Encouraging Clinical Profile of IMGN632, a Novel CD123-Targeting Antibody-Drug Conjugate, in Patients with Relapsed/Refractory Acute Myeloid Leukemia or Blastic Plasmacytoid Dendritic Cell Neoplasm

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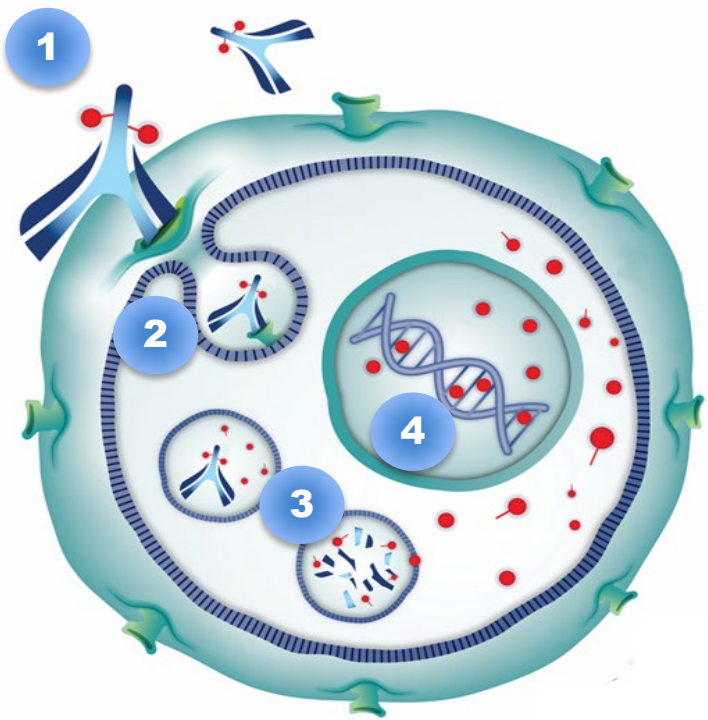
CD123 as a Therapeutic Target

- CD123, the alpha-subunit of interleukin-3 receptor (IL-3Rα), is expressed in >90% of AML, ~100% of blastic plasmacytoid dendritic cell neoplasm (BPDCN), as well as >90% of B-ALL and >75% of T-ALL and early thymic progenitor (ETP) ALL cases[1,2]
- IL3R/CD123 is a clinically-validated target in BPDCN
- CD123 expression is increased 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

[1]Testa 2014 *Biomarker Res* 2:4; [2]Angelova 2018 *Haematologica*; [3]Ehninger 2014 *Blood Cancer J* 4:e218

IMGN632: A Novel CD123-Targeting ADC



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

- **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
- Pre-clinical efficacy in AML, BPDCN, and B-ALL models
- Pre-clinical evidence for broad combination potential: Increased anti-tumor activity in combination with cytarabine, venetoclax, azacitidine and the triplet of IMGN632, venetoclax and azacitidine (2019 ASH Abstract #1375)

Kovtun 2018 *Blood Adv* 2:848-858

Study Objectives

Primary

- Establish maximum tolerated dose (MTD), recommended phase 2 dose (RP2D), and optimal schedule of IMGN632 monotherapy in relapsed and refractory AML and BPDCN

