2013 American Society of Hematology (ASH) Meeting Updates

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Disclosures

- I have received consulting fees from Sigma Tau Pharmaceuticals, Inc. and LexiComp, Inc.
- I will be discussing the off-label use of medications

Objectives

- At the conclusion of the presentation, with respect to the 2013 ASH Annual Meeting, the participant will be able to:
  - Summarize research findings of key abstracts pertinent to the field of hematopoietic cell transplantation (HCT)
  - List important breakthroughs in hematology expected to impact HCT practice
  - Identify select data presented as part of the scientific programming of interest to HCT pharmacists
  - Summarize key points and data from select sessions of the education program applicable to the care of HCT patients

55th ASH Annual Meeting & Exposition

- Held December 6-10, 2013 in New Orleans, LA
- Numbers
  - More than 4500 abstracts
- Main themes/topics
  - Personalized medicine
    - How to pick the best therapy for an individual patient
  - Precision medicine
    - Identification of targets to identify novel therapies

http://www.cancernetwork.com/ash-2013/ash-annual-meeting-highlights-exciting-advances-hematology

Select Data Pertaining to HCT

- Areas of discussion
  - Approach/role/type of transplant
  - Conditioning regimens
  - Graft-versus-host disease (GVHD)
  - Supportive care
  - Relapse
  - Survivorship
  - Patient populations/referrals
- Abstracts
  - Oral presentation – indicated by "O" after number
  - Poster display – indicated by "P" after number

Approach/Role/Type of Transplant

Approach/Role/Type of HCT

- Abstract 158 O – Encouraging Outcomes In Older Patients (Pts) Following Nonmyeloablative (NMA) Haploidentical Blood or Marrow Transplantation (haploBMT) With High-Dose Post-transplantation Cyclophosphamide (PT/Cy)
- Abstract 302 O – Alternative Donor Hematopoietic Transplantation For Patients Older Than 50 Years With AML In First Complete Remission: Unrelated Donor and Umbilical Cord Blood Transplantation Outcomes
- Abstract 160 O – Unrelated Cord Blood Transplantation For Infant Acute Leukemia Diagnosed Within 1 Year of Age: Outcomes and Risk Factor Analysis On Behalf Of Eurocord and PDWP-EBMT

Haploidentical HCT in Older Patients (158)

- Obstacles to success with allo-HCT[1]
  - Lack of a matched donor
  - Disproportional cases of hematologic malignancies in older patients
- Related haplo-HCT can overcome obstacles, but historically[2]:
  - High rate of transplant-related mortality (TRM)
  - Older recipient age associated with poorer leukemia-free survival (LFS)
- Reduced-intensity conditioning (RIC) related haplo-HCT has been found to be safe and effective[3]
  - Incorporation of post-transplant cyclophosphamide (PT/Cy)

1. Fuchs EJ. *Hematology.* 2012;2012:230-36. 2. Szydlo R, et al. *J Clin Oncol.* 1997;15:1767-77 . 3. Luznik L, et al. *Biol Blood Marrow Transplant.* 2008;14:641-50.

Haploidentical HCT in Older Patients (158)

- Study
  - Rationale
    - PT/Cy reduces risks of haplo-HCT
    - Limited data on haplo-HCT in older patients
  - Objective
    - Evaluate impact of older patient age on outcomes following RIC related haplo-HCT that utilizes PT/Cy
- Eligibility
  - Age 50-75 years with a hematologic malignancy
  - No prior allo-HCT
  - First degree relative or half-sibling donor
    - Haploidentical at HLA-A, -B, -Cw, -DRB1, -DQB1

Kasamon YL, et al. *Blood.* 2013;122(21): Abstract 158.

Haploidentical HCT in Older Patients (158)

Patient Characteristics[1]

Characteristic	N = 273
Age, years	
50-59	119 (44%)
≥ 60	154 (56%)
60-69	127 (47%)
70-75	27 (10%)
Diagnosis	
Lymphoma	153 (56%)
Acute leukemia or myelodysplastic syndrome (MDS)	96 (35%)
Myeloproliferative disorder (MPD)	17 (6%)
Myeloma	7 (3%)
Prior auto-HCT	41 (15%)
HCT-Comorbidity Index high risk (≥ 3)	138 (51%)
Disease risk index (DRI) category[2]	
Low risk	32 (12%)
Intermediate risk	197 (72%)
High risk	44 (16%)

1. Kasamon YL, et al. *Blood*. 2013;122(21): Abstract 158. 2. Armand P, et al. *Blood*. 2012;120:905-13.

Haploidentical HCT in Older Patients (158)

HCT Characteristics

Characteristic	N = 273
Regimen	
Flu/Cy/TBI	98%
2 doses Cy/MMF/Tacro	96%
Bone marrow graft	99.6%
Total nucleated dose infused/ kg, median	4.03 x 10^8
CMV mismatch	110 (41%)
Post-HCT rituximab	55/126 B cell (44%)

CMV – cytomegalovirus, Cy – cyclophosphamide, Flu – fludarabine, Tacro – tacrolimus, TBI – total body irradiation

Kasamon YL, et al. *Blood*. 2013;122(21): Abstract 158.

Haploidentical HCT in Older Patients (158)

- Safety data
  - Rapid recovery of counts
    - Neutrophil recovery
      - Median time of 16 days
      - 89% recovered by D +30
    - Platelet recovery
      - Median time of 26 days
      - 85% recovered by Day +60
  - Low risk of acute GVHD (aGVHD)
    - Grade II-IV = 32% Grade III-IV = 3%
  - Low risk of chronic GVHD (cGVHD)
    - 12% at 1 year
  - Low risk of non-relapse mortality (NRM)
    - NRM at 6 months = 11% Relapse at 1 year = 37%

Kasamon YL, et al. *Blood*. 2013;122(21): Abstract 158.

Haploidentical HCT in Older Patients (158)

- Outcome data
  - Comparable outcome of older patients to patients in their 50's (median follow-up of 2.1 years)

Age, years	Number	Estimated 2-year Progression-Free Survival (PFS)	Estimated 2-year Overall Survival (OS)
50-59	119	39%	51%
60-69	127	36%	56%
70-75	27	39%	44%

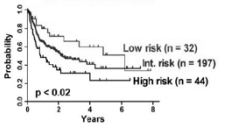
  - NRM was comparable across all age groups
    - Patients age 70-75 years old (n = 27)
      - 4 non-relapse deaths (15%) 9 relapses (33%)
      - 14 alive without relapse (52%) at a median of 11 months after HCT

Kasamon YL, et al. *Blood.* 2013;122(21): Abstract 158.

Haploidentical HCT in Older Patients (158)

DRI useful for risk stratification in RIC haploBMT with PT/Cy

OVERALL SURVIVAL BY DRI CATEGORY



Multivariate analyses of PFS:
- Independent association with PFS (p = 0.01)
- BMT year (p < 0.001) and CMV status (p ≤ 0.05) also significant

Kasamon YL, et al. *Blood.* 2013;122(21): Abstract 158. *Used with permission.*

Haploidentical HCT in Older Patients (158)

- Conclusions
  - Advanced age does not appear to prohibit HCT in patients that are otherwise eligible for the procedure
  - No apparent decrement in overall outcomes in older patients compared to those in their 50's
  - With likelihood of not having a suitable matched sibling donor, haplo-HCT may be an attractive option
    - Toxicities with haplo-HCT utilizing PT/Cy are similar to those seen with matched HCT

1. Kasamon YL, et al. *Blood.* 2013;122(21): Abstract 158. 2. Hamaker ME, et al. *Leuk Res.* 2013 Dec 30, Epub ahead of print.
3. Wildes TM, et al. *J Natl Compr Canc Netw.* 2014;12:128-36.

