ASH 2021 Update
Novel Agents in CLL

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Treatment Evolution for CLL

1960s

Alkylating agents
- Chlorambucil
- Cyclophosphamide

1970s

Purine nucleosides
- Fludarabine
- Pentostatin
- Cladribine

1980s

1990s

Purine nucleosides and alkylators

2000s

Chemoimmunotherapy (FCR, BR)
Alemtuzumab
Lenalidomide

2014-

BTK inhibitors (Ibrutinib, Acalabrutinib)
PI3K inhibitors (Idelalisib, Duvelisib)
BCL-2 inhibitor (Venetoclax)
Novel CD20 mAb (Obinutuzumab)

2022+

BTK inhibitors (Zanubrutinib, Pirtobrutinib)
PI3K inhibitor (Umbralisib)
CAR-T

Novel Agents in CLL

- Non Covalent BTKi
  - Pirtobrutinib (LOXO-305)
  - Nemtabrutinib (MK-1026, ARQ 531)
- Covalent BTKi – Zanubrutinib
- Novel PI3Ki – Umbralisib
- Novel BCL2i
  - Lisaftoclax (APG-2575)
  - BGB-11417
  - LP-118 (dual BCL2/Bcl-xl inhibitor)
- PKCβ inhibitor – MS553
- BTK degrader – NX-2127
- CAR-T – Liso-cel (CD19 CAR)
- CD20 BiTEs

Pirtobrutinib, A Highly Selective, Non-covalent (Reversible) BTK Inhibitor In Previously Treated CLL/SLL: Updated Results From The Phase 1/2 BRUIN Study

Anthony R. Mato[1], John M. Pagel[2], Catherine C. Coombs[3], Nirav N. Shah[4], Nicole Lamanna[5], Talha Munir[6], Ewa Lech-Maranda[7], Toby A. Eyre[8], Jennifer A. Woyach[9], William G. Wierda[10], Chan Y. Cheah[11], Jonathan B. Cohen[12], Lindsey E. Roeker[1], Manish R. Patel[13], Bita Fakhri[14], Minal A. Barve[15], Constantine S. Tam[16], David J. Lewis[17], James N. Gerson[18], Alvaro J. Alencar[19], Chaitra S. Ujjani[20], Ian W. Flinn[21], Suchitra Sundaram[22], Shuo Ma[23], Deepa Jagadeesh[24], Joanna M. Rhodes[25], Justin Taylor[19], Omar Abdel-Wahab[1], Paolo Ghia[26], Stephen J. Schuster[18], Denise Wang[27], Binoj Nair[27], Edward Zhu[27], Donald E. Tsai[27], Matthew S. Davids[28], Jennifer R. Brown[28], Wojciech Jurczak[29]

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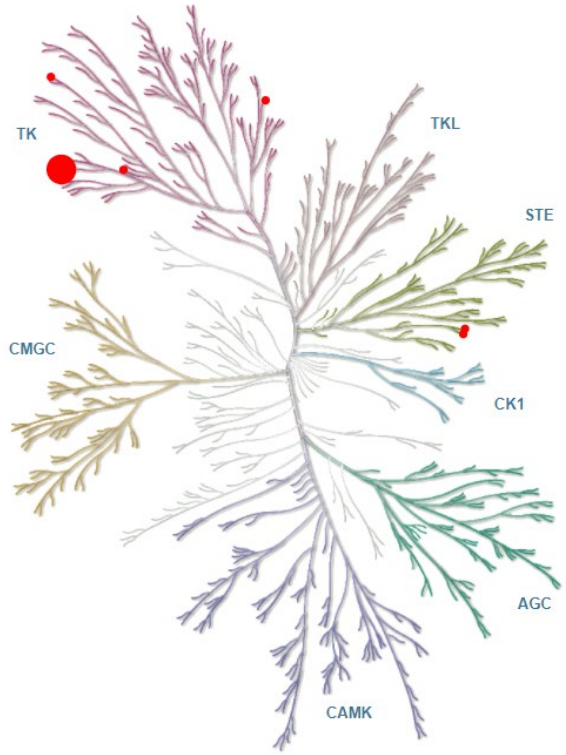
Pirtobrutinib is a Highly Potent and Selective Non-Covalent (Reversible) BTK Inhibitor

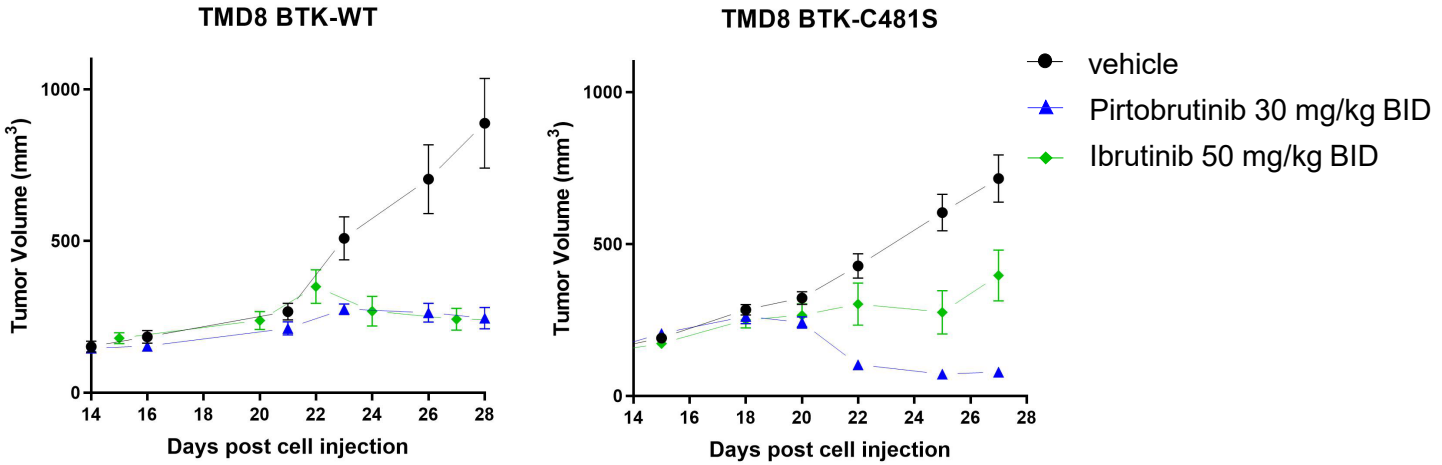
Kinome selectivity[1]

