The Next Frontier of Targeted Therapy in Lymphoma

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Disclosures

Advisory/Honorarium

Abbvie, ADC Therapeutics, AstraZeneca/Acerta, Beigene, BMS, Genentech, GenMab, Gilead/Kite, Incyte, Janssen, Lilly, Morphosys, Pharmacyclics

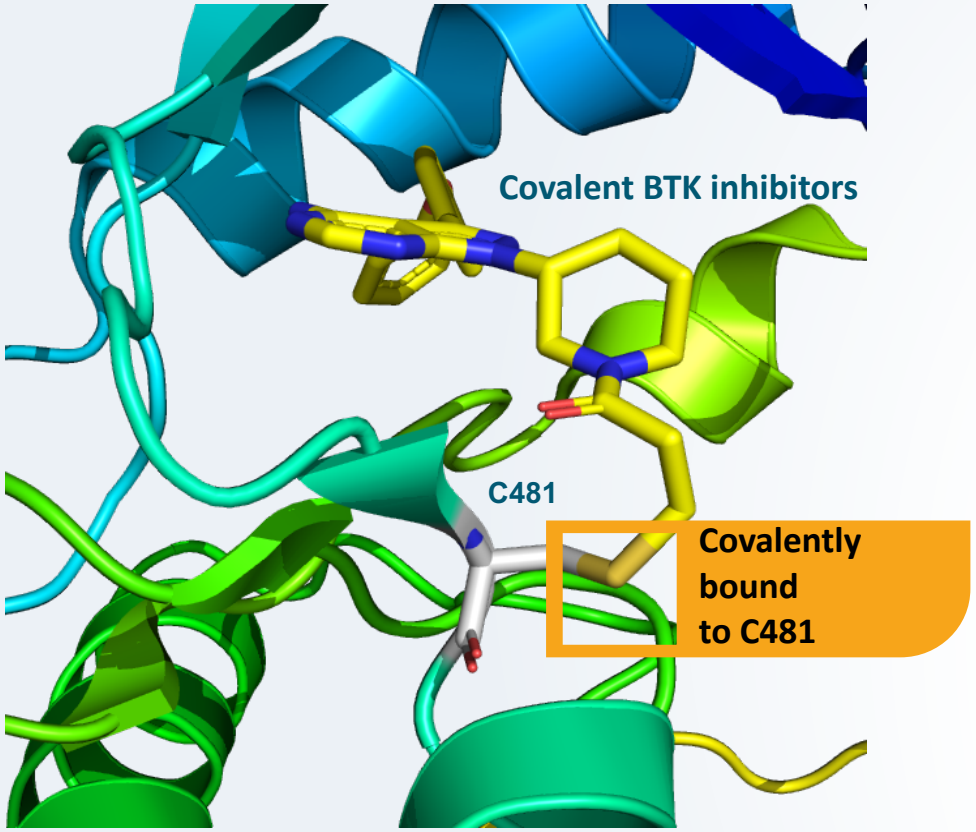
Novel Targets

- Non-Covalent BTKi
- BTK degraders
- BCL2 inhibitors
- MALT1 inhibitors
- EZH2 inhibitors
- Immunomodulator

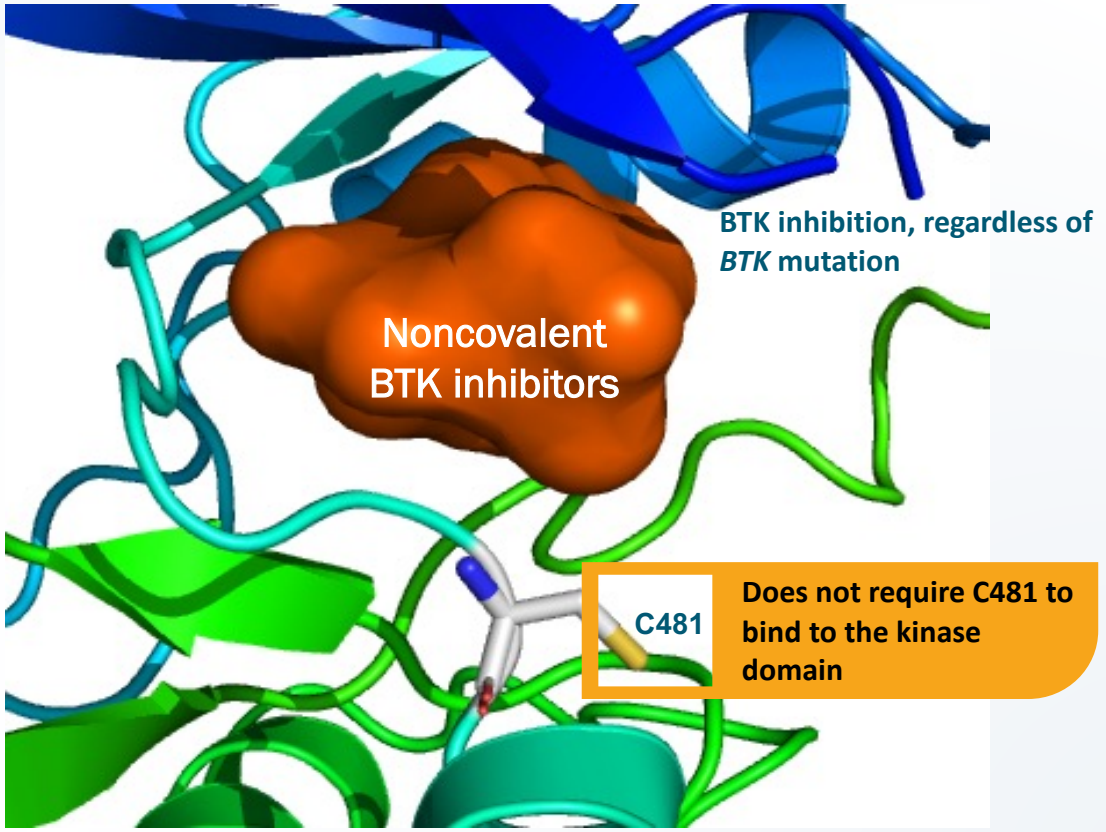
Non-covalent BTKi

Noncovalent BTK Inhibition

Covalent BTK Inhibitors (Ibrutinib, Acalabrutinib, Zanubrutinib) Require C481 WT *BTK* for Activity

