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

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Abstr #O-029. Presented by: Lorenza Rimassa

September 6th, 2015. Paris, France

Supported by: ArQule, Inc, and Daiichi-Sankyo

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[1-3]. Recently failed 2nd line studies consistently showed survival on placebo of 7-8 months[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 2nd line HCC patients [7-10]

[1]Jemal A, CA Cancer J Clin 2011. [2]Llovet J, N Engl J Med 2008. [3]Cheng AL, Lancet Oncol 2009. [4]Llovet J, J Clin Oncol 2013. [5]Zhu AX, JAMA 2014. [6]Zhu AX, Lancet Oncol 2015. [7]Son G, *J Hepatol* 2006. [8]You H, *Hepatol* 2011. [9]Chau G-Y, *Eur J Surg Oncol* 2008. [10]Santoro A, Lancet Oncol 2013

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

[1]Eathiraj S, J Biol Chem 2011. [2]Munshi N, Mol Cancer Ther 2010. [3]Santoro A, Lancet Oncol 2013. [4]Scagliotti G, J Clin Oncol 2015. [5]Eng C, J Clin Oncol 2013;31 suppl, abstr 3508. [6]Monk P, J Clin Oncol 2015;33 suppl 7, abstr 146

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

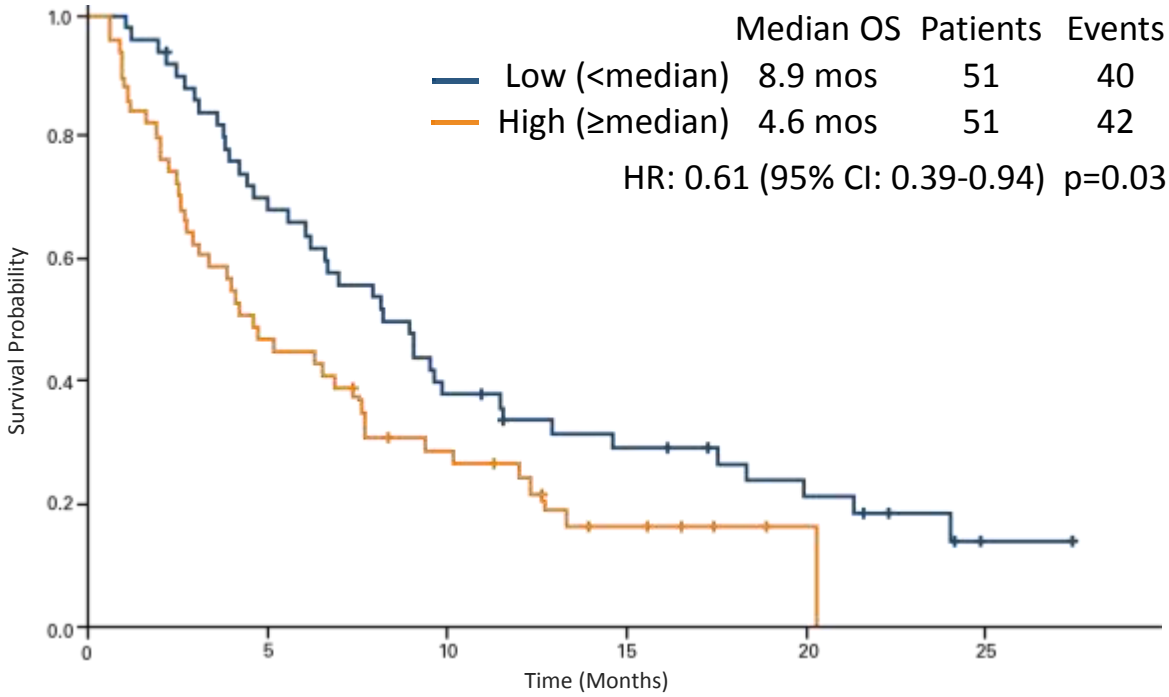
Median biomarker values were used as cut-offs to determine High or Low status except for AFP, where 75th percentile (Q3) was used

