La terapia con anti-BCL2 nelle LAM

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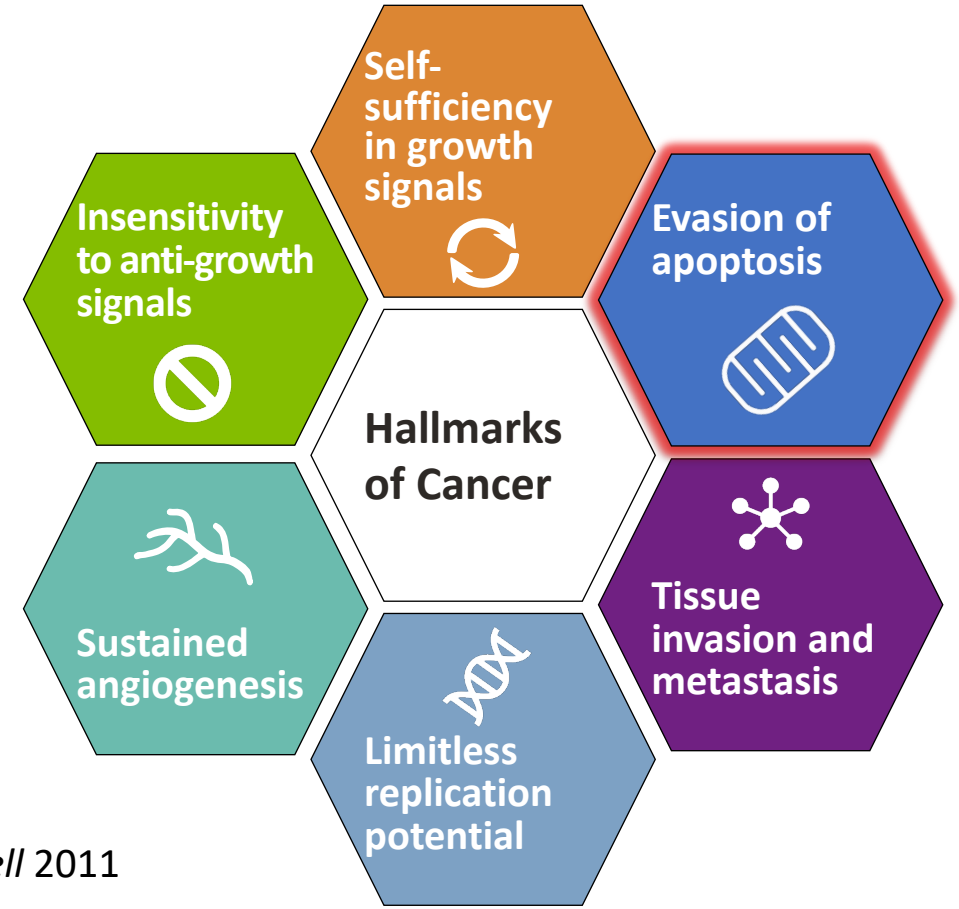
Disclosures of Name Surname

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Amgen						x	
Pfizer					x	x	
Astellas					x		
Abbvie						x	
Novartis					x	x	
Blueprint						x	
GSK						x	
BerGenBio						x	
Incyte						x	
Janssen						x	

Cancer pathogenesis is dependent on many mechanisms

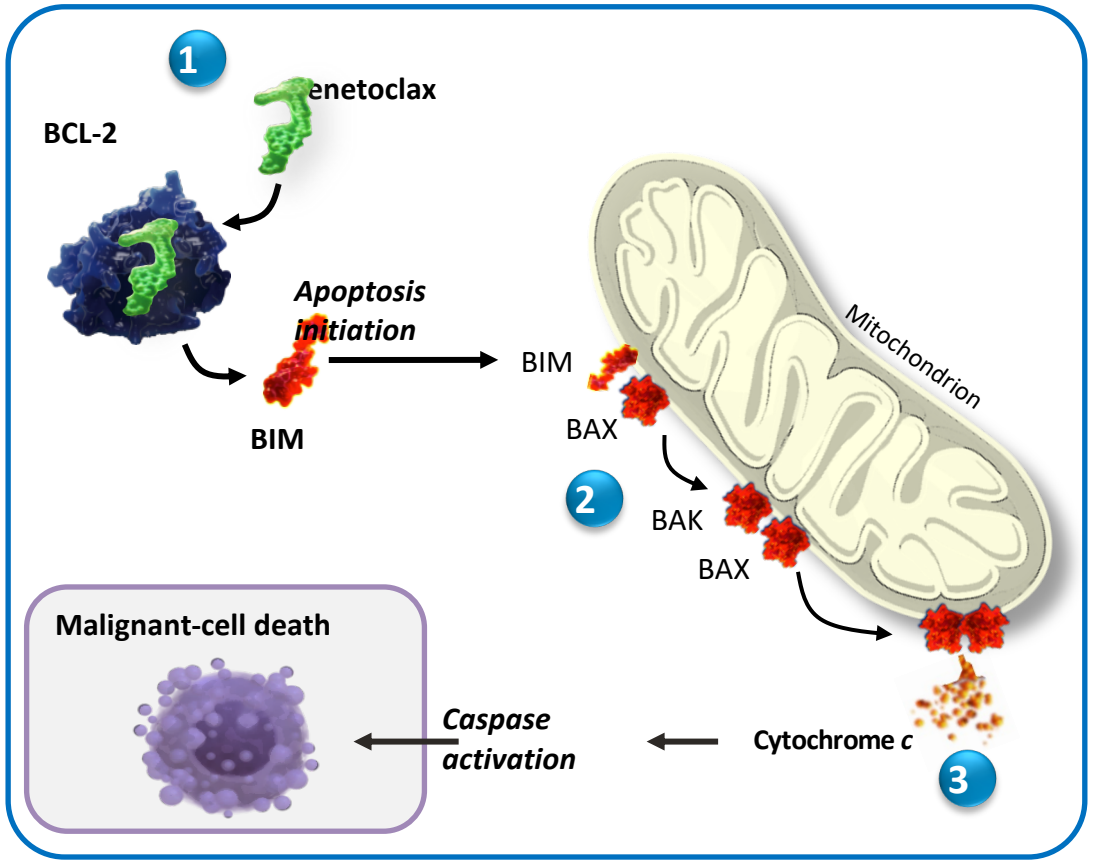
Hematologic malignancies are driven by a complex interplay of genetic alterations and mechanisms that ensure cell survival and proliferation



Evasion of apoptosis is a hallmark of malignant cell survival

Hanahan D & Weinberg RA. *Cell* 2011

Venetoclax induces apoptosis in malignant cells

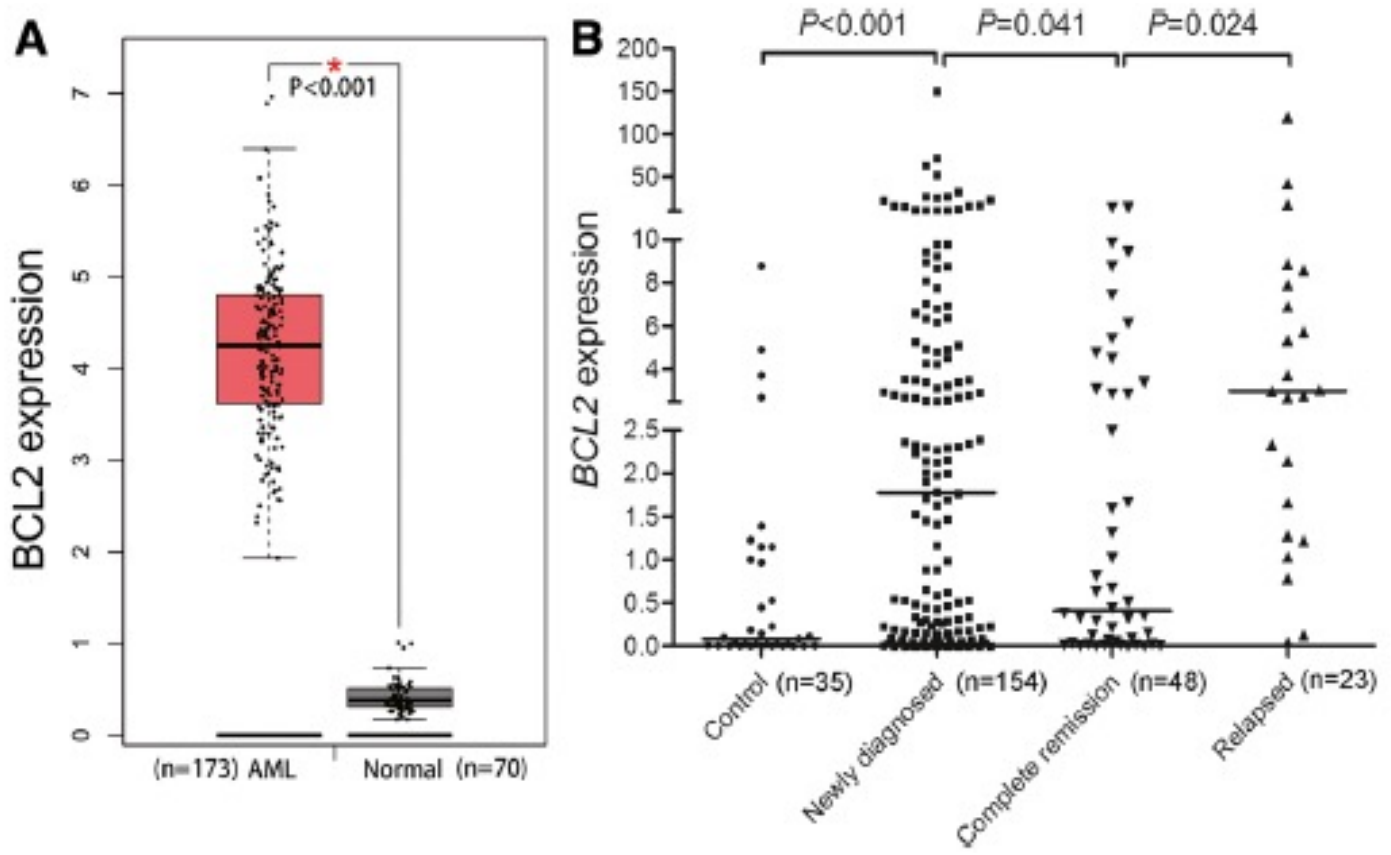


1. Venetoclax binds to BCL-2 and frees pro-death proteins (BIM, BAX)
2. The freed pro-death proteins interact and initiate an apoptotic cascade, which results in formation of a pore in the outer mitochondrial membrane
3. Cytochrome *c* is released from mitochondria and activates caspases, which dismantle the cell, resulting in malignant-cell death (apoptosis)

Letai A, *et al. Cancer Cell* 2002; Adams JM & Cory S. *Oncogene* 2007;
Souers AJ, *et al. Nat Med* 2013; Leverson JD, *et al. Cancer Discov* 2017

BCL2 in AML

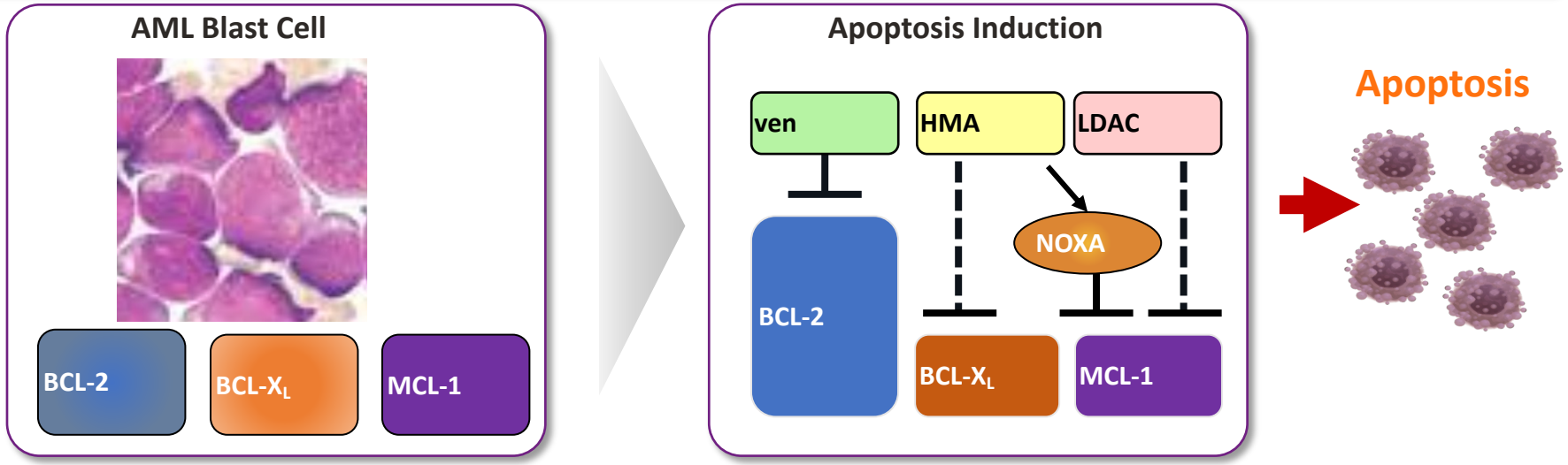
✓ Overexpression of BCL2 supports the survival of AML cells, conferring a poor prognosis and inducing treatment resistance



Zhou J et al, *Diagnostic Pathology* 2019

Venetoclax induces apoptosis in AML cells in combination with other agents

BCL-2 dependency is common in AML;[1] however, AML cells can be co-dependent on other BCL-2 family members for survival[2,3]



Size of rectangles indicates relative dependency on specific protein for survival
Dotted lines indicate an indirect therapeutic effect on BCL-2 family member dependency

- HMAs (azacitidine and decitabine[4,5]) and cytarabine[6] indirectly increase sensitivity to BCL-2 inhibition in AML cells by modifying the relative levels of BCL-2 family members

1. Pan R, *et al. Cancer Discov* 2014; 2. Valentin R, *et al. Blood* 2018; 3. Leverson JD, *et al. Cancer Discov* 2017;
4. Bogenberger JM, *et al. Leuk Lymphoma* 2015; 5. Cojocari D, *et al.* ASH 2018; poster 2644; 6. Niu X, *et al. Clin Cancer Res* 2016

VIALE-A: study design

Eligibility

Inclusion

- Patients with newly diagnosed confirmed AML
- Ineligible for induction therapy defined as **either**
  - ❖ ≥75 years of age
  - ❖ 18 to 74 years of age with at least one of the co-morbidities:
    - CHF requiring treatment or Ejection Fraction ≤50%
    - Chronic stable angina
    - DLCO ≤ 65% or FEV1 ≤ 65%
    - ECOG 2 or 3

Exclusion

- Prior receipt of any HMA, venetoclax, or chemotherapy for myelodysplastic syndrome
- Favorable risk cytogenetics per NCCN
- Active CNS involvement

Treatment

Randomization 2:1
N=433*

Venetoclax + Azacitidine (N=286)
Venetoclax 400 mg PO, daily, days 1–28 +
Azacitidine 75 mg/m² SC /IV days 1–7

Placebo + Azacitidine (N=145)
Placebo daily, days 1–28
+ Azacitidine 75 mg/m² SC /IV days 1–7

Endpoints

Primary

- Overall survival

Secondary

- CR+CRi rate
- CR+CRh rate
- CR+CRi and CR+CRh rates by initiation of cycle 2
- CR rate
- Transfusion independence
- CR+CRi rates and OS in molecular subgroups
- Event-free survival

Randomization Stratification Factors Age (<75 vs. ≥75 years); Cytogenetic Risk (intermediate, Poor); Region

Venetoclax dosing ramp-up
Cycle 1 ramp-up Day 1: 100 mg, Day 2: 200 mg, Day 3 - 28: 400 mg
Cycle 2 Day 1-28: 400 mg

