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City of Hope Comprehensive Cancer Center

Targeted Therapies in NHL…..BTKi and Beyond

Outline

- BTKi
  - Covalent
  - Non-Covalent
- BCL-2
  - Venetoclax
- PI3Ki
  - What's left
- CelMods
- BTK degraders

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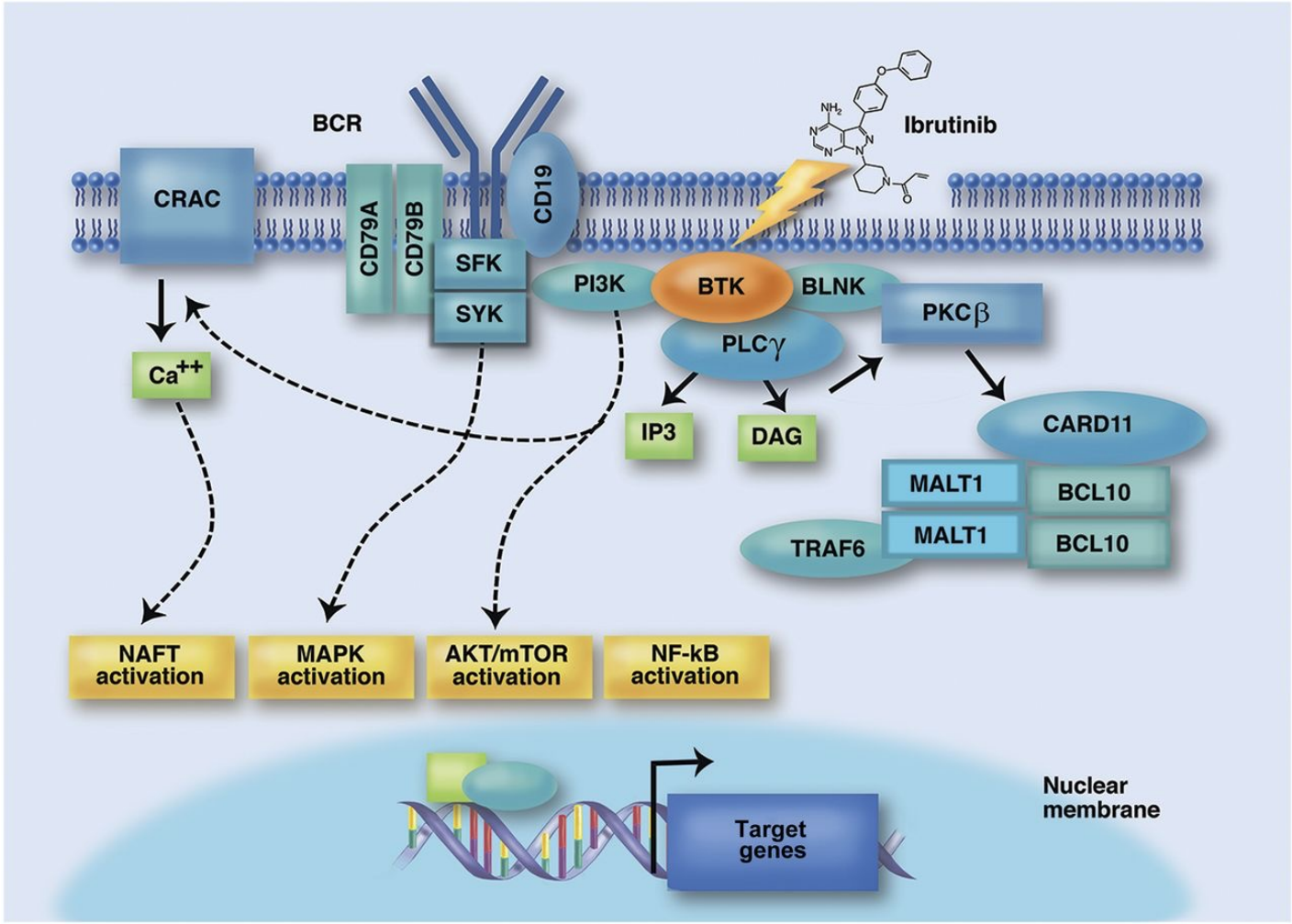
B-Cell Signaling



Davide Rossi, and Gianluca Gaidano Blood 2014;123:1772-1774

Kinome Map

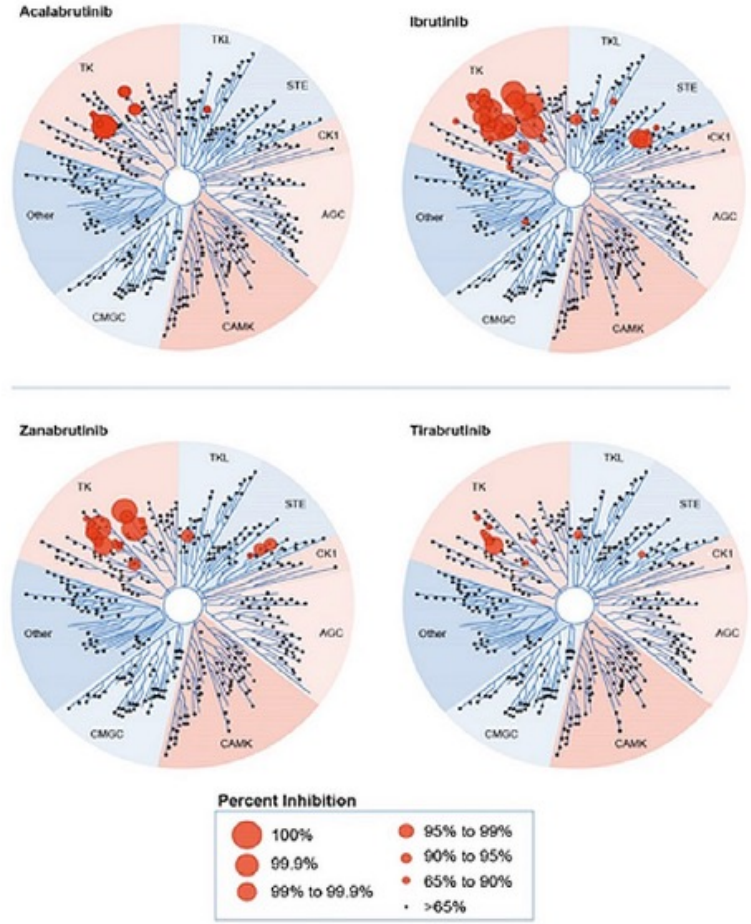


FIGURE 1 Kinome profiling of Bruton tyrosine kinase (BTK) inhibitors at a single dose of 1 µmol/L. Adapted with permission from Figure 1 in Kaptein *et al.*, 2018[24].

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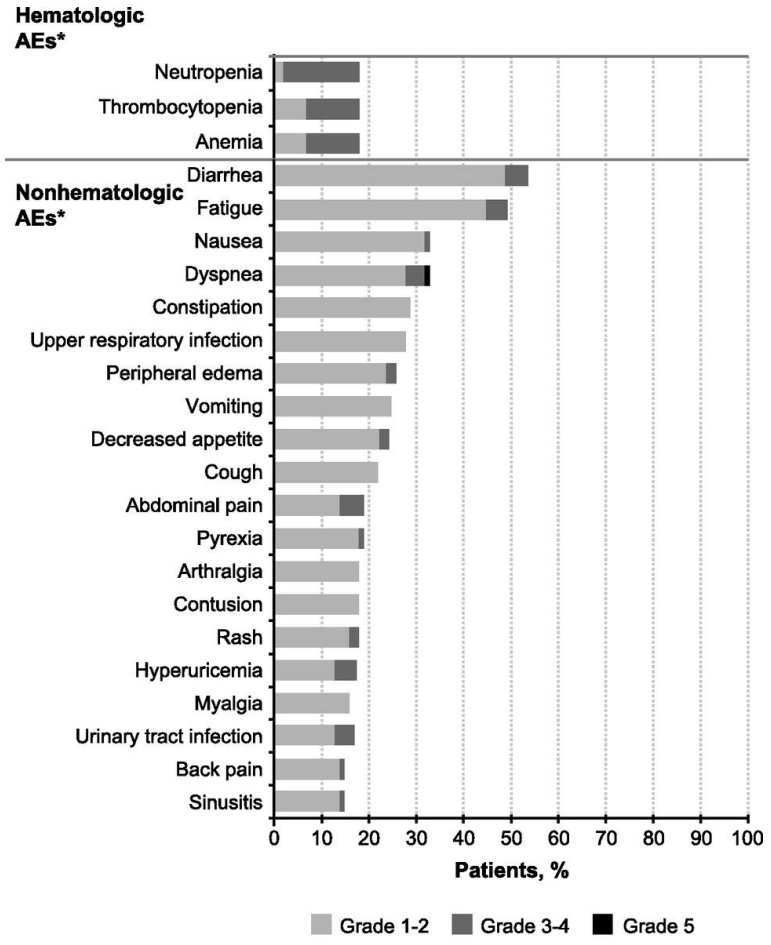
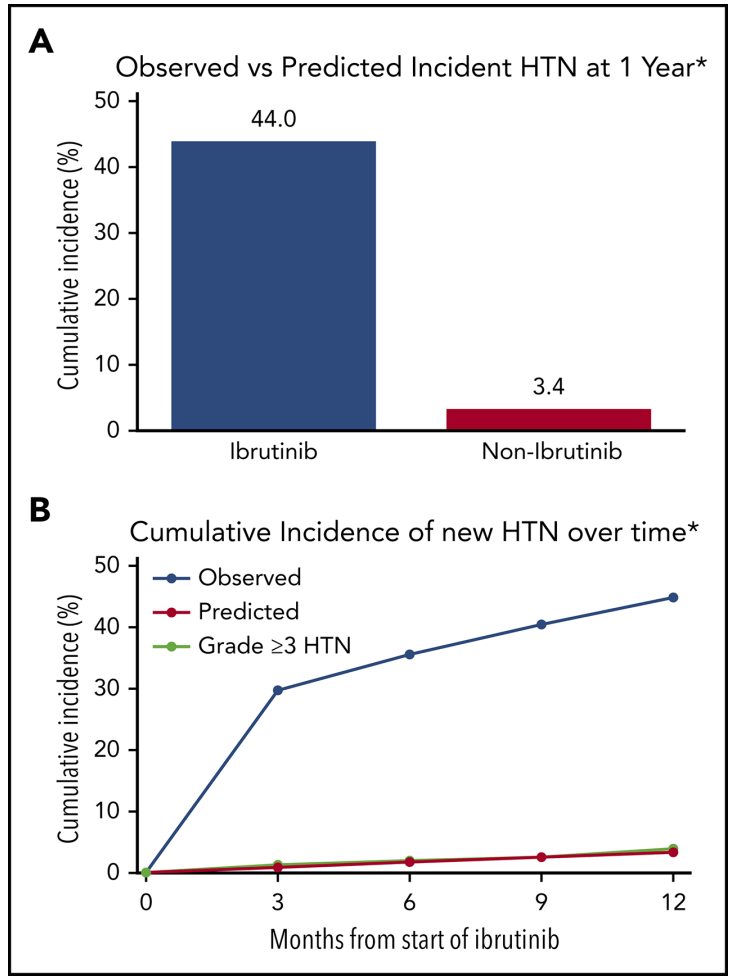
Covalent in BTKi in NHL

- Ibrutinib the first generation BTKi and was explored in several B cell malignancies
  - Initial study indicated efficacy across subtypes
    - CLL, DLBCL, MCL, WM, MZL
    - Further studies led to FDA approval in MCL, MZL and WM
  - CLL revolutionized treated
    - Replaced chemotherapy as preferred 1L option for most patients
  - Failed to demonstrated efficacy in FL, especially in rituximab resistant patients
  - DLBCL more complex

When the Toll is Due…Issues with Ibrutinib



*AEs were updated with an estimated median follow-up of 26.7 months.



