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ORAL ABSTRACTS

623.MANTLE CELL, FOLLICULAR, AND OTHER INDOLENT B CELL LYMPHOMAS: CLINICAL AND EPIDEMIOLOGICAL

Pirtobrutinib in Relapsed/Refractory (R/R) Mantle Cell Lymphoma (MCL) Patients with Prior cBTKi: Safety and Efficacy Including High-Risk Subgroup Analyses from the Phase 1/2 BRUIN Study

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Background: Despite the efficacy of covalent (c) Bruton tyrosine kinase inhibitors (BTKi) in R/R MCL, disease relapse arises through evolution of resistance mechanisms or development of cBTKi intolerance. Pirtobrutinib, a highly selective, non-covalent (reversible) BTKi has favorable oral pharmacology that enables continuous BTK inhibition throughout the daily dosing interval regardless of the intrinsic rate of BTK turnover. Pirtobrutinib is the first BTKi to demonstrate durable efficacy following prior cBTKi therapy in heavily pre-treated R/R MCL and was well-tolerated with a low frequency of treatment discontinuation due to toxicity (Wang *et al*., JCO, 2023). Pirtobrutinib is approved in the USA to treat relapsed or refractory MCL after at least two lines of systemic therapy including a prior cBTKi. Here, we report updated results of pirtobrutinib therapy in all patients (pts), including those with biologically high-risk R/R MCL with a median survival follow-up of 24.2 months (range, 18.2-29.8).
Methods: Pts with R/R MCL received pirtobrutinib monotherapy in the multicenter Phase 1/2 BRUIN trial (NCT03740529). Efficacy was assessed in all cBTKi pre-treated pts, as well as in cBTKi treatment-naïve pts. Key endpoints included overall response rate (ORR) as assessed by independent review committee per Lugano 2014 criteria, duration of response (DOR), progression-free survival (PFS), overall survival (OS), and safety. Pts were included across the dose escalation range and expansion (25-300 mg/day) with 93% (n=141) receiving at least one dose of 200 mg/day, the FDA-approved dose. A data cut of 05 May 2023 was utilized.
Results: Among all 152 pts with R/R MCL who received a prior cBTKi, the median age was 70 years (range, 46-88), and 52% had intermediate-risk and 28.3% had high-risk sMIPI scores. Median prior lines of therapy were 3 (range, 1-9), including an anti-CD20 antibody (96.7%), chemotherapy (90.1%), immunomodulator (17.1%), stem cell transplant (21.7%), BCL-2 inhibitor (15.8%), CAR-T cell therapy (8.6%), and PI3K inhibitor (3.9%). Among pts with high-risk biomarker data available, 30/60 (50%) had *TP53* mutations and 45/63 (71%) had a Ki-67 index of ≥30%. The ORR for cBTKi pre-treated pts was 49.3% (95% CI, 41.1-57.6), including 15.8% complete responses (n=24) and 33.6% partial responses (n=51), whilst cBTKi naïve pts (n=14) had an ORR of 85.7% (95% CI, 57.2-98.2). The ORR among 128 pts who had discontinued a prior cBTKi due to PD and 21 pts who had discontinued for toxicity/other reasons was 43.0% and 90.5%, respectively. Among the 75 responding cBTKi pre-treated pts, the median DOR was 21.6 months (95% CI, 9.2-27.2) at a median follow-up of 24 months. The 18- and 24-month DOR rates were 51.9% (95% CI, 37-64.8) and 38.9% (95% CI, 22.7-54.8), respectively. ORR and DOR by high-risk subgroups (including blastoid/pleomorphic variants, Ki-67 index ≥30%, and *TP53* mutations) are shown in Table 1. The 18- and 24-month DOR rates among 12 responding cBTKi naïve pts were both 90.0% (95% CI, 47.3-98.5). The median PFS and OS for cBTKi pre-treated pts was 5.6 months (95% CI, 5.3-9.2), and 23.5 months (95% CI, 17.1-NE), respectively. In the MCL cohort (n=166), the most frequent treatment-emergent adverse events (TEAEs) were fatigue (31.9%), diarrhea (22.3%), and dyspnea (17.5%). The most common Grade ≥3 TEAE was neutropenia/neutrophil count decreased (13.3%) and the rate of Grade ≥3 infections was (19.9%). Grade ≥3 hemorrhage/hematoma (2.4%) and all-grade atrial fibrillation/flutter (3.6%) were infrequent. Overall, 8 pts (5%) had treatment-related AEs leading to dose reductions and 5 (3%) had treatment-related AEs leading to pirtobrutinib discontinuation.
Conclusion: Pirtobrutinib continues to demonstrate durable efficacy and a favorable safety profile in heavily pre-treated R/R MCL pts with prior cBTKi therapy. High ORRs were observed in pts who had PD on a prior cBTKi, and in pts with high-risk disease features including blastoid/pleomorphic variants, elevated Ki-67 index, and *TP53* mutations.

