Transplantation & Cellular Therapy: Are there changes to the Standards of Care? Reflections on ASH 2022

Richard Maziarz MD
January 20, 2023
Overview

• Introduction
• ASH highlights
  • Nonmalignant
  • HCT Lymphoma
  • HCT Myeloma
  • HCT GVHD
  • CAR-T
Indications for Hematopoietic Cell Transplant in the US, 2018

- **Myeloma / PCD**
- **NHL**
- **AML**
- **MDS / MPN**
- **ALL**
- **HD**
- **Non-malignant disease**
- **Other Cancer**
- **Aplastic Anemia**
- **CML**
- **CLL**

**Number of Transplants**

- **Allogeneic**
- **Autologous**

*excludes aplastic anemia.*
Number of HCTs by Indications in the US, 2020

Abbreviations –
MM: Multiple myeloma;
PCDs: Plasma cell disorders;
AML: Acute myelogenous leukemia;
NHL: Non-Hodgkin lymphoma;
MDS: Myelodysplastic syndromes;
MPN: Myeloproliferative neoplasms;
ALL: Acute lymphoblastic leukemia;
HL: Hodgkin lymphoma;
CML: Chronic myeloid leukemia

*excludes Aplastic anemia
Number of COVID-19 Infections in HCT Recipients in the US Reported to CIBMTR by Transplant Type

![Graph showing the number of COVID-19 infections in HCT recipients in the US, with a peak in 2020.11.](image)

- **Allogeneic HCT**
- **Autologous HCT**

Data as of 12/01/2021; data may not complete for October due to data reporting lag.
Number of CAR T cell infusions: 2016-2021
(5,364 patients and 5,625 infusions)

Cumulative

Data Incomplete for 2020 & 2021
## OHSU Adult HCT & CAR T activity

<table>
<thead>
<tr>
<th>Year</th>
<th>HCT Count</th>
<th>CAR T Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>2018</td>
<td>233</td>
<td>17</td>
</tr>
<tr>
<td>2019</td>
<td>234</td>
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</tr>
<tr>
<td>2020</td>
<td>216</td>
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<td>2021</td>
<td>230</td>
<td>43</td>
</tr>
<tr>
<td>2022</td>
<td>236</td>
<td>68</td>
</tr>
<tr>
<td>2023 (Jan)</td>
<td>20</td>
<td>7</td>
</tr>
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</table>

**2023 Annualized**

240         84 (Anticipate > 90)
As a part of our federal contract to operate the Stem Cell Therapeutic Outcomes Database (SCTOD), the Center for International Blood & Marrow Transplant Research (CIBMTR) is required each year to perform a center-specific survival analysis providing one-year survival rates among U.S. centers. This report contains outcomes for transplants using both related and unrelated donors.
OHSU Pt: Relapsed, refractory DLBCL; no prior HCT

Maximal Survival estimates of R/R DLBCL: Scholar trial: <7% CR, 15% OS at 2 yrs, Crump et al, Blood, 2017
Prediction: cell and gene landscape rapid growth

- Fewer than 10 cell and gene therapies currently approved and in use, but with another 10+ expected annually in 2021 and beyond
- 1,000+ clinical trials for cell and gene therapies underway in the U.S. (asgct.careboxhealth.com)
- 24+ conditions on the near-term pipeline and constantly changing
- Number of manufacturers in cell and gene therapy market growing exponentially including big players
- Constantly shifting market; Not all cancer

Forecast (2021-2022 Pipeline)

<table>
<thead>
<tr>
<th>Blood Disorders</th>
<th>Ocular Disorders</th>
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<tbody>
<tr>
<td>• Hemophilia B (gene)</td>
<td>• Choroideremia (gene)</td>
</tr>
<tr>
<td>• Hemophilia A (gene)</td>
<td>• Leber hereditary optic neuropathy (gene)</td>
</tr>
<tr>
<td>• Transfusion dependent β-thalassemia (gene)</td>
<td>• Wet &amp; dry age-related macular degeneration (gene/cell)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Metabolic Disorders</th>
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<tbody>
<tr>
<td>• Follicular lymphoma (CAR-T expanded indications)</td>
<td>• Cerebral adrenoleukodystrophy (gene)</td>
</tr>
<tr>
<td>• Multiple myeloma (CAR-T)</td>
<td>• Mucopolysaccharidosis type III (gene)</td>
</tr>
<tr>
<td>• Bladder cancer (gene)</td>
<td></td>
</tr>
<tr>
<td>• Epstein-Barr virus-associated post-transplant lymphoproliferative disease (CTL)</td>
<td></td>
</tr>
<tr>
<td>• Cervical cancer (TIL)</td>
<td></td>
</tr>
<tr>
<td>• Metastatic melanoma (TIL)</td>
<td></td>
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<tr>
<td>• Marginal zone lymphoma (CAR-T expanded indications)</td>
<td></td>
</tr>
<tr>
<td>• Diffuse large B-cell lymphoma (CAR-T)</td>
<td></td>
</tr>
<tr>
<td>• Acute lymphoblastic leukemia (CAR-T)</td>
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<tr>
<td>• Synovial sarcoma (TCR T-Cell)</td>
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</table>

