5.1 Amendment #4 Efficacy Summary

As of the clinical cut-off date of July 31, 1998, 11/12 patients had completed the early study period (Day –7 to Day +28) and follow-up through Day +100. Myeloablation was induced in all patients on study, and engraftment was reported in all patients treated under this Amendment as well. The median time to engraftment of the 3 patients treated with autologous transplantation was Day +9, and the median time to engraftment for the 9 patients who had allogeneic transplantation was Day +14 (a day later that seen in the larger 61 patient population treated prior to Amendment #4). As of the median follow-up of 177 days in the 11 patients who had completed 28 days on study, there were no relapses observed. Two of the patients treated with allogeneic transplantation had died at the time of the clinical cut-off, and will be discussed below with the safety information.

5.2 Amendment #4 Safety Summary

Two of the 12 patients treated under this amendment had died by the time of the clinical cut-off. Both received allogeneic transplants. One died on Day +21 with sepsis, and the other died on Day +162 with chronic active hepatitis complicated with cirrhosis. There were thirteen SAE's reported on study – including two infection-related AE's, two GVHD-related AE's, and a new left bundle branch block that developed after the first dose of cyclophosphamide. The remaining SAE's were hyperbilirubinemia, diarrhea, esophagitis, and stomatitis. The hyperbilirubinemia SAE occurred in the patient whose death was attributed to sepsis on Day +21. The maximum bilirubin was noted in this patient on Day +14 when it peaked at 8.5. A diagnosis of VOD was not made despite a CT that revealed ascites and bilateral pleural effusions on Day +18 and complaints of abdominal pain. The patient is said to have developed sepsis on Day +17. Ten patients had elevated bilirubin's observed in the study period, but an actual diagnosis of VOD was not made. The patient who subsequently died with chronic active hepatitis had normal serum bilirubin's during the first 28 days on study. She had no known history of hepatitis, but at the time of diagnosis prior to her death had a liver biopsy that revealed hepatitis C RNA by polymerase chain reaction.

There are no new relevant safety findings in this small group of patients treated under Amendment #4 to the two phase 2 studies.

6. Dimethylacetamide Toxicity

The busulfan in BUSULFEX™ is dissolved in N,N-dimethylacetamide (33% wt/wt) and polyethylene glycol 400 (67% wt/wt). The reader should refer to the Pharmacology/Toxicology review for a thorough discussion of the toxicological profile of this inactive ingredient. Dimethylacetamide (DMA) was investigated in the early 1960's as a potential chemotherapeutic agent. A publication of a phase 1 evaluation of this compound was reviewed (Weiss AJ, et al: Cancer Chemotherapy Reports, No. 16, February 1962). [4] The total number of patients treated in this study was 17. The major toxicities observed were transient elevation in serum transaminases and neurological changes that included somnelence, lethargy, confusion and hallucinations. The hallucinations were described as predominately visual, but auditory hallucinations were described. They persisted in severe form for an additional 24 hours, and then gradually disappeared. The patients were said to be normal "within several days". Hallucinations were

associated with EEG changes that were particularly prominent in the frontal regions and maximal on the day of most striking hallucinatory activity. These changes were described as slow waves of moderate to high voltage that tended to occur in simultaneous bursts in all leads. The brain of one patient was examined at subsequent autopsy and was found to be without abnormality.

In the following table the DMA dose delivered to each patient on this phase 1 study has been expressed relative to the total overall 4 day cumulative dose anticipated to be delivered in a conditioning regimen of Busulfex 0.8 mg/kg/dose q 6h x 4 days.

Table 17 Summary of Dimethylacetamide Phase 1 Dose Related Toxicity as Published by Weiss, et. al. Relative to a BUSULFEX™ Conditioning Regimen Dose

