Memorial Sloan Kettering Cancer Center

Pirtobrutinib

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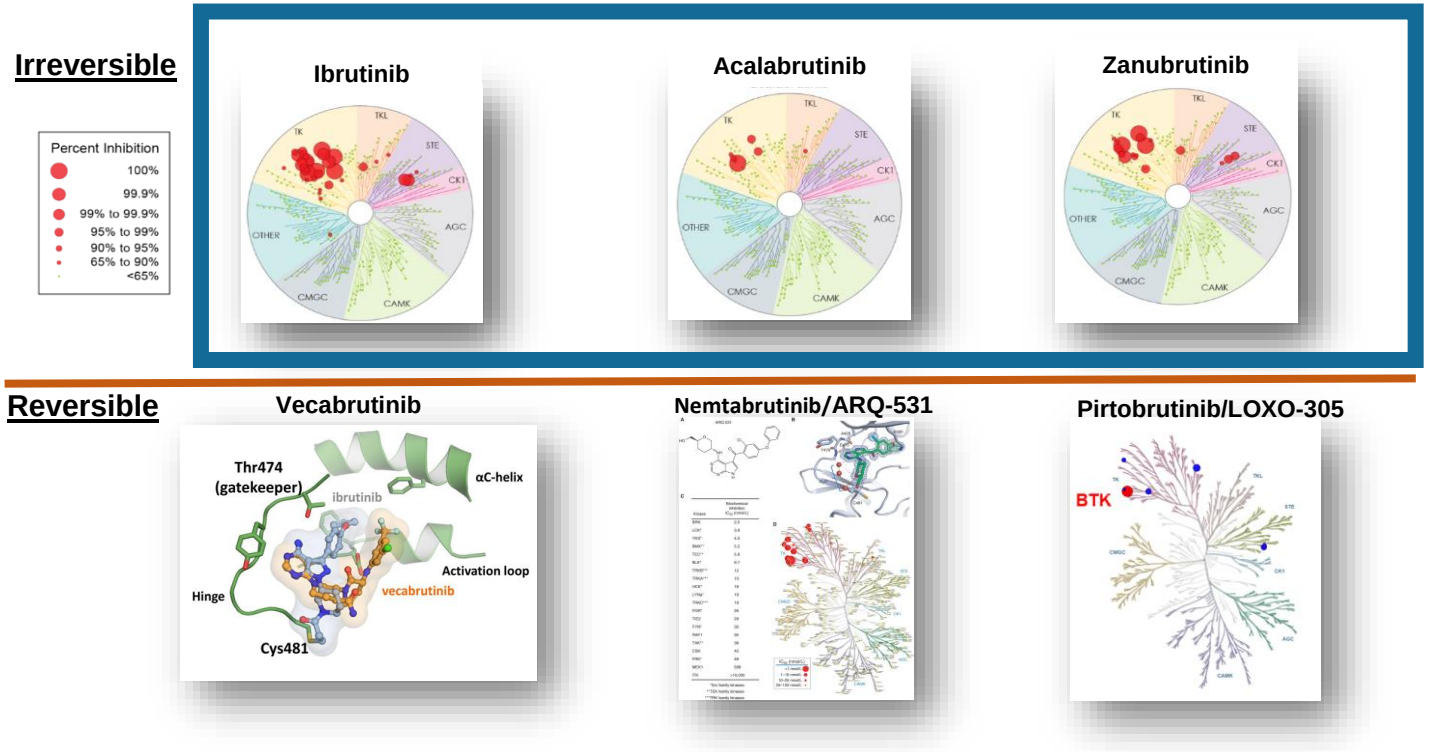
What are the unmet needs in the R/R setting?

Limitations of covalent BTK inhibitors?

No standard of care for double-refractory disease?

Several BTKi options to consider with differences in BTKi specificity, MOA, and potential for off-target effects.

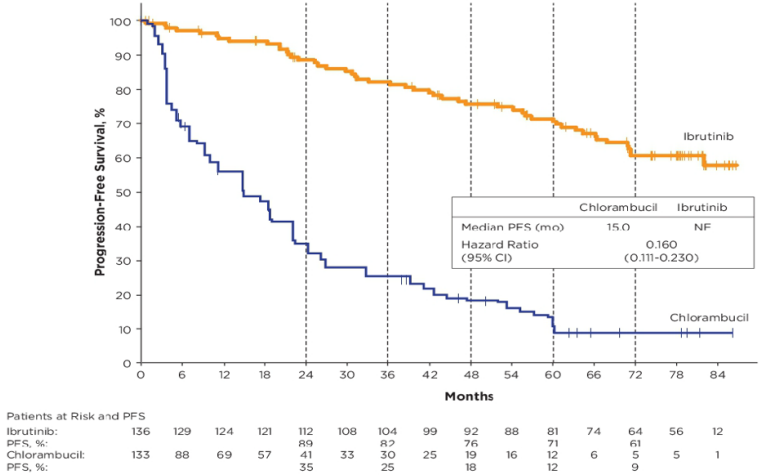


BTKi, Bruton tyrosine kinase inhibitors; MOA, mechanism of action.

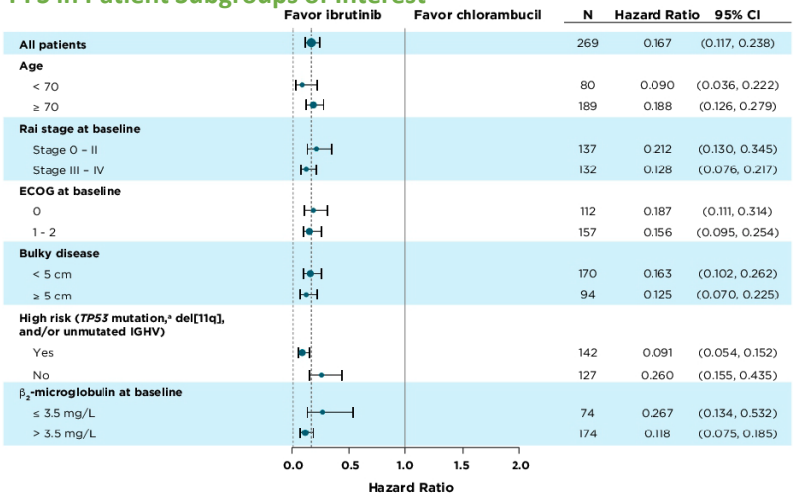
Kaptein A, de Bruin G, Emmelot-van Hoek M et al. *Blood.* 2018;132(Supplement 1):1871.

Up to 7 Years of Follow-Up in the RESONATE-2 Study of Ibrutinib for Patients With TN CLL: Efficacy

PFS: Ibrutinib vs Chlorambucil



PFS in Patient Subgroups of Interest



Efficacy

- Ibrutinib-treated patients had an 84% reduction in risk of progression or death
- Ibrutinib led to a 97% reduction in risk of PD or death in patients with del(11q) and 80% for those without del(11q) vs chlorambucil
- Ibrutinib led to an 89% and 80% reduction in risk of PD or death in patients with unmutated and mutated *IGHV*, respectively, vs chlorambucil

Barr PB, et al. ASCO 2020. Abstract 7523.

Overall discontinuation rate at 7 years = 53%

Ibrutinib discontinuation for intolerance

ARTICLES

Toxicities and outcomes of 616 ibrutinib-treated patients in the United States: a real-world analysis

41% of patients discontinued ibrutinib at a median follow-up of 17 months

Toxicity accounted for the **majority** of discontinuations (over half) in both F/L and R/R CLL patients

Most common toxicities in R/R population: **atrial fibrillation 12.3%, infection 10.7%, pneumonitis 9.9%, bleeding 9%, and diarrhea 6.6%**

Reason for ibrutinib discontinuation	Ibrutinib in front-line (n=19)	Ibrutinib in relapse (n=231)
Toxicity	63.1% (n=12)	50.2% (n=116)
CLL progression	15.8% (n=3)	20.9% (n=49)
Other/unrelated death	5.3% (n=1)	12.1% (n=28)
Physician's or patient's preference	10.5% (n=2)	6.7% (n=15)
RT DLBCL	5.3% (n=1)	4.6% (n=10)
Stem cell transplantation/CAR T-cell	0	3.3% (n=8)
Financial concerns	0	0.8% (n=2)
Secondary malignancy	0	0.8% (n=2)
RT Hodgkin lymphoma	0	0.4% (n=1)

