Phase II study of pazopanib as second-line treatment after sunitib
In patients with metastatic renal cell cancer .
Mian Xie et al. Guangzhou Medical University Hospital, China

RECORD-4: Multicenter phase 2 trial of second-line everolimus (EVE) in patients (pts) with metastatic renal cell carcinoma (mRCC): Asian versus non-Asian population subanalysis
L. Yang et al. Multinational Consortium

Prof Winald R. Gerritsen

Radboud University Medical Center

Department of Medical Oncology

Nijmegen, the Netherlands

Disclosure slide

Speaker fees

Astellas, Bayer, Bavarian Nordic, Bristol-Myers Squibb, Janssen-Cilag

Advisory boards

Amgen, Astellas, Bayer, Bristol-Myers Squibb, Dendreon, Janssen-Cilag, Morphosys, Sanofi, Transgene

Ad hoc Consultancy

Aglaia Biomedical Ventures, Psioxus Therapeutics, ORCA Pharmaceuticals, Sotio, Transgene

Founder: Carcinos (global oncology education: immunotherapy of cancer)

Phase II study of pazopanib as second-line treatment after sunitinib in patients with metastatic renal cell carcinoma: A Southern China Urology Cancer Consortium Trial *Mian Xie, Chao sheng He, Jin Kun Huang, Qi zhan Lin*

European Journal of Cancer Volume 51, Issue 5, Pages 595-603 (March 2015)

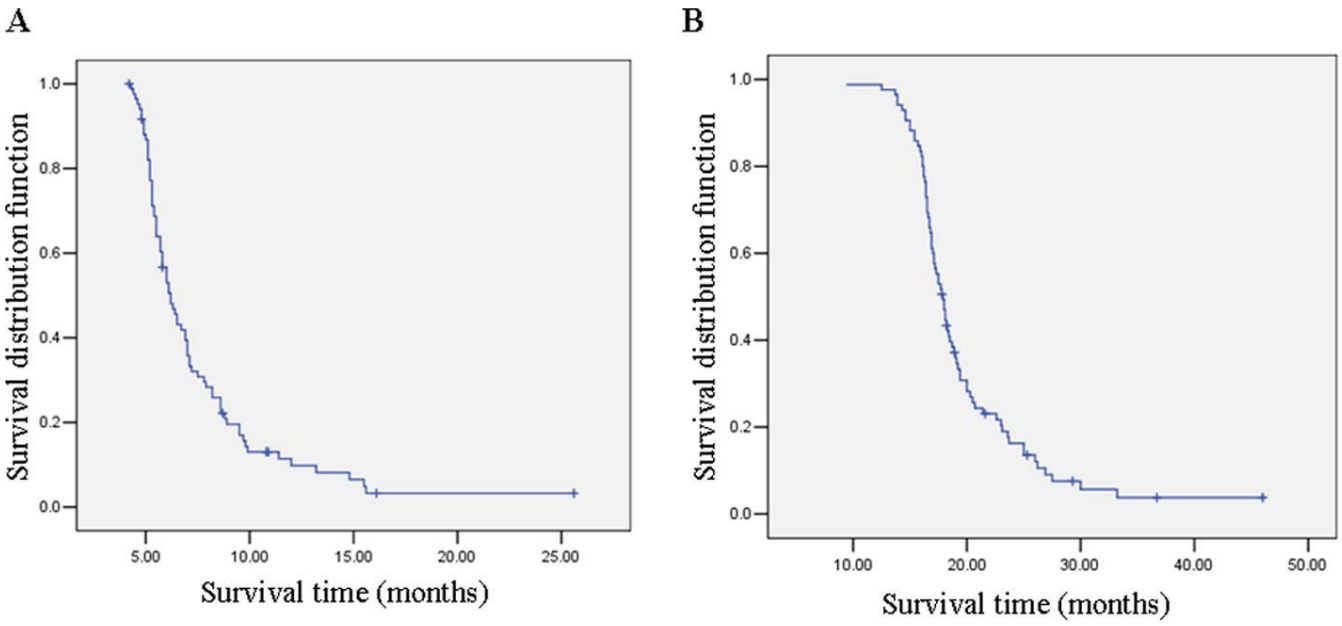
86 patients enrolled in this study

Table 2
Overview of response rate by independent review ($n = 85$).[†]

Response	Response rate	
	No.	%
ORR[a]	13	15.3
CR[b]	0	0
PR[c]	13	15.3
SD[d]	47	55.3
PD[e]	16	18.8
Unknown[f]	9	10.6

Phase II study of pazopanib as second-line treatment after sunitinib in patients with metastatic renal cell carcinoma: A Southern China Urology Cancer Consortium Trial *Mian Xie, Chao sheng He, Jin Kun Huang, Qi zhan Lin*

European Journal of Cancer Volume 51, Issue 5, Pages 595-603 (March 2015)

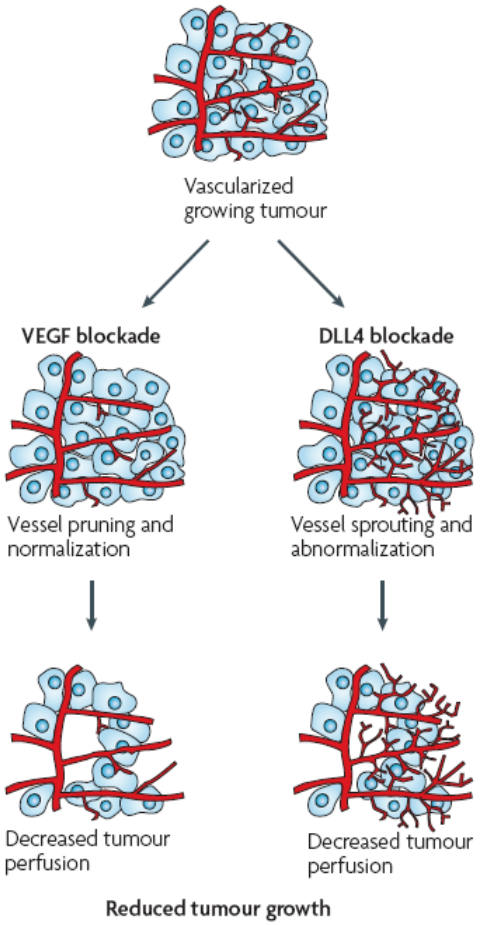


This study: Median PFS 5.6 months Median OS 18.1 months

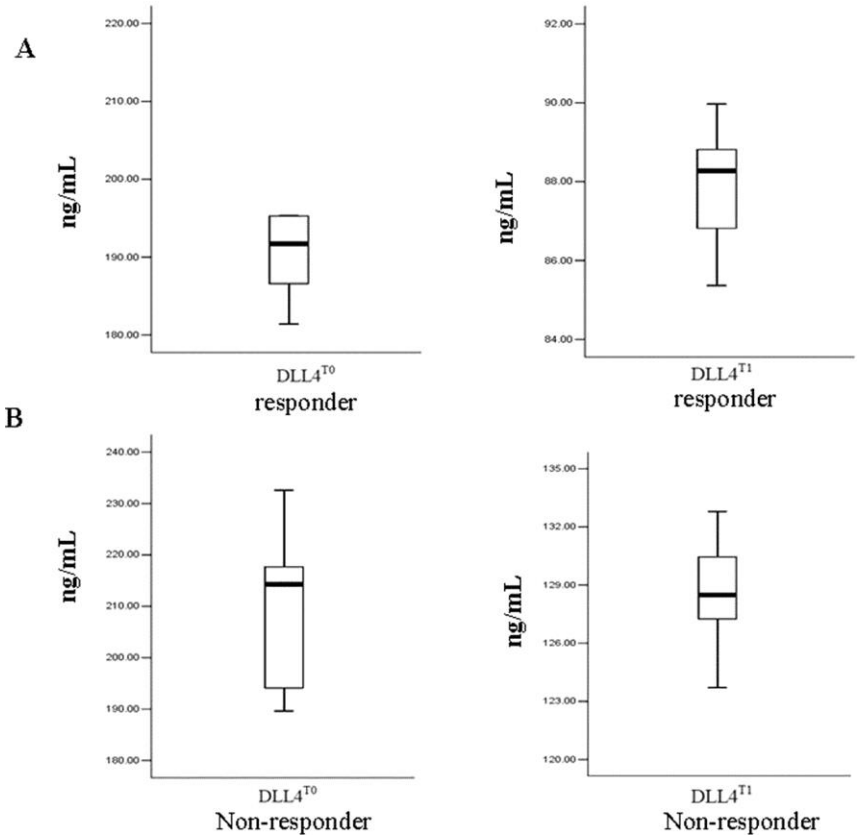
Other Study Median PFS 7.5 months Median OS 24.2 months*