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

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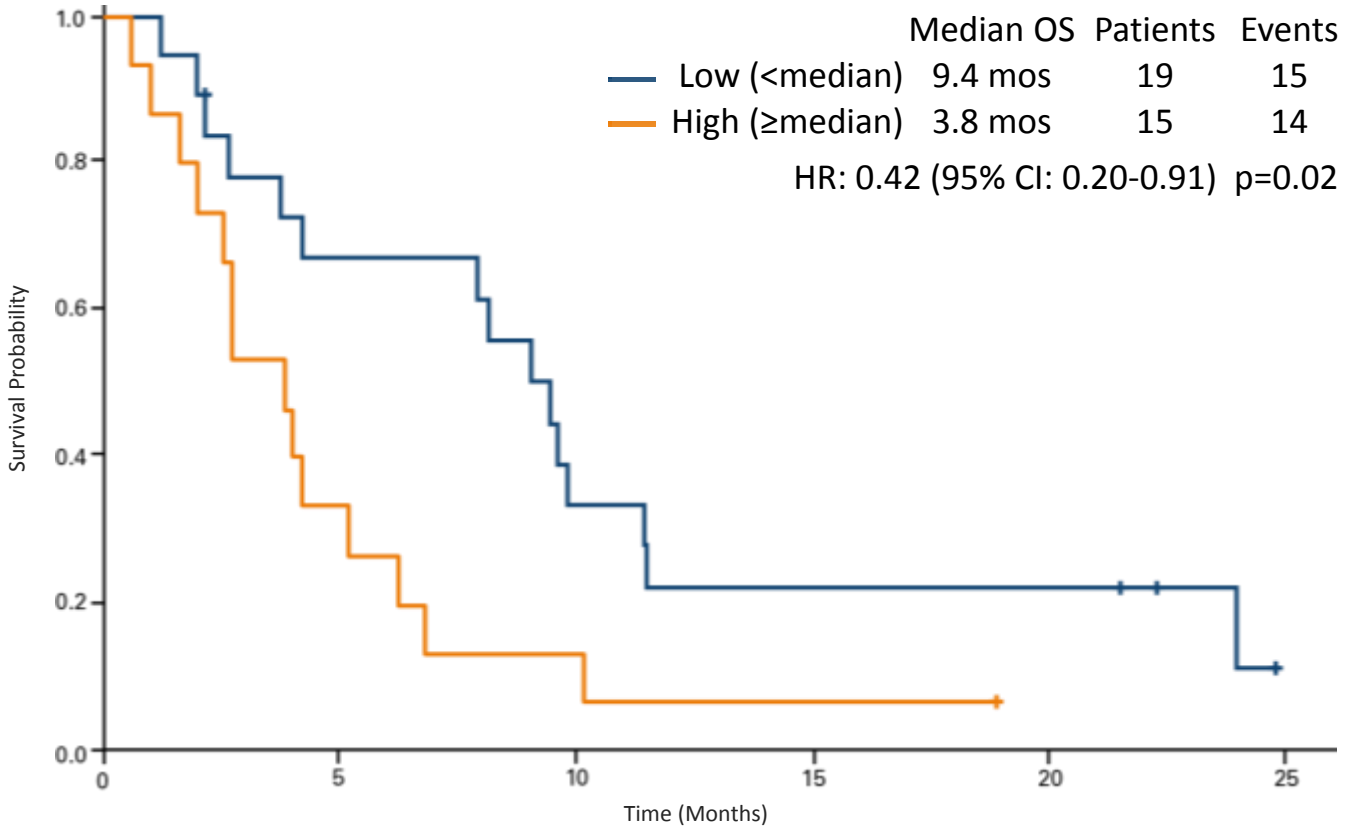
Circulating MET as a Prognostic Factor (Placebo)



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

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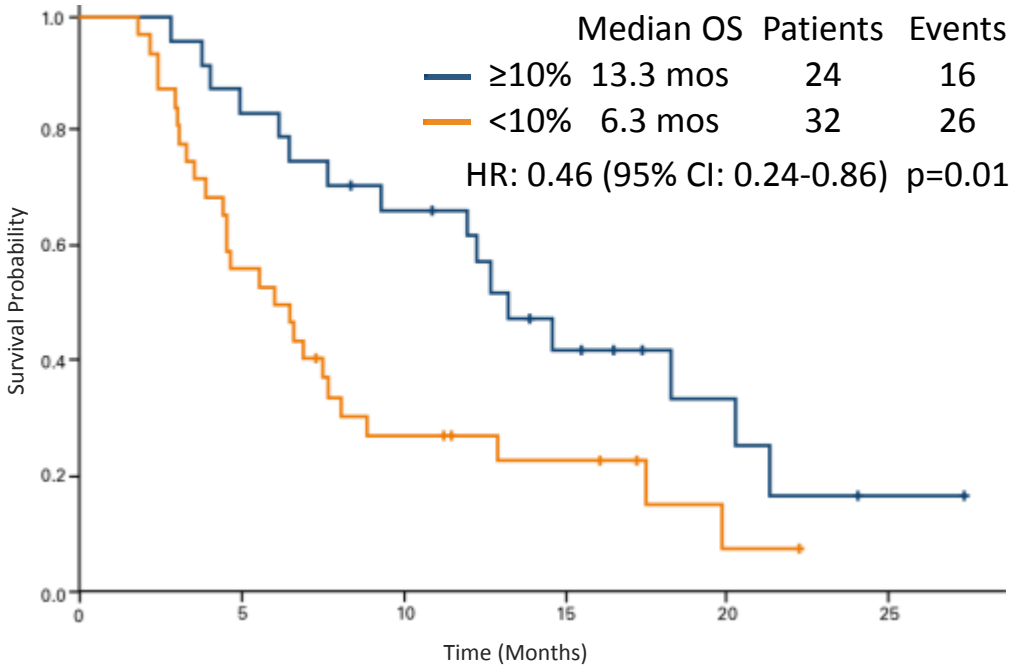
Circulating MET as a Pharmacodynamic Biomarker

