Akut Lösemilerde BCL-2 inhibitörleri

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6. Hematolojik Onkoloji Kongresi

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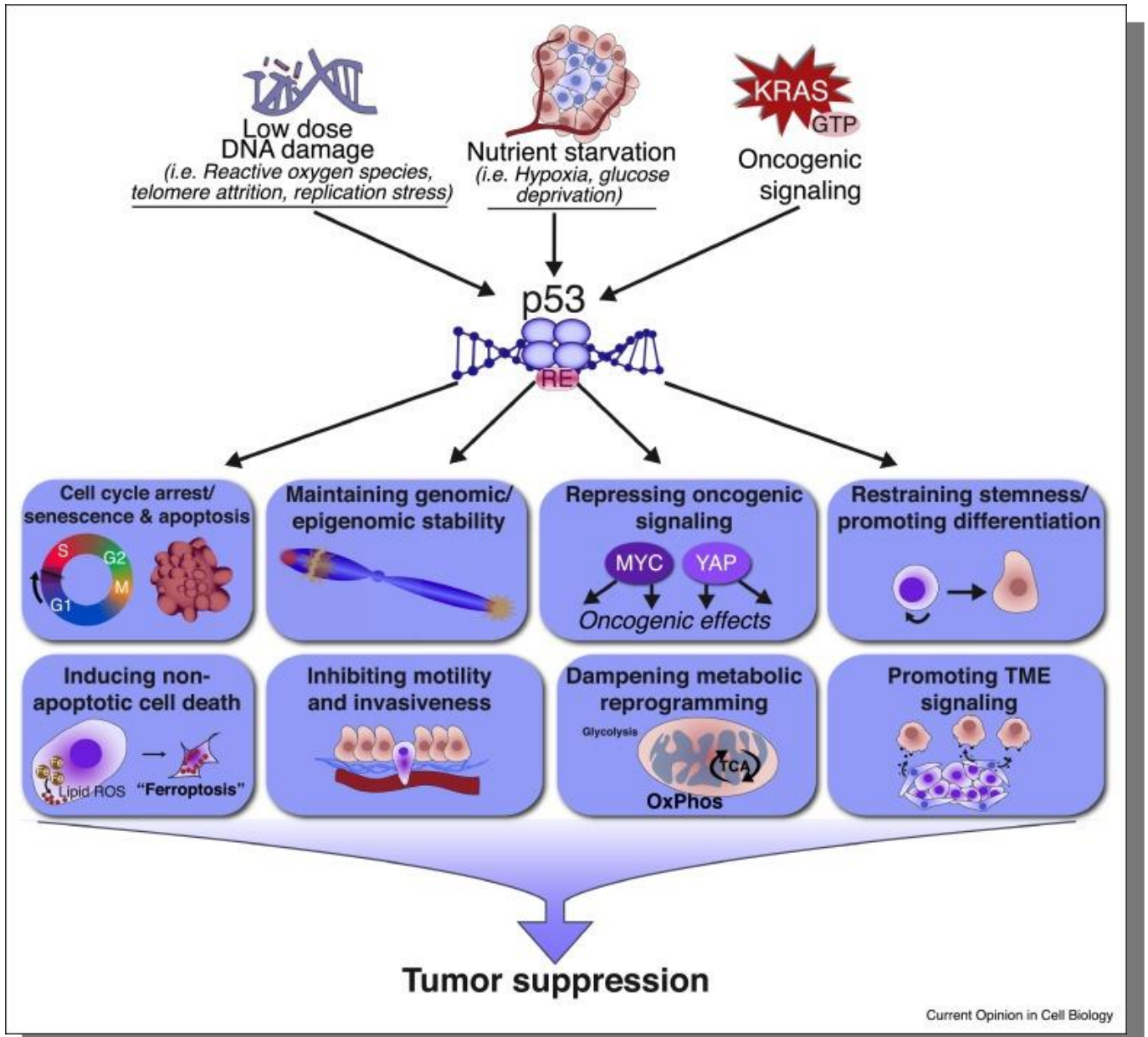
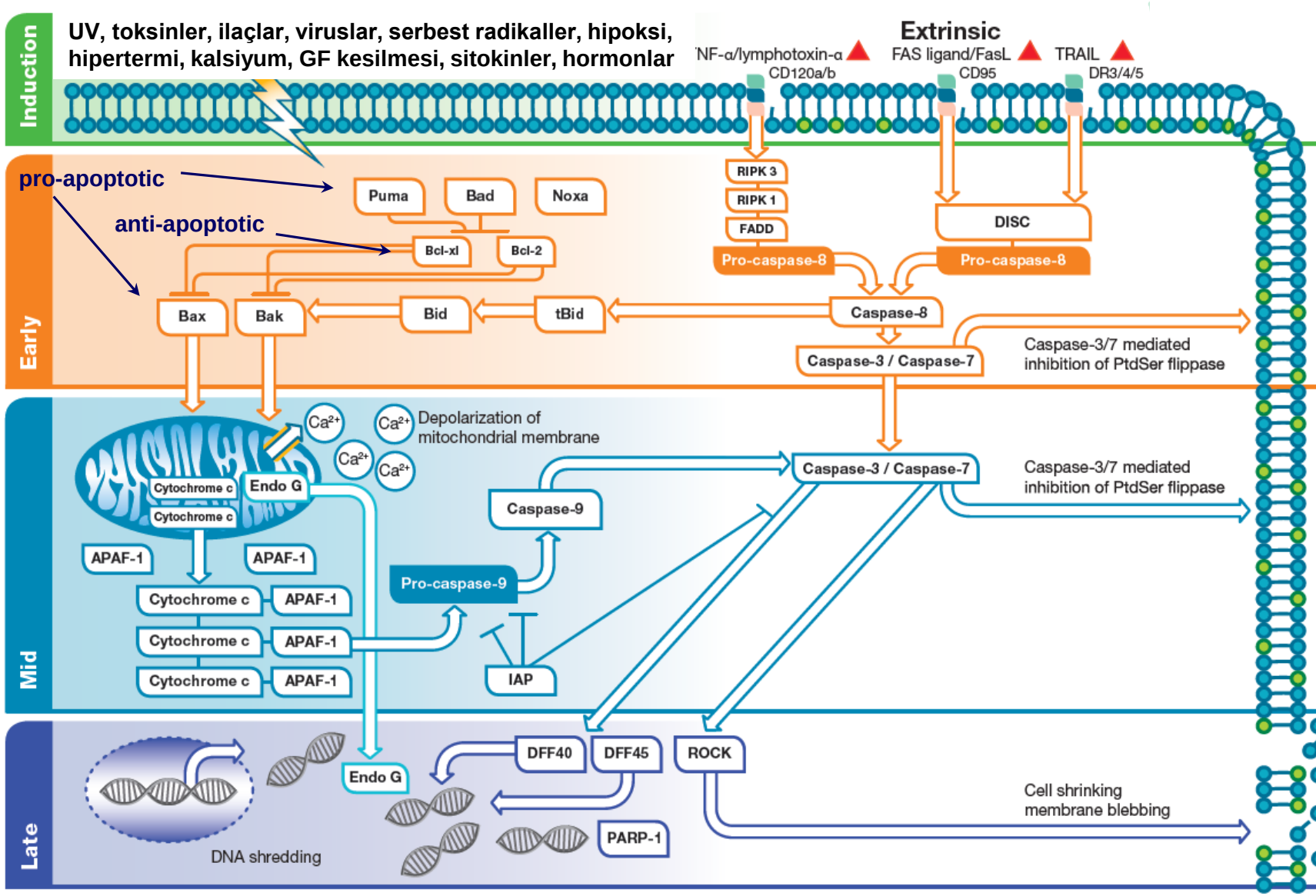
İntrinsik tümör baskılanması



Bieging KT et al. *Nat Rev Cancer* 14, 2014

Apoptotik yolak



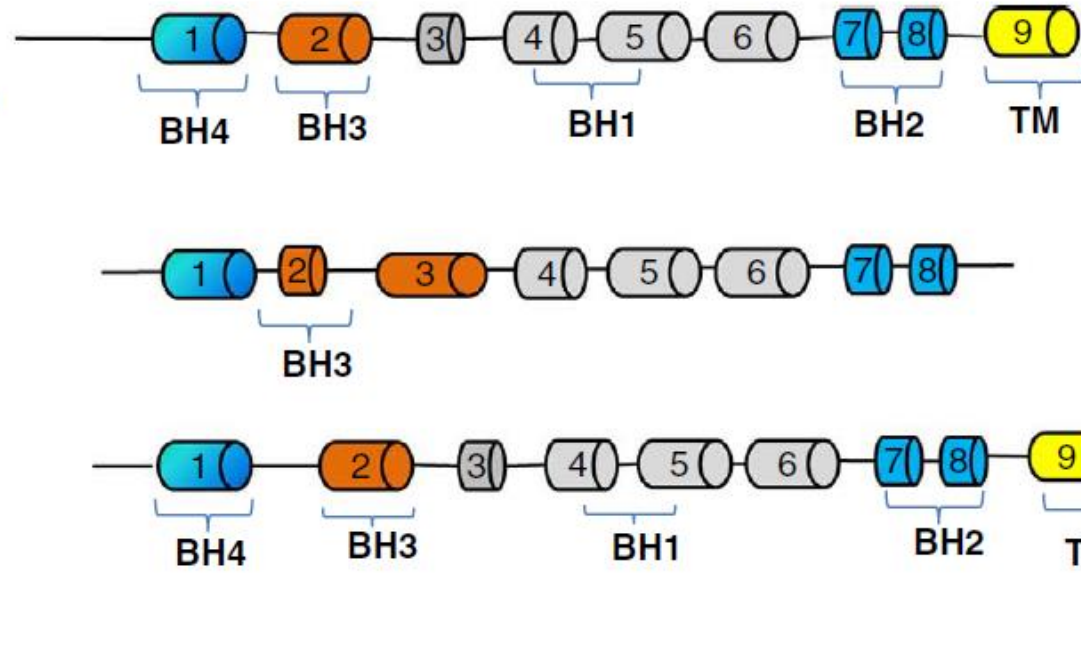
BCL-2 (B-Cell Lymphoma) protein ailesi

Anti-apoptotic proteins
(BCL-2, BCL-XL, BCL-W, MCL1, A1 and BCL-B)

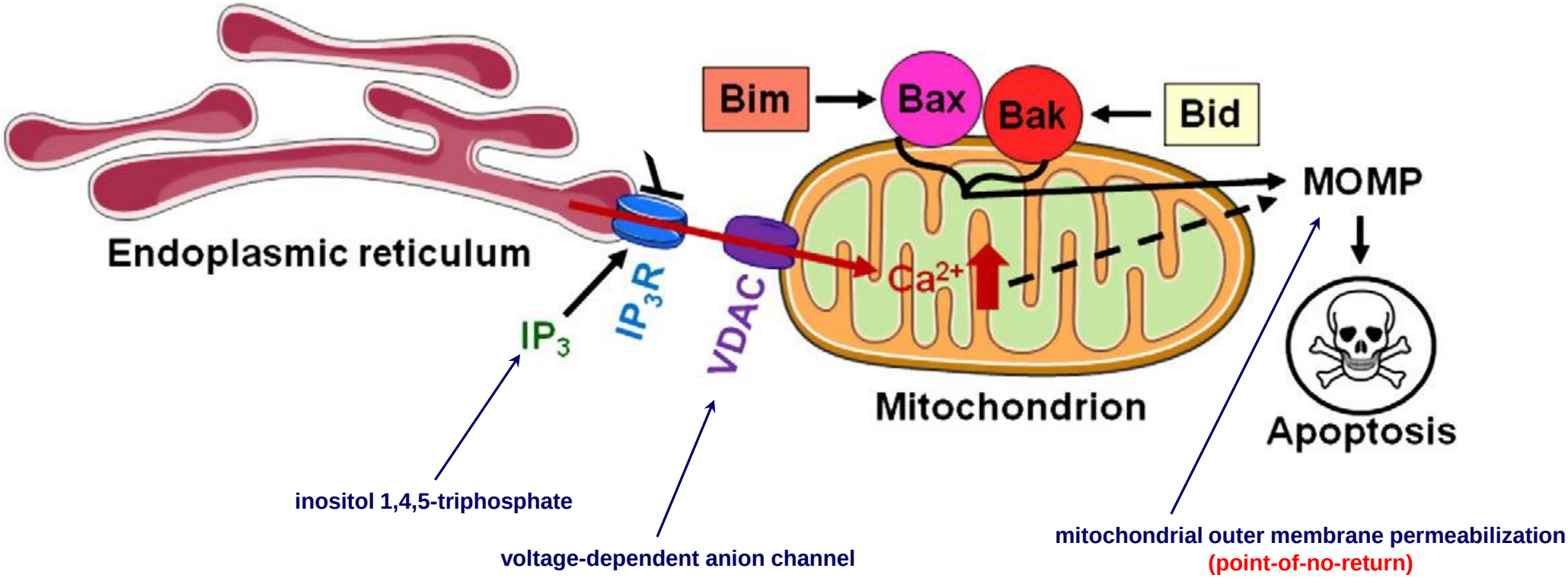
BH-3 only proteins

- Activators (BIM, PUMA, NOXA, tBID)
- Sensitizers (BAD, BMF, BIK, HRK)

