Clinical Profile of IMGN632, a Novel CD123-Targeting Antibody-Drug Conjugate (ADC), in Patients with Relapsed/Refractory (R/R) Blastic Plasmacytoid Dendritic Cell Neoplasm (BPDCN)

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BPDCN Background

- BPDCN is a rare, aggressive hematologic malignancy characterized by historically poor overall survival and limited therapeutic options

- Overexpression of CD123 (IL-3Rα) is present in all BPDCN cases, thereby establishing this surface marker as a rational target for therapeutic intervention

- Despite the recent approval of tagraxofusp-erzs, outcomes remain poor in the setting of relapsed and refractory (R/R) BPDCN and novel approaches are urgently needed
IMGN632: A Novel CD123-Targeting ADC

- Novel Anti-CD123 Antibody
  - High affinity binding to CD123
  - Unique epitope in extracellular domain
- Novel IGN Payload (DGN549)
  - DNA-alkylating activity, single strand DNA breaks (vs. double strand)
  - Uniform drug antibody ratio (DAR=2)
- Novel Peptide Linker
  - Confers greater stability in circulation
  - Efficient intracellular payload release

IMGN632 demonstrated 22-40% ORR in R/R AML at the RP2D of 0.045 mg/kg every 3 weeks, in subgroups of de novo and relapsed patients (ASH 2019)

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

Kovtun Blood Adv 2018, Daver ASH 2019
IMGN632 in BPDCN, abstract #167
Efficacy in refractory BPDCN PDX models

- IMGN632 rapidly cleared BPDCN in the bone marrow
- IMGN632 dramatically extended the lifespan of BPDCN tumor-bearing mice

Zhang Konopleva ASH.2018
IMGN632 in BPDCN, abstract #167
Study Design and Objectives

Study Design
• Patients ≥18 years old
• BPDCN, R/R or frontline
• Any CD123 positivity (flow cytometry or IHC)
• Up to 4 prior lines of therapy
• No minimum serum albumin requirement
• IMGN632 (0.045 mg/kg) is administered IV in under 30 minutes on day 1 of a 21-day cycle

Objectives
• Establish safety and tolerability and initial efficacy of IMGN632 in patients with BPDCN
## Patient Characteristics (n=29)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age years, median (range)</strong></td>
<td>72y (19-82)</td>
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<tr>
<td><strong>Gender, % (n)</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>76% (22)</td>
</tr>
<tr>
<td>Female</td>
<td>24% (7)</td>
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<tr>
<td><strong>Disease, % (n)</strong></td>
<td></td>
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<tr>
<td>Compartment involvement</td>
<td></td>
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<tr>
<td>Skin</td>
<td>69% (20)</td>
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<tr>
<td>Bone marrow</td>
<td>62% (18)</td>
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<tr>
<td>Lymph node/visceral</td>
<td>52% (15)</td>
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<tr>
<td>Prior/concurrent malignancy</td>
<td>24% (7)</td>
</tr>
<tr>
<td><strong>Baseline status, % (n)</strong></td>
<td></td>
</tr>
<tr>
<td>First relapse</td>
<td>21% (6)</td>
</tr>
<tr>
<td>Primary refractory</td>
<td>59% (17)</td>
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<tr>
<td>Relapsed</td>
<td>17% (5)</td>
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<tr>
<td>Untreated</td>
<td>3% (1)</td>
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<tr>
<td><strong>Prior therapy, % (n)</strong></td>
<td></td>
</tr>
<tr>
<td>Pts with &gt;2 prior therapies</td>
<td>45% (13)</td>
</tr>
<tr>
<td>Intense (e.g. HyperCVAD, FLAG, CHOP)</td>
<td>52% (15)</td>
</tr>
<tr>
<td>Prior exposure to tagraxofusp-erzs</td>
<td>45% (13)</td>
</tr>
<tr>
<td>Prior allogeneic stem cell transplant</td>
<td>24% (7)</td>
</tr>
</tbody>
</table>

*IMGN632 in BPDCN, abstract #167*
Favorable safety profile (TEAEs >15%) (n=29)

- No capillary leak syndrome (CLS)
- No drug related discontinuations
- No drug related deaths, 30-day mortality 0%
- The most common grade ≥3 AEs were thrombocytopenia, febrile neutropenia, and hyperglycemia (10% each)
- Rare liver-related AEs
  - One (3%) grade ≥3 LFT elevation: Gr3 ALT for >7 days (DLT), resolved
  - One (3%) grade 3 hyperbilirubinemia and weight gain: “Grade 2 clinical VOD” resolved and went to HSCT
Efficacy in R/R BPDCN

• In all R/R BPDCN patients:
  – Overall response rate (ORR) 29% (8/28, 2 CR, 2 CRc*, 1 CRi, 3 PR)
  – Composite complete remission rate (CCR#) of 18% (5/28)

• Importantly, in patients with prior tagraxofusp exposure:
  – ORR was 31% (4/13, 1 CR, 1CRi, 2 PR)
  – CCR of 15% (2/13)

• Among 15 patients with bone marrow response assessment to date, 60% (9/15) achieved a bone marrow complete remission (blasts <5%), most (78%, 7/9) also achieving an overall response

* = clinical CR: CR criteria EXCEPT limited residual skin disease “marked clearance of all skin lesions from baseline; residual hyperpigmentation or abnormality with BPDCN identified on biopsy (or no biopsy performed)”
# CCR = CR+CRc+CRi

IMGN632 in BPDCN, abstract #167
Time on treatment and response

• 39% (11/28) remain on treatment

• Responses are often rapid: mean time to response 1.1 months (range 0.7-3.5)

• Durable responses seen (up to 9.2 months) without HSCT
Responses in refractory patients

- 63yo female with BPDCN, refractory to tagraxofusp x2 presented with extensive marrow and skin involvement.

- 69yo female with MDS/BPDCN, refractory to tagraxofusp, CLAG-M, CLAG and presented with extensive skin/PET/BM involvement.
Conclusions

• This clinical trial represents the largest-to-date prospective group of uniformly treated patients with R/R BPDCN

• Favorable safety profile with no cases of CLS, limited grade ≥3 TEAEs, no treatment-related discontinuations, 0% 30-day mortality, and no treatment-related deaths
  – IMGN632 administered every 3 wks, typically given in the outpatient setting

• IMGN632 demonstrated a 29% (8/28) ORR, with 5 complete responses, including patients who had failed prior tagraxofusp-erzs
  – Multiple durable responses observed in the absence of HSCT

• FDA Breakthrough Therapy Designation (BTD) granted in R/R BPDCN
• Enrollment is open for patients with R/R and frontline BPDCN