<table>
<thead>
<tr>
<th>Neurodegenerative</th>
<th>Skin Disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Aromatic L-amino acid decarboxylase (AADC) deficiency (gene)</td>
<td>• Recessive dystrophic epidermolysis bullosa (gene)</td>
</tr>
<tr>
<td>• Spinal muscular atrophy (expanded indications-gene)</td>
<td>• Sclerodema (gene)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Inherited Immunodeficiencies</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Wiskott-Aldrich syndrome (gene)</td>
<td></td>
</tr>
<tr>
<td>• Leukocyte adhesion deficiency type I (gene)</td>
<td></td>
</tr>
</tbody>
</table>
In 2022, US could see these annualized numbers of patients (or higher) in need of services:

<table>
<thead>
<tr>
<th>Category</th>
<th>Patients / 50 Million Lives*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organ Transplant</td>
<td>4,850</td>
</tr>
<tr>
<td>Bone Marrow Transplant</td>
<td>3,400</td>
</tr>
<tr>
<td>Leukemia / Lymphoma (CAR-T)</td>
<td>23,000</td>
</tr>
<tr>
<td>Spinal Muscular Atrophy (SMA)</td>
<td>120</td>
</tr>
<tr>
<td>Multiple Myeloma</td>
<td>3,300</td>
</tr>
<tr>
<td>Hemophilia A</td>
<td>4,000</td>
</tr>
<tr>
<td>Bladder Cancer</td>
<td>13,700</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>52,370</strong></td>
</tr>
</tbody>
</table>

*US population currently estimated at 333 million
Non-malignant diseases taking center stage

- Aplastic anemia
- Immune deficiency
- Hemoglobinopathies
FDA Approves First Cell-Based Gene Therapy to Treat Adult and Pediatric Patients with Beta-thalassemia Who Require Regular Blood Transfusions: August 17, 2022

Zynteglo is a one-time gene therapy product administered single dose. Each dose of Zynteglo → customized treatment created using the pt’s own bone marrow stem cells, genetically modified to produce functional beta-globin

Zynteglo is cleared for transfusion-dependent beta thalassemia, but will come at a cost of $2.8 million per patient.
Gene Therapy is here to stay
Abst #11: Lovo-cel (bb1111) Gene Therapy for Sickle Cell Disease, Walters et al

• Lovo-cel (bb1111; LentiGlobin for sickle cell disease [SCD]) gene therapy (GT) uses auto HCT of HSPC transduced with the BB305 lentiviral vector, coding for modified β-globin gene, →sickling hemoglobin (Hb), HbAT87Q

• Eligibility: SS pts, aged 12-50, recurrent vaso-occlusive episodes

• Results- 35 pts highlighted (Gr C), med f/u 20.9 mos
Abst #11: Lovo-cel (bb1111) Gene Therapy for Sickle Cell Disease, Walters et al

Gene therapy for SS disease will also be costly.
Lymphoma advances

- Mantle cell
- Primary CNS lymphoma
Mantle cell lymphoma

• Accounts for approximately 4-6% of NHL
• Median age at diagnosis: 63-68 yrs
• Improvement in outcomes in past 10-20 yrs
  • 10-20 yrs ago, median survival was 2-3 yrs
  • now can expect 7-10 yr first remission in younger patients with low/intermediate risk disease by MIPI score
Evolution of First-line Induction Therapy For Younger MCL Patients

- Regimens involving R-CHOP-like therapy combined with R-AraC, consolidation with auto-HCT
  - Nordic, R-CHOP/R-DHAP, CALGB 59909;
  - median PFS of 5 – 9 yrs.

- Several novel induction regimens under evaluation
  - Len/Rituximab; RBAC; Benda/Rituximab +/- Bortezomib (E1411); others
  - Some of these regimens produce high (>70-80%) rates of MRD-negativity

- However, unclear whether auto-HCT confers survival benefit, especially after highly active modern induction regimens
Nordic MCL2 trial update: six-year follow-up after intensive immunochemotherapy for untreated mantle cell lymphoma followed by BEAM or BEAC + autologous stem-cell support: still very long survival but late relapses do occur

![Graph showing survival rates](http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2141.2012.09174.x/full#bjh9174-fig-0004)
Prognostic importance of MRD in MCL
CALGB 59909

Kaplan et al, ASH 2015, #337

N = 47 with MRD data (out of 151)
Maintenance rituximab after ASCT: LYMA

- N=299 enrolled
- 257 (86%) got AutoHCT
- 238 (80%) randomized
- Median f/u 52 mo after randomization

