

# Renal Cell Cancer: Present and Future

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[HKIOF May 2017]

# Disclosures

- Compensated advisory boards
  - Novartis, Roche, BMS, Pfizer, Exelixis, Ipsen, Acceleron
- Speaker honoraria
  - Novartis, Bayer, BMS, Pfizer, Ipsen

# Renal cell carcinoma



**Accounts for 3.7% of all cancer diagnoses and 2.4% of all cancer deaths worldwide**

- Seventh most common cancer in men
- Tenth most common cancer in women<sup>1</sup>



**Incidence highest in the USA, Western Europe and other developed countries<sup>2</sup>**



**Median age at diagnosis is 64 years for kidney and renal pelvis cancer<sup>3</sup>**



**Cancer stage at diagnosis determines treatment options and has a strong influence on the length of survival**

- 5-year relative survival rate: localised = 93% vs metastatic = 12%<sup>3</sup>



**Median OS ~12 months in metastatic RCC before targeted agents<sup>4</sup>**

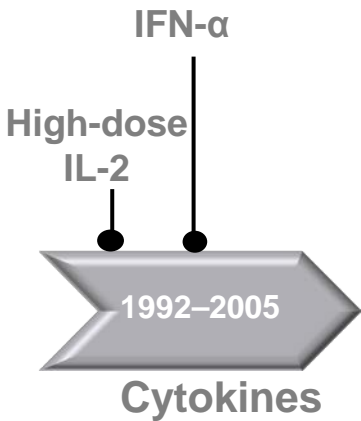
**Median OS ~30 months in most recent studies, highly dependent on prognostic factors<sup>5</sup>**

1. Siegel et al. CA Cancer J Clin 2016; 2. Ferlay et al. Int J Cancer 2015

3. SEER Stat Fact Sheets: Kidney and Renal Pelvis Cancer

4. Soerensen et al. Eur J Cancer 2014; 5. Motzer et al. N Engl J Med 2013

# The evolving treatment landscape of mRCC

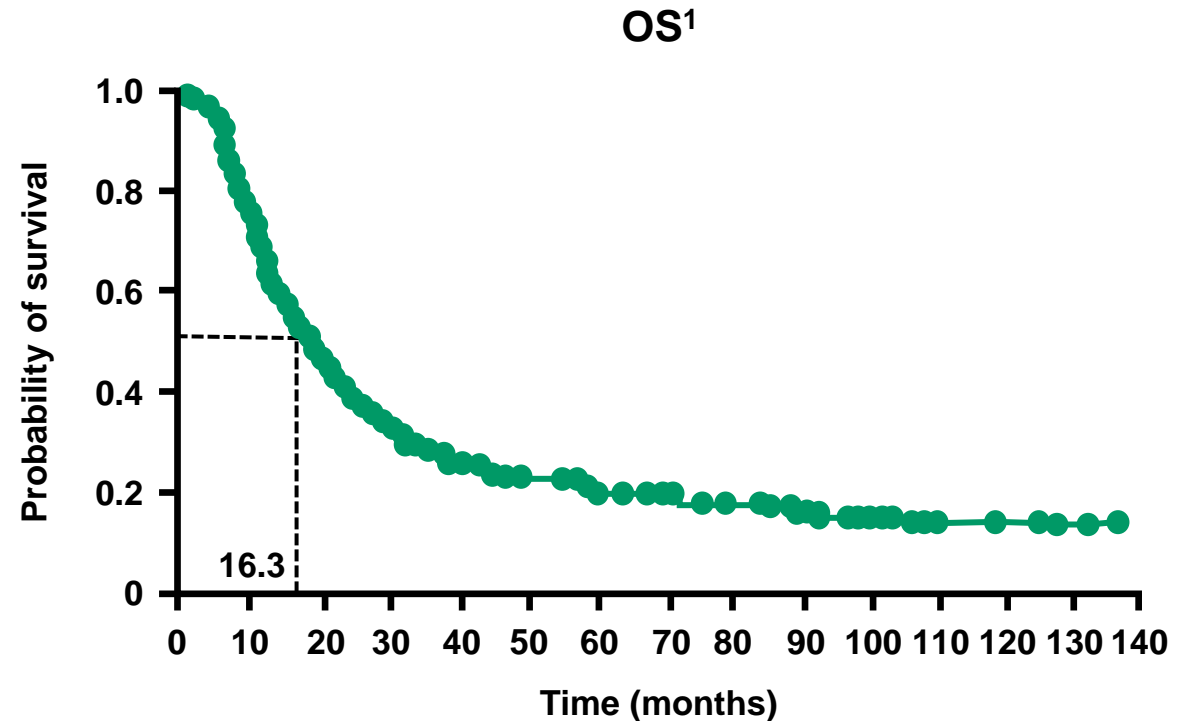
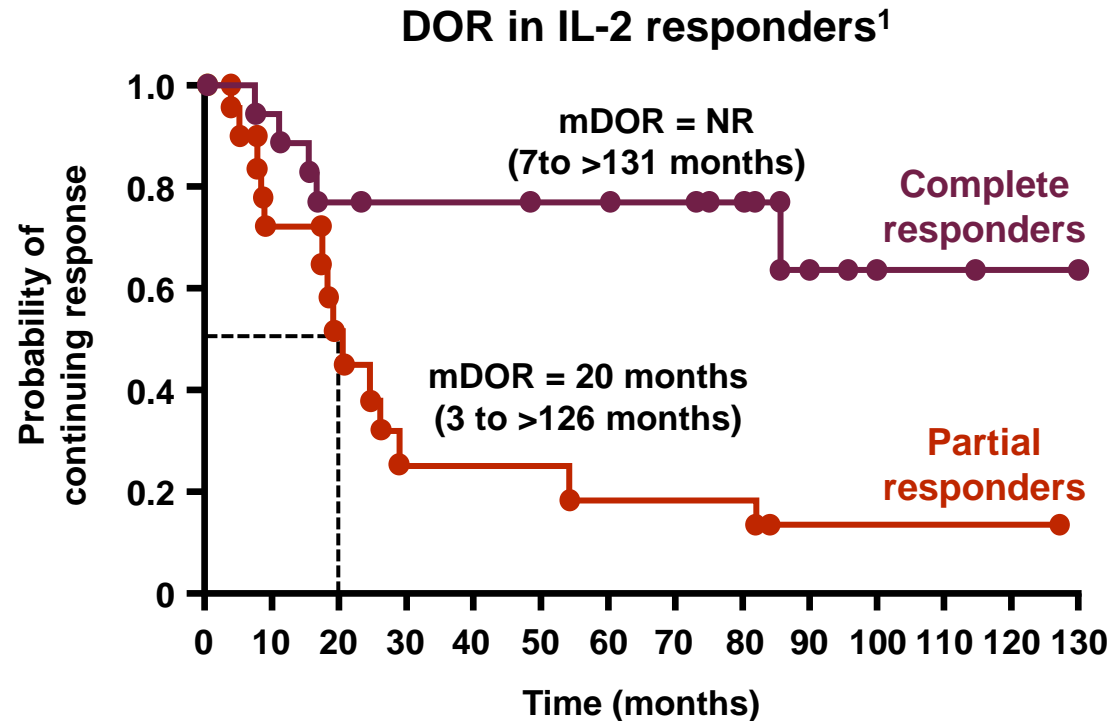


aRCC, advanced renal cell carcinoma; FDA, US Food and Drug Administration; IFN- $\alpha$ , interferon  $\alpha$ ; IL-2, interleukin-2; mTOR, mammalian target of rapamycin; VEGF, vascular endothelial growth factor.

\*Approved by the FDA in RCC.

1. Escudier B, et al. *N Engl J Med.* 2007;356:125-134;
2. Motzer RJ, et al. *N Engl J Med.* 2007;356:115-124;
3. Hudes G, et al. *N Engl J Med.* 2007;356:2271-2281;
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10. Choueiri TK, et al. *N Engl J Med.* 2015;373(19):1814-23;
11. Motzer RJ, et al. *Lancet Oncol.* 2015;16(15):1473-1482.

# Cytokines have played an important role in mRCC for >20 years



IL-2 associated with durable responses: ORR=15% (CR=7% and PR=8%)<sup>1</sup>

10–20% of patients alive after 5–10 years of treatment<sup>1</sup>

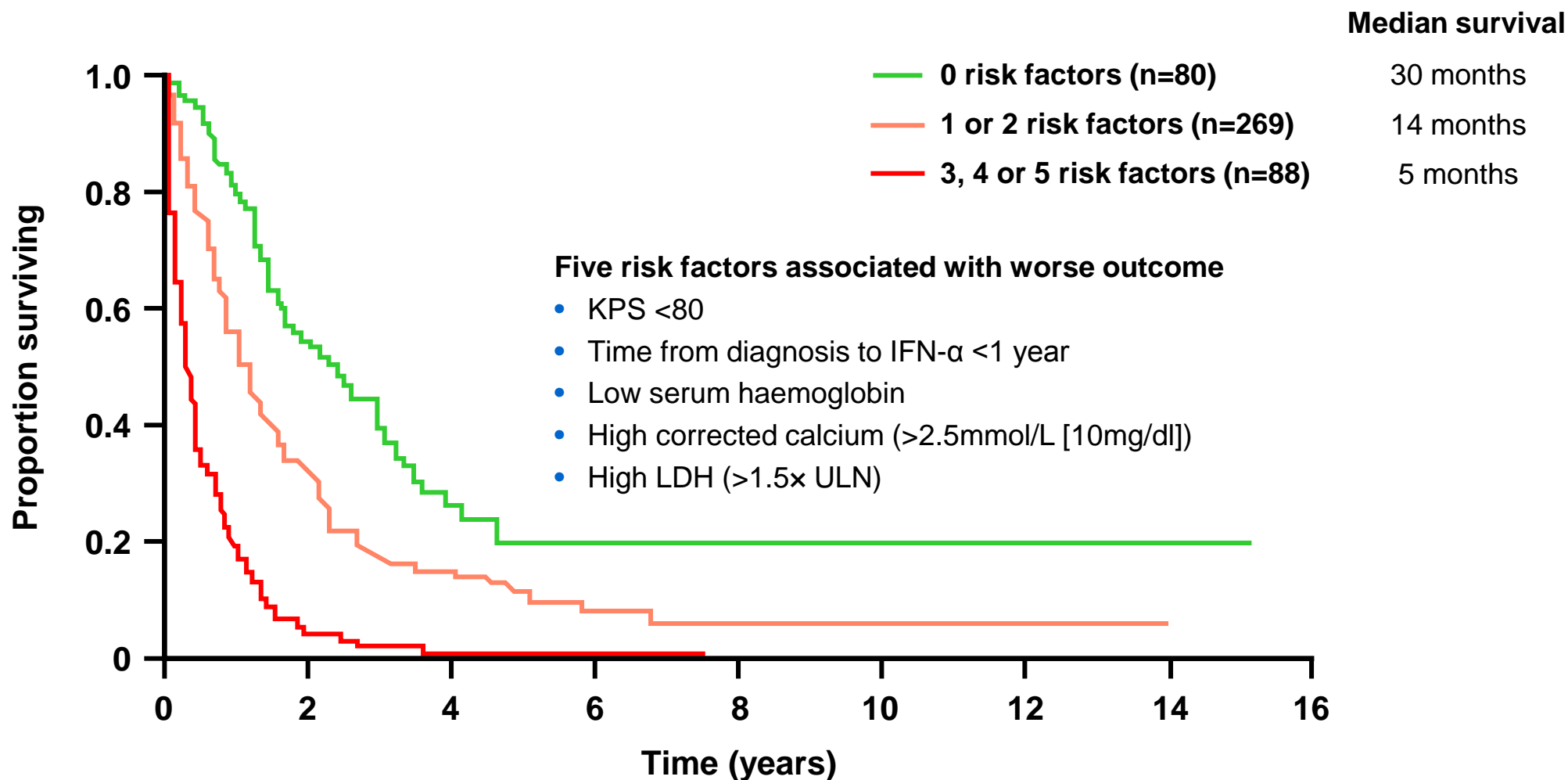
BUT

associated with substantial toxicity<sup>2</sup>

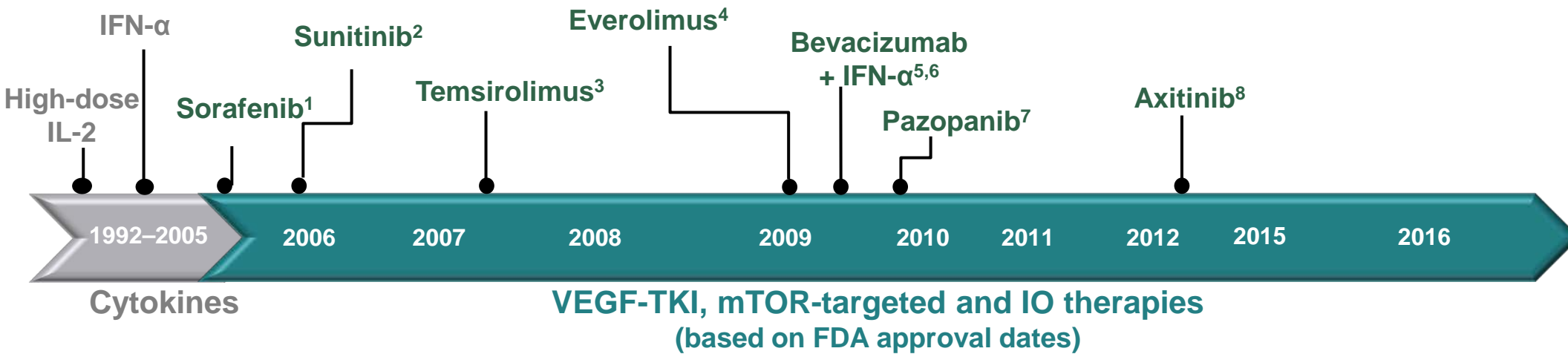
1. Fisher et al. Cancer J Sci Am 2000

2. McDermott et al. J Clin Oncol 2005

# Survival with IFN- $\alpha$ in mRCC (by MSKCC risk)



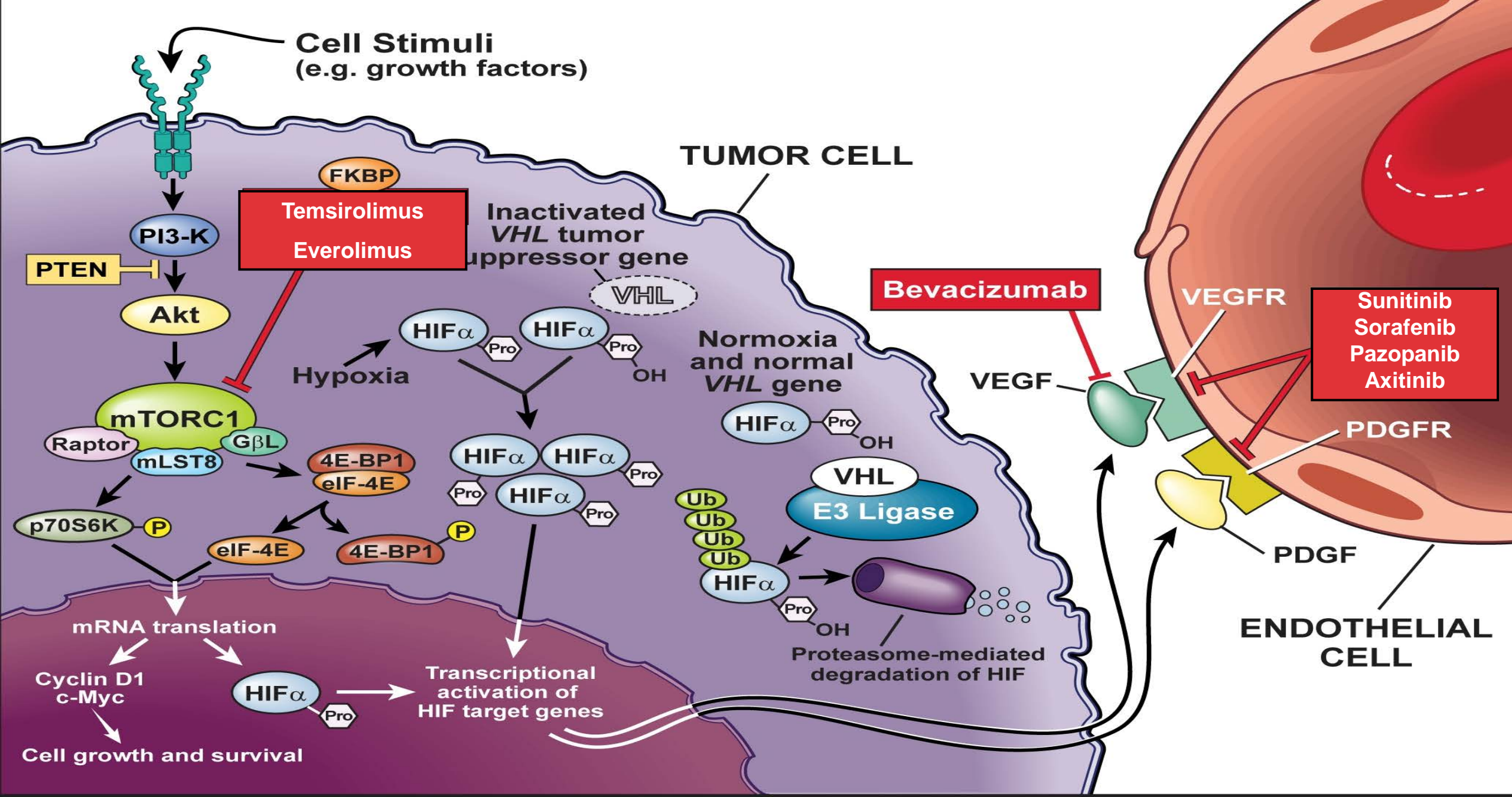
# The evolving treatment landscape of mRCC



