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SYSTEMIC THERAPY FOR KIDNEY CANCER

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24/04/2021

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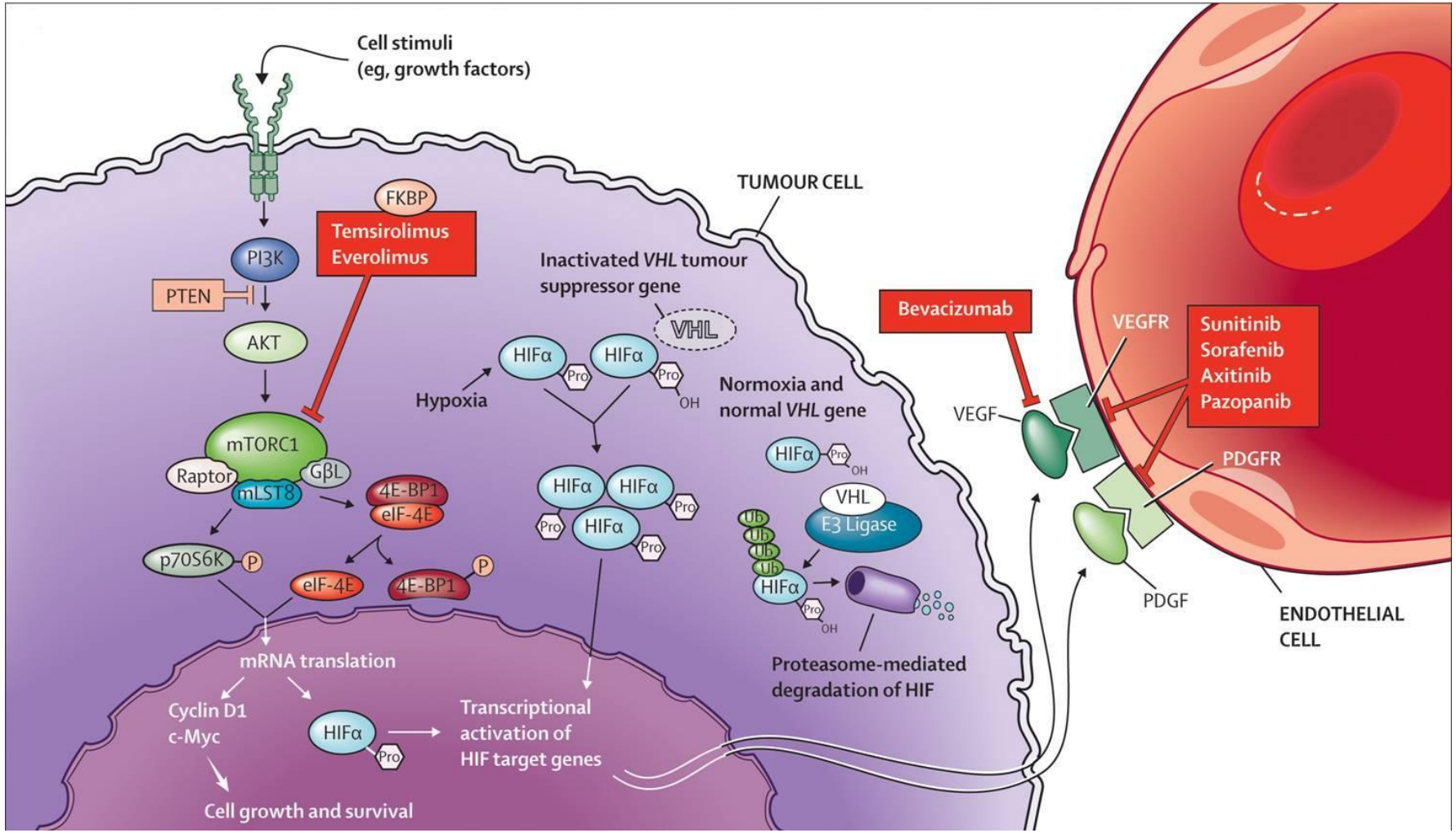
Clear-cell renal cell carcinoma

ccRCC: SENSITIVE TO VEGF-INHIBITION AND IMMUNE CHECKPOINT INHIBITION



Rini et al. Lancet Oncology 10/2009

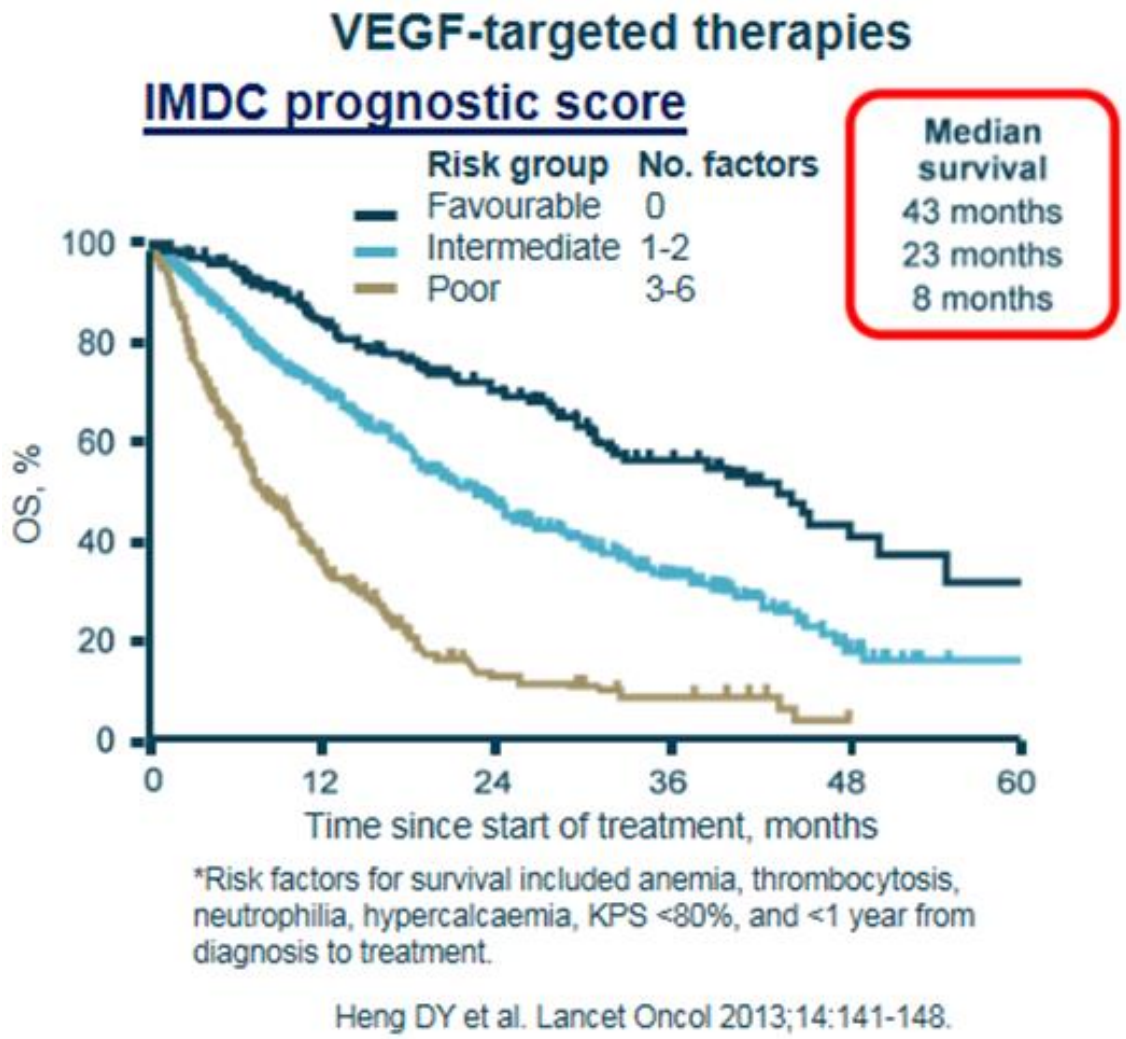
IMDC RISK GROUPS

Most frequently used prognostic scores for OS in mRCC: IMDC

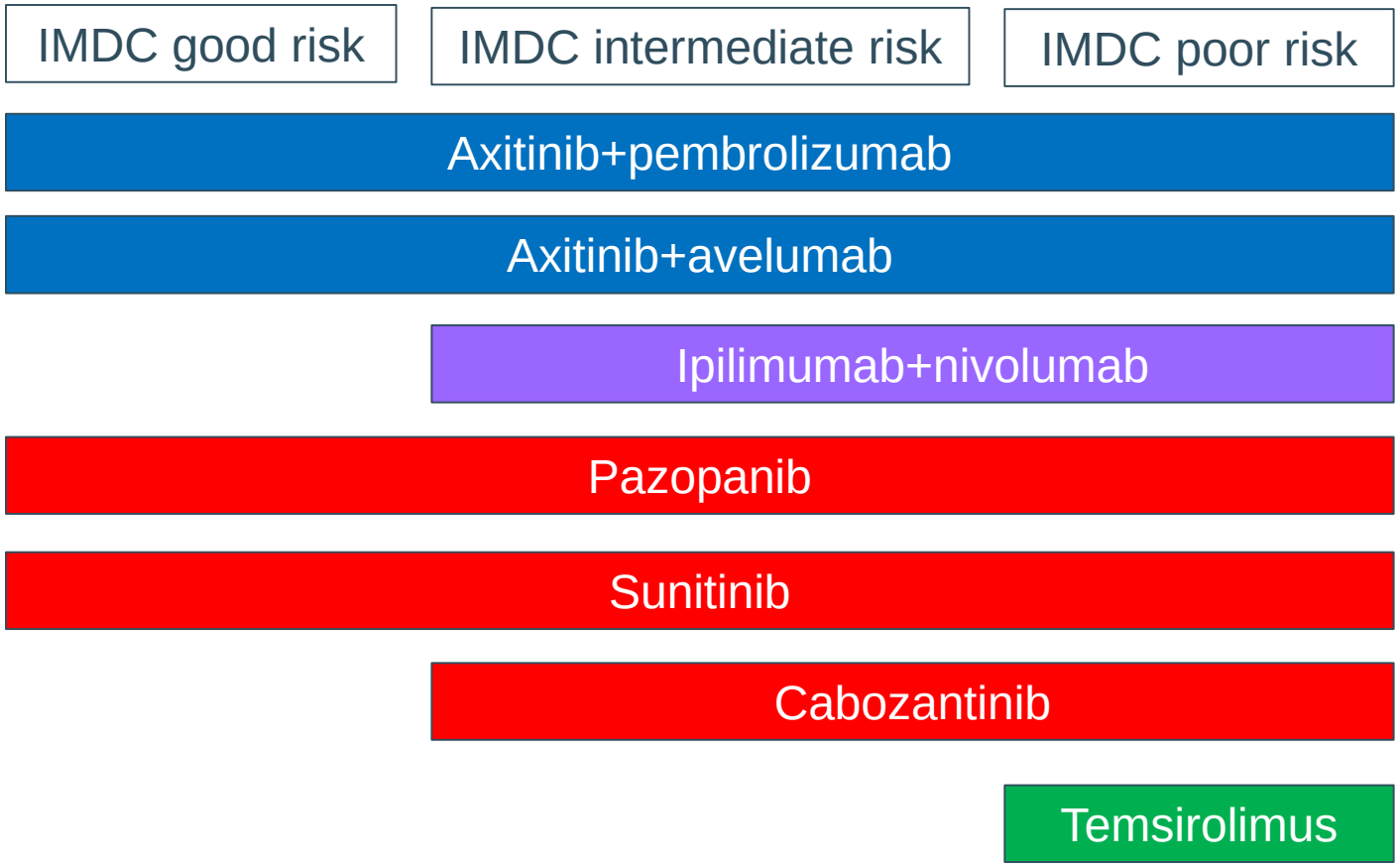
Both combine several clinical and biochemical factors

- correlated to the aggressiviness of the tumor and its impact on the general shape of the patient
- correlated to inflammation

FACTOR	ONE POINT IF
Karnofsky PS	<80
Interval between diagnosis and start of systemic therapy	<12 months
Haemoglobin	<LLN
Neutrophils	>ULN
Thrombocytes	>ULN
Corrected calcium	>ULN



LICENSED 1st LINE THERAPIES IN m-ccRCC



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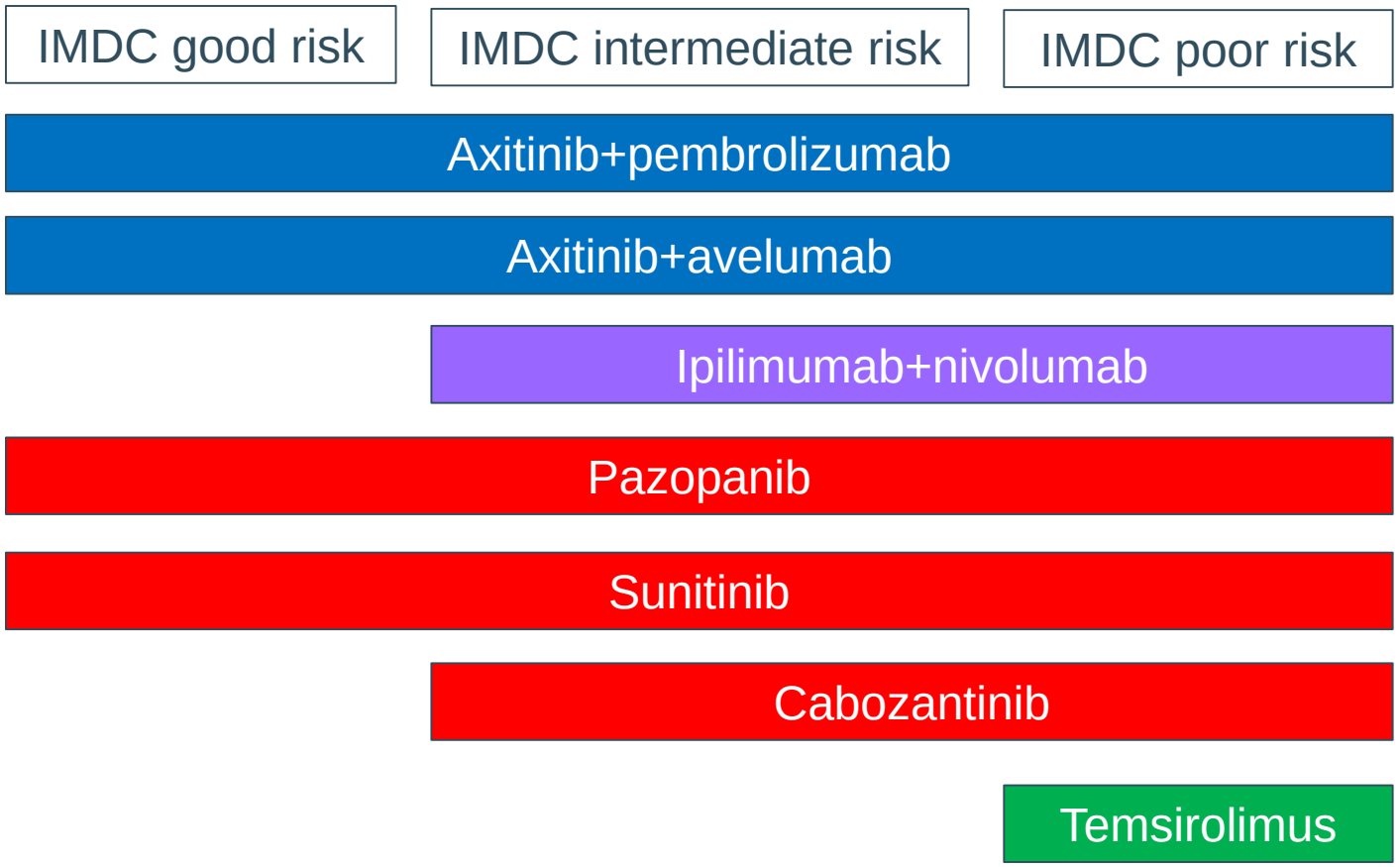


