Treatment Beyond First Line:

Which is the best sequence in 2018?

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FDA approved second line therapies for RCC

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Agent	Target	Approval	Comparator	Following	Line of therapy	Endpoint
Everolimus	mTOR (mTORC1)	2009	Placebo	Sunitinib or sorafenib or both Previous bevacizumab, IL2 or IFNα permitted	2nd/3rd	PFS
Axitinib	VEGFR1-3, c-KIT, PDGFR	2012	Sorafenib	Sunitinib, bevacizumab/IFNα , temsirolimus, or cytokine	2nd	PFS
Cabozantinib	c-MET, VEGFR2, AXL, RET	2016	Everolimus	At least one VEGFR-targeting tyrosine kinase inhibitor	2nd/3rd	PFS, OS
Nivolumab	PD-1	2015	Everolimus	One or two previous regimens of antiangiogenic therapy	2nd/3rd	OS
Lenvatinib + everolimus	VEGFR1-3, FGFR1-4 PDGFRα, c-KIT, RET	2016	Lenvatinib or everolimus	One prior VEGF targeted therapy	2nd	PFS

Adapted and updated from Modi, Trans Cancer Res, 2016

RECORD-1

Metastatic RCC

Clear cell component

Prior sunitinib or sorafenib or both

Previous bevacizumab, IL2 or IFNα permitted

No prior mTOR inhibitor

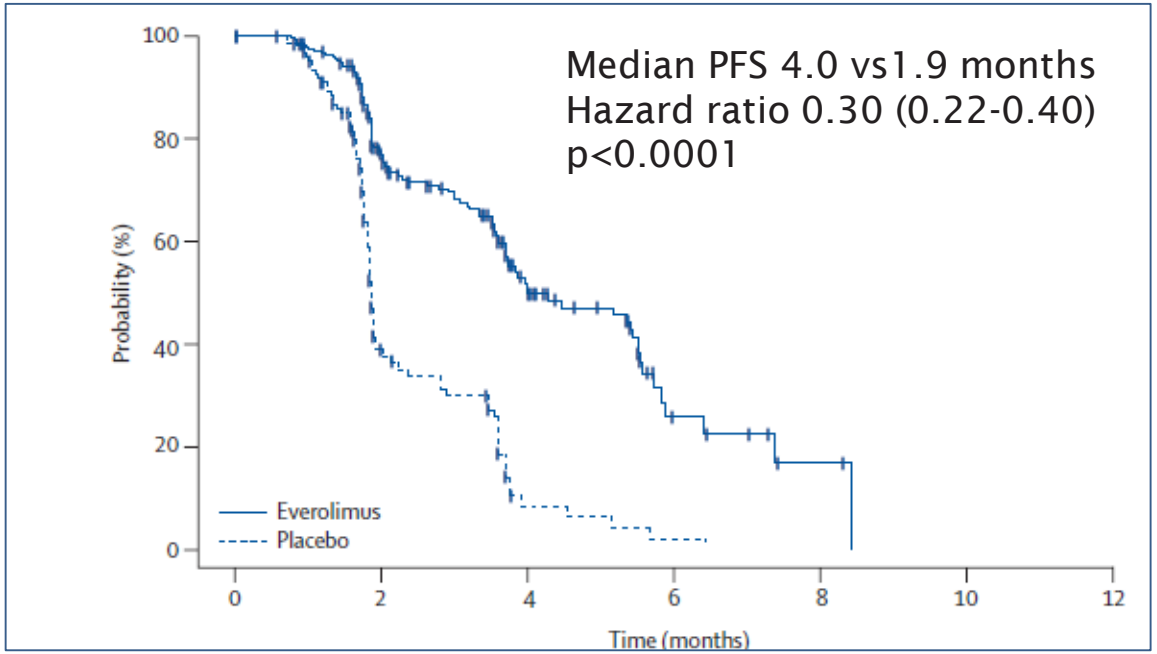
Karnofsky PS ≥ 70

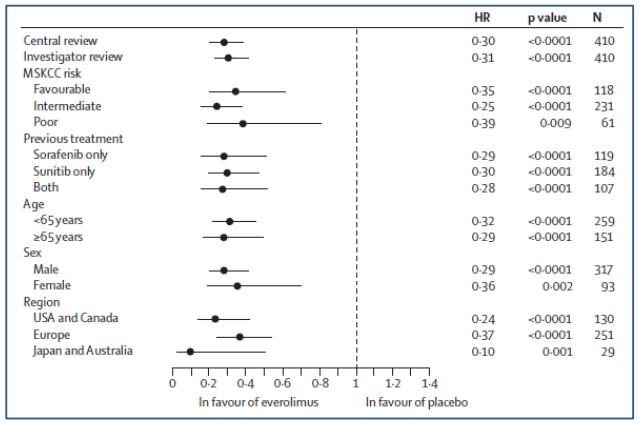
R

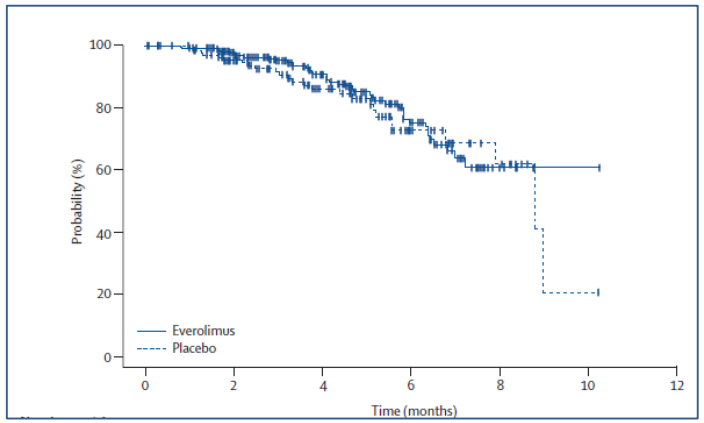
Everolimus 10mg PO daily (n=272)

Placebo (n=138)

Primary end point: progression free survival by blinded independent central review