- 4 yr PFS 83% for maint rituximab arm (vs 64% for obsv)
- 4 yr OS
  - 89% (rituximab) vs 80% (obsv)
- Now SOC at most centers

LeGouill et al, NEJM 2017
Mantle cell lymphoma – role of autoHCT

• Despite improved PFS, unclear if intensive therapy actually *improves survival*
  • patient selection bias as to who gets intensive therapy
  • other improvements in care over time have occurred
  • Remains an *area of controversy in the field* with some respected lymphoma experts not recommending up front autoHCT

• Many MCL pts are at upper age limit for intensive therapy and therefore at high risk of toxicities

• **Ideal population to develop a “risk-adapted” approach**
  • Identify those most likely to benefit from intensive treatment and spare the others the risk/ toxicities
Step 0
- Submit diagnostic tissue for molecular testing
- Any induction regimen
- Enroll before, during, or after induction

Clonal Marker Present?
- Yes
  - Post-induction restaging + Submission of blood for MRD assessment
  - MRD-neg CR
  - MRD-neg PR or MRD-pos CR

- No
  - No informative marker: MRD indeterminate

Stratify:
- MIPI-c
- Intensive vs non-intensive induction

Step 1
- Arm A Auto-HCT + Rituximab x 3 years
- Arm B Rituximab x 3 years
- Arm C Auto-HCT + Rituximab x 3 years
- Arm D Auto-HCT + Rituximab x 3 years

ECOG-ACRIN
cancer research group
Reshaping the future of patient care
ASH Abstr #1: Efficacy & Safety of Ibrutinib Combined with Standard 1st-line Rx or Substitute for Autologous HCT in Younger Patients with Mantle Cell Lymphoma: Randomized Triangle Trial By the European MCL Network, Dreyling et al.

- Randomized, open-label, 3-arm TRIANGLE trial to evaluate addition of ibrutinib to SOC (arm A+I) in comparison to the previous SOC (arm A) and an ibrutinib containing treatment without ASCT (arm I)
- Untreated, advanced stage II-IV MCL, up to 65 years
- Study treatment: 3 cycles R-CHOP/R-DHAP without (arm A) or with ibrutinib added to R-CHOP and 2 years maintenance (arms A+I, I). ASCT planned for responding pts of arms A and A+I. Rit maintenance applied according to national guidelines in all responding patients irrespective of the trial arm [A (n=288), A+I (n=292), and I (n=290)]
ASH Abstr #1: Efficacy & Safety of Ibrutinib Combined with Standard 1st-line Rx or Substitute for Autologous HCT in Younger Patients with Mantle Cell Lymphoma: Randomized Triangle Trial By the European MCL Network, Dreyling et al.
Primary CNS lymphoma-ChemoimmuneRX vs HDC & autoHCT (MATRix trial, Illerhaus et al, ASH LBA)

Open label, randomized, multicenter Ph III
Eligibility: new dx PCNSL, up to age 70, HIV-,

Induction: MATRix x 4. Pts with PR or better → 2 cycles R-DeVIC* vs BCNU/Thio + auto HCT

368 registered: 260 completed induction (75%), 229 randomized

After induction→ 27% CR, 52% PR
After consolidation→ R-DEVIC 65%, HCT 68% CR

PFS at 3 yrs: 53% vs 79 % (p=.0003)
OS at 3 yrs: 71% vs 86% (p = .01) HR = .42
Neurocognitive assessment- No difference in arms

*R-DeVIC regimen (375 mg/m² Rit day 0; dexamethasone 40 mg/d days 1 to 3; etoposide 100 mg/m²/d days 1 to 3; ifosfamide 1500 mg/m²/d days 1 to 3; carboplatin 300 mg/m² day 1)
Myeloma
Does ASCT improve outcomes for New Dx MM patients receiving triplet induction (RVd) and lenalidomide maintenance until disease progression?

- ASCT with HD melphalan is a SOC for transplant-eligible NDMM patients
- Optimal use of induction therapy, ASCT, maintenance in transplant-eligible NDMM patients continues to evolve
  - Triplet induction regimens are highly efficacious, with high response rates, high rates of MRD-negative responses, and prolonged clinical benefit
  - Long-term maintenance therapy with lenalidomide also improves outcomes through prolonged disease control
- In this context, how much does first-line ASCT enhance efficacy in NDMM, and can its use be delayed in selected patients?

ASCT, autologous stem cell transplantation; HD, high-dose; MRD, minimal residual disease; NDMM, newly diagnosed multiple myeloma; RVd, lenalidomide, bortezomib, dexamethasone.

