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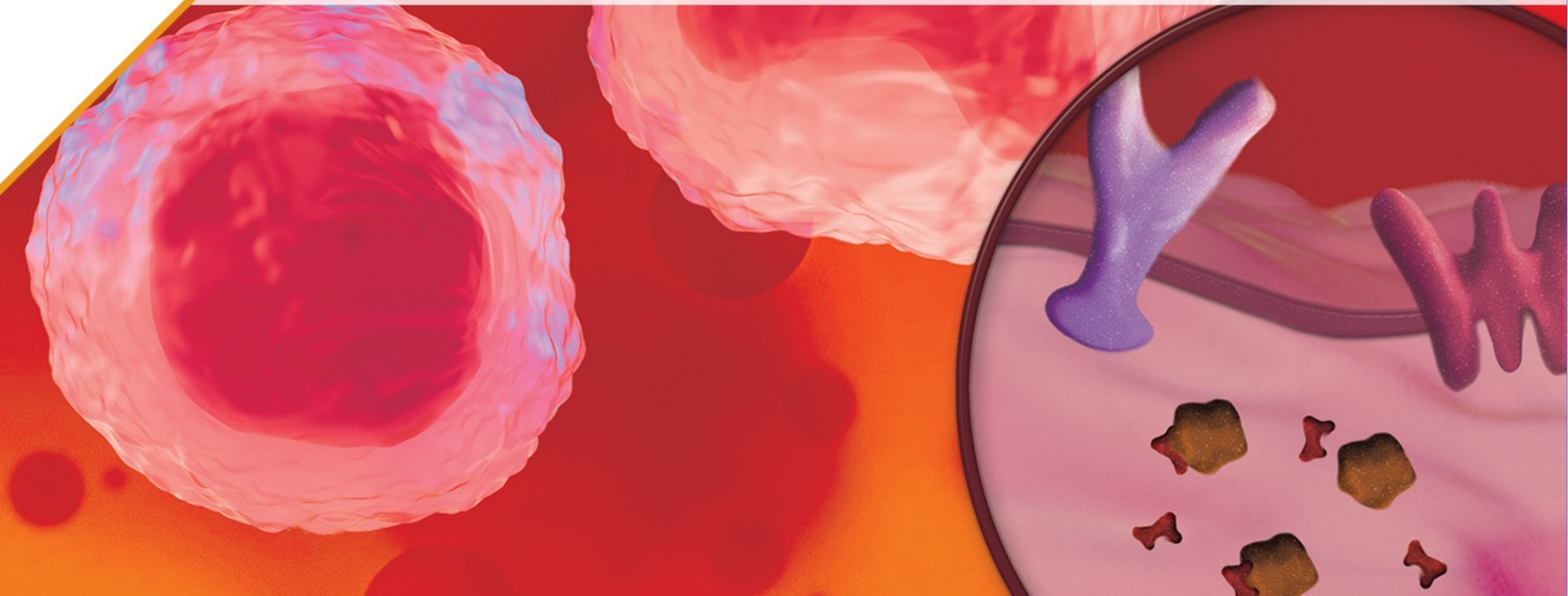
Non-Covalent BTK Inhibitors for B-Cell Malignancies (MCL/CLL):

Setting the Stage for Future Use



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- TG Therapeutics, Pharmacyclics, Abbvie, Adaptive Biotechnologies, Johnson and Johnson, Acerta / AstraZeneca, DTRM BioPharma, Sunesis, BeiGene, Genentech, Genmab, Janssen, Loxo Oncology, Nurix

Advisory/Consultancy/DSMB

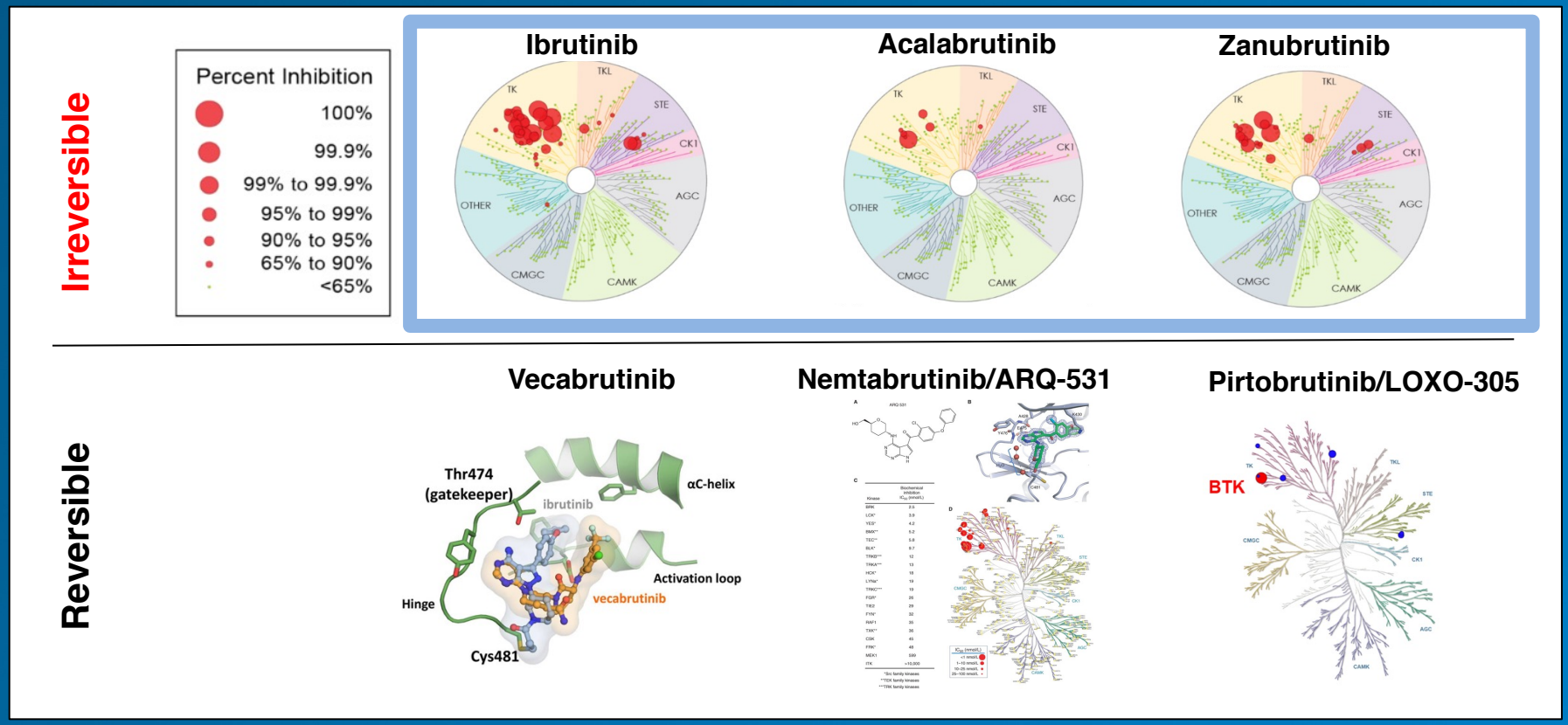
- TG Therapeutics, Pharmacyclics, Adaptive Biotechnologies, Abbvie, Johnson and Johnson, Acerta / AstraZeneca, DTRM BioPharma, Sunesis, AstraZeneca, BeiGene, Genentech, Janssen, Loxo Oncology

Treatment of CLL in 2022

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

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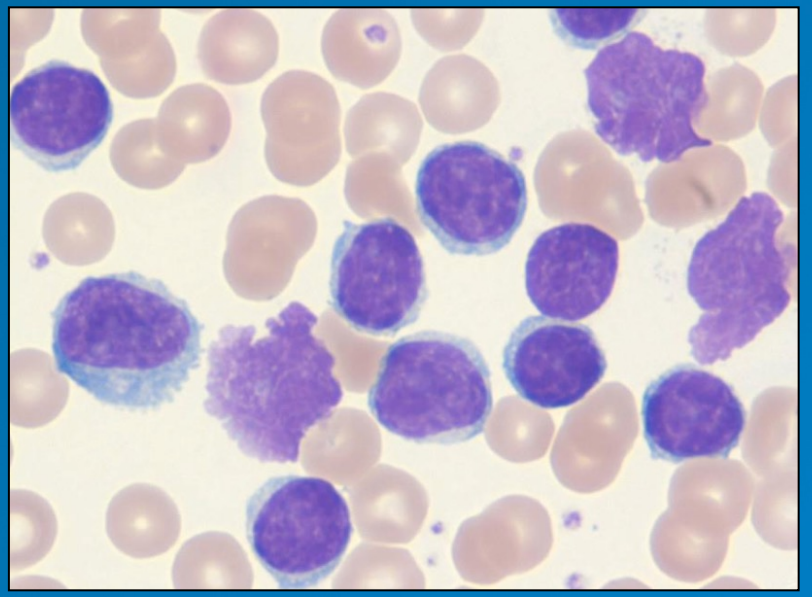
Chronic Lymphocytic Leukemia

- CD5+ mature B-cell neoplasm
- Peripheral blood, lymph node, and bone marrow compartments
- Median age at diagnosis: 72 years
- Most common leukemia in Western countries
- Heterogenous clinical presentation



Remarkable Basic, Translational and Clinical Scientific Advances

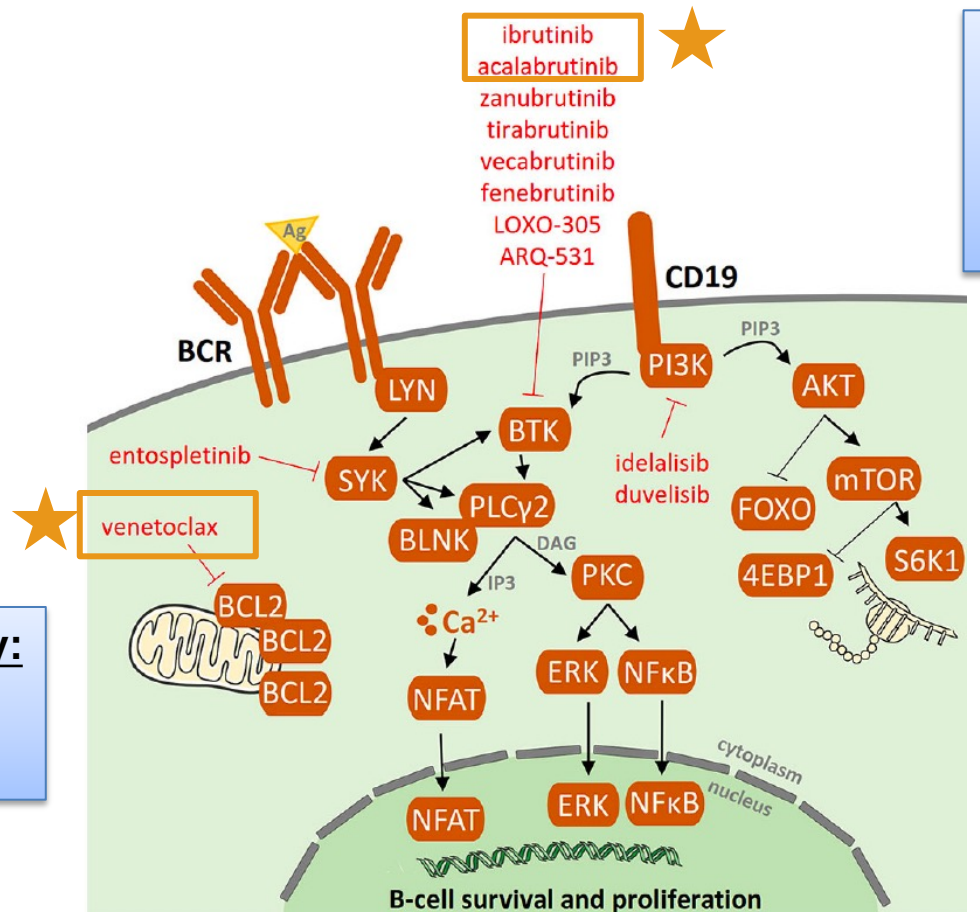
An era of targeted therapy for treatment of CLL

Burger. *N Engl J Med* 2020383:460-473; Image: Carrll TC and Venkataraman G, ASH Image Bank 2018.

Era of Targeted Therapies

Targeted therapies are now standard of care options in the front-line and relapsed/refractory settings

B-cell receptor signaling:
Covalent, irreversible Bruton tyrosine kinase Inhibitors:
ibrutinib & acalabrutinib



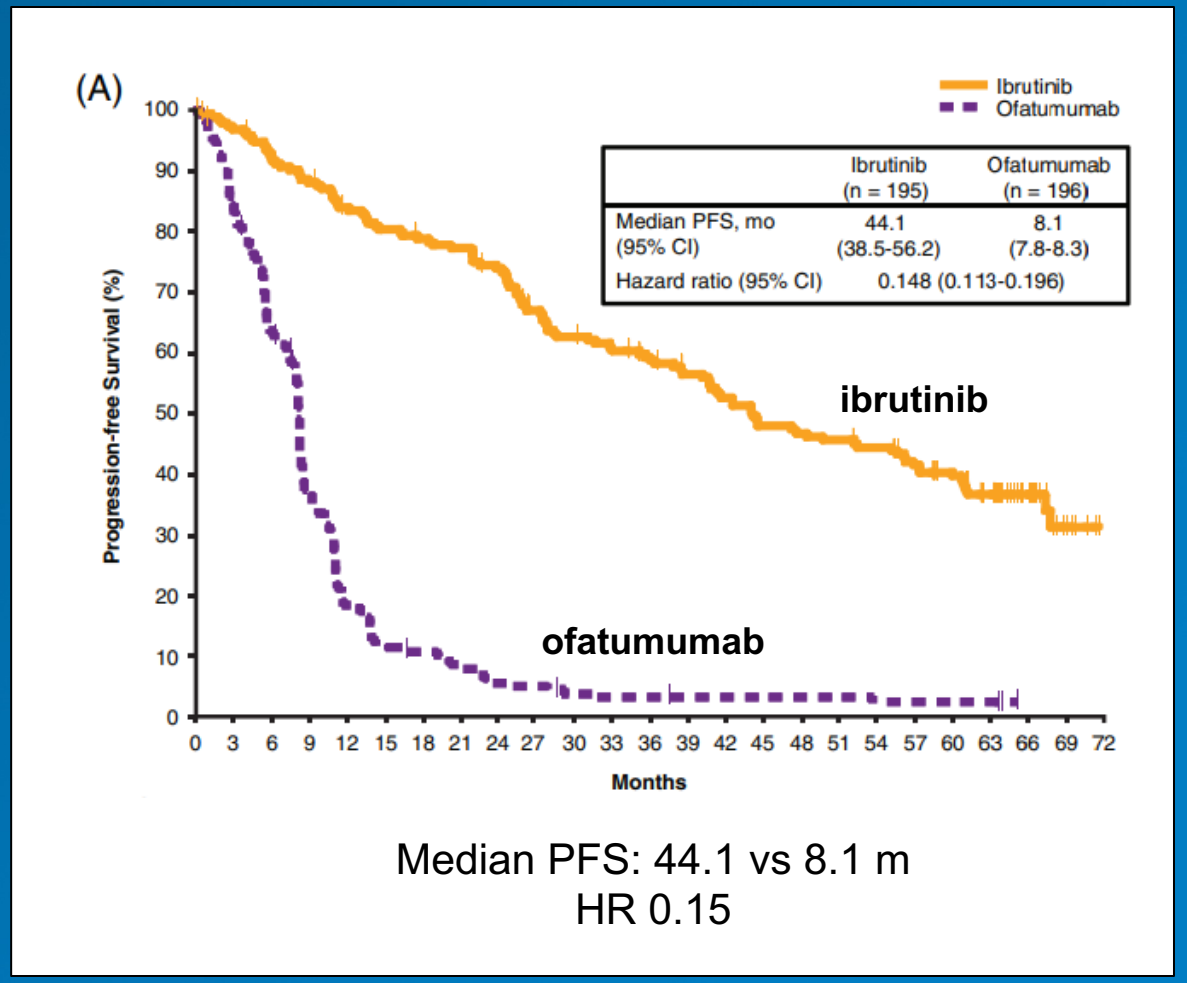
Apoptotic Pathway:
BCL-2 inhibitor
venetoclax

Figure from Sedlarikova et al. *Front Oncol*. 2020;10:894.

