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SYSTEMIC THERAPY FOR KIDNEY CANCER

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UZ Leuven
24/04/2021

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Immune checkpoint inhibitors and pre-existing auto-immune diseases

ICP-INHIBITORS AND PRE-EXISTING AUTOIMMUNE DISEASES

Oncologists and rheumatologists use the opposite therapies

Stimulation of immune system	Immunosuppression
Anti-CTLA4-mab	CTLA4
Anti-PD1-mab	
	Anti-TNF-mab

Oncologists are giving work to rheumatologists and rheumatologists to oncologists …

Limited retrospective data on the safety of checkpoint inhibitors in pts with an underlying autoimmune disorder suggest that they can be given safely.

Given the life-threatening nature of the malignancies and the potential benefits of checkpoint-blocking antibodies => discuss the possible benefits and risks of immunologic checkpoint blockade

ICP-INHIBITORS AND PRE-EXISTING AUTOIMMUNE DISEASES

52 pts with melanoma with a pre-existing autoimmune disorder treated with PEMBRO or NIVO

- 38%: flare of the autoimmune disorder requiring immunosuppression
- Majority of flares relatively mild
- Only 2 pts required discontinuation of anti-PD-1

30 pts with melanoma and a pre-existing autoimmune disorder treated with IPI:

- Rheumatoid arthritis, inflammatory bowel disease, and psoriasis
- 27%: exacerbation of underlying autoimmune conditions
- All successfully managed with corticosteroids

45 pts (mostly melanoma some NSCLC and others) with pre-existing auto-immune diseases treated with anti-PD1-mabs

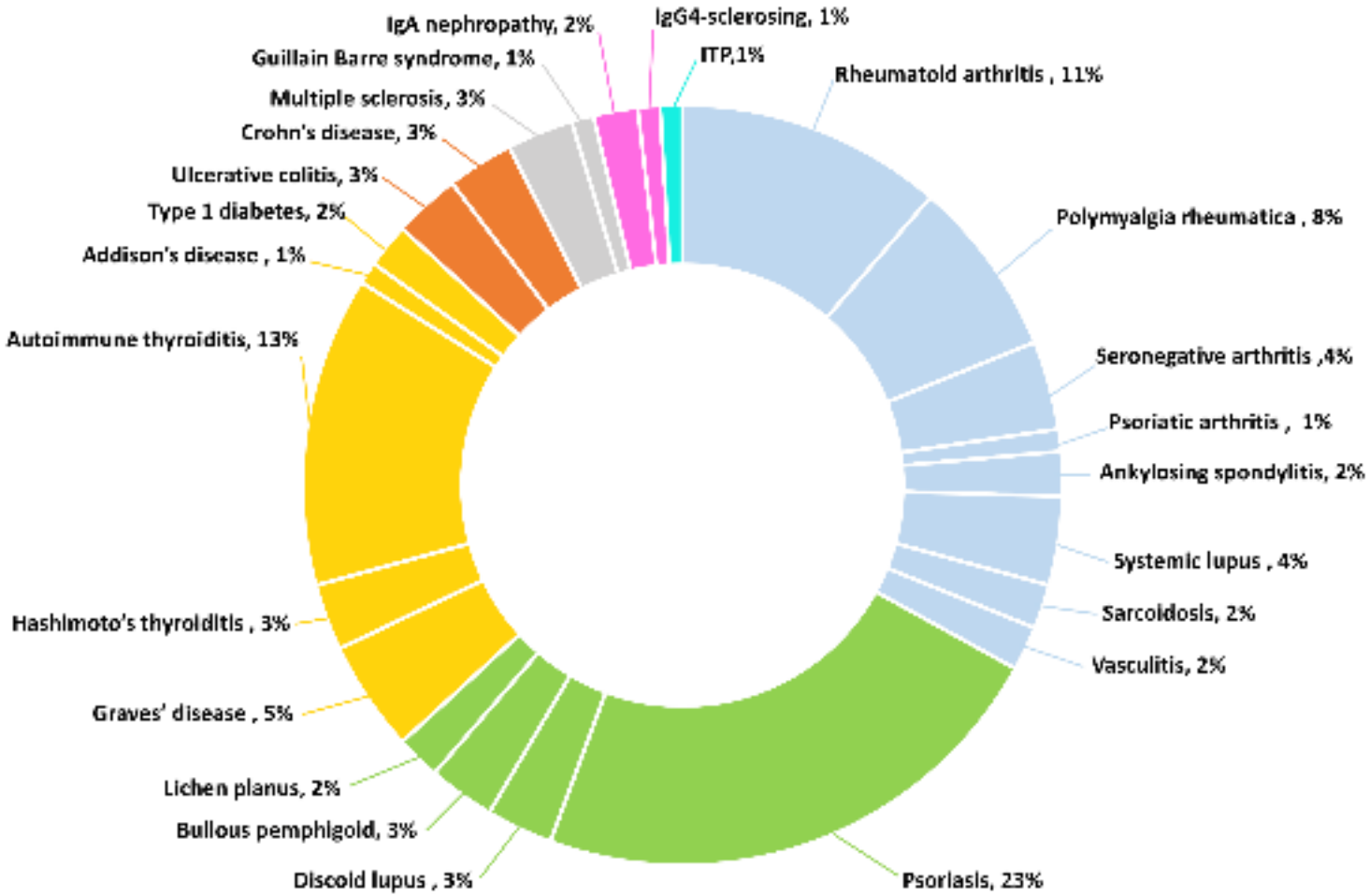
- Vitiligo, psoriasis, thyroiditis, Sjögren, rheumatoid arthritis
- 44%: at least one irAE, 55% of them “flare” of a pre-existing auto-immune disease, 75% anti-PD1-mabs were continued
- Pts with pre-existing auto-immune diseases (n=45) vs pts without auto-immune diseases (n=352): irAE-free survival time significantly shorter (median 5,4M vs 13M; p=0,0002)
- EFFICACY: Pts with pre-existing auto-immune diseases (n=45) vs pts without auto-immune diseases (n=352): No difference in ORR (38% vs 28%; p=0,098) , no difference in OS (p=0,38)

Danlos FX et al. Eur J Cancer 2018.

Menzies AM et al. Ann Oncol 2016.
Johnson DB et al. JAMA Oncol 2016; 2:234.

ICP-INHIBITORS AND PRE-EXISTING AUTOIMMUNE 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).

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ICP-INHIBITORS AND PRE-EXISTING AUTOIMMUNE DISEASES

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

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

RCC cohort (n=58)

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

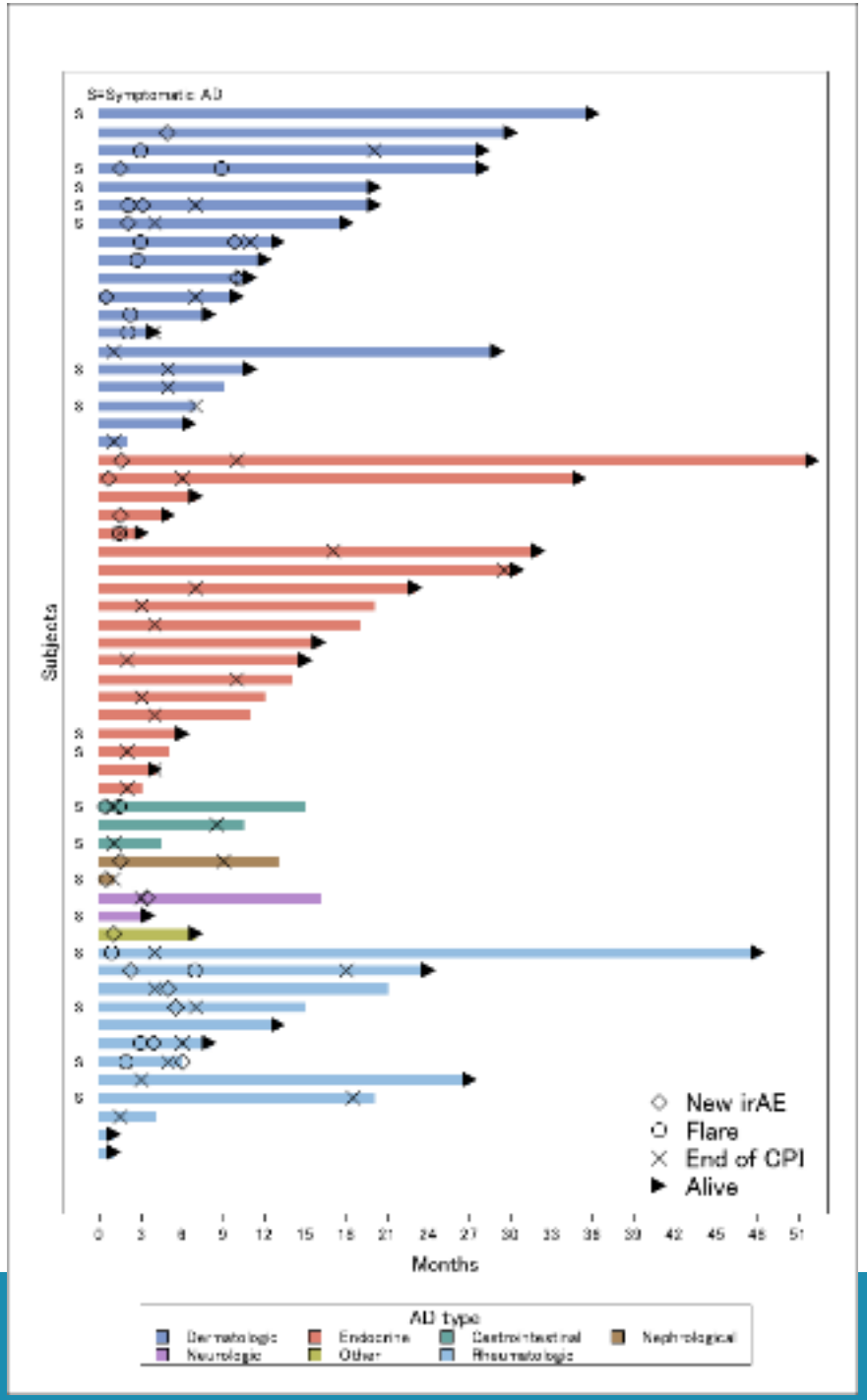
8/40 pts (20%): requiring discontinuation of ICPI.

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.



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

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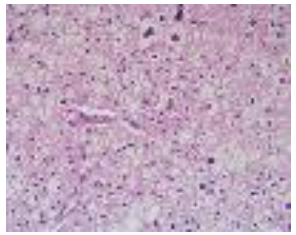
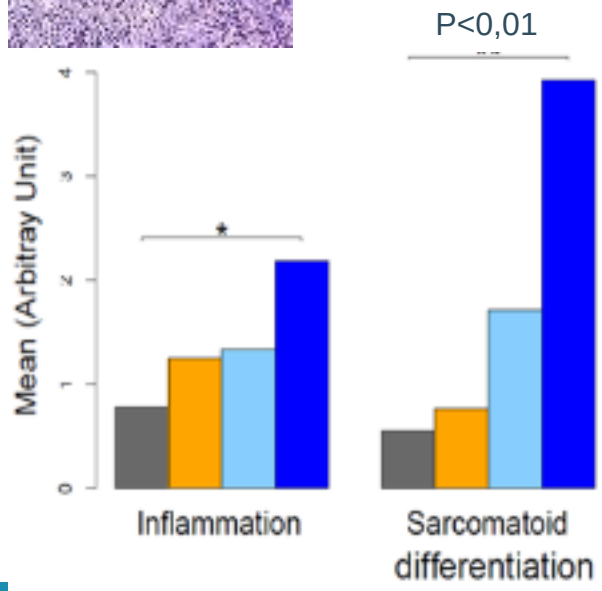
Clear-cell renal cell carcinoma Biomarkers

SARCOMATOID DEDIFFERENTIATION



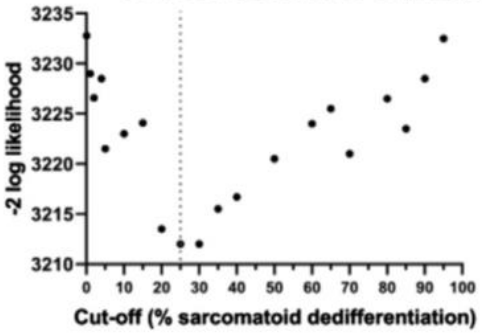


On 366 m-ccRCC pts treated with pazopanib or sunitinib in 1L

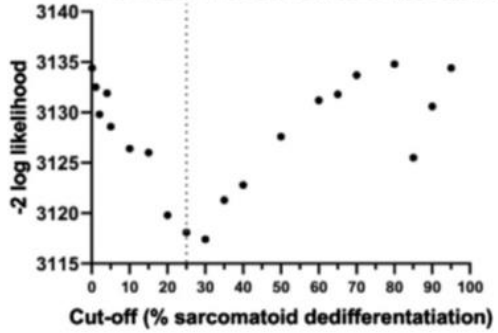
On 92 m-ccRCC pts treated with ICIs

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

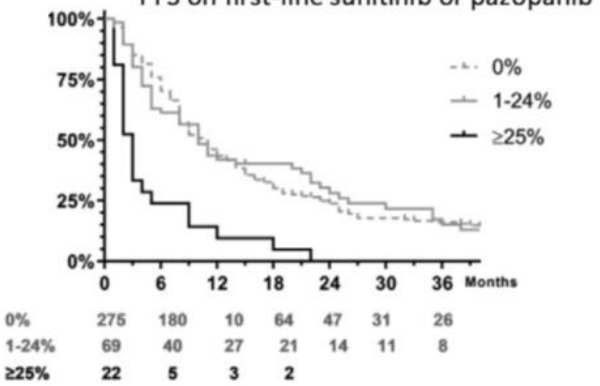
Discriminative power for PFS on first-line sunitinib or pazopanib



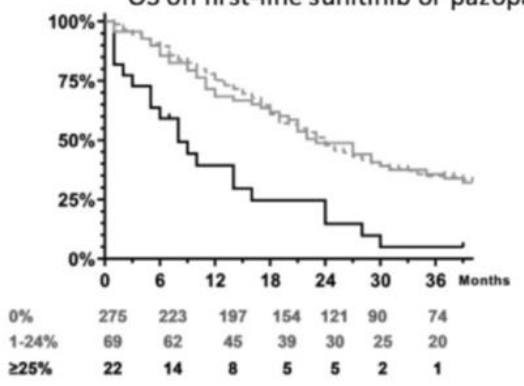
Discriminative power for OS on first-line sunitinib or pazopanib



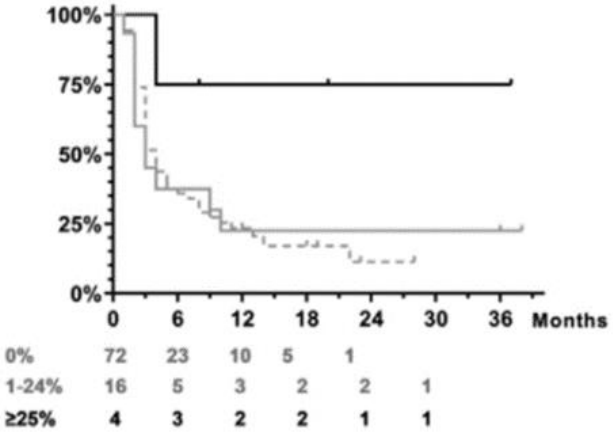
PFS on first-line sunitinib or pazopanib