Alternative Donor HCT in Older AML (302)

- Background[1,2]
  - Alternative donor HCT poorly studied in older patients with AML
  - Lack of available healthy related donors
  - Previous studies suggest benefit with unrelated donor HCT in this patient population
- CIBMTR/Eurocord study[3]
  - 740 patients (≥ 50 years old, AML in CR1)
  - 1st alloHCT from non-family donors
    - Unrelated BM or PBSC (URD) (HLA match of 7-8/8) = 535
    - Unrelated cord blood (UCB) = 205

1. Yee KW, et al. *Expert Rev Hematol.* 2010; 3:755-74. 2. Pollyea DA, et al. *Br J Haematol.* 2011;152:524-42. 3. Weisdorf DJ, et al. *Blood.* 2013;122(21): Abstract 302.

Alternative Donor HCT in Older AML (302)

		URD (8/8)	URD (7/8)	UCB
Patient Demographics	Number	441	94	205
	Median age (years)	58	58	59
	50-60	60%	62%	57%
	61-75	40%	38%	43%
	Gender, male	59%	56%	48%
	CMV seropositive	59%	62%	62%

		URD (8/8)	URD (7/8)	UCB
AML Characteristics	WBC at diagnosis, < 25 x 10^9/L	74%	77%	63%
	Time to CR1, < 8 weeks	70%	70%	51%
	Cytogenetic risk			
	Favorable	3%	1%	2%
	Intermediate	25%	35%	46%
	Unfavorable	30%	33%	37%

Weisdorf DJ, et al. *Blood.* 2013;122(21): Abstract 302.

Alternative Donor HCT in Older AML (302)

HCT Characteristics

	URD (8/8)	URD (7/8)	UCB
Conditioning regimen			
Myeloablative	50%	46%	21%
Reduced Intensity	50%	54%	79%
GVHD prophylaxis			
Tacro/CSA + MMF	30%	41%	88%
Tacro/CSA + MTX	62%	54%	3%
Tacro/CSA alone	10%	5%	6%
In vivo T-cell depletion	39%	50%	32%
Transplant period			
2005-2007	56%	61%	20%
2008-2010	44%	39%	80%
Median follow-up, months	50	61	37

CSA – cyclosporine, MMF – mycophenolate mofetil, MTX – methotrexate, Tacro - tacrolimus

Weisdorf DJ, et al. *Blood.* 2013;122(21): Abstract 302.

Alternative Donor HCT in Older AML (302)

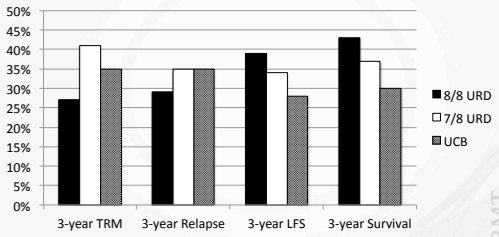
Results

	URD (8/8)	URD (7/8)	UCB	P value
Neutrophil recovery, > 500/microL at Day +28	97%	91%	69%	< 0.0001
Platelet recovery, > 20,000/microL at Day +90	91%	89%	69%	< 0.0001
aGVHD II/IV	36%	44%	35%	Not significant
cGVHD at 3 years	53%	59%	28%	0.0001

Weisdorf DJ, et al. *Blood.* 2013;122(21): Abstract 302.

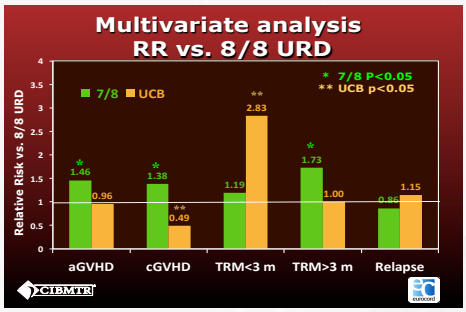
Alternative Donor HCT in Older AML (302)

Results



Weisdorf DJ, et al. *Blood.* 2013;122(21): Abstract 302.

Alternative Donor HCT in Older AML (302)



Weisdorf DJ, et al. *Blood.* 2013;122(21): Abstract 302.

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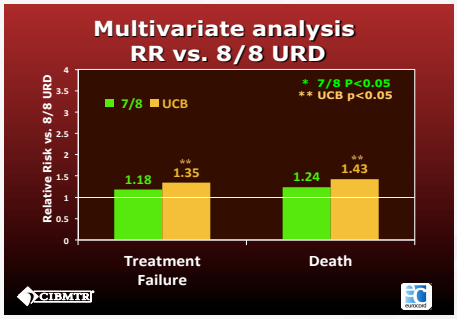
Alternative Donor HCT in Older AML (302)



Weisdorf DJ, et al. *Blood.* 2013;122(21): Abstract 302.

Used with permission.

Alternative Donor HCT in Older AML (302)

- Conclusions
  - Neutrophil and platelet recovery slower with UCB
  - 3-year cGVHD lowest with UCB
  - 3-year LFS lowest with UCB but similar with 8/8 and 7/8 URD
  - 3-year relapse similar between groups
  - 3-year TRM lowest with 8/8 URD
  - 3-year survival was greatest with 8/8 URD
- Implications
  - UCB can provide extended survival in the absence of an 8/8 HLA-matched URD
  - Lower frequency of cGVHD with UCB may be of particular value in older patients

Weisdorf DJ, et al. *Blood.* 2013;122(21): Abstract 302.

ARS Question #1

In the study reported by Ruggeri and colleagues at the 2013 ASH meeting, infants with ALL had better outcomes following allo-HCT than those with AML (like what has been observed for older pediatric patients).

A. True
B. False

UCB Transplant in Infant Leukemia (160)

- Infant acute leukemia
  - Occurs rarely and distinctly different from other pediatric acute leukemias
  - Very poor prognosis secondary to chemotherapy resistance and treatment-associated toxicities
  - Role of HCT
    - Allo-HCT indicated in ALL in CR1
    - No consensus for AML in CR1
    - UCB attractive graft source
      - High stem cell content
      - Readily available

1. Zweidler-McKay PA, et al. *Curr Probl Pediatr Adolesc Health Care.* 2008;38:78-94. 2. Hunger SP, et al. *Biol Blood Marrow Transplant.* 2009;15(1 Suppl):S79-83. 3. Carpenter PA, et al. *Biol Blood Marrow Transplant.* 2012;18(1 Suppl):S33-9.

UCB Transplant in Infant Leukemia (160)

- Study
  - Aim: evaluate outcomes and risk factors of acute leukemias diagnosed within first year of life and treated with UCB transplant (UCBT)
  - Conducted 1995 – 2012 in EBMT centers
    - Single myeloablative UCBT in 254 patients
      - 159 with ALL
      - 95 with AML
    - Median age at diagnosis = 5.7 months (0.03 – 12 months)
    - Median age at UCBT = 13.8 months (3.6 months – 11 years)
    - Median follow-up = 42 months

Ruggeri A, et al. *Blood.* 2013;122(21): Abstract 160.

UCB Transplant in Infant Leukemia (160)

Patient Characteristics

Characteristic	N = 254
Disease status	
CR1	138 (54%)
CR2	81 (32%)
Advanced	35 (14%)
Risk classification [cytogenetic data available for 182 (72%) of patients]*	
Intermediate	44 (24%)
Poor	138 (76%)

*Of those patients with ALL,
82 had chromosome 11 abnormalities defined as t(4;11)
47 had 11q23 abnormalities not otherwise specified

Ruggeri A, et al. *Blood.* 2013;122(21): Abstract 160.

