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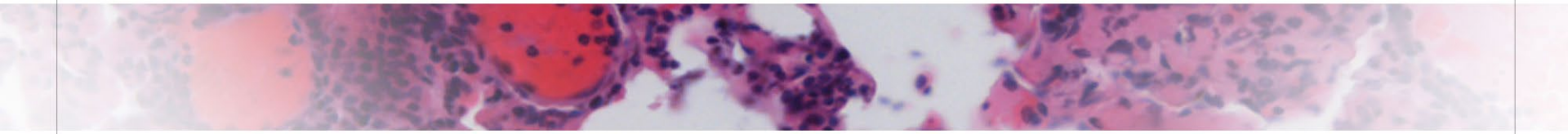

Safety and Efficacy from a Phase 1b/2 Study of IMGN632 in Combination with Azacitidine and Venetoclax for Patients with CD123-Positive Acute Myeloid Leukemia

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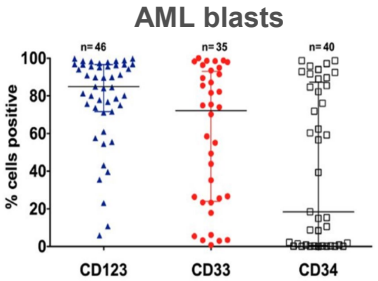
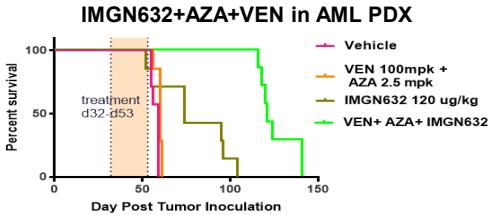
Background

- Azacitidine (AZA) and venetoclax (VEN) improved outcome in frontline older/unfit AML but long-term survival remains poor[1]
- HMA with VEN with CR/CRi rates 20-42% in VEN-naïve R/R AML[2,3]
- Overexpression of CD123, the alpha subunit of the IL-3 receptor, is observed on the majority of AML blasts cells[4]
- CD123 expression is low on normal hematopoietic stem cells
- Preclinical data have demonstrated synergy between IMGN632 and AZA and/or VEN, including overcoming AZA/VEN resistance in murine AML models[5]
- IMGN632 demonstrated single agent CR/CRi rates of 22-40% in R/R AML patient subgroups (ASH 2019)[6]
- Doublets of IMGN632 with both AZA and VEN were studied in AML patients and supported testing of the triplet of IMGN632, AZA, and VEN



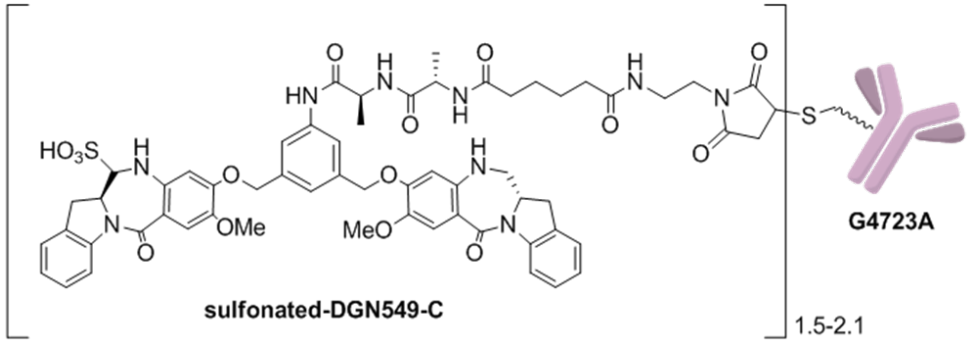
[4]Gill, *Blood*. (2014); 123(15): 2343–2354

