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Investigational Agents

All Company product candidates described or mentioned herein are investigational and have not yet been approved for marketing by any regulatory authority.
Welcome & Introduction

Scott Koenig, M.D., Ph.D.
President and Chief Executive Officer, MacroGenics
<table>
<thead>
<tr>
<th><strong>ASH 2019 Flotetuzumab Conference Call Agenda</strong></th>
</tr>
</thead>
</table>
| **Welcome & Introduction** | **Scott Koenig, M.D., Ph.D.**  
President & Chief Executive Officer |
| **Immune Landscapes:** Chemotherapy Resistance and Anti-Leukemic Activity of Flotetuzumab in Patients with Relapsed/Refractory AML | **Sergio Rutella, M.D., Ph.D., FRCPath**  
Professor, Cancer Immunotherapy, John van Geest Cancer Research Centre, Nottingham Trent University, UK |
| **Acute Myeloid Leukemia (AML):** Current Treatment Paradigm | **Geoff Uy, M.D.**  
Associate Professor, Bone Marrow Transplantation & Leukemia, Washington University School of Medicine, St. Louis |
| **Flotetuzumab Clinical Update:** Salvage Therapy for Primary Refractory and Early Relapsed AML Patients |  |
| **Future Development** | **Jan Davidson-Moncada, M.D., Ph.D.**  
Senior Clinical Research Director |
| **Key Takeaways** | **Scott Koenig, M.D., Ph.D.**  
President & Chief Executive Officer |
| **Q&A** |  |
MacroGenics is Committed to Developing Life-changing Medicines

- Engineering antibodies that leverage the immune system to fight cancer
- A leader in bispecific antibodies, including redirected T-cell killing
  - Flotetuzumab (CD3 x CD123 bispecific DART® molecule) being developed in acute myeloid leukemia (AML)

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Fc-Optimized Antibody</th>
<th>Antibody Drug Conjugate</th>
<th>DART® Molecules</th>
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</thead>
<tbody>
<tr>
<td>• MGA012 (anti-PD-1)</td>
<td>• margetuximab (anti-HER2)</td>
<td>• MGC018 (anti-B7-H3)</td>
<td>• flotetuzumab (CD123 x CD3)</td>
</tr>
<tr>
<td></td>
<td>• enoblituzumab (anti-B7-H3)</td>
<td></td>
<td>• MGD013 (PD-1 x LAG-3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• MGD019 (PD-1 x CTLA-4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• MGD009 (B7-H3 x CD3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• MGD007 (gpA33 x CD3)</td>
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</tbody>
</table>
Immune Landscapes

Sergio Rutella, M.D., Ph.D., FRCPATH
Professor, Cancer Immunotherapy, John van Geest Cancer Research Centre, Nottingham Trent University, UK
Immune Landscapes Predict Chemotherapy Resistance and Anti-Leukemic Activity of Flotetuzumab, an Investigational CD123 × CD3 Bispecific DART® Molecule, in Patients with Relapsed/Refractory Acute Myeloid Leukemia

Sergio Rutella1,2, Jayakumar Vadakekolathu1, Mark D. Minden3, Tressa Hood4, Sarah E. Church4, Stephen Reeder1, Heidi Altmann5, Amy H. Sullivan4, Elena J. Viboč4, Tasleema Patel6, Narmin Ibrahimova3, Sarah E. Warren4, Andrea Arruda3, Yan Liang4, Marc Schmitz7, Alessandra Cesano4, Peter J.M. Valk8, Bob Löwenberg8, A. Graham Pockley1, Martin Bornhäuser5, Sarah K. Tasin6, Michael P. Rettig9, Jan Davidson-Moncada10, John F. DiPersio9

1John van Geest Cancer Research Centre and 2Centre for Health, Ageing and Understanding Disease (CHAUD), School of Science and Technology, Nottingham Trent University, Nottingham, UK; 3Princess Margaret Cancer Centre, Toronto, Canada; 4NanoString Technologies, Inc., Seattle, WA; 5Department of Internal Medicine I, University Hospital Carl Gustav Carus, Technische Universität Dresden, Germany; 6Division of Oncology and Centre for Childhood Cancer Research, Children's Hospital of Philadelphia and University of Pennsylvania School of Medicine, PA; 7Institute of Immunology, Medical Faculty, Technische Universität Dresden, Dresden, Germany; 8Department of Hematology, Erasmus University Medical Centre, Rotterdam, The Netherlands; 9Division of Oncology, Department of Medicine, Washington University School of Medicine, St Louis, MO; 10MacroGenics, Inc., Rockville, MD

sergio.rutella@ntu.ac.uk
• Cytotoxic chemotherapy remains the standard-of-care for most patients with acute myeloid leukemia (AML), despite the recent approval of novel agents.

