Emerging Therapies for Relapsed / Refractory CLL

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WGW Disclosures

- Consultancy fees
  - None
- Honoraria
  - None
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  - None
- Stock ownership
  - None
- Royalties
  - None

Standard Treatments for Rel / Ref CLL by Disease Characteristics

- **Relapsed / Refractory CLL - Durable disease control**
  - Del(17p) / m-*TP53*
  - Age / comorbidities
  - Prior CIT
  - Prior BTK-inhibitor ± CIT
  - Fludarabine-refractory (CIT)
  - BTKi-refractory / m-BTK/m-PLCG2
  - Idelalisib-refractory

Treatment Options:

- BTK-inhibitor
- BCL-2-inhibitor ± CD20 mAb
- PI3K-inhibitor + rituximab
- Lenalidomide ± CD20 mAb
- ~~CIT~~
- Allo-SCT
- Clinical Trial

BTKi- *vs.* BCL-2i-based Treatment

BTK Inhibitor[1-4]

- Easy initiation
- Continuous and indefinite therapy
- Very low TLS risk
- More cardiac risk
- Some favor in del(17p)/ mutated-*TP53*
- Activity in nodal disease

BCL-2 Inhibitor[4,5]

- Risk for TLS requires monitoring for initiation
- Includes CD20 mAb – immunosuppression
- Fixed duration
- GFR sensitivity
- Concern for del(17p)/mutated-*TP53*
- Activity in BM and blood

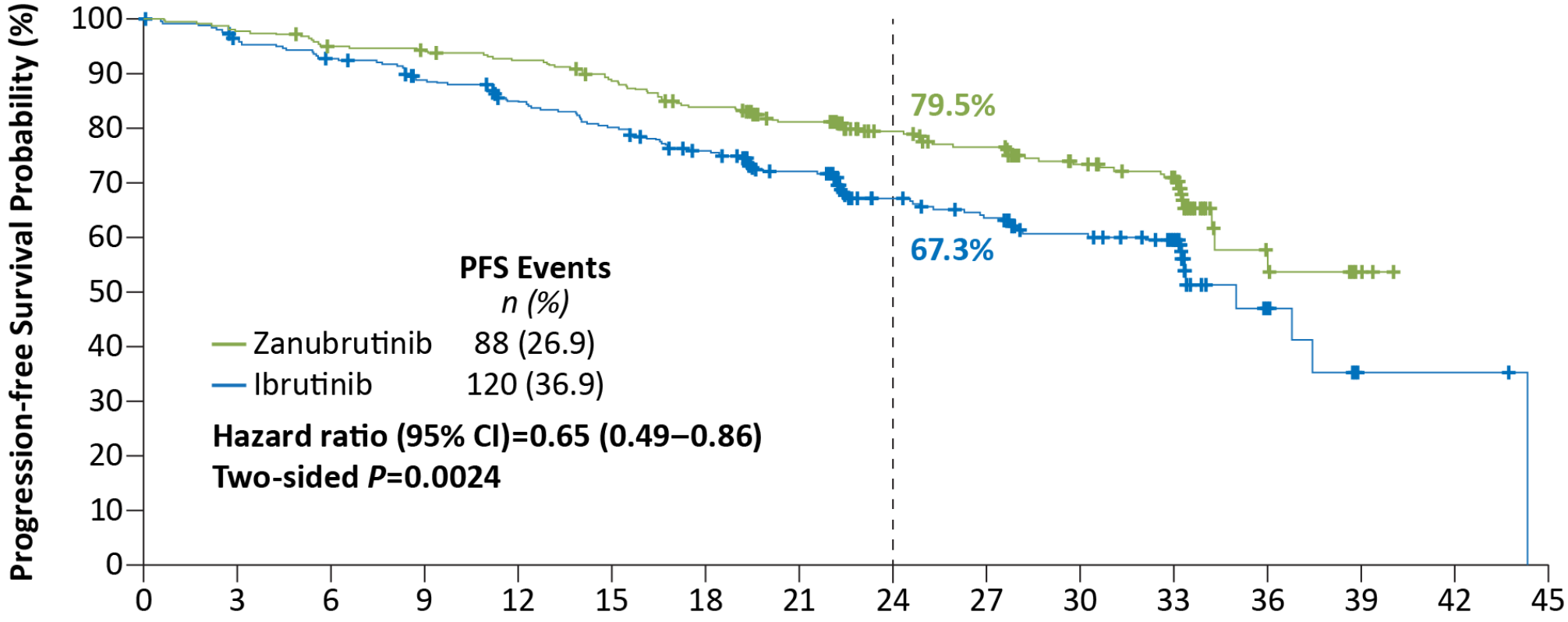
1. Acalabrutinib PI. 2. Ibrutinib PI. 3. Zanubrutinib PI. 4. Awan. Am Soc Clin Oncol Educ Book. 2020;40:1. 5. Venetoclax PI.

Advances in Treatments for Rel / Ref CLL
ASH 2022

- **ALPINE: Zanubrutnib superior PFS and ORR over ibrutinib in R/R CLL**
- **Combined IBR + VEN (CLARITY) highly active in R/R CLL**
- **Venetoclax consolidation feasible in patients on IBR ≥12 months with potential for clinical benefit (discontinue treatment, long remission)**
- **Pirtobrutinib effective for prior BTKi-treated CLL, including with C481 mutation**
- **BTK-degrader (NX-2127) tolerated with activity – novel mechanism of action**
- **New BCL2 inhibitors (BGB-11417 and Lisaftoclax) have activity and being combined with cBTKi and CD20 mAb**
- **Protein kinase C-beta inhibitor (PKCβi) - MS-553 tolerated with activity in BTKi-treated CLL being evaluated alone and in combinations**

ALPINE: Zanubrutinib PFS by IRC Superior to Ibrutinib

Median study follow-up of 29.6 months

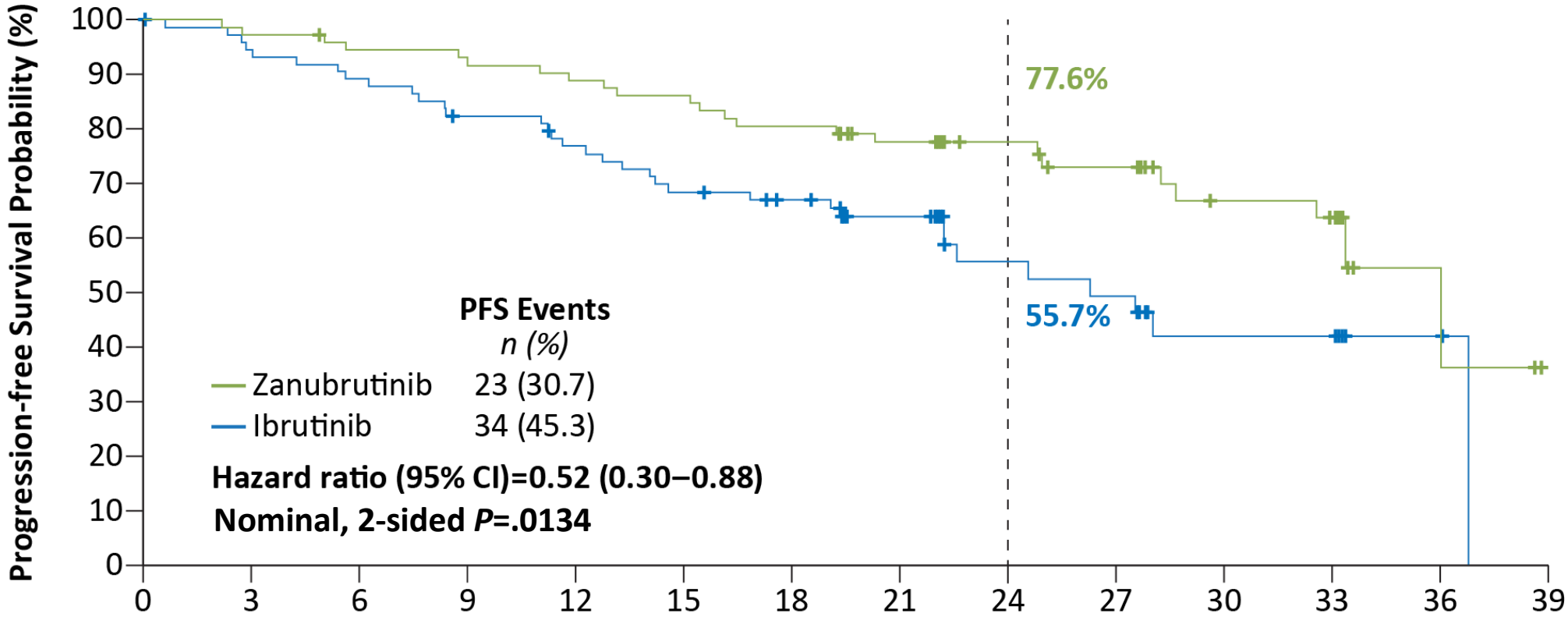


No. at Risk															
Zanubrutinib	327	315	304	301	294	280	263	226	172	161	125	113	14	2	0
Ibrutinib	325	305	293	277	260	246	228	191	133	123	98	87	9	2	2	0

Data cutoff: 8 Aug 2022

Brown et al. ASH 2022, LBA-6

ALPINE: Zanubrutinib Improved PFS in Patients with del(17p)/*TP53*^{mut}

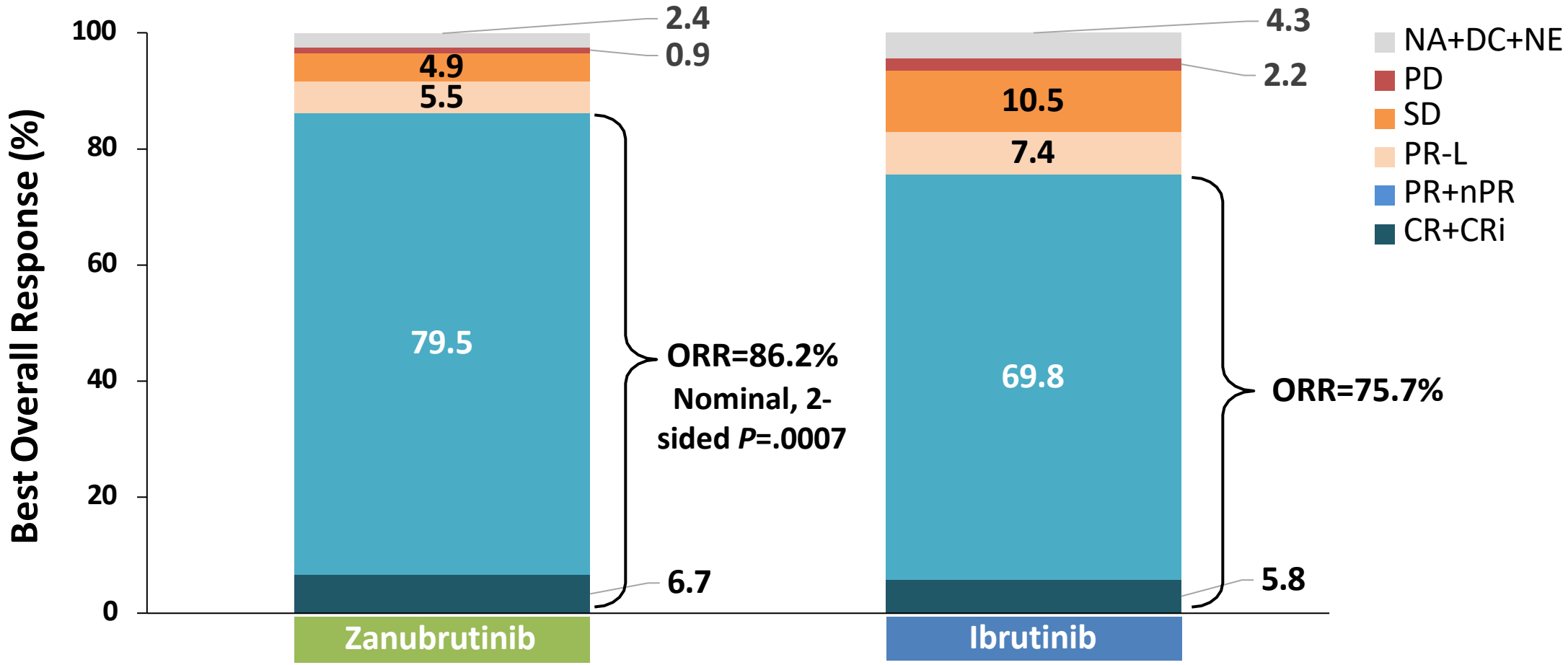


No. at Risk														
Zanubrutinib	75	71	68	67	64	62	58	49	35	30	21	19	3	0
Ibrutinib	75	70	66	60	55	49	45	34	18	16	10	10	2	0

PFS data assessed by IRC

Data cutoff: 8 Aug 2022

ALPINE: Zanubrutinib Showed Higher ORR Assessed by IRC

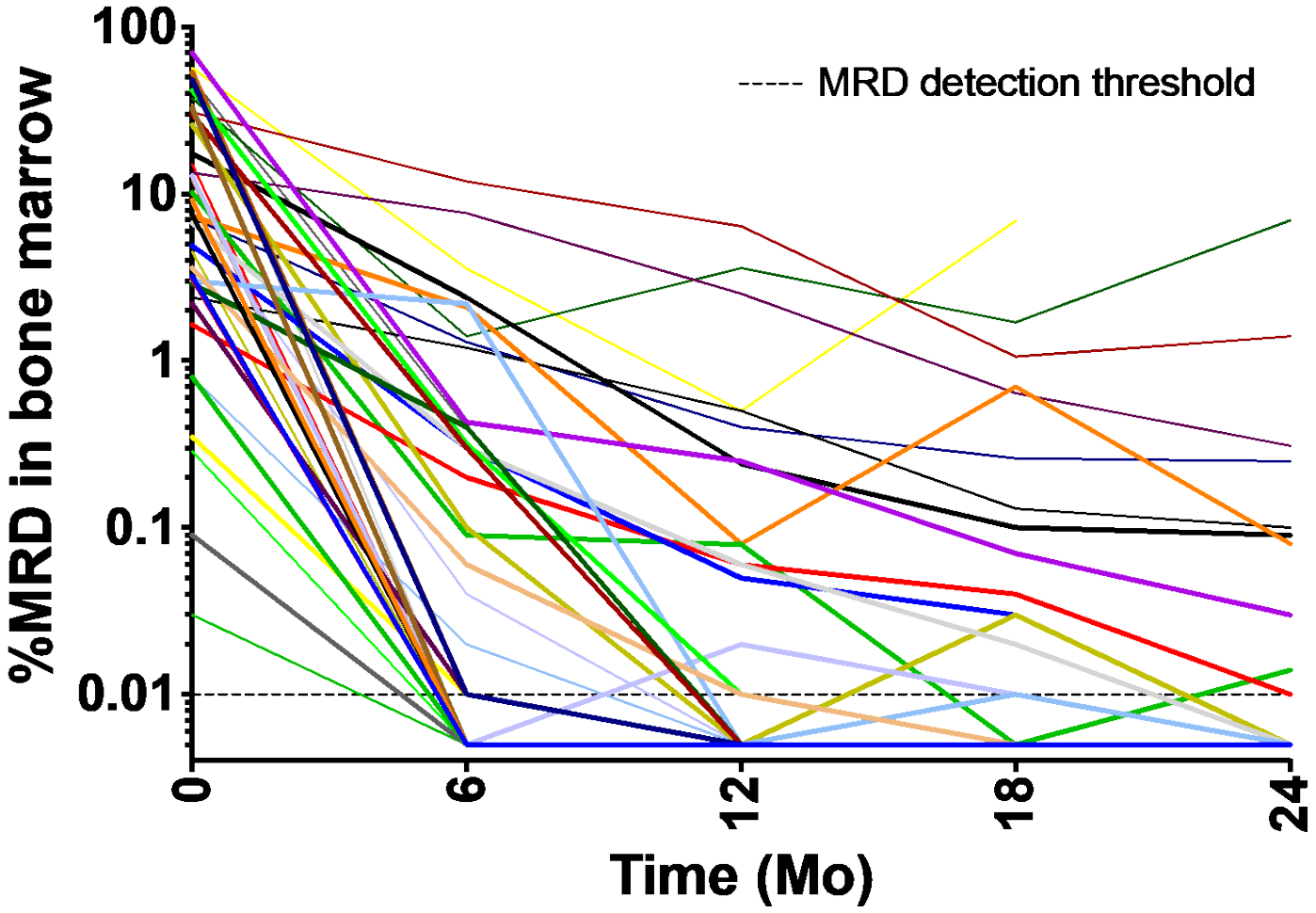


CR, complete response; CRi, complete response with incomplete bone marrow recovery; nPR, nodular partial response; PR, partial response; PR-L, partial response with lymphocytosis; SD, stable response; PD, progressive disease; NA, not assessed; DC, discontinued prior to first assessment; NE, not evaluable.

