IDH inhibitors in mutant IDH AML

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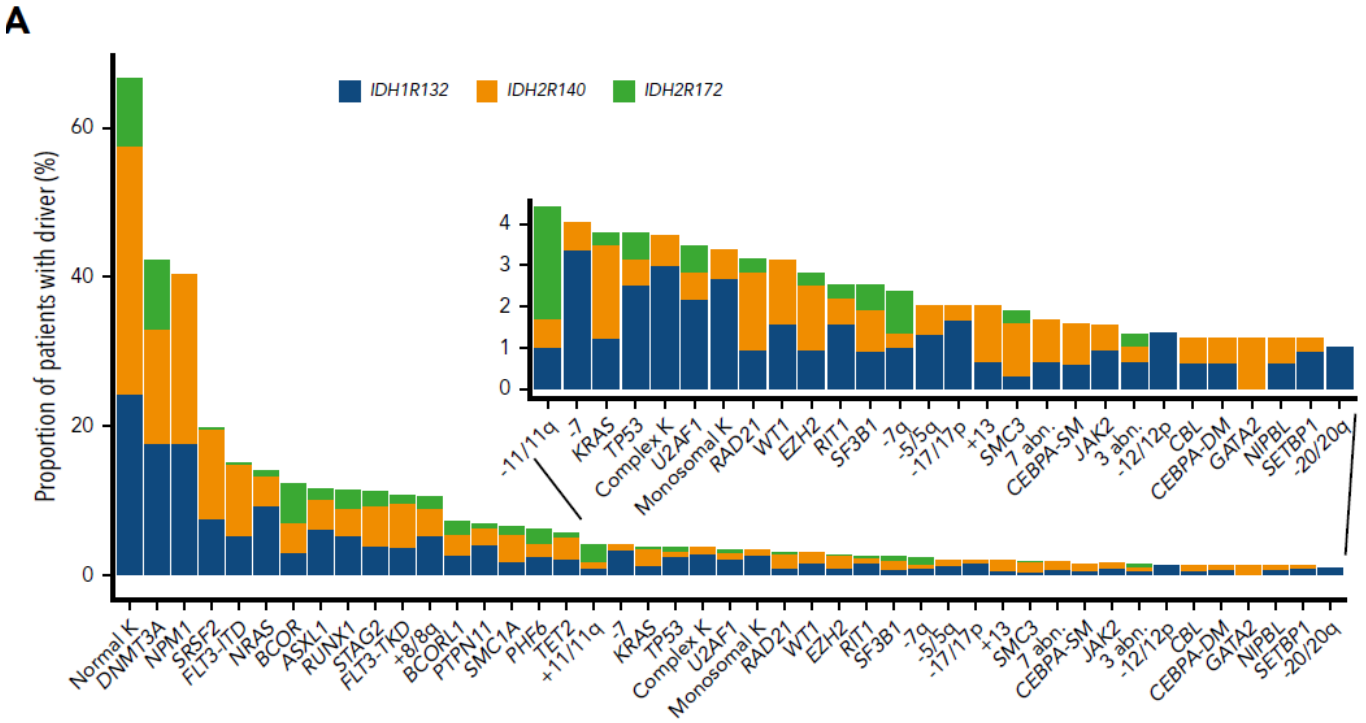
Disclosures of Stephane De BOTTON

Name of Company	Research support	Employee	Consultant	Stockholder	Speaker's Bureau	Advisory Board	Other	
Auron	X					X		
FORMA	X					X		
PFIZER						X		
SYROS						X		
ASTELLAS						X		
ABBVIE						X		
JAZZ						X		
BMS						X		
SERVIER	X					X		
REMIX						X		
FOGHORN	X							
JANSSEN							X	

IDH1/2 mutant proteins are good targets

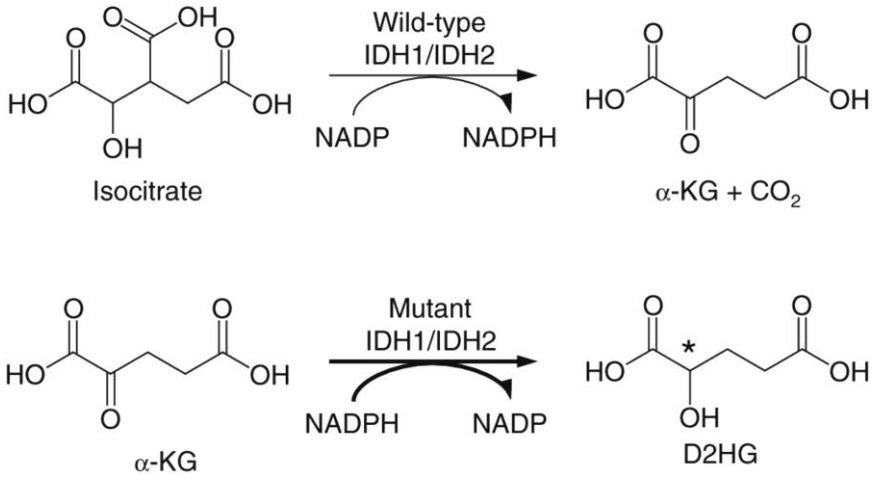
- Play a substantial role in AML pathophysiology and *IDH1/2* mutations are considered as early events in leukemogenesis
- Frequent events # 20 % AML
- They are druggable

Concurrent gene mutations in patients with IDH-mutated AML



Duchmann M et al; Blood (2021) 137 (20): 2827–2837.

IDH1/2 mutants produce D-2-HG



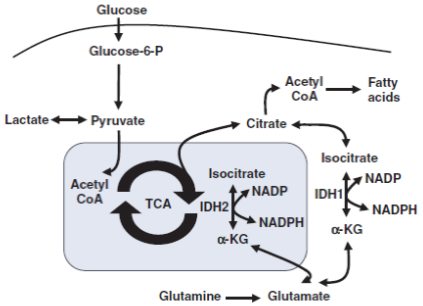
Highly similar molecules

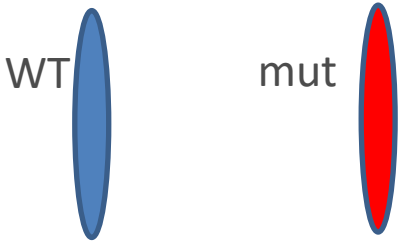
2-HG Occupies the Same Space as α-KG Does in the Active Site

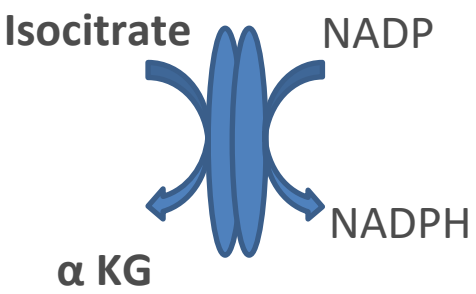
INHIBITION OF α-KG-dependent dioxygenases (control of demethylases)

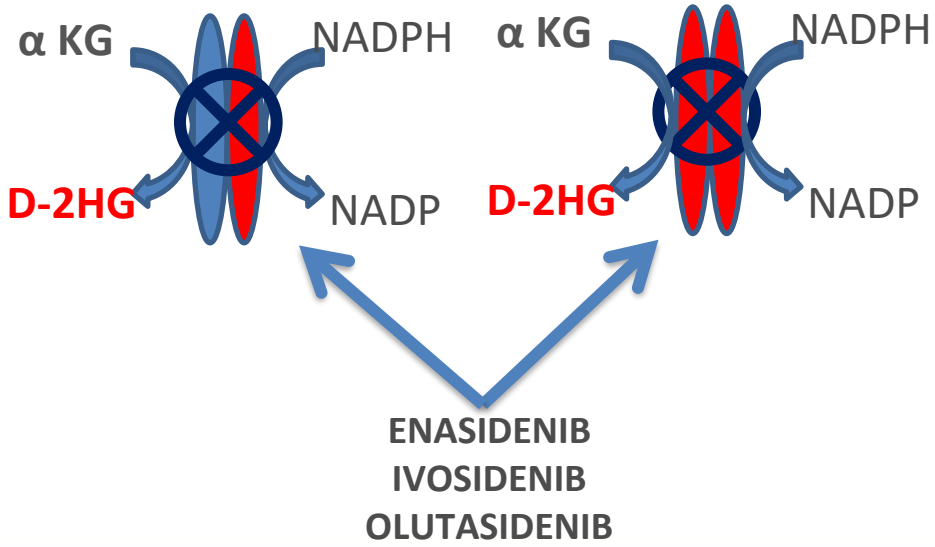
IDH1 and IDH2 Mutations Alter Histone and DNA Methylation

Block of differentiation


Glucose
Glucose-6-P
Lactate
Pyruvate
Acetyl CoA
Fatty acids
Citrate
Isocitrate
Acetyl CoA
TCA
Isocitrate
IDH2
NADP
NADPH
α-KG
Isocitrate
IDH1
NADP
NADPH
α-KG
Glutamine
Glutamate


WT
mut


Isocitrate
NADP
NADPH
α KG


α KG
NADPH
D-2HG
NADP
α KG
NADPH
D-2HG
NADP
ENASIDENIB
IVOSIDENIB
OLUTASIDENIB

IDH-mutated R/R AML

IDH1	IDH2
Tibsovo	Enasidenib
Olutasidenib	

FLT3 inhibitor if FLT3 positive

IDH inhibitors are FDA approved in R/R AML
High response rate

Table 2. Investigator-reported efficacy outcomes and survival in patients with R/R AML