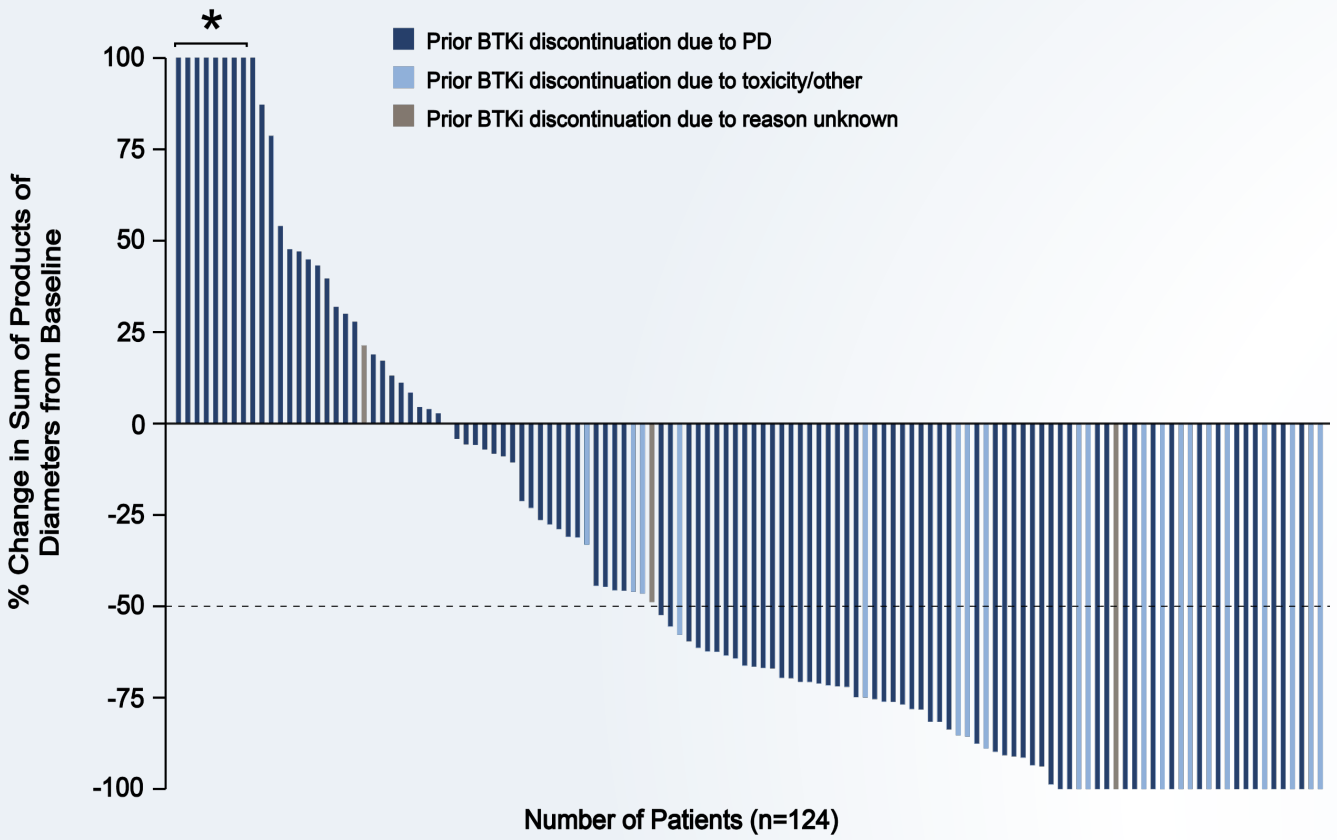


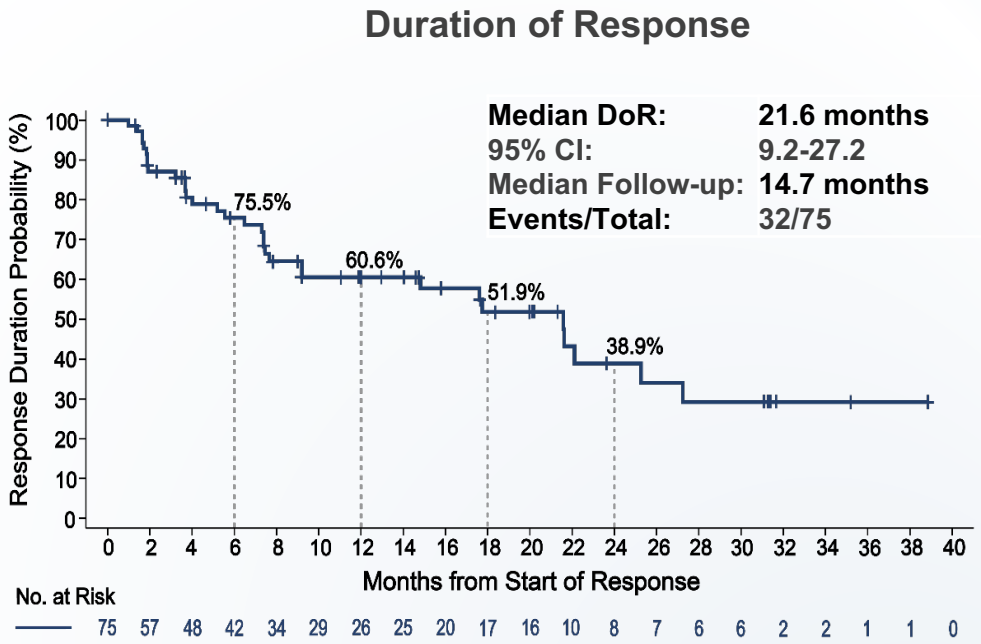
Noncovalent BTK Inhibitors (Pirtobrutinib, Nemtabrutinib) Are Active Against Both WT and C481-Mutated *BTK*



Pirtobrutinib in MCL

Prior cBTKi	n=152
ORR[a], % (95% CI)	49.3 (41.1-57.6)
Best Response[b], n (%)	
CR	24 (15.8)
PR	51 (33.6)



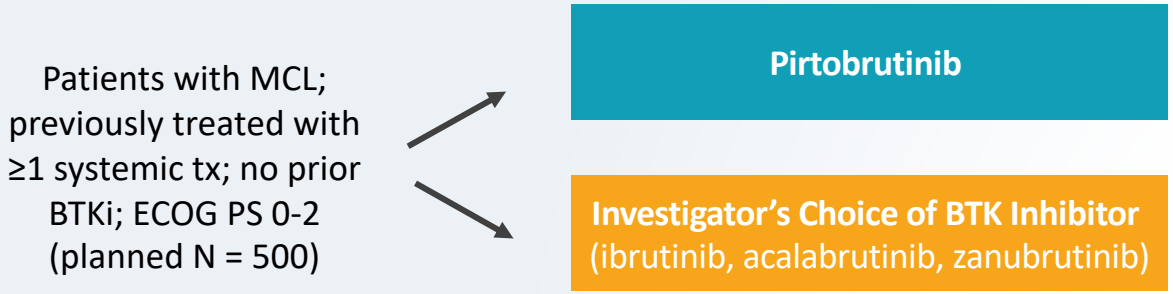


- Median time-to-response was 1.8 months (range, 0.8-13.8)

Cohen J et al ASH 2023

Phase III BRUIN-MCL-321: Pirtobrutinib vs Investigator's Choice of BTK Inhibitor in R/R MCL

