CLINICAL REVIEW

Application Type	BLA
Division / Office	DCEPT/OCTGT
Reviewer Name(s) Team Leader	Maura O'Leary, M.D. Bindu George, M.D.
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Established Name	Hematopoietic progenitor cells-cord
Therapeutic Class	Allogeneic cord blood hematopoietic progenitor cell therapy
Formulation(s)	Cell suspension for infusion
Indication(s) Intended Population(s)	Hematological Malignancies Adult and Pediatric

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AC	Advisory Committee
ALL	Acute Lymphocytic Leukemia
Allo-HCT	Allogeneic Hematopoietic Stem Cell Transplant
AL	Acute Leukemia
AML	Acute Myelogenous Leukemia
AP	Accelerated Phase
APML	Acute Promyelocytic Leukemia
Auto-HCT	Autologous Hematopoietic Stem Cell Transplant
BC	Blast Crisis
BLA	Biologics Licensing Application
BM	Bone Marrow
BMT	Bone Marrow Transplant
BRMAC	Biological Response Modifiers Advisory Committee
CCG	Childrens Cancer Group
CFR	Code of Federal Regulations
CIBMTR	Center for International Blood and Marrow Transplant Research
CML	Chronic Myelogenous Leukemia
COBLT	Cord Blood Transplantation Study
COG	Childrens Oncology Group
CP	Chronic Phase
CR	Complete Remission
CR1	First Complete Remission
CR2	Second Complete Remission
CTGTAC	Cellular, Tissue and Gene Therapies Advisory Committee
EFS	Event-Free Survival
DSI	Division of Scientific Investigations
FR	Favorable-risk
FDA	Food and Drug Administration
FR	Federal Register
GCP	Good Clinical Practice
GCSF	Granulocyte Colony Stimulating Factor
GvHD	Graft versus Host Disease
GVT	Graft versus Tumor
HCT	Hematopoietic Stem Cell Transplantation
HCT/P	Human Cell & Tissue Products
HD	Hodgkin Disease
HDCT	High-Dose Chemotherapy
HLA	Human Leukocyte Antigens
HPC-C	Hematopoietic progenitor cells – cord (umbilical cord blood)
HR	High-risk
IBMTR	International Bone Marrow Transplant Registry
IND	Investigational New Drug Application

IR	Intermediate-Risk
ITT	Intent to Treat
JMML	Juvenile Myelomonocytic Leukemia
Kg	Kilogram
K-M	Kaplan-Meier
LFS	Leukemia-Free Survival
LR	Low-risk
MDS	Myelodysplastic Syndrome
MRC	Medical Research Council
MRD	Matched Related Donor
MSD	Matched Sibling Donor
MUD	Matched Unrelated Donor
NC	Nucleated Cells
NCBP	National Cord Blood Program
NHLBI	National Heart, Lung, and Blood Institute
NIH	National Institutes of Health
NMDP	National Marrow Donor Program
NYBC	New York Blood Center
OS	Overall Survival
PBSC	Peripheral Blood Stem Cell
Ph+ALL	Philadelphia chromosome-positive Acute Lymphocytic Leukemia
PIF	Primary Induction Failure
POG	Pediatric Oncology Group
RFS	Relapse-Free Survival
RIC	Reduced Intensity Conditioning
RR	Relapse Rate
SDTM	Standard Data Tabulation Model
SR	Standard-Risk
T-UBMT	T cell-depleted Unrelated Bone Marrow Transplant
TKI	Tyrosine Kinase Inhibitors
TNC	Total Nucleated Cells
TRM	Transplant-Related Mortality
UBMT	Unrelated Donor Bone Marrow Transplant
UCB	Umbilical Cord Blood

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This review is limited to an assessment of the efficacy of Umbilical Cord Blood (UCB) as a stem cell source for allogeneic hematopoietic stem cell transplantation (allo-HCT) for hematological malignancies. There is sufficient evidence of efficacy to support marketing approval of UCB for the treatment of hematological malignancies.

However, a recommendation regarding a regulatory action on a specific biologics licensing application (BLA) for UCB to treat hematological malignancies should consider not only the conclusions from this review, but also the conclusions from Dr. Przepiorka's review of safety of UCB, and a review of the specific BLA. Therefore, this review does not make any recommendations on regulatory action.

See Section 6, Efficacy Summary, Hematological Malignancies for further discussion of the efficacy evidence.

1.2 Risk Benefit Assessment

Since this review is limited to efficacy and does not consider safety, a risk benefit assessment is not possible.

2 Introduction and Regulatory Background

This review is intended to be considered with the reviews by Drs. Hyde and Przepiorka and each applicant's specific BLA submission when recommending a regulatory action for the marketing approval of UCB.

2.1 Product Information

Please refer to Dr. Hyde's review of the efficacy of non-malignant UCB-HCT.

In general, HPC-C is a minimally manipulated placental/cord blood product (UCB) containing live human cord blood cells for unrelated allogeneic use. The cord blood is collected for banking from newborns with maternal consent. It is cryopreserved for storage and shipping.

2.2 Currently Available Treatments for Hematological Malignancies

Table 1: Available Treatments for Hematological Malignancies

FDA-Approved Therapies	Other Available Treatments
Chemotherapy, Immunotherapy Targeted Biologic Agents	HCT with matched, mismatched related and unrelated donors HCT with matched, mismatched related and unrelated donors (+/- GCSF stimulation)

2.3 Availability of Proposed Active Ingredient in the United States

Umbilical Cord Blood has been used as a source of hematopoietic stem cells for allo-HCT for over 20 years in the United States. The FDA issued a Guidance in 2009 on the use of UCB: *Guidance for Industry: Minimally Manipulated Unrelated Allogeneic Placental-Umbilical Cord Blood Intended for Hematopoietic Reconstitution for Specified Indications*; October 20, 2009 (74 FR 53753). As of October 20, 2011, per the Guidance, distribution of UCB in the United States will require an IND or BLA.

2.4 Summary of Pre-Submission Regulatory Activity Related to Submission

Please refer to Dr. Hyde's efficacy review of non-malignant indications for UCB.

2.5 Other Relevant Background Information

2.5.1 Product Comparability

After review of the published literature, the October 2009 Guidance stated that HPC-Cs (or UCB) were found to have sufficient evidence of effectiveness for the indication of HCT in hematological malignancies.

However, related-donor bone marrow, unrelated-donor bone marrow, and peripheral blood stem cells have recognized differences from each other and from UCB regarding likelihood of engraftment, rates of engraftment, and incidence of various complications.

2.5.2 Combination Therapy Issues

For patients who received UCB transplantation for the treatment of hematological malignancies, a preparative regimen is used to reduce the disease burden. This regimen also provides a permissive environment for engraftment of the donor hematopoietic stem cells. Thus, the preparative regimen may be a contributory factor in the effectiveness of any allo-HCT in the treatment of hematological malignancies. This review acknowledges that differences in preparative regimens may influence outcomes. The scope of this review does not include evaluation of differences in outcomes resulting from these differences in preparative regimens.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

3.1.1 Organization

This review relies on published literature instead of submitted data. Thus no comments are made on the quality of the organization of the data submitted to the docket.

3.1.2 Deficiencies

Reports in the published literature are not designed to support a BLA review. Consequently, the information in the published literature has deficiencies that limit this review. Those deficiencies include the following:

- Individual subject data are lacking. Characteristics of the individual subjects and specific aspects of the disease (e.g., disease stage; number of treatments needed to induce remission) were lacking. Independent clinical assessment by the reviewer to ensure that subjects met entry criteria was not possible.

- The published studies used to compare UCB to other donor sources were retrospective in nature and are subject to selection bias.

- These publications did not provide sufficient information to verify whether the control cohorts for alternate donor sources were matched to the UCB cohorts. There was insufficient information to confirm whether the cohorts in these registry studies were matched for prognostic factors.

- The p-values cited in this document were obtained from the individual citations. Many of the studies cited were retrospective and the meaningfulness of a p-value in this context is unclear. In addition, the FDA did not have access to the raw data; therefore, the FDA was unable to reproduce and confirm the results of the statistical tests.

- The types of preparative regimens, GvHD prophylaxis, and GvHD treatment affect peri-transplant outcomes, which in turn affect long-term outcomes. The details of the preparative regimens, GvHD prophylaxis, and GvHD treatment were not available in some of the studies reviewed. Thus, the confounding effects on long-term outcomes due to the difference in preparative regimens between matched cohorts could not be assessed.

Section 5.2 presents review strategies that were applied to improve reliability of the published literature.

3.2 Compliance with Good Clinical Practices

Compliance with Good Clinical Practices cannot be adequately assessed from the review of published literature.

3.3 Financial Disclosures

Financial disclosures were not available for the literature reviewed. Therefore, this review does not consider whether financial conflicts of interest might have influenced the results in the published literature.

5 Sources of Clinical Data

The data submitted to the docket was primarily to evaluate engraftment and peri-transplant morbidity. This data was inadequate to meet the primary objective of this review which was to evaluate the long-term outcomes. Thus a formal review of docket data was not performed for the review.

5.1 Tables of Studies/Clinical Trials

This review is not based on specific studies conducted under an IND, but based on review of extensive scientific literature for allo-HCT as a therapeutic modality for the treatment of hematological malignancies. Once allo-HCT is established as a treatment modality for a hematological malignancy, then the review documents the available literature on the use of UCB as the stem cell source for the allo-HCT. In ALL, AML and CML there is extensive scientific literature on the use of allo-HCT for the treatment of these hematologic malignancies. These studies are described in Section 6 under disease types.

5.2 Review Strategy

5.2.1 Regulatory Standards for Review of Effectiveness for UCB for Long-term Outcomes in Hematological Malignancies

Per the FDA Guidance to Industry: *Providing Clinical Evidence of Effectiveness for Human Drugs and Biologics*, proof of effectiveness would consist of clinical investigations as defined in the provision for "adequate and well-controlled studies" for new drugs (21 CFR 314.126), unless waived as not applicable to the biological product or essential to the validity of the study when an alternative method is adequate to substantiate effectiveness (21 CFR 601.25 (d) (2)). UCB now considered for licensure is unique in that the class of HPC-Cs are HCT/Ps

that have been utilized in medical practice as alternative sources of hemato-poietic stem cells for the last twenty years.

The data submitted to the docket consists of outcomes reported retrospectively to the blood banks from multiple treatment sites to the cord blood banks. The nature of this reporting was voluntary. As a result, the reports of long-term outcomes to the blood banks database are incomplete. The strength of the literature review is large studies that provide overall survival and leukemia-free survival (LFS) in patients from large national and international transplantation databases. Thus evaluation of effectiveness to support approval of UCB for long-term outcomes is based mainly on review of the published literature.

5.2.2 Review Strategy to Improve Reliance on Published Literature

To provide sufficient reliability to this review based on published literature, data from randomized studies comparing allo-HCT to chemotherapy were reviewed to establish that allo-HCT was an appropriate treatment option. Registry or single institution retrospective studies comparing UCB to alternate stem cell sources were then reviewed. The endpoints of interest are overall survival (OS) and disease-free survival (DFS) or leukemia-free survival (LFS).The role of allo-HCT is an evolving field. Risk categorization in current practice has changed from the categorization used in previous publications. It is therefore important to consider a review of literature which is consistent with current practice. Where multiple studies were available, the reviews that are included contain large sample sizes. This review includes the most recent updates to studies where the accounting of enrolled subjects was optimal. The availability of data in acute leukemias and chronic myelogenous leukemia (CML) was considered sufficient and reliable to evaluate for effectiveness in these disease sub-types.

In other disease sub-types, the sample size was relatively small. The data is considered insufficient to determine efficacy based on long-term outcomes. The review of the literature suggests that it is not feasible to conduct randomized studies to evaluate long-term outcomes in these diseases. Thus, for these diseases the review relied on the detailed outcomes from hematopoietic reconstitution from a single uncontrolled prospective study of unrelated UCB transplantation. This study was the COBLT Study (Cord Blood Transplantation Study) (Kurtzberg J, Prasad VK et al, 2008). This review strategy was consistent with the review procedures for evidence of effectiveness as suggested in the above guidance, since hematopoietic reconstitution is considered the general purpose of UCB transplantation for acute leukemias, CML, and other hematological malignancies where allo-HCT is indicated.

5.2.3 General Organization of the Efficacy Review and Modifications to the Review Template

All discussion of clinical studies is located in subsections of Section 6.

The discussion of efficacy of UCB for hematological malignancies is in three major sections for AML, ALL, and CML and other hematological malignancies. Within the ALL and AML major sections, the discussion for pediatric and adult diseases is included under separate categories.

A separate section (6.8) of the review examines the relationship of efficacy outcomes to cell dose and HLA disparity.

Evaluation of efficacy in older subjects, where data is limited, is reviewed under section 6.9.1.

Sections 7 and 8 of the review template relate to safety and are omitted because the Docket safety data are addressed in a separate safety review by Dr. Przepiorka. Sections 9.2 and 9.3 of the review template are omitted because the review is not for a specific BLA.

5.2.4 General Approach to the Review of Efficacy of UCB

Use of UCB in the past twenty years has been driven by the need to find an alternate donor source for allo-HCT. In practice, the approach to using UCB in both adults and pediatric patients has been as a source of allo-HCT when related or unrelated donor sources were unavailable. This practice limits the feasibility of conducting studies that provide control groups that use related and unrelated donor sources as comparator groups. Thus the evaluation of efficacy of UCB is based on retrospective studies from registries that compare UCB transplantation against related and unrelated donor transplantation. The first step of the efficacy review was evaluation of the benefit of allo-HCT for each of the acute leukemias and CML. Randomized studies comparing the long-term outcomes in allo-HCT with chemotherapy and/or auto-HCT were selected for this purpose. Subsequently, the efficacy of UCB transplantation was compared to related and/or unrelated donor in retrospective studies. Thus, the review of efficacy for the acute leukemias and CML is based on a two-part approach: 1) review of efficacy of allo-HCT; 2) review of efficacy of UCB compared to other allo-HCT donor sources.

5.3 Discussion of Individual Studies/Clinical Trials

See the discussions for each hematologic malignancy (ALL, AML, CML, other) in the subsections of Section 6.

5.4 Methods

See section 9.1 for literature search methods.

6 Review of Efficacy

6.1 Summary of Reviewer Conclusions Regarding Effectiveness

This clinical efficacy review of the literature for UCB as a stem cell source for allo-HCT concludes that:

- LFS and/or OS outcomes are comparable for UCB to alternate donor sources in acute leukemias (ALL, AML) and CML.
- Evidence of effectiveness for these LFS and/or OS outcomes does not exist for the other hematological malignancies.
- In general, the purpose of UCB-HCT is hematopoietic reconstitution. The COBLT study (Kurtzberg J, Prasad VK et al, 2008) provides sufficient evidence for UCB transplantation for hematopoietic reconstitution in other hematological malignancies.
- There is no conclusive data to support specific recommendations regarding cell dose and HLA disparity based on long-term outcomes.
- The use of UCB-HCT for treatment of hematological malignancies in older subjects who receive reduced-intensity conditioning regimens provides long-term outcomes comparable to UCB-HCT in younger subjects.

6.2 Nature and Scope of Efficacy Review for Hematological Malignancies

This efficacy review focuses on the scientific literature regarding the role of allo-HCT in the treatment of hematological malignancies with emphasis on the efficacy of UCB. In hematological malignancies, where allo-HCT is considered an acceptable treatment option, this review will address the pediatric and adult populations separately. Related transplantation, unrelated transplantation, and

umbilical cord blood transplantation (UCB) are reviewed. The review considers the risks and comparability of these different donor sources of hematopoietic stem cell transplant in the treatment of hematological malignancies. Where the availability of scientific literature was substantial, the scope of the review is limited to literature with relevant updates with a preference for studies that were multi-national and included large sample sizes.

6.3 General Background: Hematological Malignancies

Hematological malignancies are a diverse group of neoplasms. Table 2 below provides the disease types, incidence, median age at diagnosis, distribution by sex, and 5-year survival rates based on the SEER database (*Howlander and Noone et al., 2011).

Table 2: Hematological Malignancies (SEER database 2004-2008)*

Disease	% of hematological malignancies	Incidence per 100,000	Median Age	M:F	5-yr Survival Rates (%)	Comments
AML	8.7%	3.5	67	M>F	22.6	AML & ALL constitute approximately 13% of all hematological malignancies.
ALL	4.2%	1.7	13	M>F	64.4	
CLL	10.4%	4.2	72	M>F	78	
CML	4%	1.6	65	M>F	57.2	
Acute Monocytic Leukemias	0.7%	0.3	61	M=F	24.0	
Other Leukemias	1.7%	0.7	75	M>F	26	
NHL	49.1%	19.8	66	M>F	67.3	Lymphomas constitute approximately 56% of all hematological malignancies.
Hodgkin Disease	7%	2.8	38	M>F	83.9	
Myeloma	14.1%	5.7	69	M>F	39.7	

AML = Acute myelogenous leukemia
ALL = Acute lymphocytic leukemia
CLL = Chronic lymphocytic leukemia
CML = Chronic myelogenous leukemia
NHL = Non-Hodgkin lymphoma

Prognosis is variable and dependent on the specific disease, stage, cytogenetic factors, response to treatment, and stem cell transplant options. If left untreated,

hematologic malignancies are fatal (Applebaum and Forman et al., 2008). Available treatments include chemotherapy, targeted therapies, and autologous and/or allogeneic stem cell transplant (allo-HCT).

6.4 Allogeneic Stem Cell Transplantation in Hematological Malignancies

Allogeneic hematopoietic stem cell transplant (allo-HCT) has evolved from being a source of rescue following high-dose chemotherapy to a treatment used to eradicate hematological malignancies based on the graft vs. tumor (GVT) effect. The initial adoption of allo-HCT as standard clinical practice in the treatment of acute leukemias was based primarily on published literature with limited controlled comparisons of bone marrow transplantation (BMT) to conventional chemotherapy in the most common hematological malignancies.

Improvements over time to reduce the co-morbidities of transplant have included the use of non-myeloablative or reduced intensity regimens, treatment and mitigation of severe graft vs. host disease (GvHD) through a better understanding of HLA matching, and improvements in post-grafting immunosuppressive regimens and supportive care, all of which have decreased transplant-related mortality (TRM). As the clinical experience with allo-HCT evolved and with improvements in TRM, the role of allo-HCT in clinical practice was generalized from acute leukemias to other hematological malignancies.