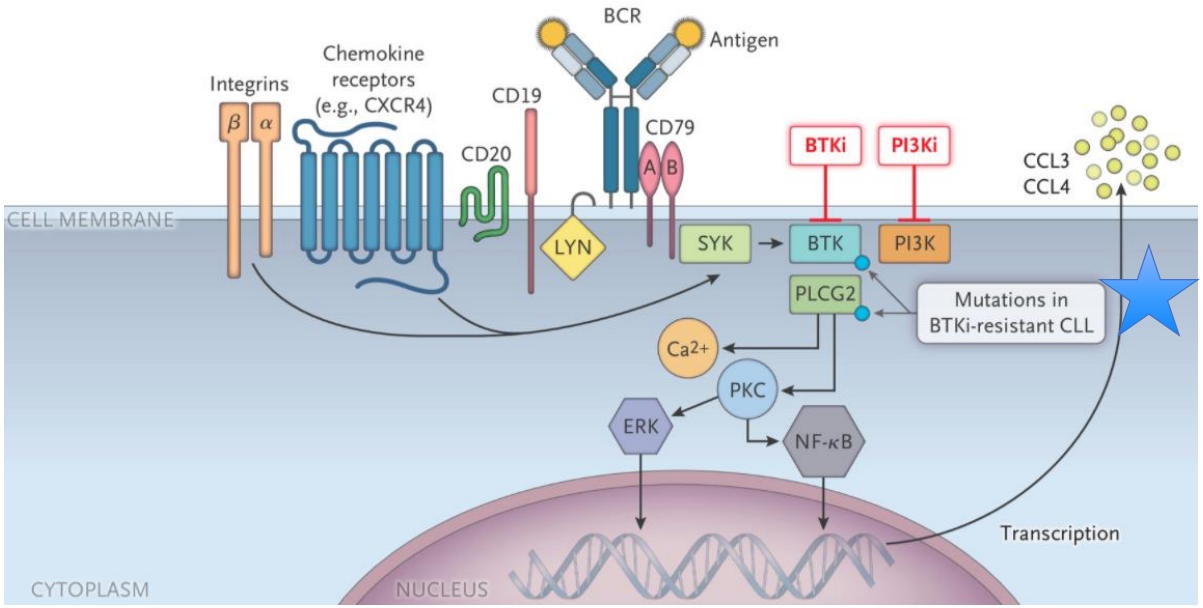
CLL: chronic lymphocytic leukemia; RT DLBCL: Richter transformation to diffuse large B-cell lymphoma; CAR T-cell: chimeric antigen receptor T-cell); RT: Richter transformation.

This study identified covalent BTK inhibitor **intolerance** as a major emerging issue in the field of CLL

BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; F/L, first line; R/R, relapsed/refractory.

Mato et al *Haematologica* 2018;103:874-879.

Acquired Resistance to Covalent BTKi



- Majority of patients have identified mutations in ***BTK*C481** at the time of disease progression on ibrutinib; ~53-87% of patients
- Mutations also identified in PLCG2, immediately downstream of BTK
- *BTK*C481 mutations are also mechanism of resistance for acalabrutinib; 69% of patients

Figure from Burger et al *NEJM* 2020; Woyach et al *NEJM* 2014; Woyach et al *JCO* 2017; Scarfo et al EHA 2020; Ahn et al *Blood* 2017; Woyach et al ASH 2019; Burger *Nature Communications* 2016

Treatment of CLL after Covalent BTKi

- **Venetoclax:** oral BCL2-inhibitor
- Front-line setting and relapsed setting including after cBTKi
- Approved as **fixed-duration** therapy (24 months in R/R setting)

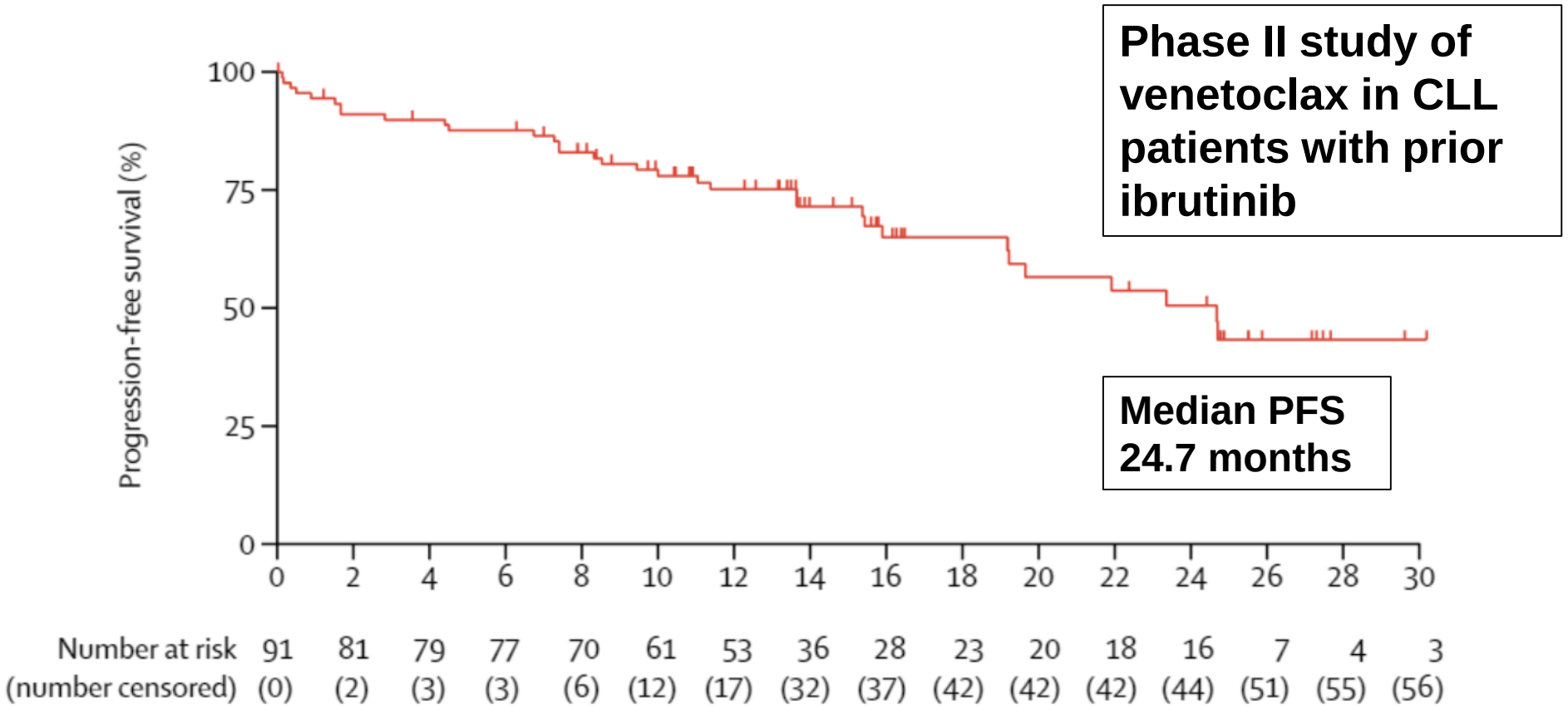


Figure from Jones et al *Lancet Oncology* 2018;
Seymour et al *NEJM* 2020; Fischer et al *NEJM* 2020

“Double Exposed” Patient: Unmet Need

A subset of patients will ultimately have **progressive CLL** following treatment with both venetoclax and covalent BTK inhibitor (cBTKi)

Standard of care options:

Chemo+/-immunotherapy (CIT)

Phosphoinositide-3-kinase inhibitors (PI3Ki) idelalisib, duvelisib

Clinical trial options:

Non-covalent BTKi (ncBTKi)

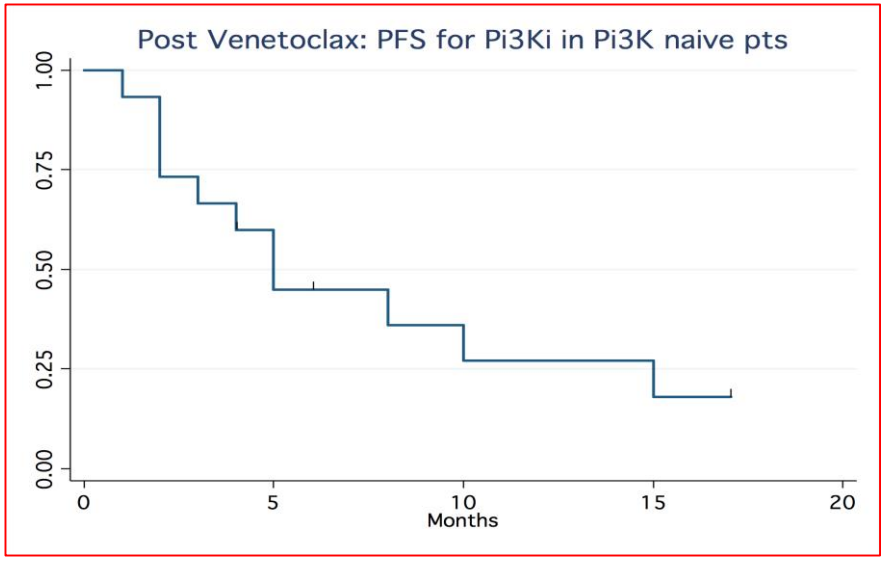
CAR T-cell therapy

Several other investigational agents

Landmark trials leading to approvals of CIT and PI3Ki did not include patients previously treated with cBTKi or venetoclax.

