Second-Line Tivantinib vs Placebo in Patients with MET-High Hepatocellular Carcinoma: Results of the METIV-HCC Phase 3 Trial

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Abstract # 4000

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Background

Sorafenib and regorafenib are approved systemic agents for patients with advanced hepatocellular carcinoma (HCC). Lenvatinib has shown non-inferiority compared to sorafenib

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

Tivantinib (ARQ 197), a selective, oral MET inhibitor, improved overall survival (OS) and progression-free survival (PFS) versus placebo in a phase 2 study in MET-High HCC patients

Llovet JM, N Engl J Med 2008. Cheng AL, Lancet Oncol 2009. Bruix J, Lancet 2017. Cheng AL, ASCO 2017 Abstract 4001. Santoro A, Lancet Oncol 2013.

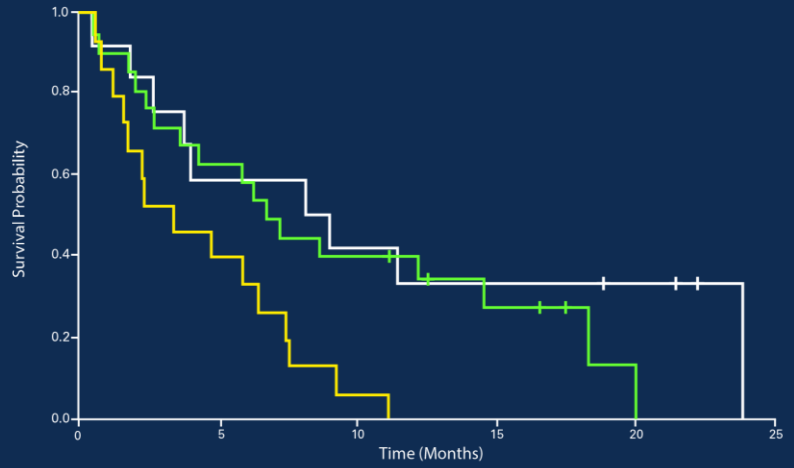
Background: Tumor MET as a Predictive Factor

	Median OS	Patients	Events
Placebo MET-Low	9.0 mos	13	9
Placebo MET-High	3.8 mos	15	15

HR: 0.34 (95% CI: 0.13-0.86) p=0.02

	Median OS	Patients	Events
Placebo MET-Low	9.0 mos	13	9
Tivantinib MET-High	7.2 mos	22	17

HR: 0.72 (95% CI: 0.30-1.70) p=0.45



Tivantinib vs placebo in 37 MET-High patients: HR: 0.43 (95% CI: 0.19-0.97), p=0.03

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)

Rimassa L, GI Cancers Symposium 2016, abstr 197

METIV-HCC Study Design

(ARQ 197-A-U303) NCT01755767

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

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

Stratified by:
- Extra-hepatic spread*
- Vascular invasion
- AFP (> / ≤ 200 ng/mL)

Endpoints
1° OS**
2° PFS, Safety
3° TTP, ORR, DCR, Type of PD, PK, Biomarkers, PRO

*includes perihepatic lymph nodes >2cm in smallest diameter
**90% power to detect OS difference with a HR 0.65 (assuming median placebo OS of 5 months)
PFS/TTP/ORR/DCR at central radiology, by RECIST 1.1, based on scans every 8 weeks

Study Design and Conduct

Key Eligibility Criteria

- Histologically confirmed advanced HCC, radiographic progression or intolerance to sorafenib
- MET-High (MET ≥2+ in ≥50% of tumor cells) tissue by immunohistochemistry (Ventana SP-44 antibody) at central laboratory (Labcorp)
- ECOG PS ≤1, Child-Pugh A cirrhotic status; adequate bone marrow, liver, kidney functions
- Measurable disease according to RECIST 1.1; no pleural effusion or clinically evident ascites

Enrolment and dosing

- Between Jan 2013 and Aug 2013, 43 patients were dosed at 240mg BID (new tablet formulation). Due to drug-related G≥3 neutropenia, dose was reduced to 120mg BID (ITT population), a modified dose reduction schema was implemented, and 340 patients were dosed between Sep 2013 and Mar 2016
- Treatment continued until confirmed radiographic disease progression, intolerable AEs or death

Baseline Characteristics (1)

