# 2014 American Society of Hematology (ASH) Meeting Updates

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## Disclosures

- Employee of Takeda Oncology
  - Please note the information in this presentation and any observations and opinions offered by me do not reflect the views of Takeda Oncology
- I will be discussing the off-label use of medications

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## Learning Objectives

- Summarize research findings of key abstracts pertinent to the field of hematopoietic stem cell transplantation (HCT).
- Examine important breakthroughs in hematology expected to impact HCT practice.
- Identify select data presented as part of the scientific programming of interest to HCT pharmacists.
- Evaluate key points and data from select sessions of the education program applicable to the care of HCT patients.

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## 56th ASH Annual Meeting & Exposition

- Held December 6-9, 2014 in San Francisco, CA
- Numbers:
  - More than 5600 abstracts
- Main themes/topics:
  - Immunotherapy

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## Immunotherapy

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## Immunotherapy

Abstract 379 O – BLAST: A Confirmatory, Single-Arm Phase 2 Study of Blinatumomab, a Bispecific T-Cell Engager (BiTE®) Antibody Construct, in Patients with Minimal Residual Disease B-Precursor Acute Lymphoblastic Lymphoma (ALL)

Abstract 965 O – Allogeneic Hematopoietic Stem Cell Transplantation Following Anti-CD19 BiTE® Blinatumomab in Adult Patients with Relapsed/Refractory B-Precursor Acute Lymphoblastic Leukemia (ALL)

Education Session – Transplantation: Adoptive T-Cell Strategies

Abstract 380 O – T Cells Engineered with a Chimeric Antigen Receptor (CAR) Targeting CD19 (CTL019) Have Long Term Persistence and Induce Durable Remissions in Children with Relapsed, Refractory ALL

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## Blinatumomab

- Bispecific T-cell Engager (BiTE®) antibody construct
- Simultaneously binds to CD3 and CD19
- Redirects T-cells to lyse CD19-expressing malignant and non-malignant B-cells
- Triggers expansion of CD8+ and CD4+ T-cell populations and serial lysis of target cells
- FDA approved: December 3, 2014.

Stein A, et al. *Blood* 2014;124(21):Abstract 965.; Goekbuget N, et al. *Blood* 2014;124(21):Abstract 379.; Baeuerle P, et al. *Cancer Res* 2009;69(12):4941-4

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## BLAST: Blinatumomab in MRD ALL (379)

- Study Objectives/Background:
  - Evaluate the efficacy, safety and tolerability of blinatumomab in MRD+ B-precursor ALL
  - In a previous phase 2 (n=21), 80% achieved complete MRD response
- Study Design:.
  - Phase 2, single-arm
  - Patients had received ≥ 3 prior therapies with MRD
  - Primary endpoint: complete MRD response
  - Secondary endpoints: overall survival, relapse-free survival, duration of complete MRD response, incidence of adverse events

MRD = minimal residual disease

Goekbuget N, et al. *Blood* 2014;124(21):Abstract 379.

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## BLAST: Blinatumomab in MRD ALL (379)

- Blinatumomab: 15 µg/m²/day continuous IV infusion for 4 weeks, followed by a 2-week treatment-free period
- Responders could receive ≤ 4 cycles or undergo HCT after ≥ 1 cycle

| | Baseline, n (%) (N=116) | MRD Response (%, 95% CI) (n=113) |
|---|---|---|
| CR in which blinatumomab was given | | |
| First | 75 (65) | 82 (72–90) |
| Second | 39 (34) | 71 (54–85) |
| Third | 2 (2) | 50 (1–99) |
| Baseline MRD levels† | | |
| ≥$10^{-1}$ to <1 | 9 (8) | 67 (30–93) |
| ≥$10^{-2}$ to <$10^{-1}$ | 45 (39) | 82 (67–92) |
| ≥$10^{-3}$ to <$10^{-2}$ | 52 (45) | 78 (65–89) |

†10 (9%) patients had MRD <$10^{-3}$, below the lower limit of quantitation, or unknown MRD status.

Goekbuget N, et al. *Blood* 2014;124(21):Abstract 379. Table used by permission of Dr. Goekbuget.

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## BLAST: Blinatumomab in MRD ALL (379)

Safety and Tolerability

| | Blinatumomab n = 116 |
|---|---|
| Patients experiencing ≥ 1 adverse event | 100% |
| Common AEs: | |
| Pyrexia | 88% |
| Headache | 38% |
| Tremor | 29% |
| Chills | 25% |
| Fatigue | 24% |
| Nausea | 22% |
| Vomiting | 22% |
| Patients experiencing ≥ 1 serious adverse event | 60% |
| Commons SAEs: | |
| Pyrexia | 15% |
| Tremor | 7% |
| Aphasia, Encephalopathy, and Overdose | Each 5% |

Goekbuget N, et al. *Blood* 2014;124(21):Abstract 379.

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## BLAST: Blinatumomab in MRD ALL (379)

- Conclusions:
  - First international multicenter trial with MRD-based patient inclusion and the endpoint of central MRD assessment
  - 78% of patients achieved a complete MRD response within 1 cycle of treatment
  - 98% of patients achieved a response after 1 cycle of treatment
  - Rapid MRD response has the potential to improve patient survival and overall outcomes

Goekbuget N, et al. *Blood* 2014;124(21):Abstract 379.

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## HCT After Blinatumomab in R/R ALL (965)

- Background:
  - OS dismal in r/r ALL
  - AlloHCT only treatment option associated with long-term survival
  - Blinatumomab has efficacy in this population
- Analysis:
  - To characterize patients undergoing HCT after CR/CRh within 2 cycles of blinatumomab
  - Assessment of mortality post-HCT

r/r = relapsed/refractory; CRh = complete remission with partial hematologic recovery

Stein A, et al. *Blood* 2014;124(21):Abstract 965.; Fielding A, et al. *Blood* 2007;109(3):944-50.

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## HCT After Blinatumomab in R/R ALL (965)

| | All Patients n = 189 |
|---|---|
| Median (range) age, years | 39 (18 – 79) |
| Prior salvage therapy | |
| None | 20% |
| 1 | 41% |
| 2 | 22% |
| ≥ 3 | 17% |
| Prior allogeneic HCT | 34% |

Stein A, et al. *Blood* 2014;124(21):Abstract 965.

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## HCT After Blinatumomab in R/R ALL (965)

Safety

| | Blinatumomab n = 189 |
|---|---|
| Any grade ≥ 3 adverse event | 82% |
| Febrile neutropenia | 25% |
| Neutropenia | 16% |
| Anemia | 14% |
| Pneumonia | 9% |
| Thrombocytopenia | 8% |
| Hyperglycemia | 8% |
| Leukopenia | 8% |

*Grade 5 AEs: 28/189 (15%) – 27 of 28 did not achieve CR/CRh

Stein A, et al. *Blood* 2014;124(21):Abstract 965.