Lymphomas constitute approximately 56% of all hematological malignancies. However, the role of allo-HCT in lymphoma is limited, due in part to the availability of other curative therapies, the availability of sibling donors, the role of autologous HCT and the toxicities associated with the conditioning regimens. Currently, acute leukemias, predominantly AML and ALL, constitute the most common hematological malignancies in which allo-HCT is used as a treatment option. New effective therapies for the treatment of specific hematological malignancies diseases (CML, MDS) provide prolonged remissions and expanded treatment options for patients. In CML, the tyrosine kinase inhibitors (TKIs), and in MDS, lenalidomide, have changed the treatment paradigm. Allo-HCT in these diseases is now reserved for patients who fail these therapies. There is limited scientific literature for the use of UCB in these disease types, especially where the role of allo-HCT is reserved for advanced disease. However, use of allo-HCT in earlier phases of these diseases was an accepted standard practice prior to the availability of these new effective therapies.

Improvements in TRM and donor selection have resulted in the increasing use of allo-HCT in the treatment of hematological malignancies. The inventory of suitable stem cell sources remains limited despite the availability of bone marrow, peripheral blood and UCB as stem cell sources.

Allo-HCT is presently considered for individual patients on a risk-based approach. This risk-based approach considers the stage and prognostic factors associated with the specific disease, available curative options, availability of related and unrelated HLA-matched donors, the conditioning regimen, and the source of the allo-HCT.

6.5 Indication: Acute Lymphocytic Leukemia (ALL)

6.5.1 Pediatric ALL: Background

Acute Lymphoblastic Leukemia (ALL) is the most common malignancy of childhood and represents about twenty-five percent of all childhood malignancies (Margolin JF, Rabin K et al, 2011). The peak incidence is between ages 2-8 years with a gradual decline until late adulthood (over 60) when the incidence again begins to increase (Howlader N, Noone AM, 2011). The choice of consolidation therapy for childhood ALL is dependent on two important evaluations performed at diagnosis and after assessment of response to initial induction therapy. Patients with primary induction failure have a poor prognosis. The overall 5-year event-free survival (EFS) for childhood ALL is 75-85 percent and can be predicted by the risk status at diagnosis and response to induction therapy (Margolin JF, Rabin K et al, 2011).

6.5.2 General approach to treatment: Pediatric ALL

General approach to allo-HCT in Pediatric ALL

Cure rates of approximately 75-85% are achieved with chemotherapy alone in Pediatric ALL, suggesting that patients in CR1 are likely to have favorable long-term outcomes without consolidation treatments like allo-HCT. The role of allo-HCT is primarily in second remission (CR2) after early relapse (less than 36 months from diagnosis) or very high-risk ALL. Very high-risk ALL is defined as:

- hypo-diploid (<44 chromosomes) in CR1
- patients who fail to respond to initial induction therapy (PIF) as indicated by poor marrow response (M2, M3 at end of induction)
- and/or the presence of minimal residual disease (Mehta PA, Davies SM, 2008; Schultz KR, Bowman WP et al, 2009, Schrappe M, Reiter A et al 2000).

With the identification and validation of new risk factors, targeted therapies and detection of early relapse, the determination of when to recommend allo-HCT is changing for pediatric ALL. The definition of "very high-risk ALL in CR1" has

changed in the past decade. For example, Philadelphia chromosome (Ph+) ALL in CR1 is no longer considered as an indication for allo-HCT in CR1. Presently, allo-HCT is not recommended as a consolidation therapy for Ph+ ALL patients (Schultz KR, Bowman WP et al, 2009, Pui CH, Carroll WL et al 2011). In this review, the discussion of the role of allo-HCT in high-risk and very high-risk disease in CR1 is limited due in part to the newer approaches to therapy and in part to the small proportion of patients that constitute this group.

Review Strategy for Efficacy of UCB-HCT as a Treatment in Pediatric ALL

As stated in Section 5.2, this review takes a two-step approach to evaluating efficacy of UCB in pediatric ALL was to first evaluate the benefit of allo-HCT in this disease and subsequently evaluate the benefit of UCB as an alternate donor source of allo-HCT.

- Three randomized studies were selected to evaluate the benefit of allo-HCT in pediatric ALL as compared to chemotherapy and/or auto-HCT. Two of these studies (Barrett et al and Eapen et al, 2006) evaluated the benefit of allo-HCT for subjects in CR2. The third study by Oudot et al evaluated the benefit of allo-HCT in subjects with Primary Induction Failure (PIF).

- Retrospective registry studies by Rocha et al and Eapen et al were selected to assess the long-term benefit of UCB transplantation as compared to other donor sources of allo-HCT in acute leukemias. These studies only provided for limited evaluation outcomes separately for pediatric ALL and AML. However, at least half of the enrolled population was diagnosed with pediatric ALL, providing for evaluation of the benefit of UCB in a large sample size in this disease.

6.5.3 Comparison of Matched Sibling Allo-HCT Donor (MSD) to Chemo-therapy in Pediatric ALL in CR2

Barrett 1994 (Barrett AJ, Horowitz MM et al, 1994)

Objective:
The objective of this study was to compare the LFS for matched sibling donor transplant (MSD) to chemotherapy in children with ALL in CR2 from data in two registry studies.

Study design:

Retrospective registry analysis from IBMTR and POG studies evaluating LFS outcomes in subjects who received an MSD allo-HCT compared to subjects who received chemotherapy from 1983-1991.
376 subjects from the International Bone Marrow Transplant Registry (IBMTR) were selected and compared to 540 subjects from the Pediatric Oncology Group (POG) group to identify variables associated with treatment failure in both groups. Subjects received transplant from 1983-1991. A subset of 255 matched pairs were selected from both registries and analyzed for treatment effect for LFS at 5 years.

Figure 1: Probability of LFS in the Matched Pair Cohort
(Barrett AJ, Horowitz MM et al, 1994)

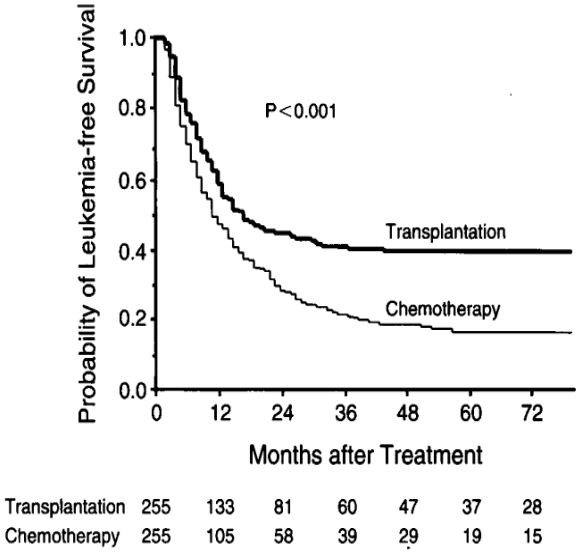


Table 3: Estimated LFS for Allo-HCT vs. Chemotherapy in Pediatric ALL
(Barrett AJ, Horowitz MM et al, 1994)

LFS at 5 years	Allo-HCT	Chemotherapy	p-value
Matched pair cohort (n=510)	40%	17%	<0.001
Unmatched pair cohort (n=916)	36%	16%	<0.001

Study Conclusions:

- There were less relapses and an increased LFS in pediatric patients with ALL in CR2 who received a MSD allo-HCT. This benefit was for patients who experienced their first relapse before or after 36 months.

Reviewer Comments and Conclusions:

- There was a greater likelihood of LFS for subjects receiving HLA donor MSD HCT at five years compared to chemotherapy. This affirms the benefit of allo-HCT for pediatric ALL in CR2.

Eapen 2006 (Eapen M, Raetz E et al 2006)
Objective:
The objective of this study was to evaluate treatment options for pediatric subjects less than 18 years with relapsed B precursor ALL. Efficacy outcomes of interest for the purpose of this review were treatment failure and overall mortality.

Design:
Patients who received chemotherapy were selected from the Pediatric Oncology Clinical Trials (POG) registry, and patients receiving transplant were selected from the Center for International Bone Marrow Transplant Research (CIBMTR) registry. The patients were drawn from the years 1991-1997. All patients had at least bone marrow relapse with or without extramedullary relapse and were in second CR. Allo-HCT recipients had a HLA MSD.
One hundred and eighty-eight chemotherapy recipients and 186 MSD HCT recipients were identified and reviewed. Within the HCT group, 82% of subjects received Total Body Irradiation (TBI) in the conditioning regimen. Time from primary induction to relapse is a known prognostic factor for pediatric ALL. This study evaluated the effect of the treatment type on long-term outcomes. Subjects with pediatric ALL in CR2 who experienced relapse within 36 months of initial CR1 are considered to have early relapse. Subjects with relapses at or beyond 36 months are considered to have late relapse.

Results:
The 8-year overall survival for children in early relapse was 32% and 44% after chemotherapy alone or transplantation with radiation (TBI), respectively. In late first-relapse patients, the overall survival at 8-years for these same groups was 66% and 63%.

Table 4: Treatment Failure and OS of Chemotherapy vs. MSD BM-HCT in Pediatric B-precursor ALL
(Eapen M, Raetz E et al, 2006)

Outcome	Treatment	Early relapse (<36 mo)			Late relapse (≥36 mo)		
		N1/N2	RR (95% CI)	p-value	N1/N2	RR (95% CI)	p-value
Treatment Failure	Chemotherapy	85/110	1.00	<0.001	32/78	1.00	<0.001
	TBI regimen HCT	50/92	0.55 (0.39-0.79)	<0.001	24/61	1.10 (0.66-1.84)	0.70
	Non-TBI regimen HCT	17/19	1.56 (0.92-2.48)	0.06	9/14	3.11 (1.72-5.62)	<0.001
Overall mortality	Chemotherapy	77/110	1.00	<0.001	26/78	1.00	<0.001
	TBI regimen HCT	48/92	0.58 (0.41-0.83)	0.003	22/61	1.10 (0.66-1.84)	0.49
	Non-TBI regimen HCT	15/19	1.51 (0.94-2.43)	0.09	9/14	3.11 (1.72-5.62)	<0.001

N1: number of events
N2: number evaluable

Study Conclusions:

- For patients with pediatric ALL in CR2, the timing of first relapse and the type of conditioning regimen are important in determining the role of MSD Allo-HCT.
- Patients with early relapse who received a TBI-containing conditioning regimen followed by MSD allo-HCT appeared to have improved LFS and OS as compared to patients receiving chemotherapy alone or MSD allo-HCT preparative regimens without TBI.
- For those subjects with late relapse, the LFS and OS outcomes were similar with transplant containing TBI as against chemotherapy, while subjects receiving a MSD allo-HCT without TBI fared worse.

Reviewer Comments and Conclusions:

- The sources of patients for the Barrett and Eapen studies were similar but did not overlap in the years from which the subjects were chosen.

- This study differs from the Barrett study in that it identifies a specific group of subjects in CR2 (early relapse) who are likely to benefit from MSD transplants.

- This study also highlights the possible potential effects of HCT conditioning regimens on outcomes. However, conclusions about the effect of a conditioning regimen must be interpreted with caution since the sample size for the non-TBI containing arm was small. Non-randomized allocation of subjects to transplantation with selection being at the discretion of the transplant center could potentially have produced a selection bias that may have influenced the outcomes.

6.5.4 Comparison of Matched Related Allo-HCT in Patients with Primary Induction Failure (PIF) in CR1 (Oudot C, Auclerc M et al, 2008)

Patients with PIF are often refractory to salvage therapy with no likelihood of survival. In those patients with PIF who achieve a CR with salvage induction treatment, post-remission therapies are important to decrease the risk of relapse.

Objective:
The objective of this study was to compare outcomes for MSD allo-HCT to outcomes for auto-HCT or chemotherapy in subjects with PIF.

Results:
One thousand three hundred and ninety five children with newly diagnosed ALL were enrolled in the FRALLE 93 study conducted in France and Belgium. Ten of 53 patients in PIF failed to reach CR1 with salvage therapy. Overall survival in those 10 patients was 0%. Forty-three patients responded to salvage treatment and achieved CR1. DFS at 5 years in the group that received MSD allo-HCT was 50% (five of ten patients). DFS at 5-years after auto-HCT was 50% (four of eight patients) while the DFS rates in the chemotherapy group was 25% (three of twelve) at less than 5 years (≥ 53 months).

Study Conclusions:

- Five-year OS for patients with PIF was poor when compared to patients who responded to initial therapy (30% vs. 85%).

- Allo-HCT and auto-HCT for PIF in ALL provided the best treatment options after salvage therapy.

Reviewer Comments and Conclusions:

- Even with the small sample size, the study supports the use of allo-HCT in pediatric subjects with ALL with PIF who are able to achieve CR1.
- The imbalance in prognostic factors may have affected the outcomes.

6.5.5 Summary Comments and Conclusions from the Review of the Literature for the Role of Allo-HCT in the Treatment of Pediatric ALL

- In pediatric ALL, MSD allo-HCT is an effective treatment option for patients in CR2 and in CR1 after salvage therapy for PIF.
- The risk factors associated with identifying very high-risk (HR) patients with pediatric ALL have changed in the past decade. The comparative studies supporting the use of allo-HCT in very HR pediatric ALL were conducted at a time prior to the current practice of selection for very HR patients. This change in the treatment paradigm poses a challenge in assessing the appropriateness of allo-HCT in very HR pediatric ALL in CR1 depending on risk factor.

6.5.6 Efficacy of UCB in Comparison with Other Allo-HCT Donor Sources in Pediatric ALL

Studies that have evaluated the efficacy of UCB-HCT in pediatric acute leukemias (ALL, AML) are summarized in a review by Brunstein CG, Weisdorf DJ, 2009. These studies are not a comparison of UCB to other allogeneic donor sources and will not be included in this efficacy review.

General Approach to Evaluation of UCB in Treatment of Pediatric ALL

The purpose of this portion of the efficacy review is to compare the efficacy of UCB to other allogeneic donor sources for the treatment of pediatric ALL. The selection of the stage of pediatric ALL in this review is guided by the current standard practice of use of allo-HCT in this disease. The impact of selection based on a threshold cell dose on the variability of the results is probably minimal. This is due to the fact that pediatric UCB transplants are likely to meet the cell dose thresholds because of the size of the patients. Thus it appears

prudent to include registry studies from the 1990's in the discussion of the role of pediatric leukemia (ALL and AML) as well as analyses from more recent data.

The single institution analysis by Barker compares long-term outcomes between UCB and unrelated or related matched BM donor sources in pediatric subjects with a variety of pediatric diseases for which allo-HCT is generally used (Barker JN, Davies SM et al, 2001). This study is not included in the review of efficacy comparing different allogeneic donor sources on outcomes due to small sample size and lack of disease-specific outcome data.

Two studies have been included in the efficacy review of UCB as a donor source in pediatric ALL. These are retrospective registry analyses from Europe and the United States. The Rocha study (Rocha V, Cornish J et al, 2001) compared two broad categories of UCB against matched and mismatched unrelated HCT. The Eapen study (Eapen M, Rubinstein P et al, 2007) compared sub-categories of UCB and unrelated HCT donor sources and attempted to evaluate the impact of cell dose on outcomes.

Comparative analysis of Allogeneic Bone Marrow Donor Sources on Long-term Outcomes in Pediatric ALL

Rocha 2001 (Rocha V, Cornish J et al, 2001)

Objective:
Rocha et al published a retrospective registry study predominantly from the Eurocord transplantation registry. The objective of this study was to compare outcomes of unrelated donor transplants using either Umbilical Cord Blood (UCB) or Unrelated Bone Marrow (UBM) as donor source in pediatric subjects under 16 years of age for HCT in the Acute Leukemias (AL).

Study design:
UBM-HCT was grouped further into T cell depleted (T-UBM HCT) and un-manipulated UBM-HCT. In both UBM groups, the source of the BM was unrelated to the recipient. Subjects were treated between 1994 and 1998. Efficacy outcomes evaluated were Event-Free Survival (EFS) and Overall Survival (OS).

Results:
Pediatric patients with ALL and AML were included in this study. In patients with ALL, 195 received an Unmanipulated UBM-HCT, 145 received a T – UBM- HCT and 65 received a UCB-HCT.

Table 5: Efficacy Outcomes of UCB-HCT vs. BM-HCT for Pediatric Acute Leukemia
(Rocha V, Cornish J et al, 2001)

Outcomes for AL at 2 yrs	UCB-HCT (n=99)	Unmanipulated UBM-HCT(n=262)	T-UBM-HCT (n=180)
Relapse	38%	39%	47%
EFS	31%	43%	37%
OS	35%	49%	41%

Study Conclusions:

- Neutrophil recovery and platelet recovery were associated with cell dose for UCB-HCT. A cell dose of 3.7 x 10e7 TNC/kg was associated with increased probability of engraftment.
- In patients who received a UCB-HCT, relapse was associated with younger patients, AML, and advanced stage of disease at time of HCT.
- UCB-HCT had less cGvHD than the unmanipulated UBM-HCT.
- The main differences in outcomes occurred in the first 100 days post-HCT. In the UCB-HCT group; this was reflected in delayed engraftment, failed engraftment, and an increase in TRM.

Reviewer Comments and Conclusions:

- Long-term outcomes of EFS and OS are comparable between UCB-HCT and UBM-HCT. In patients without a suitable UBM-HCT donor, UCB-HCT provides an alternative donor source.
- This is not a randomized study. Differences in prognostic factors, treatment regimens and selection bias could have impacted outcomes. Outcomes for ALL were not reported separately. However, more than half of these subjects with AL were of the ALL sub-type.

Eapen 2007 (Eapen M, Rubinstein P et al, 2007)

Objective:
The objective of this study was to compare 5-year LFS outcomes of UCB-HCT to allele matched unrelated BM HCT in children less than 16 years old with AL. The source of subjects is the Center for International Blood and

Marrow Transplant Research (CIBMTR) and the National Cord Blood Program (NCBP) of the New York Blood Center (NYBC).

Design:
The study selected pediatric subjects with either AML or ALL. Subjects received a single unit of cord blood. HLA mismatches up to two HLA loci were permitted. Time of transplant ranged from 1995-2003.

Results:
Five hundred and three children who received a UCB-HCT were compared with 282 BM-HCT recipients. Of the subjects receiving UCB, 201 mismatched at one antigen level and 267 at two antigen levels. For the BM-HCT recipients, 44 subjects are mismatched at one allele level, and 122 subjects are mismatched at two allele levels. Approximately 60% of the patients were ALL, of whom 55% were transplanted in CR2. Cell dose in the UCB group ranged from 2.2-6.9 x 10^7 TNC/kg. LFS outcomes were similar in all groups.