*Hainsworth JD et al.
Clin Genitourin Cancer 2013;11:270

Phase II study of pazopanib as second-line treatment after sunitinib in patients with metastatic renal cell carcinoma: A Southern China Urology Cancer Consortium Trial *Mian Xie, Chao sheng He, Jin Kun Huang, Qi zhan Lin*



Thuston, G. et al NCR 2006



RECORD-4: Multicenter Phase 2 Trial of Second-Line Everolimus in Patients With Metastatic Renal Cell Carcinoma: Asian Vs Non-Asian Population Subanalysis

Lin Yang,[1] Anna Alyasova,[2] Dingwei Ye,[3] Andrey Karpenko,[4] Hanzhong Li,[5] Boris Alekseev,[6] Liping Xie,[7] Galina Kurteva,[8] Ruben Kowalyszyn,[9] Oleg Karyakin,[10] Yeni Neron,[11] Thomas Cosgriff,[12] LaTonya Collins,[13] Thomas Brechenmacher,[14] Chinjune Lin,[13] Liza Morgan,[13] Robert J. Motzer[15]

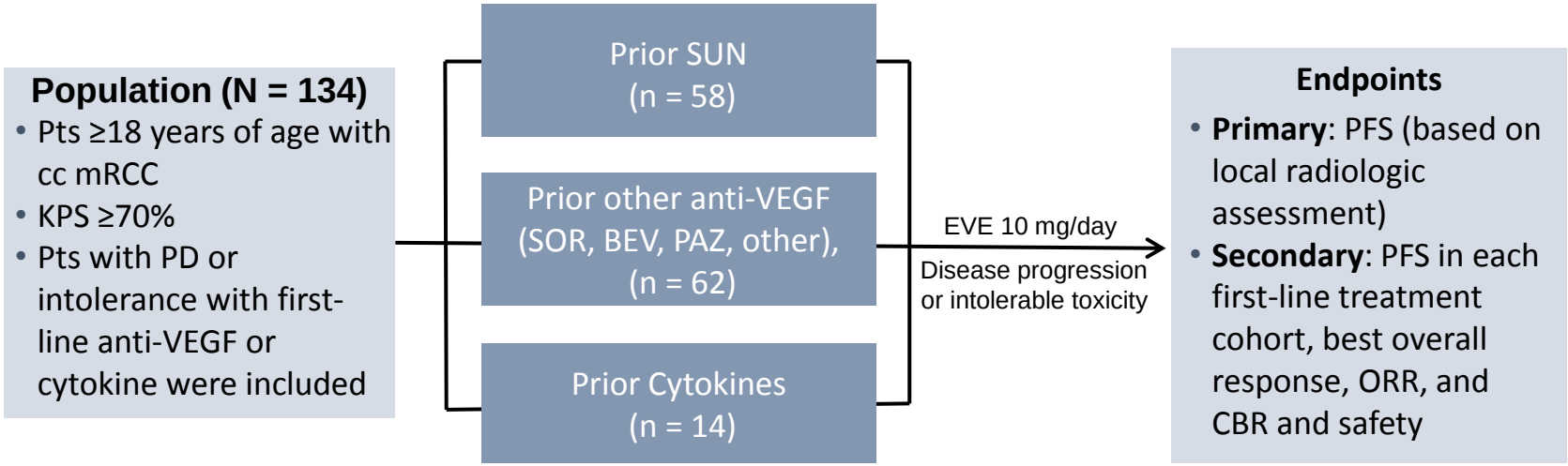
[1]Cancer Institute and Hospital, Chinese Academy of Medical Science, Beijing, China; [2]Prevoljskiy Region Medical Centre, Novgorod, Russia; [3]Fudan University Shanghai Cancer Center, Shanghai, China; [4]Leningrad Regional Oncologic Dispensary, Saint Petersburg, Russia; [5]Peking Union Medical College Hospital, Beijing, China; [6]Moscow Hertzen Oncology Institute, Moscow, Russia; [7]First Affiliated Hospital, School of Medicine, Zhejiang University, Zhejiang Province, China; [8]Center of Oncology, Sofia, Bulgaria; [9]Centro de Investigaciones Clinicas Clinica Viedma, Viedma, Argentina; [10]Medical Radiological Research Center, Oncology Department, Obninsk, Russia; [11]Centro de Pesquisas Oncológicas-CEPON, Florianopolis-SC, Brazil; [12]Crescent City Research Consortium, Marrero, Louisiana, USA; [13]Novartis Oncology, East Hanover, New Jersey, USA; [14]Novartis Pharma S.A.S., Rueil-Malmaison, France; [15]Memorial Sloan Kettering Cancer Center, New York, New York, USA

SINGAPORE 2015 ESMO ASIA 18-21 DECEMBER SINGAPORE

Study Design

Study Design and Patients

Open label, Multicenter, International phase II study*



*Primary analysis data cutoff was September 1, 2014

BEV, Bevacizumab; ccmRCC, clear cell metastatic renal cell carcinoma; CBR, clinical benefit rate; KPS, Karnofsky performance status; ORR, objective response rate; PAZ, pazopanib; PD, progressive disease; PFS, progression-free survival; Pts, patients; SOR, sorafenib; SUN, sunitinib; VEGF, vascular endothelial growth factor

