Het niercarcinoom in 2020: een update

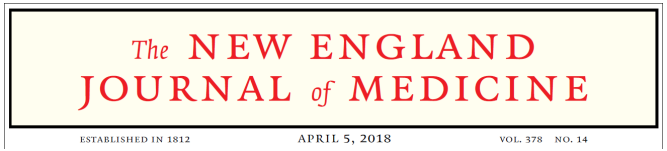
Nieuwe systeemtherapie in gemetastaseerde setting voor heldercellig en papillair RCC

Prof Dr Benoit Beuselinck
UZ Leuven
20/02/2020

FIRST LINE CCRCC

FIRST CHOICE	
IMDC G/I/P	Axitinib/pembrolizumab or axitinib/avelumab
IMDC I/P	Ipilimumab/nivolumab
IF CONTRA-INDICATION FOR ICPIs: AI DISEASES	
IMDC G	Sunitinib or pazopanib
IMDC I/P	Cabozantinib
IF CONTRA-INDICATION FOR ICPIs: ELDERLY (80+?)	
IMDC G	Sunitinib or pazopanib > nivolumab
IMDC I/P	Cabozantinib > nivolumab

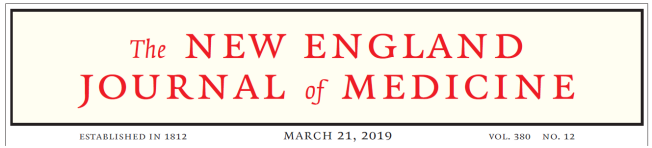
FIRST LINE CCRCC



Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma

The NEW ENGLAND JOURNAL of MEDICINE

Pembrolizumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma



Avelumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma

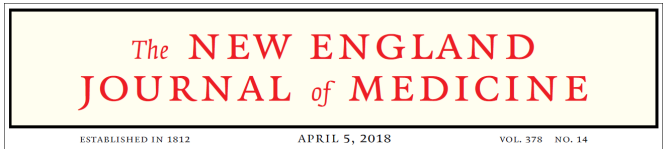
A

B

C

What will be your prefered 1L option from 01/03/2020 ?

FIRST LINE CCRCC

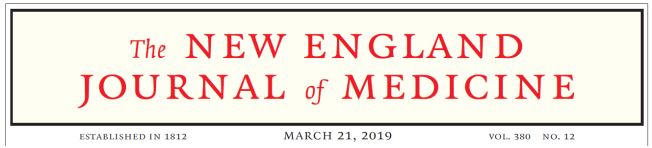


Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma

A

Pembrolizumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma

B



Avelumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma

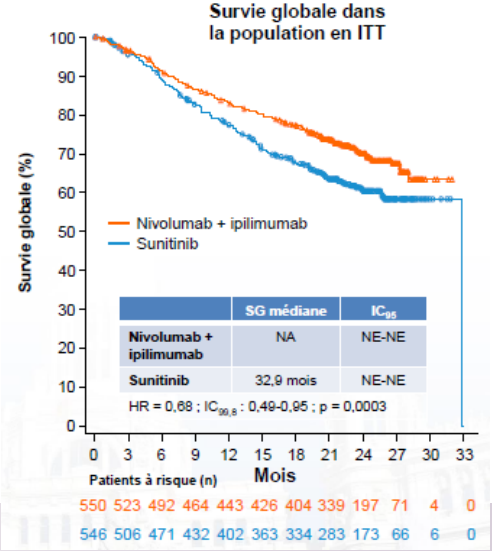
C

FIRST LINE CCRCC: IPILIMUMAB/NIVOLUMAB

CA209-214 phase III study: 1L m-ccRCC: ipilimumab/nivolumab versus sunitinib

In all patients

	IPI/NIVO	SUN	
RR	39%	32%	p=0,0191
PFS	12,4	12,3	p=0,85
OS	NR	32,9	p=0,0003

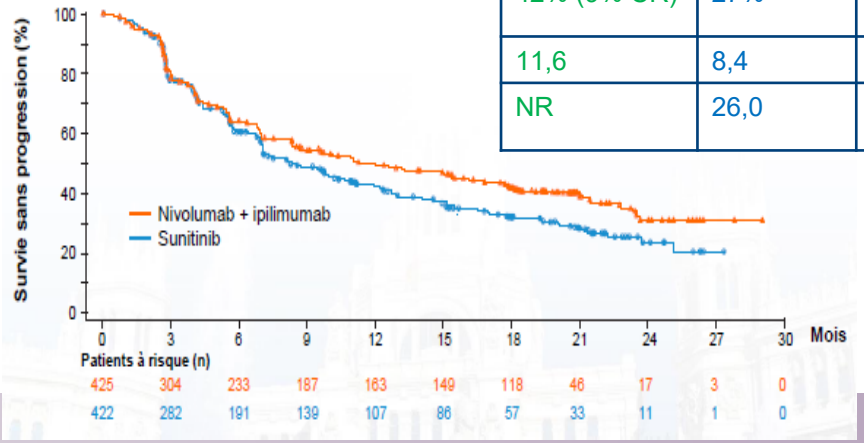


In good risk patients

IPI/NIVO	SUN	
29%	52%	P=0.0002
15,3	25,1	P<0,0001
NA	NA	NA

In intermediate and poor risk patients

IPI/NIVO	SUN	
42% (9% CR)	27%	P<0,0001
11,6	8,4	p=0,03
NR	26,0	P<0,0001

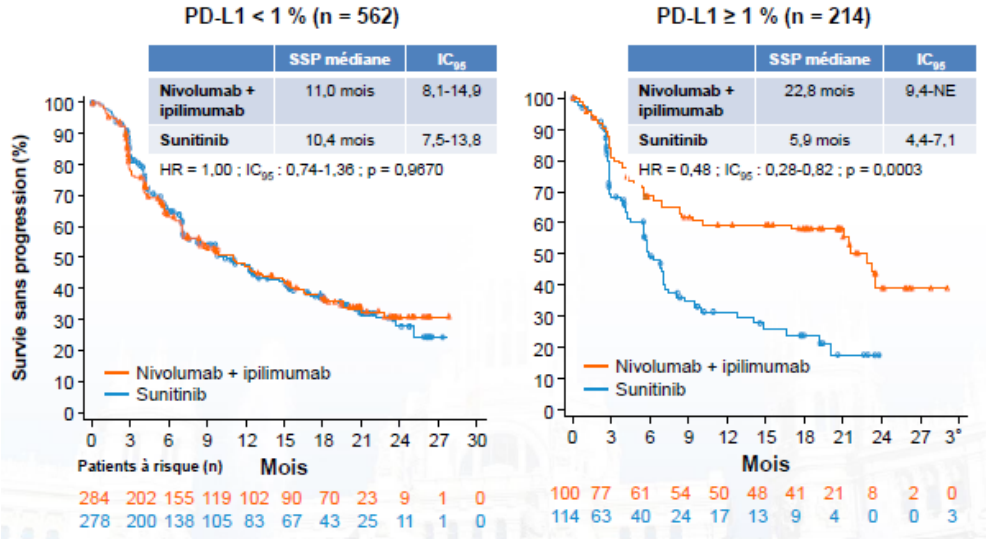


Escudier et al. ESMO 2017

FIRST LINE CCRCC: IPILIMUMAB/NIVOLUMAB

CA209-214 phase III study: 1L m-ccRCC: ipilimumab/nivolumab versus sunitinib

In intermediate/ poor risk pts



	ALL			PDL1<1%			PDL≥1%		
	IPI/NIVO	SUN		IPI/NIVO	SUN		IPI/NIVO	SUN	
RR	42% (9% CR)	27%	P<0,0001	37%	28%	P=0,03	58% (CR 16%)	22%	P<0,001
PFS	11,6	8,4	p=0,03	11,0	10,4	P=0,96	22,8	5,9	P=0,0003
OS	NR	26,0	P<0,0001	NR	NR	HR 0,73 (95%CI 0,56-0,96)	NR	19,6	HR 0,45 (95%CI 0,29-0,71)

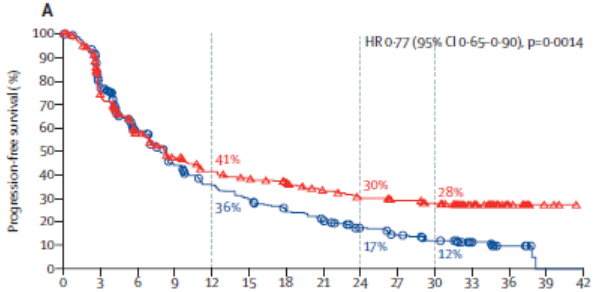
Escudier et al. ESMO 2017

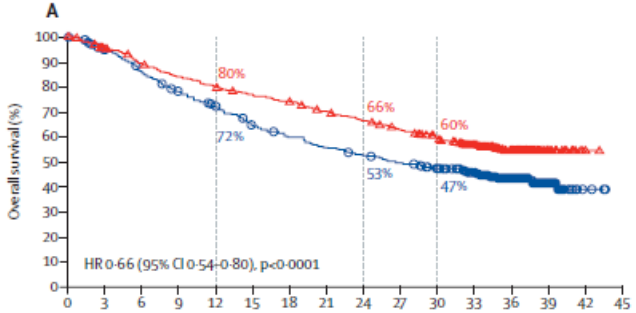
FIRST LINE CCRCC: IPILIMUMAB/NIVOLUMAB

CA209-214 phase III study: 1L m-ccRCC: ipilimumab/nivolumab versus sunitinib

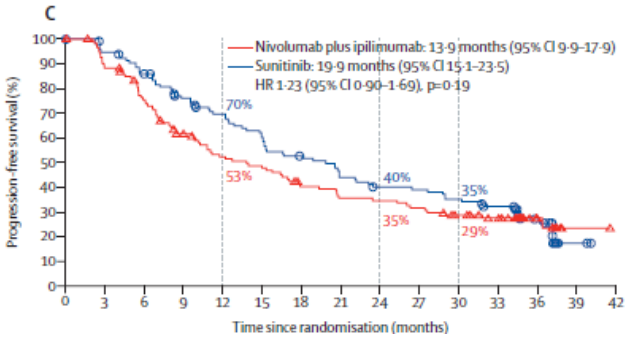
30 months follow up

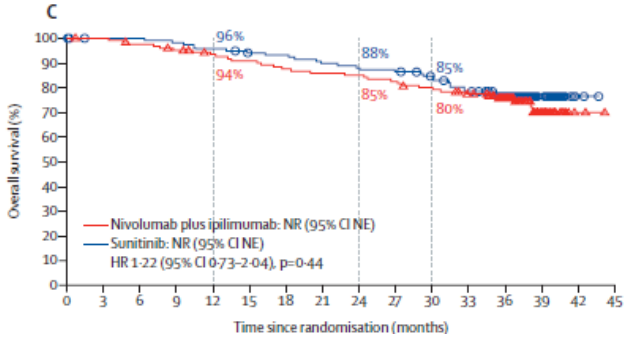
IMDC Intermediate and poor risk





IMDC Good risk





	IPI/NIVO	SUN
RR	31% **(CR 8%)**	**46%** (CR 4%)

Better RR and PFS does not translate into better OS …
CR rate is double in ipi/nivo in IMDC good risk patients
Ipi/nivo only available in 1L … an opportunity not to miss?

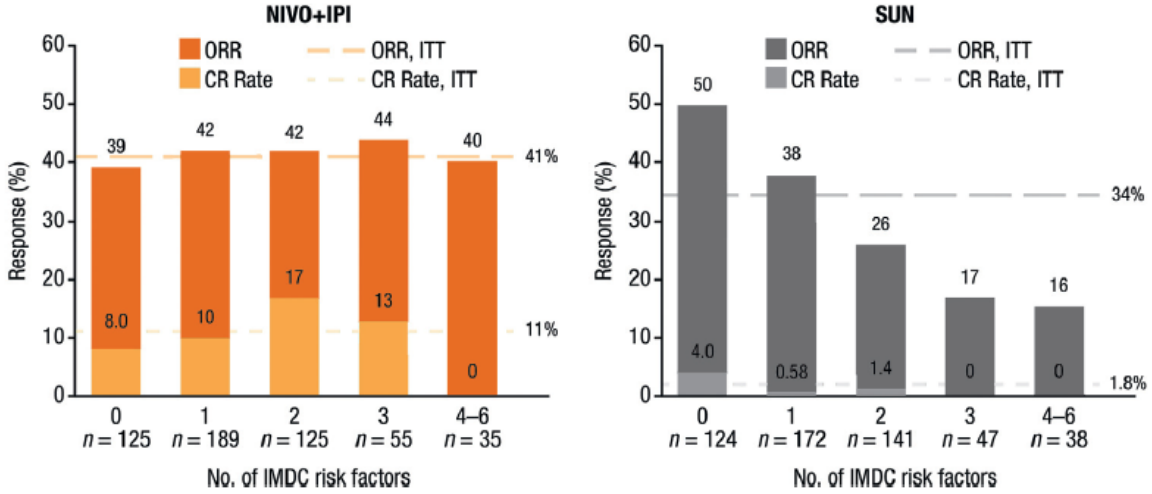
Motzer, Beuselinck, et al, Lancet Oncology 2019

FIRST LINE CCRCC: IPILIMUMAB/NIVOLUMAB

CA209-214 phase III study: 1L m-ccRCC: ipilimumab/nivolumab versus sunitinib

Number of IMDC risk factors

- ORR on ipi/nivo are equal across all IMDC risk groups, but decrease on sun with increasing IMDC risk factors
- The OS benefit from ipi/nivo versus sun increases with the number of IMDC risk factors
- However, global prognosis is not inverted … IMDC intermediate/poor still have poorer outcome than IMDC good risk patients

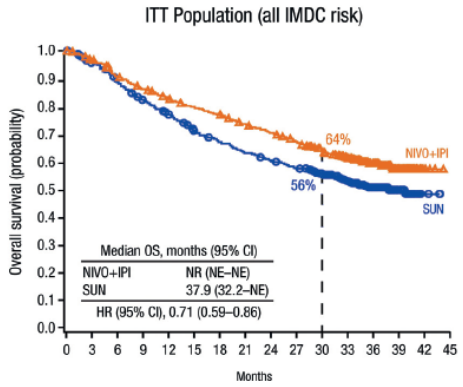


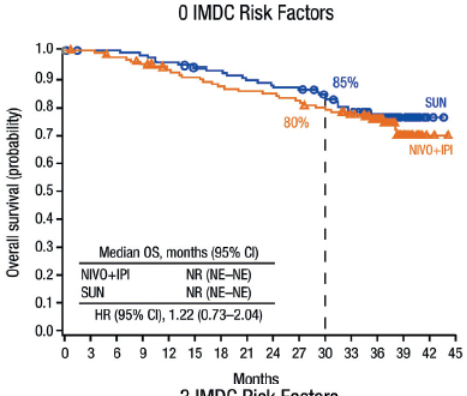
Escudier et al. Eur Uro 2019

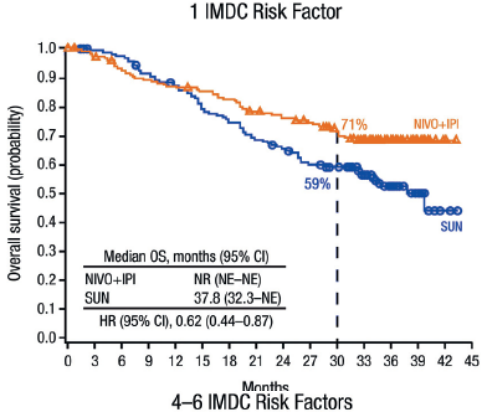
FIRST LINE CCRCC: IPILIMUMAB/NIVOLUMAB

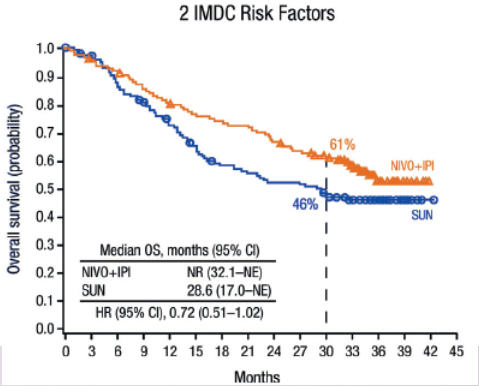
CA209-214 phase III study: 1L m-ccRCC: ipilimumab/nivolumab versus sunitinib

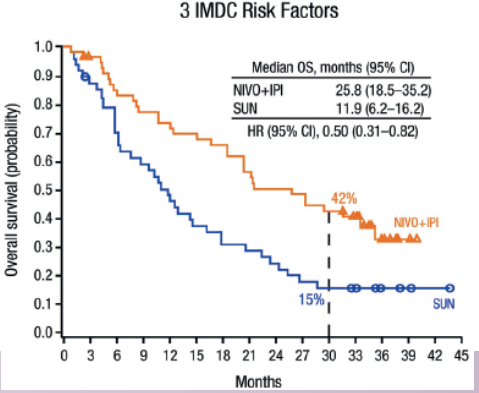
Number of IMDC risk factors

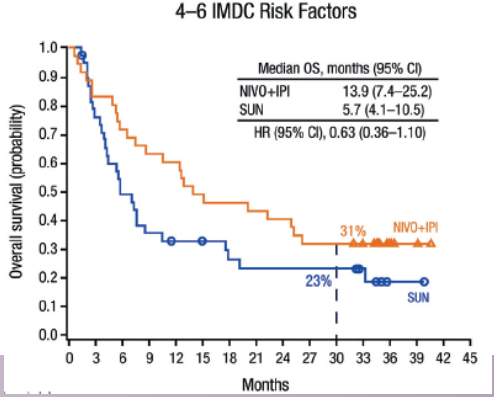








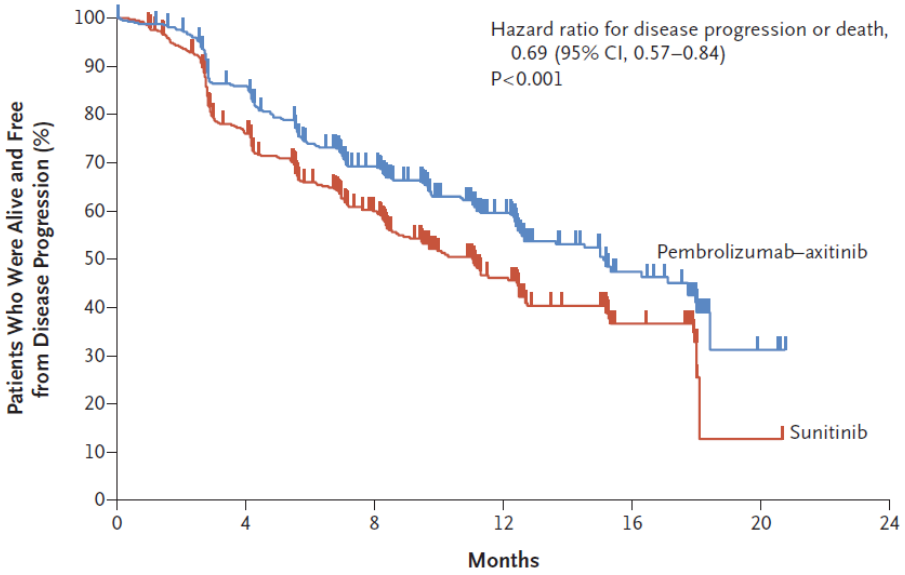


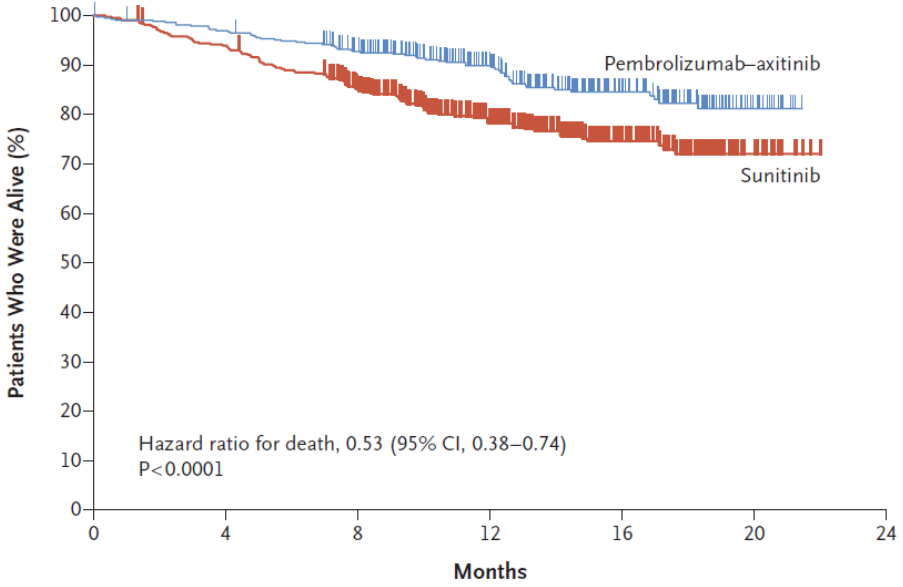


Escudier et al. Eur Uro 2019

FIRST LINE CCRCC: AXITINIB/PEMBROLIZUMAB VERSUS SUNITINIB

KEYNOTE 426: Pembrolizumab 200 mg Q3W en axitinib 2x 5 mg/d versus sunitinib 50 mg/d





Rini et al. NEJM 2019.

FIRST LINE CCRCC: AXITINIB/PEMBROLIZUMAB VERSUS SUNITINIB

KEYNOTE 426: Pembrolizumab 200 mg Q3W en axitinib 2x 5 mg/d versus sunitinib 50 mg/d

Table 2. Summary of Confirmed Objective Response.*

Variable	Pembrolizumab–Axitinib (N = 432)	Sunitinib (N = 429)
Objective response rate — % (95% CI)†	59.3 (54.5 to 63.9)	35.7 (31.1 to 40.4)
Best overall response — no. (%)		
Complete response	25 (5.8)	8 (1.9)
Partial response	231 (53.5)	145 (33.8)
Stable disease	106 (24.5)	169 (39.4)
Progressive disease	47 (10.9)	73 (17.0)
Could not be evaluated‡	8 (1.9)	6 (1.4)
Not assessed§	15 (3.5)	28 (6.5)
Median time to response (range) — mo¶	2.8 (1.5 to 16.6)	2.9 (2.1 to 15.1)
Median duration of response (range) — mo‖	Not reached (1.4+ to 18.2+)	15.2 (1.1+ to 15.4+)

Rini et al. NEJM 2019.

