First Line Therapy in Metastatic Kidney Cancer: State of the Art in 2018

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FDA approved first line therapies for RCC

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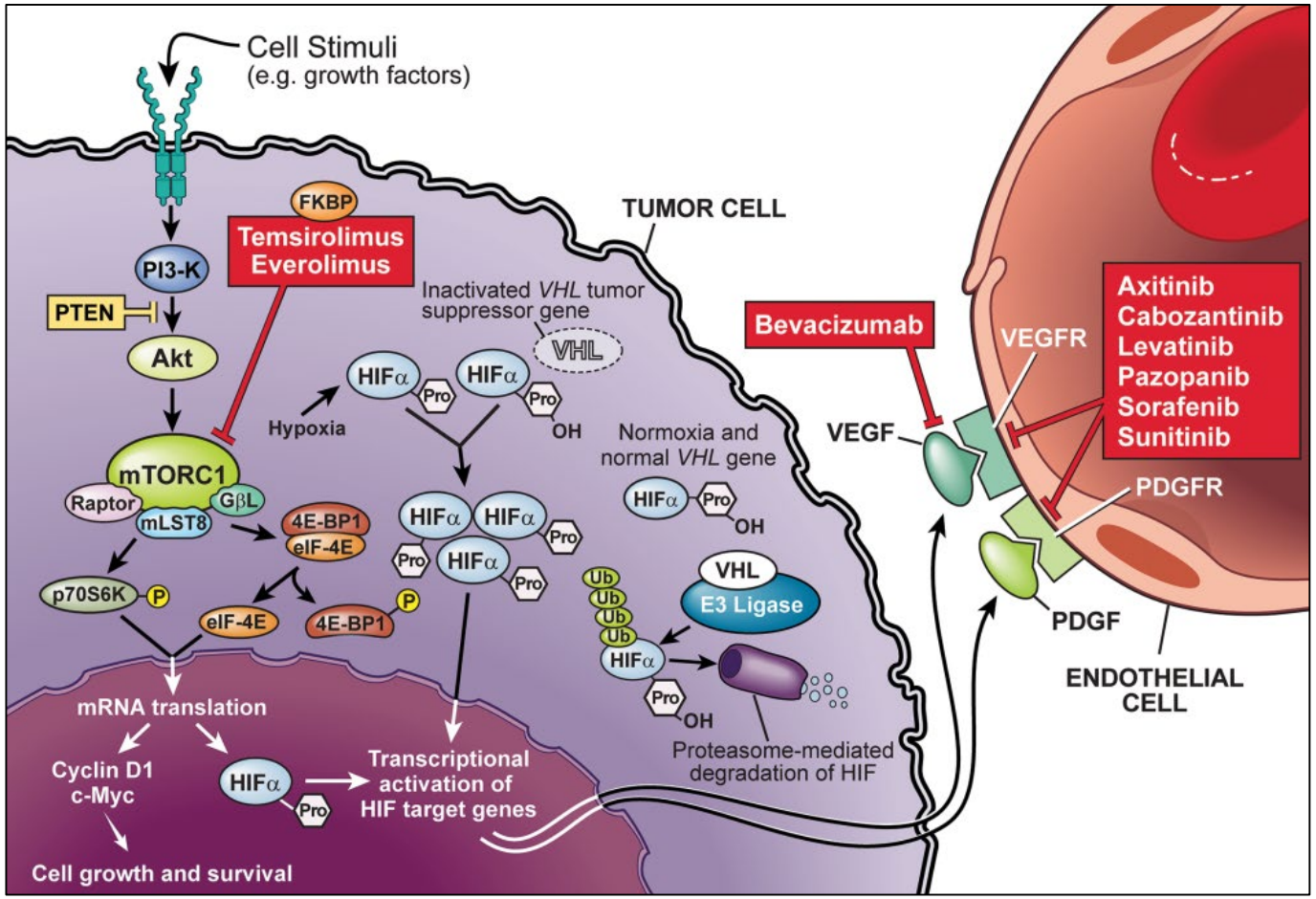
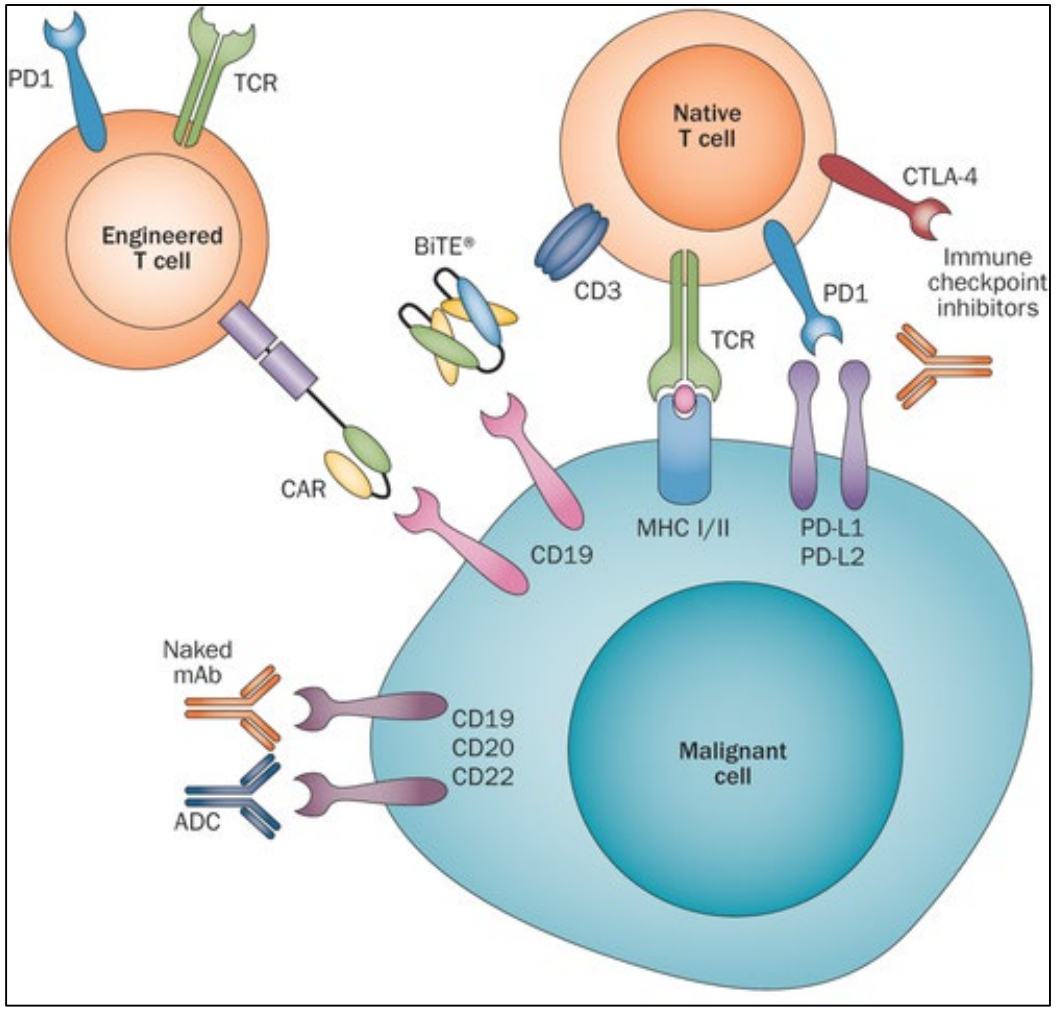
Agent	Target	Approval	Comparator	Endpoint	Risk group
IL-2	Cytokine immunotherapy	1992	None	ORR	
Sunitinib	VEGFR, PDGFR	2006	Placebo	OS	
Temsirolimus	mTOR	2007	IFNα	OS	Poor risk
Pazopanib	VEGFR, PDGFR, RET, KIT	2009	Placebo	PFS	
Bevacizumab + IFNα	Anti VEGF	2009	IFNα + placebo	OS	
Cabozantinib	c-Met, VEGFR2, AXL, RET	2017	Sunitinib	PFS	Intermediate / poor
Ipilimumab + Nivolumab	CTLA4/PD1	2018	Sunitinib	OS, ORR	Intermediate / poor