	R/R AML	
	Enasidenib, 100 mg/d (n = 214)	All doses (N = 280)
ORR, % (n/N) [95% CI]*	38.8 (83/214) [32.2%-45.7%]	39.6 (111/280) [33.9%-45.6%]
CR + CRi/CRp rate, % (n/N)	29.0 (62/214)	27.9 (78/280)
Best response		
CR, n (%) [CR rate 95% CI]	42 (19.6) [14.5-25.6]	53 (18.9) [14.5-24.0]
CRi/CRp, n (%)	20 (9.3)	25 (8.9)
PR, n (%)	9 (4.2)	17 (6.1)
MLFS, n (%)	12 (5.6)	16 (5.7)
SD, n (%)†	98 (45.8)	122 (43.6)
PD, n (%)‡	19 (8.9)	26 (9.3)
Not evaluable, n (%)	3 (1.4)	4 (1.4)
Time to first response, median (range), mo	1.9 (0.5-9.4)	1.9 (0.5-9.4)
Duration of response, median (95% CI), mo	5.6 (3.8-7.4)	5.6 (4.6-6.5)
Time to best response, median (range), mo	3.7 (0.6-14.7)	3.7 (0.5-14.7)
Time to CR, median (range), mo	3.7 (0.7-14.7)	3.8 (0.5-14.7)
OS, median (95% CI), mo	8.8 (7.7-9.6)	8.8 (7.8-9.9)
EFS, median (95% CI), mo§	4.7 (3.7-5.6)	4.6 (3.7-5.6)

*Responses were evaluated by study investigators and classified according to the 2003 revised IWG criteria for AML.[16] ORR consists of CR, CRi, CRp, PR, and MLFS.

†SD was defined as failure to achieve a response but not meeting criteria for disease progression for >8 consecutive weeks.

‡For patients with 5% to 66% bone marrow blasts at nadir, a >50% increase in bone marrow blast count percentage from the nadir with percentage ≥ 20%; and for patients with ≥67% bone marrow blasts at nadir, a doubling of the nadir absolute peripheral blood blast count with a final absolute peripheral blood blast count >10×10^9/L

§Date of first documented response to date of relapse, disease progression, or death.

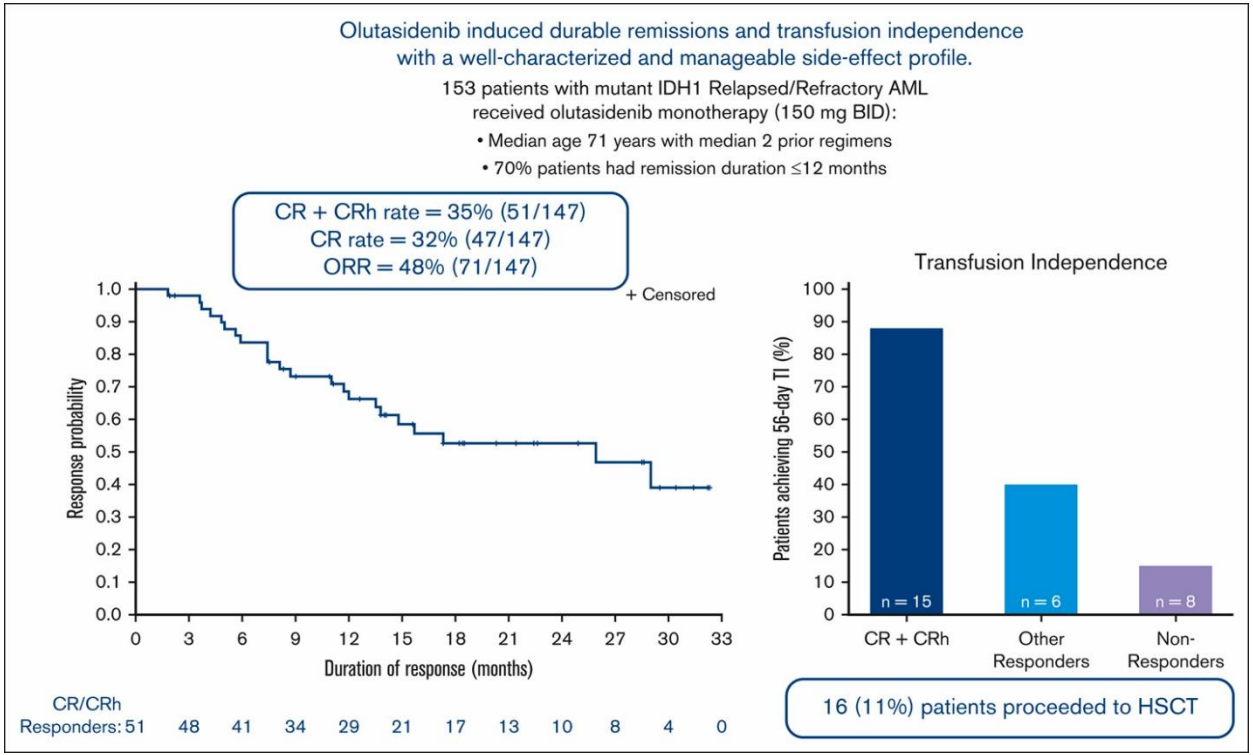
Eytan M. Stein et al. Blood 2019;133:676-687

Table 3. Investigator-Reported Hematologic Response, Time to Response, and Response Duration in Patients Receiving 500 mg of Ivosidenib Daily.*

Response	Primary Efficacy Population (N=125)	Relapsed or Refractory AML (N=179)	Untreated AML (N=34)†	MDS (N=12)‡
CR or CRh				NA
No. of patients	38	54	12	NA
% (95% CI)	30.4 (22.5–39.3)	30.2 (23.5–37.5)	35.3 (19.7–53.5)	NA
Median time to CR or CRh (range) — mo	2.7 (0.9–5.6)	2.0 (0.9–5.6)	2.8 (1.9–2.9)	NA
Median duration of CR or CRh (95% CI) — mo	8.2 (5.5–12.0)	6.5 (5.5–11.1)	NE (1.0–NE)	NA
CR				
No. of patients	27	39	7	5
% (95% CI)	21.6 (14.7–29.8)	21.8 (16.0–28.6)	20.6 (8.7–37.9)	41.7 (15.2–72.3)
Median time to CR (range) — mo	2.8 (0.9–8.3)	2.8 (0.9–8.3)	2.8 (1.9–3.7)	1.9 (1.0–5.6)
Median duration of CR (95% CI) — mo	9.3 (5.6–18.3)	9.3 (5.6–12.5)	NE (5.6–NE)	NE (2.8–NE)
Overall response				
No. of patients	52	70	19	11
% (95% CI)	41.6 (32.9–50.8)	39.1 (31.9–46.7)	55.9 (37.9–72.8)	91.7 (61.5–99.8)
Median time to first response (range) — mo§	1.9 (0.8–4.7)	1.9 (0.8–4.7)	1.9 (0.9–2.9)	1.6 (1.0–2.8)
Median duration of response (95% CI) — mo	6.5 (4.6–9.3)	6.5 (4.6–9.3)	9.2 (1.9–NE)	NE (2.3–NE)
Best response — no. (%)				
CR	27 (21.6)	39 (21.8)	7 (20.6)	5 (41.7)
CRi or CRp	16 (12.8)	21 (11.7)	7 (20.6)	0
Partial remission	0	0	1 (2.9)	0
MLFS or bone marrow CR¶	9 (7.2)	10 (5.6)	4 (11.8)	6 (50.0)
Stable disease	44 (35.2)	69 (38.5)	10 (29.4)	0
Progressive disease	13 (10.4)	15 (8.4)	3 (8.8)	1 (8.3)
Could not be evaluated	0	0	0	0
Not assessed	16 (12.8)	25 (14.0)	2 (5.9)	0

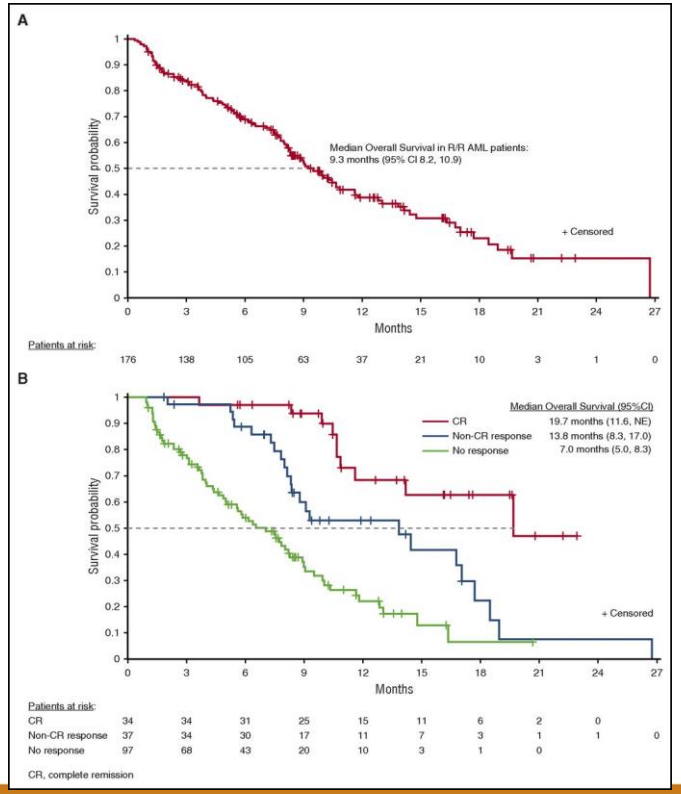
Courtney DiNARDO N Engl J Med 2018; 378:2386-2398