Baseline Demographics and Disease Characteristics

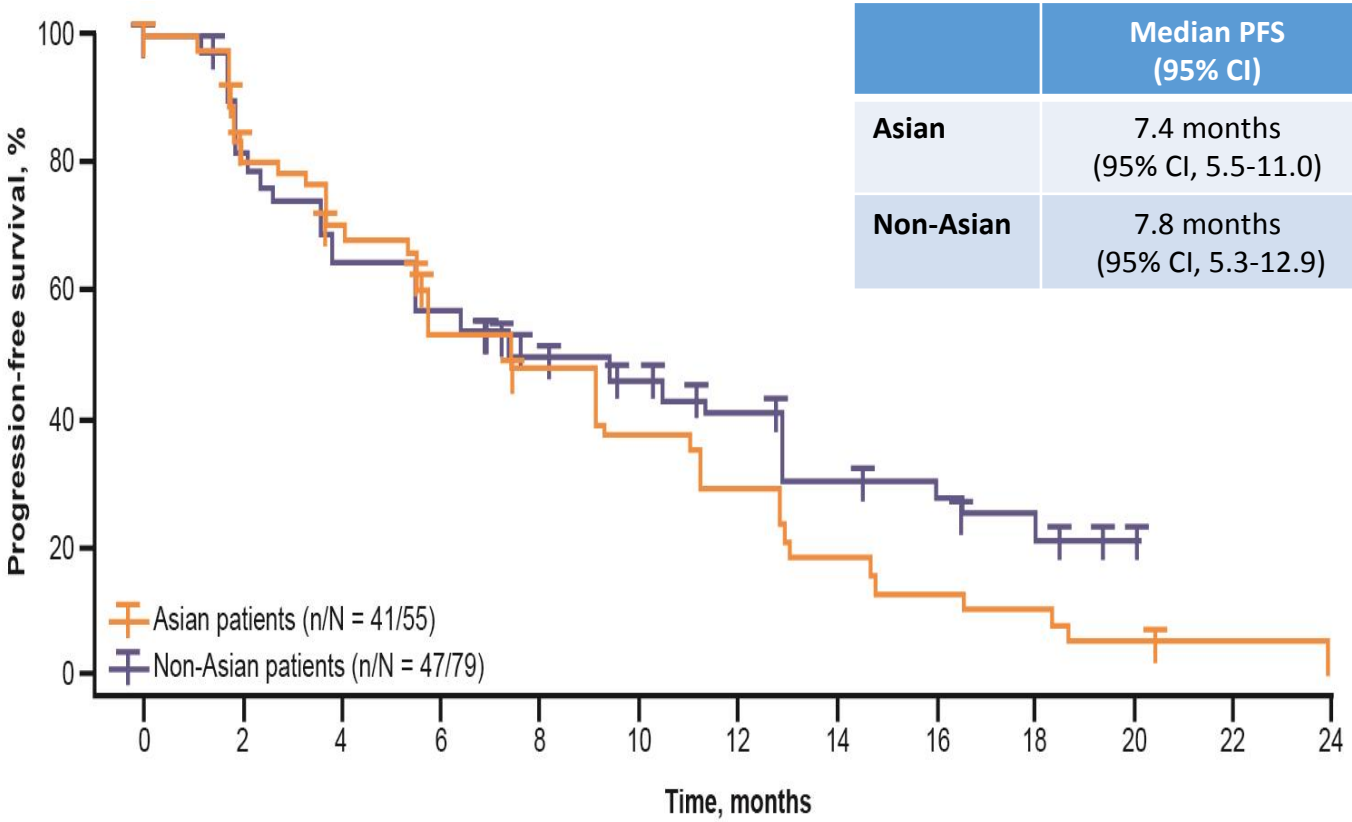
- Median duration of exposure: Asian vs non-Asian = 5.5 months vs 6.0 months

	Overall Population (N = 134)	
	Asian (n = 55)	Non-Asian (n = 79)
Age, median (range), years	55 (18-78)	60 (23-79)
< 65 y, n (%)	47 (85)	58 (73)
Sex, n (%)		
Men	40 (73)	51 (65)
Women	15 (27)	28 (35)
MSKCC prognosis,[a] n (%)		
Favorable	40 (73)	30 (38)
Intermediate	14 (25)	36 (46)
Poor	1 (2)	13 (17)
Median time since RCC diagnosis , months	25.1	41.4
Median duration of exposure, months	5.5	6.0

[a] Patients in the favorable group had no risk factors, pts in the intermediate group had 1 risk factor, and pts in the poor group had 2 or 3 risk factors.

PFS in Asian and Non-Asian populations

	Median PFS (95% CI)
Asian	7.4 months (95% CI, 5.5-11.0)
Non-Asian	7.8 months (95% CI, 5.3-12.9)



Number of patients still at risk

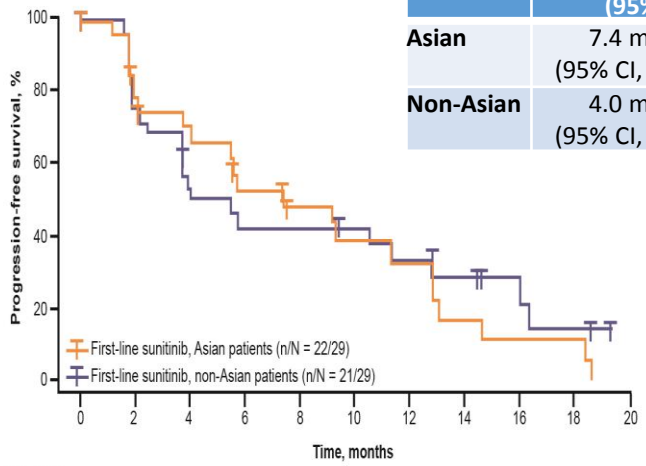
Asian patients	55	41	31	22	18	14	11	7	5	4	2	1	0
Non-Asian patients	79	61	46	37	27	21	17	12	9	7	2	0	0

CI, confidence interval; PFS, progression-free survival

PFS by First-Line Cohorts

PFS by First-Line Sunitinib

	Median PFS (95% CI)
Asian	7.4 months (95% CI, 3.7-12.8)
Non-Asian	4.0 months (95% CI, 2.5-12.9)

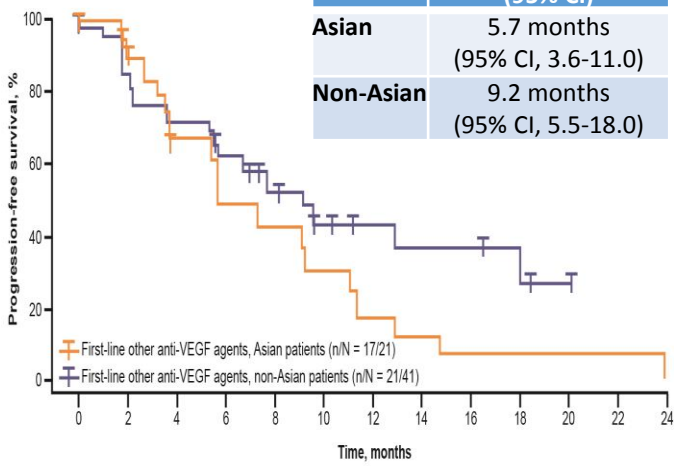


Number of patients still at risk

First-line sunitinib, Asian patients	29	20	17	12	9	7	6	3	2	2	0
First-line sunitinib, non-Asian patients	29	21	13	11	11	10	8	6	3	2	0

PFS by First-Line Other anti-VEGF Agents

	Median PFS (95% CI)
Asian	5.7 months (95% CI, 3.6-11.0)
Non-Asian	9.2 months (95% CI, 5.5-18.0)



Number of patients still at risk

First-line other anti-VEGF agents, Asian	21	17	11	8	7	5	3	2	1	1	1	0
First-line other anti-VEGF agents, non-Asian	41	32	26	21	13	8	6	5	5	4	2	0	0

CI, confidence interval; PFS, progression-free survival; VEGF, vascular endothelial growth factor

Best Response by RECIST 1.0 (Local Review)

	Overall Population		Prior Therapy					
			Sunitinib		Other anti-VEGF Agents		Cytokines	
	Asian (n = 55)	Non-Asian (n = 79)	Asian (n = 29)	Non-Asian (n = 29)	Asian (n = 21)	Non-Asian (n = 41)	Asian (n = 5)	Non-Asian (n = 9)
Best overall response, n (%)								
Partial response	6 (11)	4 (5)	2 (7)	2 (7)	3 (14)	0 (0)	1 (20)	2 (22)
Stable disease	35 (64)	55 (70)	19 (66)	18 (62)	13 (62)	32 (78)	3 (60)	5 (56)
Progressive disease	9 (16)	13 (17)	6 (21)	9 (31)	2 (10)	4 (10)	1 (20)	0 (0)
Unknown	5 (9)	6 (8)	2 (7)	0 (0)	3 (14)	4 (10)	0 (0)	2 (22)
Missing	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)
ORR,[a] n (%) [95% CI]	6 (11) [4-22]	4 (5) [1-13]	2 (7) [1-23]	2 (7) [1-23]	3 (14) [3-36]	0 (0) [0-9]	1 (20) [1-72]	2 (22) [3-60]
CBR,[b] n (%) [95% CI]	41 (75) [61-85]	59 (75) [64-84]	21 (72) [53-87]	20 (69) [49-85]	16 (76) [53-92]	32 (78) [62-89]	4 (80) [28-100]	7 (78) [40-97]

[a] ORR, complete response + partial response.
[b] CBR, complete response + partial response + stable disease.

