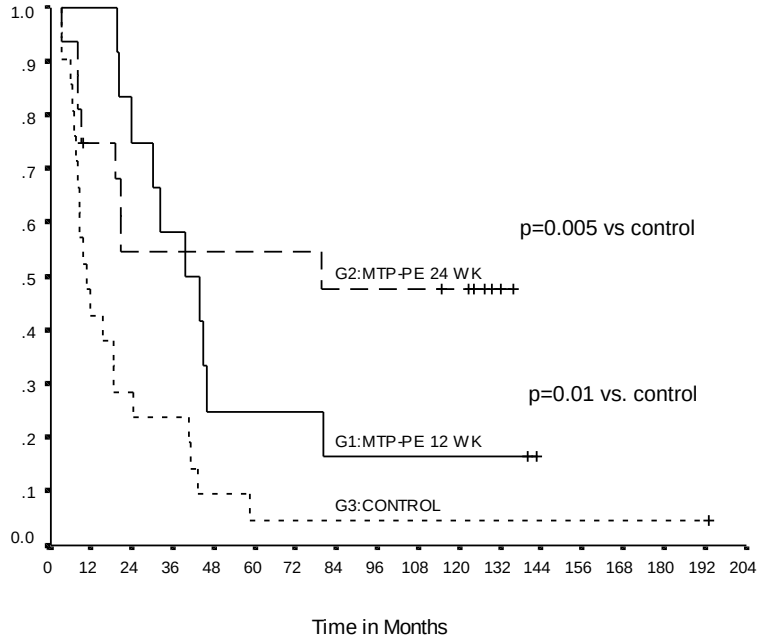
Section A. Clarification on effectiveness data

A1. Please provide justification for the length (36 weeks, 48 infusions) of MEPACT treatment.

Treatment duration is important in the efficacy of immune response modifier agent-based regimens, since long term immune activation may be required to obtain optimal biological effects. This was also shown by the results of a phase 2 study with MEPACT. In the study, 24 weeks of treatment (twice weekly for 12 weeks then once weekly for an additional 12 weeks) was more effective than 12 weeks of twice weekly treatment. When it was observed that this longer treatment period was associated with a better survival outcome and without increased toxicity (Figure A1), the treatment schedule was further extended to 36 weeks in the phase 3 study (once weekly for an additional 12 weeks beyond 6 months) so that the administration of MEPACT would extend slightly beyond the longest chemotherapy administration.

Figure A1: Survival Follow-up of Patients in Phase 2 Study 08
(Dr. E. Kleinerman, personal communication)



The proposed treatment regimen, 2 mg/m^2 twice weekly for 12 weeks and then once weekly for 24 weeks, was shown to provide significant and sustained survival benefit in the phase 3 study. This longer treatment duration is consistent with the underlying biological mechanism of action, and the understanding that immune activation may be necessary for a relatively long period of time to optimise the efficacy of agents with immunomodulatory properties.

Section 6.1.

A2. Please clarify the number of citations identified for clinical effectiveness through MEDLINE. When the ERG reran this search it identified 302 studies. Please explain the discrepency between this figure and the 186 citations reported in your submission.

Our searches of MEDLINE identified 300 references and searches of MEDLINE in Process, Embase and the Cochrane Library identified a further 34 references after deduplication, bringing the total to 334 articles as previously specified in Section 6.2. The 186 articles cited in Appendix 2 is in error and reflects an early iteration of the search strategy. Note, the search strategy presented in the report is an amalgam of two separate searches which were presented together in the report for ease of viewing.

Section 6.3.1.1.

A3. Please clarify whether outcome assessments were blinded in INT-0133.

Blinding is not needed to assess patient survival, which was the first stated aim of study INT-0133. Blinding of treatment was not considered feasible in study INT-0133 because (i) it is not acceptable to expose children or adolescents to 48 placebo injections and (ii) the low grade side effects that usually result from initial MEPACT doses, including fever, chills and headache, would make blinding difficult. The outcome assessments used are consistent with the European regulatory standards set out in the Note for Guidance on the Evaluation of Anticancer Medicinal Products in Man (CPMP/EWP/205/95 Rev.3) and the Addendum on Paediatric Oncology (CPMP/EWP/569/02).

In addition, central third party reading of relapse scans is not standard practice for paediatric osteosarcoma studies, because relapse is identified as newly detectable disease in a patient previously in remission rather than by assessment of disease response or progression based on tumour size.

Section 6.3.1.2.

A4. Please clarify whether INT-0333 uses the most effective combination (dosage and timing) of high dose methotrexate, doxorubicin and cisplatin. In addition, do the dosage and timings of ifosfamide in the INT-0133 trial reflect current practice in (including in EURAMOS trial) or outside the UK for first and second line therapy?

The dosage and timing of methotrexate, doxorubicin and cisplatin were essentially the same in study INT-0133 as in the comparator arms for the ongoing EURAMOS study (Tables A4a-c). This reflects current clinical practice in the UK as well as in many other geographical locations, such as Member States of the European Union. The regimen used represents the most effective chemotherapy combination currently available, as evidenced by use in the EURAMOS trial comparator treatment arms.

Table A4a: Chemotherapy Doses in INT-0133 and EURAMOS

	INT-0133		**EURAMOS**	
	Dosage	**Total dose**	**Dosage**	**Total dose**
Doxorubicin (A)	25 mg/m^2/d x 3d	450 mg/m^2	37.5 mg/m^2/day x 2d	450 mg/m^2
Cisplatin (P)	120 mg/m^2	480 mg/m^2	60 mg/m^2/day x 2d	480 mg/m^2
Methotrexate (M)	12 g/m^2	144 g/m^2	12 g/m^2	144 g/m^2
Ifosfamide (I) **Regimen B only**	1.8 g/m^2/day x 5d	45 g/m^2	1.8 g/m^2/day x 5d (l) 2.8 g/m^2/day x 3d	43.8 g/m^2
Etoposide	-	-	100 mg/m^2/day x 5d	1500 mg/m^2

Table A4b: Induction Chemotherapy INT-0133 and EURAMOS

	Week					
	0	**3**	**4**	**5**	**8**	**9**
INT-0133 Regimen A	AP	M	M	AP	M	M
INT-0133 Regimen B	IP	M	M	IP	M	M
EURAMOS	AP	M	M	AP	M	M

Table A4c: Maintenance (Adjuvant) Chemotherapy INT-0133 and EURAMOS

WEEK	12	15	16	17	19	20	21	22	23	24	25	26	27	28	29	30	31	32	35	36	38	39	40
INT-0133 Regimen A	AP	M	M	AP		M	M	A			M	M	A			M	M						
INT-0133 Regimen B	AP	M	M	AI		M	M	AP			M	M	AI			M	M	P	I		P		
EURAMOS comparator arms	AP	M	M	AP		M	M	A		M	M	A		M	M								
Group 1 Arm 2	AP	M	M	AP		M	M	A		M	M	A		M	M	IFN Wks 30-104							
Group 2 Arm 2	AP	M	IE		M	AI (l)			M	IE			M	AP			M	IE	M	AI (l)		M	M

In all regimens, the total doses of doxorubicin, cisplatin, methotrexate and ifosfamide (when used) were the same (A, C, M) or very similar (I). In INT-0133 Regimen B all doses of cisplatin were given during maintenance treatment whereas in Regimen A and in EURAMOS,

they were split between the induction and maintenance periods, although total doses were identical for all regimens. The maintenance chemotherapy schedule was extended in INT-0133 Regimen B to accommodate the addition of ifosfamide; in EURAMOS Group 2, Arm 2 the schedule is extended to accommodate the addition of both etoposide and ifosfamide.

Section 6.3.1.2 and 6.4.2.

A5. Please provide justification on the protocol amendment to extend MEPACT treatment in the INT-0133 trial from 36 to 48 weeks. In addition, as a result of the amendment, were the numbers of infusions increased? What were the reasons for patients not receiving the full 48 infusions? Do survival rates differ according to the number of doses received? What were the major reasons for patients receiving more than the 48 doses (Table 2, p47)?

The phase 2 study in which treatment duration was shown to be important (see response to A1) was completed at the same time as study INT-0133 was being initiated. Based on the improvement in outcomes associated with longer duration MEPACT monotherapy in the phase 2 study and the decision to extend MEPACT treatment beyond the completion of chemotherapy, a very early study INT-0133 protocol amendment supported an increase in the number of MEPACT doses from 36 to 48 and the treatment duration from 24 to 36 weeks.

Eleven patients in the INT-0133 intent-to-treat population were randomised to MEPACT prior to the protocol amendment. The protocol amendment was implemented close enough to study initiation that all patients randomised to MEPACT had the opportunity to receive the extended treatment schedule.

Some patients did not receive the full MEPACT treatment schedule during maintenance therapy for a number of reasons including:

- Voluntary withdrawal or non-compliance (refusal) by patient or parents.
- Withdrawal from treatment due to chemotherapy toxicity.
- Disease recurrence.
- Withdrawal by the physician.
- A major protocol violation.

Attempts were made to analyse cumulative MEPACT dose response relationships versus survival for the phase 3 study. While the outcomes of these analyses generally favoured MEPACT (either in terms of p-value or the direction of the hazard ratio), full analysis was problematical as MEPACT is given with several other chemotherapies and a higher cumulative MEPACT dose is also associated with longer treatment duration with other agents.

Sixty one of 338 patients randomised to receive MEPACT were reported to have received one (n=29), two (n=27) or more (n=5) extra MEPACT doses. The reason for this may be

due to patients receiving MEPACT at both a major oncology centre (trial participant) and at a local facility under the direction of their local physician; the administration of extra MEPACT doses may have been due to problems with sites notifying each other on the number of doses received.

Section 6.3.1.2.

A6. Please provide the number of patients in each MEPACT group who had dose escalation to 2mg/m^2 +1mg and then to 2mg/m^2 +2mg. Also provide data on the number of people who exceeded a dose of 2mg/m^2.

Only a small number of patients (<10%) in the phase 3 study underwent MEPACT dose escalation. Twenty-eight patients in the intent-to-treat population received doses exceeding 2 mg/m^2, 11 randomised to Regimen A + MEPACT and 17 randomised to Regimen B + MEPACT. In the Regimen A group, 4 patients had a maximum MEPACT dose of 2 mg/m^2 + 1 mg and 7 patients had a maximum dose of 2 mg/m^2 + 2 mg. In the Regimen B group, 3 patients had a maximum MEPACT dose of 2 mg/m^2 + 1 mg and 14 patients had a maximum dose of 2 mg/m^2 + 2 mg. In three instances, the higher dose was due to a dosing or labeling error, as documented in the case report form, and all subsequent doses were administered at 2 mg/m^2. The small proportion of patients (<10%) who underwent dose escalation supports the observation that 2 mg/m^2 is a biologically active dose of MEPACT. The SPC agreed with the CHMP (that essentially forms a basis of the terms of the centralised marketing authorisation) stipulates a fixed MEPACT dose of 2 mg/m^2.

Section 6.3.3.

A7. Please clarify the number of patients randomised in the INT-0133 trial, and explain the discrepancies between the manufacturers submission, Meyer et al 2005, and Meyer et al 2008.

A total of 793 patients were randomised into study INT-0133. The primary analysis group included 678 patients, aged ≤30 with newly diagnosed non-metastatic high-grade resectable osteosarcoma. This was the intent-to-treat population as defined by the study protocol. The study also allowed patients with metastatic or unresectable disease to be enrolled, with the study design stipulating that they be analysed separately. Sixteen of the 793 randomised patients were deemed ineligible by the COG after randomisation. US cooperative groups are required to exclude data from ineligible patients in all analyses and reports, thus the total number of patients reported by COG was 777 and the intent-to-treat group analysed by the COG (in the 2008 publication) comprised 662 patients. A true intent-to-treat analysis includes all randomised patients and IDM Pharma's analysis, therefore, included COG-ineligible patients (giving n=793 in total and n=678 as the intent-to-treat population). However, the study findings and conclusions were the same

irrespective of inclusion or exclusion of COG-ineligible patients. The 2007 dataset was independently verified by the inspectors assigned by the European Medicines Agency during centralised regulatory review, and showed compliance with good clinical practice and providing the most up-to-date and comprehensive information that could be reliably used for evaluation of the clinical benefits of MEPACT.

The 2005 publication apparently excluded ineligible patients and patients with metastatic disease but included some patients with unresectable non-metastatic disease at diagnosis. This error was corrected in the 2008 analysis and publication.

Section 6.3.4.

A8. Please confirm the following: Primary endpoint = Disease Free Survival; Secondary endpoints = Overall survival, histological response and adverse events. Please provide precise definitions of the survival outcomes in terms of events and time period.

The first stated aim of pivotal study INT-0133 was to improve survival (OS), as indicated on the first page of the study protocol. OS was defined as the time from study randomisation to death from any cause. The US National Cancer Institute (NCI) cooperative group convention at the time the protocol was written was to justify in the document the number of patients enrolled and the time at which the initial analysis would be available. For INT-0133, the first analysis planned was based upon an intermediate endpoint and the study was sized against that intermediate endpoint. The intermediate endpoint was Disease-Free Survival (DFS). DFS was defined as the time from study randomisation to disease progression/recurrence of osteosarcoma, or death from any cause.

Improvement in OS was the primary study aim, is the goal of MEPACT treatment, and is the most important outcome measure for young people with osteosarcoma. While an intermediate endpoint such as DFS is frequently used in assessing efficacy, this is an intermediate or surrogate outcome for OS; OS remains the gold-standard for assessment of a cancer therapy, as noted in the CHMP Guideline on the Evaluation of Anticancer Medicinal Products in Man (CPMP/EWP/205/95/Rev.3/Corr.2).

Consistent with the standard rules of setting censoring times, patients without events were censored on the date of last contact. Of the 678 patients in the intent-to-treat (ITT) analysis, 173 were reported to have died with survival being measured to the date of death. Survival for the remaining 505 patients in the ITT analysis was measured until the date of censoring. These 505 patients were censored on the documented last contact date. All patients were known to be alive on the date used for censoring and no assumptions were made concerning the survival status of any patient.

The primary and first stated aim of INT-0133 was to improve OS. As listed in the study protocol, included comparison of the results (including histological response) from the two chemotherapy regimens (three vs. four agent regimens) to determine: whether

histological response after a long pre-operative chemotherapy regimen was as strong a predictor of DFS as histological response after a short pre-operative chemotherapy regimen; if addition of MEPACT improved DFS; and if multiple drug resistance gene-encoded P-glycoprotein was a useful factor for consideration when assigning therapy or determining prognosis.

Section 6.3.5

A9. Please clarify the definition of intent-to-treat (ITT) as being from randomisation (study entry) rather than from receipt of neoadjuvant treatment.

The intent-to-treat analyses performed by IDM Pharma are defined as starting at the date of randomisation (study entry), as prospectively planned.

Section 6.3.6.

A10. Please provide a tabulated summary of the suggested critical appraisal criteria as noted in the NICE STA specification guide to manufacturers.