Data cutoff: 8 Aug 2022

Venetoclax added to ibrutinib in high-risk CLL

MRD results



- **CLL/SLL on IBR ≥12 mo with measurable MRD, no PD, ≥1 high-risk feature:**
  - Del(17p) and/or TP53-m
  - Del(11q)
  - Complex karyotype
  - Elevated B2M

- 17/45 pts (38%) post-C6 and 26/45 (57%) post-C12 achieved U-MRD4.

- 6/16 patients MRD+ at C12 converted to U-MRD4 at C24

- Best cumulative rate of U-MRD4 in bone marrow was 33/45 (73%)

- 32/45 (71%) had U-MRD4 at the completion of venetoclax

Thompson et al. ASH 2022, Abstract #96

Venetoclax added to ibrutinib in high-risk CLL

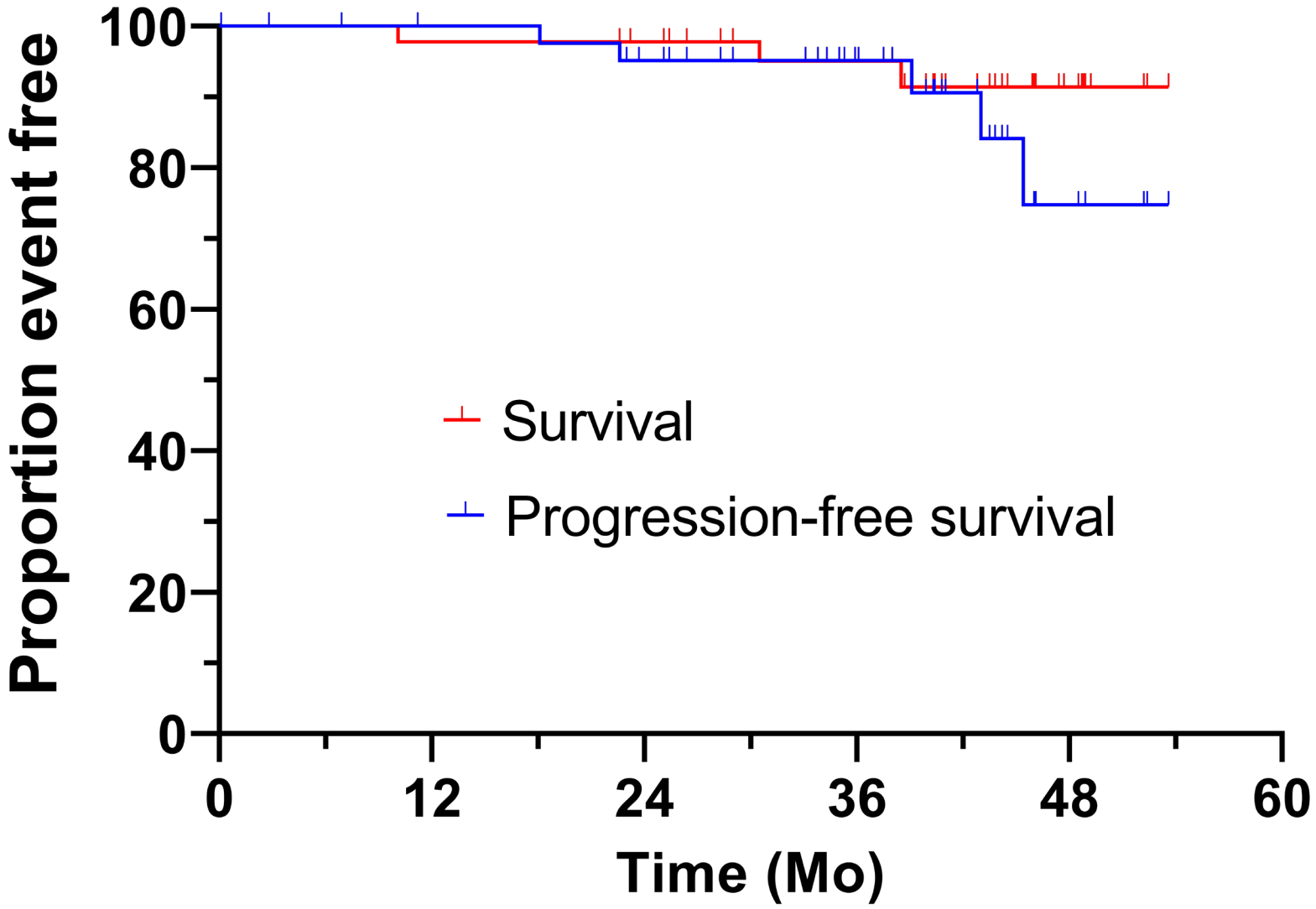
U-MRD according to pre-treatment characteristics

Pre-treatment characteristic (N=45 unless stated)	Number with U-MRD4	Odds ratio, P value
TP53 deletion and/or mutation, n=41	n (%) unless stated	
Yes, n=26	17 (65%)	0.5 (0.1-2.0), p=0.32
No, n=15	12 (80%)	
Complex Karyotype, n=38		
Yes, n=11	8 (73%)	1.3 (0.3-6.3), p=0.61
No, n=27	18 (67%)	
Treatment prior to ibrutinib		
Treatment-naïve, n=22	18 (82%)	0.3 (0.1-1.4), p=0.12
Previously treated, n=23	14 (61%)	

Thompson et al. ASH 2022, Abstract #96

Venetoclax added to ibrutinib in high-risk CLL

PFS and OS

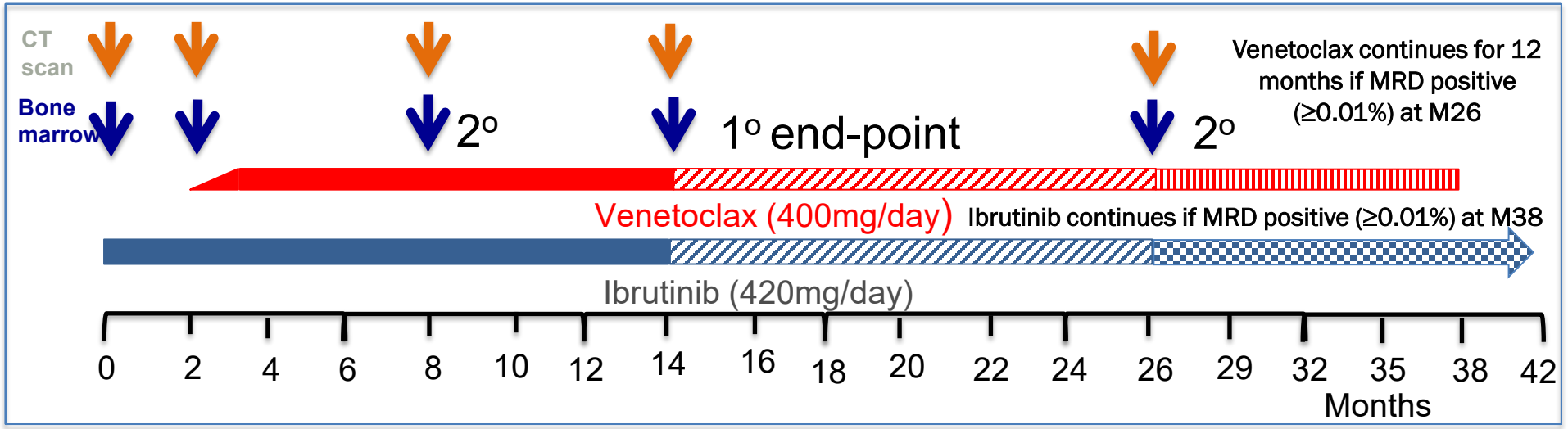


Causes of death:

1. Metastatic melanoma.
2. AML.
3. Unknown in a patient who was lost to follow-up

Thompson et al. ASH 2022, Abstract #96

Treatment Schedule and Stopping Rules- Amendment allowed addition of 3rd year of Venetoclax

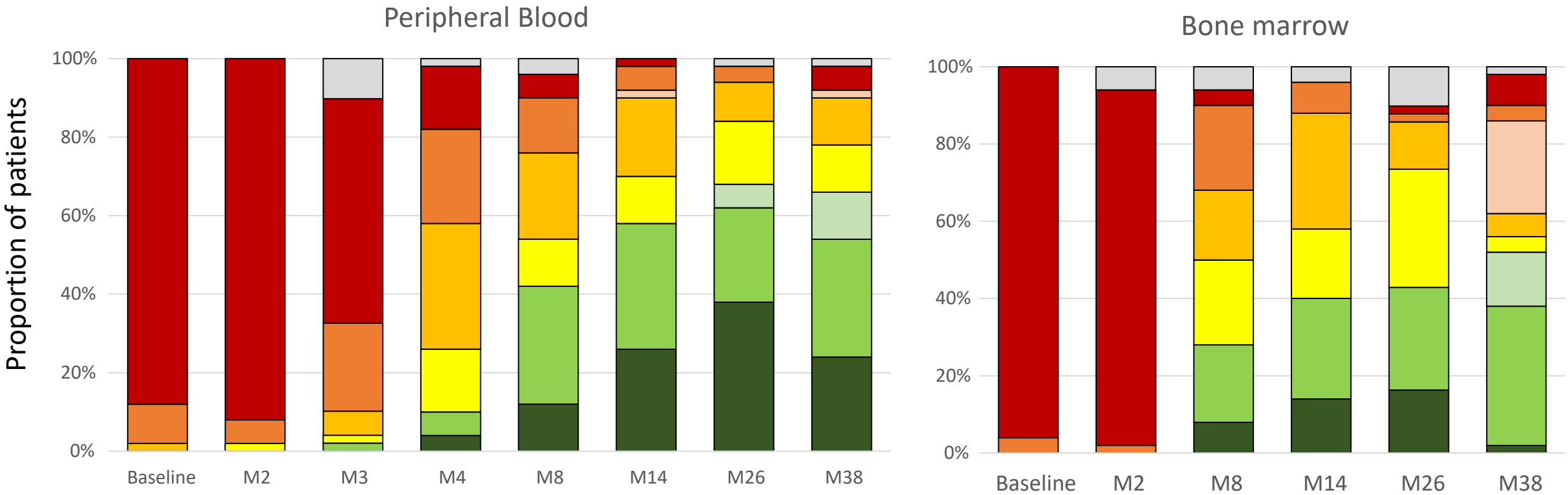


<u>Duration of VEN therapy</u>: 3 consecutive MRD4 (<0.01% CLL) in PB confirmed in BM:
MRD <0.01% at M8 → stop I+V at M14; MRD <0.01% at M14 → stop I+V at M26
MRD negative (<0.01%) at M26 → stop I+V at M26, if MRD positive (≥0.01%) continue IBR till PD
<u>Amendment:</u> if MRD positive (≥0.01%) at M26, Additional Ven for 12 months.

Munir et al. ASH 2022, Abstract #91

IBR + VEN for R/R CLL

PB and BM MRD responses at various time points

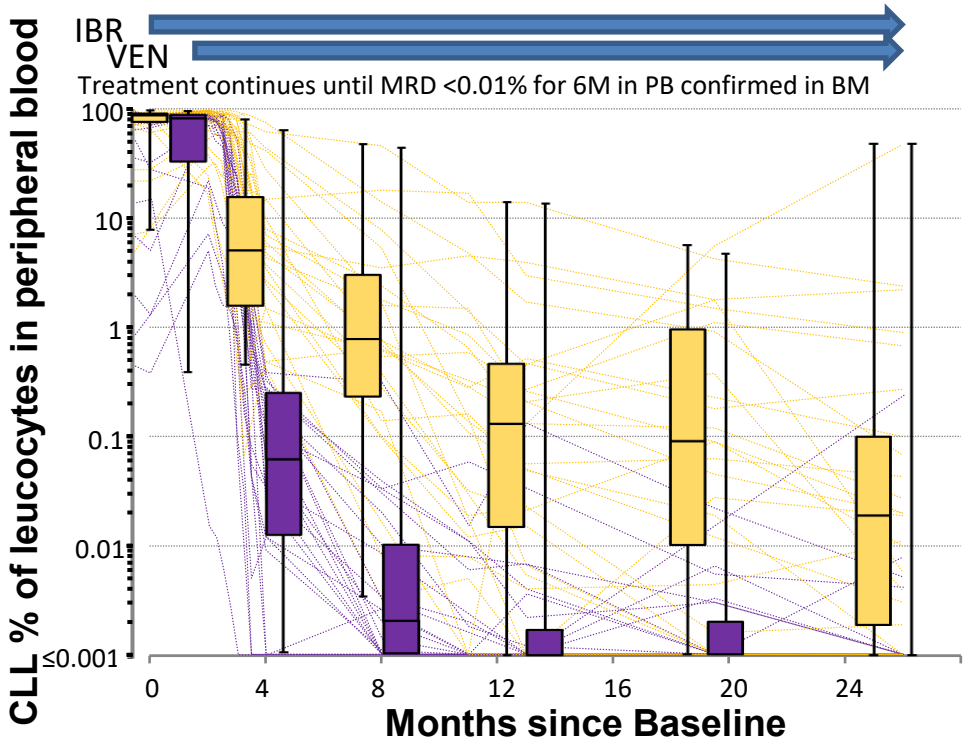


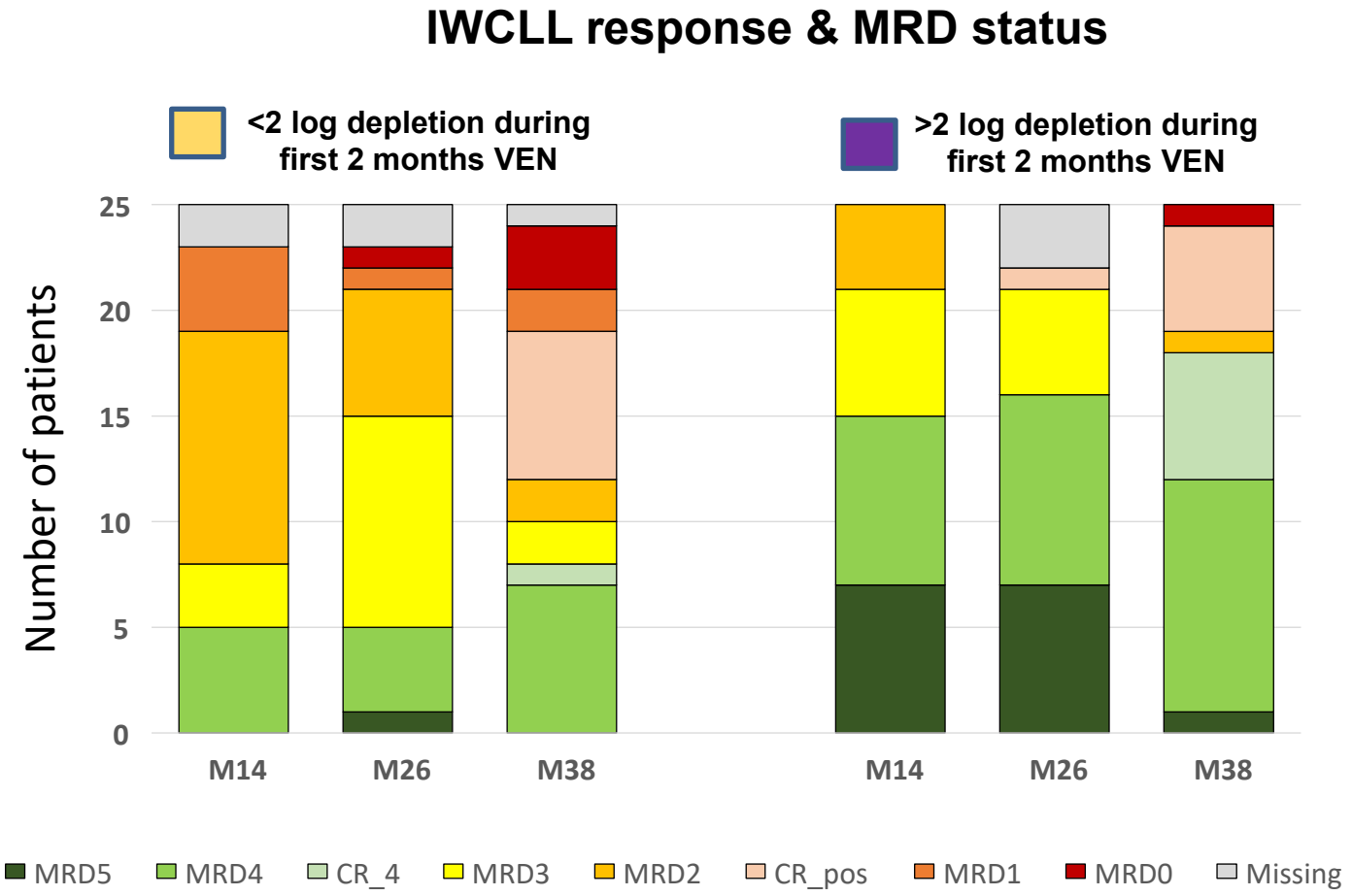
MRD4 includes imputed MRD4 (previous BM <0.01% and current PB <0.001%)
CR_4: previous BM MRD4/5 and remains in clinical remission with PB MRD4/5 where tested
CR_pos: remains in clinical remission with MRD>0.01% or not known
MRD0 includes MRD status unknown but clinical PR
Missing includes 1 dead

