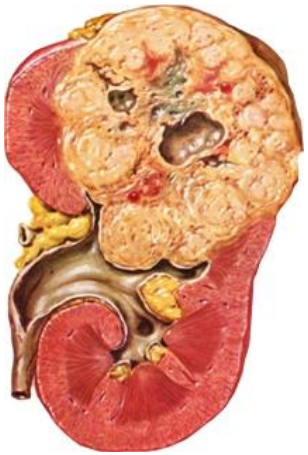
12th Belgian Symposium on the Integration of Molecular Biology Advances into Oncology Clinical Practice

Saturday 24th November 2018 Morning

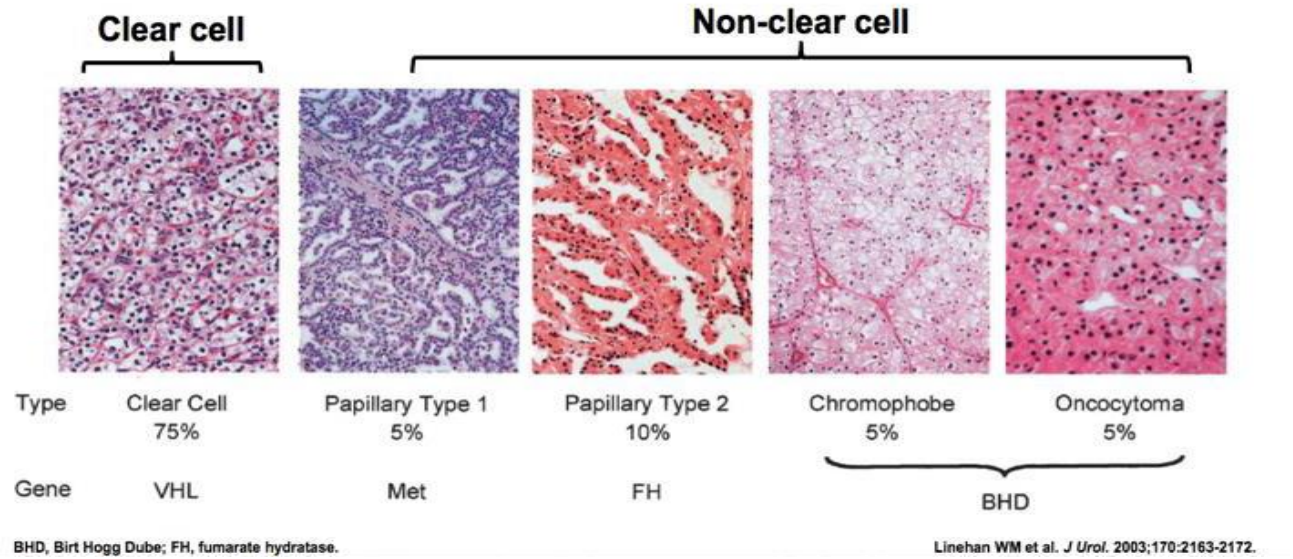


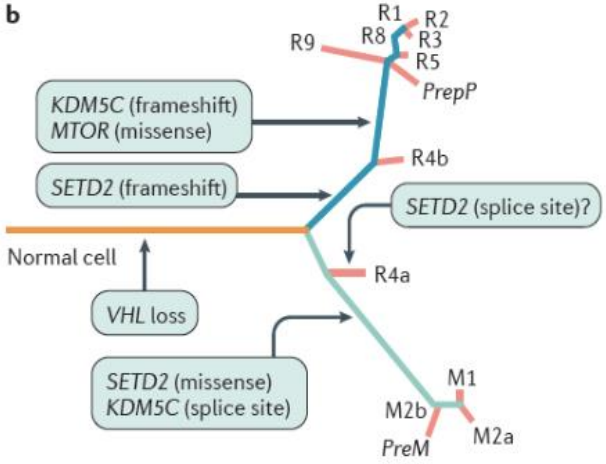
Focus in advanced RCC:

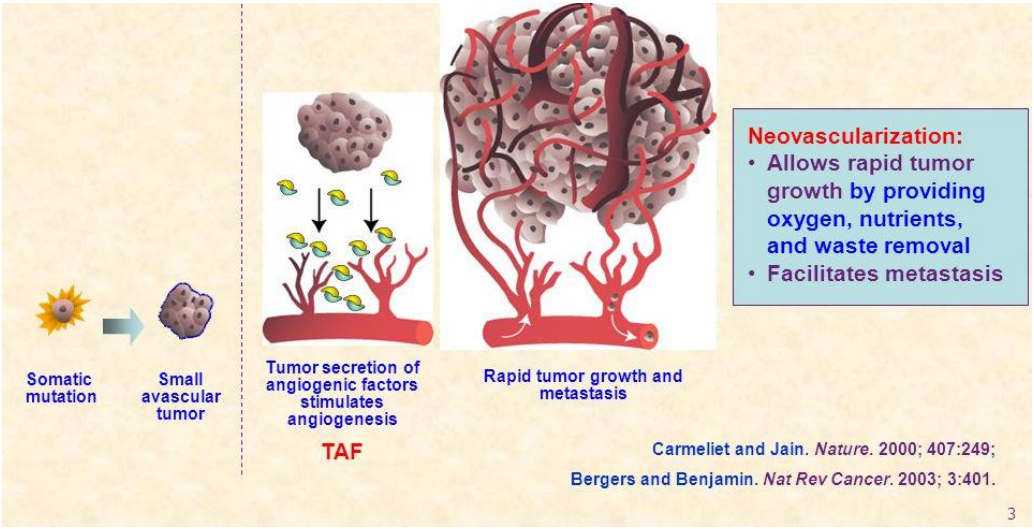
future directions in patient selection

Seront Emmanuel, MD PhD

Medical Oncologist


Clear cell
Non-clear cell
Type
Clear Cell
75%
Papillary Type 1
5%
Papillary Type 2
10%
Chromophobe
5%
Oncocytoma
5%
Gene
VHL
Met
FH
BHD
BHD, Birt Hogg Dube; FH, fumarate hydratase.
Linehan WM et al. J Urol. 2003;170:2163-2172.

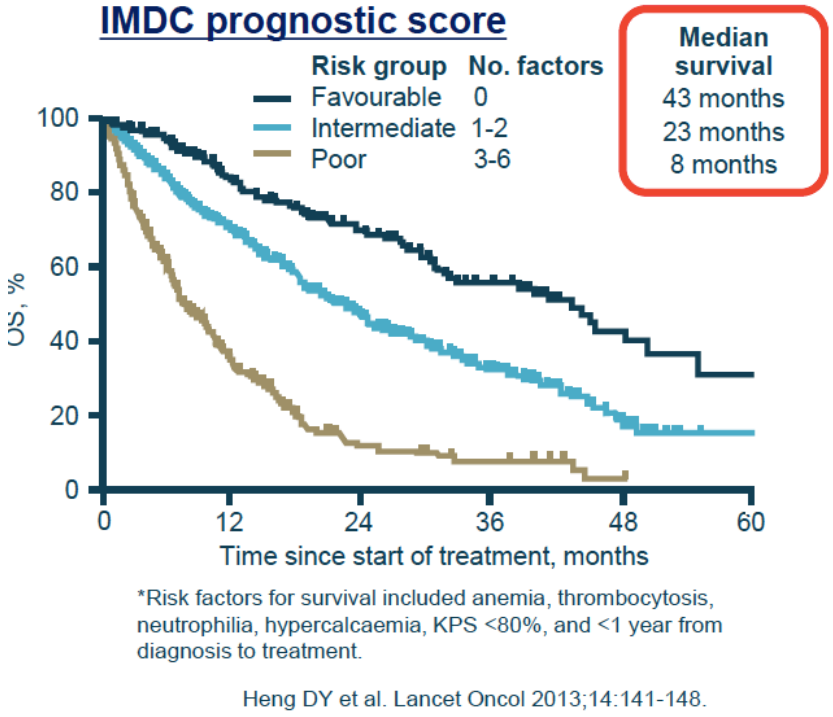

b
R1
R2
R3
R5
R8
R9
PrepP
KDM5C (frameshift)
MTOR (missense)
SETD2 (frameshift)
R4b
SETD2 (splice site)?
Normal cell
R4a
VHL loss
SETD2 (missense)
KDM5C (splice site)
M1
M2b
M2a
PreM


Somatic mutation
Small avascular tumor
Tumor secretion of angiogenic factors stimulates angiogenesis
TAF
Rapid tumor growth and metastasis
Neovascularization:
• Allows rapid tumor growth by providing oxygen, nutrients, and waste removal
• Facilitates metastasis
Carmeliet and Jain. Nature. 2000; 407:249;
Bergers and Benjamin. Nat Rev Cancer. 2003; 3:401.
3

	Treatment group	Standard recommendation
First line	Good or intermediate risk	Sunitinib Bevacizumab + IFN-α Pazopanib
	Poor risk	Temsirolimus

VEGFR Blockade

➔ VEGF-targeted therapies



*Risk factors for survival included anemia, thrombocytosis, neutrophilia, hypercalcaemia, KPS <80%, and <1 year from diagnosis to treatment.

Heng DY et al. Lancet Oncol 2013;14:141-148.

Heng Criteria IMDC prognostic score

Prognostic Factor
Karnofsky performance status < 80
Time from diagnosis to treatment with TKI < 12 months
Hemoglobin < Lower limit of laboratory's reference range
Platelets > Upper limit of normal
Neutrophils > Upper limit of normal

	Treatment group	Standard recommendation
First line	Good or intermediate risk	Sunitinib Bevacizumab + IFN-α Pazopanib
	Poor risk	Temsirolimus
Second line	Post-TKIs	Nivolumab Cabozantinib [Axitinib]

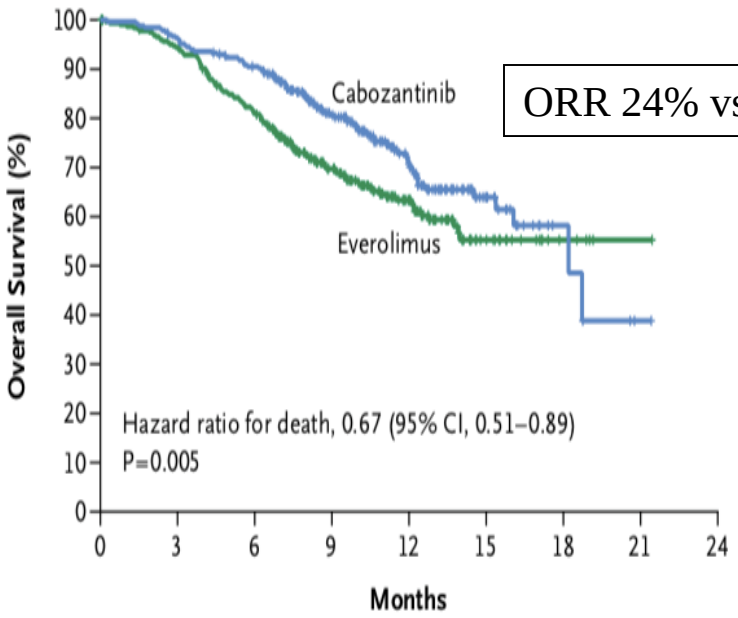
VEGFR Blockade

PD-1 Inhibitor

ORIGINAL ARTICLE

Cabozantinib versus Everolimus in Advanced Renal-Cell Carcinoma

T.K. Choueiri, B. Escudier, T. Powles, Paul N. Mainwaring, B.I. Rini, F. Donskov, H.

