A Phase 3 Placebo-Controlled Trial with Tivantinib (ARQ 197), in Patients with Second-Line, MET-High, Inoperable Hepatocellular Carcinoma

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ILCA
International Liver Cancer Association

4-6 September 2015 - Paris, France
**Background**

**Hepatocellular Carcinoma (HCC)**

is a leading cause of cancer-related death, and sorafenib is the only approved systemic agent for unresectable patients\(^1\)-\(^3\)

Due to lack of placebo, 2\(^{nd}\) line single arm phase 2 studies often provide encouraging but unreliable results, biased by patient selection\(^4\)-\(^6\)

All 2\(^{nd}\) line phase 3 studies failed so far. All were conducted in unselected patients and based on small, open-label phase 2 studies\(^7\)-\(^9\)

**MET**

is the receptor tyrosine kinase for hepatocyte-growth factor (HGF) and is involved in cancer progression and metastasis

MET expression is also triggered by factors such as hypoxia and is associated with more aggressive disease

MET is often dysregulated in HCC, may be involved in resistance to anti-angiogenic agents and correlates with poor prognosis in HCC patients who underwent resection\(^10\)-\(^12\)

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\(^1\) Jemal A, CA Cancer J Clin 2011.  
\(^3\) Cheng AL, Lancet Oncol 2009.  
\(^4\) Fornaro L et al, Fut Oncol 2014.  
\(^5\) Shao YY et al, J Hepatol 2014.  
\(^6\) Finn R, J Hepatol 2014.  
\(^7\) Llovet J, J Clin Oncol 2013.  
\(^8\) Zhu AX, JAMA 2014.  
Tivantinib (ARQ 197)
is an oral, ATP-independent MET inhibitor with activity in MET-High patients in four randomized, placebo controlled studies in:

- Hepatocellular Carcinoma (HCC): ARQ 197-215 double-blind randomized phase 2 study in 107 second-line HCC patients with tivantinib vs placebo1

- Non-squamous, non small cell lung cancer (NSCLC): MARQUEE phase 3 study in 1048 pre-treated non-squamous NSCLC patients with erlotinib plus tivantinib vs erlotinib plus placebo2

- Colorectal cancer (CRC): ARQ 197-252 double-blind randomized phase 2 study in 120 metastatic pre-treated CRC patients with irinotecan plus cetuximab plus tivantinib vs irinotecan plus cetuximab plus placebo3

- Castration-resistant prostate cancer (CRPC): An NIH-sponsored double-blind randomized phase 2 study in 80 metastatic CRCP patients with tivantinib vs placebo4

ARQ 197-215

met the primary endpoint of time to progression (TTP) in the intent-to-treat (ITT) 2nd line HCC population

Tumor samples available at study entry were mandatory and tumor MET was found to be a strong independent prognostic factor

The pre-determined secondary efficacy endpoints in MET-High patients were reached, with no activity seen in MET-Low patients

Survival in MET-High patients on tivantinib was comparable to survival in MET-Low patients on placebo

Exploratory endpoints included relationship between biomarkers and key efficacy endpoints, results presented at ILCA 2015\(^1\)

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**Survival Probability vs. Time (Months)**

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<tr>
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<th>Median OS</th>
<th>Patients</th>
<th>Events</th>
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<tbody>
<tr>
<td>Placebo MET-High</td>
<td>9.0 mos</td>
<td>13</td>
<td>9</td>
</tr>
<tr>
<td>Placebo MET-Low</td>
<td>3.8 mos</td>
<td>15</td>
<td>15</td>
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<tr>
<td>HR: 0.34 (95% CI: 0.13-0.86)</td>
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<td>p=0.02</td>
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<th></th>
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</thead>
<tbody>
<tr>
<td>Tivantinib MET-High</td>
<td>9.0 mos</td>
<td>13</td>
<td>9</td>
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<tr>
<td>Tivantinib MET-High</td>
<td>7.2 mos</td>
<td>22</td>
<td>17</td>
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<tr>
<td>HR: 0.72 (95% CI: 0.30-1.70)</td>
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<td>p=0.45</td>
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\(^1\)Rimassa L et al, ILCA 2015
Approximately 303 adult pts with MET-High, Child A, ECOG 0-1, inoperable, measurable HCC progressed or intolerant to 1 prior therapy with sorafenib

2:1 Randomization

Tivantinib*
120mg PO BID
202 pts

Placebo*
PO BID
101 pts

Endpoints

1° OS

2° PFS**, Safety

3° TTP, ORR, DCR, Type of PD, PK, Biomarkers, Patient-Reported Outcomes

*Supplied as tablets, administered once in the morning and once in the evening

**Tumor assessment based on independent radiology review of scans performed every 8 weeks
Immunohistochemistry (IHC) is assessed by a central lab using the Ventana SP-44 antibody.

