中國醫藥大學附設醫院
China Medical University Hospital

臨床Bcl2 抑制劑用於 AML和CLL的治療價值

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Outline

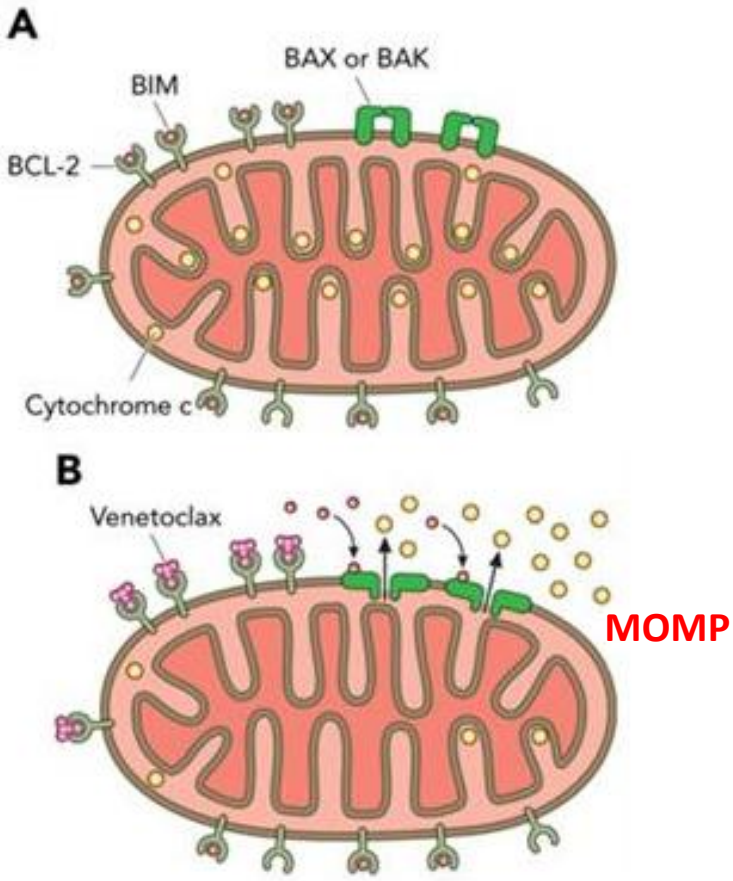
Introduction of Anti-/Pro-apoptotic Proteins

- Basic science introduction

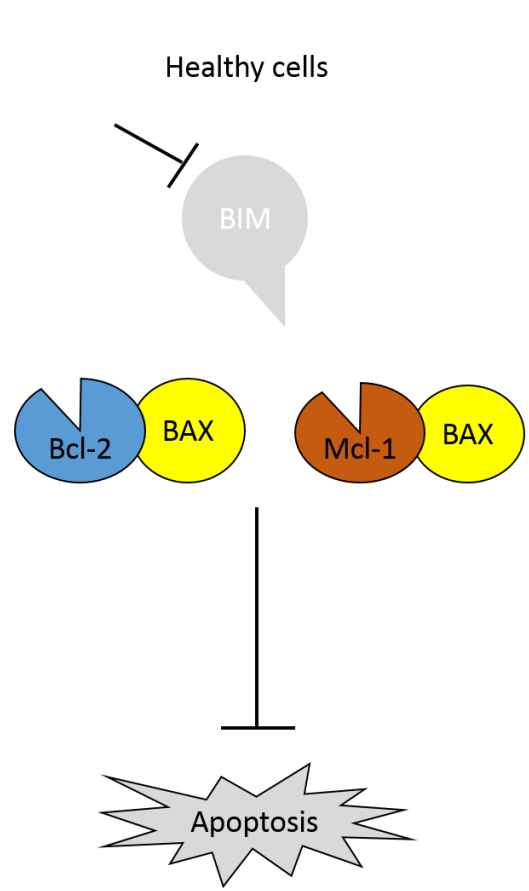
Bcl2 inhibitor (Venetoclax) for AML and CLL

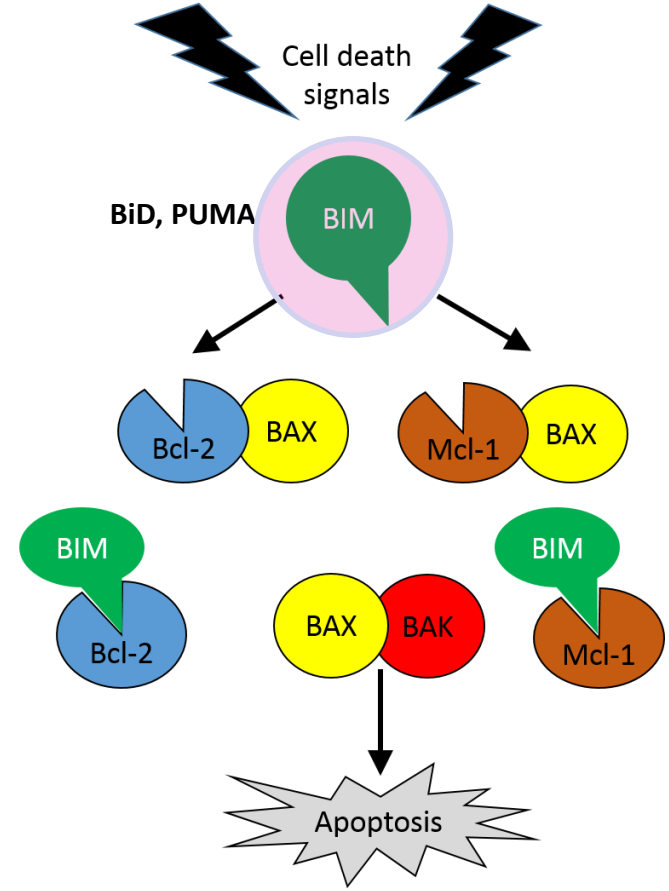
- Data review
- CMUH experience

Anti-/Pro-apoptotic Proteins



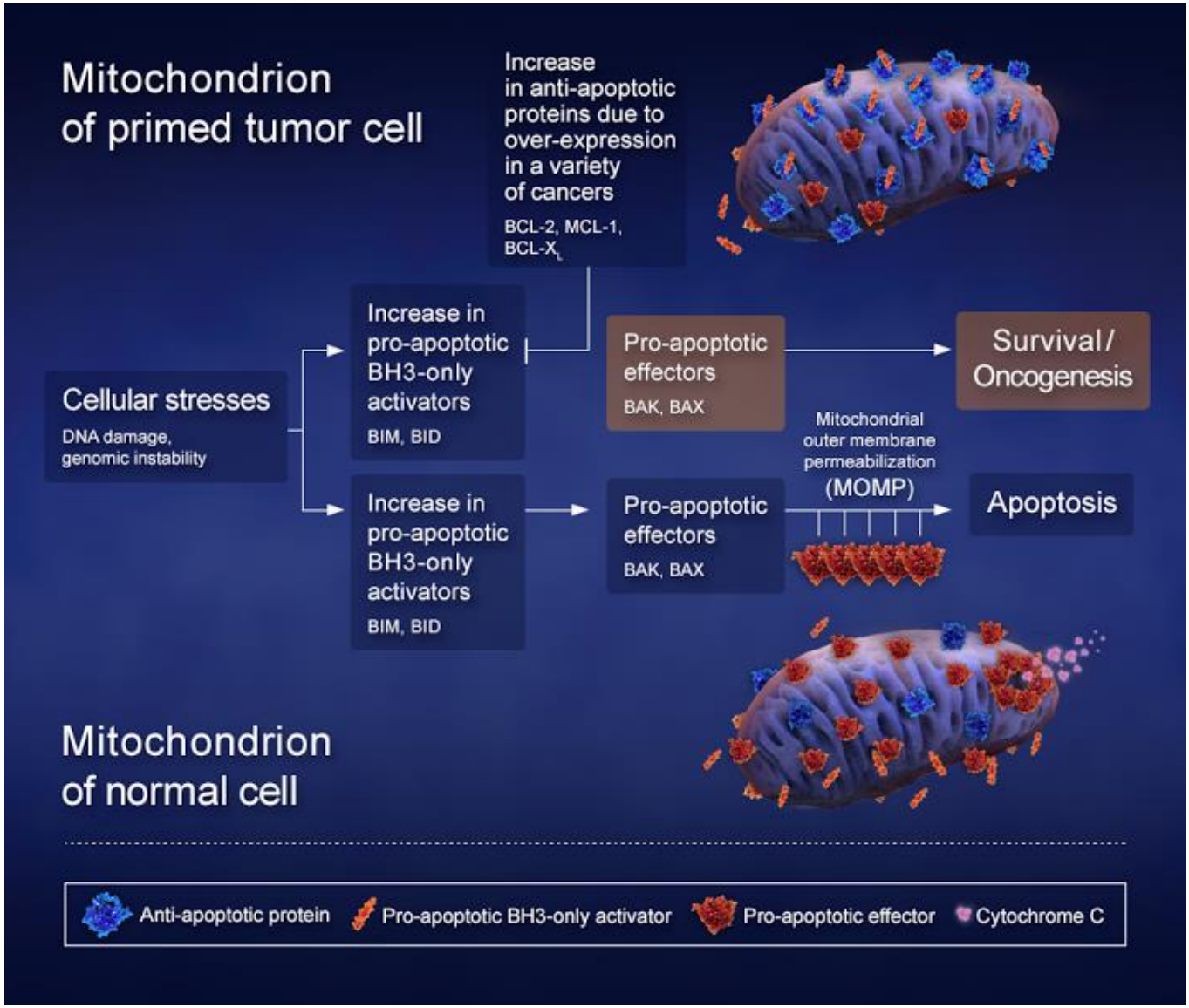
MOMP: Mitochondria outer membrane permeabilization