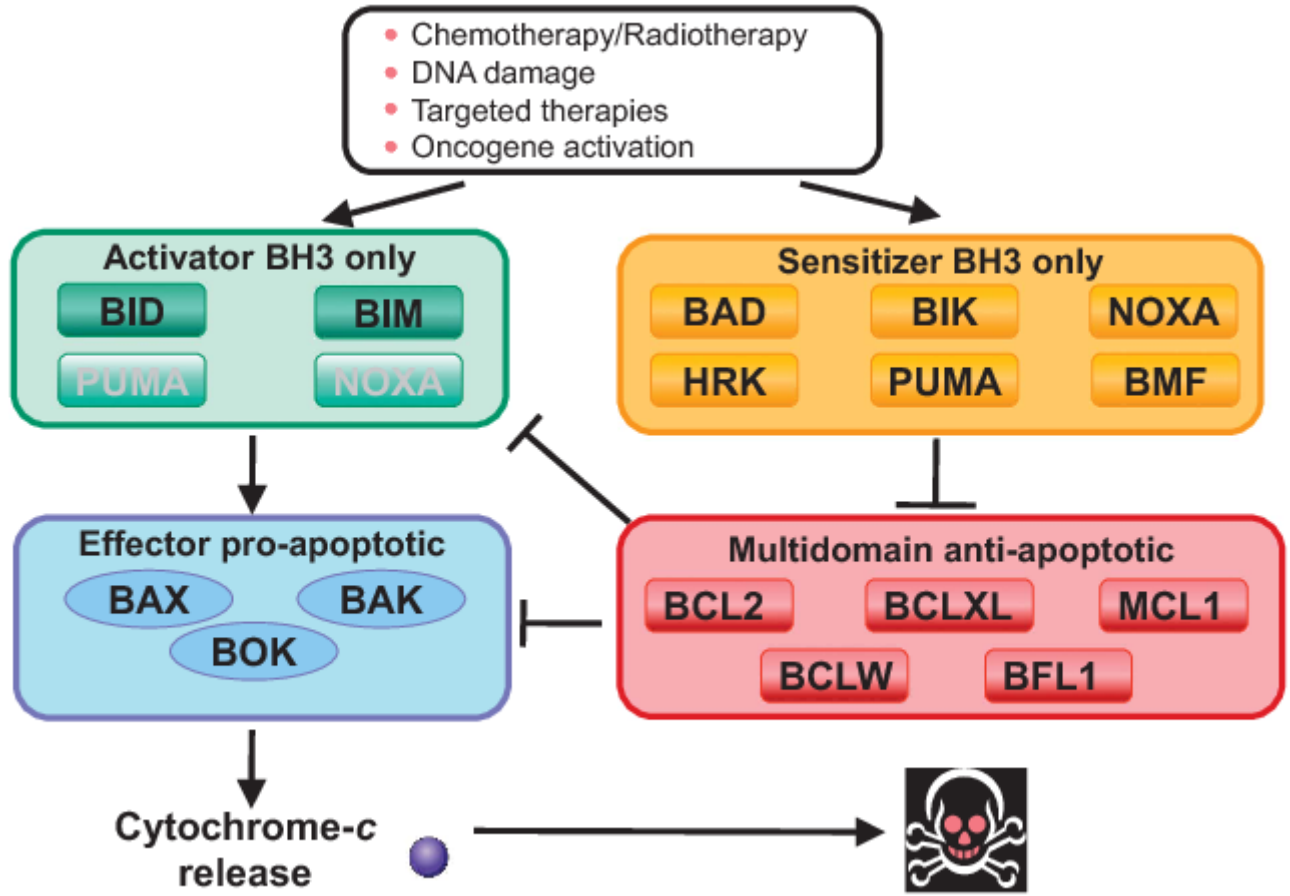
Multi-domain pro-apoptotic proteins effectors (BAX, BAK and BOK)



Wu H et al. *Blood Reviews*, 2018



Akl H et al. *Biochimica et Biophysica Acta,* 2014



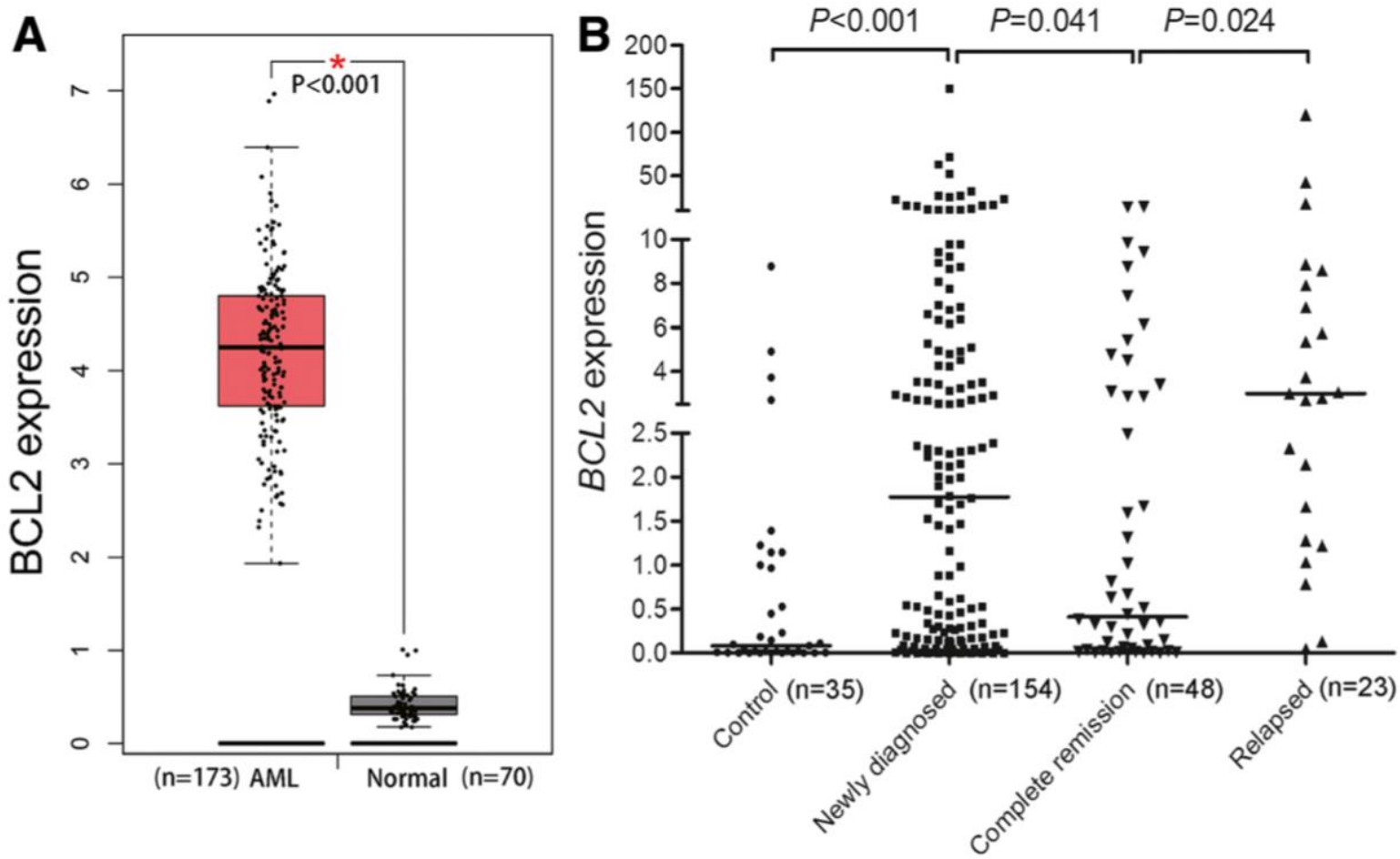
Montero J et al. *Cell Death Diff,* 2018

BCL-2 RNA yıkımını sağlayan miRNA'ları kodlayan genlerde;

* downregülasyon/delesyon,
* amplifikasyon,
* kromozomal translokasyonlar

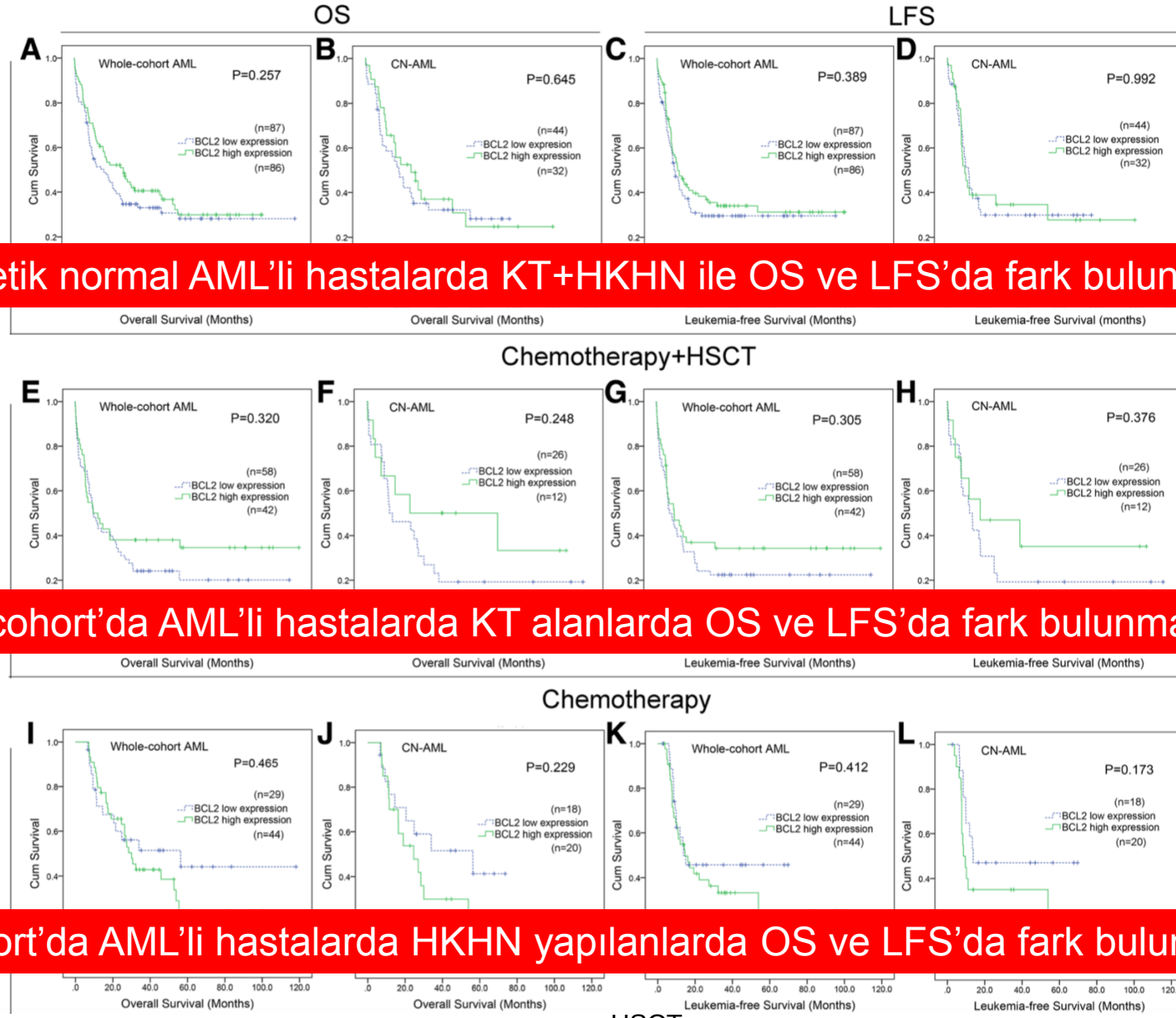
Tümör	Yüksek düzeyde BCL-2 ekspresyonu
Kronik Lenfositer Lösemi (KLL)	Vakaların %95'inde bildirilmiş
Akut Myeloid Lösemi (AML)	Kemoterapiye kötü yanıt ile ilişkili
Akut Lenfositik Lösemi (ALL)	Neredeyse tüm hastalarda
Foliküler Lenfoma (FL)	Yaklaşık hastaların %90'ında
Diffüz Büyük B Hücreli Lenfoma (DBBHL)	Hastaların yaklaşık %20'sinde Toplam sağkalımı kötü etkiliyor
Solid tümörler	Prostat, meme, küçük hücreli ve küçük hücreli dışı akciğer kanserleri, over, mesane, kolorekral, baş boyun tümörleri ve nöroblastom