DiNardo C et al, *NEJM* 2020

VIALE-A: responses

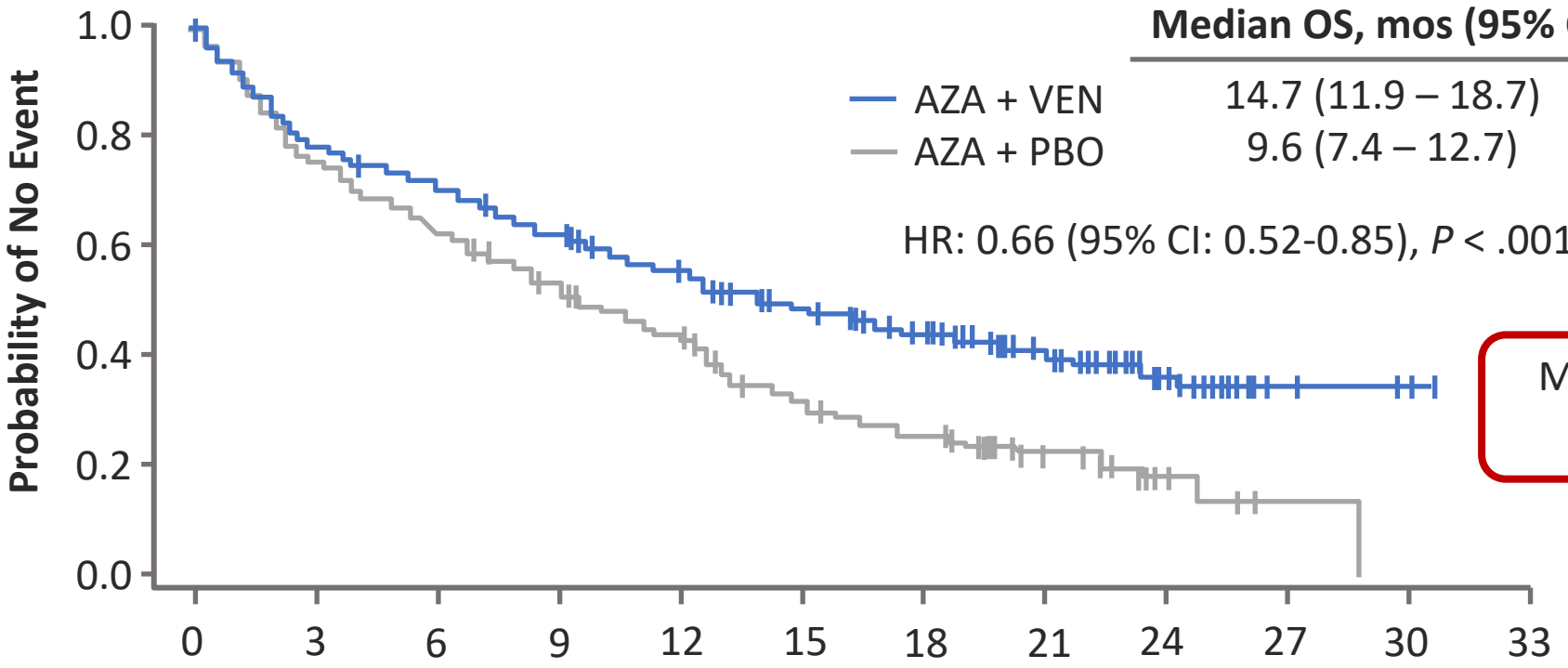
	Aza + Ven (n = 286)	Aza + Pbo (n = 145)	p value
CR + CRi rate (95% CI), %	66.4 (60.6-71.9)	28.3 (21.1-36.3)	<.001
CR + CRi by start of cycle 2 (95% CI), %	43.4 (37.5-49.3)	7.6 (3.8-13.2)	<.001
CR rate (95% CI), %	36.7 (31.1-42.6)	17.9 (12.1-25.2)	<.001
Transfusion independence* (95% CI), %			
▪ RBC	59.8 (53.9-65.5)	35.2 (27.4-43.5)	<.001
▪ Platelets	68.5 (62.8-73.9)	49.7 (41.3-58.1)	<.001
CR + CRi rate in subgroups (95% CI), %			
▪ IDH1/2	75.4 (62.7-85.5)	10.7 (2.3-28.2)	<.001
▪ FLT3	72.4 (52.8-87.3)	36.4 (17.2-59.3)	.021
▪ NPM1	66.7 (46.0-83.5)	23.5 (6.8-49.9)	.012
▪ TP53	55.3 (38.3-71.4)	0	<.001
EFS (95% CI), mo	9.8 (8.4-11.8)	7.0 (5.6-9.5)	<.001

- Median age (range): 76 yrs (49-91)

*defined as ≥ 56 days with no RBC or platelet transfusion between first and last day of treatment

DiNardo C et al, *NEJM* 2020

VIALE-A: Overall Survival



Median OS, mos (95% CI)	
AZA + VEN	14.7 (11.9 – 18.7)
AZA + PBO	9.6 (7.4 – 12.7)

HR: 0.66 (95% CI: 0.52-0.85), $P < .001$

Median Follow-up: 20.5 months

No. at Risk												
Aza + Ven	286	219	198	168	143	117	101	54	23	5	3	0
Aza + Pbo	145	109	92	74	59	38	30	14	5	1	0	0

DiNardo C et al, *NEJM* 2020

VIALE-A: safety

Table 2. Adverse Events.*

Event	Azacitidine–Venetoclax Group (N = 283)		Azacitidine–Placebo Group (N = 144)	
	All Grades†	≥Grade 3‡	All Grades†	≥Grade 3‡
	number of patients (percent)			
All adverse events	283 (100)	279 (99)	144 (100)	139 (97)
Hematologic adverse events	236 (83)	233 (82)	100 (69)	98 (68)
Thrombocytopenia	130 (46)	126 (45)	58 (40)	55 (38)
Neutropenia	119 (42)	119 (42)	42 (29)	41 (28)
Febrile neutropenia	118 (42)	118 (42)	27 (19)	27 (19)
Anemia	78 (28)	74 (26)	30 (21)	29 (20)
Leukopenia	58 (21)	58 (21)	20 (14)	17 (12)
Nonhematologic adverse events				
Nausea	124 (44)	5 (2)	50 (35)	1 (1)
Constipation	121 (43)	2 (1)	56 (39)	2 (1)
Diarrhea	117 (41)	13 (5)	48 (33)	4 (3)
Vomiting	84 (30)	6 (2)	33 (23)	1 (1)
Hypokalemia	81 (29)	30 (11)	41 (28)	15 (10)
Peripheral edema	69 (24)	1 (<1)	26 (18)	0
Pyrexia	66 (23)	5 (2)	32 (22)	2 (1)
Fatigue	59 (21)	8 (3)	24 (17)	2 (1)
Decreased appetite	72 (25)	12 (4)	25 (17)	1 (1)
Infections	239 (84)	180 (64)	97 (67)	74 (51)
Pneumonia	65 (23)	56 (20)	39 (27)	36 (25)
Serious adverse events§	235 (83)	232 (82)	105 (73)	102 (71)
Febrile neutropenia	84 (30)	84 (30)	15 (10)	15 (10)
Anemia	14 (5)	14 (5)	6 (4)	6 (4)
Neutropenia	13 (5)	13 (5)	3 (2)	3 (2)
Atrial fibrillation	13 (5)	10 (4)	2 (1)	2 (1)
Pneumonia	47 (17)	46 (16)	32 (22)	31 (22)
Sepsis	16 (6)	16 (6)	12 (8)	12 (8)

DiNardo C et al, *NEJM* 2020

What about real life?

NIH U.S. National Library of Medicine
ClinicalTrials.gov

Gimema AML 2320

Prospective and retrospective observational evaluation of **real world** outcome of unfit AML patients treated with the combination of Venetoclax plus HMAs, under the italian law no.648/96

Italian observational study of patients with AML treated with small Molecule inhibiting BCL-2 **(AVALON)**

Venetoclax+HMAs: for which patients?

Spediz. abb. post. - art. 1, comma 1
Legge 27-02-2004, n. 46 - Filiale di Roma

Anno 161° - Numero 61

GAZZETTA UFFICIALE

DELLA REPUBBLICA ITALIANA

PARTE PRIMA **Roma - Lunedì, 9 marzo 2020** SI PUBBLICA TUTTI I GIORNI NON FESTIVI

Denominazione: VENETOCLAX.

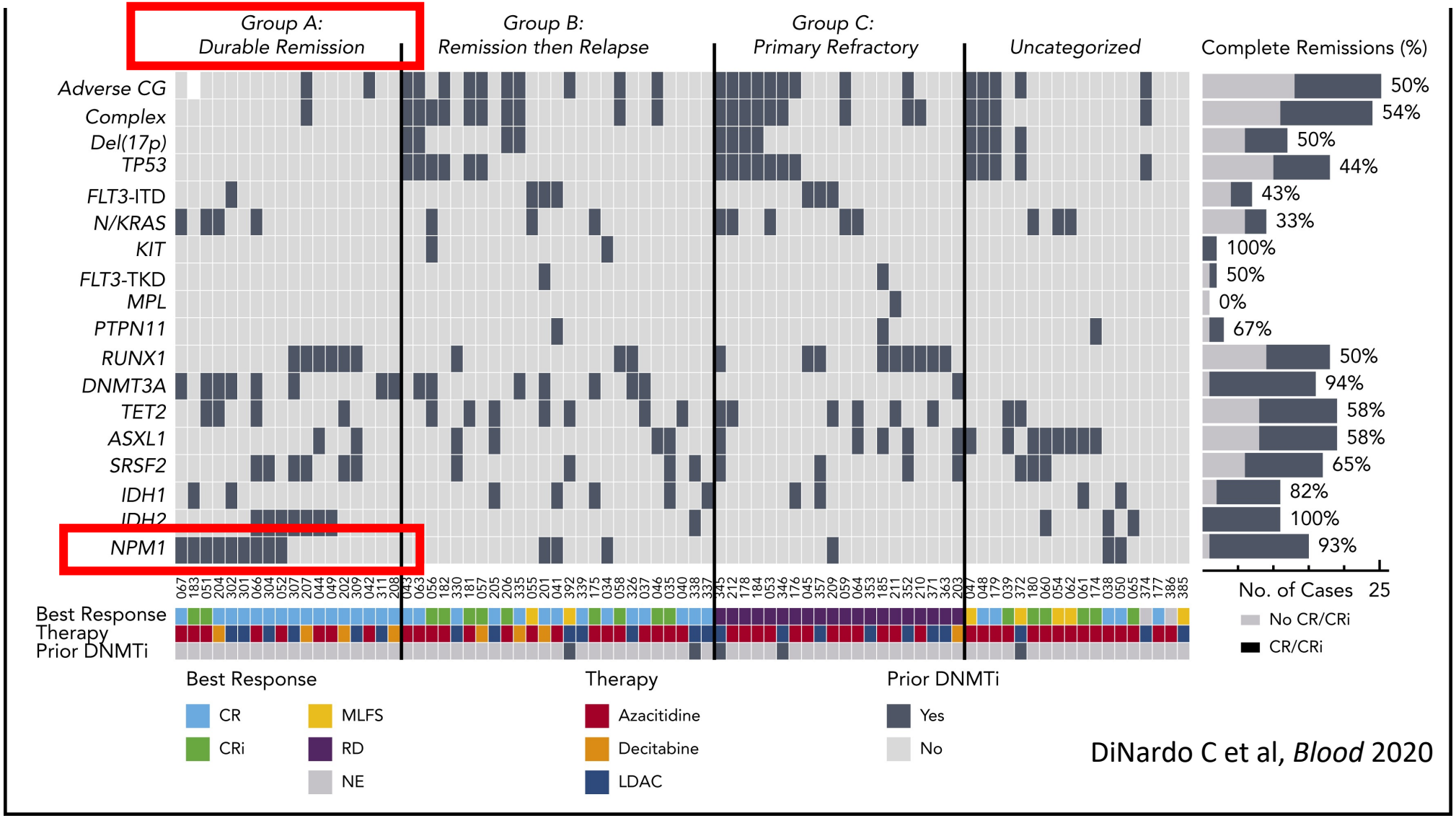
Indicazione terapeutica: in combinazione con «Azacitidina» o «Decitabina», nel trattamento di pazienti adulti con leucemia mieloide acuta di nuova diagnosi non candidabili a chemioterapia intensiva di induzione o con età ≥ 75 anni.

Criteri di inclusione:

1) pazienti di età > di 18 anni con nuova diagnosi di leucemia mieloide acuta, non eleggibili a chemioterapia intensiva di induzione;

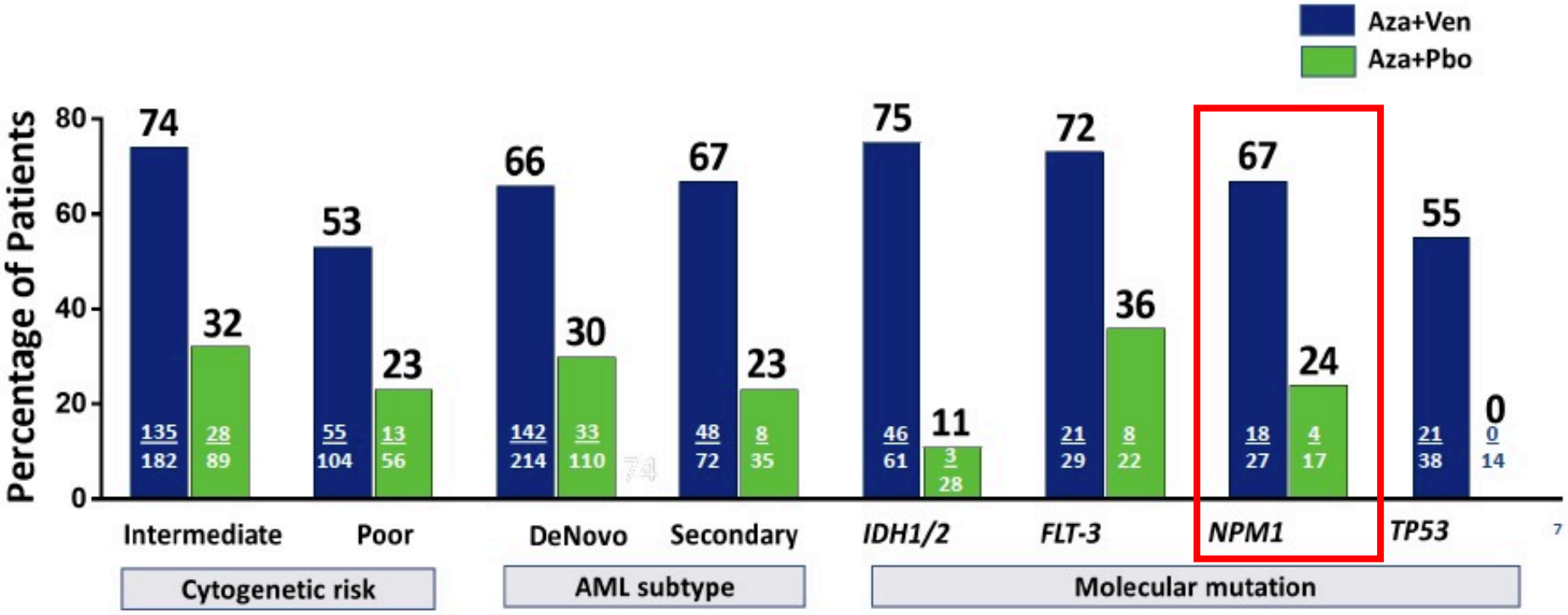
2) pazienti di età ≥ a 75 anni con nuova diagnosi di leucemia mieloide acuta.