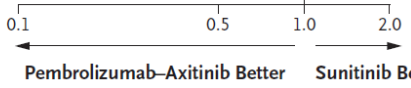
FIRST LINE CCRCC: AXITINIB/PEMBROLIZUMAB VERSUS SUNITINIB

KEYNOTE 426: Pembrolizumab 200 mg Q3W en axitinib 2x 5 mg/d versus sunitinib 50 mg/d

Benefit across subgroups: IMDC G/I/P and PDL1+ or PDL1-

Progression-free Survival According to Subgroup

Subgroup	No. of Instances of Disease Progression or Death/No. of Patients	Hazard Ratio for Disease Progression or Death (95% CI)
Overall	395/861	0.69 (0.57–0.84)
Age		
<65 yr	248/538	0.70 (0.54–0.90)
≥65 yr	147/323	0.63 (0.45–0.88)
Sex		
Male	287/628	0.77 (0.61–0.97)
Female	108/233	0.54 (0.37–0.81)
Region of enrollment		
North America	75/207	0.79 (0.50–1.25)
Western Europe	97/210	0.59 (0.39–0.89)
Rest of the world	223/444	0.71 (0.54–0.92)
IMDC risk category		
Favorable	90/269	0.81 (0.53–1.24)
Intermediate	232/484	0.70 (0.54–0.91)
Poor	73/108	0.58 (0.35–0.94)
Karnofsky performance-status score		
90 or 100	292/688	0.69 (0.54–0.87)
70 or 80	102/172	0.67 (0.45–1.00)
PD-L1 combined positive score		
<1	137/325	0.87 (0.62–1.23)
≥1	240/497	0.62 (0.47–0.80)
No. of organs with metastases		
1	75/210	0.54 (0.33–0.87)
≥2	317/646	0.73 (0.58–0.91)



Rini et al. NEJM 2019.

FIRST LINE CCRCC: AXITINIB/PEMBROLIZUMAB VERSUS SUNITINIB

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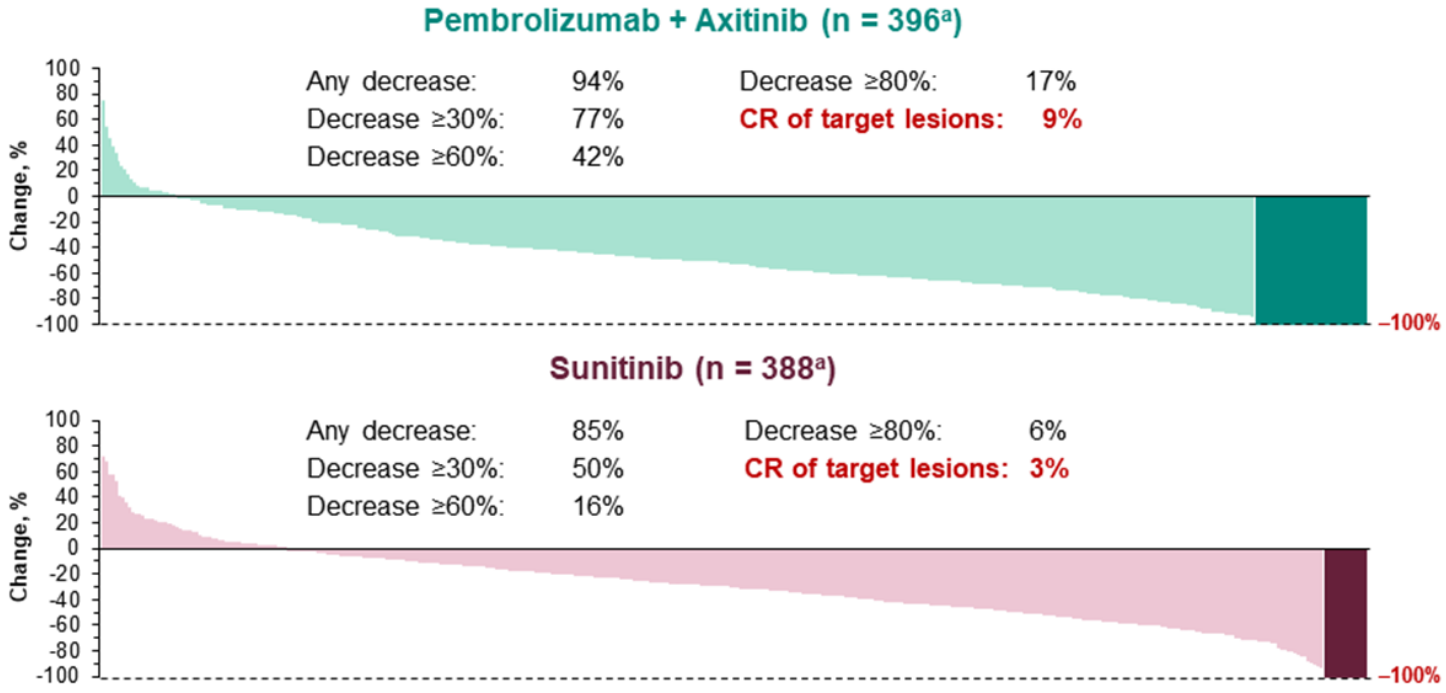
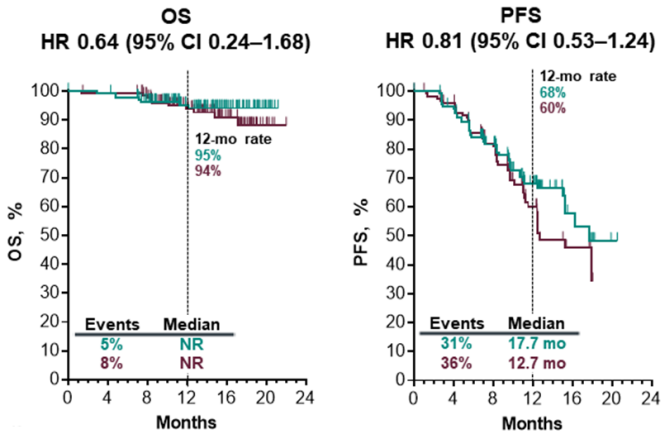


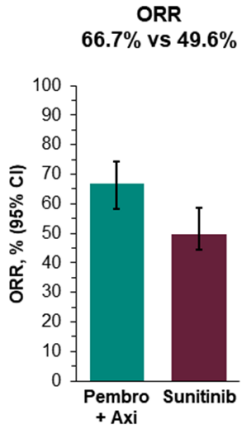
Rini et al. NEJM 2019.

FIRST LINE CCRCC: AXITINIB/PEMBROLIZUMAB VERSUS SUNITINIB

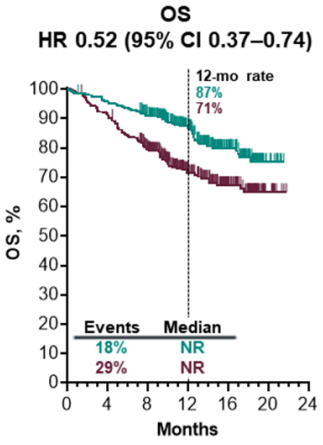
Keynote 426: phase III pembrolizumab+axitinib versus sunitinib

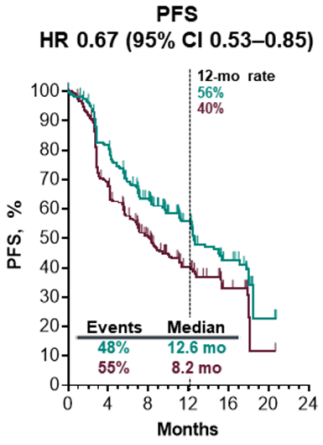
IMDC Favorable Risk

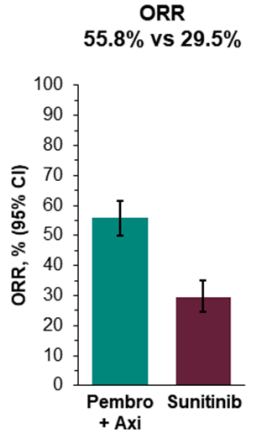




IMDC Intermediate/Poor Risk

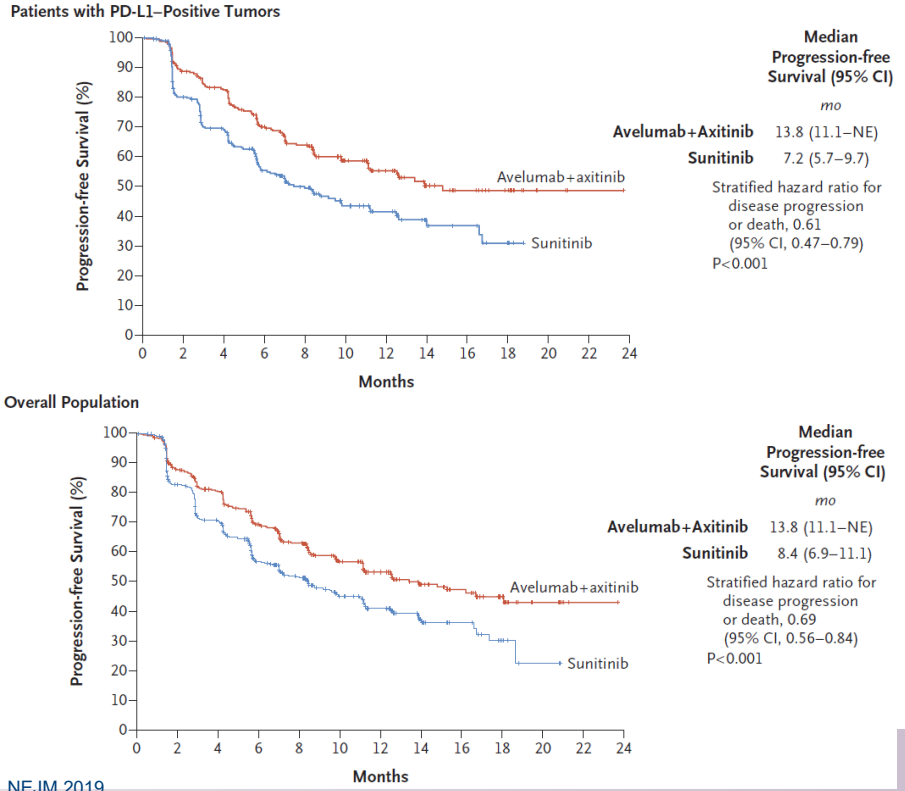


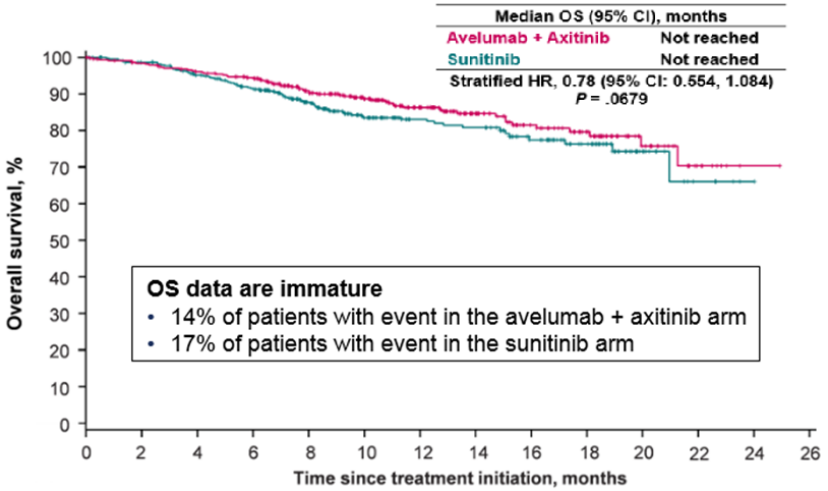




FIRST LINE CCRCC: AVELUMAB+AXITINIB

JAVELIN 101: Avelumab 10 mg/kg Q2W + Axitinib 2x 5 mg/d versus sunitinib 50 mg/d





Motzer et al. NEJM 2019.

FIRST LINE CCRCC: AVELUMAB+AXITINIB

JAVELIN 101: Avelumab 10 mg/kg Q2W + Axitinib 2x 5 mg/d versus sunitinib 50 mg/d

Table 2. Antitumor Activity among Patients with PD-L1–Positive Tumors and in the Overall Population.*

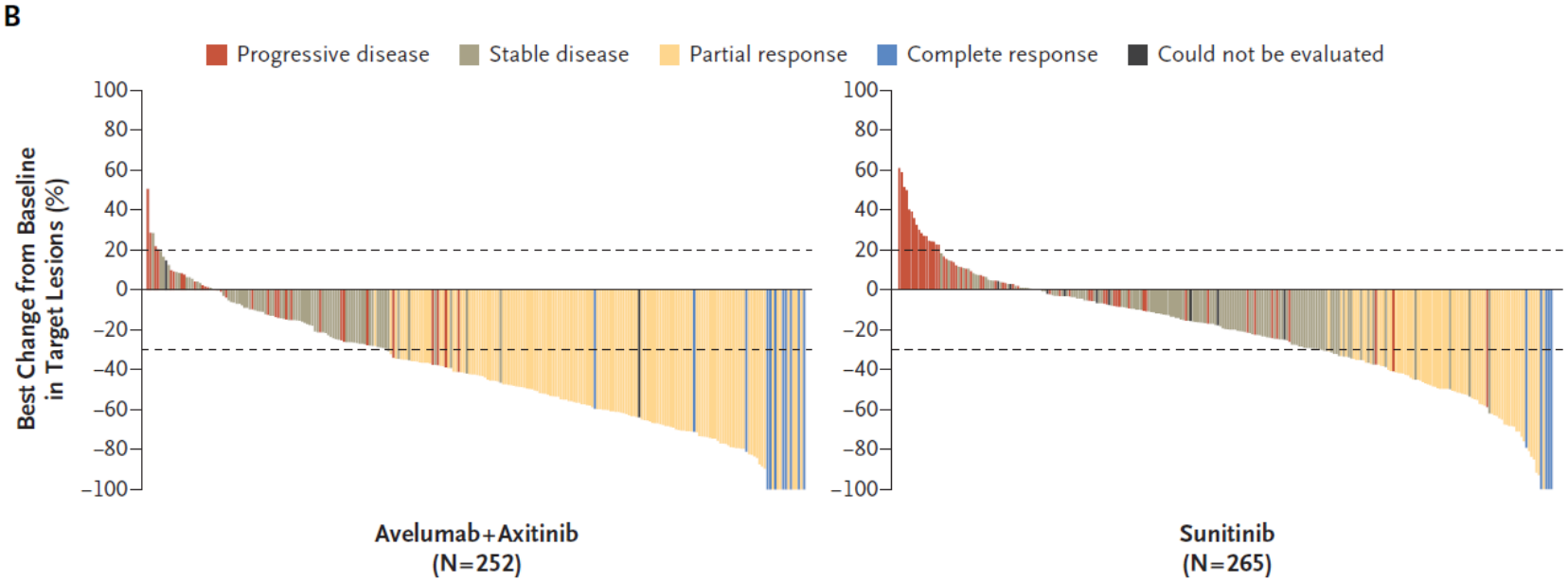
Variable	Patients with PD-L1–Positive Tumors		Overall Population	
	Avelumab plus Axitinib (N=270)	Sunitinib (N=290)	Avelumab plus Axitinib (N=442)	Sunitinib (N=444)
Confirmed objective response rate (95% CI) — %	55.2 (49.0–61.2)	25.5 (20.6–30.9)†	51.4 (46.6–56.1)	25.7 (21.7–30.0)‡
Confirmed best overall response — no. (%)				
Complete response	12 (4.4)	6 (2.1)	15 (3.4)	8 (1.8)
Partial response	137 (50.7)	68 (23.4)	212 (48.0)	106 (23.9)
Stable disease	72 (26.7)	125 (43.1)	131 (29.6)	202 (45.5)
Progressive disease	30 (11.1)	63 (21.7)	51 (11.5)	83 (18.7)
Could not be evaluated	12 (4.4)§	21 (7.2)¶	25 (5.7)‖	35 (7.9)**
Other††	7 (2.6)	7 (2.4)	8 (1.8)	10 (2.3)
Median time to response (range) — mo	1.6 (1.2–10.1)	3.0 (1.2–11.6)	2.6 (1.2–13.8)	3.2 (1.2–11.6)
Median duration of response (95% CI) — mo	NR (NE)	NR (10.9–NE)	NR (NE)	NR (11.2–NE)
Patients with ongoing response — no./total no. (%)	108/149 (72.5)	48/74 (64.9)	158/227 (69.6)	81/114 (71.1)

Motzer et al. NEJM 2019.

FIRST LINE CCRCC: AVELUMAB+AXITINIB

JAVELIN 101: Avelumab 10 mg/kg Q2W + Axitinib 2x 5 mg/d versus sunitinib 50 mg/d

Best % change from baseline in PDL1+ tumors



Motzer et al. NEJM 2019.

FIRST LINE CCRCC: COMPARISON OF EFFICACY

Table 1. Comparisons among Trials of Combination Therapy vs. Sunitinib for Patients with Metastatic Renal-Cell Carcinoma.*

Variable	Trial of Pembrolizumab plus Axitinib vs. Sunitinib[5] (N=861)	Trial of Avelumab plus Axitinib vs. Sunitinib[4] (N=886)	Trial of Nivolumab plus Ipilimumab vs. Sunitinib[3] (N=1096)
IMDC prognostic risk (% of patients)†			
Favorable	31.2	21.4	23
Intermediate	56.2	61.8	61
Poor	12.6	16.2	17
Quantifiable tumor PD-L1 expression ≥1% (% of patients)	60.5	63.2	24
Overall survival			
Hazard ratio for death	0.53	0.78	0.68
CI	95% CI, 0.38–0.74	95% CI, 0.55–1.08	99.8% CI, 0.49–0.95
P value	<0.0001	0.14	<0.001
Median progression-free survival (mo)			
Combination therapy group	15.1	13.8	12.4
Sunitinib group	11.1	8.4	12.3
Objective response in combination-therapy group (% of patients)	59.3	51.4	39.0
Complete response in combination-therapy group (% of patients)	5.8	3.4	10.2
Median follow-up (mo)	12.8	11.6	25.2

Escudier et al. NEJM 2019.

FIRST LINE CCRCC: COMPARISON OF TOXICITY

	Ipilimumab/ nivolumab	Avelumab/ axitinib	Pembrolizumab/ axitinib
All grades	93%	99,5%	98,4%
Grade ≥3	46%	71,2%	75,8%
Diarrhea all grades	27%	62,2%	54,3%
Diarrhea Grade ≥3	4%	6,7%	9,1%
Stomatitis all grades	4%	23,5%	15,6%
Stomatitis Grade ≥3	0%	1,8%	0,7%
Handfootsyndrome all G	<1%	33,4%	28,0%
Handfootsyndrome G≥3	0%	5,8%	5,1%
Hypertension all G	2%	49,5%	44,5%
Hypertension G≥3	<1%	25,6%	22,1%
Hypothyroidism all G	16%	24,9%	35,4%
Hypothyroidism G≥3	<1%	0,2%	0,2%
Pruritus all G	28%	14,1%	15,2%
Pruritus G≥3	<1%	0%	0,2%
Dysgeusia	6%	13,1%	11,0%
Anorexia all G	14%	26,3%	29,6%
Anorexia G≥3	1%	2,1%	2,8%

Motzer et al. NEJM 2019.

SECOND LINE CCRCC

FIRST LINE		SECOND LINE
IMDC G/I/P	Axitinib/pembrolizumab or axitinib/avelumab	Cabozantinib
IMDC I/P	Ipilimumab/nivolumab	Cabozantinib or axitinib
IF CONTRA-INDICATION FOR ICPIs: AI DISEASES (SEVERE)		
IMDC G	Sunitinib or pazopanib	Cabozantinib or axitinib
IMDC I/P	Cabozantinib	Axitinib
IF CONTRA-INDICATION FOR ICPIs: ELDERLY (80+?)		
IMDC G	Sunitinib or pazopanib	Nivolumab
IMDC I/P	Cabozantinib	Nivolumab

- Cabozantinib: ook cMET
- Axitinib: optitratie mogelijk

SECOND LINE CCRCC

Efficacy of VEGFR-TKIs after ICPIs

		n	mPFS	PR	CR	SD	PD
VEGFR-TKIs in 2L after ICPIs in 1L							
1L ICPIs (1)	2L VEGFR-TKI	70	13.2M	40%	2%	53%	7%
1L IPI/NIVO (2)	2L VEGFR-TKI	28	5.4M (TTF)	45%	NR	NR	NR
1L IPI/NIVO (3)	2L VEGFR-TKI	33	8.0M	36%	NR	39%	15%
VEGFR-TKIs after ICPIs (not strictly 1L)							
ICPIs (4)	VEGFR-TKI	276	6.1M	NR	NR	NR	NR
ICPIs (5)	Axitinib	40	8.8M	45%	3%	45%	10%
ICPIs (6)	VEGFR-TKI	47	8.4M	36%	NR	43%	21%

YES! VEGFR-TKIs are efficient after ICIs!

