Venetoclax in MCL

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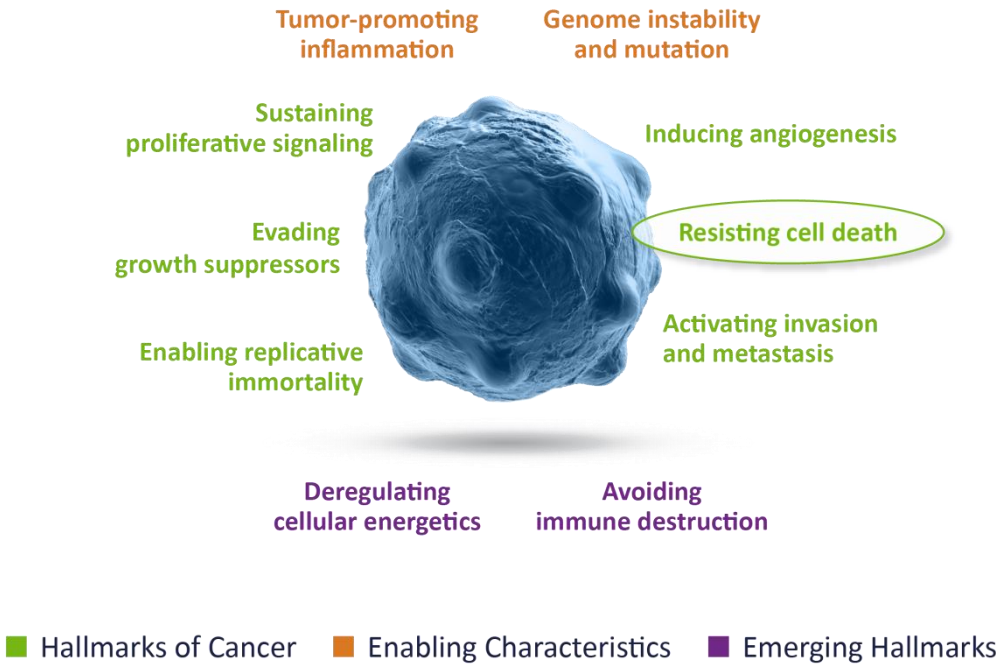
Lysa
THE LYMPHOMA STUDY ASSOCIATION

Evasion of Apoptosis, or Cell Death, is One Hallmark of Cancer

1. **Resisting Cell Death**
2. Sustained angiogenesis for growth and survival (primarily solid tumors)
3. Self-sufficiency in growth signals
4. Insensitivity to anti-growth signals
5. Tissue invasion and metastasis
6. Limitless replication potential

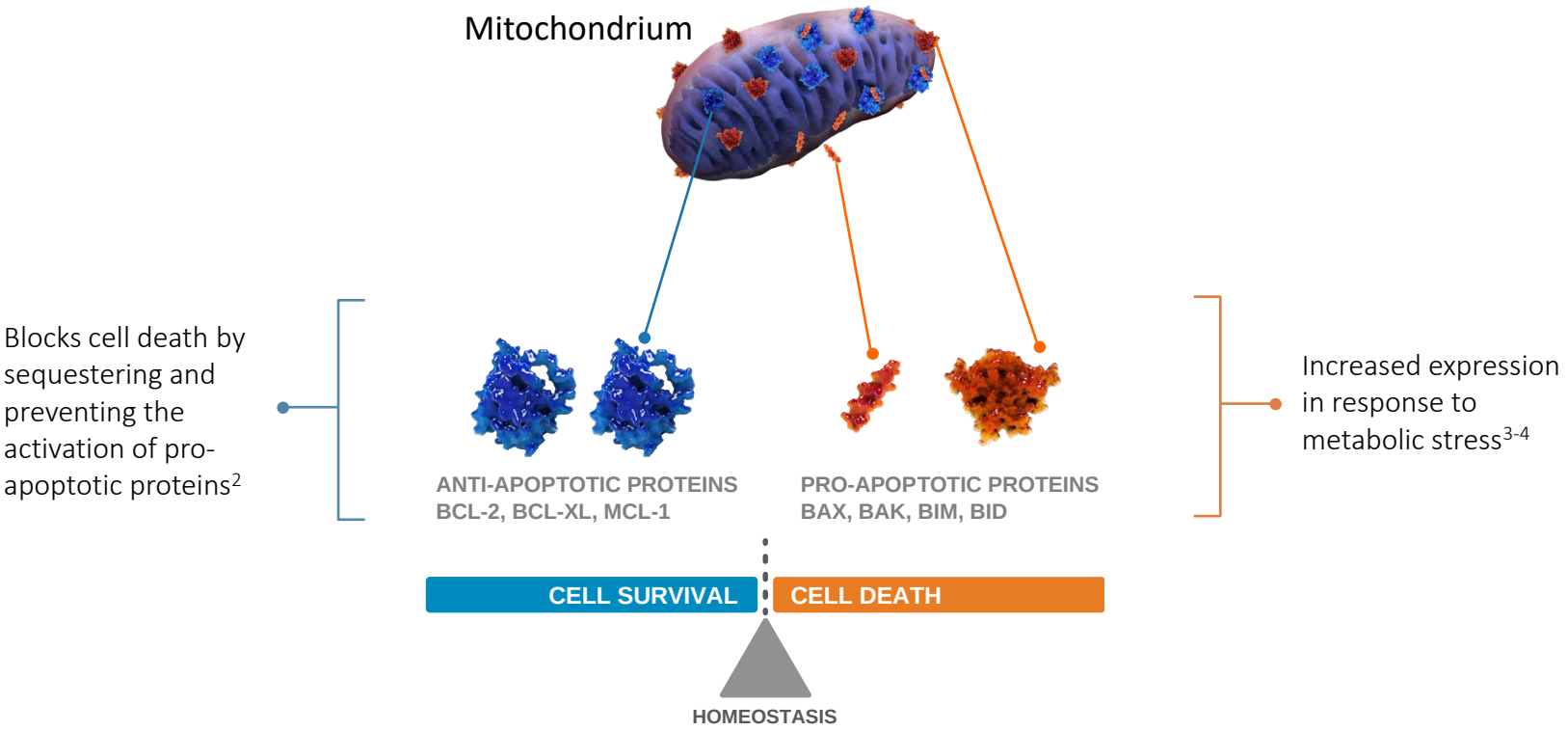
Others: Evasion of immune system



Hanahan, Weinberg. *Cell*. 2000;100:57-70.