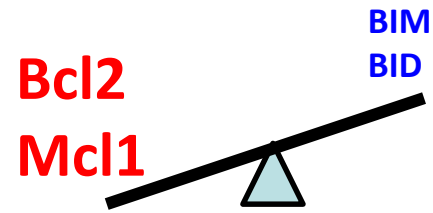


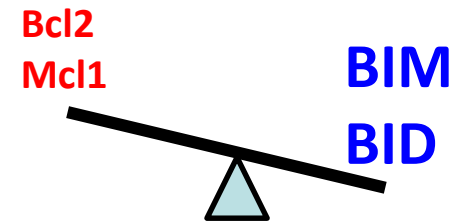


Blood (2018) 132 (10): 1007–1012

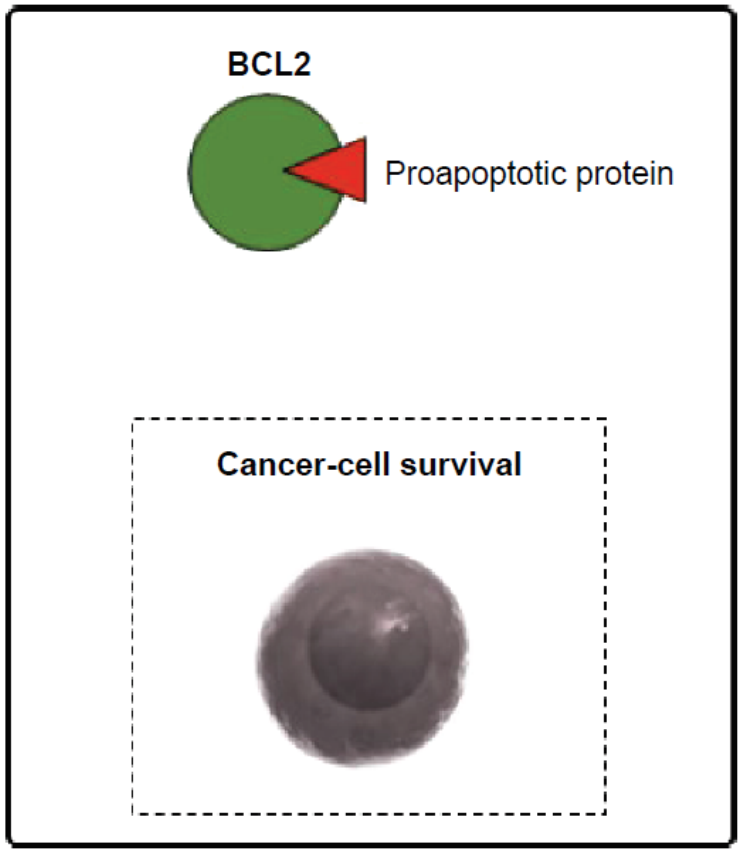
Normal Cells vs Cancer Cells



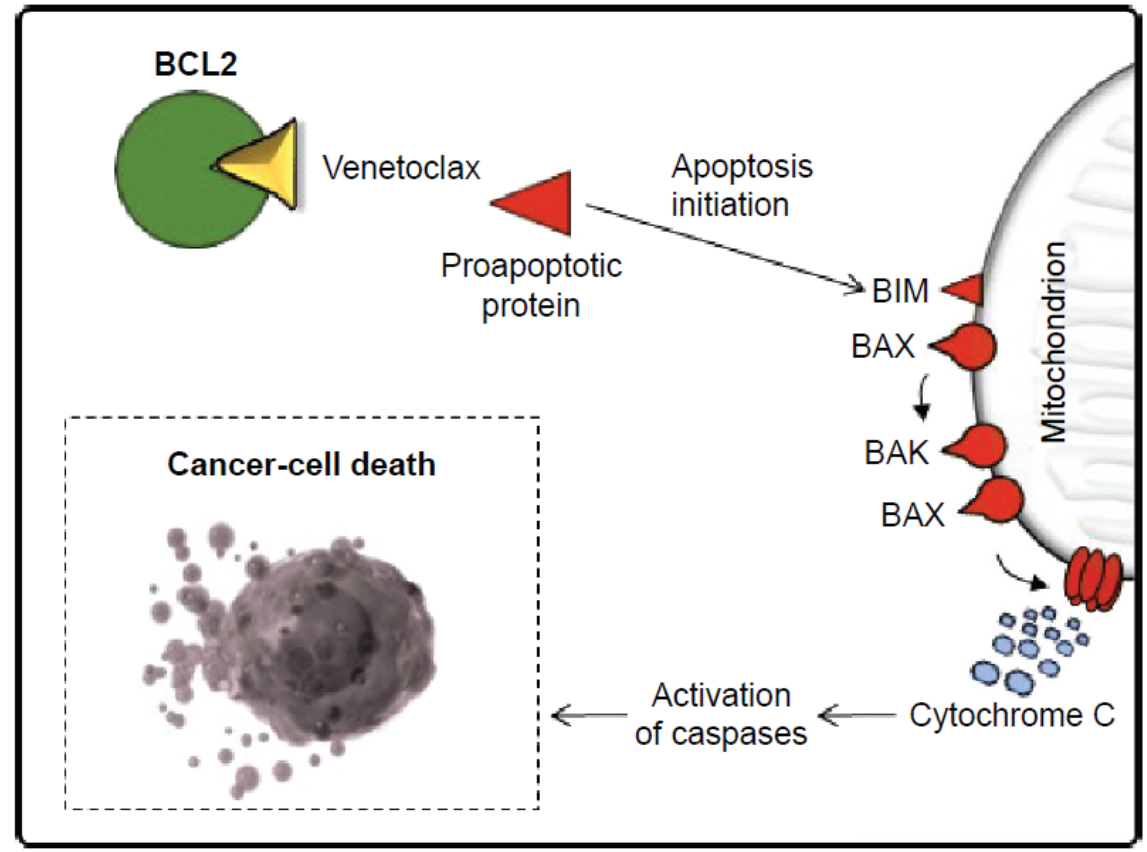




Venetoclax: Mechanism



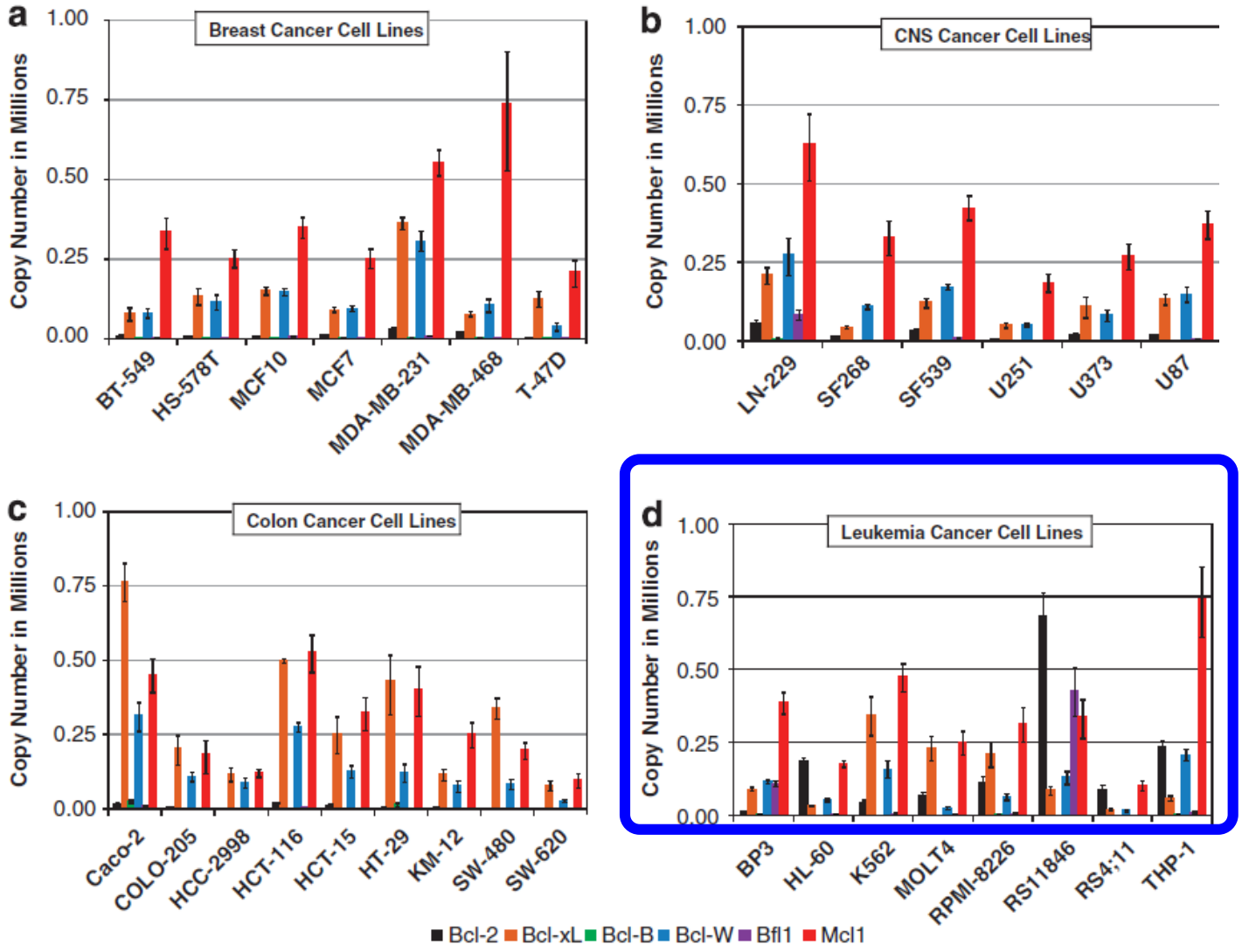
Under BCL2 overexpression cancer cells evade apoptosis by sequestering proapoptotic proteins



Venetoclax selectively binds to BCL2 and liberates proapoptotic proteins that initiate apoptosis

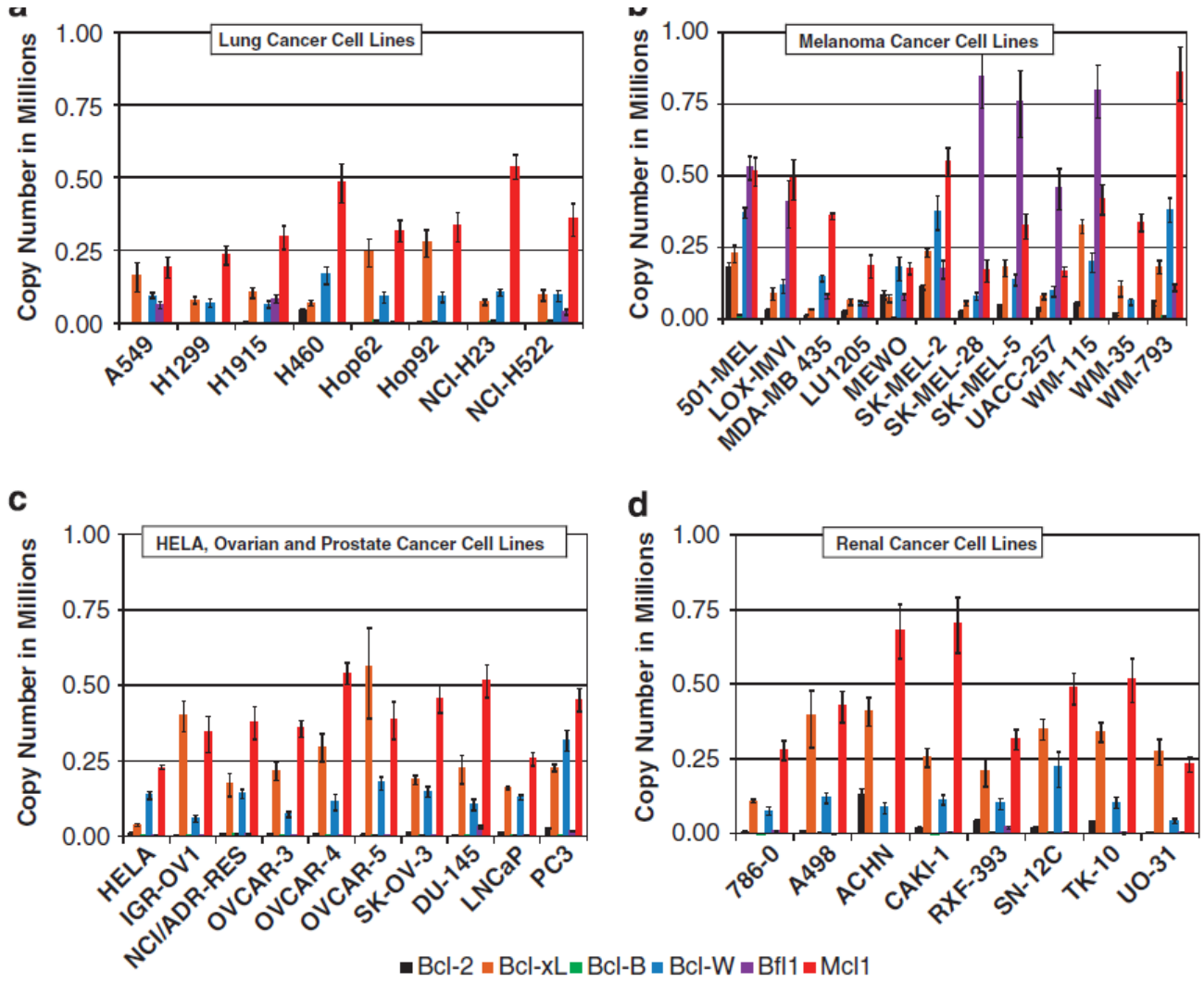
OncoTargets and Therapy 2017:10

Expression of Bcl2 family in Cancers



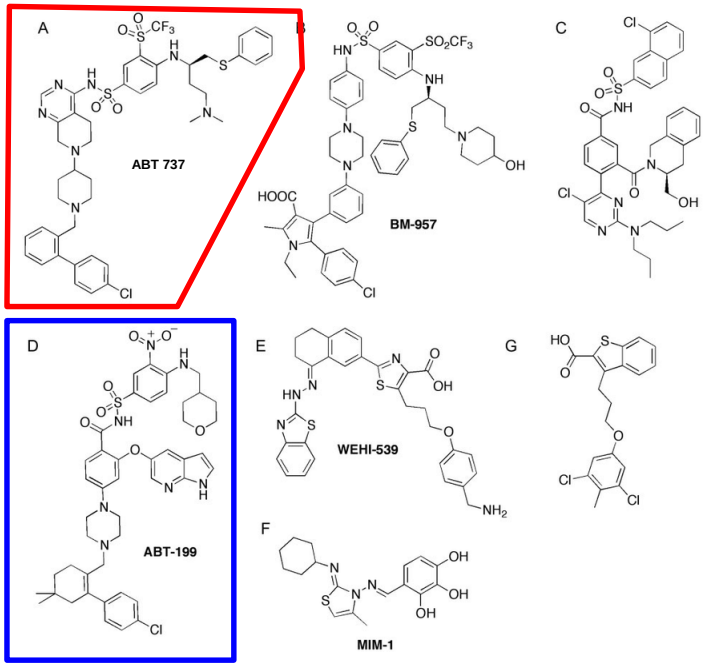
Cell Death and Disease (2010) 1, e40; doi:10.1

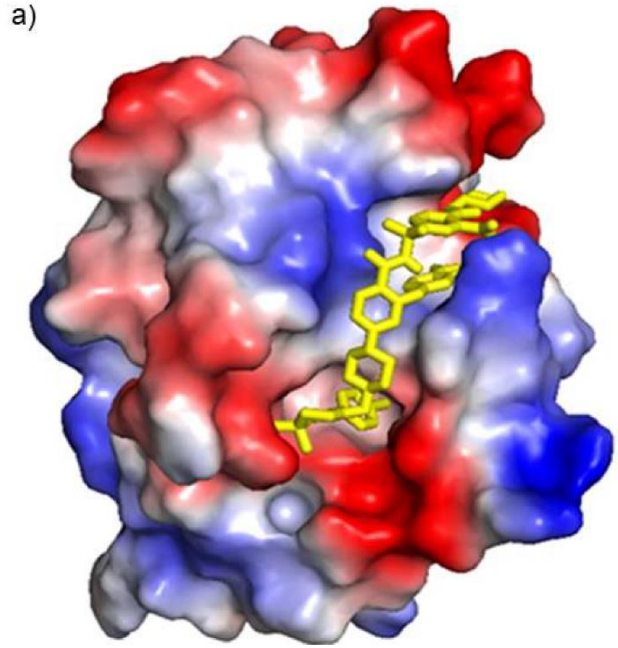
Expression of Bcl2 family in Cancers

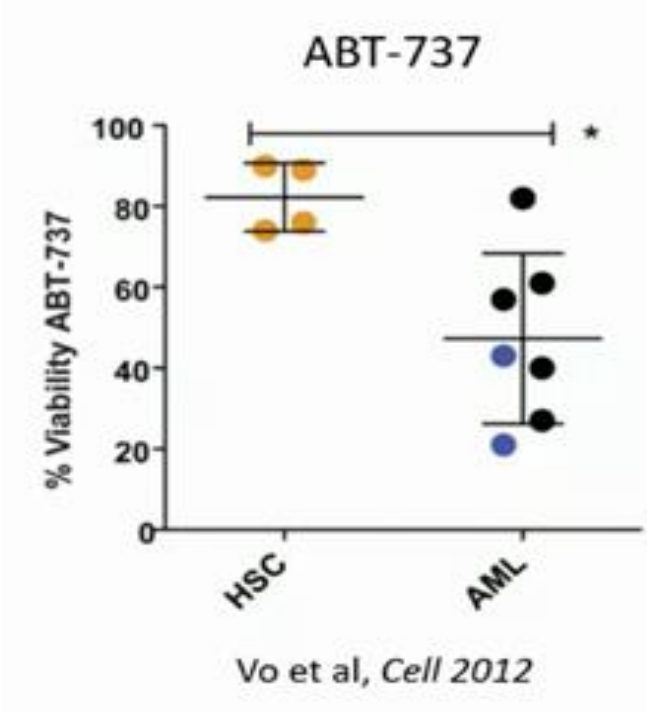


Cell Death and Disease (2010) 1, e40; doi:10.1

BH3 Mimetics & Bcl-2/Bcl-X_L Interaction







ABT-737/ABT-263: Bcl-2/Bcl-X_L inhibitor ➔ severe thrombocytopenia due to Bcl-X_L inhibition

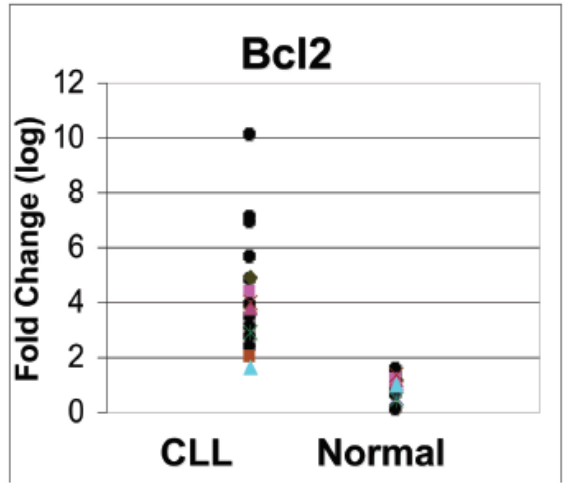
ABT-199: Selective Bcl-2 inhibitor ➔ Venetoclax

Bcl2 Expression in CLL

A

Chip	Fold	T-Test
U133	20.02	4.21E-06
U133	14.19	5.46E-14
U133	7.51	3.01E-05
U95	3.88	3.14E-07
U95	3.12	2.85E-05
U95	2.22	4.59E-05