AML'de BCL-2 ifadesi



Zhou JD et al. *Diag Pathol,* 2019

AML'de BCL-2 ifadesinin OS ve LFS'a etkisi



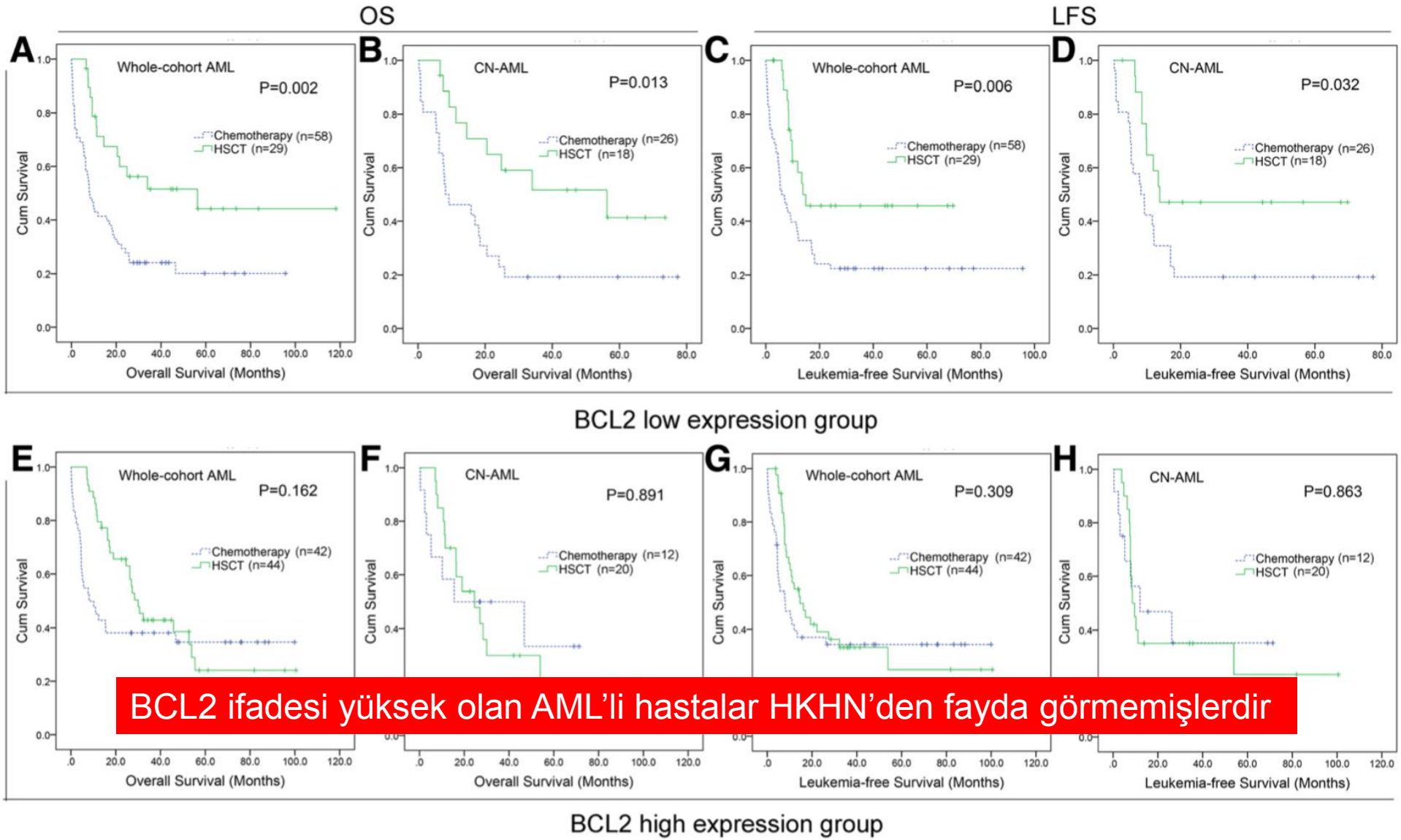
Sitogenetik normal AML'li hastalarda KT+HKHN ile OS ve LFS'da fark bulunmamıştır

Tüm cohort'da AML'li hastalarda KT alanlarda OS ve LFS'da fark bulunmamıştır

Tüm cohort'da AML'li hastalarda HKHN yapılanlarda OS ve LFS'da fark bulunmamıştır

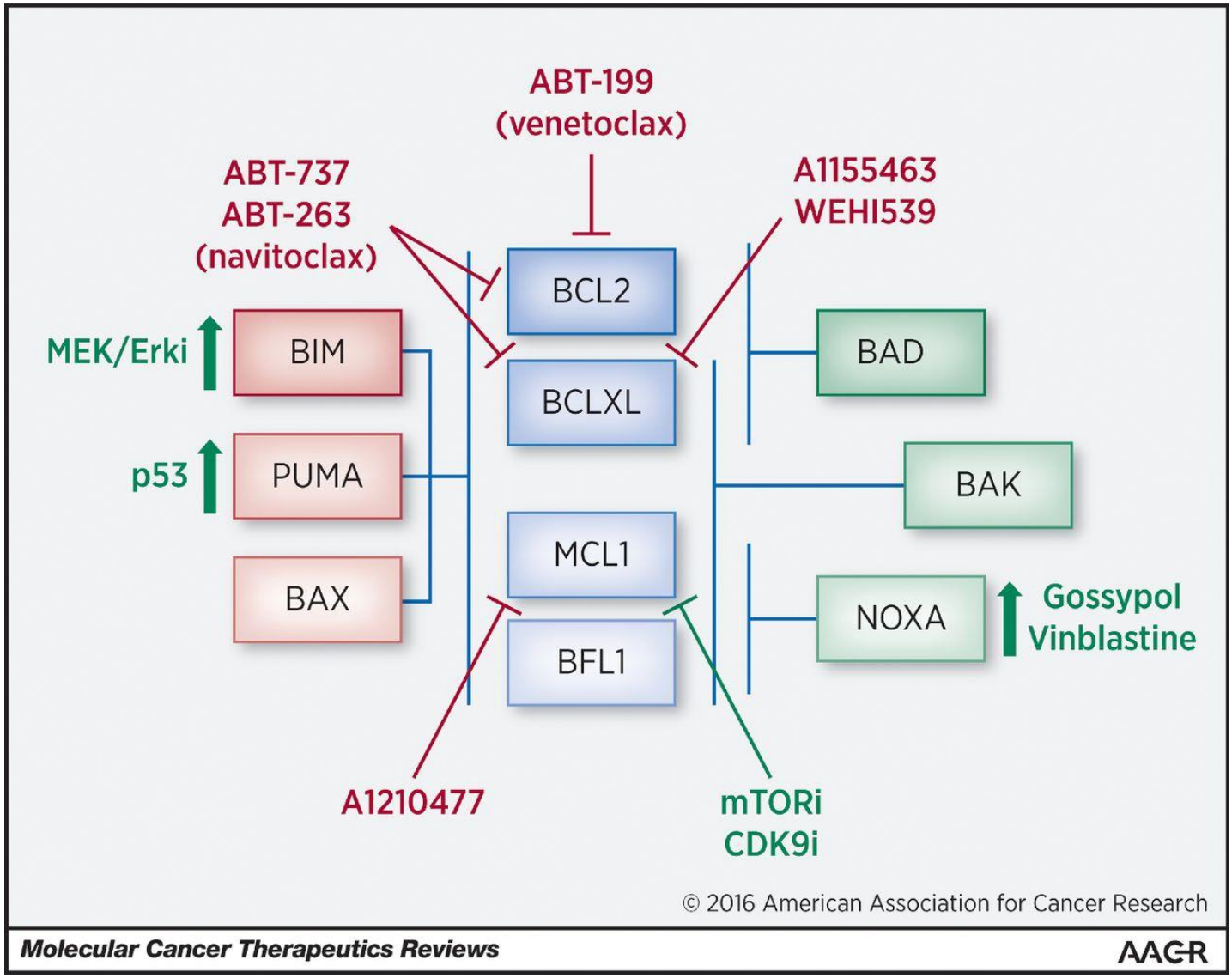
Zhou JD et al. *Diag Pathol*, 2019

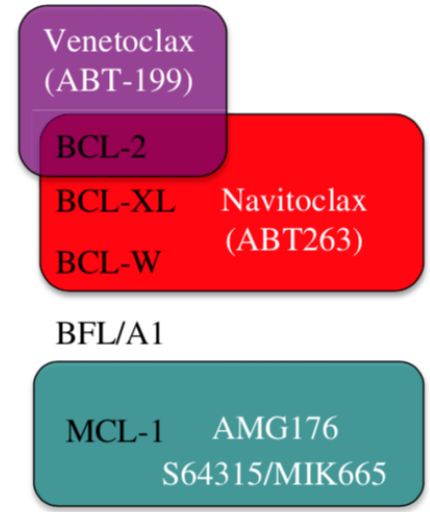
AML'de BCL-2 ifadesinin OS ve LFS'a etkisi