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

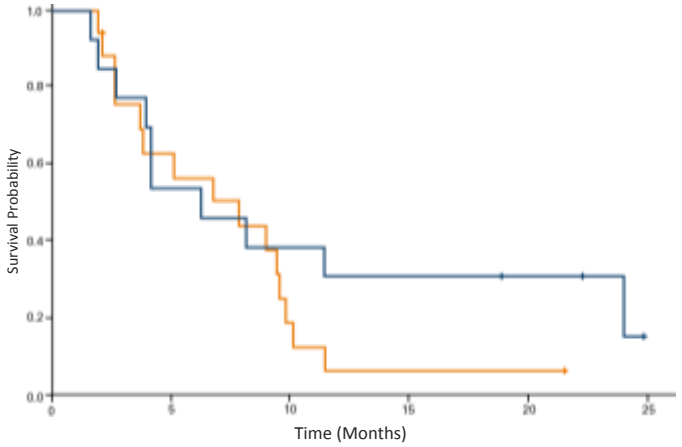
Tivantinib



	Median OS	Patients	Events
≥10%	13.3 mos	24	16
<10%	6.3 mos	32	26

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

Placebo



	Median OS	Patients	Events
≥10%	6.2 mos	13	10
<10%	7.9 mos	17	15

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

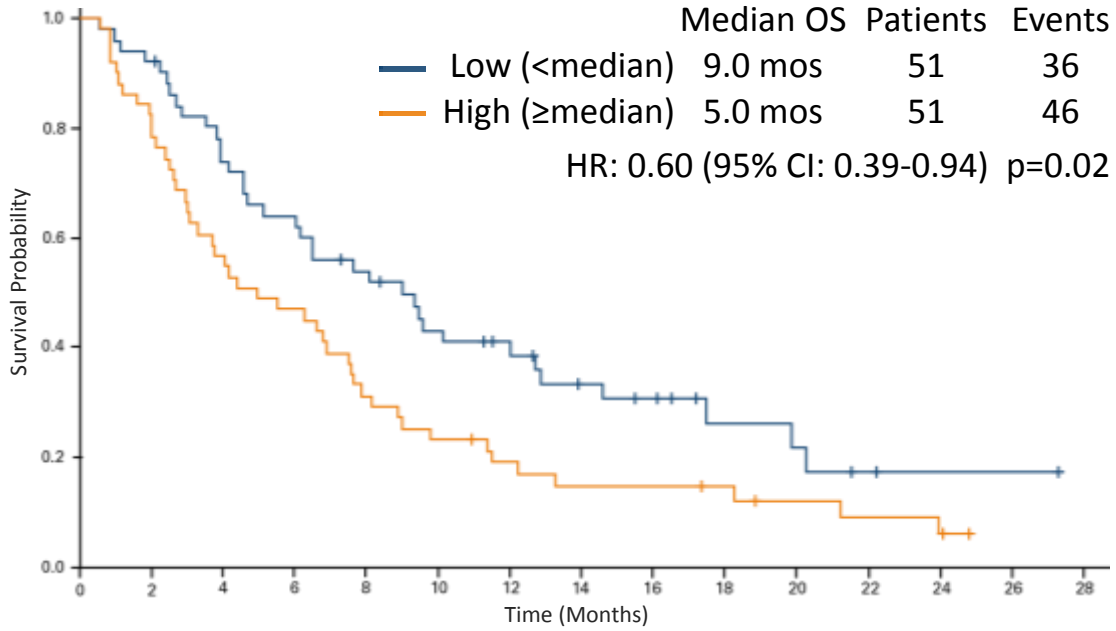
Overall: 12.3 mos in 37 pts ≥10%, 6.6 mos in 49 pts <10% HR: 0.50 (95%CI: 0.30-0.83), p=0.006

Median change from baseline in circulating MET in patients stable at first scan: -37.9% on tivantinib, +18.4% on placebo

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

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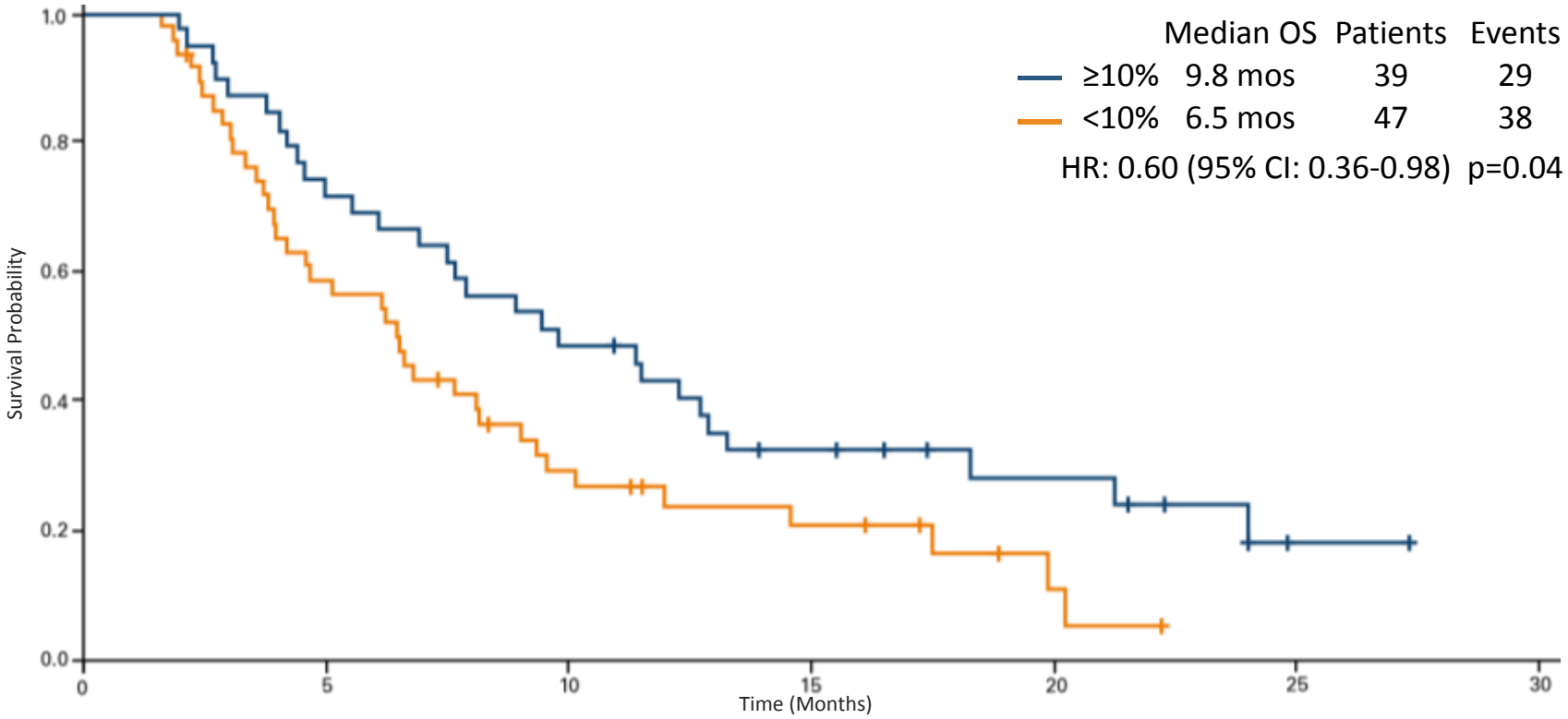
Circulating HGF as a Predictive Factor