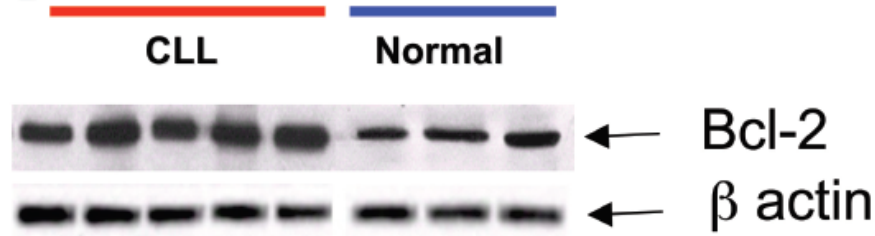
B



C

QPCR	Fold	n
Bcl2	5.53	36

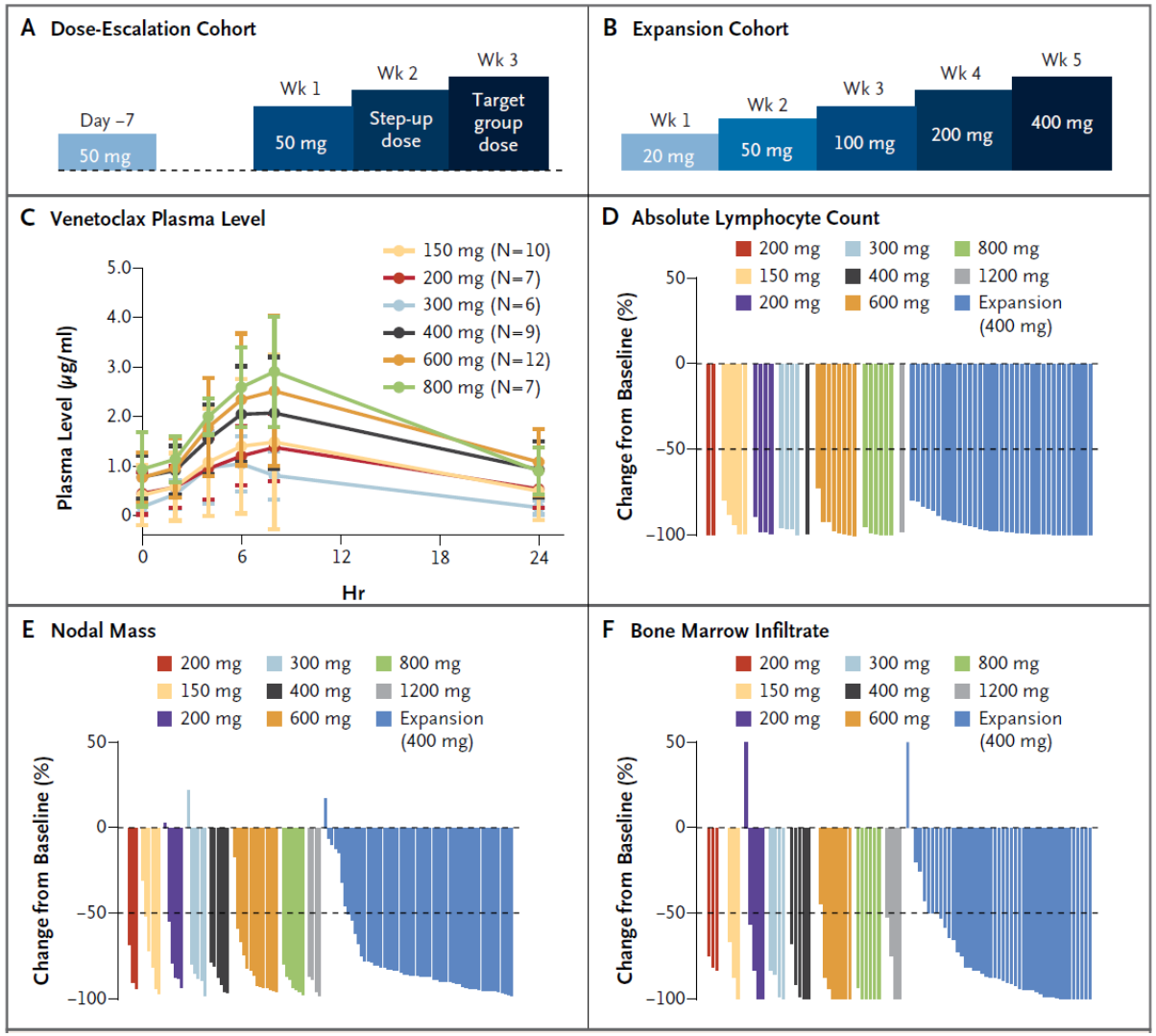
D



Mol Med 2008, 14 (9 - 10): 618 - 627

Venetoclax for RR-CLL

Phase 1: Dose escalation phase + Expansion cohort



3+3 design initially

Why changed to “Intra”-patient dose escalation protocol?

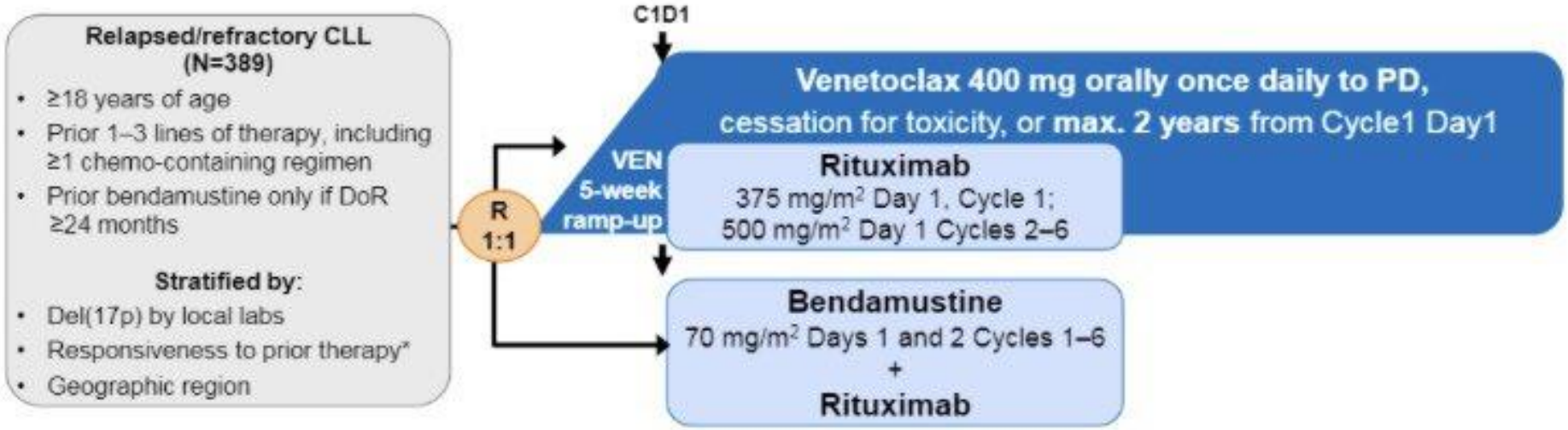
All the first 3 patients had laboratory evidence of tumor lysis!

In the dose escalation cohort, 2 died of TLS!

N Engl J Med 2016;374:311-22

Venetoclax-R vs Bendamustine-R for RR-CLL

MURANO Study Design (V ~ "fixed duration" 2Y)

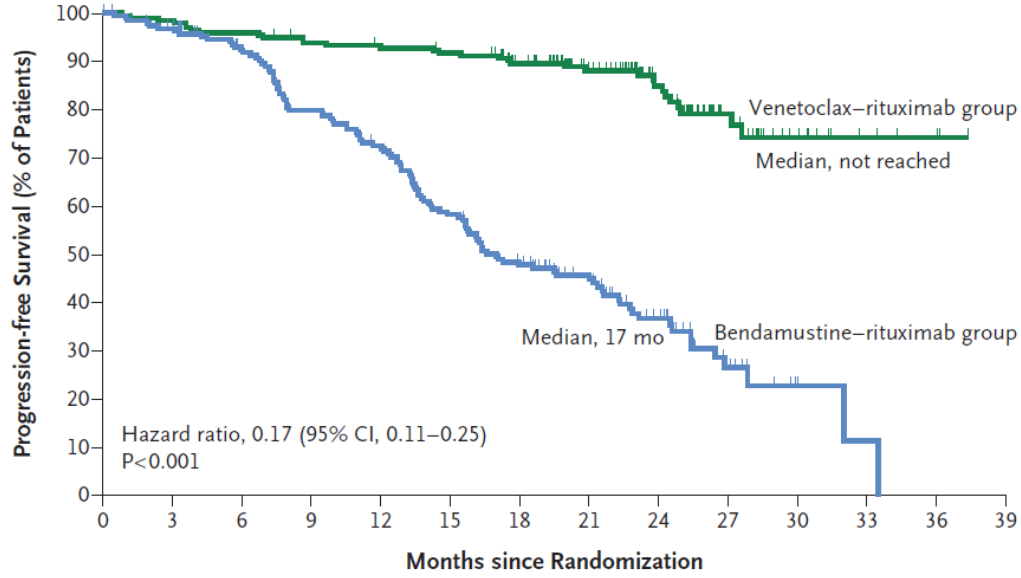


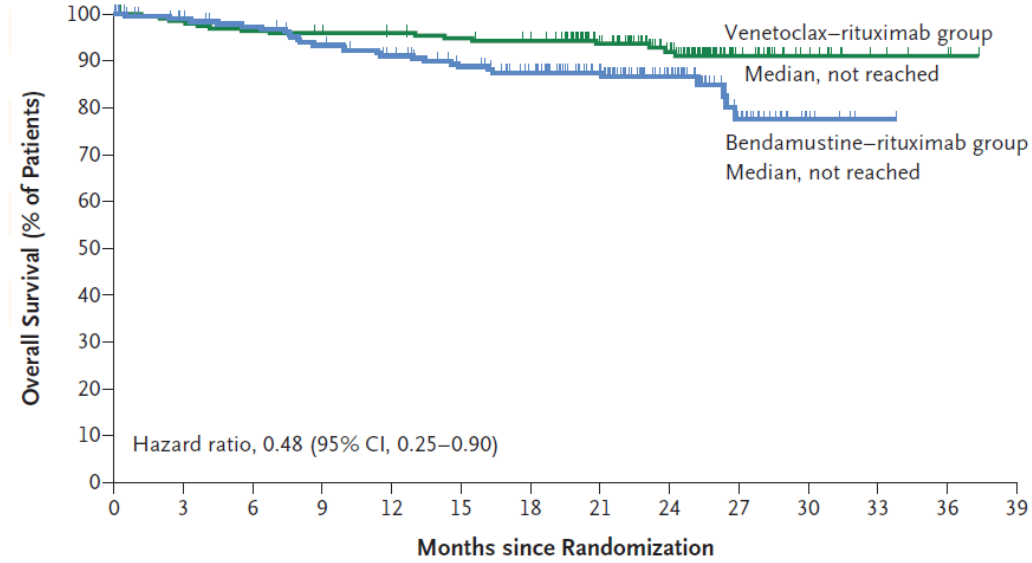
Primary Endpoint	INV-assessed PFS
Major Secondary Endpoints	• IRC-CR ⇒ IRC-ORR ⇒ OS (hierarchical testing) • IRC-assessed PFS and MRD-negativity
Key Safety Endpoints	Overall safety profile, focusing on serious adverse events and Grade ≥3 adverse events
Interim Analysis	Approximately 140 INV-assessed PFS events (75% of total information)

NCT02005471

*High-risk CLL – any of following features: del(17p) or no response to front-line chemotherapy-containing regimen or relapsed ≤12 months after chemotherapy or within ≤24 months after chemoimmunotherapy.

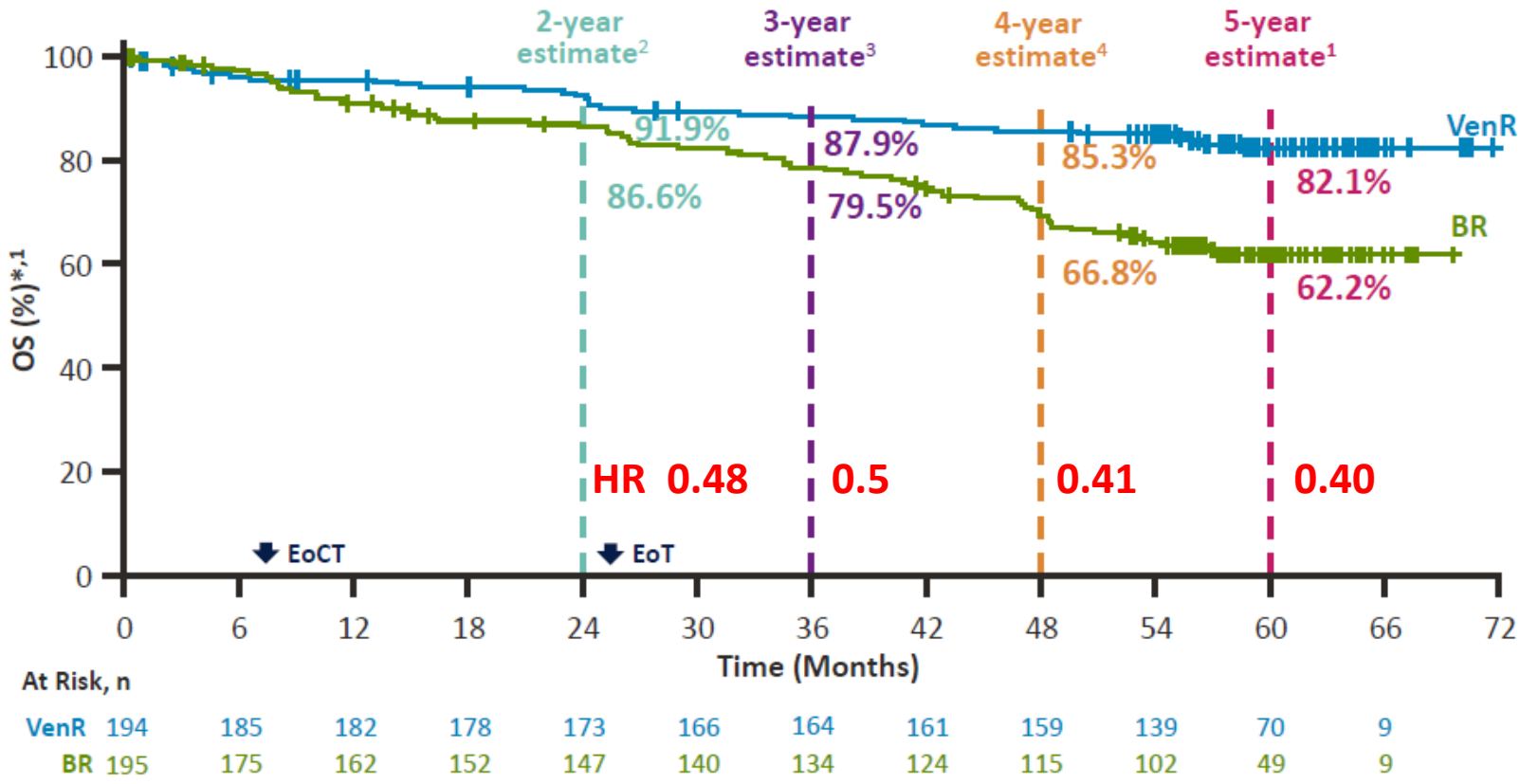
VR vs BR for RR-CLL





N Engl J Med 2018;378:1107-20

MURANO 5Y F/U: OS (ITT)