Motzer, Lancet, 2008

AXIS primary endpoint

Metastatic RCC

Clear cell component

Prior sunitinib, bevacizumab/IFNα , temsirolimus, or cytokine

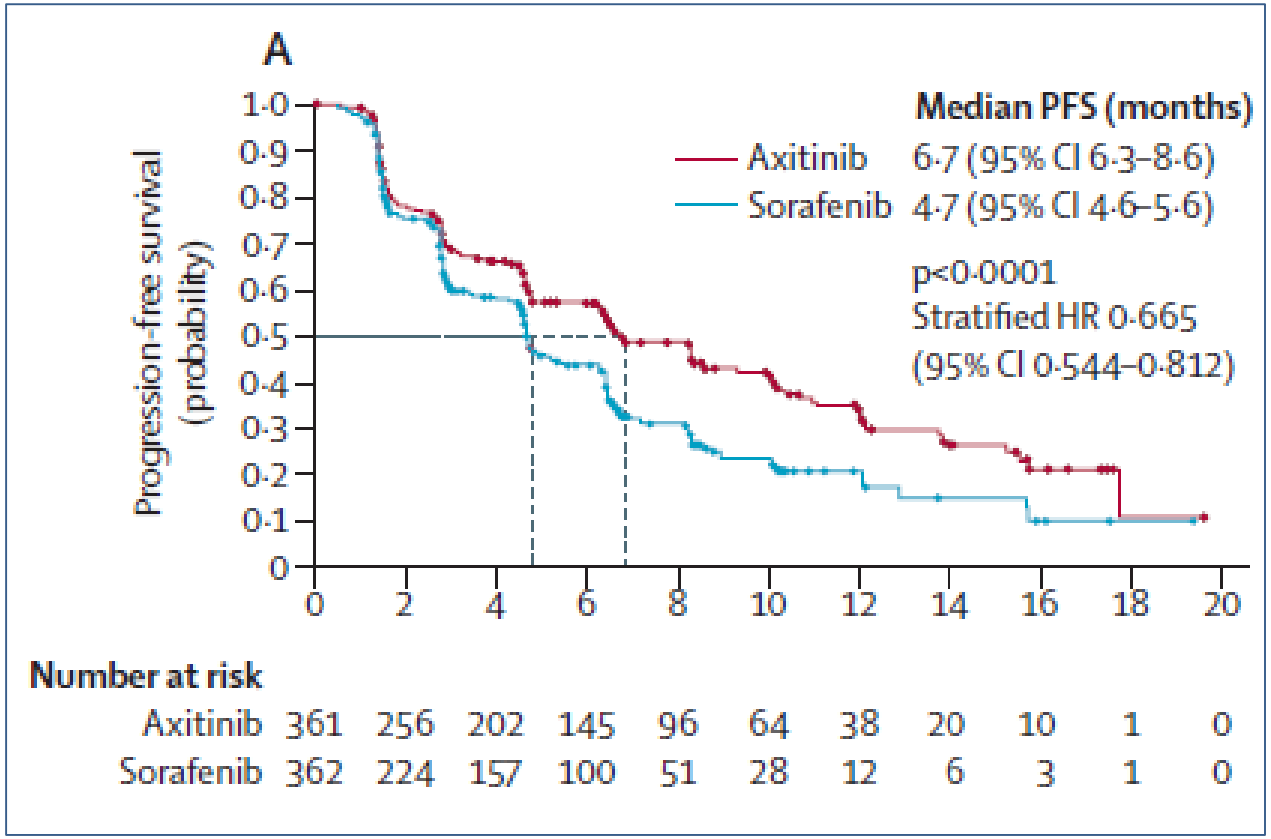
ECOG PS 0 or 1

R

Axitinib 5mg BID (n=361)

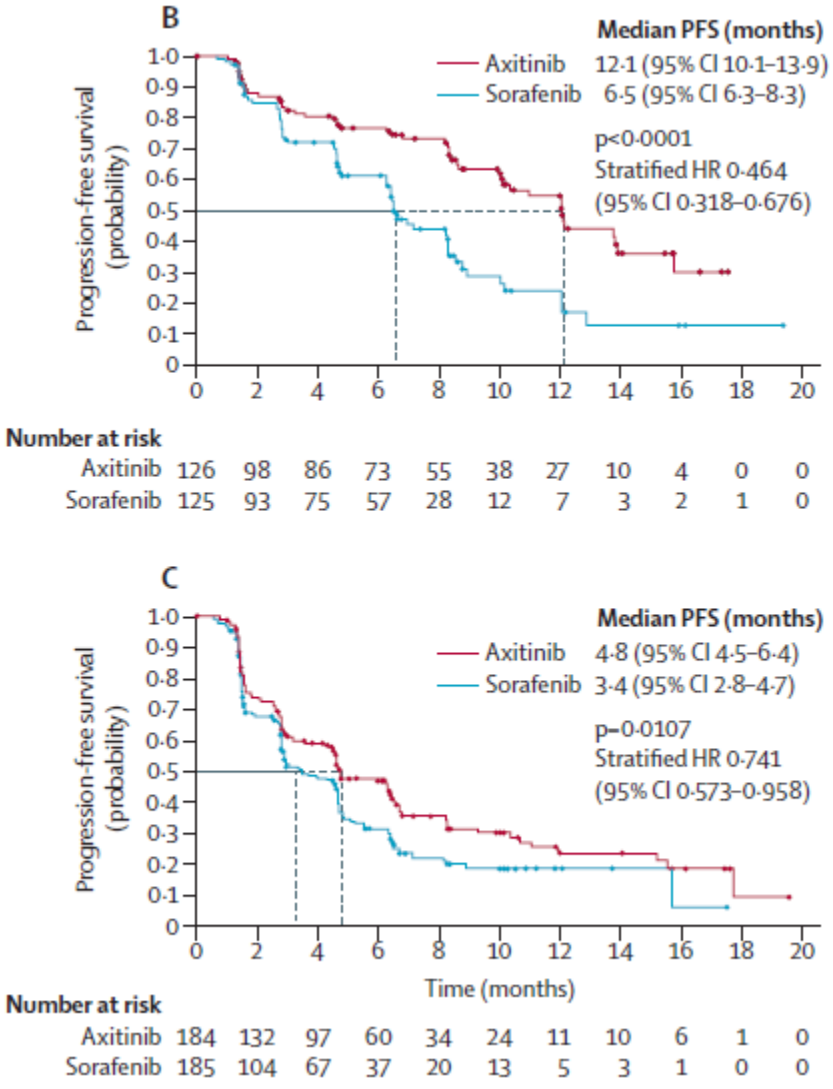
Everolimus 10mg OD (n=362)

