EURAMOS-1

De EURAMOS studie is **gesloten**.
Het advies van de protocol commissie is om patiënten te behandelen volgens de standaardarm van het Euramos1 protocol tot er gekozen is voor een nieuw protocol.
Voor vragen kunt u zich wenden tot Dr. J.H.M. Merks, Prinses Máxima Centrum, Utrecht.

Protocolcommissie: Osteosarcomen

EURAMOS-1

ISRCTN67613327
EudraCT no. 2004-000242-20

A randomized trial of the European and American Osteosarcoma Study Group to optimize treatment strategies for resectable osteosarcoma based on histological response to pre-operative chemotherapy

Clinical trial protocol
Version: 2.1
Date: 21st April 2009

1. General Information

1.1. Important Note

This document describes a randomized trial for resectable osteosarcoma and provides information about the procedures for entering patients into it. It is not intended for use as an aide-memoir or guide for the treatment of other patients; every care was taken in its drafting but corrections or amendments may be necessary. These will be circulated to known investigators in the trial, but centers entering patients for the first time are advised to contact their appropriate Trials Center (see below and section 1.5) to confirm the correctness of the protocol, and to obtain the necessary authorization to enter patients into the trial. Participants are required to maintain confidentiality regarding the contents of this protocol. No part of this protocol may be reproduced or circulated without prior authorization by the appropriate Chief Investigator. Responsibility for the administration of the protocol treatments lies with the participants. Before entering patients into the trial, investigators must ensure that the study protocol has received ethical committee clearance. Please note that this trial is a collaboration between American and European trial groups; for consistency, American spellings are used throughout the protocol.

This protocol was developed using the Master protocol of the Deutsche Krebsgesellschaft e.V. and the Deutsche Krebshilfe e.V., versions 05/05/01 and 05/22/03.

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1.9. Committee Membership

Committee membership for each participating group, and the constitution and remit of the Trial Management Group (TMG), Trial Steering Committee (TSC) and Independent Data Monitoring Committee (IDMC) are listed in Appendix A.1.

1.10. Signature Page

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31 Dec 2008	..... Dr Neyssa Marina (for COG)
31 Dec 2008	..... Dr Sigbjørn Smeland (for SSG)
31 Dec 2008	..... Dr Jeremy Whelan (for EOI)
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1.11. Summary

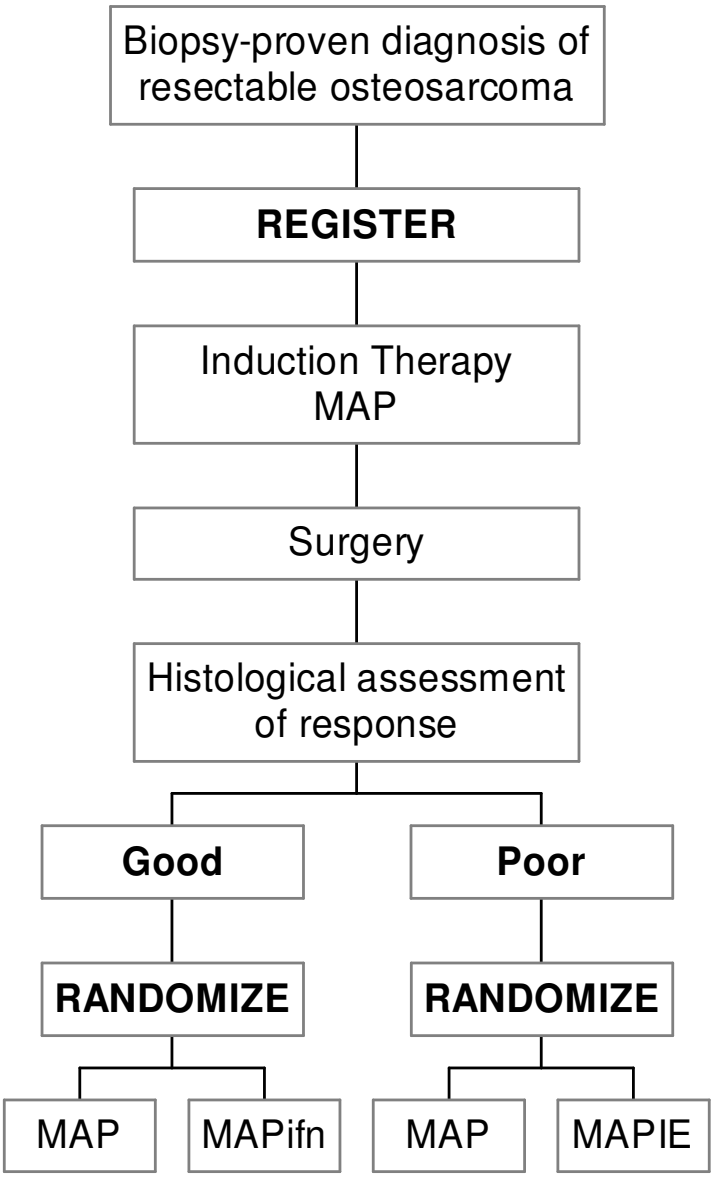
1.11.1. Summary

EURAMOS-1 is a joint protocol of four of the world's leading multi-institutional osteosarcoma groups: the North American Children's Oncology Group (COG), the German-Austrian-Swiss Cooperative Osteosarcoma Study Group (COSS), the European Osteosarcoma Intergroup (EOI) and the Scandinavian Sarcoma Group (SSG). The collaboration's main aim is to optimize the treatment of patients suffering from osteosarcoma. The EURAMOS-1 trial is open for all patients with resectable high-grade osteosarcoma of the limbs or axial skeleton, whether the tumor is localized or primarily metastatic, who are considered suitable for neo-adjuvant chemotherapy. The trial takes into account the strong prognostic value of tumor response to preoperative chemotherapy and divides patients accordingly. All patients registered will receive a standard three-drug induction regimen consisting of two cycles of cisplatin and doxorubicin along with four cycles of methotrexate (**MAP**). After recovery from chemotherapy, patients then proceed to surgical resection. Post-operative therapy is determined by the histological response of the tumor. Good responders (< 10% viable tumor) will be randomized to continue with **MAP**, or receive pegylated interferon α-2b as maintenance therapy after MAP (**MAPifn**). Poor responders (≥ 10% viable tumor) will be randomized to continue with **MAP** or to receive the same regimen with the addition of ifosfamide and etoposide (**MAPIE**). Event-free survival is the primary endpoint.

1.11.2. Zusammenfassung (German)

EURAMOS-1 ist ein von vier der weltweit führenden multizentrischen Osteosarkomgruppen (COG, COSS, EOI, SSG) gemeinsam durchgeführtes Projekt. Hauptziel der Zusammenarbeit ist die Optimierung der Therapie bei Patienten mit Osteosarkomen. EURAMOS-1 ist offen für alle Patienten mit operablen Osteosarkomen der Extremitäten oder des Körperstamms, ob lokalisiert oder primär metastatisch, bei denen keine Kontraindikation gegen die geplante neo-adjuvante Chemotherapie vorliegt. Das Behandlungskonzept berücksichtigt die hohe prognostische Aussagekraft des Tumoransprechens auf die präoperative Chemotherapie und stratifiziert die postoperative Chemotherapie dementsprechend. Alle registrierten Patienten erhalten initial eine Standard-Induktionstherapie mit drei Medikamenten, die präoperativ aus zwei Zyklen Cisplatin/Doxorubicin und vier Zyklen Methotrexat besteht (**MAP**). Nach ausreichender Erholung von den Nebenwirkungen dieser Therapie erfolgt die Operation des Primärtumors. Die Zusammenstellung der postoperativen Therapie hängt vom histologischen Ansprechen des Tumors ab. Bei Patienten mit gutem Tumoransprechen (< 10% vitaler Resttumor) wird zwischen einer Therapiefortsetzung mit **MAP** und einer Therapiefortsetzung mit MAP plus Erhaltungstherapie mit Interferon-α (**MAPifn**) randomisiert. Bei Patienten mit schlechtem Tumoransprechen (≥ 10% vitaler Resttumor) wird zwischen einer Therapiefortsetzung mit **MAP** und einer Salvage-therapie aus MAP plus Ifosfamid/Etoposid (**MAPIE**) randomisiert. Primärer Endpunkt ist das ereignisfreie Überleben.

1.12. Flow Chart



1.13. Contents

2. Introduction

2.1. Background

Osteosarcoma is the commonest bone tumor in children and adolescents. The most frequent primary sites are the distal femur and proximal tibia, and 15-20% of patients have clinically detectable metastases at the time of diagnosis. The outcome for patients with osteosarcoma was poor before the use of effective chemotherapy, with 2-year overall survival in the range of 15-20%. The administration of multi-agent chemotherapy has dramatically improved the outcome for these patients. Most current series report 3-year disease-free survival rates of 60-70% following the administration of pre-operative multi-agent chemotherapy followed by surgical resection and continuation of chemotherapy post-operatively.

The most active chemotherapeutic agents for osteosarcoma are cisplatin, doxorubicin and methotrexate. In recent years, ifosfamide, usually in combination with etoposide, has also shown activity in this disease. In osteosarcoma, it is possible to assess response to pre-operative chemotherapy via examination of the resected tumor specimen. It is known that patients who achieve a good histological response to pre-operative chemotherapy, defined as < 10% viable tumor, experience considerably better survival than those who have a poor response (≥ 10% viable tumor). Five-year survival for good responders is in the region of 75-80%, compared to 45-55% for poor responders (Bielack et al, 2002; Whelan et al, 2000).

2.2. Rationale for common trial

This protocol represents a collaboration between four major research groups in osteosarcoma: the North American Children's Oncology Group (COG), the German-Austrian-Swiss Cooperative Osteosarcoma Study Group (COSS), the European Osteosarcoma Intergroup (EOI) and the Scandinavian Sarcoma Group (SSG). The most recent results of the studies undertaken by the four groups are detailed in section 2.3. They are similar - and it is evident that further improvements will depend on refinements of therapy whose impact will be assessable only in large patient groups, or by the use of biologically based therapeutic developments, which may require refinements of traditional clinical investigative methods.

As a result, each group has agreed on the merits of trying to conduct an intergroup randomized trial. The power of such collaboration is the ability to conduct large trials with rapid accrual which would allow investigation of new agents to be undertaken quickly and effectively. In acknowledgement of the difficulties that face the establishment of a new collaboration such as this, and with the knowledge that there is no new chemotherapy agent immediately available for trial, it has been agreed that a first trial should be relatively simple. We are, therefore, undertaking a randomized trial with widely inclusive eligibility criteria which will address the question of whether chemotherapy should be changed on the basis of histological response to pre-operative chemotherapy.

Behind these developments lies a considerable degree of pragmatism and an acceptance for each group that there will need to be areas of constructive compromise to make such a collaboration work. The reward from the successful establishment of such a major collaboration will derive in the first place from closer international communication between experts, from parallel biological studies and the innovative trials that may follow.

The World Health Organization has proclaimed the current decade 2000-2010 the “Bone and Joint Decade”, to improve the health-related quality of life for people with musculoskeletal disorders throughout the world. One of the aims is to advance understanding of musculoskeletal disorders through research to improve prevention and treatment. Forty-four national governments have endorsed the Bone and Joint Decade, including ten of the European countries represented in the EURAMOS-collaboration (Austria, Belgium, Denmark, Finland, Germany, Hungary, The Netherlands, Sweden, Switzerland, and United Kingdom) as well as Canada and the United States. In his endorsement speech for the Bone and Joint Decade, UN Secretary General Kofi Annan said, "There are effective ways to prevent and treat these disabling disorders, but we must act now". This is what the EURAMOS collaborators are aiming to do.

2.3. History of participating groups

The North American Children’s Oncology Group (COG) was formed by the merger of the Children’s Cancer Group (CCG), National Wilm’s Tumor Study Group (NWTSG), Intergroup Rhabdomyosarcoma Study Group (IRSG), and the Pediatric Oncology Group (POG) in 2000. COG recently reported the results of INT 0133, a 2×2 factorial design trial examining the addition of ifosfamide and muramyl tripeptide (MTP), a biological agent, to a control regimen of methotrexate, doxorubicin, and cisplatin (MAP). Preliminary results of INT 0133 indicate that although neither treatment offers an event-free survival benefit when added to MAP individually, there is a synergistic effect when ifosfamide and MTP are administered together (Meyers et al, 2001). However, it is felt that ifosfamide was administered sub-optimally in the trial, and MTP has not been made commercially available. Thus, COG still considers MAP to be the most suitable standard chemotherapy regimen in this disease.

The Cooperative Osteosarcoma Study Group (COSS), consisting of centers in Germany, Austria and Switzerland, has performed a series of studies since 1977 incorporating multi-agent chemotherapy and surgical resection. Neoadjuvant chemotherapy was first incorporated into trial COSS-80, which turned out to be the first multi-institutional study to confirm the close correlation between histological response to preoperative treatment and the development of metastatic disease (Winkler et al, 1984). The follow-up study, COSS-82, failed to demonstrate a salvage effect for aggressive postoperative chemotherapy in patients who – in an effort to spare them from the drugs most likely to cause late effects – had received a ‘mild’, low-toxicity pre-operative regimen devoid of doxorubicin and cisplatin (Winkler et al, 1988).

The best results from COSS were achieved with the use of methotrexate, cisplatin, doxorubicin and ifosfamide, with a 10-year survival of 71% (Fuchs et al, 1998). This trial also evaluated the use of intra-arterial cisplatin and found no benefit compared to intravenous administration (Winkler et al, 1990). More recently, COSS has reduced chemotherapy associated late effects by altering doxorubicin and cisplatin administration to continuous infusions. Neither resulted in a measurable reduction of efficacy (Bielack et al, 1999a). An attempt to abbreviate chemotherapy for presumed good prognostic patients in the current trial, COSS-96, had to be abandoned prematurely because of an unexpectedly high number of relapses.

Based on 1702 patients entered into COSS trials until 1998, it was concluded that incomplete surgery was the most important negative prognostic indicator, followed by poor response, primary metastases, and axial location (Bielack et al, 2002), as well as tumor size in those patients where it could be evaluated (Bieling et al, 1996; Bielack et al, 2002).

For the last twenty years, UK and mainland European centers have participated in trials under the auspices of the European Osteosarcoma Intergroup (EOI) consisting of the National Cancer Research Institute (NCRI) Sarcoma Clinical Studies Group, the Soft Tissue and Bone Sarcoma Group of the European Organization for the Research and Treatment of Cancer (EORTC), the United Kingdom Children's Cancer Study Group (UKCCSG) and the International Society of Paediatric Oncology (SIOP). The cornerstone of EOI trials has been a two-drug regimen consisting of six cycles of cisplatin and doxorubicin. Two randomized trials conducted by EOI during the 1980s and 1990s have demonstrated that this regimen is not inferior to more complex schedules incorporating methotrexate (Bramwell et al, 1992; Souhami et al, 1997). EOI have recently concluded the BO06 trial comparing the two-drug regimen with the same regimen intensified under G-CSF cover. Preliminary results have shown that intensifying treatment in this manner does not improve progression-free or overall survival (Lewis and Nooij, 2003).

Despite the fact that it has never been shown to be inferior to other treatments for osteosarcoma in a randomized setting, many clinicians in EOI are uneasy about continuing to base therapy on the two-drug regimen. This is because other groups in Europe and the US have reported superior results using regimens including other agents such as methotrexate and ifosfamide (Bacci et al, 1998; Fuchs et al, 1998; Meyers et al, 1998).

The Scandinavian Sarcoma Group (SSG) comprises the Scandinavian countries (Denmark, Finland, Iceland, Norway and Sweden) with a population of about 25 million people. Since 1979, SSG has performed three non-randomized neo-adjuvant chemotherapy trials for high-grade osteosarcoma localized to the extremities. The first, SSG II, was based on the Memorial Sloan Kettering's T-10 protocol and included high-dose methotrexate and doxorubicin in the pre-operative chemotherapy regimen. 17% of the patients obtained a good histological response and the difference in outcome between good and poor responders was 28% (Sæter et al 1991). The second osteosarcoma trial (SSG VIII) utilized a three-drug combination of methotrexate, doxorubicin and cisplatin. The 5-year projected overall survival was 74%, which represented an improvement of 9% compared to the SSG II study (Smeland et al, 2003a). With a relatively low dose of ifosfamide (4.5 g/m^2) the combination of ifosfamide and etoposide failed to improve outcome for poor histological responders and the data did not support the strategy used with discontinuation and exchange of all drugs used pre-operatively in the salvage regimen. The following trial, the first joint Italian/Scandinavian study (ISG/SSG I), was undertaken to explore the benefit of adding high-dose ifosfamide (15 g/m^2) to the induction therapy. Preliminary analyses suggest that this attempt with maximum dose-intensity of conventional chemotherapy does not improve outcome compared to previous trials (Smeland et al, 2003b).

2.4. Rationale for EURAMOS-1

The aim of EURAMOS-1 is to investigate whether it is feasible to improve outcome for both good and poor responders through the addition of extra agents into the post-operative treatment schedule. The control arm for this trial will be the MAP regimen which served as the control arm of INT 0133.

Poor responders will be randomized between MAP and the MAPIE regimen: MAP with the addition of ifosfamide and etoposide. Good responders will be randomized between MAP and MAPifn, consisting of MAP followed by maintenance therapy with pegylated interferon α-2b.

A POG study incorporating ifosfamide with standard multi-agent chemotherapy and surgical resection for patients with clinically detectable metastases at diagnosis resulted in 5-year event-free survival (EFS) of 47% (Harris et al, 1998). In addition, the EFS for patients treated by COSS investigators is superior when ifosfamide is incorporated into the standard three-drug regimen with a 10-year survival of 71% (Fuchs et al, 1998; Winkler et al, 1990). Although INT-0133 suggested that the addition of ifosfamide to standard multi-agent therapy did not improve outcome, the results were complicated by the interaction between ifosfamide and MTP. However, careful evaluation of the INT-0133 study reveals that ifosfamide was administered at a lower dose than that given for the treatment of patients with metastatic osteosarcoma (Harris et al, 1998; Goorin et al, 2002), and some of those studies have suggested the presence of a dose-response with more favorable responses at ifosfamide dosages > 11 g/m^2. Furthermore, a recent trial from POG incorporating high-dose ifosfamide and etoposide into the standard three-drug regimen for patients with metastatic osteosarcoma reported a response rate of 62% and a 2-year EFS of 45% (Goorin et al, 2002). In addition, a previous non-randomized Italian trial reported that the addition of ifosfamide and etoposide to standard chemotherapy for patients with a poor histological response resulted in a similar outcome to that reported for patients with a good histological response (Bacci et al, 1993). This would suggest that the combination of ifosfamide and etoposide has significant activity and might improve the outcome for patients with a poor histological response. However, there is considerable difficulty interpreting these data since variations exist in patient selection and the dose of ifosfamide.

Thus, although a few studies have evaluated the role of altering post-operative therapy in poor histological responders, the role of high-dose ifosfamide and etoposide in this setting has not been investigated in a large controlled trial. It is important to determine in a randomized trial whether this drug combination improves the outcome for patients with poor histological response since the combination has significant activity in metastatic osteosarcoma. This trial randomizes patients who have had a poor histological response to pre-operative chemotherapy to post-operative therapy with either the standard three-drug regimen, MAP, or the three drugs plus ifosfamide and etoposide, MAPIE. COG has previously performed a pilot study adding this combination to the standard three-drug regimen and it is well tolerated (Mark Bernstein, personal communication).

Preliminary analysis of INT-0133 reveals that 45% of patients had a good histological response (< 10% viable tumor) to pre-operative therapy and these patients have a 3-year EFS of 75%. The additional toxicity of the ifosfamide and etoposide combination may be hard to justify in this group to further improve their outcome.

The rationale for using pegylated interferon α-2b is to maintain remission in a significant proportion of patients who have previously had a good response to chemotherapy. Interest in the value of this agent in osteosarcoma has continued since the *in vitro* effects of interferon-α on osteosarcoma cells were demonstrated more than twenty years ago. Observations since have consistently supported the growth inhibiting effect on osteosarcoma both in cell lines and animal models (Strander and Einhorn, 1977; Brosjo et al, 1985; Bauer HC et al, 1987).

As yet, interferon-α has not been widely tested in clinical trials in osteosarcoma though its role as maintenance treatment in other tumors has been extensively studied (Allen et al, 2001; Bjorkstrand et al, 2001). Most information comes from a Scandinavian series where 64 consecutive patients were treated with interferon-α as single adjuvant to surgery. 69% of patients remained in complete remission during the treatment period 1985 to 1990 (Strander et al, 1995). A pegylated preparation of interferon-α with an extended half-life offers particular advantages, less frequent administration and higher dose delivery (Bukowski et al, 2002). The tolerability of this preparation has now been demonstrated and there is additional extensive data of the tolerability of interferon-α in children treated for chronic hepatitis (Bunn et al, 2000; Wozniakowska-Gesicka et al, 2001).

2.5. Metastatic, axial and secondary osteosarcoma

Most osteosarcoma studies have exclusively focused on patients with *de novo*, localized extremity disease, thereby neglecting a significant proportion of the total patient population, namely those with axial primaries, primary metastatic disease, or secondary osteosarcomas. Altogether, they make up approximately 15 to 20% of all osteosarcoma patients. This restriction was mainly based on the belief that the latter patients have a poor prognosis regardless of therapeutic interventions, so that their inclusion into randomized trials might obscure differences between chemotherapy regimens. Recent analyses, however, have convincingly demonstrated that a significant proportion of these patients may well be cured, provided a complete surgical remission is achieved, and that the poor outlook so often associated with these situations is restricted to inoperable disease.

A recent trial has shown that the prognosis of patients with localized axial osteosarcoma in whom surgery achieved effective local control is comparable to that for patients with extremity tumors (Bielack et al, 1995). 53 patients with localized axial primaries and complete surgery had a 5-year survival rate of 53%, compared to 4% in 42 patients with inoperable localized axial disease (Flege et al, 2001). For patients with metastases at diagnosis, the 5-year survival rate was 49% (95% Confidence Interval 39%-59%) in 96 patients in whom a complete surgical remission was achieved, while it was only 4% (95% Confidence Interval 2%-6%) in 110 others (Kager et al, 2003). As for osteosarcoma arising as a second malignancy, including those arising after therapeutic irradiation, two European groups have been able to demonstrate cure rates similar to those seen in primary osteosarcoma if they arose in resectable locations (Bielack et al, 1999b; Tabone et al, 1999). Additionally, although there is no randomized evidence, early-phase trials suggest that ifosfamide and etoposide may be useful in the treatment of metastatic osteosarcoma (Gentet et al, 1997; Michelagnoli et al, 1999, Goorin et al, 2002).

In conclusion, there is good evidence that axial, primary metastatic, and secondary osteosarcomas can be cured if they are resectable, i.e. a complete surgical remission of all affected sites can be obtained. Patients with metastatic disease will be separately stratified and randomized. There is no reason to believe that their inclusion into randomized trials would obscure the assessment of survival endpoints. This will offer the opportunity to learn more about less commonly reported aspects of osteosarcoma. The EURAMOS investigators have, therefore, decided that all patients with resectable osteosarcoma should be eligible for participation in the trial, regardless of tumor site, primary metastatic status, or history of a previous malignancy.

In order to avoid interference of prior therapies with protocol chemotherapy, of the latter, only those who had not received chemotherapy for their previous cancer will be eligible. Some trial groups may have their own protocol for metastatic patients, participating clinicians should check with the relevant Trials Center before registering patients.

2.6. Quality of life

Quality of life (QL) will be assessed in EURAMOS-1 using self- and parent-assessed questionnaires. The main objective of QL assessment is to determine the impact on QL in both the short- and long-term for two groups of patients: for poor responders, the impact of the addition of ifosfamide and etoposide to standard chemotherapy; and for good responders, the addition of maintenance therapy with pegylated interferon α-2b. Describing and comparing the impact of these regimens on QL will lead to a better understanding, from the patients' perspective, of the nature of treatment related side-effects, both short- and long-term. These data will help define future treatment options for these patients.

The medical late effects of therapy have been studied extensively in children (Bhatia et al, 2003) and young adults while the impact of these late effects on the QL of the patients has been less studied, particularly in patients with osteosarcoma (Hudson et al, 1998; Nicholson et al, 1992; Postma et al, 1992; Weddington et al, 1991). Survivors of osteosarcoma are particularly vulnerable to medical late effects because of the intensity of their treatment (surgery and chemotherapy) and this may lead to a more significant impact on QL.

Additionally, the assessment of QL within EURAMOS-1 will allow more global concerns to be addressed, for example whether QL is affected by surgical factors, patient maturity (emotional and physical) and other characteristics such as gender and site of primary tumor (Nagarajan et al, 2002).

2.7. Potential toxicities

Treatment of osteosarcoma is associated with both short and long-term toxicities from chemotherapy as well as functional disability as a consequence of skeletal reconstruction necessary after resection of the primary tumor. The toxicity profile of the standard chemotherapy in this protocol is well known but additional toxicities, particularly renal and neurological, may be anticipated with the salvage chemotherapy (MAPIE) as well as for patients treated with pegylated interferon α-2b. Criteria for dose adjustment for all agents are set out in this protocol which allow a uniform approach to drug adjustment while preserving dose and schedule wherever possible. Major toxicities will be reported as serious adverse events (SAE) and circulated to investigators according to good clinical practice (GCP).

In addition to myelosuppression which is largely ameliorated by G-CSF, ifosfamide can cause renal damage – both glomerular and tubular – which appears to be at least in part dose-related. Encephalopathy is also more common at higher doses. Using higher doses than proposed in this protocol, Goorin et al reported profound myelosuppression as the principal toxicity when the combination of ifosfamide (17.5 g/m^2) and etoposide (500 g/m^2/cycle) were given pre-operatively to patients with osteosarcoma. When continued post-operatively at 12 g/m^2/cycle, additional extra-medullary toxicities such as electrolyte disturbance and Fanconi syndrome affected only a small proportion of patients (Goorin et al, 2002).

In a subsequent COG pilot study using this combination at the doses proposed in this study, toxicity has been limited allowing the delivery of planned chemotherapy (COG Meeting Book Report). As expected, severe toxicity was mostly hematological in spite of G-CSF support. Grade 3-4 neutropenia occurred in 67-90% of all courses; while about 20-30% were complicated by febrile neutropenia; up to 25% of all courses were complicated by infection with or without neutropenia. Non-hematologic toxicities were uncommon and included grade 3-4 hypokalemia in 8-17% of all courses, while grade 3-4 hypophosphatemia occurred in 3-14%. Neurotoxicity was very rare and was only reported in 2% of courses; while grade 3-4 renal dysfunction was reported in up to 1.5% of courses. In the Italian/Scandinavian ISG/SSG 1 study high-dose ifosfamide (15 g/m^2) was combined with high-dose methotrexate, doxorubicin and cisplatin as first line treatment. The scheduled treatment was feasible with a mean dose delivery of 92%. The hematological toxicity after high-dose ifosfamide was considerable and grade 4 neutropenia and thrombocytopenia occurred in 79% and 33% of all courses, respectively. Grade 2-4 neuro- or nephrotoxicity were rare and reported for 5% and 2.5 % of the patients respectively.

The toxicities commonly associated with pegylated interferon α-2b include flu-like symptoms, fatigue, anorexia, fever and mood disturbances. Myelosuppression and abnormalities of liver function may also occur. These are manageable with appropriate supportive measures and dose modification. Treatment can be sustained for many months in the majority of patients. Pegylated interferon preparations have the advantage of once weekly administration and are well tolerated even at the higher dose exposure arising from the prolonged half-life. At a reported maximum tolerated dose of 6 μg/kg/week (equivalent to approximately 180 mIU/week of pegylated interferon α-2b) the most common side effects were mild to moderate fatigue, anorexia and rigors. Grade 3/4 toxicities were uncommon and appeared to be dose-related. In this same study, 29 patients were eligible for treatment for up to one year of whom 15 discontinued due to progressive disease, 6 because of toxicity including 3 treated at 7.5 μg/kg/week, and 8 completed treatment for 12 months. Again, toxicity appeared dose-related for those treated for more prolonged periods (Bukowski et al, 2002). For this study, the selection of a dose escalation schema and a low maximum dose should ensure that most patients will receive both a tolerable and clinically valuable dose.

3. Objectives

3.1. Primary objectives

- In a randomized trial, to examine whether the addition of ifosfamide and etoposide (IE) to post-operative chemotherapy with cisplatin, doxorubicin and methotrexate improves event-free survival for patients with resectable osteosarcoma and a poor histological response to 10 weeks of pre-operative chemotherapy.

- In a randomized trial, to examine whether the addition of pegylated interferon α-2b (ifn) as maintenance therapy after post-operative chemotherapy with cisplatin, doxorubicin and methotrexate improves event-free survival for patients with resectable osteosarcoma and a good histological response to 10 weeks of pre-operative chemotherapy.

3.2. Secondary objectives

- To investigate whether the addition of IE to post-operative therapy for poor responders, and the addition of ifn as maintenance therapy for good responders, leads to an improvement in the following outcomes:
  - Overall survival
  - Short-term toxicity
  - Long-term toxicity
  - Quality of life

- To investigate whether the addition of IE to post-operative therapy for poor responders, and the addition of ifn as maintenance therapy for good responders, leads to an improvement in event-free and overall survival in patients with localized osteosarcoma at entry.

- To investigate whether biological or clinical correlates to histological response and outcome can be identified.

- To establish whether this international cooperation in clinical trials for osteosarcoma is feasible.

- To examine the outcome of the entire cohort of patients.

4. Trial Design

4.1. Trial Type

EURAMOS-1 is a phase III, open-label, randomized controlled trial of parallel groups with the intention of optimizing therapy for patients with osteosarcoma.

4.2. Trial Organization

4.2.1. Size of the trial

The target for EURAMOS-1 is to randomize a minimum of 1260 patients: 567 good responders and 693 poor responders. It is anticipated that around 2000 patients will need to be registered to achieve this.

4.2.2 Time Schedule

The date of activation for this trial is 15 December 2004. The recruitment period is expected to last for 5 years. The analysis of the primary endpoint, event-free survival, is scheduled to commence around two years after the trial closes to accrual.

4.2.3. Feasibility of Recruitment

EURAMOS-1 is a collaboration of four of the leading worldwide groups involved in clinical research in osteosarcoma: COG, COSS, EOI and SSG. Each of these groups has considerable experience in conducting large, multi-center studies in the disease.

Based on experience in previous trials, the four participating groups expect to register around 400 per year in total. Thus, accrual is expected to take 5 years.

Anticipated accrual per year, based on previous trial experience, is shown below:

Trials Group	***Anticipated accrual/year***
COG	170
COSS	120
EOI	100
SSG	30

4.2.4. Registration and Randomization Principles

Patients will be registered according to the practice of each group (see Appendix B.3). Registration and commencement of chemotherapy must take place within 30 days of diagnostic biopsy.

Surgery will be performed after 10 weeks of pre-operative chemotherapy. Once histological response to pre-operative chemotherapy has been evaluated, patients will be randomized by contacting the relevant trials center. Randomization must be performed within 35 days from date of definitive surgery. Treatment will be allocated using permuted blocks, stratified by group, site of primary tumor and presence of metastases. Registration and randomization for each group will be conducted by that group's Trials Center. Randomization procedures will be the same for each group.

Patients will be required to give informed consent twice: at registration and randomization. At randomization, the reference pathologist's assessment of histological response should be obtained whenever possible. However, if this is not obtained within 35 days of surgery, the local pathologist's assessment should be reported.

4.2.5 Ancillary Studies

Parallel biological studies will be performed in selected groups for this trial. Blood and tumor DNA will be collected and will be used to try to identify factors that influence response to therapy and its side effects, and potentially also susceptibility to the disease. Information from these studies may be used to develop improved treatment stratification and novel therapeutic approaches (see Appendix A.9).

5. Participating Researchers/Institutions

This trial has been approved by four major research groups in osteosarcoma: COG, COSS, EOI and SSG (see above, section 1.5). Any center treating osteosarcoma within Europe and North America that has been accredited by the appropriate research group may participate in this trial. Each Trials Center will have responsibility for the accreditation of institutions wishing to participate.

Participating investigators/centers must fulfill a set of basic criteria and witness this by signature of the EURAMOS-1 Commitment Form (see Appendix B.2). Criteria that are common to all groups are:

- Accreditation with one of the participating groups according to the rules set forth by that group
- Ethical approval to participate in the trial according to their national and, for European centers, European rules and regulations
- Identification of a principal investigator responsible for the institution's participation in EURAMOS-1 who fulfills the legal requirements for investigators in biomedical research of the country in which the institution is situated
- Local infrastructure sufficient to guarantee that the investigations and treatment measures required by the protocol can be performed without undue delay
- Local infrastructure sufficient to guarantee follow-up
- Willingness to allow monitoring (source data verification)
- Willingness to comply with the protocol in all aspects of patient care, specimen handling and data management, as witnessed by signature(s) on the commitment form (Appendix B.2)
- Familiarity with the chemotherapy agents under investigation, and the standard of supportive care required for these patients

6. Patient Selection Criteria

6.1. Registration

Patients must fulfill the following criteria for registration into the trial:

1. Histological evidence of high grade osteosarcoma of the extremity or axial skeleton including those arising as second malignancies
2. Resectable disease (defined as disease that is amenable or may become amenable to complete and potentially curative resection. Referral to a recognized specialist center may be appropriate)
3. Age ≤ 40 years at date of diagnostic biopsy
4. Registration within 30 days of diagnostic biopsy
5. Start chemotherapy within 30 days of diagnostic biopsy
6. Neutrophils $\geq 1.5 \times 10^9$/L (or WBC $\geq 3 \times 10^9$/L if neutrophils are not available) and platelet count $\geq 100 \times 10^9$/L
7. Glomerular Filtration Rate ≥ 70 mL/min/1.73 m^2
8. Serum bilirubin ≤ 1.5 × ULN
9. Sufficient cardiac function to receive anthracyclines: SF ≥ 28% or EF ≥ 50%
10. Adequate performance status (Karnofsky score ≥ 60 or WHO ≤ 2 for patients (age ≥ 16), Lansky score ≥ 60 (age < 16). Patients whose performance status is adversely affected by a pathologic fracture but who are able to undergo treatment are eligible (see Appendix A.2 for details)
11. Patient fit to undergo protocol treatment and follow-up
12. Written informed consent

Exclusion criteria are as follows:

1. Unresectable disease, primary or metastatic or both
2. Low grade osteosarcoma
3. Juxtacortical (periosteal, parosteal) osteosarcoma
4. Craniofacial osteosarcoma
5. Any previous treatment for osteosarcoma
6. Any previous chemotherapy for any disease
7. Any other medical condition precluding treatment with protocol chemotherapy (for example HIV, psychiatric disorder etc)
8. Pregnant or lactating women

Metastatic disease is defined in section 8.2.3.

6.2. Randomization

Patients must fulfill the following criteria for randomization into the trial:

1. Registered before definitive surgery to take part in EURAMOS-1 according to section 6.1
2. Assessment of histological response in primary tumor and randomization within 35 days of definitive surgery (assessment by reference pathologist where possible)
3. Exactly two courses of cisplatin and doxorubicin must have been administered before surgery
4. At least two courses and no more than six courses of methotrexate must have been administered before surgery
5. Recovery from prior therapy allowing administration of chemotherapy as detailed in the protocol
6. No evidence of local disease progression according to definition in Appendix A.6
7. No progression of metastatic disease or new metastatic disease
8. Macroscopically complete surgical resection of the primary tumor
9. In patients with metastatic disease, complete removal of all metastases or complete removal planned and deemed feasible
10. Age ≥ 5 at biopsy for patients with good response
11. Essential data collection will be provided (entry form, pre-operative chemotherapy forms, surgery and pathology report)
12. Written consent to undergo randomization

7. Patient Entry and Randomization

7.1. Registration

Patients should be registered by contacting the appropriate Data Center as soon as consent is obtained. Contact details for each Data Center are given in the inside cover of the protocol. Registration should take place within 30 days of biopsy according to group practice (see Appendix B.3).

7.2. Randomization

Randomization should occur as soon as histological response has been verified, according to the criteria defined in Section 6.2. Patients should be randomized by contacting the appropriate Data Center. Concealment of allocation is guaranteed as all treatment allocation is undertaken at the relevant Data Center. Treatment will be allocated using permuted blocks with appropriate stratification. Patients should be immediately informed which treatment they will be receiving. A letter confirming allocated treatment will follow within 7 days of randomization.

8. Assessment and Procedures

8.1. Key Timepoints

Registration	According to group practice (see Appendix B.3)
Surgery for primary tumor	Week 11
Re-starting chemotherapy after surgery	Week 12 or as soon as recovery allows
Randomization	Week 12-16 when histology available
Surgery for metastases	Week 11 to 20 (see section 9.2.2.5), preferably before non-MTX chemotherapy

8.2. Assessment before start of treatment

8.2.1. Basic patient information

1. Height, weight and surface area
2. Karnofsky or WHO performance status (patients ≥ 16 years) or Lansky play scale (patients < 16 years) (See Appendix A.2)
3. Menstrual history and pregnancy test if indicated

8.2.2. Disease assessment (primary tumor)

1. Plain radiograph in two planes
2. MRI of primary site, including, at least, entire involved bone and adjacent joints.

Other baseline investigations (dynamic bone scans, dynamic MRI, PET scans etc) may be carried out and used for pre-operative assessment of response (see Appendix B.9).

8.2.3. Disease assessment (metastases)

1. Chest X-ray
2. CT scan thorax
3. Radionuclide scan of skeleton with X-rays or MRI scans of affected areas

Definition of lung metastases: minimum criteria determined by spiral CT scanning are 3 or more lesions, which are ≥ 5 mm in maximum diameter or a single lesion ≥ 1 cm. These patients will be classified as having “certain” pulmonary metastases. Scans of patients registered as having metastatic disease with fewer or smaller lesions will be classified as “possible” metastatic disease and may be called for central review (see Appendix B.9).

Definition of bone metastases: must include confirmation of bone scintigraphy or plain radiograph abnormalities either by MRI scan or biopsy or both.

8.2.4. Recommended baseline assessment of organ function

1. Full blood count and differential white count
2. Blood chemistry (creatinine, urea, sodium, potassium, calcium, magnesium, phosphate, alkaline phosphatase, albumin, bicarbonate, liver transaminase, bilirubin)
3. Coagulation profile
4. Urinanalysis (dip stick) for blood, protein and glucose
5. Urine phosphate and creatinine
6. Measurement of glomerular filtration rate (GFR) either by estimation (see Appendix A.3 for suggested formulae) or direct measurement
7. Left ventricular ejection fraction or fractional shortening (echocardiogram or radionuclide scan)
8. Audiometry

Sperm storage is recommended for male patients of reproductive age.

8.3. Assessment during treatment

8.3.1. Prior to each course of chemotherapy

See section 9

8.3.2. Assessment prior to surgery

1. MRI of primary site
2. X-ray of primary tumor
3. Chest X-ray or chest CT scan
4. Appropriate imaging of known metastatic disease

8.3.3. Assessment during post-operative chemotherapy

1. Chest X-ray every 2 months
2. X-ray of primary site every 4 months

8.3.4. After last cycle of chemotherapy

1. Full blood count and differential white count
2. Blood chemistry (creatinine, urea, sodium, potassium, calcium, magnesium, phosphate, alkaline phosphatase, albumin, bicarbonate, liver transaminase, bilirubin)
3. Measurement of glomerular filtration rate (GFR) either by estimation (see Appendix A.3 for suggested formulae) or direct measurement (e.g. by radionuclide determination)
4. Measurement of renal tubular function (optional) e.g. Tubular phosphate reabsorption Tm_P/GFR (see Appendix A.3)
5. CT scan thorax (preferred) or chest X-ray
6. Appropriate imaging of former primary tumor site
7. Audiogram

8.4. After treatment

8.4.1. Disease-related follow-up after completion of chemotherapy

8.4.1.1. Follow-up schedule

Participating institutions will follow all patients indefinitely for relapse and survival, regardless of protocol violation. The following are minimum guidelines for timing of follow-up visits *from diagnostic biopsy* to ensure consistency in the detection of relapse or progression. The date of relapse will be defined as the date on which evidence of relapse is confirmed, whether radiologically or clinically. For the purposes of the study, patients will be followed-up for a minimum of five years after the end of the trial.

- **Clinic visits after end of chemotherapy**

Years 1-2	every 6 weeks-3 months
Years 3-4	every 2-4 months
Years 5-10	every 6 months
Thereafter	every 6-12 months according to local practice

- **Investigations at follow-up visits**

1. Physical examination at each visit
2. Chest X-ray at each visit
3. X-ray of the primary tumor site every 4 months until the end of year 4

Chest CT scan is optional, but should always be performed if chest X-ray shows metastasis or is inconclusive.

Bone scan and plain X-ray should be performed on clinical suspicion of bone metastases; if inconclusive, supplement with CT and/or MRI.

If relapse is detected at any site, a complete diagnostic investigation (chest CT scan, bone scan, imaging of primary tumor site) must be undertaken. Refer to Appendix B.9 for an overview over scheduled imaging studies.

8.4.2. Toxicity/Late – Effects Related Follow-Up

Multimodal therapy of osteosarcoma may be associated with permanent alterations of cardiac, renal, auditory, reproductive function, orthopedic problems and other late effects including secondary malignancies. Appropriate additional investigations must therefore be performed in order to ensure optimal patient care. Some of the cooperating groups recommend or require participation in national or international Late Effects Follow Up programs. Late effects of chemotherapy will be documented for EURAMOS-1, and will include cardiac toxicity, renal toxicity and ototoxicity.

For EURAMOS-1 the following investigations should be performed annually during follow-up and toxicity reported for a minimum of five years:

- Blood chemistry (creatinine, urea, sodium, potassium, calcium, magnesium, phosphate, alkaline phosphatase, albumin, bicarbonate, liver transaminase, bilirubin)
- Left ventricular ejection fraction or fractional shortening (echocardiogram or radionuclide scan)

8.5. Technical Guidance on Imaging studies

All imaging studies should be performed in a manner to ensure optimal quality. Refer to guidelines of competent national and international organizations for guidance. Some groups may chose to give detailed recommendations about the way in which particular imaging studies should be performed. If so, these are found in Appendix B.9. These recommendations are not mandatory parts of the protocol, but may assist to obtain optimal images.

8.6. Quality of Life

Quality of life (QL) data will be collected for all randomized patients in EURAMOS-1 via self- and parent-administered questionnaires as appropriate. The main objective of QL assessment within this clinical trial is to determine the impact on QL of the addition of IE to chemotherapy for poor responders and the addition of maintenance therapy with ifn for good responders. Describing and comparing the impact of the these regimens on QL will lead to a better understanding, from the patients' perspective, of the nature of treatment related side-effects, both short- and long-term. These data will help define future treatment options for these patients.

For patients aged 16 and over, QL will be assessed using the EORTC QLQ-C30 questionnaire (Aaronson et al, 1993; Fayers et al, 1995). For patients aged 15 and under, there is no pediatric QL measure that has been validated in all participating countries. Thus, QL for patients aged 15 and under will be assessed using either the generic PedsQL questionnaire (Varni et al, 2002), or the PEDQOL questionnaire (Calaminus et al, 2000), according to group practice.

The initial QL assessment will take place in protocol week 5, as early as the end of the second M course but before the second AP course. Assessments will then take place at 3 months after definitive surgery to primary tumor and at 18 months and 3 years after commencement of protocol therapy. Full details of QL administration are contained in Appendix A.8.

9. Trial Medication and Treatment Plan

9.1. Chemotherapy

9.1.1. Agents used

The following agents will be used as part of osteosarcoma treatment according to EURAMOS-1:

- **Doxorubicin**
  (Adriamycin) NSC #123127
- **Cisplatin**
  (Cis-diaminedichloroplatinum II, CDDP, Platinol) NSC #119875
- **Methotrexate**
  (MTX, amethopterin) NSC #000740
- **Ifosfamide**
  (IFX, IFOS, IFO) NSC #109724
- **Etoposide**
  (VP-16, VePesid) NSC #141540
- **Pegylated interferon α-2b**
  (Peg-Intron) NSC # 720033

9.1.2. Agent Availability

Doxorubicin, methotrexate, cisplatin, ifosfamide, and etoposide preparations from various manufacturers are commercially available in all countries participating in EURAMOS-1. Most of the preparations which are commercially available include osteosarcoma or sarcoma among the indications for which they were licensed. The agents will be obtained from the (hospital) pharmacies of the investigators' institutions according to local practice. The choice of the specific preparation which is to be given to a particular patient is left at the discretion of his treating physician and the protocol does not include recommendations to use or not use the preparations of specific manufacturers. The chosen supplier's recommendations regarding storage, stability, dilution, incompatibilities, and measures of caution should be followed (see appropriate package inserts and Appendix A.5 for further information).

Pegylated interferon α-2b (Peg-Intron) will be supplied for this trial by Integrated Therapeutics Group Inc (ITGI), a wholly-owned subsidiary of Schering-Plough. Contact information for individual Schering-Plough country operations and request of supply is included in Appendix B.5. Drug will be supplied as follows.

Identification of Product and Packaging:

- Supply type: Open-label drug supply
- Product Identity: Pegylated interferon α-2b (Peg-Intron / SCH 054031)
- Supplied by Schering Corporation in single use vials containing a label dose strength of 50 µg or 100µg of Peg-Intron
- Kit Configuration: Peg-Intron supply is delivered in boxes containing 6 vials per box.

9.1.3. Labeling

Peg-Intron Powder for Injection is supplied for this study by ITGI and will be labeled with the following information:

- Product Identity: Pegylated interferon α-2b (Peg-Intron / SCH 054031)
- Vials of dose strength of 50µg or 100µg PEG-Intron
- Lot and/or packaging/shipment request (PSR) number
- Study number: "EURAMOS-1"
- Appropriate storage conditions
- The appropriate investigational use statement
- Will contain a caution statement in compliance with local requirement
- ITGI Identification

As only licensed chemotherapy agents are used, there will be no trial-specific labeling of the chemotherapy medication in addition to the labels of the commercial products.

9.1.4. Side effects

The known side effects of the agents which are to be used as part of protocol therapy are specified in Appendix A.5. Investigators are requested to refer to the package inserts for additional information.

9.1.5. Medical Emergencies associated with trial medication

Investigators should refer to the detailed information given in section 9.1, Appendix A.5, the chemotherapy administration sheets (Appendix B.6) and to the appropriate package insert for information about the handling of emergencies which might arise in connection with trial medication, such as anaphylaxis, extravasation, acute methotrexate intoxication, or accidental overdose. Investigators are requested to contact the appropriate Trials Center for assistance in case of such emergencies.

9.1.6. Drug Accountability

Peg-Intron is an investigational agent in this setting, it will require appropriate drug accountability according to ICH-GCP.
As all chemotherapy agents are licensed in the countries in which the trial will be performed, drug accountability measures for chemotherapy agents as required for clinical trials with unlicensed experimental agents will not be necessary.

9.1.7. Treatment Regimen

9.1.7.1. Definition of abbreviations used

- A (DOX) Doxorubicin (Adriamycin) 37.5 mg/m^2/day × 2 (Σ 75 mg/m²)
- E (ETO) Etoposide 100 mg/m^2/day × 5 (Σ 500 mg/m²)
- P (DDP) Cisplatin 120 mg/m^2/course (Σ 120 mg/m²)
- I (IFO14 g) Ifosfamide 14 g 2800 mg/m^2/day × 5 (Σ 14000 mg/m²)
- i (IFO9 g) Ifosfamide 9 g 3000 mg/m^2/day × 3 (Σ 9000 mg/m²)
- M (MTX) Methotrexate 12000 mg/m^2 (Σ 12000 mg/m²)
  with leucovorin (folinic acid) rescue
- ifn (IFNα) Pegylated interferon α-2b 0.5-1.0 µg/kg s.c. once weekly
  (Peg-Intron)

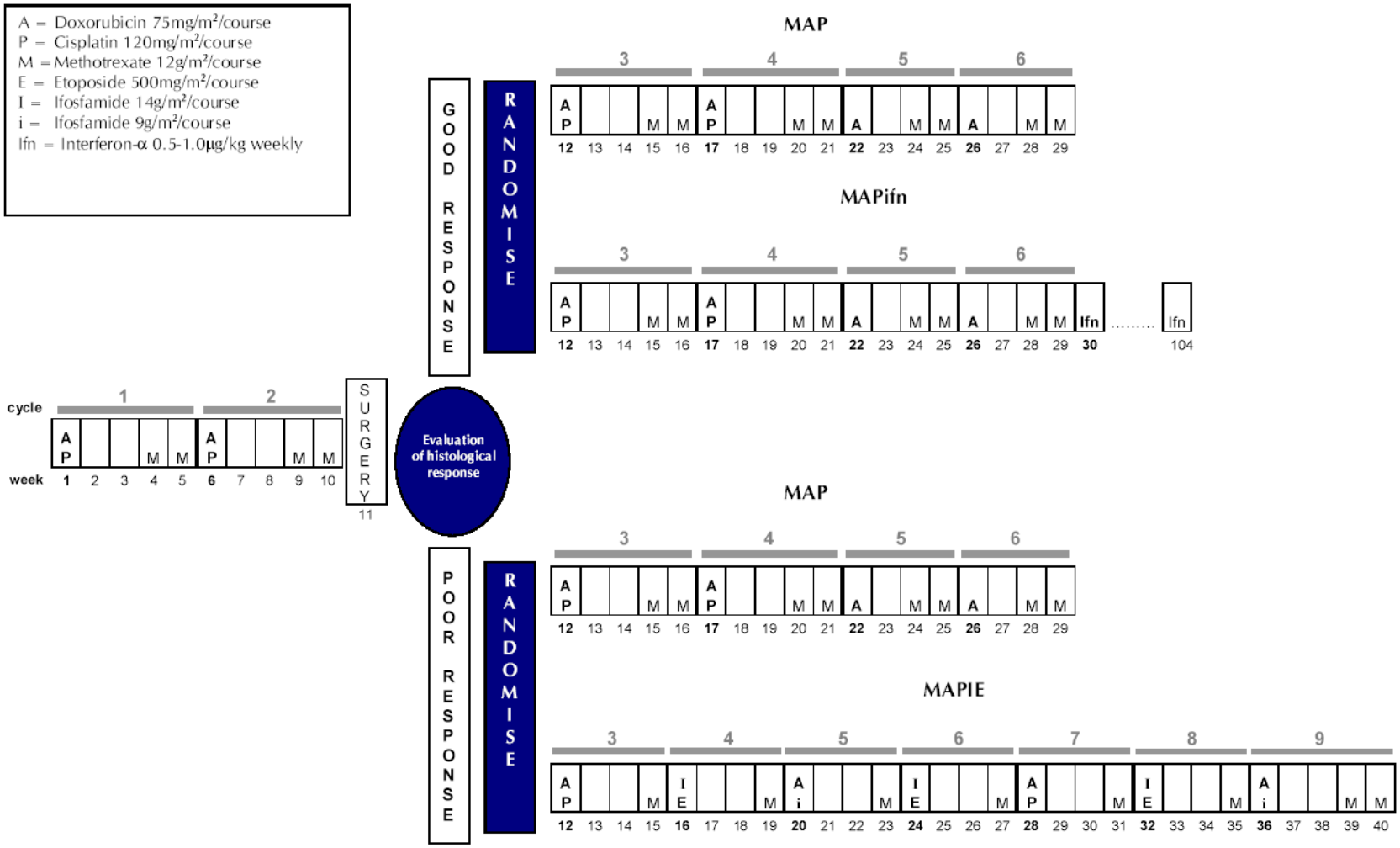
(all drugs given IV except pegylated interferon α-2b)

9.1.7.2. Definition of treatment courses

- A = Doxorubicin (Adriamycin) 37.5 mg/m^2/day × 2 (Σ 75 mg/m²)
- Ai = Doxorubicin (Adriamycin) 37.5 mg/m^2/day × 2 (Σ 75 mg/m²)
  \+ Ifosfamide 9 g 3000 mg/m^2/day × 3 (Σ 9000 mg/m²)
- AP = Doxorubicin (Adriamycin) 37.5 mg/m^2/day × 2 (Σ 75 mg/m²)
  \+ Cisplatin 120 mg/m^2/course (Σ 120 mg/m²)
- IE = Ifosfamide 14 g 2800 mg/m^2/day × 5 (Σ 14000 mg/m²)
  \+ Etoposide 100 mg/m^2/day × 5 (Σ 500 mg/m²)
- M = Methotrexate 12000 mg/m^2 (Σ 12000 mg/m²)
  with leucovorin rescue
- ifn Pegylated interferon α-2b 0.5-1.0 µg/kg s.c.
  (Peg-Intron)

(all drugs given IV except Pegylated interferon α-2b)

9.1.7.3. Scheduled treatment dates



Note: A third preoperative course of AP should not be given, as this renders the patient ineligible for randomisation. It is permissible to administer up to two additional MTX courses and have the patient remain eligible for randomization (see randomisation criterion 3 and 4). Surgery for metastases should take place between weeks 11-20. See section 9.2.2.5

9.1.7.4. Cumulative dosages (mg/m²)

	MTX Methotrexate	**DOX** Doxorubicin (Adriamycin)	**DDP** Cisplatin	**IFO** Ifosfamide	**ETO** Etoposide	**IFNα** Interferon-α
MAP	144000	450	480	-	-	-
MAPifn	144000	450	480	-	-	
MAPIE	144000	450	480	60000	1500	-

9.1.8. Treatment administration details

All participating groups have extensive experience with the chemotherapeutic agents used in EURAMOS-1. Each group has previously developed detailed guidelines about the administration of the drugs and supportive care measures. These guidelines are identical in many aspects, such as the necessity for hydration routines for methotrexate, cisplatin, and ifosfamide, for mesna administration with ifosfamide, or for serum level adapted leucovorin rescue with high dose methotrexate. The guidelines given below apply to all participating groups. Details, which may differ slightly between groups, are elaborated in the group specific administration appendices (Appendix B.6).

Body surface area should be estimated from a standard nomogram: DO NOT attempt to correct for amputation. For obese subjects, no alterations or dose capping are recommended.

A third pre-operative course of AP should not be given as this renders the patient ineligible for randomization. It is permissible to administer up to two additional MTX courses and have the patient remain eligible for randomization (see randomization criterion 3 and 4).

Drug dosage should be modified as little as possible. If necessary, delay treatment in order to administer full doses. Decisions regarding the possibility of proceeding with chemotherapy after a delay should be re-evaluated at least every 3-4 days. In the absence of prohibitive toxicity, an attempt to give any omitted chemotherapy should be made after the end of scheduled protocol chemotherapy (i.e. after week 29 in arms MAP and MAPifn and after week 40 in arm MAPIE).

9.1.8.1. Course name: AP

9.1.8.1.1. Course definition

Doxorubicin (adriamycin)	75 mg/m^2
Cisplatin	120 mg/m^2

9.1.8.1.2. Course timing

Weeks	1, 6, 12, 17 (MAP, MAPifn) 1, 6, 12, 28 (MAPIE)

9.1.8.1.3. Mandatory tests

- Height, weight and surface area
- Clinical examination
- Full blood count and differential white count
- Blood chemistry (creatinine, urea, sodium, potassium, calcium, magnesium, phosphate, alkaline phosphatase, albumin, bicarbonate, liver transaminase, bilirubin)
- Beyond cumulative dose of doxorubicin 300 mg/m^2: Left ventricular ejection fraction or fractional shortening (echocardiogram or radionuclide scan)
- Measurement of GFR either by estimation (see Appendix A.3 for suggested formulae) or direct measurement (e.g. radio-isotopic method)
- Audiometry before 3rd and 4th AP cycle

9.1.8.1.4. Minimum requirements

General clinical condition permitting chemotherapy

Neutrophils	≥ 0.75 x10^9/L
or WBC	≥ 2.0 x10^9/L
Platelets	≥ 75 x10^9/L
Bilirubin	≤ 1.25 x ULN
GFR	≥ 70 mL/min/1.73m^2
Cardiac function	FS ≥ 28% or LVEF ≥ 50% at last scheduled assessment
Hearing	< Grade 2 at ≤2 kHz

9.1.8.1.5. Administration

Note: commence A-containing cycles at full dose unless previous dose reduction for A-containing cycles for gastrointestinal cardiotoxicity. In those circumstances continue A at previous reduced dose

Doxorubicin	48 hour continuous IV infusion = 37.5 mg/m^2/day administered by 48 hour continuous infusion.
Cisplatin	Continuous 72 hour IV infusion Or 4 hour infusion (60 mg/m^2) x 2 days (COG).
Hydration	Sufficient hydration is mandatory. Details of individual Groups' practice are in Appendix B.6.

9.1.8.1.6. Supportive care

G-CSF	G-CSF is recommended when a previous AP cycle has been complicated by fever and neutropenia with non-catheter related sepsis or prolonged hospitalization (>7 days). Begin at least 24 hours after the completion of chemotherapy. Continuation until WBC > 5.0 x 10^9/L is recommended.
Cardioprotection	Wherever possible use prolonged continuous infusion. Dexrazoxane may be used if a confirmed 10% fall within the normal range of LVEF or similar fall within the normal range of FS occurs (see Appendices A.5 and B.6).

9.1.8.1.7. Dose Modifications for AP

Toxicity	Grade	Action
Myelosuppression	On Day 1 of cycle ANC < 0.75 x 10^9/L or WBC < 2.0 x10^9/L Plts < 75 x 10^9/L	Delay and repeat within 3-4 days until criteria are met. Retreat at full dose unless previous dose reduction. For repeated delay (> 7 days) use G-CSF. If delayed > 7 days in spite of G-CSF reduce cisplatin by 25%.
Febrile Neutropenia with or without documented infection	All grade 4, consider for grade 3	Add G-CSF. Further episodes despite G-CSF: reduce cisplatin by 25%.
-Mucositis -Severe abdominal pain -Diarrhea -Typhlitis	Grade 4 mucositis or typhilitis or repeated Grade 3 mucositis	Delay until resolved & decrease subsequent doxorubicin to 60 mg/m^2/cycle.
Hearing	≥ Grade 2	Discontinue cisplatin if hearing loss extends to 2kHz or lower frequencies.
Cardiotoxicity	LVEF < 50% or SF < 28%	Repeat echo or MUGA in one week. If echo or MUGA within normal range proceed with chemotherapy. If LVEF does not normalize, omit all further doxorubicin.
Renal Toxicity	Serum creatinine > 1.5 x baseline or GFR <70mL/min/1.73 m^2	Delay for one week. If renal function does not improve, omit cisplatin and give doxorubicin alone. Resume cisplatin at future courses if GFR ≥ 70 mL/min/1.73 m^2.
Hepatic Toxicity	Raised Bilirubin	Reduce doxorubicin as follows: **Concentration** — **% Dose** 0 – 21 µmol/L (0 -1.24 mg/dL) 100% 22 – 35 µmol/L (1.25-2.09 mg/dL) 75% 36 – 52 µmol/L (2.1 -3.05 mg/dL) 50% 53 – 86 µmol/L (3.06-5.0 mg/dL) 25% > 87 µmol/L (> 5.0 mg/dL) 0%
Neuropathy	Grade 1 ≥ Grade 2	Reduce cisplatin by 25% for all future courses. Omit cisplatin for all future courses.

9.1.8.2. Course name: M

9.1.8.2.1. Course definition

Methotrexate	12 g/m^2

9.1.8.2.2. Course timing

Weeks	4, 5, 9, 10, 15, 16, 20, 21, 24, 25, 28, 29 (MAP, MAPifn) 4, 5, 9, 10, 15, 19, 23, 27, 31, 35, 39, 40 (MAPIE)

9.1.8.2.3. Mandatory tests

- Height, weight and surface area
- Clinical examination
- Full blood count and differential white count
- Blood chemistry (creatinine, urea, sodium, potassium, calcium, magnesium, phosphate, alkaline phosphatase, albumin, bicarbonate, liver transaminase, bilirubin)
- Measurement of GFR either by estimation (see Appendix A.3 for suggested formulae) or direct measurement (e.g. radio-isotopic method)
- Urinary pH

9.1.8.2.4. Minimum requirements

General clinical condition permitting chemotherapy including resolving mucositis ≤ grade 1
No serous effusions or other '3rd space'

Neutrophils	≥ 0.25 x10^9/L
Or WBC	≥1.0 x10^9/L
Platelets	≥ 50 x10^9/L
Bilirubin	≤ 1.25 x ULN
Transaminases	may be any value in the absence of other causes of liver dysfunction
GFR	≥ 70 mL/min/1.73 m^2
Urinary pH	> 7.0 immediately prior to MTX
Monitoring	Availability of serum MTX level monitoring

9.1.8.2.5. Administration

Methotrexate	4 hour infusion.
Hydration	Adequate fluid with electrolytes and bicarbonate must be given to maintain urine output and alkalinization. This should be maintained until MTX serum level is considered safe according to group practice (generally either <0.1 μmol/L or <0.2 μmol/L). For details see Appendix B.6.
Urine pH	A urinary pH >7 must be achieved before starting the MTX infusion and maintained until serum level is considered safe according to group practice (generally either <0.1 μmol/L or <0.2 μmol/L). For details see Appendix B.6.