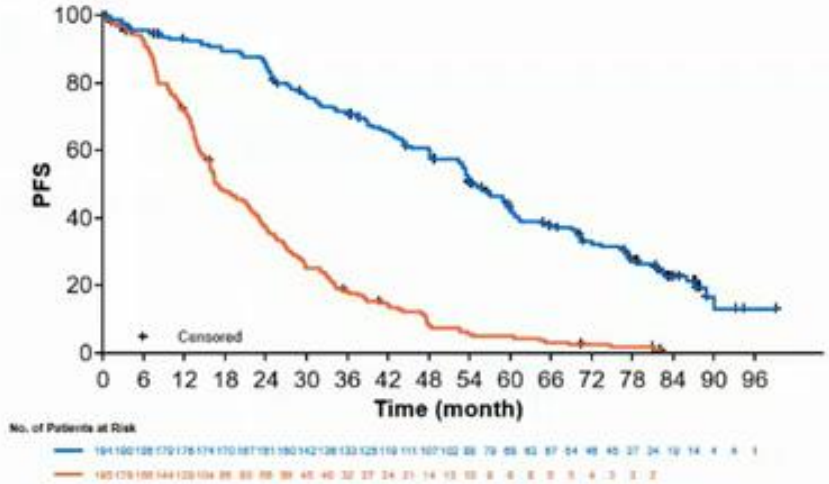


BR → 80% novel agent after PD, OS remains inferior to VR

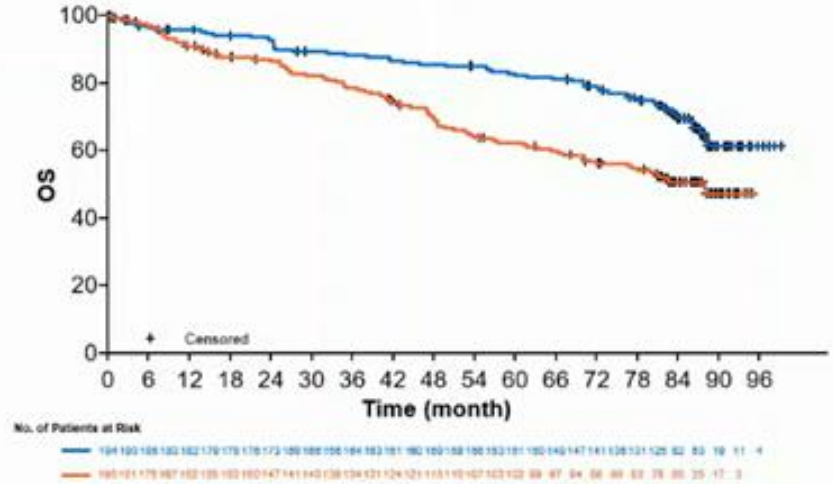
ASH 2020, abstract 125

PFS and OS benefits with VenR over BR were sustained at 7 years

	Median PFS (95% CI), months	HR* (95% CI)	7-year PFS (%)
VenR (n=194)	54.7 (52.3–59.9)	0.23 (0.18–0.29) Stratified P-value <0.0001†	23.0
BR (n=195)	17.0 (15.5–21.7)		NE



	Median OS (95% CI), months	HR‡ (95% CI)	7-year OS (%)
VenR (n=194)	NE	0.53 (0.37–0.74) Stratified P-value <0.0002†	69.6
BR (n=195)	87.8 (70.1–NE)		51.0



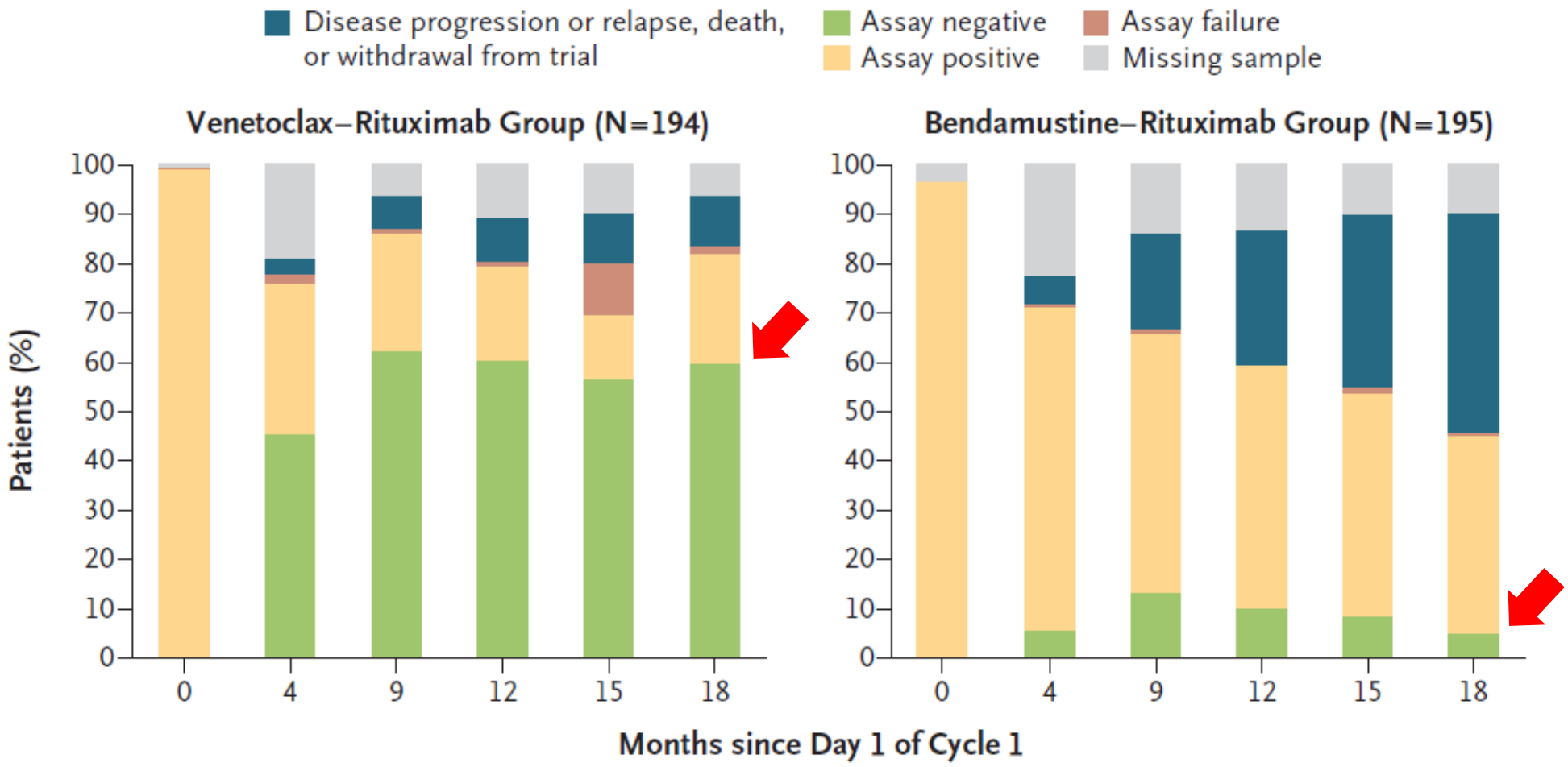
- Median follow up for efficacy (range) was 86.8 months (0.3–99.2) for VenR and 84.4 months (0.0−95.0) for BR
- No new safety signals were identified since the 5-year data cut,[1] with all patients outside of the AE reporting window§

*Stratified HR is presented, unstratified HR=0.25. †P-values are descriptive only. ‡Stratified HR is presented, unstratified HR=0.54. §All AEs were reported until 28 days after the last dose of Ven or 90 days after last dose of R, whichever was longer. After this, only deaths, serious AEs, or AEs of concern that were believed to be Ven-related were reported. AE, adverse event; CI, confidence interval; HR, hazard ratio; NE, not estimable.

1. Seymour JF, et al. Blood 2022;140(8):839–50.

Arnon Kater, et al. 2023 EHA

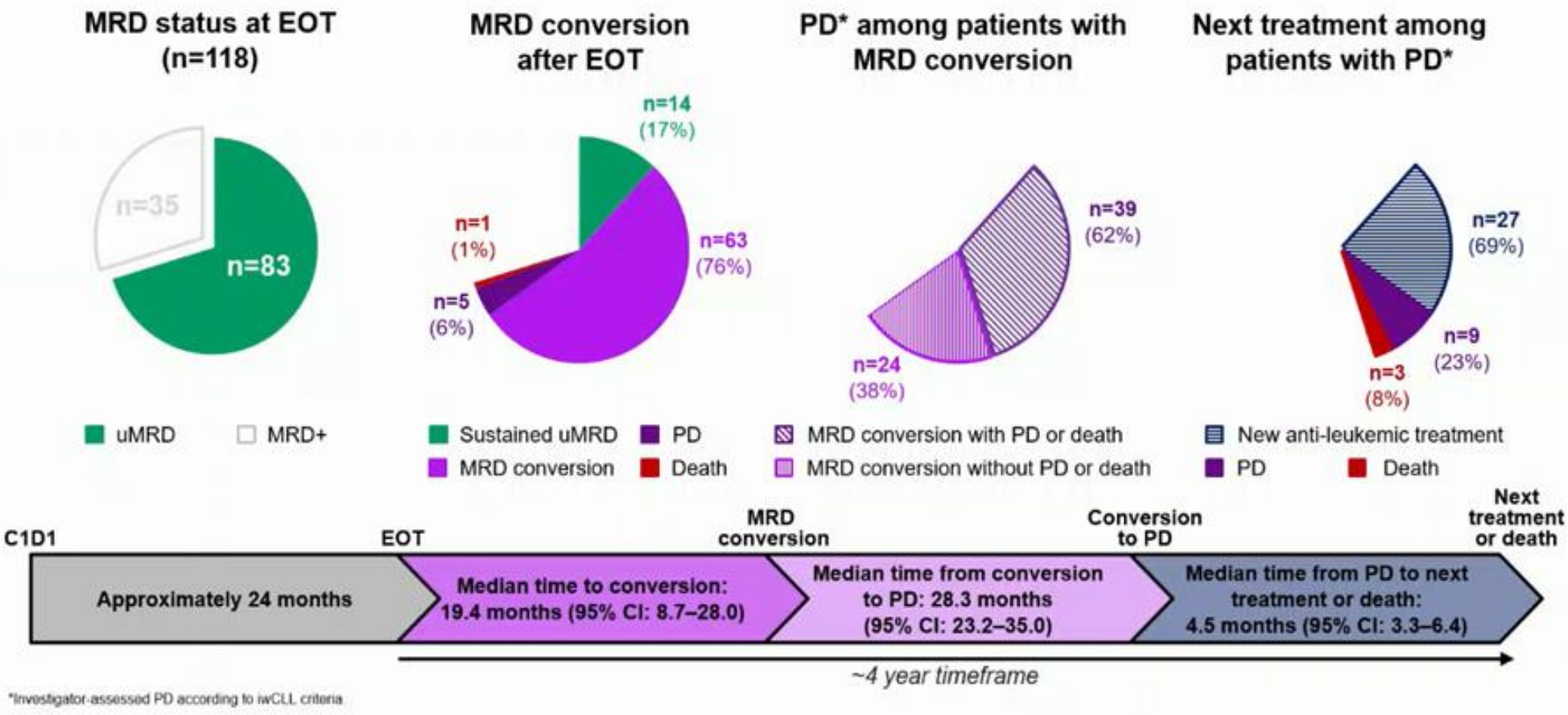
VR vs BR for RR-CLL



MRD negativity (PB) at M18: 60% vs 5%

N Engl J Med 2018;378:1107-20

Most patients who received the full 2 years of VenR treatment had uMRD at EOT; generally MRD conversion with subsequent PD did not occur until ~4 years post EOT



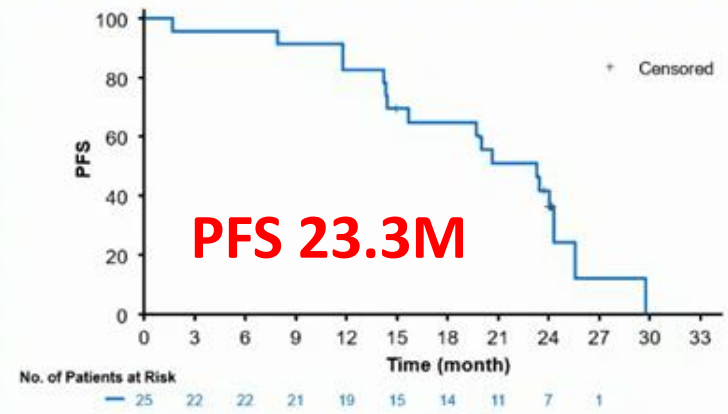
Arnon Kater, et al. 2023 EHA

MURANO retreatment/crossover substudy

- Amongst VenR-retreated patients, median follow up (range) was 33.4 months (2.7–44.0)
  - Median PFS (95% CI) was 23.3 months (15.6–24.3)
  - Best ORR was high at **72%** CR rate was 24%
  - Median OS was not reached

Response rates indicate that VenR retreatment is a viable option for pretreated patients

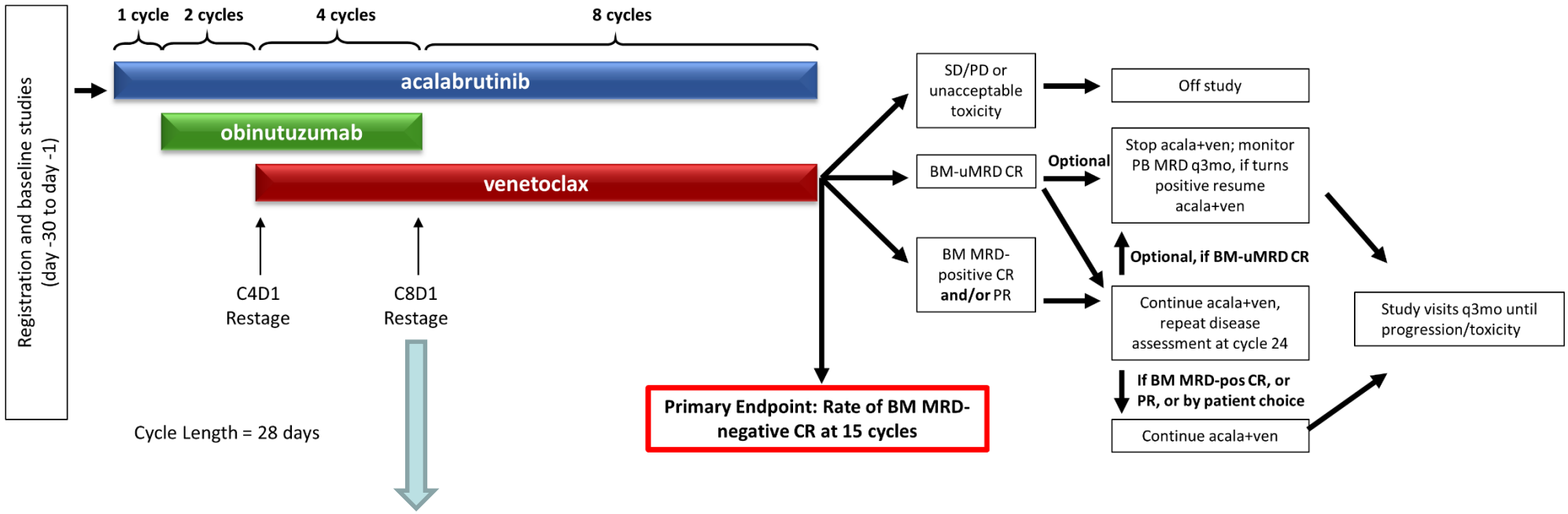
PFS for VenR-retreated patients in the substudy