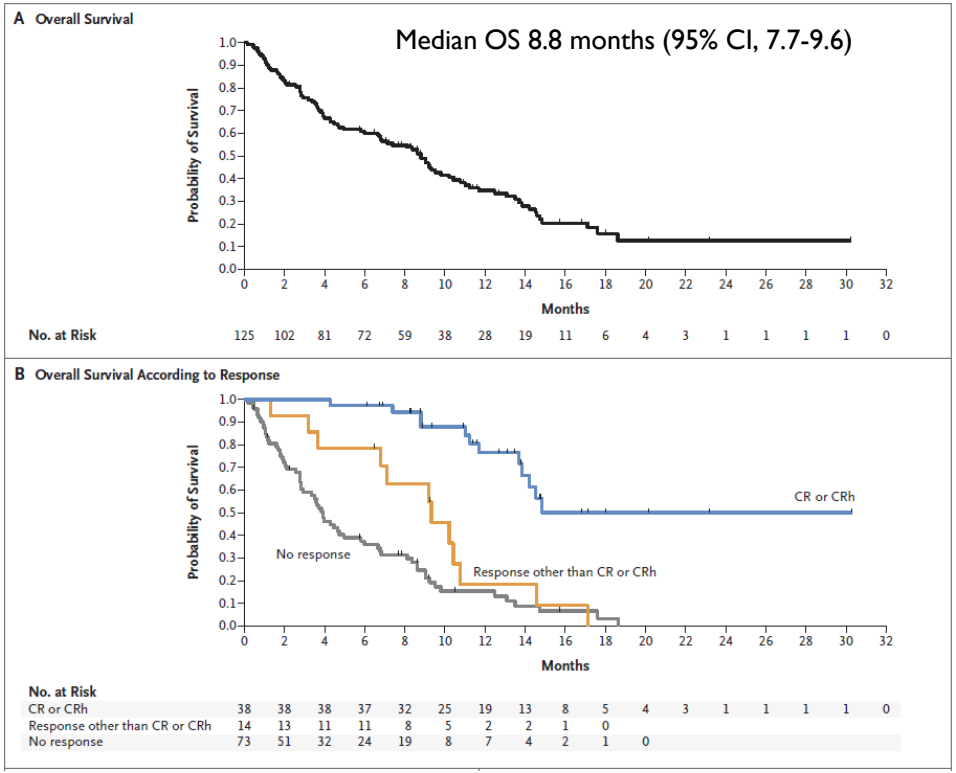
IDH inhibitors are FDA approved in R/R AML
High response rate



de Botton S, et al., Blood Adv, 2023,

IDH inhibitors are FDA approved in R/R AML
Durable responses



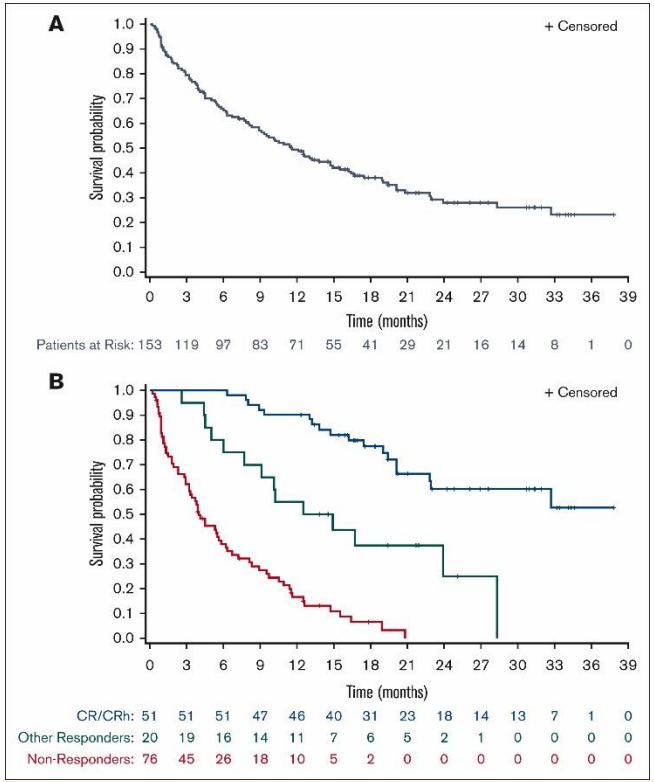


Eytan M. Stein et al. Blood 2017;130:722-731

Courtney DiNARDO N Engl J Med 2018; 378:2386-2398

IDH inhibitors are FDA approved in R/R AML
Durable responses

median OS 11.6 months



de Botton S, et al., Blood Adv, 2023,

IDH inhibitors are FDA approved in R/R AML
SAFE

Supplementary Table S3. Treatment-related adverse events (any grade) occurring in ≥5% of all patients.

	Relapsed / refractory AML		
	Enasidenib 100 mg/day (n=214)	All doses (n=280)	All patients (N=345)
Preferred term	n (%)		
Hyperbilirubinemia*	71 (33)	97 (40)	139 (40)
Nausea	59 (28)	76 (27)	95 (28)
Decreased appetite	41 (19)	50 (18)	61 (18)
Vomiting	37 (17)	46 (16)	52 (15)
Diarrhea	33 (15)	45 (16)	52 (15)
Fatigue	31 (14)	41 (15)	51 (15)
IDH differentiation syndrome	27 (13)	33 (12)	38 (11)
Dysgeusia	22 (10)	26 (9)	34 (10)
AST increased	20 (9)	24 (9)	29 (8)
Dyspnea	20 (9)	21 (8)	27 (8)
Leukocytosis	16 (8)	22 (8)	25 (7)
Anemia	14 (7)	18 (6)	25 (7)
ALT increased	15 (7)	18 (6)	21 (6)
Rash	13 (6)	14 (5)	20 (6)
Hyperuricemia	12 (6)	14 (5)	18 (5)

*Contains multiple preferred terms under the Standardized MedDRA Query (SMQ) "Biliary system related investigations, signs and symptoms"

ALT, alanine aminotransferase; AST, aspartate aminotransferase; IDH, isocitrate dehydrogenase

Eytan M. Stein et al. Blood 2019;133:676-687

Table S4. Most common adverse events (≥5%) considered to be related to ivosidenib by the investigator.

Event, n (%)	Overall population, N=258	
	Any grade	Grade ≥3
Any treatment-related adverse event	163 (63.2)	66 (25.6)
Nausea	37 (14.3)	2 (0.8)
Diarrhea	32 (12.4)	3 (1.2)
Electrocardiogram QT prolongation	32 (12.4)	18 (7.0)
Fatigue	32 (12.4)	2 (0.8)
IDH differentiation syndrome	27 (10.5)	12 (4.7)
Decreased appetite	25 (9.7)	2 (0.8)
Leukocytosis	18 (7.0)	3 (1.2)
Vomiting	18 (7.0)	1 (0.4)

Courtney DiNARDO N Engl J Med 2018; 378:2386-2398

IDH inhibitors are FDA approved in R/R AML
SAFE

Differentiation Syndrome

All Grades:
14% (21 pts)

Grades 3/4:
7% (11 pts) / 1% (1 pt)

- 3 pts discontinued treatment
  - Event was fatal in 1 pt
- 18 pts had concomitant leukocytosis

QTc Prolongation

All Grades:
8% (13 pts)

Grades 3/4: < 1%
(1 pt, Grade 3)

- No events led to discontinuation

Liver Abnormalities

TEAEs[a]:

All Grades: 21% (32 pts)

Grades 3/4:
10% (16 pts)/2% (3 pts)

- 7 pts (Grade 3/4) discontinued treatment; 4 pts after recurrence post-rechallenge
- 25 pts had no dose modification or continued after a rechallenge

No Hy's law cases

Laboratory Abnormalities[b]:

N=153, n (%)	All Grades	Grade ≥ 3
AST increased	65 (42)	12 (8)
ALT increased	63 (41)	19 (12)
ALP increased	60 (39)	9 (6)
Bilirubin increased	42 (27)	4 (3)

[b] **Based on worst post-baseline laboratory values**

[a] **Summary of relevant PTs from Hepatobilliary Disorders and Investigations SOCs**

ALP, alkaline phosphate; ALT, alanine aminotransferase; AST, aspartate aminotransferase, PT, preferred term; SOC, system organ class

Differentiation Syndrome Associated With Enasidenib # 12% of the R/R AML

AT Fathi et al. JAMA Oncol. 2018 Jan 18.

Table 1. Frequency of Signs and Symptoms Consistent With IDH-DS[a]

Sign or Symptom	Patients With IDH-DS, No. (%) (n = 33)[b]
Dyspnea	28 (85)
Unexplained fever (body temperature of 38.0°C for 2 d)	26 (79)
Pulmonary infiltrates	24 (73)
Hypoxia	19 (58)
Acute kidney injury (CTCAE grade ≥2)	14 (42)
Pleural effusion	14 (42)
Bone pain or arthralgia	9 (27)
Lymphadenopathy	8 (24)
Rash	8 (24)
Disseminated intravascular coagulopathy	7 (21)
Edema or weight gain of >5 kg from screening	7 (21)
Pericardial effusion	5 (15)

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events[14]; IDH-DS, isocitrate dehydrogenase differentiation syndrome.

[a] Signs and symptoms included in this table are based on retrospective differentiation syndrome review committee review of clinical records.

