Tumor and Plasma Biomarker Analysis from the Randomized Controlled Phase 2 Trial of Tivantinib in Second-line Hepatocellular Carcinoma


Abstract # 197

Supported by: ArQule, Inc, and Daiichi-Sankyo

Presented by: Lorenza Rimassa, MD
Disclosures

• **Consulting or Advisory Role:**
  – Lilly
  – Merck Serono

• **Travel, Accommodations, Expenses** (to present accepted abstracts at conferences):
  – ArQule
Outline

Role of biomarkers in second-line hepatocellular carcinoma (HCC)

ARQ 197-215 Phase 2 randomized, placebo-controlled trial (RCT)
  • Circulating biomarkers (MET, HGF, AFP)
  • Tumor biomarker (MET)

ARQ 197-A-U303 (METIV-HCC) Phase 3 RCT
  • Tumor biomarker (MET)
Background

Sorafenib is the only approved systemic agent for advanced HCC

**MET** is the HGF tyrosine kinase receptor, involved in HCC progression and metastasis

**Tivantinib (ARQ 197)** is an oral, ATP-independent MET inhibitor active in MET-High patients in 4 RCT in HCC, NSCLC, CRC, CRPR\(^1\) - \(^4\)

**ARQ 197-215**, a multi-center, phase 2 RCT of tivantinib in 107 2\(^{nd}\) line HCC patients, met the primary endpoint of TTP in the ITT population and the pre-defined secondary efficacy endpoints in MET-High patients. Tumor MET was found to be prognostic\(^1\)

**Exploratory endpoints** included biomarkers correlation with efficacy endpoints


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Methods

**Circulating MET, HGF, and AFP** were centrally tested in serum (ELISA):

- MET and HGF were collected before the first dose on cycle 1 day 1, and post dose on day 1 of every cycle thereafter (q4 weeks)
- AFP was collected at screening and every 8 weeks thereafter

Median biomarker values were used as cut-offs to determine High or Low status except for AFP, where 75\textsuperscript{th} percentile was also used.

**Tumor MET** was centrally analyzed after randomization and prior to un-blinding. Immunohistochemistry was performed with the Ventana SP-44 antibody. Strict criteria were used for MET-High status: $\geq 2+$ staining within $\geq 50\%$ of tumor cells.

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Patient characteristics were balanced between groups except for minor imbalances.

<table>
<thead>
<tr>
<th>Imbalanced Baseline Characteristics</th>
<th>Circulating</th>
<th>Tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MET (N=102)</td>
<td>HGF (N=102)</td>
</tr>
<tr>
<td>Vascular Invasion</td>
<td>29 (High)</td>
<td>41 (High)</td>
</tr>
<tr>
<td></td>
<td>35 (Low)</td>
<td>24 (Low)</td>
</tr>
<tr>
<td>HBV+</td>
<td>20 (High)</td>
<td>12 (High)</td>
</tr>
<tr>
<td></td>
<td>20 (Low)</td>
<td>28 (Low)</td>
</tr>
<tr>
<td>HCV+</td>
<td>57 (High)</td>
<td>47 (High)</td>
</tr>
<tr>
<td></td>
<td>33 (Low)</td>
<td>46 (Low)</td>
</tr>
</tbody>
</table>

In red, factors differing by ≥10% between High and Low subgroups; all other factors were well balanced.
Circulating MET as a Prognostic Factor

Baseline median circulating MET concentration: 13.26ng/mL (1.29-49.8ng/mL)

**ITT Baseline** N=102
- Median OS: Low (<median) 8.9 mos, High (≥median) 4.6 mos
- Patients: Low 51, High 51
- Events: Low 40, High 42
- HR: 0.61 (95% CI: 0.39-0.94) p=0.03

**Placebo Baseline** N=34
- Median OS: Low 9.4 mos, High 3.8 mos
- Patients: Low 19, High 15
- Events: Low 15, High 14
- HR: 0.42 (95% CI: 0.20-0.91) p=0.02

Trend in predictive value for circulating MET-High: tivantinib vs placebo HR: 0.55, p=0.07
(interaction test not significant)

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Circulating MET as a Pharmacodynamic Biomarker

Patients with best circulating MET reduction from baseline by ≥10% versus <10%

ITT: 12.3 mos in 37 pts ≥10%, 6.6 mos in 49 pts <10%, HR: 0.50 (95%CI: 0.30-0.83), p=0.006

<table>
<thead>
<tr>
<th></th>
<th>Tivantinib N=56</th>
<th>Placebo N=30</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥10%</td>
<td>13.3 mos</td>
<td>6.2 mos</td>
</tr>
<tr>
<td>&lt;10%</td>
<td>6.3 mos</td>
<td>7.9 mos</td>
</tr>
<tr>
<td>Patients</td>
<td>24</td>
<td>13</td>
</tr>
<tr>
<td>Events</td>
<td>16</td>
<td>10</td>
</tr>
<tr>
<td>HR: 0.46 (95% CI: 0.24-0.86) p=0.01</td>
<td>HR: 0.64 (95% CI: 0.28-1.49) p=0.3</td>
<td></td>
</tr>
</tbody>
</table>

Median best MET change in patients stable at 6 weeks: -37.9% on tivantinib, +18.4% on placebo

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Circulating HGF as a Prognostic Factor

Baseline median circulating HGF concentration: 2307 pg/mL (421-58080 pg/mL)

- **ITT Baseline N=102**
  - Low (<median): 9.0 mos, 51 patients, 36 events
  - High (≥median): 5.0 mos, 51 patients, 46 events
  - HR: 0.60 (95% CI: 0.39-0.94), p=0.02