Secondary

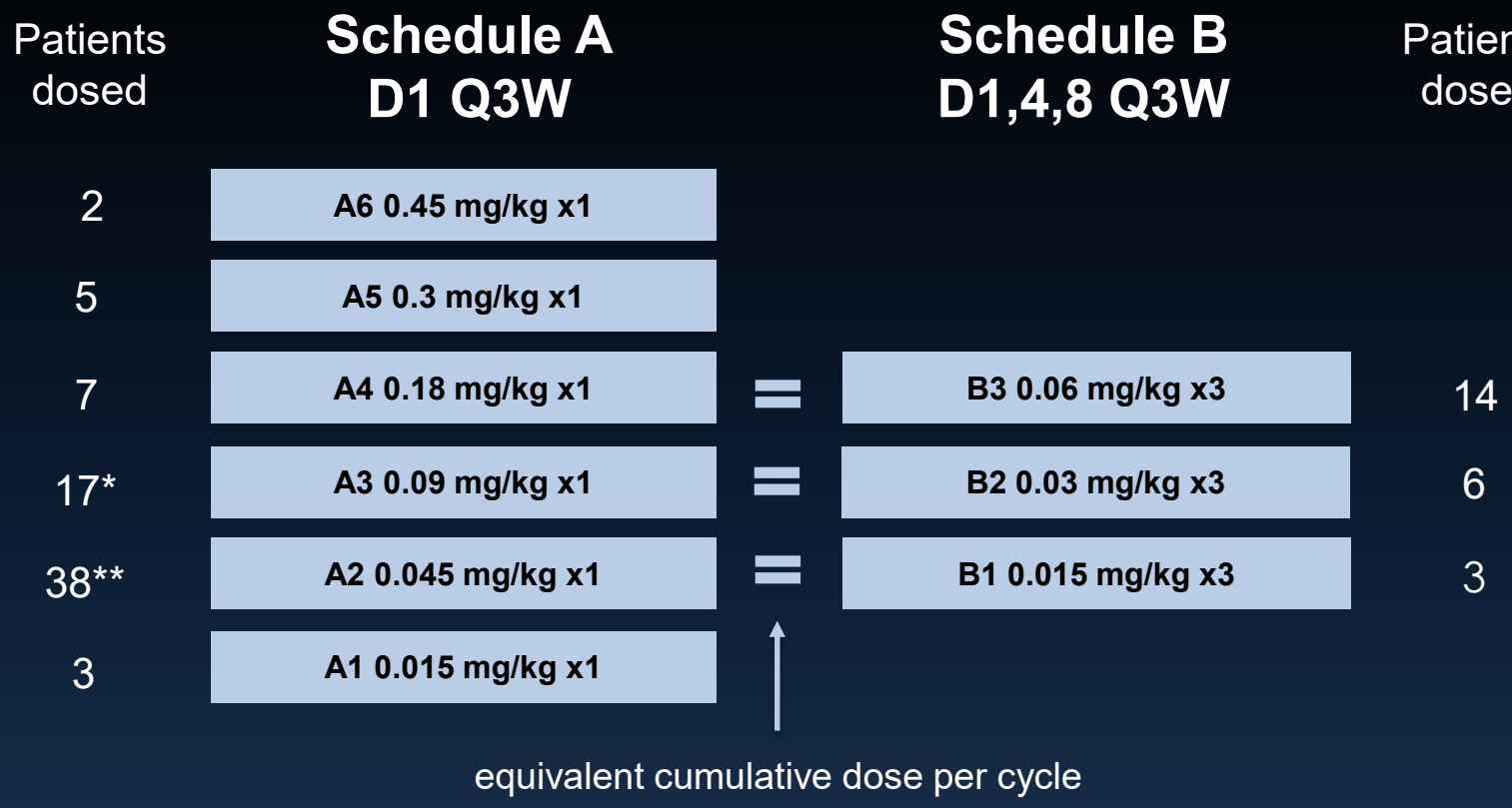
- Determine safety and tolerability of IMGN632, including dose-limiting toxicities (DLTs)

- Characterize preliminary antileukemia activity (ORR) and pharmacokinetic (PK) profile of IMGN632 in AML and BPDCN

Study Design

- Patients ≥18 years with CD123-positive (local lab, 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 to optimize RP2D selection
- IMGN632 administered IV on two schedules:
  - A: Day 1 of a 3 week cycle (D1 Q3W)
  - B: Days 1, 4 and 8 of a 3 week cycle (D1,4,8 Q3W)
    - Fractionated schedule from Schedule A
- Starting dose 0.015 mg/kg, with escalation using a modified Fibonacci schema

Enrollment (n=95)