	Tivantinib N=226 (%)	Placebo N=114 (%)
Median age (yrs, range)	65.6 (19 - 87)	64.7 (26 - 84)
Males	199 (88.1)	107 (93.9)
Caucasian	162 (71.7)	86 (75.4)
ECOG PS 0	141 (62.4)	66 (57.9)
BCLC stage A / B / C	15 (6.6) / 27 (11.9) / 184 (81.4)	7 (6.1) / 17 (14.9) / 90 (78.9)
Extrahepatic spread*	130 (57.5)	67 (58.8)
Vascular invasion*	79 (35.0)	38 (33.3)
Extrahepatic spread and/or vascular invasion	160 (70.8)	81 (71.1)
AFP >200ng/mL*	97 (42.9)	48 (42.1)
HBV+ / HCV+	40 (17.7) / 73 (32.3)	21 (18.4) / 33 (28.9)
Child-Pugh A	215 (95.1)	108 (94.7)

*Stratification factors

Baseline Characteristics (2)

	Tivantinib N=226 (%)	Placebo N=114 (%)
Prior sorafenib for <60 days	25 (11.1)	11 (9.6)
Median time on sorafenib (months, range)	6.3 (0.4 - 46.5)	5.8 (0.7 - 65.0)
Median time from last sorafenib dose (months, range)	2.2 (0.43 - 32.4)	2.2 (0.46 – 43.0)
Reason for sorafenib discontinuation		
Intolerance	38 (16.9)	24 (21.1)
Radiographic progression	186 (82.7)	89 (78.1)
Increased size of existing lesions	148 (65.8)	64 (56.1)
New intrahepatic lesions	66 (29.3)	42 (36.8)
New distant metastasis	28 (12.4)	20 (17.5)
New vascular invasion	12 (5.3)	3 (2.6)

Baseline Tumor MET at Immunohistochemistry

Tested Tumor Samples (overall)	MET-High N (%)	MET-Low N (%)
N=1125	591 (53)	534 (47)
Biopsied before sorafenib (N=558)	197 (35)	361 (65)
Biopsied after sorafenib (N=567)	394 (69)	173 (31)
Median H-score (range)	170 (120 - 300)	90 (0 - 180)

MET-High Tumor Samples	Biopsied Pre-sorafenib N (%)	Biopsied Post-sorafenib N (%)
N=591	197 (33)	394 (67)
Median H-Score (range)	170 (130 - 290)	170 (120 - 300)

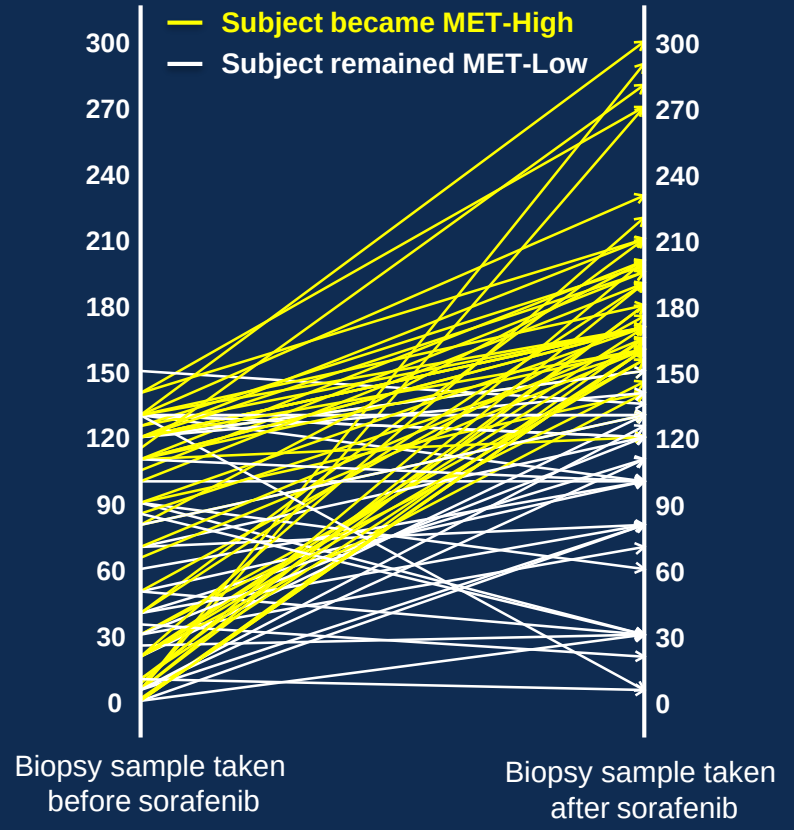
Per-protocol IHC was performed by the central lab; subsequent analysis by an independent lab on a subset of samples was not conclusive due to reader and assay differences; final results are pending

