NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Mifamurtide for the treatment of osteosarcoma
Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the manufacturer or sponsor of the technology, national professional organisations, national patient organisations, the Department of Health and the Welsh Assembly Government and relevant NHS organisations in England. Consultee organisations are invited to submit evidence and/or statements and respond to consultations. They are also have right to appeal against the Final Appraisal Determination (FAD). Consultee organisations representing patients/carers and professionals can nominate clinical specialists and patient experts to present their personal views to the Appraisal Committee.

Clinical specialists and patient experts – Nominated specialists/experts have the opportunity to make comments on the ACD separately from the organisations that nominated them. They do not have the right of appeal against the FAD other than through the nominating organisation.

Commentators – Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement. They are invited to respond to consultations but, unlike consultees, they do not have the right of appeal against the FAD. These organisations include manufacturers of comparator technologies, NHS Quality Improvement Scotland, the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Information Authority and NHS Purchasing and Supplies Agency, and the *British National Formulary*).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but may be summarised by the Institute secretariat – for example when many letters, emails and web site comments are received and recurring themes can be identified.

Comments received from consultees

Consultee	Comment	Response
Takeda	*i) Whether you consider that all of the relevant evidence has been taken into account?*	
	We consider that all of the evidence submitted by Takeda UK on the 10th December 2009 and the 8th February 2010 has been taken into account. However, we do not consider the appraisal committee's interpretation of what is the appropriate comparator in the UK to be correct.	Comment noted
	In the UK the current standard of care is entry into a randomised multicentre intergroup clinical trial (such as EURAMOS I.) Currently it is estimated that 80-90% of patients diagnosed with osteosarcoma in the UK are entered into the European and US osteosarcoma trial EURAMOS I trial as part of an adjuvant regimen (with ifosfamide, etoposide, cisplatin, doxorubicin and methotrexate) for patients with tumours showing a poor histological response to pre-operative chemotherapy. Hence it is important to differentiate from what is perceived to be routinely used, and what is actually used in the NHS. In the EURAMOS I trial, the adjuvant treatment regimen employed includes ifosfamide which equates to 4 agent chemotherapy. As a result it is incorrect to assume that 3 agent combination chemotherapy is the current standard of care and it is the opinion of Takeda UK that the appraisal committee should consider both 3 agent and 4 agent combination chemotherapy treatment as the standard of care in England and Wales.	Comment noted. The Committee heard from clinical specialists that only patients with tumours showing a poor histological response to pre-operative chemotherapy may receive ifosfamide within the EURAMOS 1 study, and patients would not be eligible for mifamurtide while they are receiving the study drug regimens. The Committee concluded that the current standard chemotherapy regimen in England and Wales is doxorubicin, methotrexate and cisplatin, and that ifosfamide is not routinely used in UK clinical practice outside the EURAMOS 1 study. Please see FAD section 4.4.
	These considerations are further elaborated upon in section 3 of this response to ACD.	
	ii) Do you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence, and that the preliminary views on the resource impact and implications for the NHS are appropriate?	
	Takeda UK do not consider the summaries of clinical and cost effectiveness presented within the ACD to be generally reasonable interpretations for this appraisal for two key reasons:	
	1. As highlighted above, we do not consider NICE's interpretation of the standard of care to be appropriate.	Comment noted. The Committee concluded that the current standard chemotherapy regimen in England and Wales is doxorubicin, methotrexate and cisplatin, and that ifosfamide is not routinely used in UK clinical practice outside the EURAMOS 1 study. Please see FAD sections 4.3 & 4.4.

	2. We do not consider NICE's approach to assessing the results of the INT-0133 trial as appropriate either scientifically or philosophically. NICE have analysed the trial's 2 x 2 factorial design as four separate arms. However, the trial was not designed nor statistically powered to be analysed in this way. The post-hoc analysis under-taken by NICE was not statistically significant in any of the arms – this is not surprising as the trial was not designed nor powered to be analysed in this way. Additionally, given the substantial time commitments in researching rare and ultra orphan diseases, the limited sample sizes and often the relative uncertainty related to such results, it seems philosophically wrong to sub divide the data of a rare disease to the point where results cannot be significant and favourable decision making is impossible. It is the opinion of Takeda UK that the INT-0133 trial should be analysed as it was statistically planned to do so in line with good clinical and statistical practice.	The Committee considered the most appropriate comparison and the most appropriate analysis of mifamurtide from INT-0133. The Committee considered the most appropriate comparison and the most appropriate analysis of mifamurtide from INT-0133. The Committee concluded that the comparison that best reflected current UK clinical practice was the individual mifamurtide containing regimen (A+) compared with a regimen reflecting UK clinical practice (A). However, for the reasons given in section 4.6 of the FAD, the Committee accepted that the combined analysis of all the INT-0133 data may be more appropriate in determining the effect of adding mifamurtide to the standard UK regimen than the post hoc analysis directly comparing regimen A+ with regimen A. Please see FAD sections 4.7 and 4.8.
	3. Given the considerations raised in points 1 and 2 above, we do not consider the summaries of cost effectiveness to be reasonable nor logical interpretations.	The Committee considered the additional analyses carried out by the manufacturer and concluded that the manufacturer's best-case ICERs were substantially higher than those normally considered to be an acceptable use of NHS resources. See FAD section 4.16.
	These considerations are further elaborated upon in section 1, 2, 3, 4 and 5 of this response to ACD.	
	iii) Whether you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS?	
	Takeda UK do not consider the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for guidance to the NHS. In particular it is not clear from the ACD how the rarity of osteosarcoma has been considered in this appraisal. Takeda UK believe it is important for NICE to be transparent in any future documentation recommending the use of mifamurtide (FAD and guidance documents) as to NICE's policy for assessing medicines for rare and ultra orphan disease and how in this case the Social Value Judgements[1] endorsed by the NICE Board have been employed for consideration for this appraisal.	Comment noted. The Committee considered that mifamurtide is indicated for a small patient population with a rare disease, and noted that NICE had not received direction from the Department of Health that treatments for rare conditions ('orphan' or 'ultra-orphan') should be appraised differently from any other treatments. See FAD section 4.19. The Committee agreed that the best-case ICER based on the evidence available was £70,100 per
	Takeda UK are committed to making mifamurtide available to patients in England	

	and Wales; however at this stage it is not clear what is required to accomplish this for an ultra orphan medication. Indeed, using the standard appraisal committee cost per QALY threshold for acceptance of under £30,000 would suggest that patients with osteosarcoma and other rare illnesses will be underserved until NICE have a transparent policy for assessment of rare illnesses to which manufacturers can work towards. These considerations are further elaborated upon in section 5 of this response to ACD. Given these considerations, it is the opinion of Takeda UK that the provisional recommendations of the ACD do not constitute a suitable basis for guidance to the NHS. In addition, Takeda UK would encourage NICE to consider some of the previous thinking regarding the appraisal of ultra orphan medications for this appraisal, or alternatively, and as per stated in the Social Value Judgements, allow the other mechanisms in the NHS to assess the availability of ultra-orphan drugs, and to terminate this NICE appraisal. Takeda UK's response to the ACD is provided in following five sections: Section 1: We summarise the main findings from the pivotal trial INT-0133, and the quality and robustness of findings in the context of an ultra-orphan indication. Section 2: We address concerns expressed in the ACD over specific methodology in INT-0133 relating to the analyses of A/B vs. A+/B+, and related uncertainty over the estimates of survival. We present further information pertaining to the statistical plan for INT-0133 and robustness of the trial methodology. Section 3: We address the issue of the appropriate comparison relevant for UK practice for assessing clinical effectiveness from the INT-0133 trial. Section 4: We address issues and concerns over the plausible ICER for mifamurtide vs. standard therapy. Section 5: We place the clinical and cost-effectiveness results in the context of the unmet need of children, teenagers and young adults with the ultra-orphan disease osteosarcoma.	QALY gained. Although the Committee accepted that there may be a case for accepting a higher ICER for children, adolescents and young people, this ICER was too high to allow the Committee to recommend mifamurtide, even when taking into account a number of other considerations such as other aspects of health-related quality of life not adequately captured in the QALY, the innovative nature of the drug, the rarity of the condition, and possible discount rates. See FAD section 4.22. Comment noted.

	Section 1: Summary of clinical effectiveness issues. 1.1 Methodology related to INT-0133 Paragraph 4.5 of the NICE ACD states: *"The Committee considered the evidence on the clinical effectiveness of mifamurtide as presented in the manufacturer's submission and the ERG's critique. It considered the evidence from the only relevant randomised clinical trial (INT-0133). The Committee noted that the study was relatively well conducted, but it agreed that there were substantial methodological issues identified by the ERG which led to uncertainty around the estimates of survival."* Page 9 of the Evidence Review Group (ERG) report[2] states the following methodological issues suggested of the INT-0133 trial: – open label design. – delayed adminstration and failure to receive mifamurtide after randomisation. – imbalance of histological response to neoadjuvant therapy. – disparity of survival events in the subset of patients who did not enter the maintenance phase. – interpretation of the statistical analyses. Responses to these ERG concerns relating to the robustness of the data are addressed in turn through this section. Information provided is not new evidence, but has been previously submitted in response to clarification questions to IDM (December 2008), Takeda UK (January 2010) and response to the ERG Report from Takeda UK (February 2010):	Comment noted.
	1.1.1. "open label design" 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 mifamurtide doses, including fever, chills and headache, would make blinding	Comment noted.

	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)[3] and the Addendum on Paediatric Oncology (CPMP/EWP/569/02)[4]. The ERG Report from 2009[2] acknowledges that: *"With many cytotoxic cancer drugs, the nature of the interventions precludes blinding (i.e. drug toxicities or manner of administration) for the practical and ethical reason that informed dose monitoring and adjustment is required."* *1.1.2. "delayed adminstration and failure to receive mifamurtide after randomisation"* The ERG refers to the delayed administration of mifamurtide within the trial due to the lack of availability of the specialist filter required for reconstitution and administration of mifamurtide (was not available from 15 June 1995 to 15 January 1996.) During this period only 8 of the 51 patients randomised to a mifamurtide group did not receive mifamurtide therapy. These 8 patients were retained in the intention to treat analysis and therefore would have if anything, a minimal negative effect on the results against mifamurtide. Also, the expected result from such a delay would be to diminish the observed efficacy of mifamurtide, not exaggerate it *1.1.3. "imbalance of histological response to neoadjuvant therapy"* The ERG refers to the imbalance in histological response to neoadjuvant therapy between treatment groups. This was particularly pronounced for those patients assigned to regimen A+, where a greater proportion of tumours showed a poor [greater than 5% remaining viable tumour] histological response. Takeda UK agree with the appraisal committee that there is evidence of a link between poor histological response and prognosis and it is not clear the impact that this makes upon the A/A+ arms. However, this imbalance would again reduce the positive effect on patient survival from mifamurtide, not exaggerate it. *1.1.4. "disparity of survival events in the subset of patients who did not enter the maintenance phase"* Takeda UK refer to the response to the NICE clarification questions submitted by IDM on the 8th December 2008 and detailed below.	Comment noted. Comment noted. Comment noted

	The requested information regarding the number of patients who did not enter maintenance (adjuvant treatment phase) in INT-0133 is included in the following table for intent-to-treat patients *(Table A11a provided by Takeda but not reproduced here)*. Reasons for patients not progressing onto the maintenance phase included disease progression or protocol violation. The majority of documented protocol breaks were due to voluntary withdrawal either by the patient/parent or by the physician. Such withdrawals are fairly representative of that observed in any other oncology clinical research.[5] The number of DFS and death events is summarised by treatment arm in the subset of patients who did not enter the maintenance phase *(Table A11b provided by Takeda but not reproduced here).* Takeda UK confirm that this data is included in the intention to treat analysis as previously submitted and there is no disparity of survival events as suggested. The overall number of patient who withdrew before the maintenance (adjuvant) treatment phase (74) are very low; when subdivided per the 4 arms the numbers are too low to make any significant conclusions regarding a disparity of survival events. It would be appreciated if the Appraisal Committee can please explain where the proposed disparity in survival events may lay.	
	1.1.5 "interpretation of the statistical analyses." Takeda UK refer to Section 2 of this document: Summary of statistical plan and robustness of trial methodology.	Comment noted
	1.2 <u>Regulatory interrogation and approval of INT-0133</u> As previously noted, the licence application was based on the results of one clinical trial, and therefore the European Medicines Agency (EMA), Committee for Medicinal Products for Human Use (CHMP) considered that the data needed to be of high quality and the results robust[6]. Initially in their assessment, the CHMP raised a number of concerns with respect to the above study[6]. The CHMP convened the scientific advisory group (SAG) for oncology to advise on these including site visits to lead investigating centres in the USA. The main findings from their review were as follows[6]: • The CHMP Scientific Advisory Group (SAG) for oncology confirmed the data	Comment noted. The criteria used by other organisations to recommend a technology may be different from those used by NICE. The Committee only consider technologies that have received a positive CHMP opinion. An appraisal process requests healthcare professionals to provide a view of the technology within the context of current clinical practice. This view is important because it extends the evidence that is derived from pre- and post-licensing studies, which often relates to efficacy and safety under clinical trial conditions

	was of high quality and the results robust. • The CHMP finally concluded that the risk benefit of mifamurtide was favourable in this indication. • From the data presented on overall survival it was deemed possible that there exists a quantitative interaction with ifosfamide. However, the SAG agreed that this quantitative interaction was likely to be small and of little clinical importance. What was felt to be important was that the clinical data presented were reassuring about the fact that there is no important qualitative interaction. • The SAG agreed by consensus that the benefits of mifamurtide were consistent regardless of the treatment arm used in the pivotal trial, although the treatment effect might be slightly different. • Overall, the SAG considered that the unexplained observations and uncertainties were well within the range of what is observed with other cancer products. • The SAG and the EMA agreed that based on the clinical efficacy data presented; treatment with mifamurtide was associated with clinically significant benefits in the proposed indication. The SAG also agreed that the observed toxicity profile raised no particular concern, given the large unmet medical need and the sufficiently convincing efficacy data.[6]	rather than effectiveness in routine clinical practice. See 'Guide to the methods of technology appraisal' section 4.4.2.
	Key points concerning methods and results are as follows[7, 8]: • 6-year survival probability was 78% in patients who received mifamurtide compared with 70% in patients who did not. • There is an approximate 30% reduction in the risk of death with the addition of mifamurtide. • An improvement in overall survival is the gold-standard endpoint for a new osteosarcoma drug, showing a significant clinical benefit for paediatric and young adult patients with osteosarcoma. • The primary endpoint stated in the protocol was overall and disease-free survival for both treatment comparisons (mifamurtide maintenance and ifosfamide induction, respectively). • Disease free and overall survivals are considered the most relevant endpoints for studies in cancer in general, and for high mortality cancers, such as osteosarcoma, in particular.	Comment noted.

	• All analyses (disease free survival and overall survival) show a consistent patient benefit across 2003, 2006, and 2007 INT-0133 datasets for the addition of mifamurtide to standard chemotherapy. • Trend direction and magnitude are consistent across all end points with statistical analysis (identical statistical methodology) on datasets at three specified time intervals. **Section 2: Summary of statistical plan and robustness of trial methodology.** Paragraph 4.6 of the NICE ACD states: *"The Committee noted that the manufacturer had presented a pooled analysis of the two mifamurtide-containing regimens (comparing chemotherapy plus mifamurtide [regimen A+ or B+] versus chemotherapy without mifamurtide [regimen A or B]) for overall survival and a number of post hoc efficacy analyses. The Committee discussed whether it was reasonable for the manufacturer to have pooled the data from the three- and four -agent chemotherapy arms (regimens A and B, and regimens A+ and B+). The Committee considered that the analysis had methodological flaws and the data should have been analysed as four separate and independent treatment regimens."* *"The Committee discussed the uncertainty around the pooled analysis and noted the ERG's concerns that although the addition of mifamurtide to multi-agent chemotherapy (regimens A+ and B+ combined) increased overall survival compared with multi-agent chemotherapy alone (regimens A and B combined), the size of the treatment effect of mifamurtide was uncertain, partly related to the disparity of survival events in the subset of patients who did not enter the maintenance phase. The Committee noted that a greater proportion of patients assigned to regimen A+ had tumours showing a poor (greater than 5% remaining viable tumour) histological response to neoadjuvant pre-operative therapy. It accepted the view of the clinical specialists that there was evidence of a link between poor histological response to neoadjuvant therapy and prognosis, but concluded that it was not possible to establish whether, or to what extent, this variation in histological response before adjuvant therapy in the different treatment groups might have affected the results".* *"The Committee also noted the ERG's concerns that there may have been interaction between treatments (that is, ifosfamide may be required to ensure activity of mifamurtide). However the Committee accepted that based on the 95% confidence intervals observed there was no strong*	Comment noted.

	evidence to suggest that there was interaction, and it accepted the clinical specialists' views that there was no biologically plausible reason for such an effect." 2.1 *"The Committee considered that the analysis had methodological flaws and the data should have been analysed as four separate and independent treatment regimens."* Takeda UK confirm that the pre-specified and documented clinical and statistical analysis of INT-0133 was to compare overall survival (OS) and disease free survival (DFS) in a 2 x 2 factorial analysis of A/B v A+/B+ (and A/A+ v B/B+). This was done to answer two separate clinical questions using the same limited data set, a particularly appropriate method given the ultra-orphan and serious nature of this disease. This is unquestionably a more statistically robust analysis than splitting the trial post-hoc to perform separate sub-group analyses for comparisons which it was not powered for. To try and argue otherwise is both statistically inaccurate & manifestly perverse. *(The 1992 original protocol document for INT-0133 was provided by Takeda but is not reproduced here)*: Statistical analysis was pre-specified in the INT-0133 trial protocol and performed as planned to ensure credibility in line with good clinical trial practice. Hence, the approach to analyse the INT-0133 trial as planned is in line with good clinical trial practice and statistical methodology from the ICH-GCP, the Declaration of Helsinki, the EU Clinical Trials Directive (EUCTD) and the FDA Regulations Relating to Good Clinical Practice and Clinical Trials; it is inappropriate to carry out sub group analysis if not pre-specified in the statistical protocol. Moreover, sub group or secondary outcome analysis is only considered valid for hypothesis generation if the primary outcome measure meets significance and the original hypothesis proven and accepted. NICE have analysed the trial's 2 x 2 factorial design as four separate arms. However, the trial was not designed nor statistically powered to be analysed in this way. The post-hoc analysis under-taken by NICE was not statistically significant in any of the arms – this is not surprising as the trial was not designed nor powered to be analysed in this way. It took 14 years to recruit sufficient patients into the INT-0133 trial to enable a valid statistical analysis of the primary end point - it would take decades to statistically power the secondary analysis of the 4 individual arms. Hence, sub group analysis as suggested by the NICE ERG and Appraisal Committee (paragraph 4.6) has to be recognised as a post-hoc analysis that was not pre-specified and therefore is of minimal relevance when trying to determine efficacy.	The Committee considered the most appropriate comparison and the most appropriate analysis of mifamurtide from INT-0133. The Committee concluded that the comparison that best reflected current UK clinical practice was the individual mifamurtide containing regimen (A+) compared with a regimen reflecting UK clinical practice (A). However, for the reasons given in section 4.6 of the FAD, the Committee accepted that the combined analysis of all the INT-0133 data may be more appropriate in determining the effect of adding mifamurtide to the standard UK regimen than the post hoc analysis directly comparing regimen A+ with regimen A. Please see FAD sections 4.7 and 4.8.

