Disease	No. with Active Disease	No. with Prior Transplant	No. with ≥3 Prior Chemotx Regimens	No. with Prior Radiotherapy	No. with Both Prior Radiotherapy and ≥3 Chemotx
Acute Leukemia (N = 26)					
> CR#1 (N = 14)	5	1	7	0	1
CR#1 with high risk for relapse (N=8)	2	0	0	3	1
Induction Failure	3	0	0	0	0
CML (N = 17)					
	17	2	2	1	2
Lymphoma (N = 10)					
Hodgkin's Disease (N=4) Primary Refractory or Resistant Relapse	3	1	0	1	2
Non-Hodgkin's Lymphoma (N=6) Primary Refractory or Resistant Relapse	4	2	0	0	4
MDS (N=9)					
	9	2	0	3	2
TOTAL	**43**	**8**	**9**	**8**	**12**

Reviewer Comment: Heavy pretreatment in the setting of transplantation has its greatest impact on observed regimen related toxicity and relapse of disease. As the study was designed to primarily examine engraftment after transplantation, only the regimen related toxicity would be expected to be readily discernible from data collected through Day +28.

4.8 On-Study Therapy

All but one of 62 patients enrolled received the planned 16 doses of intravenous busulfan on study (as full dose). The one who did not, withdrew prior to receiving any treatment on study. One patient did not receive the second dose of cyclophosphamide because of hypotension that developed after the first dose. That patient received melphalan in lieu of the second dose of cyclophosphamide.

The protocol cautioned against rapid infusion of busulfan as a bolus or IV push. Review of busulfan infusion ACCESS dataset reveal that there were two patients who received single doses in under an hour (50 minutes). No unusual evidence of toxicity was found in the adverse event records for these patients on the short infusion date.

4.9 Endpoints/Statistical Considerations

The efficacy variables selected for analysis in this study were **myeloablation, engraftment , relapse, and survival.** The endpoints of myeloablation and time to engraftment were accepted as primary surrogate endpoints by the Division of Oncology Drug Products in a pre-NDA meeting with the sponsor

4.9.1Definitions of Efficacy Endpoints

- **Myeloablation** was defined as any one or combination of the following:

(a) Absolute neutrophil count (ANC) $<0.5 \times 10^9$/L.
(b) Absolute lymphocyte count (ALC) $<0.1 \times 10^9$/L.
(c) Platelet count $<20{,}000/mm^3$ or bleeding requiring platelet transfusion.

The first of two consecutive days for which cell counts dropped to below these cut-off levels was recorded as the date of myeloablation. In addition, for the purpose of the sponsor's study report, because some institutional guidelines allowed platelet transfusion before platelet counts fell below $20{,}000/mm^3$, thrombocytopenia was defined as the first day a patient required platelet transfusion.

- Engraftment was defined as the day that ANC was $>0.5 \times 10^9$/L.
- **Nonengraftment** was defined as failure to reach an ANC $>0.5 \times 10^9$/L by BMT Day +100.
- **Late Graft Failure or Late Rejection** was defined as development of ANC $<0.5 \times 10^9$/L after having engrafted within the first 100 days.
- **Relapse** was recorded as the day it was detected.
- **Survival** was recorded as the date of death. Cause of death was to be recorded.

The statistical analysis plan treated patients who did not complete the study period (through BMT Day +28) because of death, withdrawal of consent, failure to engraft, or disease progression with subsequent alternative treatment as censored.

4.10 Efficacy Analysis

4.10.1 Myeloablation

The definitions used to describe this endpoint were described in the preceding section, 4.9.1 Definitions of Efficacy Endpoints. The median time to achieving myeloablation based on neutrophil count was BMT Day +4. The median time to myeloablation based on the first platelet transfusion was BMT Day +5. All but one patient on study required platelet transfusion The median time to lymphopenia-defined myeloablation was BMT Day +3.

Reviewer Comment: A query of the sponsor's ACCESS database (Table-Laboratory Hematology and Table- Transfusion) revealed that the majority of patients received their first platelet transfusion on study when the platelet count was <20,000/mm^3. Twelve patients were exceptions.

4.10.2 Engraftment

Engraftment was recorded as the day that ANC exceeded 0.5 x 10^9/L. All **evaluable** patients (60/60) treated in this study are reported to have engrafted. The median time to engraftment was BMT Day +13 (range = 9-29). The patient who received no treatment on study was not considered in this analysis, and Pt. who died on Day +20 before engraftment took place from a fungal pneumonia was not included in the analysis either.

