Tivantinib in Pretreated Hepatocellular Carcinoma (HCC): Tumor and Plasma Biomarker Analysis from the Randomized Controlled Phase 2 Trial (RCT) ARQ 197-215


Abstr #O-029. Presented by: Lorenza Rimassa

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Disclosures

Lorenza Rimassa, MD

No disclosures to report
Background

Hepatocellular Carcinoma (HCC) is among the leading causes of cancer-related death, and sorafenib is the only approved systemic agent for patients with unresectable disease\textsuperscript{1-3}. Recently failed 2\textsuperscript{nd} line studies consistently showed survival on placebo of 7-8 months\textsuperscript{4-6}

MET, the receptor tyrosine kinase for hepatocyte-growth factor (HGF), is involved in cancer progression and metastasis; its dysregulation correlates with poor prognosis in early stage and 2\textsuperscript{nd} line HCC patients\textsuperscript{7-10}

Background

**Tivantinib (ARQ 197)** is an oral, ATP-independent MET inhibitor with activity in MET-High patients in four randomized, placebo controlled studies in HCC, NSCLC, CRC, and prostate cancer\(^1\)-\(^6\)

**ARQ 197-215** was a multi-center, phase 2, placebo RCT of tivantinib:
- The study enrolled 107 HCC patients who had progressed or were intolerant to one prior systemic therapy
- The primary endpoint of time to progression (TTP) in the intent-to-treat (ITT) population and the pre-determined secondary efficacy endpoints in MET-High patients were reached
- Tumor MET was also found to be a strong independent prognostic factor\(^3\)
- Exploratory endpoints included relationship between biomarkers and key efficacy endpoints

Methods

Circulating MET, HGF, and AFP were centrally tested in plasma (ELISA):
• MET and HGF serum samples 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 after randomization, as well as at the end of treatment

Median biomarker values were used as cut-offs to determine High or Low status except for AFP, where 75\textsuperscript{th} percentile (Q3) was used

Tumor MET was centrally analyzed after randomization and prior to study un-blinding. Immunohistochemistry was performed using the Ventana SP-44 antibody. Strict reading criteria were followed to determine MET-High status in patients: ≥2+ staining within ≥50% of tumor cells
Circulating MET as a Prognostic Factor (ITT)

N=102 (68 on tivantinib, 34 on placebo)
Baseline median circulating MET concentration: 13.26ng/mL (1.29-49.8ng/mL)

No observed correlation between circulating and tumor MET
Circulating MET as a Prognostic Factor (Placebo)

Non-statistical trend in predictive value for circulating MET:

In circulating MET-High: 7.0 mos in 36 pts on tivantinib, 3.8 mos in 15 pts on placebo; HR: 0.55 (95% CI: 0.28-1.06), p=0.07

Median OS Patients Events
Low (<median) 9.4 mos 19 15
High (≥median) 3.8 mos 15 14
HR: 0.42 (95% CI: 0.20-0.91) p=0.02
Circulating MET as a Pharmacodynamic Biomarker

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

**Tivantinib**

- **Median OS**
  - ≥10%: 13.3 mos
  - <10%: 6.3 mos

- **Patients**
  - ≥10%: 24
  - <10%: 32

- **Events**
  - ≥10%: 16
  - <10%: 26

- **HR**: 0.46 (95% CI: 0.24-0.86) \( p=0.01 \)

**Placebo**

- **Median OS**
  - ≥10%: 6.2 mos
  - <10%: 7.9 mos

- **Patients**
  - ≥10%: 13
  - <10%: 17

- **Events**
  - ≥10%: 10
  - <10%: 15

- **HR**: 0.64 (95% CI: 0.28-1.49) \( p=0.3 \)

**Overall**

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

**Median change from baseline in circulating MET in patients stable at first scan**

- -37.9% on tivantinib, +18.4% on placebo

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Circulating HGF as a Prognostic Factor

N=102 (68 on tivantinib, 34 on placebo)
Baseline median circulating HGF concentration: 2307 pg/mL (421-58080 pg/mL)

On placebo: 21 High, 13 Low: HR: 0.80 (95% CI: 0.37-1.73), p=0.56
On tivantinib: 30 High, 38 Low: HR: 0.57 (95% CI: 0.33-0.98), p=0.04
Circulating HGF as a Predictive Factor