Table 6: Estimated 5-year LFS Outcomes of UCB-HCT vs. BM-HCT in Pediatric Acute Leukemia (Eapen M, Rubinstein P et al, 2007)

Registry source/ Author/ Age range	Stem cell source based on HLA disparity (n)	Disease (n)	LFS probability (%)	Outcome summary
CIBMTR (Pediatric) Eapen 2007[1] Age 0-16 yrs	M UCB (35)	AML (16) ALL (19)	5-yr LFS: 60%	No statistically significant differences for LFS were noted between matched, low or high cell dose mismatched UCB, mismatched BM compared to matched BM
	MM UCB-1L (44)	AML (8) ALL (36)	5-yr LFS: 36%	
	MM UCB-1H (157)	AML (69) ALL (88)	5-yr LFS: 45%	
	MM UCB-2 (267)	AML (101) ALL (166)	5-yr LFS: 33%	
	M UBM (116)	AML (36) ALL (80)	5-yr LFS: 37%	
	MM UBM (166)	AML (60) ALL(106)	5-yr LFS: 38%	

M UCB = Matched UCB
MM UCB-1L = Mismatched UCB at 1/6 HLA loci with low cell dose (low cell dose was ≤ $3x10^7$ TNC/kg
MM UCB-1H = Mismatched UCB at 1/6 HLA loci with high cell dose (high cell dose was > $3x10^7$ TNC/kg
MM UCB-2 = Mismatched UCB at 2/6 HLA loci with any cell dose for Eapen 2007
M UBM = Unrelated BM Matched at 8/8 HLA Loci
MM UBM = Matched at 6/8 and 7/8

Study Conclusions:

- HLA matched or 1-2-antigen mismatched UCB is a suitable stem cell source for pediatric acute leukemia.

- The patients with HLA-matched UCB-HCT had the best 5-year LFS (60%) but the numbers were small. For the remaining donor sources the 5-year LFS was similar.

- Cell dose and HLA match affected the rate of TRM in UCB-HCT.

- GvHD rates both acute and chronic were similar for matched and mismatched UCB-HCT and allele matched BM-HCT.

Reviewer Comments and Conclusions:

- The results of this study suggest that LFS outcomes for mismatched BM-HCT, matched BM-HCT and mismatched UCB-HCT were similar.

6.5.7 Summary Comments and Conclusions from the Review of the Literature for the Role of Allo-HCT and UCB-HCT in the Treatment of Pediatric ALL

- In pediatric ALL, MSD allo-HCT is an effective treatment option for patients in CR2 and in CR1 after salvage therapy for PIF.

- The risk factors associated with identifying very high-risk (HR) patients with pediatric ALL have changed in the past decade. The comparative studies supporting the use of allo-HCT in very HR pediatric ALL were conducted at a time prior to the current practice of selection for very HR patients. This change in the treatment paradigm poses a challenge in assessing the appropriateness of allo-HCT in very HR pediatric ALL in CR1 depending on risk factor.

- The two registry retrospective analyses of long-term outcomes suggest that UCB-HCT may be comparable to other unrelated allogeneic donor sources. The degree of HLA matching for UCB donors does not seem to impact outcomes in pediatric ALL if the number of mismatches is restricted to no more than two HLA loci.

6.5.8 Adult ALL: Background

In adults, ALL represents 20 percent of all leukemias seen in persons over 20 years of age (Margolin JF, Rabin K et al, 2011 and carries a five-year mortality

rate of 65 percent (Margolin JF, Rabin K et al, 2011). Treatment for adult ALL is also based on risk categorization (Bassan R, Hoelzer D, 2011; Forman SJ, 2008).

6.5.9 General Approach to Treatment: Adult ALL

As with pediatric ALL, risk factors at the time of diagnosis impact the type of treatment that may be needed to achieve the greatest benefit to the patient. In adult ALL, the overall survival with best available therapy is in the range of 25-35% (Thiebaut A, Vernant JP et al, 2000).

General Approach to Allo-HCT in Adult ALL

Adult high-risk patients in CR1 after induction therapy are candidates for hematologic stem cell transplantation from various graft sources. The joint study by the Medical Research Council (MRC) and the Eastern Cooperative Oncology Group (ECOG) found that MSD allo-HCT is beneficial in CR1 for standard risk ALL. (Goldstone AH, Richards SM et al, 2008). This study also concluded that in the absence of sibling donor sources, chemotherapy or auto-BMT was preferable to Allo-HCT in standard risk ALL. The majority of adult patients with ALL are considered high-risk due to the advanced median age at diagnosis (Bassan R, Hoelzer D, 2011). Therefore, the applicability of the study by Goldstone 2008 is limited and the study has not been considered in detail in this review. Studies that evaluated benefit in high-risk adult ALL were selected for review and will discussed below.

Review Strategy for Efficacy of UCB-HCT in Adult ALL

As stated in Section 5.2, this review takes a two-step approach to evaluating efficacy of UCB in adult ALL was to first evaluate the benefit of allo-HCT in this disease and subsequently evaluate the benefit of UCB as an alternate donor source of allo-HCT.

- The assessment of the efficacy of allo-HCT is based on two randomized studies selected to evaluate the benefit of allo-HCT in the treatment of adult ALL with high-risk disease. These studies (Sebban et al and Hunualt et al, 1994) compared allo-HCT against auto-HCT and/or chemotherapy. These studies were selected because they were prospective randomized studies based on the donor vs. no donor analysis (ITT).

- The efficacy of UCB compared to other allo-HCT sources was based on four retrospective registry or single institution studies in adult leukemia. Two of these studies (Tomblyn 2009 and Atsuta 2009) evaluated the benefit specifically in adult ALL while the other two studies by Laughlin 2004 and Rocha 2004 evaluated outcomes in Acute Leukemia in general in which

approximately half the total number of subjects had ALL. The large sample sizes from the registry studies and the use of matched cohorts for controls were major advantages of these two studies.

6.5.10 Evidence Based Approach to Use of Allo-HCT in Adult ALL

Non-randomized retrospective studies comparing outcomes of MSD allo-HCT to chemotherapy have been published (Horowitz MM, Messerer D et al, 1991 and Oh H, Gale RP et al 1998). These studies have not been included in this review because the studies were retrospective. Studies by Sebban (Sebban C, Lepage E et al, 1994) and Hunault (Hunault M, Harousseau JL et al, 2004) are randomized prospective studies that evaluated the benefit of Allo-HCT in high-risk adult ALL. These studies are discussed below.

6.5.11 Comparison of Allo-BM-HCT against Chemotherapy or Auto-BM-HCT (Sebban C, Lepage E et al, 1994)

Objective:
The objective of the LALA87 study, a French prospective study, was to evaluate auto-HCT or chemotherapy vs. MSD allo-HCT as optimal post-remission therapy in adults with ALL in CR1 or subsequent CR.

Study design:
Enrollment period was between 1986 and 1991. Subjects between 15-40 years of age in CR after either induction therapy CR1 or salvage therapy were allowed to participate. Subjects with HLA MSDs were assigned to the BM-HCT group and subjects without an MSD were assigned to the control group. Subjects in the control group were randomized after consolidation treatment to receive chemotherapy or auto-HCT. Conditioning regimens were the same for auto-HCT and allo-HCT. Based on available literature, high-risk ALL was defined as:

- Presence of Philadelphia chromosome (Ph+)
- Undifferentiated or Null leukemia
- Other leukemias with one or more adverse features of either age >35 years, WBC count >30x10^9, or time to CR>4 weeks.

Results:
One hundred and sixteen subjects were assigned to the BM-HCT group and 141 to the control group. Subjects were well balanced in both arms for the high-risk factors except for the presence of Ph+ALL. The control group had more subjects with Ph+ALL (13% vs. 6%) than the BM-HCT group. Ninety-two subjects (81%) in the BM-HCT group were transplanted in CR1; 33 of

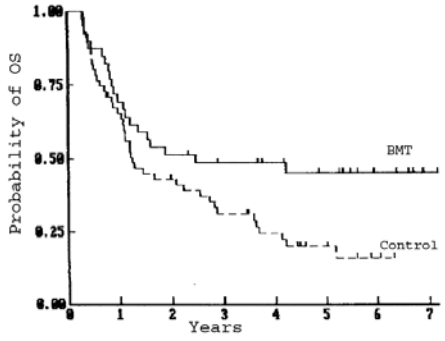
these subjects had high-risk ALL. In the control group, only 83% were randomized to either maintenance chemotherapy or auto-HCT. Of those randomized to auto-HCT only 69% received the allocated treatment. The primary cause for the failure to treat with auto-HCT was early relapse. The median duration of follow-up was 62 months.

Table 7: OS and DFS in BM-HCT vs. Control (Auto-HCT/Chemotherapy)
(Sebban C, Lepage E et al, 1994)

Allocation	n	Median Survival (mo) (95% CI)	p-value (OS)	Median DFS (mo) (95% CI)	p-value (DFS)
BM HCT	116	51 (30-NR)	0.08	24 (15-NR)	0.1
Control	141	30 (21-43)		22 (13-29)	
HR-ALL	96	19 (13-34)	<0.001	12 (9-23)	<0.001
Standard risk	161	57 (34-NR)		29 (21-NR)	
HR-ALL (BM HCT)	41	30 (13-NR)	0.03	21 (11-NR)	0.01
HR-ALL(Control)	55	15 (13-31)		9 (6-20)	
SR-ALL (BM HCT)	75	NR (32-NR)	0.7	27 (16-NR)	0.9
SR-ALL (Control)	86	56 (28-NR)		30 (21-NR)	

n = Sample size based on treatment Allocation
CI = Confidence interval
DFS = Disease-Free Survival
NR = Not reached
HR = High-risk
SR = Standard Risk ALL

Figure 2: Probability of OS in High-risk Leukemia Subjects for BM-HCT vs. Auto-HCT/Chemotherapy
(Sebban C, Lepage E et al, 1994)



Study Conclusions:

- Allo-HCT did not improve survival in patients with standard-risk ALL.
- Allo-HCT did provide a significant improvement in median DFS (p=0.01) and OS (p=0.03)

Reviewer Comments and Conclusions:

- When the results are analyzed as BM-HCT (MSD) vs. chemotherapy, there is no statistically significant advantage to BM allo-HCT (MSD).
- The study suggests that the OS and DFS benefit for MSD allo-HCT is limited to high-risk ALL. Outcomes were similar for standard-risk ALL.
- Since age >35 years is considered an independent high-risk factor in subjects with ALL other than the Ph+, undifferentiated and null type ALL, most adult subjects with ALL are likely to be considered as high-risk ALL. This study was not designed to assess age as a risk factor in OS with allo-HCT.
- This study had a small percentage of older (>35) age patients (HCT: 16%; control: 18%), so the conclusions from this study are primarily for HR factors other than age.

6.5.12 Comparison of MSD Allo-HCT Against High Dose Chemotherapy and Auto-HCT in Adult ALL (Hunualt M, Harousseau JL, et al, 2004)

Objective:
The objective of the study by Hunault et al. is to examine the role of MSD allo-HCT in both older and younger adults with high-risk ALL and to compare long-term outcomes to those of auto-HCT after high-dose chemotherapy.

Study design:
This was a randomized prospective trial conducted between 1994 and 1998. High-risk features were similar to the Sebban study, but differed in the inclusion of additional poor-risk cytogenetic abnormalities (t(4:11) or t(1:19) and did not include null or undifferentiated ALL sub-types. Subjects who entered CR1 after first induction or salvage induction were eligible. All subjects received the same induction (Berlin-Frankfurt-Muenster-BFM) and consolidation regimens. Subjects who were 50 years or younger without a 6/6 matched sibling donor were assigned to receive auto-HCT after high-dose conditioning treatment (HDT). Subjects in the auto-HCT arm underwent a

second randomization to maintenance interferon-α or no further therapy after hematopoietic recovery.

Results:
Median follow-up was 5.1 years. Pre-treatment characteristics were well balanced in both groups. The number of subjects alive in CR1 at the end of induction was 156. Thirty-nine of forty-one subjects in the allo-HCT group and 91 of 115 subjects in the auto-HCT group received per-protocol treatment. Four subjects in the auto-HCT group received a matched unrelated allo-HCT. The most common reason for not receiving the assigned treatment was early relapse.

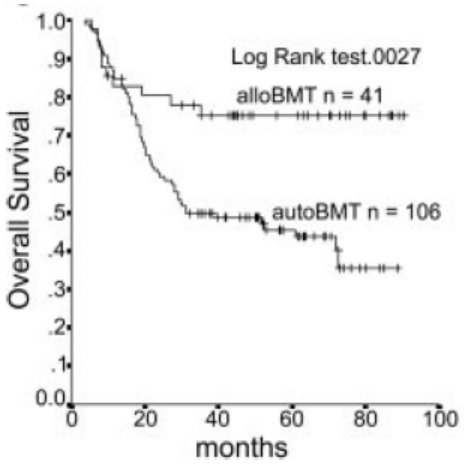
Table 8: OS and DFS Outcomes for Allo-HCT and Auto-HCT in Adult ALL
(Hunualt M, Harousseau JL, et al, 2004)

Outcomes	Allo-HCT (n=41) (months)	Auto-HCT (n=106*) (months)	p-value
DFS	NR	20.9	0.0027
OS	NR	31.2	0.0004

NR=Not Reached

*Of the 115 subjects assigned to Auto-HCT, 106 subjects were used for ITT analysis to provide an age-matched cohort to the Allo-HCT arm. Exclusion of subjects > 50 years old for Allo-HCT is an accepted practice due to the risks associated with Allo-HCT in patients with advanced age.

Figure 5: OS in the Allo-HCT and Auto-HCT in the ITT groups
(Hunualt M, Harousseau JL, et al, 2004)



Study Conclusions:

- Allo-HCT (MSD) provided better outcomes than auto-HCT for adult ALL subjects in CR1.

Reviewer Comments and Conclusions:

- The two prospective studies by Sebban et al and Hunualt et al suggest that MSD Allo-HCT is beneficial in adult ALL in CR1 with high-risk features.

- Direct comparisons of the Sebban study and Hunualt study are difficult to assess since individual patient data regarding prognostic factors and other eligibility criteria are not available.

- The mortality risk for the subjects in the control arm of the Sebban study was higher even though the age group was younger than in the Hunualt study.

6.5.13 Comparison of the Impact of Graft Source for HCT on Outcomes in Adult ALL

Prospective comparative studies of UCB-HCT to other donor sources for allo-HCT have not been done. Selection of studies for comparison of long-term outcomes of HCT with UCB was based on sample sizes from either registries or large single institutions. Analysis of registry studies helps to assess the effectiveness of UCB-HCT as compared to unrelated bone marrow (BM) or peripheral blood stem cells (PBSC) in allo-HCT. They also provide large sample sizes to look for crucial differences in the incidence of relapse, TRM and GvHD. Single-institution studies had a consistent approach to the management of transplant-related complications, conditioning regimens and GvHD prophylaxis between subjects. These factors affect peri-transplant related mortality, which in turn affects long-term outcomes. Reducing the variability in these factors is expected to reduce their impact on differences in long-term outcomes.

The data evaluating outcomes by specific donor sources in adults with ALL is limited. The single-institution study by Tomblyn et al compares outcomes for various graft sources in both adult and pediatric ALL. Registry studies by Rocha (Rocha V, Labopin M et al, 2004), Laughlin (Laughlin MJ, Eapen M et al, 2004), Atsuta (Atsuta Y, Suzuki R et al, 2009) and Eapen (Eapen M, Rocha V et al, 2010) report outcomes for acute leukemia (ALL and AML) by various donor sources in adults. Limited disease-specific outcome data for ALL and AML are presented. These four studies are discussed below to provide supportive data for the use of UCB as compared to other Allo-HCT

stem cell sources in ALL. Since both ALL and AML are included in the registry studies, this portion of the efficacy review is also applicable to the review of the impact of donor sources on outcomes in adult subjects with AML.

Tomblyn 2009 (Tomblyn MB, Arora M et al, 2009)

Objective:

The objective of this study was to evaluate 5-year outcomes based on OS, LFS and relapse rates in high-risk or recurrent ALL comparing various graft sources: autologous donor, related donor (RD), unrelated donor (URD) and umbilical cord blood donor (UCB).

Design:

This is a single institution study from the University of Minnesota. This study retrospectively reviews their experience with patients with ALL from 1980-2005 who received myeloablative allo-HCT from multiple graft sources. Ninety percent of the subjects received a cyclophosphamide/TBI-based HCT preparative regimen. A subset analysis was performed that included a cohort of subjects (n=242) undergoing allo-HCT restricted to CR1 and CR2 receiving transplants between 1990-2005 and aimed at evaluating contemporary practices of allo-HCT in the treatment of ALL.

Results:

The median age was 13 yrs, with range from 6-55 yrs. The total sample size was 623 subjects. Of the 69 subjects receiving UCB transplants, 21 received double-cord units. The overall study results included outcomes for both the autologous and allogeneic groups. In brief, OS was poorest for autologous or mismatched URD sources of stem cells. The analysis of outcomes for patients with ALL suggested that LFS was similar for matched donor, well matched or partially matched URD, and UCB. Disease status at time of allo-HCT was associated with decreased OS if the patients were CR2 or greater (58% of the patients). Late events after two years were rare. TRM was highest in the recipients of mismatched unrelated donor transplant.