	NICE Appraisal Committees in the past have sited statistical analysis issues with primary and sub group analysis and suggested it as poor clinical trial practice, refuting to accept the clinical case on this basis. Recent examples include NICE technology appraisal guidance 160 and 161 assessing technologies in the treatment of primary and secondary prevention of osteoporotic fragility fractures in postmenopausal women. In both of these cases NICE criticised the manufacturer for reliance on post-hoc subgroup analyses. In particular NICE state in TA 161: • *"The Committee noted that strontium ranelate was effective in preventing vertebral and non-vertebral fractures, and the drug resulted in a non-significant 15% reduction in hip-fracture risk. The Committee was also aware of the result of a post-hoc subgroup analysis showing a statistically significant reduction in the incidence of hip fractures in women over the age of 74 years who had a T-score of –2.4 SD or below".* • *"The Committee did not accept the estimate of efficacy for strontium ranelate in preventing hip fracture from the post-hoc subgroup analysis, but it accepted the statistically non-significant RR of 0.85 for hip fracture to acknowledge an effect on this important type of fracture".* Consequently, the most robust evidence base for assessment of the disease free survival and overall survival benefit associated with mifamurtide is to use the whole patient population in INT-0133 where A+/B+ is compared to an A/B regimen. 2.2 *"the size of the treatment effect of mifamurtide was uncertain, partly related to the disparity of survival events in the subset of patients who did not enter the maintenance phase".* Takeda UK refer to the response previously provided in section 1.14 of this document. Takeda UK confirm that this data is included in the intention to treat analysis as previously submitted and there is no disparity of survival events as suggested. Takeda UK confirm that this data is included in the intention to treat analysis as previously submitted and there is no disparity of survival events as suggested. There are also no significant differences in the percentage of patients in each group who progressed to the maintenance phase. Reasons for patients not progressing onto the maintenance phase included disease progression or protocol violation. The majority of documented protocol breaks were due to voluntary withdrawal either by the patient/parent or by the physician. Given the small numbers of patients involved in each sample and the randomised nature of the study, any disparities are likely the	Comment noted. This has not been included in the FAD.

	result of chance. 2.3 *"It (the appraisal committee) accepted the view of the clinical specialists that there was evidence of a link between poor histological response to neo-adjuvant therapy and prognosis, but concluded that it was not possible to establish whether, or to what extent, this variation in histological response before adjuvant therapy in the different treatment groups might have affected the results".* Takeda UK agree with the appraisal committee that there is evidence of a link between poor histological response and prognosis and it is not clear the impact that this makes upon the A/A+ arms. Indeed information presented at the request of the EMA clearly show the imbalance of patients with tumours grades I/II (unfavourable) and grades III/IV (favourable) between the A and A+ arms *(Table 2.2.1 and Table 2.2.2 were provided by Takeda but not reproduced here*). There was no imbalance present in the B/B+ arms of the study or in those patients less than 16 years old; these may be more accurate reflection of mifamurtide efficacy. Given it is not clear the quantitative impact of poor histological response and prognosis upon the A/A+ arms then it would seem most appropriate to either assume efficacy as reported in the B/B+ arms (where there was no imbalance in histological response) or as Takeda UK suggest, to use the overall A/B vs. A+/ B+ analysis to assume efficacy data of which the INT-0133 trial was statistically powered. 2.4 *"The Committee also noted the ERG's concerns that there may have been interaction between treatments (that is, ifosfamide may be required to ensure activity of mifamurtide). However the Committee accepted that based on the 95% confidence intervals observed there was no strong evidence to suggest that there was interaction, and it accepted the clinical specialists' views that there was no biologically plausible reason for such an effect".* Takeda UK agree with the appraisal committee that there is no strong evidence to suggest there was interaction, and that there was no biological plausible reason for such an effect. To analyze the study in accordance with the initial factorial design, there had to be no interaction between the two study questions. For event free survival the proportional hazards regression analysis P value associated with the test of the hypothesis of no interaction between the chemotherapy intervention and the MTP intervention was 0.102, which does not meet the conventional level of significance of less than 0.1 (Table 2.4.1).	The Committee considered the most appropriate comparison and the most appropriate analysis of mifamurtide from INT-0133. The Committee concluded that the comparison that best reflected current UK clinical practice was the individual mifamurtide containing regimen (A+) compared with a regimen reflecting UK clinical practice (A). However, for the reasons given in section 4.6 of the FAD, the Committee accepted that the combined analysis of all the INT-0133 data may be more appropriate in determining the effect of adding mifamurtide to the standard UK regimen than the post hoc analysis directly comparing regimen A+ with regimen A. Please see FAD sections 4.7 and 4.8. Comment noted. See detailed response above and FAD section 4.7.

	For overall survival, the proportional hazards regression analysis P value associated with the test of the hypothesis of no interaction between the chemotherapy intervention and the MTP intervention was .60, which definitely does not meet a conventional level of significance *(Table 2.4.1 was provided by Takeda but not reproduced here).* The stratified analysis was performed as prospectively defined. There is no evidence of an interaction. Given the committee's conclusion, it is only appropriate to then interpret the results of INT-0133 using the pre-specified factorial analyses of A/B vs. A+/B+ rather than doing a post-hoc subset analysis of the 4 separate arms. **Section 3: Confirmation of appropriate comparison relevant for UK practice for assessing clinical effectiveness from the INT-0133 trial.** Paragraph 4.7 of the NICE ACD states: *"The NICE Committee concluded that the most appropriate analysis compared the individual mifamurtide-containing regimen (A+) with a regimen reflecting UK clinical practice (regimen A). The Committee also concluded that given that ifosfamide is only administered in a clinical trial setting in the UK, the analysis of B+ versus B and the pooled analysis including A+ and B+ combined versus A and B combined were not considered to represent UK clinical practice."* In Section 2 we have confirmed that the most appropriate comparison for adjuvant mifamurtide is versus regimen A/B on the basis of the pre-specified statistical plan and the original trial design. It is also the opinion of Takeda UK that the appraisal committee should consider both 3 agent and 4 agent combination chemotherapy treatment as the standard of care in England and Wales which reflects the trial design of INT-0133. The clinical standard of care for osteosarcoma patients within the UK is in line with national and international recommendations. The European Society for Medical Oncology (ESMO) Osteosarcoma Guidelines: ESMO Clinical Recommendations for diagnosis, treatment and follow-up[10] state: *"Patients with osteosarcoma should be treated in reference centres able to provide access to the full spectrum of care or shared with such centres within reference networks. There, therapy is usually given within the framework of prospective, often collaborative, clinical studies, or established treatment protocols."* British Sarcoma Group Guidelines on the treatment of osteosarcoma[11] state:	Comment noted. The Committee heard from clinical specialists that only patients with tumours showing a poor histological response to pre-operative chemotherapy may receive ifosfamide within the EURAMOS 1 study. It noted that patients in the EURAMOS study would not be eligible for mifamurtide while receiving study drug regimens. The Committee concluded that the current standard chemotherapy regimen in England and Wales is doxorubicin, methotrexate and cisplatin, and that ifosfamide is not routinely used in UK clinical practice outside the EURAMOS 1 study. Please see FAD sections 4.3 and 4.4.

	"Curative treatment for high-grade osteosarcoma consists of surgery and chemotherapy. All patients should be considered for inclusion into National or International clinical trials." Takeda UK confirms that the clinical standard of care for osteosarcoma patients within the UK is entry into a randomised multicenter intergroup clinical trial (such as EURAMOS I) and this is suggested by NICE within the ACD. Currently it is estimated that 80-90% of patients diagnosed with osteosarcoma in the UK are entered into the European and US osteosarcoma trial EURAMOS I trial as part of an adjuvant regimen (with ifosfamide, etoposide, cisplatin, doxorubicin and methotrexate) for patients with tumours showing a poor histological response to pre-operative chemotherapy. Therefore, key points to note of relevance for the comparisons as discussed in the ACD are as follows: • Regimens with and without ifosfamide represent the current and future standard of care for the treatment of osteosarcoma in England and Wales. Even though many patients are currently treated within the context of a clinical trial, given the rarity of the condition the treatment provided within clinical trials (i.e. the EURAMOS I trial) represents the standard of care across treatment centres in the UK. • The most robust evidence base for assessment of the disease free survival and overall survival benefit associated with mifamurtide is that using the whole patient population in INT-0133 where A+/B+ is compared to an A/B regimen. • The survival benefit associated with A/B v A+/B+ provides a more realistic proxy for the clinical benefits associated with A+ v A, and B+ v B than splitting the trial to perform separate sub-group analyses for these comparisons. For reasons explained above (Sections 2), we do not feel a reliable assessment of cost-effectiveness can be performed for A+ vs. A, or B+ vs. B. Hence it is important to differentiate from what is perceived to be routinely used, and what is actually used in the NHS. It is incorrect to assume that 3-agent chemotherapy is the current standard of care when only a minority of patients receive non protocol, non RCT (EURAMOS I) care. The majority of patients receive care through an RCT and this treatment includes ifosfamide and is more akin to treatment arms B/B+ in the INT-0133 trial. Hence, it is the opinion of Takeda UK that the appraisal committee should consider both 3-agent and 4-agent combination chemotherapy treatment as the standard of care in England and Wales.	The Committee considered the most appropriate comparison and the most appropriate analysis of mifamurtide from INT-0133. The Committee concluded that the comparison that best reflected current UK clinical practice was the individual mifamurtide containing regimen (A+) compared with a regimen reflecting UK clinical practice (A). However, for the reasons given in section 4.6 of the FAD, the Committee accepted that the combined analysis of all the INT-0133 data may be more appropriate in determining the effect of adding mifamurtide to the standard UK regimen than the post hoc analysis directly comparing regimen A+ with regimen A. Please see FAD sections 4.7 and 4.8. The Committee heard from the clinical specialists that the standard adjuvant multi-agent chemotherapy regimen in the UK is doxorubicin, methotrexate and cisplatin, and that ifosfamide is not routinely used in UK clinical practice outside the EURAMOS 1 study. The 'Guide to the methods of health technology appraisal' states that relevant comparator treatments are those routinely used in

	Section 4: Summary of comparative health economic evidence. Information provided in sections 1-3 of this response document have reiterated the rigour of the INT-0133 trial, and the relevant comparisons appropriate for analysis. It is important to bring these factors to account for health economic modelling and determining a reliable base case cost effectiveness relevant for publication in future NICE documentation (FAD and guidance documents). In consideration of the evidence on cost-effectiveness for this comparison the Appraisal Committee considered that it was appropriate to include the following parameters in the cost-effectiveness analysis: age dependent utility values, post recurrence mortality rates set to those of the age-matched population if patients were disease free for 5 years, and amputation and limb salvage costs (section 4.16 of the ACD). It was stated that this increased the ICER from £56,700 to £91,400 (with PAS), although this also included the cost of treating hearing loss adverse events. The committee did not consider it was necessary to include hearing loss attributed to mifamurtide but an ICER without hearing loss in the revised base case was not available or presented in the ACD. Takeda UK have re-run the model based on the following assumptions: • *Clinical data as per the pooled datasets of A/B versus A+/B+* • *Comparator in the UK is 3 agent and 4 agent chemotherapy.* • *60 year time horizon.* • *100% of the population starting in the Disease-free health state.* • *Amputation and limb salvage costs included (changed as per ACD).* • *Hearing loss adverse event not included (not changed as per ACD);* • *Mortality risk reverting to general population after a given time period included (changed as per ACD);* • *Age related utility weights included (as per ACD);* • *Discounting rates of 3.5% for both costs and outcomes applied;* • *PASLU approved PAS.* When we re-run the model with the revised base case but without the hearing loss	the NHS and that evidence from expert statements may also help to outline the treatments that are currently used in routine NHS practice and whether these are different from what is considered to be best practice, particularly when published trials are not recent or do not closely follow UK practice. Comment noted Comment noted. Section 4.16 of the FAD states

	AE, this produces an ICER of £70,062 (deterministic analysis) or £66,982 (probabilistic analysis) *(Table 4.1 was provided by Takeda but is not reproduced here*), with a 54% probability of cost-effectiveness at a willingness to pay threshold of £70K (or 25% at £50K). We believe it is appropriate that this figure is cited in the ACD rather than the current statement that the "most plausible ICER would be less than £91,400" (section 4.16) which is somewhat vague and misrepresentative. As the committee is concerned over the uncertainty associated with the survival benefit it is also appropriate to consider the sensitivity of the ICER to more pessimistic survival outcomes. One way this can be handled simply in the economic model is to adjust the time horizon. The base case time horizon is 60 years, which has been considered appropriate by the ERG. However, applying a shorter time horizon reduces the mean survival benefit estimated by the model. Hence, using our original base case the survival estimate with a 60 year time horizon is a mean of 4.02 life year (undiscounted) or 1.57 discounted, whereas with a 50 year time horizon the estimated undiscounted survival benefit is a mean of 3.39 life years (a 16% LYG reduction from the base case), the 40 year time horizon the estimated survival benefit from the model is 2.68 years on average (a 33% reduction in survival benefit from the base case). The mean life years gained are slightly lower in the NICE appraisal committee base case. The impact these sizeable hypothetical reductions in survival benefit have is to increase the deterministic ICER to up to £67,000 per QALY gained using our original base case or £80,000 using the appraisal committee preferred base case *(Table 4.2 was provided by Takeda but is not reproduced here*) and a 40 year time horizon. As the 60 year time horizon has been accepted as an appropriate base case the calculations in Table 4.2 are hypothetical illustrations to show the relatively limited sensitivity of survival benefit on the ICER. The cost-effectiveness results are particularly sensitive to the choice of discount rate for benefits (QALYs). Applying a 1.5% discount rate to future QALYs the ICER based on the NICE preferred base case decreases from £70,062 to £44,222 (and from £67,982 to £42,599 in probabilistic analysis) whilst 0% discounting of QALYs and costs produces an ICER of £31,043 per QALY gained (£27,823 in probabilistic analysis). In section 4.15 of the ACD it is stated that for consistency across all technology appraisals a 3.5% discount rate should be applied. It is, however, legitimate to vary the discount rate in sensitivity analysis. Despite the sensitivity of the ICER for mifamurtide to the discount rates selected for QALYs (more so than survival), there is no mention in the ACD of the actual impact varying the discount rate has on the ICER (only brief mentions in section 3.16 and 4.15). Therefore, we strongly feel	that the Committee considered the additional analyses carried out by the manufacturer. It concluded that the manufacturer's best-case ICERs of £70,100 per QALY gained (deterministic analysis) and £67,000 per QALY gained (probabilistic analysis), both including the PAS, were substantially higher than those normally considered to be an acceptable use of NHS resources. Comment noted. The Committee discussed the sensitivity of the manufacturer's original base-case ICER to the discount rate applied to outcomes, and how this would affect the ICERs estimated in the manufacturer's additional analyses. The Committee noted that no formal case had been made for varying the discount rate. The Committee was aware of the policy relating to the NICE reference case and section 5.6.2 of the 'Guide to the methods of technology appraisal', which specifies that a discount rate of 3.5% should be used for both costs and outcomes. The Committee was aware that it also states that consideration should be given to sensitivity analyses that use different rates for costs

	more attention should be given in the ACD to the impact varying the QALY discount rate has on the ICER. In conclusion, whilst the base case ICER is above £30,000/QALY and we agree with the appraisal committee that it is also likely to be at least £50,000/QALY assuming a base case discount rate of 3.5%. We have provided an estimate of £70,000 per QALY (£66,982 probabilistic analysis) gained using the parameters in the NICE appraisal committee base case. Certainly, we feel that the ICER is not likely to exceed £100,000 per QALY gained (section 4.19 of the ACD). This is based on a comparison with regimen A/B which we have argued is the most appropriate comparison consistent with actual best clinical practice for the treatment of osteosarcoma in the UK.	and outcomes and/or that vary the rate between 0% and 6%. The Committee considered that in some situations discounting may have a large effect on ICERs, but it concluded that the discount rate recommended for the reference case were the most appropriate to use in this appraisal. See FAD section 4.19.
	Section 5: Orphan drug environment in the UK and identifying a reasonable cost effectiveness threshold.	
	Takeda UK do not consider the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for guidance to the NHS. In particular it is not clear from the ACD how the rarity of osteosarcoma has been considered in this appraisal. Takeda UK believe it is important for NICE to be transparent in any future documentation recommending the use of mifamurtide (FAD and guidance documents) as to NICE's policy for assessing rarity and ultra orphans indications and how in this case the social value judgements have been employed for consideration in this appraisal.	Comment noted. The Committee considers that treatment for rare conditions should be appraised in the same way as any other treatments. NICE appraises topics that are formally referred by the Department of Health.
	In particular, Takeda UK are concerned regarding the appraisal committees preference to consider post hoc sub group analyses to inform decision making for treatments of rare diseases. Given the substantial time commitments in researching rare diseases and the limited sample size's produced, it seems philosophically wrong to sub divide the data of a rare disease to the point where results cannot be significant and favourable decision making is impossible. There is already relative uncertainty related to the clinical trial results of a rare disease without further subdividing the available information. It is the opinion of Takeda UK that the INT-0133 trial should be analysed as it was statistically planned to do so.	The Committee considered the most appropriate comparison and the most appropriate analysis of mifamurtide from INT-0133. The Committee concluded that the comparison that best reflected current UK clinical practice was the individual mifamurtide containing regimen (A+) compared with a regimen reflecting UK clinical practice (A). However, for the reasons given in section 4.6 of the FAD, the Committee accepted that the combined analysis of all the INT-0133 data may be more appropriate in determining the effect of adding mifamurtide to the standard UK regimen than the post hoc analysis directly comparing regimen A+ with regimen A. Please see FAD sections 4.7 and 4.8.