9.1.8.2.6. Supportive care

MTX serum levels: Must be taken at 24 - 28 hours from start of MTX then daily until level is considered safe according to group practice (generally either <0.1 μmol/L or <0.2 μmol/L).

Leucovorin Rescue: This must begin 24 - 28 hours after start of MTX infusion and be continued until serum MTX level is considered safe according to group practice (generally either <0.1 μmol/L or <0.2 μmol/L). For details see Appendix B.6.

9.1.8.2.7. Methotrexate toxicity — recommendations for management

The groups collaborating in EURAMOS-1 have each developed detailed guidelines about how to handle such hazardous situations. Adherence to these guidelines has led to positive results in previous studies.

Methotrexate toxicity and delayed methotrexate excretion can pose a significant and immediate threat to any patient receiving high dose methotrexate.

SEVERE TOXICITY REQUIRES PROMPT INTERVENTION.

All group's Methotrexate guidelines include provisions for adequate hydration and alkalinization of the urine, for the serial determination of methotrexate serum levels, and for leucovorin administration. All groups require adaptations of the leucovorin dose to methotrexate levels and clinical toxicity. All guidelines include nomograms which assist in finding the correct leucovorin dose for specific situations. All groups allow alternate approaches such as a 24 hour continuous infusion of leucovorin or carboxypeptidase G_2 to be used at the discretion of investigator in cases where there is evidence of significantly delayed methotrexate excretion or severe clinical toxicity. **Contact appropriate Trials Center and/or CI in case of significantly delayed methotrexate excretion or severe toxicity.** Patients with severe Methotrexate toxicity may experience renal failure, hepatic dysfunction and myelosuppression. Patients may have severely delayed MTX excretion with MTX levels > 0.1 μM and elevated serum creatinine for more than 21 days.

Carboxypeptidase G_2 (Voraxaze™, Glucarpidase) is an effective agent for the treatment of severe or life-threatening MTX-induced toxicity. Its use should be always considered early for patients developing acute impairment of renal function after MTX. Details of indications, supply and administration are in Appendix A.5.

The group specific guidelines for the management of methotrexate administration, methotrexate toxicity, and delayed excretion are given in Appendix B.6.

It is expected that patients receiving high dose Methotrexate will develop hypertransaminasemia and occasionally hyperbilirubinemia. These elevations can last up to two weeks following the infusion and will not be considered toxicity requiring discontinuation of the drug. Persistent hyperbilirubinemia and/or Grade 3 or 4 hypertransaminasemia for longer than 3 weeks should result in discontinuation of MTX if no other etiology is apparent. Notify appropriate CI or Trials Center.

In the event of severe toxicity or recurrent moderate toxicity that does not have an obvious correctable cause, contact the appropriate CI or Trials Center.

9.1.8.2.8. Dose Modifications for M

Note that no dose **reductions** will apply

Toxicity	Grade	Action
Myelosuppression	On Day 1 of cycle ANC < 0.25 x 10^9/L Or WBC < 1.0 x10^9/L Plts < 50 x 10^9/L	Delay until recovery according to group practice (see Appendix B.6).
- Mucositis - Severe abdominal pain - Diarrhea	Grade 3-4 mucositis or diarrhea after MTX If persists for >1 Wk & is present on Day 29 of MAP cycle	Consider leucovorin rescue adjustment. Reminder: exclude drugs interfering with excretion. Omit Day 29 methotrexate (of this cycle only) & proceed to next cycle (or surgery).
Renal Toxicity	GFR <70mL/min/1.73m^2	Delay until recovery. If renal function does not improve within 1 week, omit MTX & proceed to next possible cycle. If renal function subsequently improves, MTX can be resumed. (Patients receiving A alone may continue with doxorubicin).
Abnormal LFTs	Not MTX induced LFTs elevated Probably MTX induced i.e. up to 3 weeks after MTX Bilirubin > 1.25 x ULN	Delay one week. Give if ALT < 10 x ULN. It is expected that patients receiving high dose Methotrexate will develop hypertransaminasemia and occasionally hyperbilirubinemia. These elevations can last up to two weeks following the methotrexate infusion and will not be considered toxicity requiring discontinuation of the drug. Persistent hyperbilirubinemia for longer than three weeks will result in discontinuation of MTX.

9.1.8.3. Course name: IE

9.1.8.3.1. Course definition

Ifosfamide	14 g/m^2
Etoposide	500 mg/m^2

9.1.8.3.2. Course timing

Weeks	16, 24, 32 MAPIE only

9.1.8.3.3. Mandatory tests

- Height, weight and surface area
- Clinical examination
- Full blood count and differential white count
- Blood chemistry (creatinine, urea, sodium, potassium, calcium, magnesium, phosphate, alkaline phosphatase, albumin, bicarbonate, liver transaminase, bilirubin)
- Measurement of GFR either by estimation (see Appendix A.3 for suggested formulae) or direct measurement (e.g. radio-isotopic method)
- Urine dipstick for blood before and at least once daily during ifosfamide administration
- Bicarbonate before and at least once daily during ifosfamide administration

Elective Tests
- Measurement of urinary phosphate re-absorption (TmP/GFR) to assess renal tubular function (see Appendix A.3)

9.1.8.3.4. Minimum requirements

General clinical condition permitting chemotherapy

Neutrophils	≥ 0.75 x10^9/L
or WBC	≥ 2.0 x10^9/L
Platelets	≥ 75 x10^9/L
Bilirubin	≤ 1.25 x ULN
GFR	≥ 70 mL/min/1.73 m^2
Urine	No hematuria

9.1.8.3.5. Administration

Ifosfamide	4 hour IV infusion = 2.8 g/m^2/day x 5.
Etoposide	1 hour IV infusion = 100 mg/m^2/day x 5.
mesna	Continuous IV infusion (2.8 g/m^2/day x 5) and continuing for a minimum of 12 hours after the final dose of ifosfamide (loading dose allowed).
Hydration	Adequate hydration throughout ifosfamide infusion and for a minimum of 12 hours after end of ifosfamide infusion.

9.1.8.3.6. Supportive care

G-CSF	Use G-CSF after ALL IE cycles. Begin at least 24 hours after completion of chemotherapy. Continuation until WBC > 5.0 x 10^9/L is recommended.
Encephalopathy	This will occasionally occur and vary in degree from mild agitation to coma and seizures. Risk factors are poor renal function, low albumin and pelvic tumors. See appendix A.5 for information on methylene blue and dose modifications for adjustment of subsequent ifosfamide-containing cycles (IE or Ai).

9.1.8.3.7. Dose Modifications for IE

Toxicity	Grade	Action
Myelosuppression	On Day 1 of cycle ANC $< 0.75 \times 10^9$/L Or WBC $< 2.0 \times 10^9$/L	Delay and repeat within 3-4 days Retreat at full dose unless previous dose reduction. Consider reduction if cycle is delayed > 7 days in spite of G-CSF (20% dose reduction by omitting the last day of the cycle).
Febrile neutropenia after previous IE	All grade 4 Consider for grade 3	Reduce both drugs by 20% i.e. omit last day of cycle. If a second episode occurs, omit etoposide.
- Mucositis - Severe abdominal pain Diarrhea Typhlitis	Grade 4 mucositis after previous IE Repeated Grade 3 mucositis	Reduce etoposide by 50%.
Renal Toxicity – glomerular	Serum Creatinine 1.5 x baseline or GFR < 70 mL/min/1.73 m^2	Delay for one week. If renal function does not improve, discontinue ifosfamide, confirm GFR and consider substituting cyclophosphamide and mesna, both 500mg/m^2 x 5 days.
Renal Toxicity – tubular (based on GFR, serum bicarbonate, need for electrolyte replacement, or TmP/GFR)	Grade 1 Grade 2 Grade 3/4	No change. Consider reduction of ifosfamide by 20% i.e. omit last day. No further ifosfamide. Consider substituting cyclophosphamide and mesna, both 500 mg/m^2 x 5 days.
Hemorrhage, GU - Bladder (Hematuria) - exclude vaginal bleeding and if microscopic, confirm where possible by microscopy	Dipstick positive prior to ifosfamide Microscopic during ifosfamide ≥ 2 occasions ≥ Grade 2	Exclude other causes; double mesna dose +/- increase hydration. Give additional bolus 600 mg/m^2 then continuous infusion at double dose. If persists, discontinue ifosfamide and contact CI. Discontinue ifosfamide, continue double dose mesna and hydration for 24 hours after ifosfamide; consider cystoscopy; contact CI if CTCAE grade 3 or 4
Neurological toxicity – confusion or depressed level of consciousness	Grade 2 Grade 3 Grade 4	No change unless persistent and distressing. Then decrease ifosfamide by 20% (omit last day's dose). If persists, reduce by a further 20%. Stop ifosfamide for this cycle. Decrease next cycle of ifosfamide by 20% (omit last day's dose). If persists, reduce by a further 20%. No further ifosfamide. Consider substituting cyclophosphamide and mesna, both 500 mg/m^2 x 5 days.
Neurological toxicity - seizures	Grade 2 Grade 3 Grade 4	Consider anticonvulsants (benzodiazepines preferred) and/or stopping ifosfamide for this cycle. Continue future cycles at same dose. Stop ifosfamide for this cycle. Consider future cycles at same dose with anticonvulsant coverage. No further ifosfamide. Consider substituting cyclophosphamide and mesna, both 500 mg/m^2 x 5 days.
Neurological toxicity – peripheral neuropathy (exclude other causes)	≥ Grade 2	Omit further ifosfamide. Consider substituting cyclophosphamide and mesna, both 500 mg/m^2 x 5 days.

9.1.8.4. Course name: Ai

9.1.8.4.1. Course definition

Doxorubicin (adriamycin)	75 mg/m^2
Ifosfamide	9 g/m^2

9.1.8.4.2. Course timing

Weeks	20, 36 MAPIE only

9.1.8.4.3. Mandatory tests

- Height, weight and surface area
- Clinical examination
- Full blood count and differential white count
- Blood chemistry (creatinine, urea, sodium, potassium, calcium, magnesium, phosphate, alkaline phosphatase, albumin, bicarbonate, liver transaminase, bilirubin)
- Beyond cumulative dose of doxorubicin 300 mg/m^2: Left ventricular ejection fraction or fractional shortening (echocardiogram or radionuclide scan)
- Measurement of GFR either by estimation (see Appendix A.3) or direct measurement (e.g. radio-isotopic method)
- Urine dipstick for blood before and at least once daily during ifosfamide administration
- Bicarbonate before and at least once daily during ifosfamide administration

Elective Tests
- Measurement of urinary phosphate re-absorption (TmP/GFR) to assess renal tubular function (see Appendix A.3)

9.1.8.4.4. Minimum requirements

General clinical condition permitting chemotherapy

Neutrophils	≥ 0.75 x10^9/L
or WBC	≥ 2.0 x10^9/L
Platelets	≥ 75 x10^9/L
Bilirubin	≤ 1.25 x ULN
Cardiac function	FS ≥ 28% or LVEF ≥ 50% at last scheduled assessment
GFR	≥ 70 mL/min/1.73 m^2
Urine	No hematuria

9.1.8.4.5. Administration

Note: commence A-containing cycles at full dose unless previous dose reduction for A-containing cycles for gastrointestinal cardiotoxicity. In those circumstances continue A at previous reduced dose

Doxorubicin	48 hour continuous IV infusion = 37.5 mg/m^2/day administered by 48 hour continuous infusion.
Ifosfamide	4 hour IV infusion = 3 g/m^2/day x 3.
mesna	Continuous IV infusion (3 g/m^2/day x 3) and continuing for a minimum of 12 hours after the final dose of ifosfamide (loading dose allowed).

Hydration — Adequate hydration throughout ifosfamide infusion and for a minimum of 12 hours after end of ifosfamide infusion.

9.1.8.4.6. Supportive care

G-CSF — The use of G-CSF after all Ai cycles is recommended. Begin at least 24 hours after completion of chemotherapy. Continuation until WBC > 5.0 x 10^9/L is recommended.

Encephalopathy — This will occasionally occur and vary in degree from mild agitation to coma and seizures. Risk factors are poor renal function, low albumin and pelvic tumors. See appendix A.5 for information on methylene blue and dose modifications for adjustment of subsequent ifosfamide-containing cycles (IE or Ai).

Cardioprotection — Wherever possible use prolonged continuous infusion. Dexrazoxane may be used if a confirmed 10% fall within the normal range of LVEF or similar fall within the normal range of FS occurs (see Appendices A.5 and B.6).

9.1.8.4.7. Dose Modifications for Ai

Toxicity	Grade	Action
Myelosuppression	On Day 1 of cycle ANC < 0.75 x 10^9/L or WBC < 2.0 x10^9/L Pts < 75 x 10^9/L	Delay and repeat within 3-4 days. Retreat at full dose unless previous dose reduction. For repeated delay use G-CSF.
Febrile Neutropenia after previous Ai	All grade 4, consider for grade 3	If occurs despite G-CSF, reduce ifosfamide to 6g/m^2 by eliminating the last day of the cycle.
- Mucositis - Severe abdominal pain - Diarrhea - Typhlitis	Grade 4 mucositis after Ai or AP or repeated Grade 3 mucositis	Delay until resolved & decrease subsequent doxorubicin to 60 mg/m^2/cycle Note: if previous doxorubicin dose reductions other than for cardiotoxicity or grade 4 mucositis, contact CI.
Cardiotoxicity	LVEF < 50% or SF ≤ 28%	Repeat echo or MUGA in one week. If echo or MUGA within normal range proceed with chemotherapy. If LVEF does not normalize, omit all further doxorubicin.
Hepatic Toxicity	Raised Bilirubin	Reduce doxorubicin as follows: **Concentration** — **% Dose** 0 – 21 µmol/L (0 -1.24 mg/dL) 100% 22 – 35 µmol/L (1.25-2.09 mg/dL) 75% 36 – 52 µmol/L (2.1 -3.05 mg/dL) 50% 53 – 86 µmol/L (3.06-5.0 mg/dL) 25% > 87 µmol/L (> 5.0 mg/dL) 0%
Renal Toxicity – glomerular	Serum Creatinine 1.5 x baseline or GFR < 70 mL/min/1.73 m^2	- Delay for one week. If renal function does not improve, omit ifosfamide, confirm GFR and consider substituting cyclophosphamide and mesna, both 500 mg/m^2 x 3 days for future cycles.

Renal Toxicity – tubular (based on GFR, serum Bicarbonate, need for electrolyte replacement, or TmP/GFR)	Grade 1	No change.
	Grade 2	Reduce ifosfamide to 6 g/m^2 (by eliminating last day).
	Grade 3/4	No further ifosfamide Consider substituting cyclophosphamide 500 mg/m² x 3 days.
Hemorrhage, GU - Bladder (Hematuria) - exclude vaginal bleeding and if microscopic, confirm where possible by microscopy	Dipstick positive prior to ifosfamide	Exclude other causes; double mesna dose +/- increase hydration.
	Microscopic during ifosfamide ≥ 2 occasions	Give additional bolus 600 mg/m^2 then continuous infusion at double dose. If persists, discontinue ifosfamide and contact CI.
	≥ Grade 2	Discontinue ifosfamide, continue double dose mesna and hydration for 24 hours after ifosfamide consider cystoscopy; contact CI if CTCAE grade 3 or 4
Neurological toxicity – confusion or depressed level of consciousness	Grade 2	No change unless persistent and distressing. For further cycles decrease ifosfamide to 6 g/m^2. (eliminating last day of cycle) If persists further, omit ifosfamide. Consider substituting cyclophosphamide and mesna, both 500 mg/m^2 x 3 days.
	Grade 3	Stop ifosfamide for this cycle. Decrease next cycle of ifosfamide to 6 g/m^2 (eliminating last day of cycle). If persists further, omit ifosfamide. Consider substituting cyclophosphamide and mesna, both 500 mg/m^2 x 3 days.
	Grade 4	No further ifosfamide. Consider substituting cyclophosphamide and mesna, both 500 mg/m^2 x 3 days.
Neurological toxicity - seizures	Grade 2	Consider anticonvulsants (benzodiazepines preferred) and/or stopping ifosfamide for this cycle. Continue future cycles at same dose.
	Grade 3	Stop ifosfamide for this cycle. Consider future cycles at same dose with anticonvulsant coverage.
	Grade 4	No further ifosfamide. Consider substituting cyclophosphamide and mesna, both 500 mg/m^2 x 3 days.
Neurological toxicity – peripheral neuropathy (exclude other causes)	≥ Grade 2	Omit further ifosfamide. Consider substituting cyclophosphamide and mesna, both 500 mg/m^2 x 3 days.

9.1.8.5. Course name: A

9.1.8.5.1. Course definition

Doxorubicin (adriamycin) 75 mg/m^2

9.1.8.5.2. Course timing

Weeks 22, 26 MAP and MAPifn only

9.1.8.5.3. Mandatory tests

- Height, weight and surface area
- Clinical examination
- Full blood count and differential white count
- Blood chemistry (creatinine, urea, sodium, potassium, calcium, magnesium, phosphate, alkaline phosphatase, albumin, bicarbonate, liver transaminase, bilirubin)
- Beyond cumulative dose of 300 mg/m^2: Left ventricular ejection fraction or fractional shortening (echocardiogram or radionuclide scan)

9.1.8.5.4. Minimum requirements

General clinical condition permitting chemotherapy:

Neutrophils	≥ 0.75 x10^9/L
or WBC	≥ 2.0 x10^9/L
Platelets	≥ 75 x10^9/L
Bilirubin	≤ 1.25 x ULN
Cardiac function	FS ≥ 28% or LVEF ≥ 50% at last scheduled assessment

9.1.8.5.5. Administration

Note: commence A-containing cycles at full dose unless previous dose reduction for A-containing cycles for GI toxicity. In those circumstances continue A at previous reduced dose

Doxorubicin	48 hour continuous infusion = 37.5 mg/m^2/day administered by 48 hour continuous infusion.
Hydration	No additional hydration is necessary.

9.1.8.5.6. Supportive care

G-CSF	Consider the use of G-CSF if already used for previous AP cycles.
Cardioprotection	Wherever possible use prolonged continuous infusion. Dexrazoxane may be used if a confirmed 10% fall within the normal range of LVEF or similar fall within the normal range of FS occurs (see Appendices A.5 and B.6).

9.1.8.5.7. Dose Modifications for A

Toxicity	Grade	Action
Myelosuppression	On Day 1 of cycle ANC $< 0.75 \times 10^9$/L or WBC $< 2.0 \times 10^9$/L Plts $< 75 \times 10^9$/L	Delay and repeat within 3-4 days. For repeated delay consider decreasing doxorubicin to 60 mg/m^2/cycle.
Febrile Neutropenia	All grade 4, consider for grade 3	Add G-CSF. Further episodes despite G-CSF: reduce doxorubicin to 60 mg/m^2/cycle.
-Mucositis -Severe abdominal pain - Diarrhea - Typhlitis	Grade 4 mucositis after AP Repeated Grade 3 mucositis	Delay until resolved & decrease subsequent doxorubicin to 60 mg/m^2/cycle Note: if previous doxorubicin dose reductions other than for cardiotoxicity or grade 4 mucositis, contact CI.
Cardiotoxicity	LVEF ≤ 50% or SF ≤ 28%	Repeat echo or MUGA in one week. If echo or MUGA within normal range proceed with chemotherapy. If LVEF does not normalize, omit all further doxorubicin.
Hepatic Toxicity	Raised Bilirubin	Reduce doxorubicin as follows: **Concentration** **% Dose** 0 – 21 µmol/L (0 -1.24 mg/dL) 100% 22 – 35 µmol/L (1.25-2.09 mg/dL) 75% 36 – 52 µmol/L (2.1 -3.05 mg/dL) 50% 53 – 86 µmol/L (3.06-5.0 mg/dL) 25% > 87 µmol/L (> 5.0 mg/dL) 0%

9.1.8.6. Course name: ifn

9.1.8.6.1. Course definition

Pegylated interferon α-2b 0.5-1.0 μg/kg s.c. once weekly.

9.1.8.6.2. Course timing

Weekly from week 30 (or recovery from toxicity from MAP) until week 104 with a total duration of all therapy of two years from 1st day of chemotherapy. MAPifn only.

9.1.8.6.3. Monitoring

At least every 2 weeks for 8 weeks,
1-2 monthly thereafter.

9.1.8.6.4. Mandatory tests

- Weight
- Clinical examination with particular attention to neuropsychiatric assessment
- Full blood count and differential white count
- Blood chemistry (creatinine, urea, sodium, potassium, calcium, magnesium, phosphate, alkaline phosphatase, albumin, bicarbonate, liver transaminase, bilirubin)
- Thyroid function tests
- Triglycerides and evaluation for AST/ALT evaluation
- Pancreatic enzyme tests
- Ophthalmolgic evaluation

9.1.8.6.5. Minimum requirements

General clinical condition permitting treatment:

Hb	≥ 8.0 g/dL
Neutrophils	≥ 0.75 $x10^9$/L
or WBC	≥ 2.0 $x10^9$/L
Platelets	≥ 75 $x10^9$/L
Bilirubin	≤ 1.5 x ULN
Creatinine	≤ 1.5 x ULN
Triglycerides	< 8.5 x ULN
Amylase	WNL
Pancreatic fraction amylase or lipase	WNL
Baseline ophthalmologic Evaluation (Fundoscopy)	WNL
Performance status	Karnofsky score ≥ 60, WHO ≤ 2 (age ≥ 16), or Lansky score ≥ 60 (age < 16).

Autoimmune hepatitis is a contraindication for drug administration. Any AST/ALT elevation > Grade 3 would preclude administration of ifn. Decompensated liver disease is a contraindication for use of ifn.

9.1.8.6.6. Administration

Weekly subcutaneous injection

Starting dose	0.5 µg/kg/wk (maximum dose 50 µg) for 4 weeks, if well tolerated (no more than grade 2 flu-like symptoms with no other toxicity more than grade 1),
	then
Dose escalation	to1.0 µg/kg/wk (maximum dose 100 µg).

9.1.8.6.7. Supportive care

Systemic symptoms such as fever, chills, headache are expected particularly in the first few weeks of treatment. Pre-treatment with Acetaminophen/paracetamol (250-1000 mg to be given 30-60 minutes before each dose of ifn) is recommended.

9.1.8.6.8. Dose Modifications for ifn

Toxicity	Grade	Action
Fever, chills, fatigue, headache etc	Any	May improve with continued treatment. Treat with paracetamol/acetaminophen and if severe, NSAID providing platelet count is maintained. Dose reduction appropriate only if sustained and not relieved by above.
Hemoglobin	≥ Grade 3	Persistent and symptomatic. Reduce to starting dose (0.5 µg/kg/wk), or, if at starting dose level decrease by 25%. If no resolution within 4 weeks, stop ifn.
Leucocytes	Grade 3 Grade 4	Reduce to starting dose (0.5 µg/kg/wk), or, if at starting dose level decrease by 25%. If resolves to ≤ grade 2, resume the previous dose level and, if at the starting dose level (0.5 ug/kg/wk), the planned dose escalation 4 weeks later. If no resolution within 4 weeks, stop ifn until resolved to ≤ Grade 2, then resume at reduced dose level (starting dose level 0.5 µg/kg/wk ,or, at 25% below the starting does level if toxicity was encountered at starting dose level). If toxicity recurs, stop ifn Stop ifn until toxicity has resolved to ≤ Grade 2, then resume ifn at starting dose (0.5 µg/kg/wk), or, if at starting dose level decrease by 25%. If grade 3 or greater toxicity recurs, stop ifn.
Neutrophils	Grade 3 Grade 4	Reduce to starting dose (0.5 µg/kg/wk), or, if at starting dose level decrease by 25%. If resolves to ≤ grade 2, resume the previous dose level and, if at the starting dose level (0.5 ug/kg/wk), the planned dose escalation 4 weeks later. If no resolution within 4 weeks, stop ifn until resolved to ≤ Grade 2, then resume at reduced dose level (starting dose level 0.5 µg/kg/wk, or, at 25% below the starting does level if toxicity was encountered at starting dose level). If toxicity recurs, stop ifn Stop ifn until toxicity has resolved to ≤ Grade 2, then resume ifn at starting dose (0.5 µg/kg/wk), or, if at starting dose level decrease by 25%. If grade 3 or greater toxicity recurs, stop ifn.
Platelets	Grade 2 ≥ Grade 3	Reduce to starting dose (0.5 µg/kg/wk), or, if at starting dose level decrease by 25%. If resolves to ≤ grade 1, resume the previous dose level and, if at the starting dose level (0.5 ug/kg/wk), the planned dose escalation 4 weeks later. If no resolution within 4 weeks, stop ifn until resolved to ≤ Grade 1, then resume at reduced dose level (starting dose level 0.5 µg/kg/wk, or, at 25% below the starting does level if toxicity was encountered at starting dose level). If toxicity recurs, stop ifn Stop ifn until toxicity has resolved to ≤ Grade 1, then resume ifn at starting dose (0.5 µg/kg/wk), or, if at starting dose level decrease by 25%. If grade 2 or greater toxicity recurs, stop ifn.
Renal toxicity – Creatinine	Grade 2 ≥ Grade 3	Reduce to starting dose (0.5 µg/kg/wk), or, if at starting dose level decrease by 25%. If no resolution within 4 weeks, stop ifn. Discontinue.

Neurotoxicity incl. Mood alteration	≥ Grade 2 Any mood alteration	Reduce to starting dose (0.5 µg/kg/wk), or, if at starting dose level decrease by 25%. If no resolution within 4 weeks, stop ifn. Undertake psychiatric assessment. Consider discontinuation.
Cardiotoxicity e.g. arrhythmia	Grade 2 ≥ Grade 3	Reduce to starting dose (0.5 µg/kg/wk), or, if at starting dose level decrease by 25%. If no resolution within 4 weeks, stop ifn. Discontinue.
Pancreatitis		Elevated triglycerides can result in pancreatitis. Ifn should be discontinued in patients who develop pancreatitis.
Hepatic Toxicity - Bilirubin,	Grade 3 Grade 4	Reduce to starting dose (0.5 µg/kg/wk), or, if at starting dose level decrease by 25%. If no resolution within 4 weeks, stop ifn. Discontinue.
Gastrointestinal e.g. vomiting or diarrhea	Grade 2 for > 2 weeks or ≥ grade 3	Reduce to starting dose (0.5 µg/kg/wk), or, if at starting dose level decrease by 25%. If no resolution within 4 weeks, stop ifn.
Thyroid dysfunction	Any	Assess and treat thyroid as appropriate. Continue ifn unless not controlled.
Triglycerides	>8.5 x ULN	Stop ifn until triglycerides < 8.5 ULN

9.1.9. Recommendations for supportive care

9.1.9.1. Venous Access

A permanent indwelling venous access device is recommended. This is not a trial requirement.

9.1.9.2. Antiemetics

All patients must be treated with appropriate antiemetics according to institutional practice.

9.1.9.3. Neutropenia

9.1.9.3.1. Neutropenic fever

Antibiotic coverage is at the discretion of the investigator. Broad spectrum antibiotics should be chosen in consideration of local microbials. Since nephrotoxic agents are used in this therapy, aminoglycosides should be used with caution.

9.1.9.3.2. G-CSF

Since treatment intensity is important, G-CSF support is preferable to dose reduction. The recommended dose and schedule indicated in the package insert should be used at the discretion of the investigator. Chemotherapy should not be given until a patient has been off G-CSF for 2 days.

9.1.9.4. Anemia and thrombocytopenia

Transfuse to maintain hemoglobin levels according to institutional practice. Erythropoietin is not recommended as standard therapy but may be used at the discretion of the investigator e.g. for patients who refuse transfusion on religious grounds.

Give platelet transfusions for bleeding associated with thrombocytopenia. Give platelet transfusions prophylactically when counts drop below 10 000/μL. Some institutions may use higher thresholds for platelet transfusion, e.g. 20 000/μL. Higher thresholds should also be used during septic episodes.

Appropriate national and institutional guidelines should be followed regarding filtering and irradiation of blood products.

9.1.9.5. Pneumocystis carinii

Pneumocystis carinii prophylaxis is not routinely recommended as the risk of pneumocystis infection in this population is relatively low, although group and institutional practice may vary.

Trimethoprim/Sulfamethoxazole (TMP/SMX) should not be administered with or close to the administration of high dose methotrexate. Sulfonamides can displace methotrexate from plasma binding sites and increase free methotrexate. Trimethoprim can interfere with the microbiological DHFR assay for methotrexate; no interference occurs with the RIA.

In addition, both agents have similar toxicities, and the administration of TMP/SMX increases the risk of high dose methotrexate toxicity.

9.1.9.6. Magnesium supplementation

It may be helpful to supplement magnesium beginning with the first cisplatin-containing course and up to approximately three months after completion of chemotherapy.

Intravenous magnesium supplementation in the hydration fluids should be considered during administration of cisplatin or ifosfamide. See appropriate administration sheets in the Appendix B.6.

9.1.9.7. Neurotoxicity associated with ifosfamide

Guidance for dose adjustment is found in section 9.1.8.3 and 9.1.8.4. Further information about treatment and prevention of neurotoxicity may be found in the Appendix B.6.

9.1.9.8. Hydration Routines

Hydration routines for chemotherapy administration are detailed in section 9.1 and appendix B.6.

9.1.9.9 Bisphosphonates

Some investigators may choose to use bisphosphonates after surgery. The benefits of this have as yet not been prospectively evaluated in this group of patients. Administration of bisphosphonates should be recorded on End of Treatment Form.

9.2. Surgery

9.2.1. Biopsy

The diagnosis of high-grade osteosarcoma must be verified histologically before initiation of chemotherapy. In order to ensure appropriate biopsy techniques and an appropriate evaluation of the obtained material, it is strongly recommended that biopsies should only be performed in specialized centers. Open biopsy may be performed in order to obtain sufficient material for histological evaluation and ancillary studies. The biopsy specimen should be forwarded to the pathologist without prior fixation. Further recommendations about how to proceed in specific situations and various tumor locations may vary between groups. Individual groups' recommendations are summarized in Appendix B.7.

9.2.2. Definitive Surgery

For osteosarcoma, surgery is the local treatment of choice. Complete surgical removal of all affected sites is mandatory whenever feasible.

9.2.2.1. Definitive Surgery of the Primary Tumor

Surgery of the primary tumor is scheduled for 11 weeks after the commencement of chemotherapy. Surgery should be performed in a manner which guarantees wide or radical margins according to Enneking's classification (Enneking et al, 1980). While it is most often possible to reach such margins without sacrificing the affected limb, mutilating surgery may become necessary if this is not the case. The indication for limb-salvage must be made with particular caution if a poor tumor response to preoperative chemotherapy is anticipated by clinical investigations or appropriate imaging studies. Marginal or intralesional surgery should be avoided whenever possible and must be restricted to situations where wide or radical margins are not achievable by any means. As inappropriate surgery may easily lead to local recurrence and death in otherwise curable patients, it is strongly recommended that osteosarcoma surgery should only be performed in specialized centers. Further recommendations about how to proceed in specific situations and various tumor locations may vary between groups (Appendix B.7).

9.2.2.2. Definitive Surgery Guidelines

Prior to definitive surgery the following parameters are recommended:
Neutrophils > 1.0×10^9/L
Platelets > 80×10^9/L

Indications for limb salvage surgery:

1. Tumor resectable with wide margins
2. Reconstruction possible and likely to be successful
3. Patient aware of risks/ benefits of limb salvage

Indications for amputation:

1. Inability to completely resect the tumor without leaving residual disease
2. Extensive involvement of neurovascular bundle
3. Patient preference

There will be many situations where the decision is not easy, in particular when there has been a poor response to chemotherapy, there is extensive soft tissue involvement and the tumor is adjacent to the main neurovascular bundle. In these situations seek a second opinion from one of the main surgical centers.

9.2.2.3. Reconstruction after limb salvage surgery

There are many types of limb salvage reconstruction available. Remember that the principle aim of the surgeon is to completely resect the tumor with wide margins. This principle should never be sacrificed in order to make limb salvage reconstruction easier. The patient will want a reconstruction that will function well and have few complications. In some situations an amputation may give a better and more predictable result than attempts at reconstruction (e.g. distal tibia).

The following reconstruction options represent standard treatment but are NOT meant to exclude other options:

Distal Femur - in most cases use of an endoprosthesis will give a good result. If the tumor involves the knee joint an extra-articular resection should be carried out.

Proximal Tibia - use of an endoprosthesis will work well if the extensor mechanism is reconstructed. A gastrocnemius muscle flap should be part of the soft tissue reconstruction.

Proximal Femur – modular endoprostheses work well. Because of the significant risk of dislocation a large unipolar or bipolar head is recommended.

Proximal Humerus – reconstructive options include the use of a prosthesis, a fibula graft (vascularised) or a turn down of the clavicle (*claviculo pro humero*).

Pelvis – all surgical reconstructions are high risk and should be carried out at a center with appropriate expertise.

Diaphyseal tumor – When the joints can be spared above and below a tumor in a long bone then a biological reconstruction is preferred – either using an allograft or an autograft (or a combination).

Young children with long bone tumors – extendable endoprostheses have proved useful but have a significant risk of complications. Families must be fully informed about risks/benefits and the inevitability of the need for further surgery. Rotation plasty should be considered in these cases.

If there is insufficient local expertise, refer to a member of the Surgical Panel (Appendix A.1).

9.2.2.4. Surgery of pelvic and other axial tumors

Osteosarcomas arising in the axial skeleton (excluding craniofacial bones) that are deemed resectable with curative intent are eligible for inclusion in this protocol. Subsequent surgical management of such tumors may include amputation (fore or hind quarter for shoulder girdle and pelvic tumors) or complex reconstruction. The chosen approach should be anticipated to achieve the safest oncological margin and at least macroscopic resection.

If there is insufficient local expertise, refer to a member of the Surgical Panel (Appendix A.1).

9.2.2.5. Surgery of primary metastases

If primary metastases are present, all of these must also be resected completely, regardless of their number and site, if the patient is treated with curative intent. Resection is strongly recommended for patients felt to have definite or possible pulmonary metastases at initial diagnosis. The preferred time-point for surgery of primary metastases may be between protocol weeks 11 and 20, but other dates may be chosen at the discretion of the treating physicians. For pulmonary metastases, thoracotomy with manual exploration of both lungs is strongly recommended, even when imaging studies suggest unilateral disease. The use of thoracoscopic techniques is strongly discouraged, as they lack sensitivity and may be associated with an increased risk of intraoperative tumor dissemination.

In order to avoid complications associated with delayed methotrexate excretion due to third-spacing into pleural effusions, thoracotomy should not be followed by high-dose methotrexate, but rather by other chemotherapeutic agents.

9.3. Radiotherapy

As stated above, complete surgery is the local treatment of choice in osteosarcoma. Radiotherapy is reserved for situations where complete surgery cannot be achieved. Radiotherapy is, however, recommended for inoperable sites or those that could only be operated with inadequate margins. It is strongly suggested that participating institutions use the information and consulting systems set up by their respective groups before assuming inoperability, because some lesions which at first seem inoperable may turn out to be operable by specialized tumor surgeons. Further recommendations about how to proceed in specific situations may vary between groups. When radiotherapy is indicated, chemotherapy should not be interrupted for radiotherapy which is generally best deferred until the end of chemotherapy. Radiotherapy may be administered during treatment with pegylated interferon α-2b but it is not anticipated that the need will arise except in most uncommon circumstances. See also Appendix B.10.

9.4. Treatment of Relapsed Disease

EFS is the primary endpoint of EURAMOS-1 and therapy of relapsed disease is not prescribed in this trial. In order to achieve a homogeneous standard of patient care, the EURAMOS investigators have summarized their joint opinion about how patients who experience a relapse following therapy on the EURAMOS-1 trial might be treated in Appendix A.7.

10. Trial Pathology

Before entering patients in this trial, clinicians should discuss this protocol with their pathologist and provide them with appropriate documents.

EURAMOS-1 is served by a panel of appointed review pathologists (names and addresses listed in Appendix A.1). The panel's purpose is to ensure uniform histopathological criteria according to the WHO classification (2002) for admission to the trial and the assessment of response to chemotherapy.

10.1. Biopsy

Biopsy sections are to be reviewed by individual Panel members. Panel members are appointed to cover cases entered in the trial as designated within study groups (see Appendix A.1).

Biopsies are classified as high grade central or surface osteosarcomas in accordance with the WHO classification of Tumours Volume 5 (2002). Low-grade central, periosteal and parosteal osteosarcomas are excluded from the trial.

Biopsies are classified as conventional, telangiectatic, small cell or high grade surface osteosarcoma, secondary osteosarcoma or non-osteosarcoma. Conventional osteosarcomas will be divided into the following subtypes: osteoblastic, chondroblastic,

fibroblastic, unusual type, or not specified. Unusual types of conventional osteosarcoma consist of one of the following: osteoblastic osteosarcoma - sclerosing type, osteosarcoma resembling osteoblastoma, chondromyxoid fibroma-like osteosarcoma, chondroblastoma-like osteosarcoma, clear-cell osteosarcoma, malignant fibrous histiocytoma-like osteosarcoma, giant cell rich osteosarcoma and epithelioid osteosarcoma.

The review pathologist should be supplied with adequate radiographs in addition to tumor material. If there is still a diagnostic problem these cases should be circulated among the review pathologists.

Unless otherwise specified in the group specific appendix, five unstained sections on coated slides suitable for immunohistochemistry and one H&E from each block of the initial biopsy will be required by a review pathologist. A minimum of one representative H&E stained section from the initial biopsy will be required. It is the responsibility of the clinician entering patients in the trial to ensure that the pathologist is informed of each patient included and request him/her to forward the relevant material to the review pathologist. It is NOT the responsibility of the review pathologist to chase slides.

It is advisable that, in addition to routine decalcification in formic acid or other solution as practiced by individual institutions, part of the biopsy material should be placed in EDTA for decalcification for preservation of DNA which may be useful for future analysis.

It is recommended that tumor material surplus to diagnostic requirements is snap-frozen and stored at –70^{o}C or in liquid nitrogen for future diagnosis and/or research.

10.2. Resection/amputation

Given the goals of the present trial, timely resection specimen analysis is of paramount importance. This means that at all times the handling of the resected specimens are of peak priority including the initial handling, decalcification, administration and dispatching the material for central review. With regard to decalcification times and procedures please see Appendix B.8.

The examination has three objectives:
1) Assessment of resection margins
2) Assessment of the response to chemotherapy
3) Estimation of the amount of cartilaginous differentiation being more or less than 30% of the tumor volume

To provide documentation of the soft tissue margins, the initial gross examination should be performed on the fresh specimen. Measurement of the narrowest resection margin (mm) is of most value. Histological sections should be taken in any area where excision margins appear dubious. Ideally, the specimen should be prepared by dividing it <u>longitudinally</u> in the plane of maximum tumor diameter, and the <u>whole</u> of this slab should be divided into blocks for preparation of histological sections. Radiological imaging of the specimen is of value in determining the maximum tumor diameter. A photograph and a diagrammatic map of the specimen should be prepared indicating the site of individual blocks. For quantitating the effects of chemotherapy, *only* the sections where tumor was present or was thought to have been present should be assessed. Normal adjacent bone and soft tissue areas should *not*

be included in the area quantitated. If there is difficulty in handling specimens at any stage, the review pathologists are anxious to help.

One H&E stained section from each block encompassing the largest diameter of the resected tumor (not the complete specimen) will be required by a review pathologist, as well as the map indicating from which point the sections are taken. If indicated in the group specific appendix, the submitting pathologist is asked to provide five unstained sections mounted on coated slides, in addition to the one H&E of each tumor block of the resected specimen. Moreover, the pathology report including the size of the tumor in two dimensions and margins of excision (mm) from the contributing pathologist should be added with a conclusion in either English, French or German or the language of the review pathologist. It is the responsibility of the clinician entering patients in this trial to request the submitting pathologist to send the appropriate set of forms, local pathology report including the schematic block map and slides to the review pathologist.

10.3. Procedure for Quantitation

The amount of viable tumor is reported as less than 10% of the tumor area in cases showing a good response and greater than or equal to 10% in cases showing a poor response.

In most cases, the amount of viable remnant tumor is obvious (<10% vital or nearly all vital). In these instances, one can assign response to one of the above mentioned categories. For problematic (non-obvious) cases, graph paper with 2 mm squares can be photocopied (actual size) on to acetate sheets for overhead projection. This may be cut into rectangles and fixed over the cover slip using double-sided sellotape. The entire tumor-bearing areas can thus be measured and totaled.

The same method may be used for quantifying the amount of cartilaginous differentiation. When more than 30% of an osteosarcoma is composed of chondroblastic areas, intimately associated and mixed with non-chondroid-elements it is considered as chondroblastic osteosarcoma. Viable chondroblastic areas are characteristically composed of nodular, bluish hyaline cartilage, with moderately to severely pleomorphic malignant cells. The microscopic appearance is of chondrosarcoma grade 2-3. Necrotic cartilaginous areas are recognized as a confluent, very pale to light eosinophilic homogeneous matrix with vesicular-appearing lacunae in which shadows of necrotic cells can be seen. Grossly, an overt chondroid appearance is rare so the diagnosis is made on histology.

Please note that special amendments for COG and COSS are provided in the additional histopathology appendices.

11. Withdrawal of patients from protocol treatment

The planned duration of the MAP regimen is 29 weeks and the duration of the MAPIE regimen is 40 weeks. In the MAPifn arm, duration of therapy will be two years in total. Surgery is intended to be performed at week 11 in all arms.

Patients may withdraw from protocol treatment for the reasons listed below:

- Death, relapse or tumor progression
- Serious adverse events or other major toxicity prohibiting continuation of protocol therapy
- Pregnancy
- Personal wish of the patient
- Any other situation where continued protocol treatment may not be in the best interest of the patient

The reason for terminating treatment should be recorded on the End of Treatment Form (Appendix FORMS), along with all other post-treatment investigations (see section 8.4).

Patients for whom histological response information is not available, or who did not receive sufficient chemotherapy to allow randomization (see section 6.2) are recommended to receive post-operative chemotherapy according to the MAP schedule. Patients who experience tumor progression during pre-operative treatment are recommended to receive post-operative treatment according to the MAPIE schedule. Patients who are not eligible for randomization as surgery is not macroscopically complete should receive radiotherapy and/or experimental treatments as appropriate. For the purpose of the trial, all patients will remain on follow-up for a minimum of five years after the end of the trial.

12. Determination of Efficacy

12.1. Timing

Remission status and survival will be assessed at the time intervals specified in section 8.4.1.1.

12.2. Methods

Remission status will be assessed clinically and by the imaging studies defined in Appendix B.9. Survival will be ascertained by direct contact of the participating institutions with the trial subjects.

12.3. Quantification of Disease Status

At each follow-up visit scheduled by the protocol, surviving patients will be characterized as either being in complete remission or alive with disease by members of the local investigator team.

12.4. Continuity of methods

The same methods for assessment of disease status will be recommended by the protocol throughout the whole duration of the trial.

12.5. Evaluation Criteria/Remission Criteria

Detailed definitions of complete remission and disease progression, as used in EURAMOS-1 are given in Appendix A.6. No other remission criteria will be used.

13. Determination of Safety

13.1. Adverse Event

An adverse event (AE) is any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does **not necessarily have a causal relationship** with this treatment.

An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product. AEs are documented on the case report forms (CRF) and graded for severity according to Common Terminology Criteria for Adverse Event v. 3.0 (CTCAE).

13.2. Adverse Reaction (AR)

An adverse reaction (AR) is an AE which is judged by the investigator as having a reasonable suspected causal relationship to an investigational medicinal product (IMP).

13.3. Unexpected Adverse Reaction

An ‘unexpected adverse reaction’ (UAR) is an AR, the nature or severity of which is not consistent with the applicable product information.
Examples of UARs include:

- an expected /labeled AR with an unexpected outcome (e.g. a fatal outcome)
- “acute renal failure” is a labeled AR, a subsequent new report of “interstitial nephritis” is more specific and, therefore, unexpected
- an increase in the rate of occurrence of an expected, AR, which is judged to be clinically important is considered as unexpected

13.4. Serious Adverse Event or Reaction

A serious adverse event (SAE) or serious adverse reaction (SAR) is any untoward medical occurrence or effect that at any dose:

- results in death regardless of its cause – see below
- is life-threatening – see below
- requires hospitalization or prolongation of an existing hospitalization Not every hospitalization constitutes a reportable serious adverse event. For exceptions see below
- results in persistent or significant disability or incapacity– For exceptions see below
- is a congenital anomaly or birth defect
- any other medically important condition such as abnormal biological or vital signs and secondary malignancies (cancer) - For exceptions see below:

DEFINITIONS and EXCEPTIONS for EURAMOS:

- **All deaths** including death due to disease progression during protocol treatment and for 30 days after the last protocol treatment, including treatment with pegylated interferon α-2b, will be reported as an SAE. Death due to progression of disease will not constitute a SAE if it occurs at least 30 days after the last protocol treatment.

- The term "life-threatening" refers to an event where the patient is at IMMEDIATE risk of death at the time of the event (e.g. requires IMMEDIATE intensive care treatment). It does not refer to an event which hypothetically might cause death if it were more severe e.g. drug induced hepatitis which, if resolved, is not life threatening although it could lead to liver failure and death.

- **Hospitalization** is defined as at least one overnight admission

a) Hospitalization for chemotherapy is not reported as an SAE. In addition expected side effects of chemotherapy, which are listed in the product information, will not be reported on an SAE form for the purposes of this clinical trial unless in the opinion of the investigator they unexpectedly prolonged the hospitalization or required intensive care therapy.

b) Hospitalization for procedures required by the protocol e.g. biopsy or surgery are not considered serious adverse events until one of the above criteria are met.

c) Hospitalization due to signs and symptoms associated with disease progression are not considered an SAE unless outcome leads to DEATH during protocol treatment and for 30 days after the last protocol treatment, including treatment with pegylated interferon α-2b.

d) Elective hospitalization for a pre-existing condition that has not worsened does not constitute a SAE.

- **Disability** is defined as a substantial disruption in a person's ability to conduct normal life functions (e.g. blindness, deafness). Disability resulting from tumor surgery does not constitute an SAE.

- **Other medically important conditions** are important medical events that in the opinion of the investigator may not be immediately life-threatening or result in death or

hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm or convulsions. Secondary malignancies are also considered to be medically important e.g. skin cancers, myelodysplastic syndrome (MDS) and are reportable on an SAE form during protocol treatment and for 30 days after the last protocol treatment, including treatment with pegylated interferon α-2b. Abnormal biological or vital signs commonly occur under chemotherapy and will only be reported as serious when considered CLINICALLY RELEVANT BY THE INVESTIGATOR (unexpected) e.g. severe nephrotoxicity (CTCAE Grade 4) or severe cardiac toxicity (CTCAE Grade 4). Expected serious adverse reactions (SAR) such as hematological toxicity or increase in liver enzymes under methotrexate which resolve are examples of SARs which are not considered reportable on an SAE Form by the investigator.

13.5. Serious Adverse Event and Reaction Reporting

All SAEs and SARs, regardless of causal relationship, must be reported to the EURAMOS Intergroup Safety Desk (EISD), Münster, Germany within 1 business day directly by fax +49 (0) 251 83 57112 on the SAE Form. SAEs and SARs will be reported following the first dose of chemotherapy throughout the clinical trial and for 30 days after the last protocol treatment, including treatment with pegylated interferon α-2b. The EISD will inform regional data centers immediately of all SAEs. The national coordinators or their designee (e.g. regional data centers) are responsible for promptly notifying the Ethics Committee and the competent authorities of all unexpected serious adverse reactions.

All SAE reports which occur for patients on the Peg-Intron treatment arm, whether or not deemed drug-related or expected, must be reported by the EURAMOS Intergroup Safety Desk (EISD) to the Schering Plough Global Pharmocovigilance Department Safety Surveillance Department via FAX at 973-921-7423 within 24 hours (one working day) of first becoming aware of the event.

13.5.1 Clarification procedure for SAE reporting

Institutional investigators may be asked to clarify submitted serious adverse event reports.

Note: The following section refers to calendar days unless explicitly reported as working days

Within one business day of receiving the SAE notification, EISD will request any necessary clarifications.

The initial request for clarification will be sent to the identified institutional investigator. The institution is asked to respond within 2 business days.

If there has been no response within 7 days, then the institutional investigator and the institutional principal investigator (if a different individual) will be contacted for clarification.

A reminder will be sent 7 days later (14 days from the initial request for clarification). The reminder will state that if there has been no response within an additional 7 days (21 days from the initial demand for clarification), then the institution will be suspended from further

registration of new patients on EURAMOS I, although continued data submission will be required for patients already enrolled on study. This reminder (14 days from the initial request for clarification), will also notify the group principal investigator and the Trials Office. If there has been no response within a further 7 days, (21 days after the initial request for clarification), the institution will be suspended from registering new patients until the clarification has been supplied, along with a letter outlining the corrective measures that have been put in place to prevent a subsequent similar delay in response. The notice of suspension will be sent by the group Chief Investigator.

13.6. Late effects of chemotherapy

Late effects of chemotherapy will be documented on follow-up forms and include:

- cardiac toxicity
- renal toxicity
- ototoxicity

13.7. Systematic evaluation of organ toxicity

13.7.1. Timepoints

Details on how and when to grade organ toxicities during treatment are given in Section 8. During follow-up, long-term toxicities will be recorded on the six-monthly follow-up form.

13.7.2 Grading of toxicity

All toxicities will be classified according to the CTCAE Version 3.0, June 10, 2003 (see Appendix A.4).

13.7.3. Safety Monitoring (Independent Data Monitoring Committee)

Toxicity information will be reviewed by the Independent Data Monitoring Committee (IDMC) at their regular meetings. If the IDMC have any concerns regarding the safety of patients in this trial, they will report these concerns to the Trial Steering Committee (TSC).

14. Duration of the Trial

It is intended that EURAMOS-1 will remain open until it has completed accrual for both good and poor responders. The trial will be monitored regularly by the IDMC who will review confidential interim analyses of the trial as well as issues surrounding accrual. If they have any grave concerns regarding the trial, for example if one treatment arm is demonstrably inferior to another, the IDMC will report the findings to the TSC who will decide upon the trial's future.

The trial will end on the date of the last treatment visit for the last patient undergoing protocol treatment. Long term follow-up will continue for a minimum of five years after the end of the trial.

15. Statistical Methods

15.1. Endpoints

The primary endpoint for EURAMOS-1 is event-free survival (EFS); secondary endpoints are overall survival (OS), toxicity and quality of life. For the statistical comparison of the randomized arms, EFS and OS will be measured from date of randomization to date of event or date of death as appropriate; surviving patients will be censored at date last known to be alive. For reporting EFS and OS estimates at specific timepoints, these measures will be calculated from date of diagnostic biopsy. Treatment comparisons of EFS and OS will also be conducted in the subgroup of localized patients. Trial conclusions will be based on all endpoints. Events are defined as death, detection of local recurrence or metastasis, progression of metastatic disease, or detection of a secondary malignancy. Toxicity will be assessed using the CTCAE (Appendix A4). Good histological response is defined as < 10% viable tumor.

15.2. Sample Size

Sample size calculations for this trial have been calculated using the method of George and Desu (George and Desu, 1974). The good histological response rate for the MAP induction regimen, estimated from INT 0133, is 45%. Analysis of EFS is planned to take place around two years after the closure recruitment to of the trial, analysis of OS is planned for around four years after closure.

Based on the previous experience of the participating groups, 3-year EFS for the MAP regimen is expected to be 70% for good responders and 45% for poor responders; 5-year OS is also expected to be 70% for good responders and 45% for poor responders.

Setting a two-sided significance level of 5% and 80% power, around 525 events are required. Assuming 400 patients registered per year, it is proposed that 1260 patients be randomized into EURAMOS 1. Of these, 567 are anticipated to be good responders and

693 poor responders. Previous data from COSS suggested that 10% of patients registered at the start of treatment are not randomized following surgery because of disease progression. In EURAMOS-1 the non randomization rate has been higher at around 30-35% for many reasons including disease progression, insufficient pre-operative chemotherapy and withdrawal of consent. Thus randomization of 1260 patients will require around 2000 patients to be registered over a period of around 5 years.

To detect an absolute improvement of 10% in good responders, from 70% to 80% (hazard ratio 0.63), in 3-year EFS and 5-year OS requires around 147 events. To detect an absolute improvement of 10% in poor responders, from 45% to 55% (hazard ratio 0.75), in 3-year EFS and 5-year OS requires around 378 events. Randomisation of around 1260 patients over 5 years with approximately half being good responders allows for sufficient events after around 1-2 years for good responders and 3-4 years for poor responders.

15.3. Sample size for patients with localized disease

At least 85% of patients randomized into EURAMOS-1 are expected to have localized disease at registration. A minimum of 482 good responders with localized disease and 590 poor responders with localized disease may thus be available for analysis. Due to the better prognosis for localized disease, EFS and OS are expected to be slightly higher for this cohort compared to the whole trial population.

In good responders with localised disease, assuming a two-sided significance level of 5% and 80% power, 98 events are required to detect an improvement of 10%, from 75% to 85% (hazard ratio 0.56) in 3-year EFS and 5-year OS. In poor responders with localised disease, 270 events are required to detect an improvement of 11%, from 50% to 61% (hazard ratio 0.71), in 3-year EFS and 5-year OS (2-sided significance level of 5%, 80% power). With the assumed proportion of patients having localised disease, it is expected to have reasonable power in the localised disease setting when the main analyses are performed.

15.4. Intended Analysis

The two arms will be compared on an intention-to-treat basis. Differences in event-free survival and overall survival will be assessed using the logrank test and expressed using hazard ratios with appropriate confidence intervals. Proportions of patients experiencing grade 3 and 4 toxicities will be compared using chi-square tests or Fisher's exact tests where appropriate. Differences in EFS and OS will be assessed for the subgroup of patients with localized disease. No other subgroup analyses are planned but the consistency of treatment effect within specified groups, e.g. site of disease, will be examined. A full Statistical Analysis Plan will be developed separately.

15.5. Interim Analyses

The data will be reviewed and formal interim analyses performed at regular intervals (approximately 6-monthly) by an IDMC who will be asked to give advice on whether the accumulated data from the trial, together with results from other relevant trials, justifies continuing recruitment of further patients.

A decision to discontinue recruitment, in all patients or in selected subgroups will be made only if the result is likely to convince a broad range of clinicians including participants in the trial and the general clinical community. If a decision is made to continue, the IDMC will advise on the frequency of future reviews of the data on the basis of accrual and event rates.

The Haybittle-Peto stopping rule will be adopted for this trial (Haybittle, 1971; Peto et al, 1976). The trial will be stopped for good or poor responders if the p-value for the analysis of EFS is below 0.001. This approach has the advantage of not requiring the number of interim analyses to be specified, and not increasing the Type I error of the final analysis by more than a nominal amount. The IDMC will make recommendations to the TSC as to the continuation of the trial.

It is important that interim analyses of EURAMOS-1 examine the safety of the patients who have been entered into it. If, at interim analysis, the lower bound of the 95% confidence interval for the proportion of patients in each arm who died due to toxicity exceeds 3%, the future of the trial will be discussed with the TSC. The minimum number of toxic deaths for which the lower bound of the 95% Confidence Interval exceeds 3% is shown in the table below:

Number of patients	**Number of toxic deaths**
50	5
100	8
150	10
200	12
250	14
300	16

At each interim analysis, all reported grade 4 CTCAE toxicities will be presented by arm. Any perceived excess in grade 4 toxicity, in any arm, will lead to further investigation to determine the safety of that arm. As the toxicity profiles of MAP and MAPIE are known from the results of INT 0133 and P9754, further stopping rules for chemotherapy toxicity are not warranted.

The role of the TSC is to provide overall supervision for the trial and provide advice through its independent Chairman. The ultimate decision for the continuation of the trial lies with the TSC. See Appendix A.1 for details on trial committees.

15.5.1. Stopping rules for pegylated interferon α-2b

Experience from the Karolinska Hospital in Sweden suggests that interferonα is not associated with major acute or long-term toxicity in osteosarcoma patients (Strander et al, 1995). Interferon-α has an excellent safety record in other diseases, and we would not expect to see major toxicities arising from it in this trial. However, it would be prudent to monitor the safety of patients who receive pegylated interferon α-2b carefully.

If any toxic death occurs that is attributable to pegylated interferon α-2b, the IDMC and TSC will be consulted within 7 days with a view to discontinuing this arm. If, at interim analysis, > 25% of patients who started pegylated interferon α-2b have subsequently ceased

treatment for any reason other than disease progression, relapse or death, the TMG will discuss whether to discontinue this arm with the IDMC and TSC. Permanent, early discontinuation of pegylated interferon α-2b should be discussed with the regional CI whenever possible. At interim analysis, all grade 4 toxicities observed during treatment with pegylated interferon α-2b will be reported. If any individual non-hematological toxicity criterium is associated with grade 4 toxicity in more than 5% of patients, the continuation of this arm will be reviewed with the IDMC and TSC.

16. Data Management

16.1. Patient Identification

Upon registration, every patient will be assigned a unique patient identification number by the appropriate Trials Center, which, in addition to their initials, date of birth, and gender will allow unambiguous identification. Local investigators will keep a confidential patient identification list connecting these with the full patient name. Some study groups will record full names. If so, the authorization to record full names will be included in the appropriate Informed Consent form (see Appendix B.13).

16.2. Data Collection/Case Report Forms

Data will be recorded on case report forms (CRFs) supplied by the appropriate Trials Center, or submitted electronically according to group practice (Appendix B.2). Copies of pathology reports and surgical reports and other notes will also be collected by some groups (see Appendix B.4). All variables on which information is to be collected for the purpose of the trial and the manner in which this information is to be coded will be predefined by the Coordinating Data Center London (CDC) after discussion with the TMG. Groups are free to collect additional information according to their respective practice. Patients initials, but not name or address, will be recorded on the CRFs (when used) for identification purposes, unless otherwise specified. This information will be treated with strict confidentiality by the relevant trials center. The data to be recorded and the schedule for submitting data can be viewed in Appendix B. Participating Trials Centers may also chose to abstract data directly from original reports submitted by participating institutions (e.g.: surgical reports or pathology reports) or to use remote data entry systems. The type of data to be recorded is detailed in the Assessments and Procedures section (Section 8). The CDC will provide all Trials Centers with a list of data to be collected, the timepoints at which these are to be collected and an exact definition of terms. Groups for whom English is not the main language are allowed to translate this information into their respective languages for easier data collection, provided that the definitions used are not altered in meaning and that the collected data is not affected by this translation.

CRFs, when used, must be filled out with ink. Corrections should be performed as follows: A single line should be drawn through the incorrect information, the correct information written next to it and dated and signed by the investigator, if necessary giving reasons for the correction. Data fields which can not be filled because of lack of information should be commented. The CRFs are to be filled out in a timely fashion, signed by the local investigator. The top copy of all CRFs should be sent in a timely fashion to the relevant Trials Center for data entry and a copy kept at the participating institution.

16.3. Data Processing

At the relevant Trials Center, the data provided by the local investigators and information obtained directly by reference pathologists, surgeons, radiologists, or radiotherapists (see Appendix A.1) will be processed, checked for consistency, and entered into an electronic database. Implausible or missing data will be corrected or supplemented after contacting the local investigator. Correction notes will be stored in such a way as to accommodate the retrieval of all data submitted by a local investigator. The validated data will be entered into

a database and stored electronically using the software of choice of the relevant Trials Center.

