Updates from the American Society of Hematology Annual Meeting 2019: Part I

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Faculty Disclosure

- I have no pertinent disclosures
- Off-label and non-FDA approved medications will be discussed

Objectives

- Describe relevant data and research in hematopoietic cell transplantation (HCT) and cellular therapy presented at the 2019 American Society of Hematology (ASH) Meeting
- Identify significant advances in hematology anticipated to impact HCT and cellular therapy clinical practice
- Select an evidence-based treatment plan for a patient based on the data presented at the 2019 ASH meeting
ASH 61st Annual Meeting & Exposition

- December 7 – 10, 2019 in Orlando, Florida

- Program highlights
  - Educational sessions: > 30
  - Oral abstracts: > 1,000
  - Poster presentations: > 3,800

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Program Highlights

- Acute GVHD
  - Abstracts 39, 367, 368, 369

- Chronic GVHD
  - Abstract 872

- AML HCT Outcomes
  - Abstract 264

- HCT Complications
  - Abstract 40

- HCT Conditioning
  - Abstracts 42, 258

- AML (Pre-HCT)
  - Abstract 260

- CAR-T (non-MM)
  - Abstracts 199, 243, 245, 780

- CAR-T (MM)
  - Abstract 204

- NHL/ALL-related (Post-HCT)
  - Abstract 778

- PD-1
  - Abstract 775

- NHL HCT Outcomes
  - Abstract 319

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ALL, acute lymphoid leukemia; AML, acute myeloid leukemia; CAR-T, chimeric antigen receptor T-cell; GVHD, graft versus host disease; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; PD-1, programmed death-1
39 Pre-Transplant Serum Claudin-3 Predicts Intestinal Graft-Versus-Host Disease and Non-Relapse Mortality-Host after Allogeneic Hematopoietic Cell Transplantation

Background and Objective

- GI acute GVHD
  - Difficult to identify patients at risk
  - Intestinal damage
  - Chemotherapy
  - Infections

- Biomarkers: ST2/REG3a/TNFR1
  - At onset of symptoms
  - Post HCT

- Determine association of serum pre-HCT biomarkers on GI GVHD and 1-year NRM

- Gut barrier
  - REG3a, citrulline, claudin-3, EGF, lipopolysaccharide

- Inflammation
  - AREG, ST2, TIM-3

- Patients undergoing first allogeneic HCT (N=528) from 2010-2018

Results

<table>
<thead>
<tr>
<th>Patient Demographics</th>
<th>Frequency (%)</th>
<th>Patient Demographics</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>323 (61%)</td>
<td>Female</td>
<td>195 (39%)</td>
</tr>
<tr>
<td>Median age (range), IQR</td>
<td>41 (&lt;75, 11-60)</td>
<td>Low risk</td>
<td>40 (9%)</td>
</tr>
<tr>
<td>Source</td>
<td></td>
<td>Intermediate risk</td>
<td>281 (53%)</td>
</tr>
<tr>
<td>Marrow</td>
<td>140 (27%)</td>
<td>High risk</td>
<td>58 (11%)</td>
</tr>
<tr>
<td>PBSC</td>
<td>149 (29%)</td>
<td>Very high risk</td>
<td>5 (1%)</td>
</tr>
<tr>
<td>UCB</td>
<td>239 (46%)</td>
<td>Non-malignant</td>
<td>140 (27%)</td>
</tr>
<tr>
<td>Conditioning</td>
<td></td>
<td>HCT-CI</td>
<td></td>
</tr>
<tr>
<td>MAC TBI</td>
<td>169 (32%)</td>
<td>0</td>
<td>261 (49%)</td>
</tr>
<tr>
<td>MAC non-TBI</td>
<td>73 (14%)</td>
<td>1-2</td>
<td>145 (27%)</td>
</tr>
<tr>
<td>RIC/NMA</td>
<td>286 (54%)</td>
<td>3+</td>
<td>122 (23%)</td>
</tr>
</tbody>
</table>

DRI, disease risk index; HCT-CI, hematopoietic cell transplant – comorbidity index; IQR, interquartile range; MAC, myeloablative; NMA, nonmyeloablative; PBSC, peripheral blood stem cell; RIC, reduced intensity; TBI, total body irradiation.


Results

<table>
<thead>
<tr>
<th>Factors</th>
<th>GI GVHD: Odds Ratio</th>
<th>NRM: Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>NA</td>
<td>1.04</td>
</tr>
<tr>
<td>ST2</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>EGF</td>
<td>NA</td>
<td>0.99</td>
</tr>
<tr>
<td>AREG</td>
<td>0.99</td>
<td>NA</td>
</tr>
<tr>
<td>Claudin-3</td>
<td>1.16</td>
<td>1.38</td>
</tr>
<tr>
<td>TIM-3</td>
<td>NA</td>
<td>1.59</td>
</tr>
<tr>
<td>Citrulline</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>AREG/EGF</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

GI GVHD cut-off: 24.5 pg/ml
- 37% (28% - 39%) if >
- 18% (13% - 26%) if < (P<.01)

NRM cut-off: 27.1 pg/ml
- 34% (17% - 21%) if >
- 12% (8% - 18%) if < (P<.01)

Factors associated with Claudin-3:
- Female, age <50 years, (DRI) non-malignant, HCT-Ci 0

