Phase 1 Cohort Expansion of Flotetuzumab, a CD123 x CD3 Bispecific DART® Protein, in Patients with Relapsed/Refractory Acute Myeloid Leukemia (AML)

Geoffrey L. Uy, MD, Michael P Rettig, PhD, Norbert Vey, MD, John Godwin, MD, Matthew Foster, MD, David A. Rizzieri, MD, Martha L. Arellano, MD, Max S. Topp, MD, Gerwin Huls, MD, PhD, Mojca Jongen-Lavrencic, MD, PhD, Giovanni Martinelli, MD, Stefania Paolini, MD, PhD, Fabio Ciceri, MD, Matteo Giovanni Carrabba, MD, Kendra Sweet, MD, Farhad Ravandi, MBBS, Sarah E Church, PhD, Jayakumar Vadakekollathu, PhD, Sergio Rutella, MD, PhD, FRCPath, Jichao Sun, PhD, Kang Yang, Jan Baughman, MPH, Teia Curtis, PhD, Erin Timmeny, Kerri Cali, Kathy Tran, John Muth, MS, Ross La Motte-Mohs, PhD, Camille Poirot, Pharm.D., Athanasios Pallis, MD, Alessandra Cesano, MD, PhD, Ezio Bonvini, MD, Jon Wigginton, MD, Bob Löwenberg, MD, PhD, Jan K Davidson Moncada, MD, PhD and John F DiPersio, MD, PhD
Flotetuzumab (MGD006): CD123 x CD3 Bispecific DART® Protein

- Bivalent, investigational bispecific molecule that co-engages T cells (anti-CD3) with a tumor associated antigen (anti-CD123)

- CD123 is low affinity IL-3 receptor
  - Normally expressed on plasmacytoid dendritic cells (pDCs), basophils, monocytes, and hematopoietic progenitor cells (HPCs)
  - Over-expressed on leukemic stem cells (LSCs) in AML and other hematologic malignancies

- Flotetuzumab designed to:
  - Redirect T-cells to kill tumor cells
  - Recognize tumors independent of TCR & MHC
Flotetuzumab Phase 1 Study Design

**Dose Escalation**

- **Single Patient Dose Escalation**
  - N=14

- **3 + 3 Multi-patient Dose Escalation**
  - N=33

**Expansion Cohort**

- R/R AML
- Recommended Phase 2 Dose (RP2D)
  - N=31

**Key entry criteria**

- Relapsed/Refractory AML unlikely to benefit from cytotoxic chemotherapy
  - Refractory to ≥ 2 induction attempts
  - 1st relapse with initial CR duration of < 6 months or any prior unsuccessful salvage
  - 2nd relapse or higher
  - HMA failure
- No prior allogeneic hematopoietic cell transplant

**Study objectives**

- Safety and preliminary clinical activity
- Optimize delivery and supportive care (manage CRS while minimizing corticosteroid use)
- Define PK, PD and PK/PD relationships
Methods

- Patients receive RP2D of 500 ng/kg/day by continuous infusion

![Flotetuzumab Dose and Dosing Schedule]

- Disease status assessed by modified IWG criteria
- Samples collected to investigate candidate biomarkers, including CD123 receptor density/cell (RD)
- Gene expression profiling performed using NanoString® PanCancer IO 360™ assay
  - Assessed expression of 770 genes, including 14 immune cell types and 32 immunoncology biological signatures in bone marrow (BM) samples
## Summary of AML Patient Demographics Treated at RP2D

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Patients (n=31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Median (Range)</td>
</tr>
<tr>
<td></td>
<td>64.0 (29.0, 82.0)</td>
</tr>
<tr>
<td>Gender [n(%)]</td>
<td>Female</td>
</tr>
<tr>
<td></td>
<td>15 (48.4)</td>
</tr>
<tr>
<td>Disease Status at Time of Enrollment</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Primary Refractory§</td>
</tr>
<tr>
<td></td>
<td>19 (61.3%)</td>
</tr>
<tr>
<td></td>
<td>Relapse*</td>
</tr>
<tr>
<td></td>
<td>9 (29.0%)</td>
</tr>
<tr>
<td></td>
<td>Failed ≤ 2 cycles of HMA</td>
</tr>
<tr>
<td></td>
<td>3 (9.7)</td>
</tr>
<tr>
<td>AML Risk Stratification (ELN 2017)</td>
<td>Adverse</td>
</tr>
<tr>
<td></td>
<td>15 (48.4)</td>
</tr>
<tr>
<td></td>
<td>Intermediate</td>
</tr>
<tr>
<td></td>
<td>8 (25.8)</td>
</tr>
<tr>
<td></td>
<td>Favorable</td>
</tr>
<tr>
<td></td>
<td>5 (16.1)</td>
</tr>
<tr>
<td></td>
<td>Unknown</td>
</tr>
<tr>
<td></td>
<td>3 (9.7)</td>
</tr>
<tr>
<td># Prior Lines of Therapy</td>
<td>Median (Range)</td>
</tr>
<tr>
<td></td>
<td>2.0 (1, 9)</td>
</tr>
</tbody>
</table>