The BCL-2 Family of Proteins Regulate the Apoptotic Process

The BCL-2 family consists of pro- and anti-apoptotic proteins that function cooperatively to regulate the intrinsic pathway of apoptosis[1-2].



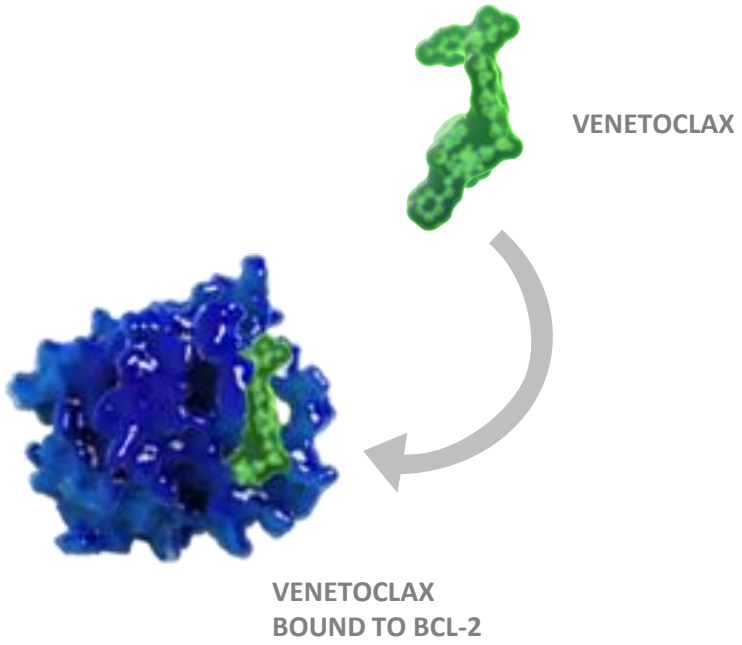
The dynamic balance between pro- and anti-apoptotic members determines whether a cell will live or die[2]

1. Cory S et al. Oncogene 2003;22:8590–8607. 2. Plati J, Bucur O, Khosravi-Far R. Integr Biol (Camb) 2011;3:279–296. 3 Deng, J., et al., Cancer Cell, 2007. 12(2): p. 171-85. 4. Certo et al, Cancer Cell 9, 351-365; 2006

Venetoclax is a Selective Inhibitor of BCL-2[1]

Venetoclax is a selective, orally available small-molecule BCL-2 inhibitor which helps restore apoptosis independent of TP53 functional status[1,2].

Venetoclax is structurally designed to bind to BCL-2, in
a manner analogous to native pro-apoptotic factors[1].

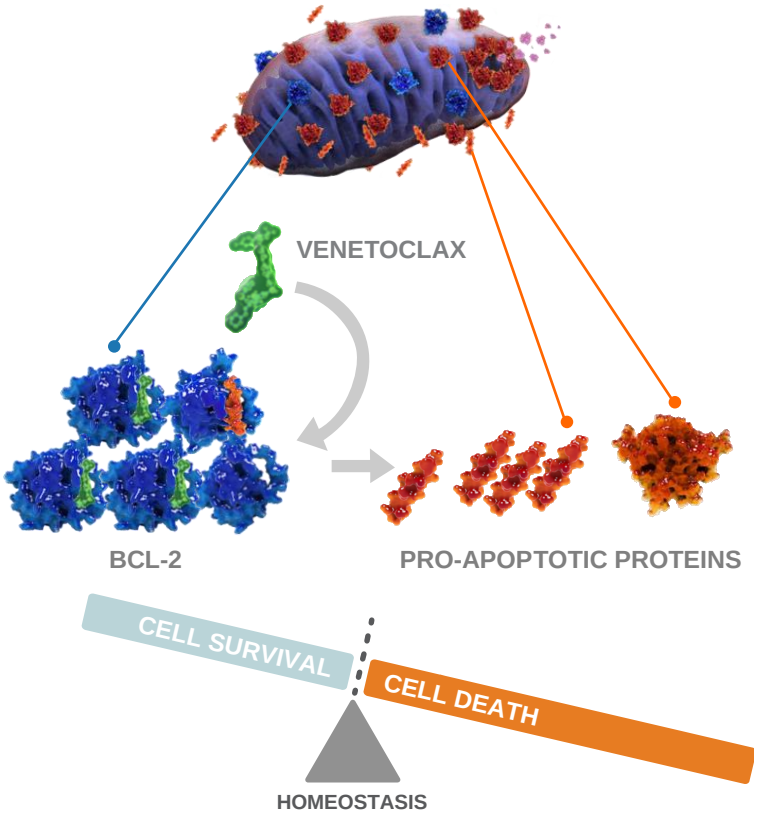


1.Souers, A.J., et al. Nat Med, 2013. 19(2): p. 202-8. 2. Anderson MA, Tam CS, Seymour JF et al. ASH Annual Meeting Abstracts 2013;122.

Venetoclax Restores Apoptosis by Helping Release Sequestered Pro-apoptotic Proteins[1-4]

Venetoclax inhibits BCL-2 and can contribute to releasing the store of pro-apoptotic proteins, helping tip the balance in favor of cell death[1-3].

Venetoclax can induce cell death irrespective of TP53 function as the effects of BCL-2 inhibition are thought to be independent of this pathway[4]



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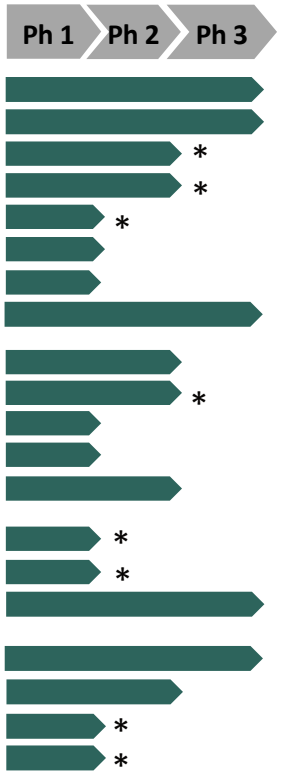
Venetoclax is developped in a Range of Hematologic Malignancies

