A Phase I, First-in-Human Study Evaluating the Safety and Preliminary Antileukemia Activity of IMGN632, a Novel CD123-Targeting Antibody-Drug Conjugate, in Patients with Relapsed/Refractory Acute Myeloid Leukemia and Other CD123-Positive Hematologic Malignancies

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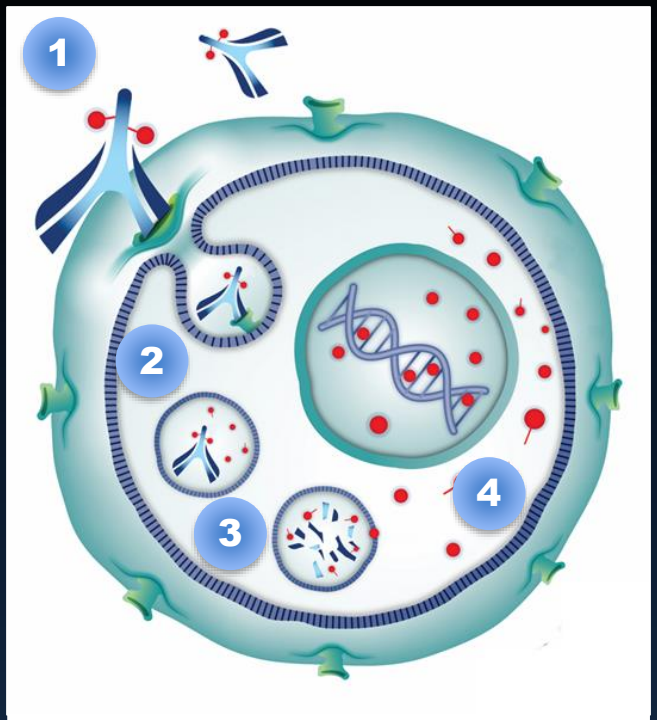
CD123 as a Therapeutic Target

- CD123, the α-subunit of interleukin-3 receptor (IL-3Rα), 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

[1]Testa 2014 *Biomarker Res* 2:4; [2]Khoury 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
  - 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

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

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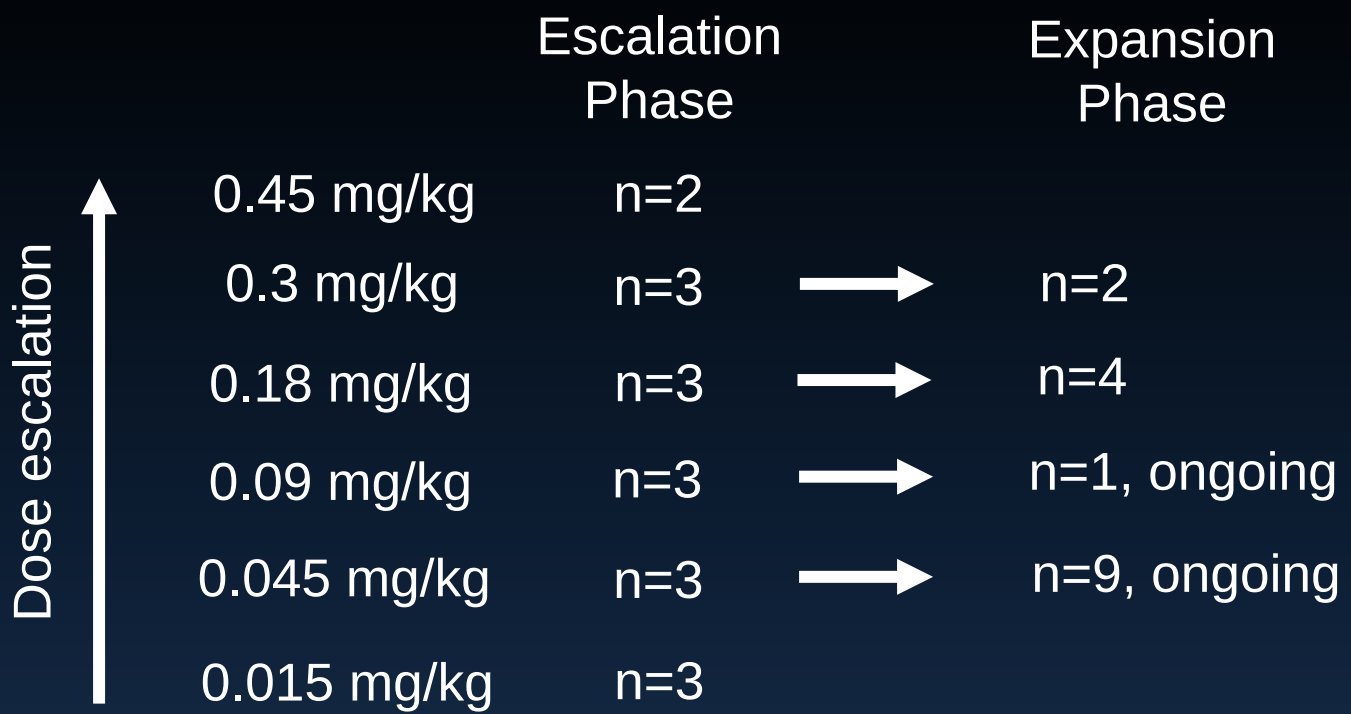
Study Design