International, open-label, randomized phase III trial



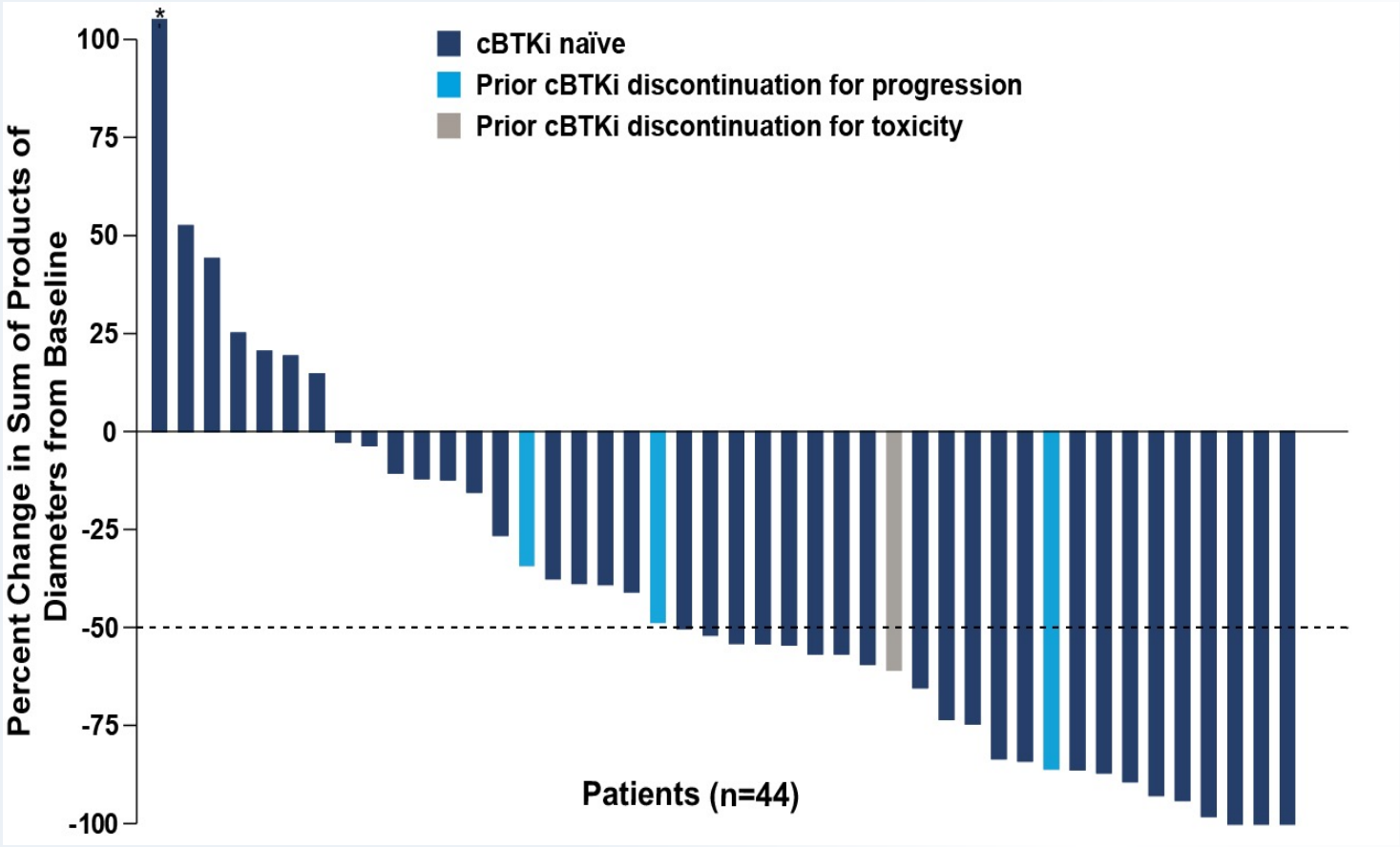
Primary endpoint: PFS

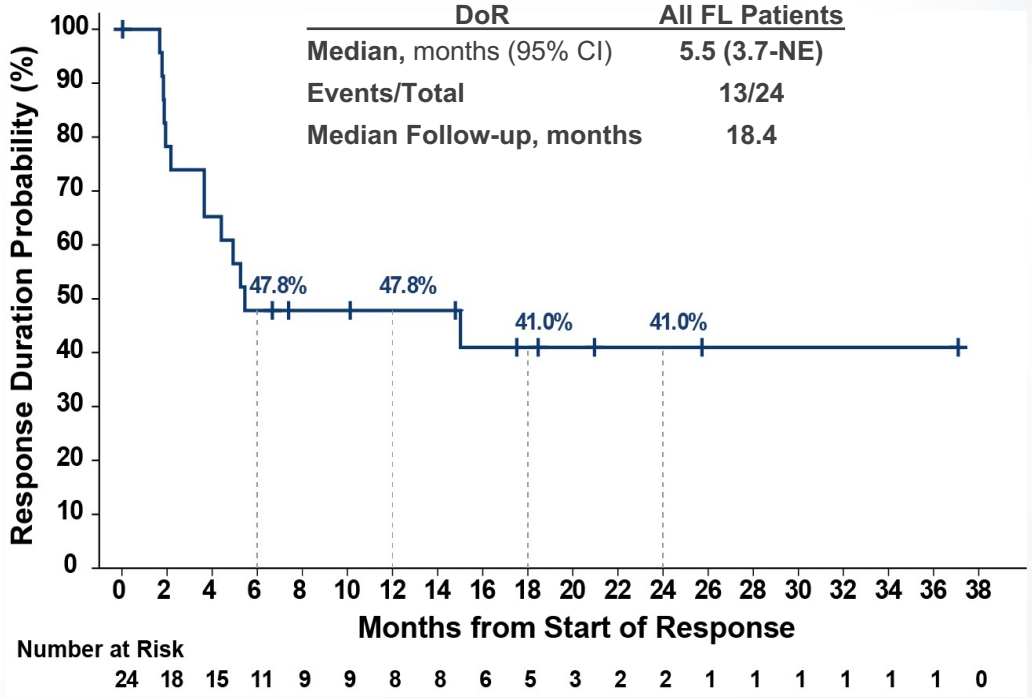
Secondary endpoints: EFS, ORR, DoR, OS, TTF, time to worsening of MCL-related symptoms, tolerability

NCT04662255

Pirtobrutinib in FL

	FL Patients (n=48)
Overall Response[a], % (95% CI)	50.0 (35.2-64.8)
Best Response, n (%)	
CR	7 (14.6)
PR	17 (35.4)