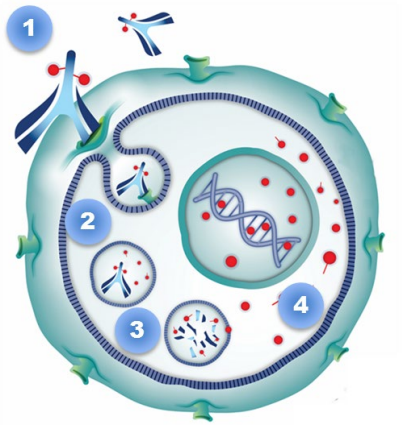


[5]Kuruvilla; *Blood* (2020) 136 (S1): 32–33

[1]DiNardo CD; *NEJM* (2020). [2]DiNardo CD; *Lancet Haematol* (2020). [3]Stahl M; *Blood Adv* (2021). [6]Daver N; *Blood* (2020) 134 (S1): 50–51

IMGN632 Background





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

- IMGN632 is a CD123-targeting antibody-drug conjugate (ADC) comprised of a high-affinity antibody coupled to a DNA-alkylating payload of the novel IGN (indolinobenzodiazepine pseudodimer) class
- IGN payloads alkylate DNA and cause single strand breaks without crosslinking. IGNs are designed to have high potency against tumor cells, while demonstrating less toxicity to normal marrow progenitors than other DNA-targeting payloads

Study Design and Objectives

- Open-label, multicenter, Phase 1b/2 study of IMGN632 in combination with AZA and VEN in patients with relapsed/refractory CD123-positive AML

- Primary Objective:
  1. Determine the safety and efficacy of IMGN632 when administered in combination with AZA and VEN in relapsed/refractory patients with AML
  2. Responses are determined using modified European LeukemiaNet (ELN) criteria with a 14-day count recovery window

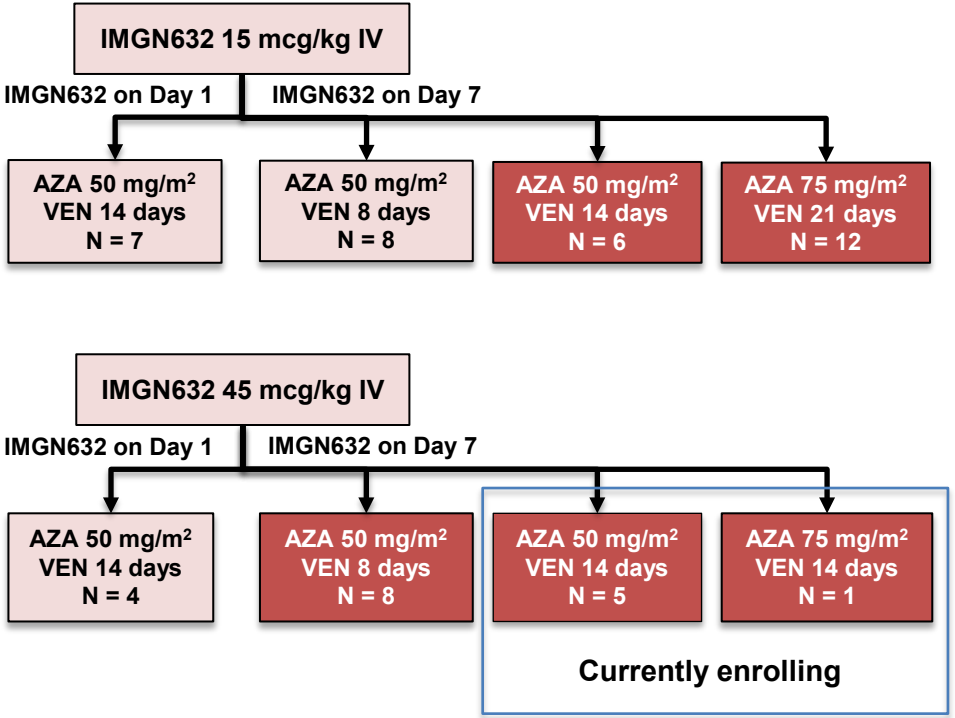
Study Scheme and Dosing Cohorts

TRIPLET regimen
(4 variable escalation)