CBR, clinical benefit rate; CI, confidence interval; ORR, objective response rate; Pts, patients; RECIST, response evaluation criteria in solid tumors; VEGF, vascular endothelial growth factor

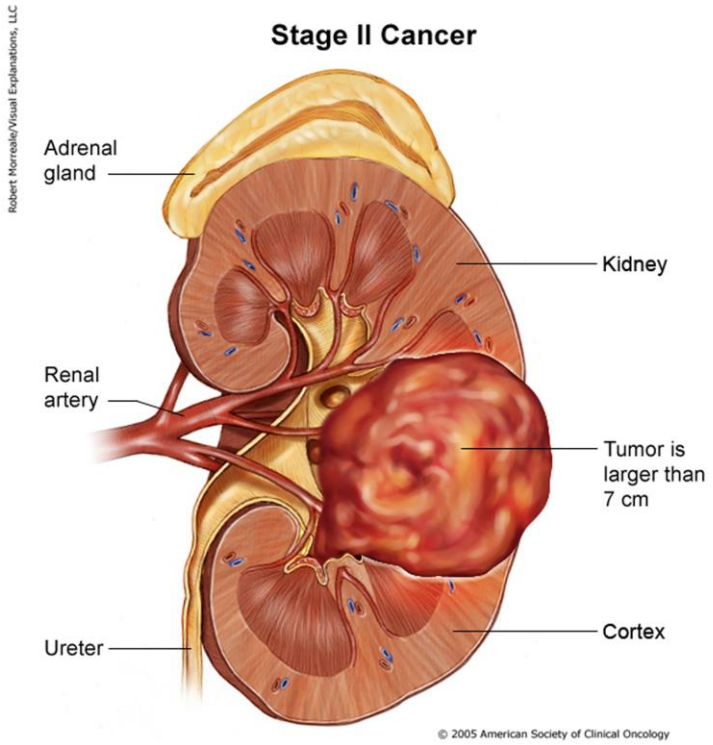
Adverse Event Profile

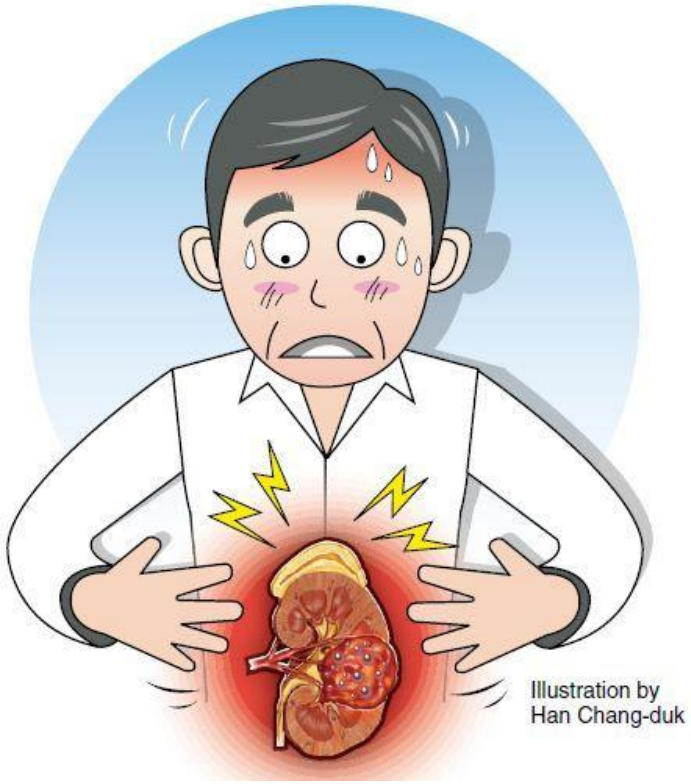
	Overall Population	
	Asian (n = 55)	**Non-Asian (n = 78)***
Overall rate of AEs, n (%)	44 (80)	58 (74)
Overall rate of grade 3 and 4 AEs, n (%)	32 (58)	42 (54)
Dose adjustment or study drug interruption to manage AEs , n (%)	22 (40)	35 (45)
Treatment discontinuation because of AEs, n (%)	11 (20)	13 (17)
On-treatment deaths, n (%)	6 (11)	7 (9)
Cause of on-treatment death	Disease progression (n = 3) Respiratory failure (n = 2) Multiorgan failure (n = 1)	Multiorgan failure (n = 2) Cardiopulmonary failure (n = 1) Disease progression (n = 1) Sepsis (n = 1) Sudden death (n = 1) Unknown cause (n = 1)

*One patient died before treatment initiation and was excluded from the safety analysis

AEs, adverse events; Pts, patients

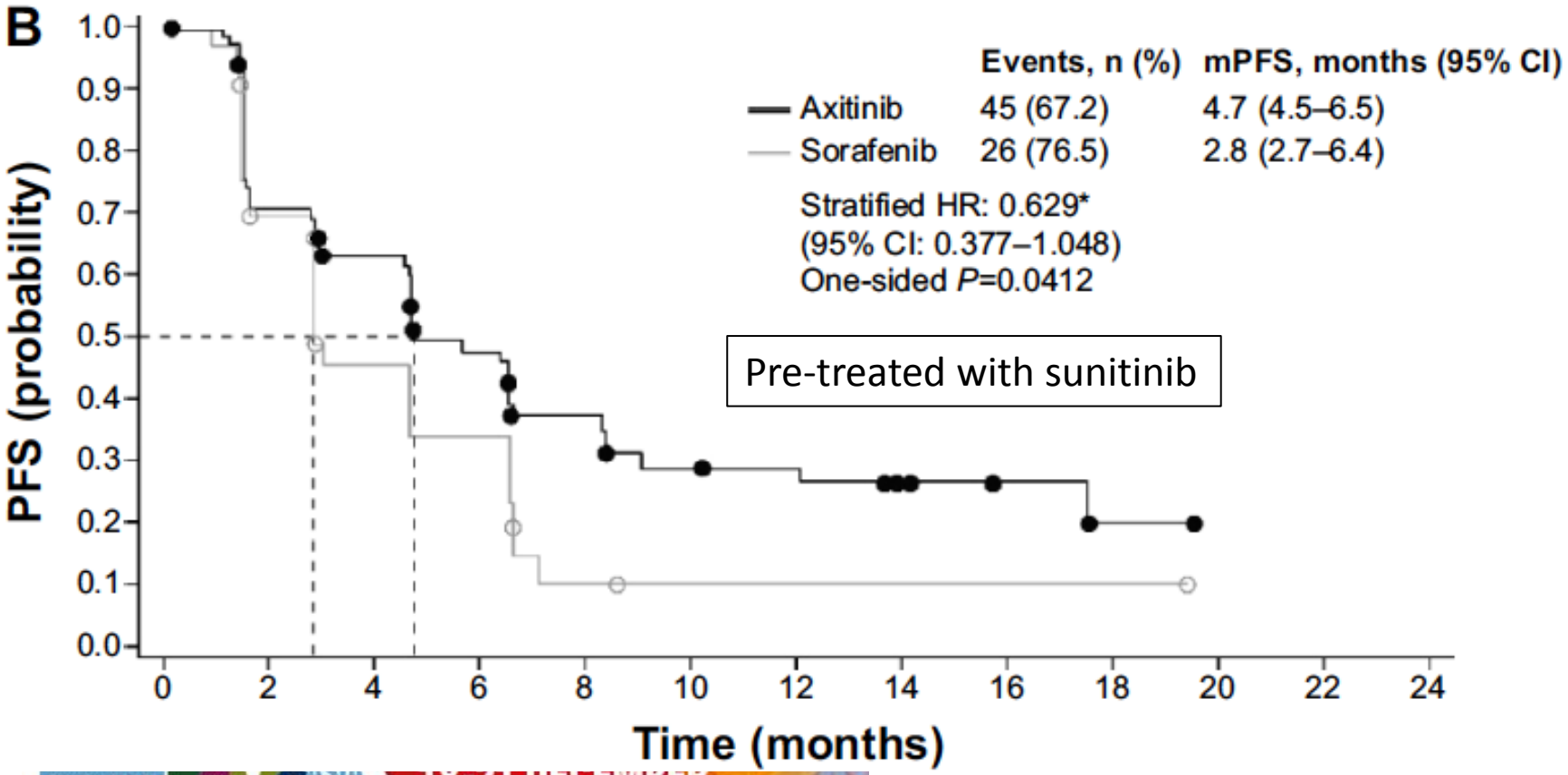
Other studies in second line therapy
Renal Cell Cancer





Axitinib versus sorafenib as a second-line therapy in Asian patients with renal Cell carcinoma: results from a randomized registrational study.