Predictive Role: None

- HGF-High: 30 on tivantinib, 21 on placebo: HR: 0.99 (95% CI: 0.55-1.79), p=0.98
- HGF-Low: 38 on tivantinib, 13 on placebo: HR: 0.75 (95% CI: 0.36-1.56), p=0.44

Interaction test: no correlation between circulating HGF and response to tivantinib, nor with circulating or tumor MET
Best Circulating HGF Response as a Prognostic Factor

No difference was evident by treatment arm

No predictive value for circulating HGF change was observed

<table>
<thead>
<tr>
<th>Group</th>
<th>Median OS</th>
<th>Patients</th>
<th>Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥10%</td>
<td>9.8 mos</td>
<td>39</td>
<td>29</td>
</tr>
<tr>
<td>&lt;10%</td>
<td>6.5 mos</td>
<td>47</td>
<td>38</td>
</tr>
</tbody>
</table>

HR: 0.60 (95% CI: 0.36-0.98) p=0.04
Circulating HGF and Best Response as Prognostic Factor

Baseline HGF - Low and ≥10% best reduction: N=11, median OS: not reached
Baseline HGF - Low and <10% best reduction: N=35, median OS: 7.65 mos
Baseline HGF - High and ≥10% best reduction: N=29, median OS: 7.77 mos
Baseline HGF - High and <10% best reduction: N=12, median OS: 3.52 mos

p=0.03
Circulating AFP as a Prognostic Factor

N=104. Prognostic trend favoring patients with AFP below median (186 IU/mL):
HR: 0.75 (95% CI: 0.48-1.15), p=0.18

Baseline AFP 75th percentile (Q3): 3507.50 IU/mL

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

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Circulating AFP as a Predictive Factor

Predictive Role: None

- AFP ≥median: 31 on tivantinib, 21 on placebo: HR: 0.78 (95% CI: 0.42-1.44), p=0.42
- AFP <median: 37 on tivantinib, 15 on placebo: HR: 1.01 (95% CI: 0.52-1.98), p=0.98
- On tivantinib: 31 AFP ≥median, 37 AFP <median: HR: 0.79 (95% CI: 0.45-1.36), p=0.39
- AFP ≥Q3: 15 on tivantinib, 11 on placebo: HR: 0.72 (95% CI: 0.31-1.63), p=0.42
- AFP <Q3: 53 on tivantinib, 25 on placebo: HR: 0.98 (95% CI: 0.57-1.71), p=0.95

Interaction test: no correlation between circulating AFP and response to tivantinib
Potential association between baseline AFP ≥median and tumor MET-High
Patient Distribution by Tumor MET Status

In tivantinib studies, patients are defined as MET-High if staining is ≥2+ within ≥50% of tumor cells. Such criterion is strict and excludes borderline staining patients.

In HCC patients from this study, values clustered towards either high or low MET expression.

Median H-Score:
- for MET-High: 175
- for MET-Low: 40

H-score is obtained by multiplying the percentage of cells staining by the intensity of the stain\(^1\), eg: (50% x 2+ = 100) + (25% x 3+ = 75) + (25% x 0 = 0) gives H-score of 175

\(^1\)Shi B, J Histochem Cytochem 2013
## Tumor MET Status by prior Therapies

<table>
<thead>
<tr>
<th></th>
<th>MET-High</th>
<th>MET-Low</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall</strong> <em>(N=77)</em></td>
<td>37 (48%)</td>
<td>40 (52%)</td>
</tr>
<tr>
<td><strong>Time on sorafenib</strong></td>
<td>6.1 months</td>
<td>4.6 months</td>
</tr>
<tr>
<td><strong>Tumor samples taken before sorafenib</strong> <em>(N=55)</em></td>
<td>22 (40%)</td>
<td>33 (60%)</td>
</tr>
<tr>
<td></td>
<td>0/9 samples taken at surgery</td>
<td>9/9 samples taken at surgery</td>
</tr>
<tr>
<td></td>
<td>12 treated with TACE: 6 biopsied before TACE, 6 after</td>
<td>13 treated with TACE: 12 biopsied before TACE, 1 after</td>
</tr>
<tr>
<td><strong>Tumor samples taken after sorafenib</strong> <em>(N=17)</em></td>
<td>14 (82%)</td>
<td>3 (18%)</td>
</tr>
<tr>
<td></td>
<td>6 treated with TACE</td>
<td>1 treated with TACE</td>
</tr>
<tr>
<td><strong>Median H-Score (0-300)</strong></td>
<td>175</td>
<td>40</td>
</tr>
</tbody>
</table>