	It has been recognised for many years that, because of the costs associated with development, special incentives are required if pharmaceutical manufacturers are to be encouraged to develop and market treatments for rare diseases (orphan indications). In both the US, and the EU, legislation has been put in place to promote the development of treatments for rare diseases such as osteosarcoma.	The Committee discussed the innovative nature of the technology. Please see FAD section 4.20.
	In the UK there have been initiatives without tangible development as to how orphan drugs may be assessed. Nonetheless NICE, despite stating clearly in section 4.4 (page 20) of their, "Social Value Judgements Principles for the development of NICE guidance" [2], under rare conditions: *"NICE considers that it should evaluate drugs to treat rare conditions, known as 'orphan drugs', in the same way as any other treatment (see Glossary).* *NICE does not expect to receive referrals from the Secretary of State for Health to evaluate 'ultra-orphan drugs' (drugs used to treat very rare diseases or conditions). This is because the Department of Health currently has other mechanisms to assess the availability of ultra-orphan drugs in the NHS".*	The Committee considers that treatment for rare conditions should be appraised in the same way as any other treatments. NICE appraises topics that are formally referred by the Department of Health.
	On this premise Takeda UK would question why NICE are assessing mifamurtide.	
	In addition, NICE have developed two key initiatives in how orphan drugs may be assessed. – NICE Recommendations for Appraisal of Orphan Products to the Department of Health, 2006. "Appraising Orphan Drugs" [12] – NICE Citizens Council report on departing from the threshold November 2008 "Departing from the threshold." [13]	
	In the 2006 report on NICE Recommendations for Appraisal of Orphan Products to the Department of Health[12], NICE submitted a proposal for appraising orphan and ultra-orphan drugs. Whilst the proposals in this report were not implemented, NICE's conclusions and recommendations in the proposal are of interest for this appraisal: • *"A number of drugs which can be categorised as "orphan drugs" have been referred to NICE and appraised successfully suggesting that for these drugs it was possible to apply NICE methodology [section 4.1.1 of the NICE report]. Therefore no changes to its processes are needed for the appraisal of conventional orphan drugs [4.1.3]. <u>However, NICE considers that there would be problems in the appraisal of "ultra-orphan drugs" largely because of their high acquisition costs [4.2]".</u>*	The Committee considered that mifamurtide is indicated for a small patient population with a rare disease, and noted that NICE had not received direction from the Department of Health that treatments for rare conditions ('orphan' or 'ultra-orphan') should be appraised differently from any other treatments (see FAD section 4.20).

	• *"Separate decision rules (i.e. the range of ICERs considered "cost effective") will need to be developed and adopted for ultra-orphan drugs if the Institute is prepared to accept substantially higher ICERs than those currently considered to be cost effective [4.9]".* • *"The Institute proposes that these ultra-orphan drug decision rules are based on the ICERs of those ultra-orphan drugs currently on the UK market. NICE states that this will provide an implicit benchmark against which new ultra-orphan products can be evaluated. NICE emphasises that a final position on cost effective ICERs will need to be confirmed through wider consultation. At current prices [2005 in the report] indicative ICERs for ultra-orphan products are in the range of £200,000 to £300,000 per QALY (i.e. a ten-fold increase on the decision rules currently applied in conventional appraisals) [4.9]".* NICE has also consulted, in November 2008, the Citizens Council on the question, "In what circumstances should NICE recommend interventions where the cost per QALY is above the threshold range of £20-30,000?" [13] Two of the 29 Council members attending the meeting took the view that there were no circumstances in which NICE appraisal committees should depart from the established threshold. Of the remaining 27 Council members, the numbers who favoured taking account of each of a list of various possible circumstances were - in order of support - as follows: *1 the treatment in question is life-saving (n=24)* *2 the illness is a result of NHS negligence (23)* *3 the intervention would prevent more harm in the future (23)* *4 the patients are children (22)* *5 the intervention will have a major impact on the patient's family (22)* *6 the illness under consideration is extremely severe (21)* *7 the intervention will encourage more scientific and technical innovation (21)* *8 the illness is rare (20)* *9 there are no alternative therapies available (19)* *10 the intervention will have a major impact on society at large (16)* *11 the patients concerned are socially disadvantaged (13)* *12 the treatment is life extending (10)*	Comment noted. Please see detailed response above.

	13 the condition being tackled is time-limited (9) *14 the illness is a result of corporate negligence (2)* Of these criterion, mifamurtide would qualify for 8/14 of these criteria (numbers 1,3,4,5,6,8,9,12) which if implemented may suggest an alternative approach to this appraisal. Takeda UK are committed to making mifamurtide available to patients in England and Wales; however at this stage it is not clear what is required to accomplish NICE approval for an ultra orphan medication. Indeed, using the standard appraisal committee cost per QALY threshold for acceptance of under £30,000 would suggest that patients with osteosarcoma and other rare illnesses will be underserved until NICE have a transparent policy for assessment of rare illnesses to which manufacturers can work towards. If NICE had adopted criteria as per the aforementioned 2006 report, then mifamurtide would easily prove a cost effective treatment. Likewise if NICE had adopted modification criteria as proposed by the citizen's council report then undoubtedly mifamurtide would have proven cost effective. Takeda UK would encourage NICE to consider some of the previous thinking regarding the appraisal of ultra orphan medications for this appraisal, or alternatively, and as per stated in the Social value Judgements, allow the other mechanisms in the NHS to assess the availability of ultra-orphan drugs, and to terminate this NICE appraisal. **<u>Summary</u>** In summary, Takeda UK Ltd believe that the NICE Appraisal Consultation Document should change to recognise the points in this response and support the use of mifamurtide in the care of appropriate patients with osteosarcoma in NHS England and Wales. In particular, it is important to recognise: – The robustness of the data which has been scrutinised in detail by the CHMP, – The lack of progress and unmet need of young patients with osteosarcoma, – Potential lifetime survival benefit for the additional responders to mifamurtide. The overall conclusion of the EMA in respect of the clinical efficacy of mifamurtide	Comment noted. Please see detailed responses above. Comment noted. Please see detailed responses above.

	was very clear and this is reflected in the EPAR where it states that "Mepact significantly increased the overall survival of patients with newly-diagnosed resectable high-grade osteosarcoma when used in conjunction with combination chemotherapy when compared to chemotherapy alone". Takeda UK Ltd believes it is totally unacceptable to use post-hoc sub-analyses to question the clinical effectiveness of mifamurtide in relation to the data scrutinised by the Regulatory Authority the EMA resulting in our product licence. Whilst the base case ICER is above £30,000/QALY, we agree with the Appraisal Committee that it is also likely to be at least £50,000/QALY assuming a base case discount rate of 3.5%. We have provided an estimate of £70,000 per QALY gained using the parameters in the NICE appraisal committee base case. Certainly, we feel that the ICER is not likely to exceed £100,000 per QALY gained (section 4.19 of the ACD). This is based on a comparison with A/B which we maintain is the only appropriate comparison consistent with actual best clinical practice for the treatment of osteosarcoma in the UK. We believe the economic case represented in the submission and the updates in the model have enabled us to increase our confidence in the boundary of the plausible impact of uncertainty in key variables on the mifamurtide cost-effectiveness ratios. If NICE had adopted criteria as per the aforementioned 2006 report, then mifamurtide would easily prove a cost effective treatment. Likewise if NICE had adopted modification criteria as proposed by the citizen's council report then undoubtedly mifamurtide would have proven cost effective. Takeda UK would encourage NICE to consider some of the previous thinking regarding the appraisal of ultra orphan medications for this appraisal, or alternatively, and as per stated in the Social Value Judgements, allow the other mechanisms in the NHS to assess the availability of ultra-orphan drugs, and to terminate this NICE appraisal.	
Sarcoma UK	**Has all of the relevant evidence been taken into account?** The evidence is limited to one clinical study which took place over 14 years. It accrued patients in one of the rarest cancers, including teenagers – a notoriously difficult group to convince about entering clinical trials. The study produced one over-riding conclusion – that mifamurtide resulted in long-term survival for an additional 7-8% of the patient group, reducing the number at risk of dying by about one-third. This was the study's primary endpoint and its statistical design was intended to arrive at a conclusion of this nature. It is worth recalling the opinion of EMA when granting marketing approval "Mepact significantly increased the overall survival of patients…"	Comment noted. The primary endpoint of the INT-0133 was overall survival. However the study was powered for the first planned analysis of the intermediate endpoint, which was disease-free survival (that is, time to progression or death). See FAD section 3.2. The Committee was aware that the combined analysis suggested a statistically significant improvement in overall survival from 71% in the

	It is worth noting that average survival in the UK is lower than in the study group comparison arms (which were largely recruited in the USA) although there is no evidence to suggest that the treatment effect in the UK might be higher as a result. Whatever else is taken into account this result is fact, it is inarguable, and is a significant statistical outcome. **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** It is acknowledged that the single study has weaknesses and that there are many valid questions which remain unanswered. The study was powered to produce an overall survival result, which it did successfully. It was not powered for sub-group analyses yet the Evidence Review for this appraisal entered into extended analysis and discussion about sub-groups. Such analysis was gratuitous. It could never deliver significance because the original study design was not powered to deliver it, and attempting to power the study to do so would have extended the duration of the trial into decades. It is notable that in other technology appraisals NICE has avoided similar sub-group analyses BECAUSE there was no statistical power. Why is NICE inconsistent on this issue ? The main difference between sub-groups is one agent in the adjuvant chemotherapy (ifosfamide) and patients in these arms (b and B+) attained a better response with mifamurtide, although this was non-significant. This additional chemotherapy is currently only available in the UK to patients entered in the EURAMOS1 clinical trial. The Committee accepted the assurance of the clinical experts that there was no biological reason for assuming that ifosfamide had a significant effect on the efficacy	control arm to 78% in the mifamurtide arm over a median follow-up period of 7.9 years. Although the study was powered for the intermediate endpoint of disease-free survival, it failed to show that regimens of chemotherapy plus mifamurtide (regimens A+ and B+ combined) significantly increased disease-free survival compared with chemotherapy alone (regimens A and B combined) (hazard ratio 0.78, 95% CI 0.61 to 1.01). See FAD section 4.7. The Committee concluded that mifamurtide plus postoperative multi-agent chemotherapy may be more clinically effective than postoperative multi-agent chemotherapy alone. However, there was substantial uncertainty around the size of this effect, particularly in the context of the standard treatment regimen used in the NHS. See FAD section 4.10. Please see above. The Committee considered the most appropriate comparison and the most appropriate analysis of mifamurtide from INT-0133. The Committee concluded that the comparison that best reflected current UK clinical practice was the individual mifamurtide containing regimen (A+) compared with a regimen reflecting UK clinical practice (A). However, for the reasons given in section 4.6 of the FAD, the Committee accepted that the combined analysis of all the INT-0133 data may be more appropriate in determining the effect of adding mifamurtide to the standard UK regimen than the post hoc analysis directly comparing regimen A+ with regimen A. Please see FAD sections 4.7 and 4.8.

	of mifamurtide. Given this acceptance there is no rational reason for the emphasis given to the sub-group analyses by the Appraisal, especially when the overall result is so clear. This is the kind of inconsistent statistical jiggery-pokery of which NICE is more usually able to accuse pharmaceutical companies. That NICE should do it in an apparent attempt to create a fog of added uncertainty around a simple and clear overarching fact is at best contrived, at worst devious. **Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** This treatment is high-cost. Given the very small patient group to which it is applicable (estimated at a maximum of 60-70 a year in England and Wales) the costs of the drug are inevitably high. We welcome the willingness of the manufacturer to agree a patient access scheme with the Department of Health and express some surprise that such an agreement carries no weight with NICE, especially as there is no secret that NICE staff are closely involved with negotiating these schemes. This approach has a two-faced quality to it – it also looks devious and dishonest. Without the support of such a scheme there was never much likelihood of an ICER for mifamurtide coming within the range that NICE usually accepts for approval. Requiring NICE to undertake a study of this kind was a mistake. NICE processes are inarguably biased against rare diseases and this is an ultra-orphan condition; NICE has never appraised a children's cancer drug before and does not have the contextual experience to do so; nor does NICE have the moral, clinical or scientific authority to pick apart the trial data in the way it has with this review. NICE has moved into an area for which its appraisal processes are unsuited and has once again demonstrated that it is incapable of operating appropriate flexibility with a rarer cancer. Given the age range of the patient group and the fact that primary treatment for osteosarcoma is nationally commissioned, there is a huge question about the sense of NICE appraising this treatment in the first place. It clearly lies within the scope of national specialist commissioning. In addition we would draw attention to the NICE Citizen's Council meeting of	Comment noted. The Committee considered the additional analyses carried out by the manufacturer. It concluded that the manufacturer's best-case ICERs of £70,100 per QALY gained (deterministic analysis) and £67,000 per QALY gained (probabilistic analysis), both including the PAS, were substantially higher than those normally considered to be an acceptable use of NHS resources. See FAD section 4.16. The Committee considers that treatment for rare conditions should be appraised in the same way as any other treatments. NICE appraises topics that are formally referred by the Department of Health. Although the Committee accepted that there may be a case for accepting a higher ICER for children, adolescents and young people, this ICER was too high to allow the Committee to recommend mifamurtide, even when taking into account a number of other considerations such as other aspects of health-related quality of life not adequately captured in the QALY, the innovative nature of the drug, the rarity of the condition, and possible discount rates. See FAD section 4.22. The Committee considers that treatment for rare

	November 2008 which considered where exceptionality to usual cost-per-QALY rules should apply. More than two-thirds of the members considered exceptional circumstances apply where: • the patients are children • the intervention will have a major impact on the patient's family • the illness under consideration is extremely severe • the intervention will encourage more scientific and technical innovation • the illness is rare 20 • there are no alternative therapies available On this basis we believe that the Department of Health should accept that the Appraisal is not sound, nor is it a suitable basis for guidance to the NHS because it conflicts which society's expectations, as independently expressed through NICE's own consultation methods. NICE must recommend that the Department should use alternative routes which recognise the clinical efficacy of the treatment and are appropriately empowered to approve it for use. **Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief?** The Appraisal Committee's discussion of this issue makes interesting reading. Whether the law on discrimination when drafted, was intended to cover the denial of effective healthcare to children threatened by a potentially fatal disease, is a pertinent question. We might expect the NHS as a whole to reflect the moral and ethical standards of society with regard to children, and we can retain the hope that it will do so. It is, however, a sad day when NICE demonstrates that it has no duty to reflect society's expectations and is prepared to sacrifice children on its self-justified altar of cost-effectiveness.	conditions should be appraised in the same way as any other treatments. NICE appraises topics that are formally referred by the Department of Health. The Committee considered that osteosarcoma predominantly affects children, teenagers and young adults, and that osteosarcoma is a rare disease. The Committee further noted that when an appraisal affects a particular age group it does not mean that a negative recommendation in that appraisal constitutes discrimination on the grounds of age. The Committee noted that no different recommendations were made for the patient population for which mifamurtide is licensed, that is, the recommendations not based on and does not vary according to the age of the patient. There was no evidence heard or submitted to suggest that different recommendations on the basis of age would be necessary to meet patient need or that a different recommendation for one or more patient groups within the overall patient population would be clinically and cost effective. The Committee was

	The self-justification extends to the press release which accompanied the public announcement of the ACD. The wording of this release seems to have been designed to mislead people reading it into believing that there is an effective alternative to mifamurtide in the treatment of osteosarcoma. This is not true and NICE should state this fact unequivocally. Why should NICE seek to tell an untruth of this kind ? It is clearly intended to explicitly support its negative decision for a treatment which is clinically effective. Using an untruth as self-justification is a reprehensible turn of events and we have separately sought a full explanation. Thus, we must ask why this appraisal should have been discriminated against to receive such treatment from NICE: is the first drug to be appraised for children's cancer the first to be treated in this way?	therefore satisfied that there were no equalities issues in relation to age in this appraisal and that the recommendations were consistent with NICE's obligations under the equalities legislation and the requirement for fairness. See FAD section 4.21. The patient experts stated that there had been few developments that had improved optimal treatment of osteosarcoma over the past 20 years. The Committee noted that the clinical specialists stated that the only development in the past 10 years had been the introduction of high-dose methotrexate and better implementation of treatment regimens, which had together improved survival rates by 10–20%, bringing them in line with those in Europe and the USA. See FAD section 4.3. The Committee noted that based on the magnitude of the additional benefit and the associated uncertainty, it was not persuaded that adjuvant chemotherapy with mifamurtide significantly and substantially changes the way that the current need is met, or that it has been shown to have an appropriate level of effectiveness, given the wide confidence intervals of the hazard ratios. The Committee concluded that although mifamurtide plus multi-agent chemotherapy for the treatment of high-grade resectable non-metastatic osteosarcoma after macroscopically complete surgical resection might represent a potentially valuable new therapy, the size of the treatment effect relative to standard UK clinical practice was uncertain. See FAD sections 4.20, 4.22. NICE appraises the clinical and cost effectiveness of technologies. For both legal and bioethical reasons those undertaking technology appraisals must take account of economic considerations (Social Value Judgements – Principles for the Development of NICE Guidance; principle 5).