- **ITT Best Change N=86**
  - ≥10%: 9.8 mos, 39 patients, 29 events
  - <10%: 6.5 mos, 47 patients, 38 events
  - HR: 0.60 (95% CI: 0.36-0.98), p=0.04

Results were overall confirmed when analyzed by treatment arm.
Circulating AFP as a Prognostic Factor

Baseline median: 186 (1.5-440008) IU/mL. Baseline 75th percentile (Q3): 3507.50 IU/mL

AFP <median vs AFP ≥median HR: 0.75 (95% CI: 0.48-1.15), p=0.18

No difference by best AFP change from baseline observed in 43 patients with AFP ≥20 IU/mL

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Baseline Tumor MET Status

H-score: percentage of cells staining per the intensity of the stain\(^1\)

<table>
<thead>
<tr>
<th>H-Score</th>
<th>Median</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>MET-High Patients</td>
<td>175</td>
<td>120</td>
<td>300</td>
</tr>
<tr>
<td>MET-Low Patients</td>
<td>40</td>
<td>0</td>
<td>125</td>
</tr>
</tbody>
</table>

Tested samples (N=77) | 37 (48%)
Samples with available biopsy date (N=72) | 36 (50%)
Tumor samples taken before sorafenib (N=55) | 22 (40%)
Tumor samples taken after sorafenib (N=17) | 14 (82%)

Correlations: none between tumor MET, circulating MET, HGF; possible between AFP and tumor and circulating MET

\(^1\)Shi B, J Histochim Cytochem 2013

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Tumor MET as a Prognostic and Predictive Factor

<table>
<thead>
<tr>
<th></th>
<th>Median OS</th>
<th>Patients</th>
<th>Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo MET-Low</td>
<td>9.0 mos</td>
<td>13</td>
<td>9</td>
</tr>
<tr>
<td>Placebo MET-High</td>
<td>3.8 mos</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>HR: 0.34 (95% CI: 0.13-0.86) p=0.02</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Median OS</th>
<th>Patients</th>
<th>Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo MET-Low</td>
<td>9.0 mos</td>
<td>13</td>
<td>9</td>
</tr>
<tr>
<td>Tivantinib MET-High</td>
<td>7.2 mos</td>
<td>22</td>
<td>17</td>
</tr>
<tr>
<td>HR: 0.72 (95% CI: 0.30-1.70) p=0.45</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Tivantinib vs placebo in 40 MET-Low patients: HR: 1.33 (95% CI: 0.58-3.04), p=0.50

Significant interaction test for tivantinib and tumor MET status in terms of OS (p=0.04)
Conclusions from ARQ 197-215

- Circulating MET, HGF, and AFP by 75th percentile hold a prognostic value

- Circulating MET is a pharmacodynamic biomarker for tivantinib

- Tumor MET is the only prognostic and predictive biomarker, and is more frequently “High” after sorafenib

- This analysis supports the use of tivantinib in MET-High patients only, and the rationale for the METIV-HCC study
METIV-HCC (ARQ 197-A-U303)*

Phase 3 clinical trial in the Americas, Australia, Europe, New Zealand

Approximately 303 adult pts with:
- MET-High, measurable HCC
- Child-Pugh A, ECOG PS 0-1, inoperable, progressed or intolerant to 1 prior therapy with sorafenib

2:1 Randomization

Oral Tivantinib 120mg BID
202 pts

Oral Placebo BID
101 pts

Overall Survival

Eligibility and IHC criteria comparable to the ARQ 197-215 phase 2 RCT (except METIV-HCC selected MET-High patients only). Accrual completed in December 2015

*Data are preliminary, from non-cleaned database, from biopsied patients regardless of their enrolment status

NCT01755767

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### METIV-HCC: Baseline Tumor MET Status*

<table>
<thead>
<tr>
<th>H-Score</th>
<th>Median</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>MET-High Patients</td>
<td>170</td>
<td>120</td>
<td>300</td>
</tr>
<tr>
<td>MET-Low Patients</td>
<td>90</td>
<td>0</td>
<td>180</td>
</tr>
</tbody>
</table>

**Table:**

<table>
<thead>
<tr>
<th>Samples Description</th>
<th>Tested samples (N=1138)</th>
<th>Samples with available biopsy date (N=925)</th>
<th>Tumor samples taken before sorafenib (N=438)</th>
<th>Tumor samples taken after sorafenib (N=487)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>576 (51%)</td>
<td>527 (57%)</td>
<td>173 (39%)</td>
<td>354 (73%)</td>
</tr>
</tbody>
</table>

*Data are preliminary, from non-cleaned database, from biopsied patients regardless of their enrolment status.

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METIV-HCC: Baseline Tumor MET Status*

MET-Low to MET-High Conversion:
71 patients were MET-Low at biopsy taken before sorafenib and were re-biopsied after sorafenib
50 out of 71 (70%) converted to MET-High at the biopsy taken after sorafenib

*Data are preliminary, from non-cleaned database, from biopsied patients regardless of their enrolment status
The only correlation found is between High MET status and prior treatment with sorafenib (p<0.0001)

No correlation found between MET status and:

- time on sorafenib
- reason for sorafenib discontinuation
- time between last sorafenib dose and biopsy
- time between diagnosis and biopsy
- prior local therapies

*Data are preliminary, from non-cleaned database, from biopsied patients regardless of their enrolment status
Conclusions

Tumor MET results are comparable in both ARQ 197-215 and METIV-HCC studies with tivantinib in second-line HCC

Strict criteria can make MET immunohistochemistry reliable across studies

Tumor MET status is more frequently (70-80%) “High” after sorafenib as the biological features of the tumor become more aggressive

Baseline tumor biomarker analysis from the ongoing phase 3 trial confirms biomarker analysis results from phase 2

The METIV-HCC trial will validate the role of the analyzed biomarkers in HCC
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