	Combination (study name)	Indication
CLL	*+Rituxan (MURANO)*	r/r CLL
	+Gazyva (CLL14)	CLL
	monotherapy	r/r CLL 17p
	monotherapy	r/r CLL after BCRi
	+Rituxan	r/r CLL & SLL
	+BR	r/r CLL & CLL
	+Gazyva	r/r CLL & CLL
	+Gazyva/Imbruvica (CLL13) [a]	1L CLL
NHL	*+Rituxan vs BR (CONTRALTO)*	r/r FL
	+R-CHOP vs R-CHOP (CAVALLI)	1L DLBCL
	+BR	r/r NHL
	monotherapy	r/r CLL & r/r NHL
	+Gazyva/polatuzumab	DLBCL & FL
MM	*monotherapy*	r/r MM
	+bortezomib/dex	r/r MM
	+bortezomib/dex [a]	r/r MM
AML	*+dec / +aza* [a]	AML
	monotherapy	AML
	+dec / +aza	AML
	+Ara-C	AML



Slide provided by Abbvie

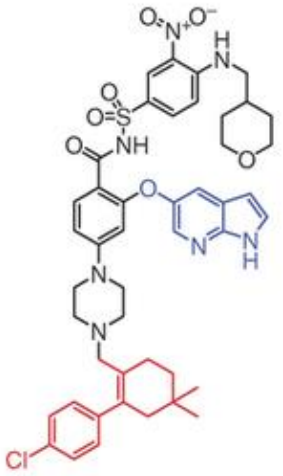
Venetoclax:
Rational in MCL