Validated EURAMOS-1 trial data will be submitted from the four Trials Centers (COSS, SSG, MRC, and COG) to the CDC in a format specified by the CDC every 6 months. All data sent to the coordinating Trials Center for analysis will be anonymized. The CDC London will keep an electronic database containing all submitted validated information, using the software of its choice. The database will be frozen after entry of all relevant data at time of each analysis. This closure will be documented. Commercially available, validated software will be used for all analyses.

16.4. Archiving of Trial Documents

Original versions of the central trial protocol and of all group-identical appendices will be kept at the CDC, which will also be supplied with and store authorized copies of group-specific appendices.

The Trials Centers of the participating groups will store original versions of the group-specific appendices. They will also be supplied with and store authorized copies of the central trial protocol and of all group-identical appendices.

The originals of all trial documents including the CRFs will be stored at the relevant Trials Centers and the CDC for the time period defined by national laws and regulations, but not shorter than 15 years after publication of the final analysis.

Local investigators and trial centers will store all administrative documents (e.g. correspondence with ethical committees, regulatory agencies, trial centers), the patient identification list, copies of the CRFs, the protocol and the amendments for the time period specified above.

Local investigators will store the patient's hospital charts for as long as required by national laws and regulations, but not less than 15 years.

17. Quality Assurance

17.1. Introduction

The EURAMOS collaborators are aware that all clinical research carries with it the obligation to ensure optimal therapy for participating patients and optimal conduct of the research such that the patients' participation is meaningful. Accurate and timely knowledge of the progress of each trial is a critical Intergroup responsibility. The multi-center and intergroup nature of the EURAMOS trial presents a variety of challenging methodological problems regarding assurance of quality and consistency in trial conduct. The collaborating groups each have well established quality control procedures and have developed a number of additional approaches to address these issues, which are described in this section.

In order to deal with assurance of quality and consistency in trial conduct for their intergroup trial, EURAMOS has formed a Coordinating Center for quality matters, located at the Koordinierungszentrum Klinische Studien (KKS) Münster, Germany.

Together with the TMG, the Münster office is responsible for the development and implementation of the trial's Quality Assurance Program, including routine monitoring procedures, on-site visits, and adverse events reporting, as well as other good clinical practice techniques. It is responsible for the development of standard operational procedures relating to quality assurance issues, based on the ICH/GCP guidelines and EU directive 2001/20/EC, which are then to be implemented for the trial as a whole.

Procedures in place for rapid reporting of treatment-related morbidity information (SAEs) and the interim evaluation of outcome measures and patient safety information are detailed in other sections of the protocol.

17.2. Data Consistency

Methods used to generate trial data in a standardized fashion across groups are described in detail in the appropriate sections of the protocol. Standardized reporting of toxicity will be according to the CTCAE Version 3.0, Publication Date: June 10, 2003 (Appendix A.4).

Data consistency will be checked at the appropriate Trials Centers by comparing information from CRFs with that from pathology reports and surgery reports and submitted progress notes. Compliance with the entry criteria and the principles of randomization, compliance with the diagnostic, therapeutic, and follow-up guidelines of the protocol, and the correct translation onto CRFs will be reviewed. Implausible or missing data will be corrected or supplemented after contacting the local investigator.

Participating investigators must agree to on site data verification on the commitment form (see Appendix B.2). Details about the organization, content, and conduct of these on site visits are given in section 17.4. and in Standard Operational Procedures. The frequency of monitoring visits will be decided after grant approval in relation to the sum allocated for these purposes.

17.3. Review of Trial Quality Indicators

An IDMC, independent of trial leadership, free of conflicts of interest, will be formed. The main objectives of the IDMC are to:

- ensure that patients in the clinical trial are protected
- ensure that evaluation of interim results and decisions about continuing, modifying, or terminating the clinical trial and reporting results are made competently and independently; and
- ensure that the credibility of clinical trial reports and the ethics of clinical trial conduct are maintained

Issues surrounding accrual, eligibility criteria, randomization, and compliance with the protocol will be reviewed during the regular meetings of the IDMC. The CDC and KKS Münster will supply the IDMC will all necessary information. If the IDMC have any grave concerns regarding the trial, they will report them to the TSC who will decide upon the trial’s future.

17.4. Monitoring

EURAMOS is a collaboration between four multi-institutional osteosarcoma groups: COG, COSS, EOI and SSG. Each group will be responsible for organizing a monitoring program of their participating institutions according to GCP. On site visits will be made at regular intervals throughout the trial as required, which may be supplemented by investigators' training and meetings. Data Centers will meet regularly to assure data consistency between centers.

17.4.1. Aim of monitoring

The purpose of these visits is:

- to verify that the rights and well-being of human subjects are protected
- to verify accuracy, completion and validity of reported trial data from the source documents
- to evaluate the conduct of the trial within the institution with regard to compliance with the currently approved protocol, GCP and with the applicable regulatory requirements

17.4.2. Notice of monitoring

The Trials Center will give the responsible investigator adequate notice of the monitoring visit to allow adequate time, space and staff for these visits.

17.5. Reference Panels

17.5.1. Pathology Review

Pathology review will be undertaken for all patients within the trial. Both the diagnostic biopsy and the resection specimen histology will be reviewed by a review pathologist (see Appendix A.1 for members of the panel). The pathology/biological studies subgroup will undertake regular audit to determine consistency of reporting.

The process of pathology review is detailed in section 10.

17.5.2. Radiology Panel

Review of thorax CT scans will be undertaken by the TMG in conjunction with a radiologist (see Appendix A.1 for radiology panel membership). Chest CT scans may be requested for patients registered as having "possible" metastatic disease i.e. fulfilling the following criteria:

a) A single lesion no greater than 1 cm or
b) less than 3 lesions of ≥ 5 mm

17.5.3. Surgical Panel

The surgical panel(s) issue(s) guidelines surrounding tumor resection and reconstruction. Some groups offer or require consultation with members of the surgical panel prior to tumor surgery. See Appendix B.7 for guidelines. See Appendix A.1 for panel membership.

17.5.4. Oncology Panel

The oncology panels of each group shall check the protocol for content, consistency and accuracy on all topics surrounding trial medication. Members of each group's oncology panel are appointed to represent the group in the TMG and the TSC. Some groups may offer or require consultation with named members of the oncology panel on issues surrounding chemotherapy. See Appendix A.1 for panel membership.

17.5.5. Radiotherapy Panel

The radiotherapy panel(s) issue(s) guidelines surrounding radiotherapy for insufficient margins or inoperable relapse. Some groups offer or require consultation with members of the radiotherapy panel prior to any radiotherapy. See Appendix B.10 for guidelines. See Appendix A.1 for panel membership.

17.5.5. Pharmacy Panel

The pharmacy panel issues guidelines surrounding trial medication. Some groups offer consultation with members of the pharmacy panel. See Appendix A.1 for panel membership.

18. Ethical Background

18.1. Declaration of Helsinki

EURAMOS-1 will be conducted in full accordance with the Declaration of Helsinki, last revised by 52nd WMA General Assembly, Edinburgh, Scotland, October 2000 (see Appendix A.11).

18.2. Ethical Approval

Before being activated by a group, the protocol, patient information sheets, and consent forms must have been reviewed and accepted by the appropriate Ethics Committee of that group, in conformity with the laws and regulations of the country of the Chief Investigator and, for European investigators, the appropriate European laws and regulations.

The group for which this version of the protocol was issued will submit protocol, patient information sheets, and consent forms to the appropriate Ethics Committee named in Appendix B.11. The trial will not be activated before approval by that committee. All investigators from the group for which this version of the protocol was issued will follow any additional guidelines which might be given in the group-specific Appendix B.11.

The Chief Investigator of the group will inform the named Ethics Committee and the competent authorities about all protocol amendments which might affect the safety of participating patients. The Ethics Committee will also be informed about all severe or unexpected adverse events made known to the Chief Investigator.

Within 90 days after the end of the trial (see section 14), the Chief Investigator(s) shall notify the competent authorities and the competent Ethics Committee that the clinical trial has ended. If the trial has to be terminated early, this period shall be reduced to 15 days and the reasons clearly explained.

Directive 2001/20/EC of the European parliament and of the council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use states that, “in the case of multi-center clinical trials carried out in more than one Member State *(of the European Union)* simultaneously, a single Ethics Committee opinion shall be given for each Member State concerned by the clinical trial” (see Appendix A.12). Member States of the European Union shall adopt and publish before 1 May 2003 the laws, regulations and administrative provisions necessary to comply with this Directive. In Member States failing to comply with these provisions and in participating countries which are not Member States of the European Union, multiple Ethics Committee opinions may be required. Before entering patients into the trial, clinicians must, therefore ensure that they have ethical approval to participate in the trial according to their national and, where applicable, European laws and regulations. It may be necessary to await the vote of the local Ethical Committee and to inform that board about protocol amendments, adverse events, and termination of the trial, as detailed above.

18.3. Patient Information

Before entry into the trial and randomization, the trial subject or, when the person is not able to give informed consent, their legal representative, will be given the opportunity, in a prior interview with the investigator or a member of the investigating team, to understand the objectives, risks and inconveniences of the trial, and the conditions under which it is to be conducted and will also be informed of their right to withdraw from the trial at any time. Minors are to receive information according to their capacity of understanding, from staff with experience with minors, regarding the trial, the risks and the benefits.

18.4. Informed consent

Prior to trial entry, the trial subject or, when the person is not able to give informed consent, their legal representative, must give their written consent after being informed of the nature, significance, implications and risks of the clinical trial, including treatment allocation and randomization. Sufficient time will be allowed to decide about trial participation and to solve open questions. If the individual is unable to write, oral consent in the presence of at least one witness may be given in exceptional cases, as provided for in national legislation.

The signature of the legal representative is required for children and adolescents below legal age. The explicit wish of a minor who is capable of forming an opinion and assessing this information to refuse participation or to be withdrawn from the clinical trial at any time is to be considered by the investigator or where appropriate the principal investigator.

Master versions of the Patient Information and Informed Consent Forms for the group for which this version of the protocol was issued are to be found in Appendix B.13. The format may need to be modified according to the requirements of the participating institution. Any modified versions may need to be submitted to the appropriate Ethical Committee for evaluation.

Patient Information and Informed Consent forms will be issued in two copies. One copy remains with the local investigator, one is handed to the patient.

18.5. Data Management, Storage and Transmission

The patients will be informed about the fact that their trial based data will be stored, transmitted and used for scientific analyses and publications, and that competent authorities may have the right to conduct an official review of documents, records, and any other resources that are deemed by the competent authority to be related to the clinical trial and that may be located at the site of the trial or at the Trials Center, or at other establishments which the competent authority sees fit to inspect.

Patients have the right to be informed about the data kept.

Consent for data management, storage and transmission will be asked for in addition to consent into trial participation (see Appendix B.13).

18.6. Consent into surgery and radiotherapy

Information about any surgical or radiotherapeutical procedures will be given by the treating surgeons or radiotherapists and informed consent into these procedures will be requested separately.

18.7. Withdrawal from the trial

The subject may without any resulting detriment withdraw from the clinical trial at any time by revoking their informed consent.

19. Legal and Administrative Guidelines

19.1. Good Clinical Practice (GCP)

The ”Recommendations of Good Clinical Practice (ICH-GCP: International Conference on Harmonisation - Good Clinical Practice, effective since 17.1.1997)” and “Directive 2001/20/EC of the European parliament and of the council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use” (see Appendix A.12) will be respected.

19.2. Legal background (National and International Regulations)

The trial will be performed in accordance with the national laws and regulations of the countries in which it is being performed and applicable European laws and regulations. Before commencing the trial, the Chief Investigator for each of the cooperating groups shall submit a valid request for authorization to the competent authority of the country in which they plan to conduct the clinical trial. The trial will not start until the Ethics Committee has issued a favorable opinion and the competent authority of the country concerned has not informed the sponsor of any grounds for non-acceptance.

The Chief Investigators for each group are required to ensure that the laws, regulations and rules of their respective countries are being followed. Details on the legal background for the group for which this version of the protocol is being issued are to be found in Appendix B.12.

The Chief Investigator for each cooperative group must be qualified for this position as required by the national laws and regulations of their country and, for European Chief Investigators, applicable European laws and regulations (for instance: adequate experience in the conduct of clinical trials).

19.3. Insurance

Each group has ensured that appropriate arrangements for indemnity to cover the liability of the investigator, including insurance where necessary, have been made according to their national guidelines (see Appendix B.12).

19.4. Finance

19.4.1. Protocol Development

Costs arising in association with protocol development were covered by a generous grant of 15 000 € from the European Science Foundation (Pan-European Clinical Trials (2001) – grant no. 01-26-DE).

19.4.2. Treatment Related Costs

Participation in oncology trials has become the “standard of care” in pediatric oncology as well as in bone sarcoma treatment in all age groups. The laboratory and clinical investigations set forth in the EURAMOS-1 protocol, as well as radiological staging and follow-up procedures are part of standard routine clinical care for osteosarcoma patients in all participating countries. No additional diagnostic tests not required as part of routine care are called for by the EURAMOS-1 protocol. No additional costs not already covered by hospital reimbursements will arise in association with diagnostic evaluation and follow-up of trial subjects. The cost of treatment in this trial will not exceed the standard cost of treating these patients.

Peg-Intron (SCH 054031) will be supplied free of charge by ITGI.

19.4.3. Cost of Trial Organization and Data Management

19.4.3.1. Costs arising within participating groups

Each of the four participating groups is required to apply for funding which covers the costs associated with data collection and the maintenance of their group's trial infrastructure.

- **COSS**

A grant has been awarded by the German Cancer Charity (Deutsche Krebshilfe e.V., Thomas-Mann-Str. 40, Postfach 1467, D-53111 Bonn). Deutsche Krebshilfe has for more than a decade generously supported the COSS trials as well as many other German Pediatric Oncology trials.

- **SSG**

The sarcoma trials of SSG are currently funded by the Swedish Cancer Society and the Nordic Cancer Union.

- **EOI**

Funding for data management and statistics in the UK has been awarded by the National Cancer Research Institute (NCRI) Clinical Trials Awards and Advisory Committee (CTAAC).

- **COG**

COG participation will be funded by a COG grant covering per case reimbursement and statistical and data center support and limited investigator support for the group's Chief Investigator. Additional funds will be applied for to cover travel expenses and data transfer.

19.4.3.2. Pan European Cooperation

Costs arising from Pan-European Cooperation within EURAMOS-1 are the subject of grants by Member Organisations of the European Science Foundation's (ESF) European Medical Research Councils (EMRC). These were provided based on the positive review of a grant application (01-26-DE) for EURAMOS-1, which was submitted in response to a call for outline proposals for pan-European controlled clinical trials, published in The Lancet (Vol. 358, 9 June 2001). Following consideration of the assessments given by external referees, the International Expert Review Panel of the EUROCORES Programme on Pan-European Clinical Trials selected EURAMOS-1 to be recommended for funding.

19.4.4. Ancillary studies

Costs associated with ancillary studies will be the subject of separate grant applications.

19.5. Compliance with the protocol

The guidelines of the protocol are to be followed. Participating investigators must document all protocol violations and must give the reasons responsible for these violations (e.g.

emergency measures). Compliance will be checked as part of the on-site monitoring process.

19.6. Protocol-Amendments

After commencement of the trial, the EURAMOS TMG may make amendments to the protocol. All amendments must be authorized by the four Chief Investigators after consultation with the TMG and the TSC. If those amendments are substantial and are likely to have an impact on the safety of the trial subjects or to change the interpretation of the scientific documents in support of the conduct of the trial, or if they are otherwise significant, the Chief Investigators shall notify the competent authorities of the countries concerned of the reasons for, and content of, these amendments and shall inform the Ethics Committee or Committees concerned. If the opinion of the Ethics Committee is favorable and the competent authorities have raised no grounds for non-acceptance of the aforementioned substantial amendments, the EURAMOS group shall proceed to conduct the trial following the amended protocol. Should this not be the case, the EURAMOS group will either take account of the grounds for non-acceptance and adapt the proposed amendment to the protocol accordingly or withdraw the proposed amendment.

Participating investigators will be informed about all amendments and have to verify knowledge of amendments by their signature. Patient information and CRFs will be adapted to include all changes specified in the amendments.

Amendments would include:
(1) The protocol version for which the amendment is applicable
(2) An exact description of all alterations made
(3) The reasons for these alterations
(4) The date of these alterations
(5) The authorization by the Chief Investigators

20. Publication policy

20.1. Final report

A final report of EURAMOS-1 will be written by the TMG. It will include the relevant clinical and statistical issues, tables detailing results and the conclusions. It will be signed by all four Chief Investigators and the statistician of the CDC.

20.2. Publication

Publication of the trial will be performed regardless of its outcome. The publication will be written in accordance with the standards of the CONSORT Statement (Begg et al, 1997) or subsequent updates. The authorship will consist of the TMG chair and the following representatives of each group: CI, pathologist, surgeon, statistician and data manager. This will be the writing committee. The order of the authors will be the four CIs followed by the others. The senior author will be the TMG chair, unless they are a member of the same group as the first author; in that case a CI from another group will be the senior author. First authorship will determined between the four CIs. The first author will provide a first draft of the report within 18 months of closure.

The trial report will be accompanied by an appendix identifying the TMG and listing contributors to the trial and all associated committees. Publication requires authorization by the TMG.

Additional publications using data analyzed by the CDC will be authorized by the TMG and published with authors and “on behalf of EURAMOS”.

No group will independently use data from EURAMOS-1 for separate publication before publication of the final trial report. After the EFS and OS reports have been published, each group can report analyses of their own data without consulting the TMG. Analyses of the whole trial data set require the permission of the TMG.

21. Glossary and Abbreviations

A	Doxorubicin (Adriamycin)
AE	Adverse event
Ai	Treatment course: Doxorubicin and Ifosfamide 9g
ANC	Absolute Neutrophil
AP	Treatment course: Doxorubicin and Cisplatin
AR	Adverse Reaction
AST/ALT	Aspartate aminotransferase/ Alanine aminotranferease
CCG	Children's Cancer Group
CDC	Coordinating Data Center London
CI	Chief Investigator
COG	Children's Oncology Group
CONSORT	
COSS	Cooperative Osteosarcoma Study Group
CRF	Case Report Form
CT	Computed Tomography
CTAAC	Clinical Trials Awards and Advisory Committee
CTCAE	Common Terminology Criteria for Adverse Events
DDP	Cisplatin
DHFR	Dihydrofolate Reductase
DOX	Doxorubicin (Adriamycin)
E	Etoposide
EDTA	Ethylene Diamine Tetra Acetate
EF	Ejection fraction
EFS	Event-Free Survival
EISD	EURAMOS Intergroup Safety Desk
EMRC	European Medical Research Councils
EOI	European Osteosarcoma Intergroup
EORTC	European Organisation for Research and Treatment of Cancer
ESF	European Science Foundation
ETO	Etoposide
EU	European Union
EURAMOS	European and American Osteosarcoma Study Group
EUROCORES	European Science Foundation Collaborative Research
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony-Stimulating Factor
GFR	Glomerular Filtration Rate
i	Ifosfamide 9 g
I	Ifosfamide 14 g
IDMC	Independent Data Monitoring Committee
IE	Treatment Course: Ifosfamide 14g and Etoposide
ifn	Pegylated interferon α-2b
IFNα	Pegylated interferon α-2b
IFO14 g	Ifosfamide 14 g
IFO9 g	Ifosfamide 9 g
IMP	Investigational medicinal product
IRSG	Intergroup Rhabdomyosarcoma Study Group
ITGI	Integrated Therapeutics Group Inc, a wholly-owned subsidiary of Schering-Plough

KKS	Koordinierungszentrum Klinische Studien
LVEF	Left Ventricular Ejection Fraction
M	Methotrexate
MAP	Treatment Arm: Methotrexate, Doxorubicin and Cisplatin
MAPIE	Treatment Arm: Methotrexate, Doxorubicin, Cisplatin, Ifosfamide and Etoposide
MAPifn	Treatment Arm: Methotrexate, Doxorubicin, Cisplatin followed by Pegylated interferon α-2b
MDS	Myelodysplastic syndrome
MRC	Medical Research Council (UK)
MRC CTU	Medical Research Council Clinical Trials Unit
MRI	Magnetic Resonance Imaging
MTP	Muramyl tripeptide
MTX	Methotrexate
MUGA	Multigated Acquisition Scan
NCRI	National Cancer Research Institute (UK)
NSAID	Non-steroidal anti-inflammatory
NWTSG	National Wilm's Tumor Study Group
OS	Overall Survival
P	Cisplatin
Participating Institutions	Accredited center
PET	Positron Emission Tomography
Plts	Platelets
POG	Pediatric Oncology Group
QL	Quality of life
RIA	Radioimmunoassay
SAE	Serious Adverse Event
SAR	Serious adverse reaction
SF	Shortening Fraction
SIOP	International Society of Paediatric Oncology
SMX	Sulfamethoxazole
SSG	Scandinavian Sarcoma Group
TMG	Trial Management Group
TMP	Trimethoprim
Trials Center	COG, COSS, EOI, SSG
TSC	Trial Steering Committee
UAR	Unexpected adverse event
UKCCSG	United Kingdom Children's Cancer Study Group
ULN	Upper Limit of Normal
UN	United Nations
WNL	Within Normal Limits
WBC	White blood cell
WHO	World Health Organization

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Appendix A - International

Appendix A.1 Trial organization and membership

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The Chief Investigators have overall responsibility for the design, coordination and management of the trial. Each CI assumes full responsibility for her/his cooperative group and will not be responsible for the other three cooperating groups.

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Trial Management Group (TMG)

The TMG is a group set up by the Chief Investigators to manage the trial on a day-to-day basis. The TMG consists of the Chief Investigators, Dr Mark Bernstein (Chair, COG bone sarcoma), a representative of the Pathology Sub-Committee (elected by the pathology panel) and statistical and data management representatives from each trials center and the coordinating data center.

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National Coordinators

A National Coordinator is required for each country participating in the EURAMOS 1 trial. The role of the National Coordinator is to ensure that EURAMOS 1 is conducted according to the principles of GCP and according to the laws and regulations by all participating institutions in that country.

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Trial Steering Committee (TSC)

The role of the TSC is to provide overall supervision for the trial. It will elect a chairperson (one of the independent members) during its first meeting. It should also provide advice through its independent chairperson to the CIs and the participating trial groups on all aspects of the trial. The involvement of independent members who are not directly involved in other aspects of the trial provides protection for both trial participants and CIs. The CIs and the independent TSC members are to be appointed are listed below in alphabetical order:

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Independent Data Monitoring Committee (IDMC)

The IDMC is the only body involved in the trial that has access to the unblinded comparative data. The role of its members is to monitor these data and make recommendations to the TSC on whether the trial should or should not continue based on any ethical or safety reasons. In addition, the IDMC may be asked by the TSC to consider data emerging from other related studies. Membership of the IDMC will be completely independent of the CIs and the TSC.

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Oncology Panel

The oncology panels of each group shall check the protocol for content, consistency and accuracy on all topics surrounding study medication. Members of each group's oncology panel are appointed to represent the group in the TMG and the TSC. Some groups may offer or require consultation with named members of the oncology panel on issues surrounding chemotherapy.

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Pathology review panel

The purpose of the Pathology Review Panel is to ensure that the histopathological criteria for admission to the trial and histological response to chemotherapy are assessed in a timely and consistent fashion for all trial groups participating in EURAMOS 1. Each of the participating groups has formed a pathology sub-panel. Together, these form the pathology panel of the EURAMOS 1 trial. Each of the 4 collaborating groups has named one representative pathologist (highlighted by asterisk) to represent their group in intergroup discussions. These four will elect one pathologist to represent pathology in the Trial Management Committee.

Pathology review will be undertaken for all patients within the trial. Both the diagnostic biopsy and the resection specimen histology will be reviewed by a study pathologist. The pathology/biological studies subgroup will undertake regular audit to determine consistency of reporting. The process of pathology review is detailed in the protocol.

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Radiology panel

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Appendix A.2 Performance status

	Lansky score (1-16 years)		Karnofsky score (> 16 years)		WHO Performance Status
100	Fully active, normal.	**100**	Normal; no complaints; no evidence of disease.	**0**	Fully active, able to carry on all pre-disease performance without restriction.
90	Minor restrictions in physically strenuous activity.	**90**	Able to carry on normal activities; minor signs or symptoms of disease.		
80	Active, but tires more quickly.	**80**	Normal activity with effort; some signs and symptoms of disease.	**1**	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light housework, office work.
70	Both greater restriction of, and less time spent in, active play.	**70**	Cares for self but unable to carry on normal activity or to do work.		
60	Up and around, but minimal active play; keeps busy with quieter activities.	**60**	Requires occasional assistance but is able to care for most of personal needs.	**2**	Ambulatory and capable of self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
50	Gets dressed, but lies around much of the day; no active play; able to participate in all quiet play and activities.	**50**	Requires frequent assistance and medical care.		
40	Mostly in bed; participates in quiet activities.	**40**	Disabled; requires special care and assistance.	**3**	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
30	In bed; needs assistance even for quiet play.	**30**	Severely disabled; hospitalization is indicated though death not imminent.		
20	Often sleeping; play entirely limited to very passive activity.	**20**	Very ill; hospitalization and active supportive care necessary.	**4**	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
10	No play, does not get out of bed. Moribund.	**10**	Moribund, fatal processes progressing rapidly.		
0	Unresponsive. Dead.	**0**	Unresponsive. Dead.	**5**	Dead.

Appendix A.3 Measuring renal function

Measurement or calculation of Glomerular Filtration Rate (GFR)

Cisplatin, Methotrexate and Ifosfamide all cause renal toxicity. Regular monitoring is essential to detect renal damage. Serum creatinine should be monitored prior to each cycle of chemotherapy. In addition, GFR should be assessed as specified within the protocol.
The optimal way to measure GFR is by radionuclide measurement/EDTA clearance. However GFR can be estimated, as follows:

Schwartz Formula [age 1-18] [1]

$$\text{Estimated Creatinine clearance (mL/Min/1.73m}^2\text{)} = \frac{F \times \text{Height [cm]} \times 88.4}{\text{Serum Cr (}\mu\text{mol/L)}}$$

OR

$$= \frac{F \times \text{Height [cm]}}{\text{Serum Cr (mg/dL)}}$$

Where **F** is proportional to body muscle mass, hence depending on age and gender:

- Low birth weight infant **F** = 0.33
- Term Infant (< 1 year of age) **F** = 0.45
- Male, 1-16 years **F** = 0.55
- Female, 1-21 years **F** = 0.55
- Male, 16-21 years **F** = 0.70

Normal values [mL/min/1.73m²]:

- mean value: 120
- Normal range: 90-150

Cockcroft – Gault Formula (>18 years) [2]

Female

$$\frac{1.05\ (140 - \text{age (yrs)})\ \text{wt (kg)}}{\text{Creatinine (}\mu\text{mol/L)}}$$

OR

$$\frac{0.85\ (140 - \text{age (yrs)})\ \text{wt (kg)}}{72 \times \text{Creatinine (mg/dL)}}$$

Male

$$\frac{1.25\ (140 - \text{age (yrs)})\ \text{wt (kg)}}{\text{Creatinine (}\mu\text{mol/L)}}\ \text{(or)}$$

OR

$$\frac{(140 - \text{age (yrs)})\ \text{wt (kg)}}{72 \times \text{Creatinine (mg/dL)}}$$

Note: the accuracy of these formulae have been incompletely evaluated in patients receiving repeated cycles of intensive chemotherapy OR in adolescents. Renal function may be over-estimated by these methods.

Calculation of Tubular Function (T_p/C_{crea} or Tm_p/GFR)

Fractionated Tubular phosphate re-absorption (T_p/C_{crea}) can be calculated from paired serum and urine samples, according to Rossi et al [3], as follows:

$$\mathbf{T_p/C_{crea}} = Phosphate_{serum} - \frac{Phosphate_{urine} \times Creatinine_{serum}}{Creatinine_{urine}} \text{ [µmol/mL]}$$

OR

$$\mathbf{T_p/C_{crea}} = \left[Phosphate_{serum} - \frac{Phosphate_{urine} \times Creatinine_{serum}}{Creatinine_{urine}}\right] \times 0.323 \text{ [mg/dL]}$$

Reference values in three age groups, "limit" refers to mean – 2 SD for T_P/C_{crea}.

	< 1 month		1-12 months		> 1 year	
	mean	limit	mean	limit	mean	limit
T_P/C_{crea} [µmol/mL]	2.13	1.90	2.10	1.00	1.50	1.07

References:

1. Schwartz, G.J., L.P. Brion, and A. Spitzer, *The use of plasma creatinine concentration for estimating glomerular filtration rate in infants, children, and adolescents.* Pediatr Clin North Am, 1987. **34**(3): p. 571-90.
2. Cockcroft, D.W. and M.H. Gault, *Prediction of creatinine clearance from serum creatinine.* Nephron, 1976. **16**(1): p. 31-41.
3. Rossi, R., et al., *Assessment of tubular reabsorption of sodium, glucose, phosphate and amino acids based on spot urine samples.* Acta Paediatr, 1994. **83**(12): p. 1282-6.

Appendix A.4 Common Terminology Criteria for Adverse Events v3.0 (CTCAE)

Toxicity	Grade 1	2	3	4	5
Allergy/immunology					
Allergic reaction/ hypersensitivity (including drug fever)	Transient flushing or rash; drug fever <38°C (100.4°F)	Rash; flushing; urticaria; dyspnea; drug fever ≥38°C (.100.4°F)	Symptomatic bronchospasm, with or without urticaria; parenteral medication(s) indicated; allergy-related edema/angioedema; hypotension	Anaphylaxis	Death
Auditory/ear					
Hearing: Patients with/without baseline audiogram and enrolled in a monitoring program	Threshold shift or loss of 15 - 25dB relative to baseline, averaged at 2 or more contiguous test frequencies in at least one ear; or subjective change in the absence of a Grade 1 threshold shift	Threshold shift or loss of >25 - 90 dB, averaged at 2 contiguous test frequencies in at least one ear	Adult only: Threshold shift or loss of >25 - 90 dB, averaged at 3 contiguous test frequencies in at least one ear Pediatric: Hearing loss sufficient to indicate therapeutic intervention, including hearing aids (e.g., ≥20 dB bilateral HL in the speech frequencies; >30 dB unilateral HL; and requiring additional speech-language related services)	Adult only: Profound bilateral hearing loss (>90 dB) Pediatric: Audiologic indication for cochlear implant and requiring additional speech-language related services	
Remark: Pediatric recommendations are identical to adults, unless specified. For children and adolescents (≤18 years of age) without a baseline test, pre-exposure/pre-treatment hearing should be considered to be <5 dB loss.					
Blood/bone marrow					
Hemoglobin (Hgb)	< LLN - 10.0 g/dl < LLN - 6.2mmol/L < LLN - 100 g/L	<10.0 - 8.0 g/dl <6.2 - 4.9 mmol/L <100 - 80 g/L	<8.0 - 6.5 g/dl <4.9 - 4.0mmol/L <80 - 65 g/L	<6.5 g/dl <4.0mmol/L <65 g/L	Death
Leukocytes (total WBC)	< LLN - 3000/mm^3 < LLN - 3.0 x 10^9 /L	<3000 - 2000/mm^3 <3.0 - 2.0 x 10^9 /L	<2000 - 1000/mm^3 <2.0 - 1.0 x 10^9 /L	< 1000/mm^3 < 1.0 x 10^9 /L	Death

Toxicity	Grade 1	2	3	4	5
Blood/bone marrow					
Neutrophils/ granulocytes (ANC/AGC)	< LLN - 1500/mm^3 < LLN - 1.5 x 10^9 /L	<1500 - 1000/mm^3 <1.5 - 1.0 x 10^9 /L	<1000 - 500/mm^3 <1.0 - 0.5 x 10^9 /L	< 500/mm^3 < 0.5 x 10^9 /L	Death
Platelets	< LLN - 75000/mm^3 < LLN - 75.0 x 10^9 /L	<75000 - 50000/mm^3 <75.0 - 50.0 x 10^9 /L	<50000 - 25000/mm^3 <50.0 - 25.0 x 10^9 /L	< 25000/mm^3 < 25.0 x 10^9 /L	Death
Cardiac arrhythmia					
Cardiac arrhythmia - Other (specify,-)	Mild	Moderate	Severe	Life-threatening; disabling	Death
Cardiac general					
Left ventricular systolic dysfunction	Asymptomatic, resting ejection fraction (EF) <60 - 50%; shortening fraction (SF) <30-24%	Asymptomatic, resting EF <50 - 40% SF <24 - 155%	Symptomatic CHF responsive to intervention; EF <40 - 20% SF <15%	Refractory CHF or poorly controlled; EF <20%; intervention such as ventricular assist device, ventricular reduction surgery, or heart transplant indicated	Death
Constitutional symptoms					
Fatigue (asthenia, lethargy, malaise)	Mild fatigue over baseline	Moderate or causing difficulty performing some ADL	Severe fatigue interfering with ADL	Disabling	_
Fever (in the absence of neutropenia, where neutropenia is defined as ANC < 1.0 x 10^9/L)	38.0 - 39.0°C (100.4 - 102.2°F)	>39.0 - 40.0°C (102.3 - 104.0°F)	> 40.0°C (>104.0°F) for ≤24hrs	> 40.0°C (>104.0°F) for >24hrs	Death
Rigors, chills	Mild	Moderate, narcotics indicated	Severe or prolonged, not responsive to narcotics	_	_
Weight loss	5 - <10% from baseline; intervention not indicated	10 - <20% from baseline; nutritional support indicated	≥20% from baseline; tube feeding or TPN indicated	_	_

Toxicity	Grade 1	2	3	4	5
Endocrine					
Thryoid function, high (hyperthyroidism, thyrotoxicosis)	Asymptomatic, intervention not indicated	Symptomatic, not interfering with ADL; thyroid suppression therapy indicated	Symptoms interfering with ADL; hospitalization indicated	Life-threatening consequences (e.g., thyroid storm)	Death
Thyroid function, low (hypothyroidism)	Asymptomatic, intervention not indicated	Symptomatic, not interfering with ADL; thyroid replacement indicated	Symptoms interfering with ADL; hospitalization indicated	Life-threatening myxedema coma	Death
Gastrointestinal					
Diarrhea	Increase of < 4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4-6 stools per day over baseline; IV fluids indicated<24 hrs; moderate increase in ostomy output compared to baseline; not interfering with ADL	Increase of ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; hospitalization; severe increase in ostomy output compared to baseline; interfering with ADL	Life-threatening consequences(e.g. hemodynamic collapse)	Death
Remark: Diarrhea includes diarrhea of small bowel or colonic origin, and/or ostomy diarrhea					
Mucositis/stomatitis (clinical exam) -Select: - Anus - Esophagus - Large Bowel - Larynx - Oral Cavity - Pharynx - Rectum - Small Bowel - Stomach - Trachea	Erythema of the mucosa	Patchy ulcerations or pseudomembranes	Confluent ulcerations or pseudomembranes; bleeding with minor trauma	Tissue necrosis; significant spontaneous bleeding; life-threatening consequences	Death

Toxicity	Grade 1	2	3	4	5
Mucositis/stomatitis (functional/ symptomatic) -Select: - Anus - Esophagus - Large Bowel - Larynx - Oral Cavity - Pharynx - Rectum - Small Bowel - Stomach - Trachea	Upper aerodigestive tract sites: Minimal symptoms, normal diet; minimal respiratory symptoms but not interfering with function Lower GI sites: Minimal discomfort, intervention not indicated	Upper aerodigestive tract sites: Symptomatic but can eat and swallow modified diet; respiratory symptoms interfering with function but not interfering with ADL Lower GI sites: Symptomatic, medical intervention indicated but not interfering with ADL	Upper aerodigestive tract sites: Symptomatic and unable to adequately aliment or hydrate orally; respiratory symptoms interfering with ADL Lower GI sites: Stool incontinence or other symptoms interfering with ADL	Symptoms associated with life-threatening consequences	Death
Typhlitis (cecal inflammation)	Asymptomatic, pathologic or radiographic findings only	Abdominal pain; mucus or blood in stool	Abdominal pain, fever, change in bowel habits with ileus; peritoneal signs	Life-threatening consequences (e.g. perforation, bleeding, ischemia, necrosis); operative intervention indicated	Death
Vomiting	1 episode in 24 hrs	2 - 5 episodes in 24 hours; IV fluids indicated < 24 hrs	≥6 episodes in 24 hrs; IV fluids, or TPN indicated ≥24 hrs	Life threatening consequences	Death
Hemorrhage/bleeding					
Hemorrhage, GU - Bladder	Minimal or microscopic bleeding, intervention not indicated	Gross bleeding, medical intervention, or urinary tract irrigation indicated	Transfusion, interventional radiology, endoscopic, or operative intervention indicated; radiation therapy (i.e. hemostasis of bleeding site)	Life-threatening consequences; major urgent intervention indicated	Death

Toxicity	Grade 1	2	3	4	5
Infection					
Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection) (ANC < 1.0 x 10^9/L, fever ≥38.5°C)	-	-	Present	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	Death
Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC < 1.0 x 10^9/L)	_	Localized, local intervention indicated	IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or operative intervention indicated	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	Death
Infection with normal ANC or Grade 1 or 2 neutrophils	_	Localized, local intervention indicated	IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or operative intervention indicated	Life-threatening consequences (e.g. septic shock, hypotension, acidosis, necrosis)	Death
Metabolic/laboratory					
AST, SGOT (Serum glutamic oxaloacetic transaminase)	> ULN - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN	_
Bilirubin (hyperbilirubinemia)	> ULN - 1.5 x ULN	> 1.5 - 3.0 x ULN	> 3.0 - 10.0 x ULN	> 10.0 x ULN	_
Creatinine	> ULN - 1.5 x ULN	> 1.5 - 3.0 x ULN	> 3.0 - 6.0 x ULN	> 6.0 x ULN	Death
Remark: Adjust to age-appropriate levels for pediatric patients					
Glomerular filtration rate (GFR)	<75 - 50% LLN	<50 - 25% LLN	<25% LLN, chronic dialysis not indicated	Chronic dialysis or renal transplant indicated	Death
Phosphate, serum-low (hypophosphatemia)	<LLN - 2.5 mg/dL <LLN - 0.8 mmol/L	<2.5 - 2.0 mg/dL <0.8 - 06 mmol/L	<2.0 - 1.0 mg/dL <0.6 - 0.3 mmol/L	<1.0 mg/dL <0.3 mmol/L	Death

Toxicity	Grade 1	2	3	4	5
Neurology					
Confusion	Transient confusion, disorientation or attention deficit	Confusion or disorientation, or attention deficit interfering with function, but not interfering with ADL	Confusion or delirium interfering with ADL	Harmful to others or self; hospitalization indicated	Death
Mood alteration -select - agitation - anxiety - depression - euphoria	Mild mood alteration not interfering with function	Moderate mood alteration interfering with function, but not interfering with ADL; medication indicated	Severe mood alteration interfering with ADL	Suicidal ideation; or danger to self or others	Death
Neuropathy- motor	Asymptomatic, weakness on exam/testing only	Symptomatic weakness interfering with function, but not interfering with ADL	Weakness interfering with ADL; bracing or assistance to walk (e.g. cane or walker) indicated	Life-threatening; disabling (e.g. paralysis)	Death
Neuropathy-sensory	Asymptomatic; loss of deep tendon reflexes or paresthesia (including tingling) but not interfering with function	Sensory alteration or paresthesia (including tingling), interfering with function, but not interfering with ADL	Sensory alteration or paresthesia interfering with ADL	Disabling	Death
Somnolence/ Depressed level of consciousness	_	Somnolence or sedation interfering with function, but not interfering with ADL	Obtundation or stupor; difficult to arouse; interfering with ADL	Coma	Death
Seizure	_	One brief generalized seizure; seizure(s) well controlled by anticonvulsants or infrequent focal motor seizures not interfering with ADL	Seizures in which consciousness is altered; poorly controlled seizure disorder, with breakthrough generalized seizures despite medical intervention	Seizures of any kind which are prolonged, repetitive, or difficult to control (e.g. status epilepticus, intractable epilepsy)	Death

Toxicity	Grade 1	2	3	4	5
Renal/Genitourinary					
Cystitis	Asymptomatic	Frequency with dysuria; macroscopic hematuria	Transfusion; IV pain medications; bladder irrigation indicated	Catastrophic bleeding; major non-elective intervention indicated	Death
Urinary electrolyte wasting (e.g., Fanconi's syndrome, renal tubular acidosis)	Asymptomatic, intervention not indicated	Mild, reversible and manageable with replacement	Irreversible, requiring continued replacement	_	_
Renal failure	-	-	Chronic dialysis not indicated	Chronic dialysis or renal transplant indicated	Death
Secondary malignancy					
Secondary malignancy - possibly related to cancer treatment (specify, -)	-	-	Non-life-threatening basal or squamous cell carcinoma of the skin	Solid tumor, leukemia or lymphoma	Death
Syndromes					
Flu-like syndrome	Symptoms present but not interfering with function	Moderate or causing difficulty performing some ADL	Severe symptoms interfering with ADL	Disabling	Death

The complete CTCAE can be found at http://ctep.info.nih.gov/reporting/index.html

Appendix A.5 Agent information

Guidance on the management of toxicity in the trial are given in Section 9.1.8. Important safety information on the individual drugs is given below, but for full prescribing information the Summary of Product Characteristics (SPC) for the individual products should be consulted.

Doxorubicin

Alternative names

Adriamycin, 14-hydroxydaunorubicin, 3-Hydroxyacetyldaunorubicin,
NSC #123127

Mechanism of action

Doxorubicin is an anthracycline antibiotic isolated from cultures of *Streptomyces peucetius* active in all phases of the cell cycle with maximal activity in S phase. It has several modes of action including intercalation to DNA double helix, topoisomerase II mediated DNA damage, production of oxygen-free radicals which cause damage to DNA and cell membranes, and complex formation with iron or copper via the hydroquinone moieties. Iron doxorubicin complexes may contribute to cardiotoxicity by toxic free radical generation.

Since it is primarily excreted by the liver, any liver impairment may enhance toxicity. 40% to 50% is excreted in the bile; <5% in the urine. The drug has a very short initial half-life of <20 minutes and a terminal half-life of 17 hours. Animal studies indicate cytotoxic levels persist in tissue for as long as 24 hours.

Considerations prior to administration

Well established robust venous access. A central venous catheter or indwelling vascular access port is recommended for prolonged infusions to reduce the risk of extravasation.

If the patients hepatic function is significantly impaired, doxorubicin dosage reduction should be considered. See section 9.1.8 of protocol for details of dose modifications.
Special Precautions: Avoid extravasation and local contact with skin or conjunctiva. Avoid mixing with other agents, especially heparin.

Adverse effects

	Common Happens to 21-100 patients out of every 100	**Occasional** Happens to 5-20 patients out of every 100	**Rare** Happens to <5 patients out of every 100
Immediate: Within 1-2 days of receiving drug	Cardiac arrhythmias[1], nausea, vomiting, worsens side effects due to radiation, local ulceration if extravasated, pink or red color to urine	–	Anaphylaxis, allergic reactions, rash
Prompt: Within 2-3 weeks, prior to the next course	Myelosuppression (L), alopecia (L)	Stomatitis (L), hepatotoxicity (L), mucositis (L)	Rash
Delayed: Any time later during therapy, excluding the above conditions	Myelosuppression (mainly leukopenia and thrombocytopenia), immunosuppression, alopecia	Cardiomyopathy (cumulative and dose dependent)[2] (L)	–
Late: Any time after completion of treatment	–	–	Secondary malignancy
Unknown Frequency and Timing: **teratogenic toxicities in breast-fed children			

[1] *Rarely clinically significant.*
[2] *Risk increases with chest radiation*
(L) Toxicity may also occur later.

**Doxorubicin is excreted into breast milk in humans. Doxorubicin is considered to be contraindicated during breast feeding because of concerns for possible immune suppression, carcinogenesis, neutropenia, and unknown effects on growth.

Modification of anthracycline therapy to limit cardiac toxicity:
Anthracycline therapy has been found to cause acute and late cardiac toxicity which may become manifest clinically as congestive heart failure or malignant arrhythmias. The risk of cardiac toxicity is related to both dose intensity and total cumulative anthracycline dose. Serial measurements of systolic left ventricular function and changes on ECG may reveal trends, which suggest subclinical cardiac toxicity. However, these measurements do not infallibly predict which patients will develop congestive heart failure. Therefore, the decision to discontinue anthracycline before the total cumulative dose planned for a protocol must be made by the study investigators after balancing the risk of further cardiac damage, as suggested by abnormal results on serial cardiac testing, against the predicted benefit of increased cure rate based on the expected efficacy against the tumor targeted by the study. See section 9.1.8 of protocol for details of dose modifications.

Recommended route

Intravenous. Due to the vesicant properties of doxorubicin, it is strongly recommended that doxorubicin is given through a central venous line.

Dose/schedule

To reduce cardiotoxicity the following schedule is recommended within this protocol.
- Administration of doxorubicin as a 48 hour infusion
- Dexrazoxane may be considered when sustained reductions within the normal range of left ventricular ejection fraction or fractional shortening occurs. For details of dexrazoxane see page 56.

Formulation

Available in some countries as 2 mg/mL solution 10 mL (20 mg) and 25 mL (50 mg) and vials. Store refrigerated between 2- 8°C. Check with local CI for details.

Also available as a freeze-dried powder in 10 mg, 20 mg, 50 mg and 100 mg vials. Store at room temperature. The contents of the vial should be reconstituted with Water for Injection BP, Sodium Chloride 0.9%, or Dextrose 5% Injection to a solution concentration of 2 mg/mL. Refrigerate, protect from light and prolonged exposure to aluminum.

Doxorubicin should not be mixed with heparin as a precipitate may form and it is not recommended that doxorubicin be mixed with other drugs. Prolonged contact with any solution of an alkaline pH should be avoided as it will result in hydrolysis of the drug.

Supplier

Commercially available. See package insert for further information.

Cisplatin

Alternative names

Cis-diaminedichloroplatinum II, CDDP, Platinol, NSC #119875

Mechanism of action

Cisplatin is a platinum complex that has been shown to have cytotoxic effects by directly binding with DNA. Inhibition of DNA synthesis is thought to be due to the formation of inter- and intra-strand crosslinks between the guanine-guanine groups. Cisplatin has synergistic cytotoxicity with radiation and other chemotherapeutic agents. Cisplatin has a rapid distribution phase of 25-80 minutes with a slower secondary elimination half-life of 60-70 hours. Its penetration into the CNS is poor.

Considerations prior to chemotherapy

Adequate hydration and diuresis must be established prior to administration

Adverse effects

	Common Happens to 21-100 patients out of every 100	**Occasional** Happens to 5-20 patients out of every 100	**Rare** Happens to <5 patients out of every 100
Immediate: Within 1-2 days of receiving drug	Nausea (L), vomiting (L)	Metallic Taste (L)	Anaphylactic reaction
Prompt: Within 2-3 weeks, prior to the next course	Anorexia (L), myelosuppression, hypomagnesemia (L), high frequency hearing loss (L), nephrotoxicity (L)	Electrolyte disturbances (L)	Peripheral neuropathy (L), tinnitus (L), seizure (L), liver toxicity (L)
Delayed: Any time later during therapy, excluding the above conditions	–	Hearing loss in the normal hearing range	–
Late: Any time after completion of treatment	–	–	Secondary malignancy

(L) Toxicity may also occur later.

Dose/schedule

IV infusion Special Precautions: To reduce risk of nephrotoxicity, maintain a high urine flow (>100 mL/h) with good hydration. Mannitol is often administered to ensure good diuresis and has advantages over frusemide (which can itself cause renal damage).

Within this protocol the cisplatin may be given as either a 4 hour infusion on 2 consecutive days or as a 72 hour continuous infusion. With 72 hour continuous infusion the use of mannitol is not necessary.

To decrease the risk of hypomagnesaemia, give magnesium supplementation either orally or in the IV fluid, or both.

Formulation

Available in some countries as a white lyophilized powder in 10 mg and 50 mg vials, and as an aqueous solution, in 1 mg/mL, 50 mL and 100 mL vials, check with local CI for details.

Reconstitute by adding 10 mL or 50 mL sterile water to 10 mg or 50 mg vials respectively. If not used within 6 hours, it must be protected from light. The solution is stable for 20 hours at room temperature. **Do not refrigerate reconstituted solution.** Further dilution can be made in solutions containing at least 0.3% sodium chloride to maintain stability. For preparation of solution for infusion, any device containing aluminium that may come in contact with cisplatin (sets for intravenous infusion, needles, catheters, syringes) must be avoided as loss of potency can occur.

Supplier

Commercially available. See package insert for further information

Methotrexate

Alternative names

MTX, amethopterin, NSC #000740

Mechanism of action

Methotrexate (MTX) is an analogue of folic acid which penetrates into cells via a specific membrane transport system used by physiological folates. Inside the cell MTX rapidly binds to and inhibits its target enzyme dihydrofolate reductase (DHFR), leading to the inhibition of the syntheses of purines and pyrimidines. Intracellular folates exist physiologically in the form of polyglutamates and MTX is also metabolized to polyglutamate forms. Recent data suggest that the syntheses of purines and thymidylate can be stopped by direct inhibition from dihydrofolate and MTX polyglutamates. Thus, following the inhibition of DHFR by MTX, increasing levels of the dihydrofolate polyglutamates may directly block the syntheses of these nucleotides. In addition to direct inhibition of DHFR by methotrexate, the formation of polyglutamyl metabolites of the drug is also thought to:

a) increase intracellular drug accumulation
b) increase intracellular drug retention
c) inhibit folate-dependent nucleotide synthesis, by effects at loci other than DHFR

High-dose methotrexate (HDMTX) regimens designed to circumvent MTX resistance are thought to act by overcoming the decreased membrane transport of MTX into tumor cells. Achieving and sustaining high plasma levels of the drug promotes MTX diffusion thus overcoming the defective MTX transport system. However, other possible mechanisms i.e. mutation or overproduction of DHFR and impaired polyglutamation have been identified.

The doses of methotrexate needed to achieve these high plasma concentrations MUST be followed by the antidote leucovorin (folinic acid) to prevent increased toxicity to normal tissues.

Leucovorin (Folinic Acid) Rescue

The clinical usefulness of leucovorin rescue regimens is based upon the selectivity of the antidote in rescuing normal but not neoplastic tissue plus the competitive nature of the rescue in that more leucovorin is required to rescue at higher MTX concentrations.

Leucovorin can interact with MTX at different levels within the cells.

Membrane interactions

Leucovorin can compete with MTX uptake into cells since both use the same transport system. This observation forms the basis for one of the hypotheses of selectivity since tumor cells with a defect in the folate transport system would not be rescued since insufficient folate would enter the cell; in contrast to normal cells with intact folate transport which could be more easily rescued.

Replenishment of reduced folates

Leucovorin provides the cell with a source of reduced folate cofactors which can be used to restore purine and pyrimidine synthesis even though the activity of DHFR remains impaired

by the presence of dihydrofolate and MTX polyglutamates. This could account for the competitive nature of leucovorin rescue.

Inhibition of polyglutamate formation

Leucovorin can inhibit the formation of MTX polyglutamates (MTXPG's). Some tumor cells containing MTXPG's can only be poorly rescued by leucovorin since nucleotide synthesis remains inhibited by the polyglutamates despite high intracellular levels of reduced folates. Since normal bone marrow precursors metabolize less MTX to polyglutamates they are less sensitive to the effects of MTX and can be more easily rescued with leucovorin.

Considerations prior to administration

To prevent renal damage, intravenous hydration and alkalinization is given before methotrexate is commenced and continued until plasma methotrexate levels are considered safe according to group practice (generally either < 0.1 μmol/L or < 0.2 μmol/L, for details see Appendix B.6).

The establishment of an alkaline diuresis during treatment is important to increase the solubility of MTX and its 7-hydroxy metabolite and prevent the nephrotoxity resulting from precipitation of these substances in the renal tubules.

The appropriate leucovorin regimen MUST be prescribed at the same time as the MTX. IV leucovorin is commenced 24 – 28 hours after the start of the MTX and treatment is continued until plasma MTX levels are considered safe according to group practice (generally either < 0.1 μmol/L or < 0.2 μmol/L, for details see Appendix B.6).

Since MTX readily enters body fluids, patients with effusion(s) can have sustained high levels and must be monitored carefully.

Adverse effects

	Common Happens to 21-100 patients out of every 100	**Occasional** Happens to 5-20 patients out of every 100	**Rare** Happens to <5 patients out of every 100
Immediate: Within 1-2 days of receiving drug	–	Nausea, vomiting, anorexia	Dizziness, malaise, blurred vision, allergic reaction, peeling, redness, and tenderness of the skin, especially the soles and palms
Prompt: Within 2-3 weeks, prior to the next course	Transaminase elevations	Diarrhea, myelosuppression, stomatitis, photosensitivity	Alopecia, folliculitis, renal toxicity, leukoencephalopathy (L), seizures, acute neurotoxicity
Delayed: Any time later during therapy, excluding the above conditions	–	–	Lung damage (L), hyperpigmentation, liver damage (L), osteoporosis (L) Learning disability (L)
Late: Any time after completion of treatment	–	–	Progressive CNS deterioration
Unknown Frequency and Timing: **Fetal and teratogenic toxicities			

(L) Toxicity may also occur later.
**Methotrexate crosses the placenta to the fetus. Fetal toxicities and teratogenic effects of methotrexate (either alone or in combination with other antineoplastic agents) have been noted in humans. The toxicities include: congenital defects, chromosome abnormalities, malformation, severe newborn myelosuppression, pancytopenia, and low birth weight.
**Methotrexate is excreted into breast milk in low concentrations. However, because the drug may accumulate in neonatal tissues, breast feeding is not recommended. Methotrexate is considered to be contraindicated during breast feeding because of several potential problems, including immune suppression, neutropenia, adverse effects on growth, and carcinogenesis.

Dose/schedule

Methotrexate will be given by IV infusion over 4 hours. Leucovorin (folinic acid rescue) will start 24 – 28 hours after the start of the 4-hour infusion.

Suggested Hydration Protocol

(Some groups have additional or slightly different hydration routines, see group specific Appendix B)
Hydration fluid:
Glucose 4%, Sodium chloride 0.18%
Potassium chloride 20 mmol/L
Sodium bicarbonate 50 mmol/L

Infusion rate: 125 mL/m^2 per hour (3 L/m^2/24 hours)

Urine pH: A urinary pH >7 must be achieved before starting the MTX infusion. It may be necessary to increase the sodium bicarbonate concentration in the hydration fluid to 70 mmol/L to maintain an alkaline urine (pH 7-8).

An alternative method of alkalinizing the urine is to use acetazolamide 500 mg four times a day starting 24 hours prior to the MTX and continuing for 72 hours (Shamash 1991). In children a dose of 250 mg/m^2 is recommended.

Pre-hydration: Recommended for at least 4 hours prior to commencement of methotrexate

Hydration during MTX infusion

The MTX must be infused at the appropriate rate, in combination with the hydration fluid at a combined rate of 125 mL/m^2/h.

Hydration after completion of methotrexate infusion

Total fluid input/day until serum MTX concentration is considered safe according to group practice (generally either < 0.1 µmol/L or < 0.2 µmol/L, for details see Appendix B.6) : ≥ 2000 mL/m^2. The patient should receive at least 1500 mL/m^2/ 24 hours as IV fluid to keep the urine alkaline.

Leucovorin (folinic acid) rescue

The leucovorin MUST be written up at the same time as the methotrexate is prescribed. Rescue starts 24 - 28 hours after start of 4 hour MTX infusion.

Leucovorin 15 mg/m^2 intravenously or orally every 6th hour, beginning 24 –28 hours after starting the methotrexate infusion. Normally, leucovorin is given by 11 - 12 doses until T84. It is sufficient to give leucovorin until 6 hours after the methotrexate concentration has fallen below 0.1-0.2 µmol/L.

Interactions

Drugs which compromise renal function e.g. aminoglycosides and cisplatin can decrease clearance of methotrexate and lead to systemic toxicity. Avoid concurrent use of NSAIDs, including salicylates and sulphonamides. Large doses of penicillin may interfere with the active renal tubular secretion of methotrexate.

Overdosage

Although High Dose MTX is generally well tolerated, unpredictable life-threatening toxicity can occur. For patients who have markedly delayed clearance of MTX secondary to renal dysfunction, therapeutic options are few and of limited efficacy. Carboxypeptidase-G2 (CPDG-2) inactivates MTX by hydrolyzing its C-terminal glutamate residue. CPDG-2 may be used to rescue patients with renal dysfunction and delayed MTX excretion.

Management of methotrexate toxicity and delayed methotrexate excretion

General considerations

Prompt intervention should prevent severe toxicity. Severe toxicity is anticipated if there is a greater than 100% rise in the serum creatinine level within 24 hours after start of the methotrexate infusion and/or the serum methotrexate levels are in the "toxicity range" on the MTX excretion curve (see below). Patients in this situation should be treated by continued hydration and alkalinization of the urine with 3,000 mL/m^2/24 h of glucose 4%, sodium chloride 0.18% with 40 mmol $NaHCO_3$/L and 20 mmol KCl/L or similar alkaline hydration fluids. In this case, the minimum diuresis should be increased to 600 mL/m^2/6h. Increase the dose of leucovorin as described below (see Appendix B.6 for group specific guidance). The

administration of potassium should be carefully monitored, depending on renal function. Body weight, fluid input and output and blood pressure should be monitored. Blood counts, serum creatinine, liver transaminases, ALP, bilirubin and serum methotrexate levels should be measured daily. If increased, serum-creatinine, kidney function should be evaluated with GFR. Records should be kept of the clinical course. Always ensure that the patient is not taking other medications that interfere with methotrexate binding or excretion.

Guidance for adjustment of leucovorin dose during delayed methotrexate excretion (see Appendix B.6 for group specific guidance)

$$\text{Total daily dose of leucovorin (mg)} = \frac{\text{Patient's actual serum MTX} \times \text{standard daily dose of leucovorin}}{\text{Upper limit of serum MTX for the actual day and time}}$$

The upper limit of serum MTX		
	at 24 hours is	20 µM
	at 48 hours is	2 µM
	at 72 hours is	0.2 µM

Example:
If the 48 hours methotrexate level was 40 µM, the leucovorin dose should be adjusted to:

$$\text{Total daily dose of leucovorin (mg)} = 1200 \text{mg/m}^2\text{/24 hours} = \frac{60 \text{ mg/m}^2 \times 40}{2}$$

It is possible to reduce the dose of leucovorin on the following days in relation to the reduction in the methotrexate level. When the methotrexate level is in the range of 0.2–0.9 µM, give leucovorin in doses of 8 mg/m^2 orally every 6 hours until one dose after the serum level is < 0.1 - 0.2 µM.
Note: Always continue to monitor urine pH and give more $NaHCO_3$ if pH < 7.

Formulation

Available in a variety of forms, all prepared as the sodium salt (yellow powder), with or without preservatives check with local CI for details.

High Dose MTX: Available as a 1 g or 5 g vial containing methotrexate 100 mg/mL, for intravenous use in high-dose therapy. After dilution – Chemical and physical in-use stability has been demonstrated in dextrose 5% and sodium chloride 0.9% infusion solutions for 30 days at 4°C in PVC containers when protected from light.

Supplier

All forms of Methotrexate are commercially available. See package insert for further information.

Reference

Shamash J, Earl H, Souhami R. Acetazolamide for alkalinisation of urine in patients receiving high-dose methotrexate. Cancer Chemother Pharmacol. 1991;28(2):150-1.

Ifosfamide

Alternative names

IFX, IFOS, IFO, NSC #109724

Mechanism of action

Ifosfamide (IFOS) is a structural analogue of cyclophosphamide. Ifosfamide requires hepatic microsomal activation for the production of the reactive 4-hydroxyoxazaphorine intermediate which serves as a carrier molecule for the ultimate intracellular liberation of phosphoramide mustard, an alkylating agent. The occurrence of another reactive metabolite, acrolein, is thought to be the cause of the hemorrhagic cystitis, identical to that seen with cyclophosphamide. The metabolism of ifosfamide is dose-dependent, with the terminal half-life varying between 7 and 16 hours at doses of 1.6-2.4 g/m² and 3.8-5.0 g/m², respectively. At 1.6-2.4 g/m²/d, 12 to 18% of the dose was excreted in the urine, whereas at 5 g/m² single-dose, 61% was excreted in the urine. Evidence also exists to suggest that metabolism is inducible, with more rapid clearance occurring in the second and later doses of fractionated courses of 3-5 times weekly. Unlike cyclophosphamide, as much as 50% of a large dose of ifosfamide may be subject to alternative metabolic degradation, with the production of reactive but non-cytotoxic species. Some of these products (chloracetaldehyde) are suggested as being the cause of ifosfamide neurotoxicity.