Hypertension and incident cardiovascular events following ibrutinib initiation

2nd Generation Agents

- Acalabrutinib and Zanubrutinib designed to have more fidelity to BTK and in theory fewer side effects compared to ibrutinib.
- What about efficacy??
  - Efficacy appears similar between all three drugs, but AE profile did appear improved with less promiscuous agents
  - Except for MZL
    - Early results from the ALPINE study demonstrated improved ORR and PFS as compared with Ibrutinib
- And safety…….bit controversial…..

Acalabrutinib

- Cardiac AE's have been reported with Acalabrutinib as well.

Event	All patients (N=762)	
	Any grade	Grade ≥3[c]
Any cardiac AE,[a] n (%),[b] [number of individual events], {rate per PEY}	129 (17), [199], {0.081}	37 (5), [51], {0.023}
Most common cardiac AE (preferred terms; occurring in ≥4 patients), n (%), [number of individual events], {rate per PEY}		
Atrial fibrillation/flutter[d]	38 (5), [48], {0.024}	11 (1.4), [12], {0.007}
Atrial fibrillation	34 (4), [44], {0.021}	10 (1), [11], {0.006}
Atrial flutter	4 (0.5), [4], {0.003}	1 (0.1), [1], {0.001}
Palpitations	23 (3), [27], {0.014}	0
Tachycardia	17[e] (2), [18], {0.011}	0
Sinus tachycardia	11[e] (1), [13], {0.007}	1 (0.1), [1], {0.001}
Angina pectoris	10 (1), [11], {0.006}	2 (0.3), [2], {0.001}
Bradycardia	9 (1), [10], {0.006}	2 (0.3), [2], {0.001}
Cardiac failure	6 (0.8), [6], {0.004}	3 (0.4), [3], {0.002}
Acute myocardial infarction	5 (0.7), [6], {0.003}	5 (0.7), [6], {0.003}
Supraventricular tachycardia	4[e] (0.5), [4], {0.003}	1 (0.1), [1], {0.001}

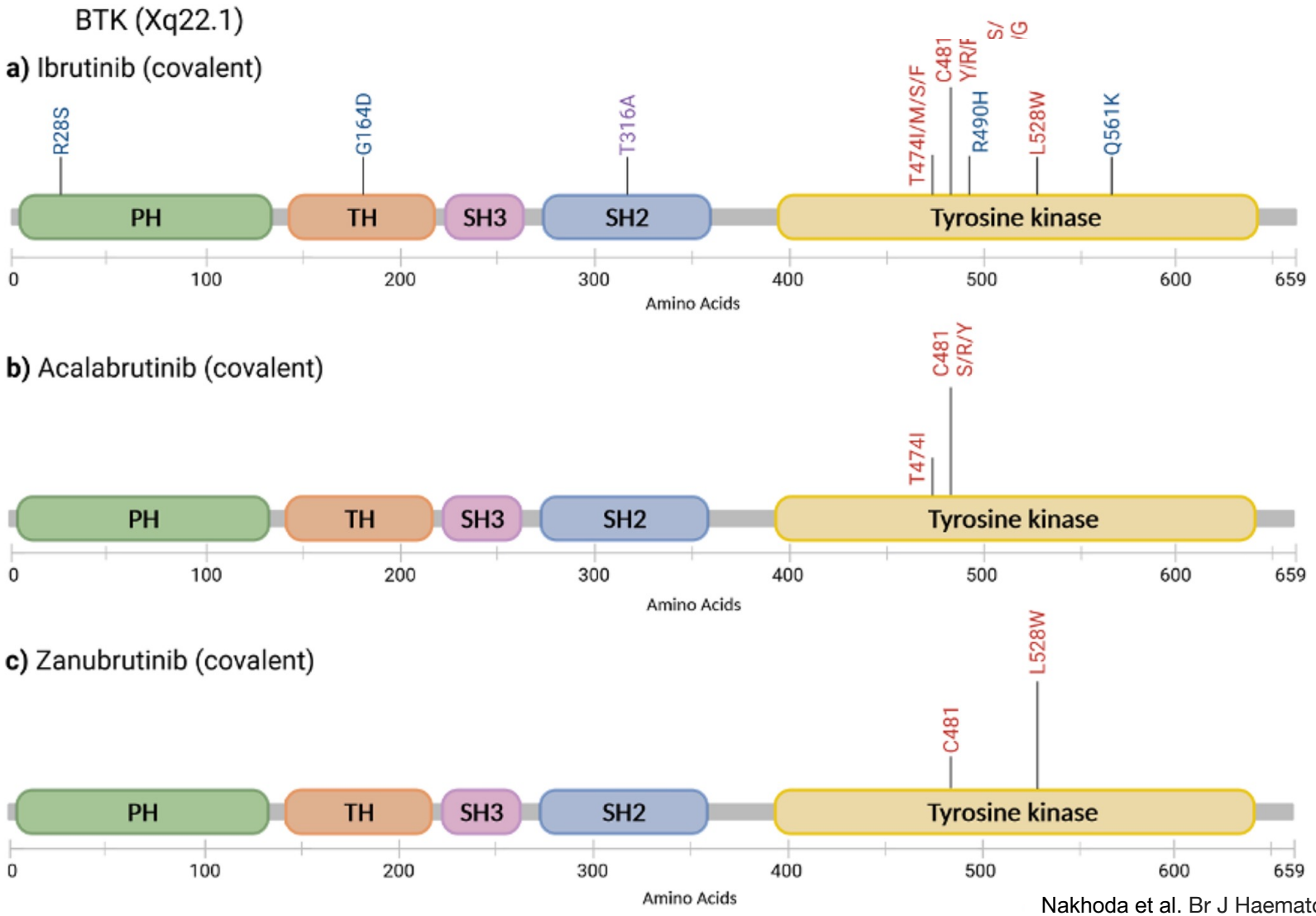
[a]Adverse events (AE) categorized under the system organ class cardiac disorders. [b]199 AE were reported in 129 patients (17%). No events under the preferred terms sudden death or sudden cardiac death were reported. [c]Other grade ≥3 AE of interest occurring in <4 patients each included complete atrioventricular (AV) block (n=2; 0.3%), acute coronary syndrome (n=1; 0.1%), second-degree AV block (n=1; 0.1%), and ventricular fibrillation (n=1; 0.1%). [d]Patients with "atrial fibrillation" or "atrial flutter" preferred terms combined. There was no overlap between patients with "atrial fibrillation" and "atrial flutter" events. [e]One patient had both "tachycardia" and "sinus tachycardia" events. Another patient had both "sinus tachycardia" and "supraventricular tachycardia" events. A third patient had both "tachycardia" and "supraventricular tachycardia" events. All other reports of "tachycardia," "sinus tachycardia," and "supraventricular tachycardia" occurred in unique patients. PEY: patient exposure years.

- Data raised questions about ventricular arrythmias in acalabrutinib

Problems of Le Resistance

- One Big issue with BTKi is the development of resistance and lack of viable options post resistance in several subtypes.
  - Most of what is know about drivers of mutations comes from CLL where several different mutations have been identified.
    - Binding site mutations (C481S)
    - Kinase Domain Mutations (V416L, A428D, M437R, T474I)
    - Gain of function PLCG2 missense mutations
    - BTK kinase dead mutation (L528W)
  - Resistance is unclear in other subtypes as well

Most Common Resistance Mutations



Nakhoda et al. Br J Haematol. 2023 Jan; 200(2): 137–149.

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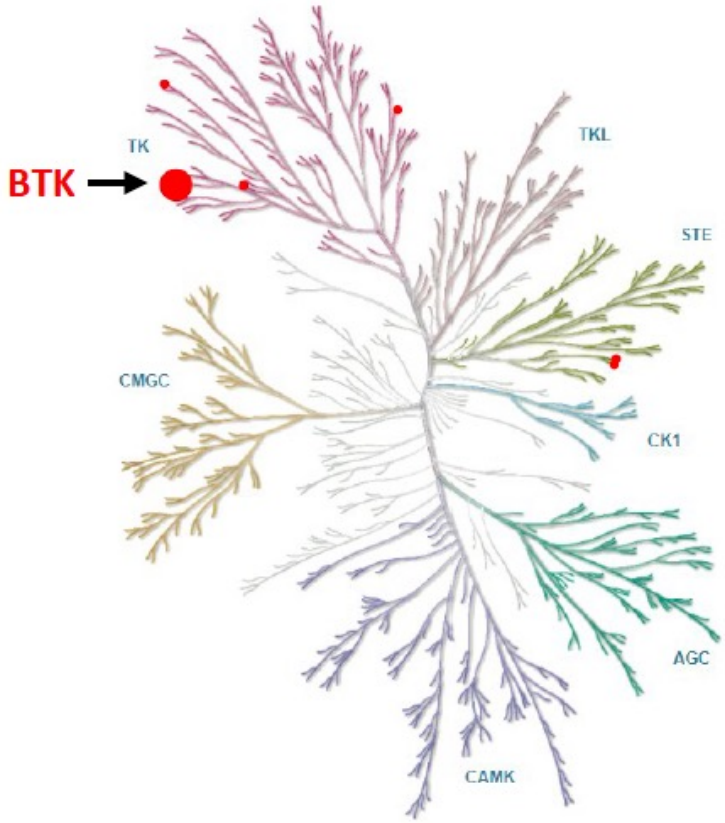
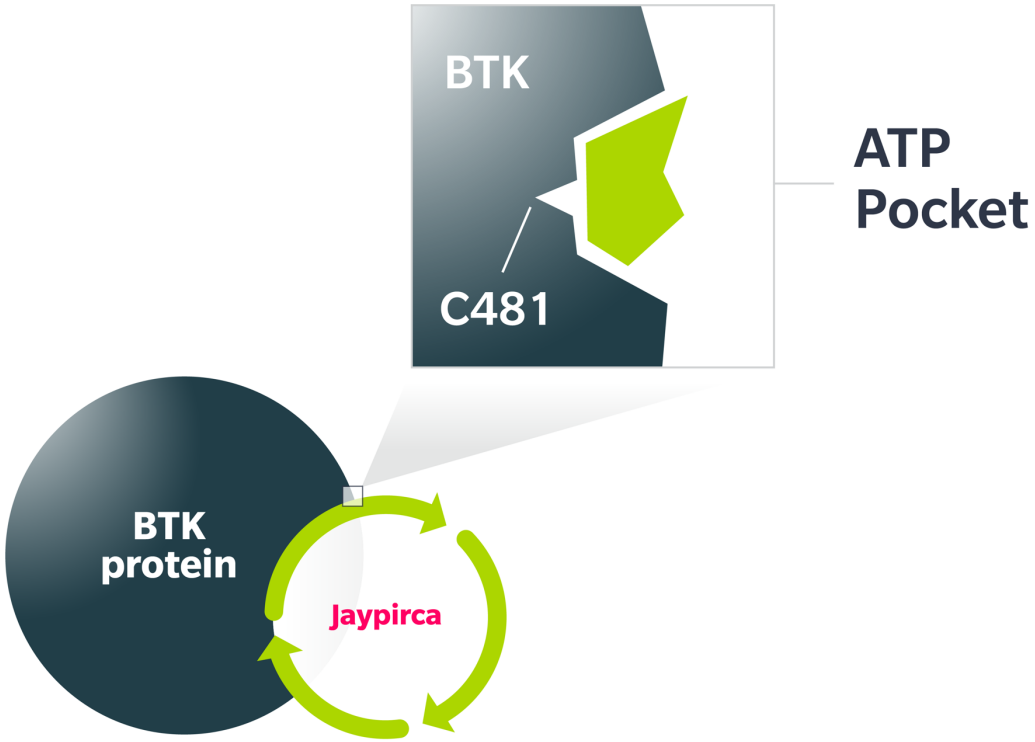
Pirtobrutinib