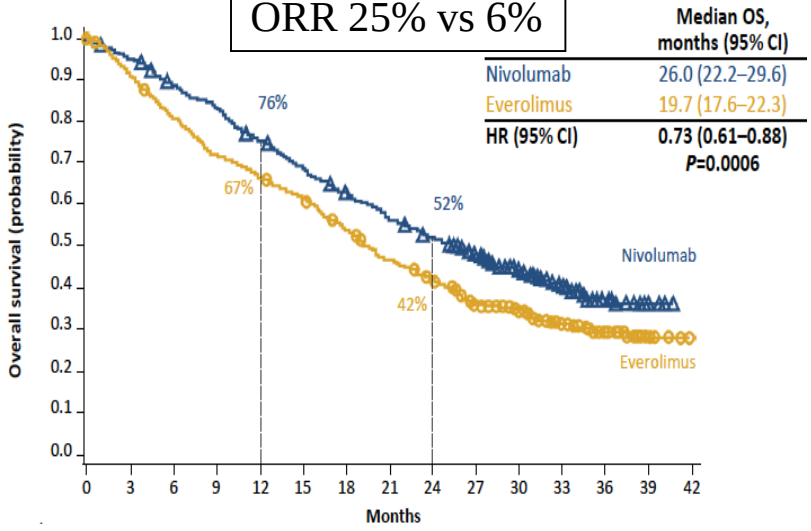


ORR 24% vs 4%

All IMDC risk group

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 NOVEMBER 5, 2015 VOL. 373 NO. 19

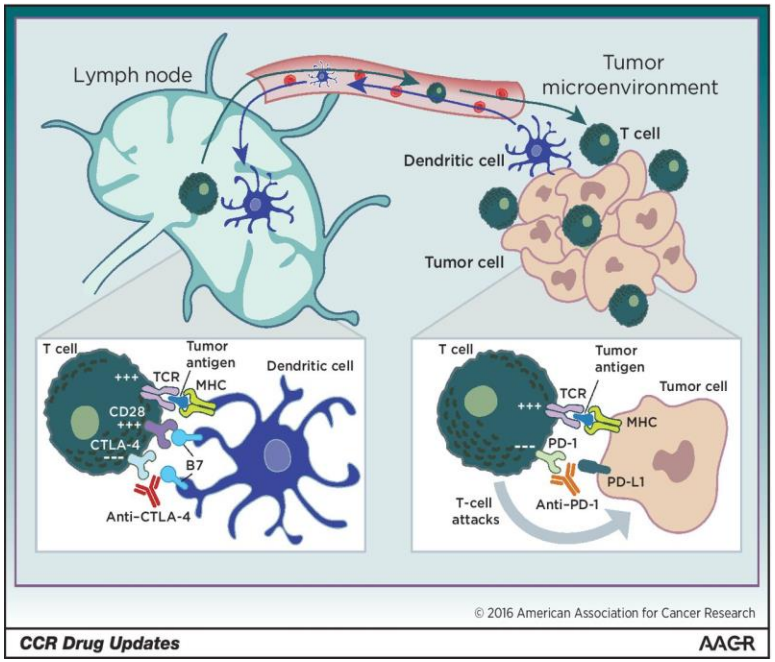
Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma



ORR 25% vs 6%

All IMDC risk group
PDL1 - and PDL1 +

New ways to improve first line treatment = Era of Combos (1)



ORIGINAL ARTICLE

Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma

R.J. Motzer, N.M. Tannir, D.F. McDermott, O. Arén Frontera, B. Melichar,

CheckMate 214: Study design

Patients

- **Treatment-naïve advanced or metastatic clear-cell RCC**
- **Measurable disease**
- **KPS ≥70%**
- **Tumor tissue available for PD-L1 testing**

Randomize 1:1

Stratified by
- IMDC prognostic score (0 vs 1–2 vs 3–6)
- Region (US vs Canada/Europe vs Rest of World)

Treatment

Arm A
3 mg/kg nivolumab IV + 1 mg/kg ipilimumab IV Q3W for four doses, then 3 mg/kg nivolumab IV Q2W

Arm B
50 mg sunitinib orally once daily for 4 weeks (6-week cycles)

Co-primary endpoints:
ORR
PFS
OS

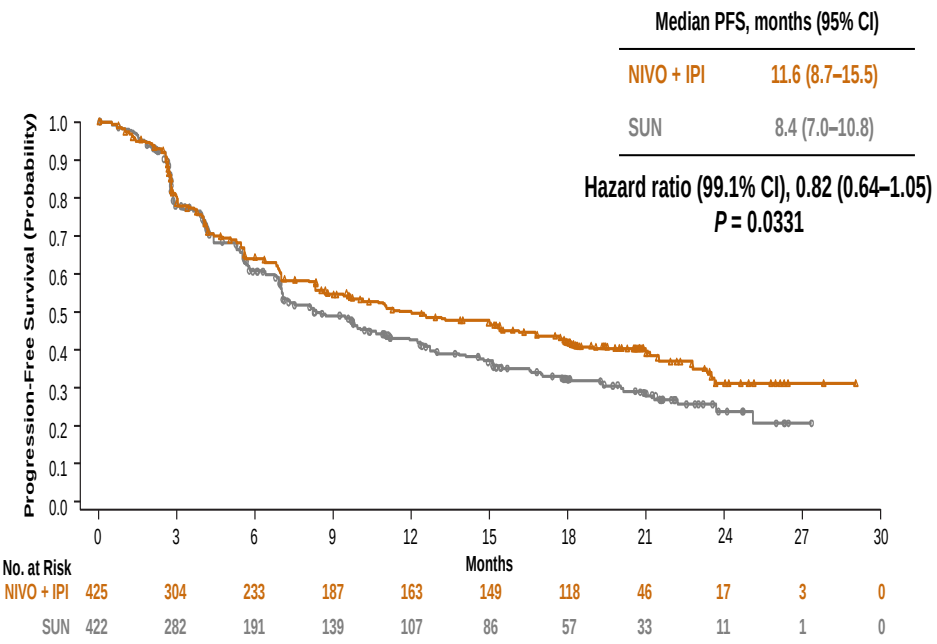
intermediate/poor risk groups

Primary endpoint in IMDC intermediate/poor risk

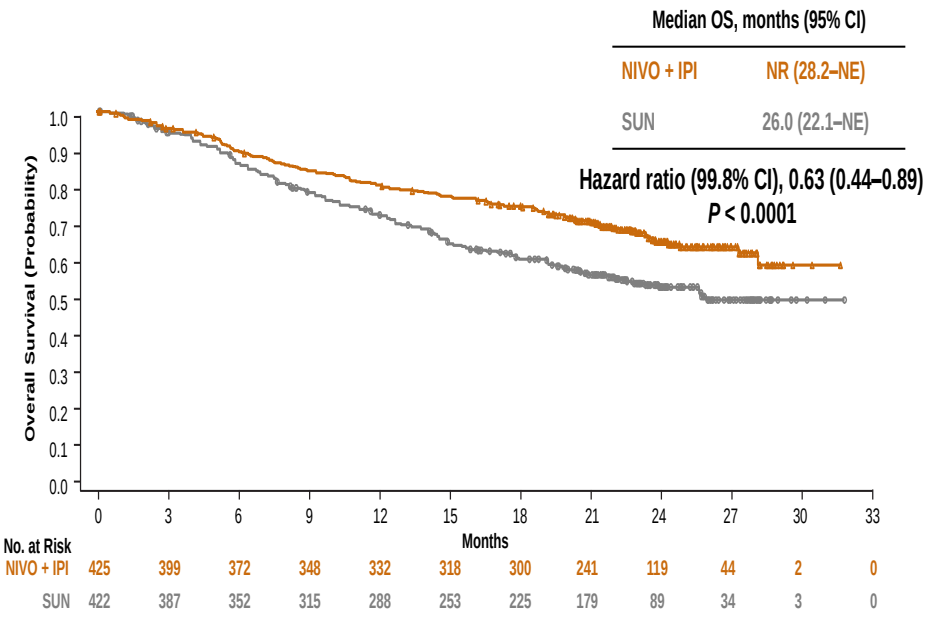
Co-primary endpoint

Outcome	N = 847	
	NIVO + IPI N = 425	SUN N = 422
Confirmed ORR,[a] % (95% CI)	**42**	**27**
	P < 0.0001	
Confirmed BOR,[a] %		
Complete response	**9[b]**	**1[b]**
Partial response	32	25

PFS: IMDC intermediate/poor risk



OS: IMDC intermediate/poor risk

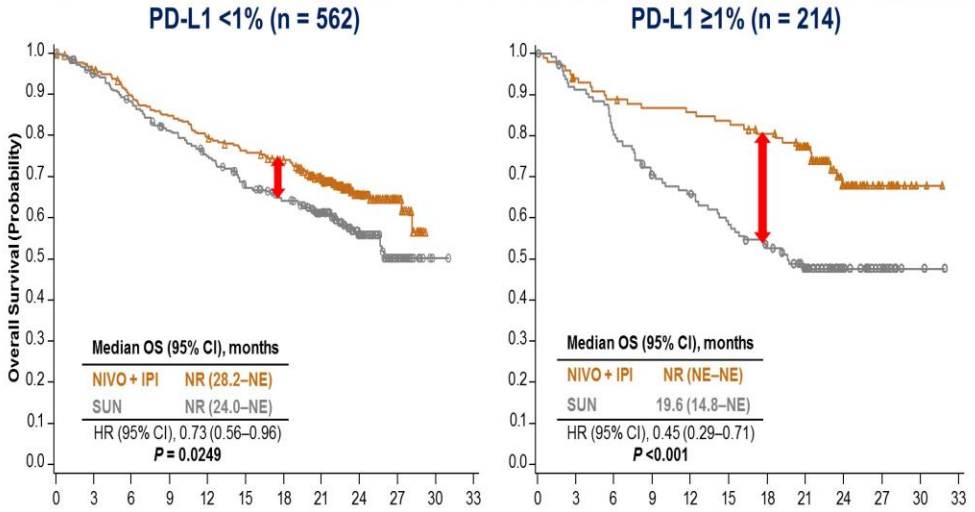


Exploratory endpoint

	IMDC intermediate/poor risk			
	PD-L1 <1%		PD-L1 ≥1%	
Outcome	NIVO + IPI N = 284	SUN N = 278	NIVO + IPI N = 100	SUN N = 114
ORR,[a] % (95% CI)	37 (32–43)	28 (23–34)	**58 (48–68)**	**22 (15–31)**
	P = 0.0252		*P* < 0.0001	
BOR,[a] %				
Complete response	7	1	**16**	1
Partial response	30	27	42	21

