Section A. IDM Clarification on Effectiveness Data

The first stated aim of pivotal study INT-0133 was to improve overall survival (OS) as indicated on the first page of the study protocol. The U.S. National Cancer Institute (NCI) cooperative group convention at the time the protocol was written was to justify in the document the number of patients enrolled and the time at which the initial analysis would be available. For INT-0133, the first analysis planned was based upon an intermediate endpoint, Disease-Free Survival (DFS).

Assessing improvement in OS as the primary aim of the Phase 3 MEPACT study is consistent with the treatment goal in osteosarcoma. While an intermediate endpoint such as DFS is frequently used when considering efficacy, OS remains the gold standard assessment for cancer therapies.

Improvements in both OS (HR 0.67-0.72) and DFS (HR 0.74-0.78) were observed following the addition of MEPACT to chemotherapy for the 2003, 2006, and 2007 datasets. One of the patient groups (Group A+) that subsequently received MEPACT as part of adjuvant chemotherapy was shown to have an excess of patients with unfavourable histopathologic response to neoadjuvant chemotherapy, which accounts for discrepancies seen between OS and DFS.

On 18 December 2008 the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, and recommending the granting of a marketing authorisation for MEPACT for the treatment of osteosarcoma. The benefits, as stated by the CHMP, for MEPACT used in conjunction with combination chemotherapy are associated with improved overall survival when compared with chemotherapy alone, as observed in the randomised controlled trial.

A1. Please clarify your response to A21 (p20 of the IDM Pharma response to clarification) by providing the following data and/or justification in the grey cells of Tables 1a and 1b on pages 4 and 5 below.

The tables have been completed as requested.

A2. Please clarify whether table A21b (p20 of the IDM Pharma response to clarification) refers to overall survival or disease survival. If A21b refers to overall survival, please provide corresponding data for disease free survival or vice versa

Table A21b refers to overall survival. The corresponding data for DFS are included in Table 1b.

A3. Please provide the overall comparison of MEPACT vs. No MEPACT in table A21b (p20 of the IDM Pharma response to clarification) for both overall survival and disease free survival.

This comparison is provided in the Tables 1a and 1b.

A4. *The median follow up between the two data sets (2006 and 2007) in Table A21a (p20 of the IDM Pharma response to clarification) appear to be very similar, please clarify if this correct.*

This is correct. The median follow up times for the two datasets are very close. The 2006 dataset was closed in August 2006 and the 2007 dataset was closed in March 2007.

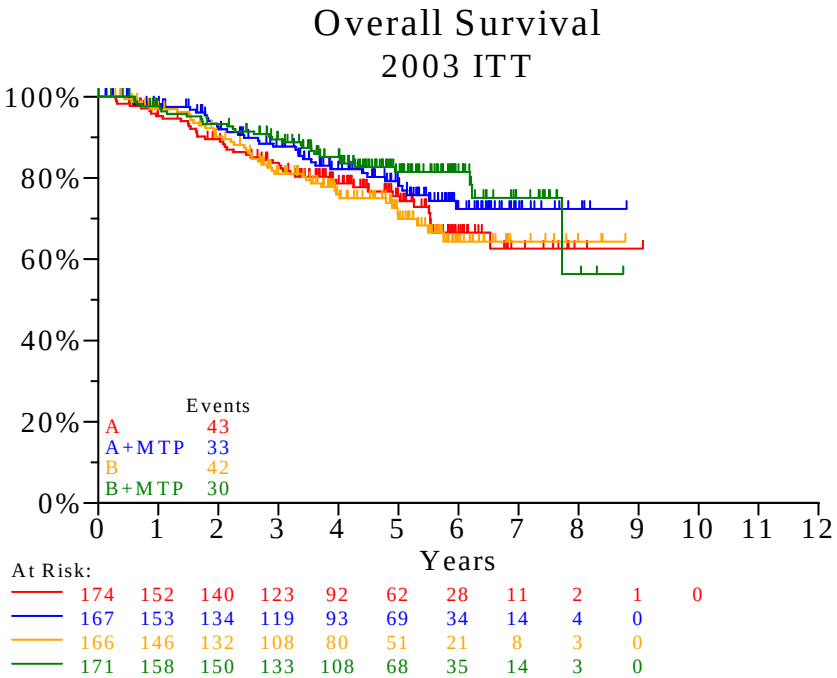
A5. *The submission by IDM Pharma (p55) also suggests that the median follow up for the 2007 data set was 7.9 years, whereas the median follow-up in the 2007 data set (Table A21a of the IDM Pharma response to clarification) suggests a range from 6.0 to 6.7 years. Please provide further clarification.*