DETERMINATION: Delayed vs Early Transplant with Revlimid Maintenance and Antimyeloma Triple Therapy

Randomization (N=722)

Stratified by:
- ISS disease stage
- Cytogenetic risk

Arm A: RVd-alone (N=357)

Arm B: RVd+ASCT (N=365)

RVd cycle 1 (N=729)

Each RVd cycle (21 days):
- R 25 mg/day PO, days 1-14
- V 1.3 mg/m² IV/SC, days 1, 4, 8, 11
- Dex 20/10 mg PO, days 1, 2, 4, 5, 8, 9, 11, 12

Induction ± ASCT + consolidation treatment duration = ~6 months

Lenalidomide maintenance
- Months 1-3: 10 mg/day
- Month 4 onwards: 15 mg/day

RVd cycles 2-3

Stem cell collection

RVd cycles 4-8

Melphalan 200 mg/m² + ASCT (N=310)

RVd cycles 4-5

Stem cell collection

R maintenance (N=291)

R maintenance (N=289)

Primary endpoint: PFS

Secondary endpoints: response rates; DOR; TTP; OS; QoL; safety

d/Dex, dexamethasone; DOR, duration of response; ISS, International Staging System; IV, intravenous; PO, orally; R, lenalidomide; SC, subcutaneous; TTP, time to progression; V, bortezomib
Primary endpoint: Progression-free survival (PFS)

<table>
<thead>
<tr>
<th></th>
<th>Events* – no. (%)</th>
<th>Median PFS, months (95% CI)</th>
<th>5-year PFS, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RVd-alone</td>
<td>189 (52.9%)</td>
<td>46.2 (38.1–53.7)</td>
<td>41.5 (35.7–47.2)</td>
</tr>
<tr>
<td>RVd+ASCT</td>
<td>139 (38.1%)</td>
<td>67.5 (58.6–NR)</td>
<td>55.6 (49.4–61.3)</td>
</tr>
<tr>
<td>HR</td>
<td>1.53 (1.23–1.91)</td>
<td></td>
<td>p&lt;0.0001</td>
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Patients at risk

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<tr>
<th></th>
<th>0</th>
<th>12</th>
<th>24</th>
<th>36</th>
<th>48</th>
<th>60</th>
<th>72</th>
<th>84</th>
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<tbody>
<tr>
<td>RVd-alone</td>
<td>357</td>
<td>250</td>
<td>187</td>
<td>160</td>
<td>126</td>
<td>96</td>
<td>60</td>
<td>40</td>
</tr>
<tr>
<td>RVd+ASCT</td>
<td>385</td>
<td>276</td>
<td>226</td>
<td>191</td>
<td>160</td>
<td>118</td>
<td>77</td>
<td>42</td>
</tr>
</tbody>
</table>

CI, confidence interval; HR, hazard ratio; Data cutoff: 12/10/21. *PFS events: disease progression or death.
PFS by stratification factor – cytogenetic risk

<table>
<thead>
<tr>
<th>Patients at risk</th>
<th>RVd-alone</th>
<th>RVd+ASCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>RVd-alone</td>
<td>68</td>
<td>36</td>
</tr>
<tr>
<td>RVd+ASCT</td>
<td>68</td>
<td>45</td>
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<th>Patients at risk</th>
<th>RVd-alone</th>
<th>RVd+ASCT</th>
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</thead>
<tbody>
<tr>
<td>RVd-alone</td>
<td>37 (56.1%)</td>
<td>28 (42.4%)</td>
</tr>
<tr>
<td>RVd+ASCT</td>
<td>37 (56.1%)</td>
<td>28 (42.4%)</td>
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<table>
<thead>
<tr>
<th>Median PFS, months</th>
<th>RVd-alone</th>
<th>RVd+ASCT</th>
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<tbody>
<tr>
<td>High-risk</td>
<td>17.1</td>
<td>55.5</td>
</tr>
<tr>
<td>HR 1.99 (95% CI 1.21–3.26)</td>
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<table>
<thead>
<tr>
<th>Median PFS, months</th>
<th>RVd-alone</th>
<th>RVd+ASCT</th>
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<tbody>
<tr>
<td>Standard-risk</td>
<td>53.2</td>
<td>82.3</td>
</tr>
<tr>
<td>HR 1.38 (95% CI 1.07–1.79)</td>
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</table>

