Randomised study of axitinib plus best supportive care (BSC) versus placebo plus BSC in patients with advanced hepatocellular carcinoma following prior antiangiogenic therapy

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***Equal contribution**

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Disclosure

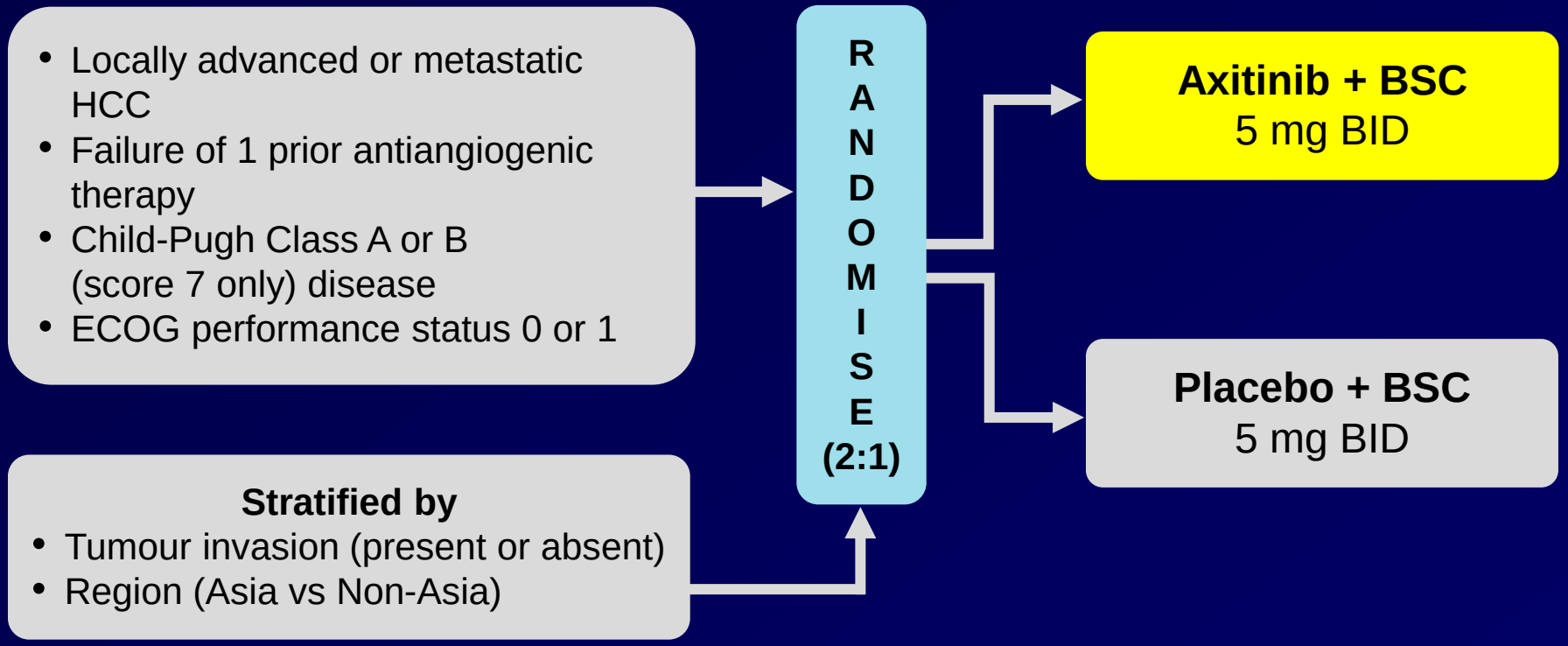
- Yoon-Koo Kang has served as a consultant for Pfizer Inc and Bayer Pharmaceuticals
- This study was sponsored by Pfizer Inc

Background

- Sorafenib, multi-targeted TKI, is the current standard treatment for advanced HCC
  - Sorafenib prolonged OS over placebo in patients with advanced HCC[1,2]
  - Other molecular targeted agents failed to show survival benefit in 1st- or 2nd-line HCC[3-7]; therefore, unmet need exists for treatment of patients with advanced HCC who progressed on or are intolerant to sorafenib
- Axitinib is a potent and selective inhibitor of VEGF receptors 1, 2, and 3 approved for 2nd-line renal cell carcinoma
  - A phase II trial was conducted to evaluate the efficacy of axitinib as 2nd-line treatment of advanced HCC