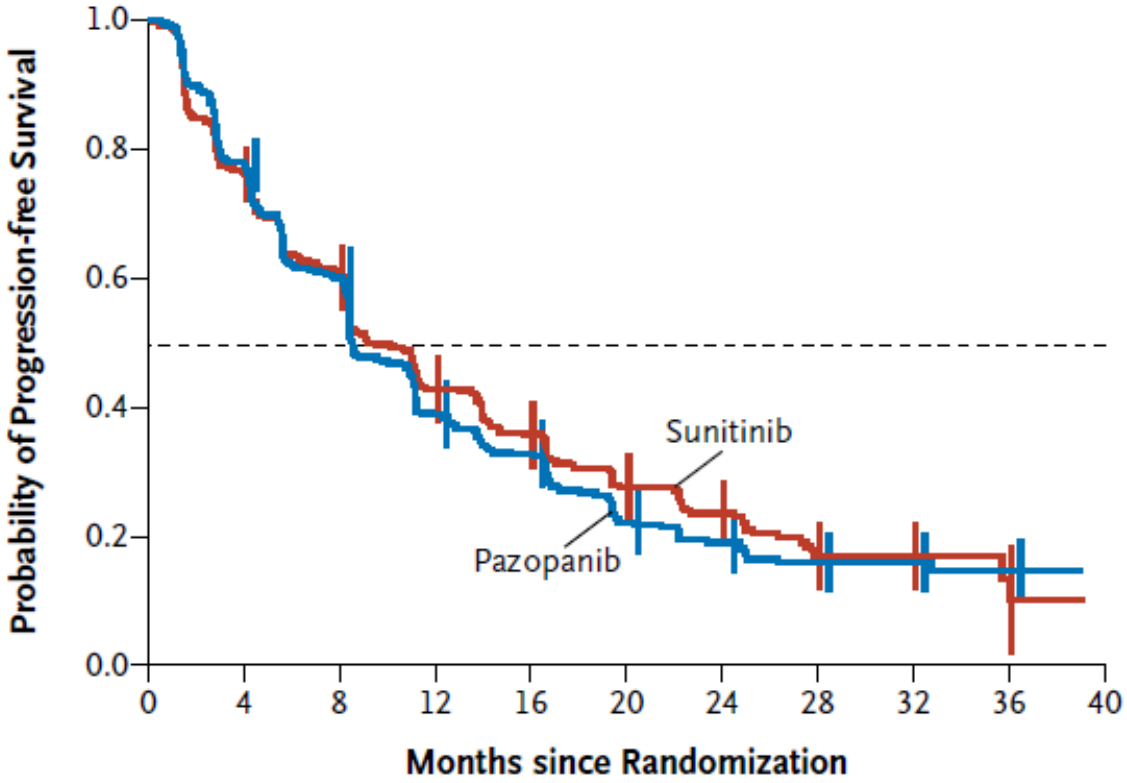
Adapted and updated from Modi, Trans Cancer Res, 2016





Barata and Rini, CA Cancer J Clin, 2017

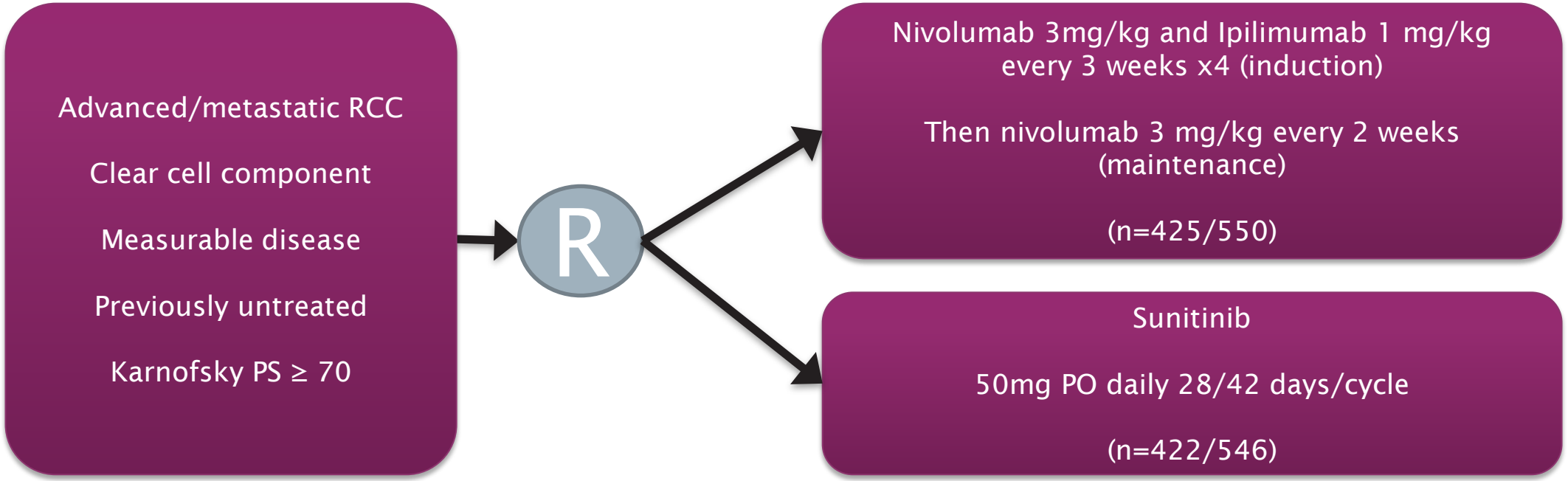
Single agent first line VEGFR directed therapy



