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MD Anderson Cancer Center
Making Cancer History®

Venetoclax

New Drugs in Hematology
Bologna October 2018

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Disclosures

- *Consultant for AbbVie, Genentech, F. Hoffman La-Roche*
- *Served as advisory board member for F. Hoffman La-Roche*
- *Equity, Reata Pharmaceuticals*
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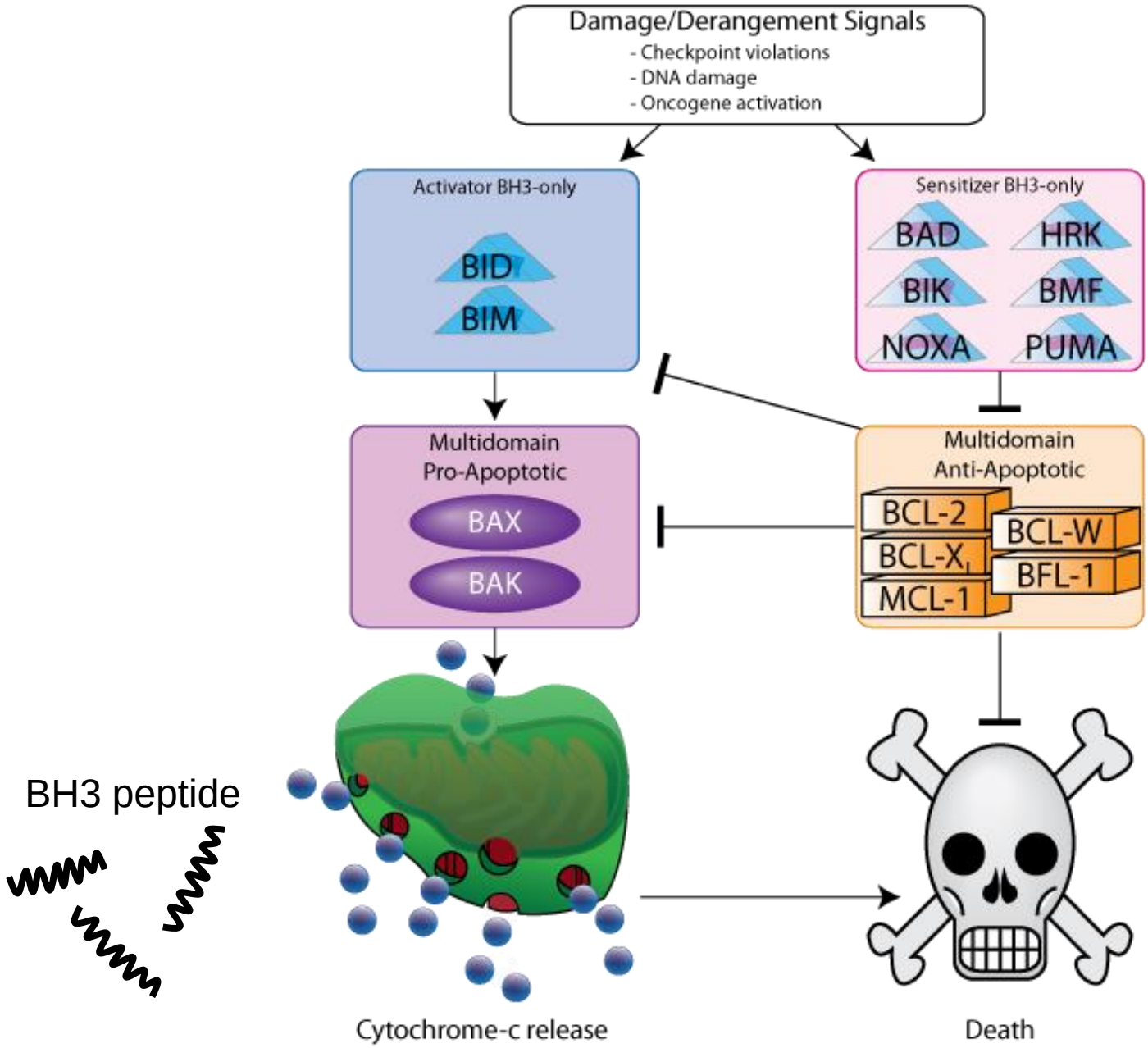
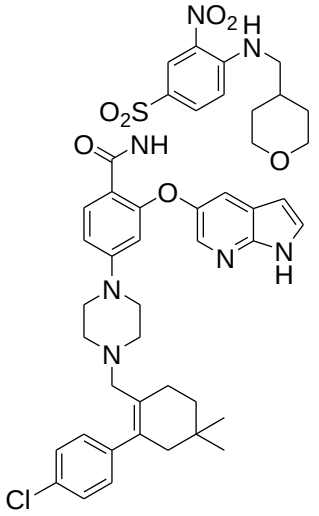
Apoptotic Signaling



Certo et al,
Cancer Cell 2006

Venetoclax (ABT-199) is a Potent and Selective BCL-2 Inhibitor

- High affinity for BCL-2
- Lower affinity for BCL-X_L, MCL-1
- >100-fold improved functional selectivity
- Orally bioavailable



ABT-199

	Binding Affinity				Cellular Efficacy, EC_{50} (nM)				
	TR FRET K_i (nM)				Engineered cell lines			Tumor cell lines	
Agents	BCL-2	BCL-X_L	BCL-w	MCL-1	BCL-2	BCL-X_L	Functional Selectivity	RS4;11 (BCL-2)	H146 (BCL-X_L)
ABT-263	0.04	0.05	7	>224	20	13	0.6	110	75
ABT-199	< 0.01	48	21	>440	4	261	87	12	3600

Abbvie ***Souers AJ et al. Nat Med. 2013 (2):202-8***

ABT-199 in AML: Preclinical

- BCL-2 is highly expressed in AML blasts
- ABT-199 effectively kills AML cells, with IC_{50}<10nM in the majority of primary AML samples tested
- Sensitivity of primary AML cells to ABT-199 positively correlates with BCL-2 protein levels
- Bcl-2 inhibition by ABT-199 effectively kills AML cells *in vivo* (AML cell line and primary AML PDX)
- **BH3 profiling: A predicative biomarker for Bcl-2 inhibition**

Pan R et al Cancer Discovery 2014; 4(3):362-75

Single Agent Venetoclax in R/R AML

Response	N=32 (%)
Objective Response (CR + CRi)*	**6 (19)**
CR	2 (6)
CRi	4 (13)
Stable Disease, SD	17 (53)
≥ 50 % blast reduction with two cell line recovery	2 (6)
≥ 50 % blast reduction with one cell line recovery	2 (6)

- **More than 50% of patients had clinical benefit**
- **5 of 6 responses occurred within the first 4 week assessment**
- **Median time on study: 63 days (range 13 – 246)**
- **Four of the 6 CR/CRi had IDH1/2 mutations (33%)**

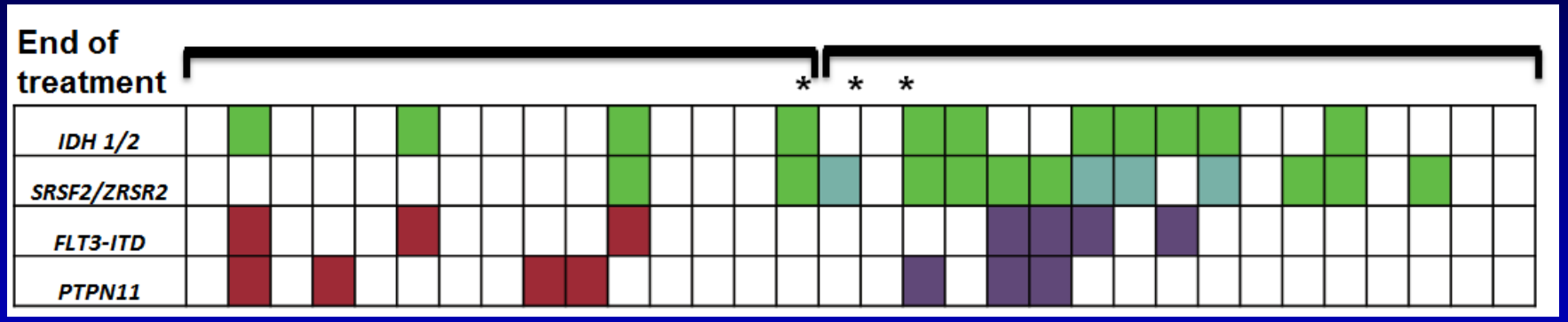
Activity in Patients with IDH mutations

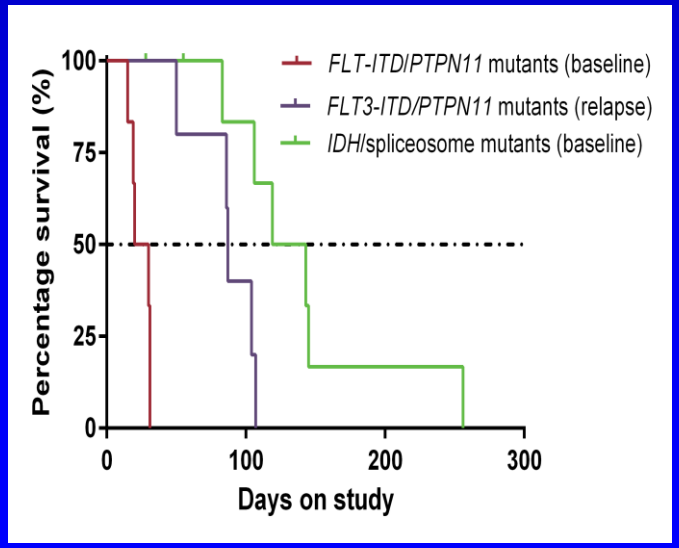
Response	N=11 (%)
Objective Response (CR + CRi)	**4 (36)**
CR	2 (18)
CRi *	2 (18)
Stable Disease ≥ 50 % blast reduction with one cell line recovery	2 (18)
Progressive Disease	4 (36)
Marrow Aplasia	1 (9)

*** One subject with IDH mutation in exon 3; dose interruption for 20 days after week 4 achieved CRi at week 24**

Konopleva et al., … Letai
Cancer Discovery 2016

Emergence of FLT3 and PTPN11 mutations in relapsing AML: Secondary Resistance

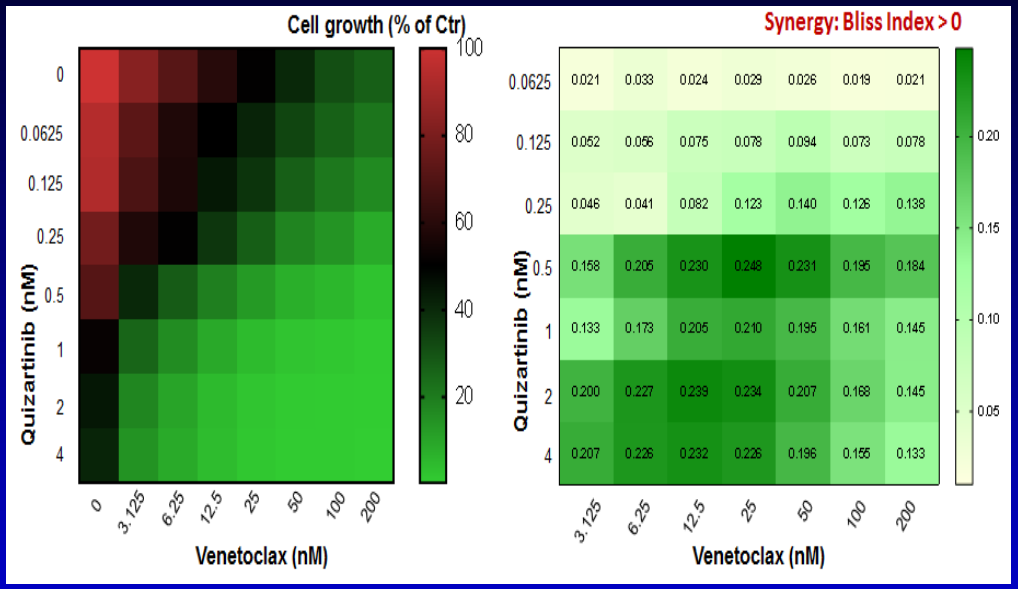


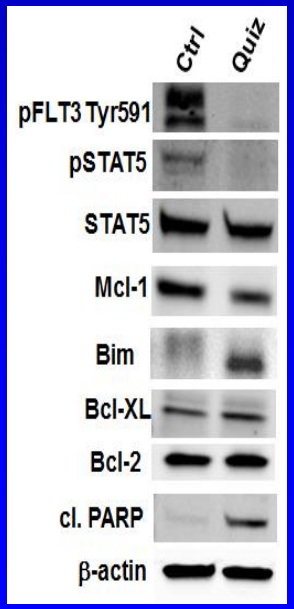


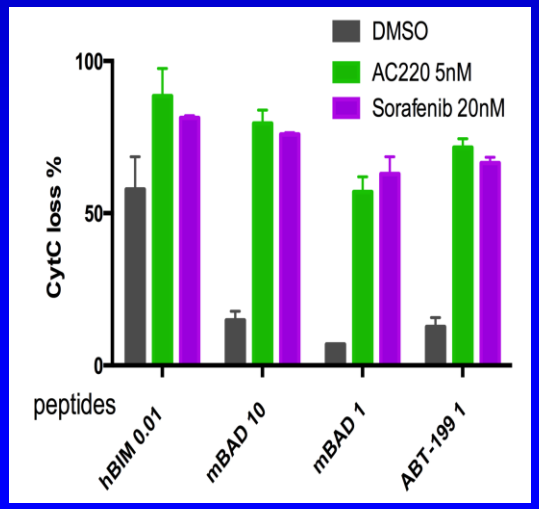
Group	N	Median time (days)
Resistant	6	25
Secondary resistance	5	87
Sensitive	8	131