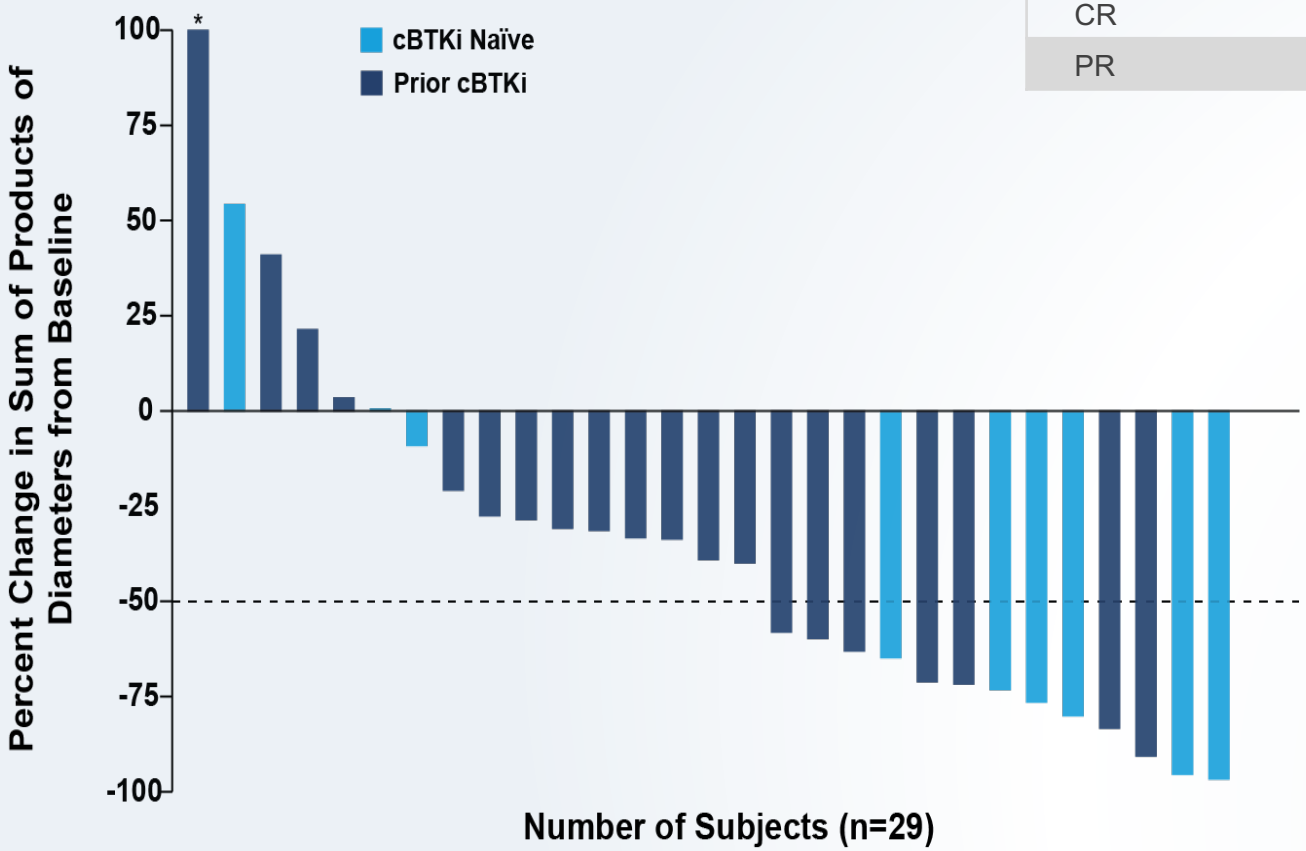


- Median time-to-response was 1.9 months (range, 1.6-7.5)
- Among 4 patients who had received prior cBTKi, 3 achieved partial response and 1 had stable disease

Shah N et al ASH 2023

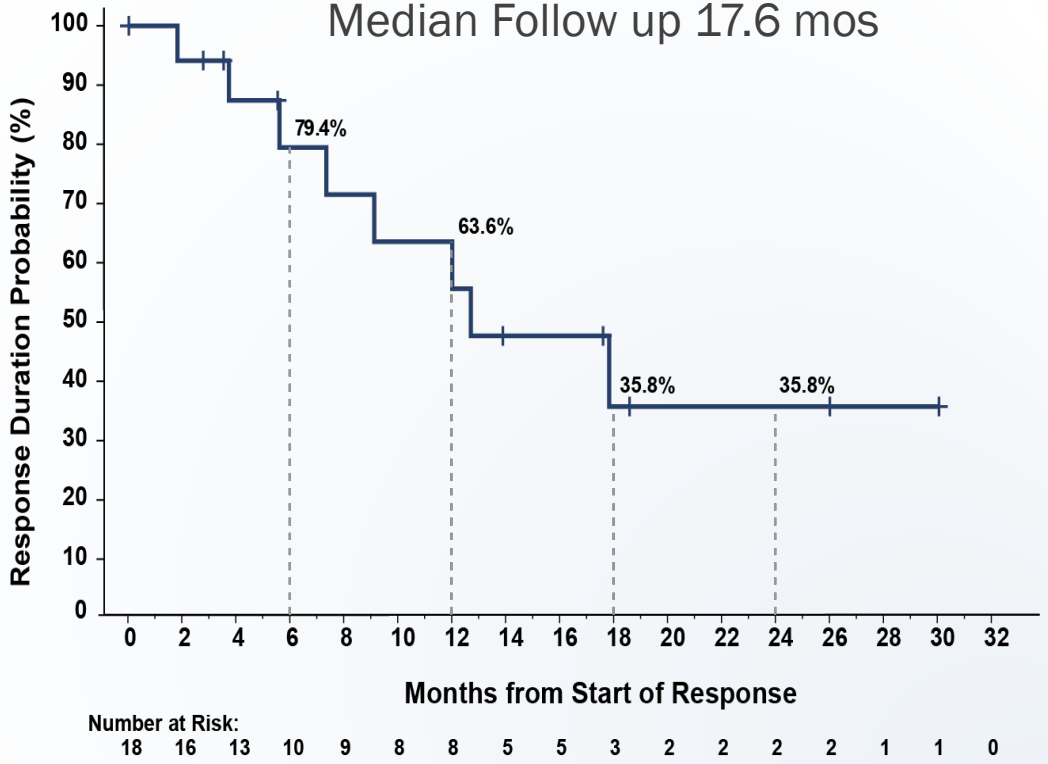
Pirtobrutinib in MZL

	All MZL Patient n=36	Prior cBTKi n= 26	cBTKi Naïve n= 10
Overall Response Rate[a], % (95% CI)	50 (32.9- 67.1)	46.2 (26.6-66.6)	60.0 (26.2-87.8)
Best Response, n (%)			
CR	1 (2.8)	0 (0.0)	1 (10.0)
PR	17 (47.2)	12 (46.2)	5 (50.0)



- Median time-to-response was 1.9 months (range, 1.6-19.3)

Median DOR was 12.7 months
Median Follow up 17.6 mos



Patel K et al ASH 2023

BTK Degraders

Targeting BTK a Different Way

Bruton's Tyrosine Kinase Degraders

- Small molecule, PROTAC (proteolysis-targeting chimera)
- Unique approach to BTKi resistance
- Induce degradation of BTK protein in cells
- Attaches to kinase, shuttles to E3 ubiquitin ligase, complex degraded

Eliminates protein rather than inhibiting protein

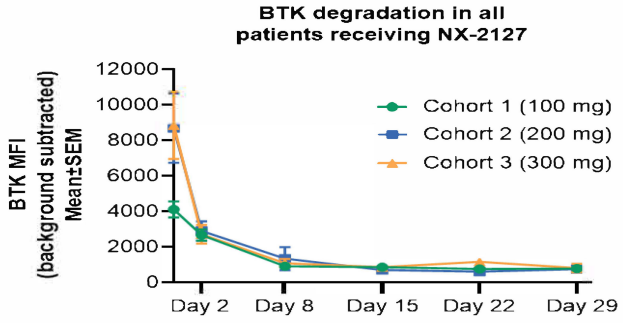
Sun Y et al *Cell Research* (2018) 28: 779–781

NX-2127, a First-in-Class Bruton's Tyrosine Kinase (BTK) Dual-Targeted Protein Degrader with Immunomodulatory Activity: Phase I FIH

Median Line of Therapy 4
3 Dose Levels
Median Follow up 9.5 months

	N = 47
CLL	29
MCL	5
MZL	3
WM	3
FL	2
DLBCL	5

Figure. BTK expression in all patients receiving NX-2127



Dose (mg)	Number of patients per day				
100	27	23	22	21	19
200	9	8	9	7	6
300	7	5	6	4*	3