COMBINATION THERAPY:
New standard of care

VEGFR-TKIs MONOTHERAPY:
Older standard of care

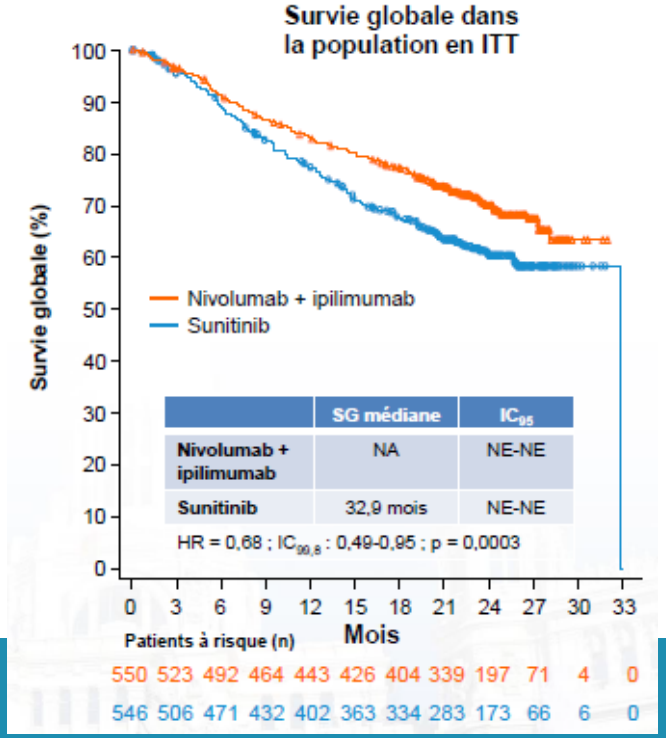
Not much used any more

RECENT PHASE III STUDIES

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

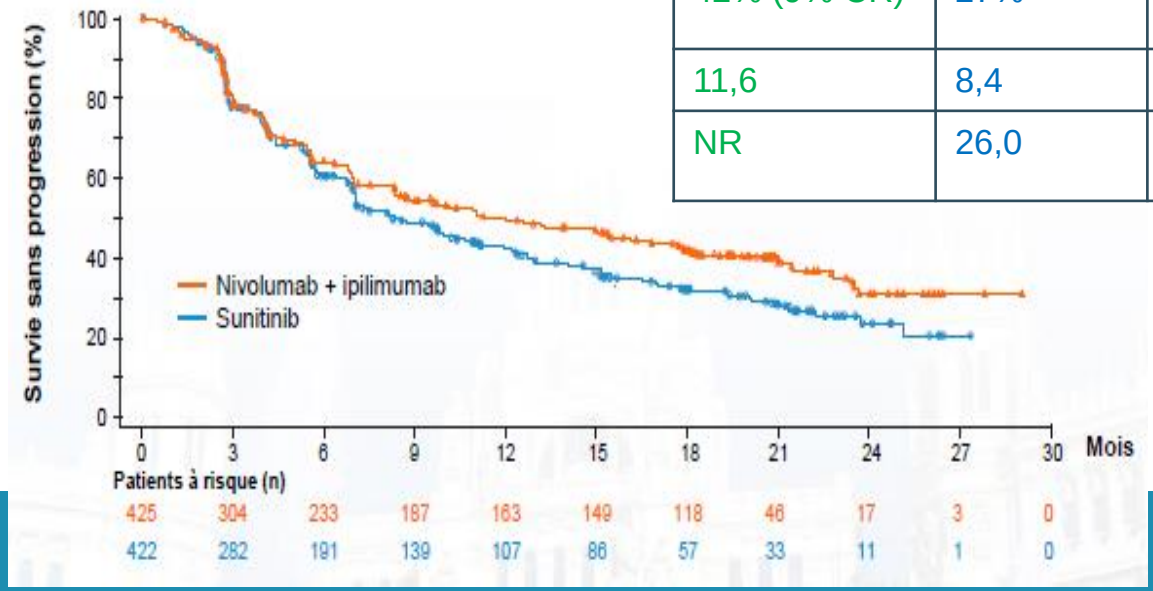


In good risk patients

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



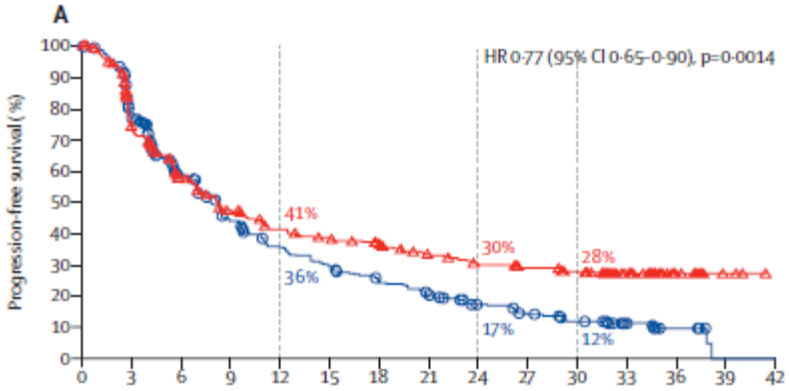
Escudier et al. NEJM 2017

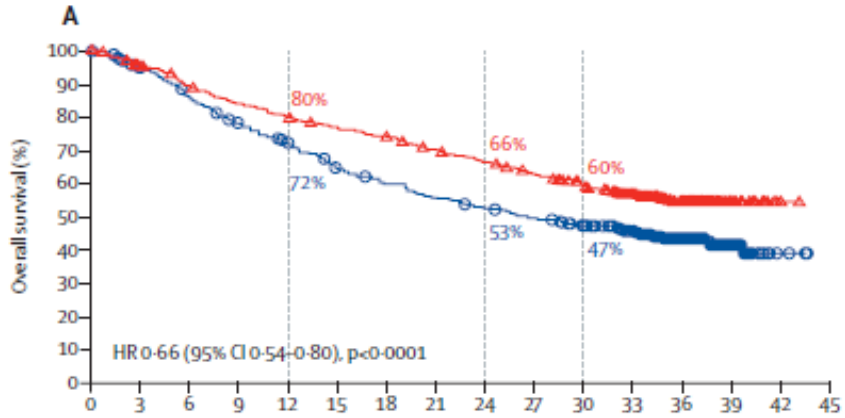
RECENT PHASE III STUDIES

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

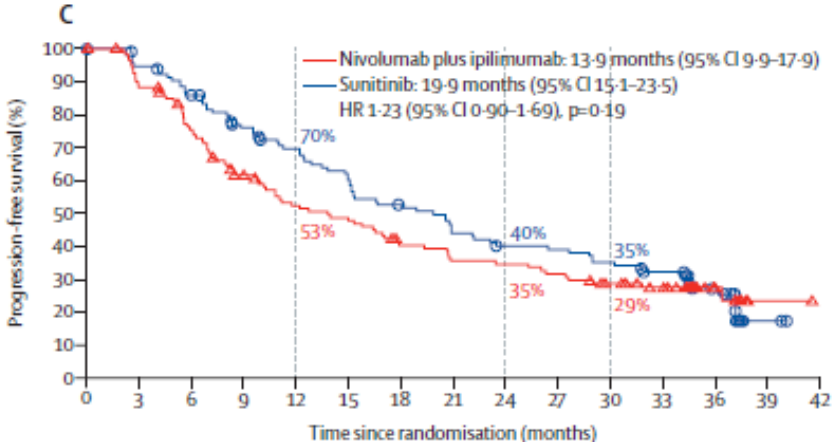
30 months follow up

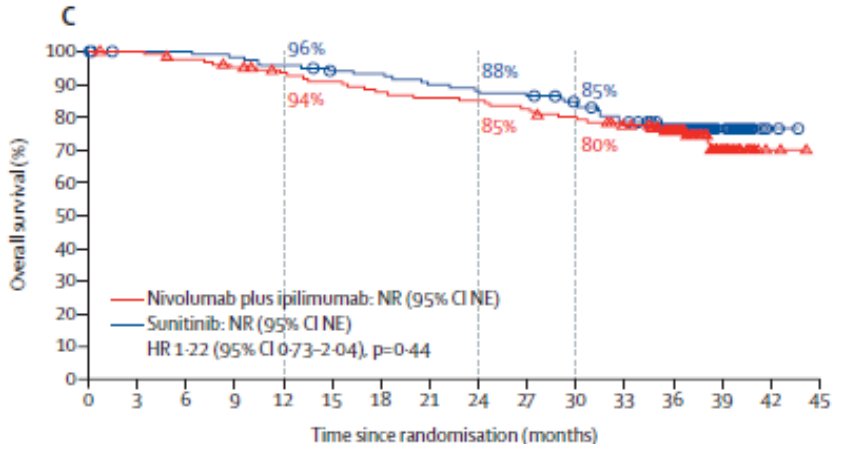
IMDC Intermediate and poor risk





IMDC Good risk





Motzer, Beuselinck, et al, Lancet Oncology 2019

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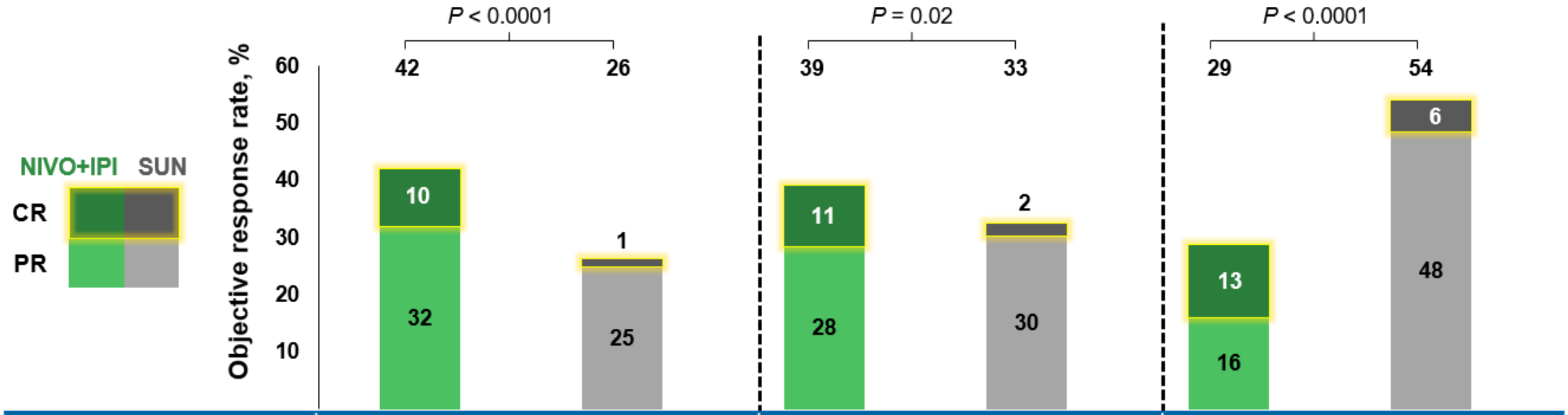
RECENT PHASE III STUDIES

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

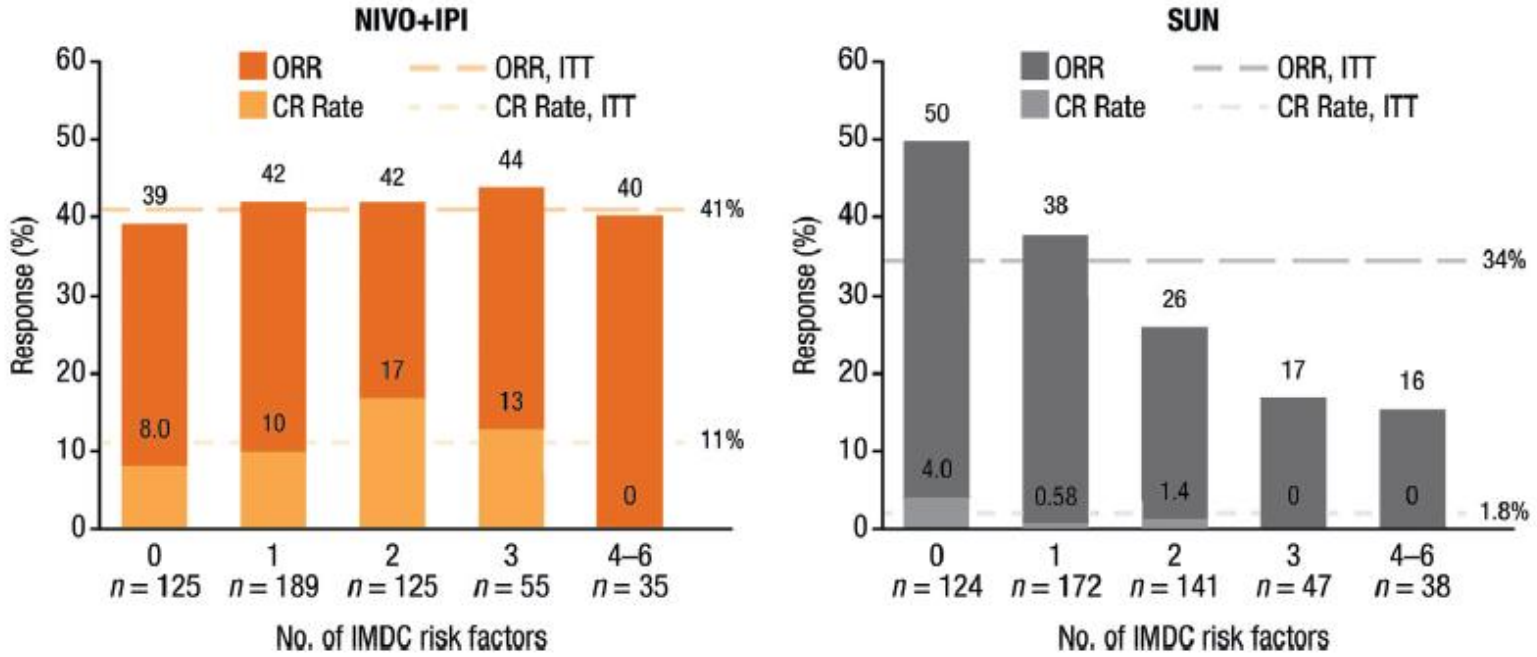


	Primary: Intermediate/poor risk		Secondary: ITT population		Exploratory: Favorable risk	
	NIVO+IPI N = 425	SUN N = 422	NIVO+IPI N = 550	SUN N = 546	NIVO+IPI N = 125	SUN N = 124
Median DOR, months (95% CI)	NR (NE)	19.7 (16.4–26.4)	NR (NE)	24.8 (19.4–27.3)	NR (40.1–NE)	27.4 (23.5–40.3)
Ongoing response, n/N (%)	121/179 (68)	58/111 (52)	146/215 (68)	94/178 (53)	25/36 (69)	36/67 (54)
Stable disease, %	31	44	36	42	54	32