Furman et al *NEJM* 2014; Flinn et al *Blood* 2018; Mato et al *Lancet* 2021; Siddiqi et al *Blood* 2021; Thompson MC et al ASH 2021

After BTKi → venetoclax: PI3Ki did not result in durable remissions and therefore is not an acceptable SOC in the 3rd line setting in modern era



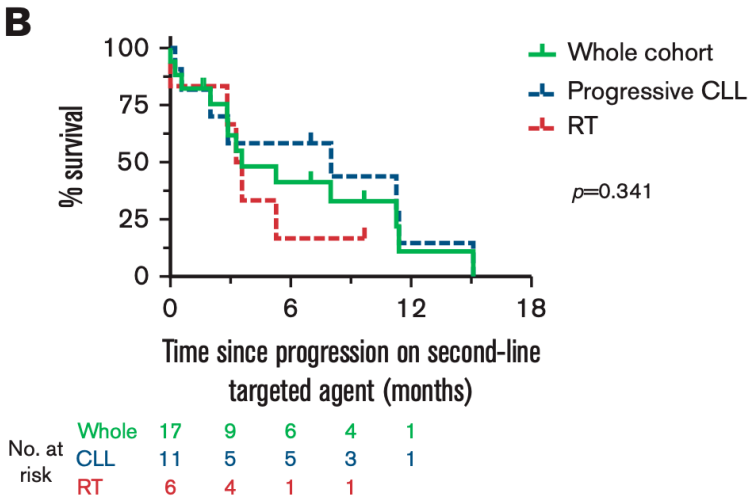
Median PFS = 4 months

Outcomes of patients with CLL sequentially resistant to both BCL2 and BTK inhibition

Thomas E. Lew,[1,2,*] Victor S. Lin,[1-3,*] Edward R. Cliff,[1] Piers Blombery,[1,3,4] Ella R. Thompson,[4] Sasanka M. Handunnetti,[1] David A. Westerman,[1,3,4] Bryone J. Kuss,[5] Constantine S. Tam,[1,3,6] David C. S. Huang,[2,3] John F. Seymour,[1,3] Andrew W. Roberts,[1-3] and Mary Ann Anderson[1,2]

[1]Department of Clinical Haematology, The Royal Melbourne Hospital and Peter MacCallum Cancer Centre, Melbourne, VIC, Australia; [2]Blood Cells and Blood Cancer Division, Walter and Eliza Hall Institute of Medical Research, Parkville, VIC, Australia; [3]Faculty of Medicine, Dentistry and Health Sciences, The University of Melbourne, Parkville, VIC, Australia; [4]Department of Pathology, Peter MacCallum Cancer Centre, Melbourne, VIC, Australia; [5]College of Medicine and Public Health, Flinders University, Adelaide, SA, Australia; and [6]Department of Haematology, St Vincent's Hospital Melbourne, Fitzroy, VIC, Australia

Double Refractory Pts

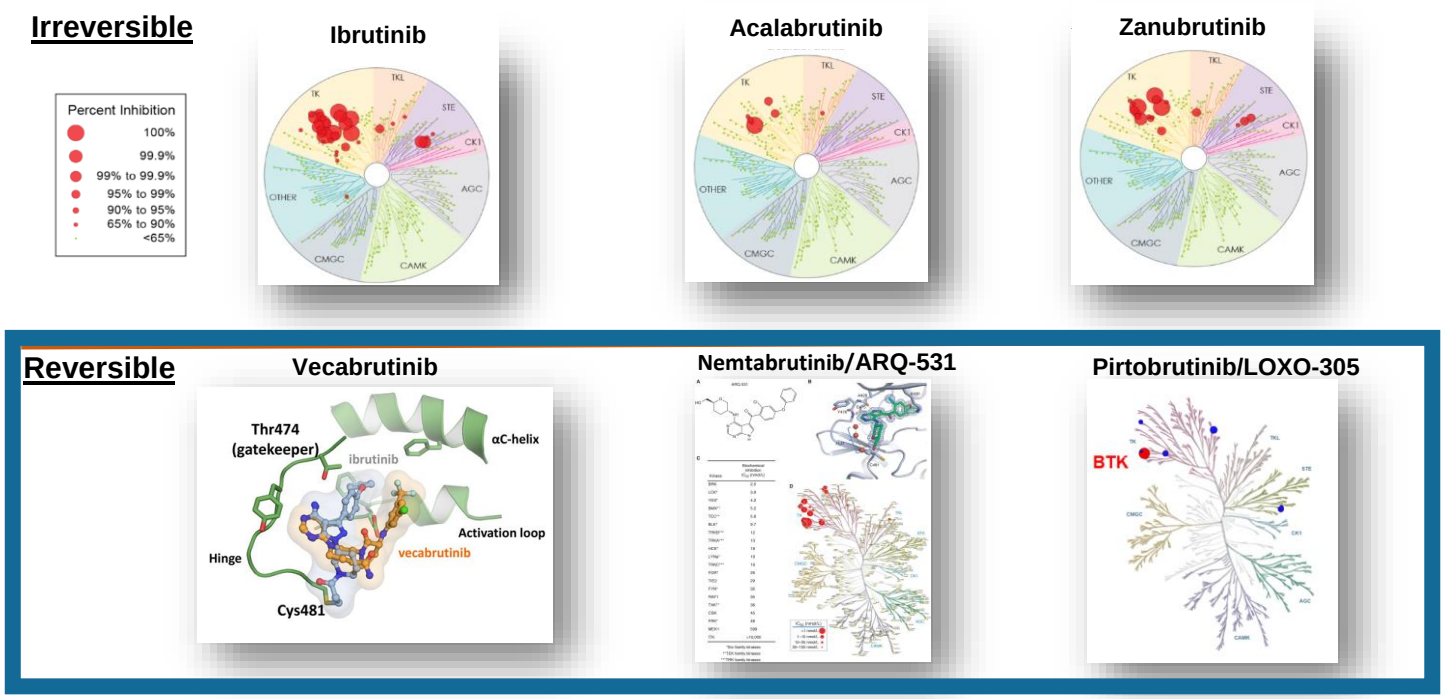


Median OS = 3.6 months

Mato et al, CCR 2020, Lew, et al Blood Advances 2022

Non-Covalent BTK Inhibitors

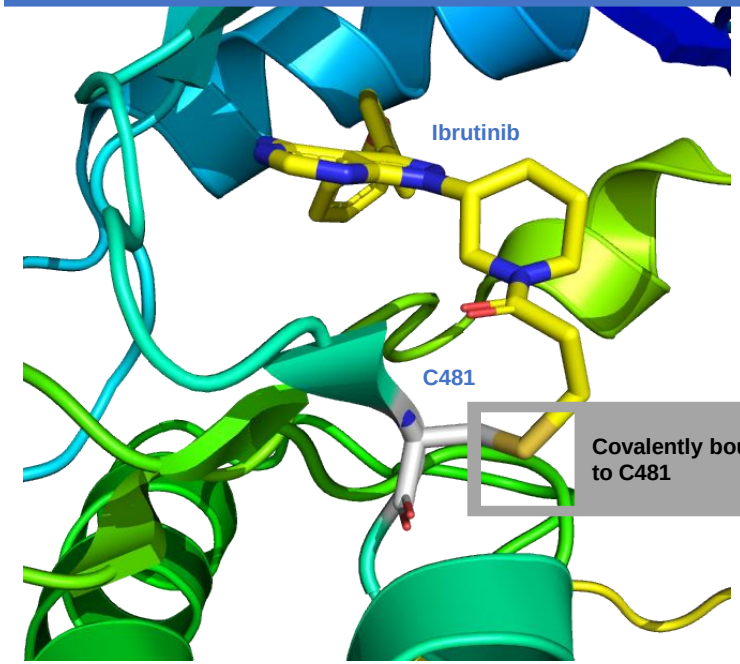
Several BTKi options to consider with differences in BTKi specificity, MOA, and potential for off-target effects.



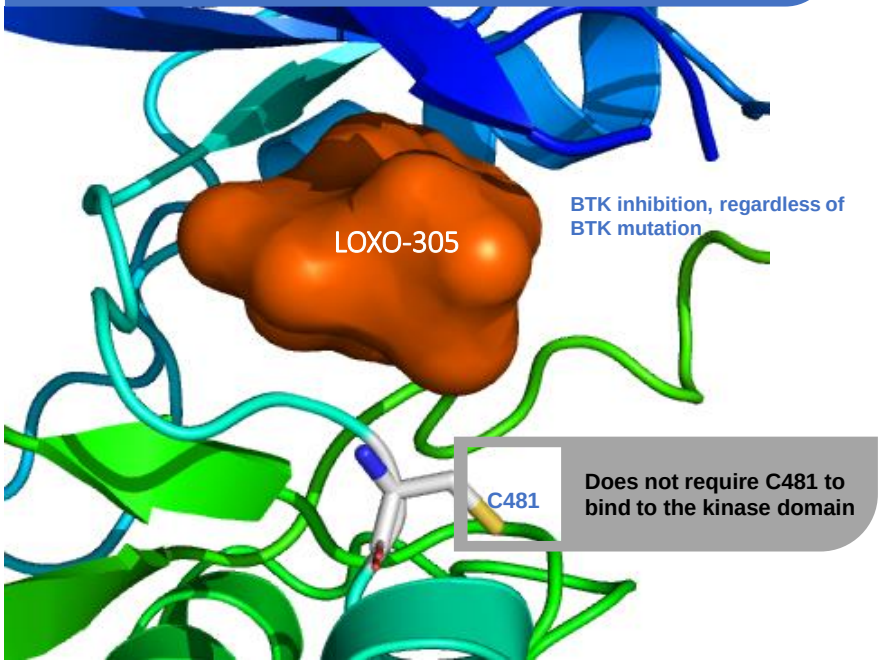
Kaptein et al. *Blood* 2018;132(suppl 1):1871.