DMA Dose	Total DMA Dose Relative to Total Busulfex Dose	No. Pt's Treated	No. of Pt's with CNS Events	Event	Onset
100 mg/kg/d x 4D	0.6x	1	0	–	–
200 mg/kg/D x 4D	1.2x	1	1	Confusion, Lethargy, Somnolence	During treatment, Day 3
200 mg/kg/d x 5D	1.5x	1	1	Lethargy, Confusion, ?Hallucination	During treatment, Day 4
300 mg/kg/d x 2D	0.9x	1	1	Confusion	1 day post-tx
320 mg/kg/D x 5D	2.4x	1	1	Hallucination, Disorientation	–
400 mg/kg/d x 4D	2.4x	2	2	Hallucination, Confusion	6 days post-tx
400 mg/kg/d x 5D	3.0x	1	1	Confusion	–
410 mg/kg/d x 4D	2.5x	1	1	Hallucination	2 days post-tx
420 mg/kg/d x 3D	1.9x	1	1	Hallucination	1 day post-tx
440 mg/kg/d x 4D	2.7x	1	1	Hallucination	1 day post-tx
450 mg/kg/d x 3D	2.1x	1	1	Hallucination	1 day post-tx
450 mg/kg/d x 4D	2.7x	1	1	Hallucination	1 day post-tx
480 mg/kg/d x 3D	2.2x	1	1	Hallucination	1 day post-tx
500 mg/kg/d x 2D	1.5x	2	1	Confusion	1 day post-tx
610 mg/kg/d x 3D	2.8x	1	1	Hallucination	1 day post-tx

In the following table the patients are tabulated according to the dosage delivered relative to the anticipated dose in a Busulfex containing conditioning regimen for transplantation.

Table 18 Tabulation of Patients Experiencing DMA Neurological Toxicity in a Phase 1 Setting Relative to a BUSULFEX™ Conditioning Regiment Dose

DMA Dose Relative to Busulfex Dose	No. Pt's	No. CNS events	Event	Onset
0.6x	1	0	–	–
0.9x	1	1	Confusion	1d post
1.2x	1	1	Confusion	During treatment, Day 3
1.5x	3	3	Confusion-2; Lethargy, Confusion, ?Hallucination	1 d post-2; During treatment, Day 4
1.9x	1	1	Hallucination	1d post
2.1x	1	1	Hallucination	1d post
2.2x	1	1	Hallucination	1d post
2.4x	3	3	Hallucination-3 Confusion-2	6d post-1; Not given-2
2.5x	1	1	Hallucination	2d post
2.7x	2	2	Hallucination-2	1d post-2
2.8x	1	1	Hallucination	1d post
3.0x	1	1	Confusion	Not given

Based on these data the reviewer went back to the study reports of OMC-BUS-3 and OMC-BUS-4 to reassess the neurological toxicity reported in these studies. The adverse event and concomitant medication ACCESS data sets were examined for event onset comparability to that reported in the DMA phase 1 trial, and to assess if other medications could have contributed to

the symptoms. In OMC-BUS-3 one patient had an adverse event of "confusion" reported 3 days (BMT Day –1) after the last day of busulfan dosing (BMT Day –4). One patient had an adverse event of hallucination reported one day after the last day of busulfan dosage (Day –3). That patient was treated with decadron on the same day (cyclophosphamide prophylaxis) and had a prn dose of Ambien ordered (but it is unknown whether it was administered).

In OMC-BUS-4 all but one of the adverse event reports of "confusion" occurred on or after BMT Day +16. The exception was in Pt. confusion was reported on BMT Day –3 (one day after the last dosing of busulfan). On that day the patient had been treated with decadron (cyclophosphamide nausea prophylaxis) as well as compazine with benadryl (BMT Day –5 through Day –2).

Hallucinations were reported in 3 patients on OMC-BUS-4. In Pt. it occurred on BMT Day –3 (one day after the last dose of busulfan). This patient was treated with Decadron on that date, but was treated subsequently during the admission with the same drug without any reported CNS changes. In addition this patient had a prn Restoril order, but it is not known whether he was actually treated with this medication. Pt. had hallucinations reported on BMT Day +10 (14 days after the last busulfan dose), and Pt. had hallucinations reported on BMT Day +12 (16 days after the last busulfan dose). Nightmares were reported as an adverse event in Pt. on BMT Day 0.

Pt. had acute delirium reported that had its onset on BMT Day –4 (last day of Busulfex dosing) and did not resolve until BMT Day +5. This patient was 55 years old and was started on Ambien on BMT Day-5. It was stopped on BMT Day –3. Compazine was administered on a scheduled q 6h dose from BMT Day –7 to BMT Day –4.