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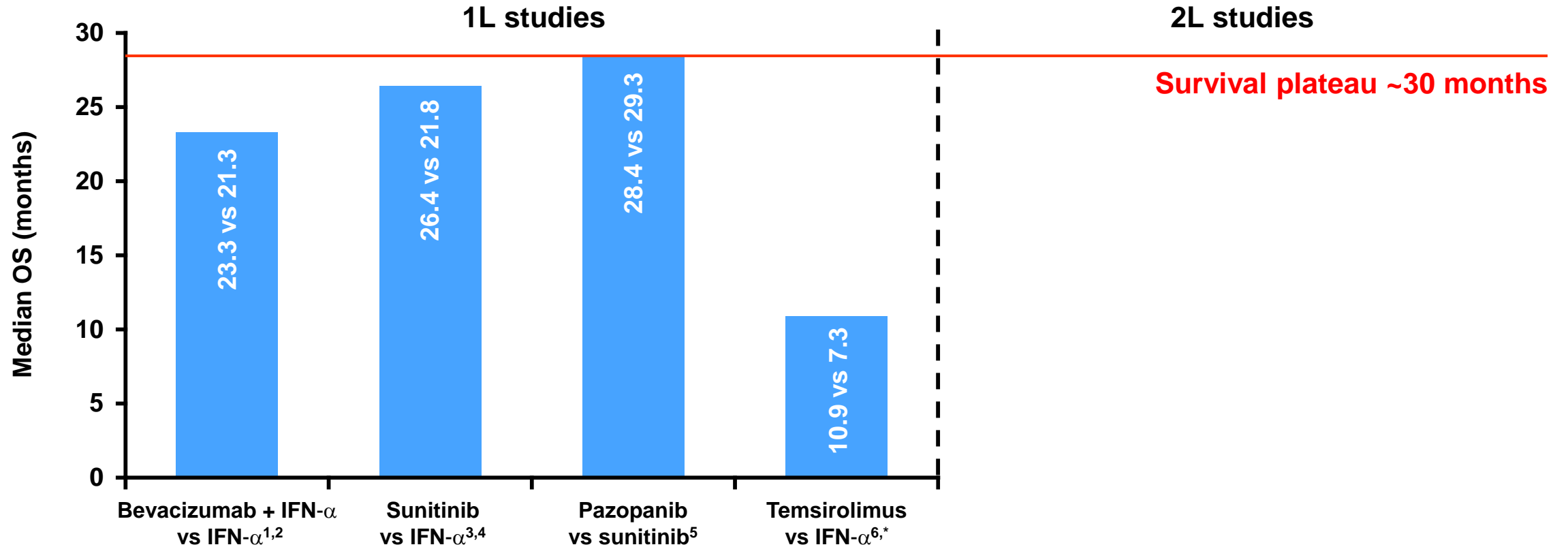
1. Escudier B, et al. *N Engl J Med.* 2007;356:125-134; 2. Motzer RJ, et al. *N Engl J Med.* 2007;356:115-124; 3. Hudes G, et al. *N Engl J Med.* 2007;356:2271-2281; 4. Motzer RJ, et al. *Lancet.* 2008;372:449-456; 5. Escudier B, et al. *Lancet.* 2007;370:2103-2111; 6. Rini BI, et al. *J Clin Oncol.* 2008;26:5422-5428; 7. Sternberg CN, et al. *J Clin Oncol.* 2010;28:1061-1068; 8. Rini BI, et al. *Lancet.* 2011;378:1931-1939; 9. Motzer RJ, et al. *N Engl J Med.* 2015;373(19):1803-1813; 10. Choueiri TK, et al. *N Engl J Med.* 2015;373(19):1814-23; 11. Motzer RJ, et al. *Lancet Oncol.* 2015;16(15):1473-1482.





# ...improving OS outcomes

Selected phase III studies of targeted therapies in mRCC

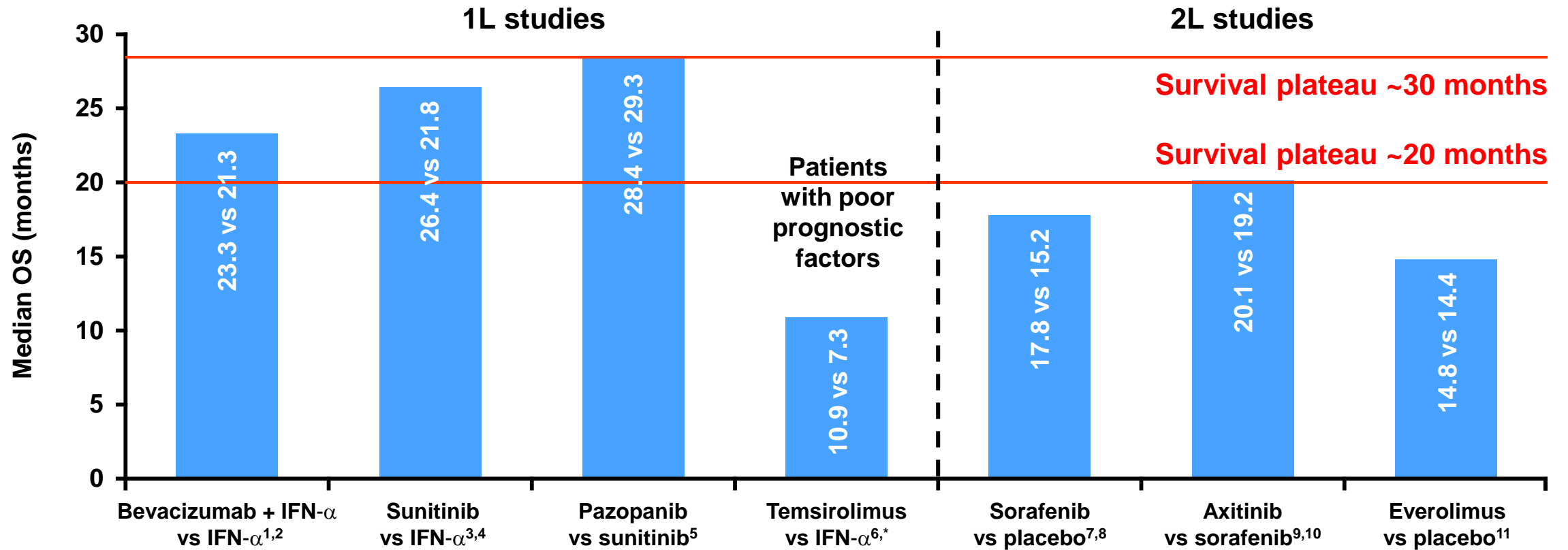


1. Escudier et al. Lancet 2007; 2. Escudier et al. J Clin Oncol 2010; 3. Motzer et al. N Engl J Med 2007; 4. Motzer et al. J Clin Oncol 2009  
5. Motzer et al. N Engl J Med 2013; 6. Hudes et al. N Engl J Med 2007; 7. Escudier et al. N Engl J Med 2007  
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\*Patients with poor prognostic factors

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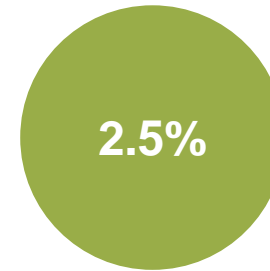
# Additional unmet needs of targeted therapies in mRCC

Up to 26% of patients refractory to 1L anti-angiogenic agents<sup>1</sup>

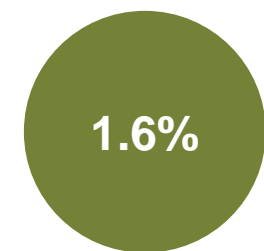


Complete responses to targeted therapies are rare<sup>2</sup>

*Bevacizumab + IFN- $\alpha$*

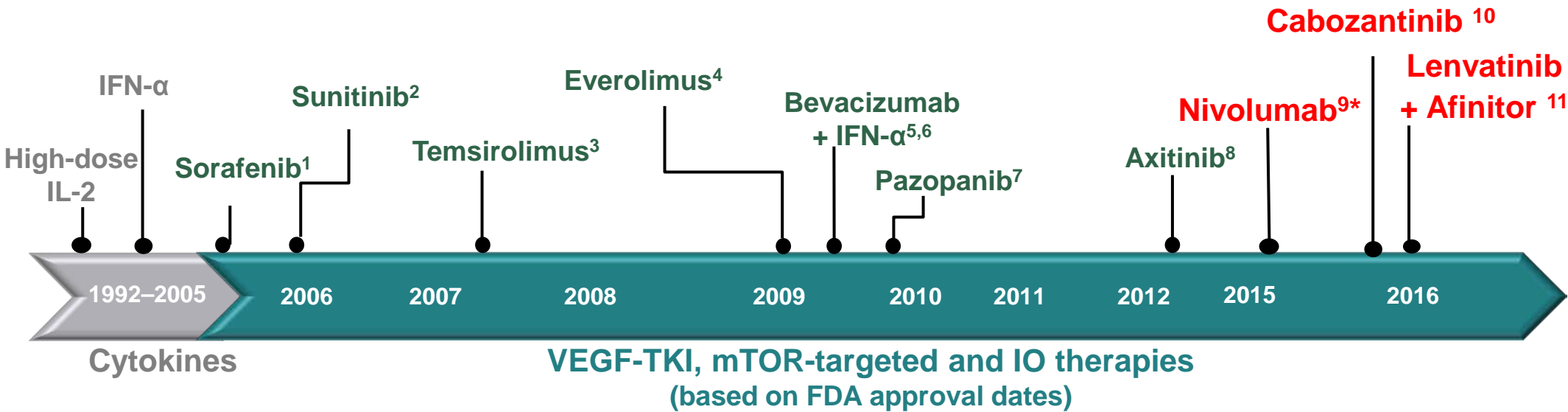


*TKIs*



Incidence of complete response

# The evolving treatment landscape of mRCC

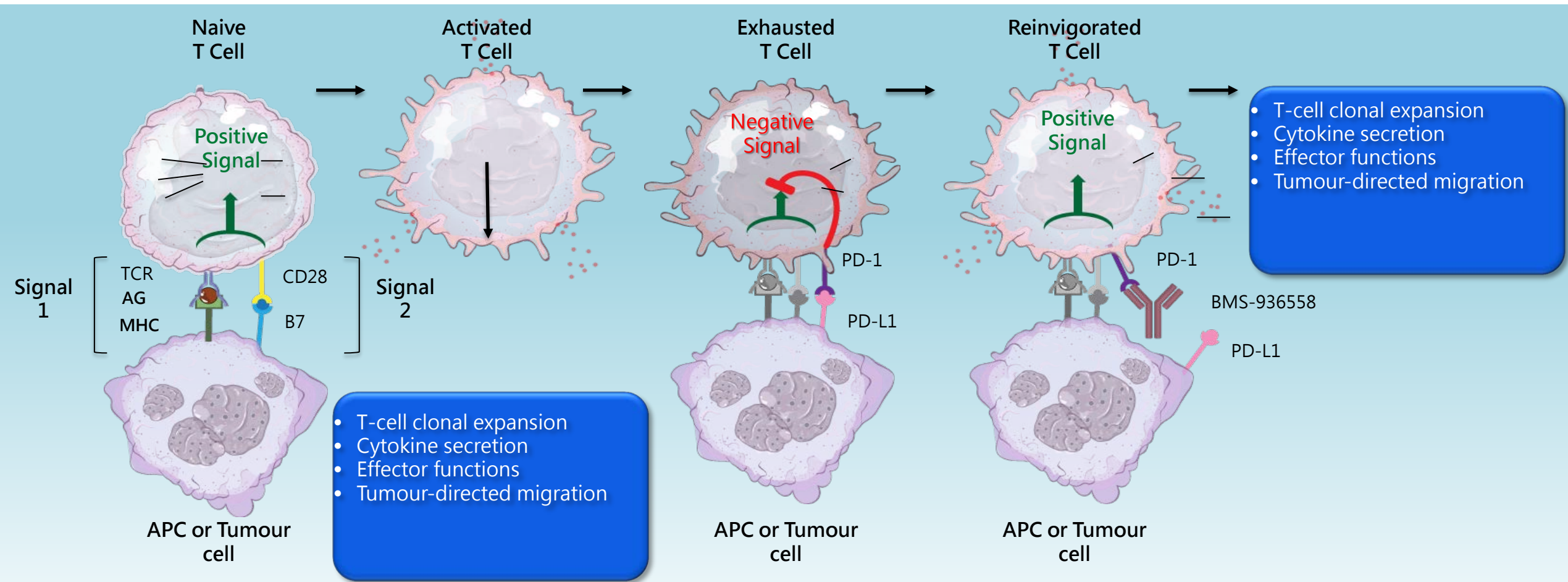


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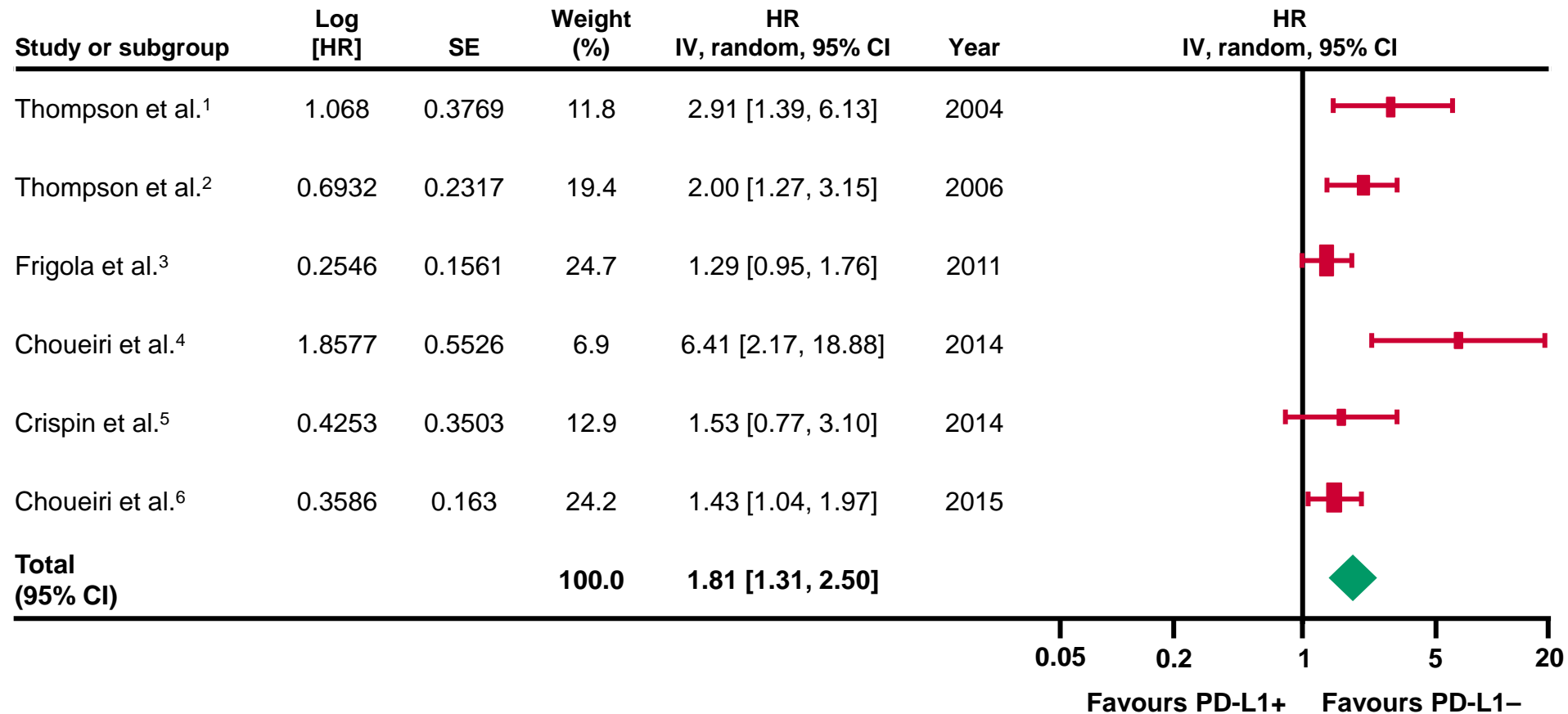
# Understanding immune resistance has been key



AG, antigen; APC, antigen presenting cell; MHC, major histocompatibility complex; PD-1, programmed death-1; TCR, T-cell receptor.

Adapted from Brahmer JR et al. *J Clin Oncol.* 2010;28:3167-3175 and Keir ME et al. *Annu Rev Immunol.* 2008;26:677-704.