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## HCT After Blinatumomab in R/R ALL (965)

- Results:
  - 81/189 (43%) of patients achieved a CR/CRh within 2 cycles of blinatumomab*
  - 32/81 (40%) of patients achieving CR/CRh after 2 cycles of blinatumomab went on to receive on-study HCT
  - 27/52 (52%) of HCT-naïve and 5/29 (17%) of previously transplanted patients received on-study HCT
  - Two-thirds of the patients who did not receive transplant were > 65 yo or had received prior HCT
  - Day +100 mortality rate for HCT-naïve patients was 12.9%

*Primary Study End Point

Stein A, et al. *Blood* 2014;124(21):Abstract 965.

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## CAR T Cell Mechanism of Action

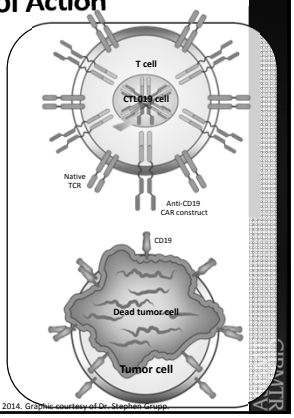
Gene transfer technology is used to stably express CARs on T cells, conferring novel antigen specificity

CTL019 therapy takes advantage of the cytotoxic potential of T cells thereby killing tumor cells in an antigen-dependent manner

Persistent CTL019 cells consist of both effector (cytotoxic) and central memory T cells

T cell are non-cross resistant to chemotherapy

Responses are cytolytic: no swelling!




Grupp S, et al. *Blood* 2014;124(21):Abstract 380. ; June C. ASH Education Session 2014. Graphic courtesy of Dr. Stephen Grupp.

## CD19: An Ideal Tumor Target in B-Cell Malignancies

- CD19 expression is generally restricted to B cells and B cell precursors
  - CD19 is not expressed on hematopoietic stem cells
- CD19 is expressed on most B cell malignancies
  - B-ALL, CLL, DLBCL, FL, MCL
- Antibodies against CD19 inhibit tumor cell growth

ALL = acute lymphoblastic leukemia; CLL = chronic lymphocytic leukemia; DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; MCL = mantle cell lymphoma

June C. ASH Education Session 2014.

## CTL019 CLL: Generalities on First 3 Treated Patients

- All 3 patients had CLL
  - Late-stage incurable leukemia
  - 3.5-7.7 pounds of tumor/patient
- Each infused CAR T cell or its progeny killed more than 1000 tumor cells
- Remissions durable to date
- Sustained antibody delivery with a single infusion of reprogrammed T cells (Beyond 4+ years)

June C. ASH Education Session 2014.

## Durable Responses with CTL019 for R/R ALL (380)

- 135 patients have been treated with CART19 for CLL, ALL, lymphoma and myeloma
- Update ALL Cohort (n = 64) as of November 2014:
  - 41 pediatric cases treated (28 post alloHCT)
  - 35 of 39 CR, 2 pending evaluation
  - 3 (of 4) responded after being refractory to blinatumomab
  - 8 electively retreated at 3-6 months for waning CARs or robust B cell activity
  - 5 off-study for alternate therapy (3 HCT)

June C. ASH Education Session 2014.

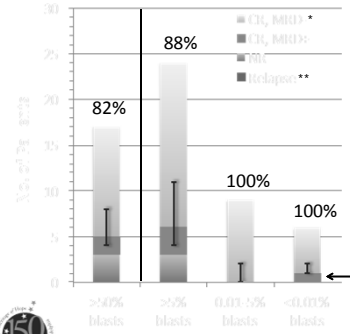
## High Rates of Remission Induction in ALL with CTL019 (380)

Over 130 patients have been treated with CTL019 (CLL, ALL, NHL)

- Pediatric ALL phase 1/2a study (N = 39):
  - 36 of 39 in complete remission (92%)
  - 10 relapses, 5 CD19+ and 5 CD19(-)
  - Median follow-up 6 months, range 1.5-31 months
  - 15 patients out 1 year or more
  - No events after 12 months
  - 3 patients have gone to HCT

Grupp S, et al. *Blood* 2014;124(21):Abstract 380. Slide courtesy of Dr. Stephan Grupp, MD.

## Disease Burden at Time of Infusion and Response (380)




Patient population

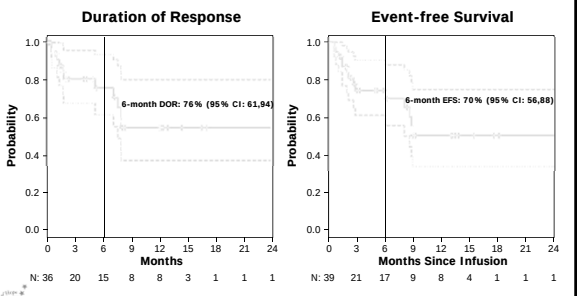
- ≥ 2nd relapse
- Majority refractory to multiple prior therapies

* <0.01% MRD by flow cytometry
** ½ CD19+, ½ CD19-

← MRD- at 3 and 6 months without further therapy

Grupp S, et al. *Blood* 2014;124(21):Abstract 380. Slide courtesy of Dr. Stephan Grupp, MD.
Abbreviations: BM, bone marrow; CR, complete response, MRD, minimal residual disease; NR, no response

## Duration of Response and EFS (380)




Grupp S, et al. *Blood* 2014;124(21):Abstract 380. Slide courtesy of Dr. Stephan Grupp, MD.

## CTL019 Toxicities (380)

- **B-cell aplasia**
  - **observed in all responding patients to date**
  - **managed with IVIg replacement therapy**
- **Cytokine release syndrome (CRS)**
  - **reversible, on-target toxicity**
  - **Controlled with anti-IL-6 therapy (tociluzumab)**
  - **Severity related to tumor burden: Treat MRD as outpatient?**
- **Macrophage activation syndrome (HLH / MAS)**
- **Neurotoxicity**
  - **Significant confusion, aphasia**
  - **Occurs in a small number of patients and after CRS**

Grupp S, et al. *Blood* 2014;124(21):Abstract 380. Slide courtesy of Dr. Stephan Grupp, MD.

## Conclusions (380)

- High rate of remission induction: 92% in a large 39 patient cohort
- Extraordinary growth of CTL019 in responding patients
- CTL019 persistence in some responding patients of up to 31 months with B cell aplasia
- Only 3 of the patients went to transplant

Grupp S, et al. *Blood* 2014;124(21):Abstract 380.; Slide courtesy Best of ASH.