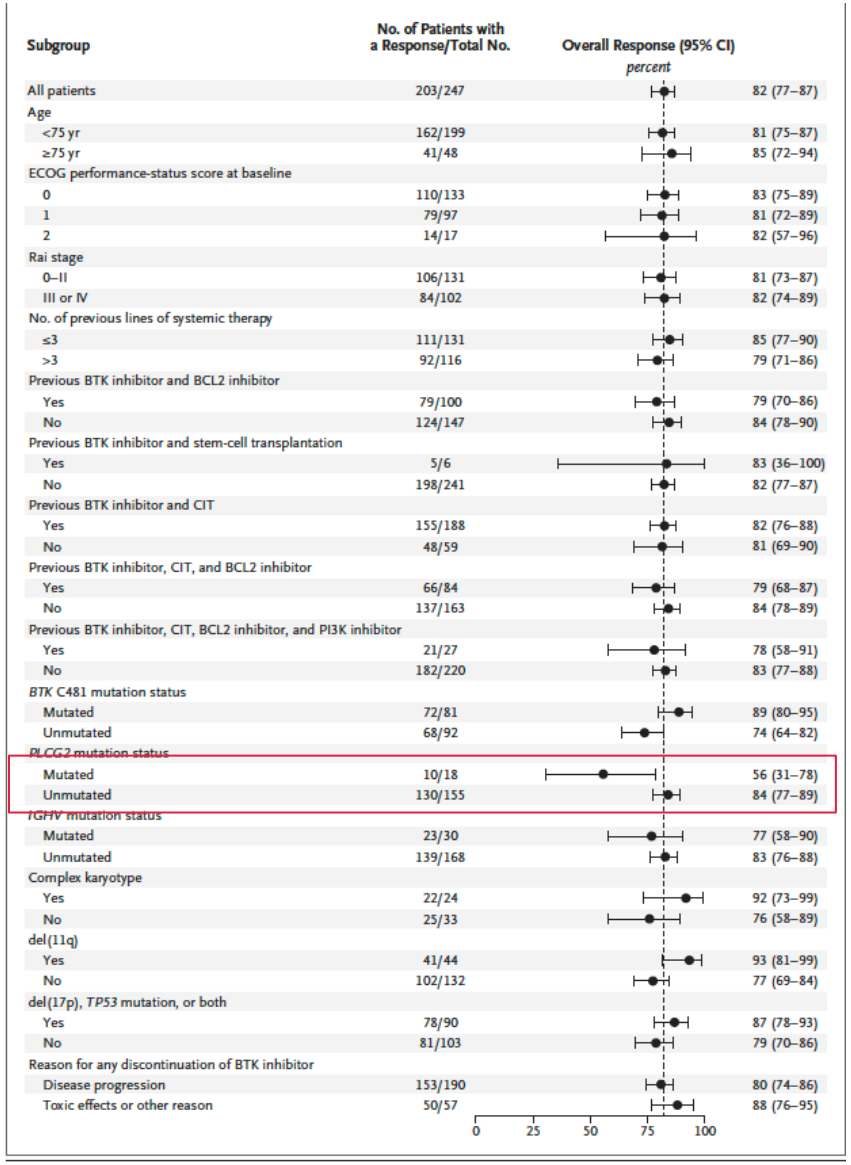




CLL

Table 2. Efficacy of Pirtobrutinib in Patients with CLL or SLL Who Had Previously Received a BTK Inhibitor.*

Variable	Previous BTK Inhibitor (N=247)	Previous BTK Inhibitor + BCL2 Inhibitor (N=100)
Overall response — % (95% CI)		
Including complete response, nodular partial response, or partial response	73.3 (67.3–78.7)	70.0 (60.0–78.8)
Including complete response, nodular partial response, partial response, or partial response with lymphocytosis	82.2 (76.8–86.7)	79.0 (69.7–86.5)
Best response — no. (%)		
Complete response	4 (1.6)	0
Nodular partial response	1 (0.4)	0
Partial response	176 (71.3)	70 (70.0)
Partial response with lymphocytosis	22 (8.9)	9 (9.0)
Stable disease	26 (10.5)	11 (11.0)
Progression-free survival		
Median (95% CI) — mo	19.6 (16.9–22.1)	16.8 (13.2–18.7)
Patients with censored data — no. (%)	126 (51.0)	44 (44.0)
Median follow-up — mo	19.4	18.2



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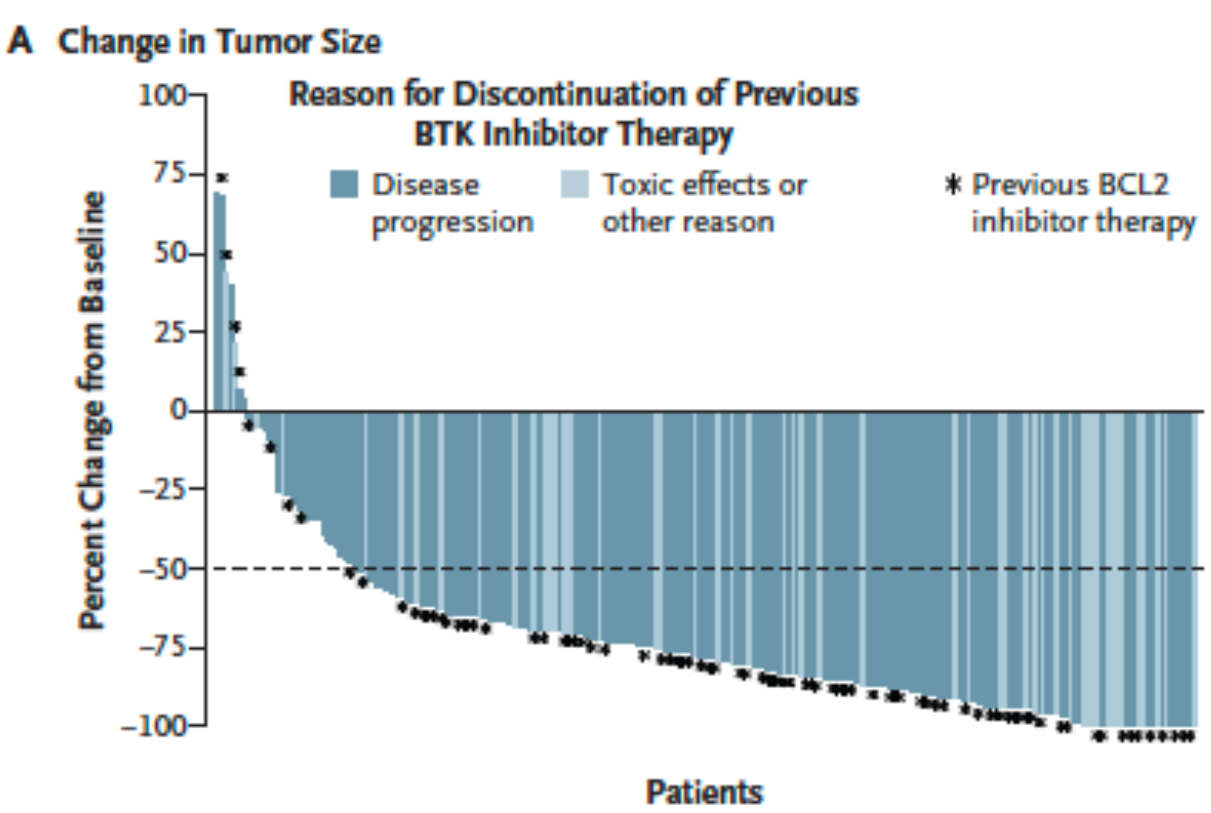
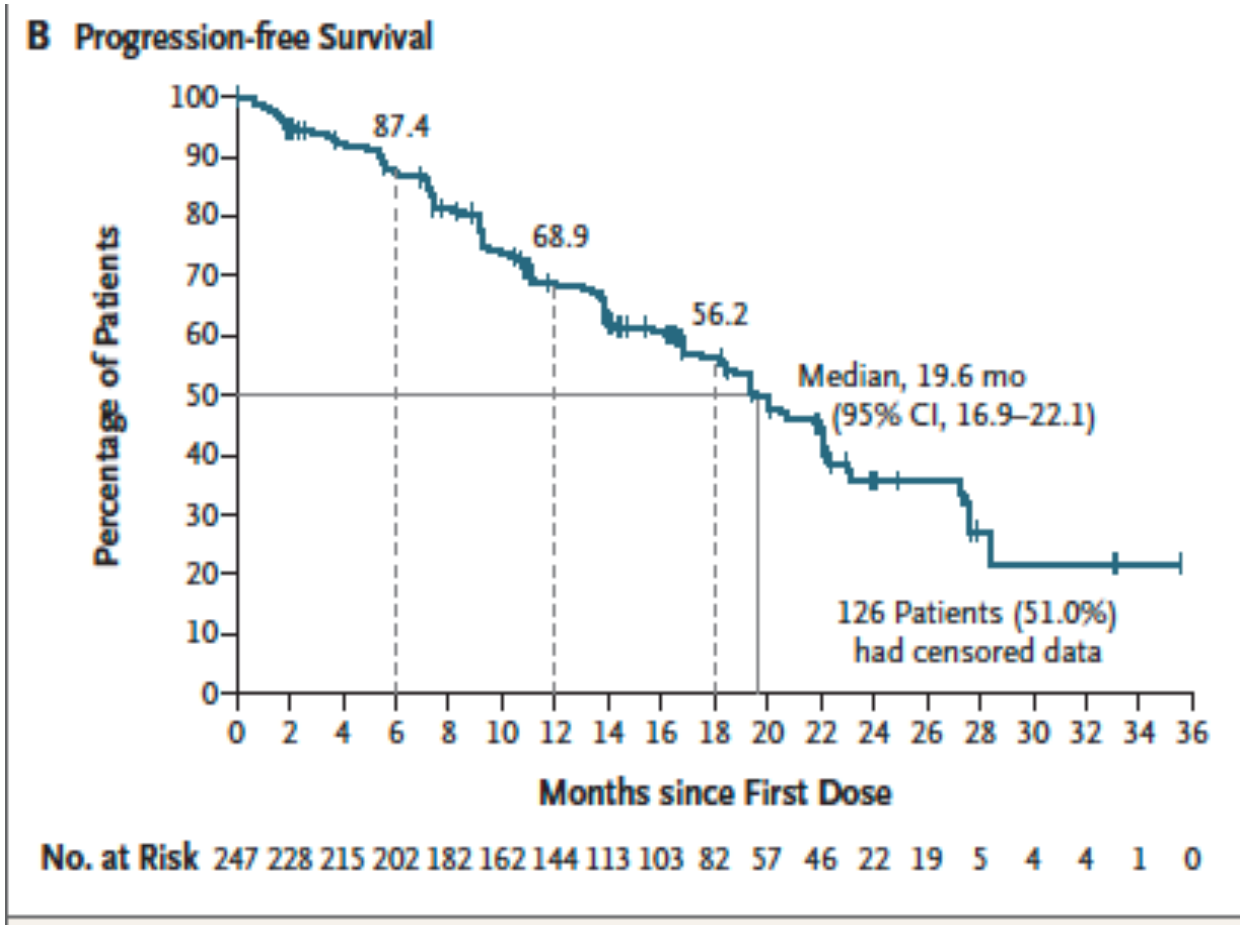
CLL Response