Considerations prior to administration

Particular risk factors have been identified as increasing the risk of encephalopathy and/or nephrotoxicity. These include impaired renal function, prior platinum treatment, nephrectomy or pelvic disease, although the absence of these does not preclude the occurrence of toxicity.

Adverse effects

	Common Happens to 21-100 patients out of every 100	**Occasional** Happens to 5-20 patients out of every 100	**Rare** Happens to <5 patients out of every 100
Immediate: Within 1-2 days of receiving drug	Nausea (L), vomiting (L), anorexia (L)	Somnolence, confusion, weakness, seizure, inappropriate ADH[1]	Encephalopathy (L)
Prompt: Within 2-3 weeks, prior to next course	Myelosuppression, arrhythmia, EKG changes	Hemorrhagic cystitis, cardiac toxicities with arrythmias[2], myocardial necrosis[2]	–
Delayed: Any time later during therapy, excluding the above conditions	Alopecia	Fanconi's renal syndrome	Peripheral neuropathy, acute renal failure, pulmonary fibrosis (L)
Late: Any time after completion of treatment	–	Infertility/sterility	Secondary malignancy, bladder fibrosis

[1] Less common with lower doses
[2] Extremely rare at doses of < 10 g/m²/course
(L) Toxicity may also occur later.

Dose/schedule

Ifosfamide by 4 hour infusion. Intravenous hydration (with glucose/saline + potassium chloride 20 - 30 mmol/L), containing mesna at 100% (mg/mg) of the prescribed daily ifosfamide dose. Infuse this solution at a rate of 3 L/m^2/24 hours. Some groups recommend commencing 4 hours before the first ifosfamide dose and continuing for a minimum of 12 hours after completion of the last ifosfamide infusion (see Appendix B for group specific guidance).

Oral mesna may be substituted for part of the intravenous dose. The package insert for mesna tablets specifies a dose of 20% of the ifosfamide dose at the time of ifosfamide administration and 40% at 2 and 6 hours following each dose of ifosfamide. Although the package insert also states that "The efficacy and safety of the ratio of IV and PO mesna has not been established as being effective for daily doses of ifosfamide higher than 2.0 g/m^2", Berardi et al have shown that in practice a dose of 100% of the ifosfamide as described in the package insert/SPC can be used safely instead of intravenous mesna for the final day of ifosfamide treatment with doses of $\geq$3 g/m^2.

Mesna tablets are available in some countries as 400 mg & 600 mg, check with local CI for details.

Oral mesna dosing for final day ifosfamide infusion

Time from end of ifosfamide infusion	Route	Dose of mesna	IE & Ai schedules
T = 0	IV bolus	20% w/w daily ifos dose	600 mg
T = 2 hrs	po	40%	1200 mg
T = 6 hrs	po	40%	1200 mg

Ifosfamide neurotoxicity - the role of Methylene blue

Methylene Blue should be considered for all patients with Grade 2 neurocortical toxicity grading, and is indicated for patients with grade 3 and 4 toxicity.

Methylene blue is contraindicated in patients with

- Glucose-6-phosphate dehydrogenase deficiency
- Pregnancy & Lactation
- Known sensitivity to the drug
- Severe renal impairment

Mechanism of action

Whilst the exact mechanisms for Ifosfamide-induced encephalopathy are not known, various metabolic pathways have been suggested. Methylene blue may act by counteracting some of these pathways

Drug Interactions

No significant drug interactions have been reported with methylene blue

Dose

Whilst there have been no studies to determine the best dose and scheduling for the treatment of Ifosfamide-induced encephalopathy with Methylene Blue, a review of the literature would suggest:

Treatment of Ifosfamide-induced encephalopathy:

Adults: 50 mg (5mL ampule of 1% solution) – 4 hourly
Pediatrics: 1 mg/kg/dose – 4 hourly

Prophylaxis of Ifosfamide-induced encephalopathy:

Adults: 50 mg (5 mL ampoule of 1% solution) – 6 hourly
Pediatrics: 1 mg/kg/dose – 6 hourly

Administration

Either as a slow IV bolus – given over several minutes, or in 100 mL normal saline over 15-30 min. The methylene blue should be filtered before use using a 0.45 micron filter.

Side Effects

Potentially life threatening effects:
- Occasionally: hypotension and cardiac arrhythmias

Symptomatic Adverse Effects
- I.V. administration may cause abdominal pain, headache, dizziness, tremors, apprehension, confusion, chest pain, dyspnoea, tachycardia, and sweating – however, several of these symptoms are also symptoms of methaemoglobinaema for which Methylene Blue is indicated.
- Nausea, vomiting, diarrhea, and dysuria have been reported with oral administration
- If MB is injected subcutaneously or extravasation occurs, necrotic abscesses may result
- Blue discoloration of urine, stools and saliva.

Supplier

Ifosfamide is commercially available. See package insert for further information.

Methylene Blue USP is available in the UK from Mayne as 5 mL ampoules or from Martindale as 10 mL ampoules containing 50 mg/mL (1% solution).

References

Berardi R, Strauss S, Blake D, Whelan J
Is it safe to substitute Oral for Intravenous Mesna? A Case Control Study
Proceedings ASCO 2000; abstract no: 2398

Watkin SM, Husband DJ, Green JA and Warenius HM (1989) Ifosfamide Encephalopathy: a Reappraisal. European Journal Cancer Clinical Oncology 25(9): 1303-1310

Cerny T, Castiglione M, Brunner K, Küpfer A, Martinelli G, and Lind M. (1990) Ifosfamide by continuous infusion to prevent encephalopathy. Lancet 335: 175

Pelgrims J, De Vos F, Van den Brande J, Schrijvers D, Prové A and Vermorken JB (2000) Methylene blue in the treatment and prevention of ifosfamide-induced encephalopathy: report of 12 cases and a review of the literature. British Journal of Cancer 82(2): 291-294

Meanwell CA, Blake AE, Kelly KA, Honigsberger L, Blackledge G (1986) Prediction of Ifosfamide/mesna Associated Encephalopathy. European Journal Cancer Clinical Oncology 22(7): 815-819.

Küpfer A, Aesclimann C, Wermuth B and Cerny T (1994) Prophylaxis and reversal of ifosfamide encephalopathy with methylene blue. Lancet 343: 763-764

Koschuth A, Spath-Schwalbe E and Possinger K (1996) Methylenblau bei Ifosfamid-induzierter Enzephalopathie. Dtsch Med Wochenschr 121: 1210

Van Tongelen K and Hawthorn J (1994) A Practical Guide to EORTC studies. EORTC. Brussels, *Cited in* Pelgrims et al (2000) Methylene blue in the treatment and prevention of ifosfamide-induced encephalopathy: report of 12 cases and a review of the literature. British Journal of Cancer 82(2): 291-294

Etoposide

Alternative names

VP-16, VePesid, NSC #141540

Mechanism of action

A semisynthetic derivative of podophyllotoxin that forms a complex with topoisomerase II and DNA which results in a single and double strand DNA breaks. Its main effect appears to be in the S and G2 phase of the cell cycle. The initial half-life is 1.5 hours and the mean terminal half-life is 4 to 11 hours. It is primarily excreted in the urine. There is poor diffusion into the CSF. The maximum plasma concentration and area under the concentration time curve (AUC) exhibit a high degree of patient variability. Etoposide is highly bound to plasma proteins (~94%), primarily serum albumin. Pharmacodynamic studies have shown that etoposide systemic exposure is related to toxicity. Preliminary data suggests that systemic exposure for unbound etoposide correlates better than total (bound and unbound) etoposide. Etoposide is well absorbed after oral administration, but a high degree of interpatient variability has been reported (25 - 75% bioavailability).

Adverse effects

	Common Happens to 21-100 patients out of every 100	**Occasional** Happens to 5-20 patients out of every 100	**Rare** Happens to <5 patients out of every 100
Immediate: Within 1-2 days of receiving drug	Nausea, vomiting		Hypotension, anaphylaxis, skin rash
Prompt: Within 2-3 weeks, prior to next course	Myelosuppression	Alopecia, enhanced damage due to radiation, diarrhea	Peripheral neuropathy, stomatitis
Delayed: Any time later during therapy, excluding the above conditions			
Late: Any time after completion of treatment			Secondary malignancy

(L) Toxicity may also occur later.

Dose/schedule

Etoposide - IV infusion over 1 hour. Caution: severe hypotension may occur if the drug is given in less than 30 minutes. **Should not be given by rapid intravenous push**. Watch for anaphylaxis.

Etopophos - IV bolus over 5 minutes or IV infusion may be used instead of etoposide.

Formulation

Etoposide

A yellow solution with a pH of 3 to 4, available in some countries in 100 mg (5 mL) or 500 mg (25 mL) multiple-dose sterile vials containing 20 mg/mL etoposide, check with local CI for details. Unopened vials of etoposide are stable for 24 months at room temperature (25°C). Dilute with 0.9% sodium chloride injection or0.5% glucose. At room temperature, the solution is thought to be stable for 48 hours at a concentration of 0.4 mg/mL and for 96 hours at a concentration of 0.2 mg/mL in both glass and plastic containers. At concentrations above 0.4 mg/mL, the stability of the solution is highly unpredictable; therefore dilution to a concentration >0.4 mg/mL is not recommended. DO NOT REFRIGERATE SOLUTION: keep agitation to a minimum.

Etopophos injection

Each vial contains a lyophilised powder for injection of 113.6 mg etoposide phosphate (equivalent to 100 mg etoposide). Immediately prior to administration, the content of each vial must be reconstituted with either 5 mL or 10 mL Water for Injection B.P., 5% Glucose Intravenous Infusion B.P. or 0.9% Sodium Chloride Intravenous Infusion BP to a concentration equivalent to 20 mg/mL or 10 mg/mL etoposide (22.7 mg/mL or 11.4 mg/mL etoposide phosphate), respectively. Following reconstitution the solution may be administered without further dilution.

When reconstituted and/or diluted as directed Etopophos solutions are chemically and physically stable for 48 hours at 37°C, 96 hours at 25°C and 7 days under refrigeration (2-8°C) under normal room fluorescent light in both glass and plastic containers.

Supplier

Commercially available. See package inserts for further information

Pegylated Interferon α–2b

Alternative names

Peg-Intron, IFN α,

Mechanism of action

The biological activity of Peg-Intron is derived from its interferon α-2b moiety. Interferons exert their cellular activities by binding to specific membrane receptors on the cell surface and initiate a complex sequence of intracellular events. These include the induction of certain enzymes, suppression of cell proliferation, immunomodulating activities such as enhancement of the phagocytic activity of macrophages and augmentation of the specific cytotoxicity of lymphocytes for target cells, and inhibition of virus replication in virus-infected cells. Interferon-α upregulates the Th1 T-helper cell subset in *in vitro* studies. The clinical relevance of these findings is not known.
IFN-α2b, a product of genetic engineering, has a plasma half-life of 4 to 7 hours. PegIntron is a protein-polymer conjugate (molecular weight: 31 300 daltons) and a monopegylated derivative of interferon α-2b (IntronA). It is a product of targeted covalent bonding of a polyethylene glycol (PEG) molecular with a molecular weight of 12 000 daltons to one of the free amino groups in the protein molecule. The addition of PEG results in longer plasma half-lives, lower immunogenicity, improved solubility in water, and less sensitivity to proteolysis.

Considerations prior to administration

Patients <5 years will not be randomized to interferon.

Adverse effects

	Common Happens to 21-100 patients out of every 100	**Occasional** Happens to 5-20 patients out of every 100	**Rare** Happens to <5 patients out of every 100
Immediate: Within 1-2 days of receiving drug	Flu-like syndrome- fever, fatigue, chills. Nausea, vomiting Pruritus, swelling, pain at injection site.	Headache Arrhythmias, hypotension paresthesia	Anaphylactic reaction
Prompt: Within 2-3 weeks of starting treatment	–	Confusion, depression, rash, diarrhea Elevated liver function tests	Seizures, Visual disturbances Pulmonary infiltrates, pneumonitis, pneumonia alopecia
Delayed: Any time later during therapy, excluding the above conditions	–	–	–
Late: Any time after completion of treatment	–	–	–
Unknown Frequency and Timing:			

Recommended route

Administer subcutaneously.

Dose/schedule

Starting dose 0.5 μg/kg/week (maximum 50 μg/wk) for 4 weeks then dose is escalated to 1.0 μg/kg/wk (maximum 100 μg/wk)

The following syringes and needles are recommended: B-D disposable syringes (tuberculin syringes), B-D #30963; needle gauge 27; length ½ inch (13 mm)

Dosage calculation

The total dose of Peg-Intron is calculated based on subject weight. The following formula should be used to calculate the dose:

$$\text{Dose in mL} = \frac{\text{Weight (kg) x Dose ("X" μg/kg)}}{\text{Reconstituted Vial Strength (μg/mL)}}$$

Example #1 Vial Strength = 50 μg/vial (100 μg/mL) Subject weight = 65 kg $\text{Dose in mL} = \frac{65\text{ kg x }0.5\text{ μg/kg}}{100\text{ μg/mL}}$ Dose = 0.33 mL PegIntron	Example #2 Vial Strength = 50 μg/vial (100 μg/mL) Subject weight = 80 kg $\text{Dose in mL} = \frac{80\text{ kg x }0.5\text{ μg/kg}}{100\text{ μg/mL}}$ Dose = 0.4 mL PegIntron

Formulation

Peg-Intron is supplied for the trial as a lyophilized powder in a strength of 50 μg, and 100 μg vials together with sterile water for injection. Peg-Intron must be stored at 2° - 8°C. Each vial must be reconstituted with 0.7 mL of water for injections for administration of up to 0.5 mL of solution. A small volume is lost during preparation of Peg-Intron for injection when the dose is measured and injected. Therefore, each vial contains an excess amount of solvent and Peg-Intron powder to ensure delivery of the labeled dose in 0.5 mL of Peg-Intron, solution for injection. The reconstituted solution has a concentration of 50 μg/0.5 mL or 100 μg/0.5 mL.

Reconstituted solution must be used immediately or within 24 hours when stored at 2° - 8°C (in a refrigerator). However, it is recommended that the solution be used within 3 hours after mixing.

Supplier

Pegylated interferon α-2b (Peg-Intron) will be supplied for this trial by Integrated Therapeutics Group Inc (ITGI), a wholly-owned subsidiary of Schering-Plough. Contact information for individual Schering-Plough country operations and request of supply is included in Appendix B.5.

Dexrazoxane

Alternative names

Zinecard®, Cardioxane®, ADR-529, ICRF-187, NSC-169780

Mechanism of action

Dexrazoxane is a synthetic chemical, a cyclic derivative of EDTA that readily penetrates cell membranes. Results of laboratory studies suggest that dexrazoxane is converted intracellularly to a ring opened chelating agent that interferes with iron mediated free radical generation thought to be responsible, in part, for anthracycline-induced cardiomyopathy.

Considerations prior to administration

- Satisfactory full blood count
- Only to be given with chemotherapy regimens containing anthracyclines. Monitor patients for cardiotoxicity during therapy with dexrazoxane and an anthracycline.

Adverse effects

	Common Happens to 21-100 patients out of every 100	**Occasional** Happens to 5-20 patients out of every 100	**Rare** Happens to <5 patients out of every 100
Immediate: Within 1-2 days of receiving drug	Pain on injection, phlebitis	Transient increases in triglycerides, amylase and ALT, mild nausea, vomiting, and diarrhea	–
Prompt: Within 2-3 weeks, prior to the next course	Myelosuppression	–	Neurotoxicity (manifested as Headache and constipation)
Delayed: Any time later during therapy, excluding the above conditions	–	–	–
Late: Any time after completion of treatment	–	–	–
Unknown Frequency and Timing: *Fetal toxicities			

*Possible adverse effects of dexrazoxane on the fertility of humans and experimental animals, male or female, have not been adequately studied. Dexrazoxane was maternotoxic, embryotoxic and teratogenic when given to pregnant rats and rabbits during the period of organogenesis. Safety and effectiveness of dexrazoxane in children have not been established.

Recommended route

The reconstituted solution should be given by slow IV push or short intravenous infusion.

Dose/schedule

The recommended dosage ratio of dexrazoxane: doxorubicin is 10:1 (for example, 500 mg/m^2 dexrazoxane: 50 mg/m^2 of doxorubicin).[1]

After completing the administration of dexrazoxane, and within 30 minutes from the beginning of the dexrazoxane administration, the intravenous injection of doxorubicin should be given.

Interactions

Dexrazoxane does not interfere with the pharmacokinetics of doxorubicin. However it may increase the myelosuppressive effects of other chemotherapeutic agents.

Formulation

There are two different formulations of dexrazoxane available on the market. Both brands have been shown to be bioequivalent.

Cardioxane®

Sterile, pyrogen-free lyophilized material in 500 mg single dose vials. When reconstituted as directed with 25 mL of sterile Water for Injections each mL contains 20 mg dexrazoxane. The pH of the resultant solution is 1.6.

To avoid the risk of thrombophlebitis at the injection site, Cardioxane should not be infused without further dilution with Ringer lactate solution or 0.16 M Sodium lactate solution USP

The reconstituted product remains stable for up to 24 hours at an ambient temperature under normal artificial light. The manufacturers recommend that it always be kept at 2-8°C protected from light and used within 4 hours.

Zinecard®

Sterile, pyrogen-free lyophilized material in 250 mg or 500 mg single dose vials. When reconstituted as directed with a 25 mL (for the 250 mg or 50 mL (for the 500 mg) vial of 0.167 M (M/6) Sodium Lactate Injection each mL contains 10 mg dexrazoxane. The pH of the resultant solution is 3.5 to 5.5. The reconstituted dexrazoxane solution may be diluted with either 0.9% Sodium Chloride Injection, USP, or 5.0% Dextrose Injection, USP, to a concentration range of 1.3 to 5.0 mg/mL in intravenous infusion bags.

[1] There are two brands of cardioxane available on the market with different dose recommendations. The Zinecard licensed dose in 10:1 dexrazoxane: doxorubicin whereas the Cardioxane licensed dose is 20:1. The 10:1 is the dose as recommended by ASCO. Both brands have been shown to be bioequivalent. See references

Reconstituted dexrazoxane, when transferred to an empty infusion bag, is stable for 6 hours from the time of reconstitution when stored at room temperature or under refrigeration. Dexrazoxane be diluted with either 0.9% Sodium Chloride Injection, USP, or 5.0% Dextrose Injection, USP, to a concentration range of 1.3 to 5.0 mg/mL is also stable for 6 hours.

Pharmacokinetics & pharmacodynamics

The disposition kinetics of dexrazoxane are dose-dependent with administered doses from 60 to 900 mg/m^2. The plasma half-life is 2-2.5 hours. Qualitative metabolism studies have confirmed the presence of unchanged drug, a diacid-diamide cleavage product, and two monoacid-monoamide ring products in the urine of animals and man. Metabolite levels were not measured in the pharmacokinetics studies.

Urinary excretion plays an important role in the elimination of dexrazoxane: 42% of the drug (500 mg/m^2) was excreted in the urine. In vitro studies have shown that dexrazoxane is not bound to plasma proteins. The pharmacokinetics of dexrazoxane have not been evaluated in patients with hepatic or renal insufficiency.

There was no significant change in the pharmacokinetics of doxorubicin (50 mg/m^2) in a crossover study in cancer patients.

Supplier

Commercially available in some of the participating countries. **References:**

Schuchter, Lynn M.; Hensley, Martee L. et al 2002 Update of Recommendations for the Use of Chemotherapy and Radiotherapy Protectants: Clinical Practice Guidelines of the American Society of Clinical Oncology. Journal of Clinical Oncology 2002:20(12); 2895-2903.

Rosing H, ten Bokkel Huinink WW, van Gijn R et al. Comparative open, randomized, cross-over bioequivalence study of two intravenous dexrazoxane formulations (Cardioxane and ICRF-187) in patients with advanced breast cancer, treated with 5-fluorouracil-doxorubicin-cyclophosphamide (FDC). Eur J Drug Metab Pharmacokinet. 1999 Jan-Mar; 24(1):69-77.

Carboxypeptidase G2

Alternative names

CPG2, Voraxaze™, Glucarpidase

Mechanism of action

Carboxypeptidase-G2 cleaves the terminal glutamate from folate and folate analogues such as methotrexate. In the case of methotrexate CPDG-2 action results in the production of an inactive metabolite (DAMPA). It was developed from the Pseudomonas strain RS16 and has no mammalian analogue. CPG2 has a much higher affinity for methotrexate than leucovorin so even high circulating leucovorin levels are unlikely to interfere with methotrexate inactivation. CPG2 can be used to treat patients with methotrexate-induced renal dysfunction and delayed methotrexate excretion and results in significantly diminished serum methotrexate levels usually within minutes.

Considerations prior to administration

Use of CPG2 is at the discretion of the treating physician in patients of any age. Its use should be considered early in the case of MTX induced renal failure and subsequently delayed MTX excretion. Severe non-renal-toxicity in the context of delayed MTX excretion is also an indication to consider the use of CPG2. The following are criteria for considering early use of CPG2:

- Plasma methotrexate concentration $\geq$ 10 μmol/L 48 hours after MTX administration
- Rise in creatinine of 100% or more within 24 hours of MTX

Adverse effects

	Common Happens to 21-100 patients out of every 100	**Occasional** Happens to 5-20 patients out of every 100	**Rare** Happens to <5 patients out of every 100
Immediate: Within 1-2 days of receiving drug	–	–	Rash, hypersensitivity reactions
Prompt: Within 2-3 weeks, prior to the next course	–	–	–
Delayed: Any time later during therapy, excluding the above conditions	–	–	–
Late: Any time after completion of treatment	–	–	–
Unknown Frequency and Timing:			

Recommended route

Intravenous

Dose/schedule

CPG2 is administered at a dose of 50units/kg x 1 dose intravenously. Further doses are unlikely to be necessary.

Formulation

CPG2 is available in some countries in 1000 unit vials (2 mg protein), check with local CI for details. This should be reconstituted with 1-2 mL sodium chloride 0.9% or water for injection and administered over 3-5 minutes.

Pharmacokinetics & pharmacodynamics

CPG2 reduces MTX levels in the body by over 98% in 15 minutes. CPG2 itself is fully eliminated from the body in 8 hours. No antibodies to CPG2 have ever been found in approximately 300 patients tested to date.

Supplier

Protherics plc, the manufacturer of Voraxaze™ (carboxypeptidase G2) has contracted with IDIS in the UK to respond to requests for product in countries in which the distribution of Voraxaze™ under “named patient basis” has been authorised. Registration with IDIS in advance of ordering is necessary to quickly process your request.
We will normally be able to deliver Voraxaze within 24 hrs of receipt of your order for shipments in Central Europe. This will effectively mean next day delivery and there will be a service during weekends and holidays (there may be an additional charge for this weekend service).
For destinations outside Central Europe delivery is normally within 48hrs
For information or order enquiries about Voraxaze (CPG2) please contact IDIS at the following numbers:

Contact telephone numbers for IDIS for information or order enquiries about Voraxe:

UK:	0044 (0) 1932 824 100
Germany:	0049 (0) 89 9700 7409
Ireland:	00353 (0) 1 6319325
International Enquiries:	0044 (0) 1932 824 123
Out of hours emergency line	0044 (0)1932 824 198
email contact during buisiness hours:	enquiries@idispharma.com
International enquiries:	internationalsales@idispharma.com

Contact your group’s CI in case of questions about emergency supply of carboxypeptidase.

Appendix A.6 Response definitions

In EURAMOS 1, complete response and progressive disease will be defined as follows:

Complete Remission (CR):

- The complete macroscopic excision of all detectable disease, **or**
- The complete macroscopic excision of the primary tumor, together with the disappearance of all previously detected lung metastases, as determined by CT scanning[1]. Complete response of bone metastases must be achieved surgically.

Progressive Disease (PD):

Primary Tumor:

- An increase of ≥ 20% in any dimension of the primary tumor when assessed radiologically IN ASSOCIATION WITH clinical features of progression such as increased pain, inflammatory signs, rising alkaline phosphatase. [2] Assessment must be repeated in no less than 3 weeks to be regarded as progressive disease.

Metastases:

- An increase of at least 20%, in the sum of the longest diameter (LD) of all pre-defined lung metastases (as defined in section 8.2.3 of the protocol), or unequivocal progression of smaller metastases, **or**
- The appearance of any new lesion.[3]

[1] If radiological CR of lung metastases is achieved, thoracotomy is recommended. See protocol section 9.2 Surgery

[2] Disease progression in the early stages of treatment of osteosarcoma may be mimicked e.g. by intratumoral haemorrhage. Therefore, clinical and radiological appearances should be interpreted together before considering early surgery. See also protocol section 6.2 Randomisation

[3] After RECIST criteria. See JNCI 2000;92:205-16

Appendix A.7 Guidance for treatment of relapsed disease

Introduction

The overall outcome for patients with osteosarcoma relapses occurring after intensive frontline treatment is poor (Saeter 1995, Arndt 1999, Ferrari 2003, Kempf-Bielack 2005) and, apart from surgery, there is currently no universally accepted standard of multimodal treatment. The two largest reported series include 162 patients with recurrent osteosarcoma of the extremity from the Rizzoli-Institute with a projected 5-year post-relapse survival rate of 28%. (Ferrari 2003) and 576 COSS patients with recurrent osteosarcoma of any site with a 5-year survival rate of 23% (Kempf-Bielack 2005). As in primary disease, complete surgery seems to be a prerequisite for cure (Goorin 1984, Saeter 1995, Ferrari 2003, Kempf-Bielack 2005). In addition to a second complete surgical remission, a long interval between first diagnosis and relapse and a small number of involved sites have been favorable prognostic indicators in most larger series (Saeter 1995, Ferrari 2003, Kempf-Bielack 2005). Re-treatment with chemotherapy, especially with agents not used during front-line treatment according to an SSG series (Saeter 1995), may be of benefit in some cases. Patients not achieving a 2nd complete surgical remission who received chemotherapy survived significantly longer than those who did not in the two largest reported series (Ferrari 2003, Kempf-Bielack 2005). The exact role which chemotherapy might have for relapsed osteosarcoma patients who achieve a 2nd remission, that is in a 2nd adjuvant situation, has not been firmly established, with no effect on overall survival detected in the Rizzoli series (Ferrari 2003) and a limited but nevertheless significant prolongation of event-free survival demonstrated in the COSS-series (Kempf-Bielack 2005).

Discussion of relapsed cases with your group's principal investigator prior to the initiation of relapse therapy is strongly recommended. The treatment recommendations given below are meant as a guidance for patients who experience a relapse following therapy on the EURAMOS 1 trial and are not being treated on specific relapse or phase II protocols. Adherence to this guidance is not a mandatory part of the protocol, but is strongly encouraged in order to achieve a homogeneously good quality of patient care and to offer affected patients a chance for cure. The same principles apply for the treatment of second and later relapses.

Diagnostic imaging in case of relapse

In case of a suspected relapse at any site, perform a complete local and systemic evaluation. The following diagnostic studies should be performed (see Appendix B.9 for guidance on how to perform the appropriate imaging studies):
- History and physical, with special attention to painful bony sites or visible or palpable tumors. Special attention should also be directed towards the former site of the primary tumor.
- Chest X-ray
- Thoracic CT-scan
- Dynamic ^{99m}Tc bone scan
- X-ray of the primary tumor site
- MRI, CT scan, and/or ultrasound of the former site of the primary tumor (choice of imaging method depending on the material used for reconstruction)

This is a baseline program to which other investigations may need to be added in specific situations.

Invasive diagnostic procedures in case of suspected relapse

If the results of imaging studies leave no room for doubt, relapse treatment can resume without prior histologic examination. If there is any doubt, the diagnosis of relapse must be verified histologically before the patient is subjected to chemotherapy, radiotherapy, or mutilating surgery.

Treatment after relapse

Surgery

Surgery is the cornerstone of successful relapse therapy. As in primary osteosarcoma, the complete surgical removal of all detectable osteosarcoma lesions is as much as a prerequisite for cure. An aggressive surgical approach, if necessary involving multiple operations, is part of every curative treatment attempt. In case of extrapulmonary lesions, this implies surgery according to the guidance for primary tumors set forth in Appendix B.7. In case of pulmonary metastases, this implies thoracotomy with removal of all palpable lesions. In general, bilateral exploration with palpation of both lungs is strongly recommended even in cases where involvement is seemingly unilateral, as the experienced surgeon will not infrequently find bilateral metastases even in such patients. Unilateral exploration should be reserved for late solitary metastases detected more than 3 years after initial diagnosis. Thoracoscopic metastasectomy is strongly discouraged, as it is a less sensitive technique and may carry an increased risk of tumor spillage. Thoracotomy with bilateral exploration is recommended even in cases where pulmonary metastases become invisible radiographically following chemotherapy, as metastases will almost certainly recur otherwise.

Chemotherapy

The EURAMOS collaborators agree that second line chemotherapy should be offered to most patients who experience a relapse within the first three years after diagnosis and those with multiple metastases. Many investigators would choose to treat late solitary pulmonary metastases occurring more than three years after diagnosis by surgery only, followed by a watch and wait strategy.

As for the choice of drugs for patients not on phase II protocols, it is recommended that patients who have not yet received the combination of high-dose ifosfamide and etoposide be treated with this combination. Tolerance permitting, a total of five courses is recommended. The therapy modification guidance set forth elsewhere in the EURAMOS 1 protocol should be observed. The choice of drugs for other patients should be made on an individual basis, preferably after discussion of the case with your group's principal investigator. COSS has generally recommended a combination of carboplatin and etoposide and would favor the use of this combination in this situation, but other agents such as gemcitabine have also been used by some investigators, and other group's recommendations may vary. It may also be reasonable to treat selected patients with interferon--α.

It may be sensible to apply one to two cycles of chemotherapy preoperatively in a neoadjuvant fashion. This should only be done if the relapse is not situated in an anatomical location where slight progression would lead to inoperability. If preoperative chemotherapy is used, imaging studies appropriate to detect or rule out such a progression should be performed after every cycle. In case of undisputed evidence of disease progression during chemotherapy, that drug or drug combination should not be used postoperatively. If there is progression following the first treatment course with a specific drug or drug combination, no second preoperative cycle should be given, but the patient should either proceed to surgery directly or receive treatment with other agents.

Radiotherapy

As stated above, complete surgery is the local treatment of choice in relapsed osteosarcoma. Radiotherapy is, however, recommended for inoperable sites or those that could only be operated with inadequate margins, as its use has been associated with prolonged survival in such situations [Kempf-Bielack 2004]. Targeted radiotherapy with Samarium-EDTMP may be an additional option for selected inoperable lesions [Anderson 2002, Franzius 2001]. It is strongly suggested that participating institutions use the information and consulting systems set up by their respective groups before assuming inoperability, because some lesions which at seem inoperable may turn out to be operable for specialized tumor surgeons. Further recommendations about how to proceed in specific situations may vary between groups. Your group's recommendations are summarized in Appendix B.10.

Documentation of relapse therapy

The European collaborators in cooperation with the Italian Sarcoma Group will enter information on all relapsed patients and their therapy into the Pan-European Relapsed Osteosarcoma (EURELOS) databank kept at the COSS study center, Universitätsklinikum Münster, Klinik und Poliklinik für Kinderheilkunde – Pädiatrische Hämatologie/Onkologie – D-48129 Münster, Germany (Tel: +49 (0)251 83 52424, Fax: +49 (0)251 83 56489). The appropriate forms can be found in Appendix FORMS RELAPSE. The forms are to be forwarded to your group's Trials Center, which will forward it to the EURELOS databank. COSS centers are also required to supply the COSS data center with copies of all letters, surgical and pathology reports. Details on EURELOS are the subject of a separate protocol for which independent ethical approval will be obtained.

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Appendix A.8 Quality of life

Background

Therapy for osteosarcoma has evolved over the past 2 to 3 decades with tremendous improvements in survival. Early therapy involved amputation only and resulted in poor survival, but the advent of effective chemotherapy improved survival from 20% to over 60% (Bacci et al, 1998; Friedman et al, 1972; Provisor et al, 1997). Additional improvements in surgical techniques and imaging technology has also improved local control of osteosarcoma, and allowed for increased use of limb sparing surgeries in extremity lesions on the pretext that avoiding amputation will improve function and quality of life (QL) (Springfield, 1991). This was important given that almost 90% of lesions occur in the extremities, with 78% of osteosarcomas occurring in the long bones of the lower extremity, most frequently the distal femur followed by the proximal tibia and proximal humerus (Ries et al, 1999).

The medical late effects of therapy have been studied extensively in children (Bhatia et al, 2003) and young adults, while the impact of these late effects on the QL of the patients has been less studied, particularly in patients with osteosarcoma (Hudson et al, 1998; Nicholson et al, 1992; Postma et al, 1992; Weddington et al, 1991). Survivors of osteosarcoma are particularly vulnerable to medical late effects because of the intensity of their treatment (surgery and chemotherapy) and this may lead to a more significant impact on QL.

The main objective of QL assessment within this clinical trial is to determine the impact on QL in the short- and long-term for two groups of patients: for poor responders, the impact of the addition of IE to chemotherapy; and for good responders, the addition of maintenance therapy with ifn. Describing and comparing the impact of these regimens on QL will lead to a better understanding, from the patients' perspective, of the nature of treatment related side-effects, both short- and long-term. These data will help define future treatment options for these patients.

Additionally, the assessment of QL within EURAMOS 1 will allow more global concerns to be addressed, for example whether QL is affected by surgical factors, patient maturity (emotional and physical) and other characteristics such as gender, and site of primary tumor (Nagarajan et al, 2002).

QL Instruments

For patients aged 16 and over, QL will be assessed using the EORTC QLQ-C30 questionnaire (Aaronson et al, 1993; Fayers et al, 1995). For patients aged 15 and under, there is no pediatric QL measure that has been validated in all participating countries. Thus, QL for such patients entered via COG will be assessed using the generic module of the PedsQL questionnaire (Varni et al, 2002) and QL for patients entered in Europe will be assessed using the PEDQOL questionnaire (Calaminus et al, 2000).

The reason for using two pediatric measures is because the PedsQL questionnaire has not been validated in all European languages, whereas PEDQOL has not been validated in North America. Data has been published to suggest that these two instruments produce convergent results (Kennedy and Calaminus, 2002).

PedsQL has questionnaires for four age groups: 2-4 years, 5-7 years, 8-12 years and 13-18 years. There are self-report questionnaires for patients aged 5 and over, and a parent proxy report for those aged 2 and over. For PEDQOL, there is a self-report questionnaire for patients aged 8 and over, and a parent proxy report for those aged 4 and over. For each instrument, both the self-reporting and the parent proxy questionnaire will be completed where appropriate. Patients who become 16 years old during the course of the trial should continue to use the pediatric instrument for further assessments, both PedsQL and PEDQOL have been validated up to the age of 18.

Timing of QL Assessments

- The initial assessment will be in protocol week 5, as early as the end of the second course of M but before the second AP course.

- 3 months after definitive surgery for primary tumor (+/- 2 weeks). For poor responders, this will allow comparison between the MAP and MAPIE arms.

- 18 months after commencement of protocol therapy (+/- 1 month). For good responders, this will allow comparison between the MAP and MAPifn arms.

- 3 years after commencement of protocol therapy (+/- 1 month). This will allow examination of the late effects of protocol therapy and surgery.

Once completed, QL forms should be returned to the relevant data center. Research staff should ensure that the patient identification number, and date of completion, is recorded on each form.

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Appendix A.9 Biological studies

Parallel biological studies will be performed in selected groups for this trial, lead by the Biological Studies Panel (see Appendix A.1). Blood and tumor DNA will be collected and will be used to try and identify factors that influence response to therapy and its side effects, and potentially also susceptibility to the disease. Information from these studies may be used to develop improved treatment stratification and novel therapeutic approaches.

All parallel biology studies conducted as part of the EURAMOS 1 study will be performed in accordance with protocols developed independently by each participating cooperative group (see group specific appendix for more details).

Critical features of each biology protocol will include specifications of:

- patient eligibility,
- specimen submission/collection requirements,
- instructions for specimen processing/mailing,
- delineation of planned research studies/planned banking,
- patient consent,
- patient study registration and
- statistical considerations.

It is anticipated that many biology studies will only be the interest of a single laboratory and therefore the study will only be conducted in the single cooperative group in which that laboratory resides. Other studies, most notably the cDNA expression arrays and comparative genomic hybridization will be performed throughout all participating cooperative groups. It is anticipated that the data for these assays will be combined to allow a common analysis. It will include all patients treated on the EURAMOS 1 study who have consented to take part in the biological study. Regular meetings of the osteosarcoma biology representatives and laboratory investigators will ensure the use of uniform methodologies that will allow data comparability. The following Table describes the planned laboratory studies for each of the cooperative groups:

Assay	All Groups	COG	SSG	COSS	EOI
MDR IHC		X			
MDR Functional Assays		X			
MRP Expression		X			
Methotrexate Transport		X			
Methotrexate Metabolism		X			
Topoisomerase II Expression		X	X		
Bcl-2/Bax expression		X	X		
Rb LOH		X	X		
RB rearrangement				X	
P53 IHC		X			
P53 sequence			X		
ErbB-2 FISH					X
HER2 IHC		X			X
HER2 RT-PCR		X	X		
MDM2 amplification		X	X		
p16 deletion		X	X		
p21 alteration		X			
LOH at 3q,18q		X			
sis, gli, fos amplification		X	X		
SV40 PCR		X		X	
SV40 serum antibody		X			
RAS mutation		X			
Myc amplification		X	X		
Metalloproteinase expression	X	X	X	X	X
c-met/HGF expression		X	X		
IGF-I/IGF-IR expression		X	X		
IGF-I serum levels		X			
Telomerase Activity		X			
Ploidy			X		
cDNA Expression - Affymetrix	X	X	X	X	X
cDNA Expression – Spotted		X	X		
CGH	X	X	X		
Conventional Cytogenetics			X		
17p amplicon arrays			X		
BAC arrays		X	X		
Spectral Karyotyping		X			X
Ezrin Expression	X	X	X	X	X
Galectin Expression		X	X		
Angiogenesis				X	
VEGF & bFGF				X	
Polymorphisms				X	X
Osteosarcoma pathogenesis				X	
6q14 & 15q21 radiation induction				X	
micrometastases				X	
dose-response model spheroids					X
DNA repair					X
Methylation (p16, p14), global			X		
Micrometastatic cells			X		
CDK4 amplification			X		
Tissue arrays		X	X		

Appendix A.10 Margins

Type	Dissection
Intralesional	within the lesion
Marginal	through the pseudocapsule or reactive tissue
Wide	lesion (including biopsy scar), pseudocapsule and/or reactive zone, and an unviolated cuff of normal tissue completely surrounding the mass removed as a single block
Radical	entire anatomic compartment containing the tumor removed as one block

Adapted from: Enneking WE, Spanier SS, Goodmann MA (1980): A system for the surgical staging of musculo-skeletal tumors. Clin Orthop 153:106-120

Appendix A.11 World Medical Association Declaration of Helsinki

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly
Helsinki, Finland, June 1964
and amended by the
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
and the
52nd WMA General Assembly, Edinburgh, Scotland, October 2000

A. Introduction

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects**.** Medical research involving human subjects includes research on identifiable human material or identifiable data.
2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.
3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."
4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.
5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.
6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.
7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.
8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.
9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. Basic principles for all medical research

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.
11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant

sources of information, and on adequate laboratory and, where appropriate, animal experimentation.
12. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.
13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.
14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.
15. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.
16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.
17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.
18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.
19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.
20. The subjects must be volunteers and informed participants in the research project.
21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient’s information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.
22. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.
23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.
24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These

groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.
25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.
26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.
27. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. Additional principles for medical research combined with medical care

28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.
29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.
30. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.
31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.
32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician’s judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

Appendix A.12 EU Directive

L 121/34 EN Official Journal of the European Communities 1.5.2001

DIRECTIVE 2001/20/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 4 April 2001

on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty establishing the European Community, and in particular Article 95 thereof,

Having regard to the proposal from the Commission [1],

Having regard to the opinion of the Economic and Social Committee [2],

Acting in accordance with the procedure laid down in Article 251 of the Treaty [3],

Whereas:

(1) Council Directive 65/65/EEC of 26 January 1965 on the approximation of provisions laid down by law, regulation or administrative action relating to medicinal products [4] requires that applications for authorisation to place a medicinal product on the market should be accompanied by a dossier containing particulars and documents relating to the results of tests and clinical trials carried out on the product. Council Directive 75/318/EEC of 20 May 1975 on the approximation of the laws of Member States relating to analytical, pharmaco-toxicological and clinical standards and protocols in respect of the testing of medicinal products [5] lays down uniform rules on the compilation of dossiers including their presentation.

(2) The accepted basis for the conduct of clinical trials in humans is founded in the protection of human rights and the dignity of the human being with regard to the application of biology and medicine, as for instance reflected in the 1996 version of the Helsinki Declaration. The clinical trial subject's protection is safeguarded through risk assessment based on the results of toxicological experiments prior to any clinical trial, screening by ethics committees and Member States' competent authorities, and rules on the protection of personal data.

(3) Persons who are incapable of giving legal consent to clinical trials should be given special protection. It is incumbent on the Member States to lay down rules to this effect. Such persons may not be included in clinical trials if the same results can be obtained using persons capable of giving consent. Normally these persons should be included in clinical trials only when there are grounds for expecting that the administering of the medicinal product would be of direct benefit to the patient, thereby outweighing the risks. However, there is a need for clinical trials involving children to improve the treatment available to them. Children represent a vulnerable population with developmental, physiological and psychological differences from adults, which make age- and development- related research important for their benefit. Medicinal products, including vaccines, for children need to be tested scientifically before widespread use. This can only be achieved by ensuring that medicinal products which are likely to be of significant clinical value for children are fully studied. The clinical trials required for this purpose should be carried out under conditions affording the best possible protection for the subjects. Criteria for the protection of children in clinical trials therefore need to be laid down.

(4) In the case of other persons incapable of giving their consent, such as persons with dementia, psychiatric patients, etc., inclusion in clinical trials in such cases should be on an even more restrictive basis. Medicinal products for trial may be administered to all such individuals only when there are grounds for assuming that the direct benefit to the patient outweighs the risks. Moreover, in such cases the written consent of the patient's legal representative, given in cooperation with the treating doctor, is necessary before participation in any such clinical trial.

(5) The notion of legal representative refers back to existing national law and consequently may include natural or legal persons, an authority and/or a body provided for by national law.

(6) In order to achieve optimum protection of health, obsolete or repetitive tests will not be carried out, whether within the Community or in third countries. The harmonisation of technical requirements for the development

[1] OJ C 306, 8.10.1997, p. 9 and OJ C 161, 8.6.1999, p. 5.
[2] OJ C 95, 30.3.1998, p. 1.
[3] Opinion of the European Parliament of 17 November 1998 (OJ C 379, 7. 12. 1998, p. 27). Council Common Position of 20 July 2000 (OJ C 300, 20.10.2000, p. 32) and Decision of the European Parliament of 12 December 2000. Council Decision of 26 February 2001.
[4] OJ 22, 9.2.1965, p. 1/65. Directive as last amended by Council Directive 93/39/EEC (OJ L 214, 24.8.1993, p. 22).
[5] OJ L 147, 9.6.1975, p. 1. Directive as last amended by Commission Directive 1999/83/EC (OJ L 243, 15.9.1999, p. 9).

of medicinal products should therefore be pursued through the appropriate fora, in particular the International Conference on Harmonisation.

(7) For medicinal products falling within the scope of Part A of the Annex to Council Regulation (EEC) No 2309/93 of 22 July 1993 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Agency for the Evaluation of Medicinal Products [1], which include products intended for gene therapy or cell therapy, prior scientific evaluation by the European Agency for the Evaluation of Medicinal Products (hereinafter referred to as the 'Agency'), assisted by the Committee for Proprietary Medicinal Products, is mandatory before the Commission grants marketing authorisation. In the course of this evaluation, the said Committee may request full details of the results of the clinical trials on which the application for marketing authorisation is based and, consequently, on the manner in which these trials were conducted and the same Committee may go so far as to require the applicant for such authorisation to conduct further clinical trials. Provision must therefore be made to allow the Agency to have full information on the conduct of any clinical trial for such medicinal products.

(8) A single opinion for each Member State concerned reduces delay in the commencement of a trial without jeopardising the well-being of the people participating in the trial or excluding the possibility of rejecting it in specific sites.

(9) Information on the content, commencement and termination of a clinical trial should be available to the Member States where the trial takes place and all the other Member States should have access to the same information. A European database bringing together this information should therefore be set up, with due regard for the rules of confidentiality.

(10) Clinical trials are a complex operation, generally lasting one or more years, usually involving numerous participants and several trial sites, often in different Member States. Member States' current practices diverge considerably on the rules on commencement and conduct of the clinical trials and the requirements for carrying them out vary widely. This therefore results in delays and complications detrimental to effective conduct of such trials in the Community. It is therefore necessary to simplify and harmonise the administrative provisions governing such trials by establishing a clear, transparent procedure and creating conditions conducive to effective coordination of such clinical trials in the Community by the authorities concerned.

(11) As a rule, authorisation should be implicit, i.e. if there has been a vote in favour by the Ethics Committee and the competent authority has not objected within a given period, it should be possible to begin the clinical trials. In exceptional cases raising especially complex problems, explicit written authorisation should, however, be required.

(12) The principles of good manufacturing practice should be applied to investigational medicinal products.

(13) Special provisions should be laid down for the labelling of these products.

(14) Non-commercial clinical trials conducted by researchers without the participation of the pharmaceuticals industry may be of great benefit to the patients concerned. The Directive should therefore take account of the special position of trials whose planning does not require particular manufacturing or packaging processes, if these trials are carried out with medicinal products with a marketing authorisation within the meaning of Directive 65/65/EEC, manufactured or imported in accordance with the provisions of Directives 75/319/EEC and 91/356/EEC, and on patients with the same characteristics as those covered by the indication specified in this marketing authorisation. Labelling of the investigational medicinal products intended for trials of this nature should be subject to simplified provisions laid down in the good manufacturing practice guidelines on investigational products and in Directive 91/356/EEC.

(15) The verification of compliance with the standards of good clinical practice and the need to subject data, information and documents to inspection in order to confirm that they have been properly generated, recorded and reported are essential in order to justify the involvement of human subjects in clinical trials.

(16) The person participating in a trial must consent to the scrutiny of personal information during inspection by competent authorities and properly authorised persons, provided that such personal information is treated as strictly confidential and is not made publicly available.

(17) This Directive is to apply without prejudice to Directive 95/46/EEC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data [2].

(18) It is also necessary to make provision for the monitoring of adverse reactions occurring in clinical trials using Community surveillance (pharmacovigilance) procedures in order to ensure the immediate cessation of any clinical trial in which there is an unacceptable level of risk.

[1] OJ L 214, 24.8.1993, p. 1. Regulation as amended by Commission Regulation (EC) No 649/98 (OJ L 88, 24.3.1998, p. 7)

[2] OJ L 281, 23.11.1995, p. 31.

(19) The measures necessary for the implementation of this Directive should be adopted in accordance with Council Decision 1999/468/EC of 28 June 1999 laying down the procedures for the exercise of implementing powers conferred on the Commission [1],

HAVE ADOPTED THIS DIRECTIVE

Article 1

Scope

1. This Directive establishes specific provisions regarding the conduct of clinical trials, including multi-centre trials, on human subjects involving medicinal products as defined in Article 1 of Directive 65/65/EEC, in particular relating to the implementation of good clinical practice. This Directive does not apply to non-interventional trials.

2. Good clinical practice is a set of internationally recognised ethical and scientific quality requirements which must be observed for designing, conducting, recording and reporting clinical trials that involve the participation of human subjects. Compliance with this good practice provides assurance that the rights, safety and well-being of trial subjects are protected, and that the results of the clinical trials are credible.

3. The principles of good clinical practice and detailed guidelines in line with those principles shall be adopted and, if necessary, revised to take account of technical and scientific progress in accordance with the procedure referred to in Article 21(2).

These detailed guidelines shall be published by the Commission.

4. All clinical trials, including bioavailability and bioequivalence studies, shall be designed, conducted and reported in accordance with the principles of good clinical practice.

Article 2

Definitions

For the purposes of this Directive the following definitions shall apply:

(a) 'clinical trial': any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more investigational medicinal product(s), and/or to identify any adverse reactions to one or more investigational medicinal product(s) and/or to study absorption, distribution, metabolism and excretion of one or more investigational medicinal product(s) with the object of ascertaining its (their) safety and/or efficacy; This includes clinical trials carried out in either one site or multiple sites, whether in one or more than one Member State;

(b) 'multi-centre clinical trial': a clinical trial conducted according to a single protocol but at more than one site, and therefore by more than one investigator, in which the trial sites may be located in a single Member State, in a number of Member States and/or in Member States and third countries;

(c) 'non-interventional trial': a study where the medicinal product(s) is (are) prescribed in the usual manner in accordance with the terms of the marketing authorisation. The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring procedures shall be applied to the patients and epidemiological methods shall be used for the analysis of collected data;

(d) 'investigational medicinal product': a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorisation but used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form;

(e) 'sponsor': an individual, company, institution or organisation which takes responsibility for the initiation, management and/or financing of a clinical trial;

(f) 'investigator': a doctor or a person following a profession agreed in the Member State for investigations because of the scientific background and the experience in patient care it requires. The investigator is responsible for the conduct of a clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the leader responsible for the team and may be called the principal investigator;

(g) 'investigator's brochure': a compilation of the clinical and non-clinical data on the investigational medicinal product or products which are relevant to the study of the product or products in human subjects;

(h) 'protocol': a document that describes the objective(s), design, methodology, statistical considerations and organisation of a trial. The term protocol refers to the protocol, successive versions of the protocol and protocol amendments;

(i) 'subject': an individual who participates in a clinical trial as either a recipient of the investigational medicinal product or a control;

[1] OJ L 184, 17.7.1999, p. 23.

(j) 'informed consent': decision, which must be written, dated and signed, to take part in a clinical trial, taken freely after being duly informed of its nature, significance, implications and risks and appropriately documented, by any person capable of giving consent or, where the person is not capable of giving consent, by his or her legal representative; if the person concerned is unable to write, oral consent in the presence of at least one witness may be given in exceptional cases, as provided for in national legislation.

(k) 'ethics committee': an independent body in a Member State, consisting of healthcare professionals and non-medical members, whose responsibility it is to protect the rights, safety and wellbeing of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, expressing an opinion on the trial protocol, the suitability of the investigators and the adequacy of facilities, and on the methods and documents to be used to inform trial subjects and obtain their informed consent;

(l) 'inspection': the act by a competent authority of conducting an official review of documents, facilities, records, quality assurance arrangements, and any other resources that are deemed by the competent authority to be related to the clinical trial and that may be located at the site of the trial, at the sponsor's and/or contract research organisation's facilities, or at other establishments which the competent authority sees fit to inspect;

(m) 'adverse event': any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment;

(n) 'adverse reaction': all untoward and unintended responses to an investigational medicinal product related to any dose administered;

(o) 'serious adverse event or serious adverse reaction': any untoward medical occurrence or effect that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect;

(p) 'unexpected adverse reaction': an adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. investigator's brochure for an unauthorised investigational product or summary of product characteristics for an authorised product).

Article 3

Protection of clinical trial subjects

1. This Directive shall apply without prejudice to the national provisions on the protection of clinical trial subjects if they are more comprehensive than the provisions of this Directive and consistent with the procedures and time-scales specified therein. Member States shall, insofar as they have not already done so, adopt detailed rules to protect from abuse individuals who are incapable of giving their informed consent.

2. A clinical trial may be undertaken only if, in particular:

(a) the foreseeable risks and inconveniences have been weighed against the anticipated benefit for the individual trial subject and other present and future patients. A clinical trial may be initiated only if the Ethics Committee and/or the competent authority comes to the conclusion that the anticipated therapeutic and public health benefits justify the risks and may be continued only if compliance with this requirement is permanently monitored;

(b) the trial subject or, when the person is not able to give informed consent, his legal representative has had the opportunity, in a prior interview with the investigator or a member of the investigating team, to understand the objectives, risks and inconveniences of the trial, and the conditions under which it is to be conducted and has also been informed of his right to withdraw from the trial at any time;

(c) the rights of the subject to physical and mental integrity, to privacy and to the protection of the data concerning him in accordance with Directive 95/46/EC are safeguarded;

(d) the trial subject or, when the person is not able to give informed consent, his legal representative has given his written consent after being informed of the nature, significance, implications and risks of the clinical trial; if the individual is unable to write, oral consent in the presence of at least one witness may be given in exceptional cases, as provided for in national legislation;

(e) the subject may without any resulting detriment withdraw from the clinical trial at any time by revoking his informed consent;

(f) provision has been made for insurance or indemnity to cover the liability of the investigator and sponsor.

3. The medical care given to, and medical decisions made on behalf of, subjects shall be the responsibility of an appropriately qualified doctor or, where appropriate, of a qualified dentist.

4. The subject shall be provided with a contact point where he may obtain further information.

Article 4

Clinical trials on minors

In addition to any other relevant restriction, a clinical trial on minors may be undertaken only if:

(a) the informed consent of the parents or legal representative has been obtained; consent must represent the minor's presumed will and may be revoked at any time, without detriment to the minor;

(b) the minor has received information according to its capacity of understanding, from staff with experience with minors, regarding the trial, the risks and the benefits;

(c) the explicit wish of a minor who is capable of forming an opinion and assessing this information to refuse participation or to be withdrawn from the clinical trial at any time is considered by the investigator or where appropriate the principal investigator;

(d) no incentives or financial inducements are given except compensation;

(e) some direct benefit for the group of patients is obtained from the clinical trial and only where such research is essential to validate data obtained in clinical trials on persons able to give informed consent or by other research methods; additionally, such research should either relate directly to a clinical condition from which the minor concerned suffers or be of such a nature that it can only be carried out on minors;

(f) the corresponding scientific guidelines of the Agency have been followed;

(g) clinical trials have been designed to minimise pain, discomfort, fear and any other foreseeable risk in relation to the disease and developmental stage; both the risk threshold and the degree of distress have to be specially defined and constantly monitored;

(h) the Ethics Committee, with paediatric expertise or after taking advice in clinical, ethical and psychosocial problems in the field of paediatrics, has endorsed the protocol; and

(i) the interests of the patient always prevail over those of science and society.

Article 5

Clinical trials on incapacitated adults not able to give informed legal consent

In the case of other persons incapable of giving informed legal consent, all relevant requirements listed for persons capable of giving such consent shall apply. In addition to these requirements, inclusion in clinical trials of incapacitated adults who have not given or not refused informed consent before the onset of their incapacity shall be allowed only if:

(a) the informed consent of the legal representative has been obtained; consent must represent the subject's presumed will and may be revoked at any time, without detriment to the subject;

(b) the person not able to give informed legal consent has received information according to his/her capacity of understanding regarding the trial, the risks and the benefits;

(c) the explicit wish of a subject who is capable of forming an opinion and assessing this information to refuse participation in, or to be withdrawn from, the clinical trial at any time is considered by the investigator or where appropriate the principal investigator;

(d) no incentives or financial inducements are given except compensation;

(e) such research is essential to validate data obtained in clinical trials on persons able to give informed consent or by other research methods and relates directly to a life-threatening or debilitating clinical condition from which the incapacitated adult concerned suffers;

(f) clinical trials have been designed to minimise pain, discomfort, fear and any other foreseeable risk in relation to the disease and developmental stage; both the risk threshold and the degree of distress shall be specially defined and constantly monitored;

(g) the Ethics Committee, with expertise in the relevant disease and the patient population concerned or after taking advice in clinical, ethical and psychosocial questions in the field of the relevant disease and patient population concerned, has endorsed the protocol;

(h) the interests of the patient always prevail over those of science and society; and

(i) there are grounds for expecting that administering the medicinal product to be tested will produce a benefit to the patient outweighing the risks or produce no risk at all.

Article 6

Ethics Committee

1. For the purposes of implementation of the clinical trials, Member States shall take the measures necessary for establishment and operation of Ethics Committees.

2. The Ethics Committee shall give its opinion, before a clinical trial commences, on any issue requested.

3. In preparing its opinion, the Ethics Committee shall consider, in particular:

(a) the relevance of the clinical trial and the trial design;

(b) whether the evaluation of the anticipated benefits and risks as required under Article 3(2)(a) is satisfactory and whether the conclusions are justified;

(c) the protocol;

(d) the suitability of the investigator and supporting staff;

(e) the investigator's brochure;

(f) the quality of the facilities;

(g) the adequacy and completeness of the written information to be given and the procedure to be followed for the purpose of obtaining informed consent and the justification for the research on persons incapable of giving informed consent as regards the specific restrictions laid down in Article 3;

(h) provision for indemnity or compensation in the event of injury or death attributable to a clinical trial;

(i) any insurance or indemnity to cover the liability of the investigator and sponsor;

(j) the amounts and, where appropriate, the arrangements for rewarding or compensating investigators and trial subjects and the relevant aspects of any agreement between the sponsor and the site;

(k) the arrangements for the recruitment of subjects.

4. Notwithstanding the provisions of this Article, a Member State may decide that the competent authority it has designated for the purpose of Article 9 shall be responsible for the consideration of, and the giving of an opinion on, the matters referred to in paragraph 3(h), (i) and (j) of this Article.

When a Member State avails itself of this provision, it shall notify the Commission, the other Member States and the Agency.

5. The Ethics Committee shall have a maximum of 60 days from the date of receipt of a valid application to give its reasoned opinion to the applicant and the competent authority in the Member State concerned.

6. Within the period of examination of the application for an opinion, the Ethics Committee may send a single request for information supplementary to that already supplied by the applicant. The period laid down in paragraph 5 shall be suspended until receipt of the supplementary information.

7. No extension to the 60-day period referred to in paragraph 5 shall be permissible except in the case of trials involving medicinal products for gene therapy or somatic cell therapy or medicinal products containing genetically modified organisms. In this case, an extension of a maximum of 30 days shall be permitted. For these products, this 90-day period may be extended by a further 90 days in the event of consultation of a group or a committee in accordance with the regulations and procedures of the Member States concerned. In the case of xenogenic cell therapy, there shall be no time limit to the authorisation period.

Article 7

Single opinion

For multi-centre clinical trials limited to the territory of a single Member State, Member States shall establish a procedure providing, notwithstanding the number of Ethics Committees, for the adoption of a single opinion for that Member State.

In the case of multi-centre clinical trials carried out in more than one Member State simultaneously, a single opinion shall be given for each Member State concerned by the clinical trial.

Article 8

Detailed guidance

The Commission, in consultation with Member States and interested parties, shall draw up and publish detailed guidance on the application format and documentation to be submitted in an application for an ethics committee opinion, in particular regarding the information that is given to subjects, and on the appropriate safeguards for the protection of personal data.

Article 9

Commencement of a clinical trial

1. Member States shall take the measures necessary to ensure that the procedure described in this Article is followed for commencement of a clinical trial.

The sponsor may not start a clinical trial until the Ethics Committee has issued a favourable opinion and inasmuch as the competent authority of the Member State concerned has not informed the sponsor of any grounds for non-acceptance. The procedures to reach these decisions can be run in parallel or not, depending on the sponsor.

2. Before commencing any clinical trial, the sponsor shall be required to submit a valid request for authorisation to the competent authority of the Member State in which the sponsor plans to conduct the clinical trial.

3. If the competent authority of the Member State notifies the sponsor of grounds for non-acceptance, the sponsor may, on one occasion only, amend the content of the request referred to in paragraph 2 in order to take due account of the grounds given. If the sponsor fails to amend the request accordingly, the request shall be considered rejected and the clinical trial may not commence.