## ARS Question #1

In the study reported by Grupp and colleagues, patients treated with CTL019 demonstrated improvement in duration of response but not event-free survival

A. True
B. False

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## Infectious Diseases

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## Infectious Diseases

Abstract 1133 P – A Phase III, Randomized, Double-Blind Trial to Evaluate Efficacy and Safety of Isavuconazole Versus Voriconazole in Patients with Invasive Mold Disease (SECURE): Outcomes in Hematopoietic Stem Cell Transplant Patients with Invasive Aspergillosis

Abstract 2482 P – Intravenous Immunoglobulin Post Allogeneic Stem Cell Transplantation Is Associated with Lower Levels of CMV Reactivation

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## SECURE: Isavuconazole vs. Voriconazole (1133)

- Background:
  - High risk of invasive fungal diseases, including invasive aspergillosis (IA), in the HCT population with significant mortality
  - Isavuconazole (ISA) is a novel, broad-spectrum, triazole antifungal
    - Available IV and PO
    - *In vitro* activity: *Candida* spp., *Cryptococcus* spp., *Aspergillus* spp., etc.
  - SECURE – non-inferiority of ISA vs. Voriconazole (VRC) for day 42 all-cause mortality for treatment of IFD by *Aspergillus* spp.
  - Sub-group analysis in HCT patients

IFD = invasive fungal disease

Heinz W, et al. *Blood* 2014;124(21):Abstract 1133.

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## SECURE: Isavuconazole vs. Voriconazole (1133)

- Analysis:
  - SECURE – 527 patients randomized
  - 67 patients with proven or probable IA had a history of HCT (ISA n=38, VRC n=29)
  - No survival benefit with isavuconazole vs. voriconazole (P=0.428)

Heinz W, et al. *Blood* 2014;124(21):Abstract 1133.

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## SECURE: Isavuconazole vs. Voriconazole (1133)

Safety

| | ISA n = 38 | VRC n = 29 |
|---|---|---|
| Pyrexia | 26% | 41% |
| Diarrhea | 29% | 28% |
| Abdominal Pain | 11% | 35% |
| Vomiting | 21% | 21% |
| Cardiac Disorders | 16% | 41% |

Heinz W, et al. *Blood* 2014;124(21):Abstract 1133.

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## SECURE: Isavuconazole vs. Voriconazole (1133)

- Conclusions:
  - Highest mortality in HCT patients with neutropenia (37%) vs. no neutropenia (14%)*
  - Mortality also higher in patients without GVHD (33%) vs. with GVHD (15%)
  - Overall efficacy similar between ISA and VRC
  - Similar rates of AEs, significantly fewer cardiac disorders with ISA
    - Cardiac toxicity largely TEAE tachycardia, reported in 34.5% of VRC arm but none with ISA

*Observed results independent of treatment group

Heinz W, et al. *Blood* 2014;124(21):Abstract 1133.

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## IVIG Associated with Less CMV Reactivation (2482)

- Background:
  - CMV common post alloHCT resulting in significant cost, morbidity and potential mortality
  - 2012, funding withdrawn for routine IVIG use post alloHCT in Australia
- Analysis:
  - CMV reactivation, time to first CMV reactivation and cumulative days of major CMV reactivation

Yannakou C, et al. *Blood* 2014;124(21):Abstract 2482.

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## IVIG Associated with Less CMV Reactivation (2482)

| | IVIG n=50 | No IVIG n=50 |
|---|---|---|
| CMV reactivation | 37 (74%) | 39 (78%) |
| Major reactivation | 13 (26%) | 25 (50%)* |
| Minor reactivation | 28 (56%) | 25 (50%) |
| Median time to CMV reactivation - days | 38 | 35 |
| Cumulative duration of CMV reactivation - days | 181 | 604† |
| Median duration of CMV reactivation per patient - days | 13 | 21 |

*RR 0.52, 95% CI [0.30-0.90], p=0.018
†RR 0.30, 95% CI [0.25-0.35], p<0.0001

Yannakou C, et al. *Blood* 2014;124(21):Abstract 2482.

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## IVIG Associated with Less CMV Reactivation (2482)

- Conclusions:
  - Routine IVIG use resulted in no reduction in the rate of latency of CMV reactivation
  - Routine IVIG use was associated with a lower magnitude of CMV reactivation and a reduced requirement for anti-CMV therapy
  - IVIG use post alloHCT may assist in reducing CMV viral burden

Yannakou C, et al. *Blood* 2014;124(21):Abstract 2482.

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## ARS Question #2

What impact does the routine use of IVIG have on CMV reactivation after alloHCT?

A. IVIG use increased the latency of CMV reactivation
B. IVIG use was associated with an increased requirement for anti-CMV therapy
C. IVIG use was associated with a lower magnitude of CMV reactivation
D. IVIG use reduced overall survival post alloHCT

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## Graft vs Host Disease (GVHD)

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## GVHD

Abstract 188 O – A Refined Clinical Risk Score at Onset of Treatment for Acute GVHD That Predicts Response to Initial Therapy, Survival and Transplant-Related Mortality

Abstract 661 O – A Biomarker Algorithm Defines Onset Grades of Acute Graft-vs-Host-Disease with Distinct Non-Relapse Mortality

Abstract 2492 P – Drug Metabolism Gene Polymorphisms Influence Tacrolimus/Sirolimus Blood Levels and Incidence of Graft-Versus-Host Disease Following Allogeneic Hematopoietic Stem Cell Transplantation

Abstract 2553 P – Sirolimus, Tacrolimus and Antithymocyte Globulin Are Associated with Improved Overall Survival When Compared to Methotrexate, Tacrolimus and Antithymocyte Globulin in Mismatched Unrelated Allogeneic Hematopoietic Cell Transplantation

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## Refined Clinical Risk Score for Acute GVHD (188)

- Background:
  - Acute GVHD remains a major cause of morbidity and mortality after alloHCT
  - Corticosteroid-based therapy only effective in ~50% of patients
  - Methods needed to identify patients unlikely to respond to initial standard therapies
- Hypothesis:
  - Initial GVHD organ stage would better identify highest risk patients than initial organ grade

MacMillan M, et al. *Blood* 2014;124(21):Abstract 188.; MacMillan M, et al. *Biol Blood Marrow Transplant* 2015. Ahead of print.

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## Refined Clinical Risk Score for Acute GVHD (188)

- Establishing GVHD Risk Categories by Initial Organ Stage (n = 1723)
  - Organ stage for each patient determined at the time of steroid treatment
    - Skin 0-4
    - Liver 0-4
    - Lower GI 0-4
    - Upper GI 0-4
  - 67 categories generated
  - Collapsed into 17 larger categories clustered as clinically similar cohorts with comparable CR/PR at day 28
  - Endpoints: CR/PR at day 28; TRM and survival at 6 months

PR = partial response; TRM = treatment-related mortality

MacMillan M, et al. *Blood* 2014;124(21):Abstract 188.; MacMillan M, et al. *Biol Blood Marrow Transplant* 2015. Ahead of print.