Critical Appraisal Criteria	**INT-0133 (Non-metastatic resectable osteosarcoma, ITT)**
How was allocation concealed?	Randomisation was performed centrally by the COG Data Center. Randomisation assignment was not concealed (see response A3).
What randmoisation technique was used?	Prior to the start of the study, a randomisation assignment sheet was constructed for each stratum. The treatments were assigned on the sheet in permuted block sizes of 4. The assignments were generated using the CCG-developed, FORTRAN-based program RANDTAB. When a patient was to be enrolled from an institution, an institutional Clinical Research Associate called the Telephone Study Registrar at the COG Operations Center.
Was a justification of sample size provided?	The convention for the cooperative group at the time the protocol was written was to justify in the document the number of patients enrolled and the time at which the initial analysis would be available. For INT-0133, the first analysis planned was for an intermediate endpoint and the study was sized for that endpoint. This is described and justified based on observations from prior studies.
Was follow up adequate?	Yes, in the 2006 and 2007 datasets, almost 95% of patients are accounted for at 3 years and more than 80% are accounted for beyond 5 years. The 2007 dataset was the subject of a satisfactory inspection carried out by the EMEA.
Were the individuals undertaking the outcomes assessment aware of	Blinding is not needed to assess patient survival, which was the first stated aim of study INT-0133. Blinding of treatment was not considered feasible in study INT-0133 because (i) it was not

Critical Appraisal Criteria	INT-0133 (Non-metastatic resectable osteosarcoma, ITT)
allocation?	acceptable to expose children or adolescents to 48 placebo injections and (ii) the side effects that usually result from initial MEPACT doses (including low grade fever, chills and headache) would make it difficult to blind the study. In addition, central third party reading of relapse scans is not standard for paediatric osteosarcoma studies because relapse is considered in terms of newly detectable disease in a person previously in remission, rather than by an assessment of disease response or progression based on tumour size.
Was the design parallel-group or crossover?	Parallel group
What was the study design?	The study had a four-arm multi-centre, randomised and open-label design.
Was the RCT conducted in the UK; if not, is clinical practice likely to differ from UK practice?	INT-0133 was conducted in North America. The patient characteristics and clinical practices for osteosarcoma do not differ between the US and most of Europe, including the UK. This is illustrated by the ongoing EURAMOS study in which the USA and most EU cooperative groups, including those in the UK, participate.
How do the included RCT participants compare with patients who are likely to receive the intervention in the UK?	The participants in study INT-0133 are highly representative of patients likely to receive the intervention in the UK.
What dosage regimens were used in the RCT?	The four study treatment arms comprised 10 weeks of induction therapy comprising: • **Regimen A** - two doses of doxorubicin (25m g/m^2/day over 72 hours), two doses of cisplatin (120 mg/m^2) and four doses of high dose methotrexate (12 g/m^2). • **Regimen B** - two doses of doxorubicin (25 mg/m^2/day over 72 hours), two courses of ifosfamide (1.8 g/m^2/day x 5 days) and four doses of high-dose methotrexate (12 g/m^2). followed by definitive surgery and then maintenance therapy of: • **Regimen A** - four doses of doxorubicin, two doses of cisplatin and eight doses of methotrexate. • **Regimen A+** - four doses of doxorubicin, two doses of cisplatin and eight doses of methotrexate plus MEPACT. • **Regimen B** - four doses of doxorubicin, four doses of cisplatin, three courses of ifosfamide and eight doses of methotrexate. • **Regimen B+** - four doses of doxorubicin, four doses of cisplatin, three courses of ifosfamide and eight doses of methotrexate plus MEPACT. MEPACT was given as twice-weekly intravenous infusion for 12 weeks followed by once weekly intravenous infusion for 36

Critical Appraisal Criteria	INT-0133 (Non-metastatic resectable osteosarcoma, ITT)
	weeks. The starting dose of MEPACT was 2 mg/m^2, which could be dose-escalated to 2 mg/m^2 + 1 mg and then to 2 mg/m^2 + 2 mg until biological activity was seen. Other chemotherapies were used at the same doses as for induction therapy.
Are these dosage regimens used within the SPC?	Most patients in study INT-0133 (>90%) received MEPACT at 2 mg/m^2, the same dosage as recommended in the SPC. The schedule of treatment, 48 doses over 36 weeks, was the same in study INT-0133 as that recommended in the SPC, which will form part of the terms of the marketing authorisation to be granted by the European Commission.
Were the study groups comparable?	Yes, the MEPACT and no-MEPACT groups were comparable with respect to gender, age, and race. Patients were stratified at randomisation for important prognostic factors and so groups were also comparable for tumour location and LDH. The only imbalance was identified after neoadjuvant chemotherapy and definitive surgery, with more patients in the MEPACT group showing a poor histological response to neoadjuvant chemotherapy. Since this was determined after definitive surgery, it was impossible to control at randomisation.
Were the statistical analyses used appropriate	Yes, standard and appropriate statistical methodologies were used that were consistent with the statistical principles described in the various guidelines adopted by the International Conference on Harmonisation and have been accepted by the regulatory authorities in the the European Union, United States and Japan. Standard statistical methodologies were used in all efficacy analyses. The product-limit estimator of Kaplan and Meier (1958 - Kaplan EL and Meier P. Nonparametric estimation from incomplete observations. *Journal of the American Statistical Association* 1958; 53:457-481[1]) was used to estimate the survival curves, and the Cox proportional hazards regression model (1972 - Cox DR. Regression models and life tables [with discussion]. *Journal of the Royal Statistical Society B* 1972; 34:187-220[2]) was used to estimate the reduction in risk of death. The log-rank statistic, as described in the study protocol was used to test for treatment differences with respect to overall survival.
Was an intent-to-treat analysis undertaken	Yes, the primary analysis on which the conclusions wre based is an intent-to-treat analysis.
Were there any confounding factors that may attenuate the interpretaion of the results	For the primary study aim, overall survival, there were no confounding factors.

A11. Please provide details on the number of patients (for each of four treatment arms) who did not enter the maintenance phase of INT-0133. In addition, provide details on the number of disease free survival events and death (by treatment arm) in the subset of patients who did not enter the maintenance phase.

The requested information regarding the number of patients who did not enter maintenance in INT-0133 is included in the following table for intent-to-treat patients (Table A11a).

Table A11a: Patient Disposition during Induction and Maintenance Phases INT-0133 (ITT Population)

	Regimen A	**Regimen A + MEPACT**	**Regimen B**	**Regimen B + MEPACT**
	N=174	N=167	N=166	N=171
Entered Induction Phase	170	164	164[1]	169
Withdrawn				
Progressive Disease	6	6	4	3
Removed for Toxicity	0	0	2	1
Withdrawal by Parent or Patient	3	4	5	4
Withdrawal by Physician	3	1	0	0
Major Protocol Deviation	2	4	6	3
Death	2	0	0	0
Lost to Follow-Up	0	0	0	0
Other	1	4	0	0
Entered Maintenance Phase	153 (88%)	145 (87%)	148 (89%)	158 (92%)
Withdrawn				
Progressive Disease	9	8[2]	7	9
Removed for Toxicity	1	1	4	2
Withdrawal by Parent or Patient	8	20	6	26
Withdrawal by Physician	0	1	4	6
Major Protocol Deviation	2	5	5	4
Death	1	1	0	1
Lost to Follow-Up	0	1	0	1
Other	0	0	1	2
Deemed Ineligible	2	0	1	1
Completed Protocol Therapy	130	108	120	106

[1]One patient with prior surgery went directly to maintenance chemotherapy and did not have induction chemotherapy. This patient is not included in the total of 164.

[2]One patient had progressive disease documented at surgery. This patient is included among those with progressive disease.

The number of DFS and death events is summarised by treatment arm in the subset of patients who did not enter the maintenance phase in Table A11b.

Table 11b: Events Reported for ITT Patients Who Did Not Reach the Maintenance Phase

	Treatment Assignment				
	A -	**A +**	**B -**	**B +**	**Total**
DFS Event					
No	6 (28.57%)	9 (40.91%)	6 (33.33%)	7 (53.85%)	28 (37.84%)
Yes	15 (71.43%)	13 (59.09%)	12 (66.67%)	6 (46.15%)	46 (62.16%)
Total	21 (100%)	22 (100%)	18 (100%)	13 (100%)	74 (100%)
Death					
No	8 (38.10%)	15 (68.18%)	12 (66.67%)	7 (53.85%)	42 (56.76%)
Yes	13 (61.90%)	7 (31.82%)	6 (33.33%)	6 (46.15%)	32 (43.24%)
Total	21 (100%)	22 (100%)	18 (100%)	13 (100%)	74 (100%)

A12. Please provide a full breakdown of the number of withdrawals for each treatment group prior to and during the maintenance phase. Please provide details of the reasons for withdrawal (including definition and severity of toxicities etc), broken down by the four treatment arms if possible.

Table A11a presents a full breakdown of the number of withdrawals for each treatment group prior to and during the maintenance phase. Three and eight patients, respectively, were removed from the study due to toxicity during the induction and maintenance phases. Table A12 describes toxicities as recorded in the CRF. The definition of adverse event grades can be found in the Children's Cancer Group Toxicity and Complications Criteria (Attachment 1).

Table A12: Patients Removed For Toxicity in INT-0133 (ITT Population)

Regimen	Toxicity noted in CRF
Removed Prior to the Maintenance Phase	
B	Grade 4 leukoencephalopathy associated with methotrexate administration in induction course 1; removed from protocol therapy.
B	Removed from study due to grade 4 anaphylactic reaction to methotrexate during induction course 1.
B + MEPACT	Removed from therapy due to grade 3 allergic reaction to methotrexate during induction course 1.
Removed During the Maintenance Phase	
B	Removed from protocol therapy during maintenance course 1 due to severe methotrexate toxicity. Associated adverse events included grade 4 increases in SGOT and SGPT and grade 4 neurotoxicity (central cerebellar), including seizures and encephalopathy.
A	Removed from protocol therapy due to doxorubicin cardiotoxicity during maintenance courses 2 and 3, including left ventricular dilation, S4 gallop on physical examination and shortening fraction on echo (48%).
B	Removed from study due to liver failure and renal dysfunction during maintenance course 3. Associated adverse events included grade 4 platelet decrease, grade 3 SGPT, grade 4 total bilirubin abnormality, grade 3 creatinine clearance and grade 4 infection.
B + MEPACT	Patient removed having developed Fanconi's syndrome during maintenance course 3. Adverse events associated included grade 3 electrolyte abnormality (K) and urine/serum glucose levels of 14 and 109 mg/dl, respectively.
B	Removed from protocol therapy during maintenance course 4 due to grade 3 cardiotoxicity (doxorubicin) and decreased renal function (grade 4 creatinine clearance attributed to cisplatin and methotrexate).
B	Discontinued all chemotherapy during maintenance course 5 due to Staphylococcal osteomyelitis (listed as grade 4 "local" adverse event).
B + MEPACT	Removed from therapy during maintenance course 5 due to concern over renal function. The associated adverse event was grade 4 electrolyte (Mg) abnormality.
A+ MEPACT	Admitted twice for severe abdominal pain and distension, nausea and vomiting after MEPACT during the final treatment course. Discontinued MEPACT following completion of all chemotherapy.

A13. Please provide further details on compliance to study treatments, by each arm, prior to and during the maintenance phase.

There was overall good compliance to study treatments. Significant non-compliance to the study plan is referred to by the COG as a protocol break, defined as a modification in protocol therapy that is sufficiently different from the protocol plan as to make the toxicity data recorded not comparable with that for other patients at the same point during treatment. The majority of documented protocol breaks were due to voluntary withdrawal either by the patient/parent or by the physician. However some protocol breaks were related to deviations in planned therapy, for a variety of reasons. Overall, 92 protocol breaks were reported, as summarised in Table A13 (phase 1 refers to induction and phase 2 refers to maintenance).

Table A13: Reasons for Protocol Breaks in Study INT-0133

Time of Protocol Break		
Phase	**Course**	**Reason for Noncompliance**
		Regimen A + MEPACT
1	1	Patient started on the wrong regimen by mistake (B+ instead of A+)
1	2	Did not have definitive surgery at end of induction course 2 due to scheduling difficulties and varicella zoster infection; surgery was postponed until after starting maintenance therapy
2	1	MEPACT was not given, reportedly by mistake
2	1	Did not receive MEPACT during maintenance due to non-availability of filters; none was given after chemotherapy was competed. Also received an increased dose of methotrexate in phase 2, course 1 which violated protocol guidelines.
2	1	Did not receive doxorubicin due to concerns over cardiac function (not a break); cisplatin was discontinued at the family's request due to moderate hearing loss (patient/guardian refusal); ifosfamide was added (severe deviation)
2	1	Inadvertently not given MEPACT for the first 14 weeks of maintenance; it was decided not to subsequently administer MEPACT
2	1/2	Cisplatin, doxorubicin and 1 dose of methotrexate and MEPACT were not given in maintenance course 2; MEPACT was not given in maintenance course 1; all were reportedly due to surgical delays
2	2	Omitted methotrexate from the end of maintenance course 2 until the patient discontinued therapy due to mucositis; not consistent with protocol guidelines
2	3/4	No MEPACT was given during courses 3 and 4, reportedly due to chest and back pain
2	3/4	Parents refused additional MEPACT in maintenance course 3 and last two methotrexate doses in maintenance course 4
2	4	Patient did not receive 7 doses of MEPACT during maintenance course 4, reportedly due to two episodes of gram negative sepsis
		Regimen A
1	2	Second dose of methotrexate was omitted due to impending definitive surgery; adequate support for the deviation was not provided.
2	1	Courses were given out of order (3, 1, 2, 4)
2	1	Surgery was postponed until maintenance course 1
2	2	Major change from CCG protocol therapy
2	3	Not given doxorubicin during maintenance course 3, reported as due to "small body size"
		Regimen B + MEPACT
1	1	Stopped subsequent methotrexate administration after acute toxicity in induction course 1; not considered consistent with protocol guidelines
1	1	Patient had definitive surgery prior to study entry; skipped induction and went directly to maintenance due to a misinterpretation of the protocol
1	2	Removed from therapy at the end of induction due to delays in the parental decision regarding surgery
2	1	Modifications included doxorubicin given over 48 hrs, not 72 hours; methotrexate dose reduced; both methotrexate doses omitted during course 4; cisplatin omitted from course 5

Time of Protocol Break		
Phase	**Course**	**Reason for Noncompliance**
2	1	Parents elected to discontinue MEPACT
2	2	No chemotherapy after this course; surgery had not healed over 7 months due to chemotherapy side effects
2	3	Series of fever with neutropenia, and typhlitis during maintenance course 3 resulted in omission of cisplatin in accordance with protocol guidelines; omission of two MEPACT doses (in the best interest of the patient); reduced methotrexate dose by 50% (severe deviation)
2	3	Cisplatin inadvertently omitted during phase 2 course 3
2	4	Parent requested no more cisplatin due to hearing loss; replaced with carboplatin in maintenance course 5
2	4	Omitted methotrexate from maintenance course 4 due to neutropenia and fever (dose 1) and low platelet count (dose 2); omission of both doses considered not justified
2	4	Stopped MEPACT therapy due to severe neutropenia; the treating team was convinced that MEPACT may have prolonged neutropenia, which was discontinued in the best interest of patient care
2	5	Last dose of cisplatin omitted due to hearing loss at 4000 Hz (not at 2000 Hz)
2	5	MEPACT discontinued due to shaking/chills
Regimen B		
1	0	Patient missed induction due to misinterpretation of the protocol
1	1	Taken off protocol therapy due to anaphylactic reaction to methotrexate (per study chair, methotrexate could have been omitted and the patient remain on therapy)
1	2	Physician decided to give more chemotherapy before definitive surgery, despite counselling against this by the PI
2	1	Patient did not receive chemotherapy from Days 0-2 (cisplatin/doxorubicin); chemotherapy delay reportedly due to wound infection and increases in liver function tests. Patient went directly to high-dose methotrexate
2	4	Did not receive full dosage of ifosfamide and doxorubicin due to inconsistencies between medical and pharmacy accounts of the doxorubicin dispensed
2	5	Omitted ifosfamide and reduced cisplatin on the family's request
2	5	Did not receive the last dose of cisplatin due to grade 2 auditory toxicity

A14. Please provide details on rates of discontinuation for each of the four arms, prior to and during the maintenance phase.

Please see Table A11. Discontinuation rates are summarised in Table A14. It should be noted that Regimen B + MEPACT was the longest planned treatment schedule in this study. It is well recognised that in trials comparing treatments where one is significantly longer than the other, patients are more likely to cease therapy earlier than planned in the longer arm (Souhami et al *Lancet.* 1997 Sep 27;350(9082):911-7[3]).

Table A14: Discontinuation by Treatment Assignment Before and During Maintenance INT-0133 (ITT Population)

Regimen	A	A + MEPACT	B	B + MEPACT
Randomised (N)	174	167	166	171
Withdrawn before maintenance	21 (12%)	22 (13%)	18 (11%)	13 (8%)
Entered maintenance	153 (88%)	145 (87%)	148 (89%)	158 (92%)
Withdrawn during maintenance	23 (13%)	37 (22%)	28 (17%)	52 (30%)

Sections 6.3.6.4 and 6.4.2.