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ing; *Seattle Genetics:* Research Funding; *Astra Zeneca:* Consultancy, Research Funding; *Abbvie Pharmaceuticals:* Research Funding; *BridgeBio:* Current equity holder in publicly-traded company; *Janssen:* Consultancy; *Genentech:* Consultancy, Research Funding; *Celgene:* Research Funding. **Munir:** *AstraZeneca:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Janssen:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding, Speakers Bureau; *Abbvie:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding, Speakers Bureau; *Roche:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Sobi:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Alexion:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *BeiGene:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau. **Tsai:** *Eli Lilly and Company:* Current equity holder in publicly-traded company; *Loxo@Lilly:* Current Employment. **Balbas:** *Eli Lilly and Company:* Current Employment, Current equity holder in publicly-traded company. **Liu:** *Eli Lilly and Company:* Current Employment. **Ruppert:** *Eli Lilly and Company:* Current Employment, Current equity holder in publicly-traded company; *Telios Pharma:* Consultancy. **Nguyen:** *Loxo@Lilly:* Current Employment. **Roeker:** *PeerView:* Other: CME speaker; *Curio:* Other: CME speaker; *Ascentage:* Consultancy; *AbbVie:* Consultancy, Research Funding; *Adaptive Biotechnologies:* Research Funding; *Beigene:* Consultancy; *AstraZeneca:* Consultancy, Research Funding; *Pfizer:* Consultancy, Research Funding; *DAVA:* Other: CME speaker; *Janssen:* Consultancy; *Loxo Oncology:* Consultancy, Other: travel support, Research Funding; *Medscape:* Other: CME speaker; *Pharmacyclics:* Consultancy; *TG Therapeutics:* Consultancy; *Abbott Laboratories:* Current equity holder in publicly-traded company; *Genentech:* Research Funding; *Aptose Biosciences:* Research Funding; *Dren Bio:* Research Funding; *Qilu Puget Sound Biotherapeutics:* Research Funding. **Wang:** *Bristol Myers Squibb:* Consultancy, Honoraria; *BioInvent:* Consultancy, Honoraria, Research Funding; *BeiGene:* Consultancy, Honoraria, Research Funding; *Imedex:* Honoraria; *Hebei Cancer Prevention Federation:* Honoraria; *Epizyme:* Consultancy, Honoraria; *Clinical Care Options:* Honoraria; *BGICS:* Honoraria; *Anticancer Association:* Honoraria; *Vincerx:* Research Funding; *Molecular Templates:* Research Funding; *Loxo Oncology:* Consultancy, Research Funding; *Juno Therapeutics:* Research Funding; *Genentech:* Consultancy, Research Funding; *Celgene:* Other: Travel, Research Funding; *WebMD:* Honoraria; *Studio ER Congressi:* Honoraria; *Scripps:* Honoraria; *Practice Point Communications (PPC):* Honoraria; *Physicians Education Resources (PER):* Honoraria, Other: Travel; *OncLive:* Honoraria; *Oncology Specialty Group:* Honoraria; *Nurix:* Honoraria; *NIH:* Honoraria; *Moffit Cancer Center:* Honoraria; *MJH Life Sciences:* Honoraria; *MD Education:* Honoraria; *Meeting Minds Experts:* Honoraria; *Medscape:* Honoraria; *IDEOlogy Health:* Honoraria; *i3Health:* Honoraria; *Genmab:* Honoraria, Research Funding; *Eastern Virginia Medical School:* Honoraria; *Dava Oncology:* Honoraria, Other: Travel; *CAHON:* Honoraria; *Bantam Pharmaceutical:* Honoraria; *VelosBio:* Consultancy, Research Funding; *Pharmacyclics:* Consultancy, Honoraria, Research Funding; *Pepromene Bio:* Consultancy; *Parexel:* Consultancy; *Oncternal:* Consultancy, Research Funding; *Milken Institute:* Consultancy; *Miltenyi Biomedicine:* Consultancy; *Merck:* Consultancy, Honoraria; *Eli Lilly and Company:* Consultancy, Research Funding; *Leukemia & Lymphoma Society:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; *Kite, a Gilead Company:* Consultancy, Honoraria, Other: Travel, Research Funding; *Janssen:* Consultancy, Honoraria, Research Funding; *InnoCare:* Consultancy, Research Funding; *Genentech:* Consultancy, Research Funding; *DTRM Biopharma (Cayman) Limited:* Consultancy; *Deciphera:* Consultancy; *Be Biopharma:* Consultancy; *AstraZeneca:* Consultancy, Honoraria, Other: Travel, Research Funding; *Amphista Therapeutics Limited:* Consultancy; *ADC Therapeutics America:* Consultancy; *CSTone:* Consultancy; *Practice Point Communications:* Honoraria; *Physicians Education Resources:* Honoraria; *Acerta Pharma:* Consultancy, Honoraria, Research Funding; *AbbVie:* Consultancy, Honoraria; *TS Oncology:* Honoraria; *Mumbai Hematology Group:* Honoraria; *OMI:* Honoraria; *Pharmacyclics:* Honoraria.