There was one graft failure reported in this study. **Pt.** had graft failure reported on Day +34. According to her SAE narrative for LLL Pneumonia and Bilateral Effusion, this 41 yo female had graft failure diagnosed when her ANC dropped to 300. A bone marrow on Day +36 revealed 18% blasts and relapse of her AML. Because the bone marrow revealed disease relapse and a mixed chimera, the sponsor has subsequently revised this assessment of graft failure in its 120 Day Safety Update. It is its position, now, that there were no graft failures in this study.

Reviewer Comment: Deaths prior to documentation of engraftment are treated variably in BMT studies reported in the literature. Some reports consider these patients non-evaluable for the endpoint, and others handle these cases as graft failures. The statistical analysis plan in the protocol does not pre-define how these cases will be dealt with in the study analysis, but the sponsor has analyzed them as non-evaluable. The death of Pt. without engraftment occurred 7days after the median time to engraftment observed for the overall patient population in this study, but 9 days earlier than the latest day in the overall range observed. The fact that the WBC remained <0.2 without evidence of engraftment one week past the median day for engraftment on this study certainly raises the question of whether this patient would have been a graft failure if he had survived.

An ACCESS query of the sponsor's ACCESS Concomitant Medications table using "GCSF", "G-CSF", "Neupogen", and "Filgrastim" did not yield a list of the total number of patients on study. The concomitant medication list was examined for all the patients that did not appear in the query list, and 12 patients did not appear to be treated with G-CSF on study – most treated at study center #06. A review of the data listings for concomitant medications demonstrated that stop dates for G-CSF were not always provided in the data base, and multiple stop and start dates were found for some patients. In addition, when the serial WBC's and ANC's were examined by patient, the possibility was raised that not all sporadic use of G-CSF was always

recorded. For example, a patient's granulocyte could be noted to drift downward after the stop date for G-CSF in the concomitant medication data base, and then suddenly jump significantly, only to start a slow drift downward again – similar to the drift seen after the documented prior stop of G-CSF (but no G-CSF usage was documented for the subsequent rise).

Because CBC data after 28 days was not provided in most patients, the reviewer questioned whether the ANC was maintained after discharge from the hospital in those patients who had ANC's drifting significantly downward at the time of dismissal. The only means of answering that question with the datasets provided was to evaluate the Post-Study Surveillance Adverse Event ACCESS data set (BMT Day +29 to BMT Day +100). This data set was derived from a sheet in the case report form that provided a place for the investigator to record the adverse events during that time period, along with the associated grade, start and stop dates, coding for severity, relationship to busulfan, and the action taken to address the event. This was evaluated by the reviewer for reports of graft failure, leukopenia, or neutropenia post-dismissal from the hospital. This approach yielded five patients who had leukopenia reported after Day 30 : ***Pt.*** *(Grade 3 Leukopenia Day 35-37, Grade 4 Leukopenia Day 37-43, and Grade 3 Leukopenia Day 43-46, associated with thrombocytopenia grade 3-4 on Days 24-41),* ***Pt.*** *(Grade 2 Leukopenia Day 27-38 and Grade 3 Leukopenia Day 55-69),* ***Pt.*** *(Grade 3 Neutropenia Days 63-72),* ***Pt-*** *(Grade 3 Leukopenia Day 28-31), and* ***Pt-*** *(Grade 1 Leukopenia Day 27-34). Only the first three `patients in that list had leukopenia reported beyond Day 34 and their pertinent laboratory are summarized in the table below.*

Despite finding no reports of hematological adverse events in the Post-Study Surveillance (Day +29 - Day +100), the reviewer had questions about the quality of data provided regarding engraftment in six additional patients who are included in the table below as well (Pt's . The latter questions generally sprung from the fact that no G-CSF stop date was provided, or there were apparent missing data regarding G-CSF use. In patient there were no lab data beyond Day +18, and in patient the ANC dropped below 500 after the date of engraftment (meeting the study definition of graft failure), followed then by a climb to 2,560. None of these patients had hematological adverse events identified in the Post-Study Surveillance ACCESS data set derived from the Post-Study Surveillance Adverse Events Record (BMT Day +29 to BMT Day +100) sheet in the case report form described above.

