Activity of osimertinib and the selective RET inhibitor BLU-667 in an EGFR-mutant patient with acquired RET rearrangement.

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Disclosures

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BLU-667 is an investigational medicine being developed by Blueprint Medicines Corporation
Background

• Osimertinib (osi) is a selective, CNS-penetrant, 3rd gen EGFR TKI approved by FDA and EMA for front-line use\(^1\).
• Osi resistance mechanisms (MoR) include \textit{EGFR C797S}, MET amp and histologic transformations, but many patients do not have an identified MoR\(^2\).
• Fusions in \textit{RET} and other oncogenes have been described in resistant EGFR-mutant NSCLC\(^3,4\), but the functional role of \textit{RET} fusions in this context is unknown.
• BLU-667 is an highly potent and selective investigational RET inhibitor with clinical activity in NSCLCs and other cancers harboring RET alterations\(^5,6\).

\textbf{BLU-667 has broad anti-tumor activity against RET-altered cancers}

Note: Data previously presented in April 2018 at AACR Annual Meeting (Subbiah, V et al, AACR 2018).

Methods

- Molecular Analysis of Osimertinib-Resistant Biopsies (41 patients)
  - Tissue: FoundationOne and MGH Snapshot/Rearrangement panel, MET/EGFR FISH
  - Plasma: Guardant360 NGS ctDNA
- In Vitro Models focused on acquired RET fusions
  - We expressed CCDC6-RET in PC9 (EGFR del19) and MGH134 (EGFR L858R/T790M) cells by lentiviral infection.
  - Cell lines were treated with EGFR and RET TKIs
- Single-Patient IND Protocol with Osimertinib and BLU-667
  - Based on the pre-clinical efficacy of osimertinib + BLU-667, we wrote a single-patient IND protocol and treated a patient with osimertinib + BLU-667
  - Protocol was reviewed and approved by FDA and local IRB. The patient provided written consent prior to starting treatment

![Osimertinib + BLU-667 Protocol](image)

Overall Osi-Resistant Cohort (n=41)

We identified 4 osimertinib-resistant patients with fusions detected in plasma and/or tissue:

- Co-occurrence CCDC-RET and TPM3-NTRK1 fusions in ctDNA (pt 33)
- CCDC-RET fusion (tissue) (pt 1)
- PCBP2-BRAF fusion (tissue) (pt 2)
- AGK-BRAF fusion (tissue) (pt 3)
CCDC6-RET expression in EGFRm NSCLC cell lines (PC9, MGH134)

A

Proliferation (Ratio)

Time (days)

PC9

MGH134

EV

CCDC6-RET

VEHICLE

OSI 1 M

B

PC9 EV

PC9 CCDC6-RET

Afatinib

Osimertinib

Drug Concentration (nM)

% Cell Viability

C

EGFRi

BLU-667

EGFRi + BLU-667 1 µM

PC9 EV

PC9 CCDC6-RET

Downstream signaling not suppressed

Downstream signaling is suppressed

Response to Osimertinib (osi) + BLU-667 in the Clinic

- 60yo F with EGFR del19 NSCLC received afatinib x 1 year, then osi for T790M x 18 mos.
- Post-osi biopsy (MGH NGS/Rearrangement Panel) - CCDC6-RET fusion, T790M “lost”
- Treated with Osimertinib + BLU-667 on single-patient IND protocol.
  - Osimertinib 80mg QD
  - BLU-667 200mg QD x 2 weeks, then 300 mg QD
- To date, the safety profile of Osi/BLU-667 includes only grade 1 AE’s, including:
  - Fatigue, leukopenia, high BP, dry mouth, AST/ALT elevation
- Treatment with Osi/BLU-667 is ongoing.

**RECIST 1.1 Partial Response (-78%)**

*PR Pending confirmation*
Conclusions

- \textit{RET} and other oncogene fusions are a recurrent finding in EGFR\textit{m} NSCLC with acquired resistance to osimertinib and other EGFR TKIs.
- Our \textit{In vitro} models suggest that \textit{CCDC6-RET} mediates EGFR resistance and can be inhibited by combined EGFR + RET inhibition.
- We present the first example of a clinical response to combined EGFR + RET inhibition in a patient with EGFR\textit{m} NSCLC and acquired \textit{CCDC-RET} fusion after osimertinib.
- Combining potent and highly-selective inhibitors of RET and EGFR like osimertinib and BLU-667 appears to be well tolerated.
- Further study of osimertinib plus BLU-667 will be needed to define clinical activity and confirm safety in a larger cohort of patients.
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