XVIII IWCLL
International Workshop on CLL
20-23 SEPTEMBER 2019 EDINBURGH

Novel Combinations and MRD in Relapsed/Refractory Disease

Matthew S. Davids, MD, MMsc

Assistant Professor of Medicine | Harvard Medical School
Associate Director, CLL Center | Dana-Farber Cancer Institute

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Disclosures

Matthew S. Davids, MD, MMSc

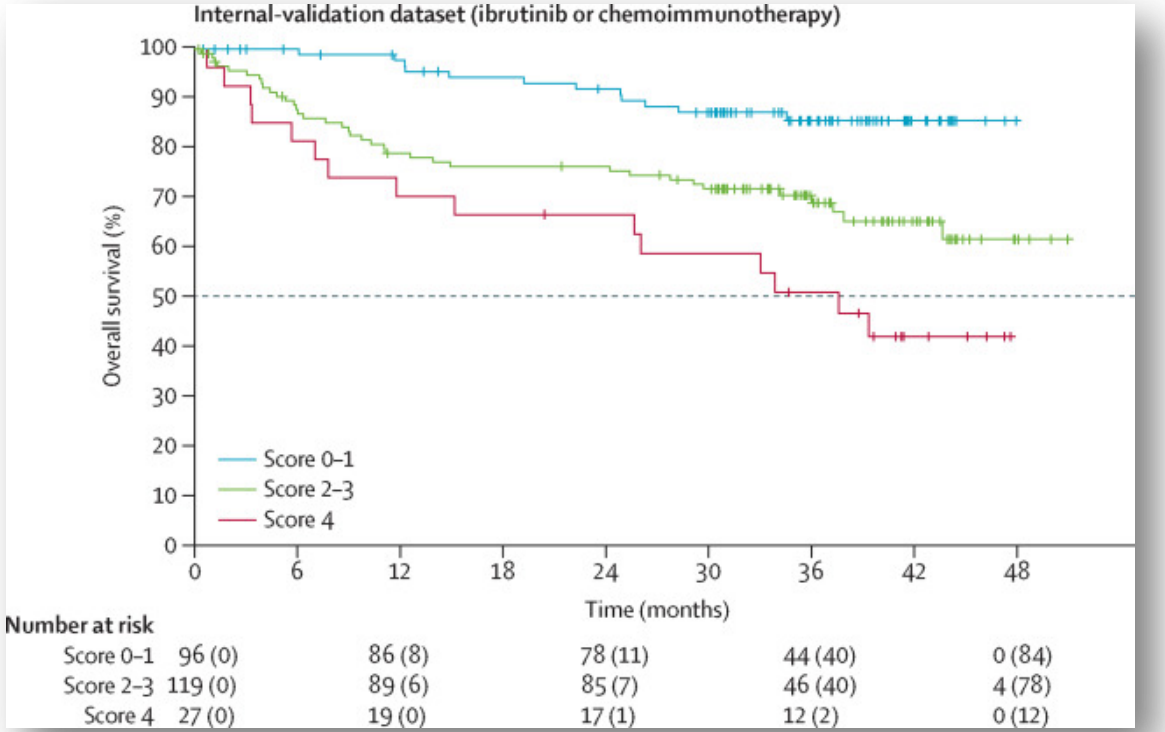
I have the following financial relationships to disclose:

Consultant for: Abbvie, Genentech, Janssen, Pharmacyclics, TG Therapeutics, Celgene, Astra-Zeneca, Verastem, MEI Pharma, Acerta, Syros, Sunesis, Adaptive Biotechnologies

Research funding: Genentech, Pharmacyclics, TG Therapeutics, Verastem, BMS, Acerta, MEI Pharma, Surface Oncology, Ascentage

High risk CLL patients have short survival with novel agent monotherapy (n=2,475)

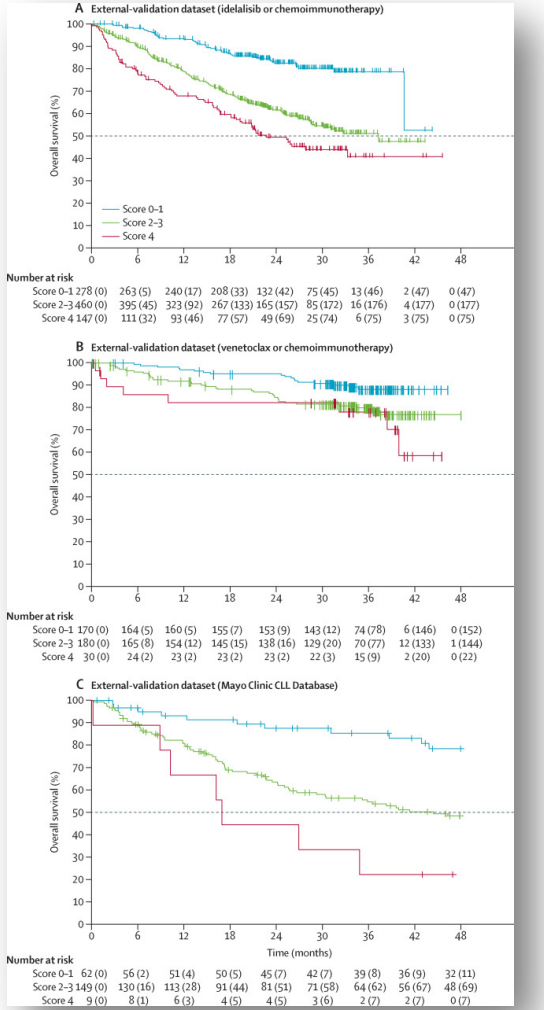
Ibrutinib



Idelalisib

Venetoclax

Mayo Clinic External Validation



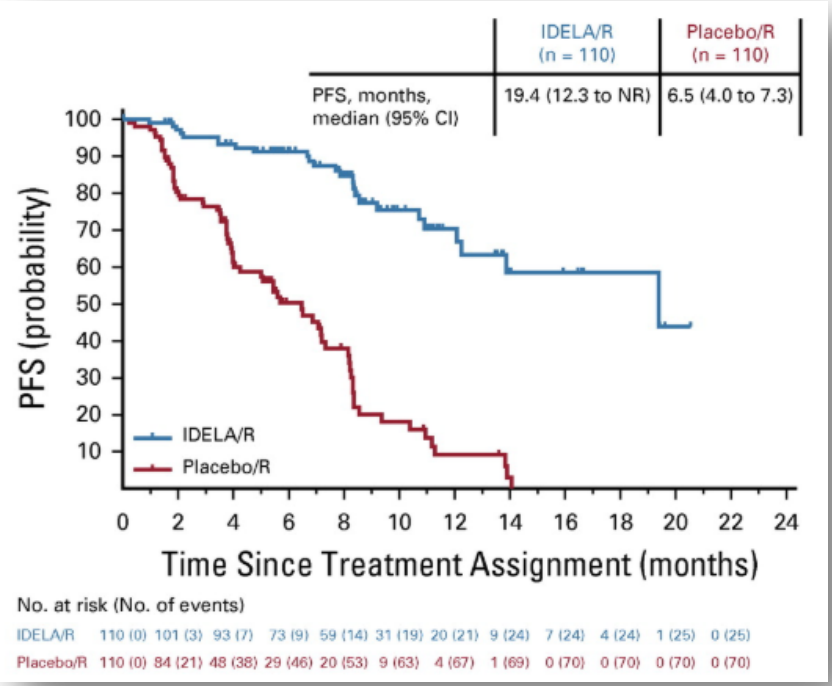
Soumerai J et al., *Lancet Haem*, 2019

Outline

- Relapsed/Refractory CLL
  - Dual BCR blockade
  - BCL-2/BCR blockade
- Richter's Syndrome
  - Novel agent plus chemoimmunotherapy
  - Novel combinations with checkpoint blockade
- Future Combinations
  - Further exploiting targeting of the Bcl-2 family

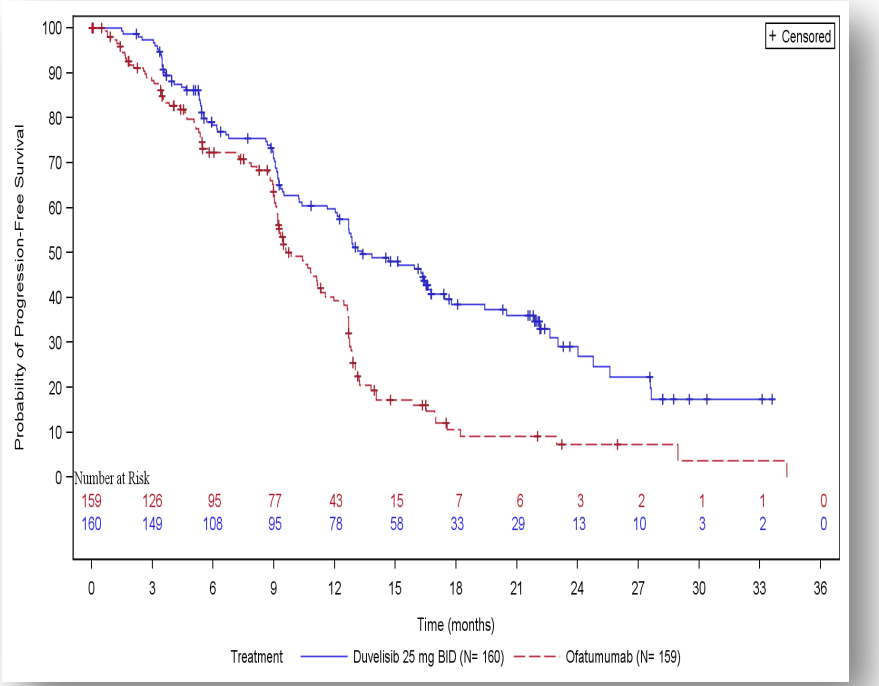
Approved PI3Ki are efficacious, with manageable toxicity in R/R CLL

Idelalisib + Rituximab



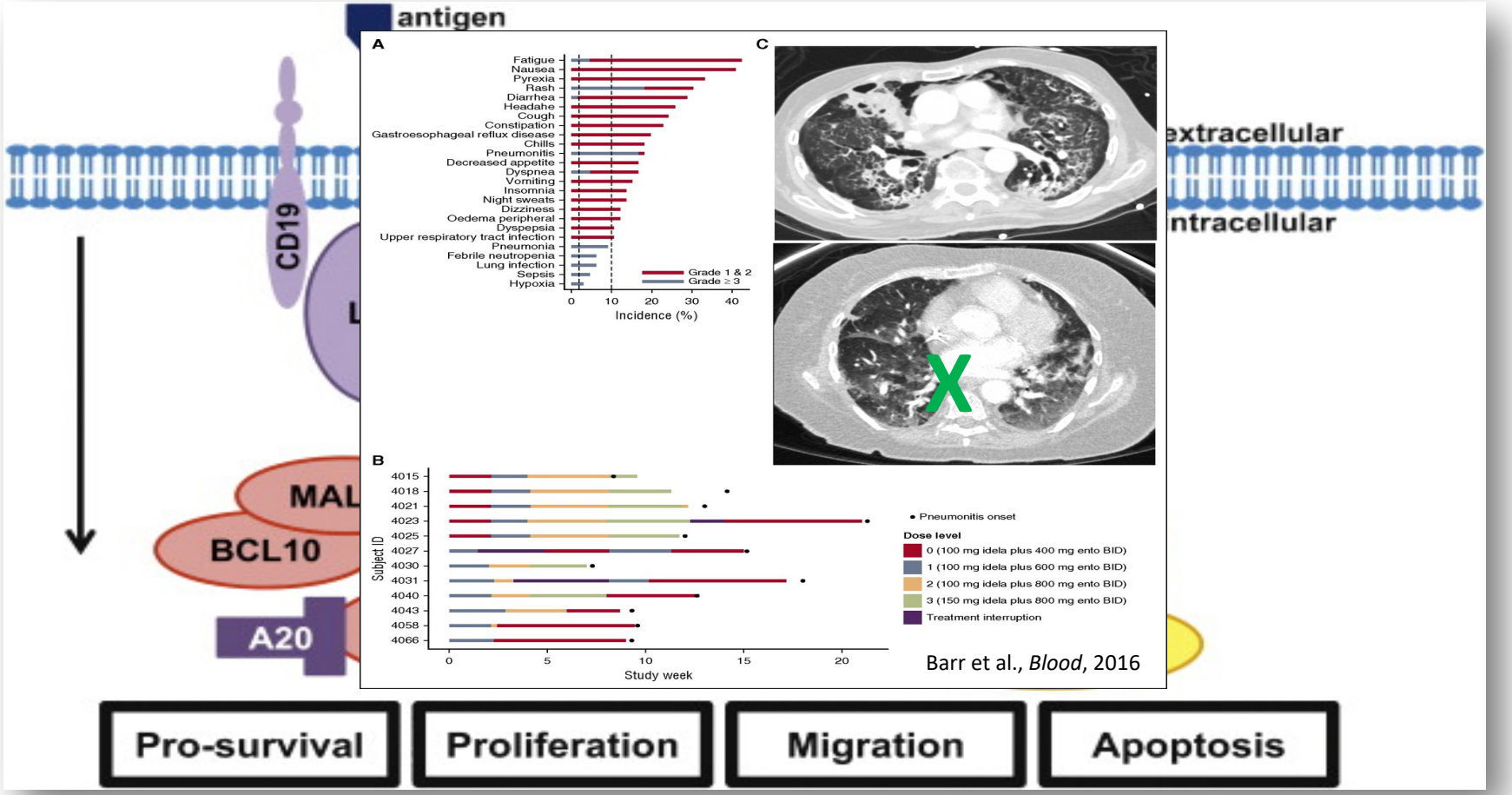
Sharman et al., J Clin Oncol, 2019

Duvelisib



Flinn et al., *Blood*, 2018

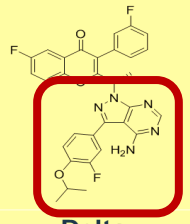
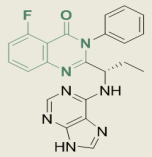
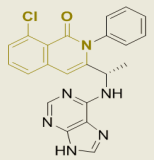
Inhibiting multiple BCR pathway kinases may deepen and prolong response and overcome resistance mutations



Barr et al., *Blood*, 2016

Niemann et al., *Seminars in Cancer Biology*, 2013

Umbralisib (TGR-1202) is a next generation PI3Kδ inhibitor with a favorable safety profile

TGR-1202	Idelalisib (GS-1101)	Duvelisib (IPI-145)
		
Delta	Delta	Delta/Gamma
QD	BID	BID

Fold-selectivity				
Isoform	PI3Kα	PI3Kβ	PI3Kγ	PI3Kδ
Umbralisib	>1000	>50	>48	1
[1]Idelalisib	>300	>200	>40	1
[2]Duvelisib	>640	>34	>11	1

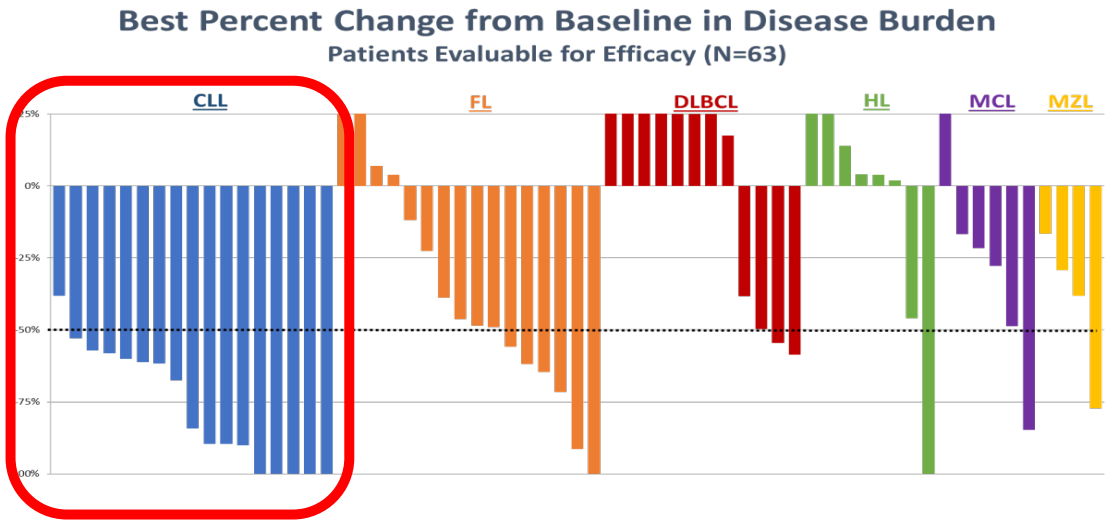
Safety

In 165 patients treated with umbralisib (TGR-1202) alone or with anti-CD20:

- Grade 3/4 AST/ALT increase was 3% (8% all grades)
- Diarrhea in 47%, mainly grade 1, with 5 patients (3%) with Grade 3/4
- 8% of patients off study due to an AE

Burris et al, ASCO 2016

Efficacy



O'Connor et al, ASH 2015

[1]Flinn et al. 2009, [2]Porter et al. 2012

Umbralisib in combination with ibrutinib in patients with relapsed or refractory chronic lymphocytic leukaemia or mantle cell lymphoma: a multicentre phase 1–1b study

Matthew S Davids, Haesook T Kim, Alyssa Nicotra, Alexandra Savell, Karen Francoeur, Jeffrey M Hellman, Josie Bazemore, Hari P Miskin, Peter Sportelli, Laura Stampleman, Rodrigo Maegawa, Jens Rueter, Adam M Boruchov, Jon E Arnason, Caron A Jacobson, Eric D Jacobsen, David C Fisher, Jennifer R Brown on behalf of the Blood Cancer Research Partnership of the Leukemia and Lymphoma Society

