Targeted Alpha-Particle Therapy for Hematologic Malignancies

Joseph G. Jurcic, MD
Professor of Medicine at CUIMC
Director, Hematologic Malignancies
Columbia University Irving Medical Center
Attending Physician, New York-Presbyterian Hospital
E-mail: jgj2110@cumc.columbia.edu
225Ac-lintuzumab is an investigational agent currently in development for use in AML, MDS, and multiple myeloma.

<table>
<thead>
<tr>
<th>Company</th>
<th>Research Support</th>
<th>Consultant</th>
<th>Advisory Board</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actinium Pharmaceuticals</td>
<td>×</td>
<td></td>
<td>×</td>
</tr>
<tr>
<td>AbbVie</td>
<td>×</td>
<td>×</td>
<td></td>
</tr>
<tr>
<td>Astellas</td>
<td>×</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AstraZeneca</td>
<td></td>
<td>×</td>
<td></td>
</tr>
<tr>
<td>Boston Biomedical</td>
<td></td>
<td>×</td>
<td></td>
</tr>
<tr>
<td>Celgene</td>
<td>×</td>
<td>×</td>
<td></td>
</tr>
<tr>
<td>Daiichi Sankyo</td>
<td>×</td>
<td>×</td>
<td></td>
</tr>
<tr>
<td>Forma Therapeutics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genentech</td>
<td>×</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kura Oncology</td>
<td>×</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Novartis</td>
<td></td>
<td>×</td>
<td></td>
</tr>
<tr>
<td>Seattle Genetics</td>
<td>×</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Syros Pharmaceuticals</td>
<td>×</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Pathogenesis of Acute Myeloid Leukemia

Normal Hematopoiesis

Leukemogenesis

1. Lack of Differentiation
   - AML1/ETO
   - PML/RARα
   - MLL rearrangements

2. Increased Proliferation
   - BCR/ABL
   - TEL/PDGFBβR
   - N-RAS, K-RAS mutants
   - FLT3, c-KIT mutations

Prognostic Factors for AML

**Survival by Age**¹

![Graph showing survival by age](image)

**Survival by Karyotype**²

![Graph showing survival by karyotype](image)

²Byrd JC *et al.* *Blood* 2002;100:4325-4336.
Acute Myeloid Leukemia in Older Patients

Incidences of AML by Age

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Percentage of New Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20</td>
<td>4.9</td>
</tr>
<tr>
<td>20-34</td>
<td>6</td>
</tr>
<tr>
<td>35-44</td>
<td>5.3</td>
</tr>
<tr>
<td>45-54</td>
<td>9.5</td>
</tr>
<tr>
<td>55-64</td>
<td>16.9</td>
</tr>
<tr>
<td>65-74</td>
<td>24.3</td>
</tr>
<tr>
<td>75-84</td>
<td>22.6</td>
</tr>
<tr>
<td>&gt;84</td>
<td>10.5</td>
</tr>
</tbody>
</table>

Treatment Options for Older Patients

<table>
<thead>
<tr>
<th>Regimen</th>
<th>CR/CRi</th>
<th>Median OS (mos.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDAC²</td>
<td>18%</td>
<td>~ 5</td>
</tr>
<tr>
<td>Decitabine³</td>
<td>18%</td>
<td>7.7</td>
</tr>
<tr>
<td>Azacitidine⁴</td>
<td>27.8%</td>
<td>12.1</td>
</tr>
<tr>
<td>Venetoclax + HMA⁵</td>
<td>67%</td>
<td>17.5</td>
</tr>
</tbody>
</table>

Abbreviations: LDAC, low-dose cytarabine; HMA, hypomethylating agent; CR, complete remission; CRi, CR with incomplete count recovery; OS, overall survival.