Good responders: NPM1+ patients



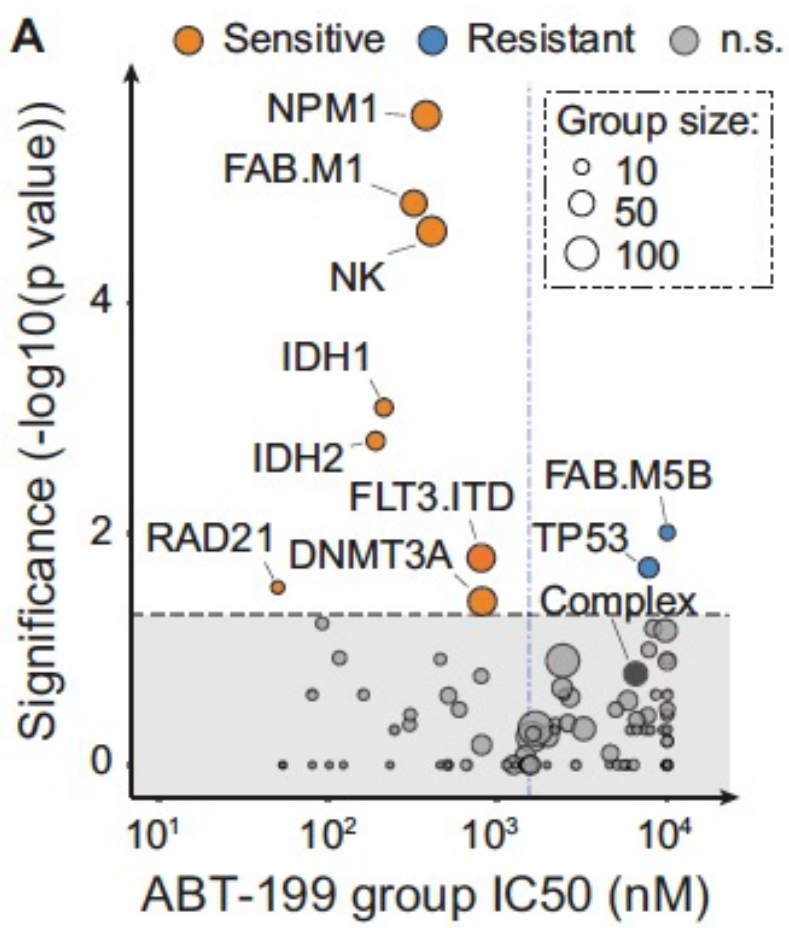
DiNardo C et al, *Blood* 2020

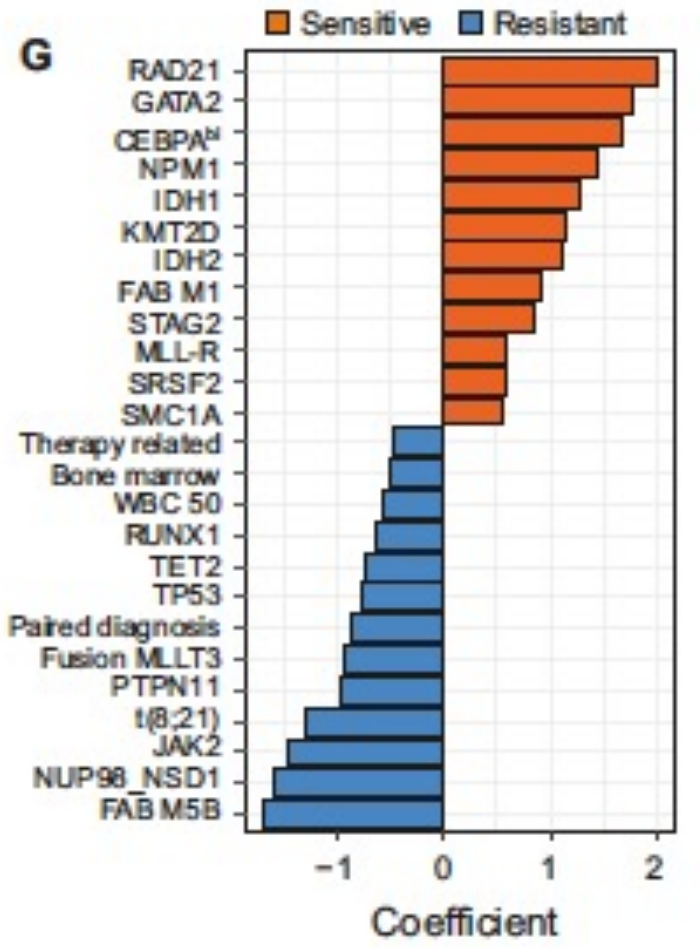
VIALE-A: high response rates in NPM1 patients



DiNardo C et al, *NEJM* 2020

Preclinical data

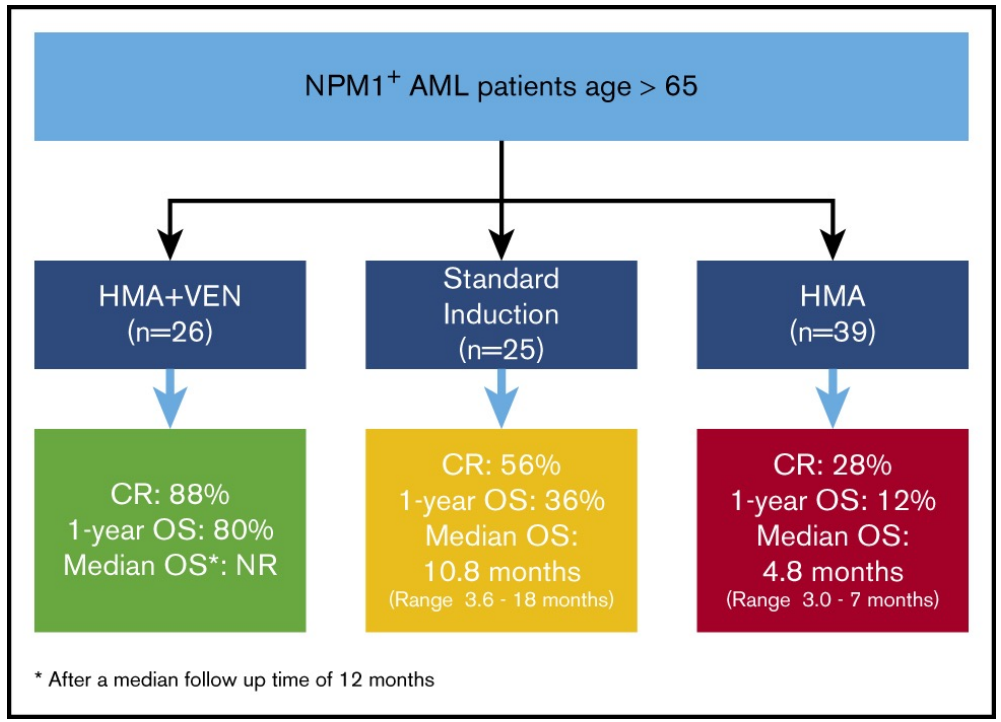


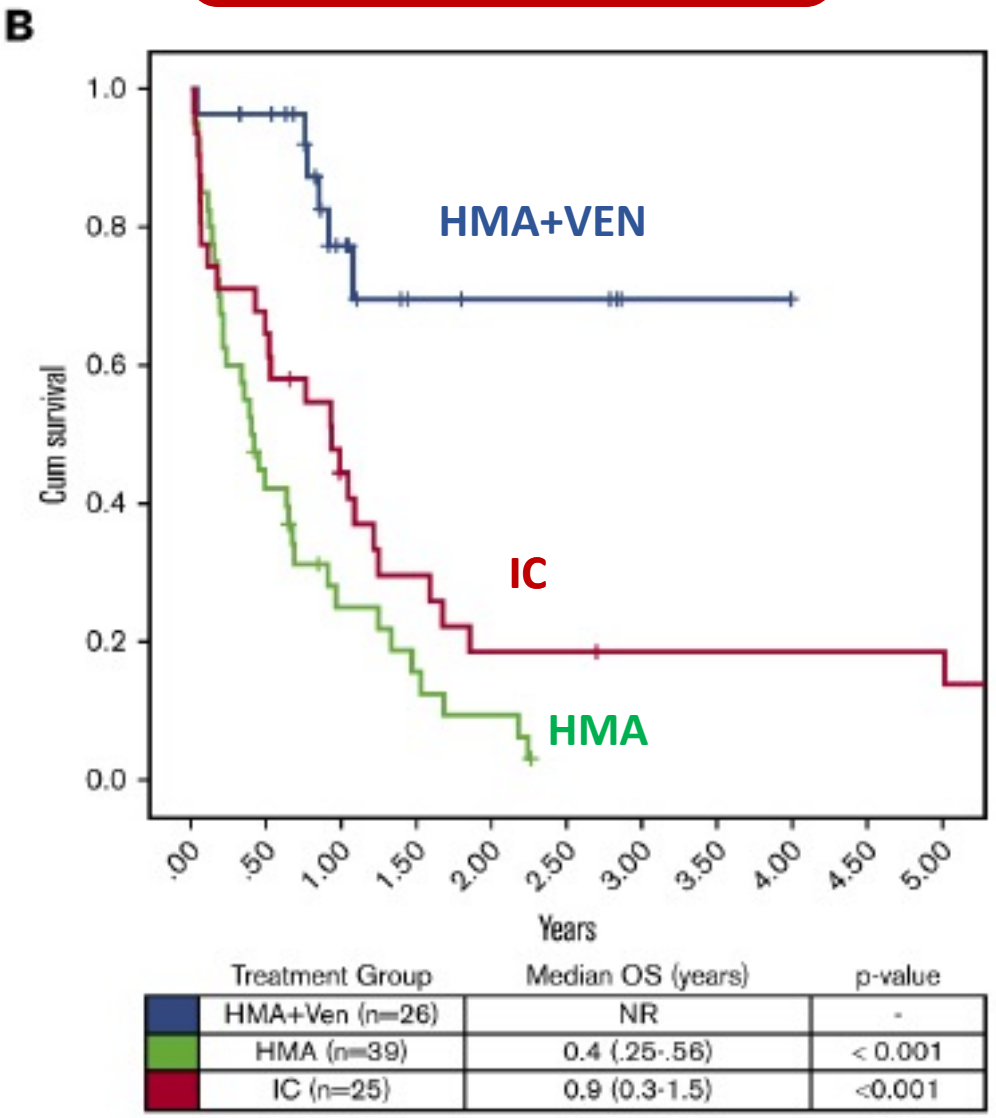


Bisaillon R et al, *Leukemia* 2020

Favourable outcome with Venetoclax+HMAs in NPM1+ AML

Median OS: NR (HMA+VEN)
0.9 years (IC)

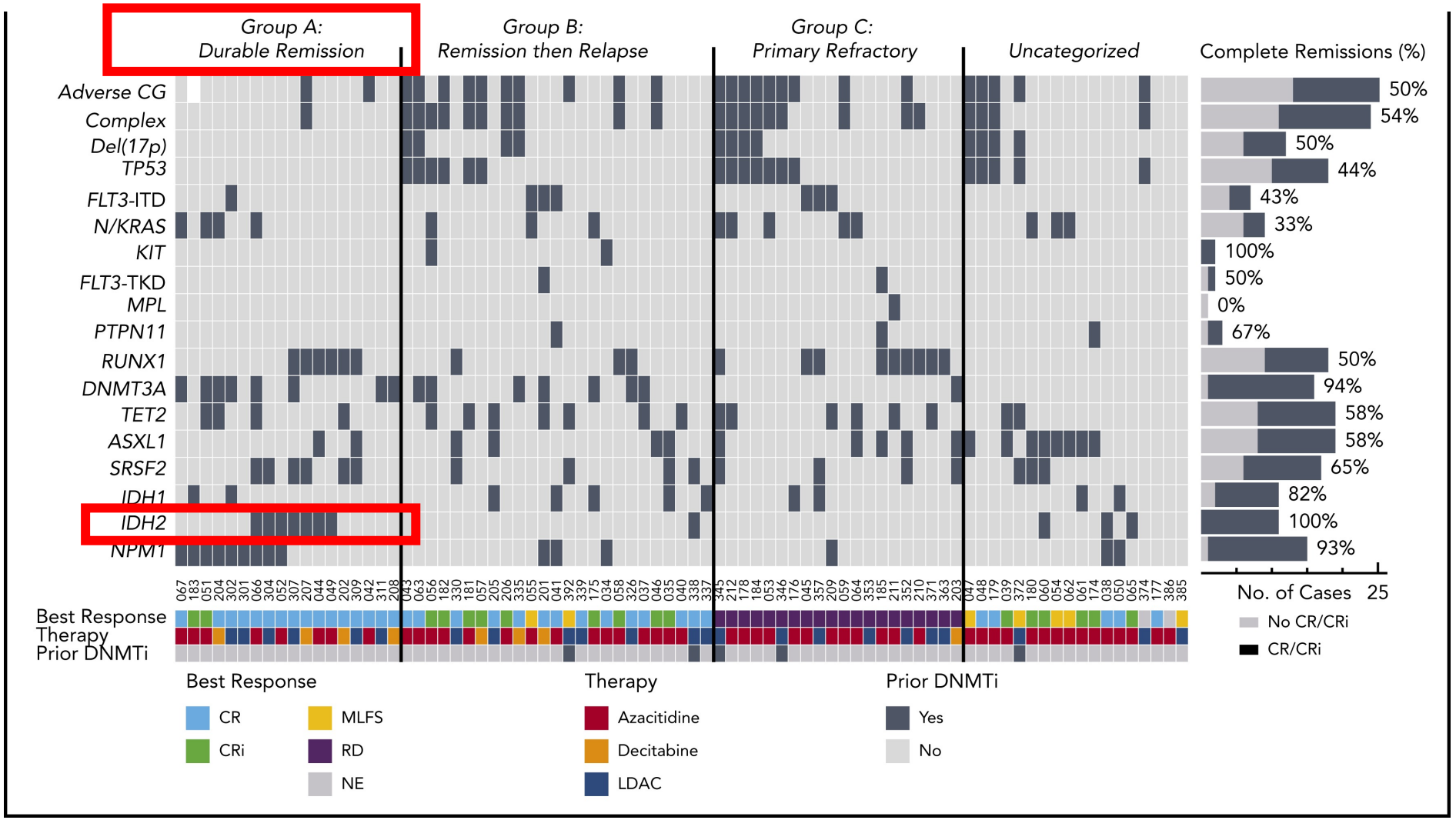




Treatment Group	Median OS (years)	p-value
HMA+Ven (n=26)	NR	-
HMA (n=39)	0.4 (.25-.56)	< 0.001
IC (n=25)	0.9 (0.3-1.5)	<0.001