Covalent BTK inhibitors

- **Ibrutinib & acalabrutinib**: bind irreversibly to BTK protein
- Oral, **continuous therapies**
- Improved PFS compared to CIT controls
  - R/R ibrutinib: RESONATE (ofatumumab)
  - F/L ibrutinib: RESONATE -2 (chlorambucil)
  - F/L acalabrutinib: ELEVATE-TN (obinutuzumab + chlorambucil)

Progression-free Survival



Median PFS: 44.1 vs 8.1 m
HR 0.15

CIT, chemoimmunotherapy; F/L, first-line; PFS, progression-free survival; R/R, relapsed/refractory.
Munir et al. Am J *Hematol* 2019;94:1353-1363; Barr et al. *J Clin Oncol*. 2021;39:7523; Sharman et al. *J Clin Oncol*. 2021;39:7509.

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Ibrutinib Discontinuation for Intolerance

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 first-line and relapsed/refractory CLL
- Most common toxicities in relapsed/refractory CLL:
  - Atrial fibrillation 12.3%
  - Infection 10.7%
  - Pneumonitis 9.9%
  - Bleeding 9%
  - 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)

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

BTK, Bruton tyrosine kinase; CAR T-cell, chimeric antigen receptor T-cell; CLL, chronic lymphocytic leukemia, RT DLBCL, Richter transformation to diffuse large B-cell lymphoma; RT, Richter transformation.

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

Acquired Resistance to Covalent BTKi

- Majority of patients have identified mutations in *BTKC481* at the time of disease progression on ibrutinib; ~53-87% of patients
- **Catalytically activating** mutations
- Mutations also identified in PLCG2, immediately downstream of BTK
- *BTKC481* mutations are also main mechanism of resistance for acalabrutinib; 69% of patients

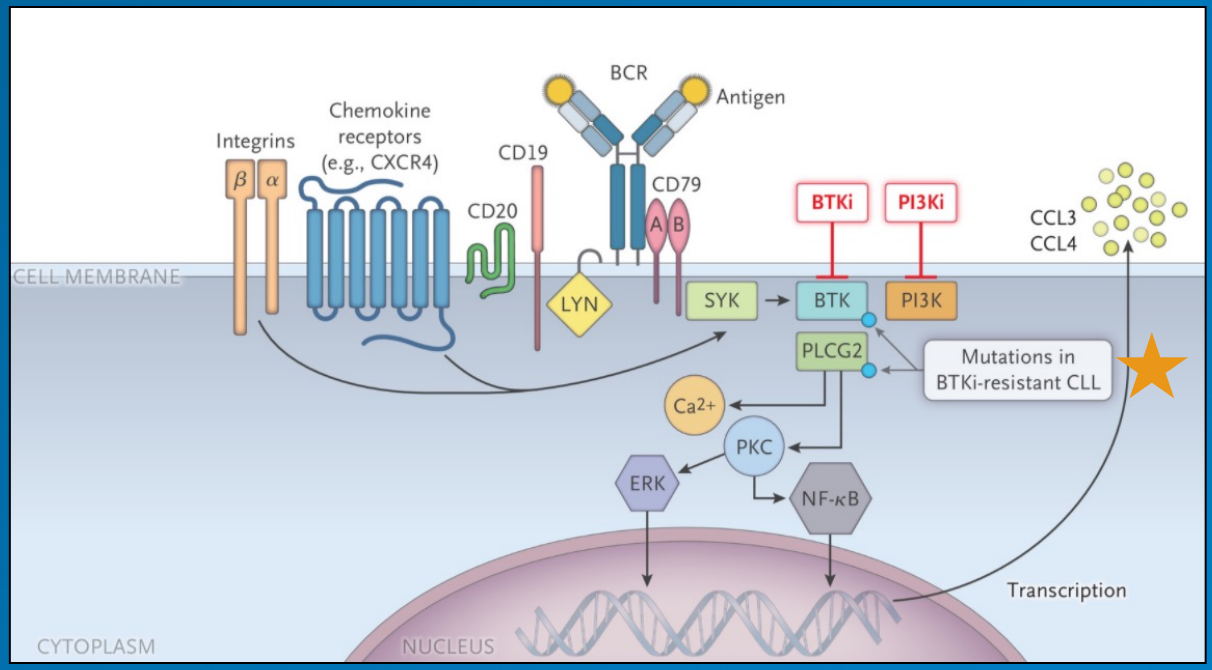
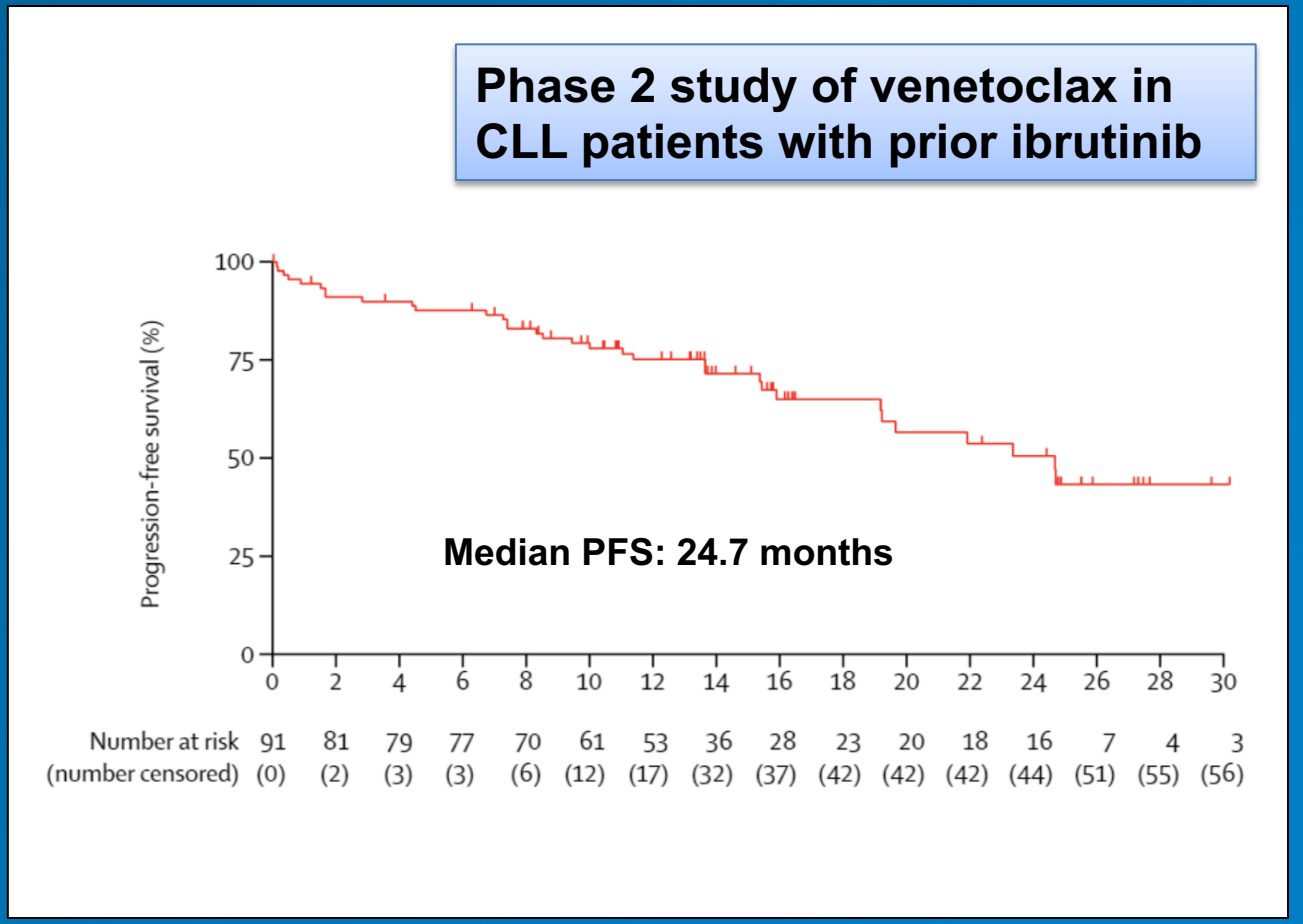


Figure from Burger. *N Engl J Med*. 2020;383:460-473.
BTKi, Bruton tyrosine kinase inhibitor.
Burger et al. *Nat Commun* 2016;7:11589. Woyach et al. *N Engl J Med*. 2014;370:2286-2294; *J Clin Oncol*. 2017;35:1437-1443; *Blood* 2019;134(suppl 1):504.
Scarfò et al. EHA 2020;4:34-35. Ahn et al. *Blood* 2017;129:1469-1479.

Treatment of CLL After Covalent BTKi

- **Venetoclax:** oral BCL-2 inhibitor
- First-line setting and relapsed setting including after cBTKi
- Approved as **fixed-duration** therapy (24 months in R/R setting)

Progression-free Survival



cBTKi, covalent Bruton tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; PFS, progression-free survival; R/R, relapsed/refractory.
Figure from Jones et al. *Lancet Oncol.* 2018;19:65-75.

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"Double Exposed" Patient: Unmet Need

- Landmark trials leading to approvals of CIT and PI3K inhibitors did not include patients previously treated with cBTKi or venetoclax
- We conducted a retrospective analysis to compare outcomes of therapies for CLL patients who have received cBTKi and venetoclax

A subset of patients will ultimately have **progressive CLL** following treatment with both venetoclax and a cBTKi

Standard of care options:

- Chemotherapy +/- immunotherapy
- PI3K inhibitors: idelalisib, duvelisib

Clinical trial options:

- Non-covalent BTKi
- CAR T-cell therapy
- Several other investigational agents

cBTKi, covalent Bruton tyrosine kinase inhibitor; CAR, chimeric antigen receptor; CIT, chemoimmunotherapy; CLL, chronic lymphocytic leukemia; PI3K, phosphoinositide 3-kinase.

Furman et al. *N Engl J Med*. 2014; Flinn et al *Blood* 2018; Mato et al *Lancet* 2021; Siddiqi et al *Blood* 2021; Thompson et al. *Blood* 2021;138(suppl 1):2628.

Response Rates to Selected Therapies

ncBTKi and cellular therapies have high overall response rates

CIT and PI3Ki have relatively low overall response rates

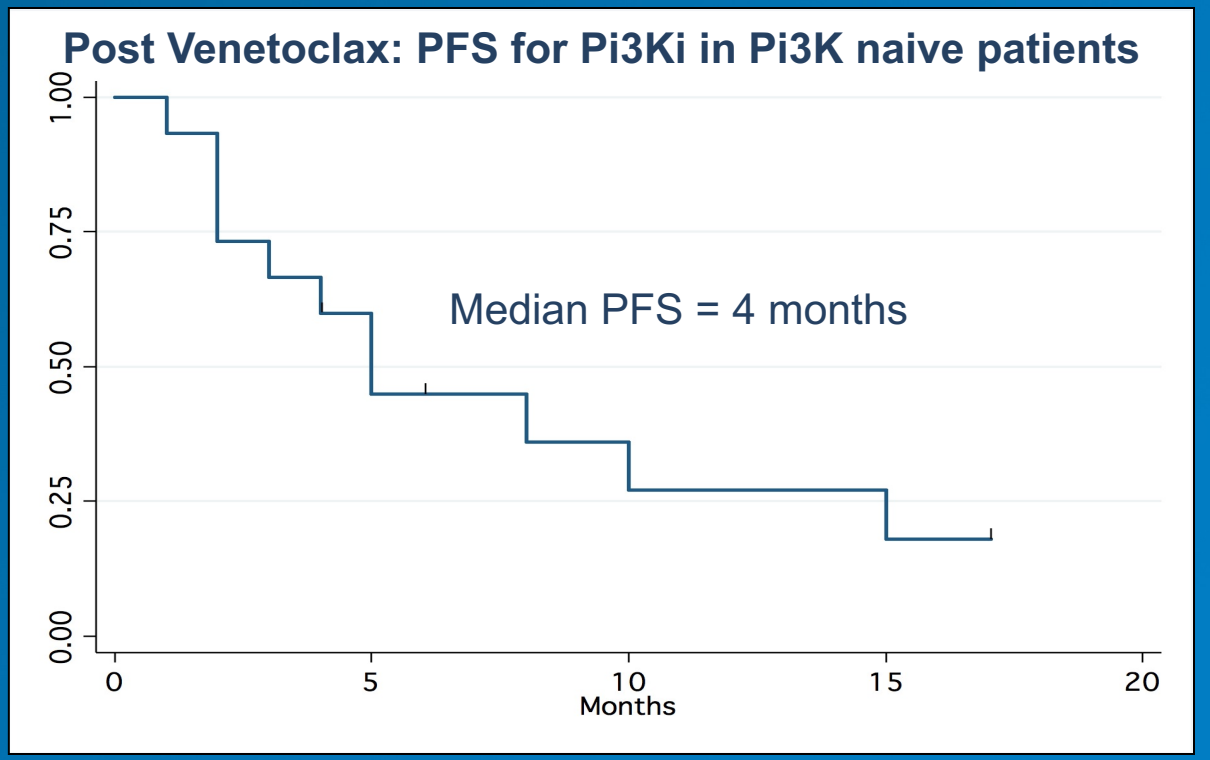
Subsequent Therapy	CAR-T	Allo SCT	ncBTKi	PI3Ki	CIT
Patients treated	**9**	**17**	**45**	**24**	**23**
ORR	**85.7%** n = 7	**76.5%** n = 17	**75.0%** n = 43	**40.9%** n = 22	**31.8%** n = 22
Median PFS (mo)	**4** n = 9	**11** n = 16	**Not reached** n = 40	**5** n = 21	**3** n = 20
Median follow-up (mo)	**3**	**6.5**	**9**	**4**	**2**

Allo SCT, allogeneic stem cell transplantation; CAR, chimeric antigen receptor; CIT chemoimmunotherapy; ncBTKi, non-covalent BTK inhibitors; ORR, overall response rate; PFS, progression-free survival; PI3K, phosphoinositide 3-kinase.