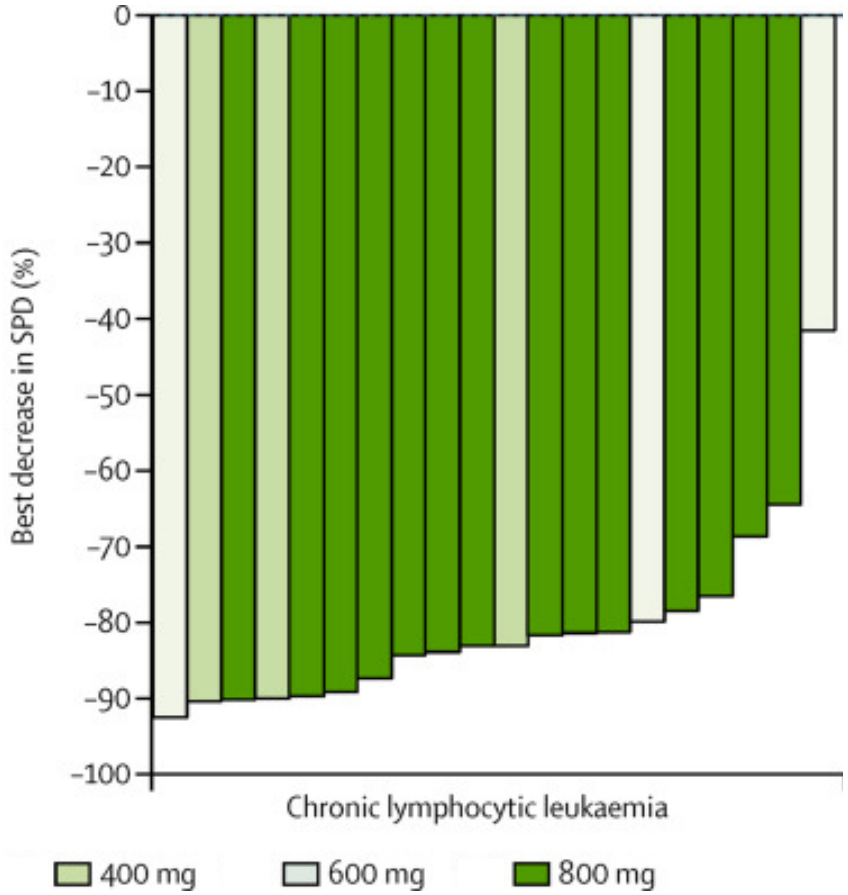
	All grades				Grade 3–4			
	400 mg (n=6)	600 mg (n=6)	800 mg (n=30)	Total (n=42)	400 mg (n=6)	600 mg (n=6)	800 mg (n=30)	Total (n=42)
Non-haematological*								
Diarrhoea	5 (83%)	3 (50%)	14 (47%)	22 (52%)	1 (17%)	0	3 (10%)	4 (10%)
Infection	4 (67%)	1 (17%)	16 (53%)	21 (50%)	1 (17%)	1 (17%)	5 (17%)	7 (17%)
Nausea	1 (17%)	3 (50%)	14 (47%)	18 (43%)	1 (17%)	0	0	1 (2%)
Fatigue	2 (33%)	5 (83%)	9 (30%)	16 (38%)	0	0	2 (7%)	2 (5%)
Hyperglycaemia	1 (17%)	2 (33%)	9 (30%)	12 (29%)	0	0	1 (3%)	1 (2%)
Transaminitis	4 (67%)	1 (17%)	5 (17%)	10 (24%)	0	0	1 (3%)	1 (2%)
Dizziness	2 (33%)	3 (50%)	4 (13%)	9 (21%)	0	0	0	0
Bruising	2 (33%)	0	5 (17%)	7 (17%)	0	0	5 (17%)	5 (12%)
Cough	1 (17%)	2 (33%)	4 (13%)	7 (17%)	0	0	0	0
Headache	2 (33%)	1 (17%)	4 (13%)	7 (17%)	0	0	0	0
Anorexia	0	3 (50%)	3 (10%)	6 (14%)	0	0	0	0
Myalgia	2 (33%)	0	4 (13%)	6 (14%)	0	0	0	0
Rash	0	0	6 (20%)	6 (14%)	0	0	1 (3%)	1 (2%)
Hypertension	0	1 (17%)	4 (13%)	5 (12%)	0	1 (17%)	0	1 (2%)
Haematological								
Neutropenia	4 (67%)	1 (17%)	12 (40%)	17 (40%)	2 (33%)	1 (17%)	2 (7%)	5 (12%)
Thrombocytopenia	3 (50%)	3 (50%)	10 (33%)	16 (38%)	1 (17%)	0	1 (3%)	2 (5%)
Anaemia	2 (33%)	3 (50%)	8 (27%)	13 (31%)	0	1 (17%)	1 (3%)	2 (5%)

Data are n (%). *Excludes asymptomatic laboratory values that resolved promptly.

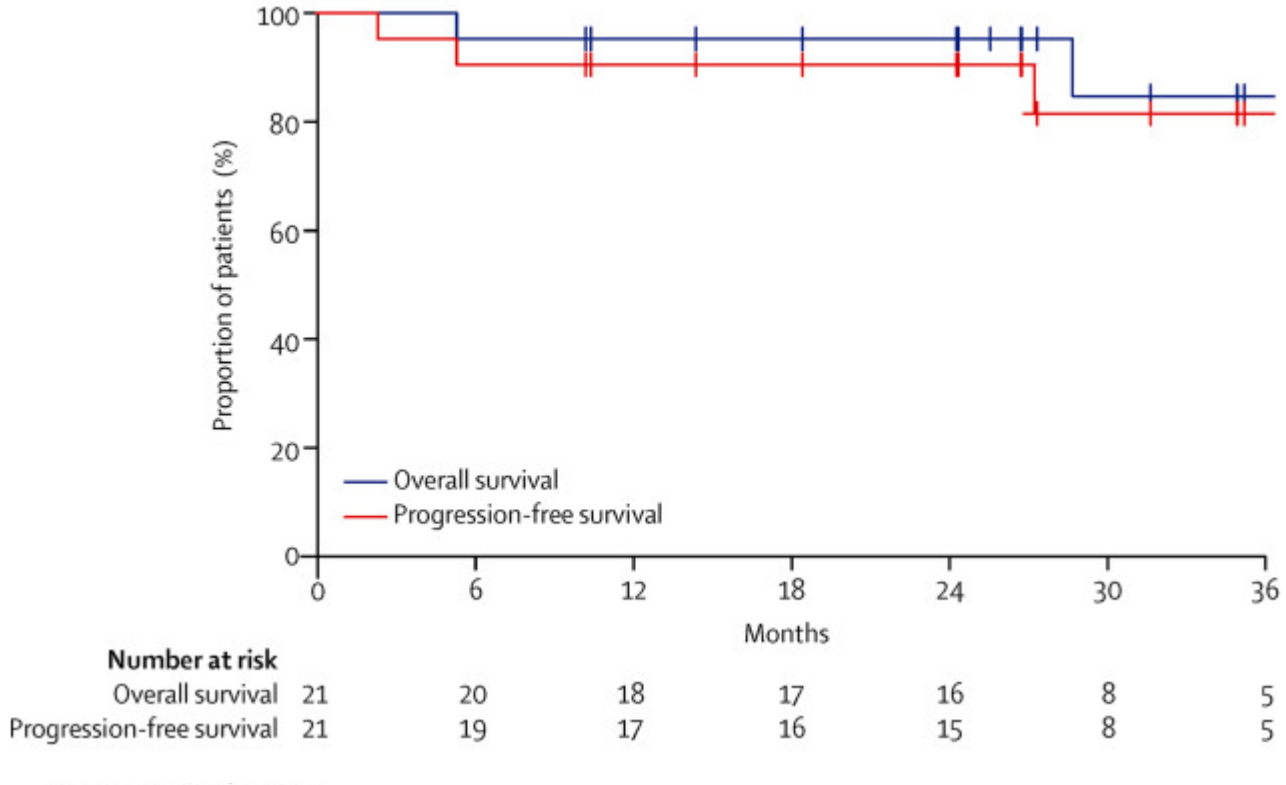
***Table 2*: All-grade adverse events in ≥10% of patients and grade 3–4 adverse events in all patients by umbralisib dose level**

Davids et al., *Lancet Haem*, 2019

Umbralisib + ibrutinib leads to a high CR rate and durable response



CR rate: 29%



2-year PFS/OS: 90%/95%

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Davids et al., *Lancet Haem*, 2019

BCL-2 and BCR pathway are the Achilles' Heels of CLL Pathophysiology

BCL-2

BCR

BTK inhibition increases CLL cell dependence on Bcl-2

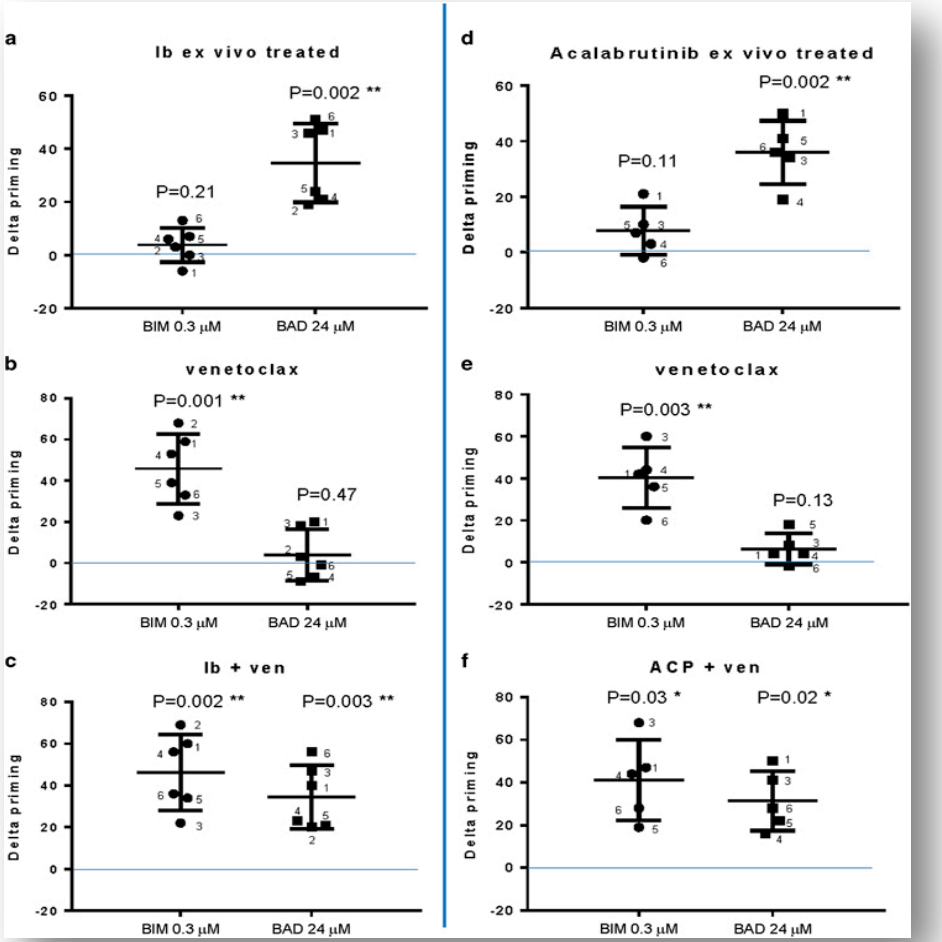
Leukemia (2017), 1–10

www.nature.com/leu

ORIGINAL ARTICLE

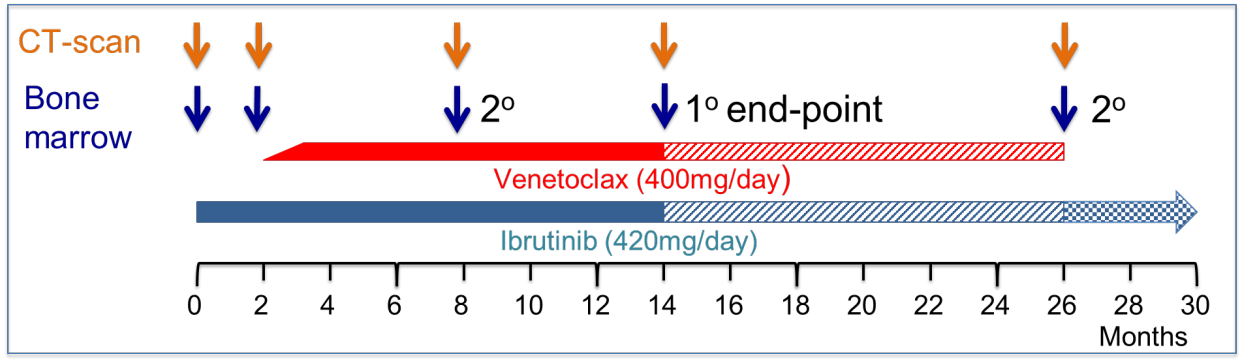
Bruton's tyrosine kinase inhibition increases BCL-2 dependence and enhances sensitivity to venetoclax in chronic lymphocytic leukemia

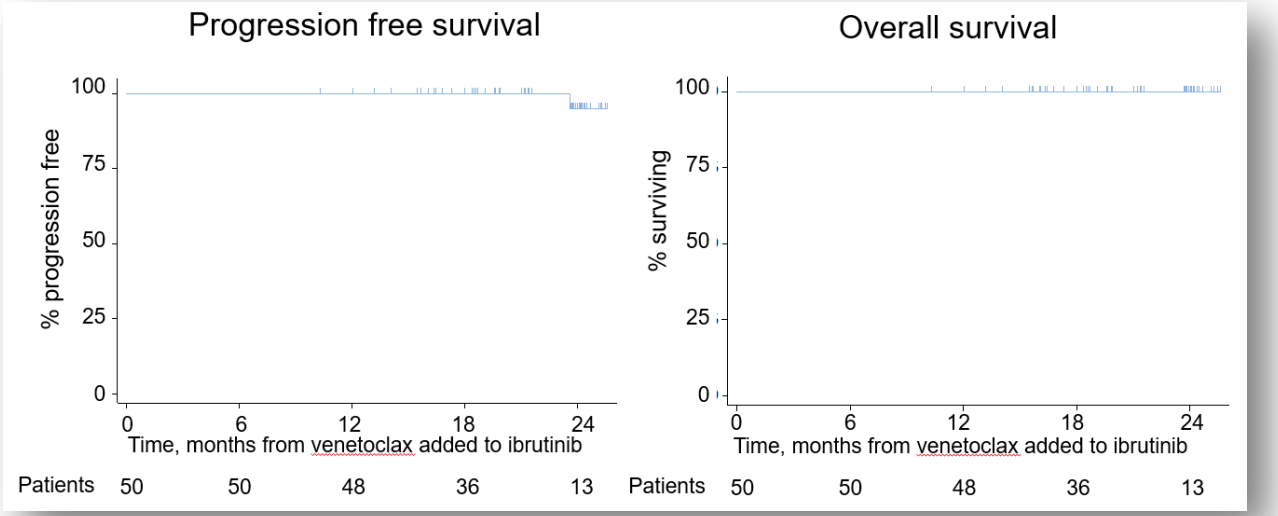
J Deng, E Isik, SM Fernandes, JR Brown, A Letai[1] and MS Davids[1]

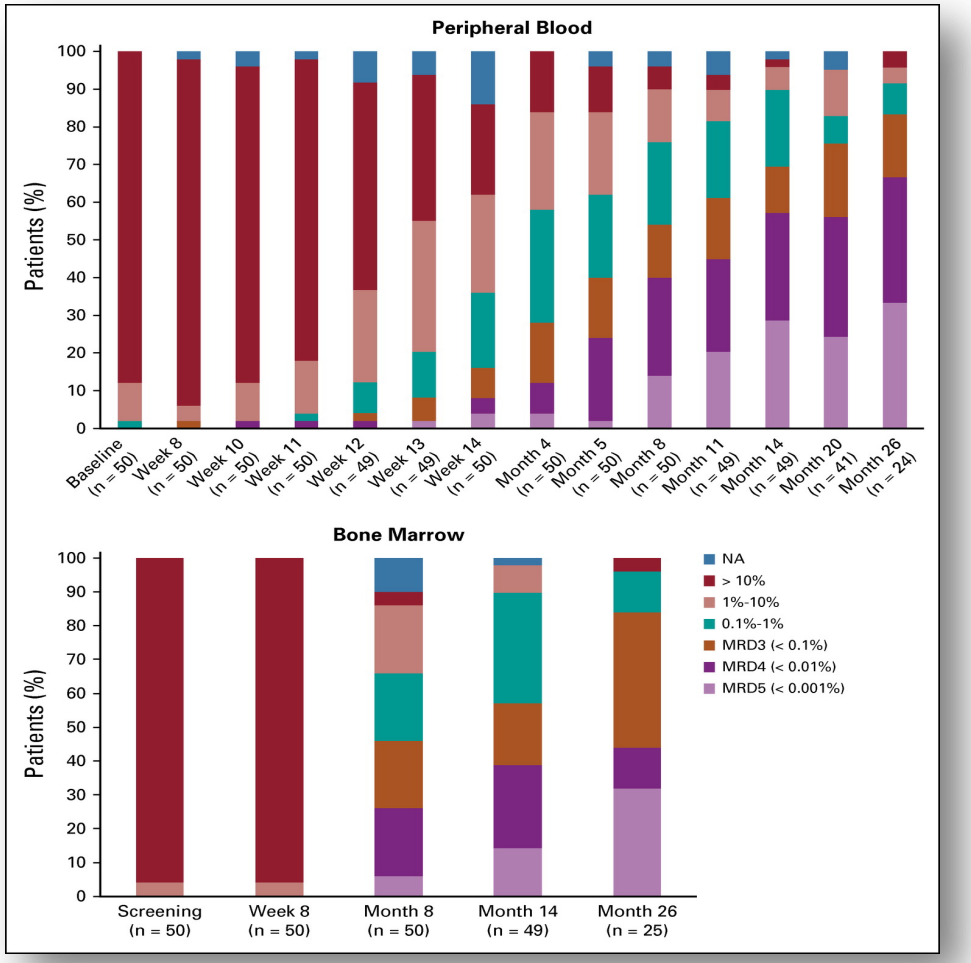


Deng et al., *Leukemia*, 2017

UK CLARITY: I + V leads to high rates of undetectable MRD which are translating into durable response