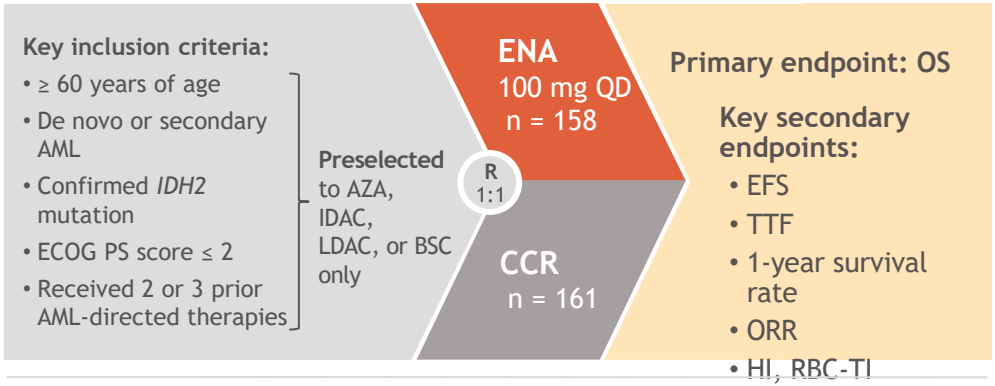
[b] Patients may have had multiple symptoms.

Table 2. Response Among Patients With and Without IDH-DS

Patient Response	IDH-DS, No. (%) (n = 33)[a]	No IDH-DS, No. (%) (n = 248)
Overall response[b]	15 (45.5)	93 (37.5)
CR	6 (18.2)	49 (19.8)
CRi/CRp	6 (18.2)	16 (6.5)
PR	2 (6.1)	14 (5.7)
MLFS	1 (3.0)	14 (5.7)
Stable disease[c]	16 (48.5)	121 (48.8)
Disease progression	1 (3.0)	14 (5.7)

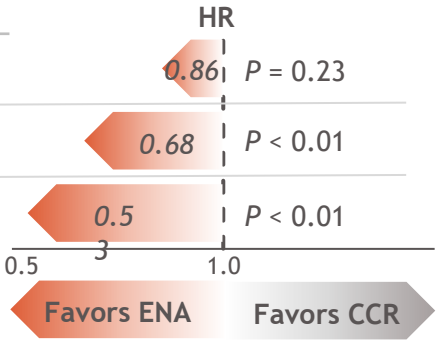
IDHENTIFY: study design and overall (ITT) results

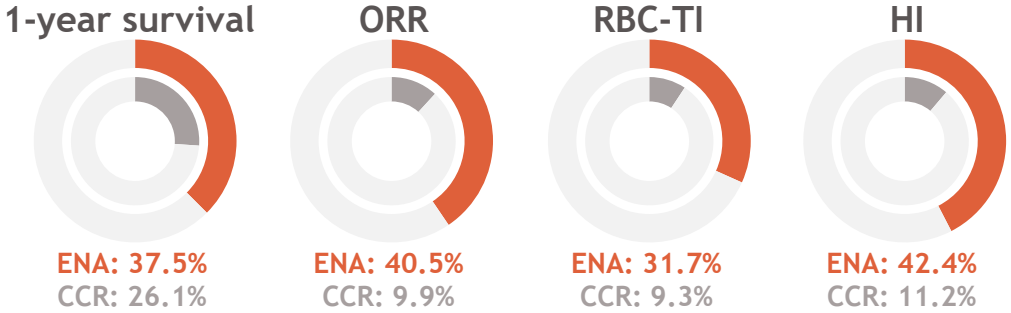
Phase 3, open-label, preselection study design



KM-estimated survival outcomes

	ENA	CCR	HR	
OS, median, mo	6.5	6.2	0.86	*P* = 0.23
EFS, median, mo	4.9	2.6	0.68	*P* < 0.01
TTF, median, mo	4.9	1.9	0.53	*P* < 0.01



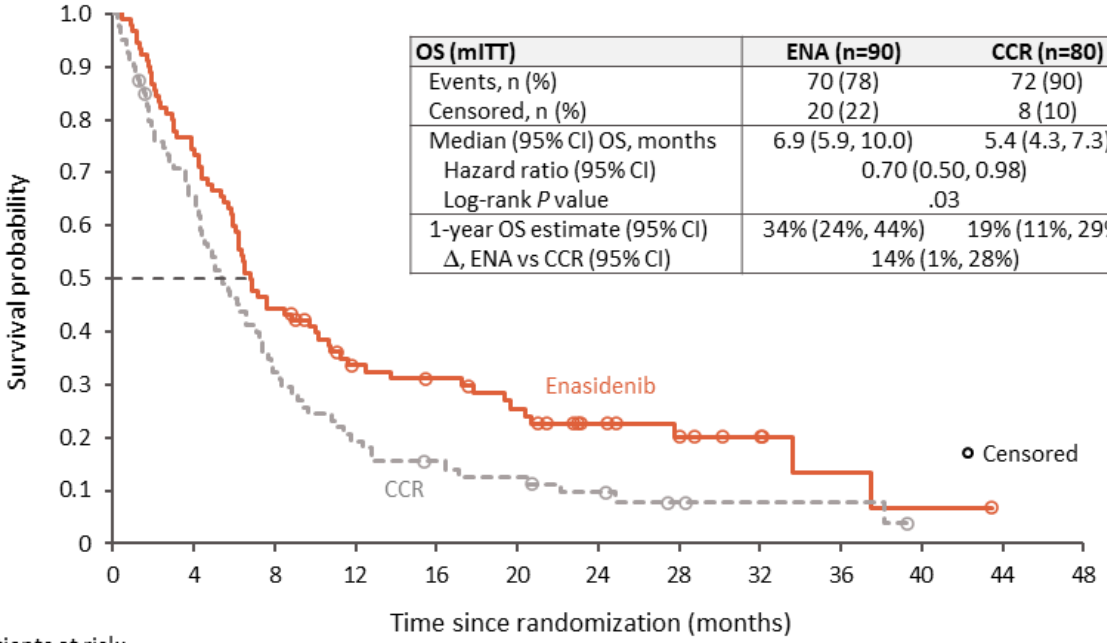


- OS was likely confounded by early Tx discontinuation and use of subsequent therapy during OS follow-up, which were more frequent in the CCR arm[1]

de Botton S, et al. *Blood* 2022

IDHENTIFY: study design and overall (mITT) results

OS (mITT)	ENA (n=90)	CCR (n=80)
Events, n (%)	70 (78)	72 (90)
Censored, n (%)	20 (22)	8 (10)
Median (95% CI) OS, months	6.9 (5.9, 10.0)	5.4 (4.3, 7.3)
Hazard ratio (95% CI)	0.70 (0.50, 0.98)	
Log-rank *P* value	.03	
1-year OS estimate (95% CI)	34% (24%, 44%)	19% (11%, 29%)
Δ, ENA vs CCR (95% CI)	14% (1%, 28%)	



Patients at risk:

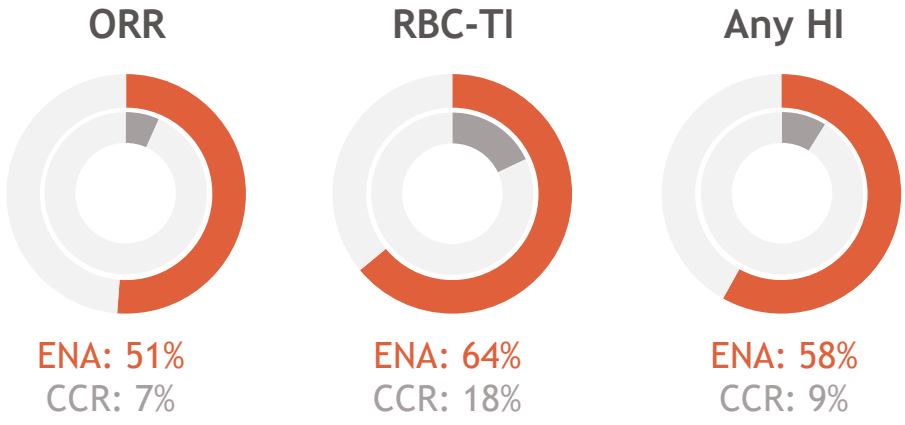
ENA	90	67	40	26	23	18	11	7	5	2	1	0	0
CCR	80	51	25	15	11	9	6	3	2	2	0		

Δ, difference; CCR, conventional care regimens; CI, confidence interval; ENA, enasidenib; mITT, modified intention-to-treat; OS, overall survival.

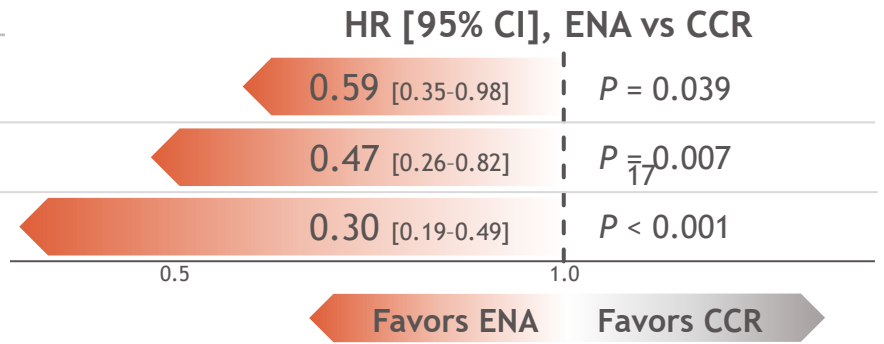
R172 subgroup summary

Baseline mutations:

- Median 4 (range, 2–8) gene mutations
- Most common co-mutations: *DNMT3A*, *RUNX1*
- *DNMT3A* and *TP53* preferentially co-mutated with R172 (vs R140)



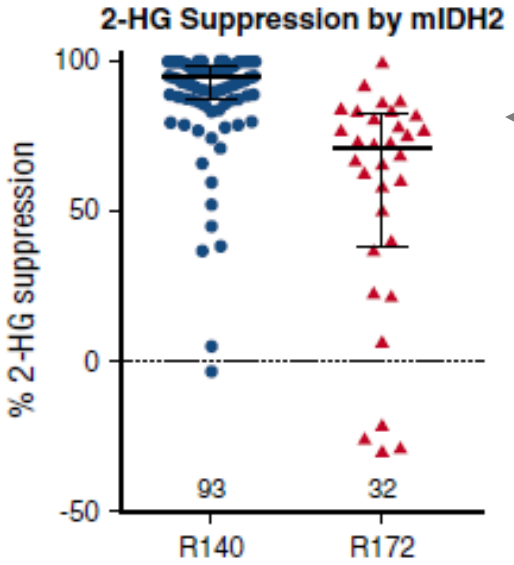
	ENA (n=43)	CCR (n=45)
OS, median, mo	14.6	7.8
EFS, median, mo	10.1	2.7
TTF, median, mo	7.5	2.2



AML, acute myeloid leukemia; CCR, conventional care regimen; ENA, enasidenib; EFS, event-free survival; HI, hematologic improvement; HR, hazard ration; mo, month; ORR, overall response rate; OS, overall survival; TTF, time to treatment failure.