A15. Please provide details which summarise, for each of the four arms, what dosage of MEPACT was actually used, and how many cycles of MEPACT were actually administered, during treatment maintenance phase.

With the exception of a small group of patients (described in the response to A6), all patients who received MEPACT in study INT-0133 received the 2 mg/m^2 dose. The number of doses of MEPACT administered for each of the two MEPACT study arms is summarised in Table A15. No MEPACT was given to patients in Regimens A and B.

Table A15: MEPACT Exposure INT-0133 (ITT Patients)

		Regimen A with MEPACT (N=167)	**Regimen B with MEPACT** (N=171)
Number of Doses of MEPACT	0	29 (17%)	16 (9%)
	1-5	8 (5%)	5 (3%)
	6-10	5 (3%)	5 (3%)
	11-15	1 (<1%)	6 (4%)
	16-20	5 (3%)	3 (2%)
	21-25	8 (5%)	10 (6%)
	26-30	6 (4%)	8 (5%)
	31-35	2 (1%)	11 (6%)
	36-40	12 (7%)	10 (6%)
	41-45	13 (8%)	17 (10%)
	46-50	75 (45%)	78 (46%)
	>50	3 (2%)	2 (1%)
Average MEPACT dose	N	138	155
	Mean (SD)	3.1 (0.8)	3.1 (0.8)
	Median	3.0	3.0
	Min – Max	1.4 – 5.8	1.4 – 5.3
Cumulative MEPACT dose	N	138	155
	Mean (SD)	120.4 (52.9)	117.6 (52.7)
	Median	132.2	117.6
	Min – Max	2.4 – 265.2	3.5 – 251.4
Including Patients with No Dose:			
Average MEPACT dose	N	167	171
	Mean (SD)	2.6 (1.4)	2.8 (1.2)
	Median	2.9	3.0
	Min – Max	0.0 – 5.8	0.0 – 5.3
Cumulative MEPACT dose	N	167	171
	Mean (SD)	99.5 (66.3)	106.6 (60.8)
	Median	115.0	110.4
	Min – Max	0.0 – 265.2	0.0 – 251.4

Section 6.3.6.6

A16. Please justify why a Gompertz model was preferred. This distribution has a hazard function which increases exponentially with time, which is unlikely to be the case for osteosarcoma. Perhaps a Weibull distribution truncated at the appropriate time may have been more appropriate, or even a log-normal distribution, which allows for a decrease in hazard after a period of time.

The Gompertz model as described by Cantor (Sample size calculations for the log rank test: a Gompertz model approach, *Journal of Clinical Epidemiology* 1992;45(10):1131-1136[4]) was used in the protocol (section 15.3) to justify the sample size. The hazard function may increase or decrease with time, depending on paramter values. The Gompertz model is commonly used to model survival data when a proportion of patients is anticipated to experience long-term survival or cure.

A17. Please clarify whether any tests were undertaken to see if a proportional hazards assumption was appropriate for estimating the treatment effect of MEPACT.

The Cox proportional hazards regression model assumes that the hazards (risk of death) for the two treatment arms are proportional to one another. The proportionality of the hazards for the MEPACT and the no MEPACT treatment arms is illustrated in Figures A17a and A17b, demonstrating the appropriateness of the analytic approach.

Figure A17a: Hazard, Overall Survival (ITT Population)

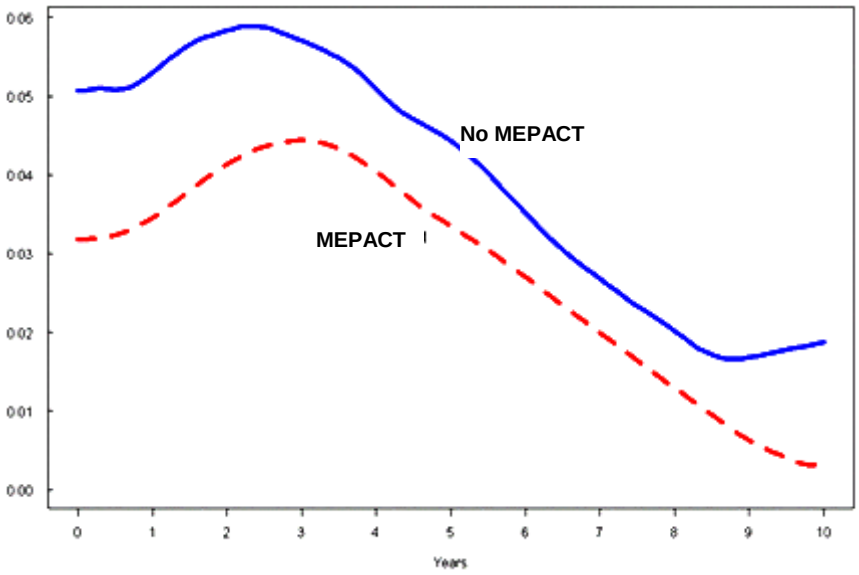
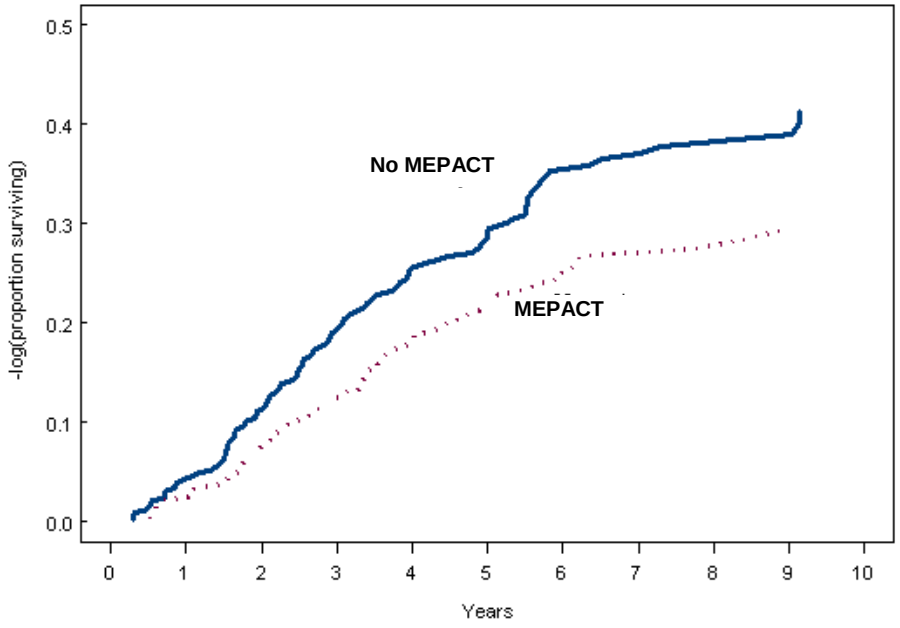


Figure A17b: Cumulative Hazard, Overall Survival (ITT Population)



A18. Please provide the p-value for the interaction test for age.

The appropriate testing procedures (Gail and Simon. Testing for qualitative interactions between treatment effects and patient subsets. *Biometrics*, 1985, 41, 361-372[5]) yielded results indicating non-significance for the interaction between MEPACT treatment and age (p = 0.210).

Section 6.4.1.

A19. Please provide distributions for age at diagnosis for each of the four treatment groups.

Since study entry was required to occur within 30 days of diagnosis, the ages of patients at study entry were equivalent to the age at diagnosis ± 30 days.

Table A19: Age Distribution by Treatment Assignment (ITT Population)

Regimen	A	A + MEPACT	B	B + MEPACT
Age (years)				
Mean	13.8	14.0	13.5	13.8
Median	13.3	14.3	13.6	13.9
Range	4.0 – 30.1	4.9 – 29.2	4.2 – 30.6	1.4 – 30.4

A20. Please provide details regarding tumour response (i.e. grades, including definitions) following the neoadjuvant treatment phase, by each of the four regimens.

Histological response to neoadjuvant treatment is summarised by regimen assignment in Table A20a. The Huvos grading system was used in study INT-0133.

Table A20a: Histological Response* to Neoadjuvant Therapy INT-0133 (ITT Population)

	Grade I	Grade IIA	Grade IIB	Grade III	Grade IV		
	No effect	>50% viable tumour	5%-50% viable tumour	<5% viable tumour	No viable tumour	**Not reported**	**Total**
A	7	21	50	50	21	25	174
A + MEPACT	6	28	59	32	20	22	167
B	4	12	62	42	26	20	166
B + MEPACT	3	18	52	53	19	26	171
Total	20	79	223	177	86	93	678

*Test that the four treatments have the same distribution: Kruskal Wallis test p-value = 0.0649 (excluding those not reported)

With respect to prognosis, Grade I and II neoadjuvant responses are considered unfavourable and Grade III and IV responses are considered favourable. Table A20b summarises patients according to favourable or unfavourable neoadjuvant response and demonstrates the excess of unfavourable responses in the Regimen A + MEPACT treatment arm. It should be noted that stratification at randomisation balanced treatment arms for other important prognostic indicators of survival in osteosarcoma, including LDH level and tumour site. Histological response was not determined until after induction therapy and surgery and could not, therefore, be controlled for at randomisation.

Table A20b: Histological Response to Neoadjuvant Therapy INT-0133 (ITT Population)

	Unfavourable 5%-100% viable tumour	Favourable 0 - 5% viable tumour	Not reported	Total
A	78	71	25	174
A + MEPACT	93	52	22	167
B	78	68	20	166
B + MEPACT	73	72	26	171
Total	322	263	93	678

<u>Section 6.4.3.</u>

A21. Please provide tabulated results (ITT analysis) for each of the treatment groups separately for disease free survival and overall survival time. Ideally data

should be reported as follows: median follow up (6 years [2006 data set - published data from Meyer et al 2008] and 7.9 years [unpublished data from 2007 data set], event rates (number of events/total number) for each arm separately (A, A+, B, B+), for each of the 2006 and 2007 data sets. In addition, provide hazard ratios, confidence intervals and p-values for each of the six possible pairs of treatment groups, separately for each of the 2006 and 2007 data sets.

Median follow-up and event rates for the 2006 and 2007 data as provided to IDM by the COG are summarised by treatment assignment in Table A21a. IDM Pharma does not have the datasets used by the COG for their publications, as they derive and analyse their datasets independently of IDM and may use statistical procedures or practices that are unique to the cooperative groups and NCI. Please note that there were no new events when comparing the 2006 and 2007 datasets.

Table A21a: Median Follow-up, and Event Rates by Treatment Assignment INT-0133, ITT (2006 and 2007)

	2006 Data			2007 Data		
	Median follow up	**DFS events**	**OS events**	**Median follow up**	**DFS events**	**OS events**
A (n=174)	5.9	62 (36%)	51 (29%)	6.0	62 (36%)	51 (29%)
A+ MEPACT (n=167)	6.2	58 (35%)	37 (22%)	6.7	58 (35%)	37 (22%)
B (n=166)	5.9	71 (43%)	49 (30%)	6.3	71 (43%)	49 (30%)
B+ MEPACT (n=171)	6.1	49 (29%)	36 (21%)	6.2	49 (29%)	36 (21%)

Table A21b summarises the comparison of the six possible pairs of treatment groups separately for each of the 2006 and 2007 datasets.

Table A21b: Comparison by Treatment Assignment INT-0133, ITT (2006 and 2007)

	2006 Data			2007 Data		
	p-value	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**
A vs A+ MEPACT	0.2172	0.76	(0.50, 1.17)	0.1949	0.75	(0.49, 1.16)
A vs B	0.9275	0.98	(0.66, 1.45)	0.8884	0.97	(0.66, 1.44)
A vs B + MEPACT	0.1190	0.71	(0.46, 1.09)	0.1093	0.70	(0.46, 1.08)
B vs A+ MEPACT	0.1943	0.75	(0.49, 1.16)	0.1832	0.75	(0.49, 1.15)
A+ vs B + MEPACT	0.6868	0.91	(0.57, 1.44)	0.7135	0.92	(0.58, 1.45)
B vs B + MEPACT	0.0832	0.68	(0.44, 1.05)	0.0825	0.68	(0.44, 1.05)

A22. Please explain the disparities between figures 2A and 3A in Meyer et al 2008 relating to event-free survival (EFS) and overall survival (OS). EFS and OS are extremely closely linked in osteosarcoma, and while both sets of survival curves show a large difference between B+ and B, this is not the case with A and A+.

When analysing the data for the 2008 publication, the test for interaction for event-free survival (EFS) did not reach the prospectively defined level of significance (Meyers, Schwartz, Krailo et al. Osteosarcoma: the addition of muramyl tripeptide to chemotherapy improves overall survival: A report from the Children's Oncology Group. *J Clin Oncol* 2008; 26:633-638[6]). The importance of this negative test was that it allowed the the COG investigators to perform the marginal analyses, as prospectively defined. Although the magnitude of the difference in EFS was greater for Regimen B than Regimen A, it is important to note that the difference between the effect of MEPACT was one of magnitude and not one of direction. This indicates that there is no qualitative interaction in the analysis of EFS.

As discussed by Meyers, Schwartz, Krailo MD et al. (in reply: *J Clin Oncol* 2008; 26 18:3104-3105[7]) EFS and OS did correlate in this study. Both EFS and OS were improved by the addition of MEPACT to chemotherapy. The hazard ratios were similar and favoured MEPACT (0.8 for EFS and 0.71 for OS). As noted in Table A20b, an excess of patients assigned to Regimen A + MEPACT experienced an unfavourable response to neoadjuvant chemotherapy. This cannot be attributed to MEPACT or to a putative interaction, since MEPACT was not introduced until after definitive surgery, but may contribute to the poorer EFS seen in the Regimen A + MEPACT group.

When the test for interaction was applied to OS there was no indication of an interaction. The hazard ratios for the addition of MEPACT to Regimen A (HR = 0.76) and Regimen B (HR = 0.66) were similar in magnitude, and both showed improved OS to be associated with the addition of MEPACT to chemotherapy.

In exploring subgroup analyses, an imbalance in histological response was also noted in patients older than 16. In this group a large proportion of individuals experienced unfavourable responses in the MEPACT arms (Table A22 left panel and response to A25). In the larger group of patients aged less than 16 (Table A22, right panel), a balance in favourable responses was seen between those receiving or not receiving MEPACT.