Pirtobrutinib Is a Non-Covalent BTK Inhibitor

Covalent BTK inhibitors (ibrutinib, acalabrutinib, zanubrutinib) require WT BTK for activity



LOXO-305 is a non-covalent BTK inhibitor that is potent against both WT and C481-mutant BTK



WT=wild-type.

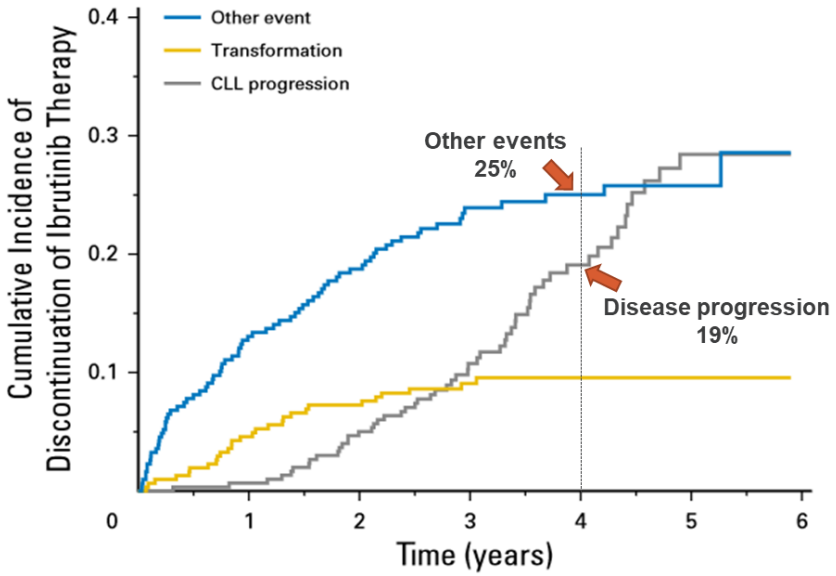
Pirtobrutinib, A Highly Selective, Non-covalent (Reversible) BTK Inhibitor In Previously Treated CLL/SLL: Updated Results From The Phase 1/2 BRUIN Study

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]

[1]Memorial Sloan Kettering Cancer Center, New York, USA; [2]Swedish Cancer Institute, Seattle, USA; [3]University of North Carolina at Chapel Hill, Chapel Hill, USA; [4]Medical College of Wisconsin, Milwaukee, USA; [5]Herbert Irving Comprehensive Cancer Center, Columbia University, New York, USA; [6]Department of Haematology, St. James's University Hospital, Leeds, UK; [7]Institute of Hematology and Transfusion Medicine, Warsaw, Poland; [8]Oxford University Hospitals NHS Foundation Trust, Churchill Cancer Center, Oxford, UK; [9]The Ohio State University Comprehensive Cancer Center, Columbus, USA; [10]MD Anderson Cancer Center, Houston, USA; [11]Linear Clinical Research and Sir Charles Gairdner Hospital, Perth, Australia; [12]Winship Cancer Institute, Emory University, Atlanta, GA, USA; [13]Florida Cancer Specialists/Sarah Cannon Research Institute, Sarasota, USA; [14]University of California San Francisco, San Francisco, USA; [15]Mary Crowley Cancer Research, Dallas, USA; [16]Peter MacCallum Cancer Center, Royal Melbourne Hospital, and University of Melbourne, Melbourne, Australia; [17]Plymouth Hospitals NHS Trust - Derriford Hospital, Plymouth, UK; [18]Lymphoma Program, Abramson Cancer Center, University of Pennsylvania, Philadelphia, USA; [19]University of Miami Miller School of Medicine, Miami, USA; [20]Fred Hutchinson Cancer Research Center, [21]Sarah Cannon Research Institute, Nashville, USA; [22]Department of Hematology and Medical Oncology, Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY, [23]Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Chicago, IL, USA; [24]Cleveland Clinic, Cleveland, OH, USA; [25]Northwell Health Cancer Institute, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell Health, New Hyde Park, NY; [26]Università Vita-Salute San Raffaele and IRCCS Ospedale San Raffaele, Milan, Italy; [27]Loxo Oncology at Lilly, Stamford, CT, USA; [28]Dana-Farber Cancer Institute and Harvard Medical School, Boston, USA; [29]Maria Sklodowska-Curie National Research Institute of Oncology, Krakow, Poland

Resistance and Intolerance Limit Covalent BTK Inhibitor Outcomes

Ibrutinib discontinuation from 4 prospective studies[1]



- Ibrutinib discontinuation rates at 5 years
  - Front line = 41%[1]
  - Relapsed/refractory = 54%[2]

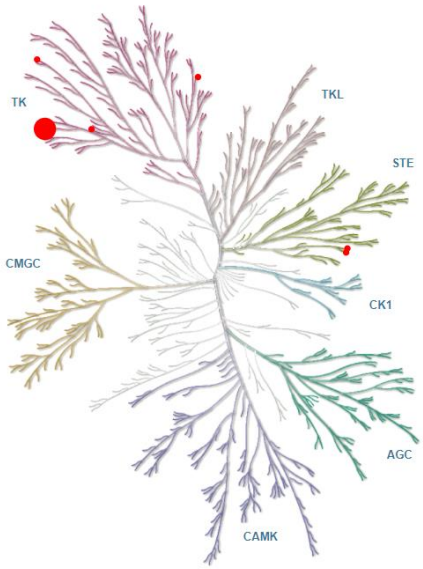
Available options following covalent BTK inhibitor treatment are limited:

- **Covalent BTK inhibitor retreatment**: Only effective in the context of covalent BTK intolerance, not progression
- **Venetoclax**: Efficacious, but complicated administration and not appropriate for all patients
- **PI3K Inhibitors**: Limited benefit in this population and significant toxicity burden
- **Chemoimmunotherapy**: Limited benefit in this population and most current patients have already received these regimens

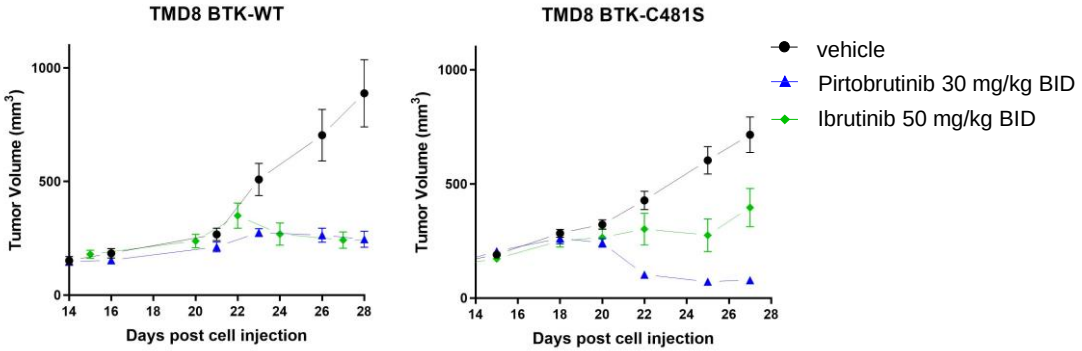
[1]Woyach et al. *J Clin Oncol*. 2017;35:1437-1443. [2]Burger. *Leukemia* 2020;34:787-7898.

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

Kinome selectivity[1]
Highly selective for BTK



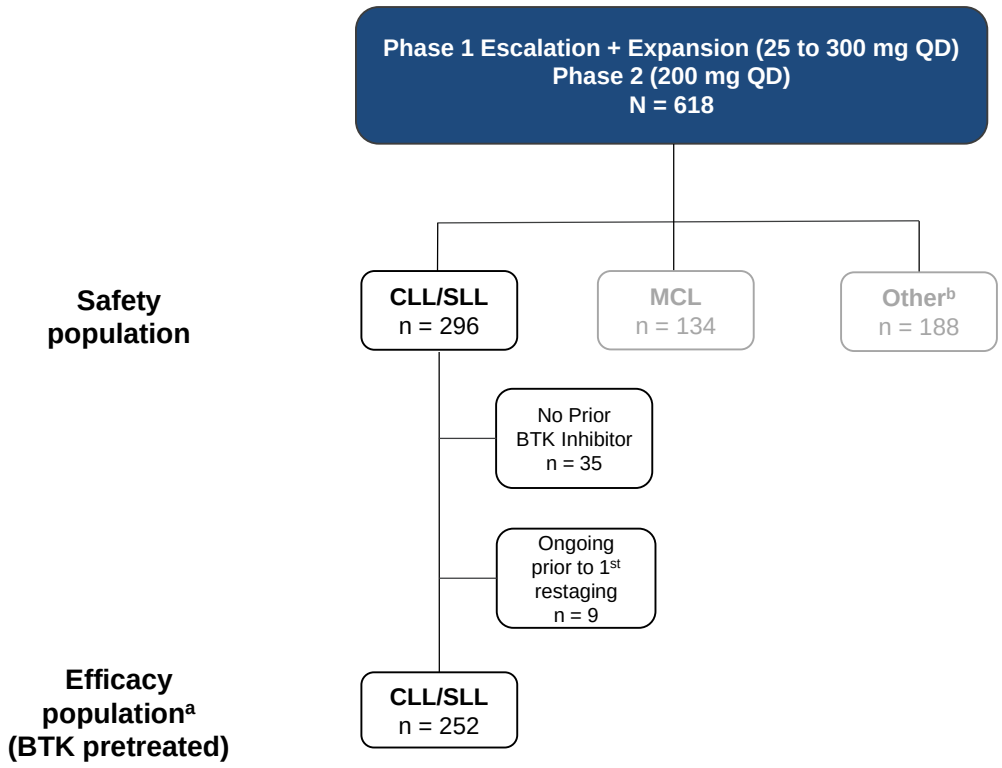
Xenograft models
In vivo activity similarly efficacious as ibrutinib in WT; superior in C481S



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

BID, twice-daily; BTK, Bruton tyrosine kinase.
[1]Mato et al. *Lancet* 2021;397:892-901. [2]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 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 July 16, 2021.

BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; MTD, maximum tolerated dose; ORR, overall response rate; QD, once daily; SLL, small lymphocytic leukemia.

[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 diffuse large B-cell lymphoma, Waldenstrom macroglobulinemia, follicular lymphoma, mantle zone lymphoma, Richter transformation, B-PLL, Hairy Cell Leukemia, PCNSL, and other transformation.

Mato et al. *Lancet* 2021;397:892-901.

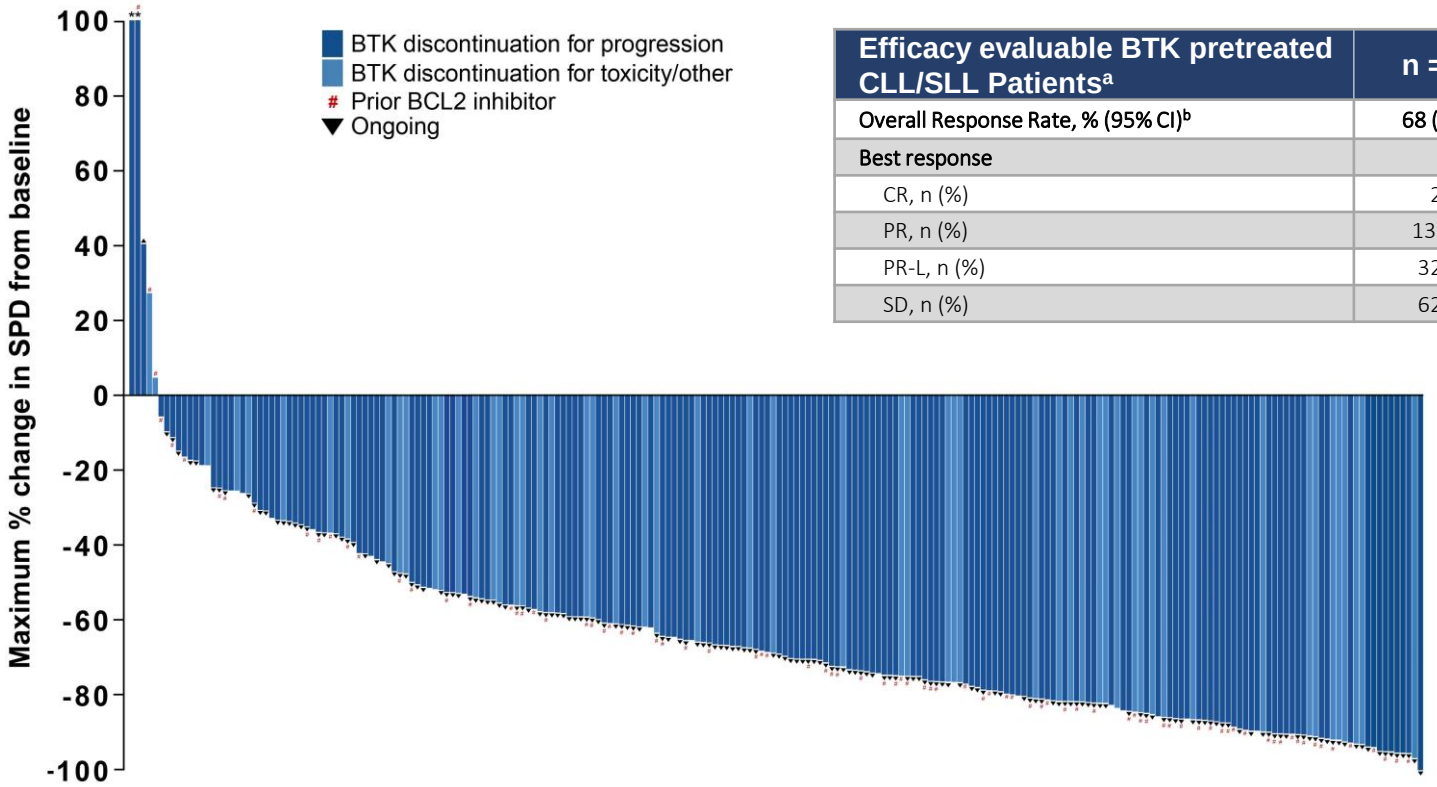
BTK Pretreated CLL/SLL Patient Characteristics

Characteristics	N = 261
Median age, y (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 July 16, 2021.
BTK, Bruton tyrosine kinase; ECOG, Eastern Cooperative Oncology group performance status;
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.
Mato et al. Abstract 391. ASH 2021. https://ash.confex.com/ash/2021/webprogram/Paper147599.html

Pirtobrutinib Efficacy in BTK Pretreated CLL/SLL Patients

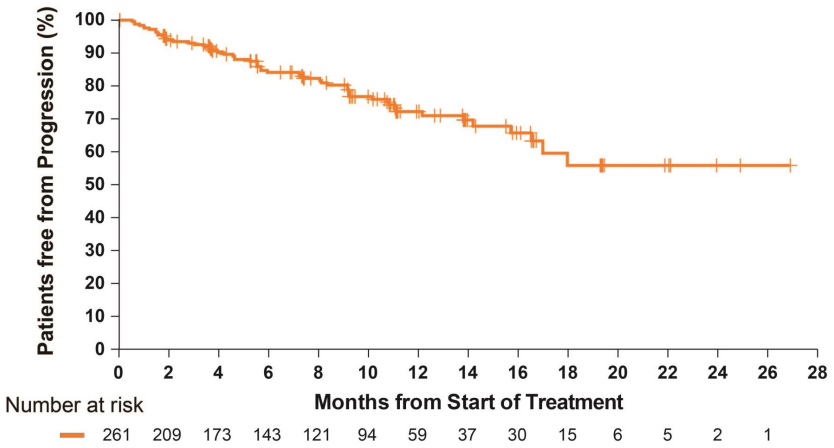


Efficacy evaluable BTK pretreated CLL/SLL Patients[a]	n = 252
Overall Response Rate, % (95% CI)[b]	68 (62-74)
Best response	
CR, n (%)	2 (1)
PR, n (%)	137 (54)
PR-L, n (%)	32 (13)
SD, n (%)	62 (25)

Data cutoff date July 16, 2021.
BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; CR, complete response; PR, partial response; SD, stable disease; SLL, small lymphocytic leukemia.
*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.
Mato et al. Abstract 391. ASH 2021. https://ash.confex.com/ash/2021/webprogram/Paper147599.html

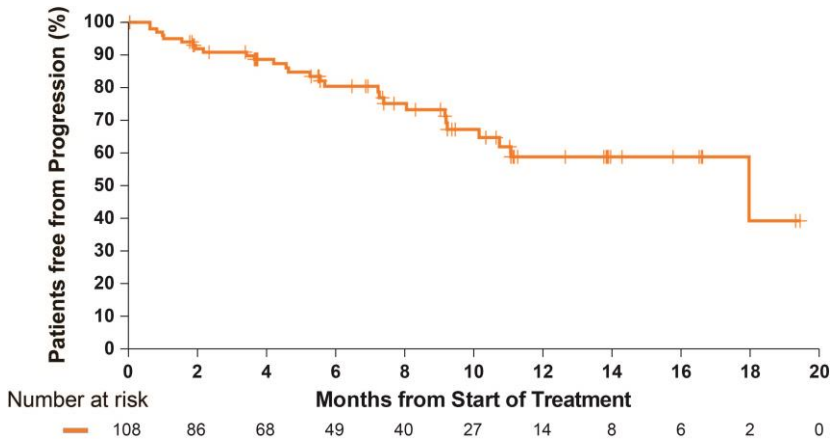
Progression-free Survival in BTK Pretreated CLL/SLL Patients