PRESENTED BY:
Paul G. Richardson, MD
## PFS by subgroup

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Median, months</th>
<th>HR (95% CI)</th>
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<tbody>
<tr>
<td><strong>All ITT analysis</strong></td>
<td></td>
<td>1.53 (1.23–1.91)</td>
</tr>
<tr>
<td><strong>Age</strong></td>
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<tr>
<td>&lt;60 years</td>
<td>47.3</td>
<td>1.49 (1.14–1.95)</td>
</tr>
<tr>
<td>≥60 years</td>
<td>46.5</td>
<td>1.59 (1.05–2.40)</td>
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<tr>
<td><strong>Sex</strong></td>
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<tr>
<td>Male</td>
<td>47.4</td>
<td>1.50 (1.11–2.02)</td>
</tr>
<tr>
<td>Female</td>
<td>45.3</td>
<td>1.54 (1.09–2.17)</td>
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<tr>
<td><strong>Race</strong></td>
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<tr>
<td>White/Caucasian</td>
<td>44.3</td>
<td>1.67 (1.29–2.15)</td>
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<tr>
<td>Black/African American</td>
<td>38.1</td>
<td>1.07 (0.61–1.89)</td>
</tr>
<tr>
<td>Other</td>
<td>NR</td>
<td>3.40 (1.00–11.5)</td>
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<tr>
<td><strong>ECOG</strong></td>
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<tr>
<td>0</td>
<td>56.7</td>
<td>1.32 (0.94–1.86)</td>
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<tr>
<td>1–2</td>
<td>37.5</td>
<td>1.72 (1.28–2.32)</td>
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<tr>
<td><strong>BMI</strong></td>
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<tr>
<td>&lt;25</td>
<td>33.6</td>
<td>2.60 (1.56–4.31)</td>
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<tr>
<td>25 to &lt;30</td>
<td>52.3</td>
<td>1.24 (0.86–1.80)</td>
</tr>
<tr>
<td>≥30</td>
<td>45.8</td>
<td>1.41 (0.98–2.02)</td>
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<td><strong>MM</strong></td>
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<tr>
<td>IgG</td>
<td>53.3</td>
<td>1.25 (0.93–1.67)</td>
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<tr>
<td>IgA</td>
<td>46.5</td>
<td>2.31 (1.43–3.74)</td>
</tr>
<tr>
<td>Light chain</td>
<td>23.3</td>
<td>2.33 (1.14–4.74)</td>
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<tr>
<td><strong>ISS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>52.0</td>
<td>1.83 (1.32–2.54)</td>
</tr>
<tr>
<td>II</td>
<td>46.2</td>
<td>1.38 (0.96–1.96)</td>
</tr>
<tr>
<td>III</td>
<td>40.3</td>
<td>1.14 (0.64–2.01)</td>
</tr>
<tr>
<td><strong>LDH</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not elevated (&lt;225 U/L)</td>
<td>47.7</td>
<td>1.45 (1.12–1.88)</td>
</tr>
<tr>
<td>Elevated (≥225 U/L)</td>
<td>41.1</td>
<td>1.77 (1.09–2.88)</td>
</tr>
<tr>
<td><strong>FISH</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High risk</td>
<td>17.1</td>
<td>1.99 (1.21–3.26)</td>
</tr>
<tr>
<td>t(4;14)</td>
<td>19.8</td>
<td>2.72 (1.19–6.24)</td>
</tr>
<tr>
<td>Del(17p)</td>
<td>16.3</td>
<td>1.44 (0.76–2.73)</td>
</tr>
<tr>
<td>Standard risk</td>
<td>53.2</td>
<td>1.38 (1.07–1.79)</td>
</tr>
<tr>
<td><strong>R-ISS</strong></td>
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</tr>
<tr>
<td>I</td>
<td>59.1</td>
<td>1.38 (0.90–2.12)</td>
</tr>
<tr>
<td>II</td>
<td>40.9</td>
<td>1.63 (1.22–2.19)</td>
</tr>
<tr>
<td>III</td>
<td>22.2</td>
<td>0.96 (0.43–2.13)</td>
</tr>
</tbody>
</table>
Key secondary endpoint: Overall survival (OS)

Median follow-up 76.0 months

<table>
<thead>
<tr>
<th>Time from randomization (months)</th>
<th>Probability of survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.0</td>
</tr>
<tr>
<td>12</td>
<td>0.95</td>
</tr>
<tr>
<td>24</td>
<td>0.88</td>
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<tr>
<td>36</td>
<td>0.78</td>
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<td>48</td>
<td>0.68</td>
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<tr>
<td>60</td>
<td>0.58</td>
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<tr>
<td>72</td>
<td>0.48</td>
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<tr>
<td>84</td>
<td>0.38</td>
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<table>
<thead>
<tr>
<th>Patients at risk</th>
<th>RVd-alone</th>
<th>RVd+ASCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time from randomization (months)</td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>RVd-alone</td>
<td>357</td>
<td>332</td>
</tr>
<tr>
<td>RVd+ASCT</td>
<td>365</td>
<td>353</td>
</tr>
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</table>

Events – no. (%) | 5-year OS, % | HR (adjusted CI*) |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>RVd-alone</td>
<td>90 (25.2%)</td>
<td>79.2</td>
</tr>
<tr>
<td>RVd+ASCT</td>
<td>88 (24.1%)</td>
<td>80.7</td>
</tr>
</tbody>
</table>