IMGN632 15 OR 45 mcg/kg
IMGN632 given on day 1 OR 7
AZA 50 OR 75 mg/m2 IV/SQ on days 1-7
VEN 400 mg PO for 8 OR 14 OR 21 days
in a 28-day cycle

Higher Intensity Cohorts:

IMGN632 on Day 7
EITHER IMGN632 dose 45 mcg/kg
OR 14-21 days of VEN



Patient Characteristics (N = 51)

Age	Median 67y < 65y ≥ 65y	Range 32-81y 49% (25) 51% (26)
Gender, % (N)	Male Female	63% (32) 37% (19)
History/Type of AML, % (N)	De Novo Secondary Missing	71% (36) 27% (14) 2% (1)
Previous Treatment %* (N)	First Relapse Primary Refractory Other Median Prior Lines of Therapy	37% (19) 35% (18) 27% (14) 2 (1-3)
ELN Risk	Adverse Intermediate Favorable Not determined/Missing	49% (25) 20% (10) 2% (1) 29% (15)
FLT3 Status, % (N)	Mutated	20% (10)
Prior Venetoclax, % (N)	Yes No	51% (26) 49% (25)

***Percent not equal to 100 due to rounding**

Safety (N=51)

Treatment Emergent Adverse Effects (TEAE)	All Grades ≥ 20%	≥ Grade 3
Infusion Related Reactions	33%	2%
Febrile Neutropenia	31%	26%
Dyspnea	28%	8%
Fatigue	28%	0%
Hypophosphatemia	26%	2%
Diarrhea	22%	0%
Hypokalemia	22%	2%
Nausea	22%	0%
Vomiting	22%	0%
Pneumonia	20%	16%

- Rates of cytopenias similar to those observed with the HMA+VEN in R/R AML[1]
- Infusion related reactions (IRR) consisting mainly of chills/rigors (16 of 17 grade 1-2)
  - One patient with grade 4 IRR (dyspnea, hypotension) on Day 1 schedule, resolved without sequelae
  - Peripheral edema grade 1-2 18%; no ≥ grade 3
- No tumor lysis syndrome (TLS), no veno-occlusive disease (VOD), no capillary leak or cytokine release
- Discontinuations due to AEs (8%)
- **30-day mortality 0%, 60-day mortality 10%**

[1]Schuler; *Annals of Hematology* (2021) 100:959-968. * HMA = Hypomethylating agent

Antileukemic Activity Observed Across All Doses/Schedules

Efficacy evaluable population[#] (All doses and schedules)	N	ORR N	CCR N	CR N (%)	CRh N (%)	CRp N (%)	CRi N (%)
	46	22 (48%)	14 (30%)	4 (9)	8 (17)	1 (2)	1 (2)
Higher intensity cohorts[#]	**N**	**ORR N**	**CCR N**	**CR N (%)**	**CRh N (%)**	**CRp N (%)**	**CRi N (%)**
	29	17 (59%)	11 (38%)	4 (14)	6 (21)	1 (3)	0

Median duration on study: 9.1 weeks (Range 3-52.4 weeks)

[#]5 patients were excluded from efficacy evaluable population as they are in their first cycle (3 of those are in the high intensity cohort)

ORR (CR + CRh + CRp + CRi + MLFS)
CCR (CR + CRh + CRp + CRi)