UCB Transplant in Infant Leukemia (160)

UCBT Characteristics

Characteristic	N = 254
HLA mismatches	
None (6/6)	40 (21%)
One (5/6)	107 (57%)
Two (4/6)	42 (22%)
Median TNC x 10^7/kg (range)	9.4 (1 – 18)
Conditioning regimen [busulfan (Bu) based]	n = 186 (75%)
Bu/Cy	68 (37%)
Bu/Cy/Melphalan	43 (23%)
Bu/Cy/Flu/Thiotepa	31 (17%)
Other	44 (23%)
Use of TBI > 6 Gy	31 (12%)
Use of antithymocyte globulin before Day 0	79%
GVHD prophylaxis	
Cyclosporine ± steroids	72%
Cyclosporine ± mycophenolate mofetil	11%

Ruggeri A, et al. *Blood*. 2013;122(21): Abstract 160.

UCB Transplant in Infant Leukemia (160)

- Results
  - Neutrophil engraftment = median time of 21 days
    - In a univariate analysis, higher cell dose was associated with better engraftment
  - aGVHD
    - 39 ± 3% cumulative incidence at Day 100
    - Median time to onset was 18 days
    - 96 patients (38%) experienced Grade II – IV aGVHD
      - Grade II = 60%
      - Grade III = 25%
      - Grade IV = 15%

Ruggeri A, et al. *Blood*. 2013;122(21): Abstract 160.

UCB Transplant in Infant Leukemia (160)

- Results
  - Relapse
    - Overall at 4 years was 26 ± 4%
      - 21% for AML vs. 28% for ALL (p = 0.32)
    - Disease status was important
      - 19 ± 4% for CR1 vs. 35 ± 5% for other (p = 0.001)
    - Diagnosis before 3 months of age
      - 36 ± 6% if < 3 months vs. 22 ± 3% if > 3 months (p = 0.06)
  - TRM
    - Overall at 4 years was 25 ± 3%
      - 31 ± 4% for ALL vs. 15 ± 4% for AML (p = 0.005)

Ruggeri A, et al. *Blood*. 2013;122(21): Abstract 160.

UCB Transplant in Infant Leukemia (160)

- Results
  - LFS
    - Overall at 4 years was 49 ± 3%
      - 41 ± 5% for ALL vs. 64 ± 5% for AML (p = 0.002)
      - 45% for ALL + chromosome 11 abnormalities
    - ALL (n = 159)
      - 50 ± 6% in CR1 vs. 30 ± 6% not in CR1 (p = 0.003)
    - AML (n = 95)
      - 82 ± 5% in CR1 vs. 40 ± 8% not in CR1 (p < 0.001)

Risk Factor	Hazard Ratio	95% CI	P-value
Diagnosis of ALL	1.8	1.2-2.7	0.004
Age at diagnosis of < 3 months	1.5	1.1-1.5	0.026
Disease status not in CR1	2.4	1.7-2.5	< 0.001

Ruggeri A, et al. *Blood*. 2013;122(21): Abstract 160.

UCB Transplant in Infant Leukemia (160)

- Results
  - Overall survival
    - At 4 years = 53 ± 3%
    - 43 ± 4% for ALL vs. 65 ± 5% for AML (p = 0.003)
    - Like LFS, being in CR1 had more favorable outcomes compared to not being CR1 for both ALL and AML
  - Cause of death [115 patients (45%)]
    - 55 relapse
    - 56 TRM
      - 52% infection, 16% GVHD, 7% multi-organ failure
    - 4 unknown

Ruggeri A, et al. *Blood*. 2013;122(21): Abstract 160.

UCB Transplant in Infant Leukemia (160)

- Conclusions
  - UCBT is a suitable option for infants with acute leukemia in remission
  - TRM higher for infants with ALL compared to AML
    - Intensity of pre-HCT therapies?
  - Patients with AML had a better prognosis than those with ALL
    - Contrasts what is seen in older pediatric patients

Ruggeri A, et al. *Blood*. 2013;122(21): Abstract 160.

Conditioning Regimens

Conditioning Regimens

- Abstract 3280 P – Pharmacokinetics Of a Generic Formulation Of Intravenous Busulfan (BUCELON 60™) In Patients Undergoing Hematopoietic Stem Cell Transplantation
- Abstract 3281 P – Impact Of Renal Insufficiency and Obesity On Safety and Outcomes Of BEAM Conditioning
- Abstract 2170 P – Use of Biosimilar G-CSF Compared With Lenograstim In Autologous Haematopoietic Stem Cell Transplant and In Sibling Allogeneic Transplant
- Abstract 3275 P – The of Tevagrastim (Biosimilar Filgrastim XMO2) For Hematopoietic Stem Cell Mobilization In HLA Matched Sibling Donors For Allogeneic Stem Cell Transplantation To AML/MDS Patients

Graft-versus-Host Disease

Graft-versus-Host Disease

- Abstract 923 O – Calcineurin Inhibitor-Free GVHD Prophylaxis with Post-Transplant Cyclophosphamide and Brief-Course Sirolimus Results in Low Rates of Non-Relapse Mortality and Chronic GVHD Following Matched Related and Unrelated Donor Peripheral Blood Stem Cell Transplantation (PBSCT)
- Abstract 909 O – A Phase II Study Of Proteasome-Inhibition For Initial Therapy Of Chronic Graft-Versus-Host Disease
- Abstract 703 O – Efficacy and Safety Of Lower-Dose Glucocorticoids For Initial Treatment Of Acute Graft-Versus-Host Disease: A Randomized Controlled Trial

Calcineurin Inhibitor-Free GVHD Prophylaxis (923)

- Background
  - GVHD preventative strategy required for allo-HCT
  - Most common strategy for GVHD prophylaxis → calcineurin inhibitor (CNI) + methotrexate[1,2]
    - Better control of aGVHD but no significant impact on cGVHD
    - Numerous challenges with this approach
      - Side effects, drug interactions, costs, etc.
  - Post-transplant cyclophosphamide (PT/Cy)[3]
    - Promotes tolerance in alloreactive host and donor T cells
    - Combination with tacrolimus and mycophenolate mofetil
    - Single agent

1. Storb R, et al. *Biol Blood Marrow Transplant*. 2010;16(1 Suppl):S18-27. 2. Martin PJ, et al. *Biol Blood Marrow Transplant*. 2012;18:1150-63. 3. Luznik L, et al. *Semin Oncol*. 39:683-93.

Calcineurin Inhibitor-Free GVHD Prophylaxis (923)

- Sirolimus
  - Novel mechanism of action
  - Potential advantages
    - Promotes generation of T-regulatory cells
    - Antineoplastic activity
    - Antiviral activity
    - Less nephrotoxicity

1. Cutler C, et al. *Curr Opin Hematol*. 2010;17:500-4. 2. Abouelnasr A, et al. *Biol Blood Marrow Transplant*. 2013;19:12-21.

