Renal Cell Cancer: Present and Future

Bernard Escudier, Gustave Roussy

[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[1]

Incidence highest in the USA, Western Europe and other developed countries[2]

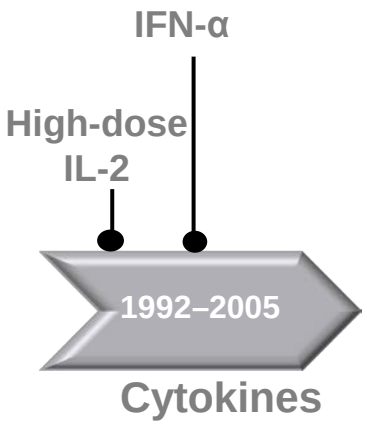
Median age at diagnosis is 64 years for kidney and renal pelvis cancer[3]

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%[3]

Median OS ~12 months in metastatic RCC before targeted agents[4]
Median OS ~30 months in most recent studies, highly dependent on prognostic factors[5]

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-α, interferon α; IL-2, interleukin-2; mTOR, mammalian target of rapamycin; VEGF, vascular endothelial growth factor.

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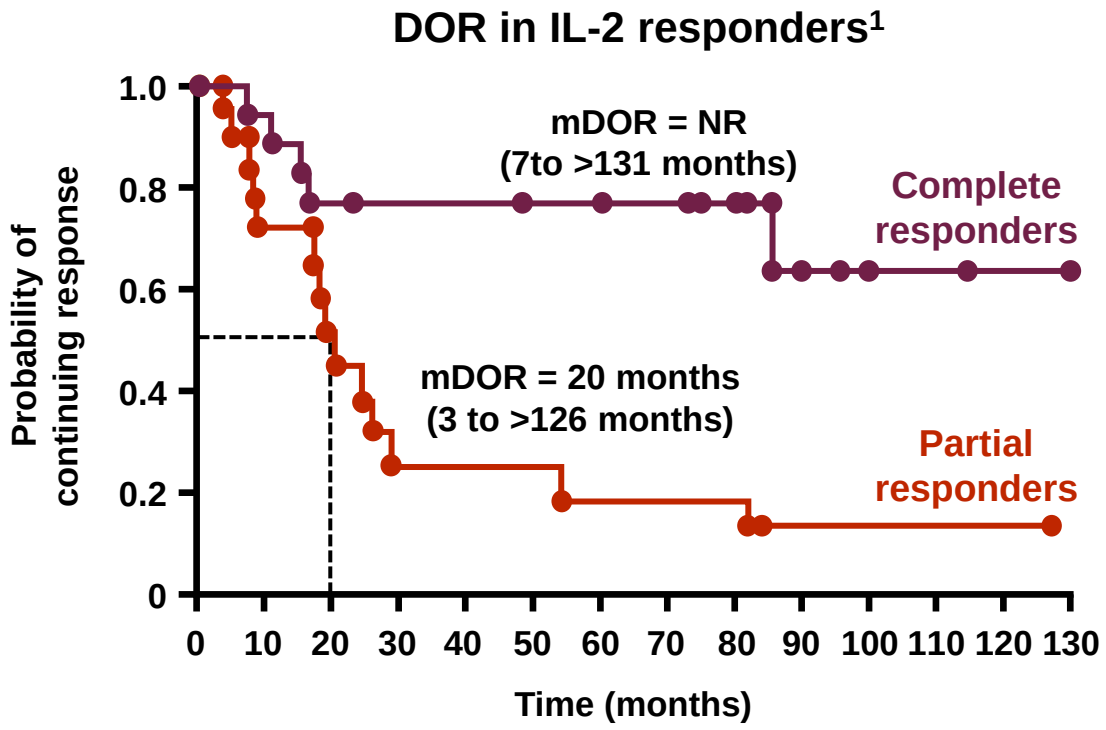
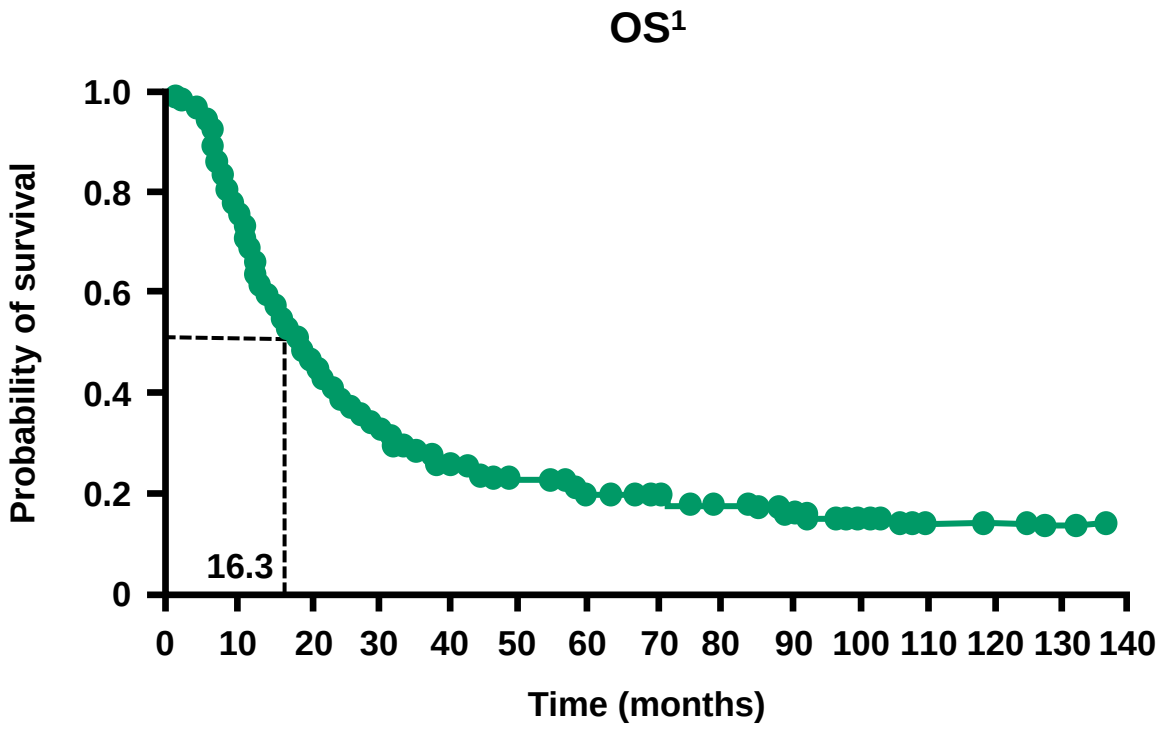
Cytokines have played an important role in mRCC for >20 years

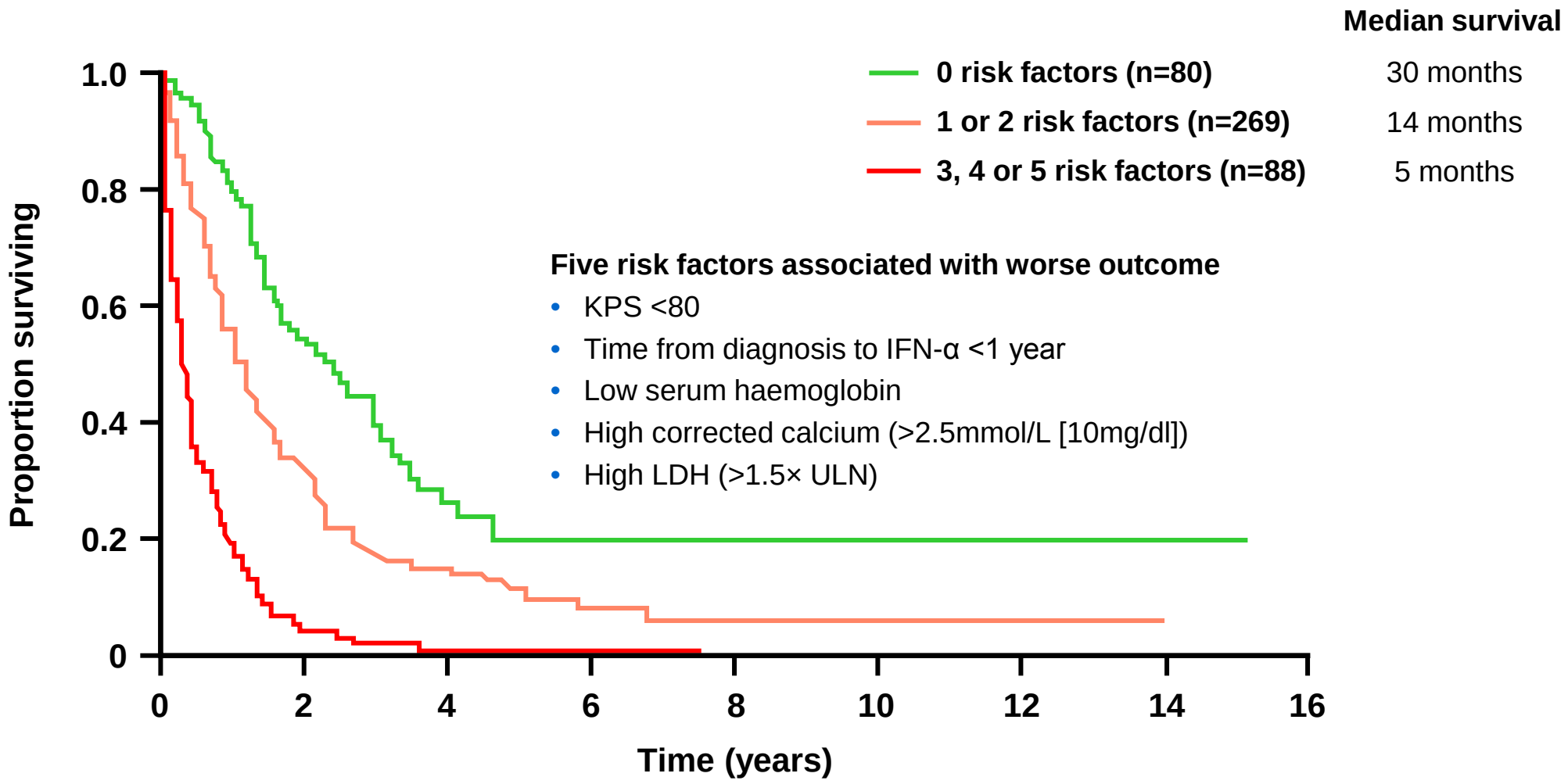




IL-2 associated with durable responses: ORR=15% (CR=7% and PR=8%)[1]
10–20% of patents alive after 5–10 years of treatment[1]
BUT
associated with substantial toxicity[2]

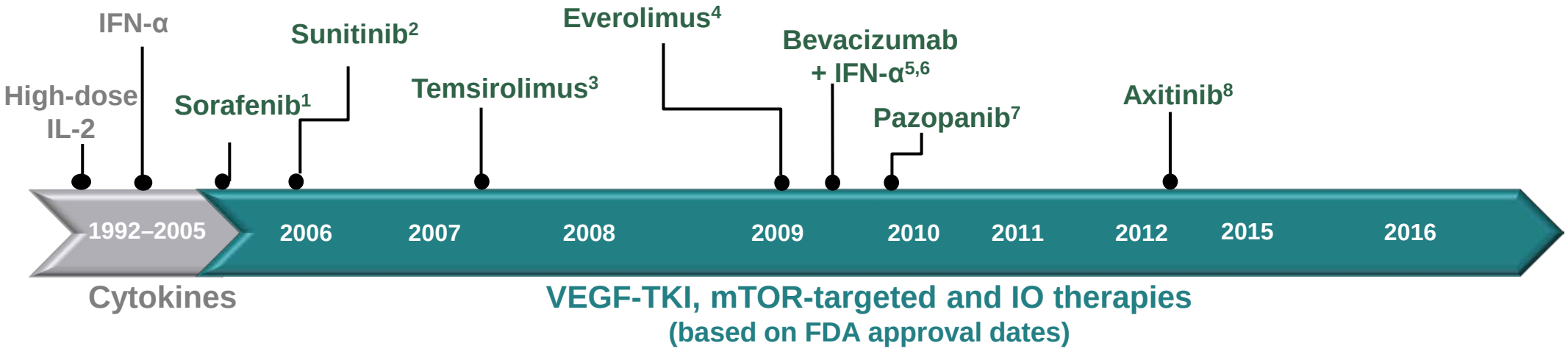
1. Fisher et al. Cancer J Sci Am 2000
2. McDermott et al. J Clin Oncol 2005

Survival with IFN-α in mRCC (by MSKCC risk)