Highly selective for BTK



Xenograft models

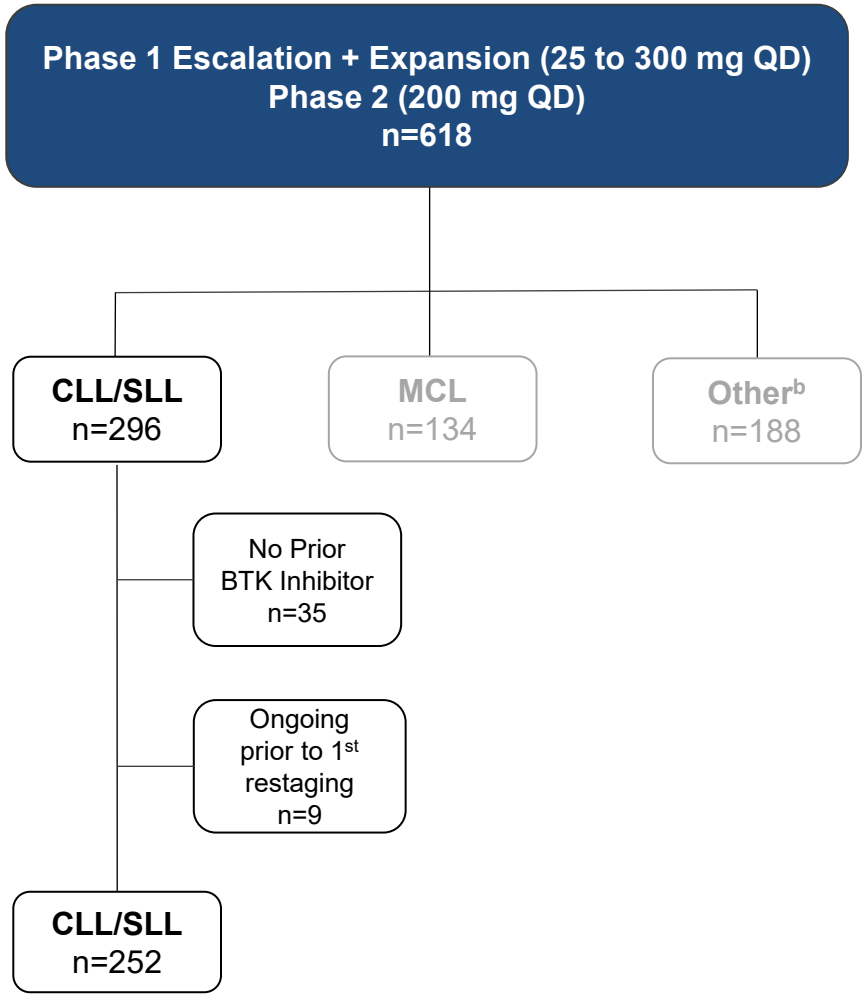
In vivo activity similarly efficacious as ibrutinib in WT; superior in C481S



- >300-fold selectivity for BTK vs 370 other kinases[2]
- Favorable pharmacologic properties allow sustained BTK inhibition throughout dosing interval[2]
- Nanomolar potency against WT & C481-mutant BTK in cell and enzyme assays[2]
- Due to reversible binding mode, BTK inhibition not impacted by a high intrinsic rate of BTK turnover[2]

BID, twice-daily; BTK, Bruton tyrosine kinase. [1]Mato et al, *Lancet*, 2021:397:892-901. [2]Brandhuber BJ, 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 0-2
- CLL or other B-cell NHL
- Active disease and in need of treatment
- Previously treated

Key endpoints

- Safety/tolerability
- Determine MTD & recommended phase 2 dose
- Pharmacokinetics
- Efficacy according to ORR & DoR based on disease criteria (iwCLL, IWWM, Lugano)

Data cutoff date of 16 July 2021. [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]Other includes DLBCL, WM, FL, MZL, Richter's transformation, B-PLL, Hairy Cell Leukemia, PCNSL, and other transformation.

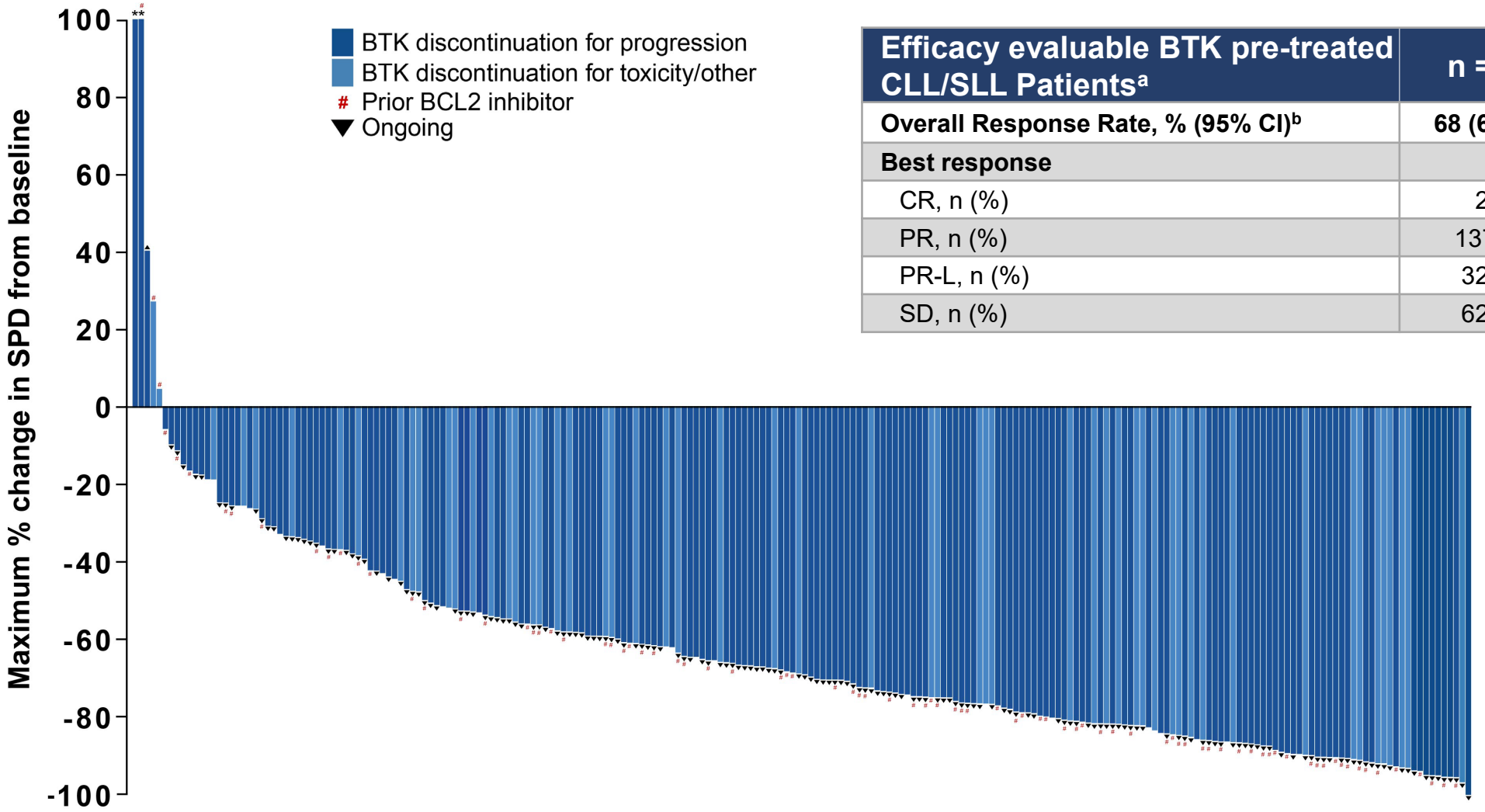
BTK Pre-treated CLL/SLL Patient Characteristics