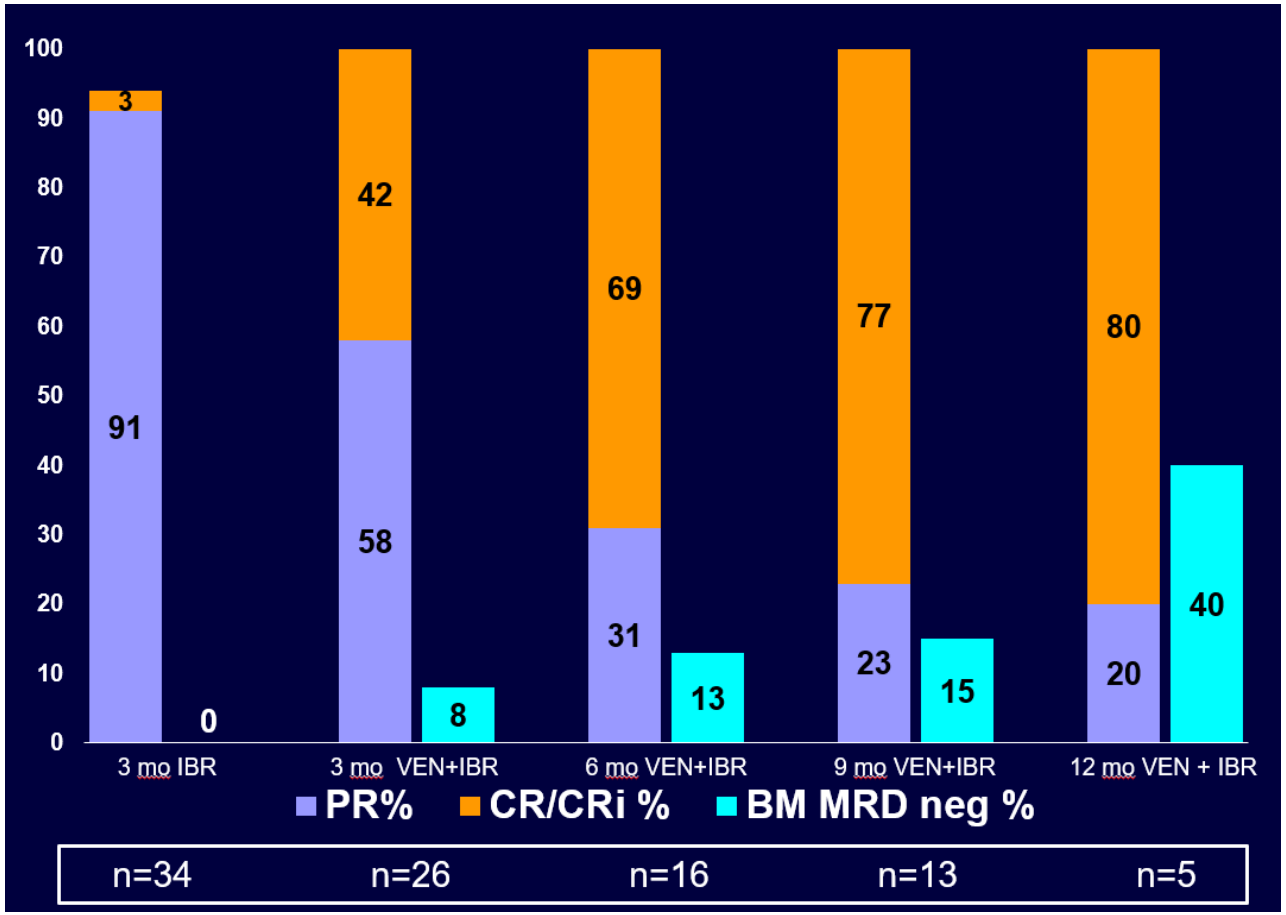




Hillmen et al., J Clin Oncol, 2019

MDACC study of ibrutinib + venetoclax in R/R CLL is also promising

	C1	C2	C3	C4 ---> C27
Ibrutinib	420mg daily	420mg daily	420mg daily	420mg daily until progression
Venetoclax	-	-	-	20mg daily x1 wk then; 50mg daily x1 wk then; 100mg daily x1 wk then; 200mg daily x1 wk then; 400mg daily continuous

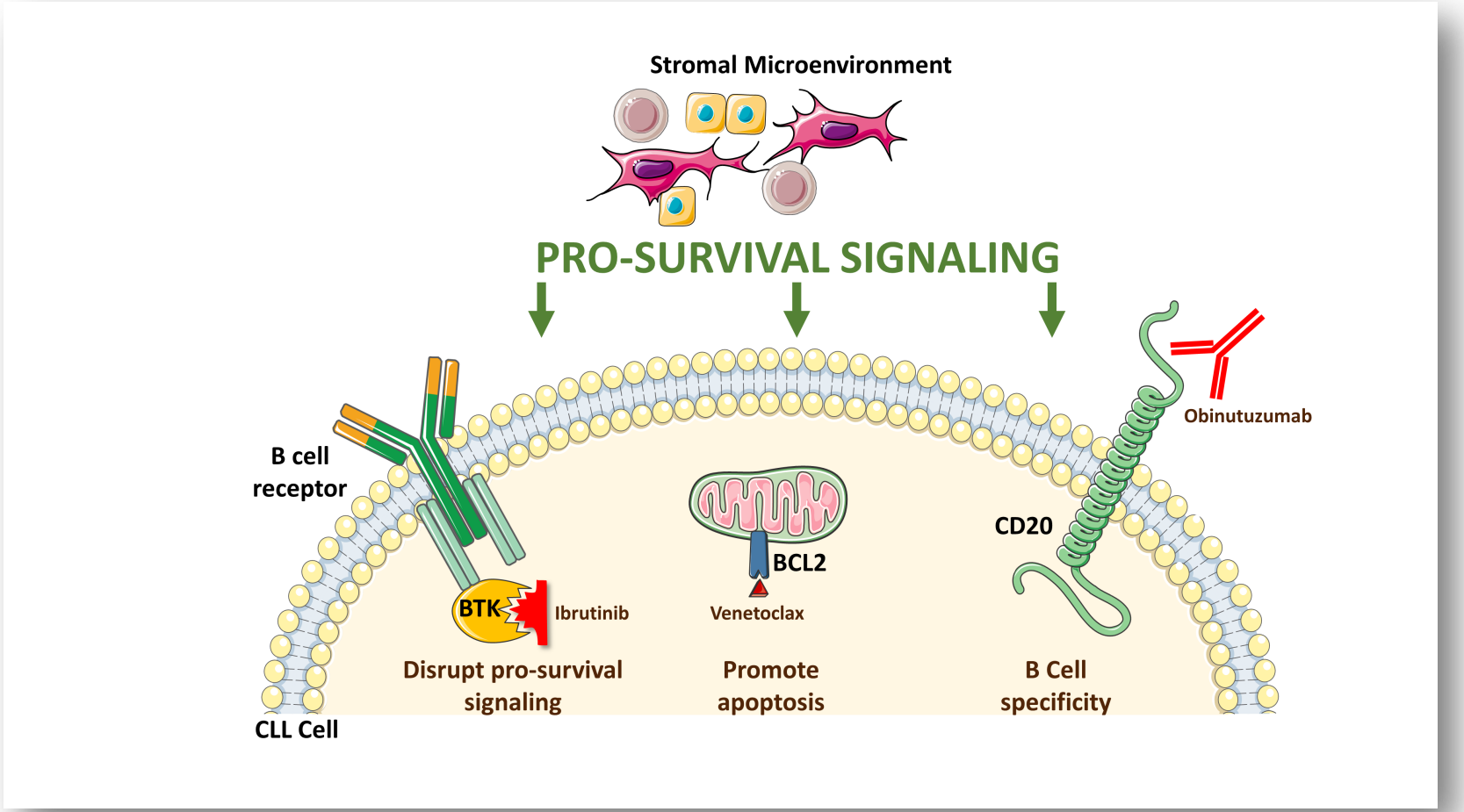


VEN duration 2 years, IBR until progression

<u>Primary endpoint: CR/CRi</u>

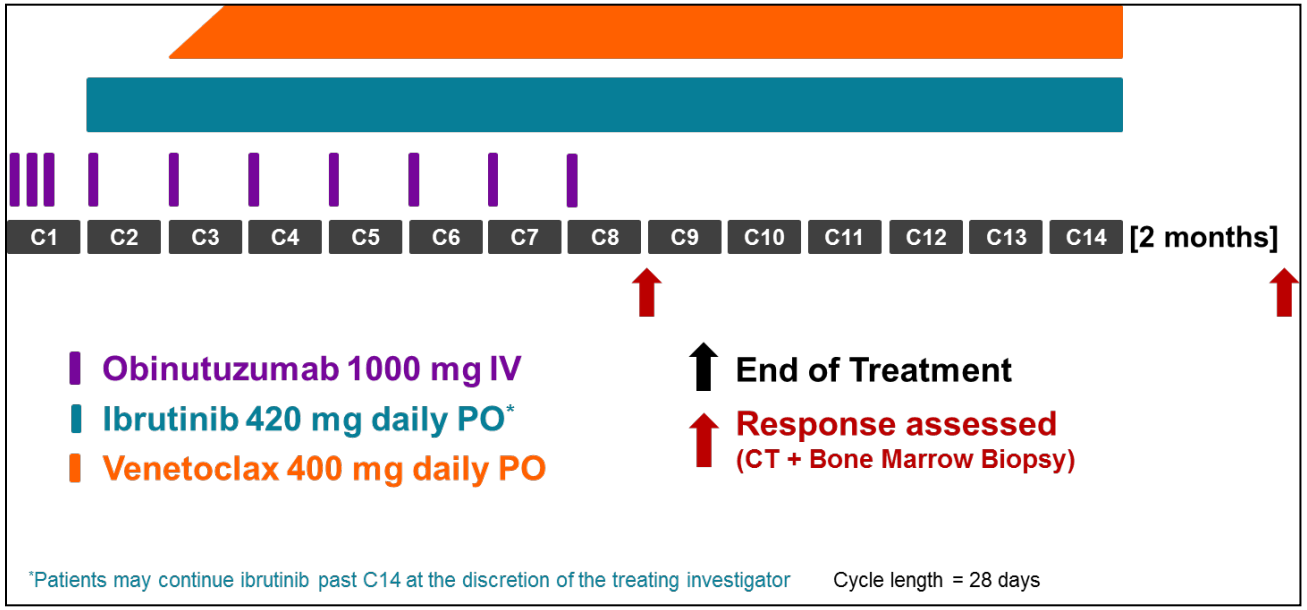
Jain *et al.* ASH 2017

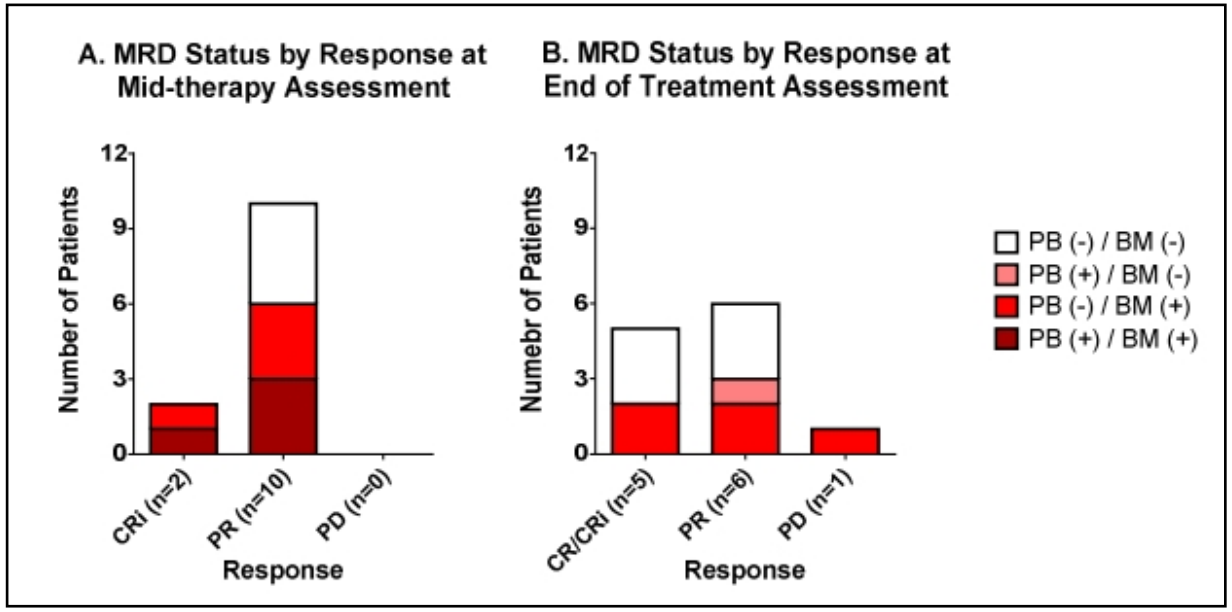
Inhibiting 3 distinct targets may result in even greater efficacy



Lampson and Davids, *Blood*, 2018

Ibrutinib/Ven/Obin was well-tolerated and active in R/R CLL





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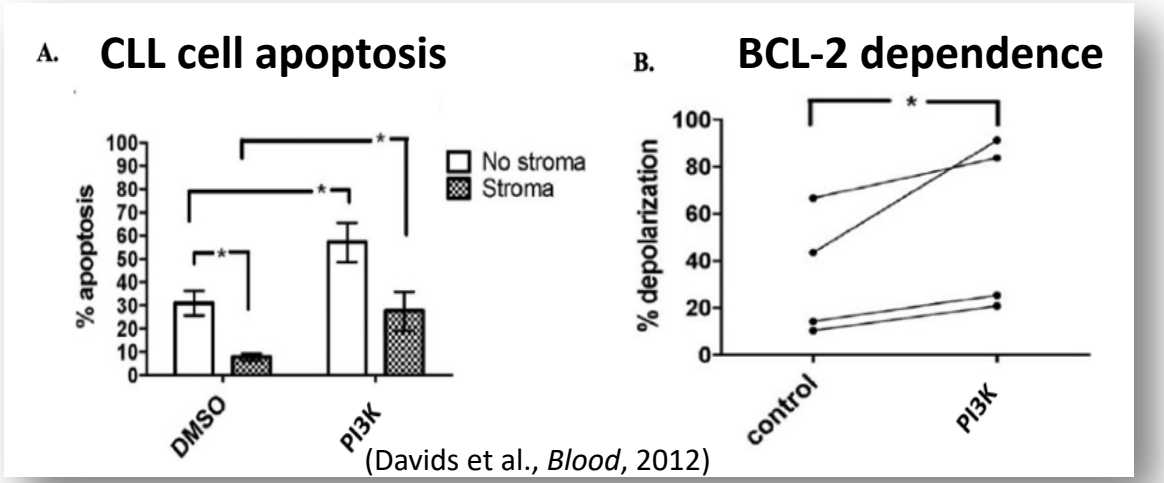
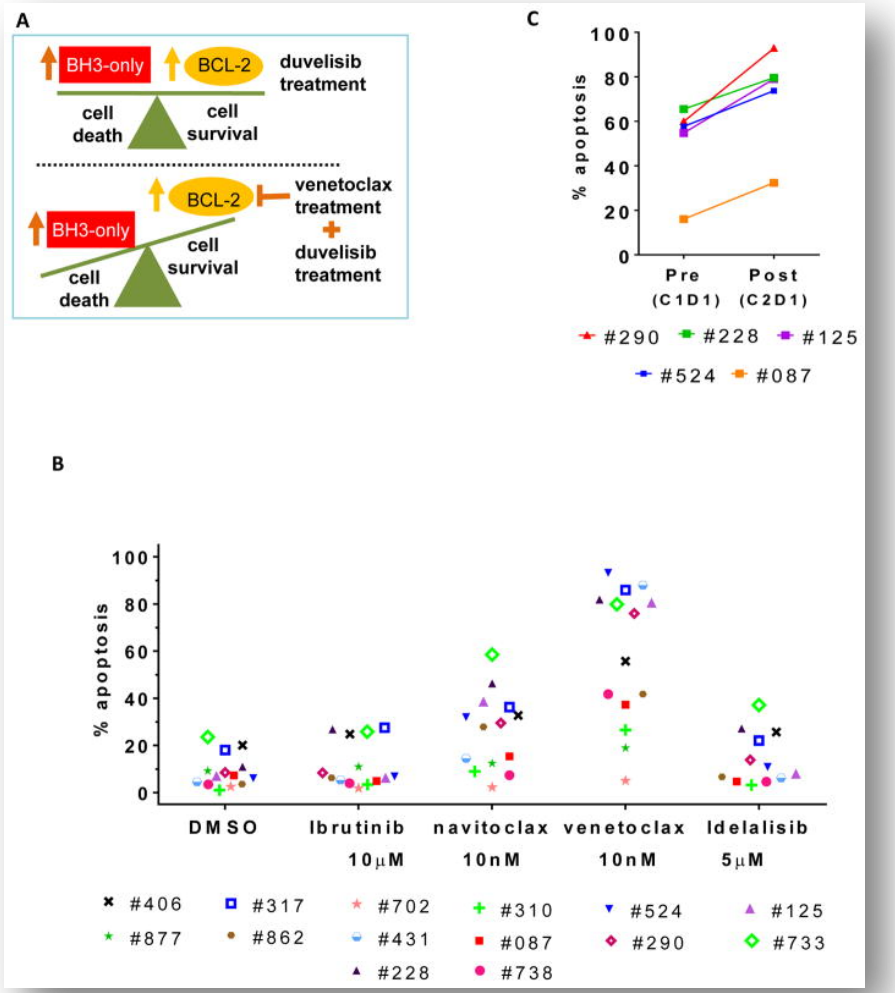
Rogers et al., *Blood*, 2018

