

MDS represented in a mixed disease study population				
Study	Level of Evidence	No. of Pt's	Study Design	Diseases

* Included in the sponsor's "overall dataset".

7.6.1 Overview of Evidence in Myelodysplastic Syndrome

The reviewer identified no level I evidence supporting the use of busulfan-based preparative therapy in transplantation for MDS. The trials that are listed involved multiple preparative regimens. Because there is no level I evidence to review, the reviewer has attempted to summarize some of the pertinent outcome data from the larger reported studies in the discussion that follows. A summary table, Table 33, has been included, that is similar in format to those used earlier for the level I evidence, in an attempt to facilitate informal comparisons among the studies.

The study reported by Nevill³⁴ is problematic as the preparative regimens used to treat the patients retrospectively analyzed in this case series are not fully outlined. Sixty patients described in this trial were all treated with either related or unrelated donor transplant. The article states that "primarily BuCY-2, was used for related-donor BMT patients", and a table indicates that 35 patients were treated with a "BuCy" conditioning regimen and 3 with "BuCy + other". The primary goal of this study was to examine the 10-year experience of Vancouver Hospital and Health Sciences Centre with MDS from the perspective of the cytogenetic categories that had been treated, and both patients with primary MDS and AML evolved from preexistent MDS were included in this analysis. Cytogenetic subgrouping was found to be the most significant correlate with event free survival on multivariate analysis. Twelve participants with AML were evaluated, but it is not clear whether these patients received a BU/CY preparative regimen. Additionally, various GVH prophylaxis regimens were employed. The 7 year Kaplan-Meier probability of relapse for patients undergoing related-donor BMT was 47% (CI=26%-74%). (Related donor BMT's were conditioned with a busulfan-based regimen.) The 7 year Kaplan-Meier probability of relapse for the entire group was 42% (CI=24%-67%). The 7y Kaplan-Meier probability of event free survival (EFS) was 30% (CI=14%-47%) in the related donor group vs. 29% (CI=16%-43%) in the group as a whole.

In the study reported by O'Donnell³⁵, et al, 38 patients were treated with the same preparative regimen, busulfan 4 mg/kg/d x 4d + cyclophosphamide 60 mg/kg/d x 2d, and transplanted with HLA-identical sibling donor marrow. Two patients had undergone induction chemotherapy for AML transformation prior to study entry. All patients treated on this study were reported to have engrafted. The Kaplan-Meier 2 year probability of disease free survival was 38% (CI=24%-55%), and the overall probability of relapse at 2 years was 24% (CI=10%-49%). The Kaplan-Meier probability of survival at 2 years was 45% (CI=30%-61%). VOD was manifested as a "complete triad" in 16% of the patients. Four of 6 patients with severe VOD died within 2 months of transplantation. Hemorrhagic cystitis occurred in 28%, and usually in the second or third month after transplantation. There were two patients who developed alveolar hemorrhage in the first 10 days post-transplant. These two had a prior history of mediastinal irradiation.

In the Ratanatharathom³⁶ study listed above, all patients were treated with a busulfan-based preparative regimen, but three different regimens were used. The majority, 24/27 patients, were

treated with busulfan 4 mg/kg x 4d + cytarabine q 12h x 2d + cyclophosphamide 60 mg/kg/d x 2 d (BAC). Patients were all \leq 55 yo. Six had transformed into AML and were treated with induction chemotherapy prior to transplantation. The majority (18) received HLA-matched sibling donor transplants. There were 3 unrelated donor transplants and the remaining were partial mismatched or phenotypically matched related marrows. The median time interval from diagnosis to transplantation was 5.6 months. One patient failed to engraft and two died from VOD. The Kaplan-Meier estimate of 4 year DFS was 56% \pm 13%.