BCL2 ifadesi yüksek olan AML'li hastalar HKHN'den fayda görmemişlerdir

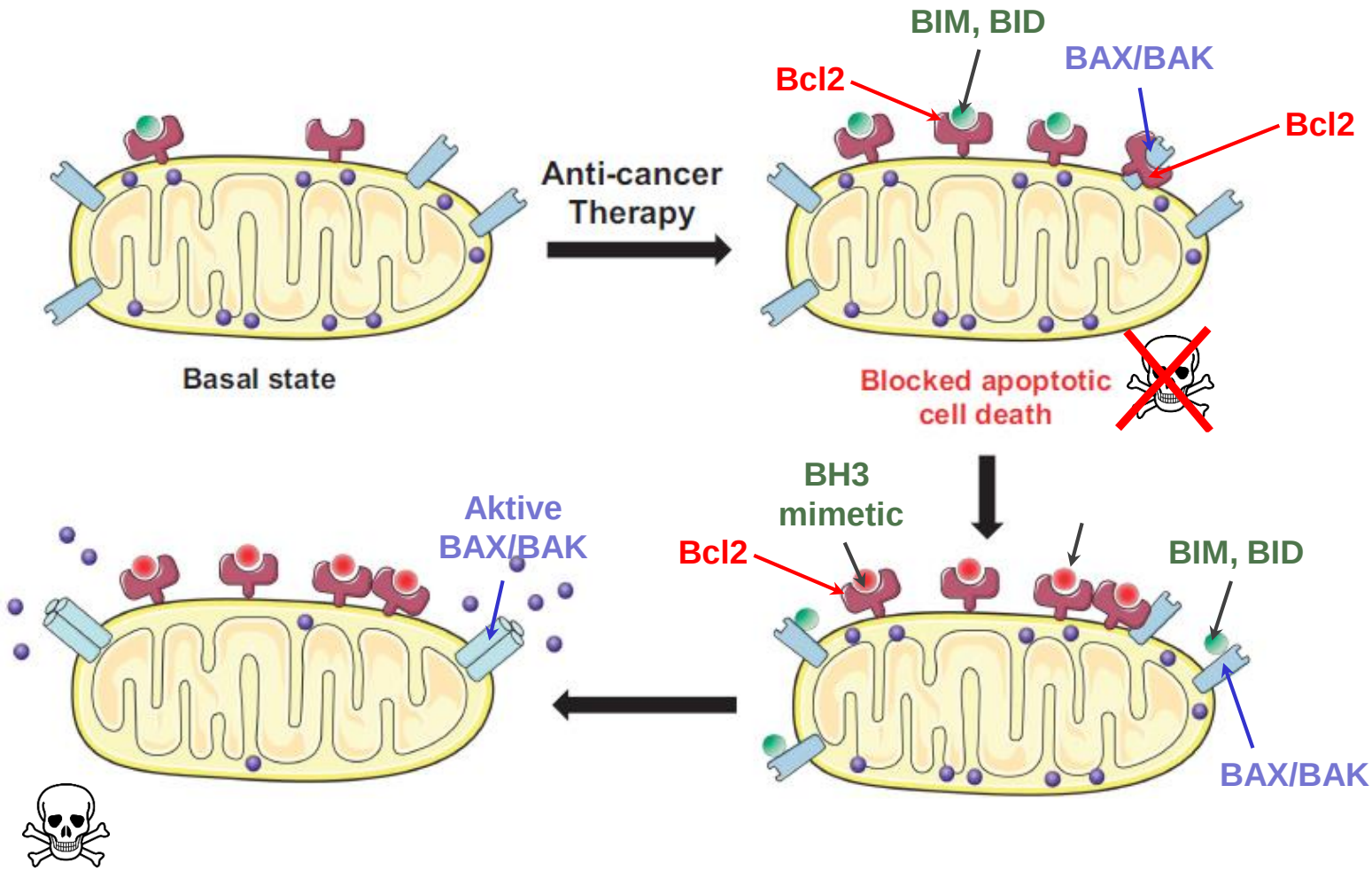
Zhou JD et al. *Diag Pathol*, 2019





Ryan S et al. *Mol Cancer Ther Rev,* 2016

BH3 mimetikler (Obatoclax, Navitoclax, Venetoclax)



Montero J et al. *Cell Death Diff,* 2018

Venetoclax

✓ VENCLYXTO®, AbbVie

* 17p del KLL, Nisan 2016
* Daha önce tedavi almış KLL'de Rituximab ile, Haziran 2016)
* ≥ 75 yaş yeni tanı AML'de Azasitidin veya Decitabin veya düşük doz AraC ile, Kasım 2018
* Daha önce tedavi almamış erişkin KLL/SLL'de, Mayıs 2019

Yeni tanı AML; VEN + LDAC (Faz I/II)

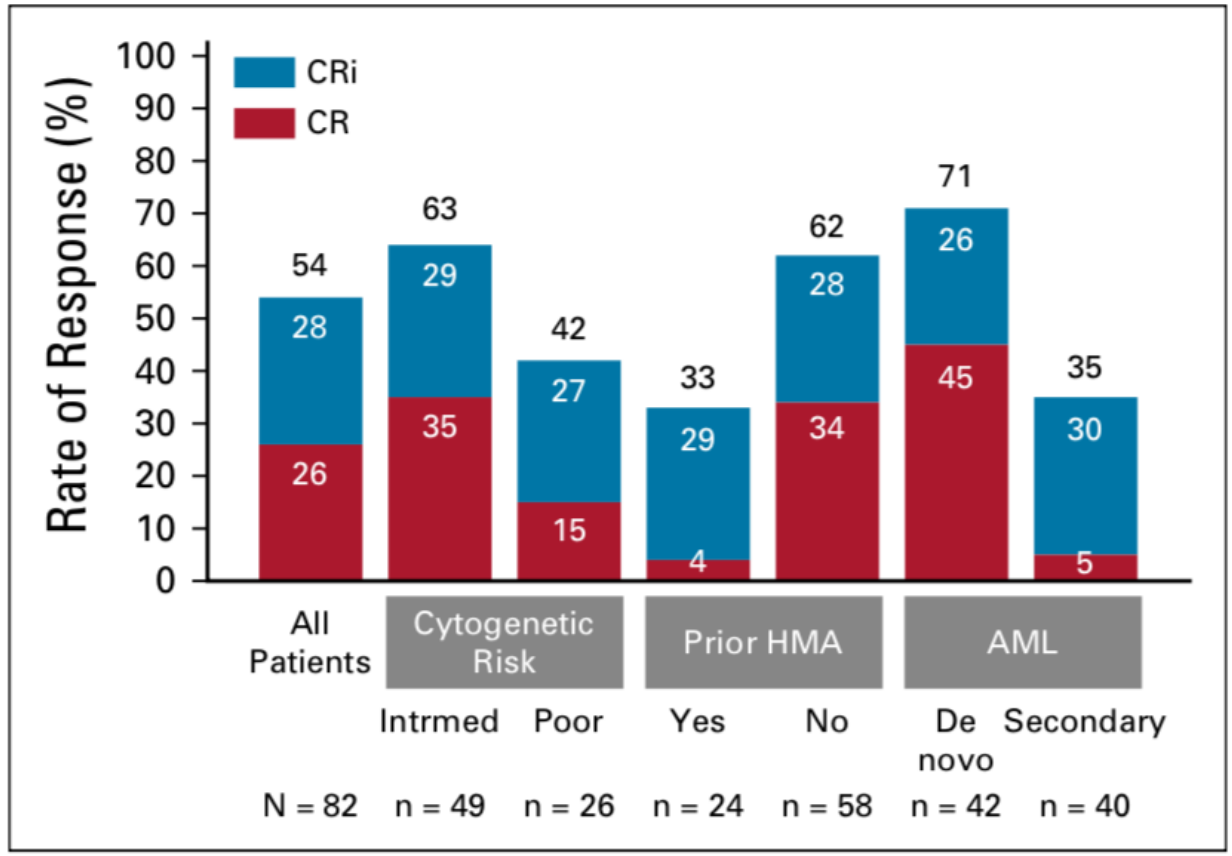
Characteristic	Venetoclax 600 mg + LDAC (n = 82)
Age, years, median (range)	74 (63-90)
≥ 65	80 (98)
≥ 75	40 (49)
Male	53 (65)
AML type	
De novo	42 (51)
Secondary	40 (49)
ECOG performance status	
0	12 (15)
1	46 (56)
2	23 (28)
3	1 (1)
Bone marrow blast count	
< 30%	27 (33)
≥ 30% to < 50%	18 (22)
≥ 50%	36 (44)
Antecedent hematologic disorder	40 (49)
Prior HMA treatment	24 (29)
Cytogenetic risk category	
Intermediate	49 (60)
Poor	26 (32)
No mitosis	7 (8)
Somatic mutations*	
TP53	10 (14)
FLT3	16 (23)
IDH1/2	18 (25)
NPM1	9 (13)

Tedavi süresi: Ortalama 4.2 ay (0.2-29 ay)

AE	Venetoclax 600 mg + LDAC (n = 82)
Any AE	82 (100)
AE with grade ≥ 3	
Febrile neutropenia	34 (42)
Thrombocytopenia	31 (38)
WBC count decreased	28 (34)
Anemia	22 (27)
Neutropenia	22 (27)
Platelet count decreased	20 (24)
Lymphocyte count decreased	15 (18)
Neutrophil count decreased	14 (17)
Hypophosphatemia	13 (16)
Hypokalemia	12 (15)
Hypertension	9 (11)
Pneumonia	9 (11)
Sepsis	9 (11)
Serious AE	
Anemia	25 (31)
Febrile neutropenia	22 (27)
Pneumonia	8 (10)
AML progression	7 (9)
Sepsis	6 (7)

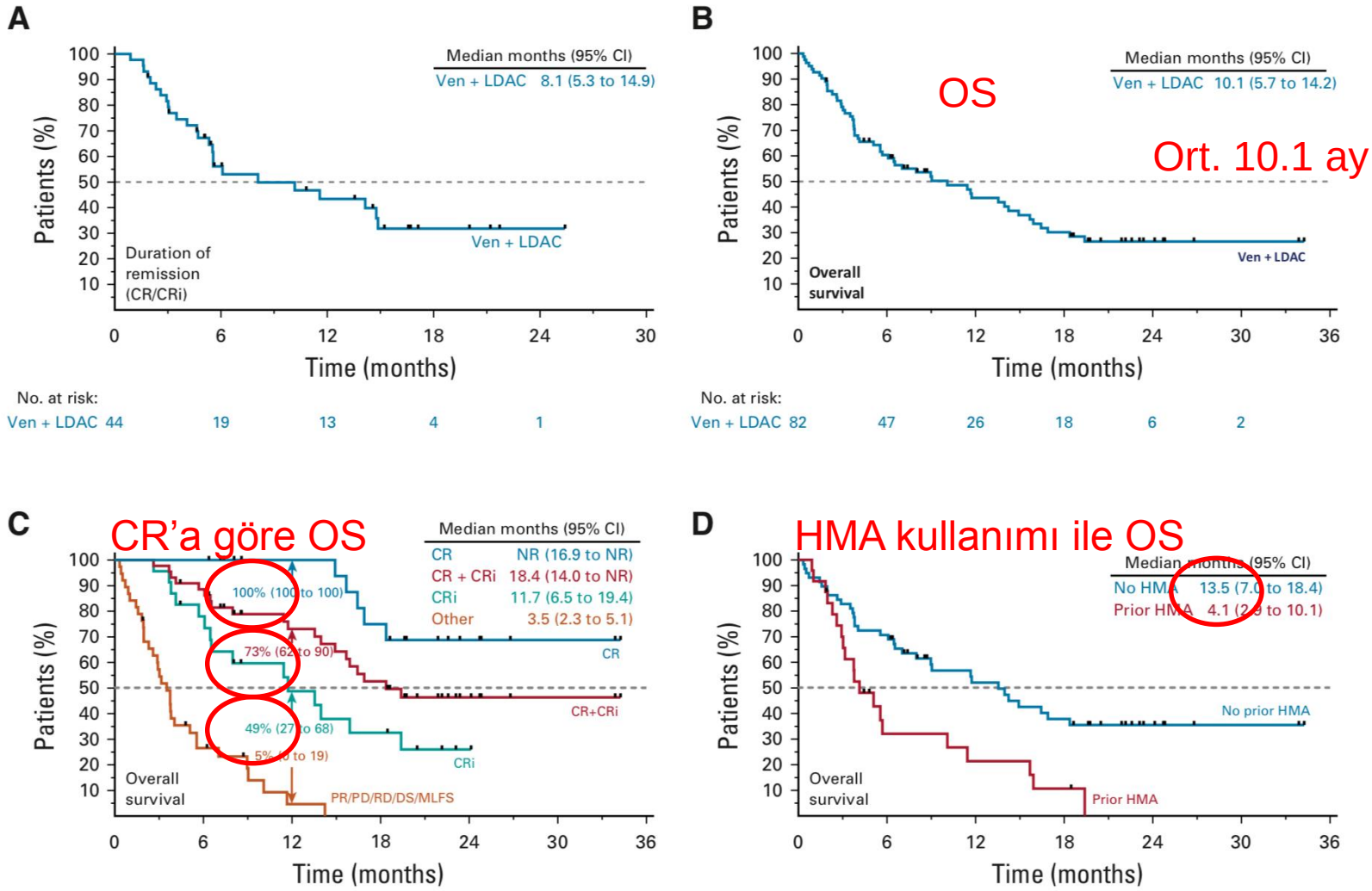
Wei AH et al. *J Clin Oncol*, 2019

Yeni tanı AML; VEN + LDAC (Faz I/II)