4. Consideration of a valid request for authorisation by the competent authority as stated in paragraph 2 shall be carried out as rapidly as possible and may not exceed 60 days. The Member States may lay down a shorter period than 60 days within their area of responsibility if that is in compliance with current practice. The competent authority can nevertheless notify the sponsor before the end of this period that it has no grounds for non-acceptance.

No further extensions to the period referred to in the first subparagraph shall be permissible except in the case of trials involving the medicinal products listed in paragraph 6, for which an extension of a maximum of 30 days shall be permitted. For these products, this 90-day period may be extended by a further 90 days in the event of consultation of a group or a committee in accordance with the regulations and procedures of the Member States concerned. In the case of xenogenic cell therapy there shall be no time limit to the authorisation period.

5. Without prejudice to paragraph 6, written authorisation may be required before the commencement of clinical trials for such trials on medicinal products which do not have a marketing authorisation within the meaning of Directive 65/65/EEC and are referred to in Part A of the Annex to Regulation (EEC) No 2309/93, and other medicinal products with special characteristics, such as medicinal products the active ingredient or active ingredients of which is or are a biological product or biological products of human or animal origin, or contains biological components of human or animal origin, or the manufacturing of which requires such components.

6. Written authorisation shall be required before commencing clinical trials involving medicinal products for gene therapy, somatic cell therapy including xenogenic cell therapy and all medicinal products containing genetically modified organisms. No gene therapy trials may be carried out which result in modifications to the subject's germ line genetic identity.

7. This authorisation shall be issued without prejudice to the application of Council Directives 90/219/EEC of 23 April 1990 on the contained use of genetically modified micro-organisms [1] and 90/220/EEC of 23 April 1990 on the deliberate release into the environment of genetically modified organisms [2].

8. In consultation with Member States, the Commission shall draw up and publish detailed guidance on:

(a) the format and contents of the request referred to in paragraph 2 as well as the documentation to be submitted to support that request, on the quality and manufacture of the investigational medicinal product, any toxicological and pharmacological tests, the protocol and clinical information on the investigational medicinal product including the investigator's brochure;

(b) the presentation and content of the proposed amendment referred to in point (a) of Article 10 on substantial amendments made to the protocol;

(c) the declaration of the end of the clinical trial.

Article 10

Conduct of a clinical trial

Amendments may be made to the conduct of a clinical trial following the procedure described hereinafter:

(a) after the commencement of the clinical trial, the sponsor may make amendments to the protocol. If those amendments are substantial and are likely to have an impact on the safety of the trial subjects or to change the interpretation of the scientific documents in support of the conduct of the trial, or if they are otherwise significant, the sponsor shall notify the competent authorities of the Member State or Member States concerned of the reasons for, and content of, these amendments and shall inform the ethics committee or committees concerned in accordance with Articles 6 and 9.

On the basis of the details referred to in Article 6(3) and in accordance with Article 7, the Ethics Committee shall give an opinion within a maximum of 35 days of the date of receipt of the proposed amendment in good and due form. If this opinion is unfavourable, the sponsor may not implement the amendment to the protocol.

If the opinion of the Ethics Committee is favourable and the competent authorities of the Member States have raised no grounds for non-acceptance of the abovementioned substantial amendments, the sponsor shall proceed to conduct the clinical trial following the amended protocol. Should this not be the case, the sponsor shall either take account of the grounds for non-acceptance and adapt the proposed amendment to the protocol accordingly or withdraw the proposed amendment;

(b) without prejudice to point (a), in the light of the circumstances, notably the occurrence of any new event relating to the conduct of the trial or the development of the investigational medicinal product where that new event is likely to affect the safety of the subjects, the sponsor and the investigator shall take appropriate urgent safety measures to protect the subjects against any immediate hazard. The sponsor shall forthwith inform the competent authorities of those new events and the measures taken and shall ensure that the Ethics Committee is notified at the same time;

(c) within 90 days of the end of a clinical trial the sponsor shall notify the competent authorities of the Member State or Member States concerned and the Ethics Committee that the clinical trial has ended. If the trial has to be terminated early, this period shall be reduced to 15 days and the reasons clearly explained.

Article 11

Exchange of information

1. Member States in whose territory the clinical trial takes place shall enter in a European database, accessible only to the competent authorities of the Member States, the Agency and the Commission:

(a) extracts from the request for authorisation referred to in Article 9(2);

(b) any amendments made to the request, as provided for in Article 9(3);

[1] OJ L 117, 8.5.1990, p. 1. Directive as last amended by Directive 98/81/EC (OJ L 330, 5.12.1998, p. 13).
[2] OJ L 117, 8.5.1990, p. 15. Directive as last amended by Commission Directive 97/35/EC (OJ L 169, 27.6.1997, p. 72).

(c) any amendments made to the protocol, as provided for in point a of Article 10;

(d) the favourable opinion of the Ethics Committee;

(e) the declaration of the end of the clinical trial; and

(f) a reference to the inspections carried out on conformity with good clinical practice.

2. At the substantiated request of any Member State, the Agency or the Commission, the competent authority to which the request for authorisation was submitted shall supply all further information concerning the clinical trial in question other than the data already in the European database.

3. In consultation with the Member States, the Commission shall draw up and publish detailed guidance on the relevant data to be included in this European database, which it operates with the assistance of the Agency, as well as the methods for electronic communication of the data. The detailed guidance thus drawn up shall ensure that the confidentiality of the data is strictly observed.

Article 12

Suspension of the trial or infringements

1. Where a Member State has objective grounds for considering that the conditions in the request for authorisation referred to in Article 9(2) are no longer met or has information raising doubts about the safety or scientific validity of the clinical trial, it may suspend or prohibit the clinical trial and shall notify the sponsor thereof.

Before the Member State reaches its decision it shall, except where there is imminent risk, ask the sponsor and/or the investigator for their opinion, to be delivered within one week.

In this case, the competent authority concerned shall forthwith inform the other competent authorities, the Ethics Committee concerned, the Agency and the Commission of its decision to suspend or prohibit the trial and of the reasons for the decision.

2. Where a competent authority has objective grounds for considering that the sponsor or the investigator or any other person involved in the conduct of the trial no longer meets the obligations laid down, it shall forthwith inform him thereof, indicating the course of action which he must take to remedy this state of affairs. The competent authority concerned shall forthwith inform the Ethics Committee, the other competent authorities and the Commission of this course of action.

Article 13

Manufacture and import of investigational medicinal products

1. Member States shall take all appropriate measures to ensure that the manufacture or importation of investigational medicinal products is subject to the holding of authorisation. In order to obtain the authorisation, the applicant and, subsequently, the holder of the authorisation, shall meet at least the requirements defined in accordance with the procedure referred to in Article 21(2).

2. Member States shall take all appropriate measures to ensure that the holder of the authorisation referred to in paragraph 1 has permanently and continuously at his disposal the services of at least one qualified person who, in accordance with the conditions laid down in Article 23 of the second Council Directive 75/319/EEC of 20 May 1975 on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products [1], is responsible in particular for carrying out the duties specified in paragraph 3 of this Article.

3. Member States shall take all appropriate measures to ensure that the qualified person referred to in Article 21 of Directive 75/319/EEC, without prejudice to his relationship with the manufacturer or importer, is responsible, in the context of the procedures referred to in Article 25 of the said Directive, for ensuring:

(a) in the case of investigational medicinal products manufactured in the Member State concerned, that each batch of medicinal products has been manufactured and checked in compliance with the requirements of Commission Directive 91/356/EEC of 13 June 1991 laying down the principles and guidelines of good manufacturing practice for medicinal products for human use [2], the product specification file and the information notified pursuant to Article 9(2) of this Directive;

(b) in the case of investigational medicinal products manufactured in a third country, that each production batch has been manufactured and checked in accordance with standards of good manufacturing practice at least equivalent to those laid down in Commission Directive 91/356/EEC, in accordance with the product specification file, and that each production batch has been checked in accordance with the information notified pursuant to Article 9(2) of this Directive;

(c) in the case of an investigational medicinal product which is a comparator product from a third country, and which has a marketing authorisation, where the documentation certifying that each production batch has been manufactured in conditions at least equivalent to the standards of good manufacturing practice referred to above cannot be obtained, that each production batch has undergone all relevant analyses, tests or checks necessary to confirm its quality in accordance with the information notified pursuant to Article 9(2) of this Directive.

Detailed guidance on the elements to be taken into account when evaluating products with the object of releasing batches within the Community shall be drawn up pursuant to the good manufacturing practice guidelines, and in particular Annex 13 to the said guidelines. Such guidelines will be adopted in accordance with the procedure referred to in Article 21(2) of this Directive and published in accordance with Article 19a of Directive 75/319/EEC.

[1] OJ L 147, 9.6.1975, p. 13. Directive as last amended by Council Directive 93/39/EC (OJ L 214, 24.8.1993, p. 22).
[2] OJ L 193, 17.7.1991, p. 30.

Insofar as the provisions laid down in (a), (b) or (c) are complied with, investigational medicinal products shall not have to undergo any further checks if they are imported into another Member State together with batch release certification signed by the qualified person.

4. In all cases, the qualified person must certify in a register or equivalent document that each production batch satisfies the provisions of this Article. The said register or equivalent document shall be kept up to date as operations are carried out and shall remain at the disposal of the agents of the competent authority for the period specified in the provisions of the Member States concerned. This period shall in any event be not less than five years.

5. Any person engaging in activities as the qualified person referred to in Article 21 of Directive 75/319/EEC as regards investigational medicinal products at the time when this Directive is applied in the Member State where that person is, but without complying with the conditions laid down in Articles 23 and 24 of that Directive, shall be authorised to continue those activities in the Member State concerned.

Article 14

Labelling

The particulars to appear in at least the official language(s) of the Member State on the outer packaging of investigational medicinal products or, where there is no outer packaging, on the immediate packaging, shall be published by the Commission in the good manufacturing practice guidelines on investigational medicinal products adopted in accordance with Article 19a of Directive 75/319/EEC.

In addition, these guidelines shall lay down adapted provisions relating to labelling for investigational medicinal products intended for clinical trials with the following characteristics:

— the planning of the trial does not require particular manufacturing or packaging processes;

— the trial is conducted with medicinal products with, in the Member States concerned by the study, a marketing authorisation within the meaning of Directive 65/65/EEC, manufactured or imported in accordance with the provisions of Directive 75/319/EEC;

— the patients participating in the trial have the same characteristics as those covered by the indication specified in the abovementioned authorisation.

Article 15

Verification of compliance of investigational medicinal products with good clinical and manufacturing practice

1. To verify compliance with the provisions on good clinical and manufacturing practice, Member States shall appoint inspectors to inspect the sites concerned by any clinical trial conducted, particularly the trial site or sites, the manufacturing site of the investigational medicinal product, any laboratory used for analyses in the clinical trial and/or the sponsor's premises.

The inspections shall be conducted by the competent authority of the Member State concerned, which shall inform the Agency; they shall be carried out on behalf of the Community and the results shall be recognised by all the other Member States. These inspections shall be coordinated by the Agency, within the framework of its powers as provided for in Regulation (EEC) No 2309/93. A Member State may request assistance from another Member State in this matter.

2. Following inspection, an inspection report shall be prepared. It must be made available to the sponsor while safeguarding confidential aspects. It may be made available to the other Member States, to the Ethics Committee and to the Agency, at their reasoned request.

3. At the request of the Agency, within the framework of its powers as provided for in Regulation (EEC) No 2309/93, or of one of the Member States concerned, and following consultation with the Member States concerned, the Commission may request a new inspection should verification of compliance with this Directive reveal differences between Member States.

4. Subject to any arrangements which may have been concluded between the Community and third countries, the Commission, upon receipt of a reasoned request from a Member State or on its own initiative, or a Member State may propose that the trial site and/or the sponsor's premises and/or the manufacturer established in a third country undergo an inspection. The inspection shall be carried out by duly qualified Community inspectors.

5. The detailed guidelines on the documentation relating to the clinical trial, which shall constitute the master file on the trial, archiving, qualifications of inspectors and inspection procedures to verify compliance of the clinical trial in question with this Directive shall be adopted and revised in accordance with the procedure referred to in Article 21(2).

Article 16

Notification of adverse events

1. The investigator shall report all serious adverse events immediately to the sponsor except for those that the protocol or investigator's brochure identifies as not requiring immediate reporting. The immediate report shall be followed by detailed, written reports. The immediate and follow-up reports shall identify subjects by unique code numbers assigned to the latter.

2. Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations shall be reported to the sponsor according to the reporting requirements and within the time periods specified in the protocol.

3. For reported deaths of a subject, the investigator shall supply the sponsor and the Ethics Committee with any additional information requested.

4. The sponsor shall keep detailed records of all adverse events which are reported to him by the investigator or investigators. These records shall be submitted to the Member States in whose territory the clinical trial is being conducted, if they so request.

Article 17

Notification of serious adverse reactions

1. (a) The sponsor shall ensure that all relevant information about suspected serious unexpected adverse reactions that are fatal or life-threatening is recorded and reported as soon as possible to the competent authorities in all the Member States concerned, and to the Ethics Committee, and in any case no later than seven days after knowledge by the sponsor of such a case, and that relevant follow-up information is subsequently communicated within an additional eight days.

(b) All other suspected serious unexpected adverse reactions shall be reported to the competent authorities concerned and to the Ethics Committee concerned as soon as possible but within a maximum of fifteen days of first knowledge by the sponsor.

(c) Each Member State shall ensure that all suspected unexpected serious adverse reactions to an investigational medicinal product which are brought to its attention are recorded.

(d) The sponsor shall also inform all investigators.

2. Once a year throughout the clinical trial, the sponsor shall provide the Member States in whose territory the clinical trial is being conducted and the Ethics Committee with a listing of all suspected serious adverse reactions which have occurred over this period and a report of the subjects' safety.

3. (a) Each Member State shall see to it that all suspected unexpected serious adverse reactions to an investigational medicinal product which are brought to its attention are immediately entered in a European database to which, in accordance with Article 11(1), only the competent authorities of the Member States, the Agency and the Commission shall have access.

(b) The Agency shall make the information notified by the sponsor available to the competent authorities of the Member States.

Article 18

Guidance concerning reports

The Commission, in consultation with the Agency, Member States and interested parties, shall draw up and publish detailed guidance on the collection, verification and presentation of adverse event/reaction reports, together with decoding procedures for unexpected serious adverse reactions.

Article 19

General provisions

This Directive is without prejudice to the civil and criminal liability of the sponsor or the investigator. To this end, the sponsor or a legal representative of the sponsor must be established in the Community.

Unless Member States have established precise conditions for exceptional circumstances, investigational medicinal products and, as the case may be, the devices used for their administration shall be made available free of charge by the sponsor.

The Member States shall inform the Commission of such conditions.

Article 20

Adaptation to scientific and technical progress

This Directive shall be adapted to take account of scientific and technical progress in accordance with the procedure referred to in Article 21(2).

Article 21

Committee procedure

1. The Commission shall be assisted by the Standing Committee on Medicinal Products for Human Use, set up by Article 2b of Directive 75/318/EEC (hereinafter referred to as the Committee).

2. Where reference is made to this paragraph, Articles 5 and 7 of Decision 1999/468/EC shall apply, having regard to the provisions of Article 8 thereof.

The period referred to in Article 5(6) of Decision 1999/468/EC shall be set at three months.

3. The Committee shall adopt its rules of procedure.

Article 22

Application

1. Member States shall adopt and publish before 1 May 2003 the laws, regulations and administrative provisions necessary to comply with this Directive. They shall forthwith inform the Commission thereof.

They shall apply these provisions at the latest with effect from 1 May 2004.

When Member States adopt these provisions, they shall contain a reference to this Directive or shall be accompanied by such reference on the occasion of their official publication. The methods of making such reference shall be laid down by Member States.

2. Member States shall communicate to the Commission the text of the provisions of national law which they adopt in the field governed by this Directive.

Article 23

Entry into force

This Directive shall enter into force on the day of its publication in the Official Journal of the European Communities.

Article 24

Addressees

This Directive is addressed to the Member States.

Done at Luxembourg, 4 April 2001.

For the European Parliament	*For the Council*
The President	*The President*
N. FONTAINE	B. ROSENGREN

Appendix B – European Osteosarcoma Intergroup (EOI)

Appendix B.1 Participating Institutions

Institutions from Belgium, the Netherlands, and the UK are invited to participate in the EURAMOS-1 trial once accredited.

Accreditation criteria are outlined in Section 5 of the protocol.

Each investigator must also complete the Commitment form (appendix B.2).

Participating institutions are already expected to be members of national or international trial groups. For example in the UK, centres will either be recognised UKCCSG centres or accredited EORTC Soft Tissue and Bone Sarcoma Group members. Other centres may participate if evidence of appropriate expertise and resources can be documented both for the clinical management of osteosarcoma and undertaking clinical trials according to GCP and EU directive standards.

For more information, contact:

EURAMOS-1 Trial
MRC Clinical Trials Unit
222 Euston Road
London NW1 2DA
Tel: 020 7670 4700
E-mail: euramos1@ctu.mrc.ac.uk

Accredited Institutions are listed on the EURAMOS-1 web site:
www.euramos.org

Appendix B.2 Commitment form

The EURAMOS Commitment form consists of 3 parts:
- Investigator statement,
- Signature list and delegation of responsibilities,
- Full contact details for all site personnel.

This must be completed by all centres wishing to participate in the UK, the Netherlands and Belgium

Investigator statement
Completed by the principal investigator at each participating institution and sent to the MRC CTU before entering any patients into this study.

Signature list and delegation of responsibilities
Completed by **all** trial staff and sent to the MRC CTU before entering any patients to this study. This must be whenever there are changes to trial staff.

Full contact details list for site personnel
Contact details are required for
- Clinicians responsible for medical care of patients
- Staff responsible for CRF completion
- Pharmacist (for PegIntron supplies)

For more information, contact:

EURAMOS-1 Trial
MRC Clinical Trials Unit
222 Euston Road
London NW1 2DA
Tel: 020 7670 4700
E-mail: euramos1@ctu.mrc.ac.uk

EURAMOS-1/BO08

MRC Clinical Trials Unit

Investigator statement

Institution: _____

I, the undersigned declare that:

1. The above named institution for which I am the named Principal Investigator regularly undertakes the treatment for osteosarcoma. Supporting evidence of this will be made available to the Trial Management Group if requested.
2. The institution for which I am the named Principal Investigator will participate in the EURAMOS-1 trial and expects to recruit approximately _____ patients per year.
3. I have read and am familiar with the current protocol.
4. I am thoroughly familiar with the appropriate use of the investigational products, as described in the protocol (and in current investigators brochure).
5. The institution has an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely.
6. I will ensure that all colleagues and supporting staff assisting with the trial are adequately informed about the protocol, the investigational products and their trial related duties.
7. I agree to conduct the study in accordance with the current protocol and will only depart from the protocol when necessary to protect the safety, rights or welfare of patients.

I agree to comply with the obligations below:

a) The trial will be conducted in compliance with GCP and applicable regulatory requirements.
b) The institution will permit monitoring and auditing by the MRC CTU or individuals or organisations appointed or agreed by them (e.g. MRC Head Office, NCRN) and inspection by the appropriate regulatory authorities. Direct access will be made available to all relevant data, documents, clinical case records and reports at the trial sites and any related sites.
c) The institution will maintain a Trial Master file, which will contain essential documents for the conduct of the trial.
d) To submit all trial data in a timely manner and as described in the protocol. Individual institutions may be suspended if data returns are poor or if trial conduct is violated in other ways.
e) To report all Serious Adverse Events (SAEs) immediately to the EURAMOS Intergroup Safety Desk, except for those that the protocol or summary of products characteristics identifies as not requiring immediate reporting (these should be reported on the CRFs for the trial). The initial SAE report shall be promptly followed by detailed written reports.
f) That no trial data will be disclosed, presented or published without the approval of the Trial Steering Committee.
g) To retain all trial related documents for 5 years after the completion of the trial.

☐ **I have no potential conflict of interest,** e.g. a professional interest, a proprietary interest or any other conflict of interest.

☐ **YES, I have a potential conflict of interest** (If you have a potential conflict of interest, we will send you an appropriate form).

Name of Principal Investigator: _____
(Print name in Capitals)

Signature: _____ **Date:** _____

EURAMOS-1/BO08 Signature list and delegation of responsibilities

Institution____

This form must be completed by all personnel managing patients and those responsible for completing CRFs (e.g oncologists, surgeons, pathologists and research nurses/data managers). <u>Only staff who are included on this form will be authorised to sign CRFs</u>.

Name	**Job title**	**Sample signature**	**Sample short signature** (initials)	**Responsibilities** (please tick all applicable boxes)
				☐ Medical care of patients ☐ Adverse event reporting ☐ Ethics/regulatory approval ☐ Registration/Randomisation ☐ Informed consent ☐ CRF completion ☐ Trial master file maintenance ☐ Pathology specimen processing ☐ Quality of Life Administration ☐ Pharmacy/ Drug accountability
				☐ Medical care of patients ☐ Adverse event reporting ☐ Ethics/regulatory approval ☐ Registration/Randomisation ☐ Informed consent ☐ CRF completion ☐ Trial master file maintenance ☐ Pathology specimen processing ☐ Quality of Life Administration ☐ Pharmacy/ Drug accountability
				☐ Medical care of patients ☐ Adverse event reporting ☐ Ethics/regulatory approval ☐ Registration/Randomisation ☐ Informed consent ☐ CRF completion ☐ Trial master file maintenance ☐ Pathology specimen processing ☐ Quality of Life Administration ☐ Pharmacy/ Drug accountability
				☐ Medical care of patients ☐ Adverse event reporting ☐ Ethics/regulatory approval ☐ Registration/Randomisation ☐ Informed consent ☐ CRF completion ☐ Trial master file maintenance ☐ Pathology specimen processing ☐ Quality of Life Administration ☐ Pharmacy/ Drug accountability
				☐ Medical care of patients ☐ Adverse event reporting ☐ Ethics/regulatory approval ☐ Registration/Randomisation ☐ Informed consent ☐ CRF completion ☐ Trial master file maintenance ☐ Pathology specimen processing ☐ Quality of Life Administration ☐ Pharmacy/ Drug accountability
				☐ Medical care of patients ☐ Adverse event reporting ☐ Ethics/regulatory approval ☐ Registration/Randomisation ☐ Informed consent ☐ CRF completion ☐ Trial master file maintenance ☐ Pathology specimen processing ☐ Quality of Life Administration ☐ Pharmacy/ Drug accountability

Please notify the MRC CTU of any changes to trial personnel by updating this form.

Full contact details list for trial personnel

Hospital: _____ **Principle Investigator:** _____

Address: _____ **Main contact person** *(e.g. data queries, general correspondence):* _____

_____

_____

- Complete this form for all trial personnel
- Notify the MRC CTU of any contact or trial personnel changes
- Use additional sheets if necessary

	Principle Investigator	Investigator
Name (title, first name/initial, surname)		
Department		
Phone		
Fax		
E-mail		
Address (if different from above)		

	Research Nurse/Data Manager	Research Nurse/Data Manager
Name (title, first name/initial, surname)		
Department		
Phone		
Fax		
E-mail		
Address (if different from above)		

	Research Nurse/Data Manager	Research Nurse/Data Manager
Name (title, first name/initial, surname)		
Department		
Phone		
Fax		
E-mail		
Address (if different from above)		

	Pharmacist	Pharmacist
Name (title, first name/initial, surname)		
Department		
Phone		
Fax		
E-mail		
Address (if different from above)		

Appendix B.3 Registration practice

Before any patients can be registered in the trial the MRC CTU must receive completed commitment form and confirmation of site-specific approval (Appendix B2.). Details of the investigators are then added to our randomisation programme. We cannot register patients until these documents are received.

NOTE: Patient/parental consent must be obtained **twice** in this trial, before registration and before randomisation.

To Register/Randomise contact:

MRC Clinical Trials Unit
Tel + 44 (0)207 670 4777
Monday - Friday
09.00 to 17.00 (UK)
10.00 to 18.00 (Belgium/Netherlands)

Registration procedure

- Patient/parental consent must be obtained before registration. The appropriate informed consent forms must be completed and signed by patient/parent.
- Patients must be registered within 30 days of diagnostic biopsy and **before** chemotherapy has started.
- Eligibility criteria will be checked during the registration procedure.
- All the information on the Registration Checklist (Form 1) will be required at registration (please complete the form before telephoning).
- The patient will be allocated a unique patient identification number. The number and the date of registration must be completed on the Registration Checklist and the form returned to the MRC CTU within 7 days of randomisation.

Randomisation procedure

- Prior to randomisation the Registration Checklist (form 1), preoperative Chemotherapy forms (form 3), Surgery form (form 4) must be completed and returned to the MRC CTU. The Diagnostic Biopsy Evaluation form (form 10) and Resected Specimen form (form 11) should be completed by the pathology review panel representative and returned to the MRC CTU.
- Patient/parental consent must be obtained before randomisation. The appropriate informed consent forms must be completed and signed by patient/parent.
- Eligible patients must be randomised within 35 days of definitive surgery.
- If possible, a review pathologist's assessment of histological response should be used for purpose of randomisation. If not, a local pathologist's assessment will be accepted, but the specimen must be reviewed as soon as possible by the appropriate review pathologist.

- All the information on the Randomisation checklist (Form 2) will be required at randomisation (please complete the form before telephoning). The Randomisation checklist must be returned to the MRC CTU within 7 days of randomisation.
- The investigator will be asked for the patient's identification number and initials provided at registration in order to identify the patient and conduct randomisation.

Patients who are not eligible for randomisation

MRC CTU must be notified by return of the Randomisation checklist (Form 2) about any patient that has not satisfied eligibility criteria for randomisation. This should be completed and returned as soon as information comes to hand.

Patients will remain in the trial for the purpose of follow-up.

Appendix B.4 Forms and procedures for data collection

Data will be recorded on case report forms (CRFs) available on the EURAMOS-1 website (www.euramos.org)

The case reports must be completed, dated and signed by the investigator or his/her authorised staff, whose sample signature has been received by the MRC CTU (see Appendix B.2).

The unique patient identification number and patients initials as given at registration must be reported on all case report forms. Local investigators must keep a confidential patient identification list connecting these with the full patient name.

CRFs must be filled out with ink. Corrections should be performed as follows: a single line should be drawn through the incorrect information, the correct information written next to it, dated and signed by the investigator, if necessary giving reasons for the correction. Data fields which cannot be filled because of lack of information should be commented. The CRFs are to be completed in a timely fashion according to the schedule (Appendix B4.) and signed by the local investigator or his/her authorised staff. A photocopy should be made of the original form and kept at the participating unit, and the original copy should be sent to the MRC CTU.

If an investigator or his/her authorised staff needs to modify a CRF after the original copy has been returned to the MRC CTU, he/she should notify the MRC CTU in writing and append a copy of the notification to his/her own copy of the CRF.

If the MRC CTU must issue a query in case of inconsistent data, the query must be promptly answered and signed by the investigator (or authorised staff). The original query must be returned to the MRC CTU and a copy must be appended to the investigators copy of the CRF.

All CRFs, CRF modifications and data queries should be promptly sent to:

EURAMOS-1 Trial
MRC Clinical Trials Unit
222 Euston Road
London NW1 2DA

Schedule for sending forms

Form	When to send	Patients Registered AND Randomised	Patients Registered and NOT Randomised
Registration Form 1	Within 7 days of registration	✓	✓
Randomisation Form 2	Within 7 days of randomisation.	✓	✓
Chemotherapy Form 3	At the end of each chemotherapy cycle. Note: All pre-operative chemotherapy forms must be received before randomisation	✓	✓ (Cycles 1 & 2 only)
Definitive Surgery Form 4	Immediately after surgery (must be received before randomisation)	✓	
End of Treatment Form 5	At the end of chemotherapy treatment (excluding interferon-α) or when the patient has discontinued chemotherapy, and return to the MRC Clinical Trials Unit.	✓	
Follow-up Form 6	Years 1-6, every 6 months (from time of biopsy)	✓	✓
Event Form 7	At the time of the first type of each event (death, local recurrence, new metastatic disease, progression of metastatic disease and secondary malignancy). This form must be completed for randomised and non-randomised patients	✓	✓
Interferon-α Form 8	Complete at 12, 15, 18, 21 and 24 months after registration.	✓	
Thoracotomy Form 9	Immediately after each thoracotomy (metastatic patients)	✓	
Quality of Life questionnaire	Protocol week 5, 3 months after definitive surgery, 18 and 36 months after registration	✓	✓
Pathology Request Letter	Send to local pathologist at registration and immediately after surgery	✓	✓

All CRFs, CRF modifications and data queries should be promptly sent to:

EURAMOS-1 Trial
MRC Clinical Trials Unit
222 Euston Road
London NW1 2DA

SAEs must be faxed to EURAMOS Intergroup Safety Desk (Germany) +49 (0) 251 83 57112 – see SAE SOP for more information

Appendix B.5 Drug supplies

1. PegIntron

a) Supplies

Pegylated interferon α-2b (PEG-Intron) will be supplied free of charge by Integrated Therapeutics Group Inc (ITGI), a wholly-owned subsidiary of Schering-Plough. MRC CTU staff will notify ITGI of any patients allocated to MAPifn arm.

In week 22 (cycle 5) of the patient's treatment, MRC CTU staff will request the first supply (i.e. 3 months) of PEG-Intron by sending a copy of the PEG-Intron request form to ITGI detailing to whom and to where the drug should be sent. A copy of this form will be forwarded for information purposes to the pharmacy contact at the institution.

PEG-Intron will be sent to pharmacies of the Investigators' institutions. The agent will be obtained from the pharmacy according to local practice. The supplier's recommendations regarding storage, stability, dilution, incompatibilities and measures of caution should be followed.

After the initial supply of PegIntron, the relevant pharmacy should order additional drug supply directly from ITGI using the Drug Re-supply Request Form (see following sample form), which can be downloaded from the EURAMOS website. If there are any concerns regarding the quality of the PegIntron delivered to the site, (e.g. broken or damaged packaging, evidence of contamination etc.) please complete the Investigational Medicinal Product Quality Complaint (IMPQC) form (see following sample form) within 1 working day of the complaint occurrence. Please read the IMPQC form instructions before completing the form. The completed form should be faxed to both the MRC CTU and the Schering Plough contact listed on the Drug Re-supply Request Form.

b) Labels

PEG-Intron will be labelled by ITGI (see following sample PEG-Intron labels)

c) Diary Cards

The purpose of the PEG-Intron Diary Card is to help with the completion of CRFs but may also be used to notify patients of the dose escalation as described in section 9.1.8.6.6 of the protocol. The PEG-Intron Diary Card can be downloaded from the EURAMOS website.

d) Drug Accountability

PEG-Intron is an investigational agent in this setting, it will require appropriate drug accountability according to ICH-GCP.

1. G-CSF - Human Granulocyte Colony-Stimulating Factor: (Granocyte™ - rHuG-CSF, Lenograstim - Chugai Pharma UK Limited)

The use of G-CSF (Human Granulocyte Colony Stimulating Factor) is recommended when chemotherapy induced myelosuppression leads to treatment delays.

Granocyte is available as lyophilised powder, each single use vial containing either 105µg of lenograstim (13.4 MIU rHuG-CSF) or 263µg of lenograstim (33.6 MIU rHuG-CSF). A pre-filled syringe of Water for Injections (1 ml) for each vial of Granocyte is provided for reconstitution before administration. Granocyte can be stored at room temperature, up to 30°C.

Lenograstim should be prescribed at a dose of 150µg/m^2/day (therapeutically equivalent to 5µg/kg/day) as a subcutaneous injection. Bone pain and injection site reaction have been associated with Lenograstim treatment in some patients.

Chugai Pharma UK Ltd has agreed that there will be a 25% retrospective stock reimbursement for GranocyteTM (rHuG-CSF, lenogastrim) used within this study for patients treated within the protocol in the UK. In the UK, Granocyte is manufactured by Chugai Pharma UK Limited and distributed by Aventis UK, tel 0870 5133347, fax 0870 5133329. For information on dosing etc, see Appendix 8.2. For reimbursement, please complete a reimbursement form (see following sample form), which can be downloaded from the EURAMOS website.

PegIntron Request Form	
Protocol Title	A randomized trial of the European and American Osteosarcoma Study Group to optimize treatment strategies for resectable osteosarcoma based on histological response to pre-operative chemotherapy.
Study Number/Identifier	EURAMOS-1/SPRI P03771

Investigator/site information	
Investigator Name	
Investigator Address	
Drug Shipment Address (pharmacy - if different than the investigator address)	
Site Number	
PI Telephone Number	
Name of Pharmacist	
Pharmacy Phone Number (if applicable)	
PI Email Address	
PI Fax number	

Patient Identification	
Patient initials	
Patient ID number	

Patient Status Dates	
Date chemotherapy started (Cycle 1 - Day 1)	
Date of Randomization (Cycle 3 – Week 12)	
Peg-IFN Drug supply Order (Cycle 5 – Week 22)	
Projected first dose of Peg-IFN (Cycle 7 – Week beginning 30)	I box (6 vials a box) Peg-Intron 50mg/ml (1 months supply) tick box ☐
	2 boxes(6 vials a box) Peg-Intron 100mg/ml (2months supply) tick box ☐
Period of drug supply to patient	3 Months

Schering Plough UK	
Marie Childs Schering Plough UK	Fax Number + 44 (0)1707 363763 Please fax 5 working days in advance of date drug required on site
Name of Person requesting Drug	Signature: Date:
Data Center contact phone	

DRUG RE-SUPPLY REQUEST FORM

This form must be completed and faxed to Marie Childs on 01707 363763
Please allow 5 working days before supplies are needed

Protocol Title	A randomized trial of the European and American Osteosarcoma Study Group to optimize treatment strategies for resectable osteosarcoma based on histological response to pre-operative chemotherapy.
Study Number/Identifier	EURAMOS-1/SPRI P03771

Investigator/site information	
Investigator Name	
Investigator Address	
Site Number	
Drug Shipment Address (pharmacy - if different than the investigator address)	
Name of Pharmacist	
Pharmacy Phone Number (if applicable)	

Patient Identification	
Patient initials	
Patient ID number	

Drug Re-supply	
Re-supply Peg-Intron	3 boxes (6 vials per box) Peg-Intron 100µg (3 months supply) tick box ☐

Schering Plough UK	
Marie Childs Schering Plough UK	Fax Number + 44 (0)1707 363763 Please fax 5 working days in advance of date drug required on site
Name of Person requesting Drug	Signature: Date:

Labels for the PEG-IFN 50 µg supply (label colour yellow):

a) Label of the vial PEG-IFN 50 µg

Study: **P03771** / **EURAMOS-1** (PSR 05I0010) Centre: _____
Patient initials: _____Patient n°: _____ Investigator_____
PEG-Interferon alfa-2b 74 µg (to yield 50 µg/0.5 ml)
Batch: ..... Expiry date: …/…
Lyophilized powder to be reconstituted with 0.7 ml of sterile water for injection.
FOR CLINICAL TRIAL PURPOSES ONLY

Please correct and translate if necessary

Sponsor: Medical Research Council, Clinical Trials Unit, 222 Euston Road, London, NW1 2DA Tel: 020 7670 4700

b) Label of the box with 6 PEG-IFN vials 50 µg

Study: **P03771** / **EURAMOS-1** (PSR 05I0010) Centre: _____
Patient initials: _____Patient n°: _____ Investigator_____
Patient weight: _____ kg
Date dispensed: _____ Date returned: _____

6 vials sterile lyophilized powder
PEG-Interferon alfa-2b 74 µg (to yield 50 µg/0.5 ml)
Batch: ..... Expiry date: …/…

Store between 2°C and 8°C.
Keep out of reach of children.
FOR CLINICAL TRIAL PURPOSES ONLY

Lyophilized powder to be reconstituted with 0.7 ml sterile water to yield a solution of **50 µg/0.5 ml** for injection. The volume of the reconstituted solution is 0.74 ml. The reconstituted solution must be refrigerated at 2°C - 8°C and used within 24 hours.

Administration: Inject ____ ml by subcutaneous injection once a week as directed.

Please correct and translate if necessary

Sponsor: Medical Research Council, Clinical Trials Unit, 222 Euston Road, London, NW1 2DA Tel: 020 7670 4700

c) Label of the carton with 5 boxes containing 6 vials PEG-IFN 50 µg

Study: **P03771** / **EURAMOS-1** (PSR 05I0010) Centre : _____

This box contains:

5 x 6 vials sterile lyophilized powder
PEG-Interferon alfa-2b 74 µg (to yield 50 µg/0.5 ml)
Batch: ..... Expiry date: …/…

Store between 2°C and 8°C.
Keep out of reach of children.
FOR CLINICAL TRIAL PURPOSES ONLY

Please correct and translate if necessary

Sponsor: Medical Research Council, Clinical Trials Unit, 222 Euston Road, London, NW1 2DA Tel: 020 7670 4700

Labels for the PEG-IFN 100 µg supply (label colour white):

d) Label of the vial PEG-IFN 100 µg

Study: **P03771** / **EURAMOS-1** (PSR 05I0010) Centre: _____
Patient initials: _____Patient n°: _____Investigator_____
PEG-Interferon alfa-2b 148 µg (to yield 100 µ g/0.5 ml)
Batch: ..... Expiry date: …/…
Lyophilized powder to be reconstituted with 0.7 ml of sterile water for injection.
FOR CLINICAL TRIAL PURPOSES ONLY

Please correct and translate if necessary

Sponsor: Medical Research Council, Clinical Trials Unit, 222 Euston Road, London, NW1 2DA Tel: 020 7670 4700

e) Label of the box with 6 PEG-IFN vials 100 µg

Study: **P03771** / **EURAMOS-1** (PSR 05I0010) Centre: _____
Patient initials: _____Patient n°: _____ Investigator_____
Patient weight: _____ kg
Date dispensed: _____ Date returned: _____

6 vials sterile lyophilized powder
PEG-Interferon alfa-2b 148 µg (to yield 100 µg/0.5 ml)
Batch: ..... Expiry date: …/…

Store between 2°C and 8°C.
Keep out of reach of children.
FOR CLINICAL TRIAL PURPOSES ONLY

Lyophilized powder to be reconstituted with 0.7 ml sterile water to yield a solution of **100 µg/0.5 ml** for injection. The volume of the reconstituted solution is 0.74 ml. The reconstituted solution must be refrigerated at 2°C - 8°C and used within 24 hours.

Administration: Inject ____ ml by subcutaneous injection once a week as directed.

Please correct and translate if necessary

Sponsor: Medical Research Council, Clinical Trials Unit, 222 Euston Road, London, NW1 2DA Tel: 020 7670 4700

f) Label of the carton with 5 boxes containing 6 vials PEG-IFN 100 µg

Study: **P03771** / **EURAMOS-1** (PSR 05I0010) Centre: _____

This box contains:

5 x 6 vials sterile lyophilized powder
PEG-Interferon alfa-2b 148 µg (to yield 100 µg/0.5 ml)
Batch: ..... Expiry date: …/…

Store between 2°C and 8°C.
Keep out of reach of children.
FOR CLINICAL TRIAL PURPOSES ONLY

Please correct and translate if necessary

Sponsor: Medical Research Council, Clinical Trials Unit, 222 Euston Road, London, NW1 2DA Tel: 020 7670 4700

Labels for the sterile water supply 0.7 ml/2 ml ampule (label colour white):

g) Labels for the ampules with sterile water for reconstitution

Study: **P03771** / **EURAMOS-1** (PSR 05I0010) Centre : _____
Patient initials: _____Patient n°: _____ Investigator_____
Sterile water for injection 0.7 ml/ampoule
Batch: ..... Expiry date: …/…
FOR CLINICAL TRIAL PURPOSES ONLY

Please correct and translate if necessary

Sponsor: Medical Research Council, Clinical Trials Unit, 222 Euston Road, London, NW1 2DA Tel: 020 7670 4700

h) Label of the boxes with 6 ampules sterile water for reconstitution

Study: **P03771** / **EURAMOS-1** (PSR 05I0010) Centre : _____
Patient initials: _____Patient n°: _____Investigator _____
Patient weight: _____ kg
Date dispensed: _____ Date returned: _____

6 ampoules

Sterile water for injection 0.7 ml/ampoule

Batch: ..... Expiry date: …/…

Store up to 30°C, do not freeze.

Keep out of reach of children.
FOR CLINICAL TRIAL PURPOSES ONLY

Please correct and translate if necessary

Sponsor: Medical Research Council, Clinical Trials Unit, 222 Euston Road, London, NW1 2DA Tel: 020 7670 4700

i) Label of the carton with 5 boxes containing 6 ampules sterile water for reconstitution

Study: **P03771** / **EURAMOS-1** (PSR 05I0010) Centre: _____

This box contains:

5 x 6 ampoules
Sterile water for injection 0.7 ml/ampoule

Batch: ..... Expiry date: …/…

Store up to 30°C, do not freeze.
Keep out of reach of children.
FOR CLINICAL TRIAL PURPOSES ONLY

Please correct and translate if necessary

Sponsor: Medical Research Council, Clinical Trials Unit, 222 Euston Road, London, NW1 2DA Tel: 020 7670 4700

Schering-Plough

Investigational Medicinal Product Quality Complaint (IMPQC) Form

Protocol No.:	Site No.:	Country (of Site):

SECTION A: Reporting the Complaint.

IMP Name(s) *(Include Schering No. if applicable. For blinded IMP, list all potential products):*

PR/ISR/Shipment No:	Unique Batch/Lot No. :	Kit No.(s) (if applicable):	Subject No. (if applicable):

Dosage Form Affected: (Check all dosage forms that are the subject of this complaint).

☐ Capsule	☐ Inhaler	☐ Lotion	☐ Cream	☐ Nasal Spray	☐ Ointment	☐ Oral Liquid	☐ Pen
☐ Tablet	☐ Vial	☐ Other (describe):					

IMP Complaint Description *(Describe problem in detail. Use additional pages as needed. Attach all relevant documents.):*

Is the IMP segregated in a secure area?	**YES** ☐	**Not Applicable (IMP not at site)** ☐		
Is the IMP available for return?	**YES** ☐	**NO** ☐	**Unknown** ☐	**Not Applicable** ☐
Was referenced IMP distributed to a subject(s)?	**YES** ☐	**NO** ☐	**Unknown** ☐	**Not Applicable** ☐
Was a serious adverse event associated with the IMPQC?	**YES** ☐	**NO** ☐	**Unknown** ☐	**Not Applicable** ☐

*NOTE: **All associated Adverse Events must be reported per protocol requirements.** For associated serious adverse events (SAEs), an SAE Form must be completed and sent with this form to the IMPQC Contact and SP Pharmacovigilance representative.*

COMPLAINT REPORTED BY:

SITE INFORMATION: Schering-Plough recognizes the importance of privacy. The personally identifiable information that you provide (such as your full name or contact information): will be stored at the local Sponsor company location; processed by company representatives including vendors, for the purposes of documenting the IMPQC reports; disclosed to regulatory agencies in the event of an inspection; and transferred and stored to the United States. We maintain appropriate security measures to protect such information.
For further information on data privacy, contact the Global Privacy Office at privacyoffice@spcorp.com.

Printed Name:	Signature:	Date (dd/mmm/yyyy):	Phone #:	FAX #:

COMPLAINT DOCUMENTED BY (if different from person reporting complaint):

Printed Name:	Signature:	Date (dd/mmm/yyyy):

FAX THE FORM WITH SECTION A COMPLETED TO THE SP IMPQC Contact at

SECTION B: FOR SP IMPQC CONTACT OR DESIGNEE USE ONLY
Reviewing the complaint information.

Printed Name of SP IMPQC Contact:	Country:	E-mail Address:	Phone No.:

Printed Name of Designee (if applicable):	Signature (of Person Completing Section B):	Date (dd/mmm/yyyy):

Fax the form to Pharmaceutical Science Quality (Note: Fax number listed on GEOS.)

SECTION C: FOR PHARMACEUTICAL SCIENCES QUALITY USE ONLY
Assigning the complaint number and providing usability or additional comments as required.

Usability: ☐ IMP May be Used OR ☐ IMP Must NOT BE USED	Additional Comments:

Complaint Number:	Signature:	Date (dd/mmm/yyyy):

Form Distribution:
Original → Investigator Site (Section A), SP IMPQC Contact (Section B), PSQ (Section C)
Copies → Official Document Repository, SP IMPQC Contact, Site, SP Pharmacovigilance as applicable

Global Clinical Form Version 1.0
FORM 0451-02
Effective Date: 31-Jul-2008

Schering-Plough

IMPQC Form Instructions for the Investigator Site and Storage Facility

Purpose of Form: To report an Investigational Medicinal Product Quality Complaint (IMPQC) through the completion of the header fields and Section A.

When Form is used:
This Form is used to report IMP Quality Issues within **1 working day** of complaint occurrence including but not limited to all issues related to:

- ✓ Deficiencies in the identity, strength, quality, purity or packaging of an Investigational Medicinal Product including commercial products. Examples include:
  - Empty capsules
  - Broken or damaged IMP packaging (e.g., subject kits, bottles or vials) on shipment receipt that may render the supplies unfit for use
  - Missing, incorrect, damaged or illegible labels
  - Removal of tamper-evident seals, unless documentation confirms it was performed by regulatory official(s) during importation (e.g. Customs officer).
  - Discoloration or taste distortion of the product from the expected product specification /description
  - Evidence of contamination (e.g. growth or crystal formation)
  - More or less than the expected number/quantity of capsules/tablets/liquid in a container/ampoule/vial being dispensed to subjects (Note: IMP supplies may continue to be dispensed unless they present a health risk to subjects; however, an IMPQC Form must be completed).
- ✓ Defects or failures in a temperature tracking device sent with an IMP shipment.
- ✓ Defects or failures in a medical device or product delivery system
- ✓ Adverse storage of IMP at the investigator site after the investigator has accepted the IMP (e.g. temperature excursions).
  Note: Please complete 1 form for each product or blinded treatment kit(s).
- ✓ Dosing of subjects with expired IMP. NOTE: It is not considered an IMPQC if subject is in possession of, but has not dosed with, expired IMP. However, these non-IMPQC issues should be reported using the IMPQC form and following the IMPQC process.

Note: Issues such as late shipments, damages limited to the outer shipping container or documented subject handling errors that don't affect the IMP packaging are NOT IMP Quality Complaints.

General Instructions:

- Only 1 type of complaint should be reported in the form.
- The header fields, if not pre-populated, and Section A must be completed by the person reporting and/or documenting the complaint.
- No fields should be left blank. If any data fields are unknown, unavailable or not applicable at the time of report completion, enter N/A or UNK as needed and complete a follow up report when available.
- The report must not contain personal subject information e.g. initials, date of birth, etc.

Schering-Plough

How to complete the form:
Header:

1. Enter the Protocol Number, Site Number and Country of Site.
   Note: Storage facilities should enter the facility's name for the Site Number.

Section A: Reporting the Complaint

1. Enter the following information:
   a. IMP Name. Include a Schering No. if available. For blinded IMP (e.g. in a treatment kit) list all the potential products.
   b. Packaging Request (PR), Investigator Shipping Request (ISR) or Shipment Number per the IMP label or IMP shipment documentation.
   c. Unique Batch or Lot Number – this is the batch or lot identifier on the IMP label or IMP shipment documentation. (Note: this field is required.)
   d. The treatment kit number per the IMP packaging label (may also be referred to as randomization or subject number).
   e. The subject or screening number of any subject who was in possession of the IMP when the event occurred.
   f. All affected dosage form(s). If selecting other, please specify.
   g. Summary of the complaint in as much detail as is known at the time of the report including any serious or non-serious adverse events that may be associated with the complaint. Use additional pages as necessary. Indicate on the form the number of additional pages used. Attach de-identified evidence or supporting documentation as needed.
   h. Whether the IMP has been segregated in a secure area. Check the "Not Applicable" box if the IMP is not at the investigator site or storage facility.
   i. Whether the IMP is available for return.
   j. Whether the IMP was distributed to a subject. (Note: If yes, ensure that the subject or screening number has been entered in the appropriate field).
   k. Whether a Serious Adverse Event (SAE) was associated with the complaint. (Note: All associated Adverse Events must be reported per protocol requirements. When there is an associated SAE, both the IMPQC and SAE forms must be completed and sent to both the S-P IMPQC Contact and the S-P Pharmacovigilance representative.)
2. The person reporting the complaint must print their name, date and sign the form to verify the information captured is accurate.
   Note: If the person reporting the complaint is from an investigator site, he/she must have signed the SP Consent to Use and Disclose Personal Data Form (or equivalent form approved by SP law department).
3. The person documenting the complaint, if different from the person reporting the complaint, should also print their name, date and sign the form.
4. FAX form to the S-P IMPQC Contact at the number provided.

Note: For questions regarding this process and/or form, contact the S-P IMPQC Contact.

PEG-INTRON DIARY CARD

Patient initials and trial number: _____

Dear Patient,

Please use this sheet to keep a record of your PEG-Intron injections as you take them. You will be taking PEG-Intron once a week.

Prepare the dose just before you intend to inject it and use it immediately. Look carefully at the solution before you inject yourself. Do not use if there is any discolouration. Discard any solution that is left in the vial after you give yourself the injection.

Inject Peg-Inton once each week on the same day. Injecting it at the same time of day each week will help you to remember to take it.

It is important to let your doctors and nurses know about any side effects so that steps can be taken to minimise any symptoms you may experience.

Dose/dose volume	Date	PEG-Intron taken (please tick box when taken)
	___/___/___	☐
	___/___/___	☐
	___/___/___	☐
	___/___/___	☐
	___/___/___	☐
	___/___/___	☐
	___/___/___	☐
	___/___/___	☐
	___/___/___	☐
	___/___/___	☐

Additional notes: (e.g. please note any side-effects or other reasons for omitting doses)

REIMBURSEMENT FORM

This form should be completed and returned to David Eves,

01383 732713 (Fax), d.eves@dial.pipex.com (email)

Mulliner House, Flanders Road, Turnham Green, London, W4 1NN

CHUGAI CLINICAL TRIAL SUPPORT REIMBURSEMENT FOR GRANOCYTE

STUDY NAME:

EURAMOS-1

A randomized trial of the European and American Osteosarcoma Study Group to optimize treatment strategies for resectable osteosarcoma based on histological response to pre-operative chemotherapy.

Hospital:	
Lead Clinician (please provide contact details):	
Pharmacist Name (please provide contact details):	
Number of patients:	
Total number of vials used:	
Number of vials for reimbursement required (25% in stock)	
Send reimbursement to (name):	
Address:	
For Chugai use only **Approved by:**	

Please return this form to:David Eves, Head of Medical Affairs, Mulliner House, Flanders Road, Turnham Green, London, W4 1NN (Fax) 01383 732713 (email) d.eves@dial.pipex.com

Appendix B.6 Chemotherapy administration

Course AP- Version 1

Schedule: Doxorubicin 75 mg/m^2 over 48 hours
Cisplatin 120 mg/m^2 72 hour infusion
Venous access: Double lumen central line

Day	Time	Drug	Dose	Fluid	Volume	Schedule
1	T= - 4 h	Prehydration		Sodium chloride 0.9%	800 mL/m^2	Over 4 h
1	T= 0 h	Doxorubicin	37.5 mg/m^2	Sodium chloride 0.9%	48 mL	Over 24 h See note 1
1	T= 0 h	Cisplatin	40 mg/m^2	Sodium chloride 0.9% + potassium 20 mmol/L	250 mL/m^2 Max 500 mL See note 2	Over 24 h See note 3
1	T= 0 h	Hydration		Sodium chloride 0.9% + potassium 20 mmol/L + Mg 10 mmol/L	2.5 L/m^2 See note 4	Over 24 h
2	T= 0 h	Doxorubicin	37.5 mg/m^2	Sodium chloride 0.9%	48 mL	Over 24 h
2	T= 0 h	Cisplatin	40 mg/m^2	Sodium chloride 0.9% + potassium 20 mmol/L	250 mL/m^2 Max 500 mL	Over 24 h
2	T= 0 h	Hydration		Sodium chloride 0.9% + potassium 20 mmol/L + Mg 10 mmol/L	2.5 L/m^2	Over 24 h
3	T= 0 h	Cisplatin	40 mg/m^2	Sodium chloride 0.9% + potassium 20 mmol/L	250 mL/m^2 Max 500 mL	Over 24 h
3	T= 0 h	Hydration		Sodium chloride 0.9% + potassium 20 mmol/L + Mg 10 mmol/L	2.5 L/m^2	Over 24 h See note 5

[1] Doxorubicin infusions should be given via a central line only.
[2] Cisplatin may be given in a smaller volume to facilitate day care treatment provided total daily combined oral / intravenous fluid intake is maintained above 3 L/24 h.
[3] Other groups may opt to give the cisplatin as 60 mg/m^2 over 4 h on two consecutive days.
[4] Hydration may be given orally provided a minimum of 3 L/24 h is given
[5] If oral intake is inadequate IV hydration may need to be extended for a further 12-24 hours

Course AP- Version 2

Schedule: Doxorubicin 75 mg/m^2 over 48 hours
Cisplatin 60 mg/m^2/day x 2
Venous access: Double lumen central line (see note 6)

Day	Time	Drug	Dose	Fluid	Volume	Schedule
1	T= - 4 h	Prehydration		Sodium chloride 0.9%	800 mL/m^2	Over 4 h
1	T= 0 h	Doxorubicin	37.5 mg/m^2	Sodium chloride 0.9%	48 mL	Over 24 h See note 7
1	T = 0 h	Mannitol	8 g/m^2 See note 8, 9			Over 30 min
1	T= 0 h	Hydration		Sodium chloride 0.9% + 20 mmol potassium/L + Mg 10 mmol/L See note 10	2.5 L/m^2	Over 24 h
1	T= 30 min	Cisplatin	60 mg/m^2	Sodium chloride 0.9% + 20 mmol potassium/L	250 mL/m^2 Max 500 mL	Over 4 h See note 11
2	T= 0 h	Doxorubicin	37.5 mg/m^2	Sodium chloride 0.9%	48 mL	Over 24 h
2	T = 0 h	Mannitol	8 g/m^2			Over 30 min
2	T= 0 h	Cisplatin	60 mg/m^2	Sodium chloride 0.9% + potassium 20 mmol/L	250 mL/m^2 Max 500 mL	Over 4 h
2	T= 0 h	Hydration		Sodium chloride 0.9% + potassium 20 mmol/L + Mg 10 mmol/L	2.5 L/m^2	Over 24 h

Suggested fluid volumes for AP

SA (m^2)	Cisplatin Prehydration (mL)	Cisplatin (mL)	Hydration (mL)
0.4	300	100	1000
0.5	400	100	1250
0.6	500	100	1500
0.7	600	250	1750
0.8	600	250	2000
0.9	750	250	2000
1	750	250	2500
1.1	1000	500	2500
1.2-1.4	1000	500	3000
1.5-1.6	1250	500	4000
≥1.7	1500	500	4000

[6] In patients with a single lumen central line or a peripheral line the cisplatin and hydration should commence after the doxorubicin has finished.
[7] Doxorubicin infusions should be given via a central line only.
[8] In adult patients this may be rounded up so that 200 mL of 10% mannitol or 100 mL of 20% mannitol is given.
[9] In paediatric patients mannitol may be given at a dose of 12g/1000ml as a continuous infusion during cisplatin infusion and continuing for 6 hours post cisplatin.
[10] In children the hydration fluid should be Glucose 5%/ sodium chloride 0.45% with potassium chloride 20 mmol/L
[11] Other groups may opt to give the cisplatin as 120 mg/m^2 over 72 h on two consecutive days see alternative schedules.

Course M

Day	Time	Drug	Dose	Fluid	Volume	Schedule
1	T= -4h	Prehydration		Glucose 5%, sodium chloride 0.45% with potassium chloride 20 mmol/L + sodium bicarbonate 50 mmol/L See note 12 & 13	800 mL/m^2	Over 4 h
When urinary pH >7 commence MTX						
1	T= 0 h	Methotrexate	12 g/m^2 See note14	Sodium chloride 0.9% or dextrose 5%	500 mL/m^2 Max 1 L	Over 4 h
If urinary pH <7 during MTX infusion start post hydration whilst MTX still running or give extra bicarbonate						
	T= 4 h	Post-hydration		Glucose 5%, sodium chloride 0.45% with potassium chloride 20 mmol/L + sodium bicarbonate 50 mmol/L	3000 mL/m^2/day until MTX level <0.1 µmol/L See note 15	
1	T=24 h	Methotrexate serum level taken. This should be repeated daily until level is <0.1 µmol/L or <0.2 µmol/L				
1	T=24 h	Leucovorin (folinic acid) 15 mg/m^2 See note 16 orally every 6 hours See note 17. This should be continued until level is <0.1 µmol/L or <0.2 µmol/L or 11 doses have been given to T=84 h				

Suggested fluid volumes for Methotrexate

SA (m^2)	Prehydration (mL)	Methotrexate (mL)	Post Hydration (mL)
0.4	300	250	1250
0.5	400	250	1500
0.6	500	250	1750
0.7	600	500	2000
0.8	600	500	2500
0.9-1.0	750	500	3000
1.1-1.2	1000	500	3500
1.3-1.4	1000	500	4000
1.5-1.6	1250	1000	4500
≥1.7	1500	1000	4500

[12] Instead of bicarbonate, acetazolamide 500 mg four times a day for 48 hours starting 24 hours prior to MTX may be used. See Methotrexate Appendix.
[13] Bicarbonate may be increased to 75 - 100 mmol/L if pH<7.
[14] All doses should be rounded up to next highest full gram value.
[15] After 48 hours from the start of the Methotrexate, ENSURE a combined oral and/or intravenous intake greater than 2 L/m^2/24 h until plasma methotrexate levels <0.1 µmol/L or <0.2 µmol/L. At least 1500 mL/m^2 should be as IV fluid.
[16] A variety of different leucovorin dose schedules have been used. There is no evidence to suggest that this influences overall outcome. Individual institutions/groups may therefore wish to follow their usual protocol for leucovorin rescue.
[17] Dose should be rounded up to the most convenient tablet size.

Guidelines for adjustment of leucovorin dose during delayed methotrexate excretion

$$\text{Total daily dose of leucovorin (mg)} = \frac{\text{Patient's actual serum MTX} \times \text{standard daily dose of leucovorin*}}{\text{Upper limit of serum MTX for the actual day and time}}$$

*Standard daily dose is 60mg/m^2

The upper limit of serum MTX	at 24 hours is	20 µM
	at 48 hours is	2 µM
	at 72 hours is	0.2 µM

Example:
If the 48 hours methotrexate level was 40 µM, the leucovorin dose should be adjusted to:

$$\text{Total daily dose of leucovorin (mg)} = \frac{60\ \text{mg/m}^2 \times 40}{2} = 1200\text{mg/m}^2\text{/24 hours}^{**}$$

** Give higher doses of leucovorin q 3 hours

It is possible to reduce the dose of leucovorin on the following days in relation to the reduction in the methotrexate level. When the methotrexate level is in the range of 0.2–0.9 µM, give leucovorin in doses of 8 mg/m^2 orally every 6 hours until one dose after the serum level is <0.1µM or < 0.2 µM.
Note: Always continue to monitor urine pH and give more $NaHCO_3$ if pH < 7 to prevent precipitation of MTX in acid urine and consequent renal damage..

