BLU-701 tumour suppression and intracranial activity as a single agent and in combination with BLU-945 in models of non-small cell lung cancer driven by EGFR mutations

Methods

- EGFR mutations are the most common targeted alterations in non-small cell lung cancer (NSCLC), occurring in ~15% of Caucasians and up to 50% of Asians.1
- There are no approved therapies for patients who have progressed while receiving a 1G TKI.3,7
- Administration of BLU-701 30 mg/kg led to sustained tumour regression not observed with osimertinib 25 mg/kg QD or any combination of agents. In osimertinib-resistant CDX and PDX models driven by mutant EGFR (EGFR ex19del/C797S Ba/F3 CDX model), tumour shrinkage in an osimertinib-resistant model (H1975 EGFR L858R/T790M IC90) was not observed with any combination of agents (Figure 4A).

Results

- Daily oral administration of BLU-701 1, 2, 10 or 30 mg/kg resulted in dose-dependent tumour regression, greater than either gefitinib 0.25 mg/kg QD or osimertinib 25 mg/kg QD (Figure 3A).
- Response to BLU-701 30 mg/kg QD was sustained even after treatment was stopped, resulting in tumour shrinkage in a gefitinib-resistant cell line (Figure 3B). BLU-701 30 mg/kg QD was effective against gefitinib-resistant cell lines (Figure 3B).
- In combination with osimertinib, BLU-701 had tumour regression, which regressed following osimertinib withdrawal (not shown) in 6 of 8 mice treated with osimertinib alone (Figure 3B).

Conclusions

- BLU-701 (NCT05153408) and BLU-945 (NCT04862780) are reversible, selective, and orally bioavailable agents targeting EGFR and HER2.13
- Administration of BLU-701 30 mg/kg led to sustained tumour regression not observed with osimertinib 25 mg/kg QD or any combination of agents in osimertinib-resistant CDX and PDX models driven by mutant EGFR (EGFR ex19del/C797S Ba/F3 CDX model).
- BLU-701 is brain penetrant and administration of single-agent BLU-701 and combination therapy with BLU-945 in resistant models of cancer cells can compromise the blood-brain-barrier (BBB), which restricts structurally intact cancer cells to penetrate the intact BBB in vivo and result in metastases.

References