	Pazopanib	Sunitinib	Hazard ratio
Median PFS (months)	8.4	9.5	1.05 (0.90 – 1.22)
Median OS (months)	28.4	29.3	0.91 (0.76 - 1.08)

Motzer, N Engl J Med, 2013

CheckMate 214 study design



Co-primary end points:	ORR (alpha level, 0.001) in intermediate- and poor-risk patients PFS (alpha level, 0.009) in intermediate- and poor-risk patients OS (alpha level, 0.04) in intermediate- and poor-risk patients
Secondary end points:	ORR, PFS, OS in ITT population Adverse events
Stratification:	Region IMDC risk group

Motzer, N Engl J Med, 2018

Heng risk groups

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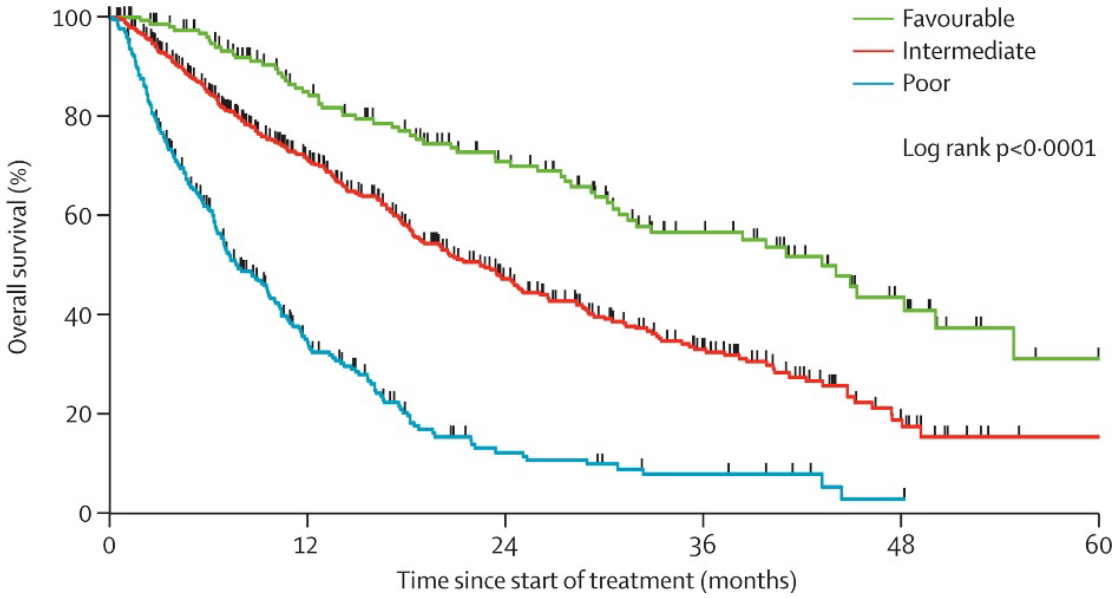
International Metastatic RCC Database Consortium risk score

Favourable:	score 0
Intermediate:	score 1 or 2
Poor:	score 3 to 6

Karnofsky performance status	< 80
Diagnosis to randomization	< 1 year
Haemoglobin	< LLN
Corrected serum calcium	> 10 mg/dL (2.5 mmol/L)
Neutrophils	> ULN
Platelets	> ULN



Overall survival

- 43·2 months (95% CI 31·4–50·1) favourable risk
- 22·5 months (18·7–25·1) intermediate risk
- 7·8 months (6·5–9·7) poor risk
- p<0·0001

Heng, Lancet Oncol, 2013

CheckMate 214 co-primary endpoints – intermediate/poor risk

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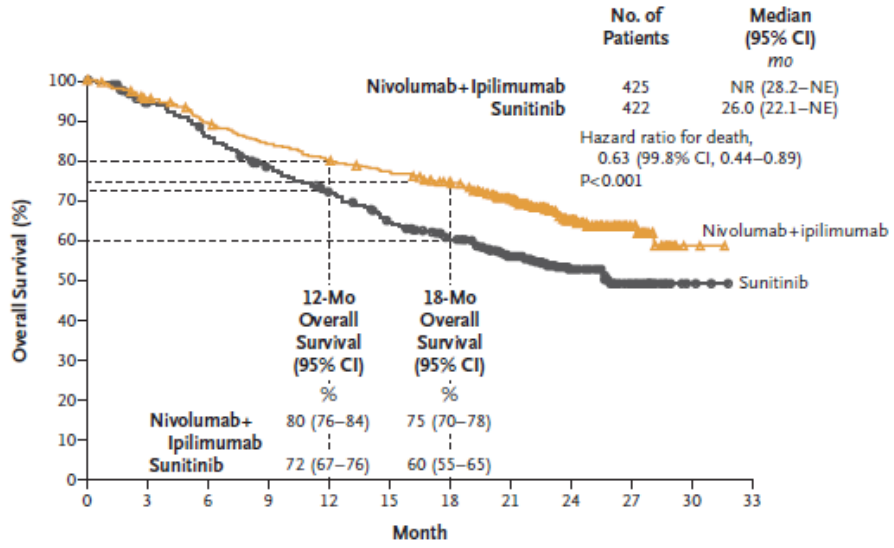
OS did met pre-specified threshold (P = 0.04) for statistical significance



PFS did not meet pre-specified threshold (P = 0.009) for statistical significance