*Biopsy date available for 72 of the 77 patients analyzed for MET status*
Tumor MET as a Prognostic Factor (Placebo)

<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>
</tbody>
</table>

HR: 0.34 (95% CI: 0.13-0.86) p=0.02
A significant interaction between tivantinib and tumor MET levels in terms of OS was observed (p=0.039)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>MET Level</th>
<th>Median OS (mos)</th>
<th>Patients</th>
<th>Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>Low</td>
<td>9.0</td>
<td>13</td>
<td>9</td>
</tr>
<tr>
<td>Tivantinib</td>
<td>High</td>
<td>7.2</td>
<td>22</td>
<td>17</td>
</tr>
</tbody>
</table>

HR: 0.72 (95% CI: 0.30-1.70) p=0.45
ARQ 197-215 Conclusions: Circulating Biomarkers

- **Prognostic value:**
  Baseline MET, HGF, AFP (75th percentile), and HGF changes

- **Prognostic trend:**
  Baseline AFP (median)

- **Pharmacodynamic biomarker:**
  Changes in circulating MET on tivantinib

- Potential association between tumor MET and circulating AFP
- No correlation between tumor and circulating MET
ARQ 197-215 Conclusions: Circulating Biomarkers

- **Predictive trend:**
  - Baseline circulating MET

<table>
<thead>
<tr>
<th>Baseline MET</th>
<th>Hazard Ratio (95% CI)</th>
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<tbody>
<tr>
<td>≥Median (N=51)</td>
<td>0.55 (0.28-1.06)</td>
</tr>
<tr>
<td>&lt;Median (N=51)</td>
<td>0.97 (0.51-1.85)</td>
</tr>
<tr>
<td>Baseline HGF</td>
<td></td>
</tr>
<tr>
<td>≥Median (N=51)</td>
<td>0.99 (0.55-1.79)</td>
</tr>
<tr>
<td>&lt;Median (N=51)</td>
<td>0.75 (0.36-1.56)</td>
</tr>
<tr>
<td>Baseline AFP</td>
<td></td>
</tr>
<tr>
<td>≥Median (N=52)</td>
<td>0.78 (0.42-1.44)</td>
</tr>
<tr>
<td>&lt;Median (N=52)</td>
<td>1.01 (0.52-1.98)</td>
</tr>
<tr>
<td>≥75th (N=26)</td>
<td>0.72 (0.31-1.63)</td>
</tr>
<tr>
<td>&lt;75th (N=78)</td>
<td>0.98 (0.57-1.71)</td>
</tr>
<tr>
<td>MET Reduction</td>
<td></td>
</tr>
<tr>
<td>≥10% (N=37)</td>
<td>0.70 (0.31-1.56)</td>
</tr>
<tr>
<td>&lt;10% (N=49)</td>
<td>0.89 (0.47-1.70)</td>
</tr>
<tr>
<td>HGF Reduction</td>
<td></td>
</tr>
<tr>
<td>≥10% (N=39)</td>
<td>0.85 (0.40-1.82)</td>
</tr>
<tr>
<td>&lt;10% (N=47)</td>
<td>0.61 (0.31-1.20)</td>
</tr>
</tbody>
</table>
ARQ 197-215 Conclusions: Tumor MET

- Tumor MET status is more frequently “High” after sorafenib
  - In line with literature: MET is more expressed in hypoxic, aggressive tumors
  - The majority of pre-sorafenib MET-Low may be MET-High after sorafenib
  - The favorable prognostic impact of true MET-Low may be underestimated
ARQ 197-215 Conclusions: Tumor MET

- Tumor MET status is more frequently “High” after sorafenib

- Tumor MET status is the only prognostic and predictive factor: tivantinib “makes” survival of MET-High comparable with the MET-Low patients

- Immunohistochemistry can be reliable when strict criteria are applied

Overall, the biomarker data from this trial support the use of tivantinib in MET-High patients only. The ongoing phase 3 METIV-HCC trial will validate the role of biomarkers in HCC
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