FDA Briefing Document

May 9, 2007
Oncologic Drugs Advisory Committee

NDA 022092
Mifamurtide
(muramyl tripeptide phosphatidyl ethanolamine, MTP-PE)
INT 0133 Cooperative Group Protocol
Immuno-Designed Molecules, Inc (IDM Pharma, Inc.)

Division of Biologic Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research, U.S.
U.S. Food and Drug Administration

Overview and Executive Summary

The review team and Division Director find that the Applicant, IDM, has failed to demonstrate that their product, mifamurtide (MTP-PE), provides substantial evidence of efficacy. The Applicant presents the results of a single, large, multicenter study conducted in approximately 600 children and young adults with newly diagnosed, resectable, high grade osteosarcoma, in whom multi-agent adjuvant chemotherapy was administered following neoadjuvant chemotherapy and surgical resection. Ordinarily, two Phase 3 studies are required for licensure. If a single randomized trial to is intended to support an NDA, the trial should be well designed, well conducted, internally consistent and provide statistically persuasive efficacy findings so that a second trial would be ethically or practically impossible to perform, as discussed in the May 1998 "Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products".

The study was designed with the following goals: (1) to demonstrate that a chemotherapy regimen containing ifosfamide results in superior Disease-free Survival (DFS) compared to the current standard-of-care adjuvant chemotherapy regimen (cisplatin, methotrexate, and doxorubicin); (2) to demonstrate superior DFS for MTP-PE plus standard chemotherapy over the standard regimen alone; and (3) to demonstrate superior DFS for the ifosfamide-containing regimen plus MTP-PE over the standard chemotherapeutic regimen. The design of the study was not discussed with FDA prior to initiation. Following completion of the study, the Applicant met with FDA on multiple occasions during which the FDA informed the Applicant of the concerns regarding study design, data collection, and analytic approach. It should be noted that the majority of these flaws were correctable and might have been rectified if an end-of-Phase 2 meeting had been held prior to study initiation.

The study demonstrated that (1) the addition of MTP-PE to standard treatment (Regimen A, the standard regimen) failed to result in superior DFS compared to the standard regimen alone (HR 0.99, p=0.96); (2) the experimental ifosfamide-containing regimen (Regimen B) was not superior to the standard regimen and the observed trend suggested poorer DFS (HR 1.18, p=0.35); and (3) the ifosfamide-containing regimen plus MTP-PE was not superior to the standard regimen (HR 0.73, p=0.11). The FDA has concluded, as did the authors who published the study results in the Journal of Clinical Oncology (Meyers PA et al. J Clin Oncol 23:2004-11, 2005), that it is inappropriate to pool results across study arms because of the qualitative differences in effects on DFS when MTP-PE is added to the standard chemotherapy as compared to when it is added to the novel chemotherapy regimen and because the results are driven by the comparison of the addition of MTP-PE to a chemotherapy regimen that performed worse than the standard chemotherapy regimen. Even if one concludes that this analytic approach is valid, the results are not robust, such that using FDA's modified

dataset (which was modified for agreement with data contained in the submitted case report forms), the result is not significant.

The findings on DFS presented by the Applicant are not robust, as demonstrated by lack of consistency across chemotherapeutic regimens, and are influenced by patients who were removed from study treatment prior to initiation of MTP-PE, by discrepancies between data in the case report forms and the electronic datasets, by lack of clarity on the timing of interim and final analyses, and by lack of a systematic and comprehensive approach to data collection over time.

With regards to the Applicant's analyses of overall survival, FDA finds that there is not sufficient evidence of a survival advantage for the addition of MTP-PE to the standard chemotherapeutic regimen. The analyses presented by the Applicant are not robust and are subject to the same concerns regarding data collection and analytic approach as those discussed in regard to DFS. Many patients not known to have died had their follow-up discontinued long before the analysis cutoff date. In addition, there is substantial concern regarding informative censoring of patients for whom there is no survival follow-up after documentation of disease recurrence.

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Appendix:

Myers PA, Schwartz CL Krailo M, Kleinerman ES, Betcher D, Berstein ML, Conrad E, Ferguson W, Gebhardt M, Goorin AM, Harris MB, Healy J, Huvos A, Link M, Montebello J, Nadel H, Nieder M, Sato J, Siegal G, Weiner M, Wells R, Wold L, Womer R, Grier H: Osteosarcoma: a randomized, prospective trial of the addition of ifosfamide and/or muramyl tripeptide to cisplatin, doxorubicin and high-dose methotrexate. J Clin Oncol 23: 2004-2011, 2005

Abbreviations Used in Document

A	Regimen A (MAP) without MTP-PE
A+	Regimen A (MAP) with MTP-PE
B	Regimen B (MAP with addition of ifosfamide) without MTP-PE
B+	Regimen B (MAP with addition of ifosfamide) with MTP-PE
BLA	Biologic License Application
CCG	Children's Cancer Group
CDDP	Cisplatin
COG	Children's Oncology Group
CRFs	Case Report Forms
DFS	Disease-free survival
DOXO	Doxorubicin
FDA	Food and Drug Administration
HDMTX	High dose methotrexate
HR	Hazard ratio
IDM	Immuno-Designed Molecules, Inc (IDM Pharma, Inc.)
IFOS	Ifosfamide
IND	Investigational new drug
ITT	Intent to treat
IRB	Institutional review board
L-MTP-PE	Liposomal Mifamurtide (muramyl tripeptide phosphatidyl ethanolamine)
MAP	Cisplatin, methotrexate, and doxorubicin [methotrexate, anthracycline (Adriamycin), platinum]
mg/m2	Milligram per meter square
MTP-PE	Mifamurtide (muramyl tripeptide phosphatidyl ethanolamine)
MTX	Methotrexate
NDA	New Drug Application
ODAC	Oncology Drug Advisory Committee
OS	Overall survival;.
POG	Pediatric Oncology Group
Reg A	Regimen A (MAP) without MTP-PE
Reg A+	Regimen A (MAP) with MTP-PE
Reg B	Regimen B (MAP with addition of ifosfamide) without MTP-PE
Reg B+	Regimen B (MAP with addition of ifosfamide) with MTP-PE

A. Background

1. Proposed Indication

"MTP-PE is indicated for the treatment of newly diagnosed resectable high grade osteosarcoma following surgical resection in combination with multi-agent chemotherapy"

2. Background on Osteosarcoma

Osteosarcoma is a bone tumor that occurs predominantly in adolescents and young adults. It accounts for about 5% of childhood tumors with approximately 400 cases diagnosed each year in the United States. Osteosarcoma is the second most common primary malignancy of bone, and it represents the fifth most common malignancy among adolescents and young adults aged 15 to 19 years. The most frequent primary sites are the distal femur and proximal tibia, and 15-20% of patients have clinically detectable metastases at the time of diagnosis.