• Immunotherapies such as monoclonal antibodies, bispecific molecules, immune checkpoint blockade (ICB) and CD123-CAR T cells are currently under investigation in AML.

• There is an urgent need to identify predictive biomarkers in the tumor immunological microenvironment (TME).

• Flotetuzumab, a CD123 × CD3 bispecific DART® molecule, is being tested in a phase 1 clinical trial of relapsed/refractory (R/R) AML (NCT#02152956).

• See also presentation #733. Monday, December 9, 2019: 2:45PM
  - Dr. Geoffrey Uy, Session #613. *Acute Myeloid Leukemia: Clinical Studies: Treatment of Relapsed/Refractory Disease*. Tangerine 3 (Orange County Convention Center).
Diversity of immune landscapes in AML

The AML tumour immunological microenvironment (TME)

1. Innate (PMN, macrophages)
2. Adaptive (T, B, NK, CTL)
3. Mast cells, exhausted CD8+ T cells

Discovery cohort (n=62)

34 non-promyelocytic de novo childhood AML
(Sarah K. Tasian, Children’s Hospital of Philadelphia, USA)
28 non-promyelocytic de novo adult AML
(Martin Bornhäuser, Dresden, Germany)
Patient series and methods

**Wet-lab cohorts**

<table>
<thead>
<tr>
<th></th>
<th>PMCC^*</th>
<th>CHOP^</th>
<th>SAL^^</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nr of patients</td>
<td>290</td>
<td>39</td>
<td>38</td>
</tr>
<tr>
<td>Age (y)</td>
<td>52 (18-81)</td>
<td>10 (0.1-20)</td>
<td>52.5 (23-75)</td>
</tr>
<tr>
<td>Disease status</td>
<td>Onset</td>
<td>Onset</td>
<td>Onset/CR/Relapse</td>
</tr>
</tbody>
</table>

**In silico cohorts**

<table>
<thead>
<tr>
<th></th>
<th>HOVON</th>
<th>Beat AML Master Trial</th>
<th>TCGA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nr of patients</td>
<td>618</td>
<td>267</td>
<td>147</td>
</tr>
<tr>
<td>Age (y)</td>
<td>Adult</td>
<td>Adult</td>
<td>Adult</td>
</tr>
<tr>
<td>Disease status</td>
<td>Onset</td>
<td>Onset</td>
<td>Onset</td>
</tr>
</tbody>
</table>

- The PanCancer Immune Profiling Panel (NanoString Technologies, Seattle, WA) was used to measure mRNA expression in bulk BM samples (n=770 immune-related genes).
- Immune signature scores and biological activity scores were calculated as pre-defined linear combinations (weighted averages) of biologically relevant gene sets.
- Gene expression data have been deposited in NCBI's Gene Expression Omnibus and will be accessible through GEO Series accession number GSE134589.

*PMCC = Princess Margaret Cancer Centre, Toronto, Canada – **Discovery cohort**

^CHOP = Children’s Hospital of Philadelphia, Philadelphia, PA

^^SAL = Studienallianz Leukämie, Dresden, Germany
Immune landscapes assist stratification


**A**

Discovery cohort (n=290 patients)

- "IFN module" gene score
- Myeloid inflammation
- Inflammatory chemokines
- Downstream IFN signaling
  - IFN-γ
  - PDL1
  - PDL2
  - MAGEs
  - IL10
- Immunoproteasome

**B**

- Immune-infiltrated (n=136) (IFN + Adaptive + Myeloid)
- Immune-depleted (n=154)

**C**

IFN-stimulated genes
- **IFN-γ mRNA**
- **PDL1 mRNA**
- **PDL2 mRNA**
- **MAGE mRNA**
- **IL10 mRNA**

T-cell and cytotoxicity markers
- **CD8+ mRNA**
- **P2RX7 mRNA**

Antigen processing and presentation
- **HLA-A mRNA**
- **HLA-B mRNA**
- **HLA-C mRNA**

Immune checkpoints and immunotherapy targets
- **B7H1 mRNA**
- **B7H2 mRNA**
- **B7H3 mRNA**

*P<0.05; ***P<0.001
Prediction of chemotherapy response

Therapy resistance (‘3+7’ backbone) was defined as failure to achieve CR in patients who survive at least 28 days (primary refractory AML) or as early relapse (less than 3 months after achieving CR).

A) PMCC discovery series (n=290)

B) Beat-AML Master Trial validation series (n=196)

Translational research question

IFN-γ-related gene signatures reflecting an immune-infiltrated TME are associated with adverse prognosis in patients with AML receiving conventional chemotherapy.