Shukui Qin et al, OncoTargets and Therapy 2015;8:1363-1373



Axitinib versus sorafenib as a second-line therapy in Asian patients with renal Cell carcinoma: results from a randomized registrational study.

Shukui Qin et al, OncoTargets and Therapy 2015;8:1363-1373

Table 2 Masked IRC-assessed best objective response rate

	Axitinib (n=135)	Sorafenib (n=69)
Overall ORR, % (95% CI)	23.7 (16.8–31.8)	10.1 (4.2–19.8)
Risk ratio (95% CI)	2.339 (1.094–5.002)	
P[a]	0.009	
Best observed response, n (%)[b]		
Complete response	0	0
Partial response	32 (23.7)	7 (10.1)
Stable disease		
≥20 weeks	34 (25.2)	19 (27.5)
<20 weeks	30 (22.2)	15 (21.7)
Progressive disease	24 (17.8)	16 (23.2)
Not assessed	5 (3.7)	4 (5.8)
Indeterminate	2 (1.5)	1 (1.4)

Axitinib versus sorafenib as a second-line therapy in Asian patients with renal Cell carcinoma: results from a randomized registrational study.

Shukui Qin et al, OncoTargets and Therapy 2015;8:1363-1373

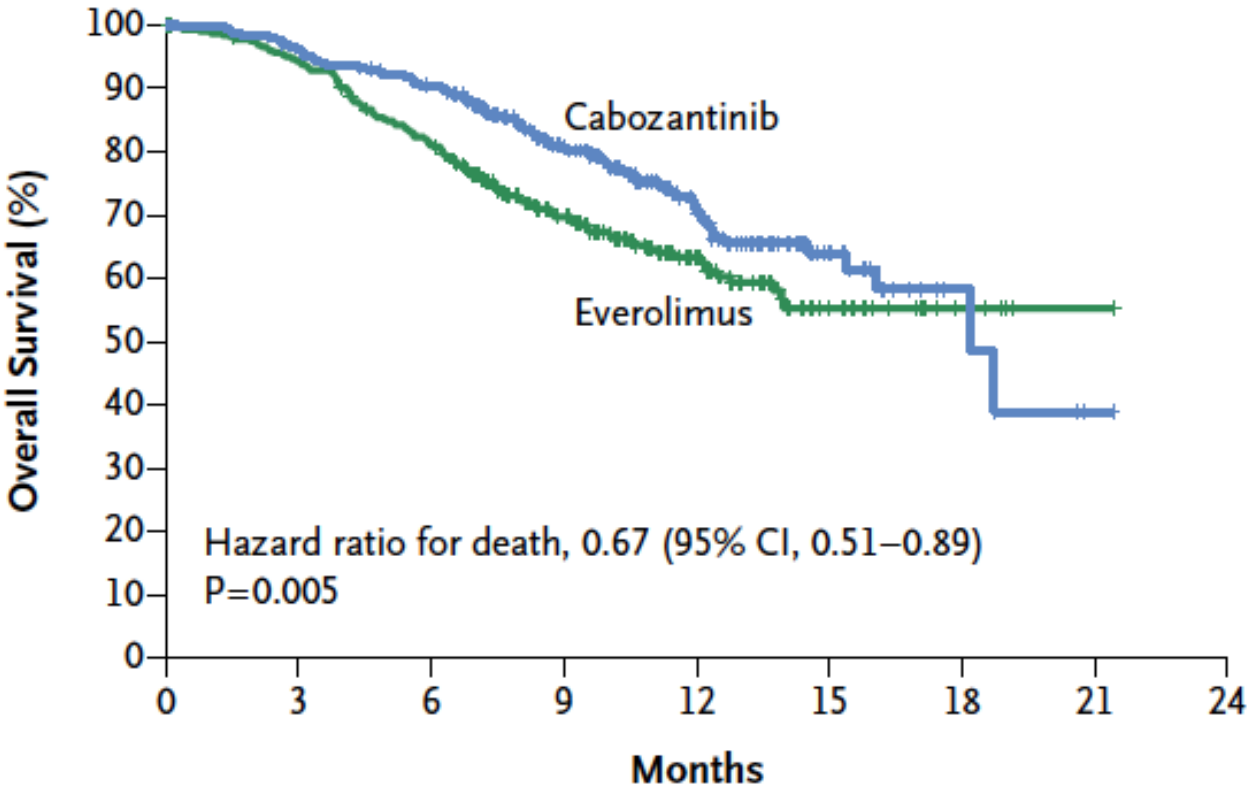
Rini BI, Escudier B, Tomczak P, et al. Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial. *Lancet*. 2011;378(9807):1931–1939.

Ueda T, Uemura H, Tomita Y, et al. Efficacy and safety of axitinib versus sorafenib in metastatic renal cell carcinoma: subgroup analysis of Japanese patients from the global randomized phase 3 AXIS trial. *Jpn J Clin Oncol*. 2013;43(6):616–628.

Cabozantinib versus Everolimus in Advanced Renal-Cell Carcinoma

T.K. Choueiri, B. Escudier, T. Powles, P.N. Mainwaring, B.I. Rini, F. Donskov, H. Hammers, T.E. Hutson, J.-L. Lee, K. Peltola, B.J. Roth, G.A. Bjarnason, L. Géczi, B. Keam, P. Maroto, D.Y.C. Heng, M. Schmidinger, P.W. Kantoff, A. Borgman-Hagey, C. Hessel, C. Scheffold, G.M. Schwab, N.M. Tannir, and R.J. Motzer, for the METEOR Investigators*

N Engl J Med 2015;373:1814-23.



No. at Risk									
Cabozantinib	330	317	294	189	101	32	6	1	0
Everolimus	328	306	260	156	88	24	5	1	0

Figure 3. Kaplan–Meier Estimates of Overall Survival.

N Engl J Med 2015;373:1814-23.

Cabozantinib versus Everolimus in Advanced Renal Cell Carcinoma
Adverse Events

Table 2. Adverse Events.*

Event	Cabozantinib (N=331)		Everolimus (N=322)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients with an event (percent)			
Any adverse event	331 (100)	226 (68)	321 (>99)	187 (58)
Diarrhea	245 (74)	38 (11)	88 (27)	7 (2)
Fatigue	186 (56)	30 (9)	148 (46)	22 (7)
Nausea	165 (50)	13 (4)	90 (28)	1 (<1)
Decreased appetite	152 (46)	8 (2)	108 (34)	3 (<1)

N Engl J Med 2015;373:1814-23.