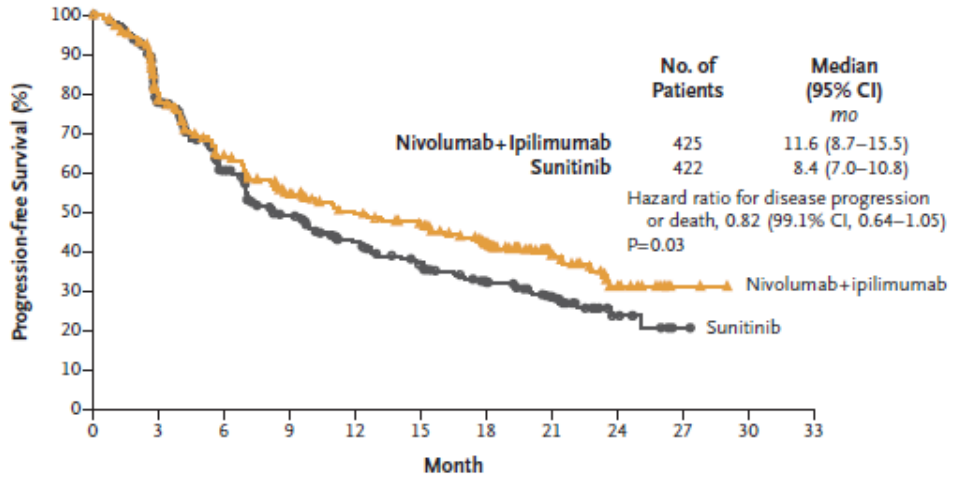


Table 2. Antitumor Activity in IMDC Intermediate- and Poor-Risk Patients.*

Variable	Nivolumab plus Ipilimumab (N=425)	Sunitinib (N=422)
Confirmed objective response rate — % (95% CI)†	42 (37–47)‡	27 (22–31)‡
Confirmed best overall response — no. (%)†		
Complete response	40 (9)‡§	5 (1)‡§
Partial response	137 (32)	107 (25)
Stable disease	133 (31)	188 (45)
Progressive disease	83 (20)	72 (17)
Unable to determine or not reported	32 (8)	50 (12)
Median time to response (range) — mo	2.8 (0.9–11.3)	3.0 (0.6–15.0)
Median duration of response (95% CI) — mo	NR (21.8–NE)	18.2 (14.8–NE)
Patients with ongoing response — no./total no. (%)	128/177 (72)	71/112 (63)

P<0.001

Reaches endpoint boundary

'Is Cure Possible?'

Curti, N Engl J Med, 2018; Motzer, N Engl J Med, 2018

CheckMate 214 - ITT and favourable risk subset

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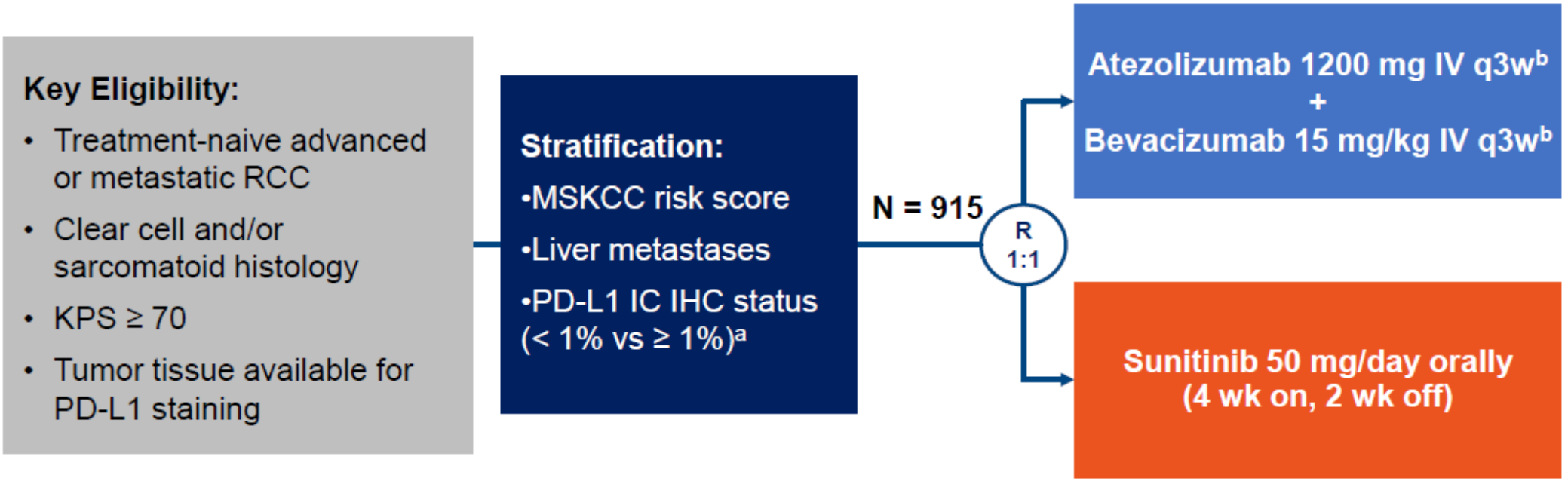
	n	Rx	18 month OS (%)	mOS (months)	HR		ORR (%)	p	mPFS (months)	HR	P
ITT	1096	I/N	78	NR	0.68	<0.001	39	0.02 (ns)	12.4	0.98	0.85
		S	68	32.9			32		12.3		
Favourable risk	249	I/N	88	NR	1.45	0.27	29	<0.001	15.3	2.18	<0.001
		S	93	32.9			52		25.1		

Handle with care!
ITT is a secondary endpoint
Favourable risk data is an exploratory analysis
Only 37 deaths in the favourable risk group (21 I/N, 16 S)

Motzer, N Engl J Med, 2018

IMmotion151 Study design



Primary endpoints:

PFS (investigators) in patients with PD-L1 ≥ 1% on infiltrating immune cells

OS in ITT population

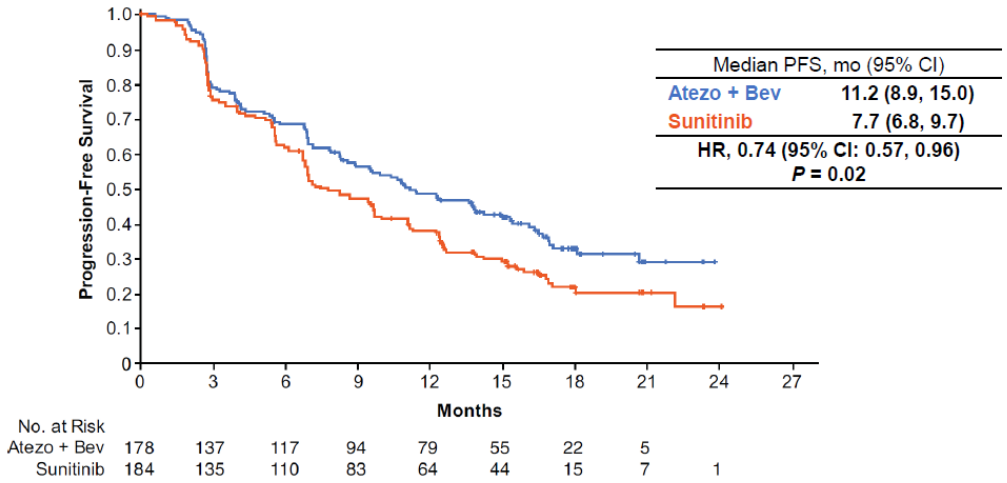
Secondary endpoints:

PFS in ITT, OS in PD-L1+, ORR, DOR, IRC assessed PFS and ORR, PROMs, safety

Motzer, GU ASCO, 2018, abstract 578

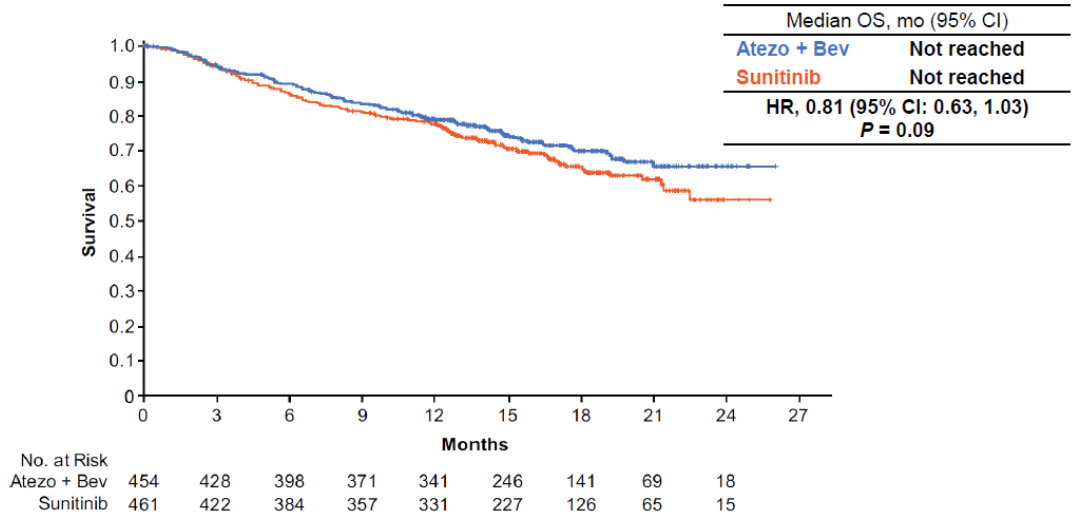
IMmotion151 - primary endpoints

Primary Endpoint
(Primary Analysis)



PFS passed the pre-specified boundary of $\alpha = 0.04$

Primary Endpoint
1st Interim Analysis



OS data are immature

29% had an OS event at data cut off

OS analysis did not pass the *P* value boundary of $\alpha = 0.0009$ at this interim analysis

Motzer, GU ASCO, 2018, abstract 578

IMmotion151 – secondary endpoints

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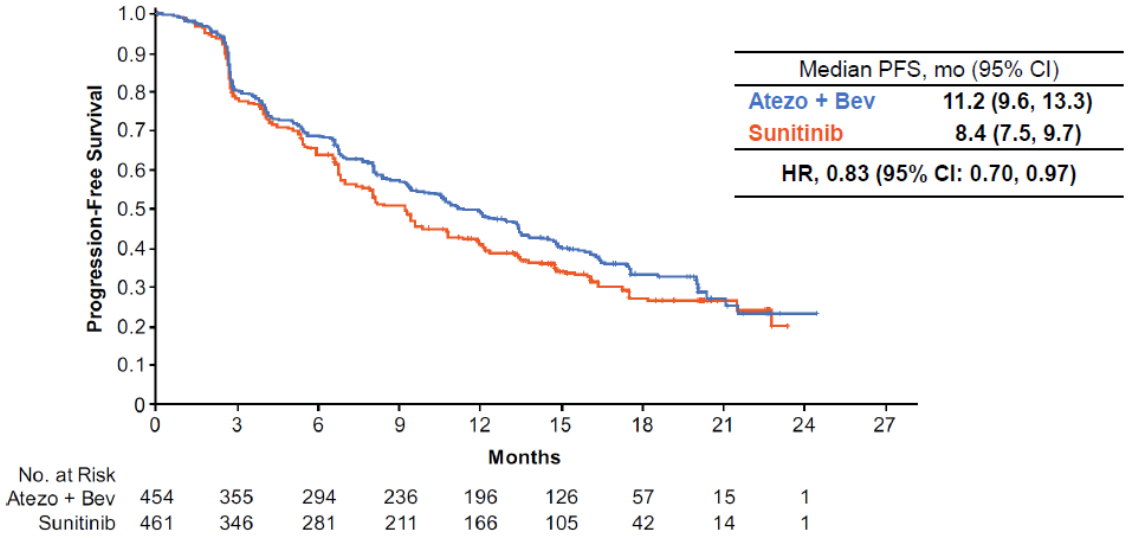
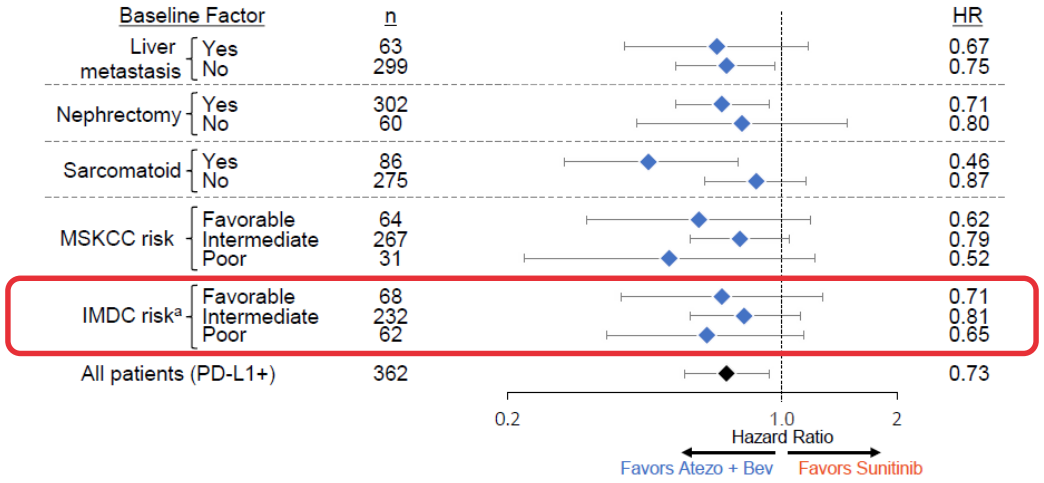
Progression-Free Survival in ITT