Lachowiez CA et al, *Blood Advances* 2020

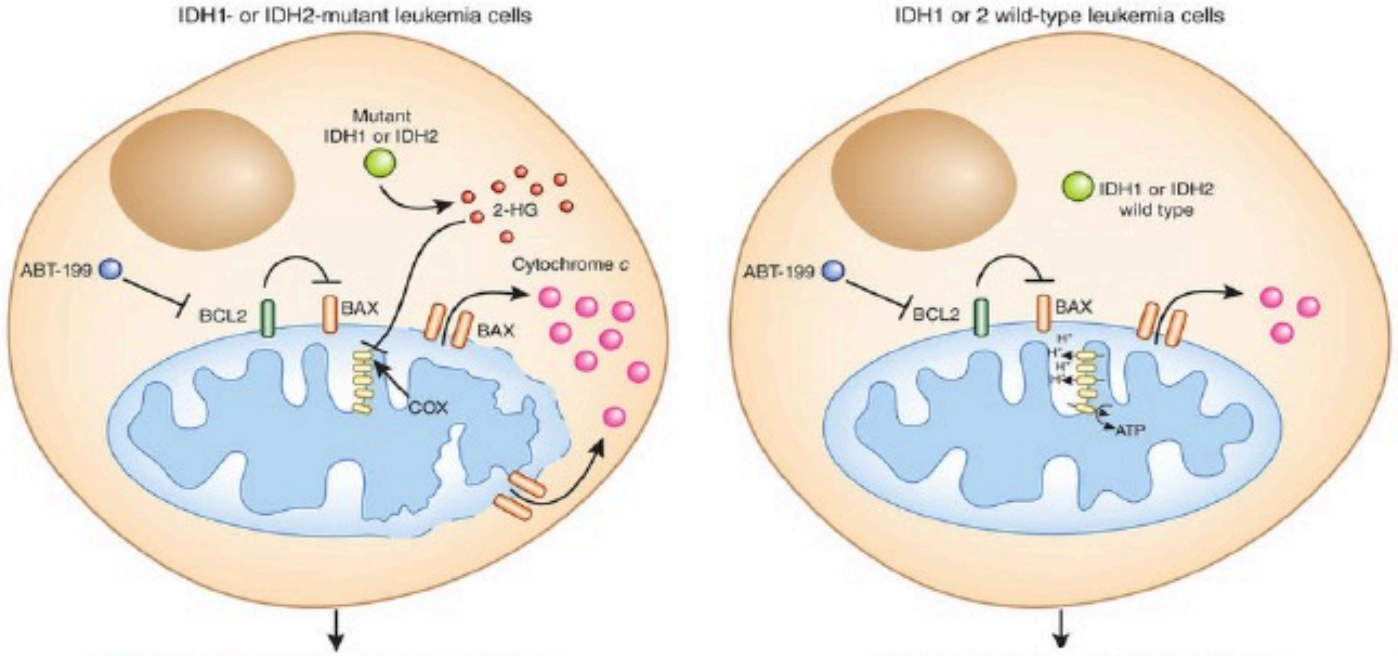
Good responders: IDH2+ patients



DiNardo C et al, *Blood* 2020

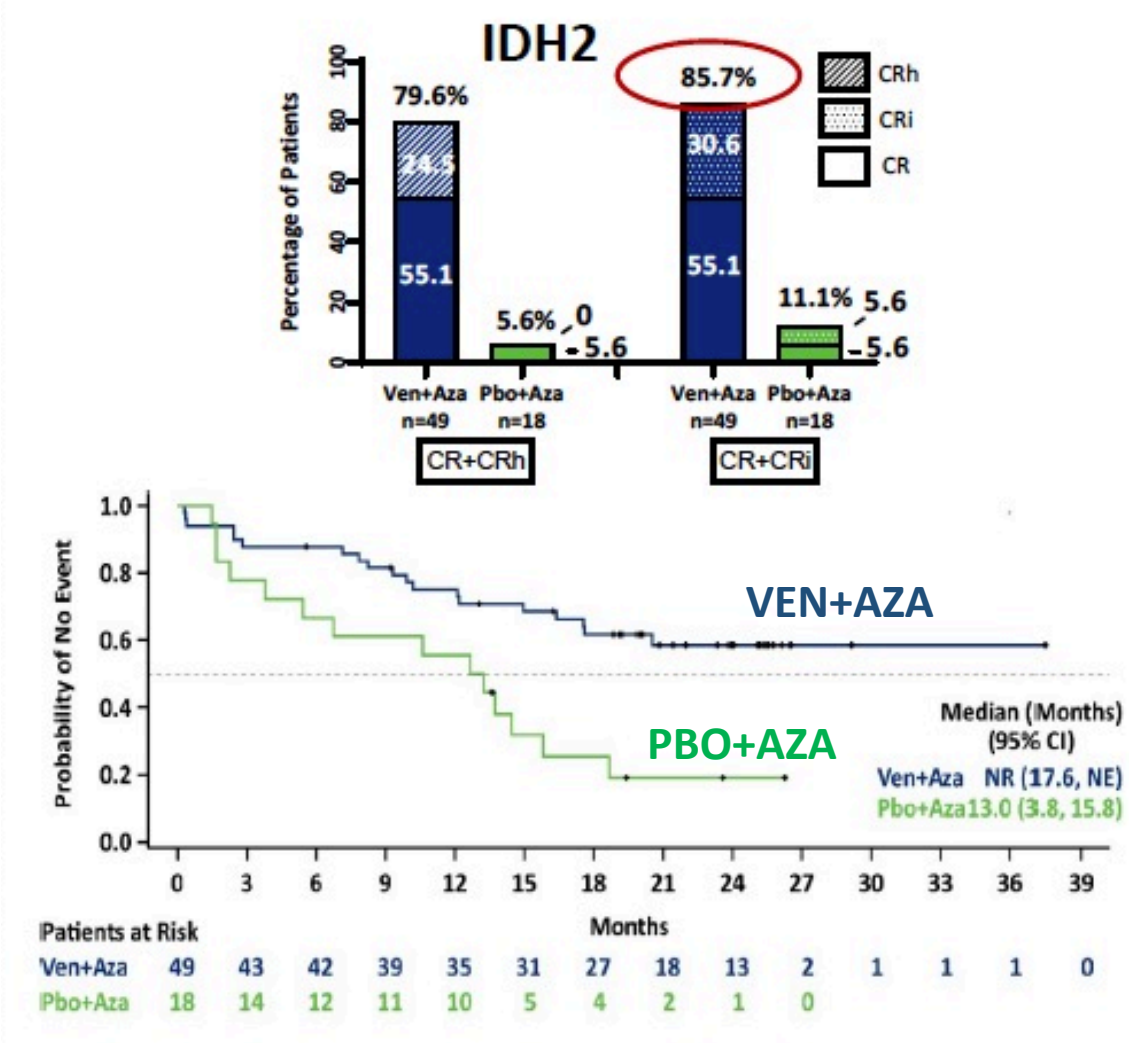
IDH mutations induce BCL-2 dependence

- 2HG-mediated inhibition of cytochrome C oxidase in the mitochondrial electron transport chain
- Leads to lower threshold to trigger apoptosis with BCL-2 inhibition (i.e. venetoclax)
- Pre-clinical data confirms synergistic activity



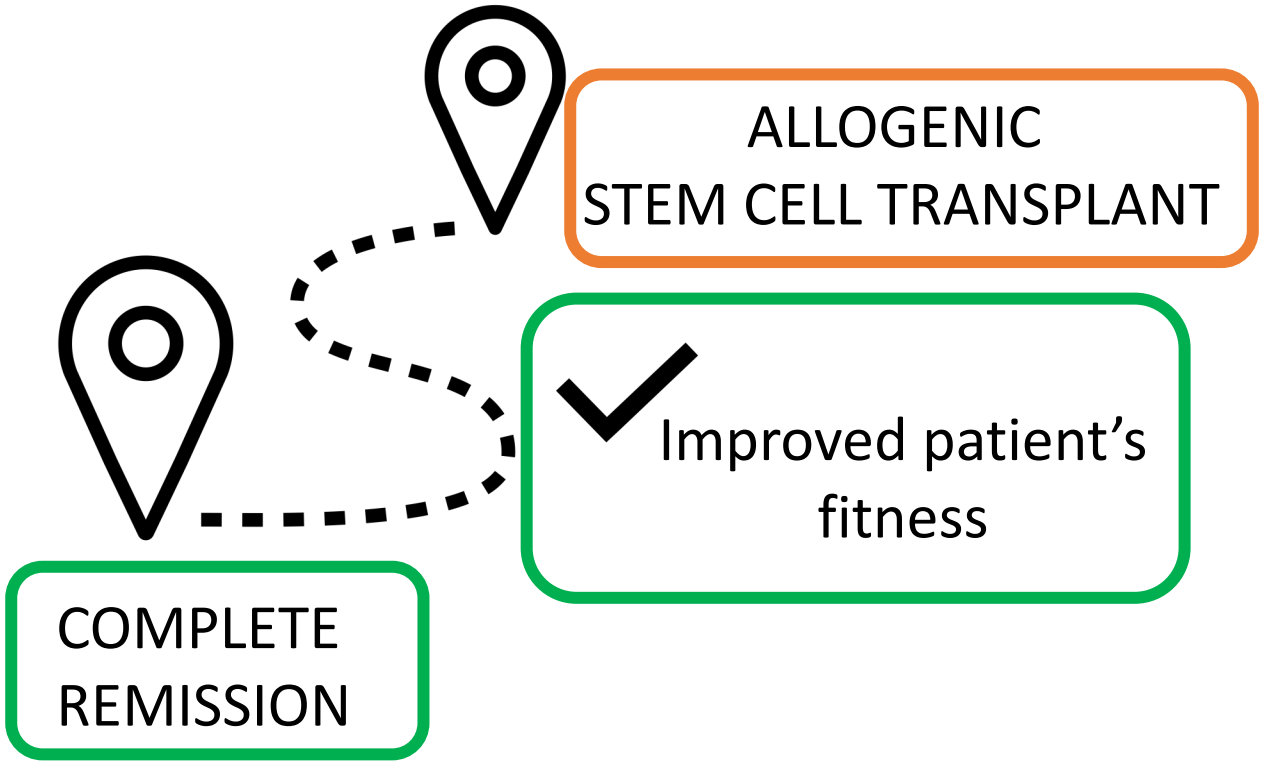
Chan SM et al, Nat Med 2015

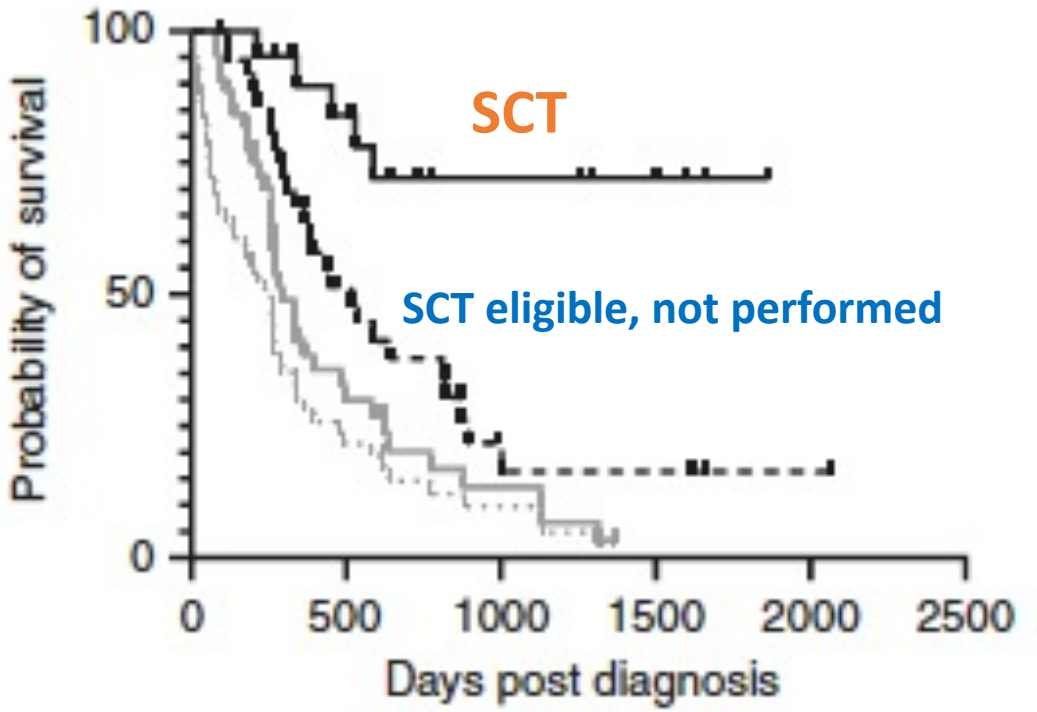
Response rates and OS of patients with IDH2 mutations



DiNardo C et al, *NEJM* 2020

Beyond complete remission in elderly patients





Pollyea D et al, *Bone Marrow Transplantation* 2021

Not only elderly/unfit patients: VEN+FLAG-IDA in young AML setting

original reports

Venetoclax Combined With FLAG-IDA Induction and Consolidation in Newly Diagnosed and Relapsed or Refractory Acute Myeloid Leukemia

Courtney D. DiNardo, MD, MSCE[1]; Curtis A. Lachowiez, MD[2]; Koichi Takahashi, MD, PhD[1]; Sanam Loghavi, MD[3]; Lianchun Xiao, MS[4]; Tapan Kadia, MD[1]; Naval Daver, MD[1]; Maria Adeoti, RN[1]; Nicholas J. Short, MD[1]; Koji Sasaki, MD[1]; Sa Wang, MD[3]; Gautam Borthakur, MD[1]; Ghayas Issa, MD[1]; Abhishek Maiti, MBBS[1]; Yesid Alvarado, MD[1]; Naveen Pemmaraju, MD[1]; Guillermo Montalban Bravo, MD[1]; Lucia Masarova, MD[1]; Musa Yilmaz, MD[1]; Nitin Jain, MD[1]; Michael Andreeff, MD, PhD[1]; Elias Jabbour, MD[1]; Guillermo Garcia-Manero, MD[1]; Steven Kornblau, MD[1]; Farhad Ravandi, MD[1]; Marina Y. Konopleva, MD, PhD[1]; and Hagop M. Kantarjian, MD[1]

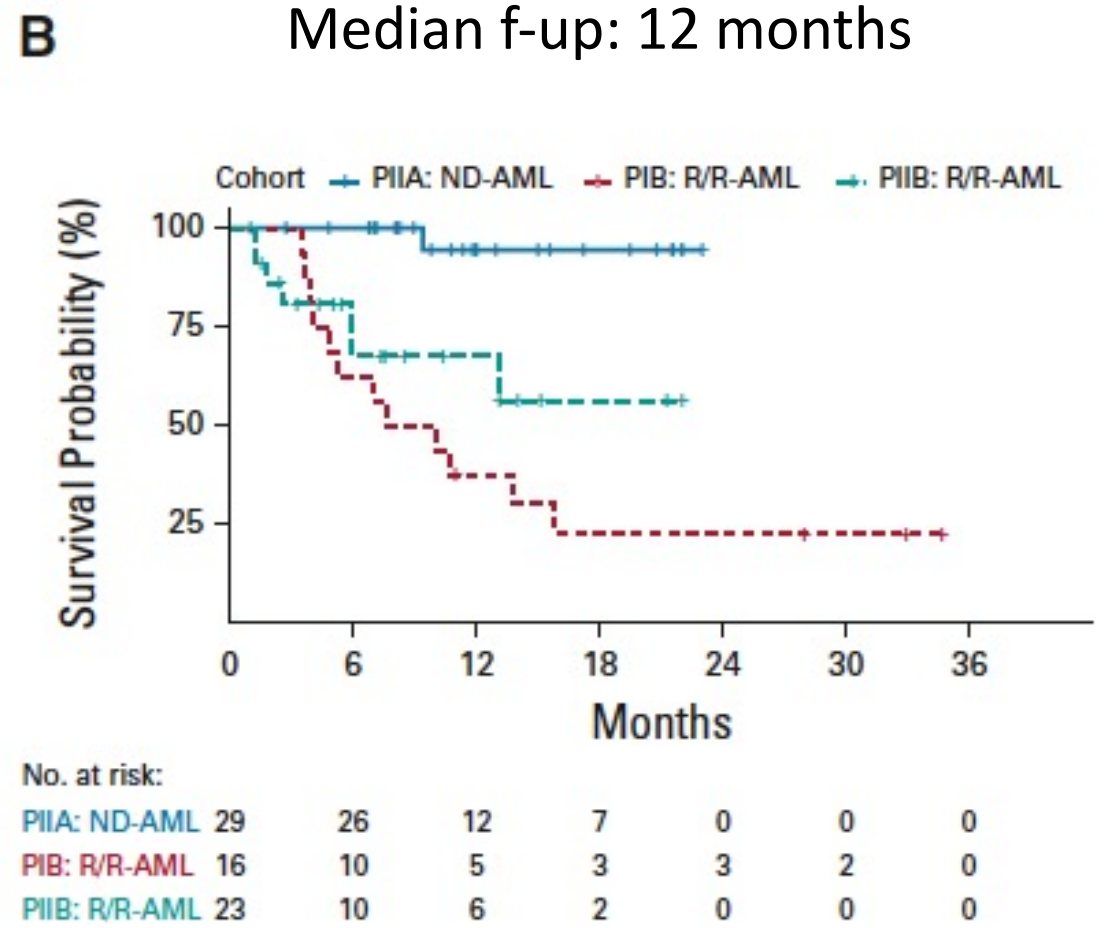
Parameter	Phase IIA ND-AML (n = 29)	Phase IB R/R-AML (n = 16)	Phase IIB R/R-AML (n = 23)
Age, years	45 (20-65)	51 (20-73)	47 (22-66)
Sex (male)	13	10	14
VEN dose level			
Dose level −1 (VEN 200 mg, D1-21)	—	8	—
Alternate dose level −1 (VEN 200 mg, D1-14)	—	5	—
Dose level 0 (VEN 400 mg, D1-14)	29	3	23
Median No. of prior therapies	—	2 (1-6)	1 (1-3)
Prior HSCT	—	7	7
Median duration of prior CR, months	—	15.1 (2.3-44)	12.6 (2.7-70)
Salvage 1	—	8	19
Salvage 2	—	3	3
Salvage 3 or greater	—	5	1
Median blast (%) at enrollment[a]	41 (4-85)	63 (6-94)	46 (1-89)
Extramedullary leukemia	3	—	1
AML type			
de novo AML	17	—	—
sAML	5	—	—
ts-AML	2	—	—
t-AML	5	—	—
R/R-AML	—	16	23
ELN risk group			
Favorable	5	6	6
Intermediate	13	2	3
Adverse	11	8	14