Are immune-infiltrated TMEs, and IFN-γ gene signatures in particular, associated with sensitivity to targeted immunotherapy with flotetuzumab, a CD123 × CD3 DART bispecific molecule?
Flotetuzumab immunotherapy

- Immune gene expression was analyzed in a subgroup of patients (n=30/50) with relapsed/refractory AML treated with flotetuzumab (NCT#02152956) at RP2D (500 ng/kg/day; Uy, et al. ASH 2017; Uy, et al. ASH 2018; Rutella, et al. ASH 2018)
  - 30 BM samples analyzed at baseline
  - 19 BM samples analyzed “on treatment” (post-cycle 1)
- The NanoString PanCancer IO360™ assay was used to interrogate the expression of 770 genes, including the abundance of 14 immune cell types and 32 immuno-oncology signatures
  - Signature scores were calculated as pre-defined linear combinations (weighted averages) of biologically relevant gene sets
## Patients and Methods

**Characteristic** | **Patients (n=30)***  
--- | ---  
Age (median and range) | 57 years (27-74)  
Gender |  
| Male | 16 (53%)  
| Female | 14 (47%)  
Disease status at study entry |  
| Relapse (CR with initial duration >6 months) | 7 (23%)  
| Refractory |  
| Primary induction failure (PIF; ≥2 induction attempts) | 17 (57%)  
| Early relapse (CR with initial duration <6 months) | 6 (20%)  
2017 ELN risk stratification |  
| Favorable | 6 (20%)  
| Intermediate | 7 (23%)  
| Adverse | 17 (57%)  
Secondary AML | 12 (40%)  
Number of prior lines of therapy (median and range) | 3 (1-9)  

*Subgroup of 30/50 patients treated at the RP2D for whom BM samples were available

Response assessment criteria employed in analysis:

- **Anti-leukemic activity (ALA):** CR/CRi, PR, “other benefit” (>30% decrease in BM blasts)
- **Non-responders (NR):** treatment failure, stable disease, progressive disease
‘Hot’ TME in chemorefractory AML

- Immune-depleted at baseline
- Immune-infiltrated at baseline

AML Type
- Refractory
- Relapse

A

B

P<0.05327
P<0.0084

Mann Whitney U test for unpaired determinations
Refractory = Primary induction failure (PIF) + early relapse (ER)
IFN-related profiles and response to flotetuzumab

Flotetuzumab modulates the TME

Matched baseline-post-C1 BMs available for 19 patients treated with flotetuzumab
Flotetuzumab modulates the TME

GeoMx Digital Spatial Profiling of 2 BM FFPEs (50+ IO proteins)

2 patients achieving CR

A

Region of interest (ROI) with no ‘T-cell clustering’

B

ROI with ‘T-cell clustering’

C

High in ROIs with ‘no T-cell clustering’

High in ROIs with ‘T-cell clustering’

CD123

CD3

DNA

Conclusions

• Transcriptional programs that reflect high immune infiltration and IFN-γ signaling enrich in a subset of patients with AML and predict chemotherapy resistance

• IFN-γ-related mRNA profiles at baseline correlate with anti-leukemic activity of flotetuzumab at the RP2D

• A subgroup of patients with an immune-infiltrated TME show high expression of immune checkpoints, including PD-L1, suggesting potential enhanced benefit from flotetuzumab in combination with ICB

  • A phase I study of flotetuzumab combined with MGA012, an anti-PD1 antibody, is ongoing in patients with R/R AML (Wei AH, et al. Poster #2662; ASH 2019)
Acknowledgements

Co-authors and Collaborators

**JVGCRC, NTU**
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Jayakumar Vadakekolathu (GEP)

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Regensburg, Germany

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Francesco M. Marincola
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**NFU**
Jan K. Davidson-Moncada
John Muth
Rockville, MD

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Mainstream QR funding, 2017-2019

**Qatar National Research Fund**
Member of Qatar Foundation

**Qatar National Priorities Research Programme, 2016-2020**
Mainstream QR funding, 2017-2019
AML Treatment Paradigm & Flotetuzumab Clinical Update

Geoffrey Uy, M.D.
Associate Professor
Bone Marrow Transplantation & Leukemia, Washington University School of Medicine, St. Louis
Background: Acute Myeloid Leukemia (AML)

• Hematopoietic stem cell (HSC) malignancy characterized by differentiation arrest and uncontrolled clonal proliferation of neoplastic precursors, preventing normal bone marrow hematopoiesis.

• Median age of 69 years at diagnosis.