Characteristics	N = 261
Median age, years (range)	69 (36-88)
Female, n (%)	84 (32)
Male, n (%)	177 (68)
ECOG PS[a], n (%)	
0	138 (53)
1	104 (40)
2	19 (7)
Median number of prior lines of systemic therapy (range)	3 (1-11)
Prior therapy, n (%)	
BTK inhibitor	261 (100)
Anti-CD20 antibody	230 (88)
Chemotherapy	207 (79)
BCL2 inhibitor	108 (41)
PI3K inhibitor	51 (20)
CAR-T	15 (6)
Stem cell transplant	6 (2)
Allogeneic stem cell transplant	5 (2)
Autologous stem cell transplant	1 (<1)
Reason discontinued prior BTKi, n (%)	
Progressive disease	196 (75)
Toxicity/Other	65 (25)

Baseline Molecular Characteristics[a]	
Mutation status, n (%)	
BTK C481-mutant	89 (43)
BTK C481-wildtype	118 (57)
PLCG2-mutant	33 (16)
High Risk Molecular Features, n (%)	
17p deletion	51 (28)
TP53 mutation	64 (37)
17p deletion or TP53 mutation	77 (36)
Both 17p deletion and TP53 mutation	38 (27)
IGHV unmutated	168 (84)
11q deletion	45 (25)

Data cutoff date of 16 July 2021. Total % may be different than the sum of the individual components due to rounding. [a]Molecular characteristics were determined centrally, in those patients with sufficient sample to pass assay quality control. 207 patients were tested for BTK and PLCG2, 180 patients for 17p deletion, 175 patients for TP53, 143 patients for 17p deletion + TP53, 200 patients for IGHV and 180 patients for 11q deletion.

Pirtobrutinib Efficacy in BTK Pre-treated CLL/SLL Patients

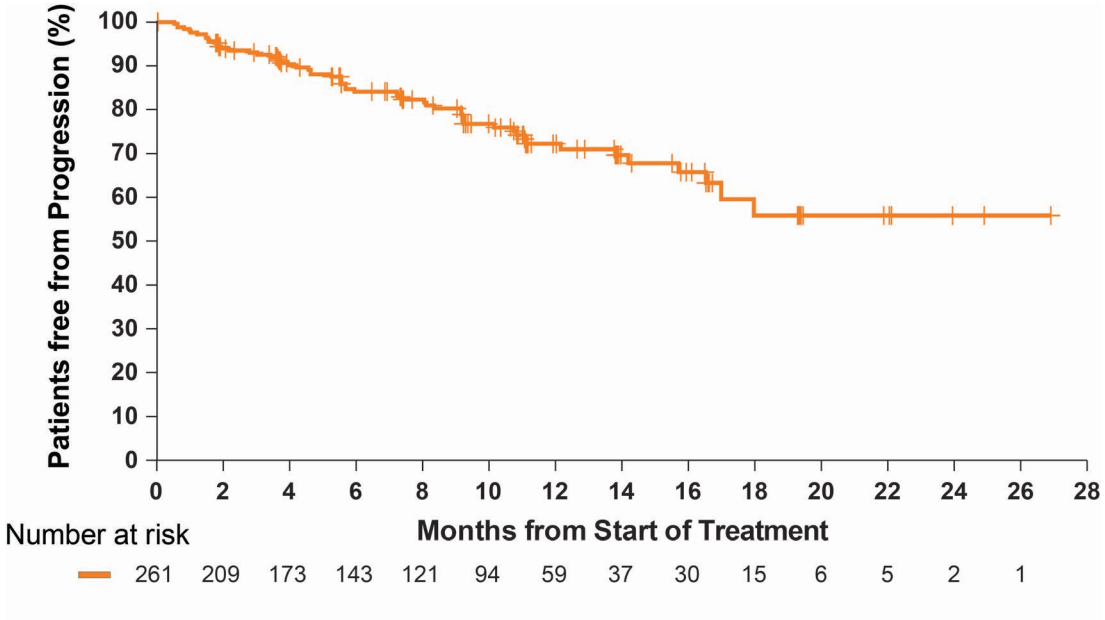


Efficacy evaluable BTK pre-treated CLL/SLL Patients[a]	n = 252
Overall Response Rate, % (95% CI)[b]	**68 (62 – 74)**
Best response	
CR, n (%)	2 (1)
PR, n (%)	137 (54)
PR-L, n (%)	32 (13)
SD, n (%)	62 (25)

Data cutoff date of 16 July 2021. *Patients with >100% increase in SPD. Data for 30 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. [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, PR, and PR-L. Response status per iwCLL 2018 according to investigator assessment. Total % may be different than the sum of the individual components due to rounding.

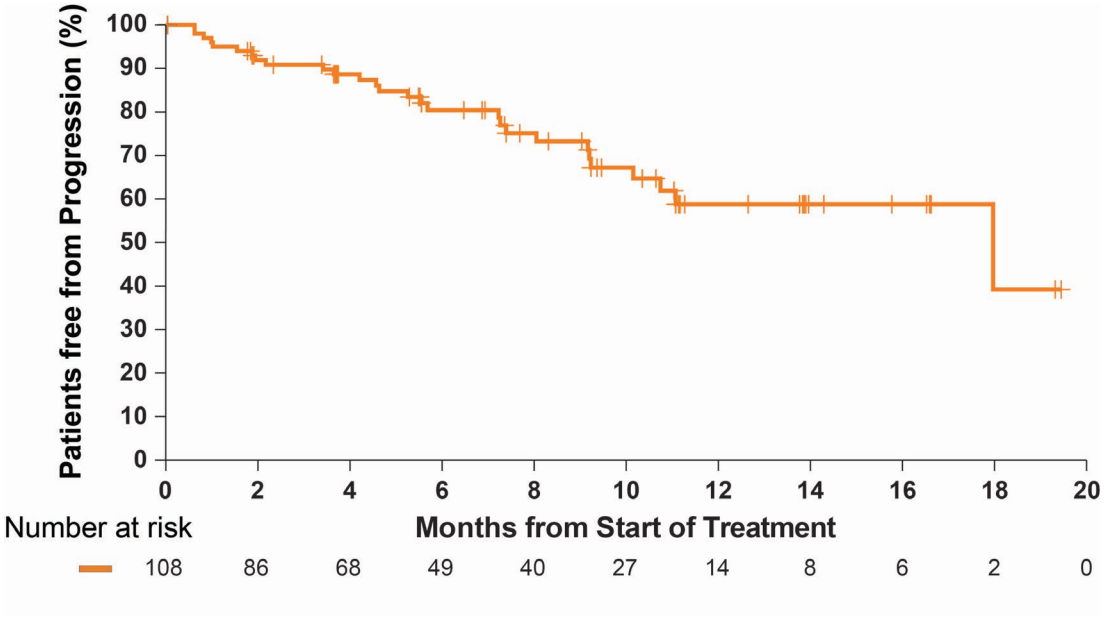
Progression-free Survival in BTK Pre-treated CLL/SLL Patients