Munir et al. ASH 2022, Abstract #91

Date of data lock: 01-Nov-2022

IBR + VEN for R/R CLL
Response correlates with initial depletion rate

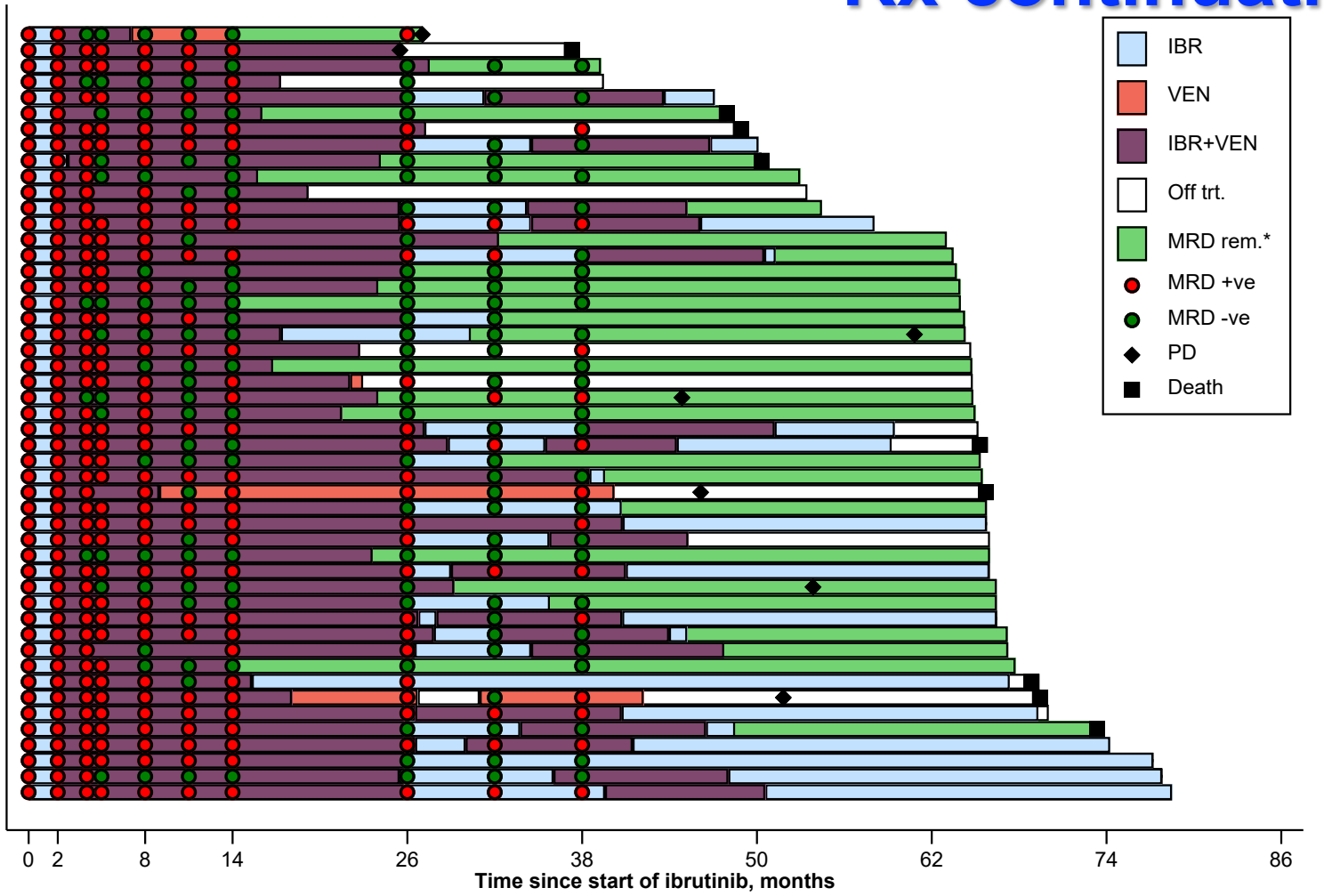




Munir et al. ASH 2022, Abstract #91

Date of data lock: 01-Nov-2022

IBR + VEN for R/R CLL
Change in MRD after Rx discontinuation and Rx continuation



* Stopped treatment due to MRD negative remission

- 9 patients continued on ibrutinib after 60 months
- 11 disease progression
- 9 Deaths
- 17 patients continue in uMRD ($<10^{-4}$) after discontinuation at any time point

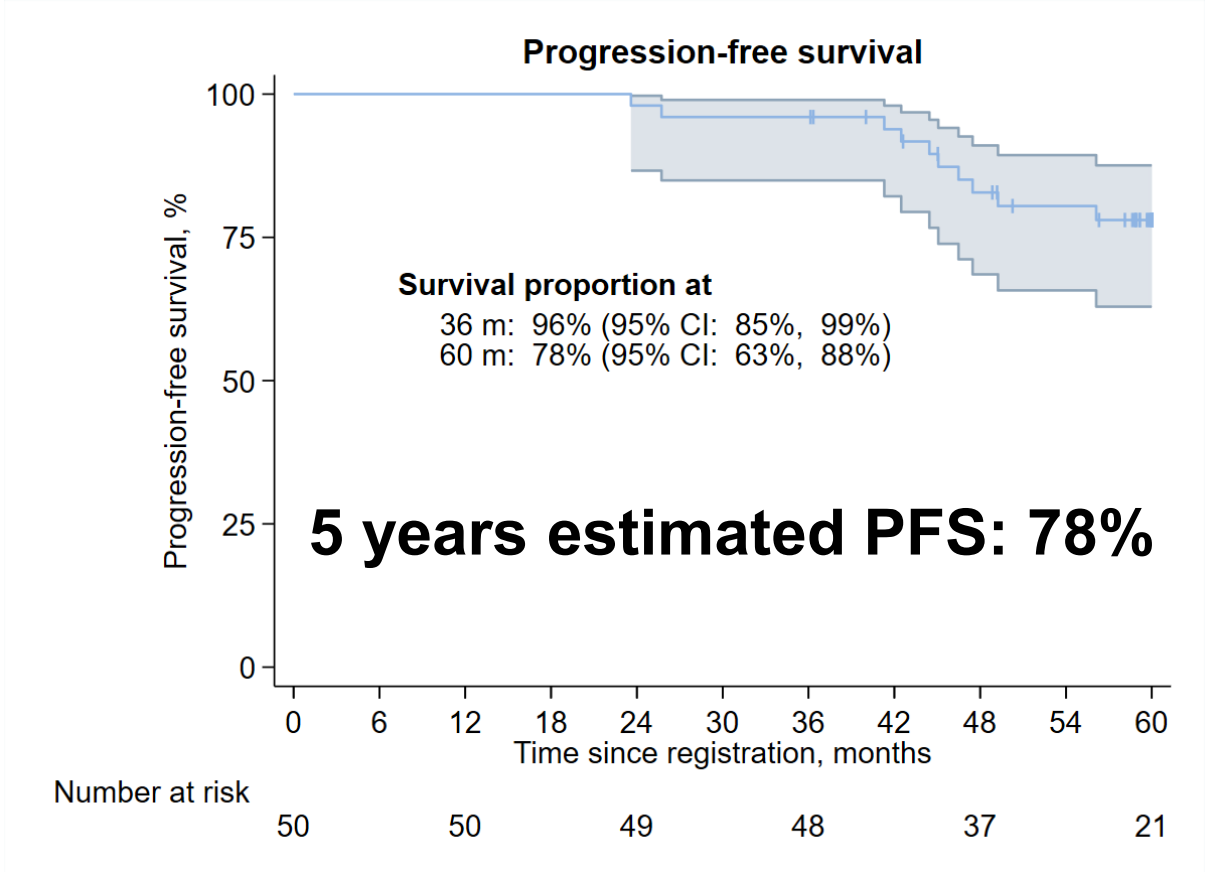
Date of data lock: 6-Nov-2020

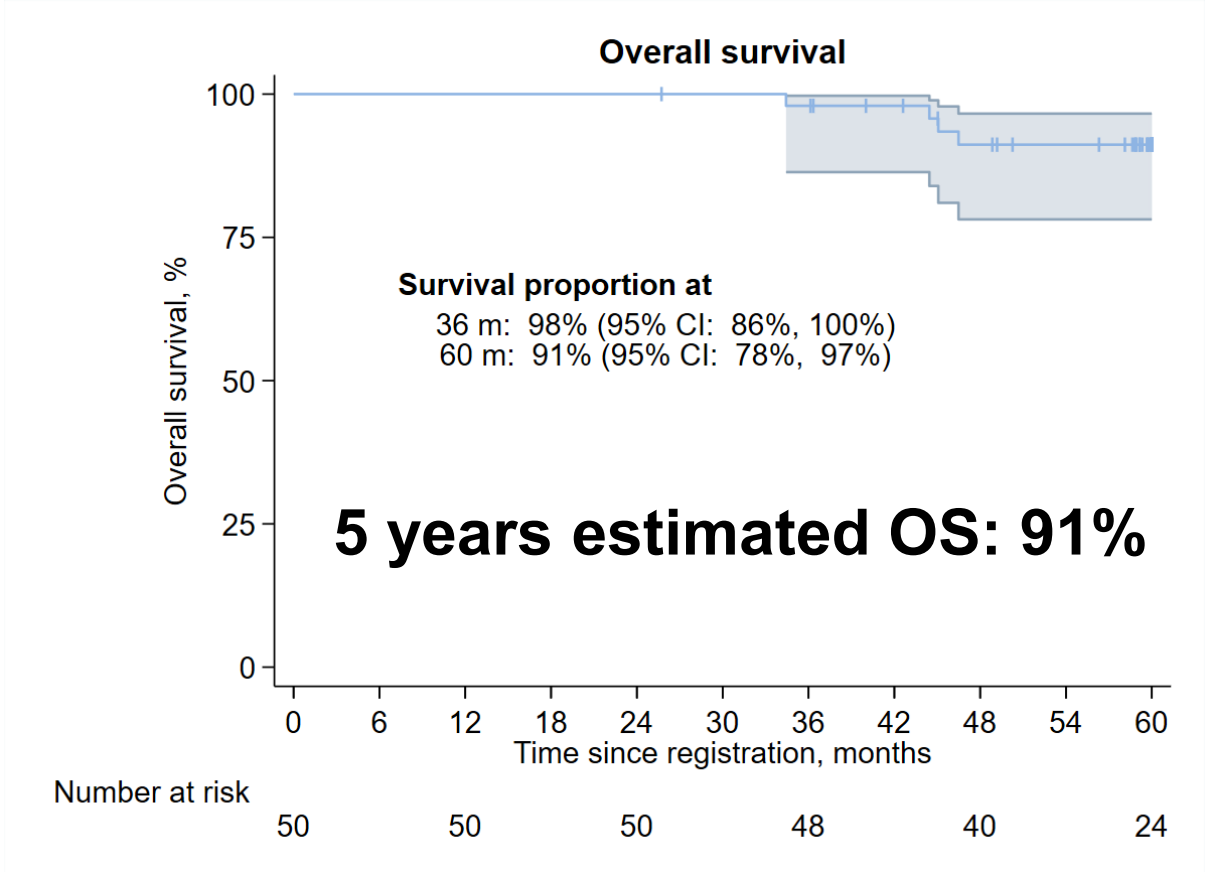
Munir et al. ASH 2022, Abstract #91

Date of data lock: 01-Nov-2022

IBR + VEN for R/R CLL Progression Free and Overall Survival (n=50)