Bone Cancer Research Trust	*Has all the relevant evidence been taken into account?* The Appraisal Committee has considered the relevant clinical trial, but it has failed to take account of important information in that trial. The trial demonstrated a reduction in mortality of 30% which, given that the current UK survival rate is about 60%, means that around 10 young people would benefit from the treatment and live a more or less normal lifespan.	Comment noted. The primary endpoint of the INT-0133 was overall survival. However the study was powered for the first planned analysis of the intermediate endpoint, which was disease-free survival (that is, time to progression or death). See FAD section 3.2. The Committee was aware that the combined analysis suggested a statistically significant improvement in overall survival from 71% in the control arm to 78% in the mifamurtide arm over a median follow-up period of 7.9 years. Although the study was powered for the intermediate endpoint of disease-free survival, it failed to show that regimens of chemotherapy plus mifamurtide (regimens A+ and B+ combined) significantly increased disease-free survival compared with chemotherapy alone (regimens A and B combined) (hazard ratio 0.78, 95% CI 0.61 to 1.01). See FAD section 4.7. The Committee concluded that mifamurtide plus postoperative multi-agent chemotherapy may be more clinically effective than postoperative multi-agent chemotherapy alone. However, there was substantial uncertainty around the size of this effect, particularly in the context of the standard treatment regimen used in the NHS .See FAD section 4.10..
	The emphasis that NICE places on relative effectiveness leads it to ignore the absolute benefit that 10 more young people with osteosarcoma will survive each year.	The treatment effect of a technology is the difference between the duration and state of health or HRQL (including the impact of any adverse effects of treatment) that would be experienced on average by patients receiving the technology and that experienced by the same group were they to receive alternative care. ('Guide to the methods of technology appraisal, section 3.2). The Committee noted that based on the magnitude of the additional benefit, it was not persuaded that adjuvant chemotherapy with mifamurtide significantly and substantially changes the way that the current need

		is met (see FAD section 4.3) or that it has been shown to have an appropriate level of effectiveness, given the wide confidence intervals of the hazard ratios (see FAD section 4.6).
	The other element which NICE has failed to take into account, and we accept that there is no published data on this, is the impact of the illness and premature death of a young person with osteosarcoma on other family members. We can say categorically that the impact is profound and remains for many years, seriously and adversely affecting the quality of life of family and friends. This impact will undoubtedly impact on the health of the family although this hasn't been formally assessed.	The Committee considered whether there were any health-related quality of life benefits that may not have been adequately captured in the estimated gained used in the QALY calculation. The Committee heard from the patient experts that supporting a young person with osteosarcoma has a substantial impact on the health-related quality of life of the family and friends of the person affected, particularly where treatment is not successful. For example, parents and siblings may develop mental health problems and family relationships may be strained. The Committee concluded that these are important issues affecting the health-related quality of life of those close to the person with osteosarcoma, but noted that these issues are not unique to the condition. For further details see FAD section 4.18.
	We note that the comment by Andrew Dillon about the outcome of the appraisal 'It is important to remember, though, that other, effective treatments are available in the NHS for treating this condition.' We would be very interested to learn what are these other treatments which deliver the same benefit as mifamurtide because we do not know of any. To the best of our knowledge, there is no alternative to mifamurtide.	The patient experts stated that there had been few developments that had improved optimal treatment of osteosarcoma over the past 20 years. The Committee noted that the clinical specialists stated that the only development in the past 10 years had been the introduction of high-dose methotrexate and better implementation of treatment regimens, which had together improved survival rates by 10–20%, bringing them in line with those in Europe and the USA. See FAD section 4.3.
	Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? BCRT absolutely refutes the Appraisal Committee's interpretation of the clinical effectiveness data considered. Trial INT-0133 was an investigator-led trial which NICE acknowledges was designed with the primary endpoint of overall survival but powered for disease—free survival	Comment noted. Please see above. The Committee considered the most appropriate comparison and the most appropriate analysis of mifamurtide from INT-0133. The Committee concluded that the comparison that best reflected current UK clinical

	as a two by two factorial design. That is, it was designed to be analysed as chemotherapy alone vs chemotherapy with mifamurtide. The ERG requested six post-hoc analyses which the study was not designed nor powered to answer. BCRT believes that this post-hoc, unplanned analysis is invalid and the numbers that result are too small to be of relevance, making these analyses unreliable and inappropriate. Notwithstanding the inappropriateness of the analysis, in the single arm comparison of regimen A vs A+ there is evidence, although it is not statistically significant, of benefit for mifamurtide. That it is not statistically significant is entirely explained by the fact that the trial was never powered for this analysis. The BCRT is prepared to provide a more detailed rebuttal of the ERG's conclusions about efficacy if requested.	practice was the individual mifamurtide containing regimen (A+) compared with a regimen reflecting UK clinical practice (A). However, for the reasons given in section 4.6 of the FAD, the Committee accepted that the combined analysis of all the INT-0133 data may be more appropriate in determining the effect of adding mifamurtide to the standard UK regimen than the post hoc analysis directly comparing regimen A+ with regimen A. Please see FAD sections 4.7 and 4.8.
	The utility values for the use of mifamurtide are based on EQ5D which is a measure completely inappropriate to the population being considered. The tool is too blunt to reflect the ability of young people to adapt to disability and whose life is not measured in the way that adults might measure life. EQ5D falsely reduces the quality of life of people with osteosarcoma and should not be used in this setting.	The Committee considered the utility values used in the manufacturers model. The Committee heard from the patient experts that young people with osteosarcoma are able to live full lives and they have a similar quality of life to their peers, with many adapting well to having a disability, and in some cases being empowered by their experience. The Committee noted that the age-adjusted utility values used in the manufacturer's updated analysis were appropriate and reflected the quality life of children, adolescents and young people as reported by the patient groups. See FAD section 4.15.
	Regardless of whether this is the first new treatment in 20 years for osteosarcoma, it is an effective treatment which saves lives. The ICER is a wholly inappropriate basis for a decision on whether or not mifamurtide should be made available.	NICE appraises the clinical and cost effectiveness of technologies. For both legal and bioethical reasons those undertaking technology appraisals must take account of economic considerations (Social Value Judgements – Principles for the Development of NICE Guidance; principle 5).
	Are the provisional recommendations sound and a suitable basis for guidance to the NHS? The conclusions drawn by the appraisal committee are unsound and based on a post-hoc analysis which in other settings NICE would criticise. For the reasons outlined above, the conclusion does not reflect the trial data and hence the	Please see detailed response above and FAD sections 4.7 and 4.8.

	recommendation is flawed. The NHS should not decide whether young people can be treated with mifamurtide based on a completely unreliable analysis performed by a technical group without expertise in treating osteosarcoma.	
	It is worth pointing out that other orphan drugs are not subject to a NICE appraisal and more expensive drugs are in routine use in the UK. It is unacceptable that young people with osteosarcoma are denied a potentially life-saving treatment because of the review mechanism to which it has been subject. NICE's appraisal should take account of these special circumstances and adjust its cost effectiveness threshold accordingly. One example, which demonstrates very well the different outcomes using different assessment methods, is the provision of the monoclonal antibody eculizumab for the treatment of patients with paroxysmal nocturnal haemoglobinuria. Introduced in April 2009 a new central funding stream, the PNH service, was added to the portfolio of the National Commissioning Group. The University of Birmingham undertook a rapid systematic review of the treatment published in 2008 and estimated that the ICERs range likely lies between £0.5M and £1.4M per life year gained for patients like those recruited to clinical trials and between £2.8M and £3.2M per life year gained for all diagnosed patients. The report also states that first year of treatment costs £252,000 and a subsequent year costs £245,700, compared to a total one-off treatment cost of £114,000 for mifamurtide.	The Committee considers that treatment for rare conditions should be appraised in the same way as any other treatments. NICE appraises topics that are formally referred by the Department of Health. Although the Committee accepted that there may be a case for accepting a higher ICER for children, adolescents and young people, this ICER was too high to allow the Committee to recommend mifamurtide, even when taking into account a number of other considerations such as other aspects of health-related quality of life not adequately captured in the QALY, the innovative nature of the drug, the rarity of the condition, and possible discount rates. See FAD section 4.22.
	Are there any aspects of the recommendations that need particular consideration to ensure NICE avoids unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief?	
	Since the population considered – young people with a limb amputation – is already disabled and if they survive will place further demands on the NHS because of their disabilities, the NICE approach to assessing the value of treatment discriminates against them. The young people for whom mifamurtide is effective will live a more or less normal lifespan and as such will need to use the NHS for aspects of their disability as well as illnesses experienced by the general population. While this may not be an unlawful discrimination it is certainly discrimination against the patients because of their age and the additional time they may hope to live.	The Committee considered that osteosarcoma predominantly affects children, teenagers and young adults, and that osteosarcoma is a rare disease. The Committee further noted that when an appraisal affects a particular age group it does not mean that a negative recommendation in that appraisal constitutes discrimination on the grounds of age. The Committee noted that no different recommendations were made for the patient population for which mifamurtide is licensed, that is, the recommendations not based on and does not vary according to the age of the patient. There was no evidence heard or submitted to suggest that different recommendations on the basis of age would be necessary to meet patient need or that a

		different recommendation for one or more patient groups within the overall patient population would be clinically and cost effective. The Committee was therefore satisfied that there were no equalities issues in relation to age in this appraisal and that the recommendations were consistent with NICE's obligations under the equalities legislation and the requirement for fairness. See FAD section 4.21.
RCN	*i) Has the relevant evidence has been taken into account?* We would ask that the evidence should include all relevant current evidence. ii) *Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence, and are the preliminary views on the resource impact and implications for the NHS appropriate?* The summaries of the clinical and cost effectiveness of this appraisal should be aligned to the clinical pathway followed by these patients. The preliminary views on resource impact and implications should be in line with established standard clinical practice. *iii) Are the provisional recommendations of the Appraisal Committee sound and do they constitute a suitable basis for the preparation of guidance to the NHS?* Nurses working in this area of health have reviewed the recommendations of the Appraisal Committee and do not have any further comments to make at this stage. *iv) Are there any equality related issues that need special consideration that are not covered in the ACD?* None that we are aware of at this stage. We would however, ask that any guidance issued should show that equality issues have been considered and that the guidance demonstrates an understanding of issues concerning patients' age, faith, race, gender, disability, cultural and sexuality where appropriate.	Comment noted. Comment noted. Comment noted. Comment noted. The Committee considered whether there were issues related to equality to be taken into account in its considerations in light of its current and future duties under the equalities legislation. See FAD section 4.21.
Royal College of Paediatrics and Child Health	<u>*Section 3.6:*</u> The College is concerned that the Evidence Review Group has negatively assessed efficacy on the basis of sub-group analysis, for which the original study was not	Comment noted. The Committee considered the most appropriate comparison and the most appropriate analysis of mifamurtide from INT-0133.

	empowered. The relevant comparison should be between chemotherapy + mifamurtide compared with chemotherapy without. The data shows a significant improvement in overall survival with the addition of the product and improvement of disease free interval (though not to the same level of statistical significance). (Reference section 3.2) The issue of efficacy is supported by the phase III data within this trial of an orphan product. This is the first major improvement in survival seen in osteosarcoma in the past one –two decades and deserves re-review. <u>*Section 3.7:*</u> We are concerned that there is excessive weight attributed to the adverse event of hearing loss in the calculation of survival morbidity. Documented objective hearing loss is a known hazard of Cisplatin based therapy; the levels of hearing loss in the whole study are less than usually documented for all groups. Rarely, patients require hearing aids to augment hearing, as functionally high frequency hearing loss is compatible with normal activities without aids. Therefore, the significance of this in the long term economics of survivorship should be adjusted more favourably in the Mifamurtide group. The statistical analysis does not take into account the known huge inter- individual variability to tolerance of Cisplatin (Pharmcogenomics Oct 2008;9(0):1521–30), which may well explain the slight increase in ototoxicity in the Mifamurtide group.	The Committee concluded that the comparison that best reflected current UK clinical practice was the individual mifamurtide containing regimen (A+) compared with a regimen reflecting UK clinical practice (A). However, for the reasons given in section 4.6 of the FAD, the Committee accepted that the combined analysis of all the INT-0133 data may be more appropriate in determining the effect of adding mifamurtide to the standard UK regimen than the post hoc analysis directly comparing regimen A+ with regimen A. Please see FAD sections 4.7 and 4.8. The Committee accepted the views of the clinical specialists that although hearing loss was the main adverse event occurring more frequently with mifamurtide treatment in the clinical study, the rate of hearing loss observed in INT-0133 was not unusual in cisplatin-containing regimens an its exclusion from the model could therefore be justified. The best-case ICERs presented in the manufacturer's additional analyses did not include hearing loss as an adverse event. See FAD sections 4.12 and 4.13.
Welsh Assembly Government	*1) Has all of the relevant evidence been taken into account?* Yes. *2) Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?* We confess that we do not have the Health Economic skills to comment reliably on the modelling performed by NICE. However, their modelling seems thorough and plausible. *3) Are the provisional recommendations sound and a suitable basis for guidance to the NHS?*	Comment noted Comment noted

	NICE felt it "was very unlikely that the cost per QALY gained was below £50,000. The most plausible ICER would be higher than £100,000 per QALY gained" [3.23]. This is above the threshold at which NICE usually concludes an intervention as cost effective. We would like to observe that progress in the development of new drugs for osteosarcoma has stalled in the last 30 years, and is likely to remain so for some time. The current EURAMOS 1 trial is unlikely to report its findings until 2020. We would argue that it is inequitable for those treated with this drug in the remaining years of the patent's life to bear the full cost of its development. We accept that this is the situation with all other new drugs. However, given the slow rate of progress in orphan drugs for rare tumours, it is likely that mifamurtide will remain indicated for some decades yet. This is unlikely to be true for most new drugs developed for the more common cancers. Additionally, given the rarity of osteosarcoma, the drug cost will need to be high to allow the manufacturer to recoup its investment. Such discrepancies disproportionately discriminate against those with rare tumours receiving new drugs, and we wonder if NICE would consider a higher threshold cost-per-QALY than is usually the case to reflect this.	Comment noted. The Committee considered the additional analyses carried out by the manufacturer. It concluded that the manufacturer's best-case ICERs of £70,100 per QALY gained (deterministic analysis) and £67,000 per QALY gained (probabilistic analysis), both including the PAS, were substantially higher than those normally considered to be an acceptable use of NHS resources. See FAD section 4.15. The Committee discussed the innovative nature of the technology and that the clinical trial was conducted in the 1990s. It noted that based on the magnitude of the additional benefit, it was not persuaded that adjuvant chemotherapy with mifamurtide significantly and substantially changes the way that the current need is met (see FAD section 4.3), or that it has been shown to have an appropriate level of effectiveness, given the wide confidence interval of the hazard ratios (see FAD section 4.6).The Committee considered that mifamurtide is indicated for a small patient population with a rare disease, and noted that NICE had not received direction from the Department of Health that treatments for rare conditions ('orphan' or 'ultra-orphan') should be appraised differently from any other treatments. See FAD section 4.19. Although the Committee accepted that there may be a case for accepting a higher ICER for a patient population of children, adolescents and young people, this ICER was too high to allow the Committee to recommend mifamurtide, even when taking into account a number of other considerations such as other aspects of health-related quality of life not adequately captured in the QALY, the innovative nature of the drug, the rarity of the condition, and possible discount rates. The Committee therefore concluded that mifamurtide could not be recommended as a cost-effective use

		of NHS resources.
	4)Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief? We believe the current recommendation could become discriminatory on grounds of age if it were changed to an acceptance of mifamurtide. The current draft NICE recommendation: "Mifamurtide in combination with postoperative multi-agent chemotherapy is not recommended in children, adolescents and young adults for the treatment of high-grade resectable non-metastatic osteosarcoma after macroscopically complete surgical resection."[1.1] reflects verbatim the EMCA licensed indication "MEPACT[mifamurtide] is indicated in children, adolescents and young adults for the treatment of high grade resectable non metastatic osteosarcoma ....." and originates from the initial clinical trial which only included osteosarcoma in patients aged 2 to 30 [Journal of Clinical Oncology 26(4), 633-638, (2008)]. However, there is no good reason to believe that osteosarcomas in younger adults over the age of 30 are biological distinct, and indeed the current EURAMOS 1 study accepts patients with osteosarcoma upto age 45. It is widely believed that "elderly" osteosarcoma, aged 60+, does behave differently, but this fact is being questioned by the current EORTC EUROBOSS study. Mifamurtide would only be used as part of combination therapy with cisplatin, doxorubicin, methotrexate and perhaps additionally ifosfamide. Such a toxic regime is unlikely ever to be used in elderly patients. If NICE were to recommend mifamurtide, it should consider dropping age recommendations as they are probably unnecessary, and are open to challenge, as suggested above.	Mifamurtide is not recommended for treatment of high-grade resectable non-metastatic osteosarcoma after macroscopically complete surgical resection in children, adolescents and young adults (FAD section 1.1). The Committee considered that osteosarcoma predominantly affects children, teenagers and young adults, and that osteosarcoma is a rare disease. The Committee further noted that when an appraisal affects a particular age group it does not mean that a negative recommendation in that appraisal constitutes discrimination on the grounds of age. The Committee noted that no different recommendations were made for the patient population for which mifamuride is licensed, that is, the recommendations not based on and does not vary according to the age of the patient. There was no evidence heard or submitted to suggest that different recommendations on the basis of age would be necessary to meet patient need or that a different recommendation for one or more patient groups within the overall patient population would be clinically and cost effective. The Committee was therefore satisfied that there were no equalities issues in relation to age in this appraisal and that the recommendations were consistent with NICE's obligations under the equalities legislation and the requirement for fairness. See FAD section 4.21.

Comments received from clinical specialists and patient experts

Nominating organisation	Comment	Response
None		

Comments received from commentators

Commentator	Comment	Response
None		

Comments received from members of the public

Role*	Section	Comment	Response
Patient1	1	Mifamurtide has shown that it offers almost a one-third reduction in the risk of dying from the disease, for those patients who have had successful surgery. This is inarguable. It was accepted when EMA (European Medicines Agency) awarded mifamurtide its license. Also, there are adults in the United States who were treated with this drug as children years ago and are now achieving their ambitions and leading normal lives. Surely they are evidence enough that the drug works? As a former osteosarcoma patient I was horrified to learn during my treatment that survival rates had not improved for 20 years. This disease affects mainly children, teenagers and young adults and if treated effectively they can go onto lead fulfilling lives contributing as equal members of society, so any drug that can improve chances of survival has to be worth having. It is morally and ethically wrong to deny children and teenagers diagnosed with osteosarcoma the chance to have a treatment that could save their lives, furthermore surely it contradicts NICE guidance on improving outcomes for children and young people with cancer.	The Committee considered all the evidence submitted, including evidence from clinical trials, patient and clinical experts, the ERG and manufacturer submissions. It also carefully considered the comments received from consultees and commentators in the response to the ACD. Comment noted. The criteria used by other organisations to recommend a technology may be different from those used by NICE. The Committee concluded that mifamurtide might represent a potentially valuable new therapy, but the size of the treatment effect relative to standard UK clinical practice was uncertain. Furthermore, the Committee agreed that the best-case ICER based on the evidence available was £70,100 per QALY gained. Although the Committee accepted that there may be a case for accepting a higher ICER for a patient population of children, adolescents and young people, this ICER was too high to allow the Committee to recommend mifamurtide, even when taking into account a number of other considerations such as other aspects of health-related quality of life not adequately captured in the QALY, the innovative nature of the drug, the rarity of the condition, and possible discount rates. Please see FAD section 4.22.

* When comments are submitted via the Institute's web site, individuals are asked to identify their role by choosing from a list as follows: 'patent', 'carer', 'general public', 'health professional (within NHS)', 'health professional (private sector)', 'healthcare industry (pharmaceutical)', 'healthcare industry'(other)', 'local government professional' or, if none of these categories apply, 'other' with a separate box to enter a description.

Role*	Section	Comment	Response
	8	Mifamurtide has shown that it offers almost a one-third reduction in the risk of dying from the disease, for those patients who have had successful surgery. This is inarguable. It was accepted when EMA (European Medicines Agency) awarded mifamurtide its license. Also, there are adults in the United States who were treated with this drug as children years ago and are now achieving their ambitions and leading normal lives. Â Surely they are evidence enough that the drug works? As a former osteosarcoma patient I was horrified to learn during my treatment that survival rates had not improved for 20 years. This disease affects mainly children, teenagers and young adults and if treated effectively they can go onto lead fulfilling lives contributing as equal members of society, so any drug that can improve chances of survival has to be worth having. It is morally and ethically wrong to deny children and teenagers diagnosed with osteosarcoma the chance to have a treatment that could save their lives, furthermore surely it contradicts NICE guidance on improving outcomes for children and young people with cancer.	Please see detailed response above.
NHS professional 1	1	Largely, we are content with the draft guidance.	Comment noted
NHS professional 1	2	The cost per QALY is above the threshold at which NICE usually concludes an intervention as cost effective. We would like to observe that progress in the development of new drugs for osteosarcoma has stalled in the last 30 years, and is likely to remain so for some time. The current EURAMOS 1 trial is unlikely to report its findings until 2020. We would argue that it is inequitable for those treated with this drug in the remaining years of the patents life to bear the full cost of its development. We accept that this is the situation with all other new drugs. However, given the slow rate of progress in orphan drugs for rare tumours, it is likely that mifamurtide will remain indicated for some decades yet. This is unlikely to be true for most new drugs developed for the more common cancers. Additionally, given the rareity of osteosarcoma, the drug cost will need to be high to allow the manufacturer to recoup its investement. Such discrepancies disproportionately descriminate against those with rare tumours receiving new drugs, and we wonder if NICE would consider a higher threshold cost-per-QALY than is usually the case to reflect this.	Comment noted. See FAD section 4.15. The Committee considered that mifamurtide is indicated for a small patient population with a rare disease, and noted that NICE had not received direction from the Department of Health that treatments for rare conditions ('orphan' or ‘ultra-orphan’) should be appraised differently from any other treatments (see FAD section 4.20).