The median follow up of patients alive at last contact was 7.9 years for the 2007 dataset. The medians presented in Table A21a by treatment regimen include patients who died. Patients known to have died are considered complete with respect to follow up. The data have been amended to include patients alive at last contact in the Tables 1a and 1b.

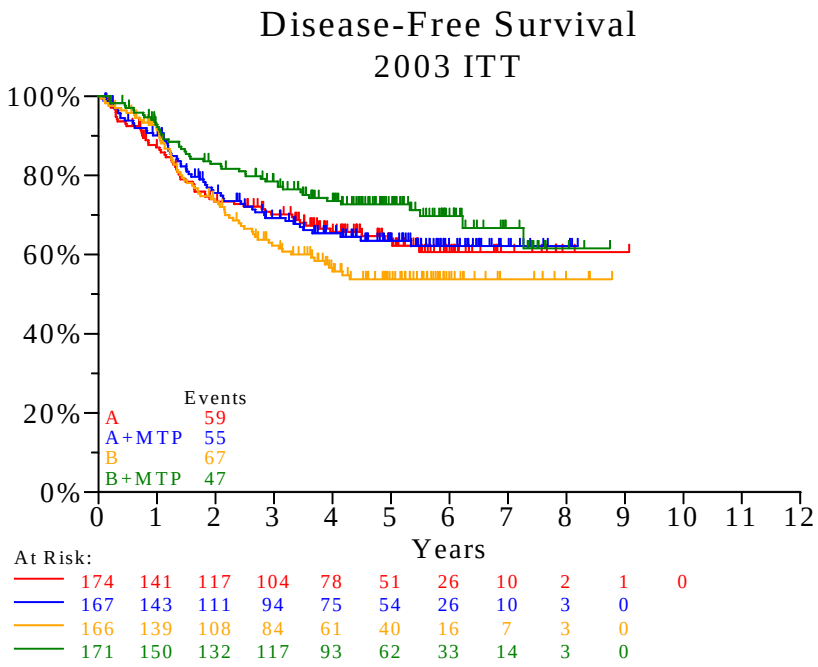
A6. *Please provide all respective data for the 2003 dataset, including Kaplan-Meier curves for the four treatment groups for the 2003 data set, including numbers at risk at each time point.*

Data for the 2003 dataset have been added to Tables 1a and 1b.

The OS and DFS Kaplan-Meier curves for the four treatment groups, including the numbers at risk at each time point, for the 2003 dataset are presented below:



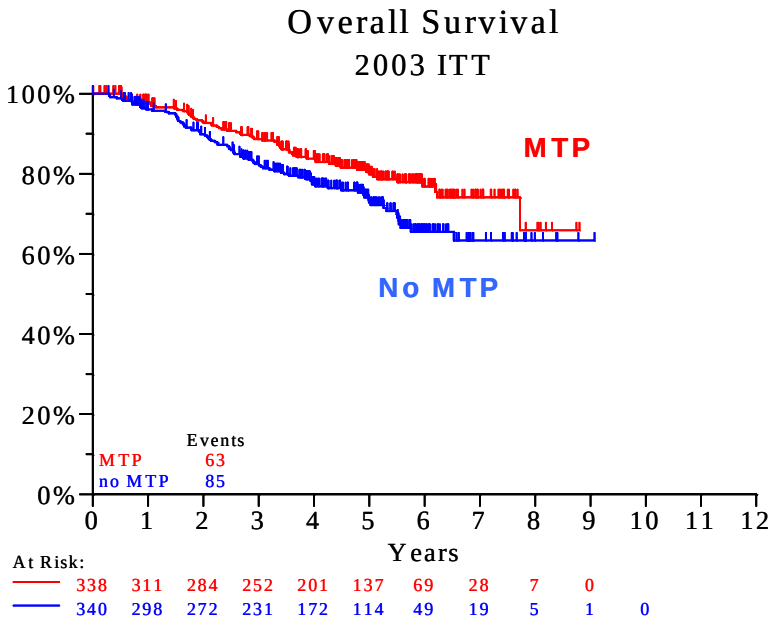
Regimen A = methotrexate, doxorubicin and cisplatin
Regimen B = methotrexate, doxorubicin, cisplatin and ifosfamide
MTP = MEPACT

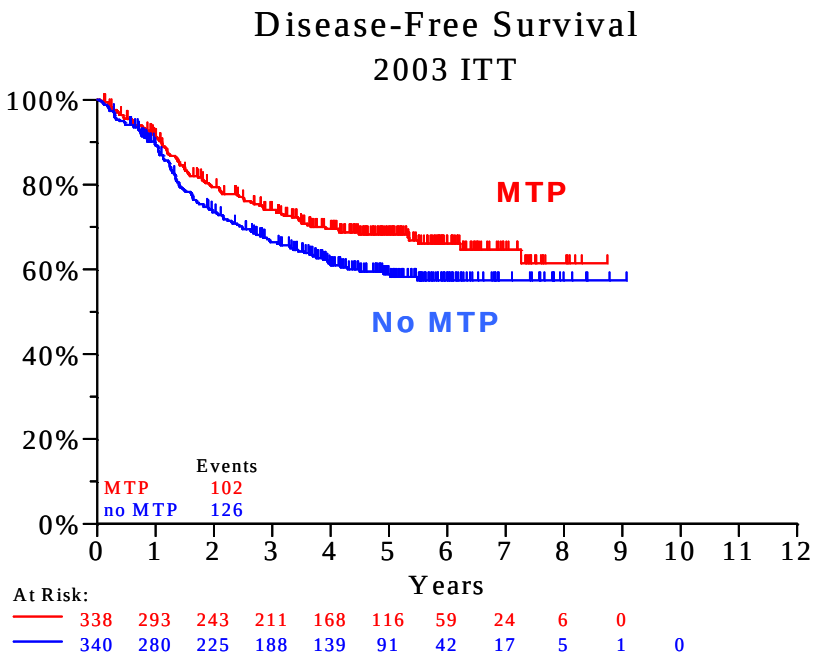


Regimen A = methotrexate, doxorubicin and cisplatin
Regimen B = methotrexate, doxorubicin, cisplatin and ifosfamide
MTP = MEPACT