Median PFS and OS not reached by 60 months

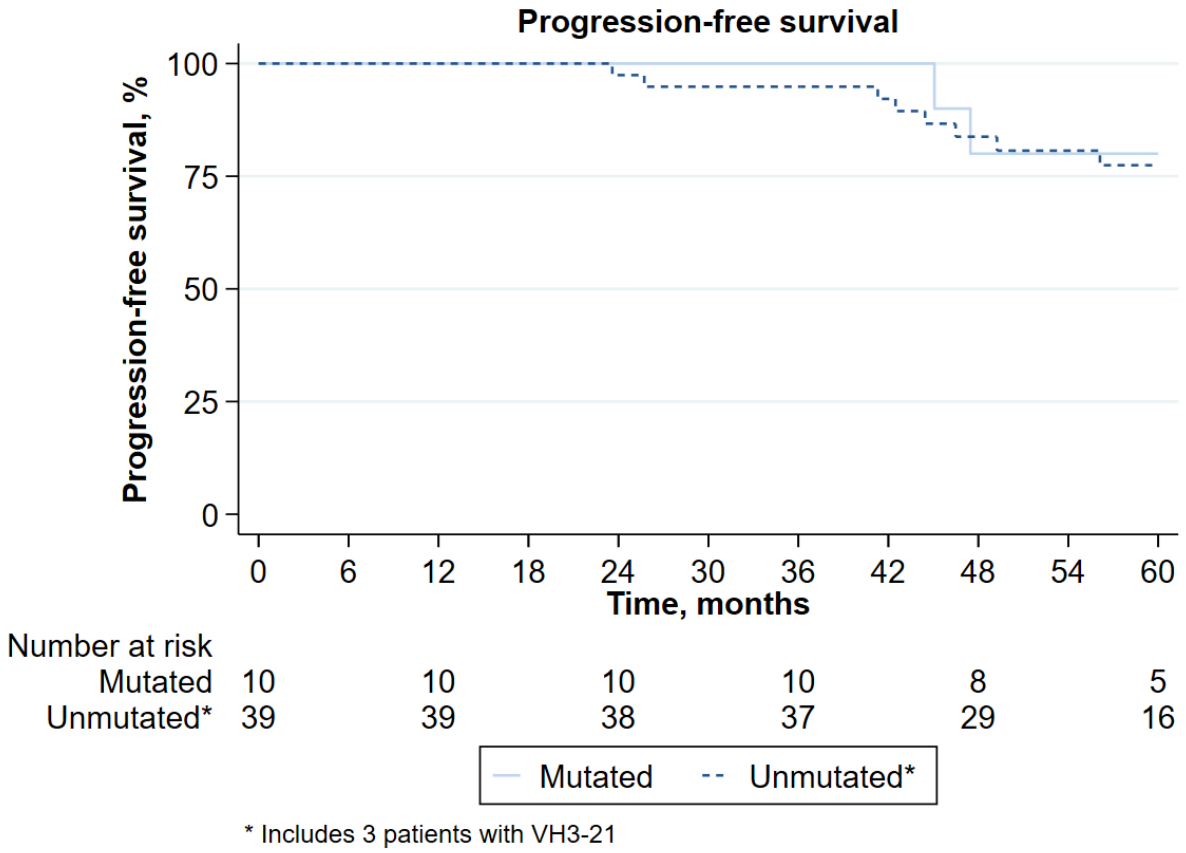


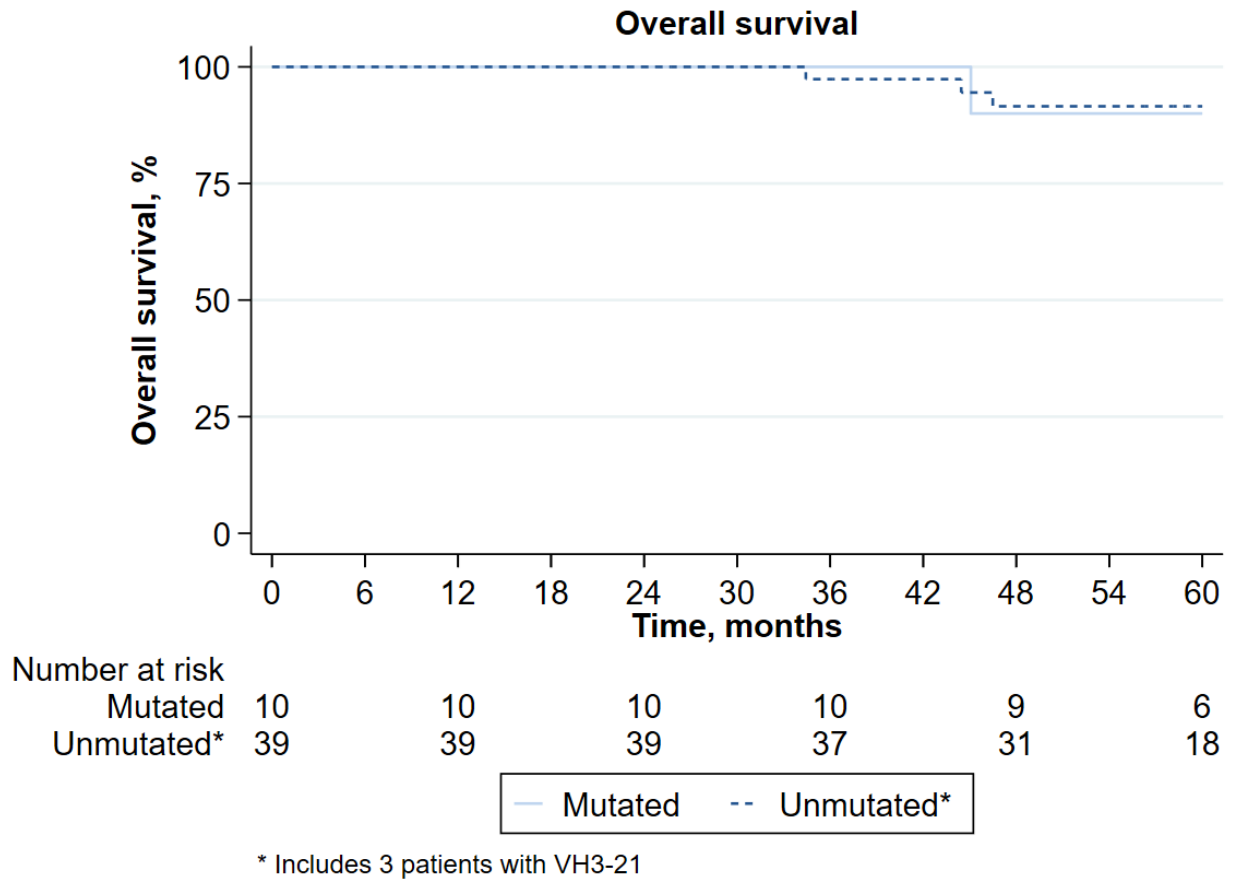


Munir et al. ASH 2022, Abstract #91

Date of data lock: 01-Nov-2022

IBR + VEN for R/R CLL Progression Free and Overall Survival based on IGHV status



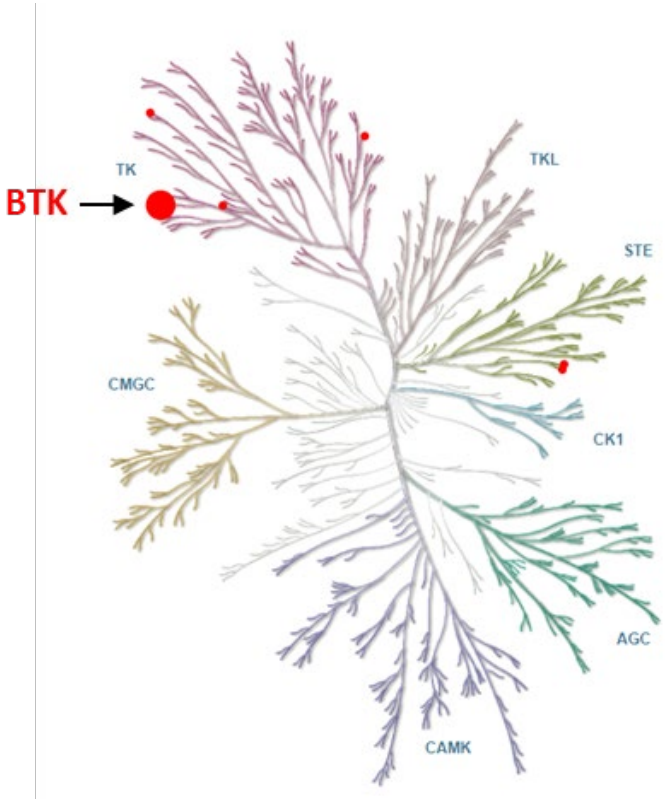


Munir et al. ASH 2022, Abstract #91

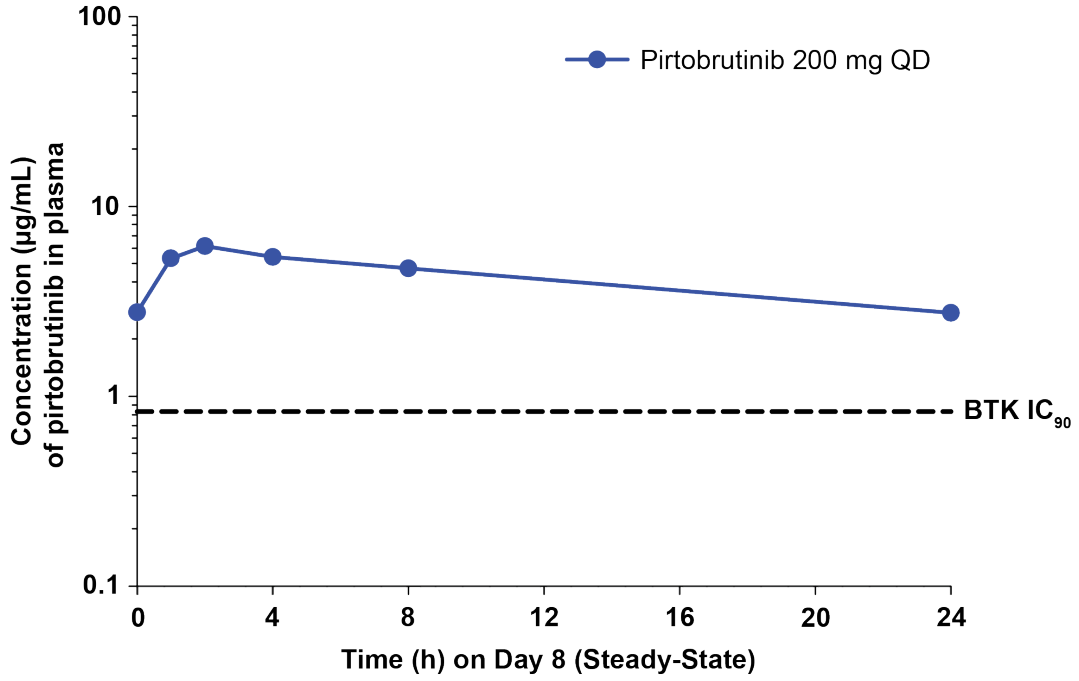
Date of data lock: 01-Nov-2022

Pirtobrutinib: Highly Selective, Non-Covalent (Reversible) BTK Inhibitor

Highly Selective for BTK[6,7]



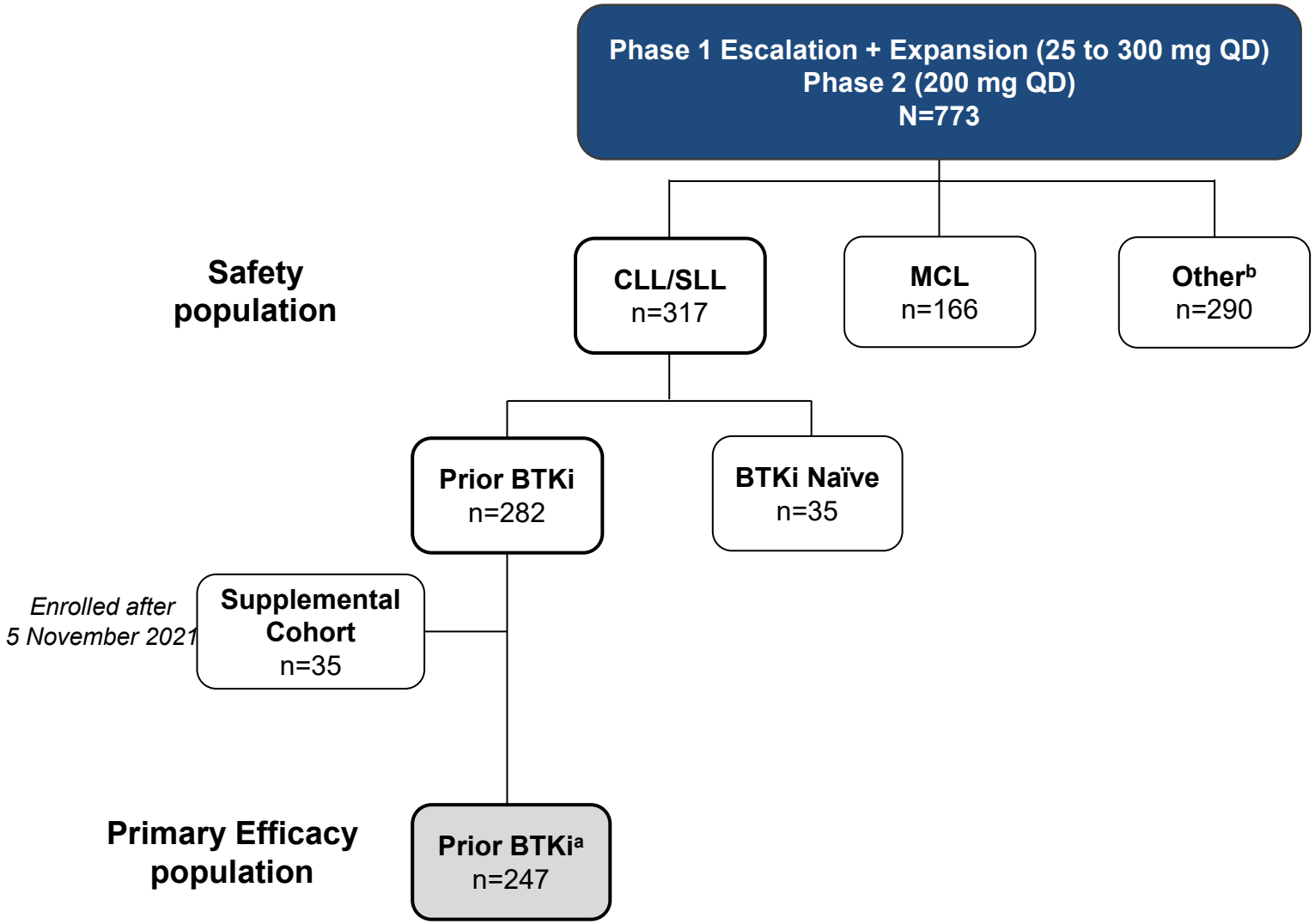
Plasma Exposures Exceeded BTK IC_{90} Throughout Dosing Interval



- Inhibits both wildtype and C481-mutant BTK with equal low nM potency, and has favorable oral pharmacology that enables continuous BTK inhibition throughout the dosing interval regardless of intrinsic rate of BTK turnover
- Pirtobrutinib is well tolerated and demonstrates promising efficacy in poor-prognosis B-cell malignancy patients following prior therapy, including prior cBTKi[1]

cBTKi, covalent Bruton tyrosine kinase inhibitor. [6]Mato et al, *Lancet*, 2021:397:892-901. [7]Brandhuber et al. *Clin. Lymphoma Myeloma Leuk*. 2018.18:S216. Illustration reproduced courtesy of Cell Signaling Technology, Inc. (www.cellsignal.com).

Phase 1/2 BRUIN Study: Design, Eligibility and Enrollment



Phase 1 3+3 design

- 28-day cycles
- Intra-patient dose escalation allowed
- Cohort expansion permitted at doses deemed safe

Eligibility

- Age ≥18
- ECOG PS 0-2
- Active disease and in need of treatment
- Previously treated

Key endpoints

- Safety/tolerability
- Determine MTD and recommended phase 2 dose
- Pharmacokinetics
- Efficacy according to ORR and DOR (iwCLL) as assessed by IRC

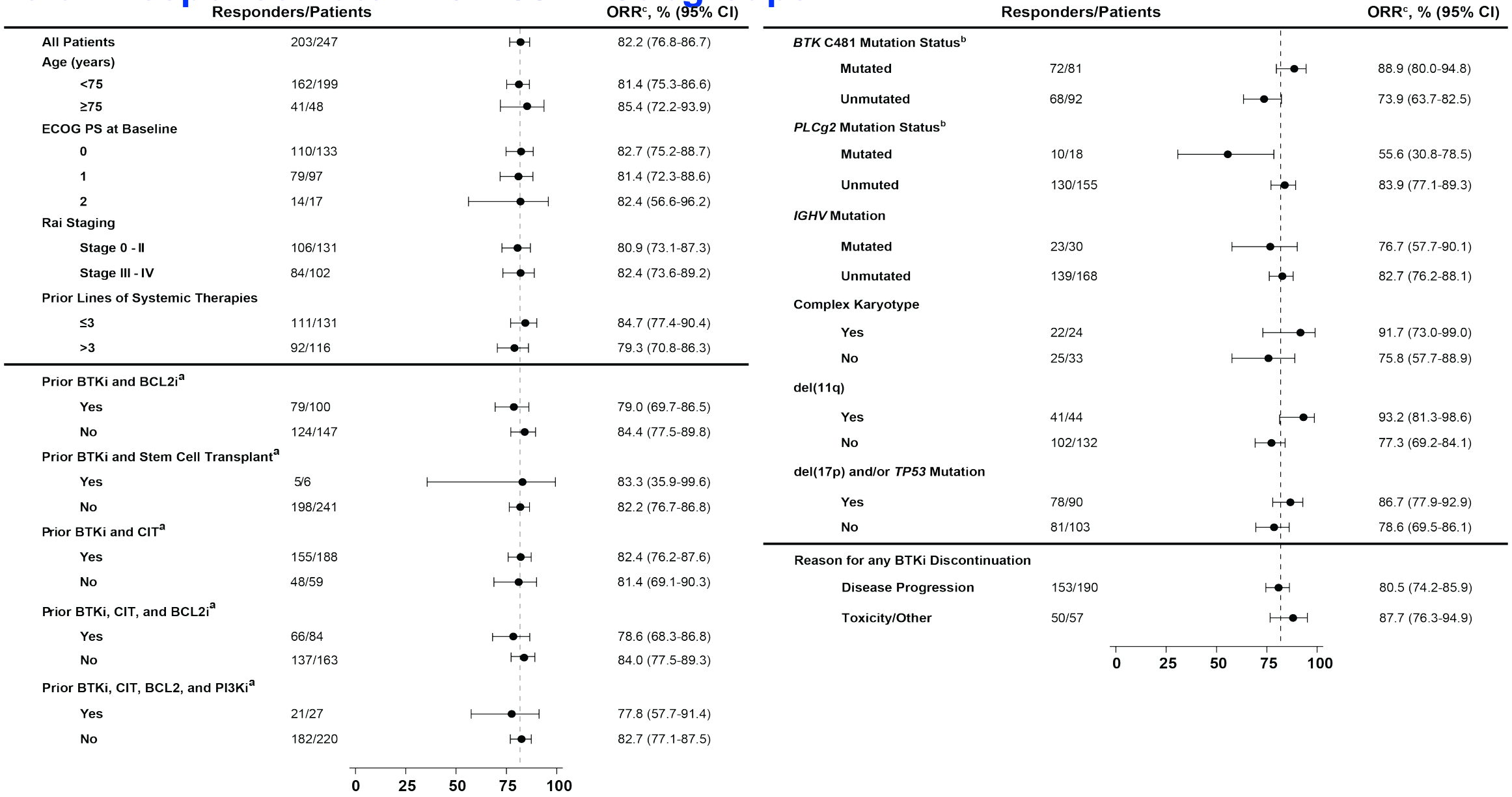
Primary efficacy population[a]

- Enrolled in phase 1 or 2
- Treated with prior BTK inhibitor containing regimen
- Received one or more doses of pirtobrutinib monotherapy

DOR, duration of response: ORR, overall response rate; ECOG PS, Eastern Cooperative Oncology Group Performance Score; MTD, maximum tolerated dose; IRC, independent review committee; QD, daily;
Data cutoff date of 29 July 2022. [a]To ensure adequate follow-up, the primary efficacy population included all CLL/SLL patients who enrolled prior to 5 November 2021. [b]Other includes DLBCL, WM, FL, MZL, Richter transformation, B-PLL, Hairy Cell Leukemia, PCNSL, and other transformation.