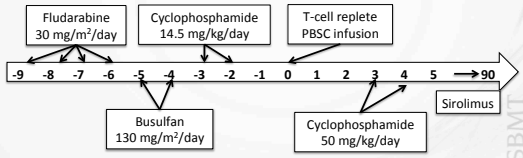
Calcineurin Inhibitor-Free GVHD Prophylaxis (923)

- Study hypothesis = using PT/Cy with short-course sirolimus after PBSCT using matched-related donor (MRD)/matched-unrelated donor (MUD) will improve outcomes
  - Reliable engraftment with rapid donor chimerism
  - Limit of a- and cGVHD with minimal NRM
  - Improve graft-versus-leukemia (GVL) effect
  - Decrease in adverse events as seen with conventional GVHD prophylaxis

Sanacore M, et al. *Blood.* 2013;122(21): Abstract 923

Calcineurin Inhibitor-Free GVHD Prophylaxis (923)

- Study
  - Patients ≤ 75 years old
  - Available 10/10 HLA-matched related or unrelated donor
  - High-risk hematologic malignancy



Sanacore M, et al. *Blood.* 2013;122(21): Abstract 923

Calcineurin Inhibitor-Free GVHD Prophylaxis (923)

Characteristics	N = 26
Age in years, median (range)	61 (25 – 73)
Gender, male	16 (62%)
Transplant type, MRD	17 (65%)
Disease status	
AML-CR1 AML-CR2 AML-PIF	4 3 1
ALL-CR1 MDS MPD	1 3 4
NHL/HD-CR2/3	3
NHL/HD refractory/relapsed	3
CLL refractory/relapsed	4
HCT-Comorbidity Index	
0 1 – 2	7 (27%) 13 (50%)
3 – 5 6 – 7	4 (15%) 2 (8%)

CR – complete remission, MPD – myeloproliferative disorder, PIF – primary induction failure

Sanacore M, et al. *Blood.* 2013;122(21): Abstract 923

Calcineurin Inhibitor-Free GVHD Prophylaxis (923)

- Results
  - Median length of hospitalization = 10 days (0 – 30)
  - Median time to neutrophil engraftment = 15 days (13 – 28)
  - Median time to platelet engraftment = 30 days (15 – 164)
  - Engraftment rate 100%
  - Median follow-up 12.7 months (3.4 – 27.5)
    - DFS 79%
    - Relapse 17%
    - NRM 4%
    - aGVHD → 42% Grade II – IV (15% Grade III – IV)
    - cGVHD → 29% (13% severe cGVHD)

Sanacore M, et al. *Blood.* 2013;122(21): Abstract 923

Calcineurin Inhibitor-Free GVHD Prophylaxis (923)

- Results
  - Time to immunosuppression discontinuation
    - 25 evaluable patients → 68% off therapy
    - 21 patients evaluable at the time of data analysis
      - 18 (86%) off therapy
      - 3 still on therapy (length = 5, 10 and 23 months)
  - Infections
    - 21% CMV reactivation in 19 patients at risk
      - No CMV disease
    - No cases of invasive molds in first 100 days
      - 1 patient with rhizopus post-HCT following relapse
    - No Epstein-Barr Virus (EBV)-associated post transplant lymphoproliferative disorder (PTLD)
    - No NRM secondary to infection
    - BK virus-associated cystitis in 31% (8/26) of patients (severe in 4 patients)

Sanacore M, et al. *Blood.* 2013;122(21): Abstract 923

Calcineurin Inhibitor-Free GVHD Prophylaxis (923)

- Results
  - Toxicity
    - 8 patients switched to tacrolimus (median time Day +51)
      - 2 due to sinusoidal obstructive syndrome
        - » Resolved spontaneously after therapy change
      - 3 due to GVHD
      - 2 as a result of cytopenias
    - 2 patients (8%) with renal insufficiency
    - Mucositis
      - 8 patients with Grade 2 and 2 patients with Grade 3
    - No cases of thrombotic microangiopathy/hemolytic-uremic syndrome

Sanacore M, et al. *Blood.* 2013;122(21): Abstract 923

Calcineurin Inhibitor-Free GVHD Prophylaxis (923)

- Conclusions
  - Achievement of
    - Consistent donor engraftment (but slower platelet recovery)
    - Low rates of infectious complications
    - Low incidence of cGVHD
    - Rapid withdrawal of immunosuppression
    - Low rate of relapse and promising DFS
  - PT/Cy + sirolimus prophylactic regimen is a safe and effective alternative to standard CNI-based immunosuppression

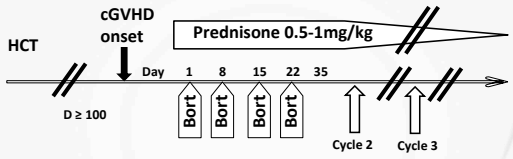
Sanacore M, et al. *Blood.* 2013;122(21): Abstract 923

Bortezomib in cGVHD (909)

- Background
  - cGVHD
  - Bortezomib clinical data
    - Improved cGVHD after treatment of post-allo-HCT relapse of multiple myeloma[1-3]
    - Effective in steroid-refractory cGVHD[4]

1. Mateos-Mazon J, et al. *Haematologica.* 2007;92:1295-6. 2. El-Cheikh J, et al. *Haematologica.* 2008;93:455-8. 3. Todisco E, et al. *Leuk Lymph.* 2007;48:1015-8. 4. Miller AM, et al. *Biol Blood Marrow Transplant.* 2011;17(Suppl 1):Abstract 530.

Bortezomib in cGVHD (909)



- Bortezomib (Bort): 1.3mg/m^2 IV D 1,8,15,22 of 35-day cycle x 3 cycles
- Prednisone: 0.5 – 1mg/kg PO daily
  - Suggested taper: 10 – 25% every 1 – 2 weeks post-C1
- 22 patients enrolled (March 2009 – November 2011)

Herrera AF, et al. *Blood.* 2013;122(21): Abstract 909. *Used with permission.*

Bortezomib in cGVHD (909)

Baseline Characteristics

Patient Characteristics	N = 22
Age in years, median (range)	51 (25 – 69)
Gender, male	10 (46%)
Primary Diagnosis	
AML	9 (41%)
NHL	4 (18%)
ALL	3 (14%)
Other	6 (27%)
Donor Source (all PBSC)	
8/8 MUD	13 (59%)
8/8 MRD	5 (23%)
7/8 MMUD	4 (18%)

MMUD – mismatched unrelated donor

Herrera AF, et al. *Blood.* 2013;122(21): Abstract 909.

Bortezomib in cGVHD (909)

Baseline Characteristics

GVHD Characteristics	N = 22
Prior aGVHD	
Grade 0 – I	19 (86%)
Grade II – IV	3 (14%)
Median platelet count, x 10^9/L (range)	197 (90 – 378)
Median time to cGVHD onset, days (range)	215 (133 – 666)
Median time to cGVHD therapy onset, days (range)	257 (186 – 2070)

Herrera AF, et al. *Blood.* 2013;122(21): Abstract 909.

Bortezomib in cGVHD (909)

- Results
  - Feasibility
    - 18 of 22 (82%) of patients completed all three cycles
    - 2 patients withdrawn from study within 2 weeks of enrollment due to progressive cGVHD
    - 2 patients on study were non-evaluable
      - 1 with relapsing AML during cycle #2
      - 1 with severe primary coccidiomycosis during cycle #1
  - Toxicity
    - 1 patient with Grade 3 peripheral neuropathy (possibly related to bortezomib)
    - No reports of
      - ≥ Grade 3 hematologic toxicities
      - Any other ≥ Grade 3 toxicities related to bortezomib
      - Increase in CMV reactivation

Herrera AF, et al. *Blood.* 2013;122(21): Abstract 909.