- Two schedules were explored
  - A: 6 dose levels given D1 Q3W (n=72, 62 AML, 10 BPDCN)
  - B: 3 dose levels given fractionated on D1,4,8 Q3W (n=23, AML only)

* includes 16 AML and 1 BPDCN patient; ** includes 29 AML and 9 BPDCN patients

Patient Characteristics (N=95)

Age, years [range]*		66 [33-83]
		% (n)
Gender*	Male	59% (56)
	Female	41% (39)
Disease	AML	n=85
	De novo AML	53% (45)
	Secondary AML/incl. therapy-related AML	47% (40)
	BPDCN	n=10
ELN Risk Category (AML only)	Favorable/Intermediate	35% (30)
	Adverse	49% (42)
	Not determined	15% (13)
Prior therapy*@	Non-intense only (e.g. HMA, IDHi)	26% (25)
	Intense (e.g. 7+3, HiDAC, SCT)	73% (69)
	Prior SCT	24% (23)
Disease status*	Primary refractory	25% (24)
	Relapsed	
	First relapse	33% (31)
	Second or greater relapse	42% (40)

*All patients (AML and BPDCN) are combined for some demographics
@Data incomplete for 1 patient

Treatment-Emergent Adverse Events
(TEAEs >15%) (N=95)

Adverse Event	Any Grade %	Treatment-Related Any Grade %	Grade ≥3 %	Treatment-Related Grade ≥3 %
Nausea	34	11	2	1
Diarrhea	31	3	0	0
Febrile Neutropenia	25	10	25	10
Infusion Related Reaction	25[#]	24	8	8
Constipation	24	2	0	0
Lung Infection	24	1	22	1
Peripheral Edema	22	3	1	0
Chills	21	8	0	0
Pyrexia	21	4	1	0
Fatigue	19	3	5	1
Insomnia	19	1	0	0
Dyspnea	17	3	3	2
Epistaxis	17	0	0	0
Abdominal Pain	16	2	1	1
ALT Increase	16	2	5	0
Decreased Appetite	16	2	1	0

