PIRTOBRUTINIB (LOXO-305), A NEXT GENERATION, HIGHLY SELECTIVE, NON-COVALENT BTK INHIBITOR IN PREVIOUSLY TREATED RICHTER TRANSFORMATION: RESULTS FROM THE PHASE 1/2 BRUIN STUDY

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Poster # EP524

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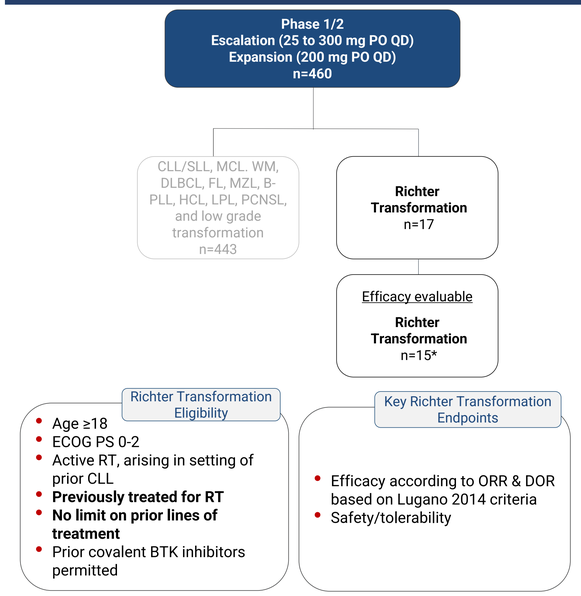
BACKGROUND

- Richter transformation (RT)
  - is commonly the development of an aggressive large cell lymphoma in the setting of underlying CLL.[1]
  - is a life-threatening event and reason for treatment failure (5-15%) among patients receiving CLL-directed therapy.[2]
- Overall survival of patients with RT is estimated at 3-11 months and there are no approved agents or defined standard of care[2]
- Pirtobrutinib (LOXO-305):
  - is a highly selective and potent non-covalent BTK inhibitor.[3]
  - has high oral bioavailability and a long half-life, resulting in robust BTK target coverage even in high-grade malignancies with high BTK protein turnover.[3]
  - is well tolerated and exhibits promising efficacy in previously treated patients with B-cell malignancies.[3]
- BRUIN (NCT03740529) is a multicenter, phase 1/2 dose escalation and expansion study evaluating pirtobrutinib in patients with previously treated, advanced B-cell malignancies.[3]
- Here, we present the safety and efficacy of pirtobrutinib in patients previously treated for RT who were enrolled in the BRUIN study.

BRUIN Study Design: RT Subgroup



*2 patients were non-evaluable for efficacy (1 ongoing prior to first post-baseline assessment, 1 ongoing with incomplete post-baseline assessment).

- 16 patients received pirtobrutinib 200 mg QD as the initial dose, and 1 patient received pirtobrutinib 150 mg QD.
- Efficacy evaluable patients were those who had at least one evaluable post baseline tumor measurement or discontinued treatment prior to first post baseline tumor measurement.
- Data cutoff date was 29 March 2021.

RESULTS

Table 1. Baseline characteristics

Characteristics	n=17
Median age, years (range)	64 (33-84)
Male, n (%) Female, n (%)	14 (82) 3 (18)
ECOG PS, n (%) 0 1 2	 8 (47) 7 (41) 2 (12)
Any *BTK* mutation status, n (%) Wildtype Unknown	 10 (59) 7 (41)
Bulky disease, n (%) < 5 cm ≥ 5 cm	 10 (59) 7 (41)
DLBCL RT histology	17 (100)
Median lines of prior systemic therapy, n (range)	6 (2-10)
Median lines of therapy for CLL prior to RT, n (range)	4 (1-9)
Median lines of prior RT-directed therapy, n (range)	2 (1-5)
All Prior therapies (CLL+RT-directed) BTK inhibitor BCL2 inhibitor	 14 (82) 10 (59)
Prior RT-directed systemic therapies, n (%)	
Chemotherapy	17 (100)
Anti-CD20 antibody	17 (100)
BTK inhibitor	6 (35)
PD/PDL-1 immunotherapies	5 (29)
mTOR inhibitor	4 (24)
PI3K inhibitor	3 (18)
Lenalidomide	3 (18)
BCL2 inhibitor	3 (18)
CAR-T	1 (6)

- Median time on treatment was 3.4 months (range 1.6-13.1+ months).