Motzer et al. J Clin Oncol 2002

The evolving treatment landscape of mRCC



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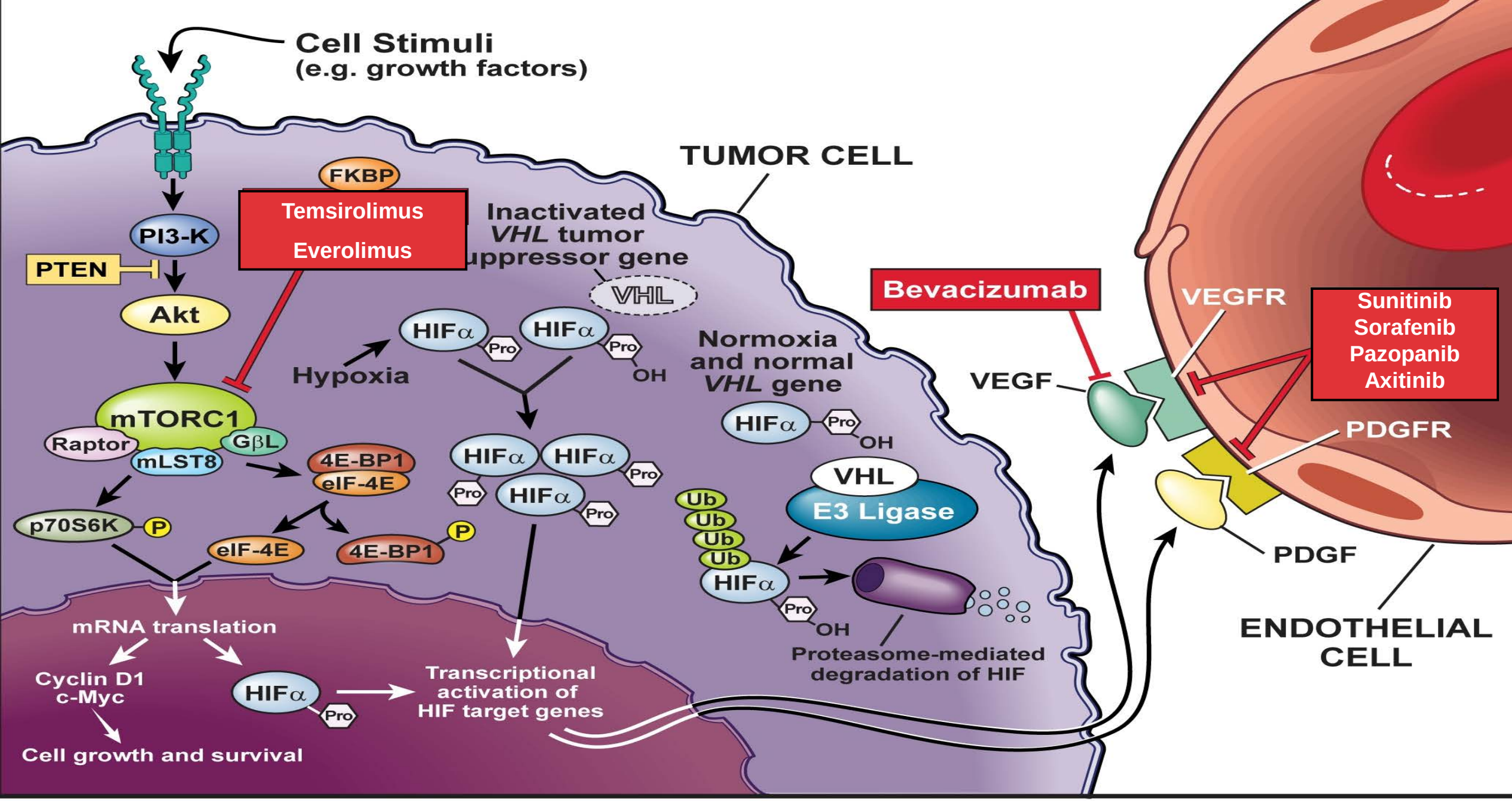
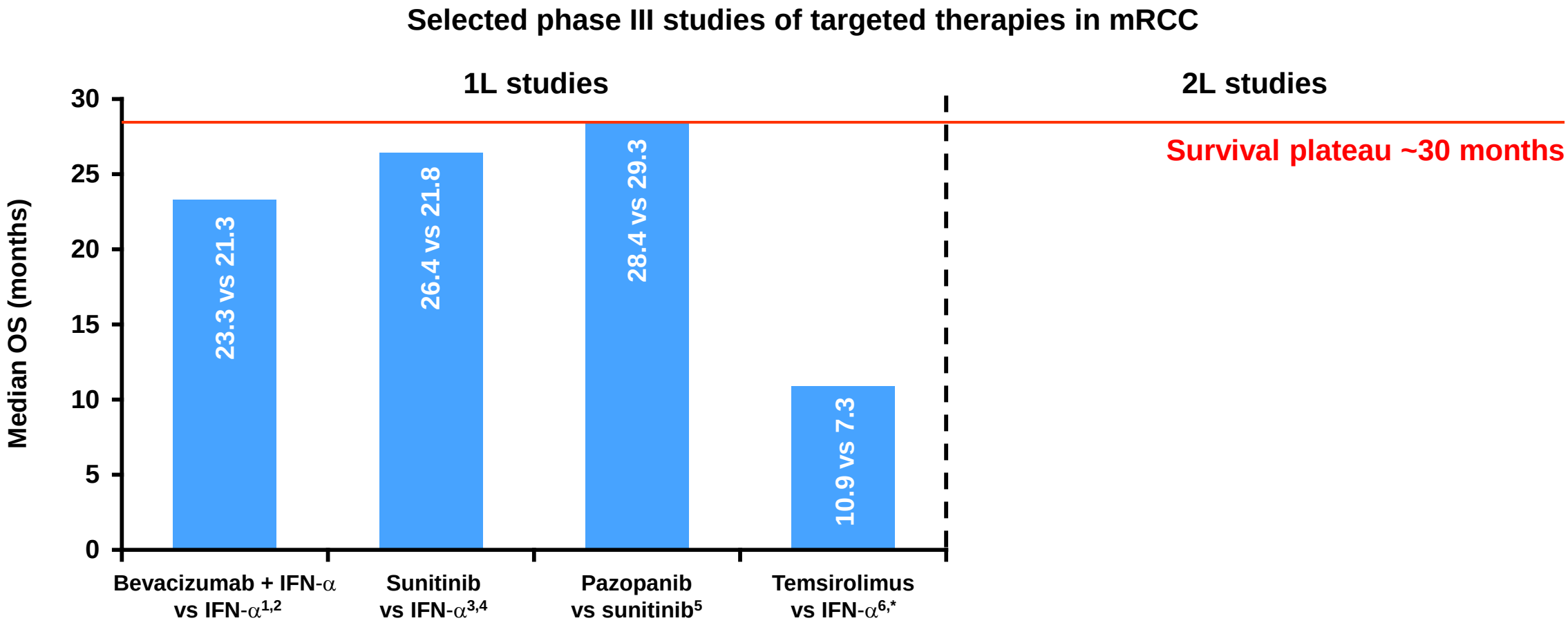


Rini BI, Campbel S and Escudier B. *Lancet.* 2009;373(9669):1119-1132.

...improving OS outcomes



*Patients with poor prognostic factors

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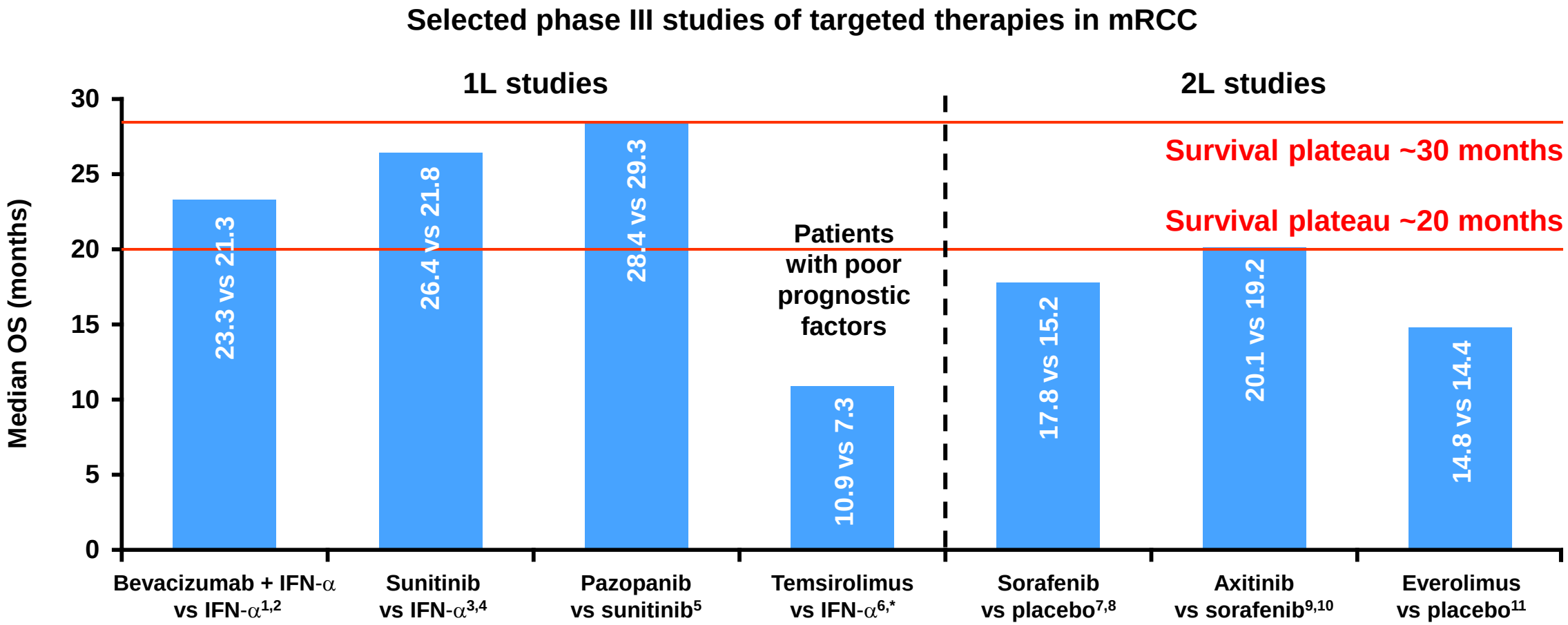

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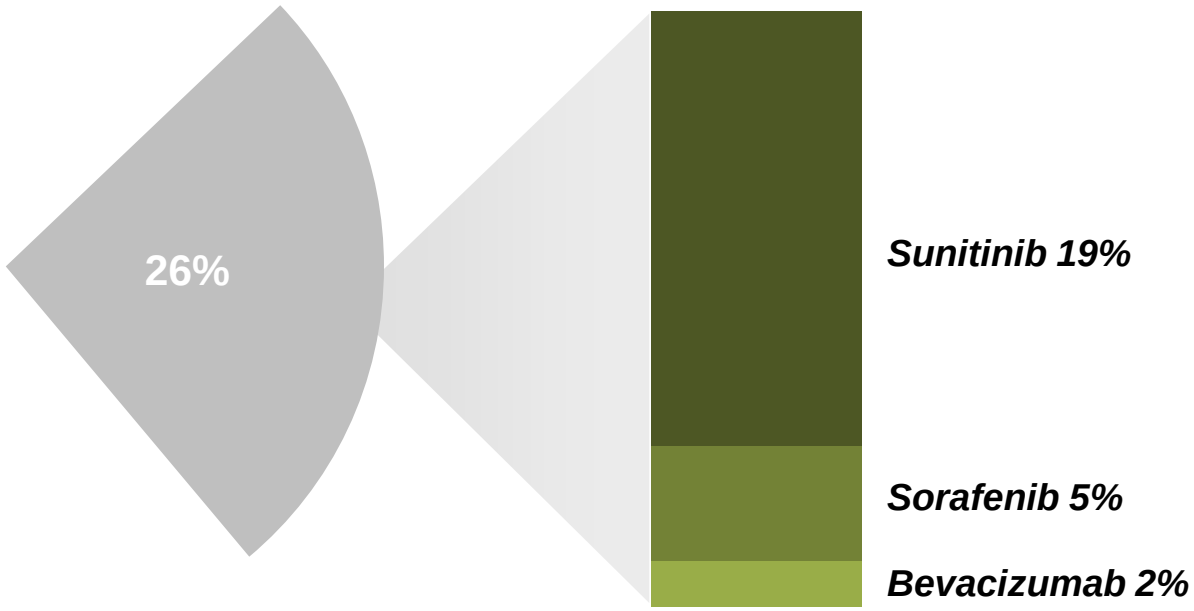
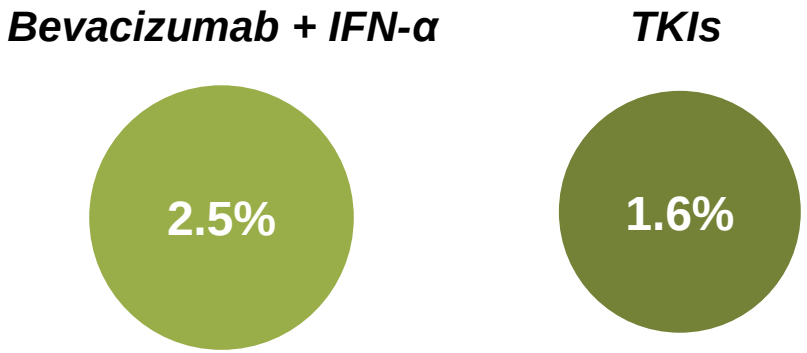
Additional unmet needs of targeted therapies in mRCC

Up to 26% of patients refractory to 1L anti-angiogenic agents[1]



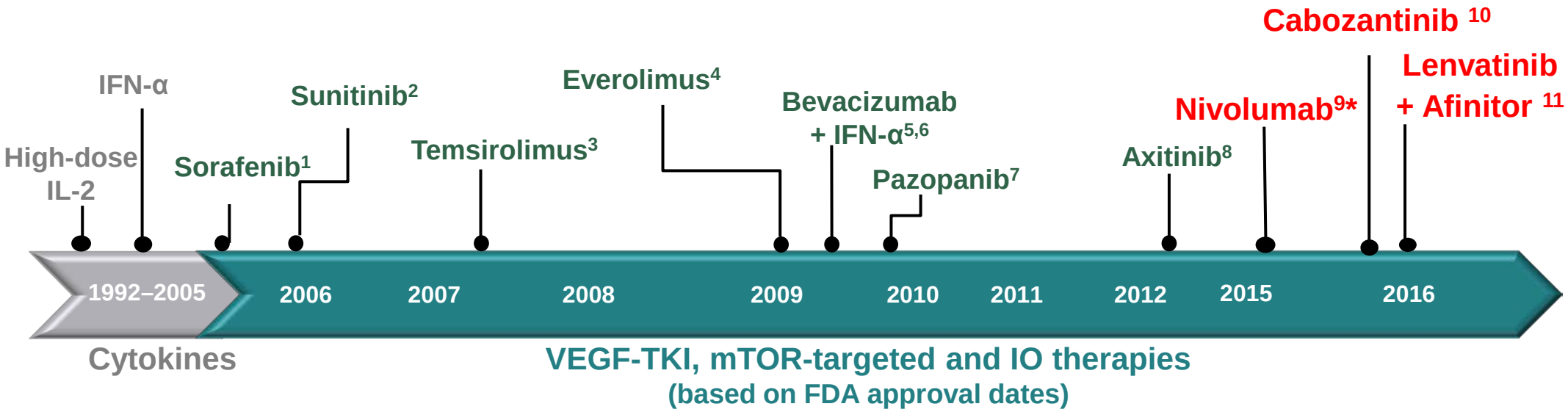
Complete responses to targeted therapies are rare[2]