Mato et al. ASH 2022, Abstract #961

Pirtobrutinib:
Overall Response Rate in CLL/SLL Subgroups



Data cutoff date of 29 July 2022. [a]Prior therapy labels indicate that patients received at least the prior therapy, rows are not mutually exclusive. [b]Patients with available mutation data who progressed on any prior BTKi. [c]Response includes partial response with lymphocytosis. Response status per iwCLL 2018 according to independent review committee assessment.

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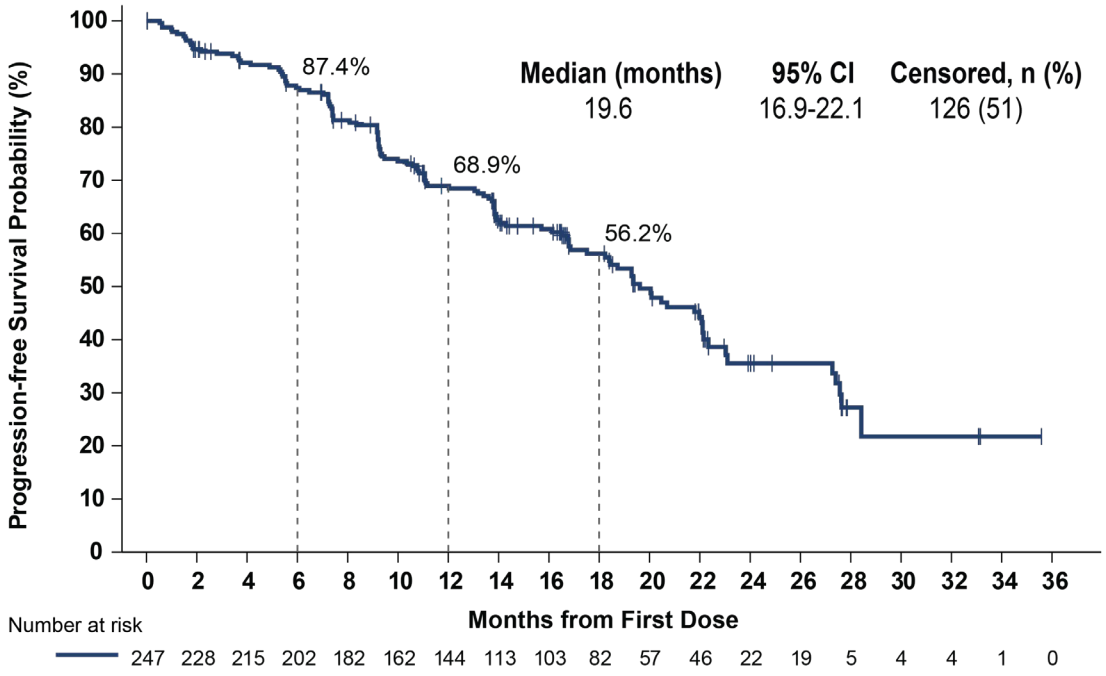
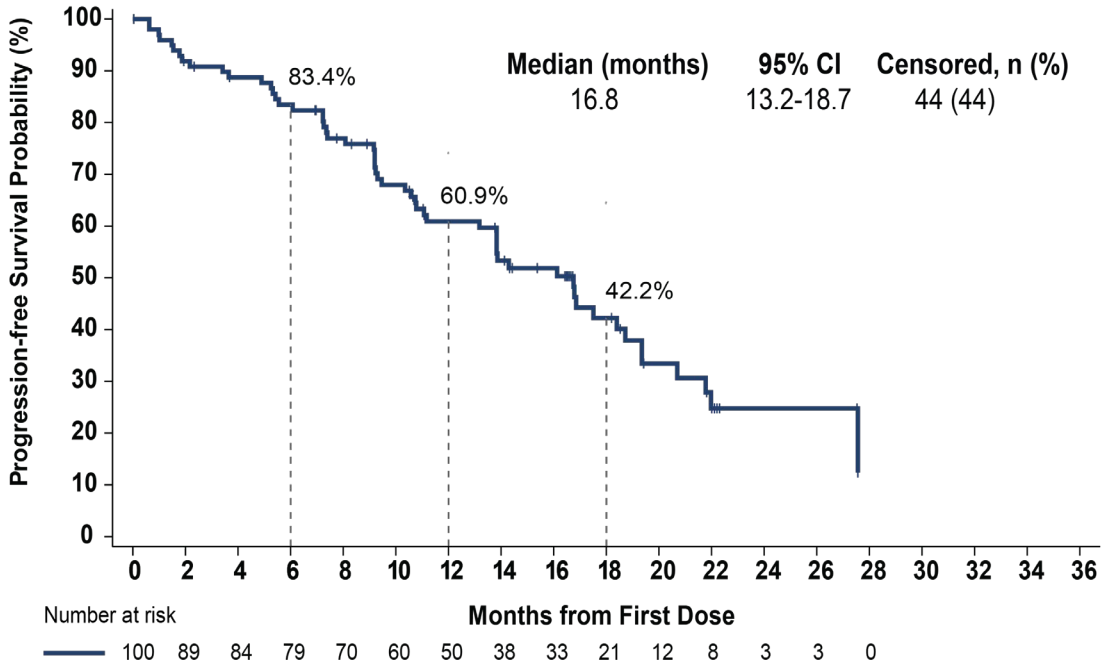
Pirtobrutinib:
Progression-Free Survival in CLL/SLL Patients who Received Prior BTKi Treatment

All prior BTKi patients
Median prior lines = 3



- Median follow-up of 19.4 months for patients who received prior BTKi

Prior BTKi and BCL2i patients
Median prior lines = 5



- Median follow-up of 18.2 months for patients who received prior BTKi and BCL2i

Data cutoff date of 29 July 2022. Response status per iwCLL 2018 according to independent review committee assessment.

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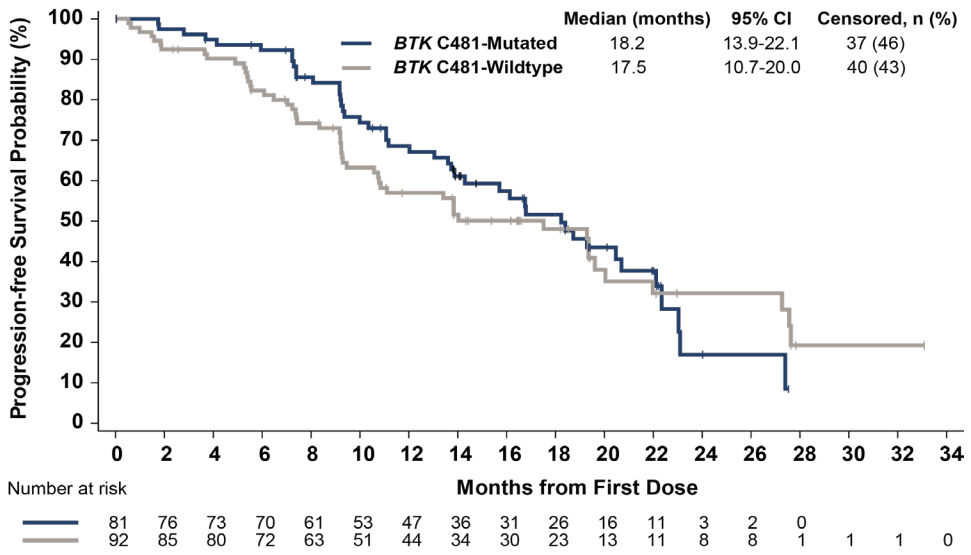
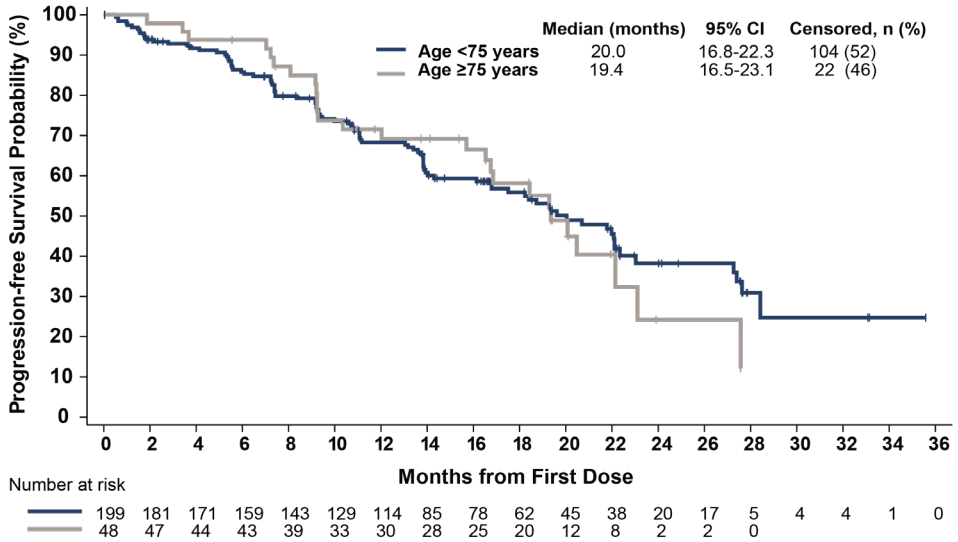
Pirtobrutinib: Progression-Free Survival in CLL/SLL Subgroups

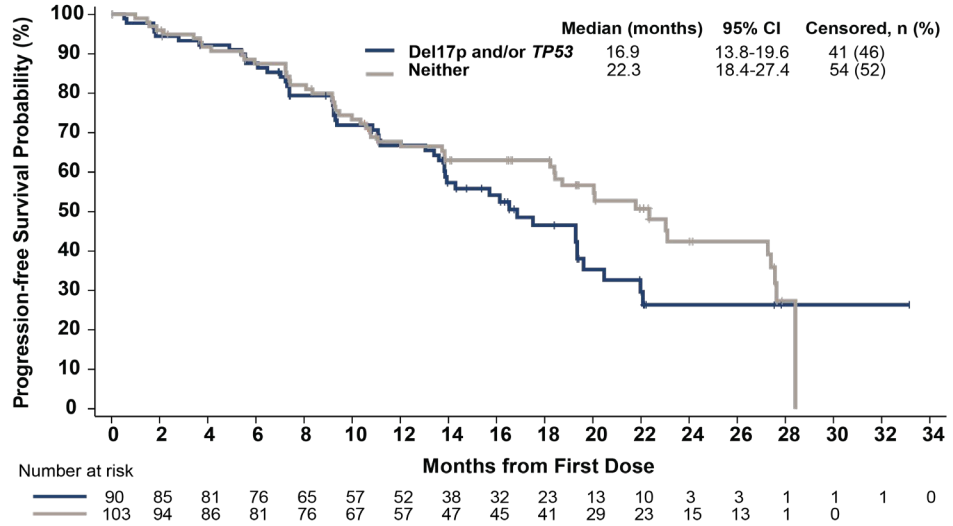
BTK C481 mutation status[a,b]



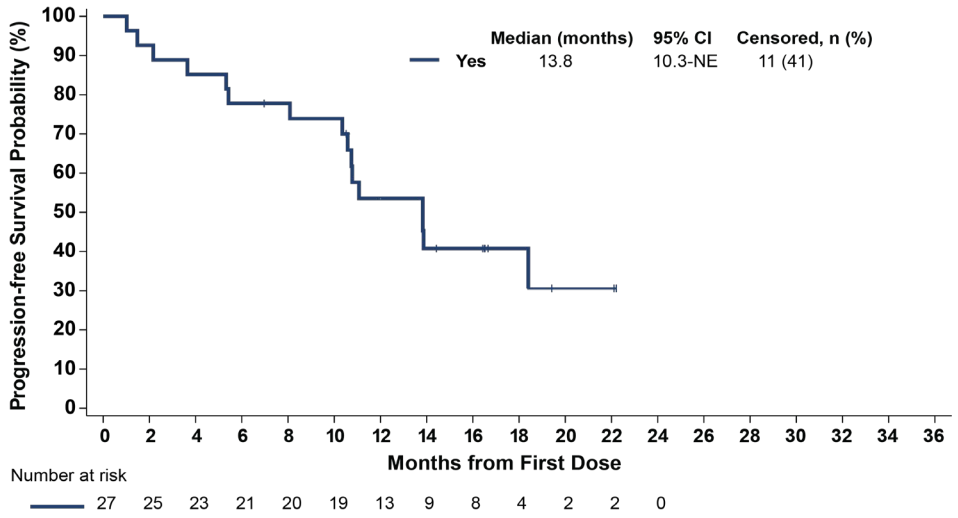
Age



del(17p) and/or *TP53* mutation[a]



Prior BTKi, CIT, BCL2i, and PI3Ki therapy



Data cutoff date of 29 July 2022. Response status per iwCLL 2018 according to independent review committee assessment. [a]*BTK* C481 mutation status, del(17p), and *TP53* mutation status were centrally determined and based on pre-treatment samples. [b]Patients with available mutation data who progressed on any prior BTKi.

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Pirtobrutinib: Safety Profile

	CLL/SLL (n=317)			
	Treatment-Emergent AEs, (≥15%), %		Treatment-Related AEs, %	
Adverse Event (AEs)	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Fatigue	31.5%	1.9%	3.5%	0.3%
Neutropenia[a]	32.5%	26.8%	19.6%	14.8%
Diarrhea	26.5%	0.6%	8.8%	0.3%
Contusion	24.3%	0.0%	16.4%	0.0%
Cough	24.3%	0.0%	1.6%	0.0%
Covid-19	24.0%	5.0%	1.6%	0.0%
Nausea	18.9%	0.0%	3.2%	0.0%
Abdominal pain	18.0%	1.6%	2.2%	0.3%
Dyspnea	17.4%	0.9%	0.6%	0.0%
Headache	17.4%	0.6%	5.4%	0.3%
Upper respiratory tract infection	16.4%	0.3%	3.5%	0.0%
Back pain	16.1%	0.9%	0.9%	0.0%
Anemia	15.1%	8.8%	4.7%	2.2%
AEs of Special Interest[b]	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Bruising[c]	30.3%	0.0%	19.6%	0.0%
Rash[d]	17.0%	0.3%	5.7%	0.3%
Arthralgia	18.3%	0.9%	4.1%	0.0%
Hemorrhage/Hematoma[e]	12.3%	2.2%	4.1%	0.9%
Hypertension	14.2%	3.5%	3.8%	0.3%
Atrial fibrillation/flutter[f,g]	3.8%	1.3%	1.3%	0.3%

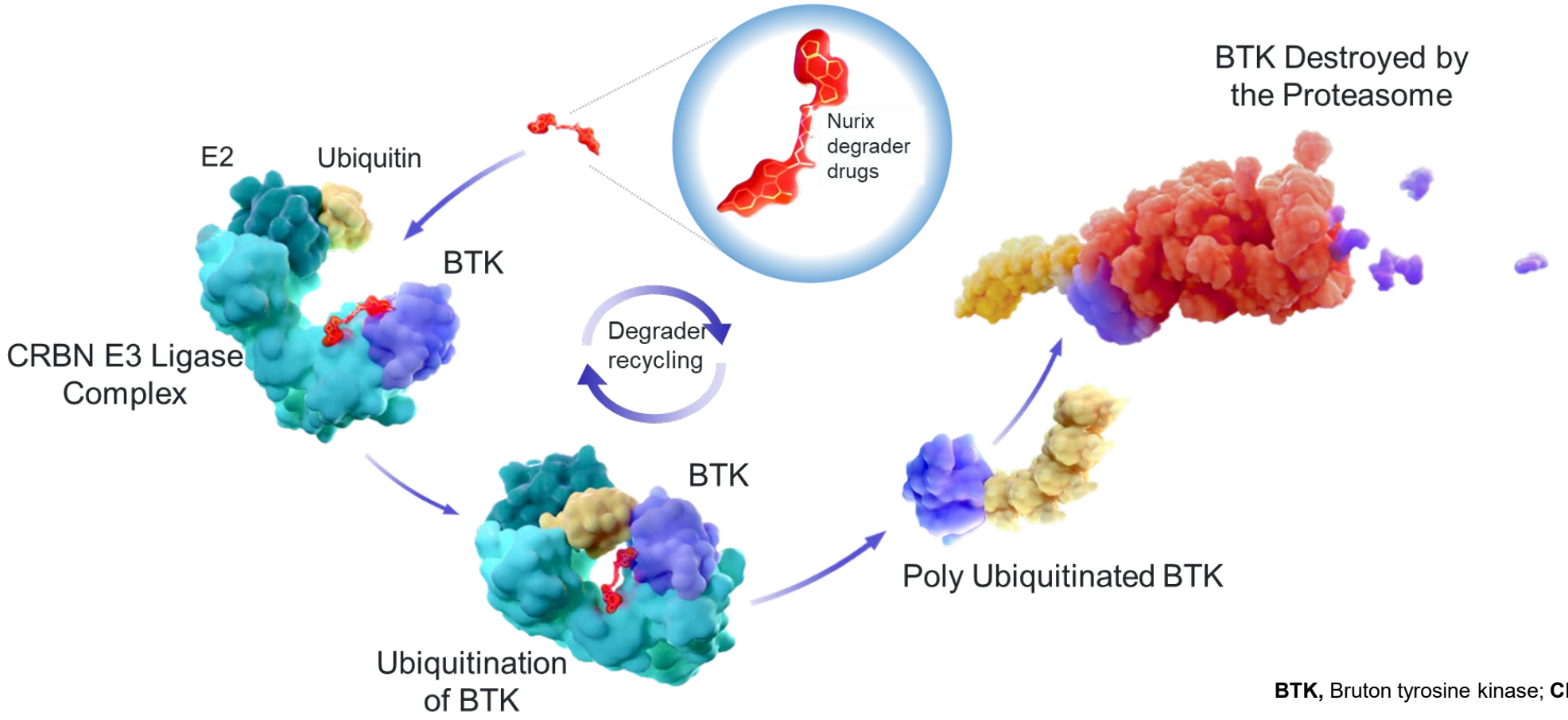
Median time on treatment for the CLL/SLL safety population was 16.5 months
Discontinuations due to treatment-related AEs occurred in 2.8% (n=9) of CLL/SLL patients
Dose reductions due to treatment-related AEs occurred in 4.7% (n=15) of CLL/SLL patients

Data cutoff date of 29 July 2022. [a]Aggregate of neutropenia and neutrophil count decreased. [b]AEs of special interest are those that were previously associated with covalent BTK inhibitors. [c]Aggregate of contusion, petechiae, ecchymosis, and increased tendency to bruise. [d]Aggregate of all preferred terms including rash. [e]Aggregate of all preferred terms including hematoma or hemorrhage. [f]Aggregate of atrial fibrillation and atrial flutter. [g]Of 12 total afib/aflutter TEAEs in the CLL/SLL safety population, 3 occurred in patients with a prior medical history of atrial fibrillation.