PFS in at least BTK pre-treated patients
Median prior lines = 3



Median PFS: Not Estimable (95% CI: 17.0 months – Not Estimable)

PFS in at least BTK and BCL2 pre-treated patients
Median prior lines = 5



Median PFS: 18 months (95% CI: 10.7 months – Not Estimable)

- 74% (194/261) of BTK pre-treated patients remain on pirtobrutinib
- Median follow-up of 9.4 months (range, 0.3 – 27.4) for all BTK pre-treated patients

Data cutoff date of 16 July 2021. Response status per iwCLL 2018 according to investigator assessment.

Pirtobrutinib Safety Profile

	All doses and patients (n=618)						
	Treatment-emergent AEs, (≥15%), %					Treatment-related AEs, %	
Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Any Grade	Grades 3/4	Any Grade
Fatigue	13%	8%	1%	-	23%	1%	9%
Diarrhea	15%	4%	<1%	<1%	19%	<1%	8%
Neutropenia[a]	1%	2%	8%	6%	18%	8%	10%
Contusion	15%	2%	-	-	17%	-	12%
AEs of special interest[b]							
Bruising[c]	20%	2%	-	-	22%	-	15%
Rash[d]	9%	2%	<1%	-	11%	<1%	5%
Arthralgia	8%	3%	<1%	-	11%	-	3%
Hemorrhage[e]	5%	2%	1%[g]	-	8%	<1%	2%
Hypertension	1%	4%	2%	-	7%	<1%	2%
Atrial fibrillation/flutter[f]	-	1%	<1%	<1%	2%[h]	-	<1%

No DLTs reported and MTD not reached
96% of patients received ≥1 pirtobrutinib dose at or above RP2D of 200 mg daily
1% (n=6) of patients permanently discontinued due to treatment-related AEs

Data cutoff date of 16 July 2021. Total % may be different than the sum of the individual components due to rounding. [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]Represents 6 events (all grade 3), including 2 cases of post-operative bleeding, 1 case each of GI hemorrhage in the setting of sepsis, NSAID use, chronic peptic ulcer disease, and one case of subarachnoid hemorrhage in setting of traumatic bike accident. [h]Of 10 total afib/aflutter TEAEs, 3 occurred in patients with a prior medical history of atrial fibrillation, 2 in patients presenting with concurrent systemic infection, and 2 in patients with both.

Conclusions

- Pirtobrutinib demonstrates promising efficacy in CLL/SLL patients previously treated with BTK inhibitors
  - Efficacy was independent of BTK C481 mutation status, the reason for prior BTKi discontinuation (i.e. progression vs intolerance), or other classes of prior therapy received (including covalent BTK inhibitors, BCL2 inhibitors, and PI3K-delta inhibitors)

- Favorable safety and tolerability are consistent with the design of pirtobrutinib as a highly selective and non-covalent reversible BTK inhibitor

- Randomized, global, phase 3 trials evaluating pirtobrutinib in CLL/SLL ongoing:
  - BRUIN CLL-321 - Pirtobrutinib vs Investigator's Choice of IdelaR or BendaR, requires prior BTK treatment (NCT04666038)
  - BRUIN CLL-322 - Pirtobrutinib + VenR vs VenR, permits prior BTK treatment (NCT04965493)
  - BRUIN CLL-313 - Pirtobrutinib vs BendaR in treatment naïve patients (NCT05023980)

IdelaR: Idelalisib and Rituximab; BendaR: Bendamustine and Rituximab; VenR: Venetoclax and Rituximab.

Preliminary Efficacy and Safety of MK-1026, a Non-Covalent Inhibitor of Wild-type and C481S Mutated Bruton Tyrosine Kinase, in B-cell Malignancies: A Phase 2 Dose Expansion Study

Jennifer Woyach,[1] Ian W. Flinn,[2] Farrukh Awan,[3] Herbert Eradat,[4] Danielle M. Brander,[5] Michael Tees,[6] Sameer A. Parikh,[7] Tycel Phillips,[8] Wayne Wang,[9] Nishitha M. Reddy,[10] Mohammed Z.H Farooqui,[10] John C. Byrd,[11] Deborah M. Stephens[12]