*Chyla B, **Daver N**,…Konopleva M, Popovic R. Am J Hematol. 2018*

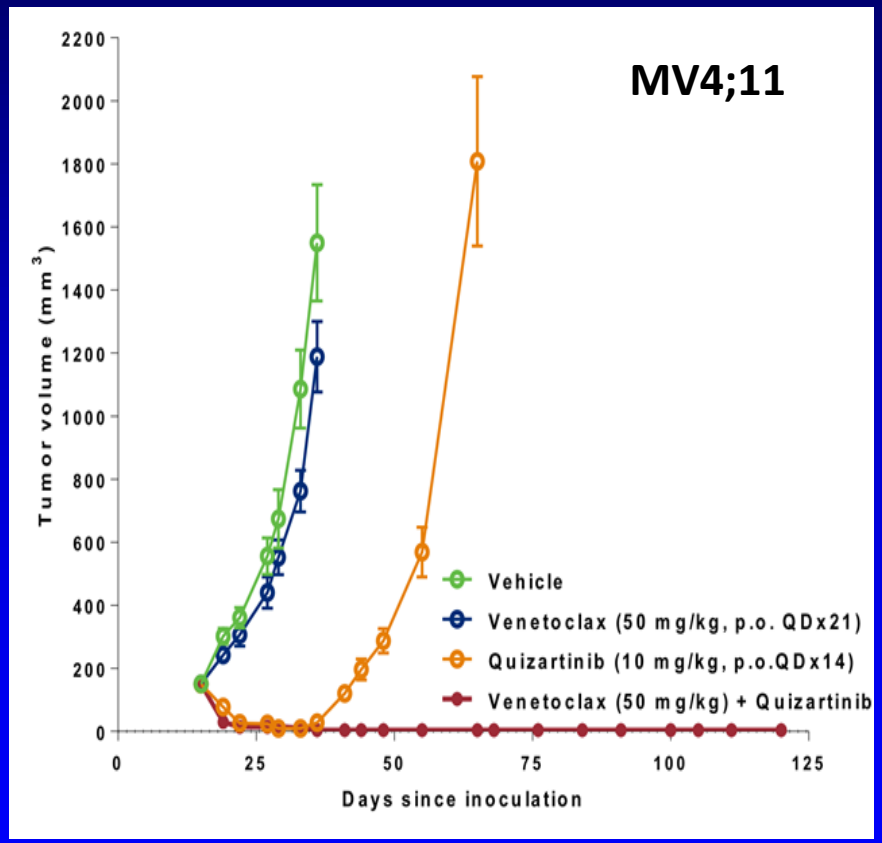
FLT3 Inhibitors and Venetoclax: Synergy and Priming





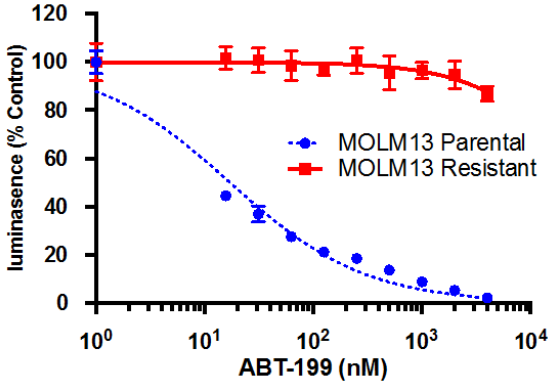


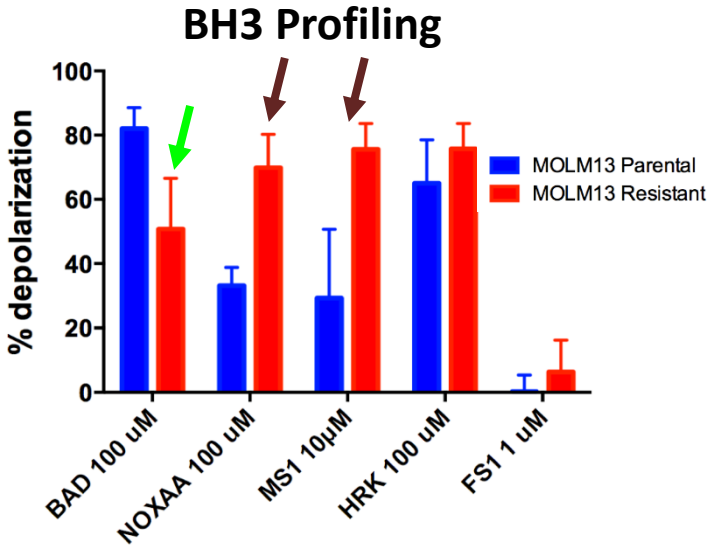
Dynamic BH3 profiling *in vitro*

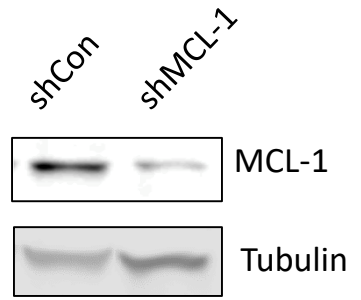


*Chyla B, **Daver N**,…Konopleva M, Popovic R. Am J Hematol. 2018*

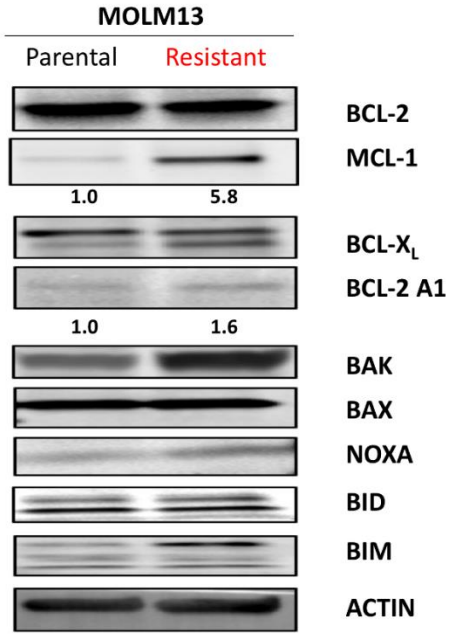
Venetoclax Resistance in AML: MCL-1 Upregulation

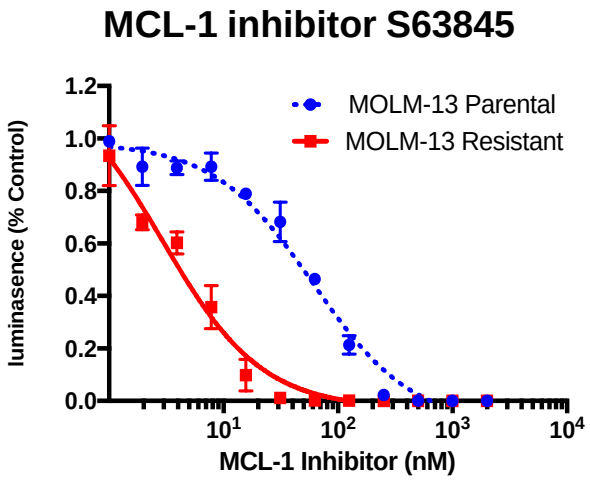


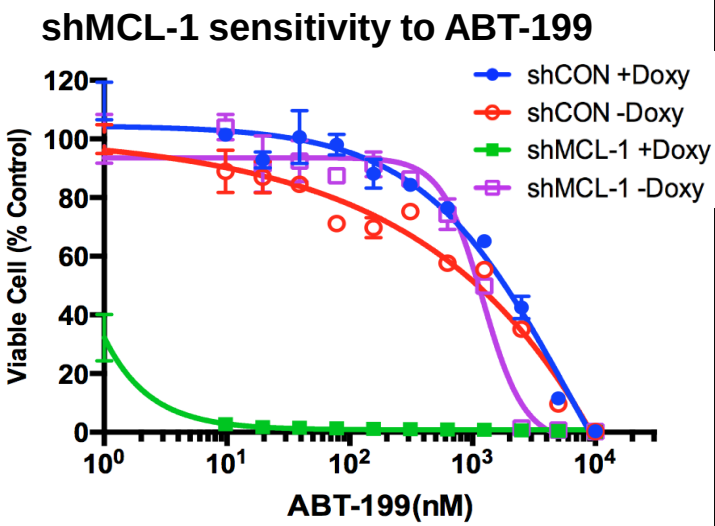




Doxycycline 100ng/ml 8h







Future Rationally Designed Venetoclax-based Combinations in AML

- Venetoclax + IDH1/2 inhibitors → later add AZA/DAC
- Venetoclax + FLT3 inhibitors → later add AZ/DAC
- Venetoclax + MCL1/CDK9 inhibitors

Frontline AZA or DAC + Venetoclax in untreated Elderly AML

Phase 1b Safety
PK & Dose Finding (45 enrolled)

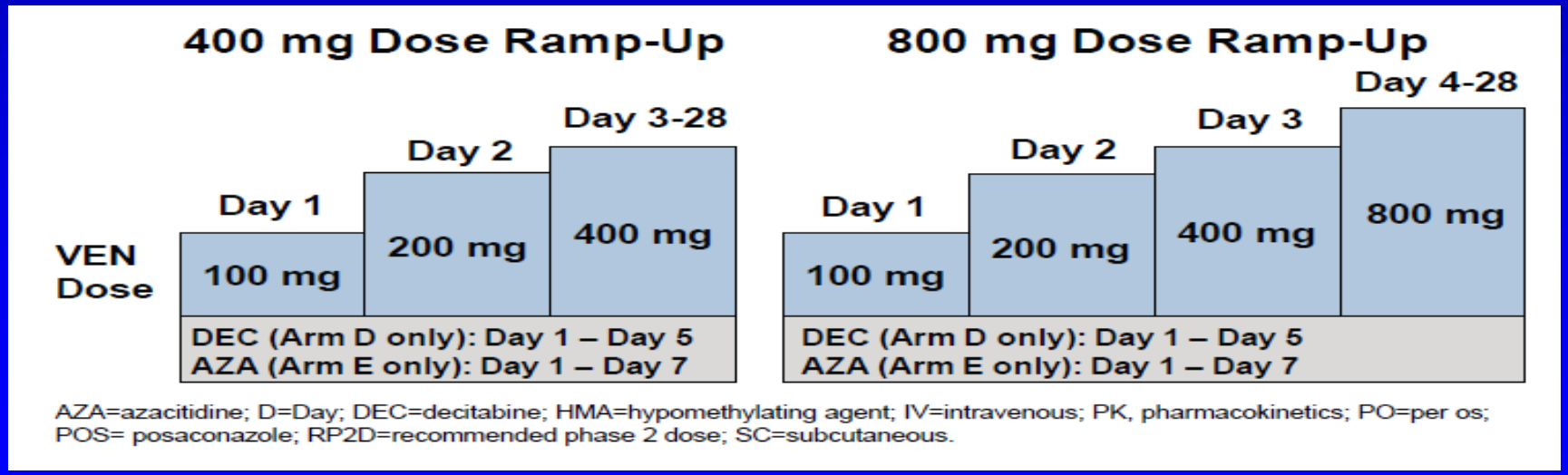
VEN + DEC (ARM A)
20 mg/m^2 D1–5, IV 28-D cycles
N=~24

VEN + AZA (ARM B)
75 mg/m^2 D1–7, IV/SC 28-D cycles
N=~24

Expansion stage →

VEN 400+ DEC/AZA
28/28 days
N=25 each

VEN 800 + DEC/AZA N=25
Cycle 1: 28/28 days
Cycle 2: 21/28 days



AZA=azacitidine; D=Day; DEC=decitabine; HMA=hypomethylating agent; IV=intravenous; PK, pharmacokinetics; PO=per os; POS= posaconazole; RP2D=recommended phase 2 dose; SC=subcutaneous.

DiNardo. Lancet Oncology 19: 216; 2018

AZA/DAC + VEN in UnRx Elderly AML - Study Group

Characteristic	N=145
Age, median (range), years	74 (65-86)
≥75 years, n (%)	52 (36)
Male, n (%)	81 (64)
ECOG performance score, n (%)	
0	32 (22)
1	90 (62)
2	23 (16)
Mutation, n (%)	
FLT3-ITD	14 (10)
IDH1/2	22 (15)
TP53	16 (11)
Cytogenetics, n (%)	
Intermediate	74 (51)
Poor	71 (49)
Secondary AML, n (%)	36 (25)

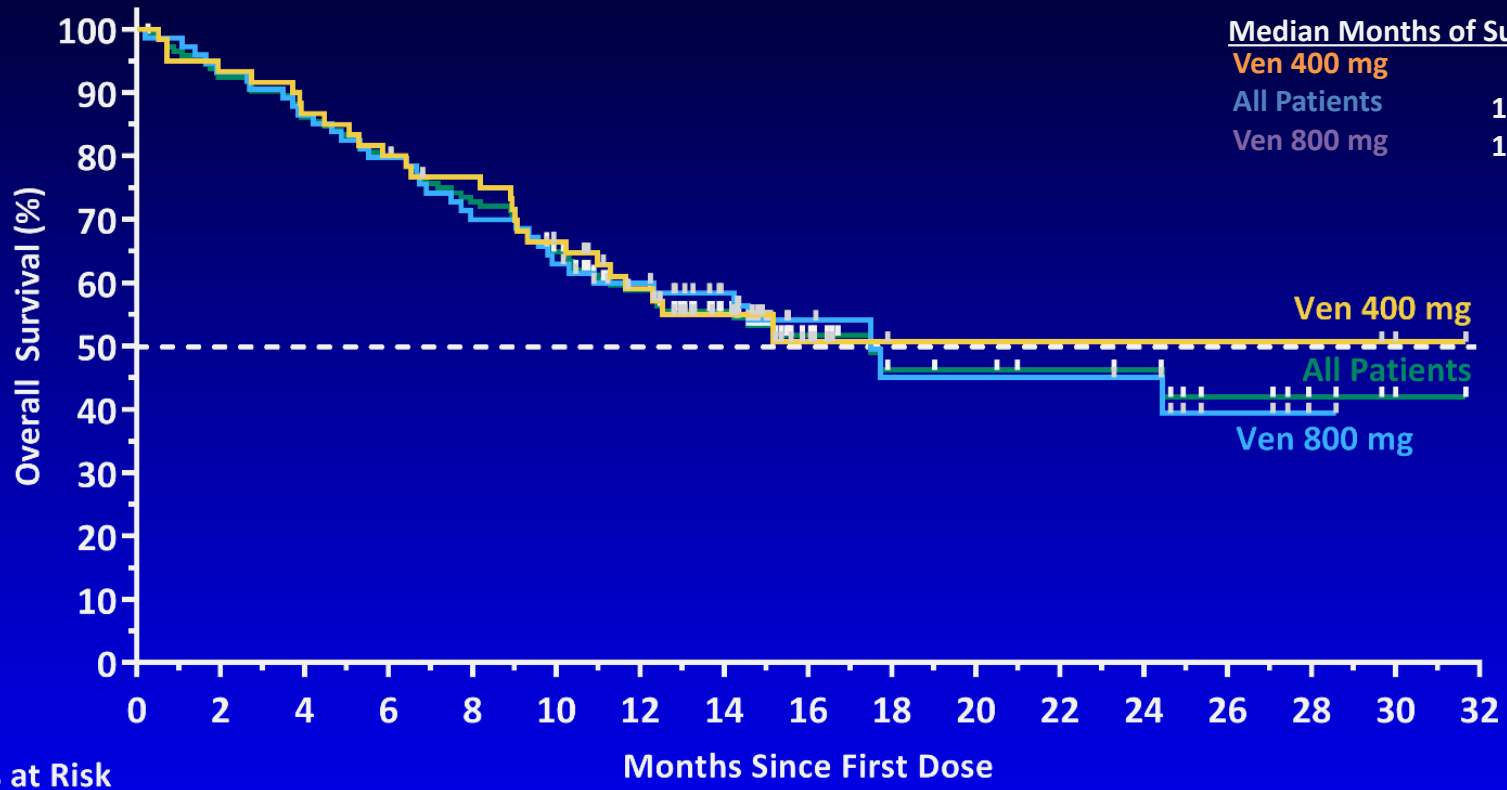
DiNardo. Lancet Oncology 19: 216; 2018

Venetoclax in UnRx Elderly AML. Response

Cohort	N	Composite Response Rate, CR/CRi n (%)	Overall Response Rate (CR+CRi+PR+MLFS), n (%)
All patients	145	97 (67)	120 (83)
VEN 400 mg	60	44 (73)	49 (82)
VEN 400 mg + AZA	29	22 (76)	24 (83)
VEN 400 mg + DEC	31	22 (71)	25 (81)
VEN 800 mg	74	48 (65)	63 (85)
VEN 800 mg + AZA	37	21 (57)	31 (84)
VEN 800 mg + DEC	37	27 (73)	32 (86)
VEN 1200 mg	11	5 (45)	8 (73)