Mato et al. ASH 2022, Abstract #961

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

Utilizing the ubiquitin-proteasome pathway to degrade BTK, a well-validated target in B-cell malignancies

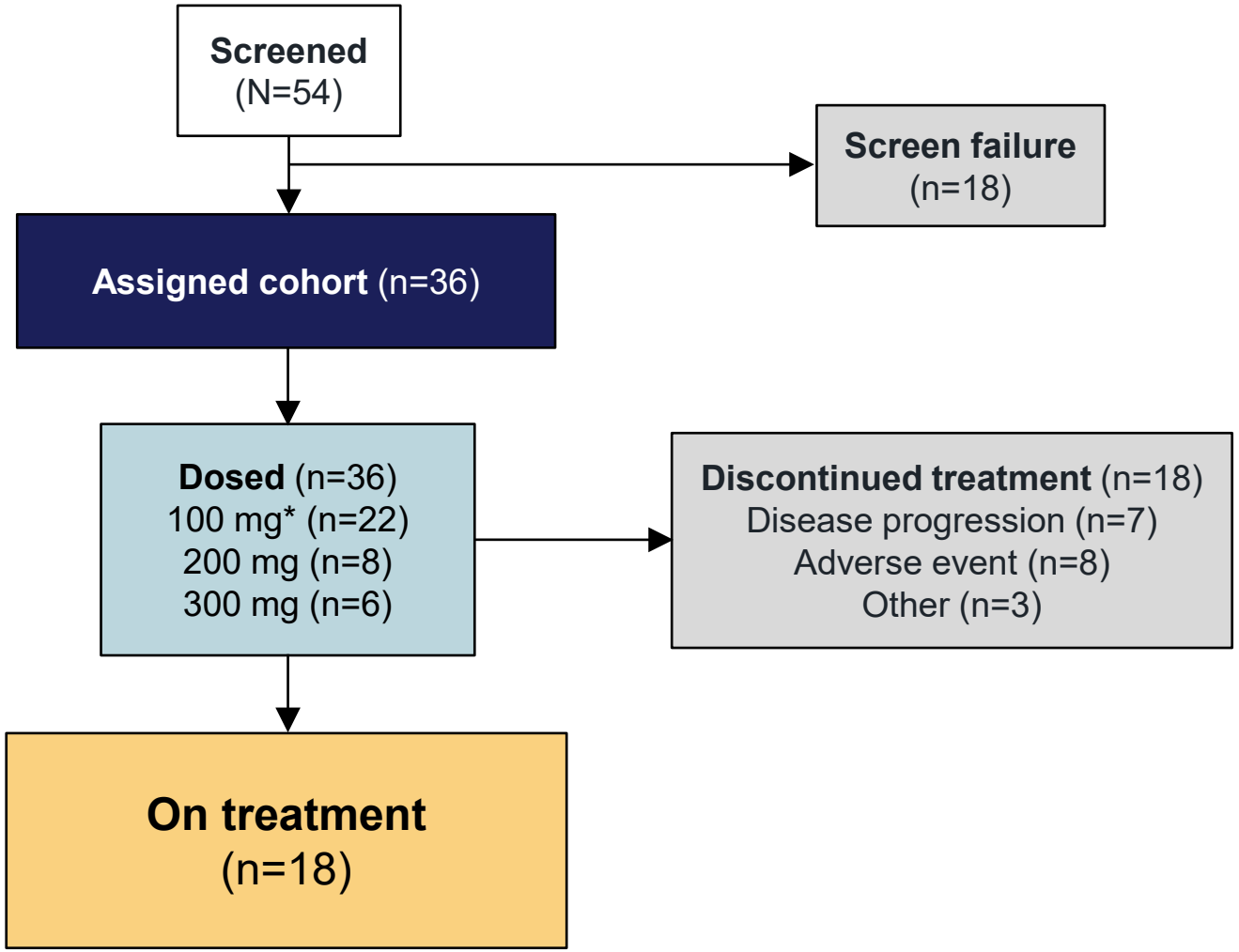


BTK, Bruton tyrosine kinase; **CRBN,** cereblon

Mato et al. ASH 2022, Abstract #965

NX-2127-001: patient disposition

Phase 1 trial in adults with relapsed/refractory B-cell malignancies



*100 mg dose includes patients from Phase 1a and Phase 1b

- **Causes for screen failure:**
  - Inadequate organ reserve (n=5)
  - Subject withdrawal (n=3)
  - Disease progression/other cancer (n=2)
  - Administration of prohibited medications (n=2)
  - Other (n=6)
- **Patients dosed include:**
  - CLL (n=23)
  - DLBCL (n=4)
  - WM (n=3)
  - FL (n=1)
  - MCL (n=4)
  - MZL (n=1)

Mato et al. ASH 2022, Abstract #965

Data cutoff: September 21, 2022

NX-2127 safety summary (all participants) by dose

AEs: all grades, n (%)	All doses (n=36)	100 mg* (n=22)	200 mg (n=8)	300 mg (n=6)
Fatigue	19 (53)	13 (59)	5 (63)	1 (17)
Neutropenia[a]	14 (39)	5 (23)	5 (63)	4 (67)
Contusion[b]	10 (28)	4 (18)	3 (38)	3 (50)
Thrombocytopenia[c]	9 (25)	5 (23)	2 (25)	2 (33)
Hypertension	9 (25)	5 (23)	2 (25)	2 (33)
Anemia	8 (22)	6 (27)	2 (25)	0
Constipation	7 (19)	7 (32)	0	0
Dyspnea	7 (19)	4 (18)	3 (38)	0
Pruritis	7 (19)	5 (23)	1 (13)	1 (17)
Atrial fibrillation/Atrial flutter[d]	6 (17)	3 (14)	2 (25)	1 (17)
Diarrhea	6 (17)	5 (23)	1 (13)	0
Petechiae	6 (17)	4 (18)	1 (13)	1 (17)
Rash	6 (17)	5 (23)	1 (13)	0

[a]Aggregate of "neutropenia" and "neutrophil count decreased" [b] Includes episodes of bruising and other similar verbatim terms [c]Aggregate of "thrombocytopenia" and "platelet count decreased" [d]Cases were confounded by risk factors such as: age >80 years (4 cases), history of hypertension (4 cases), male sex (3 cases), and history of prior AF on ibrutinib (2 cases)
*18 of the 22 patients treated at the 100 mg qd dose had CLL

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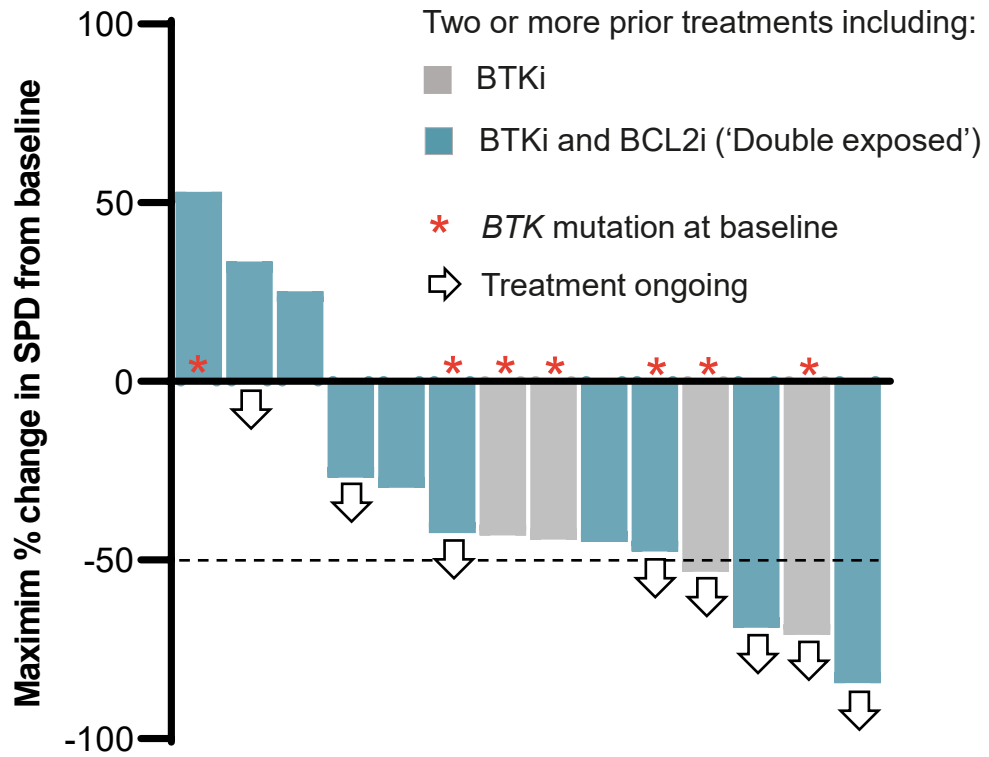
Data cutoff: September 21, 2022

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. Their treatment is ongoing with a 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

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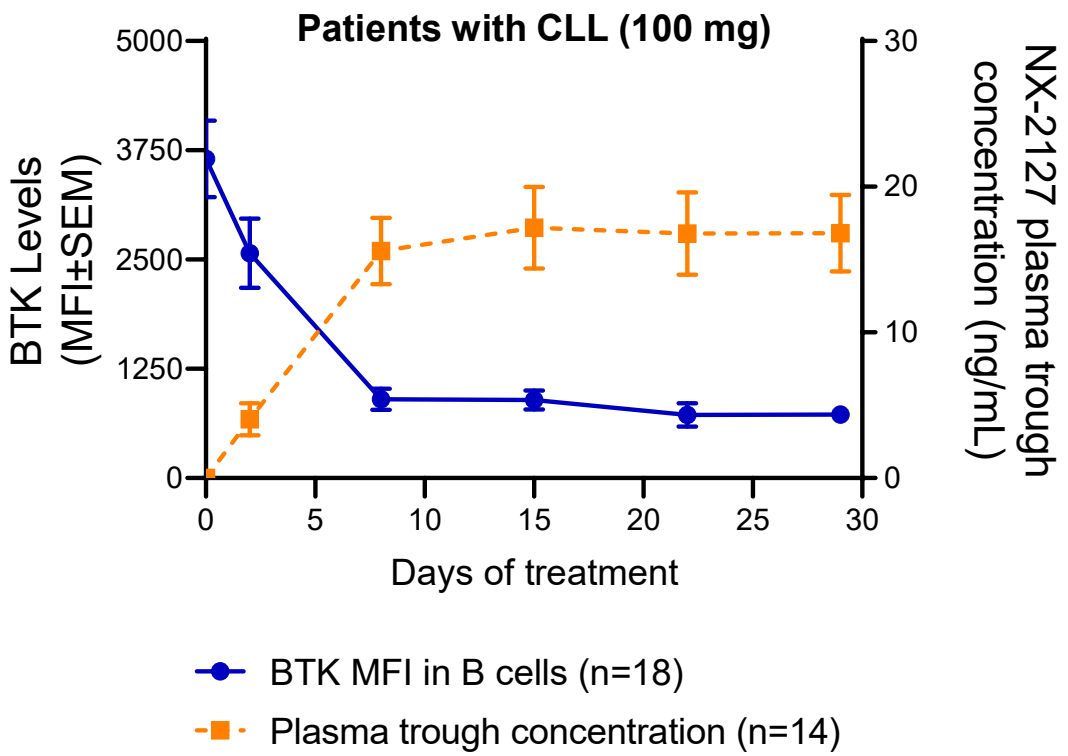
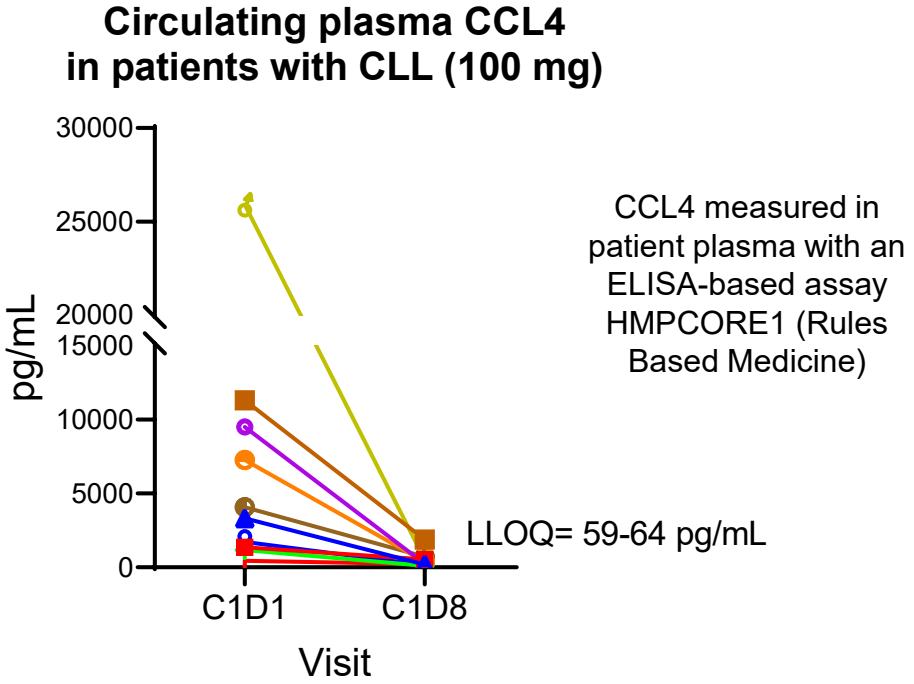
Data cutoff: September 21, 2022

NX-2127 leads to robust BTK degradation and decrease in B-cell activation





- Daily treatment with NX-2127 resulted in a fast and sustained suppression of BTK (CD19+) as measured in patient whole blood using a flow cytometry assay. BTK suppression target of 80% reached consistently (data not shown here)
- Robust decrease of plasma CCL4 by Cycle 1 Day 8 and suppression was maintained through Cycle 2 Day 1, consistent with clinically observed lymphocytosis occurring in majority of patients with nodal disease by Cycle 1 Day 8
- NX-2127 treatment also resulted in degradation of cereblon neo-substrate Ikaros

BTK, Bruton's tyrosine kinase; **CCL4**, C–C motif ligand 4; **LLOQ**, lower limit of quantification

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Data cutoff: September 21, 2022

BGB-11417 (BCL2i)
More Potent and Selective Than Venetoclax

		Bcl-2 IC_{50} nM	Bcl-2 G101V IC_{50} nM
Highly potent[2,a]	BGB-11417	0.014 ± 0.0021	0.59 ± 0.08
	Venetoclax	0.20 ± 0.015	34 ± 3.8
	Ratio (BGB-11417:venetoclax)	**1:14**	**1:57**

		Bcl-2	BCLxL	BCL-w	MCL1	BCLA1
Highly selective[2,b]	BGB-11417	1	1/2000	1/129,000	<1/714,000	<1/714,000
	Venetoclax	1	1/325	1/13,700	<1/50,000	<1/50,000
	Ratio (BGB-11417:venetoclax)	-	**1:6**	**1:9**	-	-

[a]Biochemical assays based on the time-resolved fluorescence resonance energy transfer methodology. [b]Relative selectivity compared to BCL2.