Wei AH et al. *J Clin Oncol*, 2019

Yeni tanı AML; VEN + LDAC; OS



Wei AH et al. *J Clin Oncol*, 2019

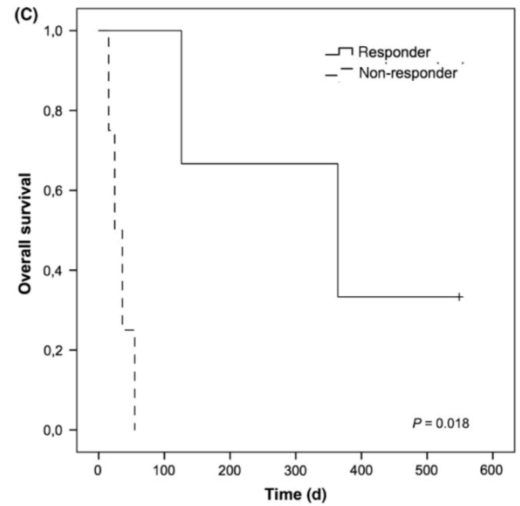
HMA-dirençli sekonder AML'de VEN

Patient	Age at AML diagnosis	Sex	Antecedent hematologic malignancy	Time to leukemic transformation (days)	Best response to HMA (IWG)	Cytogenetics	IDH1/2 mutation status	BCL-2 expression by IHC	MCL-1 expression by IHC	BIM expression by IHC
#24231	74	Female	MDS	483	TF	46 XX	IDH1 mutant	4	0	0
#8623	75	Female	MDS	1429	TF	46 XX	Wild-type	4	0.5	0.5
#6510	74	Male	MDS/MPN (CMML)	299	TF	46 XY	Wild-type	1	0	0
#25984	81	Female	MDS[a]	NA	PR	46 XX	Wild-type	1	0	1.0
#23769	65	Male	MDS[a]	NA	CRi	46 XY	Wild-type	1	0.5	1.0
#14501	73	Male	ET	1885	NA	46 XY	Wild-type	1	0	0.5
#17397	82	Male	PV	942	TF	NA	IDH2 mutant	1	1.0	1.5

Huemer F et al. *Eur J Haematol*, 2019

HMA-dirençli sekonder AML'de VEN

WBC at venetoclax start (G/L)	Best response to venetoclax (IWG)	Peripheral blast clearing during venetoclax	Survival status	PFS on prior therapy (days)	Non-hematologic venetoclax toxicity	Venetoclax dose modification	PFS on venetoclax (days)	OS from venetoclax initiation (days)
11.0	NA[b]	Day 9	Dead	222 (decitabine)	Diarrhea (III°)	Intermittent 200 mg dose (thrombocytopenia IV°)	70	126
0.7	CR	Day 21	Alive	110 (azacitidine)	None	None	505	549
9.0	TF	-	Dead	240 (azacitidine)	Fever (II°)	Temporary interruption	6	36
76.0	TF	-	Dead	325 (azacitidine)	None	None	6	15
2.0	TF	-	Dead	258 (azacitidine)	Unconjugated hyperbilirubinemia (II°)	None	18	24
269.0	TF	-	Dead	12 (azacitidine)	None	None	33	55
170.0	CR	Day 21	Dead	37 (azacitidine)	Unconjugated hyperbilirubinemia (III°)	Intermittent 200 mg dose	352	364



Huemer F et al. *Eur J Haematol*, 2019

BAYINDIR HASTANESİ- HEMATOLOJİ VE KÖK HÜCRE NAKLİ MERKEZİ

VENOTOCLAX- AZASİTİDİN PROTOKOLÜ

GÜNLER	TARİH	TEDAVİ	UYG. ŞEKLİ	DOZ	YAPILDI	UYGULAMA
1		Azasitidine 75 mg/m2	SC			Azasitidin Dextroz ile geçimsizdir !
		Venotoclax	PO	100mg		
2		Azasitidine 75 mg/m2	SC			
		Venotoclax	PO	200mg		
(3. -7.GÜNLER ARASI)		Azasitidine 75 mg/m2	SC			50 mg/2 ml steril su ile sulandırılmalıdır (100mg, 2 enjektöre)
(3. -28. GÜNLER ARASI)		Venotoclax	PO	400mg		

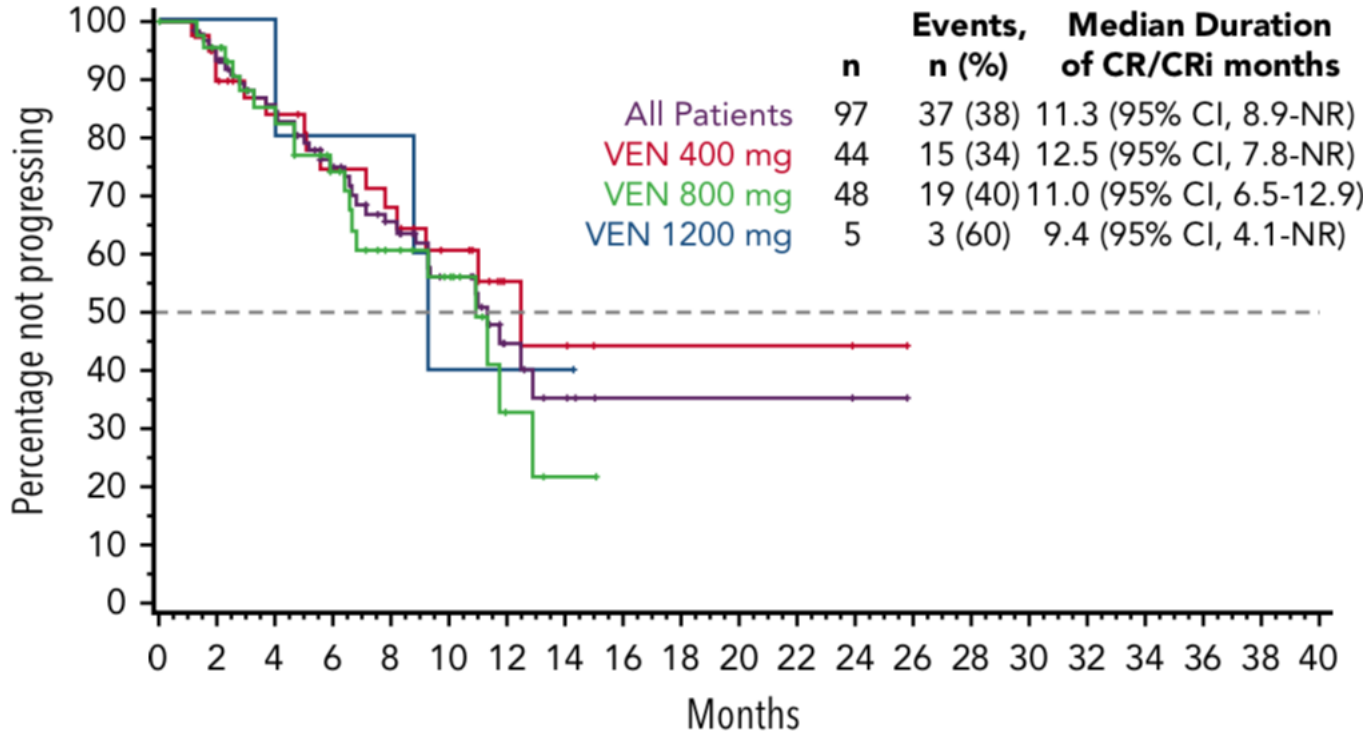
Şema 28 günde bir tekrar edilir.

Yeni tanı yaşlı AML; VEN + Desitabin/Azasitidin

Cohort	N	Composite response rate (CR + CRi) [n], n (%)	Overall response rate (CR + CRi + PR) [n], n (%)	Leukemia response rate (CR + CRi + PR + MLFS) [n], n (%)	Median duration of CR + CRi (95% CI)	Median OS (95% CI)
All patients	145	[54 + 43], 97 (67)	[54 + 43 + 2], 99 (68)	[54 + 43 + 2 + 21], 120 (83)	11.3 (8.9-NR)	17.5 (12.3-NR)
VEN 400 mg + HMA	60	44 (73)	44 (73)	49 (82)	12.5 (7.8-NR)	NR (11.0-NR)
VEN 400 mg + AZA	29	22 (76)	22 (76)	24 (83)	NR (5.6-NR)	NR (9.0-NR)
VEN 400 mg + DEC	31	22 (71)	22 (71)	25 (81)	12.5 (5.1-NR)	14.2 (7.7-NR)
VEN 800 mg + HMA	74	48 (65)	50 (68)	63 (85)	11.0 (6.5-12.9)	17.5 (10.3-NR)
VEN 800 mg + AZA	37	21 (57)	22 (59)	31 (84)	11.7 (4.6-12.9)	15.2 (9.1-NR)
VEN 800 mg + DEC	37	27 (73)	28 (76)	32 (86)	9.2 (5.9-NR)	17.5 (10.3-NR)
VEN 1200 mg + HMA	11	5 (45)	5 (45)	8 (73)	9.4 (4.1-NR)	11.4 (0.9-NR)
VEN 1200 mg + AZA	6	2 (33)	2 (33)	4 (67)	6.7 (4.1-9.4)	8.8 (0.9-NR)
VEN 1200 mg + DEC	5	3 (60)	3 (60)	4 (80)	NR (NR-NR)	NR (12.4-NR)

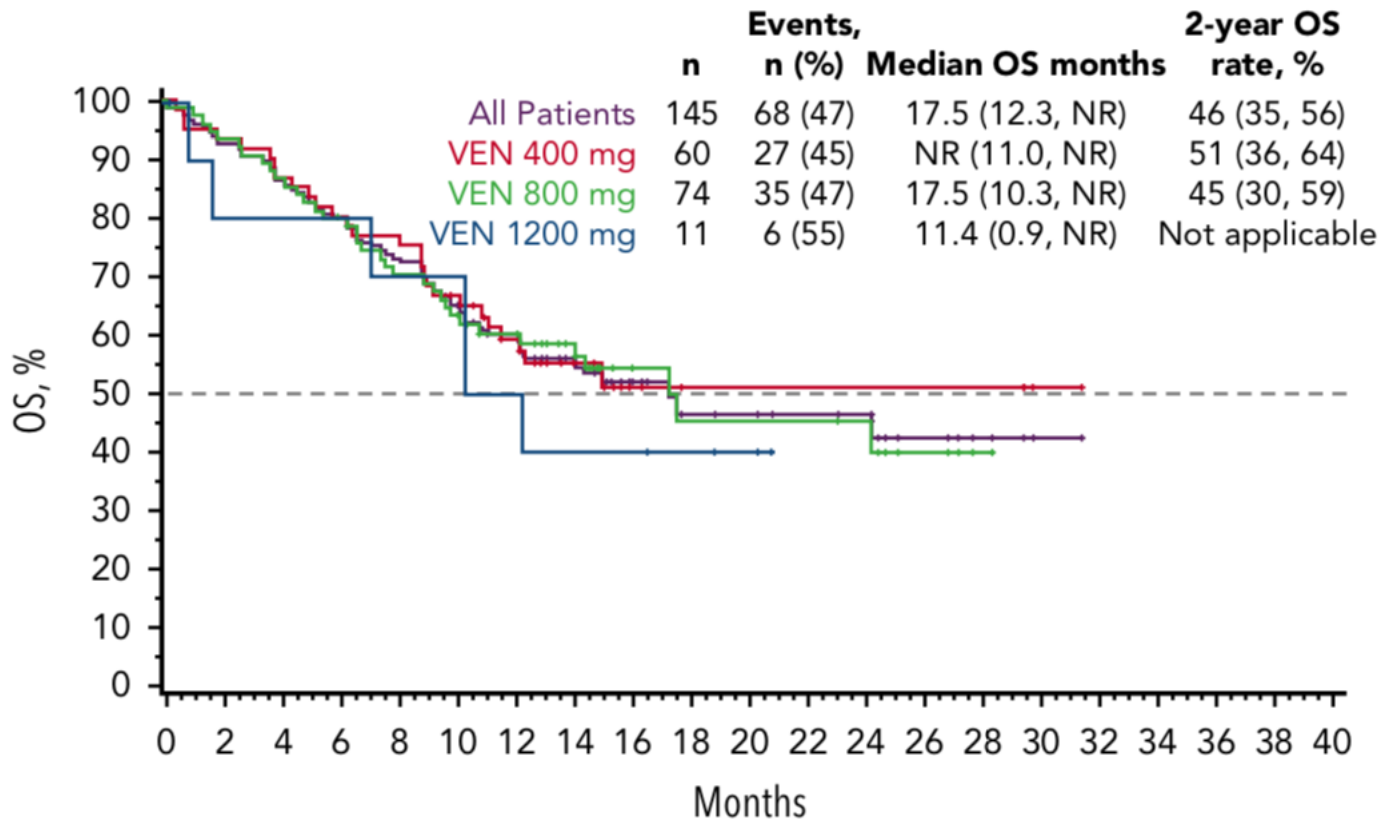
DiNardo CD et al. *Blood,* 2019

Yeni tanı yaşlı AML; VEN + Desitabin/Azasitidin: CR/CRi süresi (doz)