IDH inhibitors can suppress 2-HG

A



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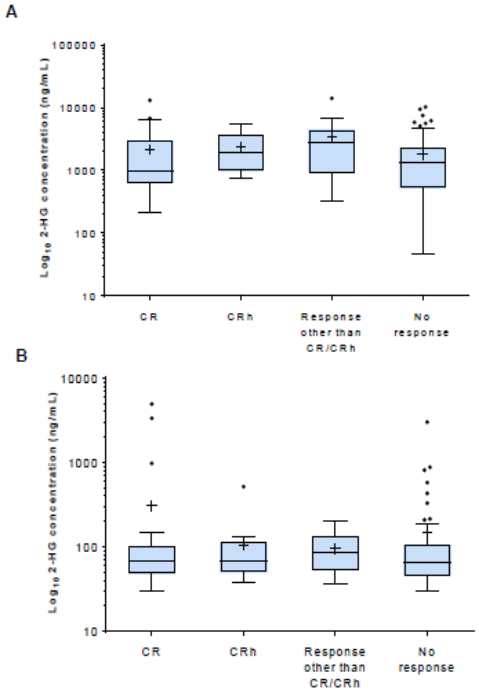
Enasidenib
acts efficiently on R140Q

Ivosidenib
acts efficiently on R132

2-HG normalized
responders and non-responders
Not a surrogate marker of response

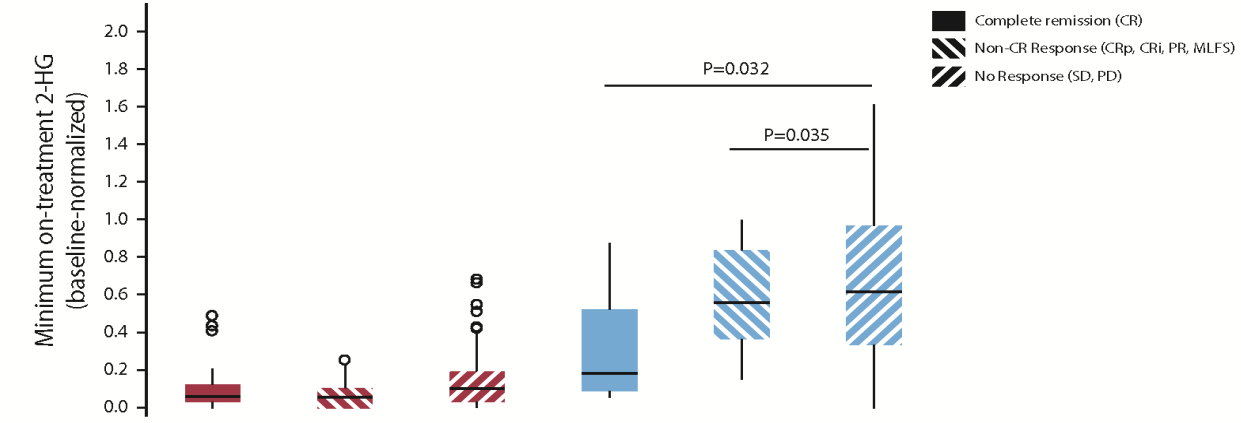
In non responders
clones are not dependent
on IDH1/2 mut

Figure S7. 2-HG levels at (A) baseline and (B) cycle 2 day 1 by best overall response in patients with R/R AML whose starting dose was 500 mg daily.



Sung Choe
Blood Adv. 2020 May 12;4(9):1894-1905

2-HG reductions were significantly greater in patients achieving CR



Best Response	CR	Non-CR response	No response	CR	Non-CR response	No response
N	23	23	72	8	11	18
Median	0.0581	0.0538	0.0999	0.1801	0.5571	0.6165
Outliers	3	1	7	0	1	0

2-HG, 2-hydroxyglutarate; CR, complete remission; CRp/CRi, CR with incomplete platelet/hematologic recovery; MLFS, morphologic leukemia-free state; PR, partial remission; PD, progressive disease; SD, stable disease

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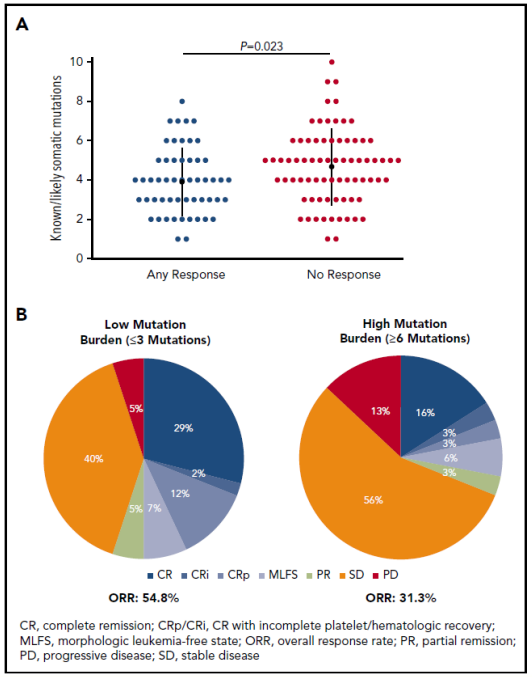
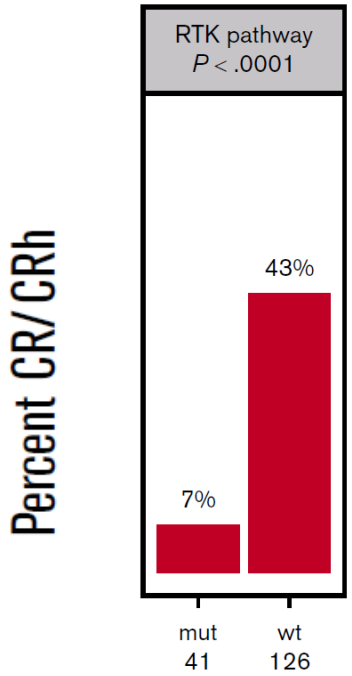
Primary resistance to IDH inhibitors

- Number of associated mutations
- Type of associated mutations

ENA





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Blood Adv
. 2020 May 12;4(9):1894-1905

IVO

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Secondary resistance to IDH inhibitors

- Clonal evolution/selection leading to IDH1/2m independence
  - Signaling pathways 35%
  - Differentiation 31%
  - Chromatin 31 %
  - Epigenetics 8%

- IDH related = 35 % (2HG addiction)
  - Gain /selection IDH1 or 2
  - Second site mutation
  - 2-HG +++

Quek et al Nature Medecine 2018; Intlekofer et al, Nature 2018

Sung Choe Blood Adv 2020 May 12;4(9):1894-1905

Combinations are required

To improve results of IDH inhibition alone

- Almost all patients relapsed
- To prevent/delay relapses IDH independent
- To improve depth of response

To ameliorate results of available therapies

- HMA are not very efficient (IDH1)
- To decrease relapse rate
- To delay relapses

Patients > 75 y and/or not eligible for intensive chemotherapy (Approved options)

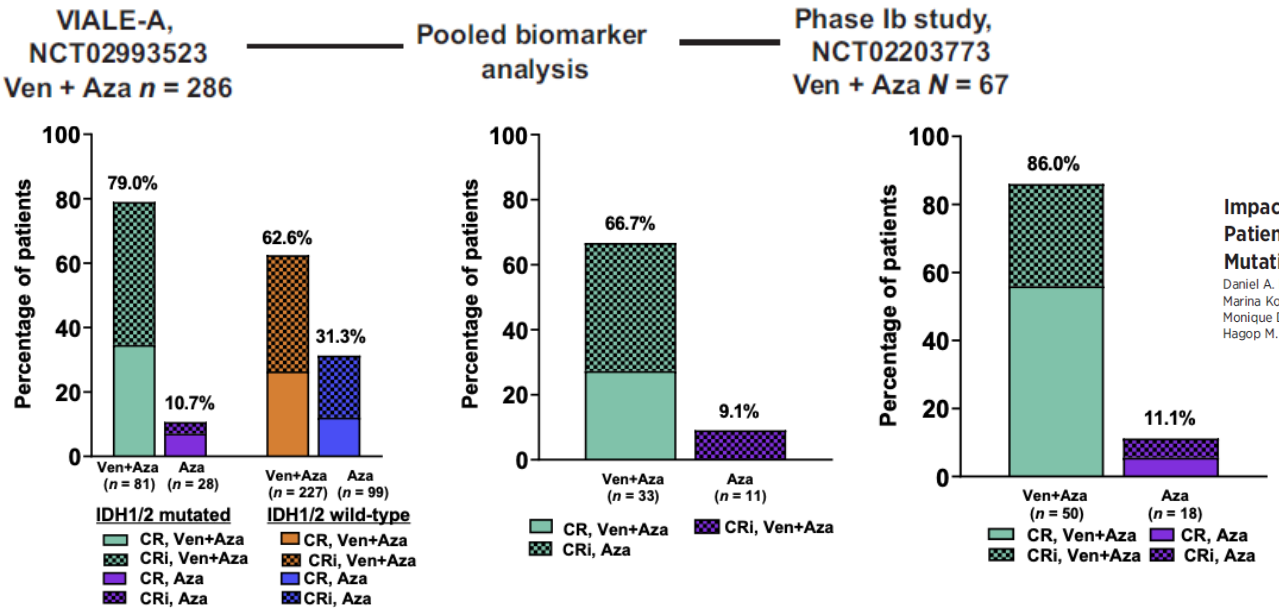
IDH1

- Tibsovo + 5-AZA
- Tibsovo alone
- Venetoclax + 5-AZA

IDH2

- Venetoclax + 5-AZA

5-AZA vs Venetoclax+ 5-AZA



Impact of Venetoclax and Azacitidine in Treatment-Naïve Patients with Acute Myeloid Leukemia and *IDH1/2* Mutations