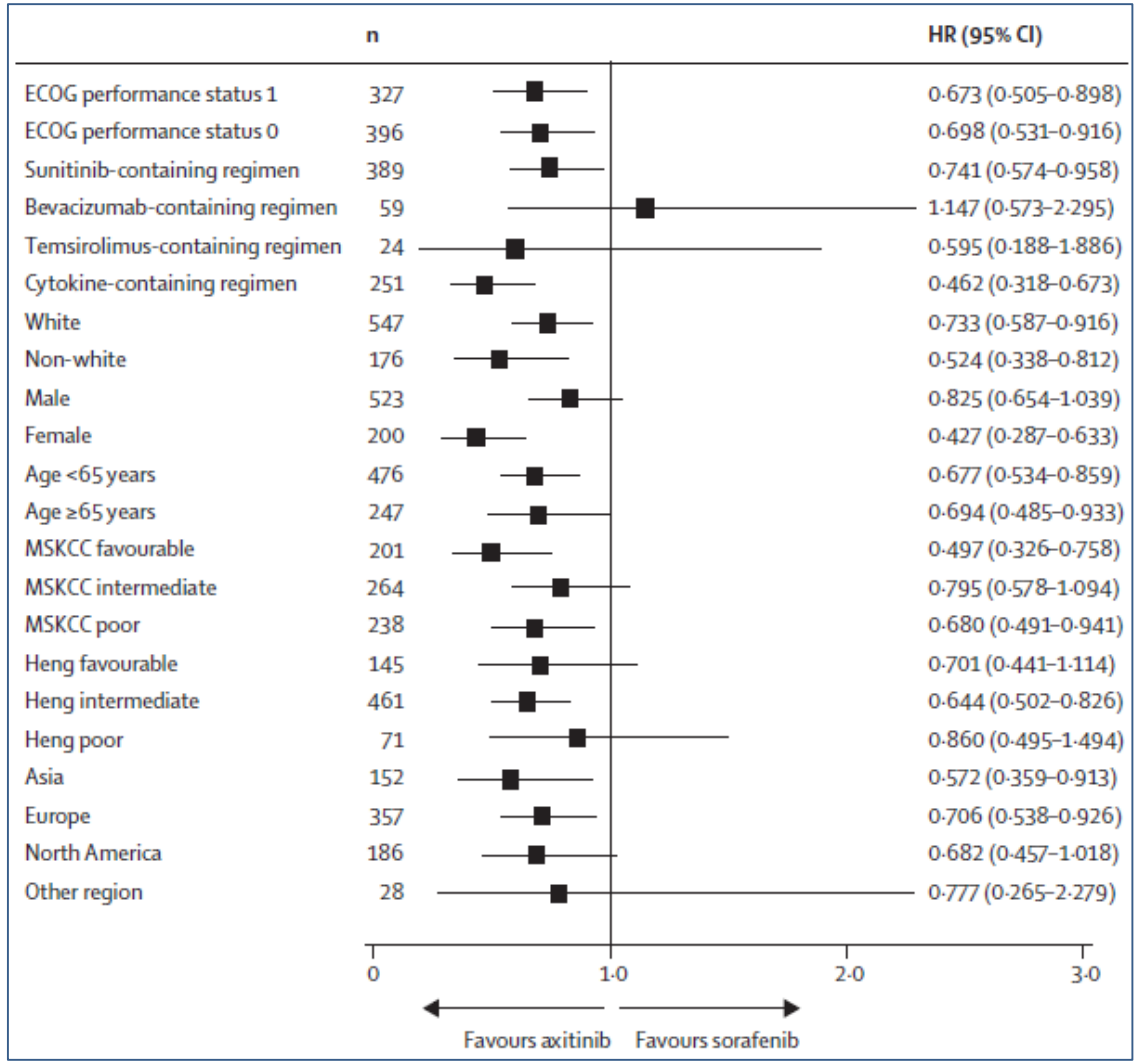
Primary end point: progression free survival by blinded independent central review