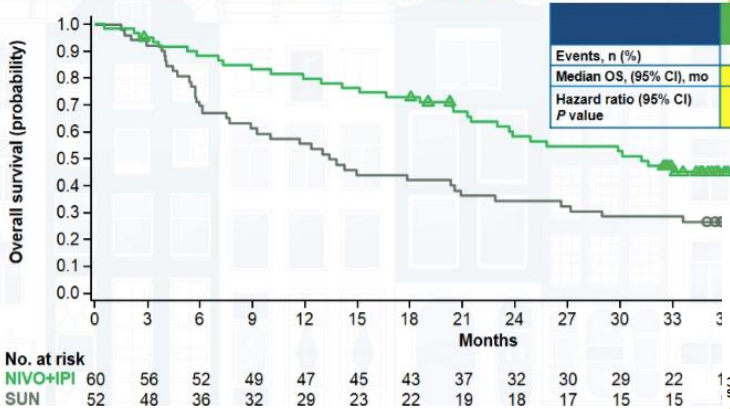
Motzer et al SITC 2017

OS by tumor PD-L1 expression: IMDC intermediate/poor risk

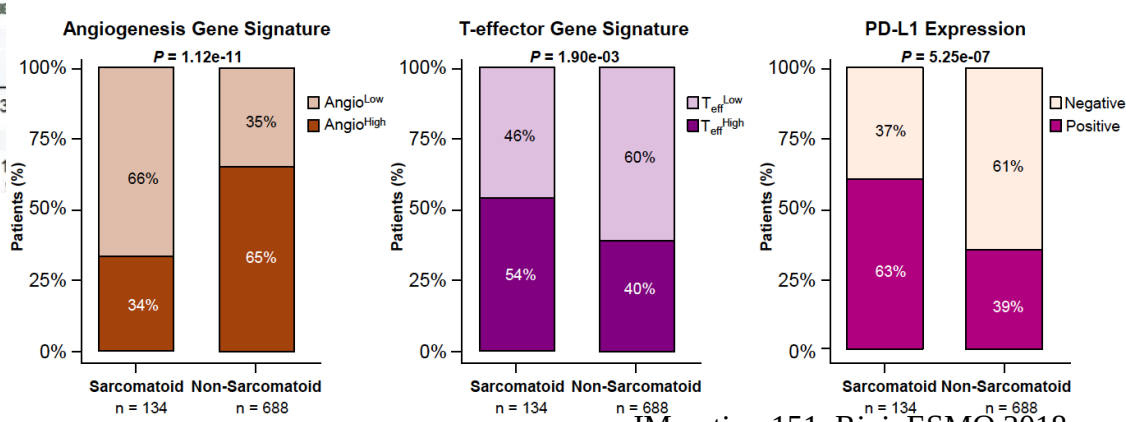


NIVO-IPI Checkmate 214 - retrospective analysis
OS: Intermediate/Poor-Risk Sarcomatoid Patients

EMUC18



	NIVO + IPI N = 60	SUN N = 52
Events, n (%)	31 (52)	39 (75)
Median OS, (95% CI), mo	**31.2 (23.0–NE)**	**13.6 (7.7–20.9)**
Hazard ratio (95% CI) *P* value	**0.55** (0.33–0.90) 0.0155	

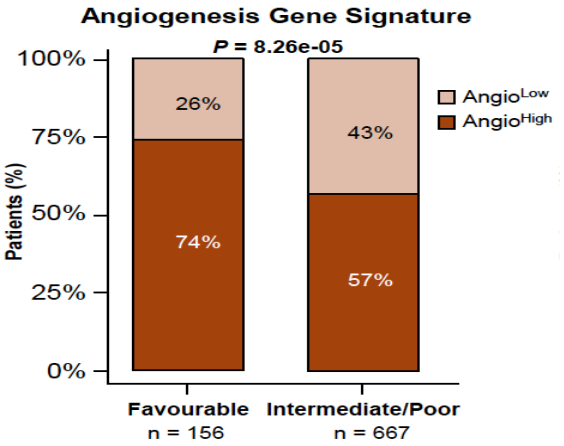


IMmotion 151, Rini, ESMO 2018

ORR and PFS: IMDC favorable risk

Outcome	N = 249[a]	
	NIVO + IPI N = 125	SUN N = 124
Confirmed ORR,[b] % (95% CI)	29 (21–38)	52 (43–61)
	P = 0.0002	
PFS,[c] median (95% CI), months	15.3 (9.7–20.3)	25.1 (20.9–NE)
	HR (99.1% CI) 2.18 (1.29–3.68) *P* < 0.0001	

Not a good option for Favorable risk



IMmotion 151, Rini, ESMO 2018

Table 3. Treatment-Related Adverse Events Occurring in 15% or More of Treated Patients in Either Group.*

Event	Nivolumab plus Ipilimumab (N=547)		Sunitinib (N=535)	
	Any Grade†	Grade 3 or 4	Any Grade‡	Grade 3 or 4
	number of patients (percent)			
All events	509 (93)	250 (46)	521 (97)	335 (63)
Fatigue	202 (37)	23 (4)	264 (49)	49 (9)
Pruritus	154 (28)	3 (<1)	49 (9)	0
Diarrhea	145 (27)	21 (4)	278 (52)	28 (5)
Rash	118 (22)	8 (1)	67 (13)	0
Nausea	109 (20)	8 (1)	202 (38)	6 (1)
Increased lipase level	90 (16)	56 (10)	58 (11)	35 (7)
Hypothyroidism	85 (16)	2 (<1)	134 (25)	1 (<1)
Decreased appetite	75 (14)	7 (1)	133 (25)	5 (<1)
Asthenia	72 (13)	8 (1)	91 (17)	12 (2)
Vomiting	59 (11)	4 (<1)	110 (21)	10 (2)
Anemia	34 (6)			
Dysgeusia	31 (6)			
Stomatitis	23 (4)			
Dyspepsia	15 (3)			
Mucosal inflammation	13 (2)			
Hypertension	12 (2)			
Palmar–plantar erythrodysesthesia	5 (<1)			
Thrombocytopenia	2 (<1)			

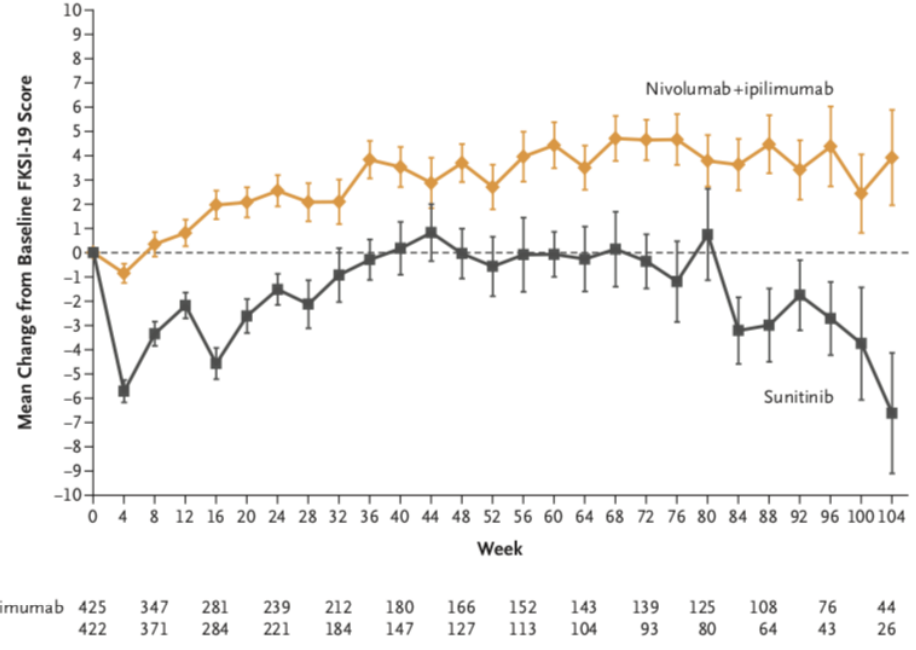
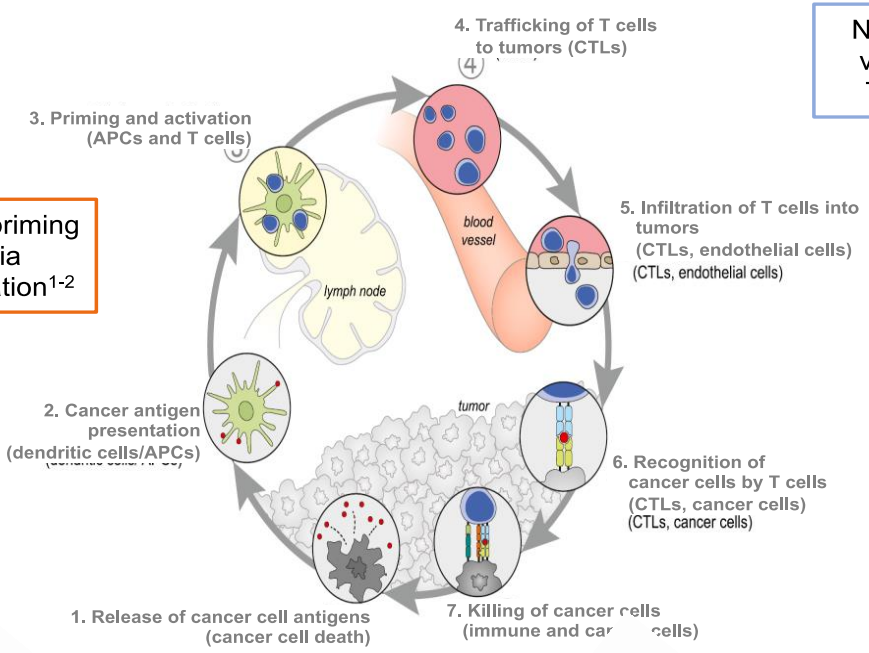


Figure 3. Health-Related Quality of Life in IMDC Intermediate- and Poor-Risk Patients.

