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IMGN632 in R/R AML and BPDCN, abstract #27
CD123 as a Therapeutic Target

- CD123, the $\alpha$-subunit of interleukin-3 receptor (IL-3R$\alpha$), is expressed in the majority of AML and nearly all BPCDN (blastic plasmacytoid dendritic cell neoplasm) and B-cell acute lymphoblastic leukemia (B-ALL) cases$^{1,2}$

- CD123 is elevated on AML blasts and leukemic stem cells compared with normal hematopoietic stem and progenitor cells$^3$

- CD123-directed therapy may be able to de-bulk and potentially eliminate the source of disease

- CD123 is rapidly internalized making it well suited for antibody-drug conjugate (ADC)-based therapeutic strategies

IMGN632: A Novel CD123-Targeting ADC

- Novel Anti-CD123 Antibody
  - Higher affinity binding to CD123
  - Unique epitope in extracellular domain

- Novel IGN Payload (DGN549)
  - DNA-alkylating activity, single strand DNA breaks (vs. double strand)
  - 10-20x more potent than the IGN in IMGN779
  - Uniform loading of 2 IGN molecules per antibody

- Stable Peptide Linker
  - Protease cleavable
  - Confers stability in circulation, and controlled intracellular payload release

1 - ADC binds target
2 - ADC internalized
3 - Payload released
4 - Payload alkylates DNA

Kovtun et al. 2018 *Blood Adv* 2:848-858
Objectives of Dose-Escalation Study

Primary
- Establish MTD and define RP2D of IMGN632 monotherapy in relapsed AML and relapsed BPDCN

Secondary
- Determine safety and tolerability of IMGN632, including dose-limiting toxicities (DLTs)
- Characterize preliminary antileukemia activity (CR+CRi) and pharmacokinetic (PK) profile of IMGN632 in AML and BPDCN

MTD, maximum tolerated dose; RP2D, recommended Phase 2 dose
Study Design

- Adult patients with CD123-positive (local, any level by flow or IHC), relapsed or refractory AML or BPDCN, with no more than 3 prior lines of therapy

- 3+3 escalation, with ability to expand multiple dose-levels

- IMGN632 administered i.v. on Day 1 of a 21-day cycle (Q3W)

- Starting dose 0.015 mg/kg, with escalation using a modified Fibonacci schema
### Enrollment (N=33)

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>Escalation Phase</th>
<th>Expansion Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.45</td>
<td>n=2</td>
<td></td>
</tr>
<tr>
<td>0.3</td>
<td>n=3</td>
<td>n=2</td>
</tr>
<tr>
<td>0.18</td>
<td>n=3</td>
<td>n=4</td>
</tr>
<tr>
<td>0.09</td>
<td>n=3</td>
<td>n=1, ongoing</td>
</tr>
<tr>
<td>0.045</td>
<td>n=3</td>
<td>n=9, ongoing</td>
</tr>
<tr>
<td>0.015</td>
<td>n=3</td>
<td></td>
</tr>
</tbody>
</table>

- Doses between 0.015 and 0.45 mg/kg Q3W were explored
- Four dose levels were expanded for efficacy and further safety assessment

*IMGN632 in R/R AML and BPDCN, abstract #27*
Pharmacokinetics and CD123 Saturation

- Sustained exposure through 48 hr post infusion at doses ≥ 0.09 mg/kg
- Continued increase in maximal concentrations and exposure with increased dose
- CD123 saturation >24 hours observed at doses ≥ 0.09 mg/kg

IMGN632 in R/R AML and BPDCN, abstract #27
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years</strong></td>
<td>70 [40-80]</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td>13 (39)</td>
</tr>
<tr>
<td><strong>Disease</strong></td>
<td>30 (91)</td>
</tr>
<tr>
<td>AML</td>
<td></td>
</tr>
<tr>
<td>BPDCN</td>
<td>3 (9)</td>
</tr>
<tr>
<td><strong>Prior therapy</strong></td>
<td>5 (15)</td>
</tr>
<tr>
<td>Non-intense only (e.g. HMA, IDHi)</td>
<td></td>
</tr>
<tr>
<td>Intense (e.g. 7+3, HiDAC, SCT)</td>
<td>19 (58)</td>
</tr>
<tr>
<td>Incomplete data</td>
<td>9</td>
</tr>
<tr>
<td><strong>Prior Transplant</strong></td>
<td>6 (18)</td>
</tr>
<tr>
<td><strong>Disease status</strong></td>
<td>9 (27)</td>
</tr>
<tr>
<td>First relapse</td>
<td></td>
</tr>
<tr>
<td>Primary refractory</td>
<td>5 (15)</td>
</tr>
<tr>
<td>Relapsed refractory (second relapse or</td>
<td>15 (46)</td>
</tr>
<tr>
<td>beyond)</td>
<td></td>
</tr>
<tr>
<td>Incomplete data</td>
<td>4</td>
</tr>
</tbody>
</table>

