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Mantle Cell Lymphoma
"The Other Agents"

Peter Martin

June 27, 2022

Conflicts of Interest

- **Consultant: AstraZeneca, ADCT, Beigene, BMS, Daiichi, Epizyme, Janssen, Takeda**
- **Research funding: Karyopharm, Roche/Genentech**

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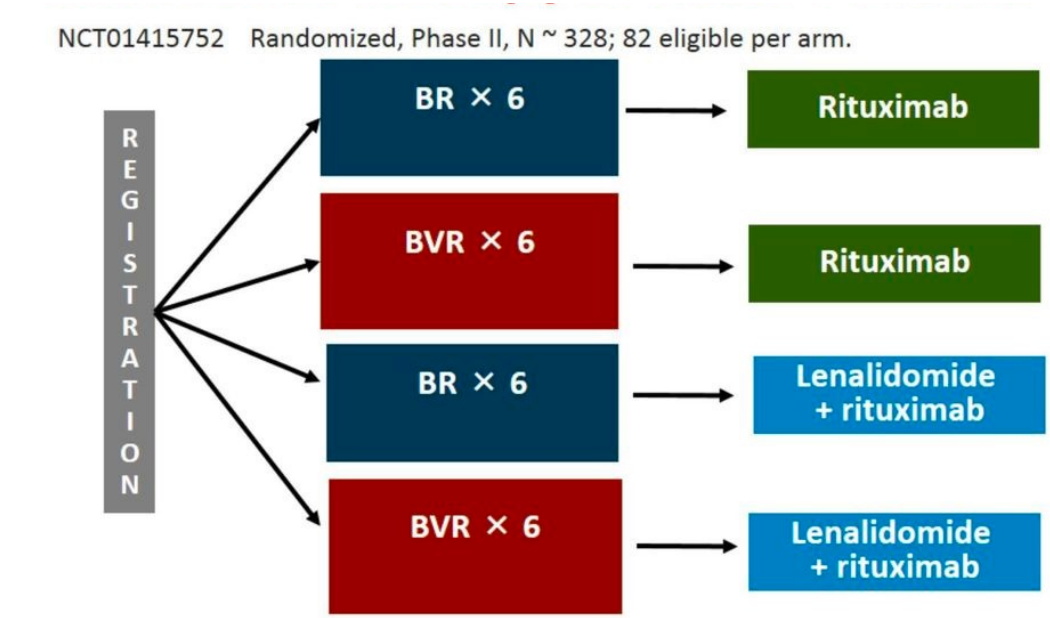
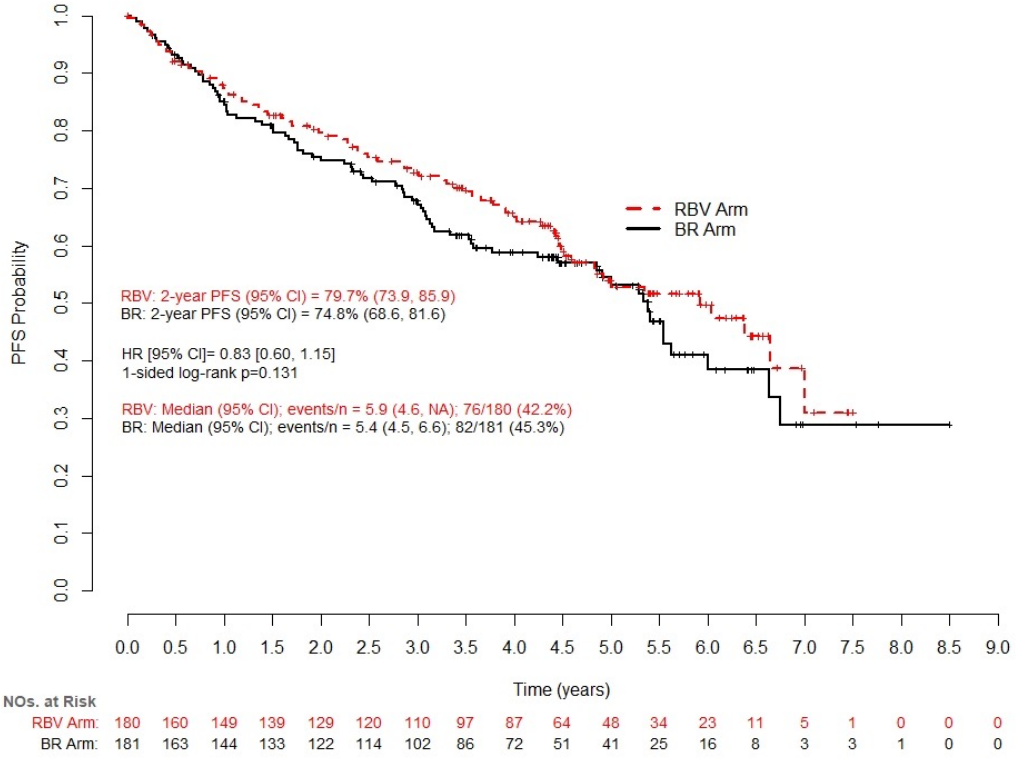
What do we do with our old “other” drugs?

E1411: US Intergroup Trial of Initial MCL Therapy in Older Patients



National Institutes of Health. https://clinicaltrials.gov/ct2/show/NCT014157.



Smith. ASCO 2021

Ibrutinib plus ixazomib is under evaluation

Phase I Study:

- Open to ibrutinib naïve and *selected* pre-treated patients**

Dose Level	Ixazomib Days 1, 8, 15 of a 28 day cycle	Ibrutinib Days 1-28 of a 28 day cycle
(-1)	3mg	420mg
1 START	3mg	560mg
2	4mg	560mg

Ibrutinib pre-treated patients must be off ibrutinib at least 3 months for Phase I

Phase II Study:

- Dosed at RP2D

→ Cohort A: Ibrutinib-Naive

→ Cohort B: Ibrutinib-Pre-Treated

NCT03323151

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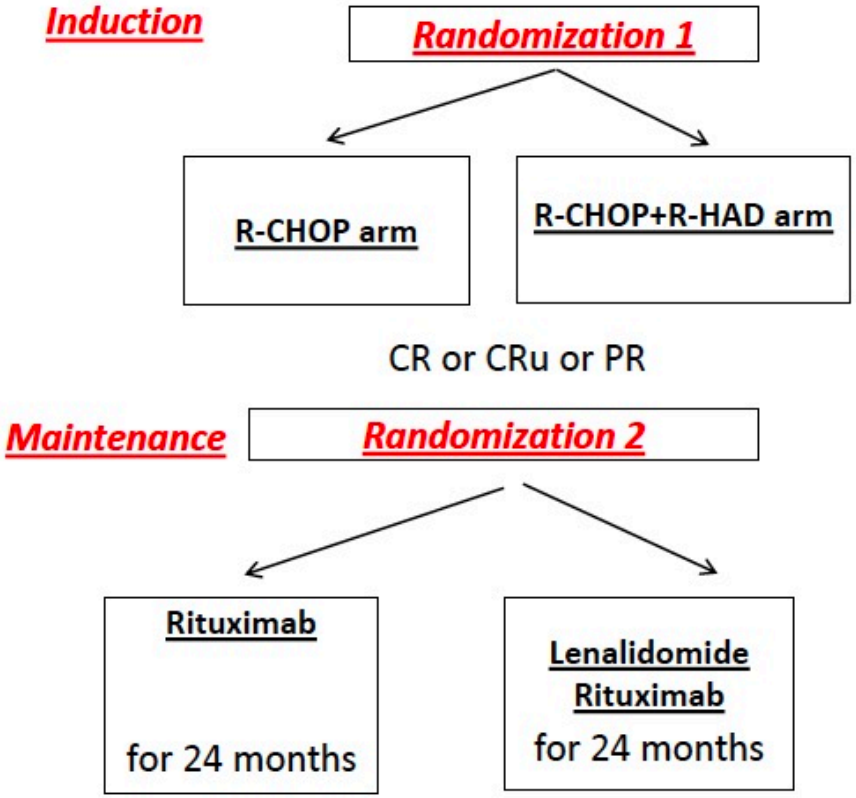
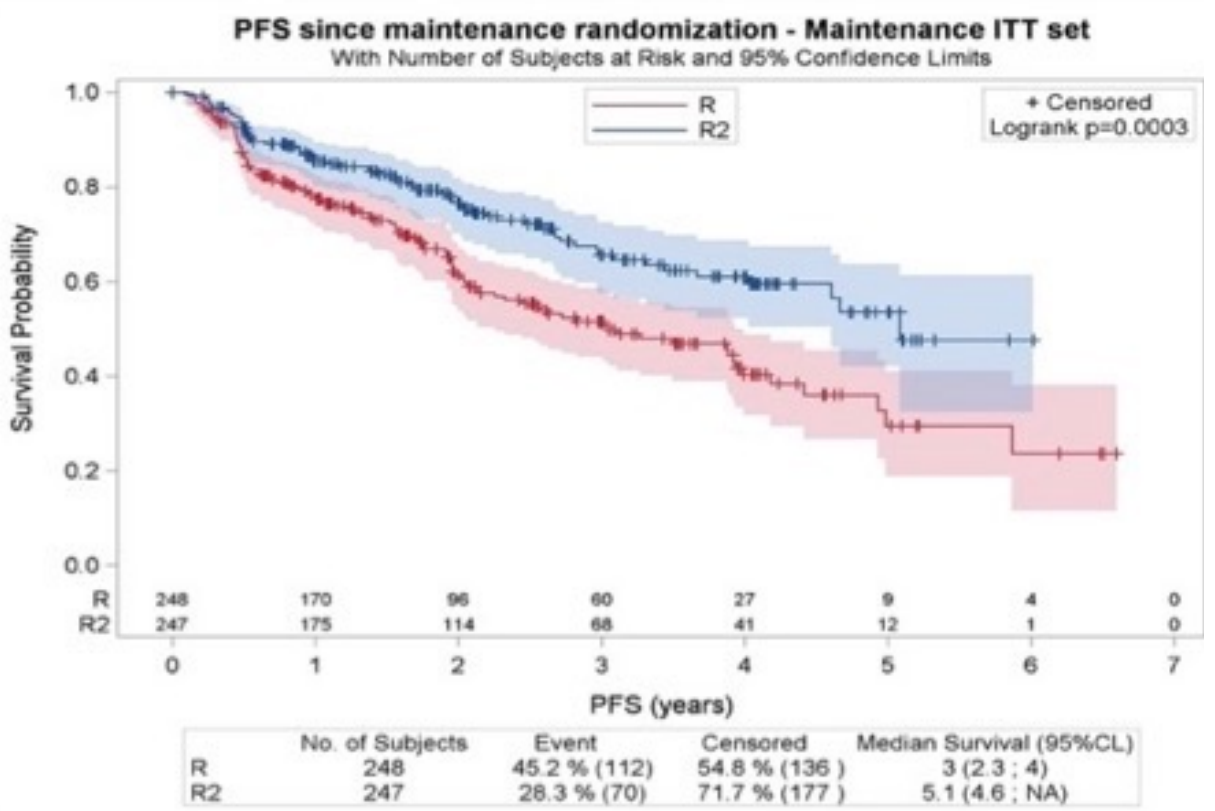
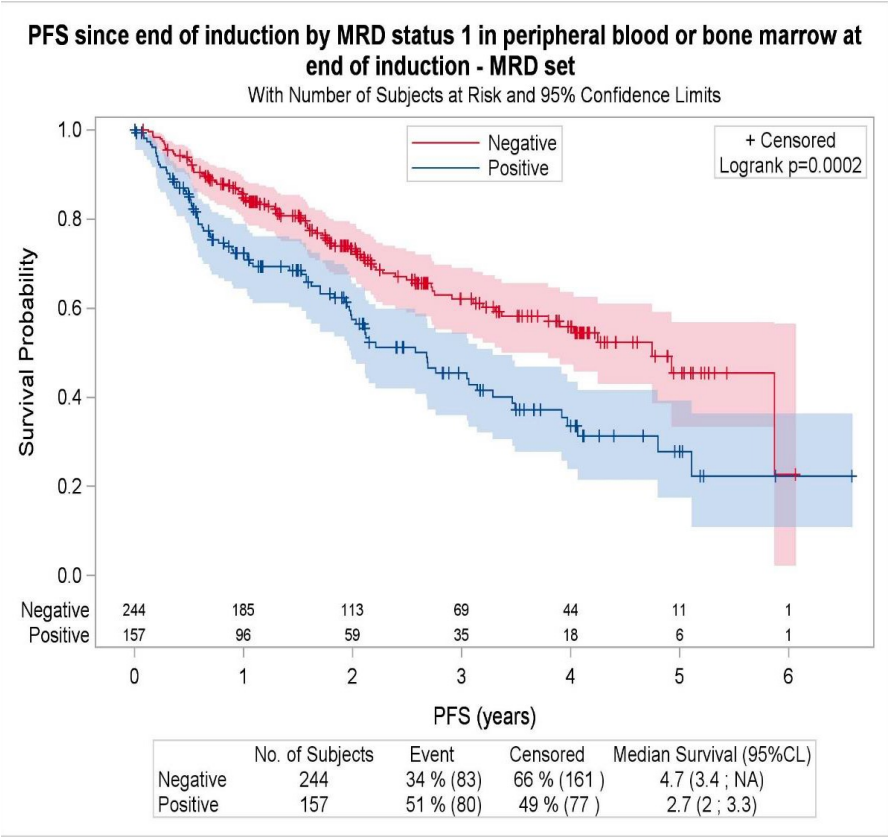
Slide courtesy of Jonathon Cohen