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



	Median OS	Patients	Events
≥10%	9.8 mos	39	29
<10%	6.5 mos	47	38

HR: 0.60 (95% CI: 0.36-0.98) p=0.04

No difference was evident by treatment arm

No predictive value for circulating HGF change was observed

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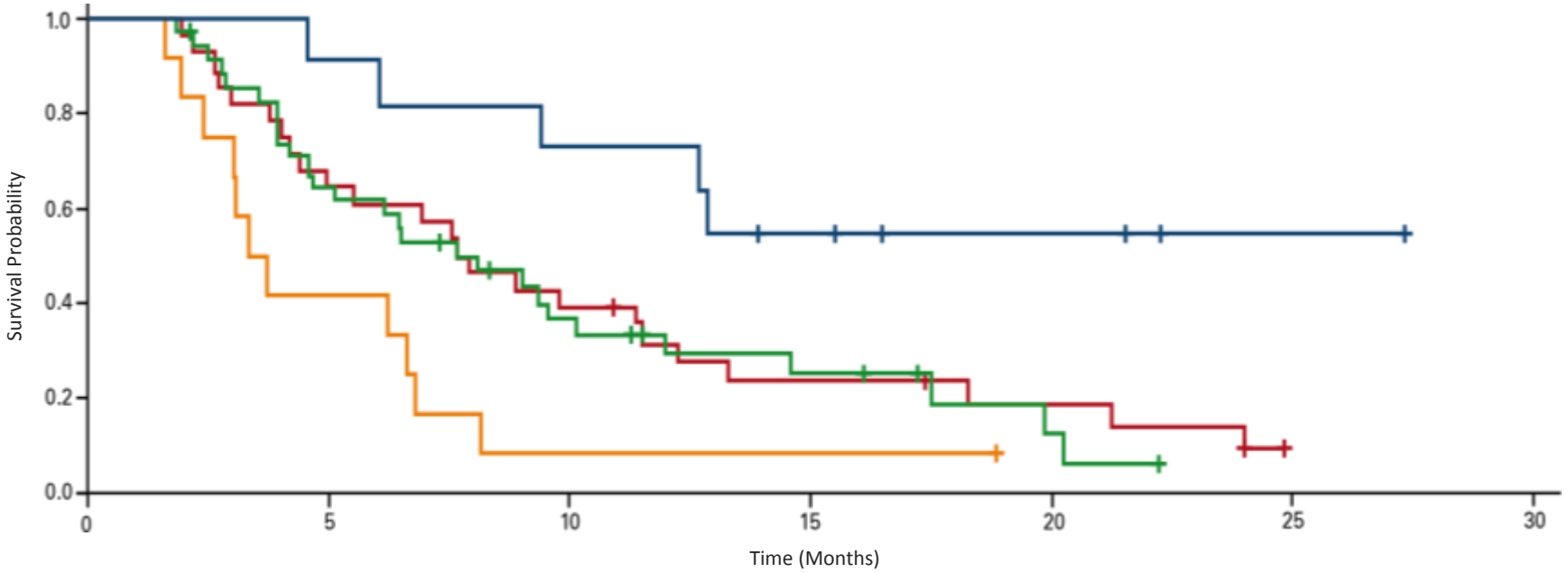
Circulating HGF and Best Response as Prognostic Factor