Incidence of complete response

1. Heng et al. Ann Oncol 2012
2. Iacovelli et al. Cancer Treat Rev 2014

The evolving treatment landscape of mRCC



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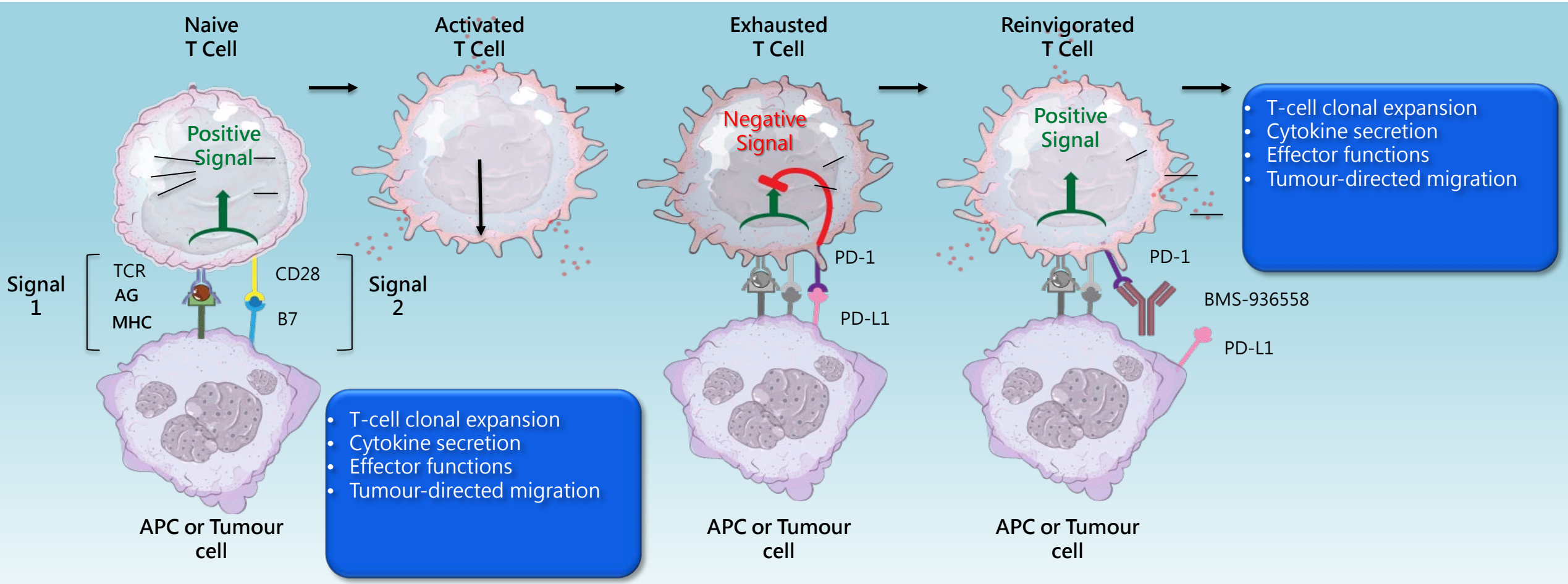
Understanding immune resistance has been key

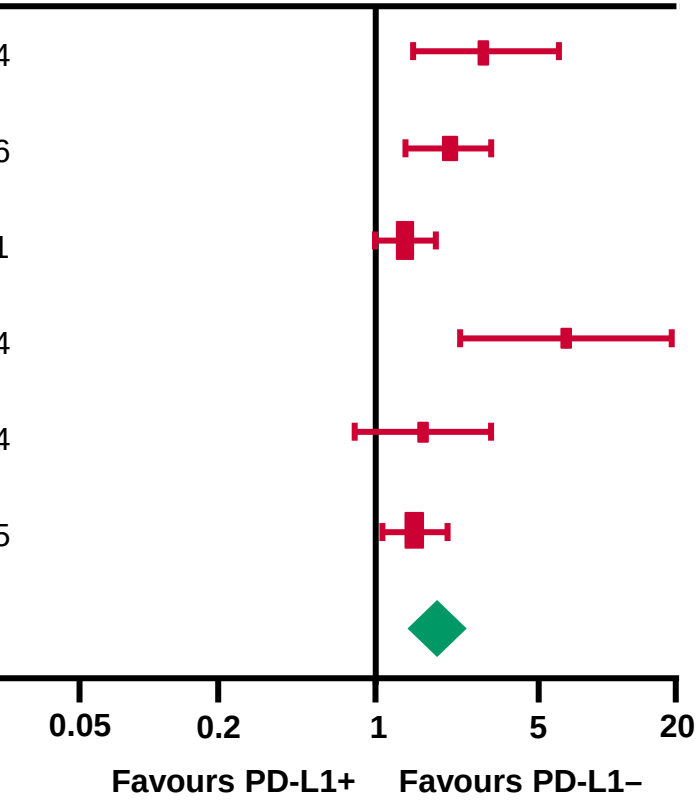


AG, antigen; APC, antigen presenting cell; MHC, major histocompatibility complex; PD-1, programmed death-1; TCR, T-cell receptor.

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

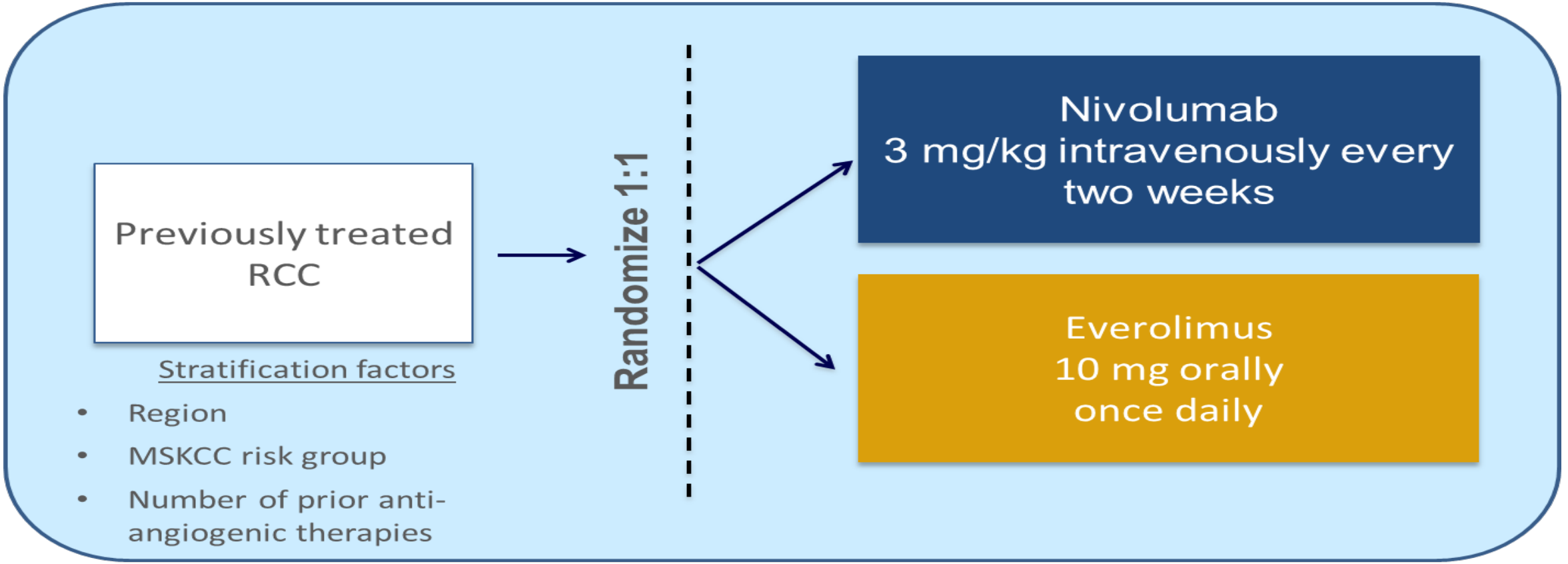
Study or subgroup	Log [HR]	SE	Weight (%)	HR IV, random, 95% CI	Year
Thompson et al.[1]	1.068	0.3769	11.8	2.91 [1.39, 6.13]	2004
Thompson et al.[2]	0.6932	0.2317	19.4	2.00 [1.27, 3.15]	2006
Frigola et al.[3]	0.2546	0.1561	24.7	1.29 [0.95, 1.76]	2011
Choueiri et al.[4]	1.8577	0.5526	6.9	6.41 [2.17, 18.88]	2014
Crispin et al.[5]	0.4253	0.3503	12.9	1.53 [0.77, 3.10]	2014
Choueiri et al.[6]	0.3586	0.163	24.2	1.43 [1.04, 1.97]	2015
Total (95% CI)			**100.0**	**1.81 [1.31, 2.50]**	



Heterogeneity: Tau²=0.08; Chi²=12.14, df=5 (p=0.03); I²=59%
Test for overall effect: Z=3.63 (p=0.0003)

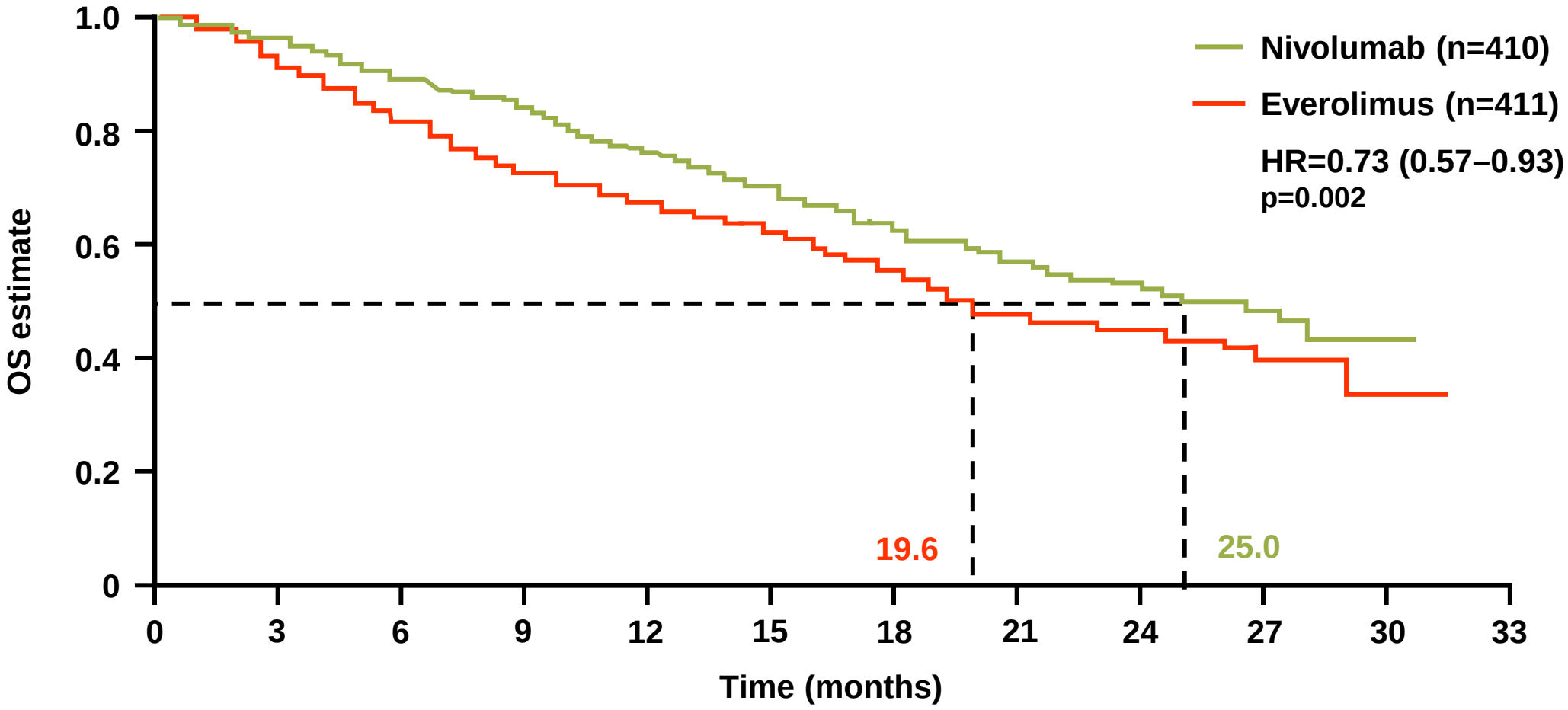
1. Thompson et al. Proc Natl Acad Sci USA 2004; 2. Thompson et al. Cancer Res 2006; 3. Frigola et al. Clin Cancer Res 2011
4. Choueiri et al. Ann Oncol 2014; 5. Crispin et al. J Clin Oncol 2014; 6. Choueiri et al. Clin Cancer Res 2015
Table adapted from Iacovelli et al. Target Oncol 2015

CheckMate 025 phase III



Motzer RJ, et al. *N Eng J Med.* 2015;373(19):1803-1813.

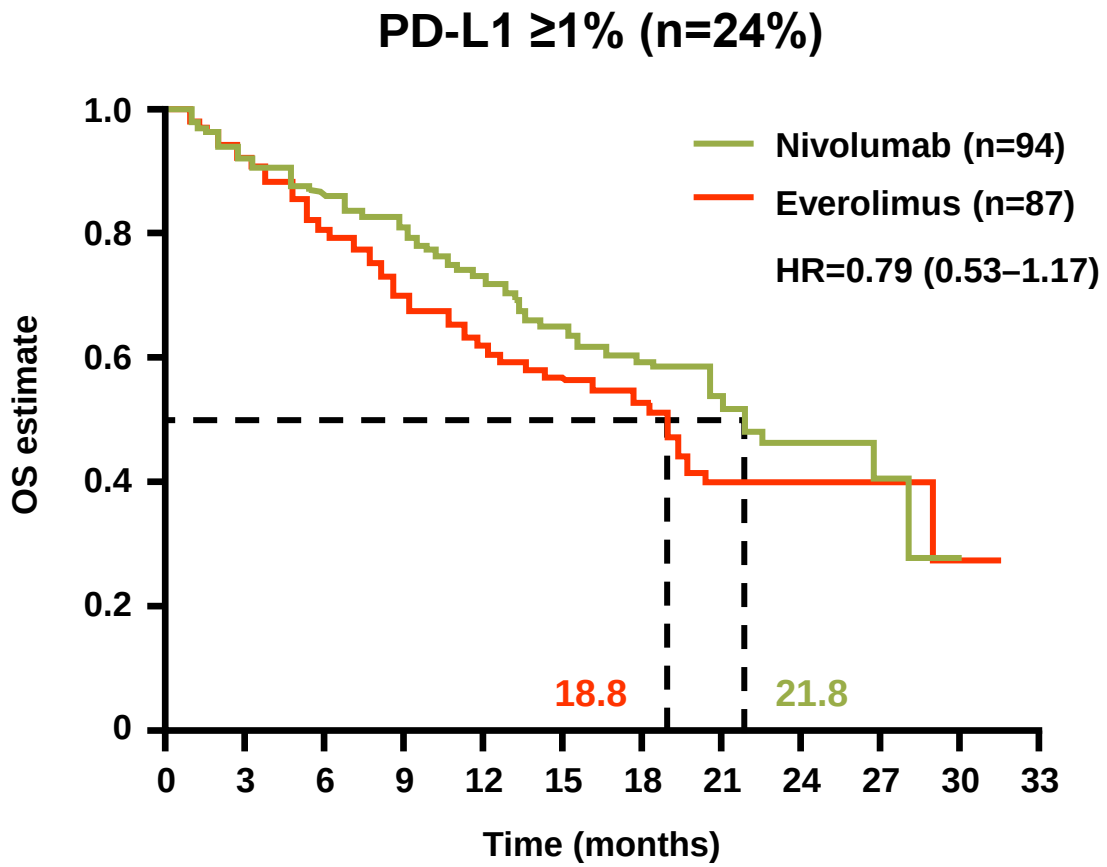
CheckMate 025 (phase III): nivolumab associated with longer OS vs everolimus in previously treated mRCC