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## Refined Clinical Risk Score for Acute GVHD (188)

| GVHD Categories Grouped by Day 28 CR/PR | N | Day 28 CR/PR | Odds Ratio of day 28 CR/PR (95% CI) | P Value | |
|---|---|---|---|---|---|
| 1. Stage 1-3 Skin only* | 901 | 68% | 1.0 | | Std Risk |
| 2. UGI only | 115 | 78% | 1.6 (1.0-2.6) | 0.04 | |
| 3. Stage 1-2 Lower GI only | 100 | 73% | 1.3 (0.8-2.1) | 0.29 | |
| 4. Stage 1-3 Skin + UGI | 90 | 69% | 1.0 (0.6-1.6) | 0.89 | |
| 5. Stage 1-3 Skin + Stage 1 Lower GI | 71 | 61% | 0.7 (0.4-1.2) | 0.16 | |
| 6. Stage 1 Lower GI + Upper GI | 64 | 64% | 0.8 (0.5-1.4) | 0.42 | |
| 7. Stage 1-3 Skin + Stage 1-4 Liver | 51 | 71% | 1.1 (0.6-2.1) | 0.71 | |
| 8. Stage 1-3 Skin + Stage 1 Lower GI + Upper GI | 62 | 61% | 0.6 (0.4-0.9) | 0.12 | |
| 9. Stage 1-2 Lower GI + Stage 1-3 Liver | 12 | 50% | 0.4 (0.1-1.4) | 0.15 | High Risk |
| 10. Stage 1-3 Skin + (Stage 1-2 Lower GI or Upper GI) + Stage 1-3 Liver | 23 | 35% | 0.2 (0.1-0.6) | 0.001 | |
| 11. Stage 3 Lower GI only | 65 | 55% | 0.5 (0.3-0.9) | 0.02 | |
| 12. Stage 1-3 Skin + Stage 2 Lower GI | 54 | 52% | 0.5 (0.3-0.9) | 0.01 | |
| 13. Stage 3-4 Lower GI + (Stage 1-3 Skin or Liver Stage 1-4) | 55 | 36% | 0.2 (0.1-0.4) | <0.001 | |
| 14. Stage 1-4 Liver alone | 25 | 48% | 0.3 (0.2-0.8) | 0.01 | |
| 15. Stage 1-3 Skin + Stage 3-4 Lower GI + Stage 1-4 Liver | 13 | 8% | 0.1 (0.01-0.3) | 0.002 | |
| 16. Stage 4 Skin only | 13 | 38% | 0.3 (0.1-0.8) | 0.02 | |
| 17. Stage 4 Lower GI only | 22 | 22% | 0.1 (0.03-0.7) | 0.02 | |

MacMillan M, et al. *Blood* 2014;124(21):Abstract 188.; MacMillan M, et al. *Biol Blood Marrow Transplant* 2015. Ahead of print. Table used with permission of Dr. MacMillan

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## Refined Clinical Risk Score for Acute GVHD (188)

| GVHD Categories Grouped by Day 28 CR/PR | N | Day 28 CR/PR | Relative Risk of TRM (95% CI) | P Value | |
|---|---|---|---|---|---|
| 1. Stage 1-3 Skin only* | 901 | 68% | 1.0 | | Std Risk |
| 2. UGI only | 115 | 78% | 0.5 (0.3-0.9) | 0.03 | |
| 3. Stage 1-2 Lower GI only | 100 | 73% | 1.6 (1.0-2.3) | 0.04 | |
| 4. Stage 1-3 Skin + UGI | 90 | 69% | 0.9 (0.6-1.5) | 0.71 | |
| 5. Stage 1-3 Skin + Stage 1 Lower GI | 71 | 61% | 1.3 (0.8-2.1) | 0.35 | |
| 6. Stage 1 Lower GI + Upper GI | 64 | 64% | 1.4 (0.9-2.4) | 0.18 | |
| 7. Stage 1-3 Skin + Stage 1-4 Liver | 51 | 71% | 1.4 (0.9-2.3) | 0.17 | |
| 8. Stage 1-3 Skin + Stage 1 Lower GI + Upper GI | 62 | 61% | 0.6 (0.3-1.3) | 0.18 | |
| 9. Stage 1-2 Lower GI + Stage 1-3 Liver | 12 | 50% | 3.2 (1.5-7.0) | 0.003 | High Risk |
| 10. Stage 1-3 Skin + (Stage 1-2 Lower GI or Upper GI) + Stage 1-3 Liver | 23 | 35% | 3.2 (1.8-5.6) | <0.001 | |
| 11. Stage 3 Lower GI only | 65 | 55% | 2.7 (1.8-4.2) | <0.001 | |
| 12. Stage 1-3 Skin + Stage 2 Lower GI | 54 | 52% | 1.6 (1.0-2.6) | 0.06 | |
| 13. Stage 3-4 Lower GI + (Stage 1-3 Skin or Liver Stage 1-4) | 55 | 36% | 3.0 (2.0-4.5) | <0.001 | |
| 14. Stage 1-4 Liver alone | 25 | 48% | 1.7 (0.8-3.8) | 0.19 | |
| 15. Stage 1-3 Skin + Stage 3-4 Lower GI + Stage 1-4 Liver | 13 | 8% | 7.4 (3.6-15.2) | <0.001 | |
| 16. Stage 4 Skin only | 13 | 38% | 2.2 (0.7-6.9) | 0.16 | |
| 17. Stage 4 Lower GI only | 22 | 22% | 3.1 (1.2-8.1) | 0.02 | |

MacMillan M, et al. *Blood* 2014;124(21):Abstract 188.; MacMillan M, et al. *Biol Blood Marrow Transplant* 2015. Ahead of print. Table used with permission of Dr. MacMillan

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## Refined Clinical Risk Score for Acute GVHD (188)

- Results/Conclusions:
  - Patients with refined high risk GVHD
    - Less likely to respond to steroid therapy (RR 0.3, p<0.001)
    - 2x increased mortality at 6 months vs. SR-GVHD (RR 2.1, p<0.001)
    - 2x increased TRM at 6 months vs. SR-GVHD (RR 2.5, p<0.001)
    - Are candidates for studies investigating new treatments

MacMillan M, et al. *Blood* 2014;124(21):Abstract 188.; MacMillan M, et al. *Biol Blood Marrow Transplant* 2015. Ahead of print.

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## Refined Clinical Risk Score for Acute GVHD (188)

- Results/Conclusions:
  - Patients with refined standard risk GVHD are candidates for studies investigating less toxic therapy
  - In contrast to biomarkers, GVHD risk score is available at bedside in real time

http://z.umn.edu/MNAcuteGVHDRiskScore

MacMillan M, et al. *Blood* 2014;124(21):Abstract 188.; MacMillan M, et al. *Biol Blood Marrow Transplant* 2015. Ahead of print.

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## ARS Question #3

An AML patient day 14 post alloHCT presents with overt signs and symptoms of GVHD. The following organ staging for GVHD is reported: skin: stage 2, lower GI: stage 1, liver: stage 1. Based upon the abstract by MacMillan and colleagues, which statement is correct? The patient:

A. Is low risk and would likely respond to steroid-based therapy
B. Should be considered for trials of less toxic GVHD therapies
C. Is high risk and would likely not respond to steroid-based therapy
D. Is at reduced risk of mortality at 6 months compared to patients with standard risk GVHD

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## Gene Polymorphisms and Tacro/Siro Levels (2492)

- Background:
  - ADME genes affect the blood level of immunosuppressants as well as clinical outcomes
- Analysis:
  - Evaluate possible associations between ADME variants and Tacro/Siro blood levels
    - Focus: ABCB1 (MDR1), CYP3A4 and CYP3A5
    - Association with other gene variants

ADME = absorption, distribution, metabolism, excretion; Tacro = tacrolimus, Siro = sirolimus
Khaled S, et al. *Blood* 2014;124(21):Abstract 2492.