Before the introduction of effective chemotherapy, the 2-year overall survival of patients with osteosarcoma was in the range of 15-20%. Multi-agent chemotherapy dramatically improved the outcome and results in 3-year disease-free survival (DFS) rates of 60-70% for patients without clinically detectable metastases at diagnosis. The current standard of care consists of a combination of effective systemic chemotherapy and complete resection of all clinically detectable disease. Randomized clinical trials have established that both neoadjuvant and adjuvant chemotherapy are effective in preventing relapse in patients with clinically non-metastatic tumors. The standard arm of the ongoing phase III International Intergroup study "A randomized trial of the European and American Osteosarcoma Study Group to optimize treatment strategies for resectable osteosarcoma based on histological response to pre-operative chemotherapy" consists of neoadjuvant chemotherapy with methotrexate, doxorubicin, and cisplatin (MAP), followed by definitive surgery and subsequent adjuvant MAP chemotherapy.

Established prognostic factors for osteosarcoma include site and size of the primary tumor, presence or absence of clinically detectable metastatic disease, adequacy of resection, and degree of necrosis observed in tumors following initial chemotherapy. Among tumors of the extremity, distal sites have a more favorable prognosis than proximal sites. Axial skeleton primary tumors are associated with the greatest risk of progression and death. Larger tumors have a worse prognosis than smaller tumors. Serum lactate dehydrogenase, which also correlates with outcome, is a likely surrogate for tumor volume.

3. Background on MTP-PE

MTP-PE is a liposomal formulation of muramyl tripeptide phosphatidyl ethanolamine, a fully synthetic lipophilic derivative of the muramyl dipeptide component of the Mycobacterium cell walls used in Freund's complete adjuvant. MTP-PE is encapsulated in multi-lameller liposomes and when delivered to macrophages stimulates tumoricidal activity. MTP-PE was

developed as a biological response modifier by Ciba-Giegy in the early 80s. Clinical development focused on osteosarcoma, as animal models suggested anti-tumor activity.

4. Regulatory Background

January 1988	Original BB IND 2803 application submitted by Ciba-Geigy.
November 1991	Study INT 0133, "Trial of Doxorubicin, Cisplatin, and Methotrexate with and without Ifosfamide and with and without Muramyl Tripeptide Phosphatidyl Ethanolamine (MTP-PE) for Treatment of Osteogenic Sarcoma: A Phase III Intergroup Study (Protocol CCG-7921, POG 9351, INT-0133)" submitted to IND.
November 1993	First patient enrolled on Study INT 0133.
July 1996	Sponsorship of IND transferred to Jenner Technologies
November 1997	Last patient enrolled on Study INT 0133.
June 1997	Protocol amendment 7 containing "final" statistical section implemented.
June 2001	Orphan designation for the treatment of children and adolescents with osteosarcoma granted for MTP-PE (#01-1433).
April 2003	Sponsorship of IND transferred to Immuno-Designed Molecules Inc. (IDM)
October 2003	IDM requested a Pre-BLA meeting with FDA to discuss the acceptabil MTP-PE.

On Nov. 26, 2003 IDM requested the meeting be postponed.

July 2004 IDM requested Fast Track Designation for MTP-PE for use in childhood and adolescent osteosarcoma. The request was denied.

September 2004 IDM and FDA met to discuss Study INT 0133, including additional animal, safety, and drug exposure data.

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November 2004	IDM and FDA met to discuss CMC requirements for license application.
April 2005	IDM and FDA met to discuss the suitability of Study INT 0133 efficacy data to support licensure; the acceptability of available non-GLP animal data, the size of the safety database available to support drug safety; and the Fast Track designation request.
June 2005	IDM requested reclassification of MTP-PE as a drug. The request was granted and BB IND 2803 was transferred to the Division of Drug Oncology Products as IND 72870.
February 2006	At a Pre-NDA meeting FDA responded to IDM question concerning the adequacy of the material to support filing of an NDA at the time the NDA was submitted.
December 2006	NDA 022-092 submitted for licensure of MTP-PE.

5. Issues for ODAC to Consider

The Applicant states that study INT 1033 has demonstrated a significant prolongation of disease-free survival (DFS) and overall survival (OS) based on an integrated analysis that compared pooled data from study Regimens A and B and pooled data from study Regimens A + MTP-PE and B + MTP-PE. The DFS results are driven by an experimental arm (Regimen B) that performed worse than the current standard of care. In addition the Applicant's primary analysis is not statistically significant when using the modified data derived from FDA review of CRFs. In regard to overall survival, as no prespecified statistical plan for the analysis of overall survival was contained in any version of the INT 0133 protocol, no meaning can be derived from the nominal p-value of the Applicant's *post hoc* overall survival analysis. In addition, the Applicant's follow-up for deaths is inadequate to permit the performance of a meaningful analysis of overall survival.

In light of the qualitative differences in outcome between the 3 experimental study arms (Regimens A+, B and B+) and the control arm (Regimen A, which represents the current standard of care), is the Applicant's pooled analyses of INT 1033 DFS data appropriate to determine the efficacy of MTP-PE?

Do the results of study INT 0133 provide substantial evidence for the efficacy of MTP-PE in the treatment of patients with resectable and non metastatic osteosarcoma? Are the effects on DFS sufficiently robust and so compelling to justify marketing approval of MTP-PE based on this single trial?

B. Study Design of INT 0133

1. Description of Trial

"Trial of Doxorubicin, Cisplatin, and Methotrexate with and without Ifosfamide and with and without Muramyl Tripeptide Phosphatidyl Ethanolamine (MTP-PE) for Treatment of Osteogenic Sarcoma: A Phase III Intergroup Study (Protocol CCG-7921, POG 9351, INT 0133)", subsequently referred to as INT 0133, was a prospective multi-center randomized study conducted by the two major American pediatric cooperative groups, the Childrens' Cancer Group (CCG) and the Pediatric Oncology Group (POG) at 164 sites. Two different cohorts were studied. The first cohort comprised patients with non-metastatic and resectable osteosarcoma. Both CCG and POG participated in this portion of the trial. The second cohort comprised patients with metastatic or non-resectable osteosarcoma. Only CCG institutions participated in this portion of the trial. IDM is supporting its claim for the efficacy of MTP-PE based on the outcome of the non-metastatic and resectable osteosarcoma cohort of patients.

