A phase Ib/II study of ivosidenib with venetoclax +/- azacitidine in *IDH1* mutated myeloid malignancies

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Study Rationale

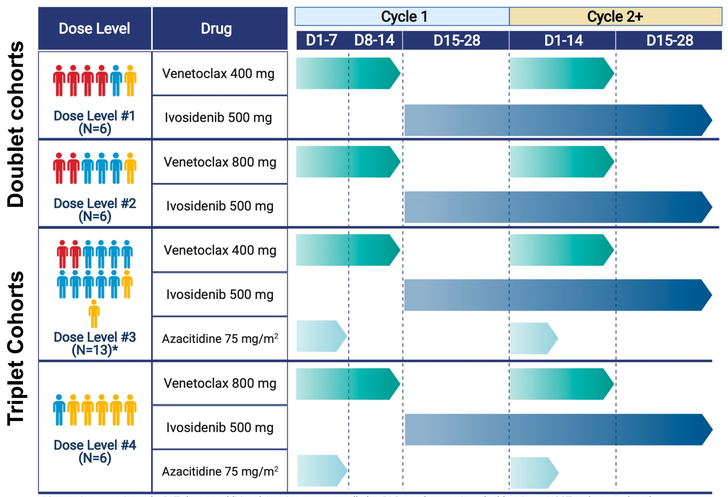
Increased BCL-2 dependency and epigenetic dysregulation may enable synergistic leukemic cell death when ivosidenib (IVO) is used in combination with the BCL-2 inhibitor venetoclax (VEN) with or without the hypomethylating agent azacitidine (AZA) [Ref 1-7].

Study objectives & inclusion criteria

Primary	Secondary
Safety and tolerability	PK analysis of IVO+VEN
Determine MTD and RP2D	Identify cellular/molecular biomarkers predictive of activity
Determine Overall Response (ORR)	Determine DOR, OS, EFS
ORR: CR+CRi+CRh+PR+MLFS	

Inclusion	Exclusion
ECOG ≤ 2	Prior ivosidenib
IDH1 R132 Mutation	Prior venetoclax
Advanced MDS or MPN (≥ 10% blasts)	CYP3A4 inducers/inhibitors in prior 72 hrs.
ND or R/R-AML	Active GVHD
Adequate renal/hepatic function	GI/Metabolic disorder with altered absorption

Dose levels



*One patient experienced a DLT, thus an additional 6 patients were enrolled at DL3, another was inevaluable prior to HSCT and was replaced

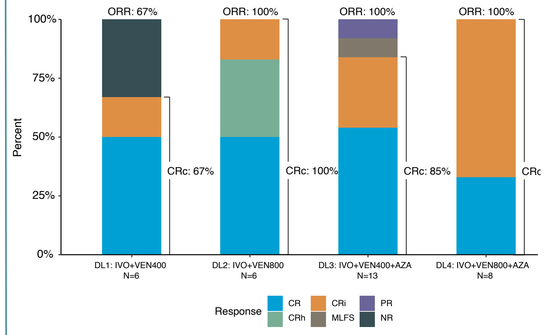
Demographics

Characteristic*	Overall N = 31	Dose level #1 N = 6	Dose level #2 N = 6	Dose Level #3 N = 13	Dose Level #4 N = 6
Age	67 (44 - 84)	69 (66 - 84)	68 (44 - 80)	65 (56 - 76)	66 (56 - 76)
Gender					
Male	20 (65%)	3 (50%)	3 (50%)	9 (69%)	5 (83%)
Baseline BM blast (%)	23 (1 - 80)	31 (1 - 64)	24 (10 - 61)	35 (7 - 80)	14 (6 - 32)
ECOG					
0	8 (27%)	1 (17%)	-	4 (31%)	3 (60%)
1	18 (60%)	4 (67%)	4 (67%)	8 (62%)	2 (40%)
2	4 (13%)	1 (17%)	2 (33%)	1 (7.7%)	-
Disease					
MDS /MPN	9 (29%)	1 (17%)	1 (17%)	2 (15%)	5 (83%)
ND-AML	14 (45%)	1 (17%)	3 (50%)	9 (69%)	1 (17%)
R/R-AML	8 (26%)	4 (67%)	2 (33%)	2 (15%)	-
2017 ELN Risk Group					
Favorable	8 (26%)	2 (33%)	3 (50%)	2 (15%)	1 (17%)
Intermediate	6 (19%)	2 (33%)	1 (17%)	2 (15%)	1 (17%)
Adverse	17 (55%)	2 (33%)	2 (33%)	9 (69%)	4 (67%)
Prior treatment	15 (48%)	5 (83%)	3 (50%)	6 (46%)	1 (17%)
# of prior Treatments					
1	9 (29%)	2 (33%)	2 (33%)	4 (31%)	1 (17%)
2	1 (3.2%)	1 (17%)	-	-	-
3	3 (9.7%)	1 (17%)	-	2 (15%)	-
4	2 (6.5%)	1 (17%)	1(17%)	-	-
Prior IDH inhibitor	3 (9.7%)	2 (33%)	1(17%)	-	-