§ Refractory includes ≥ 2 induction attempts or early relapse CR with initial duration < 6 months or refractory ≥ 4 cycles of HMA

* Relapse includes progression after initial response to HMA/late relapse CR with duration ≥ 6 months

Data cut-off Nov. 1, 2018
### Summary of Interim Safety

#### Treatment Related Adverse Events*

<table>
<thead>
<tr>
<th>Event</th>
<th>All (N=31)</th>
<th>Grade ≥ 3 (N=31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infusion related reaction/Cytokine Release Syndrome (IRR/CRS)*</td>
<td>29 (93.3)</td>
<td>4 (12.9)</td>
</tr>
<tr>
<td>Nausea</td>
<td>10 (32.3)</td>
<td></td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>9 (29.0)</td>
<td>1 (3.2)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>8 (25.8)</td>
<td>1 (3.2)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>8 (25.8)</td>
<td></td>
</tr>
<tr>
<td>C-reactive protein increased</td>
<td>6 (19.4)</td>
<td>2 (6.5)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>5 (16.1)</td>
<td>1 (3.2)</td>
</tr>
<tr>
<td>Headache</td>
<td>5 (16.1)</td>
<td></td>
</tr>
<tr>
<td>Hypotension</td>
<td>5 (16.1)</td>
<td>2 (6.5)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>5 (16.1)</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>5 (16.1)</td>
<td>2 (6.5)</td>
</tr>
<tr>
<td>Alanine aminotransferase increased</td>
<td>4 (12.9)</td>
<td>2 (6.5)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>4 (12.9)</td>
<td>1 (3.2)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>4 (12.9)</td>
<td>1 (3.2)</td>
</tr>
<tr>
<td>Edema</td>
<td>4 (12.9)</td>
<td></td>
</tr>
<tr>
<td>Lymphocyte count decreased</td>
<td>7 (22.6)</td>
<td>6 (19.4)</td>
</tr>
<tr>
<td>Anemia</td>
<td>6 (19.4)</td>
<td>6 (19.4)</td>
</tr>
<tr>
<td>Platelet count decreased</td>
<td>6 (19.4)</td>
<td>5 (16.1)</td>
</tr>
<tr>
<td>White blood cell count decreased</td>
<td>5 (16.1)</td>
<td>5 (16.1)</td>
</tr>
<tr>
<td>Neutrophil count decreased</td>
<td>4 (12.9)</td>
<td>4 (12.9)</td>
</tr>
</tbody>
</table>

* Toxicity grading for events of IRR/CRS is based upon the modified grading scale proposed by Lee et al.

Data cut-off Nov. 1, 2018, events occurring > 10%; Toxicity grading is based on CTCAE criteria version 4.0.
Most CRS Events Were Mild to Moderate Severity and Short Duration

**IRR/CRS incidence decreases with continued flotetuzumab dosing**

- 31 Patients treated, primarily low grade CRS (G1=25.8% (8/31), G2=58.1% (18/31), and G3=12.9% (4/31))
- Median duration Grade 1: 1 day, Grade 2: 2 days, Grade 3: 2.5 days
- CRS frequency decreased with time on treatment
• Baseline median percentage of CD123+ BM blasts 85% (range 1.4-100)
• Median CD123 receptor density on BM blasts 4084 (range 357-44998)
Flotetuzumab Activity in Overall RP2D Cohort

• ORR (CR/CRI/MLF/PR): 7/27 (25.9%)
• CR Rate (CR/CRI): 5/27 (18.5%)

Median DOR 3 months (1.1-5.6 months)

31 pts treated at RP2D: 27 response evaluable (2 PD on PB blasts), 25 pts in waterfall plot; 3 pts. non-evaluable (2 pts withdrew consent, 1 pt. withdrawn due to TRAE); 1 pt. ongoing.

CR=Complete Response; CRI=Complete Response with incomplete hematological improvement; MLF=Morphologic Leukemia-free state; PR=Partial Response; SD=Stable Disease; PD=Treatment Failure
* Patient subsequently underwent HSCT in remission

Data cut-off Nov. 1, 2018
Immune-Enriched TME* Associated with Resistance to Cytotoxic CTx

Is primary refractory AML (a potential surrogate for an immune-rich TME) associated with response to flotetuzumab?