CD33 Surface Antigen Expression

- Stem Cell
- CFU-GEMM
- CFU-Meg → Mega
  - Pro-normoblast → Platelets
  - Pro-myo-lymphocyte → RBC
- BFU-E → CFU-GM
  - Myelo-blast → PMN
  - Mono-blast → Mono-cytes

CD33+ and CD33−
Lintuzumab (HuM195, SGN-33)

- Humanized anti-CD33 monoclonal antibody
- Kills target cells by ADCC and fixes complement\(^1\)
- Rapidly targets leukemia cells in patients without immunogenicity\(^2\)
- Has modest activity in relapsed AML\(^3\)

\(^3\) Raza A et al. Leuk Lymph 2009; 50:1336-1344.
Alpha- vs. Beta-Particle Radioimmunotherapy

β-Particle
1-10 mm range
0.1-1 MeV

α-Particle
50-80 µm range
5-8 MeV

Tumor
Normal Endothelium
Blood Vessel
**213**Bi-Lintuzumab: A 1st Generation α-Emitting Conjugate

<table>
<thead>
<tr>
<th>Isotope</th>
<th>Alpha Decay</th>
<th>Stability</th>
</tr>
</thead>
<tbody>
<tr>
<td>225Ac</td>
<td>α 10 days</td>
<td>221Fr</td>
</tr>
<tr>
<td></td>
<td>α 4.9 min</td>
<td>217At</td>
</tr>
<tr>
<td></td>
<td>α 0.032 sec</td>
<td>213Bi</td>
</tr>
<tr>
<td></td>
<td>α 46 min</td>
<td>Stable</td>
</tr>
</tbody>
</table>

- 10.36-37 MBq/kg delivered in 3-7 fractions over 2-4 days
- Myelosuppression lasted 12-41 days (median, 22 days)
- Transient liver function abnormalities seen in 6 patients
- MTD was not reached
- 14/18 patients had reductions in marrow blasts


\[ ^{213} \text{Bi-Lintuzumab Biodistribution} \]

1st Injection  Last injection

Posterior 60-Minute Summation

Rate/Minute

Max. rate: 4.8
Min. rate: -3.9

Comparison of $^{131}$I, $^{90}$Y, and $^{213}$Bi Dosimetry for Lintuzumab

<table>
<thead>
<tr>
<th>Isotope</th>
<th>Mean Absorbed Dose (mSv/MBq)</th>
<th>Marrow/Liver/Whole Body</th>
<th>Marrow/Whole Body Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Marrow</td>
<td>Liver</td>
<td>Whole Body</td>
</tr>
<tr>
<td>$^{131}$I</td>
<td>2.7</td>
<td>0.8</td>
<td>0.16</td>
</tr>
<tr>
<td>$^{90}$Y</td>
<td>6.8</td>
<td>4.0</td>
<td>0.49</td>
</tr>
<tr>
<td>$^{213}$Bi</td>
<td>9.8</td>
<td>5.8</td>
<td>0.0004</td>
</tr>
</tbody>
</table>

Rationale for α-Particle Emitters in Cytoreduced Disease

• The short range and high LET make α-particles best suited for treatment of small-volume disease.

• Given the number of CD33 binding sites in AML and achievable specific activity, it is difficult to target adequate numbers of $^{213}$Bi atoms to each leukemia cell.

• Hypothesis: Cytoreduction with cytarabine should decrease tumor burden by 1-2 logs and increase the ratio of $^{213}$Bi atoms to target cells.
**213**Bi-Lintuzumab for Cytoreduced Disease

**Study Design**

**Cytarabine**
- 200 mg/m²/day

**Evaluate for:**
- Toxicity, maximum tolerated dose
- Biodistribution, dosimetry
- Biological effects, remission rate

**213**Bi-Lintuzumab
- **Level 1:** 18.5 MBq/kg
- **Level 2:** 27.75 MBq/kg
- **Level 3:** 37 MBq/kg
- **Level 4:** 46.25 MBq/kg

**G-CSF**
- Days 3, 4, 5, 14

$^{213}$Bi-Lintuzumab for Cytoreduced Disease

Biodistribution and Rate Imaging

Posterior 60-Minute Summation

Rate/Minute

# Results by Disease Status for $^{213}$Bi-Lintuzumab Doses ≥ 37 MBq/kg

<table>
<thead>
<tr>
<th>Disease Status</th>
<th>No. of Patients</th>
<th>CR</th>
<th>CRp</th>
<th>PR</th>
<th>Overall Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated AML, Untreated relapse</td>
<td>18</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>6 (33%)</td>
</tr>
<tr>
<td>$^{1}$ refractory, Refractory relapse</td>
<td>7</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*Abbreviations: CR, complete remission; CRp, CR with incomplete platelet recovery; PR, partial remission.*