(1) Shah et al. EJC 2019
(2) Dudani, Beuselinck et al. Eur Uro 2019
(3) Auvray et al. EJC 2019
(4) Graham, Beuselinck et al. Eur Uro Onco 2019
(5) Ornstein et al, Lancet 2019
(6) Nadal et al. Annals of Oncology 2016

SECOND LINE CCRCC

Efficacy of VEGFR-TKIs in 2L after ICPI-combo or VEGFR-TKI+ICPI in 1L

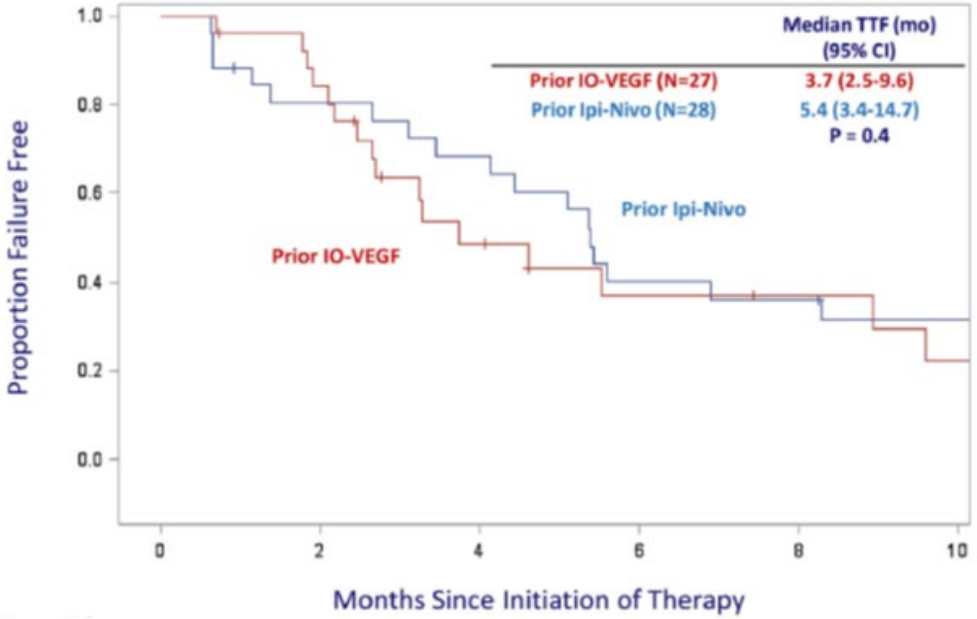


Table 3 – Outcomes with second-line VEGF-based therapy.

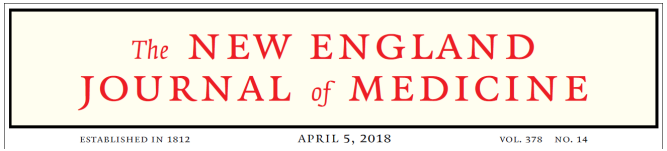
	Prior IO-VEGF ($N = 27$)	Prior Ipi-nivo ($N = 28$)	p value
Response rate	3/20 (15%)	9/20 (45%)	0.04
Time to treatment failure (mo)	3.7	5.4	0.4

IOVE = immuno-oncology and vascular endothelial growth factor; ipi-nivo = ipilimumab and nivolumab; VEGF = vascular endothelial growth factor.

FIRST LINE CCRCC

	Ipilimumab/nivolumab	Avelumab-pembrolizumab/axitinib
EFFICACY PR	39%	51,4% / 59,3%
EFFICACY CR	8% IMDC good risk 11% IMDC intermediate/poor risk 16% IMDC int/poor PDL1+	9% pembro/axitinib Increasing with longer follow-up
Easy response evaluation	Pseudo-progression in 10%	No pseudo-progression ⇒ Easier response evaluation ⇒ No myelumcompression
Toxicity	Less toxicity Decreases with time	Increasing with longer duration TKI Which product is responsible?
Sequencing	VEGFR-TKI-naive at start 2L Better RR/PFS on VEGFR-TKI in 2L	Are progressing on VEGFR-TKI … Poorer RR/PFS on VEGFR-TKI in 2L
Reimbursement criteria	Only opportunity to administer ipilimumab	VGEFR-TKIs can be given from 2L on
Price (pt of 75 kg)	1Y: 105.560 EURO 2Y: 84.890 EURO	Avelumab/axitinib: 146.393 EURO/Y Pembro/axitinib: 171.057 EURO/Y

FIRST LINE CCRCC

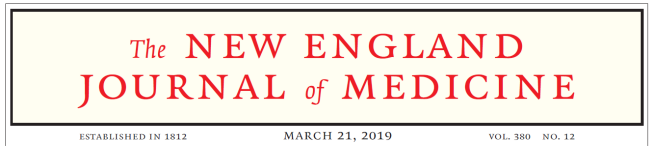


Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Pembrolizumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma



Avelumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma

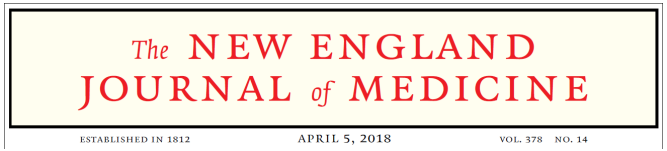
A

B

C

What will be your prefered 1L option from 01/03/2020 ?

FIRST LINE CCRCC

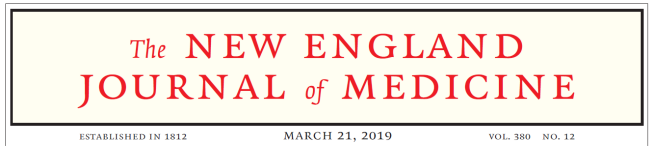


Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma

A

Pembrolizumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma

B



Avelumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma

C

THIRD LINE CCRCC

FIRST LINE		SECOND LINE	THIRD LINE
IMDC G/I/P	Axitinib/pembrolizumab or axitinib/avelumab	Cabozantinib	Everolimus?
IMDC I/P	Ipilimumab/nivolumab	Cabozantinib or axitinib	Cabozantinib or axitinib
IF CONTRA-INDICATION FOR ICPIs: AI DISEASES (SEVERE)			
IMDC G	Sunitinib or pazopanib	Cabozantinib or axitinib	Everolimus?
IMDC I/P	Cabozantinib	Axitinib	Everolimus?
IF CONTRA-INDICATION FOR ICPIs: ELDERLY (80+?)			
IMDC G	Sunitinib or pazopanib	Nivolumab	Cabozantinib or axitinib
IMDC I/P	Cabozantinib	Nivolumab	Axitinib

NON-CCRCC

For a patient with a metastatic papillary RCC if IMDC intermediate or poor risk

A. Sunitinib

B. Cabozantinib

C. Pazopanib

D. Ipilimumab/nivolumab

What will be your prefered 1L option from 01/03/2020 ?

NON-CCRCC

For a patient with a metastatic papillary RCC if IMDC intermediate or poor risk

A. Sunitinib

B. Cabozantinib

C. Pazopanib

D. Ipilimumab/nivolumab

NON-CCRCC

For a patient with a Bellini Duct RCC if IMDC intermediate or poor risk

A. Sunitinib

B. Cabozantinib

C. Ipilimumab/nivolumab

D. Cisplatin/gemcitabine

What will be your prefered 1L option from 01/03/2020 ?

NON-CCRCC

For a patient with a Bellini Duct RCC if IMDC intermediate or poor risk

A. Sunitinib

B. Cabozantinib

C. Ipilimumab/nivolumab

D. Cisplatin/gemcitabine

NON-CCRCC

BASIC PRINCIPLES:

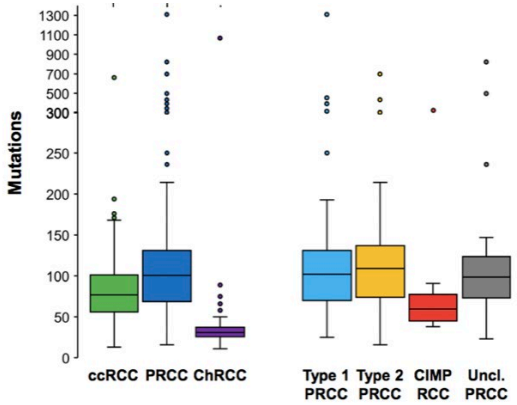
1. VEGFR-TKIs: poor performance
2. ICPIs: emerging evidence of activity
3. cMET: interesting target, but only one available cMET inhibitor: cabozantinib
4. Reimbursement conditions: ipilimumab/nivolumab allowed, but only in 1L

FIRST CHOICE		SECOND LINE
IMDC G	Sunitinib or pazopanib	Cabozantinib or nivolumab
IMDC G/I/P	Axitinib/pembrolizumab of axitinib/avelumab	Cabozantinib
IMDC I/P	Ipilimumab/nivolumab	Cabozantinib
IF CONTRA-INDICATION FOR ICPIs: AI DISEASES (SEVERE)		
IMDC G/I/P	Cabozantinib or sunitinib or pazopanib	Switch VEGFR-TKI

NON-CCRCC

Immune microenvironment in RCC

The mutation rate in RCC tumors is generally low

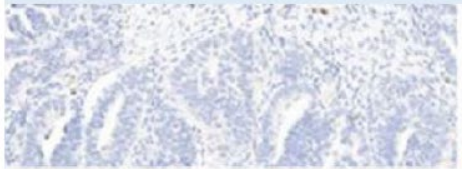


Retrospective study of PD-L1 positivity in non-ccRCC (n=101)

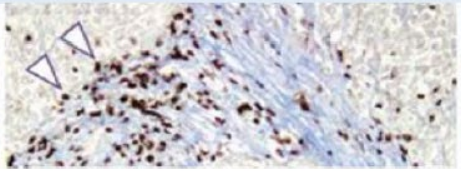
- Overall: 10.9%
- Translocation Xp11: 30%
- Collecting duct carcinoma (CDC): 20%
- Papillary: 10%
- Chromophobe: 5.6%

- PDL1+ has been associated with worse outcomes in nccRCC

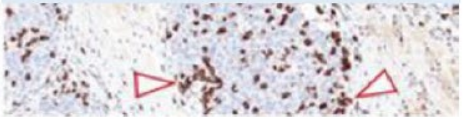
Chromophobe
Low number of immune infiltrates



Papillary
Interm. number of immune infiltrates



CDC & MC
High number of immune infiltrates but large number of potentially immunosuppressive agents



CDC: Collecting Duct Carcinoma
MC: Medullary Carcinoma

Ricketts, et al. Cell 2018; Motzer IKCS 2019
Choueiri TK, et al. Ann oncol 2014

NON-CCRCC

KEYNOTE 427 (PEMBROLIZUMAB 200 mg Q3W) PHASE II in non-ccRCC

	n	ORR	CR
Overall cohort	165	26,1%	6,1%
Papillary	118	28%	5,9%
Chromophobe	21	9,5%	4,8%
Unclassified	28	30,8%	7,7%
IMDC Favorable	53	32%	11,3%
IMDC Interm/Poor	112	23,2%	3,6%
CPS < 1	58	10,3%	5,2%
CPS ≥ 1	102	35%	6,9%

ASCO® GU 2019. McDermott DF et al.

Retrospective single center data evaluating Ipilimumab-Nivolumab in 18 patients with advanced nccRCC (78% received treatment in 1st setting)

	N	*ORR (%) **
Overall cohort	**18**	**28%**
Papillary	6	33%
Chromophobe	5	0
Unclassified	3	33%
Translocation	1	0
Medullary	1	0
Adenocarcinoma	2	50%

No CR described

Gupta R et al. ASCO 2019

NON-CCRCC

RETROSPECTIVE ANALYSIS: ICPIs in metastatic papillary RCC

- 60 pRCC patients

ICPI-TREATMENT

- 93% nivolumab
- Some pembrolizumab, avelumab, atezolizumab
- 93% monotherapy
- 1L 10%
- 2L 55%
- 3L 22%
- 4L 13%

	n	ORR	TTF (m)	OS (m)
Overall cohort	60	PR 14% SD 33% PD 53%	3.2	15
Papillary type 1	17			
Papillary type 2	36			
Papillary unclassified	7			

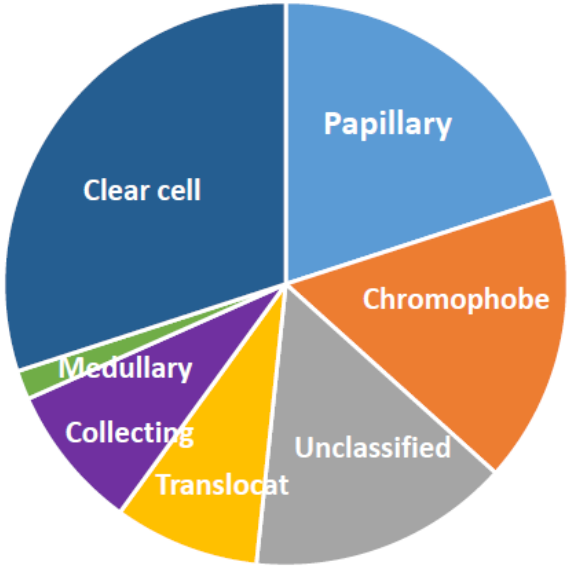
De Vries M, Beuselinck B. European Journal of Cancer 2020

NON-CCRCC

ATEZOLIZUMAB+BEVACIZUMAB for nccRCC or ccRCC with >20% sarc

- Any number of lines, 65% 1L setting
- No prior IO

Overall cohort	n = 60
nccRCC	n= 42
ccRCC sarc+	N = 18



	ORR, n (%)
Overall nccRCC	11 (26%)
• Papillary	3 (25%)
• Chromophobe	1 (10%)
• Unclassified	3 (33%)
• TFE3 Translocation	1 (20%)
• Collecting duct	2 (40%)
• Medullary	1 (100%)
Sarcomatoid differenciation	
• nccRCC	3 (38%)
PD-L1 status in nccRCC	
• Positive (n=9)	6(67%)
• Negative (n=14)	2 (14%)

Mc Gregor et al. JCO 2019

NON-CCRCC

Comparison

	ORR (%) Gupta et al	*ORR (%) McGregor et al*	*ORR (%) De Vries et al*	*ORR (%) McDermott et al*
Papillary	33%	25%	14%	28%
Chromophobe	0%	10%	NR	9,5%
Unclassified	33%	33%	NR	30,8%
Translocation	0%	20%	NR	NR
Medullary	0%	100%	NR	NR
Bellini Duct	NR	40%	NR	NR

papRCC: VEGFR-TKIs 1L

Study	n	Median PFS (months)	Overall RR	Median OS (months)
Tannir et al	14	5.7	NR	16.6
Armstrong et al	33	8.1	24%	NR
Choueiri et al	41	7.6	5%	NR
Ravaud et al	61	Type 2: 5.5 Type 1: 6.6	Type 2: 13% Type 1: 11%	Type 2: 12.4 Type 1:17.8
Connor-Wells	372	4.9	11.9%	13.9
TOTAL		+/- 6.4	13%	15.2

Chromophobe

	n		TTF (m)	ORR	OS (m)
Yip, Beuselinck et al. Kidney Cancer 2017	109	TT	6.9	21% (4% CR)	23.8

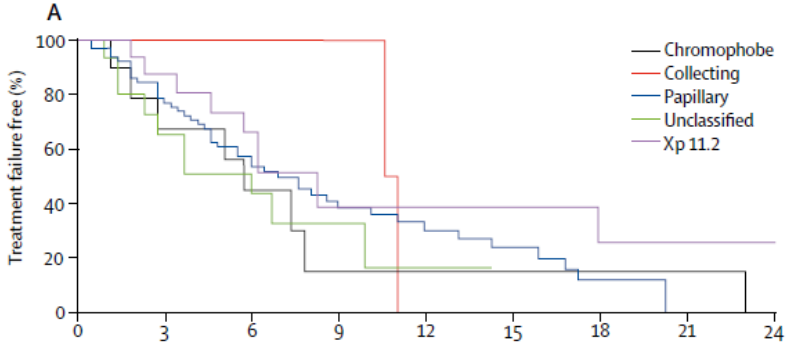
Bellini Duct (collecting duct)

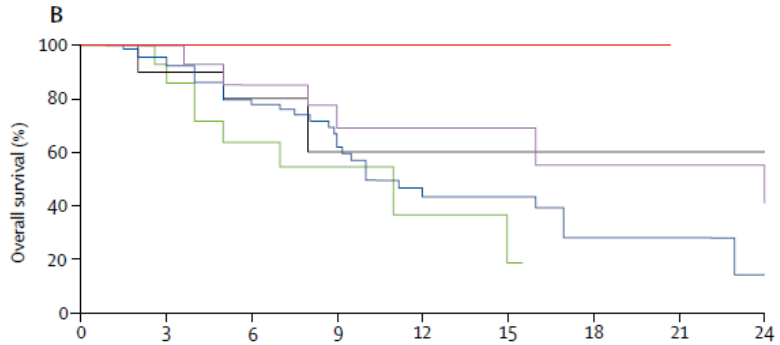
		ORR
Oudard et al. J Urol 2007	Platinum+gemcitabine	26% (1 CR + 5 PR)

NON-CCRCC

Cabozantinib retrospective analysis

	Overall response		Clinical benefit		Median time to treatment failure	12-month overall survival
	n/N	% (95% CI)	n/N	% (95% CI)		
Overall cohort	30/112	27% (19–36)	83/112	74% (65–82)	6·7 (5·5– 8·6)	51% (39–62)
Histology						
Papillary	18/66	27% (17–40)	48/66	73% (60–83)	6·9 (4·6–10·1)	46% (31–60)
Xp11.2 translocation	5/17	29% (10–56)	14/17	82% (57–96)	8·3 (4·6–NR)	69% (36–87)
Unclassified	2/15	13% (2–40)	10/15	67% (38–88)	6·0 (1·4–9·9)	36% (8–67)
Chromophobe	3/10	30% (7–65)	7/10	70% (35–93)	5·7 (1·1–7·8)	60% (16–87)
Collecting duct	2/4	50% (7–93)	4/4	100% (40–99)	NC	NC
Sarcomatoid features						
Yes	6/30	20% (8–39)	23/30	77% (58–90)	5·1 (2·8–6·2)	25% (8–47)
No	13/51	25% (14–40)	34/51	67% (52–79)	7·4 (4·6–11·0)	48% (31–64)





Martinez-Chanza N, Beuselinck B, et al. Lancet Oncology 2019

COMBINATION OF VEGFR-TKIs AND BONE RESORPTION INHIBITORS

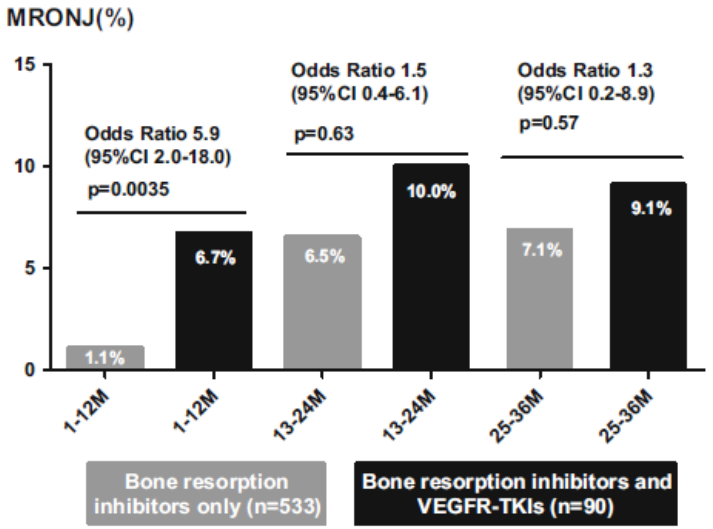
Several warnings were published, but no precise data with control series.

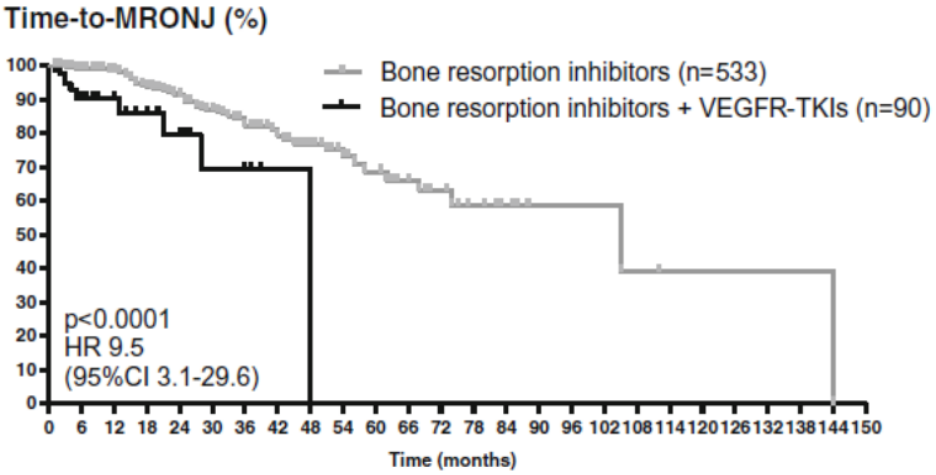
Through the induction of mucositis?

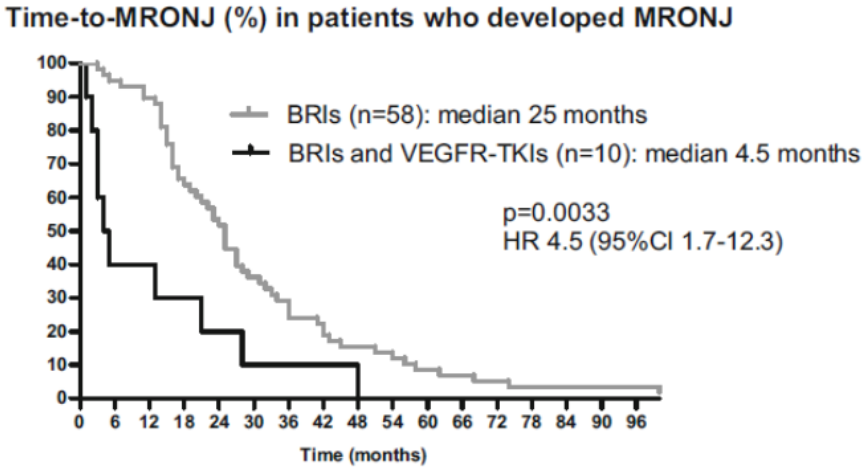
		CONTROL ARM	STUDY GROUP	p-value / OR (95%CI)
		BRI without concomitant VEGFR-TKIs (n=533)	Concomitant BRIs and VEGFR-TKI (N=90)	
TOTAL SERIES	ONJ-incidence	10.9% (58/533)	11.1% (10/90)	1.0
	Median BRI-exposure	19.0 months	5.0 months	-
	Median concomitant exposure	-	4.0 months	-
First year of exposure	ONJ-incidence	1.1% (6/533)	6.7% (6/90)	0.0035 5.9 (2.0-18.0)
	Median BRI-exposure	12.0 months	5.0 months	-
	Median concomitant exposure	-	4.0 months	-
Second year of exposure	ONJ-incidence	6.5% (22/337)	10% (2/20)	0.63 1.5 (0.4-6.1)
	Median BRI-exposure	24.0 months	24.0 months	-
	Median concomitant exposure	-	24.0 months	-
Third year of exposure	ONJ-incidence	7.1% (15/212)	9.1% (1/11)	0.57 1.3 (0.2-8.9)
	Median BRI-exposure	36.0 months	30.0 months	-
	Median concomitant exposure	-	28.0 months	-
Fourth year of exposure	ONJ-incidence	4.9% (5/103)	25.0% (1/4)	0.21 5.2 (0.8-34.5)
	Median BRI-exposure	48.0 months	38.0 months	-
	Median concomitant exposure	-	39.0 months	-

Van Cann T, Beuselinck B et al. J Supportive Care in Cancer 2018.