* TME = Tumor microenvironment
Inflammatory Signature and Increased CD123 Density in Primary Refractory AML

**Log2 fold-change 1° Refractory vs Relapse AML**

- **Inflamed**
  - CD123 RD (median)
  - CD123
  - CD46
  - Exhausted CD8
  - Immunoregulation
  - APM
  - IFN downstream
  - Myeloid inflammation
  - VEGF
  - TGF-β
  - MIR RNA

- **Exhausted**
  - Proliferation
  - JAK-STAT
  - Endothelial cells
  - B/AH3
  - APM loss
  - Glycolysis
  - Necrosis
  - Cytotoxicity
  - Cytotoxic cells
  - CD8 T cells
  - Lymphoid T cells
  - Treg
  - CTL
  - TIF
  - Th1 cells
  - TCOF
  - NK CD69+ cells
  - NK cells
  - Apolipos
  - Hypoxia
  - NSG1
  - IL10
  - IFN gamma
  - Myeloid
  - Neurotrophs
  - PO-L2
  - Sherry
  - DC
  - MAGEA
  - B2M
  - BD cells
  - PO-1
  - NGS2
  - Inflam chemokines
  - PDL1
  - CD46

- **Inflammatory Chemokines**
  - Log2 fold-change 1° Refractory vs Relapse AML:
    - p=0.026

**Companion presentation #444, 12/2 4:30-6:00pm Grand Hall B**

*38 baseline BM including dose escalation*
Primary Refractory AML Patients Were Most Responsive to Flotetuzumab

Primary Refractory: ORR 6/17 (35.3%); CR: 5/17 (29.4%)
Relapse: ORR 1/7 (14.3%); CR Rate: 0/7

* Duration of response (DOR) = 1.4 months

CR=Complete Response; CRi=Complete Response with incomplete hematological improvement; MLF=Morphologic Leukemia-free state; PR=Partial Response;
SD=Stable Disease; PD=Treatment Failure
§ Patient subsequently underwent HSCT in remission

31 pts treated at RP2D: 27 response evaluable (2 PD on PB blasts), 25 pts in waterfall plot;
3 pts. non-evaluable pts (2 pts withdrew consent, 1 pt. withdrawn due to TRAE); 1 pt. ongoing.

Data cut-off Nov. 1, 2018
# Anti-leukemic Activity Observed in Primary Refractory AML

<table>
<thead>
<tr>
<th>Evaluable Patients</th>
<th>CR (CR/CRi)</th>
<th>ORR (CR/CRi/MLF/PR)</th>
<th>Benchmark (CR/CRi)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall R/R AML</td>
<td>19% (5/27)</td>
<td>26% (7/27)</td>
<td>17% (1); 24% (2)</td>
</tr>
<tr>
<td><strong>Primary Refractory AML</strong></td>
<td><strong>29.4% (5/17)</strong></td>
<td><strong>35.3% (6/17)</strong></td>
<td><strong>13% (3)</strong></td>
</tr>
<tr>
<td>Relapse AML</td>
<td>0% (0/7)</td>
<td>14.3% (1/7)</td>
<td></td>
</tr>
<tr>
<td>Failed ≤ 3 cycles HMA</td>
<td>0% (0/3)</td>
<td>0% (0/3)</td>
<td></td>
</tr>
<tr>
<td>Secondary AML*</td>
<td>33.3% (2/6)</td>
<td>50.0% (3/6)</td>
<td>22%-32% (4)</td>
</tr>
</tbody>
</table>

*Secondary AML: AML therapy related AML/antecedent hematological malignancy

---

(1) Medeiros, et al., Clin Lymph Myel Leuk, article in press, 2018  
(3) Kantarjian, et al., Cancer, 2018  
Conclusions

• Flotetuzumab, an investigational DART molecule, demonstrated antileukemic activity with an acceptable safety profile

• Greater activity observed among patients with primary refractory disease
  – Inflammatory chemokines and CD123 receptor density more pronounced in primary refractory disease

• Ongoing / future studies will:
  – Expand enrollment in patients enriched for primary refractory AML
  – Further characterize potential candidate biomarkers of response
  – Investigation of lead in dosing strategy on going
Acknowledgements

We thank all patients and their families for their participation

• Clinical trial team at the study centers
  • Medizinische Klinik und Poliklinik II Universitätsklinikum Würzburg, Würzburg, Germany
  • Institut Paoli-Calmettes, Marseille, France
  • Ospedale San Raffaele, Milan, Italy
  • AOUBologna Policlinico S. Orsola Malpighi, Bologna, Italy
  • Universitair Medisch Centrum Groningen, Groningen, The Netherlands
  • Erasmus University Medical Center, Rotterdam, The Netherlands
  • Barnes-Jewish Hospital, Washington University School of Medicine, St. Louis, MO, U.S.A.
  • Duke University Medical Center, Durham, NC, U.S.A.
  • Winship Cancer Institute of Emory University School of Medicine, Atlanta, GA, U.S.A.
  • UNC Lineberger Comprehensive Cancer Center, Chapel Hill, NC, U.S.A.
  • Providence Cancer Center, Earle A. Chiles Research Institute, Portland, OR, U.S.A.
  • The University of Texas M D Anderson Cancer Center, Houston, TX, U.S.A.
  • Moffitt Cancer Center, Tampa, FL, U.S.A.
  • City of Hope National Medical Center, Duarte, CA, U.S.A.

• MacroGenics, Inc., U.S.A.
  • Kenneth Jacobs, Maya Kostova, Michele Shannon, Ian Lent, Andy Giglio, Ouiam Bakkacha

• Servier, France
  • Cedric Viero, Helene Lelievre