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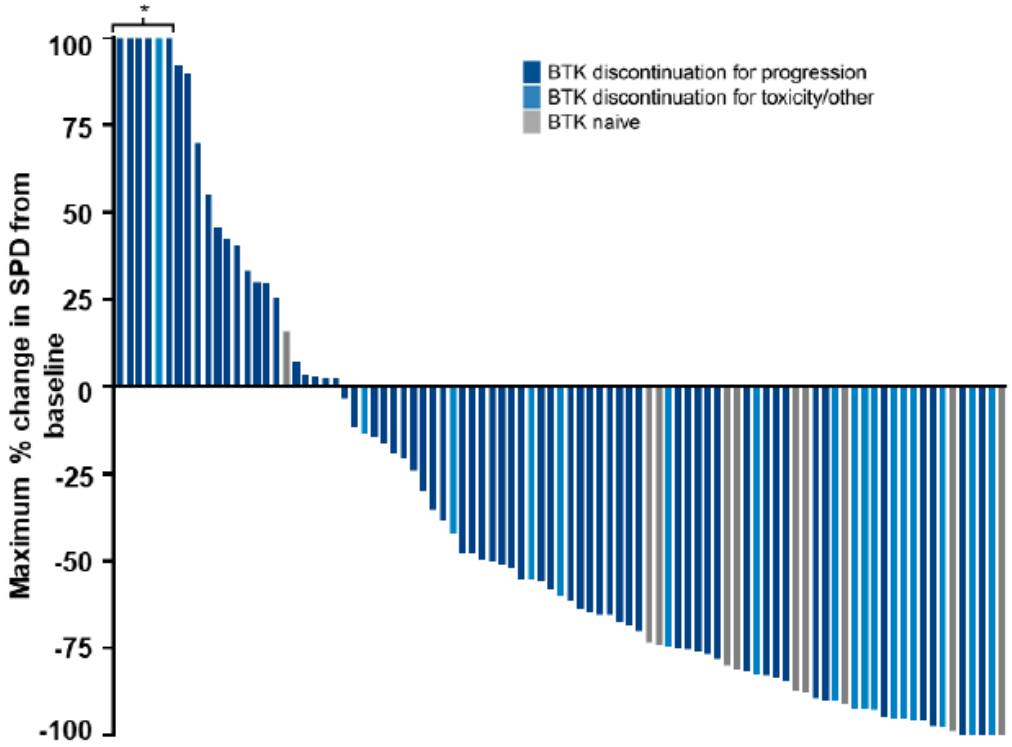
Pirtobrutinib

Pirtobrutinib Efficacy in Mantle Cell Lymphoma

200 mg daily



BTK Pre-Treated MCL Patients[a]	n=100
Overall Response Rate[b], % (95% CI)	**51% (41-61)**
Best Response	
CR, n (%)	25 (25)
PR, n (%)	26 (26)
SD, n (%)	16 (16)
BTK Naive MCL Patients[a]	**n=11**
Overall Response Rate[b], % (95% CI)	**82% (48-98)**
Best Response	
CR, n (%)	2 (18)
PR, n (%)	7 (64)
SD, n (%)	1 (9)

Efficacy also seen in patients with prior:

- Stem cell transplant (n=28): ORR 64% (95% CI: 44-81)
- CAR-T therapy (n=6): ORR 50% (95% CI: 12-88)

Data cutoff date of 16 July 2021. Data for 20 MCL patients are not shown in the waterfall plot due to no measurable target lesions identified by CT at baseline, discontinuation prior to first response assessment, or lack of adequate imaging in follow-up. *Indicates patients with >100% increase in SPD. [a]Efficacy evaluable patients are those who had at least one post-baseline response assessment or had discontinued treatment prior to first post-baseline response assessment. [b]ORR includes patients with a best response of CR and PR. Response status per Lugano 2014 criteria based on investigator assessment. Total % may be different than the sum of the individual components due to rounding.

Wang et al. ASH 2021

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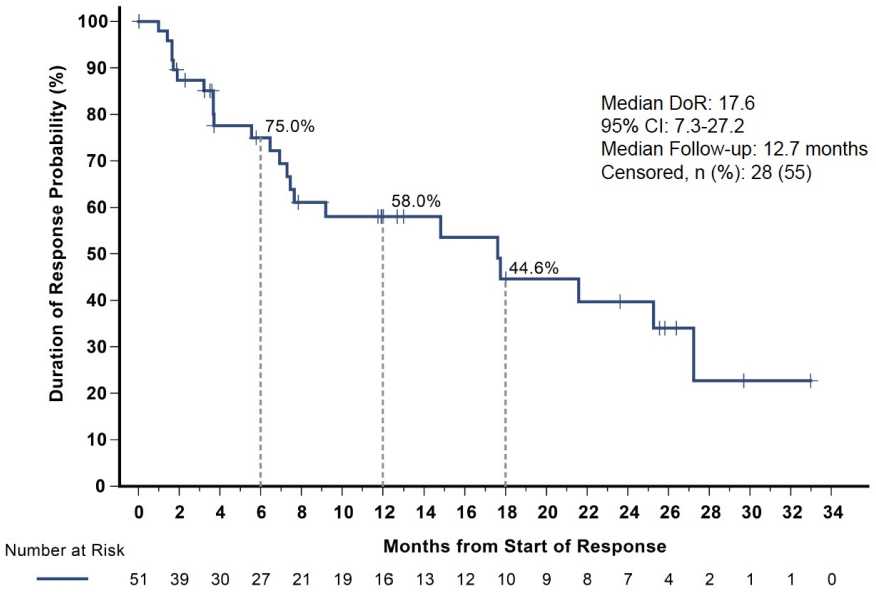
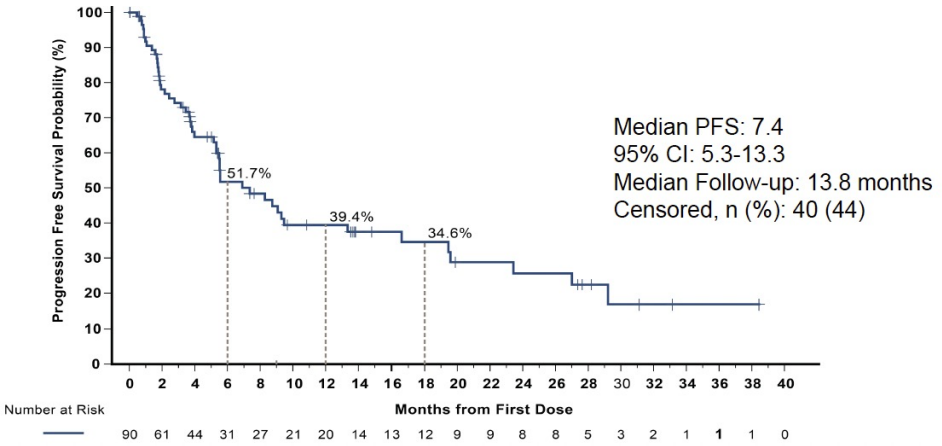
Updated Results and Subgroup Analysis From the BRUIN Phase 1/2 Study of Pirtobrutinib in Patients With R/R MCL: DOR, PFS, and OS

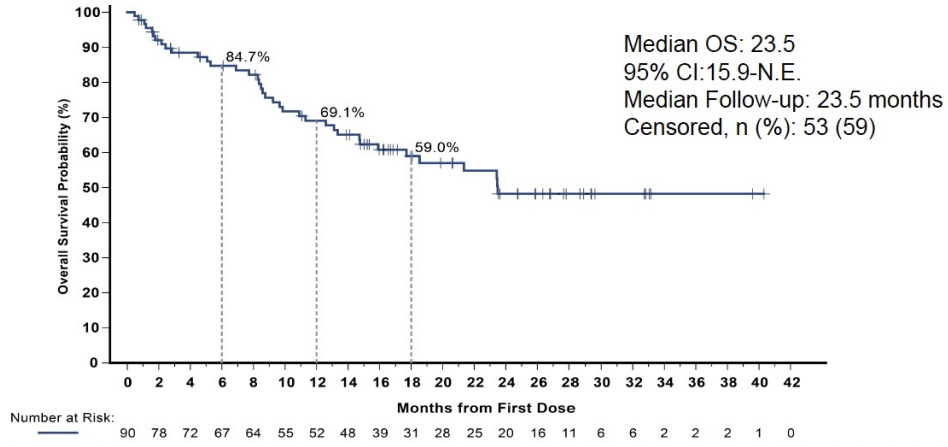
DOR in Prior cBTKi Patients



PFS in Prior cBTKi Patients



OS in Prior cBTKi Patients



- Median DOR, PFS, and OS were not reached in the cBTKi-naïve cohort
- 18-month rates (95% CI)
  - DOR: 100% (100)
  - PFS: 92.3% (56.6-98.9)
  - OS: 92.3% (56.6-98.9)

Shah NN, et al. ASCO 2023. Abstract 7514. Jurczak J, et al. EHA 2023. Abstract P1087. Cheah CY, et al. ICML 2023. Abstract 102.