Rini, Lancet, 2011

AXIS secondary endpoints and subgroups





Rini, Lancet, 2011

METEOR primary endpoint

Advanced/metastatic RCC

Clear cell component

At least one prior VEGFR-TKI

No prior mTOR inhibitor or cabozantinib

Karnofsky PS ≥ 70

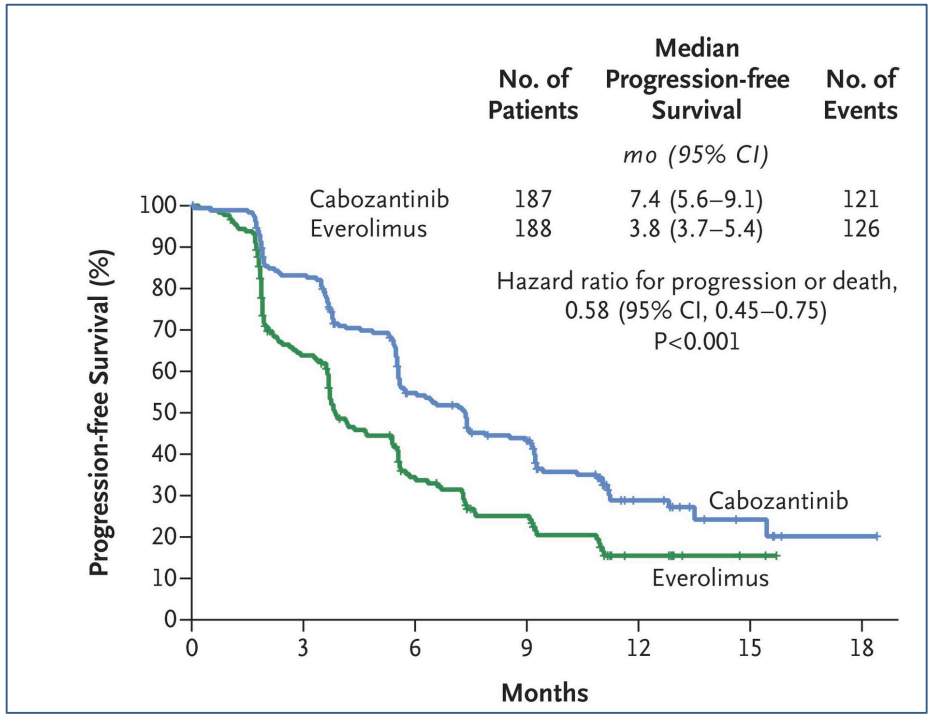
R

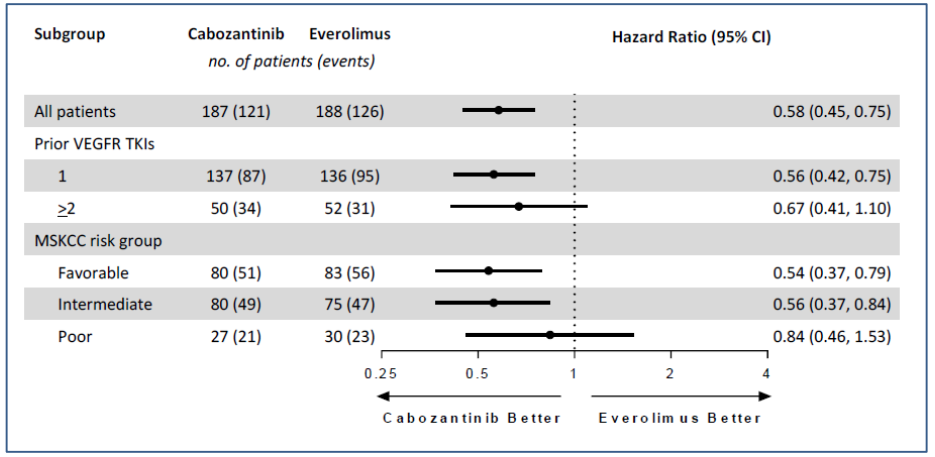
Cabozantinib 60mg PO daily (n=330)

Everolimus 10mg PO daily (n=328)

Primary end point: progression free survival by blinded independent central review

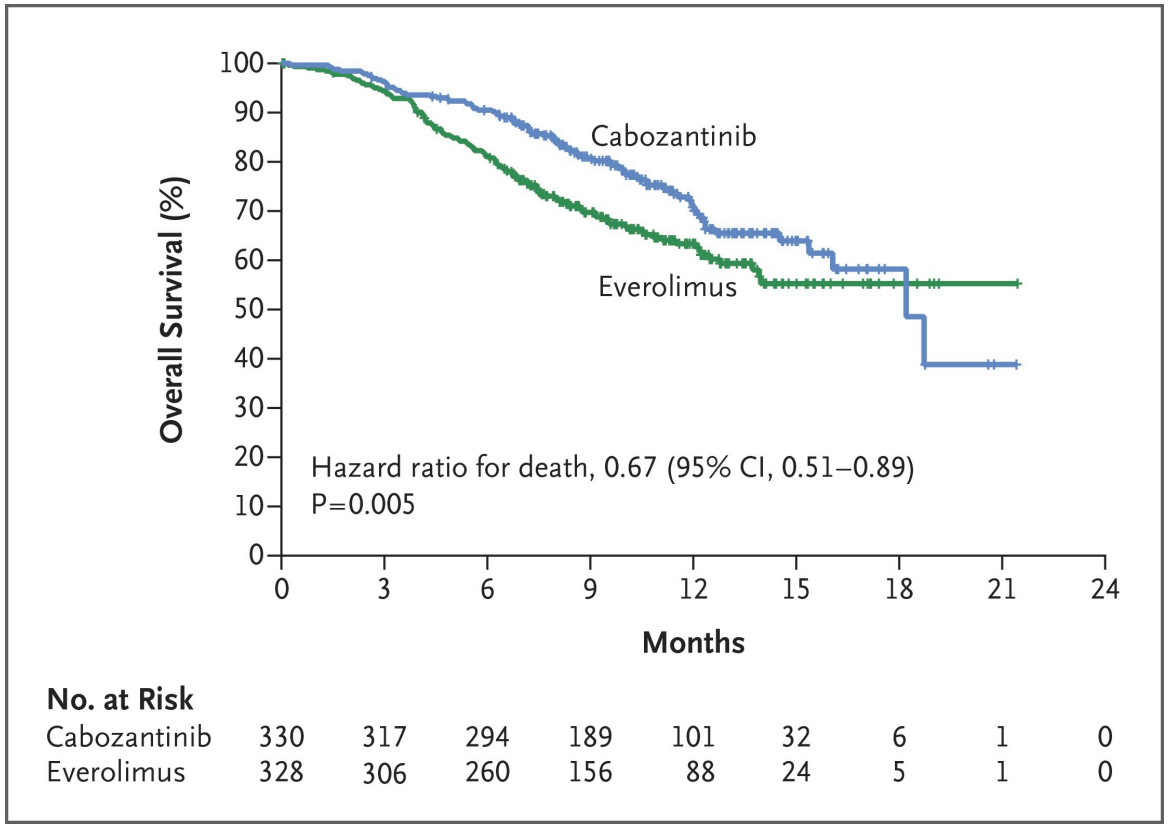
(5% had prior nivolumab)





Choueiri, N Engl J Med 2015

METEOR secondary endpoints



Updated survival analysis: 21.4 versus 16.5 months, p=0.0003, ASCO 2016

Choueiri et al, N Engl J Med 2015

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)
Palmar–plantar erythrodysesthesia syndrome	139 (42)	28 (8)	19 (6)	3 (<1)
Hypertension	122 (37)	49 (15)	23 (7)	10 (3)
Vomiting	106 (32)	7 (2)	45 (14)	3 (<1)
Weight decreased	102 (31)	6 (2)	40 (12)	0
Constipation	83 (25)	1 (<1)	60 (19)	1 (<1)
Dysgeusia	78 (24)	0	30 (9)	0
Stomatitis	73 (22)	8 (2)	77 (24)	7 (2)
Hypothyroidism	67 (20)	0	1 (<1)	0
Dysphonia	65 (20)	2 (<1)	12 (4)	0
Mucosal inflammation	63 (19)	3 (<1)	73 (23)	11 (3)
Asthenia	62 (19)	14 (4)	50 (16)	7 (2)
Dyspnea	62 (19)	10 (3)	90 (28)	13 (4)
Cough	61 (18)	1 (<1)	107 (33)	3 (<1)
Back pain	56 (17)	7 (2)	47 (15)	7 (2)
Abdominal pain	53 (16)	12 (4)	31 (10)	4 (1)
Rash	50 (15)	2 (<1)	89 (28)	2 (<1)
Pain in arms or legs	47 (14)	3 (<1)	26 (8)	1 (<1)
Muscle spasms	41 (12)	0	16 (5)	0
Dyspepsia	40 (12)	1 (<1)	15 (5)	0
Dry skin	37 (11)	0	32 (10)	0
Headache	37 (11)	1 (<1)	38 (12)	1 (<1)
Arthralgia	36 (11)	1 (<1)	45 (14)	4 (1)
Dizziness	36 (11)	0	21 (7)	0
Peripheral edema	31 (9)	0	72 (22)	5 (2)
Pyrexia	28 (8)	2 (<1)	51 (16)	1 (<1)
Pruritus	25 (8)	0	47 (15)	1 (<1)
Epistaxis	12 (4)	0	46 (14)	0
Pneumonitis	0	0	33 (10)	6 (2)
Laboratory abnormality				
Aspartate aminotransferase increased	58 (18)	6 (2)	18 (6)	1 (<1)