R2Elderly Trial,
A Mantle Cell Lymphoma Network Study



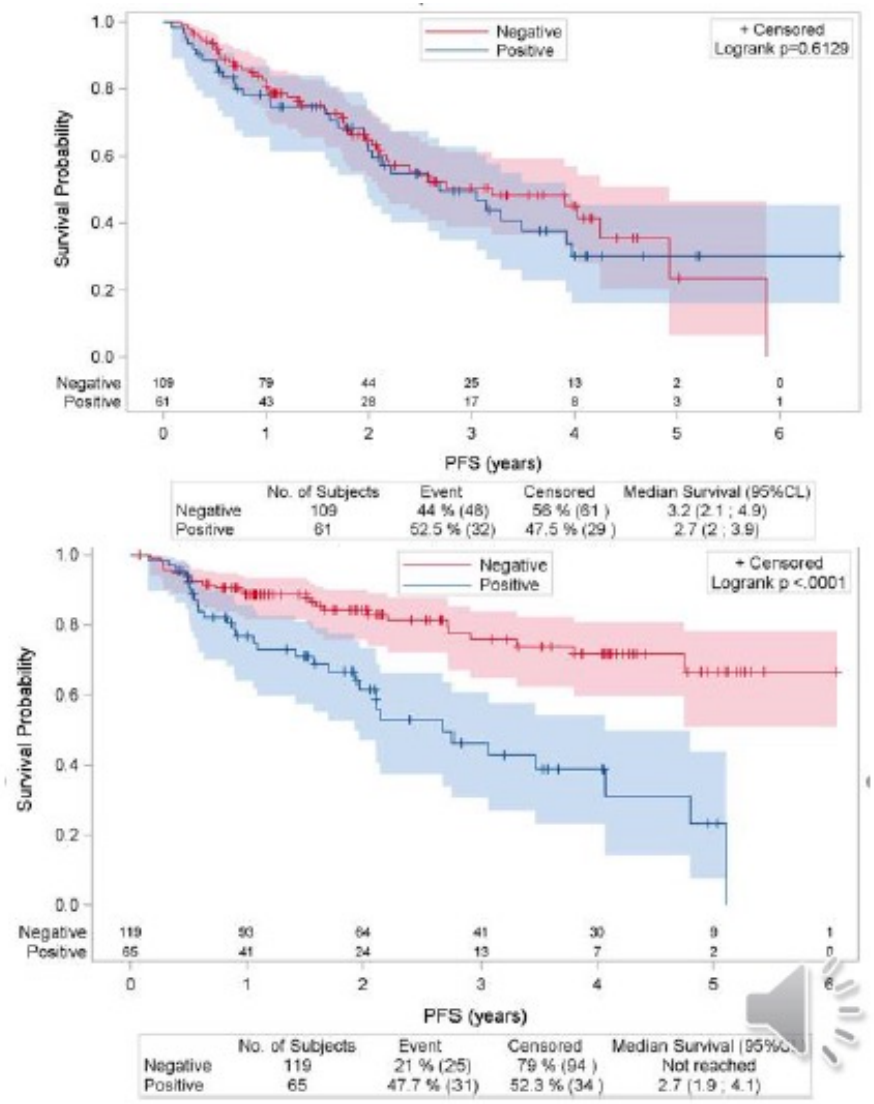


Ribrag. ASH Annual Meeting 2021



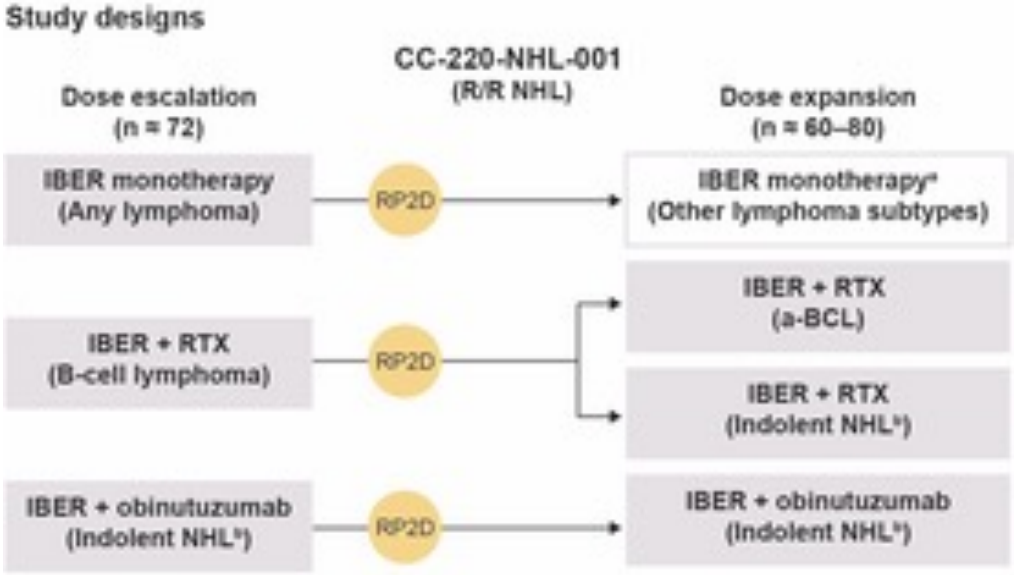
R

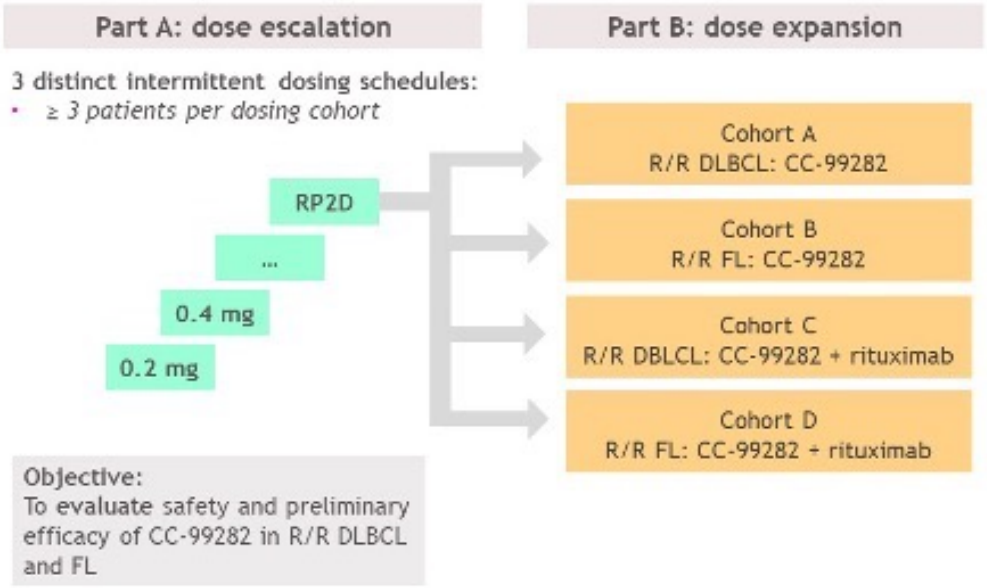
R^2



Delfau-Larue. ASH Annual Meeting 2021

New CelMods are in development, but unclear where MCL fits in





Morshchauser. ICML 2021

Where do bortezomib and lenalidomide fit?

Bortezomib

- Has a role in VR-CAP, but this regimen is not common
- No role in combination with BR
- Prolonged PFS post ASCT, but too toxic
- Possible role in combination with multiple drugs post BTKi failure

Lenalidomide

- Lenalidoimde prolongs PFS after R-HDS+ASCT and after R-CHOP-based therapy
  - Implications of MRD?
- Too early to know about maintenance post BR
- R^2 active in front-line setting, although other combinations may be more attractive
- R^2 active in combination with BTKi in r/r setting, but other combinations may be more attractive

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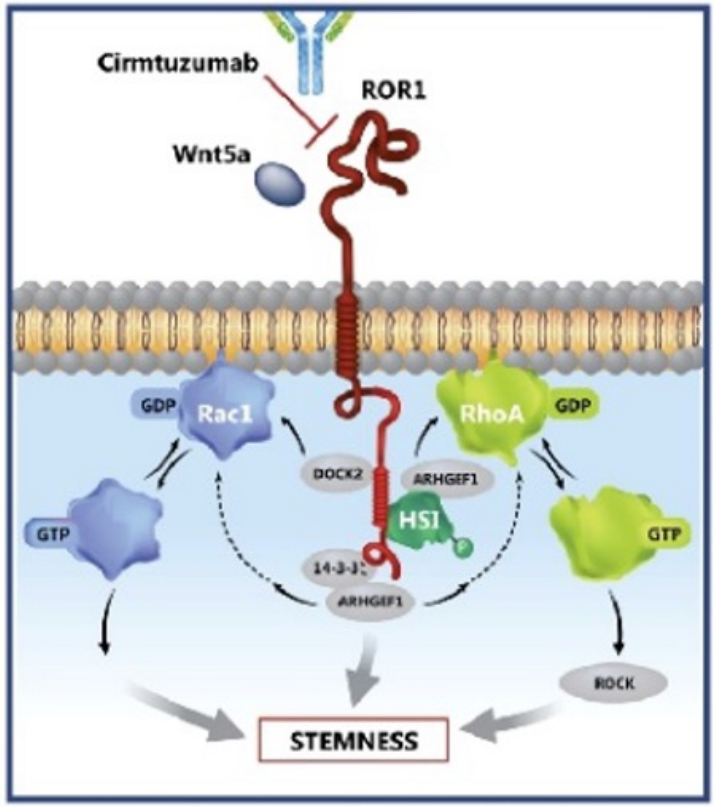
What do we do with new “other” drugs?

Receptor Tyrosine Kinase-Like Orphan Receptor 1 (ROR1) Provides an Attractive Therapeutic Target in MCL

- **ROR1 is an onco-embryonic tyrosine kinase that is re-expressed at high levels on many hematologic cancers but not on normal tissues.**
- **ROR1 binds Wnt5a, resulting in increased tumor growth, survival, metastasis, cancer cell stemness, etc.**
- **Zilovertamab (cirmtuzumab) is a humanized monoclonal antibody designed to inhibit the tumor promoting activity of ROR1.**



Zilovertamab plus ibrutinib phase 1/2 study design

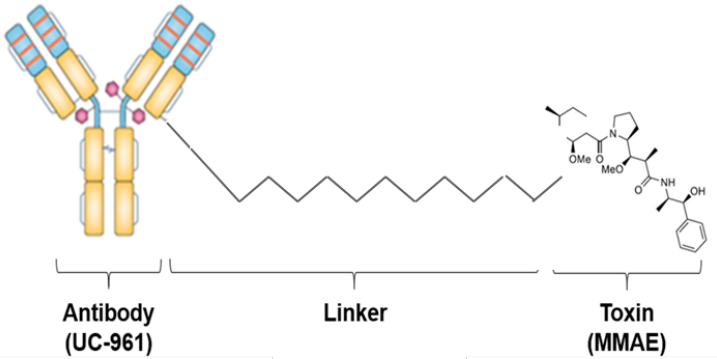
Treatment naïve (TN) or Relapsed/Refractory (R/R) CLL/SLL; R/R MCL and MZL; prior BTKi allowed for MCL and MZL

Phase 1	Phase 2	
Part 1 (MCL & CLL)	**Part 2 (MCL, CLL & MZL)**	**Part 3 (CLL)**
DOSE-FINDING COHORT ■ 2, 4, 8 & 16mg/kg and 300 & 600mg doses of zilovertamab[a] evaluated ■ Ibrutinib added after 1 month (420mg CLL, 560mg MCL, qd po) ■ No DLTs, MTD not reached ■ RDR[b]: 600mg IV q2wks X 3 then q4wks in combination with ibrutinib at approved doses per indication	**DOSE-EXPANSION COHORT** ■ Confirmed RDR[b] of zilovertamab[a] (600mg) + ibrutinib at approved dose (420mg CLL, 560mg MCL and MZL) ■ Primary objective: To further characterize safety, pharmacology, and clinical response using RDR[b]	**RANDOMIZED EFFICACY** ■ Zilovertamab[a] + ibrutinib vs. ibrutinib ■ Randomization ratio = 2:1 ■ Primary objective: Complete Response Rate
Enrolled CLL n = 18 MCL n = 12	***Enrolled*** CLL n = 16 MCL n = 21 ***MZL soon open for enrollment***	***Enrolled*** n = 31

Zilovertamab plus ibrutinib phase 1/2 activity in MCL

	Overall	Ki67 ≥ 30%	Prior BTKi[a]	Prior SCT +/- CAR-T[b]	Bulky disease (≥ 5cm)	Low sMIPI	Int sMIPI	High sMIPI	1 Prior Regimen	2 Prior Regimens	≥ 3 Prior Regimens	p53 mutation
	N=27	N=14	N=5	N=7	N=4	N=15	N=9	N=3	N=15	N=8	N=4	N=6
ORR, n (%)	23 (85.2)	12 (85.7)	4 (80.8)	7 (100.0)	4 (100.0)	13 (86.7)	8 (88.9)	2 (66.7)	13 (86.7)	6 (75.0)	4 (100.0)	5 (83.3)
CR, n (%)	11[c] (40.7)	5[c] (35.7)	2 (40.0)	5 (71.4)	3 (75.0)	5 (33.3)	5[c] (55.6)	1 (33.3)	4[c] (26.7)	5 (62.5)	2 (50.0)	1 (16.7)
PR, n (%)	12 (44.4)	7 (50.0)	2 (40.0)	2 (28.6)	1 (25.0)	8 (53.3)	3 (33.3)	1 (33.3)	9 (60.0)	1 (12.5)	2 (50.0)	4 (66.7)
SD, n (%)	2 (7.4)	0	1 (20.0)	0	0	1 (6.7)	0	1 (33.3)	0	2 (25.0)	0	0
PD, n (%)	2 (7.4)	2 (14.3)	0	0	0	1 (6.7)	1 (11.1)	0	2 (13.3)	0	0	1 (16.7)
Median Duration of Response, months (95% CI)	34.13 (13.67, NE)	NR (13.67, NE)	13.67 (11.93, NE)	34.13 (13.84, NE)	23.90 (11.93, NE)	NR (11.93, NE)	34.13 (NE)	NR (13.84, NE)	NR (11.93, NE)	NR (1.51, NE)	34.13 (13.84, NE)	13.84 (11.93, NE)

Zilovertamab Vedotin



Key Eligibility Criteria

- Histological diagnosis of CLL/SLL, lymphoplasmacytic lymphoma/Waldenström macroglobulinemia, ALL, AML, or NHL[a]

Schedule 1
Zilovertamab Vedotin
0.5-2.5 mg/kg on day 1 Q3W

Schedule 2
Zilovertamab Vedotin
1.0-2.25 mg/kg on day 1 and 8 Q3W

Schedule 3
Zilovertamab Vedotin
1.0-2.25 mg/kg on day 1, 8, and 15 Q4W

Restage by CT/MRI Q9W until cycle 11 and then Q12W thereafter

- **Primary end point:** MTD
- **Secondary end points**: safety, ORR, and DOR

Final MTD 2.5 mg/kg
DLT: Grade 4 neutropenia, Grade 3 diarrhea, Grade 3 febrile neutropenia, Grade 3 pancreatitis