Role*	Section	Comment	Response
NHS professional 1	3	We believe the current recommendation could become descriminatory on grounds of age if it were changed to an acceptance of mifamurtide. The current draft NICE recommendation reflects verbatim the EMCA licenced indication and originates from the initial clinical trial which only included osteosarcoma in patients aged 2 to 30. However, there is no good reason to believe that osteosarcomas in younger adults over the age of 30 are biological distinct, and indeed the current EURAMOS 1 study accepts patients with osteosarcoma upto age 45. It is widely believed that "elderly" osteosarcoma, aged 60+, does behave differently, but this fact is being questioned by the current EORTC EUROBOSS study. Mifamurtide would only be used as part of combination therapy with cisplatin, doxorubicin, methotrexate and perhaps additionally ifosfamide. Such a toxic regime is unlikely ever to be used in elderly patients. If NICE were to recommend mifamurtide, it should consider dropping age recommendations they are probably unnecessary, and are open to challenge, as suggested above.	Mifamurtide is not recommended for treatment of high-grade resectable non-metastatic osteosarcoma after macroscopically complete surgical resection in children, adolescents and young adults (FAD section 1.1). The Committee considered that osteosarcoma predominantly affects children, teenagers and young adults, and that osteosarcoma is a rare disease. The Committee further noted that when an appraisal affects a particular age group it does not mean that a negative recommendation in that appraisal constitutes discrimination on the grounds of age. The Committee noted that no different recommendations were made for the patient population for which mifamuride is licensed, that is, the recommendations not based on and does not vary according to the age of the patient. There was no evidence heard or submitted to suggest that different recommendations on the basis of age would be necessary to meet patient need or that a different recommendation for one or more patient groups within the overall patient population would be clinically and cost effective. The Committee was therefore satisfied that there were no equalities issues in relation to age in this appraisal and that the recommendations were consistent with NICE's obligations under the equalities legislation and the requirement for fairness. See FAD section 4.21.
NHS professional 1	8	Largely, we are content with the draft guidance	Comment noted
Other 1	1	The Appraisal Committee considered the relevant clinical trial, but failed to take account of important information in the trial. The trial demonstrated a reduction in mortality of 30% which, given that the current UK survival rate is about 60%, means that around 10 young people would benefit from the treatment and live a more or less normal lifespan. The emphasis that NICE places on relative effectiveness leads it to ignore the absolute benefit that 10 more young people with osteosarcoma will survive each year.	Comment noted. The primary endpoint of the INT-0133 was overall survival. However the study was powered for the first planned analysis of the intermediate endpoint, which was disease-free survival (that is, time to progression or death). See FAD section 3.2. The Committee was aware that the combined analysis suggested a statistically significant improvement in overall survival from 71% in the control arm to 78% in the mifamurtide

Role*	Section	Comment	Response
			arm over a median follow-up period of 7.9 years. Although the study was powered for the intermediate endpoint of disease-free survival, it failed to show that regimens of chemotherapy plus mifamurtide (regimens A+ and B+ combined) significantly increased disease-free survival compared with chemotherapy alone (regimens A and B combined) (hazard ratio 0.78, 95% CI 0.61 to 1.01). See FAD section 4.7. The Committee concluded that mifamurtide plus postoperative multi-agent chemotherapy may be more clinically effective than postoperative multi-agent chemotherapy alone. However, there was substantial uncertainty around the size of this effect, particularly in the context of the standard treatment regimen used in the NHS .See FAD section 4.10.. The treatment effect of a technology is the difference between the duration and state of health or HRQL (including the impact of any adverse effects of treatment) that would be experienced on average by patients receiving the technology and that experienced by the same group were they to receive alternative care. ('Guide to the methods of technology appraisal, section 3.2). The Committee noted that based on the magnitude of the additional benefit, it was not persuaded that adjuvant chemotherapy with mifamurtide significantly and substantially changes the way that the current need is met (see FAD section 4.3) or that it has been shown to have an appropriate level of effectiveness, given the wide confidence intervals of the hazard ratios (see FAD section 4.6).
		The other element which NICE has failed to take into account, is the impact of illness and premature death of a young person with osteosarcoma on other family members. The impact is profound and	The Committee considered whether there were any health-related quality of life benefits that may not have been adequately captured in the estimated

Role*	Section	Comment	Response
		remains for many years, seriously and adversely affecting the quality of life of family and friends. This will also impact on the health of the family and this hasn't been formally assessed.	gained used in the QALY calculation. The Committee heard from the patient experts that supporting a young person with osteosarcoma has a substantial impact on the health-related quality of life of the family and friends of the person affected, particularly where treatment is not successful. For example, parents and siblings may develop mental health problems and family relationships may be strained. The Committee concluded that these are important issues affecting the health-related quality of life of those close to the person with osteosarcoma, but noted that these issues are not unique to the condition. For further details see FAD section 4.18.
		I would be very interested to learn about the other treatments which deliver the same benefit as mifamurtide because I am led to believe there are none. To the best of my knowledge, there is no alternative to mifamurtide.	The patient experts stated that there had been few developments that had improved optimal treatment of osteosarcoma over the past 20 years. The Committee noted that the clinical specialists stated that the only development in the past 10 years had been the introduction of high-dose methotrexate and better implementation of treatment regimens, which had together improved survival rates by 10–20%, bringing them in line with those in Europe and the USA. See FAD section 4.3.

Role*	Section	Comment	Response
Other 1	8	The Appraisal Committee considered the relevant clinical trial, but failed to take account of important information in the trial. The trial demonstrated a reduction in mortality of 30% which, given that the current UK survival rate is about 60%, means that around 10 young people would benefit from the treatment and live a more or less normal lifespan. The emphasis that NICE places on relative effectiveness leads it to ignore the absolute benefit that 10 more young people with osteosarcoma will survive each year. The other element which NICE has failed to take into account, is the impact of illness and premature death of a young person with osteosarcoma on other family members. The impact is profound and remains for many years, seriously and adversely affecting the quality of life of family and friends. This will also impact on the health of the family and this hasn't been formally assessed. I would be very interested to learn about the other treatments which deliver the same benefit as mifamurtide because I am led to believe there are none. Â To the best of my knowledge, there is no alternative to mifamurtide.	Please see detailed response above.
Other 2	1	Surely the commitee cannot ignore the fact that 10 more young people will survive every year with this treatment. Also this will have an overall affect on the life of their family. I speak from experience, having lost my own son to this dreadful disease.	The Committee considered all the evidence submitted, including evidence from clinical trials, patient and clinical experts, the ERG and manufacturer submissions. It also carefully considered the comments received from consultees and commentators in the response to the ACD. Recommendations are based on both clinical and cost effectiveness.

Role*	Section	Comment	Response
Other 2	2	This treatment will save lives-fact. How can you put a cost on a young persons life.Having lost my own son, I am sure I have been more of a burden to the NHS due to depression and stress due to having lost my son.	For both legal and bioethical reasons those undertaking technology appraisals must take account of economic considerations (Social Value Judgements – Principles for the Development of NICE Guidance; principle 5). The Committee were mindful of the testimony from the patient experts that there may be an economic impact on the family, parents may experience feeling of guilt and develop mental health problem, siblings may also be affected and there may be strain on family relationships. The Committee concluded that these are important issues affecting quality of life although they are not necessarily unique to this particular condition. For further details see FAD section 4.17.
Other 2	3	I believe the conclusions drawn bt NICE are unsound. I am informed that the analysis is unreliable and therefore the NHS should not withold this drug due to flawed research done by technical people who have no expertise in Osteosarcoma.	Comment noted. The Committee considered the most appropriate comparison and the most appropriate analysis of mifamurtide from INT-0133. The Committee concluded that the comparison that best reflected current UK clinical practice was the individual mifamurtide containing regimen (A+) compared with a regimen reflecting UK clinical practice (A). However, for the reasons given in section 4.6 of the FAD, the Committee accepted that the combined analysis of all the INT-0133 data may be more appropriate in determining the effect of adding mifamurtide to the standard UK regimen than the post hoc analysis directly comparing regimen A+ with regimen A. Please see FAD sections 4.7 and 4.8.
Other 2	4	I believe witholding this drug will stop young people, starting out on their life,fulfill their dreams and ambitions and condemn them to an early death. Not to mention the anguish of their families who can do nothing but stand by and watch their loved one die.Having experienced this myself I would not like to be the person who took away their only chance of survival.My son died but with this drug his and my life could have been very different.	Comment noted

Role*	Section	Comment	Response
Other 2	5	No cost is too high for a childs life	Comment noted. For both legal and bioethical reasons those undertaking technology appraisals must take account of economic considerations (Social Value Judgements – Principles for the Development of NICE Guidance; principle 5).
Other 2	8	Surely the committee cannot ignore the fact that 10 more young people will survive every year with this treatment. Also this will have an overall affect on the life of their family. I speak from experience, having lost my own son to this dreadful disease.	The Committee considered all the evidence submitted, including evidence from clinical trials, patient and clinical experts, the ERG and manufacturer submissions. It also carefully considered the comments received from consultees and commentators in the response to the ACD. Recommendations are based on both clinical and cost effectiveness.

Role*	Section	Comment	Response
Public 1	3	The conclusions drawn by the appraisal committee are unsound and based on a post-hoc analysis which in other settings NICE would criticise. It is worth pointing out that other orphan drugs are not subject to a NICE appraisal and more expensive drugs are in routine use in the UK. One example, which demonstrates very well the different outcomes using different assessment methods, is the provision of the monoclonal antibody eculizumab for the treatment of patients with paroxysmal nocturnal haemoglobinuria. Introduced in April 2009 a new central funding stream, the PNH service, was added to the portfolio of the National Commissioning Group. The University of Birmingham undertook a rapid systematic review of the treatment published in 2008 and estimated that the ICERs range likely lies between £0.5M and £1.4M per life year gained for patients like those recruited to clinical trials and between £2.8M and £3.2M per life year gained for all diagnosed patients. The report also states that first year of treatment costs £252,000 and a subsequent year costs £245,700, compared to a total one-off treatment cost of £114,000 for mifamurtide.	Comment noted. The Committee considered the most appropriate comparison and the most appropriate analysis of mifamurtide from INT-0133. The Committee concluded that the comparison that best reflected current UK clinical practice was the individual mifamurtide containing regimen (A+) compared with a regimen reflecting UK clinical practice (A). However, for the reasons given in section 4.6 of the FAD, the Committee accepted that the combined analysis of all the INT-0133 data may be more appropriate in determining the effect of adding mifamurtide to the standard UK regimen than the post hoc analysis directly comparing regimen A+ with regimen A. Please see FAD sections 4.7 and 4.8. The Committee considered that mifamurtide is indicated for a small patient population with a rare disease, and noted that NICE had not received direction from the Department of Health that treatments for rare conditions (‘orphan’ or ‘ultra-orphan’) should be appraised differently from any other treatments. See FAD section 4.19.

Role*	Section	Comment	Response
Public 1	4	The Appraisal Committee has failed to take account of important aspects of the trial. The trial demonstrated a reduction in mortality of 30% which, given that the current UK survival rate is about 60%, means that around 10 young people would benefit from the treatment and live a more or less normal lifespan. There are serious problems with the Committee's interpretation of the trial data. The trial was designed to be analysed as chemotherapy alone vs chemotherapy with mifamurtide. The ERG requested six post-hoc analyses which the study was not designed nor powered to answer, so the resulting numbers are too small, making Â these analyses unreliable and inappropriate. Also, in the single arm comparison of regimen A vs A+ there is evidence of benefit for mifamurtide. It is not statistically significant because the trial was never powered for this analysis. EQ5D provides utility values that are too blunt to reflect the ability of young people to adapt to disability, whose life is not measured in the way that adults might measure life. EQ5D falsely reduces the quality of life of people with osteosarcoma and should not be used in this setting.	The treatment effect of a technology is the difference between the duration and state of health or HRQL (including the impact of any adverse effects of treatment) that would be experienced on average by patients receiving the technology and that experienced by the same group were they to receive alternative care. (Guide to the Methods of Technology Appraisal, section 3.2). The Committee noted that based on the magnitude of the additional benefit, it was not persuaded that adjuvant chemotherapy with mifamurtide significantly and substantially changes the way that the current need is met (see FAD section 4.3) or that it has been shown to have an appropriate level of effectiveness, given the wide confidence intervals of the hazard ratios (see FAD section 4.6). The Committee considered the utility values used in the manufacturers model. The Committee heard from the patient experts that young people with osteosarcoma are able to live full lives and they have a similar quality of life to their peers, with many adapting well to having a disability, and in some cases being empowered by their experience. The Committee noted that the age-adjusted utility values used in the manufacturers updated analysis were appropriate and reflected the quality life of children, adolescents and young people as reported by the patient groups. See FAD section 4.14.
Public 1	5	Since the population considered young people with a limb amputation is already disabled and if they survive will place further demands on the NHS because of their disabilities, the NICE approach to assessing the value of treatment discriminates against them. The young people for whom mifamurtide is effective will live a more or less normal lifespan and as such will need to use the NHS for aspects of their disability as well as illnesses experienced by the general population. Â While this may not be an unlawful discrimination it is certainly discrimination against the patients because of their age and the additional time they may hope to live.	The Committee was satisfied that there were no equalities issues in relation to age in this appraisal and that the recommendations were consistent with NICE's obligations under the equalities legislation and the requirement for fairness. See FAD section 4.21.

Role*	Section	Comment	Response
Other 3	1	I am at a loss to understand how the Committee has reached this recommendation as clearly some key factors have not been taken into consideration It is evident that nobody on the Committee has had any direct connection with the devastation that Bone Cancer causes to family and friends for life. These people mostly children and young people are very special and would certainly have put something back into society had they survived and what would they have paid in taxes etc over their lifespan would have more than compensated for the cost of treatment. My son so much wanted to live and this recommendation will deny at least 10 young people per year this chance and that cannot be fair This is the first breakthrough for 20 years being adopted in Europe why not here. We have yet to see the evidence that "other effective treatments" are available on the NHS and if this cannot be backed up the recommendation are not sound and should be reversed immediately	The Committee noted that mifamurtide might represent a potentially valuable new therapy, but the evidence of its benefit relative to standard UK clinical practice was uncertain. Furthermore, the Committee agreed that the best-case ICER based on the evidence available was £70,100 per QALY gained. Although the Committee accepted that there may be a case for accepting a higher ICER for children, adolescents and young people, this ICER was too high to allow the Committee to recommend mifamurtide, even when taking into account a number of other considerations such as other aspects of health-related quality of life not adequately captured in the QALY, the innovative nature of the drug, the rarity of the condition, and possible discount rates. The Committee therefore concluded that mifamurtide could not be recommended as a cost-effective use of NHS resources. See FAD section 4.22. The clinical specialists stated that the only development in the past 10 years had been the introduction of high-dose methotrexate and better implementation of treatment regimens, together improving survival rates by 10 -20% and bringing them in line with those in Europe and the USA. See FAD section 4.2.

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Other 3	8	I am at a loss to understand how the Committee has reached this recommendation as clearly some key factors have not been taken into consideration It is evident that nobody on the Committee has had any direct connection with the devastation that Bone Cancer causes to family and friends for life. These people mostly children and young people are very special and would certainly have put something back into society had they survived and what would they have paid in taxes etc over their lifespan would have more than compensated for the cost of treatment. My son so much wanted to live and this recommendation will deny at least 10 young people per year this chance and that cannot be fair This is the first breakthrough for 20 years being adopted in Europe why not hereWe have yet to see the evidence that "other effective treatments" are available on the NHS and if this cannot be backed up the recommendation are not sound and should be reversed immediately	Please see detailed response above.

Role*	Section	Comment	Response
Carer 1	4	1. Surely amputation and limb salvage costs are incurred whether or not Mifamurtide is given. 2. There are resulting costs to the Health Service of those left behind when a young person dies of Osteosarcoma. Parents, siblings, grandparents, wider family members and friends are all affected by mental health problems and inability to cope with what would normally be considered to be acceptable levels of stress. This leads to an increased need for support from the health service, reduced ability in the work place and relationship difficulties. These effects last for many years. 3. If a young person with an amputation lives 3 times as long as an older person with an amputation, the young person has a full life in which to earn a living and contribute to society, paying taxes etc. which contribute to the cost of extra healthcare needs resulting from the amputation. If the older person with an amputation is retired and doesn't earn and pay taxes then s/he costs the NHS more than the young person. NICE discriminates against the young people affected by Osteosarcoma in not taking this into account. Modern technology & anti discrimination laws mean amputees are able to earn a living.	Comment noted The Committee heard from the patient experts that supporting a young person with osteosarcoma has a substantial impact on the health-related quality of life of the family and friends of the person affected, particularly where treatment is not successful. For example, parents and siblings may develop mental health problems and family relationships may be strained. The Committee concluded that these are important issues affecting the health-related quality of life of those close to the person with osteosarcoma, but noted that these issues are not unique to the condition. For further details see FAD section 4.18. Comment noted. Productivity costs and costs borne by patients and carers that are not reimbursed by the NHS or PSS are not included in either the reference-case or non-reference-case analyses (See Guide to the Methods of Health Technology Appraisal – section 5.5.11).
Public 2	1	In the Bone Cancer Research Trusts response they sate that "The Appraisal Committee has considered the relevant clinical trial, but it has failed to take account of important information in that trial. The trial demonstrated a reduction in mortality of 30% which, given that the current UK survival rate is about 60%, means that around 10 young people would benefit from the treatment and live a more or less normal lifespan...	Comment noted. The primary endpoint of the INT-0133 was overall survival. However the study was powered for the first planned analysis of the intermediate endpoint, which was disease-free survival (that is, time to progression or death). See FAD section 3.2. The Committee was aware that the combined analysis suggested a statistically significant improvement in overall survival from 71% in the control arm to 78% in the mifamurtide arm over a median follow-up period of 7.9 years.