Table 11 Summary Patient Hematology Data in Patients with a Significant Drop in ANC After Engraftment

	Pt.				
BMT Day	WBC	ANC	Platelet	GCSF	Transfusion
Day +11		17		↓	Platelets
Day+12		1,159		↓	
Day +14	1.4	1,302	32	Stop	Platelets
Day +16		4,277	39		
Day +21		1,904	39		
Day+22		16,744	37		
Day +23	9.1	7,362	30		
Day +25		1,890	23		
Day +27		1,659	12		Platelets
Day +28	14.8	13,912	19		

Pt.					
BMT Day	WBC	ANC	Platelets	GCSF	Transfusion
Day +15	1.0	450	12	NO Stop Date	
Day +16	1.7	476	9	↓	Platelets
Day + 17	3.0	1320	40	↓	
Day +20	8.5	5610	18	↓	
Day +27	2.1	882	74	↓	

Pt.					
BMT	WBC	ANC	Platelets	GCSF	Transfusion
Day +12	0.6	336	9	Stop GCSF	Platelets
Day +13	1.2	679	7		Platelets
Day +14	1.5	870	7		Platelets
Day +19	2.2	1386	17		
Day +26	4.2	3486	45		

Pt.					
BMT	WBC	ANC	Platelets	GCSF	Transfusion
Day +11		102	14	↓	
Day +12		801	5	↓	Platelets
Day +14		6,552	9	Stop GCSF	Platelets
Day +17		4,380	8		Platelets
Day +20		1,612	25		Platelets
Day 21		672	17	GCSF x1	
Day 22		27,784	25		
Day 25		2,944	36		
Day 28		2,255	66		

Pt.	GRAFT FAILURE REPORTED DAY +34				
BMT	WBC	ANC	Platelets	GCSF	Transfusion
Day +16		330	6	NO Stop Date	Platelets
Day +17		518	14	↓	Platelets
Day +18		924	4	↓	Platelets
Day +21		2,254	4	↓	Platelets
Day +22		1,960	3	↓	Platelets
Day +25		1,863	2	↓	Platelets
Day +26		980	2	↓	
Day +27		1,767	1	↓	
Day +28		1,168	1	↓	Platelets

Pt.					
BMT	WBC	ANC	Platelets	GCSF	Transfusion
Day +11	0.7	490	41K	NO Stop Date	Platelets
Day +12	1.4	1,106	28K	↓	
Day +14	3.4	2,720	21K	↓	
Day +16	1.6	848	36K	↓	

Patient No.	Sponsor Day of Engraftment	Reviewer Day of Engraftment
	20	
	22	23
	16	14
	17	20
	29	29*
	21	22
	19	
	18	
	18	
	17	18
	14	
	20	
	18	19
MEDIAN	13	13

* The sponsor submitted laboratory data from Day +29 in patient that demonstrated an ANC >500 on that day. This information was submitted in correspondence dated December 28, 1998.

Note: Review of the ACCESS Concomitant Medication dataset suggests that most of the patients treated at study center #6 were not treated with G-CSF. Thirteen of the 61 evaluable patients on study were treated with G-CSF. In addition to the patients at center #6 (with the exception of), Pt's were not treated with G-CSF.

The 20 patients highlighted above, to which the sponsor and reviewer assigned differing engraftment dates, are summarized below.

Day +17: Abs. Granulocyte Count = 0.518 x 10^9/L (Time=0700)

Day +18: Abs. Granulocyte Count = 0.924 x 10^9/L

Day +13: Abs. Granulocyte Count = 0.648 x 10^9/L

Day +14: Abs. Granulocyte Count = 0.712 x 10^9/L

Day +13: Abs. Granulocyte Count = 0.504 x 10^9/L

Day +14: Abs. Granulocyte Count = 0.880 x 10^9/L

Day 11: Calc. Neutrophil Count = 0.384 x 10^9/L
WBC=0.8 % Neutrophil = 48%

Day 12: Calc. Neutrophil Count = 0.759 x 10^9/L

WBC=1.1 %Neutrophil = 69%

Day 16: Calc. Neutrophil Count = 0.440 x 10^9/L
WBC = 1.1 %Neutrophil = 40%

(Later in the day WBC is 1.5 but %Neutrophils not provided)