1. Llovet JM et al. *N Engl J Med* 2008;359:378-90; 2. Cheng AL et al. *Lancet Oncol* 2009;10:25-34; 3. Cheng AL et al. *J Clin Oncol* 2013;31:4067-75; 4. Johnson PJ et al. *J Clin Oncol* 2013;31:3517-24; 5. Cainap C et al. *J Clin Oncol* 2013;31(Suppl 4):Abstr 249; 6. Llovet JM et al. *J Clin Oncol* 2013;31:3509-16; 7. Zhu AX et al. *JAMA* 2014;312:57-67

Study Design and Endpoints



Primary endpoint: Overall survival (OS)

Secondary endpoints: Progression-free survival (PFS), Time to progression (TTP), Objective response rate (ORR), Duration of response (DR), Disease control rate (DCR), Safety, Health-related quality of life (HRQoL), Biomarkers

Statistical Assumption and Study Conduct

- The study had a 80% power to detect 67% improvement in OS with a corresponding HR 0.60 (1-sided α=0.025); this translates to a median OS of 5.0 to 8.3 months
- To achieve the targeted number of 150 events (deaths) for final analysis, 198 patients were to be enroled
- From Dec 2010 to Jul 2012, 202 subjects were randomised
- An interim analysis was performed after ~50% of OS events occurred; the independent Data Monitoring Committee recommended to proceed as per plan
- As of the data cutoff for primary analysis, 3 March 2014:
  - 151 events were reported
  - 29 patients alive; 8 on treatment: axitinib 7 vs placebo 1

Demographic and Baseline Characteristics (I)

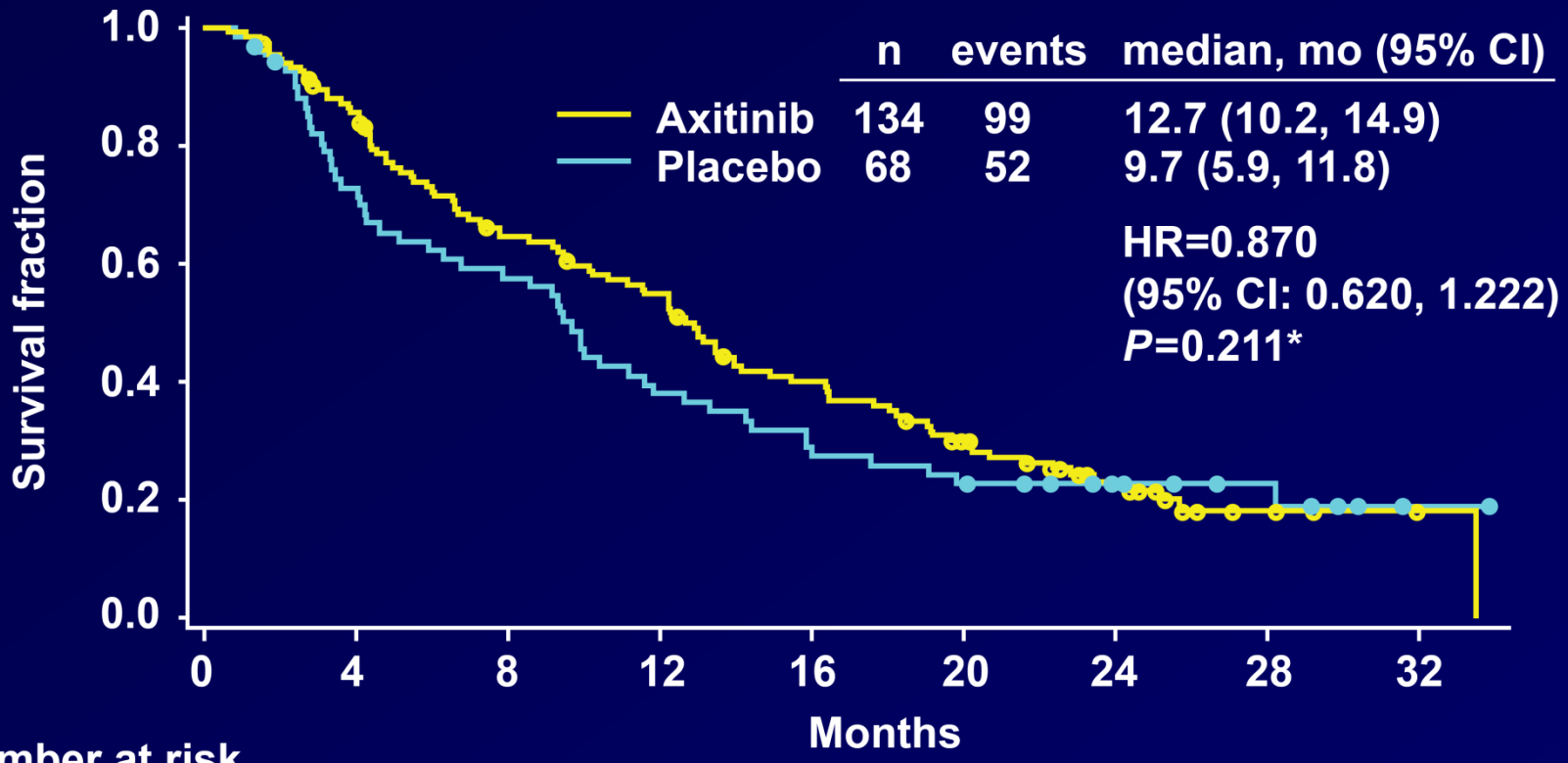
	Axitinib + BSC (n=134)	Placebo + BSC (n=68)
Age, yr, median (range)	61 (25–84)	63 (26–83)
Male, n (%)	110 (82)	56 (82)
Race, n (%)		
Caucasian	48 (36)	26 (38)
Asian	84 (63)	42 (62)
Black	2 (1)	0
Geographic region, n (%)		
Asian sites	83 (62)	41 (60)
ECOG performance status, n (%)		
0	78 (58)	39 (57)
1	56 (42)	29 (43)
Child Pugh classification, n (%)		
A	134 (100)	68 (100)