• Nearly 20,000 new cases diagnosed per year in the US

• Approximately 40-50% of patients fail to achieve remission with intensive induction therapy (primary induction failure) or experience disease recurrence after a short remission duration (<6 months; early relapsed)

• Prognosis varies based in part on clinical features (e.g. patient age, medical comorbidities, and performance status) and underlying genetic features (cytogenetic and molecular aberrations).
Current Treatment Paradigm

AML

Fit for Intensive Chemotherapy (50%)
Goal is remission / cure

Induction (1-2 cycles)

“7+3” +/- midostaurin or gemtuzumab
Vyxeos (secondary AML)

Consolidation / Transplant

CR > 6 months
Relapsed

CR < 6 months
Early Relapse

No CR
Primary Induction Failure

Unfit for Intensive Chemotherapy (50%)
Goal is to extend survival

Induction

HMA +/- venetoclax
glasdegib + LDAC
avosidenib

Salvage Chemo
HMA +/- venetoclax
Targeted Agents (FLT3, IDH1/2)
Clinical Trials

December 9, 2019 – ASH 2019 Conference Call: Flotetuzumab
At Least 50% of Patients with AML Have No Known Targetable Mutation

Cancer Facts and Figures 2019
Flotetuzumab, an Investigational CD123 x CD3 Bispecific DART® Protein, in Salvage Therapy for Primary Induction Failure and Early Relapsed Acute Myeloid Leukemia Patients

Geoffrey L. Uy, MD, Ibrahim Aldoss, MD, Matthew C Foster, MD, David A Sallman, MD, Kendra L. Sweet, MD, David A. Rizzieri, MD, Peter H. Sayre, MD, PhD, Anjali S. Advani, MD, Ashkan Emadi, MD, Matthew J. Wieduwilt, MD, PhD, Norbert Vey, MD, PhD, Fabio Ciceri, MD, Matteo Giovanni Carrabba, MD, Tamara Moyo, MD, PhD, Sarah E. Church, PhD, Michael P. Rettig, PhD, Martha L. Arellano, MD, John E. Godwin, MD, Bob Löwenberg, MD, PhD, Gerwin Huls, MD, PhD, Farhad Ravandi, MD, John Muth, MS, Kathy Tran, Ouiam Bakkacha, MD; Kenneth Jacobs, MD; Mojca Jongen-Lavrencic, MD, PhD, Erin Timmeny, Max S. Topp, MD, Stefania Paolini, MD, PhD, Kuo Guo, MSc, Teia Curtis, Jian Zhao, PhD, Jayakumar Vadakekolathu, PhD, Jon M. Wigginton, MD, Ezio Bonvini, MD, Sergio Rutella, MD, PhD, FRCPath, Roland B. Walter, MD, PhD, MS, Jan K Davidson-Moncada, MD, PhD, and John F. DiPersio, MD, PhD

ClinicalTrials.gov #NCT02152956    Abstract #733
Flotetuzumab (MGD006): CD123 x CD3 Bispecific DART® Protein

• Flotetuzumab:
  – An investigational bispecific molecule that co-engages T cells (anti-CD3) with a tumor associated antigen (CD123)
  – Designed to:
    • Redirect T cells to kill tumor cells
    • Recognize tumors independent of TCR & MHC
  – Currently being tested in a Phase 1/2 study in patients with AML

• CD123, the low-affinity IL-3 receptor (IL3Rα)
  – Normally expressed on hematopoietic progenitor cells (HPCs), plasmacytoid dendritic cells (pDCs), basophils, monocytes
  – Over-expressed on leukemic stem cells (LSCs) in AML and other hematologic malignancies
  – Increased CD123 expression associated with increased risk of relapse

T-cell Infiltration in the Bone Marrow of a Flotetuzumab-treated Patient

Baseline

Flotetuzumab (Cycle 1)

Godwin et al, ASH 2019, Abstract No. 1410
Poor outcomes for Induction Failure and Early Relapse

Primary induction failure (PIF) and early relapse (CR < 6 months) AML patients are unmet medical need:

- 40-50% of patients with newly diagnosed AML fail to achieve CR with intensive induction therapy or experience disease recurrence after a short remission duration (<6 months)
- Only < 15% achieve remission following first salvage with conventional chemotherapy
- Subsequent salvage attempts are nearly universally ineffective
Immune Infiltration Associated with Poor Prognosis in AML

Cluster A (immune-enriched)  Cluster B (immune-depleted)

Higher IFN-γ and CD123 in Refractory AML Patients Treated with Flotetuzumab

IFN-γ score (NanoString PanCancer IO 360™ panel) in baseline AML bone marrow samples (n=30; subgroup of patients treated at the RP2D for whom BM samples were available) Mann-Whitney U test for unpaired samples

CD123 receptor density (no. of binding sites/cell) in primary induction failure & early relapse (n = 22) and late relapse AML (n = 7) treated at RP2D for whom data was available. Unpaired t-test
Baseline IFN-γ-related Gene Signatures Associate with Flotetuzumab Activity