JCO 2021

VEN+FLAG-IDA in young AML setting: ORR 97%

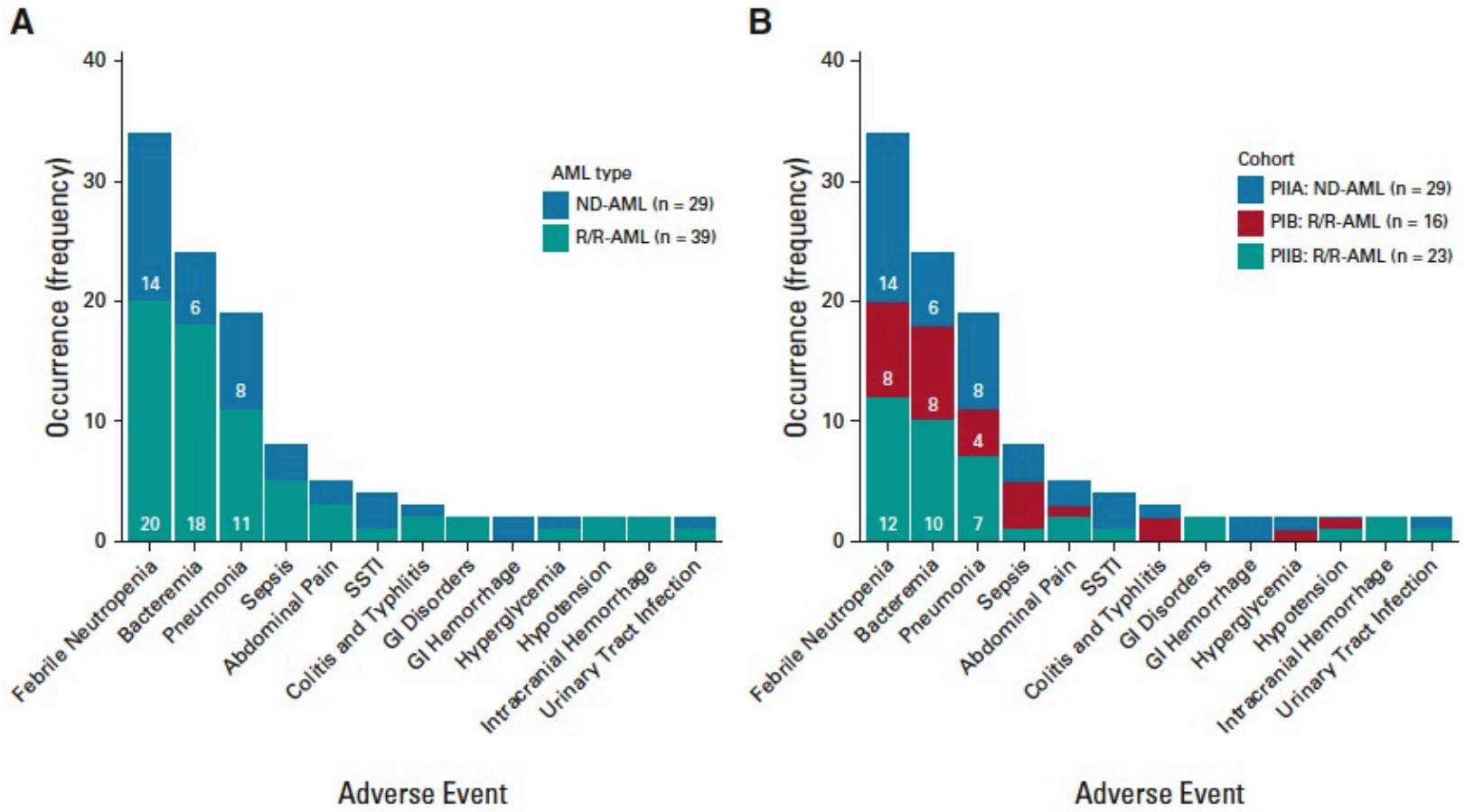
Outcome	All (N = 68)	Phase IIA ND-AML (n = 29)
ORR, No. (% [CI])	56 (82 [71 to 91])	28 (97 [85 to 99])[a]
CRc (CR + CRi + CRh), No. (% [95% CI])	52 (76 [65 to 86])	26 (90 [73 to 98])
CR, No. (%)	37 (53)	20 (69)
CRh, No. (%)	10 (15)	5 (17)
CRi, No. (%)	5 (7)	1 (3)
MRD⁻ CR (flow cytometry), No. (% [95% CI])	43 (83 [70 to 92])	25 (96 [80 to 99])
MLFS	4	2
No response	12	1
DOR (median, months)	NR	NR
EFS		
Median, months (95% CI)	18 (10.1 to NE)	NR
6-month, % (95% CI)	70 (59 to 81)	89 (78 to 100)
12-month, % (95% CI)	56 (44 to 71)	85 (72 to 100)
OS		
Median, months (95% CI)	NR	NR
6-month, % (95% CI)	81 (71 to 91)	100
12-month, % (95% CI)	70 (58 to 83)	94 (84 to 100)

Median f-up: 12 months



DiNardo C et al, *JCO* 2021

VEN+FLAG-IDA in young AML setting: Safety profile



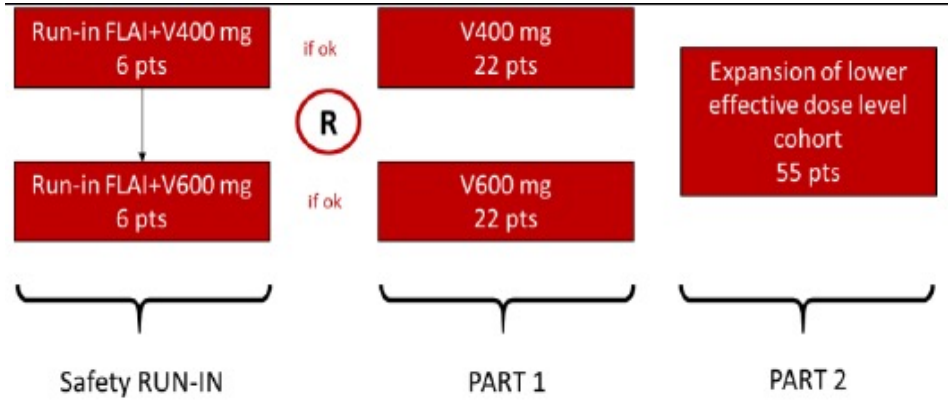
- **Three deaths in CR** (**all R/R AML**) due to systemic mucormycosis with typhlitis, SBO, perforated fistula (> Day 100), HLH complicating *E. coli* and RSV infection with no response to HLH therapy (> Day 100), and lung aspergilloma and respiratory hemorrhage (Day 51)

DiNardo C et al, JCO 2021

GIMEMA AML1718 trial for intermediate and high risk AML patients

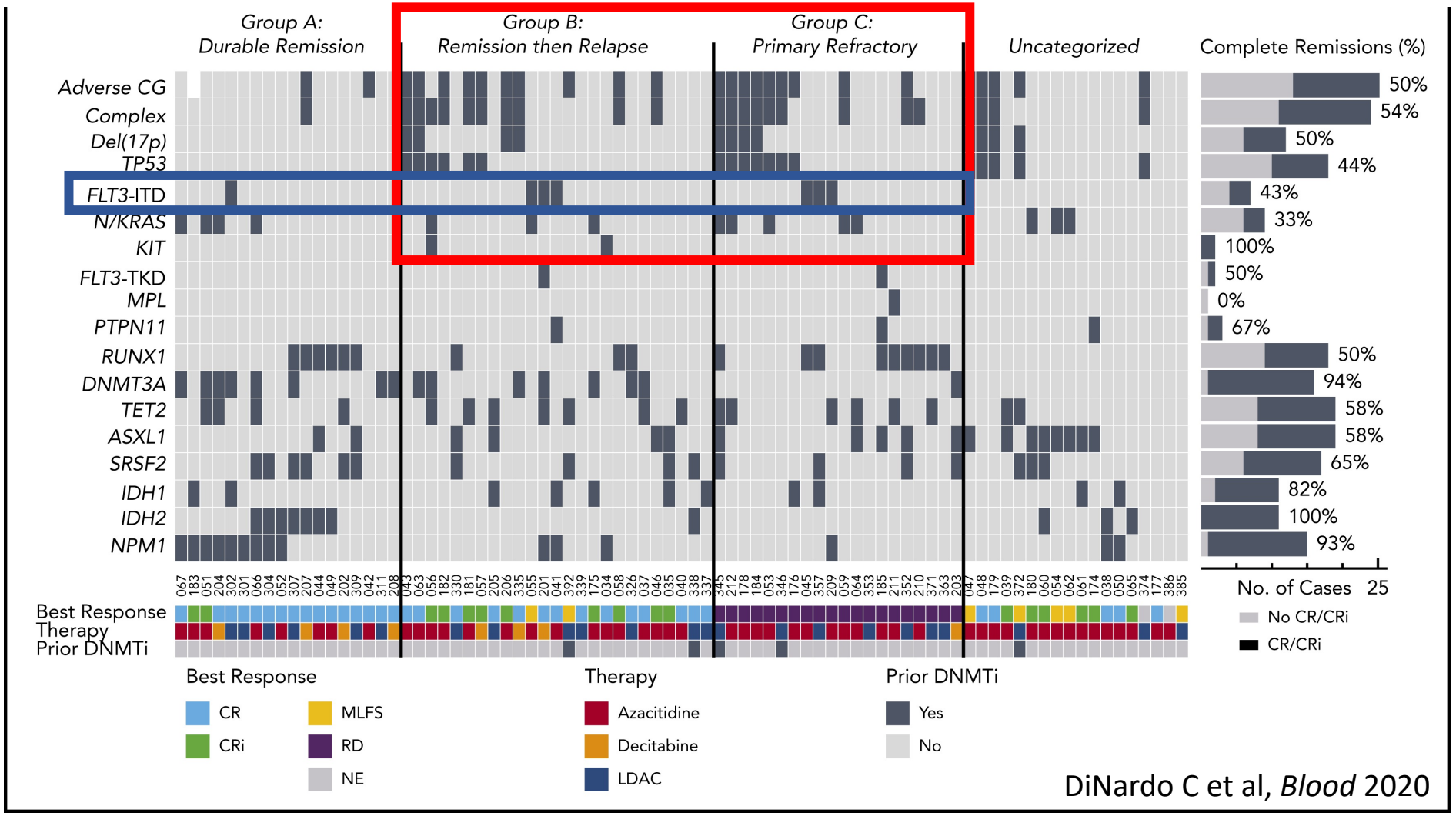
fondazione GIMEMA onlus
per la promozione e lo sviluppo della ricerca scientifica sulle malattie ematologiche. FRANCO MANDELLI

PROTOCOL TITLE:	A SAFETY RUN-IN AND PHASE 2, OPEN-LABEL, MULTICENTRE, STUDY INVESTIGATING SAFETY, TOLERABILITY AND EFFECTIVENESS OF VENETOCLAX ADD IN COMBINATION AT FLUDARABINE, CYRATABINE AND IDARUBICINE IN INDUCTION THERAPY OF NEW ONSET NON-M3 ACUTE MYELOID LEUKEMIA
SHORT NAME:	V-FIRST
PROTOCOL NUMBER:	AML1718
VERSION NUMBER:	2.0
EUDRACT NUMBER:	2018-000392-33
CLINICAL TRIAL NUMBER	NCT03455504
TEST PRODUCT:	VENETOCLAX
SPONSOR:	Fondazione GIMEMA Franco Mandelli Onlus
DATE FINAL:	February, 18th 2020



Work in progress…

A FLT3 ITD mutation is often detected at relapse after VEN+HMAs



DiNardo C et al, *Blood* 2020

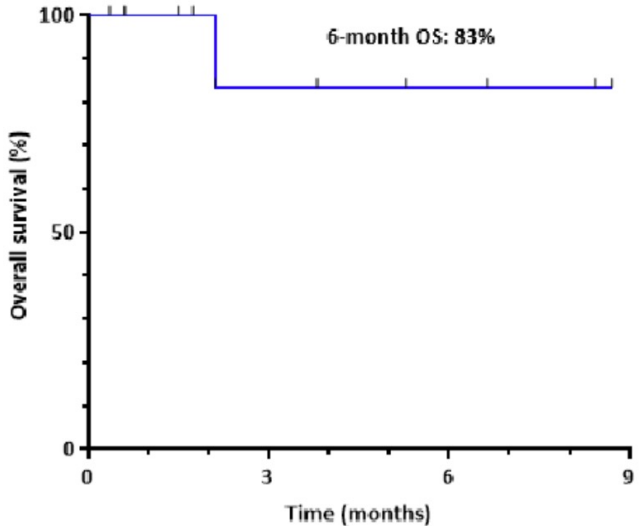
696 A Triplet Combination of Azacitidine, Venetoclax and Gilteritinib for Patients with *FLT3*-Mutated Acute Myeloid Leukemia: Results from a Phase I/II Study

Program: Oral and Poster Abstracts
Type: Oral
Session: 615. Acute Myeloid Leukemias: Commercially Available Therapies, Excluding Transplantation and Cellular Immunotherapies: Current approach to FLT3 mutated AML
Hematology Disease Topics & Pathways:
Clinical Trials, AML, Clinical Research, Clinically Relevant, Diseases, Therapies, Myeloid Malignancies