CheckMate 025 primary endpoint

Advanced/metastatic RCC

Clear cell component

Measurable disease

One or two previous antiangiogenic therapies

No prior mTOR inhibitor

Karnofsky PS ≥ 70

R

Nivolumab

3 mg/kg IV every 2 weeks*

(n=410)

Everolimus

10mg PO daily

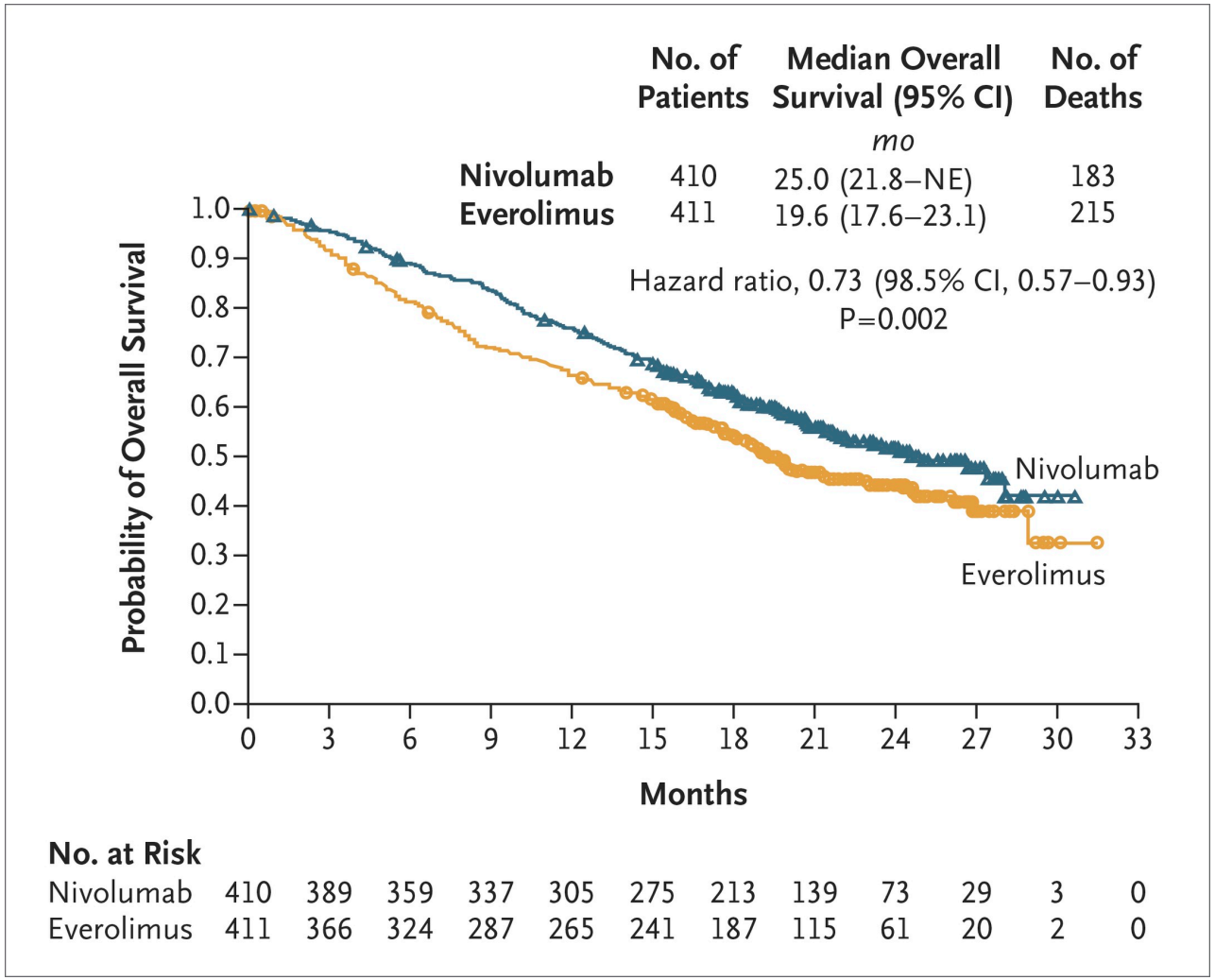
(n=411)

Primary end point: Overall survival

Secondary end points:
- ORR
- PFS
- Association between OS and tumour PD-L1 expression
- Adverse events

Stratification:
- Region, MSKCC prognostic risk group, number of previous regimens

* Nivolumab 480mg every 4 weeks now FDA and EMA approved



Motzer, N Engl J Med, 2015

CheckMate 025 secondary endpoints

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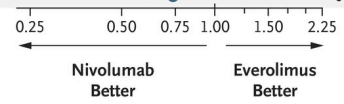
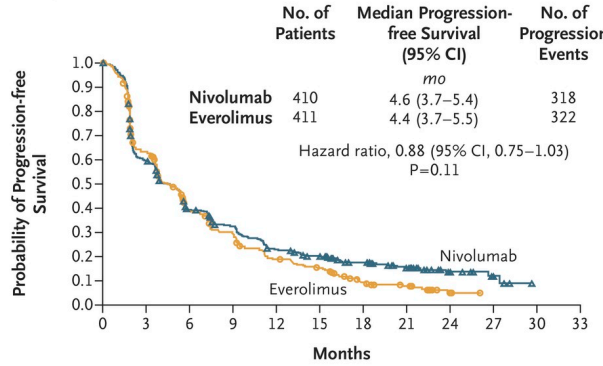
A Subgroup Analyses of Overall Survival