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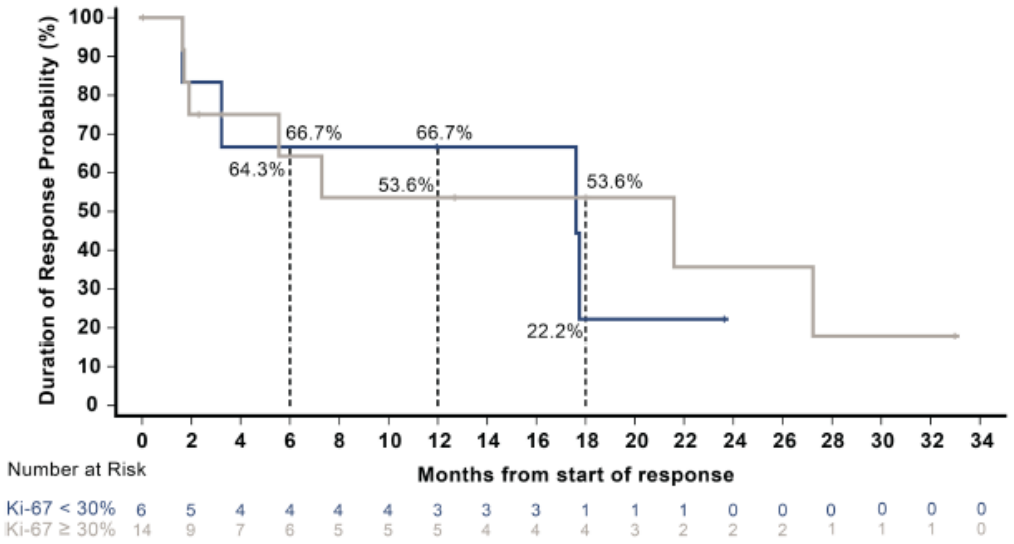
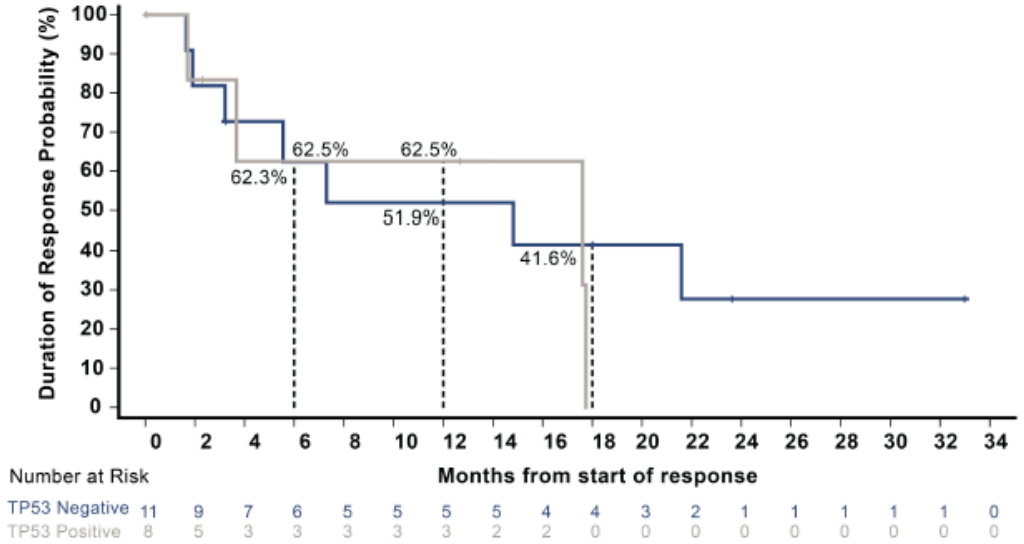
Updated Results and Subgroup Analysis From the BRUIN Phase 1/2 Study of Pirtobrutinib in Patients With R/R MCL: DOR, PFS, and OS by Subgroup

DOR by Ki-67 Index



DOR by *TP53* Status



Median DOR, PFS, and OS by High-Risk Subgroup (range), months		Median DOR	Median PFS	Median OS
Ki-67	<30%	17.6 (1.6-NE)	19.5 (0.9-NE)	NE (6.9-NE)
	≥30%	21.6 (1.7-NE)	5.2 (1.9-23.4)	NE (14.7-NE)
TP53	Negative	14.8 (1.9-NE)	7.4 (3.8-23.4)	NE (6.9-NE)
	Positive	17.6 (1.7-NE)	5.2 (1.7-19.5)	15.9 (8.3-NE)

Shah NN, et al. ASCO 2023. Abstract 7514. Jurczak J, et al. EHA 2023. Abstract P1087. Cheah CY, et al. ICML 2023. Abstract 102.

Updated Results and Subgroup Analysis From the BRUIN Phase 1/2 Study of Pirtobrutinib in Patients With R/R MCL: Safety and Summary

AEs for Patients With MCL (n=166), %		TEAEs (≥15%)		TRAEs	
		Any Grade	Grade ≥3	Any Grade	Grade ≥3
Fatigue		31.3	3.0	21.1	2.4
Diarrhea		22.3	0.0	12.0	0.0
Dyspnea		16.3	1.2	9.0	0.6
AEs of special interest	Bruising	16.3	0.0	11.4	0.0
	Rash	8.4	0.6	5.4	0.0
	Arthralgia	9.0	1.2	2.4	0.0
	Hemorrhage/hematoma	10.2	2.4	4.2	0.6
	Hypertension	3.6	0.0	1.8	0.0
	Afib/flutter	3.6	1.8	0.6	0.0

- Median time on treatment for the MCL population: 5 months
- Discontinuations due to TRAEs: 3% (n=5)
- Dose reductions due to TRAEs: 6% (n=10)

Table 3. Safety Profile of Pirtobrutinib in Patients with CLL or SLL.

Event	Adverse Events (N=317)		Treatment-Related Adverse Events (N=317)*	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number of patients (percent)			
Adverse events†				
Fatigue	100 (31.5)	6 (1.9)	11 (3.5)	1 (0.3)
Diarrhea	84 (26.5)	2 (0.6)	28 (8.8)	1 (0.3)
Contusion	77 (24.3)	0	52 (16.4)	0
Cough	77 (24.3)	0	5 (1.6)	0
Coronavirus disease 2019	76 (24.0)	16 (5.0)	5 (1.6)	0
Nausea	60 (18.9)	0	10 (3.2)	0
Abdominal pain	57 (18.0)	5 (1.6)	7 (2.2)	1 (0.3)
Dyspnea	55 (17.4)	3 (0.9)	2 (0.6)	0
Headache	55 (17.4)	2 (0.6)	17 (5.4)	1 (0.3)
Upper respiratory tract infection	52 (16.4)	1 (0.3)	11 (3.5)	0
Back pain	51 (16.1)	3 (0.9)	3 (0.9)	0
Anemia	48 (15.1)	28 (8.8)	15 (4.7)	7 (2.2)
Adverse events of special interest‡				
Atrial fibrillation or flutter§	12 (3.8)	4 (1.3)	4 (1.3)	1 (0.3)
Bleeding	135 (42.6)	7 (2.2)	75 (23.7)	3 (0.9)
Bruising¶	96 (30.3)	0	62 (19.6)	0
Hemorrhage	67 (21.1)	7 (2.2)	22 (6.9)	3 (0.9)
Hypertension	45 (14.2)	11 (3.5)	12 (3.8)	1 (0.3)
Infections	225 (71.0)	89 (28.1)	39 (12.3)	12 (3.8)
Neutropenia‖	103 (32.5)	85 (26.8)	62 (19.6)	47 (14.8)

Shah NN, et al. ASCO 2023. Abstract 7514. Jurczak J, et al. EHA 2023. Abstract P1087. Cheah CY, et al. ICML 2023. Abstract 102.

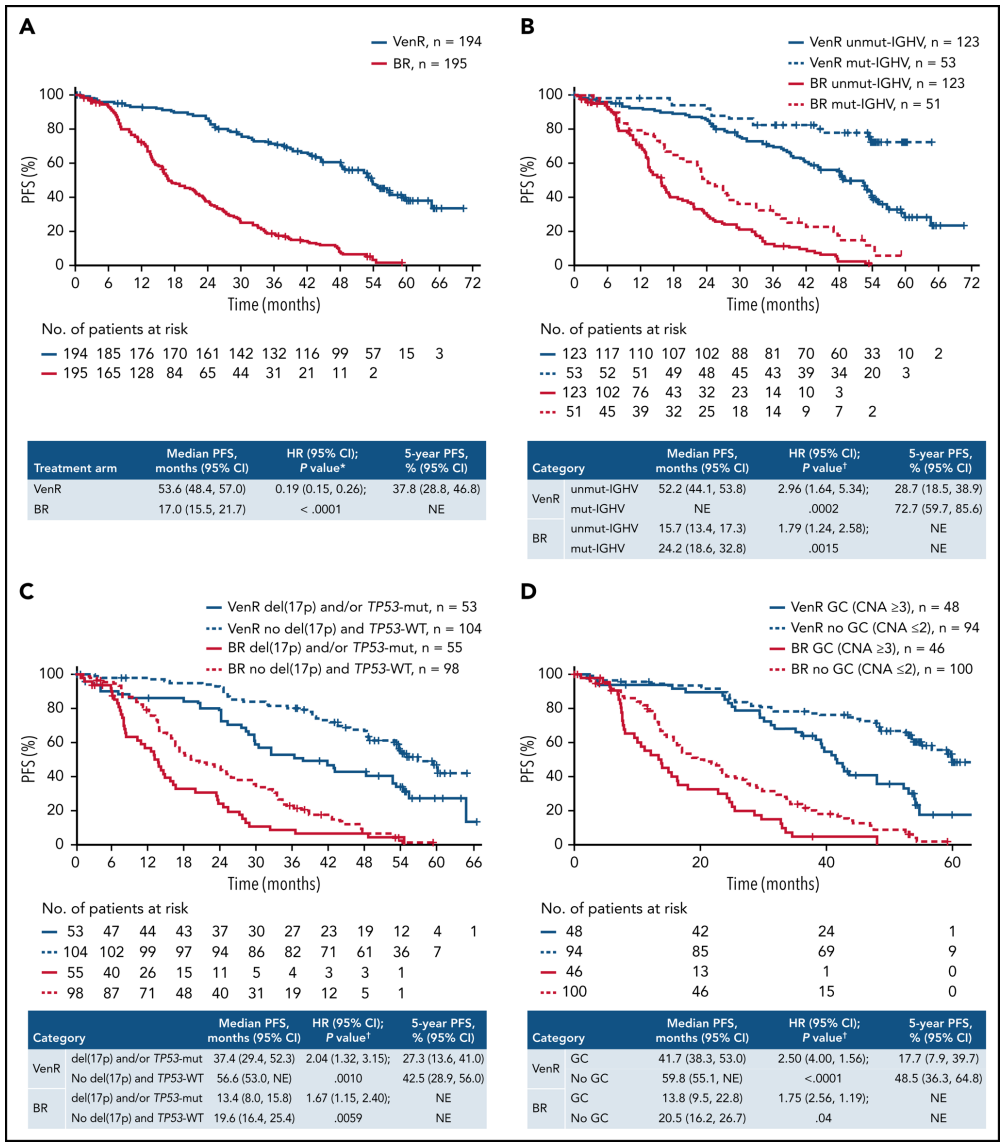
Summary

- BTKi are integral and approved in several NHL subtypes
  - Recently Ibrutinib lost indication in MCL due to results from SHINE
- Newer generation of agents available with improvement in tolerance
- Resistance is noted across all agents with most of the data from CLL
  - Clear resistance mechanism in CLL
  - Other subtypes without any clear pattern or easy strategy to overcome
- Non-covalent agents able to overcome some resistance but in CLL noted to lead to alternative resistance mutations as compared to covalent drugs.