All the adverse events reported as "lethargy" on OMC-BUS-4 occurred on or after BMT Day +4 (4, 9. 16, and 18). "Somnolence was reported in one patient, , on BMT Day +7. "Agitation" was reported in patient on BMT Day +17, and "disorientation" was reported on BMT Day +18 for Pt. All of these cases seem too remote from the busulfan dosing to be related to the DMA solvent.

It is possible that some of these CNS adverse events were related to DMA, particularly the hallucinations in Pt. , the acute delirium in Pt. , and the confusion reported in Pt. – given the similar timing of onset to that seen in the phase 1 study reported by Weiss. These patients, however, were on multiple other medications, that could have played a role in these CNS manifestations. It is difficult to definitively associate these events with DMA. It seems clear, however, that the labeling should reflect the potential of this toxicity.

7. Literature Review – High Dose Busulfan in Conditioning Regimens for Hematopoietic Stem Cell Transplantation

In a meeting held January 16,1997, the Agency agreed that a complete and comprehensive literature review establishing evidence that oral busulfan is safe and efficacious as a preparative conditioning therapy for bone marrow transplantation would be acceptable to support an application for this indication. A comparison of the efficacy and safety data for oral busulfan reported in the literature and those of intravenous busulfan observed in the submitted clinical studies would be required in such an application format. Additional correspondence from the

Agency dated April 27, 1998 clarified that, because high dose oral busulfan has not been approved for bone marrow transplantation in any disease, the literature review would have to document its efficacy in the setting of specific diseases. An approval of a global indication in bone marrow transplantation would not be forthcoming.

The sponsor has proposed the following labeled indications in this application:

This is qualified in the proposed labeling with the following statement:

In keeping with its discussions in an NDA formatting meeting held May 6, 1998, the sponsor has provided within this application an analysis and discussion of the literature-based support of each disease indication proposed in their labeling.

The wording of the proposed labeling and the content of the literature review submitted to support this labeling proposal raised the following issues, which the reviewer used as a guide for the examination of the submitted efficacy/safety data for high dose busulfan:

- Are there sufficient data to support the use of **high dose busulfan** in combination with a variety of chemotherapeutic agents? Or, alternatively, which chemotherapeutic agent combinations that include **high dose busulfan** as a component have adequate data supporting their efficacy and safety?

- Are there sufficient data to support the use of high dose busulfan in combination with radiation therapy?

- Since "hematopoietic progenitor cell transplantation" includes allogeneic bone marrow transplant, autologous bone marrow transplant, and peripheral blood stem cell transplantation (both autologous and allogeneic), are there data to support the use of high dose oral busulfan in each of these settings? Should demonstration of efficacy and safety in one, e.g. allogeneic bone marrow transplant, translate into efficacy and safety in each of the other modalities?

- Are there sufficient data to support efficacy and safety of high dose oral busulfan in bone marrow transplantation in each of the following diseases – AML, ALL, CML, MDS, non-Hodgkin's lymphoma, Hodgkin's disease, multiple myeloma, breast cancer, ovarian cancer, and genetic diseases?

- The last question implies that there is evidence to support the efficacy of bone marrow transplantation in each of these diseases. Does such evidence exist?

Confronted with the numerous efficacy issues derived from the sponsor's proposal for labeling and the 43 "core database" articles submitted by the sponsor that involved diverse patient populations with multiple diseases, varying intra-study supportive care measures (e.g. GVH prophylaxis and G-CSF/GM-CSF use), and methods of stem cell transplantation, there was a clear necessity to prospectively define the methodology for assessing the literature data base and the sponsor's overview. Principles of evidence-based medicine defined in publications by Oxman[5], Guyatt[6], Bloomfield[7], and Shaw[8] were used to provide the framework for the review. These principles are based on the recognition that only a systematic overview of existing evidence can form the basis for translation of evidence into a clinical recommendation. The overview should address a focused clinical question, use appropriate criteria to select studies for inclusion in the overview, employ a comprehensive search capable of identifying all pertinent articles, and appraise the validity of the studies included. Outcomes of interest should be similar across studies.