Ex vivo PI3K inhibition enhances mitochondrial priming and BCL-2 dependence in CLL cells



(Davids et al., *Blood*, 2012)



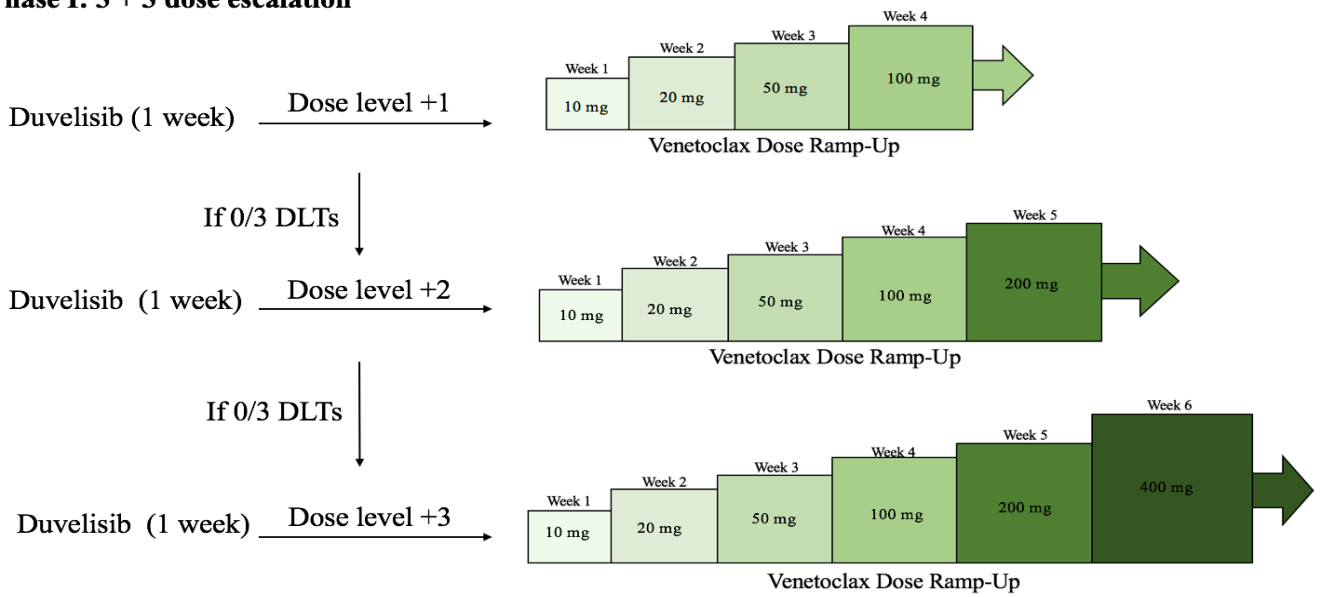
(Patel et al., *Leukemia*, 2017)

Rationale for developing a BCL2i/PI3Ki combination

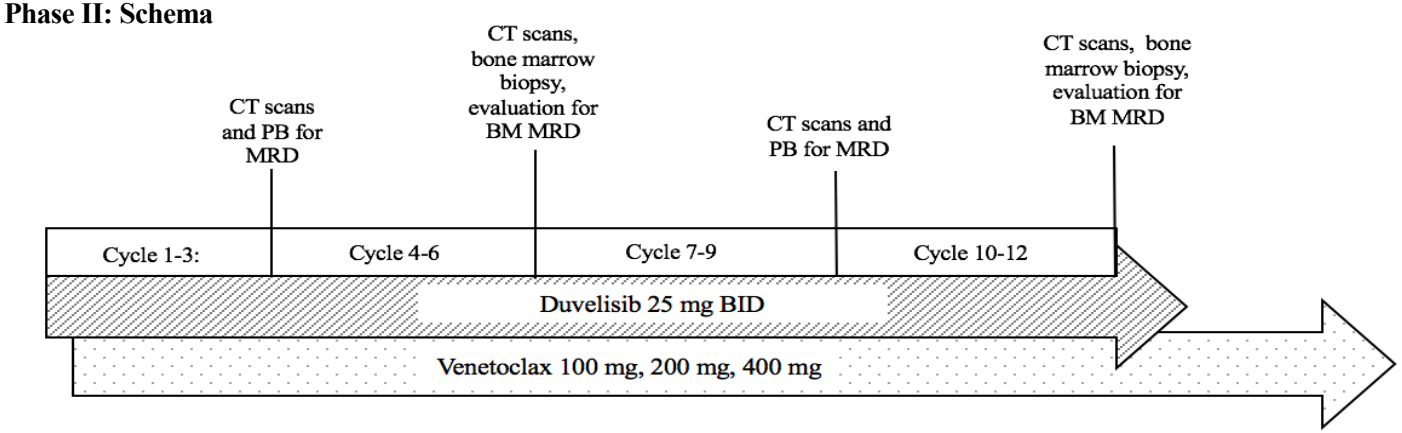
- Venetoclax and PI3Ki are efficacious single agents, but have low CR rates, require indefinite therapy
- Older CLL patients with cardiac comorbidities may not tolerate BTKi therapy
- Venetoclax and PI3Ki have non-overlapping toxicities, though potential for DDI

A Phase I/II Investigator-Initiated Study of Duvelisib + Venetoclax in Patients with R/R CLL/SLL

Phase I: 3 + 3 dose escalation



Phase II: Schema



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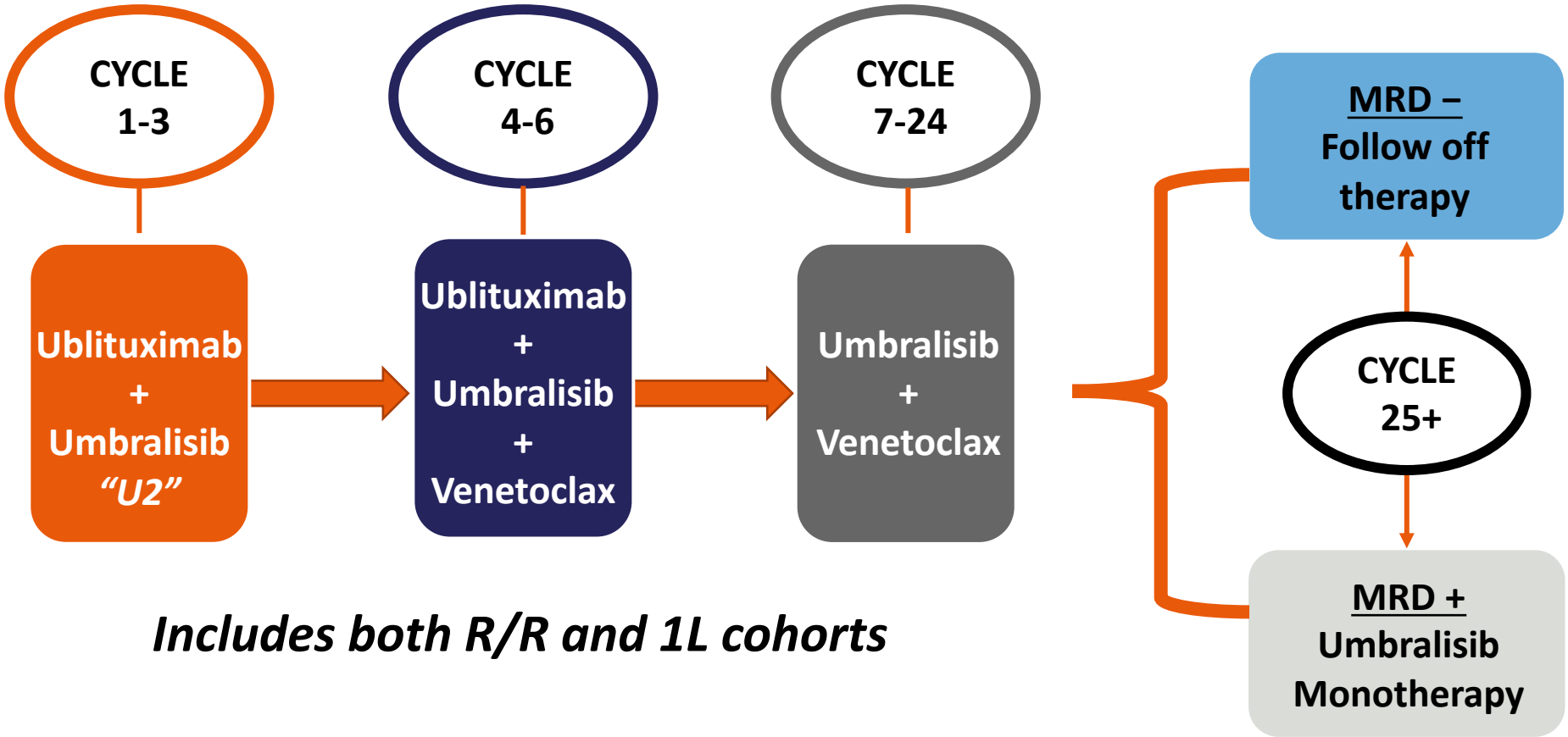
PI: Davids, DFCI

A phase 2 study of U2 + ven is now accruing (n=150)



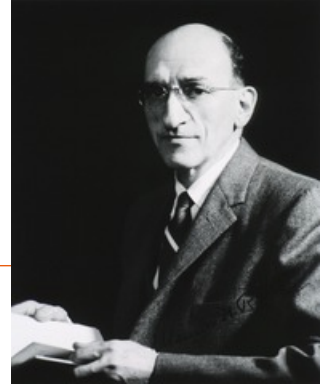
Includes both R/R and 1L cohorts

PI: Furman, Cornell

Outline

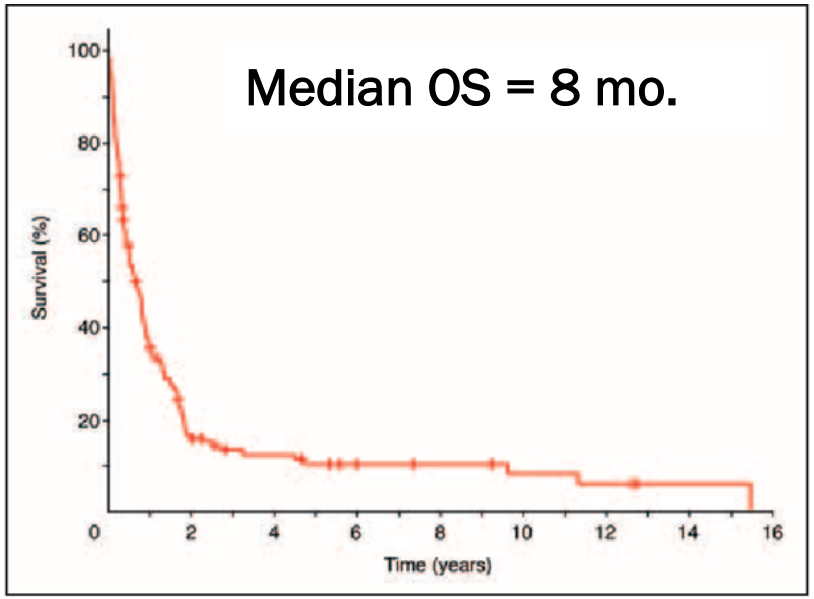
- Relapsed/Refractory CLL
  - Dual BCR blockade
  - BCL-2/BCR blockade
- **Richter's Syndrome**
  - **Novel agent plus chemoimmunotherapy**
  - **Novel combinations with checkpoint blockade**
- Future Combinations
  - Further exploiting targeting of the Bcl-2 family

Richter's Syndrome (RS) has a poor survival after CIT and particularly after novel agents (NA)

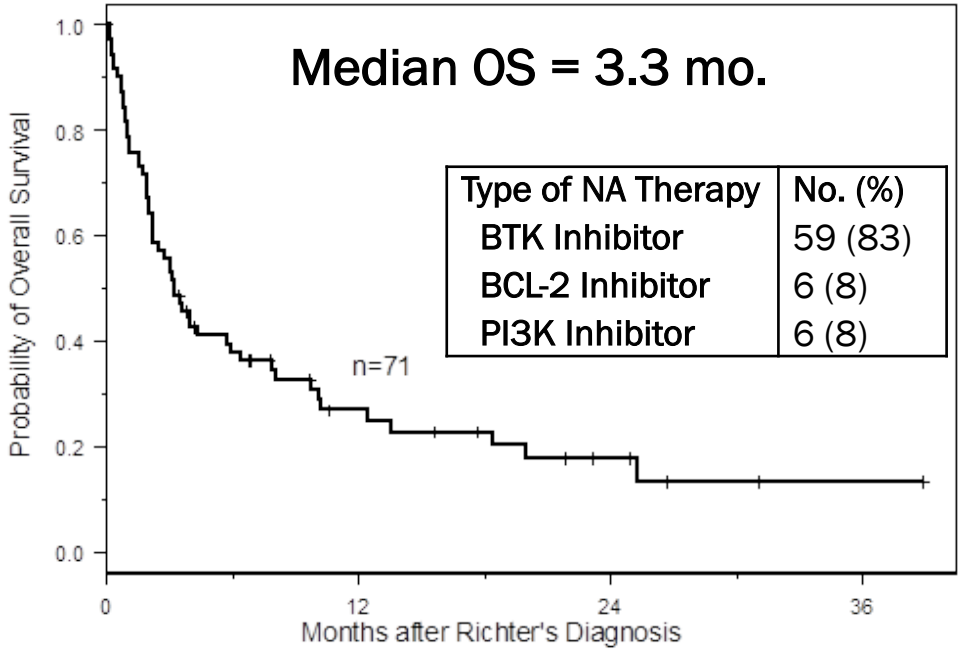


Maurice Richter, MD circa 1959

Post-CIT



Post-NA



Type of NA Therapy	No. (%)
BTK Inhibitor	59 (83)
BCL-2 Inhibitor	6 (8)
PI3K Inhibitor	6 (8)

Anthracycline-containing chemoimmunotherapy is commonly used, but outcomes are poor for most patients, and novel therapeutic approaches are urgently needed

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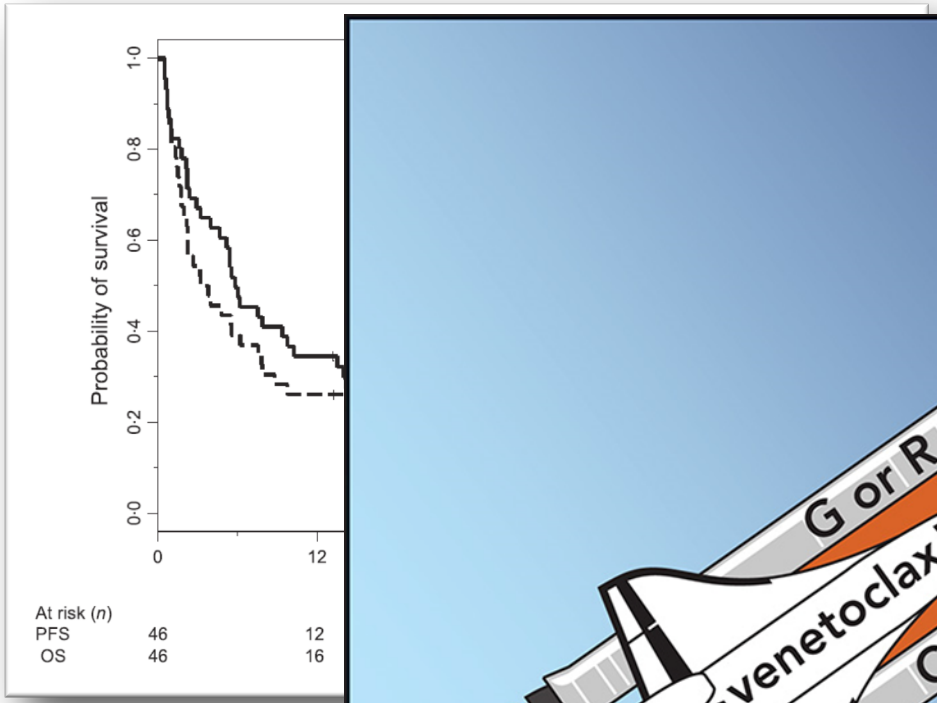
Tsimberidou et al., *J Clin Oncol,* 2006