Possibly/Probably related TEAEs ≥10% highlighted in yellow

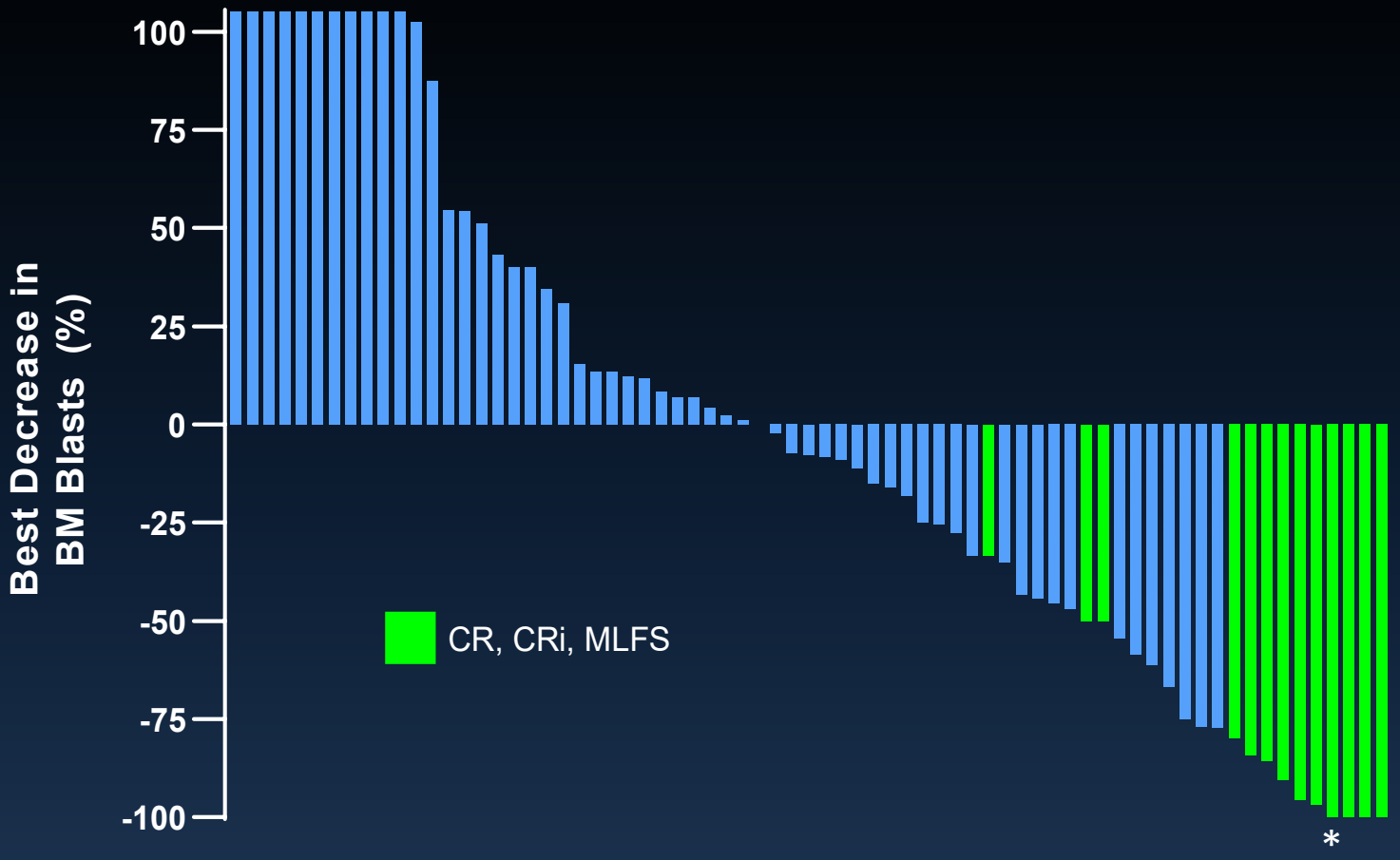
[#] one unrelated platelet transfusion IRR

Safety Summary (n=95)

- Overall well tolerated in relapsed/refractory AML and BPDCN patient population
- Most frequent treatment-related AEs were infusion-related reactions (24%; chills, tachycardia, nausea/vomiting, diarrhea). IRRs were reversible, did not require IMGN632 discontinuation in any patient
- Single DLTs seen at higher dose levels (n=4)
  - Reversible veno-occlusive disease (VOD) (n=3), two had prior SCT
    - All occurred at cumulative doses ≥0.18 mg/kg per cycle
    - Abdominal pain, ascites, variable LFT elevation
    - Liver biopsies consistent with sinusoidal obstruction
    - All reversible, improved in 1-2 weeks
    - Fractionated Schedule B did not appear to improve safety margin for VOD
  - Prolonged neutropenia (n=1): 0.3 mg/kg after 2 cycles
- Deaths: 30 day any cause mortality (6%)
  - 5 unrelated (progressive disease x2, lung infection, respiratory failure, sepsis)
  - 1 possibly related (cause unknown)

AML Efficacy

BM-evaluable patients (n=71)



- 54% of BM-evaluable patients had a reduction in BM blasts
- 13 responses (2 CR, 10 CRi, 1 MLFS*) observed across both schedules and at multiple dose levels
- Fractionated Schedule B did not appear to provide increased efficacy

BM evaluable: patients who had at least one post-dosing BM evaluation

AML Responder Analysis

Of 13 responders

- 92% had prior intense therapy, including 3 with prior SCT
- 69% had 2-3 prior lines of therapy
- 54% had ELN Adverse Risk

