CBL Mutations as Potential Mediators of EGFR TKI Resistance Effectively Treated with Sitravatinib

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BACKGROUND

- Sitravatinib (MGCD516) is an orally available, small molecule inhibitor of a spectrum of RTKs that act as oncogenic drivers
- Sitravatinib does not inhibit serine threonine kinases, but specifically targets CBL's key RTK targets

RATIONALE FOR TARGETING CBL MUTATIONS

- CBL is commonly inactivated by missense mutations in the RING domain or deletions, that result in loss of function mutations
- Loss of CBL function may be responsible for acquired resistance to 3rd generation EGFR tyrosine kinase inhibitors
- The clinical trial with sitravatinib is currently enrolling patients with malignancies harboring CBL loss of function mutations (NCT02219711)

METHODS

- S16-001 STUDY DESIGN
  - Multi-center, open label Phase 1b study evaluating Safety, PK, Metabolism, PD and Clinical activity of sitravatinib in patients with advanced solid tumor malignancies

DOSE ESCALATION

- Phase 1: Explore dose/regimen and define stable Phase 2 dose using the mFtD method

DOSE EXPANSION

- Phase 1b: Inclusion of evaluation of sitravatinib in malignancies selected patient populations:
  - Tumor Genetic Profile At Diagnostic EGFR exon 19 deletion

RESULTS

CASE HISTORY

- 77 year-old female, lifelong non-smoker, metastatic adenocarcinoma of the lung

PATIENT BACKGROUND

- Prior treatments included:
  - Erlotinib brief re-challenge
  - Carboplatin/pemetrexed
  - Osimertinib
  - Rociletinib, experimental inhibitor of EGFR T790M

SAFETY AND ACTIVITY

- Confirmed partial response (PR) for 9 months
- No further responses

CONCLUSIONS

- The ability of sitravatinib to inhibit multiple relevant oncogenic driver RTKs combined with blockade of VEGFR family kinases, likely contributes to the clinical activity observed in this case

REFERENCES

3. Post progression NGS of Tumor:
   - Loss of EGFR p.T797M
   - Presence of original EGFR exon 19 deletion
   - New CBL p.C384R hotspot mutation

TREATMENT

- Enrolled in Study S16-001 on 10 March 2017
- Treated with sitravatinib at 150mg QD in cycles of 21 days

Figure 4. Activity of sitravatinib in CBL-Mutant NSCLC

Figure 2A. Somatic mutations in CBL commonly occur in the RING domain in human cancer Figure 2B. CBL mutations correlated with sitravatinib response in 500 cancer cell line screen

Figure 3. Sitravatinib activity in NSCLC models exhibiting CBL mutations

Figure 1. CBL-dependent RTK degradative pathway and CBL's key RTK targets

Figure 4. Activity of sitravatinib in CBL-Mutant NSCLC

POTENTIAL IMPLICATIONS

- CBL p.C384R has been previously described:
  - This missense gene mutation results in an amino acid change (cysteine to arginine) in the RING finger of CBL
  - Functional consequences include the loss of CBL's E3 ubiquitin ligase function
  - We postulate that the gain of the CBL p.C384R mutation may shift the spectrum of activated receptor tyrosine kinases resulting in:
    - A shift in EGFR receptor heterodimerization patterns
    - Dependence on multiple RTKs for tumor cell growth and survival
  - The ability of sitravatinib to inhibit multiple relevant oncogenic driver RTKs combined with blockade of VEGFR family kinases, likely contributes to the clinical activity observed in this case

DATA ON FILE.

CBL, CBL loss of function mutations; EGFR, epidermal growth factor receptor; EGFR TKI, epidermal growth factor receptor tyrosine kinase inhibitor; PD, progression disease; PD-L1, programmed death ligand 1; PR, partial response; RTK, receptor tyrosine kinase; SD, stable disease; TKI, tyrosine kinase inhibitor; PD-L1, programmed death ligand 1; PR, partial response; SD, stable disease; TKI, tyrosine kinase inhibitor.