Davids et al., *J Clin Oncol* 35, no.15_suppl (May 2017) 7505

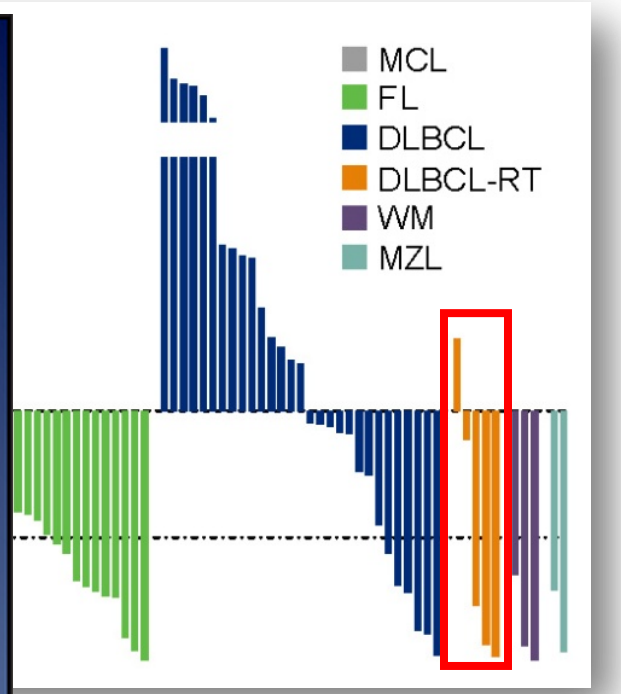
We hypothesized that adding venetoclax to R-EPOCH would be active and tolerable for patients with Richter's Syndrome

R-EPOCH for Richter's Syndrome



Treat (n=
Complete
Clinical R
Progressi
Died with

Venetoclax for Richter's Syndrome



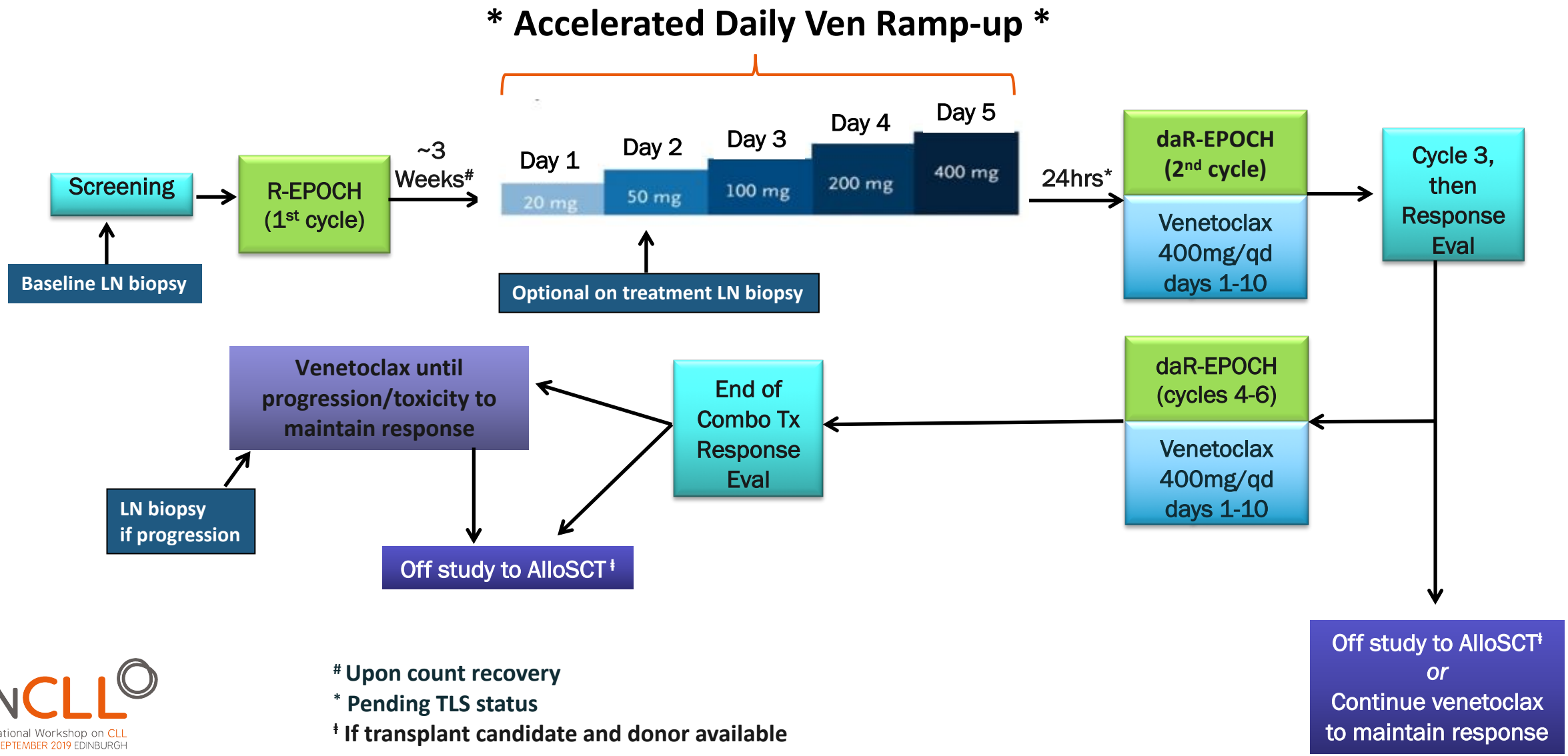
BCL-RT patients all for > 1 year

Rogers et al., *Br J Haematol*, 2017

Herbaux and Davids, *Blood*, 2019

Davids et al., *JCO*, 2017

VR-EPOCH in Richter's Syndrome: Study Schema



Upon count recovery
* Pending TLS status
‡ If transplant candidate and donor available

VR-EPOCH in RS: Patient Characteristics

- 26 patients have received at least one dose of study treatment
- Median age: 63 years (range 49-77)
- CLL Prognostic Markers:
  - Del(17p): 33%, *TP53* mutation 29%, complex karyotype: 43%, *NOTCH1* mutation: 10%
- Median # of prior CLL treatments: 2 (range 0-5)
- Prior CLL therapies:
  - CIT (n=17), ibrutinib (n=9), venetoclax (n=3), idelalisib (n=2), duvelisib (n=1)
  - 5 patients were previously untreated

Davids et al., ICML, 2019

VR-EPOCH in Richter's Syndrome: Adverse Events

≥Grade 3 Hematologic Toxicities

- Neutropenia: 45%
- Anemia: 35%
- Thrombocytopenia:25%

≥Grade 3 Non-hematologic Toxicities

- Febrile neutropenia: 20%
- Infections: sepsis (n=3, 1 fatal) during C1 of R-EPOCH (despite growth factor, prior to starting ven)
- 1 pt each with influenza A, norovirus, grade 4 infectious enterocolitis while on combination therapy
- 1 patient with sudden death in hospital during C1 prior to ven, presumed cardiopulmonary

No TLS occurred with <u>daily</u> ven ramp-up after 1 cycle of R-EPOCH (n=20)

Davids et al., ICML, 2019

VR-EPOCH in Richter's Syndrome: Preliminary Efficacy Data

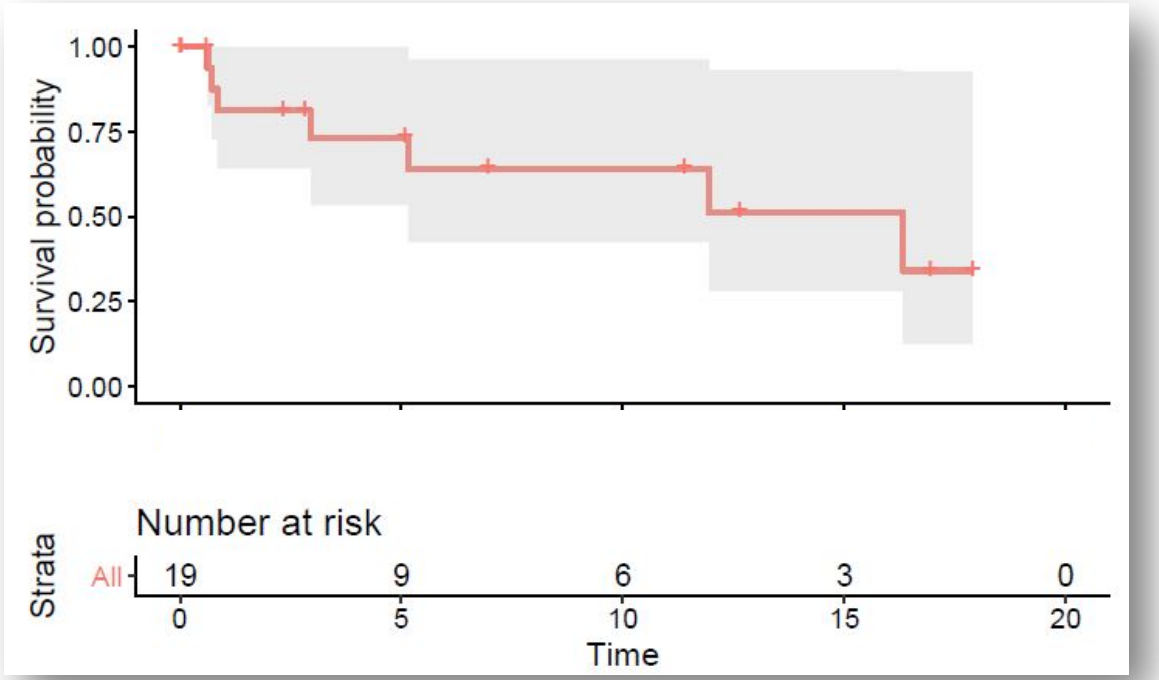
- 18 pts have started combination therapy and are evaluable for response

- **<u>CR (primary endpoint): 12/18 (67%)</u>**
  - All patients who achieved CR also had undetectable BM-MRD for CLL
  - ORR: 14/18 (78%)
  - 5/9 (56%) pts eligible for alloHCT have undergone transplant
  - 4/5 of these patients are still in CR (range 4-20 months post-alloHCT)

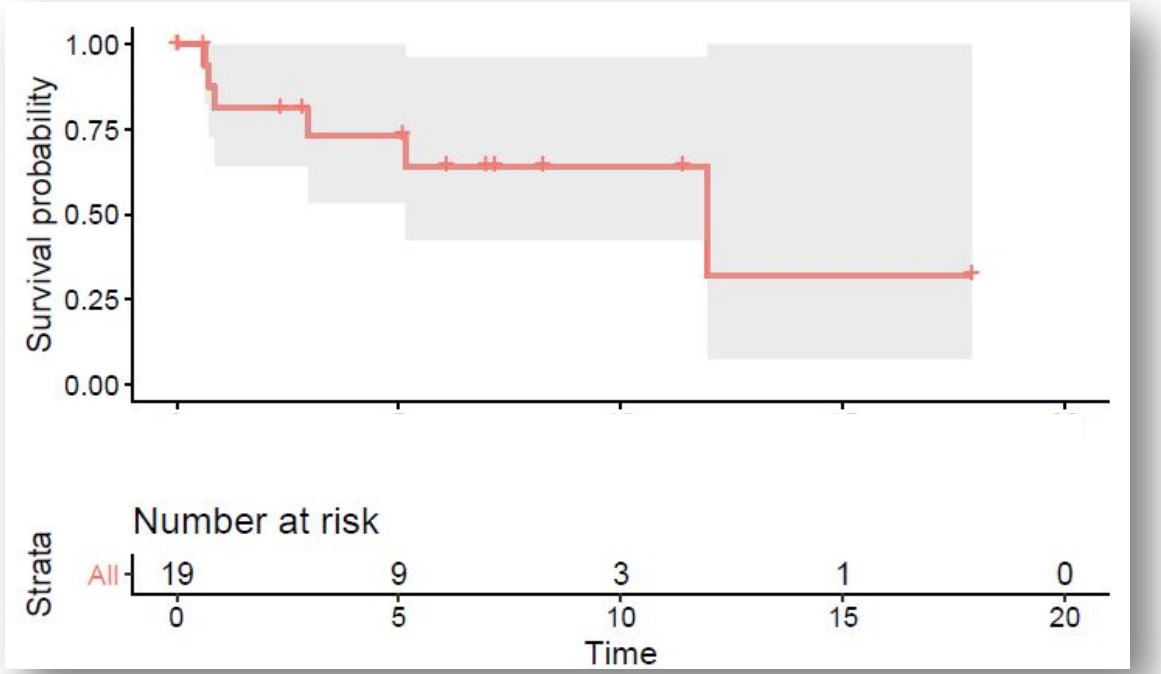
Davids et al., ICML, 2019

VR-EPOCH in Richter's Syndrome: Overall Survival

Uncensored



Censored at time of alloHCT



Median follow-up: 3 mo (range 0-17.9 mo)
Median OS: 16.3 mo

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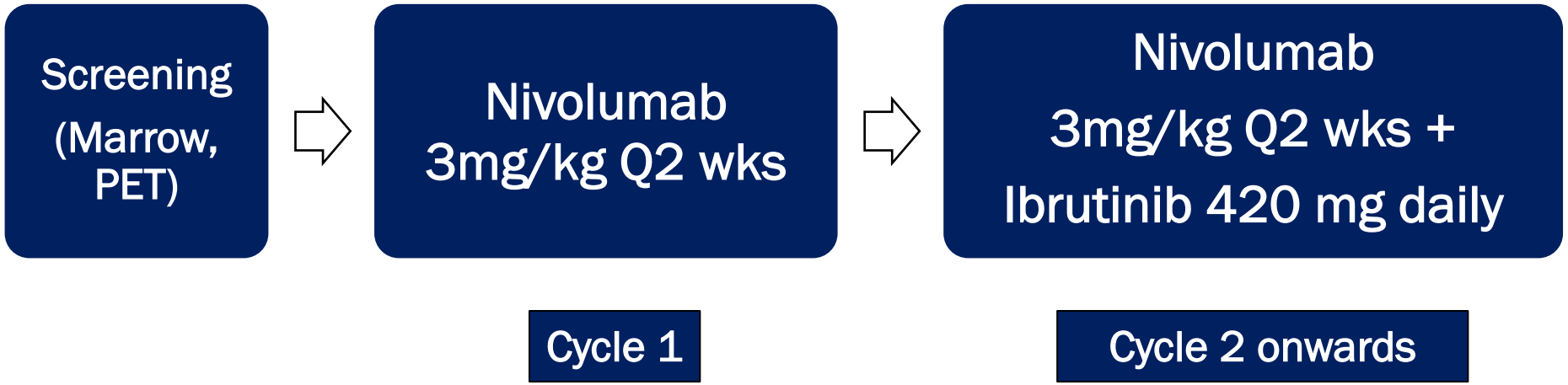
Davids et al., ICML, 2019

Checkpoint inhibition in RS

- **Pembrolizumab monotherapy (n=9)** Ding et al. Blood 2017
  - 4/9 (44%) ORR
  - Median PFS 5.4 mos; Median OS 10.7 mos
- **PD-1 mAb +/- Ibrutinib (n=10)** Rogers et al. BJH 2018
  - 1/10 (10%) ORR
- **Nivolumab + Ibrutinib (n=20)** Younes et al. Lancet Haem. 2019
  - 13/20 (65%) ORR

Nivolumab + Ibrutinib in RS: Study Design



Response Evaluation

After C1, C3, C6, C9, C12, then Q6 months

Jain et al., ASH, 2018

Nivo + Ibrutinib in RS: Baseline Characteristics (N=24)

		n (%) or median [range]
Age, years		64.5 [47-88]
Gender, M		14 (58)
Prior Therapies for CLL/RT		3 [0-10]
	Prior therapy for RT	10 (42)
	Prior therapy for CLL	20 (83)
Type of Therapy for CLL/RT	CIT	19 (79)
	BTKi*	13 (54)
	BCL2i	5 (21)
	PI3Ki	4 (17)
	Allo-SCT	3 (13)
CLL FISH (n=20)	Del(17p)	9 (45)
	Del(11q)	4 (20)
	Trisomy 12	4 (20)
	Negative	3 (15)
CLL *IGHV* status (n=18)	Unmutated	13 (72)
CLL Cytogenetics (n=19)	Complex	12 (63)
CLL Mutations (n=17)	*TP53*	8 (47)
	NOTCH1	4 (24)

* ibrutinib, n=12; acalabrutinib, n=1

Jain et al., ASH, 2018

Nivo + Ibrutinib Toxicities (N=24)

	No. of patients with event (%)	
	Grade 1-2	Grade ≥3
Skin rash	8 (33)	0
Arthralgia	6 (25)	0
Easy bruising	5 (21)	0
Diarrhea	3 (13)	0
Atrial Fibrillation	1 (4)	0

- Immune-related adverse events
  - Elevation of lipase/amylase (G4) n=1
  - Pneumonia / Pneumonitis (G3) n=2
  - Transaminitis (G3) n=1
  - Uveitis (G2) n=1

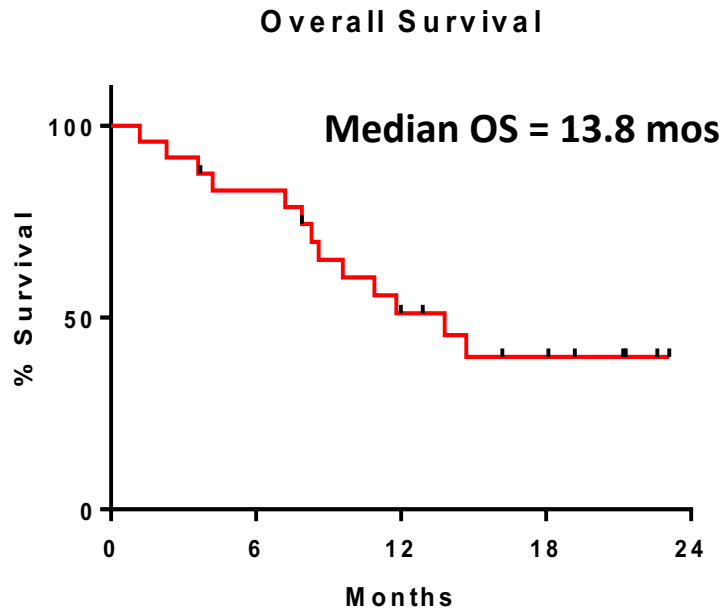
Jain et al., ASH, 2018

Nivo + Ibrutinib in RS: Responses

- 10/24 (42%) pts responded
  - Complete metabolic response, n=8
  - Partial metabolic response, n=2