Median PFS, mo (95% CI)	
Atezo + Bev	11.2 (9.6, 13.3)
Sunitinib	8.4 (7.5, 9.7)
HR, 0.83 (95% CI: 0.70, 0.97)	

PFS in Key Subgroups (PD-L1+)



Motzer, GU ASCO, 2018, abstract 578

Other TKI/immunotherapy combinations

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	IMmotion151 N=915 (362 PDL1 +ve)	
	Bevacizumab Atezolizumab	Sunitinib
PFS PDL1 +ve (months)	11.2	7.7
	HR 0.74, p = 0.02	
PFS All patients (months)	11.2	8.4
	HR 0.83	
OS PDL1+ve (months)	NR	23.3
	HR 0.68	
OS All patients (months)	NR	NR
	HR 0.81, p=0.09	
ORR (CR) PDL1 +ve (%)	43 (9)	35 (4)
ORR (CR) All patients(%)	37 (5)	33 (2)

Motzer, GU ASCO, 2018, abstract 578; Motzer, ESMO congress 2018; Merck press release 18 Oct 2018, https://bit.ly/2yLtWaC

Other TKI/immunotherapy combinations

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	IMmotion151 N=915 (362 PDL1 +ve)		JAVELIN Renal 101 N=886 (560 PDL1 +ve)	
	Bevacizumab Atezolizumab	Sunitinib	Axitinib Avelumab	Sunitinib
PFS PDL1 +ve (months)	11.2	7.7	13.8	7.2
	HR 0.74, p = 0.02		HR 0.61, p < 0.0001	
PFS All patients (months)	11.2	8.4	13.8	8.4
	HR 0.83		HR 0.69, p < 0.0001	
OS PDL1+ve (months)	NR	23.3	-	-
	HR 0.68		-	
OS All patients (months)	NR	NR	NR	NR
	HR 0.81, p=0.09		HR 0.78, p = 0.0679	
ORR (CR) PDL1 +ve (%)	43 (9)	35 (4)	55 (4)	26 (2)
ORR (CR) All patients(%)	37 (5)	33 (2)	51 (3)	26 (2)

Motzer, GU ASCO, 2018, abstract 578; Motzer, ESMO congress 2018; Merck press release 18 Oct 2018, https://bit.ly/2yLtWaC

Other TKI/immunotherapy combinations

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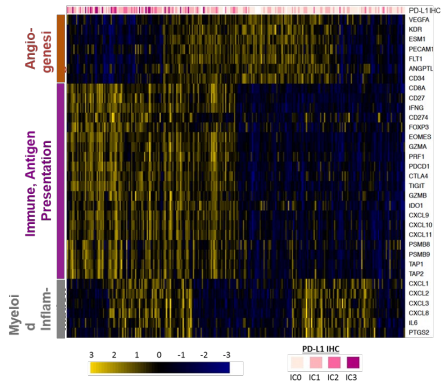
	IMmotion151 N=915 (362 PDL1 +ve)		JAVELIN Renal 101 N=886 (560 PDL1 +ve)		KEYNOTE-426 N=861	
	Bevacizumab Atezolizumab	Sunitinib	Axitinib Avelumab	Sunitinib	Axitinib Pembrolizumab	Sunitinib
PFS PDL1 +ve (months)	11.2	7.7	13.8	7.2	'Consistent regardless of PDL1 expression'	
	HR 0.74, p = 0.02		HR 0.61, p < 0.0001			
PFS All patients (months)	11.2	8.4	13.8	8.4	'Statistically significant and clinically meaningful improvements'	
	HR 0.83		HR 0.69, p < 0.0001			
OS PDL1+ve (months)	NR	23.3	-	-	'Consistent regardless of PDL1 expression'	
	HR 0.68		-			
OS All patients (months)	NR	NR	NR	NR	'Statistically significant and clinically meaningful improvements'	
	HR 0.81, p=0.09		HR 0.78, p = 0.0679			
ORR (CR) PDL1 +ve (%)	43 (9)	35 (4)	55 (4)	26 (2)	'Consistent regardless of PDL1 expression'	
ORR (CR) All patients(%)	37 (5)	33 (2)	51 (3)	26 (2)	'Significant improvements'	

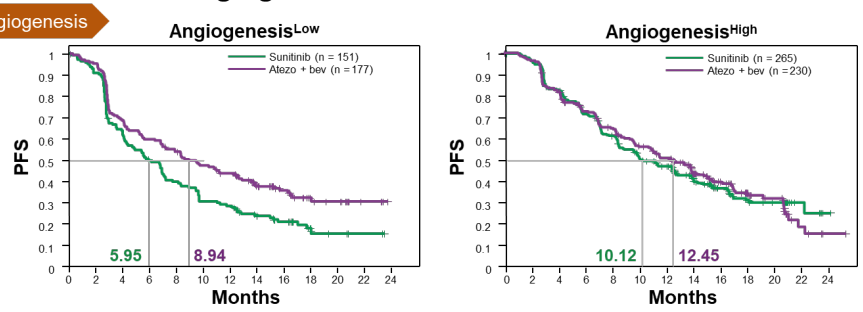
Motzer, GU ASCO, 2018, abstract 578; Motzer, ESMO congress 2018; Merck press release 18 Oct 2018, https://bit.ly/2yLtWaC