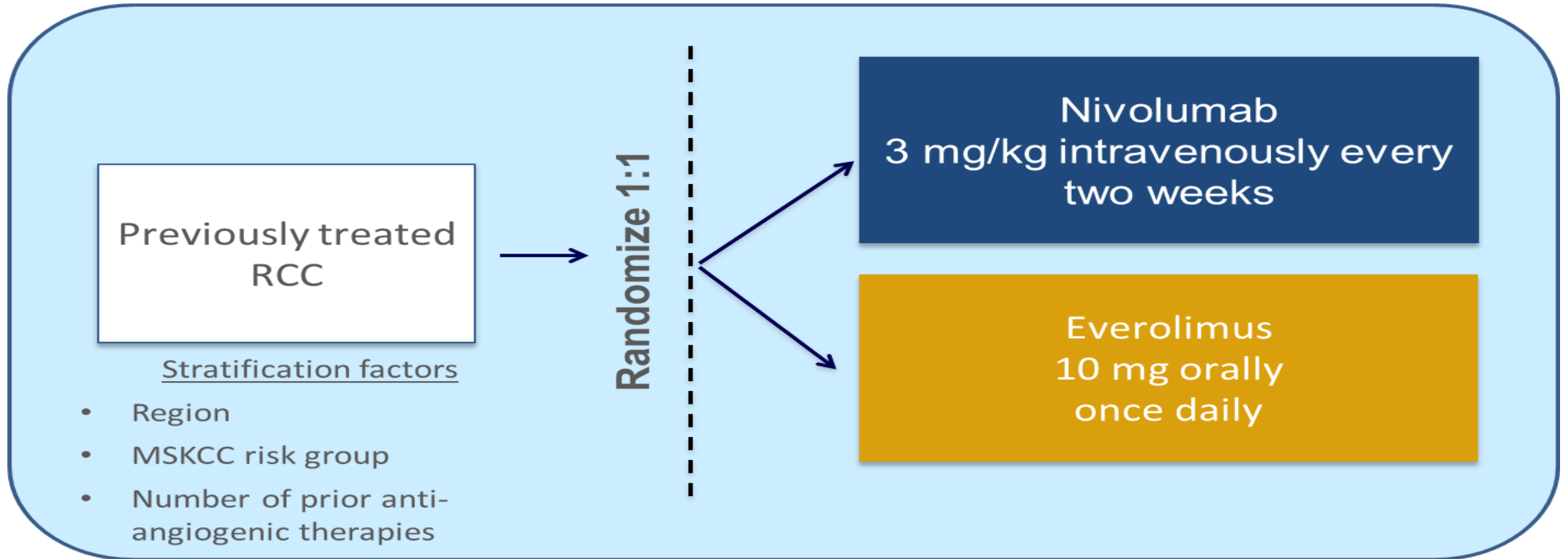
# PD-L1 expression is a negative prognostic factor in RCC



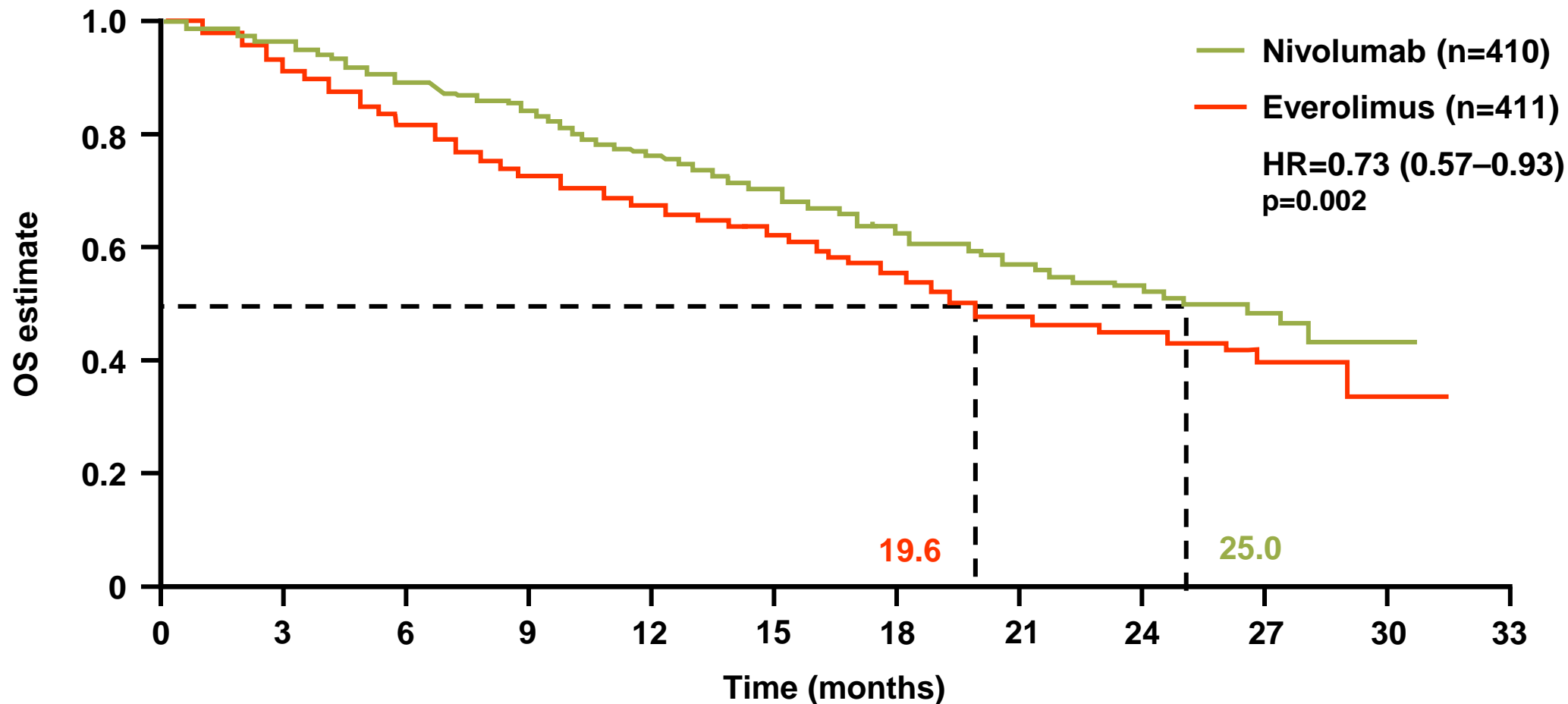
Heterogeneity: Tau<sup>2</sup>=0.08; Chi<sup>2</sup>=12.14, df=5 (p=0.03); I<sup>2</sup>=59%  
 Test for overall effect: Z=3.63 (p=0.0003)

1. Thompson et al. Proc Natl Acad Sci USA 2004; 2. Thompson et al. Cancer Res 2006; 3. Frigola et al. Clin Cancer Res 2011  
 4. Choueiri et al. Ann Oncol 2014; 5. Crispin et al. J Clin Oncol 2014; 6. Choueiri et al. Clin Cancer Res 2015  
 Table adapted from Iacovelli et al. Target Oncol 2015

# CheckMate 025 phase III

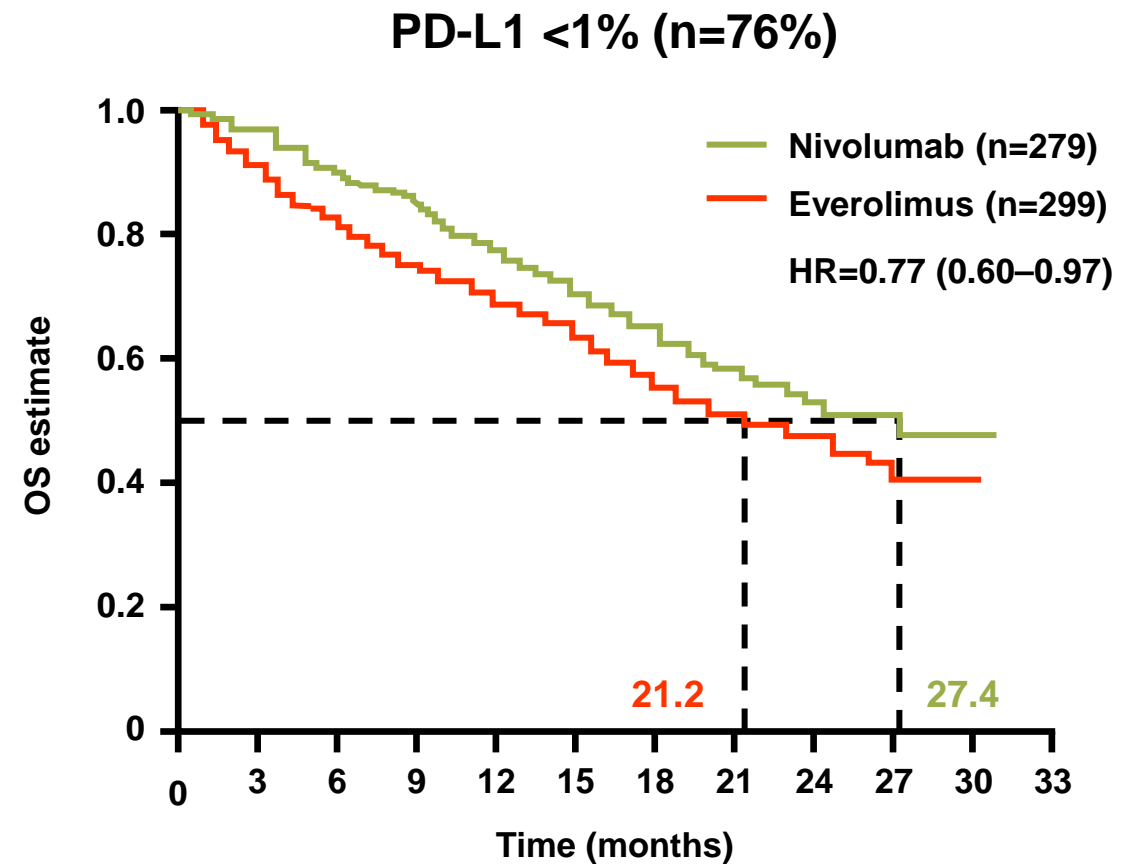
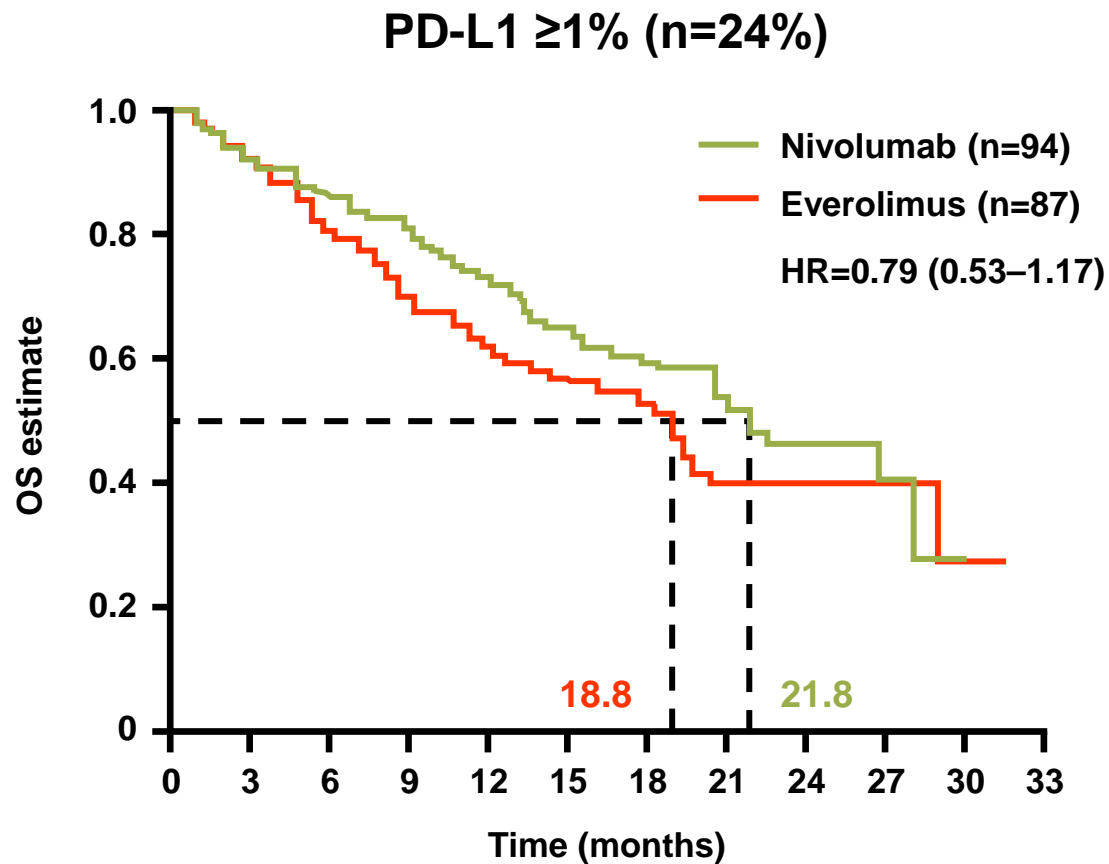


# CheckMate 025 (phase III): nivolumab associated with longer OS vs everolimus in previously treated mRCC





# CheckMate 025: OS benefit of nivolumab irrespective of PD-L1 expression



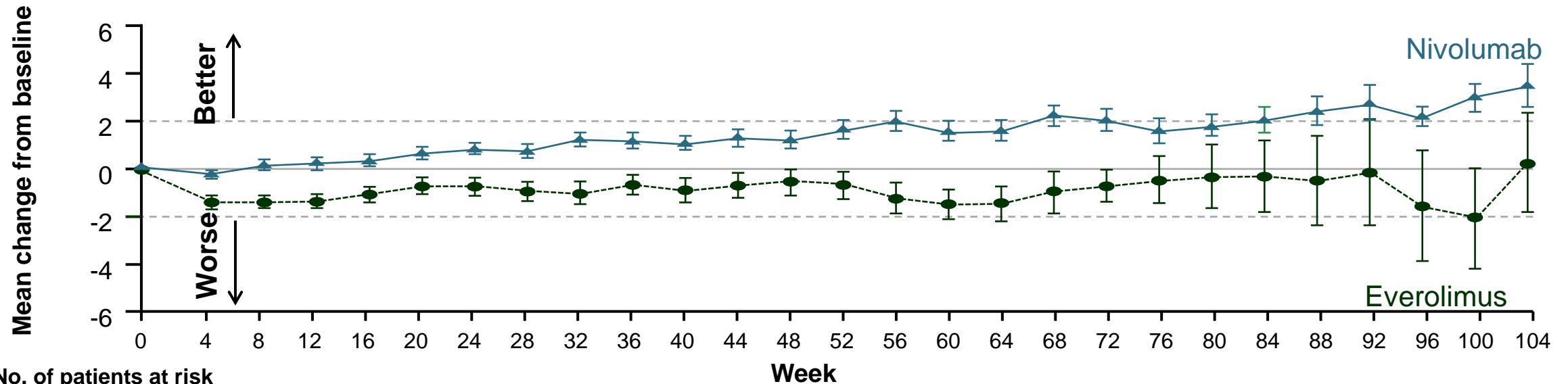
# CheckMate 025: response outcomes improved with nivolumab

	Nivolumab (n=410)	Everolimus (n=411)
ORR, %	25	5
Odds ratio (p-value)	5.98 (p<0.0001)	
Best overall response, %		
CR	<b>1</b>	<b>1</b>
PR	<b>24</b>	<b>5</b>
SD	<b>34</b>	<b>55</b>
PD	35	28
Not evaluated	6	12
Median time to response (range), months	3.5 (1.4–24.8)	3.7 (1.5–11.2)
Median DOR (range, months)	12.0 (0–27.6)	12.0 (0–22.2)
Ongoing response, %	48	45

\*For patients without progression or death, duration of response is defined as the time from the first response (CR/PR) date to the date of censoring

# QoL in CheckMate-025

Mean change from baseline in QoL scores (FKSI-DRS) in the nivolumab group increased over time and differed significantly from the everolimus group at each assessment through week 104 ( $P < .05$ )<sup>1</sup>



## No. of patients at risk

	0	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72	76	80	84	88	92	96	100	104
Nivolumab	362	334	302	267	236	208	186	164	159	144	132	119	112	97	90	89	81	72	63	59	53	44	43	31	30	26	20
Everolimus	344	316	270	219	191	157	143	122	102	97	87	74	73	63	58	49	44	35	30	28	24	21	15	12	12	9	9

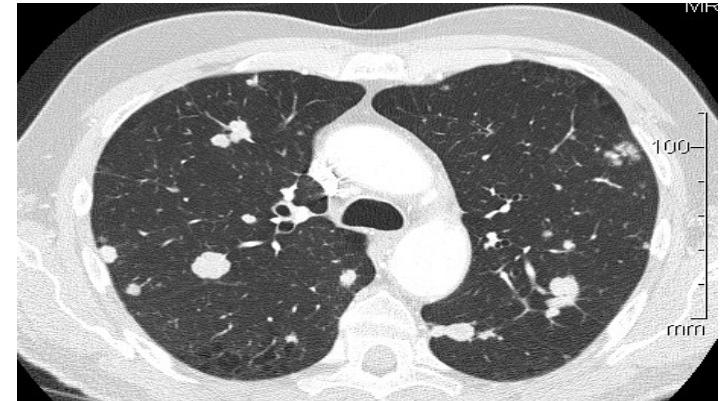
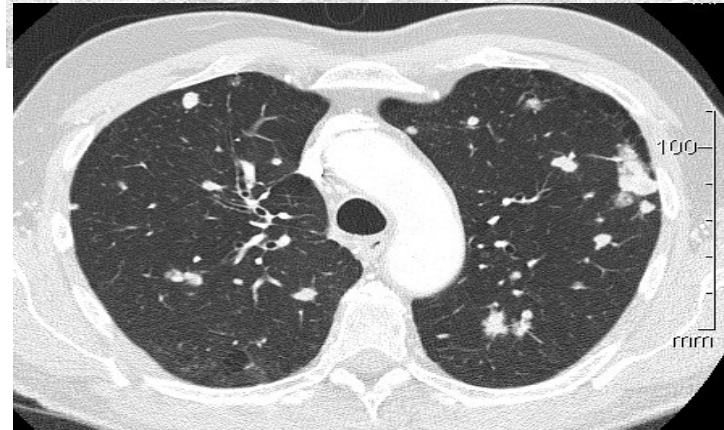
Questionnaire completion rate:  $\geq 80\%$  during the first year of follow-up.