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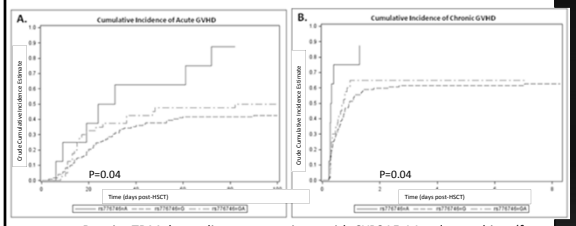
## Gene Polymorphisms and Tacro/Siro Levels (2492)

- Results:




- Despite TDM dose adjustment, patients with CYP3A5 AA polymorphism (fast drug metabolizers) were found to have increased incidence of acute and chronic GHVD. This group also found to have lower Tacro blood levels and concentration/dose ratio

Khaled S, et al. *Blood* 2014;124(21):Abstract 2492. Graphics used with permission of Dr. Khaled.

TDM = Therapeutic Drug Monitoring

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## Gene Polymorphisms and Tacro/Siro Levels (2492)

- Conclusions:
  - First study to demonstrate influence of ADME genetic variants on drug levels and clinical outcomes
  - Other potential genetic variants associated with Tacro/Siro levels but none reached statistical significance
  - Results may lead to individualized dosing of immunosuppressants based on ADME gene polymorphisms

Khaled S, et al. *Blood* 2014;124(21):Abstract 2492.

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## Siro/Tacro/ATG Associated with ↑ OS (2553)

- Background:
  - No existing data for combination of ATG with Siro/Tacro or MTX/Tacro in MMUD alloHCT
- Analysis:
  - Retrospective trial design (n=122)
  - Comparison of Siro/Tacro/ATG vs. MTX/Tacro/ATG for: NRM, RFS, OS, and incidence of EBV reactivation

Siro = sirolimus; Tacro = tacrolimus; ATG = antithymocyte globulin; MTX = methotrexate; NRM = non-relapse mortality; RFS = relapse-free survival; OS = overall survival; EBV = Epstein Barr virus

Nelson R, et al. *Blood* 2014;124(21):Abstract 2553.

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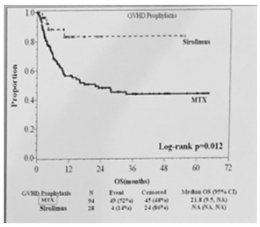
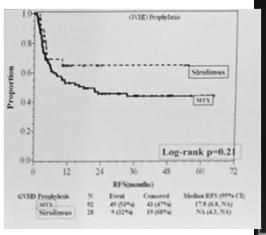
## Siro/Tacro/ATG Associated with ↑ OS (2553)

- Results:




Overall Survival




Relapse-Free Survival

Nelson R, et al. *Blood* 2014;124(21):Abstract 2553. Graphics used with permission of Dr. Nelson and Dr. Shapiro.

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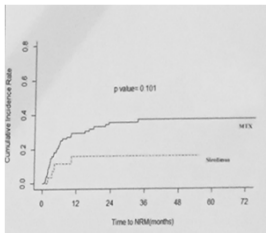
## Siro/Tacro/ATG Associated with ↑ OS (2553)

- Results:




Non-Relapse Mortality

Nelson R, et al. *Blood* 2014;124(21):Abstract 2553. Graphics used with permission of Dr. Nelson and Dr. Shapiro.

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## Siro/Tacro/ATG Associated with ↑ OS (2553)

- Conclusions:
  - Low CIBMTR disease risk was a favorable prognostic factor for better RFS and OS
  - The use of Tacro/Siro/ATG did not appear to have a protective effect on disease relapse
  - MTX/Tacro/ATG showed a two-fold higher 3-year cumulative incidence of NRM (P=NS)
  - Study suggests that combining Siro/Tacro/ATG results in improved OS in MMUD allo-HCT

NS = not significant

Nelson R, et al. *Blood* 2014;124(21):Abstract 2553.

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## Complications of Transplant

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## Complications of Transplant

Abstract 2470 P – Updated Results from a Large, Ongoing, Treatment IND Study Using Defibrotide for Patients with Hepatic Veno-Occlusive Disease

Abstract 2469 P – Defibrotide for the Treatment of Severe Hepatic Veno-Occlusive Disease: An Analysis of Clinical Benefit As Determined by Number Needed to Treat (NNT) to Achieve Complete Response and to Improve Survival

Abstract 663 O – Biomarkers for Diagnosis and Prognosis of Sinusoidal Obstruction Syndrome (SOS) after Hematopoietic Stem Cell Transplantation

Abstract 1144 P – Management Strategies for Posterior Reversible Encephalopathy Syndrome (PRES) in Patients Receiving Calcineurin-Inhibitor or Sirolimus Therapy for Hematologic Disorders and Allogeneic Transplantation

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## Defibrotide for Hepatic VOD (2470)

- T-IND-2006-05
  - >80% mortality at D+100 in patients developing veno-occlusive disease (VOD)/multi-organ failure (MOF).
  - Study initiated in 2007.
  - Largest prospective evaluation of defibrotide for the treatment of severe VOD (sVOD)/MOF in HCT patients.
  - Updated analysis based on 612 patients enrolled between December 2007 and December 2013 at 86 sites in the USA.

Richardson P, et al. *Blood* 2014;124(21):Abstract 2470.; Coppell J, et al. *Biol Blood Marrow Transplant* 2010;16:157-68.

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## Defibrotide for Hepatic VOD (2470)

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% | 35% |
| 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% |

‡CR defined as total bilirubin < 2 mg/dL and resolution of MOF
*Kaplan-Meier estimates for time-to-event analysis at Day 100

Richardson P, et al. *Blood* 2014;124(21):Abstract 2470.

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## Defibrotide for Hepatic VOD (2470)

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 postHCT

| 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 at Day 100
‡Log-rank test between subgroups

Richardson P, et al. *Blood* 2014;124(21):Abstract 2470.

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## Defibrotide for Hepatic VOD (2470)

Safety: Transplanted analysis population

| | Defibrotide (n=612) |
|---|---|
| Total patients with at least one adverse event (AE)* | 22.5% |
| Total patients with at least one serious AE | 13.4% |
| Hypotension | 5.9% |
| Hemorrhage<br>Pulmonary Hemorrhage<br>Gastrointestinal Hemorrhage<br>Epistaxis | 11.4%<br>4.7%<br>3.6%<br>3.1% |
| Related events leading to discontinuation | 13.4% |

*AEs judged to be related (possibly, probably, or definitely) to defibrotide treatment

Richardson P, et al. *Blood* 2014;124(21):Abstract 2470.