Venetoclax

- BCL-2 inhibition has been explored in NHL
  - Initial attempt with navitoclax was derailed due to thrombocytopenia given expression of Bcl-xL on platelets.
  - Study with venetoclax noted impressive ORR in CLL and BTK naïve MCL
    - Other subtypes without significant agent response including FL and DLBCL despite 14;18 translocation.
  - Only approved in CLL
  - Several newer BCL-2 inhibitors being evaluated. Data pending.

Murano - Data

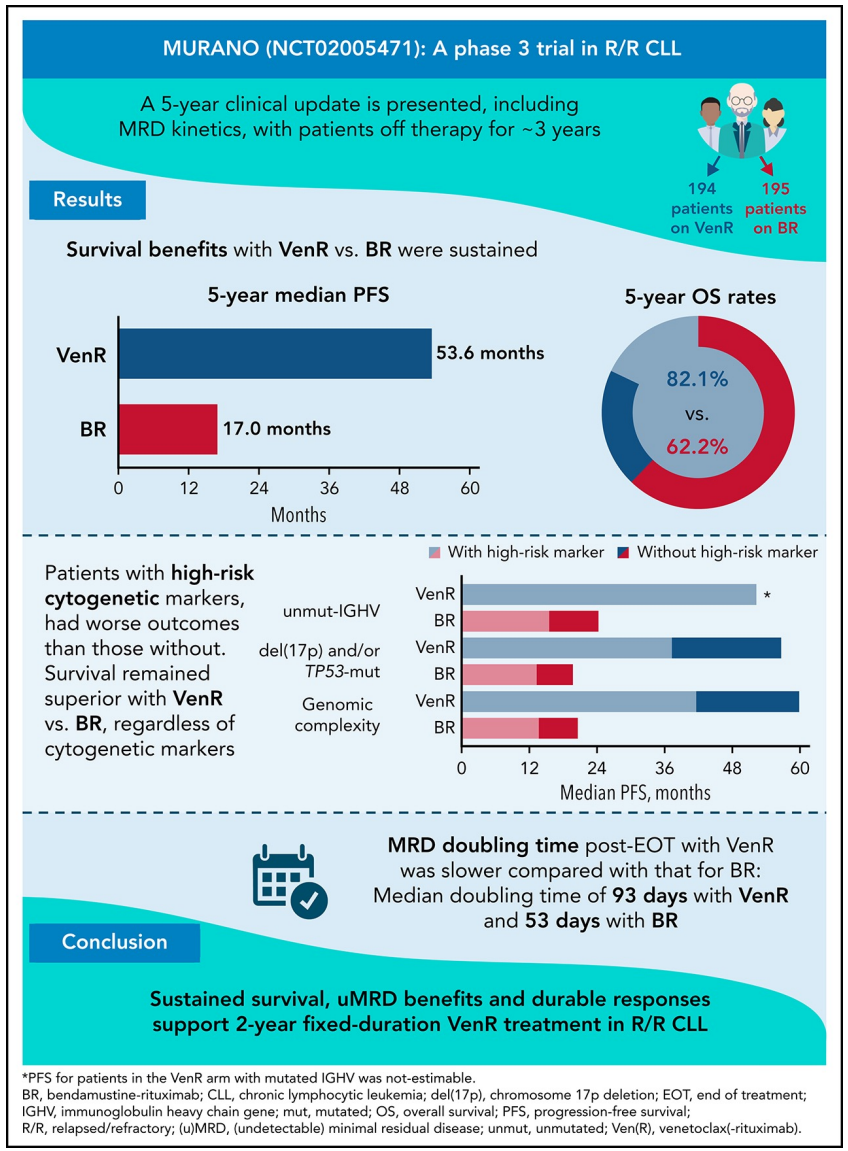


Treatment arm	Median PFS, months (95% CI)	HR (95% CI); *P* value*	5-year PFS, % (95% CI)
VenR	53.6 (48.4, 57.0)	0.19 (0.15, 0.26);	37.8 (28.8, 46.8)
BR	17.0 (15.5, 21.7)	< .0001	NE

Category		Median PFS, months (95% CI)	HR (95% CI); *P* value†	5-year PFS, % (95% CI)
VenR	unmut-IGHV	52.2 (44.1, 53.8)	2.96 (1.64, 5.34);	28.7 (18.5, 38.9)
	mut-IGHV	NE	.0002	72.7 (59.7, 85.6)
BR	unmut-IGHV	15.7 (13.4, 17.3)	1.79 (1.24, 2.58);	NE
	mut-IGHV	24.2 (18.6, 32.8)	.0015	NE

Category		Median PFS, months (95% CI)	HR (95% CI); *P* value†	5-year PFS, % (95% CI)
VenR	del(17p) and/or *TP53*-mut	37.4 (29.4, 52.3)	2.04 (1.32, 3.15);	27.3 (13.6, 41.0)
	No del(17p) and *TP53*-WT	56.6 (53.0, NE)	.0010	42.5 (28.9, 56.0)
BR	del(17p) and/or *TP53*-mut	13.4 (8.0, 15.8)	1.67 (1.15, 2.40);	NE
	No del(17p) and *TP53*-WT	19.6 (16.4, 25.4)	.0059	NE

Category		Median PFS, months (95% CI)	HR (95% CI); *P* value†	5-year PFS, % (95% CI)
VenR	GC	41.7 (38.3, 53.0)	2.50 (4.00, 1.56);	17.7 (7.9, 39.7)
	No GC	59.8 (55.1, NE)	<.0001	48.5 (36.3, 64.8)
BR	GC	13.8 (9.5, 22.8)	1.75 (2.56, 1.19);	NE
	No GC	20.5 (16.2, 26.7)	.04	NE



*PFS for patients in the VenR arm with mutated IGHV was not-estimable.
BR, bendamustine-rituximab; CLL, chronic lymphocytic leukemia; del(17p), chromosome 17p deletion; EOT, end of treatment; IGHV, immunoglobulin heavy chain gene; mut, mutated; OS, overall survival; PFS, progression-free survival; R/R, relapsed/refractory; (u)MRD, (undetectable) minimal residual disease; unmut, unmutated; Ven(R), venetoclax(-rituximab).

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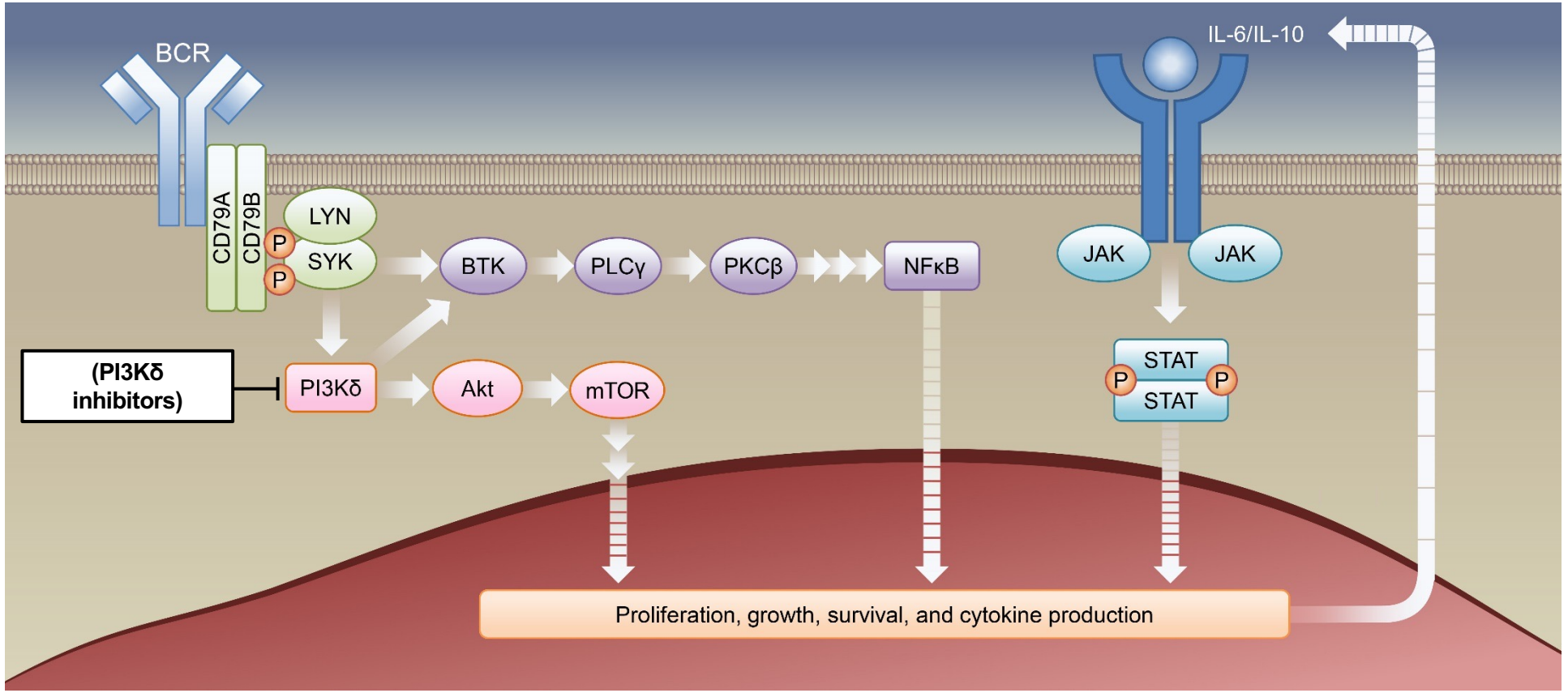
PI3K and JAK-STAT Pathways as Therapeutic Targets in B-Cell Malignancies