Thompson et al. *Blood* 2021;138(suppl 1):2628.

Post Venetoclax

- After BTKi and/or venetoclax: PI3Ki did not result in durable remissions and therefore is not an acceptable standard of care in the third-line setting in modern era



BTKi, BTK inhibitor; PI3K, phosphoinositide 3-kinase inhibitor.
Mato et al. *Clin Cancer Res.* 2020;26(14):3589-3596.

Summary: Alternate Covalent BTK Inhibitors

Intolerance

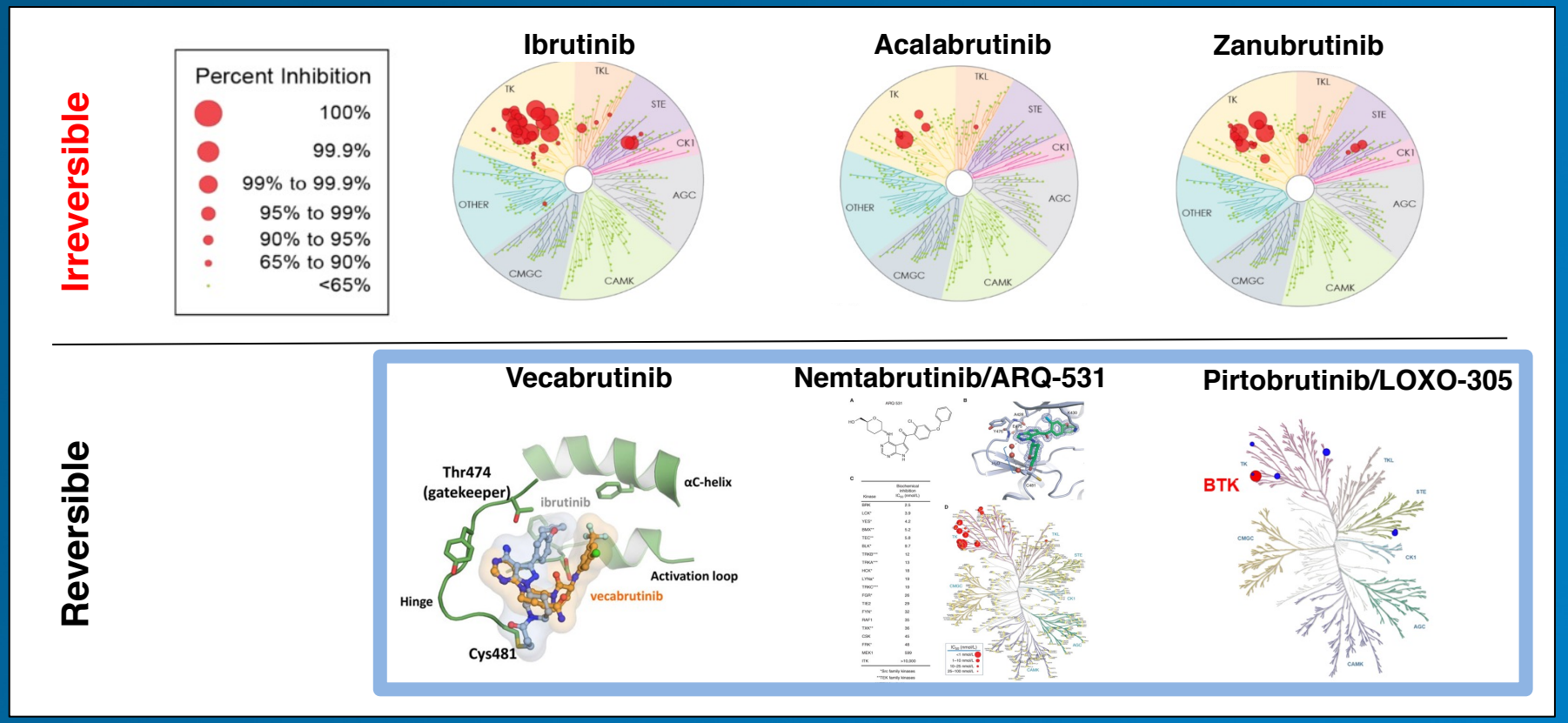
- Intolerance remains the most common reason for Ibrutinib discontinuation
- Direct comparison suggest next-generation covalent BTK inhibitors lead to lower discontinuation rates due to adverse events; early data suggest fewer adverse events lead to better progression-free survival

Resistance

- *C481* mutations are the most common cause of resistance to ibrutinib
- Limited data from more selective covalent BTK inhibitors suggest similar mechanisms of resistance

Non-Covalent BTK Inhibitors

Differences in BTKi Specificity, MOA, and Potential Off-Target Effects Among New BTK Inhibitors



BTKi, Bruton tyrosine kinase inhibitor; MOA, mechanism of action.
Kaptein et al. *Blood*. 2018;132:1871.

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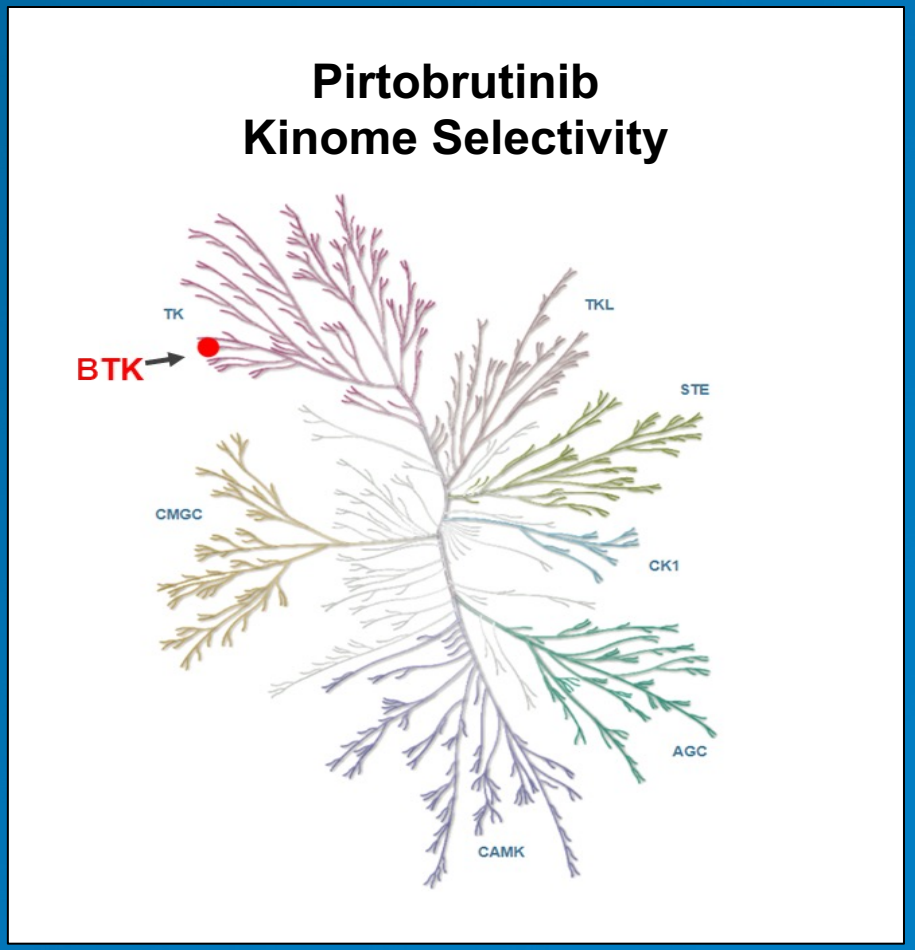
Non-Covalent BTK Inhibitors

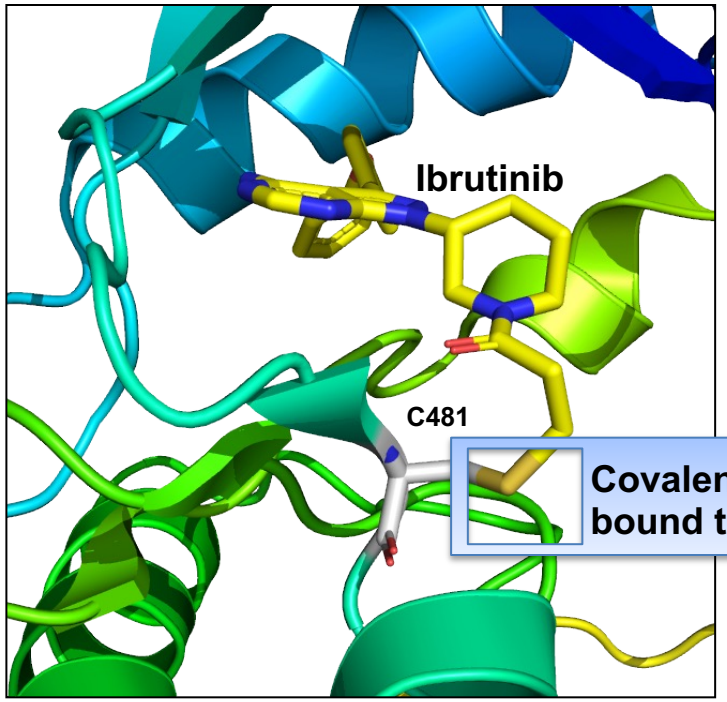
- **Reversible** binding to BTK
- Several agents in clinical development
  - Nemtabrutinib (ARQ-531/MK-1026)[1]
  - Pirtobrutinib (LOXO-305)[2]
    - Highly selective: minimal activity against non-BTK kinases
    - Longer half-life and increased BTK occupancy compared to covalent BTK inhibitors



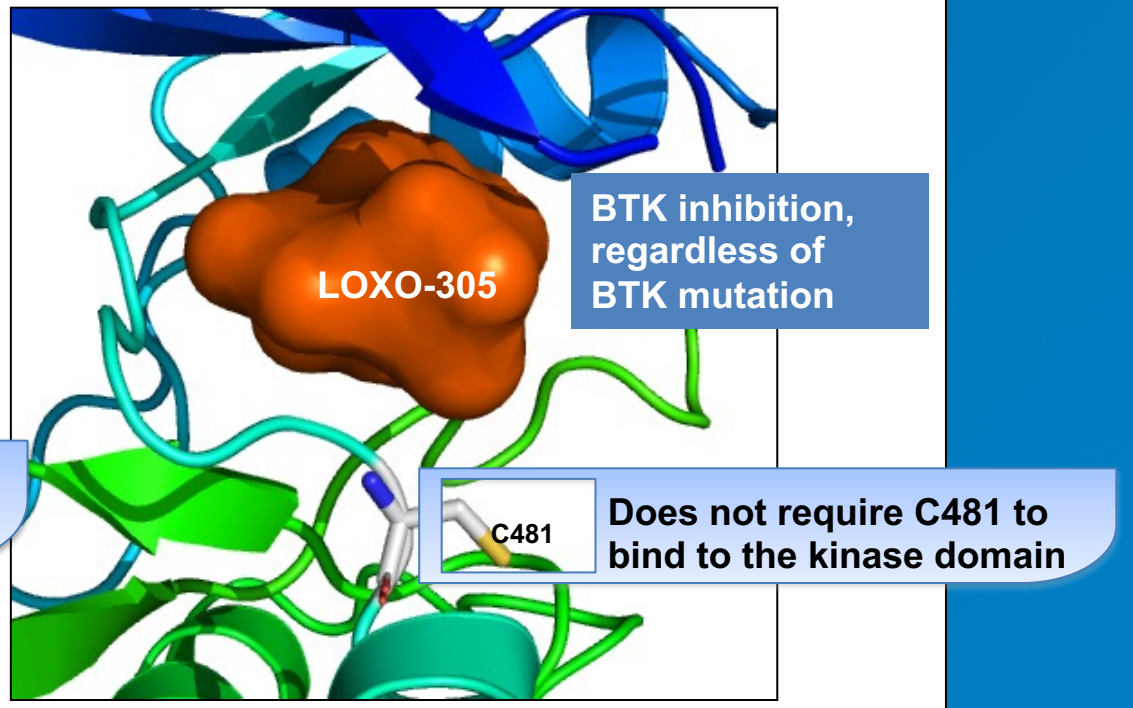
1. Reiff et al. *Cancer Discov*. 2018;8:1300-1315. 2. Mato et al *Lancet* 2021;397:892-901.
BTK, Bruton tyrosine kinase.