Response by subgroups

- Relapsed AML (excluding primary refractory AML)
  - 22% (12/54) overall response rate (ORR) in relapsed AML across all dose levels, and 26% (6/23) at 0.045 mg/kg
- Relapsed/refractory De novo AML (excluding secondary AML)
  - 28% (11/40) ORR in relapsed/refractory de novo AML across all dose levels, 40% (6/15) ORR at 0.045 mg/kg, and 46% (6/13) ORR in relapsed, de novo AML at 0.045 mg/kg
- ELN Adverse Risk (excluding ELN Fav/Int): 20% (7/35) ORR across all dose levels
- Prior SCT: 18% (3/17) ORR across all dose levels

Pharmacokinetics and pharmacodynamics

- Efficacy observed was independent of CD123 expression levels or CD123 saturation
- Efficacy observed was independent of PK parameters (Cmax, AUC)

Based on safety and efficacy data

- 0.045 mg/kg Q3W (Dose level A2) selected as the RP2D for IMGN632 monotherapy
- 0.015-0.09 mg/kg (Dose levels A1-A3) selected for continued development in combinations

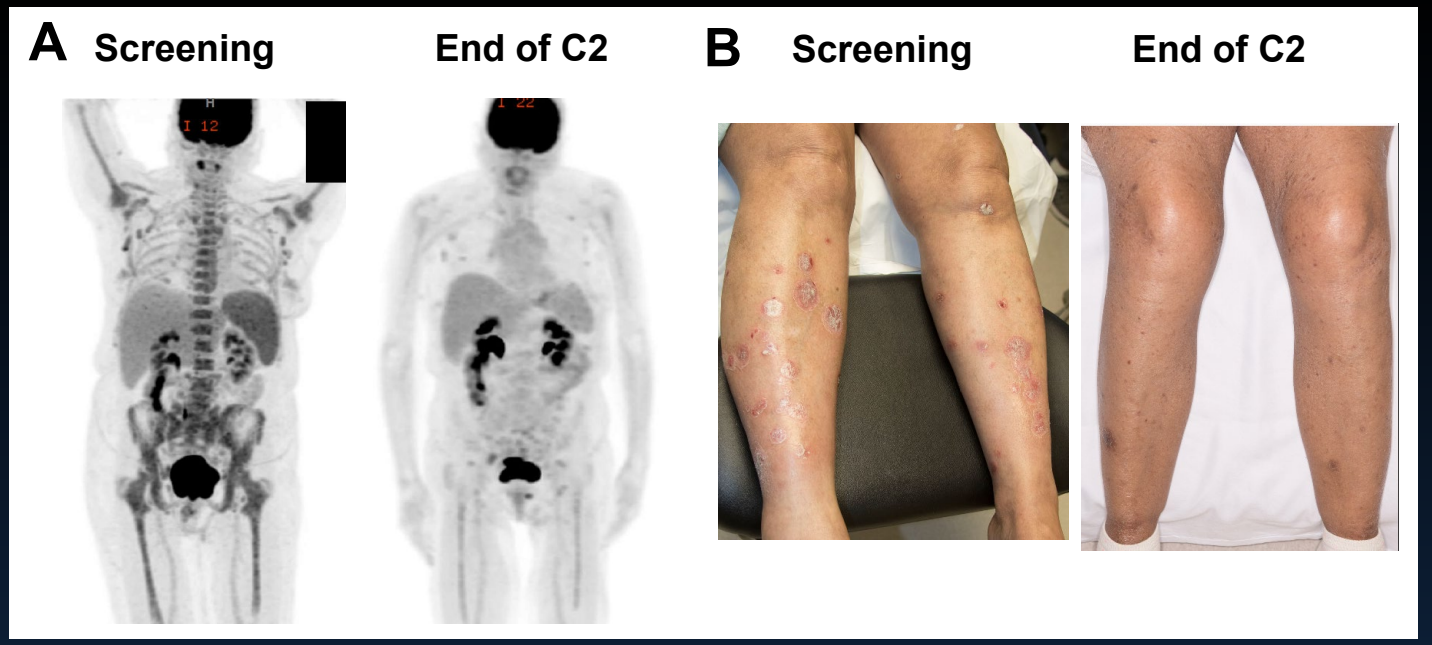
BPDCN experience

Nine of ten BPDCN patients were evaluated for response

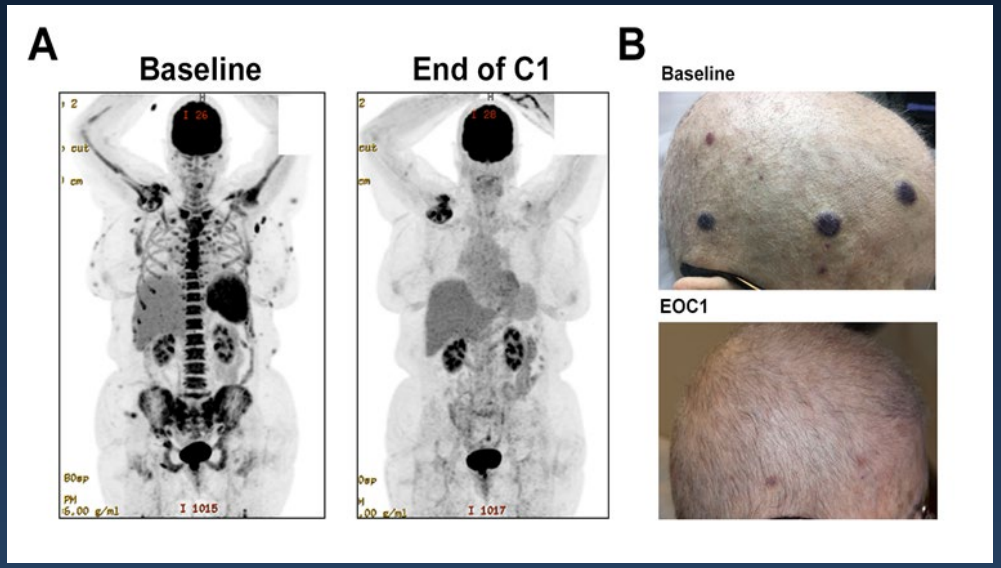
- Three responders (CR, CRi, PR)
  - All three had prior SL-401
  - Two also had prior intense chemotherapy and/or alloSCT
  - All three had skin, PET and BM disease
  - All three achieved their response with 1-2 doses of IMGN632 at dose level 0.045 mg/kg
  - BM cleared to 0% from baseline 28%, 37%, and 84% at screening, respectively

Responses in refractory BPDCN