RECENT PHASE III STUDIES

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

- 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



=> ipilimumab/nivolumab is also a good option in IMDC good risk patients

Escudier et al. Eur Uro 2019

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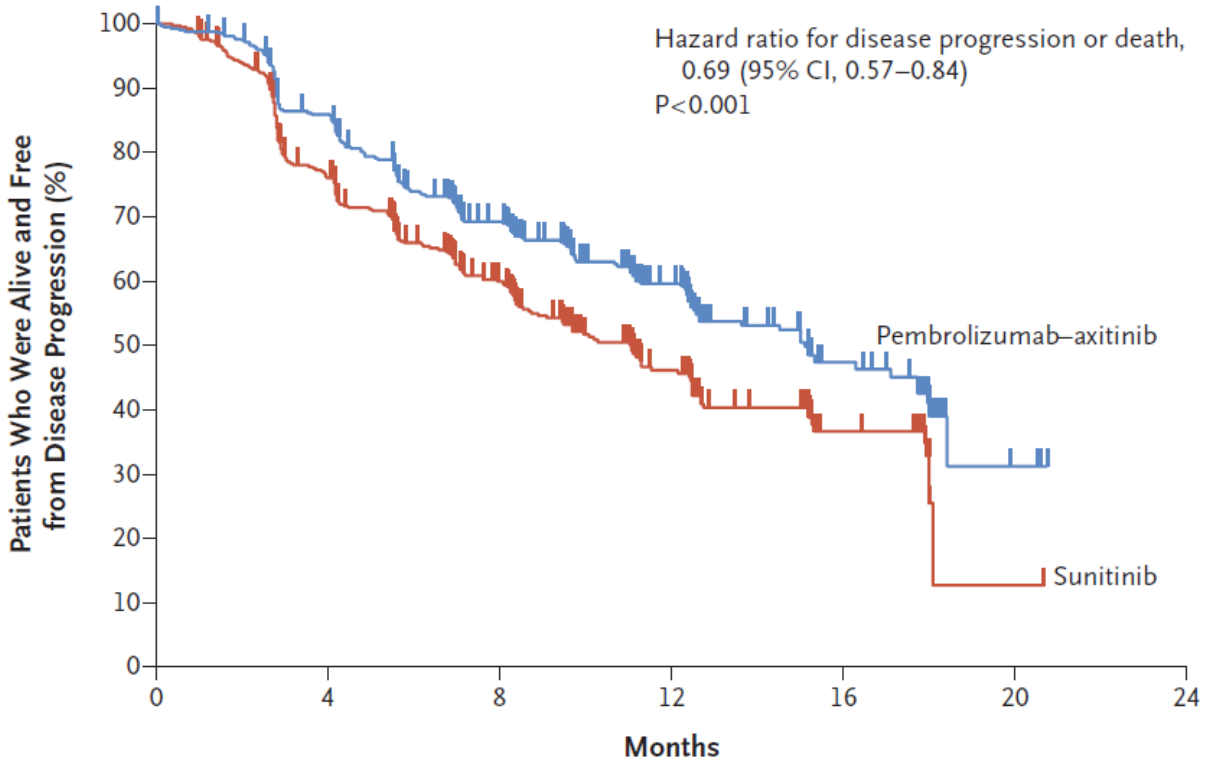
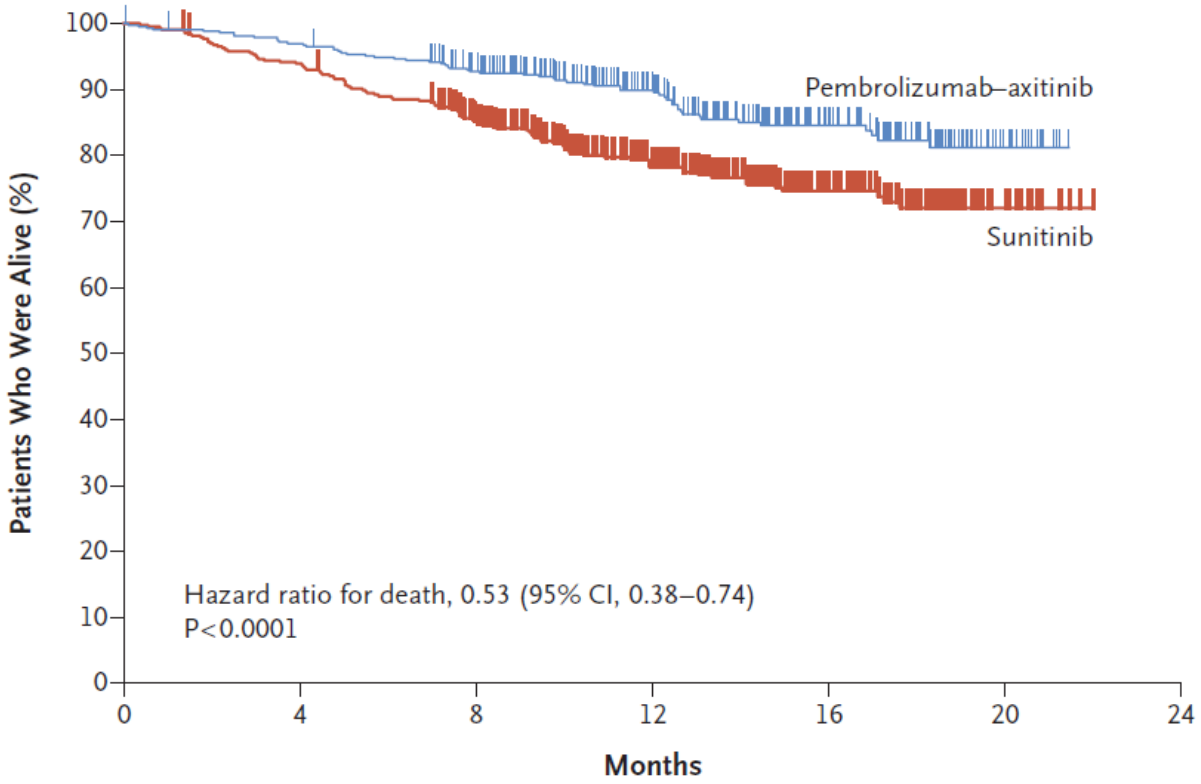
RECENT PHASE III STUDIES

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





Rini et al. NEJM 2019.

RECENT PHASE III STUDIES

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.

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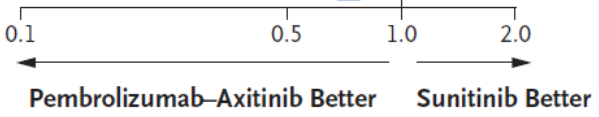
RECENT PHASE III STUDIES

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

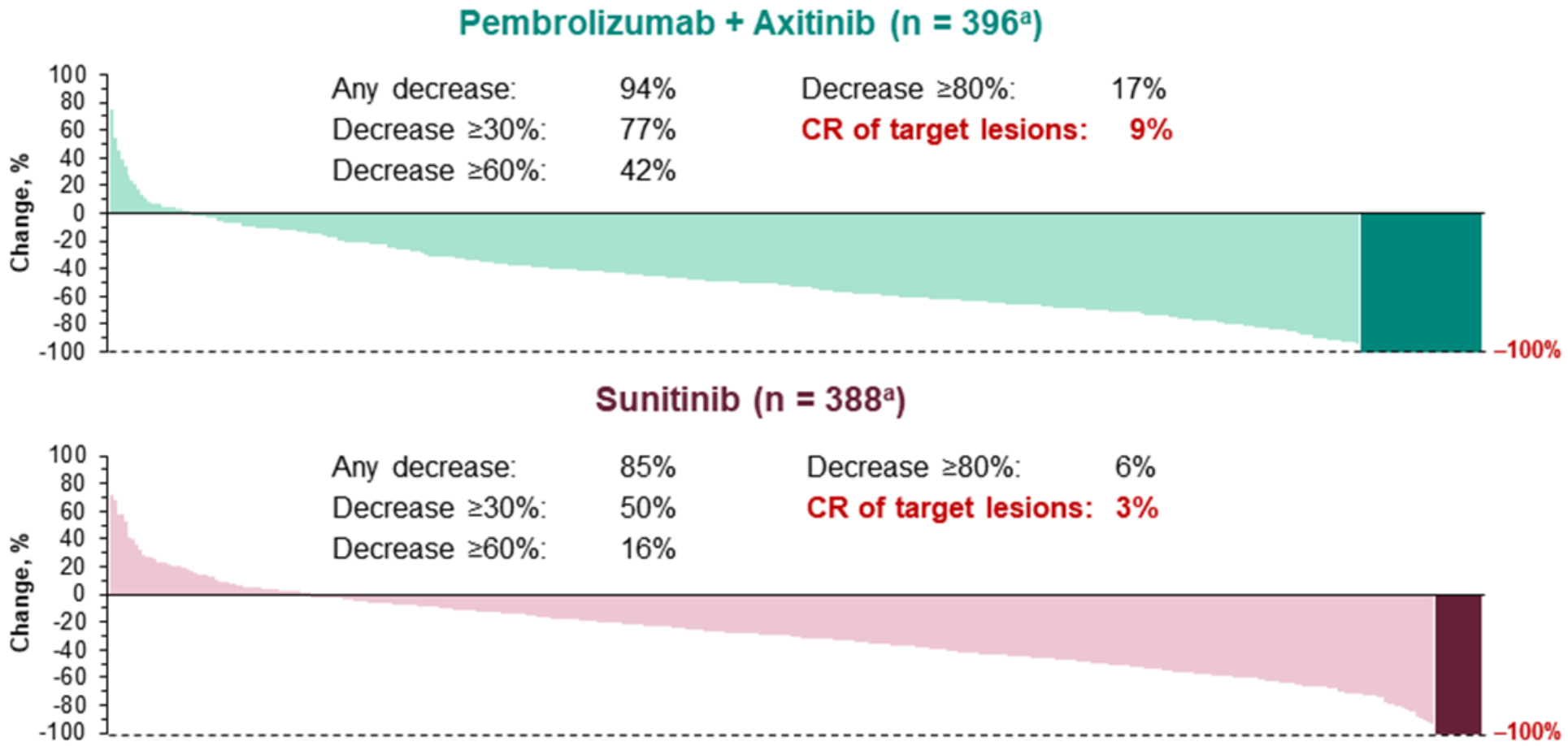
Subgroup	No. of Instances of Disease Progression or Death/No. of Patients	Hazard Ratio for Disease Progression or Death (95% CI)
Overall	395/861	0.69 (0.57–0.84)
Age		
<65 yr	248/538	0.70 (0.54–0.90)
≥65 yr	147/323	0.63 (0.45–0.88)
Sex		
Male	287/628	0.77 (0.61–0.97)
Female	108/233	0.54 (0.37–0.81)
Region 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.

RECENT PHASE III STUDIES

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



Rini et al. NEJM 2019.

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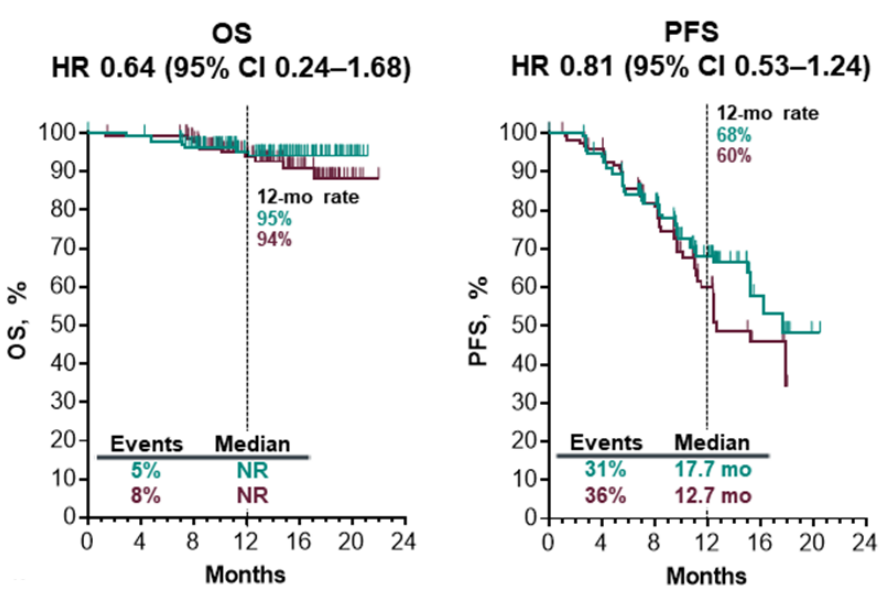
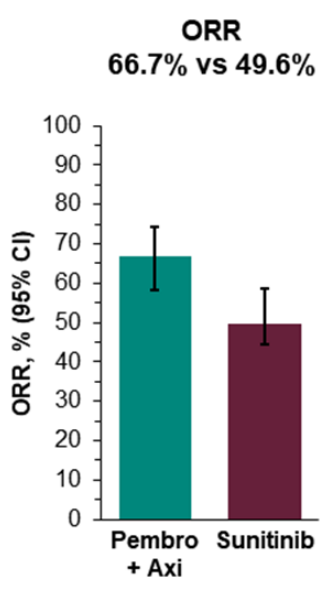
RECENT PHASE III STUDIES

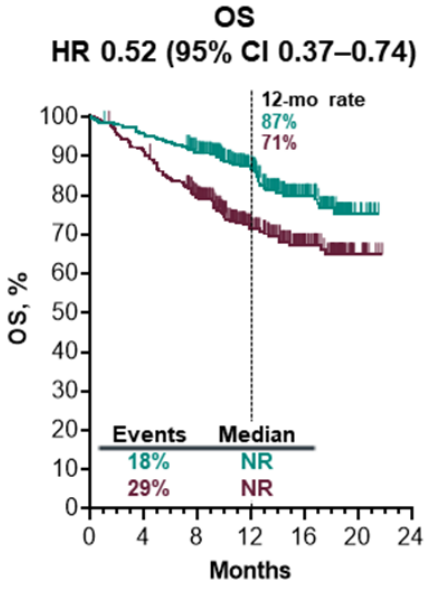
Keynote 426: phase III pembrolizumab+axitinib versus sunitinib

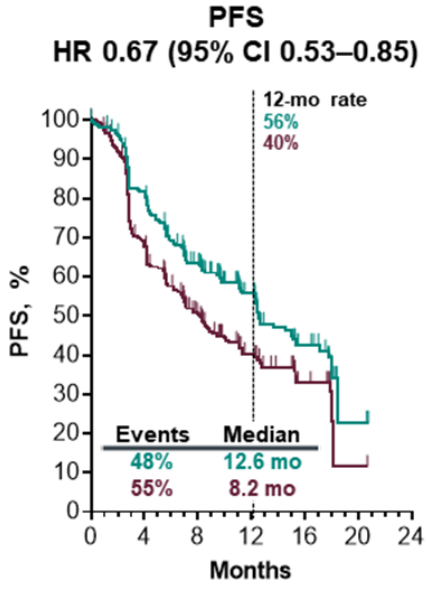
IMDC Favorable Risk

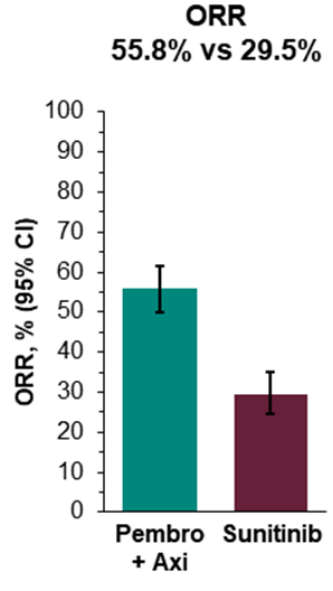




IMDC Intermediate/Poor Risk





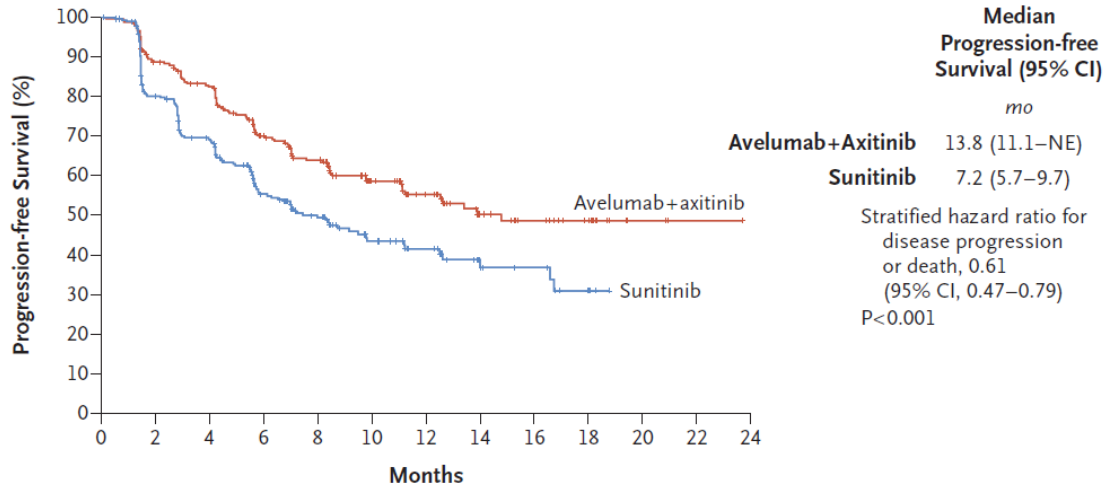


Rini et al. NEJM 2019.

