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ORAL ABSTRACTS

642.CHRONIC LYMPHOCYTIC LEUKEMIA: CLINICAL AND EPIDEMIOLOGICAL

Initial Results of a Phase 1 Dose Escalation Study of LP-168, a Novel Covalent and Non-Covalent Next-Generation Inhibitor of Bruton's Tyrosine Kinase

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Introduction: Inhibitors of Bruton's Tyrosine Kinase (BTKi) have been transformative therapies in chronic lymphocytic leukemia (CLL) and other lymphoid malignancies. Despite extended remissions, most patients (pts) will relapse. Covalent BTKi (cBTKi) including ibrutinib, acalabrutinib, and zanubrutinib, share a common resistance mechanism, acquisition of a C481 mutation in BTK. Non-covalent BTKi (ncBTKi) can overcome this, however, second-site mutations, notably T474 gatekeeper and kinase-dead mutations, have been observed. LP-168 is a selective next generation inhibitor of BTK that can bind wild-type and C481-mutated BTK covalently and non-covalently, respectively, with preclinical activity in resistant CLL models (submitted to ASH 2023). This dual activity is hypothesized to allow efficacy against cells with wild-type BTK through covalent activity while preventing expansion of the most common resistance mechanisms through non-covalent activity. Here we describe initial results of a phase 1 study of LP-168, with safety evaluation focusing on DLT evaluable pts, and efficacy evaluation focusing on the cohort of pts with CLL.

Methods: NCT04775745 is a multicenter phase 1 dose escalation study of LP-168 monotherapy in pts with relapsed/refractory B-cell malignancies. CLL pts must have received ≥2 prior therapies. Dose escalation was performed using 3+3 design with expansion at multiple doses. Treatment emergent adverse events (TEAEs) were assessed per NCI CTCAE v5.0. Responses were evaluated using iwCLL 2018 criteria. Intra-patient dose escalation was permitted when dose levels cleared safety evaluation.

Results: From 16 Sep 2021 to 10 Jul 2023, 43 DLT-evaluable pts were enrolled, including 35 with CLL, at doses from 100-300 mg daily as well as 150 mg twice daily. Data for this abstract were locked 10 Jul 2023. CLL pts received a median of 3 prior therapies, with 94% receiving a prior cBTKi and 11% a ncBTKi. 20 pts had alterations in *TP53*, 21 pts had C481S *BTK* mutations, 7 pts had gatekeeper mutations at T474 *BTK*, and 5 pts had mutation in *PLC γ2* (Table).

33 pts have response data with median follow-up of 12.6 months (Figure). Overall response rate (ORR) including all dose levels was 54.5% (18/33)-all were partial response (PR) or partial response with lymphocytosis (PR-L). When evaluating only pts at doses of 200 mg or higher, ORR was 66.7% (10/15). In the subgroup of pts who had received only one prior BTKi including all dose levels, ORR was 77.8% (14/18). In the subgroup of pts with both *BTK* C481 and T474 mutations at doses of 150mg BID or 300mg QD, ORR was 75% (3/4). At the time of this report, only 5 pts with CLL have discontinued the study for progressive disease.

At data lock, 43 DLT evaluable pts (with all histologies) were evaluable for safety. No DLT have been observed, and most AE have been low grade. TEAE seen in >20% of pts included diarrhea, fatigue, arthralgia, headache, constipation, cough, and dizziness; of those, grade 3 or higher AE included fatigue and constipation in 1 pt each. Serious AE were seen in 11 pts, of which 1 led to discontinuation (intracranial hemorrhage in a mantle cell lymphoma pt in complete remission). No DLT was identified at doses up to 300 mg daily and 150 mg twice daily. No atrial fibrillation/flutter has been reported. Hypertension grade 3 or higher was seen in 1 pt, and 1 pt experienced high-grade bleeding (as described). AE frequency did not increase with increasing doses.

Pharmacokinetics showed plasma exposure increases dose-dependently. Steady state AUC $_{24h}$ was between 47.1-94.6 ug/mL*h with limited accumulation. Steady state half-life was between 15.3-21.9 hours at all doses and C $_{max}$ was between 3500 and 5600 ng/mL. BTK occupancy is nearly at 100% at dose levels that were tested, with little variability among pts. Collective review demonstrates optimal Cmax to be achieved at either 200 or 300 mg dosed daily.

Conclusions: LP-168 has been well tolerated in this study, with no DLTs identified at doses up to 300 mg daily. Preliminary efficacy was observed in high risk CLL pts, including those treated with one or more BTKi. Considering safety, efficacy, and PK/PD, dose expansion will occur at 200 mg and 300 mg daily following the FDA Project Optimus guidelines to determine the recommended phase 2 dose. A separate cohort will enroll pts with gatekeeper mutations to further explore efficacy. Updated biomarker, safety, and efficacy data will be presented at the meeting.