Trial Schema

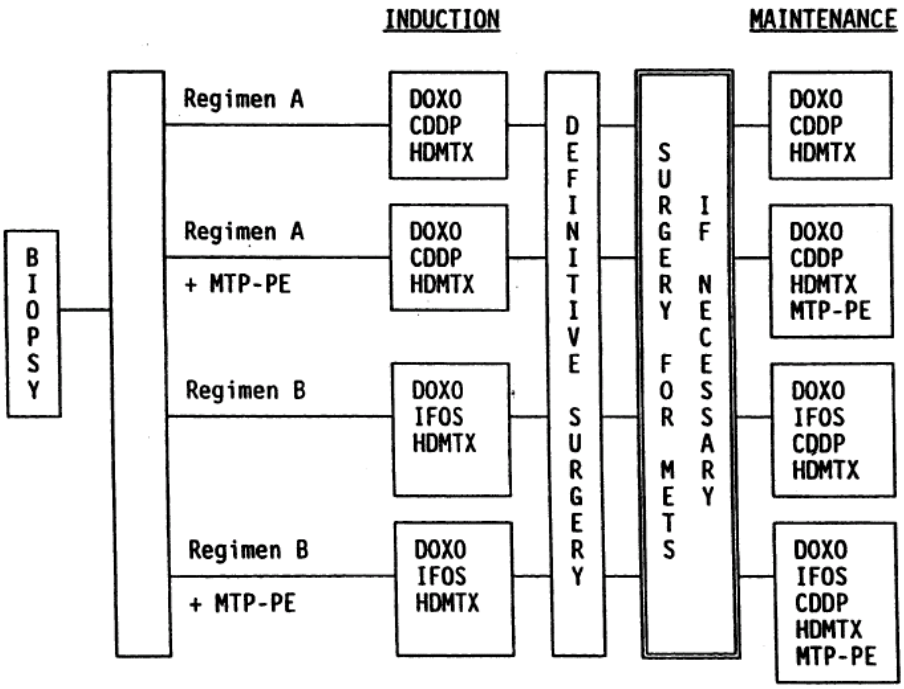
INT 0133 was a multi-center randomized open label study. Two therapy-related experimental questions were investigated in this study.

1. A comparison of two chemotherapeutic regimens: standard arm (Regimen A: high-dose methotrexate, cisplatin, and doxorubicin) and an experimental arm (Regimen B: a modification of the standard arm with the addition of ifosfamide).

2. The contribution of MTP-PE given in combination with the chemotherapeutic regimens - Regimen A with or without MTP-PE and Regimen B with or without MTP-PE.

Patients were randomized at the time of registration to one of four arms. Randomization was stratified by lactate dehydrogenase (LDH), tumor location, and prior amputation. MTP-PE was scheduled to be administered during maintenance therapy following surgical resection. See Figures 1, 2, and 3 below. For Figures 2 and 3, please note that Regimens A and B were identical to Regimens A+ and B+ (displayed) except for the absence of administration of MTP-PE.

Figure 1. Overall Study Schema Study INT 0133*



*Note: No patients in the study INT 0133 Intent to Treat (ITT) population required surgery to remove metastases.

Figure 2. Regimen A+: Standard Therapy Plus MTP-PE

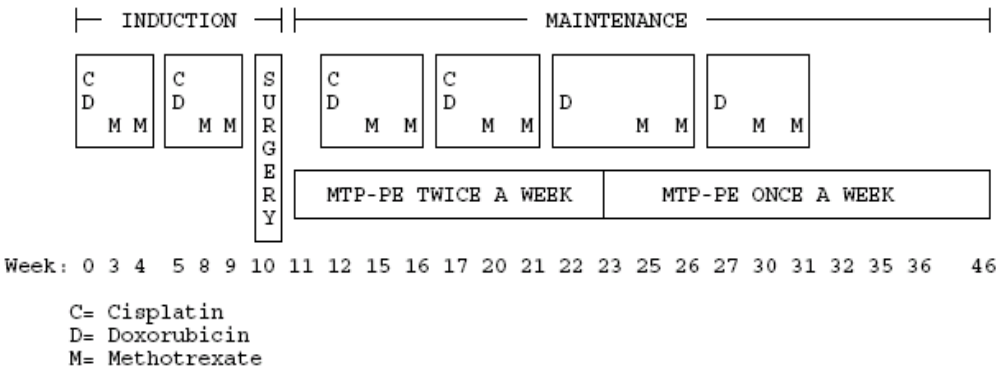
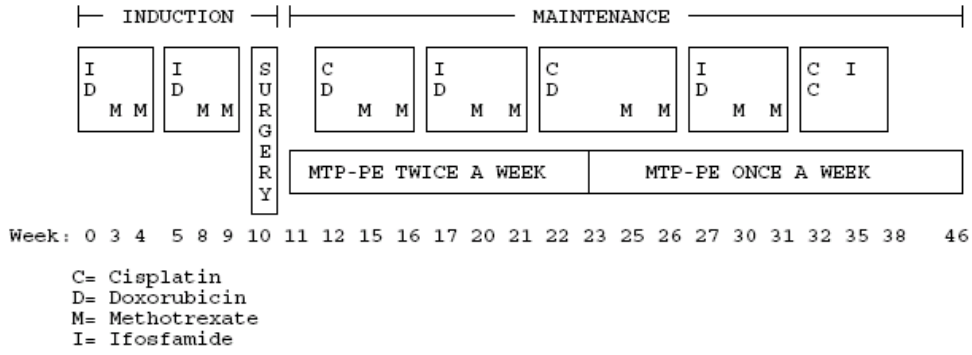


Figure 3. Regimen B+: Ifosfamide-Enhanced Chemotherapy Plus MTP-PE



The initial dose of MTP-PE was 2 mg/m^2 and was to be administered without chemotherapy. Subsequent doses were to be escalated (2 mg/m^2 + 1 mg; 2 mg/m^2 + 2 mg) until a biologic response was observed. A biologic response was defined as fever, chills or elevated C-reactive protein. Subsequent doses were to be administered twice a week for 12 weeks then weekly for 24 weeks with adjuvant chemotherapy, for a total of 48 total doses.

2. Potential Endpoints

In the original protocol for study INT 0133, no primary and secondary endpoints were explicitly specified. No detailed prospective statistical analysis plan was developed prior to the designated final analysis. Consequently, the intended primary endpoint of INT 0133 had to be inferred from evidence found in the protocol.

The following sections of the protocol are relevant to retrospectively determining the pre-specified endpoints of the trial:

"1 Specific Aims:

1.1 To improve the survival of patients with osteogenic sarcoma.

1.2 To compare the results of a prospective randomized trial of two chemotherapeutic regimens in the treatment of osteogenic sarcoma.

1.3 To compare the results of a combined chemotherapeutic regimen (high-dose methotrexate, cisplatin, and doxorubicin) given pre-operatively and post-operatively to a similar regimen using the same drugs and adding ifosfamide.

1.4 To test whether the early introduction of ifosfamide results in a higher rate of good histologic response at the time of definitive surgery.

1.5 To determine whether histologic response assessed after longer pre-operative chemotherapy with more drugs predicts disease-free survival with the same power as observed in CCG-782 which used a shorter period of pre-operative chemotherapy and fewer drugs.

1.6 To determine whether liposomal muramyl tripeptide phosphatidyl ethanolamine (MTP-PE), a stimulator of macrophage function, can improve <u>disease-free survival</u> for patients with osteogenic sarcoma. (emphasis added)

1.7 To determine whether multiple drug resistance gene-encoded P-glycoprotein expression is useful for determining prognosis or assigning therapy."