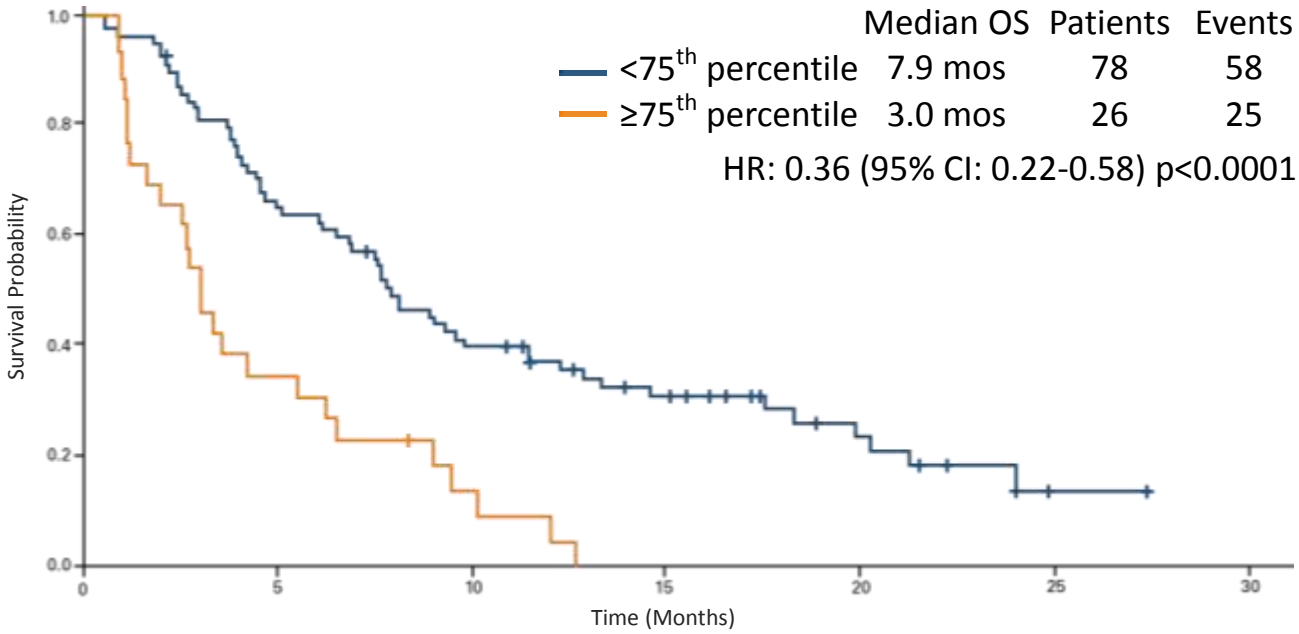
- Baseline HGF-Low and ≥ 10% best reduction: N=11, median OS: not reached
- Baseline HGF-Low and <10% best reduction: N=35, median OS: 7.65 mos
- Baseline HGF-High and ≥10% best reduction: N=29, median OS: 7.77 mos
- Baseline HGF-High and <10% best reduction: N=12, median OS: 3.52 mos

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

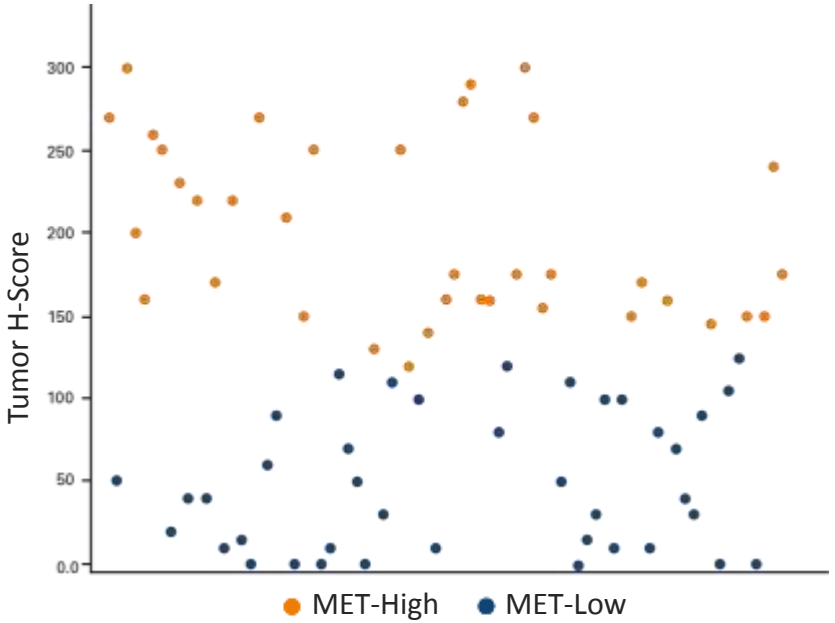
Patient Distribution by Tumor MET Status