- Prior BTKi = 3/13 (23%) (median prior therapies = 4)
- No prior BTKi = 7/11 (64%) (median prior therapies = 1)

- 4 pts went to allo-SCT in remission

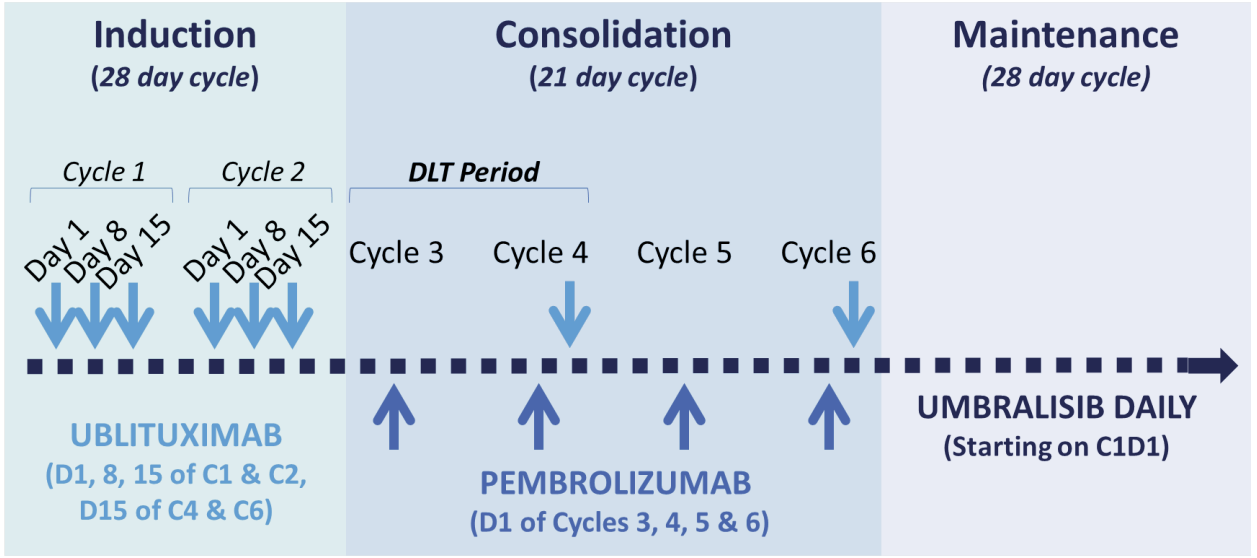


- 4 additional pts underwent allo-SCT after a subsequent salvage therapy

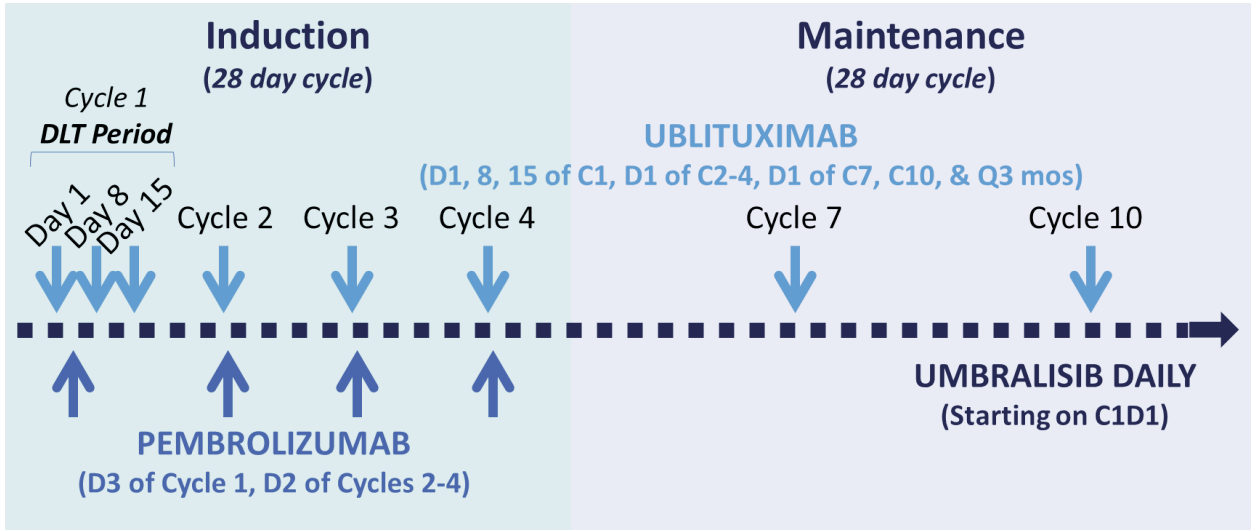
Jain et al., ASH, 2018

Phase I/II Study of Umbralisib/Ublituximab/Pembrolizumab in R/R CLL and Richter's Syndrome

CLL



RS



XVIII IWCLL
International Workshop on CLL
20-23 SEPTEMBER 2019 EDINBURGH

Mato et al., ICML, 2019

Toxicity profile of U2/pembro is manageable

Enrollment by Cohort

Pembro Dose	CLL	RT	Total
100 mg	5	4	9
200 mg	6	5	11

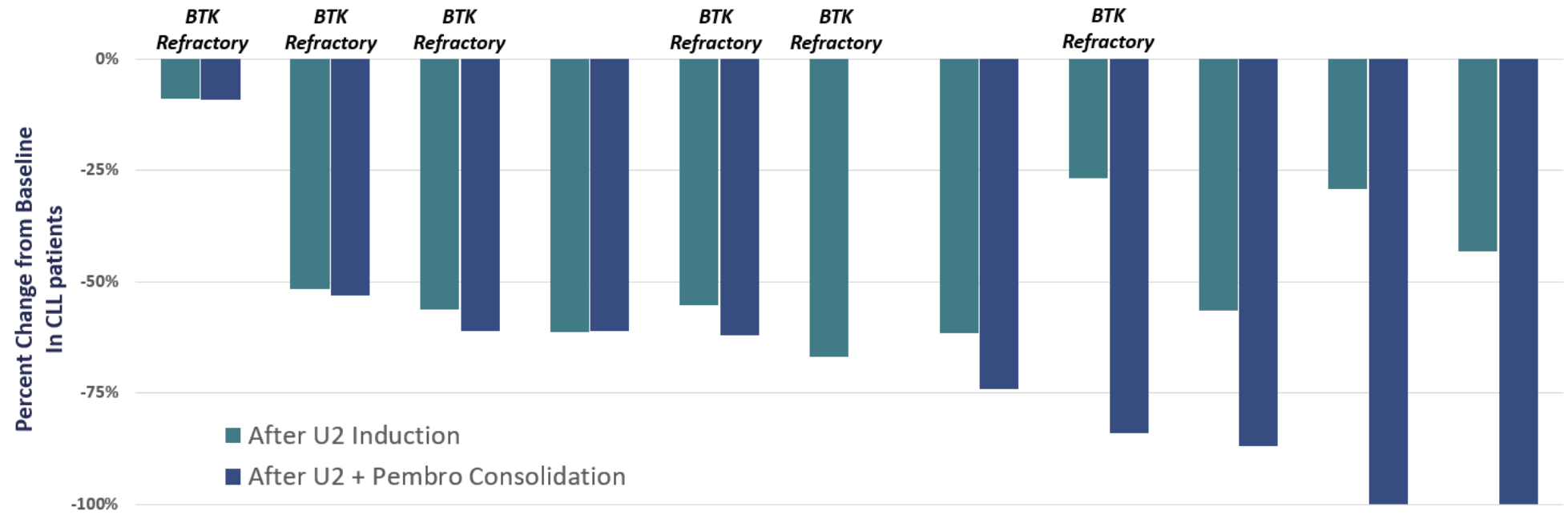
- 1 DLT at 200 mg pembro dose (transient elevated LFT - resolved); MTD not reached
- Grade 3/4 LFT elevations occurred in 4 patients (20%)
- No Grade 3/4 diarrhea and no events of colitis observed
- No Grade 3/4 pembro associated autoimmune events
- Median follow-up for all subjects: 11 mos (23 mos for CLL cohort)

Mato et al., ICML, 2019

Preliminary efficacy data in R/R CLL

Group	N	CR N (%)	PR N (%)	SD N (%)	ORR N (%)
CLL	11	1 (9%)	9 (82%)	1 (9%)	10 (91%)

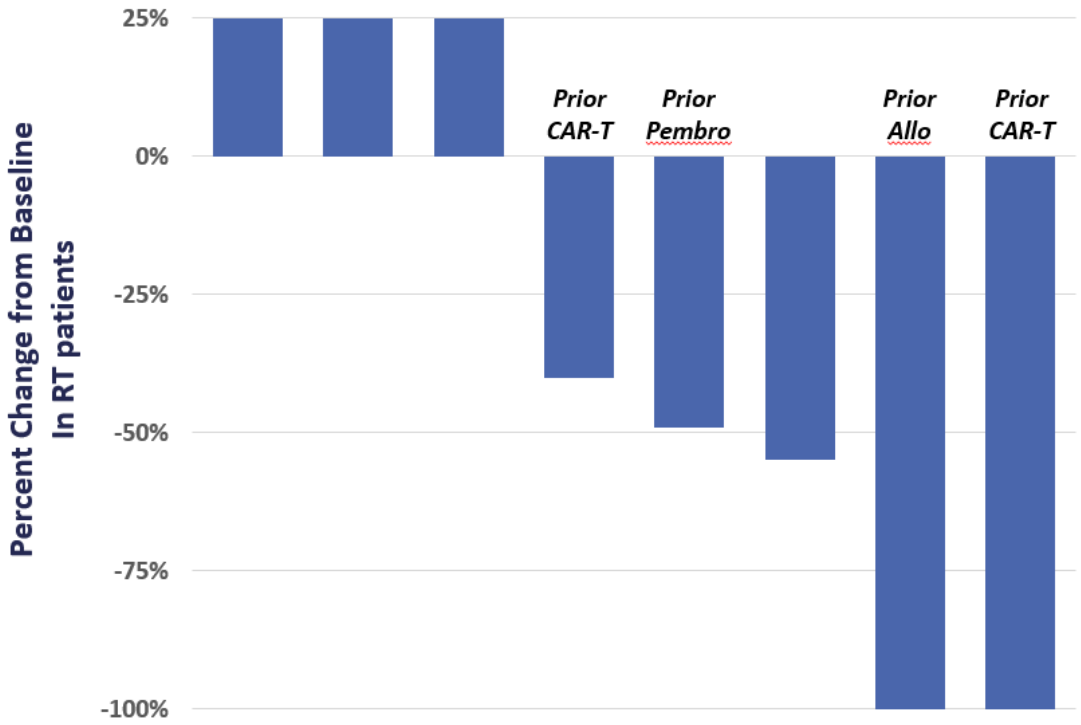
- BTK Refractory CLL
  - **ORR: 83% (5/6)**
  - 80% of BTK Refractory responders (4/5) achieved response after U2 Induction, prior to addition of pembro



XVIII IWCLL International Workshop on CLL 20-23 SEPTEMBER 2019 EDINBURGH

Mato et al., ICML, 2019

Preliminary efficacy data in RS



- Heavily refractory Richter's
  - 7/8 BTK Refractory
  - Durable responses observed

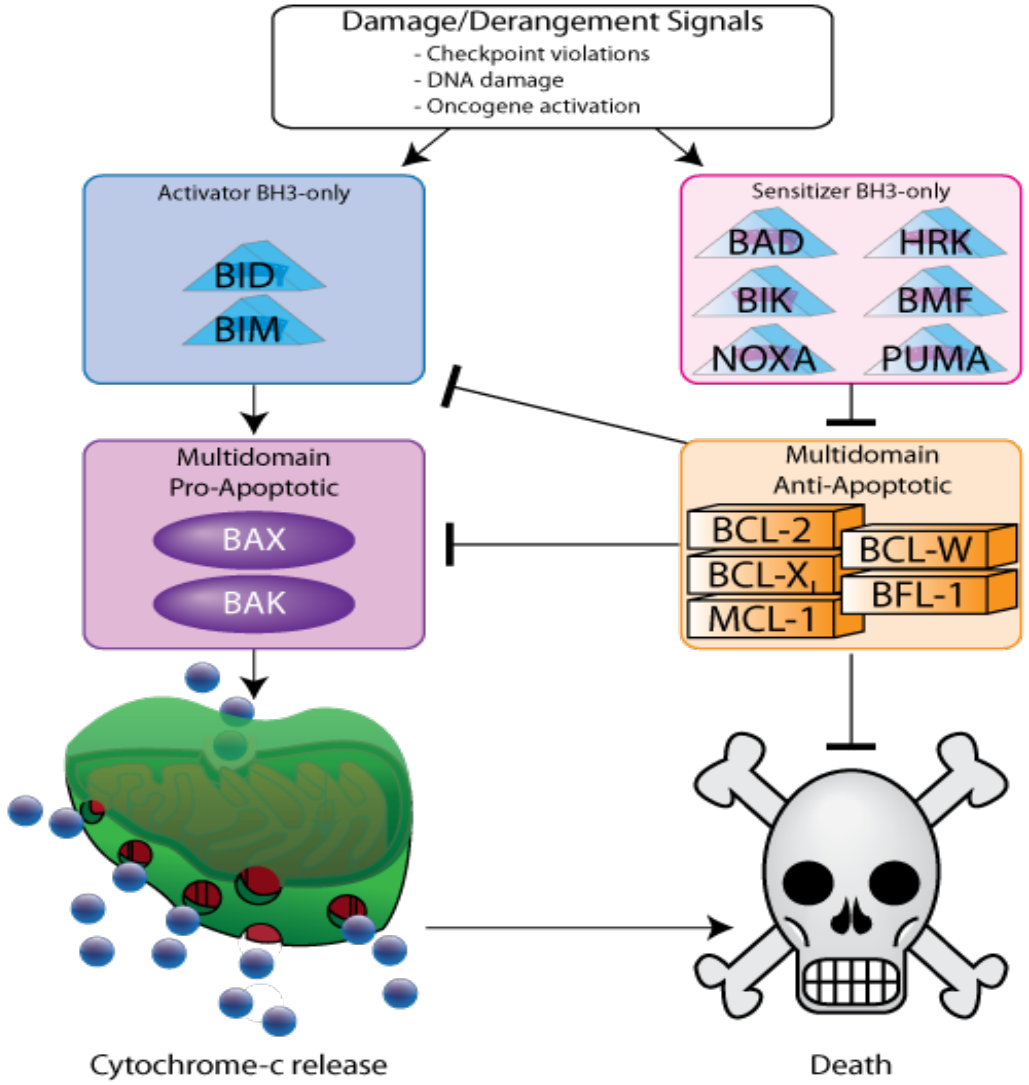
ORR N (%)	3 (38%)
CR N (%)	2 (25%)
PR N (%)	1 (12.5%)
SD N (%)	2 (25%)

Mato et al., ICML, 2019

Outline

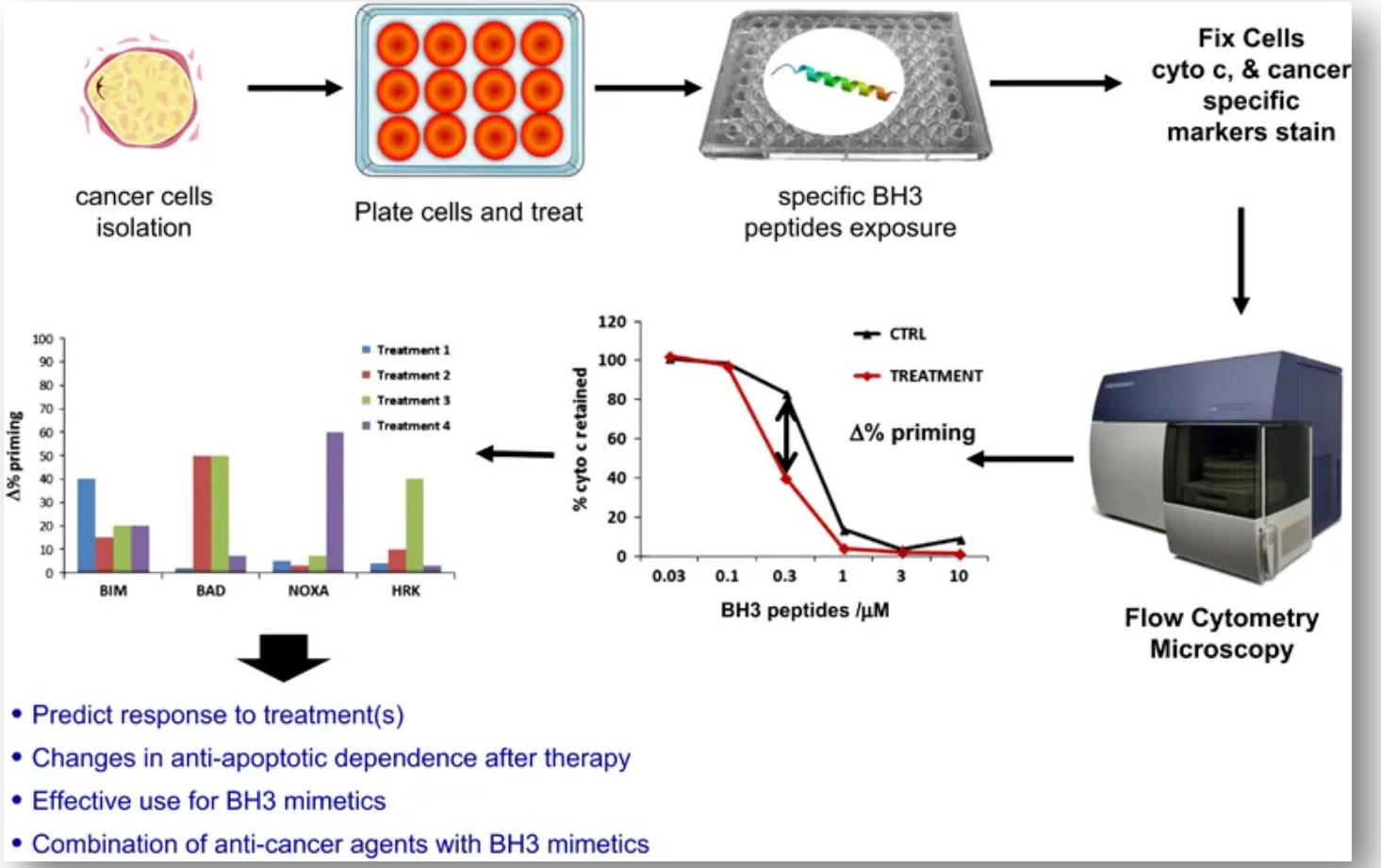
- Relapsed/Refractory CLL
  - Dual BCR blockade
  - BCL-2/BCR blockade
- Richter's Syndrome
  - Novel agent plus chemoimmunotherapy
  - Novel combinations with checkpoint blockade
- **Future Combinations**
  - **Further exploiting targeting of the Bcl-2 family**