*All patients (AML and BPDCN) are combined for demographics.*
Treatment-Emergent Adverse Events (TEAEs >10%) (N=33)
Safety Summary (n=33)

• Patients received a median of two Q3W IMGN632 doses (range, 1-6)

• Most frequent IMGN632-related AEs were infusion-related reactions (IRRs; chills, tachycardia, nausea/vomiting, diarrhea).
  – The frequency of IRRs decreased with steroid premedication

• DLTs and related SAEs:
  – febrile neutropenia (3 SAEs)
  – reversible veno-occlusive disease (VOD) (2 DLTs)
    • 0.45 mg/kg moderate VOD, alloSCT for MDS 1 year prior, after 1 dose, typical symptoms per Baltimore criteria
    • 0.18 mg/kg mild VOD, after 2 doses, only symptom was ascites, no Doppler flow changes, liver biopsy showed early VOD
  – prolonged neutropenia (1 DLT): 0.3 mg/kg after 2 doses

• Three deaths within 30 days of last dose of IMGN632: progression (n=2), unknown cause (n=1, possibly related)
Anti-leukemia Activity
BM-evaluable AML Patients (N=23)
Best Decrease from Baseline in Bone Marrow Blasts (%)

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Preliminary Responses in BPDCN patients

- 3 patients with relapsed/refractory BPDCN have been dosed at dose level 2 (0.045 mg/kg Q3W)
  - All had received SL-401 previously

- #1: Had resolution of skin lesions (cleared visually, biopsy negative), PET (significantly reduced lesions) and BM (84% to 5%) after first IMGN632 dose. After second dose, BM cleared (0%), but small PET positive lesions noted, came off treatment. Best response = PR

- #2: Had stable skin lesions, Stable PET/CT after 1 dose of IMGN632. Ongoing cycle 2. Stable disease.

- #3: Had improvement in skin lesions (nearly resolved, biopsy negative), complete resolution of PET, and BM (37% to 0%) with one dose of IMGN632. Ongoing cycle 2. Best response = unconfirmed CRi
Rapid response in a refractory BPDCN patient

- 69yo female with MDS/BPDCN, partial response to 1 cycle of SL-401 but had liver toxicity, then failed salvage with CLAG-M and enrolled on this study with diffuse bone involvement, numerous lymph node and subcutaneous lesions, and 9 skin tumors.

- A) PET images and B) skin lesions from screening and 3 weeks later, after 1 dose IMGN632 at 0.045 mg/kg (dose level 2)
### Summary of Responses and Safety

<table>
<thead>
<tr>
<th>Cohort Dose (mg/kg)</th>
<th>1 0.015</th>
<th>2 0.045</th>
<th>3 0.09</th>
<th>4 0.18</th>
<th>5 0.3</th>
<th>6 0.45</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AML Responses</strong></td>
<td>1/3 CRi</td>
<td>2/8 CR, CRi</td>
<td>1/2 CRi</td>
<td>1/6 CR</td>
<td>1/3 CRi</td>
<td>0/1</td>
<td>23</td>
</tr>
<tr>
<td><strong>BPDCN responses</strong></td>
<td></td>
<td>2/3 PR, CRi</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3</td>
</tr>
<tr>
<td><strong>DLTs</strong></td>
<td></td>
<td></td>
<td></td>
<td>1/7</td>
<td>1/5</td>
<td>1/2</td>
<td></td>
</tr>
</tbody>
</table>

*in patients with end of cycle 1 bone marrow

- AML responses are seen across a wide dose range (0.015-0.3 mg/kg)
- BPDCN responses observed
- Single DLTs have been seen at higher doses (0.18, 0.3, and 0.45 mg/kg)
  - Toxicity at 0.3 mg/kg and above is consistent with pre-clinical modeling
- Expansion continues at doses 0.045 and 0.09 mg/kg

IMGN632 in R/R AML and BPDCN, abstract #27
Conclusions

• The anti-CD123 ADC IMGN632 is tolerable at doses up to 0.3 mg/kg
  — Overall AE profile consistent with underlying disease
  — No evidence of cumulative toxicity following multiple doses (up to 6 doses)
  — Single DLTs seen at higher dose levels 0.18, 0.3, 0.45 mg/kg
    • 2 reversible VOD and 1 prolonged neutropenia

• CR/CRi in 26% of R/R AML and responses in 2 of 3 relapsed BPDCN patients
  — CR/CRis seen at a wide range of doses (0.015-0.3 mg/kg)
  — BPDCN responses after SL-401 failures

• IMGN632 demonstrates initial safety and activity in patients with AML and BPDCN
  — Ongoing enrollment on expansion cohorts and fractionated schedule
Thank You
to the patients and families