Demographic and Baseline Characteristics (II)

	Axitinib + BSC (n=134)	Placebo + BSC (n=68)
Tumor invasion[a], n (%)		
Present	102 (76)	52 (76)
BCLC stage, n (%)		
A	5 (4)	3 (4)
B	20 (15)	12 (18)
C	108 (81)	53 (78)
Prior systemic therapy, n (%)		
Sorafenib-containing regimen	124 (93)	58 (85)
Prior local therapy, n (%)	99 (74)	46 (68)
HCC etiology, n (%)		
Hepatitis B	69 (51)	34 (50)
Hepatitis C	39 (29)	11 (16)

[a] Tumor vascular invasion and/or extrahepatic spread

Overall Survival: All Randomised Patients (N=202)

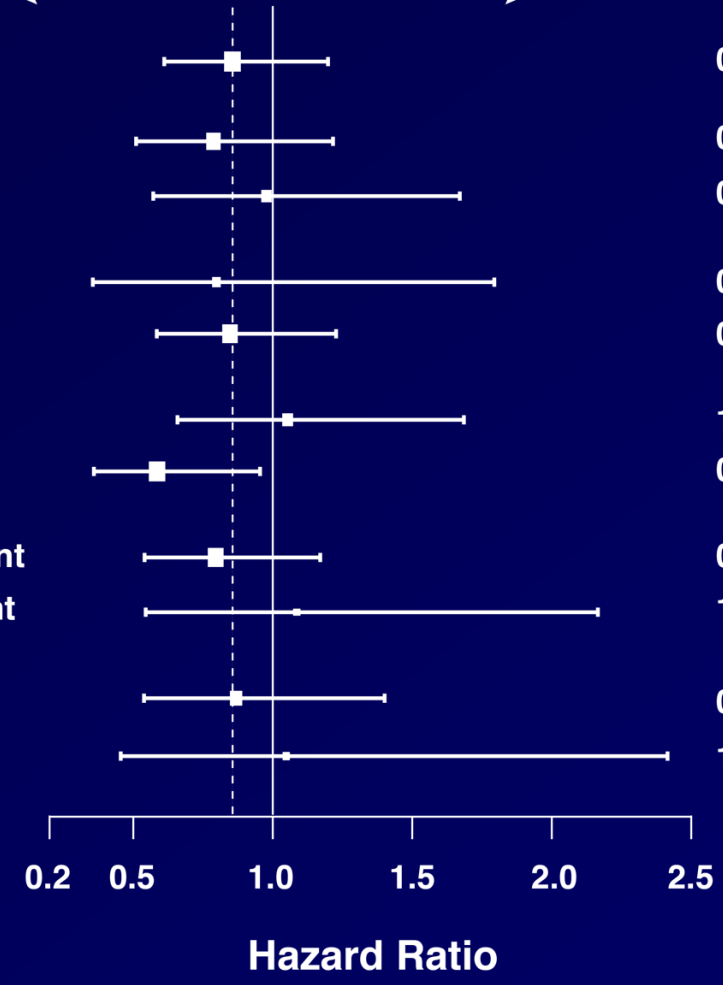


Number at risk

Axitinib	134	111	81	68	48	33	17	4	1
Placebo	68	48	38	25	18	15	9	6	1

*1-sided stratified log-rank test

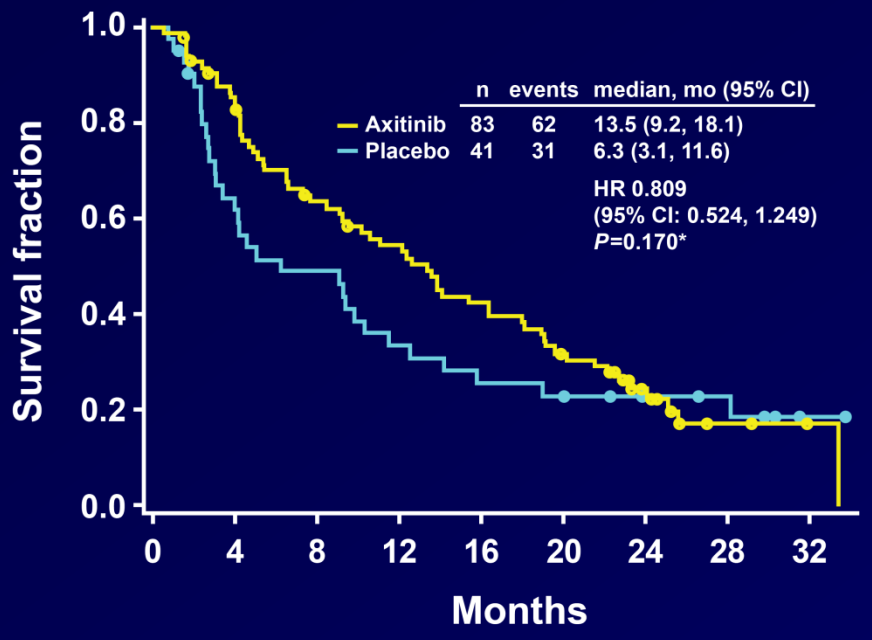
Subgroup Analysis of Overall Survival



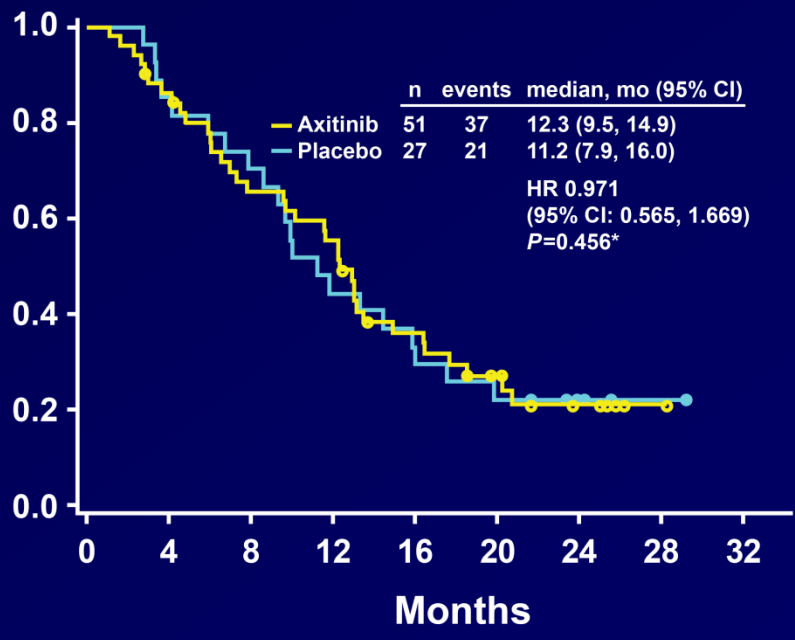
Population	Hazard Ratio [95% CI]	Sample Size (Events) Axitinib	Placebo
All patients	0.856 [0.611, 1.198]	134 (99)	68 (52)
Asian patients	0.788 [0.510, 1.216]	83 (62)	41 (31)
Non-Asian patients	0.977 [0.572, 1.670]	51 (37)	27 (21)
BCLC Stage A or B	0.798 [0.355, 1.794]	25 (15)	15 (10)