Sutton, et al³⁷, reported on a series of 71 patients with MDS referred to the French Bone Marrow Transplant Registry. 17/71 had been conditioned for transplantation with busulfan-based regimens (busulfan 4mg/kg x 4d + cyclophosphamide 60mg/kg x 2d in 13; and cyclophosphamide 50 mg/kg x 4d in 17). Twenty-six were prepared for BMT with CY/TBI. The median follow-up of patients in this report was 6 years. At the time of transplant 11/71 had progressed to AML, and 7 were in a chemotherapy-induced CR. All transplants were performed with HLA-identical sibling donor marrow. Median patient age was 37 yo (range=5-55), and 5 patients were under 15 yo. The median time interval between diagnosis of MDS and transplantation was 201 days. The 7-year Kaplan-Meier event free survival was 32%. The 7-year Kaplan-Meier estimate of relapse was 48%. The overall 7-year Kaplan-Meier TRM rate was 39%. Univariate analysis and Cox adjusted comparison showed CY/TBI yielded a significant advantage in survival outcome and relapse. The Kaplan-Meier estimate of 7-year overall survival and EFS in the BU/CY subset was 18% vs. 57% in the CY/TBI subset, ($p=0.005$). The Kaplan-Meier estimated risk of relapse at 7 years in the BU/CY subset was 69% vs. 20% in the TBI/CY group, $p=0.007$. Although the article reported that the distribution of the FAB subgroups was even between these two non-randomized preparative regimen subsets, the data was not shown.

In a case series from the Fred Hutchinson Cancer Research Center published in 1993 by Anderson, et al³⁸, 88/93 patients were treated for BMT with a CY/TBI regimen, and only 5 with BU/CY from 1981-1990. Patients with disease that had transformed to AML were not included in the analysis. Median age was 30, with a range of 1-60 yo. The median duration of disease from diagnosis to transplantation was 10 months. Transplants were performed with HLA-identical sibling marrow in 62/93, unrelated donor in 6, and partial mismatch in 20. The remainder were syngeneic or phenotypically matched family member transplants. The 4-year Kaplan-Meier estimate of DFS was 41% for the entire group. The Kaplan-Meier probability of relapse at 4 years was 28%, and the K-M probability of death from nonmalignant causes was 43% at 4 years.

The Seattle group reported a subsequent analysis of 44 patients treated with CY/TBI during the interval 1982-1990 used as a historical control for comparison to 31 patients with MDS transplanted with a BU/CY/TBI preparative regimen, which employed a busulfan dose of 1.76 mg/kg/d x 4d, between 1990-1993.³⁹ This publication was included in the sponsor's 43 article "core dataset." The patients in the BU/CY/TBI group had an older median age than the historic control group (41 vs. 36 yo in the historic control), and it included no patients less than 16 yo. There were no patients in the historic control with CMML, while 26% of the BU/CY/TBI group had this FAB subtype. The median duration of disease prior to transplant was 5 months on the BU/CY/TBI arm, and 8.5 months on the CY/TBI arm. Patients with AML were not included in the analysis of either group. All but 8 patients on the BU/CY/TBI arm underwent HLA-identical sibling transplantation. Six were unrelated donor transplants. The 3y Kaplan-Meier estimate of DFS in the BU/CY/TBI group was 23%. The 3-year Kaplan-Meier probability of relapse was 28%, and the nonrelapse mortality rate was 68% (3-y probability). [In the 1993 publication discussed above, the Kaplan-Meier estimate of survival was reported as 4 year DFS (28%).] The 3-year DFS for the historical control group was 30%, not statistically different from the

BU/CY/TBI group, $p=0.27$. The 3 year K-M probability of relapse was not significantly different between groups - 53% in the control vs. 28% for BU/CY/TBI, $p=0.27$. The control's 3 year estimated non-relapse mortality rate was 36% compared to 68% in the BU/CY/TBI group, $p=0.12$. The conclusion drawn from this non-randomized comparison was that BU/CY/TBI preparative therapy for transplantation in MDS was not an advance over CY/TBI given the lack of statistically significant difference from the previous experience in the CY/TBI group in 3y actuarial DFS. If differences in disease and transplant characteristics between the comparison groups were corrected for, the relapse rate in the BU/CY/TBI was nearly half that of the CY/TBI group, while at the same time the non-relapse mortality was nearly twice as high on the BU/CY/TBI arm, resulting in similar DFS between groups.