COMBINATION OF VEGFR-TKIs AND BONE RESORPTION INHIBITORS







Van Cann T, Beuselinck B et al. J Supportive Care in Cancer 2018.

COMBINATION OF VEGFR-TKIs AND BONE RESORPTION INHIBITORS

OR first year of exposure: 5,9

Time-to-MRONJ: 9,5

Time-to-MRONJ if MRONJ: 4,5

⇒ Incidence 5-10x higher

⇒ However life-time risk is the same … as in diseases with longer survival

⇒ This may change if RCC patient survival will increase and exposure increase (VEGFR-TKIs + ICPIs …) !

		CONTROL ARM	STUDY GROUP	p-value / OR (95%CI)
		BRI without concomitant VEGFR-TKIs (n=533)	Concomitant BRIs and VEGFR-TKI (N=90)	
TOTAL SERIES	ONJ-incidence	10.9% (58/533)	11.1% (10/90)	1.0
	Median BRI-exposure	19.0 months	5.0 months	-
	Median concomitant exposure	-	4.0 months	-

161 pts zoledronic acid and 36/161 switch to denosumab:
48 pts with concomitant angiogenesis inhibitor

Table III. Medication and risk of ONJ: multiple logistic regression analysis

	OR (95% CI)	*P*
Administration of ZA		
Increasing duration	1.00 (1.00–1.00)	.376
Total dose	1.01 (1.00-1.02)	.069
Concomitant use of angiogenesis inhibitors (+/–)	5.02 (1.56-16.17)	.007*
Replacement of ZA with denosumab (+/–)	3.81 (1.04-13.97)	.043*

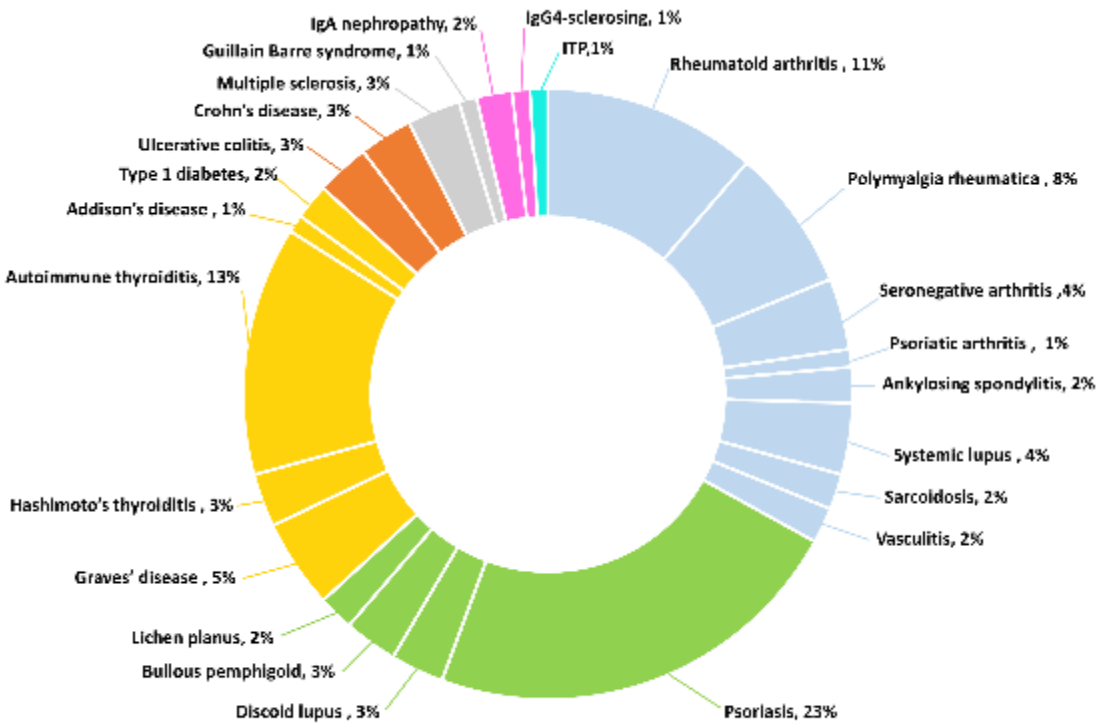
ONJ, osteonecrosis of the jaw; *OR*, odds ratio; *ZA*, zoledronic acid.
*$P < .05$.

Van Cann T, Beuselinck B et al. J Supportive Care in Cancer 2018.

Higuchi et al. Oral Medecine 2018.

ICPIs AND PRE-EXISTING AI-DISEASES

Retrospective multicenter analysis of advanced RCC (n=58) and urothelial cancer (n=48) patients with pre-existing AD treated with ICPI



Martinez-Chanza N, Beuselinck B et al. Journal for ImmunoTherapy of Cancer 2020 (accepted).

ICPIs AND PRE-EXISTING AI-DISEASES

35/106 pts (33%): G1/2 clinically active AD

10/106 pts (9%): required systemic corticosteroids or immunomodulators.

EXACERBATIONS OCCURRED IN 38/106 PTS (36%):

17/38 pts (45%): requiring steroids

6/38 pts (16%): requiring discontinuation of IPI.

NEW ONSET irAEs OCCURRED IN 40/106 PTS (38%):

22/40 pts (55%): requiring steroids

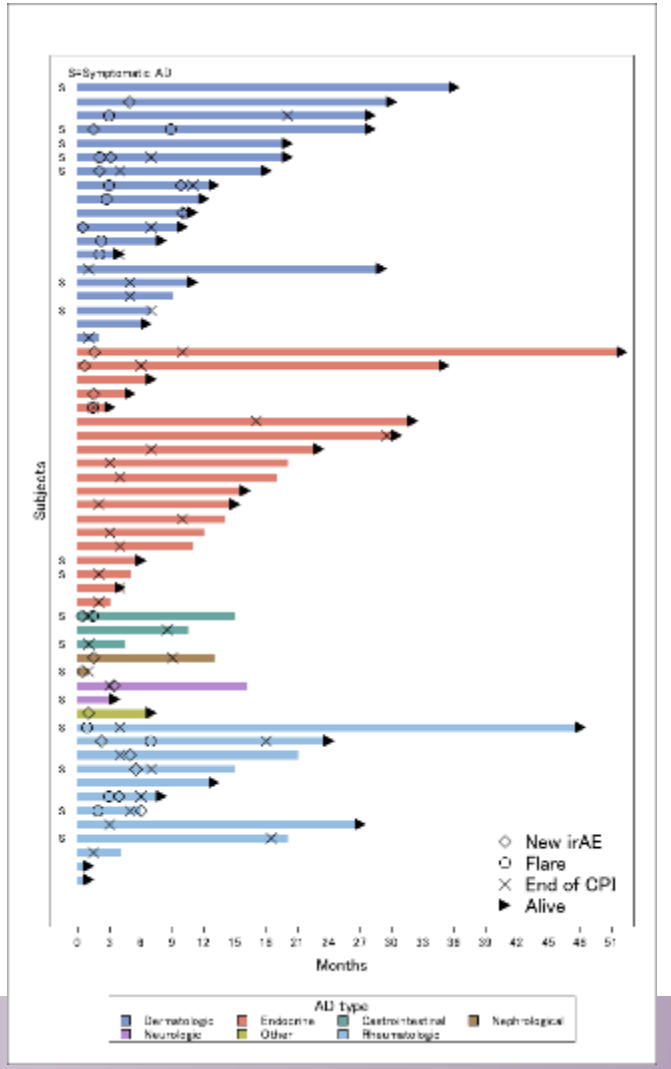
8/40 pts (20%): requiring discontinuation of ICPI.

Few G3/4 irAEs (6% exacerbations, 12% new irAEs) with no treatment-related deaths.

For RCC, ORR was 31% (95%CI 20-45), median TTF 7 months (95%CI 4-10) and 12-months OS 78% (95%CI 63-87).

CONCLUSIONS:

CPI can be administered safely in RCC patients with well-controlled AD with no increase in irAEs rates and similar degrees of clinical benefit to historical non-AD populations.



RCC cohort (n=58)

Martinez-Chanza N, Beuselinck B et al. Journal for ImmunoTherapy of Cancer 2020 (accepted).

ANY QUESTION?

I have questions to all year answers ☺

Het niercarcinoom in 2020: een update

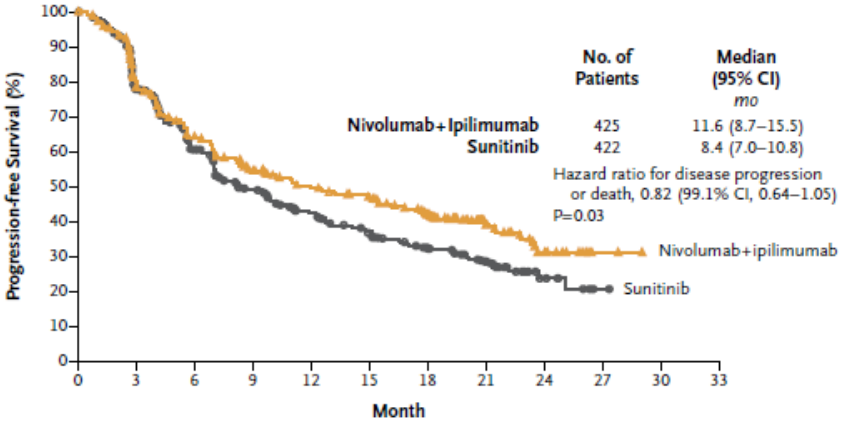
Predictieve markers bij systeemtherapie

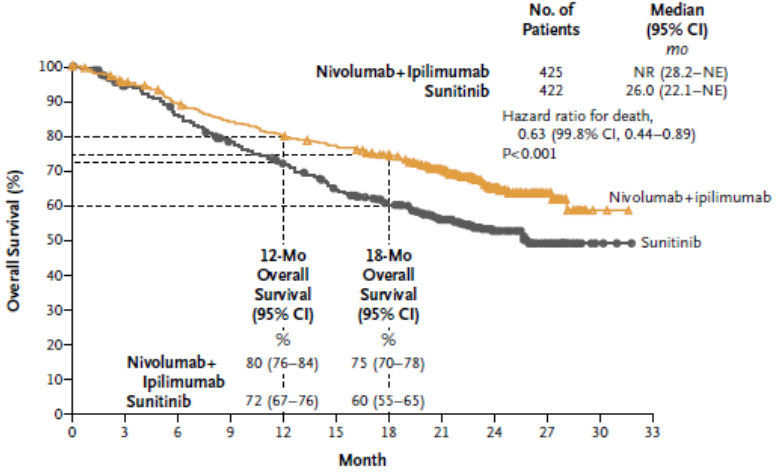
Prof Dr Benoit Beuselinck
UZ Leuven
20/02/2020

- ccRCC: ANGIOGENESIS AND IMMUNE PROFILE
- c-MET STATUS
- SARCOMATOID DEDIFFERENTIATION
- POLYBROMO-1 MUTATIONS
- MUTATIONAL BURDEN
- HISTOLOGY: PAPILLARY RCCs
- RESPONSE PREDICTION IN mTORinh

ccRCC: ANGIOGENESIS AND IMMUNE PROFILE

CA209/214 study: first results favor sunitinib in IMDC good risk and ipilimumab/nivolumab in IMDC intermediate/poor risk





	IMDC INTERM/POOR RISK		
	IPI/NIVO	SUN	
RR	42% (9% CR)	27% (1% CR)	P<0,0001
PFS	11,6	8,4	p=0,03
OS	NR	26,0	P<0,0001

	IMDC GOOD RISK		
	IPI/NIVO	SUN	
RR	29%	52%	0,0002
PFS	15,3	25,1	<0,0001
OS	NR	NR	overlapping

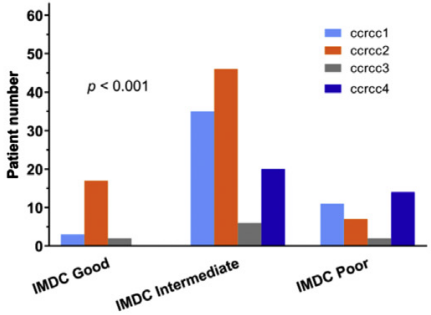
Motzer et al, NEJM 2018

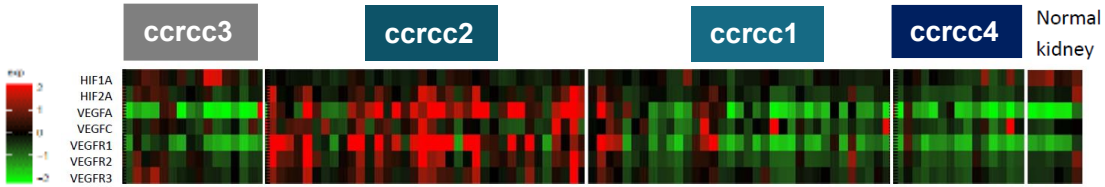
ccRCC: ANGIOGENESIS AND IMMUNE PROFILE

IMDC score is related to molecular characteristics

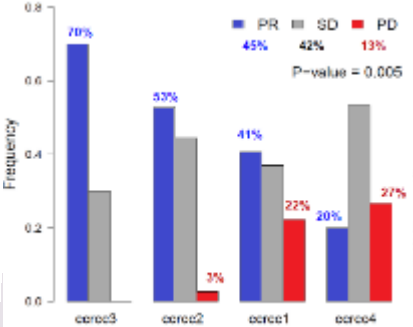
Good	Important neo-angiogenesis Allmost all ccrcc2 tumors	Explains good response on VEGFR-TKIs
Interm	Heterogeneous group	
Poor	Low neo-angiogenesis Few ccrcc2 tumors	Explains poor response on VEGFR-TKIs

Correlation between ccrcc1 to –4 molecular subtype and IMDC risk group

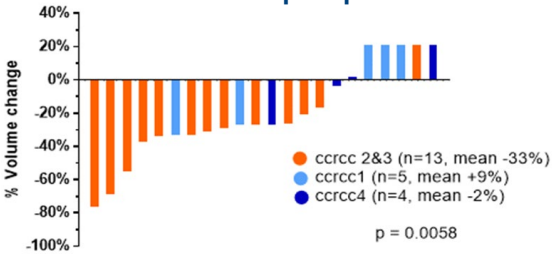




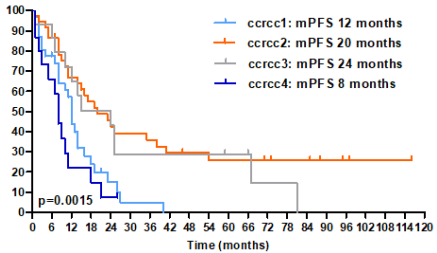
RR on sunitinib



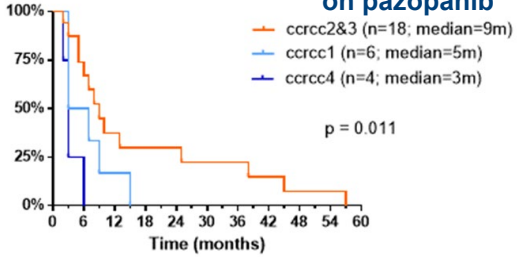
RR on pazopanib



PFS (%) on sunitinib



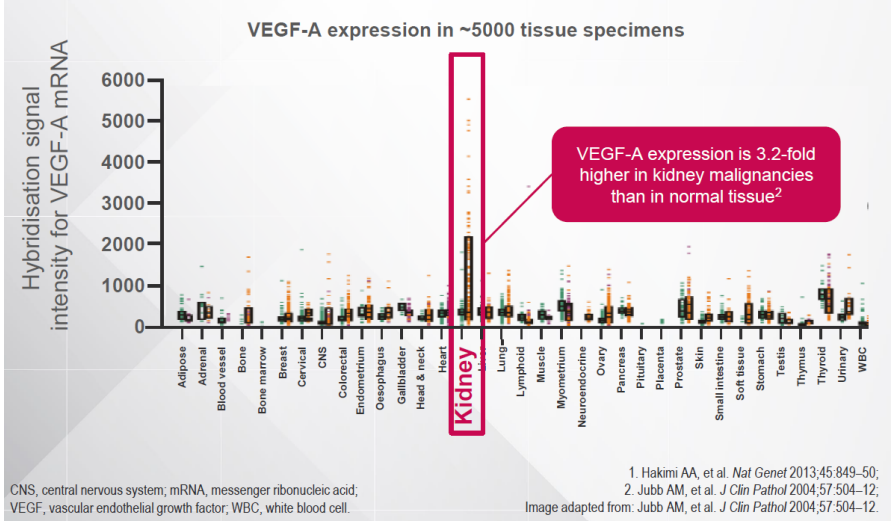
Progression free survival (%) on pazopanib



Verbiest A, Renders I, Beuselinck B et al. Clin Genitourinary Cancer 2019
Beuselinck et al. Clin Cancer Res. 2015.
Beuselinck et al. Acta Oncologica 2017
Verbiest, Beuselinck et al. Clin Genitourin Cancers 2017

ccRCC: ANGIOGENESIS AND IMMUNE PROFILE

Inhibition of the activated VEGF-dependent-pro-angiogenic pathway in hyper-vascular ccRCCs

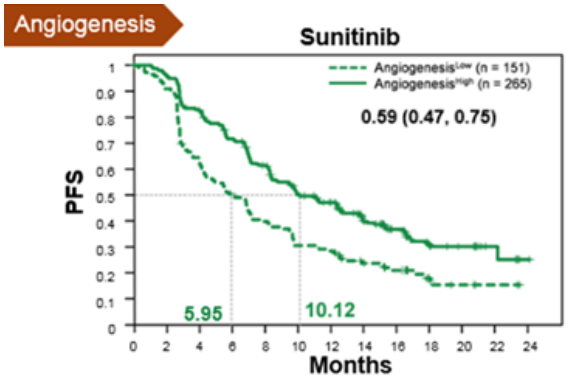


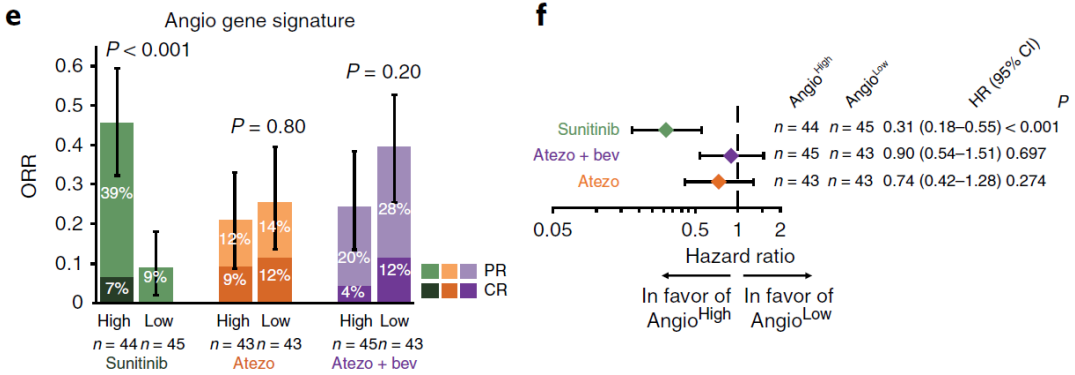
Gene	Expression	Beuselinck et al (1) (n=104)	Dornbusch et al (2) (n=42)	Garcia-Donas et al (3) (n=67)	Terakawa et al (4) (n=40)	You et al (5) (n=65)
HIF1A	High	Longer OS	Higher RR, longer PFS			
HIF2A	High	Longer PFS and OS		Higher RR, longer OS		
PDGFRB	High	Higher RR, longer PFS	Higher RR	Higher RR		
VEGFR1	High	Less patients with early PD. Longer PFS. Longer OS	Higher RR, longer OS			
VEGFR2	High	Less patients with early PD, higher RR. Longer PFS and OS	Higher RR		Longer PFS	Higher RR
VEGFR3	High	Less patients with early PD. Longer PFS and OS (UV only)	Longer PFS	Longer PFS		

(1) Beuselinck et al. Acta Oncologica 2017
(2) Dornbusch et al. Plos One 2013
(3) Garcia-Donas et al
(4) Terakawa et al
(5) You et al

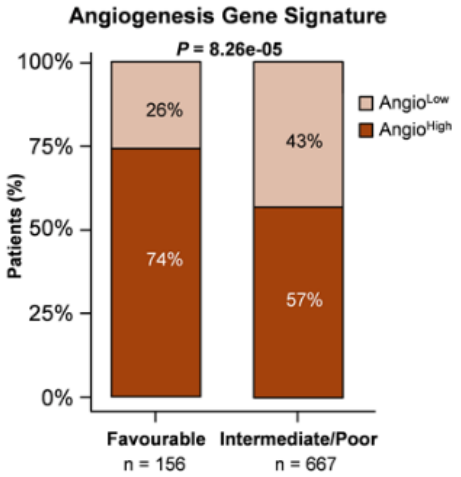
ccRCC: ANGIOGENESIS AND IMMUNE PROFILE

IMMOTION 150/151 (sunitinib vs atezolizumab/bevacizumab): angiogenesis correlated to better outcome on sunitinib and to MSKCC score