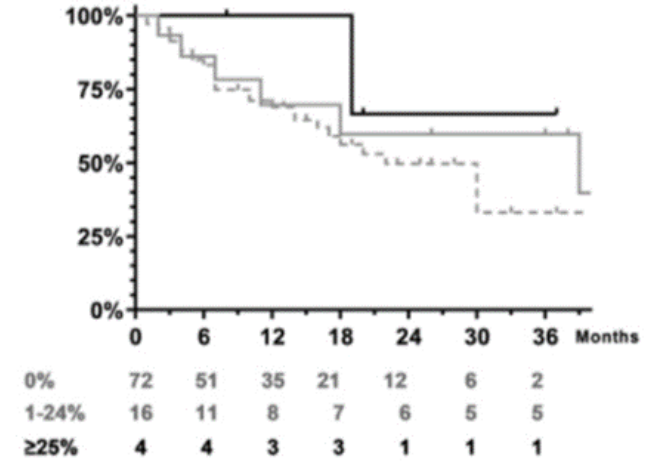
OS on first-line sunitinib or pazopanib



PFS on Immune checkpoint inhibitors



OS on immune checkpoint inhibitors



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

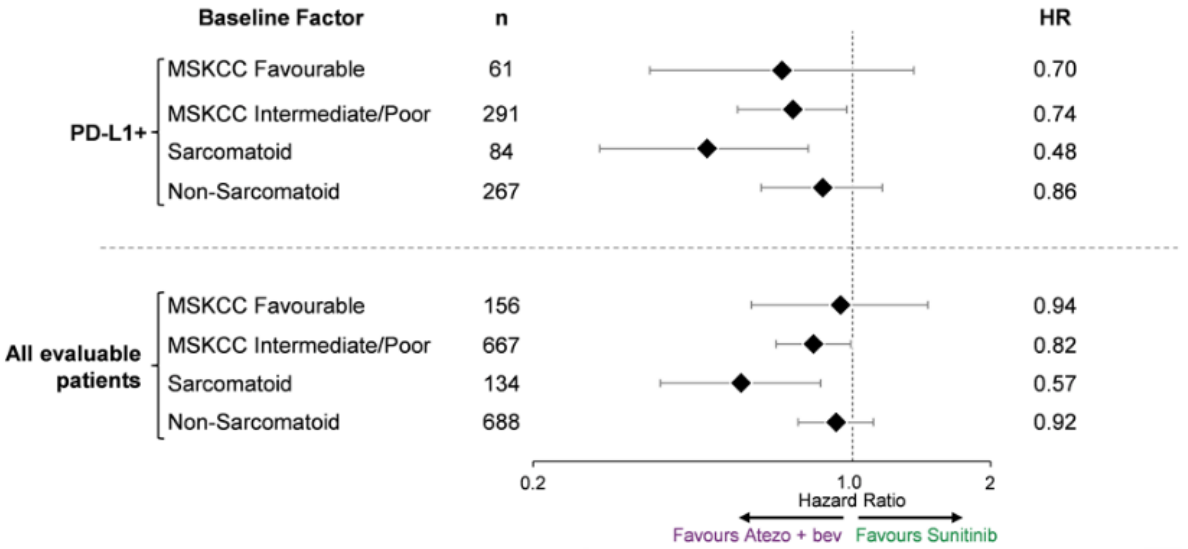
SARCOMATOID DEDIFFERENTIATION

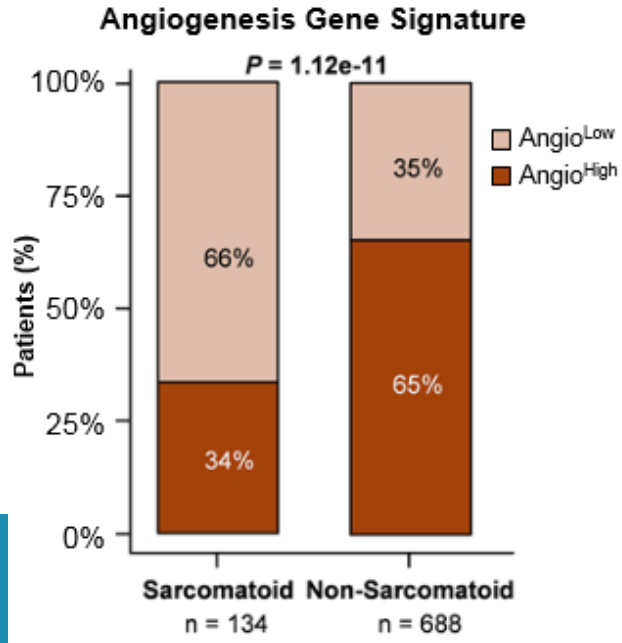
IMMOTION 151: SARCOMATOID TUMORS:

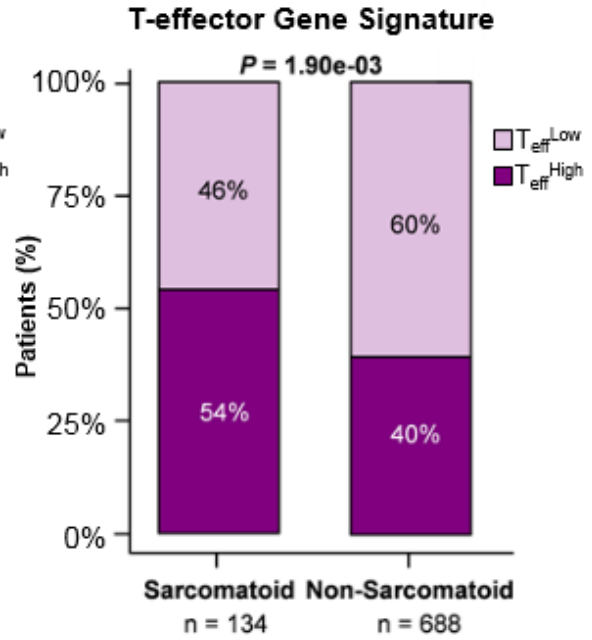
More benefit from atezolizumab/bevacizumab

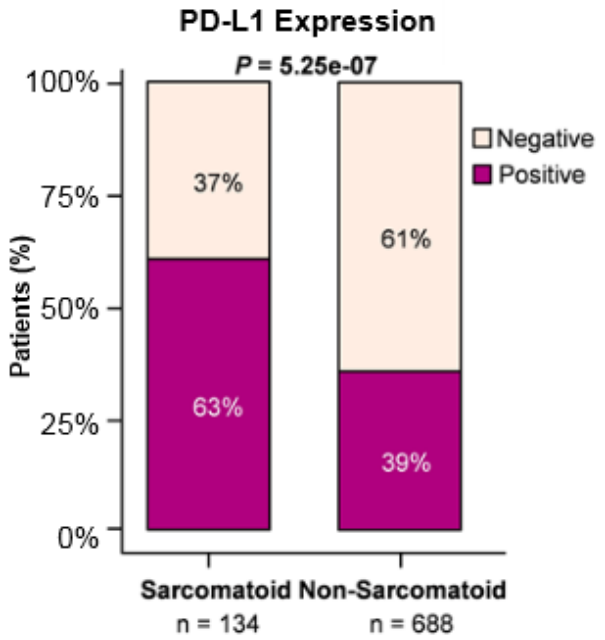
Display:

- less angiogenesis
- more Teff signature
- more PDL1 expression







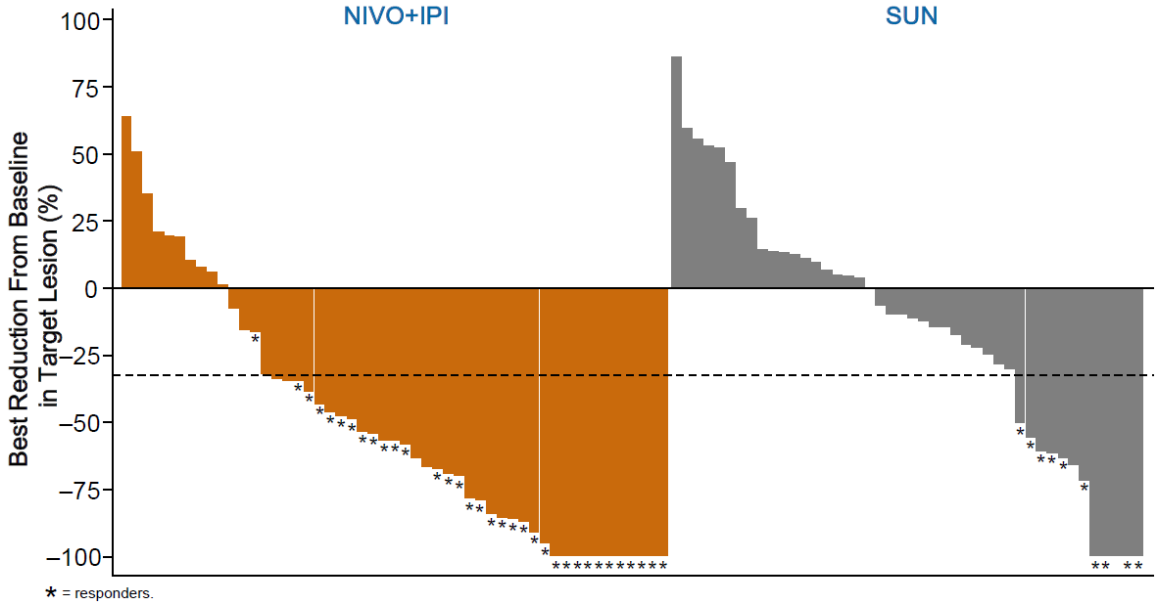


Rini et al. ESMO2018

SARCOMATOID DEDIFFERENTIATION

CA209-214 30 MONTHS FOLLOW UP

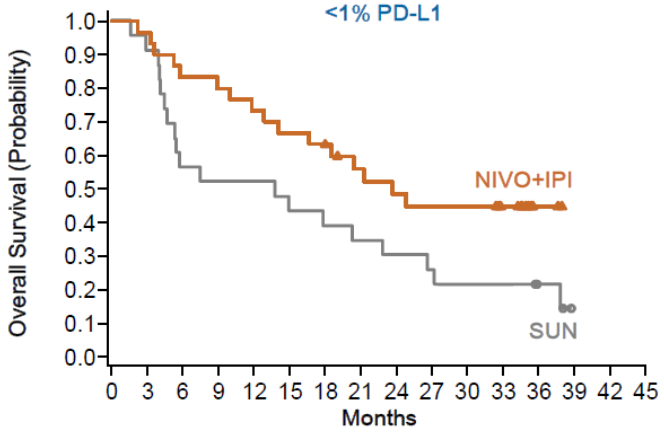
Best Tumor Reduction From Baseline in Target Lesions per Investigator: Intermediate/Poor-Risk Sarcomatoid Patients



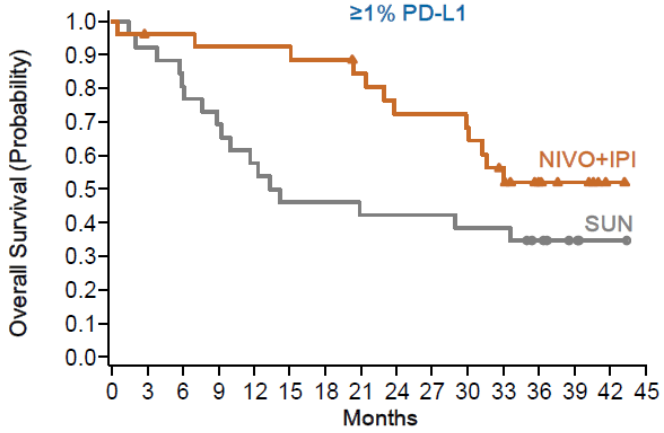
* = responders.

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)



Motzer, Beuselinck, et al, Lancet Oncology 2019

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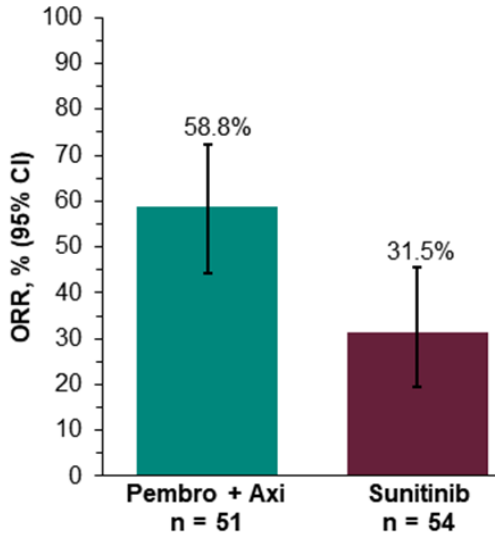
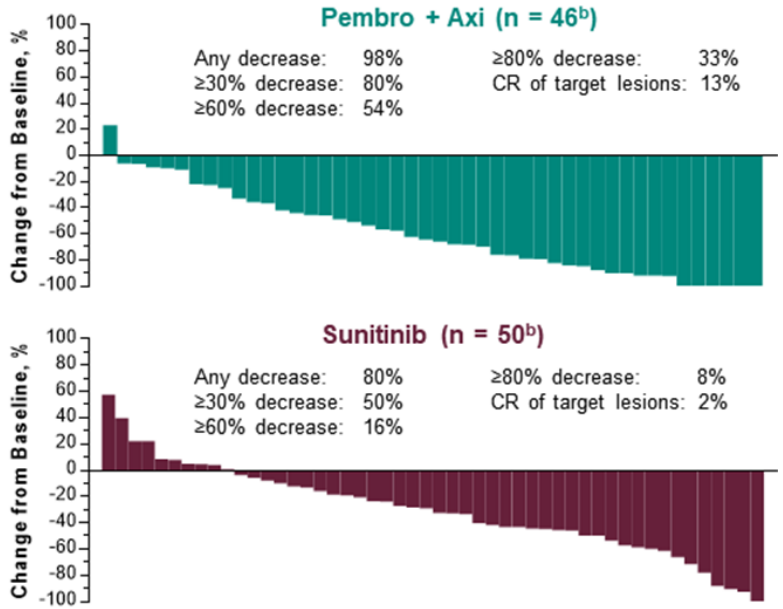
SARCOMATOID DEDIFFERENTIATION

KEYNOTE 426: PATIENTS WITH TUMORS WITH SARCOMATOID DEDIFFERENTIATION

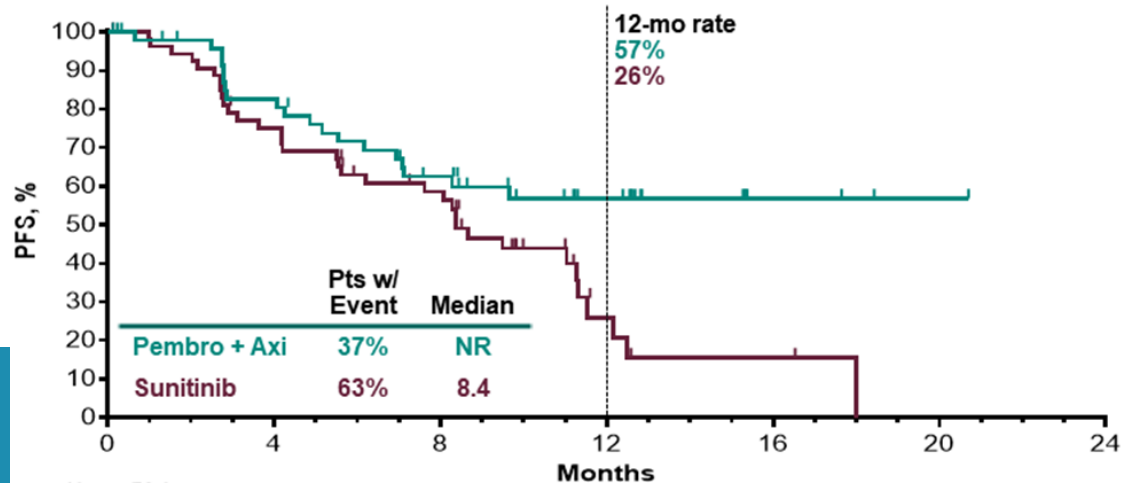
	Pembrolizumab + Axitinib N = 51	Sunitinib N = 54
IMDC risk category		
Favorable	7 (13.7%)	10 (18.5%)
Intermediate	34 (66.7%)	38 (70.4%)
Poor	10 (19.6%)	6 (11.1%)
PD-L1 CPS ≥1[b]	38 (74.5%)	43 (79.6%)