RECENT PHASE III STUDIES

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

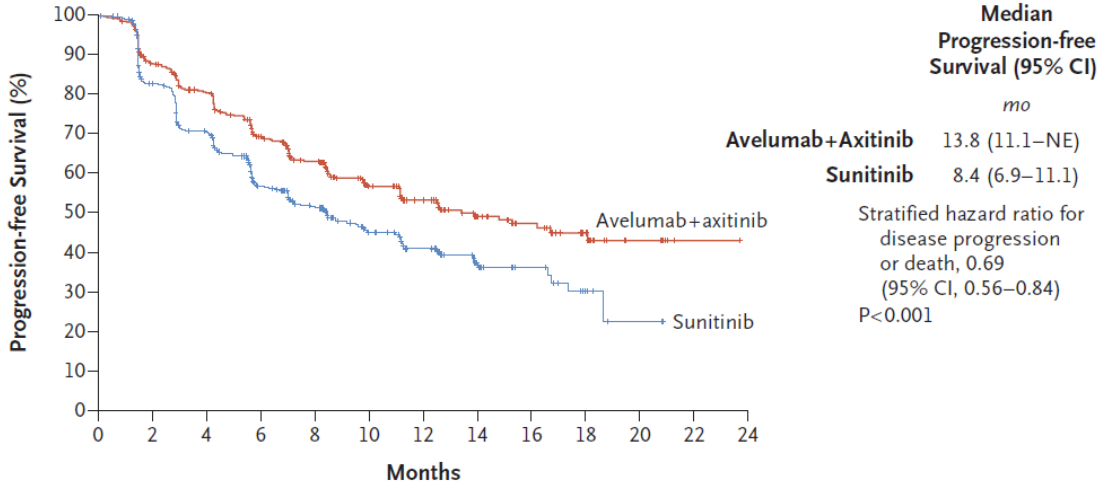
Patients with PD-L1–Positive Tumors



	Median Progression-free Survival (95% CI) *mo*
Avelumab+Axitinib	13.8 (11.1–NE)
Sunitinib	7.2 (5.7–9.7)

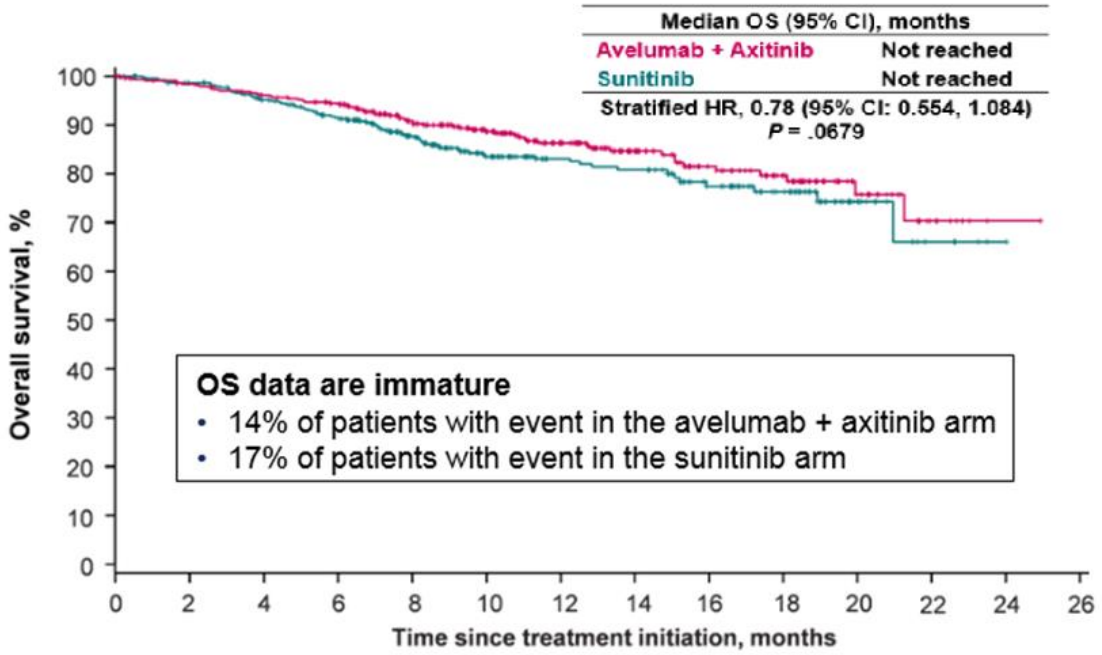
Stratified hazard ratio for disease progression or death, 0.61 (95% CI, 0.47–0.79)
P<0.001

Overall Population



	Median Progression-free Survival (95% CI) *mo*
Avelumab+Axitinib	13.8 (11.1–NE)
Sunitinib	8.4 (6.9–11.1)

Stratified hazard ratio for disease progression or death, 0.69 (95% CI, 0.56–0.84)
P<0.001



Motzer et al. NEJM 2019.

RECENT PHASE III STUDIES

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.

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RECENT PHASE III STUDIES

COMPARISON OF TOXICITY

Main difference = time of onset of adverse events

Ipilimumab/nivolumab: first months

VEGFR-TKIs: long term toxicity

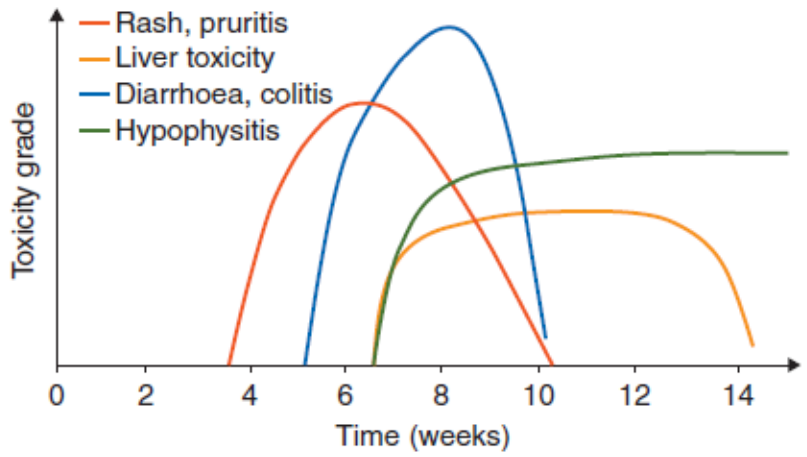

Figure 1. Timing of occurence of immune-related adverse events following ipilimumab treatment.

	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.

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RECENT PHASE III STUDIES

	Ipilimumab/nivolumab	Axitinib-avelumab or axitinib-pembrolizumab
EFFICACY PR	39%	51,4% / 59,3%
EFFICACY CR	13% IMDC good risk 10% 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
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	VEGFR-TKIs can be given from 2L on
In case of brain metastases		VEGFR-TKI can have an antiflogistic effect against cerebral edema
Pts with myelum /nerve compression		Best choice because higher PR rate and no pseudoprogression
Pts with cardiovascular antecedents	Best choice	Contra-indicated
Pts with auto-immune diseases	Contra-indicated	Best choice

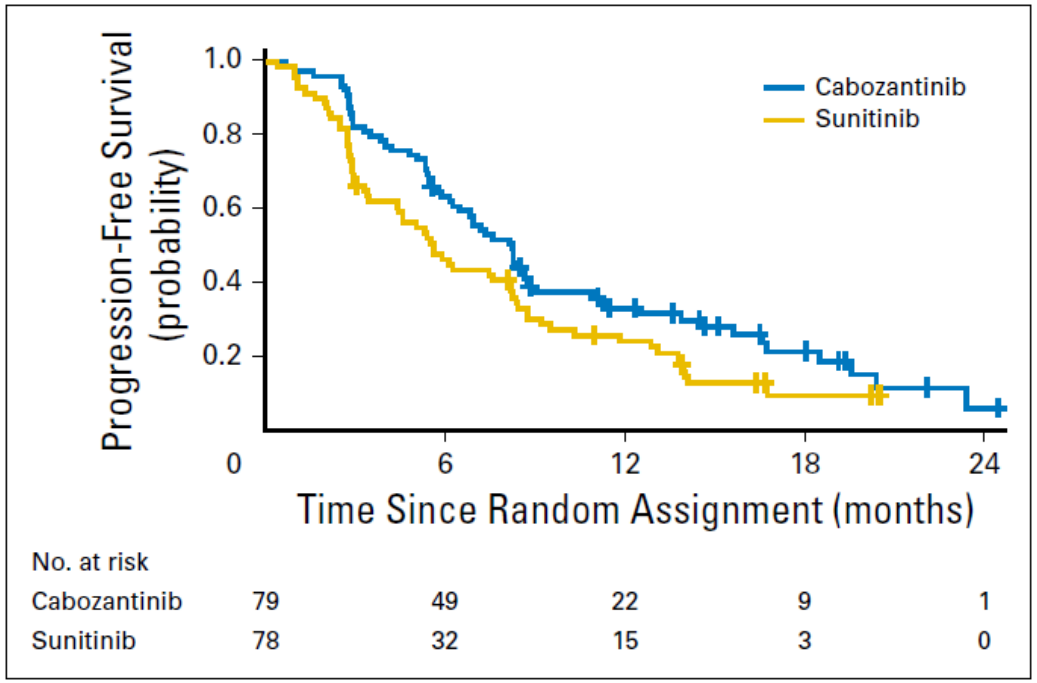
VEGFR-TKIs IN FIRST LINE IN MONOTHERAPY

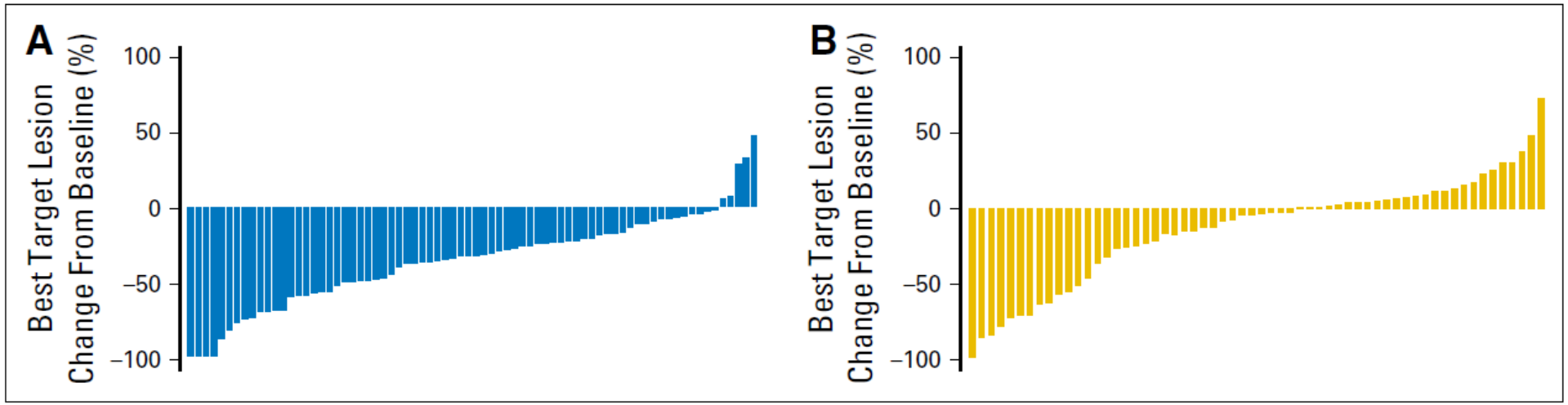
CABOSUN phase II trial in IMDC intermediate/poor risk pts

- 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

VEGFR-TKIs IN FIRST LINE IN MONOTHERAPY

AXL-expression in kidney tumor:

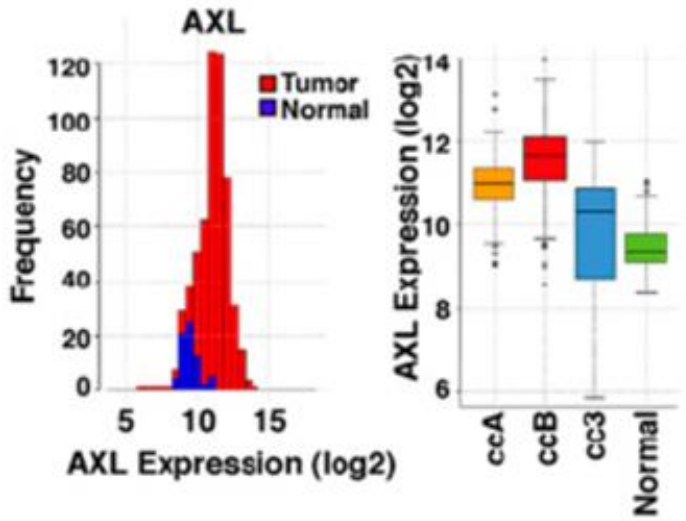
- is higher than in normal kidney tissue
- Correlates with aggressive tumor behavior (ccB>ccA)
- Is highly expressed in aggressive ccRCC
- Correlates with shorter survival

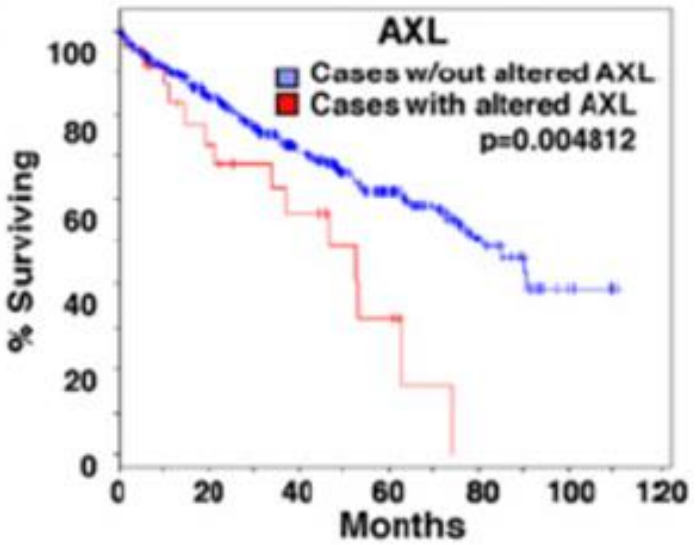
- HIF1A and HIF2A directly activate expression of AXL
- AXL activates the proto-oncogene MET.

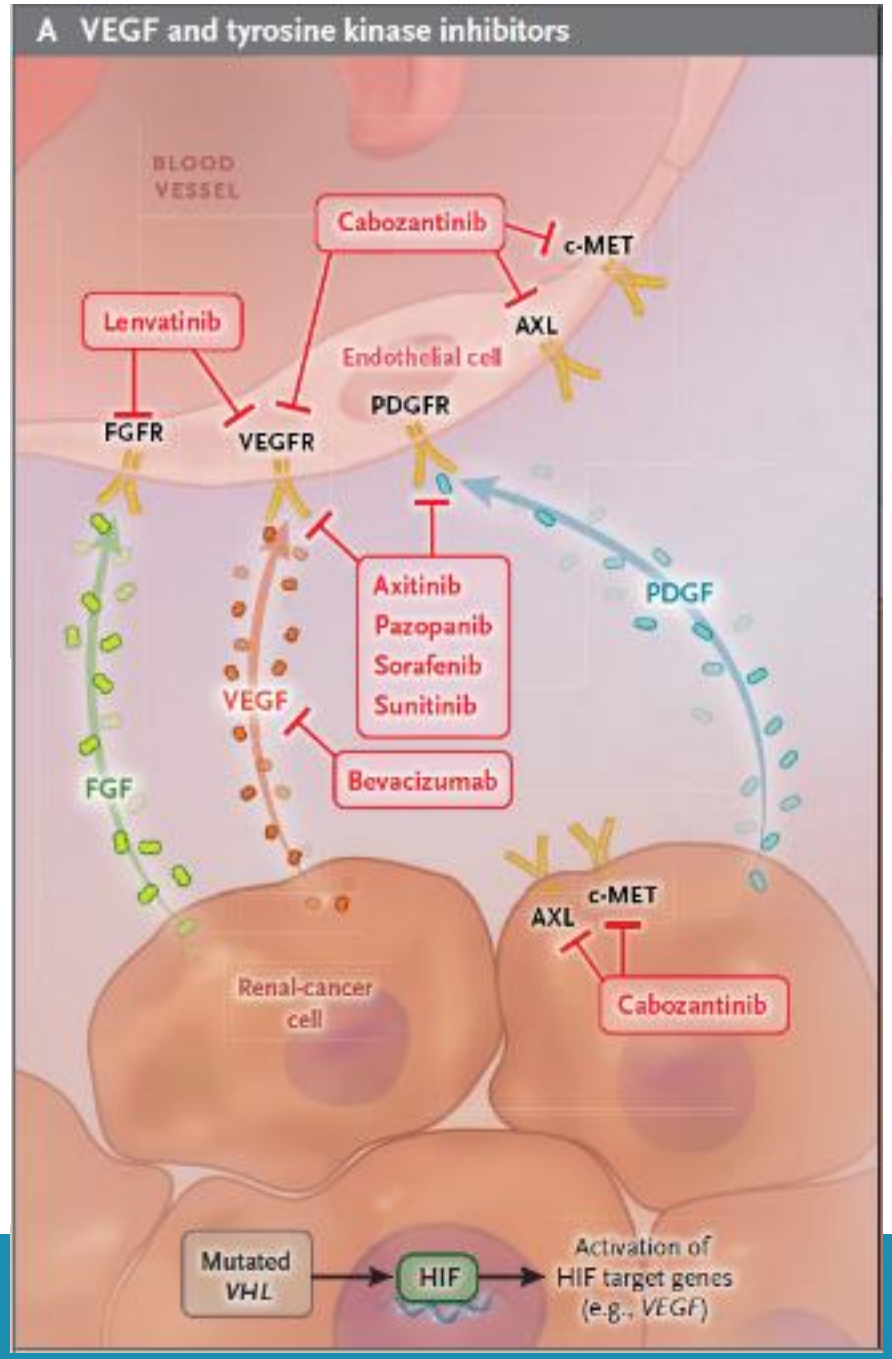
- Inactivation of AXL signaling in m-ccRCC cells reversed the invasive and metastatic phenotype in vivo.