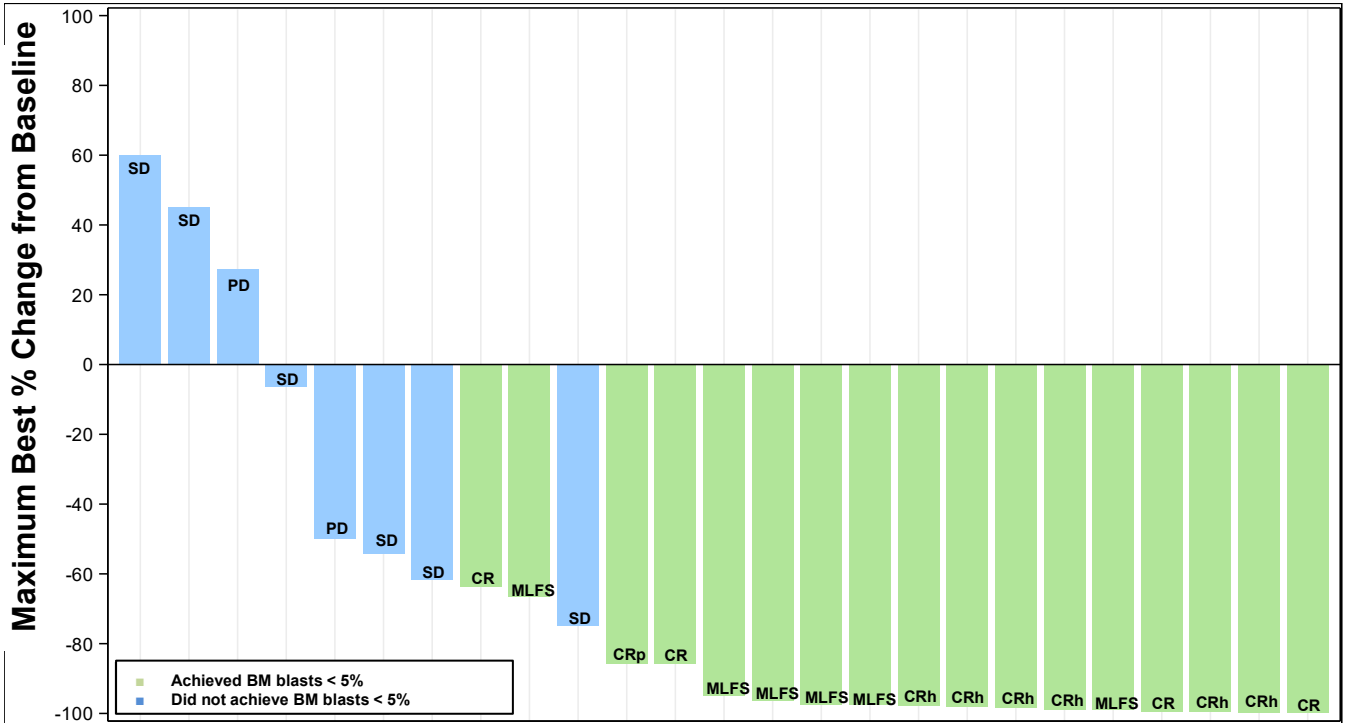
Antileukemic Activity in Higher Intensity Cohorts: Subsets of Interest

Previous Treatments	N	ORR	CCR
VEN naïve	15	73%	53%
Prior VEN	14	43%	21%
Prior HMA + VEN	12	42%	25%
Prior Stem Cell Transplant	7	71%	71%
High Risk Cytogenetics	**N**	**ORR**	**CCR**
ELN Adverse Risk	14	64%	36%
FLT-ITD	9	89%	78%

HMA = Hypomethylating agent, ITD = Internal tandem duplication

ORR (CR + CRh + CRp + CRi + MLFS)
CCR (CR + CRh + CRp + CRi)