Wang. ASH Annual Meeting 2021

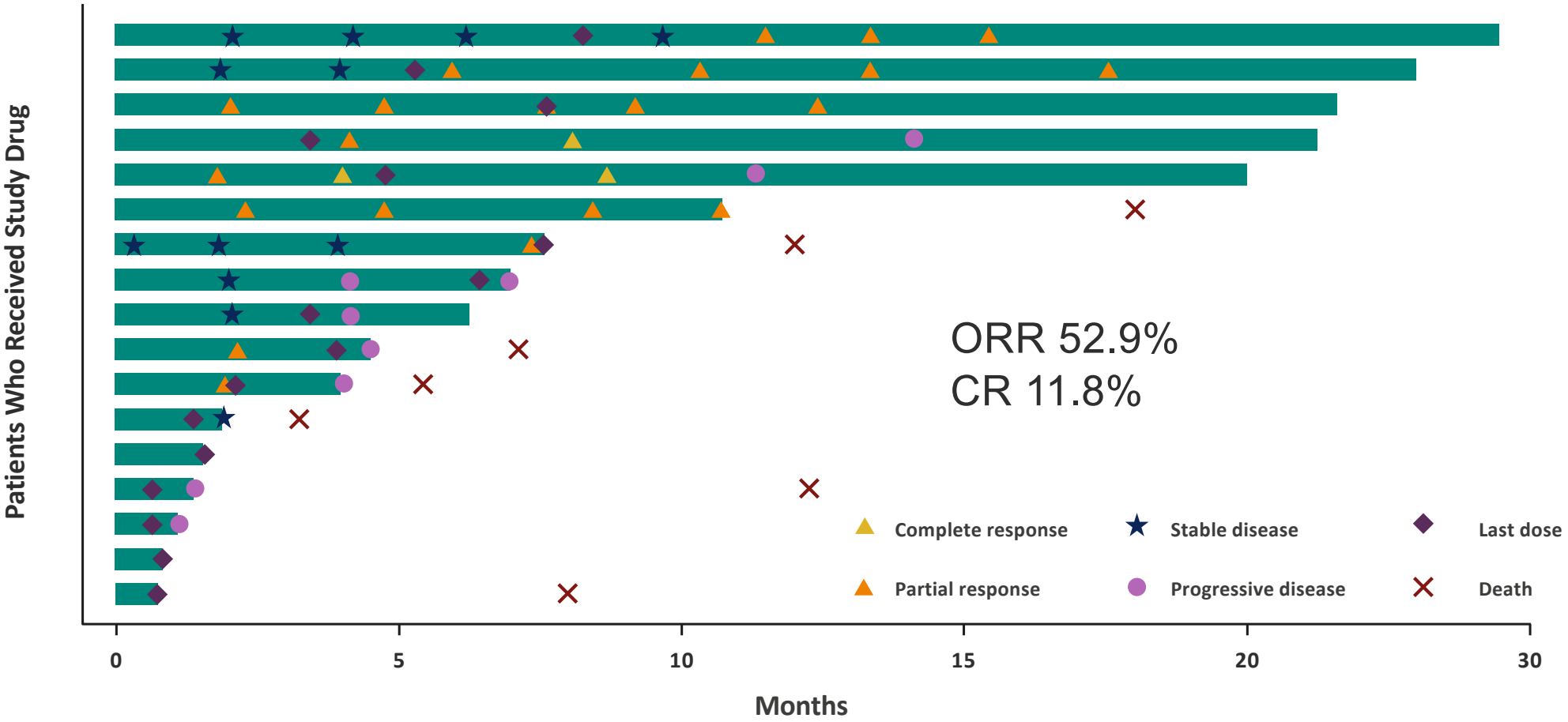
1. Borcherding N et al. *Protein Cell.* 2014;5:496-502; 2. Danesmanesh AH et al. *Leuk Lymphoma.* 2013;54:843-850.3. Vaisitti T et al. *Blood.* 2021;137:3365-3377.

Grade 3 or 4 Adverse Events in ≥3 Patients

Grade 3 or 4 AEs, n (%)	All Patients N = 51	
	All-Cause	Treatment-Related
Decreased neutrophil count	16 (31.4)	16 (31.4)
Decreased hemoglobin	8 (15.7)	3 (5.9)
Febrile neutropenia	4 (7.8)	2 (3.9)
Peripheral neuropathy[b]	4 (7.8)	4 (7.8)
Decreased platelet count	4 (7.8)	4 (7.8)
Diarrhea	3 (5.9)	2 (3.9)
Increased lipase	3 (5.9)	2 (3.9)
Pneumonia	3 (5.9)	1 (2.0)

[a]No deaths were attributed to study therapy. 1 patient died due to acute respiratory failure not related to treatment.
[b]Includes the preferred terms peripheral sensory neuropathy, peripheral neuropathy, peripheral motor neuropathy, and peripheral sensorimotor neuropathy.
Data cutoff: May 18, 2021.

Zilovertamab Vedotin Efficacy in MCL



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Glofitamab regimens investigated in R/R MCL

Dose escalation (Phase I)

Glofitamab fixed dosing

Gpt 1000mg
Glofitamab
0.6, 16 or 25mg*:
n=3

C1D–7	C2D1 up to C12D1 (Q3W)
Gpt 1000mg	*Glofitamab 0.6mg, 16mg, or 25mg*

Glofitamab SUD

Gpt 1000mg
Glofitamab
2.5/10/16mg or
2.5/10/30mg†: n=7

C1D–7	C1D1	C1D8	C2D1 up to C12D1 (Q3W)
Gpt 1000mg	*Glofitamab 2.5mg*	*Glofitamab 10mg*	*Glofitamab 16 or 30mg*

Gpt 2000mg
Glofitamab
2.5/10/30mg: n=19

C1D–7	C1D1	C1D8	C2D1 up to C12D1 (Q3W)
Gpt 2000mg	*Glofitamab 2.5mg*	*Glofitamab 10mg*	*Glofitamab 30mg*

Population characteristics:

- *Age ≥18 years*
- *≥1 prior systemic therapy*
- *ECOG PS ≤1*

Clinical cut-off date: May 18, 2021. *Two patients received Gpt 1000mg, glofitamab 0.6mg (n=1) or 16mg (n=1) plus obinutuzumab 1000mg on D1 of Cycles 2–12. †One patient received extended SUD (0.5/2.5/10/30mg) and one patient received Gpt 1000mg, glofitamab SUD 2.5/10/30mg, plus obinutuzumab 1000mg on D1 of Cycles 2–12
D, day; ECOG PS, Eastern Cooperative Oncology Group performance status; Q3W, every three weeks.

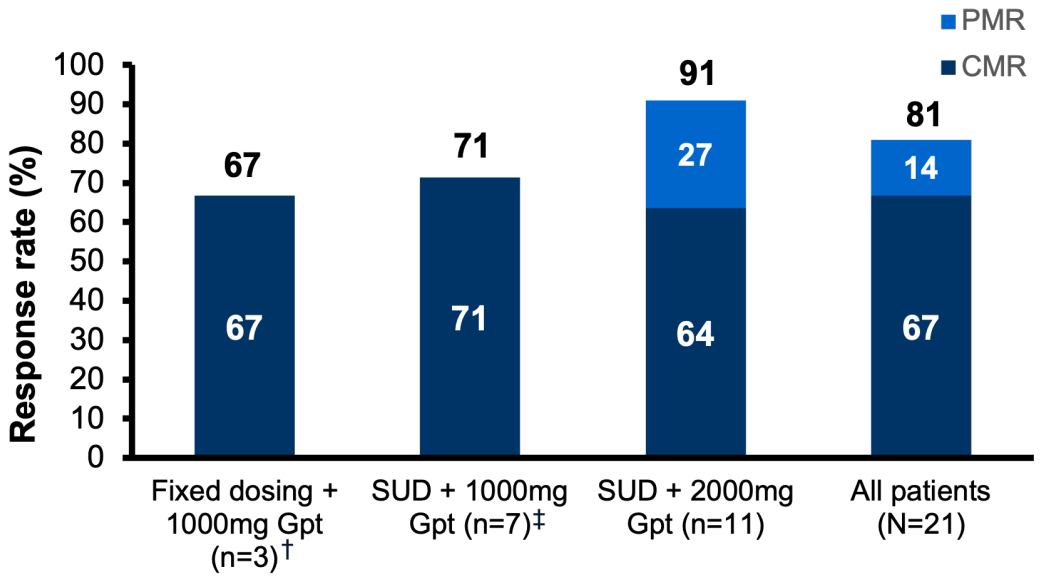
Baseline characteristics

n (%) of patients unless stated		Glofitamab fixed dosing + 1000mg Gpt (n=3)	Glofitamab SUD + 1000mg Gpt (n=7)	Glofitamab SUD + 2000mg Gpt (n=19)	All patients (N=29*)
Median age, years (range)		81.0 (66–84)	69.0 (64–75)	66.0 (41–84)	69.0 (41–84)
Male		2 (66.7)	6 (85.7)	12 (63.2)	20 (69.0)
Ann Arbor stage III–IV at study entry		2 (66.7)	6 (85.7)	16 (84.2)	24 (82.8)
MCL IPI score ≥6 at study entry		3 (100)	3 (42.9)	12 (63.2)	18 (62.1)
Prior therapy	Median time since last therapy, months (range)	1.1 (1.0–8.5)	3.4 (1.2–53.2)	1.6 (0.1–107.5)	1.7 (0.1–107.5)
	Prior lines of therapy, median (range)	3 (2–5)	4 (3–5)	3 (1–6)	3 (1–6)
	BTKi	3 (100)	6 (85.7)	11 (57.9)	20 (69.0)
	Lenalidomide	0	1 (14.3)	3 (15.8)	4 (13.8)
	Chemotherapy	3 (100)	7 (100)	18 (94.7)	28 (96.6)
	Alkylator	0	6 (85.7)	7 (36.8)	13 (44.8)
	Anti-CD20 monoclonal antibody	3 (100)	6 (85.7)	14 (73.7)	23 (79.3)
Refractory status	Refractory to any prior therapy	3 (100)	7 (100)	16 (84.2)	26 (89.7)
	Refractory to prior anti-CD20 therapy	2 (66.7)	3 (42.9)	10 (52.6)	15 (51.7)
	Refractory to first-line therapy	2 (66.7)	2 (28.6)	11 (57.9)	15 (51.7)
	Refractory to last prior therapy	2 (66.7)	5 (71.4)	13 (68.4)	20 (69.0)