BCLC Stage C	0.847 [0.584, 1.227]	108 (84)	53 (42)
Baseline ECOG 0	1.053 [0.658, 1.685]	78 (54)	39 (26)
Baseline ECOG 1	0.585 [0.359, 0.954]	56 (45)	29 (26)
Tumor Invasion Present	0.795 [0.541, 1.170]	97 (73)	50 (40)
Tumor Invasion Absent	1.086 [0.545, 2.165]	37 (26)	18 (12)
Hepatitis B Present	0.869 [0.539, 1.401]	69 (50)	34 (26)
Hepatitis C Present	1.048 [0.455, 2.415]	39 (28)	11 (7)

Overall Survival: Asian vs Non-Asian Patients

Asian Patients (n=124)



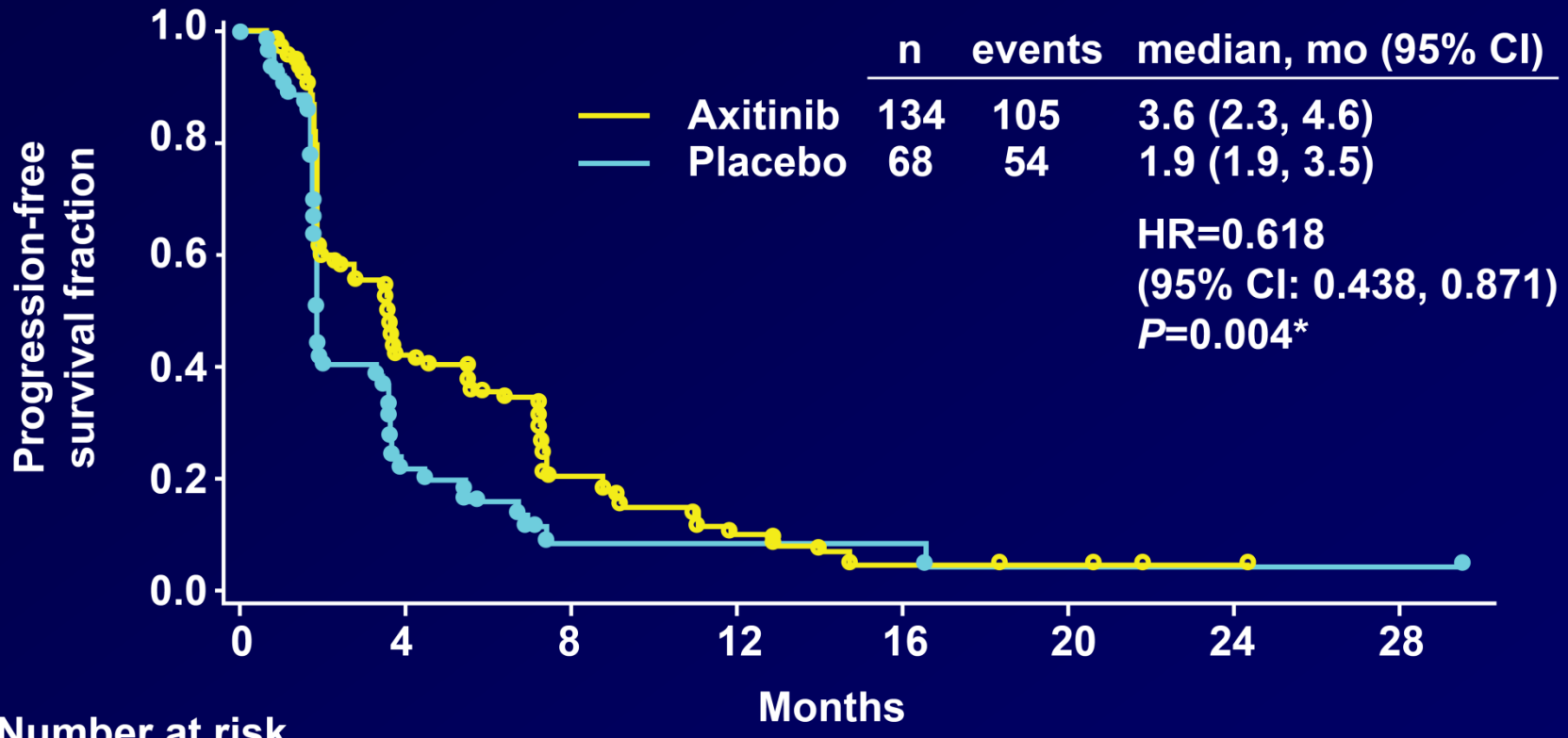
Non-Asian Patients (n=78)