*1 out of 4 patients had dose modification from Day 19 onwards

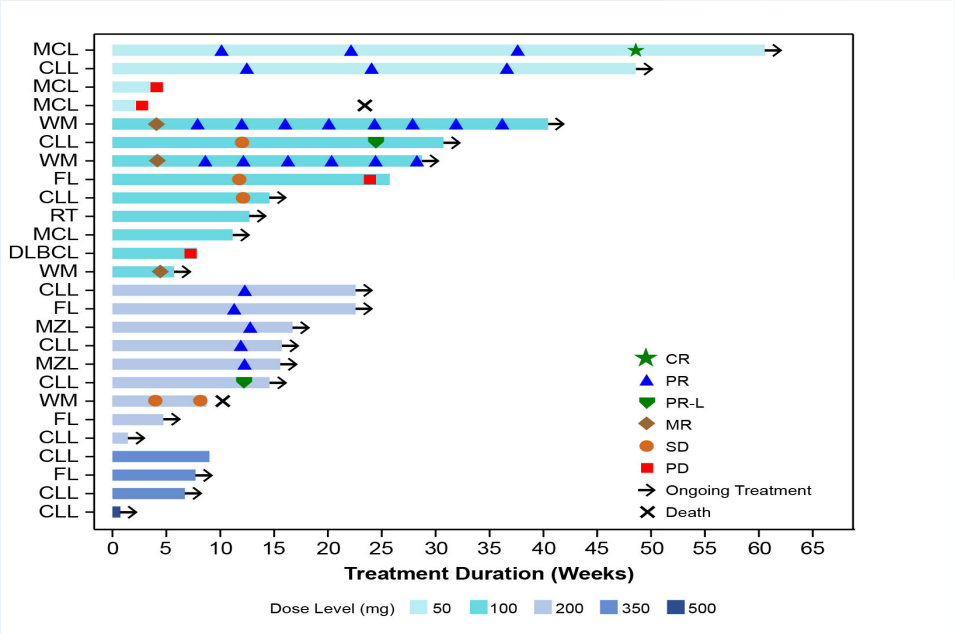
CLL	NHL
9 PR	1 PR
	2 CR

DLT Cognitive disturbance, neutropenia
Any grade fatigue (48.9%), neutropenia (42.6%) and hypertension (36.2%). The most common grade ≥3 TEAEs were neutropenia (38.3%), hypertension (14.9%) and anemia (12.8%). Atrial fibrillation 12.8%

Danilov A et al ASH 2023

Bruton's Tyrosine Kinase (BTK) Degrader Bgb-16673: Phase I FIH

Median Line of Therapy 3.5
5 Dose Levels
Median Follow up 3.5 months



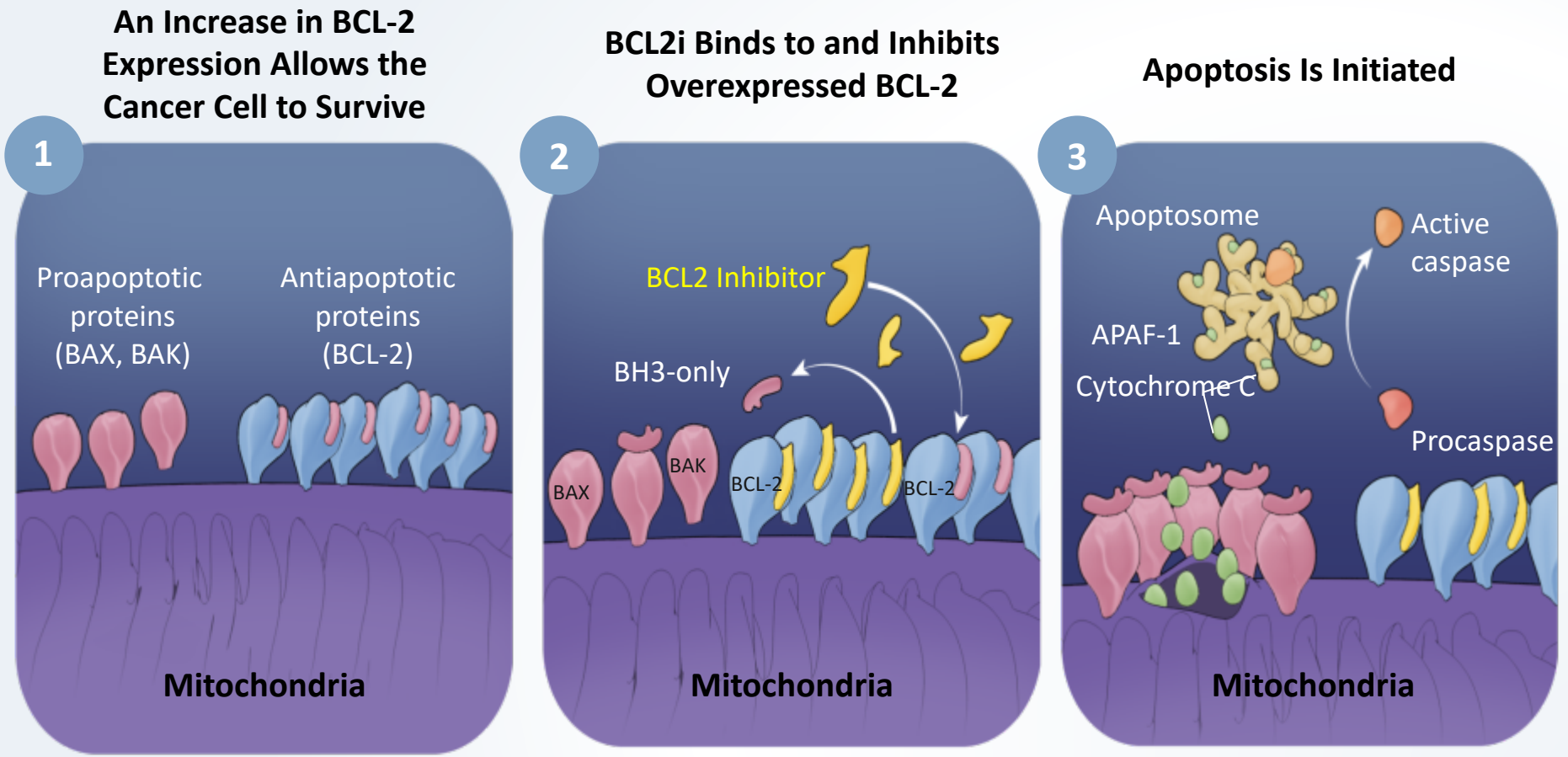
	N	Prior cBTKi	Prior BCL2i	Prior ncBTKi	ORR in evaluable pts 12/16 (67%)
CLL	10	10	9	2	5/6
MCL	4	4			1/3
MZL	2	1			2/2
WM	4	4	2	1	3/4
FL	4			1	1/2
DLBCL	1	1			0/1
RT	1	1	1		

Contusion (30.8%; no gr ≥3), pyrexia (23.1%; no gr ≥3), neutropenia/neutrophil count decreased (23.1%; gr ≥3, 15.4%), and lipase increased (23.1%; gr ≥3, 3.8%; all transient and asymptomatic)
No HTN or A Fib.

Seymour J et al ASH 2023

BCL2 Inhibitors

BCL-2 Inhibition



Kumar. ASCO 2015. Abstr 8576.