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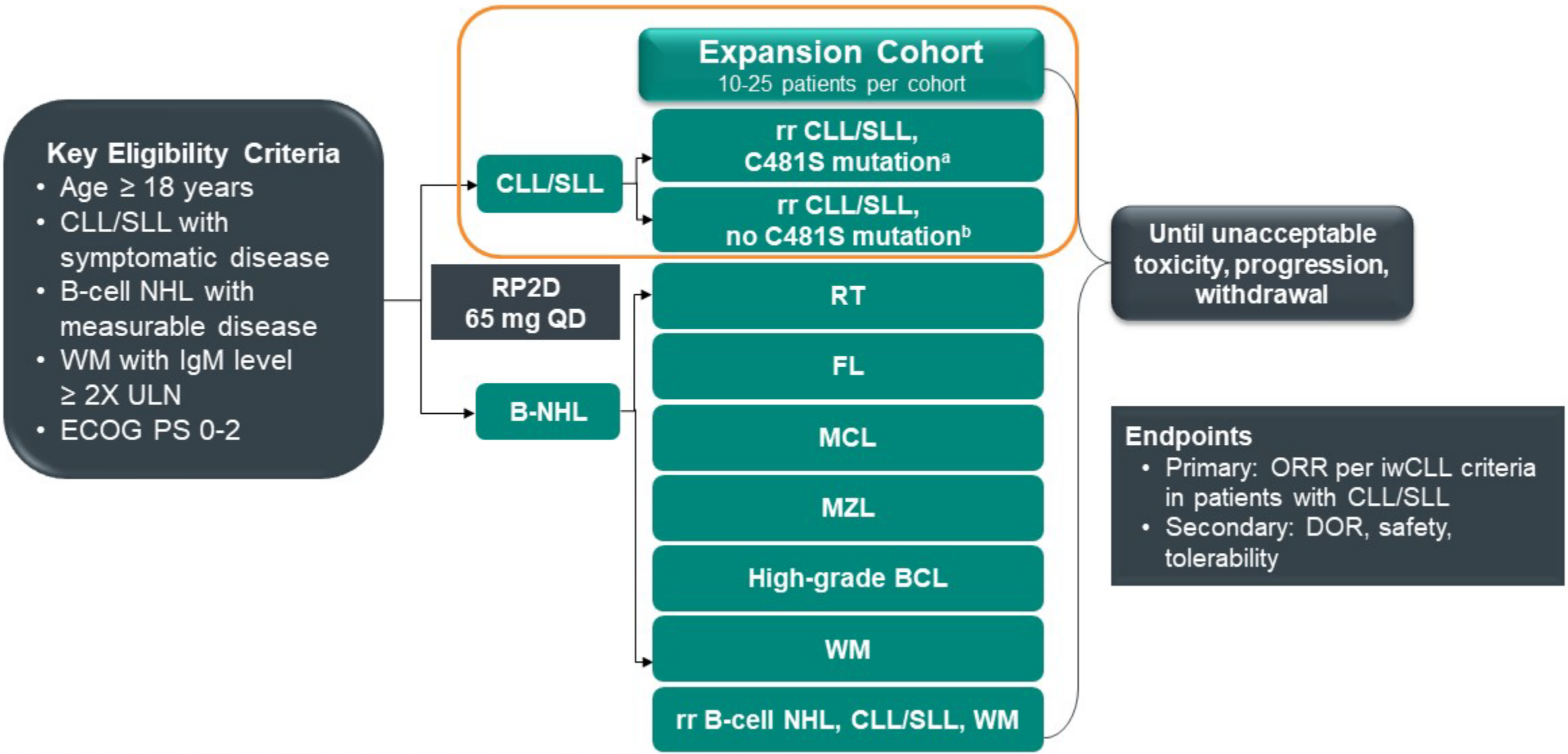
MK-1026-001 Study Design (NCT03162536)



[a]Cohort A: patients with rr CLL/SLL with ≥2 prior therapies including covalent BTKi, with C481S mutation;
[b]Cohort B includes patients with rrCLL/SLL recall with ≥2 prior therapies, progressed /intolerant to BTKi, no C481S mutation

Baseline Characteristics

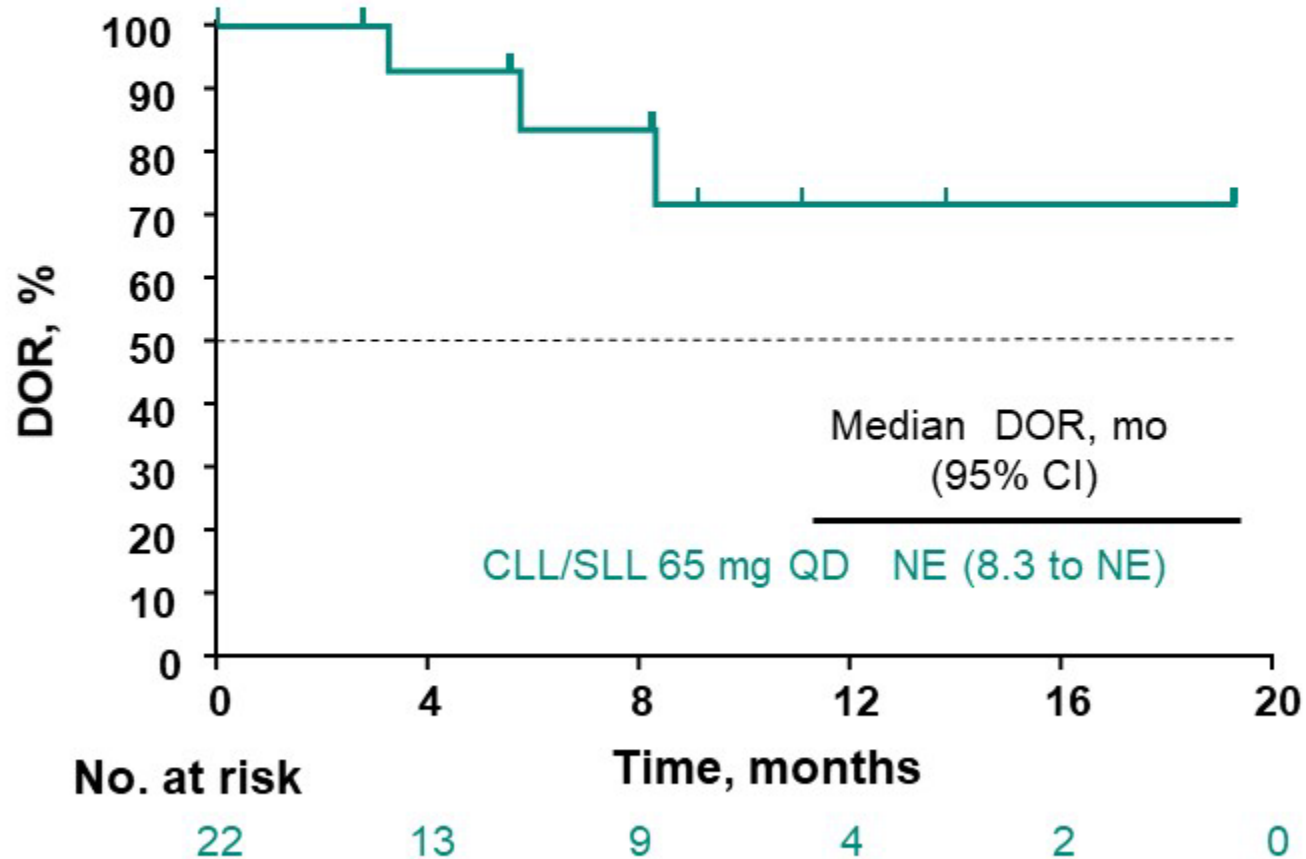
Characteristic, n (%)	Overall Population N = 118
Age, median (range), years	66.0 (38-86)
Male	91 (77.1)
White	105 (89.0)
CLL/SLL	68 (57.6)
WM	4 (3.4)
B-cell NHL	44 (37.3)
RT	16 (13.3)
FL	11 (9.3)
DLBCL	6 (5.1)
MCL	6 (5.1)
High-grade BCL	3 (2.5)
MZL	2 (1.7)
MK-1026 65 mg QD	94 (79.7)

Characteristic, n (%)	CLL/SLL 65 mg QD N = 51
Prior lines, median (range)	4 (1-18)
Prior BTK inhibitor therapy	43 (84.3)
ECOG PS 0	14 (27.5)
1	32 (62.7)
2	5 (9.8)
IGHV Unmutated	30 (58.8)
Mutated	2 (3.9)
Unknown	19 (37.3)
Del (17p) Present	12 (23.5)
Absent	33 (64.7)
Missing	6 (11.8)
BTK C481S Present	32 (62.7)
Absent	12 (23.5)
Unknown/Missing	7 (13.7)

Data cut-off: April 7, 2021.