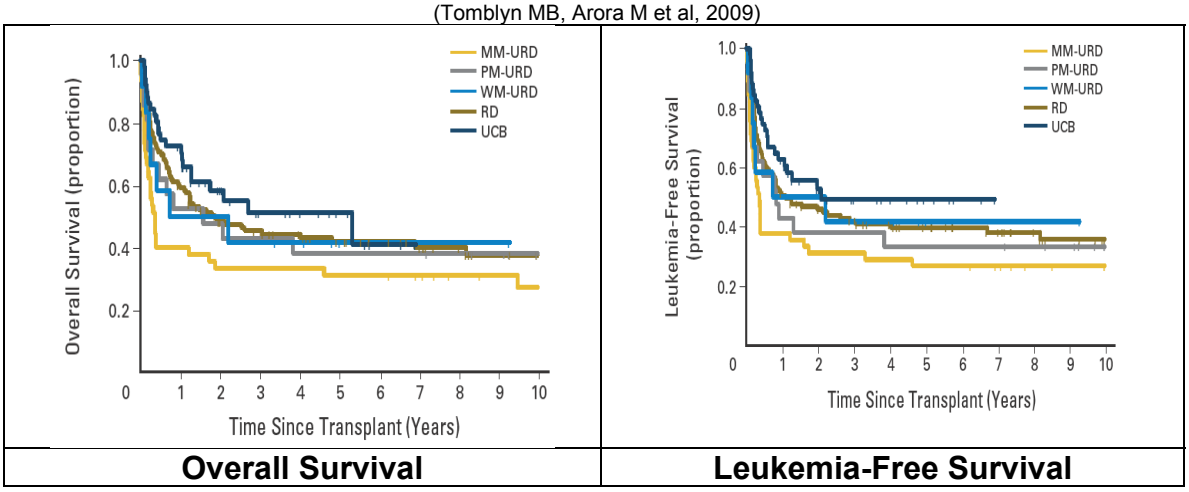
Table 9: Five-year OS and LFS in ALL in CR1 and CR2 by Allogeneic Donor Source (Tomblyn MB, Arora M et al, 2009)

Graft source (n=242)	RD (95% CI) (n=113)	WMURD (95% CI) (n=12)	PM-URD (95% CI) (n=21)	MM-URD (95% CI) (n=45)	UCB (95% CI) (n=51)
OS at 5 yrs	42% (33-51%) (RR=1.0)	42% (14-70%) (p=0.75) (RR=1.1)	38% (18-58%) (p=0.24) (RR=1.5)	31% (17-45%) (p=0.01) (RR=1.7)	51% (46-66%) (p=0.66) (RR=1.1)
LFS at 5 yrs	40% (31-48%) (RR=1.0)	42% (14-40%) (RR=1.1)	(RR=1.5)	27% (14-40%) (RR=1.7)	49% (34-64%) (RR=1.0)

RD: Related Donor PM-URD: Partially matched URD RR: Relative risk
URD: Unrelated Donor MM-URD: Mismatched URD
WM-URD: Well matched URD UCB: Umbilical Cord Blood
LFS: Leukemia Free Survival (patients alive without relapse)

Figure 3: **Five-year OS and LFS in ALL in CR1 and CR2 by Allogeneic Donor Source**

(Tomblyn MB, Arora M et al, 2009)



Overall Survival	Leukemia-Free Survival

Study Conclusions:

- The study provides evidence that durable LFS at 5 years can be achieved with allo-HCT for patients with ALL.
- Five-year OS results were similar for MM URD, WM URD, PM URD, RD and UCB donor sources. These may be considered equivalent options for patients with ALL.
- Analysis of outcomes by year of transplant suggests significant improvement in outcomes, possibly due to improvements in supportive care, recognition of critical factors in HLA matching and availability of UCB units as an alternative to poorly matched unrelated donors.
- The authors observed improvements in OS, LFS and TRM. They attributed this to improved supportive care, improved HLA matching and UCB as an alternative to URD with poor HLA match characteristics.

Reviewer Comments and Conclusions:

- Patients with ALL lacking a sibling donor can receive UCB or a well-matched URD and have acceptable long-term LFS.
- This study supports expanding the donor pool for adults with ALL in CR1 to UCB.

- Of the 69 patients in this study that received UCB, 21 received double units.

- The study results do not provide the median cell dose and the degree of mismatch for the UCB recipients. Since the median age was 13 years of age, the impact of cell dose in the adult population cannot be assessed. The selection of UCB units in current practice uses a higher median TNC/kg cell dose and lesser degree of HLA mismatch as compared to the selection of UCB in this study.

- There is limited information on the impact of prognostic factors such as age and cell dose on outcome.

Rocha 2004 (Rocha V, Labopin M et al, 2004)

Objective:
The objective of this retrospective registry study was to compare outcomes for unrelated UCB-HCT and unrelated HLA matched B- HCT in a series of 682 adults (15-55 years old) with acute leukemia (ALL and AML).

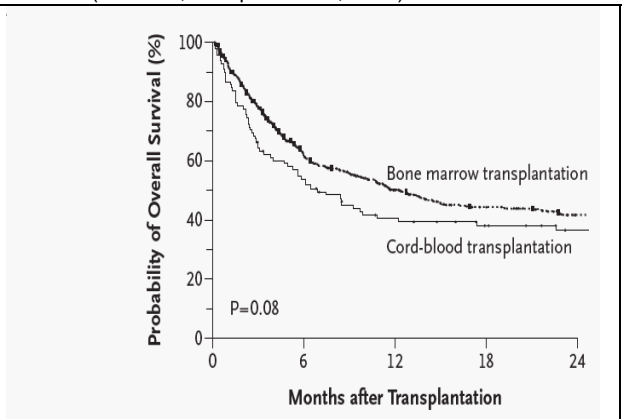
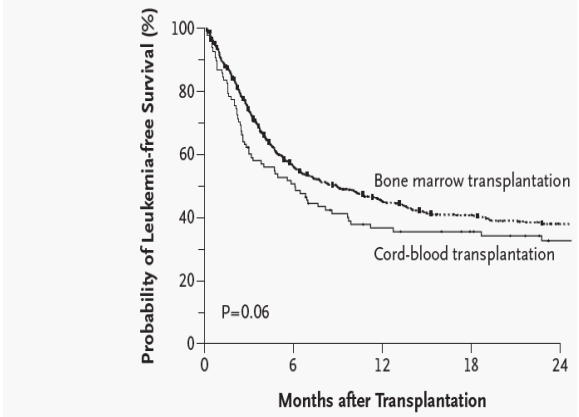
Study design:
Data was obtained from Eurocord and European Blood and Bone Marrow Transplant Group recipients who either received a single cord blood unit mismatched in up to 3 of 6 loci or HLA matched bone marrow from an unrelated donor between 1998 and 2002.

Results:
98 recipients of UCB-HCT and 584 recipients of BM-HCT were evaluable. Forty-nine percent of subjects with ALL were in CR1 and 47% were in CR2. Ninety percent of the recipients of UCB-HCT were matched at 1-2 HLA loci. The median TNC was $2.3x10^7$/kg.

Table 10: Two-year LFS Probability for Unrelated UCB-HCT and BM-HCT in Adults with ALL (Rocha V, Labopin M et al, 2004)

Disease	Unrelated UCB-HCT(n=53) Probability (95% CI)	Unrelated BM-HCT (n=267) Probability (95% CI)	p-value
ALL (overall)	34% (27-41)	33% (30-36)	0.21
ALL in CR1	43% (33-53)	49% (45-53)	0.31
ALL in CR2	44% (32-56)	47% (43-50)	0.64
Advanced ALL	23% (17-29)	19% (16-22)	0.92

Figure 4: Outcomes for Unrelated UCB-HCT and Unrelated BM-HCT in Adults with Acute Leukemia (Rocha V, Labopin M et al, 2004)

Overall survival in AML and ALL	 No. at Risk Bone marrow transplantation 584 324 224 178 148 Cord-blood transplantation 98 51 35 28 21
Leukemia-Free Survival in AML and ALL	 No. at Risk Bone marrow transplantation 584 293 202 165 138 Cord-blood transplantation 98 49 32 27 19

Study Conclusions:

- For acute leukemias, OS and LFS are similar for both unrelated UCB-HCT and unrelated BM-HCT.
- There was no difference in the 2-year cumulative incidence of relapse between UCB-HCT (44%) and BM-HCT (38%) recipients.
- The differences in the probability of 2-year LFS between recipients of UCB-HCT and unrelated matched BM-HCT for ALL in CR1 and CR2 were not statistically significant.

Reviewer Comments and Conclusions:

- The 2 year LFS for the BM-HCT group (predominantly ALL in CR1) in the Sebban study appears to be comparable to the 2-year LFS in the CR1 group for Rocha et al.

- This study supports the use of UCB as a donor source for allo-HCT in patients without an HLA-matched donor.

Laughlin 2004 (Laughlin MJ, Eapen M et al, 2004)

Objective:

The objective of this retrospective registry study was to compare outcomes of unrelated BM-HCT and unrelated UCB-HCT in patients with AL, CML or MDS. The data source was the IBMTR.

Study design:

The sources of the subjects were the IBMTR and the NYBC. One hundred and fifty single-unit UCB recipients were matched for 5/6 (34) or 4/6 (116) alleles. Four hundred and fifty UBM-HCT recipients were selected with one or no mismatches. Transplantations were performed from 1996-2001 in adult patients (16 – 60 years old). Engraftment, LFS and OS were evaluated.

Results:

The majority of the subjects were less than 40 years of age. Approximately 50% of subjects in the UBM-HCT arm and 69% of subjects in the UCB-HCT arm had acute leukemia (ALL and AML). The median cell dose for UCB was $2.2x10^7$ TNC/kg. In this analysis an effect of median cell dose on outcomes was not found. Median follow-up period for UBM-HCT and UCB-HCT were 48 and 40 months respectively. The differences in relapse rates were not statistically significant.

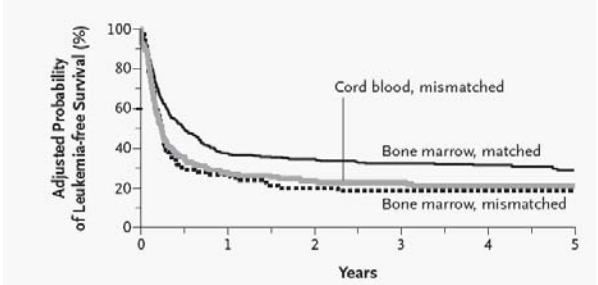
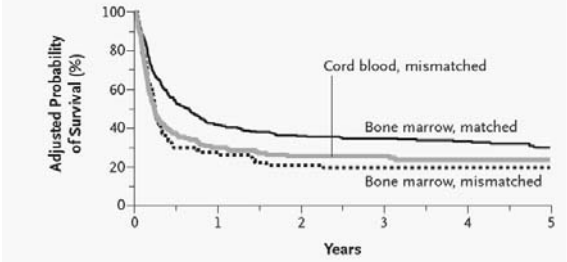
Table 11: LFS and OS in Acute Leukemia for UCB-HCT and UBM-HCT
(Laughlin M, Eapen M et al, 2004)

Survival	0-2MM UCB-HCT (n= 150)	MM-UBM-HCT (n=83)	M-UBM-HCT (n=357)	Comments
3 yr LFS	23%	19%	33%	3-yr LFS and OS outcomes favored of the M-UBM-HCT group compared to either the UCB-HCT or MM-UBM-HCT. No differences were seen between MM-UBM-HCT and UCB-HCT.
3 yr OS	26%	20%	35%	

0-2 MM UCB: Mismatched at 0, 1 or 2 HLA loci
M-UBMT: Matched unrelated BM donor
MM-UBMT: Mismatched BM at one HLA locus

Figure 5: LFS and OS in Acute Leukemia for Unrelated Matched BM-HCT, Mismatched BM-HCT and UCB-HCT

(Laughlin M, Eapen M et al, 2004)

Leukemia-Free Survival	 No. at Risk Bone marrow, matched 367 138 120 99 60 42 Bone marrow, mismatched 83 23 16 14 8 5 Cord blood, mismatched 150 38 28 24 12 5
Overall Survival	 No. at Risk Bone marrow, matched 367 153 124 104 62 42 Bone marrow, mismatched 83 24 17 15 9 6 Cord blood, mismatched 150 40 29 25 13 5

Study Conclusions:

- HLA mismatched UCB can be a source of hematopoietic stem cells if no matched donor is available.

- LFS and OS for matched unrelated allo-HCT were significantly better for matched unrelated BM-HCT as compared to UCB-HCT. However the outcomes were similar between HLA-mismatched unrelated BM-HCT and UCB-HCT (one and two loci).

- Patients who received UCB had a higher rate of cGvHD than unrelated matched BM recipients.

- Cell dose did not change the incidence of mortality and treatment failure for UCB recipients. Dose was < $3.0x10^7$ TNC/kg in 80% of the patients.

Reviewer Comments and Conclusions:

- UCB is an acceptable alternative donor source to unrelated mismatched BM for adults with AL, CML or MDS.

Atsuta 2009 (Atsuta Y, Suzuki R et al, 2009)

Objective:
The objective of this retrospective registry study was to compare unrelated UCB-HCT to unrelated matched bone marrow transplantation (MUD BM-HCT) in adults with acute leukemia from two Japanese registries.

Study design:
Patients received either a single UCB unit with 0-2 HLA mismatches or allele matched BM from unrelated donors. Patients who were registered from 2000-2005 were analyzed. Subjects were 16 years or older. Overall survival and LFS were the outcomes of interest.

Results:
The 114 UCB and 222 BM recipients were well balanced for disease status. There were more patients with poor prognostic cytogenetic risk factors for ALL in the UCB group. In the UCB group, 77% of the subjects had 2 HLA mismatched donor transplants. The preparative regimen included cyclophosphamide and total body irradiation. GvHD prophylaxis was methotrexate plus either cyclosporine or Tacrolimus; cyclosporine plus an additional agent or Tacrolimus plus an additional agent.

Table 12: Two-year OS and LFS in Adult ALL for UCB vs. Matched Unrelated Allo-HCT (MUD) (Atsuta Y, Suzuki R et al, 2009)

Outcome	UCB-HCT	BMT-HCT	p-value
2-year LFS	46%	44%	P=0.41
2-year OS	52%	53%	P=0.99

Study Conclusions:

- UCB matched or mismatched for 0-2 loci is an alternative donor source for patients without matched or mismatched BM donor.
- All patients received single units of UCB, the preparative regimens were similar and GvHD prophylaxis was similar even though this was a registry study.
- Patients with AML had lower 2-year OS and LFS than BM recipients, this was not the case for ALL patients.

Reviewer Comments and Conclusions:

- The study provides evidence that OS and LFS are similar in ALL between UCB-HCT and MUD BM-HCT. Therefore UCB is an acceptable alternative donor source for ALL patients who do not have a MUD source as an option.
- These findings are consistent with the findings from the Laughlin study. Comparison to MSD is not available.
- The Japanese donor pool is different from the IBMTR registry in that the Japanese population has a higher genetic homogeneity. Therefore, the Japanese donor pool has the possibility of decreased TRM and GvHD from any unrelated donor source including unrelated UCB.

Eapen 2010 (Eapen M, Rocha V et al, 2010)

This study provides an updated review of registry data on outcomes in acute leukemias (ALL, AML), based on graft selection from UCB, BM, or PBSC unrelated donor sources.

Objective:

The objective of this retrospective study was to evaluate whether changes in the graft selection process had improved the outcomes for UCB when compared to matched and partially matched unrelated BM or PBSC donor sources.

Study design:

CIBMTR and National Cord Blood Program (NCBP) registry data from 2002-2006 were evaluated in patients who were 16 years or older. In this study, matching at HLA-C loci was included in the selection of matched unrelated BM and PBSC. HLA mismatches were restricted to up to 2 loci. The cell dose threshold of $2.5x10^7$ TNC/kg was an eligibility requirement for the analysis. These changes to the graft selection process and minimum threshold for cell dose were expected to reduce the TRM and improve long-term outcomes.

PBSC were included in the analysis group due to the changing practice with regard to donor source.

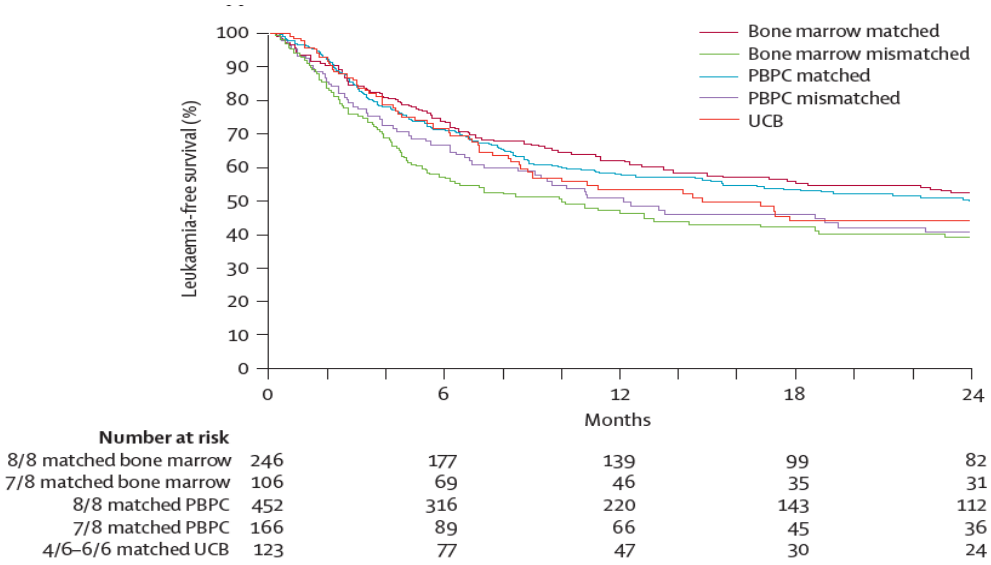
Results:

There were 888 subjects who received PBSC, 472 who received BM, and 165 who received UCB. The study was not designed to evaluate differences in outcomes between BM and PBSC group. The proportion of subjects with ALL (approximately 42%) in both the PBSC and BM groups were similar; however the UCB group had a higher proportion of subjects with ALL (54%). The proportion of subjects in CR1 or CR2 was comparable in all groups. There were no statistically significant difference in LFS and OS between UCB compared to fully or partially matched unrelated BM or PBSC. There were no differences in LFS or OS for the overall group if subjects were in CR as opposed to active disease at the time of transplantation.

Table 13: Two-year LFS for UCB-HCT and Matched and Mismatched Unrelated BM-HCT (Eapen M, Rocha V et al, 2010)

Outcome	UCB-HCT	M-UBM-HCT		MM-UBM-HCT	
		PBSC	BM	PBSC	BM
2-year LFS	44%	50%	52%	39%	41%

Figure 6: LFS Probabilities by Donor Source and HLA Match for Patients with Acute Leukemia in Remission
(Eapen M, Rocha V et al, 2010)



Study Conclusions:

- An effect of cell dose on LFS and OS outcomes was not seen. There was insufficient sample size to analyze the effect of HLA mismatch on outcomes within the UCB group.

Reviewer Comments and Conclusions:

- This study suggests that UCB is comparable in efficacy to both fully matched and partially matched unrelated BM and PBSC for allo-HCT. The comparability of UCB to fully matched unrelated donor allo-HCT differs from the results of the Laughlin 2004 study (Laughlin MJ, Eapen M et al, 2004) where fully matched allo-HCT was superior to unrelated UCB-HCT mismatched at 1 or 2 alleles.