Pirtobrutinib/LOXO-305 Is a Non-Covalent BTK Inhibitor

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

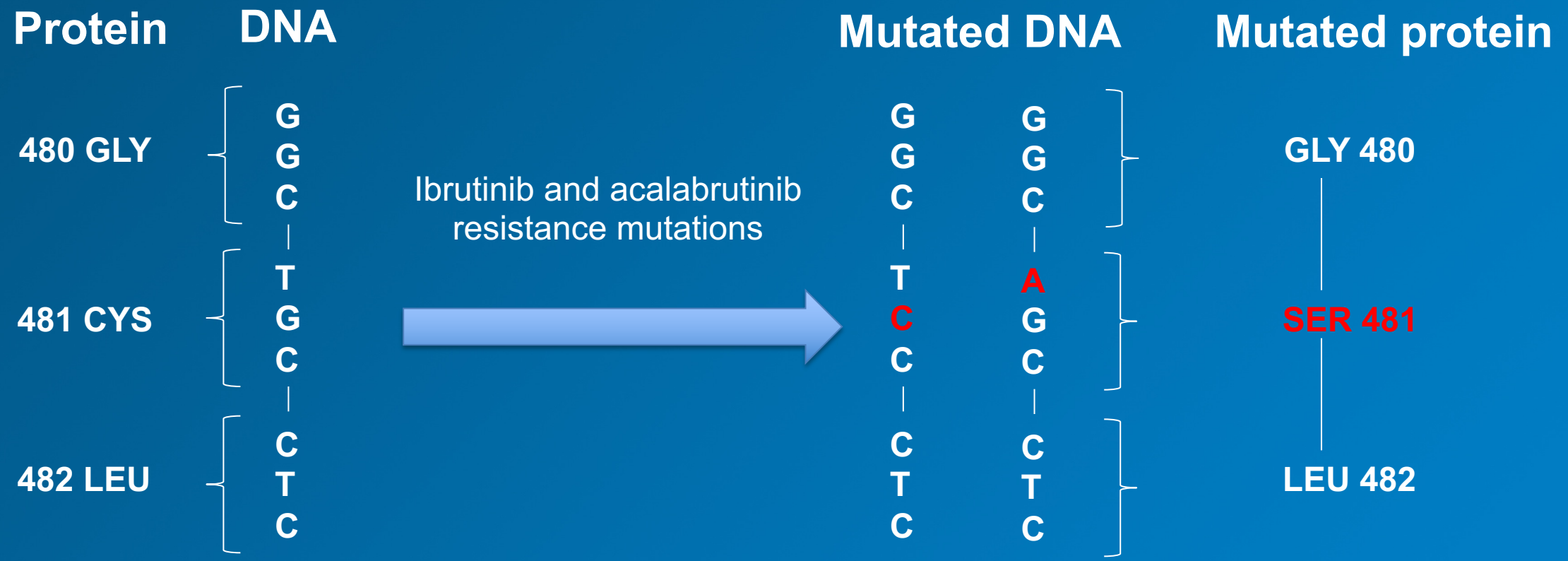


LOXO-305 is a non-covalent BTK inhibitor that is potent against both WT and C481-mutant BTK



BTK, Bruton tyrosine kinase; WT, wild-type.

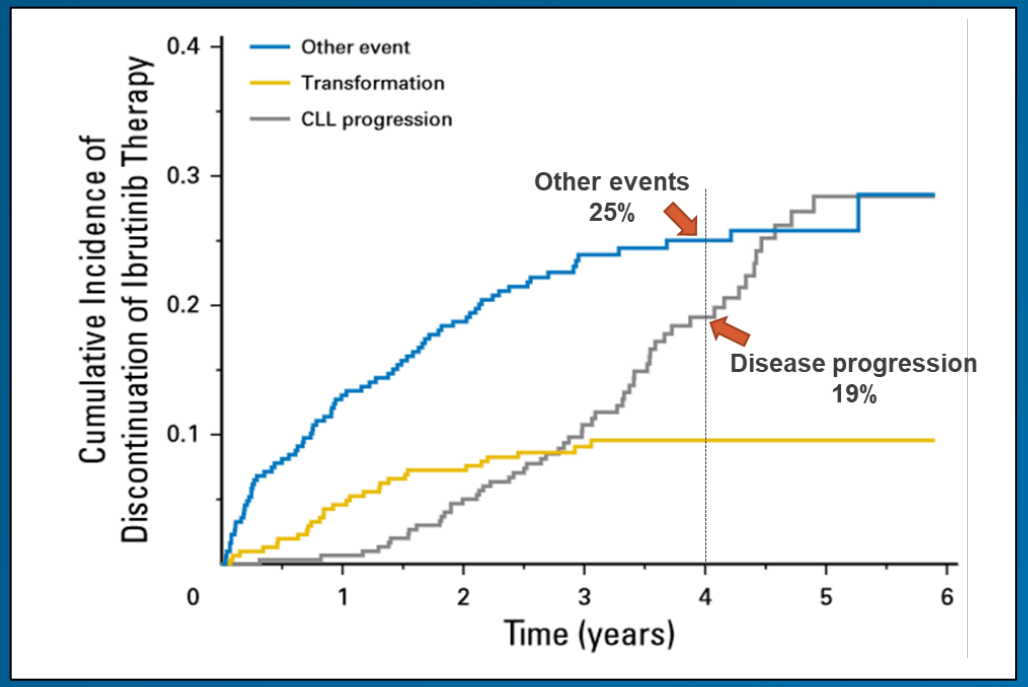
Genetic Mutations Leading to Covalent BTK Inhibitor Resistance



BTK, Bruton tyrosine kinase.

Resistance and Intolerance Limit Covalent BTK Inhibitor Efficacy

Ibrutinib Discontinuation (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 induces significant toxicity burden
  - **Chemoimmunotherapy:** Limited benefit in this population because most patients have already been exposed to these drugs

[1]Woyach et al. *J Clin Oncol*. 2017;35:1437-1443. [2]Burger. *Leukemia* 2020;34:787-7898.
BTK, Bruton tyrosine kinase; PI3K, phosphoinositide 3 kinase.

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Non-Covalent BTK Inhibitors: Promising New Agents in CLL

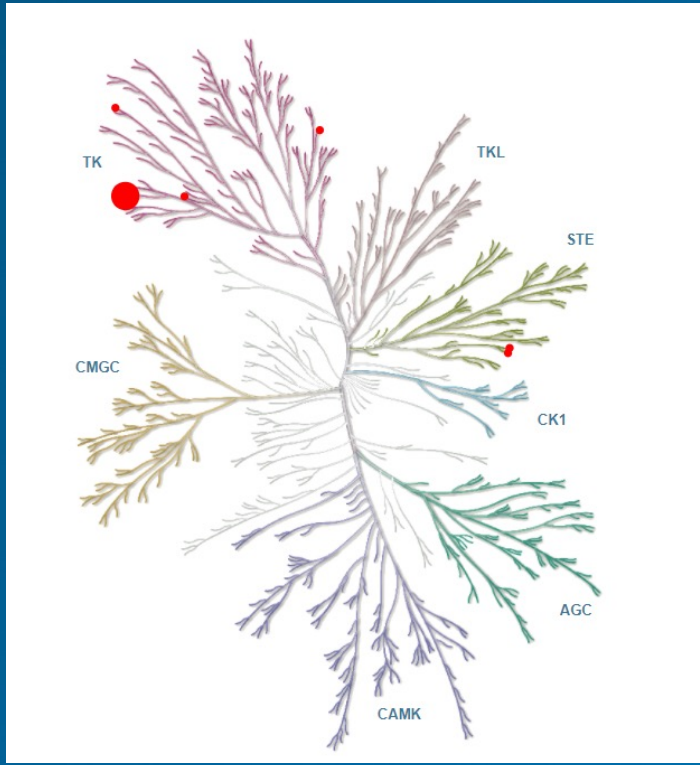
Pirtobrutinib

Nemtabrutinib

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

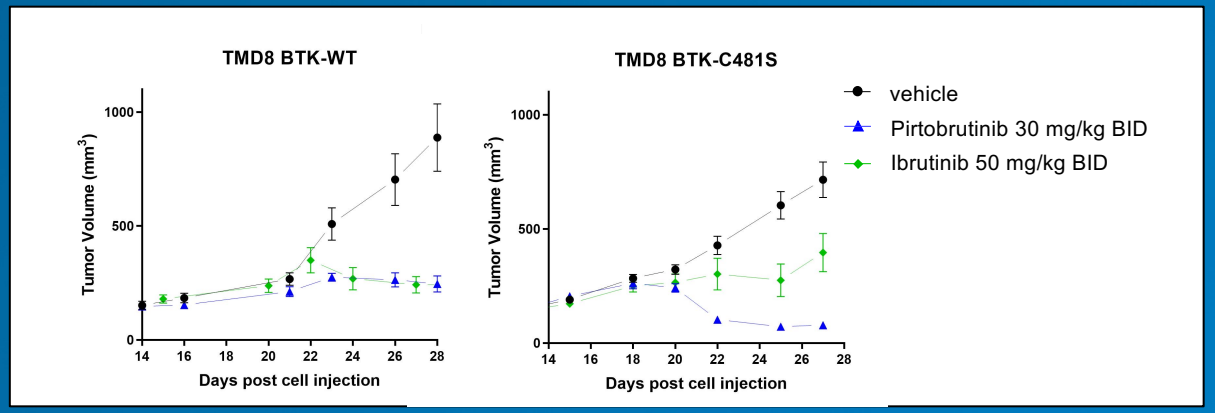
Kinome selectivity[1]

Highly selective for BTK



Xenograft models

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

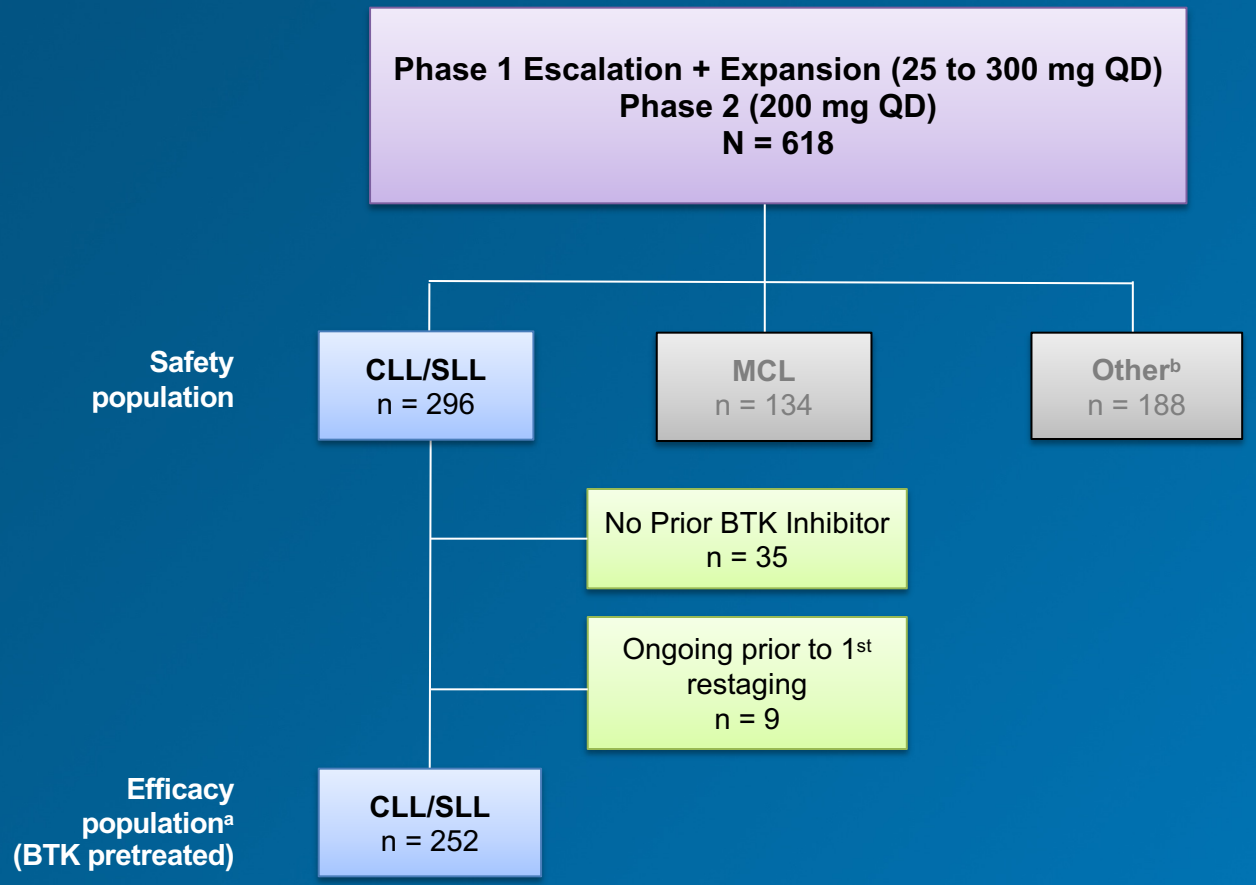


- Nanomolar potency against WT & C481-mutant BTK in cell and enzyme assays[2]
- >300-fold selectivity for BTK vs 370 other kinases[2]
- Due to reversible binding mode, BTK inhibition not impacted by intrinsic rate of BTK turnover[2]
- Favorable pharmacologic properties allow sustained BTK inhibition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

BID, twice-daily; BTK, Bruton tyrosine kinase; WT, wild type.