Data cutoff: 12/10/21

Presented by: Paul G. Richardson, MD

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What are we doing today?
US SWOG / BMT CTN Myeloma Trial

S1803: Phase III Study of Daratumumab (NSC-791647) + Lenalidomide (LD) or Lenalidomide (L) as Post-Autologous Stem Cell Transplant Maintenance Therapy in Patients with Multiple Myeloma (MM) Using Minimal Residual Disease to Direct Therapy Duration (DRAMMATIC Study)

Diagram:
- Registration/Enrollment (prior to ASCT)
  - ASCT per Institutional/PI discretion
  - Randomization (within 180 days post-ASCT)
    - Lenalidomide
    - Lenalidomide + Daratumumab
  - Continue for 2 years of Therapy
    - Assess MRD
      - MRD Negative
        - 2nd randomization
          - Continue L
          - Stop L
      - MRD Positive
        - 2nd randomization
          - Continue L
          - Stop LD
          - Continue LD
      - MRD Negative
        - Continue LD
      - MRD Positive
        - Continue LD
  - Follow until progressive disease
    - Off Protocol Therapy (Patients followed for Overall Survival (4 years))
Primary objective: To compare the overall survival (OS) between the two treatment arms.

Major Secondary Objectives of First Randomization (LD vs. L):

- To compare the best overall response rate (ORR), including partial remission (PR), very good partial remission (VGPR), and complete remission (CR, sCR) in the subset of patients not in PR at baseline (baseline is study entry pre HCT).
- To compare progression free survival (PFS) between the study arms, and to report these findings once PFS data are mature and the study accrual has been completed.
- To compare MRD-negativity on the two treatment arms at maintenance initiation, and at 24 months and 36 months post maintenance.
- To compare toxicities and tolerability of long term therapy between the study arms.

Primary Objectives of the Second Randomization:

- To compare progression free survival (PFS) between MRD negative patients randomized to indefinite L vs. discontinued L from the time of second randomization.
- To compare progression free survival (PFS) between MRD negative patients randomized to indefinite LD vs. discontinued LD from time of second randomization.
Myeloma: SOC remains $\Rightarrow$ AutoHCT early after induction therapy

- What’s next? Advanced auto HCT trials
- Master trial – Dara+KRD $\rightarrow$ MRD driven RX
- Griffin trial – Ph II VRD vs Dara + VRD $\rightarrow$ HCT $\rightarrow$ DR maint
  - 36-month PFS & OS rates were 78.1% and 93.8%, respectively
  - BUT STRINGENT CRs are being seen
Thoughts: allo HCT

• Still the mainstay of activity
• Major advances in the past half decade
• New grading scales- Minnesota/Ann Arbor aGVHD; NCI cGVHD
• FDA approvals for acute & chronic GVHD
  • Prophylaxis: Abatacept
  • Treatment: MSC, ruxolitinib in aGVHD; ibrutinib, ruxolitinib, belumosodil in cGVHD
GVHD:

- Many trials, limited success in new GVHD prophylaxis strategies over the past 3 decades
- Calcineurin inhibitor and MTX remained standard
- Other regimens equivalent outcomes- different toxicity profiles
- Previous 4 arm randomized phase II national trial- BMT CTN 1202: contemporary Tac/MTX vs Tac/MTX/Marivaroc vs Tac/MTX/Bortezomib vs Tac/MMF/ post HCT CTX
- Results: Tac/MMF/post HCT CTX appeared superior to marivaroc or bortezomib arms
- Phase III trial needed
GVHD prophylaxis with post-HCT CTX
cGVHD/Relapse-free Survival

• Good approximation to the endpoint of interest
current GVHD (or IS)/relapse-free survival at 1 year.

• Time to event composite endpoint:
  – Event = cGVHD, relapse or death

• Assumptions
  – aGVHD would have resolved by 1 year (either resulting in death, withdrawal of IS or progression to cGVHD)
  – Patients who developed cGVHD are still on IS at 1 year
At one yr, no difference in relapse rates, degree of chimerism, graft failure rates or OS.
Number of Haploidentical Donor# HCTs in the US in Recipients Aged ≥18 Years by Graft Source

Includes all mismatched related donors; Abbreviations - BM: Bone marrow; PB: Peripheral blood
Orca-T is a high-precision, immunotherapy allograft; Day 0 → CD34+ stem cells & Tregs; Day 2 → Tcon
Then Single agent GVHD proph with Tac or Siro
Total treated: n =180
127 subjects > 180 days f/u

Results: Case match contemporary control with CIBMTR cases from 2016-2018; Tac/ MTX only

Early engraftment – D13 neutrophils; D16 platelets
Low severe (Gr III) infections 11%

GRFS @ 18 months 69%
OS @ 18 months 86%
Abstr. # 4865
Estimating the Lifetime Medical Cost Burden of an Allogeneic Hematopoietic Cell Transplantation Patient and the Value of Addressing the Unmet Need, Maziarz et al

*Scenario 2 resulted in $479,297 of additional value due to chronic GVHD (versus $263,944 in Scenario 1) offsets for a total net monetary value of $911,062.