Summary of Response (CLL/SLL), Efficacy Evaluable Population

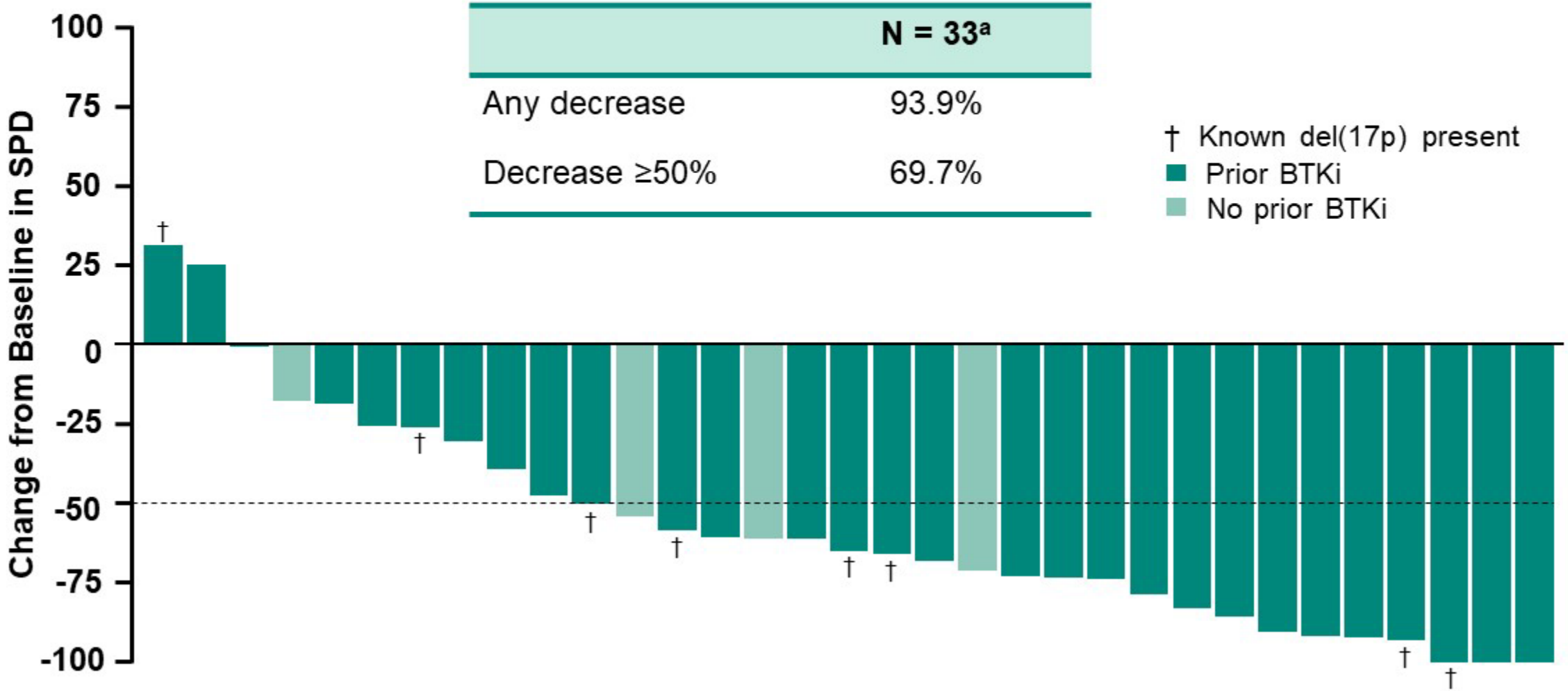
n (%) [95% CI]	CLL/SLL 65 mg QD N = 38[a]
ORR	**22 (57.9%)**
	[40.8-73.6]
CR	1 (2.6%) [0.0-13.8]
PR	12 (31.6%) [17.5-48.6]
PR-L	9 (23.7%) [11.4-40.2]
SD	15 (39.5%) [24.0-5.6]



[a]Efficacy evaluable patients with CLL/SLL who received at least one cycle of MK-1026 at preliminary RP2D of 65 mg QD and had ≥1 post-baseline assessment; Response assessed per iwCLL criteria Data cut-off: April 7, 2021.

Percent Change From Baseline in SPD (CLL/SLL), Efficacy Evaluable Population

	N = 33[a]
Any decrease	93.9%
Decrease ≥50%	69.7%



[a]33 of 38 patients with ≥1 assessment post-baseline were evaluable for change from baseline in sum of product of diameters (SPD); Data cut-off: April 7, 2021.

Treatment-Emergent AEs

Events, n (%)		All Patients N = 118
All TEAEs		114 (96.6)
Grade ≥3 TEAEs[a]		80 (68.0)
MK-1026-related TEAE		78 (66.1)
Grade ≥3 related TEAEs[b]		31 (26.3)
Related TEAEs leading to discontinuation		9 (7.6)
TEAEs ≥20%	**All**	**Grade ≥3**
Fatigue	33.1%	3.4%
Constipation	31.4%	0.8%
Dysgeusia	28.0%	0
Cough	24.6%	0
Nausea	24.6%	0.8%
Pyrexia	24.6%	0
Dizziness	22.9%	0
Hypertension	22.9%	9.3%
Peripheral edema	22.0%	0
Diarrhea	21.2%	0.8%
Arthralgia	20.3%	0

Data cut-off: April 7, 2021; [a]8 patients had grade 5 TEAEs including death after PD (n=3), sepsis (n=1), dyspnea (n=1), and respiratory failure (n=2); [b]No grade 5 drug-related TEAEs were reported.

First-in-Human Study of Lisaftoclax (APG-2575), a Novel BCL-2 Inhibitor (BCL-2i), in Patients (pts) with Relapsed/Refractory (R/R) Chronic Lymphocytic Leukemia (CLL) and Other Hematologic Malignancies (HMs)

Sikander Ailawadhi,[1] Asher Alban Akmal Chanan-Khan,[1] Aneel Paulus,[1] Zi Chen,[2] Bo Huang,[2] Marina Konopleva,[3] Danielle M. Brander,[4] David Rizzieri,[4] Masa Lasica,[5] Constantine Si Lun Tam,[5] Costas K. Yannakou,[6] H. Miles Prince,[6] Matthew Steven Davids,[7] Zhicong He,[8] Ming Lu,[9] Mohammad Ahmad,[9] Mingyu Li,[9] Eric Liang,[9] Boyd Mudenda,[9] Dajun Yang,[2,10] and Yifan Zhai[9]*