Median OS 17.5 mos; estimated 2-yr OS 48%

Overall Survival



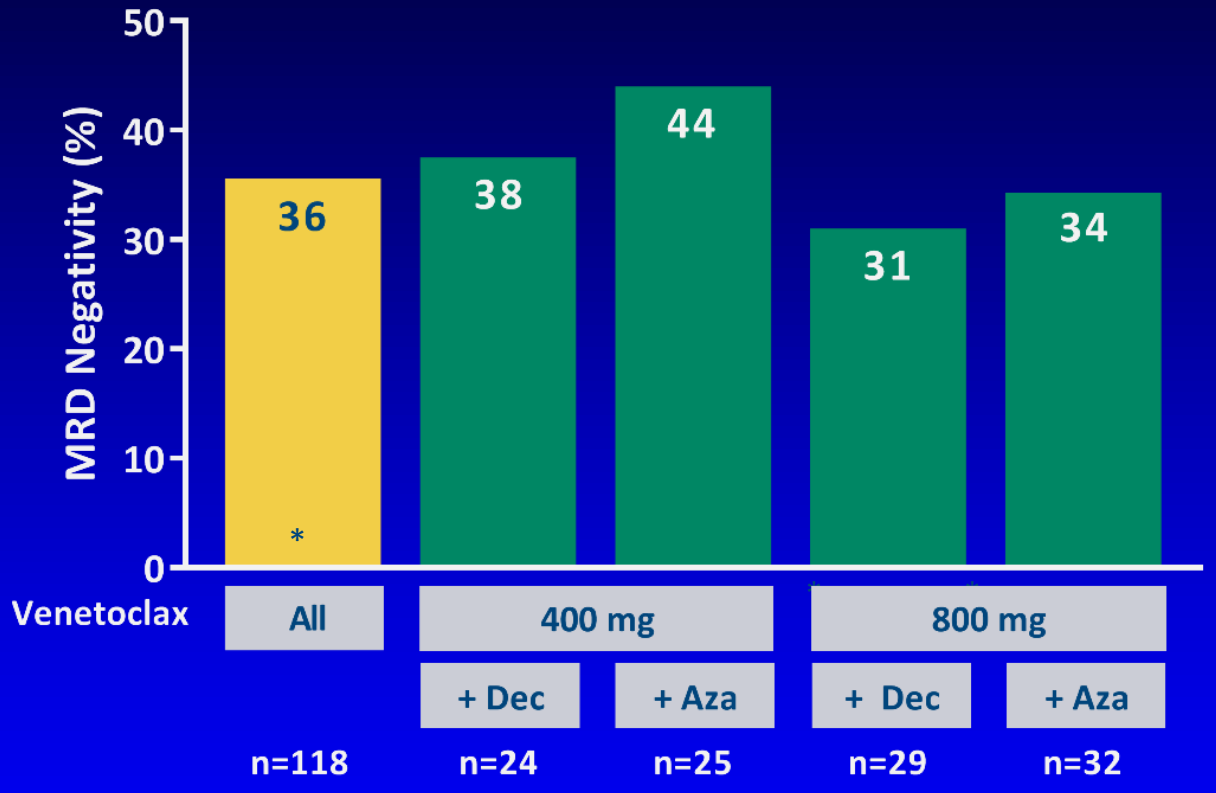
Patients at Risk

All patients	145	133	124	115	102	89	73	53	25	16	15	13	12	7	4	2
Ven 400 mg	60	56	52	48	45	38	30	20	8	3	3	3	3	3	3	2
Ven 800 mg	74	69	64	59	50	44	38	29	13	10	10	10	9	4	1	

- At a median time on study of 8.9 months (range, 0.2-31.6), the median overall survival (OS) in all treated patients was 17.5 months (95% CI, 12.3, NR-)
- The estimated 6-month, 1-year, and 2-year OS rates were 80%, 59% and 46%

DiNardo et al., ASCO 2018

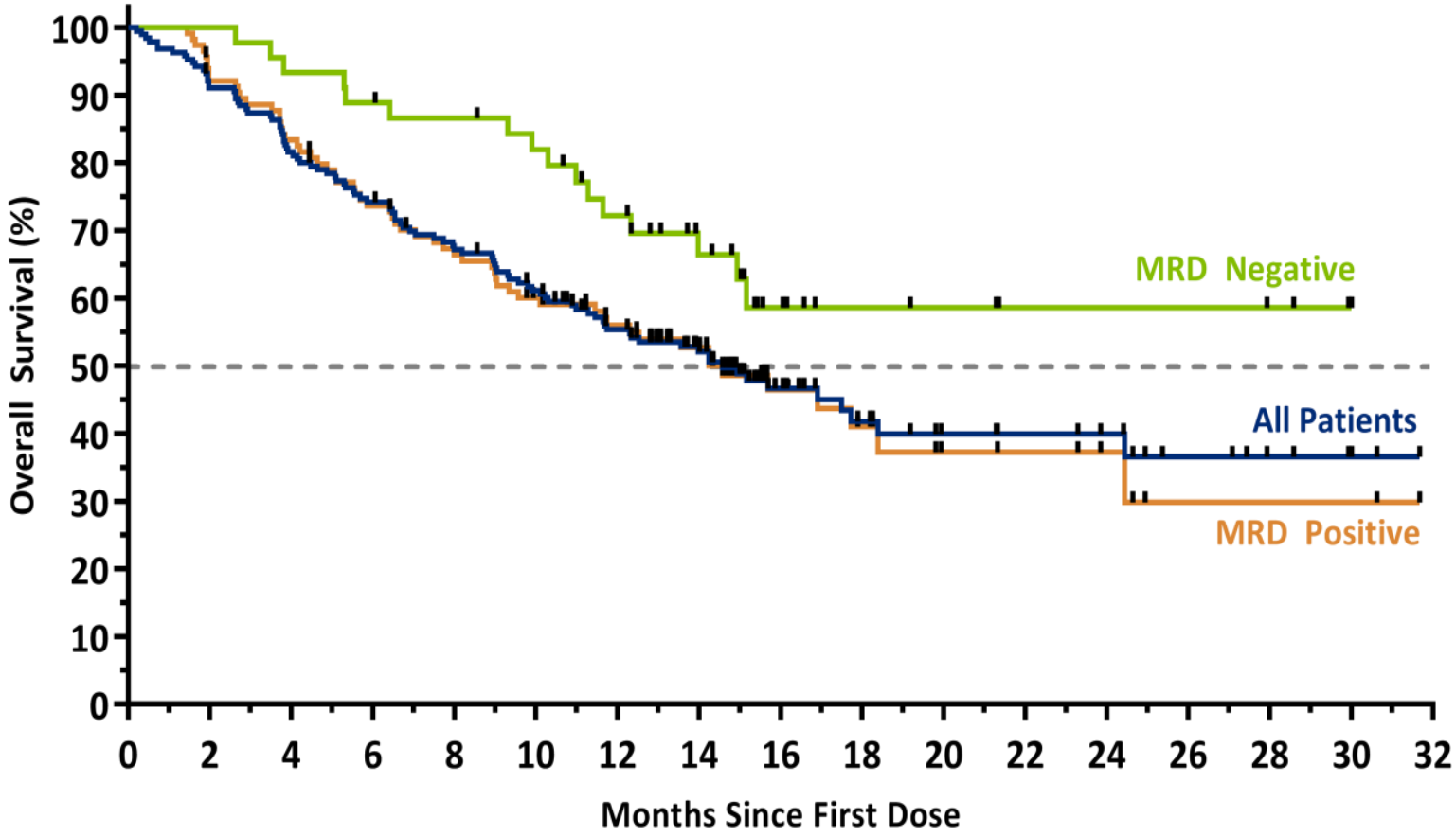
Minimal Residual Disease (MRD) Negativity



* Includes patients that received 1200 mg venetoclax

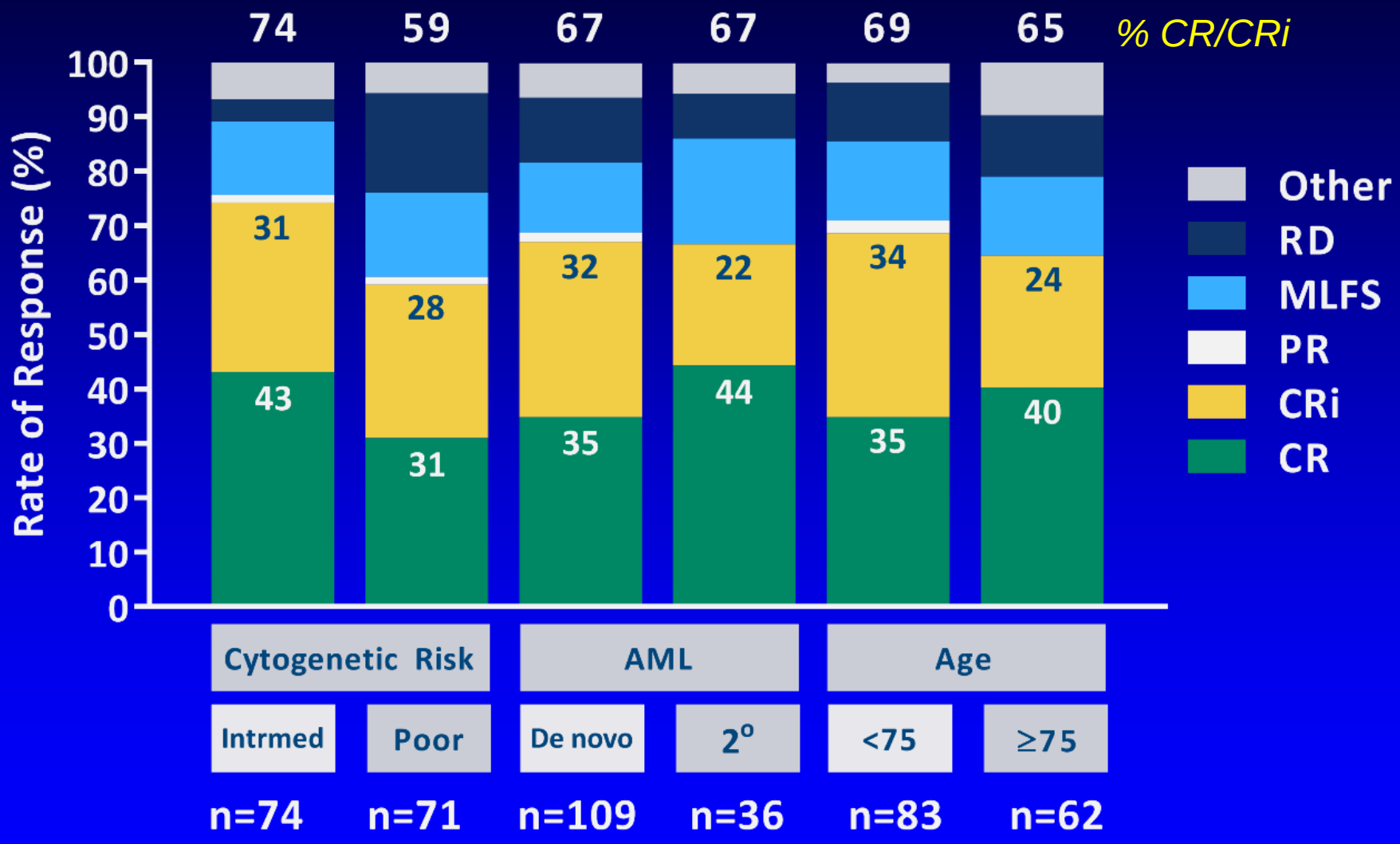
- MRD negativity was defined as less than 10^{-3} percent leukemic cells as detected by multicolor flow cytometry in bone marrow aspirates at any measurement