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

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



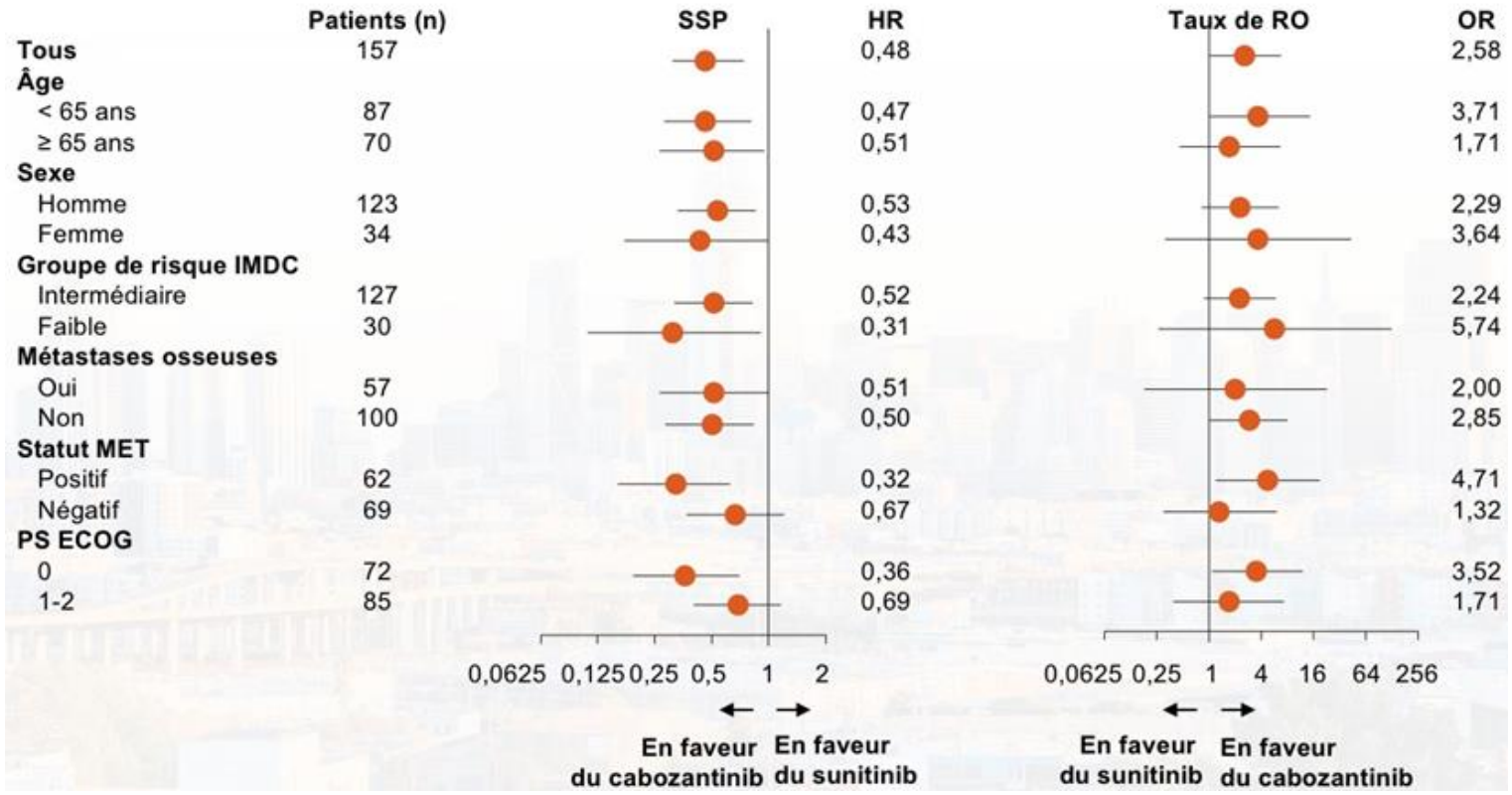


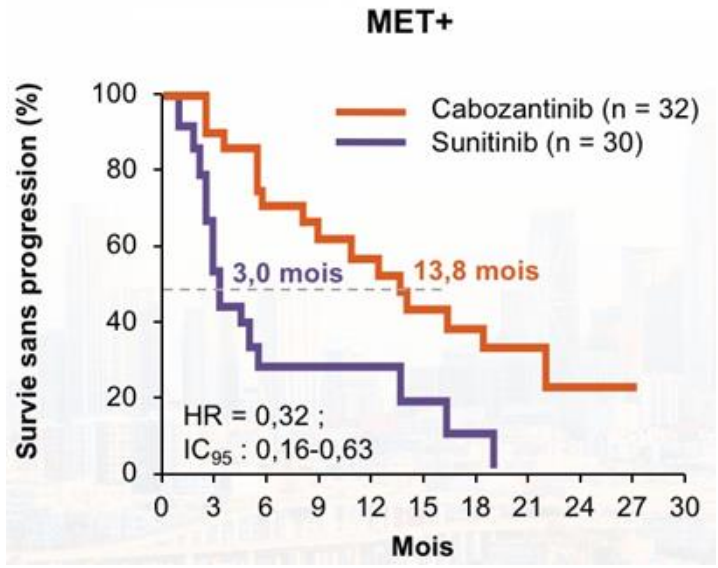


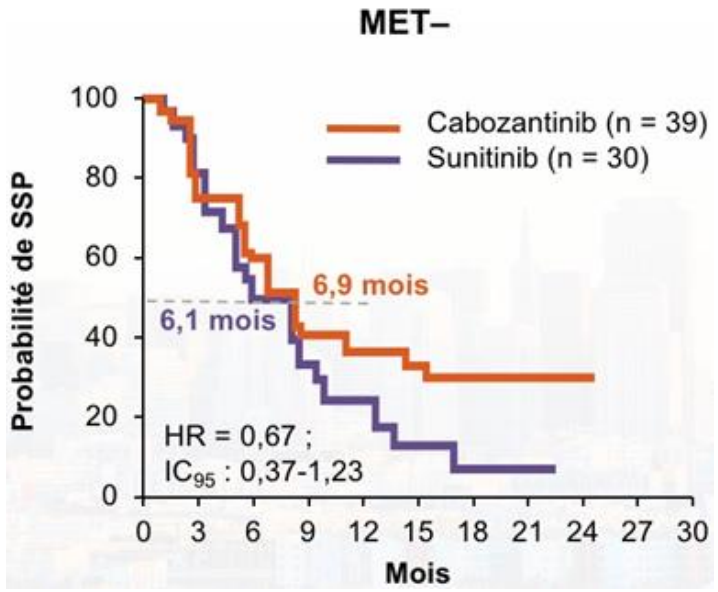
Rankin et al. PNAS 2014

VEGFR-TKIs IN FIRST LINE IN MONOTHERAPY

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







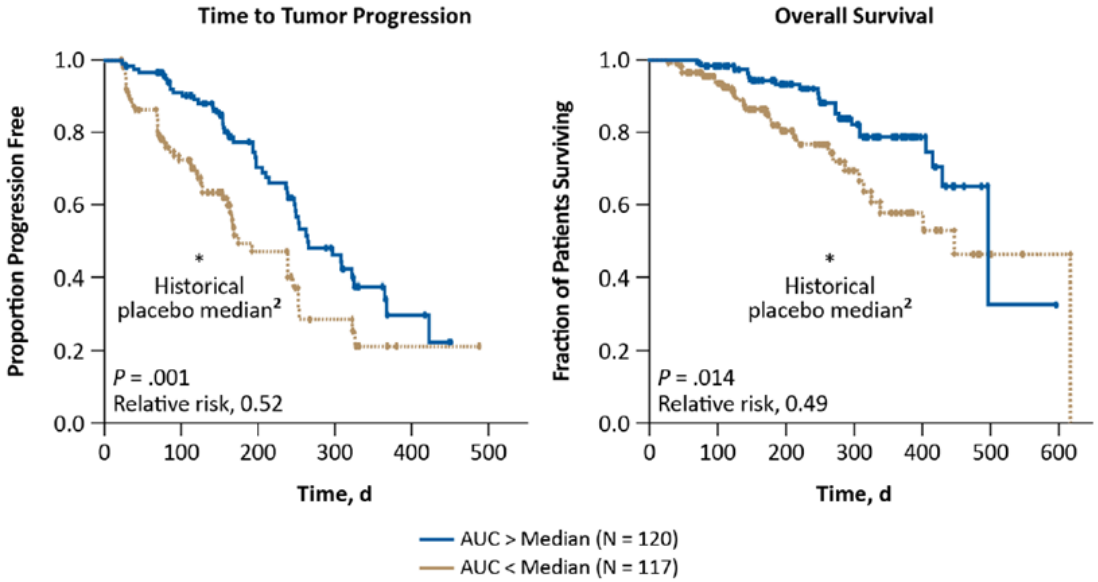
VEGFR-TKIs IN FIRST LINE IN MONOTHERAPY

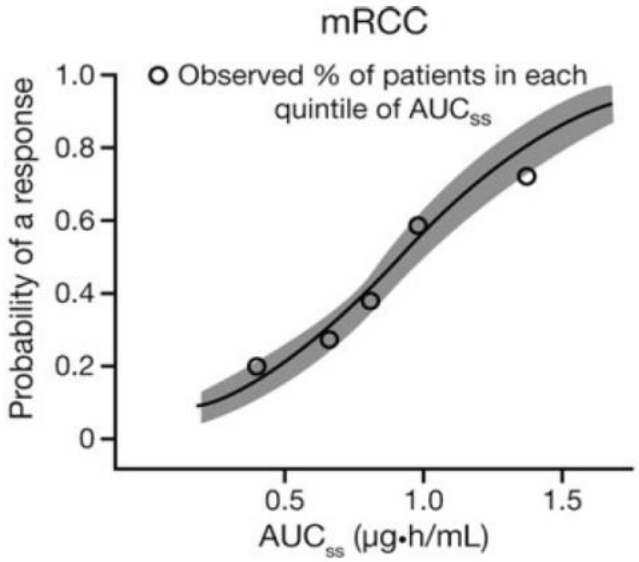
- Patients with absolute contra-indications for IO:
  - severe AI diseases
  - transplant patients

- Elderly (>80?): probably also good OS if sequentially treated with VEGFR-TKI followed by nivolumab

VEGFR-TKIs IN FIRST LINE IN MONOTHERAPY

Sunitinib Exposure and Clinical Outcome[1]





⇒ Keep the dose as high as possible
⇒ Try to take care of the adverse events

Hook et al.

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LICENSED 2d AND FURTHER LINE THERAPIES IN m-ccRCC

Nivolumab	AFTER 1L VEGFR-TKI (decreasing)
Axitinib or cabozantinib	AFTER 1L IO-COMBINATIONS And as 2L VEGFR-TKI in patients with severe contra-indications for IO Axitinib: up-titration Cabozantinib: also cMET and AXL inhibition
Sunitinib, pazopanib or sorafenib	As further line VEGFR-TKI
Everolimus	IN PATIENTS RESISTENT TO VEGFR-TKIs and IO

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

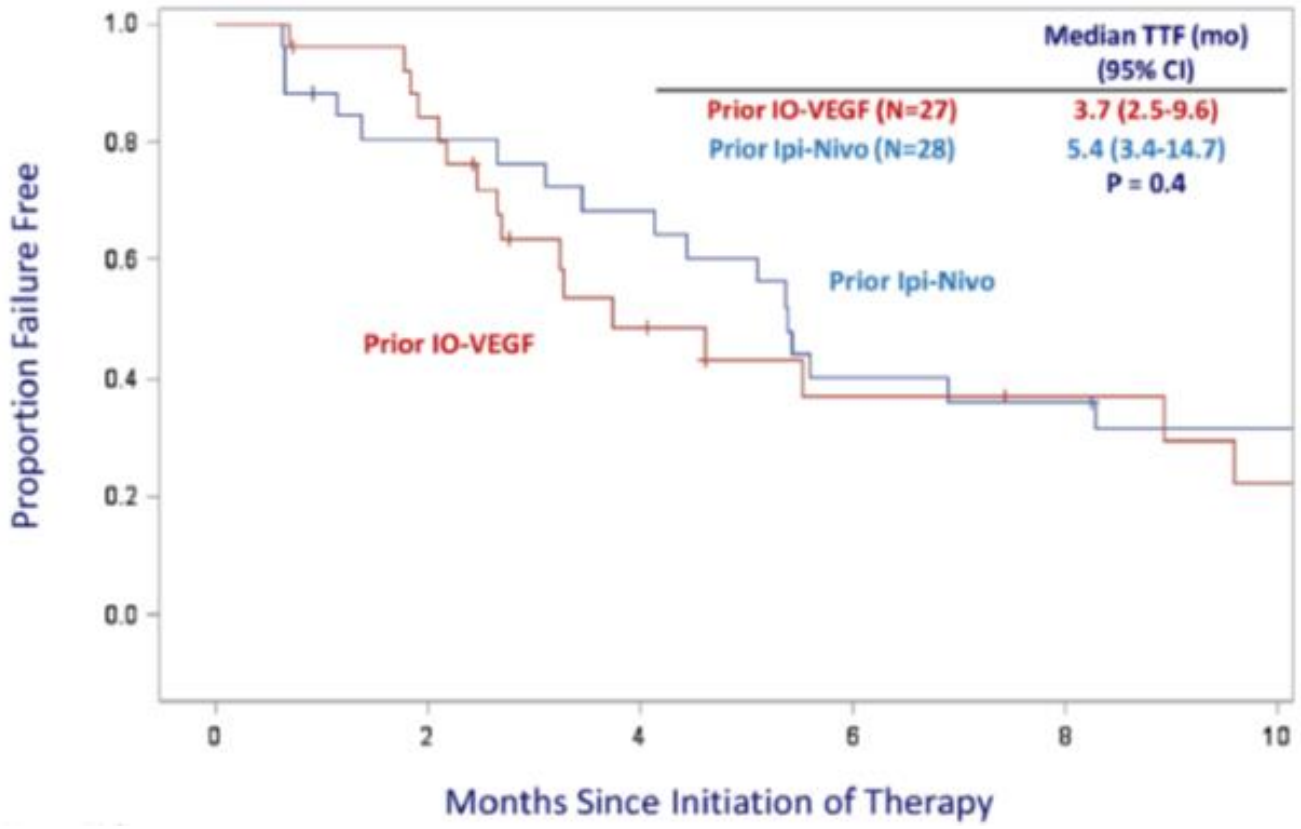

Table 3 – Outcomes with second-line VEGF-based therapy.

	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.