Guidelines for grading quality of clinical studies for their inclusion in an overview universally consider the highest level of evidence, Level I, as that derived from well-designed, randomized, controlled clinical trials. The next lower level, Level II evidence, is provided by nonrandomized, case-control or cohort studies. Uncontrolled and retrospective studies, including those with historic controls, provide the lowest levels of evidence at Level III. Randomized, controlled studies can be further assessed based on number of participants. The number should be high enough to be associated with a low risk of error.

Based on this overview, the following early review framework was outlined by the reviewer:

- Assess sponsor methodology for identification of pertinent articles for review.
- Assess the literature search for missing, potentially pertinent articles.
- Assess the abstraction of data from the core data base articles by the sponsor to see if it could be duplicated.
- Assess the study design of the "core database" articles to assign the level of evidence provided.
- Evaluate the "core database" evidence provided individually for each of the issues derived from the proposed indication tabulated above.

The review team agreed that level I evidence of efficacy/safety would form the basis for confirmation of each proposed indication. In addition, the team agreed that the clinical endpoints of interest for establishing efficacy were overall survival and disease free survival. Endpoints of interest to support safety included treatment-related mortality, VOD and time to engraftment.

The methodology used by the reviewer to assess the completeness of the literature review is included in Appendix #2 of this review. She also reabstracted the data from the sponsor's "core dataset" and checked it against that abstracted by the sponsor. The reviewer's abstraction agreed with that of the sponsor's except on some minor points, and frequently those disagreements could be attributed to editorial problems with the article itself – differing values were reported in different sections or tables of the individual paper.

The format of the critical evaluation of the sponsor's literature review that follows will be disease-based. For each disease listed in the proposed, labeled indication, the medical reviewer has tabulated the articles in the sponsor's 43 article "core database" that provide data in that disease. These articles are further sub-categorized within the disease grouping on the basis of whether the article pertains only to that disease, or whether multiple malignancies were assessed

within the confines of one study. Articles are assigned a level of evidence based on study design. This review will focus almost exclusively on evidence from randomized, controlled trials, and separate tables that summarize the features of these level I articles are provided. Any pertinent articles identified by the reviewer outside the sponsor's "core database" are similarly tabulated, in additional tables. A discussion summarizing the data from any level I studies will follow the summary tables, along with literature references regarding the general issue of whether transplantation is an accepted treatment modality in that disease setting.

7.1 Acute Myelogenous Leukemia

The following table summarizes the level of evidence provided by the core database in the proposed indication in AML. Additional pertinent articles identified by the medical reviewer's evaluation of the literature search are presented in a separate table that follows.

Table 19 Summary List of Sponsor's Core Database Articles Pertaining to AML

AML- only patient population				
Study	**Level of Evidence**	**No. of Pt's**	**Study Design**	
Blaise	I	101 (51/50)*	**Randomized Controlled Open Label**	Allo-BMT
Cassileth	Level III for AML (Level II for autologous)	58 (39/19)**	Uncontrolled, prospective (Cohort study for autologous)	Auto-BMT
Chao	Level III	50	Uncontrolled, Phase 2	Auto-BMT
Chopra	Level III	34	Retrospective, uncontrolled	Auto-BMT
Copelan	Level III	127	Uncontrolled, Retrospective?	Allo-BMT
Crilley	Level III	25	Retrospective	Allo-BMT
Demirer	Level III	23	Uncontrolled, Prospective?	Auto-BMT
Dusenbery	Level III	75	Retrospective	Auto-BMT
Geller	Level III	99	Retrospective? Uncontrolled	Allo-BMT
Miggiano	Level III	51	Retrospective Uncontrolled	Auto-BMT
Santos	Level III	51	Retrospective Uncontrolled	Allo-BMT
Sanz	Level III	28	Prospective, Uncontrolled	Auto-BMT
Selvaggi	Level III	63	Prospective, Uncontrolled	Auto-BMT
AML represented in a mixed disease study population				