Patients are deemed “MET-High” only when at least 50% of tumor cells stain positive, with a staining intensity of at least 2+

The rigorous IHC criteria employed in the METIV-HCC study were set-up for the ARQ 197-215 study, and were able to clearly discern between MET-High and MET-Low patients: median H-Score was 175 for MET-High, 40 for MET-Low patients.\(^1\)

Stratification factors are three, independent:

- Vascular invasion
- Extra-hepatic spread
- AFP (< or ≥ 200ng/mL)

Statistics

257 OS events needed, HR 0.65 (improvement from 5 to 7.7 months), interim analysis at ~60% of events

\(^1\)Rimassa L et al, ILCA 2015
Histologically confirmed, inoperable, not eligible for local therapy HCC
- MET-High tumor tissue, reported by LabCorp
- progressed or intolerant to sorafenib
- Prior systemic therapy ≥ 2 wks prior to random (3 wks for IV therapies)
- ECOG PS ≤ 1
- Ended local therapy ≥ 4 wks prior to random
- RECIST 1.1 measurable disease (lesions treated with local therapy must show clear progression to be chosen as target) within 21 days prior to random
- Hb ≥ 9.0, Plt ≥ 60k, ANC ≥ 1.5, bilirubin ≤ 2, ALT/AST ≤ 5 × ULN, creatinine ≤ 1.5 × ULN, albumin ≥ 2.8, INR 0.8 - ULN (or ≤ 3 if receiving anticoagulants)
- Life expectancy ≥ 12 weeks

- >1 prior systemic regimen (and MET inh/Ab)
- Child B-C (ascites evaluated clinically)
- Other previous or concurrent cancer
- Heart failure or arrhythmia ≥ G3 in last 6 mos
- Active clinically serious infections ≥ G3
- Known HIV
- Blood or albumin transfusion 5 days before screening
- IFN or anti-HCV therapy
- Liver transplant
- Significant GI bleeding ≤ 4 weeks before random
- Pleural effusion or clinically evident ascites
Locations

**Argentina:** Buenos Aires, Pilar

**Australia:** Camperdown, Heidelberg, Melbourne, Nedlands,

**Austria:** Graz, Innsbruck, Linz, Wien

**Belgium:** Brussels, Ghent, Leuven, Liege

**Brazil:** Barretos, Porto Alegre, Rio De Janeiro, Sao Paulo

**Canada:** Toronto, Vancouver

**France:** Amiens, Bordeaux, Caen, Clichy, Creteil, Grenoble, Lille, Marseille, Montpellier, Paris, Reims, Rennes, Toulouse, Villejuif

**Germany:** Aachen, Berlin, Bonn, Duesseldorf, Essen, Frankfurt, Hamburg, Hannover, Heidelberg, Leipzig, Magdeburg, Mainz, Munich, Regensburg, Tuebingen, Ulm, Wuerzburg

**Italy:** Benevento, Bergamo, Bologna, Catania, Firenze, Meldola, Milano, Modena, Napoli, Orbassano, Padova, Parma, Pavia, Pisa, Reggio Emilia, Roma, Rozzano, Torino

**Netherlands:** Amsterdam

**New Zealand:** Auckland

**Portugal:** Lisboa, Porto, Villa Real

**Spain:** Alicante, Barcelona, Cordoba, Madrid, Majadahonda, Oviedo, Pamplona, Sabadell, Santander, Santiago de Compostela, Valencia, Zaragoza

**Sweden:** Gothemburg, Stockholm

**Switzerland:** Bern, Zurich

**United States of America:** Boston, Charleston, Chicago, Dallas, Detroit, Gainesville, Galveston, Hackensack, Houston, Los Angeles, Minneapolis, New York, New Orleans, Orange, Philadelphia, Scarborough, Seattle, Tucson, Washington, Westwood

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