MET gene copy number gains evaluated by NGS is more predictive than other methods to enrich for papillary RCC patients sensitive to Savolitinib, a selective MET inhibitor

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Background

There is no approved therapy for the treatment of papillary renal cell carcinoma (PRCC). Advances in molecular profiling of PRCC have identified a segment of PRCC with 10q28, MET mutation rates1. Chromosome 7 gains is a hallmark of PRCC and thought to occur at 50% frequency in PRCC2. We undertook a retrospective analysis of archival tumor samples to evaluate MET pathway aberrations for correlation with efficacy in a phase II study of Savolitinib (n=26) in PRCC (NCT02127710). Archival diagnostic tumor samples were mandated for central confirmation of PRCC diagnosis, histological subtyping and for exploratory biomarker analysis.

Methods

46 archival tumors were obtained from the Ph2 Clinical Trial and profiled using four methods: H&E stain for PRCC histological subtype, immunohistochemistry (IHC) for c-Met protein expression (Ventana, CONFIRM), FISH for MET gene amplification (Abbott, Vysis), Next Generation Sequencing (NGS) as an orthogonal method for confirmation of MET amplifications, detection of HGF gene amplifications, MET mutations, chromosome 7 gains and other exploratory genomic biomarkers (Foundation Medicine Inc;T7 panel).

Biomarker Hypotheses

- MET high copy number gain is associated with response to Savolitinib
- HGF high copy number gain is not associated with response to Savolitinib
- MET high copy number gain is predictive of response to Savolitinib

Assessment of the MET Pathway by NGS

Table 1. Predictive Biomarker Hypotheses. Central tests for all submitted and evaluable archival tumor tissues at onset of trial.

Conclusions

• NGS is the most predictive test for response to Savolitinib.
• The frequency of MET Driven NGS biomarkers in the Ph2 population were 50% and captured all 8 responders, however 42% of non-responders are also MET-driven.
• Molecular characterization of MET status by NGS was more predictive of response to Savolitinib than a classification based on pathology, redefining PRCC at the molecular level and identifying MET as a target in PRCC.
• Biomarker driven patient selection should be considered for targeted therapies like the MET Receptor Tyrosine Kinase in PRCC and may apply to other indications.

Acknowledgements

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References

1. Choueiri et al. JCO 2017
2. Cooper et al. JCO 2017
3. Afghahi et al. JCO 2018
4. Choueiri et al. JCO 2017
5. 504-14-L (IC) at ESMO 2013

Figure 3. Kaplan-Meier estimate of PFS by MET-driven NGS biomarker status. Adapted from Ph2 trial publication with original legend (next).

Figure 4. Disease Stage in Ph2 Trial and TCGA PRCC patient populations. Comparisons are only observational since disease stage proportions are different.

Figure 5. MET-driven PRCC by NGS biomarker category in Savolitinib Ph2 Trial. MET and HGF loci are both located on Chromosome 7 (red). Although each biomarker was independent, some PRCC cases have co-occurrence of MET-driven NGS biomarkers.