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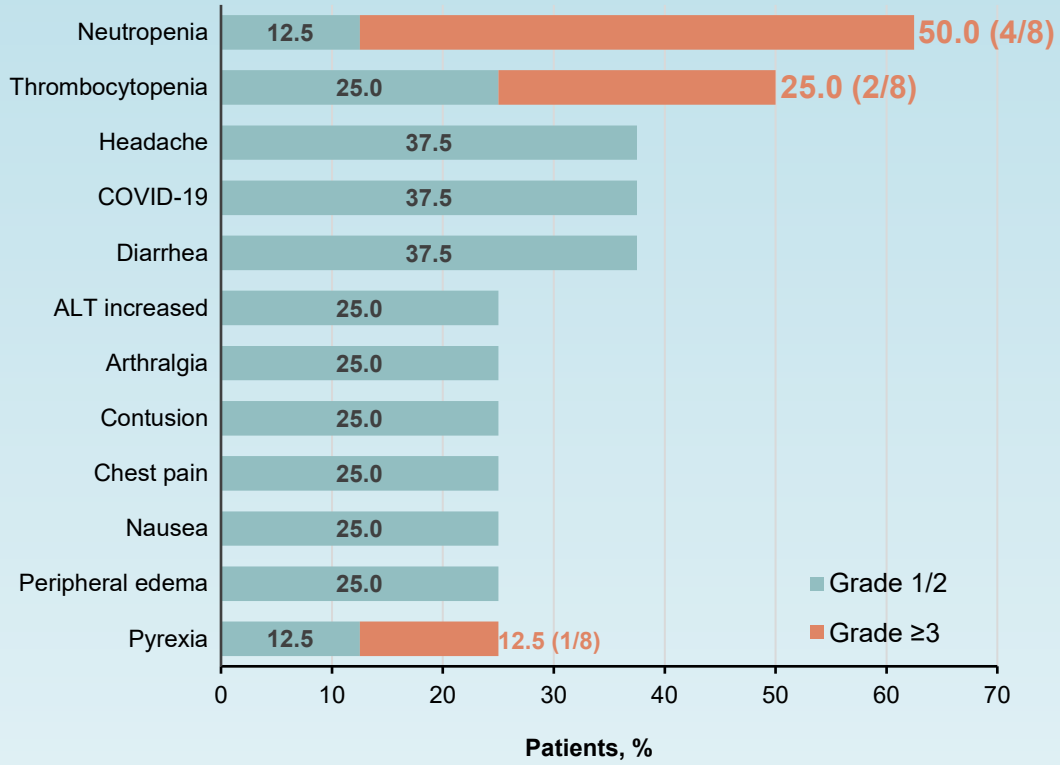
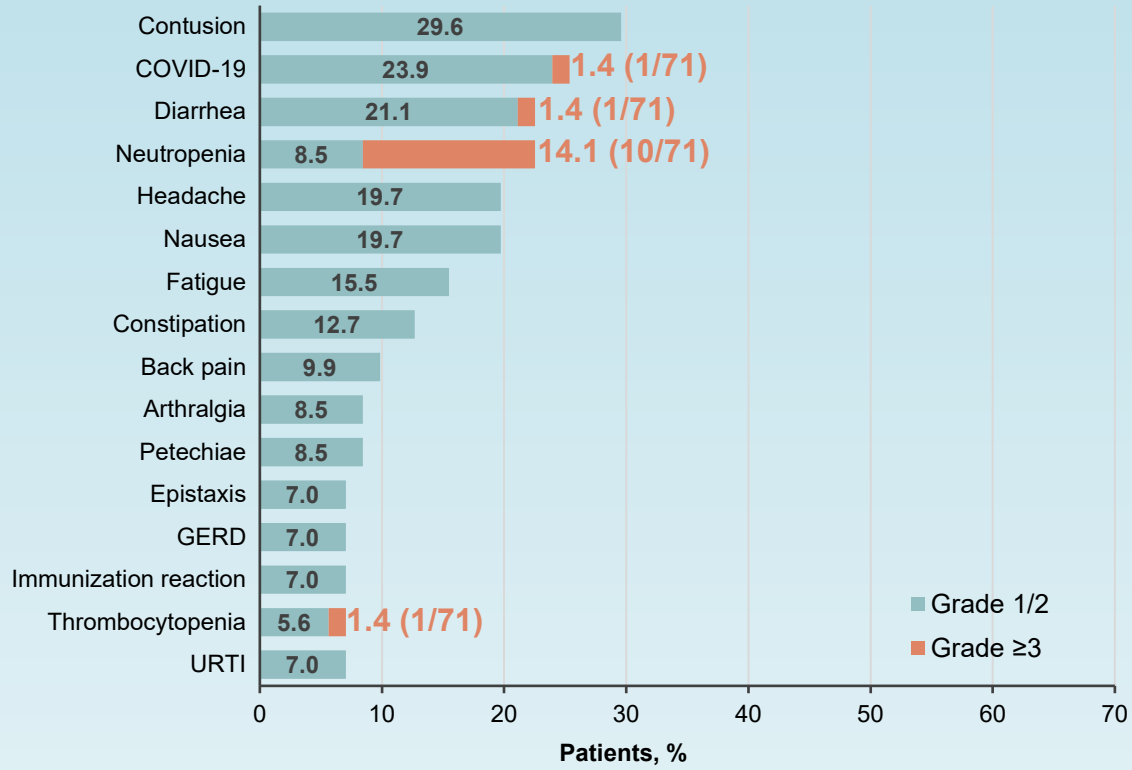
BGB-11417 (BCL2i) ± Zanubrutinib
Most Frequent Adverse Events

BGB-11417 Monotherapy, n=8
(Events in ≥2 Patients)



BGB-11417 + Zanubrutinib, n=71[a,b]
(Events in ≥5 Patients)



[a]Includes 21 patients who are still in zanubrutinib pretreatment phase and have not yet received BGB-11417. [b]Includes 46 patients who are TN.

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BGB-11417 (BCL2i) ± Zanubrutinib
Overall Response Rate

Response, n (%)	R/R BGB-11417 (n=8)	R/R BGB-11417 + zanubrutinib (n=25)	TN BGB-11417 + zanubrutinib (n=46)
Treated with BGB-11417	**8**	**24**	**26**
Efficacy evaluable	**6**	**20[a]**	**11[a]**
ORR, n (%)	4 (67)	19 (95)	11 (100)
CR	2 (33)[b]	6 (30)[c]	2 (18)[d]
PR	2 (33)[e]	13 (65)[f]	9 (82)[g]
SD	2 (33)	1 (5)	0
PD	0	0	0
Median follow-up, months (range)	13.4 (1.4-21.9)	11.1 (2.2-18.6)	3.5 (0.4-9.7)

[a]n=2 (R/R) and n=11 (TN) have responded after zanubrutinib pretreatment but have not yet had response assessment on combination treatment: they are not included here. [b]40 mg: n=1; 80 mg: n=1. [c] 40 mg: n=1; 80 mg: n=2; 160 mg: n=3. [d] 160 mg: n=2. [e]40 mg: n=1; 80 mg: n=1. [f] 40 mg: n=2; 80 mg: n=3; 160 mg: n=3 ; 320 mg: n=5. [g]160 mg: n=9.
CR, complete response; ORR, overall response rate; PR, partial response; SD, stable disease.

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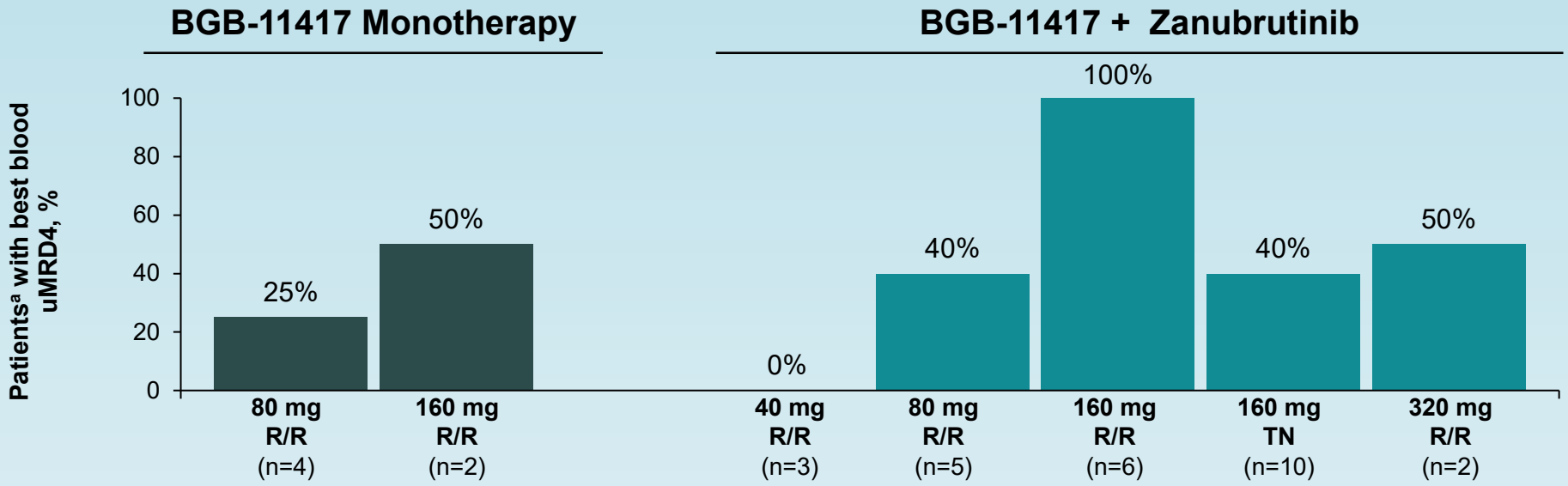
BGB-11417 (BCL2i) ± Zanubrutinib
Blood Minimal Residual Disease

- Blood MRD negativity was observed at **≥80 mg** after **6 months** (mono and combo in R/R CLL/SLL)
- **uMRD rate increased with longer follow-up and higher dose** (160 mg and 320 mg are immature)



	80 mg R/R (n=4)	160 mg R/R (n=2)	40 mg R/R (n=3)	80 mg R/R (n=5)	160 mg R/R (n=6)	160 mg TN (n=10)	320 mg R/R (n=2)
Median treatment duration months, range	**20.2** (15.9-23.8)	**14.3** (13.9-14.7)	**17.1** (16.4-17.8)	**15.0** (10.7-16.3)	**12.1** (9.8-13.7)	**8.2** (5.7-8.6)	**9.3** (9.0-9.5)
Median time to blood uMRD4[b], months, range	**12.2** (12.2-12.2)	**7.4** (7.4-7.4)	**0**	**9.5** (6.7-12.2)	**8.1** (4.6-10.4)	**6.6** (4.9-6.9)	**7.1** (7.1-7.1)

Data cutoff date: 29 October 2022.

MRD was measured by ERIC flow cytometry with 10^{-4} sensitivity. [a]In MRD-evaluable population, which was defined as patients who tested at least 1 postbaseline MRD sample. [b]From BGB-11417 first dose to first blood uMRD4; uMRD4 is defined as CLL cells out of total nucleated cells less than 10^{-4}.

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Lisaftoclax (APG-2575) (BCL2i) Study Schema

Part 1 (n = 46)
Lisaftoclax monotherapy

Dose escalation (3+3 design)

- 400 mg (n = 18)
- 600 mg (n = 16)
- 800 mg (n = 12)

- = PK ≥ 3 pts per cohort

Part 2 (n = 18)
Lisaftoclax combination therapy

Dose escalation (3+3 design)

A. Rituximab* (n=9)
+
Lisaftoclax — 400 mg (n=3)
600 mg (n=3)
800 mg (n=3)

B. Acalabrutinib** (n=9)
+
Lisaftoclax — 400 mg (n=3)
600 mg (n=3)
800 mg (n=3)

Dose expansion cohorts (n = 100)

- **Rituximab + Lisaftoclax** (n=30)
  - 400 mg (n = 10)
  - 600 mg (n = 12)
  - 800 mg (n = 8)

- **Acalabrutinib + Lisaftoclax** (n=70)
  - 400 mg (n = 13)
  - 600 mg (n = 42)
  - 800 mg (n = 15)

* Standard label rituximab was used: 375 mg/m^2 IV on C1D8 and 500 mg/m^2 on Day 1 of Cycles 2-6.
**Standard label acalabrutinib was used: 100 mg orally twice daily

- PK, pharmacokinetics; MTD/RP2D, maximum tolerated dose/recommended phase 2 dose

Clinical trial registration: NCT04215809

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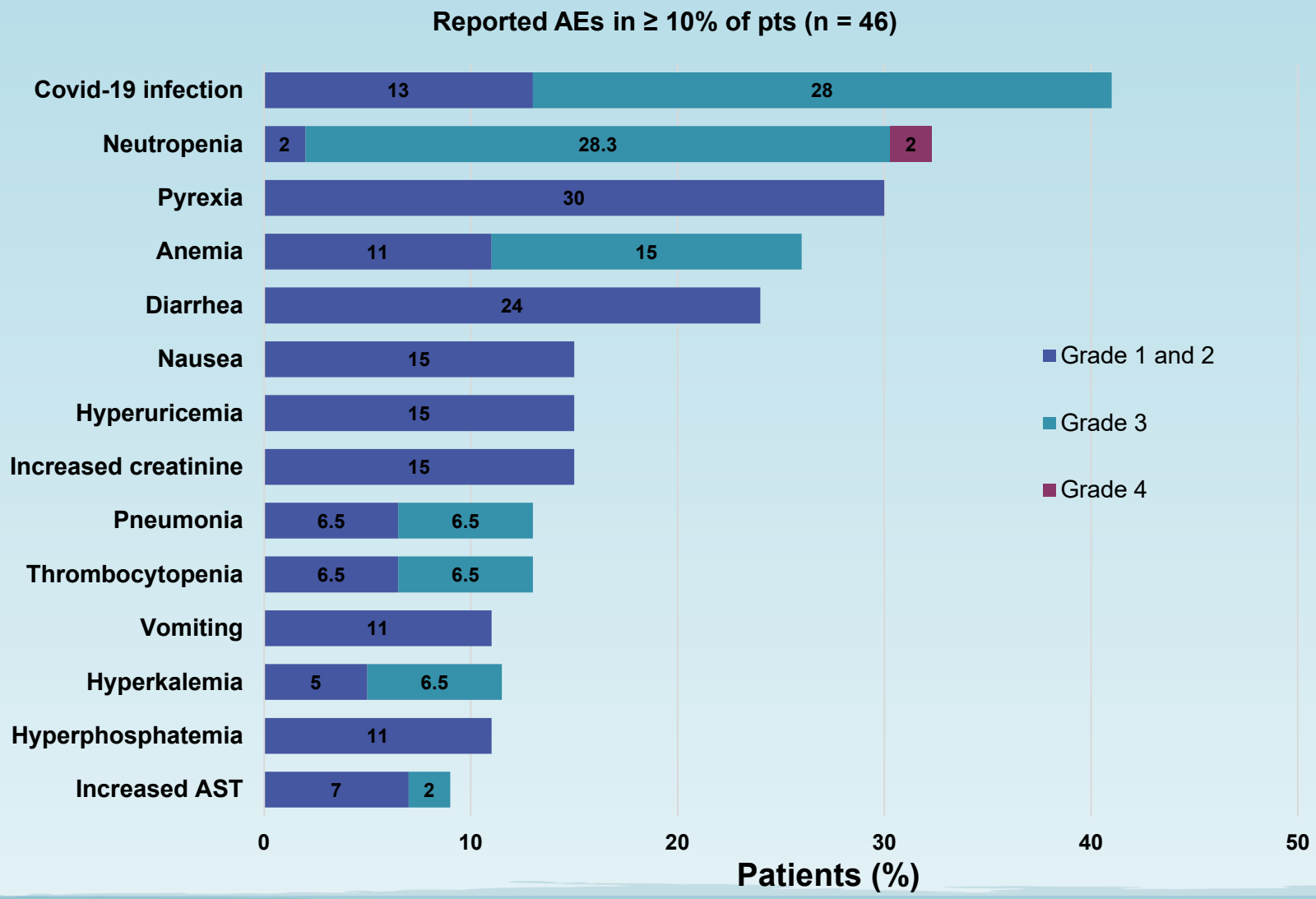
Lisaftoclax Safety: Monotherapy