PFS in at least BTK pretreated patients
Median prior lines = 3



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

PFS in at least BTK and BCL2 pretreated patients
Median prior lines = 5



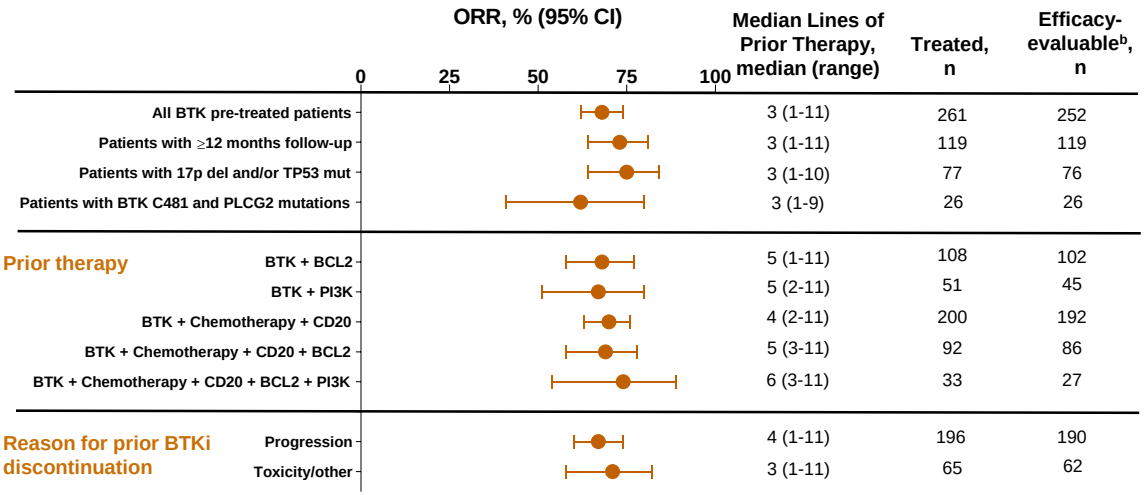
Median PFS: 18 months (95% CI: 10.7 months - Not Estimable)

- 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 pretreated patients

Data cutoff date July 16, 2021.
BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; PFS, progression-free survival.
Response status per iwCLL 2018 according to investigator assessment.
Mato et al. Abstract 391. ASH 2021. https://ash.confex.com/ash/2021/webprogram/Paper147599.html

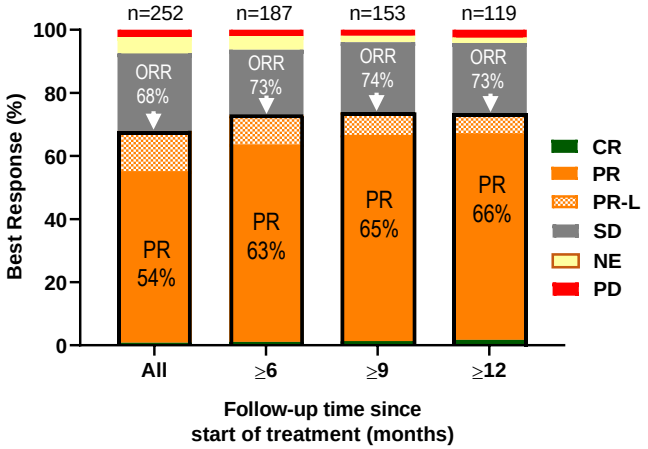
Pirtobrutinib Efficacy in BTK Pretreated CLL/SLL Patients

Pirtobrutinib Efficacy Regardless of Other Prior Therapy[a]



		Median Lines of Prior Therapy, median (range)	Treated, n	Efficacy-evaluable[b], n
All BTK pre-treated patients		3 (1-11)	261	252
Patients with ≥12 months follow-up		3 (1-11)	119	119
Patients with 17p del and/or TP53 mut		3 (1-10)	77	76
Patients with BTK C481 and PLCG2 mutations		3 (1-9)	26	26
Prior therapy	BTK + BCL2	5 (1-11)	108	102
	BTK + PI3K	5 (2-11)	51	45
	BTK + Chemotherapy + CD20	4 (2-11)	200	192
	BTK + Chemotherapy + CD20 + BCL2	5 (3-11)	92	86
	BTK + Chemotherapy + CD20 + BCL2 + PI3K	6 (3-11)	33	27
Reason for prior BTKi discontinuation	Progression	4 (1-11)	196	190
	Toxicity/other	3 (1-11)	65	62

Overall Response Rate Over Time[c]



Data cutoff date July 16, 2021.

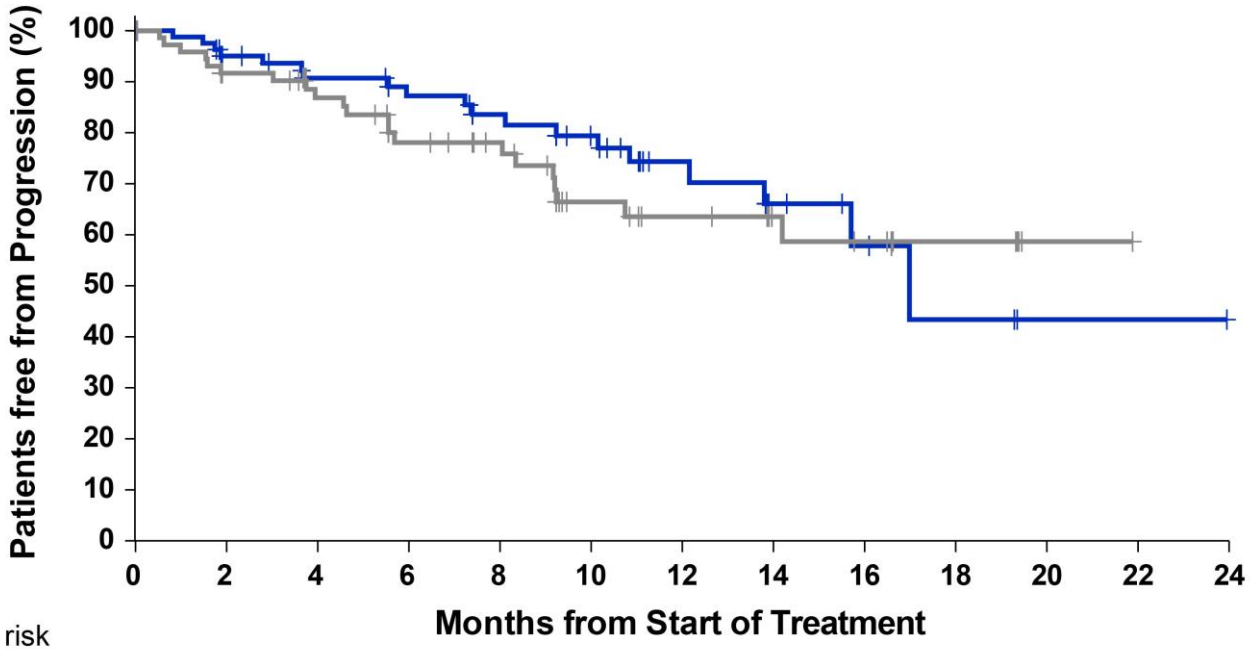
BTKi, Bruton tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease; ORR, overall response rate.

Total % may be different than the sum of the individual components due to rounding. [a]Prior therapy labels indicate that patients received at least the prior therapy, rows are not mutually exclusive. [b]Efficacy evaluable patients are those who had at least one evaluable post-baseline assessment or had discontinued treatment prior to first post-baseline assessment. [c]Includes the BTK pre-treated efficacy-evaluable CLL/SLL patients at the time of data cutoff. Data at each timepoint includes the BTK pre-treated efficacy-evaluable CLL/SLL patients who had the opportunity to be followed for at least the indicated amount of time.

Mato et al. Abstract 391. ASH 2021. https://ash.confex.com/ash/2021/webprogram/Paper147599.html

BTK C481 Mutation Status is not Predictive of Pirtobrutinib Benefit

Progression-free survival by BTK C481 mutation status[a] in CLL/SLL patients with progression on a prior BTK inhibitor



Number at risk													
BTK C481-mutated	84	68	54	49	40	33	18	10	7	3	1	1	0
BTK C481-wildtype	74	62	52	40	35	23	19	13	11	5	1	0	

Data cutoff date July 16, 2021.
BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; SLL, small lymphocytic leukemia.
Response status per iwCLL 2018 according to investigator assessment. [a]BTK C481 mutation status was centrally determined and based on pre-treatment samples.
Mato et al. Abstract 391. ASH 2021. https://ash.confex.com/ash/2021/webprogram/Paper147599.html

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 July 16, 2021.
AEs, adverse events; DLTs, dose-limiting toxicities; MTD, maximum tolerated dose.; RP2D, recommended phase 2 dose.
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.
Mato et al. Abstract 391. ASH 2021. https://ash.confex.com/ash/2021/webprogram/Paper147599.html

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 (ie, progression vs intolerance), or other classes of prior therapy received (including covalent BTK inhibitors, BCL2 inhibitors, and PI3K-delta inhibitors)