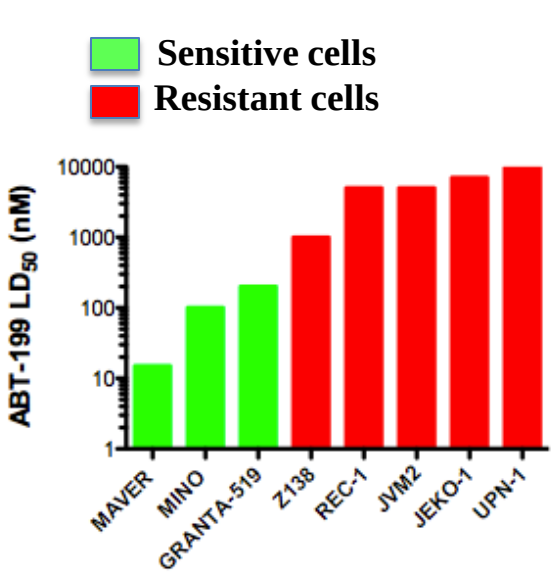
MCL: a Bcl-2-dependent tumor

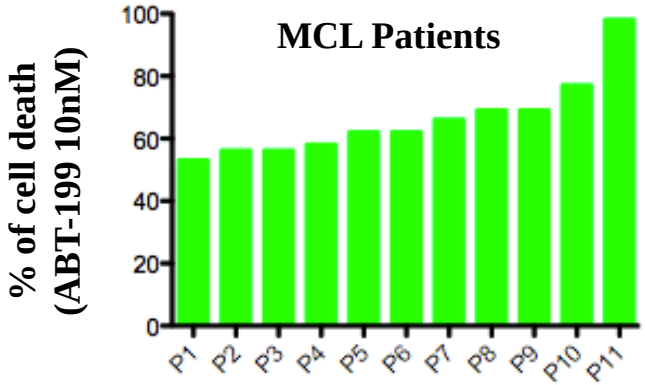
VENETOCLAX, ABT-199 Affinity

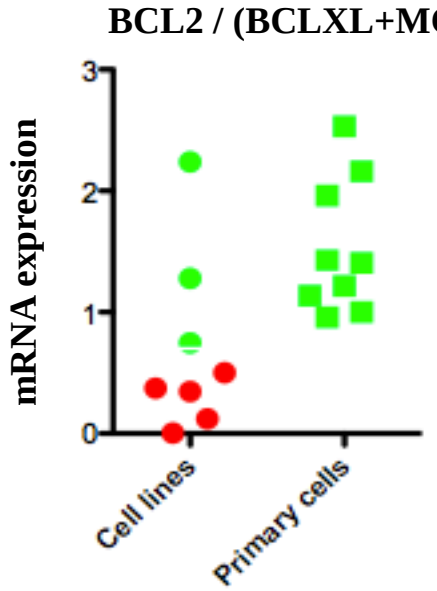
BCL2 < 0.01 nM
BCLXL = 48nM
MCL1 >444nM

Souers et al Nature Medecine 2013





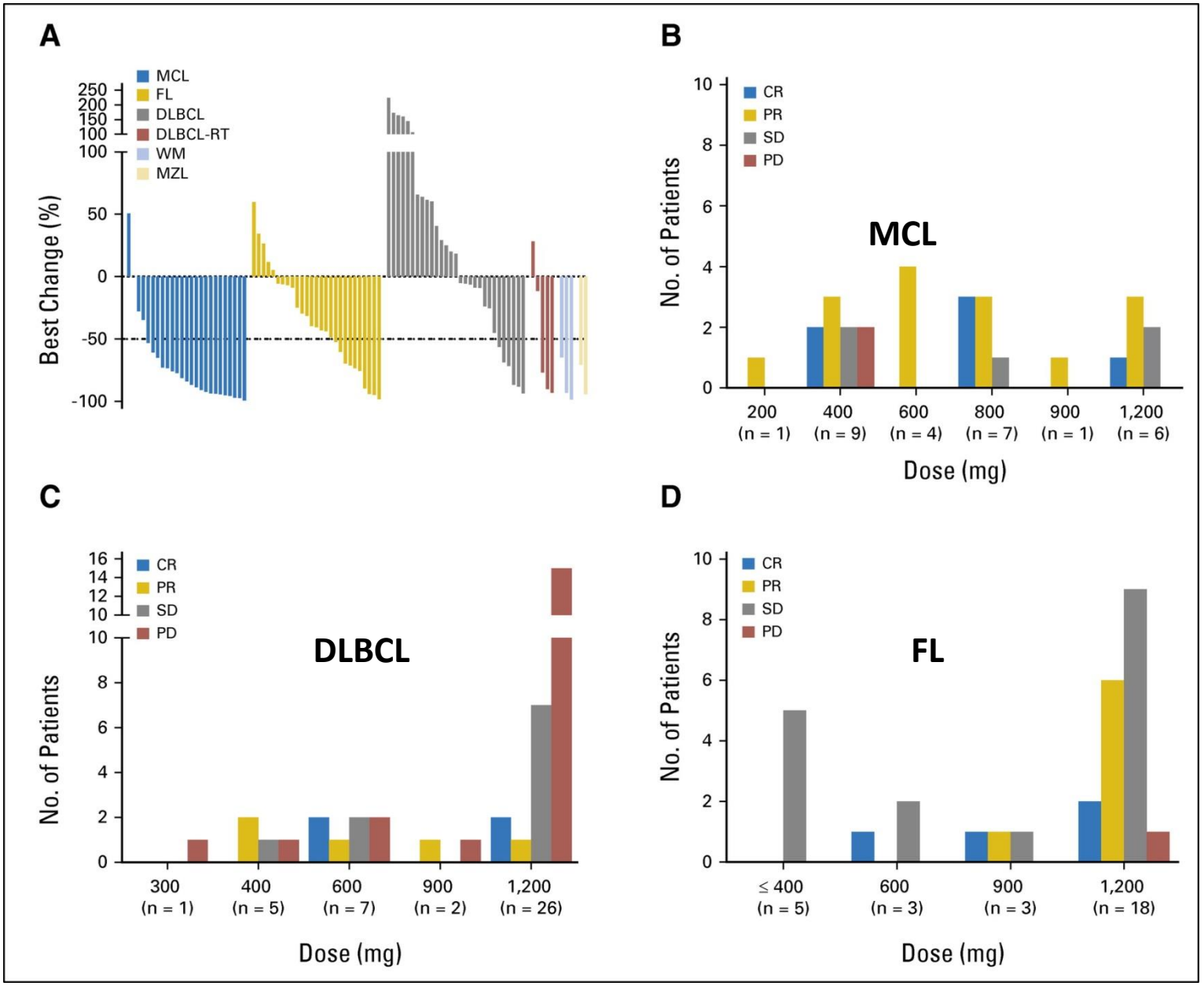




MCL sensitivity to venetoclax correlates with BCL2 / (BCLXL + MCL1) mRNA ratio

Chiron et al Oncotarget 2015

Venetoclax in monotherapy in MCL

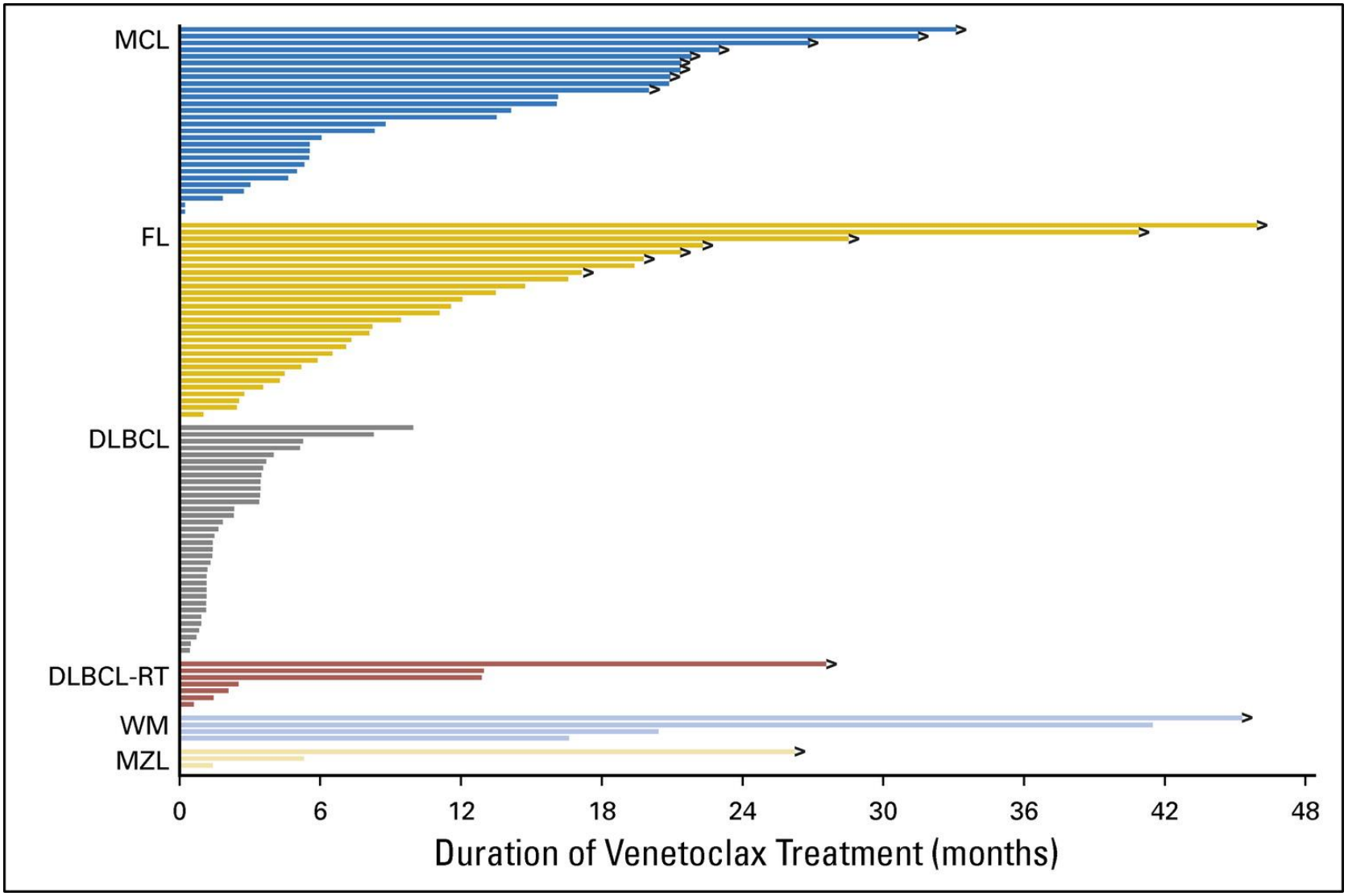


Davids MS et al. J Clin Oncol 2017

Phase I First-in-Human Study of Venetoclax in Patients With Relapsed or Refractory Non-Hodgkin Lymphoma