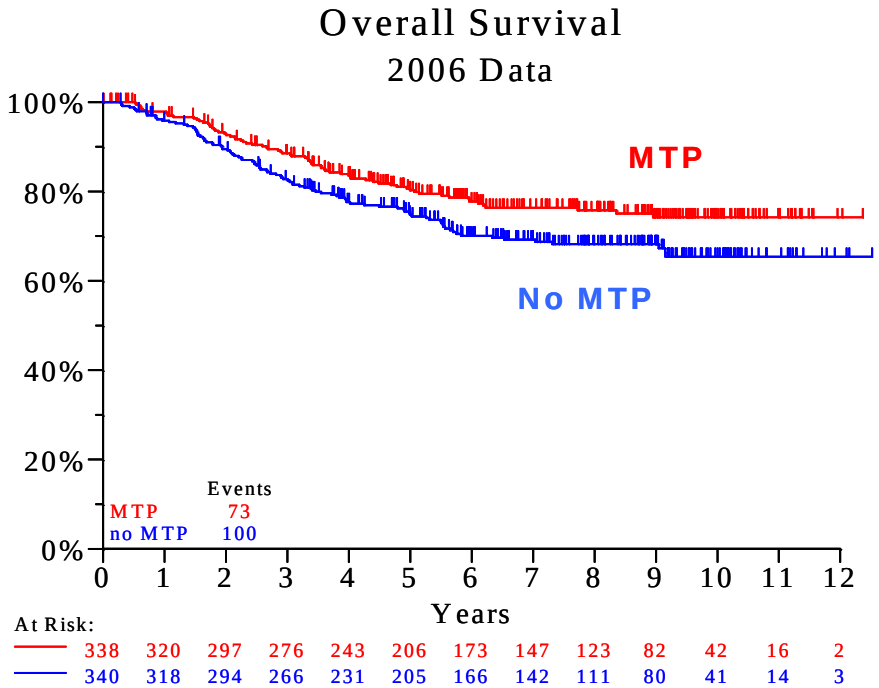
A7. *Please provide Kaplan-Meier curves for the MEPACT and no MEPACT groups for the 2003, 2006 and 2007 data set, including numbers at risk at each time point.*

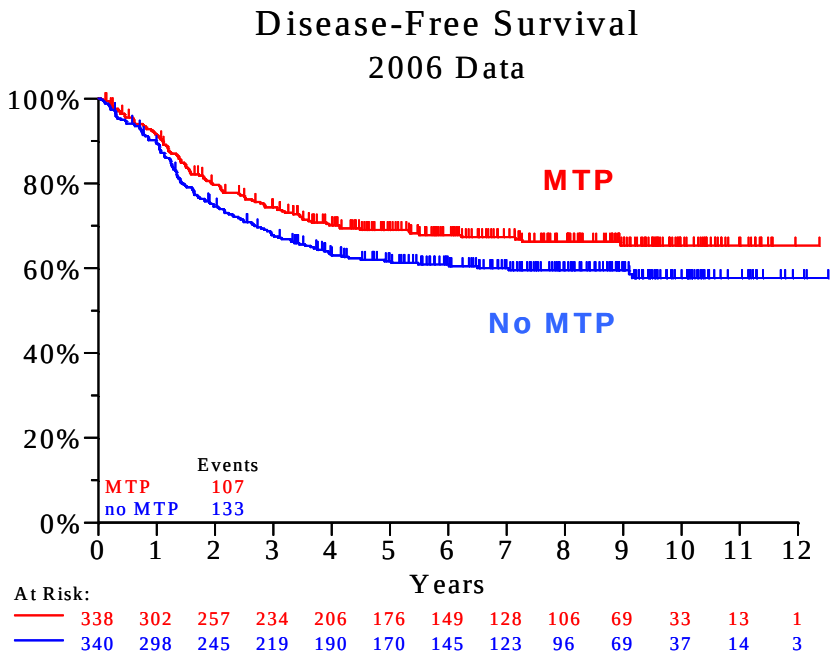
The OS and DFS Kaplan-Meier curves for the 2003 dataset for the MEPACT (MTP) and no-MEPACT (No MTP) groups, including numbers at risk at each time point are presented below:



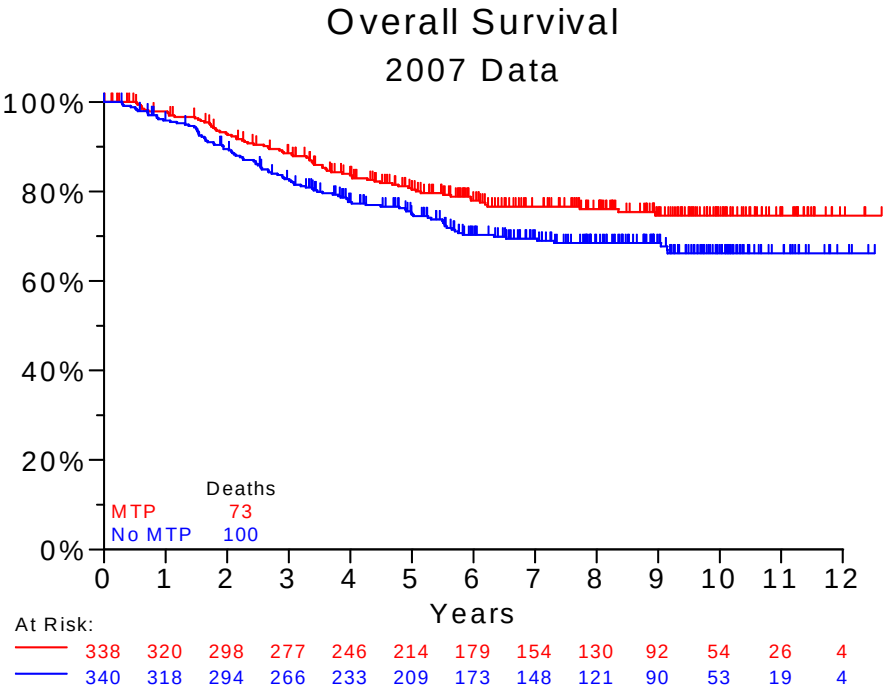


The OS and DFS Kaplan-Meier curves for the 2006 dataset for the MEPACT (MTP) and no-MEPACT (No MTP) groups, including numbers at risk at each timepoint, are presented below:





The OS and DFS Kaplan-Meier curves for the 2007 dataset for the MEPACT (MTP) and no-MEPACT (No MTP) groups, including numbers at risk at each time point, are presented below:



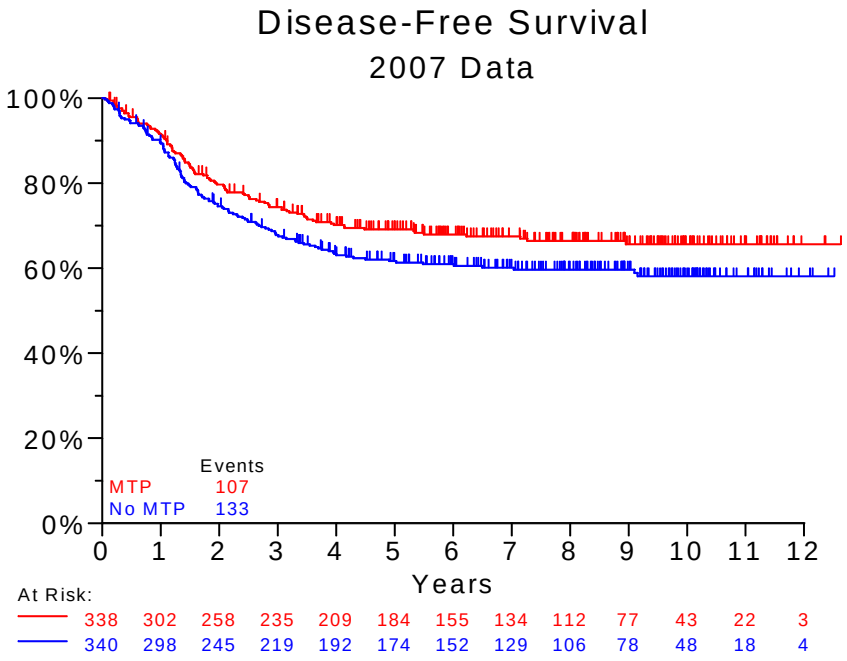

Disease-Free Survival
2007 Data
100%
80%
60%
40%
20%
0%
Events
MTP 107
No MTP 133
0 1 2 3 4 5 6 7 8 9 10 11 12
Years
At Risk:
338 302 258 235 209 184 155 134 112 77 43 22 3
340 298 245 219 192 174 152 129 106 78 48 18 4