Study	Level of Evidence	No. of Pt's	Study Design	Diseases
Ringden	I	**69***** (37/32) (167)	Randomized, Controlled, Open Label	AML, ALL, CML, "Lymphoma" Allo-BMT
Angelucci	III	**2** (30)	Retrospective, uncontrolled	ALL, ANLL, CML, MM, MDS Allo-BMT
Ballester	III	**3** (51)	Uncontrolled, Phase 1-2	Auto-BMT
Chiang	III	**2** (23)	Uncontrolled, Prospective	CML, ALL, AML, NHL, HD, MDS Allo-BMT + 1 Auto-BMT
Kapoor	III	**51** (127)	Uncontrolled, Prospective	CML, AML, ALL, MDS, Lymphoma Allo-BMT
Przepiorka	III	**8** (30)	Prospective, Phase 1-2	AML, ALL, CML, MDS, Lymphoma Allo-BMT
Przepiorka	III	**33** (85)	Uncontrolled, Prospective	AML, ALL, CML, MDS Allo-BMT
Sahebi	III	**12** (65)	Retrospective	AML, ALL, CML, MDS Allo-BMT
Spitzer	III	**22** (33)	Retrospective	AML, ALL, CML, MDS, NHL, HD, CLL, PLL Allo-BMT + Auto-BMT
Topolsky	III	**3** (25)	Retrospective	AML, CML, ALL, MDS, MM Allo-BMT
Tutschka	III	**23** (50)	Uncontrolled, Prospective	AML, CML, ALL Allo-BMT
Vaughn	III	**10** (24)	Retrospective, Historic Control	AML, ALL, CML, HD, NHL Allo-BMT
Vey	III	**12** (25)	Uncontrolled, Prospective	AML, ALL, CML, Lymphoma Allo-BMT

von Bueltzingsloewen	III	26 (101)	Retrospective	AML, ALL, CML, MDS Allo-BMT

* Number of participants in each arm; Bolded number represents the busulfan-containing arm.
** Number of participants in the comparison between autologous and allogeneic transplantation in this study. The underlined number represents the number of participants who had autologous transplantation.
***The bold number represents the number of patients with AML, the number in parentheses below is the total number of patients on study.

To summarize the evidence provided by the sponsor in AML, there are two level I studies, and the remaining 24 studies provide only level III evidence. Only one of the level I studies is restricted to patients with AML. There are eleven additional studies that are restricted to patients with AML, but they provide only level III evidence. The remaining studies included patients with a number of different hematological malignancies.

The following table summarizes the additional pertinent studies in the literature identified by the reviewer and not included in the sponsor's 43 article "core dataset".

Table 20 Summary List of Additional Pertinent AML Studies Identified by Reviewer

AML-only Patient Population				
Study	**Level of Evidence**	**No. of Pt's**	**Study Design**	
Cassileth 12/98	I	116 ABMT 117 HDAC 113 Allo-BMT	Prospective Randomized Controlled	First CR
Harousseau 10/97	I	86 ABMT 71 ICC 73 Allo-BMT	Prospective, Randomized Controlled	First CR
Ravindranath 5/96	I	115 ABMT 117 ICC 89 Allo-BMT	Prospective, Randomized Controlled	Pediatric AML First CR
Reiffers 96	I	39 ASCT 38 MCx (Allo-BMT: 14/33 Bu)	Prospective, Randomized Controlled	First CR
Zander 12/97	III	31	Retrospective, Uncontrolled	Allo-BMT
Michel 6/94	III?	42 Bu/Cy 32 TBI	Retrospective	Allo-BMT
Michel 6/97	III?	42 Bu/Cy 32 TBI	Retrospective	Update of above
AML represented in a mixed disease study population				
Study	**Level of Evidence**	**No. of Pt's**	**Study Design**	**Diseases**

Blume 4/93	I	18* (18/22) (61/61)	**Randomized, Controlled, Prospective**	AML, CML, ALL Allo-BMT
Bertz 6/97	III	10 (36)	Uncontrolled, Retrospective	AML, CML, ALL, MDS Allo-BMT
Ljungman 12/97	III	172	Uncontrolled, Prospective	AML, CML, ALL, MDS Allo-BMT
Kalaycioglu 1/95	III	93 (199)	Retrospective, Uncontrolled	AML, CML, MDS Allo-BMT

* Eighteen patients with AML were treated with a busulfan-based regimen in this study. There were 22 patients on study with AML who were not treated with a busulfan-based regimen. There were 61 total patients (representing three hematological malignancies) on each arm of this study.