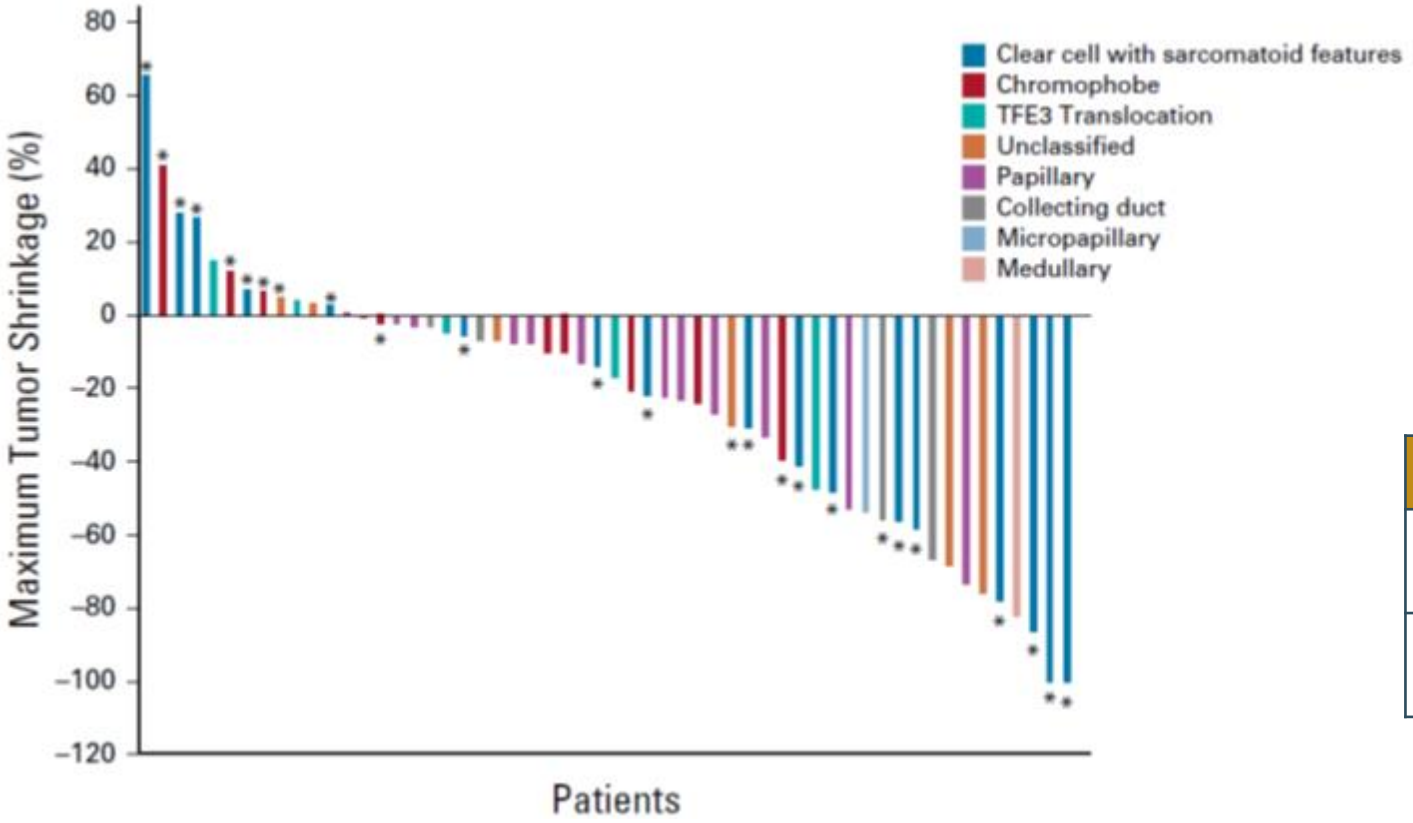
PFS: HR 0.54 (95% CI 0.29–1.00)

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



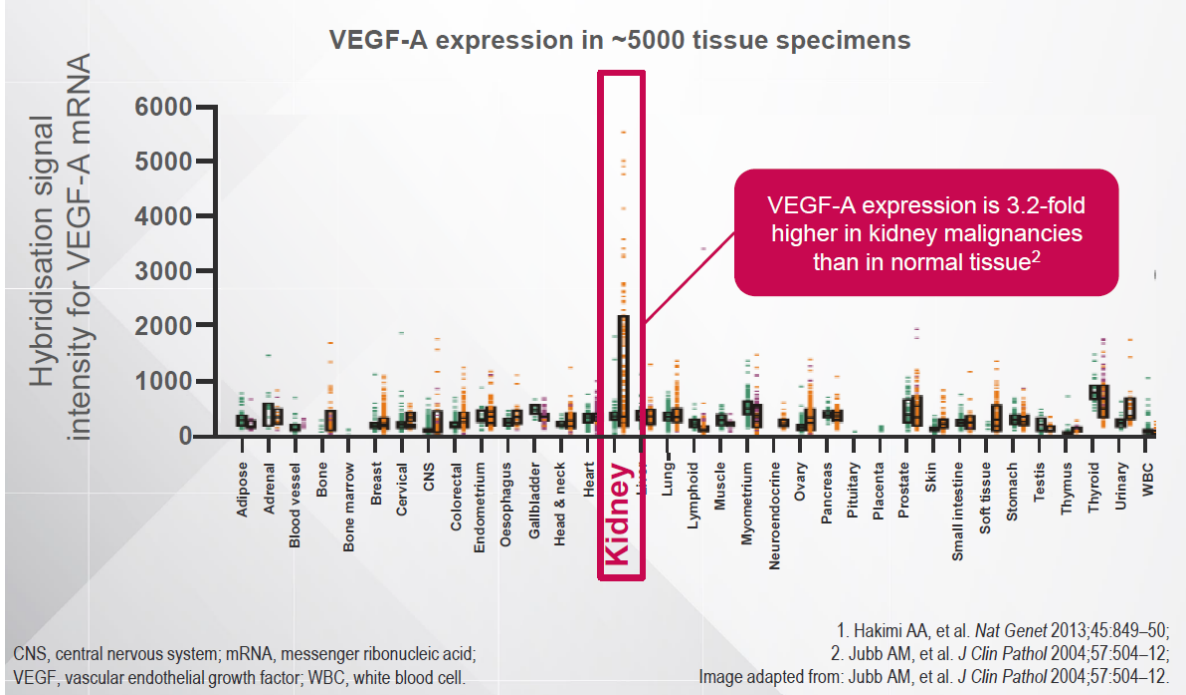
	N	RR
ccRCC sarc+	18	50%
Non-ccRCC sarc+	8	38%

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

Mc Gregor et al. JCO 2019

ANGIOGENESIS

- ccRCC are often hypervascular tumors
- Increased angiogenesis is associated with response on VEGFR-TKIs



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

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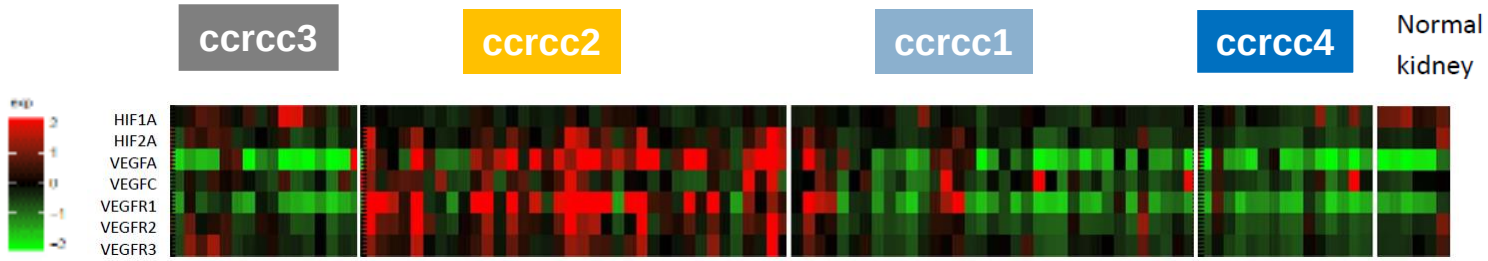
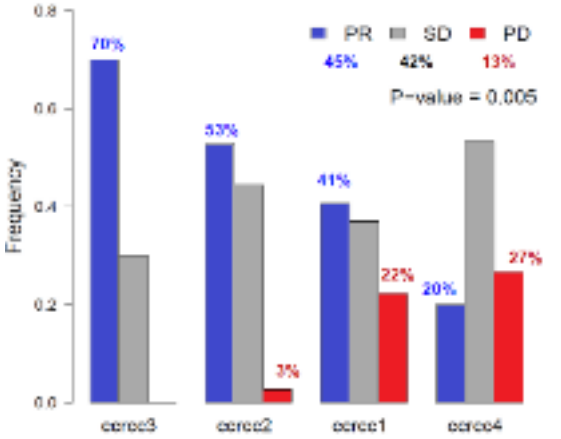
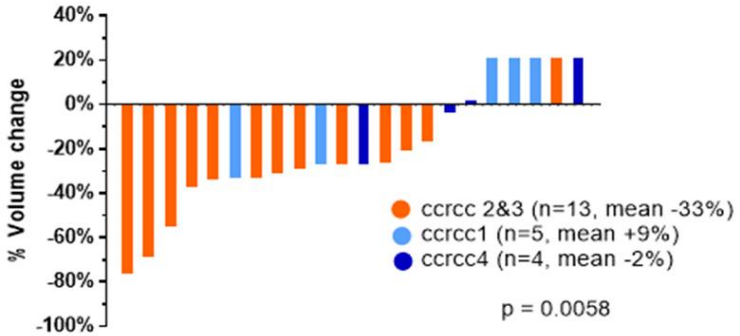


IMDC score is related to molecular characteristics

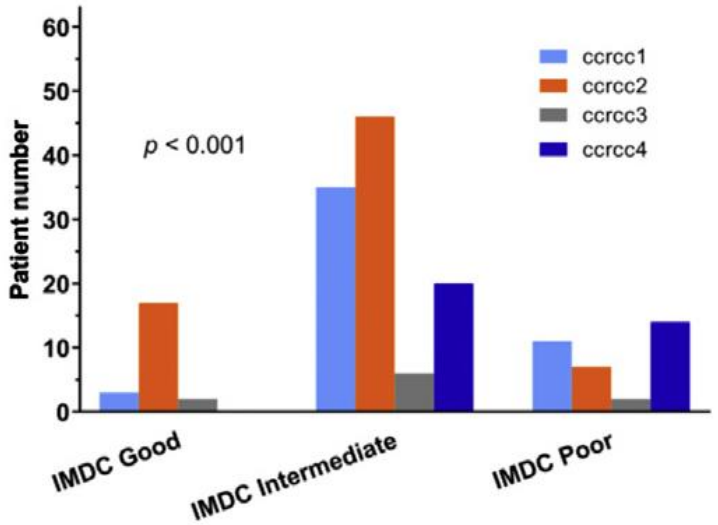
RR on sunitinib



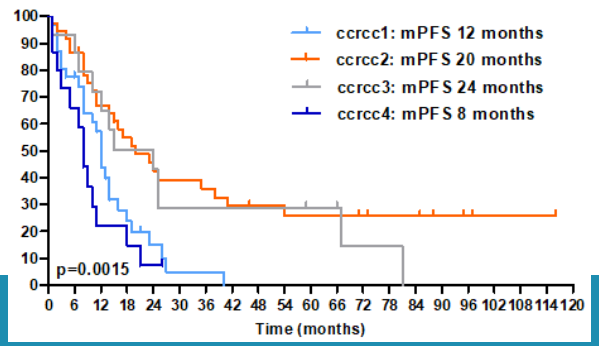
RR on pazopanib



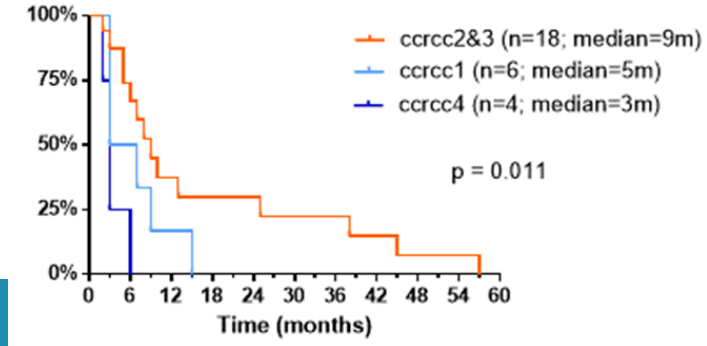
Correlation between ccrcc1 to –4 molecular subtype and IMDC risk group



PFS (%)



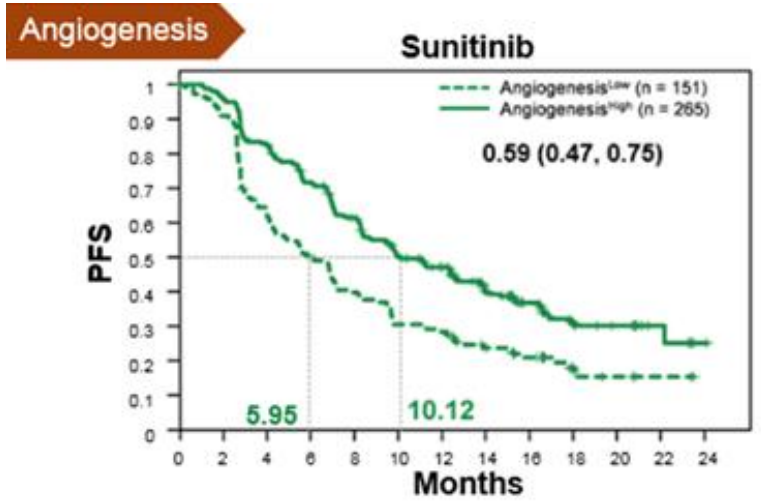
Progression free survival (%)

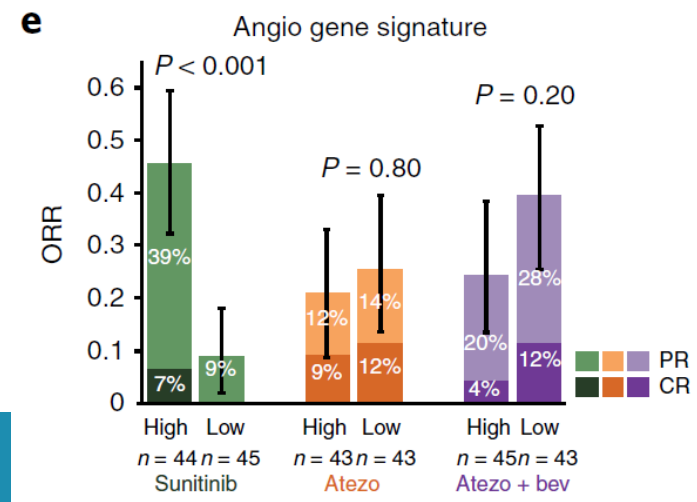


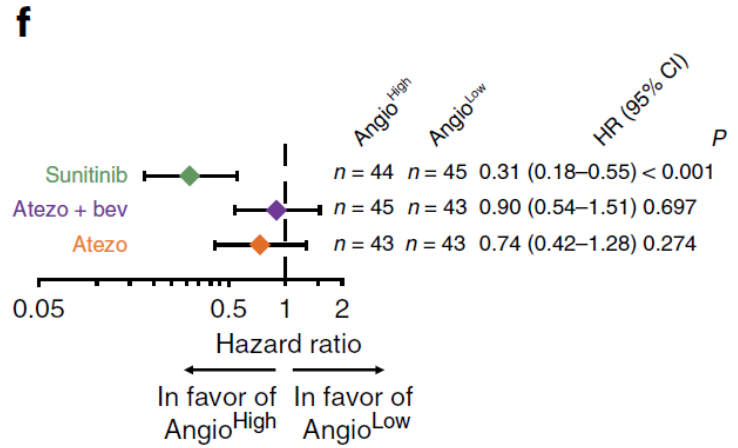
Verbiest A, Renders I, Beuselinck B et al. Clin Genitourinary Cancer 2019
Beuselinck et al. Clin Cancer Res. 2015.
Beuselinck et al. Acta Oncologica 2017
Verbiest, Beuselinck et al. Clin Genitourin Cancers 2017

ANGIOGENESIS

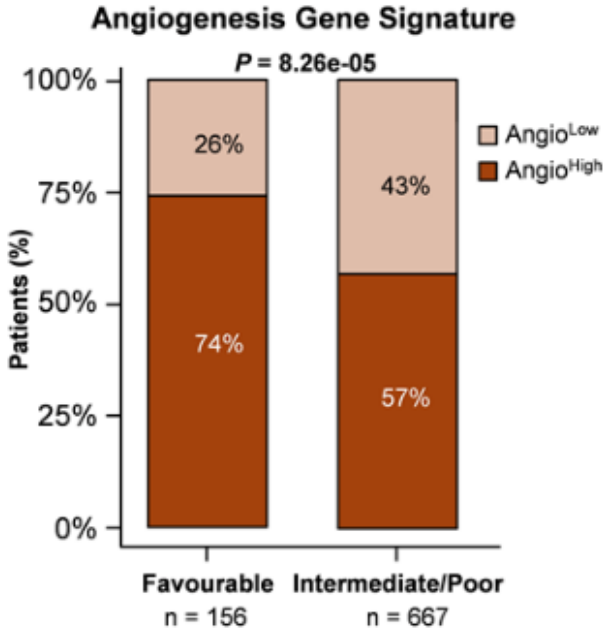
IMMOTION 150/151 (sunitinib vs atezolizumab/bevacizumab): angiogenesis correlated to better outcome on sunitinib and to MSKCC score