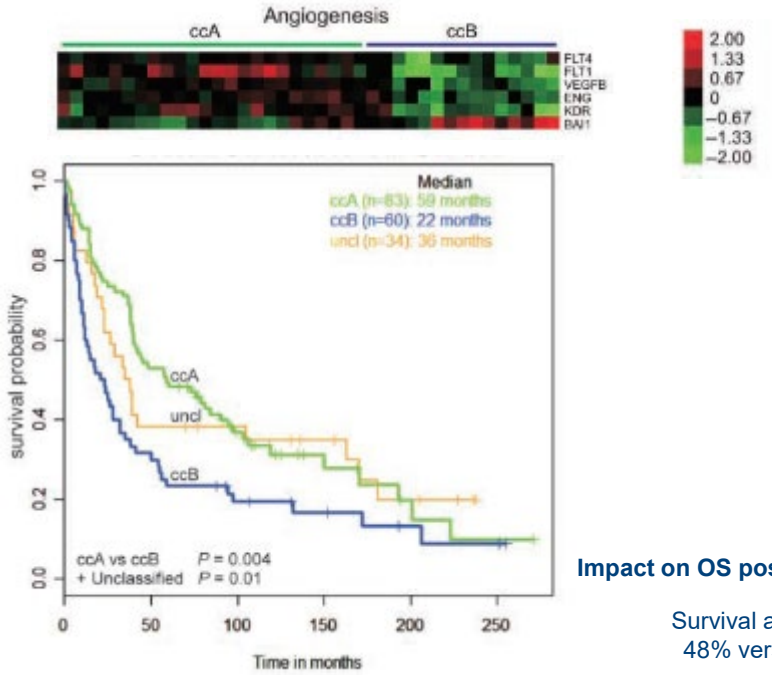
MSKCC favorable risk pts: More angiogenesis



ccRCC: ANGIOGENESIS AND IMMUNE PROFILE

ccA AND ccB EXPRESSION PROFILES

Two main clusters with a prognostic impact post-nephrectomy

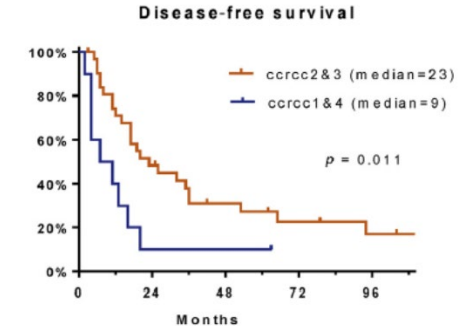


Impact on OS postnephrectomy

Survival at 5 years:
48% versus 23%

PROGNOSIS AFTER METASTASECTOMY

- 43 ccRCC pts UZLeuven: Metastasectomy with curative intent
- Ccrcc1-4 classification has a prognostic value post-metastasectomy and allows patient selection for metastasectomy

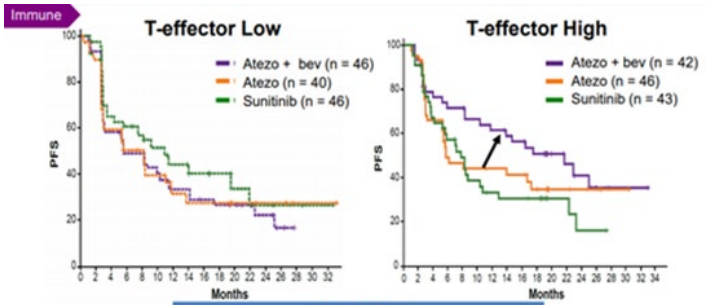


Brannon et al. Genes & Cancer 2010
Brannon et al. European Urology 2012

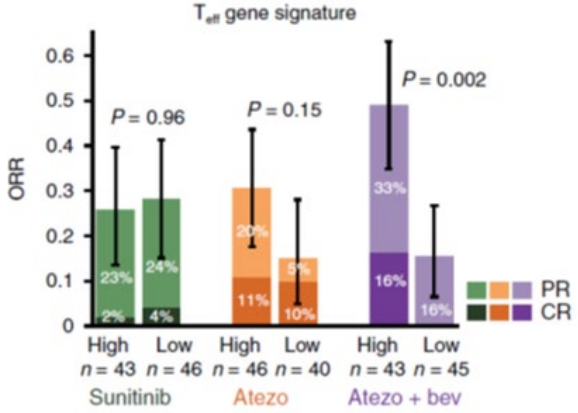
Verbiest A, Beuselinck B et al. Eur Uro 2018

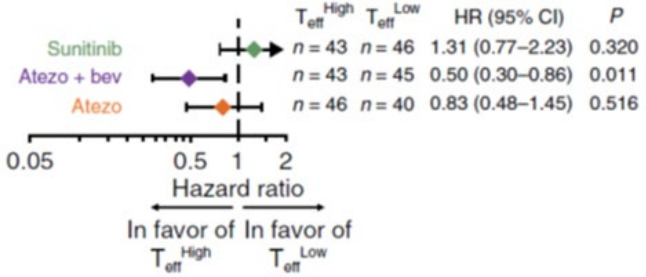
ccRCC: ANGIOGENESIS AND IMMUNE PROFILE

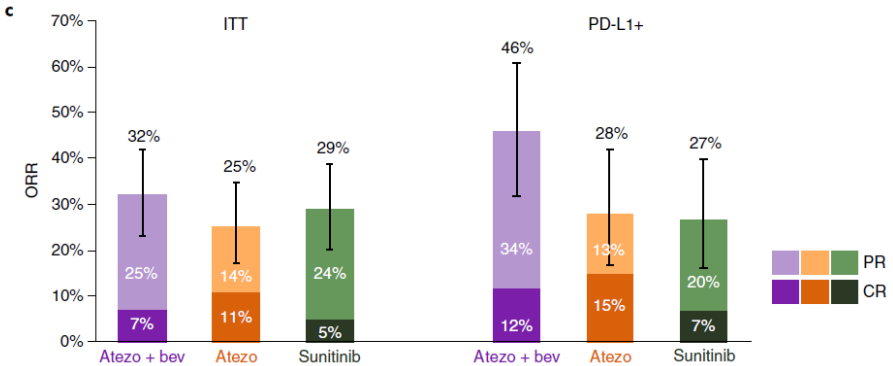
IMMOTION 150/151 (sunitinib vs atezolizumab/bevacizumab): Teff signature correlated to better outcome on atezo/bev



HR (95% CI)	T-effector Low	T-effector High
Atezo + bev vs sunitinib	1.41 (0.84, 2.36)	0.55 (0.32, 0.95)
Atezo vs sunitinib	1.33 (0.76, 2.33)	0.85 (0.50, 1.43)







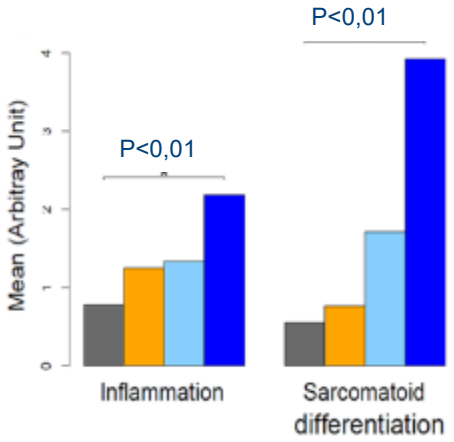
McDermott et al. Nature 2018

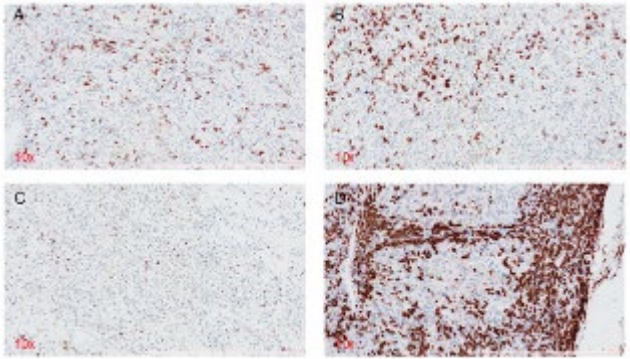
ccRCC: ANGIOGENESIS AND IMMUNE PROFILE

Ccrcc-1 to -4 EXPRESSION PROFILES

Subgroup characteristics: Cytokine analysis

=> ccrcc4: strong inflammatory, Th1-oriented but suppressive immune microenvironment.



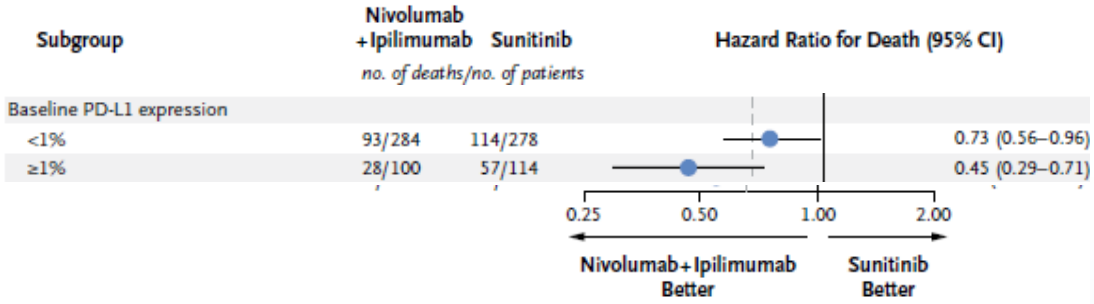


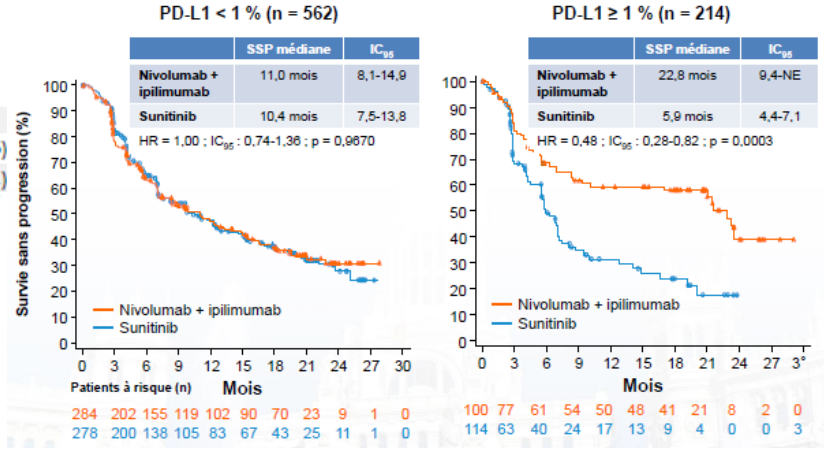
CD8+ cell infiltration in ccrcc1 (A), ccrcc2 (B), ccrcc3 (C) and ccrcc4 (D)

Beuselinck et al. Clin Cancer Res. 2015.

ccRCC: ANGIOGENESIS AND IMMUNE PROFILE

IPI/NIVO versus SUN as 1st line therapy in intermediate/poor risk pts



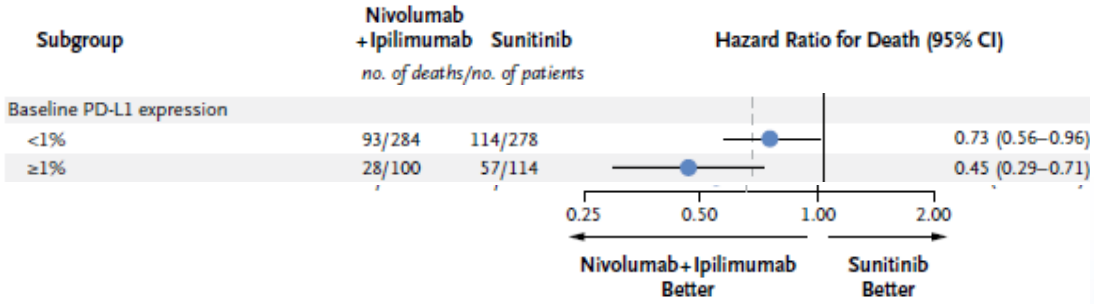


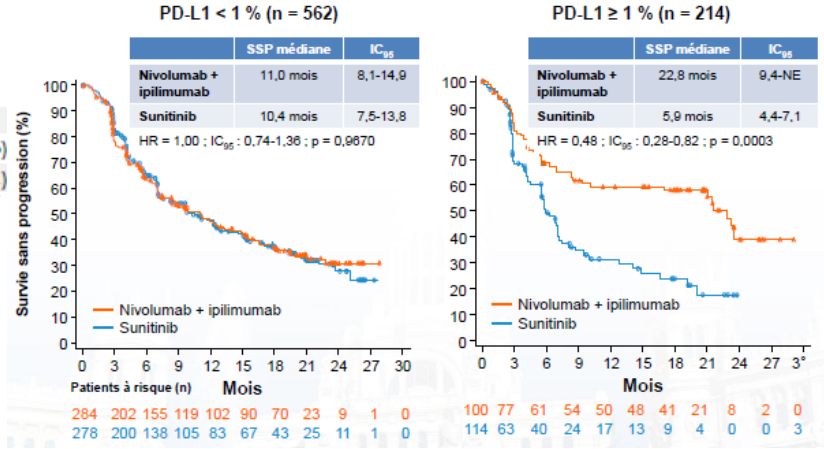
IMDC INTERM/POOR RISK PDL1<1%			IMDC INTERM/POOR RISK PDL≥1%		
IPI/NIVO	**SUN**		**IPI/NIVO**	**SUN**	
37%	28%	P=0,03	58% (CR 16%)	22%	P<0,001
11,0	10,4	P=0,96	22,8	5,9	P=0,0003
NR	NR	HR 0,73 (95%CI 0,56-0,96)	NR	19,6	HR 0,45 (95%CI 0,29-0,71)

Escudier et al. ESMO 2017

ccRCC: ANGIOGENESIS AND IMMUNE PROFILE

IPI/NIVO versus SUN as 1st line therapy in intermediate/poor risk pts





IMDC INTERM/POOR RISK PDL1<1%			IMDC INTERM/POOR RISK PDL≥1%		
IPI/NIVO	SUN		IPI/NIVO	SUN	
37%	28%	P=0,03	58% (CR 16%)	22%	P<0,001
11,0	10,4	P=0,96	22,8	5,9	P=0,0003
NR	NR	HR 0,73 (95%CI 0,56-0,96)	NR	19,6	HR 0,45 (95%CI 0,29-0,71)

FINALLY: A VALIDATED PREDICTIVE BIOMARKER?

NEO-ANGIOGENESIS => VEGFR-TKIs

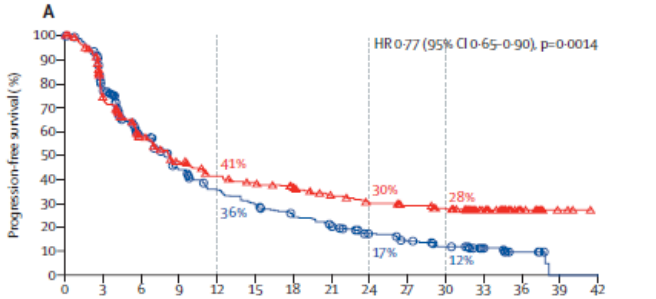
IMMUNE MARKERS => ICIs?

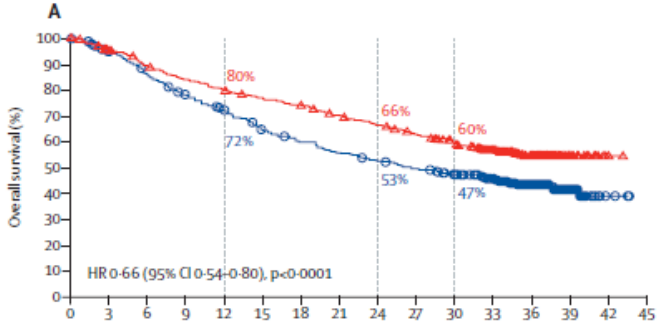
Escudier et al. ESMO 2017

ccRCC: ANGIOGENESIS AND IMMUNE PROFILE

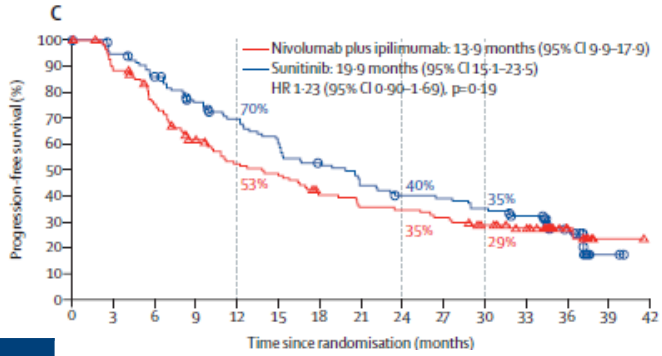
Phase III study ipi/nivo versus sunitinib in 1L: 30 months follow up

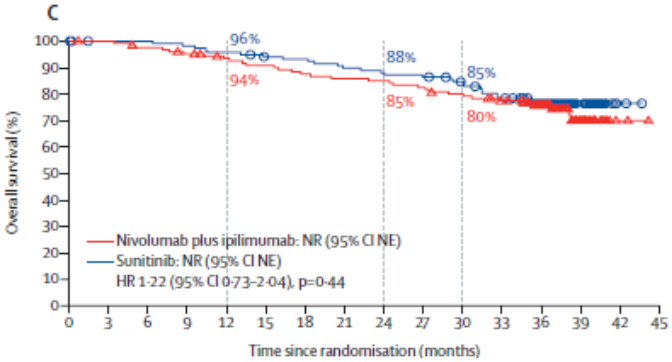
IMDC Intermediate and poor risk





IMDC Good risk





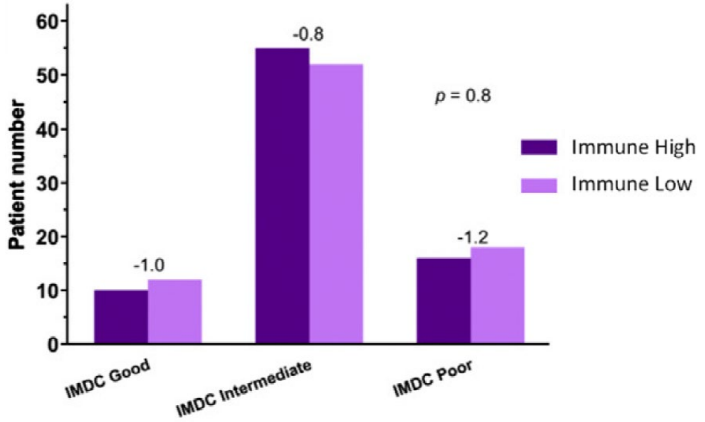
	IPI/NIVO	SUN
RR	31% **(CR 8%)**	**46%** (CR 4%)

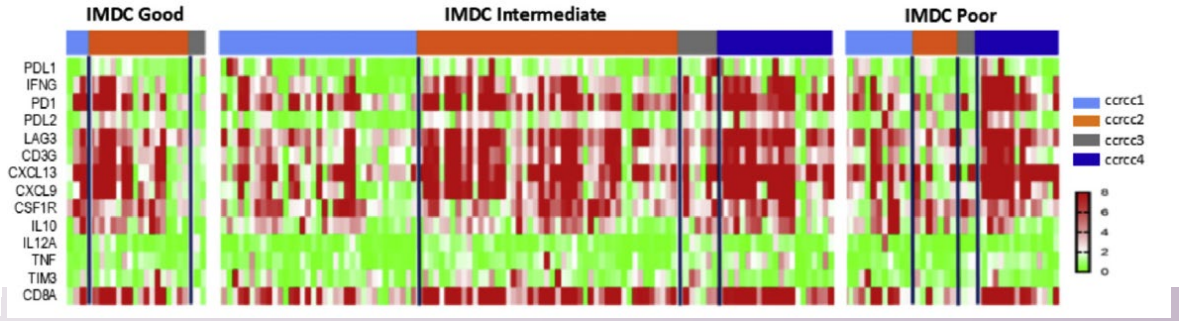
Motzer, Beuselinck, et al, Lancet Oncology 2019

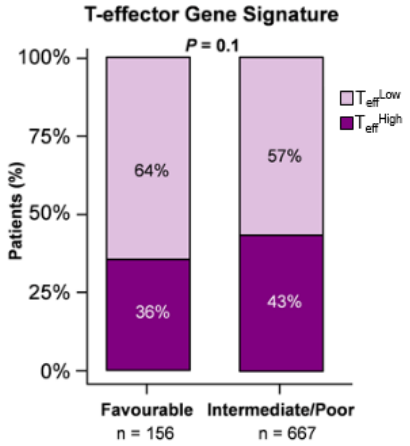
Better RR and PFS does not translate into better OS …
CR rate is double in ipi/nivo in IMDC good risk patients
Ipi/nivo only available in 1L … an opportunity not to miss?