Arnon Kater, et al. 2023 EHA

CLL 1st Line Rx: Phase 2 Acalabrutinib + G + V

Cytoreduction
Prevent TLS



25%CR, 75% PR;
65% PB, 50% BM
8 color F-MRD(-)

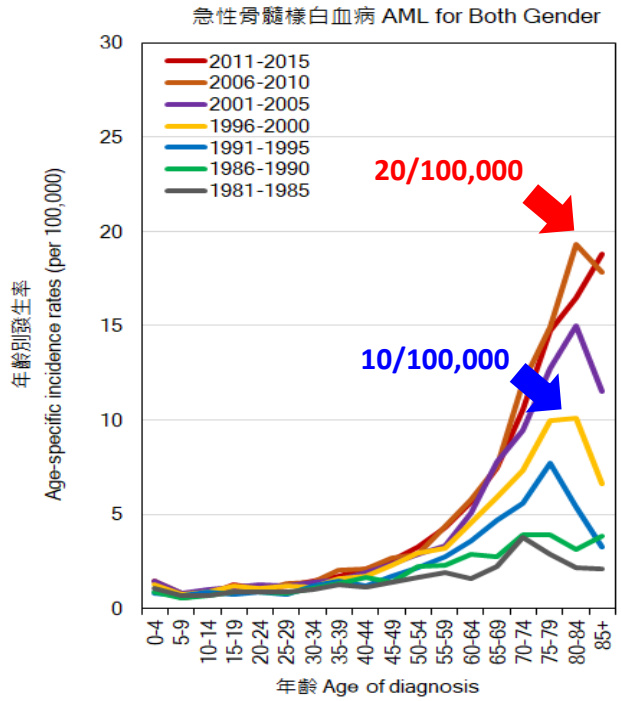
- **Very effective, with early response**
- **Del17p also good!**
- **32% Gr.3/4 neutropenia; 22% IRR**
- **5% TLS (after O; no TLS after V)**

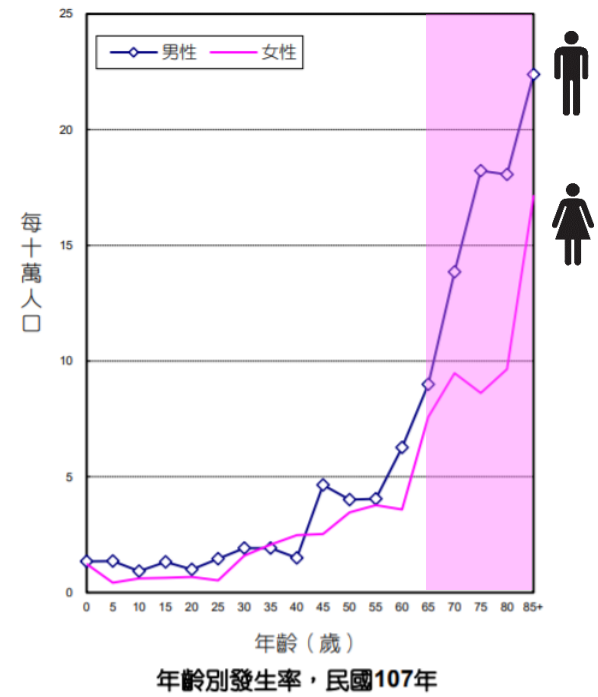
Summary 1

Venetoclax for CLL

- Fixed duration treatment possible
- Very high response rate and survival rate
- Re-treatment OK

AML in Taiwan





年齡別發生率，民國107年

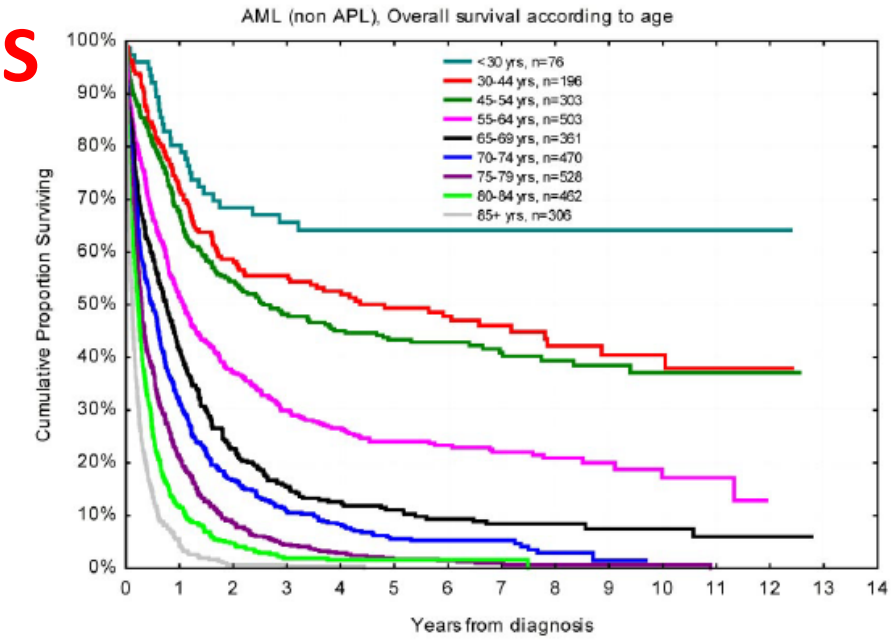
- 859 newly diagnosed AML in 2018, Median age at diagnosis: 63 (M) and 63 (F)
- Age-adjusted incidence rate: 2.62/100,000 (UK 5.2/100,000; US 4.3/100,000)

Taiwan Cancer Registry 2018

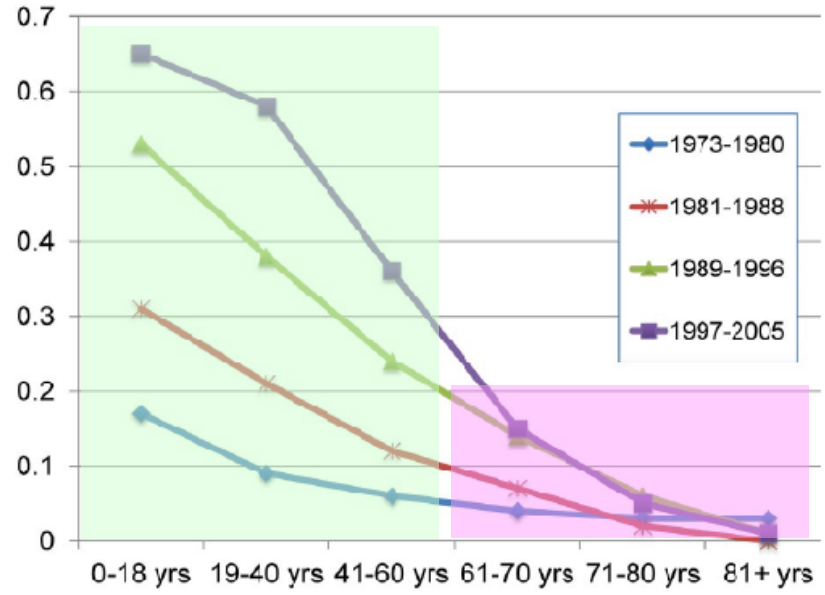
Elderly AML: Unmet Medical Need

Swedish acute leukemia registry; Dx in 1997 to 2006, F/U in 2008/12

OS



5YS



Blood. 2012; 119(17):3890-3899

Unexpected Bonus!!!

blood®

Blood Spotlight

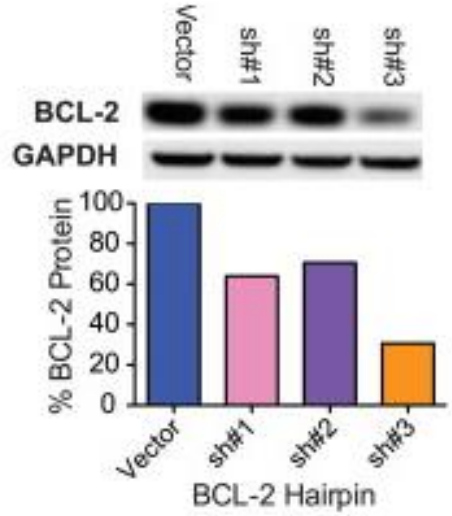
BCL-2 inhibition in AML: an unexpected bonus?

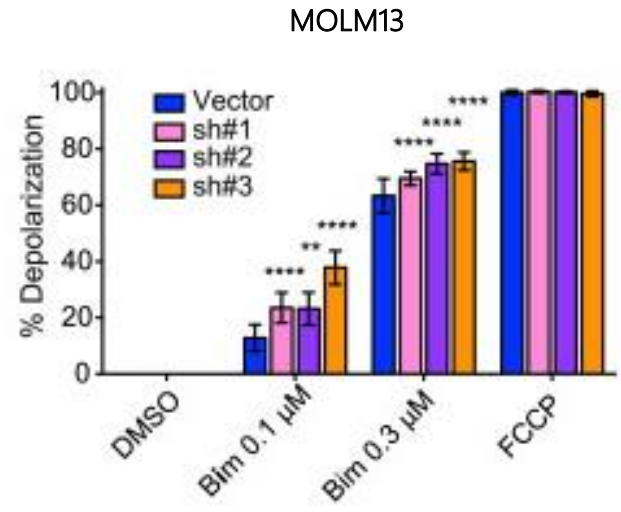
Marina Konopleva[1] and Anthony Letai[2]

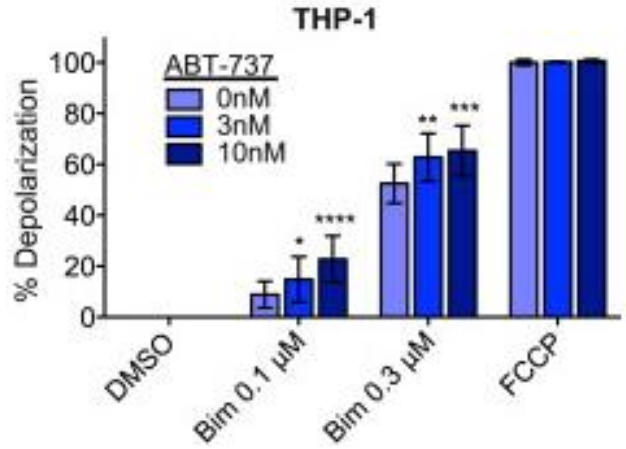
[1]The University of Texas MD Anderson Cancer Center, Houston, TX; and [2]Dana-Farber Cancer Institute, Boston, MA

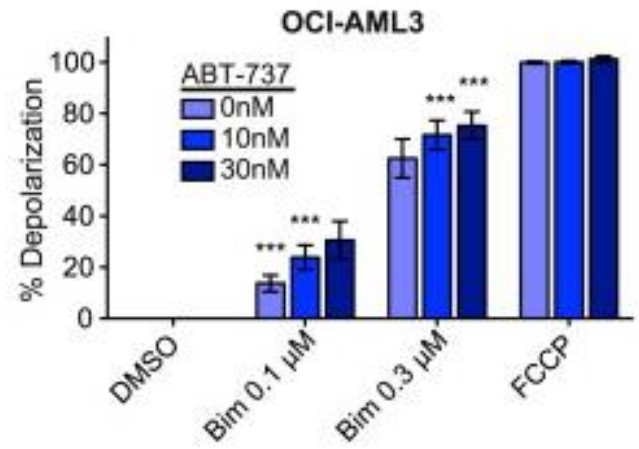
B-cell lymphoma 2 (BCL-2) was discovered at the breakpoint of the t(14;18) in follicular lymphoma >30 years ago. Although inhibition of BCL-2 first proved valuable in lymphoid malignancies, clinical progress in myeloid malignancies lagged. Here, we summarize the basic biology and preclinical results that spurred clinical BCL-2 inhibition in acute myeloid leukemia (AML). Response rates and toxicity for venetoclax in combination with standard AML agents, such as azacitidine, decitabine, and low-dose cytarabine, compare favorably with conventional induction chemotherapy. Durability of response requires further study. (*Blood*. 2018;132(10):1007-1012)

BH3 Profiling in AML Cell Line









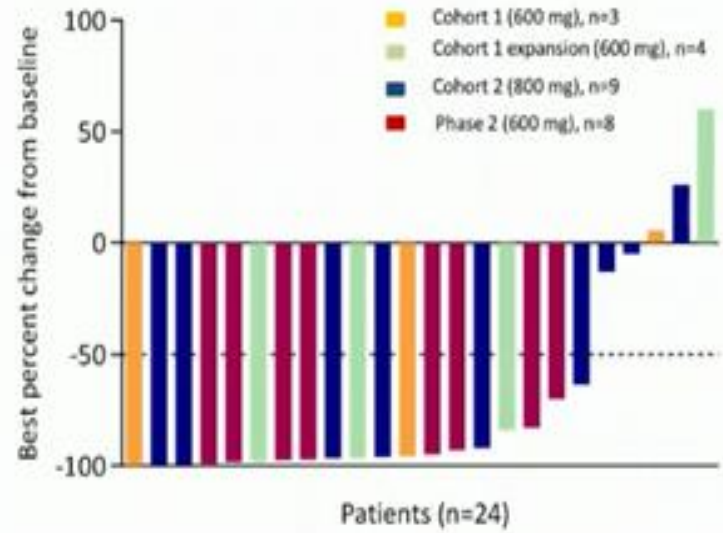
Cell 2012, 151(2): 344-355

Phase 1 Ven/AZA(DEC) and Ven/LDAc

VEN 400-800	VEN +AZA	VEN+DEC
N	16	18
CR/CRi	81%	61%

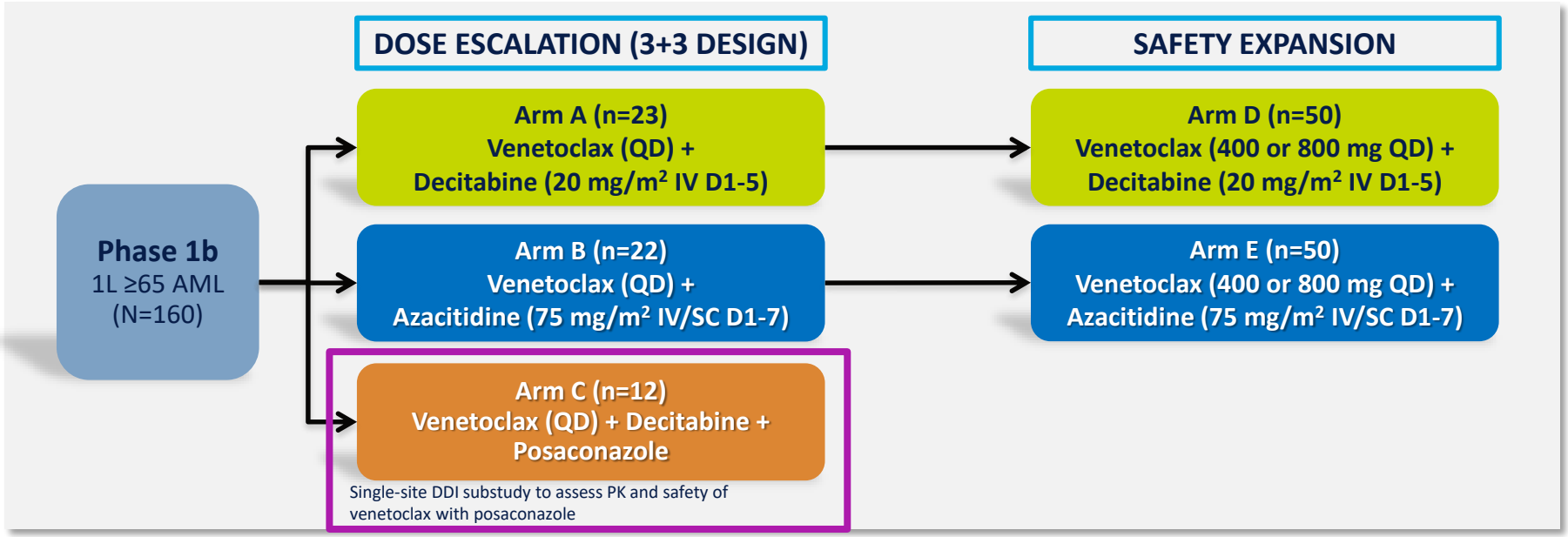
VEN 600	VEN + LDAC
N	26
CR/CRi	58%

Di Nardo et al, ASH 2015



Lin et al, ASCO 2016

M14-358 – Study Design and Endpoints



INCLUSION CRITERIA

- 1L AML (WHO criteria)
- Ineligible for treatment with standard induction regimen
- Intermediate or adverse risk cytogenetics
- ECOG PS 0-2
- No promyelocytic leukemia
- No CNS involvement