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## Defibrotide for Hepatic VOD (2470)

- Conclusions:
  - Largest prospective trial with defibrotide for severe VOD/MOF
  - Defibrotide relatively well tolerated with manageable toxicity
  - Previously reported response and survival very favorable in this high-risk population
  - Early initiation of defibrotide is important once sVOD is suspected

Richardson P, et al. *Blood* 2014;124(21):Abstract 2470.

## Defibrotide for Hepatic VOD – NNT (2469)

- Study Objectives:
  - To compare outcome, expressed by number needed to treat (NNT), of therapy with defibrotide vs. other agents used for sVOD.
- Study Design:
  - Phase 3 trial
  - Defibrotide 25 mg/kg/day for ≥ 21 days in patients with sVOD postHCT vs. historical controls
  - Primary endpoint: CR rate by day +100
  - Secondary endpoint: survival at day +100

Richardson P, et al. *Blood* 2014;124(21):Abstract 2469.

## Defibrotide for Hepatic VOD – NNT (2469)

- Historical Controls Selection:
  - VOD by Baltimore criteria by day + 21*
  - MOF (renal and/or pulmonary failure) by day +28*
  - HCT ≥ 6 months prior to first use of defibrotide at that institution
    - Patient data provided only to the time where possible sVOD was diagnosed

*Inclusion criteria also applied to prospective cohort treated with defibrotide

Richardson P, et al. *Blood* 2014;124(21):Abstract 2469.

## Defibrotide for Hepatic VOD – NNT (2469)

- A statistically significant percentage of patients treated with defibrotide achieved CR* and resolution of MOF† at day + 100, compared with control.

| | Defibrotide | Control | P-value |
|---|---|---|---|
| Complete response rate at day + 100 | 23.5% | 9.4% | 0.013 |
| Survival at day + 100 | 38.2% | 25.0% | 0.034 |

*CR defined by total bilirubin < 2 mg/dL
†Defined by resolution of renal and/or pulmonary dysfunction

Richardson P, et al. *Blood* 2014;124(21):Abstract 2469.

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## Defibrotide for Hepatic VOD – NNT (2469)

Safety

| | Defibrotide n = 102 | Historical Control n = 32 |
|---|---|---|
| Hypotension | 39% | 50% |
| Diarrhea | 25% | 41% |
| Vomiting | 21% | 25% |
| Nausea | 15% | 31% |
| Pyrexia | 15% | 34% |
| Tachycardia | 10% | 44% |
| Agitation | 11% | 28% |
| Rash | 10% | 25% |
| Generalized edema | 8% | 25% |
| Petechiae | 6% | 28% |
| Blister | 6% | 25% |

Richardson P, et al. *Blood* 2014;124(21):Abstract 2469.

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## Defibrotide for Hepatic VOD – NNT (2469)

- NNT to achieve 1 CR and to prevent 1 death by day +100 with defibrotide

| **Treatment Arms** | Patients (n) | CR (%) | ARR | NNT to Achieve 1 CR | Survival Rate (%) | ARR | NNT to Achieve 1 Death |
|---|---|---|---|---|---|---|---|
| Defibrotide | 102 | 23.5 | 0.141 | 7 | 38.2 | 0.132 | 8 |
| Historical controls | 32 | 9.4 | | | 25.0 | | |

ARR = absolute risk reduction; CR = complete response; NNT = number needed to treat

$$NNT = \frac{1}{ARR}$$

Richardson P, et al. *Blood* 2014;124(21):Abstract 2469.

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## Defibrotide for Hepatic VOD – NNT (2469)

- Conclusions:
  - Significant improvement in CR and survival at day +100 compared with historical controls
  - This analysis formed basis of defibrotide approval in EU
  - Adverse events consistent with previous trials
  - NNTs with defibrotide comparable or lower than with other therapies with sVOD

Richardson P, et al. *Blood* 2014;124(21):Abstract 2469.

## Biomarkers for Diagnosis/Prognosis of SOS (663)

- Background:
  - Complication of alloHCT, occurring in up to 20% of recipients
  - Known risk factors:
    - Conditioning regimens (busulfan, cyclophosphamide)
    - Pre-existing liver disease
    - Radiation to the abdomen
    - Use of combination of tacro/sirolimus for GVHD prophylaxis
  - Diagnosis by triad of: weight gain/ascites, hepatomegaly, elevated bilirubin +/- abdominal ultrasound
- Goal:
  - Identify and validate SOS biomarkers using a proteomics approach

Paczesny S, et al. *Blood* 2014;124(21):Abstract 663.; Slide courtesy of Dr. Sophie Paczesny, MD, PhD.

## Biomarker Discovery (663)

**Plasma Pool: 19 BMT recipients with SOS (heavy isotope)**
**vs.**
**Plasma Pool: 19 BMT recipients without SOS (light isotope)**

↓

**494 proteins identified and quantified**

↓

**151 proteins heavy/light ≥ 2 &**
**77 proteins heavy/light ≤ 0.5**

↓

**6 proteins with antibodies for ELISA**
**VCAM1↑, TIMP1↑, vWF↑, ICAM1↑, CD97↑, L-Ficolin↓**
**+ 5 previous or novel markers**
**PAI-1, thrombomodulin, HA, ANG2, ST2**

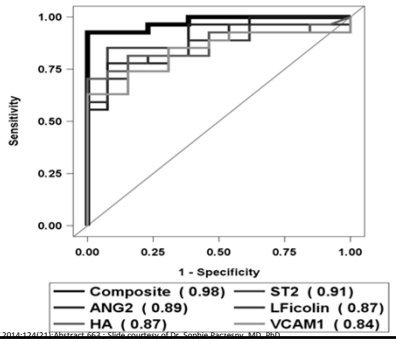
↓

**Validation set of 45 patients (32 SOS+, 13 SOS-)**

Paczesny S, et al. *Blood* 2014;124(21):Abstract 663.; Slide courtesy of Dr. Sophie Paczesny, MD, PhD.

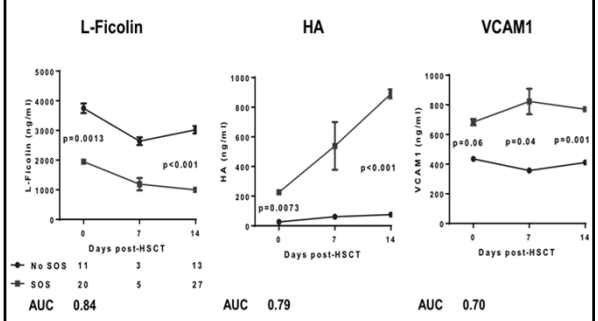
## Individual and composite ROC curves of the 5 top diagnostic biomarkers (663)

32 SOS patients [median day onset = day 11 post-HSCT (range 4-63)] vs. 13 time-matched controls [day 14 post-HSCT (range 7-41)]




Paczesny S, et al. *Blood* 2014;124(21):Abstract 663.; Slide courtesy of Dr. Sophie Paczesny, MD, PhD.

## (663)




ST2 and ANG2 that are diagnostic, are not prognostic

Paczesny S, et al. *Blood* 2014;124(21):Abstract 663.; Slide courtesy of Dr. Sophie Paczesny, MD, PhD.