The Seattle group also published a historical control comparison between a prospectively treated group of patients with refractory anemia conditioned for allogeneic transplantation between 1990 and 1993 with busulfan 4 mg/kg/d x 4d + cyclophosphamide 60 mg/kg/d x 2d, and a group of 38 patients with RA conditioned for allogeneic transplantation between 1981 and 1990 with CY/TBI.⁴⁰ The BU/CY group donors included HLA identical siblings, mismatched sibling, matched unrelated donor and minor mismatched unrelated donor. All patients treated with a BU/CY preparative regimen engrafted and the Kaplan-Meier probability of 3y DFS was 63% on the BU/CY arm. There were 2 deaths with VOD. In a univariate comparison of the BU/CY patients and the historical control group (CY/TBI), the 3 year estimates of DFS were not statistically significantly different - BU/CY= 63% and CY/TBI=60%. The 3 year probability of relapse was 0% on the BU/CY arm and 4% on the CY/TBI arm, $p=0.6$. Adjustment for potential confounding variables in Cox regression models also found no statistically significant difference in outcome between treatment groups.

Table 35 Summary of Studies Pertaining to Myelodysplastic Syndrome

Citation	Design and Dose	Disease	BMT Type	% Engrafted Median Days	% Relapse	% Survival Median Survival	Adverse Events
Anderson, J. Blood. 1993 82(2):677. Allogeneic BMT for 93 Patients with MDS	Uncontrolled	MDS. Disease transformed to AML not included in analysis. Median duration of dz = 10 mo. Med. age = 30 (1-60)	Allogeneic HLA-identical sibling = 62 Unrelated donor = 6 Partial mismatch=20 BU/CY = 5 CY/TBI = 88		K-M 4y = 28% (Entire Group)	DFS (4y K-M) Entire Group=41%	The K-M probability of death from nonmalignant causes at 4y=43% (Entire Group)
1981-1990.							
Anderson J. Allogeneic Marrow Transplantation for MDS with Advanced Disease Morphology: Phase II Study of Busulfan, Cyclophosphamide, and TBI and Analysis of Prognostic Factors. JCO 14(1):220, 1996.	Retrospective, Historical Control CY/TBI vs. BU/CY/TBI CY/TBI=44 BU/CY/TBI=31	MDS CMML: CY/TBI=0 BU/CY/TBI=26% Med. Duration of dz: CY/TBI= 8.5 mo BU/CY/TBI= 5 mo Pr's with AML not included in the analysis.	Allogeneic Median age: CY/TBI=36 BU/CY/TBI= 41 No patients < 16 yo.		3y K-M: CY/TBI= 53% BU/CY/TBI=28% P=0.27	3y K-M DFS: CY/TBI = 30% BU/CY/TBI=23% P=0.27	3y K-M non-relapse mortality: CY/TBI = 36% BU/CY/TBI = 68% P=0.12
1982-1990 vs.1990-1993							

Citation	Design and Dose	Disease	BMT Type	% Engrafted Median Days	% Relapse	% Survival Median Survival	Adverse Events
Anderson J. Allogeneic Marrow Transplantation for Refractory Anemia. A Comparison of Two Preparative Regimens and Analysis of Prognostic Factors. JCO, 14(10):220. 1996.	Retrospective, Historical Control BU/CY Vs. CY/TBI	Refractory Anemia	Allogeneic		3 y K-M: BU/CY = 0% CY/TBI = 4% P=0.6	3y K-M DFS: BU/CY = 63% CY/TBI = 60%	
vs. 1981-1990							
Nevill T. Cytogenetic Abnormalities in Primary Myelodysplastic Syndrome Are Highly Predictive of Outcome After Allogeneic BMT. Blood. 92(6):1910. 1998	Retrospective, Uncontrolled Total Patients = 60	MDS and secondary AML(12)	Allogeneic 38 Related Donor Tx's were conditioned with "Primarily BUCY-2". BU/CY = 35 BU/CY+other = 3		7 y K-M Related Donor = 47% (CI=26-74%) 7y K-M Entire Group = 42% (CI=24-67%)	7 y K-M EFS Related Donor = 30% (CI=16-43%) 7y K-M EFS Entire Group = 30% (CI=14-47%)	

