“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."
CRIZOTINIB IN PAPILLARY RCC

Laurence Albiges
Gustave Roussy
MET inhibition in pRCC

- Rational
  - Protein over expression in pRCC (Choi 2006, Gibney, 2012)
  - MET germline and somatic mutation (Smith, 2000)

- Foretinib (VEGFR2 & MET TKI) trial
  - Population : 65 metastatic pRCC type I & II
  - Median PFS >9 months in pretreated patients, OS : 70% at 1 year
  - Germline MET mutation predictive of response

![Graph showing percentage change from baseline](image)

Choueiri, JCO 2013
Refining MET receptor role in pRCC

- Germline mutation TK domain
- Somatic mutation TK domain
- Copy Number Alteration
- Fusion
- Transcript variant
Crizotinib achieves objective responses and long-lasting disease control in patients with metastatic papillary renal cell carcinoma type 1 (PRCC1) with somatic MET mutations or MET amplification

EORTC phase II trial 90101- CREATE (NCT01524926)

Patrick Schöffski, Agnieszka Wozniak, Bernard Escudier, Piotr Rutkowski, Alan Anthoney, Sebastian Bauer, Jozef Sufliasry, Winette van der Graaf, Lars Lindner, Viktor Grünwald, Branko Zakotnik, Evelyne Lerut, Sandrine Marréaud, Michela Lia, Tiana Raveloarivahy, Sandra Collette, Laurence Albiges

Presented at AACR Annual Meeting, April 17, 2016, New Orleans (LA)
EORTC 90101 CREATE study design

- Multicentre, biomarker-driven, single agent, non-randomised open-label phase II trial.
- Objective: Assessing the efficacy and safety of crizotinib in patients with locally advanced or metastatic PRCC1.
- 13 academic centres in 8 European countries
- Population:
  - Patients with the local diagnosis of advanced/metastatic PRCC1 were screened for active treatment after central confirmation of the diagnosis by a reference pathologist.
  - Patients were attributed to MET+ or MET- sub-cohorts with bi-directional Sanger sequencing of MET exons 16-19 of tumour tissue (investigator blinded).
- Eligible patients received oral crizitobin 250mg twice daily.
- The primary endpoint was response rate (RR) documented by RECIST 1.1.
- A Simon's optimal two stage design was implemented in the MET+ and MET- sub-cohorts. If at least two out of the first twelve eligible and evaluable PRCC1 MET+ patients achieved a confirmed partial (PR) or complete response (CR), a maximum of 35 patients were enrolled.
Screened pts PRCC1 per local pathology
N=41

Centrally confirmed PRCC1 and enrolled
N=23 (all started crizotinib)

MET+
N=4

MET-
N=16

MET?
N=3

MET+ analysis set
Eligible and evaluable
N=4 (incl. 1 MET amplified)

MET- analysis set
Eligible and evaluable
N=16 (incl. 1 MET amplified)

Eligible and evaluable
N=3

Other (ineligible) diagnoses:
- 4 translocation carcinomas
- 2 PRCC2
- 1 clear cell RCC
- 1 adenoid-cystic carcinoma or metanephric adenoma
- 1 non-specified malignancy

4 patients not enrolled due to brain metastasis, rapid clinical deterioration, no measurable lesion or lost to follow up

MET?: Technical failure, mutational analysis could not be done
Treatment duration (per protocol analysis)

- MET+ (mutation in exons 16-19)
- MET- (no mutation in exons 16-19)

Treatment stopped due to:
- Adverse event
- Progression
- Patient’s decision or other reason
Treatment duration (considering MET amplification)

**MET+** (mutation in exons 16-19) and/or MET amplification

**MET-** (no mutation in exons 16-19), no MET amplification

- **MET amplification (exploratory)**
- **RECIST PR first documented**
- **Treatment ongoing**
- **Treatment stopped due to**
  - Adverse event
  - Progression
  - Patient’s decision or other reason

Fifteenth International Kidney Cancer Symposium
November 4-5, 2016
Marriott Miami Biscayne Bay, Miami, Florida, USA
Treatment duration (considering \textit{MET} amplification)

\textit{MET+} (mutation in exons 16-19) and/or \textit{MET} amplification

\textit{MET-} (no mutation in exons 16-19), no \textit{MET} amplification

\textit{MET?} (technical failure)

- \textit{MET} amplification (exploratory)
- RECIST PR first documented
- Treatment ongoing
- Treatment stopped due to
  - Adverse event
  - Progression
  - Patient’s decision or other reason

\begin{itemize}
  \item \textit{MET amplification (exploratory)}
  \item RECIST PR first documented
  \item Treatment ongoing
  \item Treatment stopped due to
    \begin{itemize}
      \item Adverse event
      \item Progression
      \item Patient’s decision or other reason
    \end{itemize}
\end{itemize}
Response assessment (primary endpoint, investigator assessed)

<table>
<thead>
<tr>
<th>Best response (RECIST V1.1)</th>
<th>PRCC1 MET+, N=4</th>
<th>PRCC1 MET-, N=16</th>
<th>PRCC1 MET?, N=3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed CR</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Confirmed PR</td>
<td>2 (50.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>1 (25.0)</td>
<td>13 (81.3)</td>
<td>2 (66.7)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>1 (25.0)</td>
<td>3 (18.8)</td>
<td>1 (33.3)</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