"15 Statistical Considerations"

"15.3 The major questions which will determine the required accrual time and sample size are:

i) Do the 2 arms determined by the MTX + CDDP + DOXO ± IFOS induction randomization differ with respect to DFS?

ii) Do the 2 arms determined by the ± MTP-PE maintenance randomization differ with respect to DFS?"

"15.8 DFS and survival will be masked until accrual has ended and all patients have completed therapy."

The information and assumptions used in the original calculations of sample size and trial duration indicate that INT 0133 was powered to detect effects on DFS. In addition, in section 15.3 quoted above, both "major" questions i) and ii) were to be addressed by stratified log rank tests. Therefore, DFS appears to be the prespecified primary endpoint for study INT 0133. Overall survival (OS) can be inferred to be an additional endpoint based on the references to survival in the "Specific Aims" and "Statistical Considerations" sections of the protocol. However, no prespecified plan for overall survival analysis was included in the protocol.

3. Study Population

Inclusion Criteria

- Patients with newly diagnosed (≤ 1 month) malignant high-grade osteosarcoma of bone
- ≤ 30 years of age
- Normal Organ Function - Renal, Liver, Cardiac
- IRB approved protocol with signed consent

Exclusion Criteria

- Low grade osteosarcoma, parosteal or periosteal sarcoma
- Radiation-induced sarcoma
- Pre-malignant bony lesion (Paget's disease)
- Previous chemotherapy or radiotherapy
- Metastatic or non-resectable – POG ineligible

4. Efficacy and Safety Assessments

DFS was to be determined by periodic physical exam and chest x-ray evaluations. There was no central review or confirmation of this endpoint. After therapy was completed, the protocol specified that patients were to be evaluated every 3 months for 1 year, every 6 months for 2 years, then yearly.

Safety assessments were to be collected on end-of-phase/course report forms during therapy and on disease status and event forms when patients were no longer receiving protocol therapy. During therapy, grade 3 and 4 toxicities as defined by the CCG toxicity scale were to be collected. Myelotoxicity was not to be collected unless it led to a delay in therapy. The highest creatinine documented during the course was to be collected. During treatment and follow up phases, selected toxicities and complications specified in a list on the case report form were also to be collected (for example, auditory deficit, visual abnormality, neuropsychological deficit, significant pain, etc.).

5. Statistical Planning

In the original protocol, no primary and secondary endpoints were explicitly specified. The protocol stated that the effect of MTP-PE on DFS was to be analyzed by stratified log-rank test. In this NDA submission, the Applicant considers DFS as the primary endpoint and OS as the secondary endpoint. The primary patient group in this study, the Intent to Treat (ITT) population, was defined as patients randomized and having resectable osteosarcoma with no clinical signs of metastatic disease and with tumor considered to be resectable.

The original protocol assumed a long term DFS of 60% in the pooled MTP-PE containing arms as compared to 72% in the pooled non-MTP-PE containing arms. With this assumption, a total of 585 patients (3.9 years of accrual) and two years of follow-up are

required to demonstrate superiority of the pooled MPT-PE containing arms compared to the pooled non-MTP-PE containing arms in DFS with a two-sided significance level of .05 and power of 80%. IDM later converted the information needed (a total of 585 patients, 3.9 years of accrual, and two years of follow-up) to a total event number of 167.

An interim analysis was performed in September 1996 without any consideration of a Type I error rate adjustment. Protocol Amendment 7 on 6/16/97 contained revised statistical planning. It stipulated that two additional interim analyses would be performed using the methods of Lan and DeMets. The first additional interim analysis had been performed in February 1997. If the test comparing the chemotherapeutic or biological interventions had had a nominal p value< 0.011, the study would have been nominated for possible termination of randomization. The second additional interim analysis would be performed in September 1997. If the test comparing the chemotherapeutic or biological interventions had a nominal p value < 0.013, the study would be nominated for possible termination of randomization. At the final analysis, a nominal p value <0.040 would be considered statistically significant.

6. Trial Design Issues

Although randomization of patients to receive or not receive MTP-PE was performed at study entry, MTP-PE administration was delayed until maintenance. As a result, approximately 10% of patients enrolled and randomized to regimens containing MTP-PE did not enter the maintenance phase of therapy and therefore received no administration of MTP-PE. A number of DFS and OS events occurred in these patients. The impact of this trial design flaw on the study results will be discussed in Section C "FDA Assessment of INT 1033", subsection 1, and in the Efficacy section.

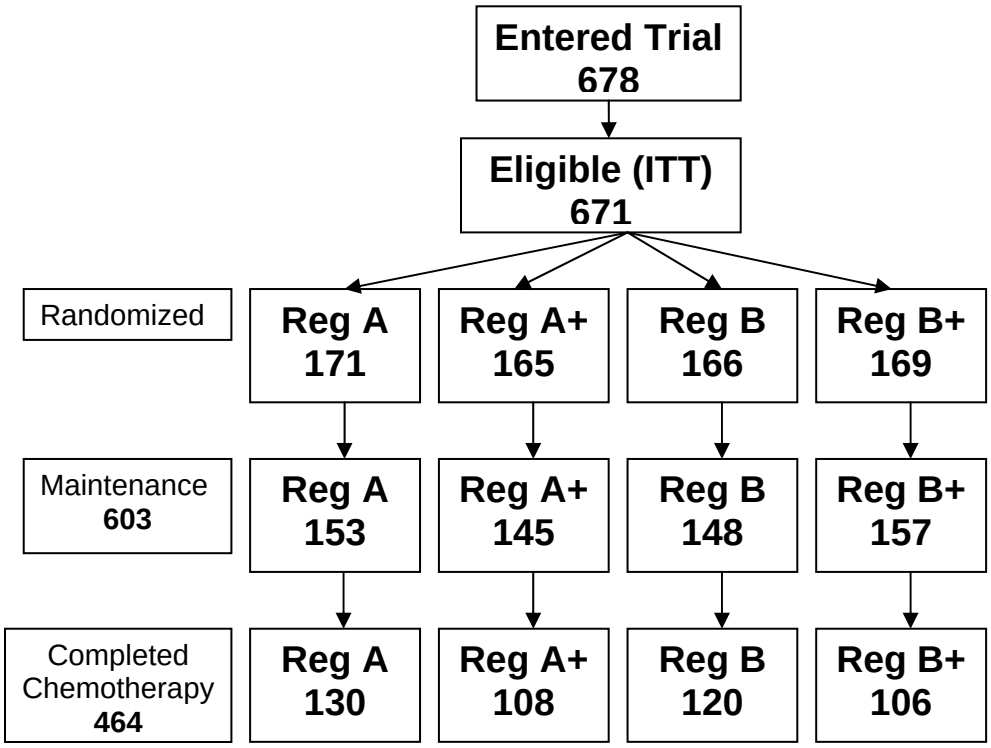
C. Review Issues Regarding INT 0133

1. Assessment of Study Conduct and Integrity and Adequacy of Data Submitted

Patient Disposition

Study INT 0133 accrued patients from October 1993 to November 1997, enrolling 678 patients to the resectable and non-metastatic high grade osteosarcoma cohort. At the February 22, 2006 pre-NDA meeting FDA agreed with IDM that the intent to treat (ITT) population was to include randomized patients with newly diagnosed, non-metastatic resectable osteosarcoma at study entry. Based on this definition, for the FDA analyses 4 patients with ineligible diagnoses (lymphoma, high grade mesenchymal chondrosarcoma, chondrosarcoma, chondroblastic osteosarcoma) and a patient determined to have metastatic disease at diagnosis were removed from the ITT population. In addition, the FDA analyses excluded two patients determined during audits not to have appropriate IRB approval. The result of randomization and disposition of patients is summarized in Figure 4 presented below.