Citation	Design and Dose	Disease	BMT Type	% Engrafted Median Days	% Relapse	% Survival Median Survival	Adverse Events
O'Donnell M. Busulfan/Cyclophosphamide as Conditioning Regimen for Allogeneic Bone Marrow Transplantation for MDS. JCO 13(12): 2973. 1995.	Uncontrolled, Prospective BU/CY N=38	MDS	HLA-identical sibling allogeneic		2 y K-M = 24% (CI=10-49%)	2y K-M DFS = 38% (CI=24-55%) 2y K-M OS = 45% (CI=30-61%)	VOD = 16% 4/6 patients died of VOD
Ratanatharathorn V. Busulfan-Based Regimens and Allogeneic BMT in Patients with Myelodysplastic Syndromes. Blood, 81(8):2194. 1993.	Uncontrolled, Prospective N=27 Bu/CY/Cytarabine = 24 Age = 55 yo	MDS Transformed AML = 6 Median Dz Duration = 5.6 mo	Allogeneic	On patient failed to engraft		4 y K-M DFS = 56% ± 13%	2 deaths from VOD

Citation	Design and Dose	Disease	BMT Type	% Engrafted Median Days	%Relapse	%Survival Median Survival	Adverse Events
Sutton L. Factors Influencing Outcome in De Novo MDS Treated by Allogeneic BMT: A Long-Term Study of 71 Patients. Blood 88(1):358. 1996.	Retrospective, Uncontrolled N=71 CY/TBI=26 BU/CY120=13 BU/CY200=17.	MDS	Allogeneic		7 y K-M= 48%	7y K-M EFS = 32%	7 y K-M TRM = 39%
1982-1991	Other=28 (25 were TBI based) Median Age=37 (5-55)	Med. Duration of Dz=201 days			BU/CY subset: 7y K-M = 69% CY/TBI subset: 7y K-M = 20% p=0.007	BU/CY subset: 7y K-M EFS = 18% CY/TBI subset: 7y K-M EFS=57% p=0.005 BU/CY subset 7y K-M OS= 18% CY/TBI subset: 7y K-M OS = 57% p=0.005	BU/CY subset 7y K-M TRM =43% CY/TBI subset 7y K-M TRM = 29% P=0.33

7.6.2 Summary and Conclusion – Myelodysplastic Syndrome

Although, allogeneic bone marrow transplantation is viewed as the only currently available treatment modality that is curative in the setting of MDS, there is no level I evidence to support the proposed indication of the use of high dose busulfan based regimen as preparative therapy in such transplantation. Comparison of available case series that included BU/CY preparative therapy to those reported using alternative regimens are difficult given the use of different efficacy endpoint analyses and differences among patient populations, or poorly defined analyses of subsets within case series. The subset analysis in the report by Sutton, suggested an inferior outcome for the BU/CY preparative regimen, but this analysis was based on small subsets, in a non-randomized trial, making definitive conclusions impossible. The historic control comparison reported by Anderson, et al, reported similar outcomes in DFS between BU/CY/TBI and CY/TBI, but is flawed on the basis that it was not a randomized comparison. Not only does a non-randomized comparison introduce multiple potential identified and unidentified differences between comparator groups, but the time periods in which treatment was delivered in each group were disparate. The evolution of supportive care capabilities over time would have to be factored into an assessment of such a comparison.

Reviewer Comment on Sponsor's Literature Review Analysis: The sponsor has concluded from their analysis of the data derived from the 43 article "core dataset" that the "totality of these data provide evidence that high-dose oral busulfan-based preparative regimens are efficacious in patients with MDS who underwent allogeneic transplantation." The sponsor combined the data from 3 of the articles in "core dataset" that included patients with MDS to perform their analysis and derive this conclusion. Those study reports by Anderson, Chiang, and Sahebi included a total of 41 patients with MDS – 31 of which were from the Anderson article. The reviewer again finds fault with the methodology employed by the sponsor for their analysis. The endpoints of overall survival, DFS, and relapse were analyzed by tallying the number of patients who met each endpoint for each study and dividing by the total number at risk from all those studies combined. The 8 patients in the study reported by Sahebi were not included in the tally for survival of DFS as that information was not included in the article. The overall crude percentage associated with a busulfan preparative regimen was then presented in a summary table. The fact that these endpoints were each described differently in reference to different time frames or with varying amounts of median follow-up among this heterogeneous group of studies, was acknowledged but discounted in this analysis methodology. The time reference for Kaplan-Meier estimates of efficacy from the studies were combined to create a time range, and associated then with a combined range of estimated probabilities for these endpoints. This range was then compared to "reference" ranges derived from the literature to derive a final summary conclusion of comparative efficacy for busulfan.