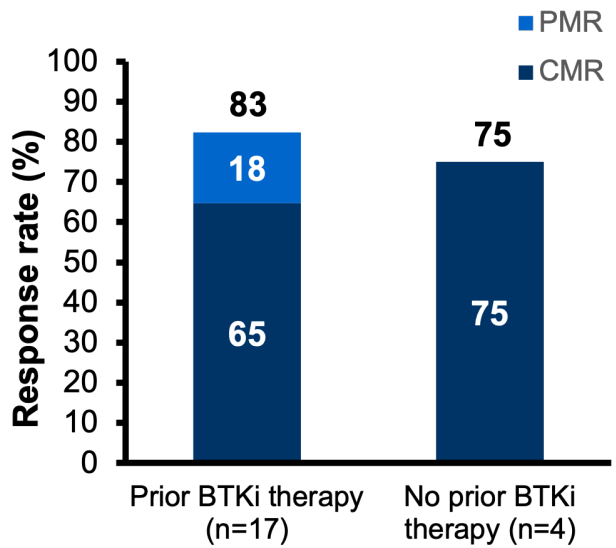
*Three patients were treated with glofitamab in combination with obinutuzumab (G-combo). IPI, International Prognostic Index.

Glofitamab Efficacy in MCL

Response rates[1] by glofitamab regimen*



Response rates[1] by prior BTKi therapy*



Phillips. ASH Annual Meeting 2021

Adverse event overview

n (%) of patients with ≥1 AE unless stated	Glofitamab fixed dosing + 1000mg Gpt (n=3)	Glofitamab SUD + 1000mg Gpt (n=7)	Glofitamab SUD + 2000mg Gpt (n=19)
Any CRS	3 (100)	5 (71.4)	9 (47.4)
Grade 1	3 (100)	2 (28.6)	5 (26.3)
Grade 2	0	2 (28.6)	4 (21.1)
Grade 3	0	0	0
Grade 4[†]	0	1 (14.3)	0
Serious AE of CRS (any grade)	2 (66.7)	5 (71.4)	4 (21.1)
Median time to first CRS event, hrs (range)	5.5 (3.0–32.7)	9.6 (6.6–21.7)	12.1 (7.7–19.8)
Tocilizumab use in patients with CRS	0	4 (57.1)	3 (15.8)

AE, n (%)	All patients (N=29)
Any grade ICANS* AE	1 (3.4)
Grade 1	1 (3.4)
Grade 2	0
Serious	0
Any grade tumor flare	3 (10.3)
Grade 1	2 (6.9)
Grade 2	1 (3.4)
Serious	2 (6.9)
Any grade neutropenia	9 (31.0)
Grade ≥3	5 (17.2)
Serious	0
Febrile neutropenia	2 (6.9)
Serious	1 (3.4)
Any grade infections	12 (41.4)
Grade ≥3	4 (13.8)[†]
Serious	3 (10.3)

Phillips. ASH Annual Meeting 2021

New immunotherapies

- **Bispecific antibodies are clearly active in r/r MCL**
  - **Initial approval possible in BTKi-pretreated pts**
  - **Could move up very quickly**
- **Zilovertamab vedotin appears active**
  - **Initial approval possible in BTKi-pretreated pts**
- **Zilovertamab**
  - **Development is less clear**

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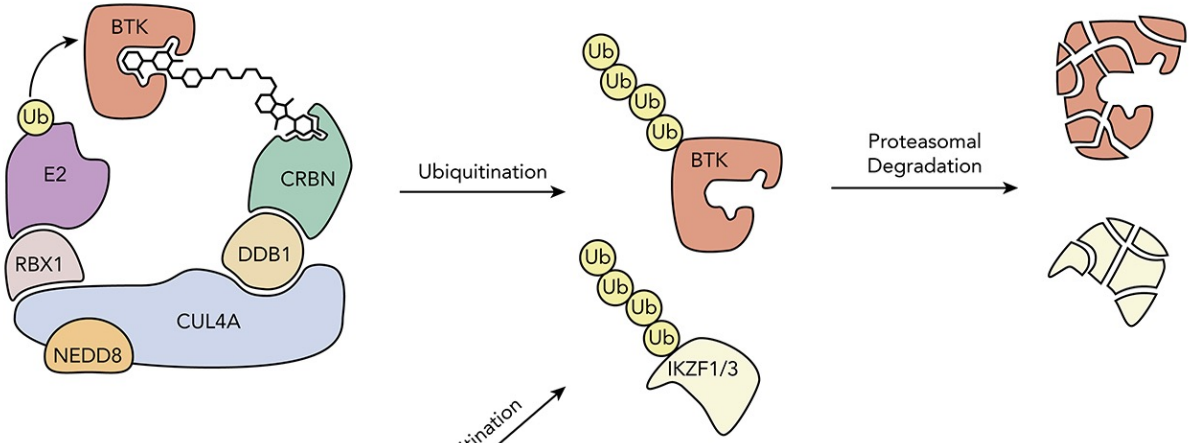
What ”other” drugs could we see in MCL?

BTK Proteolysis Targeting Chimeras



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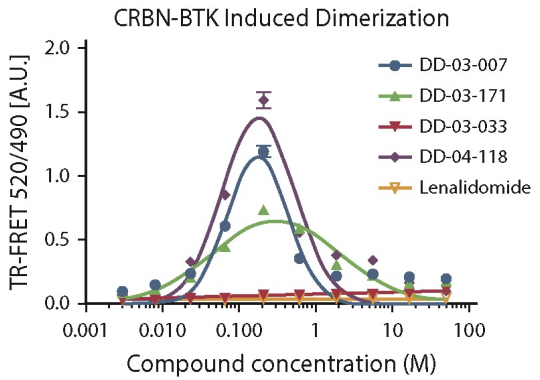

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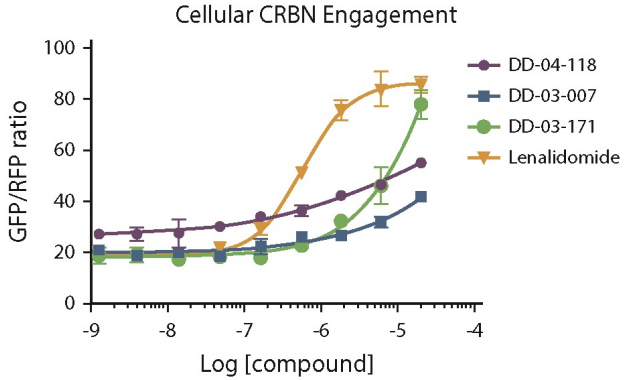
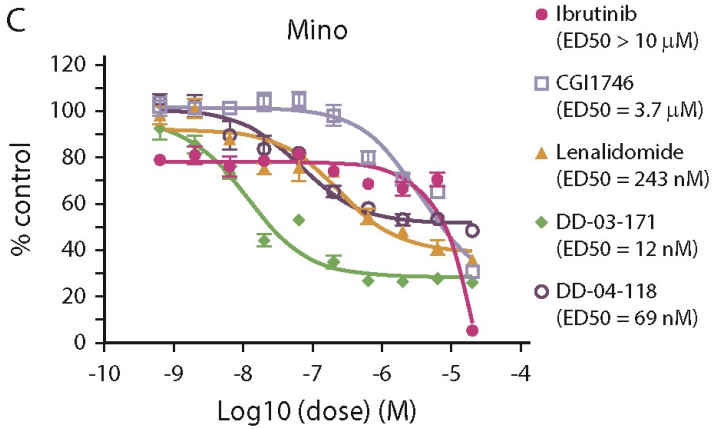
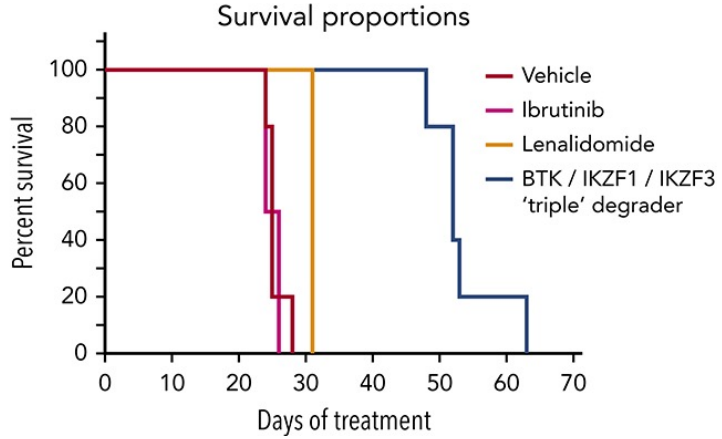
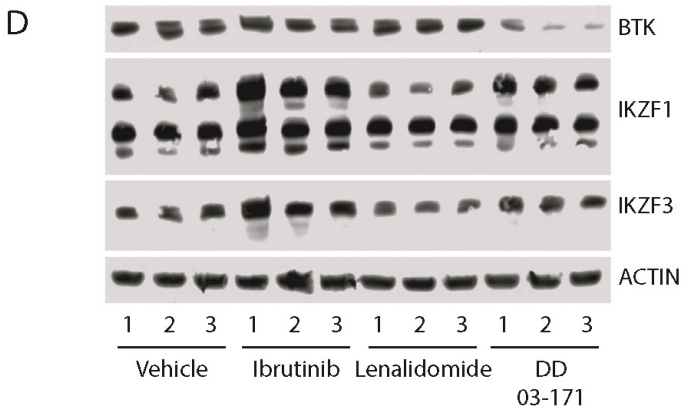