OBJECTIVES

Safety: ***Safety, PK, MTD, RP2D***

Efficacy: ***ORR, DOR, TTP, PFS, OS***

Exploratory: ***Predictive Biomarker, MRD(neg)***

1L=First Line. AML=Acute Myeloid Leukemia. CNS=Central Nervous System. D=Day. DDI=Drug-Drug Interaction. DOR=Duration of Response. ECOG PS=Eastern Cooperative Oncology Group Performance Status. IV=Intravenous. MRD(neg)=Minimum Residual Disease Negativity. MTD=Maximum Tolerated Dose. ORR=Overall Response Rate. OS=Overall Survival. PFS=Progression-Free Survival. PK=Pharmacokinetics. QD=Once Daily. RP2D=Recommended Phase 2 Dose. SC=Subcutaneous. TTP=Time To Progression. WHO=World Health Organization.

1. DiNardo CD, et al. Lancet Oncol. 12 Jan 2018. DOI: http://dx.doi.org/10.1016/S1470-2045(18)30010-X.
2. ClinicalTrials.gov. NCT02203773. https://clinicaltrials.gov/ct2/show/NCT02203773. Accessed March 2017.

M14-358 – Baseline Characteristics

Characteristic		Dose-Escalation Phase: Arm A Ven + Dec (n=23)	Dose-Escalation Phase: Arm B Ven + Aza (n=22)	Dose-Expansion Phase: Arm D Ven + Dec (n=50)	Dose-Expansion Phase: Arm E Ven + Aza (n=50)	Total (N=145)
Age, median (range), years		74 (68-85)	75 (65-82)	73 (65-86)	74 (65-86)	74 (65-86)
Age >75 years, n (%)		10 (44)	9 (41)	17 (34)	16 (32)	52 (36)
Male, n (%)		9 (39)	11 (50)	30 (21)	31 (62)	81 (64)
ECOG PS, n (%)	0	2 (9)	4 (18)	12 (24)	14 (28)	32 (22)
	1	17 (74)	14 (64)	30 (60)	29 (58)	90 (62)
	2	4 (17)	4 (18)	8 (16)	7 (14)	23 (16)
Cytogenetics*, n (%)	Intermediate Risk		12 (55)	26 (52)	21 (42)	74 (51)
	Poor Risk		10 (45)	24 (48)	29 (58)	71 (49)
Secondary AML, n (%)			6 (27)	12 (24)	15 (30)	36 (25)
Mutation, n (%)†	*FLT3*			5 (10)	6 (12)	14 (10)
	IDH 1/2		)	5 (10)	7 (14)	22 (15)
	TP53			5 (10)	7 (14)	16(11)
Antecedent hematologic disorder, n (%)		2 (9)	3 (14)	9 (18)	12 (24)	26 (18)
Baseline BM blast count, n (%)	≤50%	13 (56)	15 (68)	32 (64)	32 (64)	92 (63)
	>50%	10 (43)	7 (32)	18 (36)	18 (36)	53 (37)
Baseline median WBC, 10^9/L		2.9	2.2	2.58	2.4	2.5
Hydroxyurea prior to study initiation, n (%)		6 (26)	2 (9)	4 (8)	5 (10)	17 (12)
Median time on study (range), months		**.4**	**–30.0)**	**11.8 (0.2–16.5)**	**9.3 (0.5–16.2)**	**8.9 (0.2–31.7)**

Elderly, 74

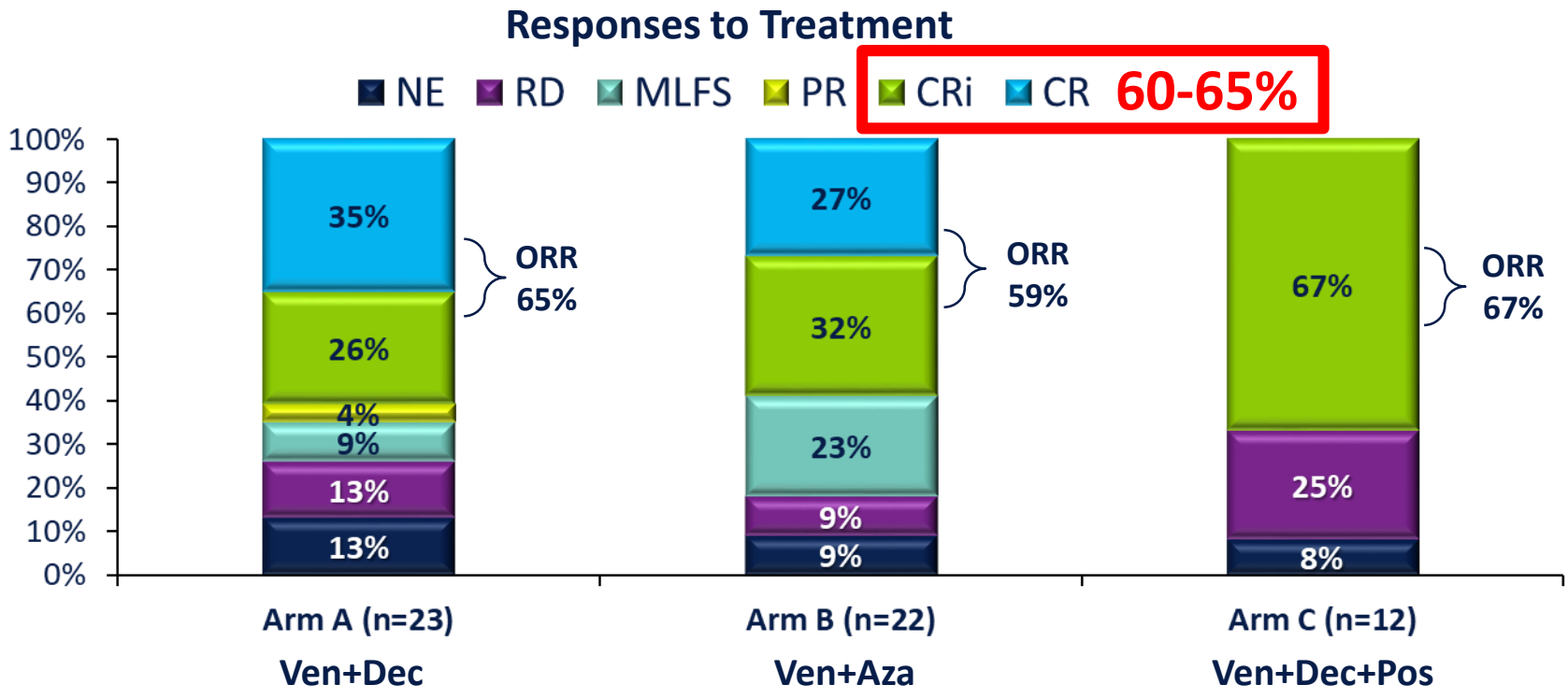
50% poor risk
25% 2nd AML

FLT3ITD, IDH1/2, TP53 mutation included

8.9M on treatment

*NCCN Risk Categorization: Guidelines for AML Version 2.2014. †Site-reported Data, to be confirmed by central laboratory. AML=Acute Myeloid Leukemia. Aza=5-Azacitidine. BM=Bone Marrow. DE=Dose Escalation. Dec=Decitabine. ECOG=Eastern Cooperative Oncology Group. PS=Performance Status. Ven=Venetoclax. WBC=White Blood Cell. DiNardo CD, et al. Poster #2628. 59th ASH Annual Meeting and Exposition; December 9-12, 2017; Atlanta, GA.

M14-358 – Response Rates (Dose Escalation Cohort)



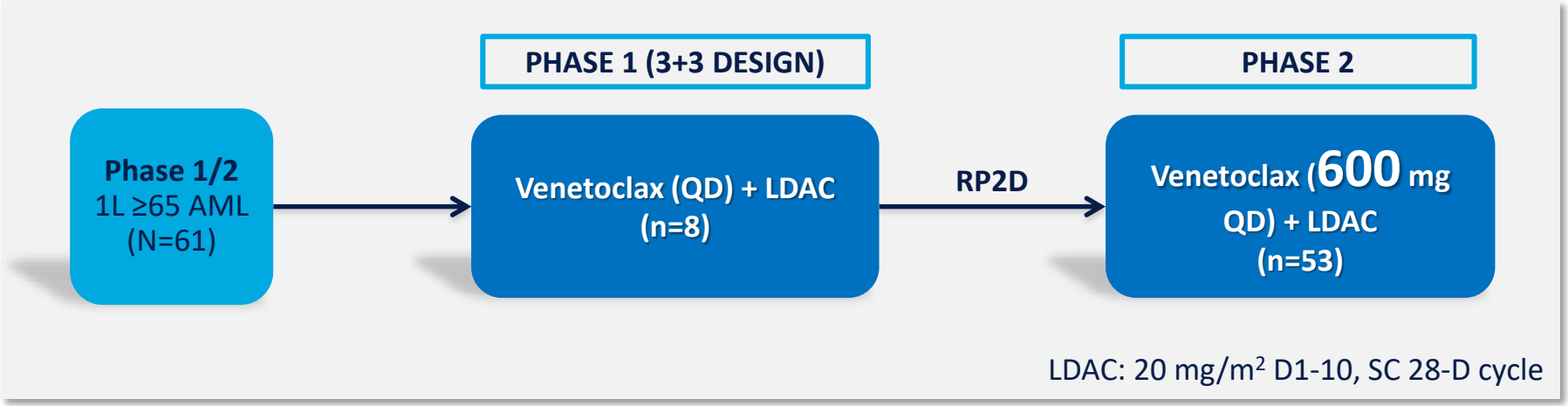
Median time to CR/CRi	**1.0 (0.9-1.8)**	**1.2 (1.0-2.4)**	**0.9 (0.8-1.5) Months**
Median DOR	**8.4 (4.2-NR)**	**12.3 (7.9-12.9)**	**4.3 (1.1-NR) Months**

The proportion of patients achieving an overall response to treatment with venetoclax was similar whether it was given in combination with decitabine or azacitidine.

Data cutoff=June 15, 2016. Aza=5-Azacitidine. CR=Complete Response. CRi=Complete Response with Incomplete Marrow Recovery. DE=Dose Escalation. Dec=Decitabine. DOR=Duration of Response. mo=Month. NE=Not Evaluable. NR=Not Reached. Pos=Posaconazole. PR=Partial Response. RD=Resistant Disease. MLFS=Morphological Leukemia-Free State. Ven=Venetoclax.

DiNardo CD, et al. Lancet Oncol. 12 Jan 2018. DOI: http://dx.doi.org/10.1016/S1470-2045(18)30010-X.

M14-387: Study Design and Endpoints



OBJECTIVES

Safety: ***Safety, PK, MTD, ORR, TPP, RP2D***

Efficacy: ***Response Rates (CR, CRi, PR, MLFS), DOR, OS***

Exploratory: ***Biomarkers Predictive of Outcome***

1L=First Line. AML=Acute Myeloid Leukemia.
CNS=Central Nervous System. CR=Complete Response. CRi=Complete Response with Incomplete Marrow Recovery.
D=Day. DLT=Dose Limiting Toxicity. DOR=Duration of Response. ECOG PS=Eastern Cooperative Oncology Group Performance Status.
LDAC=Low-Dose Cytarabine. MLFS=Morphologic Leukemia-Free State. MTD=Maximum Tolerated Dose. ORR=Overall Response Rate.
OS=Overall Survival. PK=Pharmacokinetics. PR=Partial Response. QD=Once Daily. RP2D=Recommended Phase 2 Dose. SC=Subcutaneous. TTP=Time to Progression.

1. Wei AH, et al. Oral #0890. 59th ASH Annual Meeting and Exposition; December 9-12, 2017; Atlanta, GA.
2. ClinicalTrials.gov. NCT02287233. https://clinicaltrials.gov/ct2/show/NCT02287233. Accessed March 2017.