Figure 4. Disposition as Determined by FDA Reviewer of Patients Entered in Non-metastatic Resectable Cohort



Imbalance in Events Due to Trial Design Flaw

Although randomization of patients to receive or not receive MTP-PE was performed at study entry, it is important to note that MTP-PE administration was delayed until the maintenance phase of the protocol. As a result of this design flaw, approximately 10% of patients did not enter the maintenance phase of therapy. Patients assigned to study regimens containing MTP-PE who did not enter the maintenance phase received no MTP-PE. The number of DFS events and the number of deaths in the subset of patients who did not enter the maintenance phase were not balanced between the arms containing MTP-PE and the arms not containing MTP-PE. Forty three patients (26 in arms not containing MTP-PE and 17 in arms containing MTP-PE) who did not enter the maintenance phase are known to have had a DFS event (see Table 1). Twenty eight patients (18 in arms not containing MTP-PE and 10 in arms containing MTP-PE) who did not enter the maintenance phase are known to have died (see Table 2).

These events are not attributable to regimen assignment and represent statistical "noise" occurring before the possible initiation of MTP-PE administration that by chance favored the MTP-PE containing arms. Although analyses of the ITT population, representing the only

analyses that maintain the fairness of the randomization, remain the primary analyses of DFS and OS, exploratory analyses based on data from patients who entered the maintenance phase will be presented in the Efficacy section.

Table 1. Asymmetric Distribution of DFS Events in Patients Who Did Not Enter Maintenance Phase

	DFS Events in Patients Who Did Not Enter Maintenance Phase (N = 68)
Regimen A	14
Regimen B	12
Regimen A + MTP-PE	12
Regimen B + MTP-PE	5
Difference between pooled non-MTP-PE containing arms and pooled MTP-PE containing arms	**9**

Table 2. Asymmetric Distribution of Patient Deaths in Patients Who Did Not Enter Maintenance Phase

	Deaths in Patients Who Did Not Enter Maintenance Phase (N = 68)
Regimen A -	12
Regimen B -	6
Regimen A + MTP-PE	5
Regimen B + MTP-PE	5
Difference between pooled non-MTP-PE containing arms and pooled MTP-PE containing arms	**8**

Unavailability of MTP-PE filters

MTP-PE was administered through 3-µm filters to decrease the risk of infusion of large aggregates of liposomes into patients. From June 15, 1995, to January 15, 1996 there was a problem with availability of these filters. During this period investigators were instructed to continue to initiate administration of MTP-PE when filters were available, even if the

initiation was delayed. Of patients enrolled on the trial, 93 entered maintenance during this period, including 45 on MTP-PE-containing arms. Of these 45, 7 received no MTP-PE, 13 received < 90% of doses (<43 of 48 doses), and 25 received ≥ 90% of doses (38 to 48 of 48 doses). These patients remain in the ITT analysis population and the protocol was amended to increase accrual to the study to compensate for the time filters were not available.

Data Set Integrity

The data sets submitted with the application were derived from data sets assembled by the Childrens' Oncology Group (COG) that were analyzed for the peer-reviewed article published by the cooperative group to report the results of the trial. (Meyers PA et al. J Clin Oncol 23:2004-11). The FDA reviewer compared this data set to data included in the CRFs submitted with the application. One institution submitted "supplementary follow-up forms May 2005" on all patients treated at that institution. This resulted in an increase in the mean overall survival follow-up for patients from this institution from 0.9 years to 7.5 years. There were 68 discrepancies in overall survival and 66 discrepancies in DFS identified by the FDA reviewer based on review of the CRFs, including 9 additional patients identified as having experienced disease events or deaths. Seven of these were identified in patients with "supplementary follow-up forms May 2005" from the one institution. Because of the discrepancies between the data sets submitted and the documentation in the CRFs, FDA analyses were performed using the "FDA Review" data set. This data set was constructed based on information documented in the CRFs submitted in the application. Although the Applicant submitted a revised data set on February 19, 2007 with updated patient information, this data set was not supported by primary documentation in the CRFs and was not be used for FDA analyses.

Patients with Active Disease at Last Contact – Informative Censoring and the Reliability of Overall Survival Data

The Applicant emphasizes overall survival advantage as a compelling result to support this application. There were 26 patients with active oncologic disease at last contact, either osteosarcoma or AML. There is an extremely high probability that these patients died. The assigned treatment arms for these patients were imbalanced. Sixteen of these patients were assigned to regimens containing MTP-PE and 10 to regimens that did not contain MTP-PE. This inadequate follow-up for survival represents a form of informative censoring, and diminishes the FDA reviewer's assessment of the reliability of the OS Data.

2. Demographics and Disease Characteristics

Tables 3 and 4. below present the demographic and disease characteristics of the population studied for the ITT population.

Table 3. Demographic Characteristics of the Intent to Treat Population

		Reg A N=171	Reg A + N=165	Reg B N=166	Reg B + N=169	Total N=671
Sex (%)	Male	48	57	52	62	55
	Female	52	43	48	38	45
Race (%)	White	67	65	72	61	66
	Black	15	12	15	16	14
	Hispanic	11	16	10	13	13
	Asian	3	2	0	5	3
	Other	4	5	3	5	4
Age in years	Median	13.2	14.3	13.6	13.8	13.6
	Range	4.0-30.	5.0-2.2	4.2-30.	1.4-30.	1.4-30.6

Table 4. Tumor Location in the Intent to Treat Population
(All values are %)

	Reg A N=171	Reg A + N=165	Reg B N=166	Reg B + N=169	Total N=671
Arm – Humerus	11	12	10	11	11
Arm – Radius	1		2	5 3	2
Arm – Ulna		0.6	0.6		0.3
Arm - NOS			0.6		0.1
Leg – Femur	53	55	58	54	55
Leg – Tibia	23	27	23	27	25
Leg – Fibula	4	2	1	2	2
Leg - NOS	0.5		0.6		0.3
Other	5	3	4	2	7
Unknown	3	0.6		1	1

MTP-PE was not administered until the maintenance phase of therapy. Tumor response to the preceding neoadjuvant therapy is a known prognostic factor in osteosarcoma. Therefore an analysis of tumor response by regimen is presented below in Table 5.