Patients with high pre-HCT serum Claudin-3 may benefit from intestinal barrier-focused supportive care

Background

- Acute GVHD limits benefit of allogeneic HCT
- Day 28 response predicts NRM
- Biomarkers can predict outcomes
  - Amphiregulin
  - TIM-3
  - ST2
  - REG3a

- Be validated response biomarker for GVHD
- MAP algorithm (ST2/REG3a)
  - Identified patients for severe GVHD
  - Used in predicting probability of high-risk
  - Low-risk

- Could change in MAP after 28 days of treatment predict NRM?
- Treatment of acute GVHD: N=615
  - Training cohort n=248 → Develop
  - Validation cohort n=367 → Test

367 The MAGIC Algorithm Probability (MAP): A Novel Laboratory Biomarker for the Response to Treatment of Acute Graft-Versus-Host Disease

Srinagesh H.
Patients who experienced 6 mo NRM

Patients who did not experience 6 mo NRM

MAP >0.290 = worse OS than if MAP <0.290

Predicting NRM (accuracy)
— Day 28 MAP > than clinical response (p<.0001)
— Clinical response + biomarkers = MAP

Predicts NRM in clinical responders
— High MAP worse NRM than low MAP (49% vs 12%, p<0.0001)

Predicts NRM in non-clinical responders
— High MAP worse NRM than low MAP (85% vs 24%, p<0.0001)

Conclusion

1st validated algorithm acting as a response biomarker for acute GVHD treatment
— Predicts more accurately than day-28 clinical response

Unknown if predicts response to novel therapies

Feasibility outside of a clinical trial?

Cost?
Background

- **IL-6**
  - Produced in many cell types
  - Signals via IL-6 receptor/gp130 heterodimer
  - Highly inflammatory
  - Mediates GVHD via Th17 pathway
- **Tocilizumab**
  - Anti-IL-6 receptor monoclonal antibody

Endpoints

- **Primary objective**
  - Determine efficacy in preventing grade II-IV acute GVHD at day +100

Design

- **Patients**
  - ALL, AML, MDS, CMML
- **Donors**
  - 8/8 HLA (A, B, C, DR) MSD or MUD
- **MAC Conditioning**
  - Cy/TBI or Bu/Cy
- **RIC Conditioning**
  - Fludara

- **PSSC**
- **GVHD prophylaxis**
  - CSA 140-300 ng/dL starting day -1 through day +100
  - MTX 15 mg/m² IV days +1, then 10 mg/m² days +3, +6, +11
- **Study drug:** tocilizumab or placebo
  - Tocilizumab 8 mg/kg (max 800 mg) IV over 60 minutes on day -1

CSA, cyclosporin; HLA, human leukocyte antigen; IL-6, interleukin 6; MDS, myelodysplastic syndrome; MSD, matched sibling donor; MUD, matched unrelated donor; PBSC, peripheral blood stem cell; PFS, progression free survival; OS, overall survival; TRM, transplant related mortality; TBI, total body irradiation; Bu, busulfan; CMML, chronic myelomonocytic leukemia; Cy, cyclophosphamide; Fludara, fludara; N, number; AML, acute myeloid leukemia; MSC, mesenchymal stem cell; RIC, reduced intensity conditioning; TCT, Center for T cell Therapy; TCR, T cell receptor; TMA, targeted molecular analysis.
## Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo</th>
<th>Tocilizumab</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>73</td>
<td>72</td>
<td></td>
</tr>
<tr>
<td>Age, median (years)</td>
<td>51 (19-68)</td>
<td>52 (28-61)</td>
<td>0.9</td>
</tr>
<tr>
<td>Male (%)</td>
<td>43 (59)</td>
<td>38 (53)</td>
<td>0.55</td>
</tr>
<tr>
<td>Disease (%)</td>
<td></td>
<td></td>
<td>0.12</td>
</tr>
<tr>
<td>AML</td>
<td>39 (54)</td>
<td>44 (61)</td>
<td></td>
</tr>
<tr>
<td>ALL</td>
<td>19 (26)</td>
<td>10 (14)</td>
<td></td>
</tr>
<tr>
<td>MDS</td>
<td>14 (19)</td>
<td>13 (19)</td>
<td></td>
</tr>
<tr>
<td>CMML</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td></td>
</tr>
<tr>
<td>Disease status (%)</td>
<td></td>
<td></td>
<td>0.84</td>
</tr>
<tr>
<td>CR1</td>
<td>64 (88)</td>
<td>63 (88)</td>
<td></td>
</tr>
<tr>
<td>&gt;CR1</td>
<td>4 (5)</td>
<td>7 (10)</td>
<td></td>
</tr>
<tr>
<td>Untreated (MDS)</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td></td>
</tr>
<tr>
<td>Conditioning (%)</td>
<td></td>
<td></td>
<td>0.95</td>
</tr>
<tr>
<td>Cy/TBI</td>
<td>24 (33)</td>
<td>20 (27)</td>
<td></td>
</tr>
<tr>
<td>Bu/Cy</td>
<td>9 (12)</td>
<td>9 (12)</td>
<td></td>
</tr>
<tr>
<td>Flu/Mel</td>
<td>40 (55)</td>
<td>41 (55)</td>
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</tr>
<tr>
<td>CMV status (%)</td>
<td></td>
<td></td>
<td>0.81</td>
</tr>
<tr>
<td>D+/R+</td>
<td>30 (41)</td>
<td>25 (32)</td>
<td></td>
</tr>
<tr>
<td>D+/R</td>
<td>10 (14)</td>
<td>9 (12)</td>
<td></td>
</tr>
<tr>
<td>D-</td>
<td>19 (26)</td>
<td>18 (24)</td>
<td></td>
</tr>
<tr>
<td>D- R+</td>
<td>14 (19)</td>
<td>17 (22)</td>
<td></td>
</tr>
</tbody>
</table>