New ways to improve first line treatment = Era of Combos (2)

Promotion of T-cell priming and activation via dendritic cell maturation[1-2]



Normalization of the tumor vasculature for increased T-cell tumor infiltration[3-6]

Establishing an immune-permissive tumor microenvironment by decreasing MDSC and Treg populations[6-10]

IMmotion151
PD-L1 + VE

IMmotion151: A Randomized Phase III Study of Atezolizumab Plus Bevacizumab vs Sunitinib in Untreated Metastatic Renal Cell Carcinoma

Sunitinib

Javelin Renal
NCT0268400
PD-L1 + V

JAVELIN Renal 101: Randomized Phase 3 Trial of Avelumab + Axitinib vs Sunitinib as First-Line Treatment of Advanced Renal Cell Carcinoma

Sunitinib

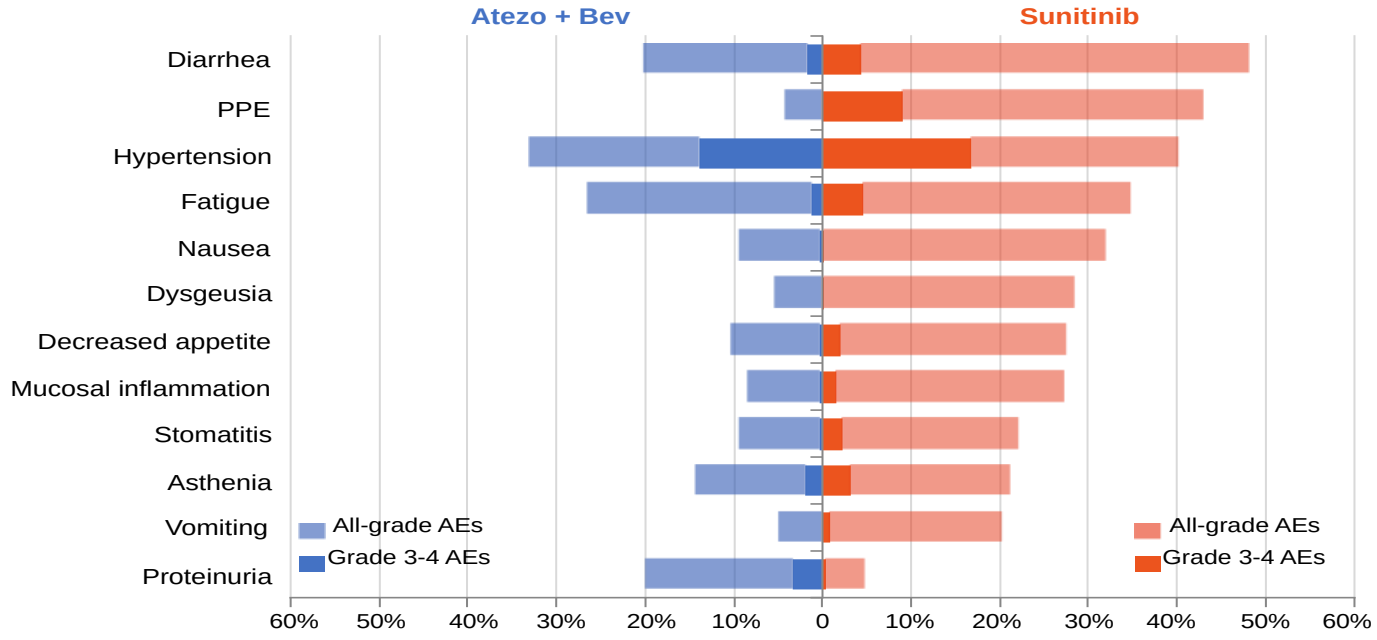
Keynote 426- NCT02853331:
PD-1 + VEGFR TKI

Phase
Co-Primary
PFS, OS

Data awaited

Pembrolizumab + Axitinib

Sunitinib

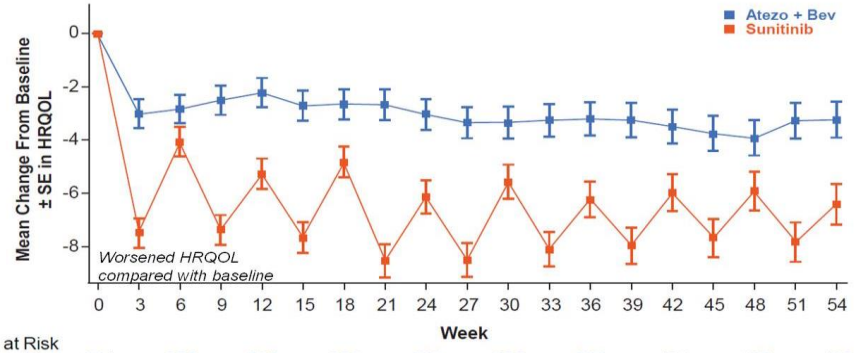


PPE, palmar-plantar erythrodysesthesia.

Atezolizumab + Bevacizumab

HRQOL (FKSI-19)

Change in Health-Related Quality of Life Over Time



No. at Risk										
Atezo + Bev	364	305	297	266	238	223	200	191	185	169
Sunitinib	345	276	253	230	210	198	173	161	146	131

- Baseline HRQOL[a] in both arms suggests minimal impairment and scores were comparable to the US general adult population[1]
- Patients treated with atezolizumab + bevacizumab reported less worsening in HRQOL[b,c] compared with patients treated with sunitinib

SE, standardized error. Score range, 0-76. Effect size ≥ 0.20 suggests a clinically important difference between arms.
[a] Mean baseline total scores (SD): atezo + bev, 59.8 (9.8) vs sunitinib, 59.5 (9.4). Mean normative FKSI-19 total score for the US general adult population, 59.8.
[b] $P < 0.05$ from repeated-measures model for atezo + bev vs sunitinib at visits until week 72; exception was at week 6.
[c] Average difference in least-squares mean estimates of score changes for atezo + bev vs sunitinib at visits through week 54 was 3.67; mean effect size, 0.42 (range, 0.16, 0.67). $P < 0.0001$ from linear mixed model of change from baseline to end of treatment; effect size, 0.35. 1. Butt et al. *Cancer.* 2013;119:429-437.

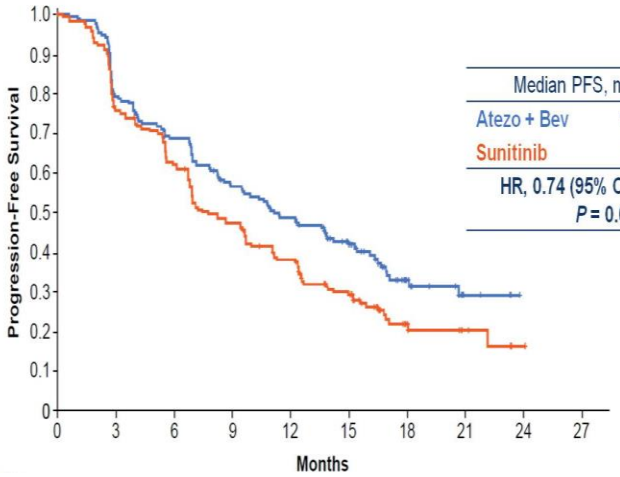
IMmotion151: A Randomized Phase III Study of Atezolizumab Plus Bevacizumab vs Sunitinib in Untreated Metastatic Renal Cell Carcinoma

Atezolizumab + Bevacizumab

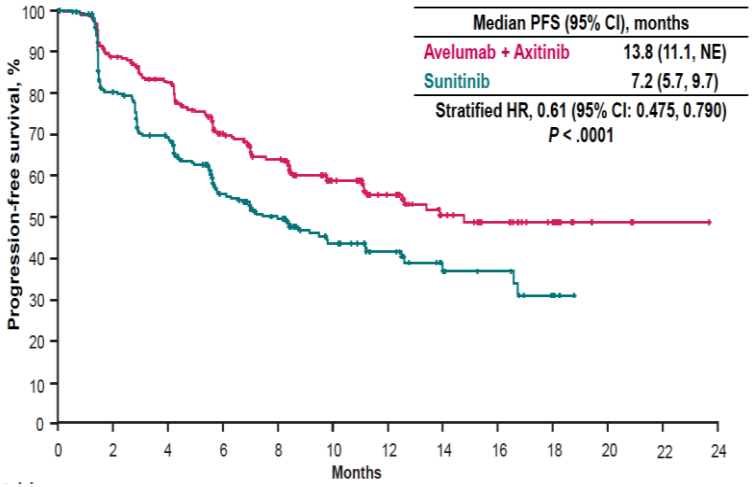
JAVELIN Renal 101: Randomized Phase 3 Trial of Avelumab + Axitinib vs Sunitinib

Avelumab + Axitinib

Primary endpoint = PFS in PD-L1 +

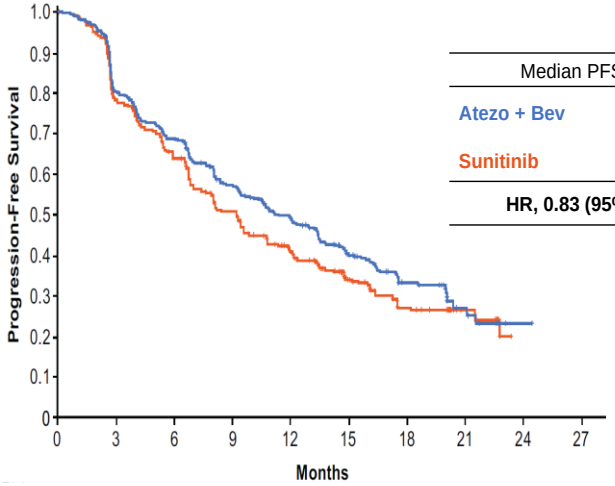


Median PFS, mo (95% CI)	
Atezo + Bev	11.2 (8.9, 15.0)
Sunitinib	7.7 (6.8, 9.7)
HR, 0.74 (95% CI: 0.57, 0.96)	
P = 0.02[a]	

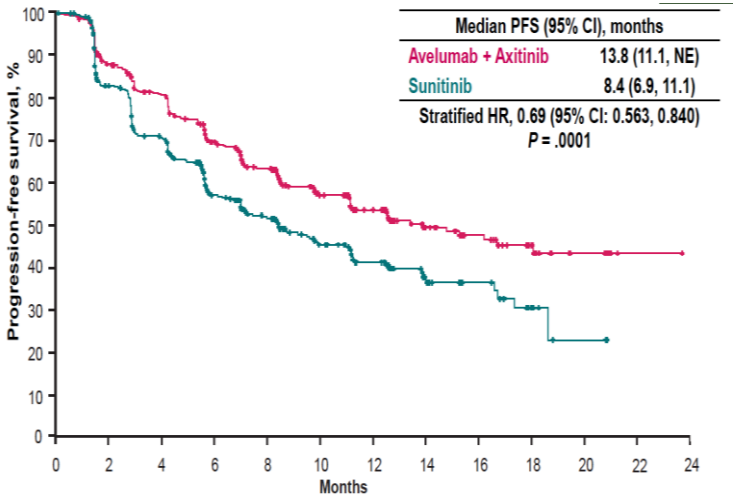


Median PFS (95% CI), months	
Avelumab + Axitinib	13.8 (11.1, NE)
Sunitinib	7.2 (5.7, 9.7)
Stratified HR, 0.61 (95% CI: 0.475, 0.790)	
P < .0001	