- 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

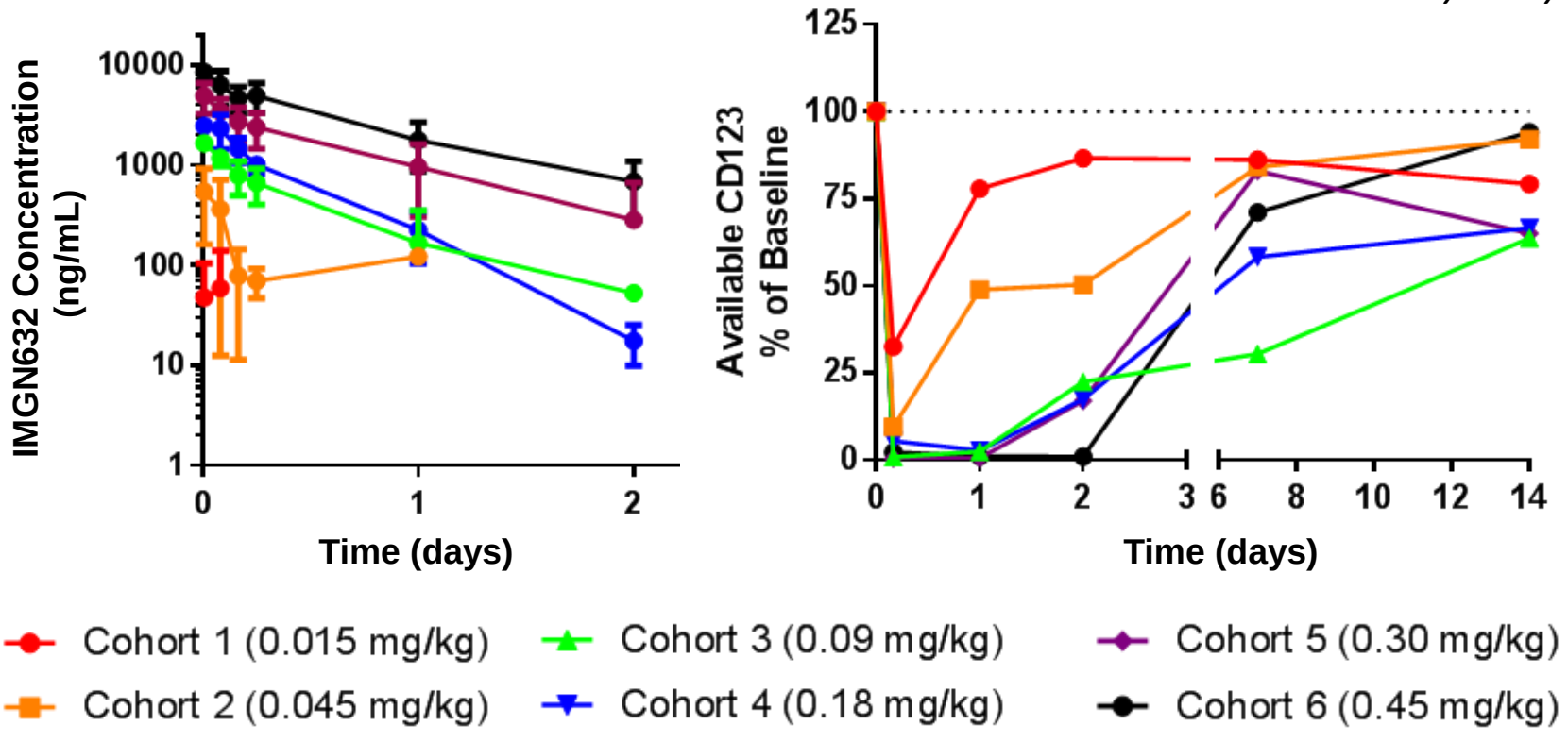
Enrollment (N=33)