Monday, December 13, 2021: 4:00 PM

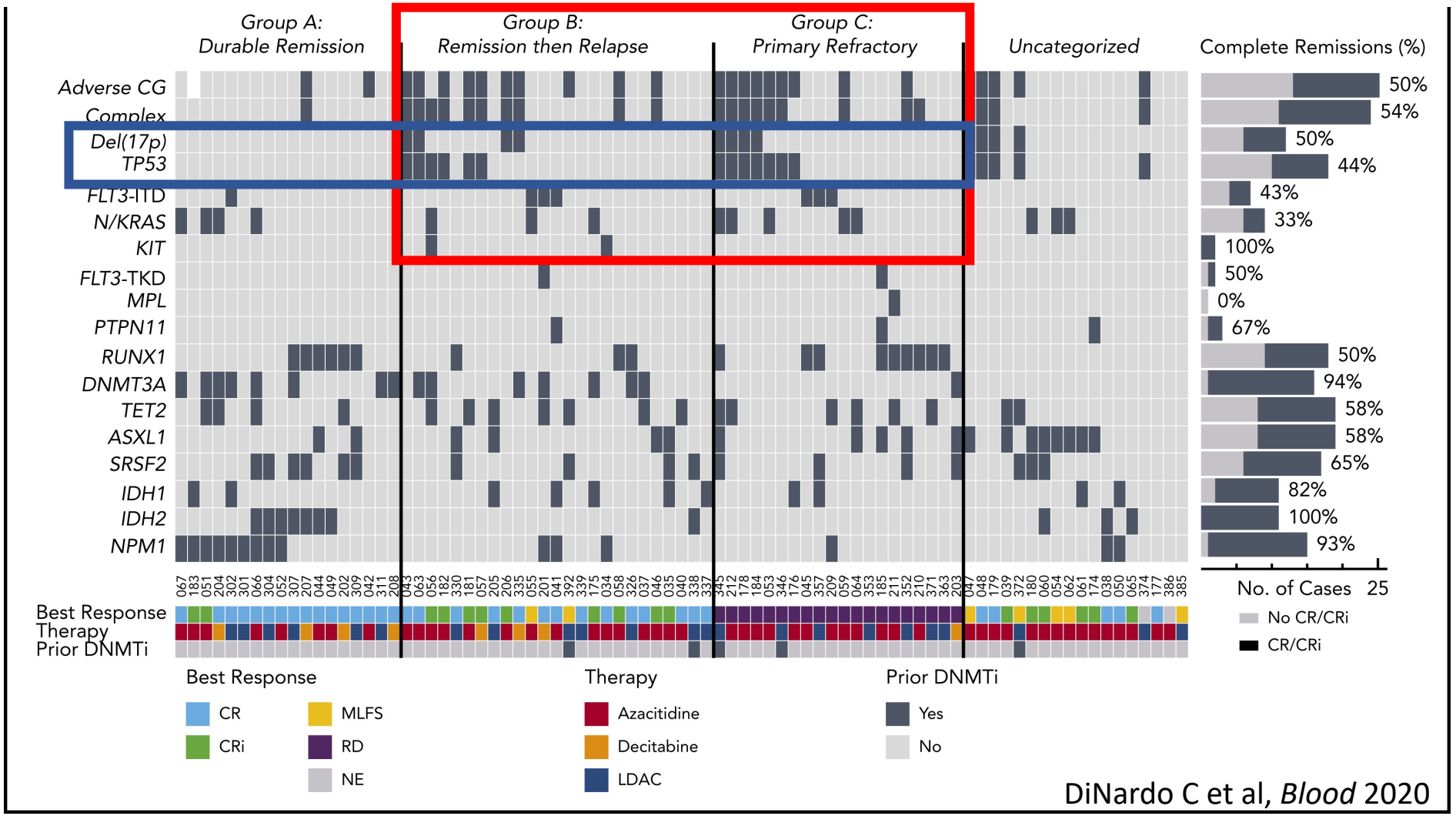
Nicholas J. Short, MD[1], *Courtney D. DiNardo, MD, MSc*[1], *Naval Daver, MD*[1], *Daniel Nguyen*[1*], *Musa Yilmaz, MD*[1], *Tapan M. Kadia, MD*[1], *Guillermo Garcia-Manero, MD*[1], *Ghayas C. Issa, MD*[1], *Xuelin Huang, PhD*[2*], *Wei Qiao, PhD*[2*], *Koji Sasaki, MD, PhD*[1], *Guillermo Montalban-Bravo, MD*[1], *Kelly S. Chien, MD*[1], *Gautam Borthakur, MD*[1], *Ricardo Delumpa, BSN*[1*], *Anna Milton*[1*], *Sherry A. Pierce, BSN, BA*[1*], *Elias J. Jabbour, MD*[1], *Marina Konopleva, MD, PhD*[1], *Hagop Kantarjian, MD*[1] *and Farhad Ravandi, MBBS*[1]

[1]*Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX*
[2]*Department of Biostatistics, The University of Texas MD Anderson Cancer Center, Houston, TX*



Characteristic, n (%) / median [range]	Frontline (N=11)
Age (years)	71 [61-79]
≥75 years	3 (27)
Diagnosis	
AML	11 (100)
MDS/CMML	0
Number of prior therapies	---
Prior FLT3 inhibitor	---
Prior HSCT	---
Type of FLT3 mutation	
ITD only	9 (82)
TKD only	2 (18)
ITD + TKD	0
FLT3 allelic ratio	
ITD	0.21 [0.04-3.35]
TKD	0.44 [0.03-0.85]
Cytogenetics	
Adverse risk (-5, -7, complex, inv(3))	3 (27)
Diploid	4 (36)
Others	4 (36)

A TP53 mutation is often detected at relapse and in primary refractory patients after VEN+HMAs



DiNardo C et al, *Blood* 2020

224 Outcomes in Patients with Poor-Risk Cytogenetics with or without *TP53* Mutations Treated with Venetoclax Combined with Hypomethylating Agents

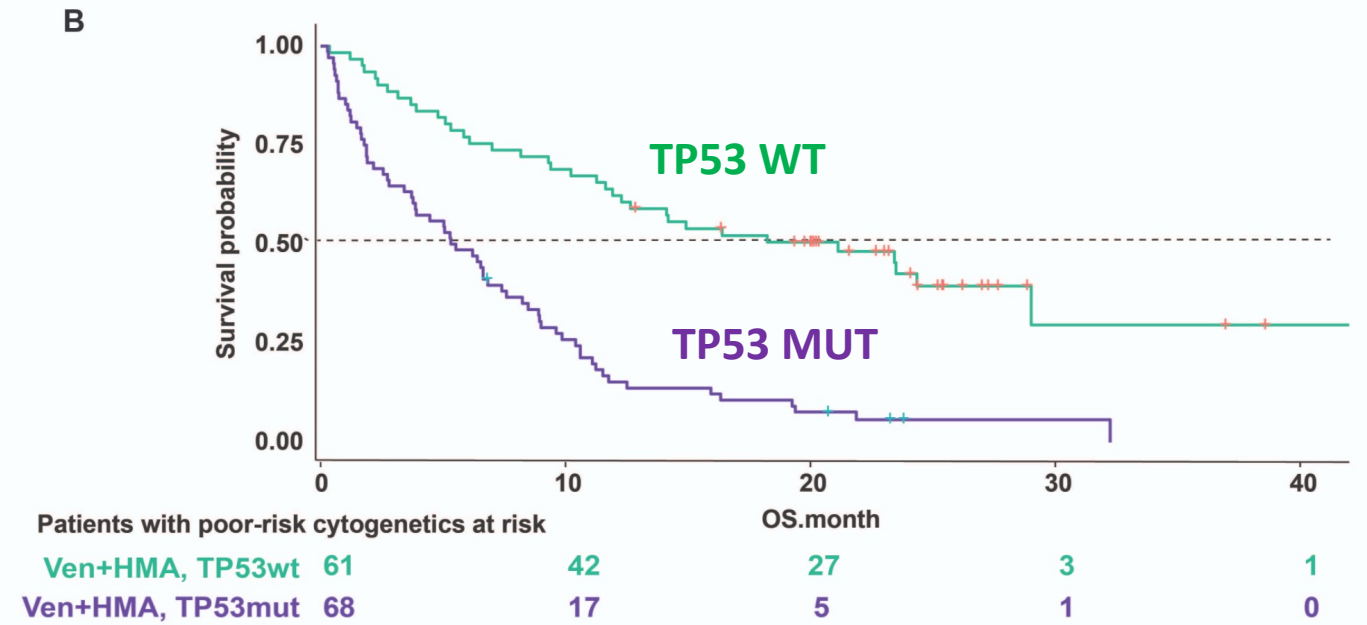
Program: Oral and Poster Abstracts
Type: Oral
Session: 617. Acute Myeloid Leukemia: Biology, Cytogenetics, and Molecular Markers in Diagnosis and Prognosis: Response Prediction across the Spectrum of DNA, RNA, Protein and Ex Vivo Cells
Hematology Disease Topics & Pathways:
Clinical Trials, Clinical Research, Clinically Relevant

Saturday, December 11, 2021: 2:15 PM

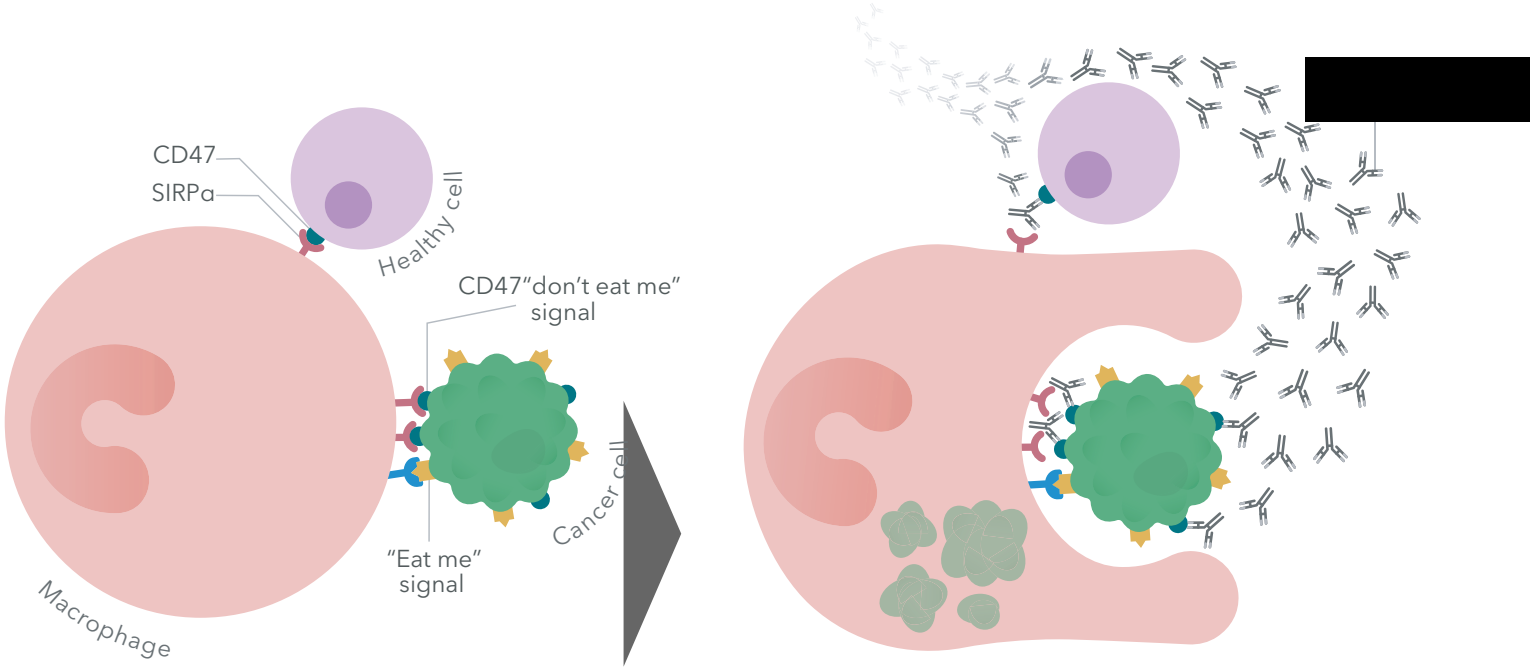
Daniel A. Pollyea, MD, MS[1], *Keith W. Pratz, MD*[2], *Andrew H. Wei, MBBS, PhD*[3], *Vinod A. Pullarkat, MD*[4], *Brian A. Jonas, MD, PhD, FACP*[5], *Christian Recher, MD, PhD*[6], *Sunil Babu*[7*], *Andre C. Schuh, MD*[8], *Monique Dail, PhD*[9*], *Yan Sun, PhD*[10*], *Jalaja Potluri, MD*[10], *Brenda Chyla, PhD*[10] *and Courtney D. DiNardo, MD, MSc*[11]

CR+ CRi: 73.8% (TP53 wt)
47% (TP53 mut)

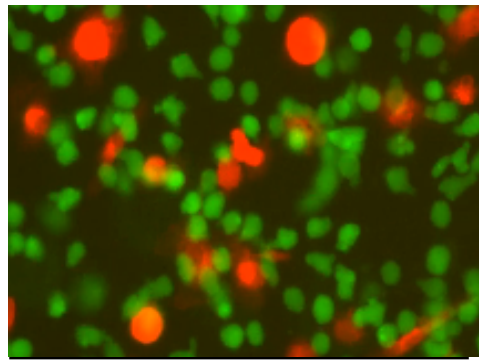
OS: 21.1 months (TP53 wt)
5.4 months (TP53 mut)



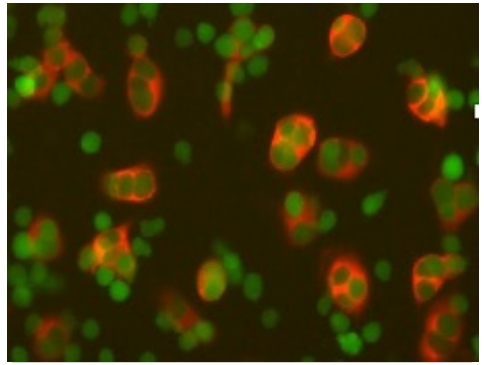
Which options for TP53 mut AML?
Magrolimab: a macrophage checkpoint inhibitor



Control mAb: No Phagocytosis



Anti-CD47 mAb: Phagocytosis

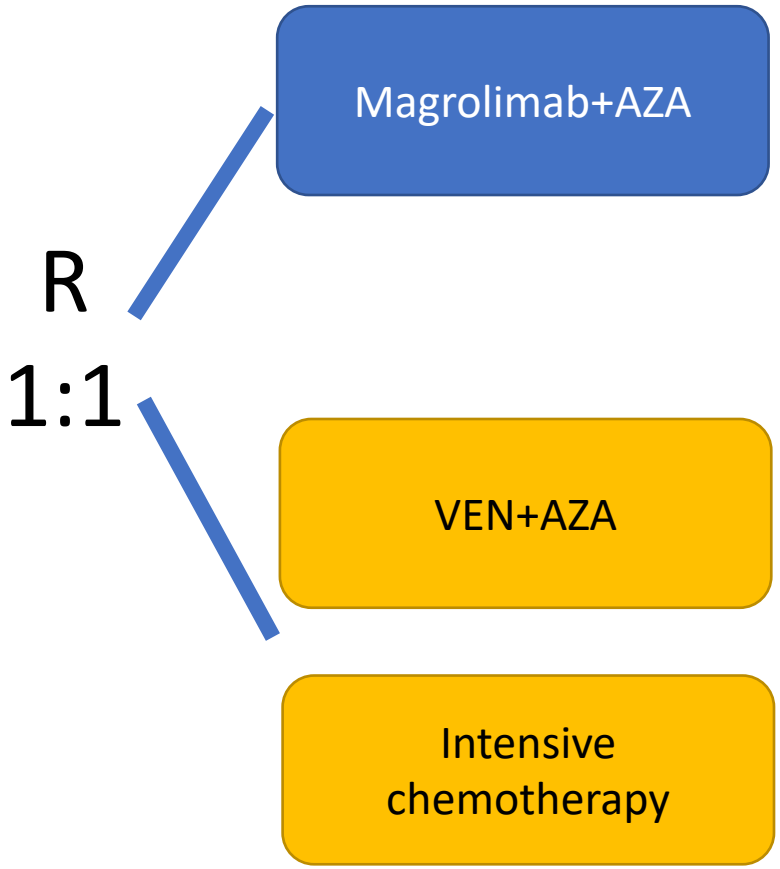


Macrophages Cancer cells

- Magrolimab is an IgG4 anti-CD47 monoclonal antibody that eliminates tumor cells through macrophage phagocytosis
- In ***TP53*** AML patients (phase 1): **ORR 71%; median OS 12.9 months**

Daver. EHA 2020. Abstr S144.