Disclosures Woyach: *Newave:* Consultancy; *Loxo:* Consultancy; *Beigene:* Consultancy; *AstraZeneca:* Consultancy; *Abbvie:* Consultancy; *Schrodinger:* Research Funding; *Morphosys:* Research Funding; *Karyopharm:* Research Funding; *Janssen:* Consultancy, Research Funding; *Pharmacyclics:* Consultancy, Research Funding. **Stephens:** *AbbVie:* Consultancy; *AstraZeneca:* Consultancy, Research Funding; *BeiGene:* Consultancy; *Bristol-Myers Squibb:* Consultancy; *Celgene:* Consultancy; *Genentech:* Consultancy; *Janssen:* Consultancy; *Lilly:* Consultancy; *Novartis:* Research Funding. **Brander:** *Genentech:* Consultancy, Other: Site PI clinical trial (grant paid to institution), Research Funding; *ArQule/Merck:* Other: Site PI clinical trial (grant paid to institution), Research Funding; *Ascentage:* Other: Site PI clinical trial (grant paid to institution), Research Funding; *Pharmacyclics:* Consultancy, Other: Site PI clinical trial (grant paid to institution), Research Funding; *AbbVie:* Consultancy, Other: Site PI clinical trial (grant paid to institution), Research Funding; *AstraZeneca/Acerta:* Other: Site PI clinical trial (grant paid to institution), Research Funding; *TG Therapeutics:* Other: Site PI clinical trial (grant paid to institution), Research Funding; *Novartis:* Other: Site PI clinical trial (grant paid to institution), Research Funding; *NeWave:* Other: Site PI clinical trial (grant paid to institution), Research Funding; *MEI Pharma:* Other: Site PI clinical trial (grant paid to institution), Research Funding; *DTRM:* Other: Site PI clinical trial (grant paid to institution), Research Funding; *Catapult:* Other: Site PI clinical trial (grant paid to institution), Research Funding; *Juno/Celgene/BMS:* Other: Site PI clinical trial (grant paid to institution, Research Funding; *Beigene:* Other: Site PI clinical trial (grant paid to institution), Research Funding; *Pharmacyclics:* Other: Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid for NCCN panel member CLL/SLL and HCL, inform-CLL registry steering committee; *AbbVie:* Other: Core registry steering committee ; *CLL Society:* Other: Alliance in Clinical Trials: Leukemia committee member & Trial Champion of S1925 . **Kittai:** *Abbive:* Consultancy; *AstraZeneca:* Consultancy, Research Funding; *BeiGene:* Consultancy, Research Funding, Speakers Bureau; *Eli Lilly:* Consultancy; *Janssen:* Consultancy; *KITE:* Consultancy; *BMS:* Consultancy. **Curran:** *Servier:* Consultancy, Other: Expert consensus panel; *Kite:* Other: Advisory board; *Amgen:* Other: Advisory board; *Jazz:* Other: Advisory board; *Incyte:* Other: Advisory board; *Pfizer:* Honoraria, Other: Advisory board. **Tan:** *Guangzhou Lupeng Pharmaceutical Co:* Current Employment, Current holder of *stock options* in a privately-held company, Membership on an entity's Board of Directors or advisory committees, Patents & Royalties: Newave Pharmaceutical Inc. **Chen:** *Newave Pharmaceutical Inc:* Current Employment, Current holder of *stock options* in a privately-held company, Honoraria, Membership on an entity's Board of Directors or advisory committees, Patents & Royalties: Newave Pharmaceutical Inc. **Anthony:** *Newave Pharmaceutical Inc:* Current Employment, Current holder of *stock options* in a privately-held company, Membership on an entity's Board of Directors or advisory committees; *Exact Sciences:* Consultancy; *Halia Therapeutics:* Consultancy; *Sumitomo Dainippon Pharma oncology:* Patents & Royalties. **Chen:** *Newave Pharmaceutical Inc.:* Current Employment, Current holder of *stock options* in a privately-held company, Membership on an entity's Board of Directors or advisory committees.

Table: Baseline Characteristics of 35 DLT evaluable patients with CLL/SLL

Characteristic	Number
Median age (range)	70.5 (53-81)
Male gender (%)	30 (86)
Median lines of prior therapy (range)	3 (2-8)
Prior Therapies, n (%)	
1 prior cBTKi	19(54)
2 prior cBTKi	10(29)
Prior cBTKi and ncBTKi	4(11)
Chemotherapy	26(74)
BCL2 inhibitor	17(49)
BCL2 + BTK inhibitors	15 (43)
CAR-T	1 (3)
Known Molecular Characteristics *	
Del(17p) and/or *TP53* mutation	20
IGHV unmutated	25
Del11q	15
BTK C481S	21
BTK C481 R/F/Y/V	5
BTK T474 I/F/H	7
BTK L528W	1
BTK wild type	11
PLCG2 known BTKi resistance mutation	5

* The known molecular characteristic information is extracted from screening FISH, medical notes, site standard of care BTK panel and NGS reports. 17 patients who didn't have any mutation analysis done at site level had their screening PBMC samples sequenced using CLL Ampliseq panel at OSU EHL laboratory.

Figure: Response and duration of treatment for 33 CLL/SLL patients who are DLT evaluable with available response data

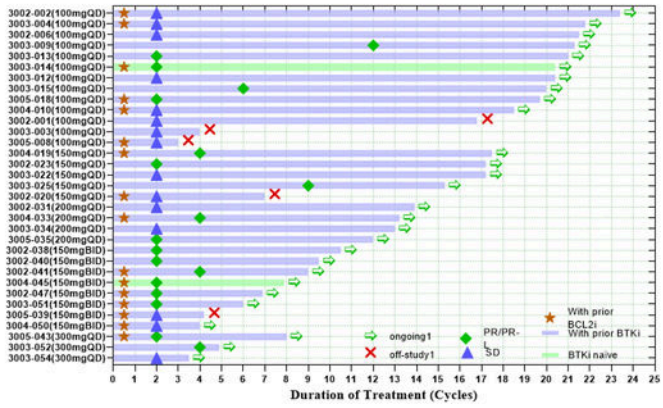

Figure 1

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