Actininium-225: An Alpha-Particle Nanogenerator

- Short half-life and need for on-site generator limit use of $^{213}$Bi.
- $^{225}$Ac can be stably conjugated to antibodies using DOTA.
- $^{225}$Ac-labeled antibodies are 1,000-10,000 times more potent *in vitro* compared to $^{213}$Bi analogs.
- Nanocurie doses of $^{225}$Ac-labeled antibodies prolong survival of mice in xenograft models.

Phase I Trial of $^{225}$Ac-Lintuzumab

- 18 patients with R/R AML received a single dose of 18.5-148 kBq/kg
- DLT was myelosuppression
- No renal toxicity was seen
- MTD was 111 kBq/kg
- Bone marrow blasts were reduced in 10/15 (67%) evaluable patients
- 8 patients (53%) had marrow blast reductions of ≥ 50%
- 3 patients achieved ≤ 5% marrow blasts at doses of 37, 111, and 148 kBq/kg

Pharmacokinetics of $^{225}$Ac-Lintuzumab

- Determined by $\gamma$ counting at energy windows for:
  - $^{221}$Fr (185-250 KeV)
  - $^{213}$Bi (360-480 KeV)

- Two-phase elimination kinetics were seen:
  - Mean plasma $t_{1/2-\alpha} = 1.9$ hrs
  - Mean plasma $t_{1/2-\beta} = 38$ hrs

- Similar to $^{131}$I- and $^{90}$Y- but distinct from $^{213}$Bi-lintuzumab

Low-Dose Cytarabine (LDAC) Plus $^{225}$Ac-Lintuzumab

Low-Dose Cytarabine 20 mg SQ BID

$^{225}$Ac-Lintuzumab
- **Level 1**: 18.5 kBq/kg/fraction
- **Level 2**: 37 kBq/kg/fraction
- **Level 3**: 55.55 kBq/kg/fraction
- **Level 4**: 74 kBq/kg/fraction

Furosemide 40 mg po daily

Spironolactone 25 mg po daily

Juricic JG et al. SNMMI 2017; abstract 456.
## LDAC plus $^{225}$Ac-Lintuzumab

### Objective Responses

<table>
<thead>
<tr>
<th>Response</th>
<th>Dose Level (kBq/kg/fraction)</th>
<th>Total (N=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>18.5 (n=3)</td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>0</td>
<td>1 (6%)</td>
</tr>
<tr>
<td>CRp</td>
<td>0</td>
<td>2 (11%)</td>
</tr>
<tr>
<td>CRi*</td>
<td>0</td>
<td>2 (11%)</td>
</tr>
<tr>
<td>Overall</td>
<td>0</td>
<td>5 (28%)</td>
</tr>
<tr>
<td></td>
<td>37 (n=6)</td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>0</td>
<td>1 (17%)</td>
</tr>
<tr>
<td>CRp</td>
<td>1 (17%)</td>
<td>2 (11%)</td>
</tr>
<tr>
<td>CRi*</td>
<td>0</td>
<td>2 (11%)</td>
</tr>
<tr>
<td>Overall</td>
<td>1 (17%)</td>
<td>5 (28%)</td>
</tr>
<tr>
<td></td>
<td>55.5 (n=3)</td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>1 (33%)</td>
<td></td>
</tr>
<tr>
<td>CRp</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>CRi*</td>
<td>1 (33%)</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>2 (67%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>74 (n=6)</td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CRp</td>
<td>1 (17%)</td>
<td>1 (17%)</td>
</tr>
<tr>
<td>CRi*</td>
<td>1 (17%)</td>
<td>1 (17%)</td>
</tr>
<tr>
<td>Overall</td>
<td>2 (67%)</td>
<td>5 (28%)</td>
</tr>
</tbody>
</table>

**Abbreviations:** CR, complete remission; CRp, CR with incomplete platelet recovery; CRi, CR with incomplete blood count recovery.