Tx Réponses / histologie (IIT)							
Best response	**All (106)**	**MCL (28)**	**FL (29)**	**DLBCL (34)**	**RT (7)**	**WM (4)**	**MZL (3)**
ORR (%)	47 (44)	21 (75)	11 (38)	6 (18)	3 (43)	4 (100)	2 (67)
CR (%)	14 (13)	8 (21)	4 (14)	4 (12)	0	0	0
PR (%)	33 (31)	15 (54)	7 (24)	2 (6)	3 (43)	4 (100)	2 (67)
SD (%)	32 (30)	5 (18)	17 (59)	8 (24)	2 (29)	0	0
PD (%)	24 (23)	2 (7)	1 (3)	19 (56)	1 (14)	0	1 (33)

Davids MS et al. J Clin Oncol 2017



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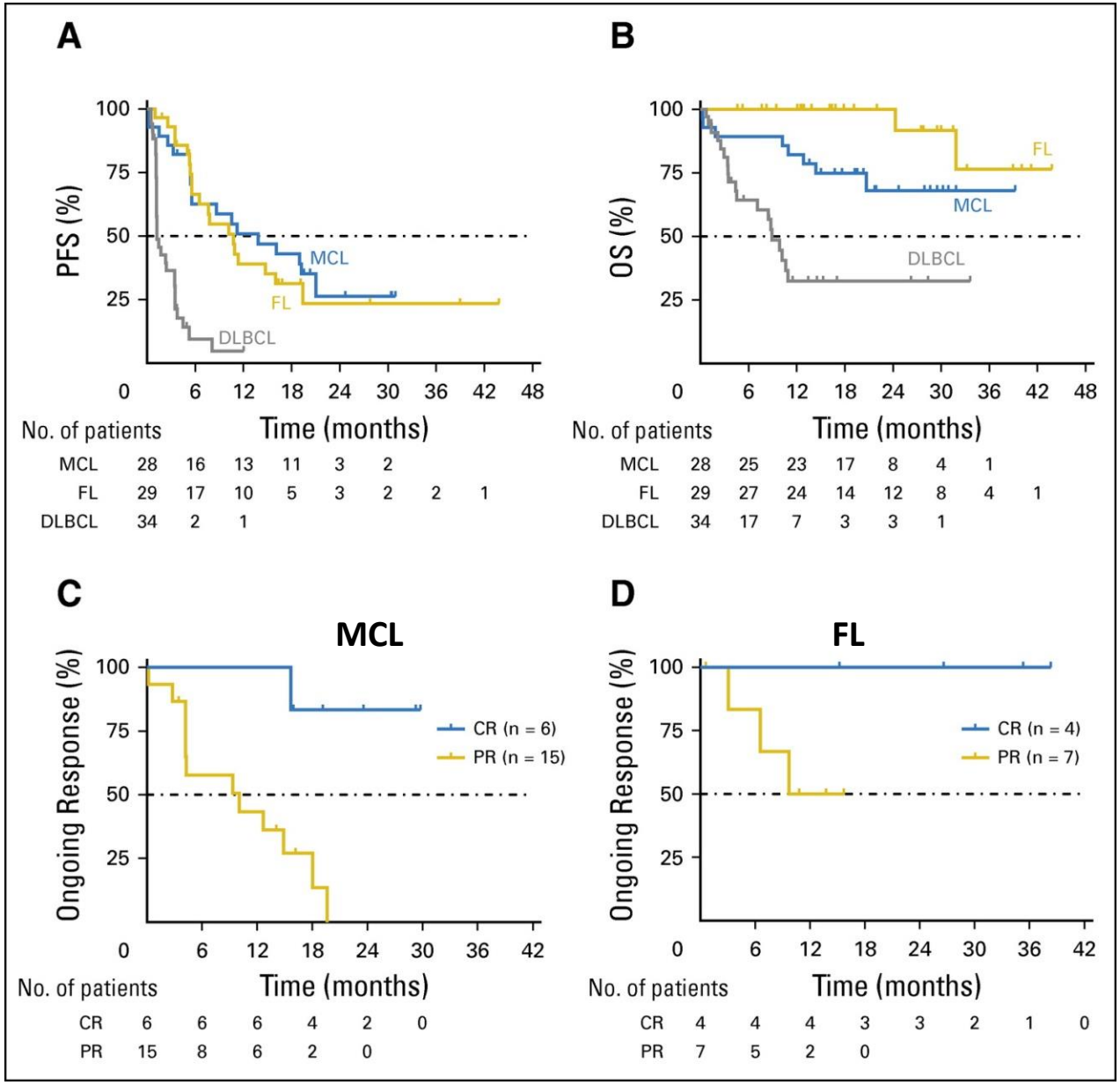


Davids MS et al. J Clin Oncol 2017

Venetoclax in combo in MCL

Initial Report of a Multi-Institution Phase I/Ib study of Ibrutinib with Venetoclax in relapsed or refractory Mantle Cell Lymphoma.

2-stages study
Until progression or unacceptable toxicity

STUDY TYPE
- Phase: 1/1b
- Accrual: 28(target)
- Location: USA
- Start enrollment : 10/2015

SPONSOR
- Graig Portell, University of Virginia, USA

STATUS
- Open, recruiting

KEY INCLUSION CRITERIA
- Confirmed diagnosis of MCL with at least one prior line of Tx
- Measurable disease
- No previous ibrutinib or BTK inhibitors

KEY ENDPOINTS
- DLT (30 d post initiation)
- Toxicity (AE/SAE)
- ORR; CR;
- PFS; OS;
- Completing 4, 16, 28, 40, 56 wks Tx

STUDY DESIGN

Venetoclax (100 – 400 mg)
Ibrutinib (280 – 560 mg)

Table 1. Zone and Arm Designation by Combination

Venetoclax (mg per day)				
	400 (week 3+) 200 (week 2) 100 (week 1)	Zone 2 / Arm C	Zone 3 / Arm E	Zone 4 / Arm F
	200 (week 3+) 200 (week 2) 100 (week 1)	Zone 1 / Arm A	Zone 2 / Arm B	Zone 3 / Arm D
All subjects 100 mg/day Venetoclax (week 0)		280	420	560
		Ibrutinib (week 1+) mg per day		