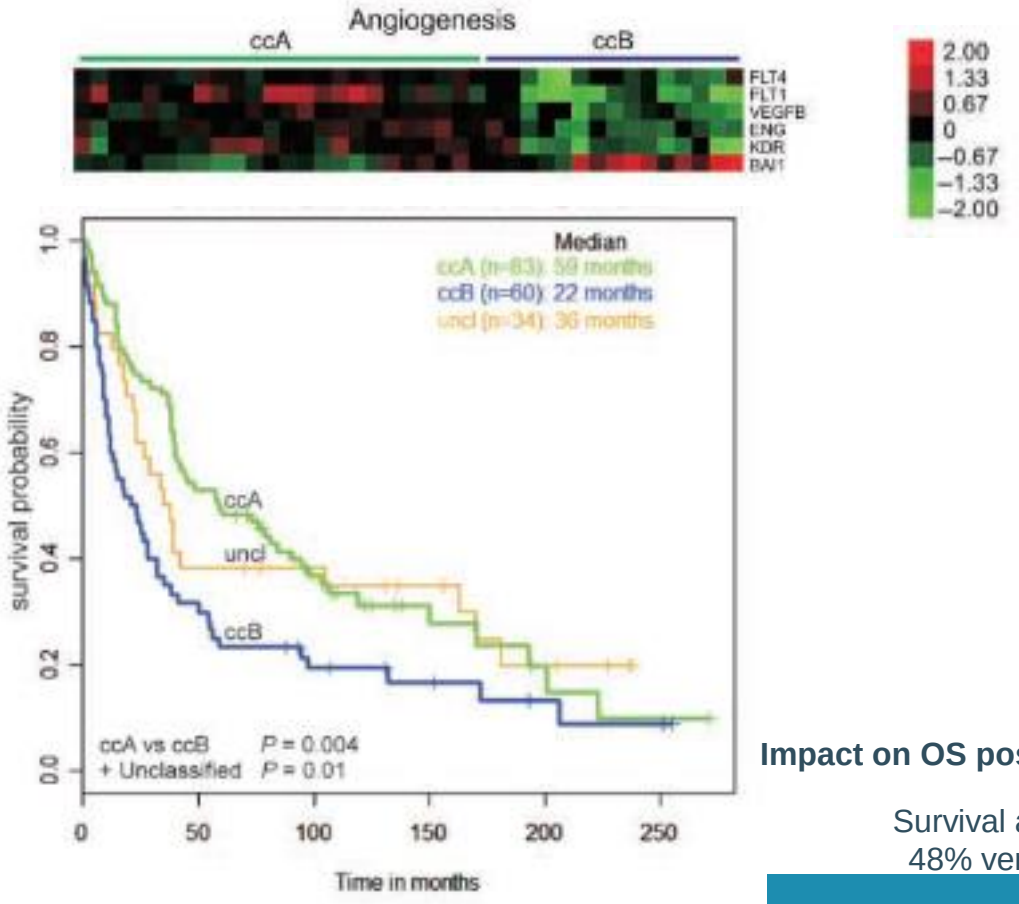
MSKCC favorable risk pts: More angiogenesis



ANGIOGENESIS

ccA AND ccB EXPRESSION PROFILES

Two main clusters with a prognostic impact post-nephrectomy

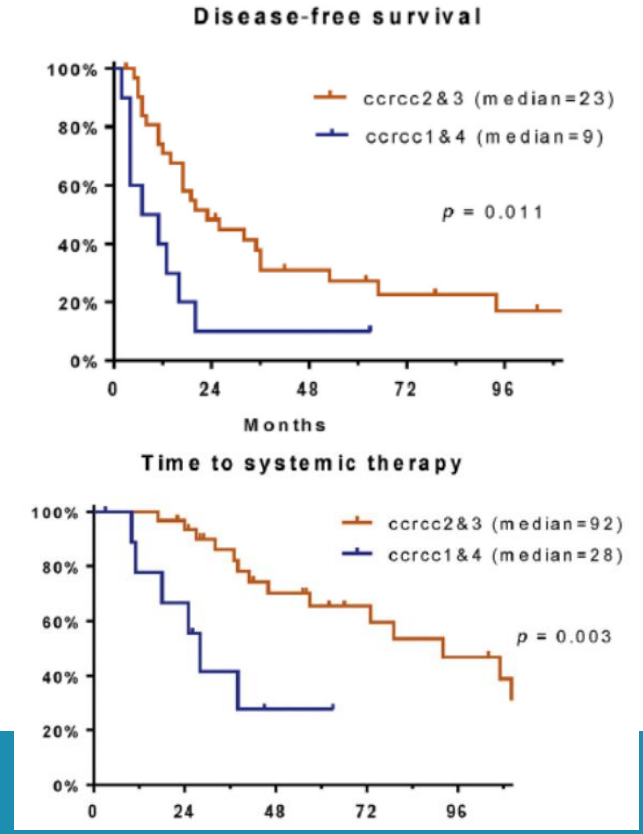


Impact on OS postnephrectomy

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

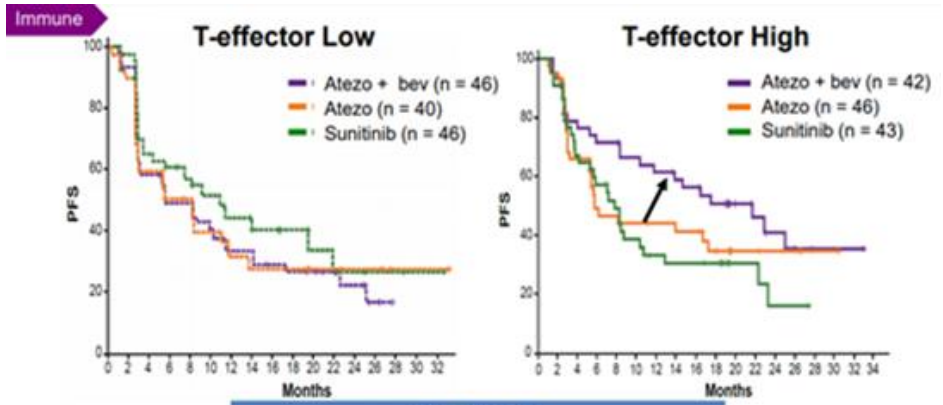


Brannon et al. Genes & Cancer 2010
Brannon et al. European Urology 2012

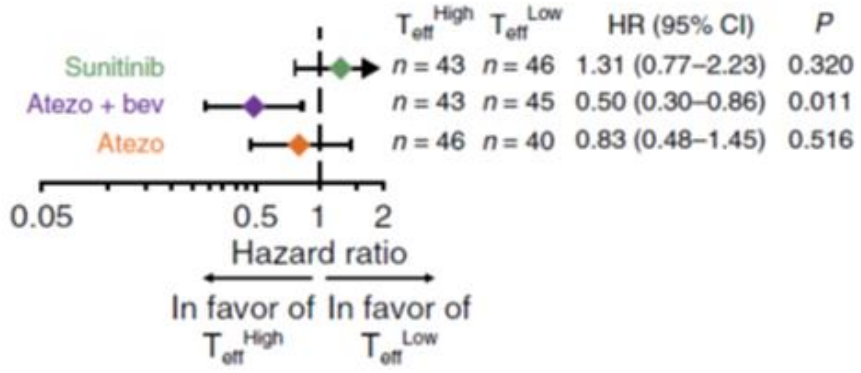
Verbiest A, Beuselinck B et al. Eur Uro 2018

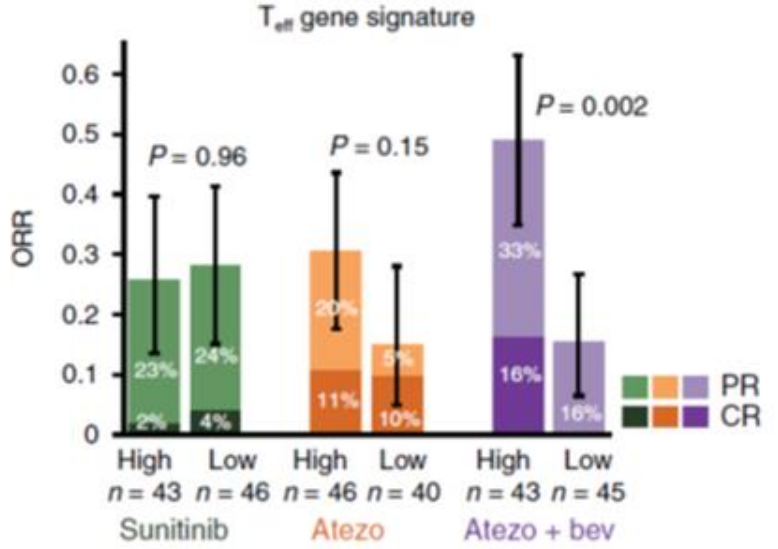
T-EFFECTOR SIGNATURE

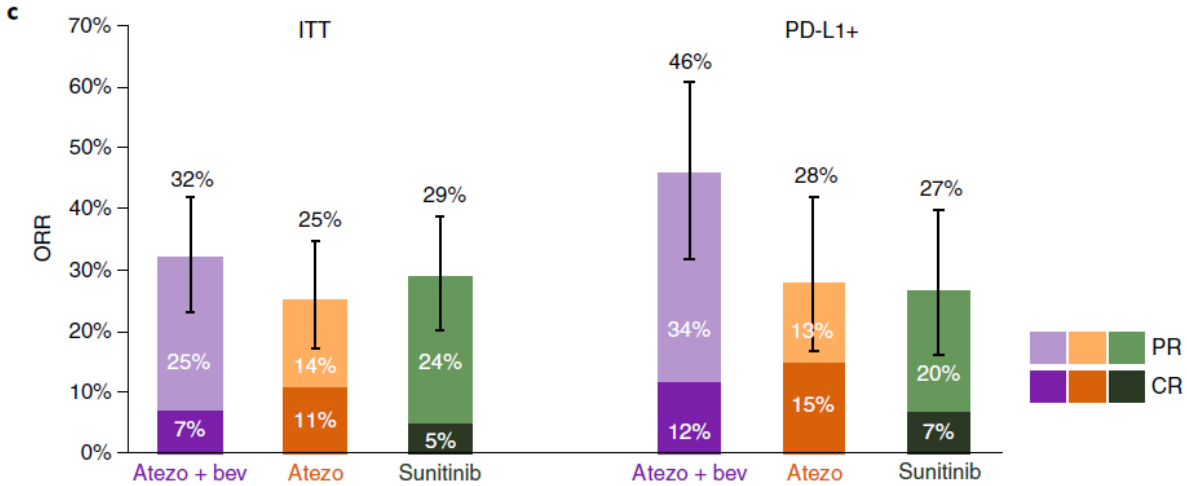
IMMOTION 150/151 (sunitinib vs atezolizumab/bevacizumab): Teff signature correlated to better outcome on atezo/bev



	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)







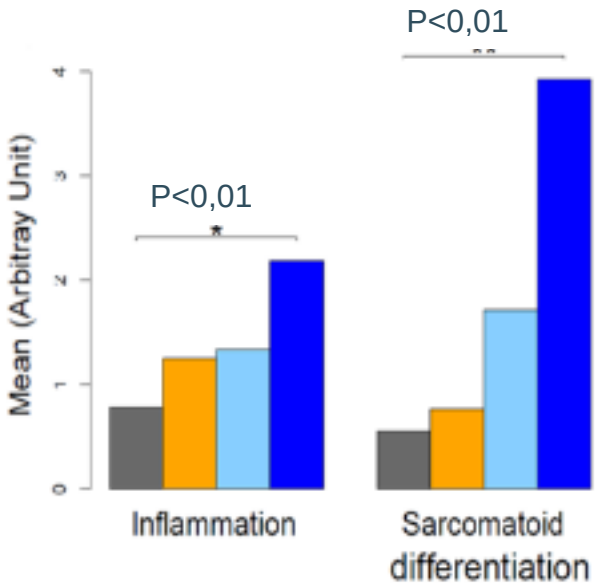
McDermott et al. Nature 2018

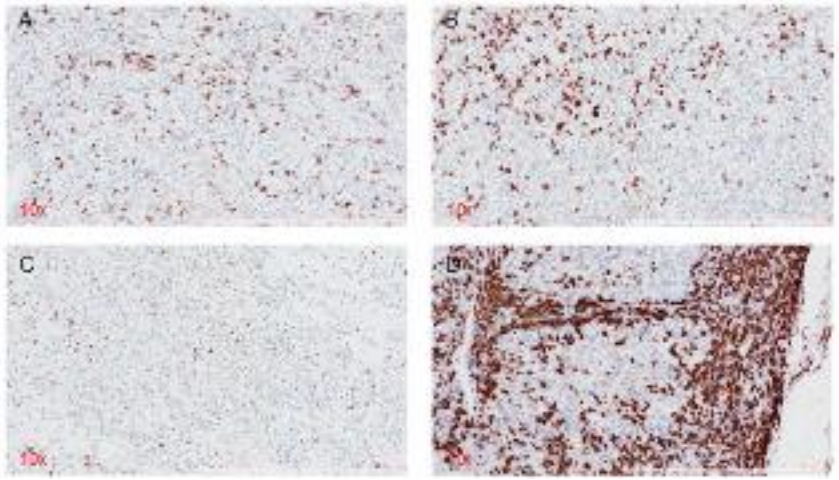
T-EFFECTOR SIGNATURE

Ccrcc-1 to -4 EXPRESSION PROFILES

Subgroup characteristics: Cytokine analysis

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

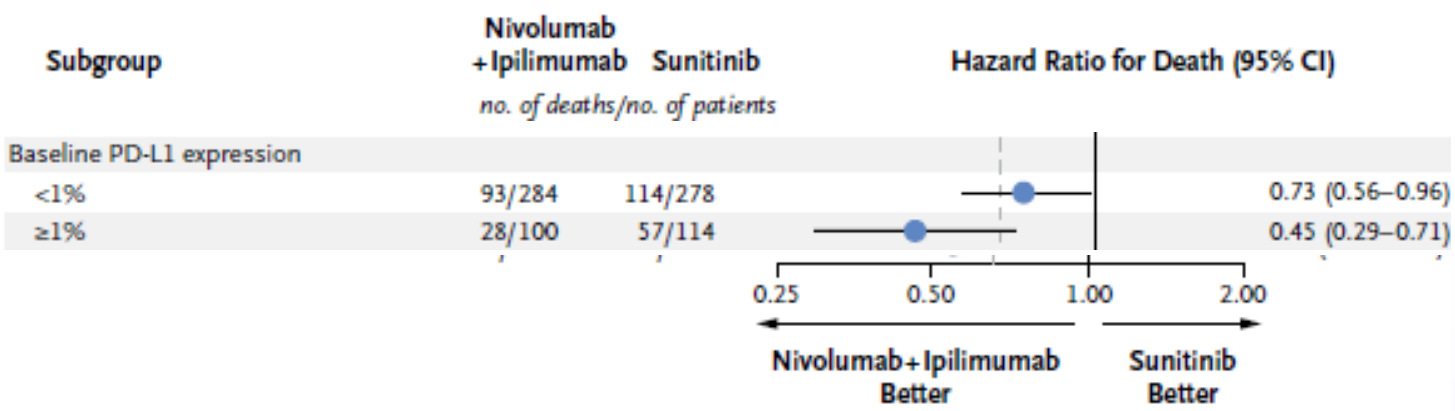


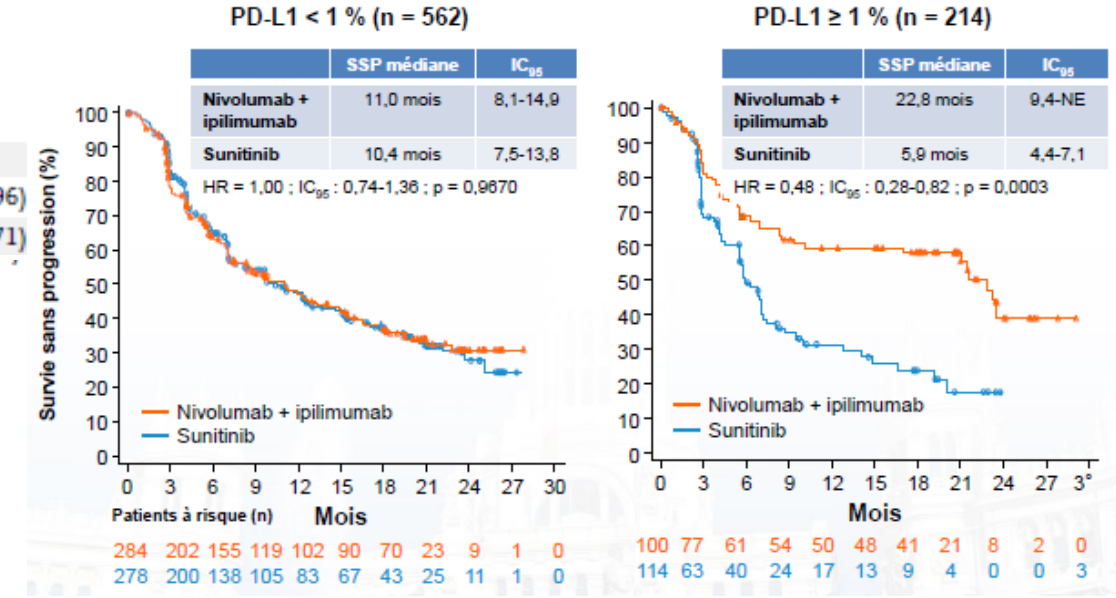


CD8+ cell infiltration in ccrcc1 (A), ccrcc2 (B), ccrcc3 (C) and ccrcc4 (D)