Role*	Section	Comment	Response
			Although the study was powered for the intermediate endpoint of disease-free survival, it failed to show that regimens of chemotherapy plus mifamurtide (regimens A+ and B+ combined) significantly increased disease-free survival compared with chemotherapy alone (regimens A and B combined) (hazard ratio 0.78, 95% CI 0.61 to 1.01). See FAD section 4.7. The Committee concluded that mifamurtide plus postoperative multi-agent chemotherapy may be more clinically effective than postoperative multi-agent chemotherapy alone. However, there was substantial uncertainty around the size of this effect, particularly in the context of the standard treatment regimen used in the NHS .See FAD section 4.10.. The treatment effect of a technology is the difference between the duration and state of health or HRQL (including the impact of any adverse effects of treatment) that would be experienced on average by patients receiving the technology and that experienced by the same group were they to receive alternative care. ('Guide to the methods of technology appraisal, section 3.2). The Committee noted that based on the magnitude of the additional benefit, it was not persuaded that adjuvant chemotherapy with mifamurtide significantly and substantially changes the way that the current need is met (see FAD section 4.3) or that it has been shown to have an appropriate level of effectiveness, given the wide confidence intervals of the hazard ratios (see FAD section 4.6).
		The other element which NICE has failed to take into account... is the impact of the illness and premature death of a young person with osteosarcoma on other family members." As the family member of a young person who died from a bone cancer, I know that this effect is devastating.	The Committee considered whether there were any health-related quality of life benefits that may not have been adequately captured in the estimated gained used in the QALY calculation. The

Role*	Section	Comment	Response
		The committee should take in to account the cost of counselling etc for family members, and the distress that families suffer for the rest of their lives following the death of a child. The lives of 10 young people a year is a significant number and the committee should reconsider its decision.	Committee heard from the patient experts that supporting a young person with osteosarcoma has a substantial impact on the health-related quality of life of the family and friends of the person affected, particularly where treatment is not successful. For example, parents and siblings may develop mental health problems and family relationships may be strained. The Committee concluded that these are important issues affecting the health-related quality of life of those close to the person with osteosarcoma, but noted that these issues are not unique to the condition. For further details see FAD section 4.18.
	8	In the Bone Cancer Research Trusts response they state that "The Appraisal Committee has considered the relevant clinical trial, but it has failed to take account of important information in that trial. The trial demonstrated a reduction in mortality of 30% which, given that the current UK survival rate is about 60%, means that around 10 young people would benefit from the treatment and live a more or less normal lifespan... The other element which NICE has failed to take into account... is the impact of the illness and premature death of a young person with osteosarcoma on other family members." As the family member of a young person who died from a bone cancer, I know that this effect is devastating. The committee should take in to account the cost of counselling etc for family members, and the distress that families suffer for the rest of their lives following the death of a child. The lives of 10 young people a year is a significant number and the committee should reconsider its decision.	Please see detailed response above.

Role*	Section	Comment	Response
Public 3	1	To whom it may concern: I am a Bone Cancer Research Trust supporter and support their view opposing your recommendation refusing Mifamurtide for the treatment of osteosarcoma as follows: Has all the relevant evidence been taken into account? The Appraisal Committee has considered the relevant clinical trial, but it has failed to take account of important information in that trial. The trial demonstrated a reduction in mortality of 30% which, given that the current UK survival rate is about 60%, means that around 10 young people would benefit from the treatment and live a more or less normal lifespan. The emphasis that NICE places on relative effectiveness leads it to ignore the absolute benefit that 10 more young people with osteosarcoma will survive each year. The other element which NICE has failed to take into account, and we accept that there is no published data on this, is the impact of the illness and premature death of a young person with osteosarcoma on other family members. We can say categorically that the impact is profound and remains for many years, seriously and adversely affecting the quality of life of family and friends. This impact will undoubtedly impact on the health of the family although this hasn't been formally assessed. We note that the comment by Andrew Dillon about the outcome of the appraisal 'It is important to remember, though, that other, effective treatments are available in the NHS for treating this condition.' We would be very interested to learn what are these other treatments which deliver the same benefit as mifamurtide because we do not know of any. To the best of our knowledge, there is no alternative to mifamurtide. Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? BCRT absolutely refutes the Appraisal Committee's interpretation of the clinical effectiveness data considered. Trial INT-0133 was an investigator-led trial which NICE acknowledges was designed with the primary endpoint of overall survival but powered for disease—free survival as a two by two factorial design. That is, it was designed to be analysed as chemotherapy alone vs chemotherapy with mifamurtide. The ERG requested six post-hoc analyses which the study was not designed nor powered to answer. BCRT believes that this post-hoc, unplanned analysis is invalid and the numbers that result are too small to be of relevance, making these analyses unreliable and inappropriate. Notwithstanding the inappropriateness of the analysis, in the single arm comparison of regimen A vs A+ there is evidence, although it is not statistically significant, of benefit for mifamurtide. That it is not statistically significant is entirely explained by the fact that the trial was never powered for this analysis. The BCRT is prepared to provide a more detailed rebuttal of the ERG's conclusions about efficacy if requested. The utility values for the use of mifamurtide are based on EQ5D which is a measure completely	Comment noted. Please see detailed response above.

Role*	Section	Comment	Response
Public 3	1	The Appraisal Committee has failed to take account of important information. The trial demonstrated a reduction in mortality of 30% which, given that the current UK survival rate is about 60%, means that around 10 young people would benefit from the treatment and live a more or less normal lifespan. The emphasis that NICE places on relative effectiveness leads it to ignore the absolute benefit that 10 more young people with osteosarcoma will survive each year. The other element which NICE has failed to take into account, and we accept that there is no published data on this, is the impact of the illness and premature death of a young person with osteosarcoma on other family members. We can say categorically that the impact is profound and remains for many years, seriously and adversely affecting the quality of life of family and friends. This impact will impact on the health of the family although this hasn't been formally assessed. for treating this condition.? I would be very interested to learn what are these other treatments which deliver the same benefit as mifamurtide because we do not know of any. To the best of our knowledge, there is no alternative to mifamurtide.	Comment noted. The Committee considered the most appropriate comparison and the most appropriate analysis of mifamurtide from INT-0133. The Committee concluded that the comparison that best reflected current UK clinical practice was the individual mifamurtide containing regimen (A+) compared with a regimen reflecting UK clinical practice (A). However, for the reasons given in section 4.6 of the FAD, the Committee accepted that the combined analysis of all the INT-0133 data may be more appropriate in determining the effect of adding mifamurtide to the standard UK regimen than the post hoc analysis directly comparing regimen A+ with regimen A. Please see FAD sections 4.7 and 4.8. The clinical specialists stated that the only development in the past 10 years had been the introduction of high-dose methotrexate and better implementation of treatment regimens, together improving survival rates by 10 -20% and bringing them in line with those in Europe and the USA. See FAD section 4.2.

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Public 3	2	BCRT absolutely refutes the Appraisal Committee?s interpretation of the clinical effectiveness data considered. Trial INT-0133 was an investigator-led trial which NICE acknowledges was designed with the primary endpoint of overall survival but powered for disease?free survival as a two by two factorial design. That is, it was designed to be analysed as chemotherapy alone vs chemotherapy with mifamurtide. The ERG requested six post-hoc analyses which the study was not designed nor powered to answer. BCRT believes that this post-hoc, unplanned analysis is invalid and the numbers that result are too small to be of relevance, making these analyses unreliable and inappropriate. Notwithstanding the inappropriateness of the analysis, in the single arm comparison of regimen A vs A+ there is evidence, although it is not statistically significant, of benefit for mifamurtide. Regardless of whether this is the first new treatment in 20 years for osteosarcoma, it is an effective treatment which saves lives. The ICER is a wholly inappropriate basis for a decision on whether or not mifamurtide should be made available.	Comment noted. Please see detailed response above. NICE appraises the clinical and cost effectiveness of technologies. For both legal and bioethical reasons those undertaking technology appraisals and developing clinical guidelines must take account of economic considerations (Social value Judgements – Principles for the development of NICE guidance; principle 5).

Role*	Section	Comment	Response
Public 3	6	Since the population considered young people with a limb amputation is already disabled and if they survive will place further demands on the NHS because of their disabilities, the NICE approach to assessing the value of treatment discriminates against them. The young people for whom mifamurtide is effective will live a more or less normal lifespan and as such will need to use the NHS for aspects of their disability as well as illnesses experienced by the general population. While this may not be an unlawful discrimination it is certainly discrimination against the patients because of their age and the additional time they may hope to live.	The Committee considered that osteosarcoma predominantly affects children, teenagers and young adults, and that osteosarcoma is a rare disease. The Committee further noted that when an appraisal affects a particular age group it does not mean that a negative recommendation in that appraisal constitutes discrimination on the grounds of age. The Committee noted that no different recommendations were made for the patient population for which mifamurtide is licensed, that is, the recommendations not based on and does not vary according to the age of the patient. There was no evidence heard or submitted to suggest that different recommendations on the basis of age would be necessary to meet patient need or that a different recommendation for one or more patient groups within the overall patient population would be clinically and cost effective. The Committee was therefore satisfied that there were no equalities issues in relation to age in this appraisal and that the recommendations were consistent with NICE's obligations under the equalities legislation and the requirement for fairness. See FAD section 4.21.
Public 3	8	The Appraisal Committee has failed to take account of important information. The trial demonstrated a reduction in mortality of 30% which, given that the current UK survival rate is about 60%, means that around 10 young people would benefit from the treatment and live a more or less normal lifespan. The emphasis that NICE places on relative effectiveness leads it to ignore the absolute benefit that 10 more young people with osteosarcoma will survive each year.	Comment noted. The primary endpoint of the INT-0133 was overall survival. However the study was powered for the first planned analysis of the intermediate endpoint, which was disease-free survival (that is, time to progression or death). See FAD section 3.2. The Committee was aware that the combined analysis suggested a statistically significant improvement in overall survival from 71% in the control arm to 78% in the mifamurtide arm over a median follow-up period of 7.9 years. Although the study was powered for the intermediate endpoint of disease-free survival, it failed to show that regimens of chemotherapy plus mifamurtide (regimens A+ and B+ combined) significantly increased disease-free survival compared with chemotherapy alone (regimens A

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			and B combined) (hazard ratio 0.78, 95% CI 0.61 to 1.01). See FAD section 4.7. The Committee concluded that mifamurtide plus postoperative multi-agent chemotherapy may be more clinically effective than postoperative multi-agent chemotherapy alone. However, there was substantial uncertainty around the size of this effect, particularly in the context of the standard treatment regimen used in the NHS .See FAD section 4.10.. The treatment effect of a technology is the difference between the duration and state of health or HRQL (including the impact of any adverse effects of treatment) that would be experienced on average by patients receiving the technology and that experienced by the same group were they to receive alternative care. ('Guide to the methods of technology appraisal, section 3.2). The Committee noted that based on the magnitude of the additional benefit, it was not persuaded that adjuvant chemotherapy with mifamurtide significantly and substantially changes the way that the current need is met (see FAD section 4.3) or that it has been shown to have an appropriate level of effectiveness, given the wide confidence intervals of the hazard ratios (see FAD section 4.6).
		The other element which NICE has failed to take into account, and we accept that there is no published data on this, is the impact of the illness and premature death of a young person with osteosarcoma on other family members. We can say categorically that the impact is profound and remains for many years, seriously and adversely affecting the quality of life of family and friends. This impact will impact on the health of the family although this hasn't been formally assessed.	The Committee considered whether there were any health-related quality of life benefits that may not have been adequately captured in the estimated gained used in the QALY calculation. The Committee heard from the patient experts that supporting a young person with osteosarcoma has a substantial impact on the health-related quality of life of the family and friends of the person affected, particularly where treatment is not successful. For example, parents and siblings may develop mental

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			health problems and family relationships may be strained. The Committee concluded that these are important issues affecting the health-related quality of life of those close to the person with osteosarcoma, but noted that these issues are not unique to the condition. For further details see FAD section 4.18.
		for treating this condition.? I would be very interested to learn what are these other treatments which deliver the same benefit as mifamurtide because we do not know of any. To the best of our knowledge, there is no alternative to mifamurtide.	The clinical specialists stated that the only development in the past 10 years had been the introduction of high-dose methotrexate and better implementation of treatment regimens, together improving survival rates by 10 -20% and bringing them in line with those in Europe and the USA. See FAD section 4.2.
Public 4	Notes	BCRT absolutely refutes the Appraisal Committee's interpretation of the clinical effectiveness data considered. Trial INT-0133 was an investigator-led trial which NICE acknowledges was designed with the primary endpoint of overall survival but powered for disease—free survival as a two by two factorial design. Â That is, it was designed to be analysed as chemotherapy alone vs chemotherapy with mifamurtide. The ERG requested six post-hoc analyses which the study was not designed nor powered to answer. BCRT believes that this post-hoc, unplanned analysis is invalid and the numbers that result are too small to be of relevance, making these analyses unreliable and inappropriate. Notwithstanding the inappropriateness of the analysis, in the single arm comparison of regimen A vs A+ there is evidence, although it is not statistically significant, of benefit for mifamurtide. That it is not statistically significant is entirely explained by the fact that the trial was never powered for this analysis. The BCRT is prepared to provide a more detailed rebuttal of the ERG's conclusions about efficacy if requested.	Please see above. The Committee considered the most appropriate comparison and the most appropriate analysis of mifamurtide from INT-0133. The Committee concluded that the comparison that best reflected current UK clinical practice was the individual mifamurtide containing regimen (A+) compared with a regimen reflecting UK clinical practice (A). However, for the reasons given in section 4.6 of the FAD, the Committee accepted that the combined analysis of all the INT-0133 data may be more appropriate in determining the effect of adding mifamurtide to the standard UK regimen than the post hoc analysis directly comparing regimen A+ with regimen A. Please see FAD sections 4.7 and 4.8.
		The utility values for the use of mifamurtide are based on EQ5D which is a measure completely inappropriate to the population being considered. The tool is too blunt to reflect the ability of young people to adapt to disability and whose life is not measured in the way that adults might measure life. Â EQ5D falsely reduces the quality of life of people with osteosarcoma and should not be used in this setting. Regardless of whether this is the first new treatment in 20 years for osteosarcoma, it is	The Committee considered the utility values used in the manufacturers model. The Committee heard from the patient experts that young people with osteosarcoma are able to live full lives and they have a similar quality of life to their peers, with many adapting well to having a disability, and in some cases being empowered by their experience.

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		an effective treatment which saves lives.	The Committee noted that the age-adjusted utility values used in the manufacturer's updated analysis were appropriate and reflected the quality life of children, adolescents and young people as reported by the patient groups. See FAD section 4.14.
		The ICER is a wholly inappropriate basis for a decision on whether or not mifamurtide should be made available. The conclusions drawn by the appraisal committee are unsound and based on a post-hoc analysis which in other settings NICE would criticise. For the reasons outlined above, the conclusion does not reflect the trial data and hence the recommendation is flawed. The NHS should not decide whether young people can be treated with mifamurtide based on a completely unreliable analysis performed by a technical group without expertise in treating osteosarcoma.	NICE appraises the clinical and cost effectiveness of technologies. For both legal and bioethical reasons those undertaking technology appraisals must take account of economic considerations (Social Value Judgements – Principles for the Development of NICE Guidance; principle 5).
		It is worth pointing out that other orphan drugs are not subject to a NICE appraisal and more expensive drugs are in routine use in the UK. It is unacceptable that young people with osteosarcoma are denied a potentially life-saving treatment because of the review mechanism to which it has been subject. NICE's appraisal should take account of these special circumstances and adjust its cost effectiveness threshold accordingly. One example, which demonstrates very well the different outcomes using different assessment methods, is the provision of the monoclonal antibody eculizumab for the treatment of patients with paroxysmal nocturnal haemoglobinuria. Introduced in April 2009 a new central funding stream, the PNH service, was added to the portfolio of the National Commissioning Group. The University of Birmingham undertook a rapid systematic review of the treatment published in 2008 and estimated that the ICERs range likely lies between £0.5M and £1.4M per life year gained for patients like those recruited to clinical trials and between £2.8M and £3.2M per life year gained for all diagnosed patients. The report also states that first year of treatment costs £252,000 and a subsequent year costs £245,700, compared to a total one-off treatment cost of £114,000 for mifamurtide.	Comment noted. The Committee considered that mifamurtide is indicated for a small patient population with a rare disease, and noted that NICE had not received direction from the Department of Health that treatments for rare conditions ('orphan' or 'ultra-orphan') should be appraised differently from any other treatments. See FAD section 4.20.

Role*	Section	Comment	Response
Public 5		Why should people be denied the chance to a longer life! My sister in-law died of an aggressive cancer in February this year, i no if she could of had some more time, she would of jumped at the chance, and spent those special times with her 15 year old daughter.	Comment noted
Other 3	1	The numbers of children suffering and as such requiring treatment from this drug is very low. The mortality rate for the disease is high with the survival rate at present around 60%. In my opinion the small numbers of sufferers compared with the improvement in the survival rate for young sufferers and the hope for future sufferers makes the availability of the treatment cost effective and worth introducing. Remember we are talking about Â YOUNG people here with the potential of many years of quality life ahead of them even if they are likely to be disabled through the loss of a limb.	Comment noted. The Committee does not consider the affordability, that is costs alone, of new technologies but rather their cost effectiveness in terms of how its advice may enable the more efficient use of available healthcare resources (NICE Guide to the Methods of Health Technology Appraisal, section 6.2).
Other 3	2	The costs above compared with the costs to the NHS for treatment of other often self induced diseases is disproportionate. Young people with this disease have not contributed to it in any way in terms of lifestyle, on the contrary they are random In developing guidance for the nHS, no priorotiy shoudl healthy individuals struck down by an illness that predominantly effects the young.As a health service I believe we should invest in the future and that means in our young people.	In developing guidance for the NHS, no priority should be given based on individual's income, social class or position in life and individual' social roles, at different ages, when considering cost effectiveness (Social Value Judgements; principle 8).
Other 3	3	I am not qualified to comment on health research and cost.	Comment noted
Other 3	4	My understanding having consulted with those who work with such patients and potential beneficieries of this treatment is that the analysis is flawed and therefore by defenition the conclusion is worthless and inaccurate. Where is the evidence of involvement in the trials of those who have expertise and experience in treating osteosarcoma ?. Independence is important but in such a specialist area of treatment the inclusion of someone with the expertise in this field is surely critical.	Comment noted. The Committee considered the most appropriate comparison and the most appropriate analysis of mifamurtide from INT-0133. The Committee concluded that the comparison that best reflected current UK clinical practice was the individual mifamurtide containing regimen (A+) compared with a regimen reflecting UK clinical practice (A). However, for the reasons given in section 4.6 of the FAD, the Committee accepted that the combined analysis of all the INT-0133 data may be more appropriate in determining the effect of adding mifamurtide to the standard UK regimen than the post hoc analysis directly comparing regimen A+ with regimen A. Please see FAD sections 4.7 and 4.8.