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

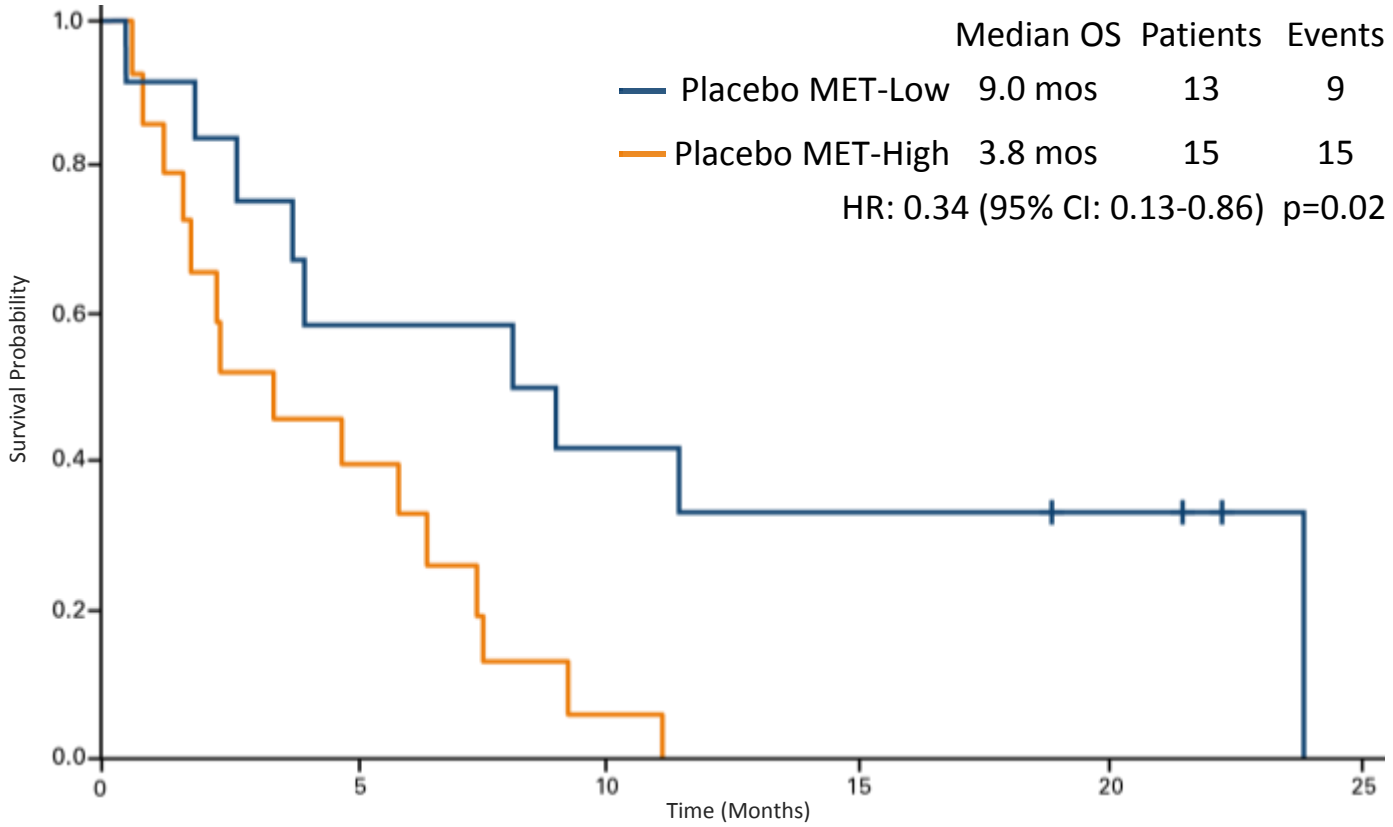
[1]Shi B, J Histochem Cytochem 2013

Tumor MET Status by prior Therapies

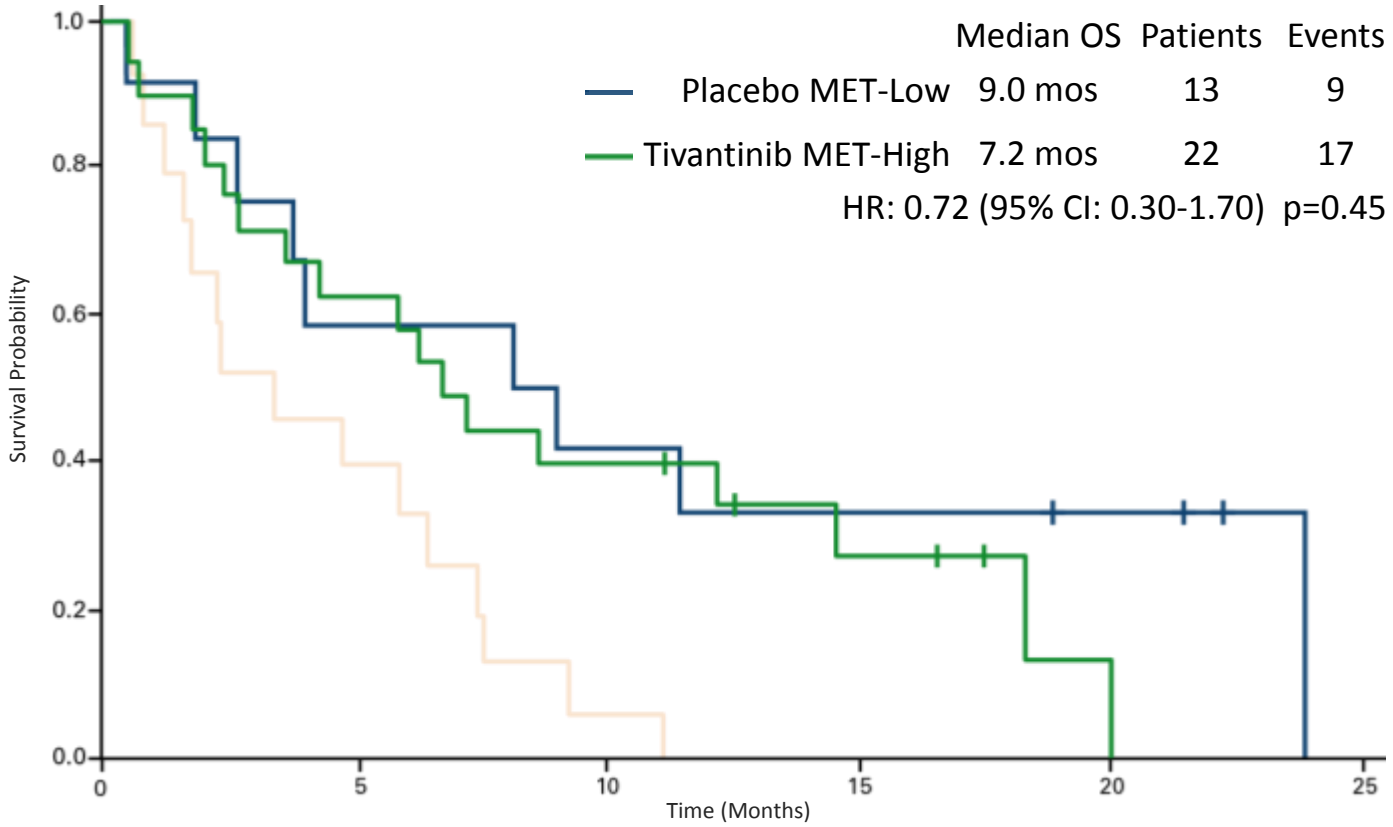
	MET-High	MET-Low
Overall* (N=77)	**37 (48%)**	**40 (52%)**
Time on sorafenib	6.1 months	4.6 months
Tumor samples taken before sorafenib (N=55)	**22 (40%)**	**33 (60%)**
	0/9 samples taken at surgery	9/9 samples taken at surgery
	12 treated with TACE: 6 biopsied before TACE, 6 after	13 treated with TACE: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