A Phase I Study of Bcl-2 inhibitor BGB-11417 in adult patients with mature B-cell malignancies

Median Line of Therapy 2 (1-7)
4 Dose Levels
Weekly or Daily Ramp up
Median Follow up 6.6 months

	N = 54
CLL	20
MZL	4
FL	7
Transformed	3
DLBCL	20

CLL 12 Evaluable 9 Response	NHL 27 Evaluable 5 Response
7 PR	4 PR
2 CR	1 CR

WM 4	MCL Combination BTKi 11
1 minor response	6 ORR

3 DLTs: Grade 3 FN, Grade 3 thrombocytopenia, Grade 3 bone pain.
Most common TEAE: all grades, white blood cell count decreased (48.1%); grade ≥3, neutropenia (25.9%).
14.8% had serious TEAEs and 14.8% had TEAEs leading to drug interruption.
No pts had TEAEs leading to death/tx discontinuation or clinical tumor-lysis syndrome events

Li C et al ASH 2022, ASCO 2023; Soumeri J et al ASH 2022

MALT1 Inhibitors

MALT1

MALT1 Inhibitor

Mucosa-associated lymphoid tissue lymphoma translocation protein 1

Component of MALT1-BCL10-CARD11 complex downstream BTK on BCR

Key mediator of NF-κB signaling

A Phase I Study of MALT1 inhibitor JNJ-67856633: FIH Phase I

Escalating Doses 50-600 mg
Loading dosing explored (BID, then QD)

Table. Summary of TEAEs

Safety	n (%)	
	Any grade	Grade 3-4
TEAEs	106 (97.2)	84 (77.1)
TEAEs in ≥20% of patients		
Hyperbilirubinemia	48 (44.0)	16 (14.7)
Anemia	39 (35.8)	18 (16.5)
Neutropenia	35 (32.1)	29 (26.6)
Diarrhea	26 (23.9)	3 (2.8)
Rash[a]	24 (22)	8 (7.3)
Thrombocytopenia	25 (22.9)	11 (10.1)
Blood creatinine increased	22 (20.2)	0 (0.0)

[a]Includes preferred terms "rash", "rash maculo-papular", "rash macular", "rash erythematous", and "rash papular".

TEAE, treatment-emergent adverse event.

	N = 109
Patients Evaluable at RP2D	36
ORR	10, 27.8%
CR	4, 11.1%
PR	6, 16.7%
Responses seen in indolent and aggressive disease	

Dose limiting toxicities were reported in 5 pts: 400 mg, G3 hyponatremia; 600 mg, G2 bradycardia; 300 mg, G3 febrile neutropenia; 400 mg LD, G3 renal failure; 300 mg LD, G3 acute renal failure
RP2D was 300 mg QD and LD 300 mg

Hertzberg M et al Lugano 2023

A Phase 1, Open-Label, Multicenter, Dose-Escalation Study of Sgr-1505 As Monotherapy in Subjects with Mature B-Cell Malignancies

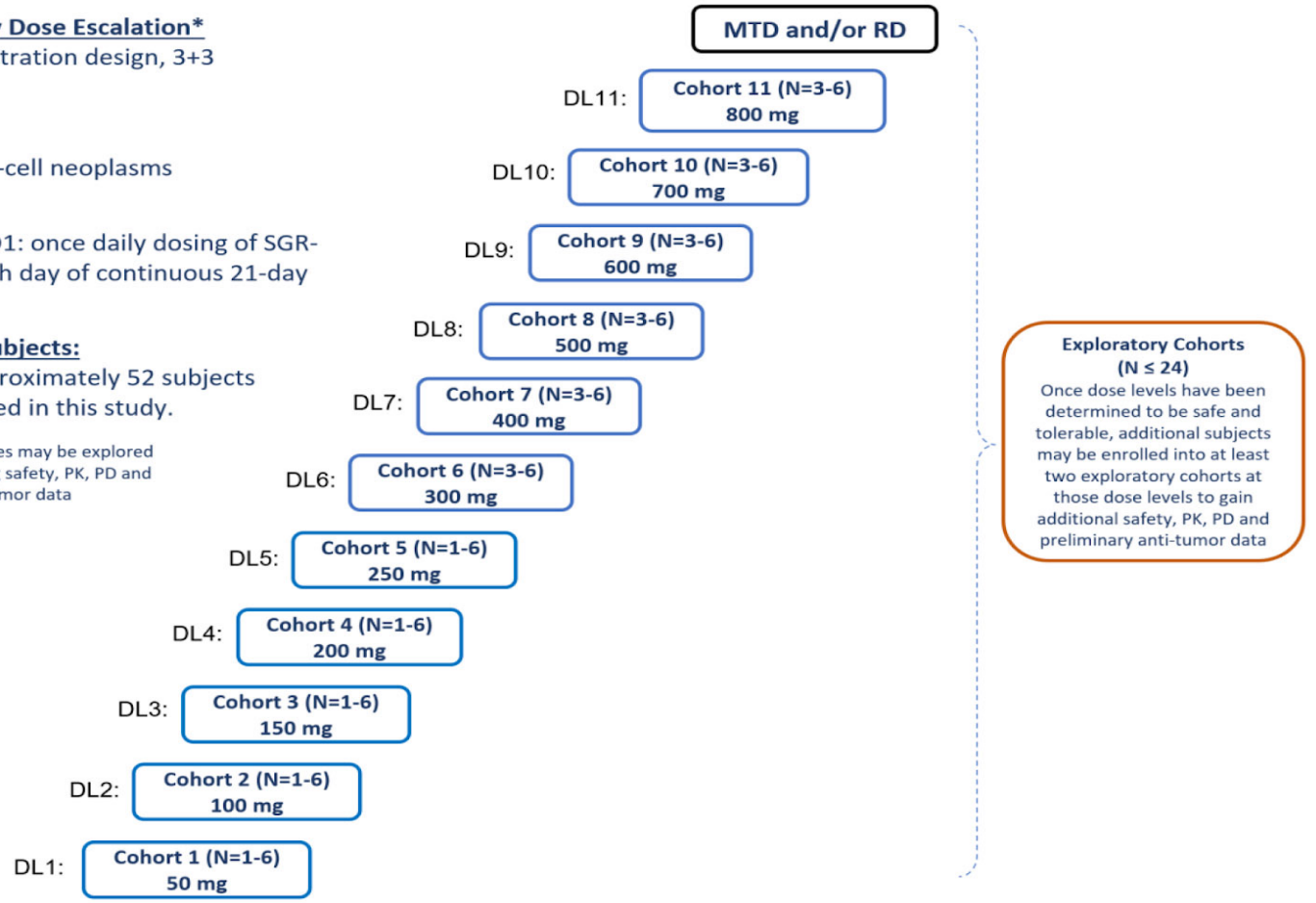
Monotherapy Dose Escalation*
Accelerated titration design, 3+3 (N=~28)

Population:
R/R mature B-cell neoplasms

Schedule:
- Start C1 D1: once daily dosing of SGR-1505, each day of continuous 21-day cycles

Number of Subjects:
A total of approximately 52 subjects will be included in this study.

*Intermediate doses may be explored based on emerging safety, PK, PD and preliminary anti-tumor data