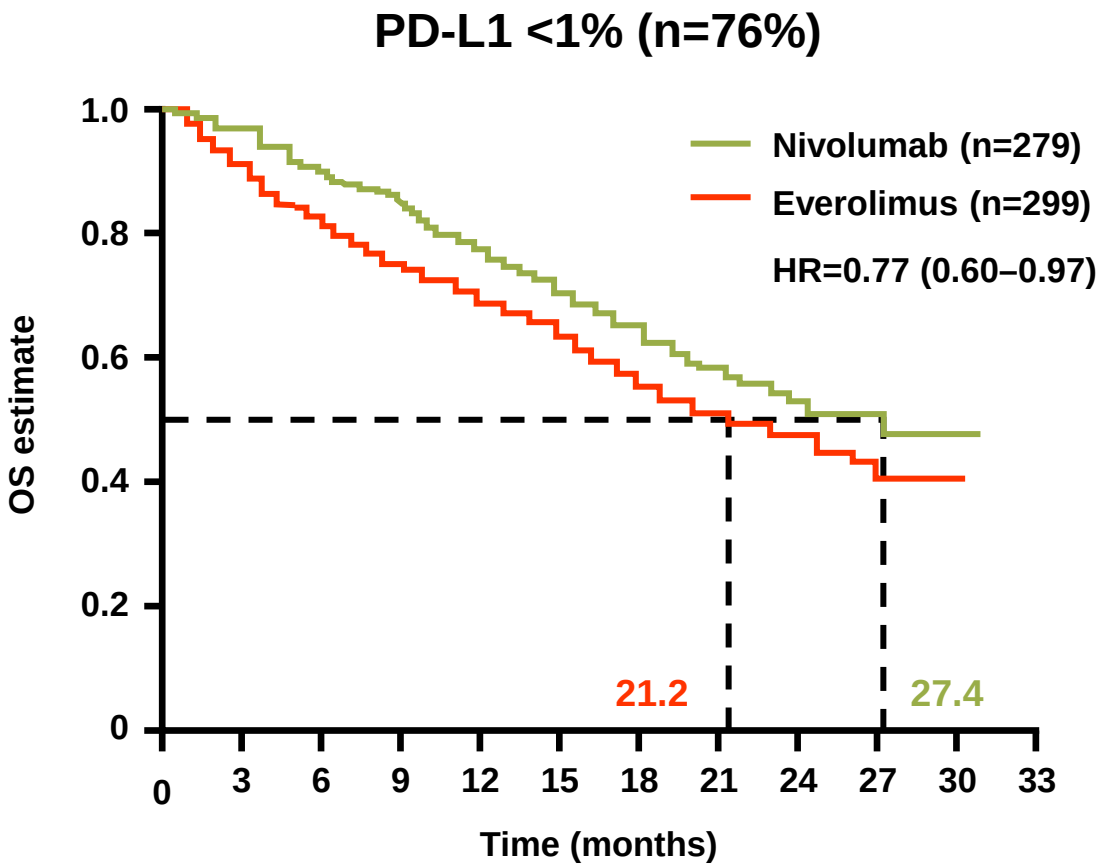


Minimum follow-up = 14 months

Sharma et al. ECC 2015; Motzer et al. N Engl J Med 2015

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





Sharma et al. ECC 2015; Motzer et al. N Engl J Med 2015

CheckMate 025: response outcomes improved with nivolumab

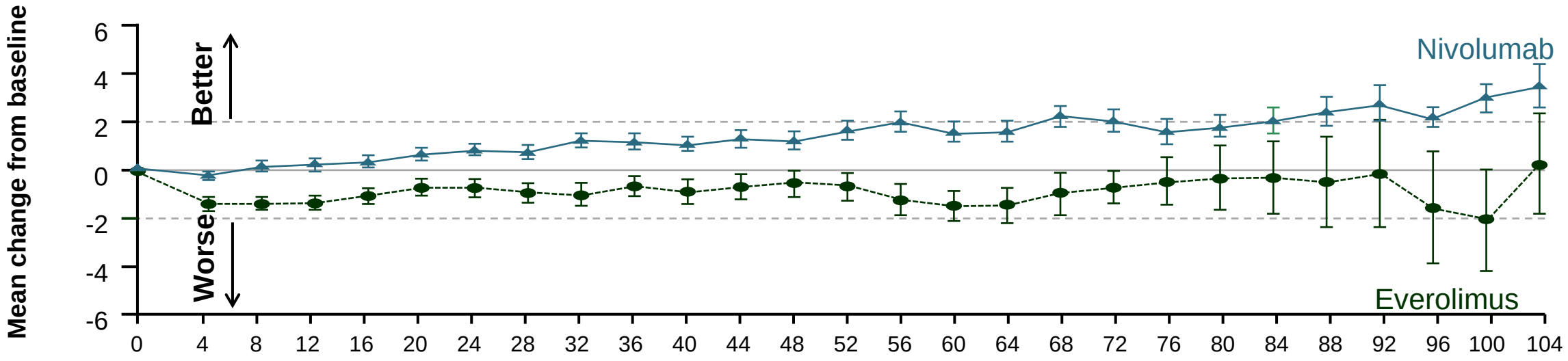
	Nivolumab (n=410)	Everolimus (n=411)
ORR, %	25	5
Odds ratio (p-value)	5.98 (p<0.0001)	
Best overall response, %		
CR	**1**	**1**
PR	**24**	**5**
SD	**34**	**55**
PD	35	28
Not evaluated	6	12
Median time to response (range), months	3.5 (1.4−24.8)	3.7 (1.5−11.2)
Median DOR (range, months)	12.0 (0−27.6)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

Sharma et al. ECC 2015

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)[1]



No. of patients at risk

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

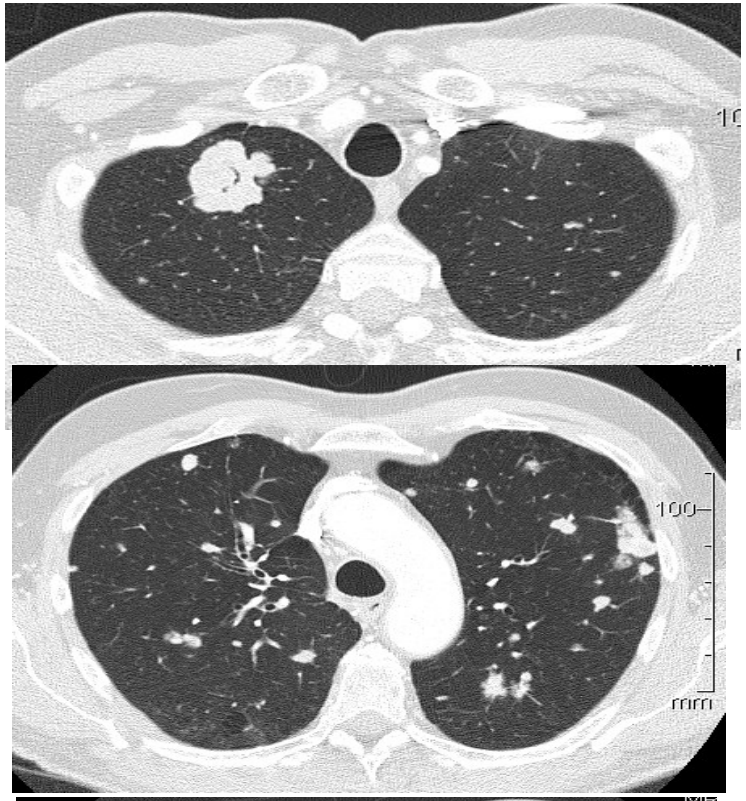
Questionnaire completion rate: ≥80% during the first year of follow-up.

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

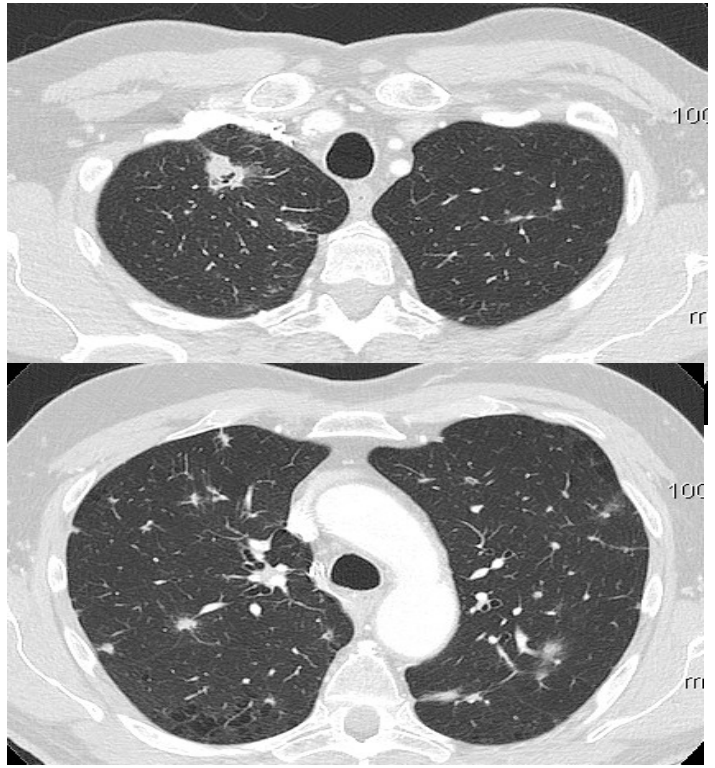


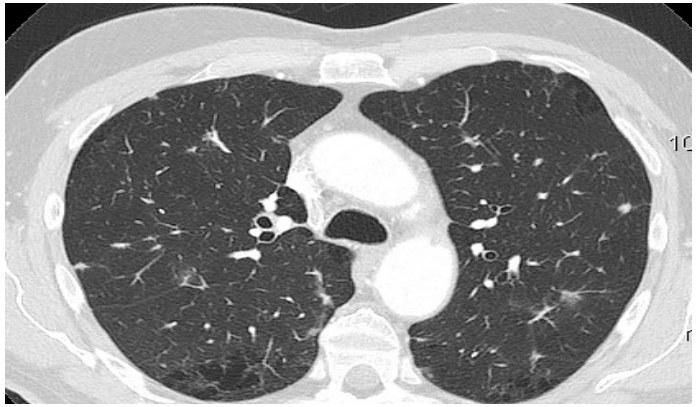
This patient improved after the first infusion