Bortezomib in cGVHD (909)

Liver

Pt	Baseline	Wk 15
6		
8		
10		
11		
12		
13		
15		
16		
7		
14		
17		
18		
20		
4		
5		
Median Score	3	0

n = 15
ORR 86%
8 CR 53%
5 PR 33%
2 PD 13%

Skin

Pt	Baseline	Wk 15
2		
8		
10		
12		
14		
15		
17		
19		
3		
1		
9		
Median Score	2	0

n = 11
ORR 82%
8 CR 73%
1 PR 9%
2 SD 18%

Joint/Muscle/Fascia

Pt	Baseline	Wk 15
14		
18		
1		
3		
9		
12		
Median Score	1	1

n = 6
ORR 50%
2 CR 33%
1 PR 17%
3 SD 50%

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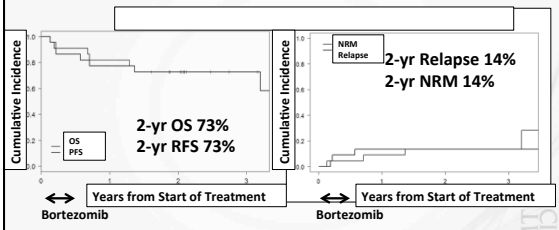
Organ
3 ☐☐☐☐ 0

Herrera AF, et al. *Blood.* 2013;122(21): Abstract 909.

Bortezomib in cGVHD (909)

Survival, Relapse, NRM



Median f/u 25 months, range (19.3 – 48.5)

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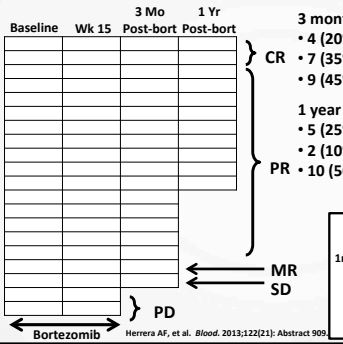
Herrera AF, et al. *Blood.* 2013;122(21): Abstract 909.

Prednisone Dose Over Time



3 months post-bortezomib end
- 4 (20%) off prednisone
- 7 (35%) ≤ 0.25mg/kg prednisone
- 9 (45%) add'l cGVHD therapy

1 year post-bortezomib end
- 5 (25%) off prednisone
- 2 (10%) ≤ 0.25mg/kg prednisone
- 10 (50%) add'l cGVHD therapy

Used with permission.

Prednisone Dose
0.5 0.25
1mg/kg ☐☐☐☐ 0 mg/kg
☐ New cGVHD therapy
☐ Death
☐ Relapse

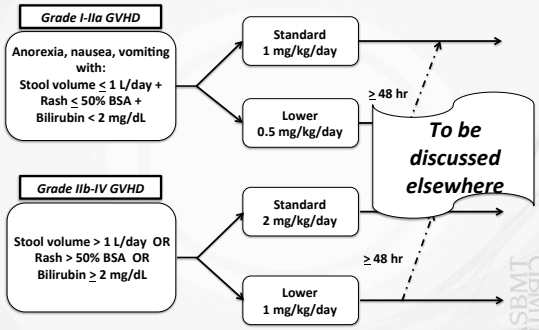
Herrera AF, et al. *Blood.* 2013;122(21): Abstract 909.

Bortezomib in cGVHD (909)

- Conclusions
  - Bortezomib + prednisone was feasible and well-tolerated as 1st line cGVHD therapy
    - High overall response rate after 15 weeks of therapy, most notably in skin and liver
    - 1 year after end of therapy
      - 25% of patients off prednisone
      - 10% on low-dose of prednisone (≤ 0.25 mg/kg)
      - 50% required additional therapy for cGVHD
  - Need to conduct a randomized controlled trial to determine whether proteasome-inhibition adds benefit

Herrera AF, et al. *Blood.* 2013;122(21): Abstract 909.

Lower Dose Steroids in aGVHD (703)



Mielcarek M, et al. *Blood.* 2013;122(21): Abstract 703.

Graft-versus-Host Disease

- Abstract 3297 P – Higher Mycophenolic Acid (MPA) Trough Levels Result In Lower Day 100 Severe Acute GVHD Without Increased Toxicity In Double-Unit Cord Blood Transplantation (CBT) Recipients
- Abstract 4571 P – A Pilot Study Of Continuous Infusion Mycophenolate Mofetil For Graft Versus Host Disease Prophylaxis
- Abstract 2067 P – Tocilizumab In The Treatment Of Steroid Refractory Graft Versus Host Disease: A Single Institutional Experience

Supportive Care

Supportive Care

- Abstract 700 O – Results Of The Large Prospective Study On The Use Of Defibrotide (DF) In The Treatment Of Hepatic Veno-Occlusive Disease (VOD) In Hematopoietic Stem Cell Transplant (HSCT). Early Intervention Improves Outcome - Updated Results Of a Treatment IND (T-IND) Expanded Access Protocol
- Abstract 4591 P – Impact Of Prophylaxis With Defibrotide On The Occurrence Of Acute GvHD In Allogeneic HSCT

ARS Question #2

On the T-IND-2006-05 study, when compared to children, adult patients treated with defibrotide for severe veno-occlusive disease had which of the following outcomes?

A. Inferior CR and survival rates
B. Superior CR and survival rates
C. Higher incidence and grades of aGVHD
D. Higher rates of graft failure and disease relapse

Defibrotide on T-IND (700)

- T-IND-2006-05[1]
  - Given the life-threatening nature of veno-occlusive disease (VOD)/multi-organ failure (MOF) with > 80% mortality at D+100,[2] study initiated in 2007
  - This study is the largest prospective evaluation of defibrotide for the treatment of severe VOD (sVOD)/ MOF in HCT patients
  - Updated analysis is based on 470 patients enrolled between December 2007 and December 2012 at 75 centers in the USA
    - The efficacy and safety of defibrotide in patients who had undergone HCT (N = 425; 90%) was presented

1. Richardson PG, et al. *Blood.* 2013;122(21): Abstract 700. 2. Coppell JA, et al. *Biol Blood Marrow Transplant.* 2010;16:157–68.

Defibrotide on T-IND (700)

35% of HCT patients had CR at Day +100
  – Survival at Day +100 was 55%

	CR Day +100	Survival Day +100*
HCT patients (n = 425)	35%	55%
HCT patients with sVOD (n = 284)	29%	48%
HCT patients with non-severe VOD (n = 141)	47%	69%
Non-HCT patients (n = 45)	40%	62%

*Kaplan–Meier estimates for time-to-event analysis by Day 100

Richardson PG, et al. *Blood.* 2013;122(21): Abstract 700.

Defibrotide on T-IND (700)

- Children (≤16 years) had higher CR rates and survival compared to adults

	Pediatric patients (n=232)	Adult patients (n=192)	p value
CR (Day +100)	41%	27%	0.0038*
Survival (Day +100)†	60%	49%	0.0203‡

*Chi-square test between subgroups
†Kaplan–Meier estimates for time-to-event analysis by Day 100
‡Log-rank test between subgroups

Richardson PG, et al. *Blood.* 2013;122(21): Abstract 700.

Defibrotide on T-IND (700)

- Delay in the initiation of defibrotide treatment of > 2 days from sVOD/VOD diagnosis results in significantly lower CR rate and higher mortality at Day +100 post-HCT

Time from VOD diagnosis to defibrotide administration (n=406)	≤2 Days (n=272)	>2 Days (n=134)	p value
CR (Day +100)	39%	25%	0.0052*
Survival (Day +100)†	61%	38%	< 0.0001‡

*Chi-square test between subgroups
†Kaplan–Meier estimates for time-to-event analysis by Day 100
‡Log-rank test between subgroups

Richardson PG, et al. *Blood.* 2013;122(21): Abstract 700.