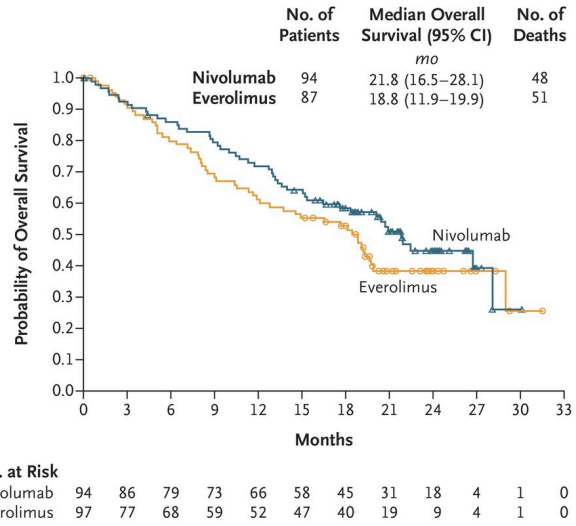
Subgroup	Nivolumab	Everolimus	Unstratified Hazard Ratio for Death (95% CI)
	no. of events/total no.		
Overall	183/410	215/411	0.76 (0.62–0.92)
MSKCC prognostic score			
Favorable	45/145	52/148	0.89 (0.59–1.32)
Intermediate	101/201	116/203	0.76 (0.58–0.99)
Poor	37/64	47/60	0.47 (0.30–0.73)
Previous antiangiogenic 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)



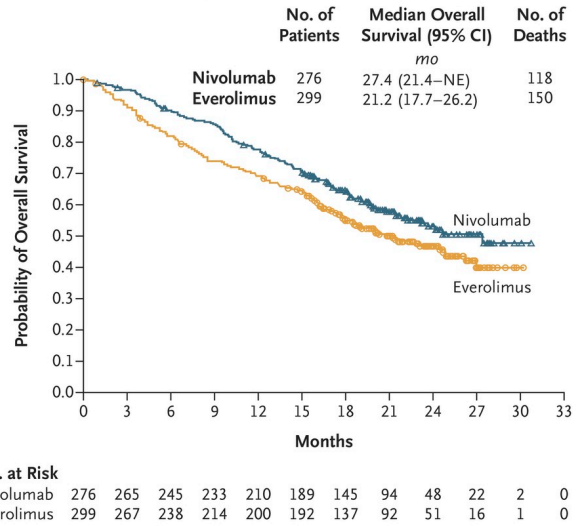
B Kaplan–Meier Curve for Progression-free Survival



A Patients with ≥1% PD-L1 Expression



B Patients with <1% PD-L1 Expression



ORR:

Nivolumab 25%
Everolimus 5%
p<0.001

CR rates 1% and <1%

Motzer, N Engl J Med, 2015

CheckMate 025 toxicity

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)
Pruritus	57 (14)	0	39 (10)	0
Diarrhea	50 (12)	5 (1)	84 (21)	5 (1)
Decreased appetite	48 (12)	2 (<1)	82 (21)	4 (1)
Rash	41 (10)	2 (<1)	79 (20)	3 (1)
Cough	36 (9)	0	77 (19)	0
Anemia	32 (8)	7 (2)	94 (24)	31 (8)
Dyspnea	30 (7)	3 (1)	51 (13)	2 (1)
Peripheral edema	17 (4)	0	56 (14)	2 (1)
Pneumonitis	16 (4)	6 (1)	58 (15)	11 (3)
Mucosal inflammation	11 (3)	0	75 (19)	12 (3)
Dysgeusia	11 (3)	0	51 (13)	0
Hyperglycemia	9 (2)	5 (1)	46 (12)	15 (4)
Stomatitis	8 (2)	0	117 (29)	17 (4)
Hypertriglyceridemia	5 (1)	0	64 (16)	20 (5)
Epistaxis	3 (1)	0	41 (10)	0

Safety profile consistent with other studies

Fewer grade 3+ treatment-related AEs (cf. cabozantinib)

Differences between arms reflective of drug class

Motzer, N Engl J Med, 2015

HOPE 205

Advanced/metastatic clear cell RCC

One prior VEGF targeted therapy

No prior mTOR inhibitor or lenvatinib

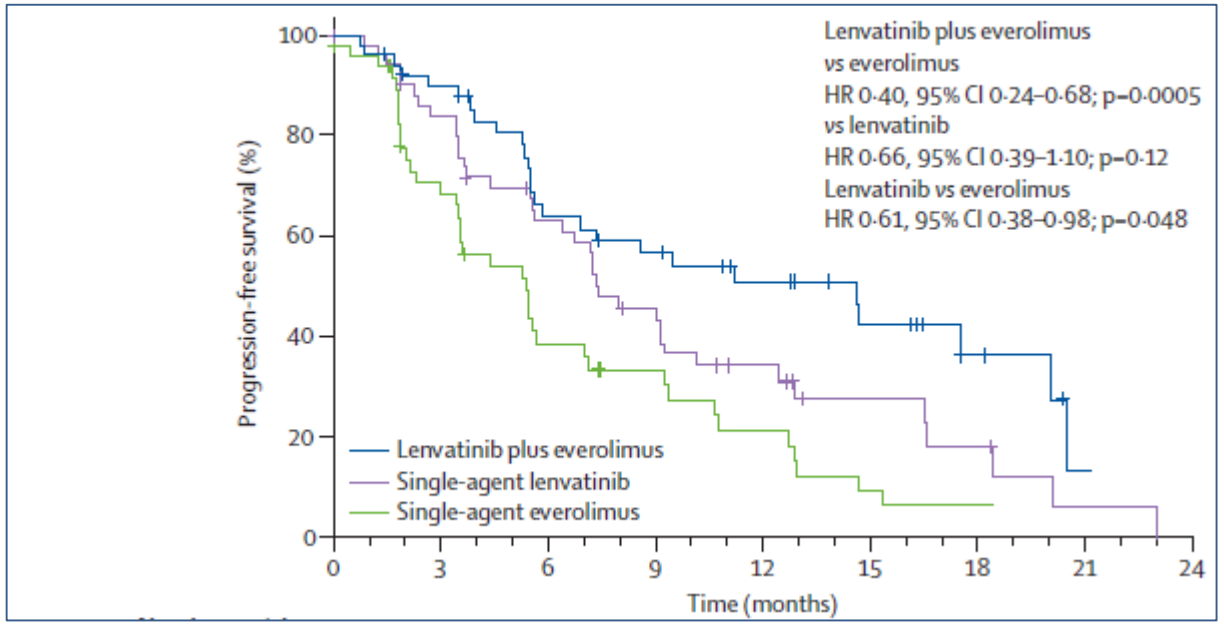
ECOG PS 0 or 1

R

Lenvatinib 18mg OD + Everolimus 10mg OD (n=51)