Table A22: Neoadjuvant Histological Response in Patients Based on Age

	Histologic Response Patients >16 Years*				**Histologic Response Patients < 16 Years****			
	Grades I/II Unfavourable	Grades III/IV Favourable	Not reported***	Total	Grades I/II Unfavourable	Grades III/IV Favourable	Not reported***	Total
MEPACT	57 (59%)	23 (24%)	17 (17%)	97	109 (45%)	101 (42%)	31 (13%)	241
No MEPACT	40 (47%)	32 (38%)	13 (15%)	85	116 (45%)	107 (42%)	32 (13%)	255
Total	97	55	30	182	225	208	63	496

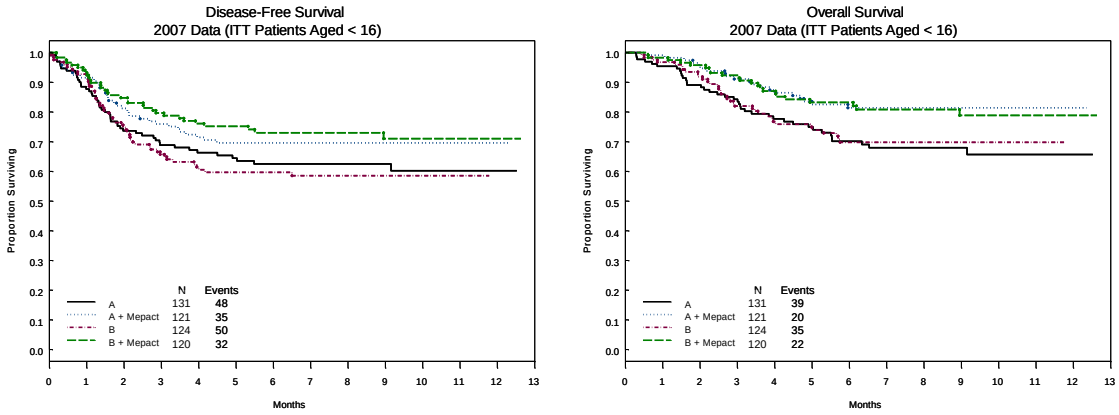
*p = 0.0626, **p = 0.9421

***Includes patients who underwent disease progression before surgery or for whom data are not available

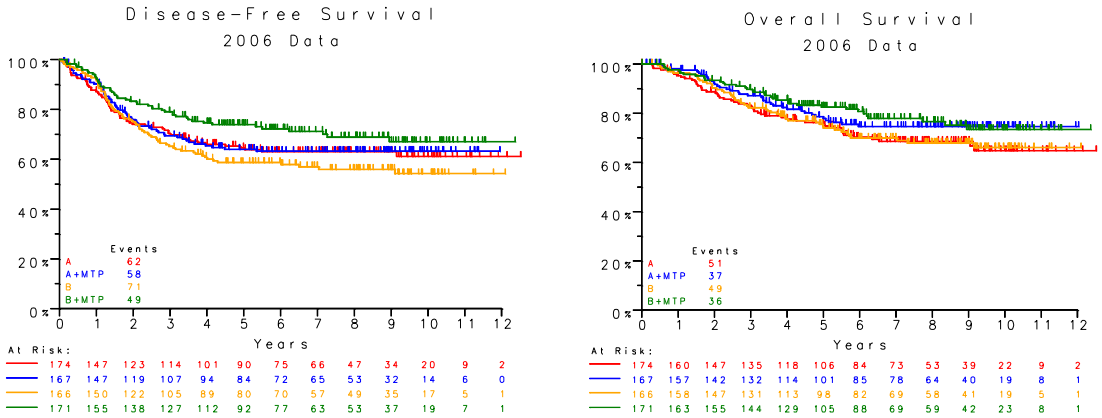
When DFS was analysed excluding patients aged over 16 years (those with the imbalance in histological response, Figure A22 left panel) any suggestion of interaction disappeared,

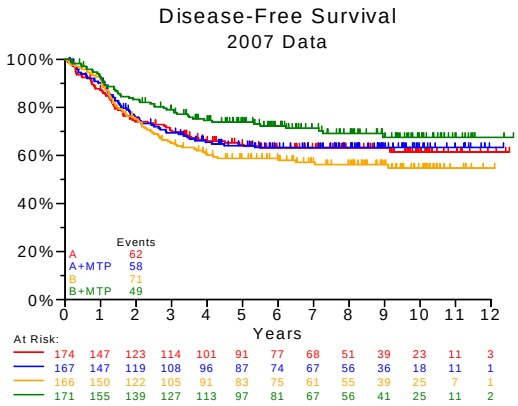
and the DFS curves were completely predictive of the OS outcome (Figure A22 right panel).

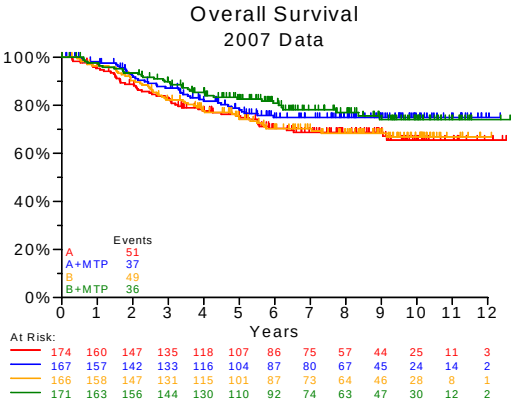
Figure A22: DFS and OS in Study INT-0133, ITT Patients <16 Years of Age



A23. Please provide Kaplan-Meier curves for the four treatment groups for 2006 and 2007 data sets (separately), including numbers at risk at each time point.







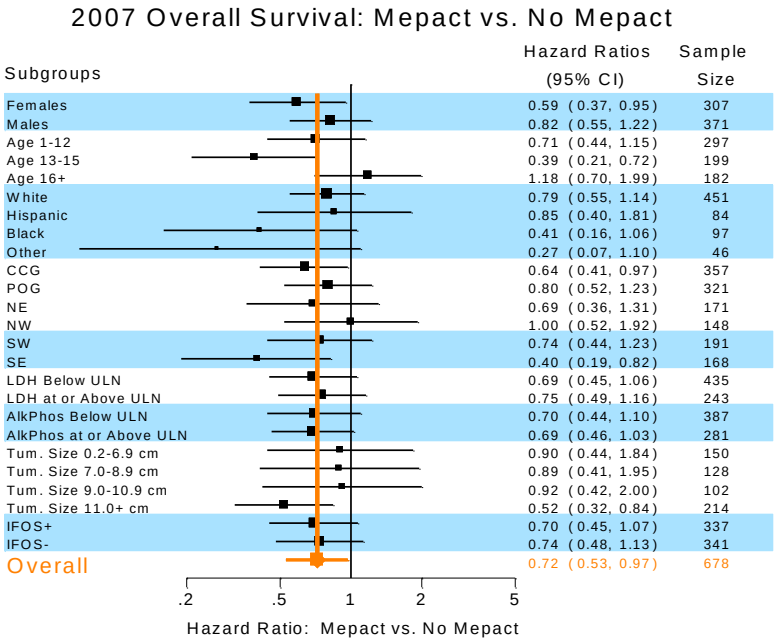
A24. Please provide detailed results (including event rates, hazard ratios, confidence intervals and P values on each subgroup analyses. Were these considered a priori or post hoc (provide evidence to support this)? Please include enough information to support the statement that exploratory findings confirm the robustness and consistency of the findings across the study population.

The standard approach to analysing and reporting randomised clinical trials is examination of the primary endpoint in the overall intent-to-treat population. Figure A24 (yellow box) identifies the statistically significant survival benefit seen with MEPACT at the p = 0.03 level, with a hazard ratio of 0.72 and an upper confidence limit of <1. This represents the best estimate of the overall drug benefit. Subsequent statistical analyses were used to examine the consistency of the effect. Such post-hoc sugroup analysis of efficacy based on demographic and other variables are standard and are the expected exploratory analyses for large randomised studies.

> "In most cases, however, subgroup or interaction analyses are exploratory and should be clearly identified as such; they should explore the uniformity of any treatment effects found overall. In general, such analyses should proceed first through the addition of interaction terms to the statistical model in question, complemented by additional exploratory analysis within relevant subgroups of subjects, or within strata defined by the covariates. When exploratory, these analyses should be interpreted cautiously; any conclusion of treatment efficacy (or lack thereof) or safety based solely on exploratory subgroup analyses are unlikely to be accepted." (Statistical Principles for Clinical Trials, September 1998, CPMP/ICH/363/96)

The Forest Plot (Figure A24) demonstrates the consistency of the MEPACT OS benefit across a broad range of demographic and prognostic factors (where a hazard ratio of <1 favours MEPACT and horizontal bars depict the 95% confidence interval for the hazard ratio).

Figure A24: Survival Benefit – Overall and Across Subgroups



These exploratory findings show a consistent benefit in favour of MEPACT, both overall and among the analysis subgroups.

A25. One subgroup analysis suggests no benefit for MEPACT treatment in patients >16 years of age. Please explain if this is correct. Is mifamurtide of no benefit to people over 16 years?

There is no evidence that the relative treatment benefit of MEPACT differs by age. Of the 25 subgroup comparisons (Figure A24), only age >16 years showed a hazard ratio of >1. The lower confidence interval (0.70) for age >16 years overlaps the overall hazard ratio of 0.72 favouring MEPACT. It is consistent with chance and expected that 1 of 25 subgroups could be on the opposite side of 1, as a result of chance alone.

As discussed above (A18) the appropriate testing procedures (Gail and Simon. Testing for qualitative interactions between treatment effects and patient subsets. *Biometrics*, 1985, 41, 361-372[5]) yielded a result of non-significance for the interaction between MEPACT and age (p = 0.210).

The need for caution in interpreting such subset analyses was emphasised by the ISIS investigators that include Sir Richard Peto and Sir Richard Doll.

> "Clearly significant overall results may therefore provide strong indirect evidence of benefit in subgroups where the results, considered in isolation, are not

conventionally significant (or even, perhaps, slightly adverse)." [ISIS-2 (Second International Study of Infarct Survival) Collaboration Group, *The Lancet* 1988, 2 (8607):349-360[8]].

Also, as noted in Section A22, of patients aged >16 a greater proportion in the MEPACT arms experienced an unfavourable response to neoadjuvant therapy. Histological response to induction therapy is one of the best predictors of survival. The smaller size of the >16 age group and the excess of poor histological responders in the MEPACT arms are likely to contribute to the findings seen in the Forest plot.

Section 6.4.4

A26. Please provide disease recurrence frequencies (Table 5) following adjuvant chemotherapy by each treatment group for the 2007 data set.

Disease recurrence frequencies for patients who reached the maintenance phase of treatment are summarised in Table A26, by treatment assignment. If a patient had multiple sites of recurrence, only one site is counted in the summary with the following priorities: pulmonary metastases first, then new bone metastases, then primary disease site. Therefore, if a patient had pulmonary metastases and new bone metastases, they were only counted as having pulmonary metastases.

Table A26: Site of Disease Recurrence for Patients who Reached Maintenance

n (%)	**A (N=153)**	**A + MEPACT (N=145)**	**B (N=148)**	**B + MEPACT (N=158)**
Patients with disease recurrence	41	41	57	39
New pulmonary metastases	24 (59)	27 (66)	37 (65)	25 (64)
New bone metastases	6 (15)	6 (15)	6 (11)	5 (13)
Primary disease site	4 (10)	3 (7)	8 (14)	2 (5)
Other	3 (7)	2 (5)	4 (7)	5 (13)
Unknown	4 (10)	3 (7)	2 (4)	2 (5)

Section 6.5.

A27. Please provide further details of the meta-analysis according to the NICE STA specification guide for manufacturers.

With reference to the NICE STA Specification Guide for Manufactures a meta-analysis was not considered appropriate as only one clinical study assessed overall survival following MEPACT therapy (study INT-0133). This has been the largest clinical trial

ever conducted by a co-operative group to evaluate the clinical efficacy of a new drug candidate for osteosarcoma, with data accrual over a period of more than 15 years. This study is described in Sections 6.3 and 6.4 of the submitted main report. The analysis referred to in Section 6.5 represents an integrated analysis of the ITT and non-ITT groups from study INT-0133 rather than a true meta-analysis.

Section 6.6

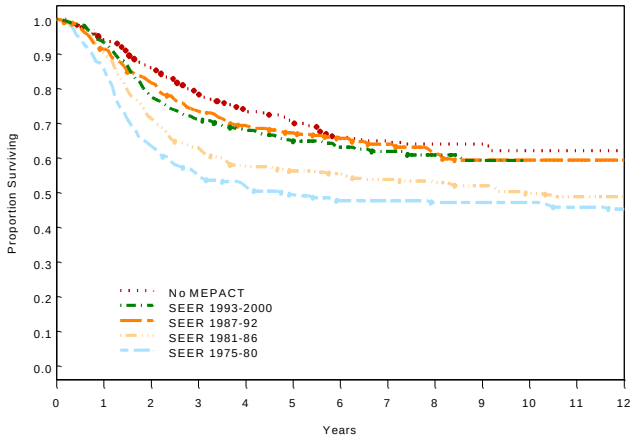
A28. Please clarify and justify why no statistical analysis was carried out for the indirect comparison. Please summarise the relevant data from the six review articles that have been cited.

Because the randomised study INT-0133 directly compares MEPACT with the relevant UK comparator (3 agent chemotherapy) in a head-to-head fashion, there was considered to be no need for indirect comparison with other RCTs.

However, comparisons with population based data from the Surveillance, Epidemiology, and End Results (SEER) Program of the US National Cancer Institute put the overall survival benefit in context. The SEER Program collects and publishes cancer incidence and survival data from population-based cancer registries. The population based SEER data provide a relevant comparison for the INT-0133 data since study INT-0133 is estimated to have included about a third of all newly diagnosed children and adolescents with osteosarcoma in the US during the study. The population of all patients in the MEPACT phase 3 study, including those with non-metastatic and metastatic disease, is comparable with patients from several treatment eras from the SEER population.

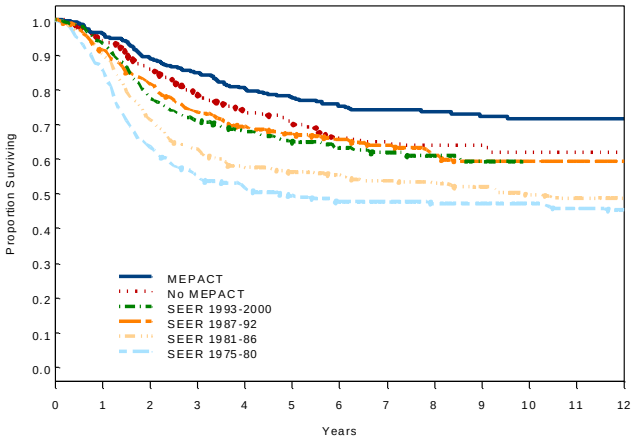
There was improvement in patient survival from 1975 to 1986, as noted in Figure A28a, due to improved surgical techniques, the availability of new chemotherapeutic agents, and the use of combination chemotherapy. However, the survival of patients with osteosarcoma has not improved since 1987. Also shown in Figure A28a is a survival analysis of all patients in the MEPACT RCT who did not receive MEPACT (in red) overlaid on the survival analysis of the comparable SEER population. This shows that the survival of those who did not receive MEPACT is similar to population-based data for osteosarcoma cases diagnosed in the USA in the years 1987 through 2000.

Figure A28a: Overall Survival: SEER Historical Data and INT-0133, No MEPACT



The superior outcome with MEPACT is not the result of an inferior survival of patients treated with chemotherapy only. The survival advantage is clearly due to the positive contribution of MEPACT (Figure A28b).

Figure A28b: Overall Survival: SEER Historical Data and INT-0133



Section 6.7.

A29. Please provide data on the degree, duration and severity of adverse events (including definitions) in the INT-0133 trial for each of the four treatment groups.

All non-haematological Grade 3 and 4 toxicities were reported to the COG regardless of frequency. Grade 3 and 4 hematologic toxicities that resulted in treatment delay were also reported. These were included in the case reports and are summarised below. Definitions

of severity are included in the Childrens Cancer Group Toxicity and Complications Criteria (Attachment 1).

As is standard for paediatric cooperative group studies, Grade 1 and 2 toxicities were not recorded in the central database but were documented locally. Reporting focused on important Grade 3 and 4 toxicities, consistent with all phase 3 paediatric oncology studies.

A summary of the Grade 3 and 4 toxicities reported for the intent-to-treat population in study INT-0133 according to treatment assignment and by MEPACT randomisation is presented in Table A29. The data demonstrate that MEPACT has a clinically manageable safety profile.