DiNardo CD et al. *Blood,* 2019

Yeni tanı yaşlı AML; VEN + Desitabin/Azasitidin: OS



DiNardo CD et al. ***Blood,*** **2019**

Yeni tanı yaşlı AML; VEN + Desitabin/Azasitidin

Subgroup	Evaluable for response/OS, n (%)	CR + CRi, n (%)	n for Median duration of CR + CRi	Median duration of CR + CRi, mo (95%CI)	Median OS, mo (95%CI)
All patients	145	97 (67)	97	11.3 (8.9, NR)	17.5 (12.3-NR)
Cytogenetic risk					
Intermediate	74 (51)	55 (74)	55	12.9 (11, NR)	NR (17.5-NR)
Poor	71 (49)	42 (60)	42	6.7 (4.1, 9.4)	9.6 (7.2-12.4)
Age					
≥75 y					
<75 y					
AML					
De novo					
Secondary					
Mutations*					
FLT3†					
IDH1 or 2‡					
NPM1					
TP53					

This study demonstrated a high CR + CRi rate of 67% (ORR, 68%) and a tolerable safety profile for venetoclax in combination with azacitidine or decitabine. Notably, the venetoclax 400 mg + HMA cohort achieved a CR + CRi rate of 73%, a median duration of CR + CRi of 12.5 months, and median OS not reached. These results warrant further evaluation of 400-mg venetoclax + HMA in a larger population.

DiNardo CD et al. *Blood,* 2019

R/R AML'de VEN + …

Characteristic	N = 43 (%)
Median age (range), *years*	68, 25–83
>65 yrs	25 (58)
Male—no. (%)	28 (65)
Diagnosis—no. (%)	
AML	39 (91)
MDS/MPN	2 (5)
BPDCN	2 (5)
Relapsed status—no. (%)	
Salvage 1	7 (16)
Salvage ≥ 2	36 (84)
Prior allogeneic SCT	5 (12)
Treated AHD	12 (31)
Cytogenetics—no. (%)	
Adverse	20 (47)
Diploid	12 (28)
Inv(16)	2 (5)
Other Intermediate	9 (21)
Molecular mutations—no. (%)	
IDH1/2[a]	11 (26)
TP53	10 (23)
TET2	10 (23)
RUNX1	8 (19)
DNMT3A	8 (19)
ASXL1	6 (14)
K/NRAS	6 (14)
FLT3	5 (12)
CEBPA	4 (9)
JAK2	4 (9)
NPM1	3 (7)
IKZF2	2 (5)
VEN combination regimen—no. (%)	
Azacitidine[b]	8 (19)
Decitabine[c]	23 (53)
Low-dose cytarabine[d]	8 (19)
Other[e]	4 (9)
VEN maintenance dose (median, range), *mg*	200 (100–800)

DiNardo CD et al. *Am J Hematol,* 2018

R/R AML'de VEN + …: Cevap veren hastalar

Patient	Cytogenetics	Molecular	Salvage	VEN dose (mg)	Chemotherapy	Best response	Cycles to respond	Total cycles[a]
1. 76F	Inv(16)	CBFB-MYH11	2	800	Azacitidine[e]	CRi	1	4
2. 74M[b]	Adverse	ASXL1, RUNX1, TET2, TP53	5	400	Decitabine[e]	MLFS	1	1
3. 60F	Diploid	CEBPA	6	100[d]	Decitabine[e]	MLFS	1	2
4. 51F[c]	Adverse	RUNX1, TP53	6[i]	100[d]	Decitabine[h]	MLFS	1	4
5. 73M[b]	Intermediate	IDH2, IZKF2	5	100[d]	LDAC[g]	CRi	1	2
6. 72M	Diploid	IDH1, IDH2, RUNX1	2	200[d]	Azacitidine[f]	CR	1	2
7. 40M	Intermediate	IDH2	1[i]	100[d]	Azacitidine[f]	MLFS[j]	1	2
8. 63M	Adverse	RUNX1	2	100[d]	Decitabine[h]	CR[j]	1	2
9. 58M[b]	Diploid	None	2	400[d]	Decitabine[h]	CRi	1	2

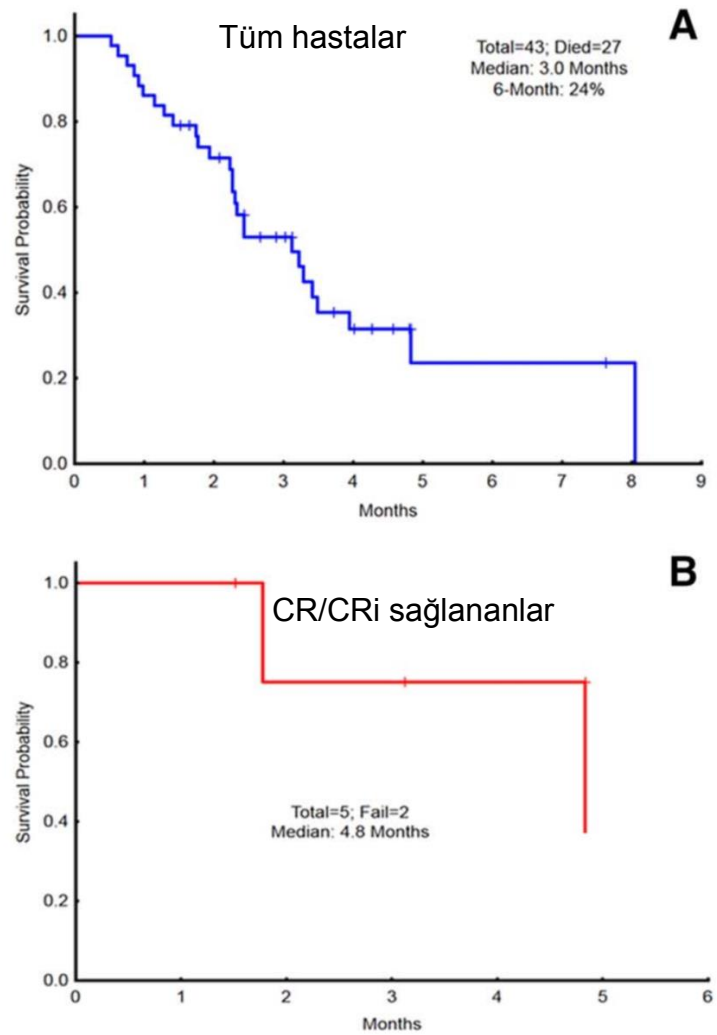
DiNardo CD et al. *Am J Hematol,* 2018

R/R AML'de VEN + …: Tedavi cevabı

Characteristic	*N* = 43 (%)
VEN combination cycles received[a]—no. (%)	
1	17 (40)
2	18 (42)
≥3	8 (19)
Response—no. (%)	
ORR	9 (21)
CR	2 (5)
CRi	3 (7)
MLFS	4 (9)
NR	34 (79)
Early death (within 30 days)	5 (12)
Median overall survival[a] (range), *months*	3.0 (0.5–8.0)

DiNardo CD et al. *Am J Hematol,* 2018

R/R AML'de VEN + …: OS



DiNardo CD et al. *Am J Hematol,* 2018

Bone Marrow Transplantation
https://doi.org/10.1038/s41409-018-0347-6

CORRESPONDENCE

Feasibility of Venetoclax-based combinations for adult patients with acute myeloid leukemia relapsing after allogenic stem cell transplantation

Nour M. Moukalled[1] · Haidar El Darsa[1] · Yolla Haibe[1] · Radwan Massoud[1] · Souha S. Kanj[2] · Rami Mahfouz[3] · Ali Bazarbachi[1] · Jean El-Cheikh[1]

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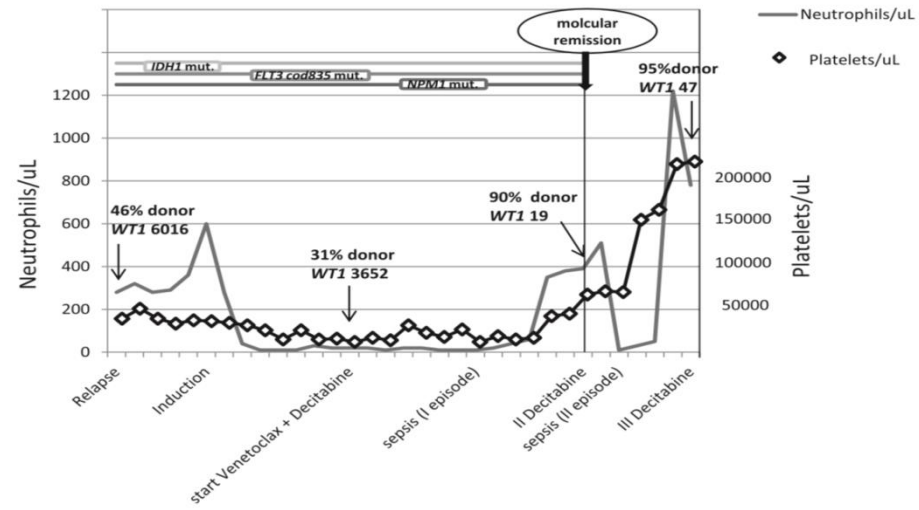
DOI: 10.1002/ajh.25352

Venetoclax plus decitabine induced complete remission with molecular response in acute myeloid leukemia relapsed after hematopoietic stem cell transplantation



ALL'de BCL-2 inhibitörleri

Hindawi
Case Reports in Hematology
Volume 2018, Article ID 6092646, 4 pages
https://doi.org/10.1155/2018/6092646

Case Report

Venetoclax in Combination with Decitabine for Relapsed T-Cell Acute Lymphoblastic Leukemia after Allogeneic Hematopoietic Cell Transplant

Leena T. Rahmat,[1] **Anna Nguyen**,[2] **Haifaa Abdulhaq**,[3] **Sonam Prakash**,[2] **Aaron C. Logan**,[1] **and Gabriel N. Mannis**[1]

Feasibility of the Combination of Venetoclax and Asparaginase-based Chemotherapy for Adult Patients With Relapsed/Refractory Acute Lymphoblastic Leukemia

Jean El-Cheikh,[1] Nour M. Moukalled,[1] Haidar El Darsa,[1] Radwan Massoud,[1] Souha S. Kanj,[2] Rami Mahfouz,[3] Ali Bazarbachi[1]

Table 1 Patients' Characteristics

Characteristics	Patient 1	Patient 2	Patient 3	Patient 4
Age/gender	23/F	21/F	53/M	27/F
Subtype	T-ALL	T-ALL	T-ALL	B-ALL
Molecular	TCR Gamma, beta, delta	TCR Gamma, beta delta	TCR Gamma, beta, delta	IgH/IgK
Karyotype	46 XX iso(21)	NA	NA	NA
Lines of therapy prior to venetoclax	5	5	2	4
Type of prior regimens	HyperCVAD; MTX + V + IT chemo; Clofa; allo-SCT; BFM	Ida + Arac; FLAG + HDArac; Clofa + Etopo + Cyclo; Aug BFM	HyperCVAD; BFM-like;	R-modified AugBFM; POMP; R-hyperCVAD; Capizzi; allo-SCT
Transplanted	Yes from MSD	Not transplanted	Not transplanted	Yes haploidentical