There were five level I studies identified by the reviewer. Only one, the study report by Blume, is similar in structure to the level I studies submitted by the sponsor in the 43 article "core dataset" – randomizing between BU/CY and CY/TBI. It is a study that enrolled a mixture of leukemia types. The remaining four level I studies in the reviewer's table all focus on AML in first CR, and examine autologous transplantation vs. maintenance chemotherapy (in one) or intensive course consolidation chemotherapy (remaining two). One of these studies evaluates pediatric AML. All four find no statistically significant difference in DFS between these treatment modalities (autologous transplantation vs. chemotherapy). One study, reported recently by Cassileth[9] found that the probability of overall survival after consolidation with high-dose cytarabine was higher than with autologous transplantation, p=0.05.

The following table summarizes the study design characteristics and efficacy findings of the level I studies identified by the sponsor and reviewer.

Table 21 Summary of Level I Studies Pertaining to AML

Citation	Design and Dose	Disease	BMT Type	% Engrafted Median Days	%Relapse	%Survival Median Survival	Adverse Events
Blaise, D. Blood. 1992 May; 79(10):2578. Allogeneic BMT for AML in first remission: a randomized trial of busulfan-cytoxan vs. Cytoxan-TBI as preparative regimen: a report from the Group d'Etudes de la Greffe de Moelle Osseuse. (1987-1990 accrual)	Prospective, Randomized BU/CY= BU 4 mg/kg x 4d + CY 60 mg/kg x 2d VS. CY 60 mg/kg x 2d + TBI (43/50 pt's fractionated; 6 fx's; + lung shielding in all)	AML in first CR Age > 14yo Mean age = 32 ± 8	Allogeneic HLA-identical sibling BU/CY = 51 CY/TBI = 50 GvH Prophylaxis: Cyclosporine+MTX Anti-p55 MoAb in 17 patients (8/9) (investigational)	ANC=500: 19± 7d BU/CY ANC= 500: 19 ± 6d CY/TBI Platelets= 50K: 30 ±26d BU/CY Platelets= 50K: 31± 18d CY/TBI 1/51 BU/CY and 3/50 CY/TBI not evaluable for engraftment for death within 1 month of BMT.	BU/CY = 34% CY/TBI= 14% P<0.04 (K-M probability at 2 years)	Mean f/u=23 months OS (2y K-M) BU/CY=51% CY/TBI= 75% (P<0.02) DFS (2y K-M) BU/CY=47% CY/TBI= 72% P<0.01	BU/CY = 27% TRM 3/6 VOD died CY/TBI = 8% TRM 1/2 VOD died p<0.06
Blume, K. Blood. 1993 April; 81(8): 2187. A Prospective Randomized Comparison of Total Body Irradiation-Etoposide VS. Busulfan-Cyclophosphamide as Preparatory Regimens for Bone Marrow Transplantation in Patients With Leukemia Who Were No in First Remission: A SWOG Study 1987-1991 accrual	Prospective, Randomized. BU/Cy= BU 4 mg/.kg x 4d + CY 60 mg/kg x 2d VS. TBI/VP-16 (60 mg/kg x 1) TBI in 11 fx's, shielding not mentioned Stratified for Good Risk=CR2 or Accelerated CML Poor Risk=CR3, Induction failure, In Relapse, Blast phase CML	Leukemia failing prior therapy at least once AML=40 BU/CY=18 TBI=22 ALL=48 BU/CY=23 TBI=25 CML=34 BU/CY=20 TBI=14	Allogeneic Sibling donor BU/CY=61 TBI/VP-16=61 GvH prophylaxis: Cyclosporine + prednisone	No Mention	RR of Relapse expressed as BU/CY:TBI/VP-16 RR=1.02 95% CI=0.56-1.86	Med. F/U= 30 mo RR of Mortality expressed as BU/CY:TBI/VP-16 Mortality RR = 0.97 (95%CI=0.64-1.48) OS and DFS were subset analyzed by good risk and poor risk – 3y actuarial Study had 89% power to detect RR 2.3	BU/CY = 3/61 VOD TBI/VP-16 = 0/61 VOD