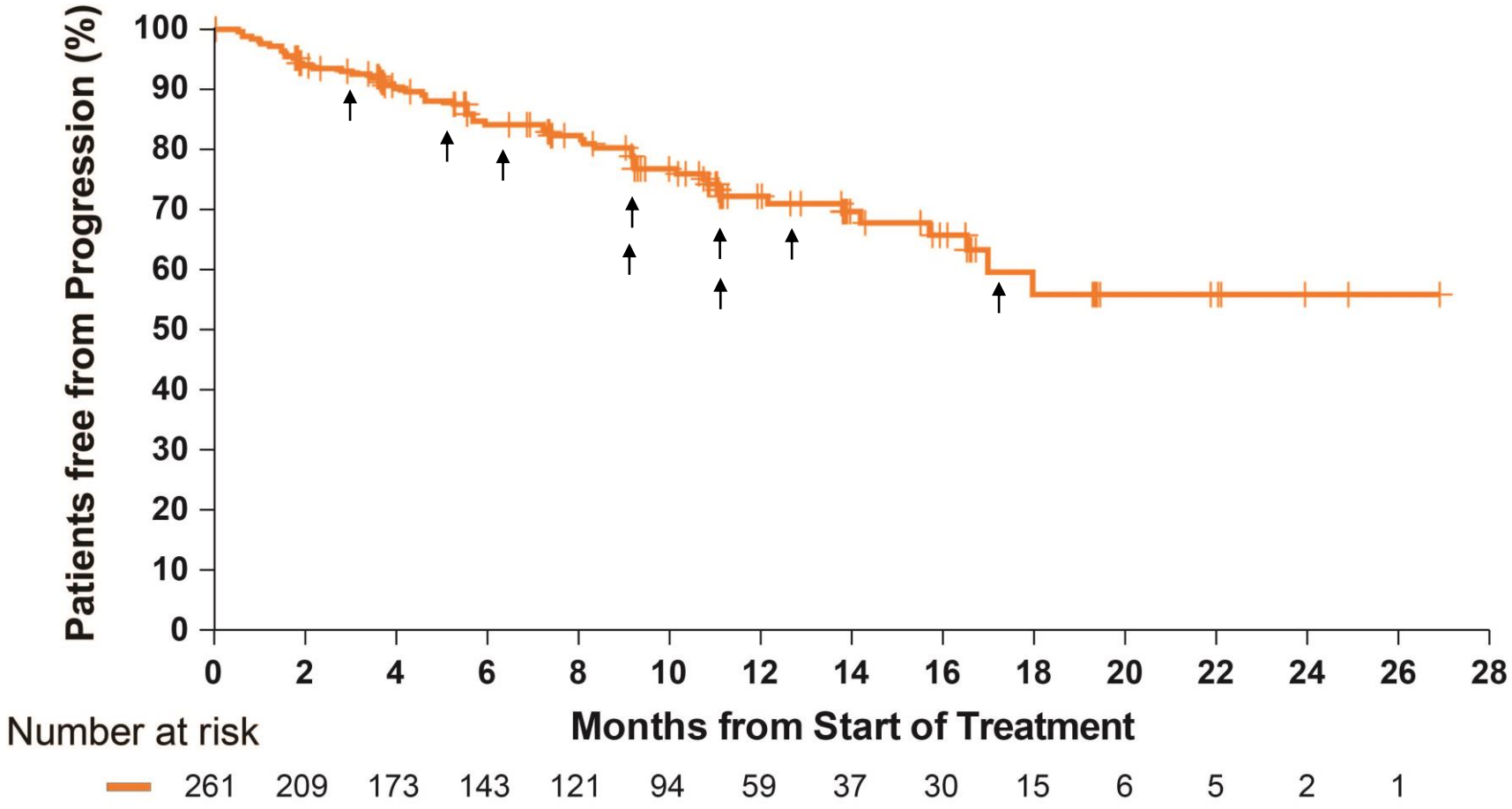
- Favorable safety and tolerability are consistent with the design of pirtobrutinib as a highly selective and non-covalent reversible BTK inhibitor

- 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)

BendaR, bendamustine and rituximab; BTKi Bruton tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; IdelaR, idelalisib and rituximab; SLL, small lymphocytic leukemia; VenR, venetoclax and rituximab.

Progression of Disease on Pirtobrutinib

Progression on Pirtobrutinib: MSK Cohort



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The NEW ENGLAND JOURNAL of MEDICINE

Mechanisms of resistance to non-covalent BTKi

ORIGINAL ARTICLE FREE PREVIEW

Mechanisms of Resistance to Noncovalent Bruton's Tyrosine Kinase Inhibitors

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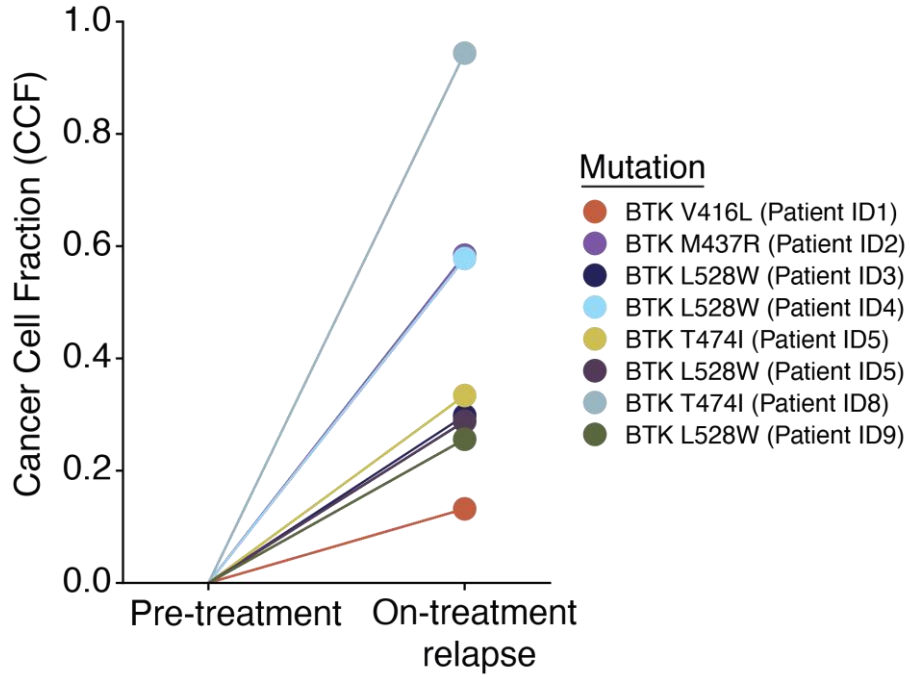
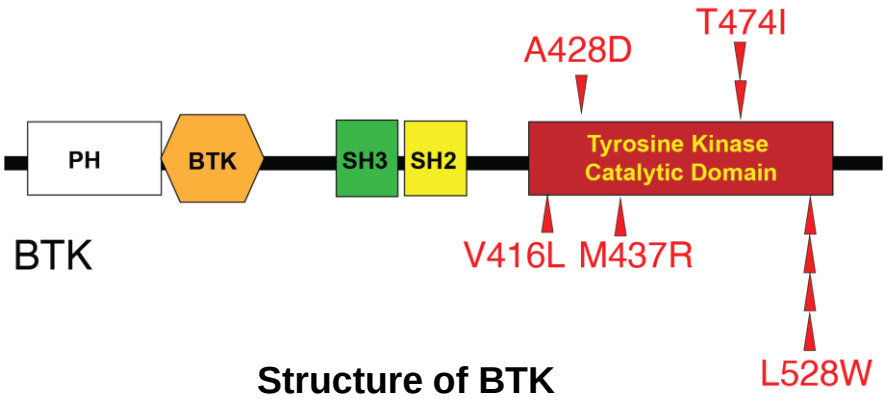
Acquired *BTK* mutations on Pirtobrutinib





Structure of BTK

We identified novel acquired mutations in BTK at the time of disease progression including:

- ***BTK* L528W**
- ***BTK* V416L**
- ***BTK* M437R**
- ***BTK* T474I**
- ***BTK* A428D**

These mutations cluster around the tyrosine kinase catalytic domain of BTK.

Additionally, several patients with progressive disease had pre-existing PLCG2 mutations.

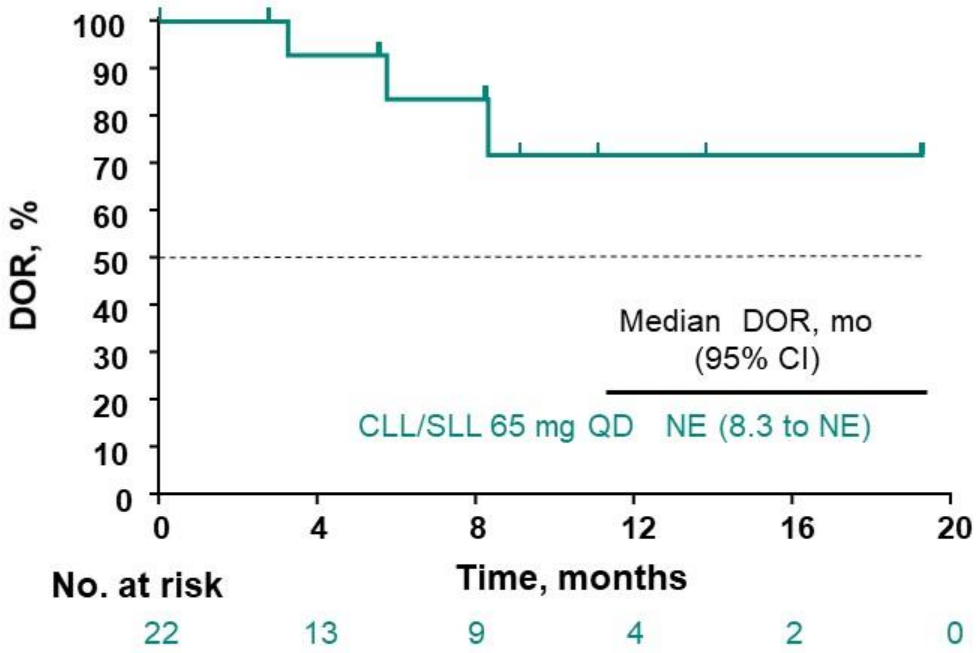
Wang E*, Mi X*, Thompson MC*… Mato, AR*, Taylor J*, Abdel-Wahab O*, NEJM 2022

Nemtabrutinib

Woyach MK-1026 ASH 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.