Reprinted with permission from Sharma P, et al. Oral presentation at 2015 ECCO/ESMO; September 25-29, 2015; Vienna, Austria, Abstract 3LBA.

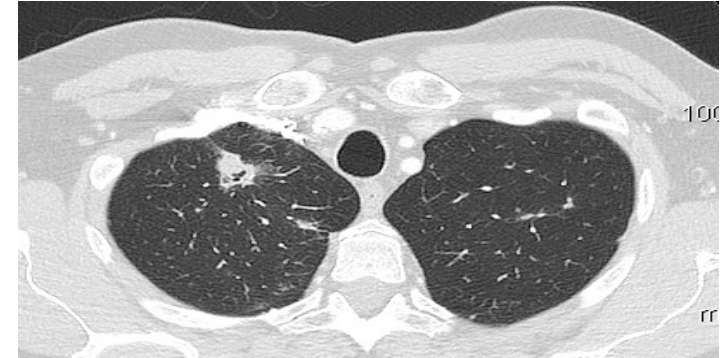
1. Motzer RJ et al. *N Engl J Med*. 2015;373(19):1803-1813. Supplementary appendix available online: <http://www.nejm.org/doi/full/10.1056/NEJMoa1510665>.

# Case 1: 4th line therapy, still in CR in May 2017

30 Oct 2015



13 Jan 2016



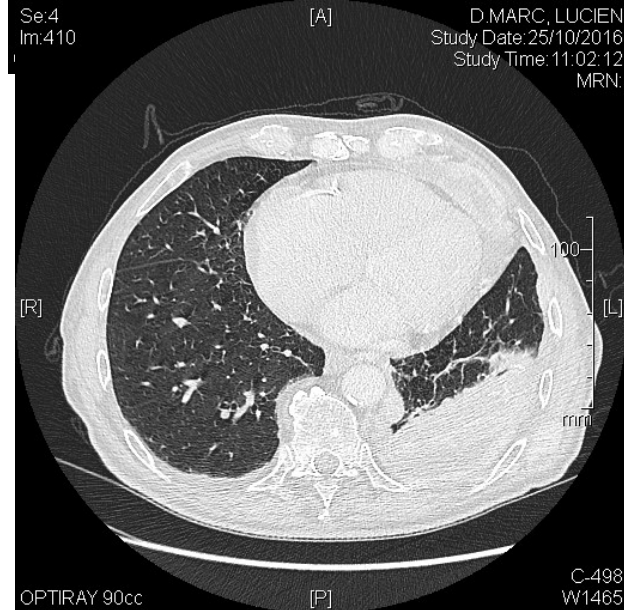
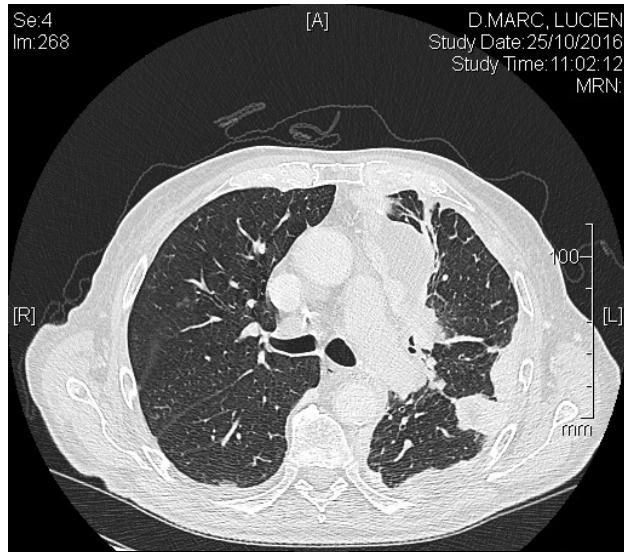
This patient improved after the first infusion

Rapid PR

Now in CR after 19 months

# Case 2: 2nd line therapy, PR ongoing for 12 months

Baseline

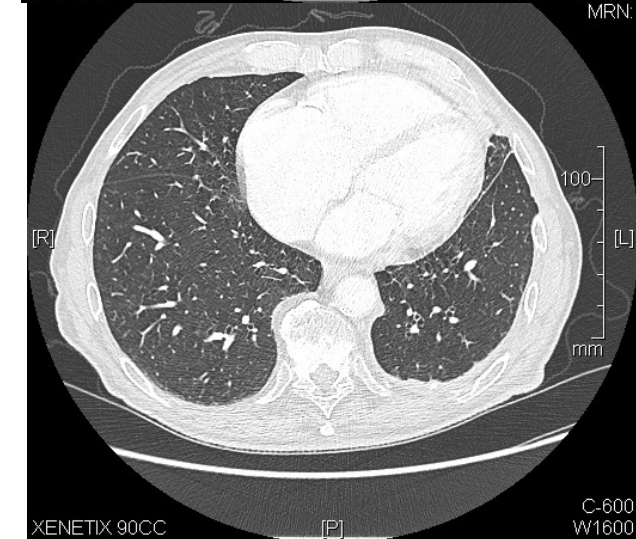
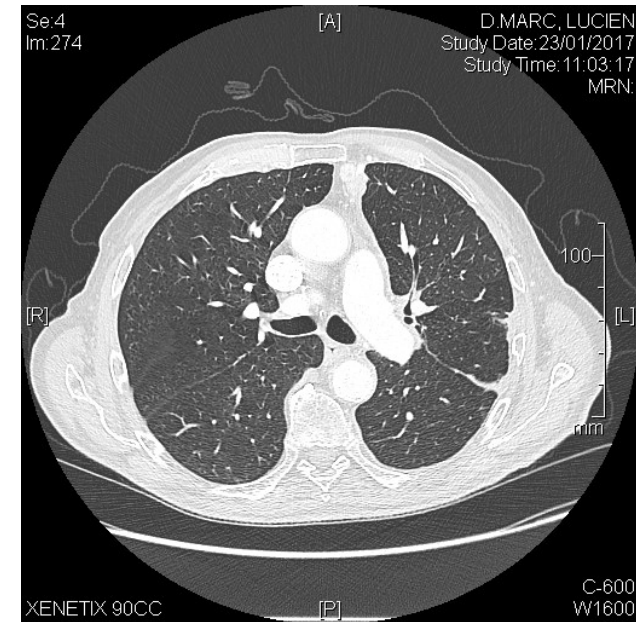


This patient develop PPR

He received steroids

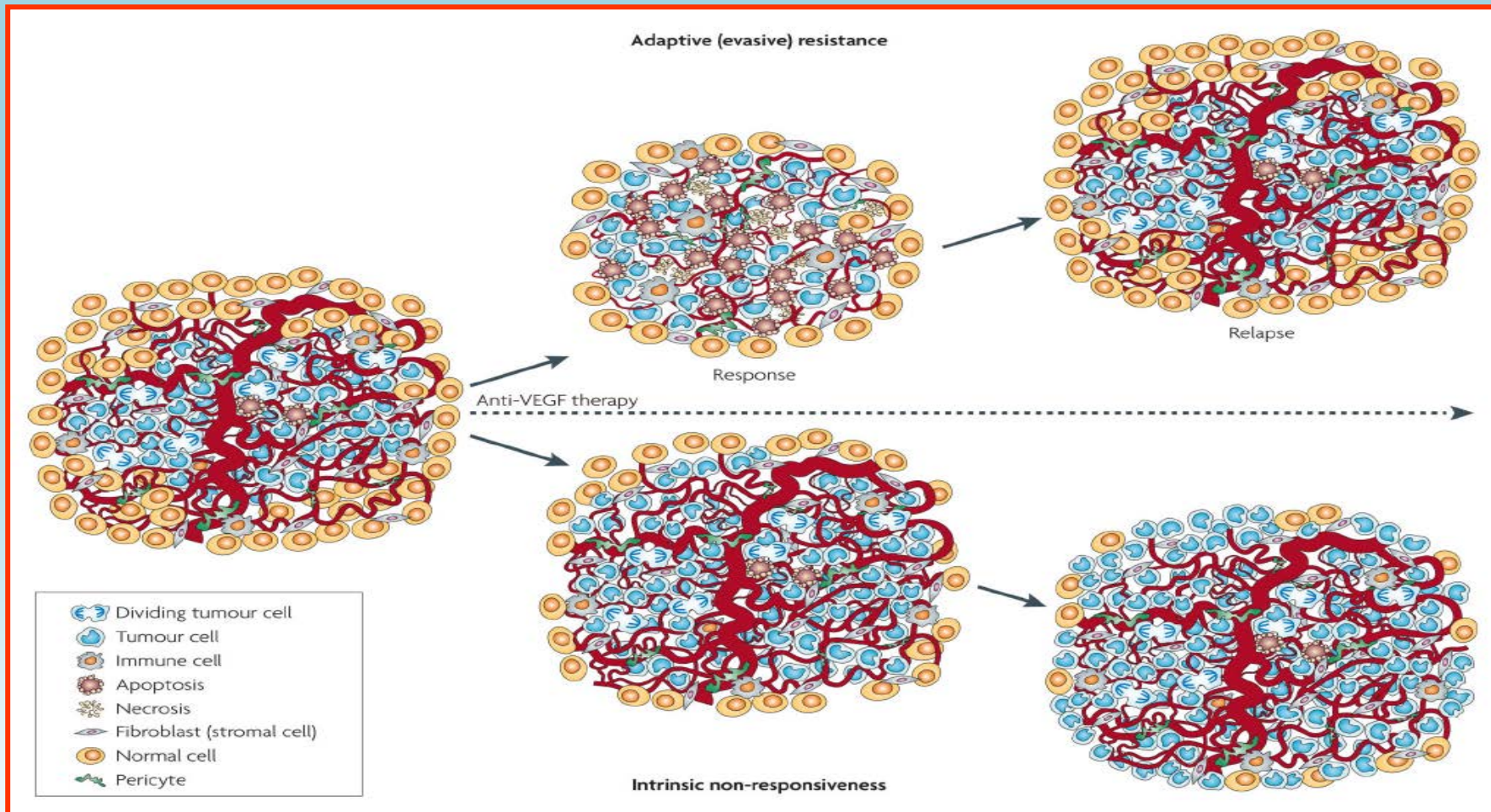
Still on Nivolumab with ongoing response

2 months





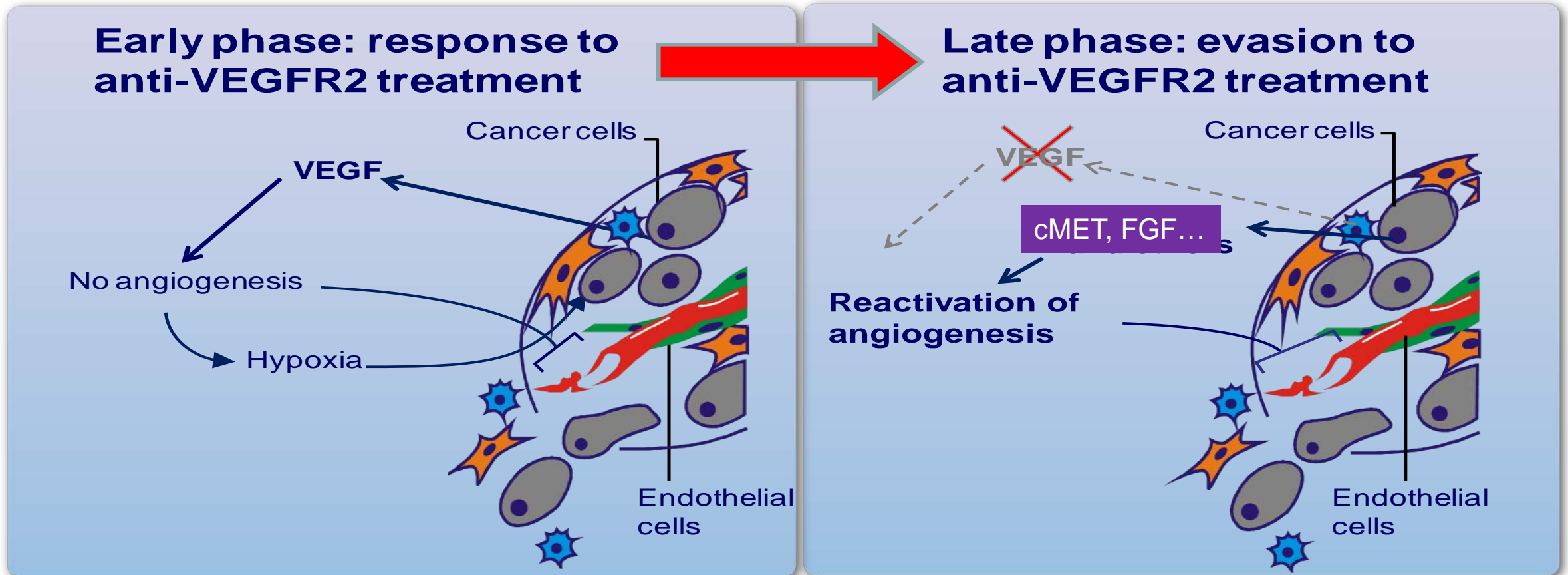
# Understanding escape mechanisms to VEGF targeted agents has also been very important



**Adaptive resistance:**  
VEGF-targeted agents fail to produce enduring clinical responses in most patients

**Intrinsic resistance:**  
No predictive biomarkers available to date

# Several pathways are involved



FGF2 is expressed by numerous tumor types and exerts its activity by interacting with TK receptors, heparan-sulfate proteoglycans, and integrins expressed on the endothelial cell surface

# Lenvatinib Study Design

## Key eligibility criteria:

- Advanced or metastatic RCC
- Measurable disease
- Progression on/after 1 prior VEGF-targeted therapy
- Progression within 9 mos of stopping prior treatment
- ECOG PS  $\leq$  1

R  
A  
N  
D  
O  
M  
I  
Z  
E

Lenvatinib  
18 mg PO qd  
+  
Everolimus  
5 mg PO qd

Lenvatinib  
24 mg PO qd

Everolimus  
10 mg PO qd

## Patients were treated until:

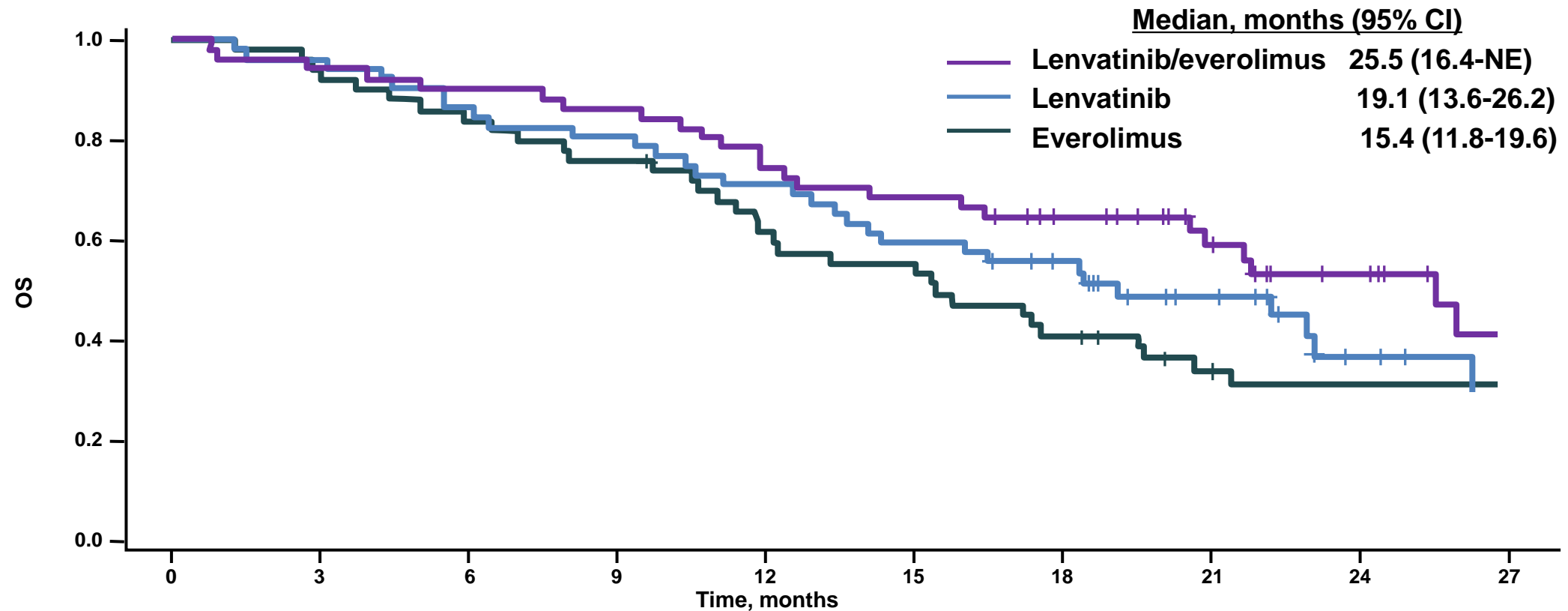
- Disease progression
- Unacceptable toxicity