IFN-γ-related gene signatures (NanoString PanCancer IO 360™ panel) in baseline BM samples
NR= no response; Data shown as mean, p-value calculated by Mann-Whitney U test for unpaired determinations
Samples n=30; subgroup of patients treated at the RP2D for whom BM samples were available
TIS: Tumor Inflammation Signature

Rutella et al. ASH 2019 Abstract # 460
Expansion in primary induction failure & early relapsed AML patients

Flotetuzumab Phase 1/2 Study Design

Key Entry Criteria (refractory AML population)

- Primary induction failure (PIF): refractory to ≥ 2 induction attempts
- Early relapse: First relapse with initial CR duration of < 6 months or any prior unsuccessful salvage
- No prior allogeneic hematopoietic cell transplant

Study Objectives

- Safety and preliminary clinical activity
- Optimize delivery and supportive care
- Define PK, PD and PK/PD relationships

Dose Escalation

- N=47

Expansion Cohort

- Relapsed/Refractory AML
- Recommended Phase 2 Dose (RP2D)
- N=50

Refractory Population

- (Primary Induction Failure & Early Relapse AML)
- N=30
Methods

- Recommended phase 2 dose (RP2D): 500 ng/kg/day by continuous infusion
  - Lead-in dose escalation (LID) during first week of treatment
  - Pre-medication includes 10-20 mg IV dexamethasone pre-dose

- Disease status assessed by modified IWG criteria
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Population (n=30)</th>
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<tbody>
<tr>
<td>Age, Median (range)</td>
<td>59 (27, 74)</td>
</tr>
<tr>
<td>Gender, Female</td>
<td>10 (33.3%)</td>
</tr>
<tr>
<td><strong>Disease Status at Study Entry</strong></td>
<td></td>
</tr>
<tr>
<td>Primary Induction Failure (≥ 2 induction attempts)</td>
<td>24 (80.0%)</td>
</tr>
<tr>
<td>Early Relapse (CR with initial duration &lt; 6 months)</td>
<td>6 (20.0%)</td>
</tr>
<tr>
<td><strong>ELN Risk Stratification (2017)</strong></td>
<td></td>
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<tr>
<td>Adverse</td>
<td>18 (60.0%)</td>
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<tr>
<td>Intermediate</td>
<td>7 (23.3%)</td>
</tr>
<tr>
<td>Favorable</td>
<td>5 (16.7%)</td>
</tr>
<tr>
<td><strong>Secondary AML</strong></td>
<td>12 (40.0%)</td>
</tr>
<tr>
<td><strong>Number of Prior Lines of Therapy, median (range)</strong></td>
<td>4 (1, 9)</td>
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<tr>
<td><strong>Failed induction therapy</strong></td>
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<tr>
<td>Cytarabine based induction chemotherapy</td>
<td>21 (70.0%)</td>
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<td>Alternative induction therapy</td>
<td>3 (10.0%)</td>
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<tr>
<td><strong>Early relapse (&lt;6 months)</strong></td>
<td></td>
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<tr>
<td>Number of patients</td>
<td>6 (20.0%)</td>
</tr>
<tr>
<td>Median duration of CR1 (range)</td>
<td>32 days (29-45)</td>
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*Data cut-off Nov 1st, 2019*
### Flotetuzumab: Phase 1/2 Population Safety

<table>
<thead>
<tr>
<th>Treatment Related Adverse Events*</th>
<th>Total RP2D Population (n=50)</th>
<th>Refractory Population (n=30)</th>
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<tbody>
<tr>
<td></td>
<td>All n (%)</td>
<td>Grade ≥ 3 n (%)</td>
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<tr>
<td>Infusion related reaction (IRR)/ Cytokine release syndrome (CRS)</td>
<td>48 (96.0)</td>
<td>4 (8.0)</td>
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<tr>
<td>Nausea</td>
<td>13 (26.0)</td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>11 (22.0)</td>
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</tr>
<tr>
<td>Diarrhea</td>
<td>11 (22.0)</td>
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<tr>
<td>Edema peripheral</td>
<td>10 (20.0)</td>
<td>1 (2.0)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>8 (16.0)</td>
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</tr>
<tr>
<td>Myalgia</td>
<td>8 (16.0)</td>
<td>2 (4.0)</td>
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<tr>
<td>Arthralgia</td>
<td>7 (14.0)</td>
<td>1 (2.0)</td>
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<tr>
<td>Dyspnea</td>
<td>9 (18.0)</td>
<td>3 (6.0)</td>
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<tr>
<td>Alanine aminotransferase increased</td>
<td>7 (14.0)</td>
<td>2 (4.0)</td>
</tr>
<tr>
<td>C-reactive protein increased</td>
<td>6 (12.0)</td>
<td>2 (4.0)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>6 (12.0)</td>
<td>1 (2.0)</td>
</tr>
<tr>
<td>Rash</td>
<td>6 (12.0)</td>
<td></td>
</tr>
<tr>
<td>Lymphocyte count decreased</td>
<td>8 (16.0)</td>
<td>7 (14.0)</td>
</tr>
<tr>
<td>White blood cell count decreased</td>
<td>8 (16.0)</td>
<td>7 (14.0)</td>
</tr>
<tr>
<td>Anemia</td>
<td>8 (16.0)</td>
<td>7 (14.0)</td>
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<tr>
<td>Platelet count decreased</td>
<td>7 (14.0)</td>
<td>7 (14.0)</td>
</tr>
</tbody>
</table>

