Poster
AML-262

Pivekimab sunirine (PVEK) triplet with azacitidine and venetoclax shows broad activity in adverse genetic subsets of relapsed/refractory AML and reduced infusion related reactions

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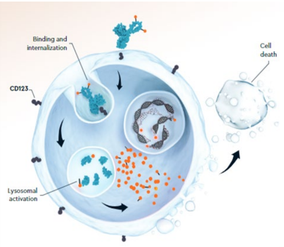
INTRODUCTION

- Hypomethylating agents (HMA) and venetoclax (VEN) demonstrate improved outcomes in frontline older/unfit patients with AML but long-term survival remains poor[1]
- HMA combined with VEN have reported complete response/complete response with incomplete count recovery (CR/CRi) rates of 20-42% in patients with VEN-naïve relapsed/refractory (R/R) AML[2,3]
- Overexpression of CD123, the alpha subunit of the IL-3 receptor, is observed on the majority of AML blast cells[4]
- Preclinical data have demonstrated synergy of PVEK when combined with AZA and/or VEN, including in AZA/VEN resistant murine AML models[5]
- PVEK demonstrated single-agent CR/CRi rates of 22-40% in subgroups of patients with R/R AML[6]

PVEK Background

- PVEK, also known as IMGN632, is a CD123-targeting antibody-drug conjugate (ADC) comprised of a high-affinity antibody coupled to a DNA-alkylating payload of the novel indolinobenzodiazepine pseudodimer (IGN) class
- The IGN payload alkylates DNA and causes 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[7]



Study Design and Endpoints

IMGN632-0802 is an open-label, multicenter, Phase 1b/2 study of PVEK in combination with AZA + VEN in patients with relapsed/refractory CD123-positive AML

- Primary objective is to determine the safety and efficacy of PVEK in combination with AZA + VEN in patients with R/R AML
  - Safety population is defined as all patients who received at least one dose
  - Efficacy-evaluable patients included all treated patients who have an efficacy assessment at baseline and at least one post-dosing efficacy assessment, or who died within 28 days of first dose and had no post-dosing efficacy assessment data
  - Responses were determined using 2017 European LeukemiaNet (ELN) criteria with the addition of CRh and CRp and a 14-day count recovery window
  - ORR is defined as CR + CRh + CRp + CRi + MLFS + PR
  - CCR is defined as CR + CRh + CRp + CRi

CR, complete response; CRh, complete response with partial hematologic recovery; CRp, complete response with incomplete platelet count recovery; CRi, complete response with incomplete count recovery; MLFS, morphologic leukemia-free state; PR, partial response

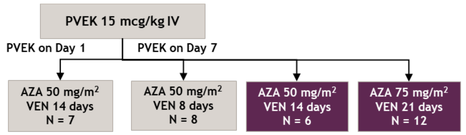
Dosing Cohorts

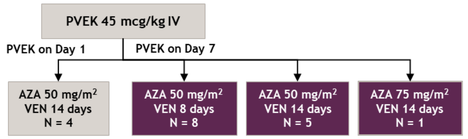
TRIPLET regimen (4 variable escalation)

PVEK 15 OR 45 mcg/kg
PVEK 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:

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





Efficacy

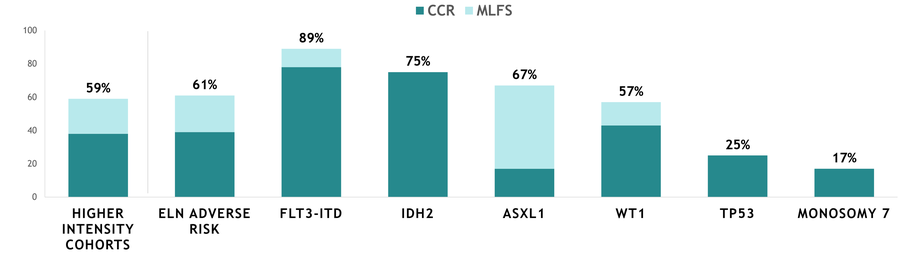
Higher Intensity Cohorts	N*	ORR	CCR	CR	CRh	CRp	CRi
	29	59%	38%	14%	21%	3%	0

*3 patients were excluded from the efficacy evaluable population as they were in their first cycle of treatment at the time of data cut
Median duration on study: 9.1 weeks (range 3-52.4 weeks)

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	18	61%	39%
FLT3-ITD	9	89%	78%
IDH2	4	75%	75%
ASXL1	6	67%	17%
WT1	7	57%	43%
TP53	4	25%	25%
Monosomy 7/del(7q)	6	17%	17%

Subgroup Analysis Overall Response Rate



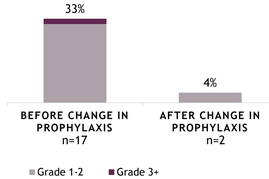
Safety

Treatment Emergent Adverse Events (TEAEs) N=51	All Grades*	Gr 3	Gr 4
Infusion Related Reactions (IRRs)	33%	-	2%
Febrile Neutropenia	31%	24%	2%
Dyspnea	28%	8%	-
Fatigue	28%	-	-
Hypophosphatemia	26%	2%	-
Diarrhea	22%	-	-
Hypokalemia	22%	-	2%
Nausea	22%	-	-
Vomiting	22%	-	-
Pneumonia†	20%	12%	2%

*reported in ≥20 of patients; †one patient with grade 5 pneumonia

- No tumor lysis syndrome, veno-occlusive disease, capillary leak, or cytokine release syndrome observed
- Prior to change in steroid prophylaxis, IRRs primarily consisted of chills/rigors; one patient with grade 4 IRR (dyspnea, hypotension) and resolved without sequelae
  - Initial IRR prophylaxis: 1 dose of dexamethasone (8 mg) on the day of PVEK administration
  - New IRR prophylaxis: 2 doses of dexamethasone (8 mg) on the day prior and 1 dose on the day of PVEK administration
    - Only 2 patients experienced an IRR after prophylaxis update

DECREASE IN INFUSION RELATED REACTIONS



CONCLUSIONS

- PVEK triplet with AZA+VEN demonstrates anti-leukemic activity across multiple high-risk genetic subsets of patients with relapsed/refractory AML
- Prophylactic steroids added on day -1 have significantly reduced IRRs. After change in prophylaxis, all IRRs observed were grade 1-2 and resolved with limited intervention
- PVEK triplet with AZA+VEN is a promising anti-leukemic combination with a manageable safety profile that warrants further investigation
- Expansion cohorts are now enrolling for patients with newly diagnosed AML (NCT04086264)

1. DiNardo, CD; *NEJM* (2020); 2. DiNardo, CD; *Lancet Haematol* (2020); 3. Stahl, M; *Blood Adv* (2021); 4. Gill, S; *Blood* (2014); 5. Kuruvilla, VM; *Blood* (2020); 6. Daver, N; *Blood* (2020); 7. Kovtun, Y; *Blood Adv* (2018)