*Biopsy date available for 72 of the 77 patients analyzed for MET status

Tumor MET as a Prognostic Factor (Placebo)



Tumor MET as a Predictive Factor



A significant interaction between tivantinib and tumor MET levels in terms of OS was observed (p=0.039)

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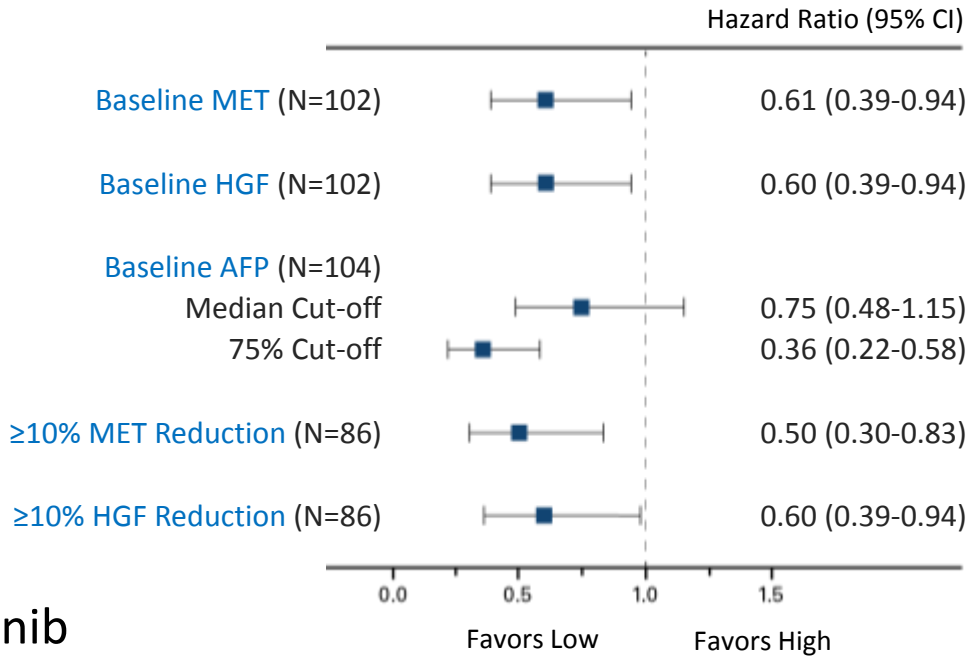
ARQ 197-215 Conclusions: Circulating Biomarkers

- **Prognostic value:**
  Baseline MET, HGF, AFP (75th percentile), and HGF changes
- **Prognostic trend:**
  Baseline AFP (median)
- **Pharmacodynamic biomarker:**
  Changes in circulating MET on tivantinib