Based on the lack of level I evidence to support efficacy for the use of a high dose busulfan based preparative regimen in allogeneic transplantation for MDS, there is not literature support available for a labeled indication in this disease.

7.7 Multiple Myeloma

The following table summarizes the level of evidence provided in the articles in the sponsor's "core dataset" that pertain to multiple myeloma.

Table 36 Summary List of Sponsor's Core Database Articles Pertaining to Multiple Myeloma

Multiple Myeloma - only patient population				
Study	Level of Evidence	No. of Pt's	Study Design	
Alegre	III	24	Uncontrolled, Prospective	
Bensinger	III	80	Uncontrolled, Retrospective	
Schiller	III	23	Uncontrolled, Prospective, Phase 1-2	
Multiple Myeloma represented in a mixed disease study population				
Study	Level of Evidence	No. of Pt's	Study Design	Diseases
Angelucci	III	1 (30)	Retrospective, uncontrolled	ALL, ANLL, CML, MM, MDS
Ballester	III	21 (51)	Uncontrolled, Phase 1-2	NHL, MM, AML, CML, ALL
Schiffman	III	7 (104)	Uncontrolled, Prospective, Phase 2	MM, Breast, Lymphoma, Ovarian, Sarcoma, others
Srivastava	III	4 (24)	Uncontrolled, Retrospective	MM, NHL, HD, ALL, Breast, Sarcoma, others
Topolsky	III	1 (25)	Uncontrolled, Retrospective	AML, CML, ALL, MDS, MM

There were no level I studies submitted by the sponsor. The 8 studies listed in the table above provide only level III evidence. The three studies that limited participation to a patient population with multiple myeloma provide the bulk of the level III evidence in this disease. The studies that allowed participation of multiple types of malignancies contain a minimal component of patients with myeloma, with the exception of the phase 1-2 study report by Ballester in which nearly half the patients had myeloma.

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 37 Summary List of Additional Pertinent Multiple Myeloma Studies Identified by the Reviewer

Multiple Myeloma - only patient population				
Study	Level of Evidence	No. of Pt's	Study Design	
Vesole, 1996	III	470 (29 allografted with Busulfan)	Uncontrolled, Retrospective	
Multiple Myeloma represented in a mixed disease study population				
Study	Level of Evidence	No. of Pt's	Study Design	Diseases

7.7.1 Overview of Evidence in Multiple Myeloma

No level I studies that employed busulfan for preparative therapy in transplantation for multiple myeloma were identified by the reviewer.

The results of a level I, prospective, randomized trial conducted by the Intergroupe Francais du Myelome comparing conventional chemotherapy to high-dose therapy combined with unpurged autologous transplantation in patients <65 yo with stage II-III myeloma⁴¹ were published in 1996. This study did not utilize a high dose busulfan conditioning regimen. Conventional chemotherapy consisted of alternating cycles of VMCP and BVAP, administered in 3 week cycles for 12 months (total of 18 cycles), with interferon alfa administered from cycle 9 until relapse. The comparator arm treated patients with 4-6 cycles of alternating MVCP and BVAP followed by autotransplantation with unpurged marrow after conditioning with TBI + melphalan 140 mg/m². Interferon was started after recovery from transplantation. This trial revealed that high-dose therapy with autotransplantation increased the response rate - 38% achieving CR + "very good" PR vs. 14% of the conventional dose treatment arm. The CR + PR was 81% on the high dose arm and 57% on conventional dose therapy, p<0.001. After a median follow-up of 37 months on the conventional dose arm and 41 months on the high-dose arm, the median overall survival was 37.4 months on conventional therapy and not reached on the high dose arm, p=0.03. Median event free survival was 18 months on the conventional arm and 27 months on the high dose arm, p=0.01. The probability of event free survival at 5 years in the high dose arm was 28%, and 10% in the conventional dose group, p=0.01. Twenty-six per cent of patients assigned to the high dose arm were unable to receive it, usually due to poor performance status and insufficient bone marrow collection.