Defibrotide on T-IND (700)

Safety: Transplanted analysis population

	Defibrotide (N=425)
Total patients with at least one adverse event (AE)*	22%
Total patients with at least one serious AE	13%
Hypotension	4%
Hemorrhage Pulmonary hemorrhage Gastrointestinal hemorrhage Epistaxis Hematuria	17% 6% 6% 3% 2%
Related events leading to discontinuation	16%
Incidence of all grade GVHD (in patients who underwent an allo-HCT)	11%

*A possible relationship with defibrotide could not be ruled out

Richardson PG, et al. *Blood.* 2013;122(21): Abstract 700.

Defibrotide on T-IND (700)

- Conclusions
  - Ongoing treatment IND provided broad access to defibrotide
  - Use of defibrotide for treatment of sVOD in HCT patients improves outcomes
  - Children had higher CR rates compared to adults
  - Early initiation of defibrotide is important once sVOD is suspected
  - Defibrotide is well tolerated with markedly lower rates of GVHD than expected

Richardson PG, et al. *Blood.* 2013;122(21): Abstract 700.

Defibrotide Effects on aGVHD (4591)

- Background
  - *In vitro* defibrotide has been shown to bind to various sites on the vascular endothelium, modulating expression status and activity of endothelial cells[1,2]
  - Vascular endothelium is one of the main target tissues identified in the pathogenesis of aGVHD[3]
  - Defibrotide has a potential role in aGVHD
- Analysis[4]
  - Effects of defibrotide on incidence and severity of aGVHD in pediatric patients receiving defibrotide prophylaxis for VOD post-HCT

1. Richardson PG, et al. *Expert Opin Drug Saf.* 2013;12:123-36. 2. Defitelio® Summary of Product Characteristics. Gentium SpA, 2013. 3. Kummer M, et al. *J Immunol.* 2005;174:1947-53. 4. Corbaciogku S, et al. *Blood.* 2013;122(21): Abstract 4591.

Defibrotide Effects on aGVHD (4591)

- Findings
  - Prophylaxis with defibrotide was found to significantly reduce the occurrence and severity of aGVHD
  - Use of corticosteroids was significantly lower in those patients receiving defibrotide
  - Defibrotide use did not seem to interfere with leukemia relapse rates at Day 100 or Day 180
- Further studies are clinically warranted

Corbaciogku S, et al. *Blood.* 2013;122(21): Abstract 4591.

Supportive Care

- Abstract 2057 P – Inhaled Cyclosporine For The Treatment Of Bronchiolitis Obliterans Following Hematopoietic Stem Cell Transplantation (HSCT) Or Lung Transplantation
- Abstract 2986 P – Evaluating Risk Factors and Outcomes For Clostridium Difficile Infection (CDI) In Stem Cell Transplant (SCT) Recipients
- Abstract 4641 P – Incidence and Risk Factors For Pneumocystis Jirovecii pneumonia (PCP) Following Haematopoetic Stem Cell Transplant (HSCT)
- Abstract 4631 P – Palifermin For Prevention Of Oral Mucositis Has No Negative Effect On Long-Term Outcome In Patients With Hematological Malignancies Undergoing HSCT - Long-Term Follow-Up

Relapse

Relapse

- Abstract 2072 P – Survival Of AML Patients Relapsing After Allogeneic Stem Cell Transplantation: A Center For International Blood and Marrow Transplant Research Study

AML Relapse After Allo-HCT (2072)

- Survival after AML relapse post-allo-HCT is poor
- Study objectives
  - Measure OS of AML patients relapsing post-allo-HCT
  - Identify prognostic factors for survival following post-HCT relapse
  - Identify clinical and disease characteristics of long-term (≥ 1 year) post-relapse survivors after allo-HCT
- Several factors associated with poor survival

Bejanyan N, et al. *Blood*. 2013;122(21): Abstract 2072.

AML Relapse After Allo-HCT (2072)

- Survival is better with:
  - Longer time from HCT to relapse
  - Age < 40 years
  - Favorable cytogenetics
  - Use of RIC
  - Related/Unrelated-Matched donor
  - No active GVHD at the time of relapse
- Survival ≥ 1 year post relapse (23%) associated with relapse > 6 months post-HCT and receiving 2nd HCT or donor lymphocyte infusion (DLI)
- Relapse/Persisting AML is the primary cause of death (71%)

Bejanyan N, et al. *Blood.* 2013;122(21): Abstract 2072.

Survivorship

Survivorship

- Abstract 916 O – Voriconazole Exposure and The Risk Of Cutaneous Squamous Cell Carcinoma In Allogeneic Hematopoietic Stem Cell Transplant Patients
- Abstract 553 O – Long-Term Health-Related Outcomes In Survivors Of Childhood Hematopoietic Cell Transplantation (HCT): A Report From The Bone Marrow Transplant Survivor Study (BMTSS)

Voriconazole and Cutaneous Squamous Cell Carcinoma In HCT (916)

- Background
  - Recommendations for prophylaxis with mold-active agents[1]
    - Role of voriconazole
  - Voriconazole and squamous cell carcinoma (SCC)[2-5]
    - Identified as an independent risk factor in solid organ transplant patients
- Study[6]
  - Examine the risk of cutaneous SCC in HCT patients receiving voriconazole
  - Retrospective review of consecutive adult patients receiving a HCT at the Mayo Clinic between 2007 and 2012

1. Freifeld AG, et al. *Clin Infect Dis.* 2011;52:e56-e93. 2. Vadnerkar A, et al. *J Heart Lung Transplant*. 2010;29:1240-4. 3. Zwald FO, et al. *Dermatol Surg*. 2012;38:1369-74. 4. Singer JP, et al. *J Heart Lung Transplant*. 2012;31:694-9. 5. Feist A, et al. J Heart Lung Transplant. 2012;31:1177-81. 6. Hashmi SK, et al. *Blood*. 2013;122(21): Abstract 916.

Voriconazole and Cutaneous Squamous Cell Carcinoma In HCT (916)

- Methods
  - Identification of cutaneous SCC by biopsy reports
  - Voriconazole exposure at anytime during disease treatment
    - Cumulative exposure was total number of days following HCT
  - Number of covariates adjusted for simultaneously was limited due to small number of patients developing cutaneous SCC
    - Gender Age at HCT TBI for conditioning
    - Skin cancer pre-HCT (yes/no) cGVHD (yes/no)

Hashmi SK, et al. *Blood*. 2013;122(21): Abstract 916.

Voriconazole and Cutaneous Squamous Cell Carcinoma In HCT (916)

Baseline Patient Characteristics	N = 381
Age at HCT, years (range)	53 (19-71)
Gender, Male	222 (58.3%)
Race, Caucasian	358 (94.0%)
Primary malignancy	
AML	137 (36.0%)
MDS/MPD	71 (18.6%)
ALL	50 (13.1%)
CLL	44 (11.5%)
Plasma Cell Disorders	30 (7.9%)
CML	23 (6.0%)
Lymphoma	17 (4.5%)
Non-Malignant Disorders	9 (2.4%)
Skin cancer pre-transplant	
Melanoma	8 (2.1%)
Non-Melanoma	25 (6.6%)
No previous history documented	348 (91.3%)

Hashmi SK, et al. *Blood*. 2013;122(21): Abstract 916.