Overall Survival by Whether a Patient Achieved MRD Negativity



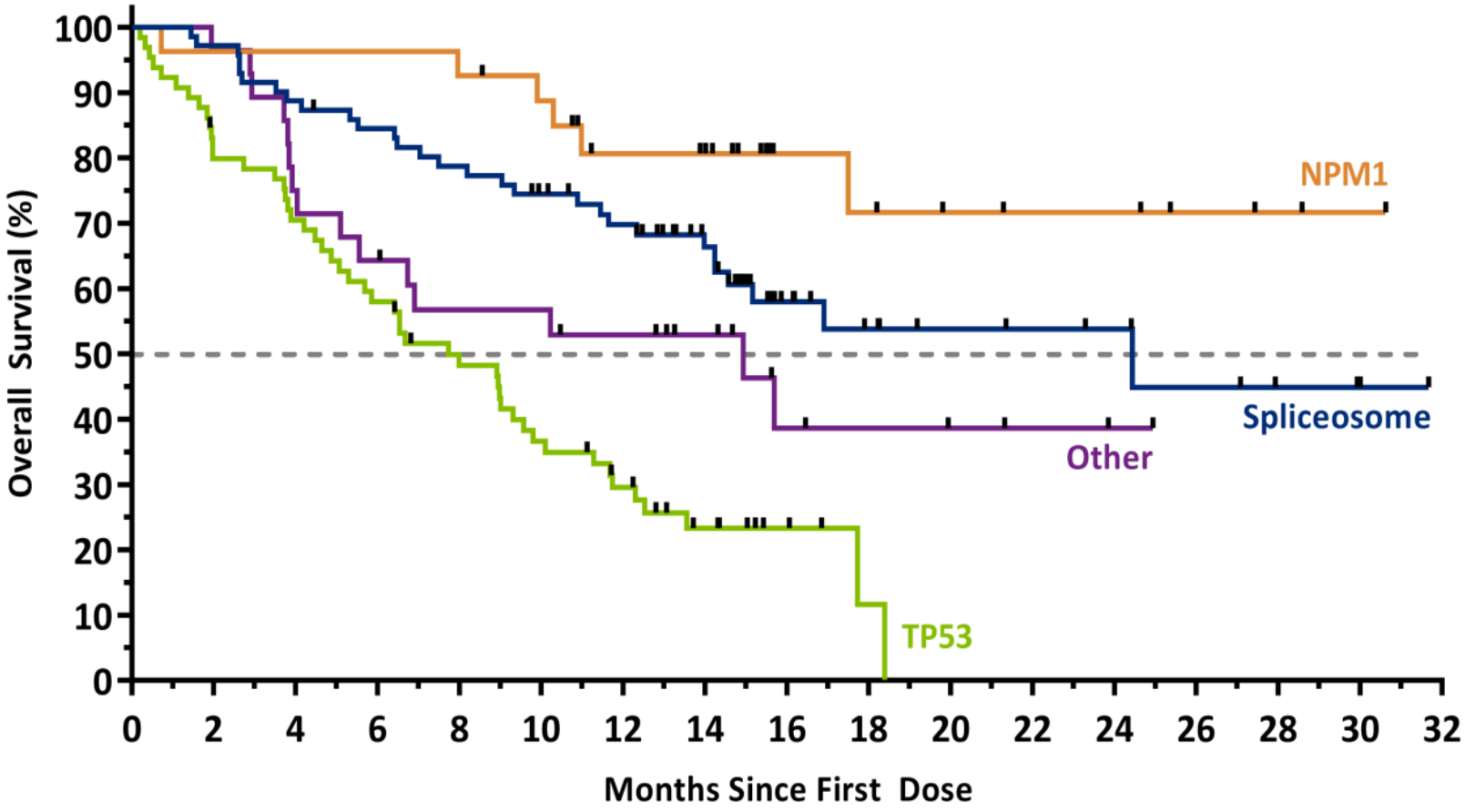
Strickland et al., EHA 2018

Response Rates by Patient Subgroups



DiNardo et al., ASCO 2018

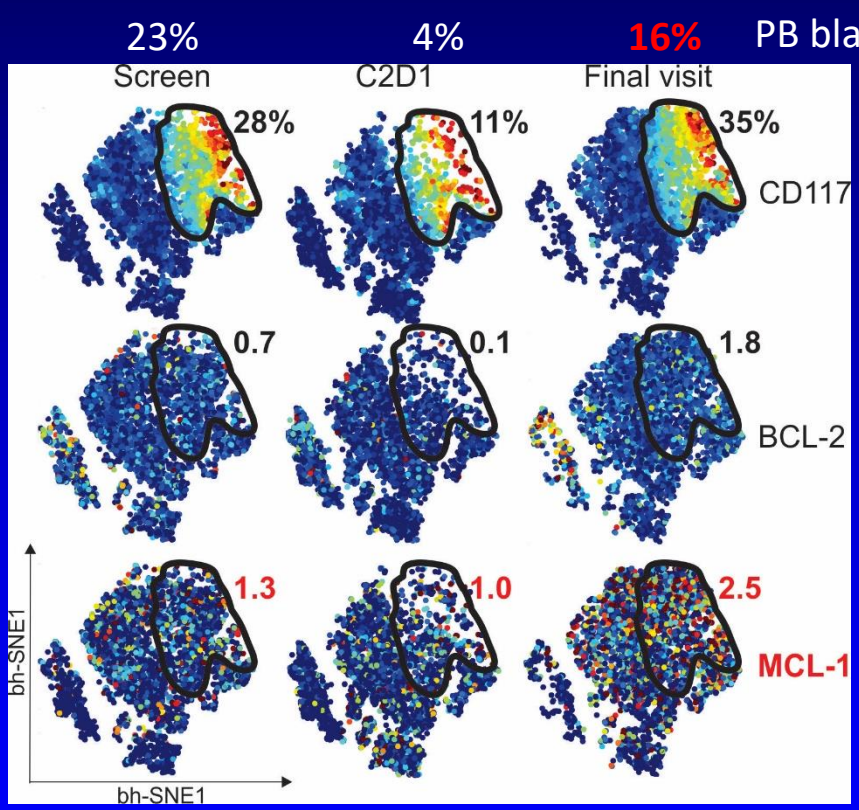
Overall Survival by Molecular Subgroup



Strickland et al., EHA 2018

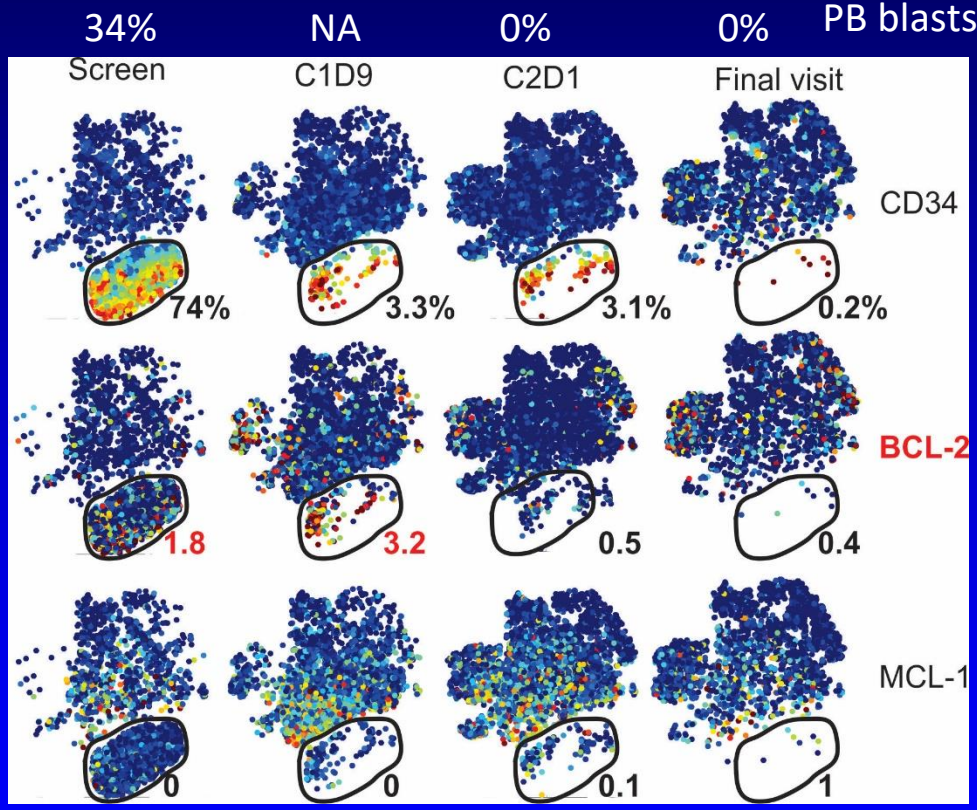
CyTOF Profiling: BCL-2 and MCL1 expression in AML stem/progenitor cells

A – Pt 15109: Relapse



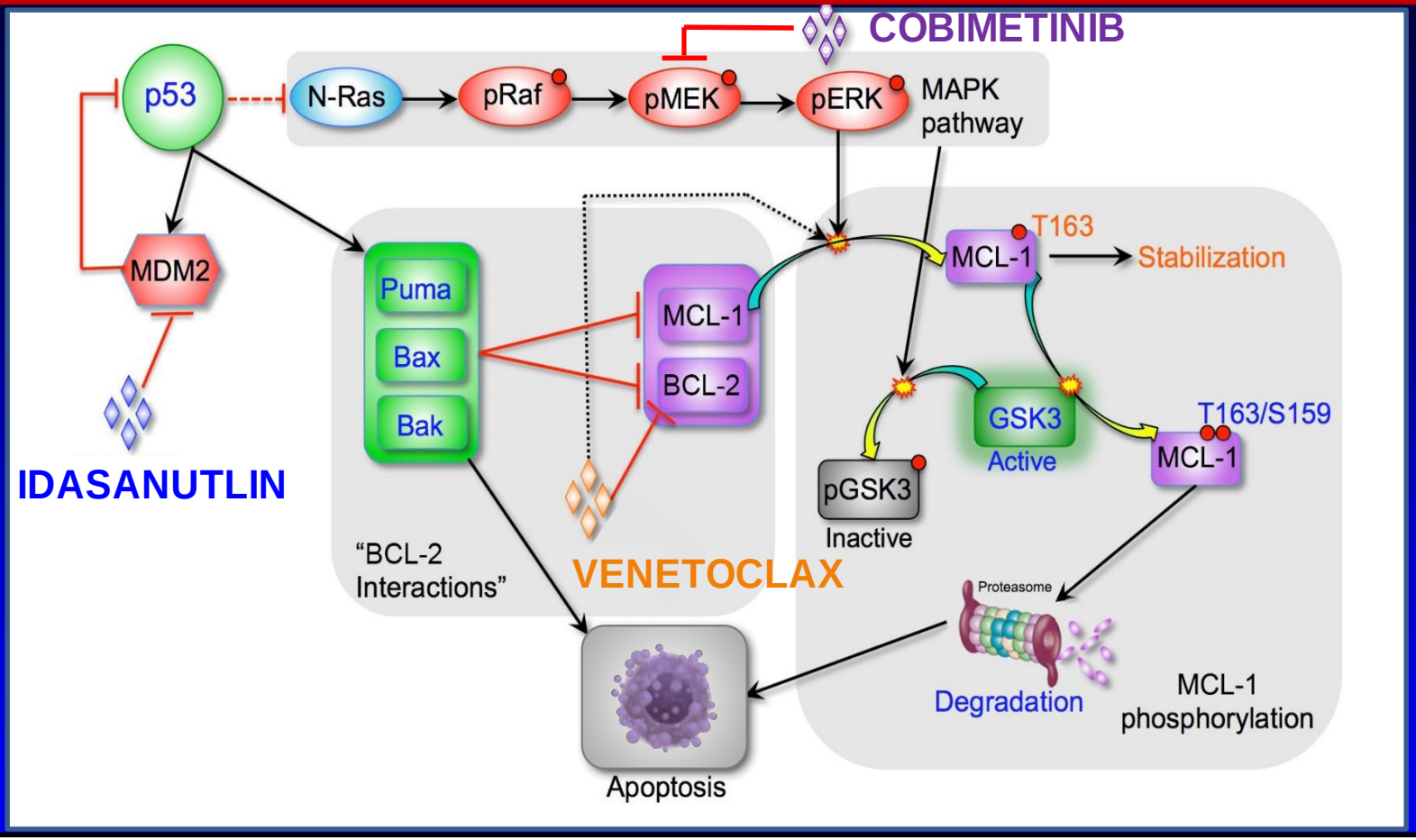
LSPCs:
CD34-CD117+ALDH1A1+CD99partial

B – Pt 20205: stable CR



LSPCs:
CD34-CD117+ALDH1A1+CD99partial

Beyond Single Pathway: Synthetic Lethality of MDM-2 and BCL-2 Inhibition



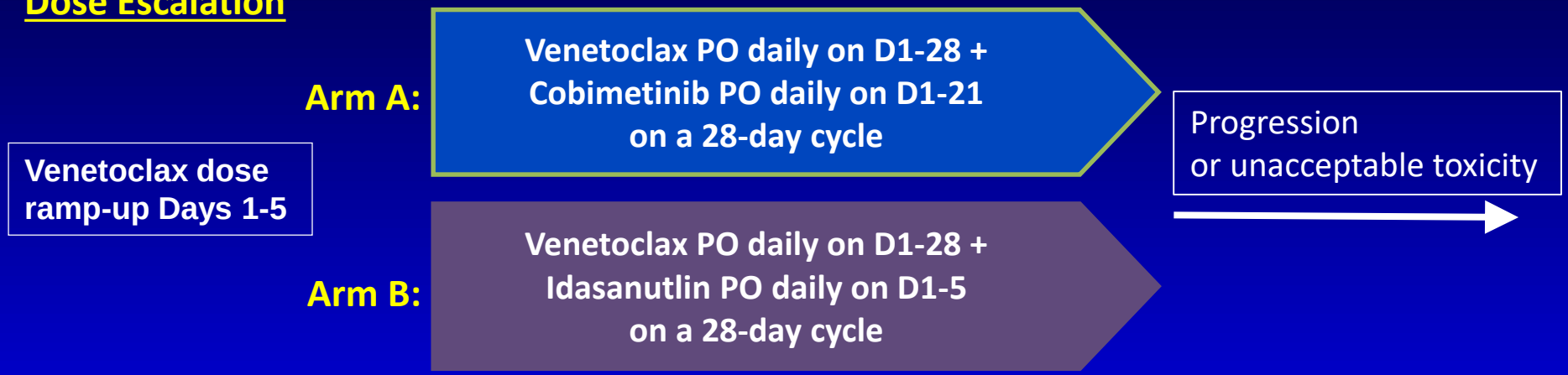
- MEKi and MDM2i inhibits MCL-1, an anti-apoptotic protein, overcoming resistance to BCL-2 inhibition in AML[1,2]

MCL-1=myeloid cell leukemia 1; MDM2=mouse double minute 2 homolog; MEK=mitogen-activated protein kinase kinase

[1]Figure adapted from Pan R, Andreeff M, et al. *Cancer Cell.* Dec 11, 2017
[2]Han L, Konopleva M, et al. *ASH* 2016.