[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 PS 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)

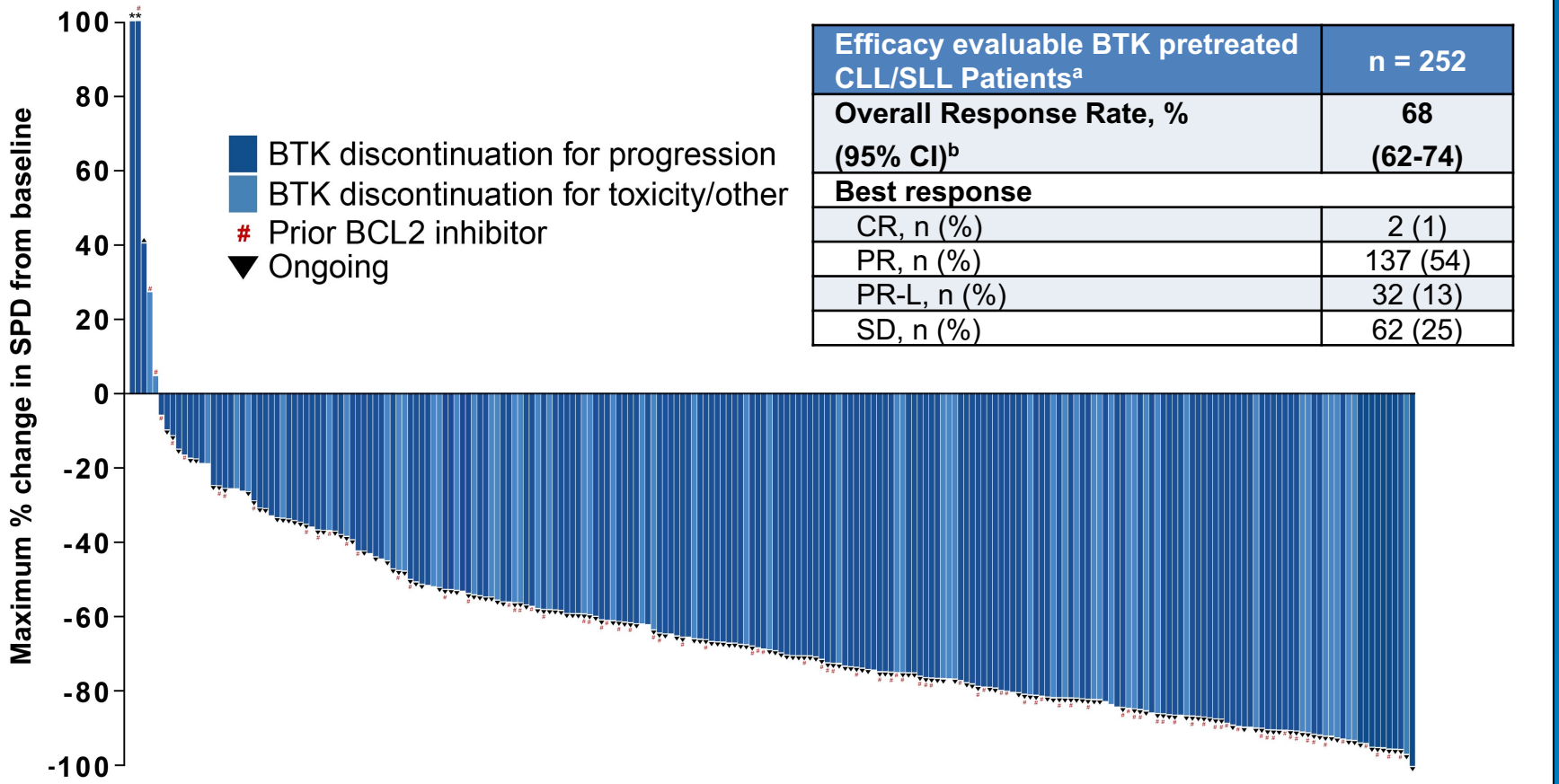
Data cutoff date July 16, 2021.

BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; IWWM, International Workshop on Waldenstrom's Macroglobulinemia; MCL, mantle cell lymphoma; MTD, maximum tolerated dose; NHL, non-Hodgkin lymphoma; 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.

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.

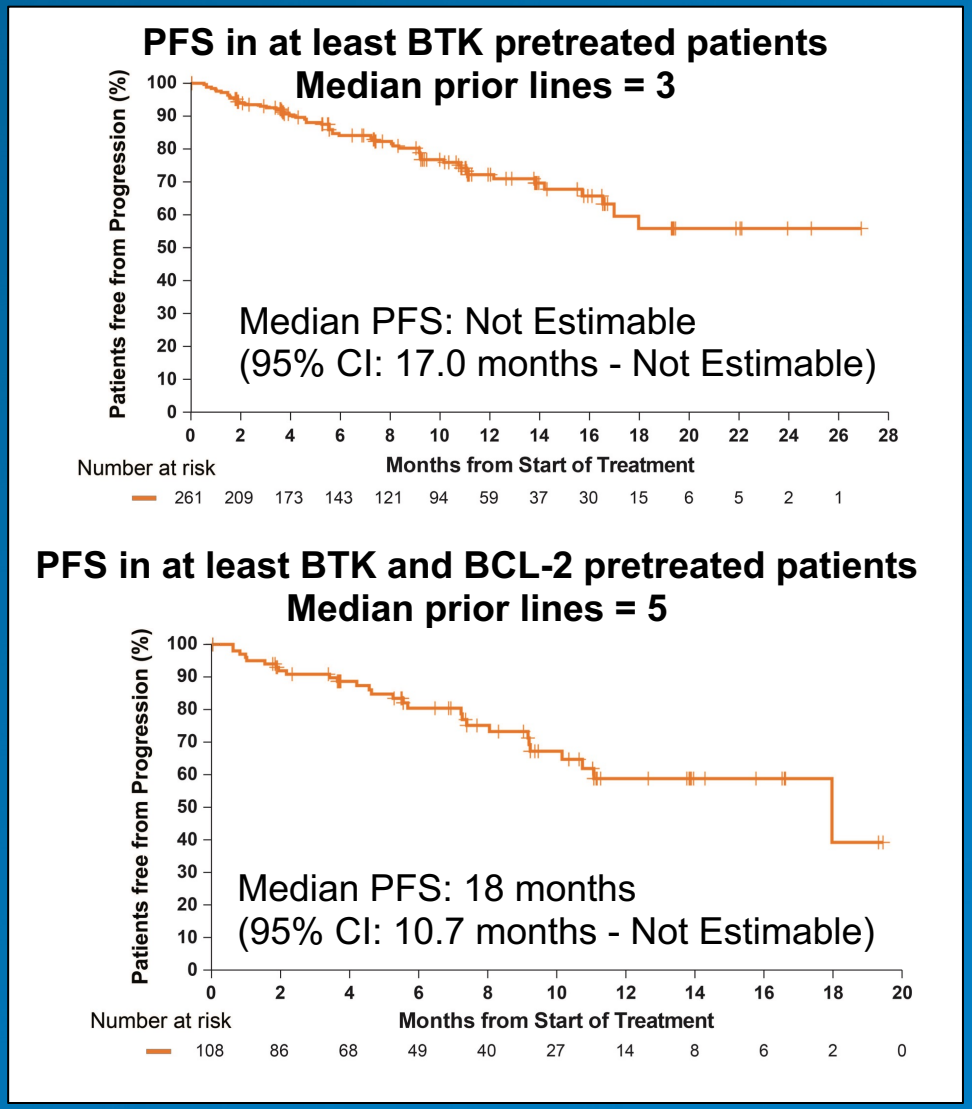
BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; CR, complete response; PR, partial response; PR-L, partial responses with ongoing lymphocytosis; SD, stable disease; SLL, small lymphocytic leukemia.

*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. *Blood* 2021;138:391.

Pirtobrutinib: Progression-free Survival in BTK Pretreated CLL/SLL Patients

- 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; SLL, small lymphocytic leukemia.
Response status per iwCLL 2018 according to investigator assessment.
Mato et al. *Blood* 2021;138:391.

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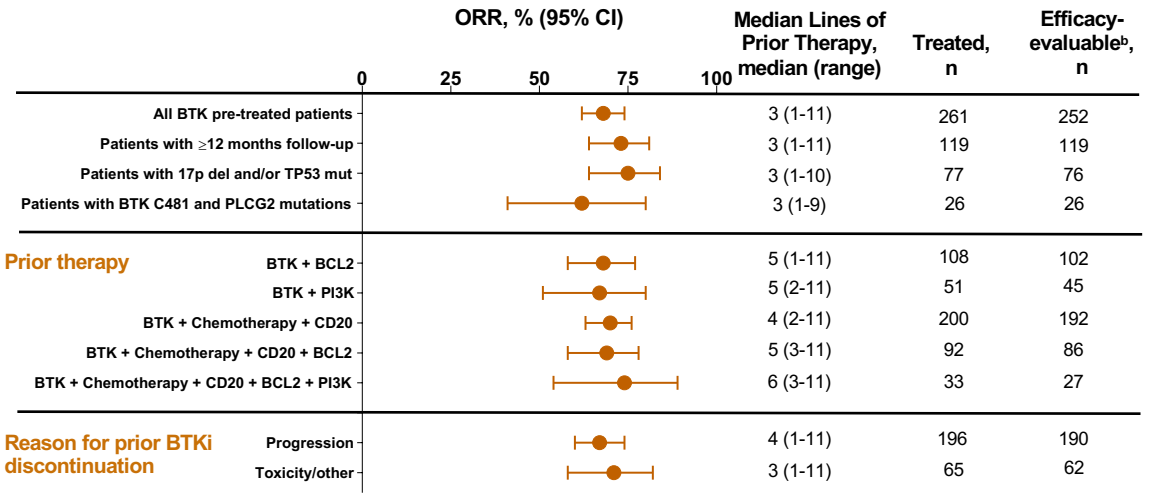
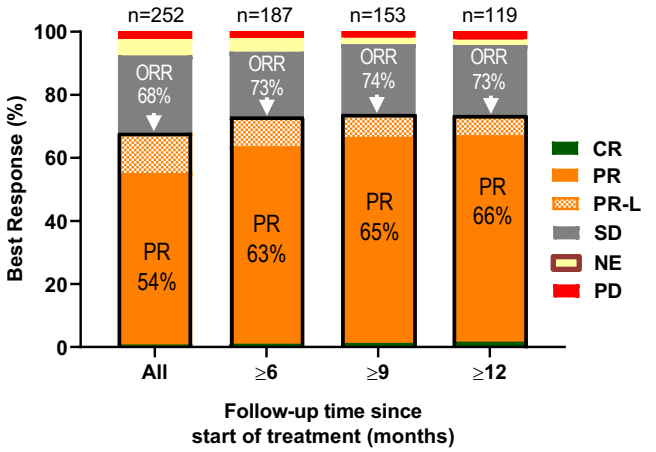
Pirtobrutinib Efficacy in BTK Pretreated CLL/SLL Patients

Pirtobrutinib Efficacy Regardless of Other Prior Therapy[a]



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; ORR, overall response rate; PD, progressive disease; PR, partial response; PR-L, PR rate with lymphocytosis; SD, stable disease; SLL, small lymphocytic lymphoma.

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. *Blood* 2021;138:391.

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. *Blood* 2021;138:391.

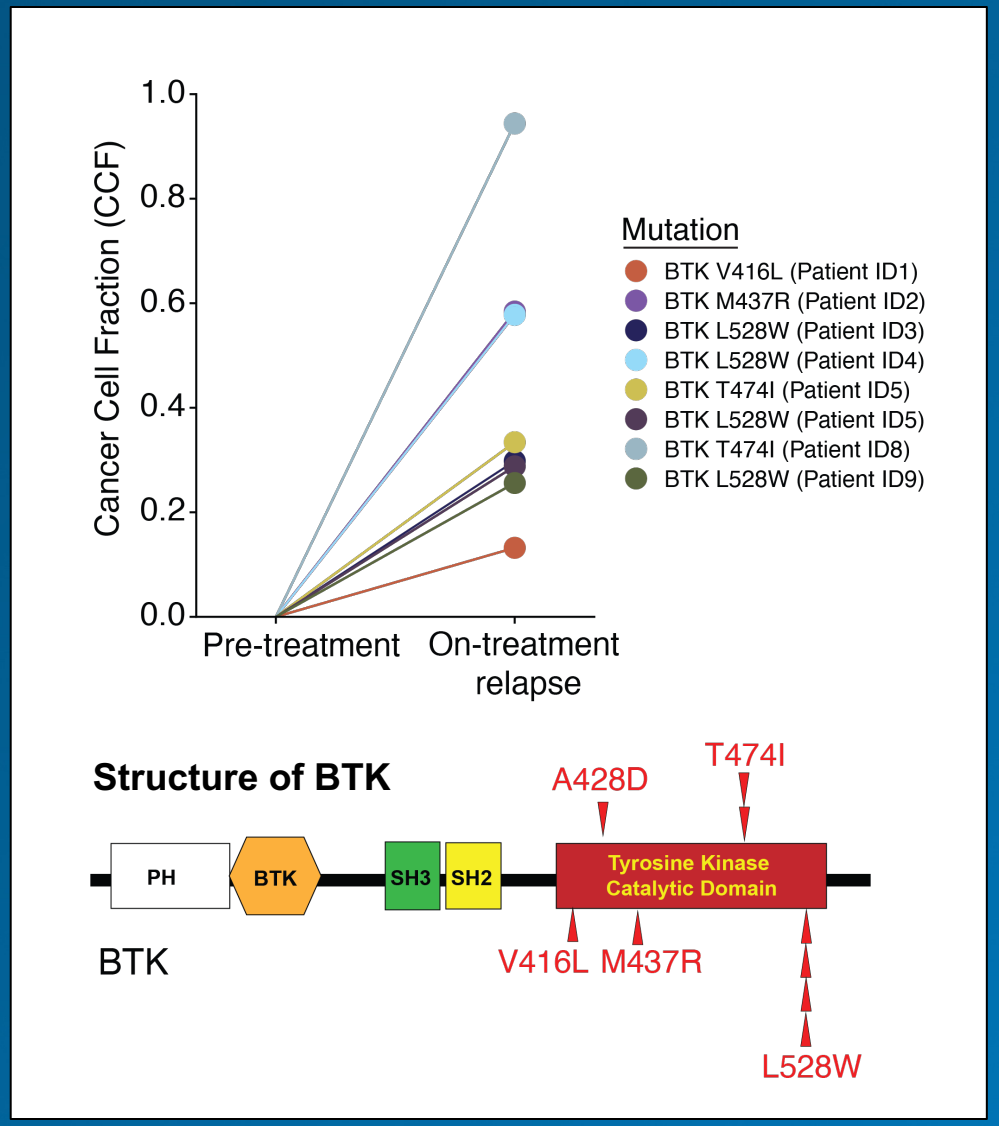
Pirtobrutinib CLL Conclusions

- 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, BCL-2 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.

Mechanisms of Resistance to Non-Covalent BTK Inhibitors

Acquired *BTK* Mutations on Pirtobrutinib



- 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 et al. In press 2022.