Citation	Design and Dose	Disease	BMT Type	% Engrafted Median Days	%Relapse	%Survival Median Survival	Adverse Events
		Age stratification for: 0-20yo 21-50yo					
Ringden, O. Blood. 1994 May; 83(9):2723. Randomized Trial Comparing Busulfan with TBI as Conditioning in Allogeneic Marrow Transplant Recipients with Leukemia: A Report from the Nordic BMT Group. (1988-1992 accrual)	Prospective, Randomized BU/CY= BU 4mg/kg x 4d + CY 60 mg/kg x 2d VS. CY/TBI (60 mg/kg x 2d) One center didn't fx TBI; other gave 3-7 fx's; +lung shielding Early dz=CML in CP, Lymphoma and Acute leukemia in first remission Advanced dz= Beyond first remission or CP.	Hematologic malignancy AML N=69 BU/CY=37 TBI=32 ALL N=38 BU/CY=18 TBI=20 CML N=57 BU/CY=30 TBI=27 Lymphoma N=4 BU/CY=3 TBI=1 Age = 1-55 Med. Age 34 yo	Allogeneic HLA Identical BU/CY = 88 CY/TBI = 79	86/88 BU/CY Engrafted 78/79 CY/TBI Engrafted ANC > 500 = 20d BU/CY (11-44) = 20d CY/TBI (12-39) Last Platelet Transfusion= Day 19 BU/CY Day 19 CY/TBI	3y Actuarial Relapse: BU/CY=22% CY/TBI=26% P=0.9	3y K-M estimated OS: BU/CY=62% CY/TBI=76% P<0.03 3y K-M estimated DFS: BU/CY = 56% CY/TBI= 67% P=0.065 DFS in Subset Analysis = Adults >17 yo (p<0.02) and Advanced disease had lower DFS on BU/CY (p=0.005) Subset analysis of the AML patients found no significant difference in 3y DFS, p=0.37. (BU/CY=61% vs. TBI=64%)	TRM = 28% BU/CY 9% TBI/CY p=0.006 VOD : BU/CY=12% TBI/CY=1% (p=0.009) Hemorrhagic Cystitis: BU/CY= 24% TBI/CU=8% (p=0.003)

Citation	Design and Dose	Disease	BMT Type	% Engrafted Median Days	%Relapse	%Survival Median Survival	Adverse Events
Cassileth, P. NEJM. 1998 December; 339(23):1649-1656. Chemotherapy Compared with Autologous or Allogeneic BMT in the Management of AML in First Remission	Prospective, Randomized Rndomization: AutoBMT v. HDAC Pt's eligible for Allo-BMT were tx'd with related donor marrow Conditioning for BMT = BU/CY BU 4mg/kg x 4d + CY 50 mg/kg x 4d HDAC consolidation= 3g/m² over 3h q 12h x 12	AML in first CR Age: 16-55	Autologous = 116 HDAC = 117 Allo = 113 Marrow purging performed with 4-hydroperoxycyclo-phosphamide	Graft failure in 1 autotransplanted patient. Median to ANC > 500: Allo = 19 d	ABMT = 48% HDAC = 61% Allo = 29%	OS 4 y Life Table: ABMT= 43%± 9% HDAC = 52%± 9% (P=0.05) Allo=46%± 10% (p=0.04 Allo v. HDAC) DFS 4y Life Table: ABMT=35%± 9% HDAC= 35%± 9% Allo= 43%± 10%	VOD: Autologous = 2/63 treated Allo = 6/92 treated TRM = Deaths within 100d of postremission therapy: Autologous = 14%; 9/63 treated HDAC= 3%; 3/106 treated Allo = 21%; 19/92 treated
Harousseau, J.L. Blood. 1997 October; 90(8): 2978. Comparison of autologous bone marrow transplantation and intensive chemotherapy as postremission therapy in adult acute myeloid leukemia. The Groupe Ouest Est Leucemies Aigues Myeloblastiques.	Prospective, Randomized. BU/CY = BU 4 mg/kg x4 d + CY 50 mg/kg x 4 d (The conditioning regimen was preceded by one course of post-remission ICC with ARA-C + anthracycline) VS. Ara-C 3g/m² q 12 h x 4d + anthracycline x 2d (ICC = 2 courses)	AML, primary. Age: 15-50	Autologous = 86 ICC = 78	ANC median duration <500 = 25d after ABMT. ANC median duration <500 = 24d after ICC (p=0.48.) Platelets median duration <30,000=109.5 days after ABMT Platelets median duration <30,000 = 18.5 days after ICC (P=0.0001)	ABMT = 45.3% ICC =54.9%.	ABMT 4 y K-M DFS=44%±5.5% OS =50%±6%. (±SE) ICC 4 y K-M DFS = 40% ±5.5%. OS = 54.5%± 6%. (±SE) [DFS p=0.41; OS p=0.72]	ABMT = 6.5% TRM. ICC = 3% TRM

