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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 ≥ 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 (Tmax 2-4 h), long half-life (> 12 hours) and exposure (AUC and Cmax) 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.