T-EFFECTOR SIGNATURE

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



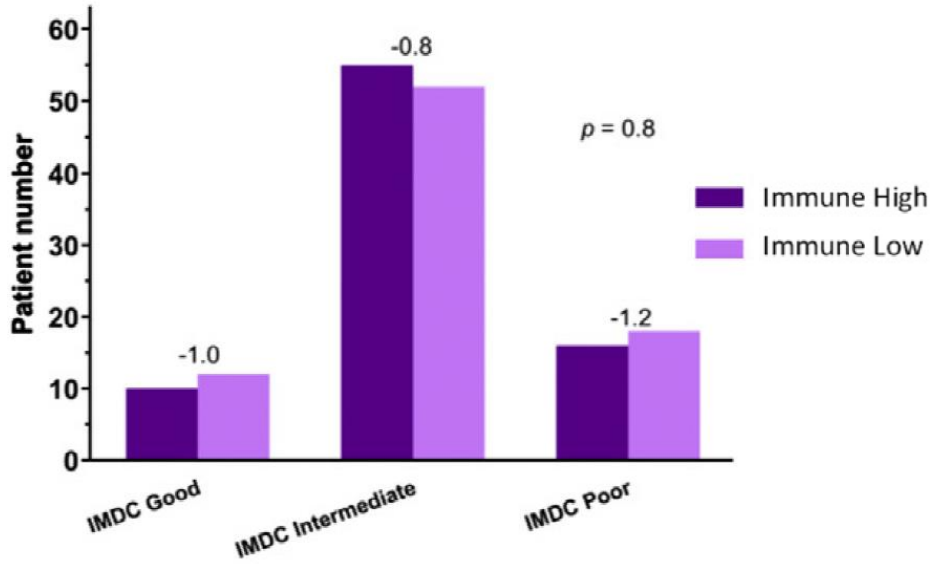


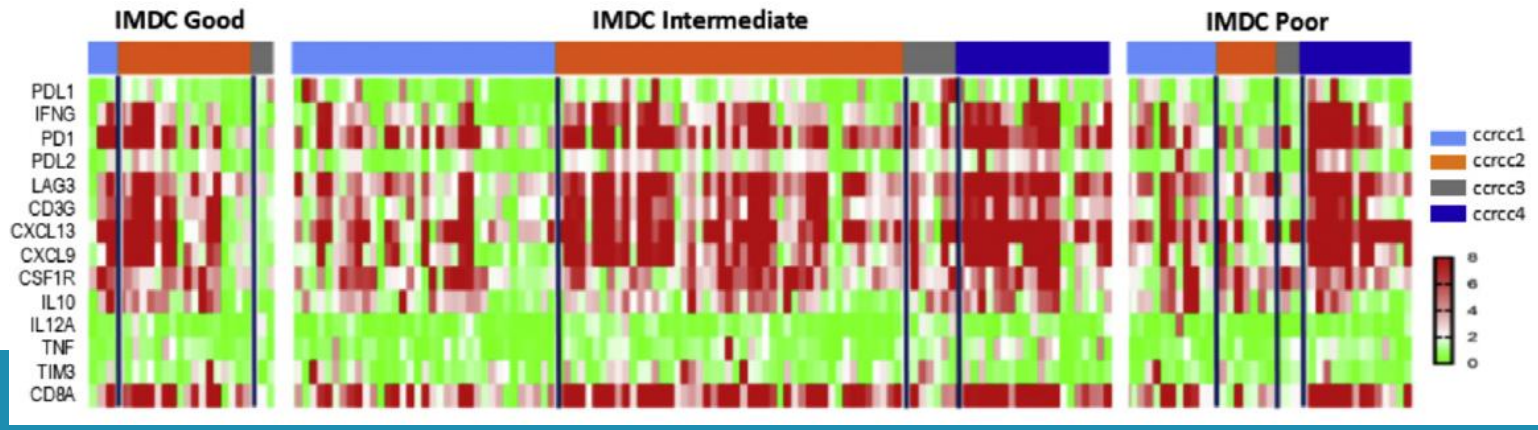
IMDC INTERM/POOR RISK PDL1<1%			IMDC INTERM/POOR RISK PDL≥1%		
IPI/NIVO	SUN		IPI/NIVO	SUN	
37%	28%	P=0,03	58% (CR 16%)	22%	P<0,001
11,0	10,4	P=0,96	22,8	5,9	P=0,0003
NR	NR	HR 0,73 (95%CI 0,56-0,96)	NR	19,6	HR 0,45 (95%CI 0,29-0,71)

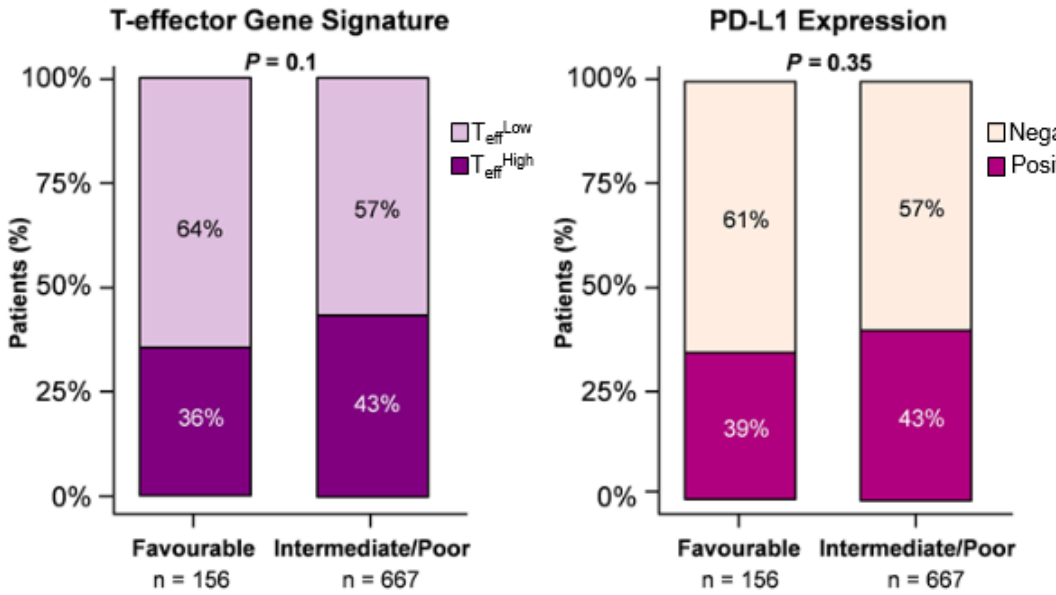
Escudier et al. ESMO 2017

T-EFFECTOR SIGNATURE

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





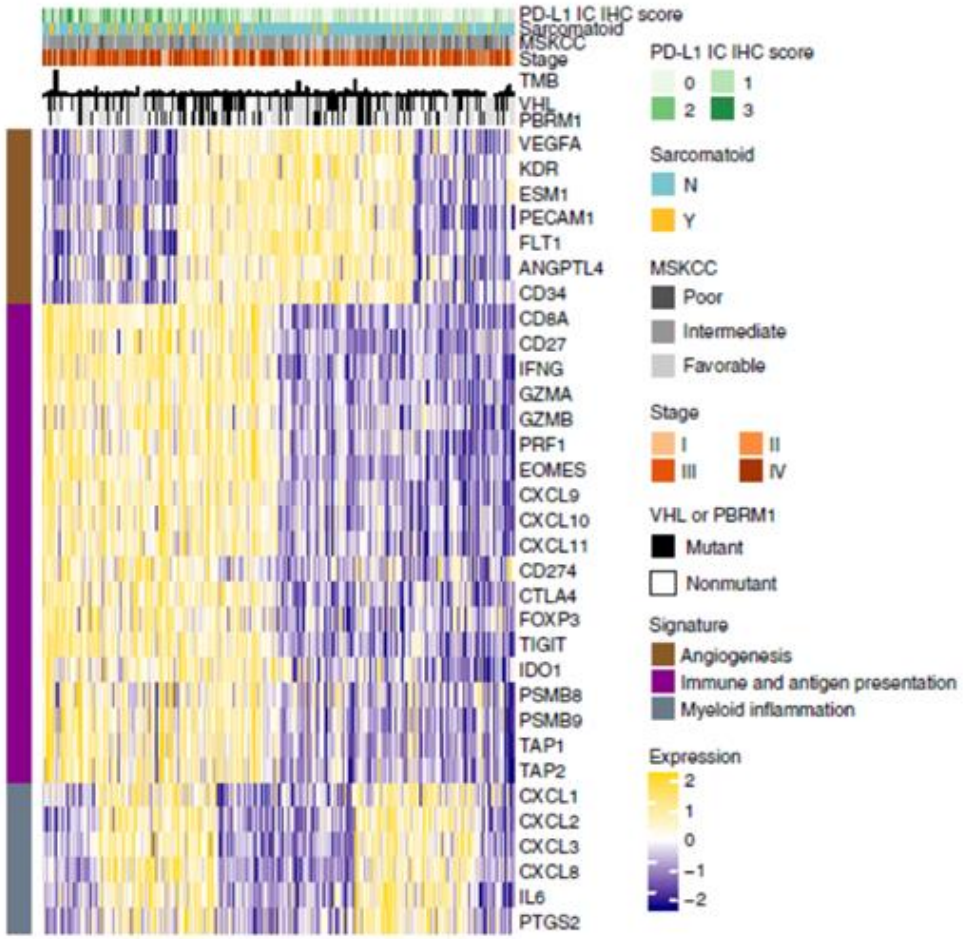


Verbiest A, Renders I, Beuselinck B et al. Clin Genitourinary Cancer 2019

Rini et al. ESMO2018

T-EFFECTOR SIGNATURE

THERE IS OVERLAP … NOT ANGIO HIGH OR IMMUNE HIGH …

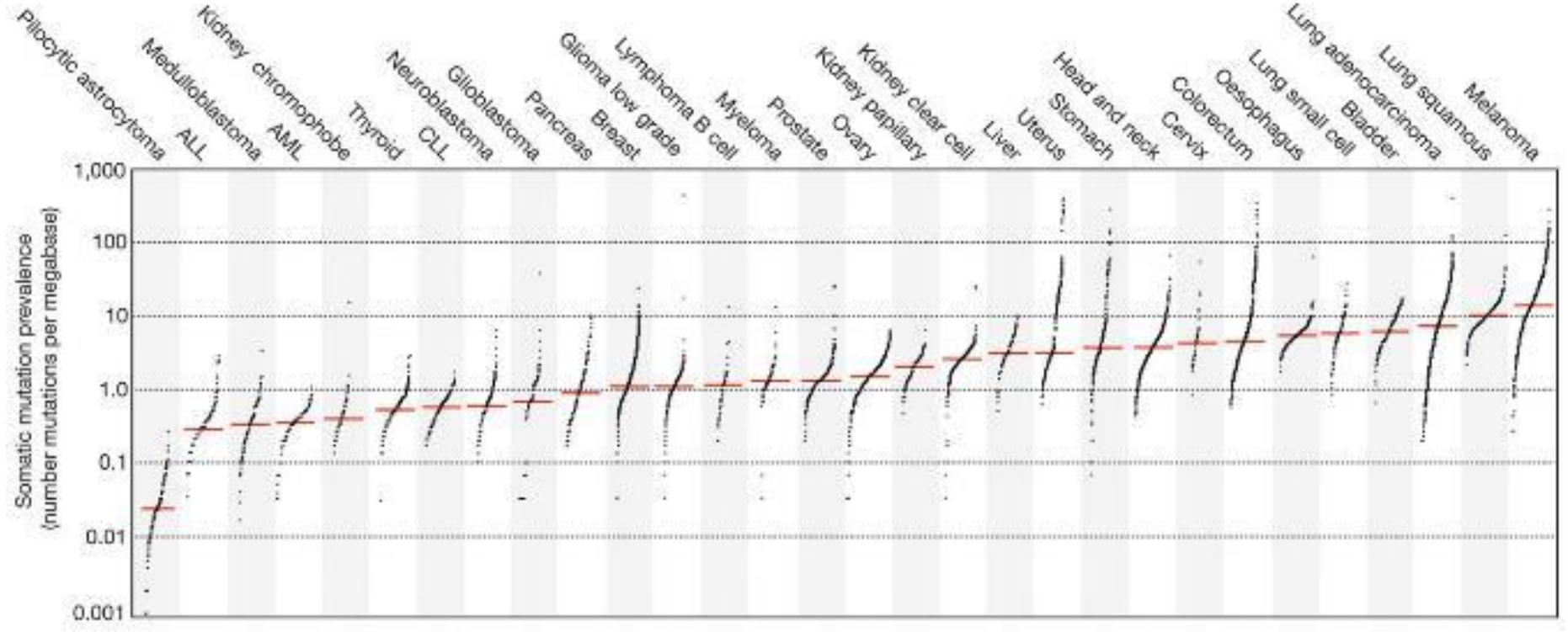


McDermott et al. Nature 2018

Beuselinck et al. Clin Cancer Res. 2015.

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

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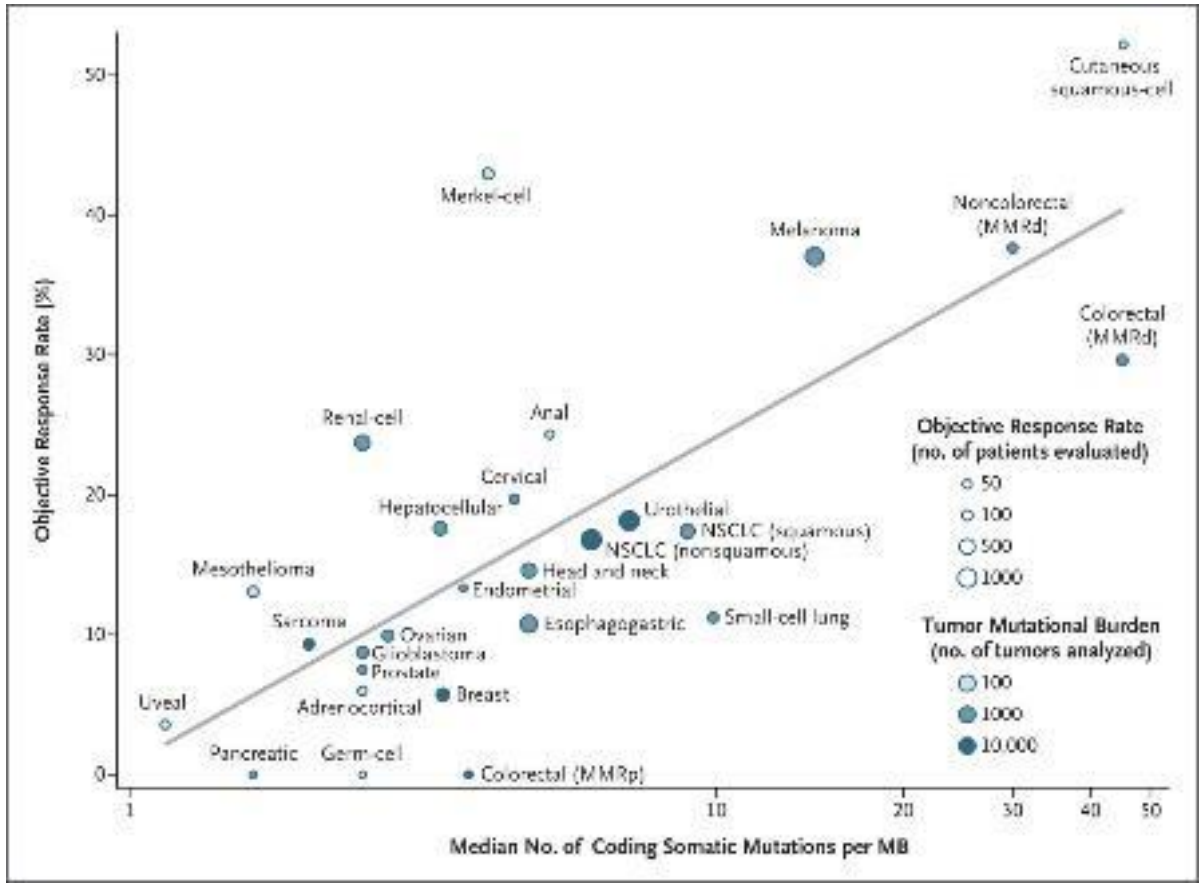
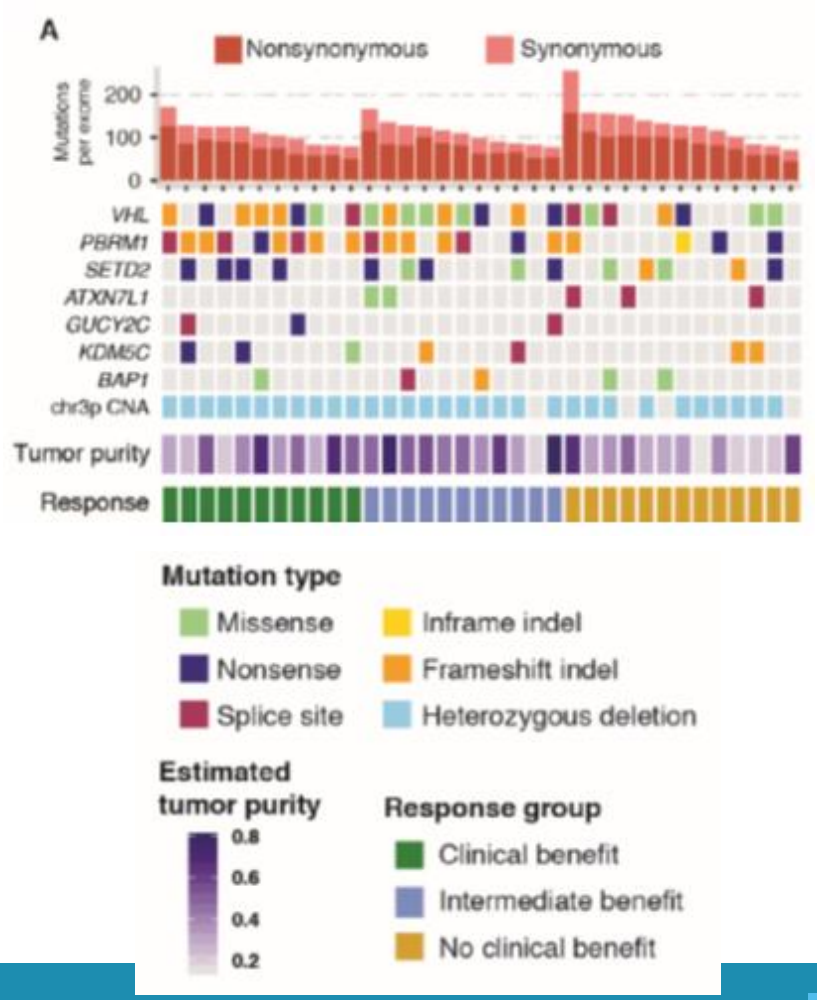
MUTATIONAL BURDEN