Dudani S, Beuselinck B, et al, European Urology 2019

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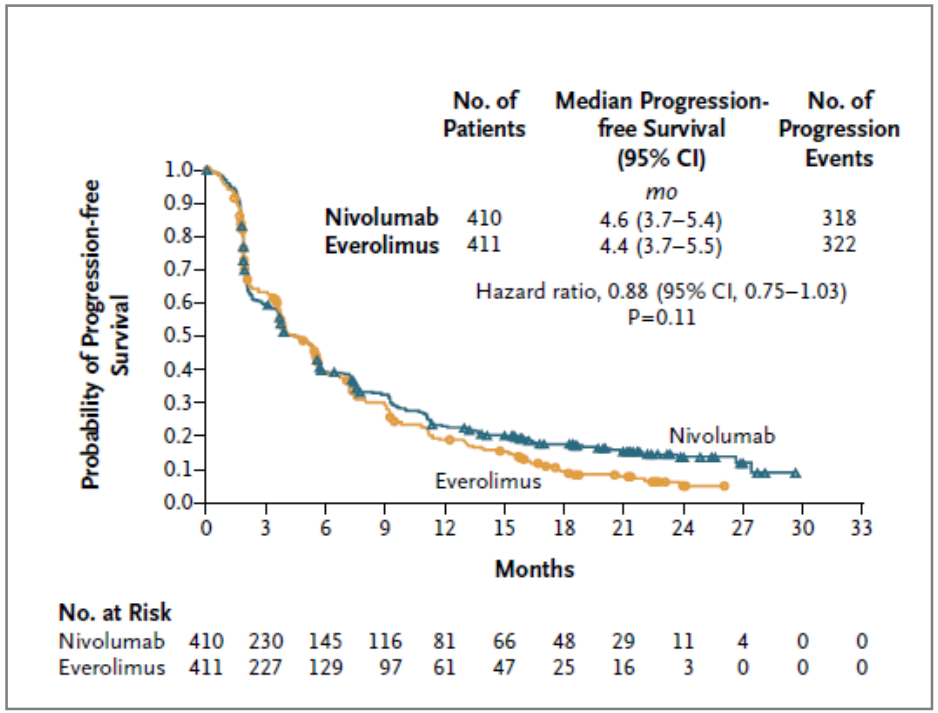
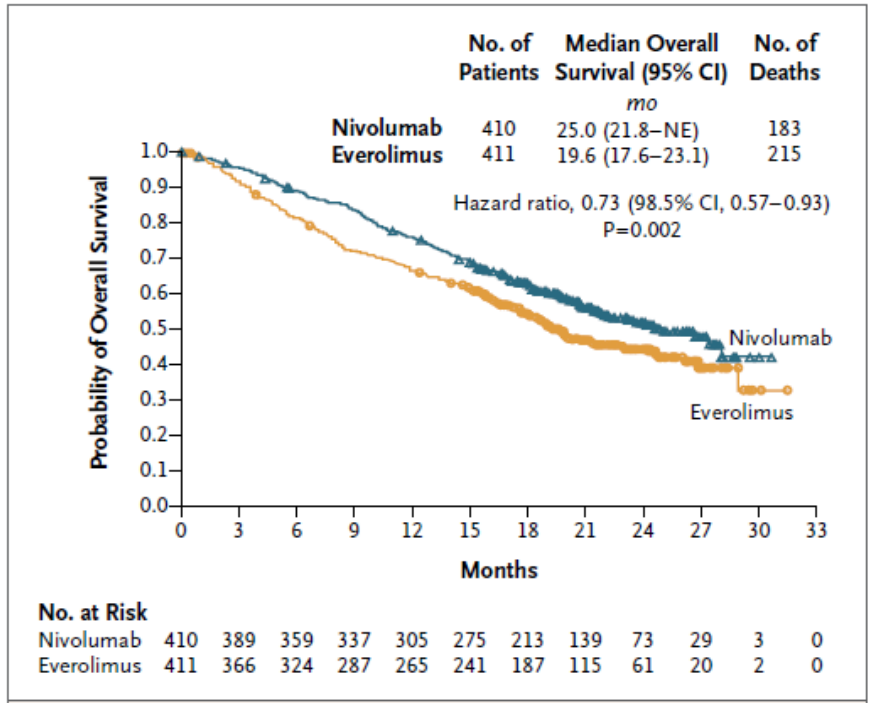
SECOND LINE CCRCC

CA 209-025: Nivolumab versus everolimus





PFS is a poor parameter for NIVO efficacy, among others because of pseudoprogression
RR 25% vs 5%

Motzer et al. NEJM 2015

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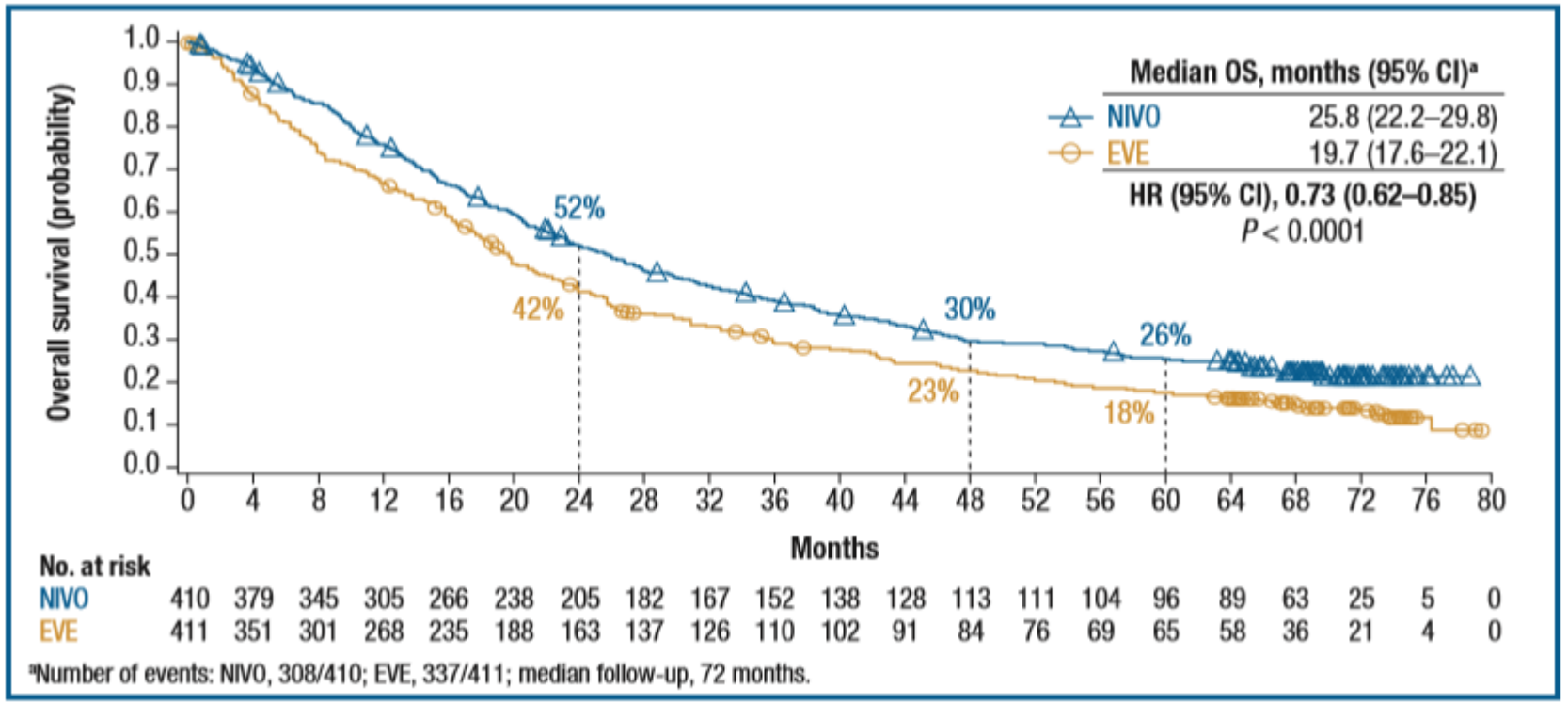
SECOND LINE CCRCC

CA 209-025: Nivolumab versus everolimus 5Y follow up

Figure 1. Overall survival



Cave cross-over everolimus > nivolumab: the tail in the curve is in both cases influenced by nivolumab

SECOND LINE CCRCC

Man, born 1959

Oncologische voorgeschiedenis:

NIERCARCINOOM
- 06-2011: Radicale nefrectomie links: clear cell RCC pT2bpN0M0 Fuhrmann III. Postoperatief inclusie in de SORCE trial maar behandeld in de placebo-arm

LONGMETASTASEN
- 03-2012: Longmetastasen: start Sutent
- 06-2012: Bilan na 2 cycli sutent: PR
- 01-2013: Progressie onder sutent. Start Axitinib
- 04-2013: Progressie onder axitinib: start everolimus.
- 06-2015: Pneumocystis pneumonia. Dosisreductie everolimus 5mg.
- 07-2015: Bilan na 29 cycli everolimus: blijvende partiële respons, dosisescalatie 10 mg.
- 03-2016: Bilan na 38 cycli everolimus: progressie. Cross-over naar nivolumab-arm.
- 04-2016: Partiële respons onder nivolumab
- 11-2016: Na 7 maanden nivolumab: CT: één longletsel neemt toe. Nivolumab verder.
- 02-2017: Verdere toename van één longletsel: Resectie longmetastase: APO: RCC. Stop nivolumab
- 01-2021: CT thorax-abdomen: no evidence of disease

Everolimus: globally poor results, but some patients respond very well …

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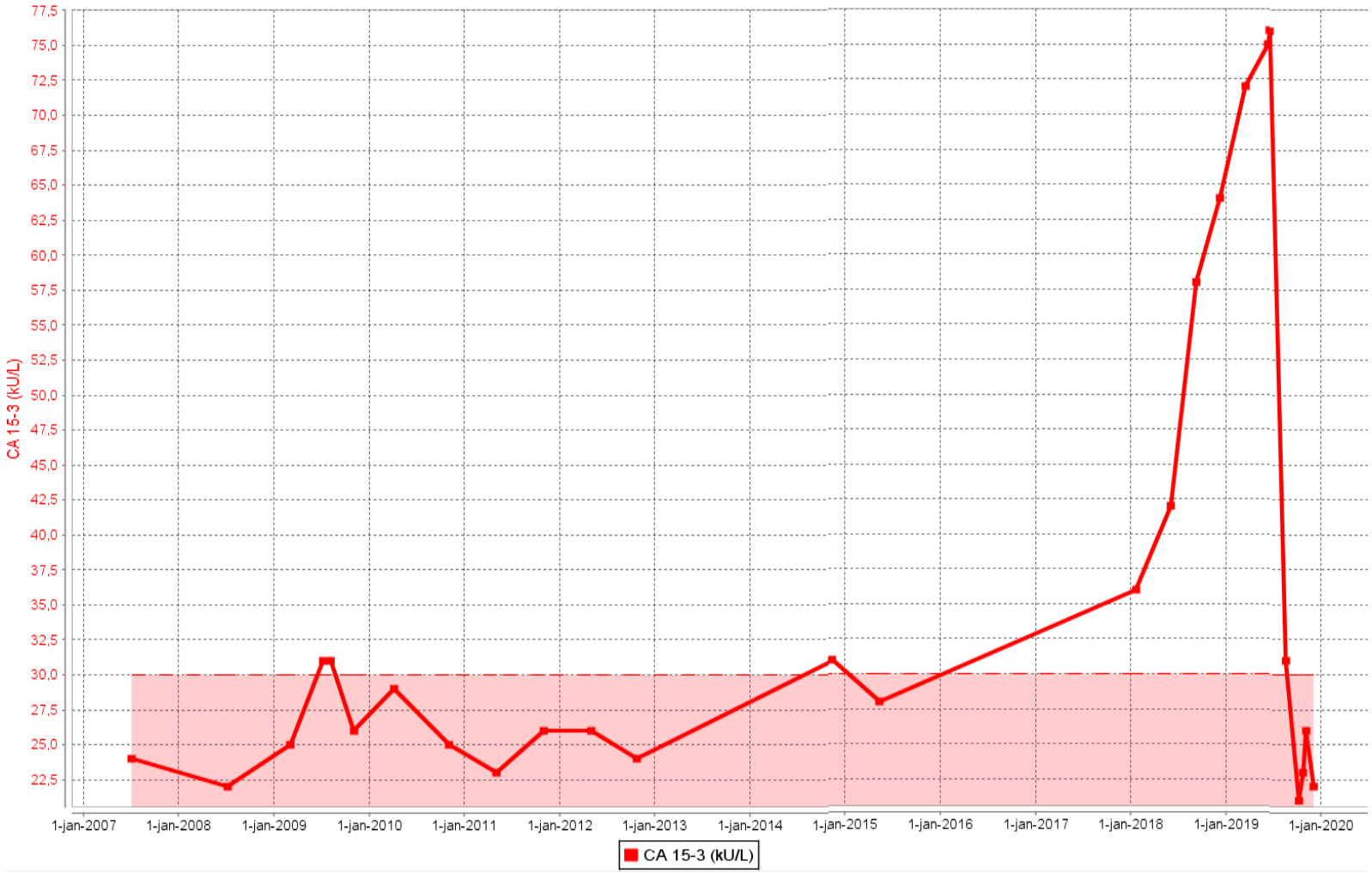
QUICK OR SLOW RESPONSES?

QUICK OR SLOW RESPONSES?

CASUS women 65 years

- Antecedents of breast carcinoma => post-op follow up with CA 15.3
- 2009: increase CA 15.3 => CT thorax/abdomen for relapse breast carcinoma: no metastases but kidney tumor
- Nefrectomy: decrease of CA 15.3!
- 2015: Development of bone metastasis of RCC in left femur
- Increase of CA 15.3
- Refuses systemic therapies (pazopanib/sunitinib) for several months
- Impressive decrease in pain/CA 15.3 after a single administration of ipi/nivo

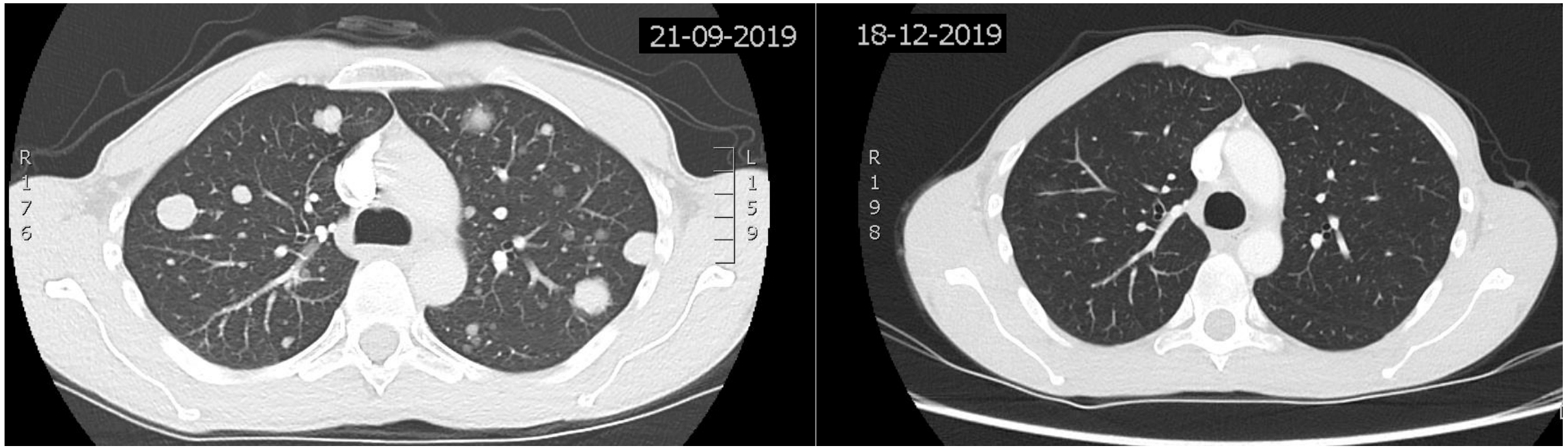


QUICK OR SLOW RESPONSES?