Coming soon: newly diagnosed TP53 AML patients



Study to Evaluate the Safety and Efficacy of **Magrolimab in Combination With Azacitidine Versus Physician's Choice of Venetoclax in Combination With Azacitidine or Intensive Chemotherapy** in Previously Untreated Adults With TP53 Mutant Acute Myeloid Leukemia **(ENHANCE-2)**

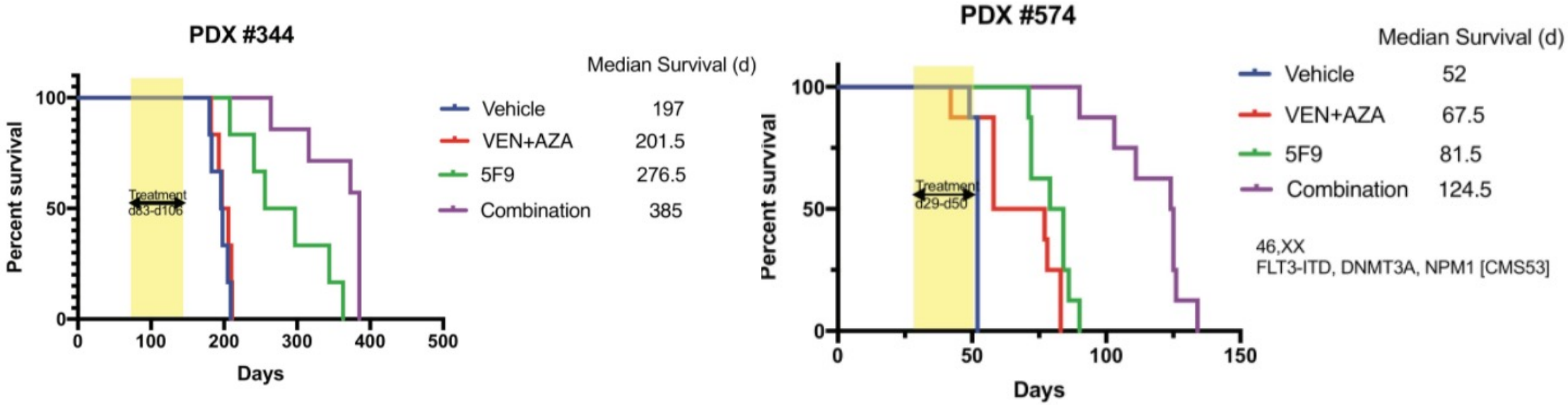
NCT04778397

510 Combined Blockade of CD47-Sirpa Interaction By 5F9 (Magrolimab) and Azacitidine/Venetoclax Therapy Facilitates Macrophage-Mediated Anti-Leukemia Efficacy in AML Pre-Clinical Models

Program: Oral and Poster Abstracts
Type: Oral
Session: 604. Molecular Pharmacology and Drug Resistance: Myeloid Neoplasms: Novel Strategies to Overcome Resistance to BCL-2 Inhibition
Hematology Disease Topics & Pathways:
Translational Research

Sunday, December 12, 2021: 5:45 PM

Yannan Jia[1*], *Qi Zhang, PhD*[1*], *Connie Weng, BA*[1*], *Cassandra L Ramage*[1*], *Yuki Nishida, MD, PhD*[2], *Mark Chao, MD, PhD*[3], *Roy Louis Maute, PhD*[3], *Shelley Herbrich, PhD*[1], *Weiguo Zhang, MD, PhD*[4], *Michael Andreeff, MD, PhD*[1], *Naval Daver, MD*[5] *and Marina Konopleva, MD, PhD*[1]



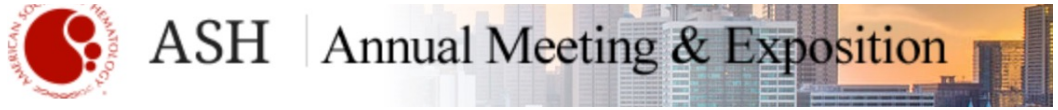
371 Phase I/II Study of Azacitidine (AZA) with Venetoclax (VEN) and Magrolimab (Magro) in Patients (pts) with Newly Diagnosed Older/Unfit or High-Risk Acute Myeloid Leukemia (AML) and Relapsed/Refractory (R/R) AML

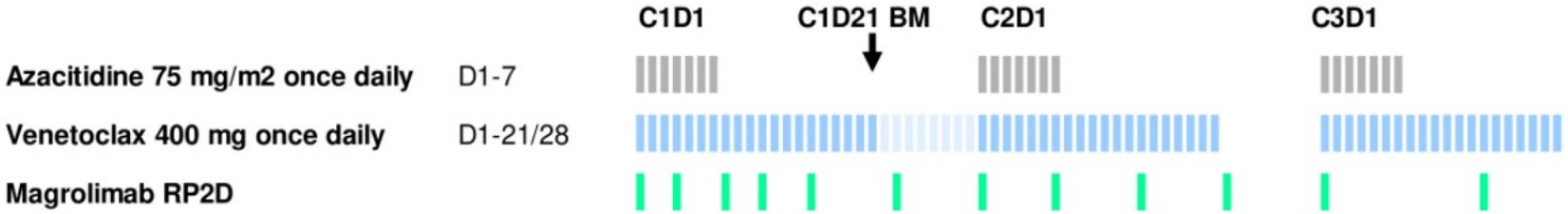
Program: Oral and Poster Abstracts
Type: Oral
Session: 616. Acute Myeloid Leukemias: Investigational Therapies, Excluding Transplantation and Cellular Immunotherapies: Triplet Combinations of Novel Therapies
Hematology Disease Topics & Pathways:
Adults, Biological, Antibody Therapy, Clinical Trials, Non-Biological, AML, Elderly, Chemotherapy, Clinical Research, Immunology, Checkpoint Inhibitor, Clinically Relevant, Diseases, Therapies, Immunotherapy, Biological Processes, Monoclonal Antibody Therapy, Myeloid Malignancies, Study Population

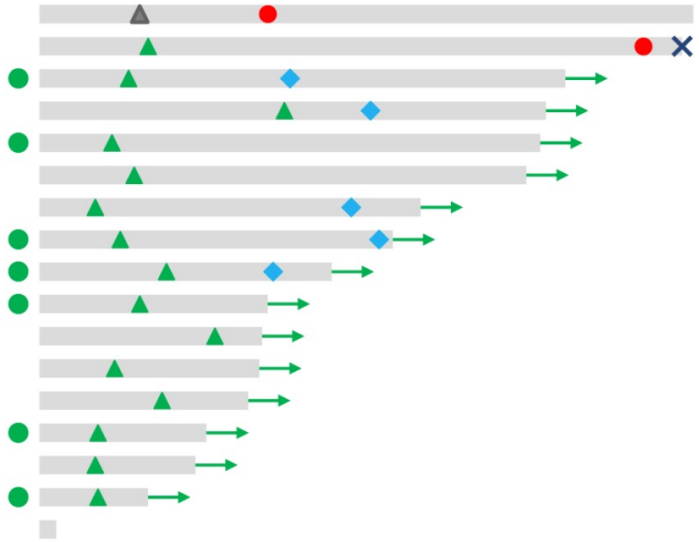
Sunday, December 12, 2021: 10:30 AM

Naval Daver, MD[1], *Marina Konopleva, MD, PhD*[2], *Abhishek Maiti, MBBS*[2*], *Tapan M. Kadia, MD*[3], *Courtney D. DiNardo, MD, MSc*[2], *Sanam Loghavi, MD*[4], *Naveen Pemmaraju, MD*[2], *Elias J. Jabbour, MD*[2], *Guillermo Montalban-Bravo, MD*[2*], *Guilin Tang, MD, PhD*[5*], *Koji Sasaki, MD, PhD*[6], *Gautam Borthakur, MD*[7], *Musa Yilmaz, MD*[8], *Joie Alvarez, BSN*[2*], *Michelle Golez*[9*], *Sherry A. Pierce, BSN, BA*[2*], *Graciela M. Nogueras González, MPH*[10*], *Jing Ning*[1] *Hussein A Abbas, MD, PhD*[12], *Farhad Ravandi, MBBS*[2], *Guillermo Garcia-Manero, MD*[2] *and Hagop Kantarjian, MD*

Characteristics	Frontline (N=17)	Relapsed / Refractory	
		Venetoclax-naïve (N=8)	Venetoclax failure (N=13)
Age, years	70 [33 - 84]	51 [28-74]	71 [36-80]
Male sex	10 (59)	4 (50)	6 (46)
ECOG PS			
0-1	9 (53)	7 (87)	10 (77)
≥2	8 (47)	1 (13)	3 (23)
Peripheral blood blasts, %	11 [1-97]	48 [1-80]	33 [1-90]
Bone marrow blasts, %	30 [9-96]	29 [11-97]	66 [6-85]
Diagnosis			
De novo AML	8 (47)	4 (50)	5 (38)
Therapy-related AML	6 (35)	3 (38)	3 (23)
Secondary AML	3 (18)	1 (12)	5 (38)
ELN 2017 risk group			
Favorable	0 (0)	0 (0)	0 (0)
Intermediate	3 (18)	1 (13)	1 (8)
Adverse	14 (82)	7 (87)	12 (92)







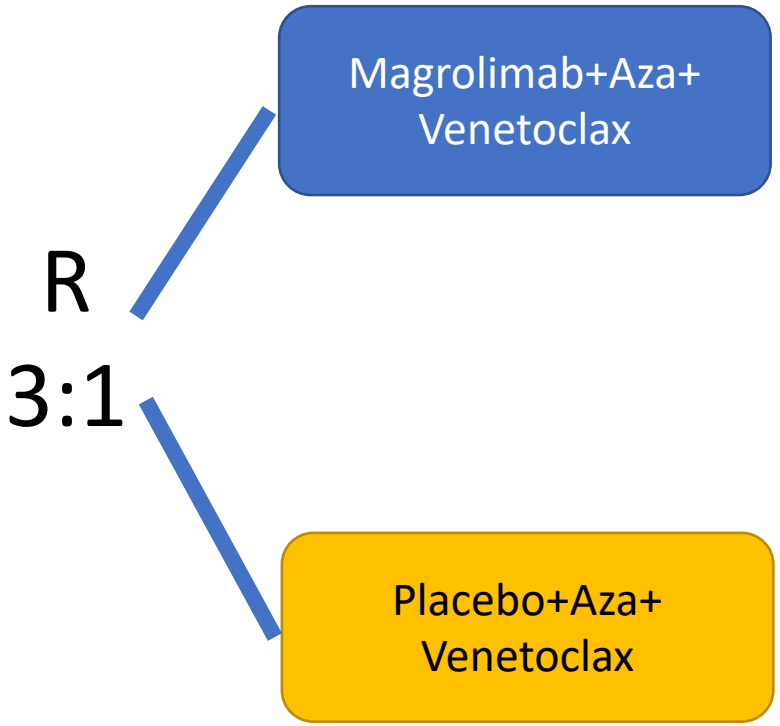
AML
- Newly diagnosed
- R/R VEN-naïve
- R/R post-VEN

Outcome
- CR/CRi
- MLFS
- MRD negative
- No response

- Relapse
- Allo-SCT
- Ongoing response
- Death

Outcomes	Frontline AML (N=16)[1]
ORR	16 (100)
CR/CRi	15 (94)
CR	13 (81)
CRi	2 (13)
MLFS	1 (6)
No response	0 (0)
Time to first response	0.7 [0.6-1.5]
Time to best response (months)	1.1 [0.7-2.9]
Median time to ANC >0.5	28 [20 – 41]
Median time to platelet >50	24 [18 – 41]
4-week mortality	0 (0)
8-week mortality	0 (0)

Coming soon: newly diagnosed unfit AML patients



Study Evaluating the Safety and Effectiveness **Magrolimab Versus Placebo in Combination With Venetoclax and Azacitidine** in Participants With Acute Myeloid Leukemia (AML) (ENHANCE-3)

NCT05079230

Towards triplets in AML

Table 2 Combination regimens with venetoclax under investigation in AML.

Doublet Venetoclax backbone	Triplet Venetoclax + HMA backbone
HMA (eg, AZA, DEC)	FLT3 inhibitor (eg, midostaurin, gilteritinib, quizartinib)
LDAC	IDH1/2 inhibitor (eg, ivosidenib, enasidenib)
FLT3 inhibitor (eg, midostaurin, gilteritinib, quizartinib)	APR-246 (TP53 target)
IDH1/2 inhibitor (eg, ivosidenib, enasidenib)	MCL1 inhibitor (CYC065, AMG 176)
MDM2 antagonist (eg, idasanutlin)	Immune therapies (CD123 ADC, CD70 antibody, PD-1 inhibitors, TIM-3 inhibitors, CD47 antibodies)
CDK9 inhibitor[a] (eg, alvocidib, voruciclib)	
MCL1 inhibitor (S64315, AZD5991)	

ADC antibody-drug conjugate, *AML* acute myeloid leukemia, *AZA* azacitidine, *CDK* cyclin-dependent kinase, *DEC* decitabine, *FLT3* FMS-like tyrosine kinase 3, *HMA* hypomethylating agent, *IDH* isocitrate dehydrogenase, *LDAC* low-dose cytarabine, *MCL1* myeloid cell leukemia-1, *MDM2* mouse double minute 2, *PD-1* programmed cell death protein 1, *TIM-3 T* cell immunoglobulin and mucin domain-containing protein 3.
[a]Data from Bogenberger et al.[24] and Luedtke et al.[25].