Central review of responses ongoing
Maximum shrinkage of target lesions (per protocol)
Progression-free survival (per protocol)

- **MET+ (mutation in exons 16-19)**: 75.0% (95% CI: 12.8, 96.1)
- **MET- (no mutation in exons 16-19)**: 34.3% (95% CI: 12.2, 58.0)

Number of pts at risk:

<table>
<thead>
<tr>
<th>Months</th>
<th>0</th>
<th>4</th>
<th>8</th>
<th>12</th>
<th>16</th>
<th>20</th>
<th>24</th>
<th>28</th>
<th>32</th>
<th>36</th>
</tr>
</thead>
<tbody>
<tr>
<td>pts</td>
<td>143</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

PFS assessed by investigator: MET+ (mutation in exons 16-19) - MET- (no mutation in exons 16-19)
Progression-free survival (considering MET amplification)

- **MET+** (mutation in exons 16-19) and/or MET amplification
  - 80.0% (95% CI: 20.4, 96.9)

- **MET-** (no mutation in exons 16-19), no MET amplification
  - 29.2% (95% CI: 8.4, 54.2)

PFS assessed by investigator

<table>
<thead>
<tr>
<th>O</th>
<th>N</th>
<th>Number of pts at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>4 4 4 4 2 2 1 0</td>
</tr>
<tr>
<td>10</td>
<td>15</td>
<td>6 1 0 0 0 0 0 0</td>
</tr>
</tbody>
</table>
## Efficacy summary (investigator assessment)

<table>
<thead>
<tr>
<th>Best response (RECIST V1.1)</th>
<th>PRCC1 MET+, N=4</th>
<th>PRCC1 MET-, N=16</th>
<th>PRCC1 MET?, N=3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Best response (RECIST v1.1), N (%):</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Confirmed CR</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>• Confirmed PR</td>
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<tr>
<td>• Progressive disease</td>
<td>1 (25.0)</td>
<td>3 (18.8)</td>
<td>1 (33.3)</td>
</tr>
<tr>
<td><strong>Treatment ongoing/stopped</strong></td>
<td>0 / 4</td>
<td>3 / 13</td>
<td>1 / 2</td>
</tr>
<tr>
<td><strong>Treatment duration (months):</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Mean (SD)</td>
<td>11.9 (9.3)</td>
<td>5.3 (6.0)</td>
<td>20.6 (16.7)</td>
</tr>
<tr>
<td>• Median (range)</td>
<td>11.1 (1.5 – 23.9)</td>
<td>3.4 (1.9 – 26.8)</td>
<td>30.3 (1.4 – 30.3)</td>
</tr>
<tr>
<td><strong>% PFS at 24 months (95% confidence interval)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>75% (12.8 - 96.1)</td>
<td>34.3% (12.2 - 58.0)</td>
<td>66.7 (5.4 - 94.5)</td>
<td></td>
</tr>
<tr>
<td><strong>% OS at 24 months (95% confidence interval)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>75% (12.8 - 96.1)</td>
<td>29.3% (5.3 - 59.9)</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

Central review of responses ongoing
Patient case 1

• Pathology
  – Type 1 papillary RCC
  – July 2010 - radical nephrectomy.
  – March 2012 - pulmonary metastases. Slow PD

• Treatment history
  – Crizotinib as first-line treatment since October 21\textsuperscript{st}, 2014.
Baseline
10/13/2014

3 Months
01/12/2015
RECIST - 30%

Best Response
05/15/2015
RECIST - 40%
Baseline
10/13/2014

3 Months
01/12/2015
RECIST - 30%

Best Response
05/15/2015
RECIST - 40%
Patient case 1

• Pathology
  – Type 1 papillary RCC
  – July 2010 - radical nephrectomy.
  – March 2012 - pulmonary metastases. Slow PD

• Treatment history
  – Crizotinib as first-line treatment since October 2014 to March 2016
  – Surgery of residual lung mets: fibrosis only – no residual tumor cells
  – Crizotinib discontinued
  – Off therapy until October 2016, localised retroperitoneal relapse
Patient Case 2

• Pathology
  – Type 1 papillary RCC
  – November 2009 - partial nephrectomy.

• Treatment history
  – Crizotinib as first-line treatment since July 13, 2015.
Baseline
07/06/2015

3 Months
10/8/2015
RECIST - 19%

Best Response
06/20/2016
RECIST - 35%
Baseline
07/06/2015

3 Months
10/8/2015
RECIST - 19%

Best Response
06/20/2016
RECIST - 35%
Patient Case 2

• Pathology
  – Type 1 papillary RCC
  – November 2010 - partial nephrectomy.
  – January 2012 - pulmonary metastases. Slow PD

• Treatment history
  – Crizotinib as first-line treatment since July 13, 2015 - ongoing
  – PR sustained as best response as of October 2016
Conclusion

• Take home Message
  • Crizotinib display significant activity in highly selected tumor type
  • MET is a valid target in type I pRCC with MET driven tumors

• A selection criteria may evolve over time (MET mut to MET mut and amplif)
• Clinical trial in rare cancer requires effective network
• Biology-driven patient selection is doable, however requires prompt tissue processing

• Open question
  • Shall we restrict MET inhibitors to type I pRCC: NO!
  • Shall we select MET inhibitors use on MET activated tumor: YES!