Voriconazole and Cutaneous Squamous Cell Carcinoma In HCT (916)

Baseline HCT Characteristics	N = 381
Graft type	
Peripheral Blood	331 (86.9%)
Bone Marrow	40 (10.5%)
Umbilical Cord Blood	10 (2.6%)
Conditioning Regimen	
Melphalan/Fludarabine	130 (34.1%)
Cyclophosphamide/TBI	106 (27.8%)
Fludarabine/TBI	43 (11.3%)
Busulfan/Cyclophosphamide	38 (10.0%)
Melphalan/TBI	24 (6.3%)
Busulfan/Fludarabine	11 (2.9%)
Cyclophosphamide/Fludarabine/TBI	8 (2.1%)
Other	21 (5.5%)
Total body irradiation	
Myeloablative	137 (36.0%)
Reduced Intensity/Nonmyeloablative	55 (14.0%)
No radiation received	189 (49.6%)

Hashmi SK, et al. *Blood.* 2013;122(21): Abstract 916.

Multivariable Cox models for SCC adjusting voriconazole exposure/cumulative use for five pre-specified covariates

Variable	History of Voriconazole Exposure			Cumulative Days of Voriconazole Use		
	Hazard Ratio	95% Confidence Interval	P Value	Hazard Ratio	95% Confidence Interval	P Value
Voriconazole	2.436	0.557 – 10.652	0.2369	1.859	1.347– 2.567	<0.001
Male Gender	3.399	1.269 – 9.106	0.0149	3.598	1.328 – 9.746	0.0118
Transplant Age	1.049	1.002 – 1.098	0.0403	1.070	1.019 – 1.123	0.0070
TBI-Conditioning (yes/no)	1.654	0.728 – 3.754	0.2291	1.861	0.827 – 4.189	0.1333
Skin Cancer Pre-HCT	2.900	1.152 – 7.302	0.0238	2.715	1.084 – 6.800	0.0330
Chronic GVHD	2.989	0.858 – 10.410	0.0855	2.047	0.549 – 7.631	0.2862

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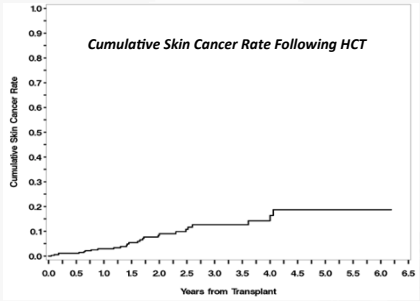
Hashmi SK, et al. *Blood.* 2013;122(21): Abstract 916.

Voriconazole and Cutaneous Squamous Cell Carcinoma In HCT (916)



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Hashmi SK, et al. *Blood.* 2013;122(21): Abstract 916.

Voriconazole and Cutaneous Squamous Cell Carcinoma In HCT (916)

- Limitations
- Conclusions
  - First study in HCT to identify relationship between cumulative days of voriconazole exposure and development of cutaneous SCC
  - No causality established
  - Risks of long-term use of voriconazole?
  - Patient counseling necessary
  - Changes in therapy may be necessary

Hashmi SK, et al. *Blood*. 2013;122(21): Abstract 916.

Bone Marrow Transplant Survivor Study (553)

- Retrospective cohort study design
- Eligibility
  - HCT between 1974 and 1988 at City of Hope or University of Minnesota
  - Age at HCT ≤ 21 years
  - Survival of ≥ 2 years post-HCT
- Instruments
  - BMT Survivor Study (BMTSS) Questionnaire
    - Medical outcomes
    - Healthcare utilization
    - Functional health status
    - Sociodemographic information

Armenian S, et al. *Blood*. 2013;122(21): Abstract 553.

Bone Marrow Transplant Survivor Study (553)

- Summary – Chronic Health Conditions
  - Cumulative incidence
    - Any chronic health condition was 56% at 15 years post-HCT
    - Severe/life threatening condition was 25% at 15 years
  - Risk factors for severe/life threatening condition
    - Female gender (1.6-fold higher risk)
    - Conditioning with TBI (2.6-fold higher risk)
  - Incidence and severity of chronic health conditions did not vary by stem cell source
  - Among allo-HCT recipients
    - Patients with cGVHD at highest risk for severe-life threatening health conditions

Armenian S, et al. *Blood*. 2013;122(21): Abstract 553.

Bone Marrow Transplant Survivor Study (553)

- Summary – Late Mortality
  - OS (having survived the first 2 years post-HCT) was 80% at 10 years
    - 68% for auto-HCT vs. 83% for allo-HCT
  - Compared to age- and sex-matched general population, the cohort was at a:
    - 22-fold increased risk of premature death
      - High risk: female, TBI conditioning, auto-HCT
    - 8-fold risk of NRM

Armenian S, et al. *Blood*. 2013;122(21): Abstract 553.

Bone Marrow Transplant Survivor Study (553)

- Summary – Health Care Utilization
  - 92% of survivors carried health insurance
  - 100% of survivors reported medical contact
  - 84% reported having had a general physical exam in the past 2 years
  - 68% reported a cancer center visit
- Interpretation
  - There is a need for lifelong contact with healthcare system
  - High proportion of survivors seen outside transplant center
  - Need to standardize long-term follow-up recommendations

1. Armenian S, et al. *Blood*. 2013;122(21): Abstract 553. 2. Majhail NS, et al. *Biol Blood Marrow Transplant*. 2012;18:348-71.

Patient Populations/Referrals

Patient Populations/Patient Referrals

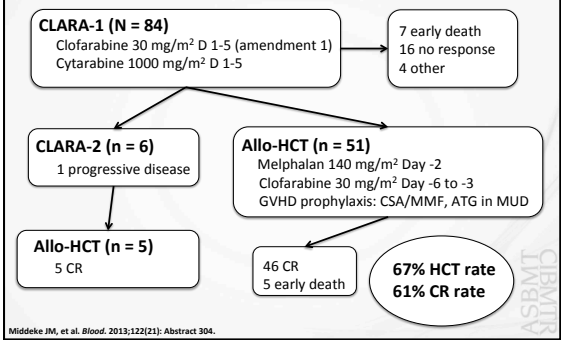
- Abstract 304 O – Clofarabine Salvage Therapy Prior To Allogeneic Hematopoietic Stem Cell Transplantation In Patients With Relapsed Or Refractory AML – Results Of The Bridge Trial

The BRIDGE Trial (304)

- Background[1-4]
  - Poor outcomes in relapsed/refractory AML
  - Clofarabine + cytarabine
- BRIDGE trial[5]
  - Intent-to-transplant study (Phase II)
  - Primary endpoint: CR after consolidation
    - Assessed on Day 42 following last dose of clofarabine
  - Major eligibility criteria
    - Relapsed/refractory AML in patients > 40 years old
      - Excluded: ≥ 2nd relapse, refractory disease after > 1 cycle of high-dose cytarabine
    - No prior HCT

1. Kubal T, et al. *Curr Opin Hematol*. 2013;20:100-6. 2, Ghanem H, et al. *Leuk* Lymph. 2013;54:688-98. 3. Mathisen MS, et al. *Clin Lymphoma Myeloma Leuk*. 2013;13:139-43. 4. Martinez-Cuadron D, et al. *Ann* Hematol. 2014;93:43-6. 5. Middeke JM, et al. *Blood*. 2013;122(21): Abstract 304.

The BRIDGE Trial (304)



Middeke JM, et al. *Blood*. 2013;122(21): Abstract 304.