Source: Kennedy GA. Blood. 2019;134:368. CR, complete response; D, donor; R, recipient

## Results

### Acute GVHD II-IV

<table>
<thead>
<tr>
<th>Time</th>
<th>Placebo</th>
<th>Tocilizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day +100</td>
<td>36%</td>
<td>27% (p=0.23)</td>
</tr>
<tr>
<td>MUD: Day +100</td>
<td>48%</td>
<td>32% (p=0.16)</td>
</tr>
<tr>
<td>MUD: Day +180</td>
<td>48%</td>
<td>32% (p=0.13)</td>
</tr>
</tbody>
</table>

### Acute GVHD III-IV

<table>
<thead>
<tr>
<th>Time</th>
<th>Placebo</th>
<th>Tocilizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day +100</td>
<td>13%</td>
<td>14% (p=0.93)</td>
</tr>
<tr>
<td>MUD: Day +100</td>
<td>10%</td>
<td>14% (p=0.59)</td>
</tr>
</tbody>
</table>

### Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Placebo</th>
<th>Tocilizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRM</td>
<td>8%</td>
<td>11% (p=0.56)</td>
</tr>
<tr>
<td>PFS</td>
<td>25%</td>
<td>33% (p=0.24)</td>
</tr>
<tr>
<td>OS</td>
<td>79%</td>
<td>71% (p=0.31)</td>
</tr>
</tbody>
</table>

Engraftment
- Neutrophil: 15 (11-24) vs 18 (9-35) (p=0.01)
- Platelet: 16 (8-36) vs 19 (11-389) (p=0.02)

No difference in grade 3 liver toxicity or grade 2 infections

## Conclusions

- Tocilizumab prophylaxis combined with CSA/MTX - Does NOT reduce grade II-IV acute GVHD - Trend in reduction at day +100 and day +180
- Grade III-IV acute GVHD was not reduced
- Neutrophil and platelet engraftment was delayed with addition of tocilizumab
- HCT-related outcomes (TRM, PFS, OS) were not improved
- Underpowered
- Influence of conditioning and immunosuppression combination unknown
- GVHD treatment - Steroid refractory GvHD
- Underpowered

369 Sirolimus Combined with Cyclosporine (CSP) and Mycophenolate Mofetil (MMF) As Graft-Vs-Host Disease (GVHD) Prophylaxis after Nonmyeloablative (NMA) Hematopoietic Cell Transplantation (HCT) Using HLA Class I or Class II Antigen Mismatched Donors: Results from a Phase II Multi-Center Trial

Background

- Phase 1/2 multicenter single arm trial
  - Single antigen HLA Class I MMUD/MMRD PBSC HCT
  - FluTBI with CSA/MMF
- Grades II-IV acute GVHD: 69%
- Chronic GVHD: 41%
- NRM: 47%
- Relapse: 26%
- OS: 29%
- PFS: 28%

- Phase 3 multicenter trial
  - HLA 10/10 MUD PBSC HCT
  - FluTBI
  - CSA/MMF (standard)
  - CSA/MMF/Sirolimus (triplet)
- Grades II-IV acute GVHD: 52% vs. 26%
- Chronic GVHD: 8% vs. 2%
- 4-yr NRM: 32% vs. 16%
- 4-yr relapse: 27% vs. 25%
- 4-yr OS: 46% vs. 64%
- 4-yr PFS: 41% vs. 59%

Objectives

- Primary
  - Decrease acute GVHD grades II-IV to <70% after NMA HLA class I or class II MMRD or MMUD HCT
  - Single antigen mismatch at HLA A, B or C +/− class I allele level mismatch
  - Mismatched at allele level for 2 HLA class I loci
  - Mismatched at the antigen or allele level for any HLA DRB1 and/or DQB1
- Secondary
  - Evaluate NRM incidence at day +100
  - Evaluate acute GVHD grades III-IV incidence
Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (%, N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range)</td>
<td>63 (21-76)</td>
</tr>
<tr>
<td>Male</td>
<td>49 (64)</td>
</tr>
<tr>
<td>Class I</td>
<td>51 (67)</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
</tr>
<tr>
<td>AML</td>
<td>23 (30)</td>
</tr>
<tr>
<td>MDS/MPD</td>
<td>20 (27)</td>
</tr>
<tr>
<td>CML</td>
<td>1 (1)</td>
</tr>
<tr>
<td>CLL</td>
<td>10 (13)</td>
</tr>
<tr>
<td>HL</td>
<td>2 (3)</td>
</tr>
<tr>
<td>MM</td>
<td>5 (7)</td>
</tr>
<tr>
<td>HLA mismatch</td>
<td></td>
</tr>
<tr>
<td>Class I</td>
<td>51 (67)</td>
</tr>
<tr>
<td>Class II</td>
<td>25 (33)</td>
</tr>
<tr>
<td>CD 34+ 10^6/kg</td>
<td>6 (2.5-24.1)</td>
</tr>
<tr>
<td>CD 3+ 10^6/kg</td>
<td>2.7 (0.4-5.4)</td>
</tr>
</tbody>
</table>