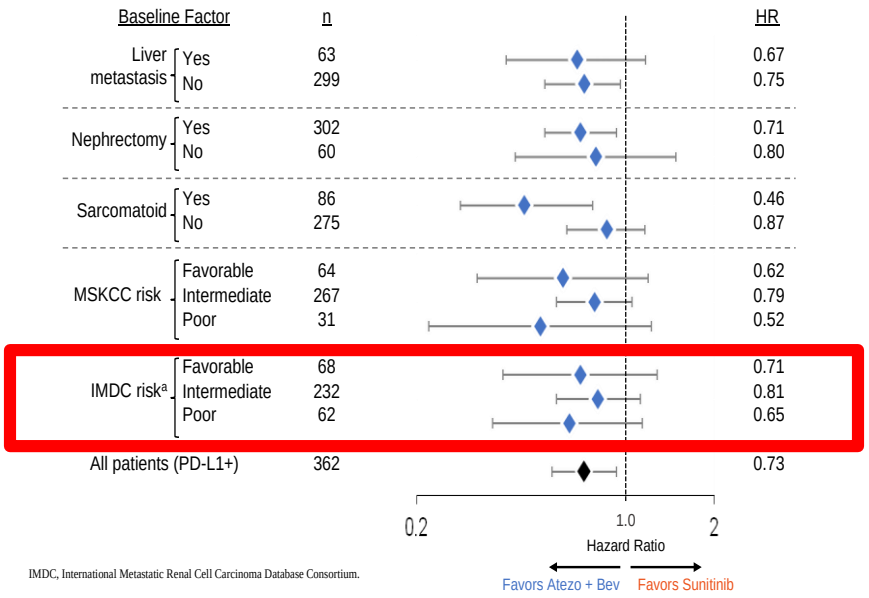
Secondary endpoint = PFS in ITT



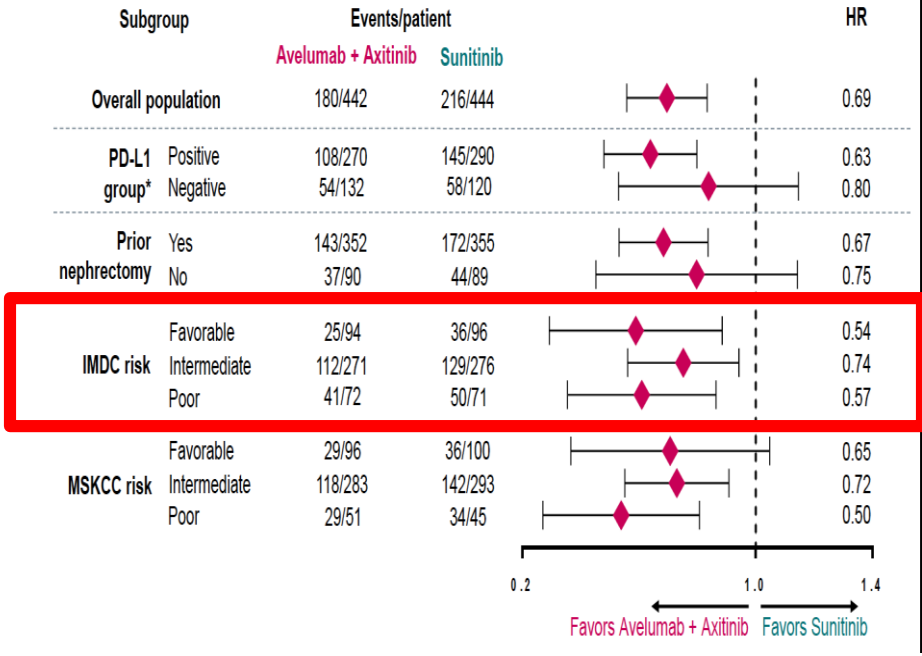
Median PFS, mo (95% CI)	
Atezo + Bev	11.2 (9.6, 13.3)
Sunitinib	8.4 (7.5, 9.7)
HR, 0.83 (95% CI: 0.70, 0.97)	



Median PFS (95% CI), months	
Avelumab + Axitinib	13.8 (11.1, NE)
Sunitinib	8.4 (6.9, 11.1)
Stratified HR, 0.69 (95% CI: 0.563, 0.840)	
P = .0001	



IMDC, International Metastatic Renal Cell Carcinoma Database Consortium.

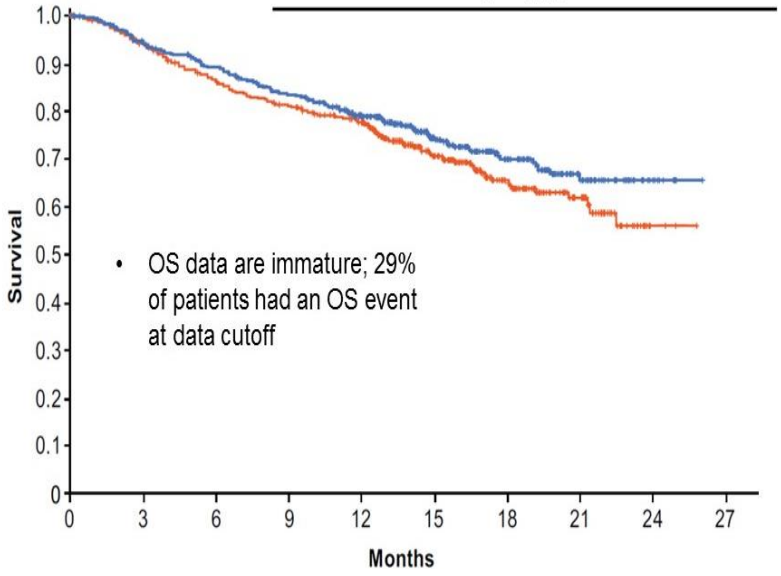


	IMmotion 151					Javelin 101			
	PDL1 +		ITT			PDL1+		ITT	
	Atezo+Beva n=178	Sun n=184	Atezo+Beva n=454	Sun n=460		Avelu +Axi n=270	Sun n=290	Avel+Axi n=442	Sun n=444
ORR %	**43**	**35**	**37**	**33**		**55**	**26**	**51**	**26**
CR	9	4	5	2		4	2	3	2
PR	34	30	31	31		51	23	48	24
SD	32	35	39	39		27	43	30	46

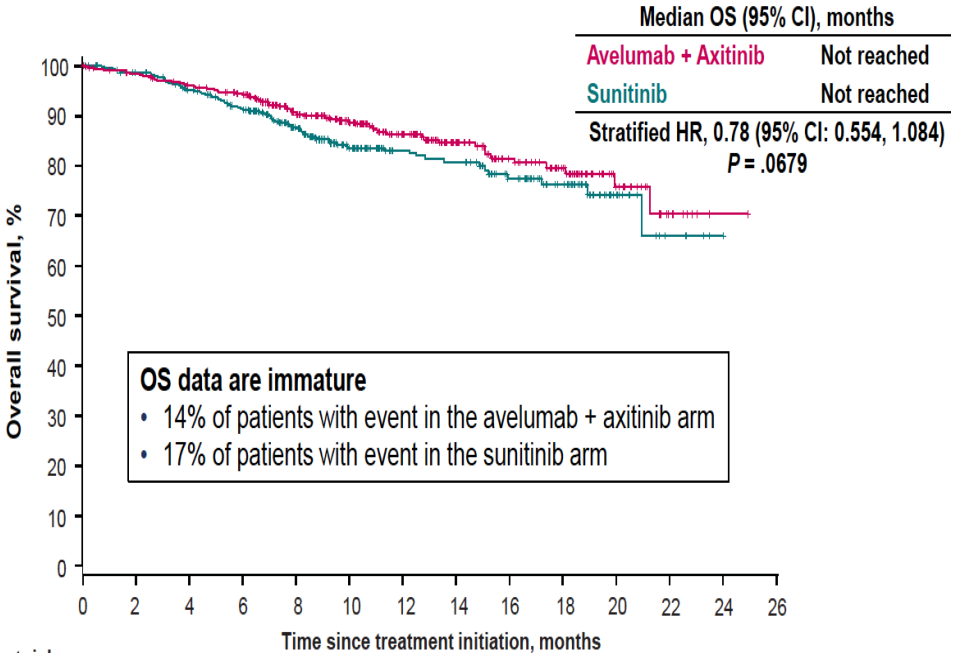
OS in ITT

ITT Median OS, mo (95% CI)	
Atezo + Bev	Not reached
Sunitinib	Not reached

HR, 0.81 (95% CI: 0.63, 1.03)
P = 0.09



OS in overall population



Of course, very important endpoint !

What next after association of TKI and ICI ?

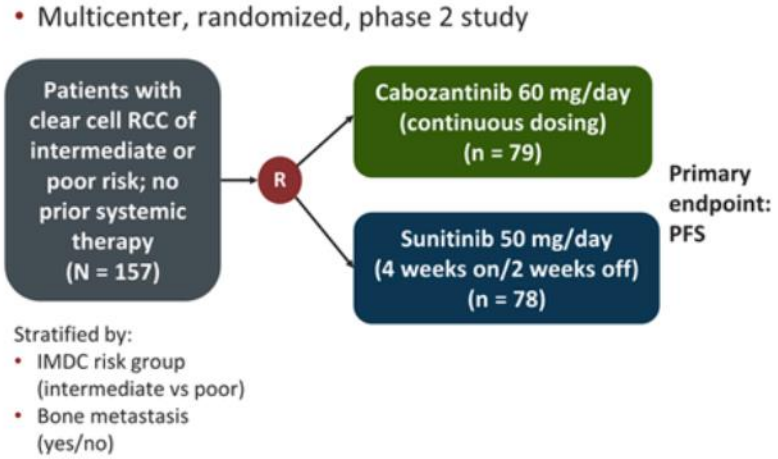
Is Sunitinib still a good comparator ?

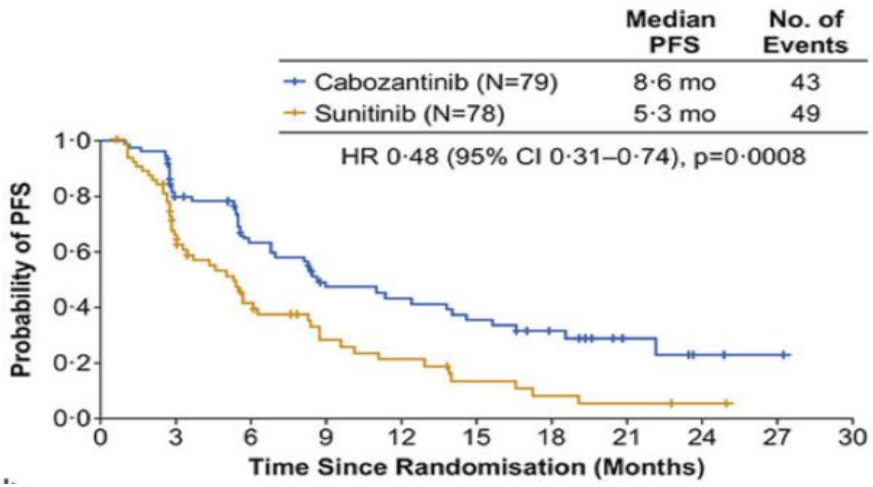
ELSEVIER journal homepage: www.ejcancer.com

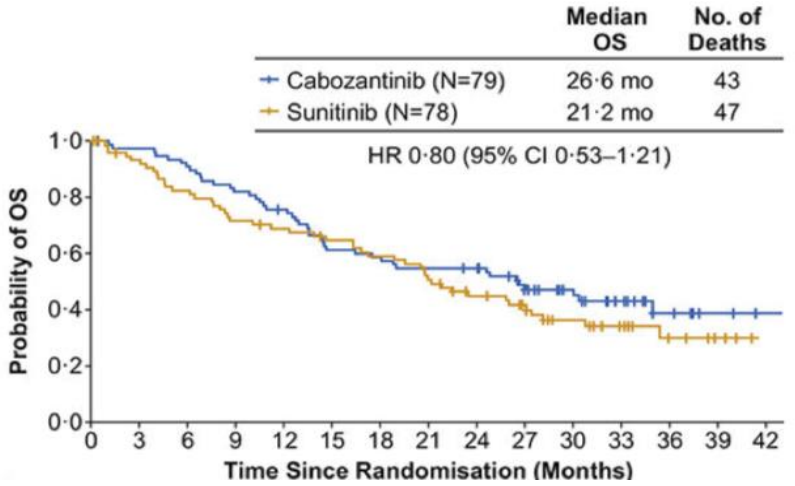
Original Research

Cabozantinib versus sunitinib as initial therapy for metastatic renal cell carcinoma of intermediate or poor risk (Alliance A031203 CABOSUN randomised trial): Progression-free survival by independent review and overall survival update