- The overall LFS rate at 2 years in Eapen 2010 appears to be better for all groups than in the Laughlin study. The Eapen 2010 study patients were treated more recently, with improved patient selection, conditioning regimens and GvHD prophylaxis.
- The Rocha 2004 study (Rocha V, Labopin M et al, 2004) did not include mismatched-UBM-HCT, but the overall LFS outcomes are comparable between this Eapen 2010 study and the Rocha 2004 study.

- Since the Rocha 2004 and Laughlin 2004 studies evaluated similar periods of transplantation, the disparity between their overall results cannot be explained by graft selection practices. It is also unclear whether the improvements in LFS for mismatched-UBM-HCT seen in the Eapen 2010 study relative to the Laughlin 2004 study were related to HLA-C locus matching or other advances in standard of care for allo-HCT patients.

6.5.14 Summary Comments and Conclusions for the Role of Allo-HCT and UCB as Donor Sources in Adult ALL

- The studies outlined above:
    - The Sebban (Sebban C, Lepage E et al, 1994) and Hunault (Hunault M, Harousseau JL et al, 2004) studies conclude that compared to conventional chemotherapy, allo-HCT from MSD provides an OS benefit in high-risk ALL in adults in all age groups.

- The Tomblyn study (Tomblyn MB, Arora M et al, 2009) is more pertinent to pediatric subjects with ALL, but the study also included adults with ALL. This study suggests that UCB may be comparable to MSD, fully and partially matched unrelated donor and mismatched donors with regard to OS outcomes.

- The Laughlin study (Laughlin MJ, Eapen M et al, 2004) suggests that matched unrelated donor transplant has superior outcomes compared to UCB or mismatched unrelated donor transplant in Acute Leukemias (AL).

- The Rocha (Rocha V, Labopin M et al, 2004) and Atsuta (Atsuta Y, Suzuki R et al, 2009) studies conclude that LFS and OS outcomes between UCB-HCT and fully matched unrelated HCT were similar for AL.

- The Eapen study (Eapen M, Rocha V et al, 2010) suggests that LFS in UCB-HCT is comparable to both fully matched and partially matched unrelated donor sources for AL

- Based on the above published studies, the reviewer conclusions are:

  - UCB may be a suitable substitute for matched or partially matched donors in the adult ALL population.

  - There is insufficient evidence to conclude that UCB is an acceptable alternative donor source if a MSD donor is available in adult ALL.

  - Thus, UCB may be an acceptable treatment option for adult ALL patients for whom a mismatched unrelated donor is the only other available option after risk vs. benefit assessments are made for the individual patient.

  - UCB may be an acceptable alternative if no other related or unrelated donor source of hematopoietic stem cells is available.

6.6 Indication: Acute Myelogenous Leukemia (AML)

6.6.1 Pediatric AML: Background

AML represents about 15-20 percent of all childhood leukemia. The peak incidence is in the first year of life and then decreases until age 4 and then remains constant throughout childhood and adolescence (Howlader N, Noone AM, 2011). In general, treatment is risk-stratified with 90% of patients achieving initial remission. Sixty percent of patients maintain long-term remission with aggressive consolidation therapy that is risk-based (Niewerth D, Creutzig U et al, 2010). Pediatric patients with AML who have Acute Promyelocytic Leukemia (APML), Down Syndrome, or favorable risk as determined by cytogenetics and response to induction therapy are not considered allo-HCT candidates in CR1.

This efficacy review in pediatric AML will focus on CR1 and CR2. Comparability of UCB to other sources of allogeneic stem cells in subjects with pediatric AML will also be assessed.

6.6.2 General Approach to the Treatment of Pediatric AML

In the last three decades, allo-HCT has been considered for consolidation therapy for pediatric and adult patients with AML. Allo-HCT is the consolidation treatment of choice post-CR1 in patients with matched sibling donors in the intermediate and high-risk groups. Exceptions are:

- the AML subtype Acute Pro-Myelocytic Leukemia [APML: t(15;17)]
- children with Down Syndrome
- patients with AML, favorable risk

Multiple clinical trials (Testi AM, Biondi A et al, 2005; Ortega JJ, Madero L et al, 2005; Zhang L, Zhao H et al, 2008) provide evidence of the efficacy of All Trans-Retinoic Acid (ATRA) in the treatment of APML. These study results led to guidelines that restrict allo-HCT to relapses and refractory disease in APML. In Rao et al, pediatric patients with Down Syndrome and AML in CR1 who received Allo-HCT were found to have increased TRM without long-term benefits on OS. The publication concluded that there is no role for consolidation treatment with Allo-HCT in children with Down Syndrome with AML in CR1 (Rao A, Hills RK et al, 2005).

Areas of controversy include the potential benefit and role of transplantation in AML with FLT3-ITD mutations where the overall survival rates are 30%. There is

also evidence of a lack of benefit of allo-HCT in infants with AML (Pui CH, Carroll WL et al, 2011). The effect of UCB-HCT or allo-HCT in the above sub-types of AML is beyond the scope of this review.

Review Strategy for Efficacy of allo-HCT as a Treatment in Pediatric AML

As stated in Section 6.0 of this review the two-step approach to evaluating efficacy of UCB in pediatric AML was to first evaluate the benefit of allo-HCT in this disease and subsequently evaluate the benefit of UCB as an alternate donor source of allo-HCT.

One meta-analysis (Horan JT, Alonzo TA et al, 2008) and two randomized studies (Woods WG, Neudorf S et al, 2001; Gibson BE, Wheatley K et al 2005) were selected to evaluate the efficacy of MSD allo-HCT in the treatment of pediatric AML.

- The two randomized studies were chosen because they were large cooperative prospective clinical trials designed to assess the benefit of allo-HCT as compared to chemotherapy and auto-HCT.
- The meta-analysis was selected because it reviewed four large prospective pediatric cooperative group trials conducted in the United States, United Kingdom, Europe and Australia to evaluate the benefit of allo-HCT in pediatric AML. This meta-analysis compared allo-HCT to chemotherapy. Two of the trials in the meta-analysis were Woods et al and Gibson et al.

Review Strategy for Efficacy of UCB-HCT as a Treatment in Pediatric AML

To compare UCB as donor source to other allo-HCT donor stem cell sources, registry studies by Rocha V, Cornish J et al, 2001 and Eapen M, Rubinstein P et al, 2007 were reviewed.

- These retrospective registry studies had large sample sizes. The studies were conducted internationally. This combination of size and scope may provide improved reliability and generalizability of the results for use in this review of efficacy.
- As discussed in the review strategy for efficacy of UCB-HCT in pediatric ALL, these studies reported outcomes in acute leukemias as a group. However, these two studies are considered acceptable to include in this AML review because approximately half of the enrolled subjects had a diagnosis of AML.

6.6.3 Role of Allo-HCT in the Treatment of Pediatric AML in Remission

Comparison of MRD Allo-HCT to Auto-HCT or Chemotherapy in Pediatric AML (Woods WG, Neudorf S et al, 2001)

Woods 2001

Objective:
The objective of this study (CCG-2891) was to compare allo-HCT to one of two control groups with regard to long-term survival in pediatric subjects with AML in remission. These control groups were high-dose chemotherapy (HDCT) and auto-HCT.

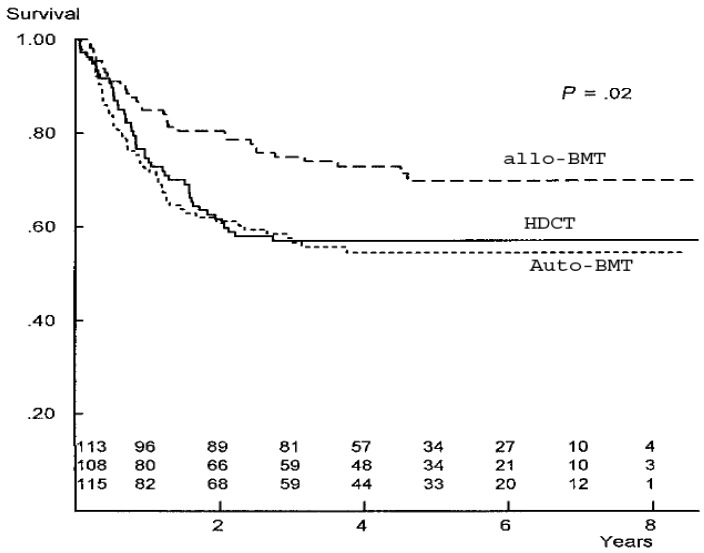
Design:
Subjects who achieved CR were eligible for allocation to allo-BM HCT if a MRD source was available. Following CR, those who did not have a MRD source were randomized to treatment with auto-BM HCT or HDCT. Survival analysis was based on an ITT (allocation to MSD allo-BMT vs. HDCT or auto-BM HCT). The study was conducted between 1989 and 1995.
Results:
Six hundred and fifty-two patients were in remission after completion of therapy. Of the 652 subjects in remission, 181 patients were to receive allo-BM HCT. Of the remaining 471 subjects in remission but without a MSD donor, 115 refused to be randomized between auto-BM HCT or HDCT. The remaining subjects were randomized to auto-BM HCT (n=177) and HDCT (n=179). There were statistically significant differences in 8-year DFS and OS in favor of the allo-BM HCT when compared to each of the two control groups.

Table 14: DFS and OS outcomes for Allo-HCT, Auto-BM-HCT and Chemotherapy (Woods WG, Neudorf S et al, 2001)

Outcomes*	Allo- BM HCT	Auto-BM HCT	Chemotherapy	p-value Allo- vs. Auto	p-value Chemo vs. Allo-HCT
All patients (n=537)	n=181	n=177	n= 179		
DFS	55%	42%	47%	0.001	0.01
OS	60%	48%	53%	0.002	0.05

- Outcomes are based on 8-year follow-up

Figure 7: OS Outcomes for Allo-HCT, Auto-BM HCT and Chemotherapy
(Woods WG, Neudorf S et al, 2001)



Allo-BMT = Allo BM HCT with a MSD
HDCT = High-dose chemotherapy
Auto-BMT = Auto-BM HCT

Study Conclusions:

- Allo-HCT for pediatric AML in CR1 was statistically significantly better (p=0.006) than auto-HCT or HDCT as consolidation therapy with 8-year follow-up for OS.
- The advantage to MSD allo-HCT was consistent when stratified for age, white blood cell count at diagnosis, FAB classification and cytogenetics.

Reviewer Comments and Conclusions:

- For patients with pediatric AML in CR1, allo-HCT as consolidation therapy provides better long-term outcomes as compared to auto-HCT or HDCT.
- The study was based on an ITT population determined by biologic randomization (depending on MRD donor availability). This is likely to reduce selection bias.
- Subjects in CR1 who received allo-HCT from MRD sources were not selected based on high-risk disease status. Risk-based selection of allo-HCT candidates is now the standard of care to determine if allo-HCT is an appropriate therapeutic plan in CR1.Thus, the applicability of the study conclusions to current practice remains to be determined.

- Despite the lack of a risk-based approach to therapeutic decisions, the patients who receive MSD allo-HCT had a statistically significant improvement in 8-year OS. The study reviewed cytogenetics at diagnosis, and the three groups were balanced. From the risk-based approach, the advantage of allo-HCT is in the intermediate-risk group. The low or favorable-risk and high-risk groups have similar outcomes, as detailed in the studies below.

Analysis of Risk-Based Outcomes Between MSD Allo-HCT and Auto-BM-HCT in MRC 10 (Gibson BE, Wheatley K et al 2005)

Gibson 2005

Objective:
The primary objective of the MRC AML 10 study was to reduce the relapse risk (RR) in pediatric AML. This study also compared long-term outcomes of allo-BMT (allo-HCT from BM source only) to auto-BM HCT (auto-HCT from BM source only) in CR1.

Study Design:
Between 1988-1995, subjects ≤ 14 years of age in CR1 with no MSD were assigned to the auto-BM HCT or no further therapy after four courses of aggressive chemotherapy. Risk-group stratification was determined by cytogenetics. There were 3 risk groups determined by cytogenetics at diagnosis and response to course one of treatment: Low-risk (LR), Standard-Risk (SR), and High-Risk (HR).

Results:
A total of 364 subjects were enrolled. Outcomes of only those subjects who achieved a remission and received a transplant will be included in the discussion of the results below. The assessment of efficacy of BM-HCT was based on an intention to treat (ITT) analysis, i.e., whether a MSD was available (donor) or not (no donor group). This assessment compared outcomes for the donor group (allo-BM HCT) versus the no donor group (auto-BM HCT or no further therapy) within each risk-based sub-group as well as for the entire group. Sixty-one of the 85 subjects with MSD received an allo-BM HCT. There was no statistically significant difference in survival at 10 years between subjects with (68%) versus without (59 %) a donor, HR=0.79, 95% CI=0.54-1.17, p=0.03). For those subjects receiving allo-BM HCT, the differences among the three risk groups with regard to both OS and DFS at 10 years from the time of CR were statistically significant. For those subjects who relapsed and likely received salvage therapy with re-induction followed by allo-BM HCT, the OS at 5 years for LR, SR and PR were 57%, 14% and 8%. These results were statistically significant.

Study Conclusions:

- The OS at 10 years was similar for allo-BM HCT, auto-BM HCT or no further therapy. The treatment-related deaths off-set the benefit of decreased relapse risk (RR) in the allo-BM HCT group.

- The MRC 10 trial for adults and children was analyzed to produce a risk-based approach to therapy use in subsequent MRC trials for all aged patients. Thirty-four percent of the patients were low-risk, 61% were Intermediate-risk and 7% were high-risk. OS at 10-years was 77%, 58% and 30%, respectively.

- The 57% OS at 5 years post-relapse for the LR group suggests that salvage therapy with allo-BM-HCT may be more appropriate in CR2 in the LR subjects. The post-relapse 5-year OS outcome for the high-risk group was low (8%). The sample size for this group was small (19% of all subjects).

Reviewer Comments and Conclusions:

- There outcomes for allo-HCT and chemotherapy were similar for subjects with AML in CR1. As with other studies that are described in the meta-analysis (Horan JT, Alonzo TA et al, 2008), the results suggest that low-risk subjects have acceptable long-term survival outcomes that may permit using allo-BM-HCT as a salvage option at relapse.

- Both the AML 10 (Gibson et al) and CCG 2891 (Woods WG, Neudorf S et al, 2001) studies compared OS outcomes between donor vs. no donor groups to evaluate the benefit of MSD allo-BMT HCT. However the results from these studies are different.
    - Unlike the CCG 2891 study, the AML 10 study did not suggest a benefit for MSD allo-BMT for the entire group. This difference may be due to the differences in post-transplant mortality associated with the AML 10 induction regimen, consisting of four induction courses, compared to the post-transplant mortality associated with the two induction courses in the CCG 2891.

    - In AML 10 the benefit of allo-BM HCT in reducing relapse may have been offset by the induction-related toxicity and peri-transplant mortality.

- This study provides justification for the use of risk-based therapy to determine the timing of MSD allo-HCT.

Meta-analysis of the Treatment of AML

Horan 2008 (Horan JT, Alonzo TA et al, 2008)

Objective:
The objective of this meta-analysis of the treatment of AML was to assess the Children's Oncology Group studies (POG 8821, CCG 2891, and CCG 2961) and the British MRC AML10 study to define prognostic and therapeutic risk categories.

Outcomes were used to define risk-categories for pediatric subjects with AML in CR1 in the context of efficacy of MRD allo-BM-HCT versus chemotherapy.

Study design:
Subjects were stratified into three risk categories (low, intermediate and high-risk) based on their cytogenetic profile at diagnosis and their response to induction therapy based on their percentage of remaining blasts after the first course of chemotherapy. Long-term outcomes of LFS and OS were compared based on assignment to MRD Allo-BM HCT or chemotherapy.

- Low-risk was defined as inv 16, t(8:21)
- High-risk was defined as monosomy 5, monosomy 7, 5q-, 3q abnormalities, ≥ 5 cytogenetic abnormalities or more than 15% blasts after first chemotherapy.

- Intermediate-risk was defined as those subjects who had cytogenetic results that were neither low-risk nor high-risk.

Results:
Of the 1,373 patients in first remission, eight hundred ninety-three patients received chemotherapy alone and 480 patients were assigned to allo-HCT. A summary of the results are provide in Table 15.

Table 15: Risk-Based Outcomes for BM HCT vs. Chemotherapy in Pediatric AML (Horan JT, Alonzo TA et al, 2008)

Sample Size and Outcomes* by risk category	BM HCT (%)	Chemotherapy (%)	HR (95% CI)	p-value
Overall group (Not-risk stratified and includes unclassified risk group)				
N	480	893		
DFS	56%	61%	0.89 (0.57-1.37)	0.58
OS	73%	71%	0.95 (0.57-1.59)	0.85
Low-Risk				
N	96	157		
DFS	63%	61%	0.89 (0.57-1.37)	0.58
OS	73%	71%	0.95 (0.57-1.59)	0.85
Intermediate-Risk				
N	204	411		
DFS	58%	39%	0.59 (0.46-0.76)	<0.001
OS	62%	51%	0.69 (0.52-0.90)	0.006
High-Risk				
N	9	38		
DFS	33%	35%	1.13 (0.38-3.38)	0.82
OS	33%	35%	0.87 (0.30-2.51)	0.80

*Outcomes reported are at 8 years. N = sample size

Conclusions:

- The study concluded that matched related donor allo-BM HCT provides a treatment benefit over chemotherapy for IR pediatric AML.

Reviewer Comments and Conclusions:

- The sample size was small for the HR group (n=47). Therefore, there is insufficient data to evaluate efficacy in the HR group. In general, the incidence of HR AML is less than 15 % of all AML (Pui CH, Carroll WL et al, 2011). Therefore, the relative sample sizes in this study reflect the relative incidences of the risk groups in the AML population.

- This retrospective meta-analysis is based on studies from three large international cooperative groups. The studies varied in study design, treatment regimens, and demographics. Individual subject data and study details are unavailable in this study report. Thus it is difficult to assess the impact of these variations on the study results.

- The meta-analysis includes studies that were conducted over a period of 15 years. Subject eligibility and selection practices based on risk-group stratification for allo-BMT evolved during this period. Individual study data and individual study criteria for subject selection are lacking in the report. Thus the conclusions from this analysis must be interpreted in light of these changes in risk stratification.