## Stratification factors:

- Hemoglobin (normal vs low)
- Corrected serum calcium ( $\geq$  vs  $<$  10 mg/dL)



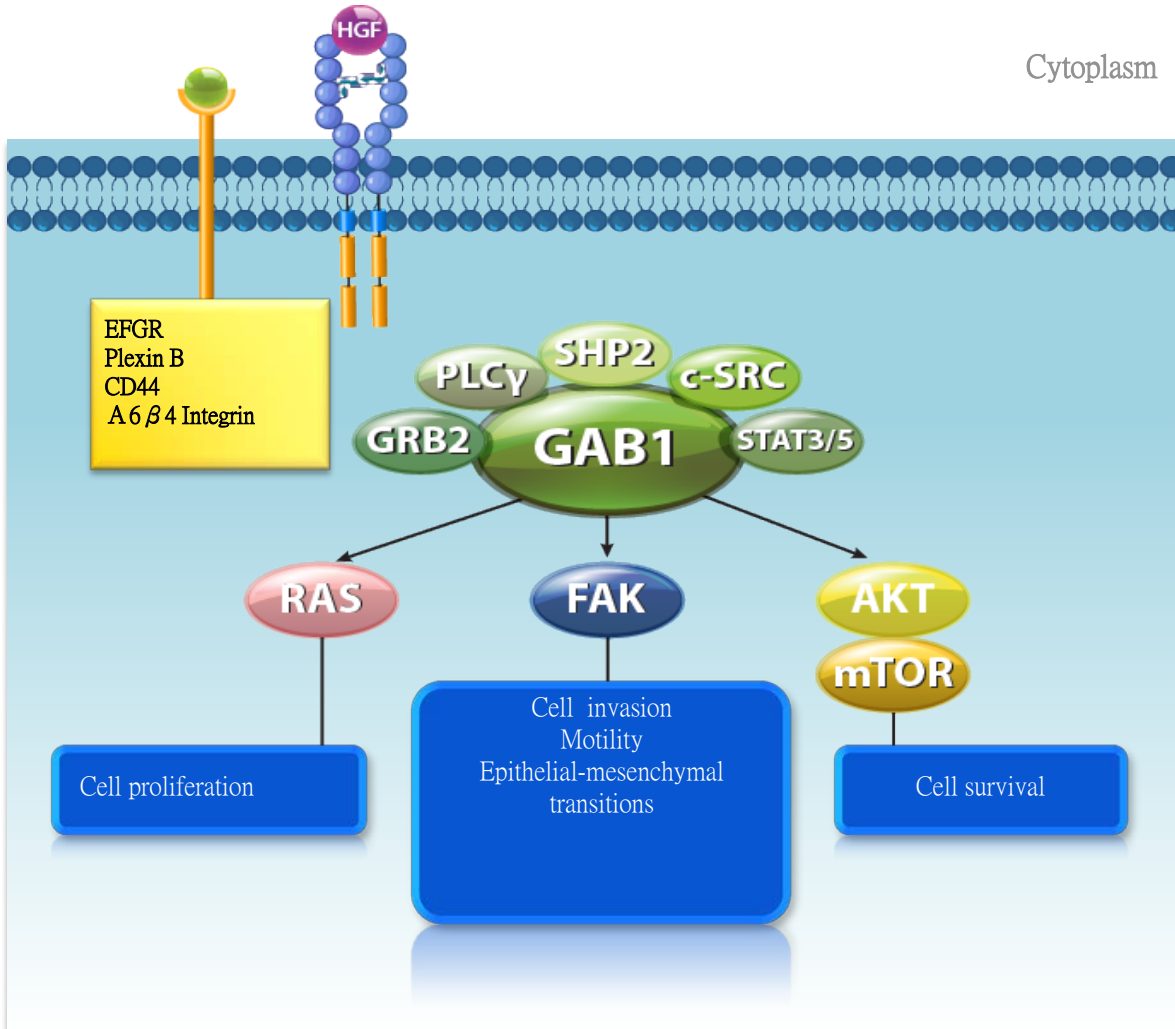
# Secondary Endpoint: OS



Lenvatinib/everolimus vs Everolimus  
HR = 0.51 (95% CI, 0.30-0.88); *P* = 0.024

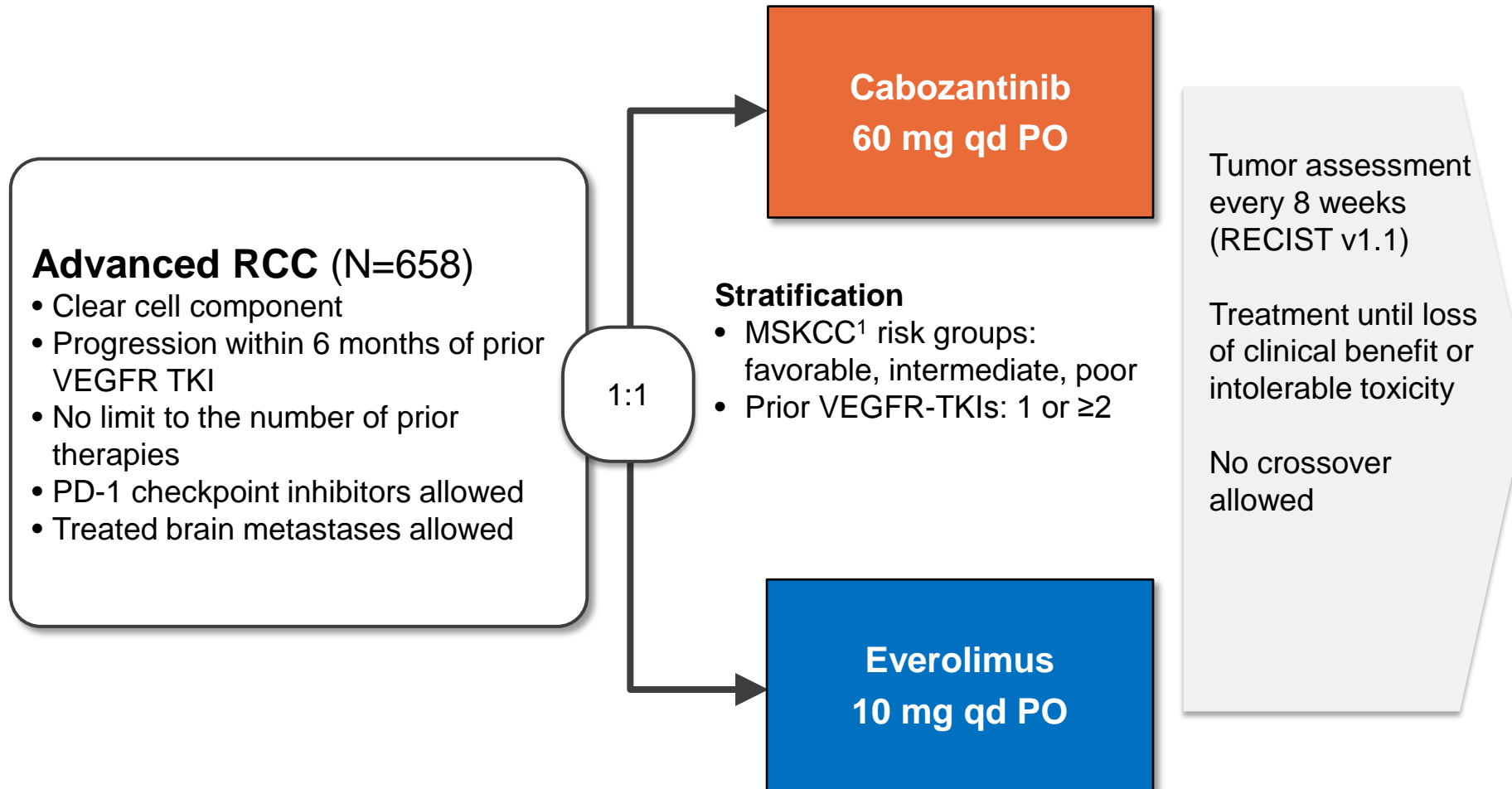
Lenvatinib vs everolimus  
HR = 0.68 (95% CI, 0.41-1.14); *P* = 0.118

# MET and Acquired Resistance to VEGF-targeted Therapies

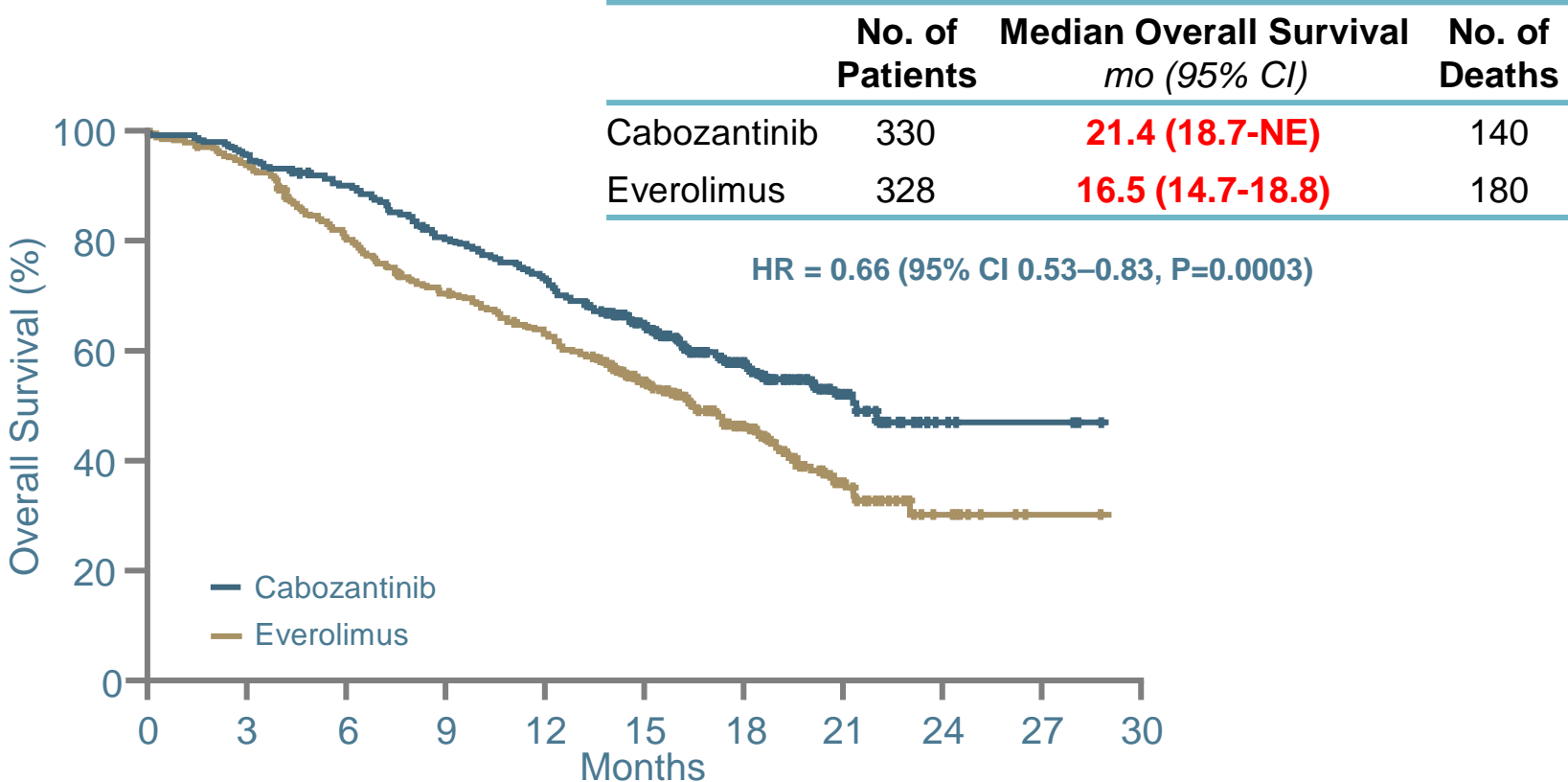


- Hypoxia triggers increase in cMET expression and activity:
  - Cell invasion and migration
  - Cell proliferation
  - Cell survival
- Inhibition of cMET may help overcome acquired resistance to the VEGF pathway
- Dual inhibitors of cMET and VEGFr2 such as Cabozantinib are active

# METEOR Study Design



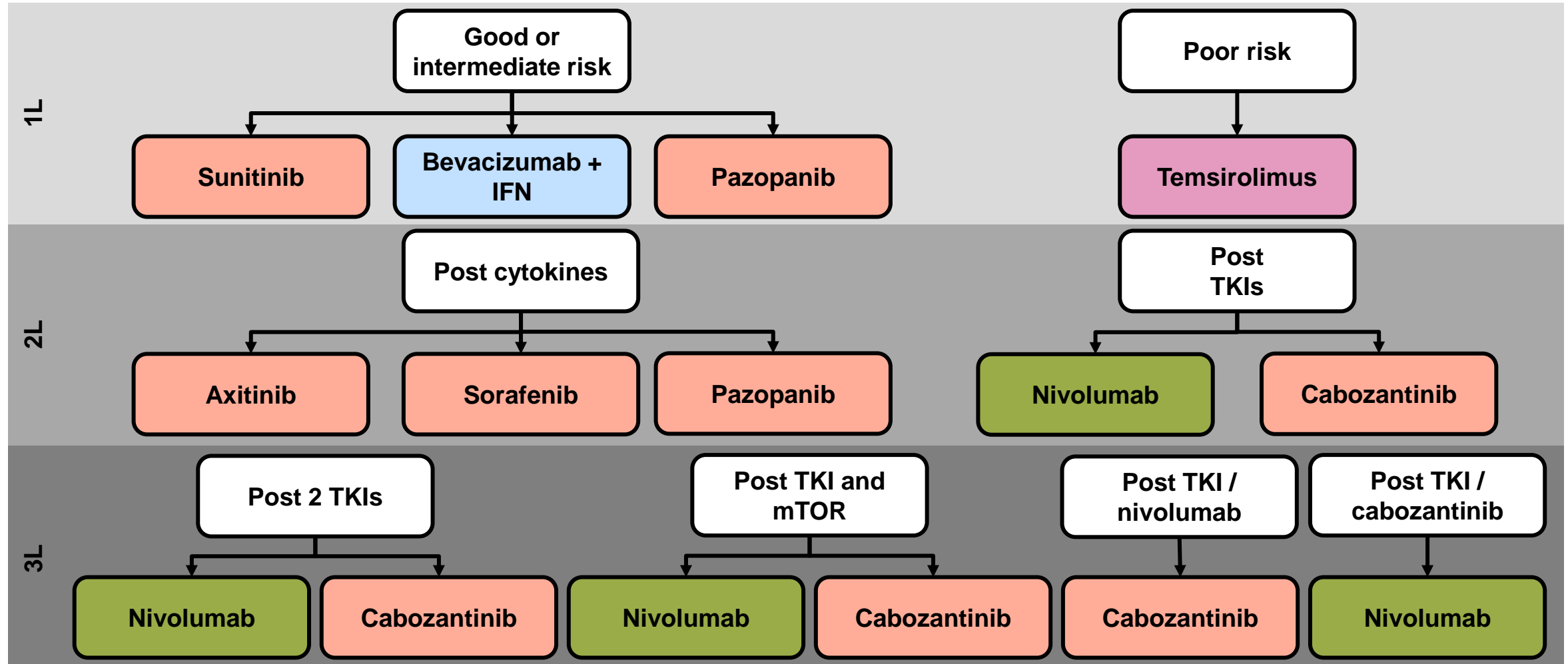
# Overall Survival



	No. of Patients	Median Overall Survival mo (95% CI)	No. of Deaths
Cabozantinib	330	<b>21.4 (18.7-NE)</b>	140
Everolimus	328	<b>16.5 (14.7-18.8)</b>	180

No. at Risk	0	3	6	9	12	15	18	21	24	27	30
Cabozantinib	330	318	296	264	239	178	105	41	6	3	0
Everolimus	328	307	262	229	202	141	82	32	8	1	0