Table A29: Grade 3 and 4 Toxicities in Study INT-0133 (ITT Population)

	Regimen A	**Regimen A + MEPACT**	**Regimen B**	**Regimen B + MEPACT**	**No MEPACT**		**MEPACT**	
					N	**%**	**N**	**%**
Number of Patients:	**174**	**167**	**166**	**171**	**340**		**338**	
Haematological								
WBC	40	29	44	53	84	24.71	82	24.26
ANC	84	75	71	85	155	45.59	160	47.34
Platelets	56	48	43	49	99	29.12	97	28.70
Haemoglobin	14	14	14	18	28	8.24	32	9.47
Lymphocytes	2	2	3	4	5	1.47	6	1.78
Second malignancy	4	4	3	3	7	2.06	7	2.07
Hepatic								
SGOT	48	52	66	60	114	33.53	112	33.14
SGPT	84	86	102	91	186	54.71	177	52.37
Alkaline phosphatase	4	0	2	5	6	1.76	5	1.48
Total bilirubin	19	12	17	16	36	10.59	28	8.28
Clinical	1	0	1	0	2	0.59	0	0.00
Pancreas								
Amylase creatinine clearance	0	0	0	1	0	0.00	1	0.30
Amylase	1	1	0	1	1	0.29	2	0.59
Glucose	14	4	12	10	26	7.65	14	4.14
Renal								
BUN	2	1	0	2	2	0.59	3	0.89
Creatinine	3	4	2	2	5	1.47	6	1.78
Creatinine clearance	5	1	9	1	14	4.12	2	0.59
Systolic BP	3	1	1	0	4	1.18	1	0.30
Diastolic BP	3	1	3	1	6	1.76	2	0.59
Hematuria	0	0	1	0	1	0.29	0	0.00
Bladder	1	0	0	0	1	0.29	0	0.00

	Regimen A	Regimen A + MEPACT	Regimen B	Regimen B + MEPACT	No MEPACT		MEPACT	
					N	%	N	%
GI								
Stomatitis	94	82	61	73	155	45.59	155	45.86
Abdominal pain	4	6	3	5	7	2.06	11	3.25
Constipation	6	7	3	3	9	2.65	10	2.96
Diarrhoea	6	3	5	11	11	3.24	14	4.14
Nausea & vomiting	36	35	23	24	59	17.35	59	17.46
Pulmonary								
Vital capacity	0	2	1	0	1	0.29	2	0.59
Functional	0	1	2	1	2	0.59	2	0.59
Clinical	0	0	2	0	2	0.59	0	0.00
Cardiac								
Rhythm	1	3	1	1	2	0.59	4	1.18
Echo	1	2	0	3	1	0.29	5	1.48
Function	0	0	1	0	1	0.29	0	0.00
Hypertension	2	1	0	0	2	0.59	1	0.30
Hypotension	3	0	4	1	7	2.06	1	0.30
Nervous								
Perpheral-sensory	0	1	5	4	5	1.47	5	1.48
Central-cerebellar	6	7	8	6	14	4.12	13	3.85
Skin	14	4	8	11	22	6.47	15	4.44
Allergy	2	3	2	3	4	1.18	6	1.78
Coagulation – PT	0	0	1	0	1	0.29	0	0.00
Coagulation - PTT	0	0	0	0	0	0.00	0	0.00
Hearing - objective	8	26	16	13	24	7.06	39	11.54
Hearing - subjective	1	10	1	2	2	0.59	12	3.55
Electrolytes								
Sodium	5	2	2	0	7	2.06	2	0.59
Potassium	10	8	11	8	21	6.18	16	4.73
Calcium	5	2	2	3	7	2.06	5	1.48
Magnesium	3	6	2	3	5	1.47	9	2.66
Infection	48	33	33	40	81	23.82	73	21.60
Fever	5	2	3	4	8	2.35	6	1.78
Local	2	0	3	1	5	1.47	1	0.30
Mood	6	7	3	2	9	2.65	9	2.66
Weight change	4	2	0	4	4	1.18	6	1.78
Performance status	1	1	0	1	1	0.29	2	0.59

Section B. Clarification on cost-effectiveness data

Briefing: Corrections to Table 9 of the Main Report

During the restructuring of the model to accommodate the annual costs of endoprosthesis and amputation (Query B9) for the 20, 40 and 60 year extended time horizon, the following was observed:

The additional discounted QALYs and monitoring costs computed for the patients remaining in the disease-free (DF) state for the 20 and 40 year extended time horizons, reported in Table 9 of the submitted main report, were inconsistently reported and incorporated into the model. Table 9 reports the additional discounted costs to be rewarded to the proportion of patients still remaining in the DF state at the end of the study horizon (for the respective extended follow up horizons). The model automatically adjusts these costs by multiplying the costs by the proportion of patients remaining in the DF state at the end of the study horizon, as expected. However, the additional discounted QALYs reported in Table 9 have already been adjusted for the proportion of patients remaining in the DF state at the end of the study horizon. When added to the model the adjustment was performed a second time, which is incorrect, and this was not observed during the model validation.

Thus the results relating to the 20 and 40 year extended horizons in the main report in Tables 15 and 16 and in the Executive summary have been revised. In the queries below the correct additional discounted QALYs are applied. Table 9 from the main report is presented below with the incorrect values and an updated Table 9 is represented with the correct values. In addition, revised tables are also presented for Tables 15 and 16. These revised tables demonstrate that the incremental cost/QALY for all three extended time horizons (20, 40 and 60 years) remain well within the ultra-orphan threshold range of £200,000 to £300,000 cost/QALY (Section 7.3.3 of main report) proposed by NICE in its paper entitled "Appraising Orphan Drugs".

Table 9:Discounts Assumed for 20- and 40-Year Time Horizons (Incorrect Values)

Extended Time Horizon	**Treatment**	**Additional Discounted QALY**	***Additional Discounted Monitoring Costs £***
20-years	MEPACT	7.7	*1706*
20-years	NO MEPACT	6.9	*1706*
40-years	MEPACT	11.5	*2564*
40-years	NO MEPACT	10.4	2564

Table 9 (new): Discounts Assumed for 20- and 40-Year Time Horizons (Correct Values)

Extended Time Horizon	**Treatment**	**Additional Discounted QALY**	***Additional Discounted Monitoring Costs £***
20-years	MEPACT	11	*1706*
20-years	NO MEPACT	11	*1706*
40-years	MEPACT	16.6	*2564*
40-years	NO MEPACT	16.6	2564
60-years	MEPACT	19.4	2995
60-years	NO MEPACT	19.4	2995

Table 15: Extrapolation to 20-Years Beyond the Reference Case Horizon

Strategy	**Cost**	**Incremental cost**	**QALY gain**	**Incremental effect**	**Cost/QALY (£)**	**Incremental C/E (ICER, £)**
No MEPACT	£35K		10.73 years		3,232	
MEPACT	£154K	£119K	12.02 years	1.29 years	12,796	92,259

Table 15 (new): Extrapolation to 20-Years Beyond the Reference Case Horizon

Strategy	**Cost**	**Incremental cost**	**QALY gain**	**Incremental effect**	**Cost/QALY (£)**	**Incremental C/E (ICER, £)**
No MEPACT	£35K		13.29 years		2,609	
MEPACT	£154K	£119K	14.31 years	1.02 years	10,749	116,879

Table 16: Extrapolation to 40-Years Beyond the Reference Case Horizon

Strategy	Cost	Incremental cost	QALY gain	Incremental effect	Cost/QALY (£)	Incremental C/E (ICER, £)
No MEPACT	£35K		12.92 years		2,726	
MEPACT	£154K	£119K	14.66 years	1.74 years	10,535	68,463

Table 16 (new): Extrapolation to 40-Years Beyond the Reference Case Horizon

Strategy	Cost	Incremental cost	QALY gain	Incremental effect	Cost/QALY (£)	Incremental C/E (ICER, £)
No MEPACT	£35K		16.79 years		2,097	
MEPACT	£154K	£119K	18.20 years	1.41 years	8,487	84,786

Section 4.1.2.3.

B1. Please provide rates of limb-salvage and amputations by the four treatment groups.

Rates of limb-salvage and amputations are provided for the ITT population in Table B1a and for the group of patients entering the maintenance phase in Table B1b.

Table B1a: Rates of Limb-Salvage and Amputation for the ITT Population

	Limb Salvage/Amputation: Intent-to-Treat Population N (%)				
	Regimen A	**Regimen A + MEPACT**	**Regimen B**	**Regimen B + MEPACT**	**Total**
Amputation	36 (20.69)	40 (23.95)	31 (18.67)	37 (21.64)	144
Limb Salvage	113 (64.94)	101 (60.48)	108 65.06)	114 (66.67)	436
Unknown	25 (14.37)	26 (15.57)	27 (16.27)	20 (11.70)	98
Total	174	167	166	171	678

Table B1b: Rates of Limb-Salvage and Amputation for Patients Entering the Maintenance Phase

	Limb Salvage/Amputation: Maintenance Phase Patients N (%)				
	Regimen A	**Regimen A + MEPACT**	**Regimen B**	**Regimen B + MEPACT**	**Total**
Amputation	33 (21.57)	37 (25.52)	28 (18.92)	37 (23.42)	135
Limb Salvage	104 (67.97)	94 (64.83)	104 (70.27)	111 (70.25)	413
Unknown	16 (10.46)	14 (9.66)	16 (10.81)	10 (6.33)	56
Total	153	145	148	158	604

For patients entering the maintenance phase, 24.4% and 67.7% of patients in the MEPACT arm had an amputation or limb salvage, respectively. In the No MEPACT arm 20.3% and 69.1% of patients had an amputation or limb salvage, respectively. An amputation rate of 25% was used in the model to reflect UK clinical practice, where the amputation rate is slightly higher than in the USA (according to UK clinical expert opinion).

B2. Please provide results for the reference case, and time horizons of 20, 40 and 60 years, assuming all surviving patients will require appropriate type of revision surgery (i.e., further limb-salvage or prosthetic corrective/replacement) after 10 years. If restructuring the model in this way is not possible please provide estimates based on appropriately discounted costs of an additional surgical intervention based on trial rates.

The model has been restructured to incorporate estimates of amputation and limb salvage and the annual costs associated with these procedures. The annual costs of amputation and limb salvage with endoprosthesis from an NHS perspective (1997 prices), are reported as part of a cost-effectiveness study[9]. The formulae used to compute these annual costs are presented below[9]:

Amputation Costs: A+B

A= Initial fixed cost of inpatient hospital stay for amputation
B= Annual package price for provision of an exoprosthesis and maintenance costs for follow up and attention to complications

Using the Consumer Price index (CPI) to convert the 1997 reported prices to 2006 prices, the fixed cost is estimated to be £6569 and the annual package cost is estimated to be £5369 (2006 prices). Within the economic model 50% of the annual package costs are included within each 6-month cycle for the 25% of patients having an amputation. The initial fixed cost (A) for amputation is not included in the model as it is incurred prior to maintenance treatment.

Endoprosthesis Costs: E + [2Fy +sSy+rRy +3r(rRy)]

E = the cost of the initial procedure

y = the number of years since the original procedure
F = the cost of follow-up attendance
s =the risk of a 'servicing' procedure in any year
S = the cost of a 'servicing' procedure
r = the risk of a revision procedure being needed
R = the cost of a revision procedure

In the above formula the annual costs of the initial endoprosthesis are represented by [2Fy +sSy+rRy +3r(rRy)]. Using the above formula and converting 1997 reported prices to 2006 prices using the CPI, the following costs have been assumed for the model:

E (initial procedure) = £14612

Annual cost = 2Fy +sSy+rRy +3r(rRy)

= 2*£189 + 0.03*£1952+0.04*£14612 +3*0.04(0.04*£14612)

The model assumes that 4% of patients will have a replacement endoprosthesis each year[9]. Due to the uncertainty of this estimate, a sensitivity analysis has been undertaken for a range of 4-8% for the reference case and 4% and 8% for the extended horizons. Within the economic model 50% of the annual costs are included within each 6-month cycle period for the 75% of patients with limb salvage. The initial fixed cost (E) is not included as this cost is incurred prior to the maintenance phase. Table B2a presents the costs applied to the model for this analysis and Table B2b presents the results of the sensitivity analyses.

Table B2a: Discounted Costs for 20, 40 and 60 Year Extended Time Horizons with Endoprothesis Rates and Amputation

Endoprosthesis Replacement Rate (Annual Costs)	**Discounted Costs for the Extended Time Horizon (£)**		
	20 years	**40 years**	**60 years**
4% (£1091)	33487	50316	58774
8% (£1886)	42258	63495	74168

The results demonstrate that increasing the rate of annual prosthesis replacements from 4-8% does not significantly impact on the ICER within the same follow-up time horizon. However for extended follow-up periods of 20, 40 and 60 years, MEPACT is demonstrated to be more cost-effective with longer time horizons. The incremental cost/QALYs are well within the ultra-orphan threshold range of £200,000 to £300,000 (Section 7.3.3 of the submitted main report) proposed by NICE.

Table B2b: Sensitivity Analysis of Annual Endoprosthesis Rates for the Reference Case and 20, 40 and 60-Year Extensions

Horizon	Rate	Strategy	Cost	Incr Cost	QALY	Incr QALY	Cost/QALY (£)	ICER (£)
Reference	4%	No MEPACT	£48,163		6.42 years		7,504	
		MEPACT	£168,248	£120,085	6.68 years	0.26 years	25,192	461,696
Reference	5%	No MEPACT	£49,102		6.42 years		7,650	
		MEPACT	£169,255	£120,153	6.68 years	0.26 years	25,343	461,959
Reference	6%	No MEPACT	£50,082		6.42 years		7,803	
		MEPACT	£170,307	£120,225	6.68 years	0.26 years	25,500	462,233
Reference	7%	No MEPACT	£51,107		6.42 years		7,962	
		MEPACT	£171,407	£120,299	6.68 years	0.26 years	25,665	462,520
Reference	8%	No MEPACT	£52,178		6.42 years		8,129	
		MEPACT	£172,555	£120,377	6.68 years	0.26 years	25,837	462,819
20	4%	No MEPACT	£69K		13.29 years		5,198	
		MEPACT	£191K	£122K	14.31 years	1.02 years	13,381	120,069
40	4%	No MEPACT	£80K		16.79 years		4,741	
		MEPACT	£203K	£124K	18.20 years	1.41 years	11,165	87,884
60	4%	No MEPACT	£85K		18.54 years		4,579	
		MEPACT	£209K	£124K	20.14 years	1.60 years	10,379	77,628
20	8%	No MEPACT	£79K		13.29 years		5,912	
		MEPACT	£202K	£123K	14.31 years	1.02 years	14,107	120,950
40	8%	No MEPACT	£92K		16.79 years		5,470	
		MEPACT	£217K	£125K	18.20 years	1.41 years	11,904	88,739
60	8%	No MEPACT	£99K		18.54 years		5,314	
		MEPACT	£224K	£125K	20.14 years	1.60 years	11,124	78,475

Section 4.1.2.6.

B3. Please provide results for a 5% recurrence rate after 5 years of follow-up for the reference case, and for time horizons of 20, 40 and 60 years. If restructuring the model in this way is not possible please vary the cost of treating any recurrence by 2% as well as 5%.

As the state transition estimates have been taken from the clinical data, it was not considered possible to factor in a 5% recurrence rate after 5 years without introducing much uncertainty and new assumptions into the model. Instead, as suggested, the cost of treating a recurrence has been increased by 2% and 5%; these include costs associated with diagnosis, surgery and palliative care. A factor variable has been included into the model to accommodate the 2% and 5% increase.

The results (Table B3a) demonstrate that increasing the cost of disease recurrence by 2% and 5% does not impact on the ICER within the same time horizon. Although, the costs are increased in both the MEPACT and No MEPACT arms, the incremental costs reduce slightly in favour of MEPACT as the cost of recurrence is increased. This is consistent for all extended time horizons.

For extended follow-up periods of 20, 40 and 60 years, MEPACT is demonstrated to be more cost-effective the longer the extended time horizon (Table B3b). The incremental cost/QALYs are well within the ultra-orphan threshold range of £200,000 to £300,000 cost/QALY (Section 7.3.3 of the main report) proposed by NICE.