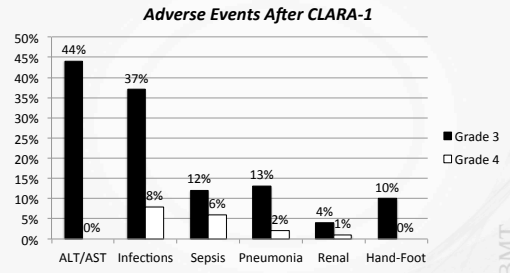
The BRIDGE Trial (304)

Patient Characteristics[1]	N = 84
Age (median) in years	61 (40 – 75)
Performance status of ECOG ≥ 2	23%
HCT-CI cycles, median (range)	1 (0 – 6)
Disease status	
Refractory	48%
Early relapse (< 6 months)	24%
Late relapse (> 6 months)	26%
ELN genetic risk group[2]	
Favorable	17%
Intermediate I	35%
Intermediate II	18%
Adverse	20%

ELN – European LeukemiaNet

1. Middeke JM, et al. *Blood.* 2013;122(21): Abstract 304. 2. Dohner H, et al. *Blood.* 2010;115:453-74.

The BRIDGE Trial (304)



Middeke JM, et al. *Blood.* 2013;122(21): Abstract 304.

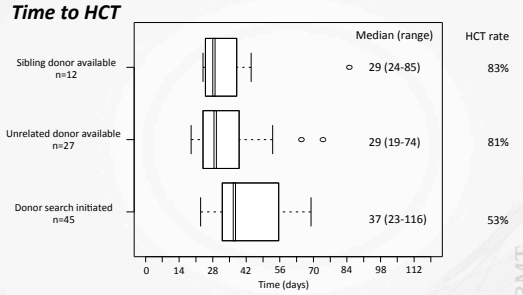
The BRIDGE Trial (304)

- Response on Day 15
  - 47% good (< 10% blasts)
  - 35% moderate (reduction in blast count and/or marrow cellularity + clearance of peripheral blood)
  - 19% no response
- Overall survival by intention to treat
  - 51% at 12 months
- DFS
  - 57% at 12 months

Middeke JM, et al. *Blood.* 2013;122(21): Abstract 304.

The BRIDGE Trial (304)

Time to HCT



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Middeke JM, et al. *Blood.* 2013;122(21): Abstract 304.

The BRIDGE Trial (304)

- Conclusions
  - Activity and toxicity of CLARA-1 reasonable
  - Salvage chemotherapy and rapid transplantation in aplasia is feasible
  - Promising DFS in transplanted patients
  - Difficult to assess for the affects of clofarabine, high-dose melphalan and GVL effect

Middeke JM, et al. *Blood.* 2013;122(21): Abstract 304.

Scientific Sessions

ARS Question #3

What impact does the ratio of B cell-activating factor (BAFF) to B cells have on GVHD after allo-HCT?

A. Increased ratio associated with aGVHD
B. Decreased ratio associated with aGVHD
C. Increased ratio associated with cGVHD
D. Decreased ratio associated with cGVHD

Platelets and Cancer

- Platelets and the role of cancer metastasis
  - Adhesion
  - Coagulation
  - Protection against natural killer (NK) cells or turbulence
- Platelet inhibitors have been shown to substantially decrease risk of tumor invasion and mortality in cancer patients
- Platelets are large reservoirs of angiogenic and oncogenic growth factors
  - Modulation of cytokines to change effects

1. Labelle M, et al. *Cancer Cell.* 2011;20:576-90. 2. Gay LJ, et al. *Nat Cancer Rev.* 2011;11:123-34. 3. Labelle M, et al. *Cancer Discov.* 2012;2:1091-9. 4. Stone RL, et al. *N Engl J Med.* 2012; 366:610-8. 5. Cho MS, et al. *Blood.* 2012;120:4869-72.

Roles of B Cells in Transplant

- After allo-HCT role of donor B cells in GVHD
  - Potential role in aGVHD
  - Clear evidence for contribution to both GVL and cGVHD
    - Several studies have demonstrated the benefits of rituximab in the management and prophylaxis of steroid-refractory cGVHD[1,2]
- B cell-activating factor (BAFF)[3,4]
  - Promotes B cell differentiation
  - Increased BAFF:B cell ratio in patients with cGVHD
- B cell reconstitution in HCT[5]
  - Inadequate recovery → development of cGVHD
  - Rapid recovery → low incidence of cGVHD
  - Response to rituximab → recovery of normal B cell homeostasis

1. Arai S, et al. *Blood.* 2012;119:6145-54. 2. Cutler C, et al. *Blood.* 2013;122:1510-7. 3. Sarantopoulos S, et al. *Blood.* 2009;113:3865-74. 4. Allen JL, et al. *Blood.* 2012;120:2529-36. 5. Kuzmina Z, et al. et al. *Blood.* 2013;122(21): Abstract 4623.

Education Sessions

ARS Question #4

The potential for immunotherapy utilizing chimeric antigen receptors (CAR) in HCT candidates includes which of the following?

A. Re-induce remission prior to HCT
B. Produce minimal residual disease (MRD) negative status prior to allo-HCT
C. Serve as a bridge to HCT
D. All of the above

Education Sessions

- Genomics in Hematology 101 for the Practicing Clinician
- Changing Paradigms in Acute Lymphoblastic Leukemia: From the Genome to the Patient
- Clinical Dilemmas in Acute Myeloid Leukemia
- Allogeneic Transplant for High Risk Myelodysplastic Syndromes and Acute Myeloid Leukemia: Are We Improving Outcomes?
- Pediatric Hematology: Insights Applicable to All!
- HIV in Hematology: What's New?
- Infectious Disease Complications Encountered by the Practicing Hematologist
- A Fresh Look at Drug Approval: Moving Away From Tradition

Featured Topic – Chimeric Antigen Receptors (CAR): Driving Immunotherapy!

- Efficacy
  - Leukemia Lymphoma Multiple myeloma
  - Solid tumors
- Outstanding issues
  - Persistence (correlates with outcome)
  - Homing (sanctuary sites)
  - On target toxicities
    - B cell aplasia, cytokine release syndrome (CRS)
  - Other toxicities
    - Macrophage activation syndrome (MAS)/hemophagocytic lymphohistiocytosis (HLH), neurotoxicity
  - Which cells should be CAR modified?

1. Grupp SA, et al. *New Engl J Med.* 2013;368:1509-18. 2. Riddell SR, et al. *Biol Blood Marrow Transplant.* 2013;19(1 Suppl):S2-5. 3. Sadelain M, et al. *Cancer Discov.* 2013;3:388-98. 4. Barrett DM, et al. *Current Opin Pediatr.* 2014;26:43-9. 5. Barrett DM, et al. *Annu Rev Med.* 2014;65:333-47. 6. *Immunol Rev.* 2014;257:5-276.

Featured Topic – Chimeric Antigen Receptors (CAR): Driving Immunotherapy!

- Potential for immunotherapy
  - Consolidate patients with minimal residual disease (MRD)
  - Re-induce remission
  - Produce MRD-negative status prior to allo-HCT
  - Serve as a bridge to HCT
  - High risk pediatric ALL

1. Grupp SA, et al. *New Engl J Med.* 2013;368:1509-18. 2. Riddell SR, et al. *Biol Blood Marrow Transplant.* 2013;19(1 Suppl):S2-5. 3. Sadelain M, et al. *Cancer Discov.* 2013;3:388-98. 4. Barrett DM, et al. *Current Opin Pediatr.* 2014;26:43-9. 5. Barrett DM, et al. *Annu Rev Med.* 2014;65:333-47. 6. *Immunol Rev.* 2014;257:5-276.

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Questions

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