Results

- Acute GVHD (day +100)
  - Grades II-IV: 34%
  - Grade III: 3%
- Chronic GVHD (2-year): 54%

- Per HLA class mismatch
  - NRM (2-year)
    - Class I: 16%
    - Class II: 28%
- Relapse (2-year)
  - Class I: 23%
  - Class II: 28%

- PFS (2-year)
  - Class I: 61%
  - Class II: 56%

- OS (2-year)
  - Class I: 67%
  - Class II: 68%

- Per HLA class mismatch
  - NRM (2-year)
    - Class I: 16%
    - Class II: 28%

Results: Sirolimus + MMF + CSA

- Reduction of acute GVHD II-IV
- Reduction of NRM
- Compared to historic data
  - Reduced acute GVHD
  - Grade III: 3%
  - No effect on relapse or progression (26%)
  - Improved NRM: 47% vs. 15%
- Improved OS and PFS
- Current RCT: Sirolimus/MMF/CSA vs. Sirolimus/PTCy/CSA

(ptcy, post transplant cyclophosphamide)
40 Soluble C5b-9 As a Prognostic Biomarker for Thrombotic Microangiopathy at the Onset of Graft-Versus-Host Disease

Background

- TMA is a complication post HCT
- GVHD is a risk factor for TMA
- Soluble C5b-9 (sC5b9) — A possible prognostic biomarker for TMA
- Nested case-control study (1:2)
  - Case: TMA with prior GVHD
  - Control: non-TMA with prior GVHD
- Similar with GVHD onset days (IQR)
- Cases: 21 (11-34)
- Controls: 21 (16-31)

Results and Conclusions

- Mean sC5b9 levels
  - Elevated during infection
- sC5b9 ↑ at onset of GVHD associated with TMA
- Limitations
  - Small sample size, rare disease
  - Lack of standardization for complement assay
872 KD025 for Patients with chronic Graft-Versus-Host Disease (cGVHD) – Long Term Follow-up of a Phase 2a Study (KD025-208)

Background

- **KD025**: ROCK2 inhibition
  - Down regulates pro-inflammatory Th17 responses
  - ↑ Treg function
  - ↓ STAT3 phosphorylation and ↑ STAT5 phosphorylation
- **Design**
  - Adults (post 1-3 lines of therapy) with
    - Steroid-dependent or refractory cGVHD
    - Persistent active cGVHD after >2 months of steroid therapy
    - Receiving glucocorticoid +/- calcineurin inhibitor
- **Cohorts**
  - 1: 200 mg daily (n=17)
  - 2: 200 mg BID (n=16)
  - 3: 400 mg daily (n=21)

Results

<table>
<thead>
<tr>
<th>Notable Baseline Characteristics</th>
<th>Cohort 1 (n=17)</th>
<th>Cohort 2 (n=16)</th>
<th>Cohort 3 (n=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;4 organs involved</td>
<td>8 (47)</td>
<td>10 (63)</td>
<td>9 (43)</td>
</tr>
<tr>
<td>Severe cGVHD</td>
<td>12 (71)</td>
<td>14 (88)</td>
<td>16 (76)</td>
</tr>
<tr>
<td>Median prednisone dose at baseline (mg/kg/day)</td>
<td>0.22</td>
<td>0.19</td>
<td>0.15</td>
</tr>
<tr>
<td>&gt;2 prior lines of therapy</td>
<td>15 (88)</td>
<td>5 (30)</td>
<td>12 (57)</td>
</tr>
<tr>
<td>Refractory to prior lines of therapy</td>
<td>10 (71)</td>
<td>6 (38)</td>
<td>16 (76)</td>
</tr>
<tr>
<td>Median treatment duration (months)</td>
<td>9</td>
<td>8</td>
<td>9</td>
</tr>
</tbody>
</table>

**Responses observed**

- Refractory to prior line: 82%
- >2 Prior lines of therapy: 90%
- Severe cGVHD: 90%
- >4 organs involved: 70%

N: ORR (%); 95% CI
Results

- Response
  - 75% of responses occurred by week 8
  - 51% maintained a response for ≥20 weeks
- FFS at 12 mo: 47%
- OS at 24 mo: 83%
- Corticosteroids
  - 19% of patients discontinued
  - 65% achieved dose reductions
  - Median reduction: 50%

<table>
<thead>
<tr>
<th>Cohort 1</th>
<th>Cohort 2</th>
<th>Cohort 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with corticosteroid dose reduction (%)</td>
<td>13 (76)</td>
<td>8 (50)</td>
</tr>
<tr>
<td>Median dose reduction (%)</td>
<td>63</td>
<td>50</td>
</tr>
</tbody>
</table>

Corticosteroids

42 Optimal Conditioning for Older Patients with Acute Myeloid Leukemia (AML) Receiving Allogeneic Hematopoietic Stem Cell Transplantation: A Propensity Score Analysis