Phase Ib Study Venetoclax in Combination with MEK Inhibitor Cobimetinib or MDM2 Inhibitor Idasanutlin in Patients with R/R AML

Study Design Overview



Key Objectives

- Safety and tolerability, determination of MTD and RP2D
- Preliminary efficacy

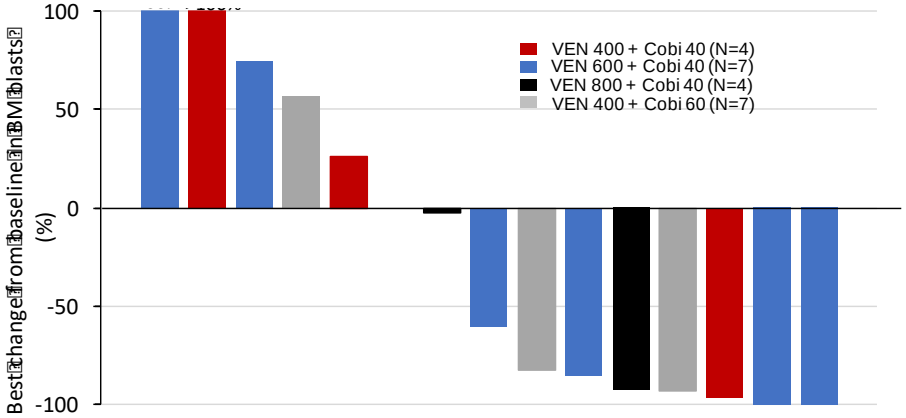
Key Eligibility Criteria

- Patients with ≥ 60 years old with relapsed/refractory AML or with previously treated antecedent hematologic disorders transformed to AML
- Ineligible for cytotoxic therapies or allogeneic stem cell transplant
- Prior allogeneic stem cell transplant allowed

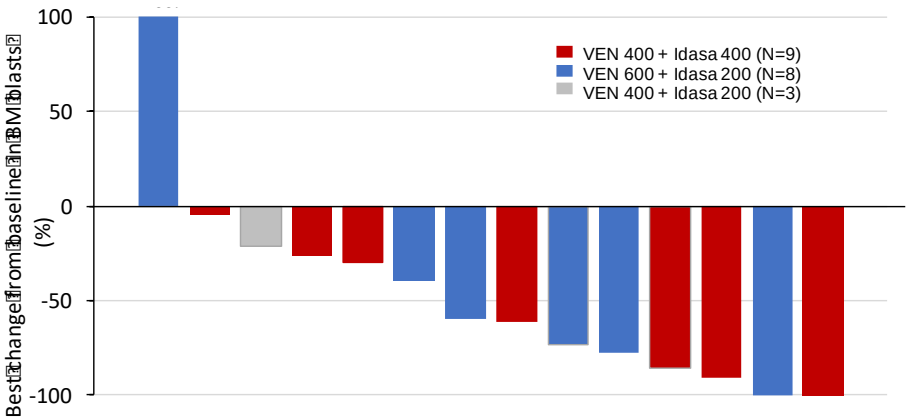
Daver et al. ASH 2017

VEN + COBI/IDASA in AML: Preliminary Efficacy

Arm A: Venetoclax + Cobimetinib



Arm B: Venetoclax + Idasanutlin



	Ven + Cobi (N=30)	Ven + Idasa (N=24)
ORR	6 (20%)	8 (33%)
CR+CRi	5 (17%)	4 (17%)
PR	0	1 (4%)
MLFS	1 (3%)	3 (13%)

Daver et al. ASH 2017

Summary

- AML cell survival is Bcl-2-dependent but is Mcl-1 co-dependent
- Venetoclax plus HMA or LDAC demonstrate a tolerable safety profile and compelling activity for elderly treatment naïve AML patients.
- Concomitant blockade of BCL-2 and MdM2 may constitute synthetic lethality in AML
- Dual Targeting of BCL-2/MCL-1 is warranted (Servier, Amgen)
- Combinations with standard chemotherapy in younger AML patients, and with targeted agents (IDH, FLT3, BET, CDK9 inhibitors) are ongoing/planned

Ongoing/Planned Trials

AML Ongoing:

- Ven+5-aza, elderly unfit Phase 3 *(DiNardo)*
- Ven/Idasanutlin/Cobimetinib *(Andreeff / Daver / Konopleva)*
- FLAG-Ida/Ven *(DiNardo/Konopleva)*
- AG120/Ven *(DiNardo/Konopleva)*
- Decitabine x 10 / Ven *(Konopleva/DiNardo)*
- ABBV-075 (BRD4-i)/Ven
- ABBV-621 (TRAIL agonist)/Ven
- Dinaciclib (CDK9-i)/Ven

AML Planned:

- 7+3 / Ven *(Stone / Konopleva)*
- Quizartinib/Ven *(Daver/Konopleva)*
- Aza/Ven/nivolumab *(Daver)*
- Clad / LD AraC/Ven *(Kadia)*

ALL Ongoing:

- Mini-HCVD/Ven elderly frontline *(Jain / DeAngelo)*
- Ven/Navitoclax/L-Asp/Dex/ VCR young R/R *(St. Jude / Jabbour)*
- Mini-HCVD/Ven R/R *(Jabbour)*
- Ven/Ponatinib Ph+ R/R *(Ravandi)*

BPDCN:

- Ven *(Pemmaraju/Lane)*

MDS Ongoing:

- MDS untreated high risk Aza/Ven *(Garcia-Manero)*
- MDS HMA failure *(Garcia-Manero)*

CML Ongoing:

- Ven/Dasatinib 50 *(Kantarjian)*

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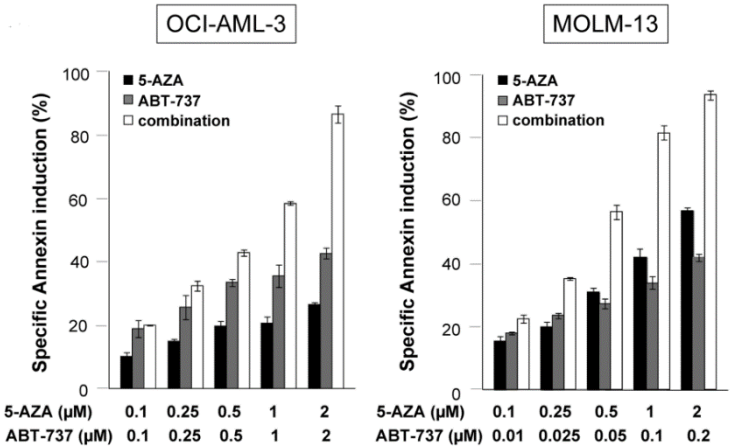
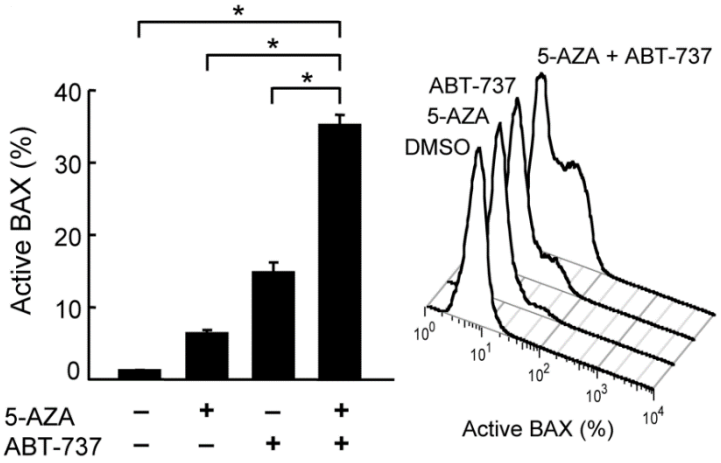
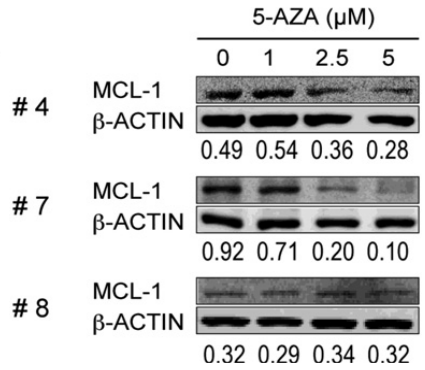
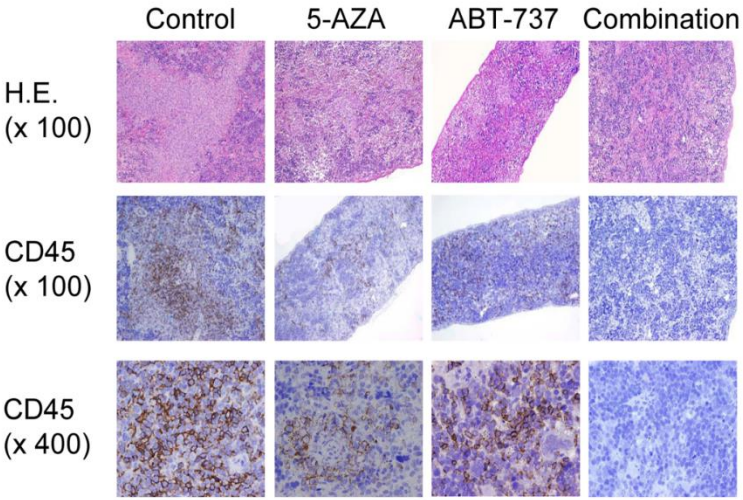
Kenna Shaw

Concomitant Inhibition of DNA Methyltransferase and Bcl-2 Synergistically Induces Apoptosis in AML