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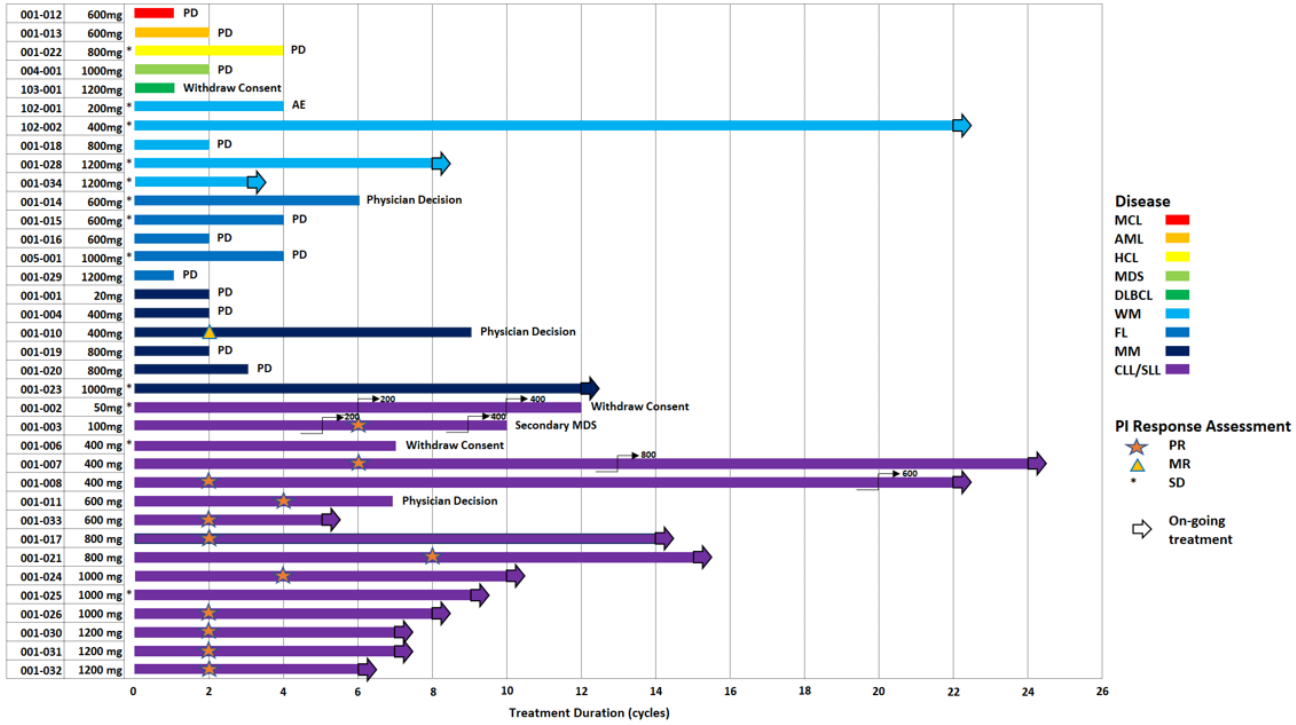
RESULTS

Table 1. Baseline characteristics and disposition for all patients

	N = 36		N = 36
Age, yr		**Median (range) no. of previous therapies**	2.0 (1–13)
Median (range)	70.0 (39–89)		
≥ 70, no. (%)	19 (52.8)		
		Treatment discontinuation, no. (% of total)	
Gender, no. (%)		No	15 (41.7)
Male	26 (72.2)	Yes	21 (58.3)
Female	10 (27.8)	Adverse event	2 (9.5)
		Progressive disease	13 (61.9)
Type of cancer, no. (%)[b]		Withdrawal by patient	3 (14.3)
CLL/SLL	15 (41.7)	Physician decision	3 (14.3)
NHL	12 (33.3)	Switch to standard of care regimen due to symptomatic anemia	1 (4.8)
MM	6 (16.7)	Switch to other treatment option due to hepatitis B reactivation	1 (4.8)
Myeloid	2 (5.6)	Switch to other treatment option due to lack of response	1 (4.8)
Hairy-cell leukemia	1 (2.8)		

Figure 2. Swimmer plot showing efficacy of APG-2575 in all patients



Venetoclax, Obinutuzumab and Atezolizumab (PD-L1 Checkpoint Inhibitor) for Treatment for Patients with Richter Transformation

Nitin Jain, Alessandra Ferrajoli, Philip Thompson, Marina Konopleva, Michael Green, Deepa Sampath, Sattva Neelapu, Koichi Takahashi, Paolo Strati, Jan Burger, Rashmi Kanagal-Shamanna, Joseph Khoury, Naveen Garg, Xiaoping Su, Xuemei Wang, Hinalben Patel, Ana Ayala, Hagop Kantarjian, Michael Keating, William Wierda

Department of Leukemia
The University of Texas MD Anderson Cancer Center
ASH 2021, Abstract 1550

Treatment Schema

	C1D1	C1D2	C1D3-4	C1D8	C1D15	C2-9D1	C2-9D2	C10-25
Atezolizumab (1680 mg IV, split over 2 days)	-	-	X	-	-	X	X	-
Obinutuzumab, mg	100	900	-	1000	1000	1000	-	-
Venetoclax	-					Weekly dose escalation starting C2D1 at 20mg daily to a target dose 800mg daily (Total 24 cycles of venetoclax, C2-C25)		

Each cycle = 28 days

Response assessment with bone marrow aspirate/biopsy and PET scan:
End of C1, C4, C9, C25

Pretreatment Characteristics and Response for Previously untreated RT (N=7)

Age, yrs	Sex	Prior CLL Rx	Prior RT Rx	IGHV status	FISH	Cytogenetics	Mutations	Best PET response	Best Marrow response	Subsequent Allo-SCT in remission	Current status
61	F	none	none	not done	17p	diploid	Not done	CMR	U-MRD	Yes	Relapsed post-SCT; receiving salvage Rx
70	M	BR	none	UM	11q	no metaphase	*NOTCH1*	CMR	U-MRD	Yes	In ongoing remission 9+ mos post-SCT
52	F	Ibrutinib	none	UM	17p	complex	*TP53*, *BTK*	PMR	H-MRD+	No	Relapsed while awaiting SCT*
75	M	Ibrutinb	none	UM	17p	complex	*TP53*	CMR	H-MRD+	No	On study C15+
61	F	Ibrutinib	none	UM	17p	complex	*TP53*	CMR	U-MRD	Yes	In ongoing remission 8+ mos post-SCT
80	F	Chl + Obin; acalabrutinib	none	UM	T12	+12	None	CMR	U-MRD	No	Died from COVID-19 PNA in C5
74	M	Ibrutinib	none	UM	Normal	diploid	*NOTCH1*	CMR	L-MRD+	No	On study C6+