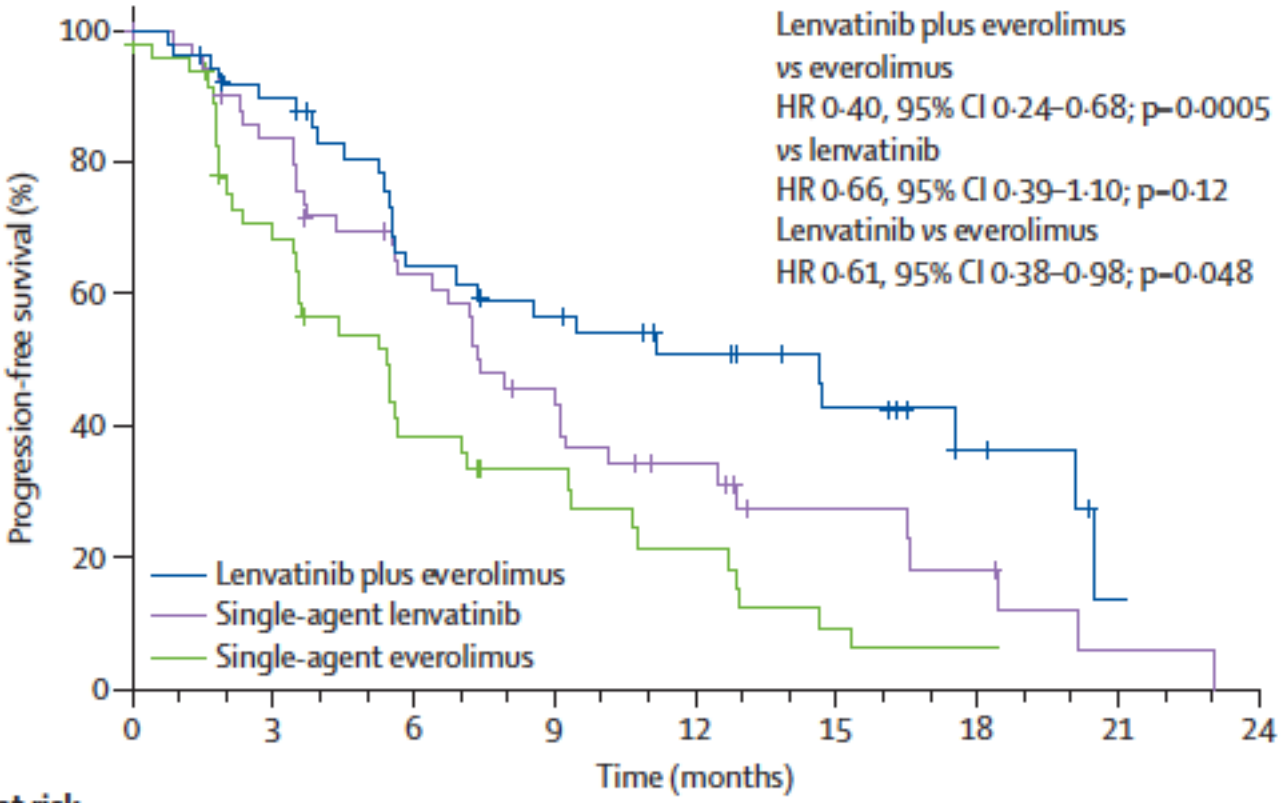
Lenvatinib, everolimus, and the combination in patients with metastatic renal cell carcinoma: a randomised, phase 2, open-label, multicentre trial

Robert J Motzer, Thomas E Hutson, Hilary Glen, M Dror Michaelson, Ana Molina, Timothy Eisen, Jacek Jassem, Jakub Zolnierek, Jose Pablo Maroto, Begoña Mellado, Bohuslav Melichar, Jiri Tomasek, Alton Kremer, Han-Joo Kim, Karen Wood, Corina Dutcus, James Larkin

Lenvatinib is another oral multitarget tyrosine kinase inhibitor

Lancet Oncol 2015; 16: 1473–82

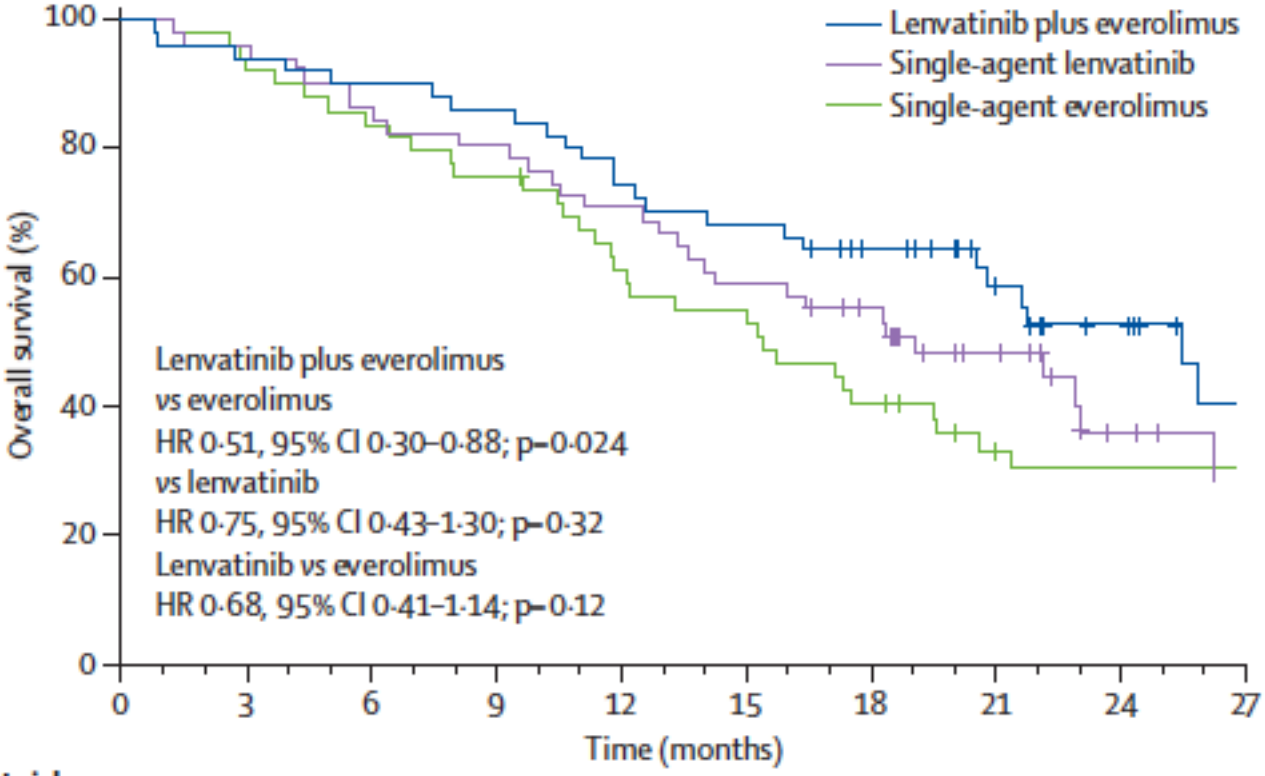
Lenvatinib, everolimus, and the combination in patients with metastatic renal cell carcinoma: a randomised, phase 2, open-label, multicentre trial



Number at risk									
Lenvatinib plus everolimus	51	41	27	23	16	10	5	1	0
Single-agent lenvatinib	52	41	29	20	11	6	4	1	0
Single-agent everolimus	50	29	15	11	7	3	1	0	0

Lancet Oncol 2015; 16: 1473–82

Lenvatinib, everolimus, and the combination in patients with metastatic renal cell carcinoma: a randomised, phase 2, open-label, multicentre trial



Number at risk										
Lenvatinib plus everolimus	51	48	46	44	38	35	29	21	14	6
Single-agent lenvatinib	52	50	45	42	37	31	26	16	7	4
Single-agent everolimus	50	46	42	38	30	27	20	14	8	2

Lancet Oncol 2015; 16: 1473–82

Lenvatinib, everolimus, and the combination in patients with metastatic renal cell carcinoma: a randomised, phase 2, open-label, multicentre trial

	Lenvatinib plus everolimus (n=51)	Single-agent lenvatinib (n=52)	Single-agent everolimus (n=50)
(Continued from previous page)			
Duration of previous VEGF-targeted therapy (months)	9·8 (2·0–66·2)	14·5 (0·7–81·8)	8·9 (1·6–57·8)
Best response for previous VEGF-targeted therapy			
Complete response	1 (2%)	0	0
Partial response	14 (28%)	10 (19%)	10 (20%)
Stable disease	20 (39%)	28 (54%)	21 (42%)
Progressive disease	7 (14%)	10 (19%)	15 (30%)
Not evaluated or unknown	9 (18%)	4 (8%)	4 (8%)
Previous checkpoint inhibitor therapy	1 (2%)	2 (4%)	2 (4%)
Previous interferon therapy	4 (8%)	3 (6%)	7 (14%)
Previous radiotherapy	6 (12%)	11 (21%)	11 (22%)

Data are number of patients (%), or median (range). ECOG=Eastern Cooperative Oncology Group. MSKCC=Memorial Sloan Kettering Cancer Center. *One patient in the lenvatinib plus everolimus group was excluded because of missing baseline laboratory values. †One patient in the lenvatinib group had two nephrectomy procedures (partial and left radical) but was only counted once. ‡All patients had one previous VEGF-targeted therapy.