Toni K. Choueiri [a,*], Colin Hessel [b], Susan Halabi [c], Ben Sanford [d],





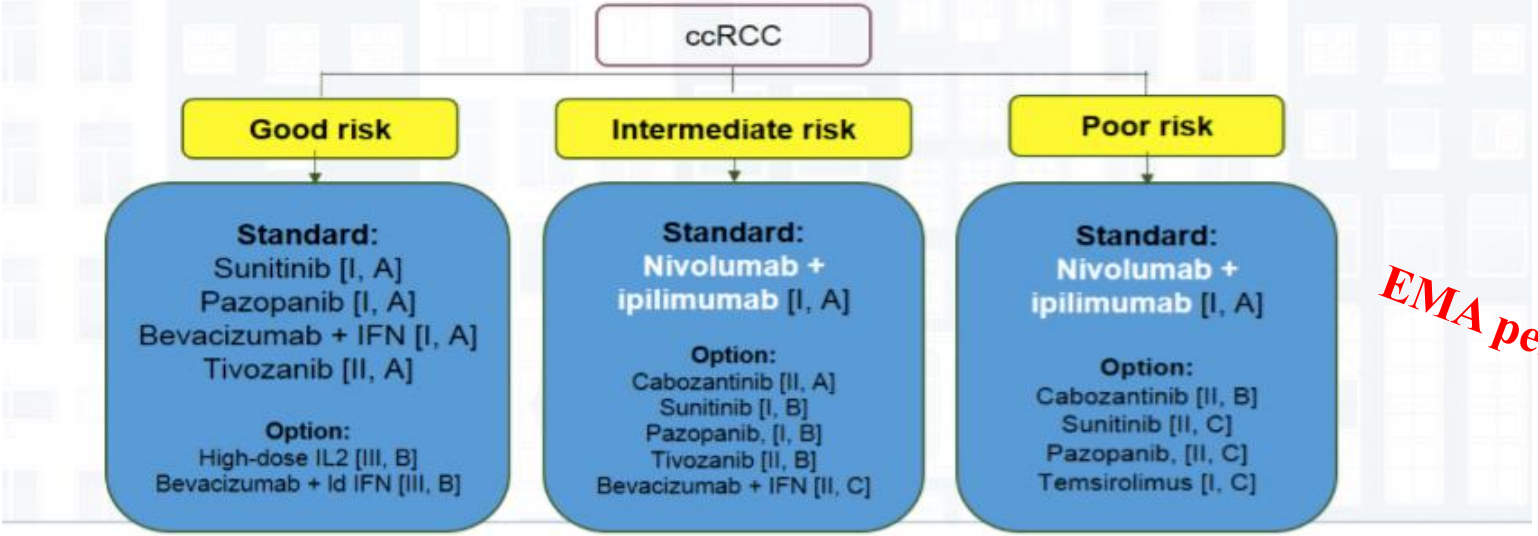


ORR : 20% vs 9%

FDA and EMA approved

ESMO GUIDELINES 2018
FIRST LINE CLEAR CELL RCC

EMUC18
8-11 November 2018
Amsterdam, The Netherlands



EMA pending

ICI + TKI ? In PDL1 + or in ITT?

Better PFS, improved RR !

TKI + ICI > sunitinib ?

➔ A good option if deep reponse required ?

➔ Maybe with Keynote 426 ???

In case of reponse (CR), what is duration of N/I administration ?

In patient refractory to TKI +ICI, what is the rescue ?

In case of CR, do we cure patients ?

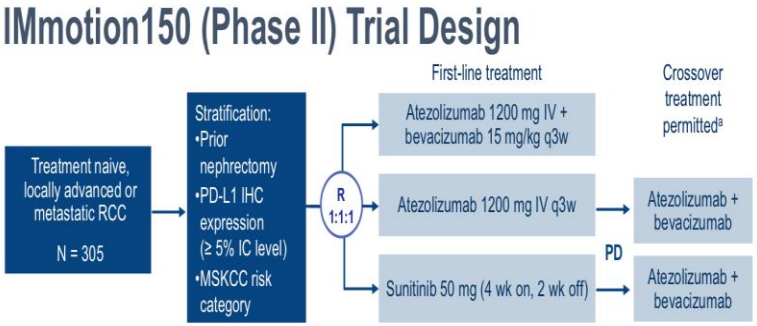
Merck's KEYTRUDA® (pembrolizumab) in Combination with Pfizer's Inlyta® (axitinib) Significantly Improved Overall Survival (OS) and Progression-free Survival (PFS) as First-Line Therapy for Advanced or Metastatic Renal Cell Carcinoma

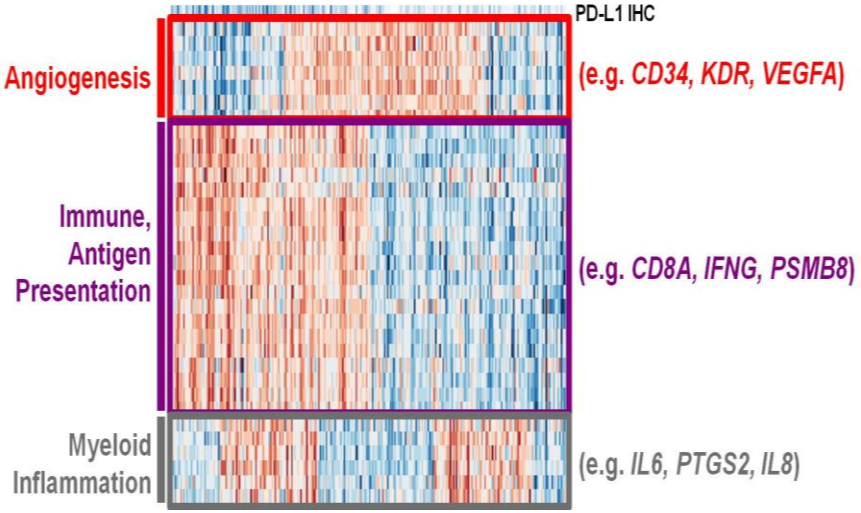
OCTOBER 18, 2018

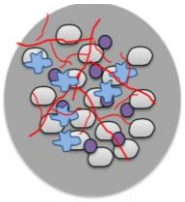
KEYTRUDA is First Anti-PD-1 Therapy in Combination to Improve Both OS and PFS in Advanced or Metastatic RCC, the Most Common Type of Kidney Cancer

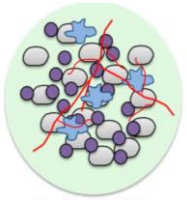
Pivotal Phase 3 KEYNOTE-426 Trial Met Both Primary Endpoints; Data to be Filed with Global Regulatory Authorities

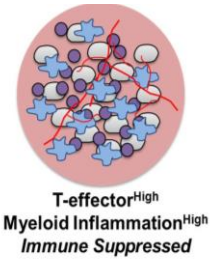
Transcriptomics to identify a potential biomarker of response.