Table B3a: Sensitivity Analysis of Increased Disease Recurrence Costs (Reference Case)

Horizon	% Cost Increase	Strategy	Cost	Incr Cost	QALY	Incr QALY	Cost/ QALY (£)	ICER (£)
Reference	0%	No MEPACT	£33,612		6.42 years		5,237	
		MEPACT	£152,639	£119,026	6.68 years	0.26 years	22,855	457,624
Reference	2%	No MEPACT	£33,640		6.42 years		5,241	
		MEPACT	£152,662	£119,021	6.68 years	0.26 years	22,858	457,606
Reference	5%	No MEPACT	£33,682		6.42 years		5,248	
		MEPACT	£152,697	£119,014	6.68 years	0.26 years	22,863	457,578

Table B3b: Sensitivity Analysis of Increased Disease Recurrence Costs for Extended Time Horizons

Horizon	% Cost Increase	Strategy	Cost	Incr Cost	QALY	Incr QALY	Cost/ QALY (£)	ICER (£)
20	0%	No MEPACT	£34,678		13.29 years		2,609	
		MEPACT	£153,822	£119,144	14.31 years	1.02 years	10,749	116,879
20	2%	No MEPACT	£34,706		13.29 years		2,611	
		MEPACT	£153,845	£119,139	14.31 years	1.02 years	10,751	116,874
20	5%	No MEPACT	£34,748		13.29 years		2,614	
		MEPACT	£153,880	£119,132	14.31 years	1.02 years	10,753	116,867
40	0%	No MEPACT	£35,214		16.79 years		2,097	
		MEPACT	£154,417	£119,203	18.20 years	1.41 years	8,487	84,786
40	2%	No MEPACT	£35,242		16.79 years		2,099	
		MEPACT	£154,441	£119,198	18.20 years	1.41 years	8,488	84,783
40	5%	No MEPACT	£35,284		16.79 years		2,102	
		MEPACT	£154,475	£119,191	18.20 years	1.41 years	8,490	84,778
60	0%	No MEPACT	£35,484		18.54 years		1,914	
		MEPACT	£154,716	£119,233	20.14 years	1.60 years	7,683	74,558
60	2%	No MEPACT	£35,512		18.54 years		1,916	
		MEPACT	£154,740	£119,228	20.14 years	1.60 years	7,684	74,555
60	5%	No MEPACT	£35,554		18.54 years		1,918	
		MEPACT	£154,775	£119,221	20.14 years	1.60 years	7,686	74,550

Section 7.2.

B4. Please provide results for a modelled time horizon of 60 years as this is considered by the ERG's clinician advisory panel to be a more plausible lifetime in a substantial proportion of cases

The results are presented for all three extended time horizons i.e. 20, 40 and 60 years (Tables B4a-B4c) and take into account the Briefing note at the beginning of Section B, highlighting the double adjustment made to the discounted QALYS in the original submission. These revised results, not surprisingly, demonstrate higher QALY gains in both the MEPACT and No MEPACT arms but a slightly lower incremental QALY gain.

MEPACT is demonstrated to be more cost-effective with longer extended time horizons. The incremental cost/QALYs for all three extended time horizons (20, 40 and 60 years) remain well within the ultra-orphan threshold range of £200,000 to £300,000 cost/QALY (Section 7.3.3 of the main report) proposed by NICE.

Table B4a: Base Case Extended by 20-Years

Strategy	Cost	Incr Cost	QALY	Incr QALY	Cost/QALY (£)	ICER (£)
No MEPACT	£35K		13.29 years		2,609	
MEPACT	£154K	£119K	14.31 years	1.02 years	10,749	116,879

Table B4b: Base Case Extended by 40-Years

Strategy	Cost	Incr Cost	QALY	Incr QALY	Cost/QALY (£)	ICER (£)
No MEPACT	£35K		16.79 years		2,097	
MEPACT	£154K	£119K	18.20 years	1.41 years	8,487	84,786

Table B4c: Base Case Extended by 60-Years

Strategy	Cost	Incr Cost	QALY	Incr QALY	Cost/QALY (£)	ICER (£)
No MEPACT	£35K		18.54 years		1,914	
MEPACT	£155K	£119K	20.14 years	1.60 years	7,683	74,558

Section 7.2.1.

B5. Please provide results for sensitivity analyses of the reference case model, assuming two vials per cycle instead of one for 5% and for 10% of patients.

The sensitivity analysis for 5% and 10% of patients receiving two MEPACT vials is presented in Table B5, with the following assumptions being made:

- Pharmacy time is incurred for the preparation of a second vial.
- The number of outpatient visits to administer MEPACT is not increased as it is assumed that two vials are required due to the patient's weight and both vials would be administered at the same outpatient visit.

The results demonstrate that when two vials instead of one are assumed for 5% of patients that the ICER increases by approximately £22,000. The same increase is observed when assuming two vials for 10% of patients.

These scenarios are considered to be highly hypothetical and unrealistic for the following reasons:

- The indication and posology authorised in the European Union for MEPACT does not permit dose-escalation (see response to A6 above). Although dose escalation was permitted in study INT-0133, the results demonstrated that 2 mg/m^2 MEPACT,delivered as one vial, is the optimal active biological dose.
- The UK population has slightly different demographics to the USA population, with UK patients being lighter. It is expected that for almost all osteosarcoma patients in the UK that a 2 mg/m^2 dose can be delivered using one vial.
- During study INT-0133, there were three instances where two vials were used; this was due to a dosing or labelling error, as documented in the CRF, rather than being driven by a clinical need.

Table B5: Sensitivity Analysis for 5% and 10% of Patients Receiving Two Vials

	Strategy	Cost	Incr Cost	QALY	Incr QALY	Cost/QALY (£)	ICER (£)
All 1-vials	No MEPACT	£33,612		6.42 years		5,237	
	MEPACT	£152,639	£119,026	6.68 years	0.26 years	22,855	457,624
5% 2 vials	No MEPACT	£33,612		6.42 years		5,237	
	MEPACT	£158,459	£124,846	6.68 years	0.26 years	23,726	480,000
10% 2-vials	No MEPACT	£33,612		6.42 years		5,237	
	MEPACT	£164,279	£130,666	6.68 years	0.26 years	24,597	502,377

Section 7.2.6.7.

B6. Please clarify the justification for not utilising a half cycle. Please confirm that varying cycle length refers to the difference between the 9-month first cycle compared to subsequent 6-month cycles. Please explain why the incremental rewards could not be accommodated under the half-cycle corrected model.

"Varying cycle length" does refer to the difference in the cycle lengths between the first cycle of 9 months and subsequent cycles of 6 months.

The half-cycle functionality within TreeAge Pro 2008, as defined in Chapter 35 of the TreeAge Pro 2008 User Manual was originally implemented. Not surprisingly, the results were favourable for MEPACT, as this correction would take drop-outs in the first cycle into account (i.e. the maintenance cycle when MEPACT is administered and most costs in the MEPACT arm are incurred). The full costs of MEPACT for those patients dropping out would then be adjusted by implementing the half-cycle correction. However the extent of favourability warranted a closer look at the methodology and assumptions behind the half-cycle functionality within TreeAge, to clarify what was going on behind the scenes. Discussions with TreeAge support highlighted that indeed the half-cycle correction functionality does not account for varying cycle lengths or varying rewards within each cycle and that any results would be unreliable. TreeAge support strongly recommended not attempting to program this manually, as the complexity would be likely lead to many model errors.

The expected consequence of non-implementation of the half-cycle correction within TreeAge would be to overestimate the Incremental Cost/QALY, as the majority of MEPACT costs are incurred in the first cycle when the half-cycle correction would take effect. Thus the reference case presented for MEPACT is expected to be overestimated.

Sections 7.2.7.4 and 10.5.2.4.

B7. Please provide separate results of sensitivity analyses for the reference case model, assuming the following values of hearing-loss rates for the four treatment groups at the end of maintenance therapy.

MEPACT arms (A+, B+)	No MEPACT arms (A, B)
15%	8%
12.5%	5.0%
19.5%	7.0%
10.5%	9.0%
19.0%	10.0%

The proposed hearing-loss rates above are considered to be inappropriate, grossly overestimated, and not supported by MEPACT clinical data. Cisplatin is known to be ototoxic, causing permanent high-tone hearing loss in 10-20% of patients[10]. All patients in both treatment groups (MEPACT and No MEPACT) received cisplatin. Clinical expert opinion considered the higher incidence of hearing loss in the MEPACT group as a data anomaly, because of its association with cisplatin use.

The results in Table B7 are, therefore, not considered to be a reflection of the cost-effectiveness of MEPACT, as the high costs and disutility associated with hearing loss are considered appropriate for a cost-effectiveness analysis of cisplatin but not for MEPACT.

The ICERs in Table B7 are driven by the rate of hearing loss and the disutility associated with hearing loss. Due to a paucity of evidence on hearing loss in osteosarcoma this disutility is assumed to remain constant for each 6-month period of the follow-up horizon. However, discussions with various experts in the field suggests that as time progresses osteosarcoma patients are likely to adapt to their hearing loss so that the associated disutility would diminish with time. This would greatly reduce the ICERs in Table B7.

Table B7: Sensitivity analysis for hearing loss rates

Hearing AE rate	Strategy	Cost	Incr Cost	QALY	Incr QALY	Cost/QALY (£)	*ICER (£)*
15%	No MEPACT	£34K		6.295 years		5,347	
8%	MEPACT	£153K	£119K	6.437 years	0.142 years	23,726	*837,214*
12.5%	No MEPACT	£34K		6.341 years		5,307	
5%	MEPACT	£153K	£119K	6.477 years	0.136 years	23,579	*875,130*
19.5%	No MEPACT	£34K		6.3102 years		5,334	
7%	MEPACT	£153K	£119K	6.3644 years	0.0542 years	23,997	*2,196,430*
10.5%	No MEPACT	£34K		6.279 years		5,360	
9%	MEPACT	£153K	£119K	6.509 years	0.230 years	23,462	*517,163*
19%	No MEPACT	£34K		6.264 years		5,373	
10%	*MEPACT*	*£153K*	*£119K*	*6.372 years*	*0.109 years*	*23,967*	*1,095,170*

Note, the hearing-loss rates represented in this table are considered to be inappropriate, grossly overestimated and unsupported by MEPACT clinical data. Cisplatin is known to be ototoxic, causing permanent high-tone hearing loss in 10-20% of patients[10]. All patients in both treatment groups (MEPACT and non-MEPACT) received cisplatin. Clinical expert opinion considered the higher incidence of hearing loss in the MEPACT group as a data anomaly, because of its association with cisplatin use. Hearing loss disutility is assumed to remain constant over time but experts in the field suggest that this may not be the case, rather the disutility may diminish with time.

Section 7.2.8.2.

B8. Please justify the decision not to adjust utility values for age.

The utilities were not age adjusted in the EQ5D survey as they related to osteosarcoma patients' actual experience of the various health states, and so are already age-specific (given certain caveats relating to the fact that they were osteosarcoma survivors recalling the relevant health state experience).

The NICE HTA review is based on health state utilities reported for adults with various types of cancer, with ages ranging from 45-75+. This population is much older than the osteosarcoma population covered by the terms of the marketing authorisation for MEPACT. Due to the small difference in overall utility values expected by performing such an age adjustment, it was not considered necessary. The base-case utilities used in the model are presented in Table 10 of the submission. As the utilities for the maintenance phase, disease-free and recurrence/disease-free health states were based on the age-specific EQ5D survey, age adjustment was not necessary.

However, base-case utilities for the following three states: recurrence, disease progression and recurrence/disease progression were derived from the NICE HTA review, due to the small numbers of patients having experienced these states in the EQ5D survey. An age adjustment has now been undertaken using population EQ5D utility norms for age <25 years for osteosarcoma patients and the utilities for older age groups from 45 years upwards, reflecting the age range of cancer patient groups from the NICE HTA review. The age-specific EQ5D utility norms were taken from Kind et al (1999)[11]. The mean EQ5D score from Kind et al is higher for younger age groups and therefore the age adjustment improves the utilities for each health state covered. The impact of adjusting these values using age specific UK population EQ5D values are shown below:

- The disease recurrence utility of 0.61 becomes an age-adjusted utility of 0.66.

- The disease progression and recurrence/disease progression utility of 0.39 becomes an age-adjusted utility of 0.49.

The results in Tables B8a and B8b demonstrate that these age adjusted utilities have little impact on the ICER ratios for all time horizons compared with the reference case.

The results in Tables B8a and B8b demonstrate that these age adjusted recurrence utilities have little impact on the ICER ratio for all time horizons compared with the reference case.

Table B8a: Sensitivity Analysis of Disease Recurrence Utility for Extended Time Horizons

Extended Horizon	Recurrence Utility	Strategy	Cost	Incr Cost	QALY	Incr QALY	C/E	ICER (£)
20	0.61	No MEPACT	£34,678		13.29 years		2,609	
		MEPACT	£153,822	£119,144	14.31 years	1.02 years	10,749	116,879
20	0.66	No MEPACT	£34,678		13.30 years		2,608	
		MEPACT	£153,822	£119,144	14.32 years	1.02 years	10,745	117,073
40	0.61	No MEPACT	£35,214		16.79 years		2,097	
		MEPACT	£154,417	£119,203	18.20 years	1.41 years	8,487	84,786
40	0.66	No MEPACT	£35,214		16.80 years		2,096	
		MEPACT	£154,417	£119,203	18.20 years	1.40 years	8,484	84,888
60	0.61	No MEPACT	£35,484		18.54 years		1,914	
		MEPACT	£154,716	£119,233	20.14 years	1.60 years	7,683	74,558
60	0.66	No MEPACT	£35,484		18.55 years		1,913	
		MEPACT	£154,716	£119,233	20.14 years	1.60 years	7,681	74,637

Table B8b: Cost-Effectiveness Results for Disease Progression Utility = 0.49

Extended Horizon	Disease Progression Utility	Strategy	Cost	Incr Cost	QALY	Incr QALY	Cost/ QALY	ICER (£)
Reference	0.39	No MEPACT	£34K		6.419 years		5,237	
		MEPACT	£153K	£119K	6.679 years	0.260 years	22,855	457,624
Reference	0.49	No MEPACT	£34K		6.422 years		5,234	
		MEPACT	£153K	£119K	6.684 years	0.262 years	22,835	453,939
20	0.49	No MEPACT	£35K		13.29 years		2,608	
		MEPACT	£154K	£119K	14.32 years	1.02 years	10,745	116,637
40	0.49	No MEPACT	£35K		16.79 years		2,097	
		MEPACT	£154K	£119K	18.20 years	1.41 years	8,484	84,659
60	0.49	No MEPACT	£35K		18.54 years		1,914	
		MEPACT	£155K	£119K	20.14 years	1.60 years	7,681	74,459

Section 7.2.8.3.

B9. Please justify the use of the utility values without exploring the effect of the following issues:

- ***recall bias as there is approximately 9 years (on average) between the age at diagnosis and when the EQ5D survey was conducted***

Osteosarcoma is an extremely rare cancer which predominantly affects children and adolescents. We extensively explored the published literature and relevant HTA/CEA databases and websites to assess the availability of directly relevant utility values in osteosarcoma, or at least in children with cancer. We did not find any plausible candidates and hence adopted the two-component strategy to utility measurement reported in the submission dossier (i.e. the EQ5D survey supported by the NICE HTA review of cancer utilities used in the independent economic models).

For the survey, we wanted to use the EQ5D instrument to best reflect the NICE reference case. We considered the use of the HUI2 paediatric version, but as osteosarcoma also affects adolescents/young adults we preferred to use the EQ5D for consistency. As we conducted the survey in osteosarcoma survivors the questionnaire was completed by adults or, for the very few cases of children completing the questionnaire, was completed on their behalf by a parent/caregiver.

We performed the survey in survivors largely for pragmatic reasons (i.e. it was easier to identify and recruit across health states) and to avoid having to administer questionnaires directly to young children. Whilst we felt this was a reasonable approach compared with interviewing patients experiencing the health state, the downside is that time that has passed since the participants experienced the health state.

It was also still difficult to find patients who had experienced the whole range of health states. The disease-free state was the current state for all participants, and represented the most reliable of the utilities generated (mean of 0.75). The value was supported by values

for childhood bone cancer using HUI data from the published literature (Alessi et al 2007[12]). It is possible that the disease-free state utility may change over time, with e.g. a lower utility in the short-term post-diagnosis but with improving status over time. However using the model time horizon of a minimum of 12 years, patients will spend most time in the long-term disease-free state of a survivor as was directly measured in the survey (i.e. no recall was needed).