Table 1a: Overall survival outcome efficacy data

Treatment***	Median follow up* (years)	Numbers followed in each group (n vs. n)	Events in each group (n vs. n)	HR (95% CI; p value**)
2003 data set for OS				
A (control)	4.5	174	43	-
A+	5.0	167	33	-
B	4.6	166	42	-
B+	4.8	171	30	-
Primary analysis				
A/B combined vs. A+/ B+ combined	4.8	340 vs. 338	85 vs. 63	0.67 (0.48,0.94; p=0.0183)
Additional analysis				
A vs. A+	-	174 v 167	43 v 33	0.78 (0.49, 1.24) p= 0.2895
A vs. B	-	174 v 166	43 v 42	1.06 (0.69, 1.63) p=0.7806
A vs. B+	-	174 v 171	43 v 30	0.69 (0.43, 1.10) p=0.1197
B vs. A+	-	166 v 167	42 v 33	0.72 (0.45, 1.13) p=0.1546
A+ vs. B+	-	167 v 171	33 v 30	0.87 (0.53, 1.43) p=0.5770
B vs. B+	-	166 v 171	42 v 30	0.58 (0.36, 0.93) p=0.0236
2006 data set for OS				
A (control)	7.5	174	51	-
A+	7.9	167	37	-
B	8.0	166	49	-
B+	6.8	171	36	-
Primary analysis				
A/B combined vs. A+/ B+ combined	7.7	340 vs. 338	100 vs. 73	0.72 (0.53, 0.98; p=0.0352)
Additional analysis				
A vs. A+	-	174 vs. 167	51 vs. 37	0.76 (0.50, 1.17) p=0.2172
A vs. B	-	174 vs. 166	51 vs. 49	0.98 (0.66, 1.45) p=0.9275
A vs. B+	-	174 vs. 171	51 vs. 36	0.71 (0.46, 1.09) p=0.1190
B vs. A+	-	166 vs. 167	49 vs. 37	0.75 (0.49, 1.16) p=0.1943
A+ vs. B+	-	167 vs. 171	37 vs. 36	0.91 (0.57, 1.44) p=0.6868
B vs. B+	-	166 vs. 171	49 vs. 36	0.68 (0.44, 1.05) p=0.0832
2007 data set for OS				
A (control)	7.8	174	51	-
A+	8.1	167	37	-
B	8.3	166	49	-
B+	7.4	171	36	-
Primary analysis				
A/B combined vs. A+/ B+ combined	7.9	340 vs. 338	100 vs. 73	0.72 (0.53, 0.97; p=0.0313)
Additional analysis				
A vs. A+	-	174 vs. 167	51 vs. 37	0.75 (0.49, 1.16) p=0.1949
A vs. B	-	174 vs. 166	51 vs. 49	0.97 (0.66, 1.44) p=0.8884
A vs. B+	-	174 vs. 171	51 vs. 36	0.70 (0.46, 1.08) p=0.1093
B vs. A+	-	166 vs. 167	49 vs. 37	0.75 (0.49, 1.15) p=0.1832
A+ vs. B+	-	167 vs. 171	37 vs. 36	0.92 (0.58, 1.45) p=0.7135
B vs. B+	-	166 vs. 171	49 vs. 36	0.68 (0.44, 1.05) p=0.0825

*for patients alive at last contact
** p-value from Cox model stratified by randomization strata for pair-wise comparisons of A/A+/B/B+. p-value from log-rank test stratified by ifosfamide use and randomization strata for Mepact vs no MEPACT.
***Regimen A = methotrexate, doxorubicin and cisplatin; Regimen A+ = A + MEPACT
Regimen B = methotrexate, doxorubicin, cisplatin and ifosfamide; Regimen B+ = B + MEPACT