Baseline Tumor MET at Immunohistochemistry

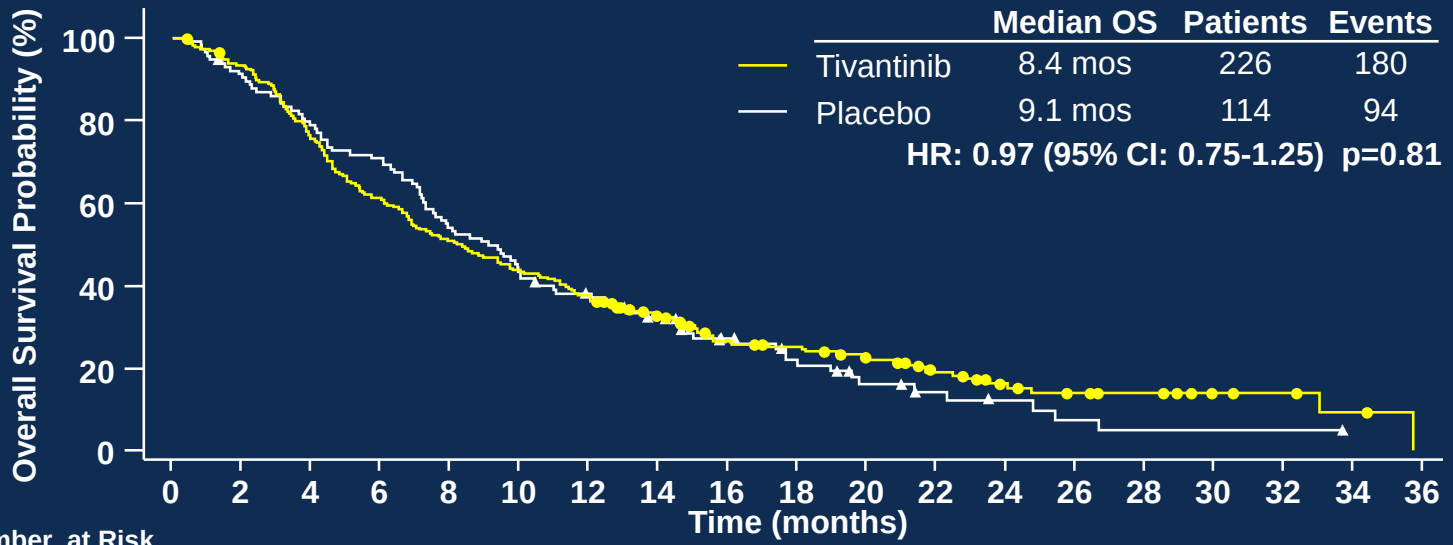
51 out of 84 (61%) patients who were MET-Low before sorafenib and were re-biopsied after sorafenib (before enrolment in METIV-HCC) converted to MET-High. In these patients, the median H-score increase was 100

A correlation was found between High MET status and treatment with sorafenib ($p<0.0001$)