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

Pharmacokinetics and CD123 Saturation

Preliminary Analyses



- 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

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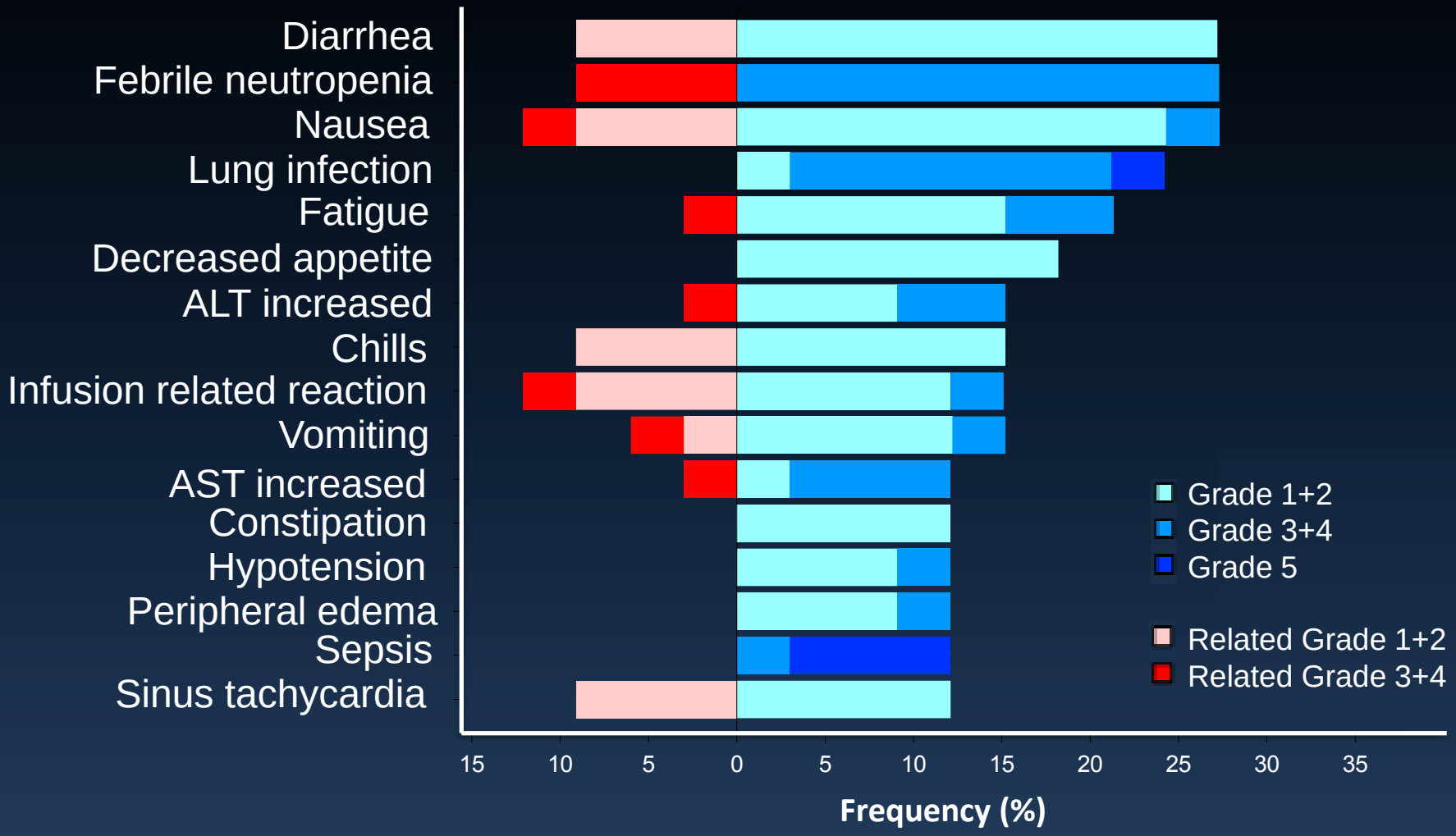
Patient Characteristics (N=33)