Table 5. Tumor Response by Regimen in Intent to Treat Population[1]
(All values are percent necrosis)

Tumor Response to Therapy Prior to MTP-PE	Reg A N=148	Reg A + N=144	Reg B N=146	Reg B + N=145	Total N=583
Grade 1: no effect	4	4	3	2	3
Grade 2A: more than 50% viable	14	19	8	12	13
Grade 2B: 5-50% tumor viable	34	41	42	36	38
Poor Response[2]	52	64	53	51	55
Grade 3: less than 5% tumor viable	34	22	29	37	30
Grade 4: no viable tumor noted	14	14	18	13	15
Good Response[3]	48	36	47	49	45

[1]No response was documented for 88 patients.
[2]Poor response: Grade 1, 2A and 2B;
[3]Good response: Grade 3 and 4

3. Drug Exposure

303 patients randomized to regimens containing MTP-PE entered the maintenance phase of the protocol (Regimen A+ n=145, Regimen B+ n=158). Ten percent of patients randomized to regimens containing MTP-PE received no doses of MTP-PE. This included 32 patients who did not enter the maintenance phase and 7 patients who entered the maintenance phase. Sixty seven percent of patients randomized to regimens containing MTP-PE received 90% of protocol-specified number of doses (43 to 48 of 48 doses).

There was no documentation that MTP-PE was administered to patients according to the dose escalation schema specified in the protocol. Five patients were escalated to $2mg/m^2$ + 1 and 21 patients were escalated to $2mg/m^2$ + 2. One patient had the dose de-escalated to 1 mg/m^2 during the second maintenance course of therapy and for all subsequent doses.

4. Efficacy

Disease Free Survival

The primary efficacy variable was DFS, defined as the time from randomization to relapse of osteosarcoma or death. If a patient experienced no event of relapse or death, the time to event is censored at the date of last report of disease event free status.

There are three main issues regarding the DFS results:

1) The Applicant's result is sensitive to changes based on FDA review of CRFs, patient's eligibility and investigator's additional follow-up data;

2) The Applicant's result is driven by an experimental arm which performs worse than the control arm; and

3) Inadequate planning and conduct of interim analyses complicate the interpretation of the DFS result.

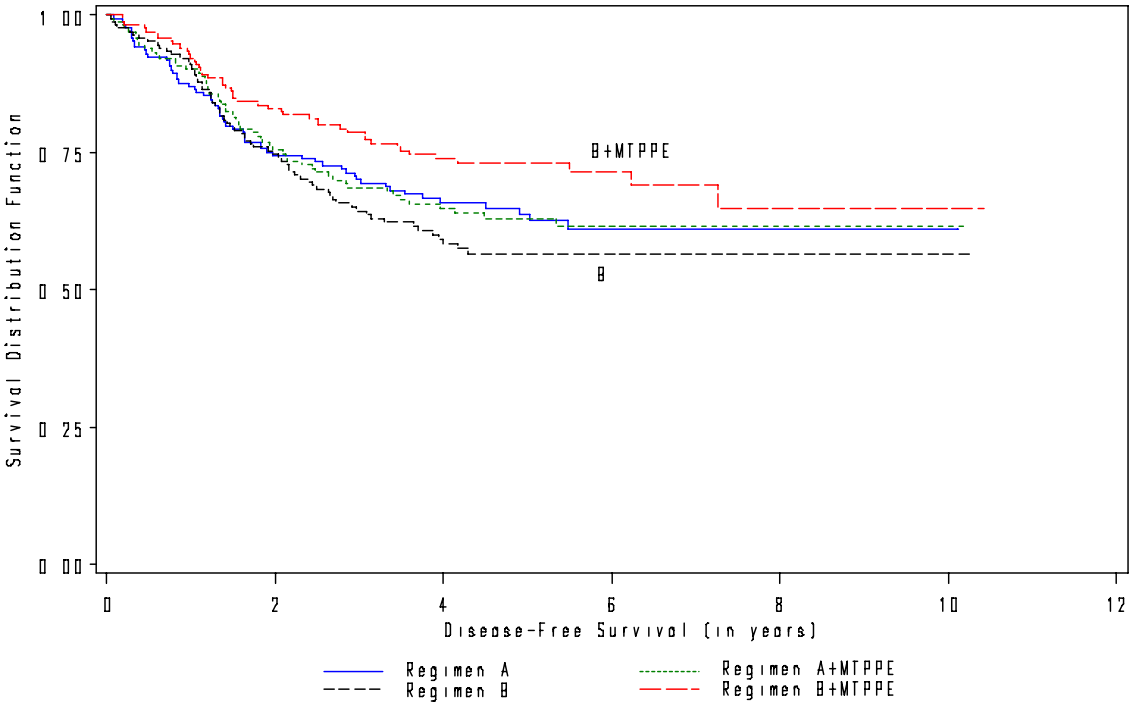
FDA analyses of DFS are based on DFS data that have been modified as a result of the findings of FDA review of case report forms and the exclusion of 7 patients.

This clinical trial involved two experimental drugs: ifosfamide and MTP-PE. Regimen A is the control regimen. Regimen A + MTP-PE, Regimen B, and Regimen B + MTP-PE are experimental regimens (each contains at least one experimental drug). DFS results are presented in Table 6 for each regimen relative to regimen A. The Kaplan-Meier curves by regimen are presented in Figure 5.

Table 6. DFS analysis by Regimen Based on FDA-modified Data

Variable	Number of Patients	Number of Events	Hazard Ratio	P-value
Regimen A	171	60	1.00	---
Regimen A + MTP-PE	165	57	0.99	0.96
Regimen B	166	67	1.18	0.35
Regimen B + MTP-PE	169	46	0.73	0.11

Figure 5. Kaplan-Meier Curves for DFS by Regimen Based on FDA-modified data



DFS was analyzed by the Applicant on pooled data using a stratified log-rank test with ifosfamide use, above/below institutional upper limit of normal LDH, involvement above the knee or elbow (yes vs. no), and prior amputation (yes vs. no) as stratification factors. By stratifying by ifosfamide use, this analysis integrates the results of a comparison of Regimen A + MTP-PE to Regimen A with a comparison of Regimen B + MTP-PE to Regimen B. Results based on the Applicant's primary analysis method are displayed in the last row of Table 7, together with the results of the individual comparisons of Regimen A + MTP-PE vs. Regimen A and Regimen B + MTP-PE vs. Regimen B. Note that there is no demonstrated improvement in DFS when comparing Regimen A + MTP-PE with the control, Regimen A (standard chemotherapy). A statistical test of an interaction effect on DFS between the background regimen and the addition of MTP-PE yielded a p-value of 0.067. This is a highly significant p-value for a test of interaction.

Table 7. Results for DFS Based on FDA-modified Data

Regimens Compared	Hazard Ratio	P-value
A + MTP-PE vs. A	0.99	0.96
B + MTP-PE vs. B	0.62	0.01
Integrated analysis [1]	0.78	0.065

[1] Applicant's method of analysis

Applicant's result is sensitive to FDA review of the primary data

When the Applicant's submitted results for DFS are compared to the results for DFS based on FDA-modified data, the hazard ratio changes from 0.76 to 0.78 and p-value changes from 0.0245 to 0.065.