# Updated ESMO guidelines: algorithm for systemic treatment in clear cell mRCC

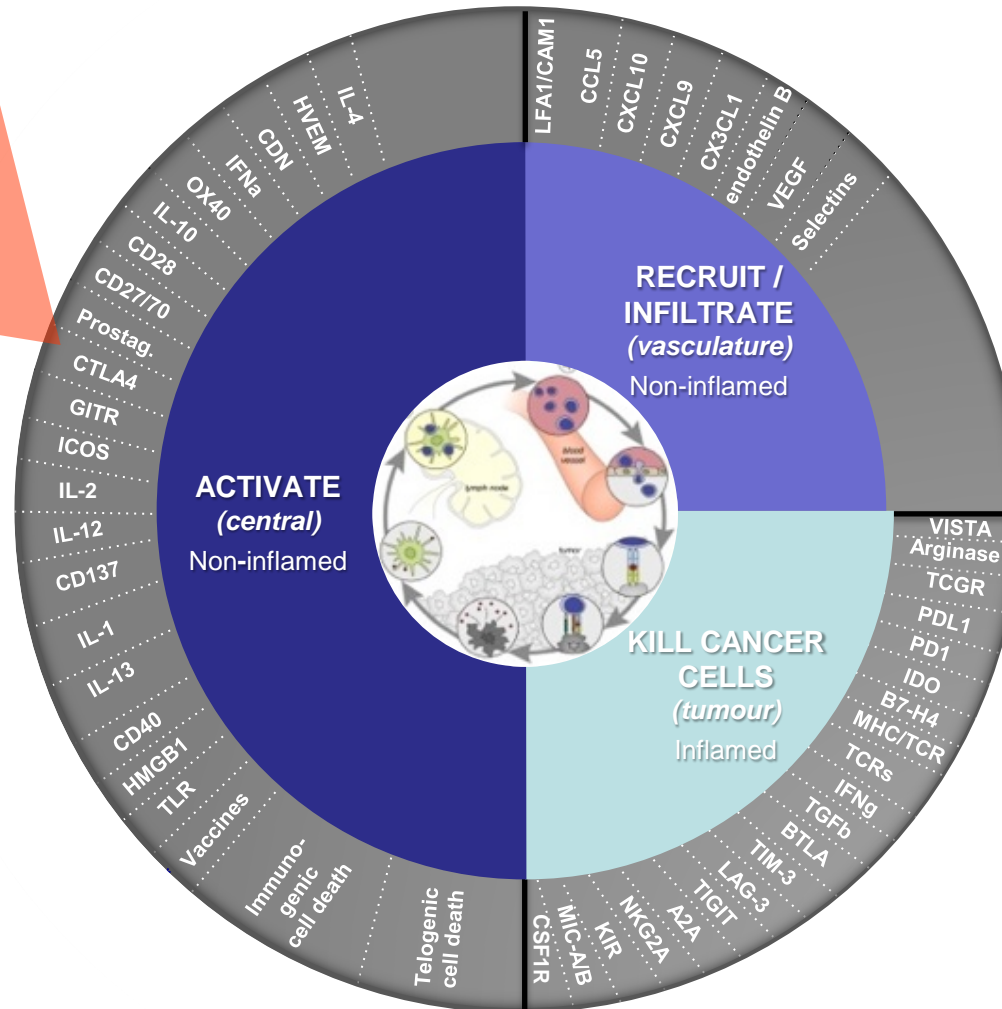


■ VEGF TKI      ■ mTOR inhibitor  
■ VEGF MAb + IFN- $\alpha$       ■ PD-1 inhibitor

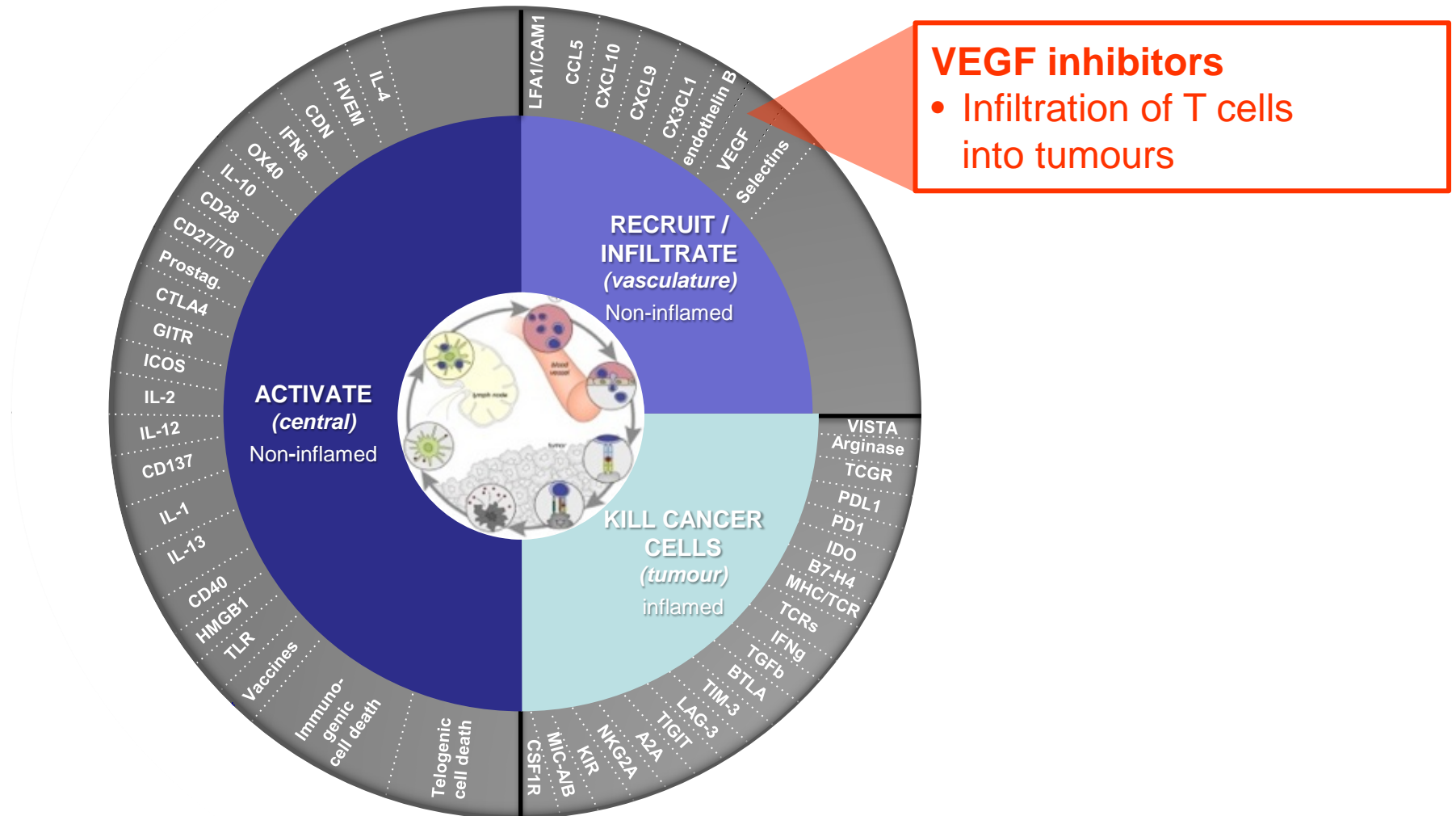
# How can we further enhance responses?

## CTLA4 inhibitors

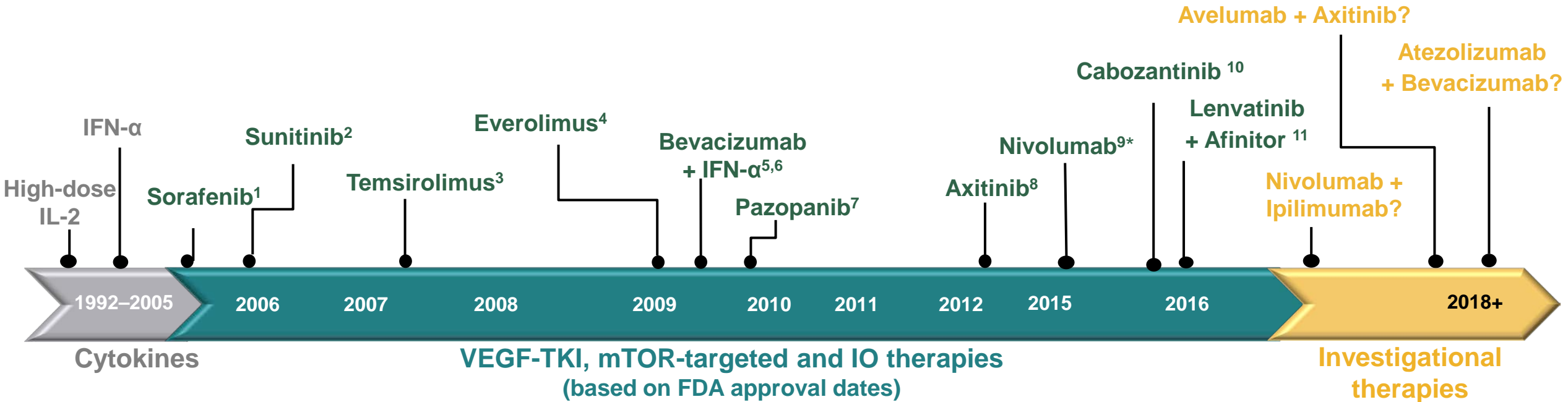
- Priming and activation of T cells



# How can we further enhance responses?



# The evolving treatment landscape of mRCC



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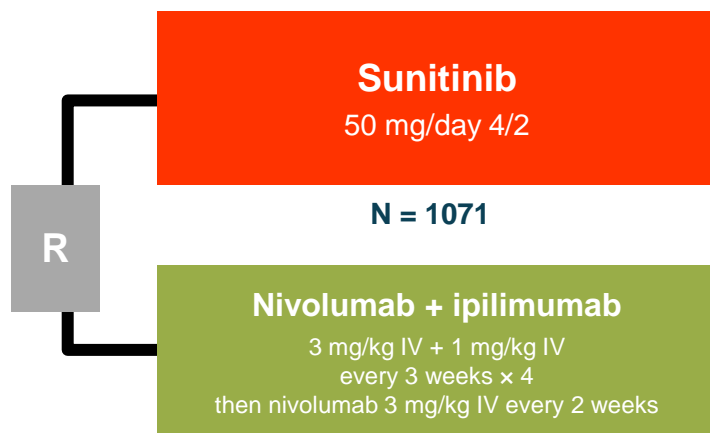
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# First-line trials expected soon

## PD1 + CTLA4 inhibition

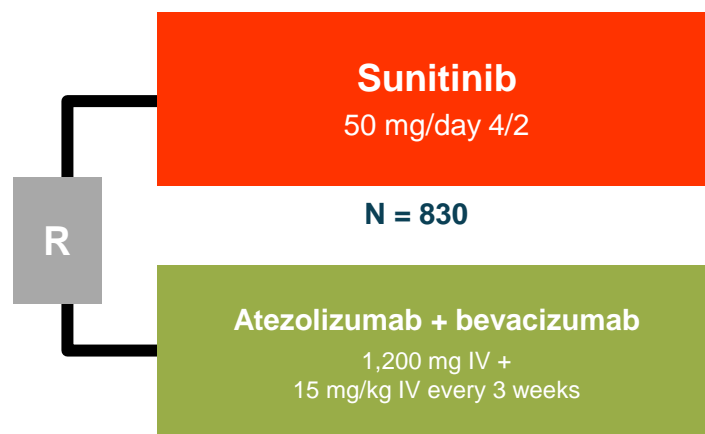
CheckMate-214<sup>1</sup>  
Phase III



Co-primary endpoint: PFS, OS

## PD-L1 + VEGF inhibition

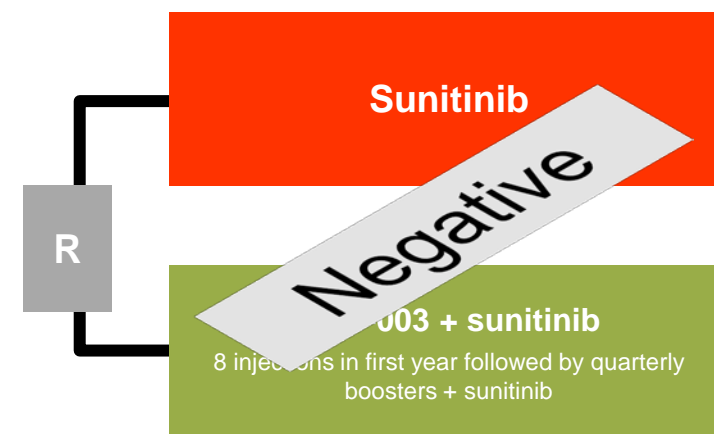
Immotion-151<sup>2</sup>  
Phase III



Co-primary endpoint: PFS, OS

## Personalized immunotherapy + VEGFR inhibition

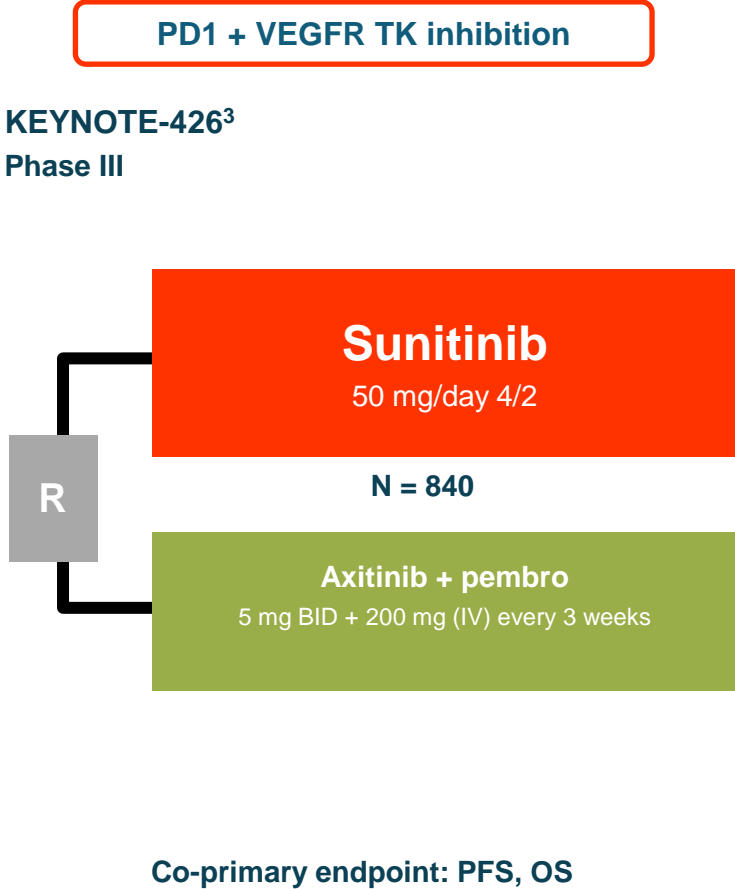
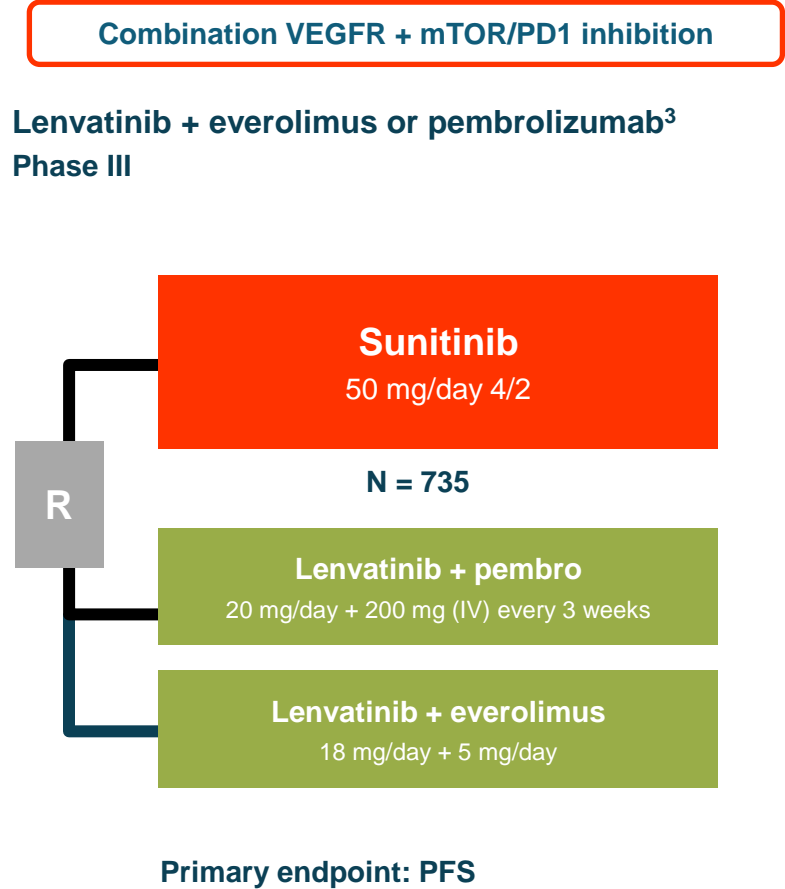
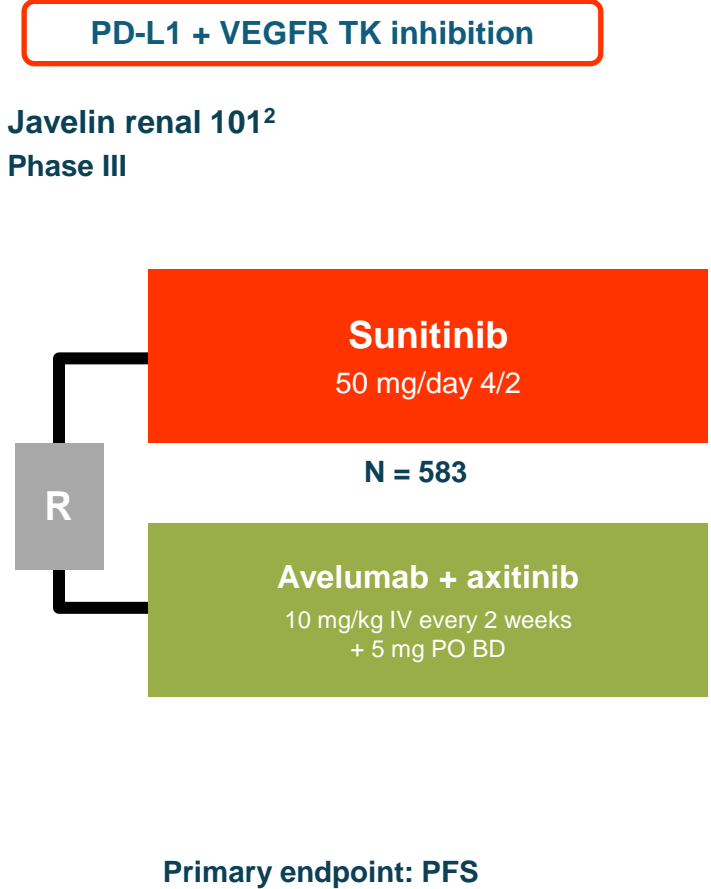
ADAPT<sup>3</sup>  
Phase III