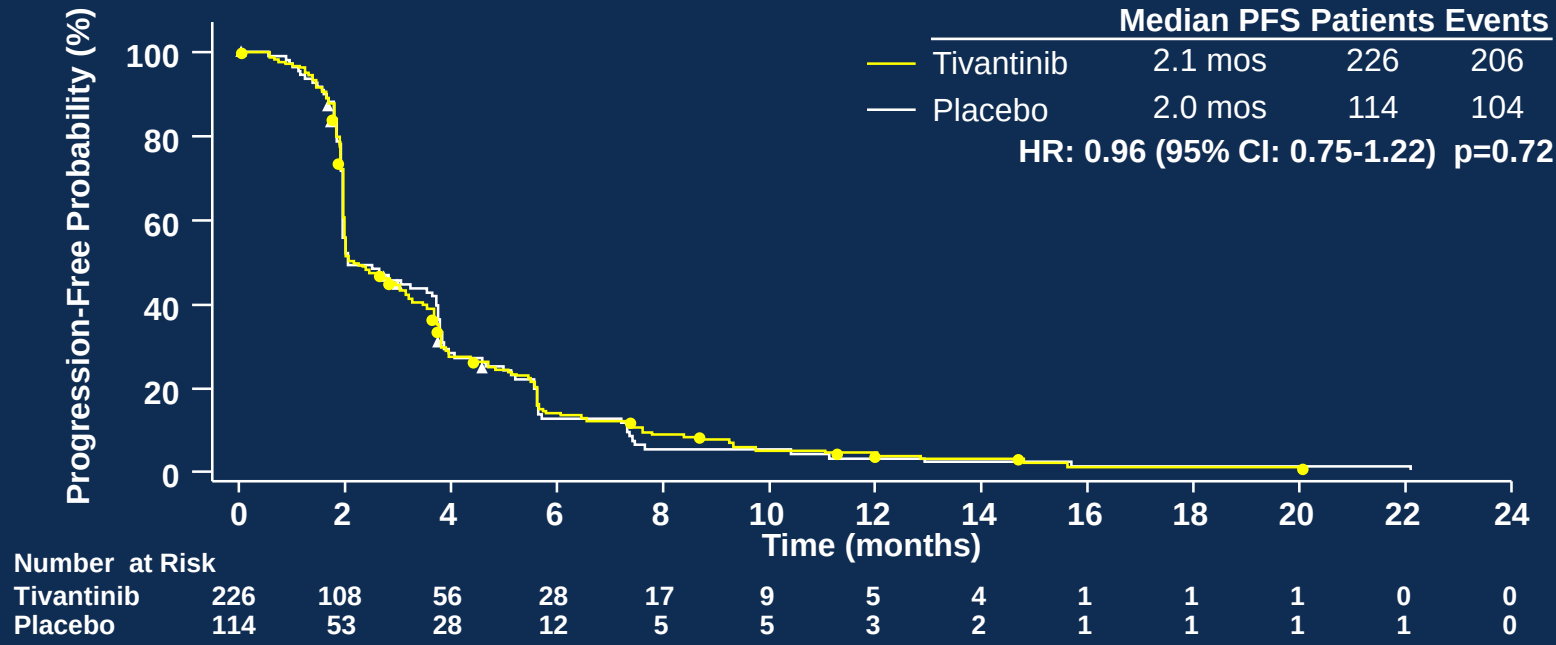
No correlation was found between MET status and other factors related to prior therapies



Primary Endpoint: Overall Survival



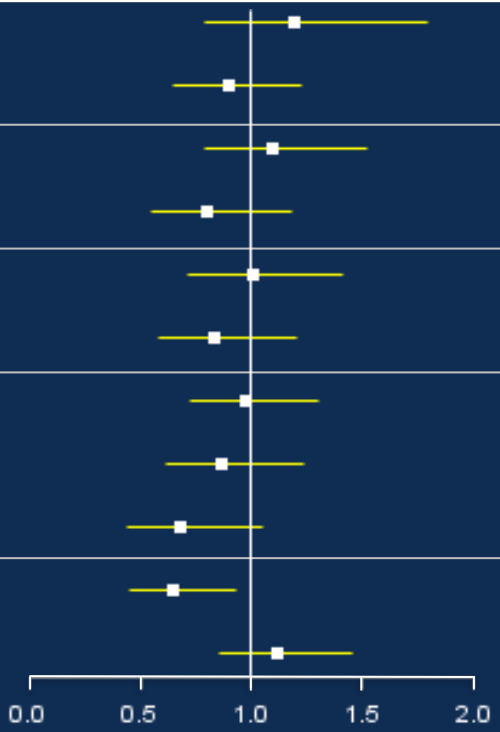
Secondary Endpoint: Progression-free Survival



Median TTP: 2.4 months on tivantinib, 3.0 on placebo; HR:0.96 (95% CI: 0.74-1.25), p=0.76
DCR: 49.5% on tivantinib, 50% on placebo (no objective responses in either arm)

OS of Selected Subgroups (1)