Rapid PR

Now in CR after 19 months

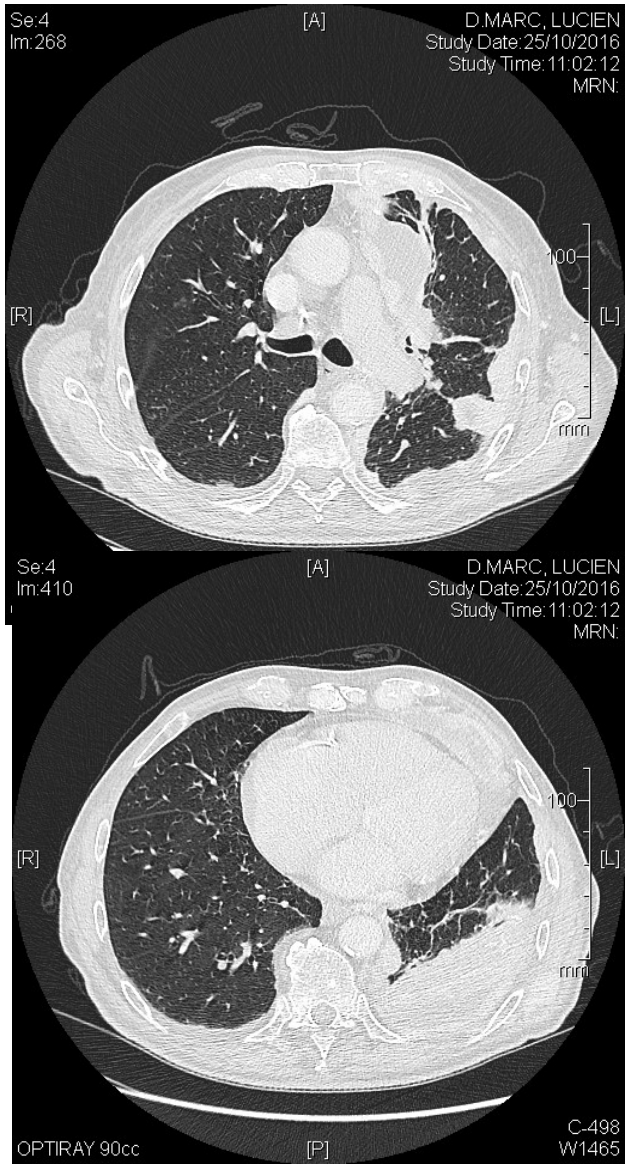
13 Jan 2016





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

Baseline

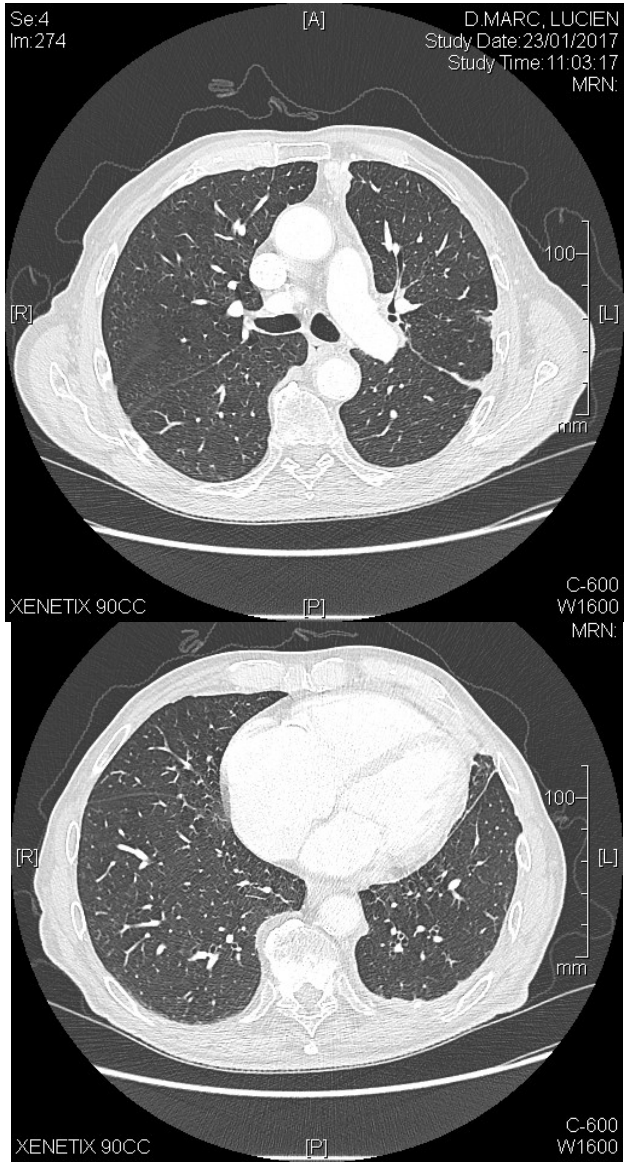


This patient develop PPR

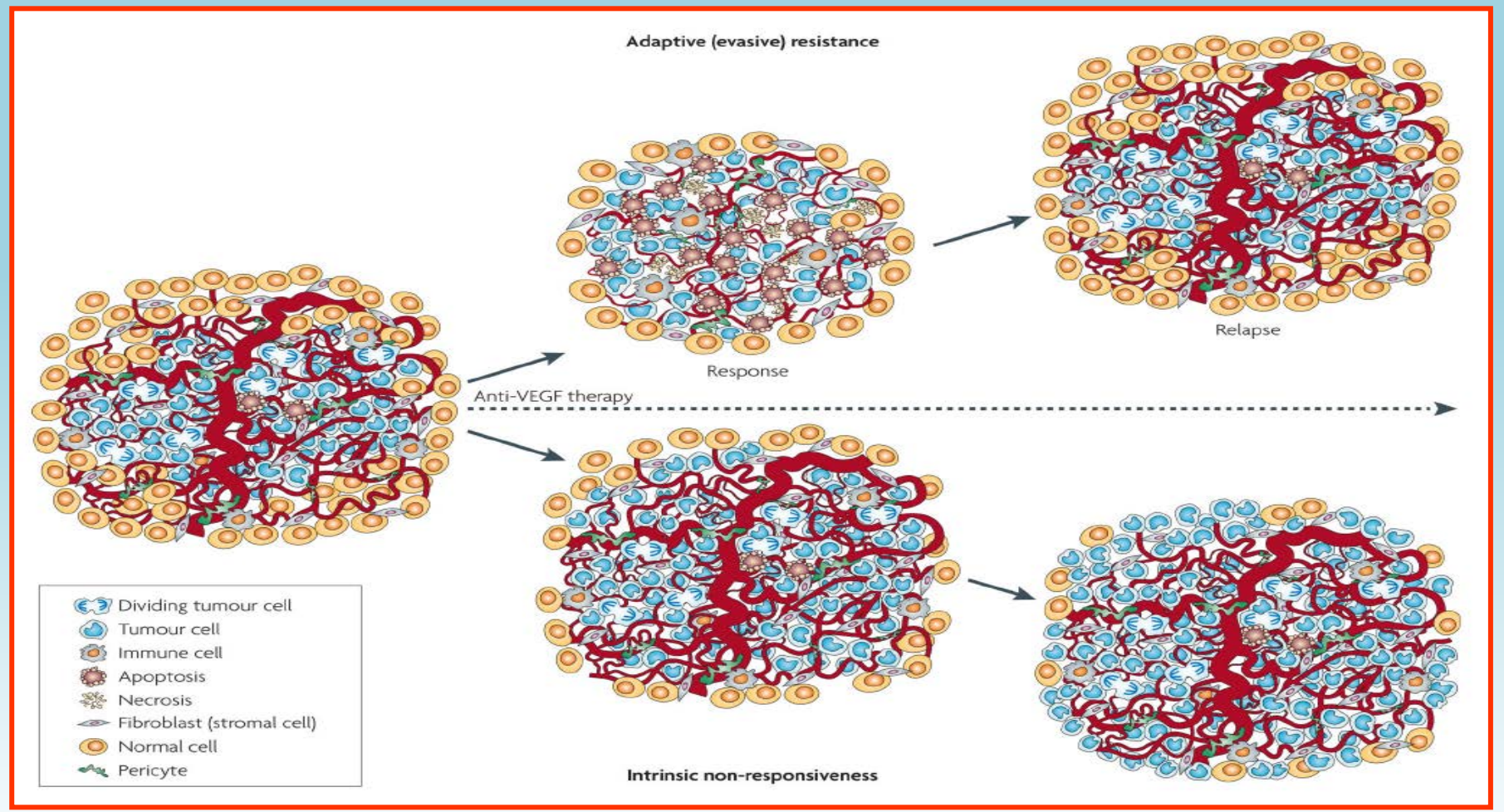
He received steroids

Still on Nivolumab with ongoing response

2 months



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

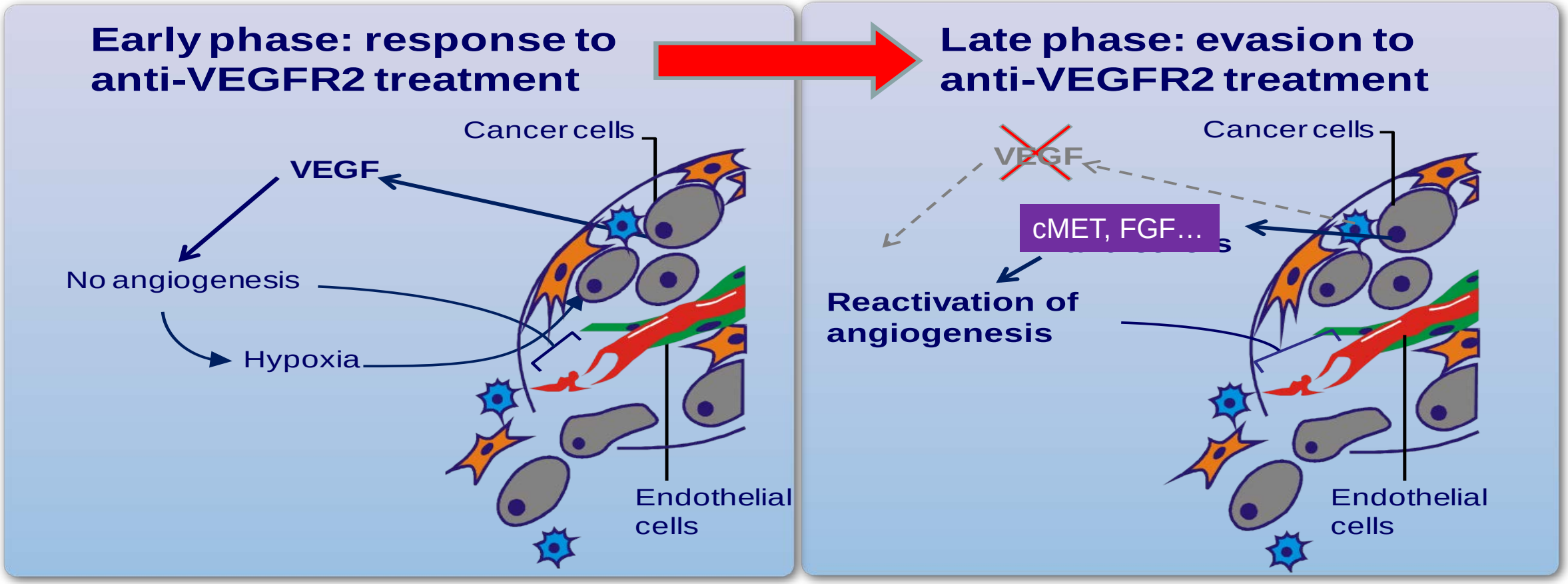


Adaptive resistance:
VEGF-targeted agents fail to produce enduring clinical responses in most patients

Intrinsic resistance:
No predictive biomarkers available to date

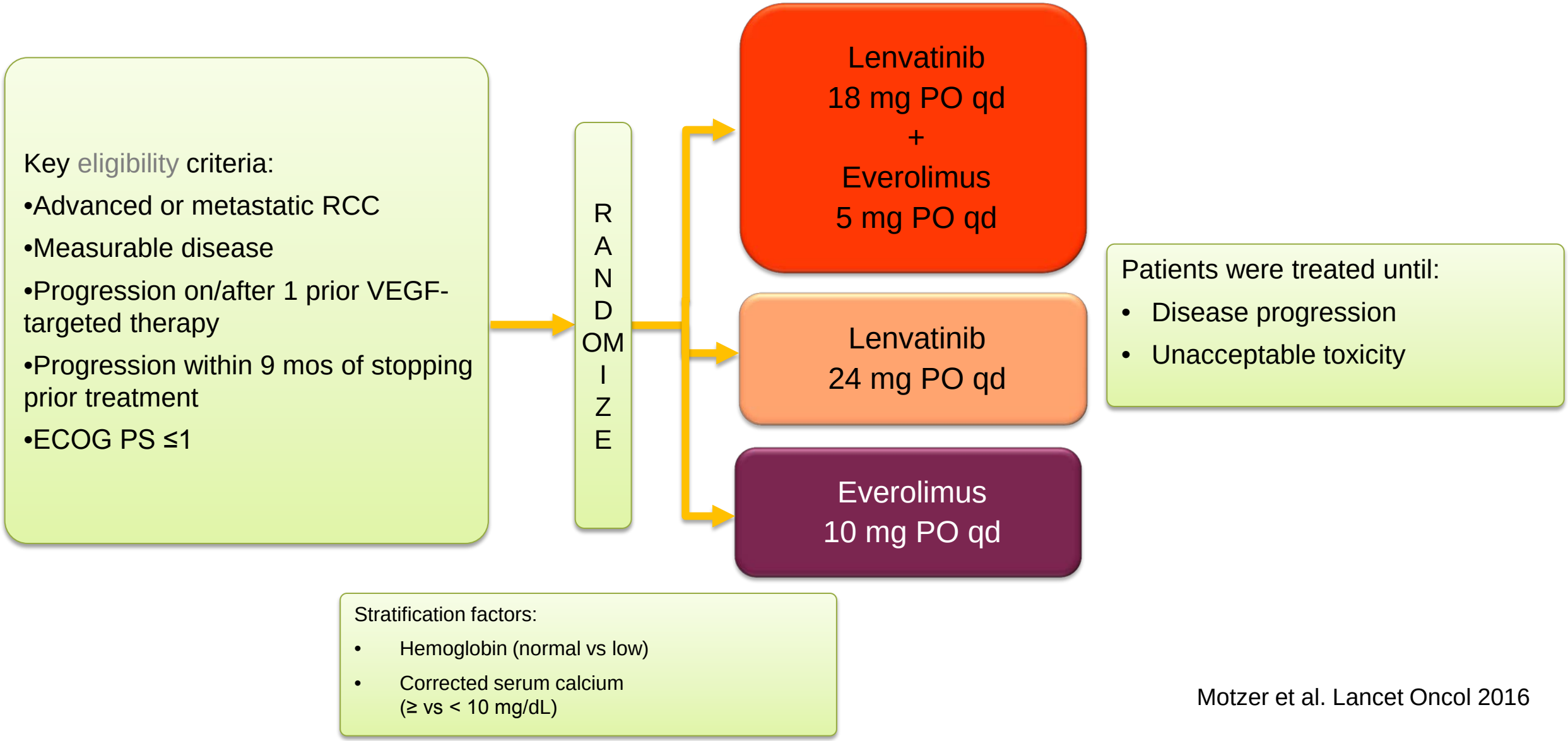
Bergers G, Hanahan D. *Nat Rev Cancer*. 2008;8:592-603.

Several pathways are involved



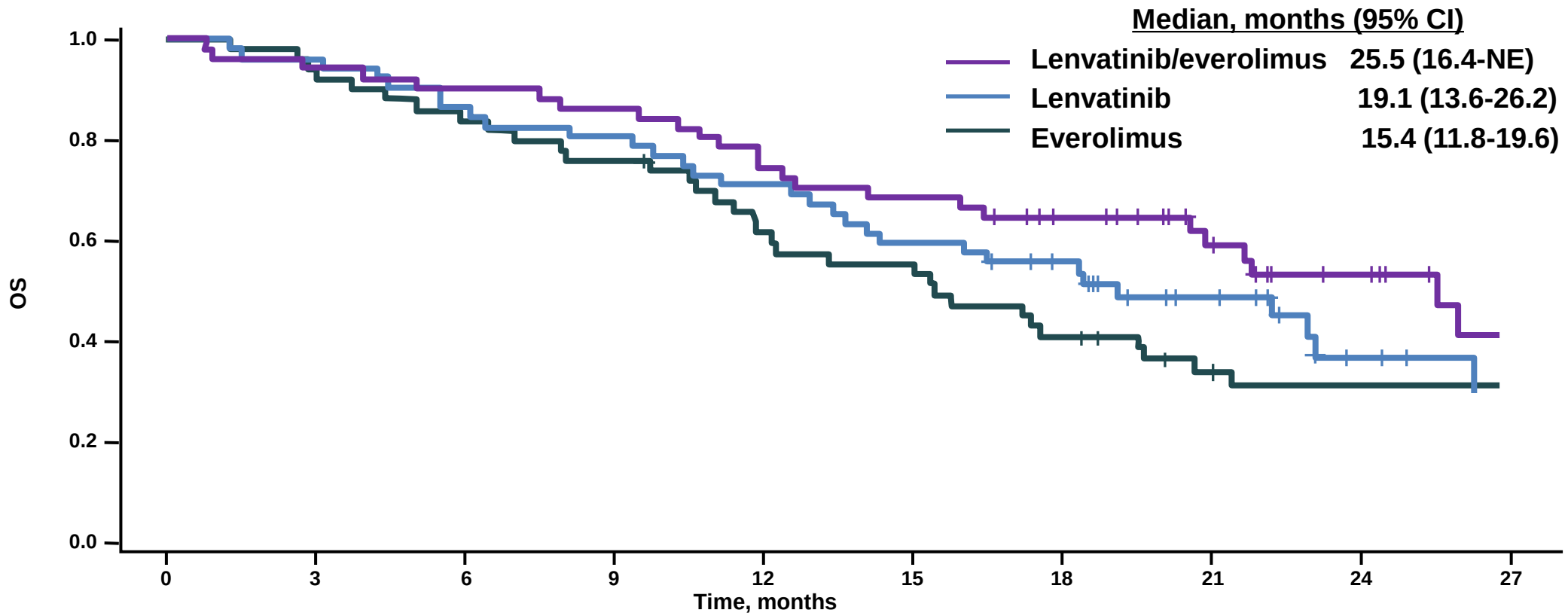
FGF2 is expressed by numerous tumor types and exerts its activity by interacting with TK receptors, heparan-sulfate proteoglycans, and integrins expressed on the endothelial cell surface

