BLU-945, a highly potent and selective 4th-generation EGFR TKI for the treatment of EGFR+/T790M/C797S resistant NSCLC

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Background
- Osimertinib, a 3rd-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI), has favorably impacted the treatment of patients with EGFR-driven non-small cell lung cancer (NSCLC) and extended survival for patients with EGFR T790M mutations through the 1st-generation agent gefitinib.
- The C797S mutation is the most frequent relapsed resistance mechanism to osimertinib and other EGFR-TKIs. A new 4th-generation TKI is expected to block the C797S gatekeeper mutation.

BLU-945 activity on EGFR mutants and EGFR wild-type (WT) was tested in biochemical assays. Osimertinib was well tolerated in the PDCX animal model. PDX (ex19del/T790M/C797S) model developed from patient with NSCLC (poorly-moderately differentiated adenocarcinoma). RNA-seq analysis of PDX model suggested EGFR amplification and allelic diversity.

Single agent BLU-945 was sufficient for tumor stasis in this model. BLU-945 single agent and combination doses were well tolerated in the animal model. BLU-945 is a highly potent and selective EGFR+ T790M/C797S inhibitor with >900-fold selectivity over EGFR WT.

Methods
- Biochemical assay on EGFR mutants and EGFR-WT proteins (WT) was tested in biochemical assays and cellular phosphorylation assays, EGFR AlphaLISA assay.
- The in vitro efficacy data for BLU-945 were developed on NC69/C797S cell line-derived tumor spheroid (CDS) model, as well as in osimertinib-resistant CDS-derived and patient-derived xenograft (PDX) models of NSCLC.

Results
- BLU-945 has antitumor activity on EGFR+/T790M and EGFR+/T790M/C797S driven cancer.
- BLU-945 has antitumor activity on EGFR+/T790M and EGFR+/T790M/C797S driven cancer.
- Single agent BLU-945 showed significant tumor regression in combination with osimertinib in a NSCLC PDX (ex19del/T790M/C797S) model with EGFR amplification and allelic heterogeneity.
- Single agent BLU-945 was sufficient for tumor stasis.
- Single agent and combination doses were well tolerated in the animal model.
- Data suggest that BLU-945 can be combined with other EGFR TKIs to address select EGFR heterogeneity.

Conclusions
- BLU-945 is a highly potent and selective drug effective in EGFR+/T790M/C797S resistant NSCLC.
- Clinical development of BLU-945 monotherapy is expected to begin with phase I clinical trials in EGFR+ NSCLC.