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

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Disclosures

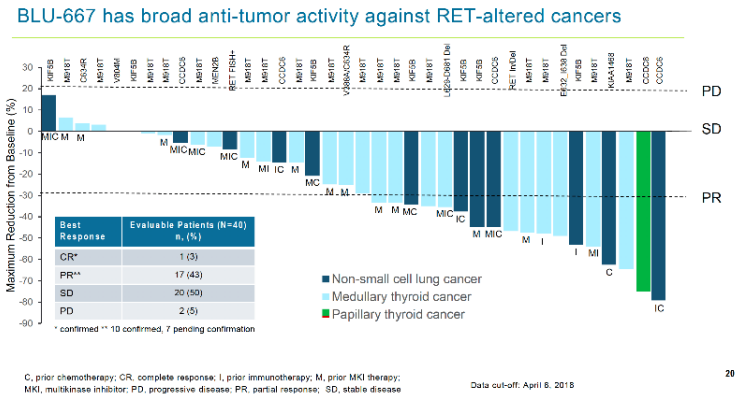
Zofia Piotrowska:

- Consulting/Advising: AstraZeneca, Ariad/Takeda, Guardant Health, Novartis, AbbVie
- Research grant (to institution): Novartis

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 *EGFR* C797S, MET amp and histologic transformations, but many patients do not have an identified MoR[2].
- Fusions in *RET* and other oncogenes have been described in resistant EGFR-mutant NSCLC[3,4], but the functional role of *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].



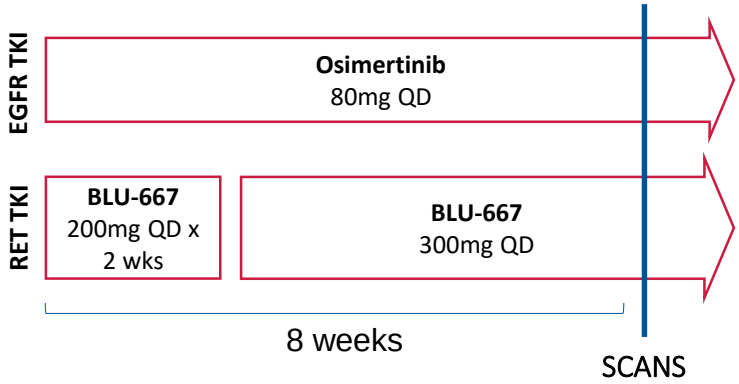
Note: Data previously presented in April 2018 at AACR Annual Meeting (Subbiah, V et al, AACR 2018)

1. Soria JC, NEJM 2018, 2. Piotrowska Z, ASCO 2017, 3. Reckamp K, AACR 2018, 4. Schrock AB, JTO 2018, 5. Subbiah V, AACR 2018, 6. Subbiah V, Cancer Discovery 2018.

Methods

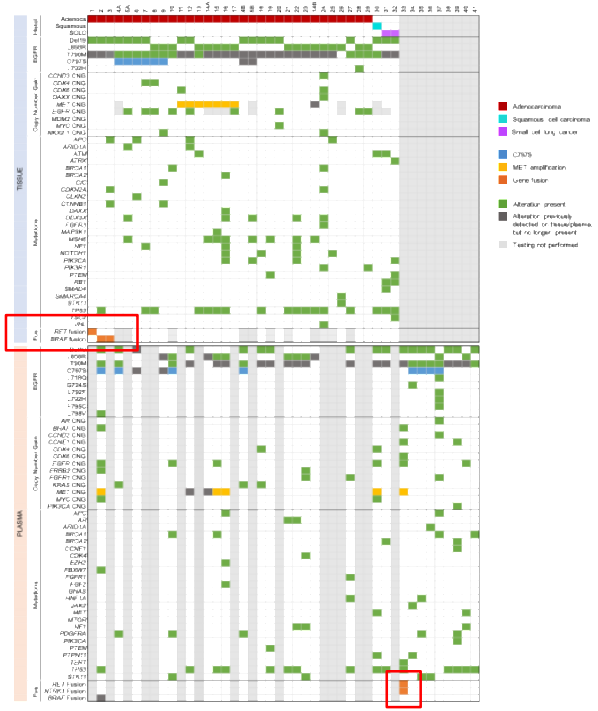
- Molecular Analysis of Osimertinib-Resistant Biopsies (41 patients)
  - Tissue: FoundationOne and MGH Snapshot/Rearrangement panel[1], MET/EGFR FISH
  - Plasma: Guardant360 NGS ctDNA
- *In Vitro* Models focused on acquired *RET* fusions
  - We expressed *CCDC6-RET* in PC9 (*EGFR* del19) and MGH134 (*EGFR* 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



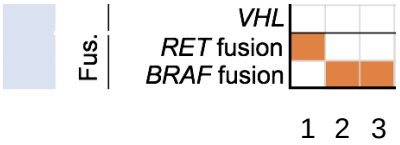
1. Zheng Z, et al, *Nat Med.* 2014;20(12):1479-1484.