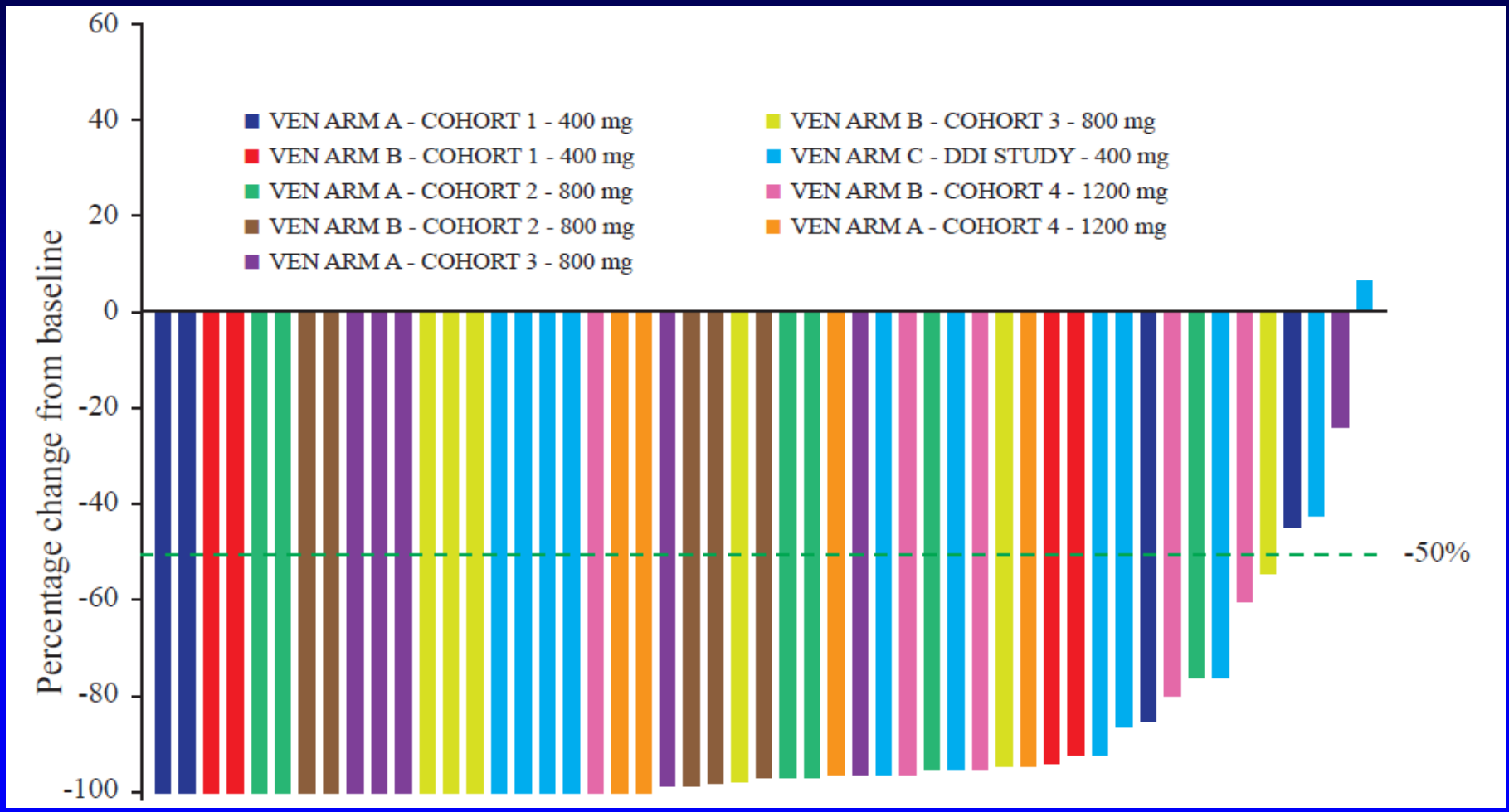






Tsao, …Konopleva. Ann Hematol. 2012, 91(12):1861-70

Venetoclax in UnRx Elderly AML. % BM Blast Reduction

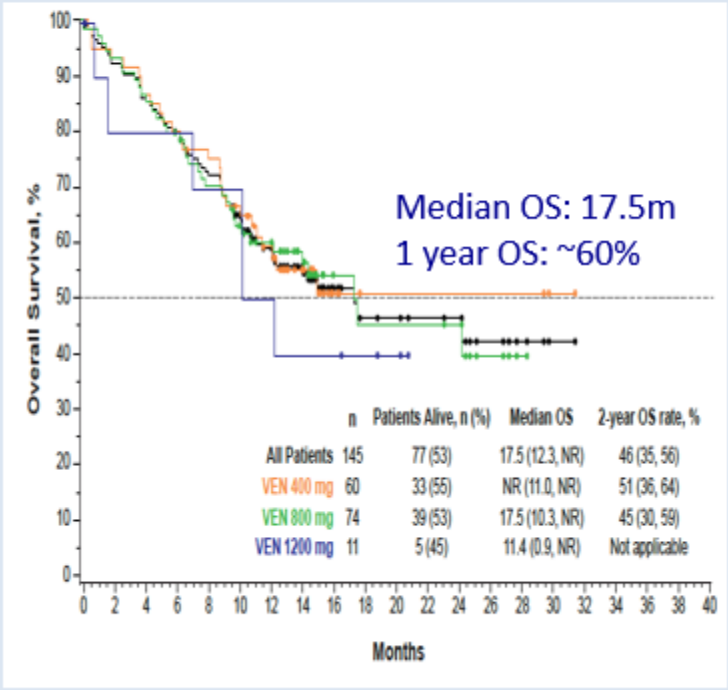


DiNardo. Lancet Oncology 19: 216; 2018

HMA + venetoclax in elderly

VEN/HMA CR/CRi 67%

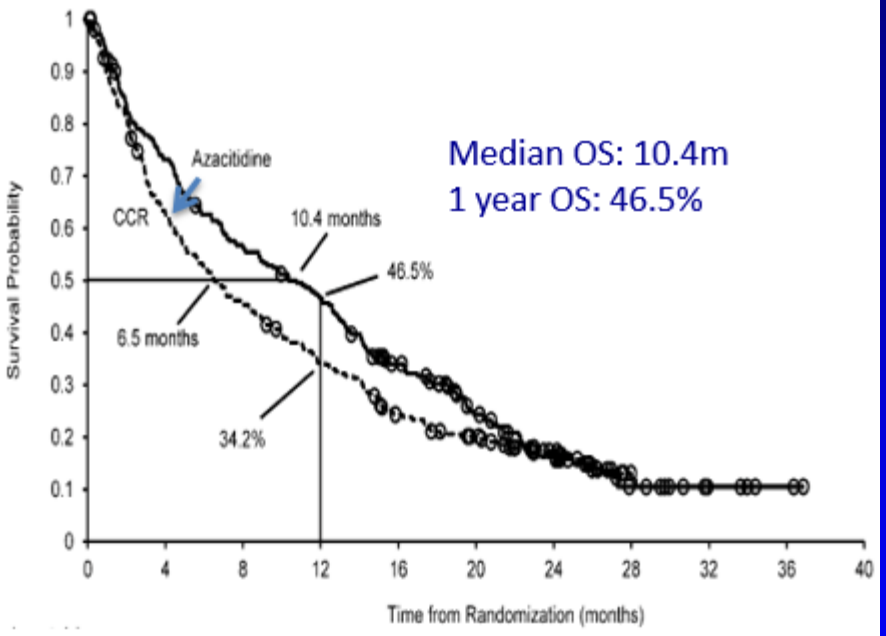
N=145, median age 73



Di Nardo, ASH 2017

AZA CR/CRi 28%

N=241, median age 75



Dombret et al, Blood 2015

FDA breakthrough designation Febr 2016

BCL-2 Inhibition and Chemotherapy: AML Primed for Cell Death?

Venetoclax + low dose cytarabine: Phase 1/2 Study in Older AML Patients

28-Day Cycles for VEN 600-mg Patients:

VEN 600 mg PO QD on days 1-28

LDAC 20 mg/m^2 SC QD on days 1-10

PRIMARY OBJECTIVE: To evaluate safety (MTD, PK) and preliminary efficacy (ORR, TTP, RP2D)

SECONDARY OBJECTIVE: To evaluate response rates, including CR, CRi, partial remission, resistant disease, and hematologic response rates, duration of response (DOR) and overall survival (OS)

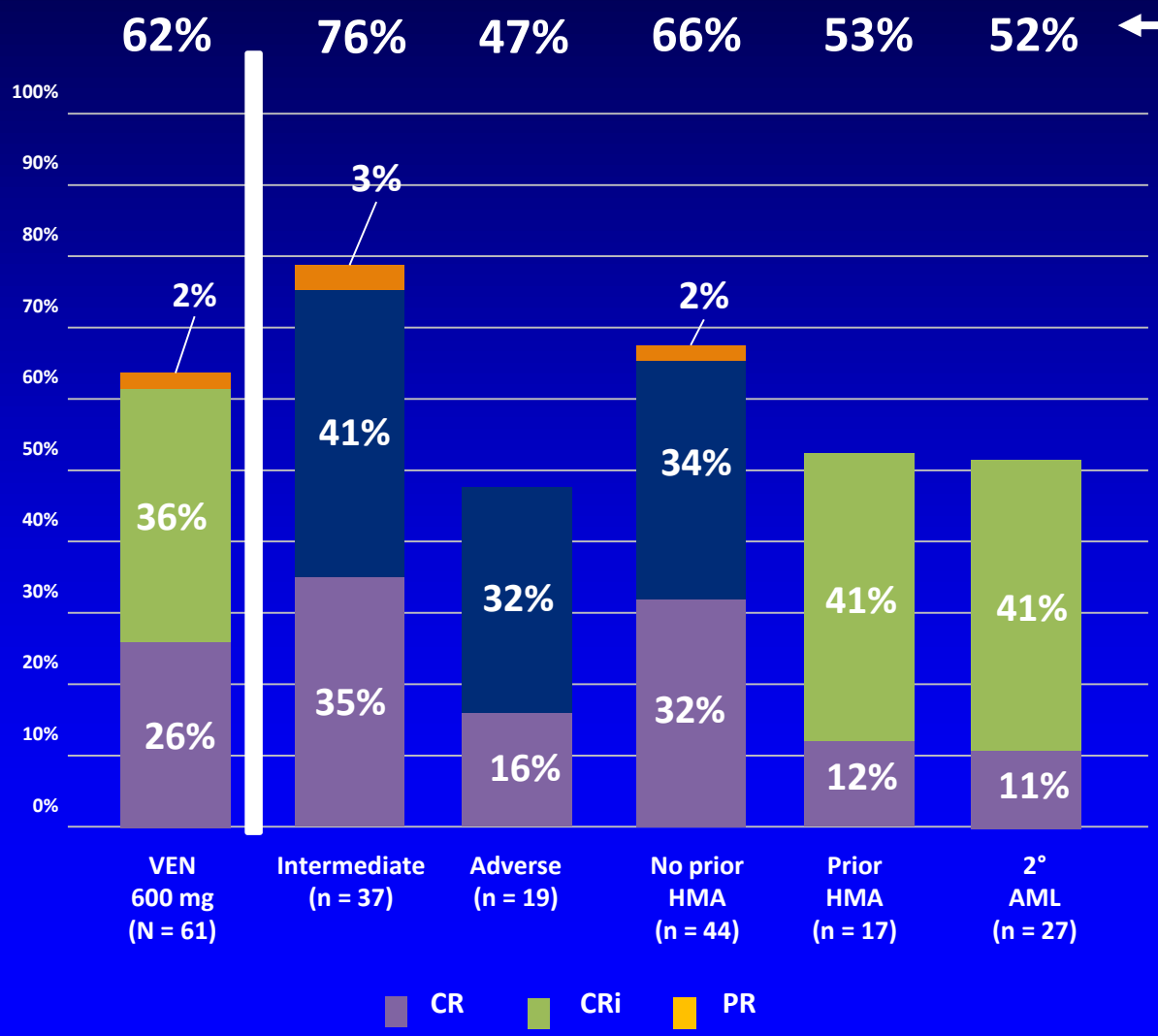
Key eligibility: age≥65; ineligible for intensive chemotherapy; prior HMA for MDS allowed (28%); WBC < 25. Secondary AML 44%.

1-year outcomes presented: VEN 600 mg + LDAC

N = 61: phase 1 (n = 8) + phase 2 (n = 53)

Wei ASH 2017

AML Response Rates



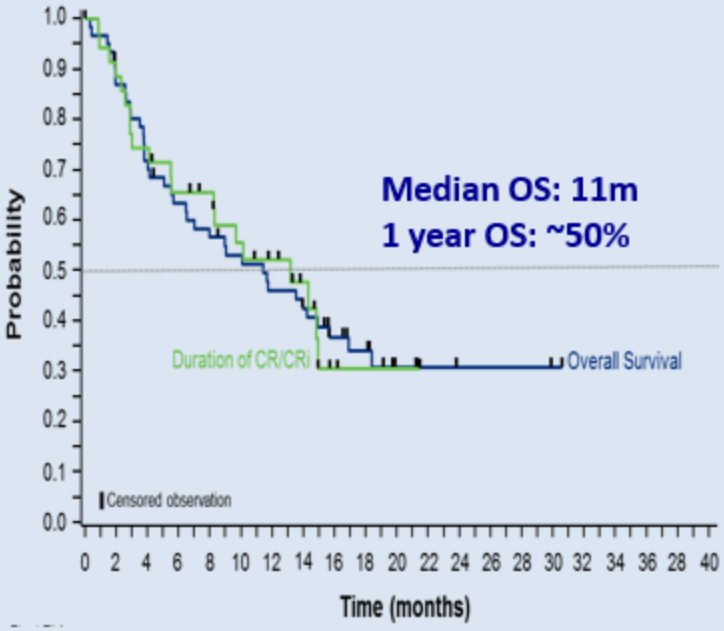
- Median time to response
  - 1 month (range: <1–9.5 months)
- Median time to best response
  - 2.6 months (range: <1–14.4 months)

Data cutoff date: 15 AUG 2017.