Lenvatinib Study Design



Motzer et al. Lancet Oncol 2016

Secondary Endpoint: OS

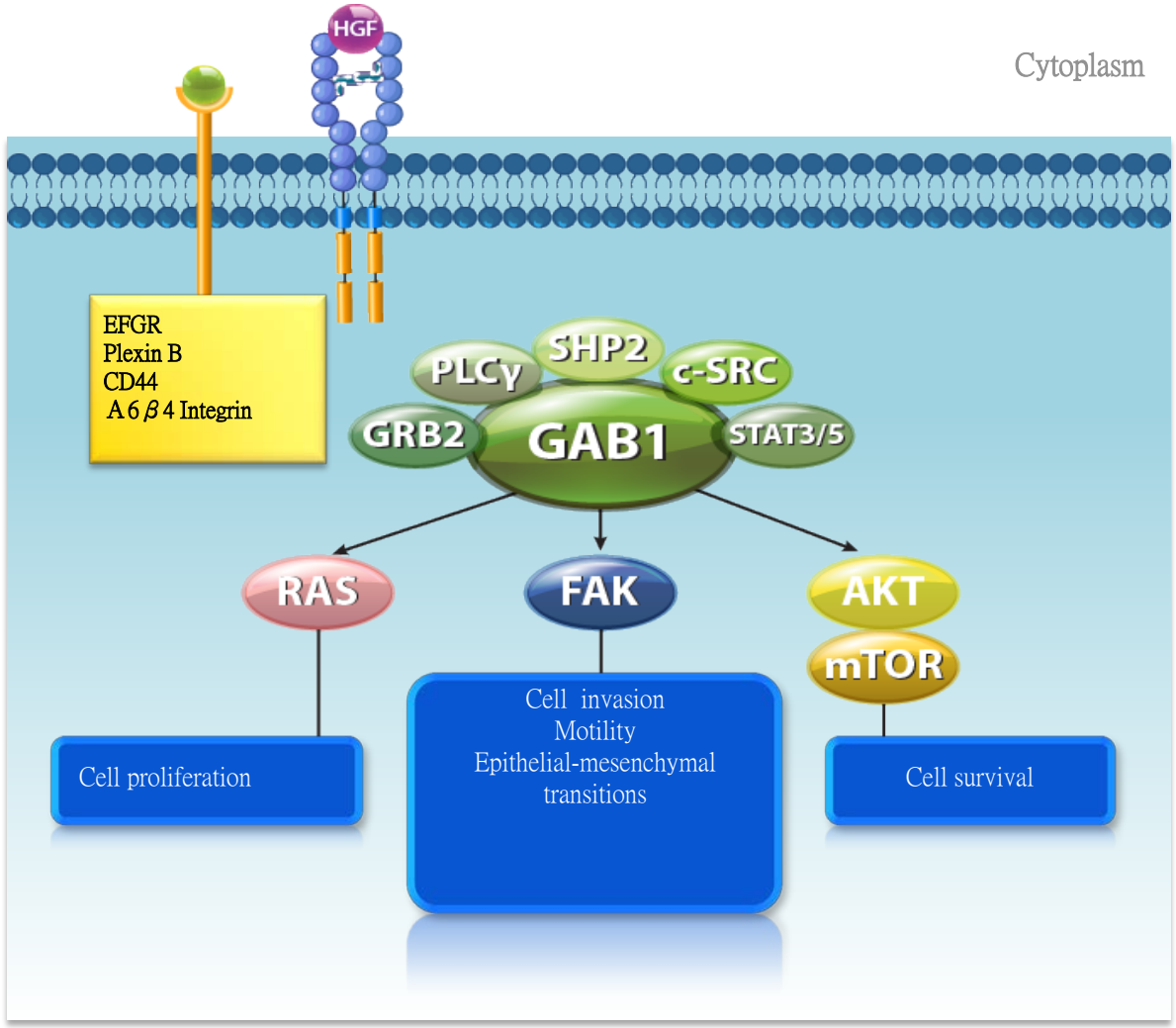


Lenvatinib/everolimus vs Everolimus
HR = 0.51 (95% CI, 0.30-0.88); *P* = 0.024

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

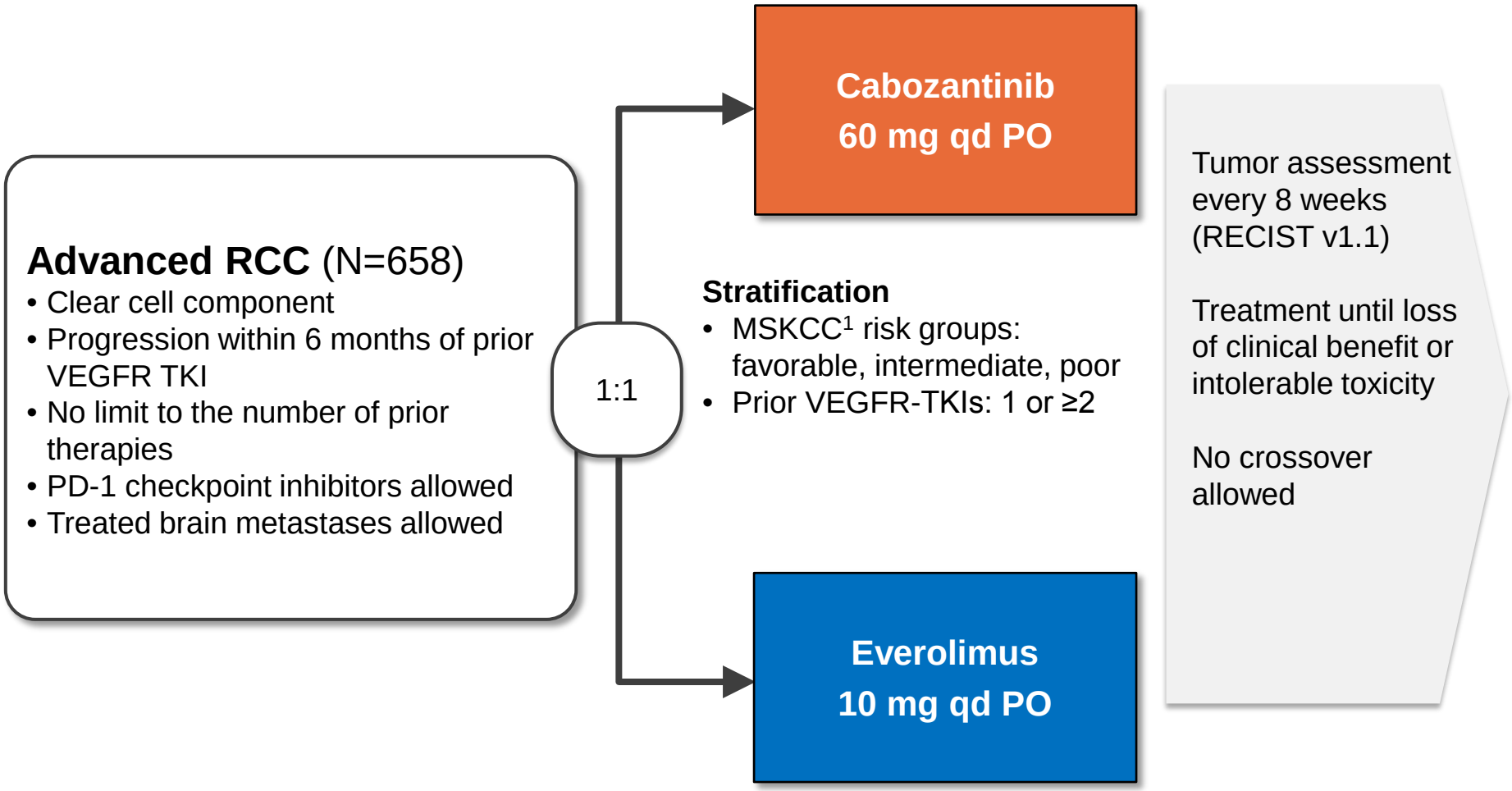
Motzer et al. Lancet Oncol 2016

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

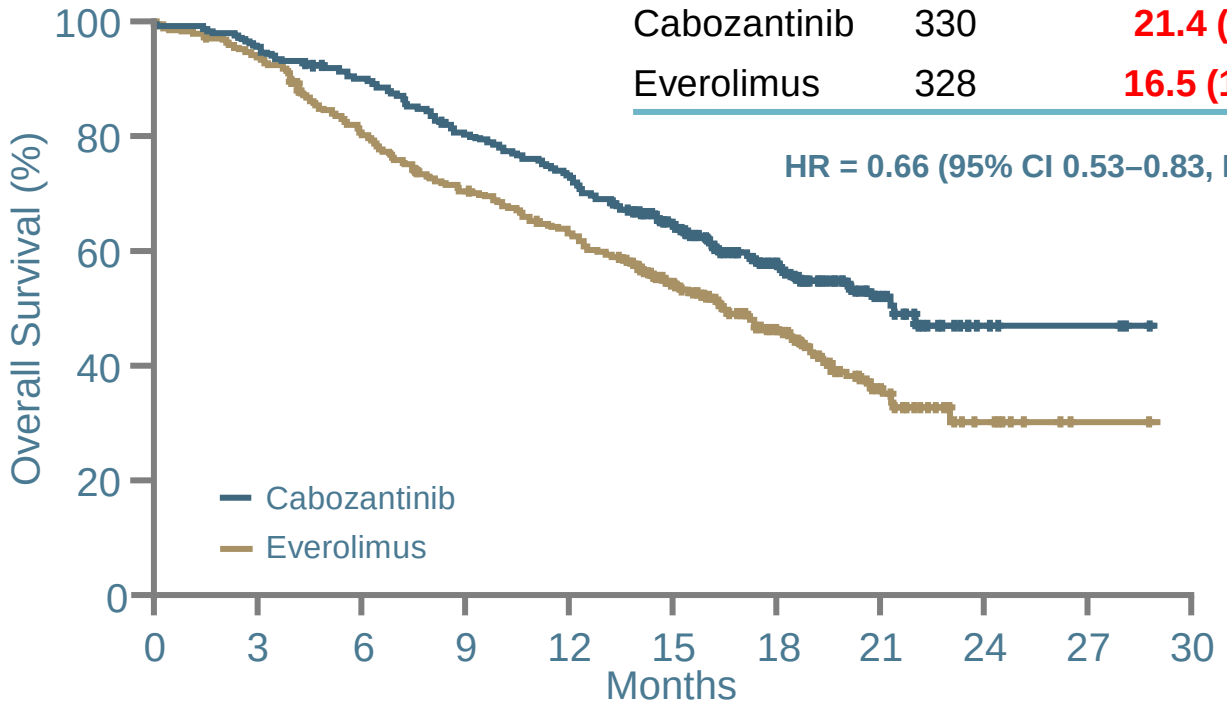
METEOR Study Design



Choueiri TK, et al. Lancet Oncol 2016;17:917–27

Overall Survival

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

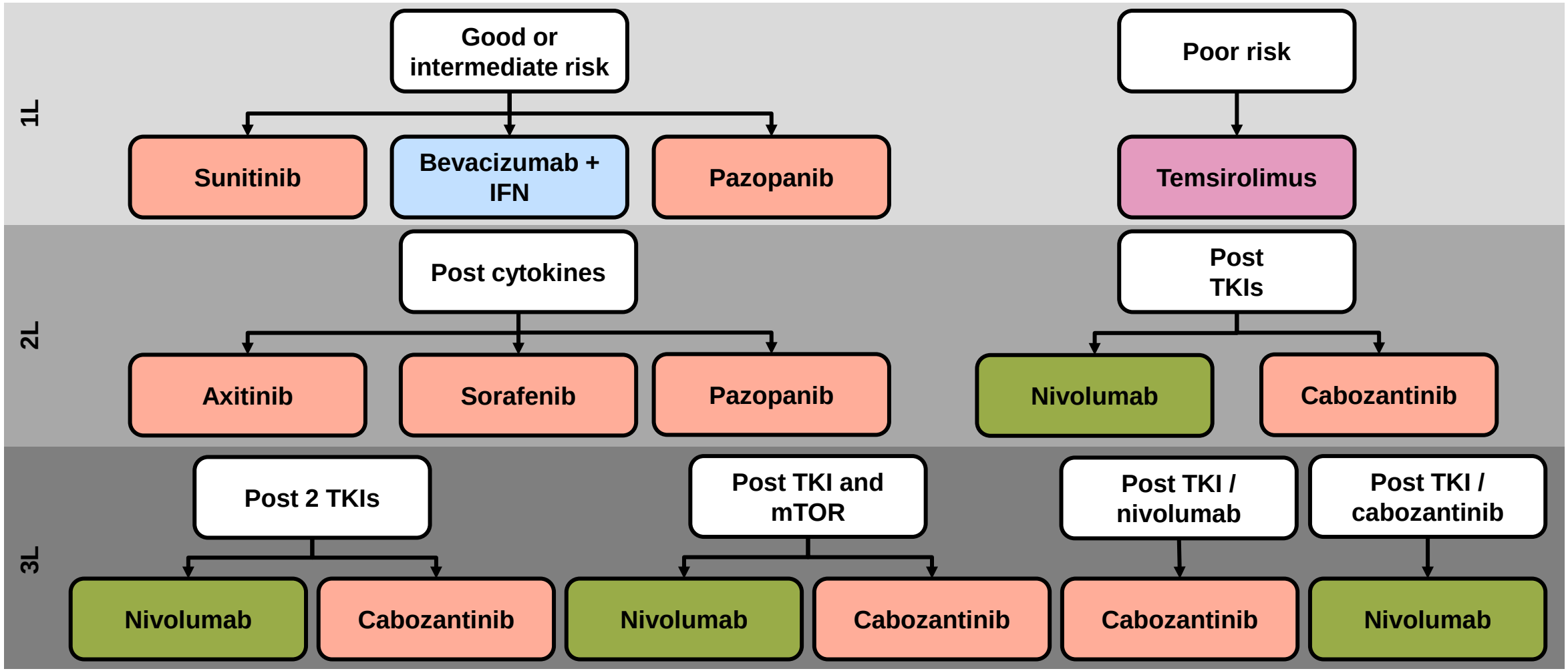


No. at Risk

Cabozantinib	330	318	296	264	239	178	105	41	6	3	0
Everolimus	328	307	262	229	202	141	82	32	8	1	0