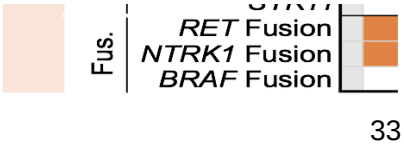
Overall Osi-Resistant Cohort (n=41)



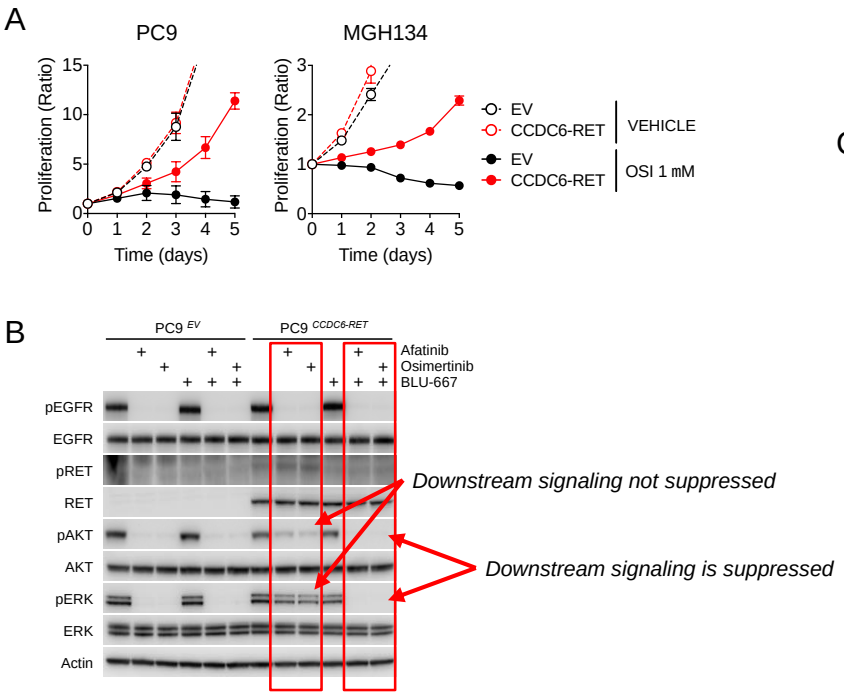
We identified 4 osimertinib-resistant patients with fusions detected in plasma and/or tissue:

- Co-occurrent *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)





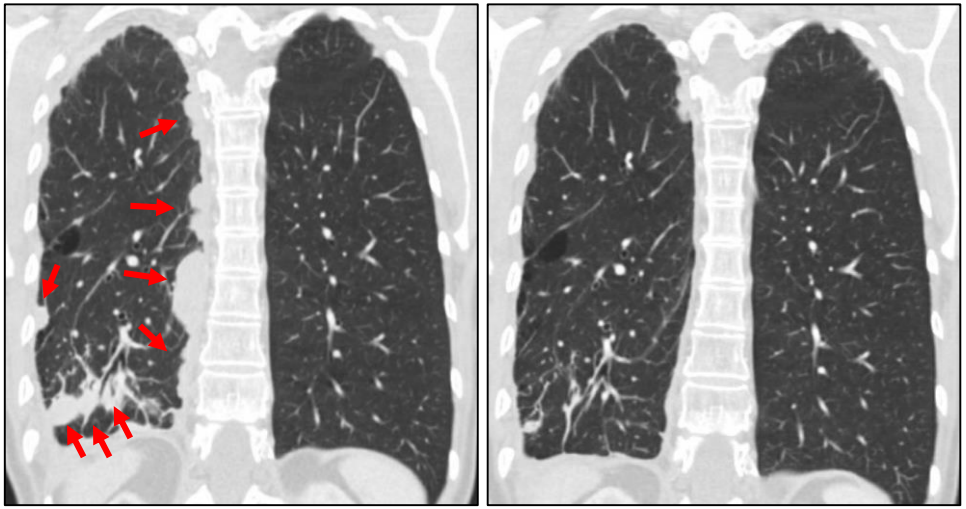
CCDC6-RET expression in EGFRm NSCLC cell lines (PC9, MGH134)



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%)*



Baseline

8 weeks

*PR Pending confirmation

Conclusions

- *RET* and other oncogene fusions are a recurrent finding in *EGFRm* NSCLC with acquired resistance to osimertinib and other EGFR TKIs.
- Our *In vitro* models suggest that *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 *EGFRm* NSCLC and acquired *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.

Acknowledgements

- We would like to thank the patients and families who participated in this study.