LDAC + venetoclax in elderly AML

LDAC/VEN CR/CRi 62%

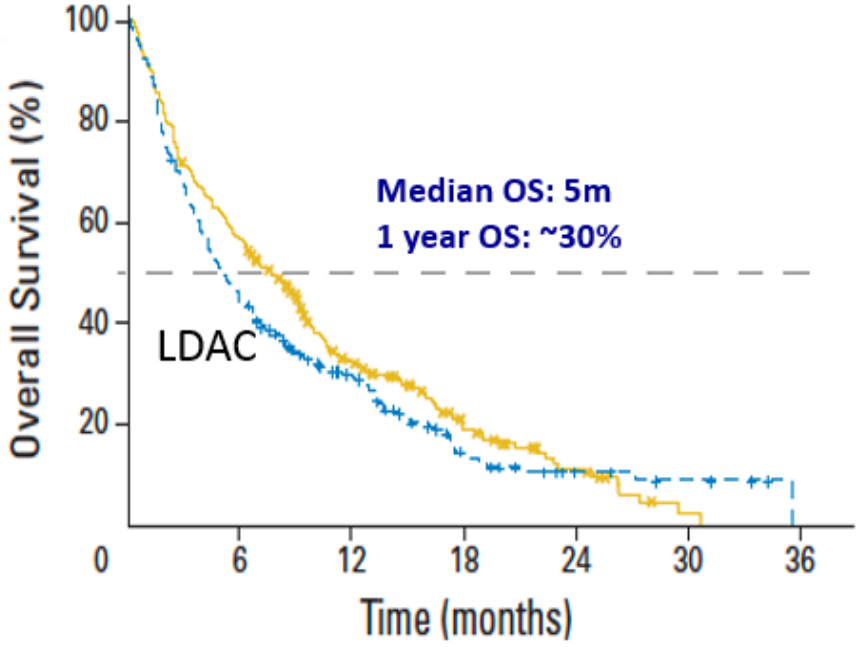
N=61, median age 74



Wei et al, ASH 2017

LDAC CR/CRi 11%

N=243, median age 73



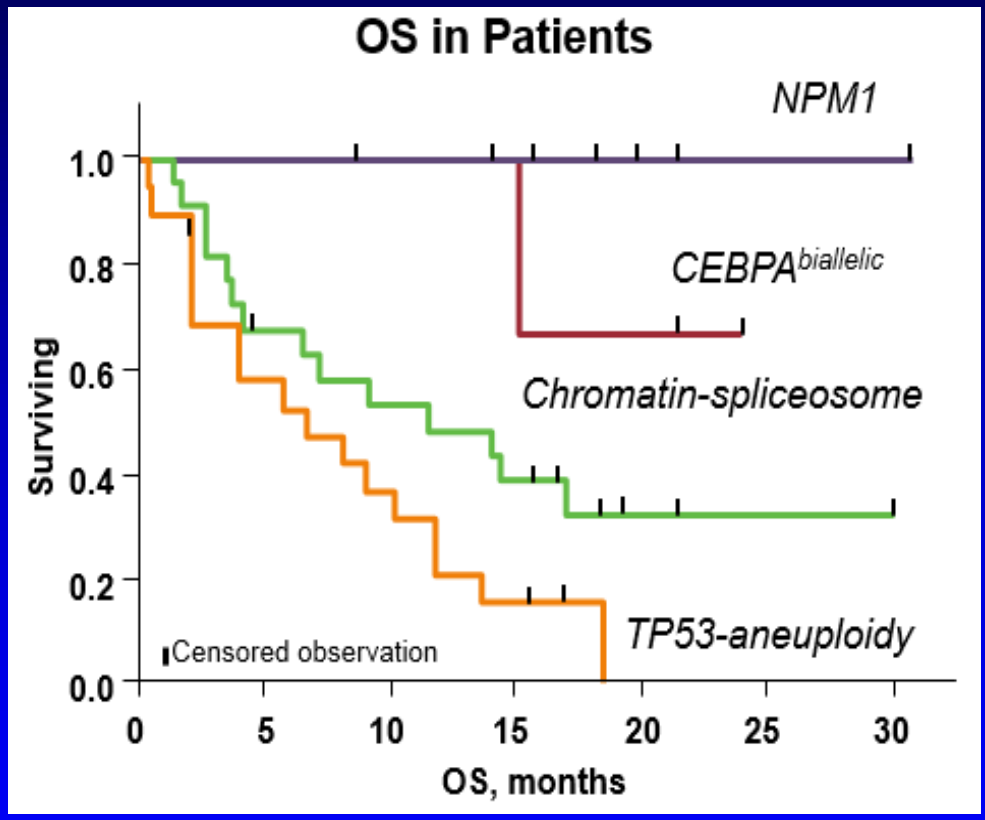
Kantarjian et al, JCO 2012

FDA breakthrough designation 28 July 2017

Wei, ASH 2017

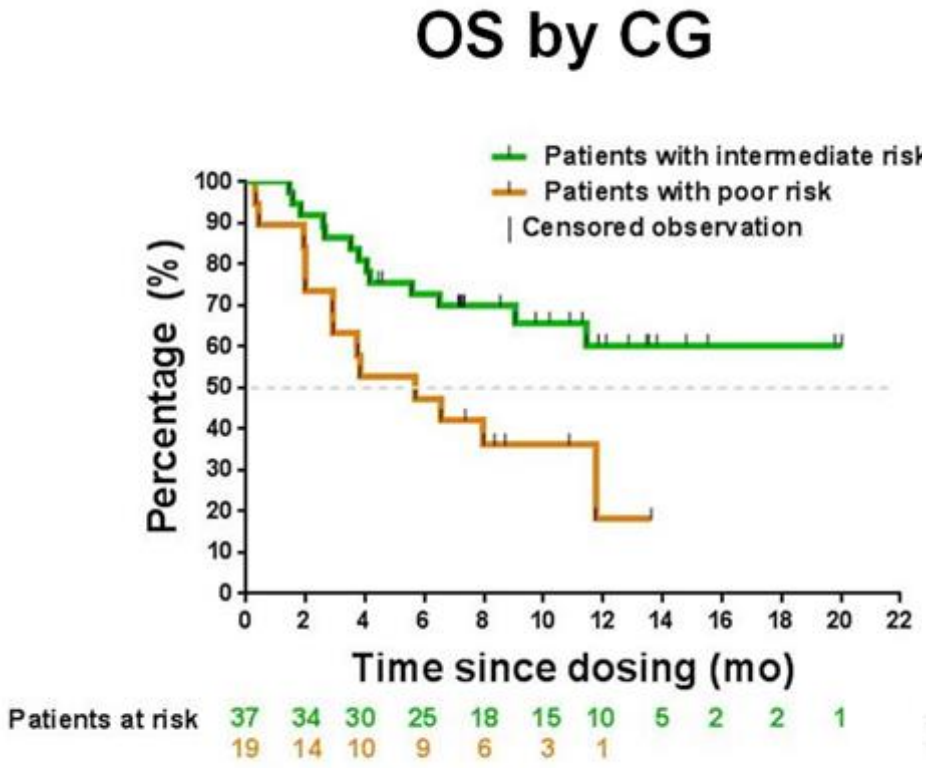
LDAC + venetoclax: Molecular Sub-group Outcomes

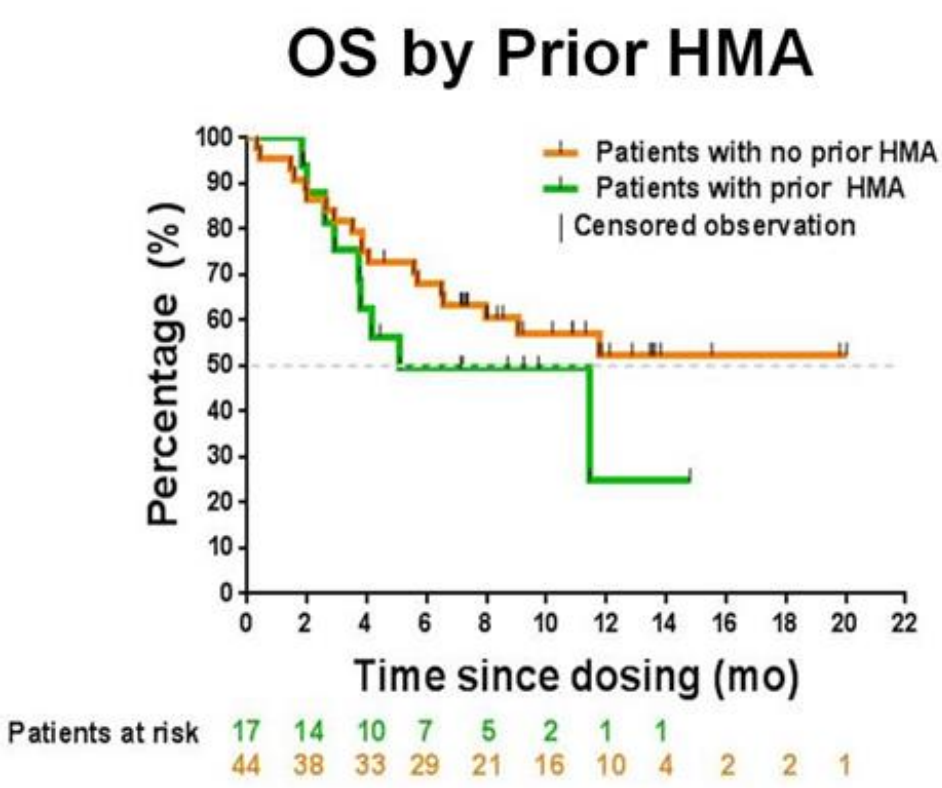
Cytogenetics	ORR (CR + CRi)	Median OS, mo
Intermediate risk n = 37	28 (76%)	15.7
Adverse risk n = 19	9 (47%)	5.7
Molecular Subgroups		
NPM1 n = 7*	7 (100%)	NR
CEBPA^{biallelic} n = 3	3 (100%)	NR
Chromatin-spliceosome n = 22	15 (68%)	11.4
TP53-aneuploidy n = 20	10 (50%)	6.5



*Four of the 7 NPM1 patients have *FLT3* mutations (3: ITD, 1: TKD).

Outcomes According to Cytogenetic Risk and Prior HMA Exposure

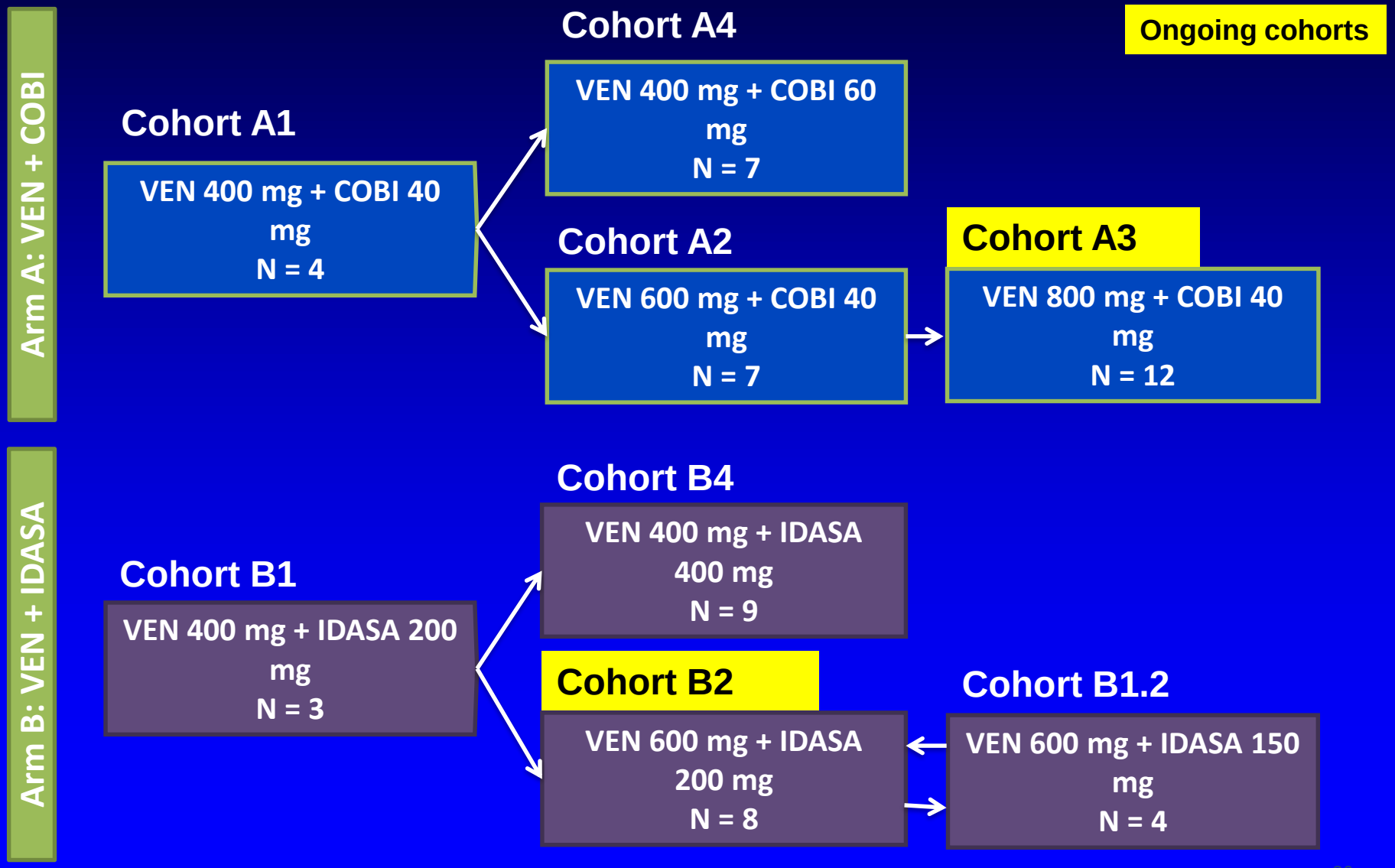




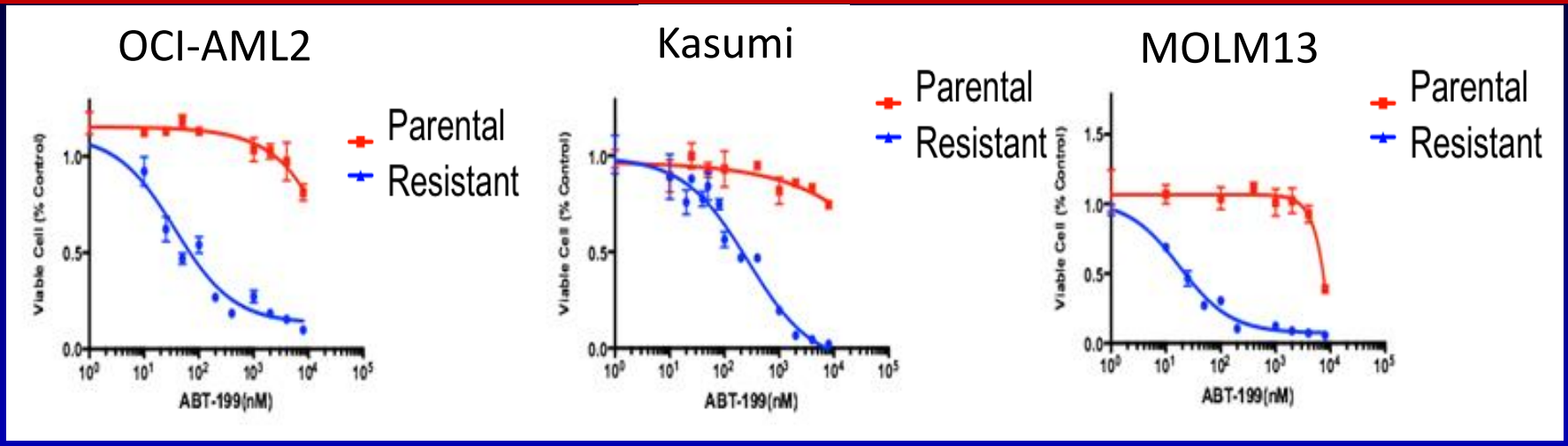
- VEN 600 mg + LDAC is well tolerated in patients ≥65 years with AML
- Early death rates (<30 days) low (3%)
- CR/CRi 62%; median OS approximately 11 months
- A planned, Phase 3 randomized trial has commenced.