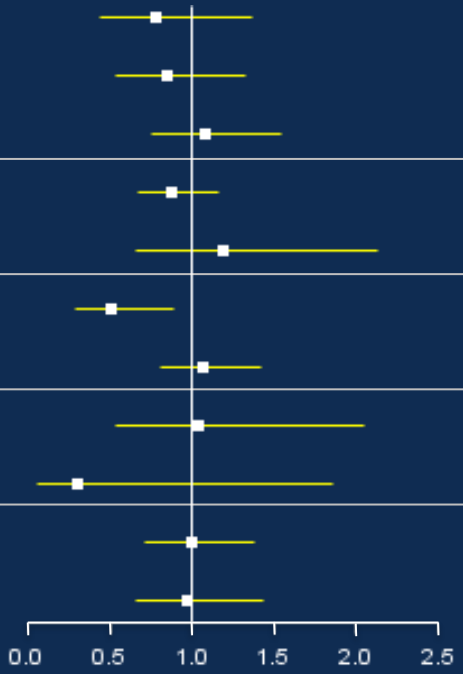
		Tivantinib	Placebo	HR (95% CI)	p
Vascular Invasion*	Yes (N=117)			1.19 (0.79 - 1.79)	0.40
	No (N=223)			0.89 (0.65 -1.22)	0.48
Extra-hepatic Spread*	Yes (N=197)			1.09 (0.78 -1.52)	0.61
	No (N=143)			0.80 (0.54 -1.18)	0.26
AFP Level*	≤200 (ng/mL) (N=194)			1.00 (0.71 -1.41)	0.99
	>200 (ng/mL) (N=146)			0.83 (0.58 -1.20)	0.33
Exposure**	AUC<26000 (N=221)			0.97 (0.73 -1.30)	0.85
	AUC ≥26000<35000 (N=175)			0.87 (0.61 -1.23)	0.43
	AUC≥35000 (N=151)			0.68 (0.44 - 1.05)	0.09
Neutropenia/Bradycardia	Yes (N=178)			0.64 (0.45 -0.92)	0.02
	No (N=276)			1.11 (0.86-1.45)	0.42



*Stratification factors; **Population PK

OS of Selected Subgroups (2)

		Tivantinib	Placebo	HR (95% CI)	p
Hepatitis	HBV Pos (N=61)			0.78 (0.44 -1.37)	0.38
	HCV Pos (HBV Neg) (N=106)			0.84 (0.53 -1.33)	0.46
	HBV and HCV Neg (N=173)			1.08 (0.76 -1.55)	0.66
Sorafenib Discont. Reason	PD (N=276)			0.88 (0.67-1.16)	0.37
	Intolerance (N=62)			1.18 (0.66 -2.13)	0.57
CYP2C19 Inhibitor Use	Yes (N=70)			0.51 (0.29 -0.89)	0.02
	No (N=270)			1.07 (0.81 -1.42)	0.64
Key Enrolment Region*	North America (N=49)			1.04 (0.53 -2.05)	0.91
	Western Europe (N=274)			0.95 (0.72 -1.26)	0.74
ECOG PS	0 (N=207)			0.99 (0.71 -1.38)	0.96
	1 (N=130)			0.97 (0.65 -1.43)	0.87



*17 patients were from Latin America, Australia, New Zealand

No OS advantage for any arms by: Age, gender, ethnicity, AST, ALT, platelets, response to sorafenib

Treatment-Emergent Adverse Events Summary

TEAE Grade	Tivantinib N=225 (%)	Placebo N=114 (%)
Any Grade	214 (95.1)	108 (94.7)
≥3	125 (55.6)	63 (55.3)
5	43 (19.1)	10 (8.8)
4	16 (7.1)	7 (6.1)
3	66 (29.3)	46 (40.4)
2	74 (32.9)	33 (28.9)
1	15 (6.7)	12 (10.5)

G5 TEAEs related to the study drug:

- 1.3% (N=3) on tivantinib, 0 on placebo

Deaths (all causes) within 30 days from last dose:

- 22.1% (N=50) on tivantinib, 15.8% (N=18) on placebo
- Most common G5 TEAEs on tivantinib: general deterioration 3.5% (N=8), hepatic failure 2.6% (N=6)