Course IE

Venous access: Double lumen central line

Day	Time	Drug	Dose	Fluid	Volume	Schedule
0	T= -4 h	mesna	2.8 g/m^2	Glucose 5% / sodium chloride 0.45% with potassium chloride 20 mmol/L	2500 mL/m^2	Over 24 h
1	T= 0 h	Etoposide See note 18	100 mg/m^2	Sodium chloride 0.9%	250 mL/m^2	Over 1 h
1	T= 0 h	Ifosfamide	2.8 g/m^2	Sodium chloride 0.9%	250-500 mL/m^2 Max 1 L	Over 4 h
1	T= 20 h	mesna	2.8 g/m^2	Glucose 5% / sodium chloride 0.45% with potassium chloride 20 mmol/L	2500 mL/m^2	Over 24 h
2	T= 0 h	Etoposide	100 mg/m^2	Sodium chloride 0.9%	250 mL/m^2	Over 1 h
2	T= 0 h	Ifosfamide	2.8 g/m^2	Sodium chloride 0.9%	250- 500 mL/m^2 Max 1 L	Over 4 h
2	T= 20 h	mesna	2.8 g/m^2	Glucose 5% / sodium chloride 0.45% with potassium chloride 20 mmol/L	2500 mL/m^2	Over 24 h
3	T= 0 h	Etoposide	100 mg/m^2	Sodium chloride 0.9%	250 mL/m^2	Over 1 h
3	T= 0 h	Ifosfamide	2.8 g/m^2	Sodium chloride 0.9%	250-500 mL/m^2 Max 1 L	Over 4 h
3	T= 20 h	mesna	2.8 g/m^2	Glucose 5% / sodium chloride 0.45% with potassium chloride 20 mmol/L	2500 mL/m^2	Over 24 h
4	T= 0 h	Etoposide	100 mg/m^2	Sodium chloride 0.9%	250 mL/m^2	Over 1 h
4	T= 0 h	Ifosfamide	2.8 g/m^2	Sodium chloride 0.9%	250-500 mL/m^2 Max 1 L	Over 4 h
4	T= 20 h	mesna See note 19	2.8 g/m^2	Glucose 5% / sodium chloride 0.45% with potassium chloride 20 mmol/L	2500 mL/m^2	Over 20 h See note 20
5	T= 0 h	Etoposide	100 mg/m^2	Sodium chloride 0.9%	250 mL/m^2	Over 1 h
5	T= 0 h	Ifosfamide	2.8 g/m^2	Sodium chloride 0.9%	250-500 mL/m^2 Max 1 L	Over 4 h

[18] Etopophos may be used instead of the etoposide infusion. This may be given as a bolus injection over 5 minutes . See Appendix A.5 for further details.

[19] Oral mesna may be substituted for the IV dose given between 4 and 24 h. See Ifosfamide appendix for details.

[20] Duration of final day mesna infusion may be reduced to 12 hours

Suggested fluid volumes for IE

SA (m^2)	Hydration (mL)	Etoposide (mL)	Ifosfamide (mL)	Mesna (mL)
0.4	200	100	100 - 200	1000
0.5-0.6	250	250	125 - 250	1500
0.7	250	250	125 - 250	2000
0.8-0.9	500	250	250 - 500	2000
1.0-1.1	500	250	250 - 500	3000
1.2	500	500	250 - 500	3000
1.3	750	500	250 - 500	3000
1.4	750	500	250 - 500	4000
1.5-1.7	750	500	500 - 1000	4000
$\geq$1.8	1000	500	500 - 1000	4000

Course Ai

Schedule: Doxorubicin 75 mg/m^2 over 48 hours
Venous access: Double lumen central line

Day	Time	Drug	Dose	Fluid	Volume	Schedule
1	T= -4 h	mesna	3 g/m^2	Glucose 5%/ sodium chloride 0.45% with potassium chloride 20 mmol/L	2500 mL/m^2 Max 4L	Over 24 h
1	T= 0 min	Doxorubicin	37.5 mg/m^2	Sodium chloride 0.9%	48 mL	Over 24 h See note 21
1	T= 0 h	Ifosfamide	3 g/m^2	Sodium chloride 0.9%	250-500 mL/m^2 Max 1L	Over 4 h
1	T= 20 h	mesna	3 g/m^2	Glucose 5%/ sodium chloride 0.45% with potassium chloride 20 mmol/L	2500 mL/m^2 Max 4 L	Over 24 h
2	T= 0 h	Doxorubicin	37.5 mg/m^2	Sodium chloride 0.9%	48 mL	Over 24 h
2	T= 0 h	Ifosfamide	3 g/m^2	Sodium chloride 0.9%	250- 500 mL/m^2 Max 1L	Over 4 h
2	T= 20 h	mesna See note 22	3 g/m^2	Glucose 5%/ sodium chloride 0.45% with potassium 20 mmol/L	2500 mL/m^2 Max 4 L	Over 24 h See note 23
3	T = 0h	Ifosfamide	3 g/m^2	Sodium chloride 0.9%	500mL/m^2 Max 1L	Over 4 h

Suggested fluid volumes for Ai

SA (m^2)	Hydration (mL)	Ifosfamide (mL)	Mesna (mL)
0.4	200	100-200	1000
0.5-0.6	250	125-250	1500
0.7	250	125-250	2000
0.8-0.9	500	250-500	2000
1.0-1.2	500	250-500	3000
1.3	750	250-500	3000
1.4	750	250-500	4000
1.5-1.7	750	500-1000	4000
$\geq$1.8	1000	500-1000	4000

[21] MUST be given via a central line. Volume of saline may be altered
[22] Oral mesna may be substituted see Appendix A.5 for details
[23] Duration of final day mesna infusion may be reduced to 12 hours

Course A
Schedule: Doxorubicin 75 mg/m^2 over 48 hours
Venous access: Central line

Day	Time	Drug	Dose	Fluid	Volume	Schedule
1	T= 0	Doxorubicin	37.5 mg/m^2	Sodium chloride 0.9%	48 mL	Over 24 h
2	T= 0	Doxorubicin	37.5 mg/m^2	Sodium chloride 0.9%	48 mL	Over 24 h

Course A + Dexrazoxane

Dexrazoxane may be used if a confirmed 10% fall within the normal range of LVEF or similar fall within the normal range of FS occurs.

Schedule: Doxorubicin 37.5mg/m^2 x 2
Venous access: Central line

Day	Time	Drug	Dose	Fluid	Volume	Schedule
1	T=0 h	Dexrazoxane	375 mg/m^2	In sodium chloride 0.9% or 0.16M sodium lactate See note 24	50 mL/m^2 max 100mL	Over 15 min
1	T=15 min	Doxorubicin	37.5 mg/m^2	Sodium chloride 0.9%	50 – 100 mL	Over 15 min
2	T=0	Dexrazoxane	375 mg/m^2	Sodium chloride 0.9% or 0.16M sodium lactate	50 mL/m^2 max 100mL	Over 15 min
2	T=15 min	Doxorubicin	37.5 mg/m^2	Sodium chloride 0.9%	50 – 100 mL	Over 15 min

[24] Depends on the brand of dexrazoxane being used. See appendix for further details

Course Ai + Dexrazoxane

Dexrazoxane may be used if a confirmed 10% fall within the normal range of LVEF or similar fall within the normal range of FS occurs.

Schedule: Doxorubicin 37.5 mg/m^2 x 2
Venous access: Double lumen central line (see note [25])

Day	Time	Drug	Dose	Fluid	Volume	Schedule
1	T= -4 h	mesna	3 g/m^2	Glucose 5%/ sodium chloride 0.45% with potassium 20 mmol/L	2500 mL/m^2	Over 24 h
1	T= 0 h	Dexrazoxane	375 mg/m^2	Sodium chloride 0.9% or 0.16 M sodium lactate See note 26	50 mL/m^2 Max 100 mL	Over 15 min
1	T= 0 h	Ifosfamide	3 g/m^2	Sodium chloride 0.9%	250-500 mL/m^2 Max 1 L	Over 4 h
1	T=15 min	Doxorubicin	37.5 mg/m^2	Sodium chloride 0.9%	50 – 100 mL	Over 15 min See notes 27
1	T= 20 h	mesna	3 g/m^2	Glucose 5%/ sodium chloride 0.45% with potassium 20 mmol/L	2500 mL/m^2 Max 4 L	Over 24 h
2	T= 0 h	Dexrazoxane	375 mg/m^2	Sodium chloride 0.9% or 0.16 M sodium Lactate	50 mL/m^2 Max 100 mL	Over 15 min
2	T=15 min	Doxorubicin	37.5 mg/m^2	Sodium chloride 0.9%	50 – 100 mL	Over 15 min
2	T= 0 h	Ifosfamide	3 g/m^2	Sodium chloride 0.9%	250- 500 mL/m^2 Max 1 L	Over 4 h
2	T=20 h	mesna See note 28	3 g/m^2	Glucose 5%/ sodium chloride 0.45% with potassium 20 mmol/L	2500 mL/m^2 Max 4 L	Over 24 h See note 29
3	T = 0 h	Ifosfamide	3 g/m^2	Sodium chloride 0.9%	250- 500 ml/m^2 Max 1L	Over 4 h

[25] In patients with a single lumen central line or a peripheral line the ifosfamide and mesna should commence after the doxorubicin has finished.
[26] Depends on the brand of dexrazoxane being used. See Appendix A.5 for further details.
[27] Doxorubicin infusion should be give via a central line only.
[28] Oral mesna may be substituted see Ifosfamide appendix for details
[29] Duration of final day mesna infusion may be reduced to 12 hours

Course AP+ Dexrazoxane - Version 1

Dexrazoxane may be used if a confirmed 10% fall within the normal range of LVEF or similar fall within the normal range of FS occurs.

Schedule: Doxorubicin 37.5 mg/m^2 x 2
Cisplatin 120 mg/m^2 72 hour infusion
Venous access: Double lumen central line (see note [30])

Day	Time	Drug	Dose	Fluid	Volume	Schedule
1	T= -4 h	Prehydration		Sodium chloride 0.9%	800 mL/m^2	Over 4 h
1	T= 0 h	Dexrazoxane	375 mg/m^2	Sodium chloride 0.9% or 0.16 M sodium lactate See note [31]	50 mL/m^2 Max 100mL	Over 15 min
1	T= 0 h	Cisplatin	40 mg/m^2	In Sodium chloride 0.9% + potassium 20 mmol/L	250 mL/m^2 Max 500 mL See note [32]	Over 24 h See note [33]
1	T= 0 h	Hydration		Sodium chloride 0.9% + potassium 20 mmol/L + Mg 10 mmol/L	2.5 L/m^2 See note [34]	Over 24 h
1	T= 15 min	Doxorubicin	37.5 mg/m^2	Sodium chloride 0.9%	50–100 mL	Over 15 min See notes [35]
2	T= 0 h	Dexrazoxane	375 mg/m^2	In sodium chloride 0.9%	50 mL/m^2 Max 100 mL	Over 15 min
2	T= 15 min	Doxorubicin	37.5 mg/m^2	In sodium chloride 0.9%	50 – 100 mL	Over 15 min
2	T= 0 h	Cisplatin	40 mg/m^2	In Sodium chloride 0.9% + 20 mmol potassium/L	250 mL/m^2 Max 500mL	Over 24 h
2	T= 0 h	Hydration		Sodium chloride 0.9% + potassium 20 mmol/L + Mg 10 mmol/Litre	2.5 L/m^2	Over 24 h
3	T= 0 h	Cisplatin	40 mg/m^2	In Sodium chloride 0.9% + potassium 20 mmol/L	250 mL/m^2 Max 500 mL	Over 24 h
3	T= 0 h	Hydration		Sodium chloride 0.9% + potassium 20 mmol/L + Mg 10 mmol/L	2.5 L/m^2	Over 24 h

[30] In patients with a single lumen central line or a peripheral line the cisplatin and hydration should commence after the doxorubicin has finished.
[31] Depends on the brand of dexrazoxane being used. See Appendix A.5 for further details.
[32] Cisplatin may be given in a smaller volume to facilitate day care treatment provided total daily combined oral / intravenous fluid intake is maintained above 2.5 L/m^2./24 h
[33] Other groups may choose to give the cisplatin as 60 mg/m^2 over 4 h on two consecutive days see alternative schedules.
[34] Hydration may be given orally provided a minimum of 2.5 L/m^2/24 h is given
[35] Doxorubicin infusions should be given via a central line only.

Course AP + Dexrazoxane - Version 2

Dexrazoxane may be used if a confirmed 10% fall within the normal range of LVEF or similar fall within the normal range of FS occurs.

Schedule: Doxorubicin 37.5 mg/m^2 x 2
Cisplatin 60 mg/m^2/day x 2
Venous access: Double lumen central line (see note [36])

Day	Time	Drug	Dose	Fluid	Volume	Schedule
1	T= -4 h	Prehydration		Sodium chloride 0.9%	800 mL/ m^2	Over 4 h
1	T= 0 h	Dexrazoxane	375 mg/m^2	Sodium chloride 0.9% or 0.16 M sodium lactate See note 37	50 mL/m^2 Max 100 mL	Over 15 min
1	T= 15 min	Doxorubicin	37.5 mg/m^2	Sodium chloride 0.9%	50 – 100 mL	Over 15 min See notes 38
1	T= 30 min	Cisplatin	60 mg/m^2	Sodium chloride 0.9% + potassium 20 mmol/L	250 mL/ m^2 Max 500 mL	Over 4 h See note 39
1	T = 0 h	Mannitol	8 g/m^2 See note 40,41			Over 30 min
1	T= 0 h	Hydration		Sodium chloride 0.9% + potassium 20 mmol/L + Mg 10 mmol/L	2.5 L/m^2 See note 42	Over 24 h
2	T= 0 h	Dexrazoxane	375 mg/m^2	Sodium chloride 0.9%	50 mL/m^2 Max 100 mL	Over 15 min
2	T= 0 h	Mannitol	8 g/m^2			Over 30 min
2	T= 0 h	Hydration		Sodium chloride 0.9% + potassium 20 mmol/L + Mg 10 mmol/L	2.5 L/m^2	Over 24 h
2	T= 15 min	Doxorubicin	37.5 mg/m^2	Sodium chloride 0.9%	50 – 100 mL	Over 15 min
2	T= 30 min	Cisplatin	60 mg/m^2	Sodium chloride 0.9% + potassium 20 mmol/L	250 mL/m^2 Max 500 mL	Over 4 h

[36] In patients with a single lumen central line or a peripheral line the cisplatin and hydration should commence after the doxorubicin has finished.
[37] Depends on the brand of dexrazoxane being used. See Appendix A.5 for further details
[38] Doxorubicin infusion should be given via a central line only.
[39] Other groups may opt to give the cisplatin as 120 mg/m^2 over 72 h see alternative schedules.
[40] In adult patients this may be rounded up so that 200 mL of 10% mannitol or 100 mL of 20% mannitol is given
[41] In paediatric patients mannitol may be given as a continuous infusion during cisplatin infusion and continuing for 6 hours post cisplatin.
[42] Hydration may be given orally provided a minimum of 2.5 L/m^2/24 h is given

Appendix B.7 Surgery

Guidelines for surgery are given in section 9.2 of the protocol. For further recommendations about how to proceed in specific situations and various tumour locations contact members of the surgical panel for EOI (see Appendix A.1)

Local Recurrence

Any patient developing local recurrence should be fully re-staged to exclude metastatic disease elsewhere. The combination of local recurrence and metastases has a particularly poor prognosis but patients with isolated local recurrence can be cured with further surgery. The aim should be to eradicate all recurrent disease. In some cases this will necessitate amputation but a wide local excision may be adequate in selected cases. If local excision is carried out then radiotherapy should also be considered to the whole of the previous operated area. Because of the increased risk of subsequent metastases further regular imaging is necessary. There is no proven role for chemotherapy if surgical re-excision is complete.

Case Report Forms (CRFs)

- A ‘Surgery Form ’ (Form 4) must be completed for all patients immediately after surgery.
- A ‘Thoracotomy Form’ (Form 9) must be completed following each thoracotomy.

See following pages for sample CRFs.

EURAMOS 1: Treatment Strategies in Osteosarcoma
SURGERY FORM

MRC B008
Form 4

Please complete this form immediately after surgery, make a copy for your records then send original copy to:
EURAMOS 1 Trial, MRC Clinical Trials Unit, 222 Euston Road, London, NW1 2DA, UK

Page 1 of 1

Patient's initials ☐☐☐☐ Date of birth ☐☐ ☐☐ ☐☐☐☐ (d m y) Patient's ID No. ☐☐☐☐☐

Hospital No. ..... Responsible clinician ..... Institution .....

1 ☐☐ ☐☐ ☐☐☐☐ **Date of surgery** (d m y)

2 ☐ **Surgeon's opinion of response to pre-operative chemotherapy**
1 = Good response
2 = Unchanged
3 = Disease progression

3 ☐ **Pathological fracture at surgery**
0 = No
1 = Yes

4 ☐ **Actual surgical procedure**
1 = Amputation
2 = Disarticulation
3 = Rotation plasty
4 = Resection with reconstruction
5 = Resection without reconstruction
6 = Other .....

5 ☐ **Was macroscopic clearance achieved?**
0 = No
1 = Yes

Signed by ..... *(authorised person only)* Date ☐☐ ☐☐ ☐☐☐☐ (d m y)

Version 1.1, July 2005

MRC Clinical Trials Unit

EURAMOS 1: Treatment Strategies in Osteosarcoma
THORACOTOMY FORM

MRC B008
Form 9

Only complete for patients with lung metatstases at Registration.
Please complete this form immediately after each thoracotomy, make a copy for your records then send original copy to:

EURAMOS 1 Trial, MRC Clinical Trials Unit, 222 Euston Road, London, NW1 2DA, UK

Patient's initials ☐☐☐☐ Date of birth ☐☐ ☐☐ ☐☐☐☐ (d m y) Patient's ID No. ☐☐☐☐☐

Hospital No. ..... Responsible clinician ..... Institution .....

1 ☐☐ ☐☐ ☐☐☐☐ **Date of thoracotomy** (d m y)

2 ☐ **Approach**
1 = Median (Sternotomy)
2 = Lateral
3 = Thoracoscopy *(not recommended - see section 9.2.2.5 of the protocol)*

3 ☐ **Side of approach**
1 = Left
2 = Right
3 = Bilateral
4 = N/A - median approach

4 ☐ **Type of resection**
1 = Pneumonectomy
2 = Lobectomy
3 = Wedge resections(s)
4 = Enucleation(s)

5 ☐ **Side of resection**
1 = Left
2 = Right
3 = Bilateral
4 = N/A - median approach

6 ☐ **Was metastatic disease histologically verified?**
0 = No
1 = Yes

7 ☐ **Was the resection macroscopically complete?**
0 = No
1 = Yes

8 ☐ **Was the resection microscopically complete?**
0 = No
1 = Yes

Number of resected suspicious lesions

9 ☐ **Left**
0 = 0
1 = 1
2 = 2-5
3 = >5

10 ☐ **Right**
0 = 0
1 = 1
2 = 2-5
3 = >5

Number of histologically verified metastases

11 ☐ **Left**
0 = 0
1 = 1
2 = 2-5
3 = >5

12 ☐ **Right**
0 = 0
1 = 1
2 = 2-5
3 = >5

13 ☐ **How did the number of histologically verified metastases compare to the number radiologically expected?**
1 = More were resected
2 = As expected
3 = Fewer were resected

14 ☐ **Were there any surgical complications?**
0 = No
1 = Yes, specify .....

Signed by ..... *(authorised person only)* Date ☐☐ ☐☐ ☐☐☐☐ (d m y)

Version 1.1, July 2005

Appendix B.8 Pathology and biological studies

Pathology Review

Please discuss this section with your local pathologist before entering your patients into the trial.

The clinical investigator or his/her designated staff is responsible for securing the co-operation of his/her local pathologist in submitting pathology material to the pathology review panel representative. Guidelines for pathology are given in section 10 of the protocol.

The following steps should be taken immediately after primary surgery:

Clinical Investigator
The clinical investigator sends to the local pathologist: 1. Pathology request letter requesting the submission of the **diagnostic biopsy** and **resected specimen*** 2. Copy of Registration Checklist (Form 1) *if surgery not performed , send diagnostic material only
Local Pathologist
The local pathologist sends to the pathology review panel representative (see following page) all items stated on the pathology request letter, namely: 1. The pathology request letter for ease of identification **Initial Biopsy** 2. Five unstained sections on poly-l-lysine coated slides and one H&E stained section from each block of the initial biopsy 3. A copy of the pathology report in English or language of review pathologist **Resected Specimen** 4. Five unstained sections on poly-l-lysine coated slides and one H&E stained section from each block of the resected tumour 5. A map of the specimen and photograph indicating the site of individual blocks 6. A copy of the pathology report in English or language of review pathologist including margin status and size of tumour in two dimensions
Pathology review panel representative
The pathology review panel representative reviews slides and sends to the MRC CTU: • Diagnostic Biopsy Evaluation Form (Form 10) • Resected Specimen Form (Form 11)

Note: When the local pathologist is a member of the pathology review panel, the pathology registration letter serves as a notification that a particular patient has been entered into the trial. The pathology review panel representative should send the pathology form as appropriate.

Pathology material should be sent as follows:

For:	The Pathology review panel representative is:
Any patient operated on at Royal National Orthopaedic Hospital, Stanmore OR Patients treated at London Southampton Cambridge Oxford Ireland	Adrienne Flanagan Institute of Orthopaedics, Royal National Orthopaedic Hospital, Stanmore Brockley Hill Stanmore Middlesex HA7 4LP UK
Any patient operated on at Royal Orthopaedic Hospital, Woodlands Birmingham OR Patients treated at Birmingham Manchester Nottingham Leeds	V P Sumathi Royal Orthopaedic Hospital Department of Musculoskeletal Pathology Robert Aitken Institute University of Birmingham Medical School Edgbaston Birmingham B15 2TT
Any patient operated on at Newcastle OR Patients treated at Newcastle	Petra Dildey Department of Cellular Pathology Royal Victoria Infirmary Queen Victoria Road Newcastle Upon Tyne NE1 4LP
Any patient operated on in Oswestry	Chas Mangham Robert Jones & Agnes Hunt Orthopaedic & District Hospital NHS Trust Oswestry Shropshire SY10 7AG
Any patient operated on in Scotland OR Patients treated at Glasgow Edinburgh Aberdeen	Robin Reid Osteo-Articular Unit Pathology Department Western Infirmary Glasgow G11 6NT
Any patient operated on in Belgium	Esther Hauben UZ Leuven campus Sint-Rafaël Minderbroedersstraat 12 B - 3000 Leuven Belgium
Any patient operated on in The Netherlands (except Amsterdam Academic Medical Centre)	Pancras Hogendoorn Leiden University Medical Centre Leiden Netherlands

Any patient operated on at the Amsterdam Academic Medical Centre	Dr J Bras Academic Medical Center University of Amsterdam Department of Pathology PO Box 22660 1100 DD Amsterdam, the Netherlands

MRC Clinical Trials Unit

EURAMOS 1: Treatment Strategies in Osteosarcoma
PATHOLOGY REQUEST LETTER

MRC B008
Letter PR

Instructions for the entering clinician: *This Request Letter* ***must*** *be sent to the local pathologist for every registered patient immediately after surgery (if surgery is not performed, send diagnostic material only).*

From: Clinician: ..... Hospital: .....

To: Pathologist: ..... Hospital: .....

Patient details

Patient's Name .....

Patient's ID Initials ☐☐☐☐

Date of birth ☐☐ ☐☐ ☐☐☐☐ (d m y)

Sex Male/Female

Hospital No. .....

Patient's ID No. ☐☐☐☐☐

Dear Dr .....

The above patient has been entered into the EURAMOS 1 study and therefore I would be extremely grateful if you could send to the review pathologist the following:

- This form for ease of identification
- The attached copy of the Registration Form 1

Diagnostic biopsy

- Five unstained sections on poly-l-lysine-coated slides and one H&E stained sectionfrom each block of the initial biopsy
- A copy of the pathology report in English, or language of review pathologist

Resected Specimen

- Five unstained sections on poly-l-lysine-coated slides and one H&E stained sectionfrom each block of the rescted specimen
- A map of teh specimen and photographindicating the site of individual blocks
- A copy of the pathology report in English, or language of review pathologist

Review Pathogist's details:

Thank you very much for your assistance in this matter

Please note: Patient's consent has been obtained for sending the material
All material not processed by the review pathologist will be returned to you, apart from slides.

Biological Studies

For patients who have consented to take part in the biological studies, the following materials should be made available on request:

- Material from the diagnostic biopsy
- Material from the primary tumour resection
- Material from the excision of metastatic disease
- 10 mL EDTA blood sample, taken before treatment begins.

Appendix B.9 Imaging

Overview of Imaging Studies

At presentation

Primary lesion: Radiographs in two planes.
MRI – appropriate long axis (coronal / sagittal / both) and axial imaging of the local lesion, with long axis T1 imaging of the whole bone to exclude skip metastases. Contrast not routinely indicated.
Assessment to include:

- Intraosseous extent – longitudinal / cm
- Extraosseous extent – longitudinal / cm
- Maximum dimensions of mass – sagittal and AP orthogonal planes / cm
- Assess if periosteum breached by tumour
- Epiphyseal extension – distance from articular surface
- Intra-articular extension
- Neurovascular bundle involvement (not involved, abutted, displaced, encased)
- Skip lesions – marrow signal intervening between primary and skip is clearly normal

CT may be diagnostically useful.

Metastases: Chest radiograph
CT chest – helical CT scan, effective slice thickness 5 – 10 mm, but preferably less than 10mm. Imaged using lung and soft tissue windows. Contrast not routinely indicated.
Definition of lung metastases: minimum criteria

- 3 or more lesions measuring 5mm or greater in max diameter
- a single lesion of 10mm or greater in max diameter.

Radioisotope bone scan of entire skeleton. Further investigation of possible bone metastases by radiographs and MRI.

Review of thorax CT scans may undertaken by the trial management group in conjunction with a radiologist (see Appendix A.1 for radiology panel membership). Chest CT scans may be requested for patients registered as having metastatic disease and fulfilling the following criteria.
a) no lesion greater than 1 cm or
b) less than 3 lesions greater than 5 mm.

Prior to surgery

Primary lesion: Radiographs in two planes.
MRI – appropriate long axis (coronal / sagittal / both) and axial imaging of the local lesion, with long axis T1 imaging of the whole bone to exclude skip metastases. Dynamic enhancement patterns may help determine chemotherapy response, but not routinely indicated.

Metastases: Chest radiograph
CT chest (see above)
MRI of metastatic disease for comparison – size / extent

Post-operative period

During post-operative chemotherapy:

Primary lesion: Initial post-op films in two planes to show the entire prosthesis
Repeat radiographs of primary site every 4 months
MRI (titanium implants) +/- ultrasound to study clinically or radiographically suspected local recurrence

Metastases: Chest radiograph every two months
CT chest on development of possible new lesion
Radiographs / MRI / radioisotope bone scan bone to study new symptoms suggesting bone metastasis.

After thoracotomy CT chest at 3 months, then 6 monthly for a minimum of 2 years

After completion of chemotherapy:

Primary lesion: Repeat radiographs of primary site every 4 months (up to 4 years).
MRI (titanium implants) +/- ultrasound to study clinically or radiographically suspected local recurrence

Metastases: Chest radiograph, frequency as per trial protocol, at each clinic visit

- Years 1-2: every 6 weeks – 3 months
- Years 3-4: every 2 – 4 months
- Years 5-10: every 6 months
- Thereafter: every 6 – 12 months according to local practice

CT chest on development of possible new lesion, or to follow previously demonstrated metastases, or after thoracotomy (see above).
Radiographs / MRI / radioisotope bone scan bone to study new symptoms suggesting bone metastasis.

Complete restaging (imaging of primary tumour site, chest CT and radioisotope bone scan) if relapse is detected at any site.

Appendix B.10 Radiotherapy

Surgical removal of all tumour tissue at any site should always be attempted and is the only proven way to achieve local control. In selected cases, however, radiotherapy plays an important role; i.e. when the tumour is unresectable for technical and/or medical reasons, or when the resection margins following surgery are involved judged by histopathological examination. Inadequate resection is defined as intralesional or margins are contaminated.

The patients treated with *post-operative irradiation* should receive a total dose of 56-62 Gy in 2 Gy fractions where margins are microscopically involved, and 64-70 Gy where macroscopic tumour tissue is left behind. For *definitive radiotherapy* of an inoperable osteosarcoma a radiation dose of 70 Gy or more should always be attempted.

Selected institutions may advocate the use of intraoperative electron boost irradiation or brachytherapy by high-dose rate after loading techniques in cases where macroscopic tumour tissues are left behind or where the surgical margins obviously are inadequate.

Practical guidelines for delivery of radiotherapy

Treatment equipment

High-energy photons generated by a linear accelerator should be used to treat deep-seated tumours; with a recommended radiation quality between 5 and 15 MV. If the target volume exceeds to the surface of the *patient*, adequate dose coverage should be obtained using bolus material rather than a mixed beam technique.

A three-dimensional computerised dose planning with inhomogeneity corrections shall be performed based on CT-scans performed on a flat tabletop. The CT-acquisition must cover all organs at risk as well as the entire target volume.

A multiple field technique, with optimal beam entry directions and beam weights, should be applied to obtain a homogenous dose to the PTV while at the same time minimise the dose to organs at risk. Normal tissue sparing should be attempted by field shaping using customised blocks (individually cut) or with a multileaf collimator.

Virtual or conventional simulation procedures are mandatory for all fields. The position of all shielding blocks should be indicated on the simulation films or on BEV-plots as overlays on DDR's.

Treatment verification

- Simulator port films or Beams Eye View-plots (BEV-plots) as overlay on Digital Reconstructed Radiographs (DDR).
- Treatment verification (portfilm or Electronic Portal Imaging (EPI) at the beginning, in the middle, and at the end of the treatment.
- Measurement of entrance dose or other equivalent methods to ensure that the correct calculated dose is given to the patient.
- Radiation treatment charts as well as the dose plan and port films shall be saved.

Abbreviations (Source: ICRU Report 50)
GTV (Gross Tumour Volume) is the gross tumour; either palpable or visible/demonstrable by imaging techniques. Its delineation should preferentially be done in collaboration with a radiologist.

CTV (Clinical Target Volume) contains a demonstrable GTV and/or sub-clinical microscopic malignant disease. Original tumour extension should guide the delineation of CTV. Ideally this should be done in collaboration with the treating surgeon. In axial tumours a safety margin of 2 cm added to GTV should be attempted. For an extremity osteosarcoma a margin of 4-5 cm may be advisable.

PTV (Planning Target Volume) is a geometrical concept defined to select appropriate beam sizes and beam arrangements, taking into considerations the net effect of all the possible geometrical variations. Margins, 0.5-1.0 cm should be added to the CTV to take into account the effects of organ and patient movements and inaccuracies in beam and patient set-up in order to ensure that the prescribed dose is actually absorbed within the CTV.

Fractionation
1.8 - 2.0 Gy/fraction given as 1 fraction per day and 5 fractions per week.
In case of bank holidays or machine breakdowns, the overall treatment time might be extended where the indication is adjuvant, whereas in case of macroscopic tumour tissue compensation by adding an extra fraction (separated by a minimum of 6 hours on a treatment day) should be considered. This may not be appropriate where spinal cord, brachial or lumbar plexus is in the high dose volume

Dose homogeneity
A maximum dose variation within the PTV between 95-105% according to the dose plan should be attempted. Hot spots outside the PTV with a maximum of 110% are acceptable only if total volume is less than 10 cm^3. Moreover, single *hot spots* should not exceed 5 cm^3.

Organs at risk & Tolerance doses for normal tissues
All structures that may be associated with serious late toxicity should be delineated and dose-volume-histograms generated. The following maximum radiation doses should be respected:
Cervical cord (more that 5 cm length) 45 Gy
Cervical cord (less 5 cm) 50 Gy
Brain tissue 60 Gy
Optic nerve/chiasm 50 Gy
Intestine 50 Gy, depending on volume
Liver:
Whole liver 20Gy: If less than ¼ volume is irradiated, 50 Gy
Kidney 20 Gy (> 1/3)
Heart 30 Gy
Lung 20 – 60 Gy depending on volume
Urinary bladder 60 Gy

Chemotherapy during radiotherapy
Chemotherapy can be continued during radiotherapy, *but enhancement of radiation toxicity is likely to occur with several agents and at the radiation doses recommended may result in severe acute and late side effects. This is of particular concern where spinal cord is in the field. High-dose methotrexate should to be avoided during radiotherapy. Adriamycin should be avoided in radiation treatment of axial tumours as intestinal toxicity will be enhanced and this agent will also increase skin toxicity. Concurrent Ifosfamide should be avoided where significant volume of bladder is in the radiation field*

Follow up
The standard guidelines pointed elsewhere in this protocol should be followed. Particular emphasis should be placed on establishing whether a local recurrence, represents an "in field" central relapse or develops outside field or as an "edge" recurrence.

CTC-score / RTOG-score vs. LENT- SOMA guidelines should be used to score normal tissue complication rates.

Quality assurance (QA)
Co-operative group multi-centre clinical trials require means to guarantee uniformity of treatment procedures and QA is a prerequisite to evaluate patients entered from various institutions. A major deviation from the protocol may jeopardise the ability to answer questions addressed in the trial.

Objectives
The aim of this QA part of the protocol is to ensure uniformity of all radiotherapy data for each patient. Specifically, this means:
- To establish a uniform description of the radiation therapy given in terms of volumes, doses and fractionation
- To evaluate compliance with the radiotherapy instructions
- To help enable a correct evaluation of the endpoints in the trial
- To create a platform for evaluation of reactions in healthy tissue, to radiation alone or in combination with the chemotherapy administered.

Elements of the QA
A final treatment evaluation of each single patient after completion of radiotherapy shall be performed. A responsible physicist will check the following parameters:
- Patient immobilisation
- 3D dose planning
- Dose prescription according to ICRU 50 and beam calibrations according to the IAEA Technical Report No. 277 or TRS 398
- Fractionation
- Volumes of GTV, CTV and PTV
- Field data for all fields
- Dose distribution in a transversal plane in or close to the centre of GTV
- Dose distribution in transversal, sagittal and frontal planes in or close to the centre of PTV
- Dose-volume histogram for all defined volumes of interest
- Copy of the treatment chart.

Appendix B.11 Ethical committee

The protocol must have ethics committee approval according to EU and national rules and regulations as described below. Evidence of ethics committee approval must be sent to the MRC CTU before randomising patients.

The patient's consent to participate in the trial should be obtained after a full explanation has been given of the treatment options, including the conventional and generally accepted methods of treatment.

The right of the patient to refuse to participate in the trial without giving reasons must be respected. After the patient has entered the trial, the clinician must remain free to give alternative treatment to that specified in the protocol, at any stage, if he/she feels it to be in the best interest of the patient. However, the reason for doing so should be recorded and the patient will remain within the trial for the purpose of follow-up and data analysis according to the treatment option to which he/she has been allocated. Similarly, the patient must remain free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing his/her further treatment.

Belgium
The Local Research Ethics Committee (LREC) in Gent (coordinating Ethics Committee for Euramos, Belgium) has approved this protocol. The responsible physician in each centre will be responsible for ensuring that this study is conducted in agreement with the Declaration of Helsinki, and that local ethical committee approval is obtained as necessary, taking advice from the decision made by the LREC in Gent. The outline of the randomised study will be explained to the patient/parent and written informed consent will be obtained. Permission to conduct the trial should be obtained from the hospital board where appropriate.

Netherlands
This protocol has been approved by the Central Committee on Research Involving Human Subjects (CCMO) in the Netherlands, and by the Local Research Ethics Committee (LREC) in Leiden. Each participating institution should gain approval from their local ethics committee who may take advice from the decision made by the LREC in Leiden. The patient information sheet must be written for each institution according to local guidelines. Permission to conduct the trial should be obtained from the hospital board where appropriate.

UK
The protocol has Multi-Centre Research Ethics Committee (MREC) approval but must be approved by the Local Research Ethics Committee (LREC) before patients are entered.

A statement of MRC policy on ethical considerations in clinical trials of cancer therapy, including the question of informed consent, is available from the MRC Head Office web site (http://www.mrc.ac.uk). This may be used to give guidance to participating investigators and to accompany applications to LREC.

Appendix B.12 Legal background

Belgium

Each hospital involved in clinical research is responsible for insurance against patient claims. The level of indemnity for non-negligent harm for clinical trial subjects will be decided by the local ethics committee and is a formal part of the ethics committee approval.

Each hospital is responsible for insurance against negligent harm. This applies to all patients regardless of whether or not they are taking part in a clinical trial, provided that the trial has been approved.

Netherlands

The rights of participants of clinical trials are protected by law in the Netherlands (the Medical Research Involving Human Subjects Act)

Each hospital involved in clinical research is responsible for insurance against patient claims. The level of indemnity for non-negligent harm for clinical trial subjects will be decided by the local ethics committee and is a formal part of the ethics committee approval.

Each hospital is responsible for insurance against negligent harm. This applies to all patients regardless of whether or not they are taking part in a clinical trial, provided that the trial has been approved.

UK

The MRC and NHS are both publicly funded bodies and are not allowed to purchase advance insurance to cover indemnity because they are backed by the resources of the Treasury. MRC will give sympathetic consideration to claims for non-negligent harm suffered by a person as a result of trial or other work supported by MRC. This does not extend to liability for non-negligent harm arising from conventional treatment where this is one arm of a trial. MRC acts as its own insurer and does not provide cover for non-negligent harm in advance for participants in MRC-funded studies.

Where studies are carried out in a hospital, the hospital continues to have a duty of care to a patient being treated within the hospital, whether or not the patient is participating in an MRC-supported study. MRC does not accept liability for any breach in the hospital's duty of care, or any negligence on the part of employees of hospitals. This applies whether the hospital is a NHS Trust or not.

Appendix B.13 Consent and Patient Information Sheets

Information sheets for adult patients
- Information sheet for adult patients. Part 1.
- Information sheet for adult patients. Part 2 - Good response.
- Information sheet for adult patients. Part 2 - Poor response

Parent information sheets
- Parent information sheet. Part 1.
- Parent information sheet. Part 2 - Good response.
- Parent information sheet. Part 2 - Poor response.

Information sheets for patients aged 14-15 (Scotland), 14-17 (England, Wales and Northern Ireland).
- Information sheet for patients aged 14-15 (Scotland), 14-17 (England, Wales and Northern Ireland). Part 1
- Information sheet for patients aged 14-15 (Scotland), 14-17 (England, Wales and Northern Ireland). Part 2 - Good response.
- Information sheet for patients aged 14-15 (Scotland), 14-17 (England, Wales and Northern Ireland). Part 2 - Poor response.

Information sheets for children aged 8-13.
- Information sheet for children aged 8-13. Part 1.
- Information sheet for children aged 8-13. Part 2 - Good response.
- Information sheet for children aged 8-13. Part 2 - Poor response.

Information sheet for patients aged under 8 years.

Consent forms for adult patients
- Consent form for adult patients - Part 1
- Consent form for adult patients - Part 2

Parent Consent forms
- Parent Consent form - Part 1.
- Parent Consent form - Part 2

Assent forms for patients aged 14-15 (Scotland), 14-17 (England, Wales and Northern Ireland).
- Assent form for patients aged 14-15 (Scotland), 14-17 (England, Wales and Northern Ireland) - Part 1
- Assent form for patients aged 14-15 (Scotland), 14-17 (England, Wales and Northern Ireland) - Part 2

Assent form for children aged 13 and under.

Sticker charts for children aged under 13
(MRC CTU will provide these charts with stickers)
- Part 1 Sticker chart
- Part 2 MAP sticker chart
- Part 2 MAPIE sticker chart

Figure 1: PEG-Intron Diary Card

GP Information Sheet
- General Practitioner Information Sheet - Part 1
- General Practitioner Information Sheet - Part 2

(to be printed on institution headed paper)

EURAMOS 1: Should chemotherapy for Osteosarcoma be changed after surgery based on the response to pre-operative chemotherapy?

(EURAMOS stands for: **Eu**ropean and **Am**erican **O**steosarcoma **S**tudy group)

Information sheet for adult patients. Part 1.

(Version No. 5.0 December 2008)

Chief Investigator: Dr Jeremy Whelan

Local Investigator:

You are being invited to take part in a research study, also called a clinical trial. This information leaflet explains what the study is all about.

Before you decide whether or not to take part it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Thank you for taking the time to read this information sheet.

1. What is the purpose of the study

You have recently been diagnosed with a rare type of bone cancer called an osteosarcoma. The standard treatment for patients with osteosarcoma is:

- MAP chemotherapy for about 10 weeks, then
- surgery, then
- MAP chemotherapy for another 18 weeks.

MAP stands for **m**ethotrexate, doxorubicin (also called **a**driamycin) and cis**p**latin.

We know that these drugs work well for many people with osteosarcoma. We are always trying to find ways to improve treatment, and to make the treatment work better for more people.

When the tumour is removed at surgery, it is possible to see how well the chemotherapy given before surgery had worked. Patients with a good response (over 90% of the tumour is killed) have a better chance of the tumour not returning than those with a poorer response (90% or less of the tumour is killed).

For patients with a poorer response to chemotherapy, we would like to see if their treatment is improved by adding extra chemotherapy drugs.

For patients with a good response, we would like to see if their treatment can be improved by giving interferon (a biological treatment) after chemotherapy has finished. Interferon is produced naturally in the body, but has been found to be an effective treatment for some cancers. The exact way interferon works is not known. It may directly kill cancer cells, or it may interfere with the blood supply to the tumour, or it may increase the response of the patient's immune system (the system that recognises and destroys "foreign" cells). We do not know if giving interferon will increase the chance of cure for patients with osteosarcoma.

2. Why have I been chosen?

Around 2000 patients will be taking part in *EURAMOS 1*, throughout the UK, Europe and America. All patients diagnosed with osteosarcoma in the participating hospitals are being invited to take part in the trial.

3. Do I have to take part?

It is up to you to decide whether or not to take part in the study. If you decide that you want to take part in this study you can keep this information sheet, and you will be asked to sign a consent form. You are still free to withdraw from the study at any time without giving a reason. A decision not to take part, or later to withdraw, will not affect the standard of care you receive.

4. What will happen to me if I take part?

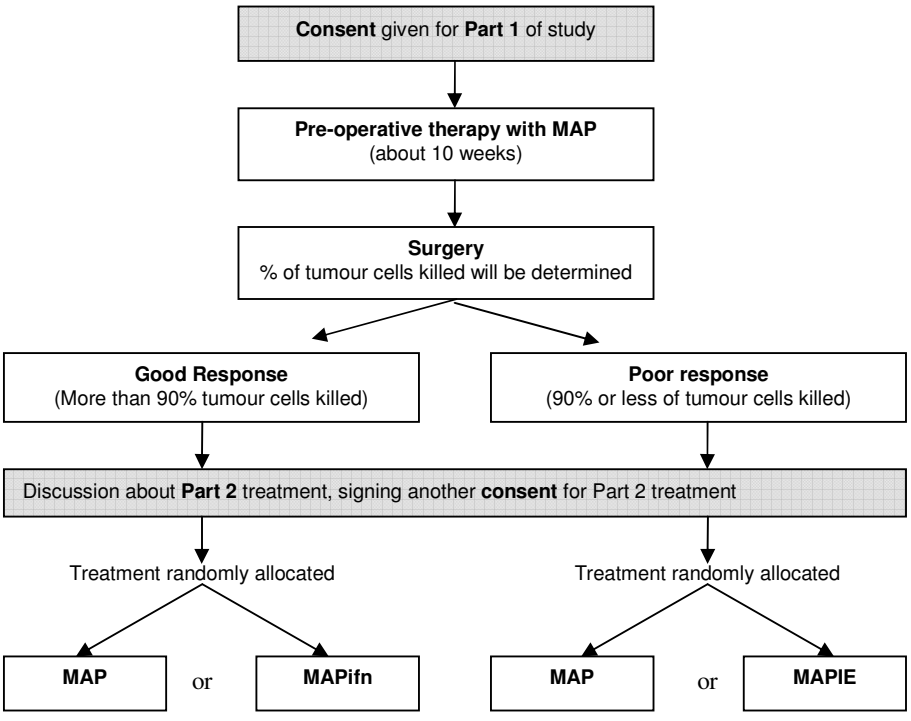
All patients who take part in this study will begin treatment with the standard 10 weeks of MAP chemotherapy, followed by surgery to remove the tumour(s).

After your operation, the tumour tissue will be looked at under a microscope to find out how many of the tumour cells have been killed. If more than 90% of the tumour cells have been killed, this will be called a good response. If 90% or less of the tumour cells have been killed, this will be called a poor response.

Your chemotherapy will restart after surgery before it is known whether you have a good or poor response, because it normally takes a few weeks to get these results. Your doctor will discuss these results with you and check you are still happy to take part in the study. The therapy you will get after surgery will depend on whether you have a good or a poor response, and then will depend on randomisation to one of two different treatments for each type of response.

Randomisation means that you are being put into a group by chance. The group you are put in is done by a computer. Neither you nor your doctor will choose which group you will be put in. You will have an equal chance of being placed in either group. Your doctor will discuss the treatments with you. You will be asked to sign another consent form for the second part of treatment.

Here is the treatment plan for the entire study:



MAP = **m**ethotrexate, doxorubicin (**a**driamycin), cis**p**latin, (the same chemotherapy as before surgery)
MAPifn = **m**ethotrexate, doxorubicin (**a**driamycin), cis**p**latin with the addition of interferon
MAPIE = **m**ethotrexate, doxorubicin (**a**driamycin), cis**p**latin with the addition of **i**fosfamide and **e**toposide

5. What will treatment involve?

The drugs for pre-operative therapy for this study are given in this way:

M = **M**ethotrexate*
Given by IV over 4 hours

A = Doxorubicin (also called **A**driamycin)
Given by IV over 48 hours

P = Cis**p**latin
Given by IV over 72 hours or by IV over 4 hours for 2 days.
These 2 methods for giving **P** have the same dose and are equally effective. Your doctor will give **P** by the method used in your hospital.

All the chemotherapy drugs will be given using a needle inserted into a vein (**intravenous or IV**). Other drugs may be given to you by tablet or liquid through the mouth (**oral**), or using a needle inserted under the skin (**subcutaneous or SC**).

Week	Day						
	1	2	3	4	5	6	7
1	AP	AP	(P)				
2							
3							
4	M						
5	M						
6	AP	AP	(P)				
7							
8							
9	M						
10	M						
11	Surgery						

***Note:** If surgery is delayed, you may get more methotrexate before surgery. If you have difficulty recovering from the effects of the methotrexate therapy you may only have methotrexate two or three times before surgery instead of four times.

Central Line

For drugs to be given by vein, your doctor will likely recommend that you have a central venous line placed. This is used to administer chemotherapy drugs and to withdraw small amounts of blood for testing during treatment. A central venous line is a type of tubing put into a large vein inside the chest by a surgeon or radiologist during a short operation. You will be anaesthetised for this procedure and get pain medication afterwards to keep you comfortable. You will be given more information about this by the doctors and nurses looking after you.

Standard Medical Tests

If you take part in this study, you will have tests that are part of regular cancer care and may be done even if you do not join in this study. These tests include blood tests, urine tests, heart and hearing tests, chest X-rays, nuclear medicine studies, CT and MRI scans.

Surgery

Surgery is a standard part of osteosarcoma treatment, which you will have even if you do not take part in this study. You will be given more information about this by your surgeon.

Some of the tissue already taken to make your diagnosis will be sent to a central review centre as part of the quality control of the study. There will also be central review of the slides used to find out how many cancer cells have been killed after the pre-operative therapy with MAP.

6. Additional Research

Biology Studies

When you have had surgery, specimens from your cancer will be stored in the hospital pathology laboratory. If you take part in the EURAMOS 1 study, we would like to ask your permission to retrieve some of that stored material in the future, for osteosarcoma research. This research is based in UK and European Universities and is only carried out after review by an independent ethics committee. It involves extracting DNA or other chemicals from the tumour to see whether it is possible to predict which patients will benefit most from each treatment. We would also like your permission to take a blood sample of 10 mL (about 2 teaspoons full) which will be used to help this research. All work is coded. Your specimens will be identified by a number, not by your name. You will not be identified or contacted. These studies will not affect your treatment in any way, and you are free to withhold this permission without affecting your participation in EURAMOS 1 or your relationship with your doctor.

Quality of Life questionnaire

As part of this study we think it is important to find out more about how patients feel both physically and emotionally during and after different treatments. In order to collect this information, brief questionnaires have been designed for you to complete. We would like you to complete questionnaires at 5 weeks, 6 months, 18 months and 3 years after you first started treatment. You can, of course, decline to complete the questionnaire at any time without affecting your relationship with your doctor.

7. How long will I be on this study?

The first part of the study will last for about 11 weeks: 10 weeks of chemotherapy followed by surgery.

If you decide to take part in this second part of the study, we think that treatment will last in total for about:

- 7 months if randomised to MAP
- 10 months if randomised to MAPIE
- 7 months for the MAP chemotherapy plus a further 17 months of therapy with weekly interferon injections if randomised to MAPifn.

However, all patients will continue to have regular check-ups and blood tests for a few years after treatment so that researchers can continue to observe any effects of treatment. In addition, we would like to continue to collect some information about how you are doing for as long as you allow us.

The researchers may decide to take you off the study if the cancer gets worse or you experience side effects from the treatment that are considered too severe.

8. What are the alternatives for treatment?

Patients who do not want to take part in this study will receive the standard treatment with MAP chemotherapy as outlined earlier.

9. What are the side effects of the proposed treatments?

All chemotherapy has side effects. The doctors and nurses looking after you will discuss these with you in more detail. They include hair loss, loss of appetite, nausea (feeling sick), vomiting, a sore mouth, tiredness, risk of infection, and risk of bleeding associated with low platelets. Many of these side effects can be controlled with drugs and your doctors and nurses will talk to you about how you can help prevent some of these side effects.

If you get an infection between courses of chemotherapy, you will need to receive antibiotic treatment in hospital. Blood and platelet transfusions can also be given when necessary. Hair loss is unfortunately inevitable but the hospital can help by providing you with a wig if you wish. Your hair will start to grow back as soon as your chemotherapy has finished.

Some of the individual drugs have additional side effects. Doxorubicin can cause damage to the heart in a small number of patients. To prevent this happening, the total dose of this drug is limited. Simple heart scans will also be done throughout your treatment so that if any changes are seen, further preventative action can be taken.

Cisplatin and methotrexate can cause damage to the kidneys. To prevent this happening, extra fluids are given with these drugs to help 'flush' them through the kidneys. You will be encouraged to drink plenty of water during your treatment. Blood tests to monitor your kidney function will be taken throughout your treatment, and adjustments will be made to your chemotherapy if necessary.

Cisplatin can cause changes in hearing. For example you may lose the ability to hear some high pitched sounds, and some patients may experience tinnitus (ringing in the ears) whilst on treatment. This usually improves when treatment is finished. You should tell your doctor if you notice changes in your hearing.

Methotrexate can cause liver irritation or damage which usually resolves a few days after its administration. Very occasionally patients receiving high dose methotrexate get a temporary rash on the soles of their feet or palms of their hands. If this occurs the doctors can prescribe anti-histamines (drugs used for allergies) to help control the rash.

As with many chemotherapy treatments it is possible that the drugs could damage an unborn child and therefore women should not become pregnant during treatment. Men should also avoid unprotected sexual intercourse whilst on treatment since the drugs could damage the sperm. For men and women there is a risk that the treatment could result in infertility. Your doctor will talk to you more about this.

As part of the chemotherapy after your operation you might also receive ifosfamide and etoposide, or interferon. Side effects of etoposide and ifosfamide are similar to MAP side effects, but some may occur more frequently, particularly infection and kidney damage. You will be monitored closely for these problems. In addition, ifosfamide can occasionally cause drowsiness or confusion in a small number of patients. Interferon may cause fever, nausea and flu-like symptoms for a few hours after the injection, and sometimes it can leave you tired and feeling down. Other side-effects associated with interferon include sleeping problems, thinning of the hair, reaction at the injection site, and less commonly decreased vision, changes in thyroid function and elevation of fats (triglycerides) in the blood.

10. What are the possible disadvantages and risks of taking part?

All cancer treatment is associated with side effects such as those described above, including potentially life-threatening problems such as infection.

11. Is this trial as safe as standard treatment?

Yes. All of these drugs have been used for patients with cancer or other diseases for a number of years. The aim of this study is not to test new drugs, but to see whether existing drugs can be given in a better way.

12. What are the possible benefits of taking part?

We hope that the treatment will help you. However, this is not certain. The information we get from this study may help us to treat future patients with osteosarcoma better, in just the same way that current treatment has been designed using information gained from previous clinical trials. We do not know whether any of the treatments described here will be better than the standard treatment in the long run.

13. What if new information becomes available?

Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. If this happens, your doctor will tell you about it and discuss with you whether you want to continue in the study. If you decide to withdraw, your doctor will make arrangements for your treatment to continue according to the best available information at the time. If you decide to continue in the study you will be asked to sign another consent form.

It is also possible that on receiving new information about treatment your doctor might consider it to be in your best interest to withdraw from the study. He/she will explain the reasons and arrange for your care to continue.

14. What happens when the research study stops?

If for any reason the research study stops, or the treatment programme needs to be changed, the reasons will be explained. Arrangements will be made for you to continue treatment according the best available information at the time.

15. What if something goes wrong?

If you are harmed as a result of your participation in this trial due to someone's negligence, then you may have grounds for legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms are available to you. Your hospital continues to have a duty of care to you as a patient being treated within the hospital whether in a trial or not.

If you are harmed as result of your participation in this study, and this is not due to negligence, the Medical Research Council would sympathetically consider any claim for compensation.

16. Will taking part in this study be kept confidential?

If you participate in EURAMOS 1, information about you will be passed to the three trials offices managing the data. The Medical Research Council Clinical Trials Unit (MRC CTU), London, are managing the main database for the study; Quality of Life questionnaires are managed by Düsseldorf University Children's Hospital, Germany; and any serious side effects are reported to regulatory agencies through University Hospital of Münster, Germany, who are managing safety information for the study. Schering Plough who are supplying interferon for the study, will be notified about any serious side effects of interferon. In each case, the forms contain little identifying information about you. Where possible, only a code number is used. Each of these units is registered under the Data Protection Act (or equivalent national laws) to hold such information on a confidential basis.

Occasionally staff from the MRC CTU or regulatory authorities will need to visit the hospital to review your notes to check that the information being provided is correct. Your GP, and the other doctors involved in your care, will be kept fully informed, but otherwise all information about you and your treatment will remain completely confidential. We will register your participation with the National Health Service Central Register (NHSCR) or similar systems. This is so we can check your health status after the trial has closed or in the event that you lose touch with your study doctor.

17. What will happen to the results of the research study?

When the trial is complete the results will be published in a medical journal, and may be presented at conferences. No individual patients will be identified.

18. Who is organising and funding the research?

In the UK this research is being organised by the National Cancer Research Institute, funded jointly by Cancer Research UK, the MRC and the NHS, and is being run together with the UK Medical Research Council Clinical Trials Unit. The research has been reviewed by those organisations, and also by an independent NHS Research Ethics Committee. Your doctor will not receive any payment for including you in this study.

All research that involves NHS patients or staff, information from NHS medical records or uses NHS premises or facilities must be approved by a NHS Research Ethics Committee before it goes ahead. Approval does not guarantee that you will not come to any harm if you take part. However approval means that the Committee is satisfied that your rights will be respected, that any risks have been reduced to a minimum and balanced against possible benefits, and that you have been given sufficient information on which to make an informed decision to take part or not.

This study is being run in collaboration with the European Osteosarcoma Intergroup (UK and Europe), the Co-operative Osteosarcoma Study Group (Europe), the Scandinavian Sarcoma Group and the North American Children’s Oncology Group.

19. Contact for Further Information

If you have any further questions about your disease or clinical trials, please discuss them with your doctor. You may also find it helpful to contact Cancerbackup, an independent patient advisory group (freephone: 0808 800 1234; address: 3 Bath Place, Rivington Street, London, EC2A 3JR; web site www.Cancerbackup.org.uk).

If you would like to see a copy of the information sheets for part 2 of this study, please ask us.

If you have private medical insurance we recommend that you contact your health insurance company about participation before agreeing to take part.

20. Local contact names and telephone numbers:

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21. What if I have any concerns?

If you have any concerns or other questions about this study or the way it has been carried out, you should contact the investigator (name), or you may contact the hospital (name) complaints department.

(to be printed on institution headed paper)

EURAMOS 1: Should chemotherapy for Osteosarcoma be changed after surgery based on the response to pre-operative chemotherapy?

(EURAMOS stands for: **Eur**opean and **Am**erican **O**steosarcoma **S**tudy group)

Information sheet for adult patients. Part 2 - Good response.

(Version No. 5.0 December 2008)

Chief Investigator: Dr Jeremy Whelan

Local Investigator:

1. What is part 2 of the study about?

Now that you have completed the first part of therapy (pre-operative chemotherapy, surgery, and evaluation) you are being asked to take part in this second part of the study.

Because you have had a good response to the pre-operative chemotherapy (more than 90% of the tumour cells have been killed) you are eligible for more MAP chemotherapy or MAP chemotherapy plus interferon (a biological therapy).

Before you decide whether or not to continue in the study it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully. Discuss it with others if you wish and if anything is not clear, or if you would like more information, don't hesitate to ask us. Take time to decide whether or not you wish to take part.

Thank you for taking the time to read this information sheet.

2. What is the purpose of Part 2 of the study?

For patients who have had a good response with standard MAP chemotherapy, continuing with MAP therapy should result in a good outcome. Researchers would like to know if adding interferon, (a biological therapy) after the MAP therapy is complete, will help make sure the tumour cells do not return later. This study will use pegylated interferon alpha-2b, interferon that has been modified to last longer in the body so it can be given less often.

3. How many people will take part in this study?

Nearly 600 patients will be participating in this part of the trial.

4. Do I have to continue to take part in this study?

It is up to you to decide whether or not to continue to take part in this study. If you do decide to continue you can keep this information sheet, and will be asked to sign a consent form allowing us to allocate your treatment by computer (randomisation). If you decide to continue to take part you are still free to withdraw from the study at any time without giving a reason. A decision not to take part, or later to withdraw, will not affect the standard of care you receive.

5. What will happen to me if I take part?

You will be assigned to one of the two treatments for good responders by randomisation. *Randomisation means that you are being put into a group by chance. The group you are put in is done by a computer. Neither you nor your doctor will choose which group you will be put in. You will have an equal chance of being placed in either group*. You will be randomised to get either standard treatment with MAP **or** treatment with MAP followed by pegylated interferon alpha-2b (MAPifn) when the chemotherapy is finished.

6. What will the treatment involve?

Both **MAP** and **MAPifn** groups will receive the same MAP chemotherapy. The drugs for the study are given in this way (the treatment weeks start at week 12 – first week of chemotherapy after surgery):

M = **M**ethotrexate
Given by IV over 4 hours

A = Doxorubicin (also called **A**driamycin)
Given by IV over 48 hours

P = Cis**p**latin
Given by IV over 72 hours or by IV over 4 hours for 2 days.
These 2 methods for giving **P** have the same dose and are equally effective. Your doctor will give **P** by the method used in your hospital

All the chemotherapy drugs will be given using a needle inserted into a vein (**intravenous or IV**). Other drugs may be given to you by tablet or liquid through the mouth (**oral**), or using a needle inserted under the skin (**subcutaneous or SC**).

Week	Day						
	1	2	3	4	5	6	7
12	AP	AP	(P)				
13							
14							
15	M						
16	M						
17	AP	AP	(P)				
18							
19							
20	M						
21	M						
22	A	A					
23							
24	M						
25	M						
26	A	A					
27							
28	M						
29	M						

MAP group: Treatment will stop when chemotherapy finishes

MAPifn group: Pegylated interferon alpha-2b – SC injection (Day 1 of each week) starting at Week 30, continuing for 17 months**.**

Standard Medical Tests

If you take part in this study, you will continue to have the tests that are part of regular cancer care and may be done even if you do not join in this study. These tests include blood tests, urine tests, heart and hearing tests, chest X-rays, nuclear medicine studies, CT and MRI scans.

Extra Medical Tests

If you take part in this study and you are randomised to receive MAPifn, you will need some extra blood tests to check your pancreatic and thyroid function and the levels of fat (triglycerides) in your blood. Additionally, your eyes will be examined. You will have these extra tests every two weeks for the first eight weeks of your treatment with interferon and every 1-2 months thereafter.

7. How long will I be on this study?

If you decide to take part in this second part of the study, we think that treatment will last for about:

- 5 months if in MAP group (a total of 7 months including pre-operative chemotherapy)
- 5 months for the MAP chemotherapy (a total of 7 months including pre-operative chemotherapy), plus a further 17 months of therapy with weekly interferon if in MAPifn group (a total of 2 years treatment).

However, you will continue to have regular check ups and blood tests for a few years after treatment so that researchers can continue to observe any effects of treatment. In addition, we would like to continue to collect some information about how you are doing for as long as you allow us.

The researchers may decide to take you off the study if the cancer gets worse or you experience side effects from the treatment that are considered too severe.

8. What are the alternatives for treatment?

Patients who do not want to take part in this study will receive the standard treatment with 5 months of MAP chemotherapy (a total of 7 months including pre-operative chemotherapy), as outlined above.