Day 17: Calc. Neutrophil Count = 0.627 x 10^9/L
WBC = 1.9 %Neutrophil = 33%

Day 15: Calc. Neutrophil Count = 450 x 10^9/L
WBC = 1.0 %Neutrophil = 45%

(Later in the day WBC is 0.9 but no % Neutrophil provided)

Day 16: Calc. Neutrophil Count = 0.504 x 10^9/L
WBC = 1.4 %Neutrophil = 36%

Day 16: Calc. Neutrophil Count = 0.308 x 10^9/L
WBC = 0.7 %Neutrophil = 44%

(Later in the day WBC is1.3 but no % Neutrophil provided)

Day 17: Calc. Neutrophil Count = 1.080 x 10^9/L
WBC = 2.0 %Neutrophil = 54%

Day 12: Calc. Neutrophil Count = 0.336 x 10^9/L
WBC = 0.6 %Neutrophil = 56%

(Later in the day WBC 0.8 but no % Neutrophil provided)

Day 13: Calc. Neutrophil Count = 0.672 x 10^9/L
WBC = 1.2 %Neutrophil = 56%

Day 12: Calc. Neutrophil Count = 0.408 x 10^9/L
WBC = 0.8 %Neutrophil = 51%

Day 13: Calc. Neutrophil Count = 1.024 x 10^9/L
WBC = 1.6 %Neutrophil = 64%

Day 17: Calc. Neutrophil Count = 0.420 x 10^9/L
WBC = 0.7 %Neutrophil = 60%

Day 18: Calc. Neutrophil Count = 0.330 x 10^9/L
WBC = 1.0 %Neutrophil = 33%

Day 19: Calc. Neutrophil Count = 0.540 x 10^9/L
WBC = 1.4 %Neutrophil = 39%

Day 13: Abs. Granulocyte Count = 0.400 x 10^9/L

Day +14: Abs. Granulocyte Count = 0.600 x 10^9/L

Day 14: Calc. Neutrophil Count = 0.104 x 10^9/L
WBC = 1.3 %Neutrophil = 8%

Day 15: THERE IS NO DAY 15 Hematology in DataSet

Day 21: Calc. Neutrophil Count = 0.693 x 10^9/L
WBC = 3.3 %Neutrophil = 21%

Day 13: Calc. Neutrophil Count = 0.380 x 10^9/L
WBC = 1.0 %Neutrophil = 38%

Day 14: Calc. Neutrophil Count = 0.846 x 10^9/L
WBC = 1.8 %Neutrophil = 47%

Day 22: Calc. Neutrophil Count = 0.288 x 10^9/L
WBC = 1.2 %Neutrophil = 24%

Day 23: Calc. Neutrophil Count = 1.776 x 10^9/L
WBC = 3.7 %Neutrophil = 48%

Day 14: Abs. Granulocyte Count = 0.580 x 10^9/L

Day 16 Abs. Granulocyte Count = 1.500 x 10^9/L

Day 17: Calc. Neutrophil Count = 0.429 x 10^9/L
WBC = 1.1 %Neutrophil = 39%

Day 18 and 19 have no %Neutrophils reported

Day 20: Calc. Neutrophil Count = 0.880 x 10^9/L
WBC = 2.2 %Neutrophil = 40%

There is no hematology data beyond Day +28 in the database. On that date the WBC=1.5, but there is no neutrophil percentage shown. The reviewer is unable Confirm the sponsor's report of engraftment on Day +29.

Day 20:	Calc. Neutrophil Count = 0.384 x 10^9/L	
	WBC = 1.2	%Neutrophil = 32%
Day 21:	Calc. Neutrophil Count = ???	
	WBC = 1.5	%Neutrophil = None Given
Day 22:	Calc. Neutrophil Count = 0.918 x 10^9/L	
	WBC = 2.7	%Neutrophil = 34%
Day 17:	Calc. Neutrophil Count = 0.490 x 10^9/L	
	WBC = 1.4	%Neutrophil = 35%
Day 18:	Calc. Neutrophil Count = 0.735 x 10^9/L	
	WBC = 2.1	%Neutrophil = 35%
Day 18:	Calc. Neutrophil Count = Unable to Calculate	
	WBC = 1.6	%Neutrophil = None Given
Day 19:	Calc. Neutrophil Count = 1.846 x 10^9/L	
	WBC = 2.6	%Neutrophil = 71%

Despite the changes in engraftment date made by the reviewer, the median time to engraftment was unchanged from that reported by the sponsor. (This is based on the assumption that Day +29 does represent the day of engraftment in Pt. who has no meaningful neutrophil data available for review. This patient's platelet count was 140K on that date, without transfusion.)