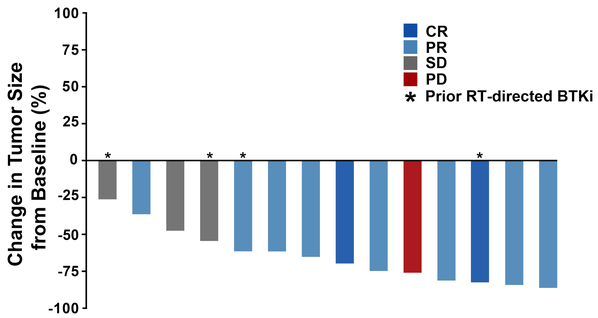
Table 2. Safety in the BRUIN study

All doses and patients (n=323)							
	Treatment-emergent AEs, (≥10%), n (%)					Treatment-related AEs, n (%)	
Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Any Grade	Grades 3/4	Any Grade
Fatigue	40 (12%)	22 (7%)	3 (1%)	-	65 (20%)	2 (<1%)	27 (8%)
Diarrhea	45 (14%)	10 (3%)	-	-	55 (17%)	-	28 (9%)
Contusion	37 (12%)	5 (2%)	-	-	42 (13%)	-	29 (9%)
AEs of special interest[a]							
Bruising	48 (15%)	5 (2%)	-	-	53 (16%)	-	37 (12%)
Rash	30 (9%)	5 (2%)	-	-	35 (11%)	-	18 (6%)
Arthralgia	13 (4%)	3 (1%)	-	-	16 (5%)	-	5 (2%)
Hemorrhage	10 (3%)	4 (1%)	1 (<1%)	-	15 (5%)	-	5 (2%)
Hypertension	2 (<1%)	9 (3%)	4 (1%)	-	15 (5%)	-	4 (1%)
Atrial fibrillation/flutter	-	2 (<1%)	-	-	2 (<1%)	-	-

Data cutoff date was 27 September 2020. Total % may be different than the sum of the individual components due to rounding. [a]AEs of special interest are those that were previously associated with covalent BTK inhibitors.

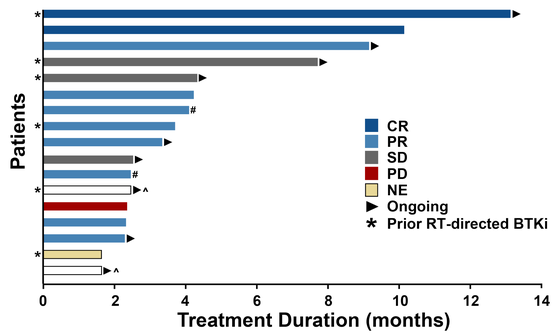
- The safety profile among the 17 RT patients was generally consistent with the overall population. The most common TEAEs in this subgroup included neutrophil count decrease and diarrhea.
- None of the 17 patients with RT discontinued treatment due to toxicity.
- Dose was reduced from 200 mg QD to 100 mg QD in 1 patient with RT due to AE (Grade 2 lipase increased).

Fig 1. Best change in tumor size and response



1 patient not shown due to discontinuation prior to first post- baseline tumor assessment.

Fig 2. Treatment duration and best response



[#]Electively discontinued in response, to pursue transplant.

^2 patients were non-evaluable for efficacy (1 ongoing prior to first post-baseline assessment, 1 ongoing with incomplete post-baseline assessment).

Table 3. ORR, BOR and TTBR

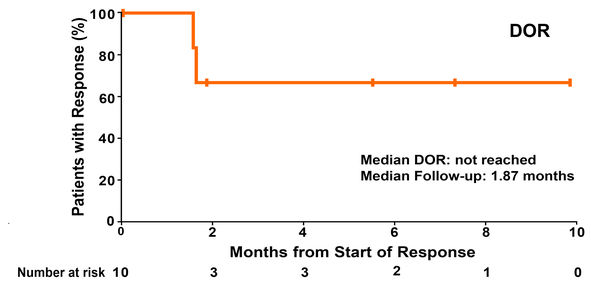
Evaluable patients with RT	n=15
Overall Response Rate **n (%)** **95% CI**	 **10 (67)** **38-88**
Best Response, n (%)	
CR	2 (13)
PR	8 (53)
SD	3 (20)
PD	1 (7)
NE	1 (7)
Time to Best Response	
Median, months (range)	1.9 (1.6-2.1)

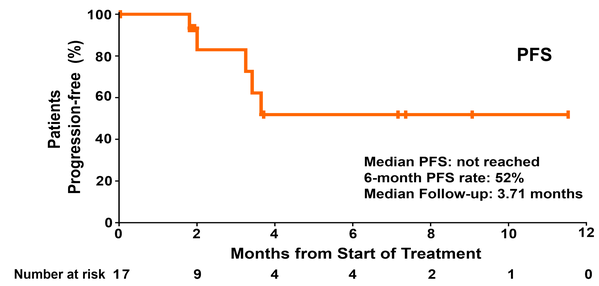
1 patient was non-evaluable due to discontinuation prior to first post-baseline tumor assessment and was counted as a non-responder. Total % may be different than the sum of the individual components due to rounding.

ORR among evaluable patients is defined as CR or PR.

Time to best response is defined as the number of months that elapsed between the date of the first pirtobrutinib dose and the first documentation of CR (if patient's BOR is CR) or PR (if patient's BOR is PR).

Fig 3. Duration of response and progression-free survival





CONCLUSIONS

- Pirtobrutinib showed encouraging efficacy in patients failing prior RT-directed therapy.
  - Promising response rate was observed (ORR = 67%).
  - Additional follow up is needed to establish durability of response.
- Pirtobrutinib showed activity in patients with RT who have received prior BTK inhibitors and chemoimmunotherapy for CLL.
- The safety profile of pirtobrutinib in patients with RT was consistent with the overall population in the BRUIN trial.

References

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