9. What are the side effects of the proposed treatment?

The side effects of chemotherapy are the same as you experienced with the treatment given before surgery.

Interferon is not a type of chemotherapy. It is a protein found naturally in the body. However, when 'additional' interferon is given, it does cause side effects, although these are not as severe as those associated with chemotherapy. It must be given as a weekly SC (under the skin) injection. The side effects include fever, nausea and flu-like symptoms for a few hours after the injection (although if this occurs it is likely to improve after the first few injections), fatigue and occasionally feelings of depression. Other side-effects associated with interferon include sleeping problems, thinning of the hair, reaction at the injection site, and less commonly decreased vision, changes in thyroid function and elevation of fats (triglycerides) in the blood.

It is important to let your doctors and nurses know about any side effects so that steps can be taken to minimise any symptoms you may experience.

10. What are the risks of taking part?

All cancer treatment is associated with side effects as described, including potentially life-threatening problems such as infection. If you are in the MAPifn group you would receive more treatment than the standard MAP treatment.

11. Are there any benefits?

We do not know whether adding interferon to the standard treatment will be better than the standard treatment in the long run. There may be differences in tumour control, or long term side effects. The information we get from this study may help us to treat future patients with osteosarcoma better.

12. What if new information becomes available?

Sometimes during the course of a research project, new information becomes available about the treatment/drug that is being studied. If this happens, your doctor will tell you about it and discuss with you whether you want to continue in the study. If you decide to withdraw, your doctor will make arrangements for your treatment to continue according the best available information at the time. If you decide to continue in the study you will be asked to sign an updated consent form.

It is also possible that on receiving new information about treatment your doctor might consider it to be in your best interests to withdraw from the study. He/she will explain the reasons and arrange for your care to continue.

13. What happens when the research study stops?

If for any reason the research study stops, or the treatment programme needs to be changed, the reasons will be explained. Arrangements will be made for you to continue treatment according the best available information at the time.

14. What if something goes wrong?

If you are harmed as a result of your participation in this trial due to someone's negligence, then you may have grounds for legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms are available to you. Your hospital continues to have a duty of care to you as a patient being treated within the hospital whether in a trial or not.

If you are harmed as result of your participation in this study, and this is not due to negligence, the Medical Research Council would sympathetically consider any claim for compensation.

15. Will taking part in this study be kept confidential?

If you participate in EURAMOS 1, information about you will be passed to the three trials offices managing the data. The Medical Research Council Clinical Trials Unit (MRC CTU), London, are managing the main database for the study; Quality of Life questionnaires are managed by Düsseldorf University Children's Hospital, Germany; and any serious side effects are reported to regulatory agencies through University Hospital of Münster, Germany, who are managing safety information for the study. Schering Plough who are supplying interferon for the study, will be notified about any serious side effects of interferon. In each case, the forms contain little identifying information about you. Where possible, only a code number is used. Each of these units is registered under the Data Protection Act (or equivalent national laws) to hold such information on a confidential basis.

Occasionally staff from the MRC CTU or regulatory authorities will need to visit the hospital to review your notes to check that the information being provided is correct. Your GP, and the other doctors involved in your care, will be kept fully informed, but otherwise all information about you and your treatment will remain completely confidential. We will register your participation with the National Health Service Central Register (NHSCR) or similar systems. This is so we can check your health status after the trial has closed or in the event that you lose touch with your study doctor.

16. What will happen to the results of the research study?

When the trial is complete the results will be published in a medical journal, and may be presented at conferences. No individual patients will be identified.

17. Who is organising and funding the research?

In the UK this research is being organised by the National Cancer Research Institute, funded jointly by Cancer Research UK, the MRC and the NHS, and is being run together with the UK Medical Research Council Clinical Trials Unit. The research has been reviewed by those organisations, and also by an independent NHS Research Ethics Committee. Your doctor will not receive any payment for including you in this study.

All research that involves NHS patients or staff, information from NHS medical records or uses NHS premises or facilities must be approved by a NHS Research Ethics Committee before it goes ahead. Approval does not guarantee that you will not come to any harm if you take part However approval means that the Committee is satisfied that your rights will be respected, that any risks have been reduced to a minimum and balanced against possible benefits, and that you have been given sufficient information on which to make an informed decision to take part or not.

This study is being run in collaboration with the European Osteosarcoma Intergroup (UK and Europe), the Co-operative Osteosarcoma Study Group (Europe), the Scandinavian Sarcoma Group and the North American Children's Oncology Group.

18. Contact for Further Information

If you have any further questions about your disease or clinical trials, please discuss them with your doctor. You may also find it helpful to contact Cancerbackup, an independent patient advisory group (freephone: 0808 800 1234; address: 3 Bath Place, Rivington Street, London, EC2A 3JR; web site www.Cancerbackup.org.uk).

If you would like to see a copy of the first patient information sheet for this study again, please ask us.

19. Local contact names and telephone numbers:

……

……

20. What if I have any concerns?

If you have any concerns or other questions about this study or the way it has been carried out, you should contact the investigator (name), or you may contact the hospital (name) complaints department.

(to be printed on institution headed paper)

EURAMOS 1: Should chemotherapy for Osteosarcoma be changed after surgery based on the response to pre-operative chemotherapy?

(EURAMOS stands for: **Eur**opean and **Am**erican **O**steosarcoma **S**tudy group)

Information sheet for adult patients. Part 2 - Poor response.

(Version No. 5.0 December 2008)

Chief Investigator: Dr Jeremy Whelan

Local Investigator:

1. What is part 2 of the study about?

Now that you have completed the first part of therapy (pre-operative chemotherapy, surgery, and evaluation) you are being asked to take part in this second part of the study.

Because you have had 90% or less tumour response to the pre-operative MAP chemotherapy you are eligible for more MAP chemotherapy, or MAP chemotherapy plus ifosfamide and etoposide (MAPIE).

Before you decide whether or not to continue in the study it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully. Discuss it with others if you wish and if anything is not clear, or if you would like more information, don't hesitate to ask us. Take time to decide whether or not you wish to take part.

Thank you for taking the time to read this information sheet.

2. What is the purpose of Part 2 of the study?

For patients who have had 90% or less tumour response with standard MAP chemotherapy before surgery, continuing with MAP therapy after surgery should result in a good outcome. Researchers would like to know if adding two other commonly used chemotherapy drugs (ifosfamide and etoposide) to the MAP will result in a better outcome and lessen the chances further of the disease returning later.

3. How many people will take part in this study?

Nearly 700 patients will be participating in this part of the trial.

4. Do I have to continue to take part in this study?

It is up to you to decide whether or not to continue to take part in this study. If you do decide to continue you can keep this information sheet, and you will be asked to sign a consent form allowing us to allocate you treatment by computer (randomisation). If you decide to continue to take part you are still free to withdraw from the study at any time without giving a reason. A decision not to take part, or later to withdraw, will not affect the standard of care you receive.

5. What will happen to me if I take part?

You will be assigned to one of the two treatments by randomisation. *Randomisation means that you are being put into a group by chance. The group you are put in is done by a computer. Neither you nor your doctor will choose which group you will be put in. You will have an equal chance of being placed in either group*. You will be randomised to get continued standard treatment with MAP **or** treatment with MAP and the addition of ifosfamide and etoposide (MAPIE).

6. What will the treatment involve?

The drugs for the study are given in this way (the treatment starts at week 12 – first week of chemotherapy after surgery):

MAP							
Week	Day						
	1	2	3	4	5	6	7
12	AP	AP	(P)				
13							
14							
15	M						
16	M						
17	AP	AP	(P)				
18							
19							
20	M						
21	M						
22	A	A					
23							
24	M						
25	M						
26	A	A					
27							
28	M						
29	M						

M = **M**ethotrexate
Given by IV over 4 hours

A = Doxorubicin (also called **A**driamycin)
Given by IV over 48 hours

P = Cis**p**latin
Given by IV over 72 hours
or by IV over 4 hours (for 2 days)
These 2 methods for giving **P** have the same dose and are equally effective. Your doctor will give **P** by the method used in your hospital

I = **I**fosfamide
Given by IV over 4 hours

E = **E**toposide
Given by IV over 1 hour

MAPIE							
Week	Day						
	1	2	3	4	5	6	7
12	AP	AP	(P)				
13							
14							
15	M						
16	IE	IE	IE	IE	IE		
17							
18							
19	M						
20	AI	AI	I				
21							
22							
23	M						
24	IE	IE	IE	IE	IE		
25							
26							
27	M						
28	AP	AP	(P)				
29							
30							
31	M						
32	IE	IE	IE	IE	IE		
33							
34							
35	M						
36	AI	AI	I				
37							
38							
39	M						
40	M						

All the chemotherapy drugs will be given using a needle inserted into a vein (**intravenous or IV**). Other drugs may be given to you by tablet or liquid through the mouth (**oral**), or using a needle inserted under the skin (**subcutaneous or SC**).

<u>Standard Medical Tests</u>

If you take part in this study, you will continue to have tests that are part of regular cancer care and may be done even if you do not join in this study. These tests include blood tests, heart and hearing tests, urine tests, chest X-rays, nuclear medicine studies, and CT and MRI scans.

7. How long will I be on this study?

If you take part in this second part of the study, we think that treatment will last for about:

- 5 months if randomised to **MAP** (a total of 7 months including pre-operative treatment)
- 7 months if randomised to **MAPIE** (a total of 9 months including pre-operative treatment)

However, patients will continue to have regular check-ups and blood tests for a few years after treatment so that researchers can continue to observe any effects of treatment. In addition, we would like to continue to collect some information about how you are doing for as long as you allow us.

The researchers may decide to take you off the study if your cancer gets worse or you experience side effects from the treatment that are considered too severe.

8. What are the alternatives for treatment?

Patients who do not want to take part in this study will receive the standard treatment with a further 18 weeks of MAP chemotherapy (the same treatment as the MAP group), as outlined above.

9. What are the side effects of the proposed treatment?

The side effects of MAP chemotherapy are the same as you experienced with the treatment given before surgery.

The side effects of ifosfamide and etoposide are similar to those you will have experienced with your pre-operative chemotherapy but some side effects may occur more frequently, particularly infections and kidney damage. You will be closely monitored for these problems. In addition, Ifosfamide can occasionally cause drowsiness or confusion in a small number of patients. Slowing down the rate of the infusion can usually help this side effect, but occasionally other medication may be needed if symptoms persist.

It is important to let your doctors and nurses know about any side effects so that steps can be taken to minimise any symptoms you may experience.

10. What are the risks of taking part?

All cancer treatment is associated with side effects as described, including potentially life-threatening problems such as infection. If you are in the MAPIE group you will receive more treatment than with standard MAP treatment.

11. Are there any benefits?

We do not know whether adding ifosfamide and etoposide to the standard treatment will be better than the standard treatment in the long run. There may be differences in control of the tumour, or long term side effects. The information we get from this study may help us to treat future patients with osteosarcoma better.

12. What if new information becomes available?

Sometimes during the course of a research project, new information becomes available about the treatment/drug that is being studied. If this happens, your doctor will tell you about it and discuss with you whether you want to continue in the study. If you decide to withdraw, your doctor will make arrangements for your treatment to continue according the best available information at the time. If you decide to continue in the study you will be asked to sign an updated consent form.

It is also possible that on receiving new information about treatment your doctor might consider it to be in your best interest to withdraw from the study. He/she will explain the reasons and arrange for your care to continue.

13. What happens when the research study stops?

If for any reason the research study stops, or the treatment programme needs to be changed, the reasons will be explained. Arrangements will be made for you to continue treatment according the best available information at the time.

14. What if something goes wrong?

If you are harmed as a result of your participation in this trial due to someone's negligence, then you may have grounds for legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms are available to you. Your hospital continues to have a duty of care to you as a patient being treated within the hospital whether in a trial or not.

If you are harmed as result of your participation in this study, and this is not due to negligence, the Medical Research Council would sympathetically consider any claim for compensation.

15. Will taking part in this study be kept confidential?

If you participate in EURAMOS 1, information about you will be passed to the three trials offices managing the data. The Medical Research Council Clinical Trials Unit (MRC CTU), London, are managing the main database for the study; Quality of Life questionnaires are managed by Düsseldorf University Children's Hospital, Germany; and any serious side effects are reported to regulatory agencies through University Hospital of Münster, Germany, who are managing safety information for the study. Schering Plough who are supplying interferon for the study, will be notified about any serious side effects of interferon. In each case, the forms contain little identifying information about you. Where possible, only a code number is used. Each of these units is registered under the Data Protection Act (or equivalent national laws) to hold such information on a confidential basis.

Occasionally staff from the MRC CTU or regulatory authorities will need to visit the hospital to review your notes to check that the information being provided is correct. Your GP, and the other doctors involved in your care, will be kept fully informed, but otherwise all information about you and your treatment will remain completely confidential. We will register your participation with the National Health Service Central Register (NHSCR) or similar systems. This is so we can check your health status after the trial has closed or in the event that you lose touch with your study doctor.

16. What will happen to the results of the research study?

When the trial is complete the results will be published in a medical journal, and may be presented at conferences. No individual patients will be identified.

17. Who is organising and funding the research?

In the UK this research is being organised by the National Cancer Research Institute, funded jointly by Cancer Research UK, the MRC and the NHS, and is being run together with the UK Medical Research Council Clinical Trials Unit. The research has been reviewed by those organisations, and also by an independent NHS Research Ethics Committee. Your doctor will not receive any payment for including you in this study.

All research that involves NHS patients or staff, information from NHS medical records or uses NHS premises or facilities must be approved by a NHS Research Ethics Committee before it goes ahead. Approval does not guarantee that you will not come to any harm if you take part However approval means that the Committee is satisfied that your rights will be respected, that any risks have been reduced to a minimum and balanced against possible benefits, and that you have been given sufficient information on which to make an informed decision to take part or not.

This study is being run in collaboration with the European Osteosarcoma Intergroup (UK and Europe), the Co-operative Osteosarcoma Study Group (Europe), the Scandinavian Sarcoma Group and the North American Children's Oncology Group.

18. Contact for Further Information

If you have any further questions about your child's disease or clinical trials, please discuss them with your doctor. You may also find it helpful to contact Cancerbackup, an independent patient advisory group (freephone: 0808 800 1234; address: 3 Bath Place, Rivington Street, London, EC2A 3JR; web site www.Cancerbackup.org.uk).

If you would like to see a copy of the first patient information sheet for this study again, please ask your doctor.

19. Local contact names and telephone numbers:

……

……

20. What if I have any concerns?

If you have any concerns or other questions about this study or the way it has been carried out, you should contact the investigator (name), or you may contact the hospital (name) complaints department

(to be printed on institution headed paper)

EURAMOS 1: Should chemotherapy for Osteosarcoma be changed after surgery based on the response to pre-operative chemotherapy?

(EURAMOS stands for: **Eur**opean and **Am**erican **O**steosarcoma **S**tudy group)

Information sheet for Parents. Part 1.
(Version No. 5.0 December 2008)

Chief Investigator: Dr Jeremy Whelan

Local Investigator:

Your child is being invited to take part in a research study, also called a clinical trial. This information leaflet explains what the study is all about.

Before you and your child decide whether or not to take part it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part. Separate information sheets are available for children aged over 14 years, aged 8-13 and under 8 years (designed to be read to the child).

Thank you for taking the time to read this information sheet.

1. What is the purpose of the study

Your child has recently been diagnosed with a rare type of bone cancer called an osteosarcoma. The standard treatment for patients with osteosarcoma is:

- MAP chemotherapy for about 10 weeks, then
- surgery, then
- MAP chemotherapy for another 18 weeks.

MAP stands for **m**ethotrexate, doxorubicin (also called **a**driamycin) and cis**p**latin.

We know that these drugs work well for many people with osteosarcoma. We are always trying to find ways to improve treatment, and to make the treatment work better for more people.

When the tumour is removed at surgery, it is possible to see how well the chemotherapy given before surgery had worked. Patients with a good response (over 90% of the tumour is killed) have a better chance of the tumour not returning than those with a poorer response (90% or less of the tumour is killed).

For patients with a poorer response to chemotherapy, we would like to see if their treatment is improved by adding extra chemotherapy drugs.

For patients with a good response, we would like to see if their treatment can be improved by giving interferon (a biological treatment) after chemotherapy has finished. Interferon is produced naturally in the body, but has been found to be an effective treatment for some cancers. The exact way interferon works is not known. It may directly kill cancer cells, or it may interfere with the blood supply to the tumour, or it may increase the response of the patient's immune system (the system that recognises and destroys "foreign" cells). We do not know if giving interferon will increase the chance of cure for patients with osteosarcoma.

2. Why has my child been chosen?

Around 2000 patients will be taking part in *EURAMOS 1*, throughout the UK, Europe and America. All patients diagnosed with osteosarcoma in the participating hospitals are being invited to take part in the trial.

3. Does my child have to take part?

It is up to you and your child to decide whether or not to take part in the study. If you decide that you want your child to take part in this study you can keep this information sheet, and you will be asked to sign a consent form on their behalf. Your child is free to withdraw from the study at any time without giving a reason. A decision not to take part, or later to withdraw, will not affect the standard of care your child receives.

4. What will happen to my child if they take part?

All patients who are enrolled on this study will begin treatment with the standard 10 weeks of MAP chemotherapy, followed by surgery to remove the tumour(s).

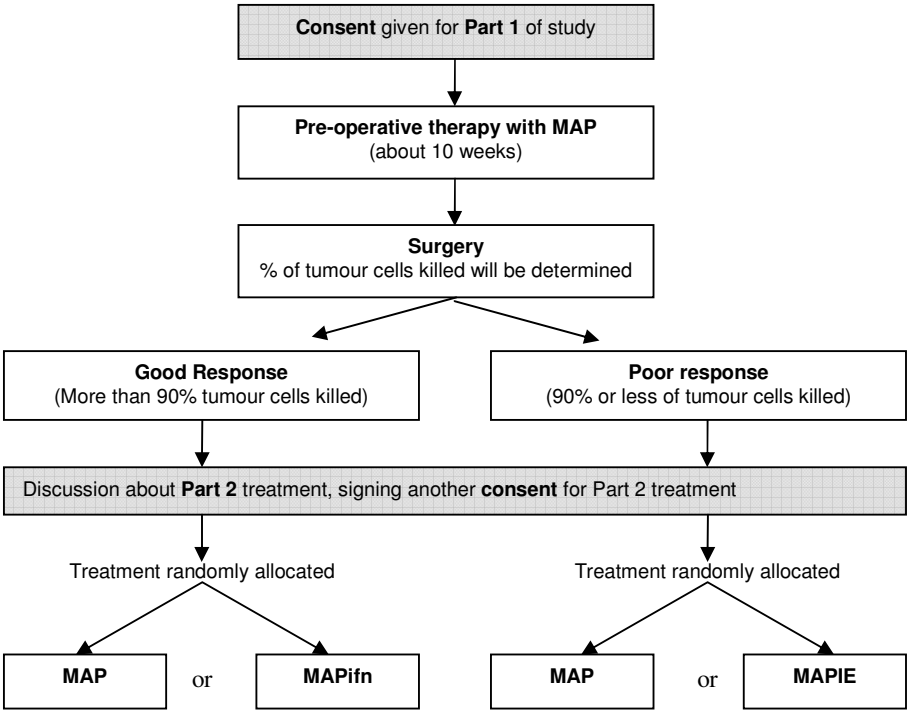
After the operation, tumour tissue will be looked at under a microscope to find out how many of the tumour cells have been killed. If more than 90% of the tumour cells have been killed, this will be called a good response. If 90% or less of the tumour cells have been killed, this will be called a poor response.

Chemotherapy will restart after surgery before it is known whether your child has a good or poor response, because it normally takes a few weeks to get these results. Your doctor will discuss these results with you and check that you are still happy for your child to take part in the study. The therapy your child will get after surgery will depend on whether they have a good or a poor response, and then will depend on randomisation to one of two different treatments for each type of response.

Please note: Long-term use of Interferon is not suitable for children under 5. Children under the age of 5 would only be allocated at random one of the trial treatments if their tumour has a poor response to chemotherapy before surgery. All children under 5 with a good response would simply continue after surgery with the same chemotherapy they had before surgery."

Randomisation means that your child is being put into a group by chance. The group your child is put in is done by a computer. Neither you nor your doctor will choose which group your child will be put in. Your child will have an equal chance of being placed in either group. Your doctor will discuss the treatments with you and your child. You will be asked to sign another consent form for the second part of treatment.

Here is the treatment plan for the entire study:



MAP = **m**ethotrexate, doxorubicin (**a**driamycin), cis**p**latin, (the same chemotherapy as before surgery)
MAPifn = **m**ethotrexate, doxorubicin (**a**driamycin), cis**p**latin with the addition of interferon
MAPIE = **m**ethotrexate, doxorubicin (**a**driamycin), cis**p**latin with the addition of **i**fosfamide and **e**toposide

5. What will treatment involve?

The drugs for pre-operative therapy for this study are given in this way:

M = **M**ethotrexate*
Given by IV over 4 hours

A = Doxorubicin (also called **A**driamycin)
Given by IV over 48 hours

P = Cis**p**latin
Given by IV over 72 hours or by IV over 4 hours for 2 days.
These 2 methods for giving **P** have the same dose and are equally effective. Your doctor will give **P** by the method used in your hospital.

All the chemotherapy drugs will be given using a needle inserted into a vein (**intravenous or IV**). Other drugs may be given by tablet or liquid through the mouth (**oral**), or using a needle inserted under the skin (**subcutaneous or SC**).

Week	Day						
	1	2	3	4	5	6	7
1	**AP**	**AP**	**(P)**				
2							
3							
4	**M**						
5	**M**						
6	**AP**	**AP**	**(P)**				
7							
8							
9	**M**						
10	**M**						
11	**Surgery**						

***Note:** If surgery is delayed, your child may get more methotrexate before surgery. If your child has difficulty recovering from the effects of the methotrexate therapy methotrexate may only be given two or three times before surgery instead of four times.

Central Line

For drugs to be given by vein, your doctor will likely recommend that your child have a central venous line placed. This is used to administer chemotherapy drugs and to withdraw small amounts of blood for testing during treatment. A central venous line is a type of tubing put into a large vein inside the chest by a surgeon or radiologist during a short operation. Your child will be anaesthetised for this procedure and get pain medication afterwards to keep them comfortable. You will be given more information about this by the doctors and nurses looking after your child.

Standard Medical Tests

If your child takes part in this study, they will have tests that are part of regular cancer care and may be done even if they do not join in this study. These tests include blood tests, urine tests, heart and hearing tests, chest X-rays, nuclear medicine studies, CT and MRI scans.

Surgery

Surgery is a standard part of osteosarcoma treatment, which your child will have even if they do not take part in this study. You will be given more information about this by your surgeon.

Some of the tissue already taken to make your child's diagnosis will be sent to a central review centre as part of the quality control of the study. There will also be central review of the slides used to find out how many cancer cells have been killed after the pre-operative therapy with MAP.

6. Additional Research

Biology Studies

When your child has had surgery, specimens from their cancer will be stored in the hospital pathology laboratory. If your child takes part in the EURAMOS 1 study, we would like to ask your permission to retrieve some of that stored material in the future, for osteosarcoma research. This research is based in UK and European Universities and is only carried out after review by an independent ethics committee. It involves extracting DNA or other chemicals from the tumour to see whether it is possible to predict which patients will benefit most from each treatment. We would also like your permission to take a blood sample of 10 mL (about 2 teaspoons full) which will be used to help this research. All work is coded. Your child's specimens will be identified by a number, not by their name. Neither you nor your child will not be identified or contacted. These studies will not affect your child's treatment in any way, and you are free to withhold this permission without affecting your participation in EURAMOS 1 or your relationship with your doctor.

Quality of Life questionnaire

As part of this study we think it is important to find out more about how patients feel both physically and emotionally during and after different treatments. In order to collect this information, brief questionnaires have been designed for you and your child to complete. We would like you and your child to complete questionnaires at 5 weeks, 6 months, 18 months and 3 years after your child first started treatment. You and your child can, of course, decline to complete the questionnaire at any time without affecting your relationship with your doctor.

7. How long will my child be on this study?

The first part of the study will last for about 11 weeks: 10 weeks of chemotherapy followed by surgery.

If your child takes part in this second part of the study, we think that treatment will last in total for about:

- 7 months if randomised to MAP
- 10 months if randomised to MAPIE
- 7 months for the MAP chemotherapy plus a further 17 months of therapy with weekly interferon injections if randomised to MAPifn.

However, all patients will continue to have regular check-ups and blood tests for a few years after treatment so that researchers can continue to observe any effects of treatment. In addition, we would like to continue to collect some information about how your child is doing for as long as you allow us.

The researchers may decide to take your child off the study if the cancer gets worse or they experience side effects from the treatment that are considered too severe.

8. What are the alternatives for treatment?

Patients who do not want to take part in this study will receive the standard treatment with MAP chemotherapy as outlined earlier.

9. What are the side effects of the proposed treatments?

All chemotherapy has side effects. The doctors and nurses looking after your child will discuss these with you in more detail. They include hair loss, loss of appetite, nausea (feeling sick), a sore mouth, vomiting, tiredness, risk of infection, and risk of bleeding associated with low platelets. Many of these side effects can be controlled with drugs and your doctors and nurses will talk to you about how you can help prevent some of these side effects.

If you get an infection between courses of chemotherapy, your child will need to receive antibiotic treatment in hospital. Blood and platelet transfusions can also be given when necessary. Hair loss is unfortunately inevitable but the hospital can help by providing your child with a wig. Your child's hair will start to grow back as soon as their chemotherapy has finished.

Some of the individual drugs have additional side effects. Doxorubicin can cause damage to the heart in a small number of patients. To prevent this happening, the total dose of this drug is limited. Simple heart scans will also be done throughout your child's treatment so that if any changes are seen further preventative action can be taken.

Cisplatin and methotrexate can cause damage to the kidneys. To prevent this happening, extra fluids are given with these drugs to help 'flush' them through the kidneys. Your child will be encouraged to drink plenty of water during their treatment. Blood tests to monitor your child's kidney function will be taken throughout their treatment, and adjustments will be made to their chemotherapy if necessary.

Cisplatin can cause changes in hearing. For example your child may lose the ability to hear some high pitched sounds, and some patients may experience tinnitus (ringing in the ears) whilst on treatment. This usually improves when treatment is finished. You should tell your doctor if you notice changes in your child's hearing.

Methotrexate can cause liver irritation or damage which usually resolves a few days after its administration. Very occasionally patients receiving high dose methotrexate get a temporary rash on the soles of their feet or palms of their hands. If this occurs the doctors can prescribe anti-histamines (drugs used for allergies) to help control the rash.

As with many chemotherapy treatments it is possible that the drugs could damage an unborn child and therefore girls should not become pregnant during treatment. Boys should also avoid unprotected sexual intercourse whilst on treatment since the drugs could damage the sperm. For boys and girls there is a risk that the treatment could result in infertility. Your doctor will talk to you more about this.

As part of the chemotherapy after your child's operation they might also receive ifosfamide and etoposide, or interferon. Side effects of etoposide and ifosfamide are similar to MAP side effects, but some may occur more frequently, particularly infection and kidney damage. Your child will be monitored closely for these problems. In addition, ifosfamide can occasionally cause drowsiness or confusion in a small number of patients. Interferon may cause fever, nausea and flu-like symptoms for a few hours after the injection, and some people can feel tired and down. Other side-effects associated with interferon include sleeping problems, thinning of the hair, reaction at the injection site, and less commonly decreased vision, changes in thyroid function and elevation of fats (triglycerides) in the blood.

10. What are the possible disadvantages and risks of taking part?

All cancer treatment is associated with side effects such as those described above, including potentially life-threatening problems such as infection.

11. Is this trial as safe as standard treatment?

Yes. All of these drugs have been used for patients with cancer or other diseases for a number of years. The aim of this study is not to test new drugs, but to see whether existing drugs can be given in a better way.

12. What are the possible benefits of taking part?

We hope that the treatment will help your child. However, this is not certain. The information we get from this study may help us to treat future patients with osteosarcoma better, in just the same way that current treatment has been designed using information gained from previous clinical trials. We do not know whether any of the treatments described here will be better than the standard treatment in the long run.

13. What if new information becomes available?

Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. If this happens, your doctor will tell you about it and discuss with you whether you want your child to continue in the study. If your child withdraws, your doctor will make arrangements for your child's treatment to continue according the best available information at the time. If your child continues in the study you will be asked to sign another consent form.

It is also possible that on receiving new information about treatment your doctor might consider it to be in your child's best interest to withdraw from the study. He/she will explain the reasons and arrange for your child's care to continue.

14. What happens when the research study stops?

If for any reason the research study stops, or the treatment programme needs to be changed, the reasons will be explained. Arrangements will be made for your child to continue treatment according the best available information at the time.

15. What if something goes wrong?

If your child is harmed as a result of their participation in this trial due to someone's negligence, then you may have grounds for legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way your child has been approached or treated during the course of this study, the normal National Health Service complaints mechanisms are available to you. Your hospital continues to have a duty of care to your child as a patient being treated within the hospital whether in a trial or not.

If your child is harmed as result of their participation in this study, and this is not due to negligence, the Medical Research Council would sympathetically consider any claim for compensation.

16. Will taking part in this study be kept confidential?

If your child participates in EURAMOS 1, information about them will be passed to the three trials offices managing the data. The Medical Research Council Clinical Trials Unit (MRC CTU), London, are managing the main database for the study; Quality of Life questionnaires are managed by Düsseldorf University Children's Hospital, Germany; and any serious side effects are reported to regulatory agencies through University Hospital of Münster, Germany, who are managing safety information for the study. Schering Plough who are supplying interferon for the study, will be notified about any serious side effects of interferon. In each case, the forms contain little identifying information about your children. Where possible, only a code number is used. Each of these units is registered under the Data Protection Act (or equivalent national laws) to hold such information on a confidential basis.

Occasionally staff from the MRC CTU or regulatory authorities will need to visit the hospital to review your child's notes to check that the information being provided is correct. Your GP, and the other doctors involved in your child's care, will be kept fully informed, but otherwise all information about your child and their treatment will remain completely confidential. We will register your child's participation with the National Health Service Central Register (NHSCR) or similar systems. This is so we can check your child's health status after the trial has closed or in the event that your child loses touch with their study doctor.

17. What will happen to the results of the research study?

When the trial is complete the results will be published in a medical journal, and may be presented at conferences. No individual patients will be identified.

18. Who is organising and funding the research?

In the UK this research is being organised by the National Cancer Research Institute, funded jointly by Cancer Research UK, the MRC and the NHS, and is being run together with the UK Medical Research Council Clinical Trials Unit. The research has been reviewed by those organisations, and also by an independent NHS Research Ethics Committee. Your child's doctor will not receive any payment for including your child in this study.

All research that involves NHS patients or staff, information from NHS medical records or uses NHS premises or facilities must be approved by a NHS Research Ethics Committee before it goes ahead. Approval does not guarantee that your child will not come to any harm if you take part. However approval means that the Committee is satisfied that your rights, your child's rights will be respected, that any risks have been reduced to a minimum and balanced against possible benefits, and that you and your child have been given sufficient information on which to make an informed decision to take part or not.

This study is being run in collaboration with the European Osteosarcoma Intergroup (UK and Europe), the Co-operative Osteosarcoma Study Group (Europe), the Scandinavian Sarcoma Group and the North American Children's Oncology Group.

19. Contact for Further Information

If you have any further questions about osteosarcoma or clinical trials, please discuss them with your doctor. You may also find it helpful to contact Cancerbackup, an independent patient advisory group (freephone: 0808 800 1234; address: 3 Bath Place, Rivington Street, London, EC2A 3JR; web site www.Cancerbackup.org.uk).

If you would like to see a copy of the information sheets for part 2 of this study, please ask us.

If you have private medical insurance we recommend that you contact your insurance company about participation in a trial agreeing to take part.

20. Local contact names and telephone numbers:

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21. What if I have any concerns?

If you have any concerns or other questions about this study or the way it has been carried out, you should contact the investigator (name), or you may contact the hospital (name) complaints department.

(to be printed on institution headed paper)

EURAMOS 1: Should chemotherapy for Osteosarcoma be changed after surgery based on the response to pre-operative chemotherapy?

(EURAMOS stands for: **Eur**opean and **Am**erican **O**steosarcoma **S**tudy group)

Information sheet for parents. Part 2 - Good response.

(Version No. 5.0 December 2008)

Chief Investigator: Dr Jeremy Whelan

Local Investigator:

1. What is part 2 of the study about?

Now that your child has completed the first part of therapy (pre-operative chemotherapy, surgery, and evaluation) you are being asked if you are happy for your child to take part in the second part of the study.

Because your child has had a good response to the pre-operative chemotherapy (more than 90% of the tumour cells have been killed) they are eligible for more MAP chemotherapy, or MAP chemotherapy plus interferon (a biological therapy).

Before you and your child decide whether or not to continue in the study it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully. Discuss it with others if you wish and if anything is not clear, or if you would like more information, don't hesitate to ask us. Take time to decide whether or not you wish to take part. Separate information sheets are available for children aged over 14 years, aged 8-13 and under 8 (designed to be read to the child).

Thank you for taking the time to read this information sheet.

2. What is the purpose of Part 2 of the study?

For patients who have had a good response with standard MAP chemotherapy, continuing with MAP therapy should result in a good outcome. Researchers would like to know if adding interferon, (a biological therapy) after the MAP therapy is complete, will help make sure the tumour cells do not return later. This study will use pegylated interferon alpha-2b, interferon that has been modified to last longer in the body so it can be given less often.

3. How many people will take part in this study?

Nearly 600 patients will be participating in this part of the trial.

4. Does my child have to continue to take part in this study?

It is up to you and your child to decide whether or not to continue to take part in this study. If you do decide that your child will continue you can keep this information sheet, and will be asked to sign a consent form allowing us to allocate your child's treatment by computer (randomisation). If your child continues to take part they are still free to withdraw from the study at any time without giving a reason. A decision not to take part, or later to withdraw, will not affect the standard of care your child receives.

5. What will happen to my child if they take part?

Your child will be assigned to one of the two treatments for good responders by randomisation. Randomisation means that your child is being put into a group by chance. The group your child is put in is done by a computer. Neither you nor your doctor will choose which group your child will be put in. Your child will have an equal chance of being placed in either group. Your child will be randomised to get either standard treatment with MAP **or** treatment with MAP and followed by pegylated interferon alpha-2b (MAPifn) when the chemotherapy is finished.

6. What will the treatment involve?

Both **MAP** and **MAPifn** groups will receive the same MAP chemotherapy. The drugs for the study are given in this way (the treatment weeks start at week 12 – first week of chemotherapy after surgery):

M = **M**ethotrexate
Given by IV over 4 hours

A = Doxorubicin (also called **A**driamycin)
Given by IV over 48 hours

P = Cis**p**latin
Given by IV over 72 hours or by IV over 4 hours for 2 days.
These 2 methods for giving **P** have the same dose and are equally effective. Your doctor will give **P** by the method used in your hospital

All the chemotherapy drugs will be given using a needle inserted into a vein (**intravenous or IV**). Other drugs may be given by tablet or liquid through the mouth (**oral**), or using a needle inserted under the skin (**subcutaneous or SC**).

Week	Day						
	1	2	3	4	5	6	7
12	AP	AP	(P)				
13							
14							
15	M						
16	M						
17	AP	AP	(P)				
18							
19							
20	M						
21	M						
22	A	A					
23							
24	M						
25	M						
26	A	A					
27							
28	M						
29	M						

MAP group: Treatment will stop when chemotherapy finishes

MAPifn group: Pegylated interferon alpha-2b – SC injection (Day 1 of each week) starting at Week 30, continuing for 17 months**.**

Standard Medical Tests

If your child takes part in this study, they will continue to have the tests that are part of regular cancer care and may be done even if your child does not join in this study. These tests include blood tests, urine tests, heart and hearing tests, chest X-rays, nuclear medicine studies, and CT and MRI scans.

Extra Medical Tests

If your child takes part in this study and they are randomised to receive MAPifn, they will need extra blood tests to check their pancreatic and thyroid function and the levels of fat (triglycerides) in their blood. Additionally, their eyes will be examined. They will have these extra tests every two weeks for the first eight weeks of interferon treatment and every 1-2 months thereafter.

7. How long will my child be on this study?

If your child takes part in this second part of the study, we think that treatment will last for about:

- 5 months if in the MAP group (a total of 7 months including pre-operative chemotherapy)
- 5 months for the MAP chemotherapy (a total of 7 months including pre-operative chemotherapy), plus a further 17 months of therapy with weekly interferon if in the MAPifn group (a total of 2 years treatment).

However, your child will continue to have regular check ups and blood tests for a few years after treatment so that researchers can continue to observe any effects of treatment. In addition, we would like to continue to collect some information about how your child is doing for as long as you allow us.

The researchers may decide to take your child off the study if the cancer gets worse or they experience side effects from the treatment that are considered too severe.

8. What are the alternatives for treatment?

Patients who do not want to take part in this study will receive the standard treatment with 5 months of MAP chemotherapy (a total of 7 months including pre-operative chemotherapy), as outlined above.

9. What are the side effects of the proposed treatment?

The side effects of chemotherapy are the same as your child experienced with the treatment given before surgery.

Interferon is not a type of chemotherapy. It is a protein found naturally in the body. However, when 'additional' interferon is given, it does cause side effects, although these are not as severe as those associated with chemotherapy. It must be given as a weekly SC (under the skin) injection. The side effects include fever, nausea and flu-like symptoms for a few hours after the injection (although if this occurs it is likely to improve after the first few injections), fatigue and occasionally feelings of depression. Other side-effects associated with interferon include sleeping problems, thinning of the hair, reaction at the injection site, and less commonly decreased vision, changes in thyroid function and elevation of fats (triglycerides) in the blood.

It is important to let your child's doctors and nurses know about any side effects so that steps can be taken to minimise any symptoms they may experience.

10. What are the risks of taking part?

All cancer treatment is associated with side effects as described, including potentially life-threatening problems such as infection. If your child is in the MAPifn group they would receive more treatment than the standard MAP treatment.

11. Are there any benefits?

We do not know whether adding interferon to the standard treatment will be better than the standard treatment in the long run. There may be differences in tumour control, or long term side effects. The information we get from this study may help us to treat future patients with osteosarcoma better.

12. What if new information becomes available?

Sometimes during the course of a research project, new information becomes available about the treatment/drug that is being studied. If this happens, your doctor will tell you about it and discuss with you whether you want your child to continue in the study. If your child withdraws, your doctor will make arrangements for your child's treatment to continue according the best available information at the time. If your child continues in the study you will be asked to sign an updated consent form.

It is also possible that on receiving new information about treatment your doctor might consider it to be in your child's best interests to withdraw from the study. He/she will explain the reasons and arrange for your child's care to continue.

13. What happens when the research study stops?

If for any reason the research study stops, or the treatment programme needs to be changed, the reasons will be explained. Arrangements will be made for your child to continue treatment according the best available information at the time.

14. What if something goes wrong?

If your child is harmed as a result of their participation in this trial due to someone's negligence, then you may have grounds for legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way your child has been approached or treated during the course of this study, the normal National Health Service complaints mechanisms are available to you. Your hospital continues to have a duty of care to your child as a patient being treated within the hospital whether in a trial or not.

If your child is harmed as result of their participation in this study, and this is not due to negligence, the Medical Research Council would sympathetically consider any claim for compensation.

15. Will taking part in this study be kept confidential?

If your child participates in EURAMOS 1, information about them will be passed to the three trials offices managing the data. The Medical Research Council Clinical Trials Unit (MRC CTU), London, are managing the main database for the study; Quality of Life questionnaires are managed by Düsseldorf University Children's Hospital, Germany; and any serious side effects are reported to regulatory agencies through University Hospital of Münster, Germany, who are managing safety information for the study. Schering Plough who are supplying interferon for the study, will be notified about any serious side effects of interferon. In each case, the forms contain little identifying information about your children. Where possible, only a code number is used. Each of these units is registered under the Data Protection Act (or equivalent national laws) to hold such information on a confidential basis.

Occasionally staff from the MRC CTU or regulatory authorities will need to visit the hospital to review your child's notes to check that the information being provided is correct. Your GP, and the other doctors involved in your child's care, will be kept fully informed, but otherwise all information about your child and their treatment will remain completely confidential. We will register your child's participation with the National Health Service Central Register (NHSCR) or similar systems. This is so we can check your child's health status after the trial has closed or in the event that your child loses touch with their study doctor.

16. What will happen to the results of the research study?

When the trial is complete the results will be published in a medical journal, and may be presented at conferences. No individual patients will be identified.

17. Who is organising and funding the research?

In the UK this research is being organised by the National Cancer Research Institute, funded jointly by Cancer Research UK, the MRC and the NHS, and is being run together with the UK Medical Research Council Clinical Trials Unit. The research has been reviewed by those organisations, and also by an independent NHS Research Ethics Committee. Your child's doctor will not receive any payment for including your child in this study.

All research that involves NHS patients or staff, information from NHS medical records or uses NHS premises or facilities must be approved by a NHS Research Ethics Committee before it goes ahead. Approval does not guarantee that your child will not come to any harm if they take part. However approval means that the Committee is satisfied that your rights, and your child's rights will be respected, that any risks have been reduced to a minimum and balanced against possible benefits, and that you and your child have been given sufficient information on which to make an informed decision to take part or not.

This study is being run in collaboration with the European Osteosarcoma Intergroup (UK and Europe), the Co-operative Osteosarcoma Study Group (Europe), the Scandinavian Sarcoma Group and the North American Children's Oncology Group.

18. Contact for Further Information

If you have any further questions about your osteosarcoma or clinical trials, please discuss them with your doctor. You may also find it helpful to contact Cancerbackup, an independent patient advisory group (freephone: 0808 800 1234; address: 3 Bath Place, Rivington Street, London, EC2A 3JR; web site www.Cancerbackup.org.uk).

If you would like to see a copy of the first patient information sheet for this study again, please ask us.

19. Local contact names and telephone numbers:

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20. What if I have any concerns?

If you have any concerns or other questions about this study or the way it has been carried out, you should contact the investigator (name), or you may contact the hospital (name) complaints department.

(to be printed on institution headed paper)

EURAMOS 1: Should chemotherapy for Osteosarcoma be changed after surgery based on the response to pre-operative chemotherapy?

(EURAMOS stands for: **Eur**opean and **Am**erican **O**steosarcoma **S**tudy group)

Information sheet for parents. Part 2 - Poor response.
(Version No. 5.0 December 2008)

Chief Investigator: Dr Jeremy Whelan

Local Investigator:

1. What is part 2 of the study about?

Now that your child has completed the first part of therapy (pre-operative chemotherapy, surgery, and evaluation) they are being asked to take part in the second part of the study.

Because your child has had 90% or less tumour response to the pre-operative MAP chemotherapy they are eligible for more MAP chemotherapy, or MAP chemotherapy plus ifosfamide and etoposide (MAPIE).

Before you decide whether or not your child will continue in the study, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully. Discuss it with others if you wish and if anything is not clear, or if you would like more information, don't hesitate to ask us. Take time to decide whether or not you wish to take part. Separate information sheets are available for children aged over 14 years, aged 8-13 and under 8 (designed to be read to the child).

Thank you for taking the time to read this information sheet.

2. What is the purpose of Part 2 of the study?

For patients who have had 90% or less tumour response with standard MAP chemotherapy before surgery, continuing with MAP therapy after surgery should result in a good outcome. Researchers would like to know if adding two other commonly used chemotherapy drugs (ifosfamide and etoposide) to the MAP will result in a better outcome and lessen the chances further of the disease returning later.

3. Why has my child been chosen?

Nearly 700 patients will be participating in this part of the trial.

4. Does my child have to continue to take part in this study?

It is up to you and your child to decide whether or not to continue to take part in this study. If your child continues you can keep this information sheet, and you will be asked to sign a consent form on their behalf, allowing us to allocate your child's treatment by computer (randomisation). If your child continues to take part they are still free to withdraw from the study at any time without giving a reason. A decision not to take part, or later to withdraw, will not affect the standard of care your child receives.

5. What will happen to my child if they take part?

Your child will be assigned to one of the two treatments by randomisation. Randomisation means that your child is being put into a group by chance. The group your child is put in is done by a computer. Neither you nor your doctor will choose which group your child will be put in. Your child will have an equal chance of being placed in either group. Your child will be randomised to get continued standard treatment with MAP **or** treatment with MAP and the addition of ifosfamide and etoposide (MAPIE).

6. What will the treatment involve?

The drugs for the study are given in this way (the treatment starts at week 12 – first week of chemotherapy after surgery):

MAP							
Week	Day						
	1	2	3	4	5	6	7
12	AP	AP	(P)				
13							
14							
15	M						
16	M						
17	AP	AP	(P)				
18							
19							
20	M						
21	M						
22	A	A					
23							
24	M						
25	M						
26	A	A					
27							
28	M						
29	M						

M = **M**ethotrexate
Given by IV over 4 hours

A = Doxorubicin (also called **A**driamycin)
Given by IV over 48 hours

P = Cis**p**latin
Given by IV over 72 hours
or by IV over 4 hours (for 2 days)
These 2 methods for giving **P** have the same dose and are equally effective. Your doctor will give **P** by the method used in your hospital

I = **I**fosfamide
Given by IV over 4 hours

E = **E**toposide
Given by IV over 1 hour

MAPIE							
Week	Day						
	1	2	3	4	5	6	7
12	AP	AP	(P)				
13							
14							
15	M						
16	IE	IE	IE	IE	IE		
17							
18							
19	M						
20	AI	AI	I				
21							
22							
23	M						
24	IE	IE	IE	IE	IE		
25							
26							
27	M						
28	AP	AP	(P)				
29							
30							
31	M						
32	IE	IE	IE	IE	IE		
33							
34							
35	M						
36	AI	AI	I				
37							
38							
39	M						
40	M						

All the chemotherapy drugs will be given using a needle inserted into a vein (**intravenous or IV**). Other drugs may be given by tablet or liquid through the mouth (**oral**), or using a needle inserted under the skin (**subcutaneous or SC**).

<u>Standard Medical Tests</u>

If your child takes part in this study, they will continue to have tests that are part of regular cancer care and may be done even if your child does not join in this study. These tests include blood tests, urine tests, heart and hearing tests, chest X-rays, nuclear medicine studies, CT and MRI scans.

7. How long will my child be on this study?

If your child takes part in this second part of the study, we think that treatment will last for about:

- 5 months if randomised to **MAP** (a total of 7 months including pre-operative treatment)
- 7 months if randomised to **MAPIE** (a total of 9 months including pre-operative treatment)

However, patients will continue to have regular check-ups and blood tests for a few years after treatment so that researchers can continue to observe any effects of treatment. In addition, we would like to continue to collect some information about how your child is doing for as long as you allow us.

The researchers may decide to take your child off the study if your cancer gets worse or your child experiences side effects from the treatment that are considered too severe.

8. What are the alternatives for treatment?

Patients who do not want to take part in this study will receive the standard treatment with a further 18 weeks of MAP chemotherapy (the same treatment as the MAP group), as outlined above.

9. What are the side effects of the proposed treatment?

The side effects of MAP chemotherapy are the same as your child experienced with the treatment given before surgery.

The side effects of ifosfamide and etoposide are similar to those your child will have experienced with their pre-operative chemotherapy but some side effects may occur more frequently, particularly infections and kidney damage. Your child will be closely monitored for these problems. In addition, ifosfamide can occasionally cause drowsiness or confusion in a small number of patients. Slowing down the rate of the infusion can usually help this side effect, but occasionally other medication may be needed if symptoms persist.

It is important to let your doctors and nurses know about any side effects so that steps can be taken to minimise any symptoms your child may experience.

10. What are the risks of taking part?

All cancer treatment is associated with side effects as described, including potentially life-threatening problems such as infection. If your child is in the MAPIE group they will receive more treatment than with standard MAP treatment.

11. Are there any benefits?

We do not know whether adding ifosfamide and etoposide to the standard treatment will be better than the standard treatment in the long run. There may be differences in control of the tumour, or long term side effects. The information we get from this study may help us to treat future patients with osteosarcoma better.

12. What if new information becomes available?

Sometimes during the course of a research project, new information becomes available about the treatment/drug that is being studied. If this happens, your doctor will tell you about it and discuss with you whether you want your child to continue in the study. If your child withdraws, your doctor will make arrangements for their treatment to continue according the best available information at the time. If your child continues in the study you will be asked to sign an updated consent form.

It is also possible that on receiving new information about treatment your doctor might consider it to be in your child's best interest to withdraw from the study. He/she will explain the reasons and arrange for your child's care to continue.

13. What happens when the research study stops?

If for any reason the research study stops, or the treatment programme needs to be changed, the reasons will be explained. Arrangements will be made for your child to continue treatment according the best available information at the time.

14. What if something goes wrong?

If your child is harmed as a result of their participation in this trial due to someone's negligence, then you may have grounds for legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way your child has been approached or treated during the course of this study, the normal National Health Service complaints mechanisms are available to you. Your hospital continues to have a duty of care to your child as a patient being treated within the hospital whether in a trial or not.

If your child is harmed as result of their participation in this study, and this is not due to negligence, the Medical Research Council would sympathetically consider any claim for compensation.

15. Will taking part in this study be kept confidential?

If your child participates in EURAMOS 1, information about them will be passed to the three trials offices managing the data. The Medical Research Council Clinical Trials Unit (MRC CTU), London, are managing the main database for the study; Quality of Life questionnaires are managed by Düsseldorf University Children's Hospital, Germany; and any serious side effects are reported to regulatory agencies through University Hospital of Münster, Germany, who are managing safety information for the study. Schering Plough who are supplying interferon for the study, will be notified about any serious side effects of interferon. In each case, the forms contain little identifying information about your children. Where possible, only a code number is used. Each of these units is registered under the Data Protection Act (or equivalent national laws) to hold such information on a confidential basis.

Occasionally staff from the MRC CTU or regulatory authorities will need to visit the hospital to review your child's notes to check that the information being provided is correct. Your GP, and the other doctors involved in your child's care, will be kept fully informed, but otherwise all information about your child and their treatment will remain completely confidential. We will register your child's participation with the National Health Service Central Register (NHSCR) or similar systems. This is so we can check your child's health status after the trial has closed or in the event that your child loses touch with their study doctor.

16. What will happen to the results of the research study?

When the trial is complete the results will be published in a medical journal, and may be presented at conferences. No individual patients will be identified.

17. Who is organising and funding the research?

In the UK this research is being organised by the National Cancer Research Institute, funded jointly by Cancer Research UK, the MRC and the NHS, and is being run together with the UK Medical Research Council Clinical Trials Unit. The research has been reviewed by those organisations, and also by an independent NHS Research Ethics Committee. Your child's doctor will not receive any payment for including your child in this study.

All research that involves NHS patients or staff, information from NHS medical records or uses NHS premises or facilities must be approved by a NHS Research Ethics Committee before it goes ahead. Approval does not guarantee that your child will not come to any harm if you take part. However approval means that the Committee is satisfied that your rights and your child's rights will be respected, that any risks have been reduced to a minimum and balanced against possible benefits, and that you have been given sufficient information on which to make an informed decision to take part or not.

This study is being run in collaboration with the European Osteosarcoma Intergroup (UK and Europe), the Co-operative Osteosarcoma Study Group (Europe), the Scandinavian Sarcoma Group and the North American Children's Oncology Group.

18. Contact for Further Information

If you have any further questions about your child's disease or clinical trials, please discuss them with your doctor. You may also find it helpful to contact Cancerbackup, an independent patient advisory group (freephone: 0808 800 1234; address: 3 Bath Place, Rivington Street, London, EC2A 3JR; web site www.Cancerbackup.org.uk).

If you would like to see a copy of the first patient information sheet for this study again, please ask your doctor.

19. Local contact names and telephone numbers:

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20. What if I have any concerns?

If you have any concerns or other questions about this study or the way it has been carried out, you should contact the investigator (name), or you may contact the hospital (name) complaints department

(to be printed on institution headed paper)

EURAMOS 1: Should chemotherapy for Osteosarcoma be changed after surgery based on the response to pre-operative chemotherapy?

(EURAMOS stands for: **Eu**ropean and **Am**erican **O**steosarcoma **S**tudy group)

Information sheet for patients aged 14-15 (Scotland), 14-17 (England, Wales and Northern Ireland). Part 1.

(Version No. 5.0 December 2008)

Chief Investigator: Dr Jeremy Whelan

Local Investigator:

You are being invited to take part in a research study, also called a clinical trial. This information leaflet explains what the study is all about.

Before you decide, please read this information sheet and talk about it with your family and friends. It is important for you to understand why the research is being done and what will happen. Ask us if there is anything you are unsure about, or if you would like more information. Take time to decide whether or not you wish to take part. We have given your parents an information sheet like this to read.

Thank you for taking the time to read this information sheet.

1. What is the purpose of the study?

You have recently been diagnosed with a rare type of bone cancer called an osteosarcoma.

The standard treatment for patients with osteosarcoma is:

- MAP chemotherapy for about 10 weeks, then
- surgery, then
- MAP chemotherapy for another 18 weeks.

MAP stands for **m**ethotrexate, doxorubicin (also called **a**driamycin) and cis**p**latin.

We know that these drugs work well for many people with osteosarcoma. We are always trying to find ways to improve treatment, and to make the treatment work better for more people.

When the tumour is removed at surgery, we can look at the tumour under a microscope to see how well the chemotherapy worked. Patients with a good response (over 90% of the tumour is killed) have a better chance of the tumour not returning than those with a poorer response (90% or less of the tumour is killed).

For patients with a poorer response to chemotherapy, we would like to see if their treatment is improved by adding extra chemotherapy drugs.

For patients with a good response, we would like to see if their treatment can be improved by giving interferon (a biological treatment) after chemotherapy has finished. Interferon is produced naturally in the body, but has been found to be an effective treatment for some cancers. The exact way interferon works is not known. It may directly kill cancer cells, or it may interfere with the blood supply to the tumour, or it may increase the response of the patient's immune system (the system that recognises and destroys "foreign" cells). We do not know if giving interferon will increase the chance of cure for patients with osteosarcoma.

2. Why have I been chosen?

Around 2000 patients will be taking part in *EURAMOS 1*, throughout the UK, Europe and America. All patients diagnosed with osteosarcoma in the participating hospitals are being invited to take part in the trial.

3. Do I have to take part?

You do not have to take part. It is up to you and your family to decide. If you decide that you want to take part in this study then you should keep this information sheet. You will sign a form to let us know that you are happy to take part, and your parents will sign a consent form on your behalf. If you decide to take part and later change your mind, nobody will mind and you will continue to get the same standard of care.

4. What will happen to me if I take part?

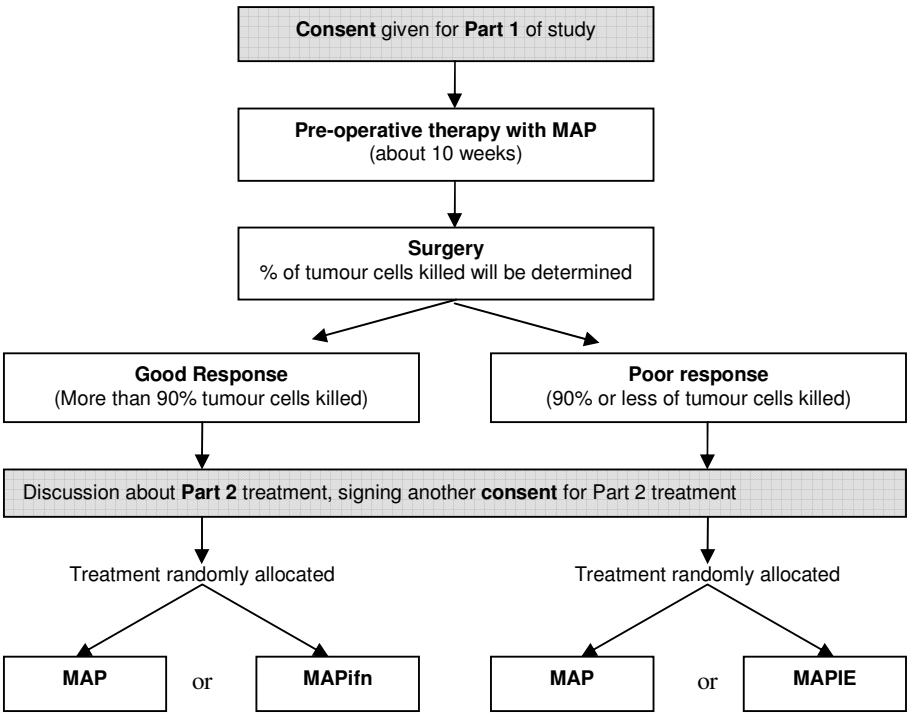
All patients who take part in this study will begin treatment with the standard 10 weeks of MAP chemotherapy, followed by surgery to remove the tumour(s).

After your operation, the tumour tissue will be looked at under a microscope to find out how many of the tumour cells have been killed. If more than 90% of the tumour cells have been killed, this will be called a good response. If 90% or less of the tumour cells have been killed, this will be called a poor response.

Your chemotherapy will restart after surgery before it is known whether you have a good or poor response, because it normally takes a few weeks to get these results. Your doctor will discuss these results with you and your parents, and check whether or not you are still happy to take part in the study. The therapy you will get after surgery will depend on whether you have a good or a poor response, and then will depend on randomisation to one of two different treatments for each type of response.

In this study, you and your doctor will not choose your treatment. Instead, a computer will choose for you. Letting the computer choose is the best way to do this study. It will put half the people in the group that gets standard treatment and half in the group that gets standard and extra treatment. The people in each group will be similar. This way, any differences between the results in the two groups must be because of the treatment.

Here is the treatment plan for the entire study:



MAP = **m**ethotrexate, doxorubicin (**a**driamycin), cis**p**latin, (the same chemotherapy as before surgery)
MAPifn = **m**ethotrexate, doxorubicin (**a**driamycin), cis**p**latin with the addition of interferon
MAPIE = **m**ethotrexate, doxorubicin (**a**driamycin), cis**p**latin with the addition of **i**fosfamide and **e**toposide

5. What will treatment involve?

The drugs for pre-operative chemotherapy for this study are given in this way:

M = **M**ethotrexate*
Given by IV over 4 hours

A = Doxorubicin (also called **A**driamycin)
Given by IV over 48 hours

P = Cis**p**latin
Given by IV over 72 hours or by IV over 4 hours for 2 days.
These 2 methods for giving **P** have the same dose and are equally effective. Your doctor will give **P** by the method used in your hospital.

All the chemotherapy drugs will be given using a needle inserted into a vein (**intravenous or IV**). Other drugs may be given to you by tablet or liquid through the mouth (**oral**), or using a needle inserted under the skin (**subcutaneous or SC**).

Week	Day						
	1	2	3	4	5	6	7
1	**AP**	**AP**	**(P)**				
2							
3							
4	**M**						
5	**M**						
6	**AP**	**AP**	**(P)**				
7							
8							
9	**M**						
10	**M**						
11	**Surgery**						

***Note:** If surgery is delayed, you may get more methotrexate before surgery. If you have difficulty recovering from the effects of the methotrexate therapy you may only have methotrexate two or three times before surgery instead of four times.

Central Line

Because your chemotherapy will be given using a needle inserted into a vein, you will need to have a central line. This is a small tube that is put into your chest so that blood samples can be taken and chemotherapy given easily. It can stay in place as long as you are having chemotherapy. It is put in while you are under an anaesthetic (which means you will be asleep). The doctors and nurses looking after you will give you more information about this.

Standard Medical Tests

While you are being treated you will have blood tests, urine tests, heart and hearing tests chest x-rays, nuclear medicine studies, CT and MRI scans. These are all part of normal cancer care and will be done to you even if you do not take part in this study.

Surgery

You will have an operation to remove your tumour. Your surgeon will explain this more and answer any of your questions.

Some of the tissue already taken to make your diagnosis will be sent to a central review centre as part of the quality control of the study. There will also be central review of the slides used to find out how many cancer cells have been killed after the chemotherapy with MAP.

6. Additional Research

Biology Studies

When you have had your operation, the tumour that has been taken out will be stored in the hospital. We would like your permission to use some of this tumour for more research.

Scientists will extract DNA and chemicals from the tumour to see if they can tell which patients will do best from the chemotherapy. They can also find this out by looking at blood, so we would also like your permission to take a small blood sample.