Applicant's result is driven by an experimental regimen performing worse than the control regimen

Even had the p-value been very small from the integrated analysis, it would not have been sufficient. One of the comparisons (Regimen B + MTP-PE vs. Regimen B) does not involve the control regimen, but rather is a comparison of an experimental regimen containing MTP-PE with another experimental regimen (Regimen B). If Regimen B does not perform similar to Regimen A, the integrated comparison will not reliably evaluate the efficacy of the MTP-PE containing regimens (relative to the control regimen). To examine the impact on the integrated analysis of Regimen B performing worse than the control regimen (Regimen A), an integrated analysis was performed in which the results for Regimen A are substituted for the results for Regimen B. The results from this analysis are provided in Table 8.

Table 8. Integrated Analysis of DFS if Regimen B Had the Same Results as Regimen A

Regimens Compared	Hazard Ratio	P-value
A + MTP-PE vs. A	0.99	0.96
B + MTP-PE vs. B=A	0.73	0.11
Integrated analysis[1]	0.86	0.28

[1] Applicant's method of analysis

The poorer performance of Regimen B relative to Regimen A reduced the estimate of the hazard ratio from 0.86 to 0.78 and reduced the p-value from 0.28 to 0.065.

Issues involving the Type I error rate (alpha)

The last protocol amendment, Amendment 7 on 6/16/1997, stated that one interim analysis had been conducted and two additional interim analyses were planned. The details of the conducted (first) interim analysis were not provided, including the amount of alpha spent. The two-sided nominal significance levels for the additional interim analyses are 0.011 and 0.013. These analyses were performed in February 1997 and September 1997 and the timings of these analyses were not based on a prespecified number of events.

The report for the second interim analysis stated that the primary endpoint was Event-free survival (EFS) with the analysis based on 56 events. The report for the third interim analysis again treated EFS as the primary endpoint and stated that "the analysis was performed when 55% of the information had been accrued". It is unclear how the information level was determined since the original protocol was powered based on DFS. The statistical boundaries were not crossed in either the 2nd or the 3rd interim analyses.

Results were not provided for the formally planned final analysis at 167 DFS events. An analysis was performed after more than 220 events based on the available data as of 7/10/2003. An integrated analysis based on the time of the 167th DFS event is not statistically significant. It is not clear whether the Type I error rate was controlled at a two-sided 0.05 level. If the timing of the final analysis was influenced by the results of the previous analyses, the Type I error rate will be impacted.

Imbalance in Events Due to Trial Design Flaw

As detailed in section C, "Review Issues Regarding INT 0133", subsection 1, "Assessment of Study Conduct and Integrity and Adequacy of Data Submitted", randomization regarding MTP-PE assignment was performed at study entry; however, MTP-PE administration was not initiated until the maintenance phase of the protocol approximately 3 months later. As a result of this delay, DFS events that are not attributable to regimen assignment occurred in a number of patients who did not enter the maintenance phase, including several assigned to study regimens containing MTP-PE who received no MTP-PE. The number of DFS events

in the subset of patients who did not enter the maintenance phase was not balanced between the MTP-PE containing arms and the non-MTP-PE containing arms. Forty three patients (26 in non MTP-PE containing arms and 17 in MTP-PE containing arms) who did not enter the maintenance phase are known to have had a DFS event

Results of exploratory analyses of DFS conducted on the subset of patients who entered the maintenance phase of the protocol is displayed in Table 9..

Table 9. Patients Who Entered Maintenance: Analysis of DFS by Regimen Based on FDA-modified Data

Variable	Number of Patients	Number of Events	Hazard Ratio	P-value
Regimen A	153	46	1.00	---
Regimen A + MTP-PE	145	45	1.02	0.91
Regimen B	148	55	1.30	0.19
Regimen B + MTP-PE	157	41	0.83	0.39

If the Applicant's primary analysis method is used on these data, the p-value equals 0.12 with a hazard ratio equal to 0.80.

Overall Survival

OS is an additional endpoint in this study. The main issues/comments involving OS are

1) The primary endpoint of the study was not met.

2) Follow-up on OS was inadequate to perform a meaningful analysis. OS analysis was not formally planned.

Inadequate follow-up

Five hundred thirty (530) patients had their OS censored based on the data provided the FDA having a cutoff date of July 10, 2003. For these patients, Table 10 provides the year that follow-up was discontinued. Note that over 95% of these patients had their follow-up for OS end in 2002 or earlier and 70% of these patients had their follow-up end in 2001 or earlier.

Table 10. Year Overall Survival Follow-up Discontinued for Patients Having Censored Overall Survival. July 10, 2003 Cutoff Date.

Year follow-up stopped	Number of patients lost to follow-up	Cumulative Number of patients lost to follow-up	Cumulative Percent of patients lost to follow-up
1994	**6**	**6**	**1.13**
1995	**17**	**23**	**4.34**
1996	**22**	**45**	**8.49**
1997	**14**	**59**	**11.13**
1998	**36**	**95**	**17.92**
1999	**75**	**170**	**32.08**
2000	**99**	**269**	**50.75**
2001	**102**	**371**	**70.00**
2002	**133**	**504**	**95.09**
2003	**26**	**530**	**100.00**

An updated OS data set was also submitted to the FDA. Five hundred five (505) patients had their OS censored based on the updated data. For these patients Table 11 provides the year that follow-up was discontinued. Note that 43% of these patients had their follow-up for OS end in 2002 or earlier. This represents 32% of all the patients in the study. In a well conducted trial for registration with OS as a primary endpoint, the proportion of patients lost to follow-up for survival is less than 5%.

Table 11. Year Overall Survival Follow-up Discontinued for Patients having Censored Overall Survival. Updated data

