Title: Activity of Osimertinib and the Selective RET Inhibitor BLU-667 in an EGFR-Mutant Patient with Acquired RET Rearrangement
Session Title: New Therapies and Emerging Data in ALK, EGFR and ROS1
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Background
The spectrum of acquired resistance (AR) to osimertinib is not yet fully characterized. We present a single-center cohort of osimertinib AR biopsies and results of a patient with RET-mediated AR treated with the investigational RET-specific TKI BLU-667 and osimertinib.

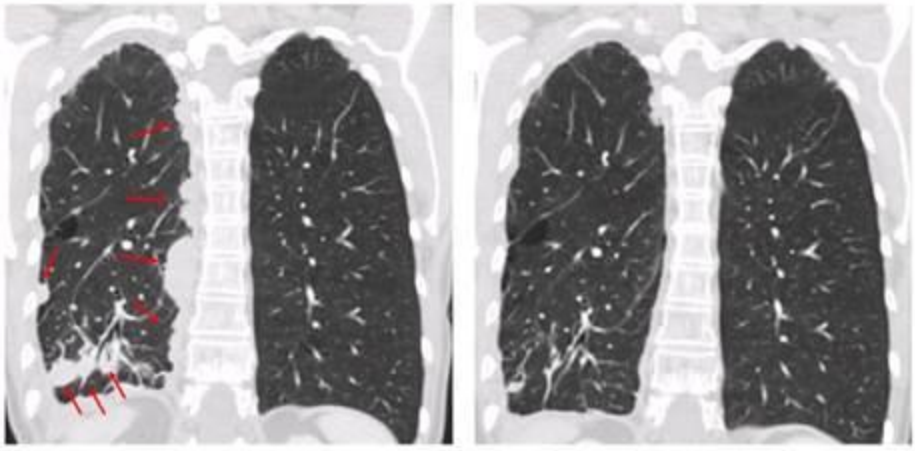
Method
We assayed tissue via SNaPshot or Foundation One next-generation sequencing (NGS) and plasma via Guardant360 NGS under an IRB-approved protocol. In vitro studies assessed implications of RET fusions in EGFR-mutant cancers. We treated one patient with osimertinib/BLU-667 using an IRB and FDA-approved compassionate use protocol.

Result
41 EGFR-mutant patients with AR to osimertinib were assessed histologically and queried by tissue NGS (n=22), plasma NGS (n=9) or both (n=10). Key AR findings: SCLC transformation (2/32 tissue); EGFR C797S (5/32 tissue, 5/19 plasma, all cis with T790M); MET amplification (7/32 tissue, 3/19 plasma); BRAF rearrangement (2/32 tissue) and CCDC6-RET rearrangement (1/32 tissue, 1/19 plasma [distinct case]).

CCDC6-RET was expressed in PC9 (EGFR del19) and MGH134 (EGFR L858R/T790M) cells, which maintained MAPK signaling and conferred resistance to osimertinib and afatinib. Inhibition of RET by BLU-667 or cabozantinib resensitized cells expressing CCDC6-RET to EGFR inhibition.

A 60-year-old woman with EGFR del19 progressed on afatinib (T790M+), then osimertinib. Tissue biopsy at osimertinib AR showed acquired CCDC6-RET (T790-wt). She began osimertinib 80mg/BLU-667 200mg daily x2 weeks, then BLU-667 was increased to 300mg daily. Her dyspnea improved within days of initiation. Scans after 8 weeks revealed a marked response with RECIST tumor shrinkage of 78% (Figure). She experienced only grade 1 toxicities of fatigue, leukopenia, hypertension, dry mouth, and elevated transaminases.

Conclusion
RET rearrangements are rare but recurrent in EGFR-mutant patients with AR to osimertinib. In vivo models suggest they mediate AR and this patient provides proof-of-concept that combination EGFR+RET inhibition with osimertinib/BLU-667 is a well-tolerated and effective regimen for RET-mediated AR. Further study is ongoing.



Pre-treatment

After 8 weeks osimertinib and BLU-667