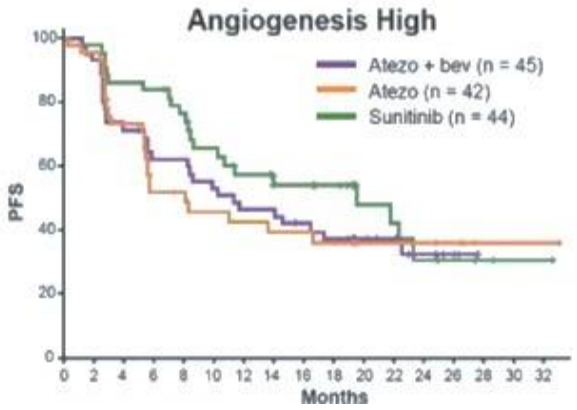


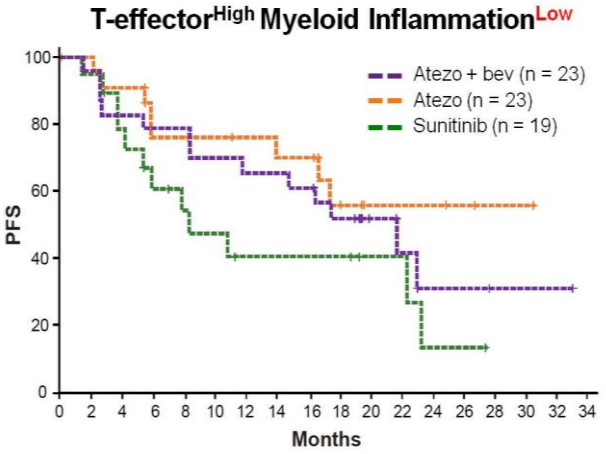


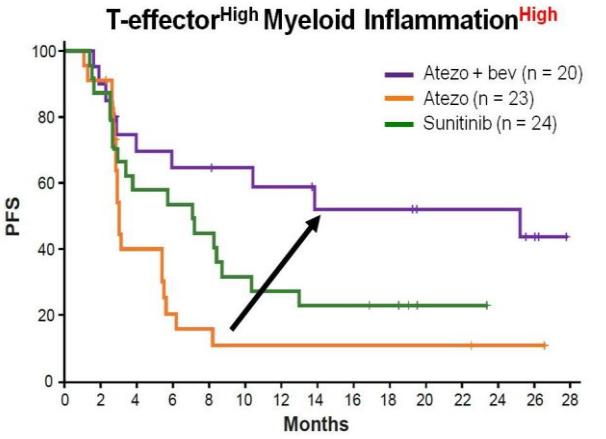




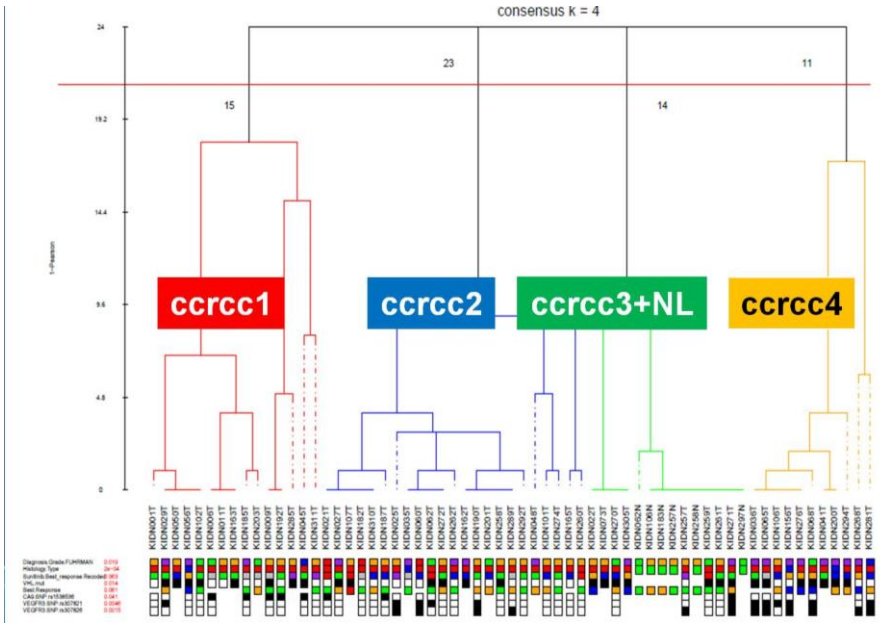


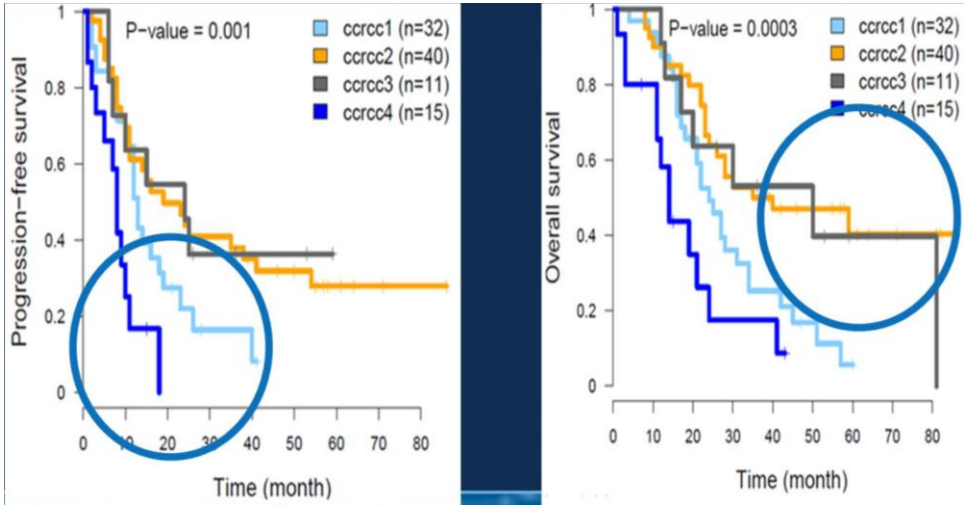




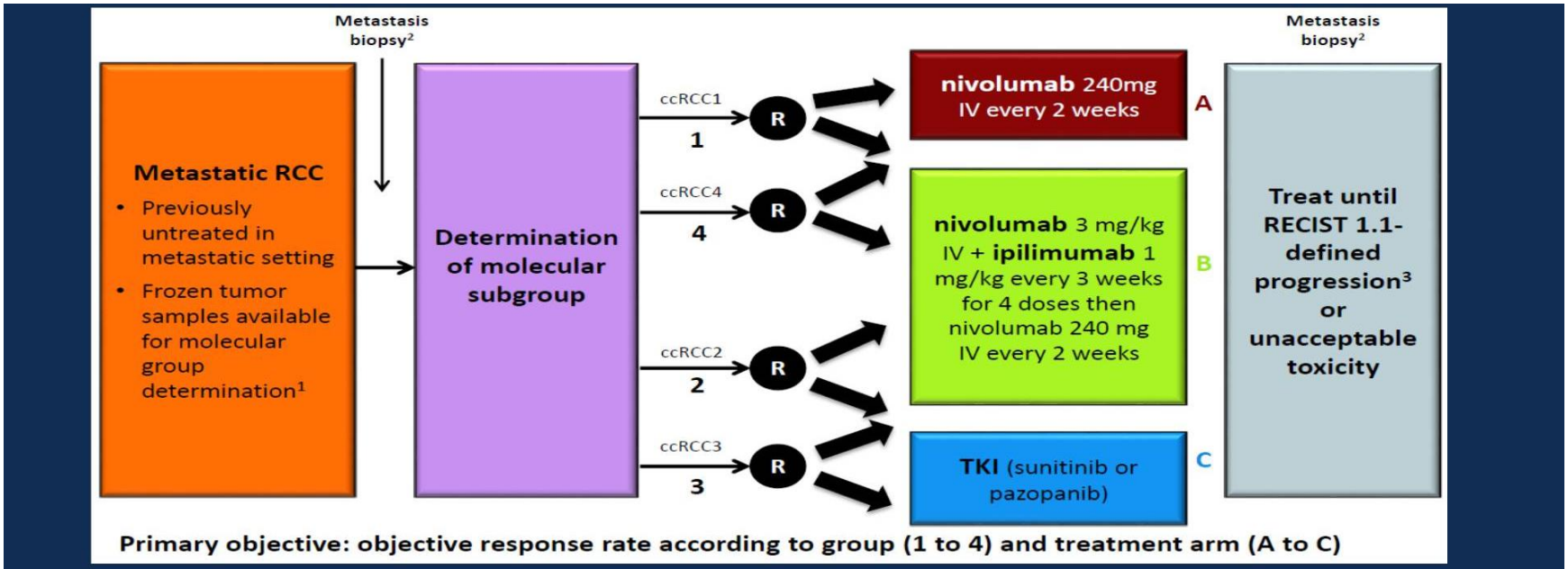


McDermott, D.F., et al. 2018. Nat. Med. 24:749–757.





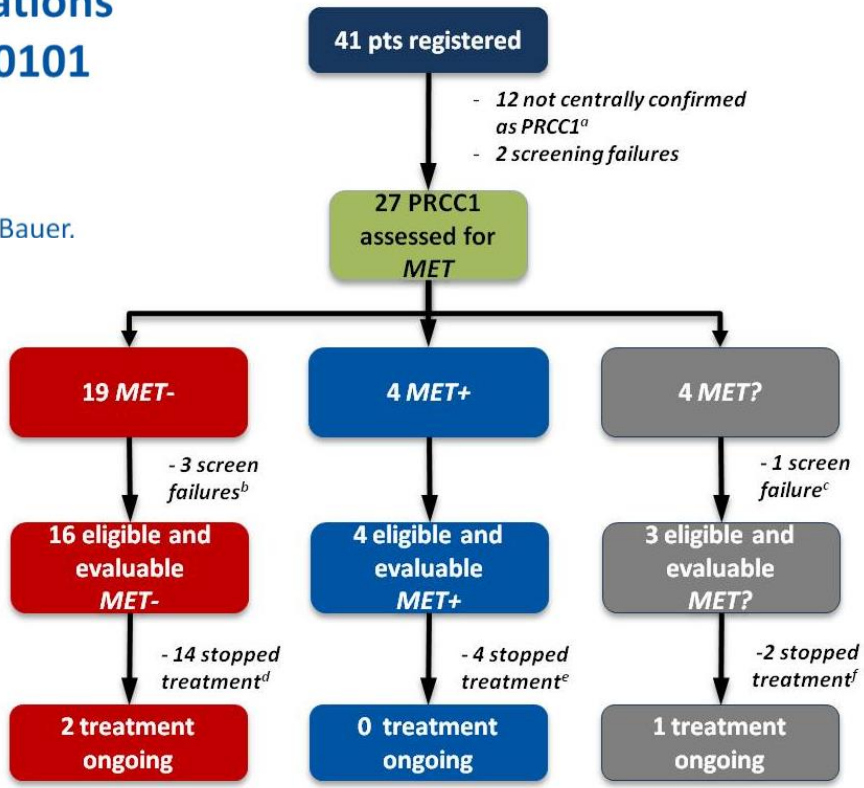
Beuselinck et al. CCR 2015



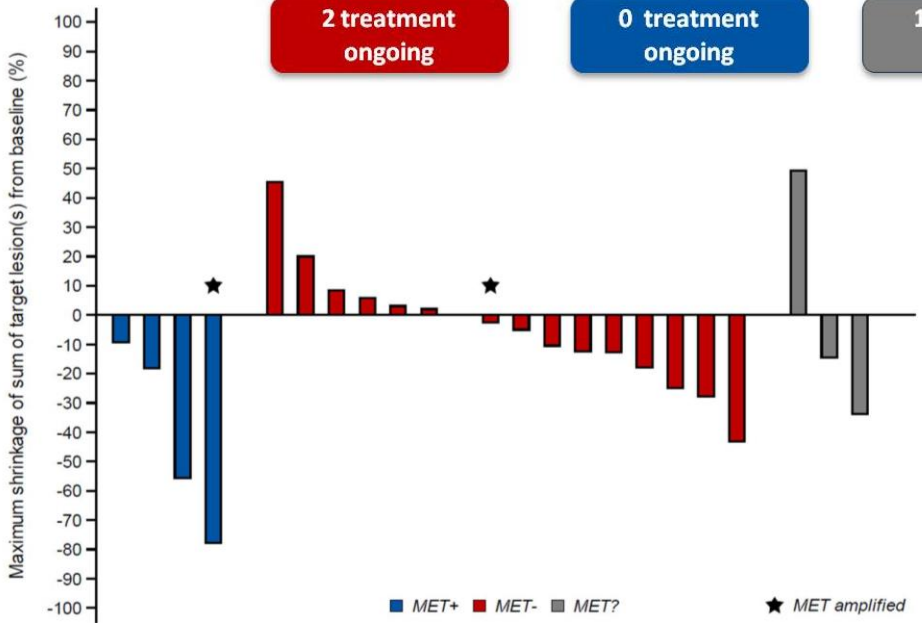
Crizotinib in patients with advanced papillary renal cell carcinoma type 1 with *MET* mutations or amplification: Final results of EORTC 90101 "CREATE"

P. Schöffski. A. Wozniak. B. Escudier. P. Rutkowski. A. Anthonev. S. Bauer.

- Sporadic and hereditary PRCC1 is associated with alterations of the *MET* proto-oncogene
  - Activating mutations in the kinase domain of *MET* (7q31.2) in 13-15% of non-hereditary PRCC
  - *MET* copy number alterations
  - Gains of chromosome 7 in up to 81% of cases

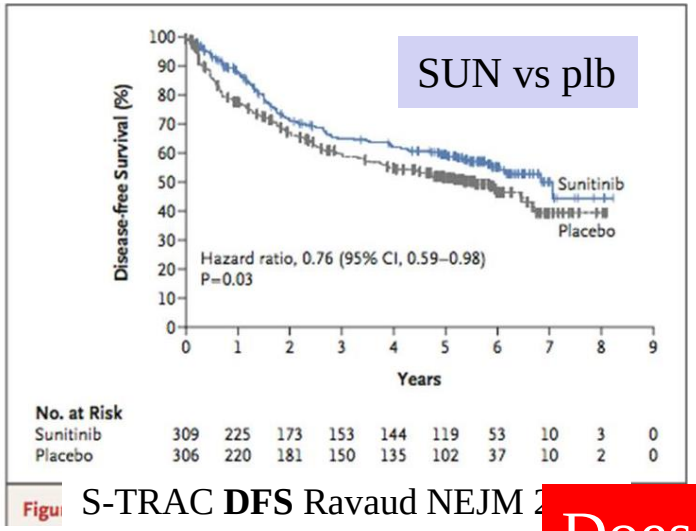


Crizotinib
= TKI Anti-Met

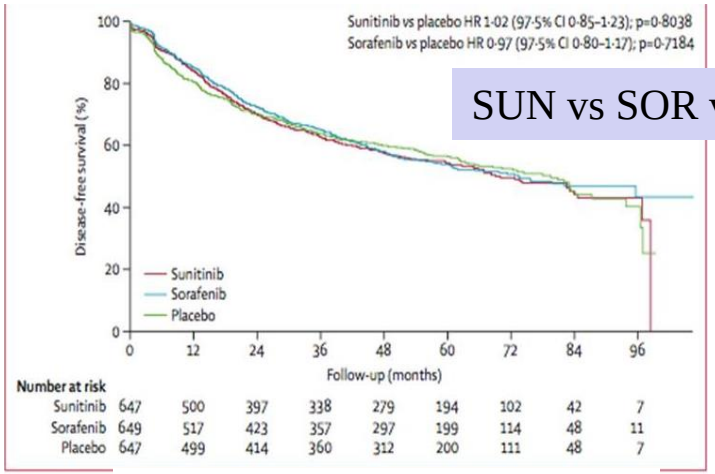


Localized Renal Cancer

TKI in Adjuvant setting ?