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

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Non-clear-cell renal cell carcinoma

- Papillary RCC (type 1 and 2)
- Chromophobe RCC
- Bellini Duct carcinoma
- Not otherwise classified

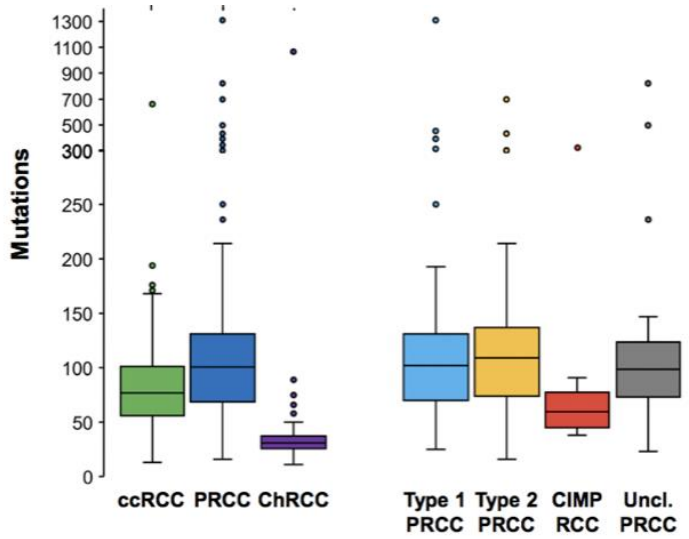
NON-CCRCC: BASIC PRINCIPLES

1. VEGFR-TKIs: poor performance
2. mTOR-inhibitors: poor performance, everolimus not reimbursed
3. ICPIs (+/- VEGFR-TKI): emerging evidence of activity, reimbursed!
4. cMET: interesting target, but only one available cMET inhibitor: cabozantinib

FIRST CHOICE		**SECOND LINE**
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	Sunitinib or pazopanib	Cabozantinib
IMDC I/P	Cabozantinib	

NON-CCRCC: IMMUNE CHECKPOINT INHIBITORS

The mutation rate in RCC tumors is generally low

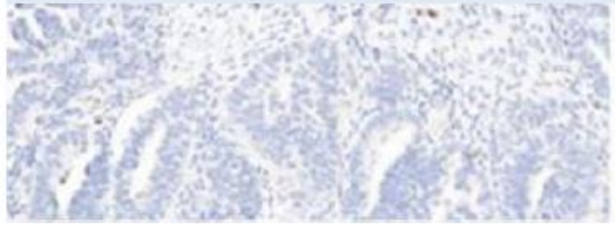


Retrospective study of PD-L1 positivity in non-ccRCC (n=101)

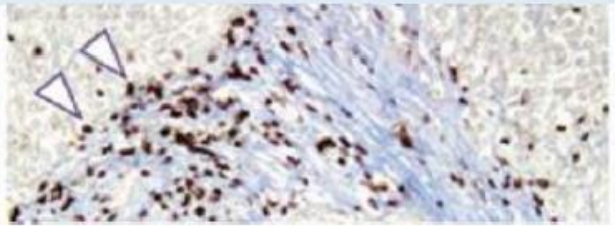
- Overall: 10.9%
- Translocation Xp11: 30%
- Collecting duct carcinoma (CDC): 20%
- Papillary: 10%
- Chromophobe: 5.6%

- PDL1+ has been associated with worse outcomes in nccRCC

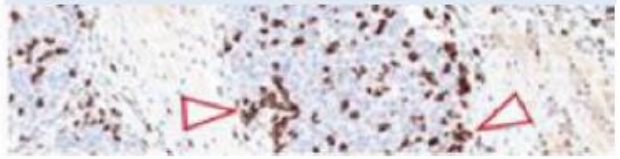
Chromophobe
Low number of immune infiltrates



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

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NON-CCRCC: IMMUNE CHECKPOINT INHIBITORS

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%

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

ASCO® GU 2019. McDermott DF et al.

NON-CCRCC: IMMUNE CHECKPOINT INHIBITORS

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%

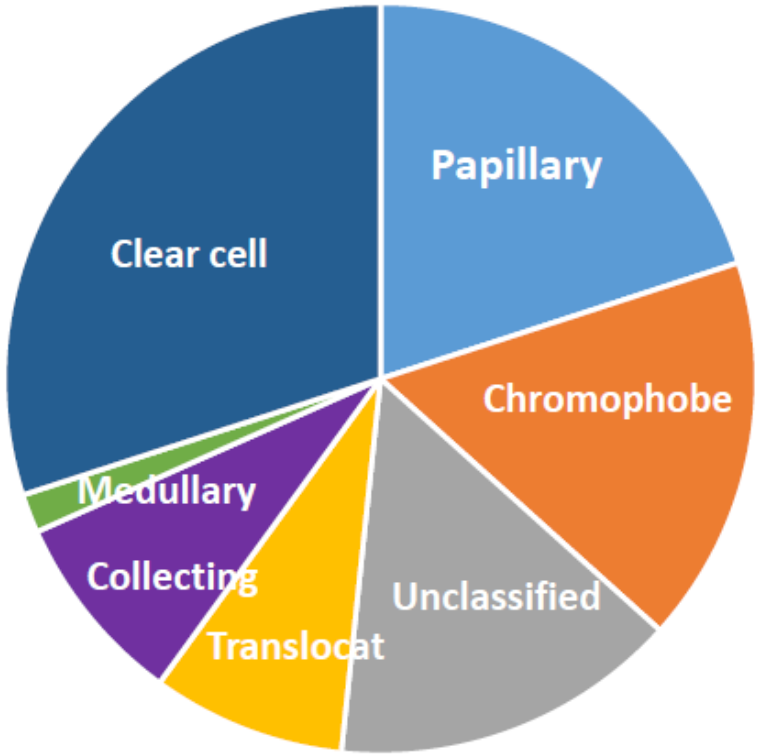
	n	ORR	TTF (m)	OS (m)
Overall cohort	60	PR 14% SD 33% PD 53%	3.2	15
Papillary type 1	17			
Papillary type 2	36			
Papillary unclassified	7			

NON-CCRCC: IMMUNE CHECKPOINT INHIBITORS

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: IMMUNE CHECKPOINT INHIBITORS

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: IMMUNE CHECKPOINT INHIBITORS

Complete response to nivolumab/ipilimumab for metastatic collecting duct carcinoma of the kidney.

- CDC patient with multiple lymph node metastases who underwent cytoreductive open nephrectomy and subsequently, received nivolumab/ipilimumab.
- Following four courses, all nodal metastases had shrunk to < 1 cm in diameter, and thus this patient was judged to show a CR.

Nivolumab therapy for metastatic collecting duct carcinoma after nephrectomy: A case report.

- After nephrectomy for CDC , multiple lung metastases were found in the following month
- First-line chemotherapy of gemcitabine/cisplatin was administered.
- At PD: targeted therapy with axitinib (10mg/body)
- At PD: second-line chemotherapy of paclitaxel and carboplatin were subsequently administered.
- However, the lung metastases progressed and new metastases spread to the right adrenal gland, liver, and lymph nodes.
- High expression of PDL1 in tumor cells => start nivolumab.
- After 2 courses of treatment: PR and improved performance status.
- To date, the patient is on his fifth course of treatment as an outpatient without disease progression.

Response to nivolumab in metastatic collecting duct carcinoma expressing PDL1: A case report.

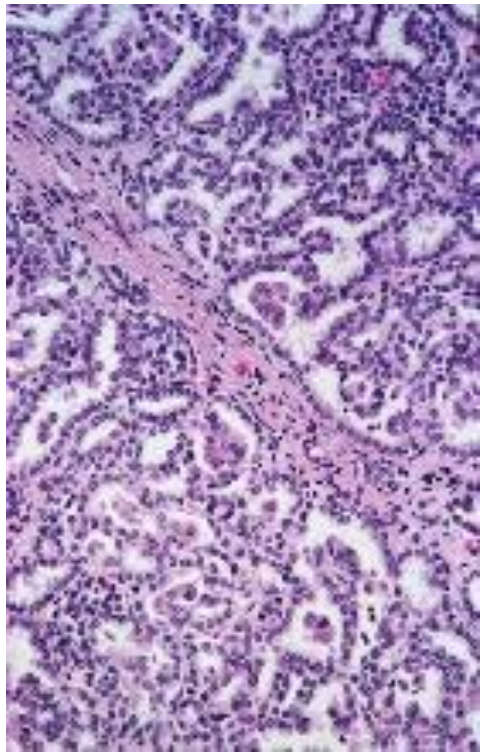
- The patient underwent right radical nephrectomy and segmentectomy of the lung following chemotherapy.
- Fifteen months following the first surgery, segmentectomy and subsequent second-line chemotherapy were performed for recurrence in the lung.
- Temsirolimus for recurrence of the lung and lymph node metastases was ultimately used for 30 months. However, the temsirolimus treatment failed to suppress the growth of metastatic lesions.
- Nivolumab resulted in CR of the lung metastasis, and it stabilized the lymph node metastasis.
- PD-L1 was highly expressed in both primary tumor and the metastatic regions.
- Therapy with nivolumab is ongoing.

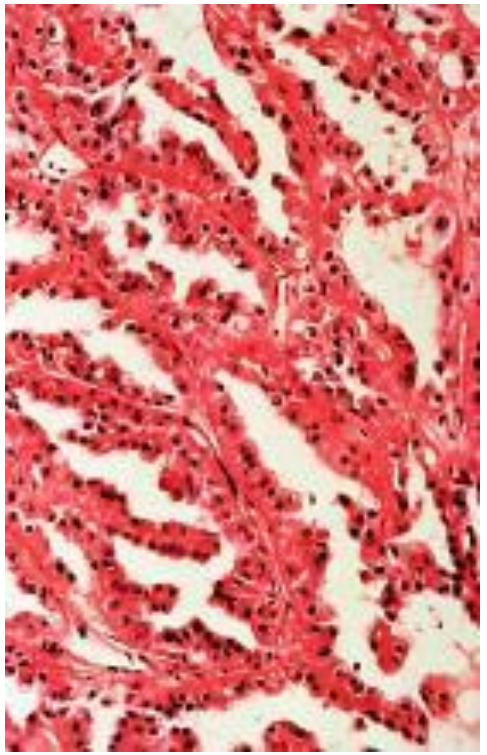
(1) Watanabe K et al. Int Cancer Conf J 2019.
(2) Yasuoka S et al. Medicine (Baltimore) 2018.
(3) Mizutani K et al. Mol Clin Oncol 2017.

cMET IN PAPILLARY RCCs

Papillary RCC (15% of all RCCs): display a papillary growth pattern

- 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%

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

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

cMET IN PAPILLARY RCCs

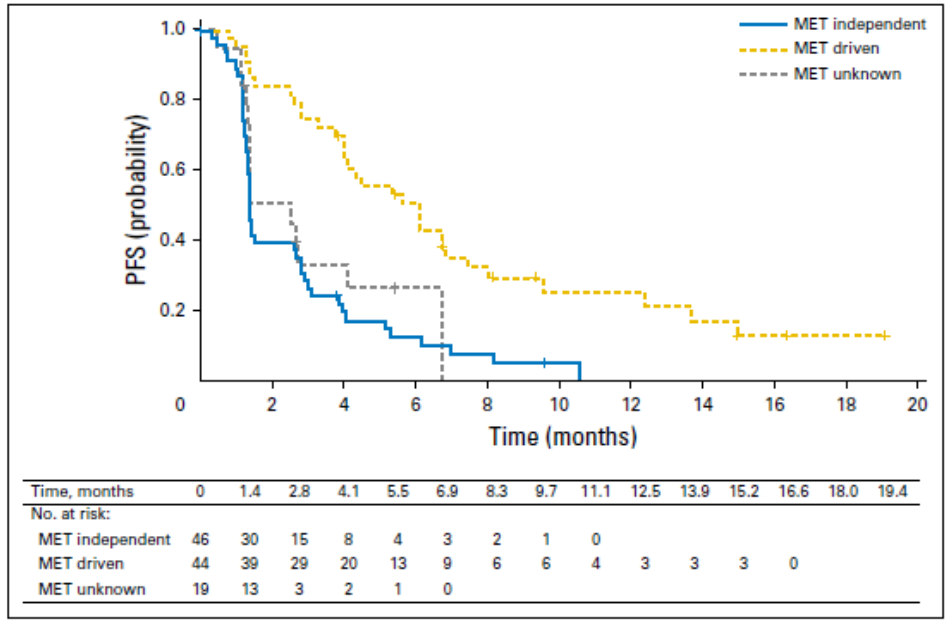
Phase II Trial of Savolitinib in 109 papRCC pts