6.6.4 The Role of UCB-HCT in Pediatric AML: Background

As with the efficacy review of the literature for pediatric ALL, the discussion of UCB as a donor source will be restricted to studies that provide comparative data in AML or acute leukemia.

Studies evaluating UCB in pediatric AML are summarized in a review by Brunstein CG, Baker KS et al, 2007. These are retrospective studies lacking control groups. Therefore, these studies are not included in this review of published literature.

UCB as a Comparable Allogeneic Donor Source in Acute Leukemia

The studies by Rocha (Rocha V, Cornish J et al, 2001) and Eapen (Eapen M, Rubinstein P et al, 2007) compare UCB to various other donor sources for allo-

BM-HCT. These studies have been discussed in detail in the efficacy review of UCB compared to other donor sources in pediatric ALL (Section 6.5.7).
In summary, Rocha 2001concluded that UCB was comparable to matched unrelated donor allo-BM HCT with regard to LFS and OS in pediatric AML.
Eapen 2007 concluded that LFS outcomes were similar for matched UCB-HCT, mismatched UCB-HCT, matched unrelated BM HCT and mismatched unrelated BM HCT.

6.6.5 Summary Comments and Conclusions for the Role of Allo-HCT and UCB-HCT in the Treatment of Pediatric AML

- In the studies outlined above:
    - The MRC AML 10 trial (Gibson BE, Wheatley K et al 2005) and the meta-analysis study (Horan JT, Alonzo TA et al, 2008) suggest that allo-HCT is unlikely to provide long-term benefit over chemotherapy for subjects with AML in the low- (or favorable-) risk group. This is because the improved outcomes and lower toxicities associated with consolidation chemotherapy outweigh the risks of peri-transplant mortality from allo-HCT.
    - The MRC 10 trial and Horan meta-analysis suggest that outcomes appear to be similar between chemotherapy and allo-HCT for pediatric AML.
    - The Horan meta-analysis provides evidence to support the use of allo-HCT in intermediate-risk pediatric ALL.

- Based on the above published studies, the reviewer concludes that in pediatric subjects with AML in CR2:
    - In the absence of other post-remission therapy, allo-HCT is a suitable option for consolidation therapy. However, individual patients should be evaluated for their suitability for allo-HCT after assessment of their risks and benefits of allo-HCT compared to consolidation chemotherapy.
    - Based on review of the published literature, UCB may be comparable as a donor source to matched and mismatched unrelated BM and PBSC donor sources in the treatment of acute leukemia (AL) including AML. However disease-specific efficacy data from prospective studies in pediatric AML for UCB-HCT is lacking. The evidence comparing UCB to other donor sources comes from retrospective analyses and is subject to various biases.
    - Standard practice for this indication for allo-HCT has changed since the period of the retrospective studies (Rocha 2001, Eapen 2007) and the meta-analysis of Horan. The role of UCB as a donor source has

only been compared within the group of subjects in whom bone marrow transplantation is indicated.

- The efficacy of UCB as a treatment in AL is a "derived comparison" directly dependent on the evidence of efficacy of allo-HCT. UCB-HCT may not be indicated in certain sub-types of acute leukemia (e.g. low-risk pediatric AML) where recent advances have suggested a lack of benefit for allo-HCT.

6.6.6 Adult AML: Background

For adult AML patients with unfavorable cytogenetics achieving CR, the probability of disease recurrence is 80%. Since fewer than 20% of adult patients with high-risk adult AML are able to receive allo-HCT in CR2, transplants should preferentially be prior to relapse after CR1 (Rowe JM, 2009). Curative potential is approximately 25%-30% in a highly selected group of patients in CR2 (Schlenk RF, Dohner K et al, 2008). Approximately half of subjects in the LR AML group in CR1 have favorable long-term outcomes without allo-HCT. The majority of subjects in the IR group have normal cytogenetics. Thus, it became necessary to establish other predictive prognostic factors to select patients with normal cytogenetics who were likely to benefit from allo-HCT. Identification of molecular classification markers of AML such as NPM1, FLT3-ITD, CEBPA and c-kit have further defined the indication of allo-HCT to this group (Schlenk RF, Dohner K et al, 2008; Dohner K, Dohner H, 2008). This efficacy review for Adult AML will focus on the role of allo-HCT in patients with AML in CR1, and the comparability of UCB to other sources of allogeneic stem cells in subjects with AML.

6.6.7 General Approach to Treatment of Adult AML

The treatment of adult AML depends on risk categorization for post-remission therapy. Risk categorization is based on cytogenetic karyotyping and/or molecular typing. Three main risk categories exist in the current standard practice, including favorable, intermediate and high-risk groups. These risk categories are prognostic. With emerging biologic data, risk classification in the intermediate risk group has changed. These changes impact the interpretation of results from older studies when compared to more recent studies in adult AML. The groups within the risk categories may not be comparable across publications.

Review Strategy for Efficacy of allo-HCT as a Treatment in Adult AML

As stated in Section 5.2, this review takes a two-step approach to evaluating efficacy of UCB-HCT for AML. The first step is to evaluate the benefit of allo-HCT in adult AML. The second step is to evaluate the benefit of UCB as an alternate donor source of Allo-HCT.

- One meta-analysis (Koreth J, Schlenk R et al, 2009) and two randomized studies (Burnett AK, Wheatley K et al, 2002 and Basara N, Schulze A et al, 2009) were selected to evaluate the efficacy of allo-HCT (MRD) as compared to a no MRD donor control group. This constitutes our first step in the review process to evaluate the efficacy of allo-HCT in the treatment of adult AML. The treatments offered to the no donor group differed between studies and included observation, auto-HCT, and conventional chemotherapy.

    - The meta-analysis was selected because it allowed for analysis across many studies, included international sites, and the retrospective studies included in the analyses were selected by independent reviewers. All of these factors were expected to reduce bias and provide a larger sample population.

    - The two other studies were selected because they were prospective randomized controlled studies. The study by Burnett 2002 was the first study to evaluate the efficacy of allo-HCT in risk-based groups. The study by Basara 2009 evaluates the efficacy of allo-HCT in the high-risk group.

Review Strategy for Efficacy of UCB-HCT as a Treatment in Adult AML

Two retrospective studies by Rocha V, Labopin M et al, 2004 and Atsuta Y, Suzuki R et al, 2009 were selected to compare the efficacy of UCB-HCT to matched unrelated allo-HCT donor sources. This comparison constitutes the second step of our review process, as stated in section 5.2.

- The study by Rocha 2004 was selected because it was a registry studies that compared UCB-HCT from international cord blood registries to matched controls from bone marrow registries. Results from analyses using control groups and multiple sites are expected to be more reliable.

- The study by Atsuta 2009 is from a single registry with a matched control group in Japan. The Japanese population is more genetically homogeneous than the populations included in other international registries, which decreases the likelihood of GvHD and peri-transplant mortality as competing risks to long-term outcomes.

6.6.8 Role of Allo-HCT for Adults with AML in CR1

The role of allo-HCT for adults with AML in CR1 is reviewed in the context of the Burnett and Basara studies and the meta-analysis by Koreth. It should be noted

that data from the Burnett study was included in the meta-analysis. It is reported separately here because the study had a considerable impact in excluding the use of allo-HCT for patients in CR1 who are favorable-risk. Three meta-analysis studies have been published evaluating the role of allo-HCT in AML in CR1. These studies include:

- Koreth J, Schlenk R et al, 2009
- Cornelissen JJ, van Putten WLJ et al, 2007
- Yanada M, Matsuo K et al , 2005

The Koreth study includes the majority of the studies considered in Cornelissen and Yanada. Therefore, detailed reports for the meta-analyses by Cornelissen and Yanada are not provided in this review.

Koreth 2009 (Koreth J, Schlenk R et al, 2009)

This study (Koreth J, Schlenk R et al, 2009) is a meta-analysis of outcomes in adult AML risk categories in donor vs. no donor groups.

Objective:
The objective of the meta-analysis was to assess RFS and/or OS outcomes in donor vs. no-donor groups. The no donor groups included auto-HCT and/or consolidation chemotherapy.

Design:
Twenty-four retrospective trials were selected by two independent reviewers based on study characteristics, interventions and outcomes. Enrollment periods for these international studies were from 1982-2006. Adult subjects with AML in CR1 were assigned to undergo allo-HCT or non-allo-HCT treatment (auto-HCT, chemotherapy or observation) based on donor availability. The cytogenetic risk criteria used were based on existing practice guidelines for risk stratification. There were only minor variations in risk stratification criteria between studies. RFS outcomes based on all cytogenetic risk groups were reported in eighteen trials. RFS outcomes for favorable-, intermediate-, and high-risk AML were reported in ten, fourteen and fourteen trials, respectively. OS outcomes based on cytogenetic risk groups were reported in fifteen trials.

Results:
Of the 6007 subjects analyzed, 5951 subjects were included in the RFS analysis and 5606 subjects were included in the OS analysis. Cytogenetic risk analysis was available in 3638 subjects, including 547 FR, 2499 IR, and 591 HR subjects.

Table 16: Meta-analysis of RFS and OS Outcomes by Risk Category for Donor vs. No-Donor Group in Adult AML (Koreth J, Schlenk R et al, 2009)

Outcome	Overall group HR (95% CI) Donor (n=1909) vs. No-Donor (n=3225)	Favorable-Risk HR (95% CI) Donor (n=188) vs. No-Donor (n=359)	Intermediate-Risk HR (95% CI) Donor (n=864) vs. No-Donor (n=1635)	High -Risk HR (95% CI) Donor (n=226) vs. No-Donor (n=366)
RFS	0.80 (0.74-0.86) P<0.01	1.06 (0.80-1.42) P=0.68	0.76 (0.68-0.85) P<0.01	0.69 (0.57-0.84) P<0.01
OS	0.90 (0.82-0.97) P<0.01	1.06 (0.64-1.76) P=0.81	0.84 (0.71-0.99) P=0.03	0.60 (0.40-0.90) P=0.01

Study Conclusions:

- The meta-analysis of the overall group showed a statistically significant benefit for RFS and OS in favor of allo-HCT for adult AML. The authors further state that for allo-HCT, there is a statistically significant benefit for subjects with intermediate- and high-risk AML. There was no benefit in favorable-risk patients.

Reviewer Comments and Conclusions:

- The treatment of AML in CR1 changed from 1982 to 2006. The enrollment characteristics of later studies included in this analysis tended to restrict allo-HCT options to intermediate- and high-risk groups. Overall, the study conclusions are consistent with the current treatment of AML in CR1, but the individual trials in the analysis varied with regard to the time for patient selection, chemotherapy backbone, risk-stratification and timing of MSD allo-HCT.

- Cytogenetic and molecular risk profiling in AML is an evolving field that can further stratify outcomes. Molecular risk profiling was not available at the time of the above studies. It is therefore unclear whether the results favoring allo-HCT in the intermediate-risk group could be the result of differences in molecular prognostic factors.

Burnett 2001 (Burnett AK, Wheatley K et al, 2002)

This study compares donor vs. no donor groups with regard to outcomes in adult AML patients who were treated on MRC AML-10.

Objective:
The objective of the study (MRC AML-10) was to evaluate the role of allo-HCT compared to other post-remission therapies (auto-BMT or chemotherapy) in AML.

Design:
The study enrolled patients ≤ 55 years of age, including pediatric ages, from UK, Ireland and New Zealand. All subjects had to be in CR1 to proceed to allo-HCT, auto-HCT or chemotherapy. The enrollment period was from 1988 and 1995. Subjects who achieved CR1 were assigned to allo-HCT if they had an HLA-matched sibling donor. Those without a MSD underwent randomization to either auto-HCT or consolidation chemotherapy. Risk categorization was based on cytogenetic karyotyping.

Results:
The majority of the patients in the analysis were adults. Of the 1063 subjects achieving CR1, 428 had a MSD, and 269 of these patients underwent allo-HCT. Patients with favorable-risk and MSD did not always receive allo-HCT because of the comparable benefit and decreased risk of chemotherapy consolidation. Outcome analysis was based on donor vs. no-donor groups.

Table 17: LFS and OS by Donor vs. No Donor Group in AML
(Burnett AK, Wheatley K et al, 2002)

Outcome	Overall group Donor (428) vs. No-Donor (877)	Favorable-risk cytogenetics t(8:21) and inv (16) Donor (n=51) vs No-Donor (n=94)	Intermediate-risk cytogenetic Donor (n=230) vs No-Donor (n=483)	High-risk cytogenetics Donor (n=23) vs. No-Donor (n=60)	Unknown cytogenetics Donor (n=77) vs. No-Donor (n=139)
DFS*	49 vs. 41% p=0.02				
OS*	54 vs. 48% P=0.1 HR=0.88 (95% CI 0.75, 1.03)	59 vs. 72% HR=1.76 (95% CI 0.96, 3.25)	54 vs. 42% HR=0.76 (95% CI 0.62, 0.94)	22 vs. 30% HR=1.14 (95% CI 0.64, 2.01)	48 vs. 45% HR=0.89 (95% CI 0.61, 1.29)

*All point estimates are at 10 yrs from CR.

Study Conclusions:

- The author's conclusions were that for subjects with favorable-risk and high-risk characteristics, there were no DFS and OS benefits to consolidation with allo-HCT.

- Subjects with intermediate-risk cytogenetics may benefit from allo-HCT with improved OS.

Reviewer Comments and Conclusions:

- This study was one of the first to use a risk-stratification in the analysis of their results. This risk-based system was based on diagnostic cytogenetics and did not direct therapeutic decisions.

- This study provides supportive evidence that AML patients with favorable-risk cytogenetics, based on the definition in the study, in CR1 should not be offered allo-HCT. Subjects with intermediate-risk benefit from allo-HCT with improved OS and lower relapse rates.

- The changes to risk-stratification from the time of the above study to current practice should be taken into consideration before recommending allo-HCT for the individual subject.

- There was insufficient evidence from this study to support the use of allo-HCT in the high-risk group.

Basara 2009 (Basara N, Schulze A et al, 2009)

This study evaluates the role of allo-HCT in high-risk AML.

Objective:
The objective of this study was to evaluate the impact of matched related and unrelated allo-HCT on DFS and OS in high-risk AML in CR1.

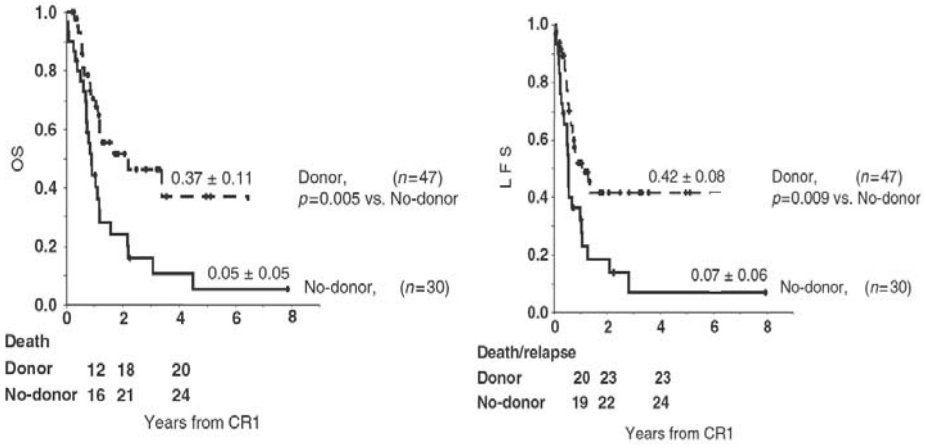
Study design:
This was a retrospective review of subjects in East German Study trials AML 96 and AML 02. High-risk determination was based on accepted karyotypes for categorization. Allo-HCT was done after consolidation chemotherapy.

Results:
Of the 138 HR patients, 77 achieved CR1 and were eligible for HCT. Median duration of follow-up was 19 months. Results for the DFS and OS analyses per donor versus no donor group (ITT) and per treatment (allo-HCT vs. chemotherapy or auto-BMT) were statistically significant in favor of allo-HCT.

The TRM in the allo-HCT group did not differ significantly from treatment related mortality in the chemotherapy group.

Figure 8: Two-Year DFS and OS for Donor vs. No Donor Group in HR AML

(Basara N, Schulze A et al, 2009)



Study Conclusions:

- The study concluded that matched allo-HCT from related or unrelated BM source provided superior OS and LFS outcomes for high-risk AML in CR1.

- The treatment related mortality from chemotherapy was not different from the TRM in allo-BMT. The outcomes related to the treatments were similar. The OS and LFS benefit for allo-HCT was probably related to reduction in the relapse rates.

Reviewer Comments and Conclusions:

- The study by Burnett et al was not conclusive regarding the role of allo-HCT in high-risk adult AML. The meta-analysis by Koreth et al and this study (Basara et al) provide evidence to support the benefit of Allo-HCT with regard to OS in high-risk adult AML.

6.6.9 Summary Comments and Conclusions for the benefit of Allo-HCT in Adult AML

- Allo-HCT provides long-term benefit in adult subjects with intermediate- and high-risk AML. Allo-HCT is not superior to chemotherapy in subjects with low-risk adult AML.

- Stratification of these risk groups has evolved from the time that these studies were conducted to the present. Thus, the recommendations for allo-HCT should also be weighed in the context of the suitability of the individual subject based on these changes in risk stratification.

6.6.10 UCB-HCT Adult AML: Background

Discussions of the efficacy of UCB-HCT compared to various other donor sources in acute leukemia have been provided under Section 6.5.13 for Rocha 2004 (Rocha V, Labopin M et al, 2004), Laughlin 2004 (Laughlin MJ, Eapen M et al, 2004), Atsuta 2009 (Atsuta Y, Suzuki R et al, 2009) and Eapen 2010 (Eapen M, Rocha V et al 2010). The discussion in this section will focus on efficacy data specifically for AML for the studies by Atsuta 2009 and Rocha 2004.

Efficacy of UCB-HCT Compared to Other Donor Sources for Allo-HCT

Rocha 2004 (Rocha V, Labopin M et al, 2004)

This is a brief summary of the data provided regarding adult AML and UCB-HCT. The objective of this retrospective analysis was to compare UCB-HCT with mismatches in up to two HLA loci to fully matched unrelated BM (UBM-HCT) donor sources.
Forty-six percent of a total of 98 subjects with Acute Leukemia who received single-unit UCB-HCT were diagnosed with AML. Fifty-four percent of 584 subjects with Acute Leukemia who received unrelated fully matched Allo-HCT were diagnosed with AML. The difference in two-year LFS, comparing UCB-HCT (32%) and UBM-HCT (42%), was not statistically significant.