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PI3Ki

- Idelalisib
- Duvelisib
- Copanlisib
- Umbralisib
- Zandelisib
- AZD8186

- Thought we might have had something with Zandelisib

The End of a Class

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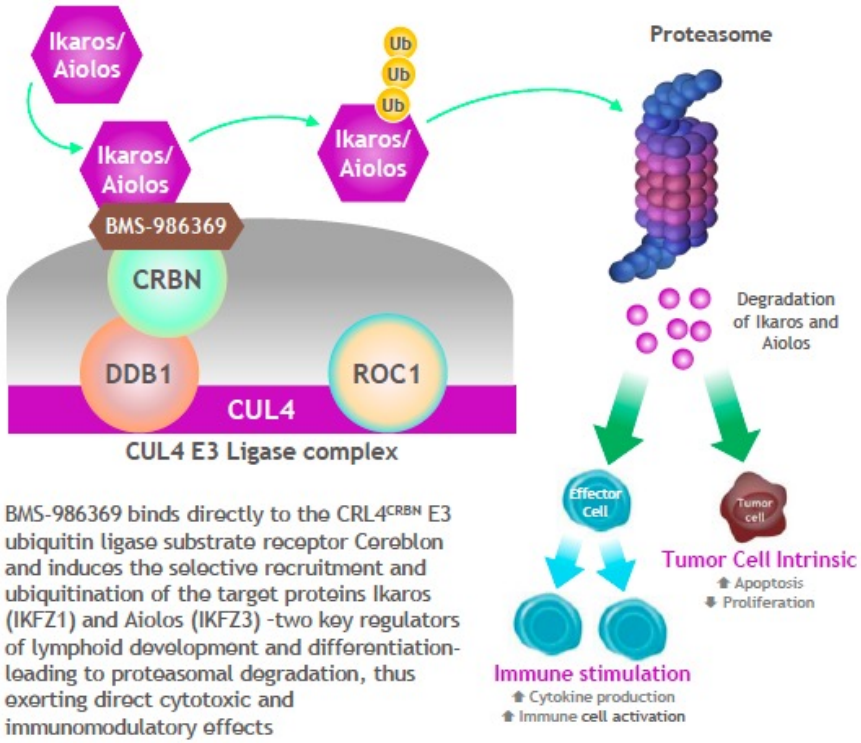
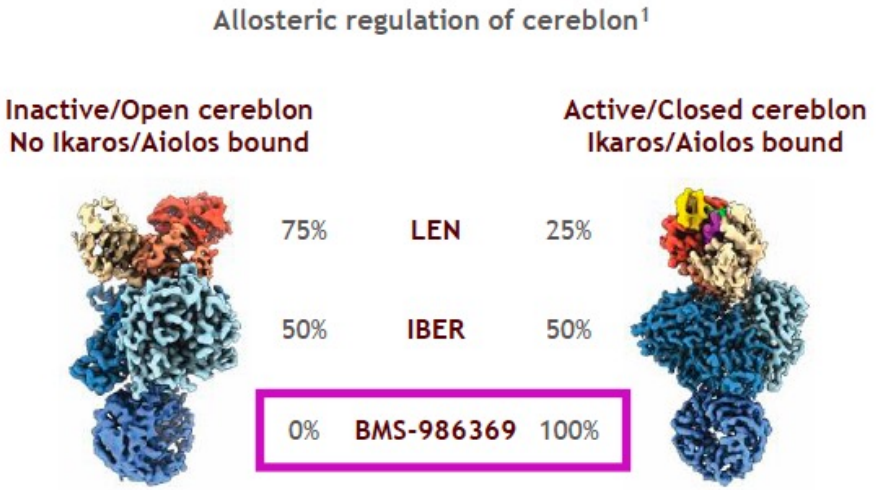
CELMoD

CC-99282 is a potent first-in-class lymphoma Cereblon E3 ligase modulator (CELMoD®) with pleotropic MoA



BMS-986369 binds directly to the CRL4^{CRBN} E3 ubiquitin ligase substrate receptor Cereblon and induces the selective recruitment and ubiquitination of the target proteins Ikaros (IKFZ1) and Aiolos (IKFZ3) -two key regulators of lymphoid development and differentiation- leading to proteasomal degradation, thus exerting direct cytotoxic and immunomodulatory effects



- Recent cryo-EM data indicates that the cereblon complex has both an *open, inactive state* and a *closed, active state* and that IMiDs and CELMoDs drive the closed conformation[1]
- Due to the unique binding modes of BMS-986369 it is more efficient than LEN at driving the closed conformation,[1] leading to deeper and more rapid degradation of Ikaros/Aiolos

CRBN, Cereblon; cryo-EM, cryo-electron microscopy; DDB1, DNA damage-binding protein 1; IKFZ3, Zinc finger protein Ikaros; IKFZ3, Zinc finger protein Aiolos; IMiDs, immunomodulatory imide drugs; LEN, lenalidomide; ROC1, regulator of cullins 1; Ub, ubiquitin.

1. Watson ER, et al. *Science* 2022;378:549-553

Michot JM, et al. ICML 2023 [Presentation #90]

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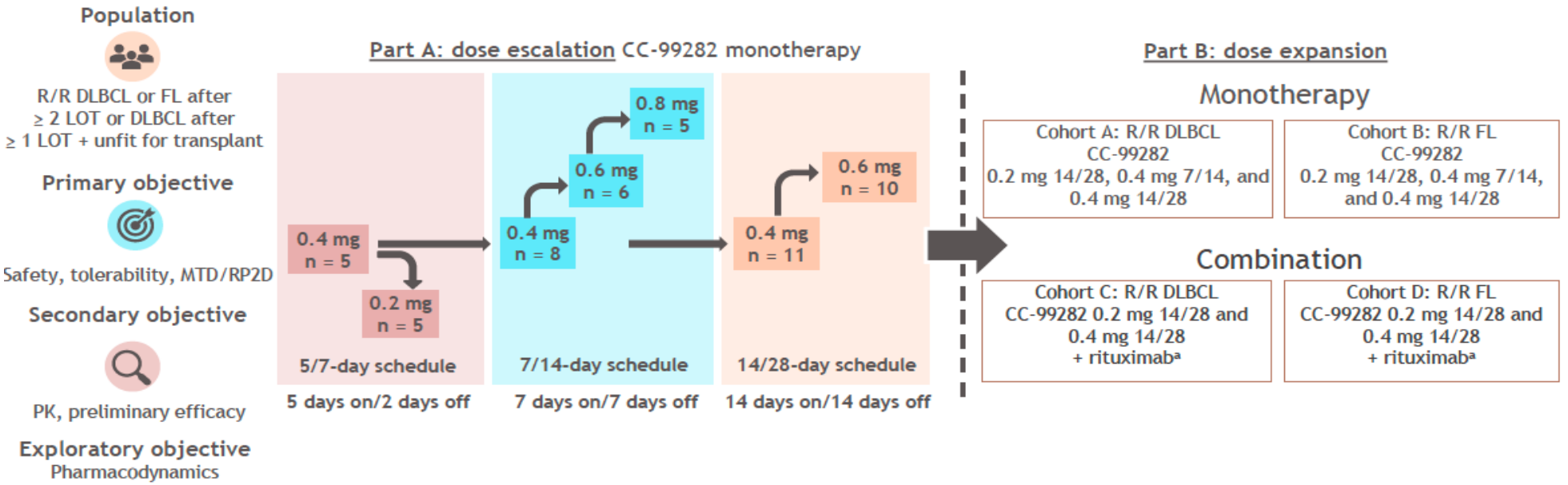
Schema

CC-99282-NHL-001 (NCT03930953) is a multicenter, phase 1, open-label, dose-finding, first-in-human study evaluating CC-99282 in patients with R/R NHL



- Duration of treatment is up to 2 years

[a]Rituximab dosing was 375 mg/m² on Days 1, 8, 15, and 22 of Cycle 1, and Day 1 of Cycles 2-5.

DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; LOT, line of therapy; MTD, maximum tolerated dose; NHL, non-Hodgkin lymphoma; PK, pharmacokinetics; R/R, relapsed or refractory; RP2D, recommended phase 2 dose.

Michot JM, et al. ICML 2022 [Presentation #901]

Treatment history	No. of prior lines of therapy, median (range)	3 (1-8)	4 (2-11)
	Prior stem cell transplant, n (%)	10 (20)	2 (17)
	Prior CAR T-cell therapy, n (%)	14 (28)	8 (67)
	Prior lenalidomide/avadomide treatment, n (%)	11 (22)	8 (67)
	Refractory[b] to last regimen, n (%)	25 (50)	7 (58)

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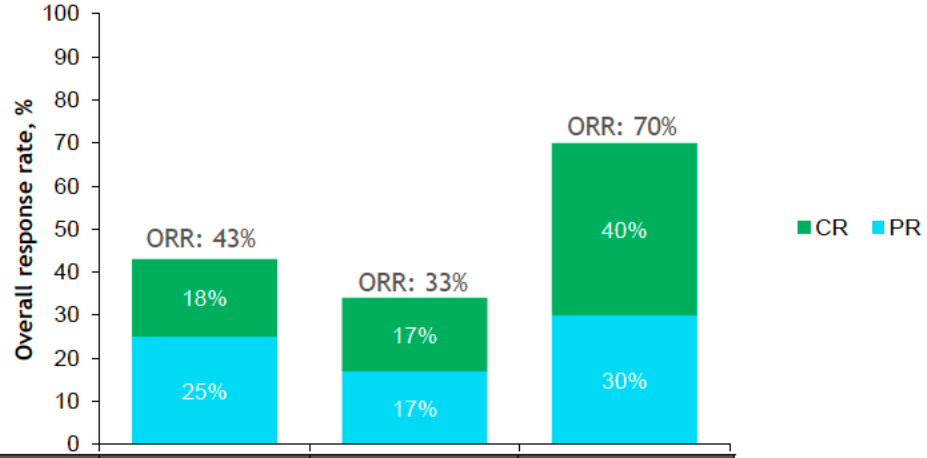
Response

Preliminary activity of CC-99282 monotherapy[a] in heavily pretreated patients with R/R NHL



Median values, days (range)	DLBCL + FL (n = 40)	DLBCL (n = 30)	FL (n = 10)
Median DOR	309 (48-930)	299 (48-898)	448 (135-930)
Median follow-up	362 (26-1004)	293 (26-1004)	572 (269-983)

- In the 7/14 day-schedule (n = 19), 3 (16%) patients had CR and 5 (26%) had PR
- In the 14/28 day-schedule (n = 21), 4 (19%) patients had CR and 5 (24%) had PR

Treatment disposition	Part A CC-99282 monotherapy (N = 50)	Part B CC-99282 + RTX (N = 12)
Completed	3 (6)	0
Ongoing	7 (14)	10 (83)
Discontinued	40 (80)	2 (17)
Primary reason for discontinuation, n (%)		
Progressive disease	33 (66)	2 (17)
Symptomatic deterioration	4 (8)	0
Adverse event	1 (2)	0
Withdrawal by patient	1 (2)	0
Physician's decision	1 (2)	0

- Median (range) CC-99282 treatment duration was 6 weeks (4-28) for Part B

Data cutoffs: Part A, 14 Sep 2022; Part B, 28 Oct 2022. [a]Part A, 7/14- and 14/28-day schedules, doses ≥ 0.4 mg.
CR, complete response; DOR, duration of response; DLBCL, diffuse large B cell lymphoma; FL, follicular lymphoma; NHL, non-Hodgkin lymphoma; PR, partial response; R/R, relapsed refractory; RTX, rituximab.