63yo female with BPDCN, refractory to SL-401 x2 presented with extensive marrow and skin involvement. After 1 dose, BM cleared from 84% to 0%. After 2 cycles, skin cleared active lesions and "Partial Remission" based on lymph nodes reduction.



69yo female with MDS/BPDCN, refractory to SL-401, CLAG-M, CLAG and presented with extensive skin/PET/BM involvement. After 1 cycle, in CRi, BM cleared from 37% to 0%.



Conclusions

- **IMGN632 is well tolerated at dose levels 0.015-0.09, including the RP2D 0.045 mg/kg Q3W**
  - Manageable IMGN632-related infusion related reactions in 24% of patients, none requiring IMGN632 discontinuation
  - Most doses given as outpatient with <30 minute IMGN632 infusion Q3W
- **Responses in R/R AML**
  - The majority of AML responders were ELN Adverse risk with 2-3 prior lines of therapy, including three with prior SCT
  - 26-46% ORR in R/R AML at the RP2D in subgroups of de novo and relapsed patients
- **Responses in R/R BPDCN**
  - BPDCN responses in 3 of 9 patients; all with prior SL-401 and two with intense chemo
- **This trial continues to enroll AML, BPDCN, and recently opened to ALL patients**
- **Further development of IMGN632 includes an open Phase Ib/II trial (TiP abstract 2601 ASH 2019)**
  - Combinations with AZA, with VEN and with AZA+VEN (supported by pre-clinical abstract 1375 ASH 2019)
  - IMGN632 monotherapy in MRD+ frontline patients

Thank You
to our patients and their families