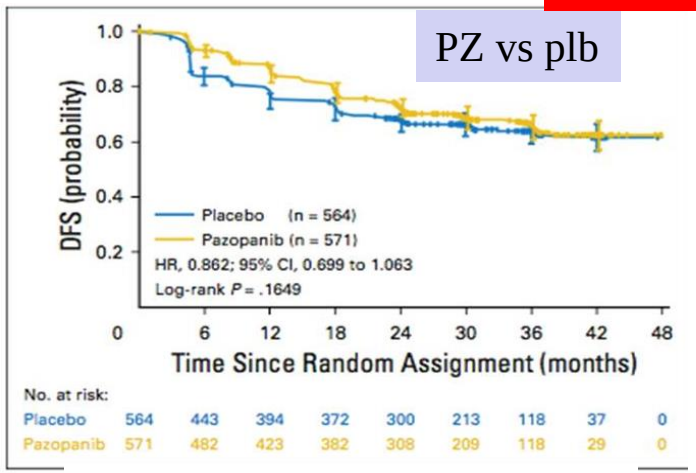


S-TRAC **DFS** Ravaud NEJM 2

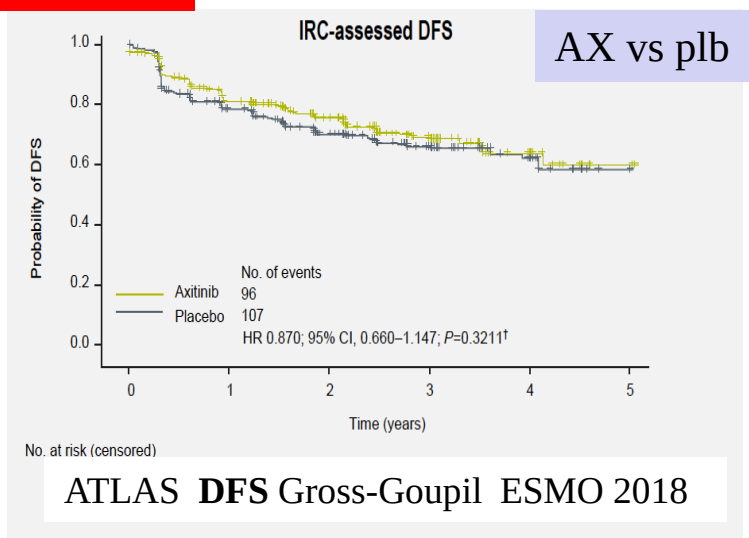


SURE **DFS** Haas Lancet 2016

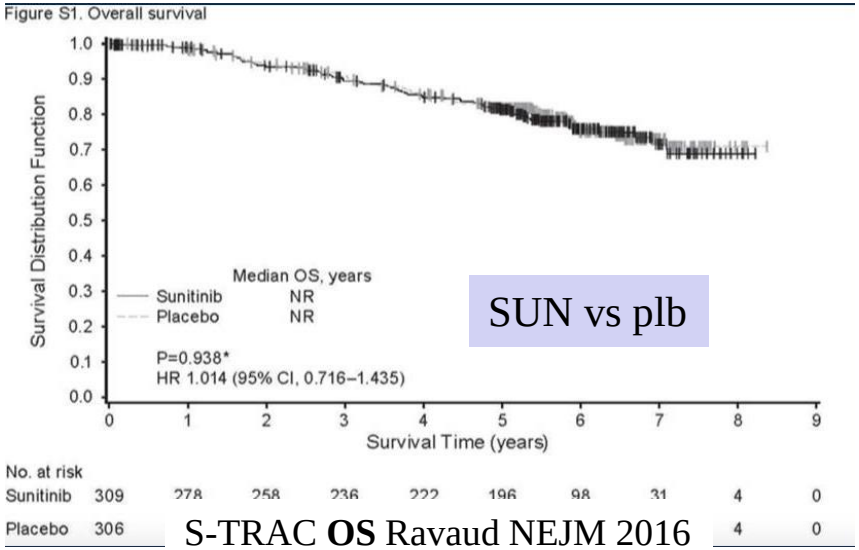
Does not CURE !!!



PROTECT **DFS** Motzer JCO 2017

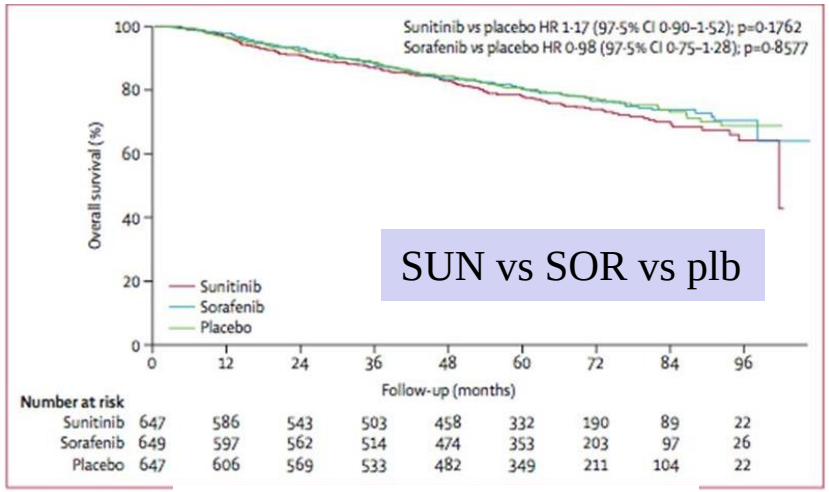


ATLAS **DFS** Gross-Goupil ESMO 2018



SUN vs plb

S-TRAC **OS** Ravaud NEJM 2016

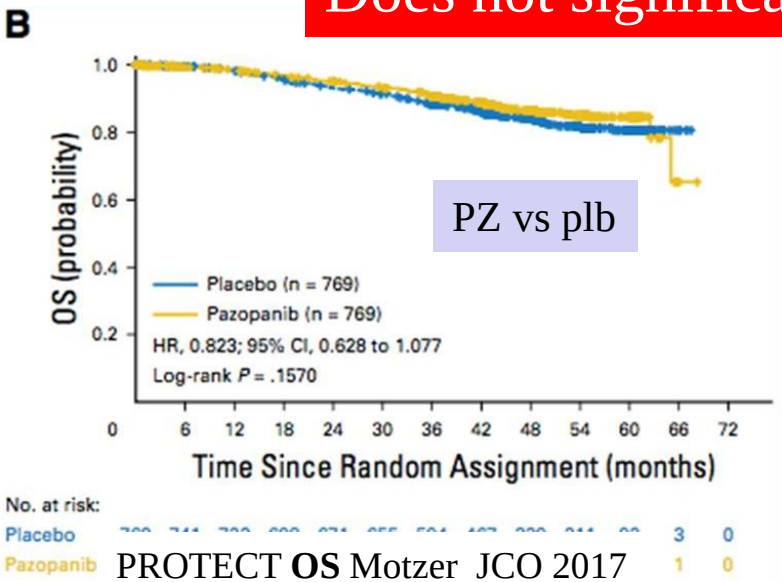


SUN vs SOR vs plb

Figure 3: Overall surviv
HR=hazard ratio.

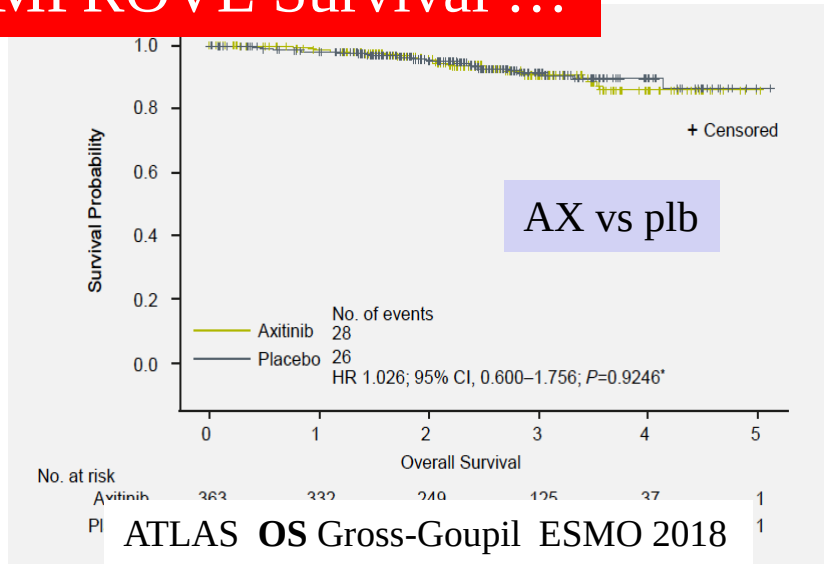
ASSURE **OS** Haas Lancet 2016

Does not significantly IMPROVE Survival !!!



PZ vs plb

PROTECT **OS** Motzer JCO 2017



AX vs plb

ATLAS **OS** Gross-Goupil ESMO 2018

	Sunitinib	Sorafenib	Placebo
grade	>3	>3	>3
ASSURE	63 %	70 %	24 %
S-TRAC	56.9 %	-	19.4 %
	Pazopanib		**Placebo**
grade	>3	-	>3
PROTECT	60 %	-	21 %

Assure Haas Lancet 2016 Protect OS Motzer JCO 2017 S-TRAC OS Ravaud, NEJM 2016

ADVERSE EVENTS !!!

No TKI in adjuvant setting in Europe !! (>< FDA)

Maybe better results with ICIs (cure ? Lessa AEs ?)

TKI remain a standard of care in RCC treatment

Nivo/ipilimumab is the new standard of care in Intermediate/poor risk group ccRCC

Awaiting Survival data for TKI + ICIs

Selection of patients is important, transciptomic, molecular, immunogram,…

Thank you