Background

- HCT is potential cure for AML
- Young, fit patients should receive MAC regimen
- RIC regimens may be better tolerated in elderly patients with more comorbidities
- Optimal regimen for older AML
Methods and Outcomes

- Analysis of 404 consecutive patients
  - With AML
  - Age ≥ 60 years
  - Receiving HCT between 1/2005 – 8/2018

- Conditioning
  - FM100: Flu 160 mg/m² + Mel 100 mg/m² N=89
  - FM140: Flu 160 mg/m² + Mel 140 mg/m² N=78
  - Bu20000: Flu (+/- clofarabine) 160 mg/m² + IV Bu x4 days N=131
    - AUC ≥ 5000 µM*L/min/day or 130 mg/m²/day
  - Bu16000: Flu (+/- clofarabine) 160 mg/m² + IV Bu x4 days N=106
    - AUC ≥ 4000 µM*L/min/day or 110 mg/m²/day

- Primary outcome: 5-yr PFS
- Secondary outcomes:
  - Relapse
  - NRM
  - GRFS

Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>FM100 (N=89)</th>
<th>FM140 (N=78)</th>
<th>Bu20000 (N=131)</th>
<th>Bu16000 (N=106)</th>
<th>Adjusted P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median</td>
<td>67 (60-79)</td>
<td>64 (60-78)</td>
<td>66 (60-73)</td>
<td>65 (60-77)</td>
<td>0.06</td>
</tr>
<tr>
<td>Disease status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR with MRD (%)</td>
<td>12 (13.5)</td>
<td>2 (2.6)</td>
<td>21 (16.0)</td>
<td>11 (10.4)</td>
<td>1.00</td>
</tr>
<tr>
<td>CR with MRD +</td>
<td>37 (41.6)</td>
<td>3 (3.9)</td>
<td>42 (32.1)</td>
<td>28 (26.4)</td>
<td></td>
</tr>
<tr>
<td>CR unknown/MRD (%)</td>
<td>29 (32.6)</td>
<td>37 (47.4)</td>
<td>44 (33.6)</td>
<td>33 (31.1)</td>
<td></td>
</tr>
<tr>
<td>Active (%)</td>
<td>11 (12.4)</td>
<td>36 (46.2)</td>
<td>24 (18.3)</td>
<td>34 (32.1)</td>
<td></td>
</tr>
<tr>
<td>Favorable risk (%)</td>
<td>15 (16.9)</td>
<td>5 (6.4)</td>
<td>24 (18.3)</td>
<td>14 (13.2)</td>
<td>0.77</td>
</tr>
<tr>
<td>Intermediate risk (%)</td>
<td>20 (22.5)</td>
<td>36 (46.3)</td>
<td>40 (30.1)</td>
<td>40 (38.6)</td>
<td></td>
</tr>
<tr>
<td>Adverse (%)</td>
<td>45 (50.6)</td>
<td>37 (47.4)</td>
<td>65 (49.6)</td>
<td>50 (47.2)</td>
<td>1.00</td>
</tr>
<tr>
<td>HCTG, median</td>
<td>3 (3-6)</td>
<td>3 (3-9)</td>
<td>3 (3-9)</td>
<td>3 (3-10)</td>
<td>1.00</td>
</tr>
<tr>
<td>KPS, median</td>
<td>60 (0-100)</td>
<td>60 (0-100)</td>
<td>56 (0-100)</td>
<td>50 (0-100)</td>
<td>0.65</td>
</tr>
<tr>
<td>MRD (%)</td>
<td>17 (19.1)</td>
<td>23 (27.4)</td>
<td>51 (38.9)</td>
<td>35 (33.3)</td>
<td>0.94</td>
</tr>
<tr>
<td>MLD (%)</td>
<td>39 (45.6)</td>
<td>43 (53.1)</td>
<td>71 (54.2)</td>
<td>65 (61.3)</td>
<td></td>
</tr>
<tr>
<td>Haploidentical (%)</td>
<td>30 (33.7)</td>
<td>8 (10.3)</td>
<td>2 (1.5)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>MMUD (%)</td>
<td>3 (3.4)</td>
<td>4 (5.1)</td>
<td>7 (5.3)</td>
<td>6 (5.7)</td>
<td></td>
</tr>
</tbody>
</table>

HCT Outcomes

<table>
<thead>
<tr>
<th></th>
<th>FM100 (%)</th>
<th>FM140 (%)</th>
<th>Bu20000 (%)</th>
<th>Bu16000 (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-year NRM</td>
<td>19 (21)</td>
<td>39 (46)</td>
<td>30 (23)</td>
<td>27 (25)</td>
<td>0.500</td>
</tr>
<tr>
<td>3-year CIR</td>
<td>32 (36)</td>
<td>32 (39)</td>
<td>30 (23)</td>
<td>55 (51)</td>
<td>0.003</td>
</tr>
<tr>
<td>5-year PFS</td>
<td>49 (56)</td>
<td>30 (34)</td>
<td>34 (26)</td>
<td>23 (22)</td>
<td>0.02</td>
</tr>
<tr>
<td>5-year GRFS</td>
<td>28 (32)</td>
<td>18 (21)</td>
<td>18 (14)</td>
<td>3 (3)</td>
<td>0.006</td>
</tr>
<tr>
<td>5-year PFS for patients with KPS&lt;90%</td>
<td>41 (47)</td>
<td>27 (32)</td>
<td>32 (24)</td>
<td>22 (21)</td>
<td>0.007</td>
</tr>
<tr>
<td>5-year PFS for patients &gt; 65 years</td>
<td>43 (49)</td>
<td>28 (32)</td>
<td>29 (22)</td>
<td>16 (16)</td>
<td>0.008</td>
</tr>
</tbody>
</table>
Results