Other anti-apoptotic proteins could mediate functional resistance to Bcl-2 selective inhibition



Certo et al, Cancer Cell 2006

BH3 profiling assesses the functional dependence of a cell on specific anti-apoptotic proteins



Anti-apoptotic protein dependencies

	Activators		Sensitizers					
	BIM	BID	BAD	BIK	NOXA	HRK	PUMA	BMF
BCL-2								
BCL-XL								
BCL-w								
MCL-1								
BFL-1								

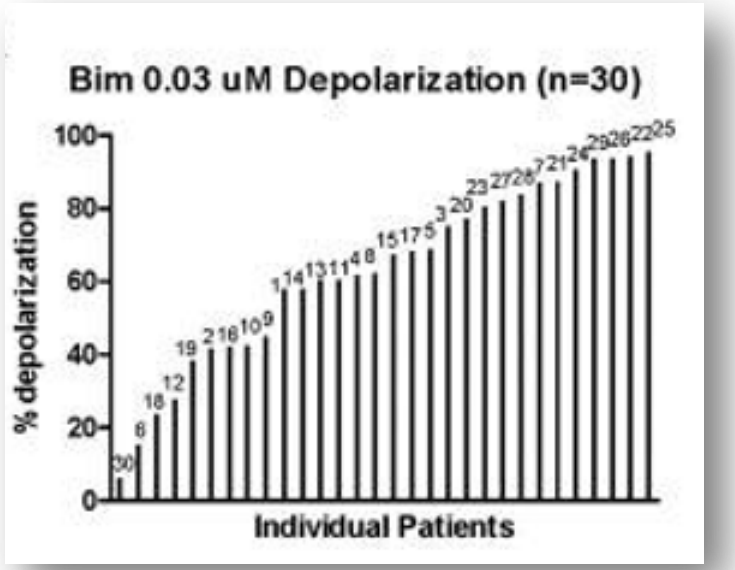
High affinity binding

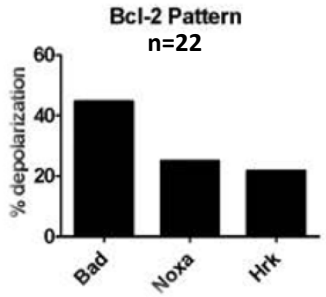
Intermediate affinity binding

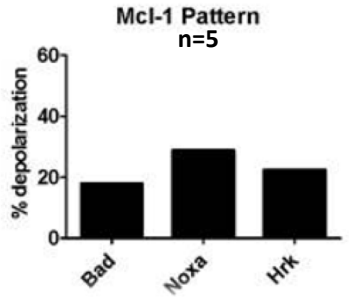
Low affinity binding

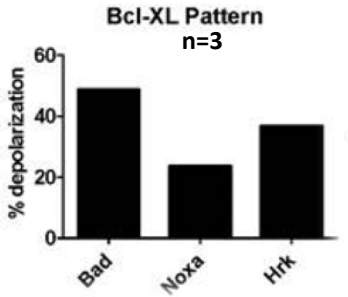
Montero and Letai, *Cell Death Differ.*, 2018

PB-derived CLL cells are generally primed for apoptosis and Bcl-2 dependent, but heterogeneity occurs



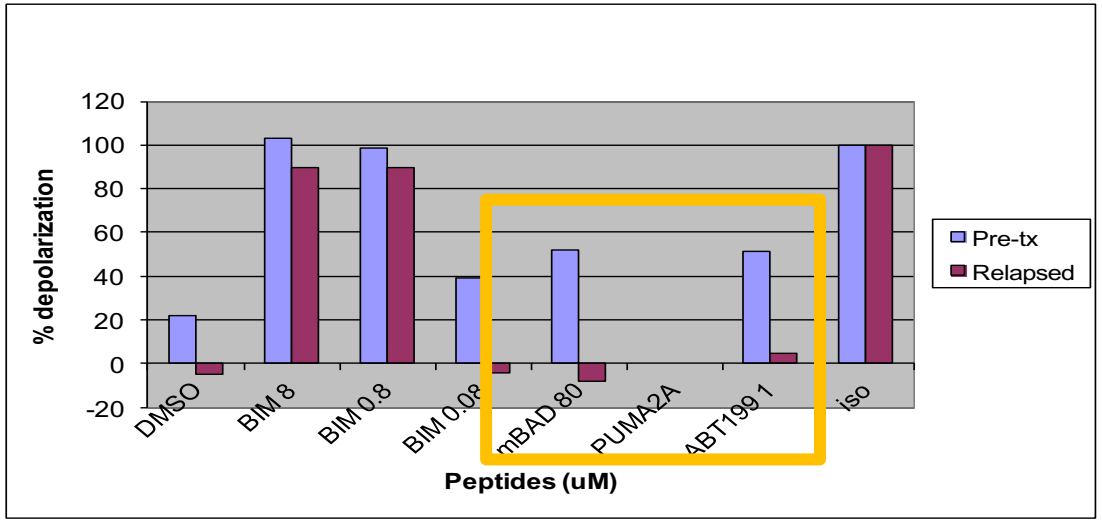


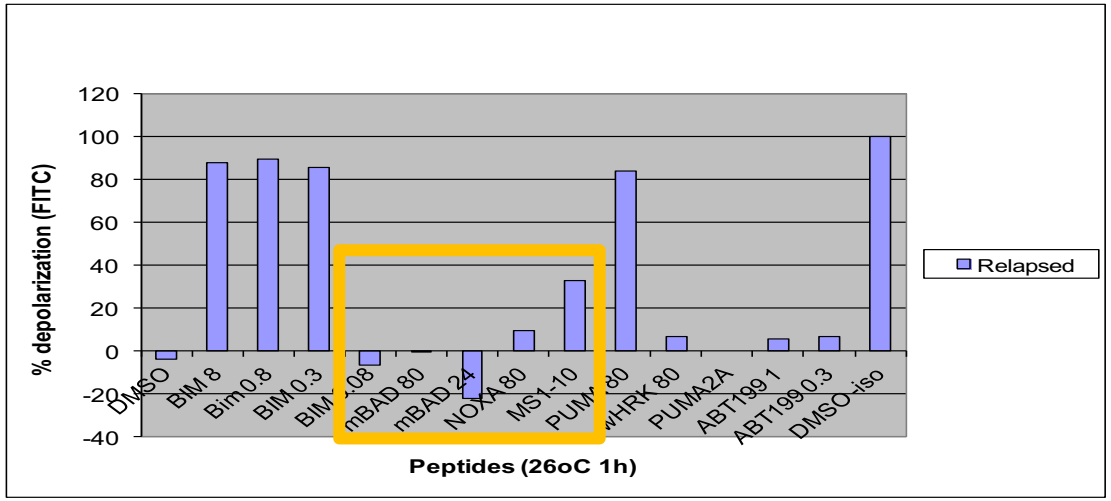




Davids et al, *Blood*, 2012

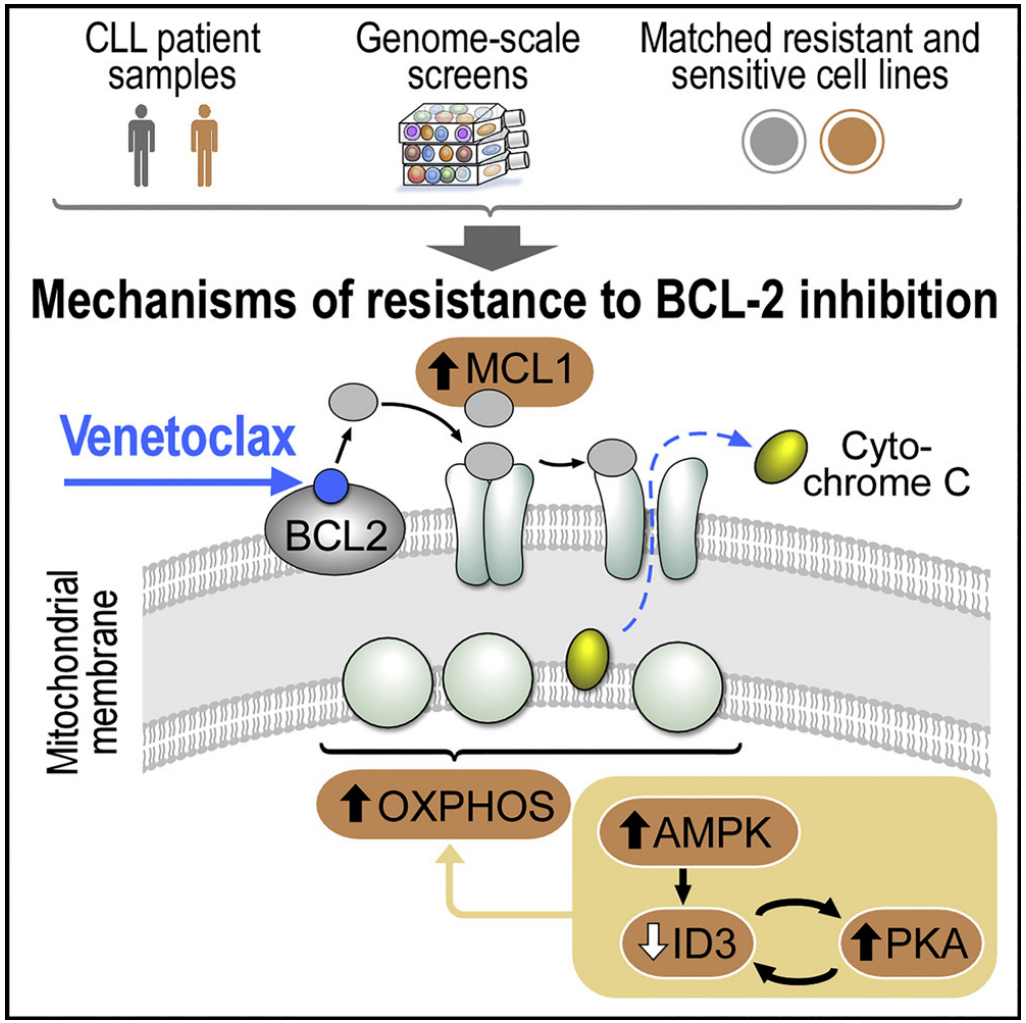
Mitochondria from patients who progress on venetoclax may be less sensitive to Bcl-2 inhibition and more Mcl-1 dependent





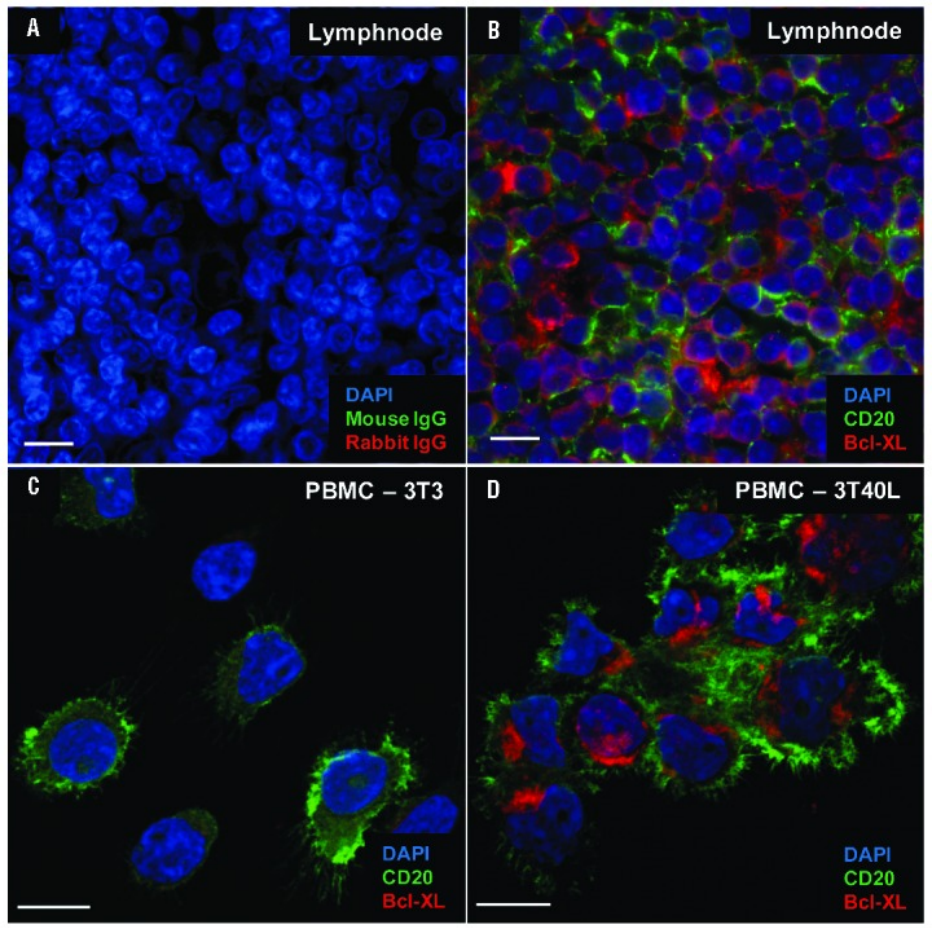
J. Deng, unpublished data

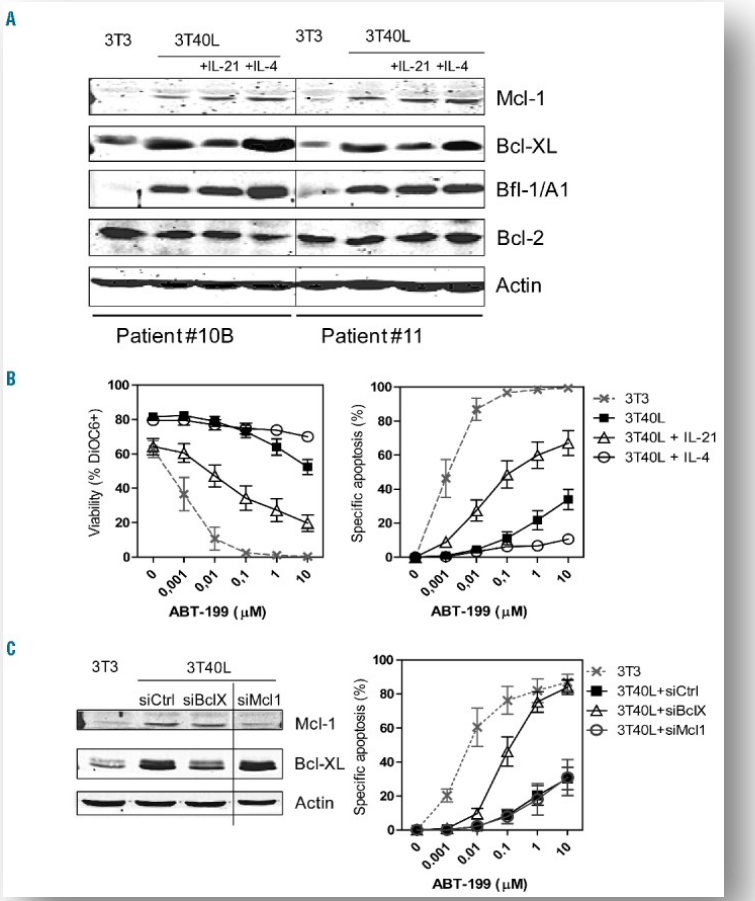
There are likely multiple drivers of venetoclax resistance, including increased MCL-1 dependence