Patient Characteristics

Characteristic	VEN 600 mg, N=61
Age, median (range), y	74 (66-87)
Male, n (%)	39 (64)
ECOG performance score, n (%) 0 1 2	 18 (30) 30 (49) 13 (21)
Secondary AML, n (%)	27 (44)
Prior HMA treatment, n (%)	17 (28)
Baseline bone marrow blast count, n (%)* ≤30 31-50 >50	 20 (34) 11 (19) 27 (47)
Cytogenetics, n (%) Intermediate Poor No mitoses	 37 (61) 19 (31) 5 (8)

*N=58

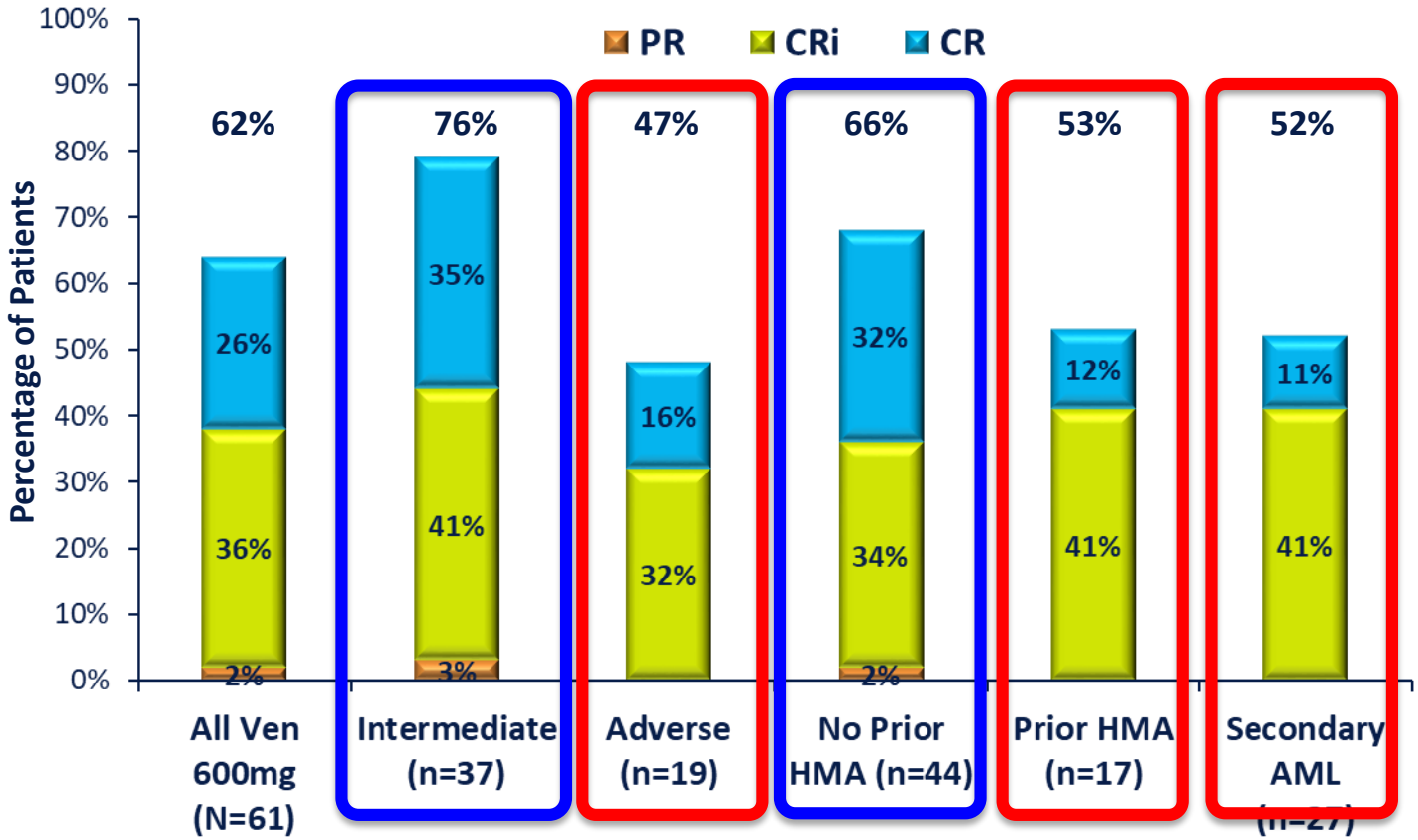
Elderly, 74

44% 2nd AML
28% HMA+

31% poor risk AML

All data as of 30-Nov-2016

Response Rates and Median Time to Response



CR+CRi 50-70%

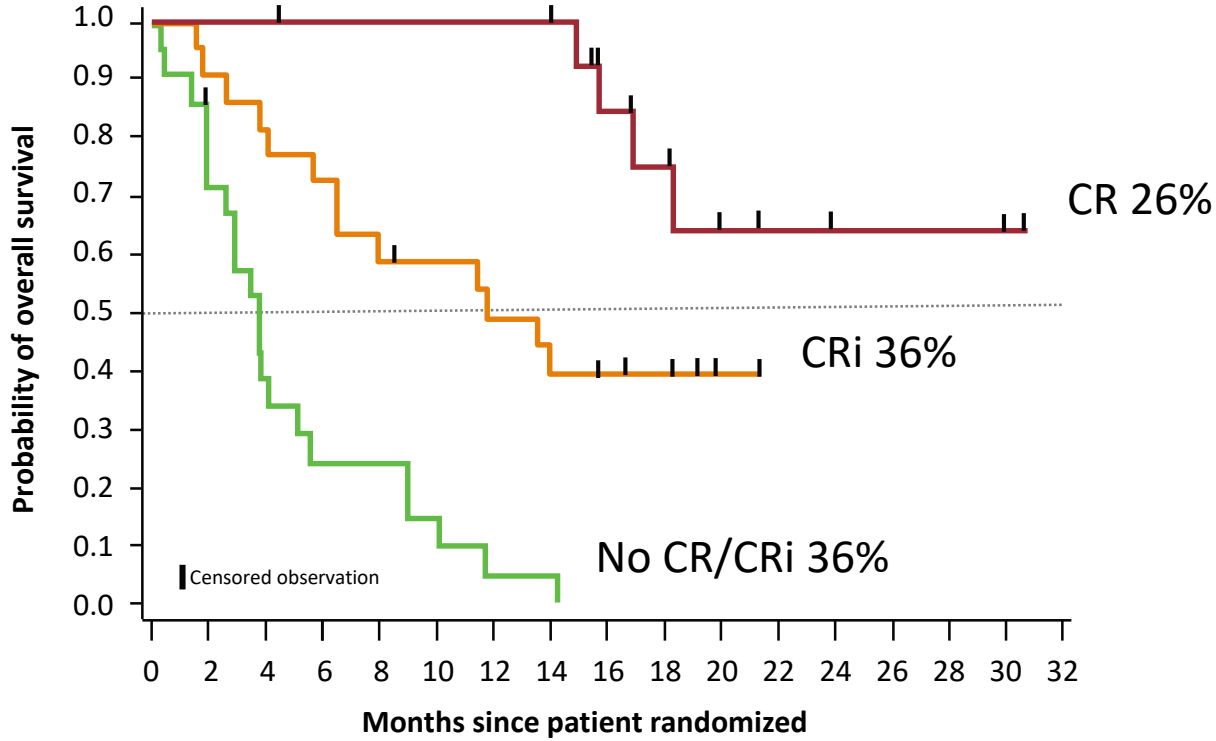
- **Median time to response – 1 month** (<1–9.5 months)
- **Median time to best response - 2.6 months** (<1–14.4 months)
- **Early death 4%**

ORR in all patients was 64% with 62% being CR/CRi. Activity was also observed in patients with prior HMA exposure, secondary AML, including those with poor cytogenetics.

Data Cutoff Date: August 15, 2017

AML=Acute Myeloid Leukemia. CR=Complete Remission.
CRi=Complete Remission with Incomplete Marrow Recovery. HMA=Hypomethylating Agent. PR=Partial Response.
PR=Partial Remission. Ven=Venetoclax. Wei AH, et al. Oral #0890. 59th ASH Annual Meeting and Exposition; December 9-12, 2017; Atlanta, GA.

Importance of CR on OS (LDAC + Ven)



	CR (n = 16)	CRi (n = 22)	RD/PD/DS/NR (n = 22)
Median OS, mo (95% CI)	NR (16.9 – NR)	11.7 (5.7 – NR)	3.8 (2.0 – 5.1)
12-month OS, % (95% CI)	100 (100 – 100)	49.2 (27.3 – 68.0)	4.8 (0.3 – 19.8)
Median no. of treatment cycles	15	7.5	2

Data cutoff date: 15 AUG 2017.

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=431*

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

Randomization Stratification Factors

- Age (<75 vs. ≥75 years);
- Cytogenetic Risk (intermediate, Poor);
- Region (US, EU, China, Japan, other regions)

Endpoints

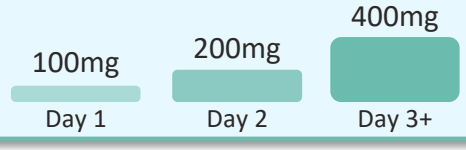
Primary

- **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

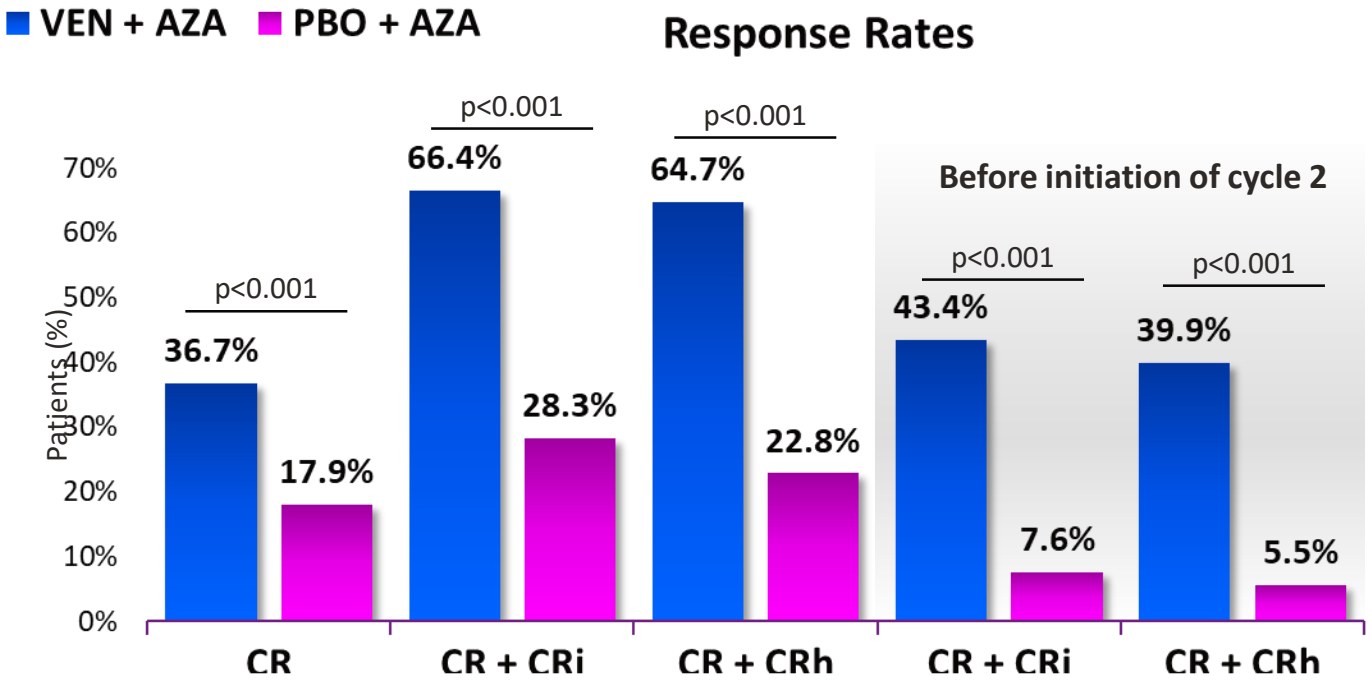
Venetoclax Ramp-Up (Cycle 1)



* 6 patients did not receive treatment after randomization but included in the efficacy analysis

AML: Acute myeloid leukemia; CHF: Congestive heart failure; CNS: Central nervous system; CR: Complete remission; CRi: CR+ incomplete marrow remission; CRh: CR+ incomplete hematologic recovery; DCLO: diffusion lung capacity for carbon monoxide; ECOG: Eastern Cooperative Oncology Group; FEV1 : Forced expiratory volume; HMA: Hypomethylating agent; NCCN: National Comprehensive Cancer Network

Responses



Median months (range)	VEN + AZA (N=286)	PBO + AZA (N=145)
Time to first response (CR or CRi)	**1.3** (0.6-9.9)	**2.8** (0.8-13.2)
Time to first response (CR or CRh)	**1.0** (0.6-14.3)	**2.6** (0.8-13.2)

In patients with CR + CRi, **MRD negativity** occurred in:

- **23.4%** receiving **VEN + AZA vs**
- **7.6%** receiving **PBO + AZA**

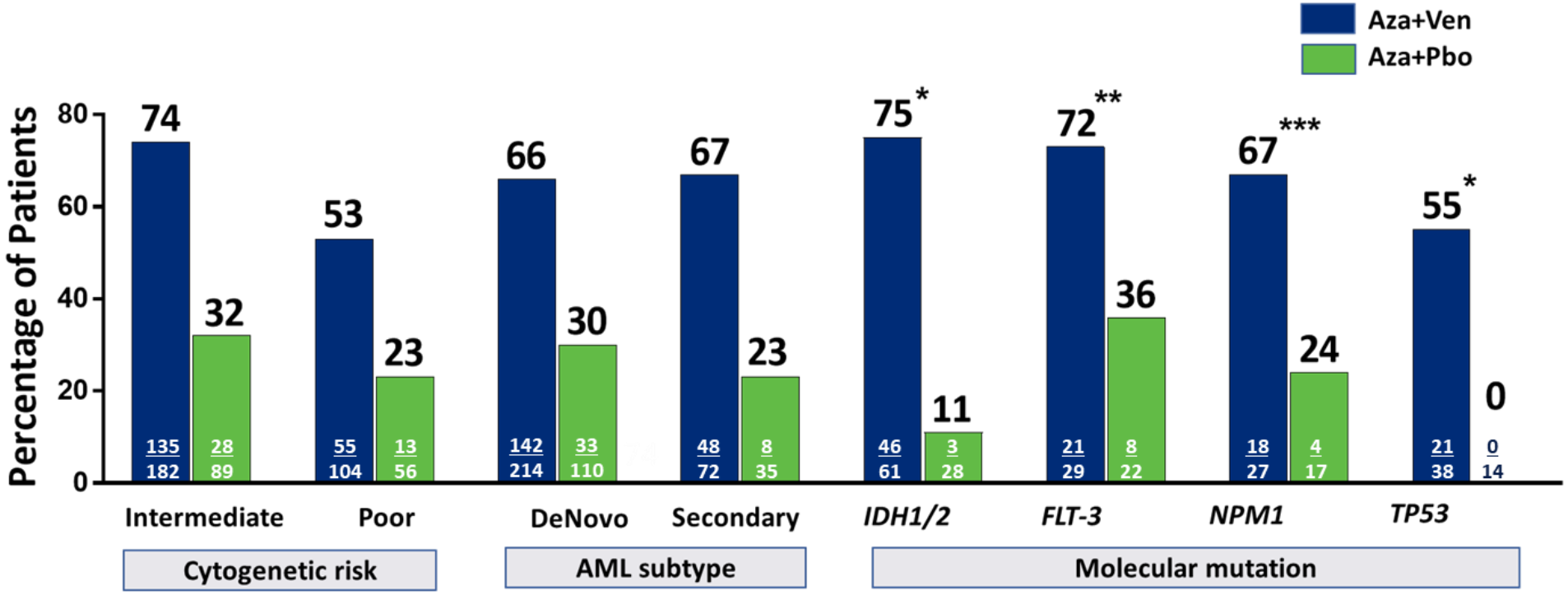
CR + CRi was achieved in 66.4% receiving VEN + AZA vs 28.3% receiving PBO + AZA (p<0.001), while CR + CRi before initiation of cycle 2 was achieved by 43.4% vs 7.6% (p<0.001), respectively

AZA=Azacitidine. CI=Confidence Interval. CR=Complete Remission. CRi=CR with Incomplete Blood Count Recovery. CRh=CR with Partial Hematologic Recovery. MRD=Measurable Residual Disease. NR=Not Reached. PBO=Placebo. VEN=Venetoclax.

Data cutoff date: January 4, 2020.