The median number of platelet transfusions on study was 6. The range was The red blood cell transfusion median was 4, with a range of The median days to discharge after transplantation was 17 (range = days). The latter time to hospital dismissal is taken from the sponsor's 120 Day Safety Update.

The results for time to engraftment observed in this study (median=13 days) that involved a heavily pretreated population undergoing transplantation with allogeneic stem cells is favorably comparable to published data in a 43 article "core data set" literature review provided by the sponsor that will be discussed later in the literature review section.

4.10.3 Late Graft Failure

The sponsor reported a single instance of late graft failure in the original study report. That patient, met the study protocol definition of late graft failure by experiencing a drop in the ANC to <500 on Day +34. Because 18% blasts (disease recurrence) were found on a bone marrow performed on Day +36 that also revealed mixed chimera, the sponsor has changed the assessment of late graft failure in the Safety Update, and now reports that there were no episodes of graft failure in this study. Because hematology laboratory beyond Day +28 is not generally provided in this application, the reviewer cannot audit the later laboratory surveillance to confirm the report of no graft failures beyond Day +28. The serious adverse event reports were reviewed

for any indication of late graft failure, and the reviewer detected none. January 9,1998 was the clinical data cut-off date for all patients (N=42) that had completed the "Study Period." There were Short-Term Post-Study Surveillance data (through Day +100) available through January 9, 1998 on 31/42 patients participating, and Long-Term Post-Study Surveillance data (> Day +100) available on 18/42 patients.

In the 120-Day Safety Update there were no changes regarding late engraftment failure.

4.10.4 Relapse

At the time of the clinical cut-off, 77% of patients had been observed to BMT Day +100, and 33% had been observed beyond Day +100. The median follow-up of patients who were still disease free at the time of the clinical cut-off was 82 days. Fifty-five patients were disease free at that time (90% of the 61 patients who actually received study drug). The median time to relapse in the 6 patients whose disease relapsed in that time was 87 days. There were no relapses in the first 28 days of the study. Three patients relapsed between Day +28 and Day +100 (the limited surveillance period of the study) – on Day +34, Day +39, and Day +68. The 3 remaining observed relapses occurred on Day +106, +114, and +255. The Kaplan-Meier probability of freedom from relapse at 100 days, as calculated by the sponsor, was 0.93 (5% CI: 0.84 – 1.0). Five of the six relapses occurred in patients with acute leukemia, and the remaining patient had CML. None of the relapsed acute leukemias were considered to have been heavily pretreated at the time of entering this study, and none had been treated with previous transplantation. Two of the patients had active disease at the time of treatment on OMC-BUS-4, and the remaining 3 were in remission. The patient with CML was considered heavily pretreated at the time of study entry. This patient had been treated with prior radiation, ≥3 prior chemotherapy regimens, and transplantation.

In the 120-Day Safety Update obtained by the reviewer on 12/9/98, the sponsor noted that as of the Safety Update Report clinical cut-off date of July 31, 1998, 82% (50/61) of the patients had been observed through Day +100. The eleven patients not followed through that point included the 3 patients who withdrew on Days +39, +49, and +65, and eight who died. Two of those eight died before Day +28. Seventeen of the 50 who completed 100 day post-transplant surveillance subsequently became unavailable for follow-up, including 7 who withdrew consent, and 10 who died. All patients who withdrew from the study had relapse or disease progression when they withdrew.

The sponsor reports in the Safety Update that as of July 31, 1998, 38/61 were progression-free, with a median follow-up of 261 days post-transplant. Seventeen additional patients had relapsed since the clinical cut-off date for the original study report, resulting in a total of 23 relapses on study. The median time to relapse in the revised report was 183 days. Six of the total 23 relapses occurred in the short-term surveillance period of Day +29 to Day +100, and 17 occurred after Day +100. The disease distribution within the 23 total relapses included 13 AML's, 5 CML's, 2 MDS, and 3 lymphoma. The revised Kaplan-Meier probability of freedom from relapse at 1 year is 0.51 (95% CI: 0.35-0.67).