Daniel A. Pollyea[1], Courtney D. DiNardo[2], Martha L. Arellano[3], Arnaud Pigneux[4], Walter Fiedler[5], Marina Konopleva[2], David A. Rizzieri[6], B. Douglas Smith[7], Atsushi Shinagawa[8], Roberto M. Lemoli[9,10], Monique Dail[11], Yinghui Duan[12], Brenda Chyla[12], Jalaja Potluri[12], Catherine L. Miller[12], and Hagop M. Kantarjian[2]

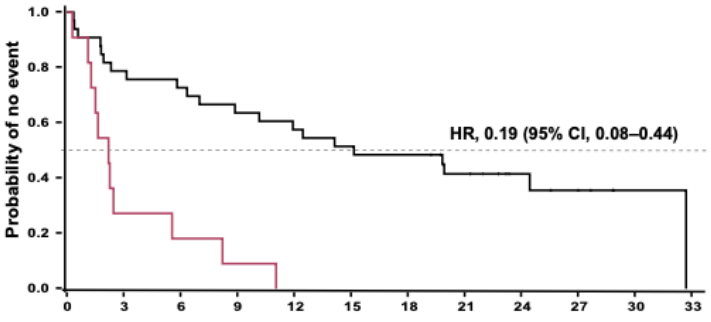
Figure 2.

A, Remission rates in patients with *IDH1/2* mutations and *IDH1/2* wild-type by treatment groups. **B,** Remission rates in patients with *IDH1* mutations in the venetoclax and azacitidine group. **C,** Remission rates in patients with *IDH2* mutations in the venetoclax and azacitidine group.

doi: 10.1158/1078-0432.CCR-21-3467

5-AZA vs Venetoclax+ 5-AZA

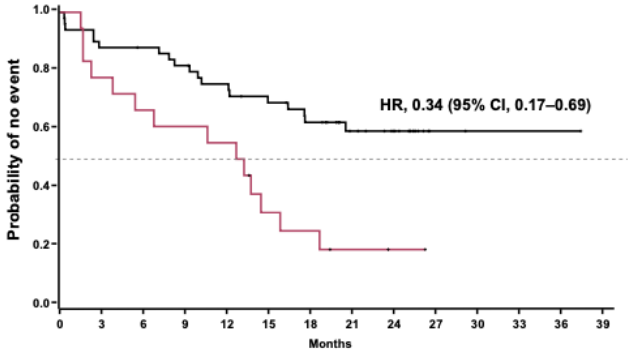
B



Patients at risk												
Ven+Aza	33	26	24	21	19	17	16	12	7	5	1	0
Aza	11	3	2	1	0							

	Events	Survival estimate (%) (95% CI) Month 6	Month 12	Month 24	Median (months) (95% CI)
Ven+Aza (*N* = 33)	21	72.7 (54.1–84.8)	57.6 (39.1–72.3)	41.6 (24.6–57.7)	15.2 (7.0, -)
Aza (*N* = 11)	11	18.2 (2.9–44.2)	NA	NA	2.2 (1.1–5.6)

C



Patients at risk													
Ven+Aza	50	44	43	40	36	32	28	19	14	2	1	1	1	0
Aza	18	14	12	11	10	5	4	2	1	0				

	Events	Survival estimate (%) (95% CI) Month 6	Month 12	Month 24	Median (months) (95% CI)
Ven Aza (*N* = 50)	19	88.0 (75.2–94.4)	75.6 (61.0–85.3)	59.5 (43.9–72.2)	- (17.6, -)
Aza (*N* = 18)	14	66.7 (40.4–83.4)	55.6 (30.5–74.8)	19.0 (4.8–40.3)	13.0 (3.8–15.8)

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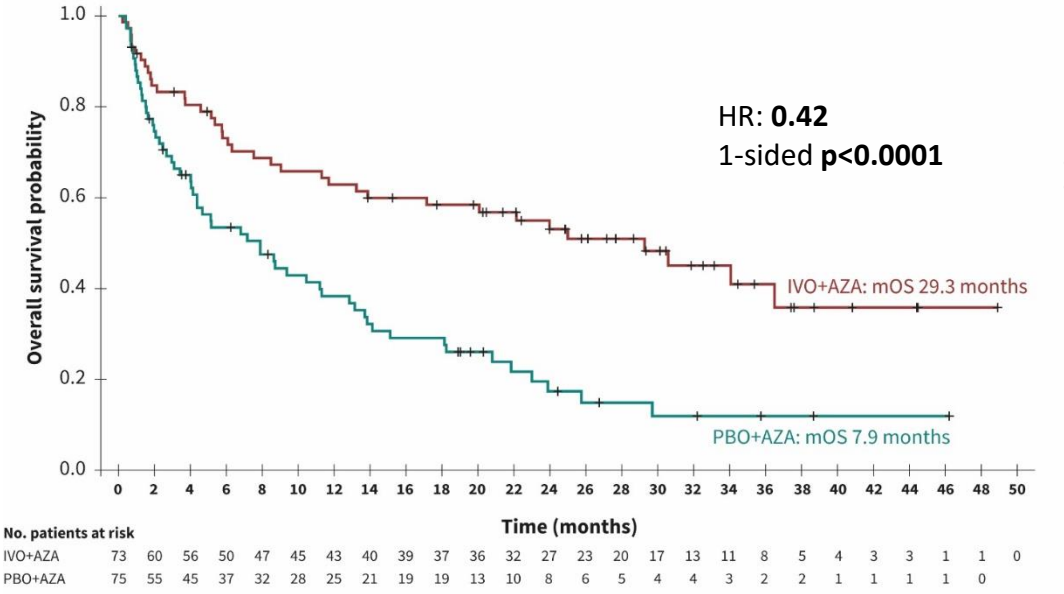
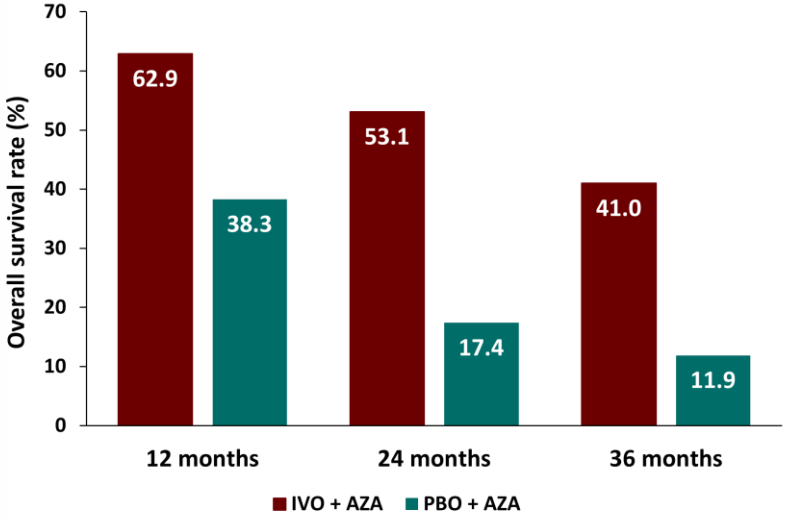
5-AZA + IVO

At a median follow-up (28.6 months)





De Botton et al. ASCO 2023. Abstract #7012

Enasidenib + 5-AZA in Patients With Newly Diagnosed AML

	Enasidenib plus azacitidine (n=68)	Azacitidine only (n=33)	p value
Overall response*	50 (74%; 95% CI 61–84)	12 (36%; 95% CI 20–55)	0·0003
Complete remission	37 (54%; 95% CI 42–67)	4 (12%; 95% CI 3–28)	<0·0001
Complete remission or complete remission with partial haematological recovery	39 (57%)	6 (18%)	0·0002
Complete remission with incomplete blood count or platelet recovery	6 (9%)	6 (18%)	..
Partial remission	4 (6%)	2 (6%)	..
Morphological leukaemia-free state	3 (4%)	0	..
Stable disease	13 (19%)	16 (48%)	..
Disease progression	1 (1%)	1 (3%)	..
Not evaluable or missing data	4 (6%)	4 (12%)	..
Time to first response, months	1·9 (1·1–3·9)	3·6 (1·9–4·4)	..
Time to complete remission, months	5·4 (3·8–7·6)	4·4 (3·8–5·6)	..
Duration of response, months	24·1 (95% CI 10·0–NR)	9·9 (95% CI 5·5–13·6)	..
Duration of complete remission, months	NR (95% CI 7·7–NR)	12·7 (95% CI 11·7–NR)	..

Data are n (%; 95% CI), n (%), median (IQR), or median (95% CI). Data cutoff Aug 20, 2019. NR=not reached. *Overall response defined as proportion of patients with complete remission, complete remission with incomplete blood count or platelet recovery, partial remission, or morphological leukaemia-free state.