Study Conclusions:

- The study concluded that LFS at two years was comparable between UCB-HCT and Unrelated BM-HCT in AML.

Reviewer Comments and Conclusions:

- There were more subjects with advanced disease (beyond CR2) in the UCB-HCT group than in the unrelated BM-HCT group. More subjects in the UCB-HCT arm had received auto-HCT as prior therapy. The number of prior therapies is an adverse prognostic factor. Thus, the UCB-HCT group had more subjects with unfavorable prognostic factors.

- This evidence supports the conclusion that UCB may have similar outcomes to fully matched unrelated allo-HCT in adult AML.

Atsuta (Atsuta Y, Suzuki R et al, 2009)
The details of this study have been provided under Section 6.5.13

The objective of this retrospective analysis study was to compare UCB-HCT to unrelated matched allo-HCT in adults with AL. The study included 477 subjects with AML receiving allo-HCT following CR1, CR2, relapse or induction failure, between 2000-2005.
One hundred and seventy-three subjects received UCB-HCT, and 311 subjects received BM HCT. The two groups were comparable with regard to disease status. Risk categories were favorable, normal, other and unknown,

Table 18: OS, LFS in AML According to Disease Status at Transplantation for UCB-HCT and UBM-HCT (Atsuta Y, Suzuki R et al 2009)

Outcome	UCB-HCT (%) n= 173	UBM-HCT (%) n=311	p-value (UCB-HCT vs. UBM-HCT)
2-yr OS	43%	60%	p<0.001
2-yr LFS	36%	54%	p<0.001

UBM = Unrelated fully matched BM donor
n = sample size

Study Conclusions:

- In patients with AML who received UCB-HCT, early mortality is high, and improvement in supportive measure could improve outcomes.

- The 2-year OS and LFS fro unrelated BM-HCT were statistically significantly better than UCB-HCT (p<0.001). See Table 21.

Reviewer Comments and Conclusions:

- The number of patients in the UCB-HCT arm with favorable cytogenetics was almost half that in the UBMT arm. The patients in the UCB-HCT arm

had more advanced disease. These are adverse prognostic factors which could have negatively affected the relapse rates and the long-term outcomes.

- The group receiving UCB-HCT had better hematopoietic recovery and chronic GvHD of the extensive type. Thus, peri-transplant mortality is unlikely to have impacted the OS outcomes.

- The evidence from this study suggests that unrelated matched allo-HCT is superior to UCB in AML. However, this conclusion should be interpreted with caution due to imbalances in adverse prognostic factors between the two treatment groups.

6.6.11 Summary Comments and Conclusions for the Role of Allo-HCT and UCB-HCT in Adult AML

- Allo-HCT provides long-term benefit in Adult AML for subjects with intermediate- and high-risk AML. Allo-HCT is not superior to chemotherapy in subjects with favorable-risk adult AML.

- Changes to stratification to the risk groups (favorable or low, intermediate and high) have evolved from the time. The studies that were conducted to validate these risk groups were conducted in a different therapeutic era. Thus, the recommendations regarding the use of allo-HCT should be weighed in the context of the suitability for the individual patient, with consideration of available risk information.

- UCB-HCT may be considered an acceptable alternative to matched unrelated allo-HCT for treatment of AML, based on the evidence from the Rocha 2004 study in Acute Leukemia and from the Laughlin 2004 study (discussed in the section under Adult ALL). The results of the Atsuta 2009 study favoring allo-HCT from matched unrelated donors over UCB is interpreted with caution due to imbalances in adverse prognostic factors between the two arms.

6.7 Indications: Chronic Myelogenous Leukemia (CML) and Other Hematological Malignancies

The evidence of effectiveness of UCB-HCT as an alternative to a matched related or unrelated donor transplant for hematological malignancies is based primarily on data in acute leukemias. The feasibility of obtaining data for each

hematological malignancy is limited due to the small population sizes. The general practice of the use of allo-HCT in hematological malignancies is based on its efficacy in the treatment of acute leukemias. The accepted medical practice is to utilize UCB-HCT in specific diseases where allo-HCT is indicated and no other stem cell donor is available. In the case of UCB, cell dose and HLA matching are considered (Stanevsky A, Goldstein G et al, 2009, Wall DA, Chan KW, 2008, Smith AR, Wagner JE, 2009) when deciding on the donor.

6.7.1 CML: Background

Chronic Myelogenous Leukemia (CML) represents approximately 15% of adult leukemias, and there are 4000-5000 new cases a year in the United States (Howlader N, Noone AM et al, 2011). CML occurs in all age groups. The incidence of CML increases with age. The median age at diagnosis is 66 years. Advances in cytogenetics and molecular characterization have enabled the clinician to identify the Philadelphia chromosome and the *BCR-ABL* chimeric gene. Tyrosine kinase inhibitors (TKIs) produce long-term outcomes in CML without allo-HCT. Ninety percent of the CML patients have the Ph+ chromosome, and an additional 5% can be detected using FISH for the *BCR-ABL* gene. These patients will respond to targeted treatment with TKIs with favorable long-term outcomes. These changes pose challenges regarding the evaluation of efficacy of allo-HCT in specific groups of subjects with CML. The challenges include:

- Limited sample sizes for studies of allo-HCT in patients who are not eligible for treatment with TKIs (TKI refractory CML or have Philadelphia chromosome-negative CML) (Druker BJ, Lee SJ, 2005).

- Previously published literature that supports the use of allo-HCT in CML. These publications did not compare allo-HCT to TKI therapy. They also did not consider cytogenetic and molecular characterization. Therefore, the efficacy review for CML did not include an extensive review of the published literature from a period prior to the availability of TKIs and cytogenetic and/or molecular characterization.

General Approach to Management of CML

CML in the pediatric population occurs after age four and is rare compared to the incidence in the adult population. Treatment principles are the same as in adults. The discussion for the treatment of pediatric CML will refer to the treatment in the adult CML population.

Following FDA approval of imatinib mesylate (a TKI) in 2001, the use of allo-HCT in CML decreased. Although allo-HCT is considered curative (Goldman JM, Mijhail NS et al, 2010), the risk vs. benefit issues of allo-HCT outweigh those of imatinib. Imatinib has been shown to result in prolonged hematologic, cytogenetic

and molecular remissions (Deininger M, O'Brien et al 2009). Allo-HCT is no longer recommended as first-line treatment in chronic phase (NCCN Guidelines v2.2012 Chronic Myelogenous Leukemia). With the development of other TKIs that target other *BCR-ABL* mutations, second-line treatments with these therapies are also considered acceptable prior to consideration of allo-HCT.

Role of Allo-HCT in CML: Current Practice

Thus, despite reduction in morbidity and mortality from TRM, the role of allo-HCT is restricted to patients with specific mutations of *BCR-ABL* (T3151) that predict resistance to TKIs or patients who have failed TKIs or have other unfavorable *BCR-ABL* mutations.

Review Strategy for Efficacy of allo-HCT as a Treatment in CML

As stated in Section 5.2, this review is a two-step approach to evaluating the efficacy of UCB-HCT in CML. The first step is to evaluate the benefit of allo-HCT in CML. The second step is to evaluate the benefit of UCB as an alternate donor source of allo-HCT.

- To evaluate data for the role of allo-HCT as first-line therapy in CML, the study by Hehlmann (Hehlmann R, Berger Ute et al, 2007) was reviewed. No additional prospective and well-controlled study of the role of Allo-HCT in second CP was identified.

- A retrospective analysis by Boehm (Boehm A, Walcherberger B at al, 2011) was reviewed to assess whether subjects undergoing allo-HCT (related and unrelated BM donor) in the post-TKI era could serve as historical controls for single-arm studies with UCB as a donor source.

6.7.2 Comparison of Allo-HCT to Drug Therapy as First Line Therapy in Chronic Phase of CML (Hehlmann R, Berger Ute et al, 2007)

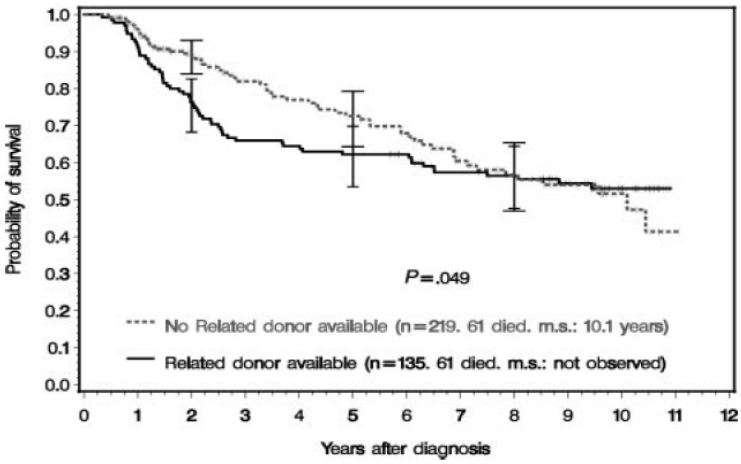
Hehlmann 2007

Objective:
The objective of this study was to compare matched related allo-HCT to IFN-gamma with regard to OS in subjects with newly diagnosed CML. Therapy with IFN-gamma was later modified to best available drug treatment, which included imatinib after 2000. To be eligible for the randomization, patients had to be eligible for allo-HCT.

Study design:
This was a prospective study from 1996 through 2001. There were two groups: subjects with matched related donors (MRD) and subjects with no MRD. Subjects who were in Chronic Phase (CP) with MRD received allo-HCT. Subjects in CP without MRD in whom a matched unrelated donor (MUD-HCT) was identified received an allo-HCT from that donor if they were unresponsive to best available drug therapy. If no MUD was found, they received best available drug treatment, which after 1999 included imatinib.

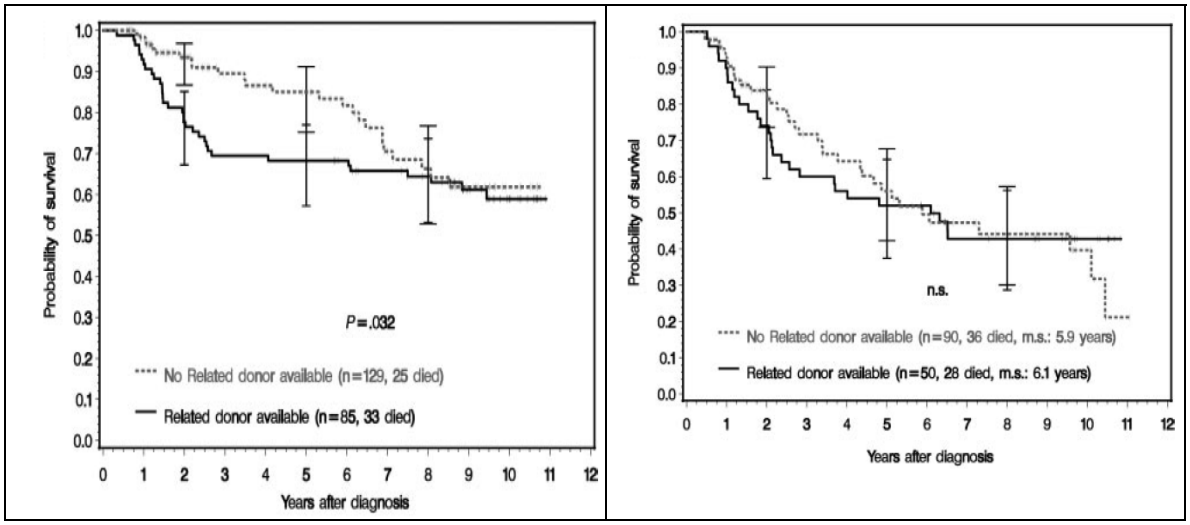
Results:
The results of the comparison of MRD to best available therapy are illustrated in Figure 17. Three hundred fifty-four eligible patients were analyzed in the entire group and then stratified by prognostic risk categories (low-, intermediate- and high-risk) (Hasford J, Pfirrmann M et al, 1998). Median follow-up is 8.9 years. Sixty-two of 122 subjects in the no donor arm received imatinib therapy; the remaining subjects received the best available therapy, which consisted mostly of interferon. The differences in the OS at 8 years between the two groups (donor vs. no donor group) were statistically significant for the low-risk subgroup (45 vs. 56%) and in the overall groups (57% vs. 56%). There was no difference between the donor and no donor groups with regard to OS in the intermediate and high-risk groups. Sample sizes were smaller for this intermediate and high-risk group than for the low-risk group.

Figure 9: OS for Subjects with Available MRD Compared to Subjects without MRD. (Hehlmann R, Berger Ute et al, 2007)



Overall group [Low, intermediate and High-risk (HR)]

Figure 10: OS for Low-Risk, and Non-Low-Risk Groups with Available MRD-HCT Compared to Those without MRD-HCT
(Hehlmann R, Berger Ute et al, 2007)



Low-risk (LR) subjects **Intermediate and HR subjects**

Study Conclusions:

- In this study, the results are statistically significant in favor of imatinib (or best available therapy) in the low-risk group and the overall group. The limited sample sizes for the intermediate and high-risk groups may have contributed to the results seen in these groups.

- The survival curves for donor vs. no donor in the intermediate and high-risk groups cross each other in the later phases of follow-up, with a downward trend in mortality for the no donor arm. An analysis of OS at 11 years suggests statistically significant results in favor of the no-donor group. It may be possible that an extended period of observation may detect a benefit for allo-HCT. However the number of subjects at risk is small, making it difficult to draw any meaningful conclusions.

Reviewer Comments and Conclusions:

- The introduction of imatinib therapy may have contributed to the late-phase plateau in the survival curves for the overall group.

- In this study, approximately half of the subjects in the no donor arm received drugs other than TKIs. This raises the possibility that the statistically significant results for OS in the no donor group could have

been the result of therapies other than TKIs. However multiple studies have established the superiority of imatinib over interferon in CML (Deininger M, O'Brien et al 2009). Therefore, it is unlikely that the improved OS in the no donor group in this study was driven by the subjects who received interferon or drugs other than TKIs.

- The conclusions from this study are applicable in the TKI era. Thus there is no role for allo-HCT as first-line therapy of CML in CP in the TKI era. It may be reasonable to reserve allo-HCT for specific groups in whom TKIs are not a viable options (TKI refractory disease and Ph-negative CML). This review of the literature did not find studies that compared the benefit of allo-HCT to therapies other than TKIs for such patients in whom TKIs are not a viable option.

- The use of imatinib or best available drug treatment is superior to allo-HCT in newly diagnosed patients with CML in CP.

6.7.4 Outcome of Allo-HCT in CML in the post-TKI era (Boehm A, Walcherberger B et al, 2011)

Boehm 2011

Objective:
The objective of this study was to evaluate OS and other transplant-related outcomes in subjects who received allo-HCT from BM or PBSC.

Design:
This was a retrospective analysis from a single center. Enrollment was from 1963-2007; however OS in specific cohorts is analyzed based on period of transplant. The study included MRD or matched or mismatched unrelated donor (URD) sources.

Results:
The discussion of the results is limited to subjects who received imatinib prior to HCT. These subjects were imatinib failures, had imatinib toxicity, or had high-risk disease (e.g., CP2 or greater). Seven of these subjects had sibling donor allo-HCT while the remainder underwent URD Allo-HCT. OS was 66% at a median follow-up time of 19 months. As seen in Figure 12, OS results for the imatinib group and the group that did not receive imatinib (predominantly in the period prior to 2001) prior to allo-HCT are similar.

Figure 11: OS Outcomes in Adult CML Undergoing Allo-HCT Performed in Specific Years (Boehm A, Walcherberger B et al, 2011)

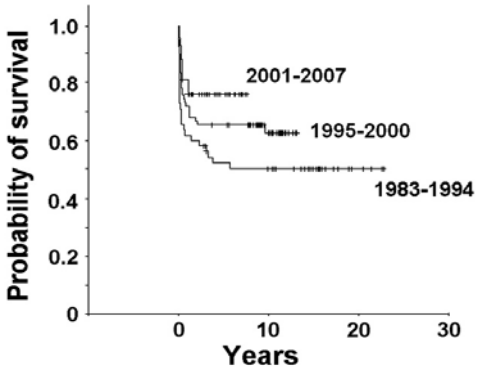
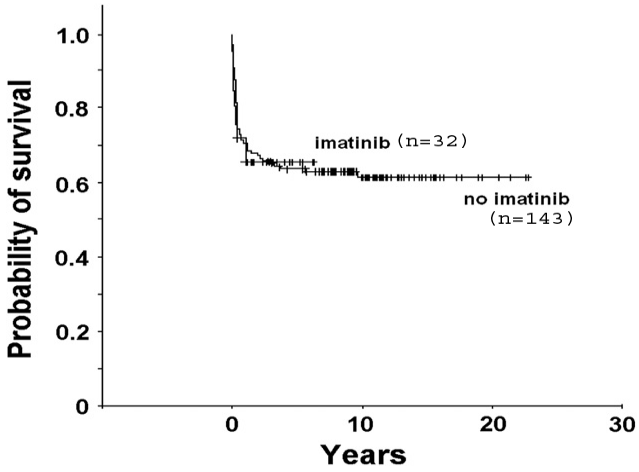


Figure 12: OS Outcomes in CML Subjects with and without Imatinib Exposure Prior to Allo-HCT (Boehm A, Walcherberger B et al, 2011)



Study Conclusions:

- The authors concluded that prior imatinib exposure did not impact the OS outcomes for allo-HCT transplant.

Reviewer Comments and Conclusions:

- The differences in outcomes among the time periods suggest that historical data from the pre-TKI era should not be used as controls for comparison to outcomes in more recent UCB studies.

- The survival data from the 32 subjects in the post-TKI era who received allo-HCT could be considered as historical controls for the purpose of comparing UCB-HCT to allo-HCT (with MRD and URD donors). This would be interpreted within the context of a median

follow-up period of 19 months. Such a control group would include subjects who by current guidelines are considered candidates for allo-HCT (high-risk or intolerant or refractory to imatinib and in disease stages beyond CP1).

- The above data illustrate a problem with retrospective analysis to determine efficacy of allo-HCT in CML, when the standard treatment paradigm for CML has changed.