Michot JM, et al. ICML 2023 [Presentation #90]

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AEs

TEAE, n (%)	All cause (N = 50)		Related to CC-99282 (N = 50)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Neutropenia	36 (72)	32 (64)	34 (68)	30 (60)
Infections	28 (56)	12 (24)	8 (16)	2 (4)
Anemia	20 (40)	11 (22)	11 (22)	4 (8)
Thrombocytopenia	18 (36)	10 (20)	12 (24)	6 (12)
Fatigue	18 (36)	2 (4)	9 (18)	1 (2)
Pyrexia	17 (34)	1 (2)	2 (4)	0
Cough	12 (24)	0	2 (4)	0
ALT increased	11 (22)	1 (2)	3 (6)	0
Constipation	10 (20)	0	4 (8)	0

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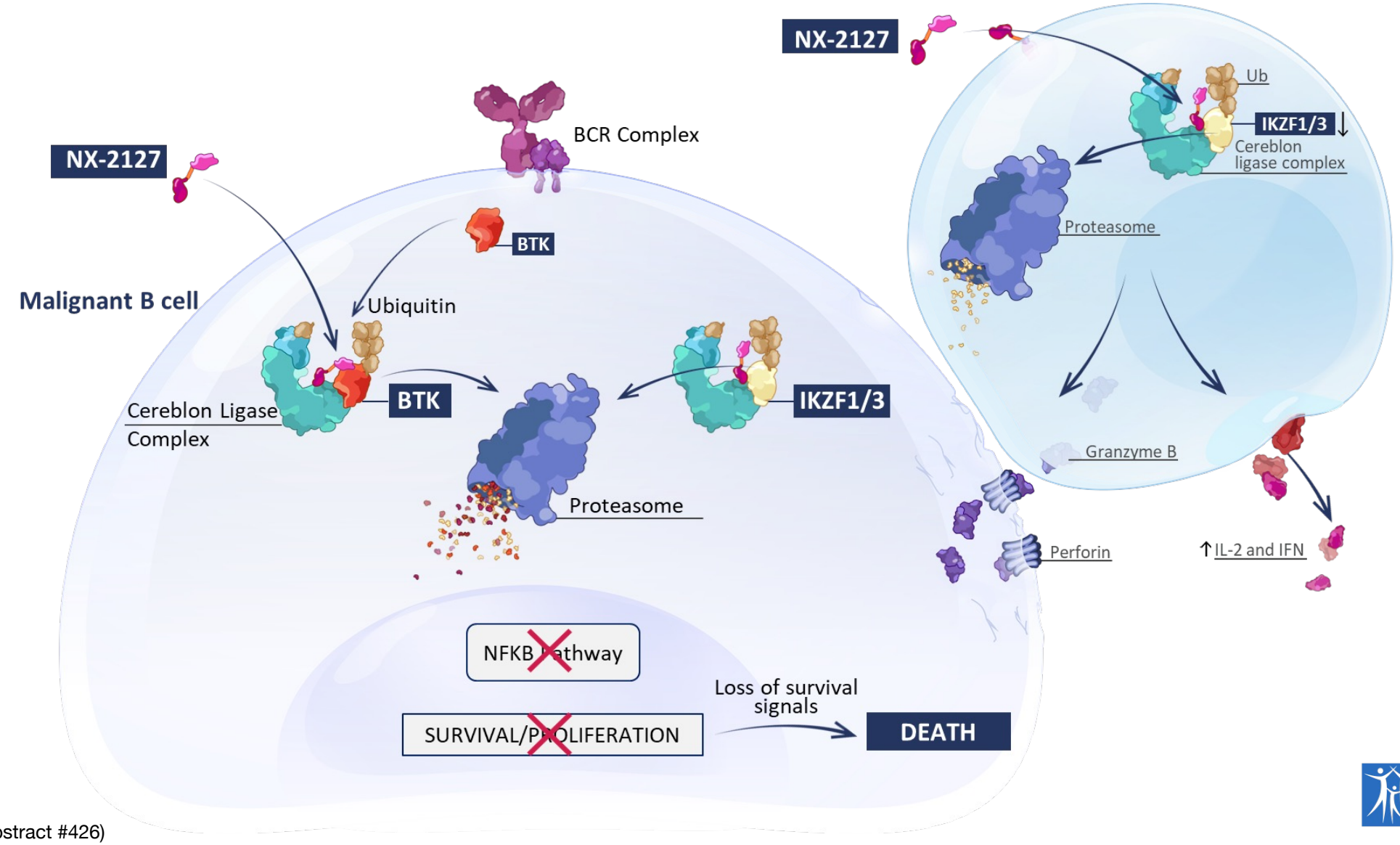
NX-2127: first-in-class targeted protein degrader of BTK



Danilov A et al, ICML 2023 (abstract #426)

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Baseline Characteristics

Elderly population with multiple prior lines of targeted therapies and acquired mutations

Characteristics	CLL (n=23)	Overall population (N=36)
Median age, years (range)	75 (61–90)	75 (50–92)
Female, n (%)	9 (39.1)	13 (36.1)
Male, n (%)	14 (60.9)	23 (63.9)
Lines of prior therapy, median (range)	5 (2–11)	4 (2–11)
BTKi, n (%)	23 (100)	31 (86.1)
Pirtobrutinib, n (%)	8 (34.8)	11 (30.6)
BTKi and BCL2i, n (%)	18 (78.3)	19 (52.8)
cBTKi, ncBTKi, and BCL2i, n (%)	7 (30.4)	7 (19.4)
***BTK* mutation present**[a], n (%)	10 (48)	11 (35)
C481	5 (24)	5 (16)
L528W	4 (19)	4 (13)
T474	3 (14)	4 (13)
V416L	1 (5)	1 (3)
***BCL2* mutation present**[a], n (%)	4 (19)	4 (13)
***PLCG2* mutation present**[a], n (%)	0 (0)	1 (3.2)

[a]Specific mutations are not additive as some patients have multiple *BTK* mutations
Mutations were tested by NGS centrally in those patients with available samples (n=31 in total population; n=21 in CLL population)

Mato et al., ASH 2022
Data cutoff: September 21, 2022

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Most common all-grade TEAEs in all patients enrolled in the NX-2127-001 trial

- The most common TEAEs were fatigue (51.4%), neutropenia (45.9%), and hypertension (32.4%).

Treatment-emergent AEs occurring in >15% of total population, n (%)	Any grade (N=37)	Grade 3+ (N=37)	SAE (N=37)
Fatigue	19 (51.4)	–	–
Neutropenia[a]	17 (45.9)	16 (43.2)	–
Hypertension	12 (32.4)	3 (8.1)	–
Constipation	9 (24.3)	–	–
Contusion[b]	9 (24.3)	–	1 (2.7)
Dyspnea	9 (24.3)	1 (2.7)	–
Thrombocytopenia[c]	9 (24.3)	3 (8.1)	–
Anemia	7 (18.9)	5 (13.5)	1 (2.7)
Diarrhea	7 (18.9)	–	–
Headache	7 (18.9)	–	–
Pruritis	7 (18.9)	–	–
Atrial fibrillation/Atrial flutter[d]	6 (16.2)	3 (8.1)	2 (5.4)
Confusional state	6 (16.2)	–	1 (2.7)
Nausea	6 (16.2)	–	–
Petechiae	6 (16.2)	–	–
Rash maculo-papular	6 (16.2)	–	–

[a]Aggregate of "neutropenia" and "neutrophil count decreased"; [b]Contusion includes episodes of bruising and other similar terms; [c]Aggregate of "thrombocytopenia" and "platelet count decreased"; [d]Cases were confounded by risk factors such as: previous BTKi, previous atrial fibrillation, pulmonary infection, hypertension, and age.

Two additional subjects were dosed, but not included in the total count of N=37 since their dosing information was not available at data cutoff.

Data cutoff: January 14, 2023

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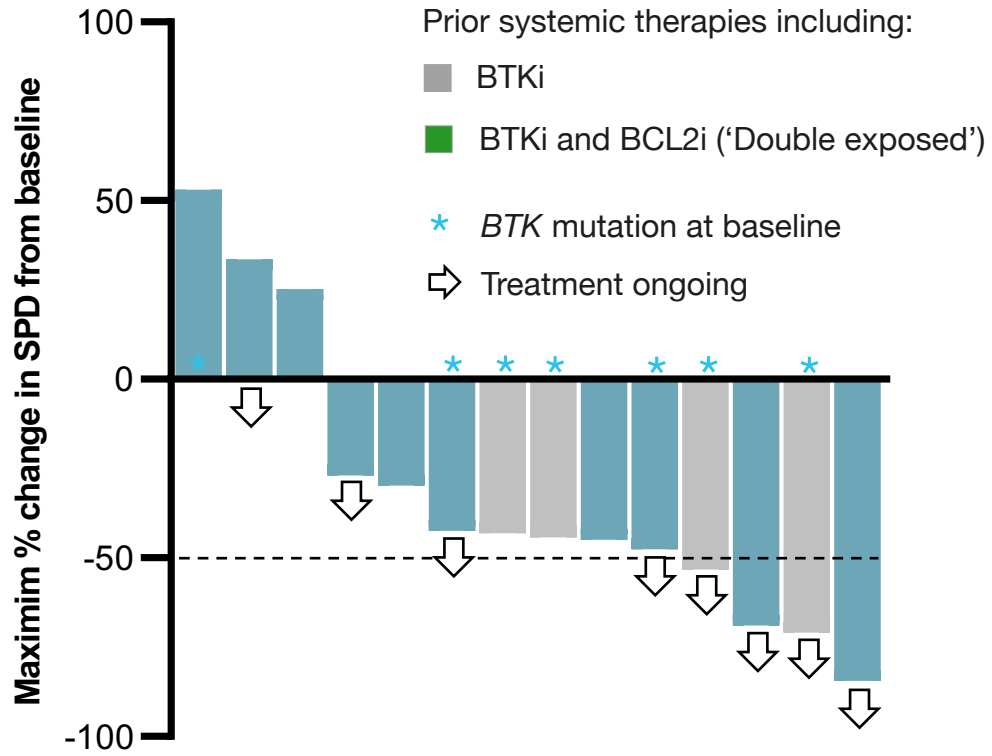
Danilov A et al, ICML 2023 (abstract #426)

NX-2127 preliminary efficacy (patients with CLL)

Disease-evaluable patients	n=15
Objective response rate,[a] % (95% CI)	33 (12–62)
Best response, n (%)	
CR	0 (0)
PR	5 (33.3)
SD	5 (33.3)
PD	2 (13.3)
NE[b]	3 (20)

[a]Objective response rate includes CR + CRi + nPR + PR-L + PR
[b]Patients who discontinued after a single assessment of SD are considered as NE



***One patient, not shown above, with prior BTKi and BCL2i treatment and with a *BTK* mutation detected at baseline, had no nodal disease at baseline and is currently ongoing with PR**

BCL2i, B cell lymphoma-2 inhibitor; **BTK**, Bruton's tyrosine kinase; **BTKi**, BTK inhibitor; **CR**, complete response; **CRi**, complete response with incomplete count recovery; **NE**, not evaluable; **PD**, progressive disease; **PR**, partial response; **SD**, stable disease

Data cutoff: September 21, 2022

Mato A et al, ASH 2022

Conclusions

- Targeted agents have always been sought for the treatment of patients with cancer
  - BTKi closest to fulfilling this dream
    - Covalent BTKi
    - Non-Covalent BTKi
    - BTK degraders
  - Resistance and toxicity remain issues
- BH3 mimetics (BCL-2i) with established role in CLL and being explored in other NHL subtypes in combination
- CELMoDs present a potential upgrade with respect to IMiDs but data is immature thus far.
- PI3Ki have copa for now and possible Duvelisib for CLL only

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- Alexey Danilov MD, PhD
- Leslie Popplewell MD
- CRNs and CRCs

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Questions

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