“The following presentation should not be regarded as an endorsement of a particular product/drug/technique by the speaker. The presentation topics were assigned to the speakers by the scientific committee of the KCA, to be presented/interpreted as part of a comprehensive scientific debate. Therefore, this presentation should not be viewed/interpreted in isolation, and should be considered in context with the other presentations in the same session."
Savolitinib (volitinib, AZD6094, HMPL-504): Future Directions

Toni K. Choueiri

Lank Center for Genitourinary Oncology
Dana-Farber Cancer Institute,
Boston MA
USA
Disclosures

- Presenting author: T.K. Choueiri
- Advisory/Consultancy Role
  - Pfizer, Exelixis, Novartis, Merck, BMS, Bayer, Roche, Prometheus, Calithera, Peloton, Foundation Medicine
- Research Funding (institutional)
  - Exelixis, Pfizer, Novartis, BMS, Merck, Roche, Tracon, Peloton, AZ
- No Speakers Bureau
Savolitinib

- Savolitinib is a potent (4 nM IC50 in kinase assay) and selective cMET inhibitor
- Ph1 studies in Australia and China (Lung, PRCC and Gastric) in 2012–2013

\[
\text{Inhibition} > 90\% \text{ at 1\,µM}
\]
\[
\text{Inhibition} > 50\% \text{ at 1\,µM}
\]
\[
\text{Inhibition} < 50\% \text{ at 1\,µM}
\]

Preclinical platform of evidence in MET-driven cancers: Papillary Renal Cell Cancer (PRCC)

- PRCC is a subset of kidney cancer (10–15%) with 6–9,000 new cases per year of PRCC in US
- Marked by high incidence of chromosome 7 trisomy, where both MET and its ligand, HGF, reside

RESULT
Savolitinib is more efficacious than standard of care in PRCC PDX models

Ph1 dose escalation study
PRCC patients

Baseline

5 months

Baseline

5 months

Biomarker assessment:
- Chromosome 7 gain
- Focal MET gene
- No changes

Clinicaltrials.gov identifier NCT01773018.
Gan et al. J Clin Oncol 32:5s, 2014 (suppl; abstr 11111)
PRCC Ph2 open label single savolitinib arm trial design

- **FPI May 2014**
  - Primary endpoint: ORR
  - Secondary endpoint: PFS, OS, safety, tolerability, PK, PD (paired biopsies)
  - Exploratory endpoints: biomarkers, HRQoL

- **90 patients recruited in 17 months (North America and EU)**

Week:

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Screening</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cycle 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cycle 2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Response assessment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cycle 3</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cycle 4</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Response or stable disease (RECIST 1.1); continue treatment, restage every 6 weeks (up to 12 weeks) until progressive disease or unacceptable toxicity**

- **Progressive disease**
  - Discontinue study drug

Clinicaltrials.gov identifier NCT02127710.
Refining MET-driven PRCC in Ph2 PRCC savolitinib trial

- Next Generation Sequencing (NGS) assay (Foundation Medicine Inc) identifies responders as “MET-driven” where any one of the following biomarkers alone or in combination are detected in archival/diagnostic tumor:
  1. Chromosome 7 copy number gain
  2. MET amplification
  3. HGF amplification
  4. MET kinase mutation

**EXAMPLES** Savolitinib Responder Patient tumor profiles

<table>
<thead>
<tr>
<th>MET AMP (CN=12)</th>
<th>Chr7 ploidy (CN=4)</th>
<th>Chr7 none (genome ploidy 4)</th>
<th>MET mutation (M1131T)</th>
</tr>
</thead>
<tbody>
<tr>
<td>E9228006 unclassified</td>
<td>E9228023 PRCC Type 1</td>
<td>E9117128 Unclassified</td>
<td>E9295081 PRCC Type 2</td>
</tr>
<tr>
<td>Tumor change (05/18/16) -42.06%</td>
<td>Tumor change (05/18/16) -66.07%</td>
<td>Tumor change (05/18/16) -63.89%</td>
<td>Tumor change (05/18/16) -65.96%</td>
</tr>
</tbody>
</table>

**FMI assay includes 400 gene panel (27 genes on Chr7) + 4200 SNPs with BioInformatic analytics**

Clinicaltrials.gov identifier NCT02127710.
Ph2 PRCC savolitinib trial: patient case

- 56 year old female
- High grade, poorly differentiated Type II PRCC
- Plasma samples collected every 6 weeks

- NGS archival tissue
- Known and likely sequence variants (green)
- Variants of unknown significant (grey)
  - **MET L1195F variant was detected at 24% allele frequency**

Clinicaltrials.gov identifier NCT02127710.
Frigault et al Poster presented at ESMO 2016, Copenhagen
Patient case: novel MET L1195F kinase domain mutation

- MET L1195F mutant is sensitive to both type 1 potent and selective MET inhibitors (capmatinib/INC280 and savolitinib) and type 2 inhibitor crizotinib
- Changes in MET L1195F AF were detected over time with savolitinib treatment
Conclusions

- Phase II primary results to be presented at a congress soon