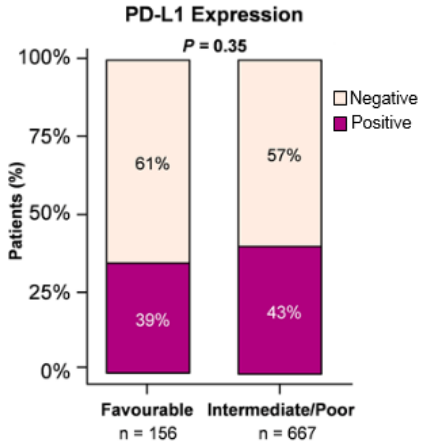
ccRCC: ANGIOGENESIS AND IMMUNE PROFILE

PDL1 expression or immune signature are present in ALL IMDC risk groups …









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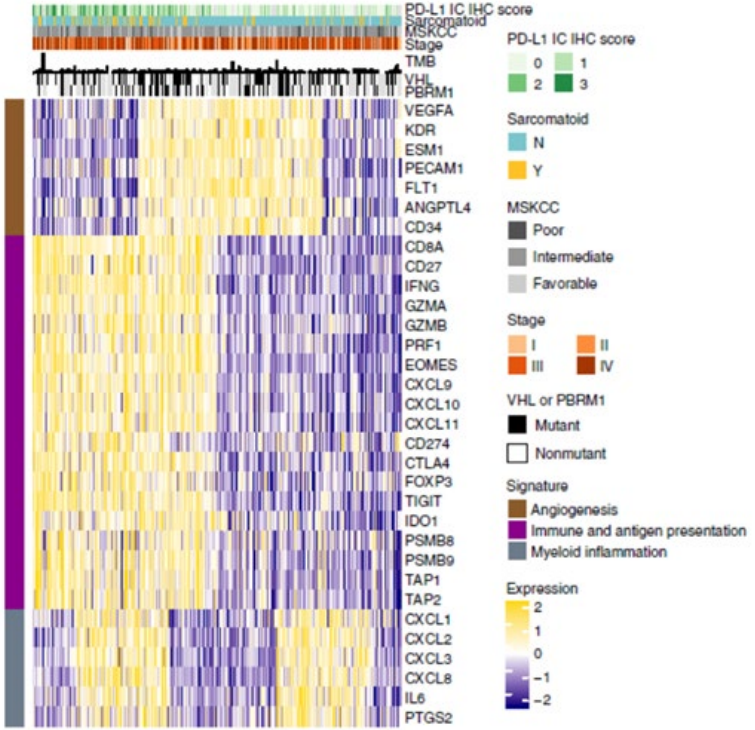
THERE IS OVERLAP … NOT ANGIO HIGH OR IMMUNE HIGH …



McDermott et al. Nature 2018

Beuselinck et al. Clin Cancer Res. 2015.

ccRCC: ANGIOGENESIS AND IMMUNE PROFILE

IN SUMMARY …

1. CA209-214 longer follow up: ICIs also work very well in IMDC good risk patients …
2. Molecular analysis: overlap: not angio high or immune high …
3. Reimbursement conditions … First-line = the only chance to give doublet ICIs
4. Indolent ccRCCs compared to agressive ccRCCs: more sensitive to VEGFR-TKIs
5. Aggressive ccRCCs compared to indolent ccRCCs: relative advantage of ipi/nivo over sunitinib is higher in agressive ccRCCs, but indolent ccRCC can also respond to ICPIs

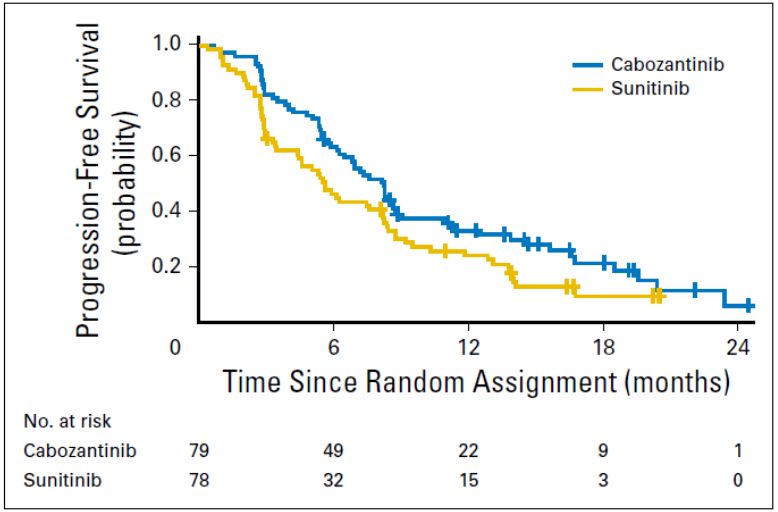
c-MET STATUS

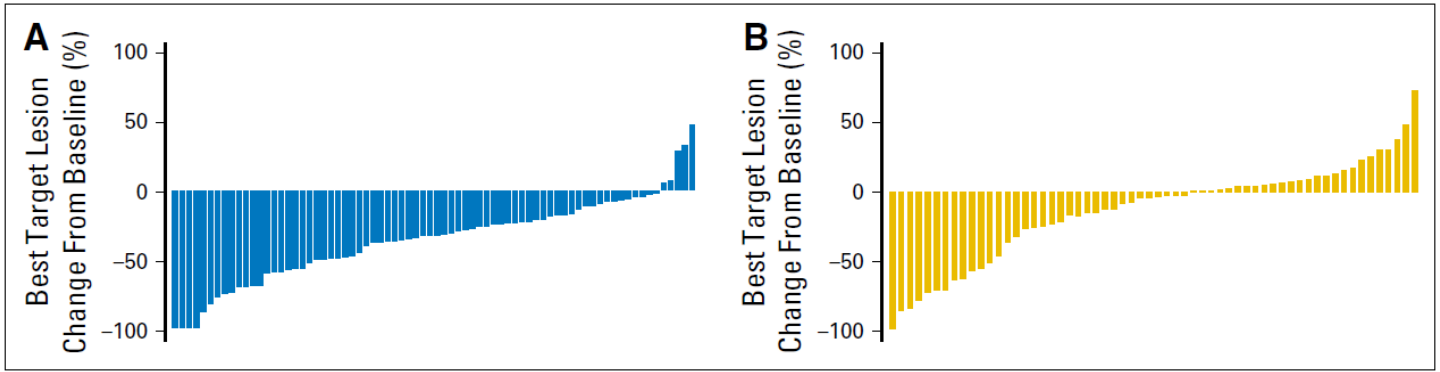
CABOSUN phase II trial in IMDC intermediate/poor risk pts

- 157 m-ccRCC pts IMDC intermediate or poor risk
- Sunitinib 50 mg/d 4W/6W vs cabozantinib 60 mg/d
- PFS 5,6 vs 8,2M (HR 0,66 95%CI 0,46-0,95) (p=0,012)

Table 2. Tumor Response

Response	Cabozantinib (n = 79)	Sunitinib (n = 78)
ORR, % (95% CI)*	33 (23 to 44)	12 (5.4 to 21)
Best overall response, No. (%)		
Confirmed CR	1 (1.3)	0
Confirmed PR	25 (31.6)	9 (11.5)
Stable disease	36 (45.6)	33 (42.3)
Progressive disease	14 (17.7)	20 (25.6)
Not evaluable or missing†	3 (3.8)	16 (20.5)





Choueri et al. JCO 2016

c-MET STATUS

AXL-expression in kidney tumor:

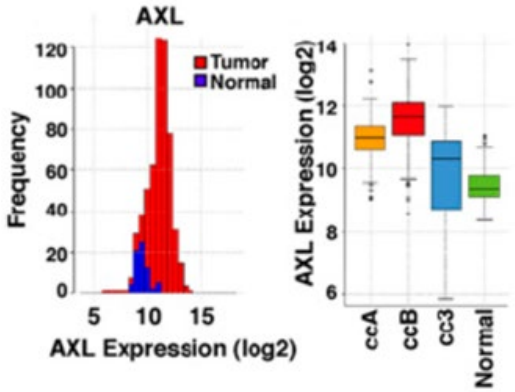
- is higher than in normal kidney tissue
- Correlates with aggressive tumor behavior (ccB>ccA)
- Is highly expressed in aggressive ccRCC
- Correlates with shorter survival

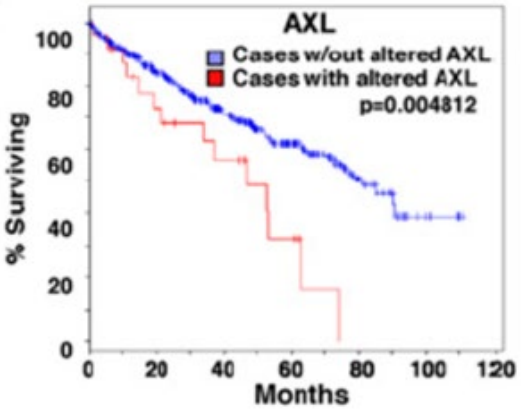
- HIF1A and HIF2A directly activate expression of AXL
- AXL activates the proto-oncogene MET.

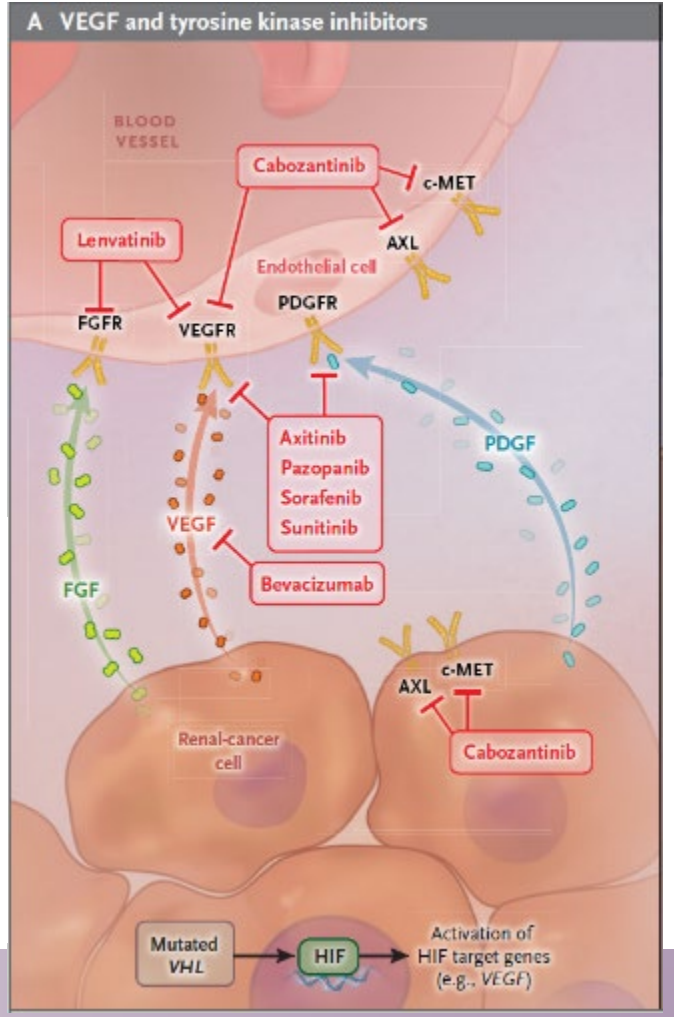
- Inactivation of AXL signaling in m-ccRCC cells reversed the invasive and metastatic phenotype in vivo.

- AXL and c-MET are upregulated in VEGFR-TKI resistent ccRCCs.

- Cabozantinib targets the VEGFR, but also AXL and c-MET



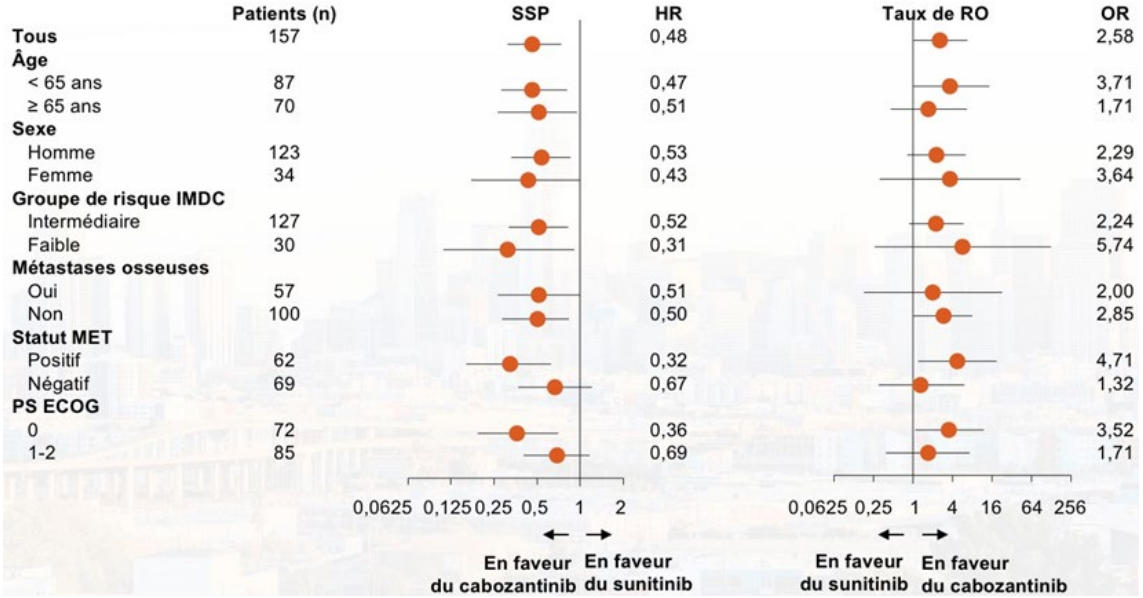


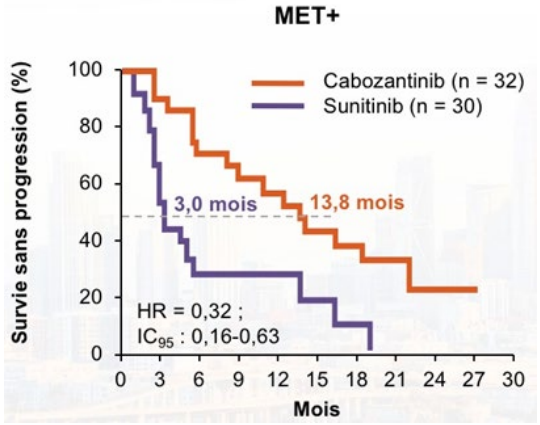


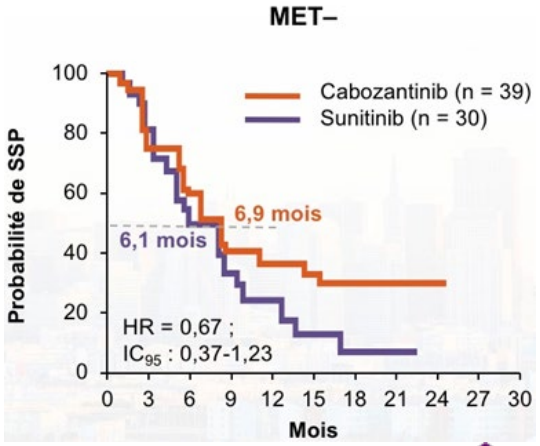
Rankin et al. PNAS 2014

c-MET STATUS

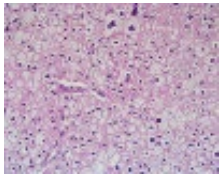
Predictive impact of c-MET status on cabozantinib efficacy (CABOSUN)

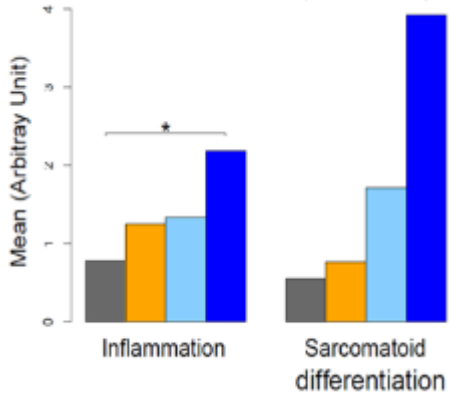






SARCOMATOID DEDIFFERENTIATION

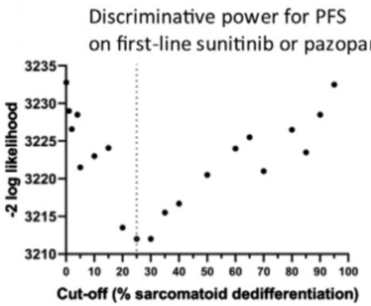


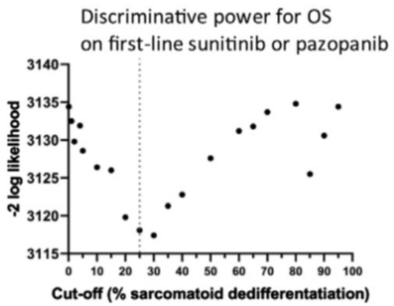


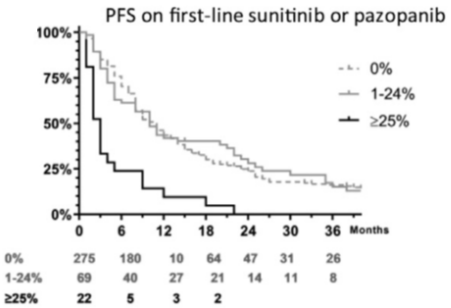
On 366 m-ccRCC pts treated with pazopanib or sunitinib in 1L

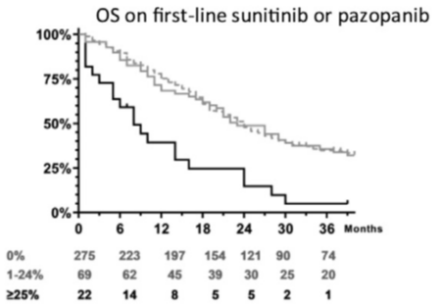
On 92 m-ccRCC pts treated with ICIs

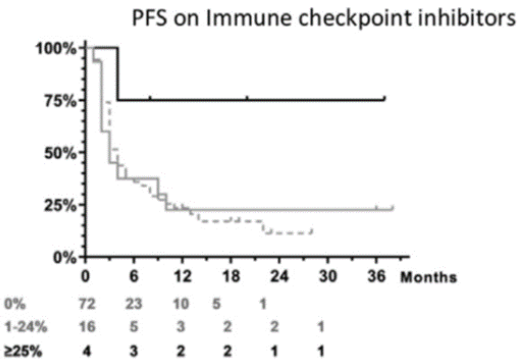
Establishing 25% as the optimal cut-off percentage for sarcomatoid dedifferentiation

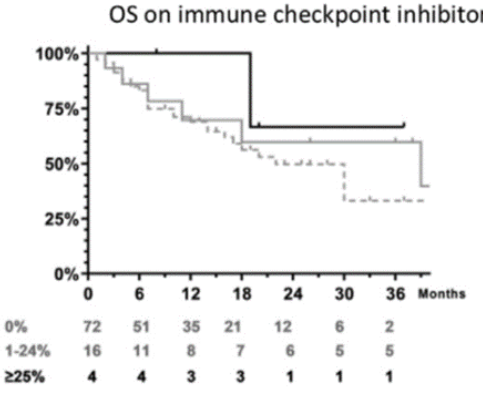












Beuselinck B et al. Clinical Genitourinary Cancer 2014.
Verbiest A, Renders I, Beuselinck B et al. Clin Genitourinary Cancer 2019

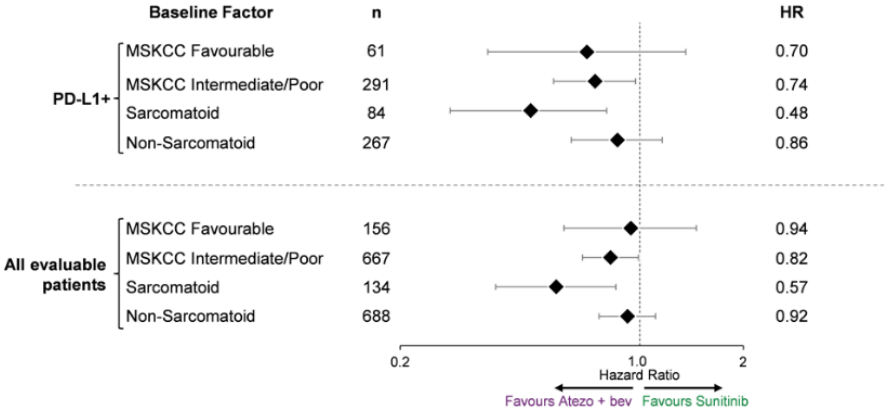
SARCOMATOID DEDIFFERENTIATION

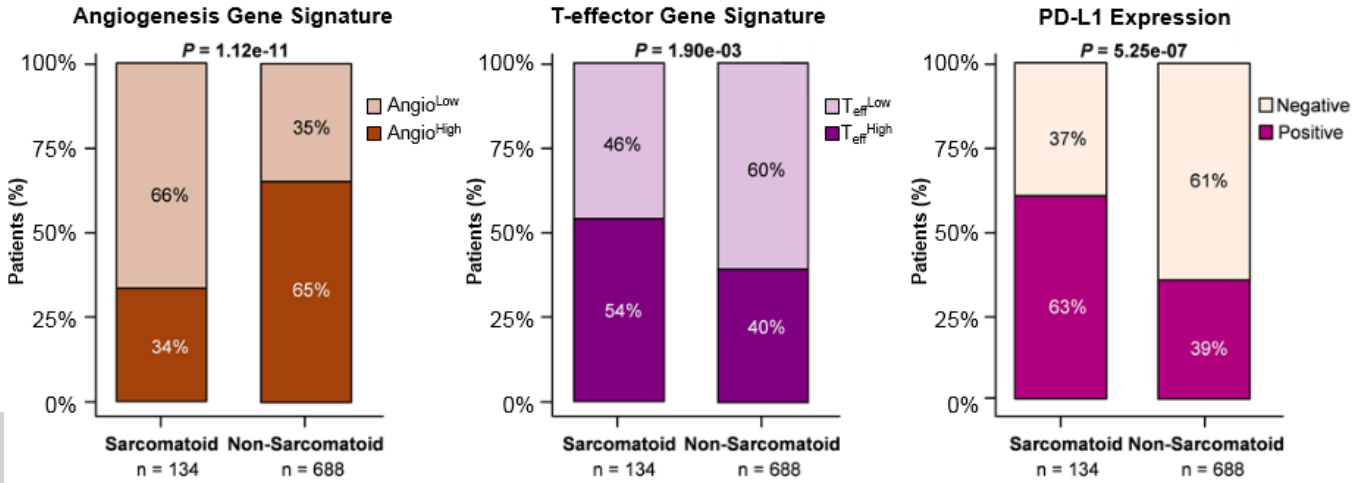
IMMOTION 151: SARCOMATOID TUMORS:

More benefit from atezolizumab/bevacizumab

Display:

- less angiogenesis
- more Teff signature
- more PDL1 expression

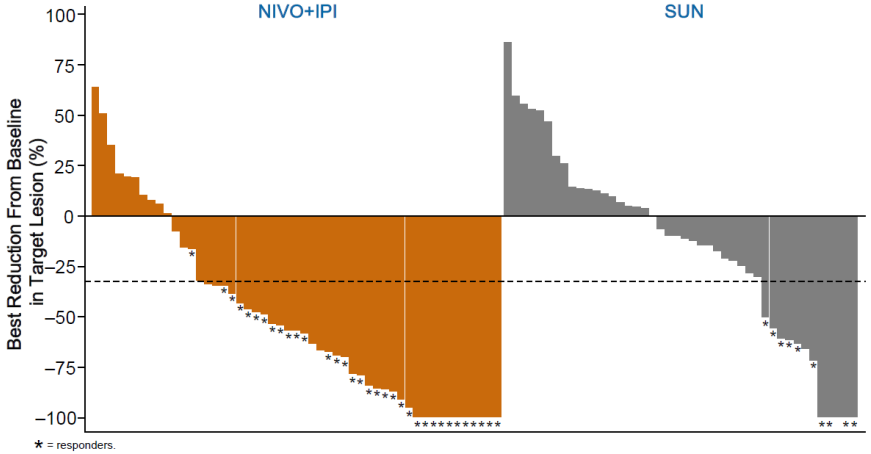




SARCOMATOID DEDIFFERENTIATION

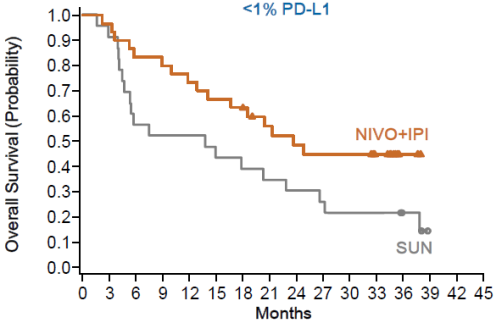
CA209-214 30 MONTHS FOLLOW UP

Best Tumor Reduction From Baseline in Target Lesions per Investigator: Intermediate/Poor-Risk Sarcomatoid Patients

