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Abstract Title:

Highly potent and selective RET inhibitor, BLU-667, achieves proof of concept in a phase I study of advanced, *RET*-altered solid tumors

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Abstract Body

Background: The receptor tyrosine kinase, RET, activated via point mutation or genomic rearrangement, is a bona fide oncogene in multiple cancers, including medullary thyroid cancer (MTC) and non-small cell lung cancer (NSCLC). However, no approved therapies target RET potently and selectively. We initiated a phase 1 study (NCT03037385) in advanced solid tumors to define the MTD, safety, pharmacokinetics (PK) and anti-tumor activity of BLU-667, a highly potent and selective oral inhibitor that targets oncogenic RET-fusions, point mutations and resistance mutations.

Methods: Adult patients (pts) with unresectable, advanced solid tumors received BLU-667 once daily on a 4-week cycle following a Bayesian Optimal Interval design, which allowed additional accrual to dose levels declared safe. Adverse events (AEs), PK, biomarkers, and radiographic anti-tumor activity were assessed.

Results: At a 13FEB18 cutoff, 43 pts (15 RET-fusion NSCLC [7 KIF5B, 4 CCDC6, 5 other]; 26 RET-mutant MTC [15 M918T, 7 other]; 2 non-RET) have been treated with BLU-667 at doses of 30 to 400 mg/day. The median number of prior anti-neoplastic therapies was 1 (range 0-8). BLU-667 showed broad anti-tumor activity across multiple RET genotypes at doses \geq 60 mg with radiographic tumor reductions (-2 to -70%) demonstrated in 83% (25/30) of RET-altered pts with at least 1 post baseline response assessment. The best overall response rate per RECIST 1.1 was 37% (11/30 pts; 95% CI 20% - 56%) with 5 PR (4 confirmed) in 11 NSCLC pts and 5 PR (3 confirmed) and 1 CR (pending confirmation) in 19 MTC pts . Rapid decline in blood (calcitonin; RET ct-DNA) and tumor (RET pathway mRNAs) biomarkers accompanied anti-tumor activity. PK showed rapid

BLU-667 absorption (T_{max} 2-4 h), long half-life (> 12 hours) and exposure (AUC and C_{max}) in the expected therapeutic range based on tumor xenograft models.

An MTD has not been reached and dose escalation continues. Most AEs were CTCAE grade (gr) 1, these included constipation (23%), ALT increase (16%), AST increase (16%), diarrhea (14%) fatigue, creatinine increase, WBC decrease, and hypertension (12% each). 3 DLTs were observed (1 gr 3 ALT increase, 1 gr 3 tumor lysis syndrome and 1 gr 3 hypertension). There

were no gr 4/5 BLU-667-related AEs. 10 pts discontinued treatment (6 PD, 2 AEs [1 drug-related], 1 death [not drug-related], 1 other); 33 remain on treatment with duration 21-11 cycles.

Conclusion: BLU-667, a highly potent and selective RET inhibitor has been well tolerated and demonstrates promising clinical activity in RET-altered solid tumors, including pts who have failed multikinase inhibitor therapy. These encouraging phase 1 data validate selective targeting of RET and warrant expanded clinical testing of BLU-667 in RET-altered cancers.