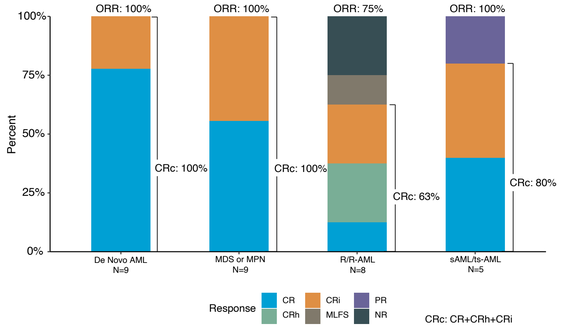
*All variables reported as N (%) or median (range) unless otherwise specified

Treatment response

Response by dose level



Response by disease



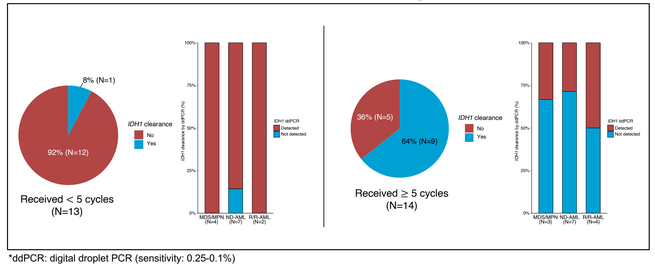
Safety of IVO+VEN +/- AZA

Grade 3-5 adverse events*				
Adverse event	**Overall (N = 31)**	**Grade 3**	**Grade 4**	**Grade 5**
Febrile neutropenia	9 (29%)	8 (26%)	-	1 (3%)
Lung infection	6 (19%)	6 (19%)	-	-
Abdominal pain	3 (10%)	3 (10%)	-	-
Differentiation syndrome (IDH-DS)	3 (10%)	3 (10%)	-	-
Musculoskeletal pain	3 (10%)	3 (10%)	-	-
Otitis media	2 (6.5%)	2 (6.5%)	-	-
Tumor lysis syndrome (TLS)	2 (6.5%)	2 (6.5%)	-	-

AE of special interest*	Onset days (range)	Grade 1/2	Grade 3/4	DLT**
TLS (N=2)	14 (0-27)	-/-	2/0	1 (50%)
IDH-DS (N=4)	39 (17-95)	0/1	3/0	0 (0%)

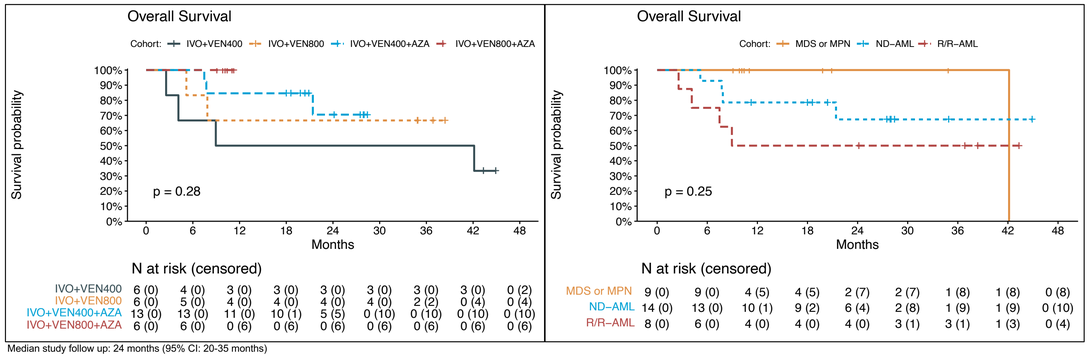
*All variables reported as N (%) or median (range); One patient in DL3 experienced G3 TLS attributed as a DLT