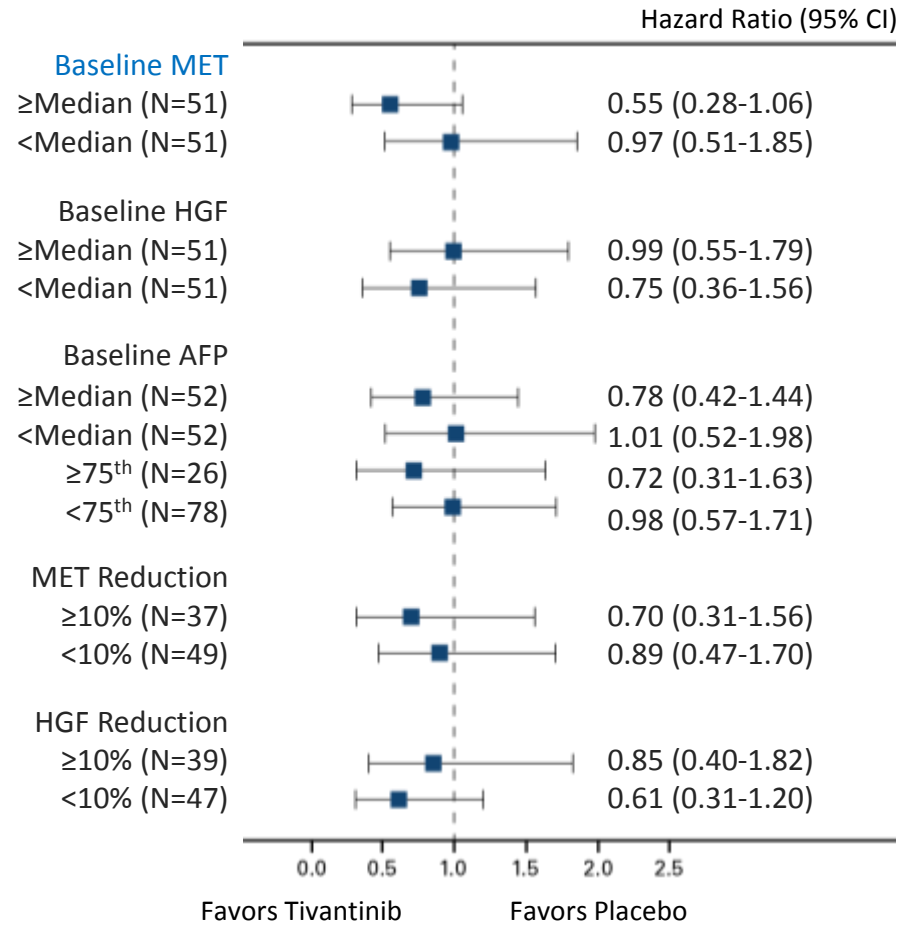


- Potential association between tumor MET and circulating AFP
- No correlation between tumor and circulating MET

ARQ 197-215 Conclusions: Circulating Biomarkers

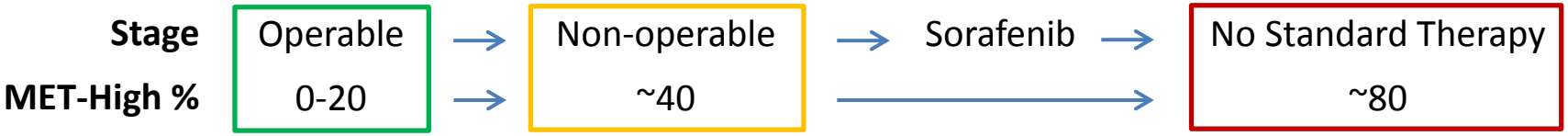
- Predictive trend:

  Baseline circulating MET



ARQ 197-215 Conclusions: Tumor MET

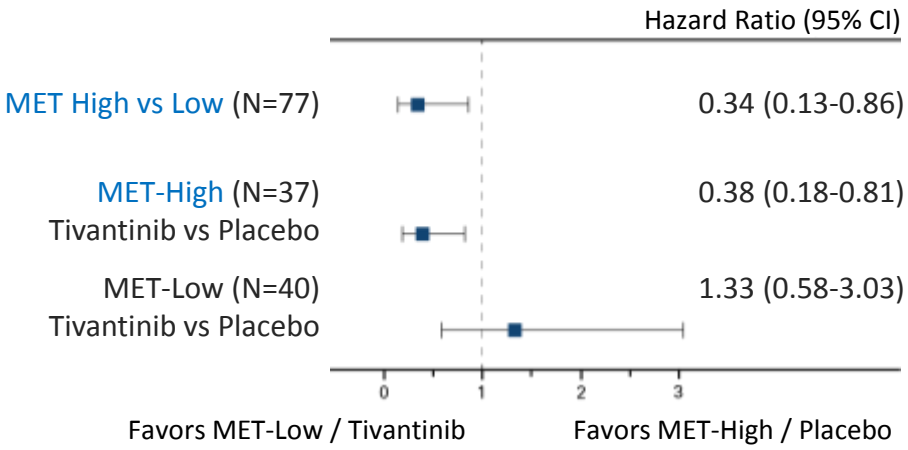
- Tumor MET status is more frequently “High” after sorafenib
  - ✓ In line with literature: MET is more expressed in hypoxic, aggressive tumors
  - ✓ The majority of pre-sorafenib MET-Low may be MET-High after sorafenib
  - ✓ The favorable prognostic impact of true MET-Low may be underestimated



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

WE THANK THE PATIENTS, THEIR FAMILIES, AND THE INVESTIGATORS

Humanitas Cancer Center, Rozzano, Milan, Italy (A Santoro, L Rimassa, N Personeni)

Humanitas University, Rozzano, Milan, Italy (A Santoro); University of Milan, Italy (N Personeni)

Fondazione IRCCS Policlinico San Matteo, Pavia, Italy (C Porta)

Cliniques Universitaires Saint-Luc, Brussels, Belgium (I Borbath)

G Rummo Hospital, Benevento, Italy (B Daniele)

Azienda Ospedaliera Parma, Italy (S Salvagni)

Erasme University Hospital, Brussels, Belgium (JL Van Laethem)

Ghent University Hospital, Belgium (H Van Vlierberghe)

J W Goethe-University Hospital, Frankfurt, Germany (J Trojan)

Klinikum der Universitat Munchen-Groshadern, Munich, Germany (E De Toni)

Vancouver General Hospital, British Columbia Cancer Clinic, Canada (A Weiss)

Cedar Sinai, Los Angeles, CA, USA (S Miles)

Policlinico Universitario Agostino Gemelli, Rome, Italy (A Gasbarrini)

Azienda Ospedaliero-Universitaria di Pisa, Italy (M Lencioni)

Daiichi Sankyo, Edison, NJ, USA (R Von Roemeling)

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