## Conclusions (663)

**Together ST2, ANG2, L-Ficolin, HA, and VCAM1 represent a biomarker panel for reliable, non-invasive diagnosis of SOS (AUC = 0.98)**

**L-Ficolin, HA, and VCAM1 are prognostic biomarkers of SOS (elevated before the appearance of clinical signs)**

**L-Ficolin, HA, and VCAM1 can stratify patients at risk of SOS as early as the day of HSCT which has therapeutic consequences including potential preemptive interventions**

**L-Ficolin's mechanism of action implicates pathways in SOS other than those related to hemostasis and endothelial injury. It has recently been shown to be involved in homeostatic clearance of mitochondria in the liver (*Brinkmann et al., JBC, 2013)***

Paczesny S, et al. *Blood* 2014;124(21):Abstract 663.; Slide courtesy of Dr. Sophie Paczesny, MD, PhD.

## Management of PRES in HCT (1144)

- Background:
  - PRES is a life-threatening complication of calcineurin-inhibitors (CNI) and Sirolimus (Siro)
  - PRES associated with hypertension and symptomatic features including: headaches, seizures, intracranial hemorrhage or ischemic stroke
  - Finding on MRI: leuko-encephalopathy with vasogenic edema and diffusion restriction in the subcortical white matter in the occipital cerebrum
- Analysis:
  - Patient comorbidities, features at PRES presentation, clinical management decisions and outcomes

PRES = posterior reversible encephalopathy syndrome
Cerejo M, et al. *Blood* 2014;124(21):Abstract 1144.

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## Management of PRES in HCT (1144)

- Results:
  - Majority of patients that developed PRES in association with CNI/Siro therapy were solid organ transplant patients followed by alloHCT patients
  - Most common symptoms at onset: hypertension, seizure, headache, intracranial hemorrhage, CVA
  - At time of PRES presentation: 22% of patients had supratherapeutic CNI/Siro levels

PRES = posterior reversible encephalopathy syndrome; CNI = calcineurin inhibitor; Siro = sirolimus; CVA = cerebrovascular accident
Cerejo M, et al. *Blood* 2014;124(21):Abstract 1144.

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## Management of PRES in HCT (1144)

- Conclusions:
  - The vast majority of patients (77%) tolerated continuation of the same CNI or changing to alternative CNI therapy with careful attention to management of hypertension
  - 11% of patients tolerated conversion from CNI to Siro
  - Only 3/27 (11%) discontinued CNI/Siro therapy indefinitely, and the recurrence rate with continuation of CNI/Siro therapy was low at 2/24 (8.3%)
  - No patients experienced fatal complications of PRES suggesting that this management strategy is safe

CNI = calcineurin inhibitor; Siro = sirolimus
Seftel M, et al. *Blood* 2014;124(21):Abstract 319.; Slide courtesy of Dr. Matthew Seftel, MD.

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## Pharmacokinetics/Pharmacodynamics

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## Pharmacokinetics/Pharmacodynamics

Abstract 425 O – Pharmacokinetics/Pharmacodynamic Relationship in Busulfan Conditioning Regimen: Results from a Large Pediatric Cohort Undergoing Hematopoietic Stem-Cell Transplantation

Abstract 3869 P – Pharmacokinetic Modeling of Fludarabine to Control Exposure and Improve Outcomes after Reduced Intensity Conditioning Transplantation

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## Pk/Pd in Busulfan Conditioning (425)

- Background:
  - Busulfan (BU) is a cornerstone of HCT conditioning regimens
  - Graft rejection, relapse and toxicities are associated with BU in HCT
  - Large variability in children
- Goals:
  - Study Pk/Pd relationship of BU in HCT, BU-based CR in pediatric population
  - Define specific therapeutic windows according to patient-specific characteristics

Paci A, et al. *Blood* 2014;124(21):Abstract 425.

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## Patients (425)

- 296 patients:

Patients with 2nd or 3rd transplantation (n = 20) were excluded from the PD analysis → 276 patients

- Follow-up:
  - Median follow-up of 32.8 months [1.4;103]
- Pathologies:
  - 6 groups of pathologies
  - 257 allogeneic HSCT
  - 41 autologous BMT
- Age:
  - Median age: **18 months** [1 ; 289]
    - 102 patients (34%) ≤1 yr, **208 patients (70%) below 3 yrs**
- Weight
  - Median weight: **10.8 kg** [3;117]
    - **101 patients (34%) ≤ 9 kg**, 204 patients (74%) below 16 kg

| Group | Pathologies | Number (%) |
|---|---|---|
| **Group 1** | Lymphohistiocytosis (LHF) | **39 (13)** |
| **Group 2** | Immunodeficiencies (CID & granulocyte ID) | **87 (30)** |
| **Group 3** | SCID | **17 (5)** |
| **Group 4** | Metabolic disease & Osteopetrosis | **49 (17)** |
| **Group 5** | Leukemias and solid tumors | **77 (26)** |
| **Group 6** | Others | **27 (9)** |

Weight and age are highly correlated (p(Rhô) = <.0001 (0.92))

GUSTAVE ROUSSY CANCER CAMPUS GRAND PARIS

Paci A, et al. *Blood* 2014;124(21):Abstract 425.; Slide courtesy of Dr. Angelo Paci, PharmD.
*56th ASH Annual Meeting, 8th December 2014 – Pk/Pd study of the French Observatoire – Paci et al.*

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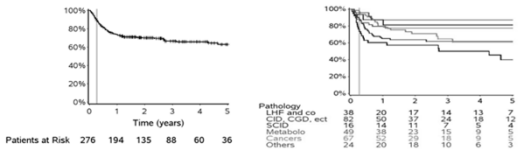
## Results on Pharmacodynamy: Overall survival (OS) (425)

- All patients (n = 276)
  - OS was 70% at 2 yrs and 63% at 5 yrs
  - not significantly associated with CR or weight(age)
  - associated with pathologies: p = 0.023 (multivariate analysis)
    - OS was 57% at 2 yrs and 40% at 5 yrs for LHF

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Paci A, et al. *Blood* 2014;124(21):Abstract 425.; Slide courtesy of Dr. Angelo Paci, PharmD.
*56th ASH Annual Meeting, 8th December 2014 – Pk/Pd study of the French Observatoire – Paci et al.*

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## Conclusion & Perspectives (425)

*Pharmacodynamy*
- OS is dependent of pathologies but not weight(age) neither conditioning
- DFS is not dependent of pathologies, weight or conditioning
- Toxicities are dependent of pathologies, weight (age) and conditioning

*Pharmacokinetics*
- Accumulation occurs during conditioning with higher exposure at AUC D9
- TDM and dose-adjustment allow to control this accumulation and a better targeting of the chosen TW, especially in children below 9 kg (*Objective of the Observatoire study*)

*Pk/PD*
- Exposure is not correlated to OS or DFS
- Exposure is correlated to HVOD but not niPD

*Perspectives*
- Enrichment of each specific populations to further explore PK/PD relationship
- Complete PK/PD analysis on sub-populations including GST polymorphism