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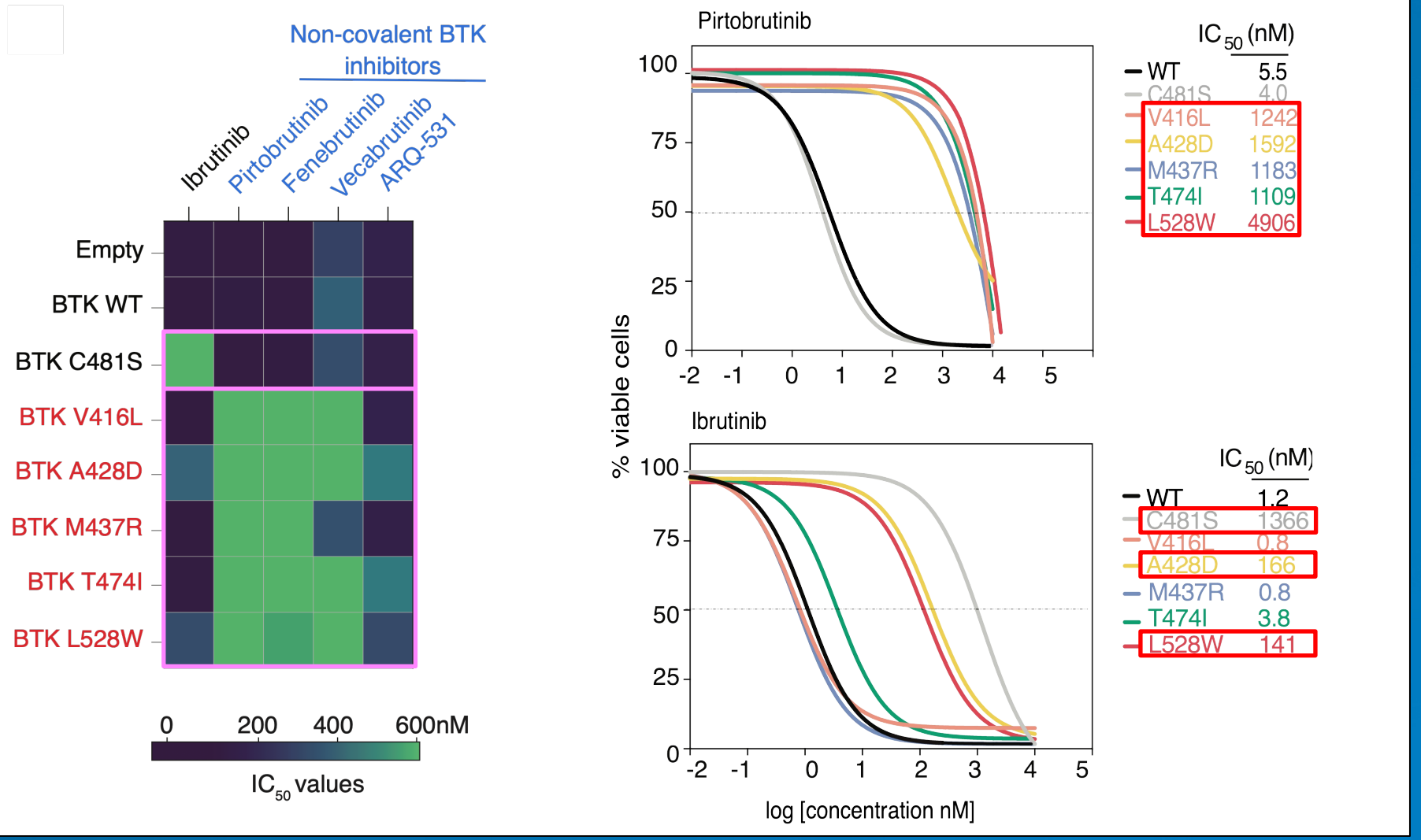
Novel *BTK* Mutations Confer Broad Resistance to Non-covalent BTK Inhibitors



Wang et al. In press 2022.

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MK-1026-001: Study Design (NCT03162536)

Key Eligibility Criteria
- Age ≥ 18 years
- CLL/SLL with symptomatic disease
- B-cell NHL with measurable disease
- WM with IgM level ≥ 2X ULN
- ECOG PS 0-2

RP2D
65 mg QD

CLL/SLL
- **Rr CLL/SLL, C481S mutation[a]**
- **Rr CLL/SLL, no C481S mutation[b]**

B-NHL
- **RT**
- **FL**
- **MCL**
- **MZL**
- **High-grade BCL**
- **WM**
- **rr B-cell NHL, CLL/SLL, WM**

Expansion Cohort
10-25 patients per cohort

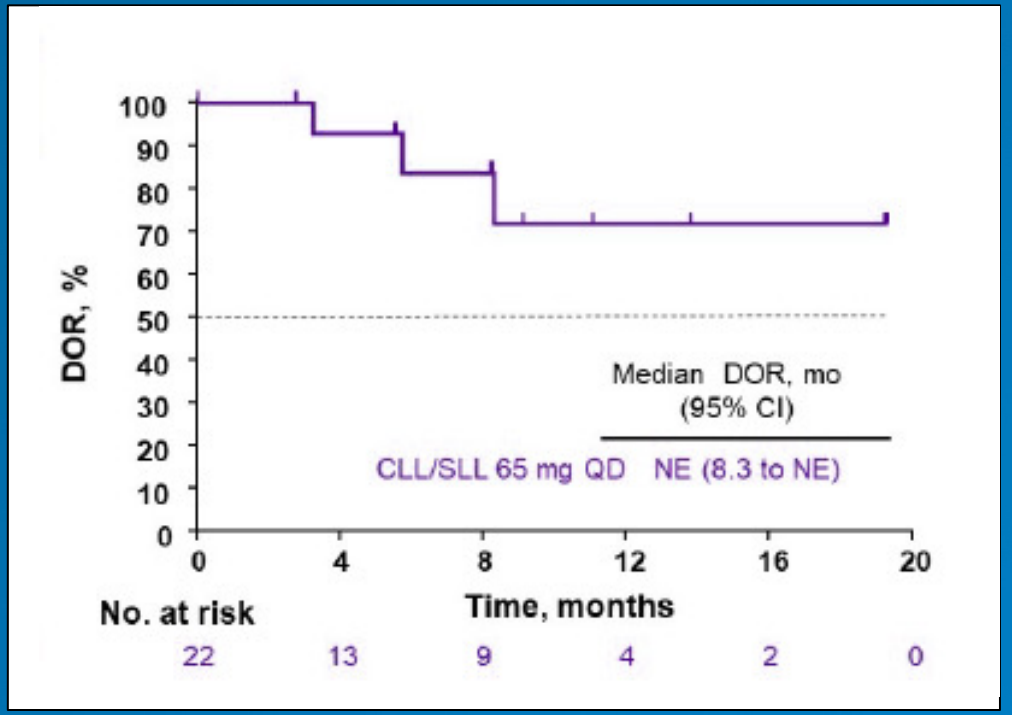
Until unacceptable toxicity, progression, withdrawal

Endpoints
- Primary: ORR per iwCLL criteria in patients with CLL/SLL
- Secondary: DOR, safety, tolerability

[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.
BCL, B-cell lymphoma; CLL, chronic lymphocytic leukemia; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; FL, follicular lymphoma; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; MCL, mantle cell lymphoma; MK-1026, nemtabrutinib; MZL, marginal zone lymphoma; NHL, non-Hodgkin lymphoma; ORR, overall response rate; rr, relapsed/refractory;
RP2D, recommended phase 2 dose; RT, Richter transformation; SLL, small lymphocytic leukemia; ULN, upper limit of normal; WM, Waldenstrom macroglobulinemia.
Adapted from Woyach et al. *Blood* 2021;138:392.

MK-1026/Nemtabrutinib: 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.

CLL, chronic lymphocytic leukemia; CR, complete response; DOR, duration of response; ORR, overall response rate; PD, progressive disease; PR, partial response; PR rate with lymphocytosis; QD, once daily; SD, stable disease; SLL, small lymphocytic leukemia.

Adapted from Woyach et al. *Blood* 2021;138:392.

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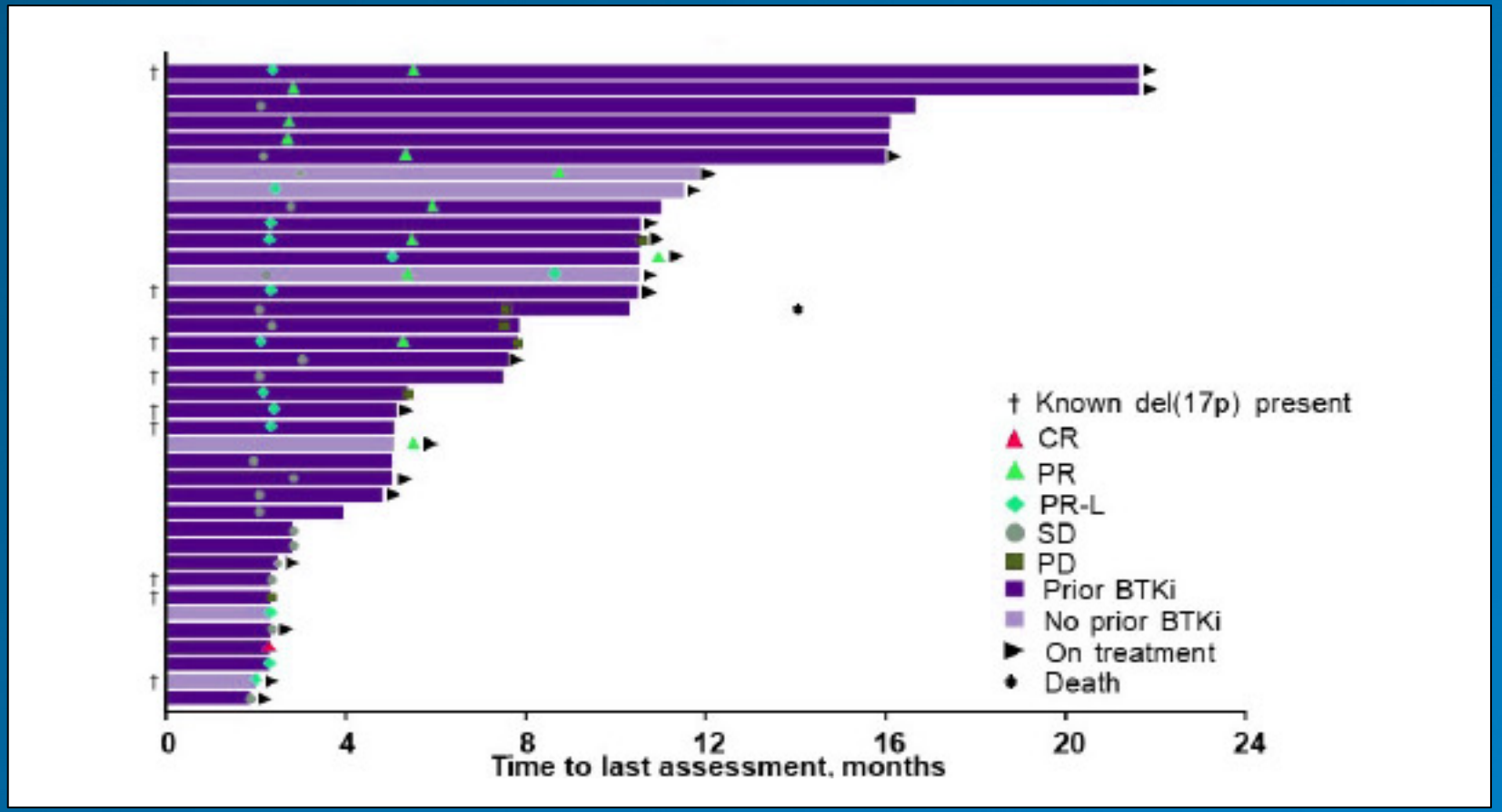
MK-1026/Nemtabrutinib: Treatment Duration Response (CLL/SLL), Efficacy Evaluable Population



Patietns with CLL/SLL treated at preliminary RP2D of 65 mg QD; PR-L, PR rate with lymphocytosis; Green bars indicate time from screening to date of last assessment; Patients not on treatment had discontinued due to progression, adverse event, patient or physician decision, or other reason. Data cut-off: April 7, 2021.
BTKi, Bruton tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; CR, complete response; DOR, duration of response; ORR, overall response rate; PD, progressive disease; PR, partial response; QD, once daily; SD, stable disease; SLL, small lymphocytic leukemia.
Adapted from Woyach et al. *Blood* 2021;138:392.

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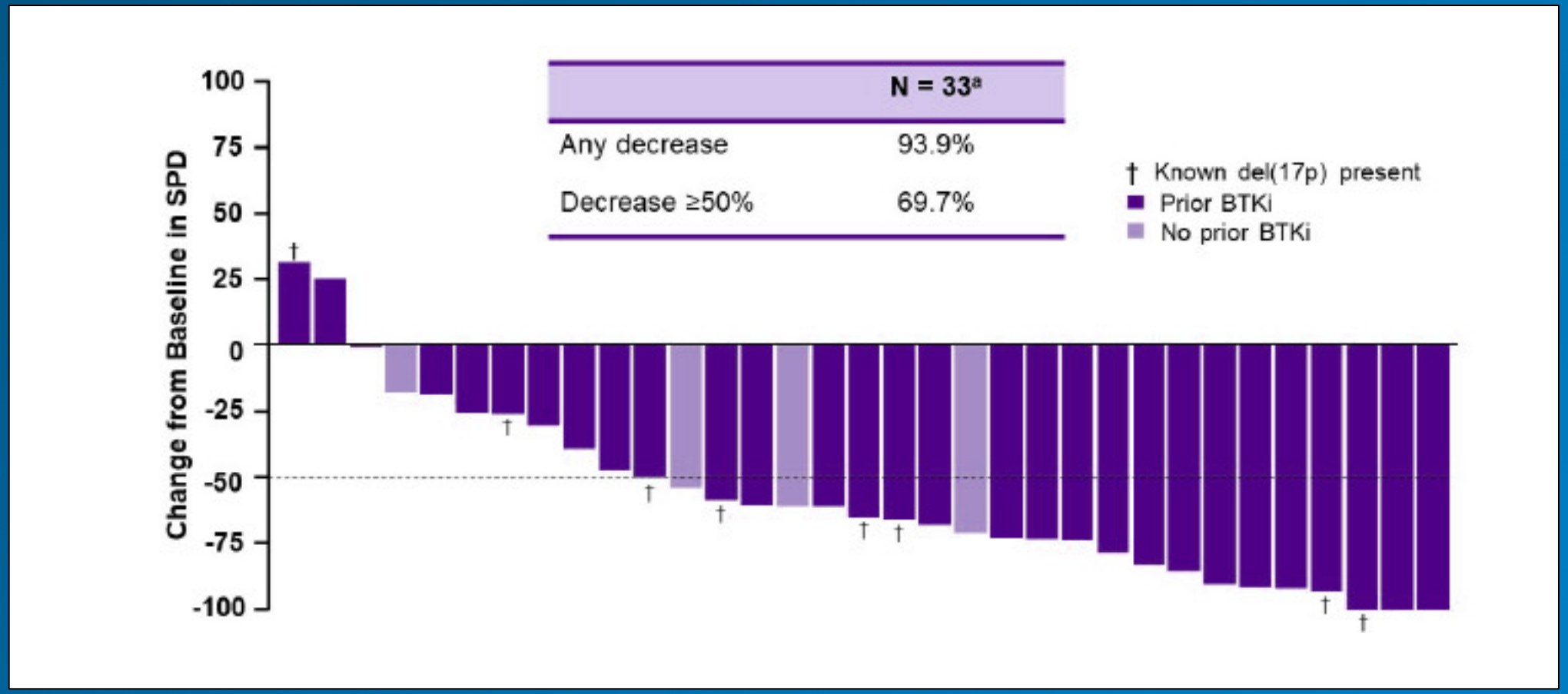
MK-1026/Nemtabrutinib: Percent Change from Baseline in SPD (CLL/SLL), Efficacy Evaluable Population



A33 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.
BTKi, Bruton tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; SLL, small lymphocytic leukemia; SPD, sum of the products of lymph node diameters.
Adapted from Woyach et al. *Blood* 2021;138:392.