A report of a comparison of tandem autologous PBSC transplantation to a historic control treated with standard therapy - 116 patients registered on SWOG studies 8229 and 8624, matched for age, β_2 -microglobulin level, and serum creatinine - was published by Barlogie in 1997.⁴² Again, there was no high dose busulfan conditioning utilized in this study. Patients on SWOG 8229 were treated with VMCP-VBAP, and on SWOG 8624 the arms were VMCP/VBAP vs. VMCPP/VBAPP vs. VAD. Eligibility for the autotransplant study included age \leq 70 yo. At the time of the study report 87% of the 123 patients who were not denied insurance coverage or who did not select allograft for the second transplant, had undergone one autotransplant, and 76% had completed two autotransplants. The preparative regimen for the first transplant was melphalan 100 mg/m² x 2d. The preparative regimen for the second transplant was melphalan 200 mg/m² for patients who had achieved \geq PR. For patients who had not achieved at least a PR with the

first autotransplant, further therapy was delivered with melphalan 140 mg/m² + TBI or high-dose combination chemotherapy with autotransplant. Prior to first autotransplant patients were treated with VAD, then high-dose cyclophosphamide for PBSC collection, and EDAP (etoposide, dexamethasone, cytarabine, and cisplatin). All treatment was followed by interferon until relapse.

An "intent to treat" analysis was applied to the 123/134 registered patients who were not denied insurance coverage and who did not opt for allograft at second transplant. Response (CR+PR) was 78% after one transplant and 85% after the second transplant. This compared to a PR from the historical control standard therapy group of 52%, p=0.001. The CR rates were not available from the historic control patients. CR was 25% after the first autotransplant and 40% after the second. Median EFS was 49 months on the transplant arm vs. 22 months on the historic control arm (p=0.0001), and median overall survival was 62 months compared to 48 months on the control arm (p=0.01). The projected 5 year EFS was 36%±16% compared to 19% on the control. The estimated 5 year overall survival was 61% ±14% compared to 39% on the control. The transplant overall treatment related mortality was reported as 7%. Based on pilot data from the "total therapy" treatment plan employed in the autologous arm in this study, the intergroup study, INT141, which compares a single PBSC autotransplant after melphalan 140 mg/m² + TBI to standard VBMCP chemotherapy, was altered to require early PBSC collection in patients randomized to the standard therapy arm, and transplants were recommended on relapse or progression on VBMCP.

The study reported by Vesole⁴³ in the reviewer's table above, is a report of tandem transplantation in 496 patients with multiple myeloma, utilizing the treatment described by Barlogie above. In this case series, 31/55 patients who were ≤ 60 yo and had an HLA-matched sibling donor underwent allo-transplantation in the second transplant. The preparative regimen for allo-transplantation was busulfan 14 mg/kg + cyclophosphamide 120 mg/kg in 29/31 of the allo-transplants. CY/TBI was used in two. Most patients undergoing allotransplant in this study had experienced an inferior response to therapy up to the time of second transplant. After the first autotransplant 15/31 had had no response, 14 had experienced PR and only two had had CR. This compared to a 24% CR rate in the group as a whole, and no response in 32% of the group as a whole. Treatment related mortality (reported within 100 days of transplant) was 19% in the 31 patients who were allo-transplanted. The treatment related mortality for the entire study group was 6%. CR was achieved in 42% and median EFS was 19 months, while overall survival was 24 months. Projected EFS for the allo-transplant group at 3 years was 28%. As a whole, 36% of the study group achieved CR.

A retrospective matched case-control analysis of 378 patients reported to the European Group for Blood and Marrow Transplantation Myeloma Registry between 1983 and 1994 was performed to compare outcomes for autologous stem cell transplantation and allotransplant in myeloma.⁴⁴ The allotransplants examined in this comparison were 189 HLA-matched sibling marrow donor transplants performed between 1983 and 1994. The autologous transplants (bone marrow or blood stem cell grafts) were performed from 1986-1994. The median follow-up after transplant was 46 months in the allo-transplant group and 30 months in the autotransplant group. The median age of the patients undergoing allotransplant was significantly lower than that of patients who underwent autotransplant — 43 vs. 49, p=0.0001. The preparative regimen for allotransplant was TBI-based in a majority of the 189 patients treated with this modality. However, 40/189 did receive a busulfan/cyclophosphamide preparative regimen. In the autotransplant group, BU/CY was used in only 9/189 of patients.