Table 2: **Haematological responses in the randomised phase 2 study portion**

*ORR = (CR, Cri/CRp, PR, MLFS)

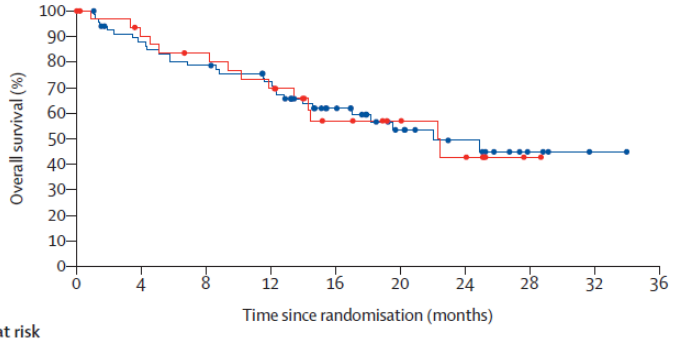
DiNardo, et al. Lancet Oncol. 2021 Nov;22(11):1597-1608. doi: 10.1016/S1470-2045(21)00494-0.

Enasidenib + AZA in Patients With Newly Diagnosed AML

OS

B

	Enasidenib plus azacitidine (n=68)	Azacitidine only (n=33)
Events	29 (43%)	14 (42%)
Censored	39 (57%)	19 (58%)
Median overall survival, months	22·0 (95% CI 14·6–NR)	22·3 (95% CI 11·9–NR)
Hazard ratio	0·99 (95% CI 0·52–1·87)	
Log-rank p value	0·97	

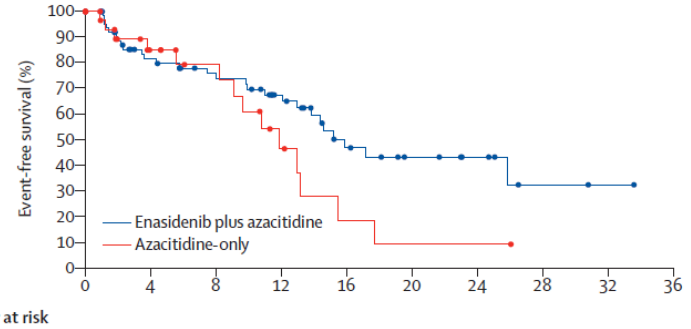


Number at risk (number censored)										
Enasidenib plus azacitidine	68 (0)	57 (3)	51 (3)	44 (6)	28 (16)	16 (25)	11 (29)	4 (35)	1 (38)	0 (39)
Azacitidine only	33 (0)	27 (3)	24 (4)	20 (4)	12 (9)	9 (12)	6 (13)	1 (18)	0 (19)	..

EFS

A

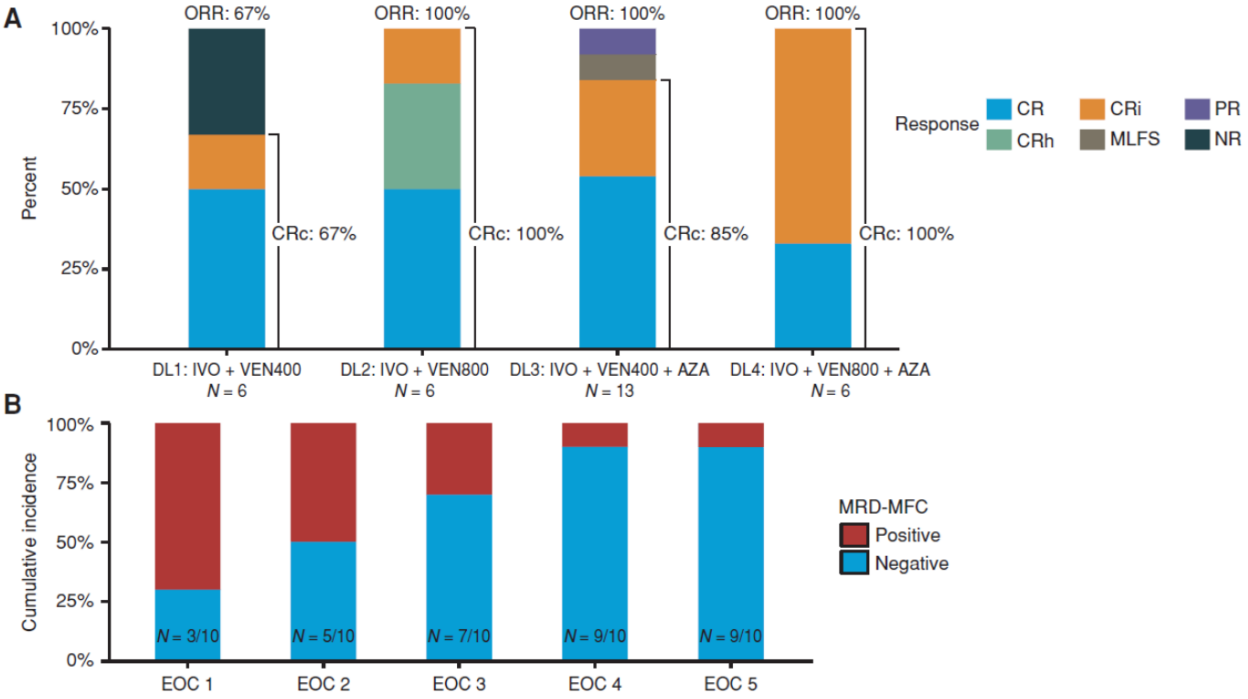
	Enasidenib plus azacitidine (n=68)	Azacitidine only (n=33)
Events	27 (40%)	14 (42%)
Censored	41 (60%)	19 (58%)
Median event-free survival, months	15·9 (95% CI 13·0–NR)	11·9 (95% CI 8·2–15·5)
Hazard ratio	0·59 (95% CI 0·30–1·13)	
Log-rank p value	0·11	



Number at risk (number censored)										
Enasidenib plus azacitidine	68 (0)	45 (12)	37 (17)	27 (23)	14 (29)	9 (33)	6 (36)	2 (39)	1 (40)	0 (41)
Azacitidine only	33 (0)	18 (11)	13 (15)	6 (17)	2 (18)	1 (18)	1 (18)	0 (19)	..	..

DiNardo, et al. Lancet Oncol. 2021 Nov;22(11):1597-1608. doi: 10.1016/S1470-2045(21)00494-0.

ivosidenib with venetoclax +/- azacitidine in IDH1-mutated



- Lachowiez et al. JCO 2022. Abstract #7018

enasidenib with venetoclax +/- azacitidine in IDH1-mutated

Table 2. Outcomes in newly diagnosed and relapsed/refractory patients with *IDH2* mutant acute myeloid leukemia.

Response	Newly diagnosed $n = 7$	Relapsed/ refractory $n = 19$
CRc	7 (100)	11 (58)
CR	5 (72)	5 (26)
CRi	2 (28)	6 (32)
MRD negativity by FCM	7/7 (100)	2/9 (22)
Not evaluable	0	1 (5)
No response	0	7 (37)
Median number of cycles given (range)	3 (1–8)	4 (1–17)
Median time to best response, months (range)	1.6 (1.0–4.2)	1.8 (0.8–5.4)

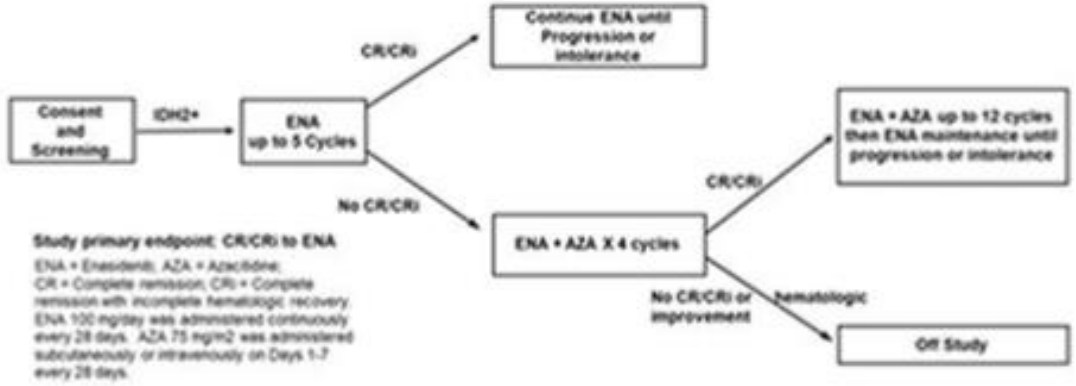
CRc -composite complete remission rate = CR + CRi, *CR*- complete remission, *CRi* -CR with incomplete hematologic recovery, *MRD*- measurable residual disease, *FCM*- flowcytometry
All results expressed as No. (%) or median [Minimum–maximum], unless specified.