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MK-1026/Nemtabrutinib: 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), and respiratory failure (n=2).
[b]No grade 5 drug related TEAEs were reported.
TEAEs, treatment-emergent adverse events.
Adapted from Woyach et al. *Blood* 2021;138:392.

Non-Covalent BTK Inhibitors in Mantle Cell Lymphoma

Outcomes in MCL Are Extremely Poor Following Covalent BTK Inhibitor Progression

- Covalent BTK inhibitor resistance in MCL and other lymphomas is incompletely understood[1-10]
- *BTK* C481-mutations are uncommon; bypass alterations and epigenetic changes implicated in some patients[7]
- Overall survival following covalent BTK inhibitor therapy is poor[3,4,11]

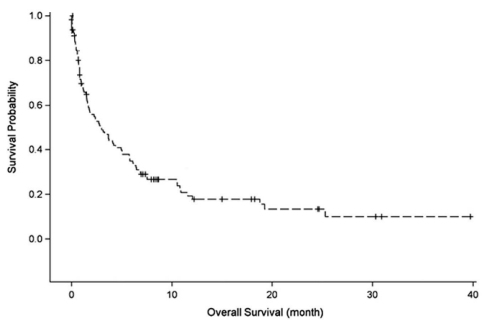


Fig 1[4]

Analysis of n = 114 global patients
Median OS = 2.9 months

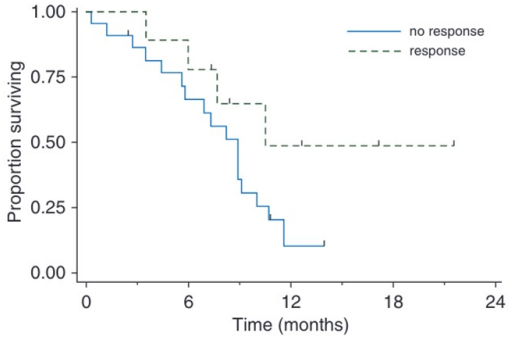


Fig 2[3]

Analysis of n = 31 US patients
Median OS = 8.4 months

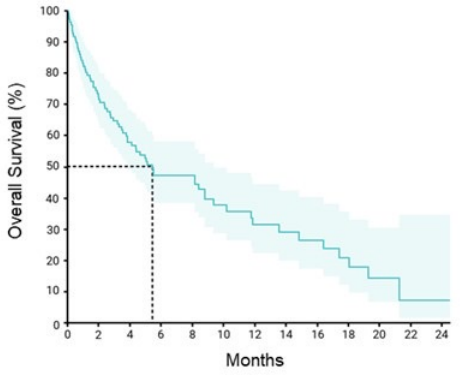


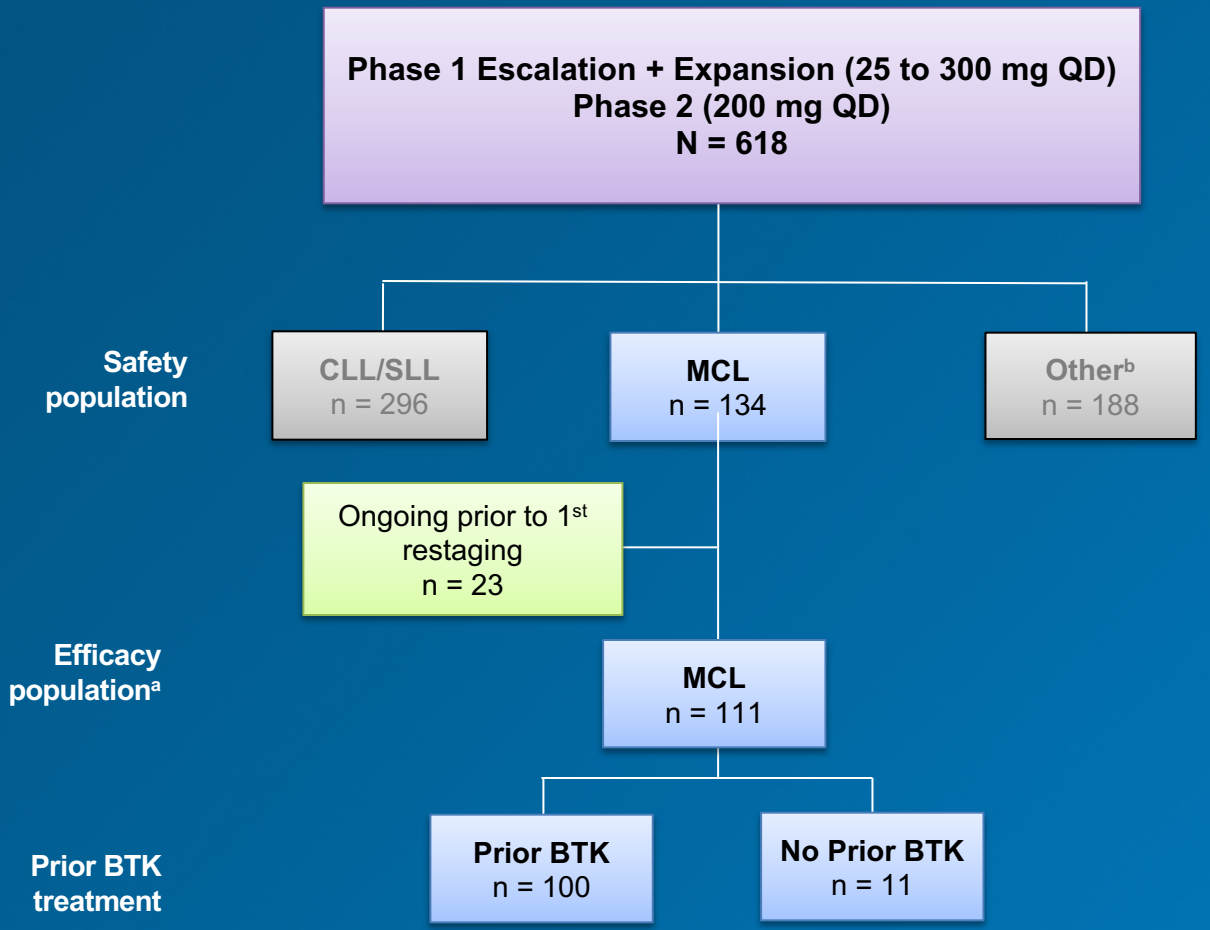
Fig 3[11]

Analysis of n = 108 Japanese patients
Median OS = 5.46 months

BTK, Bruton tyrosine kinase; MCL, mantle cell lymphoma; OS, overall survival.

[1]Hershkovitz-Rokah et al. *Br J Haemtol*. 2018;181:306-19. [2]Wang et al. *N Engl J Med*. 2013;369:507-16. [3]Cheah et al. *Ann Oncol*. 2015;26:1175-79. [4]Martin et al. *Blood* 2016;127:1559-63. [5]Dreyling et al. *Lancet* 2016;387:770-8. [6]Epperla et al. *Hematol Oncol*. 2017;35:528-35. [7]Ondrisova L and Mraz M, *Front Oncol*. 2020;10. [8]O'Brien et al. *Clin Lymphoma Myeloma Leuk*. 2018;18:648-57. [9]Byrd et al. *Blood* 2017;130(Suppl 1):4326. [10]Tam et al. *Blood* 2020;136:2038-50. [11]Rai et al. *Clin Lymphoma Myeloma Leuk*. 2021; 21(Suppl 1):S407-S408.

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
- CLL or other B-cell NHL
- Active disease and in need of treatment
- Previously treated

Key endpoints

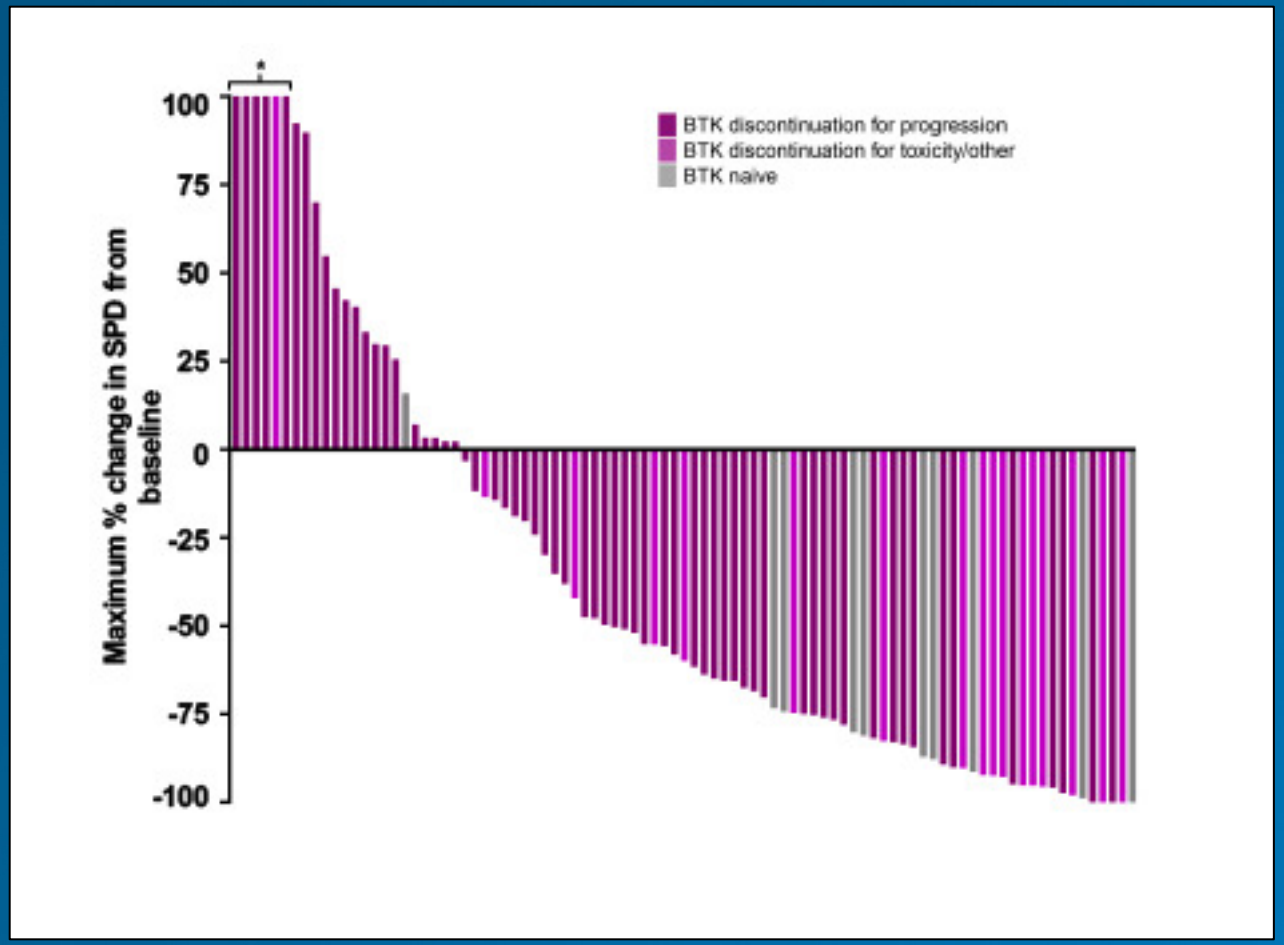
- Safety/tolerability
- Determine MTD & recommended phase 2 dose
- Pharmacokinetics
- Efficacy according to ORR & DoR based on disease criteria (iwCLL, IWWM, Lugano)

Data cutoff date July 16, 2021. [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, marginal zone lymphoma, Richter's transformation, B-PLL, Hairy Cell Leukemia, PCNSL, and other transformation.

BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; IWWM, International Workshop on Waldenstrom's Macroglobulinemia; MCL, mantle cell lymphoma; MTD, maximum tolerated dose; NHL, non-Hodgkin lymphoma; ORR, overall response rate; QD, once daily; SLL, small lymphocytic leukemia.

Wang et al. *Blood* 2021;138:381.