Choueiri TK, et al. Lancet Oncol 2016;17:917–27

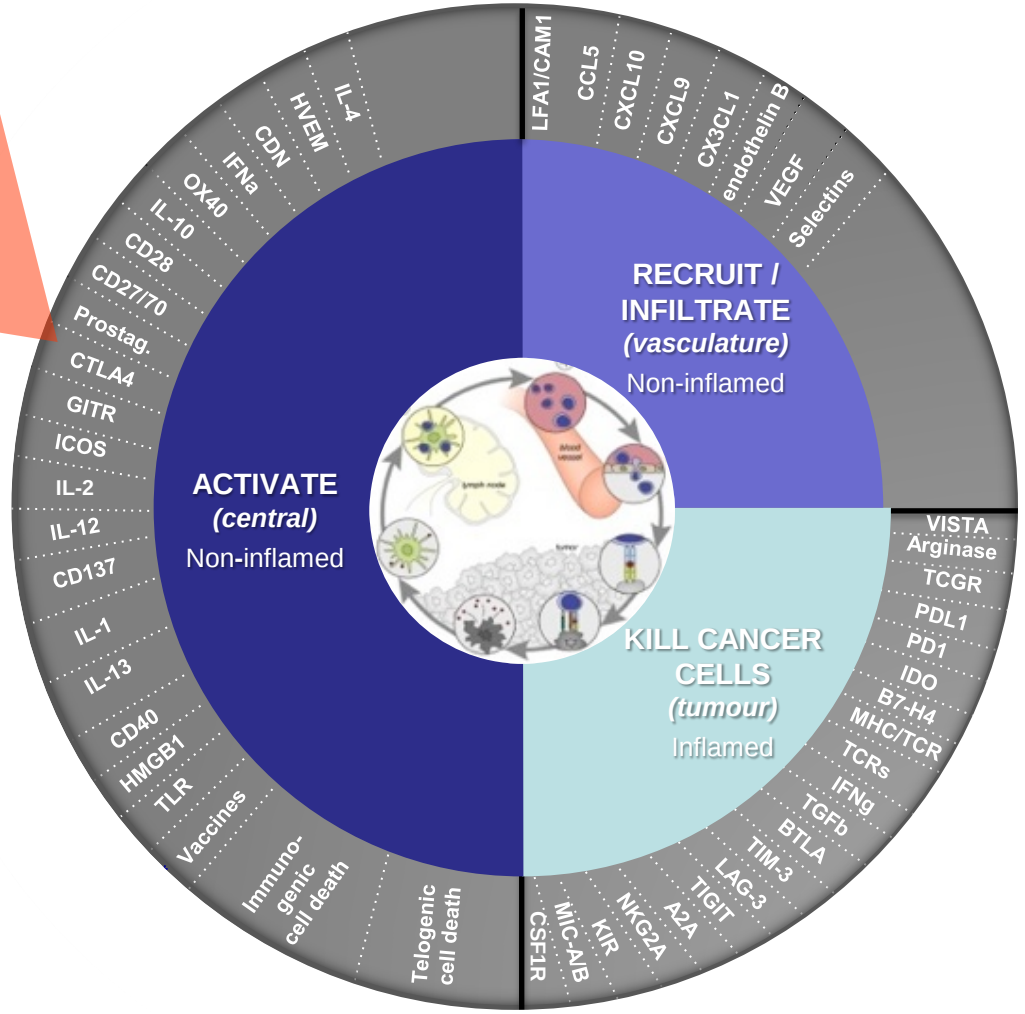
Updated ESMO guidelines: algorithm for systemic treatment in clear cell mRCC



Escudier et al. Ann Oncol 2016

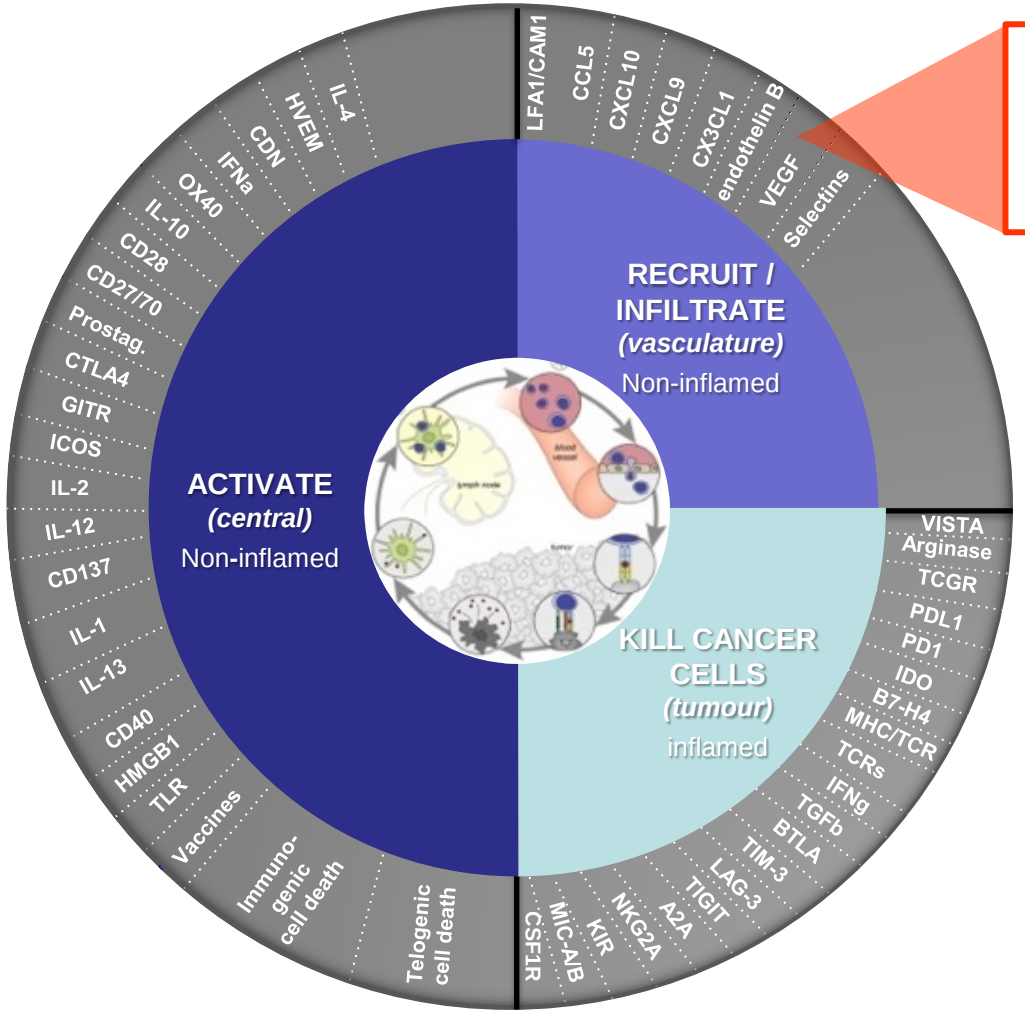
How can we further enhance responses?

CTLA4 inhibitors
- Priming and activation of T cells



Chen and Mellman. Immunity 2013

How can we further enhance responses?

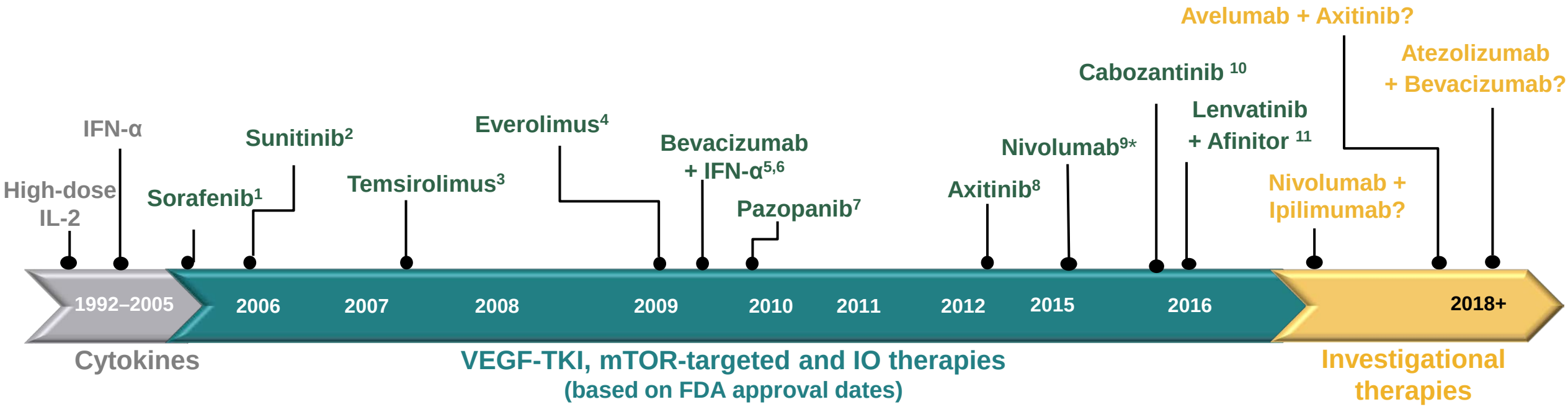


VEGF inhibitors

- Infiltration of T cells into tumours

Chen and Mellman. Immunity 2013

The evolving treatment landscape of mRCC



aRCC, advanced renal cell carcinoma; FDA, US Food and Drug Administration; IFN-α, interferon α; 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; 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.

First-line trials expected soon

PD1 + CTLA4 inhibition

CheckMate-214[1]
Phase III

R

Sunitinib
50 mg/day 4/2

N = 1071

Nivolumab + ipilimumab
3 mg/kg IV + 1 mg/kg IV
every 3 weeks × 4
then nivolumab 3 mg/kg IV every 2 weeks

Co-primary endpoint: PFS, OS

PD-L1 + VEGF inhibition

Immotion-151[2]
Phase III

R

Sunitinib
50 mg/day 4/2

N = 830

Atezolizumab + bevacizumab
1,200 mg IV +
15 mg/kg IV every 3 weeks

Co-primary endpoint: PFS, OS

Personalized immunotherapy + VEGFR inhibition

ADAPT[3]
Phase III

R

Sunitinib

Negative

003 + sunitinib
8 inje ns in first year followed by quarterly
boosters + sunitinib

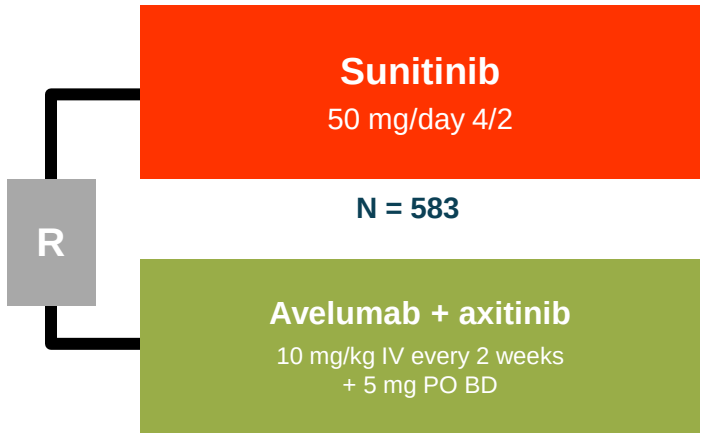
Primary endpoint: OS

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

PD-L1 + VEGFR TK inhibition

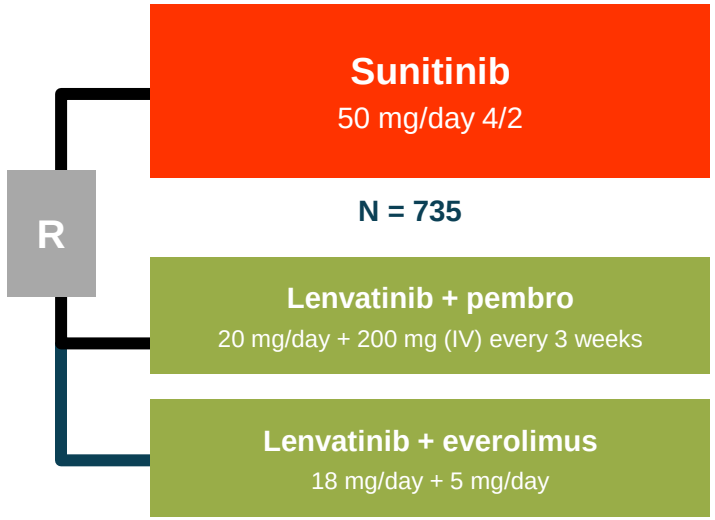
Javelin renal 101[2]
Phase III



Primary endpoint: PFS

Combination VEGFR + mTOR/PD1 inhibition

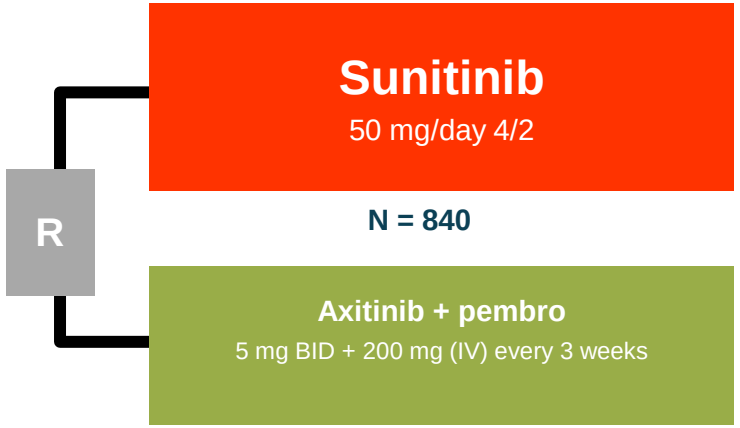
Lenvatinib + everolimus or pembrolizumab[3]
Phase III