The tumour and blood sample will be labelled with a number, so the scientists won't know your name.

You can say no to this part of the study and still take part in the main study.

Quality of Life questionnaire

As part of this study we think it is important to find out more about how patients feel during and after different treatments. To collect this information, brief questionnaires have been designed that can be completed by you or your parents. We would like you to complete questionnaires at 5 weeks, 6 months, 18 months and 3 years after you first started treatment. You can say no to doing these questionnaires and still take part in the main study.

7. How long will I be on this study?

The first part of the study will last for about 11 weeks: 10 weeks of chemotherapy followed by surgery.

If you decide to take part in this second part of the study, we think that treatment will last for about:

- 7 months if randomised to MAP
- 10 months if randomised to MAPIE
- 7 months for the MAP chemotherapy plus a further 17 months of therapy with weekly interferon if randomised to MAPifn.

However, all patients will continue to have regular check-ups and blood tests for a few years after treatment so that researchers can continue to see any effects of treatment. In addition, we would like to continue to collect some information about how you are doing for as long as you allow us.

The doctors may decide to take you off the study if the cancer gets worse or if you experience side effects from the treatment that are considered too severe.

8. What are the alternatives for treatment?

Patients who do not want to take part in this study will receive the standard treatment with MAP chemotherapy as outlined earlier.

9. What are the side effects of the proposed treatments?

All chemotherapy has side effects. The doctors and nurses looking after you will talk about these with you in more detail. MAP chemotherapy may have these side effects:

- You may feel sick, and sometimes vomit.
- You may be more likely to get an infection.
- You may bleed a bit more if you cut yourself.
- Your hair will fall out. This will grow back when you finish your treatment.
- You may not feel like eating.
- You may get a sore mouth.
- You may get rash on the soles of your feet and/or palms of your hands
- You will feel tired a lot of the time.
- You may not be able to hear high pitched sounds as well as before.

Some of the chemotherapy may cause kidney, liver and heart problems. You will be monitored closely and your treatment can be adjusted if there are any problems. You should tell your doctors and nurses if you have any side effects, they can help you with some of them. Most of the side effects will go away when you have finished your chemotherapy.

As with many chemotherapy treatments it is possible that the drugs could damage an unborn child and therefore girls should not become pregnant during treatment. Boys should also avoid unprotected sexual intercourse whilst on treatment since the drugs could damage the sperm. For boys and girls there is a risk that the treatment could result in infertility. Your doctor will talk to you more about this.

As part of the chemotherapy after your operation you might also receive ifosfamide and etoposide, or interferon. Side effects of etopsoside and ifosfamide are similar to MAP side effects, but some may occur more often. You will be monitored closely for these problems. In addition, ifosfamide can occasionally cause drowsiness or confusion in a small number of patients. Interferon may cause fever, nausea and flu-like symptoms for a few hours after the injection and some people can feel tired and down. Other side-effects associated with interferon include sleeping problems, thinning of the hair, reaction at the injection site, and less commonly decreased vision, changes in thyroid function and elevation of fats (triglycerides) in the blood.

10. What are the possible disadvantages and risks of taking part?

All cancer treatment is associated with side effects such as those described above, including potentially life-threatening problems such as infection.

11. Is this trial as safe as standard treatment?

Yes. All of these drugs have been used for patients with cancer for a number of years. The aim of this study is not to test new drugs, but to see whether existing drugs can be given in a better way.

12. What are the possible benefits of taking part?

We hope that the treatment will help you. However, this is not certain. The information we get from this study will help us to treat children and young people with osteosarcoma better in the future.

13. What if new information becomes available?

Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. If this happens, your doctor will tell you about it and discuss with you and your parents whether you want to continue in the study.

14. What happens when the research study stops?

If for any reason the research study stops, or the treatment programme needs to be changed, the reasons will be explained. Arrangements will be made for you to continue treatment according to the best available information at the time.

15. What if something goes wrong?

We are not expecting anything to go wrong, but if there are any problems please tell us. If you are still unhappy in any way about the study your parents can contact the hospital complaints department on your behalf.

16. Will taking part in this study be kept confidential?

If you participate in EURAMOS 1, information about you will be passed to the three trials offices managing the data. The Medical Research Council Clinical Trials Unit (MRC CTU), London, are managing the main database for the study; Quality of Life questionnaires are managed by Düsseldorf University Children's Hospital, Germany; and any serious side effects are reported to regulatory agencies through University Hospital of Münster, Germany, who are managing safety information for the study. Schering Plough who are supplying interferon for the study, will be notified about any serious side effects of interferon. In each case, the forms contain little identifying information about you. Where possible, only a code number is used. Each of these units is registered under the Data Protection Act (or equivalent national laws) to hold such information on a confidential basis.

Occasionally staff from the MRC CTU or regulatory authorities will need to visit the hospital to review your notes to check that the information being provided is correct. Your GP, and the other doctors involved in your care, will be kept fully informed, but otherwise all information about you and your treatment will remain completely confidential. We will register your participation with the National Health Service Central Register (NHSCR) or similar systems. This is so we can check your health status after the trial has closed or in the event that you lose touch with your study doctor.

17. What will happen to the results of the research study?

When the trial is complete the results will be published in a medical journal, and may be presented at conferences. No individual patients will be identified.

18. Who is organising and funding the research?

In the UK this research is being organised by the National Cancer Research Institute, funded jointly by Cancer Research UK, the MRC and the NHS, and is being run together with the UK Medical Research Council Clinical Trials Unit. The research has been reviewed by those organisations, and also by an independent NHS Research Ethics Committee. Your doctor will not receive any payment for including you in this study.

All research that involves NHS patients or staff, information from NHS medical records or uses NHS premises or facilities must be approved by a NHS Research Ethics Committee before it goes ahead. Approval does not guarantee that you will not come to any harm if you take part. However approval means that the Committee is satisfied that your rights will be respected, that any risks have been reduced to a minimum and balanced against possible benefits, and that you have been given sufficient information on which to make an informed decision to take part or not.

This study is being run by four different osteosarcoma study groups in the UK, Europe and America.

19. Contact for Further Information

If you have any questions, don't be afraid to talk to your doctors and nurses about it. The doctors and nurses get asked questions all the time, they won't mind. There is a lot for you to try to understand.

You may also find it helpful to contact Cancerbackup, an independent patient advisory group (freephone: 0808 800 1234; address: 3 Bath Place, Rivington Street, London, EC2A 3JR; web site www.Cancerbackup.org.uk).

20. Local contact names and telephone numbers:

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21. What if I have any concerns?

If you have any concerns or other questions about this study or the way it has been carried out, you should contact the investigator (name), or you may contact the hospital (name) complaints department

(to be printed on institution headed paper)

EURAMOS 1: Should chemotherapy for Osteosarcoma be changed after surgery based on the response to pre-operative chemotherapy?

(EURAMOS stands for: **Eu**ropean and **Am**erican **O**steosarcoma **S**tudy group)

Information sheet for patients aged 14-15 (Scotland), 14-17 (England, Wales and Northern Ireland). Part 2 - Good response.

(Version No. 5.0 December 2008)

Chief Investigator: Dr Jeremy Whelan

Local Investigator:

1. What is part 2 of the study about?

Now that you have completed the first part of therapy (pre-operative chemotherapy, surgery, and evaluation) you are being asked to take part in this second part of the study.

Because you have had a good response to the pre-operative chemotherapy (more than 90% of the tumour cells have been killed) you are eligible for more MAP chemotherapy or MAP chemotherapy plus interferon (a biological therapy).

Before you decide, please read this information sheet and talk about it with your family and friends. It is important for you to understand why the research is being done and what will happen. Ask us if there is anything you are unsure about, or if you would like more information. Take time to decide whether or not you wish to take part. We have given your parents an information sheet like this to read.

Thank you for taking the time to read this information sheet.

2. What is the purpose of Part 2 of the study?

For patients who have had a good response with standard MAP chemotherapy, continuing with MAP therapy should result in a good outcome. Researchers would like to know if adding interferon (a biological therapy), after the MAP therapy is complete, will help make sure the tumour cells do not return later. This study will use pegylated interferon alpha-2b, interferon that has been modified to last longer in the body so it can be given less often.

3. How many people will take part in this study?

Nearly 600 children and young people will be participating in this part of the trial.

4. Do I have to continue to take part in this study?

You do not have to take part. It is up to you and your family to decide. If you decide that you want to take part in this study then you should keep this information sheet. You will sign a form to let us know that you are happy to take part, and your parents will sign a consent form on your behalf. If you decide to take part and later change your mind, nobody will mind and you will continue to get the same standard of care.

5. What will happen to me if I take part?

In this study, you and your doctor will not choose your treatment. Instead, a computer will choose for you. Letting the computer choose is the best way to do this study. It will put half the people in the group that gets standard treatment and half in the group that gets standard and extra treatment. The people in each group will be similar. This way, any differences between the results in the two groups must be because of the treatment.

6. What will the treatment involve?

Both **MAP** and **MAPifn** groups will receive the same MAP chemotherapy. The drugs for the study are given in this way (the treatment weeks start at week 12 – first week of chemotherapy after surgery):

M = **M**ethotrexate
Given by IV over 4 hours

A = Doxorubicin (also called **A**driamycin)
Given by IV over 48 hours

P = Cis**p**latin
Given by IV over 72 hours or by IV over 4 hours for 2 days.
These 2 methods for giving **P** have the same dose and are equally effective. Your doctor will give **P** by the method used in your hospital

All the chemotherapy drugs will be given using a needle inserted into a vein (**intravenous or IV**). Other drugs may be given to you by tablet or liquid through the mouth (**oral**), or using a needle inserted under the skin (**subcutaneous or SC**).

Week	Day						
	1	2	3	4	5	6	7
12	AP	AP	(P)				
13							
14							
15	M						
16	M						
17	AP	AP	(P)				
18							
19							
20	M						
21	M						
22	A	A					
23							
24	M						
25	M						
26	A	A					
27							
28	M						
29	M						

MAP group: Treatment will stop when chemotherapy finishes

MAPifn group: Pegylated interferon alpha-2b – SC injection (Day 1 of each week) starting at Week 30, continuing for 17 months**.**

Standard Medical Tests

While you are being treated you will have blood tests, urine tests, heart and hearing tests, chest x-rays, nuclear medicine studies, CT and MRI scans. These are all part of normal cancer care and will be done to you even if you do not take part in this study.

Extra Medical Tests

If you take part in this study and you are randomised to receive MAPifn, you will need extra blood tests to check your pancreatic and thyroid function and the levels of fat (triglycerides) in your blood. Additionally, your eyes will be examined. You will have these extra tests every two weeks for the first eight weeks of your treatment with interferon and every 1-2 months thereafter.

7. How long will I be on this study?

If you decide to take part in this second part of the study, we think that treatment will last for about:

- 5 months if randomised to MAP (a total of 7 months including pre-operative chemotherapy)
- 5 months for the MAP chemotherapy (a total of 7 months including pre-operative chemotherapy) plus a further 17 months of therapy with weekly interferon injections if randomised MAPifn.

However, you will continue to have regular check ups and blood tests for a few years after treatment so that researchers can continue to observe any effects of treatment. In addition, we would like to continue to collect some information about how you are doing for as long as you allow us.

Your doctors may decide to take you off the study if the cancer gets worse or you experience side effects from the treatment that are considered too severe.

8. What are the alternatives for treatment?

Patients who do not want to take part in this study will receive the standard treatment with 5 months of MAP chemotherapy (a total of 7 months including pre-operative chemotherapy), as outlined above.

9. What are the side effects of the proposed treatment?

The side effects of chemotherapy are the same as you experienced with the treatment given before surgery.

Interferon is not a type of chemotherapy. It is a protein found naturally in the body. However, when 'additional' interferon is given, it does cause side effects, although these are not as severe as those associated with chemotherapy. It must be given as a weekly SC (under the skin) injection The side effects include fever, nausea and flu-like symptoms for a few hours after the injection (although if this occurs it is likely to improve after the first few injections), fatigue and occasionally feelings of depression. Other side-effects associated with interferon include sleeping problems, thinning of the hair, reaction at the injection site, and less commonly decreased vision, changes in thyroid function and elevation of fats (triglycerides) in the blood.

It is important to let your doctors and nurses know about any side effects, so they can help you with some of the side effects.

10. What are the risks of taking part?

All cancer treatment is associated with side effects as described, including potentially life-threatening problems such as infection. If you are in the MAPifn arm you will receive more treatment than the standard MAP treatment.

11. Are there any benefits?

We hope that the treatment will help you. However, this is not certain. The information we get from this study will help us to treat children and young people with osteosarcoma better in the future.

12. What if new information becomes available?

Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. If this happens, your doctor will tell you about it and discuss with you and your parents whether you want to continue in the study.

13. What happens when the research study stops?

If for any reason the research study stops, or the treatment programme needs to be changed, the reasons will be explained. Arrangements will be made for you to continue treatment according to the best available information at the time.

14. What if something goes wrong?

We are not expecting anything to go wrong, but if there are any problems please tell us. If you are still unhappy in any way about the study your parents can contact the hospital complaints department on your behalf.

15. Will taking part in this study be kept confidential?

If you participate in EURAMOS 1, information about you will be passed to the three trials offices managing the data. The Medical Research Council Clinical Trials Unit (MRC CTU), London, are managing the main database for the study; Quality of Life questionnaires are managed by Düsseldorf University Children's Hospital, Germany; and any serious side effects are reported to regulatory agencies through University Hospital of Münster, Germany, who are managing safety information for the study. Schering Plough who are supplying interferon for the study, will be notified about any serious side effects of interferon. In each case, the forms contain little identifying information about you. Where possible, only a code number is used. Each of these units is registered under the Data Protection Act (or equivalent national laws) to hold such information on a confidential basis.

Occasionally staff from the MRC CTU or regulatory authorities will need to visit the hospital to review your notes to check that the information being provided is correct. Your GP, and the other doctors involved in your care, will be kept fully informed, but otherwise all information about you and your treatment will remain completely confidential. We will register your participation with the National Health Service Central Register (NHSCR) or similar systems. This is so we can check your health status after the trial has closed or in the event that you lose touch with your study doctor.

16. What will happen to the results of the research study?

When the trial is complete the results will be published in a medical journal, and may be presented at conferences. No individual patients will be identified.

17. Who is organising and funding the research?

In the UK this research is being organised by the National Cancer Research Institute, funded jointly by Cancer Research UK, the MRC and the NHS, and is being run together with the UK Medical Research Council Clinical Trials Unit. The research has been reviewed by those organisations, and also by an independent NHS Research Ethics Committee. Your doctor will not receive any payment for including you in this study.

All research that involves NHS patients or staff, information from NHS medical records or uses NHS premises or facilities must be approved by a NHS Research Ethics Committee before it goes ahead. Approval does not guarantee that you will not come to any harm if you take part. However approval means that the Committee is satisfied that your rights will be respected, that any risks have been reduced to a minimum and balanced against possible benefits, and that you have been given sufficient information on which to make an informed decision to take part or not.

This study is being run in collaboration with the European Osteosarcoma Intergroup (UK and Europe), the Co-operative Osteosarcoma Study Group (Europe), the Scandinavian Sarcoma Group and the North American Children's Oncology Group.

18. Contact for Further Information

If you have any questions, don't be afraid to talk to your doctors and nurses about it. The doctors and nurses get asked questions all the time, they won't mind. There is a lot for you to try to understand.

You may also find it helpful to contact Cancerbackup, an independent patient advisory group (freephone: 0808 800 1234; address: 3 Bath Place, Rivington Street, London, EC2A 3JR; web site www.Cancerbackup.org.uk).

19. Local contact names and telephone numbers:

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20. What if I have any concerns?

If you have any concerns or other questions about this study or the way it has been carried out, you should contact the investigator (name), or you may contact the hospital (name) complaints department.

(to be printed on institution headed paper)

EURAMOS 1: Should chemotherapy for Osteosarcoma be changed after surgery based on the response to pre-operative chemotherapy?

(EURAMOS stands for: **Eu**ropean and **Am**erican **O**steosarcoma **S**tudy group)

Information sheet for patients aged 14-15 (Scotland), 14-17 (England, Wales and Northern Ireland). Part 2 - Poor response.

(Version No. 5.0 December 2008)

Chief Investigator: Dr Jeremy Whelan

Local Investigator:

1. What is part 2 of the study about?

Now that you have completed the first part of therapy (pre-operative chemotherapy, surgery, and evaluation) you are being asked to take part in this second part of the study.

Because you have had a 90% or less tumour response to the pre-operative MAP chemotherapy you are eligible for more MAP chemotherapy or MAP chemotherapy plus ifosfamide and etoposide (MAPIE).

Before you decide, please read this information sheet and talk about it with your family and friends. It is important for you to understand why the research is being done and what will happen. Ask us if there is anything you are unsure about, or if you would like more information. Take time to decide whether or not you wish to take part. We have given your parents an information sheet like this to read.

Thank you for taking the time to read this information sheet.

2. What is the purpose of Part 2 of the study?

For patients who have had a 90% or less tumour response with standard MAP chemotherapy before surgery, continuing with MAP therapy after surgery should result in a good outcome. Researchers would like to know if adding two other commonly used chemotherapy drugs (ifosfamide and etoposide) to the MAP will improve the outcome and prevent the disease from returning later.

3. Why have I been chosen?

Nearly 700 patients will be participating in this part of the trial.

4. Do I have to continue to take part in this study?

You do not have to take part. It is up to you and your family to decide. If you decide that you want to take part in this study then you should keep this information sheet. You will sign a form to let us know that you are happy to take part, and your parents will sign a consent form on your behalf. If you decide to take part and later change your mind, nobody will mind and you will continue to get the same standard of care.

5. What will happen to me if I take part?

In this study, you and your doctor will not choose your treatment. Instead, a computer will choose for you. Letting the computer choose is the best way to do this study. It will put half the people in the group that gets standard treatment and half in the group that gets standard and extra treatment. The people in each group will be similar. This way, any differences between the results in the two groups must be because of the treatment.

6. What will the treatment involve?

Methods for Giving Drugs

The drugs for the study are given in this way (the treatment starts at week 12 – first week of chemotherapy after surgery):

MAP							
Week	**Day**						
	1	**2**	**3**	**4**	**5**	**6**	**7**
12	**AP**	**AP**	**(P)**				
13							
14							
15	**M**						
16	**M**						
17	**AP**	**AP**	**(P)**				
18							
19							
20	**M**						
21	**M**						
22	**A**	**A**					
23							
24	**M**						
25	**M**						
26	**A**	**A**					
27							
28	**M**						
29	**M**						

M = **M**ethotrexate
Given by IV over 4 hours

A = Doxorubicin (also called **A**driamycin)
Given by IV over 48 hours

P = Cis**p**latin
Given by IV over 72 hours
or by IV over 4 hours (for 2 days)
These 2 methods for giving **P** have the same dose and are equally effective. Your doctor will give **P** by the method used in your hospital

I = **I**fosfamide
Given by IV over 4 hours

E = **E**toposide
Given by IV over 1 hour

MAPIE							
Week	**Day**						
	1	**2**	**3**	**4**	**5**	**6**	**7**
12	**AP**	**AP**	**(P)**				
13							
14							
15	**M**						
16	**IE**	**IE**	**IE**	**IE**	**IE**		
17							
18							
19	**M**						
20	**AI**	**AI**	**I**				
21							
22							
23	**M**						
24	**IE**	**IE**	**IE**	**IE**	**IE**		
25							
26							
27	**M**						
28	**AP**	**AP**	**(P)**				
29							
30							
31	**M**						
32	**IE**	**IE**	**IE**	**IE**	**IE**		
33							
34							
35	**M**						
36	**AI**	**AI**	**I**				
37							
38							
39	**M**						
40	**M**						

All the chemotherapy drugs will be given using a needle inserted into a vein (**intravenous or IV**). Other drugs may be given to you by tablet or liquid through the mouth (**oral**), or using a needle inserted under the skin (**subcutaneous or SC**).

Standard Medical Tests

While you are being treated you will have blood tests, urine tests, heart and hearing tests, chest x-rays, nuclear medicine studies, CT and MRI scans. These are all part of normal cancer care and will be done to you even if you do not take part in this study.

7. How long will I be on this study?

If you take part in this second part of the study, we think that treatment will last for about:

- 5 months if randomised to **MAP** (a total of 7 months including pre-operative treatment)
- 7 months if randomised to **MAPIE** (a total of 9 months including pre-operative treatment)

However, patients will continue to have regular check-ups and blood tests for a few years after treatment so that researchers can continue to observe any effects of treatment. In addition, we would like to continue to collect some information about how you are doing for as long as you allow us.

The researchers may decide to take you off the study if your cancer gets worse or you experience side effects from the treatment that are considered too severe.

8. What are the alternatives for treatment?

Patients who do not want to take part in this study will receive the standard treatment with a further 5 months of MAP chemotherapy (the same treatment as the MAP group), as outlined above.

9. What are the side effects of the proposed treatment?

The side effects of MAP chemotherapy are the same as you experienced with the treatment given before surgery.

The side effects of ifosfamide and etoposide are similar to those you will have experienced with your pre-operative chemotherapy, but some side effects may occur more frequently, particularly infections and kidney damage. You will be closely monitored for these problems.

In addition, ifosfamide can occasionally cause drowsiness or confusion in a small number of patients. Slowing down the rate of the infusion can usually help this side effect, but occasionally other medication may be needed if symptoms persist.

It is important to let your doctors and nurses know about any side effects, so they can help with some of the side effects.

10. What are the risks of taking part?

All cancer treatment is associated with side effects as described, including potentially life-threatening problems such as infection. If you are in the MAPIE group you will receive more treatment than with standard MAP treatment.

11. Are there any benefits?

We hope that the treatment will help you. However, this is not certain. The information we get from this study will help us to treat children and young people with osteosarcoma better in the future.

12. What if new information becomes available?

Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. If this happens, your doctor will tell you about it and discuss with you and your parents whether you want to continue in the study.

13. What happens when the research study stops?

If for any reason the research study stops, or the treatment programme needs to be changed, the reasons will be explained. Arrangements will be made for you to continue treatment according to the best available information at the time.

14. What if something goes wrong?

We are not expecting anything to go wrong, but if there are any problems please tell us. If you are still unhappy in any way about the study your parents can contact the hospital complaints department on your behalf.

15. Will taking part in this study be kept confidential?

If you participate in EURAMOS 1, information about you will be passed to the three trials offices managing the data. The Medical Research Council Clinical Trials Unit (MRC CTU), London, are managing the main database for the study; Quality of Life questionnaires are managed by Düsseldorf University Children's Hospital, Germany; and any serious side effects are reported to regulatory agencies through University Hospital of Münster, Germany, who are managing safety information for the study. Schering Plough who are supplying interferon for the study, will be notified about any serious side effects of interferon. In each case, the forms contain little identifying information about you. Where possible, only a code number is used. Each of these units is registered under the Data Protection Act (or equivalent national laws) to hold such information on a confidential basis.

Occasionally staff from the MRC CTU or regulatory authorities will need to visit the hospital to review your notes to check that the information being provided is correct. Your GP, and the other doctors involved in your care, will be kept fully informed, but otherwise all information about you and your treatment will remain completely confidential. We will register your participation with the National Health Service Central Register (NHSCR) or similar systems. This is so we can check your health status after the trial has closed or in the event that you lose touch with your study doctor.

16. What will happen to the results of the research study?

When the trial is complete the results will be published in a medical journal, and may be presented at conferences. No individual patients will be identified.

17. Who is organising and funding the research?

In the UK this research is being organised by the National Cancer Research Institute, funded jointly by Cancer Research UK, the MRC and the NHS, and is being run together with the UK Medical Research Council Clinical Trials Unit. The research has been reviewed by those organisations, and also by an independent NHS Research Ethics Committee. Your doctor will not receive any payments for including you in this study.

All research that involves NHS patients or staff, information from NHS medical records or uses NHS premises or facilities must be approved by a NHS Research Ethics Committee before it goes ahead. Approval does not guarantee that you will not come to any harm if you take part. However approval means that the Committee is satisfied that your rights will be respected, that any risks have been reduced to a minimum and balanced against possible benefits, and that you have been given sufficient information on which to make an informed decision to take part or not.

This study is being run in collaboration with the European Osteosarcoma Intergroup (UK and Europe), the Co-operative Osteosarcoma Study Group (Europe), the Scandinavian Sarcoma Group and the North American Children's Oncology Group.

18. Contact for Further Information

If you have any questions, don't be afraid to talk to your doctors and nurses about it. The doctors and nurses get asked questions all the time, they won't mind. There is a lot for you to try to understand.

You may also find it helpful to contact Cancerbackup, an independent patient advisory group (freephone: 0808 800 1234; address: 3 Bath Place, Rivington Street, London, EC2A 3JR; web site www.Cancerbackup.org.uk).

19. Local contact names and telephone numbers:

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20. What if I have any concerns?

If you have any concerns or other questions about this study or the way it has been carried out, you should contact the investigator (name), or you may contact the hospital (name) complaints department

(to be printed on institution headed paper)

EURAMOS 1: A study of ways to treat bone cancer depending on how well chemotherapy works at first
(EURAMOS stands for: **Eur**opean and **Am**erican **O**steosarcoma **S**tudy group)

Information sheet for children aged 8-13. Part 1.
(Version No. 5.0 December 2008)

Chief Investigator: Dr Jeremy Whelan
Local Investigator:

We are asking you if you would be happy to take part in a research study. Research means finding out things. Please read this information sheet and talk about it with your family and your friends. Ask us if there is anything that you are not sure about. Take plenty of time to decide whether or not you want to take part. We have information for older and younger children, if you would like to see this just ask.

1. What is osteosarcoma?

Osteosarcoma is a type of cancer that grows in bones. If you have cancer it means that some of the cells in your body have stopped working properly, and are growing too quickly. More cancer cells are made and this can cause a lump or tumour (another name some people call cancer).

2. What is the research for?

The doctors want to find out if there is a better way of treating cancer like yours.

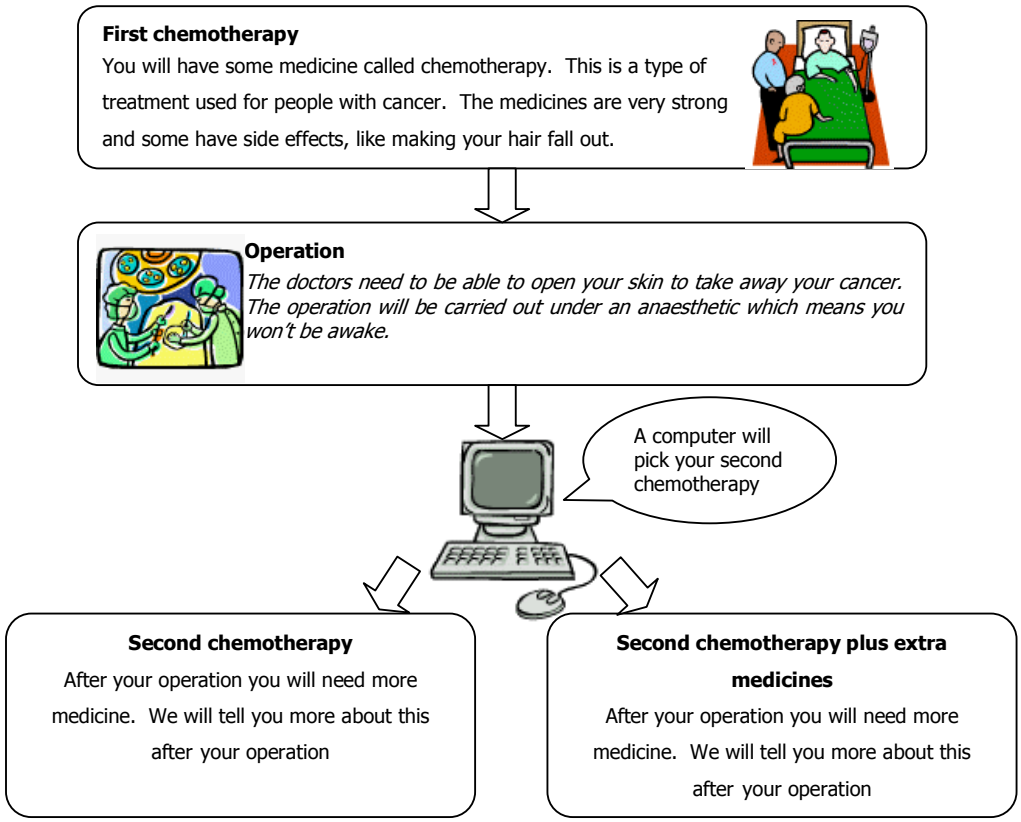
3. Why me?

We are asking you because you have bone cancer. We are asking all patients with your type of bone cancer if they would like to take part. Almost 2000 children and young people from the UK, Europe and America will take part.

4. Do I have to take part?

You do not have to take part. It is up to you and your family to decide. If you take part but then change your mind that is okay. No one will be upset with you.

5. What happens?



6. What will happen to me?

For your first chemotherapy you will have 3 different medicines. The 3 medicines are called **M**ethotrexate, Doxorubicin (also called **A**driamycin) and Cis**p**latin - or MAP for short. This will take about 10 weeks. It may be given to you like this:

Week	1	2	3	4	5	6	7	8	9	10	11
	Chemotherapy			Chemotherapy	Chemotherapy	Chemotherapy			Chemotherapy	Chemotherapy	Operation

Your chemotherapy will be given into your blood through a special thin tube called a central line. The doctors and nurses will tell you more about this. This will stay in your body until your chemotherapy is finished. The tube will be put in under an anaesthetic which means you will be asleep.

You will need to come into hospital every few weeks for a few days to have your chemotherapy. Your mum or dad will be able to stay with you.

After your operation the doctors will be able to see how well your chemotherapy worked. This will help them decide which treatment to give you next.

While you are being treated we would like to know how you are feeling. We will ask you or your parents to answer a few questions while you are having your treatment. You do not have to answer these questions if you do not want to.

7. What is being tested?

All of the medicines in this study are already being used to treat bone cancer or other diseases. We are looking at different ways to give these medicines.

8. Can this be done another way?

Your doctors will have talked with you and your parents about any treatments they can give you. It is up to you and your parents to decide which is best for you.

9. Will the medicine upset me?

Chemotherapy medicines can cause some of these side effects:

- You may feel sick, and sometimes be sick
- You may be more likely to get an infection
- You may bleed a bit more if you cut yourself
- Your hair will fall out. This will grow back when you finish your treatment
- You may not feel like eating
- You may get a sore mouth
- You may get a rash on your hands and feet
- You will feel tired a lot of the time
- You may not be able to hear some high pitched sounds as well as before

We can help you with some of these side effects and most of them will go away when you have finished your chemotherapy.

10. What if something goes wrong?

We are not expecting anything to go wrong but if there are any problems please tell us. If you are still unhappy in any way about the study your family can contact the hospital complaints department on your behalf.

11. Will joining the study help me?

We hope that the treatment will help you. However this is not certain. The information we get from this study **will** help us to treat children and young people, like you, with bone cancer better in the future.

12. Will anyone else know I'm doing this?

All information about you will be kept secret from anybody not working on the study. You can tell people if you want to, but we won't!

13. What happens to what the researchers find out?

When the study is finished, the results will be published in a medical journal (a special magazine for doctors). The results may be talked about at meetings. None of the children will be named.

14. How can I find out more about this study?

If you have any other questions, don't be afraid to talk to your doctors and nurses about them. Doctors and nurses get asked questions all the time, they won't mind. There is a lot for you to try to understand. Your mum and dad have also been given a sheet like this to read.

Thanks for taking the time to read this information sheet.

(to be printed on institution headed paper)

EURAMOS 1: A study of ways to treat bone cancer depending on how well chemotherapy works at first

(EURAMOS stands for: **Eur**opean and **Am**erican **O**steosarcoma **S**tudy group)

Information sheet for children aged 8-13. Part 2 – good response
(Version No. 5.0 December 2008)

Chief Investigator: Dr Jeremy Whelan
Local Investigator:

We are asking you if you would be happy to take part in a research study. Research means finding out things. Please read this information sheet and talk about it with your family and your friends. Ask us if there is anything that you are not sure about. Take plenty of time to decide whether or not you want to take part.

1. What is the research for?

The doctors want to find out if there is a better way of stopping the cancer you had from coming back.

2. Why me?

Now that you have had your operation, you can join the second part of this study if you want to. Nearly 600 children and young people will be in this part of the study.

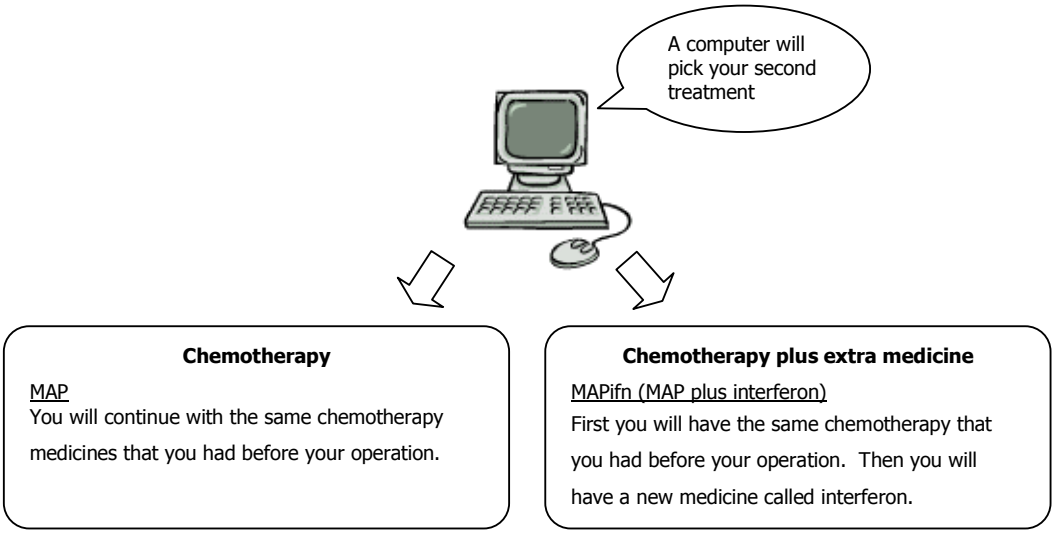
3. Do I have to take part?

You do not have to take part. It is up to you and your family to decide. If you take part but then change your mind that is okay. No one will be upset with you.

4. What happens?

Now that you have had your operation, you need to have more chemotherapy like you had before your operation. As before, you will need to come into hospital every few weeks for a few days to have your chemotherapy. Your mum or dad will be able to stay with you.

For this part of your treatment there are 2 different types of treatment you might get. You might just have the same chemotherapy you had before, or your might get the same chemotherapy plus some extra medicine (called interferon). A computer will pick which treatment you will have. This is called randomisation. There are two different treatments. You will have the same chance of getting either treatment:



5. What will happen to me?

The chemotherapy part of your treatment is the same 3 medicines that you had before your operation. The 3 medicines are called **M**ethotrexate, Doxorubicin (also called **A**driamycin) and Cis**p**latin - or MAP for short. The chemotherapy will take about 18 weeks. It may be given to you like this:

Week	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
	Chemotherapy			Chemotherapy	Chemotherapy	Chemotherapy			Chemotherapy	Chemotherapy	Chemotherapy		Chemotherapy	Chemotherapy	Chemotherapy		Chemotherapy	Chemotherapy

If you are given the **MAP** treatment, your treatment will finish now.

If you are given the **MAPifn** (MAP plus interferon) treatment, you will start your interferon treatment after you have finished your MAP chemotherapy. Interferon is given as a small injection once a week. This can be given at home. Your treatment with interferon will last for about 1½ years.

Whichever treatment you have, your doctors will keep giving you check-ups to make sure you are ok.

6. What is being tested?

We are testing these treatments because we want to find out if interferon will help keep the cancer from coming back.

7. Can this be done another way?

Letting the computer choose your treatment is the best way to do this study. The children who get each treatment will be similar. This makes it easiest to see which treatment was best.

8. Will the medicine upset me?

The side effects of the chemotherapy will be the same as before your operation.
If you are taking interferon after you have finished chemotherapy, the interferon can cause different side effects:

- You may feel a bit hot and shivery for a few hours after your injection, or you may feel a bit achy. This will get better after the first few weeks.
- The interferon may make you feel a bit tired.
- You may feel a bit sad or weepy.

If these side effects happen, the doctors will try to make them better.

9. What if something goes wrong?

We are not expecting anything to go wrong but if there are any problems please tell us. If you are still unhappy in any way about the study your family can contact the hospital complaints department on your behalf.

10. Will joining in help me?

We hope that the treatment will help you. However this is not certain. The information we get from this study **will** help us to treat children and young people like you with bone cancer better in the future.

11. Will anyone else know I'm doing this?

All information about you will be kept secret from anybody not working on the study. You can tell people if you like, but we won't!

12. What happens to what the researchers find out?

When the study is finished, the results will be published in a medical journal (a special magazine for doctors). The results may be talked about at meetings. None of the children will be named.

13. How can I find out more about this study?

If you have any other worries, don't be afraid to talk to your doctors and nurses about them. Doctors and nurses get asked questions all the time, they won't mind. There is a lot for you to try to understand.

Your mum and dad have also been given a sheet like this to read.

Thanks for taking the time to read this information sheet.

(to be printed on institution headed paper)

EURAMOS 1: A study of ways to treat bone cancer depending on how well chemotherapy works at first

(EURAMOS stands for: **Eur**opean and **Am**erican **O**steosarcoma **S**tudy group)

Information sheet for children aged 8-13. Part 2 – poor response
(Version No. 5.0 December 2008)

Chief Investigator: Dr Jeremy Whelan
Local Investigator:

We are asking you if you would be happy to take part in a research study. Research means finding out things. Please read this information sheet and talk about it with your family, and your friends. Ask us if there is anything that you are not sure about. Take plenty of time to decide whether or not you want to take part.

1. What is the research for?

The doctors want to find out if there is a better way of stopping the cancer you had from coming back.

2. Why me?

Now that you have had your operation, you can join the second part of this study if you want to. Nearly 700 children and young people will be in this part of the study.

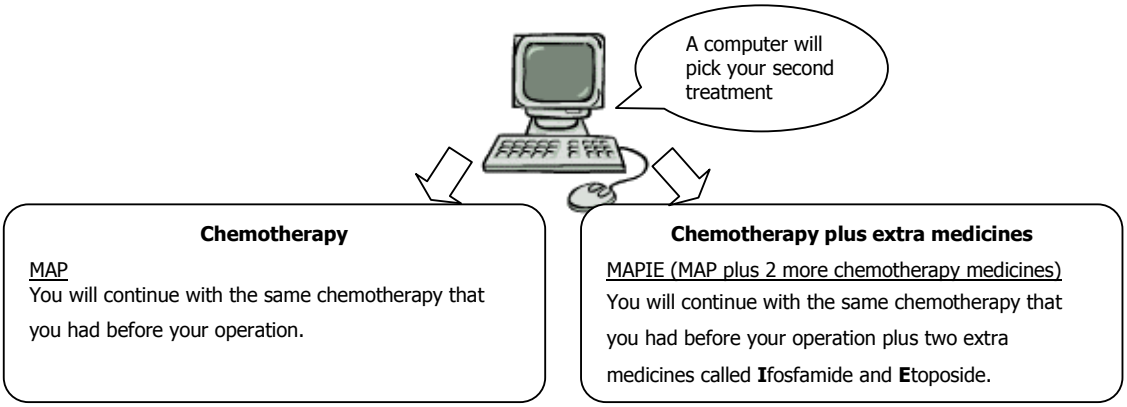
3. Do I have to take part?

You do not have to take part. It is up to you and your family to decide. If you take part but then change your mind that is okay. No one will be upset with you.

4. What happens?

Now that you have had your operation you need to have more chemotherapy like before your operation. You will need to come into hospital every few weeks for a few days to have your chemotherapy. As before, your mum or dad will be able to stay with you.

For this part of your treatment there are 2 different types of treatment you might get. You might just have the same chemotherapy you had before, or your might get the same chemotherapy plus 2 extra chemotherapy medicines (called ifosfamide and etoposide). A computer will pick which treatment you will have. This is called randomisation. There are two different treatments. You will have the same chance of getting either treatment:



5. What will happen to me?

If you are given MAP:

The chemotherapy part of your treatment is the same 3 medicines that you had before your operation. The 3 medicines are called **M**ethotrexate, Doxorubicin (also called **A**driamycin) and Cis**p**latin - or MAP for short. The chemotherapy will take about 18 weeks. It may be given to you like this:

Week	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
	Chemotherapy			Chemotherapy	Chemotherapy	Chemotherapy			Chemotherapy	Chemotherapy	Chemotherapy		Chemotherapy	Chemotherapy	Chemotherapy		Chemotherapy	Chemotherapy

If you are given MAPIE:

The chemotherapy part of your treatment is 5 medicines. The 5 medicines are called **M**ethotrexate, Doxorubicin (also called **A**driamycin), Cis**p**latin, **I**fosfamide and **E**toposide - or MAPIE for short. The chemotherapy will take about 29 weeks. It may be given to you like this:

week	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29
	Chemotherapy			Chemotherapy	Chemotherapy			Chemotherapy	Chemotherapy			Chemotherapy	Chemotherapy			Chemotherapy	Chemotherapy			Chemotherapy	Chemotherapy			Chemotherapy	Chemotherapy			Chemotherapy	Chemotherapy

Whichever treatment you have, your doctors will keep giving you check-ups to make sure you are ok.

6. What is being tested?

We want to find out if giving the 2 extra medicines is more helpful in keeping the cancer from coming back.

7. Can this be done another way?

Letting the computer choose your treatment is the best way to do this study. The children who get each treatment will be similar. This makes it easiest to see which treatment was best.

8. Will the medicine upset me?

If you are given **MAP**, the side effects of the chemotherapy will be the same as before your operation.

If you are given **MAPIE,** the side effects of the chemotherapy will be similar to before your operation. The 2 new medicines can have extra side effects. It can make some people feel a bit drowsy or muddled and confused. If this happens it will only be while you have chemotherapy.

9. What if something goes wrong?

We are not expecting anything to go wrong but if there are any problems please tell us. If you are still unhappy in any way about the study your family can contact the hospital complaints department on your behalf.

10. Will joining in help me?

We hope that the treatment will help you. However this is not certain. The information we get from this study **will** help us to treat children and young people like you with bone cancer better in the future.

11. Will anyone else know I'm doing this?

All information about you will be kept secret from anybody not working on the study. You can tell other people if you like, but we won't!

12. What happens to what the researchers find out?

When the study is finished, the results will be published in a medical journal (a special magazine for doctors). The results may be talked about at meetings. No one will be named.

13. How can I find out more about this study?

If you have any other worries, don't be afraid to talk to your doctors and nurses about them. Doctors and nurses get asked questions all the time, they won't mind. There is a lot for you to try to understand.

Your mum and dad have also been given a sheet like this to read.

Thanks for taking the time to read this information sheet.

(to be printed on institution headed paper)

EURAMOS 1: A study of drug treatment after surgery for osteosarcoma, guided by the amount of tumour killed by chemotherapy before surgery

(EURAMOS stands for: **Eur**opean and **Am**erican **O**steosarcoma **S**tudy group)

Information sheet for patients aged under 8 years.

(Version No. 5.0 December 2008)

Chief Investigator: Dr Jeremy Whelan

Local Investigator:

(To be read to child by parent/guardian)

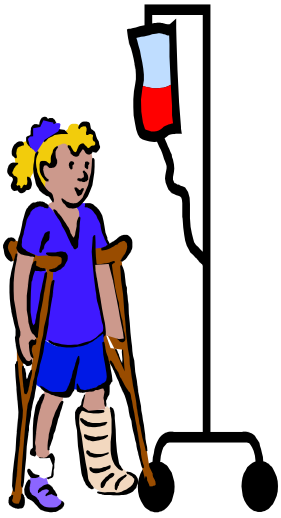
You have come into hospital because you have a lump in one of your bones that may be very sore or making you feel poorly.

This is called an osteosarcoma.

In a few weeks you will have an operation to take the bone with the lump away, but first you need medicine to help make the lump get smaller.

The medicine we need to give you is called “chemotherapy”.

Chemotherapy is given as a “drip”, usually through your central line. You will need to come into hospital every few weeks for a few days to have your chemotherapy. Your mum or dad will be able to stay with you.



Sometimes the chemotherapy can make you feel sick, but we will give you medicine to make this better. The chemotherapy will also make your hair fall out, but this will grow back once all the treatment has finished. The chemotherapy may make you feel poorly, but you will feel better once it has finished.

In a few weeks you will have an operation to take the bone with the lump away.

You will then go on to have a few more months of chemotherapy.

The doctors want to find out if there is a better way of treating osteosarcoma lumps like yours, so they are asking all children with osteosarcoma and their parents, in this country, Europe and America if they will join what is called a “trial”.

This means that all the children will get the best chemotherapy medicines, but some will also get extra medicines. The doctors will then be able to see which treatment is the best. If your parents agree we would like to ask you to join this trial.

Your doctors, nurses and play specialists will talk to you and your mum or dad more about your treatment. If you have any questions you can ask them, or get your mum or dad to ask for you.

Thank you for listening or reading this with your mum or dad.

Part 1 Sticker chart

Week	Day 1	2	3	4	5	6	7
1	chemo	chemo	chemo				
2							
3							
4	chemo						
5	chemo						
6	chemo	chemo	chemo				
7							
8							
9	chemo						
10	chemo						
11	chemo	chemo	chemo				
12	Operation						
13	chemo						
14	chemo						
15	chemo	chemo					
16							
17	chemo						
18	chemo						

Part 2 MAP Sticker chart

Week	Day 1	2	3	4	5	6	7
16	Chemo						
17	Chemo	Chemo	Chemo				
18							
19							
20	Chemo						
21	Chemo						
22	Chemo	Chemo					
23							
24	Chemo						
25	Chemo						
26	Chemo	Chemo					
27							
28	Chemo						
29	Chemo						

Part 2 MAPIE Sticker chart

Week	Day						
	1	2	3	4	5	6	7
16	Chemo	Chemo	Chemo	Chemo	Chemo		
17	Chemo	Chemo	Chemo				
18							
19	Chemo						
20	Chemo	Chemo	Chemo				
21							
22							
23	Chemo						
24	Chemo	Chemo	Chemo	Chemo	Chemo		
25							
26							
27	Chemo						

Part 2 MAPIE Sticker chart

Week	Day 1	2	3	4	5	6	7
28	Chemo	Chemo	Chemo				
29							
30							
31	Chemo						
32	Chemo	Chemo	Chemo	Chemo	Chemo		
33							
34							
35	Chemo						
36	Chemo	Chemo	Chemo				
37							
38							
39	Chemo						
40	Chemo						

(*Form to be on headed paper)*

Study Number: **EURAMOS 1/BO08**
Patient Identification Number for this trial: | | | | | |

Consent form for adult patients. Part 1.
(Version No. 3.0 December 2008)

Title of Project: **EURAMOS 1:Treatment strategies in osteosarcoma**

Name of Researcher: _____

Please initial boxes:

1. I confirm that I have read and understand the information sheet (**dated December 2008 version 5.0**) for the above study and have had the opportunity to ask questions. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand that sections of any of my medical notes may be looked at by responsible individuals from the Medical Research Council or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. ☐
4. I give permission for some of the tissue from my diagnosis and surgery to be sent to a central review centre for quality control of the study. ☐
5. I give permission for a sample of my blood, and for any stored pathological specimens, to be used for future osteosarcoma research. (If you do not wish to give this permission, do not initial the box – you can still participate in the trial). ☐
6. I will take part in the quality of life study. (If you do not wish to give this permission, do not initial the box – you can still participate in the trial). ☐
7. I am happy for a copy of this consent form to be sent to the Medical Research Council. ☐
8. I agree to take part in the above study ☐

Name of Patient	Date	Signature
Name of Person taking consent (if different from researcher)	Date	Signature
Researcher	Date	Signature

(1 copy for patient; 1 for researcher; 1 to be kept with hospital notes, 1 copy for MRC)

(*Form to be on headed paper)*

Study Number: EURAMOS 1/BO08
Patient Identification Number for this trial: | | | | | |

Consent form for adult patients. Part 2.

(Version No. 3.0 December 2008)

Title of Project: **EURAMOS 1:Treatment strategies in osteosarcoma**

Name of Researcher: _____

Please initial boxes:

1. I confirm that I have read and understand the information sheet (**dated December 2008 version 5.0**) for the above study and have had the opportunity to ask questions. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand that sections of any of my medical notes may be looked at by responsible individuals from the Medical Research Council where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. ☐
4. I am happy for a copy of this consent form to be sent to the Medical Research Council. ☐
5. I agree to take part in the above study ☐

Name of Patient	Date	Signature
Name of Person taking consent (if different from researcher)	Date	Signature
Researcher	Date	Signature

(1 copy for patient; 1 for researcher; 1 to be kept with hospital notes, 1 copy for MRC)

(*Form to be on headed paper)*

Study Number: EURAMOS 1/BO08
Patient Identification Number for this trial: | | | | | |

Parent consent form- Part 1

(Version No. 4.0 December 2008)

Title of Project: **EURAMOS 1:Treatment strategies in osteosarcoma**

Name of Researcher: _____

Please initial boxes:

1. I confirm that I have read and understand the information sheet (**dated December 2008 version 5.0)** for the above study and have had the opportunity to ask questions. ☐
2. I understand that my child's participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my child's medical care or legal rights being affected. ☐
3. I understand that sections of any of my child's medical notes may be looked at by responsible individuals from the Medical Research Council or from regulatory authorities where it is relevant to my child's taking part in research. I give permission for these individuals to have access to my child's records. ☐
4. I give permission for some of the tissue from my child's diagnosis and surgery to be sent to a central review centre for quality control of the study. ☐
5. I give permission for a sample of my child's blood, and for any stored pathological specimens, to be used for future osteosarcoma research. (If you do not wish to give this permission, do not initial the box – you can still participate in the trial). ☐
6. My child will take part in the quality of life study. (If you do not wish to give this permission, do not initial the box – you can still participate in the trial). ☐
7. I am happy for a copy of this consent form to be sent to the Medical Research Council. ☐
8. I agree for my child to take part in the above study ☐

Name of Parent / Guardian	Date	Signature
Name of Person taking consent (if different from researcher)	Date	Signature
Researcher	Date	Signature

(1 copy for patient; 1 for researcher; 1 to be kept with hospital notes, 1 copy for MRC)

(*Form to be on headed paper)*

Study Number: EURAMOS 1/BO08
Patient Identification Number for this trial: | | | | | |

Parent consent form- Part 2

(Version No. 4.0 December 2008)

Title of Project: **EURAMOS 1:Treatment strategies in osteosarcoma**

Name of Researcher: _____

Please initial boxes:

1. I confirm that I have read and understand the information sheet (**dated December 2008 version 5.0**) for the above study and have had the opportunity to ask questions. ☐
2. I understand that my child's participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my child's medical care or legal rights being affected. ☐
3. I understand that sections of any of my child's medical notes may be looked at by responsible individuals from the Medical Research Council where it is relevant to my child's taking part in research. I give permission for these individuals to have access to my child's records. ☐
4. I am happy for a copy of this consent form to be sent to the Medical Research Council. ☐
5. I agree for my child to take part in the above study ☐

Name of Parent / Guardian	Date	Signature
Name of Person taking consent (if different from researcher)	Date	Signature
Researcher	Date	Signature

(1 copy for patient; 1 for researcher; 1 to be kept with hospital notes, 1 copy for MRC)

(*Form to be on headed paper)*

Study Number: EURAMOS 1/BO08
Patient Identification Number for this trial: | | | | | |

Assent form for patients aged 14-15 (Scotland), 14-17 (England, Wales and Northern Ireland)- part 1

(Version No. 3.0 December 2008)

Title of Project: **EURAMOS 1:Treatment strategies in osteosarcoma**

Name of Researcher: _____

Please initial boxes:

1. I confirm that I have read and understand the information sheet (**dated December 2008 version 5.0**) for the above study and have had the opportunity to ask questions. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand that sections of any of my medical notes may be looked at by responsible individuals from the Medical Research Council or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. ☐
4. I give permission for some of the tissue from my child's diagnosis and surgery to be sent to a central review centre for quality control of the study. ☐
5. I give permission for a sample of my blood, and for any stored pathological specimens, to be used for future osteosarcoma research. (If you do not wish to give this permission, do not initial the box – you can still participate in the trial). ☐
6. I will take part in the quality of life study. (If you do not wish to give this permission, do not initial the box – you can still participate in the trial). ☐
7. I am happy for a copy of this consent form to be sent to the Medical Research Council. ☐
8. I agree to take part in the above study ☐

Name of patient	Date	Signature
Name of Person taking consent (if different from researcher)	Date	Signature
Researcher	Date	Signature

(1 copy for patient; 1 for researcher; 1 to be kept with hospital notes, 1 copy for MRC)

(*Form to be on headed paper))*

Study Number:EURAMOS 1/BO08
Patient Identification Number for this trial: | | | | | |

Assent form for patients aged 14-15 (Scotland), 14-17 (England, Wales and Northern Ireland) - Part 2.

(Version No. 3.0 December 2008)

Title of Project: **EURAMOS 1:Treatment strategies in osteosarcoma**

Name of Researcher: _____

Please initial boxes:

1. I confirm that I have read and understand the information sheet (**dated December 2008 version 5.0**) for the above study and have had the opportunity to ask questions. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand that sections of any of my medical notes may be looked at by responsible individuals from the Medical Research Council where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. ☐
4. I am happy for a copy of this consent form to be sent to the Medical Research Council. ☐
5. I agree to take part in the above study ☐

Name of patient	Date	Signature
Name of Person taking consent (if different from researcher)	Date	Signature
Researcher	Date	Signature

(1 copy for patient; 1 for researcher; 1 to be kept with hospital notes, 1 copy for MRC)

(*Form to be on headed paper)*

Study Number: EURAMOS 1/BO08
Patient Identification Number for this trial: | | | | | |

Assent form for children aged 13 and under.
(Version No. 3.0 December 2008)
Title of Project: **EURAMOS 1:Treatment strategies in osteosarcoma**

Name of Researcher: _____

	Please tick the box
Have you read about the project?	☐
Has somebody else told you about the project?	☐
Do you understand what the project is about?	☐
Have you asked any questions you want?	☐
Have you had your questions answered?	☐
Are you happy to take part?	☐

- If you **don't** want to take part, **don't** sign your name!
- If you do want to take part, please write your name and today's date. If you don't like writing, you could draw a smiley face instead. Someone else can fill in your name for you.

Your name: _____

Date: _____

Your parent or guardian must write their name here too if they are happy for you to do the project. This is called giving consent.

Print Name: _____

Sign: _____

Date: _____

The person who explained this project to you needs to sign too:

Print Name: _____

Sign: _____

Date: _____

EURAMOS 1: Treatment strategies in osteosarcoma
(Version No. 2.0 October 2006)

PEG-Intron Diary Card

Patient initials and trial number: _____

Dear Patient,

Please use this sheet to keep a record of your PEG-Intron injections as you take them. You will be taking PEG-Intron once a week.

Figure 2: Prepare the dose just before you intend to inject it and use it immediately. Look carefully at the solution before you inject yourself. Do not use if there is any discolouration. Discard any solution that is left in the vial after you give yourself the injection.

Inject Peg-Inton once each week on the same day. Injecting it at the same time of day each week will help you to remember to take it.

It is important to let your doctors and nurses know about any side effects so that steps can be taken to minimise any symptoms you may experience.

Dose/dose volume	Date	PEG-Intron taken (please tick box when taken)
	___/___/___	☐
	___/___/___	☐
	___/___/___	☐
	___/___/___	☐
	___/___/___	☐
	___/___/___	☐
	___/___/___	☐
	___/___/___	☐
	___/___/___	☐
	___/___/___	☐

Additional notes: (e.g. please note any side-effects or other reasons for omitting doses)

Thank you. Please return this sheet next time you come to the hospital.

EURAMOS 1 – A randomised trial of the European and American Osteosarcoma Study Group to optimise treatment strategies for resectable osteosarcoma based on histological response to pre-operative chemotherapy

General Practitioner Information Sheet - Part 1

(Version No. 2.0 October 2006)

Dear Doctor

As you are aware, your patient…… has been diagnosed as having an Osteosarcoma. I am writing to inform you that he/she has been entered into a National Cancer Research Institute study aiming to optimise treatment strategies based on histological response to pre-operative chemotherapy.

Osteosarcoma is the most common bone tumour in children and adolescents, with a long-term survival of approximately 50-60%. In osteosarcoma, it is possible to assess response to pre-operative chemotherapy via examination of the resected tumour specimen. It is known that patients who achieve a good histological response to pre-operative chemotherapy, defined as > 90% tumour necrosis, experience considerably better survival than those who have a poor response ($\leq$ 90% tumour necrosis). The aim of this trial is to investigate whether it is feasible to improve outcome for both good and poor responders through the addition of extra agents into the post-operative treatment schedule.

The standard chemotherapy for osteosarcoma is with 3 chemotherapy drugs, Methotrexate, Doxorubicin (Adriamycin) and Cisplatin, (abbreviated to MAP for short). All patients will receive 10 weeks of chemotherapy with MAP, followed by surgery to remove the primary tumour, which will be with limb-salvage therapy in the majority of patients. Poor responders will be randomised between MAP and the MAPIE regimen, which is: methotrexate, doxorubicin and cisplatin with the addition of ifosfamide and etoposide, the other two active agents in this disease. Good responders will be randomised between MAP and MAPifn, consisting of MAP followed by maintenance therapy with interferon-α, which is continued for up to 2 years from first diagnosis.

Side effects of chemotherapy include:

1. Methotrexate

Common:

- Stomatitis
- Elevated transaminases

Occasional:

- Rash, usually soles and palms

2. Doxorubicin

Common:

- Myelosuppression
- Nausea & vomiting
- Stomatitis
- Alopecia

Occasional:

- Cardiotoxicity – (cumulative and dose dependent) **(L)**

3. Cisplatin

Common:

- Myelosuppression
- Nausea & vomiting
- Hypokalaemia & Hypomagnesaemia
- Alopecia
- High frequency hearing loss

Occasional:

- Peripheral Neuropathy
- Hearing loss in the normal hearing range
- Renal Toxicity **(L)**

4. Ifosfamide

Common

- Nausea & vomiting
- Haematuria

Occasional:

- Renal Toxicity **(L)**
- Lethargy, disorientation, confusion, dizziness

5. Etoposide

- Myelosuppression

(L) – May also occur as a late effect

The side effects of interferon-α include fever, nausea, flu-like symptoms (more common with the first few injections), fatigue and feelings of depression. Should your patient develop any evidence of an infection whilst on treatment, please contact the treating centre immediately. Other side effects associated with interferon include sleeping problems, thinning of hair, reaction at the injection site and, less commonly, decreased vision, changes in thyroid function and elevation of triglycerides in the blood.

In addition to these side effects it is possible that fertility may be affected in both males and females as a result of one or more of these chemotherapy drugs. All males of a suitable age are offered sperm banking before commencing chemotherapy.

In total the treatment is likely to last 7 months for those randomised to receive MAP chemotherapy alone, and 9 months for those randomised to receive chemotherapy with MAPIE. Patients randomised to MAP + Interferon will receive 7 months of treatment with MAP, followed by interferon for up to 2 years from diagnosis.

Your treatment centre will keep you informed about your patient's progress. Should you have any questions about this study, or about your patient's treatment, your treatment centre would be happy to answer any questions you may have.

EURAMOS 1 – A randomised trial of the European and American Osteosarcoma Study Group to optimise treatment strategies for resectable osteosarcoma based on histological response to pre-operative chemotherapy

General Practitioner Information Sheet - Part 2

(Version No. 2.0 October 2006)

Dear Doctor

As you are aware, your patient…… has been diagnosed as having an Osteosarcoma and is taking part in a National Cancer Research Institute study aiming to optimise treatment strategies based on histological response to pre-operative chemotherapy.

Your patient has had a good/poor response to pre-operative chemotherapy and has been allocated the MAP/MAPifn/MAPIE regimen

Your treatment centre will keep you informed about your patient's progress. Should you have any questions about this study, or about your patient's treatment, your treatment centre would be happy to answer any questions you may have.