	Median OS, months (Axitinib vs Placebo)	HR (95% CI)	*P**
Asian	13.5 vs 6.3	0.809 (0.524, 1.249)	0.170
Non-Asian	12.3 vs 11.2	0.971 (0.565, 1.669)	0.456

*1-sided stratified log-rank test

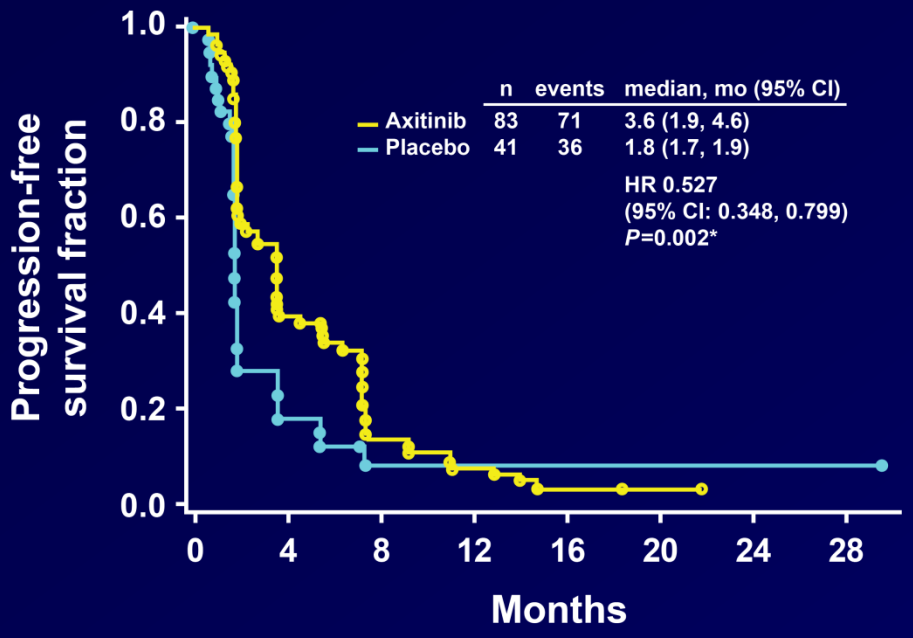
Progression-Free Survival: All Randomised Patients (N=202)