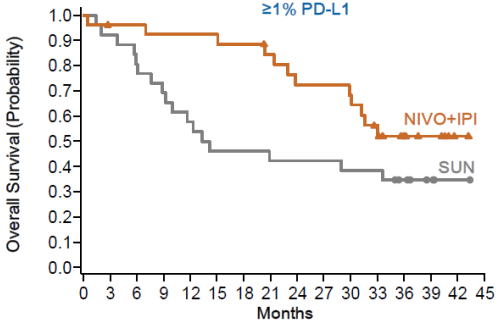


OS: PD-L1–Evaluable Sarcomatoid Patients

<1% PD-L1 Expression	NIVO+IPI N= 30	SUN N=23
Events, n (%)	16 (53)	19 (83)
Median OS, (95% CI), mo	23.7 (14.1–NE)	13.8 (4.7–22.9)



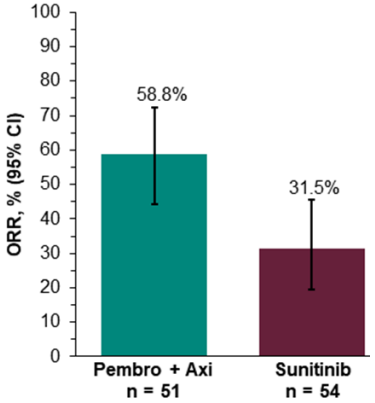
≥1% PD-L1 Expression	NIVO+IPI N= 27	SUN N= 26
Events, n (%)	12 (44)	17 (65)
Median OS, (95% CI), mo	NR (29.9–NE)	13.8 (8.9–NE)

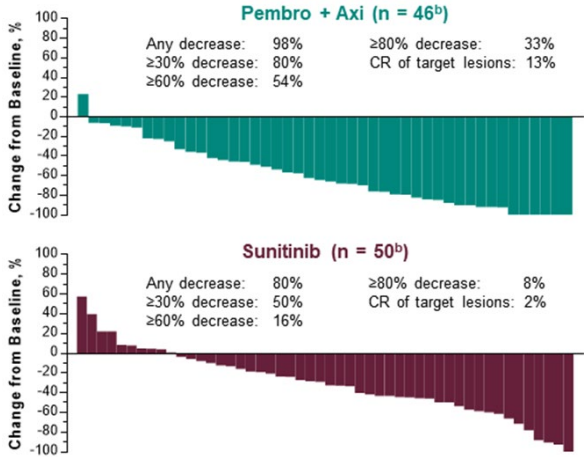


SARCOMATOID DEDIFFERENTIATION

KEYNOTE 426: PATIENTS WITH TUMORS WITH SARCOMATOID DEDIFFERENTIATION

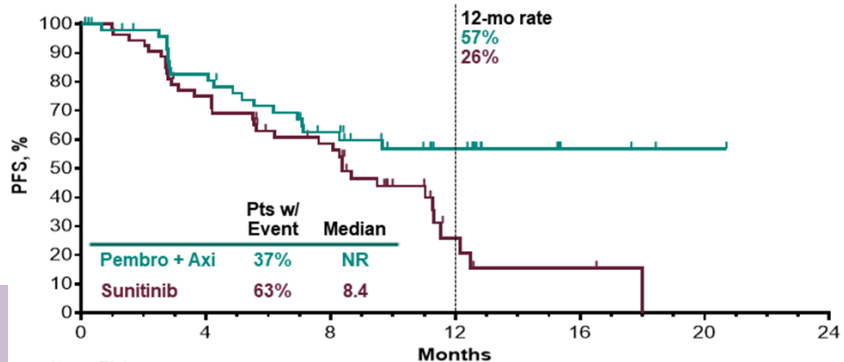
	Pembrolizumab + Axitinib N = 51	Sunitinib N = 54
IMDC risk category		
Favorable	7 (13.7%)	10 (18.5%)
Intermediate	34 (66.7%)	38 (70.4%)
Poor	10 (19.6%)	6 (11.1%)
PD-L1 CPS ≥1[b]	38 (74.5%)	43 (79.6%)





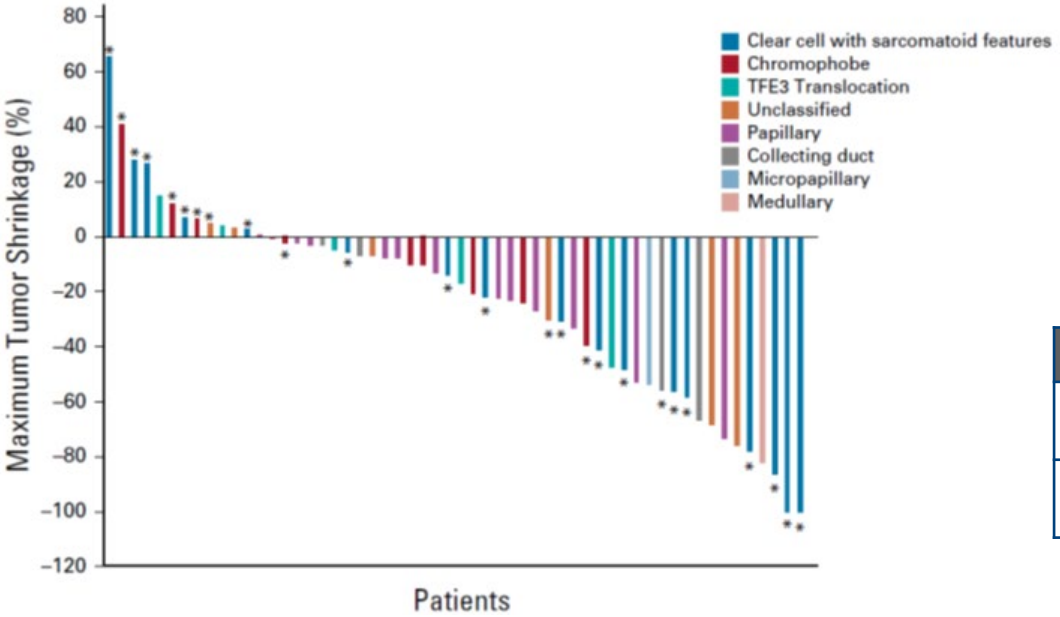
PFS: HR 0.54 (95% CI 0.29–1.00)

OS: HR 0.58 (95% CI 0.21–1.59); median NR in either arm[b]



SARCOMATOID DEDIFFERENTIATION

Atezolizumab and bevacizumab in mRCC with variant histology and/or sarcomatoid features



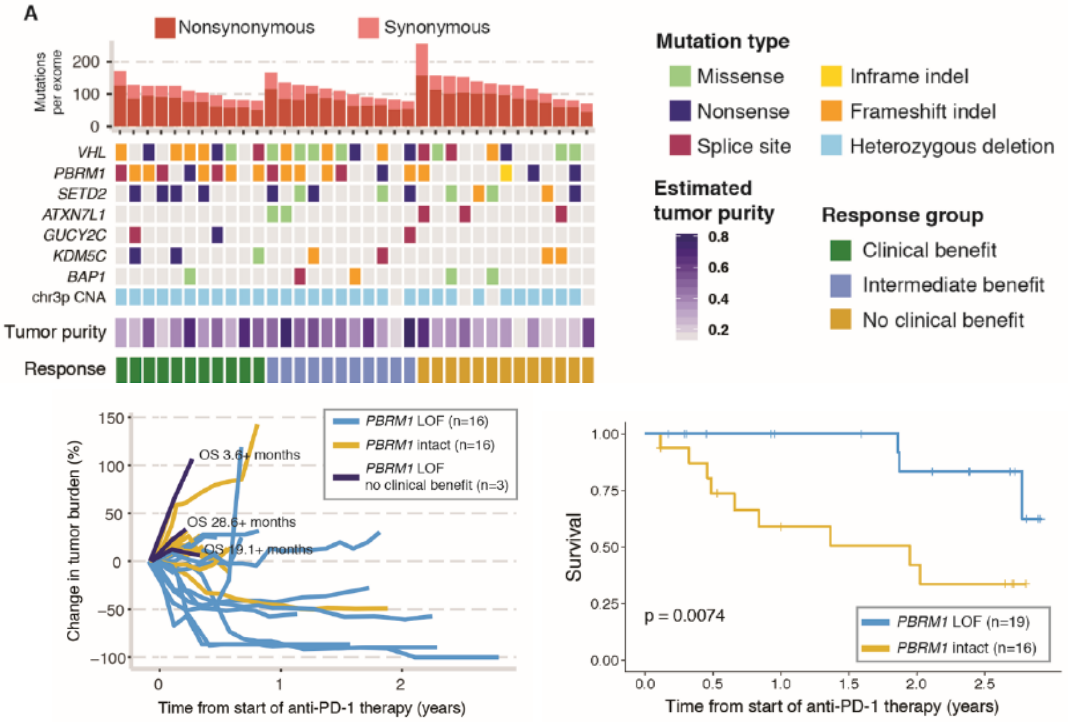
	N	RR
ccRCC sarc+	18	50%
Non-ccRCC sarc+	8	38%

(*) sarcomatoid dedifferentiation
Sarc defined as ≥20% of tumor volume

Mc Gregor et al. JCO 2019

POLYBROMO-1 MUTATIONS

WES 35 pts anti-PD1 monotherapy: PBRM1 loss of function associated with clinical benefit on ICIs



Miao et al. Science 2018

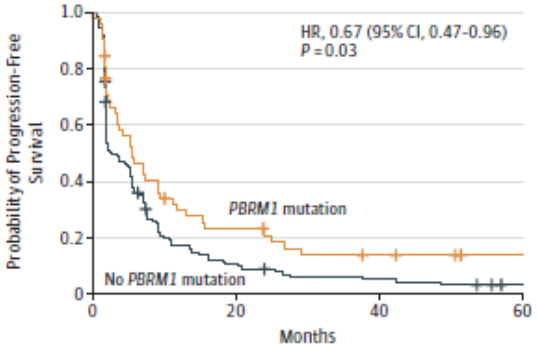
Confirmed in 63 pts anti-PD(L)1 +/- anti-CTLA4

POLYBROMO-1 MUTATIONS

189 pts nivolumab: PBRM1 mutation associated with PFS/OS

A Progression-free survival

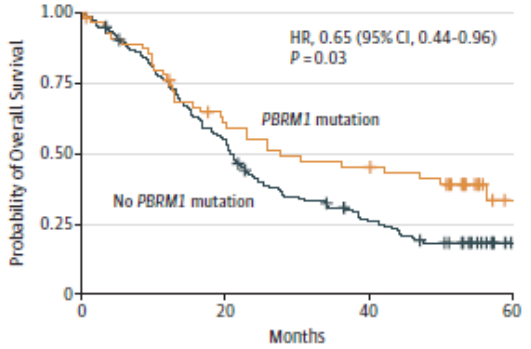
	Median PFS (95% CI), mo	No. of Events
No *PBRM1* mutation	2.9 (2.0-5.6)	118
PBRM1 mutation	5.6 (3.6-11.2)	42



No. at risk				
No *PBRM1* mutation	134	13	6	1
PBRM1 mutation	55	11	5	2

B Overall survival

	Median OS (95% CI), mo	No. of Events
No *PBRM1* mutation	20.9 (18.3-24.8)	106
PBRM1 mutation	27.9 (19.9-NE)	33



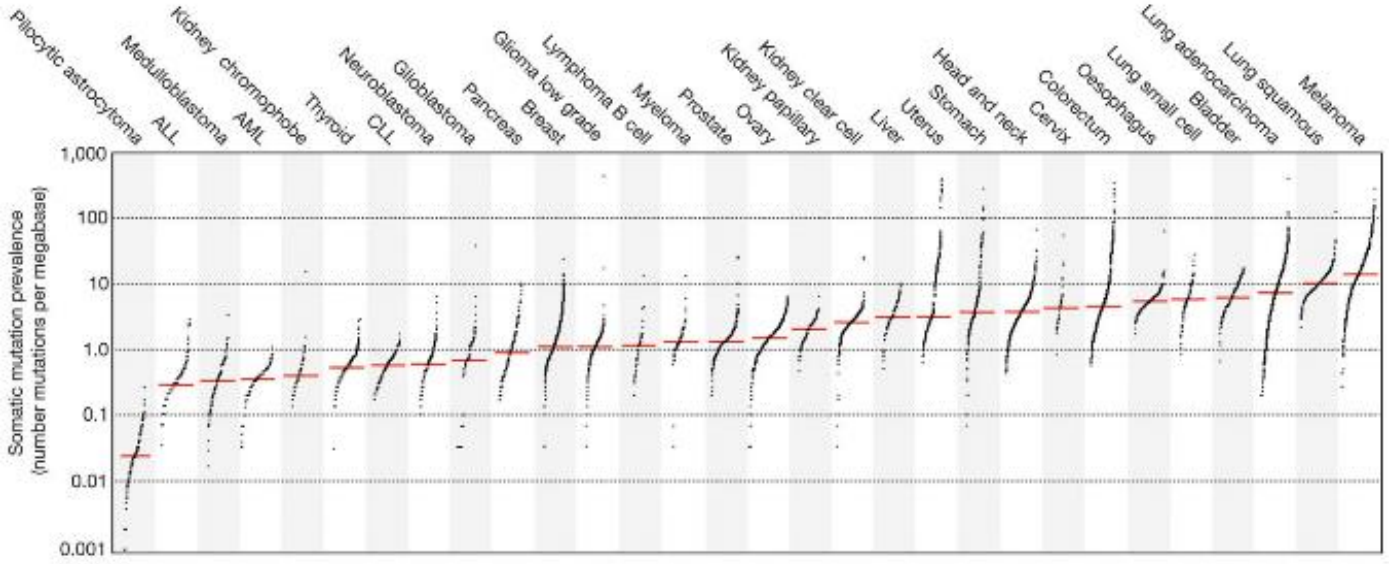
No. at risk				
No *PBRM1* mutation	134	72	32	7
PBRM1 mutation	55	31	23	4

A, Progression-free survival (PFS) with and without a *PBRM1* mutation in patients treated with nivolumab. B, Overall survival (OS) with and without a *PBRM1* mutation in patients treated with nivolumab. NE Indicates not estimable.

However: associated remains weak and does not help to exclude some pts from nivolumab …

MUTATIONAL BURDEN

Tumours with high mutational loads seem to respond particularly well to ICIs, and tend to be highly resistant to traditional treatments (1).

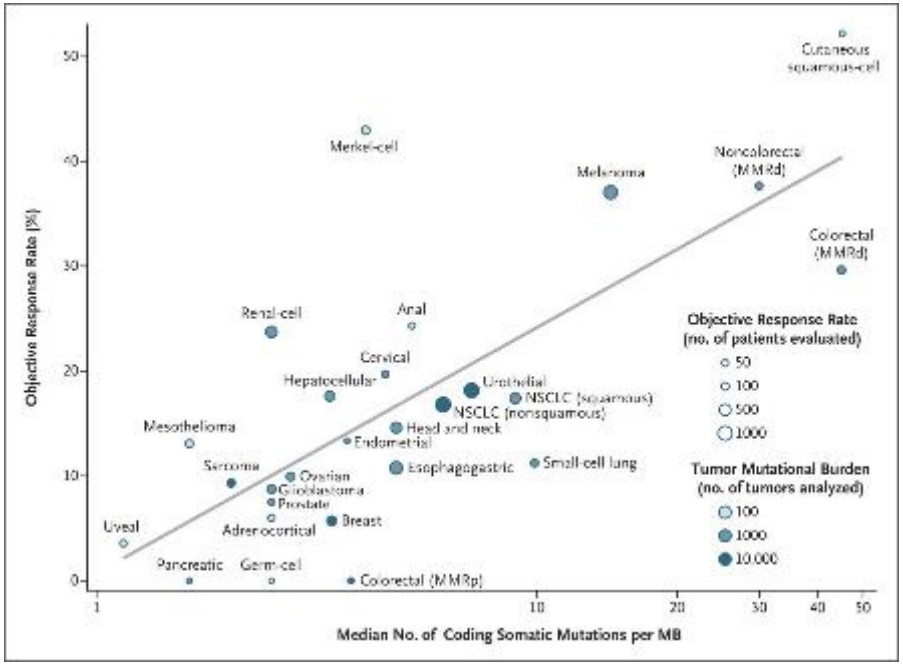


Colorectal carcinoma with mismatch repair deficiency: anti-PD1 is very active and mutational burden high (compared to CRC with mismatch repair proficiency) (2)(3).

(1) Alexandrov et al. Nature 2013.
(2) Le DT et al. NEJM 2015
(3) Le DT et al. Science 2017

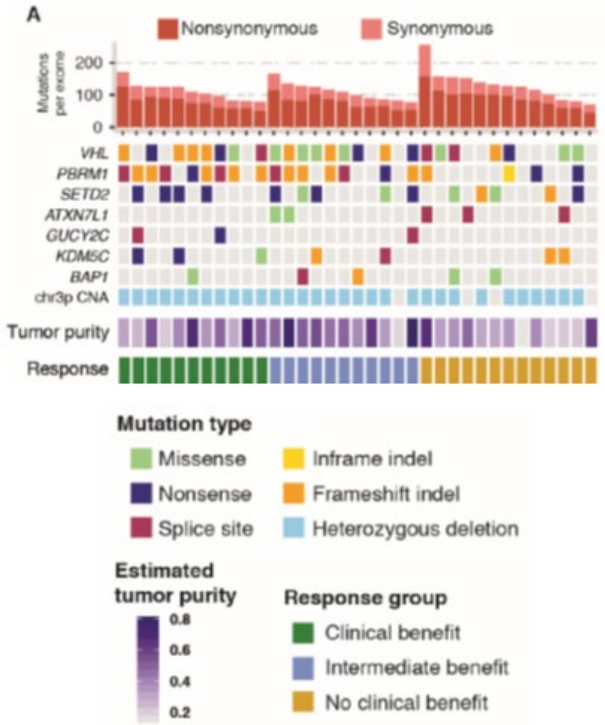
MUTATIONAL BURDEN

27 tumor types with response data on ICP-inhibitors and data on mutational burden



Correlation p<0.001

No correlation between mutational burden and outcome



Yarchoan et al. NEJM 2017

Miao et al. Science 2018

MUTATIONAL BURDEN

A: YES

B: NO

MUTATIONAL BURDEN

Case Report

Immunogenomics of Metastatic Clear-Cell Renal Cell Carcinoma: Remarkable Response to Nivolumab in a Patient With a Pathogenic Germ Line *BRCA1* Mutation

Yana Beulque,[1] Anne-Leen Deleu,[1] Kevin Punie,[1] Liesbeth De Wever,[2] Marcella Baldewijns,[3] Stefano Caruso,[4] Gabrielle Couchy,[4] Jessica Zucman-Rossi,[4] Benoit Beuselinck[1]

Clinical Practice Points

- In a subgroup of patients with metastatic clear-cell renal cell carcinoma (m-ccRCC), immune checkpoint (ICP) inhibitors can induce considerable and long-lasting responses. However, predictive biomarkers are lacking.
- We report a case of a long-lasting deep partial response with nivolumab treatment in an m-ccRCC patient with a germ line pathogenic breast cancer-1 mutation.
- This observation is consistent with 2 patient series presented recently at the annual genitourinary cancer symposium of the American Society of Clinical Oncology (ASCO-GU 2019), showing favorable outcomes with ICP inhibitors in m-ccRCC patients with somatic or germ line mutations in DNA damage repair genes.

Clinical Genitourinary Cancer, Vol. ■, No. ■, ■-■ © 2019 Elsevier Inc. All rights reserved.
Keywords: *BRCA1* mutation, Immune checkpoint inhibitors, Predictive biomarkers, Renal cell carcinoma

Nivolumab after sunitinib and axitinib: CR lasting for 27 months

Mismatch repair (Microsatelite instable/Lynch syndrome):

- Well known to respond better on ICPIs across tumor types

DNA damage repair gene mutations: some reports

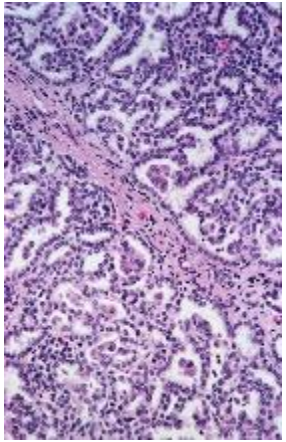
- Series of 6 heavily pretreated ovarian carcinoma pts, with a germline BRCA mutation: nivolumab led to 3 CRs and 1 PR (1).
- Metastatic cutaneous angiosarcoma in a pt with xeroderma pigmentosum (germline XPC mutation) treated with pembrolizumab after 3 lines of chemotherapy: almost CR after 4 cycles (2).
- 3 heavily pretreated prosCA pts treated with ICPIs: 3 responses: one pt with germline BRCA2, one with somatic ATM frameshift mutation and one with somatic BRCA2 mutation (3).

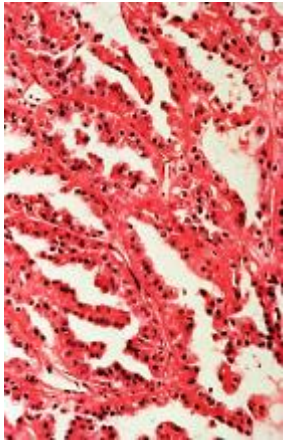
(1) Matsuo K et al. Gynecol Oncol Rep. 2018.
(2) Momen et al. Cold Spring Harb Mol Case Stud 2019.
(3) Markowski et al. The prostate 2020.