There could be an element of recall bias associated with estimates of the initial disease phase. However evidence on the impact of recall bias in cancer is mixed, with one prostate cancer study suggesting that QoL recall is good with no major bias[13]. Another, assessing the same cancer, suggested that recall bias could lead to the baseline utility being higher than it actually was[14]. Both studies asked for QoL recall at a shorter follow-up time than in our osteosarcoma survey, but were in elderly patients for whom recall would be expected to be poorer. Indeed, Litwin and McGuigan[14], 1999 found recall to be better in younger patients. Feedback from the study nurse who conducted the interviews was that, in general, patient recall was remarkably good given the time since diagnosis.

To conclude, we do not think recall bias is likely to have a major impact on the utilities generated. Recall bias applies less to the disease-free state and the direction of any recall bias for the initial disease phase is uncertain, but we feel the net effect of any such possible bias would be small.

- the survey was conducted on survivors only

We feel it was justifiable to conduct the survey in survivors as the predominant health state over the time horizon of the economic model was disease-free and this was directly estimated by the patients surveyed (see comments above).

- the small number surveyed

We acknowledge that the number of patients surveyed was small. As osteosarcoma is rare the EQ5D survey was pragmatic and sought to obtain utilities using the instrument recommended in the NICE reference case, from as many patients as was possible in a short time frame. As osteosarcoma is a rare condition, 22 patients represents a reasonable sample size and in line with the sample size in a number of published health-related QoL studies reported in the submission. To obtain data for this number required the full co-operation and support of a key treatment centre. This is also the only utility study that has been conducted in osteosarcoma patients and so represents a novel finding. Ideally more research is needed, with the survey being continued and extended to other treatment centres if possible to increase the sample size.

B10. Please clarify whether utilty values derived for six-month periods were applied to cycle 1? If so please explain the rationale behind this decision.

Utility values derived for 6-month periods were not applied to cycle 1; two utilty values are relevant to cycle 1 which is of 9-months duration. The first is the utility derived from the EQ5D survey for the 9-month maintenance period when patients receive adjuvant treatment. This utility value was just below zero in the EQ5D survey but was reset to zero in the model to avoid using negative utilities. The second, the disutility associated with hearing loss, was not specific to the duration of hearing loss but to the occurrence of the event.

Section 7.2.11.3.

B11. Please justify and explain how model inputs other than survival probabilities are affected by the way survival data are handled.

Survival probabilities are represented in the model through the use of transition probabilities between the model states. These transition probabilities are taken directly from the clinical study. During the trial horizon, in the case of withdrawals, assumptions are made about the transition probabilities based on clinical expert opinion. When such assumptions are made, the effect is to reallocate patients who withdraw to the Disease-Free or Recurrence state. The impact this has on other model inputs is that patients then incur the cycle costs and effects from the time of entering that state.

B12. Please explore the results using PSA (if possible), and provide results based on a PSA of the reference case model, as well as that for time horizons of 20, 40 and 60 years, for the variables in Tables 12 and 14 (pages 81 and 83, respectively). Please justify any omission from the list of variables in the two tables, and any choice of distribution.

See B14

B13. If PSA is used please ensure that correlations between model inputs are appropriately modelled where necessary, rather than using modelling inputs as uncorrelated quantities.

See B14

B14. If PSA is not possible, please confirm that all model inputs are estimated mean values on the scale that they are applied. For example, if the distribution of an input is assumed to be normal on a logarithm (log) scale, i.e. log-normal, and the input is applied on the original scale, the required mean is generally not the maximum-likelihood estimate on the log scale, transformed back to the original scale, but the back-transform of the maximum-likelihood estimate plus half the estimated variance (on the log scale).

Due to the ultra-orphan nature of osteosarcoma, there was a dearth of published evidence to support the choice of distribution for many of the variables outlined in Tables 12 and 14 and to inform on the reference case e.g. recurrence of lung metastases, number of second-line chemotherapy cycles. Therefore the sensitivity analyses performed imlemented the most extreme values, as informed by UK clinical expert opinion, and should represent the most conservative (extreme) ICERs for MEPACT. The survival distribution representing the clinical trial horizon is reflected in the computation of transition probabilities.

No inputs were assumed to be normal on the log scale. Model inputs were assumed as estimated means and any uncertainty was addressed by sensitivity analysis.

Section 7.3.

B15. Please provide ICERs comparing each of the six pairs of the four treatment groups, for the reference case and for 20, 40 and 60 year time horizons.

The six paired comparisons are:

1. RegA+Mepact vs Reg A
2. RegA+Mepact vs Reg B
3. RegB+Mepact vs Reg B
4. RegB+Mepact vs Reg A
5. Reg A+Mepact vs Reg B+Mepact: This comparison does not permit an economic evaluation of MEPACT with a relevant UK comparator.
6. Reg A vs Reg B: This comparison neither considers MEPACT nor permits an economic evaluation of MEPACT with a relevant UK comparator.

The results show that when MEPACT is added to Regimen A and Regimen B adjuvant chemotherapy regimens it is cost-effective compared to Regimen B alone over each of the extended follow-up periods of 20, 40 and 60 years. MEPACT is demonstrated to be more cost-effective with longer time horizons (ICERs in the range £44k-£77k) and the incremental cost/QALYs are well below the ultra-orphan threshold range of £200,000 to £300,000 (Section 7.3.3 of the submitted main report) proposed by NICE.

When MEPACT is added to Regimen A and Regimen B adjuvant chemotherapy regimens and compared to Regimen A alone, it is demonstrated to be cost-effective over the 40 and 60-year extended follow-up periods. MEPACT is demonstrated to be more cost-effective with longer time horizons and the incremental cost/QALYs for 40 and 60-year extended horizons are within the ultra-orphan threshold range of £200,000 to £300,000 (Section 7.3.3 of the submitted main report) proposed by NICE.

When comparing Regimen A+MEPACT with Regimen B+MEPACT, Regimen B+MEPACT is dominated for the 20, 40 and 60 year extended time horizons. For these extended time horizons Regimen A+MEPACT is less costly and more effective than Regimen B+MEPACT. This comparison does not permit an economic evaluation of MEPACT with a relevant UK comparator.

When comparing Regimen A adjuvant chemotherapy with Regimen B, Regimen B is dominated for each extended time horizon and the reference case. In these cases Regimen A is less costly and more effective than Regimen B for all extended time horizons and the reference case. This comparison does not permit an economic evaluation of MEPACT with a relevant UK comparator.

Table B15a: Regimen A+MEPACT versus Regimen A for Extended Time Horizons

Extended Horizon	Strategy	Cost	Incr Cost	QALY	Incr QALY	Cost/QALY (£)	ICER (£)
Reference	No MEPACT	£31K		6.508 years		4,780	
	MEPACT	£151K	£119K	6.673 years	0.165 years	22,564	724,313
20	No MEPACT	£32K		13.946 years		2,313	
	MEPACT	£152K	£119K	14.317 years	0.371 years	10,599	322,278
40	No MEPACT	£33K		17.733 years		1,852	
	MEPACT	£152K	£120K	18.208 years	0.476 years	8,367	251,297
60	No MEPACT	£33K		19.626 years		1,688	
	MEPACT	£153K	£120K	20.154 years	0.528 years	7,574	226,372

Table B15b: Regimen A+MEPACT versus Regimen B for Extended Time Horizons

Extended Horizon	Strategy	Cost	Incr Cost	QALY	Incr QALY	Cost/QALY (£)	ICER (£)
Reference	No MEPACT	£36K		6.359 years		5,672	
	MEPACT	£151K	£114K	6.673 years	0.314 years	22,564	364,934
20	No MEPACT	£37K		12.72 years		2,914	
	MEPACT	£152K	£115K	14.32 years	1.60 years	10,599	71,692
40	No MEPACT	£38K		15.95 years		2,354	
	MEPACT	£152K	£115K	18.21 years	2.25 years	8,367	50,917
60	No MEPACT	£38K		17.57 years		2,151	
	MEPACT	£153K	£115K	20.15 years	2.58 years	7,574	44,481

Table B15c: Regimen B+MEPACT versus Regimen B for Extended Time Horizons

Extended Horizon	Strategy	Cost	Incr Cost	QALY	Incr QALY	Cost/QALY (£)	ICER (£)
Reference	No MEPACT	£36K		6.359 years		5,672	
	MEPACT	£155K	£119K	6.685 years	0.325 years	23,149	364,637
20	No MEPACT	£37K		12.72 years		2,914	
	MEPACT	£156K	£119K	14.28 years	1.56 years	10,922	76,250
40	No MEPACT	£38K		15.95 years		2,354	
	MEPACT	£157K	£119K	18.14 years	2.19 years	8,628	54,399
60	No MEPACT	£38K		17.57 years		2,151	
	MEPACT	£157K	£119K	20.07 years	2.50 years	7,812	47,589

Table B15d: Regimen B+MEPACT versus Regimen A for Extended Time Horizons

Extended Horizon	Strategy	Cost	Incr Cost	QALY	Incr QALY	Cost/QALY (£)	ICER (£)
Reference	No MEPACT	£31K		6.508 years		4,780	
	MEPACT	£155K	£124K	6.685 years	0.177 years	23,149	699,943
20	No MEPACT	£32K		13.946 years		2,313	
	MEPACT	£156K	£124K	14.276 years	0.330 years	10,922	374,930
40	No MEPACT	£33K		17.733 years		1,852	
	MEPACT	£157K	£124K	18.141 years	0.408 years	8,628	303,262
60	No MEPACT	£33K		19.626 years		1,688	
	MEPACT	£157K	£124K	20.073 years	0.447 years	7,812	276,810

Table B15e: Regimen A+MEPACT versus Regimen B+MEPACT for Extended Time Horizons

Extended Horizon	Strategy	Cost	Incr Cost	QALY	Incr QALY	Cost/QALY (£)	ICER (£)
Reference	MEPACT A+	£150.6K		6.6730 years		22,564	
	MEPACT B+	£154.7K	£4.2K	6.6847 years	0.0117 years	23,149	356,702
20	MEPACT A+	£151.8K		14.3169 years		10,599	
	MEPACT B+	£155.9K	£4.2K	14.2760 years	-0.0409 years	10,922	(Dominated)
40	MEPACT A+	£152.3K		18.208 years		8,367	
	MEPACT B+	£156.5K	£4.2K	18.141 years	-0.068 years	8,628	(Dominated)
60	MEPACT A+	£152.6K		20.154 years		7,574	
	MEPACT B+	£156.8K	£4.2K	20.073 years	-0.081 years	7,812	(Dominated)

Table B15f: Regimen A versus Regimen B for Extended Time Horizons

Extended Horizon	Strategy	Cost	Incr Cost	QALY	Incr QALY	Cost/QALY (£)	ICER (£)
Reference	No MEPACT A-	£31.2K		6.464 years		4,824	
	No MEPACT B-	£36.1K	£4.9K	6.359 years	-0.105 years	5,672	(Dominated)
20	No MEPACT A-	£32.3K		13.83 years		2,337	
	No MEPACT B-	£37.1K	£4.7K	12.72 years	-1.11 years	2,914	(Dominated)
40	No MEPACT A-	£32.9K		17.58 years		1,872	
	No MEPACT B-	£37.6K	£4.7K	15.95 years	-1.62 years		(Dominated)
60	No MEPACT A-	£33.2K		19.45 years		1,706	
	No MEPACT B-	£37.8K	£4.6K	17.57 years	-1.88 years	2,151	(Dominated)

B16. Please provide survival curves for the model output and please compare to the trial results.

The economic model assumptions for handling withdrawals with and without recurrence were not based on assumptions of the hazard function extrapolated to the Cox regression model. Rather the assumptions to account for withdrawals in the presence or absence of recurrence with lung metasteses were taken from the clinical literature and clinical expert advice. The assumptions regarding the longer-term time horizons of 20, 40 and 60 years assumed that patients remaining in the disease-free state at the end of the clinical trial horizon would remain disease-free. Therefore, as the economic model assumptions were not based on the statisitcal requirements to fulfill the underlying assumptions of a Cox regression modelling approach, such Kaplan-Meier survival curves cannot be produced from the economic model.

B17. Please provide disaggregated costs and QALYs for your base case and for time horizons of 20, 40 and 60 years. The disaggregation should include factors such as QALYs gained from each health state and costs broken down to include drug acquistion costs and administration.

The disaggregated costs and QALYs are presented in the embedded Excel sheet below:

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<u>Section 7.6.2.1</u>

B18. Please cite exact passage(s) of Section 10.5 which is relevant to each item in table 8, in a separate column.

Table 8 of main report: Variables Used in the Model

Variable Name	Description	Value	Range	Section
C_2nd_chemo_cycle	Cost of second-line chemotherapy cycle	1636		10.5.4.1
C_AE_hearing	Cost of hearing AE (cycle 1)	50		10.5.2.5
C_AE_infus	Cost of infusion reaction AE (cycle 1)	1.91		10.5.2.5
C_catheter	Cost of central line insertion	2281		10.5.5.1/10.5.5.2
C_chemo_A	Cost of adjuvant chemotherapy regimen A	26832		10.5.2.3/10.5.2.4
C_chemo_B	Cost of adjuvant chemo regimen B	31181		10.5.2.3/10.5.2.4
C_ct_scan	Cost of CT scan	100		10.5.5.1/10.5.5.2
C_isotope_scan	Cost of bone isotope scan	183		10.5.5.1/10.5.5.2
C_mepact_dose	Cost of a MEPACT dose	2375		10.5.2.3
C_mepact_outvisit	Cost of an outpatient visit for MEPACT dosing	189		10.5.5.2
C_MRI	Cost of MRI scan	278		10.5.5.1/10.5.5.2
C_NHS_palliative_care	Cost of NHS palliative care	3403		10.5.4.2
C_other_pulm_surg	Cost of other non-pulmonary surgery only	6168		10.5.5.2
C_outpat	Cost of outpatient visit - no treatment	189		10.5.5.2/10.5.3.1*
C_palliative_care	Cost of all palliative care (33% added) for hospice care provided by voluntary/charity	5105		10.5.4.2
C_pharm_time	Cost of pharmacy time to prepare a MEPACT dose	50		10.5.2.3**
C_pulm_surg	Cost of pulmonary surgery	5426		10.5.5.2
du_hearing_loss	Disutility associated with hearing loss	0.18		10.5.10.2
du_hearing_loss_mainten	Disutility for hearing loss in maintenance phase	0		7.2.8.2
du_limb_salvage	Disutility associated with limb-salvage	0		7.2.8.3
initial_lifegain	Life gain in first cycle of 9 months	0.75		7.2.6.1
Lifegain	Life gain for cycle 2 onwards 6 months	0.5		7.2.6.1
no_2nd_chemo_cycles	Number of second-line chemotherapy cycles	5	4-10	10.5.4.1
no_mepact_doses	Number of MEPACT doses	48	36-48	10.5.2.1
P_AE_hearing_MEPACT	Probability of hearing loss AE MEPACT	0.15		10.5.2.5
P_AE_hearing_NOMEPACT	Probability of hearing AE NOMEPACT	0.8		10.5.2.5
P_AE_infus_MEPACT	Probability of infusion AE MEPACT	0.98		10.5.2.5
p_AE_infus_NOMEPACT	Probability of an infusion AE No MEPACT	0		10.5.2.5
p_limbsalvage	Proportion of patients in UK with limb-salvage	0.75		Table 33
p_mepact_outvisit	Proportion of outpatient visits required for MEPACT	0.3	0-0.3	10.5.2.1
p_recur_lungmets	Probability of recurrence with lung metastases	0.5	0.75	10.5.5.2 & Table 33
p_startdiseasefree_MEPACT	Proportion of patients starting in DF state	0.983498		10.5.8
p_startdiseasefree_NOMEPACT	Proportion starting in DF No MEPACT	0.993355		10.5.8
p_startdisease_MEPACT	Proportion of patients starting in DP state	0.016502		10.5.8
p_startdisease_NOMEPACT	Proportion starting in DP with NO MEPACT	0.006645		10.5.8
u_death	Utility for death	0		10.5.10. 2&7.2.8.3
u_disease	Utility for disease-progression	0.39	0.22	10.5.10. 2&7.2.8.3
u_diseasefree	Utility for disease-free state	0.75		10.5.10. 2 &7.2.8.3
u_maintain	Utility for maintenance phase (cycle 1)	0	0.20	10.5.10. 2 &7.2.8.3
u_postrecurr_disease	Utility post-recurrence disease-progression	0.39	0.22	10.5.10. 2 &7.2.8.3
u_postrecurr_disease_free	Utility post-recurrence DF	0.75		10.5.10. 2 &7.2.8.3
u_recurrence	Utility for recurrence	0.61	0.22	10.5.10. 2 &7.2.8.3

*Note for computation of outpatient visits without MEPACT dosing a cost of £116 was assumed. A cost of £189 was assumed for an outpatient visit with treatment.