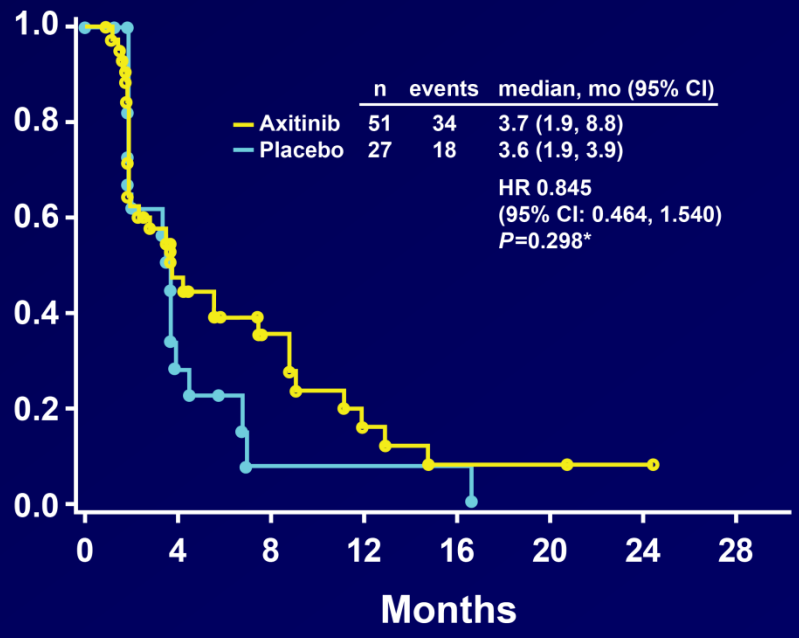
*1-sided stratified log-rank test

Progression-Free Survival: Asian vs Non-Asian Patients

Asian Patients (n=124)



Non-Asian Patients (n=78)



	Median PFS, months (Axitinib vs Placebo)	HR (95% CI)	*P**
Asian	3.6 vs 1.8	0.527 (0.348, 0.799)	0.002
Non-Asian	3.7 vs 3.6	0.845 (0.464, 1.540)	0.298

*1-sided stratified log-rank test

Tumour Response per RECIST 1.1

	Axitinib + BSC (n=134)	Placebo + BSC (n=68)
Best overall response, n (%)		
CR	1 (0.7)	0
PR	12 (9.0)	2 (2.9)
SD	49 (36.6)	20 (29.4)
PD	55 (41.0)	38 (55.9)
Indeterminate	11 (8.2)	5 (7.4)
Overall ORR (CR + PR), n (%)	13 (9.7)	2 (2.9)
	P=0.083*	
Overall DCR (CR + PR + SD), n (%)	42 (31.1)	8 (11.8)
	P=0.002*	

*1-sided unstratified Pearson chi-square test

Summary of Adverse Events (All-Causality)

n (%)	Axitinib + BSC (n=133)	Placebo + BSC (n=68)
Any AE	131 (99)	63 (93)
Serious AE	62 (47)	16 (24)
Grade ≥3 AE	109 (82)	26 (38)
Discontinued treatment due to AE	38 (29)	10 (15)
Reduced dose due to AE	46 (35)	5 (7)
Died on study[a]	16 (12)	8 (12)

[a] During the period from 1st dose until 28 days after the last dose of study drug

Common Adverse Events (All-Causality)

n (%)	Axitinib + BSC (n=133)		Placebo + BSC (n=68)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Diarrhoea	72 (54)	27 (20)	8 (12)	0
Hypertension	72 (54)	34 (26)	9 (13)	1 (1)
Decreased appetite	62 (47)	16 (12)	14 (21)	4 (6)
Fatigue	46 (35)	10 (8)	18 (26)	7 (10)
Abdominal pain	45 (34)	9 (7)	14 (21)	1 (1)
HFSR	45 (34)	20 (15)	4 (6)	0
Weight decrease	36 (27)	5 (4)	2 (3)	0
Nausea	35 (26)	6 (5)	7 (10)	0
Dysphonia	33 (25)	0	0	0
Hypothyroidism	33 (25)	0	0	0

HFSR=Hand Foot Skin Reaction

Conclusions

- Primary endpoint (OS) did not meet statistical significance
  - Median OS in all randomised patients: 12.7 vs 9.7 mo, axitinib vs placebo; stratified HR 0.870 (95% CI: 0.620, 1.222)
- There was a statistically significant improvement in secondary endpoints of investigator-assessed PFS and DCR
- Regional differences in the efficacy were noticeable
  - Asian patients had 7.2 mo benefit of median OS (median 13.5 vs 6.3 mo; HR 0.809, *P*=0.170) and 1.8 mo benefit of median PFS (median 3.6 vs 1.8 mo; HR 0.527, *P*=0.002)
  - No significant benefit in either OS or PFS in non-Asian patients
- No new safety signals identified in advanced HCC patients
  - Safety profile of axitinib in these patients is consistent with known safety profile of axitinib

Acknowledgements

- 202 patients who participated in this study and their families
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  - Samuel H. Whiting (Member)
  - Mengling Liu (Member)
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