Nemtabrutinib

Woyach MK-1026 ASH 2021

Treatment-Emergent AEs

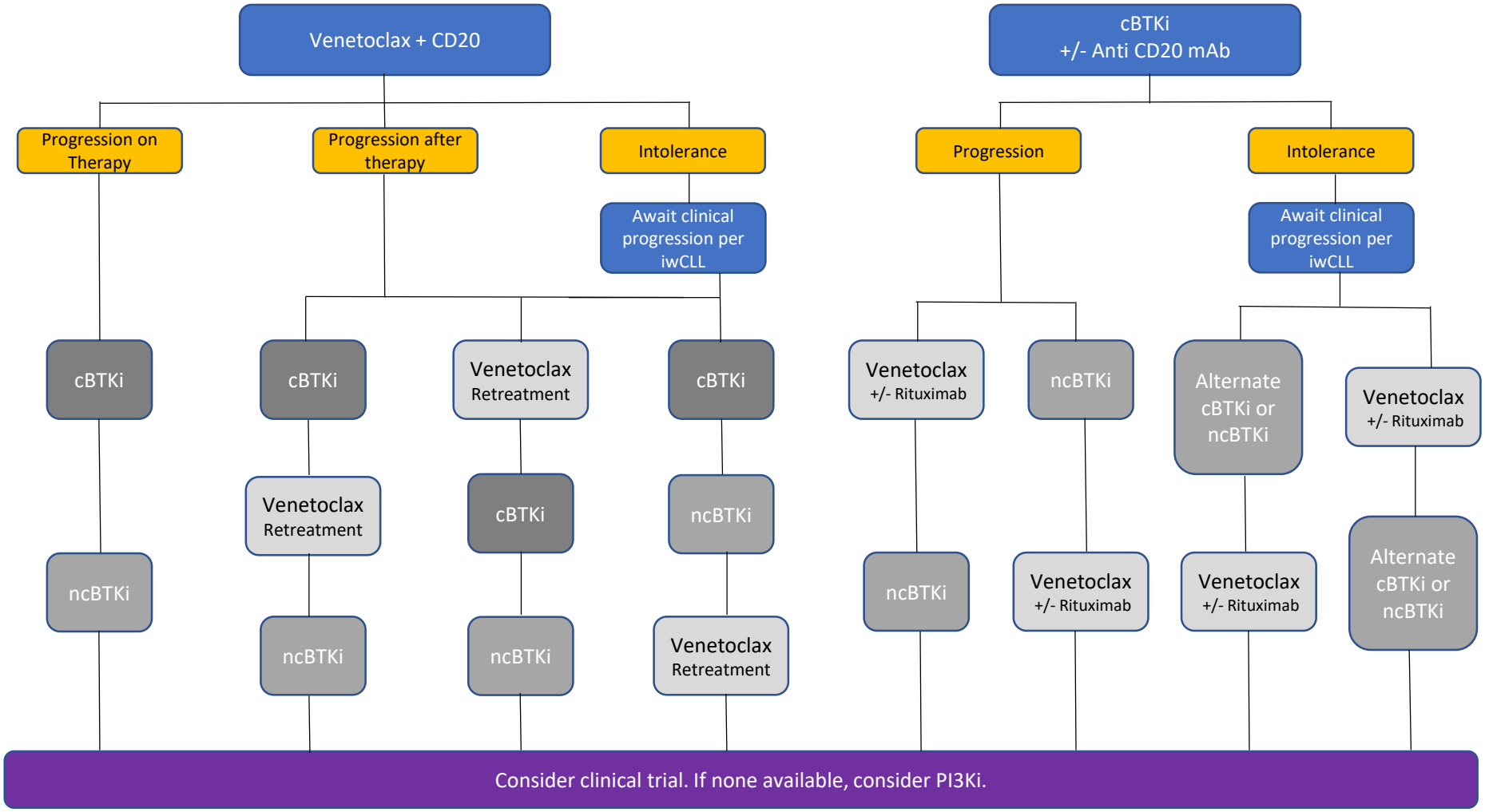
Events, n (%)		All Patients N = 118
All TEAEs		114 (96.6)
Grade ≥3 TEAEs[a]		80 (68.0)
MK-1026-related TEAE		78 (66.1)
Grade ≥3 related TEAEs[b]		31 (26.3)
Related TEAEs leading to discontinuation		9 (7.6)
TEAEs ≥20%	**All**	**Grade ≥3**
Fatigue	33.1%	3.4%
Constipation	31.4%	0.8%
Dysgeusia	28.0%	0
Cough	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.

Summary: Pirtobrutinib

- **Intolerance:** Promising safety data with favorable AE profile and low discontinuation rates due to AEs.
  - Head-to-head comparison planned vs Ibrutinib.
- **cBTKi Resistance:** Promising Phase 1-2 data suggestive Pirto can overcome C481 mutant CLL and possibly other cBTKi mechanisms of resistance.
- **Double exposed patients:** Durable remissions observed in a patient population with the largest unmet need.

From Bench to Practice: Treatment Algorithms which include ncBTKis


Venetoclax + CD20
Progression on Therapy
Progression after therapy
Intolerance
Await clinical progression per iwCLL
cBTKi
ncBTKi
cBTKi
Venetoclax Retreatment
ncBTKi
cBTKi
Venetoclax Retreatment
cBTKi
ncBTKi
ncBTKi
Venetoclax Retreatment
cBTKi +/- Anti CD20 mAb
Progression
Intolerance
Await clinical progression per iwCLL
Venetoclax +/- Rituximab
ncBTKi
Alternate cBTKi or ncBTKi
Venetoclax +/- Rituximab
ncBTKi
Venetoclax +/- Rituximab
Venetoclax +/- Rituximab
Alternate cBTKi or ncBTKi
Consider clinical trial. If none available, consider PI3Ki.

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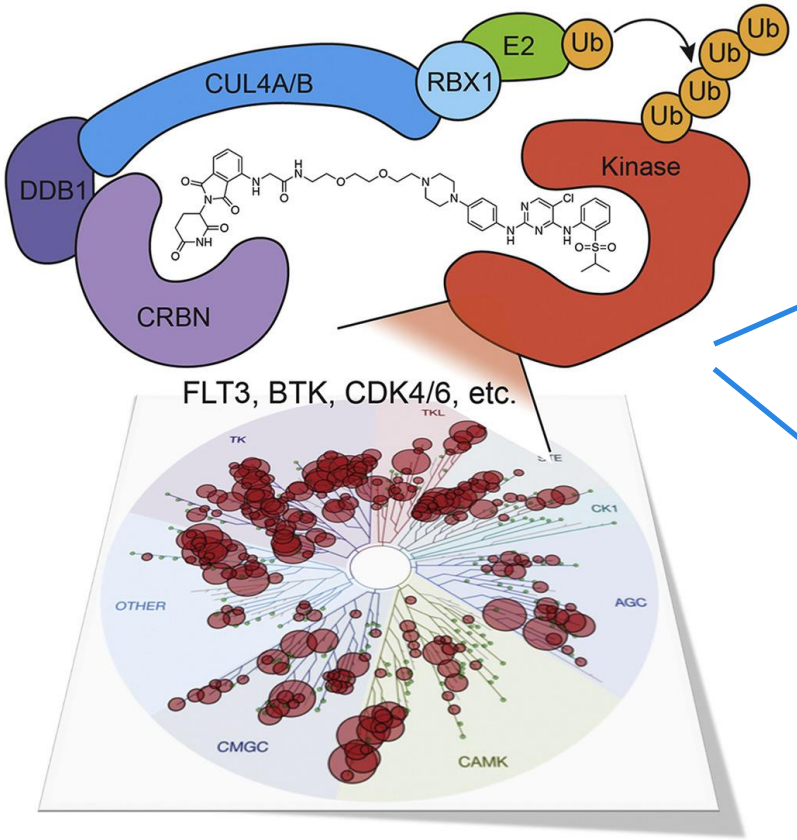
Next steps & new means to inhibit BTK in double BTKi (covalent and non covalent) refractory CLL?

Chemical Degradation of BTK in cBTK or ncBTK resistant patients?



BTK, IKZF1, IKZF3 degraders → NX2127

BTK single degraders

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