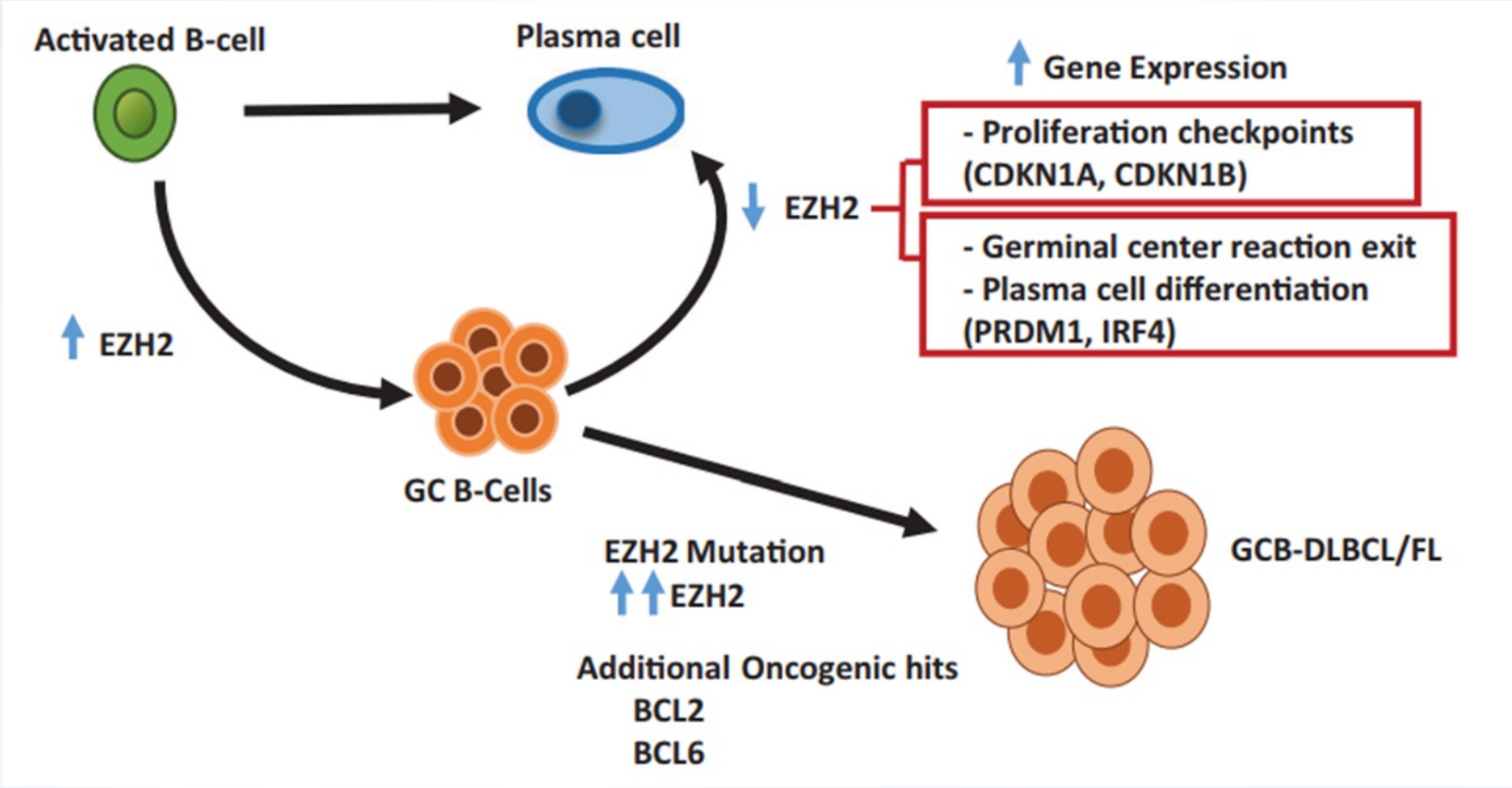


Olszewski A et al ASH 2023

EZH2 Inhibitors

Tazemetostat – Oral EZH2 Inhibitor

Recurrent gain-of-function mutations have been reported in ~25% of patients with FL.



Italiano A et al, Lancet Oncology 2018. Gulati et al, Leukemia & Lymphoma 2018

Tazemetostat – Oral EZH2 Inhibitor

Phase II trial, single arm
99 patients with FL grade 1-3b

Most common toxicities GI, infection, cytopenias

45 Patients with mutant *EZH2*

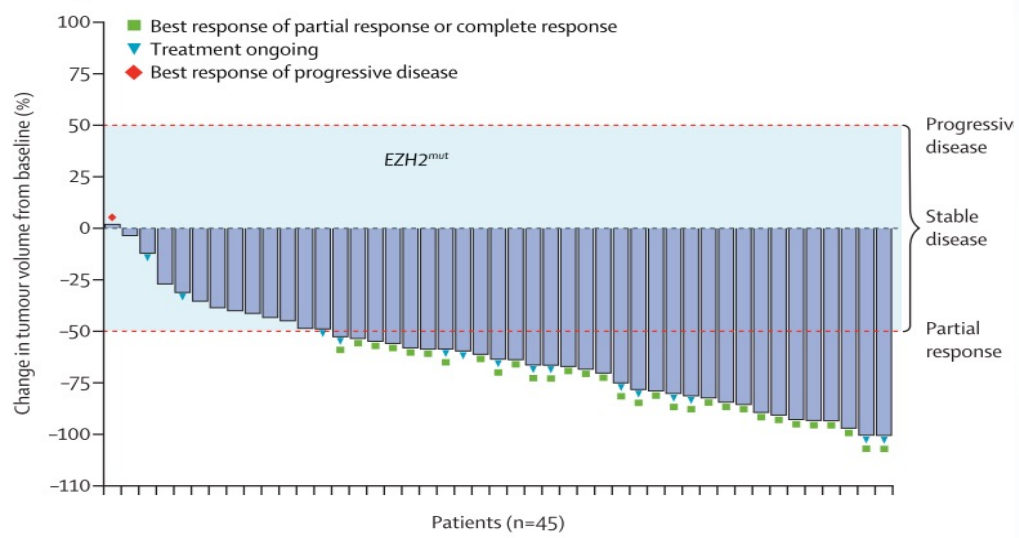
Median of 2 prior therapies; 47% ≥3

Refractory to rituximab-containing tx 99%

ORR = 69%, CR = 13%

Median DOR = 10.9 months

Median PFS = 13.8 months



54 Patients with wild-type *EZH2*

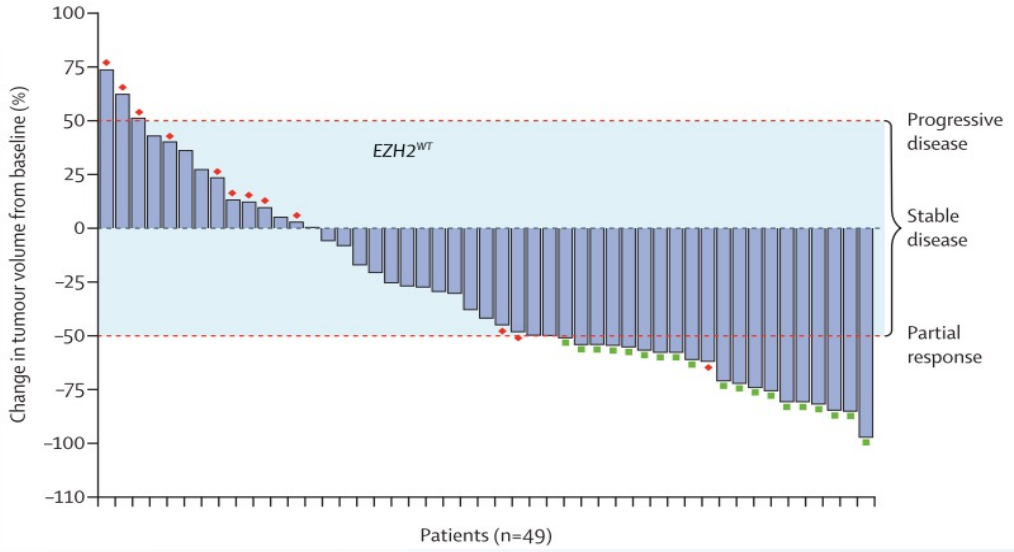
Median of 3 prior therapies; 68% ≥3

Refractory to rituximab-containing tx 59%

ORR = 35%, CR = 4%

Median DOR = 13 months

Median PFS = 11 months



Morschhauser F et al, Lancet Oncology 2020

Tazemetostat Development

Relapsed Refractory Combinations

Rixuximab

Venetoclax

Rituximab-lenalidomide

Frontline Combinations

Mosunetuzumab

Bendamustine-Rituximab

Slide credit: clinicaloptions.com

Immunomodulator

CELMoD

CC-92292

Novel, oral CELMod

Interacts with CRBN, a $CRL4^{CRBN}$ E3 ubiquitin ligase substrate receptor, to induce recruitment and ubiquitin-mediated proteasomal degradation of the transcription factors Ikaros and Aiolos