Treatment-Emergent Adverse Events Summary

Most Common (>15%) TEAEs	Tivantinib All grades	Tivantinib Grade ≥3	Tivantinib Grade 5	Placebo All grades	Placebo Grade ≥3	Placebo Grade 5
Abdominal Pain	69 (30.7)	9 (4.0)	0 (0.0)	44 (38.6)	5 (4.4)	0 (0.0)
Fatigue	58 (25.8)	3 (1.3)	0 (0.0)	31 (27.2)	5 (4.4)	0 (0.0)
Asthenia	48 (21.3)	7 (3.1)	1 (0.4)	25 (21.9)	2 (1.8)	0 (0.0)
Ascites	46 (20.4)	16 (7.1)	0 (0.0)	24 (21.1)	9 (7.9)	1 (0.9)
Decreased Appetite	36 (16.0)	2 (0.9)	0 (0.0)	21 (18.4)	3 (0.6)	0 (0.0)
Pruritus	24 (10.7)	3 (1.3)	0 (0.0)	21 (18.4)	0 (0.0)	0 (0.0)
Edema peripheral	54 (24.0)	1 (0.4)	0 (0.0)	19 (16.7)	0 (0.0)	0 (0.0)
Anemia	42 (18.7)	11 (4.9)	1 (0.4)	17 (14.9)	7 (6.1)	0 (0.0)
Diarrhea	50 (22.2)	4 (1.8)	0 (0.0)	17 (14.9)	2 (1.8)	0 (0.0)
Nausea	50 (22.2)	1 (0.4)	0 (0.0)	13 (11.4)	1 (0.9)	0 (0.0)
Other TEAEs of relevance:						
Neutropenia	28 (12.4)	9 (4.0)	0 (0.0)	5 (4.4)	1 (0.9)	0 (0.0)
Bradycardia	31 (13.8)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Patient Disposition and Treatment

		Tivantinib N=226 (%)	Placebo N=114 (%)
Median time on therapy (months, range)		3.3 (0.2-24.5)	3.7 (0.1-27.9)
Reason for discontinuation	Radiographic progressive disease	134 (59.3)	70 (61.4)
	Clinical progression	29 (12.8)	20 (17.5)
	Death	15 (6.6)	4 (3.5)
	Adverse event	28 (12.4)	11 (9.6)
	Subject decision or consent withdrawal	12 (5.3)	4 (3.5)
	Other	2 (0.1)	1 (0.9)
Dose interruption / reduction due to AE		34 (15.0) / 77 (34.1)	13 (11.4) / 35 (30.7)
Ongoing as of the data cutoff date		5 (2.2)	2 (1.8)
Post-study systemic therapies	Sorafenib / regorafenib	6 (2.7) / 5 (2.2)	2 (1.8) / 9 (7.9)
	Cabozantinib or crizotinib	3 (1.3)	6 (5.3)
	Nivolumab	10 (4.4)	1 (0.9)
	Other (hormones, chemotherapy)	37 (16.4)	20 (17.5)

Initial 240mg BID Dose Cohort

N=43 (28 on tivantinib, 15 on placebo)

Mean AUC (ngh/mL):

- 240mg BID: 31939 (90% CI: 27730 - 36147)
- 120mg BID: 26106 (90% CI: 24790 - 27422)

Most Common (>15%) AEs	Tivantinib N (%) All grades	Tivantinib N (%) Grade ≥3	Placebo N (%) All grades	Placebo N (%) Grade ≥3
Neutropenia	14 (50)	13 (46.4)	2 (13.3)	-
Alopecia	7 (25)	-	-	-
Asthenia/Fatigue	7 (25)	2 (7.2)	4 (26.7)	1 (6.7)
Edema peripheral	6 (21.4)	2 (7.1)	1 (6.7)	-
Ascites	4 (14.3)	1 (3.6)	4 (26.7)	1 (6.7)
No reported neuropathy of any grade				

	Median OS (mos)	Median PFS (mos)
Tivantinib	5.2	2.1
Placebo	5.8	2.1
HR (95% CI)	1.2 (0.64 – 2.33)	1.2 (0.39 – 3.65)
p	0.54	0.75

Mean AUC in the ARQ 197-215 phase 2 study with tivantinib 240mg BID capsules in HCC was 26000 ng.h/mL
Mean predicted AUC in non-HCC patients receiving tivantinib 360mg BID capsules: 13530 ng.h/mL

Daniele B, ESMO 2012

Conclusions

Tivantinib at 120mg BID did not improve survival in MET-High HCC patients who have progressed on or were intolerant to sorafenib

Survival of MET-High patients on placebo was longer than expected (mOS: 9.1 months)

Adverse events were manageable at the final established dose of 120mg BID

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