HISTOLOGY: PAPILLARY RCCs

Papillary RCC : displays a papillary growth pattern

- 15% of all RCCs
- 5% type 1 papRCC: basophilia
- 10% type 2 papRCC: eosinophilia, usually more aggressive





Often c-MET driven

	MET copy number gain	MET kinase domain mutation
PAP1	72%	15%
PAP2	46%	2%

Phase II studies with savolitinib (cMET-TKI), crizotinib (cMET-TKI) or foretinib (cMET-and VEGFR-TKI)

- Responses and improved PFS or DOR noted in cMET-driven papRCCs
- However, these compounds are not available.

Cabozantinib is the only available cMET-TKI …

Choueri et al. JCO 2017
Choueri et al. JCO 2013
Schöffski et al. Eur J Cancer 2017

HISTOLOGY: PAPILLARY RCCs

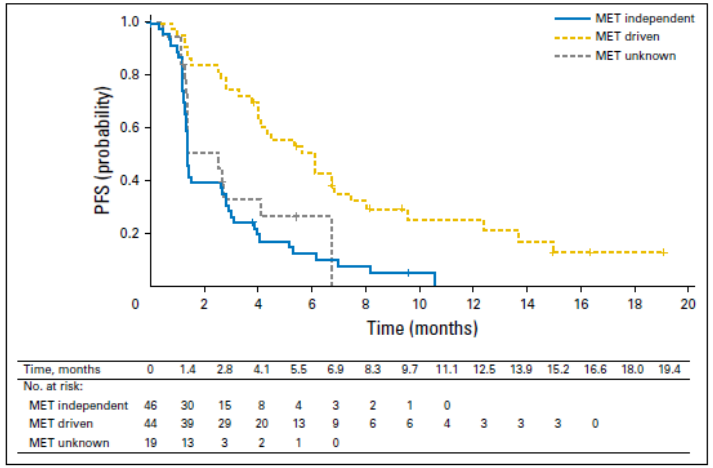
Phase II Trial of Savolitinib in 109 papRCC pts

Savolitinib 600 mg/d : highly selective MET tyrosine kinase inhibitor.

MET-driven PRCC defined as any of the following: chromosome 7 copy gain, focal MET or HGF gene amplification, MET kinase domain mutations.

Characteristic	No. (%)			
	MET Driven (n = 44)	MET Independent (n = 46)	MET Unknown (n = 19)	Total (N = 109)
Type 1 PRCC	12 (27)	2 (4)	2 (11)	16 (15)
Type 2 PRCC	23 (52)	37 (80)	8 (42)	68 (62)
Subtype unclassifiable	9 (21)	7 (15)	9 (47)	25 (23)

	PR	SD	PD	PFS
MET+ (n=40)	18%	50%	25%	6,2M
MET- (n=46)	0%	24%	61%	1,4M
				p=<0,001

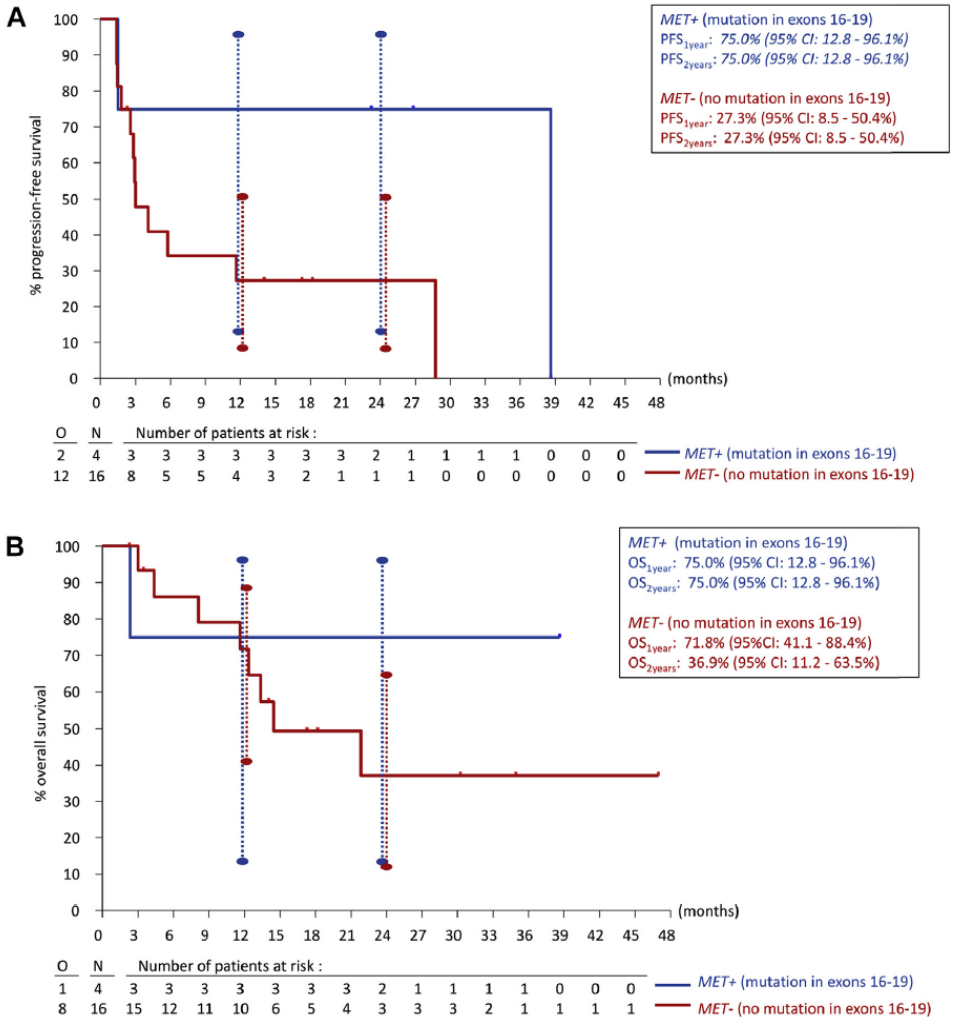


Choueri et al. JCO 2017

HISTOLOGY: PAPILLARY RCCs

Phase II study crizotinib in papRCC type 1

	RR	DOR
MET+ (n=4)	50% PR 25% SD	21,8 and 37,3M
MET- (n=16)	6% PR 69% SD	9,9M



Schöffski et al. Eur J Cancer 2017

HISTOLOGY: PAPILLARY RCCs

Phase II study of the MET/VEGFR2 inhibitor foretinib in papRCC

Foretinib: oral multikinase inhibitor targeting MET, VEGF, RON, AXL, and TIE-2 receptors.

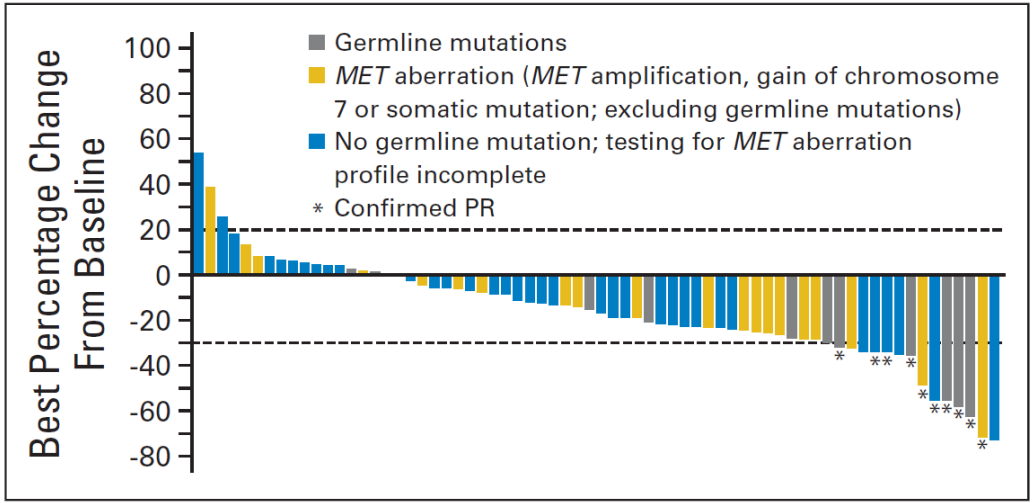
- Cohort A, 240 mg once per day on days 1 through 5 every 14 days (intermittent arm);
- Cohort B, 80 mg daily (daily dosing arm).

Patients stratified on the basis of MET pathway activation (germline or somatic MET mutation, MET [7q31] amplification, or gain of chromosome 7).

RESULTS:

74 pts enrolled, 37 in each dosing cohort.

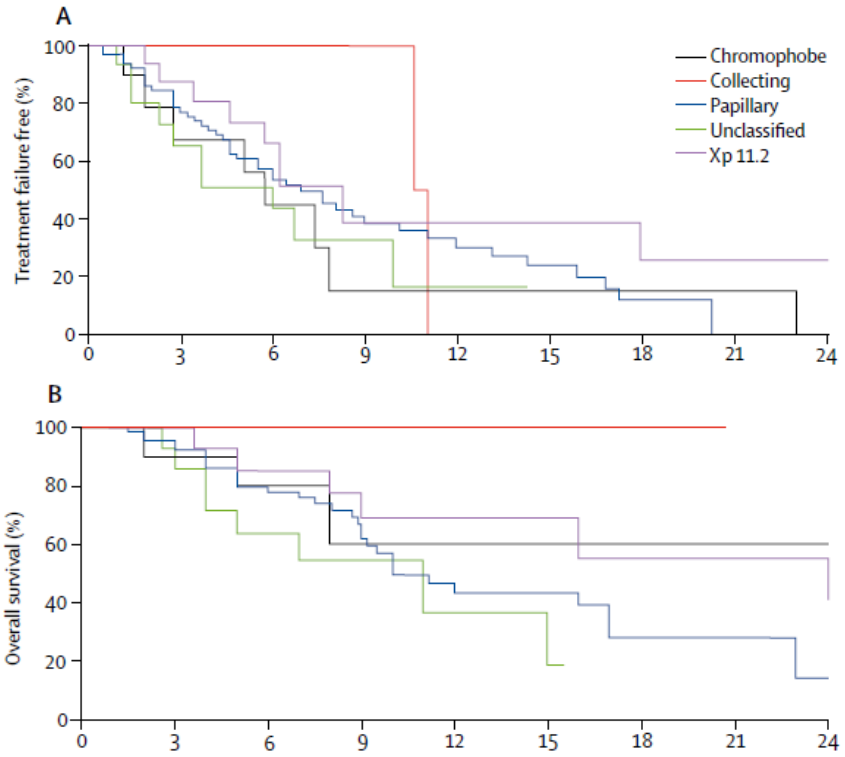
- ORR: 13.5%
- If germline MET mutation: 5/10 responses (50%)
- If no germline MET mutation: 5/57 responses (9%)
- mPFS 9.3 months
- mOS not reached.



Choueri et al. JCO 2013

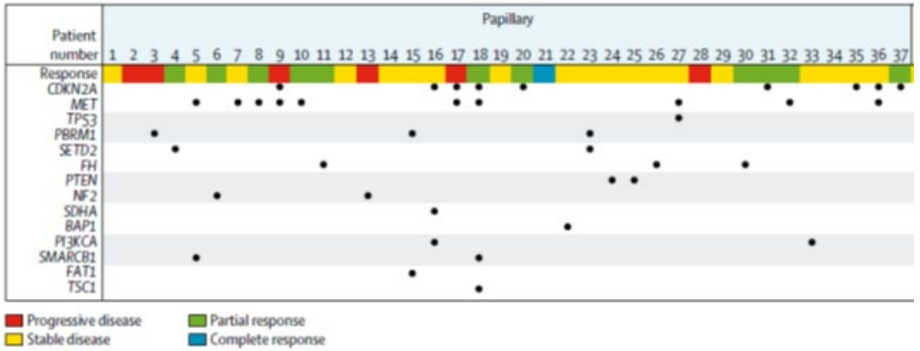
HISTOLOGY: PAPILLARY RCCs

Cabozantinib retrospective analysis (n=112)



	Overall response		Clinical benefit		Median time to treatment failure	12-month overall survival
	n/N	% (95% CI)	n/N	% (95% CI)		
Overall cohort	30/112	27% (19–36)	83/112	74% (65–82)	6·7 (5·5– 8·6)	51% (39–62)
Histology						
Papillary	18/66	27% (17–40)	48/66	73% (60–83)	6·9 (4·6–10·1)	46% (31–60)
Xp11.2 translocation	5/17	29% (10–56)	14/17	82% (57–96)	8·3 (4·6–NR)	69% (36–87)
Unclassified	2/15	13% (2–40)	10/15	67% (38–88)	6·0 (1·4–9·9)	36% (8–67)
Chromophobe	3/10	30% (7–65)	7/10	70% (35–93)	5·7 (1·1–7·8)	60% (16–87)
Collecting duct	2/4	50% (7–93)	4/4	100% (40–99)	NC	NC
Sarcomatoid features						
Yes	6/30	20% (8–39)	23/30	77% (58–90)	5·1 (2·8–6·2)	25% (8–47)
No	13/51	25% (14–40)	34/51	67% (52–79)	7·4 (4·6–11·0)	48% (31–64)

10 MET-altered papRCCs: 4 PR (40%)



RESPONSE PREDICTION IN mTORinh

PTEN expression and mutations in TSC1, TSC2 and MTOR are associated with response to rapalogs in patients with RCC (n=105)

11/87 (13%): **mTOR pathway mutations** (8 in MTOR, 1 in TSC1 and 2 in TSC2) by NGS

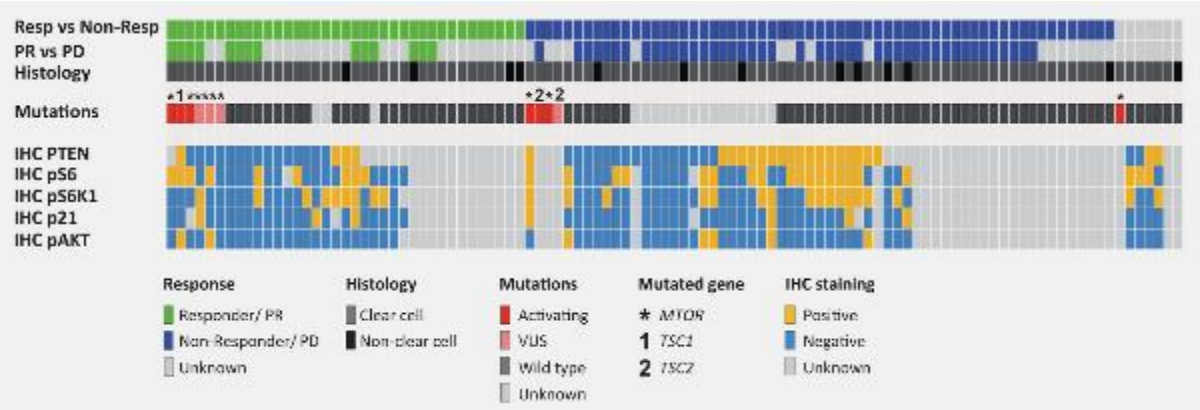
- PR more frequent if mTOR pathway mutations (OR = 0.08, 95%CI = 0.008-0.79, p=0.038)
- Among the mutated patients, some showed remarkable sensitivity to rapalogs, including two cases with 89 and 21 months PFS in third and fourth line of treatment.
- PFS not associated with mutational status in global population
- In pts with more extreme phenotypes (PR or PD as best response): better PFS in case of mTOR pathway mutations (p = 0.044)

58% of the tumors had negative **PTEN staining** (by IHC)

- Negative PTEN staining more frequent in responders (OR = 0.24, 95%CI = 0.065-0.86, p=0.029)
- PFS not associated with PTEN IHC

Mutations and PTEN IHC

- Not mutually exclusive events.
- Its combination improved response prediction (OR = 0.16, 95%CI = 0.04-0.62, p=0.013)



Roldan-Romero JM, Beuselinck B, et al. Int J Cancer 2019.

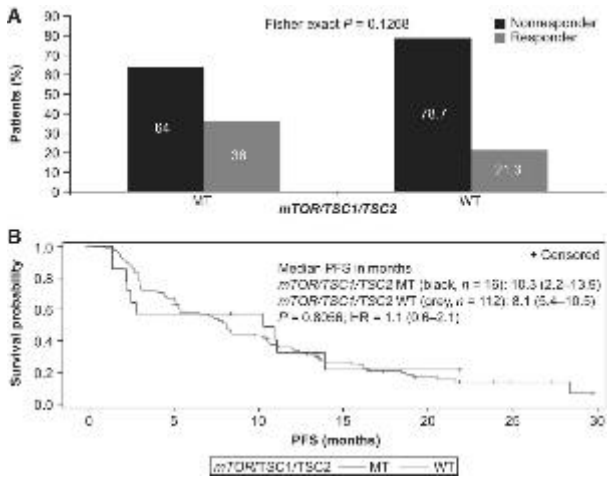
RESPONSE PREDICTION IN mTORinh

PTEN expression, not mutations in *TSC1, TSC2*, or *mTOR*, correlates with the outcome on everolimus in RCC pts treated on the randomized RECORD-3 trial (n=184).

- **Mutation rates**: 6% (*TSC1*), 4.4% (*TSC2*), and 8.2% (*mTOR*).
- 44% harbored alterations in ≥1 PI3K pathway component.
- Presence versus absence of mutations in *TSC1, TSC2*, or *mTOR* : no significant difference in RR or PFS

- **PTEN expression**
- Lost in 50% of the pts
- Retained (*n* = 50) versus lost (*n* = 50) PTEN IHC expression:
- mPFS of 5.3 vs 10.5 months (HR, 2.5; *P* < 0.001).
- (Such differences were not seen with sunitinib).

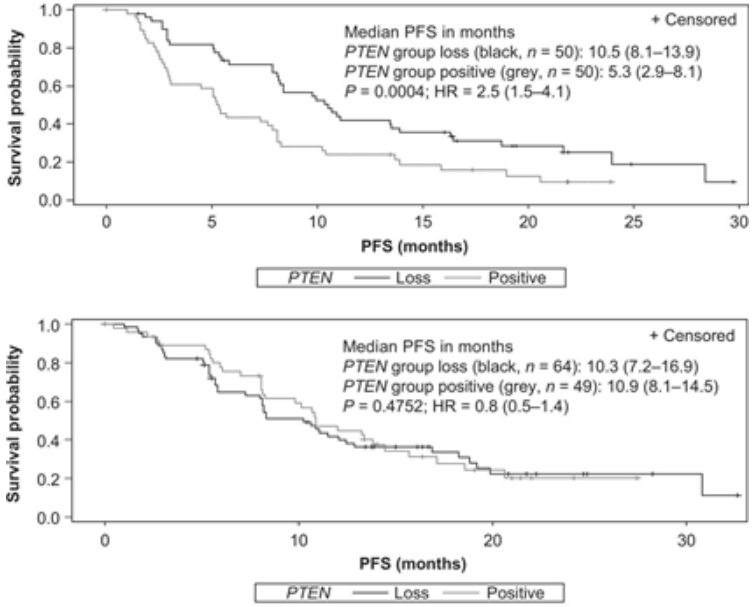
IMPACT OF mTOR/TSC1/TSC2 mutations



IMPACT OF PTEN IHC on PFS

A: in everolimus treated patients

B: in sunitinib treated patients



RESPONSE PREDICTION IN mTORinh

Mutations in TSC1, TSC2, and MTOR Are Associated with Response to Rapalogs in Patients with mRCC (n=79)

- Responders: PR by RECIST or SD with any tumor shrinkage for ≥6 months
- Non-responders: disease progression during the first 3 months of therapy.

Mutations in MTOR, TSC1, or TSC2:

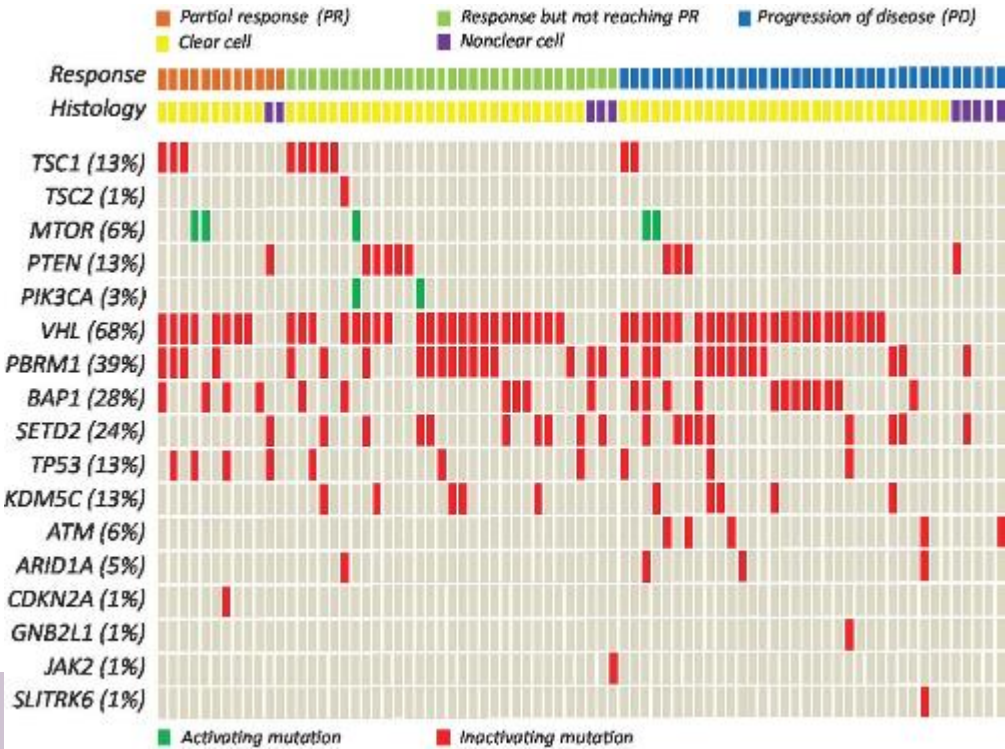
- More common in responders (12/43; 28%)
- Than non-responders (4/36; 11%)(p=0.06).

Responders:

- 42% (5/12) of pts had mutations in MTOR, TSC1, or TSC2

Non-responders:

- 11% (4/36) of pts had mutations in MTOR, TSC1, or TSC2 (p=0.03).



Kwiatkowski DJ et al. Clin Cancer Research 2016

ANY QUESTION?