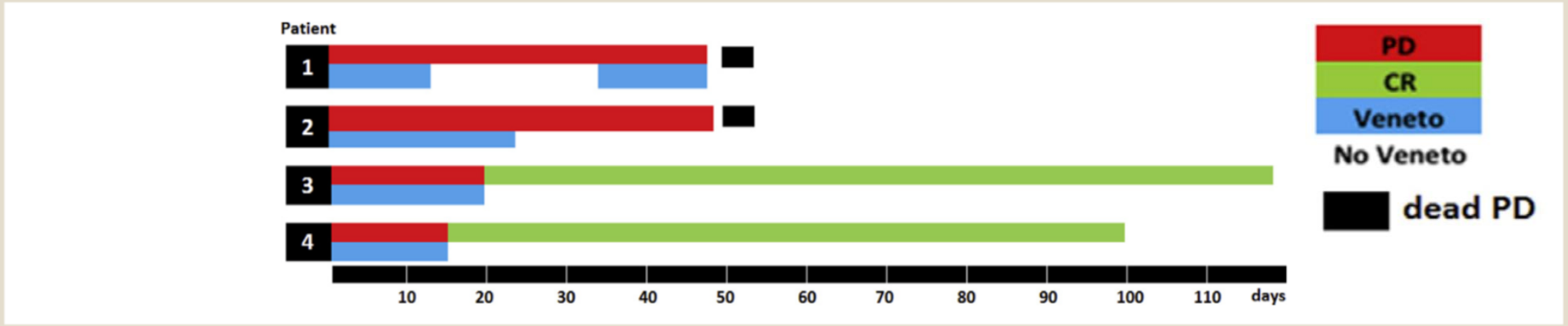
El-Cheikh et al. ***Clinical Lymphoma, Myeloma & Leukemia,*** **2018**

Table 2 Venetoclax Characteristics

Characteristics	Patient 1	Patient 2	Patient 3	Patient 4
Ramp-up venetoclax 5 days	Yes daily five days	Yes daily 5 days	Yes daily 5 days	Yes daily 3 days
Dose of venetoclax, mg	400	400	400	100
Concomitant azole	No	No	No	Voriconazole
Duration of venetoclax, d	45	24	20	14
Concomitant chemotherapy	BFM-like	Augmented BFM	BFM-like	Capizzi
Response	Hematologic CR Positive TCR gamma, beta, delta	No Response Residual 16% blasts	Hematologic CR Molecular CR	Hematologic CR Molecular CR
Adverse events	Yes	Yes	Yes	Yes
Treatment interruptions/ timing/duration	Yes/After 14 days/20 days	Yes/After 24 days/discontinued	Yes/After 20 days/discontinued	Yes/After 14 days/discontinued
Anemia/grade	Yes/severe	Yes/severe	Yes/severe	Yes/severe
Thrombocytopenia/grade duration	Yes/severe/persistent	Yes/severe/persistent	Yes/severe/21 days	Yes/severe/20 days
Neutropenia/grade/	Yes/severe/persistent	Yes/severe/persistent	Yes/severe/21 days	Yes/severe/21 days
Febrile neutropenia	Yes	Yes	No	No
Other toxicities	TLS; Organ failure	Fulminant Asperigellosis	No	No
Infection	Yes	Yes	Yes	No
CR achieved	Yes	No	Yes	Yes
Follow-up since start of venetoclax	45 days	49 days	111 days	99 days
Disease status at last follow-up	Progressive disease	Residual blasts	CR	CR
Alive at last follow-up	Dead	Dead	Alive	Alive

El-Cheikh et al. *Clinical Lymphoma, Myeloma & Leukemia,* 2018

Figure 1 Dynamics of Response to Venetoclax



these results suggest that venetoclax appears feasible in combination with chemotherapy in the treatment of R/R ALL.

El-Cheikh et al. *Clinical Lymphoma, Myeloma & Leukemia,* 2018

R/R ALL'de VEN + Nav

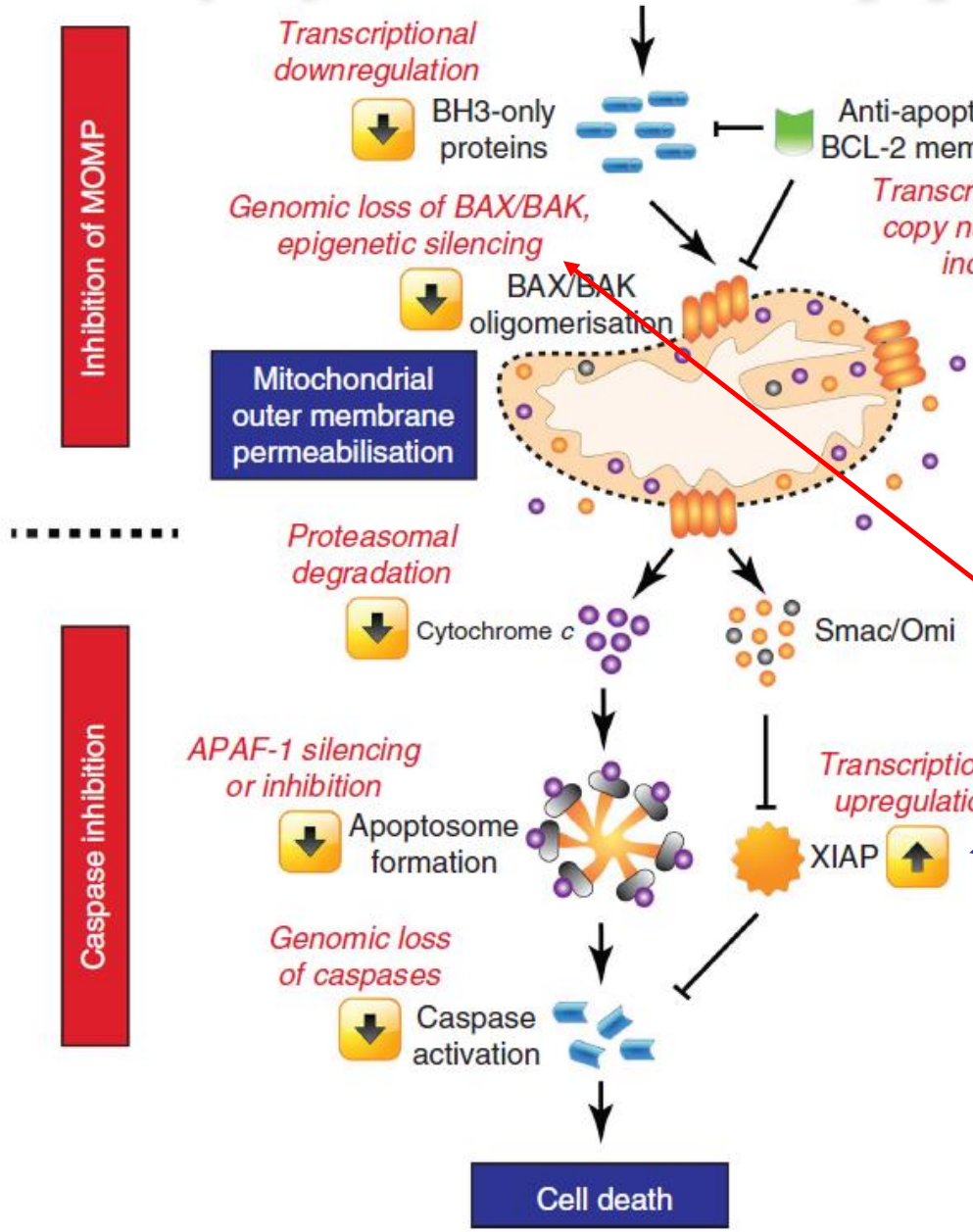
	Patient								
	A	B	C	D	E	F	G	H	I
ALL Immuno-phenotype (initial diagnosis)	Pre-B	Pre-B	Pre-B	Pre-B	Pre-B	T-ALL: ETP	T-ALL: ETP	T-ALL: medullary	T-ALL: medullary
Age, years	45	19	25	22	31	29	36	25	43
Sex	M	F	M	F	M	M	M	M	M
Number prior anti-ALL therapies	6	4	3	2	1	8	3	1	3
Prior stem cell transplant	Y	N	Y	N	N	N	N	N	N

Abbreviations: ALL, acute lymphoblastic leukemia; ETP, early T cell precursor; F, female; M, male

	B-Cell ALL Patients					T-Cell ALL Patients			
	A	B	C	D	E‡	F	G	H	I
Best response* (MRD, % cells)†	CR (neg)§	CRp (0.7)§	CR (neg)§	SD (0.53)¶	CRi (NA)§	CR (1)§	SD (NA)¶	SD (NA)¶	PR (8.9)¶
Time to first response, months	0.3	1.2	1.2	–	1.1	1.2	–	–	0.3
DOR, months	5.1 ongoing#	1.8	3.5 ongoing	–	0.1	2.3	–	–	0.3 ongoing
Time on study, months	5.9	5.4	5.1	1.2	1.2	4.0	0.8	0.6	0.6

Alexander T et al. *Blood,* 2018

Apoptosis'den Kaçış Mekanizmaları



Loss-of-function

BIM: BL, MCL
PUMA: BL
NOXA: DLBCL
BAD: DLBCL
BAX: BL, PCL, **ALL**

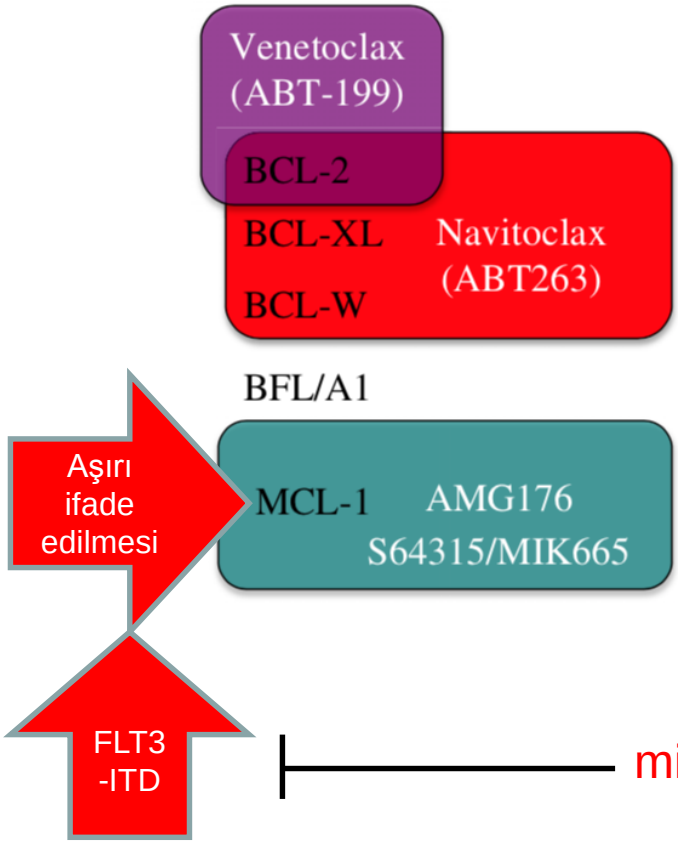
Gain-of-function

BCL-2:
FL t(14;18), KLL,
MM t(11;14), **AML**,
MCL (18q21), DLBCL
MCL-1:
AML, MCL, DLBCL,
MM
A1:
ALL, KLL, MCL
BCL- XL:
Çeşitli B- lenfomalar