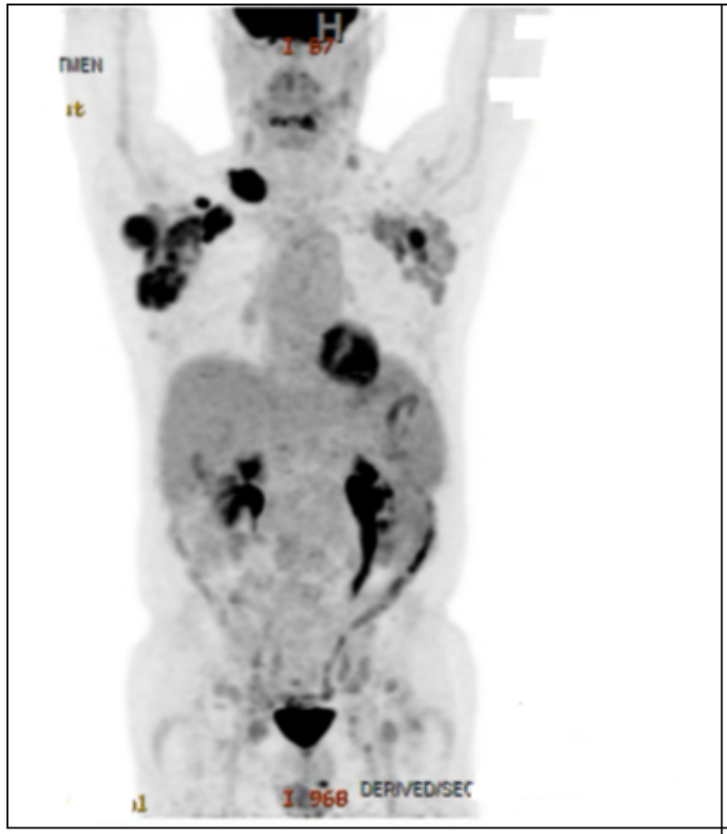
*Pt achieved PMR and relapsed in C8, prior to a planned allo-SCT; she then achieved remission after non-covalent BTK inhibitor and proceeded to allo-SCT

Note: One pt (58-year-old male) with previously untreated CLL (unmutated IGHV, del(17p), TP53 mutation, NOTCH1 mutation) developed RT and received R-CHOP for 3 cycles with no response. The pt was subsequently enrolled on the current trial but did not respond.

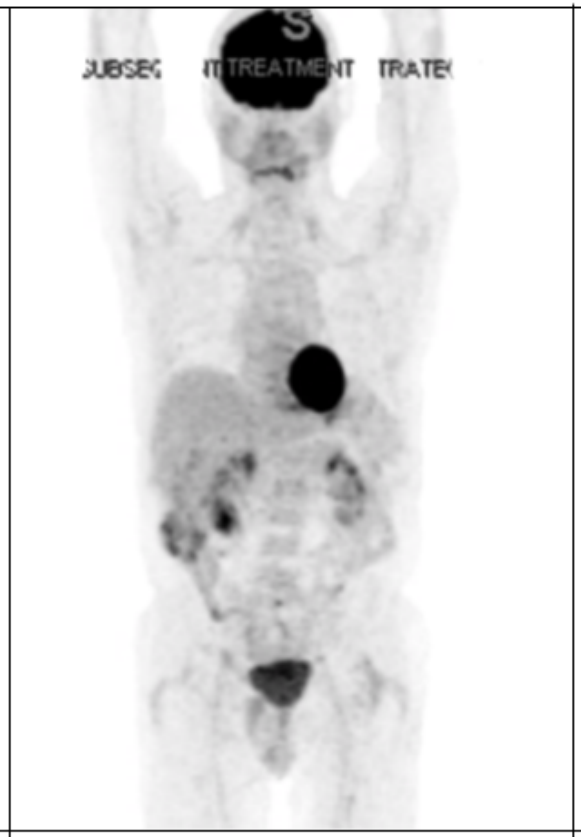
U-MRD: undetectable MRD at 10^{-4}; L-MRD+: MRD 0.01 to <1%; H-MRD+: MRD ≥1%

Patient Response (1)

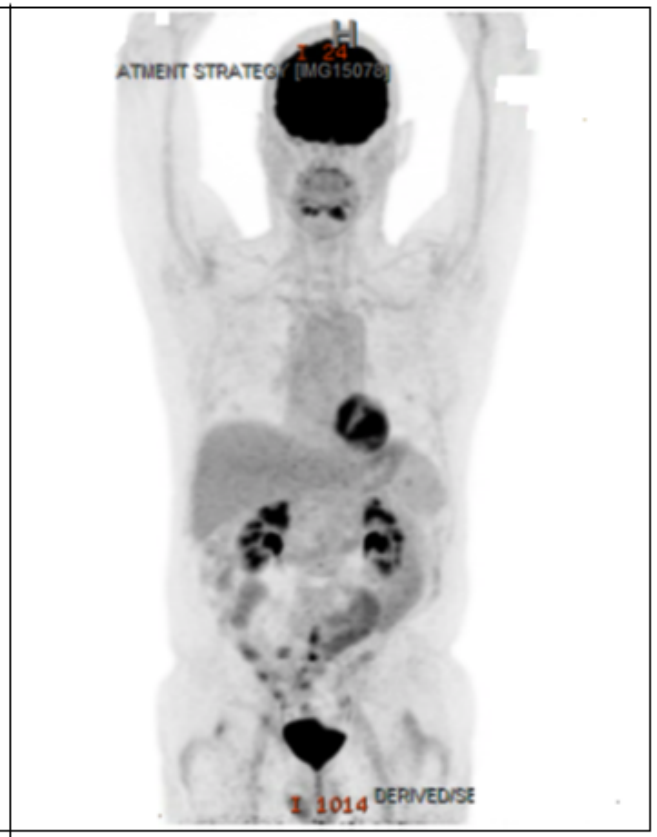
- 70-yr-old
- del(11q), *NOTCH1*-m, IGHV-UM
- BR for CLL
- RT June 2020
- Atezo + VEN + Obin as frontline therapy for RT
- Underwent allo-SCT in Feb 2021 in CMR and marrow U-MRD remission



Baseline (July 2020)



End of C4 (Nov 2020)



End of C6 (pre-SCT) (Feb 21)

Marrow baseline – 70% CLL	0.06% MRD CLL	U-MRD

Novel Agents in CLL

- Non Covalent BTKi
  - Pirtobrutinib (LOXO-305)
  - Nemtabrutinib (MK-1026, ARQ 531)
- Covalent BTKi – Zanubrutinib
- Novel PI3Ki – Umbralisib
- Novel BCL2i
  - Lisaftoclax (APG-2575)
  - BGB-11417
  - LP-118 (dual BCL2/Bcl-xl inhibitor)
- PKCβ inhibitor – MS553
- BTK degrader – NX-2127
- CAR-T – Liso-cel (CD19 CAR)
- CD20 BiTEs

Thank you!

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