Guize, et al., *Cancer Cell*, 2019

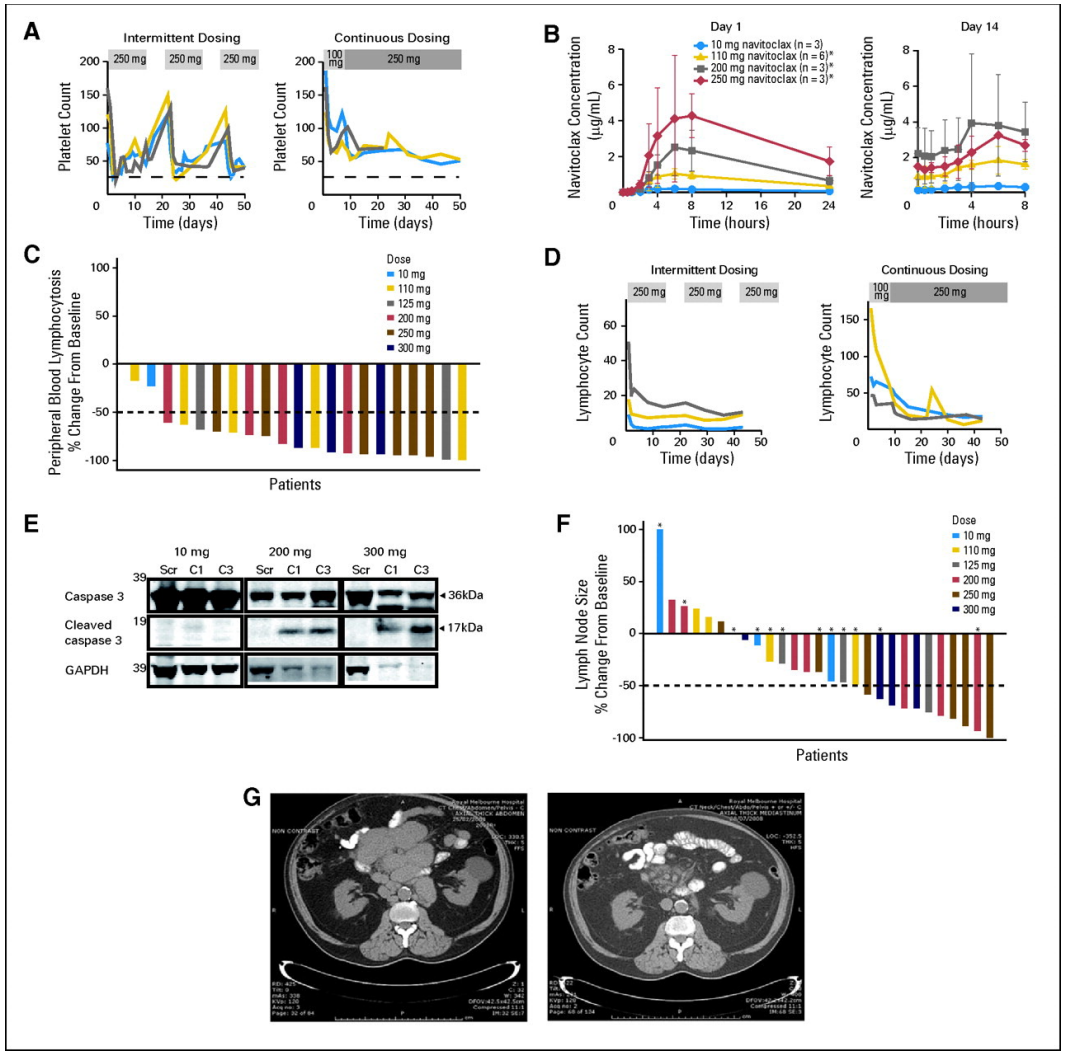
BCL-X_L is expressed in CLL cells in lymph nodes and Bcl-X_L, Mcl-1, and BFL-1 expression increases with CD40 stimulation, leading to venetoclax resistance





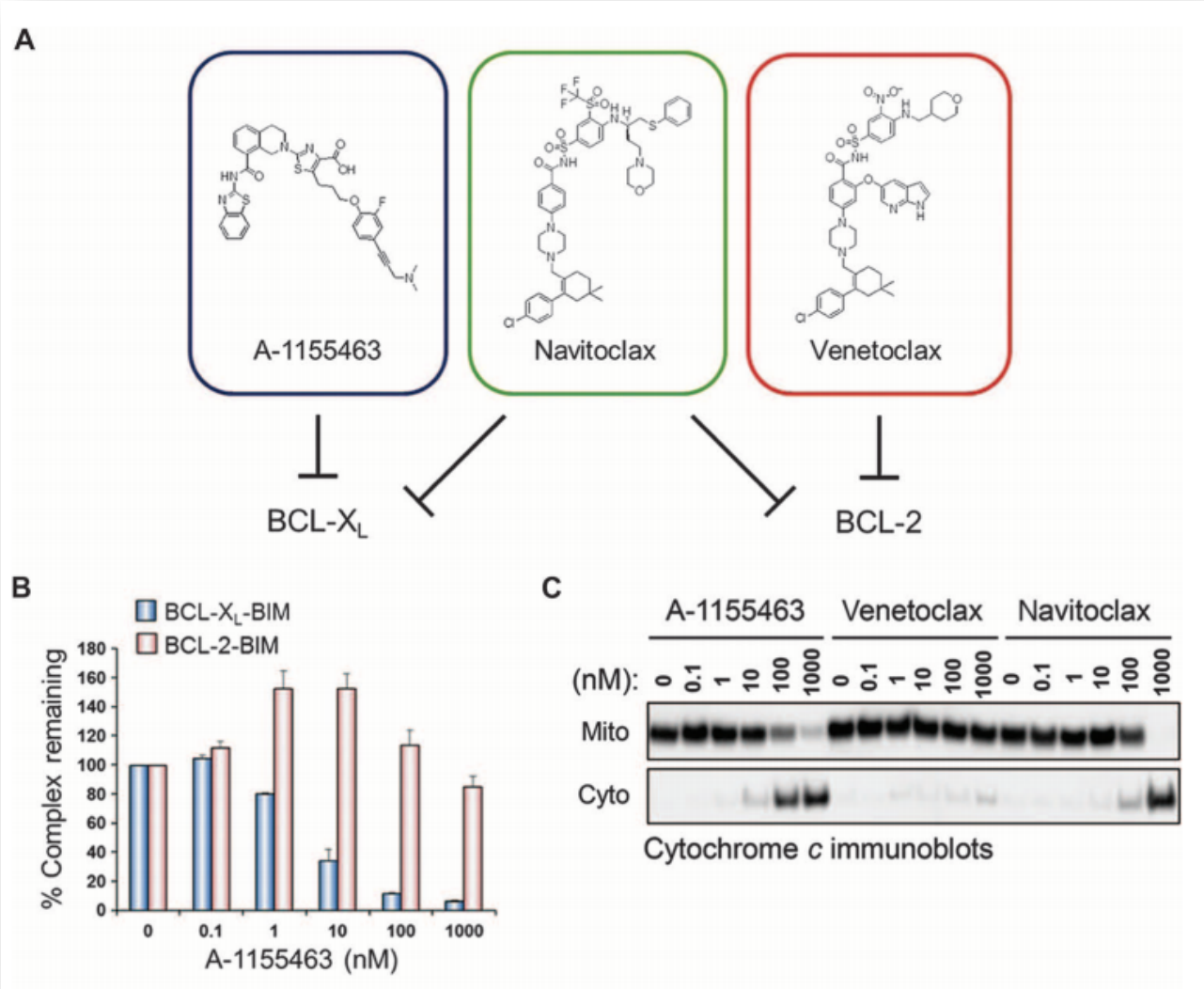
Thijssen et al., Haematologica, 2015

Navitoclax targets both Bcl-2 and Bcl-XL and is active but can cause significant thrombocytopenia



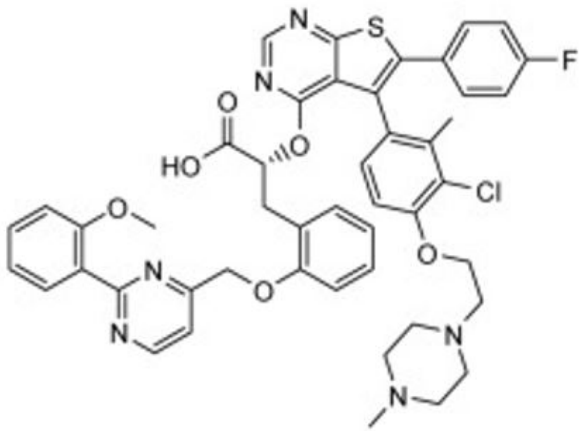
Roberts et al, *J Clin Oncol.*, 2012

A BCL-X_L selective inhibitor could overcome toxicity issues but maintain efficacy

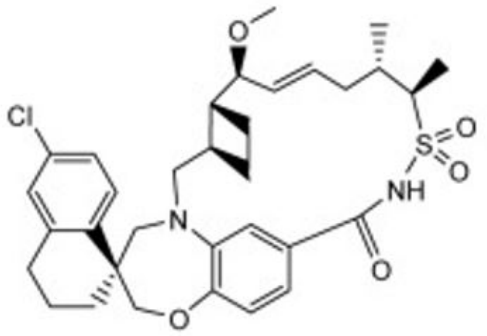


Leverson et al., Sci Trans Med, 2015

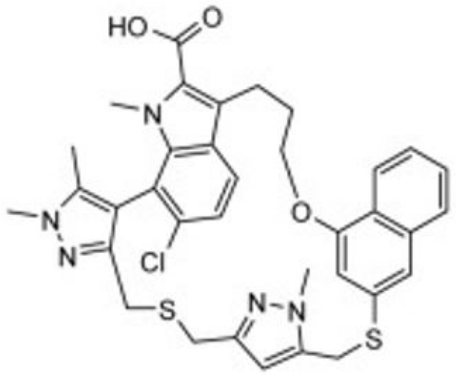
Three promising direct MCL-1 inhibitors recently entered the clinic



MIK665/S64315
Phase I



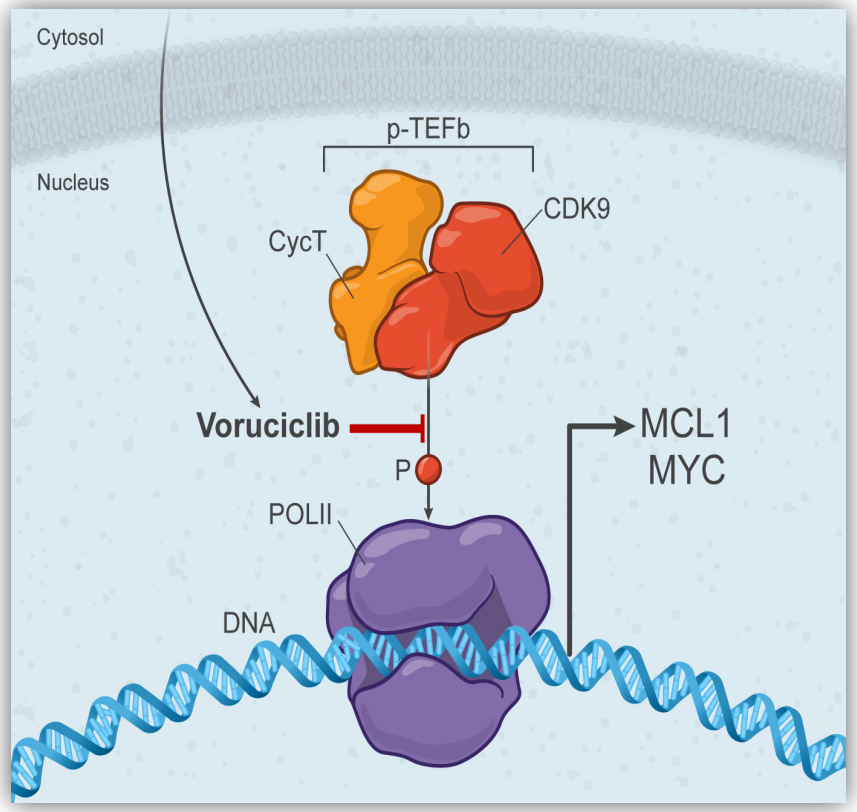
AMG176
Phase I



AZD5991
Phase I

Xiang et al., *Onco Targets Ther*, 2018

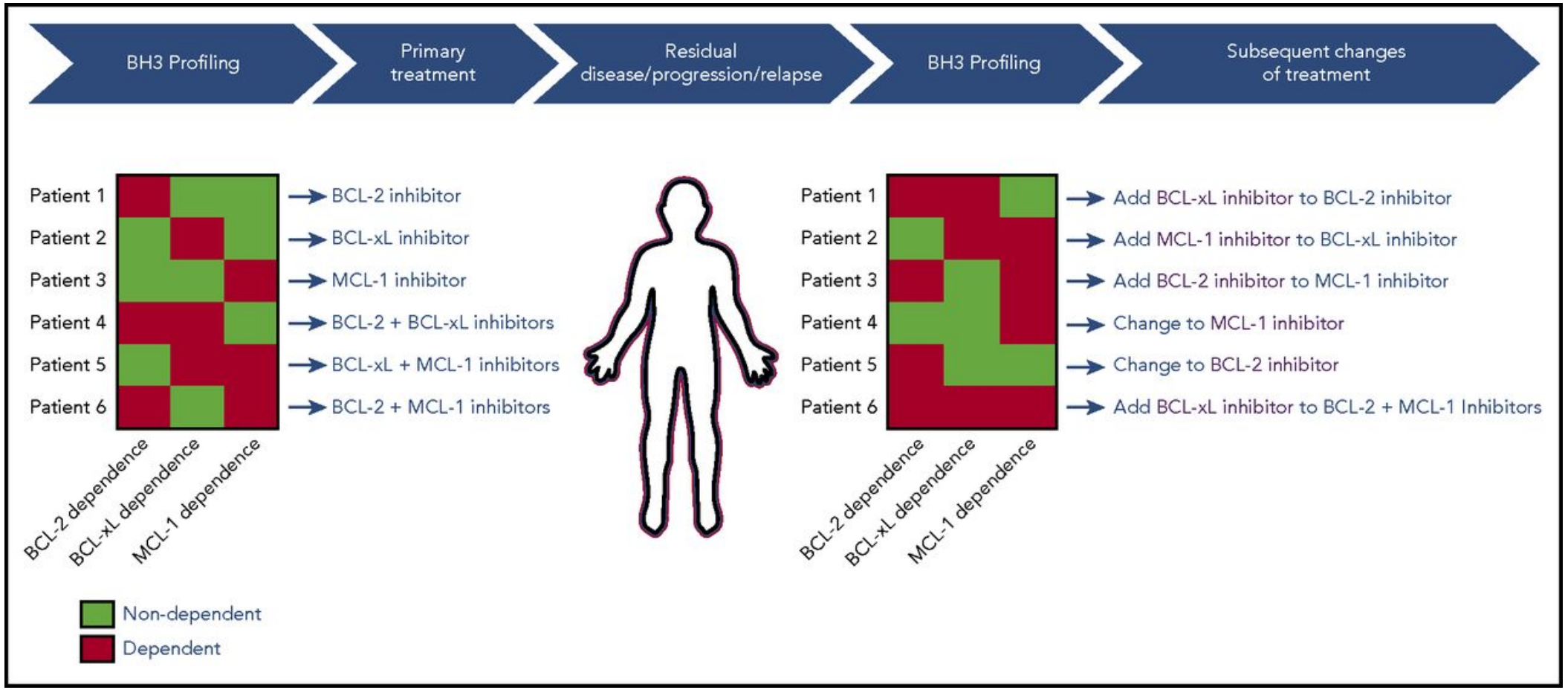
CDK inhibitors may indirectly inhibit MCL-1



Voruciclib

- Inhibits CDK9, 4, 6, and 1 at low nM conc.
- Transcriptional regulator of MCL-1 and MYC
- Orally bioavailable
- Favorable safety profile in solid tumor studies
- Phase 1 study in B-cell malignancies now open (NCT03547115)

BH3 profiling may allow for individualized BH3-mimetic therapy



Valentin, Grabow, Davids, *Blood*, 2018

Conclusions: Novel combinations in R/R CLL

- **Several promising novel combinations are in development for R/R CLL**
  - Dual BCR blockade
  - Combination BCR pathway inhibitors plus BCL-2 inhibition
- **Novel approaches for Richter's Syndrome include chemosensitization and checkpoint blockade plus BCR pathway inhibition**
- **A promising future approach may be to combine agents selectively targeting anti-apoptotic proteins, individualizing therapy based on functional and/or genomic assays**

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davidslab.dana-farber.org

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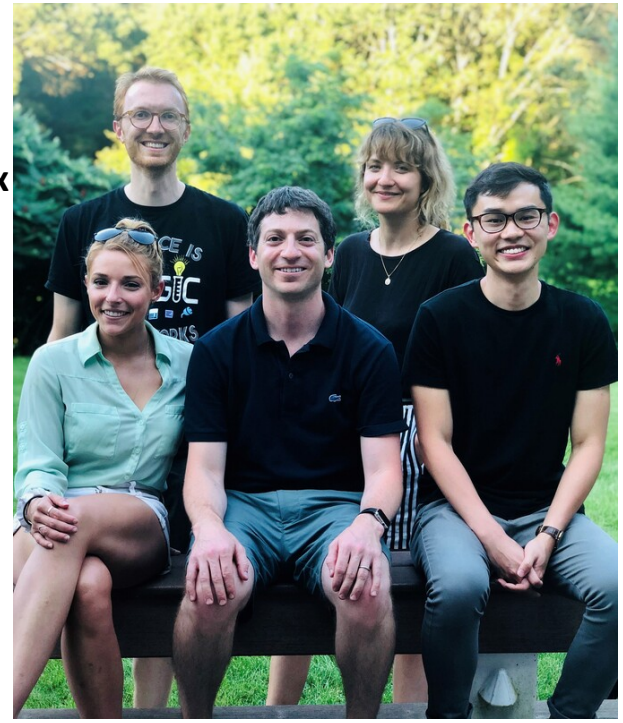

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