Table 1: **Baseline characteristics**

Lancet Oncol 2015; 16: 1473–82

Lenvatinib, everolimus, and the combination in patients with metastatic renal cell carcinoma: a randomised, phase 2, open-label, multicentre trial

	Lenvatinib plus everolimus (n=51)			Lenvatinib (n=52)			Everolimus (n=50)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Any TEAE	14 (28%)	29 (57%)	7 (14%)	8 (15%)	38 (73%)	3 (6%)	23 (46%)	21 (42%)	4 (8%)
Diarrhoea	33 (65%)	10 (20%)	0	31 (60%)	6 (12%)	0	16 (32%)	1 (2%)	0
Decreased appetite	23 (45%)	3 (6%)	0	28 (54%)	2 (4%)	0	9 (18%)	0	0
Fatigue or asthenia	23 (45%)	7 (14%)	0	22 (42%)	4 (8%)	0	18 (36%)	0	1 (2%)
Vomiting	19 (37%)	3 (8%)	0	18 (35%)	2 (4%)	0	5 (10%)	0	0
Nausea	18 (35%)	3 (6%)	0	28 (54%)	4 (8%)	0	8 (16%)	0	0

Lancet Oncol 2015; 16: 1473–82

The NEW ENGLAND JOURNAL of MEDICINE

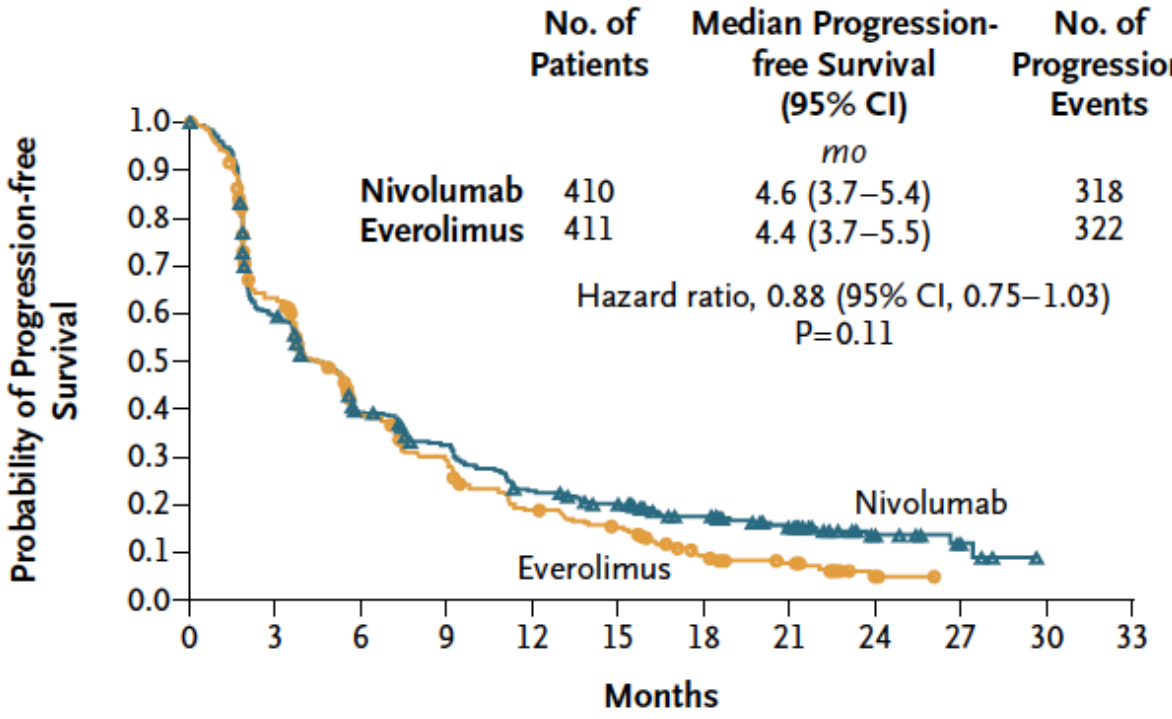
ESTABLISHED IN 1812 NOVEMBER 5, 2015 VOL. 373 NO. 19

Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma

R.J. Motzer, B. Escudier, D.F. McDermott, S. George, H.J. Hammers, S. Srinivas, S.S. Tykodi, J.A. Sosman, G. Procopio, E.R. Plimack, D. Castellano, T.K. Choueiri, H. Gurney, F. Donskov, P. Bono, J. Wagstaff, T.C. Gauler, T. Ueda, Y. Tomita, F.A. Schutz, C. Kollmannsberger, J. Larkin, A. Ravaud, J.S. Simon, L.-A. Xu, I.M. Waxman, and P. Sharma, for the CheckMate 025 Investigators*