- MVA for PFS
  — With propensity score adjustment

<table>
<thead>
<tr>
<th>Condition</th>
<th>HR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FM100</td>
<td>0.57</td>
<td>0.36-0.89</td>
<td>0.013</td>
</tr>
<tr>
<td>Secondary AML</td>
<td>1.68</td>
<td>1.25-2.26</td>
<td>0.001</td>
</tr>
<tr>
<td>CR with MRD =</td>
<td>1.62</td>
<td>1.08-2.58</td>
<td>0.044</td>
</tr>
<tr>
<td>CR unknown</td>
<td>1.96</td>
<td>1.02-3.82</td>
<td>0.043</td>
</tr>
<tr>
<td>Active disease</td>
<td>2.95</td>
<td>1.53-5.63</td>
<td>0.001</td>
</tr>
<tr>
<td>KPS (continuous)</td>
<td>0.98</td>
<td>0.95-0.99</td>
<td>0.005</td>
</tr>
<tr>
<td>MMUD</td>
<td>2.46</td>
<td>1.90-3.17</td>
<td>0.002</td>
</tr>
</tbody>
</table>

- Pairwise comparisons for PFS
  — With propensity score adjustment

<table>
<thead>
<tr>
<th>Condition</th>
<th>Ref</th>
<th>Adjusted HR</th>
<th>Adjusted P value</th>
<th>Adjusted HR</th>
<th>Adjusted P value</th>
<th>Adjusted HR</th>
<th>Adjusted P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FM100</td>
<td>Ref</td>
<td>0.73</td>
<td>0.137</td>
<td>0.77</td>
<td>(0.55 - 1.09)</td>
<td>0.57</td>
<td>(0.36 - 0.89)</td>
</tr>
<tr>
<td>Bu16000</td>
<td>Ref</td>
<td>1.25</td>
<td>0.554</td>
<td>1.20</td>
<td>(1.03 - 1.42)</td>
<td>1.20</td>
<td>(1.03 - 1.42)</td>
</tr>
<tr>
<td>Bu20000</td>
<td>Ref</td>
<td>1.68</td>
<td>0.044</td>
<td>1.68</td>
<td>(1.25 - 2.26)</td>
<td>1.68</td>
<td>(1.25 - 2.26)</td>
</tr>
</tbody>
</table>

Conclusions

- FM100 improved PFS compared with others
  — Due to lower NRM without increase relapse rate

- Benefit seen in intermediate risk disease

- FM100 better survival
  — KPS <90%
  — Age <65 years

- More intense conditioning # improved survival in elderly

258 A Phase 1 Dose-Escalation Study of Adding Venetoclax to a Reduced Intensity Conditioning (RIC) Regimen Prior to Allogeneic Hematopoietic Cell Transplantation for Patients with High Risk Myeloid Malignancies
Background

- Relapse risk high with RIC
- MAC does not guarantee less relapse in patients with high risk mutations
  —TP53
- Venetoclax (highly selective BCL-2 inhibitor)
  —FDA-approved: in combination with azacitidine, decitabine or low-dose cytarabine in newly-diagnosed AML in adults ≥75 years of age, or who have comorbidities that preclude use of intense induction chemotherapy
  —Increased response in non-HCT setting
    - CR + CRi rate = 28% azacitidine alone vs. 73% azacitidine + venetoclax
- Question: Can adding venetoclax upfront to conditioning (FluBu2) provide benefit?

![Design Diagram](image1.png)

### Design

**FluBu2**
- Flu 30 mg/m² daily days -5 to -2
- Bu 0.8 mg/kg BID days -5 to -2
- Tacrolimus 0.05 mg/kg PO BID
- MTX 5 mg/m² IV

**HCT**
- Day -8 -7 -6 -5 -4 -3 -2 -1 0 +1 +3 +6 +11

![Objective Diagram](image2.png)

### Objective

- **Primary**
  - Determine dose and schedule of venetoclax when added to FluBu2 for patients going to HCT
    - High-risk AML
    - High-risk MDS
    - High-risk MDS/MPN
- **Secondary**
  - Determine efficacy
    - Remission
    - 12-mo PFS
    - 12-mo OS
    - 12-mo CIR
    - Acute GVHD
    - Chronic GVHD
Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N=16 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>10 (62.5)</td>
</tr>
<tr>
<td>Age, median year</td>
<td>60 (25-71)</td>
</tr>
<tr>
<td>ECOG 1</td>
<td>8 (50)</td>
</tr>
<tr>
<td>ECOG 2</td>
<td>8 (50)</td>
</tr>
<tr>
<td>AML</td>
<td>6 (37.5)</td>
</tr>
<tr>
<td>MDS</td>
<td>8 (50)</td>
</tr>
<tr>
<td>MDS/MPN</td>
<td>2 (12.5)</td>
</tr>
<tr>
<td>TP53 mutation</td>
<td>10 (62.5)</td>
</tr>
<tr>
<td>Prior venetoclax treatment</td>
<td>2 (12.5)</td>
</tr>
<tr>
<td>HLA-MUD</td>
<td>14 (87.5)</td>
</tr>
<tr>
<td>Donor gender (male)</td>
<td>6 (37.5)</td>
</tr>
</tbody>
</table>