IDH1 clearance by ddPCR



*ddPCR: digital droplet PCR (sensitivity: 0.25-0.1%)

Survival outcomes



Median study follow up: 24 months (95% CI: 20-35 months)

Survival by dose level*				
Survival	**DL#1 (N=6)**	**DL#2 (N=6)**	**DL#3 (N=13)**	**DL#4 (N=6)**
Median EFS	7.9 (0-NR)	8.7 (7-NR)	NR (23-NR)	NR (-)
Median OS	26 (3-NR)	NR (5-NR)	NR (21-NR)	NR (-)
12-month EFS	50% (20%)	50% (20%)	77% (12%)	NA
12-month OS	50% (20%)	67% (19%)	85% (10%)	NA

Survival by disease			
Survival	**MDS or MPN (N=9)**	**ND-AML (N=14)**	**R/R-AML (N=8)**
Median EFS	NR (14-NR)	36.4 (23-NR)	6 (2-NR)
Median OS	42.1 (-)	NR (21-NR)	9 (8-NR)
12-month EFS	89% (11%)	71% (12%)	50% (18%)
12-month OS	100% (-)	79% (11%)	50% (18%)

*All variables reported as % (standard error) or median (95% CI)

MRD outcomes

Outcome	Doublet	Triplet
MRD-negative (MFC*)	4/8 (50%)	6/8 (75%)
IDH1 clearance cycle 5+ (ddPCR)	3/7 (43%)	6/7 (86%)
IDH1 undetected/MRD-negative**	5/8 (63%)	

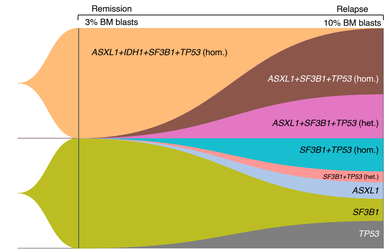
*MFC: Multiparameter flow cytometry (sensitivity: 0.1-0.01%); ** In patients receiving 5+ cycles of treatment

MRD-negative median: NR
24-month OS: 100%

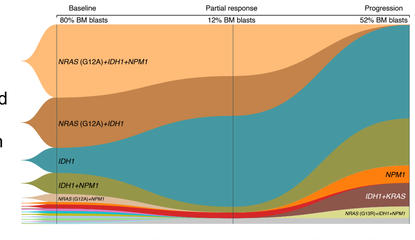
MRD-positive median: 8 months

Molecular drivers of relapse (scDNAseq)

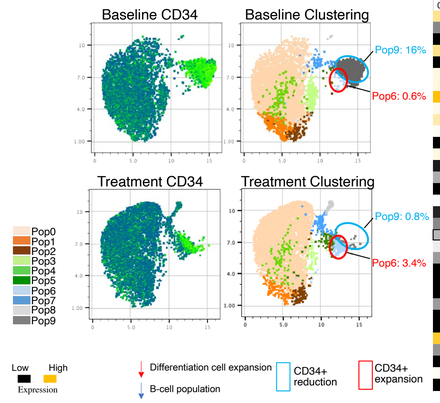
Outgrowth of *TP53* mutated clones observed with elimination of *IDH1* containing clone



Development of *KRAS* and *NRAS* G13R signaling mutations with elimination of *NRAS* G12A clones



Cellular mechanisms of relapse (CyTOF)



Emergence of CD34+ cell population with increased MCL1 expression observed following cycle 7 of treatment in patient with ND-AML

IVO+VEN+/-AZA associated with...

Expected and tolerable safety profile

High MRD-negative CRc rates in triplet combination

Durable responses and survival across disease groups

Clearance of *IDH1*-mutated clone in 64% of patients receiving ≥ 5 treatment cycles

IVO+VEN 400 mg + AZA selected as RP2D

Molecular/cellular correlates of relapse being defined

References: **1.** Papaemmanuil et. al. NEJM. 2016 Jun 9;374(23):2209-21; **2.** Mardis et. al. NEJM. 2009 Sep 10;361(11):1058-66; **3.** Paschka et. al. JCO. 2010 Aug 1;28(22):3636-43; **4.** DiNardo et. al. AJH. 2015 Aug;90(8):732-6; **5.** Ward et. al. Cancer cell. 2010 Mar 16;17(3):225-34; **6.** Chan et. al. Nature medicine. 2015 Feb;21(2):178-84; **7.** Lachowiez et. al. ASCO annual meeting (2021): 7012-7012.