A PHASE II STUDY OF ENASIDENIB WITH VENETOCLAX +/- AZACITIDINE IN IDH2-MUTATED MYELOID MALIGNANCIES
Venugopal S et al, *Blood Cancer Journal* volume 12, Article number: 10 (2022)

Phase 2 (n= 60)
enasidenib 100 mg/d

CR 37%
CRi 10 %
ORR 50 %

Duration of response : NR
OS : 24.4 months



Phase 1b (n=17)
Enasidenib + 5-AZA

CR 18 %
CRi 24 %
ORR 47 %

OS = 8.9 months

Eytan M. Stein et al ; A Completed Phase 2/1b Sub-Study of the Beat AML Master Trial, Blood, 2020,

Response to 5-AZA + VEN in R/R AML

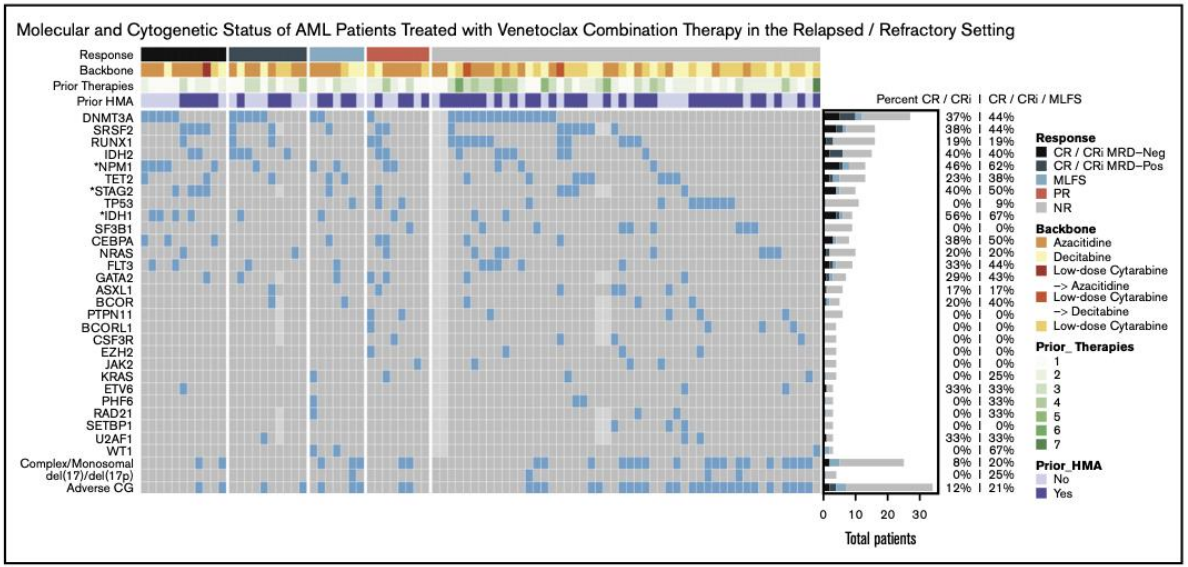


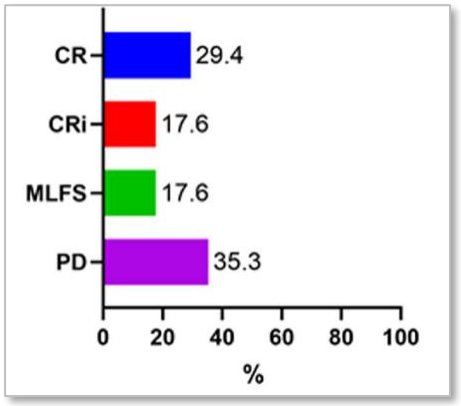
Figure 3. Molecular predictors of response. Oncoprint showing mutational and cytogenetic characteristics at diagnosis for 86 patients treated in the RR setting. Light gray boxes represent missing data. Patients are grouped by best response, annotated with colored bars above the grid. The type of backbone used in combination with venetoclax, the number of previous lines of therapy, and previous exposure to HMA are also annotated at the top. The filled bar plot on the right shows the number of patients with each mutation who achieved CR, CRi, and MLFS, with percentages to the right. Asterisks indicate genes with $P < .05$ for either percent CR/CRi MRD negative, CR/CRi, or ORR.

IDH1 (n=9)
CR/CRi = 56 %
ORR = 67 %

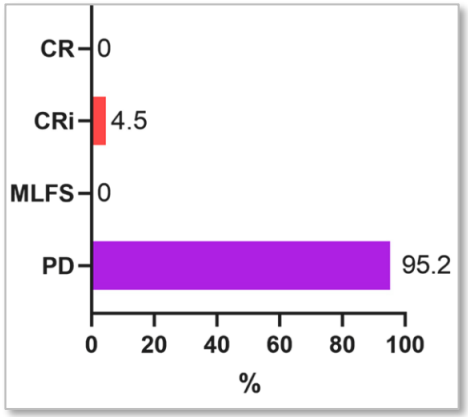
IDH2 (n=15)
CR/Cri = 56 %
ORR = 67 %

Stahl et al 2021 Mar 9;5(5):1552-1564. doi: 10.1182/bloodadvances.2020003734.

5-AZA + VEN AFTER IDH inhibitor



5-AZA + VEN BEFORE IDH inhibitor



Bewersdorf Leukemia Lymphoma 2022

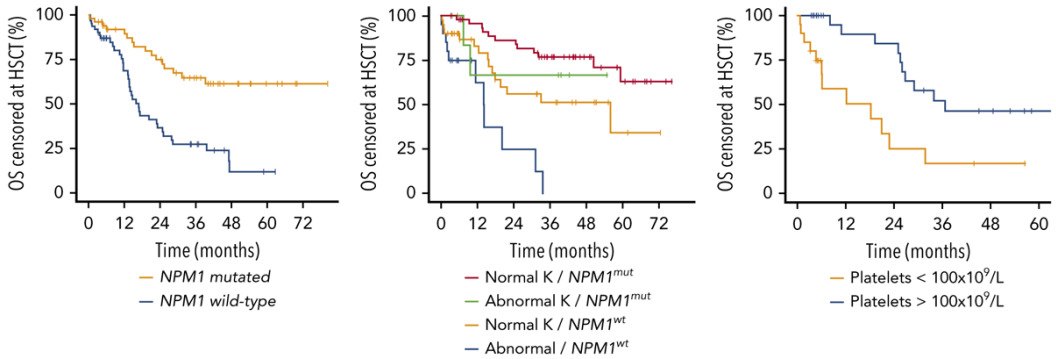
Prognostic significance of concurrent gene mutations in intensively treated patients

1502 newly diagnosed AML pts
Treated by intensive chemotherapy
- ALFA-0701: 280 pts
- ALFA-0702: 713 pts
- ALFA-1200: 509 pts

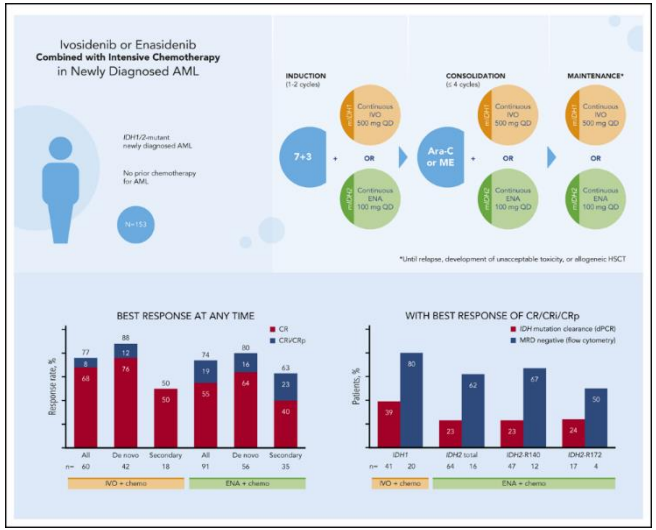
→ **319 *IDH$_{1/2}$*-mutated AML pts**

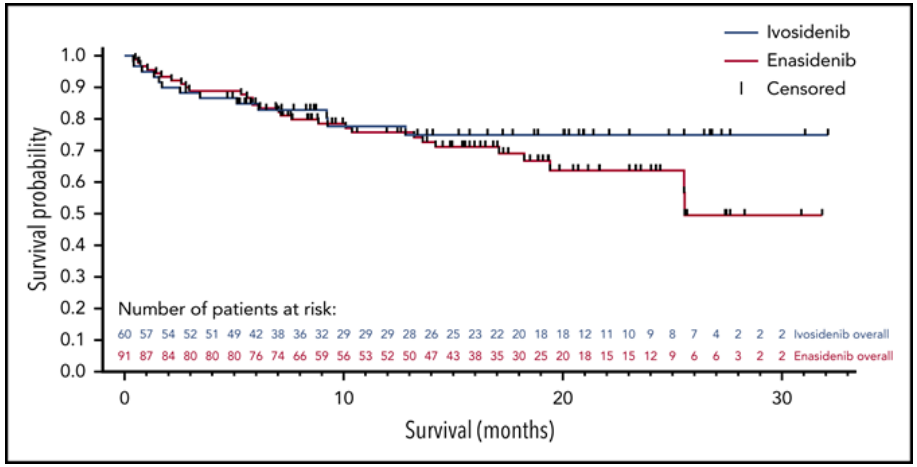
***IDH1* (n=127)**	***IDH2R140* (n=135)**	***IDH2R172* (n=57)**
Stratifiers *NPM1* mutations	*NPM1* mutations Normal Karyotype	*Platelets < 100 x 10^9/L*

Overall survival censored at HSCT



Combination studies





Study	*n*	Age, y (range)	Median OS, mo	ORR/CR/CR + CRi (%)	Median FU, mo
Stein et al[41] 3+7 and enasidenib	93	63 (27-77)	25.6	86.8/55/74[a]	14.5
Stein et al[41] 3+7 and ivosidenib	60	62.5 (24-76)	NR (78% at 12 mo)	86.7/68/77[a]	9.3

Stein et al; Blood (2021) 137 (13): 1792–1803. https://doi.org/10.1182/blood.2020007233

CONCLUSIONS

Results of combination therapies are very encouraging

Favourable safety profile
synergistic effects inducing high response rate
Translates into a significant improvement in EFS and in OS

CONCLUSIONS

Results of combination therapies are very encouraging

WHEN /HOW incorporate Bcl2 inhibitors ?