Primary endpoint: OS

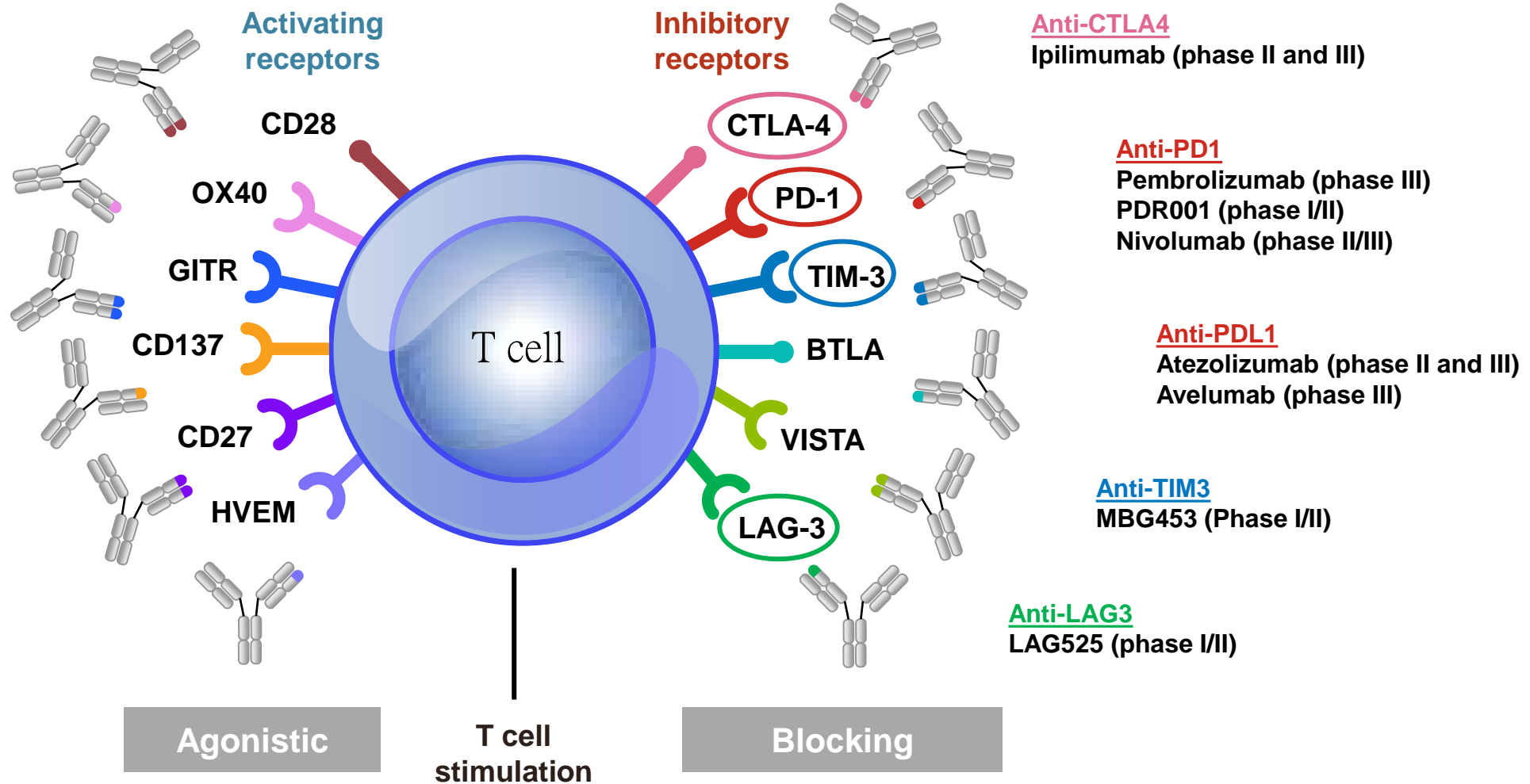
1. <https://clinicaltrials.gov/ct2/show/NCT02231749>
2. <https://clinicaltrials.gov/ct2/show/NCT02420821>
3. <https://clinicaltrials.gov/ct2/show/NCT01582672>

# First-line ongoing trials



1. <https://clinicaltrials.gov/ct2/show/NCT02684006>  
2. <https://clinicaltrials.gov/ct2/show/NCT02811861>  
3. <https://clinicaltrials.gov/ct2/show/NCT02853331>

# Multiple targets for checkpoint inhibitor in clinical development for mRCC



# What is the future of immunotherapy in RCC?

How best to integrate newer agents into routine clinical practice?

Can we predict response?

How long should we treat our patients?

How to best manage toxicities?

## EAU Guidelines on Renal Cell Carcinoma

B. Ljung  
S. Ca  
M.A.  
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NCCN Clinical Practice Guidelines in Oncology

## Kidney C

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### Renal cell carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up<sup>1</sup>

B. Escudier<sup>1</sup>, C. Porta<sup>2</sup>, M. Schmidinger<sup>3</sup>, N. Rioux-Leduc<sup>4</sup>, A. Bex<sup>5</sup>, V. Kluth<sup>6</sup>, V. Grunewald<sup>7</sup> & A. Horwich<sup>8</sup> on behalf of the ESMO Guidelines Committee<sup>1</sup>

#### incidence and epidemiology

Kidney cancer accounts for 5% and 3% of all adult malignancies in men and women, respectively, representing the 7th most common cancer in men and the 10th most common cancer in women [1]. However, available data include only two population-based registries, but also included cases of the rare papillary renal cell carcinoma (RCC) accounts for ~20% of all kidney cancers.

After over two decades of increasing incidence, RCC incidence worldwide has shown signs of plateauing or decreasing in recent years. Furthermore, kidney cancer mortality has overall been low. These patterns are consistent with reports of incidental diagnosis and decreasing rates of tumour stage and size, indeed, the widespread use of non-invasive radiological techniques (e.g. ultrasonography (US), computed tomography (CT)) allows the frequent detection of very small RCCs, which are potentially curable.

Beyond well-known risk factors for RCC, such as cigarette smoking, obesity and hypertension, evidence is accumulating to suggest an aetiological role for the dietary, a protein-rich diet, for additional factors [2], such as nephrotic syndrome. Furthermore, RCC also appears to be more common in patients with end-stage renal failure or acquired cystic disease, and in patients with dialysis, those who have had kidney transplantation, or those with tuberous sclerosis syndrome.

Approximately 25–30% of all RCCs are hereditary and several autosomal dominant syndromes are described, associated with distinct genetic hallmarks and phenotypes, the most common one being Von Hippel Lindau (VHL) disease.

#### diagnosis

As stated above, >50% of RCCs are currently detected incidentally, making the standardised trial of early-stage genetic biomarkers and perhaps additional biomarkers, important. In the past, despite the fact that RCC accounts for the 7th most common cancer, population-based studies on hepatocellular carcinoma, colorectal, endometrial and lung cancer, and breast cancer, have failed to identify additional biomarkers of the liver or urinary tract disease, which typically involve the kidney tumour, associated with being clinically frequent.

Suspicion of RCC should prompt laboratory investigations of serum creatinine, haemoglobin, uric acid and platelet counts, liver enzymes to normalise uric acid, serum electrolytes, C-reactive protein (CRP) and serum corrected calcium, in addition to other symptom-derived tests (V, D). Some of these tests are prerequisites for arterial and/or renal (or both) assessment with different purposes (see section on follow-up).

Most cases of RCC are strongly suspected by imaging findings. It is usually suggested by US and further investigated by CT, scans, which allows for assessment of local invasion, lymph node involvement, or distant metastases. Magnetic resonance imaging (MRI) may provide additional information re investigating local invasion and venous involvement by tumour thrombus.

For accurate staging of RCC, contrast-enhanced chest, abdominal, and pelvic CT is mandatory (III, A), unless indicated by clinical or laboratory signs or symptoms. The use of bone scan or CT for MRI of the brain is not recommended for routine clinical practice (III, A). In case of an allergy to CT contrast medium, adequate support should include a premedication (I, score 2) by the chest without contrast medium, together with an abdominal MRI. Thorax radiography provides additional information re lymph node involvement. <sup>125</sup>I-MIBI-CT is not a standard investigation in the diagnosis and staging of RCC. PET-CT and should not be used. For all cases, genetic biomarkers investigations only.

A renal tumour, once biopsy-proven (biopsy-negative) confirmation of malignancy with high sensitivity and specificity, is

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# What is the future of immunotherapy in RCC?

How best to integrate newer agents into routine clinical practice?

Can we predict response?

How long should we treat our patients?

How to best manage toxicities?

## EAU Guidelines on Renal Cell Carcinoma

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<sup>1</sup>Department of Medical Oncology, Gustave Roussy Institute, Villejuif, France; <sup>2</sup>Department of Medical Oncology, Institut Jules Kunkin, Paris, France; <sup>3</sup>Department of Medical Oncology, University Hospital of Vienna, Vienna, Austria; <sup>4</sup>Department of Medical Oncology, Institut Gustave Roussy, Villejuif, France; <sup>5</sup>Department of Medical Oncology, Institut Gustave Roussy, Villejuif, France; <sup>6</sup>Department of Medical Oncology, Institut Gustave Roussy, Villejuif, France; <sup>7</sup>Department of Medical Oncology, Institut Gustave Roussy, Villejuif, France; <sup>8</sup>Department of Medical Oncology, Institut Gustave Roussy, Villejuif, France

### incidence and epidemiology

Kidney cancer accounts for 5% and 3% of all adult malignancies in men and women, respectively, thus representing the 7th most common cancer in men and the 10th most common cancer in women [1]. However, available data are limited to only some geographical regions, but also included cases of the rare papillary renal cell carcinoma (RCC) accounts for ~20% of all kidney cancers.

Age over 50 years is a factor of increasing risk. RCC tends to occur worldwide but shows signs of increasing incidence in recent years. Furthermore, kidney cancer mortality has overall been low. These features are consistent with reports of incidental diagnosis and decreasing rates of distant stage and, in fact, the widespread use of non-invasive radiological techniques (e.g. ultrasonography [US], computed tomography [CT]) allows the frequent detection of early and small RCCs, which are potentially curable.

Beyond well-known risk factors for RCC, such as cigarette smoking, obesity and hypertension, evidence is accumulating to suggest an aetiological role for the dietary, protective role for additional factors [2], such as fish oils. Furthermore, RCC also appears to be more common in patients with end-stage renal failure or acquired cystic disease, and in patients with dialysis, those who have had kidney transplantation, or those with tuberous sclerosis syndrome.

Approximately 25–30% of all RCCs are hereditary and several autosomal dominant syndromes are described, most with a clear genetic basis and phenotype, the most common one being Von Hippel Lindau (VHL) disease.

### diagnosis

As stated above, 50% of RCCs are currently detected incidentally, making the standardised trial of early-stage, gross haematuria and palpable abdominal mass less important than in the past. Despite this, RCC remains the 8th most common cancer with para-neoplastic syndromes such as hypercalcaemia, unexplained weight loss, anorexia and night sweats, and the presence of haematuria are often the major indicators of the disease. In contrast to lung cancer, which typically involves the kidney, metastases will bring a variety of signs.

Suspicion of RCC should prompt laboratory investigations of serum creatinine, haemoglobin, uric acid and platelet counts, liver enzymes to normalise uric acid, serum electrolytes, C-reactive protein (CRP) and serum corrected calcium, in addition to other symptom-derived tests (V, D). Some of these tests are recommended for arterial and/or renal (or both) assessment until disease progression is evident (see later).

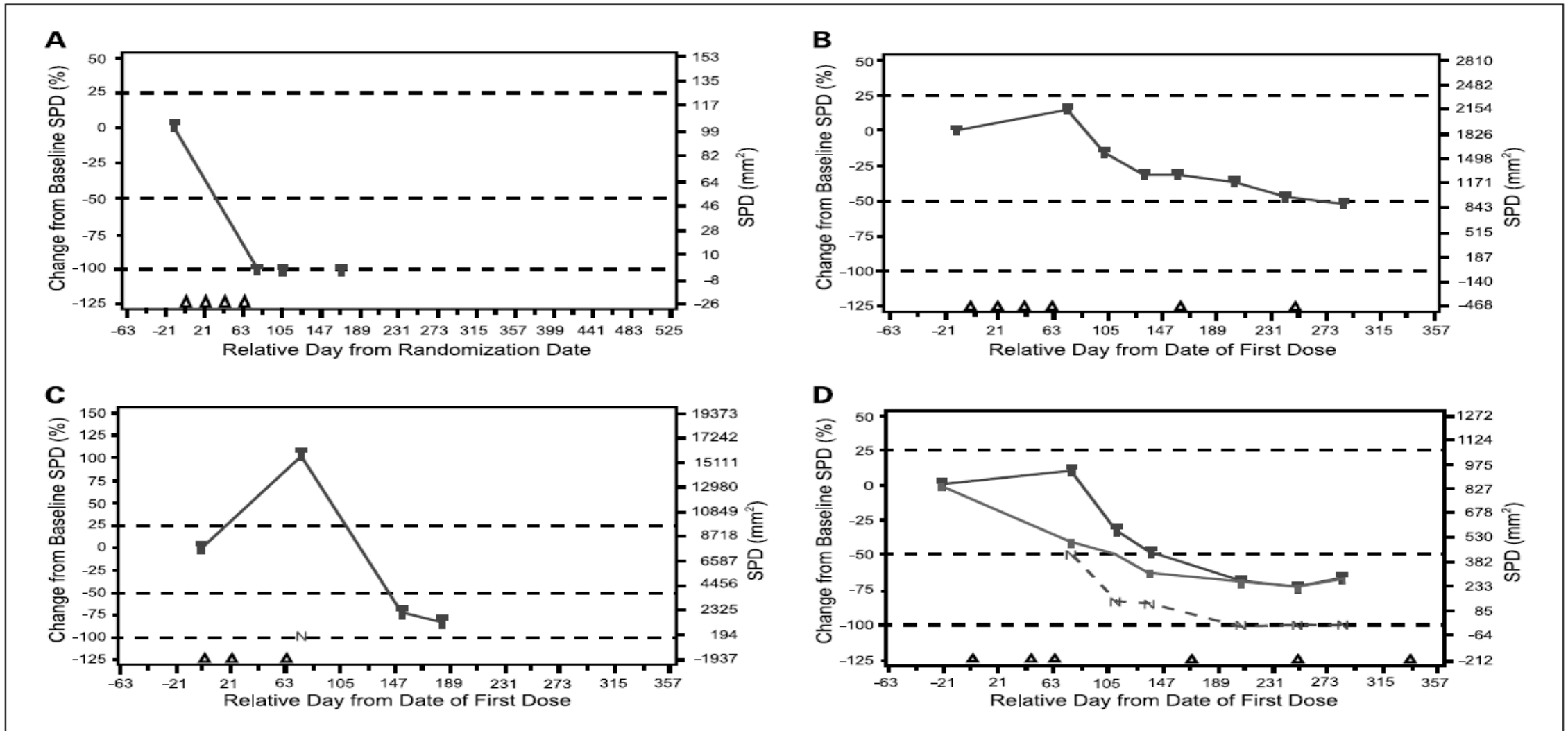
Most cases of RCC are strongly suspected by imaging. Diagnosis is usually suggested by US and further investigated by CT, which allows for assessment of local invasion, lymph node involvement, or distant metastases. Magnetic resonance imaging (MRI) may provide additional information on investigating local invasion and venous involvement by tumour thrombus.

For accurate staging of RCC, contrast-enhanced chest, abdominal, and pelvic CT is mandatory (III, A), unless contraindicated by clinical or laboratory signs or symptoms. The use of bone scan or CT for MRI of the brain is not recommended for routine clinical practice (III, A). In case of an allergy to CT contrast medium, adequate support should include a premedication with corticosteroids without contrast medium, together with an additional MRI. If renal dysfunction prevents routine imaging, <sup>125</sup>I-labelled <sup>125</sup>I-FAPI-42 is not a standard investigation in the diagnosis and staging of RCC. (RCC) and should not be used. For clinical trials, novel imaging techniques may be used. For clinical trials, novel imaging techniques may be used.