Phase III Data
Immune Checkpoint Blockade Has Clinical Efficacy in RCC

B **Kaplan–Meier Curve for Progression-free Survival**

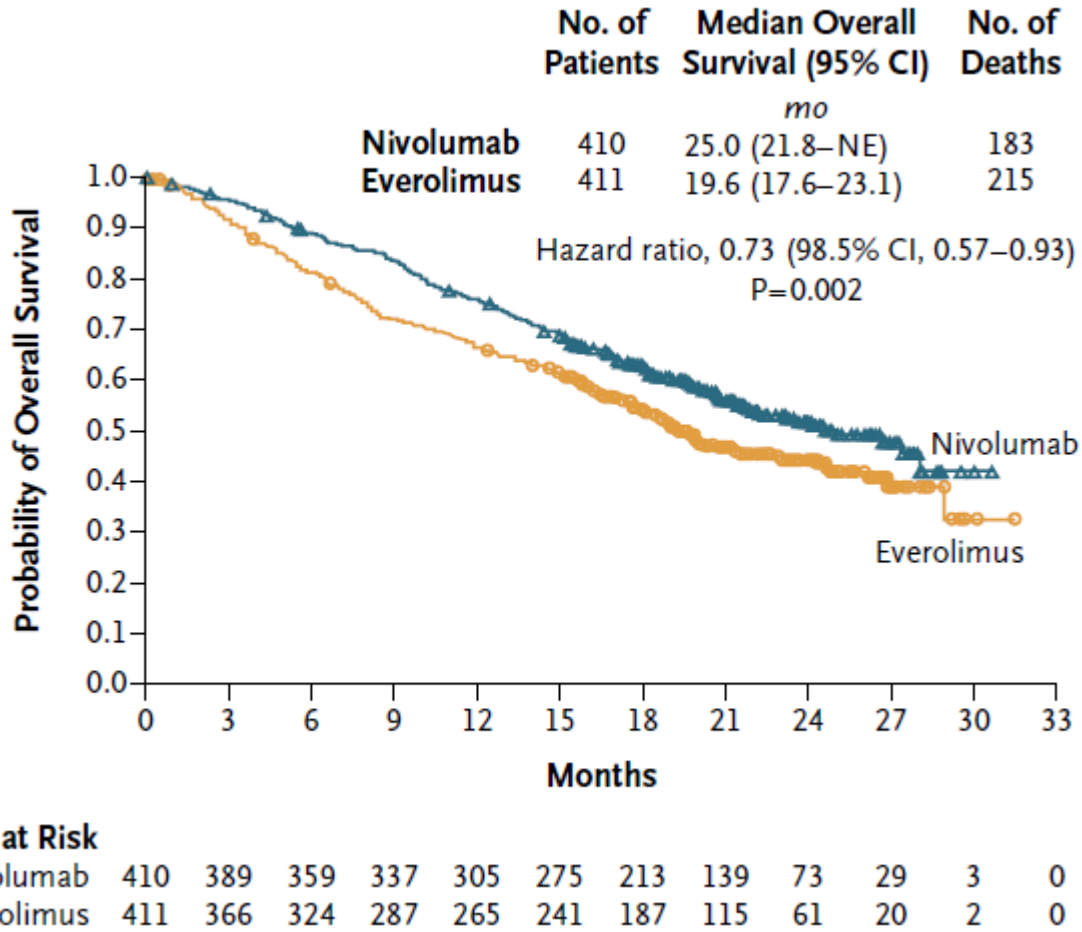


No. at Risk

Nivolumab	410	230	145	116	81	66	48	29	11	4	0	0
Everolimus	411	227	129	97	61	47	25	16	3	0	0	0

Motzer et al *NEJM* 2015

Phase III Data
Immune Checkpoint Blockade Has Clinical Efficacy in RCC

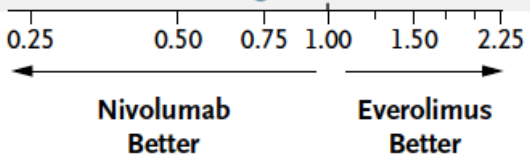


Motzer et al *NEJM* 2015

Phase III Data
Immune Checkpoint Blockade Has Clinical Efficacy in RCC

A Subgroup Analyses of Overall Survival

Subgroup	Nivolumab	Everolimus	Unstratified Hazard Ratio for Death (95% CI)
	no. of events/total no.		
Overall	183/410	215/411	0.76 (0.62–0.92)
MSKCC prognostic score			
Favorable	45/145	52/148	0.89 (0.59–1.32)
Intermediate	101/201	116/203	0.76 (0.58–0.99)
Poor	37/64	47/60	0.47 (0.30–0.73)
Previous antiangiogenic regimens			
1	128/294	158/297	0.71 (0.56–0.90)
2	55/116	57/114	0.89 (0.61–1.29)
Region			
United States or Canada	66/174	87/172	0.66 (0.48–0.91)
Western Europe	78/140	84/141	0.86 (0.63–1.16)
Rest of the world	39/96	44/98	0.78 (0.51–1.20)
Age			
<65 yr	111/257	118/240	0.78 (0.60–1.01)
≥65 to <75 yr	53/119	77/131	0.64 (0.45–0.91)
≥75 yr	19/34	20/40	1.23 (0.66–2.31)
Sex			
Female	48/95	56/107	0.84 (0.57–1.24)
Male	135/315	159/304	0.73 (0.58–0.92)



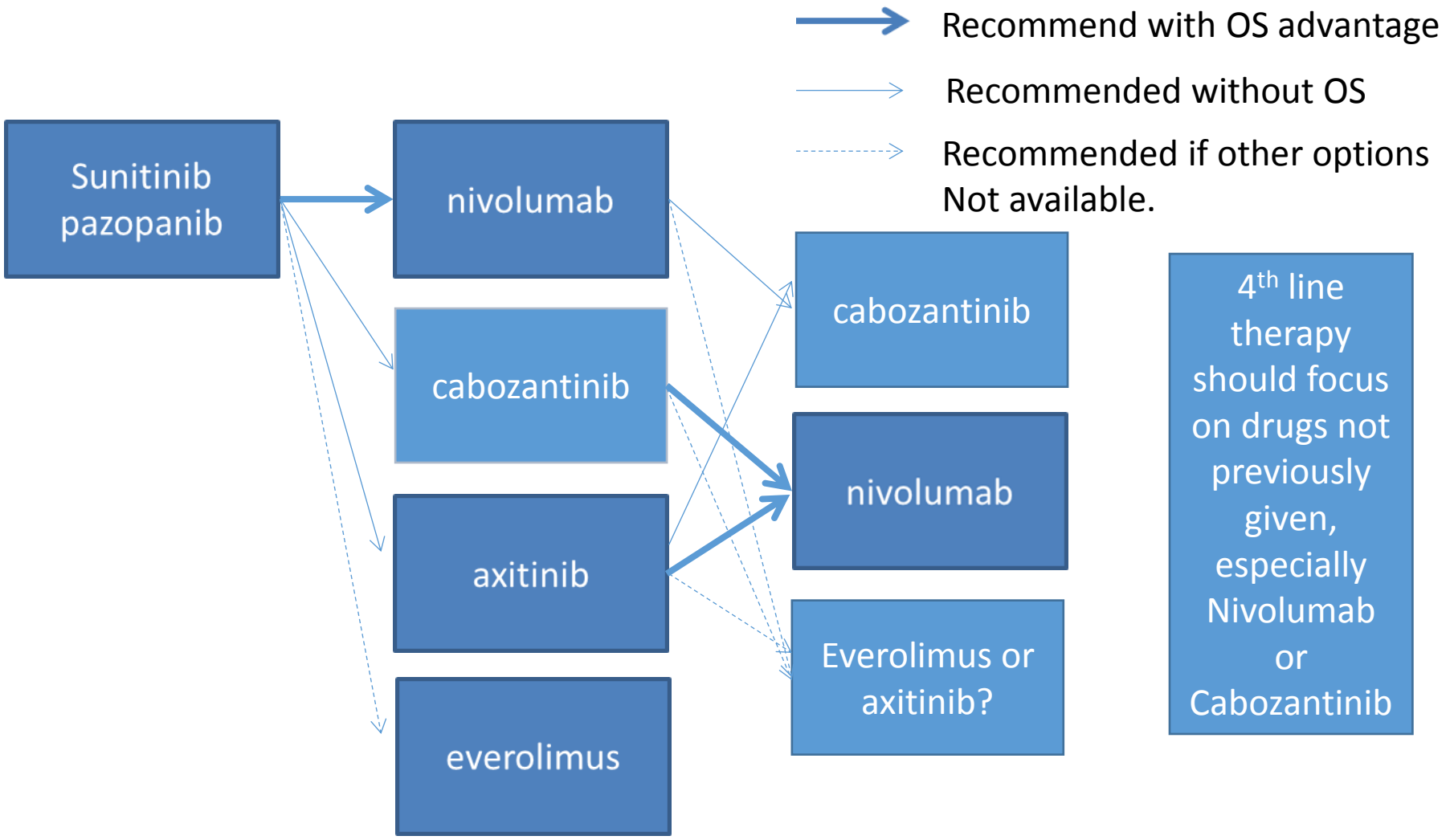
Motzer et al *NEJM* 2015

Phase III Data
Immune Checkpoint Blockade Has Clinical Efficacy in RCC

Table 2. Treatment-Related Adverse Events Reported in 10% or More of Treated Patients in Either Group.

Event	Nivolumab Group (N=406)		Everolimus Group (N=397)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients (percent)			
All events	319 (79)	76 (19)	349 (88)	145 (37)
Fatigue	134 (33)	10 (2)	134 (34)	11 (3)
Nausea	57 (14)	1 (<1)	66 (17)	3 (1)

Motzer et al *NEJM* 2015



Prof Tom Powles, ESMO 2015

Cost management