Daver N et al, *Blood Cancer Journal* 2020

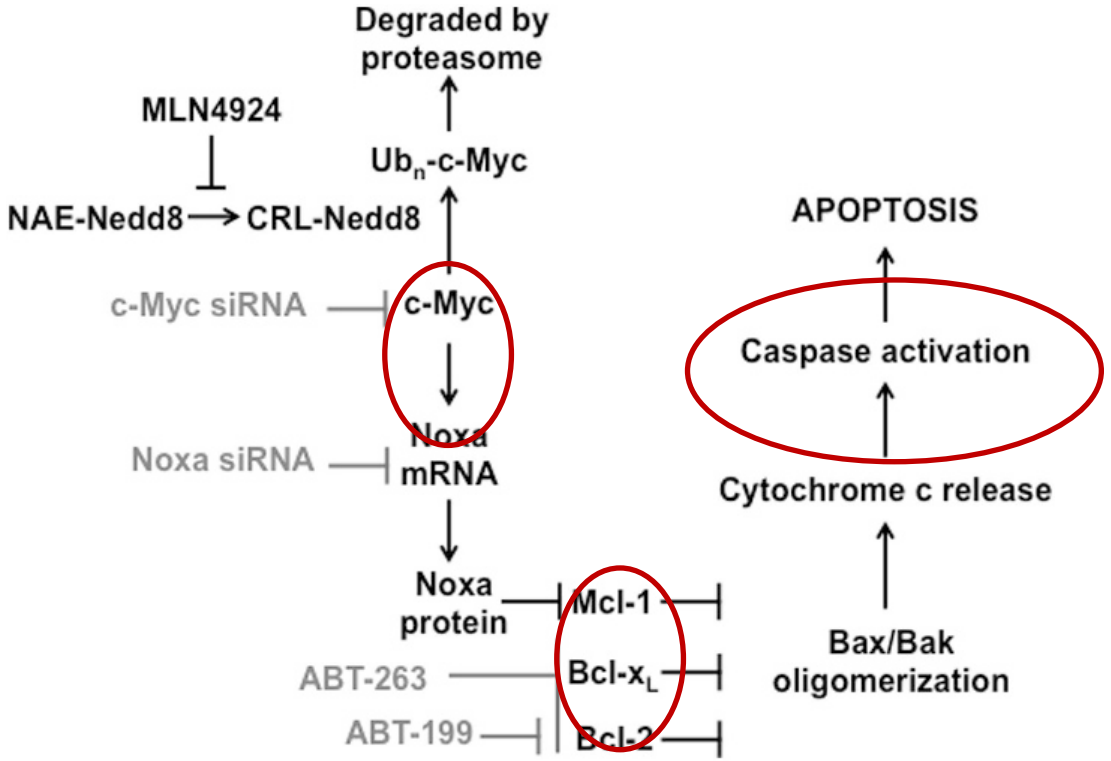
Pevonedistat in AML

Cell Death and Differentiation (2015) 22, 2133–2142

www.nature.com/cdd

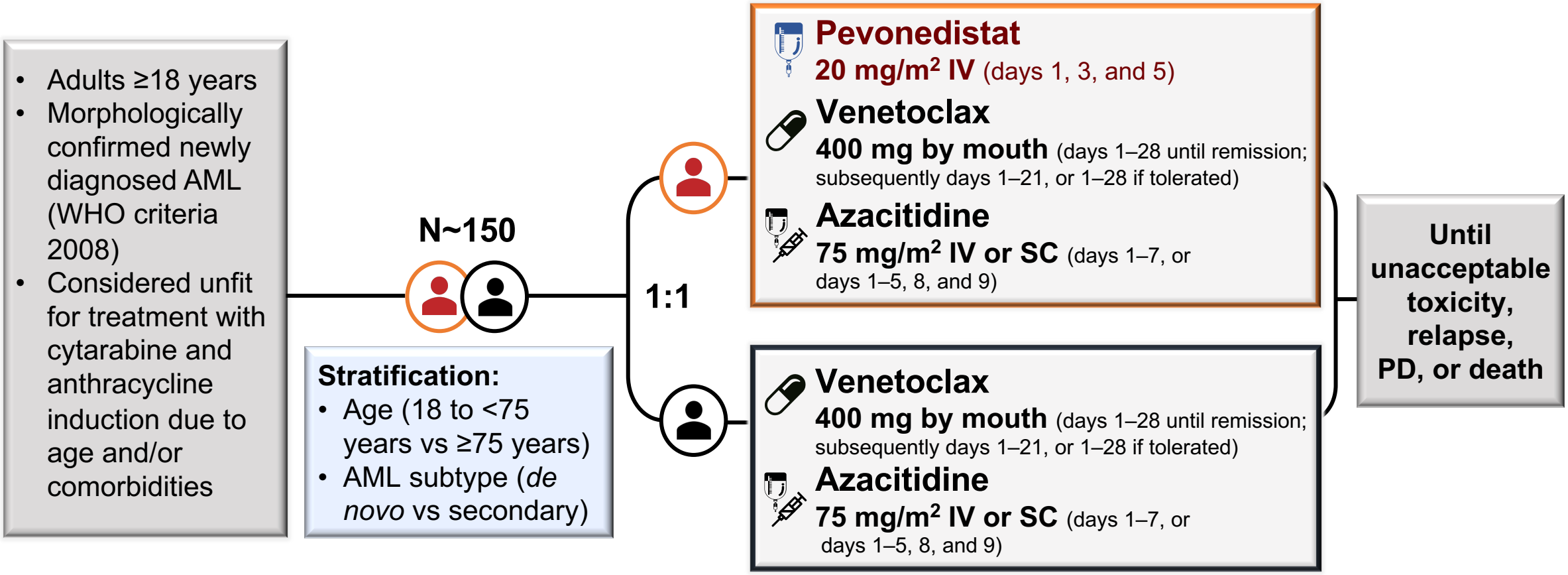
MLN4924 induces Noxa upregulation in acute myelogenous leukemia and synergizes with Bcl-2 inhibitors

KLB Knorr[1], PA Schneider[2], XW Meng[1,2], H Dai[1,2], BD Smith[3], AD Hess[3], JE Karp[3] and SH Kaufmann*[,1,2]



PEVENAZA: study design

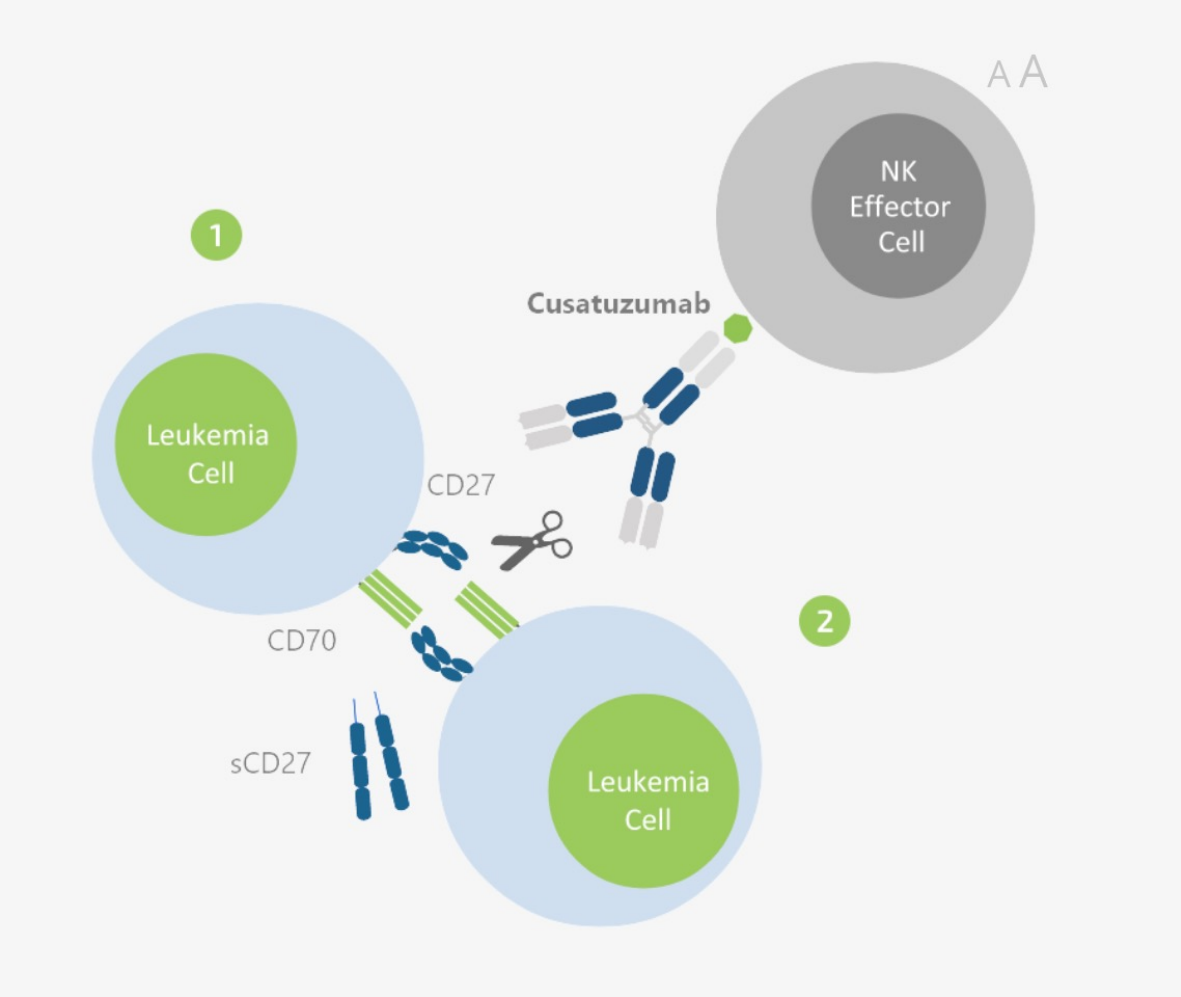
Randomized, open-label, controlled, phase 2 study (NCT04266795)[1]



IV, intravenous; PD, progressive disease; SC, subcutaneous; WHO, World Health Organization.

1. Clinicaltrials.gov. https://clinicaltrials.gov/ct2/show/NCT04266795.

Cusatuzumab: an anti CD70 antibody



Proposed Mechanism Of Action

1. Blocking CD70-CD27 signaling, which leads to myeloid differentiation and stops proliferation of leukemic stem cells; and blocking release of soluble CD27, which is generated by CD70-CD27 ligation

2. Killing cells via Fc-dependent complement dependent cytotoxicity and enhanced antibody-dependent cellular cytotoxicity (ADCC)

369 Safety and Efficacy of Cusatuzumab in Combination with Venetoclax and Azacitidine (CVA) in Patients with Previously Untreated Acute Myeloid Leukemia (AML) Who Are Not Eligible for Intensive Chemotherapy; An Open-Label, Multicenter, Phase 1b Study

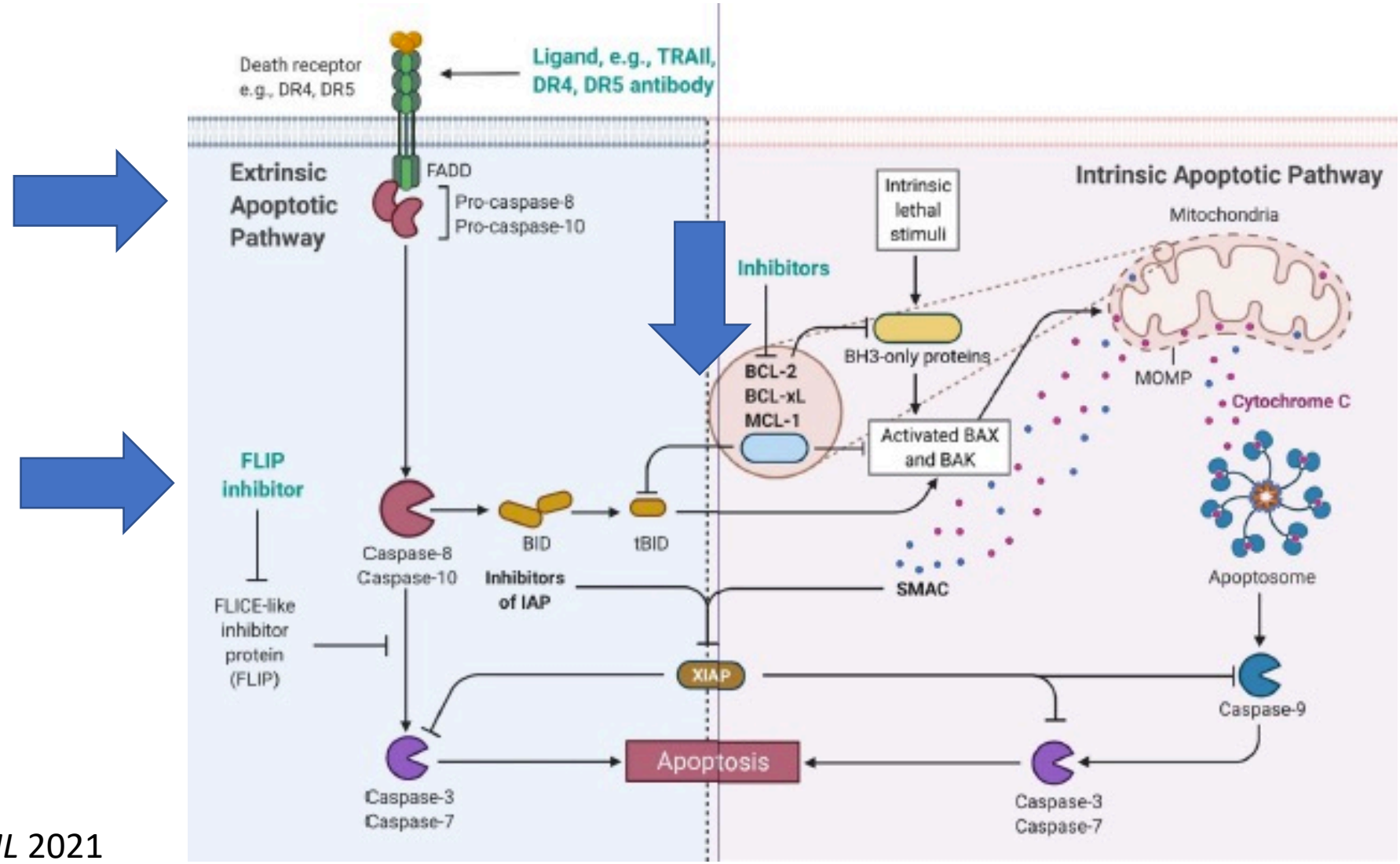
Program: Oral and Poster Abstracts
Type: Oral
Session: 616. Acute Myeloid Leukemias: Investigational Therapies, Excluding Transplantation and Cellular Immunotherapies: Triplet Combinations of Novel Therapies
Hematology Disease Topics & Pathways:
Clinical Trials, Acute Myeloid Malignancies, Biological, Adults, AML, Clinical Research, Elderly, Diseases, Therapies, Myeloid Malignancies, Monoclonal Antibody Therapy, Study Population

Sunday, December 12, 2021: 10:00 AM

Gail J. Roboz, MD[1], *Thomas Pabst, MD*[2], *Ahmed Aribi, MD*[3], *Joseph M. Brandwein, MD*[4*], *Hartmut Döhner, MD*[5], *Walter Fiedler, MD*[6], *Domenica Gandini, MD, PHD*[7*], *Michelle Geddes, MD, FRCPC*[8*], *Jing-Zhou Hou, MD, PhD*[9], *Angela J. Howes, BSc, PhD*[10], *Anna Hultberg, PhD*[7*], *Eric Huselton, MD*[11], *Julie Jacobs, PhD*[12*], *Colleen Kane, PhD, VMD*[13], *Ewa Lech-Marańda, MD, PhD*[14*], *Marieke Louwers, PhD*[7*], *Kerri Nottage, MD, MPH*[15*], *Uwe Platzbecker, MD*[16], *Raajit Rampal, MD, PhD*[17], *Mariya Salman, PhD*[15*], *Priya Shah, MBBS*[18*], *Don Stevens, MD*[19], *Monic Stuart, MD, MPH*[7*], *Marion Subklewe, MD*[20], *Anne Sumbul, MSc*[7*], *Eunice S. Wang, MD*[21], *Agnieszka Wierzbowska, MD, PhD*[22*], *Bin Yao*[7*], *Karen Yee, MD*[23], *Hagop Kantarjian, MD*[24] *and Gautam Borthakur, MD*[25]

	Intention-to-treat, N (%)*	Response evaluable, N (%)*
Number of subjects	44	42
Best response		
Complete remission (CR)	20 (45.5)	20 (47.6)
CR with partial hematologic recovery (CRh)†	10 (22.7)	10 (23.8)
CR with incomplete hematologic recovery (CRi)	14 (31.8)	14 (33.3)
CR + CRh† + CRi	34 (77.3)	34 (81.0)
Morphologic leukemia-free state (MLFS)	5 (11.4)	5 (11.9)
Partial remission (PR)	0	0
Stable disease (SD)‡	3 (6.8)	3 (7.1)
Progressive disease (PD)	0	0
Not evaluable (NE)*	2 (4.5)	0

How to overcome resistance to BCL2 inhibitors



Maiti et al, *CLML* 2021

- ✓ **HMAs+VEN** can be considered the **backbone** for unfit AML patients
- ✓ Real life data are required for a **better understanding of safety profile and toxicity management**
- ✓ Unmet medical need: **TP53 mutated** AML, but new approaches are coming
- ✓ **Moving to triplets**
- ✓ Better understanding of mechanisms of resistance to new drugs
- ✓ Integration between molecular and immunotherapy approaches

Thank you!

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