Predictive biomarkers? – IMmotion151



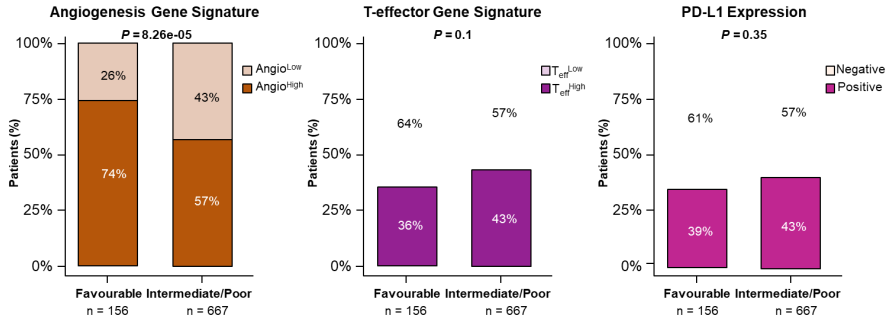
Atezolizumab + Bevacizumab Improved PFS vs Sunitinib in the Angiogenesis^{Low} Subset

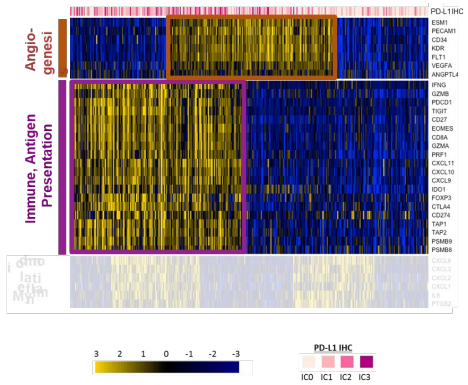
Angiogenesis



HR (95% CI)		
	Angiogenesis^{Low}	Angiogenesis^{High}
Atezo + bev vs sunitinib	0.68 (0.52, 0.88)	0.95 (0.76, 1.19)

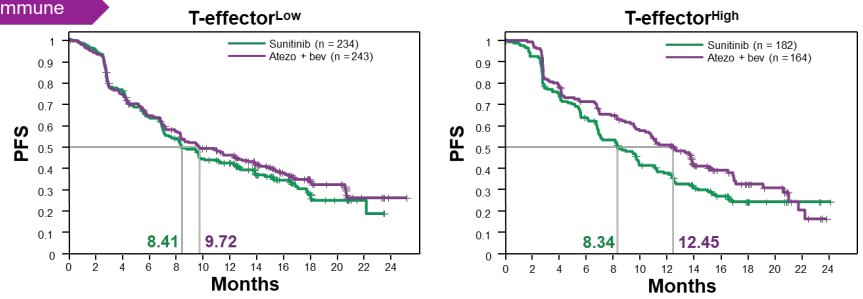
Angiogenesis Gene Expression Is Higher in Favourable MSKCC Risk Group





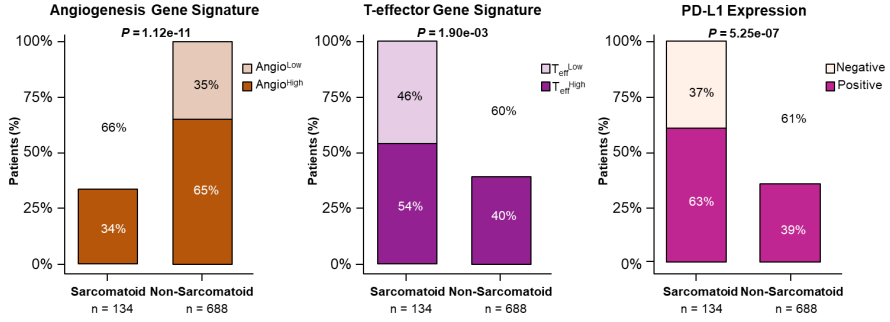
Atezolizumab + Bevacizumab Demonstrated Improved PFS vs Sunitinib in T_{eff}^{High} Subset

Immune



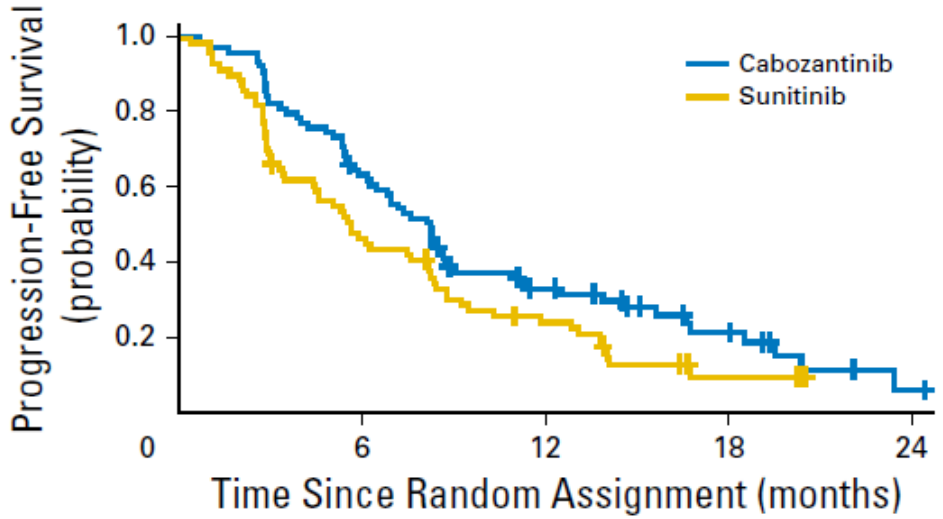
HR (95% CI)		
	T-effector^{Low}	T-effector^{High}
Atezo + bev vs sunitinib	0.91 (0.73, 1.14)	0.76 (0.59, 0.99)