Pirtobrutinib Efficacy in Mantle Cell Lymphoma



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)

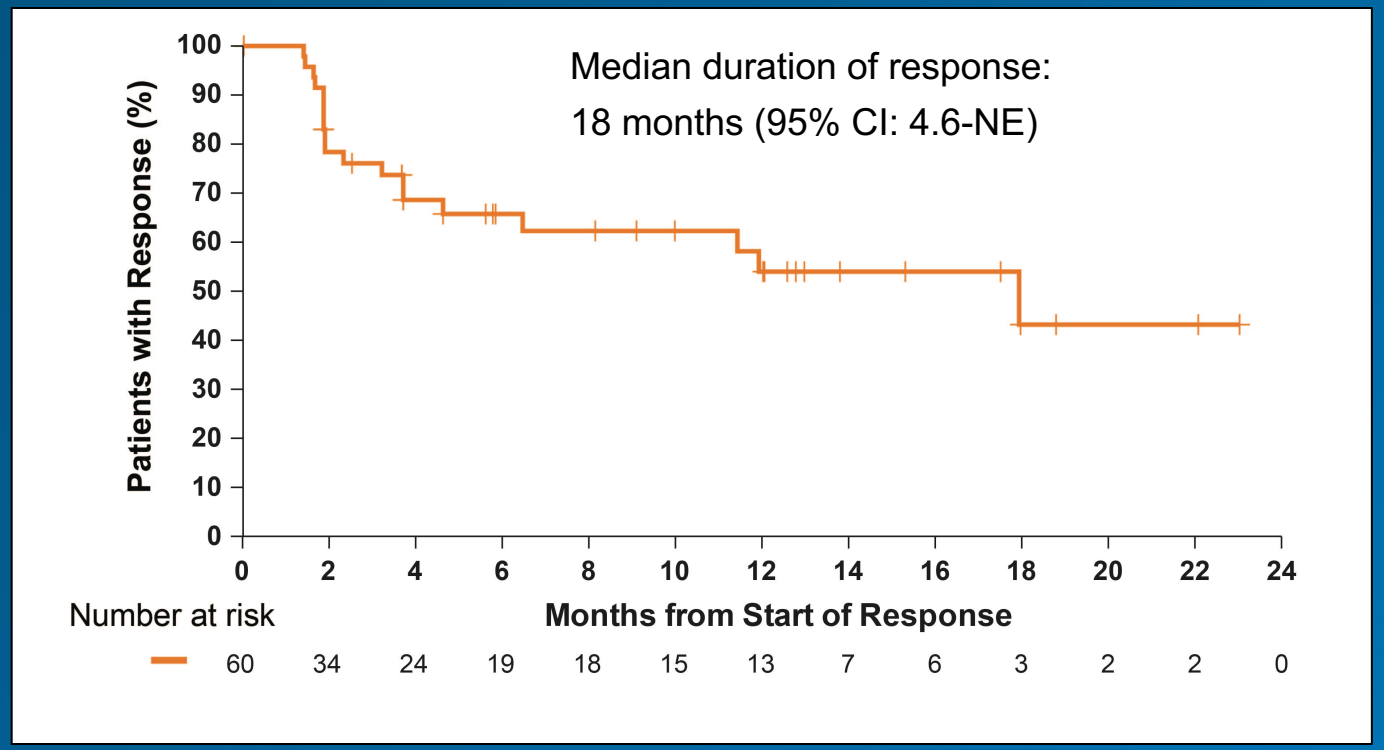
Data cutoff date July 16, 2021.

BTK, Bruton tyrosine kinase; CAR, chimeric antigen therapy; CR, complete response; MCL, mantle cell lymphoma; ORR, overall response rate; PR, partial response; SD, stable disease; SPD, sum of the products of diameters.

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.

Adapted from Wang et al. *Blood* 2021;138:381.

Pirtobrutinib Duration of Response in Mantle Cell Lymphoma



- Median follow-up of 8.2 months (range, 1.0 - 27.9 months) for responding patients
- 60% (36 of 60) of responses are ongoing

Data cutoff date July 16, 2021. Response status per Lugano 2014 criteria based on investigator assessment.
NE, not estimable.
Wang et al. *Blood* 2021;138:381.

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Mantle Cell Lymphoma Conclusions

- Pirtobrutinib demonstrates promising efficacy in patients with MCL previously treated with covalent BTK inhibitors, a population with extremely poor outcomes
- Favorable safety and tolerability are consistent with the design of pirtobrutinib as a highly selective and non-covalent BTK inhibitor
- **BRUIN MCL-321:** A randomized, global, phase 3 trial comparing pirtobrutinib with investigator's choice of covalent BTK inhibitors in BTK-naïve relapsed MCL is ongoing (NCT04662255)

BTK Bruton tyrosine kinase; MCL, mantle cell lymphoma.

From Bench to Practice: Treatment Algorithms

Summary: Alternate Non-Covalent BTK Inhibitors

Intolerance

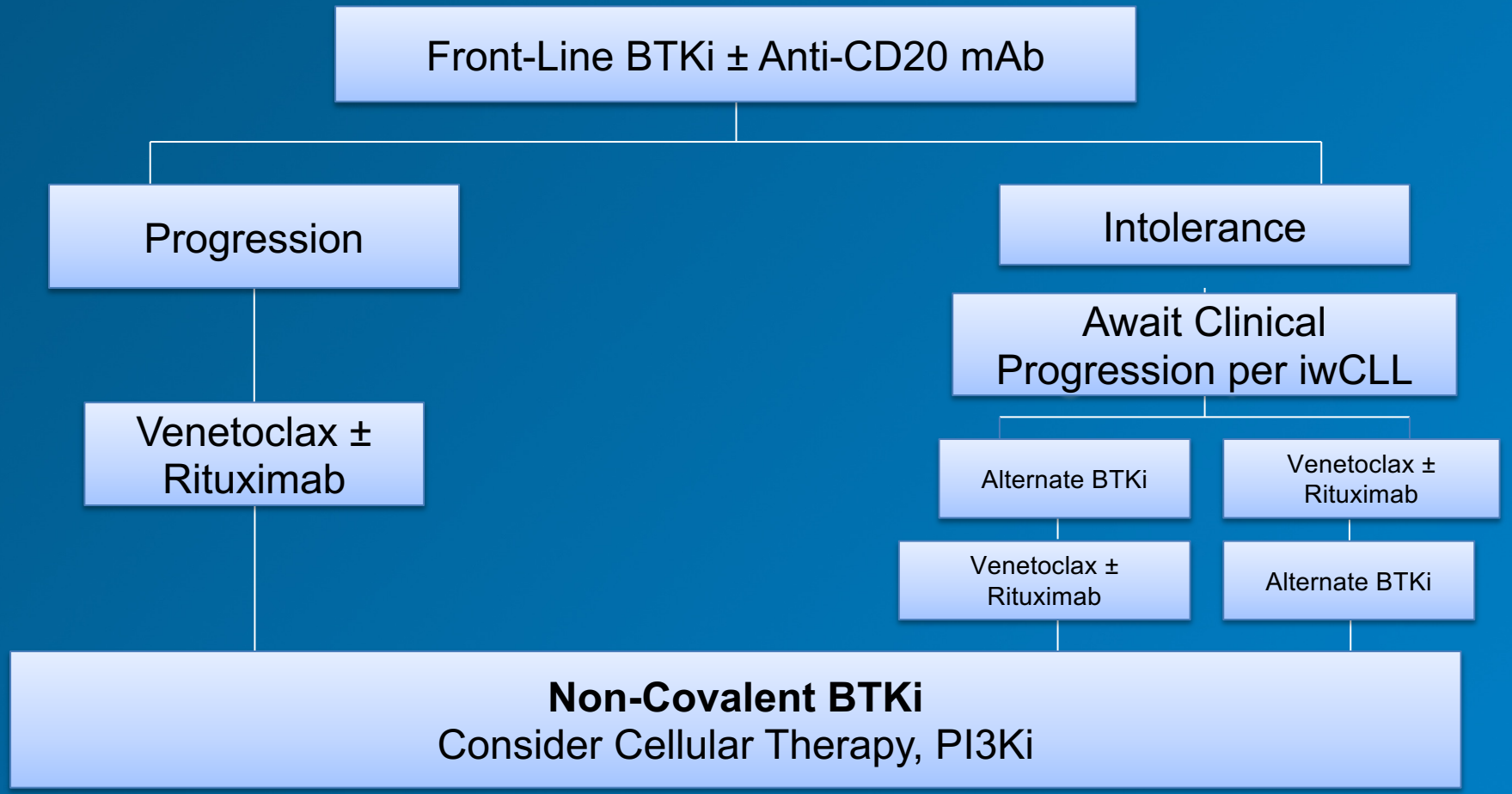
- Promising safety data with favorable AE profile and low discontinuation rates due to AEs
- Head-to-head comparison planned vs ibrutinib

Resistance

- Promising phase 1-2 data suggestive reversible BTKis can overcome *BTK* C481 mutant CLL and possible other cBTKi mechanisms of resistance

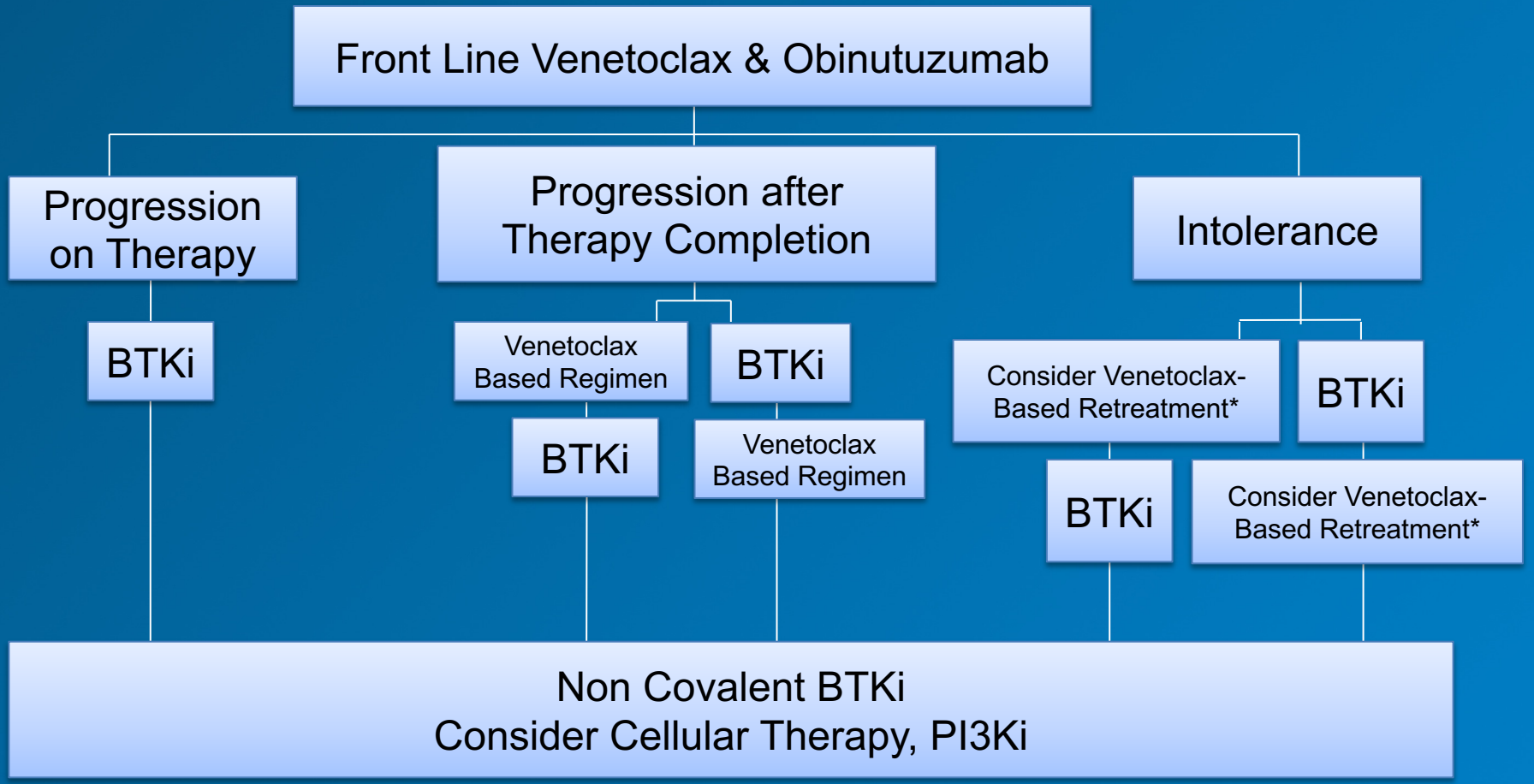
AEs, adverse events; BTKi, Bruton tyrosine kinase inhibitor; cBTKi, covalent BTKi; CLL, chronic lymphocytic leukemia.

Treatment Algorithm After Failure of BTKi and Anti-CD20 mAb



BTKi, Bruton tyrosine kinase inhibitor; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; mAb, monoclonal antibody; PI3Ki, phosphoinositide 3-kinase.

Treatment Algorithm After Failure of Venetoclax and Obinutuzumab



*With adequate supportive care and/or dose reduction.
BTKi, Bruton tyrosine kinase inhibitor; mAb, monoclonal antibody; PI3Ki, phosphoinositide 3-kinase.

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From Bench to Case-based Practice

Case Example

- A 64-year-old woman presents to your clinic with a history of Rai Stage III (Binet Stage C) del 17p CLL diagnosed 8 years ago
- Treated initially with fludarabine, cyclophosphamide, and rituximab
- Disease relapse occurred 5 years later and was treated with single-agent ibrutinib for 9 months
  - Discontinued secondary to persistent headaches, vomiting, and diarrhea
- She was then switched to venetoclax plus obinutuzumab
  - Eventually discontinued because of refractory pancytopenia
- Her absolute lymphocyte count is 135K/mL, her hemoglobin level is 9.2 g/dL, and her platelet count is 78K
- She has palpable lymphadenopathy in both axilla and a large left neck mass
- She also complains of drenching night sweats and unintentional weight loss of 20 pounds in the past 3 months
- She prefers oral medications to IV drugs and would prefer not to lose her hair

- Mindful of her preferences, what is the most appropriate and potentially most efficacious treatment to offer this patient?
  a) Single-agent idelisib
  b) Restart venetoclax
  c) Chlorambucil
  d) Acalabrutinib
  e) Unsure

Case Example, Cont.

- The patient is started on oral acalabrutinib (100 mg PO q 12 hours)
- Minor headaches develop that are readily controlled with acetaminophen
- She reports no diarrhea or nausea
- However, her lymphocyte count remains elevated after 6 months of treatment and her B-symptoms have persisted
- Molecular testing discloses a *BTK* C481 mutation

- Which of the following treatment options would you recommend?
  a) Oral chlorambucil
  b) Enroll in a phase 2 clinical trial with zanubrutinib plus obinutuzumab
  c) Enroll in a phase 2 clinic trial with single-agent pirtobrutinib
  d) Refer to a transplant center for autologous stem cell transplant
  e) Unsure

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Non-Covalent BTK Inhibitors for B-Cell Malignancies (MCL/CLL):

Setting the Stage for Future Use