4.10.5 Survival

Again, the fact that 77% of patients on study had been followed through Day +100 and only 43% past Day +100 by the time of the clinical cut-off date (January 9, 1998) should be noted before considering the survival data. The median follow-up from transplant for the patients who were survivors at the time of the clinical cut-off date was only 88 days. There were two deaths during the first 28 days after transplantation. One occurred on BMT Day +20, and the other on Day +27. One patient had acute leukemia and the other had NHL that had previously been treated with BMT and radiation. Both had had ≥3 prior chemotherapy regimens, and both died with pneumonia. Six patients died during the follow-up period between Day +29 and Day +100 (on days +30, +31, +42, +62. +80, and +98), and there were two deaths during the long-term surveillance period beyond BMT Day +100 (on Days +164 and +275). Two of the deaths that occurred in the Day +29 to Day +100 interval were attributed to VOD, one to disease progression, and the remaining 3 were respiratory related – pneumonia, respiratory failure, and diffuse alveolar hemorrhage. Only two of these patients were not considered heavily pretreated at the time of study entry. The deaths that occurred in the long-term surveillance period were attributed to disease progression (1) and infection (1). The sponsor's Kaplan-Meier estimated probability of survival at 100 days was 0.82 (95% CI: 0.69-0.94). The sponsor's Kaplan-Meier probability of disease free survival at 100 days was 0.80 (95% CI: 0.67 – 0.92).

In the Safety Update, 43/61 (70%) of patients were alive through the July 31, 1998 cut-off. The median follow-up at that point was 288 days for the survivors. All 8 additional deaths reported in the Safety Update occurred after Day +100. The median time to death was 139 days. Of the 8 new deaths reported in this update, 2 had had acute leukemia in remission at the time of transplantation, and 1 active AML, one active lymphoma, and 4 CML. The cause of death reported in this group of patients is discussed later in the safety analysis. The Safety Update's revised Kaplan-Meier probability of survival at 1 year was 0.67 (95% CI = 0.54-0.80), and the Kaplan-Meier estimate of DFS at 1 year was 0.42 (95% CI = 0.28-0.57).

4.11 Safety Analysis

4.11.1 Adverse Events

The most commonly reported adverse events were those that could be anticipated, considering that these patients had been treated with high-dose chemotherapy followed by stem cell stem cell transplantation. They were thrombocytopenia (90%), leukopenia (95%), anemia (87%), stomatitis (97%), nausea (98%), and vomiting (95%). The following table is derived from the sponsor's Adverse Event Summary Table 14.3.4 and Table 14.3.6 Summary of Grade 3 and 4 Toxicities. The Grade 3 and 4 Toxicity and SAE's columns (darkly shaded) represents the Grade 3 and 4 toxicities reported from Day –7 through Day +100 in the sponsor's Table 14.3.6, while the unshaded columns represent the adverse events for the early portion of the study – Day –7 to Day +28. The following table is not a complete listing of all adverse events. The reviewer has selected out the more common and/or pertinent adverse events to a high-dose busulfan-containing regimen.

Table 7: Summary of Adverse Events (BMT Day –7 to Day +28) AND Grade 3 / 4 Toxicities, and SAE's (BMT Day –7 to BMT Day +100)