All responses seen after Cycle 1.

Effect of Peripheral Blasts on Response

- 36 patients from initial 2 trials analyzed for response by:
  - Age
  - Disease characteristics
    - Newly diagnosed vs. relapsed
    - De novo vs. secondary AML
    - Genetic risk category
  - Disease burden
    - Bone marrow blast percentage
    - Peripheral blood blast count
  - Treatment regimen
    - Administered activity
    - Single vs. fractionated dose
    - Monotherapy vs. prior LDAC
- Only significant predictor of response was peripheral blood blast count
  - Circulating blasts may alter biodistribution leading to decreased delivery of isotope to marrow

Phase II Trial of $^{225}$Ac-Lintuzumab Monotherapy

Study Design

**Key Eligibility Criteria:**

- Patients $\geq 60$ years with untreated AML unfit for standard chemotherapy
  - Patients 60-74 years were required to have significant co-morbidities
  - All patients $\geq 75$ years were eligible
- Patients with antecedent hematologic disorders (AHDs) allowed
  - CD33 expression by $> 25\%$ of blasts
  - Hydroxyurea permitted prior to treatment

Finn LE *et al.* *Blood* 2017; 130:2638; Atallah EL *et al.* *Blood* 2018; 130:1457; Berger M *et al.* TAT 11 2019; poster 61.
## Phase II Trial of $^{225}$Ac-Lintuzumab Monotherapy

### Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of patients (N=40)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range), years</td>
<td>75 (60-87)</td>
<td></td>
</tr>
<tr>
<td>Antecedent hematologic disorder (AHD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myelodysplastic syndrome (MDS)</td>
<td>23</td>
<td>58</td>
</tr>
<tr>
<td>Chronic myelomonocytic leukemia</td>
<td>16</td>
<td>40</td>
</tr>
<tr>
<td>Atypical chronic myeloid leukemia</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>Therapy-related myeloid neoplasm</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Myelofibrosis</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Prior therapy for ADH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypomethylating agents</td>
<td>18</td>
<td>78</td>
</tr>
<tr>
<td>Immunomodulatory imid drug (IMiD)</td>
<td>13</td>
<td>57</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>Ruxolitinib</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>Cytogenetic and molecular features</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Favorable-risk</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Intermediate-risk</td>
<td>21</td>
<td>53</td>
</tr>
<tr>
<td>Adverse-risk</td>
<td>10</td>
<td>25</td>
</tr>
<tr>
<td>Unknown</td>
<td>6</td>
<td>15</td>
</tr>
</tbody>
</table>

Berger M et al. TAT 11 2019; poster 61.
# Phase II Trial of $^{225}$Ac-Lintuzumab Monotherapy

## Clinical Results

<table>
<thead>
<tr>
<th>Dose (kBq/kg)</th>
<th>Response Rate</th>
<th>Patients with Gr 4 Thrombocytopenia $&gt; 6$ weeks</th>
<th>Patients with Gr 4 Neutropenia $&gt; 6$ weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>74 (n=13)</td>
<td>69% 1 CR, 2 CRp, 6 CRi</td>
<td>46%</td>
<td>38%</td>
</tr>
<tr>
<td>55.5 (n=27)</td>
<td>22% 3 CRp, 3 CRi</td>
<td>30%</td>
<td>40%</td>
</tr>
</tbody>
</table>

*Abbreviations:* CR, complete remission; CRp, CR with incomplete platelet recovery; CRi, CR with incomplete blood count recovery.