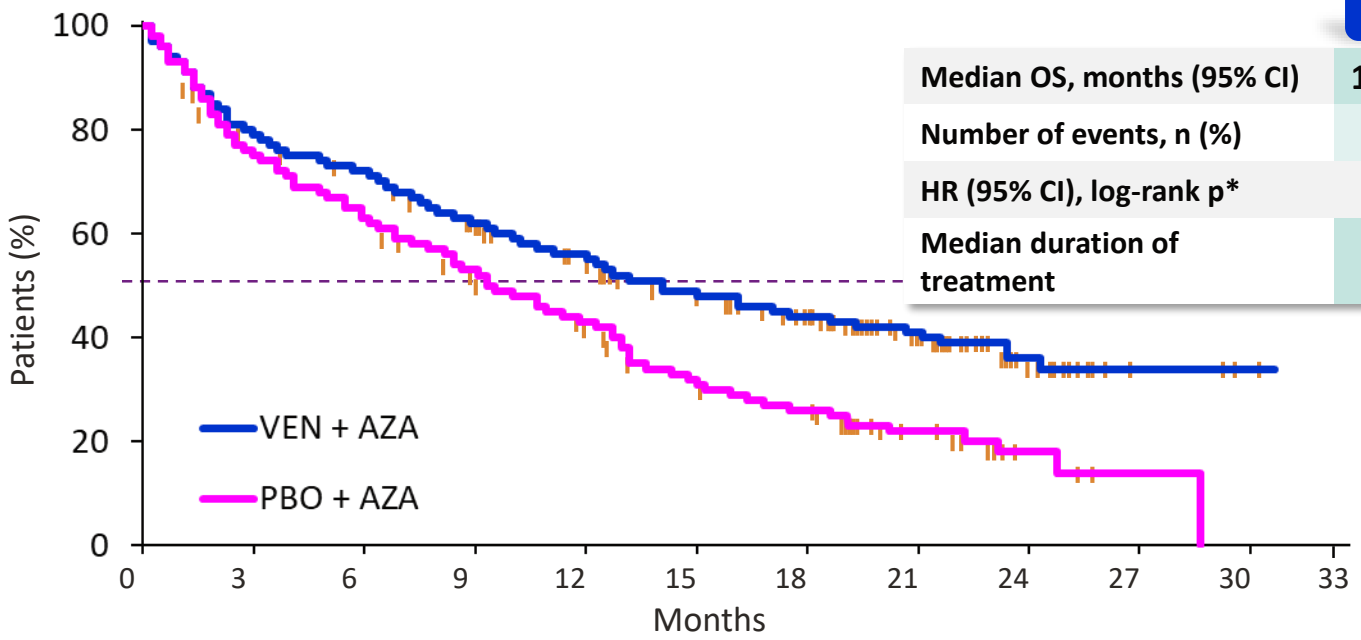
DiNardo CD, et al. N Engl J Med. 2020;383(7):617-29.

Response Rates (CR+CRi) by Subgroups



*p<0.001, **p=0.021, ***p=0.012;
P-value is from Fisher's exact test

Overall Survival



	VEN + AZA (N=286)	PBO + AZA (N=145)
Median OS, months (95% CI)	**14.7** (11.9-18.7)	**9.6** (7.4-12.7)
Number of events, n (%)	161 (56)	109 (75)
HR (95% CI), log-rank p*	0.66 (0.52-0.85), p<0.001	
Median duration of treatment	7.6 (<0.1-30.7)	4.3 (0.1-24.0)

Median follow-up:

20.5 months
(range <0.1 - 30.7 months)

VEN + AZA	286	219	198	168	143	117	101	54	23	5	3	0
PBO + AZA	145	109	92	74	59	38	30	14	5	1	0	0

The median OS (95% CI) for patients receiving VEN + AZA vs PBO + AZA was 14.7 (11.9–18.7) vs 9.6 (7.4–12.7) months, respectively. The hazard ratio was 0.66 (0.52–0.85, p<0.001).

Data cutoff date: January 4, 2020. 1. DiNardo CD, et al. N Engl J Med. 2020;383(7):617-29. 2. DiNardo CD, et al. Oral LB2601. 25th EHA Congress. June 11-21, 2020.

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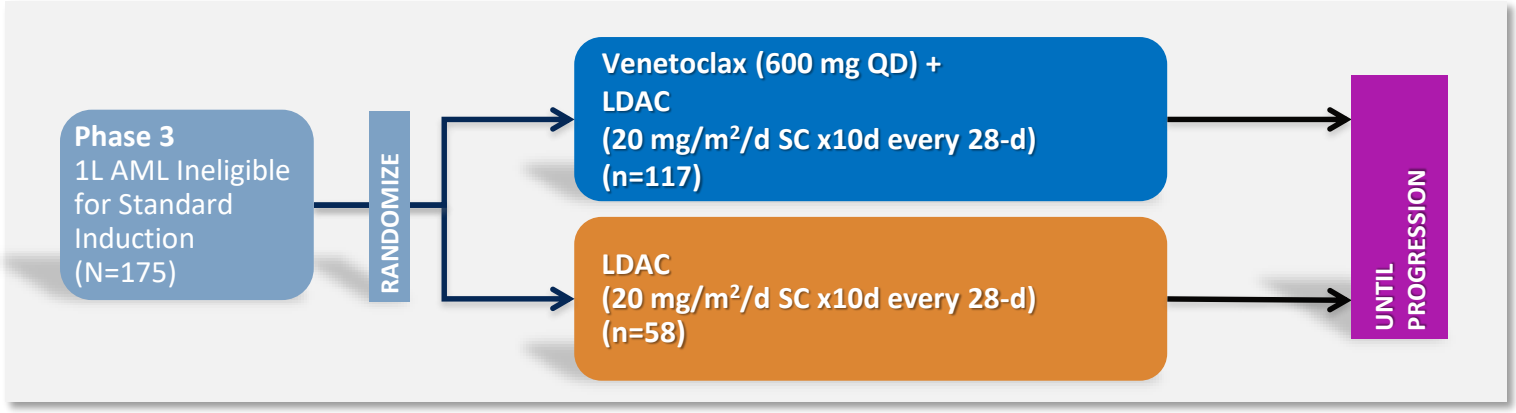
Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia

C.D. DiNardo, B.A. Jonas, V. Pullarkat, M.J. Thirman, J.S. Garcia, A.H. Wei, M. Konopleva, H. Döhner, A. Letai, P. Fenaux, E. Koller, V. Havelange, B. Leber, J. Esteve, J. Wang, V. Pejsa, R. Hájek, K. Porkka, Á. Illés, D. Lavie, R.M. Lemoli, K. Yamamoto, S.-S. Yoon, J.-H. Jang, S.-P. Yeh, M. Turgut, W.-J. Hong, Y. Zhou, J. Potluri, and K.W. Pratz

Standard Treatment for AML patients unfit for intensive chemotherapy (NCCN/ESMO/Taiwan Hematology Society)

M16-043 – Phase III

Venetoclax Trial in AML with Cytarabine



OBJECTIVES

Primary: ***OS***

Secondary: ***CR/CRi, EFS, Time to CR/CRi, Fatigue Reduction***

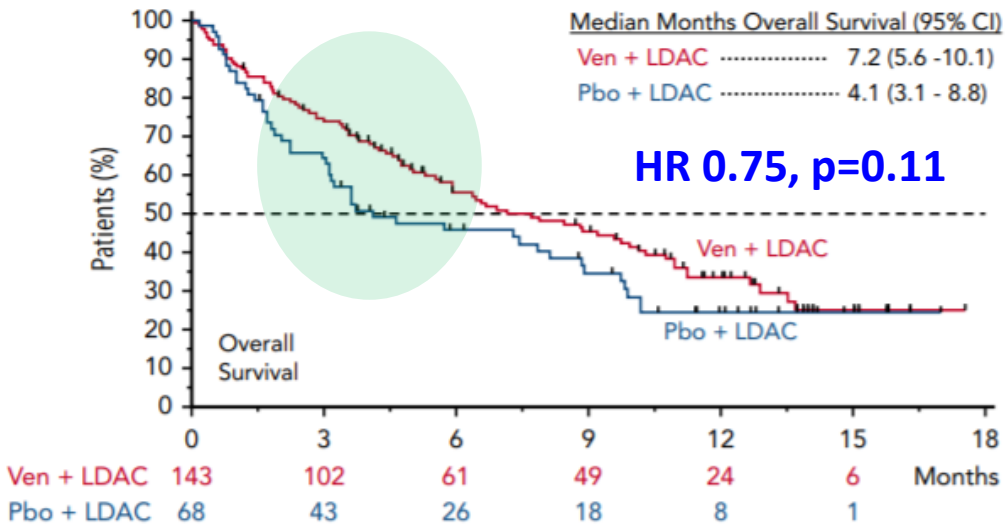
Exploratory: ***Predictive Biomarker, HRQoL***

1L=First Line. AML=Acute Myeloid Leukemia. CR=Complete Remission. CRi=Complete Remission with Incomplete Blood Count Recovery. d=Day. EFS=Event-free survival. HRQoL=Health Related Quality of Life. LDAC=Low-Dose Cytarabine. OS=Overall Survival. QD=Once Daily. SC=Subcutaneous.

ClinicalTrials.gov. NCT03069352. https://clinicaltrials.gov/ct2/show/NCT03069352. Accessed July 2017.

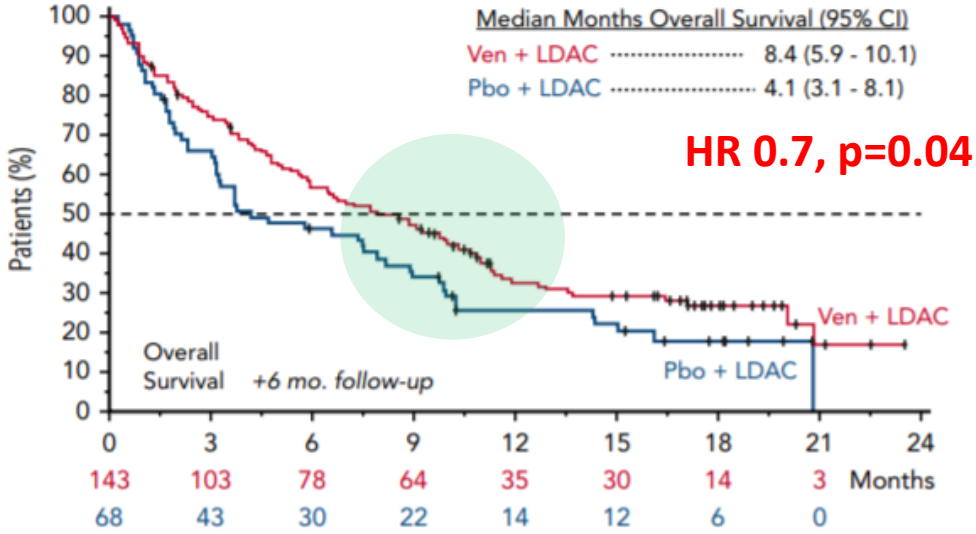
M16-043 – Phase III (Viale-C)

Preplanned analysis



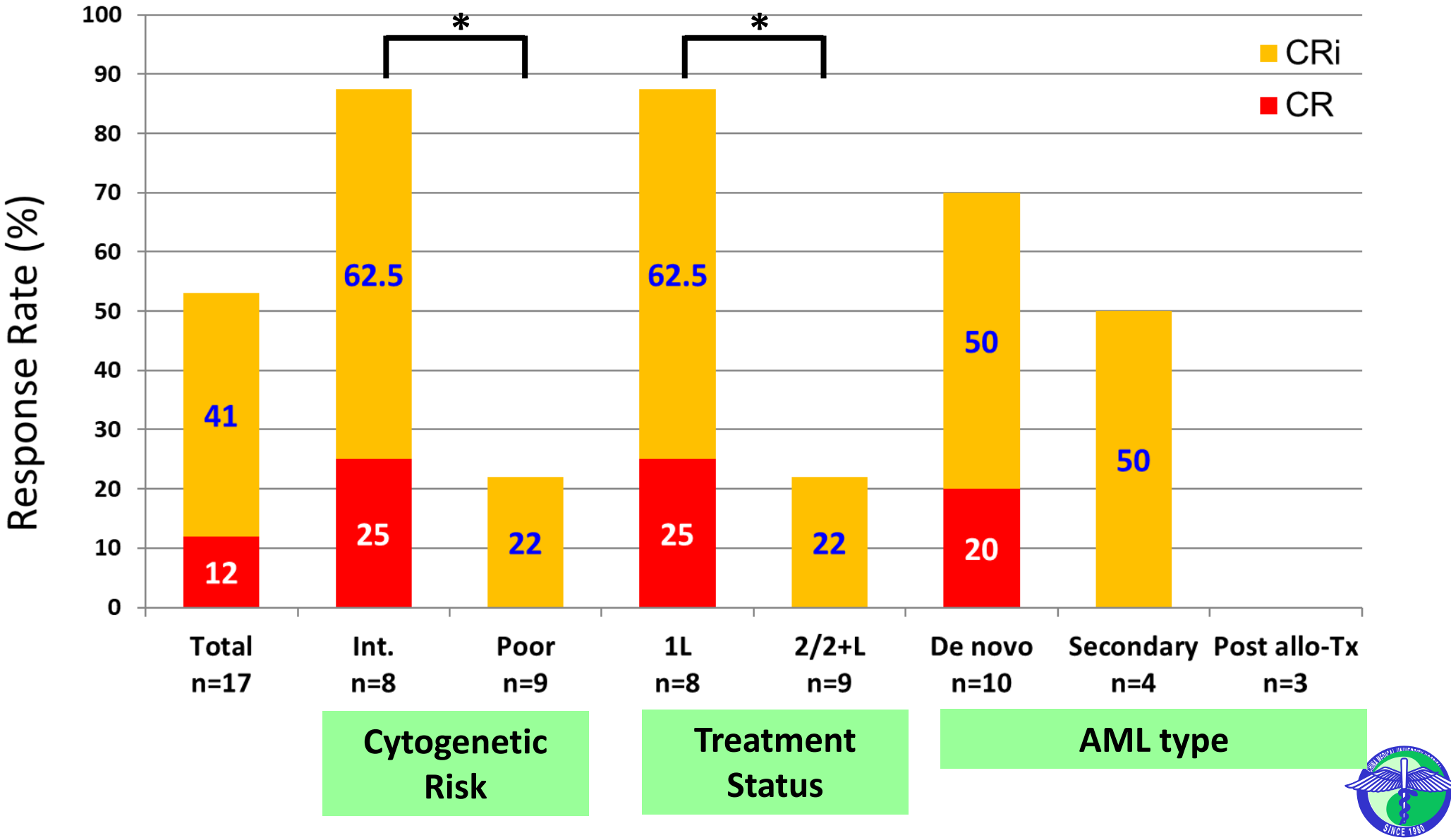
Additional 6Mo analysis

mOS: 8.4M



Blood. 2020; 135(24):2137-2145

Best Response of Evaluable Patients



Summary -2

- **Venetoclax + HMA or LDAC** as **frontline** Rx for elderly AML
  - Very high CR rate (CR+CRi): around 70%
  - Very short time to response (1-2M to CR)
  - Duration of response around 1-2+Y
  - Good tolerability
  - Bridging to alloSCT, ***cure of disease possible!***

Unanswered Questions …

- Venetoclax/AZA as induction for younger patients? Probaby ***NOT!***
- Quality of CR after Venetoclax/Aza comparing to I3A7/HDAc? Probably ***NOT*** the same!
- Timing/Selection of patients for alloHSCT?
- Maintenance therapy after alloHSCT?