COSTART term	Mild No. (%)	Moderate No. %	Severe No. %	Total Number	Grade 3&4 Toxicity	SAE's
Body as a Whole						
Fever	18 (30%)	29 (48%)	2 (3%)	49 (80%)	1 (2%)	4 (7%)
Chills	19 (31%)	8 (13%)	1 (2%)	28 (48%)	3 (5%)	
Abdominal Pain	33 (54%)	9 (15%)	2 (3%)	44 (72%)	3 (2%)	
Abdominal Enlargement	11 (18%)	3 (5%)		14 (23%)		
Ascites		1 (2%)		1 (2%)		
Inflammation Injection Site	12 (20%)	3 (5%)		15 (25%)		
Chest Pain	1 (2%)			1 (2%)	1 (2%)	
Edema General	14 (23%)	3 (5%)		17 (28%)		
Allergic Reaction	13 (21%)	2 (3%)	1 (2%)	16 (26%)	1 (2%)	1 (2%)
Headache	16 (26%)	23 (38%)	3 (5%)	42 (69%)	6 (10%)	
Cardiovascular						
	Mild	**Moderate**	**Severe**	**Total Number**	**Grade 3&4 Toxicity**	**SAE's**
Tachycardia	23 (38%)	4 (7%)		27 (44%)		
Hypotension	4 (7%)		2 (3%)	6 (10%)	2 (3%)	1 (2%)
Vasodilation	15 (25%)			15 (25%)		
Thrombosis	17 (28%)	2 (3%)		19 (31%)		1 (2%)
Postural Hypotension		1 (2%)		1 (2%)		
Left Heart Failure		1 (2%)		1 (2%)	1 (2%)	
Arrhythmia	2 (3%)	1 (2%)		3 (5%)	1 (2%)	1 (2%)
Pericardial Effusion				1 (2%)		
Digestive						
	Mild	**Moderate**	**Severe**	**Total Number**	**Grade 3&4 Toxicity**	**SAE's**
Nausea	30 (49%)	26 (43%)	4 (7%)	60 (98%)	4 (7%)	
Vomiting	32 (52%)	26 (43%)		58 (95%)	1 (2%)	
Stomatitis	15 (25%)	34 (56%)	10 (16%)	59 (97%)	16 (26%)	
Diarrhea	32 (52%)	14 (23%)	4 (7%)	50 (82%)	3 (5%)	
Hepatomegaly	2 (3%)	2 (3%)		4 (7%)		
Jaundice	6 (10%)	1 (2%)		7 (11%)		
VOD		2 (3%)	1 (2%)	3 (5%)	4 (7%)	4 (7%)
Pancreatitis		1 (2%)		1 (2%)		
Metabolic and Nutritional						
	Mild	**Moderate**	**Severe**	**Total Number**	**Grade 3&4 Toxicity**	**SAE's**
Bilirubinemia	8 (13%)	12 (20%)	10 (16%)	30 (49%)	18 (30%)	3 (5%)

SGPT Increase	10 (16%)	7 (11%)	2 (3%)	19 (31%)	4 (7%)	1 (2%)
Edema Peripheral	9 (15%)			9 (15%)	1 (2%)	
Weight Increase	2 (3%)	3 (5%)		5 (8%)		
Hypervolemia	2 (3%)	2 (3%)		4 (7%)		
Creatinine Increase	8 (13%)	4 (7%)		12 (20%)		

Nervous System

	Mild	Moderate	Severe	Total Number	Grade 3&4 Toxicity	SAE's
Coma			1 (2%)	1 (2%)	1 (2%)	

Respiratory

	Mild	Moderate	Severe	Total Number	Grade 3&4 Toxicity	SAE's
Lung Disease	19 (31%)	2 (3%)		21 (34%)		
Cough Inc.	14 (23%)	3 (5%)		17 (28%)		
Dyspnea	11 (18%)	2 (3%)	1 (2%)	14 (23%)	1 (2%)	
Asthma	5 (8%)			5 (8%)		
Hemoptysis	1 (2)	1 (2%)		2 (3%)	1 (2%)	1 (2%)
Heme Lung			1 (2%)	1 (2%)	3 (5%)	2 (3%)
Epistaxis	15 (25%)			15 (25%)		
Pleural Effusion	1 (2%)	1 (2%)		2 (3%)	1 (2%)	
Interstitial Pneumonitis	1 (2%)			1 (2%)	1 (2%)	1 (2%)
Respiratory Distress Syndrome					1 (2%)	1 (2%)
Pneumonia	1 (2%)	1 (2%)	2 (3%)	4 (7%)	4 (7%)	4 (7%)

Skin

	Mild	Moderate	Severe	Total Number	Grade 3&4 Toxicity	SAE's
Rash	29 (48%)	6 (10%)		35 (57%)		

Urogenital

	Mild	Moderate	Severe	Total Number	Grade 3&4 Toxicity	SAE's
Dysuria	4 (7%)			4 (7%)		
Hematuria	**3 (5%)**	**2 (3%)**		**5 (8%)**	**1 (2%)**	**1 (2%)**
Hemorrhagic Cystitis			**1 (2%)**	**1 (2%)**	**4 (7%)**	**4 (7%)**
Oliguria	7 (11%)	2 (3%)		9 (15%)		

Shaded Columns = Day –7 through Day +100
Unshaded Columns = Day –7 through Day +28

- <u>Hematologic Adverse Events</u>: The cytopenias observed on study were anticipated considering the therapy involved marrow ablation. Thrombocytopenia was graded severe in 49 (80%) patients. Leukopenia was graded "life threatening" in one, and severe in 89%.