CBL Mutations as Potential Mediators of EGFR TKI Resistance Effectively Treated with Sitravatinib
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RATIONALE FOR TARGETING CBL MUTATIONS

Sitravatinib (MKC-447) is an orally available, small-molecule inhibitor of a spectrum of related receptor tyrosine kinases (RTKs) including:
- TAM (famil, AXL, and MER)
- Target cellular IC50: 1nM
- Split family RTKs (VEGFR2, PDGFR and Kit)
- Target cellular IC50: 1t-50 nM
- RET, MET, DDR2, TRA
- Target cellular IC50: 0.25-10 nM
- Sitravatinib does not inhibit wild-type kinases and other receptor tyrosine kinases

SOMATIC ALTERATIONS IN CBL MUTATIONS

- CBL is an E3-ubiquitin ligase that regulates the internalization and degradation of activated RTKs including EGFR, MET, PDGFR, KIT, and TAM RTKs, thus serving as a mechanism for signal attenuation

- Loss of function mutations in CBL result in increased target RTK activation in tumor cells and may act as oncogenic drivers

- CBL is commonly inactivated by missense mutations in the RING domain or deletions, that occur in selected human cancers including NSCLC, melanoma, and sarcomas (Fig. 2A)

- Here we report on a subject with NSCLC harboring an inactivating CBL mutation treated with sitravatinib in Study 516-001

- Sitravatinib induced tumor regression in NSCLC models harboring inactivating CBL mutations (Fig. 3)

- Sitravatinib is currently being evaluated in Study 516-001, a Phase I/II study with cohorts of molecularly selected patients having advanced solid tumor malignancies

- Here we report on a subject with NSCLC harboring an inactivating CBL mutation treated with sitravatinib in Study 516-001

- Inactivating CBL mutations (Fig. 3) in combination with EGFR T790M mutations (Fig. 4) suggest that it may act as a newly described mediator of resistance to EGFR inhibition

- We postulate that the gain of the CBL 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 EGFR family kinases, likely contributes to the clinical activity observed in this case

RESULTS

Case History

- 77-year-old female, lifelong non-smoker, metastatic adenocarcinoma of the lung
- Tumor Genetic Profile At Diagnosis: EGF R exon 19 deletion

Patient Background

- Enrolled in Study 516-001 on 15 March 2017

- Baseline CT - 12 March 2017

- Somatic mutations in CBL commonly occur in the RING domain in human cancers including NSCLC, melanoma, and sarcomas (Fig. 2A)

- Sitravatinib correlates with sitravatinib response in a 500 cancer cell line screen

- Sitravatinib-induced activity in NSCLC models exhibiting CBL mutations

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REFERENCES

1. Adapted from Protein tyrosine kinase regulation by ubiquitination: Critical roles of CBL-family ubiquitin ligases. 2. COSMIC: somatic cancer genetics at high-resolution. S.A. Forbes, B. Mohapatra

516-001 STUDY DESIGN

- Multi-center, open label Phase I/II study evaluating Safety, PK, PD, and clinical activity of sitravatinib in patients with advanced solid tumor malignancies

DOSE ESCALATION

- Phase I: Explore dose/registry and define eligible Phase I dose using the mTD treatment design

DOSE EXPANSION

- Phase II: Inclusion of evaluation of sitravatinib in molecularly selected patient populations:
  - Primary focus on: NSCLC with inactivating genetic alteration in RET or amplification of C-Met8.13 (PDGFR, KIT, KDR)
  - NSCLC with inactivating mutation in CBL

- An optimal Simon 2-stage trial design will be applied to each molecularly selected Phase II cohort, ensuring n = 15 + 3 x 0.25

- Stage 1: 8 patients

- Stage 2: Additional 16 patients to total of 24. Potential to expand up to 70 patients

- Phase 1: Explore dose/registry and define eligible Phase I dose using the mTD treatment design

TREATMENT

- Enrolled in Study 516-001 on 15 March 2017

SAFETY AND ACTIVITY

- Treated with sitravatinib at 15mg QD in cycles of 21 days

- 14 treatment cycles

- Confirmed partial response with 77% decrease in target lesions

- Stable disease for approximately 4 months

- No response

- Carboplatin/pemetrexed

- Site of disease for approximately 4 months

- 2. COSMIC: somatic cancer genetics at high-resolution. S.A. Forbes, B. Mohapatra

- Loss of function mutations in CBL represent a unique class of mutations

- Sitravatinib is a potent inhibitor of several RTKs that act as oncogenic drivers

- Sitravatinib demonstrated clinical activity in a patient with NSCLC characterized by EGFR exon 19del and CBL p.C384R mutations

- Sitravatinib lso demonstrated clinical activity in a patient with NSCLC harboring CBL p.C384R mutation

- The clinical trial with sitravatinib is currently enrolling patients with malignancies harboring CBL loss of function mutations. (NCIT2219711)