Role*	Section	Comment	Response
Other 3	5	Investment in our young people is key and should override this not unreasonable cost. The benefits of what these young people can potentially bring to society far outweighs the cost of the treatment. Where within the report is any consideration given for the parents/carers of these young people and the cost to the NHS of dealing with those who have lost children and have as a result fallen themselves off the track due to the huge and immense impact of this disease, surely the NHS should take this into account and reconsider its provisional decision.	The Committee heard from the patient experts that supporting a young person with osteosarcoma has a substantial impact on the health-related quality of life of the family and friends of the person affected, particularly where treatment is not successful. For example, parents and siblings may develop mental health problems and family relationships may be strained. The Committee concluded that these are important issues affecting the health-related quality of life of those close to the person with osteosarcoma, but noted that these issues are not unique to the condition. For further details see FAD section 4.18.
Other 3	8	The numbers of children suffering and as such requiring treatment from this drug is very low. The mortality rate for the disease is high with the survival rate at present around 60%. In my opinion the small numbers of sufferers compared with the improvement in the survival rate for young sufferers and the hope for future sufferers makes the availability of the treatment cost effective and worth introducing. Remember we are talking about YOUNG people here with the potential of many years of quality life ahead of them even if they are likely to be disabled through the loss of a limb.	The Committee accepted that there may be a case for accepting a higher ICER for a patient population of children, adolescents and young people, but it was unable to reach a positive decision given the very high ICERs presented. See FAD section 4.16.
Other 4	notes	From what I have read, this is a drug that can help save the lives of young people suffering from Osteosarcoma. My daughter is 19 months post chemotherapy, we have lived in fear every day since her diagnosis in February 2008. If this drug can help, it MUST be given as an option.	Comment noted
NHS professional 2		I believe this to be wrong.Osteosarcoma is a devastating condition with a survival rate wuch has not improved in the past 30years. This is the first drug to show survival benefit and I feel that within the particular age group usually affected , every chance of improved survival must be welcomed. The health economic calculations which may be valid for older adults should not be applied for drugs introduced for a rare cancer in this most critical age group	The Committee accepted that there may be a case for accepting a higher ICER for a patient population of children, adolescents and young people, but it was unable to reach a positive decision given the very high ICERs presented. See FAD section 4.16.
NHS professional 2		AS above, I believe that as the group of patients involved are small in number but at a critical stage in their life, £114,000 is an acceptable amount to invest in the improvement in survival expected from initial trial results.	The Committee does not consider the affordability, that is costs alone, of new technologies but rather their cost effectiveness in terms of how its advice may enable the more efficient use of available healthcare resources (NICE Guide to the Methods of Health Technology Appraisal, section 6.2).

Role*	Section	Comment	Response
NHS professional 2		On the basis of 3.4 of this evidence, I would wish approval of this drug while further trials of survival are encouraged	Comment noted
NHS professional 2		The £100.000 per QALY gained is in this case a rather crude (and cruel) measure to decide for or against approval. The key point is that the only drug to provide any real hope of improved survival for this most unfortunate group is to be denied to them. This does NICE no favours and one can only hope that an opportunity is taken now to reverse this decision	Considerations about cost effectiveness are explained in the Guide to the Methods of Technology Appraisal section 6.2.
NHS professional 2		2013 is too late for all those likely to be denied this drug	Comment noted.
NHS professional 2		I believe this to be wrong.Osteosarcoma is a devastating condition with a survival rate wuch has not improved in the past 30years. This is the first drug to show survival benefit and I feel that within the particular age group usually affected , every chance of improved survival must be welcomed. The health economic calculations which may be valid for older adults should not be applied for drugs introduced for a rare cancer in this most critical age group	Comment noted. The Committee accepted that there may be a case for accepting a higher ICER for a patient population of children, adolescents and young people, but it was unable to reach a positive decision given the very high ICERs presented. See FAD section 4.16.
Other 5	1	Why not?	Comment noted
Other 5	2	In 1984 I had cisplat and as a result, had a certain amount of hearing loss. Even if hearing loss is a result of this new drug, the benefits in additional survival rates far outway the potential, and not guaranteed loss to hearing	Comment noted. See FAD section 4.9.
Other 5	3	notwithstanding costs - what are the forecast long term effects on cardiac function and other long-term potential problems? If better than current treatment using Doxorubicin and Cisplatin, I would suggest that the new treatment be seriously considered. The long term overall albeit perhaps at this stage, small, increase in survivor rates should offset the additional costs	Comment noted. The Committee considered all evidence submitted, including evidence from clinical trials, patient and clinical experts, the ERG and manufacturer submissions. It also carefully considered the comments received from consultees and commentators in the response to the ACD.
Other 5	8	Why not?	Comment noted
Other 6	1	I note the comment by Andrew Dillon about the outcome of the appraisal. It is important to remember, though, that other, effective treatments are available in the NHS for treating this condition. What are these other treatments which deliver the same benefit as mifamurtide I havent come across any. There is no alternative to mifamurtide. The trial demonstrated a reduction in mortality of 30% which, given that the current UK survival rate is about 55%, means that around 10 young people would benefit from the treatment and	The treatment effect of a technology is the difference between the duration and state of health or health related quality of life (including the impact of any adverse effects of treatment) that would be experienced on average by patients receiving the technology and that experienced by the same group were they to receive alternative care. (Guide to the Methods of Technology Appraisal, section 3.2). The Committee noted that based on the

Role*	Section	Comment	Response
		live a more or less normal lifespan. This is an absolute benefit	magnitude of the additional benefit, it was not persuaded that adjuvant chemotherapy with mifamurtide significantly and substantially changes the way that the current need is met (see FAD section 4.3) or that it has been shown to have an appropriate level of effectiveness, given the wide confidence intervals of the hazard ratios (see FAD section 4.6).
Other 7	2	The side-effects listed in 2.2 are so similar to the side-effects of the chemotherapy regimes currently being administered by the NHS that these would not be any worse a problem to a young person fighting cancer than the treatment and side-effects they already undergo. This is not a significant criteria. Some other orphan drugs are not subject to a NICE appraisal.There are more expensive drugs in routine use in the UK. This flawed review means that young people with osteosarcoma are denied a potentially life-saving treatment. NICE's appraisal should take account of these special circumstances and adjust its cost effectiveness threshold accordingly. One example, which demonstrates different outcomes using different assessment methods, is the provision of the monoclonal antibody eculizumab for the treatment of patients with paroxysmal nocturnal haemoglobinuria. Introduced in April 2009 a new central funding stream, the PNH service, was added to the portfolio of the National Commissioning Group. The life costs were higher and first year of treatment costs were £252,000 with a subsequent year costs of £245,700, compared to a total one-off treatment cost of £114,000 for mifamurtide.	Comment noted. The Committee accepted that there may be a case for accepting a higher ICER for a patient population of children, adolescents and young people, but it was unable to reach a positive decision given the very high ICERs presented. See FAD section 4.16.

Role*	Section	Comment	Response
Other 7	3	The interpretaion of the data is flawed.Trial INT-0133 was an investigator-led trial which was designed with the primary endpoint of overall survival but powered for disease free survival as a two by two factorial design. It was designed to be analysed as chemotherapy alone vs chemotherapy with mifamurtide. The ERG requested six post-hoc analyses which the study was not designed to answer. This post-hoc, unplanned analysis is invalid and the numbers that result are too small to be of relevance. These analyses are unreliable and inappropriate.In the single arm comparison of regimen A vs A+ there is evidence, of benefit for mifamurtide. It is not statistically significant because the trial was never powered for this analysis.The utility values for the use of mifamurtide are based on EQ5D, a measure inappropriate to the population being considered. The tool is too blunt to reflect the ability of young people to adapt to disability. Their life is not measured in the way that adults might measure life. EQ5D falsely reduces the quality of life of people with osteosarcoma and should not be used in this setting	Comment noted. The Committee considered the most appropriate comparison and the most appropriate analysis of mifamurtide from INT-0133. The Committee concluded that the comparison that best reflected current UK clinical practice was the individual mifamurtide containing regimen (A+) compared with a regimen reflecting UK clinical practice (A). However, for the reasons given in section 4.6 of the FAD, the Committee accepted that the combined analysis of all the INT-0133 data may be more appropriate in determining the effect of adding mifamurtide to the standard UK regimen than the post hoc analysis directly comparing regimen A+ with regimen A. Please see FAD sections 4.7 and 4.8.

Role*	Section	Comment	Response
Other 7	4	The NHS should not decide whether young people can be treated with mifamurtide based on a completely unreliable analysis performed by a technical group without expertise in treating osteosarcoma. Since the disease is rare and effects predominantly children and young people and the drug is aimed at cure, the implication of the decision appears to be that if the patient is given the drug which saves their life, because they have had limb saving or amputation procedures and so are by definition disabled, they will have a potentially longer life span than an adult, they will need more medical care over their lifespan, just because they will live longer. This is blatantly discriminatory on the basis of age and disability. Also the effect of the death of a young person from osteosarcoma is devastating and has an impact on the health of all family members, in itself putting more pressure on NHS funds.The conclusions drawn by the appraisal committee are unsound and based on a post-hoc analysis which in other circumstances NICE would criticise. The conclusion does not reflect the trial data and hence the recommendation is flawed.	Comment noted. Please see detailed response above. The Committee was satisfied that there were no equalities issues in relation to age in this appraisal and that the recommendations were consistent with NICE's obligations under the equalities legislation and the requirement for fairness. See FAD section 4.21.
Other 7	6	Outcomes for patients with sarcoma have not improved for 20 years even where the NICE current guidance is being followed. To improve outcomes, drugs such as Mifamurtide, must be allowed to be used. If new drugs/protocols are not introduced there will never be any improvement of outcomes.	Comment noted.

Role*	Section	Comment	Response
Other 7	8	I note the comment by Andrew Dillon about the outcome of the appraisal. It is important to remember, though, that other, effective treatments are available in the NHS for treating this condition. What are these other treatments which deliver the same benefit as mifamurtide I haven't come across any. There is no alternative to mifamurtide. The trial demonstrated a reduction in mortality of 30% which, given that the current UK survival rate is about 55%, means that around 10 young people would benefit from the treatment and live a more or less normal lifespan. This is an absolute benefit	The treatment effect of a technology is the difference between the duration and state of health or HRQL (including the impact of any adverse effects of treatment) that would be experienced on average by patients receiving the technology and that experienced by the same group were they to receive alternative care. ('Guide to the methods of technology appraisal, section 3.2). The Committee noted that based on the magnitude of the additional benefit, it was not persuaded that adjuvant chemotherapy with mifamurtide significantly and substantially changes the way that the current need is met (see FAD section 4.3) or that it has been shown to have an appropriate level of effectiveness, given the wide confidence intervals of the hazard ratios (see FAD section 4.6).
Carer 2	1	As a full trial on a large enough group has not been conducted i feel preliminary recommendations to be far too dismissive and appear to be based on cost savings not life saving. The efficasy of the clinical trial NICE have made a recommendation on clearly shows that young peoples lives can be considerably extended with this treatment.	Comment noted. The primary endpoint of the INT-0133 was overall survival. However the study was powered for the first planned analysis of the intermediate endpoint, which was disease-free survival (that is, time to progression or death). See FAD section 3.2. The Committee was aware that the combined analysis suggested a statistically significant improvement in overall survival from 71% in the control arm to 78% in the mifamurtide arm over a median follow-up period of 7.9 years. However, the study failed to show that regimens of chemotherapy plus mifamurtide (regimens A+ and B+ combined) significantly increased disease-free survival compared with chemotherapy alone (regimens A and B combined) (HR 0.78, 95% CI 0.61 to 1.01). See FAD section 4.6. The Committee concluded that mifamurtide plus postoperative multi-agent chemotherapy may be more clinically effective than postoperative multi-agent chemotherapy alone. However, there was substantial uncertainty around the size of this effect, particularly in the context of the standard treatment regimen used in the NHS.

Role*	Section	Comment	Response
			The treatment effect of a technology is the difference between the duration and state of health or HRQL (including the impact of any adverse effects of treatment) that would be experienced on average by patients receiving the technology and that experienced by the same group were they to receive alternative care. (Guide to the Methods of Technology Appraisal, section 3.2). The Committee noted that based on the magnitude of the additional benefit and associated uncertainty, it was not persuaded that adjuvant chemotherapy with mifamurtide significantly and substantially changes the way that the current need is met (see section 4.3), or that it has been shown to have an appropriate level of effectiveness, given the wide confidence intervals of the hazard ratios (see section 4.7).
Carer 2	2	2.2 The adverse effects of the drug are often present with many patients undergoing chemotherapy (Cisplatin, Doxorubicin, Methotrexate etc.) 2.4 More expensive drugs have been recommended and are in use by the NHS now. It has been shown both in the United States and by ERG that this treatment saves lives and outweighs the cost of mental/physical care costs the friends and family that are adversely affected by the loss of a youngster.	Comment noted. The Committee noted that mifamurtide might represent a potentially valuable new therapy, but the evidence of its benefit relative to standard UK clinical practice was uncertain. Furthermore, the Committee agreed that the best-case ICER based on the evidence available was £70,100 per QALY gained. Although the Committee accepted that there may be a case for accepting a higher ICER for children, adolescents and young people, this ICER was too high to allow the Committee to recommend mifamurtide, even when taking into account a number of other considerations such as other aspects of health-related quality of life not adequately captured in the QALY, the innovative nature of the drug, the rarity of the condition, and possible discount rates. See FAD section 4.22.
Carer 2	3	A more detailed rebuttal of the ERG conclusions i s available from the BCRT and should be considered before any final decision is made.	Comment noted

Role*	Section	Comment	Response
Carer 2	8	As a full trial on a large enough group has not been conducted i feel preliminary recommendations to be far too dismissive and appear to be based on cost savings not life saving. The efficacy of the clinical trial NICE have made a recommendation on clearly shows that young peoples lives can be considerably extended with this treatment.	Comment noted
Other 8	Notes	The trial demonstrated a reduction in mortality of 30% which, given that the current UK survival rate is about 60%, means that around 10 young people would benefit from the treatment and live a more or less normal lifespan. The emphasis that NICE places on relative effectiveness leads it to ignore the absolute benefit that 10 more young people with osteosarcoma will survive each year. This is an incredibly relevant number to any parent/brother/sister/family member affected by someone they love getting the disease. Regardless of whether this is the first new treatment in 20 years for osteosarcoma, it is an effective treatment which saves lives. Â The ICER is a wholly inappropriate basis for a decision on whether or not mifamurtide should be made available.	The treatment effect of a technology is the difference between the duration and state of health or HRQL (including the impact of any adverse effects of treatment) that would be experienced on average by patients receiving the technology and that experienced by the same group were they to receive alternative care. (Guide to the Methods of Technology Appraisal, section 3.2). The Committee noted that based on the magnitude of the additional benefit and associated uncertainty, it was not persuaded that adjuvant chemotherapy with mifamurtide significantly and substantially changes the way that the current need is met (see section 4.3), or that it has been shown to have an appropriate level of effectiveness, given the wide confidence intervals of the hazard ratios (see section 4.7).
Carer 3	Notes	The trial of this drug demonstrated a reduction in mortality of 30% which, given that the current UK survival rate is about 60%, means that around 10 young people would benefit from the treatment and live a more or less normal lifespan. There has been no significant increase in the survival rates for bone cancer in the last 20yrs, now these children are being given a chance and its taken away from them - incredible !!!	Please see detailed response above.
Carer 3	2	What price do you put on the life on your child !!!	Comment noted
Patient 2	Notes	Diagnosed with Osteosarcoma in February 2007, received the standard chemotherapy treatment, which has not progressed in the last 20 years. The hope of a new drug and to better survival rates would be of huge benefit to newly diagnosed patients.	Comment noted

Role*	Section	Comment	Response
Patient 2	1	The Appraisal Committee has considered the relevant clinical trial, but it has failed to take account of important information in that trial. The trial demonstrated a reduction in mortality of 30% which, given that the current UK survival rate is about 60%, means that around 10 young people would benefit from the treatment and live a more or less normal lifespan. The emphasis that NICE places on relative effectiveness leads it to ignore the absolute benefit that 10 more young people with osteosarcoma will survive each year. The other element which NICE has failed to take into account, and we accept that there is no published data on this, is the impact of the illness and premature death of a young person with osteosarcoma on other family members. Â We can say categorically that the impact is profound and remains for many years, seriously and adversely affecting the quality of life of family and friends. Â This impact will undoubtedly impact on the health of the family although this hasn?t been formally assessed.	The treatment effect of a technology is the difference between the duration and state of health or HRQL (including the impact of any adverse effects of treatment) that would be experienced on average by patients receiving the technology and that experienced by the same group were they to receive alternative care. (Guide to the Methods of Technology Appraisal, section 3.2). The Committee noted that based on the magnitude of the additional benefit and associated uncertainty, it was not persuaded that adjuvant chemotherapy with mifamurtide significantly and substantially changes the way that the current need is met (see section 4.3), or that it has been shown to have an appropriate level of effectiveness, given the wide confidence intervals of the hazard ratios (see section 4.7).
Patient 2	2	Regardless of whether this is the first new treatment in 20 years for osteosarcoma, it is an effective treatment which saves lives. The ICER is a wholly inappropriate basis for a decision on whether or not mifamurtide should be made available.	NICE appraises both clinical and cost effectiveness. For both legal and bioethical reasons those undertaking technology appraisals must take account of economic considerations (Social Value Judgements – Principles for the Development of NICE Guidance; principle 5).

Role*	Section	Comment	Response
Patient 2	4	It is worth pointing out that other orphan drugs are not subject to a NICE appraisal and more expensive drugs are in routine use in the UK. It is unacceptable that young people with osteosarcoma are denied a potentially life-saving treatment because of the review mechanism to which it has been subject. NICE?s appraisal should take account of these special circumstances and adjust its cost effectiveness threshold accordingly. One example, which demonstrates very well the different outcomes using different assessment methods, is the provision of the monoclonal antibody eculizumab for the treatment of patients with paroxysmal nocturnal haemoglobinuria. Â Introduced in April 2009 a new central funding stream, the PNH service, was added to the portfolio of the National Commissioning Group. The University of Birmingham undertook a rapid systematic review of the treatment published in 2008 and estimated that the ICERs range likely lies between £0.5M and £1.4M per life year gained for patients like those recruited to clinical trials and between £2.8M and £3.2M per life year gained for all diagnosed patients.	Comment noted. The Committee considered that mifamurtide is indicated for a small patient population with a rare disease, and noted that NICE had not received direction from the Department of Health that treatments for rare conditions (‘orphan’ or ‘ultra-orphan’) should be appraised differently from any other treatments. See FAD section 4.20.
Patient 2	6	Since the population considered young people with a limb amputation is already disabled and if they survive will place further demands on the NHS because of their disabilities, the NICE approach to assessing the value of treatment discriminates against discriminates against them. The young people for whom mifamurtide is effective will live a more or less normal lifespan and as such will need to use the NHS for aspects of their disability as well as illnesses experienced by the general population. While this may not be an unlawful discrimination it is certainly discrimination against the patients because of their age and the additional time they may hope to live.	Comment noted.