Berger M *et al.* TAT 11 2019; poster 61.
Tailored $^{225}\text{Ac}$ dose for specific clinical application

Post-Phase II Monotherapy Trial Strategy

High-Dose

- Targeted Conditioning
  - Conditioning for HCT in High-Risk MDS

Low-Dose

- Combination Therapy
  - Combination with Venetoclax
  - Combination with CLAG-M
  - Minimal Residual Disease in AML
  - CD33$^+$ Multiple Myeloma

Single-Agent
Targeted HCT Conditioning in MDS

- Single-agent activity seen in Phase II study in patients with prior MDS
- $^{225}$Ac-lintuzumab added to reduced-intensity conditioning (RIC) before HCT for high-risk MDS
- High-dose single-agent outpatient administration
- Brief dose-confirming Phase I followed by randomized pivotal trial
Combination Trials: Venetoclax

- Venetoclax is a BCL-2 inhibitor approved for advanced CLL\(^1\) and unfit AML patients\(^2\)
- \(^{225}\text{Ac-lintuzumab}\) synergizes with venetoclax by decreasing MCL-1
- \(^{225}\text{Ac-lintuzumab with venetoclax for R/R AML}\)
- \(^{225}\text{Ac-lintuzumab with venetoclax + azacitidine for R/R AML}\)

Combination Trials: CLAG-M

- CLAG-M is a salvage chemotherapy regimen consisting of:
  - Cladribine
  - Cytarabine (Ara-C)
  - Mitoxantrone
  - G-CSF
- Produces remission in ~50% of patients with R/R AML
- $^{225}$Ac-lintuzumab with CLAG-M adds a new modality of targeted radiation to chemotherapy in a radiation sensitive malignancy

**Single Agent Trials: Minimal Residual Disease**

- AML patients in remission but with detectable MRD are at high risk for relapse

- $^{225}$Ac-lintuzumab at low doses in patients with AML who achieve CR but have MRD
  - Multiple monthly doses
  - Follow MRD by flow cytometry

Single Agent Trials: Multiple Myeloma

- 25% of MM patients are CD33+
- CD33 expression is associated with a poor outcome
- $^{225}$Ac-lintuzumab for patients with R/R MM
- First anti-CD33 antibody study in MM

Conclusions

• Early studies with $^{213}$Bi-lintuzumab provided proof-of-principle that systemically administered targeted $\alpha$-particle therapy is feasible.

• $^{225}$Ac-lintuzumab is active against advanced AML.

• $^{225}$Ac-lintuzumab has produced remissions in older patients with untreated AML as a single agent and in combination with LDAC.

• These studies provide the rationale for use of $^{225}$Ac-lintuzumab in combination with other agents in AML and in other hematologic malignancies such as MDS and multiple myeloma.
Acknowledgments

Columbia University Medical Center
   Todd L. Rosenblat
   Chaitanya R. Divgi
   Mark Frattini

Memorial Sloan-Kettering Cancer Center
   David A. Scheinberg
   Jorge Carrasquillo
   Suzanne Chanel
   Michael Curcio
   Dan Douer
   John Humm
   Jaspreet S. Jaggi
   Katherine S. Kolbert
   Steven M. Larson
   Michael R. McDevitt
   Neeta Pandit-Taskar
   Shutian Ruan

National Cancer Institute
   Martin Brechbiel
   Otto Gansow

Johns Hopkins University
   George Sgouros

Institute for Transuranium Elements
   Christos Apostolidis
   Roger Molinet
   Alfred Morgenstern

U.S. Department of Energy
   John McClure
   Saed Mizradeh

Actinium Pharmaceuticals, Inc.
   Mark S. Berger
   Dale Ludwig

Multicenter Trial Investigators
   Ehab Atallah, Medical College of Wisconsin
   Kebede H. Begna, Mayo Clinic
   Michael Craig, West Virginia University
   Laura E. Finn, Ochsner Medical Center
   Sharif S. Khan, Bon Secours St. Francis Cancer Center
   M. Yair Levy, Baylor University
   Raya Mawah, Swedish Cancer Institute
   Johnnie J. Orozco, Fred Hutchinson Cancer Research Center
   John Pagel, Swedish Cancer Institute
   Jae Park, Memorial Sloan Kettering Cancer Center
   Alexander Perl, University of Pennsylvania
   Farhad Ravandi, MD Anderson Cancer Center
   David A. Rizzieri, Duke University
   Gail Roboz, Weill Cornell Medical College
   B. Douglas Smith, Johns Hopkins University
   William Tse, University of Louisville

Patients participating in these studies