CLINICAL UPDATE [ASH 2016, Abstr # 2958]

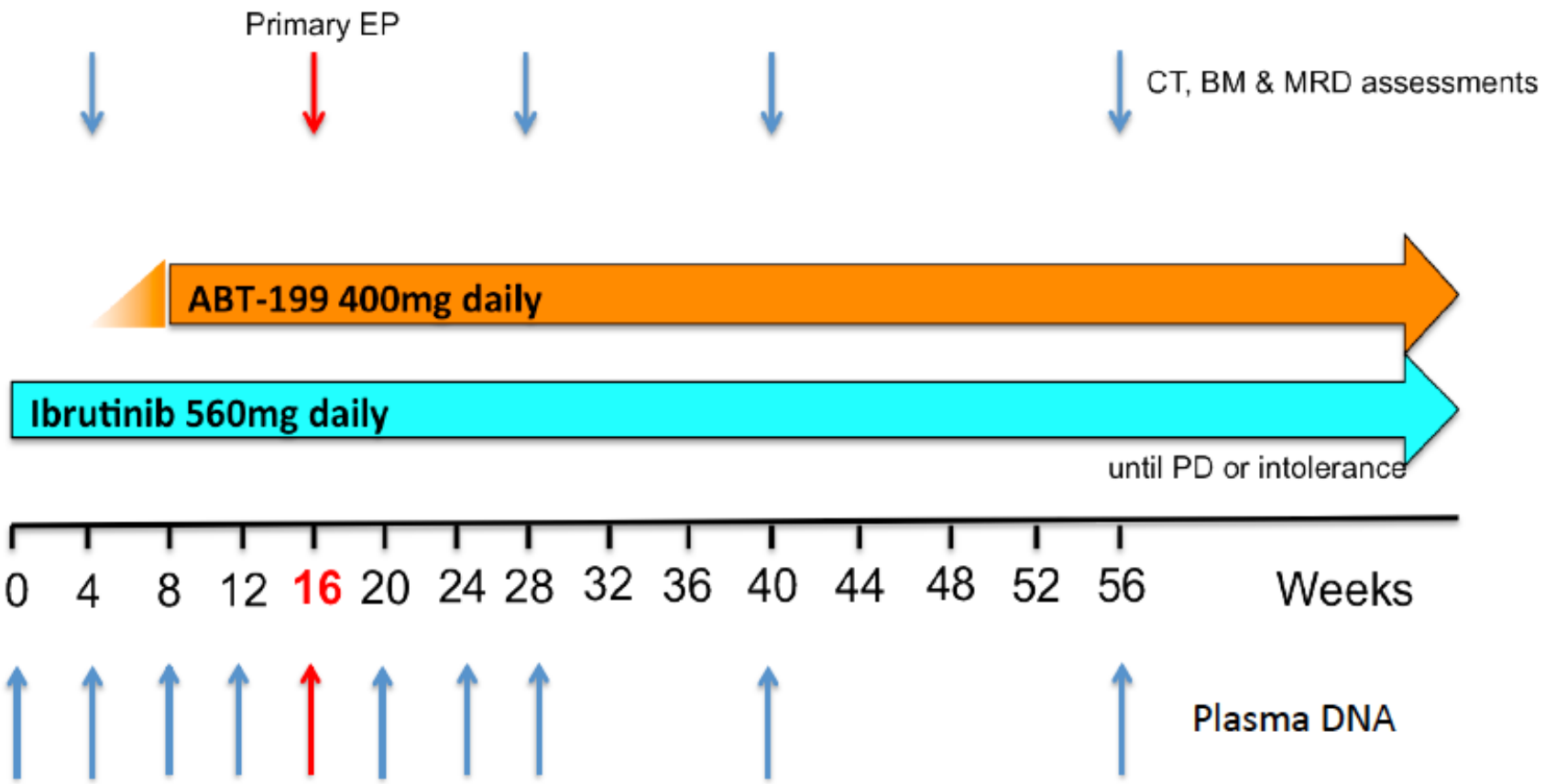
- 8 pts reported and finished stage I (Arms A to E)
- Mean age = 63 y (49-81). M / F = 7/1. 5 pts refractory / 3 pts relapsed after ASCT
- 7/8 evaluable for AE. 15 AE (14 grade ½). No TLS, 1 DLT (grade 4 neutropenia),
- 3 pts evaluable for response: 3 PR (1 pt achieving CR at 4 Mo)

Portell GA, ASH 2016. Abst # 2958

Ibrutinib + ABT-199 for MCL (AIM Study)

Con Tam
Victorian Comprehensive Cancer Center

AIM: ABT-199 & Ibrutinib Study



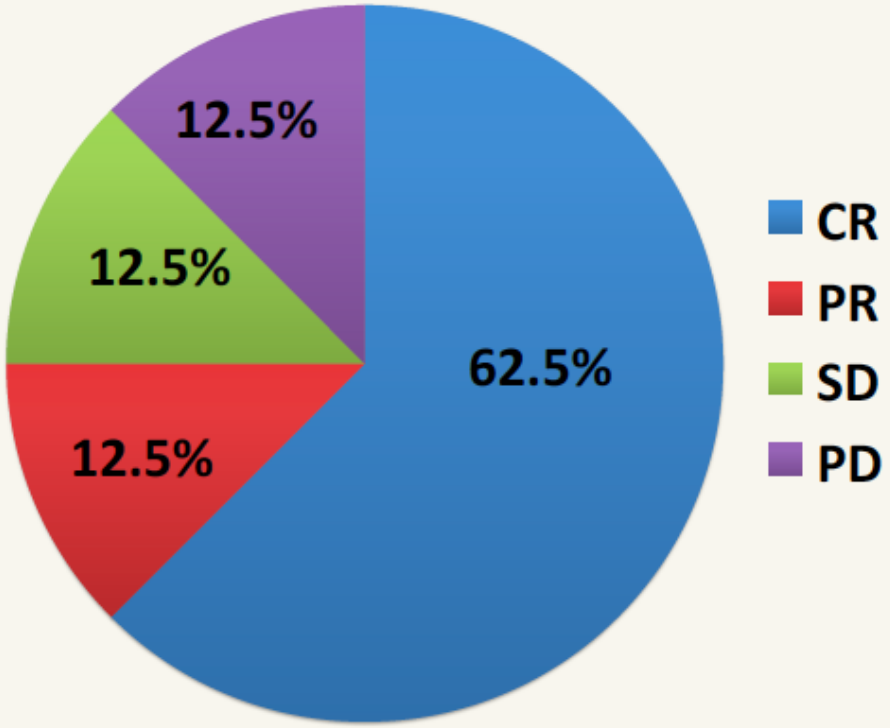
Con tam et al.