Grade 3/4 AEs in ≥ 2% of pts, no. (%)	
Neutropenia	13 (30.3)
Covid-19 infection	13 (28)
Pneumonia	3 (6.5)
Febrile neutropenia	2 (4)
Multiorgan failure	1 (2)
Clinical TLS	1 (2)

AST, aspartate aminotransferase
TLS, tumor lysis syndrome

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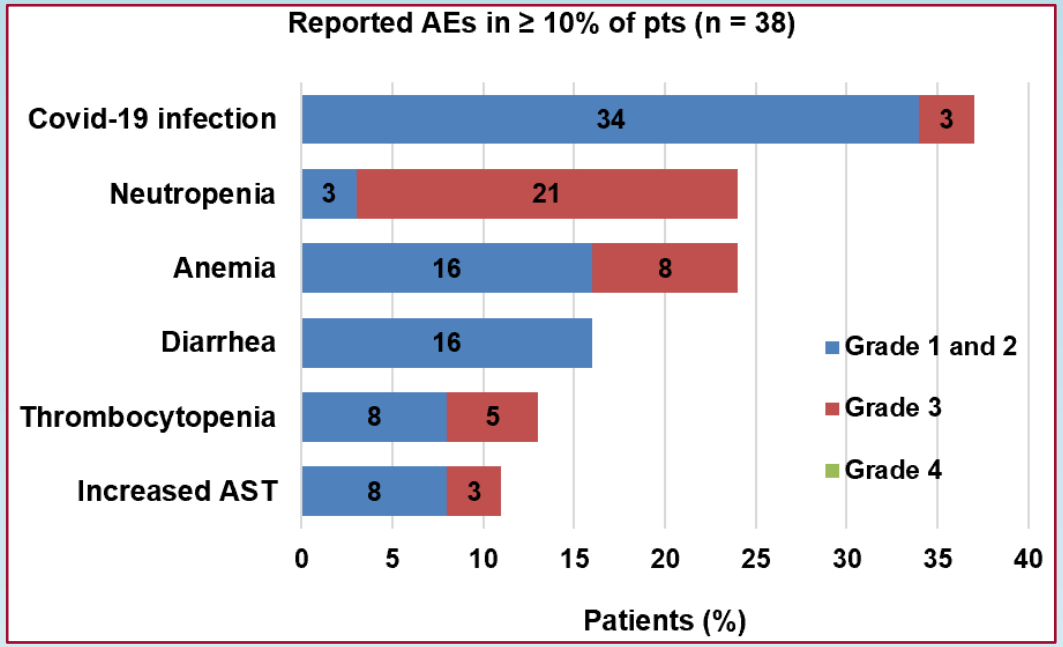
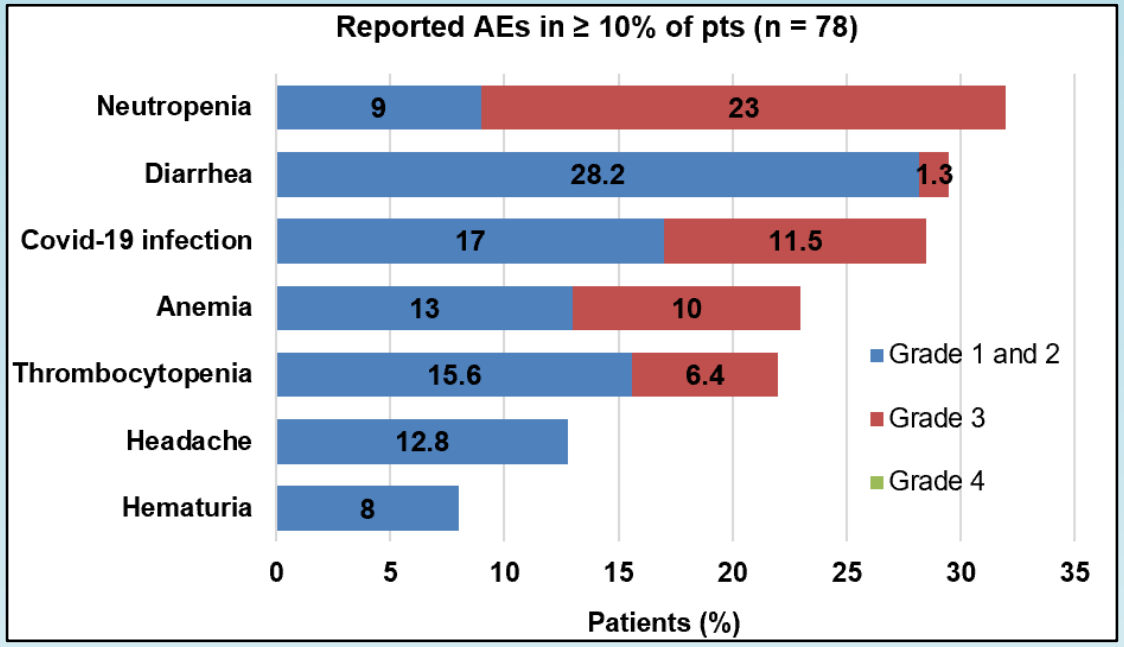
Lisaftoclax Safety: Combinations

Rituximab + Lisaftoclax



Grade 3/4 AEs in ≥ 2% of pts, no. (%)	
Neutropenia	8 (21)
Clinical TLS	1 (2.7)

Acalabrutinib + Lisaftoclax



Grade 3/4 AEs in ≥ 2% of pts, no. (%)	
Neutropenia	18 (23)
Covid-19 infection	9 (11.5)
Atrial fibrillation	3 (3.8)
Abscess	2 (3)

AST, aspartate aminotransferase
TLS, tumor lysis syndrome

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Lisaftoclax: Efficacy Summary

	Monotherapy	Combined with rituximab	Combined with acalabrutinib	
Response Evaluable	**R/R n=43**	**R/R n=34**	**R/R n=57**	**TN n=16**
Median (range) treatment duration	16.5 (1-36)	11 (1-21)	12 (1-24)	7 (5-11)
Overall Response Rate n, (%)	29/43 (67)	27/34 (79)	56/57 (98)	16/16 (100)
Biological Characteristics, no. (%)				
TP53-mutated and/or del(17p)	N/A	5/6 (83)	11/12 (92)	4/4 (100)
Complex karyotype (≥ 3 abnormities)	N/A	5/5 (100)	15/16 (94)	7/7 (100)
Unmutated IGHV	N/A	N/A	23/25 (92)	9/9 (100)
Mutated IGHV	N/A	N/A	13/13 (100)	3/3 (100)
BTKi resistant or intolerant	4/6 (67)	0/4 (0)	7/8 (88)	N/A

Data on iwCLL CR and MRD rates not yet available

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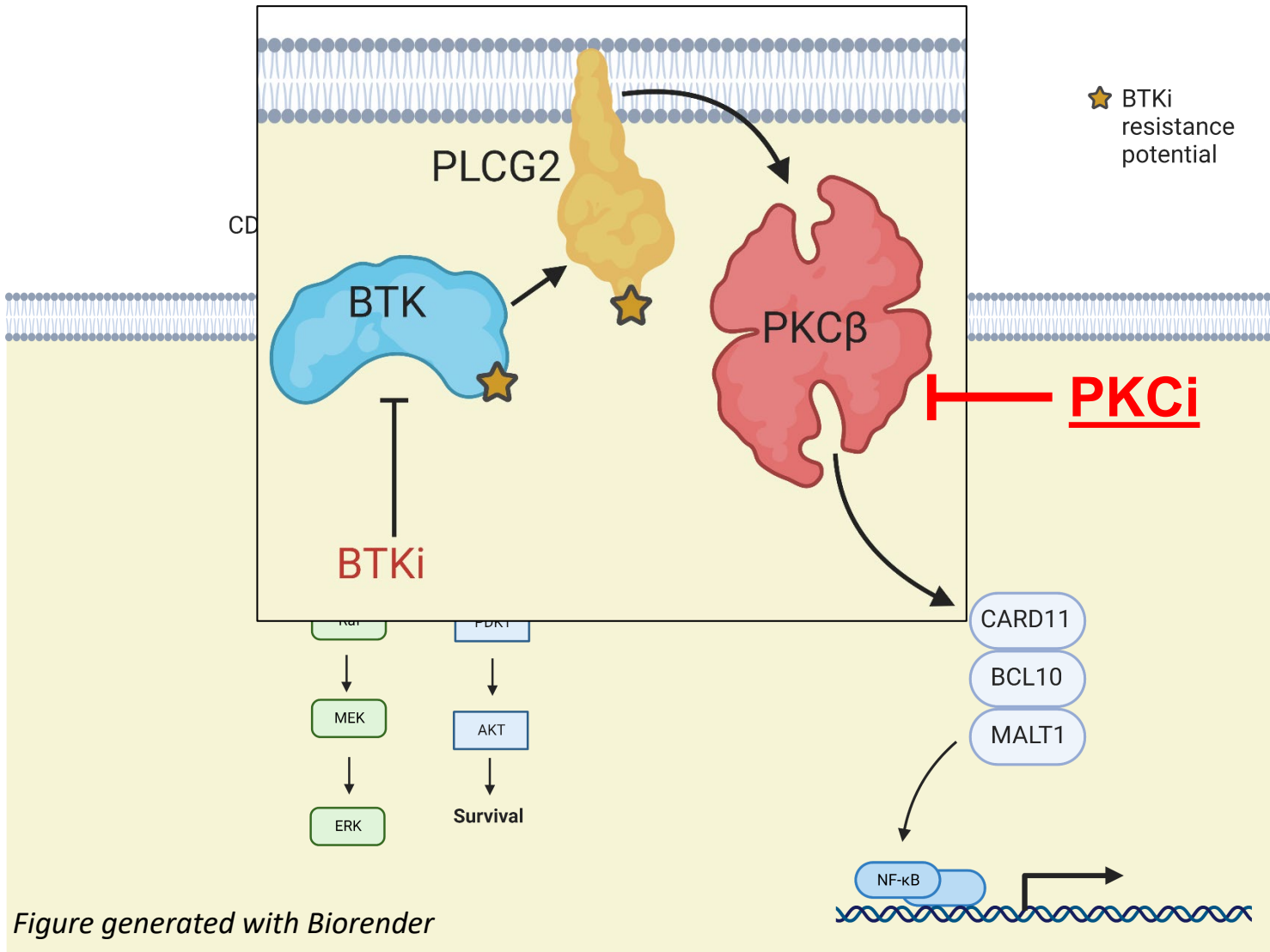
Protein Kinase C-beta Background

Resistance mutations are upstream of PKCβ

Inhibition of PKCβ has potential to overcome mutation-driven resistance



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PKCβi (MS-553)

Safety Profile in Depth

- 14 pts (33%) had Gr 3-4 TR-AE
- One Grade 4 related AE: Neutropenia
- One DLT occurred at 350 mg BID
- MTD was not reached
- RP2D of 250 mg BID was selected
- Six patients were dosed at above RP2D with drug withdrawn on 3 patients

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PKCβi (MS-553)
Efficacy

	R/R Mono	
Efficacy evaluable patients*	CLL/SLL N=23	Richter's N=3
Best Response	n(%)	
CR	0	0
PR	6 (26)	1 (33)
PRL	5 (22)	0
SD	11 (48)	0

48

* Efficacy evaluable patients are patients who have completed at least one cycle of study drug treatment or had at least one response assessment with data cutoff as of June 20, 2022

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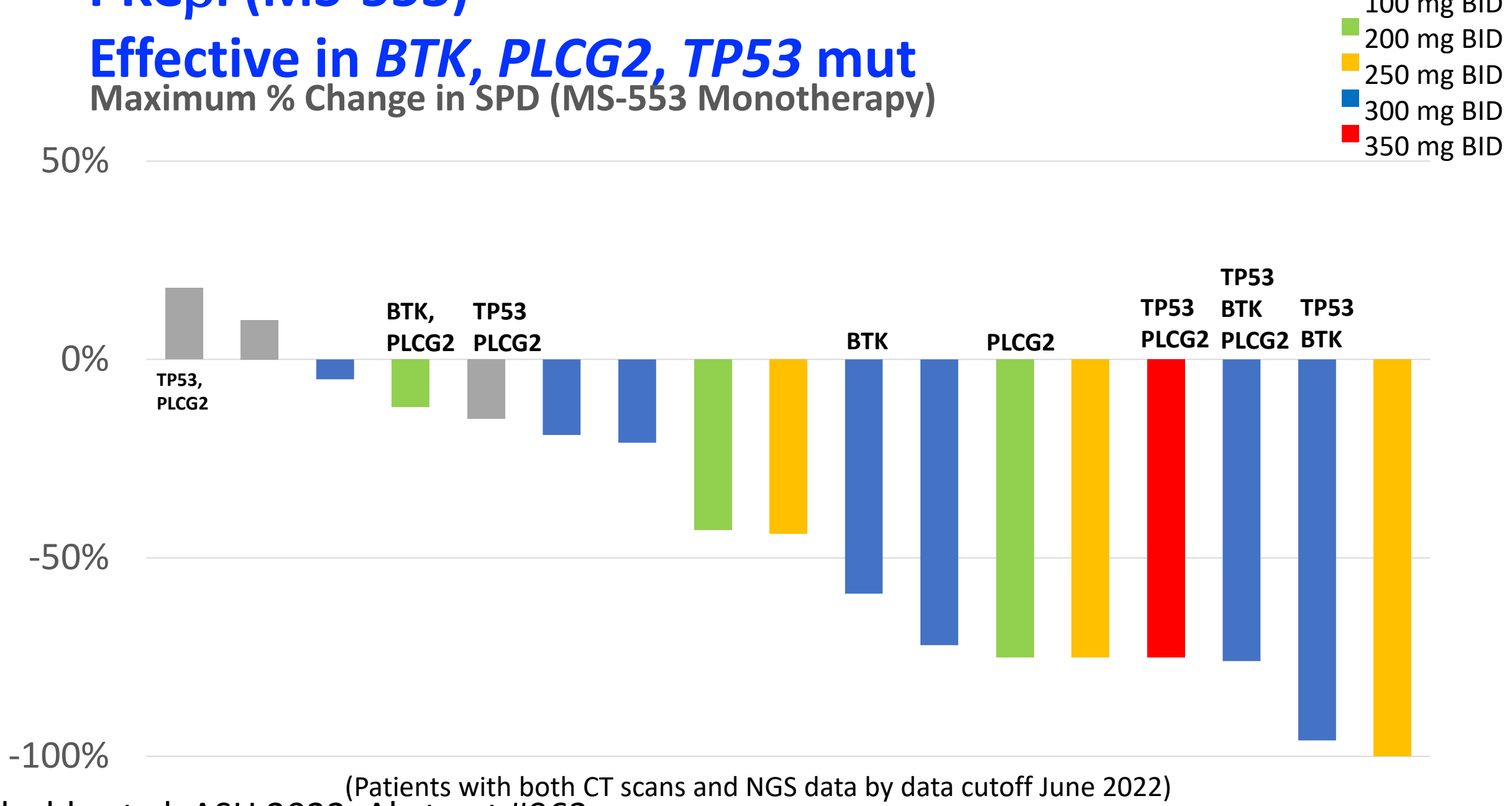
PKCβi (MS-553)

Effective in *BTK*, *PLCG2*, *TP53* mut

Maximum % Change in SPD (MS-553 Monotherapy)



(Patients with both CT scans and NGS data by data cutoff June 2022)

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Conclusions

- Consolidation with venetoclax feasible in patients on IBR ≥12 months with potential clinical benefit
- Combined IBR + VEN (CLARITY) highly active in R/R CLL
- Pirtobrutinib efficacy in prior BTKi-treated CLL
- BTK-degrader (NX-2127) tolerated with activity
- New BCL2 inhibitors (BCL2i) (BGB-11417 and Lisaftoclax) have activity and being combined with BTKi and CD20 mAb
- Protein kinase C-beta inhibitor (PKCβi) - MS-553 tolerated with activity in BTKi-treated CLL

Thank you!

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