Best Decrease in BM Blast for Higher Intensity Cohorts

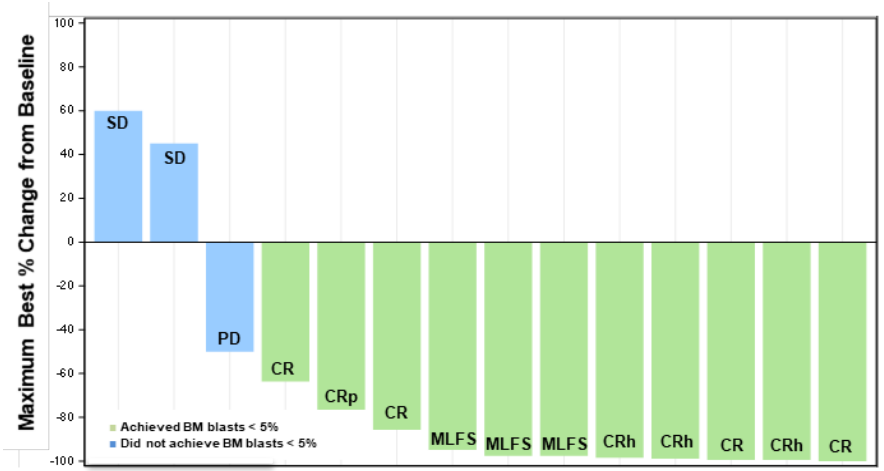


Four patients with clinical progression not included due to lack of BM assessment

- 35% (6/17) of responders in the higher intensity cohorts went on to receive a transplant after the IMGN632 triplet

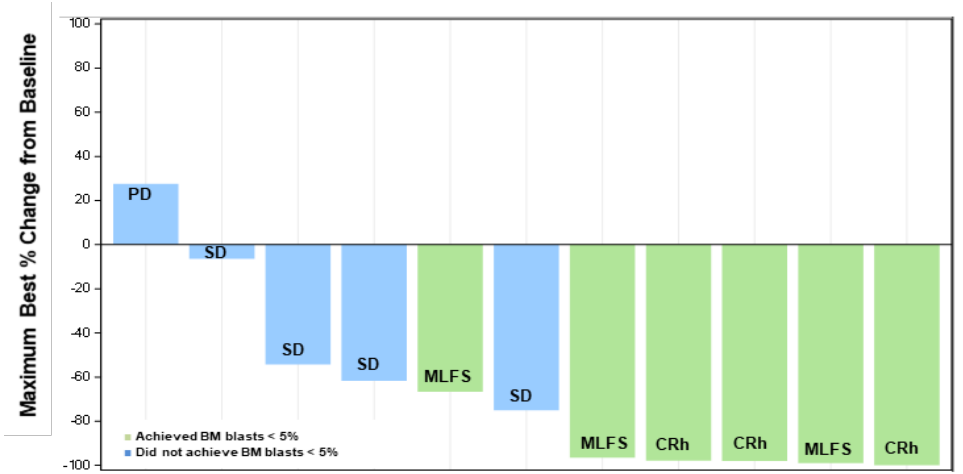
Best Decrease in BM Blast for Higher Intensity Cohorts by Prior VEN Exposure

VEN Naïve (N=15)



One patient with clinical progression not included due to lack of BM assessment

VEN Treated (N=14)



Three patients with clinical progression not included due to lack of BM assessment

Conclusions

- IMGN632+AZA+VEN with manageable safety profile in high-risk R/R AML
  - Grade 1-2 IRRs and peripheral edema
  - No TLS, VOD, capillary leak or cytokine release were observed
  - 0% 30-day mortality

- Promising anti-leukemia activity, particularly in higher intensity cohorts: ORR 59% and CCR rate 38%
  - VEN naïve patients: ORR of 73% and CCR of 53%, which compares favorably with HMA+VEN in VEN naïve R/R AML, CCR 20-42%
  - Responses noted in prior HMA+VEN failures: ORR 42%, CCR 25%
  - Patients with FLT-ITD demonstrated compelling response rates: ORR 89%, CCR 78%

- Nearing completion of the triplet escalation
  - Enrollment continues at the putative RP2D (IMGN632 45 mcg/kg IV on day 7, AZA 50 or 75 mg/m^2 IV/SQ on days 1-7, and VEN 400 mg PO on days 1-14)
  - Expansion phase 2 cohorts are planned in both relapsed and frontline AML patients (NCT04086264)