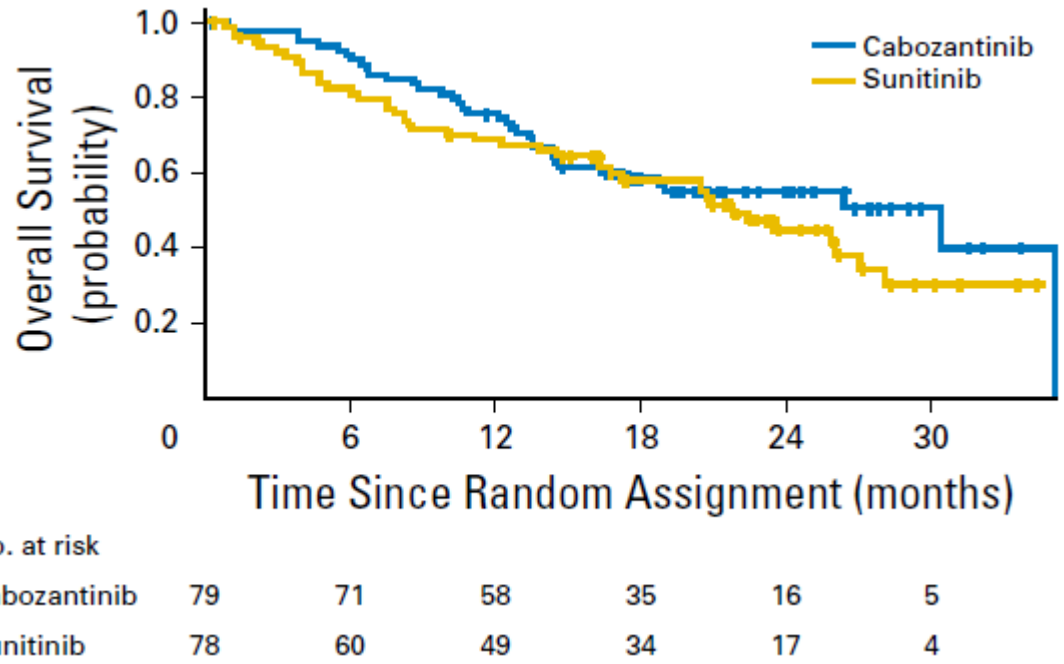
Angiogenesis Gene Expression Is Lower and PD-L1 Expression Is Higher in Sarcomatoid Tumours



Rini, ESMO 2018, Abstract LBA31, http://bit.ly/2yaVgyl

Cabozantinib (intermediate or poor risk)





	PFS (months)*	ORR (%)	OS
Cabozantinib	8.2	33 (23-44)	30.3
Sunitinib	5.6	12 (5.4-21)	21.8
HR	0.66 (0.46-0.95)		0.80 (0.50-1.26)
p	0.012		

*primary endpoint

Choueiri, J Clin Oncol, 2017

cMET inhibition in papillary mRCC

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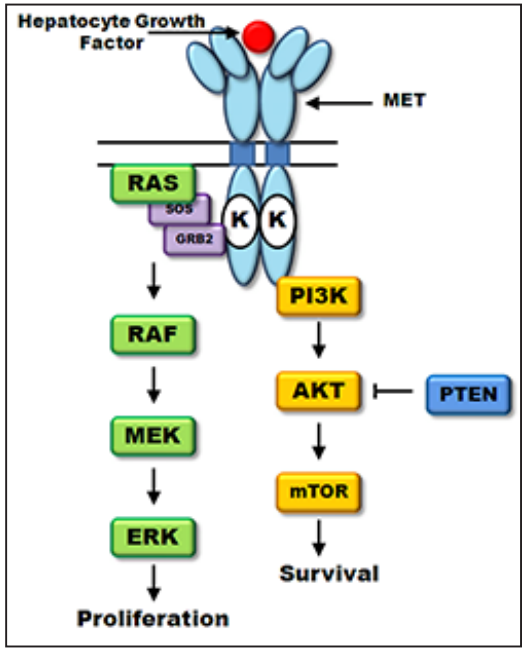
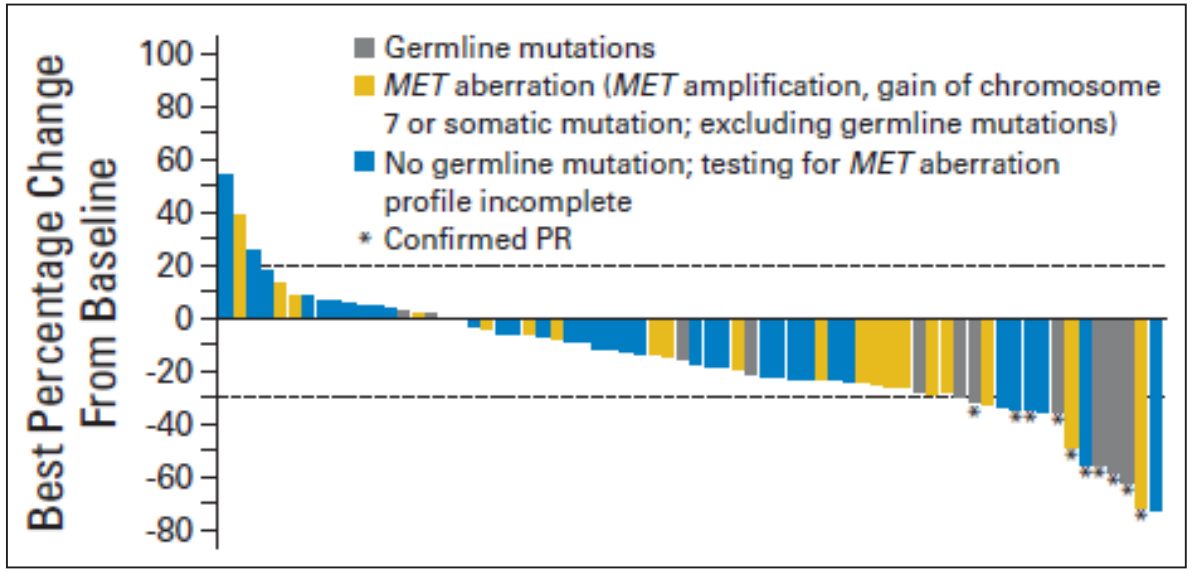
- Papillary RCC associated with activating MET gene mutations
- Foretinib: multikinase inhibitor targeting MET, VEGF, RON, AXL, TIE-2
- ORR 13.5%, median PFS 9.3 months
- Germline MET mutation predictive of response
  - 5/10 v 5/57





Choueiri, J Clin Oncol 2012

Conclusions

- Nivolumab/ipilimumab, atezolizumab/bevacizumab and axitinib/avelumab are new options for first line treatment for mRCC with a clear cell component
- They are superior to sunitinib (and possibly first line TKIs generally although we lack data for this) and appear to have a favourable and manageable safety profile
- My view is that nivolumab/ipilimumab is the current standard of care option for intermediate and poor risk disease if available
- My view is that atezolizumab/bevacizumab or axitinib/avelumab are the current standard of care options for favourable risk disease if available
- There are no validated predictive biomarkers for treatment choice but emerging data for immune and angiogenesis signatures are promising
- We have only limited data for treatment options in non-clear cell RCC histologies