**504 should read £50[4]

Section 8.1.

B19. Please provide results of the effect on budget impact of an uptake rate of 80%. It appears that until recruitment into EURAMOS I study ceases, the final uptake rate (estimated at 50-60%) is unknown. As this is the only new treatment for osteosarcoma is it possible that the uptake could exceed this estimate?

Table B19a: Budget Impact of 50% Uptake in 2009/2010 and 80% Uptake Thereafter

POPULATION DATA		**2009**	**2010**	**2011**	**2012**	**2013**
Total UK population (millions)		61	61.5	62	62.5	63
England and Wales population (89% of UK)	0.89	54.3	54.7	55.2	55.6	56.1
Incidence in children (0-14 years)*	0.7	38	38	39	39	39
Incidence in adolescents (15-19 years)*	0.7	35	36	36	36	36
Incidence in young adults (>20years)*	0.3	14	14	14	14	14
Total metastatic and non-metastatic		87	88	88	89	90
% of patients with non-metastatic	80%					
POTENTIAL PATIENT POPULATION		**69**	**70**	**71**	**71**	**72**
UPTAKE RATE		50%	50%	80%	80%	80%
Treated patients		**35**	**35**	**57**	**57**	**57**
MEPACT	**/dose**	**Cost/cycle of 48 doses**				
	£2375	114000				
BUDGET IMPACT (Worse case scenario; all patients have full cycle of 48 doses). Includes VAT @17.5%		**£4,657,371**	**£4,695,520**	**£7,571,952**	**£7,632,990**	**£7,694,028**

*Per million of population

Table B19b: Budget Impact of 80% Uptake in 2009-2013

POPULATION DATA		**2009**	**2010**	**2011**	**2012**	**2013**
UPTAKE RATE		80%	80%	80%	80%	80%
Treated patients		**56**	**56**	**57**	**57**	**57**
BUDGET IMPACT (Worse case scenario; all patients have full cycle of 48 doses). Includes VAT @17.5%		**£7,449,875**	**£7,510,913**	**£7,571,952**	**£7,632,990**	**£7,694,028**

The current EURAMOS I study is not due to complete until the end of 2010. As this reflects current standard of care for UK patients, it is likely that a 50% uptake rate in 2009 and 2010 is an over estimation. Increasing the rate from 50% to 80% for 2011-2013 increases the budget impact from approximately £5.7 million to £7.7 million in 2013. It is unknown if the uptake rate of MEPACT will exceed 80% on completion of the EURAMOS I study. If a further EURAMOS study was initiated after 2010 then the uptake rate would reflect any future study design. If patients were to receive MEPACT in all treatment arms in a future study, then the uptake rate may be >80%, assuming all patients consent to entering such a study. However, this would not be the case if all treatment arms did not include MEPACT, in which case the uptake rate might be below 50%.

Section 10.5.9.

B20. Please provide a breakdown of frequency of withdrawals by treatment arm (4 groups) and health status (disease-free, disease-progression, and recurrence) at time of withdrawal.

Tables B20a-c summarise patient health states prior to withdrawal. Note, patients can stay in the recurrence state for one cycle only. In this state they incur diagnostic costs and costs of additional surgery or chemotherapy (see Section 10.5.5 of the submitted main report). The post-recurrence column represents patients in the "Recurrence/Disease-Free" health and "Recurrence/Disease Progression" health states.

Table B20a: Frequency of Withdrawals, Based on Column Percentages

Treatment Group	Disease Progression	Disease-Free	Recurrence	Post-Recurrence	Row Totals
A+MEPACT	0 (0.00%)	102 (24.64%)	1 (33.33%)	12 (27.27%)	115 (24.84%)
A-	1 (50.00%)	107 (25.85%)	0 (0.00%)	7 (15.91%)	115 (24.84%)
B+MEPACT	1 (50.00%)	115 (27.78%)	1 (33.33%)	11 (25.00%)	128 (27.65%)
B-	0 (0.00%)	90 (21.74%)	1 (33.33%)	14 (31.82%)	105 (22.68%)
Column Totals	2 (100.00%)	414 (100.00%)	3 (100.00%)	44 (100.00%)	463 (100.00%)

Table B20b: Frequency of Withdrawals, Based on Row Percentages

Treatment Group	Disease Progression	Disease-Free	Recurrence	Post-Recurrence	Row Totals
A+MEPACT	0 (0.00%)	102 (88.70%)	1 (0.87%)	12 (10.43%)	115 (100.00%)
A-	1 (0.87%)	107 (93.04%)	0 (0.00%)	7 (6.09%)	115 (100.00%)
B+MEPACT	1 (0.78%)	115 (89.84%)	1 (0.78%)	11 (8.59%)	128 (100.00%)
B-	0 (0.00%)	90 (85.71%)	1 (0.95%)	14 (13.33%)	105 (100.00%)
Column Totals	2 (0.43%)	414 (89.42%)	3 (0.65%)	44 (9.50%)	463 (100.00%)

Table B20c: Frequency of Withdrawals, Based on Count Percentages

Treatment Group	Disease Progression	Disease-Free	Recurrence	Post-Recurrence	Row Totals
A+MEPACT	0 (0.00%)	102 (22.03%)	1 (0.22%)	12 (2.59%)	115 (24.84%)
A-	1 (0.22%)	107 (23.11%)	0 (0.00%)	7 (1.51%)	115 (24.84%)
B+MEPACT	1 (0.22%)	115 (24.84%)	1 (0.22%)	11 (2.38%)	128 (27.65%)
B-	0 (0.00%)	90 (19.44%)	1 (0.22%)	14 (3.02%)	105 (22.68%)
Column Totals	2 (0.43%)	414 (89.42%)	3 (0.65%)	44 (9.50%)	463 (100.00%)

Section 10.5.9.1.

B21. Please clarify whether the transition from disease-free (DF) status to withdrawal is handled by reallocation to disease-progression (DP) or recurrence, or whether this is handled by reallocation to DP and DF states?

Transition from Disease-Free status to withdrawal is handled by reallocation to the Disease-Free or Recurrence state. Note, in the model patients cannot progress from the Disease-Free state to Disease-Progression. Patients can only transition from the Disease-Free to Disease-Progression, via the Recurrence state.

The first sentence of Section 10.5.9.1 should read:

"On the advice of expert opinion, patients who transitioned from the Disease-Free state to Withdrawal were reallocated to: Disease-Free or Recurrence"

Section 10.5.9.3.

*B22. **Please provide results for sensitivity analyses of the reference case model when all withdrawals from this state are reallocated to DP and when half are reallocated to DP and half to DF.***

In order for 100% of withdrawals from the recurrence state to be reallocated to the DP state, the following changes have been implemented in the model.

- The probability of surgical remission after recurrence with lung metastases has been changed from 0.75 to 0.
- The probability of surgical remission after recurrence with other than lung metastases alone has been changed from 0.57 to 0.

The results demonstrate that by assigning 100% of withdrawals from the recurrence state to the DP state, the QALY gain in the MEPACT arm is reduced from 6.679 to 6.666 and the ICER is slightly increased from £457,624 to £468,571. For the case when 50% of withdrawals from the recurrence state are assigned to the DP state, the impact on the ICER is very small (£460,232).

Table B22a: 100% of Withdrawals from Recurrence State Reallocated to DP

Strategy	Cost	Incr Cost	Eff	Incr QALY	Cost/QALY (£)	ICER (£)
No MEPACT	£34K		6.412 years		5,242	
MEPACT	£153K	£119K	6.666 years	0.254 years	22,898	468,571

In order for 50% of withdrawals from the recurrence state to be reallocated to the DP state and 50% to the DF state, the following changes have been implemented in the model.

- The probability of surgical remission after recurrence with lung metastases has been changed from 0.75 to 0.5.
- The probability of surgical remission after recurrence with other than lung metastases alone has been changed from 0.57 to 0.5.

Table B22b 50% of Withdrawals from Recurrence State reallocated to DP

Strategy	Cost	Incr Cost	Eff	Incr QALY	Cost /QALY (£)	ICER (£)
No MEPACT	£34K		6.417 years		5,238	
MEPACT	£153K	£119K	6.676 years	0.259 years	22,865	460,232

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Attachment 1

Childrens Cancer Group
Toxicity and Complications Criteria

Site	Measure	GRADE				
		0/WNL	1 (Mild)	2 (Moderate)	3 (Severe)	4 (Unacceptable)
A. Blood	1. WBC/µl	≥4.0	3.0-3.9	2.0-2.9	1.0-1.9	<1.0
	2. ANC/µl	≥2.0	1.5-1.9	1.0-1.4	0.5-0.9	<0.5
	3. PLT/µl	WNL	75.0-normal	50.0-74.9	25.0-49.9	<25.0
	4. HGB g/dl	WNL	10.0-normal	8.0-10.0	6.5-7.9	<6.5
	5. LYMPHS/µl	≥2.0	1.5-1.9	1.0-1.4	0.5-0.9	<0.5
B. Marrow	1. CELLULARITY	normal	mildly hypo. 25%↓	mod. Hypo. 50%↓	marked hypo. 75%↓ 3 wks to recovery	aplastic >3 wks to recovery
C. Liver	1. SGOT	WNL	≤2.5xN	2.6-5.0xN	5.1-20.0xN	>20.0xN
	2. SGPT	WNL	≤2.5xN	2.6-5.0xN	5.1-20.0xN	>20.0xN
	3. ALK PHOS-PHATASE	WNL	≤2.5xN	2.6-5.0xN	5.1-20.0xN	>20.0xN
	4. TOTAL BILI	WNL	--	<1.5xN	1.5-3.0xN	>3.0xN
	5. LIVER-CLIN.	WNL	--	--	precoma	hepatic coma
D. Pancreas	1. Amylase/Cr.Cl.	WNL	<1.5xN	1.5-2.0xN	2.1-5.0xN	>5.0xN
	2. Amylase	WNL	<1.5xN	1.5-2.0xN	2.1-5.0xN	>5.0xN
	3. Glu mg/dl	WNL	55-64/116-160	40-54/161-250	30-39/251-500	<30/>500/ketoacid
	4. Ultrasound size & sonolucency	normal normal	normal increased	increased incr. localized	increased incr. generalized	pseudocyst hermorrhagic
E. Renal and Genitourinary	1. BUN	<20	20 - 39	40 - 59	60 - 79	≥80
	2. Creatinine	WNL	<1.5xN	1.5-3.0xN	3.1-6.0xN	>6.0xN
	3. Creatinine Clearance	WNL	75%	50 - 74%	25-49	<25%
	4. Blood pressure-systolic	baseline	±10%	±20%	±30%	±40%
	5. Blood pressure-diastolic	baseline	±5%	±10%	±15%	±20%
	6. Proteinuria	neg	1+/or <3 g/l	2-3+/or 3-10 g/l	4+/or >10g/l	nephritic synd.
	7. Hematuria	neg	micro only	gross+clots	gross+clots	Trans. Req'd
	8. Bladder – frequency & dysuria	none	slight	moderate responses to Rx	severe, no response to Rx	Incapacitating with severe hemorrage
F. Gastro-instestinal	1. Stomatitis	none	erythema, or mild soreness	painful/edema can eat	cannot eat or drink	requires parental or enteral support
	2. Abdominal pain: severity treatment	none --	mild not required	moderate required—helps	moderate—severe required—no help	severe hospitalization, heavy sedation
	3. Constipation	no chg	mild ileus	mod. Ileus	severe ileus	
	4. Diarrhea	none	↑2-3stools/day	↑4-6 stools/day or mod. cramps	↑7-9 stools.day or severe cramps	ileus>96 hrs ↑≥10 stools/day bloody, parenteral
	5. Nausea	none	reasonable intake	decreased intake	no sig. intake 6-10x/day	support required

Childrens Cancer Group
Toxicity and Complications Criteria

Site	Measure	GRADE				
		0/WNL	1 (Mild)	2 (Moderate)	3 (Severe)	4 (Unacceptable)
	%STI	<0.35	--	<.40	>0.40	--
	3. -Ischemia	none	non-specific T-wave flattening	asymptomatic/EKG chg sugg ischemia	agina/without evidence of infarct.	acute myocardial infraction
	-Pericard. Effusion	none	asympt. effusioin no Rx required	pericarditis	drainage required	tamponade; drainage urgently required
	4. Card. Function	WNL	asymptomatic/ ↓ej. Fr. <20	asymptomatic/ej. fr. <80% basline	mild CHF/ responds to Rx	severe or refractory CHF
	5. hypertension	no chg	asympt./transient ↑20% no Rx req'd	recur./persist. ↑20%, no Rx req.	requires therapy	hypertensive crisis
	6. Hypotension	no chg	no Rx. req'd.	Rx but no hosp.	Rx+ hosp. <48hrs after stop agent	Rx+ hosp. >48 hrs after stop agent
I. Nervous System	1. peripheral: sensory	no chg	mild parestihesias, loss tendonreflex	mod. sensory loss, mod. paresthesias	interferes with function	--
	Motor	no chg	subj. weakness/no obj. findings	mild obj.weakness/ no signif. impair	obj. weakness/ function impar	paralysis
	2. Central: Cerebellar	no chg	slight incoodination/ dysdiadokinesis	intention tremor/ dysmetria/ slurred speech/ nystagmus	locomotor ataxia	cerebellar necrosis
	CNS-general	no chg	drowsy/nervous	confused	seizures/psychosis	comatose
	-headache	no chg	mild	transient/mod/severe	severe, unrelenting	--
	Cortical	no chg	mild somnolence/ agitation	mod. somnolence/ agitation	severe somnolence/ agitation/ confusion/ hallucination	coma/seizures/ toxic psychosis
J. Skin	1. Skin	no chg or WNL	scattered eruption or erythema, asympt.	urticar/scattered erupt, sympt.	generalized eruption, req. Rx	exfol/ulcer dermatisis
	Alpecia	no loss	mild hair loss	marked/total hair loss	--	--
K. Allergy		none	transient rash	mild bronchospasm	mod. bronchospasm, serum sickness	hypotension, anaphylaxis
L. Coagulation	1. Fibrinogen	WNL	0.99-0.75xN	0.74-0.50xN	0.49-0.25xN	≤0.24xN
	2. PT	WNL	1.01-1.25xN	1.26-1.50xN	1.51-2.00xN	>2.00xN
	3. PTT	WNL	1.01-1.66xN	1.67-2.33xN	2.34-3.00xN	>3.00xN
	4. hemorrhage (clin)	None	mild/no tranf	gross- 1-2 trans/ episode	gross- 3-4 trans/ episode	massive->4 trans/ episode
M. Hearing	1. Objective	no chg	20-40db loss >4Khz	>40db loss >4 Khz	>40db loss <2 Khz	>40db loss<2 Khz
	2. Subjective	no chg	loss of audiometry only	tinnitus, softspeech	loss correctable with hearing aide	deafness not correctable
N. Electrolytes	1. Na mEq/l	WNL	↓130-134/ ↑146-149	125-129/150-155	116-124/156-164	<115/>165
	2. K mEq/l	WNL	↓3.1-3.4/↑5.5-5.9	2.6-3.0/6.0-6.4	2.1-2.5/6.5-6.9	<2.0/>7.0
	3. Ca mg/dl	WNL	8.4-7.8/10.6-11.5	7.7-7.0/11.6-12.5	6.9-6.1/12.6-13.5	≤6.1/≥13.5