This study found the overall response rate associated with autotransplant was higher than allo-transplant — 86% vs. 72%, p=0.001, but the CR rates were not significantly different between the

modalities – 48% for allo- and 40% for autotransplant, $p=0.12$. Treatment related mortality was significantly higher in the allotransplant group – 41% at 36 months vs. 13% in the autotransplant group, $p=0.0001$. VOD was the cause of death in 4 patients in the allo-BMT group. There were two VOD deaths in the autotransplant group. Median survival post-transplant was 34 months on the autotransplant arm and 18 months on the allo-arm, $p=0.001$. The actuarial relapse rate at 48 months was 70% on the autotransplant arm, and 50% on the allo-arm, $p=0.04$. The authors concluded that this non-randomized, retrospective analysis demonstrated that overall survival was superior with autotransplantation, and that this superiority could be attributed to higher treatment related mortality on the allotransplant group, which a lower relapse rate did not compensate.

7.7.2 Summary and Conclusion – Multiple Myeloma

In summary, although there is a level I study supporting a therapeutic role for transplantation in multiple myeloma, this study did not employ busulfan as preparative therapy for transplantation. The major trials that have attempted to examine the efficacy of transplantation in this disease through comparison to historical controls describe minimal use of busulfan preparative regimens. In those studies that employed busulfan, it was primarily in the allotransplant setting. There is no level I evidence to support allotransplant in this disease, and the retrospective analysis of the European Registry to examine comparative efficacy of allo- vs. autotransplantation in myeloma, found superior overall survival associated with autotransplantation. The latter study report, however, was not a randomized trial, and the allogeneic transplantation was performed at an earlier time interval than the autologous comparator group. Overall, there do not appear to be adequate data to support an indication for busulfan as preparative therapy for transplantation in multiple myeloma.

Reviewer Comment on Sponsor's Literature Review Analysis: The sponsor has concluded from their analysis of the data derived from the 43 article "core dataset" that the "totality of these data provide evidence that high-dose oral busulfan-based preparative regimens are efficacious in patients with multiple myeloma who underwent autologous and allogeneic transplantation." The sponsor combined the data from 4 of the articles in the "core dataset" that focused on patients treated with autologous transplantation and two articles from the "core dataset" that focused on treatment with allogeneic transplantation to perform their analysis and derive this conclusion. The allogeneic study reports from Bensinger and Angelucci had a combined patient population of 81 (80 of these from the Bensinger article) who received varying BU/CY and BU/CY/TBI regimens. The combined autologous study reports of Ballester, Alegre, Srivastava, and Schiffman produced a total population of 46 who were treated with various regimens, including BU/CY, BU/Melphalan, and BU/Melphalan/Thiotepa. The reviewer again finds fault with the methodology employed by the sponsor for their analysis. Not only were these not randomized, controlled trials, but the patients were treated with various regimens. The endpoints of overall survival, DFS, and relapse were analyzed by tallying the numbers of patients who met each endpoint for each study and dividing by the total number at risk from all those studies combined. The resulting overall crude percentage associated with a busulfan preparative regimen was then presented in a summary table. The fact that these endpoints were each described over different time frames or differing amounts of median follow-up among this heterogeneous group of studies, was acknowledged, but not factored into this analysis. Such a compilation of outcomes from multiple studies is meaningless.

7.8 Breast carcinoma

The following table summarizes the level of evidence provided in the articles in the sponsor's "core dataset" that pertain to breast carcinoma.

Table 38 Summary List of Sponsor's Core Database Articles Pertaining to Breast Carcinoma

Breast carcinoma - only patient population				
Study	Level of Evidence	No. of Pt's	Study Design	
Ghalie	III	44	Uncontrolled, prospective	
Breast carcinoma represented in a mixed disease study population				
Study	Level of Evidence	No. of Pt's	Study Design	Diseases
Schiffman	III	48* (104)	Uncontrolled, Prospective, Phase 2	MM, Breast, Lymphoma, Ovarian, Sarcoma, others
Srivastava	III	1 (24)	Uncontrolled, Retrospective	MM, NHL, HD, ALL, Breast, Sarcoma, others
Weaver	III	13 (28)	Uncontrolled, Prospective, Phase 1	Breast, HD, NHL, Sarcoma, others

* Bold number represents the number of patients with breast carcinoma on study. The number in parentheses is the total number of patients on the study.