Faster, deeper, and more sustained degradation of transcription factors Ikaros and Aiolos

Efficacy and Safety of Golcadomide, a Novel Cereblon E3 Ligase Modulator (CELMoD) Agent, Combined with Rituximab

Phase I/II

Dose escalation and expansion

0.2 and 0.4 mg

Single agent and Combination with Rituximab

R/R DLBCL and R/R FL

Chavez J et al ASH 2023

Efficacy and Safety of Golcadomide, a Novel Cereblon E3 Ligase Modulator (CELMoD) Agent, Combined with Rituximab

R/R DLBCL: N = 3, 16 evaluable

Median age 60 (35-80)

Median Prior Therapy 4.5 (1-11)

Prior CAR-T 68% (23/34)

Safety:
Neutropenia most common any-grade TEAE, 15 (44%) patients, all grade 3/4.
No febrile neutropenia occurred
Occurred at both dose levels, 26% 0.2 mg and 60% 0.4 mg
GCSF used in 14 (41%) patients.

Response	0.2 mg N = 9	0.4 mg N = 7
Overall Response Rate (n, %)	4 (44)	4 (57)
Complete Response	1 (11)	1 (14)
Partial Response	3 (33)	3 (43)
Stable Disease	1 (11)	0
Progressive Disease	4 (44)	3 (43)
Median Duration of Response, weeks (range)	20.4 (7.4-45.9)	16.6 (8.1-30.3)

Chavez J et al ASH 2023

Golcadomide (GOLCA; CC-99282), a Novel CELMoD Agent, Plus R-CHOP in Patients with Previously Untreated Aggressive B-Cell Lymphoma: Safety and Efficacy Results from Phase 1b Dose Expansion

- R-CHOP + GOLCA in 21 Day cycles
- GOLCA DL: 0.2 mg D1–7 (DL-1), 0.4 mg D1–7 (DL1), and 0.4 mg D1–10 (DL2) DL2 met the dose-limiting toxicity threshold and was not
- Dose expansion, pts were randomized 1:1 to R-CHOP plus GOLCA at DL-1 or DL1
- Primary Endpoint Safety
- Secondary Endpoints ORR and CMR

Hoffmann M et al ASH 2023

Golcadomide (GOLCA; CC-99282), a Novel CELMoD Agent, Plus R-CHOP in Patients with Previously Untreated Aggressive B-Cell Lymphoma: Safety and Efficacy Results from Phase 1b Dose Expansion

- 78 patients
- DL-1=35; DL1=37; DL2=6
- Median Age 63
- High-intermediate/High IPI 64.1%
- Stage III-IV 83.3%
- 3 discontinued due to AE (one each DL)
- Relative Dose Intensity R-CHOP > 90%

Hoffmann M et al ASH 2023

Golcadomide (GOLCA; CC-99282), a Novel CELMoD Agent, Plus R-CHOP in Patients with Previously Untreated Aggressive B-Cell Lymphoma: Safety and Efficacy Results from Phase 1b Dose Expansion

ORR at EOT

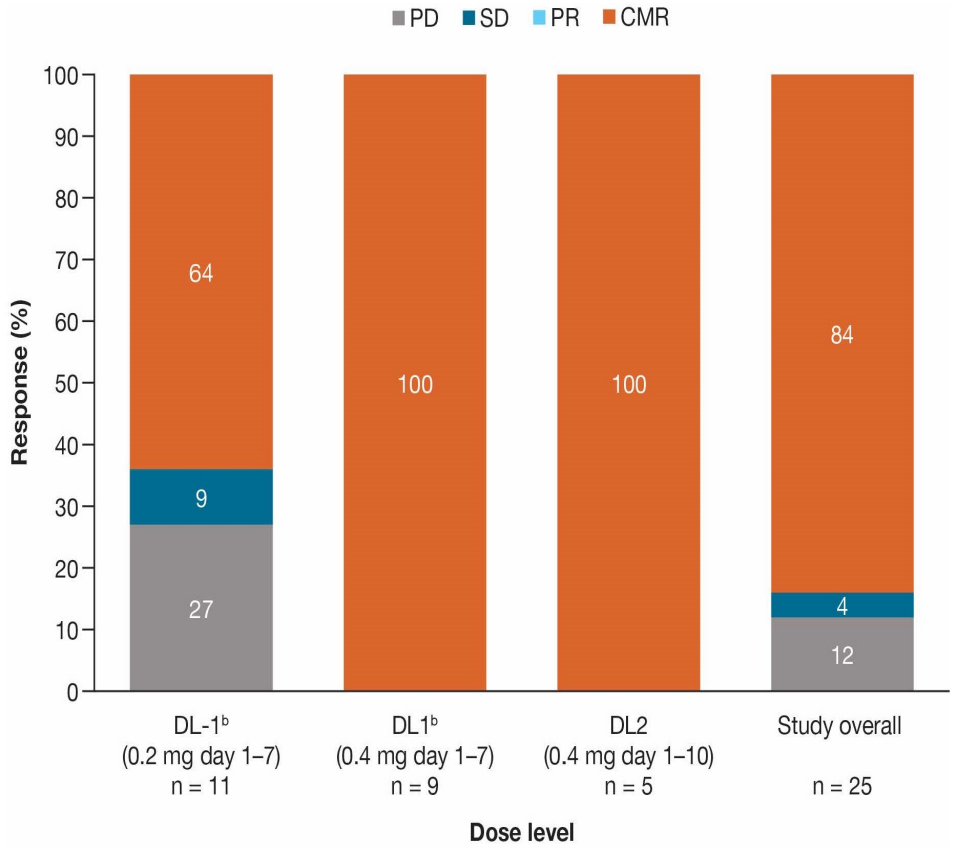


Table. Grade 3/4 TEAEs of interest[a]

System organ class Preferred term, n (%)	DL-1[b] (0.2 mg D1–7) n = 35	DL1[b] (0.4 mg D1–7) n = 37	Overall[c] (all doses) N = 78
Patients with ≥ 1 grade 3/4 TEAE	**31 (88.6)**	**29 (78.4)**	**65 (83.3)**
Blood and lymphatic system disorders	**30 (85.7)**	**28 (75.7)**	**63 (80.8)**
Neutropenia	28 (80.0)	27 (73.0)	60 (76.9)
Thrombocytopenia	4 (11.4)	17 (45.9)	25 (32.1)
Anemia	5 (14.3)	12 (32.4)	20 (25.6)
Febrile neutropenia	4 (11.4)	6 (16.2)	11 (14.1)
Lymphopenia	4 (11.4)	4 (10.8)	10 (12.8)
Infections and infestations[d]	**7 (20.0)**	**4 (10.8)**	**12 (15.4)**

Hoffmann M et al ASH 2023

Conclusions

Novel small molecule inhibitors have advanced treatment landscape for many lymphomas

BTKi, BCL2, PI3k

Newer agents in development with same targets, alternative targets

Combination therapies continue to be of high interest