Baseline Characteristics (n=8 eval)

Characteristic	Value
Age in years (median, range)	72 (53 – 77)
Male / Female	7 / 1
Performance Status (ECOG) ≥ 1	6
MIPI High / Intermediate **Blastic Morphology**	6 / 2 1
Prior Lines of Therapy (median) • Chemorefractory (%) • Prev hyperCVAD or autoSCT (%)	2 (1 – 7) 63 25
Current Status • Died of progressive disease • Alive and continuing therapy • Time on therapy (days)	 1 7 120 (54 – 285)

Con tam et al.

Response Rates at Week 16 (n = 8)



- Complete remissions in 5 (62.5%) patients - 4 had marrow involvement at baseline, all 4 were MRD-negative at <0.01% by flow cytometry* in the marrow at wk 16.

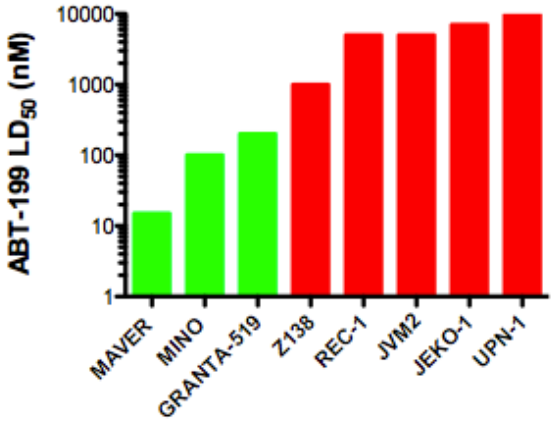
Con tam et al.

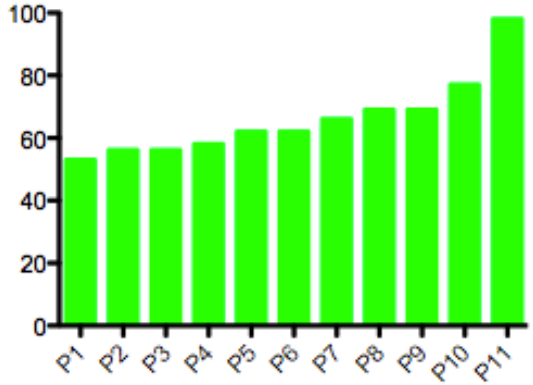
CONCLUSIONS

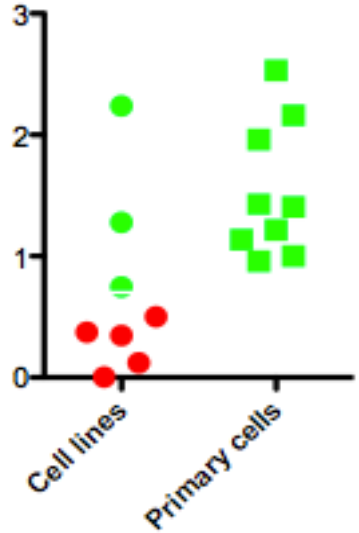
- The combination of ibrutinib and staggered introduction of venetoclax is safe and deliverable without unexpected toxicities.
- The major toxicities are gastrointestinal.
- Achievement of deep responses of <0.01% MRD opens up possibilities for treatment cessation.

Con tam et al.

Mechanisms of resitance to venetoclax in MCL



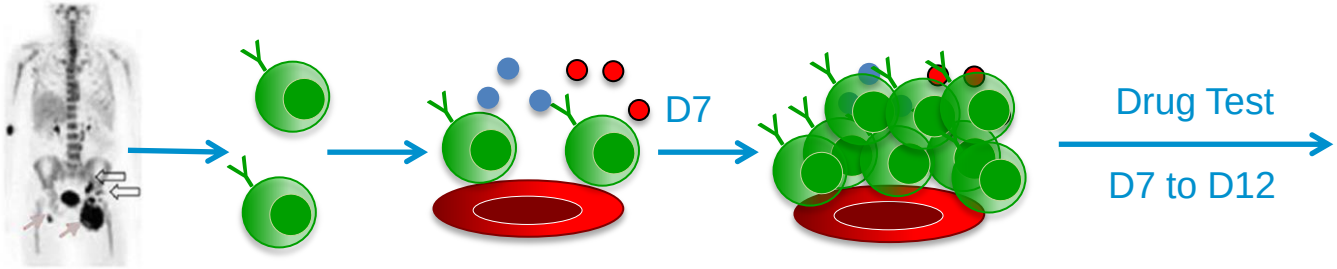


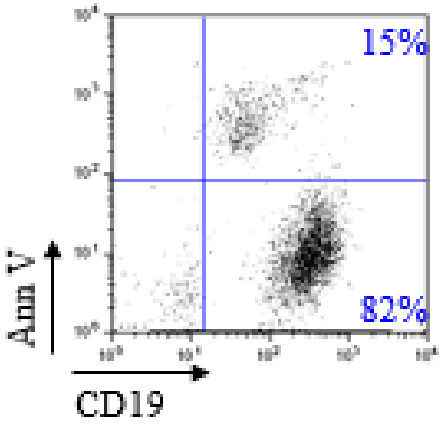


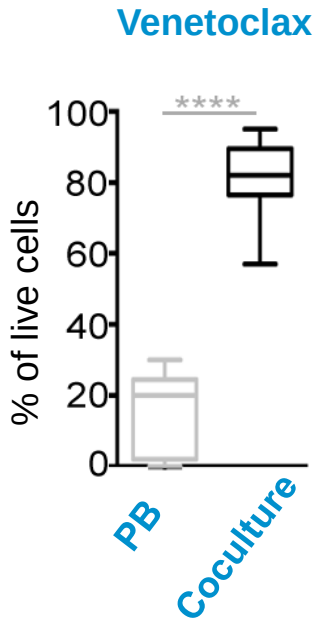
MCL sensitivity to venetoclax correlates with BCL2 / (BCLXL + MCL1) mRNA ratio