Safety

CTCAE v5.0 Toxicity Grade 3 4

- Acute kidney injury 1
- Alanine aminotransferase ↑ 3
- Aspartate aminotransferase ↑ 2
- Bone pain 1
- Diarrhea 2
- Fatigue 1
- Hyperglycemia 1
- Metabolism and nutrition disorders 1
- Mucositis oral 1
- Pleural effusion 1
- Rash maculo-papular 1
- Sepsis 1

\[ \text{GVHD} \]

- Acute: G1, skin/oral (n=4)
  - Chronic:
    - Moderate (n=2)
    - Severe (n=1)
- Death: n=1
  - Complications from chronic GVHD
- No dose limiting toxicities

Results

- Chimerism at day +28:
  - Granulocyte 100 (97-100)
  - Leukocyte 96 (92-100)
  - T cell 78 (49-92)
- Median time to ANC ≥ 500:
  - 14 days (8-25)
- Median time to PLT > 20K:
  - 14 days (13-18)
- PFS (6 mo): 63% (95% CI: 28-84%)
- OS (6 mo): 76% (95% CI: 33-94%)
- CIR (6 mo): 37.5% (95% CI: 10-66%)
- NRM (6 mo): 0%
Conclusions

- Venetoclax 400 mg daily safe and well tolerated with FluBu2
- Engraftment not impaired
- GVHD not induced
- Encouraging outcomes
- Trial amended: azacytidine + venetoclax as maintenance

264 Outcomes after Stem Cell Transplant in Older Patients with Acute Myeloid Leukemia Treated with Venetoclax-Based Therapies

More on Venetoclax...

- Objective
  - Assess outcomes of HCT after venetoclax-based treatment in newly-diagnosed AML
- Included analyses
  - Open-label phase 1b → venetoclax + azacitidine/decitabine
  - Open-label phase 1/2 → venetoclax + LDAC
- Endpoints
  - Best response
  - Time to best response
  - Time from last dose of venetoclax until HCT
  - 12-mo post-HCT survival

LDAC, low-dose cytarabine
Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Patients N=304</th>
<th>HCT Patients n=31</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venetoclax + azacitidine, n (%)</td>
<td>127 (42)</td>
<td>19 (61)</td>
</tr>
<tr>
<td>Venetoclax + decitabine</td>
<td>85 (28)</td>
<td>11 (35)</td>
</tr>
<tr>
<td>Venetoclax + LDAC</td>
<td>90 (30)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Age, median (range)</td>
<td>74 (61-90)</td>
<td>69 (63-76)</td>
</tr>
<tr>
<td>Bone marrow blasts $&gt;$50%, n (%)</td>
<td>125 (41)</td>
<td>13 (42)</td>
</tr>
<tr>
<td>Secondary AML, n (%)</td>
<td>100 (33)</td>
<td>9 (29)</td>
</tr>
<tr>
<td>ECOG 0</td>
<td>50 (16)</td>
<td>10 (32)</td>
</tr>
<tr>
<td>ECOG 1</td>
<td>175 (58)</td>
<td>11 (35)</td>
</tr>
<tr>
<td>Cyto genetic risk: Intermediate</td>
<td>172 (57)</td>
<td>18 (58)</td>
</tr>
<tr>
<td>Cyto genetic risk: Adverse</td>
<td>123 (40)</td>
<td>12 (39)</td>
</tr>
<tr>
<td>TP53, n/N (%)</td>
<td>49/218 (23)</td>
<td>3/18 (17)</td>
</tr>
<tr>
<td>FLT3</td>
<td>38/218 (17)</td>
<td>6/18 (22)</td>
</tr>
<tr>
<td>NPM1</td>
<td>34/218 (16)</td>
<td>6/18 (22)</td>
</tr>
<tr>
<td>IDH1/2</td>
<td>54/218 (25)</td>
<td>6/18 (22)</td>
</tr>
</tbody>
</table>

Median time from last dose of venetoclax to HCT
1.2 mo, range (0.4-10)

Median time on study drug for patients that had HCT
3.7 mo, range (0.9-20)

Best Response Rate: HCT Recipients

<table>
<thead>
<tr>
<th>Best response prior to HCT</th>
<th>(n=31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR/CRh</td>
<td>26 (84)</td>
</tr>
<tr>
<td>CR</td>
<td>16 (52)</td>
</tr>
<tr>
<td>CR1</td>
<td>10 (32)</td>
</tr>
<tr>
<td>CRh</td>
<td>6 (19)</td>
</tr>
<tr>
<td>MLFS</td>
<td>2 (6)</td>
</tr>
<tr>
<td>RD</td>
<td>3 (10)</td>
</tr>
</tbody>
</table>

Median time to best response
- CR/CRh: 2.3 months (range: 0.9-7.1)
- CR: 2.8 months (range: 1.0-7.1)