		N (%)
Age, years		70 [40-80]
Sex	Male	13 (39)
Disease	AML	30 (91)
	BPDCN	3 (9)
Prior therapy	Non-intense only (e.g. HMA, IDHi)	5 (15)
	Intense (e.g. 7+3, HiDAC, SCT)	19 (58)
	Incomplete data	*9*
Prior Transplant		6 (18)
Disease status	First relapse	9 (27)
	Primary refractory	5 (15)
	Relapsed refractory (second relapse or beyond)	15 (46)
	Incomplete data	*4*

*All patients (AML and BPDCN) are combined for demographics

Treatment-Emergent Adverse Events
(TEAEs >10%) (N=33)



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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

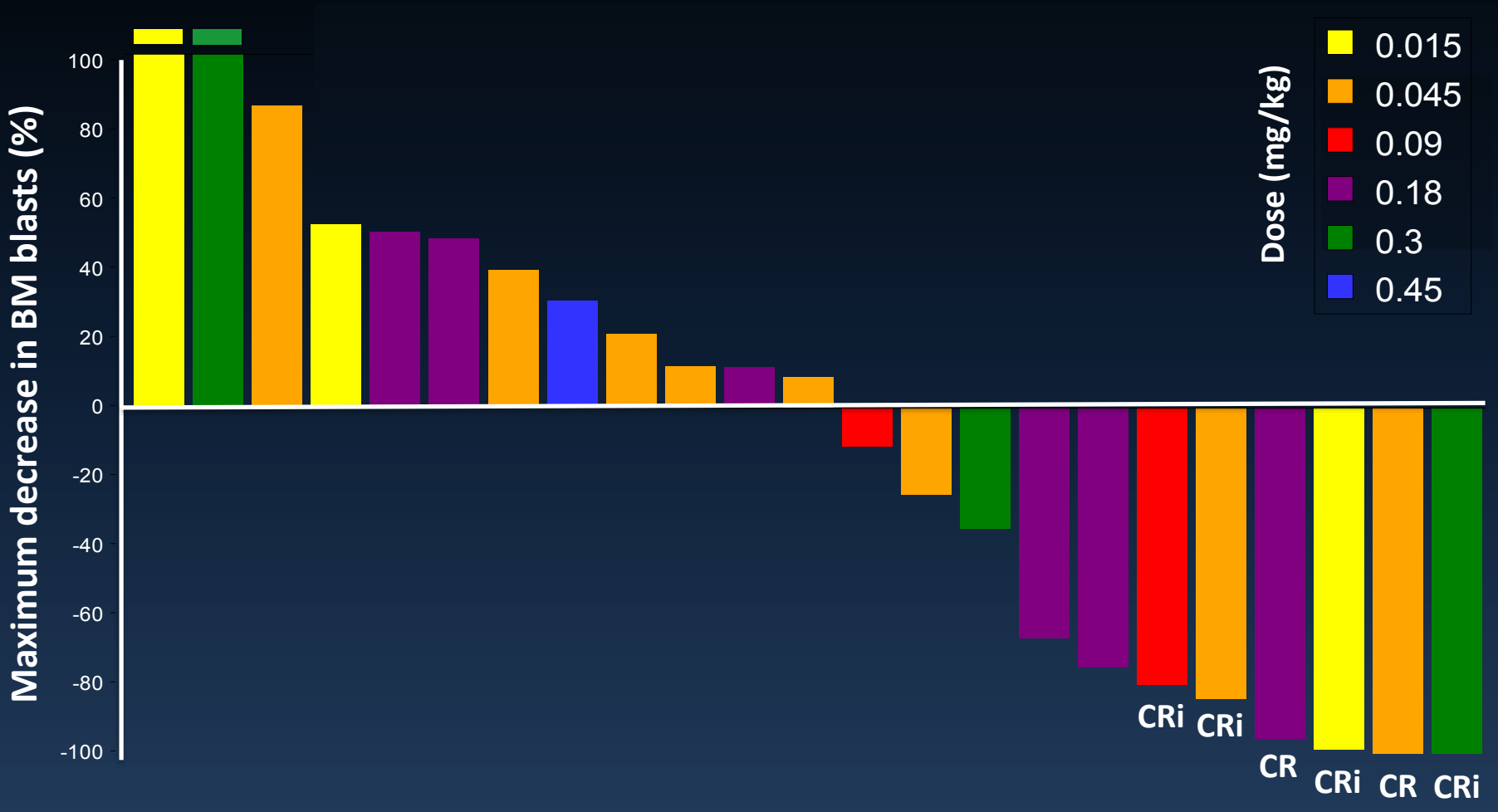
- DLTs and related SAEs:
  - febrile neutropenia (3 SAEs)
  - reversible veno-occlusive disease (VOD) (2 DLTs)
    - 0.45 mg/kg moderate VOD, alloSCT for MDS 1 year prior, after 1 dose, typical symptoms per Baltimore criteria
    - 0.18 mg/kg mild VOD, after 2 doses, only symptom was ascites, no Doppler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