*Events occurring >10%; Toxicity grading is based on CTCAE criteria version 4.0. Toxicity grading for events of IRR/CRS is based upon the modified grading scale proposed by Lee et al.

Data cut-off Nov 1st, 2019
Flotetuzumab: Strategy for Mitigation of Cytokine Release Syndrome

Several key interventions have helped mitigate CRS severity

- Introduction of early use of tocilizumab to forestall CRS development and limit use of more aggressive treatments
- Sequential increment in steps of lead-in dose (LID) schedules (from 1 step, to 2-step, to multi-step LID) have decreased CRS severity and incidence and increased the total flotetuzumab dose administered (dose intensity)
CRS Events Were Mild to Moderate in Severity in the PIF & Early Relapse AML

CRS was conservatively managed

Distribution of CRS Events by Grade

- Grade 1: 57.0% (57 patients)
- Grade 2: 42.0% (42 patients)
- Grade 3: 1.0% (1 patient)

Duration of CRS Events by Grade

- Median duration:
  - Grade 1: 1 day
  - Grade 2: 2 days
  - Grade 3: 3 days

- There were no grade 4 events

- CRS events were of short duration.
  - Median duration: Grade 1 = 1 day; Grade 2 = 2 days; Grade 3 = 3 days

- 19/30 patients received tocilizumab (10 dose for G1, 15 doses for G2, and 1 dose for G3 events)
- 5/30 patients have required steroids (3 doses for G1 and 3 doses for G2 events)
- 2/30 patients have required vasopressors (3 doses for G2 events)
Flotetuzumab is Active in Primary Induction Failure & Early Relapsed AML Patients

Benchmark analysis suggests historical CR+CRh rates in this setting of ~12.5%¹

<table>
<thead>
<tr>
<th>Responders (N)</th>
<th>ITT Population (N = 30)</th>
<th>Evaluable Pts (N = 28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>5</td>
<td>16.6%</td>
</tr>
<tr>
<td>CR + CRh</td>
<td>8</td>
<td>26.7%</td>
</tr>
<tr>
<td>CR + CRh + CRi</td>
<td>9</td>
<td>30.0%</td>
</tr>
</tbody>
</table>

Four responders (3 CR, 1 CRh) received allo-HSCT consolidation

30 refractory / early relapse pts treated at RP2D:
- 28 pts response evaluable
- 1 pt withdrew consent, 1 pt withdrawn due to non-treatment related AE
- 24 pts in waterfall plot: 4 pts were PD on circulating blasts

CR: complete response; CRh: complete response with partial hematological recovery
CRI: complete response with incomplete hematological improvement

Data cut-off Nov 1, 2019

¹ Unpublished analysis of the CLASSIC I, VALOR, ADMIRAL trials and additional trials that included venetoclax, gemtuzumab-ozogamicin, and IDH1/2 inhibitors; (n=1328): CR/CRh = 12.5% [95% CI = 7.7%, 19.6%]
Response to Flotetuzumab after Prior Lines of Therapy in PIF & Early Relapse AML

Greater response rates accrued in patients with up to 4 lines of prior therapy

<table>
<thead>
<tr>
<th>Prior Lines of Tx</th>
<th>Flotetuzumab (CR/CRh/CRi Rate)</th>
<th>Fractional</th>
<th>Cumulative</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td></td>
<td>55.6% (5/9)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>25.0% (1/4)</td>
<td>46.2% (6/13)</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>37.5% (3/8)</td>
<td>42.9% (9/21)</td>
</tr>
<tr>
<td>≥5</td>
<td></td>
<td>0.0% (0/7 )</td>
<td>32.1% (9/28)</td>
</tr>
</tbody>
</table>

Data cut-off Nov 1, 2019
## Flotetuzumab: Duration of Response in PIF & Early Relapsed AML Patients