Lenvatinib 18mg OD (n=52)

Everolimus 10mg OD (n=50)



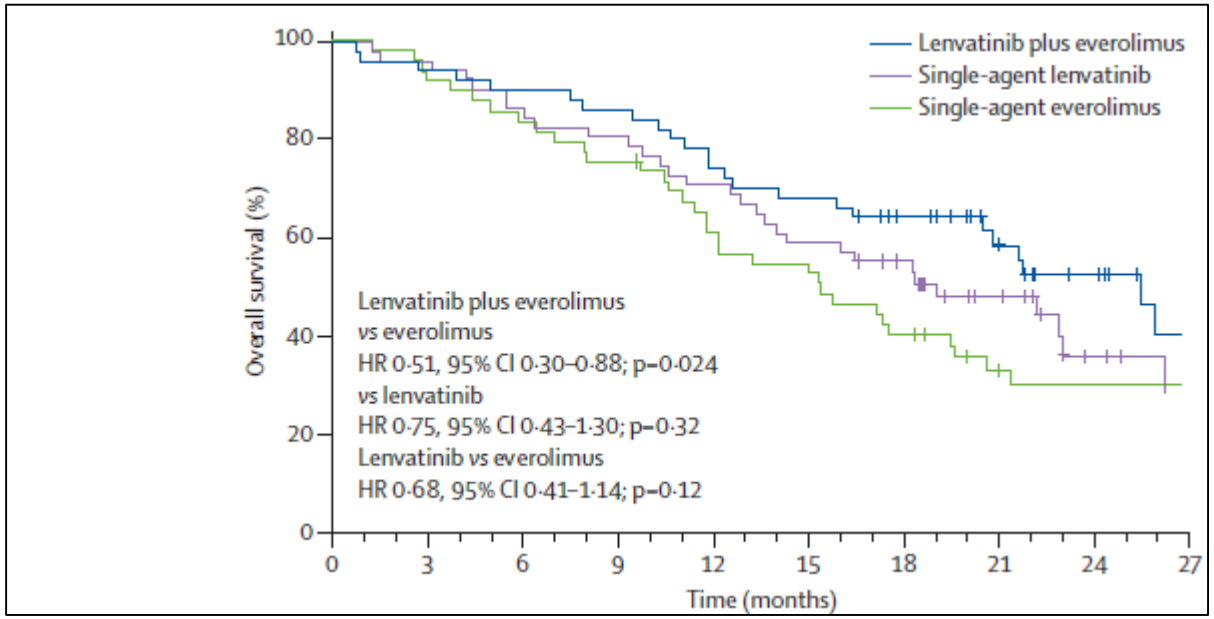
Median PFS (months):		
L+E	14.6	
E	5.5	HR 0.40 (0.24-0.68, p=0.0005)
L	7.4	HR 0.66 (0.39-1.10, p=0.12)