Role*	Section	Comment	Response
Patient 2	8	The Appraisal Committee has considered the relevant clinical trial, but it has failed to take account of important information in that trial. The trial demonstrated a reduction in mortality of 30% which, given that the current UK survival rate is about 60%, means that around 10 young people would benefit from the treatment and live a more or less normal lifespan. The emphasis that NICE places on relative effectiveness leads it to ignore the absolute benefit that 10 more young people with osteosarcoma will survive each year. The other element which NICE has failed to take into account, and we accept that there is no published data on this, is the impact of the illness and premature death of a young person with osteosarcoma on other family members. We can say categorically that the impact is profound and remains for many years, seriously and adversely affecting the quality of life of family and friends. This impact will undoubtedly impact on the health of the family although this hasn?t been formally assessed.	The treatment effect of a technology is the difference between the duration and state of health or HRQL (including the impact of any adverse effects of treatment) that would be experienced on average by patients receiving the technology and that experienced by the same group were they to receive alternative care. (Guide to the Methods of Technology Appraisal, section 3.2). The Committee noted that based on the magnitude of the additional benefit and associated uncertainty, it was not persuaded that adjuvant chemotherapy with mifamurtide significantly and substantially changes the way that the current need is met (see section 4.3), or that it has been shown to have an appropriate level of effectiveness, given the wide confidence intervals of the hazard ratios (see section 4.7).
NHS professional 3	Notes	I believe the drug should definitely be made available. My brother had a limb prosthesis fitted (£16,000 worth), only to find that the chemotherapy had only killed 30% of the tumour. The cancer therefore spread after his operation and he died, age 16, 1 year after completing rehab for his knee prosthesis. Surely anything that can help prolong life expectancy and improve young peoples chance of survival would be worth the time and money.	Comment noted

Role*	Section	Comment	Response
Other 8	1	Has all the relevant evidence been taken into account? The Appraisal Committee has considered the relevant clinical trial, but it has failed to take account of important information in that trial. Â The trial demonstrated a reduction in mortality of 30% which, given that the current UK survival rate is about 60%, means that around 10 young people would benefit from the treatment and live a more or less normal lifespan. The emphasis that NICE places on relative effectiveness leads it to ignore the absolute benefit that 10 more young people with osteosarcoma will survive each year.	The Committee considered all the evidence submitted, including evidence from clinical trials, patient and clinical experts, the ERG and manufacturer submissions. It also carefully considered the comments received from consultees and commentators in the response to the ACD. The treatment effect of a technology is the difference between the duration and state of health or HRQL (including the impact of any adverse effects of treatment) that would be experienced on average by patients receiving the technology and that experienced by the same group were they to receive alternative care. (Guide to the Methods of Technology Appraisal, section 3.2). The Committee noted that based on the magnitude of the additional benefit and associated uncertainty, it was not persuaded that adjuvant chemotherapy with mifamurtide significantly and substantially changes the way that the current need is met (see section 4.3), or that it has been shown to have an appropriate level of effectiveness, given the wide confidence intervals of the hazard ratios (see section 4.7).

Role*	Section	Comment	Response
Other 8	2	Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? Trial INT-0133 was an investigator-led trial which NICE acknowledges was designed with the primary endpoint of overall survival but powered for disease?free survival as a two by two factorial design. Â That is, it was designed to be analysed as chemotherapy alone vs chemotherapy with mifamurtide. Â The ERG requested six post-hoc analyses which the study was not designed nor powered to answer. BCRT believes that this post-hoc, unplanned analysis is invalid and the numbers that result are too small to be of relevance, making these analyses unreliable and inappropriate. Notwithstanding the inappropriateness of the analysis, in the single arm comparison of regimen A vs A+ there is evidence, although it is not statistically significant, of benefit for mifamurtide. That it is not statistically significant is entirely explained by the fact that the trial was never powered for this analysis.	Please see above.
Other 8	3	Are the provisional recommendations sound and a suitable basis for guidance to the NHS? The conclusions drawn by the appraisal committee are unsound and based on a post-hoc analysis which in other settings NICE would criticise. Â For the reasons outlined above, the conclusion does not reflect the trial data and hence the recommendation is flawed. The NHS should not decide whether young people can be treated with mifamurtide based on a completely unreliable analysis performed by a technical group without expertise in treating osteosarcoma. It is worth pointing out that other orphan drugs are not subject to a NICE appraisal and more expensive drugs are in routine use in the UK. It is unacceptable that young people with osteosarcoma are denied a potentially life-saving treatment because of the review mechanism to which it has been subject.	Comment noted. Please see above. The Committee considered the most appropriate comparison and the most appropriate analysis of mifamurtide from INT-0133. The Committee concluded that the comparison that best reflected current UK clinical practice was the individual mifamurtide containing regimen (A+) compared with a regimen reflecting UK clinical practice (A). However, for the reasons given in section 4.6 of the FAD, the Committee accepted that the combined analysis of all the INT-0133 data may be more appropriate in determining the effect of adding mifamurtide to the standard UK regimen than the post hoc analysis directly comparing regimen A+ with regimen A. Please see FAD sections 4.7 and 4.8.

Role*	Section	Comment	Response
Other 8	5	Are there any aspects of the recommendations that need particular consideration Since the population considered ? young people with a limb amputation ? is already disabled and if they survive will place further demands on the NHS because of their disabilities, the NICE approach to assessing the value of treatment discriminates against them. The young people for whom mifamurtide is effective will live a more or less normal lifespan and as such will need to use the NHS for aspects of their disability as well as illnesses experienced by the general population. While this may not be an unlawful discrimination it is certainly discrimination against the patients because of their age and the additional time they may hope to live.	The Committee was satisfied that there were no equalities issues in relation to age in this appraisal and that the recommendations were consistent with NICE's obligations under the equalities legislation and the requirement for fairness. See FAD section 4.21.
Other 8	8	Has all the relevant evidence been taken into account? The Appraisal Committee has considered the relevant clinical trial, but it has failed to take account of important information in that trial. ÂThe trial demonstrated a reduction in mortality of 30% which, given that the current UK survival rate is about 60%, means that around 10 young people would benefit from the treatment and live a more or less normal lifespan. The emphasis that NICE places on relative effectiveness leads it to ignore the absolute benefit that 10 more young people with osteosarcoma will survive each year.	The treatment effect of a technology is the difference between the duration and state of health or HRQL (including the impact of any adverse effects of treatment) that would be experienced on average by patients receiving the technology and that experienced by the same group were they to receive alternative care. (Guide to the Methods of Technology Appraisal, section 3.2). The Committee noted that based on the magnitude of the additional benefit and associated uncertainty, it was not persuaded that adjuvant chemotherapy with mifamurtide significantly and substantially changes the way that the current need is met (see section 4.3), or that it has been shown to have an appropriate level of effectiveness, given the wide confidence intervals of the hazard ratios (see section 4.7).

Role*	Section	Comment	Response
Other 9	1	Mifamurtide has shown that it offers almost a one-third reduction in the risk of dying from the disease, for those patients who have had successful surgery. This is inarguable. It was accepted when EMA (European Medicines Agency) awarded mifamurtide its license. Also, there are adults in the United States who were treated with this drug as children years ago and are now achieving their ambitions and leading normal lives. Surely they are evidence enough that the drug works?	Comment noted. The criteria used by other organisations to recommend a technology may be different from those used by NICE.
Other 9	2	Has all the relevant evidence been taken into account? The Appraisal Committee has considered the relevant clinical trial, but it has failed to take account of important information in that trial. Â The trial demonstrated a reduction in mortality of 30% which, given that the current UK survival rate is about 60%, means that around 10 young people would benefit from the treatment and live a more or less normal lifespan. The emphasis that NICE places on relative effectiveness leads it to ignore the absolute benefit that 10 more young people with osteosarcoma will survive each year. The other element which NICE has failed to take into account, and we accept that there is no published data on this, is the impact of the illness and premature death of a young person with osteosarcoma on other family members. Â We can say	The Committee considered all the evidence submitted, including evidence from clinical trials, patient and clinical experts, the ERG and manufacturer submissions. It also carefully considered the comments received from consultees and commentators in the response to the ACD. The treatment effect of a technology is the difference between the duration and state of health or HRQL (including the impact of any adverse effects of treatment) that would be experienced on average by patients receiving the technology and that experienced by the same group were they to receive alternative care. (Guide to the Methods of Technology Appraisal, section 3.2). The Committee noted that based on the magnitude of the additional benefit and associated uncertainty, it was not persuaded that adjuvant chemotherapy with mifamurtide significantly and substantially changes the way that the current need is met (see section 4.3), or that it has been shown to have an appropriate level of effectiveness, given the wide confidence intervals of the hazard ratios (see section 4.7). The Committee considered whether there were any health-related quality of life benefits that may not have been adequately captured in the estimated gained used in the QALY calculation. The

Role*	Section	Comment	Response
		categorically that the impact is profound and remains for many years, seriously and adversely affecting the quality of life of family and friends. Â This impact will undoubtedly impact on the health of the family although this hasn?t been formally assessed. (contd in next comment box)	Committee heard from the patient experts that supporting a young person with osteosarcoma has a substantial impact on the health-related quality of life of the family and friends of the person affected, particularly where treatment is not successful. For example, parents and siblings may develop mental health problems and family relationships may be strained. The Committee concluded that these are important issues affecting the health-related quality of life of those close to the person with osteosarcoma, but noted that these issues are not unique to the condition. For further details see FAD section 4.18.
Other 9	3	We note that the comment by Andrew Dillon about the outcome of the appraisal. It is important to remember, though, that other, effective treatments are available in the NHS for treating this condition. We would be very interested to learn what are these other treatments which deliver the same benefit as mifamurtide because we do not know of any. To the best of our knowledge, there is no alternative to mifamurtide. (contd in next box)	The patient experts stated that there had been few developments that had improved optimal treatment of osteosarcoma over the past 20 years. The Committee noted that the clinical specialists stated that the only development in the past 10 years had been the introduction of high-dose methotrexate and better implementation of treatment regimens, which had together improved survival rates by 10–20%, bringing them in line with those in Europe and the USA. See FAD section 4.3.

Role*	Section	Comment	Response
Other 9	4	BCRT absolutely refutes the Appraisal Committee?s interpretation of the clinical effectiveness data considered. Trial INT-0133 was an investigator-led trial which NICE acknowledges was designed with the primary endpoint of overall survival but powered for disease?free survival as a two by two factorial design. That is, it was designed to be analysed as chemotherapy alone vs chemotherapy with mifamurtide. Â The ERG requested six post-hoc analyses which the study was not designed nor powered to answer. BCRT believes that this post-hoc, unplanned analysis is invalid and the numbers that result are too small to be of relevance, making these analyses unreliable and inappropriate. Notwithstanding the inappropriateness of the analysis, in the single arm comparison of regimen A vs A+ there is evidence, although it is not statistically significant, of benefit for mifamurtide. That it is not statistically significant is entirely explained by the fact that the trial was never powered for this analysis. contd in next comments box	The Committee considered the most appropriate comparison and the most appropriate analysis of mifamurtide from INT-0133. The Committee concluded that the comparison that best reflected current UK clinical practice was the individual mifamurtide containing regimen (A+) compared with a regimen reflecting UK clinical practice (A). However, for the reasons given in section 4.6 of the FAD, the Committee accepted that the combined analysis of all the INT-0133 data may be more appropriate in determining the effect of adding mifamurtide to the standard UK regimen than the post hoc analysis directly comparing regimen A+ with regimen A. Please see FAD sections 4.7 and 4.8.

Role*	Section	Comment	Response
Other 9	5	The BCRT is prepared to provide a more detailed rebuttal of the ERGs conclusions about efficacy if requested. The utility values for the use of mifamurtide are based on EQ5D which is a measure completely inappropriate to the population being considered. The tool is too blunt to reflect the ability of young people to adapt to disability and whose life is not measured in the way that adults might measure life. EQ5D falsely reduces the quality of life of people with osteosarcoma and should not be used in this setting. Regardless of whether this is the first new treatment in 20 years for osteosarcoma, it is an effective treatment which saves lives. The ICER is a wholly inappropriate basis for a decision on whether or not mifamurtide should be made available. The conclusions drawn by the appraisal committee are unsound and based on a post-hoc analysis which in other settings NICE would criticise. For the reasons outlined above, the conclusion does not reflect the trial data and hence the recommendation is flawed. (contd in next box)	Comment noted. See detailed response above. NICE appraise clinical and cost effectiveness. For both legal and bioethical reasons those undertaking technology appraisals must take account of economic considerations (Social Value Judgements – Principles for the Development of NICE Guidance; principle 5).

Role*	Section	Comment	Response
Other 9	6	The NHS should not decide whether young people can be treated with mifamurtide based on a completely unreliable analysis performed by a technical group without expertise in treating osteosarcoma. It is worth pointing out that other orphan drugs are not subject to a NICE appraisal and more expensive drugs are in routine use in the UK. Â It is unacceptable that young people with osteosarcoma are denied a potentially life-saving treatment because of the review mechanism to which it has been subject. Â NICE's appraisal should take account of these special circumstances and adjust its cost effectiveness threshold accordingly. One example, which demonstrates very well the different outcomes using different assessment methods, is the provision of the monoclonal antibody eculizumab for the treatment of patients with paroxysmal nocturnal haemoglobinuria.	The Committee considered the most appropriate comparison and the most appropriate analysis of mifamurtide from INT-0133. The Committee concluded that the comparison that best reflected current UK clinical practice was the individual mifamurtide containing regimen (A+) compared with a regimen reflecting UK clinical practice (A). However, for the reasons given in section 4.6 of the FAD, the Committee accepted that the combined analysis of all the INT-0133 data may be more appropriate in determining the effect of adding mifamurtide to the standard UK regimen than the post hoc analysis directly comparing regimen A+ with regimen A. Please see FAD sections 4.7 and 4.8. The Committee considers that treatments for rare conditions should be appraised in the same way as any other treatments. NICE appraises topics that are formally referred by the Department of Heath. The Committee considered that mifamurtide is indicated for a small patient population with a rare disease, and noted that NICE had not received direction from the Department of Health that treatments for rare conditions ('orphan' or 'ultra-orphan') should be appraised differently from any other treatments (see FAD section 4.20).
Other 9	7	Introduced in April 2009 a new central funding stream, the PNH service, was added to the portfolio of the National Commissioning Group. The University of Birmingham undertook a rapid systematic review of the treatment published in 2008 and estimated tha	Comment noted

Role*	Section	Comment	Response
Other 9	8	Mifamurtide has shown that it offers almost a one-third reduction in the risk of dying from the disease, for those patients who have had successful surgery. This is inarguable. It was accepted when EMA (European Medicines Agency) awarded mifamurtide its license. Also, there are adults in the United States who were treated with this drug as children years ago and are now achieving their ambitions and leading ?normal? lives. Surely they are evidence enough that the drug works?	The Committee considered the most appropriate comparison and the most appropriate analysis of mifamurtide from INT-0133. The Committee concluded that the comparison that best reflected current UK clinical practice was the individual mifamurtide containing regimen (A+) compared with a regimen reflecting UK clinical practice (A). However, for the reasons given in section 4.6 of the FAD, the Committee accepted that the combined analysis of all the INT-0133 data may be more appropriate in determining the effect of adding mifamurtide to the standard UK regimen than the post hoc analysis directly comparing regimen A+ with regimen A. Please see FAD sections 4.7 and 4.8. Comment noted. The criteria used by other organisations to recommend a technology may be different from those used by NICE.
Public 6	3	After having had the experience of a friends daughter go through treatment and then die of osteosarcoma and having another of my friends go through treatment for osteosarcoma who is thankfully still with us, any evidence that mifamurtide will increase survival rates for osteosarcoma is welcome. Â Surely if it means one person and one family doesnt have to go through the trauma of losing someone they love then its worth it.	Comment noted

Role*	Section	Comment	Response
NHS professional 4	1	I am particularly concerned by the Appraisal committees conclusions in relation to efficacy. I have had extensive opportunity to review the data from the key INT trial. The trial was designed with the primary aim of improving survival for this young population. The trial was designed as a factorial design to test the efficacy of ifosfamide and mifamurtide. The data is clear. Mifamurtide reduces mortality by approximately 30%. The appraisal committee has based its conclusion on a series of post hoc unplanned analyses. This is poor statistical practice and unacceptable particularly as the study investigators have published evidence which refutes any suggestion of an interaction. (Meyers et al 2008). In addition there is extensive evidence that the A+ arm had a much higher number of patients with poor histological response compared to all other arms. This was a problem with the original study design but should not be used to prevent affected young patients having access to this agent I am clear that mifamurtide is expensive and I would prefer it to be cheaper so that it could be made available to patients	Comment noted. The Committee considered the most appropriate comparison and the most appropriate analysis of mifamurtide from INT-0133. The Committee concluded that the comparison that best reflected current UK clinical practice was the individual mifamurtide containing regimen (A+) compared with a regimen reflecting UK clinical practice (A). However, for the reasons given in section 4.6 of the FAD, the Committee accepted that the combined analysis of all the INT-0133 data may be more appropriate in determining the effect of adding mifamurtide to the standard UK regimen than the post hoc analysis directly comparing regimen A+ with regimen A. Please see FAD sections 4.7 and 4.8.

Role*	Section	Comment	Response
NHS professional 4	3	Most of my comments pertinent to this section are included in section 1. Whilst NICE is primarily concerned with cost benefit I am particularly concerned about the interpretation of efficacy based on unplanned post hoc analysis after the investigators have presented evidence that there was no interaction between ifosfamide and mifamurtide As previously stated The only additional point I would add is that the committee has been partial in which evidence it was prepared to accept it accepted post hoc analysis of underpowered assessment of A+ v A but did not apparently accept the analysis which demonstrated that in patients 16 years of age A+ and B+ were equally effective for both EFS and OS when compared to A- and B- This occurred because there was no histological response imbalance in patients less than 16years. All the histological imbalance was in those over the age of 16years. The committee could and should have commented more favourably about this. It was prepared to state the lack of impact of mifamurtide in those over 16 without making it clear to less informed observers that this was the group with the major imbalance in histological response. Lastly I wish to comment on Andrew Dillons reported observation that there is an alternative to mifamurtide. There isnt.	Please see detailed response above.

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NHS professional 4	8	I am particularly concerned by the Appraisal committees conclusions in relation to efficacy. I have had extensive opportunity to review the data from the key INT trial. The trial was designed with the primary aim of improving survival for this young population. The trial was designed as a factorial design to test the efficacy of ifosfamide and mifamurtide. The data is clear. Mifamurtide reduces mortality by approximately 30%. The appraisal committee has based its conclusion on a series of post hoc unplanned analyses. This is poor statistical practice and unacceptable particularly as the study investigators have published evidence which refutes any suggestion of an interaction. (Meyers et al 2008). In addition there is extensive evidence that the A+ arm had a much higher number of patients with poor histological response compared to all other arms. This was a problem with the original study design but should not be used to prevent affected young patients having access to this agent I am clear that mifamurtide is expensive and I would prefer it to be cheaper so that it could be made available to patients	Please see detailed response above.