<table>
<thead>
<tr>
<th>Prior Rx Lines</th>
<th>Prior Rx Included:</th>
<th>Response to Flotetuzumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>7+3/HiDAC</td>
<td>CRh→</td>
</tr>
<tr>
<td>2</td>
<td>HiDAC/Venetoclax</td>
<td>* CR→</td>
</tr>
<tr>
<td>3</td>
<td>HiDAC (x2)</td>
<td>* CR→</td>
</tr>
<tr>
<td>2</td>
<td>AZA/Midostaurin</td>
<td>* CR→</td>
</tr>
<tr>
<td>4</td>
<td>HiDAC (x2)/MEC</td>
<td>CR</td>
</tr>
<tr>
<td>2</td>
<td>7+3 (x2)</td>
<td>CR</td>
</tr>
<tr>
<td>2</td>
<td>HiDAC/Venetoclax</td>
<td>CRh</td>
</tr>
<tr>
<td>4</td>
<td>7+3/FLAG-Ida/FLAG</td>
<td>CRi</td>
</tr>
<tr>
<td>4</td>
<td>AZA/CD33xCD3 (Amv564)</td>
<td>CRh</td>
</tr>
</tbody>
</table>

- **Duration of Response**
- **Ongoing Response**
- **Survival**
- **HSCT**

**Data cut-off Nov 1, 2019**
Conclusions

- Flotetuzumab treatment in AML showed a manageable safety profile:
  - Lead-in dosing strategies and early tocilizumab usage have helped to blunt the severity of CRS

- An IFN-related gene-expression signature in baseline BM was associated with resistance to cytotoxic chemotherapy and response to flotetuzumab

- Flotetuzumab elicited clinical response (~30% CR/CR/CRi) in heavily pretreated patients who failed AML induction therapy or showed early relapse within 6 months of induction therapy
  - Historical data indicate a best response to salvage therapy of ~12.5%

- Enrollment has been expanded in patients with primary induction failure and early relapse AML
  - Parallel analysis will continue to identify flotetuzumab response-associated biomarkers
Acknowledgements

We are grateful to the patients who participated in this study and their families

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Future Development

Jan Davidson-Moncada, M.D., Ph.D.
Senior Clinical Research Director, MacroGenics
Ongoing and Planned Flotetuzumab Development

Pivotal monotherapy study planned; combination study with anti-PD-1 initiated

Phase 1/2 Dose Escalation
- Single Patient Dose Escalation
  - (3, 10, 30, 100ng/kg/day starting dose, N=14)

Phase 1/2 Expansion
- R/R AML
  - (N=50 at RP2D)

Pivotal
- Primary Induction Failure and Early Relapsed AML

- 3 + 3 Multi-patient Dose Escalation
  - 4-week cycles
  - (N=33)

Initiated
- R/R AML in Combination with MGA012 (Anti-PD-1)
  - (N=43)

*Pending ongoing discussions with FDA
**Strong Rationale for Combining Flotetuzumab with Anti-PD-1**

*Pending ongoing discussions with FDA*

MGA012 (also known as INCMGA00012) was exclusively licensed to Incyte Corporation in 2017 under a global collaboration and license agreement. MacroGenics retains the right to develop its pipeline molecules with MGA012.

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**Phase 1/2 Dose Escalation**
- Single Patient Dose Escalation (3, 10, 30, 100ng/kg/day starting dose, N=14)

**Phase 1/2 Expansion**
- 3 + 3 Multi-patient Dose Escalation 4-week cycles (N=33)
- R/R AML (N=50 at RP2D)

**Pivotal**
- Primary Refractory and Early Relapse AML

**Initiated**
- R/R AML in Combination with MGA012 (Anti-PD-1) (N=43)
Checkpoint Blockade May Enhance Anti-leukemic Activity of Flotetuzumab

- Checkpoint inhibition has changed the paradigm of cancer therapy, however treatment of AML with anti-PD-1 mAb has not been successful.

- Patients with an immune-infiltrated tumor microenvironment show high expression of immune checkpoints, including PD-L1 in a subgroup of patients.

- Based on internal analysis, a small subset of AML patients (~10-15%) express PD-L1 at baseline.

- The challenge is how to incorporate CPI in the treatment of patients with AML.