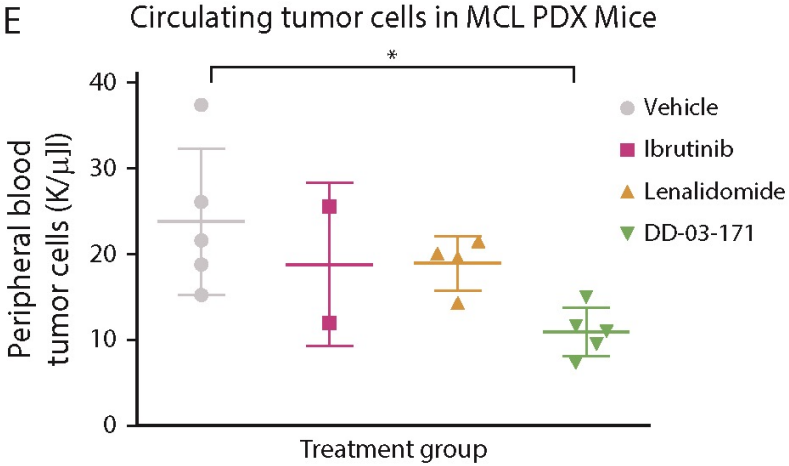
Dobrovolsky. Blood, 2019;133:952

BTK degraders have activity in MCL







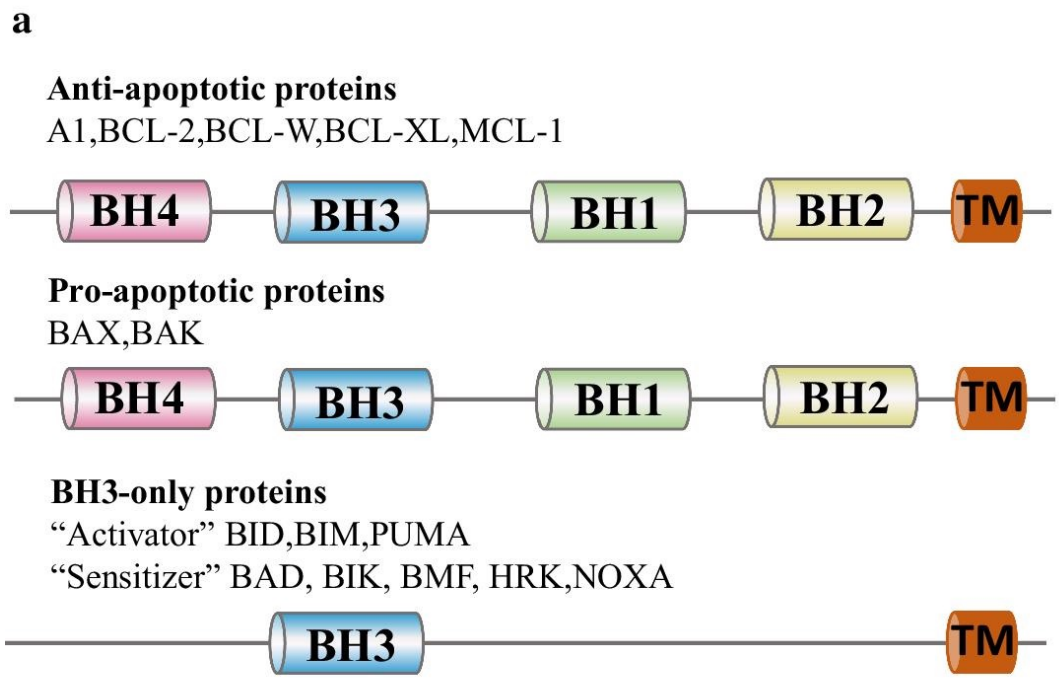


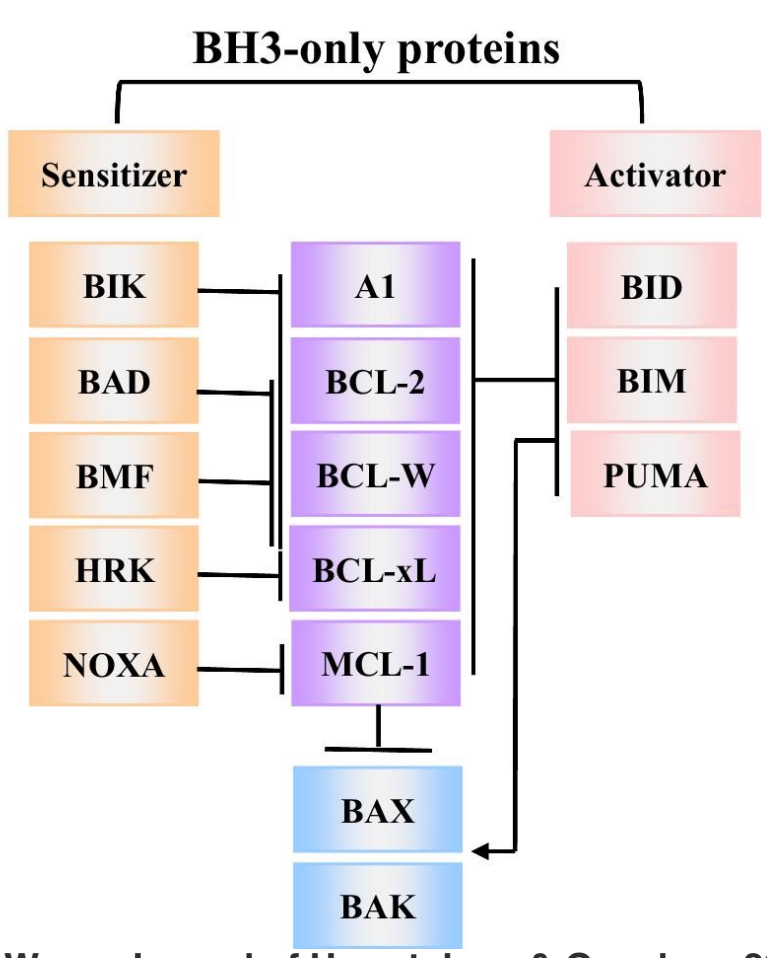
Dobrovolsky. Blood, 2019;133:952

Current BTK PROTACs in Trials

Drug	Phase	Start date	Patients	Identifier
BGB-16673	I	09/2021?	MZL, CLL, FL, MCL, WM	NCT05006716
Nx-2127	I	04/2021	MZL, CLL, FL, MCL, WM, DLBCL	NCT04830137
HSK29116	Ia/Ib	06/2021?	B-cell malignancies	NCT04861779