Scenario 1 modeled as doubled improvement in GRFS (69% GRFS in year 1 as opposed to 34%) with 15% of chronic GVHD patients remaining on treatment after two years.

Scenario 2 modeled as doubled improvement in GRFS (69% GRFS in year 1 as opposed to 34%) with 39% of chronic GVHD patients remaining on treatment after two years.
OHSU PT: Relapsed, Refractory DLBCL- post auto HCT
Baseline       Day 30       Day 90
Approved CAR-T Products & Indications

• R/R DLBCL- 3rd line- Tisagenlecleucel, Axicabtagene, Lisocabtagene
• R/R DLBCL- 2nd line- Axicabtagene
• R/R Follicular Lymphoma- 3rd line Axicabtagene
• Mantle cell lymphoma- Brexucabtagene
• Pediatric/young adult ALL- > 2nd line- Tisagenlecleucel
• Adult ALL- Brexucabtagene
• Myeloma- Beyond 4th line- Idecabtagene, Ciltacabtagene
• R/R – 2nd line- Lisocabtagene
• R/R Follicular Lymphoma- Tisagenlecleucel

Anticipated 2023- TIL for Advanced Melanoma- Lifileucil
CAR- T cell therapy: who & when
Age & Outcome of HCT for Older Patients With AML in CR1 or MDS, McClune et al, JCO 2010
Increasing use of allogeneic hematopoietic cell transplantation in patients aged 70 years and older in the United States, Muffly et al, Blood, 2017
Who?

Abstr # 2024: CAR T outcomes and age, Mirza et al

CIBMTR analysis
Retrospective
Real World
N = 1916 adults
Axicabtagene- 1438; Tisagenlecleucel- 481
Median age – 63 (range: 18-91)

<table>
<thead>
<tr>
<th>CRS</th>
<th>18-54 years</th>
<th>55-64 years</th>
<th>65-74 years</th>
<th>75+ years</th>
<th>18-54 years</th>
<th>55-64 years</th>
<th>65-74 years</th>
<th>75+ years</th>
</tr>
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<tbody>
<tr>
<td>0.3933</td>
<td>0.821</td>
<td>1.031</td>
<td>0.914</td>
<td>0.100</td>
<td>0.606</td>
<td>1.113</td>
<td>0.762</td>
<td>1.396</td>
</tr>
</tbody>
</table>

CIBMTR

Overall Survival

Progression-Free Survival

Adjusted Probability %

100  
10  
0  

Years

1  
2  

18-54 years 55-64 years 65-74 years 75+ years
When-Paradigm shift?
CAR T for first relapse DLBCL w/in 12 months of 1⁰ therapy
CORAL trial data

60% of early relapse do not respond to 1st salvage
- If respond & proceed to autoSCT, then 3 yr EFS = 39%

Gisselbrecht, JCO, 2010
Axicabtagene ciloleucel vs chemo/auto HCT for first & early relapse of DLBCL

Locke et al, NEJM, 2022
ASH #655: Liso-cel vs SOC for second line rx for R/R DLBCL: Transform study, update, Abramson et al.

N = 184 randomized; 92 / arm
CAR T arm- bridging/ CAR T
SOC- chemo x 3 → autoHCT

CR: 74 vs 43%-- CAR T vs SOC
PFS: Not reached @ 12.6 mos vs 6.2 mos

Of 91 pts on SOC arm, 67% cross over to Lisocel

Conclusion: with med f/u 17.5 months, Stat signif increase in EFS, CR and PFS.
Second line CAR T for R/R DLBCL is new SOC

• Clinical Considerations:
  • In randomized trials → CAR T is superior to chemo/auto HCT. Was not compared to auto HCT. If one treats with chemo intervention → PR or better, auto HCT still can be beneficial
  • Only applies to pts who relapse within 12 mos of completing R-CHOP or equivalent
  • Axicabtagene and Lisocabtagene met endpoints. Tisagenlecleucel in a similar, but significantly different designed trial, did not.
  • Different products have subtle differences in FDA label guiding choice
  • Apheresis before chemotherapy salvage may be ideal. Early referral is beneficial to all
Salvage therapy can impact CAR T outcomes: Iacoboni et al, ASH #658

Retrospective, multicenter study
Commercial CAR T products
N=370

Bendamustine treated N= 74
Characteristics: older, higher ECOG score

Results: Benda cohort → lower & delayed CART expansion
Lower central & effector Tmem
CR rates: recent benda vs late benda → 45 vs 67%
PFS rates: recent benda vs late benda → 1.5 vs 7.1 mos
How to improve on outcomes?
Potential trial candidates