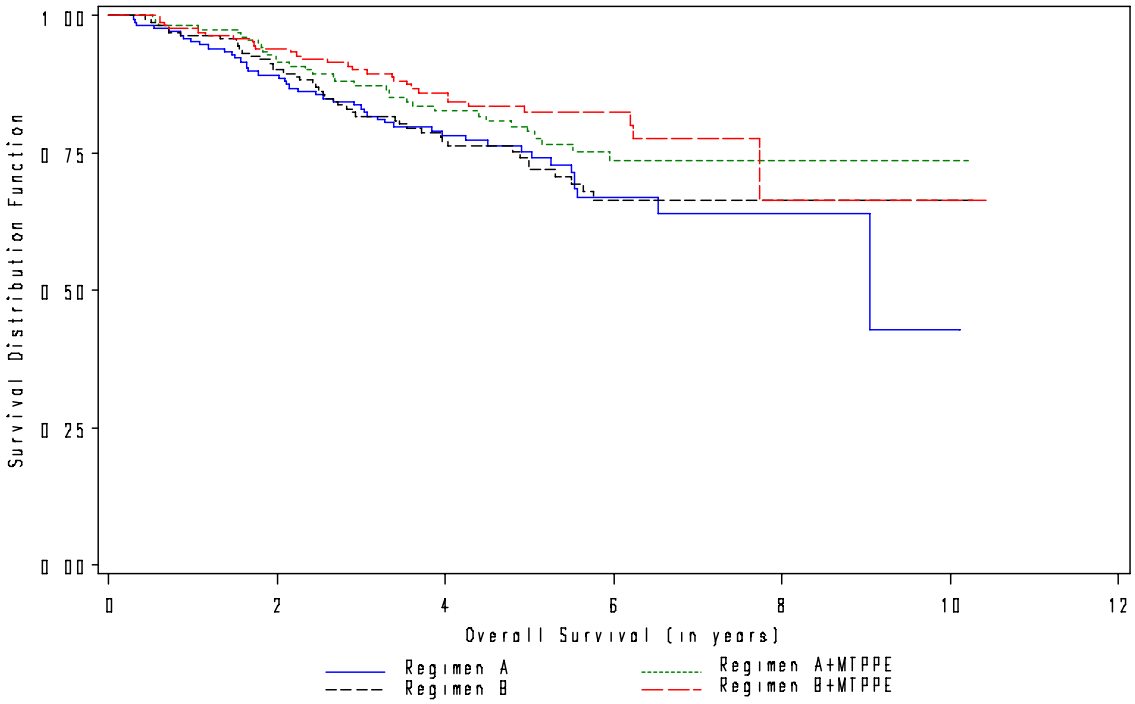
Year follow-up stopped	Number of patients lost to follow-up	Cumulative Number of patients lost to follow-up	Cumulative Percent of patients lost to follow-up
1994	**4**	**4**	**0.79**
1995	**6**	**10**	**1.98**
1996	**12**	**22**	**4.36**
1997	**6**	**28**	**5.54**
1998	**20**	**48**	**9.50**
1999	**42**	**90**	**17.82**
2000	**39**	**129**	**25.54**
2001	**39**	**168**	**33.27**
2002	**50**	**218**	**43.17**
2003	**41**	**259**	**51.29**
2004	**56**	**315**	**62.38**
2005	**78**	**393**	**77.82**
2006	**112**	**505**	**100.00**

OS results are presented in Table 12 for each regimen relative to Regimen A. The Kaplan-Meier curves by regimen are presented in Figure 6.

Table 12. Overall Survival Results by Regimen Relative to Regimen A Based on FDA-modified Data

Variable	Number of Patients	Number of Events	Hazard Ratio	P-value
Regimen A	171	46	1.00	---
Regimen A + MTP-PE	165	33	0.72	0.16
Regimen B	166	44	0.97	0.89
Regimen B + MTP-PE	169	29	0.61	0.03

Figure 6. Kaplan-Meier Curves for Overall Survival by Regimen Based on FDA-modified Data



If the Applicant's primary analysis method is used on these data, the p-value equals 0.015 with a hazard ratio equal to 0.667.

Imbalance in Events Due to Trial Design Flaw

As discussed for DFS, the delay from randomization to initiation of MTP-PE resulted in a number of patients who did not enter the maintenance phase contributing OS events that are not attributable to regimen assignment to the ITT analysis. This included patients assigned to study regimens containing MTP-PE who received no MTP-PE. The number of OS events in the subset of patients who did not enter the maintenance phase was not balanced between the MTP-PE containing arms and the non-MTP-PE containing arms. Twenty eight patients (18 in non MTP-PE containing arms and 10 in MTP-PE containing arms) who did not enter the maintenance phase are known to have died.

Results of exploratory analyses of OS conducted on the subset of patients who entered the maintenance phase of the protocol are displayed in Tables 13 and 14.

Table 13. Patients Who Entered Maintenance: Analysis of Overall Survival by Regimen Based on FDA-modified data

Variable	Number of Patients	Number of Events	Hazard Ratio	P-value
Regimen A	153	34	1.00	---
Regimen A + MTP-PE	145	28	0.84	0.49
Regimen B	148	38	1.15	0.55
Regimen B + MTP-PE	157	24	0.65	0.11

If the Applicant's primary analysis method is used on these data, the p-value equals 0.04 with a hazard ratio equal to 0.68.

5. Safety

Common adverse events associated with treatment with MTP-PE were identified in the phase I/II development. These include chill, fever, fatigue, nausea, tachycardia, and headache. Most of these were mild to moderate severity.

The INT 0133 study did not capture detailed data on adverse events associated with MTP-PE. The Applicant did not submit the adverse event data that was captured in a format that facilitated substantive analysis.

There were no deaths that appeared to be associated with treatment with MTP-PE. There was an imbalance between the pooled MTP-PE containing arms and the pooled non-MTP-PE containing arms in patients removed from therapy based on parent/patient or physician request as can be seen in Table 14.

Table 14. Reasons Captured on CRF's for Early Termination

	Prior to Maintenance n = 671	Entered Maintenance n = 603
No therapy	7	
Death	2	3
Major Deviation of Therapy	17	19
Unacceptable Toxicity	3	8 --5 on non-MTP-PE containing arms --3 on MTP-PE containing arms
Progressive Disease	19	33
Parent or Patient Request	16	60 --14 on non-MTP-PE containing arms --46 on MTP-PE containing arms
Physician Request	4	11 --4 on non-MTP-PE containing arms --7 on MTP-PE containing arms
Deemed Ineligible		3
Lost to Follow-up		2

Specific reasons documented on CRFs for the patients discontinued by parent, patient or physician choice included allergy, chills, fatigue, malaise, pain, arrhythmia, erythema multiforme, nausea, vomiting, intolerable reactions, rigors, and "too burdensome."

D. Conclusions

This study does not support approval of MTP-PE for the treatment of newly diagnosed resectable high grade osteosarcoma following surgical resection in combination with multi-agent chemotherapy.

The 1962 Kefauver-Harris Amendments to the Food, Drug and Cosmetic Act require a manufacturer to provide "substantial evidence" of effectiveness from "adequate and well-

controlled trials" before a new drug can be approved for commercial marketing. In general, this is interpreted as requiring the results of two adequate and well-controlled trials that meet their prespecified primary endpoint at $p< 0.05$. For marketing approval to be granted based on the results of a single randomized trial, the trial should be well designed, well conducted, internally consistent and provide sufficiently robust and statistically persuasive efficacy findings that a second trial would be ethically or practically impossible to perform.

The results from Study INT 1033 do not meet the threshold of singularly providing substantial evidence demonstrating that MTP-PE is effective for the requested indication. As detailed in section C.4, "Review Issues Regarding INT 0133: Efficacy", the results on DFS were neither robust nor highly statistically significant. The analysis of OS, performed *post hoc* on data that were substantially incomplete due to inadequate follow-up for survival, is not persuasive.