Rutella et al, ASH 2019 (Abstract #460); Rettig et al. ASH 2017 (Abstract #1365)
Checkpoint Molecules are Upregulated by Flotetuzumab In Vitro

CD4 and CD8 T cells from an AML patient express PD-1 after exposure to flotetuzumab

AML blasts express checkpoint molecules after exposure to flotetuzumab
**IFNγ Secretion and PD-L1 Expression in Patients Treated with Flotetuzumab**

Circulating IFNγ in AML patients treated with flotetuzumab

**PD-L1 expression on circulating AML blasts**

<table>
<thead>
<tr>
<th>Cohort (dose ng/kg/day)</th>
<th>IFNγ (pg/mL, mean ± SEM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>300</td>
<td>10 ± 1</td>
</tr>
<tr>
<td>500</td>
<td>20 ± 2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cohort (dose ng/kg/day)</th>
<th>PD-L1+ AML Blasts (% of total)</th>
</tr>
</thead>
<tbody>
<tr>
<td>300</td>
<td>0.5 ± 0.1</td>
</tr>
<tr>
<td>500</td>
<td>1.5 ± 0.2</td>
</tr>
</tbody>
</table>
Residual AML blasts from bone marrow of patients treated with flotetuzumab showed increased expression of PD-L1 compared to baseline.
PD-L1 Expression is Associated with Decreased Flotetuzumab Activity In Vitro

T cell activation and depletion of AML blasts by flotetuzumab in vitro.

Expression of immune checkpoint inhibitors on AML blasts was associated with lower anti-leukemic activity of flotetuzumab.
Patients who progressed early (<15 days) on flotetuzumab treatment had higher baseline levels of PD-L1 on AML cells than patients who had evidence of antileukemic activity.
PD-1/PD-L1 Blockade Enhances Flotetuzumab Anti-leukemic Activity In Vitro

Flotetuzumab combined with an anti-checkpoint antibody showed synergistic T-cell mediated cytotoxicity of an AML cell line (KG1A)
*p<0.05
Checkpoint Blockade May Enhance Anti-leukemic Activity of Flotetuzumab

- Flotetuzumab, in clinical and/or preclinical studies, led to:
  - increased T cell infiltration and activation in the bone marrow,
  - enhanced secretion of IFNγ,
  - upregulation of checkpoint molecules on subset of AML blasts.

- PD-L1 is upregulated in residual AML blasts after treatment with flotetuzumab

- Flotetuzumab combined with an anti-checkpoint antibody in vitro showed synergistic T-cell mediated cytotoxicity of an AML cell line.

- Flotetuzumab combined with PD-1 inhibition aims to obviate pathways of AML resistance and harness positive changes of immune modulation induced by flotetuzumab.
Flotetuzumab + MGA012 (Anti-PD-1 mAb) Combination Study in R/R AML

Phase 1 dose escalation study design

- **Induction** with flotetuzumab is administered by step-up, lead-in dosing, followed by continuous infusion, starting at week 2 and continuing through 28-day cycles.

- **Consolidation or second induction** with flotetuzumab based on response.

- **Maintenance** with MGA012 monotherapy for up to 12 months for eligible patients who achieved a complete remission during induction/consolidation.

Study is being conducted ex-US (in Australia, Spain and Israel).

Capturing Full Potential of Flotetuzumab and CD123 x CD3 Bispecific Molecules

Future Development Opportunities
- Other CD123+ Hematologic Malignancies
- 2nd Gen. Molecule in Preclinical Development
  - Fc-bearing; alternate CD3 binder

Expand Through Combinations
- Relapsed/Refractory AML (w/checkpoints)
  - Combination with MGA012 initiated

Potential First Indication
- Primary Induction Failure/Early Relapsed AML
  - Pivotal monotherapy study being planned*

*Pending ongoing discussions with FDA
Key Takeaways

Scott Koenig, M.D., Ph.D.
President and Chief Executive Officer, MacroGenics
Flotetuzumab Potential First-in-Class Molecule for the Treatment of AML

• **Path to a potential approval in primary refractory and early relapse patients**
  – Significant anti-leukemic activity observed (~32% CR/CRh/CRi rate) in hard-to-treat population
  – Immune signature supports mechanism and may predict response
  – Pivotal study being planned, discussions with FDA ongoing, update anticipated 1H2020

• **Significant patient opportunity**
  – No agents specifically approved for primary refractory population
  – Agnostic to known, targetable, disease-associated mutations
  – Continuous infusion not a barrier to implementation and helps exposure
  – 2nd generation molecule to expand addressable indications

• **Compelling rationale for combination with anti-PD-1**
  – May enhance the effect of flotetuzumab and obviate resistance
  – Phase 1/2 study in relapsed/refractory AML initiated (ex-US)

CR=complete remission. CRh=CR with partial hematologic recovery. CRi=CR with incomplete hematological recovery.
Q&A Session

Scott Koenig, M.D., Ph.D.  President & Chief Executive Officer, MacroGenics

Jan Davidson-Moncada, M.D., Ph.D.  Senior Clinical Research Director, MacroGenics

Geoff Uy, M.D.  Associate Professor, Bone Marrow Transplantation & Leukemia, Washington University School of Medicine, St. Louis

Sergio Rutella, M.D., Ph.D., FRCPtach  Professor, Cancer Immunotherapy, John van Geest Cancer Research Centre, Nottingham Trent University, UK
Thank You!

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