OffLabel Disclosure: Pirtobrutinib is approved for MCL treatment by FDA in USA to treat relapsed or refractory MCL after at least two lines of systemic therapy including prior BTK inhibitor treatment.

Overall Response Rate and Duration of Response by Subgroup

		cBTKi pre-treated MCL (n)	Number with Response (n)	ORR, % (95% CI)	DOR, median (95% CI)
Overall		152	75	49.3 (41.1-57.6)	21.6 (9.2-27.2)
MCL histology	Classic/Leukemic	120	61	50.8 (41.5-60.1)	17.7 (7.7-NE)
	Blastoid	15	6	40.0 (16.3-67.7)	NE (1.4-NE)
	Pleomorphic	17	8	47.1 (23.0-72.2)	21.6 (3.7-NE)
TP53 mutation[a]	Yes	30	13	43.3 (25.5-62.6)	17.6 (1.7-NE)
	No	30	15	50.0 (31.3-68.7)	14.8 (1.9-NE)
Ki-67 Index[a]	<30%	18	12	66.7 (41.0-86.7)	17.7 (1.9-NE)
	≥30%	45	20	44.4 (29.6-60.0)	21.6 (5.6-27.2)
sMIPI	Low	30	20	66.7 (47.2-82.7)	27.2 (6.5-NE)
	Intermediate	79	42	53.2 (41.6-64.5)	17.7 (7.4-NE)
	High	43	13	30.2 (17.2-46.1)	14.8 (5.2-21.6)
Discontinuation from any prior BTKi[a, b]	Disease Progression	128	55	43.0 (34.3-52.0)	14.8 (7.3-27.2)
	Toxicity/Other	21	19	90.5 (69.6-98.8)	25.3 (9.2-NE)

Table 1. ORR and DOR in cBTKi pre-treated pts and high-risk subgroups

[a]Patients with missing data were not included in the analysis.

[b]Disease Progression" is selected if "PD" for any prior BTK; otherwise "Toxicity" is selected if toxicity from any prior BTK; otherwise "Other".

Figure 1

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