Citation	Design and Dose	Disease	BMT Type	% Engrafted Median Days	%Relapse	%Survival Median Survival	Adverse Events
Reiffers, J. Leukemia 1996; 10:1874. Allogeneic vs. Autologous Stem Cell Transplantation vs. Chemotherapy in Patients with AML in First Remission: the BGMT 87 Study.	Prospective, Randomized Induction (n=204)→ Consolidation (n=162) ↓ Age and Donor Status (n=136)→Allogeneic BMT if ≤45 yo and with donor (33/36 with donor go to tx), Otherwise→→→ Intensification (n=99) →Randomize (n=77) Autologous Stem Cell Transplant with BU/Melphalan prep Bu= 4 mg/kg x 4d Melphalan 140mg/m² VS. Maintenance chemotherapy for 2 years with Ara-C 50 mg/m² q 12 h x 5 d+ Daunorubicin 1 mg/kg/d x 1 on months 1, 3, 6, 9, 12 and 6-MP 70 mg/m²/d x 10 d + methotrexate 15 mg/m² IM 3x/10d	AML in first CR ASCT=39 (33 tx'd) Chemo=38 (Allo=33) Age:15-55 Median = 39.8	Autologous marrow or peripheral blood stem cells No purging	No Mention	3 y K-M estimated: ASCT=45%±16% Chemo=58%±16%	<u>3 y K-M estimated</u> <u>OS:</u> ASCT=56%±16% Chemo=55%±16% Allo = Not Given Auto vs. Chemo=NS <u>DFS:</u> ASCT=51%±17% Chemo=42%±16% Allo=66.5%±16% Auto vs. Chemo p>0.5 Allo vs.Chemo p<0.02 Allo vs. Auto p=0.09	2 deaths from VOD and Infection on the ASCT arm No deaths on Chemo arm that were not related to relapse

Citation	Design and Dose	Disease	BMT Type	% Engrafted Median Days	%Relapse	%Survival Median Survival	Adverse Events
Ravindranath, Y. NEJM. 1996 May; 334:1428. Autologous Bone Marrow Transplantation VS. Intensive Consolidation Chemotherapy for AML in Childhood	Prospective, Randomized Induction (649)> Remission (552)> Eligible for randomization (343)> Randomized (232): Autologous Transplantation with preparative regimen BU/Cy BU=4 mg/kg x4d CY= 50 mg/kg x 4d Marrow purged with 4-hydroperoxy-cyclophosphamide Vs. Intensive Consolidation Chemotx with 6 courses q 3 weeks Daunorubicin 45 mg/m^2 + cytarabine and thioguanine x 5d	AML, Untreated Randomized in CR1 ABMT=115 ICC=117 Age= 1d – 20.9y	Autologous BMT Purged with 4-hydroxyperoxy-Cyclophosphamide	ANC > 500 AND Platelets >50,000 = ABMT = 43 d (median) 11/115 ABMT patients died before engraftment. (2 required attempt at second transplant)	Not Mentioned	<u>EFS (3y K-M)</u> ABMT=38%±6.4% ICC=36%± 5.8% (P=0.2) Allo=52%±8% Allo vs ICC p=0.06 Allo vs Auto p=0.01 <u>OS (3y K-M)</u> ABMT=40%± 6.1% ICC=44%± 6% (P=0.10) Allo % not given Allo vs ICC p=0.15 Allo vs Auto p=0.007 (EFS=time to relapse, failure to enter remission, or death)	TRM: ABMT = 15% ICC = 2.7% (p=0.005)