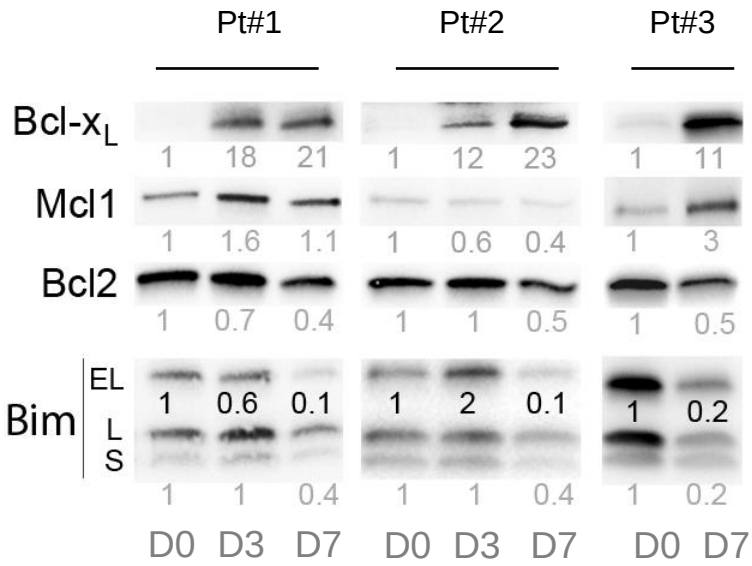
Chiron et al Oncotarget 2015

lymphoma ecosystem protect again venetoclax-induced apoptosis





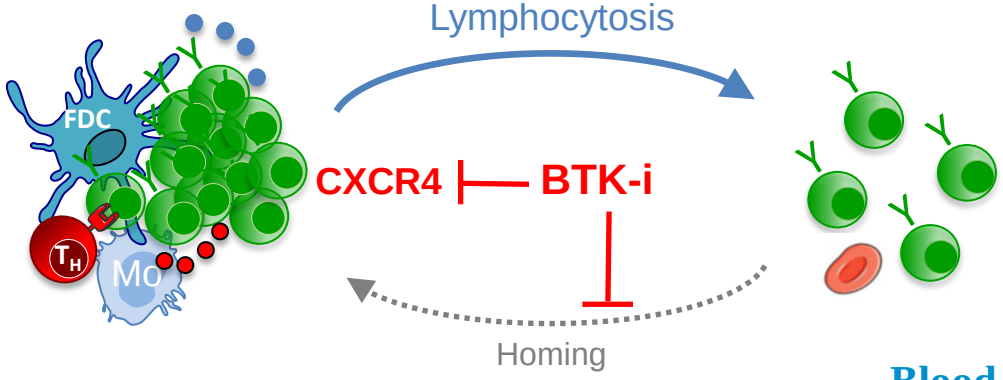




Chiron et al Blood Oct 2016

Indirectly targeting BCLXL in lymphoma

Egress from lymph nodes using a BTKi (neutralization of BCR and CXCR4 axis)



Rapid loss of BCLXL expression in PB

Lymph Nodes
BCLXL ^{high}
Venetoclax Resistance

Blood
BCLXL ^{low}
Venetoclax Sensitivity

Chiron et al Oncotarget 2015

Clinical Trial

Oasis Trial

NTC#02558816

PI : Pr. S Le Gouill

2016

CHU de Nantes

BTK-i (Ibrutinib) // anti-CD20 (GA101) // Venetoclax

Plymouth Hospitals NHS
NHS Trust

A PHASE I/II TRIAL OF OBINUTUZUMAB, ABT-199 (GDC-0199) PLUS IBRUTINIB IN RELAPSED / REFRACTORY MANTLE CELL LYMPHOMA PATIENTS

2014				2015				2016				2017				2018				2019				2020				2021			
Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4

Oct-15 **P1/2: Venetoclax + Ibrutinib, Obinutuzumab, NHL (OAsIs) - VEN029** May-18

STUDY TYPE
- Phase: 1/2
- Accrual: 33 (target)
- Location: France; UK

SPONSOR
- J&J/Janssen; Roche; Nantes University Hospital

STATUS
- Open

KEY INCLUSION CRITERIA
- Mantle cell lymphoma expressing CD5, CD20 and cyclin D1 or t(11,14) translocation
- Relapsed/refractory after at least one line of Tx
- ECOG PS 0-2

KEY ENDPOINTS
- DLT/MTD
- ORR; CRR, PRR; OS; TTP
- AE/Serious AE incidence
- Laboratory abnormalities incidence
- Tumor lysis syndrome incidence, severity
- Bio-bank for biomarker analysis

STUDY DESIGN

Step A (9 pts)

Ibrutinib 560 mg QD
d2-28 c1; d1-28 c2-6
Obinutuzumab 1000 mg
d1/2,8,15 c1; d1 c2-6

▶

Step B (24 pts)

Venetoclax QD: 100 mg w1, 200 mg w2, 400 mg w3, 400 – 1000 mg w3
Ibrutinib and Obinutuzumab as in Step A

▼ **Maintenance (c7+, 18 mos)** ▼

Ibrutinib 560 mg QD d1 - 28
Obinutuzumab 1000 mg d1 c8+
(every 2 cycles)

Venetoclax 400, 600, 800 or 1000 mg QD d1-28
Ibrutinib 560 mg QD d1 - 28
Obinutuzumab 1000 mg d1 c8+
(every 2 cycles)

CLINICAL UPDATE

- No clinical update

Conclusion

- There is a strong rational tu use Venetoclax in MCL
- The tumor niche may protects against Venetoclax-induced apoptosis
- Ibrutinib + Venetoclax trial is ongoing (AIM)
- Ibrutinib + Venetoclax+Obinutuzumab trial is ongoing (Oasis)
- Venetoclax is porbably one of the most promising new drug in MCL

CRCNA
Centre de Recherche en Cancérologie Nantes Angers

Basic Research

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D. Chiron (PhD)

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B. Tessoulin
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Translational Research

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Collaborations

Cornell University

Micronit

NiT microenvironment of tumor niches
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