Primary end point: progression free survival

Supported by a post hoc retrospective independent radiology review

Motzer, Lancet Oncol, 2015

HOPE 205

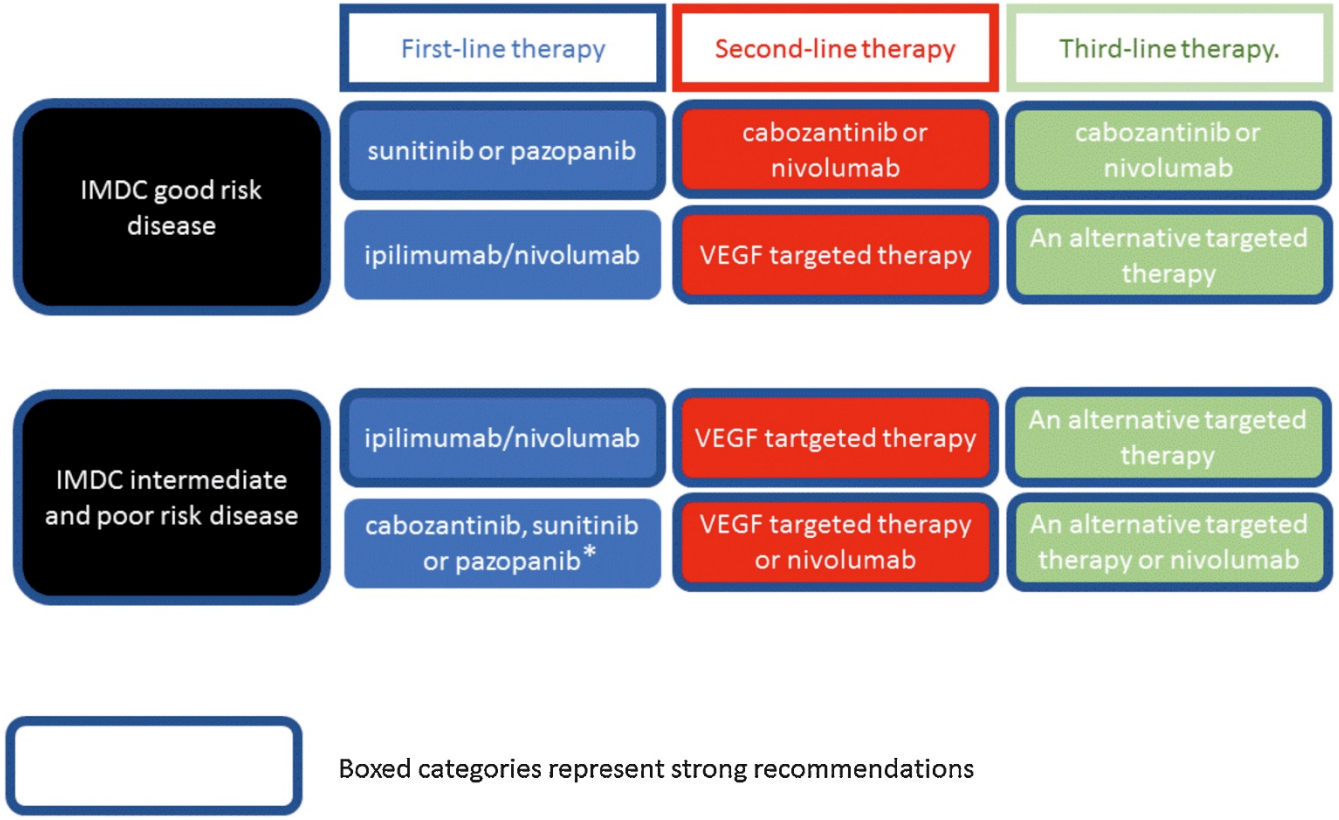


	Lenvatinib plus everolimus (n=51)			Lenvatinib (n=52)			Everolimus (n=50)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Any TEAE	14 (28%)	29 (57%)	7 (14%)	8 (15%)	38 (73%)	3 (6%)	23 (46%)	21 (42%)	4 (8%)
Diarrhoea	33 (65%)	10 (20%)	0	31 (60%)	6 (12%)	0	16 (32%)	1 (2%)	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
Cough	19 (37%)	0	0	8 (15%)	1 (2%)	0	15 (30%)	0	0
Hypercholesterolaemia	16 (31%)	1 (2%)	0	5 (10%)	0	1 (2%)	8 (16%)	0	0
Decreased weight	15 (29%)	1 (2%)	0	22 (42%)	3 (6%)	0	4 (8%)	0	0

Overall survival (at June 13, 2014)			
Events	19 (37%)	26 (50%)	26 (52%)
Median (95% CI) overall survival (months)	25·5 (20·8–25·5)	18·4 (13·3–NE)	17·5 (11·8–NE)
Overall survival (95% CI)			
At 12 months	74% (60–84)	71% (57–82)	62% (47–74)
At 18 months	67% (51–78)	54% (39–67)	47% (31–62)
Overall survival (at Dec 10, 2014)			
Events	24 (47%)	31 (60%)	33 (66%)
Median (95% CI) overall survival (months)	25·5 (16·4–NE)	19·1 (13·6–26·2)	15·4 (11·8–19·6)
Overall survival (95% CI)			
At 12 months	75% (60–84)	71% (57–82)	62% (47–74)
At 18 months	65% (50–76)	56% (41–68)	41% (27–54)

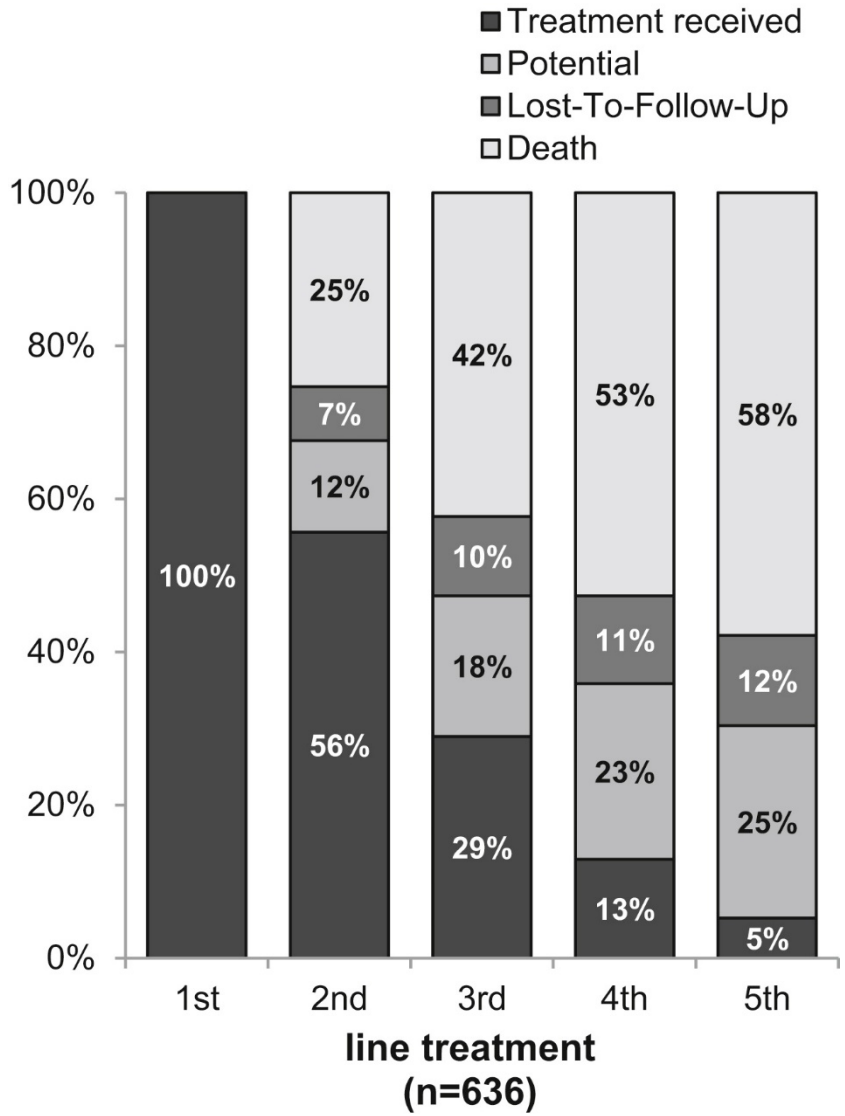
Motzer, Lancet Oncol, 2015

Guidelines: EAU update



Powles, Eur Urol, 2018

‘Drop off’ in patient's – German Cancer Registry 2007-2017



Goebell, Clin Genitourin Cancer, 2018

Summary

- Agents with positive efficacy data after prior VEGF directed therapy include everolimus, axitinib, cabozantinib, nivolumab and levatinib/everolimus
- There is (almost) no data for treatment after prior immunotherapy
- Nivolumab and cabozantinib have an established OS benefit and should perhaps therefore be prioritised
- Most patients do not get beyond 2nd line, so prioritise the 'best' treatments
- We lack any validated predictive biomarkers to aid decisions
- Outcomes remain poor