MAN 56Y

Oncologische voorgeschiedenis:

07-2019: Palpabele niertumor rechts verdacht voor RCC met multiple longmetastasen. Macroscopische hematurie en lichte flankpijn rechts.
09-2019: Nefrectomie rechts: APO: helderceelig RCC, geen sarcomatoide dedifferentiatie
09-2019: Belangrijke toename longmetastasen. Start ipilummab/nivolumab
12-2019: Bilan na 4x ipilimumab/nivolumab: complete remissie



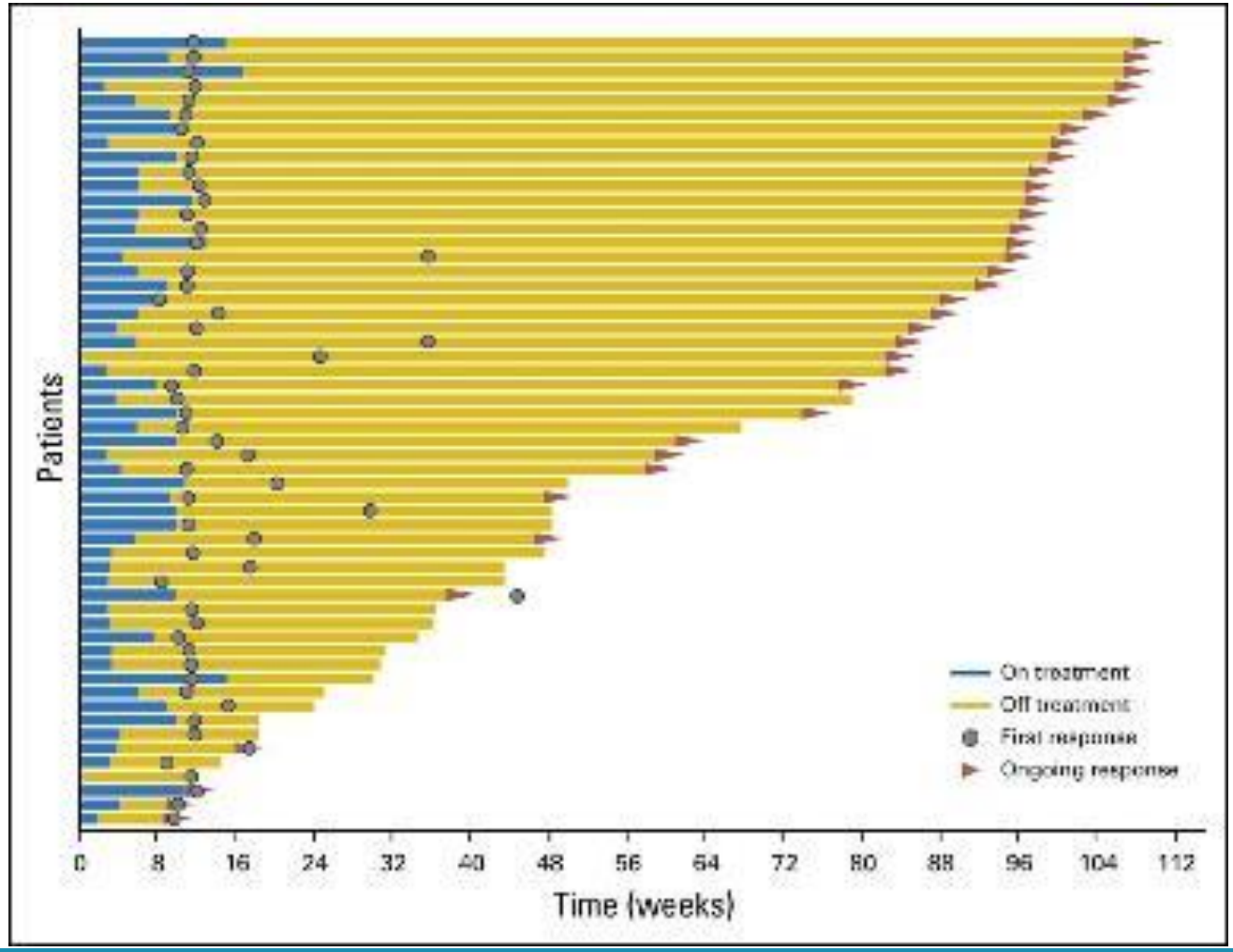
QUICK OR SLOW RESPONSES?

Responses can occur very lately …

<u>331 pts with melanoma treated with ipilimumab/nivolumab in first-line</u>

98 pts: discontinued because of irAE

Time to and duration of response in patients who discontinued treatment because of AE during the induction phase of treatment



QUICK OR SLOW RESPONSES?

MAN 67Y

Oncologische voorgeschiedenis:

- 01-2015: Niertumor rechts cT4N1M1: metastasen long + huid + paravertebrale spier links. Start Sutent 50 mg/d
- 12-2015: Radicale nefrectomie rechts + deel diafragma/M. psoas/leverkapsel: APO: pT3a Heldercellig RCC, cT4, Fuhrmann graad 4
- 07-2016: Pause Sutent
- 10-2016: Ontstaan van 2 longletsels. Stabiele metastase in de paravertebrale spier links
- 12-2016: Stereotactic Body Radiation Therapy (SBRT) spiermetastase en twee longletsels links tot 42 Gy (3x 14 Gy).
- 10-2017: Diagnose speekselkliermetastase submandibulair rechts (bewezen op biopsie)
- 12-2017: Herstart Sutent 25 mg (4 ziektelocalisaties: speekselklier, rugspier, adenopathie hoog interaortacavaal, adenopathie supraclaviculair rechts)
- 02-2018: Goede respons op Sutent: afname van alle letsel doch intolerantie (ernstige vermoeidheid). Stop Sutent
- 05-2018: Macroscopisch volledige resectie van solitaire metastase rechts frontaal (Bonheiden). APO: metastase RCC.
- 07-2018: Radiotherapie tot 3x 9 Gy op de resectieholte cerebraal rechts frontaal
- 09-2018: CT: Oncologische ziekteprogressie met volumetoename van de massa rechts supraclaviculair en interaortocavaal.
- 10-2018: Start nivolumab
- 11-2018: MR hersenen: geen hersenmetastasen
- 01-2019: CT: lichte toename maar globaal stabiele ziekte
- 04-2019: CT: lichte toename
- 06-2019: CT: lichte afname. Speekselkliermetastase is verdwenen
- 09-2019: CT: partiële response: RECIST -40%! Stop nivolumab (vermoeidheid en diarree). Vitiligo!
- 11-2019: Normaal hormonaal bilan en normaal cardiaal nazicht
- 12-2019: CT na 3 maanden therapiepause: partiële respons (RECIST -58%)

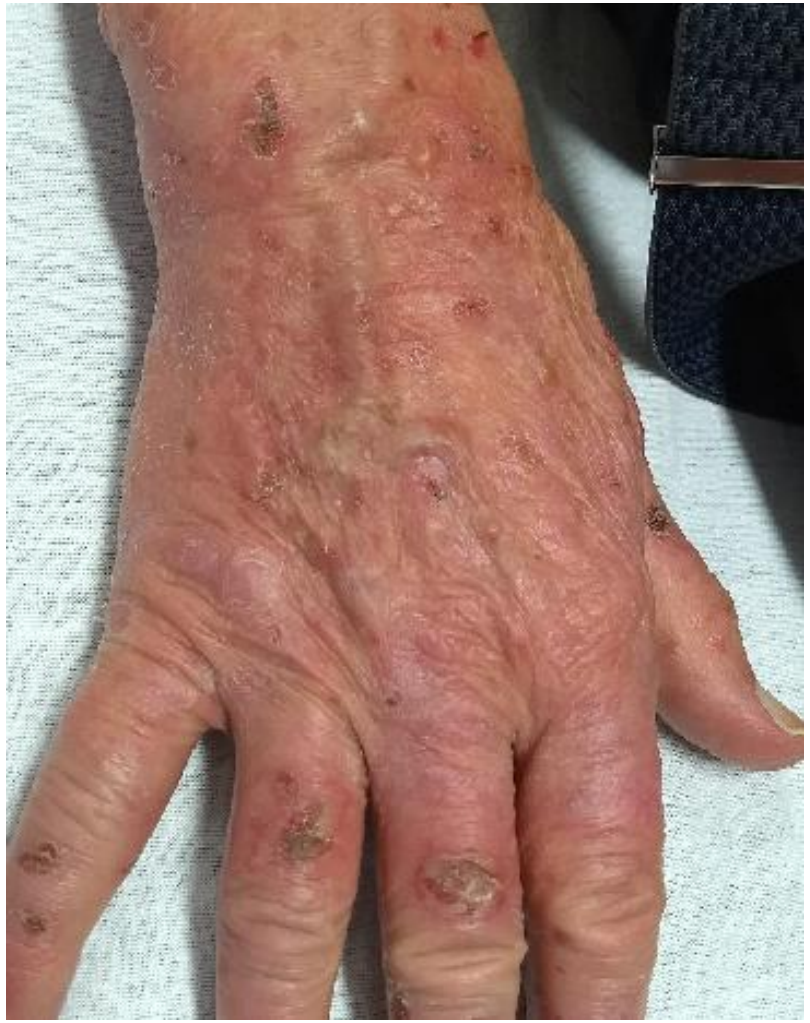
QUICK OR SLOW RESPONSES?

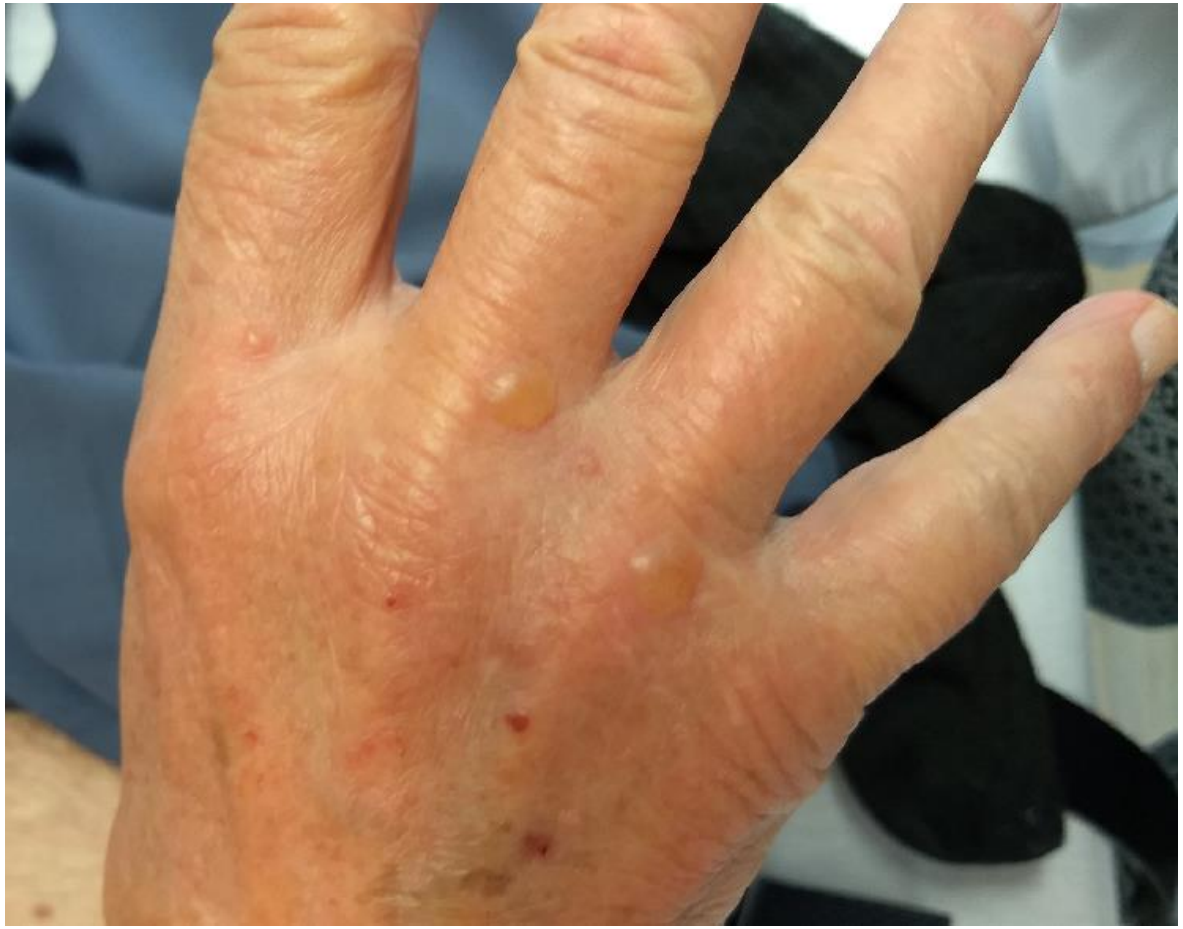
MAN 88Y

(III) RENAAL CELL CARCINOMA
11-2000: Radicale nefrectomie links met lymfadenectomie: pT1N1G4 heldercellig renaal celcarcinoma (aanvankelijk beoordeeld als waarschijnlijk chromofoob)
05-2007: CT thorax-abdomen: geen metastasen
11-2008: Echo abdomen: geen levermetastasen
02-2013: CT abdomen: levermetastasen en lokaal recidief. Biopsie nefrectomieloge: heldercellig RCC, Fuhrman graad 3.
04-2013: MR-WB: geen botmetastasen: verder afwachtende houding
02-2015: toename levermetastasering. Start Sutent
07-2015: Respons (RECIST -42%). Dosisreductie naar 37.5 mg /d gezien vermoeidheid
06-2017: Bilan na 20 cycli Sutent: ziekteprogressie lever: start Axitinib
09-2017: Bilan na 3 cycli axitinib: lichte toename, maar stabiel volgens RECIST
11-2017: Radiotherapie op botmetastase sternum 1x 8Gy
11-2017: Progressieve ziekte onder Axitinib; start Nivolumab. Tevens opstart Xgeva.
12-2017: Radiotherapie op wervel D9 1 x 8 Gy
01-2018: CT na 3 maanden nivolumab: beperkte toename van abdominale adenopathieën, stabiele levermetastasen. Nivolumab verder gezien mogelijkheid van pseudoprogressie
03-2018: CT na 5 maanden nivolumab: afname adenopathieën, tumorale implanten linker crus diafragmaticus en posterieur van de linker m. psoas, levermetastasen. Botmetastasen onveranderd.
08-2018: CT na 10 maanden nivolumab: verdere afname (Partiële response RECIST -65%)
09-2018: Stop Xgeva wegens wortelextractie
11-2018: CT na 12 maanden nivolumab: verdere afname (Partiële response RECIST -74%)
02-2019: behouden partiële respons
05-2019: behouden partiële respons, verlenging toedieningsinterval naar 6 weken.
09-2019: CT na 22 maanden nivolumab: verdere afname. Onderbreking nivolumab wegens bulleuse letsels handen

QUICK OR SLOW RESPONSES?

MAN 88Y





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PSEUDOPROGRESSION

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08/2012: Male patient 67Y
Diagnosis metastatic ccRCC

01/2016: progression bone and adrenal metastases) after sunitinib, everolimus and axitinib

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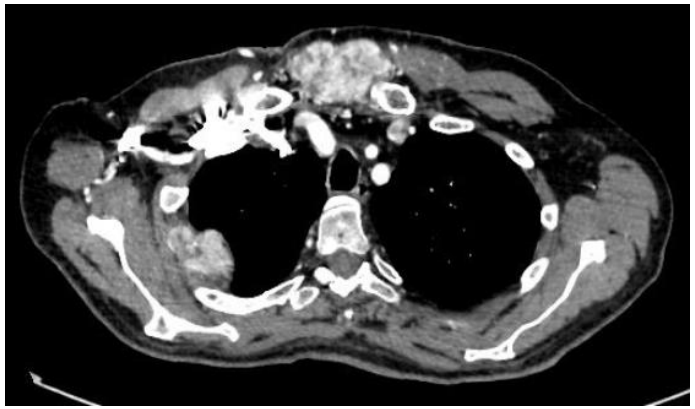
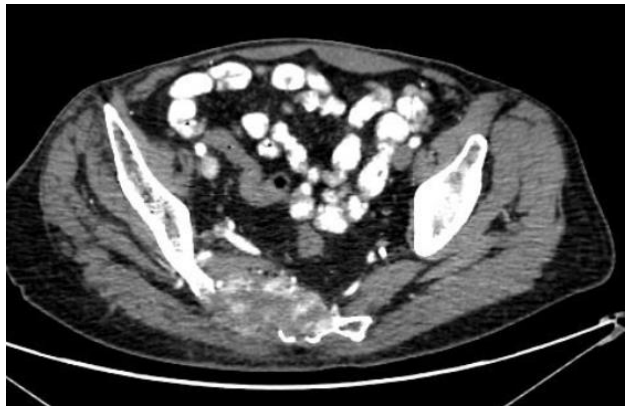
03/2016: no AE, less pain, but ECOG, QOL and weight decreased





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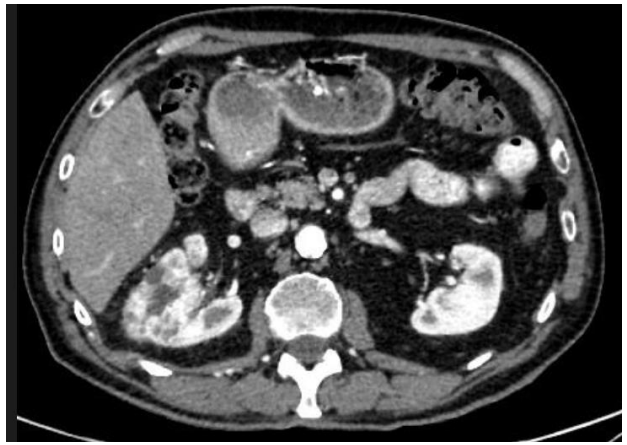