6.7.5 Summary Comments and Conclusions for Role of Allo-HCT in CML

- There is no role for allo-HCT as first-line therapy in CML.
- Allo-HCT is considered an appropriate therapy in patients who have failed TKI therapy and have no further options for curative potential other than allo-HCT. The curative potential for allo-HCT in advanced disease has been established in a study conducted in the pre-TKI era (Goldman JM, Majhail NS et al, 2010).
- Due to the shift in the standard treatment paradigm for CML, selection of an appropriate allo-HCT historical control group for comparison to UCB-HCT will be difficult.

6.7.6 Review Strategy for Efficacy of UCB-HCT as a Treatment in CML

This is the second step to evaluate the benefit of UCB as an alternate donor source of allo-HCT in patients with CML.

- Studies comparing UCB to other donor sources were not available.
- Outcomes from one more recent single-arm study using UCB allo-HCT (Nagamure-Inoue T, Kai S et al, 2008) were reviewed. The study was assessed to determine if a study that consisted of subjects with prior TKI treatment could be compared to historical controls from the study by Boehm.

Retrospective single-arm study of Umbilical Cord Blood (UCB) in CML (Nagamura-Inoue T, Kai S, et al, 2008)

Nagamura-Inoue 2008

Objective:
The objective of this study was to evaluate prognostic factors for UCB-HCT and to determine if UCB-HCT is an appropriate therapy for CML.

Design:
Retrospective study from the Japan Cord Blood Bank Network in subjects receiving UCB-HCT after prior therapies from 1997-2006. Both pediatric and adult subjects were included.

Results:
Eighty-six subjects who did not have a related or unrelated matched donor were selected. Prior treatments included imatinib, Interferon-alpha (IFN-α), chemotherapy and other therapies. The median age was 39 years. Thirty-eight of these subjects were in chronic phase (29 in CP2). The remaining subjects had more disease advanced beyond CP. The median TNC dose was 2.5 x 10e7/kg. Event-free survival (EFS) assessments included graft failure, relapse or death in patients achieving a CR. Factors associated with favorable risk for LFS outcomes included TNC >$3x10^7$/kg and CP or AP stage of disease. OS outcomes were affected by disease stage at the time of UCB-HCT. The estimated 2-year EFS, LFS and OS for all subjects were 34%, 38% and 53%. At 2 years, the probability of OS and LFS for subjects in CP were 71% and 52% respectively.

Figure 13: K-M Estimates of OS, LFS, and EFS Following UCB-HCT for Subjects with CML (Nagamura-Inoue T, Kai S, et al, 2008)

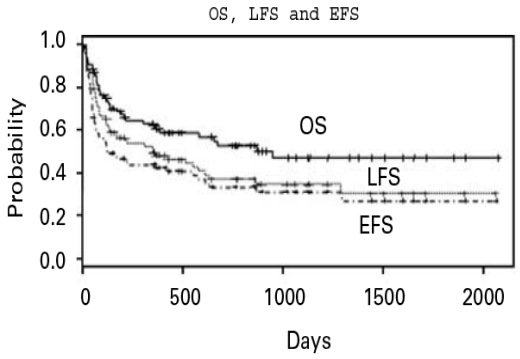
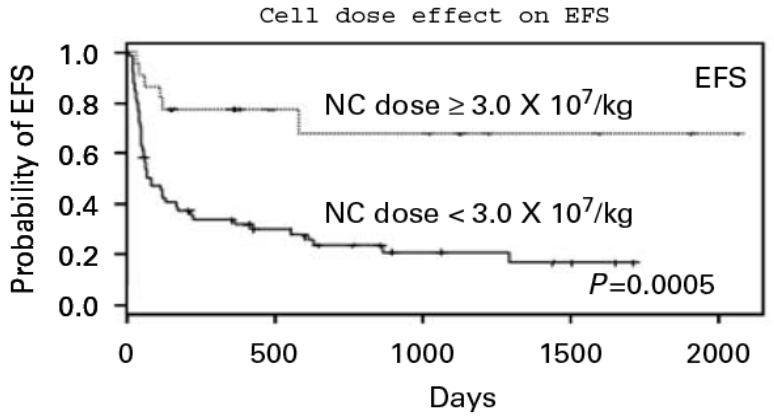
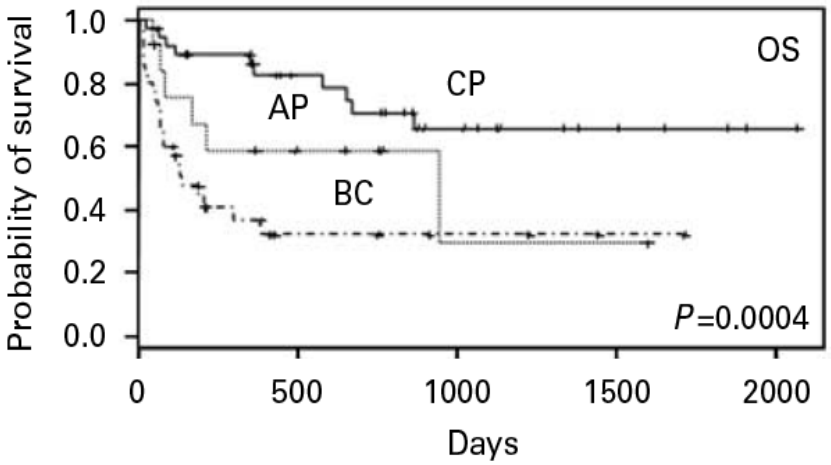


Figure 14: K-M Estimates of EFS in CML Based on TNC /kg
(Nagamura-Inoue T, Kai S, et al, 2008)



NC=nucleated cell

Figure 15: **K-M estimates of EFS by CML disease stage**
(Nagamura-Inoue T, Kai S, et al, 2008)



Study Conclusions:

- The subjects in this study met the current guidelines for allo-HCT. These results suggest that 2-year OS rates of 71% in the group who received UCB-HCT is comparable to 2-year OS rates of 44-77% in CP with unrelated allo-HCT from published studies.

Reviewer Comments and Conclusions:

- For subjects in CP, the overall survival at 2 years (71%) in this study using UCB-HCT is comparable to OS (76%) in the Allo-BMT group in the study by Boehm et al. With the limited data available in CML and the above studies, the OS outcomes may be comparable between UCB-HCT and other cell sources for Allo-HCT. The evidence from published literature is weak due to the absence of direct comparisons and the absence of data regarding detailed subject characteristics.

- UCB-HCT may be considered for CML patients who are intolerant or resistant to TKIs (T3151 mutation) and do not have a MRD or an available alternative suitably matched unrelated donor. UCB-HCT is not recommended for CML patients in CP who have not received treatment with TKIs.

6.7.7 Summary Comments and Conclusions for Role of Allo-HCT and UCB-HCT in CML

- There is no role for allo-HCT as first-line therapy in CML.

- Allo-HCT is considered an appropriate therapy in patients who have failed TKI therapy and have no further options for curative potential other than allo-HCT. This curative potential for allo-HCT in advanced disease has been established in a study conducted in the pre-TKI era (Goldman JM, Majhail NS et al, 2010).

- Changes in the standard treatment paradigm pose a challenge for the selection of an appropriate historical allo-HCT control group for comparison to UCB-HCT for the treatment of CML.

- Comparison using a historical control group of allo-HCT provides some evidence of comparability of UCB to other donor sources, especially in subjects with CP2 or beyond. The utility of UCB-HCT in accelerated phase or blast crisis is unclear.

- The evidence for effectiveness of UCB-HCT in CML is restricted to single-arm retrospective reports such as Nagamura et al. However, the available data may be sufficient to conclude that the benefit of UCB-HCT is comparable to Allo-HCT in subjects in CP2.

6.7.8 Review Strategy for Efficacy of UCB as a Treatment in Other Hematological Malignancies

As stated in Section 5.2, this review takes a two-step approach to evaluating the efficacy of UCB-HCT in other hematological malignancies. The first step would be to evaluate the benefit of allo-HCT in other hematological malignancies. The second step is to evaluate the benefit of UCB as an alternate donor source of allo-HCT. However, randomized studies and adequate comparative studies evaluating the role of allo-HCT in hematological malignancies other than for acute leukemia and CML are not available.

A single prospective study by Kurtzberg (Kurtzberg J, Prasad VK et al, 2008) is discussed below. This study does not evaluate long-term outcomes. It does provide evidence of hematopoietic reconstitution in various pediatric hematological malignancies. The primary objective of this trial was to assess overall survival (OS) at 180 days. However, considering that the general purpose of UCB-HCT is for hematopoietic reconstitution, this study is being considered for review.

Outcomes of Unrelated UCB in Pediatric Hematological Malignancies
(Kurtzberg J, Prasad VK et al, 2008):

Kurtzberg 2008

Objective:
The objective of this study was to determine survival outcomes at 180 days after transplant for unrelated UCB-HCT in children with primarily hematological malignancies.

Design:
Prospective multi-center study to evaluate OS at 180 days, engraftment, rate of relapse at two years, and two-year survival probabilities.

Results:
191 subjects were evaluated of 193 enrolled. One hundred nine subjects had ALL; 51 had AML; 13 had MDS; 7 had CML; 6 had lymphoblastic non-Hodgkin Lymphoma; 2 subjects had MDS with congenital agranulocytosis; and 1 subject had JMML. A minimum cell dose of $1x10^7$/kg was required and mismatches at up to two HLA loci were permitted. OS was 67.4% at 180 days and 49.5% at 2 years. The cumulative incidence of neutrophil recovery at Day 42 was 79.9%. Failure to engraft rate was 12%.

Study Conclusions:
- The OS at 180 days and the engraftment rate for UCB are comparable to other sources of allo-HCT.

Reviewer Comments and Conclusions:

- Thus hematopoietic reconstitution rates with UCB-HCT in hematological malignancies are comparable to other sources of allo-HCT.

Table 19 below presents the results for neutrophil recovery in the docket dataset. The cumulative incidence of neutrophil recovery at day 42 was similar for the docket dataset [all diagnoses except Hodgkin Disease (HD)] and the Kurtzberg 2008 study. These results support the efficacy of UCB for hematopoietic reconstitution to other hematological malignancies. Please see Dr. Przepiorka's safety review.

Table 19: Hematologic Recovery in Hematological Malignancies (Docket Data)

Table 1: Hematopoietic Recovery by Indication (TNC≥2.5)			
	N	Median time to ANC>500[+]	CumInc at Day 42 (%, 95%CI)[+,*]
ALL	363	27 days	78.4% (74.8-82.3%)
AML	301	26 days	75.8% (70.6-80.3%)
CML	40	30 days	69.2% (52.2-81.2%)
HD	7	42 days	57.1% (17.2-84.7%)
HIST	31	19 days	87.1% (69.2-95.0%)
MDS	65	27 days	70.3% (57.5%-79.9%)
MPD	12	23 days	75.0% (40.8-91.2%)
NHL/CLL	24	25 days	87.0% (64.8-95.6%)
OTHER	19	24 days	78.9% (53.2-91.5%)

6.7.9 Summary Comments and Conclusions for the Role of Allo-HCT and UCB in CML and Hematological Malignancies other than the Acute Leukemia

- Prospective controlled studies comparing long-term outcomes of allo-HCT and chemotherapy do not exist for hematological malignancies other than acute leukemia and CML.

- Single-arm studies of UCB-HCT with small sample sizes exist but have limited long-term outcome data.

- At best, there may be evidence of efficacy of UCB in adult CML subjects in second chronic phase.

- If the general purpose of UCB-HCT is considered to be hematopoietic reconstitution, then the evidence for effectiveness based on hematopoietic recovery in acute leukemia may be considered supportive for effectiveness in hematological malignancies other than leukemia. However, this review focuses on the assessment of long-term outcomes for efficacy rather than hematopoietic recovery.

6.8 Analysis of Clinical Information Relevant to Dosing Recommendations

6.8.1 Evidence to Support a Specific Cell Dose for UCB Use in Hematological Malignancies

In two of the four studies discussed below, dose was predetermined as a factor in the analysis. The Eapen 2010 study had a minimum cell dose of 2.5 x 10e7 TNC/kg and the Atsuta 2009 study examined efficacy in adult acute leukemias at median dose of $2.5x10^7$ TNC/kg.

The degree of HLA disparity is likely to impact the minimum cell dose that may be needed to produce a favorable efficacy outcome. Therefore, to provide support for a specific cell dose for UCB in the treatment of hematological malignancies, the effect of HLA disparity on cell dose should be considered. These four registry studies assessed the relationship of HLA matching and cell dose to outcome (LFS and OS) in hematological malignancies: Cohen YC and Scaradavou 2011; Eapen 2007; Eapen 2010; Barker 2010.

- The Cohen study (Cohen YC and Scaradavou A et al. 2011) did not find an effect of HLA disparity on OS. However, OS results were unfavorable for cell doses of $< 2.5 \times 10^7$ TNC/kg. LFS was not evaluated in the Cohen study.

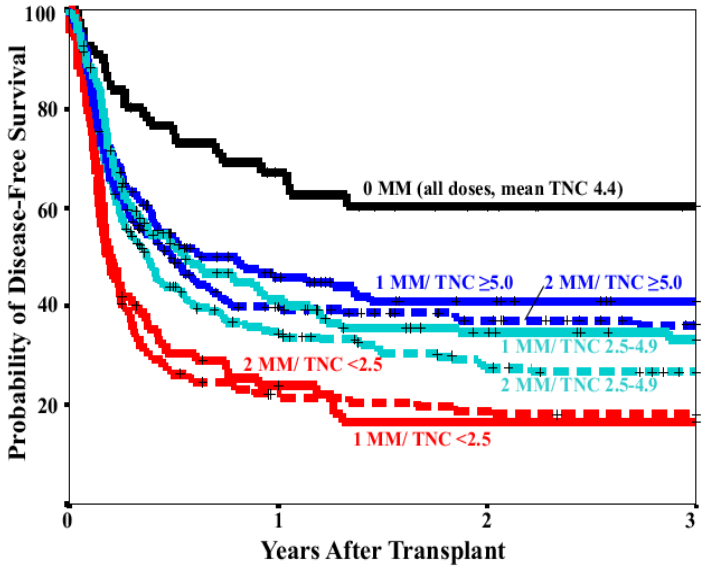
- The Eapen studies in pediatric and adult leukemia (2007 and 2010) evaluated the effect of varying degrees of HLA disparity and cell doses for UCB on outcomes compared to varying degrees of HLA disparity for bone marrow sources. The Eapen 2010 study (adults) aimed at selecting for $\geq 2.5 \times 10^7$ TNC/kg as the minimum cell dose for eligibility. Neither study found an effect of dose on LFS.

- The Barker study (Barker and Scaradavou et al 2010) compared outcomes in groups with varying degrees of HLA disparity and varying UCB cell doses. The study used a single HLA locus

mismatch and cell dose of 2.5 - 4.9x10^7 TNC/kg for the reference group.

- In the Barker study, the matched UCB group had the most favorable LFS outcomes, while the groups mismatched at 1 or 2 HLA loci receiving <2.5x10^7 TNC/kg, and the group with 3 HLA loci mismatches for UCB at any cell dose, had worse outcomes than the reference group (1 mismatch and cell dose ≥2.5x10^7 TNC/kg). LFS outcomes from the Barker study by dose are summarized in Figure 17 below.

Figure 16: Probability of Disease-Free Survival by Dose
(Barker and Scaradavou et al 2010)



Reviewer Comments and Conclusions:

- The Barker and Cohen studies support a relationship between HLA disparity and cell dose on outcomes in adult hematological malignancies. However, the results are not consistent across all four studies discussed above.

6.9 Sub-populations

6.9.1 Evidence in the Geriatric Population

The evidence of the efficacy of allo-HCT and UCB-HCT in hematological malignancies is predominantly in patients younger than 55 years of age. The study by Majhail (Majhail NS, Brunstein CG et al, 2011) is reviewed to evaluate efficacy of UCB in older subjects. In an attempt to decrease TRM, reduced intensity conditioning (RIC) regimens were used.

Majhail 2011

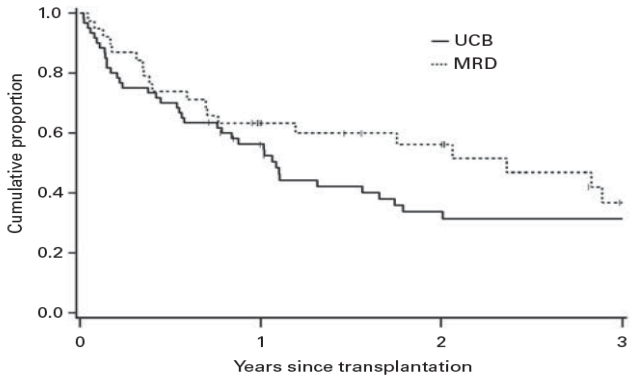
Objective:
The objective of this study was to compare MSD allo-HCT to UCB-HCT with regard to OS in subjects over age 55 years.

Design:
This was a prospective study of 98 consecutive subjects undergoing either MSD-HCT (n=38) or UCB-HCT (n=60) for AML or MDS between 2001 and 2009. MSD grafts were fully matched, while UCB matching was at 4-6/6 HLA loci. 95% of UCB recipients received two UCB units with a median cell dose of $4x10^7$ TNC/kg. All subjects received the same reduced intensity chemotherapy (RIC) regimen. The median age for subjects receiving MSD was 63; for UCB, the median age was 61 years.

Table 20: OS Comparing MSD vs. UCB in older subjects after RIC
(Majhail NS, Brunstein CG et al, 2011)

Outcome	MSD (n=38)	UCB (n=60)	p-value
OS at 3 years	37%	31%	0.21
LFS at 3 years	34%	22%	0.23

Figure 17: OS Outcomes after RIC Comparing UCB vs. MSD in Older Subjects (Majhail NS, Brunstein CG et al, 2011)



Study Conclusions:

- The results of this study suggest that UCB-HCT is comparable to MSD-allo-HCT with respect to LFS and OS in older subjects with AML and MDS who received RIC.

Reviewer Comments and Conclusions:

- This study provides supportive data for consideration of UCB as an alternate donor source for subjects who are >55 years and who are eligible for allo-HCT for the treatment of hematological malignancies. In this study, all recipients received RIC which would also affect OS and DFS. Safety data for this group has not been evaluated in this review.

9 Appendices

9.1 Literature Review

The literature search was conducted to identify historical experience and prospective clinical trial experience for hematologic malignancies. The search focused on acute leukemias because the published literature contained more information on the role of hematopoietic stem cell transplantation for acute leukemias than for other disorders. The searches were conducted through PubMed.

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