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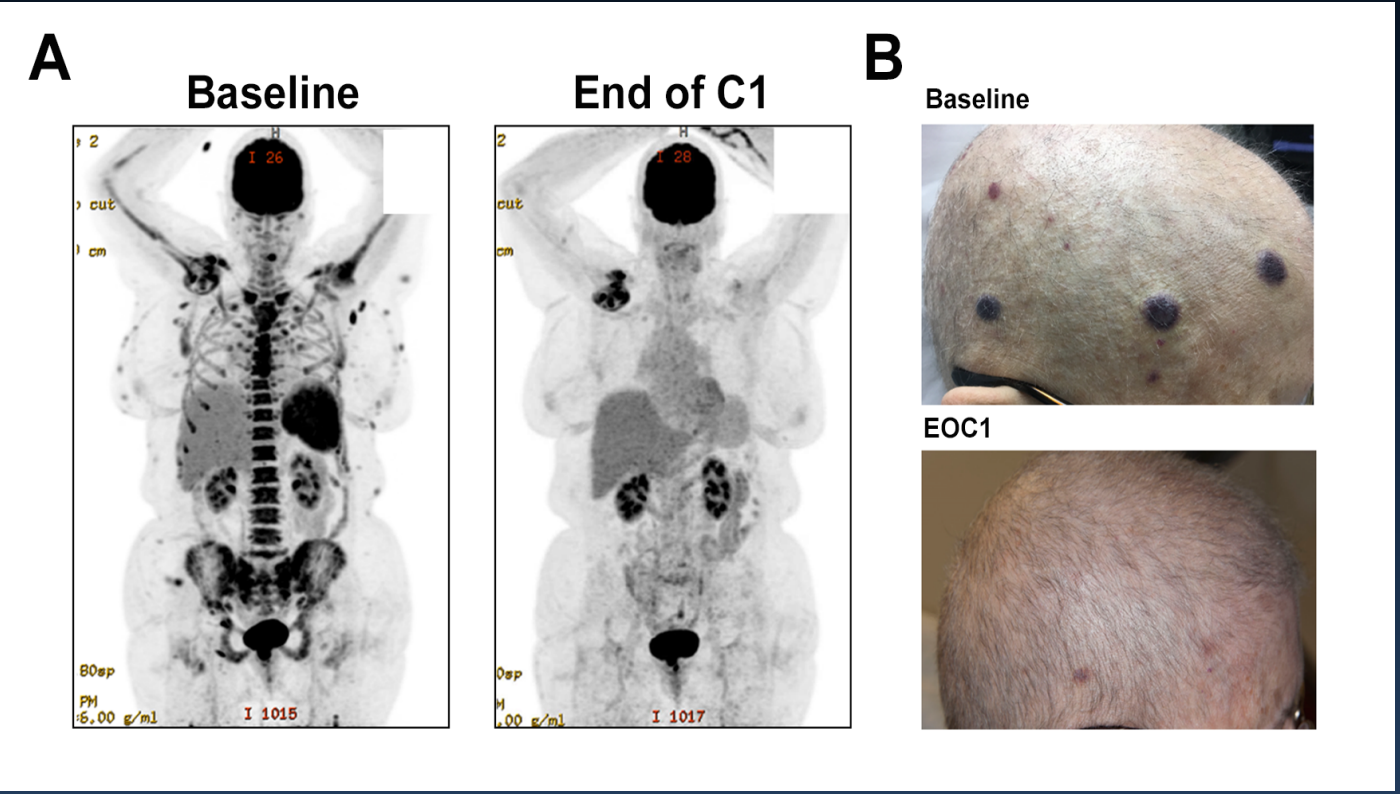
Rapid response in a refractory BPDCN patient

- 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

Cohort Dose (mg/kg)	1 0.015	2 0.045	3 0.09	4 0.18	5 0.3	6 0.45	Total
AML Responses*	1/3 CRi	2/8 CR, CRi	1/2 CRi	1/6 CR	1/3 CRi	0/1	23
BPDCN responses		2/3 PR, CRi					3
DLTs				1/7	1/5	1/2	

*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

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

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Thank You
to the patients and families