IAP:
MALT t(11;18),
ErişkinT-hücreli lösemi
AML
Pediatrik T-ALL

Lopez J et al. B*JC*, 2015

VEN ve Nav direncinin geri çevrilmesi

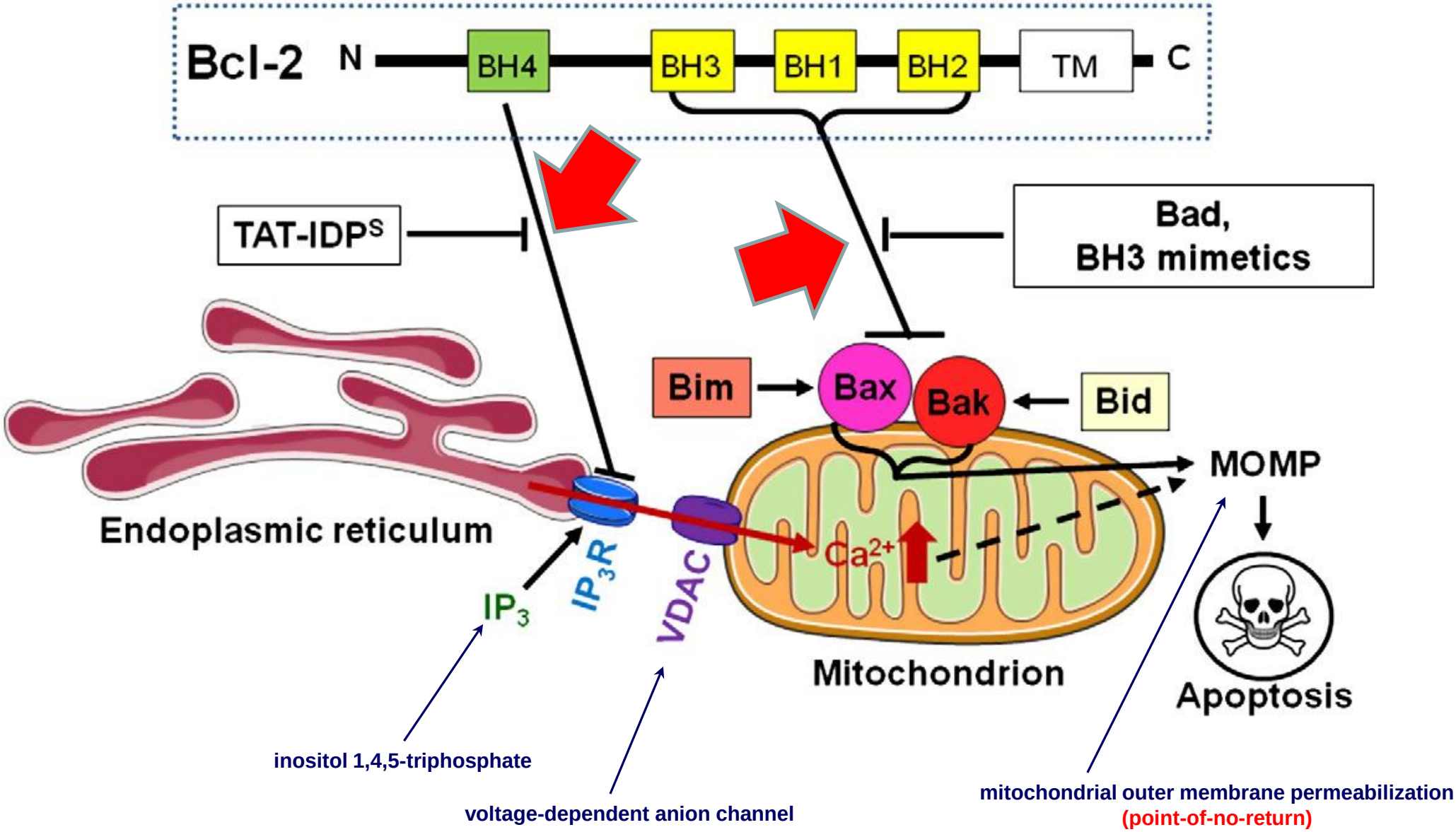


veya MCL1'in transkripsiyonel regülatörü olarak cyclin-dependent kinaz 9

veya XPO1 inhibisyonu (selinexor) ile MCL1 ifadesinin azaltılması

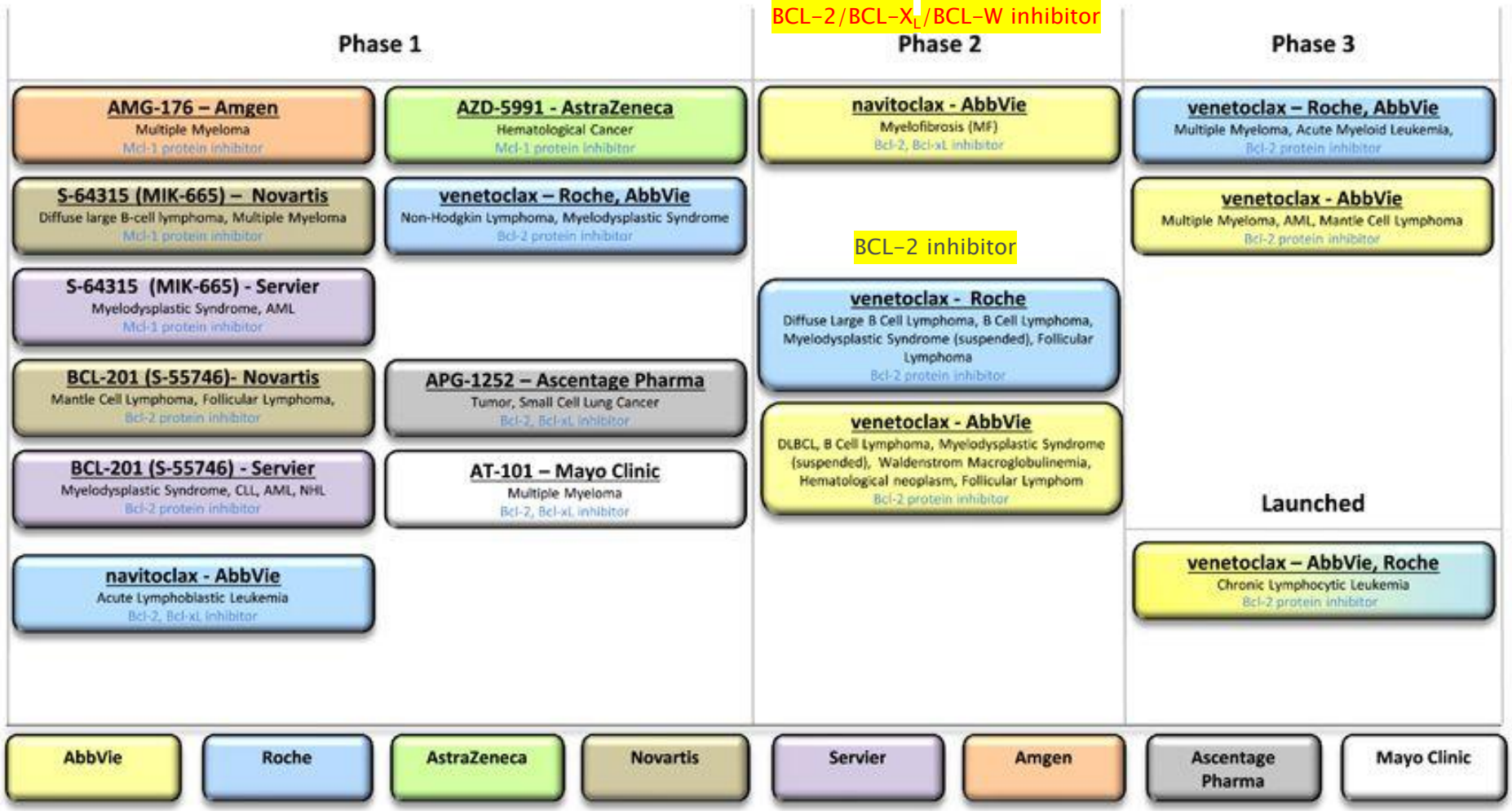
veya dounorubicin ile MCL1 seviyesinin azaltılması

midostaurin, gilteritinib



Akl H et al. *Biochimica et Biophysica Acta,* 2014

BCL-2 ailesini hedefleyen moleküller



Apoptosis'den Kaçış Mekanizmaları

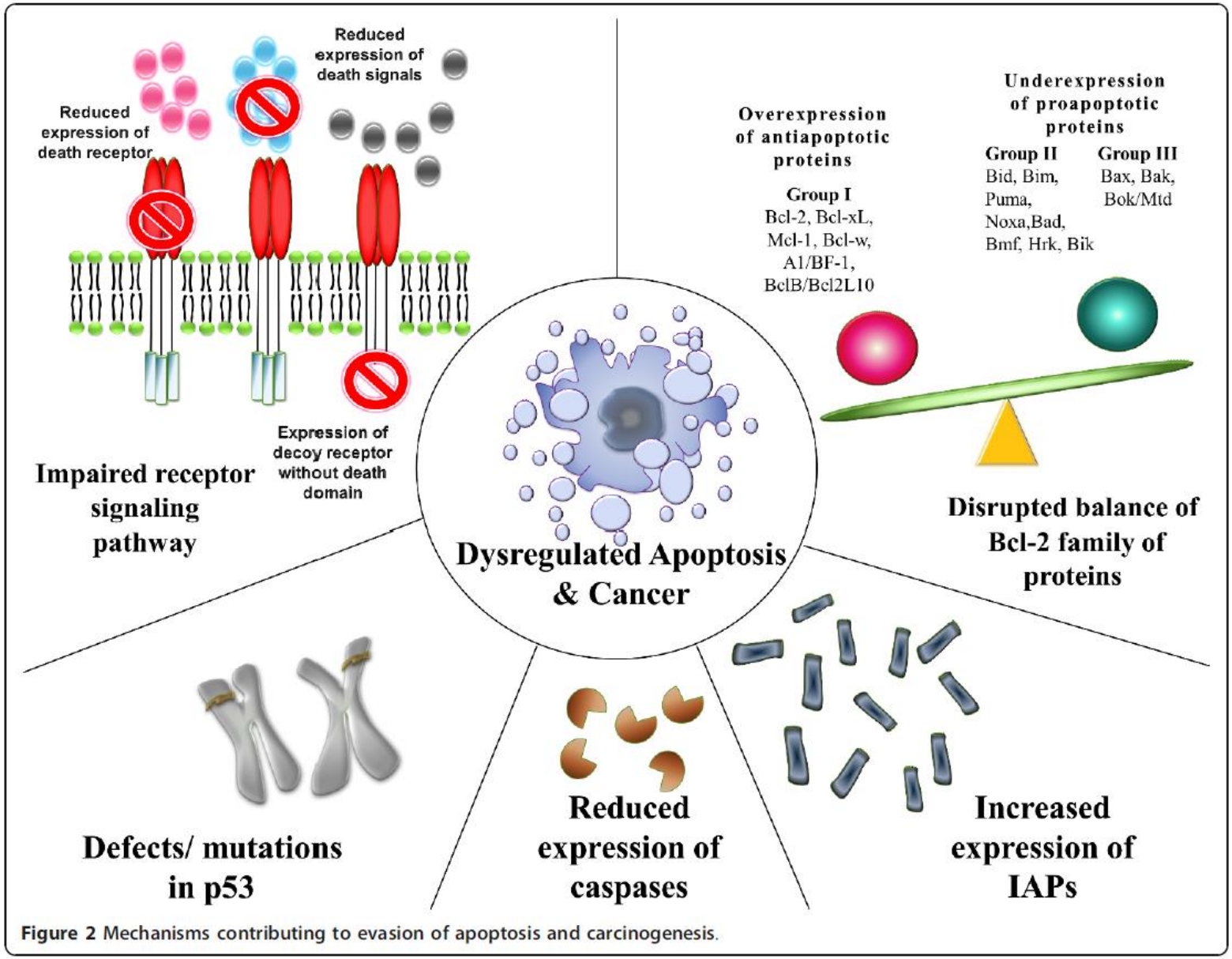


Figure 2 Mechanisms contributing to evasion of apoptosis and carcinogenesis.

Wong RSY. *J Exp Clin Cancer Res*, 2011