A renal tumour, once biopsy-proven, histopathological confirmation of malignancy with high sensitivity and specificity, is

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# New response types with immunotherapy



## Immune-Related Response Criteria

# There is a large evidence that

1. Treatment can be stopped:

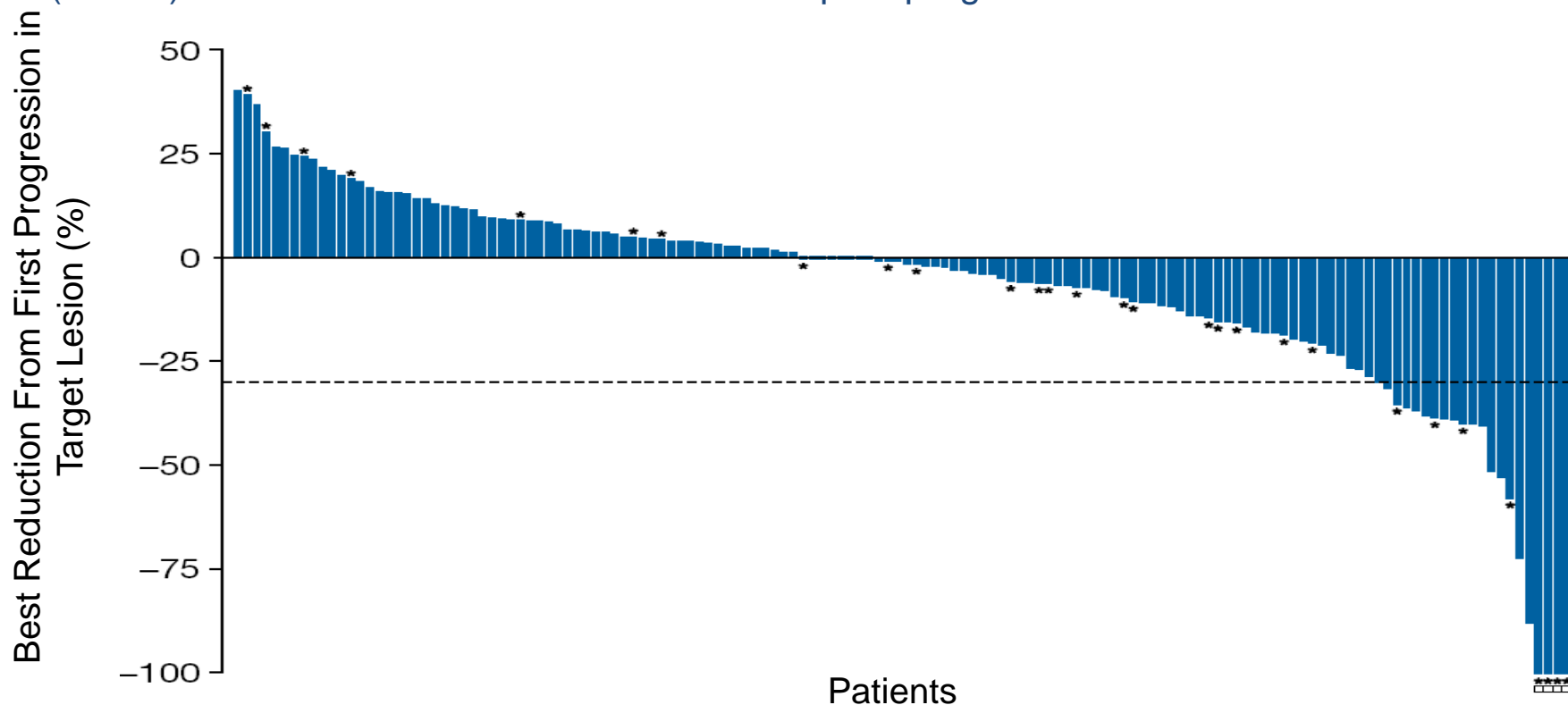
- Especially in case of CR
- In case of severe toxicity
- Ongoing discontinuation trials are needed

2. Some patients should be treated beyond progression

# Should we treat beyond progression?

A total of 142 of 153 patients treated with nivolumab beyond progression had tumor measurements pre- and post-progression

Of these 142 patients, approximately half had a reduction in tumor burden post-progression and 14% (n = 20) had  $\geq 30\%$  reduction in tumor burden post-progression



Asterisks represent responders before first progression. Square symbol represents % change truncated to 100%

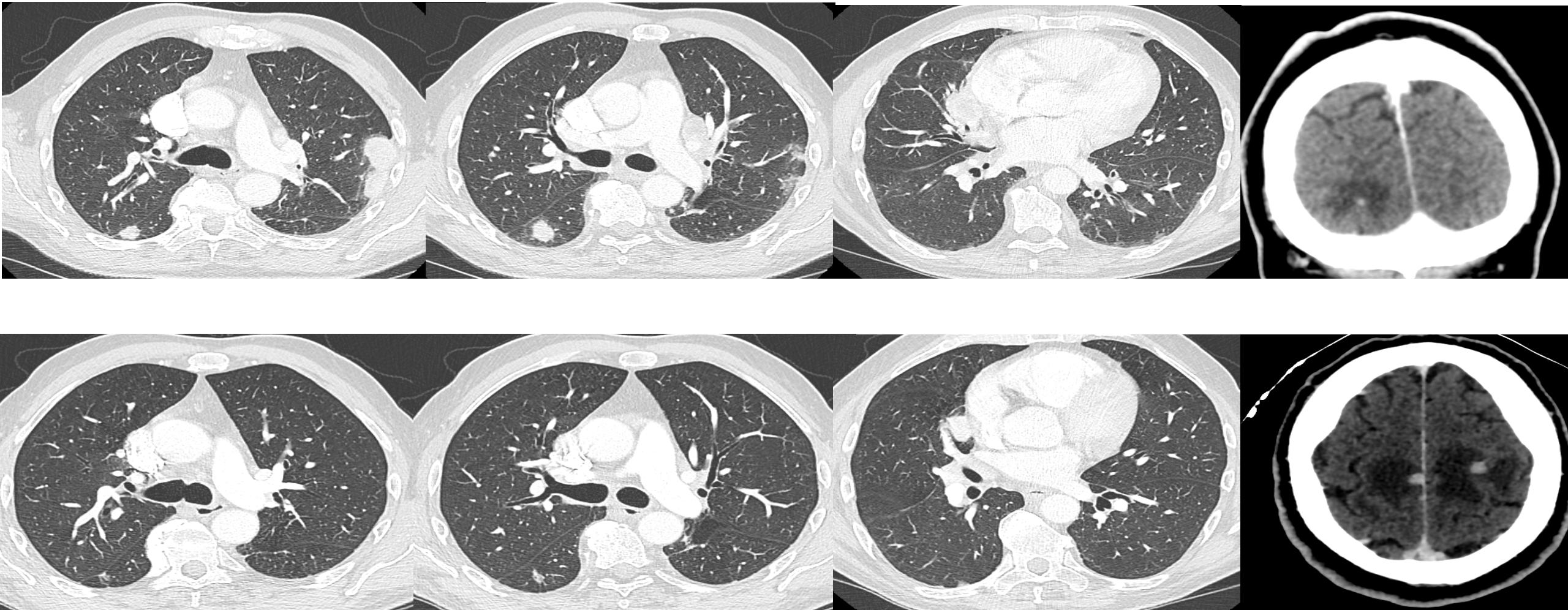


# Who should we treat beyond progression?

- Patients with good safety profile
- Patients with « clinical benefit »
  - No impairment of general condition
  - No major progression
- Commonly those with dissociated responses

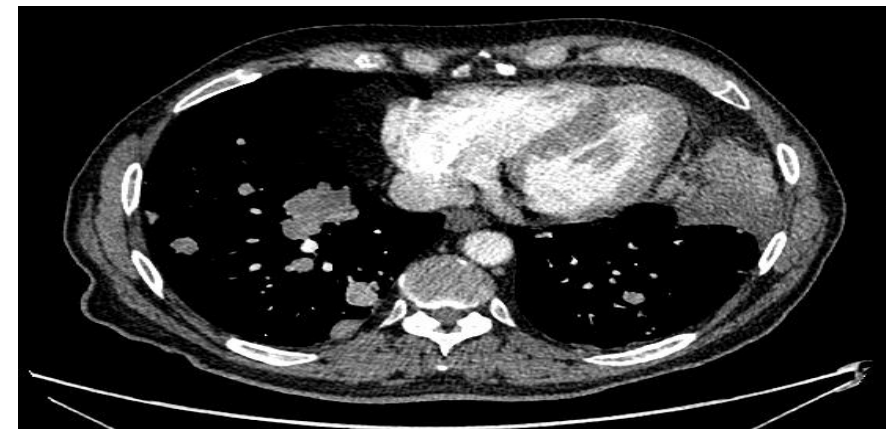
# Good patients to treat beyond progression

- Case 1



# Good patients to treat beyond progression

- Case 2



**BL**

**8w**

**16w**



# What is the future of immunotherapy in RCC and melanoma?

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Kidney cancer accounts for 5% and 3% of all adult malignancies in men and women, respectively, thus representing the 7th most common cancer in men and the 10th most common cancer in women [1]. However, available data include only two population-based registries, but also included cases of the uterine cervix, end, six countries. RCC accounts for 70% of all kidney cancers.

Age over 50 and a history of smoking are the most common risk factors for developing RCC. RCC is most commonly diagnosed in white men aged 60–70 years. Furthermore, kidney cancer mortality has increased over time. These patterns are consistent with reports of increased diagnosis and awareness of RCC of various ages and sites. Indeed, the widespread use of non-invasive radiological techniques (e.g. ultrasonography [US], computed tomography [CT]) allows the frequent detection of very small RCCs, which are potentially curable.

Beyond well-known risk factors for RCC, such as cigarette smoking, obesity and hypertension, evidence is accumulating to suggest an aetiological role for the dietary, protein-rich diet, for additional factors [2], such as nephrotic syndrome. Furthermore, RCC also appears to be more common in patients with end-stage renal failure or acquired cystic disease, and in patients with dialysis, those who have had kidney transplantation, or those with tuberous sclerosis syndrome.

Approximately 25–30% of all RCCs are hereditary and represent autosomal dominant syndromes. The most common ones being Von Hippel Lindau (VHL) disease.

### diagnosis

As stated above, 50% of RCCs are currently detected incidentally, making the standardised trial of early-stage, gene locational and prognostic laboratory tests less important than in the past. Despite this, RCC remains the 16th most common cancer with parasitic aetiology, such as lymphocytic interstitial nephritis, myeloma, and multiple myeloma. The use of laboratory tests to monitor laboratory of the liver or kidney function, which may identify earlier-stage kidney tumours, remains still being clearly frequent.

Suspicion of RCC should prompt laboratory investigations of serum creatinine, haemoglobin, uric acid and platelet counts, liver enzymes to monitor renal, ureter, cholangiocarcinoma, C-reactive protein (CRP) and serum corrected calcium, in addition to other symptom-derived tests (V, D). Some of these tests are recommended for arterial and/or renal for the assessment of renal dysfunction and/or systemic disease.

Most cases of RCC are strongly suspected by imaging findings. Imaging is usually suggested by US and further investigated by CT scan, which allows for assessment of local invasion, lymph node involvement, or distant metastases. Magnetic resonance imaging (MRI) may provide additional information in investigating local invasion and venous involvement by tumour thrombus.

For accurate staging of RCC, contrast-enhanced chest, abdominal, and pelvic CT is mandatory (III, A), unless contraindicated by clinical or laboratory signs or symptoms. The use of bone scan or CT for MRI of the brain is not recommended for routine clinical practice (III, A). In case of an allergy to CT contrast medium, adequate support should include a premedication with corticosteroids without contrast medium, together with an alternative MRI. Thoracic radiography provides additional information in the diagnosis and staging of disease. CT (IV, C) and should not be used for routine clinical practice (IV, C) only.

A renal tumour, once biopsy-proven, should undergo confirmation of malignancy with high sensitivity and specificity, in

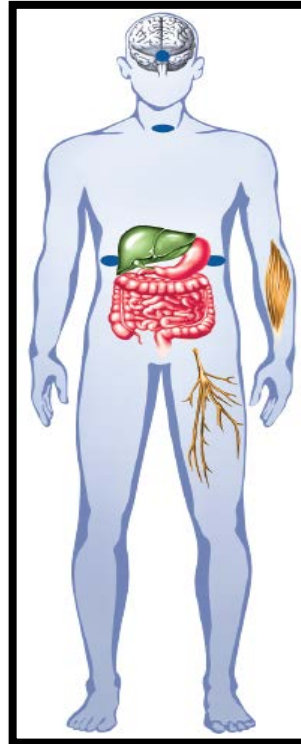
# Treatment-Related AEs Occurring in $\geq 10\%$ of Patients in Either Arm

Event	Nivolumab N=406		Everolimus N=397	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
<b>Treatment-related AEs, %</b>	79	<b>19</b>	88	37
Fatigue	33	2	34	3
Nausea	14	<1	17	1
Pruritus	14	0	10	0
Diarrhea	12	1	21	1
Decreased appetite	12	<1	21	1
Rash	10	<1	20	1
Cough	9	0	19	0
Anemia	8	2	24	8
Dyspnea	7	1	13	<1
Edema, peripheral	4	0	14	<1
Pneumonitis	4	1	15	3
Mucosal inflammation	3	0	19	3
Dysgeusia	3	0	13	0
Hyperglycemia	2	1	12	4
Stomatitis	2	0	29	4
Hypertriglyceridemia	1	0	16	5
Epistaxis	1	0	10	0

# Toxicity With Immunotherapy Agents

Activation of the immune system against tumors can result in a novel spectrum of irAEs<sup>1</sup>

- May be due to cytokine release by activated T cells<sup>1</sup>
- May be unfamiliar to clinicians
- Requires a multidisciplinary approach
- Can be serious<sup>2</sup>
- Requires prompt recognition and treatment<sup>2</sup>
- Requires patient and HCP education<sup>3</sup>

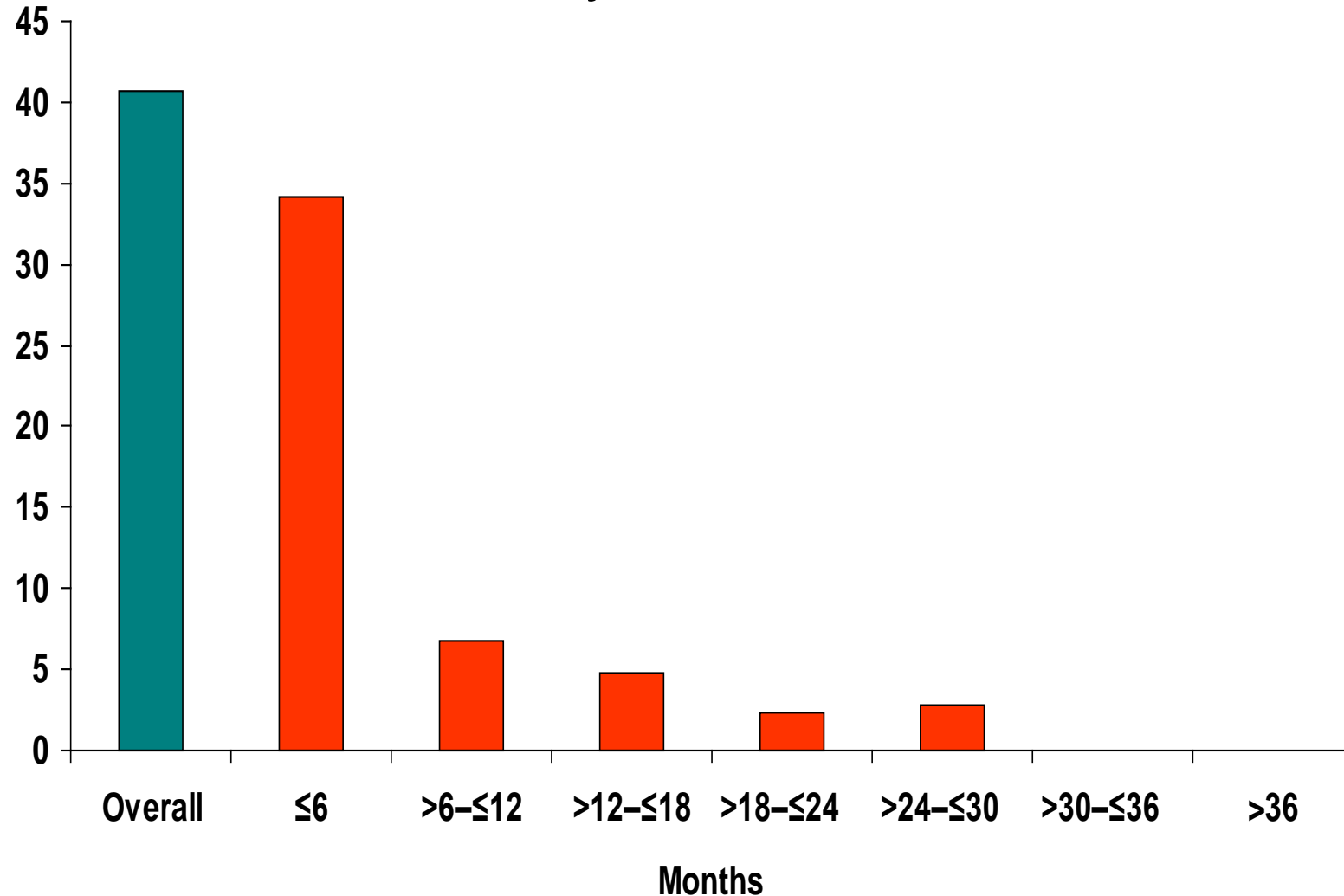


## irAEs occur in certain organ systems:<sup>1</sup>

- Skin
- Endocrine system
- Liver
- Gastrointestinal tract
- Nervous system
- Eyes
- Respiratory system
- Hematopoietic cells

## Some key messages

- Most of the toxicities occur early on



## Some key messages

- Most of the toxicities occur early on
- They are rapidly reversible on steroids (1mg/kg mostly IV)
- Steroids do not decrease the efficacy, when needed



# Summary

- Monotherapy with PD-L1/PD-1 inhibitors has demonstrated activity in mRCC
  - Nivolumab approved as 2L therapy
- Ongoing investigations using combinations with other compounds
  - Immunotherapy combinations
    - PD-1 + CTLA-4 inhibition
  - Immunotherapy + anti-VEGF inhibition
    - PD-1 + TKIs (or bevacizumab)
- Biomarkers, duration of therapy are still under investigation
- Management of side effects is important