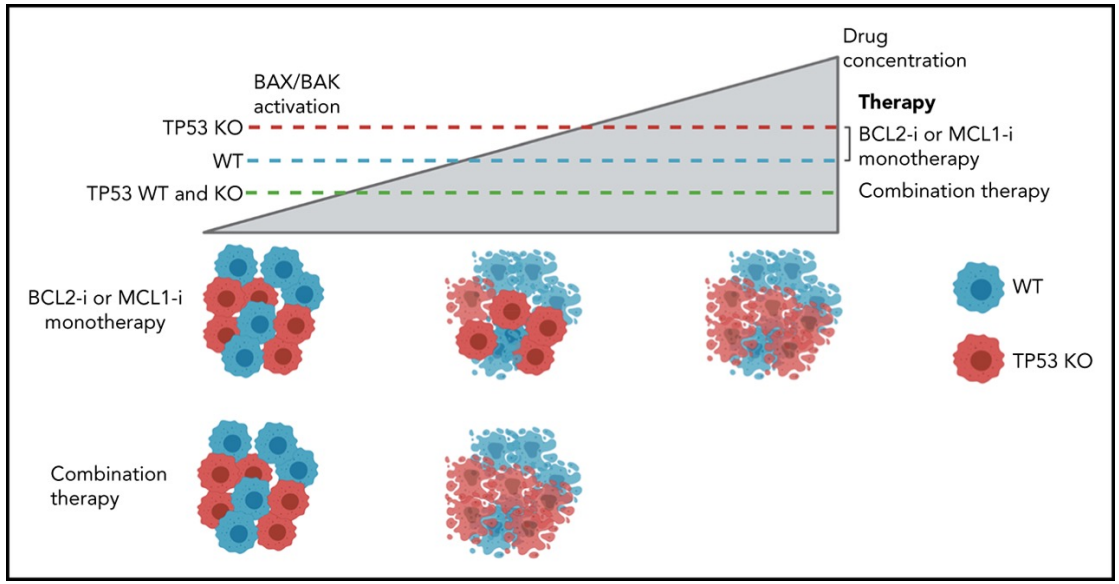
Combination BH3-mimetics

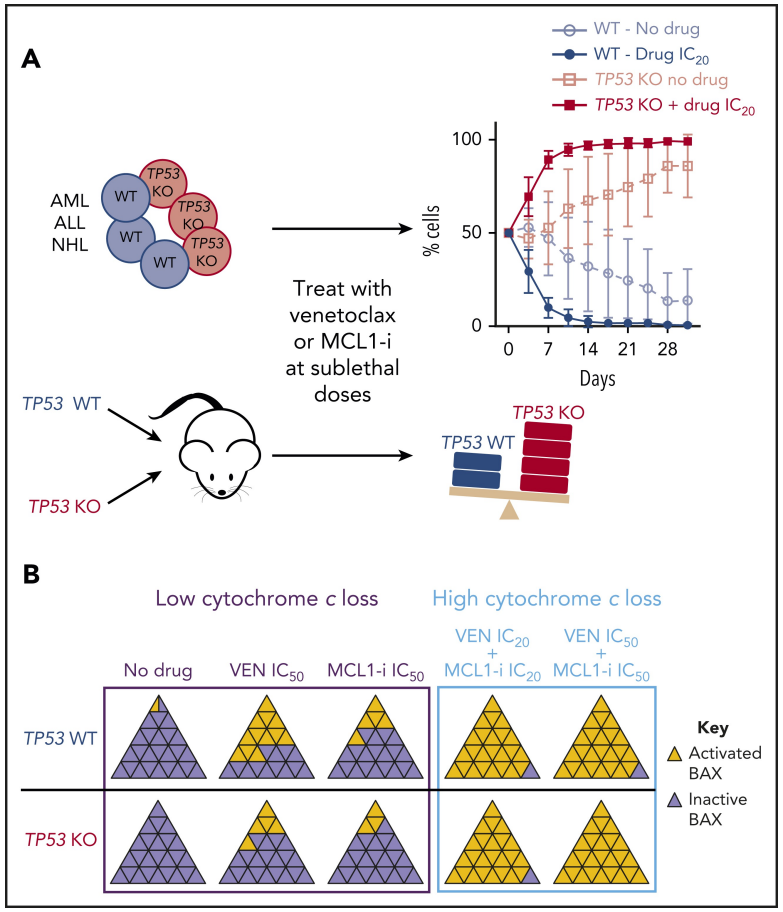




Wang. Journal of Hematology & Oncology 2021;14:67

BCL2i plus MCL1i is active in AML/NHL

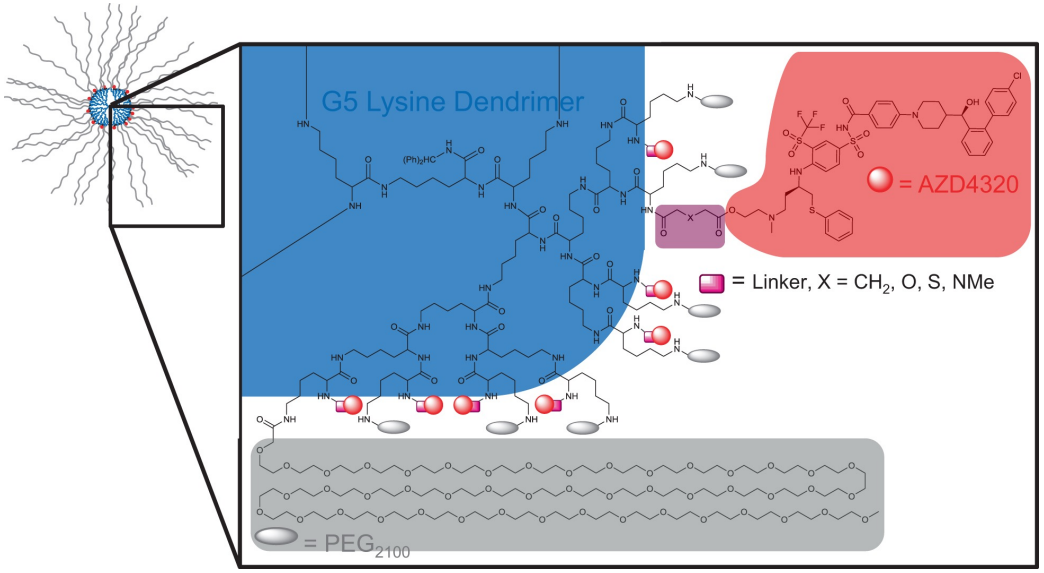


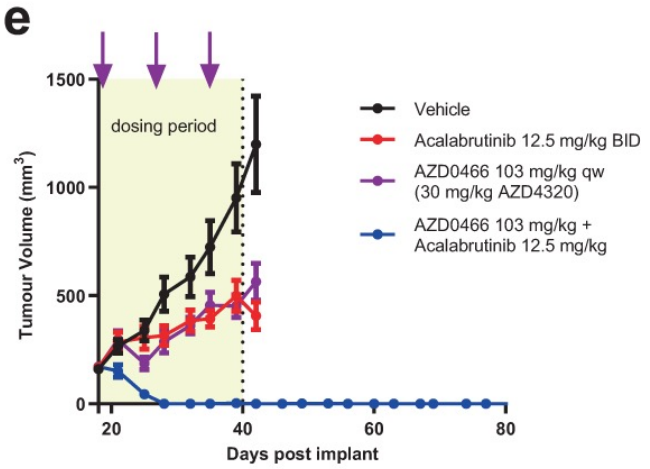


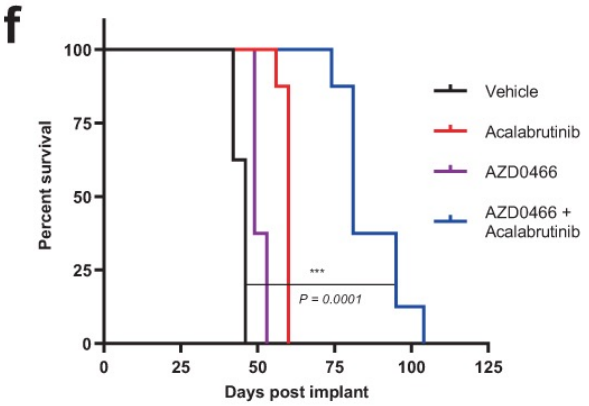
Thijssen. Blood 2021;137:2721

Brown. Blood 2021;137:2711

BCL2i plus BCLxLi is active in NHL

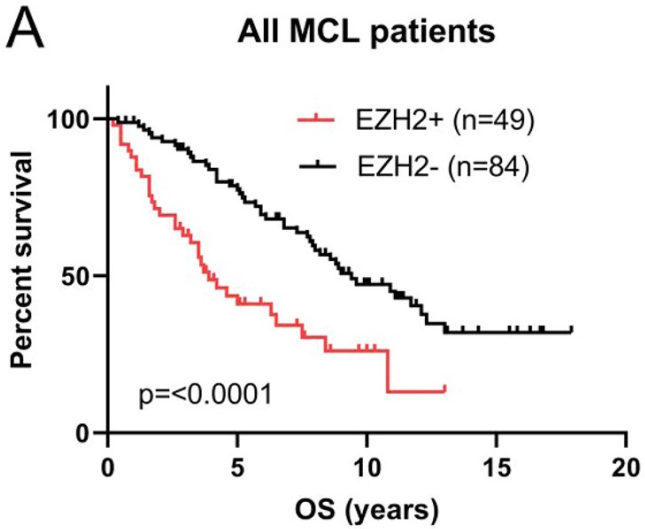


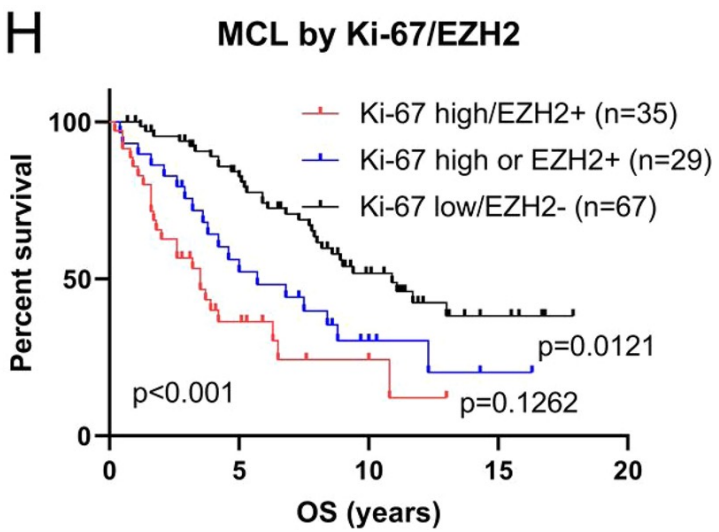




Patterson. Communications Biology 2021;4:112

EZH2 overexpression is associated with poor survival



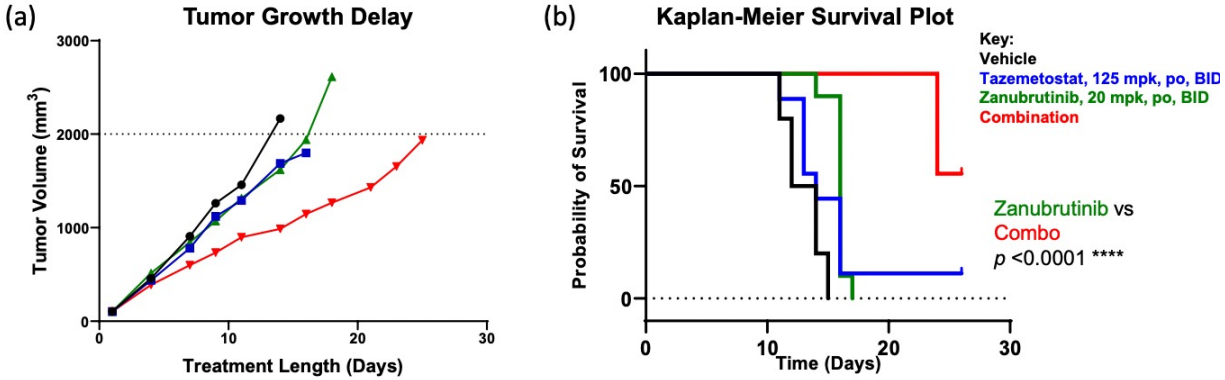


		Univariate			Multivariate	
	HR	**95% CI**	***p* value**	**HR**	**95% CI**	***p* value**
EZH2+	2.037	1.306–3.178	0.002	1.559	0.668–3.636	0.305
Ki-67 high	2.47	1.616–3.773	<0.001	2.315	0.960–4.749	0.063
P53 overexpression	1.947	1.058–3.584	0.032	1.41	0.613–3.244	0.419
Aggressive cytology	1.564	1.027–2.381	0.037	0.619	0.276–1.389	0.245