Table 1b: Disease free survival outcome efficacy data

Treatment***	Median follow up* (years)	Numbers followed in each group (n vs. n)	Events in each group (n vs. n)	HR (95% CI; p value)**
2003 data set for DFS				
A (control)	4.5	174	59	-
A+	5.0	167	55	-
B	4.6	166	67	-
B+	4.8	171	47	-
Primary analysis				
A/B combined vs. A+/ B+ combined	4.8	340 vs.338	126 vs. 102	0.74 (0.57, 0.96) p=0.0245)
Additional analysis				
A vs. A+	-	174 v 167	59 v 55	0.97 (0.67, 1.40) p=0.8622
A vs. B	-	174 v 166	59 v 67	1.25 (0.88, 1.77) p=0.2207
A vs. B+	-	174 v 171	59 v 47	0.74 (0.50, 1.09) p=0.1309
B vs. A+	-	166 v 167	67 v 55	0.76 (0.53, 1.09) p=0.1332
A+ vs. B+	-	167 v 171	55 v 47	0.77 (0.52, 1.13) p=0.1817
B vs. B+	-	166 v 171	67 v 47	0.57 (0.39, 0.82) p=0.0029
2006 data set for DFS				
A (control)	7.5	174	62	-
A+	7.9	167	58	-
B	8.0	166	71	-
B+	6.8	171	49	-
Primary analysis				
A/B combined vs. A+/ B+ combined	7.7	340 vs.338	133 vs. 107	0.78 (0.61, 1.01) p=0.0623
Additional analysis				
A vs. A+	-	174 vs. 167	62 vs. 58	0.97 (0.68, 1.39) p=0.8763
A vs. B	-	174 vs. 166	62 vs. 71	1.18 (0.84, 1.66) p=0.3409
A vs. B+	-	174 vs. 171	62 vs. 49	0.77 (0.53, 1.12) p=0.1651
B vs. A+	-	166 vs. 167	71 vs. 58	0.81 (0.57, 1.15) p=0.2413
A+ vs. B+	-	167 vs. 171	58 vs. 49	0.77 (0.53, 1.13) p=0.1850
B vs. B+	-	166 vs. 171	71 vs. 49	0.63 (0.44, 0.91) p=0.0139
2007 data set for DFS				
A (control)	7.8	174	62	-
A+	8.1	167	58	-
B	8.3	166	71	-
B+	7.4	171	49	-
Primary analysis				
A/B combined vs. A+/ B+ combined	7.9	340 vs.338	133 vs. 107	0.78 (0.61, 1.01) p=0.0586
Additional analysis				
A vs. A+	-	174 vs. 167	62 vs. 58	0.96 (0.67, 1.38) p=0.8357
A vs. B	-	174 vs. 166	62 vs. 71	1.17 (0.83, 1.65) p=0.3588
A vs. B+	-	174 vs. 171	62 vs. 49	0.76 (0.52, 1.11) p=0.1612
B vs. A+	-	166 vs. 167	71 vs. 58	0.81 (0.57, 1.15) p=0.2354
A+ vs. B+	-	167 vs. 171	58 vs. 49	0.78 (0.53, 1.14) p=0.1985
B vs. B+	-	166 vs. 171	71 vs. 49	0.63 (0.44, 0.91) p=0.0144

*for patients alive at last contact
** p-value from Cox model stratified by randomization strata for pair-wise comparisons of A/A+/B/B+. p-value from log-rank test stratified by ifosfamide use and randomization strata for Mepact vs no MEPACT.
***Regimen A = methotrexate, doxorubicin and cisplatin; Regimen A+ = A + MEPACT
Regimen B = methotrexate, doxorubicin, cisplatin and ifosfamide; Regimen B+ = B + MEPACT***