Outcomes and Conclusions

- 12-mo OS: 84% (95% CI: 60-95)
- Patients alive 12-mo post HCT 66%
- HCT patients with CR/CRh and remission $\geq$12 mo: 55%
- HCT patients with CR/CRh and remission $\geq$6 mo: 96%
- High rates of responses in untreated AML patients
  - Early
  - Durable
- Future studies for Venetoclax
  - Added to azacitidine for AML treatment post HCT
  - NCT04128501
  - Maintenance post HCT in combination with androgenic steroid of care
  - NCT04161885

260 Additional Cytotoxic Chemotherapy Is Unlikely to Eliminate Measurable Residual Acute Myeloid Leukemia (AML)

**Background**
- MRD positivity at HCT has similar outcomes to active disease
  - 3 yr-relapse: MRD-positive 67% vs. MRD-negative 22%
  - 3 yr-OS: MRD-positive 26% vs. MRD-negative 73%
- Treatment for MRD positive patients
  - HCT
  - Early vs. late HCT?

**Design and Patient Characteristics**

<table>
<thead>
<tr>
<th>Age (median)</th>
<th>HCT</th>
<th>Chem</th>
<th>None</th>
</tr>
</thead>
<tbody>
<tr>
<td>60 [17,91]</td>
<td>59</td>
<td>60</td>
<td>61</td>
</tr>
<tr>
<td>Male [Female]</td>
<td>85 (157)</td>
<td>37</td>
<td>39</td>
</tr>
<tr>
<td>Race (White, Black, or Other)</td>
<td>32 (20%)</td>
<td>40 (24%)</td>
<td>37 (23%)</td>
</tr>
<tr>
<td>ECOG (≤2)</td>
<td>165 (78%)</td>
<td>89 (78%)</td>
<td>78 (67%)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>45%</td>
<td>43%</td>
<td>48%</td>
</tr>
<tr>
<td>Adverse</td>
<td>42%</td>
<td>38%</td>
<td>38%</td>
</tr>
<tr>
<td>No prior chemo</td>
<td>60%</td>
<td>59%</td>
<td>67%</td>
</tr>
<tr>
<td>1-stress</td>
<td>22%</td>
<td>23%</td>
<td>16%</td>
</tr>
<tr>
<td>&gt;2-stress</td>
<td>18%</td>
<td>19%</td>
<td>16%</td>
</tr>
<tr>
<td>Prior HCT</td>
<td>15%</td>
<td>11%</td>
<td>16%</td>
</tr>
</tbody>
</table>
Results

- Median follow-up time = 31.1 mo
- Survival from initial treatment
  - HCT 13.8 mo
  - Chemo 11.6 mo
  - None 5.4 mo
  - $P = .009$
- Survival from HCT in Early vs. Late HCT groups
  - HCT 10.3 mo
  - Chemo 4.3 mo
  - $P = .017$
- Effect of MRD reduction on survival post HCT
  - Chemo $\rightarrow$ MRD negative 4.3 mo
  - Chemo $\rightarrow$ MRD positive 4.6 mo

Conclusions

- Chemotherapy
  - Intensive: eliminated MRD in 36%
  - No effect on HCT outcome
  - Reduces, delays HCT
- Early HCT = longer survival

ARS Question #1

- The biomarker identified by Holtan and colleagues to be associated with GI GVHD and NRM is
  - A. Reg3a
  - B. ST2
  - C. Claudin-3
  - D. AREG
ARS Question #2

• True/False: The MAP laboratory test was less accurate than combining both clinical response and biomarkers.
  A. True
  B. False

ARS Question #3

• Based on the phase II study conducted by Kornblit and colleagues, the recommended immunosuppression prophylaxis suggested for patients undergoing a hematopoietic cell transplantation using HLA Class I or Class II antigen mismatched donors is the following:
  A. Sirolimus/post transplant cyclophosphamide/cyclosporine
  B. Sirolimus/mycophenolate mofetil/cyclosporine
  C. Sirolimus/mycophenolate mofetil/post transplant cyclophosphamide
  D. Sirolimus/mycophenolate mofetil/tacrolimus

Additional Abstracts

• Plenary Session. Oral abstract #1: Annock E.C. Groen. Post-Transplantation Cyclophosphamide after Unrelated Hematopoietic Stem Cell Transplantation: Results of the Prospective Randomized HOVON 96 Trial in Recipients of Matched Related and Unrelated Donors

• Oral Presentation Session 732: Clinical Allogeneic Transplantation. Oral abstract #148: Giorgia Battipaglia. Post-Transplant Cyclophosphamide Versus Antithymocyte Globulin in Patients with Acute Myeloid Leukemia Undergoing Allogeneic Stem Cell Transplantation from HLA-Identical Sibling Donors: A Retrospective Analysis from the Acute Leukemia Working Party of the EBMT

• Oral Presentation Session 701: Experimental Transplantation. Oral abstract #195: Alison Moe. Recipient Signaling through the Cannabinoid Type 2 Receptor Regulates LPS-Independent Neuroinflammation during Graft Versus Host Disease

• Oral Presentation Session 722: Clinical Allogeneic Transplantation. Oral abstract #371: Cornelis N. De Jong. Time-Restricted Versus Standard Question Prophylaxis after Allogeneic Hematopoietic Stem Cell Transplantation: Results from the Prospective Randomized Phase II ADIVO98 Trial
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- Dr. Keith Pratz
- Dr. Jacob Appelbaum

Updates from the American Society of Hematology Annual Meeting 2019

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