Martinez-Baquero. Modern Pathol 2021

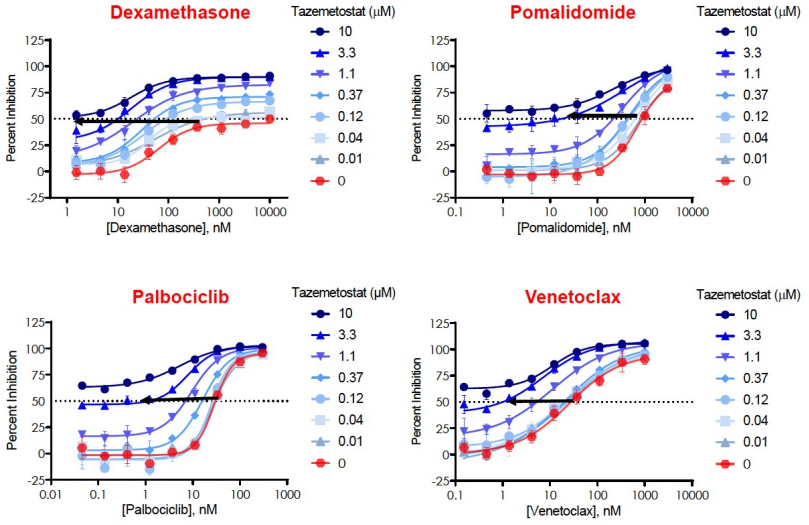
Tazemetostat combinations have preclinical activity in MCL

1. TAZEMETOSTAT ENHANCES ANTITUMOR ACTIVITY OF BTKi ZANUBRUTINIB IN MCL CELL LINE MOUSE XENOGRAFT



Mino Cell Line Mouse Xenograft Summary. EZH2 inhibitor EPZ011989 and BTKi ibrutinib have previously shown to have tumor growth inhibitory effects as single agents in the Mino xenograft model (Hood *et al.*). Here we confirm that **(a)** Tazemetostat and zanubrutinib both demonstrated antitumor activity as single agents in this model as shown by tumor growth delay (TGD). **(b)** Tazemetostat demonstrates significant tumor growth delay when administered in combination with BTKi zanubrutinib in this model. Statistical significance was analyzed for the combination using tumor growth delay rates observed by treatment with the standard of care alone (zanubrutinib) vs the respective combination with tazemetostat using the Log-rank (Mantel-Cox) test method.

(b) **COMBINATORIAL ACTIVITY IN MINO IBRUTINIB-RESISTANT MODEL**

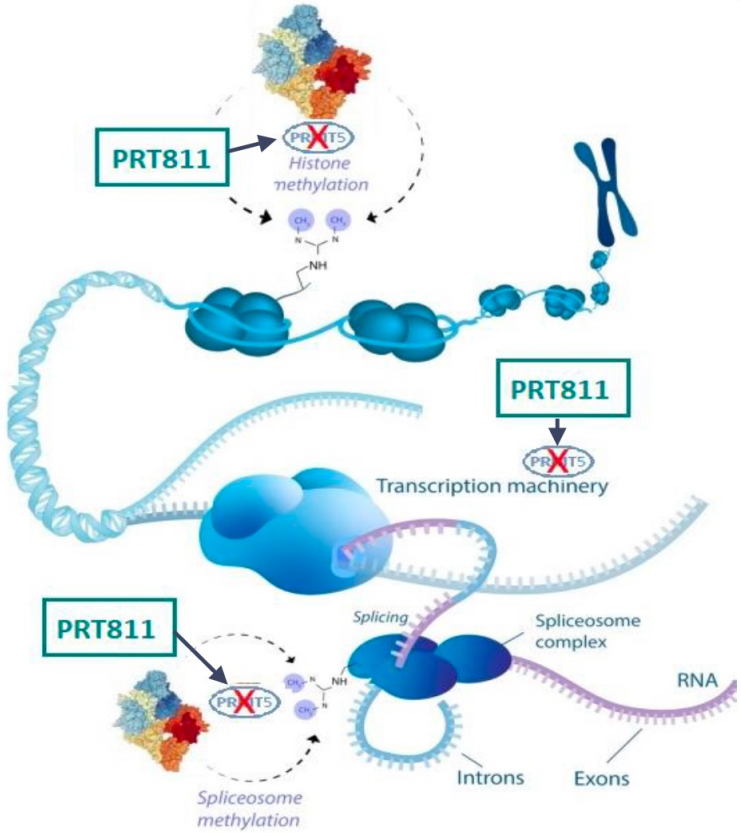


Tazemetostat Shows Combination Benefit in Mino Parental and BTKi Acquired Resistance Cell Lines in the 7-Day Pretreatment Plus 7-Day Cotreatment Model. (a) Table showing combinatorial results when tazemetostat was combined with MCL standards of care, or emerging therapies in the 7-Day Pretreatment plus 7-Day Cotreatment combination assay. **(b)** Dose response plots depicting the IC_{50} shifts (leftward arrows) upon addition of tazemetostat to the second agents in the MINO ibrutinib-resistant cell line

Keats. AACR 2021

Protein Arginine Methyltransferase 5 (PRMT5)

- PRMT5 catalyzes symmetric arginine dimethylation of protein substrates with important roles in the cell cycle, including histone modification, transcription, and spliceosome assembly
- PRMT5 is overexpressed in a variety of cancers
- PRT811 inhibits PRMT5 enzymatic activity
  - In preclinical studies, the biochemical and cellular sDMA IC_{50} were 3.9 nM and 17 nM, respectively
  - Importantly, PRT811 is brain-penetrant



>2-fold Higher Brain Exposure Compared to Plasma in Rodents

Species	Time (hr)	Plasma (μM)	Brain (μM)	Brain/ plasma
Mouse	2	0.196	0.408	2.08
	4	0.105	0.261	2.49
	8	0.018	0.082	4.56
Rat	4	2.02	4.11	2.26

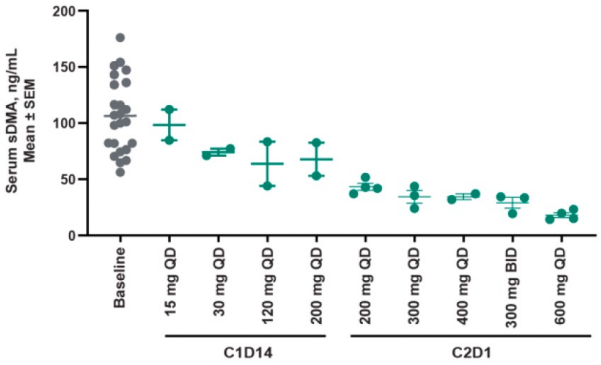
IC_{50}, half maximal inhibitory concentration; PRMT, protein arginine methyltransferase; sDMA, symmetric dimethylarginine.
Adapted from Zhang Y, et al. (2020, June 22-24). AACR Virtual Meeting. Poster 2919; Kim H. and Ronai ZA. *Cell Stress*. 4(8):199-215.

Falchook. AACR 2021

Protein Arginine Methyltransferase 5 (PRMT5)

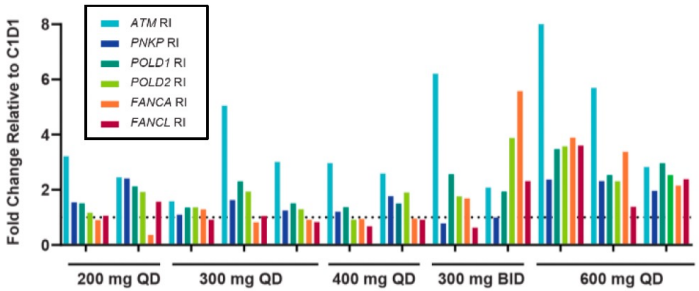
	All Patients (N=45)	
AE, n (%)	Any Grade	Grade ≥3
Patients with events	31 (69)	5 (11)
Nausea	17 (38)	0
Vomiting	12 (27)	1 (2)
Fatigue	9 (20)	1 (2)
Thrombocytopenia[a]	8 (18)	3 (7)
Anemia	7 (16)	1 (2)
Anorexia	6 (13)	1 (2)
Diarrhea	5 (11)	0
Hypophosphatemia	4 (9)	0
Pruritus	3 (7)	0
Weight loss	3 (7)	0

Dose-dependent Inhibition of Serum sDMA



- 83% decrease observed at 600 mg QD by C2D1

Intron Retention in PBMCs[a]



- PRMT5 plays a crucial role in mRNA splicing fidelity
- At higher dose levels, PRT811 treatment induced retention of introns in transcripts regulated by PRMT5

Falchook. AACR 2021

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