Poster # CLL-120

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

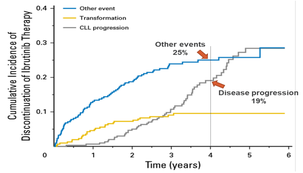
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BACKGROUND

- 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

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

Kinome selectivity[3]
Highly selective for BTK

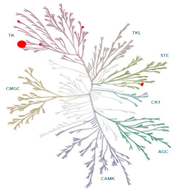
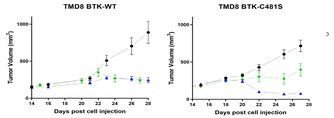


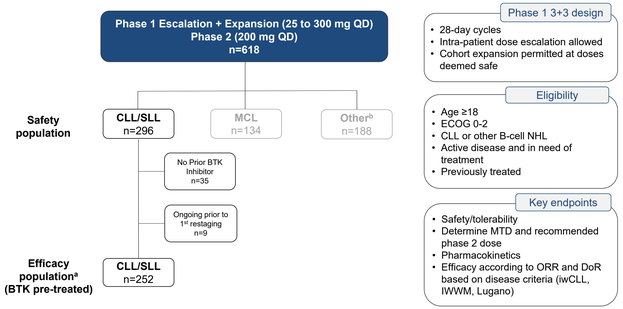
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Xenograft models
In vivo activity similarly efficacious as ibrutinib in WT; superior in C481S



- Nanomolar potency against WT and C481-mutant BTK in cell and enzyme assays[4]
- >300-fold selectivity for BTK vs 370 other kinases[4]
- Favorable pharmacologic properties allow sustained BTK inhibition throughout dosing interval[4]

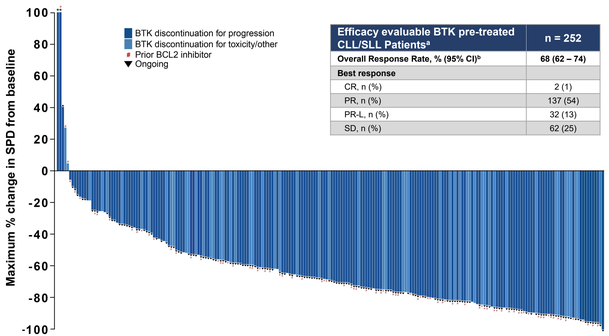
STUDY DESIGN



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.

KEY RESULTS

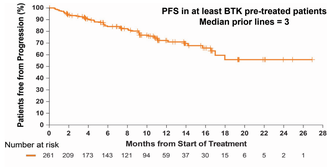
Pirtobrutinib Efficacy in BTK Pre-Treated CLL/SLL Patients



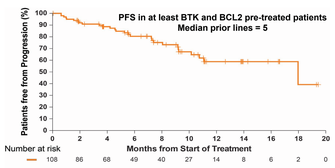
Efficacy evaluable BTK pre-treated CLL/SLL Patients[a]	n = 252
Overall Response Rate, % (95% CI)[b]	**68 (62 – 74)**
Best response	
CR, n (%)	2 (1)
PR, n (%)	137 (54)
PR-L, n (%)	32 (13)
SD, n (%)	62 (25)

Data cutoff date of 16 July 2021. [a]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. [b]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. [c]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



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

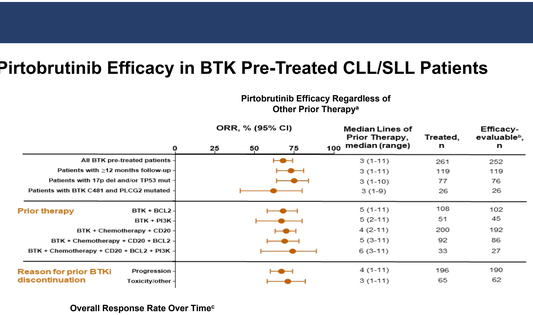


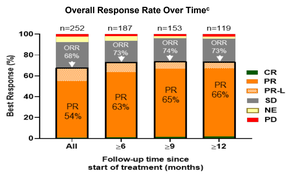
Median PFS: 18 months (95% CI: 10.7 months – Not Estimable)

- 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 Efficacy in BTK Pre-Treated CLL/SLL Patients





Data cutoff date of 16 July 2021. 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.

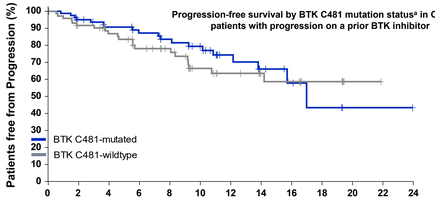
RESULTS

BTK Pre-Treated CLL/SLL Patient Characteristics

Characteristics	N = 261
Median age, years (range)	69 (36-88)
Female, n (%) Male, n (%)	84 (32) 177 (68)
ECOG PS[a], n (%) 0 1 2	 138 (53) 104 (40) 19 (7)
Median number of prior lines of systemic therapy (range)	3 (1-11)
Prior therapy, n (%) BTK inhibitor Anti-CD20 antibody Chemotherapy BCL2 inhibitor PI3K inhibitor CAR-T Stem cell transplant Allogeneic stem cell transplant Autologous stem cell transplant	 261 (100) 230 (88) 207 (79) 108 (41) 51 (20) 15 (6) 6 (2) 5 (2) 1 (<1)
Reason discontinued prior BTKi, n (%) Progressive disease Toxicity/Other	 196 (75) 65 (25)
Baseline Molecular Characteristics[a]	
Mutation status, n (%) BTK C481-mutant BTK C481-wildtype PLCG2-mutant	 89 (43) 118 (57) 33 (16)
High Risk Molecular Features, n (%) 17p deletion TP53 mutation 17p deletion or TP53 mutation Both 17p deletion and TP53 mutation IGHV unmutated 11q deletion	 51 (28) 64 (37) 77 (36) 38 (27) 168 (84) 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.

BTK C481 Mutation Status is not Predictive of Pirtobrutinib Benefit



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[c]							
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 atrial/flutter 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)
  - BRUIN CLL-314 – Pirtobrutinib vs Ibrutinib in BTKi naïve patients (NCT05254743)

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

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