Andrew Wei EHA 2017

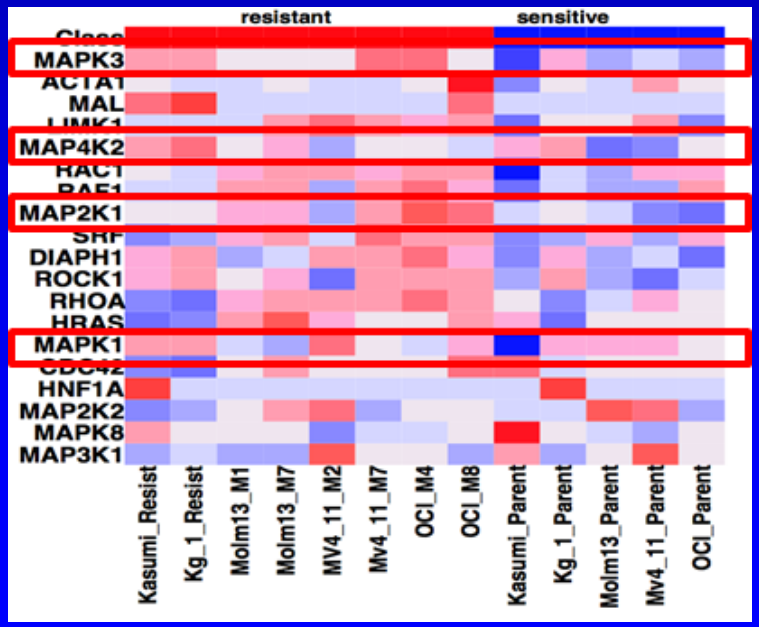
Cohort Dose Escalation Scheme

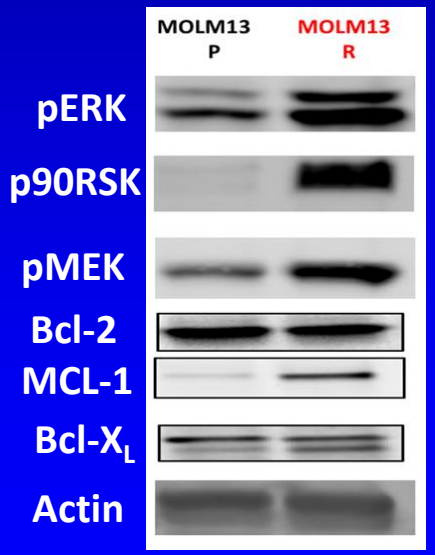


Venetoclax-Resistant AML Cell Lines: Activated MAPK and Increased MCL-1

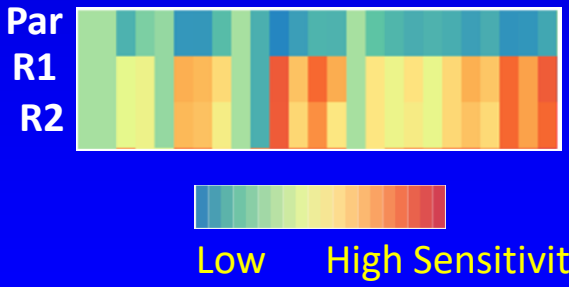


RNAseq ABT Sensitive/Resistant



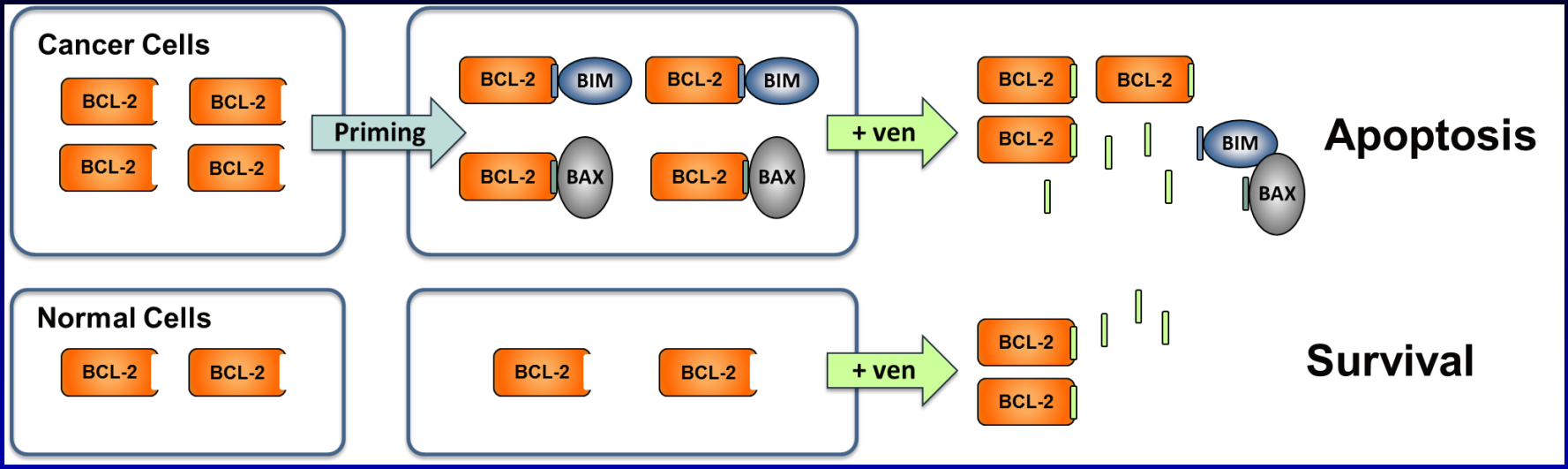


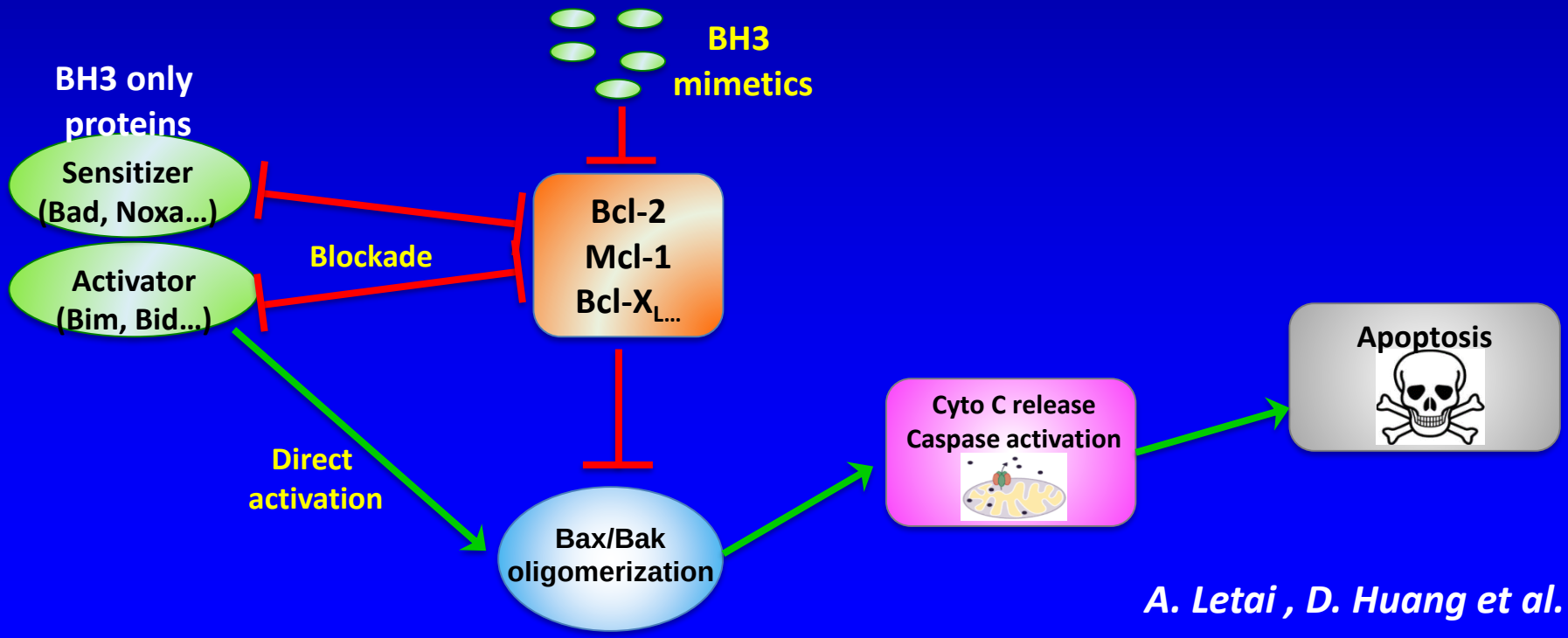
MAPK Inhibition Scores (screen, J. Tyner OHSU)



Qi Zhang

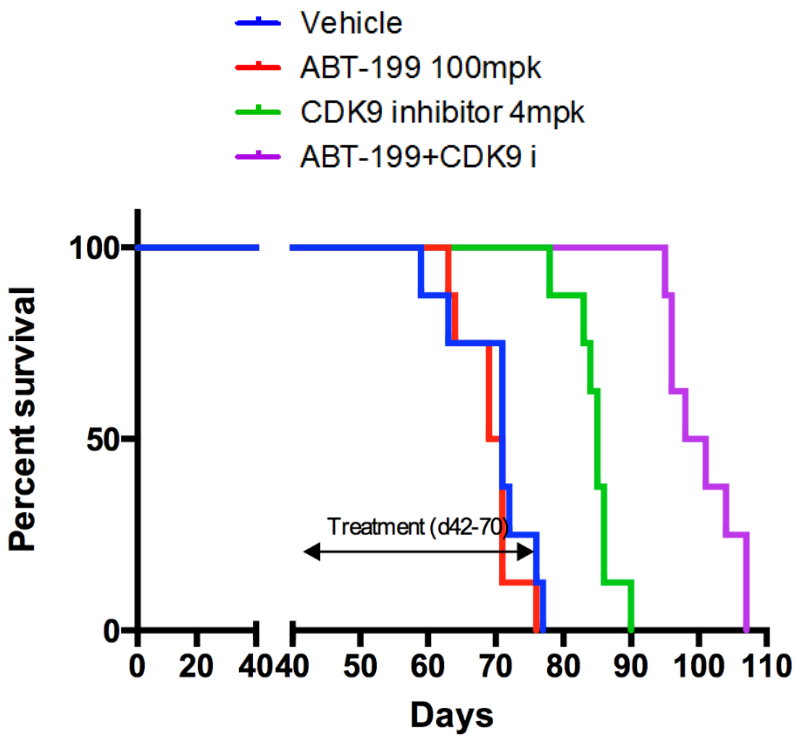
The Bcl-2 Apoptotic Switch in AML Therapy



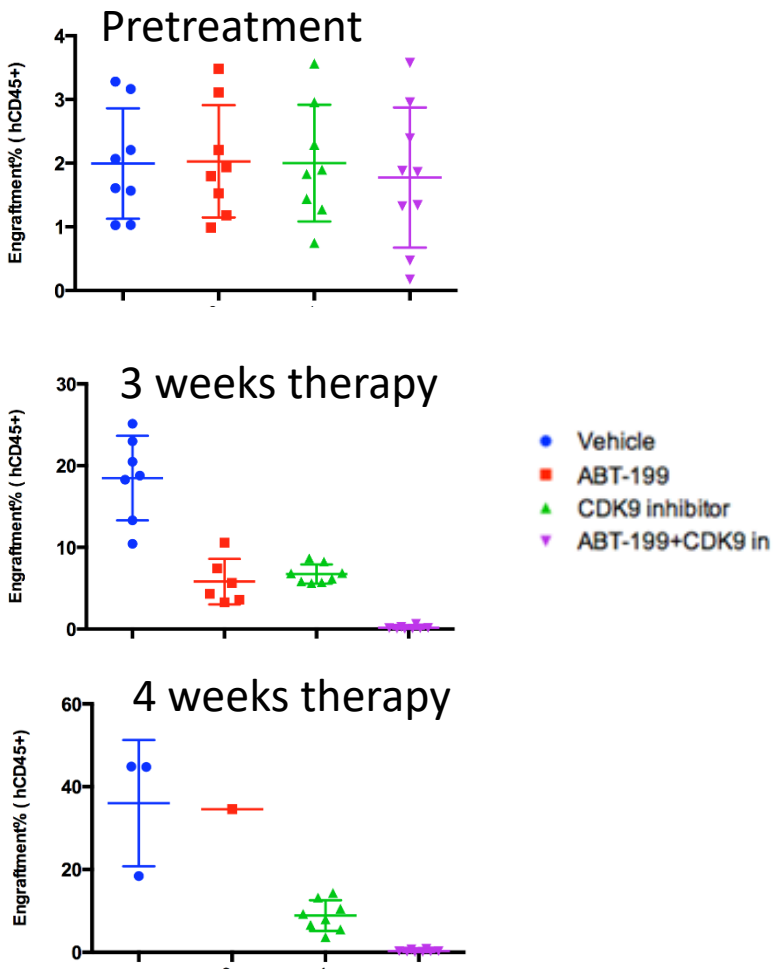


A. Letai , D. Huang et al.

Combination of ABT-199 and CDK9 Inhibitor Efficacy in FLT3-mut AML PDX in vivo



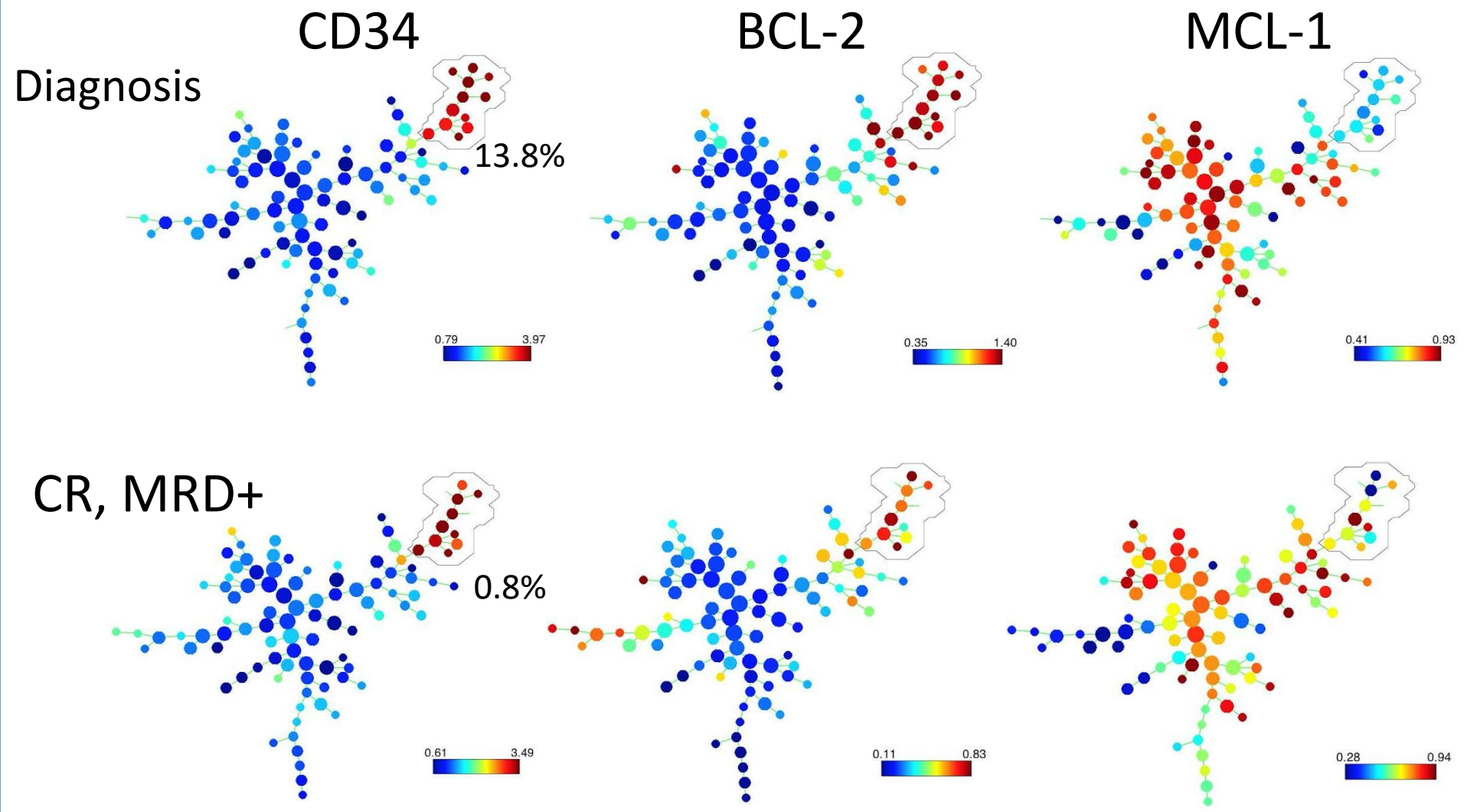
AML PDX 4095636
FLT3-ITD, DNMT3A, IDH1, NPM1



4 weeks treatment
ABT-199 100mpk qd PO QD
CDK9 inhibitor 4mpk PO BIW

Qi Zhang

Bcl-2 is highly expressed in AML MRD cells



CyTOF analysis
Lina Han