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

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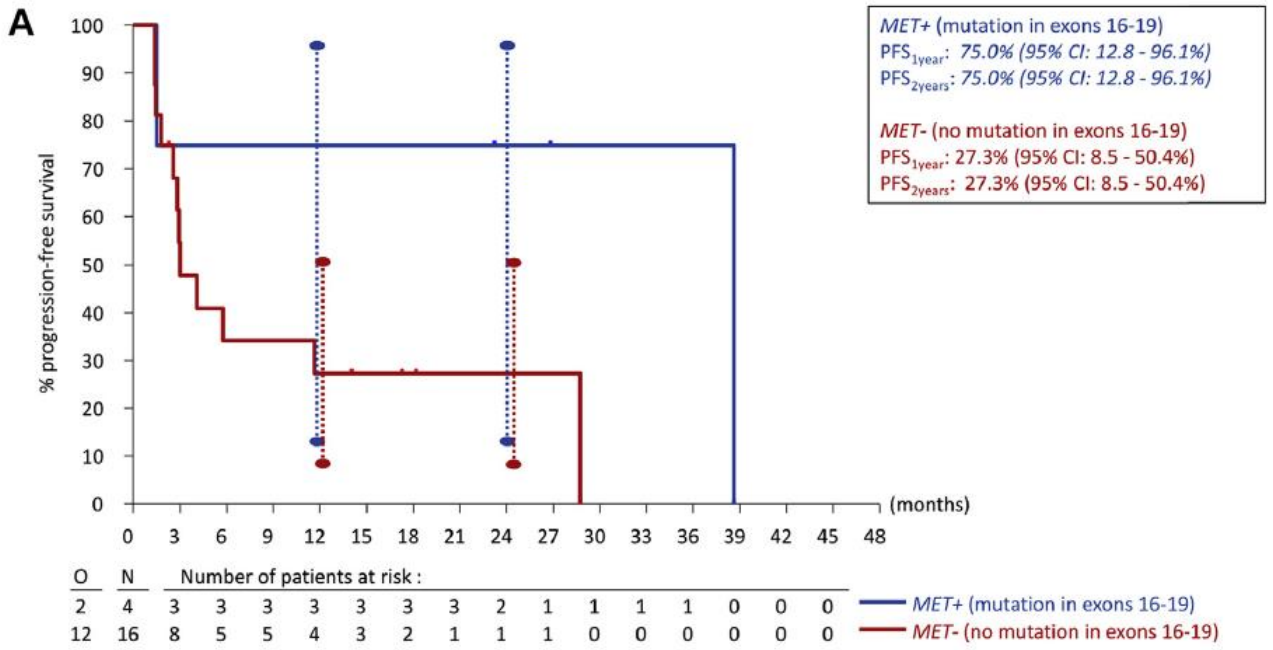
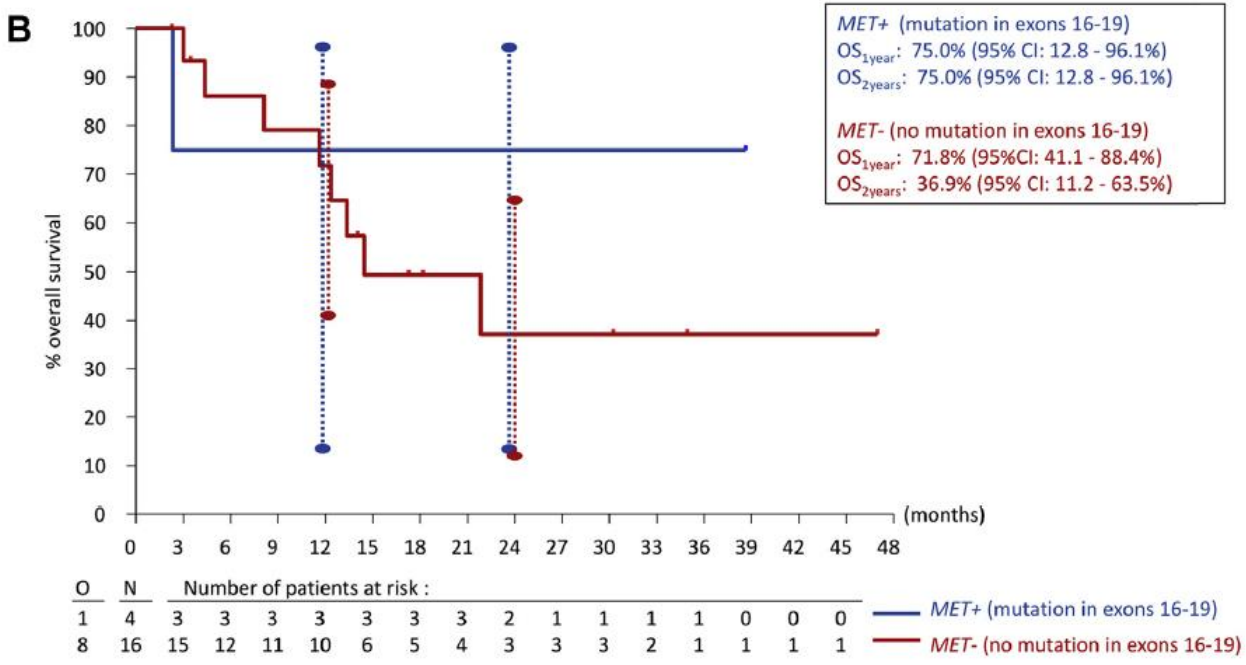
cMET IN PAPILLARY RCCs

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

cMET IN 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.

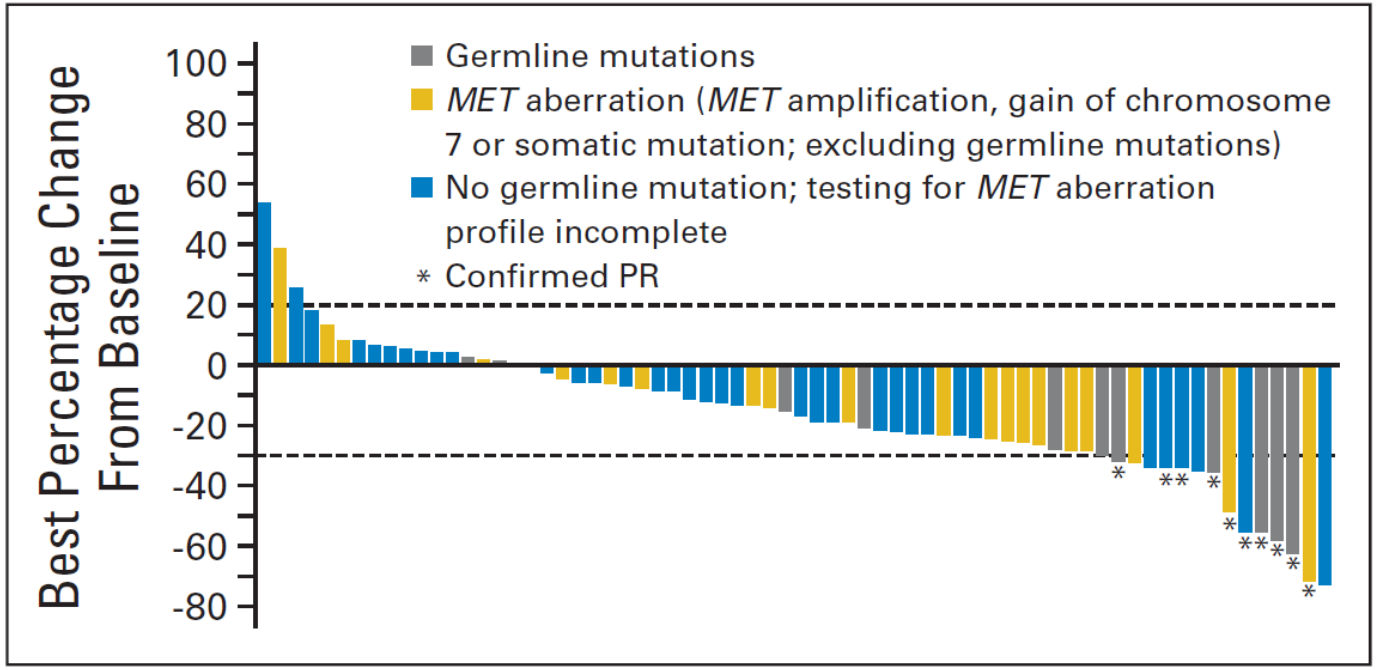
- Cohort A, 240 mg once per day on days 1 through 5 every 14 days (intermittent arm);
- Cohort B, 80 mg daily (daily dosing arm).

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.

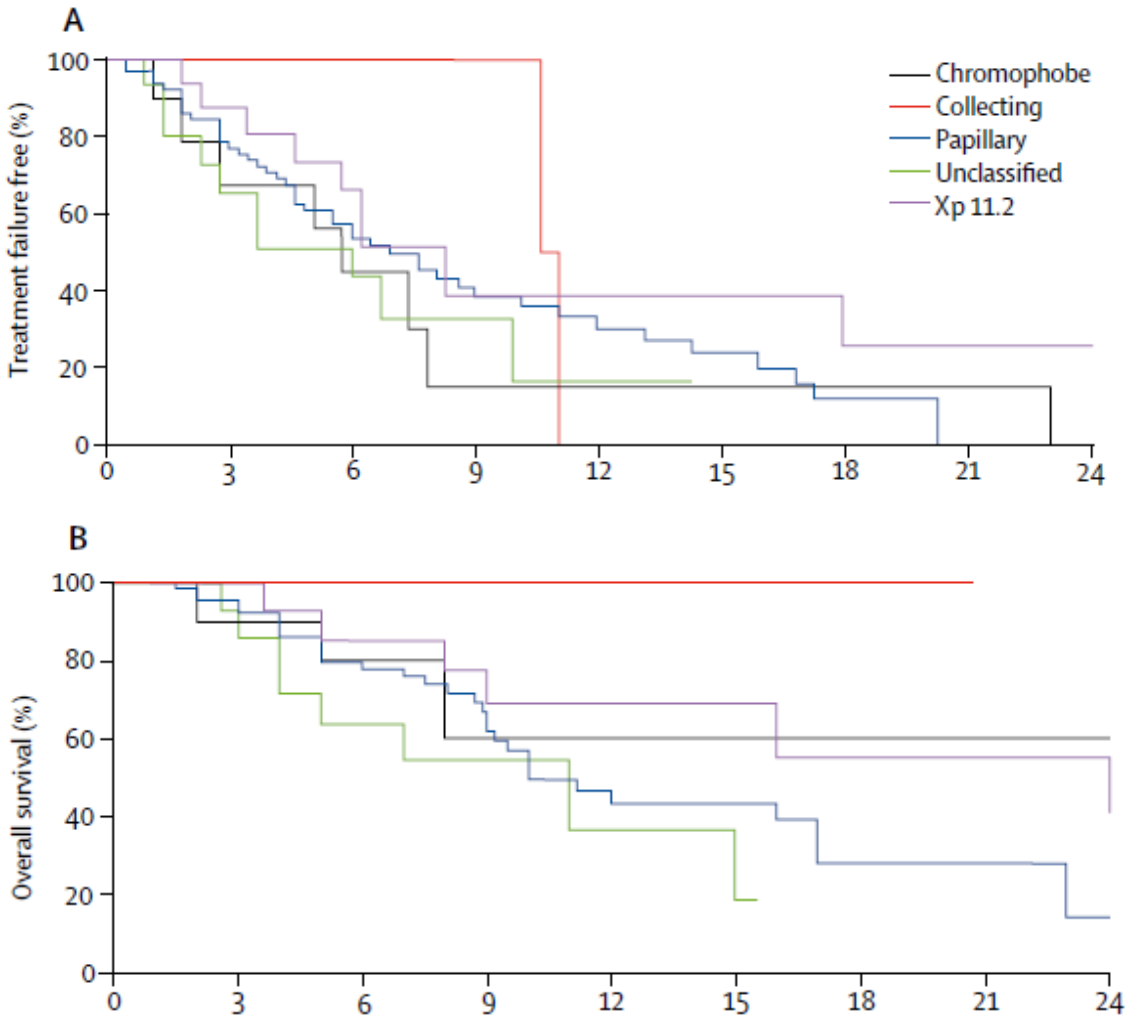
- ORR: 13.5%
- If germline MET mutation: 5/10 responses (50%)
- If no germline MET mutation: 5/57 responses (9%)
- mPFS 9.3 months
- mOS not reached.



Choueri et al. JCO 2013

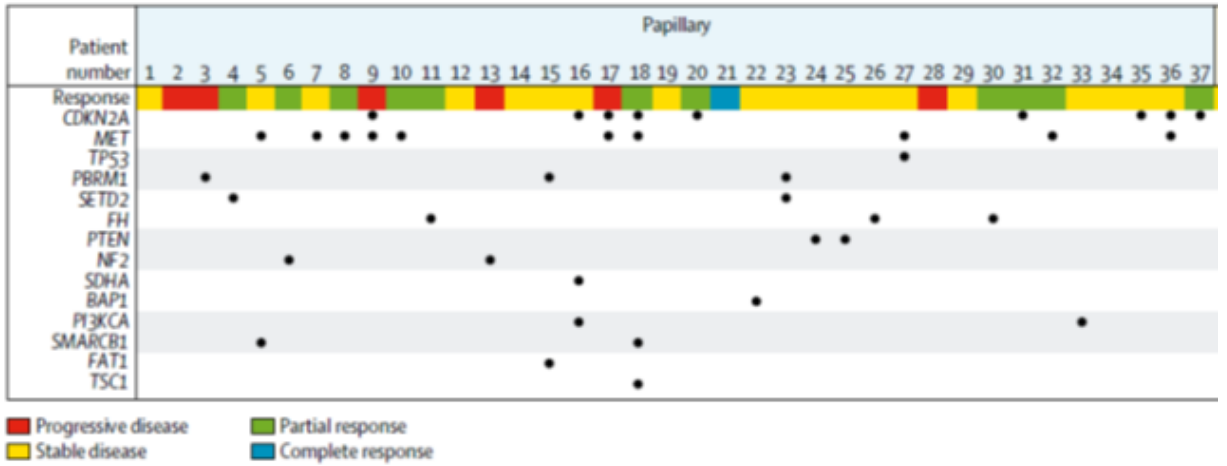
cMET IN PAPILLARY RCCs

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%)



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

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cMET IN PAPILLARY RCCs

Cabozantinib casus UZLeuven

Oncologische voorgeschiedenis:

- 01-2016: Tumor linkernieronderpool op echografie. Groot para-aortisch klierpakket en osteolytische botmetastasen L2+L3+Th11.
- 04-2016: Cytoreductieve nefrectomie links met klierevidement. APO: papillair RCC met 80% sarcomatoide dedifferentiatie
- 05-2016: Start Xgeva
- 06-2016: Stereotactische bestraling 3x9 Gy op 3 botmetastasen (T11+L3+L2)
- 07-2016: Preventieve nageling van botmetastase in proximale femurdiafyse rechts.
- 07-2016: CT thorax-abdomen: bijniermetastase rechts alsook vermoeden levermetastase. Gekende multifocale botmetastasen.
- 08-2016: Radiotherapie op rechter femur na nageling (30 gy)
- 09-2016: Start AVELUMAB fase I studie. Langdurige ziektestabilisatie.
- 09-2017: Hemorrhagie rechter bijnier, onderliggend mogelijks progressie, echter niet evalueerbaar
- 10-2017: Bilan: stabiele ziekte, bijnier niet evalueerbaar gezien bloeding
- 11-2017: Belangrijke progressie van de bijniermetastase, rest stabiel. Stop AVELUMAB
- 12-2017: Surrenalectomie rechts: APO: papillair renaal cell carcinoom
- 01-2018: Bilan 2 maand na stoppen Avelumab: Stabiele botmetastasering.
- 08-2018: progressieve ziekte: start PAZOPANIB. Stop Xgeva.
- 08-2018: Dysarthrie na episode van hypertensie en hoofdpijn en braken. Nierinsuffiscientie. Stop PAZOPANIB.
- 08-2018: Start CABOZANTINIB 40 mg/d
- 09-2018: Tijdelijke onderbreking en dan dosisreductie naar 20 mg/d wegens diarree
- 01-2019: Bilan na 5 maanden cabozantinib: Partiële respons (RECIST -35%). Herstart Xgeva
- 04-2019: Bilan na 8 maanden cabozantinib: Partiële respons (RECIST -62%). Start Elthyroxine
- 03-2020: Bilan na 19 maanden cabozantinib: Partiële respons (RECIST -70%).

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INTERACTIONS BETWEEN THERAPIES

COMBINATION OF VEGFR-TKIs AND BONE RESORPTION INHIBITORS

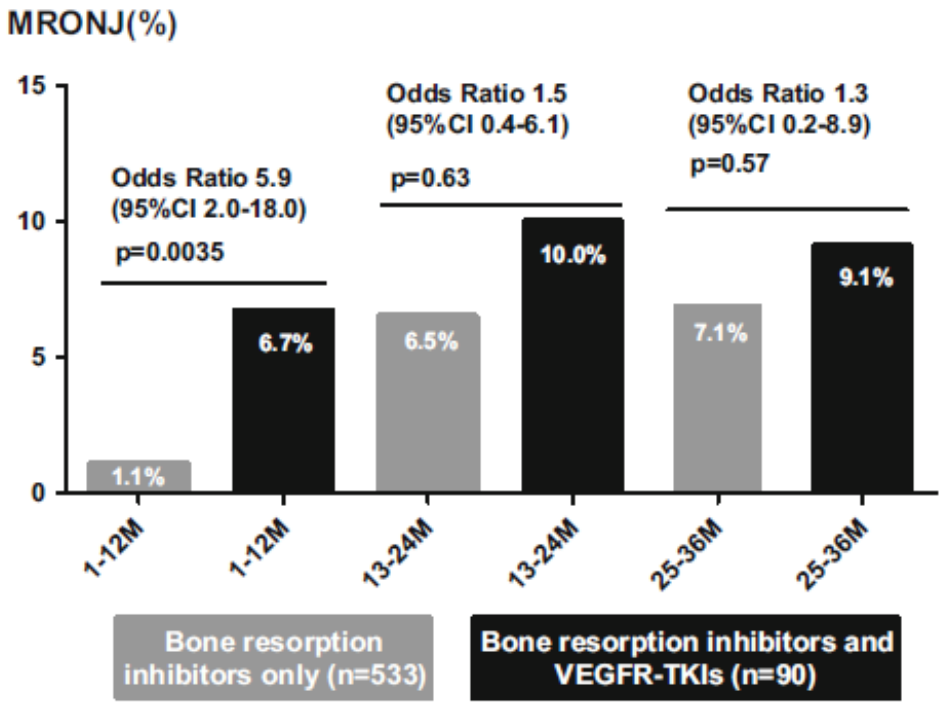
Several warnings were published, but no precise data with control series.

