Emerging evidence of activity of BLU-945 in patients with advanced EGFR-mutant NSCLC utilizing circulating tumor DNA in the phase 1/2 SYMPHONY study

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Background

- Epithelial growth factor receptor mutations (EGFRm) are the most frequent oncogenic drivers of non-small cell lung cancer (NSCLC) and are found in up to 50% of Caucasian and up to 30% of Asian patients.1

- Use of osimertinib, a third-generation EGFR (EGFRm) TKI, has improved survival in patients with EGFRm NSCLC.2

- However, EGFR-mutant NSCLC is a heterogenous disease characterized by recurrent resistance mechanisms

- Further clinical development of third-generation TKIs is needed to address this challenge.

- BLU-945 is an investigational, oral next-generation TKI, selective for EGFRm TKIs with A858P, T790M, and C797S mutants.

- This phase 1/2 SYMPHONY study evaluated the efficacy, safety, and tolerability of BLU-945 as monotherapy or in combination with osimertinib.

Method

- SYMPHONY (NCT04662972) is an ongoing phase 1/2, open-label, multi-center, phase 2 study in patients with advanced NSCLC harboring EGFRm, conducted in the US and Japan (Figure 1).

- In the phase 1 dose escalation part of the study, 50 patients were enrolled in 5 cohorts: 25 mg, 50 mg, 100 mg, 200 mg, and 400 mg. Patients could receive escalation on a patient-by-patient basis as determined by the investigator.

- In the phase 2 dose expansion part of the study, over 70 patients with advanced NSCLC harboring EGFRm were enrolled to further evaluate the safety and efficacy of BLU-945, with patient characteristics shown in Table 1.

- Safety was assessed in the phase 1 dose escalation part of the study, and tolerability was assessed in the phase 2 dose expansion part of the study.

- Key findings for the phase 2 dose expansion part of the study were as follows:

- BLU-945 and osimertinib combination treatment resulted in ORR of 40% (CR 10%, PR 30%)

- Safety

- Treatment-related adverse events (AEs) were noted: dry mouth (20%), nausea (16%), vomiting (12%), diarrhea (8%), and rash (2%)

- AE(s) deemed to be related to the study drug included 1 grade 3 vomiting and 1 grade 1 diarrhea

- Pharmacokinetics

- Cmax and AUC0−12 were determined for BLU-945 monotherapy in the 400 mg and 800 mg QD dosing arms

- Median Cmax was 1000 ng/mL and 1810 ng/mL, respectively

- Median AUC0−12 was 2662 ng·hr/mL and 4916 ng·hr/mL, respectively

- Figure 4: Reduced T790M and C797S ctDNA levels with BLU-945 treatment

- Baseline and post-treatment values are shown for T790M (top) and C797S (bottom) mutant allele fractions as assessed by ctDNA after 14 days of therapy in every dose-escalating cohort

- In the 400 mg cohort, all detectable T790M and C797S alleles showed >90% reduction in mutant allele fractions

- Safety and pharmacodynamics

- Key AEs associated with BLU-945 treatment included dry mouth, nausea, vomiting, and diarrhea

- AEs associated with osimertinib treatment included rash, increased transaminases, and diarrhea

- There were no grade 5 AEs

- Conclusions

- BLU-945 is an investigational, oral next-generation EGFR TKI that demonstrated antitumor activity in combination with osimertinib, with best response of stable disease (SD) to all prior therapies

- Further clinical development of BLU-945 as monotherapy and in combination with osimertinib is needed to determine optimal dosing and to assess efficacy in patients who have progressed on prior EGFR TKIs

References