There were no level I studies provided by the sponsor in breast carcinoma. The 4 studies listed in the table above provide only level III evidence. There is only one study with a patient population limited to breast carcinoma. The two studies reported by Ghalie and Schiffman provide the bulk of the patient numbers, and these studies are uncontrolled phase 2 trials.

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". There were no level I studies identified by the reviewer in the literature regarding the use of high dose busulfan as preparative therapy for transplantation in breast carcinoma.

Table 39 Summary List of Additional Pertinent Breast Carcinoma Studies Identified by the Reviewer

Breast carcinoma - only patient population				
Study	Level of Evidence	No. of Pt's	Study Design	
Bensinger June 1997	III	51	Uncontrolled, Prospective	
Breast carcinoma represented in a mixed disease study population				

Study	Level of Evidence	No. of Pt's	Study Design	Diseases

7.8.1 Overview of Evidence in Breast Carcinoma

The patients in the study reported by Bensinger⁴⁵, et al, in the reviewer's table above were treated with busulfan 4 mg/kg/d x 3d + melphalan 50 mg/m²/d x 2d + thiotepa 250 mg/m²/d x 2d prior to peripheral blood stem cell infusion. Twenty-six of the 51 patients reported in this article had been previously included in an analysis of this regimen in multiple malignancies by Schiffman – which is listed in the sponsor's "core dataset" summary Table above. These women's stage IV disease was refractory in 32 and responsive in 19. Eleven presented with previously untreated metastatic disease, and were treated with 1-2 courses of various intermediate-dose chemotherapy regimens or conventional doxorubicin-based chemotherapy for stem cell collection and cytoreduction prior to transplantation. Patients with hormone receptor positive disease were treated with tamoxifen for at least a year after transplantation.

All patients, except one who died on day 6 after transplantation, engrafted. One patient developed VOD. Two patients died from regimen related toxicity within 100 days of treatments (4%) and two additional patients died from complications of transplantation by day 100 (total = 8%). In terms of response, 12/51 had no evidence of disease at the time of transplantation and were considered not evaluable for tumor response to high dose chemotherapy. CR+PR was achieved in 34% of the evaluable patients. Seven of the responders were considered to have refractory disease at the time of transplant, resulting in a 25% RR in the refractory disease patients. The median follow-up in the evaluable patients (non-NED at transplant) was 423 days, and 367 days in the patients who were NED at transplant. The probability of survival for the entire study group at 1.5 year was 26%, and progression free survival, PFS, was 24%. Subset analysis of tumors responsive to therapy at the time of transplantation and those tumors that were refractory revealed that the 1.5 year probability of PFS in the responsive tumor group was 53%, compared to 23% in those with refractory tumors. The median follow-up of the responsive tumor group was 612 days.

The sponsor's core dataset article by Schiffman described the use of this same conditioning regimen in a study population with mixed malignancies that included 22 patients with stage II-III breast cancer and 26 patients with refractory breast cancer. This phase 2 study reported that 37% of the total 104 participants developed VOD and 6 patients (6%) died of regimen related toxicity within 100 days of transplant. Three deaths were attributed to VOD, two to GI toxicity, and one to IPS. Transplant complications resulted in the death of 9% on study. There were no grade III-IV regimen-related toxicities reported in the patients with stage II-III breast carcinoma. Seventeen of the 26 stage IV breast carcinoma patients were considered to have refractory disease, and 7 (41%) responded – one with a CR. In the patients with disease considered responsive prior to transplantation, 4/9 were evaluable and all 4 achieved CR. It is worth noting that the response rate in refractory patients dropped from 41% in this study to 25% in the subsequent report by Bensinger, with the increase in number of this subgroup from 17 to 32 in the later report.

The role of high dose therapy with stem cell support in the treatment of breast carcinoma has not as yet been clearly defined, although autotransplants have increased six-fold in the six years from