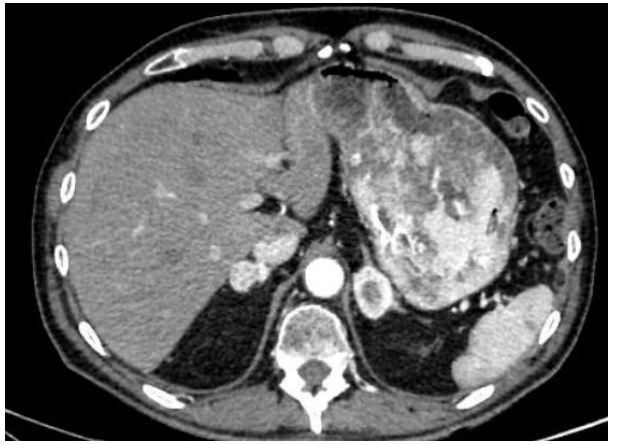

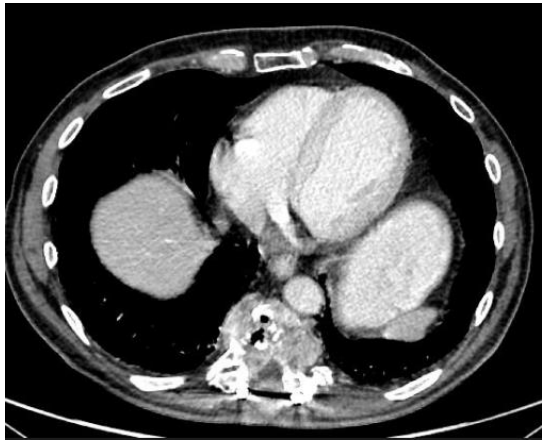

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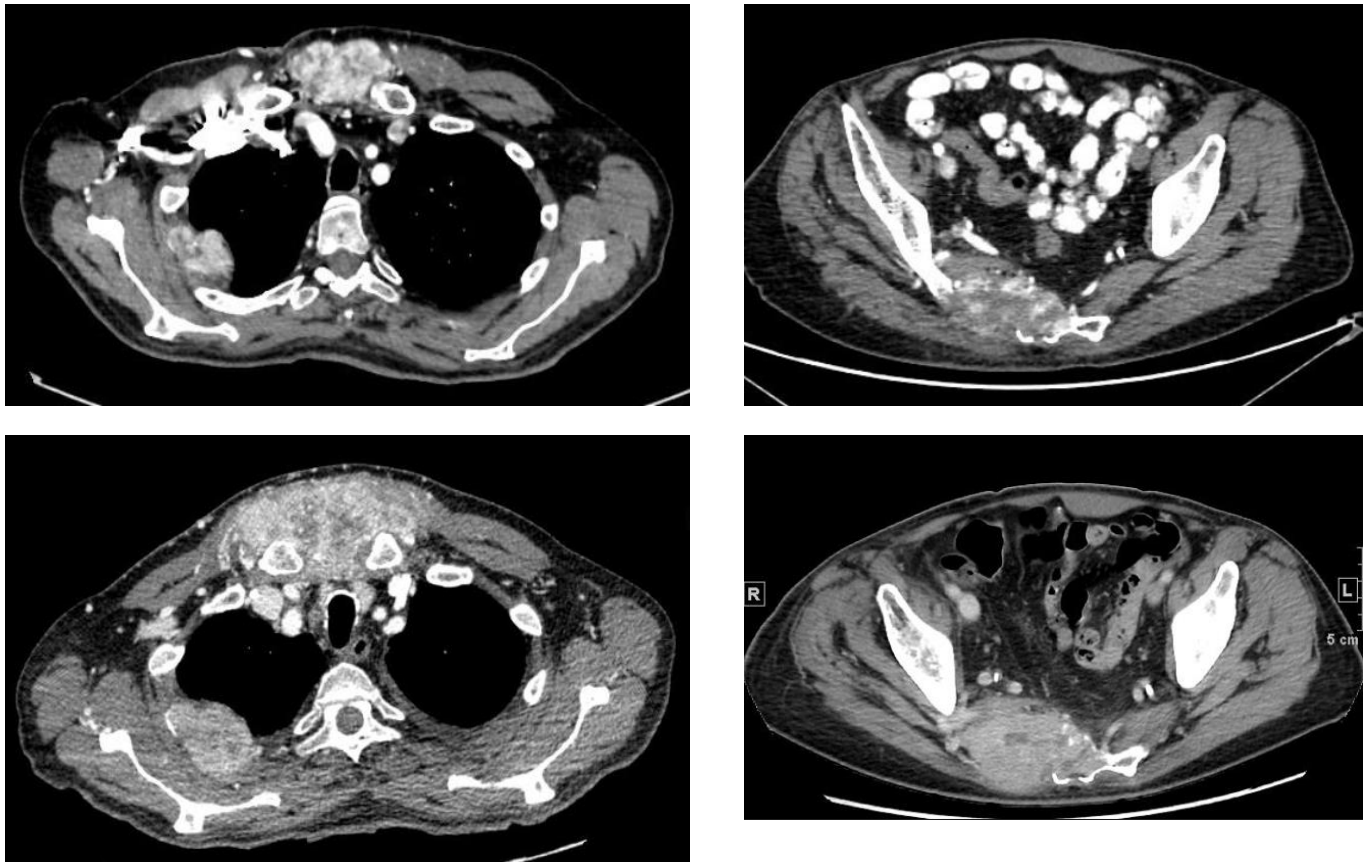
Sternal metastasis clinically evaluable

Stop nivolumab, BSC



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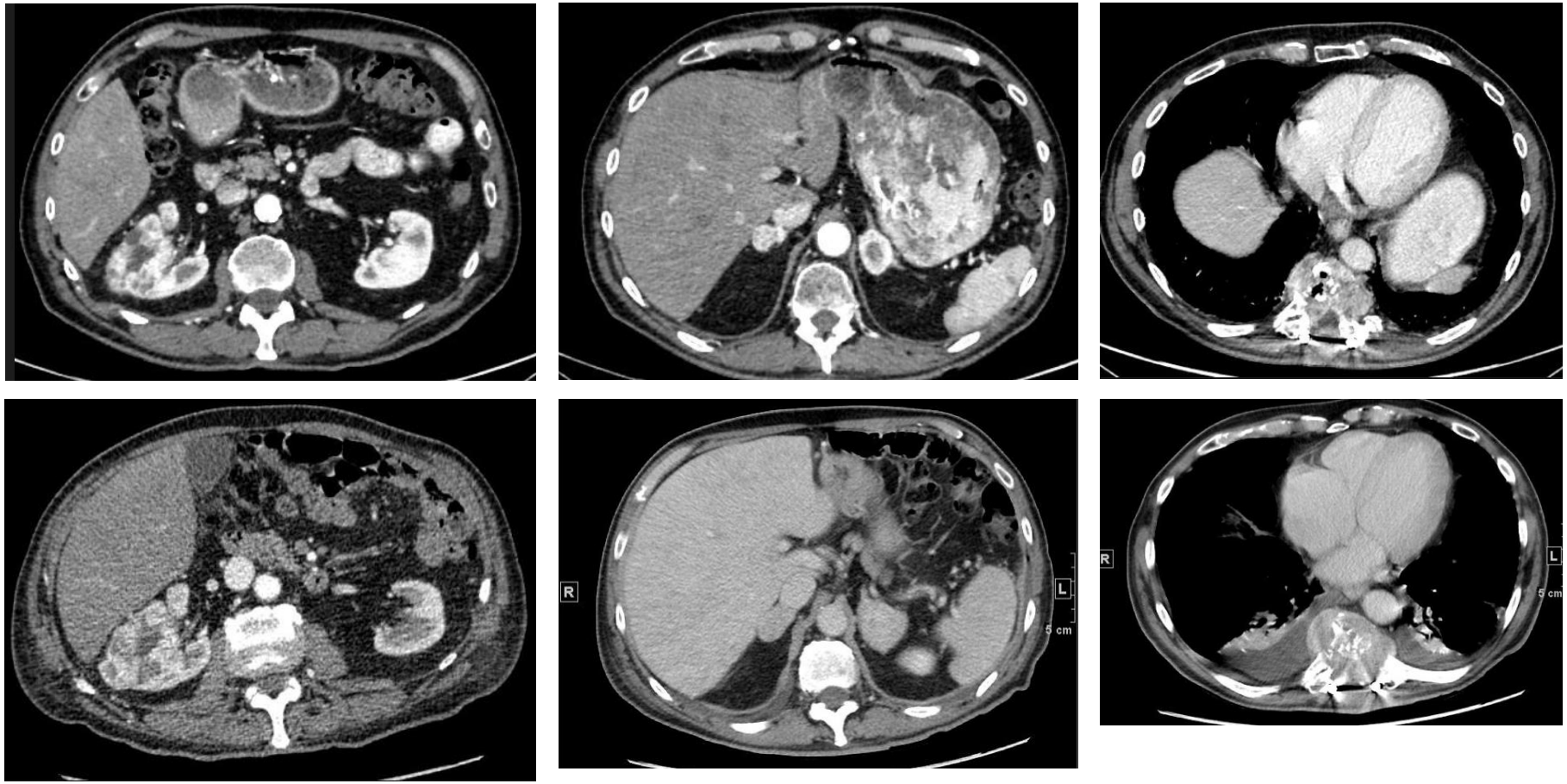

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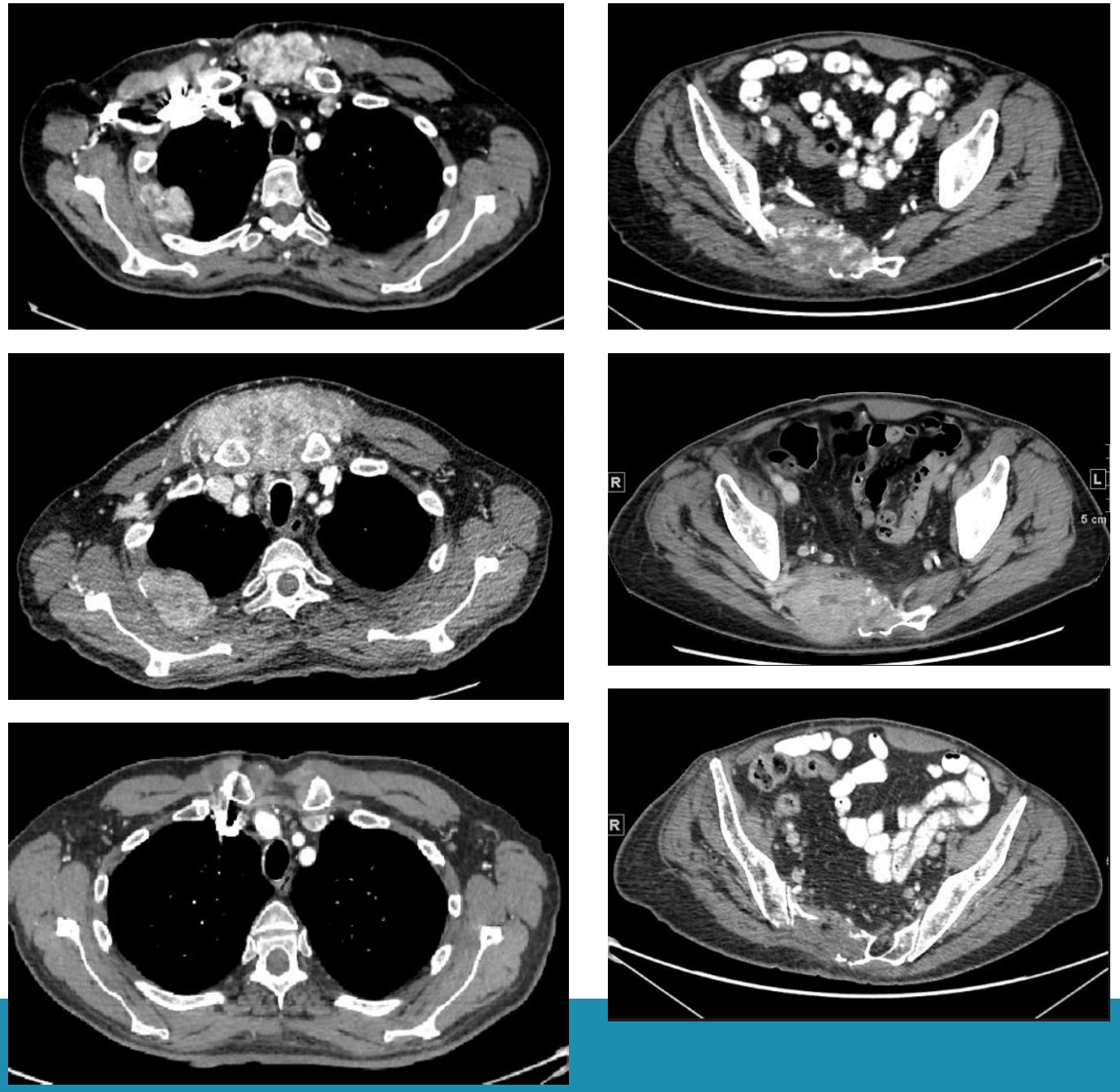
10/2016: weight, QOL and pain spontaneously improved



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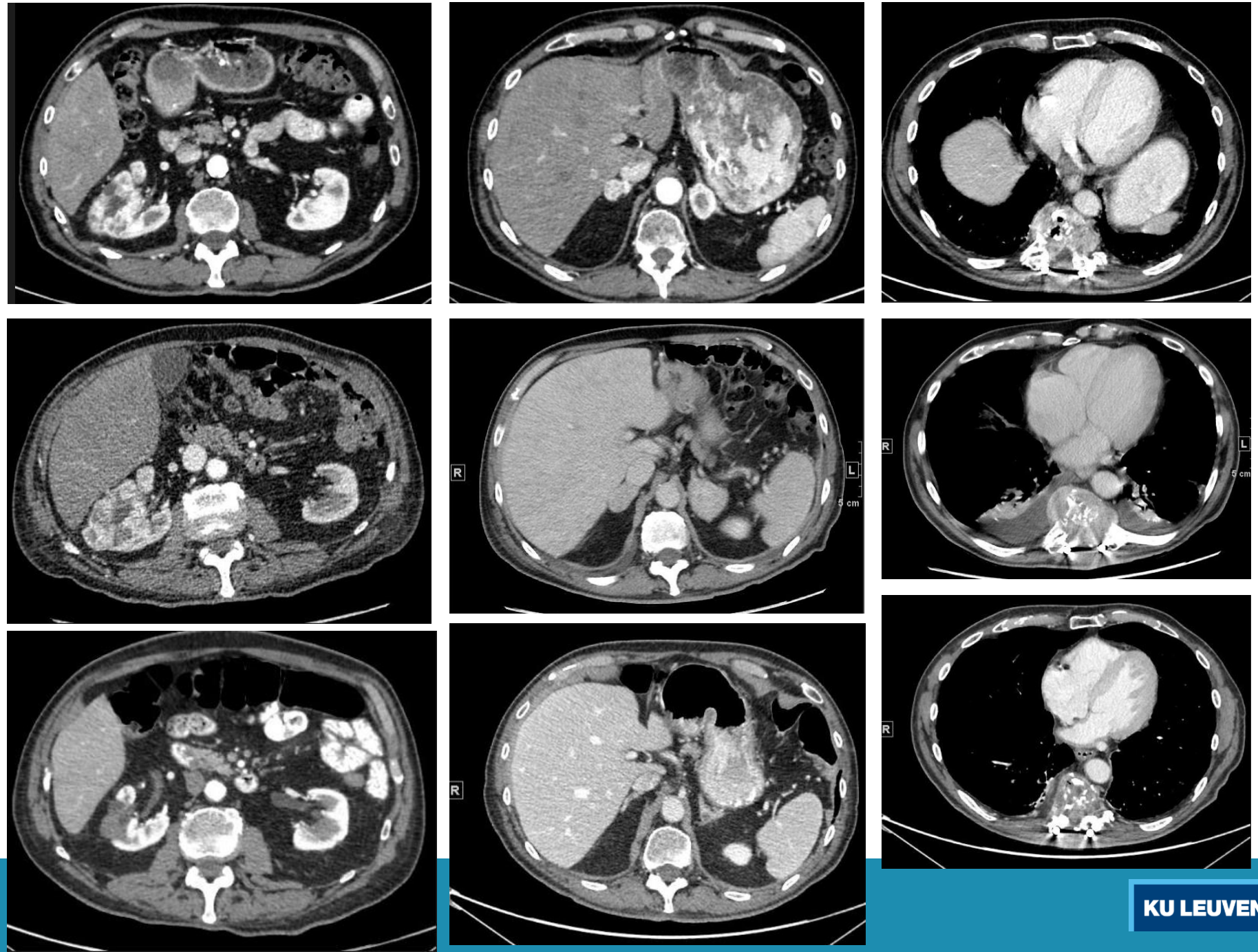

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