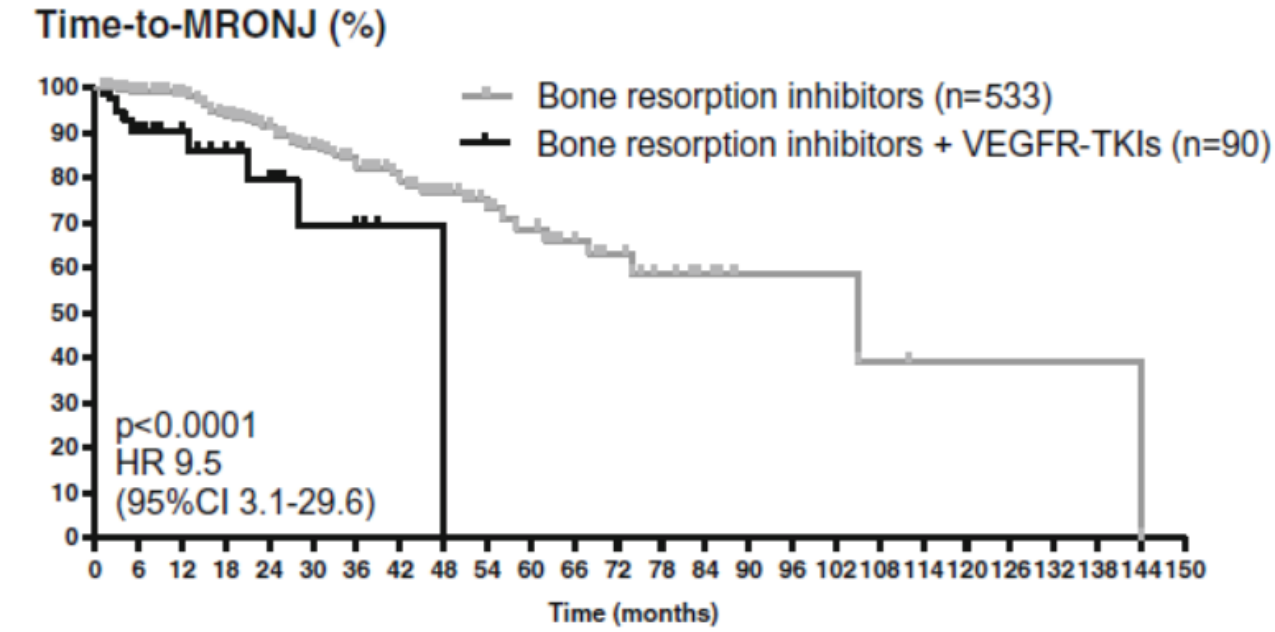
Through the induction of mucositis?

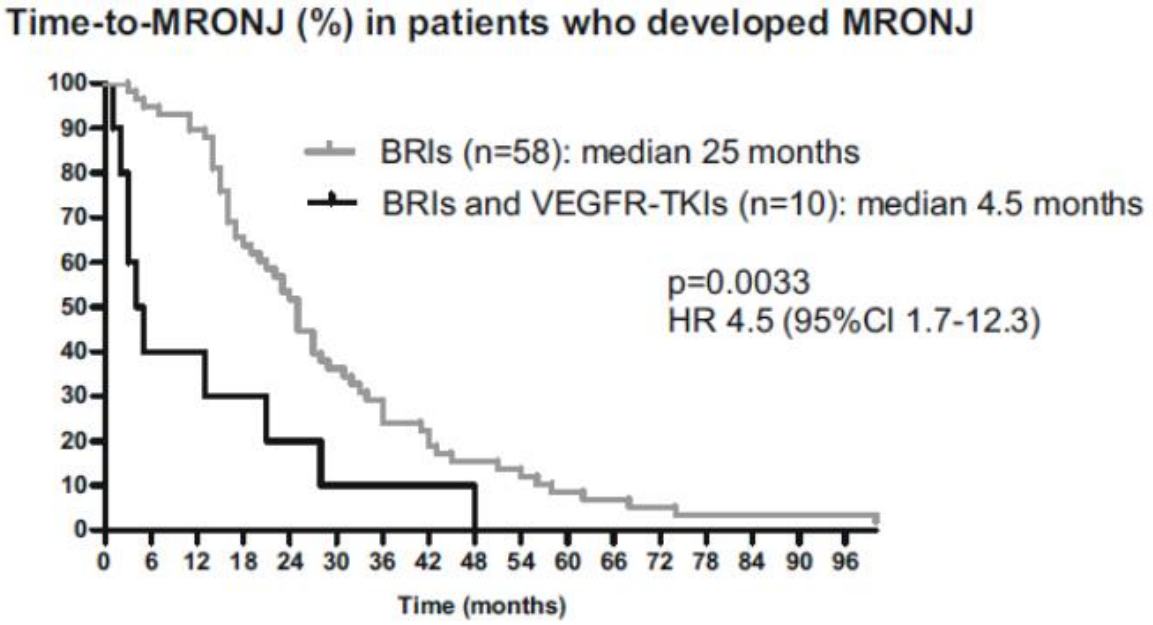
		CONTROL ARM	STUDY GROUP	p-value / OR (95%CI)
		BRI without concomitant VEGFR-TKIs (n=533)	Concomitant BRIs and VEGFR-TKI (N=90)	
TOTAL SERIES	ONJ-incidence	10.9% (58/533)	11.1% (10/90)	1.0
	Median BRI-exposure	19.0 months	5.0 months	-
	Median concomitant exposure	-	4.0 months	-
First year of exposure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

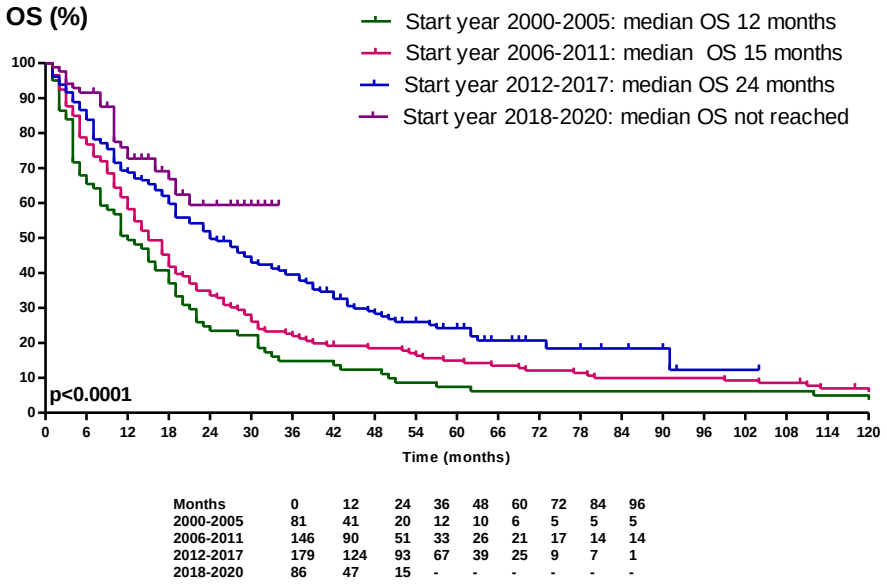
Higuchi et al. Oral Medecine 2018.

KU LEUVEN

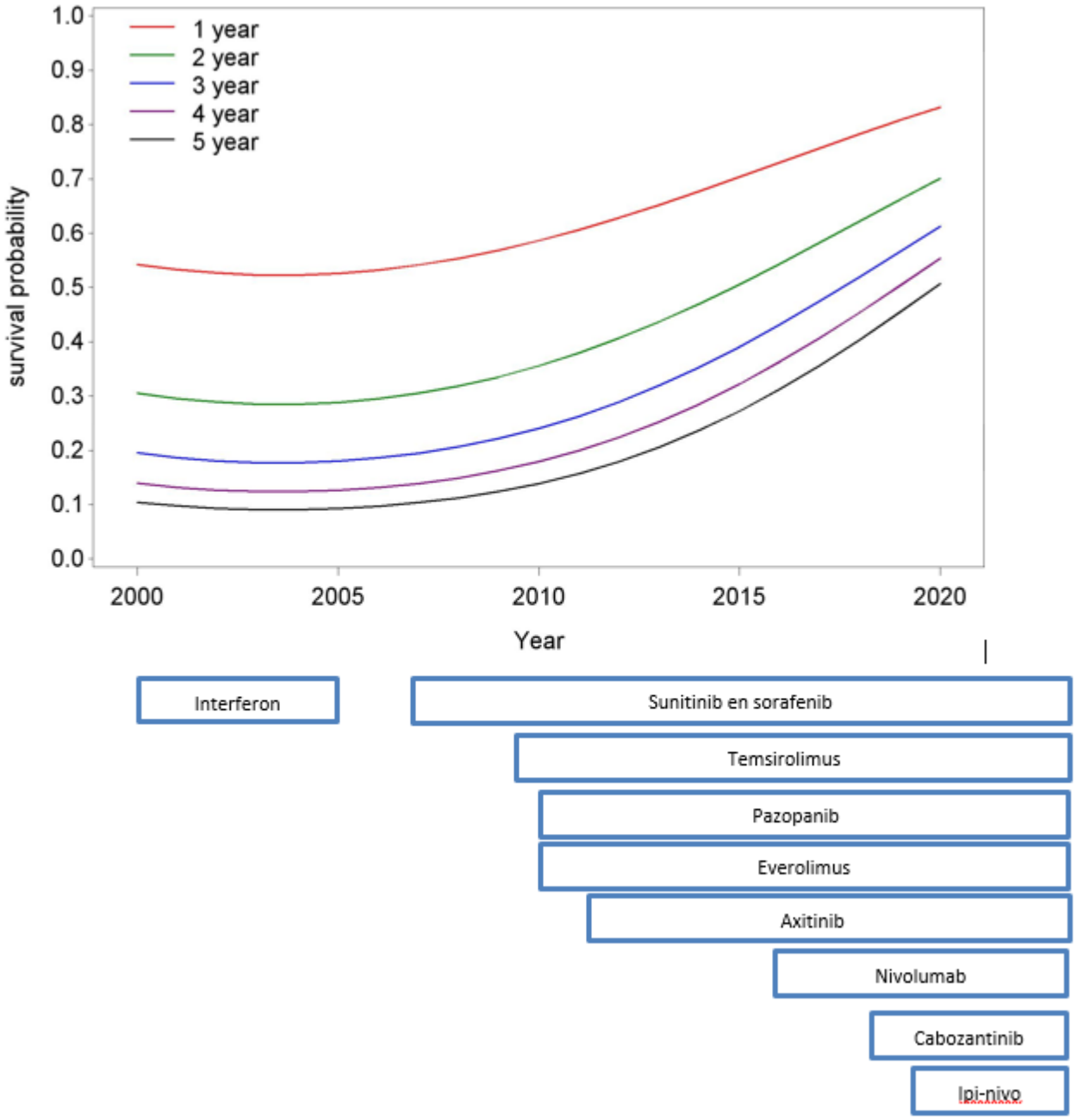
IMPROVED OS 2000-2020

500 m-ccRCC pts
Treated with systemic therapies in

- UZ Leuven
- AZ Imelda-Bonheiden
- AZ Groeninge-Kortrijk



Months	0	12	24	36	48	60	72	84	96
2000-2005	81	41	20	12	10	6	5	5	5
2006-2011	146	90	51	33	26	21	17	14	14
2012-2017	179	124	93	67	39	25	9	7	1
2018-2020	86	47	15	-	-	-	-	-	-



Demasure S, Beuselinck B et al. Manuscript in preparation.

FUTURE THERAPIES

UPCOMING COMBINATIONS

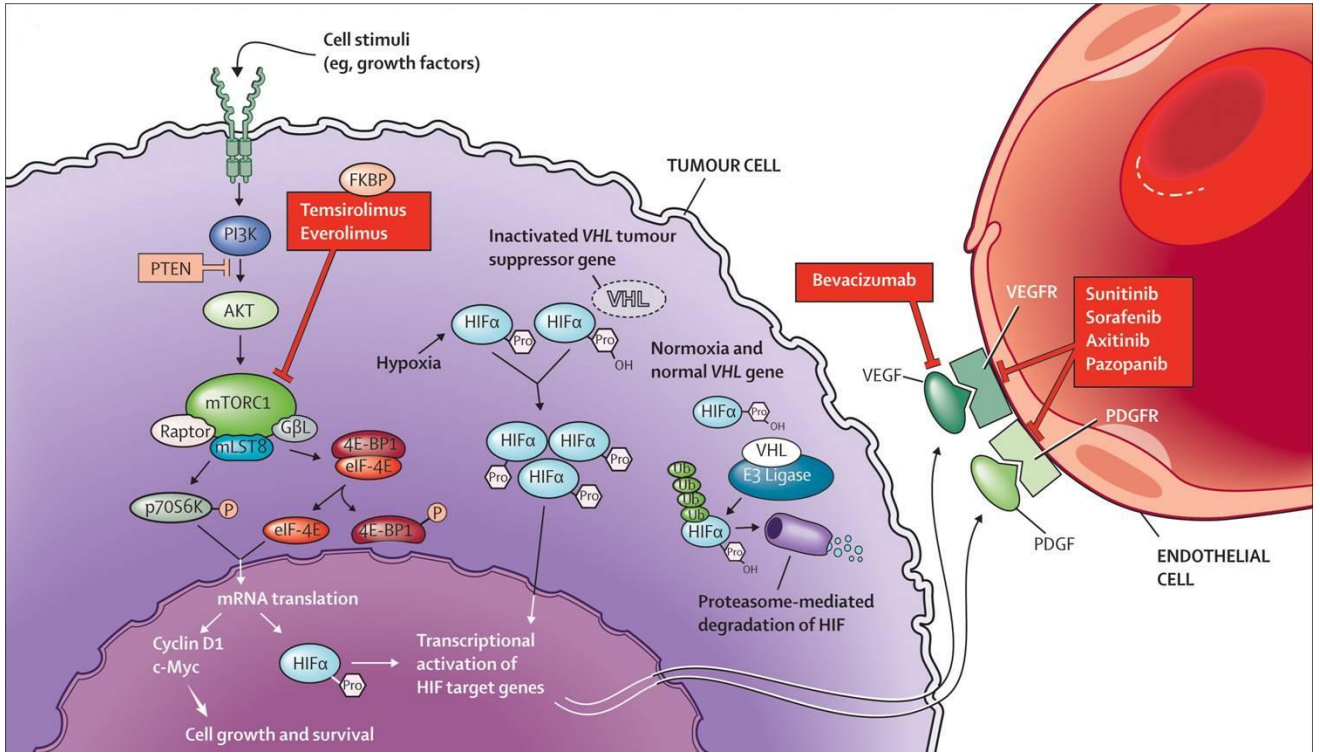
- Cabozantinib+nivolumab
- Cabozantinib+nivolumab+ipilimumab
- Lenvatinib+pembrolizumab

IMPROVED “ANGIOGENESIS INHIBITOR”

- Oral HIF2a inhibitor belzutifan
- Potent
- Less adverse events compared to VEGFR-TKIs

ADJUVANT IMMUNE CHECKPOINT INHIBITORS

- Studies with adjuvant VEGFR-TKIS failed



DON’T FORGET …

Other therapeutic options in m-RCC

1. RCC is considered radioresistent, however at higher dose, it is sensitive to radiation therapy.
2. Metastasectomy can be performed in selected patients, in order to cure or to delay start of systemic therapy
3. Watchfull waiting can be considered in patients with indolent disease: try to estimate disease velocity
4. Debulking nephrectomy still can be performed, despite CARMENA, in patients in whom the start of systemic therapy can be delayed

I have questions to all your answers!