There is an internal message: WORK IS NOT DONE
CAR T still does not cure all!!!!!
Patient Identified for Commercial CAR-T LD chemo and CAR-T infusion 1st imaging response (Day +30)

PR/SD PD

ARM 1: Mosunetuzumab
ARM 4: Observation

Treatment per discretion of treating MD

ARM 2: Polatuzumab
ARM 3: Mosun + Pola

Step 2 Post-CAR (Treatment) registration: for patients w/ SD and PR only

Step 1 (Pre-CAR) registration

• Day 30 PET-CT will be centrally reviewed (72 hours turn around time) – response criteria per Lugano
• Treatment vs observation (1:1:1:1 randomization)
• 1 year PFS: 20.0% (observation) vs 44.7% (consolidation) \( \rightarrow \) 120 patients (30 per arm)

For Arm D (observation arm) only: 
\( \rightarrow \) Will be eligible for Mosun+Pola combination upon relapse after randomization up until 1 year post CAR-T infusion

*Not a candidate for 2nd step treatment registration. Will be followed for response assessment and biomarker studies and survival.

*Not a candidate for 2nd step treatment registration. Will be followed for survival.
Other CAR T futures: New advances
Primary CNS lymphoma

Axicabtagene ciloleucel
Pilot study
N = 9
6/9 1o PCNSL
Mostly parenchymal
Prior therapies (1-6)
ORR- 86%
Evaluable at 3 months-all in CR

Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N (%)</th>
</tr>
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<tbody>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>4 (44)</td>
</tr>
<tr>
<td>Female</td>
<td>5 (56)</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
</tr>
<tr>
<td>Median (Range)</td>
<td>60 (33-74)</td>
</tr>
<tr>
<td>Primary v Secondary CNSL</td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>6 (67)</td>
</tr>
<tr>
<td>Secondary</td>
<td>3 (33)</td>
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<tr>
<td>Cell of Origin</td>
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<tr>
<td>GCB</td>
<td>1 (12)</td>
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<tr>
<td>Non-GCB</td>
<td>5 (56)</td>
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<tr>
<td>Unknown</td>
<td>3 (33)</td>
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<tr>
<td>DLB/LH</td>
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<td>Yes</td>
<td>0 (0)</td>
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<tr>
<td>No</td>
<td>6 (67)</td>
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<tr>
<td>Unknown</td>
<td>3 (33)</td>
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<tr>
<td>Double Expresor</td>
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<tr>
<td>Yes</td>
<td>1 (13)</td>
</tr>
<tr>
<td>No</td>
<td>4 (44)</td>
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<tr>
<td>Unknown</td>
<td>2 (22)</td>
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<tr>
<td>Tumor Location</td>
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<tr>
<td>Parenchymal only</td>
<td>8 (89)</td>
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<td>Leptomeningeal only</td>
<td>6 (69)</td>
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<tr>
<td>Both</td>
<td>1 (11)</td>
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<tr>
<td>Ocular</td>
<td>1 (11)</td>
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<td>CSF cytology positive</td>
<td>4 (44)</td>
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<tr>
<td>Tumor location</td>
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<tr>
<td>N=1</td>
<td>2 (1-5)</td>
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<tr>
<td>Number or prior systemic therapies</td>
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<tr>
<td>Median (Range)</td>
<td>2 (1-6)</td>
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<tr>
<td>Disease status to last line of therapy</td>
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<tr>
<td>Relapsed</td>
<td>4 (44)</td>
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<tr>
<td>Refractory</td>
<td>5 (56)</td>
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<td>Time from CNSL diagnosis to enrollment</td>
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<tr>
<td>Days (range)</td>
<td>281 (121-8666)</td>
</tr>
<tr>
<td>Time from last therapy to enrollment</td>
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<tr>
<td>Days (range)</td>
<td>57 (16-302)</td>
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</table>

Figure 1. Swimmer Plot of Response to Axi-cel Over Time

CR: complete response; uCR: unconfirmed complete response; PR: partial response; SD: stable disease (SD); PD: progressive disease
Abstr: 2023
DVRd Followed By Ciltacabtagene Autoleucel Versus DVRd Followed By ASCT in Patients with Newly Diagnosed Multiple Myeloma Who Are Transplant Eligible: A Randomized Phase 3 Study (EMagine/CARTITUDE-6)

Novel trial ➔ future studies that may change the standard of care
1:1 randomization

1º endpoints:
- PFS
- Sustained MRD neg state > 12 mos

Key 2º endpoints:
- ORR
- CR rate
- OS
- AEs
- QOL
Thanks for listening!

Memorial Day weekend, 2022- Commissioning of the USS Oregon