GUSTAVE ROUSSY CANCER CAMPUS GRAND PARIS

Paci A, et al. *Blood* 2014;124(21):Abstract 425.; Slide courtesy of Dr. Angelo Paci, PharmD.
*56th ASH Annual Meeting, 8th December 2014 – Pk/Pd study of the French Observatoire – Paci et al.*

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## Pk of Fludarabine in RIC (3869)

- Background:
  - RIC and non-myeloablative conditioning regimens have reduced TRM in elderly and those with comorbidities
  - Fludarabine is rapidly dephosphorylated to its metabolite, F-ara-A
  - Patients with renal impairment accumulate F-ara-A
  - Dosing based upon an equation using CrCl and IBW allows for estimation of an individualized dose
- Analysis:
  - Retrospectively test this equation by assessing relationship between equation-predicted AUC and TRM, acute and chronic GVHD and engraftment

RIC = reduced intensity conditioning; TRM = treatement-related mortality; CrCl = creatinine clearance; IBW = ideal body weight

Sanghavi K, et al. *Blood* 2014;124(21):Abstract 3869.

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## Pk of Fludarabine in RIC (3869)

F-ara-A CL (L/hr) = $[7.04 + 3.9 \times \{(CrCl/85) \times (70/IBW)\}] \times (IBW/70)^{0.75}$

- Results:
  - Relationship between AUC and Clinical Outcomes
    - Overall TRM was 8% and 13% at day 100 and 6 months respectively
    - Median time to TRM was 165 days
    - Cumulative incidence of TRM was significantly higher at day 100 in those with lower F-ara-A clearance and higher F-ara-A AUC
  - Acute GVHD
    - Lower F-ara-A CL was associated with higher risk of aGVHD after adjusting for donor source
  - Engraftment
    - None of the pharmacokinetic parameters was associated with engraftment

AUC = area under the curve; CL = clearance; IBW = ideal body weight; TRM = treatment-related mortality

Sanghavi K, et al. *Blood* 2014;124(21):Abstract 3869.

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## Pk of Fludarabine in RIC (3869)

- Conclusions:
  - F-ara-A clearance and a high F-ara-A AUC are significantly associated with TRM and aGVHD
  - F-ara-A clearance and AUC was not associated with engraftment
  - The dosing equation, taking into account CrCl and IBW, is supported by this data
  - Need to define optimal plasma exposure and the minimal amount of F-ara-A needed for efficacy

Sanghavi K, et al. *Blood* 2014;124(21):Abstract 3869.

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## Acute Lymphoblastic Leukemia (ALL)

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## ALL

- Abstract 319 O – Superiority of Pediatric Chemotherapy over Allogeneic Hematopoietic Cell Transplantation for Philadelphia Chromosome Negative Adult ALL in First Complete Remission: A Combined Analysis of Dana-Farber ALL Consortium and CIBMTR Cohorts

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## Superiority of Peds Chemo for Adult ALL (319)

- Background:
  - Outcomes for adult ALL are poorer than for children & adolescents
  - AlloHCT considered superior to conventionally-dosed chemotherapy
  - Pediatric-style regimens given to young adults may obviate the need for alloHCT
- Analysis:
  - Comparison of overall survival and disease-free survival in patients with Ph negative ALL in CR1

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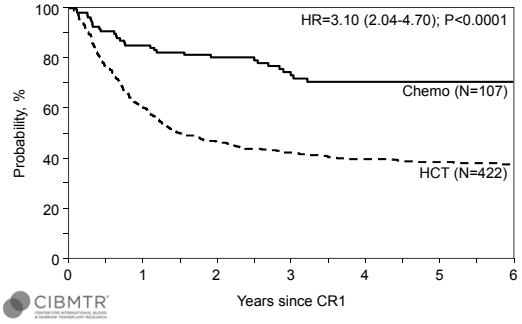
Seftel M, et al. *Blood* 2014;124(21):Abstract 319.; Slide courtesy of Dr. Matthew Seftel, MD.

## Disease-Free Survival

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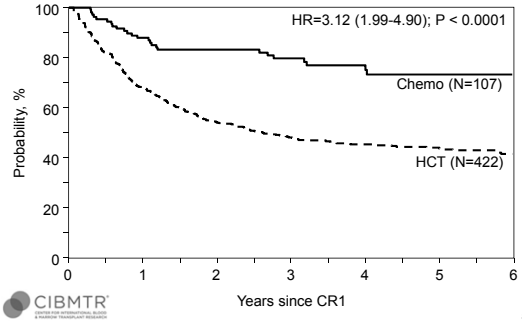
Seftel M, et al. *Blood* 2014;124(21):Abstract 319.; Slide courtesy of Dr. Matthew Seftel, MD.

## Overall Survival

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Seftel M, et al. *Blood* 2014;124(21):Abstract 319.; Slide courtesy of Dr. Matthew Seftel, MD.

## Conclusions

- In younger adults with Ph neg ALL, post-remission therapy with pediatric chemo yielded superior OS & DFS compared to HCT.
- High TRM is the major limitation after HCT.
- These data support the need for controlled clinical trials in Ph neg ALL comparing intensive chemo regimens to HCT.

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Seftel M, et al. *Blood* 2014;124(21):Abstract 319.; Slide courtesy of Dr. Matthew Seftel, MD.

## ARS Question #4

Which of the following statements is true with regard to the use of pediatric-style post-remission chemotherapy regimens for adults with Ph negative ALL?

A. Older patients experienced a reduction in OS but an increase in DFS.
B. Younger patients experienced an increased OS and DFS
C. Younger patients experienced a reduction in OS and DFS
D. Older patients experienced an increased OS and DFS

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## Other Abstracts of Interest:

#676: SWOG 0410/BMT-CTN 0703
#673: AETHERA Trial
#430: Changes in HCT Practice Influences Risk of Therapy-related MDS/AML after autoHCT
#675: GELTAMO Registry Study
#321: Post-remission alloHCT Improves Outcomes in Patients ≥ 60 years old with AML in First Remission
#280: OSHO-AML 2004 Study
#320: Dose-reduced vs Standard Conditioning Following by AlloHCT in Patients with AML or sAML
#674: AutoHCT in Patients with Chemo-Sensitive Relapsed Refractory HIV-Associated Lymphoma
#193: Improved Outcomes of AutoHCT for Light Chain Amyloidosis
#678: AutoHCT for Waldenstrom's: A Risk Factor Analysis
#198: AutoHCT vs Chemotherapy + Lenalidomide in Newly Diagnosed Multiple Myeloma According to Patient Prognosis
#79: ASPIRE

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## Acknowledgements

Susannah Koontz, PharmD, BCOP
Stephan Grupp, MD
John Levine, MD
Sophie Paczesny, MD, PhD
Angelo Paci, PharmD
Matthew Seftel, MD
Keith Stewart, MD
Rebecca Nelson, PharmD
Jamie Shapiro, PharmD
Samer Khaled, MD
Margaret MacMillan, MD
Nicola Goekbuget, MD

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