Primary endpoint: PFS

PD1 + VEGFR TK inhibition

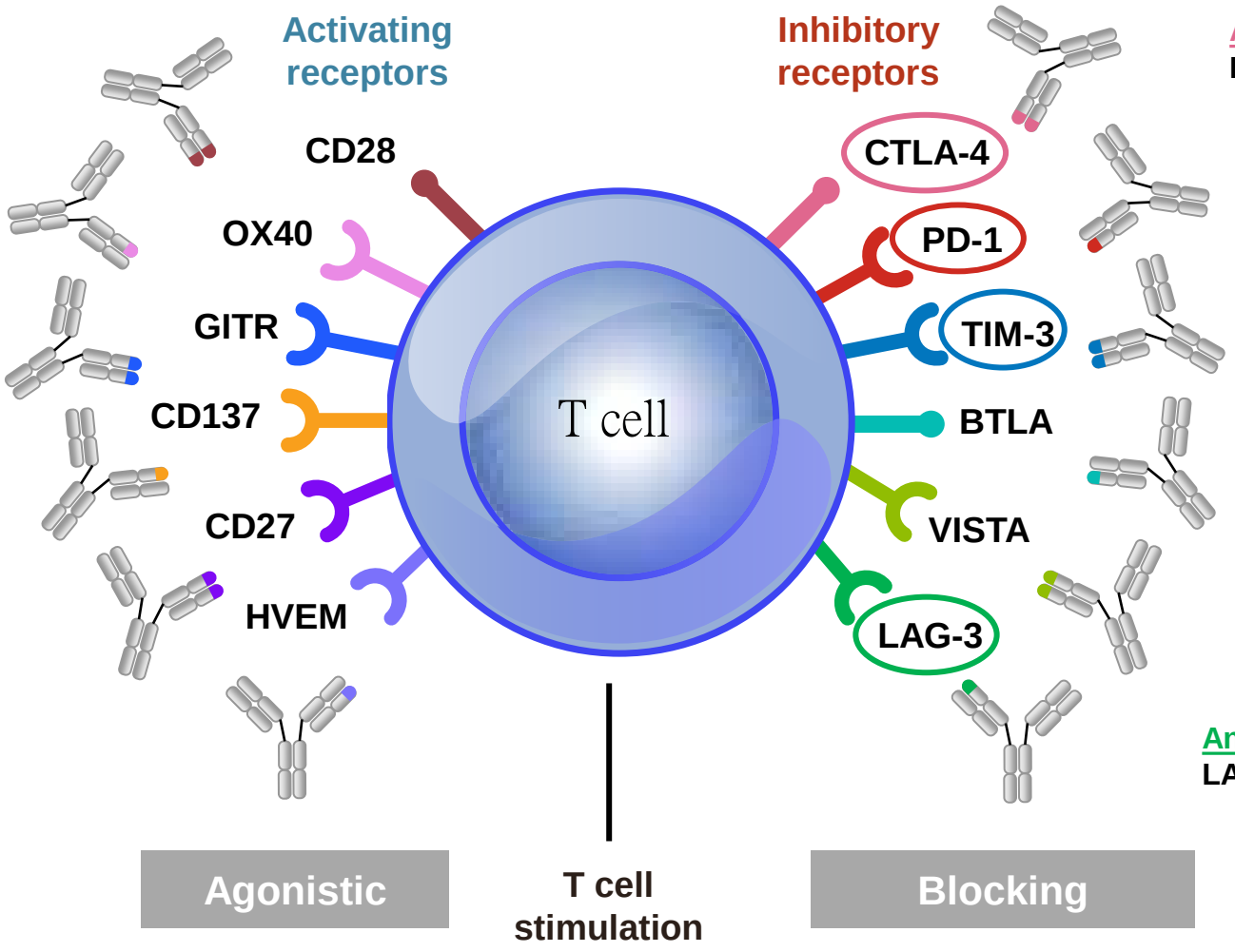
KEYNOTE-426[3]
Phase III



Co-primary endpoint: PFS, OS

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



Anti-CTLA4
Ipilimumab (phase II and III)

Anti-PD1
Pembrolizumab (phase III)
PDR001 (phase I/II)
Nivolumab (phase II/III)

Anti-PDL1
Atezolizumab (phase II and III)
Avelumab (phase III)

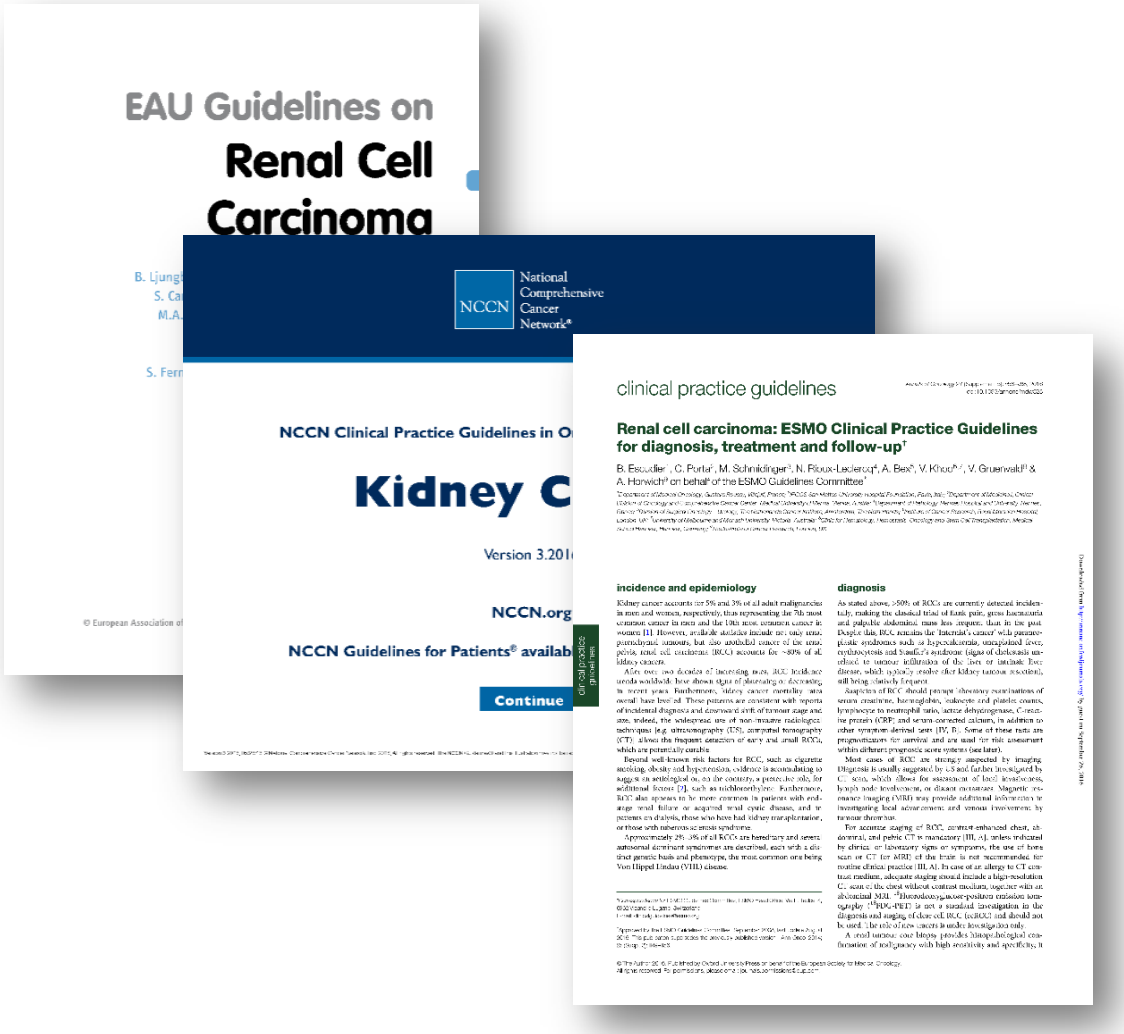
Anti-TIM3
MBG453 (Phase I/II)

Anti-LAG3
LAG525 (phase I/II)

Mellman et al. Nature 2011

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?



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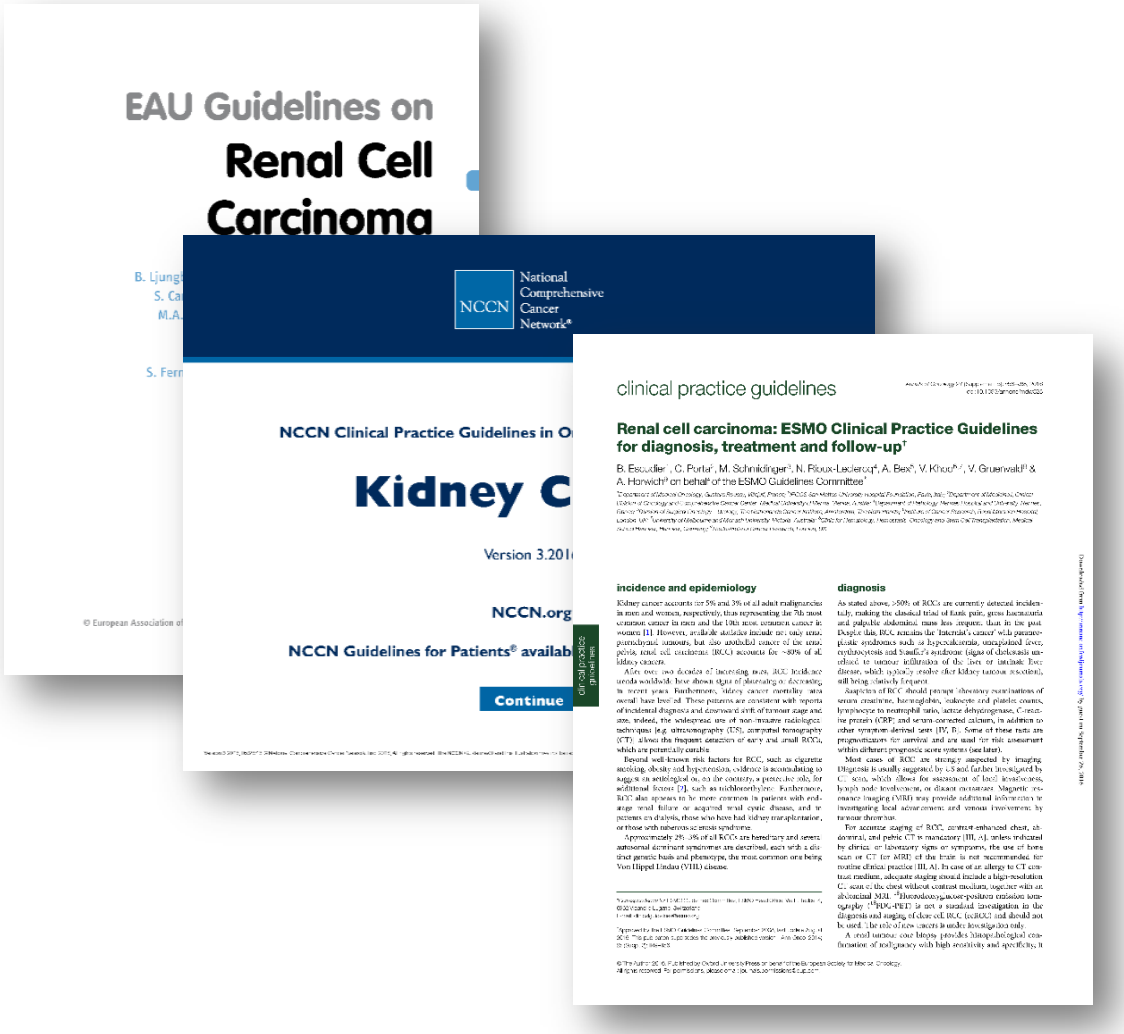
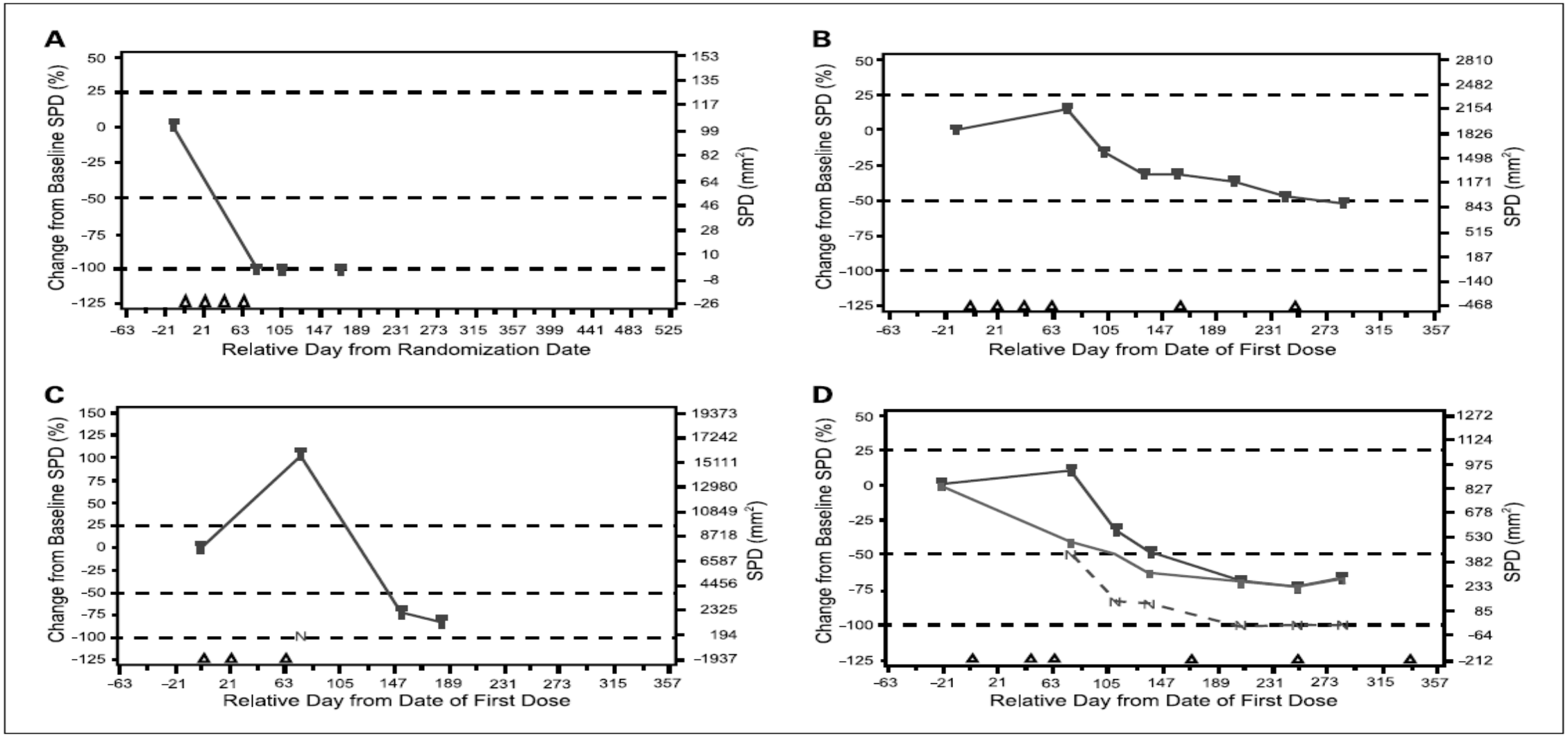


New response types with immunotherapy



Immune-Related Response Criteria

Wolchok et al Clin Cancer Res 2009

There is a large evidence that

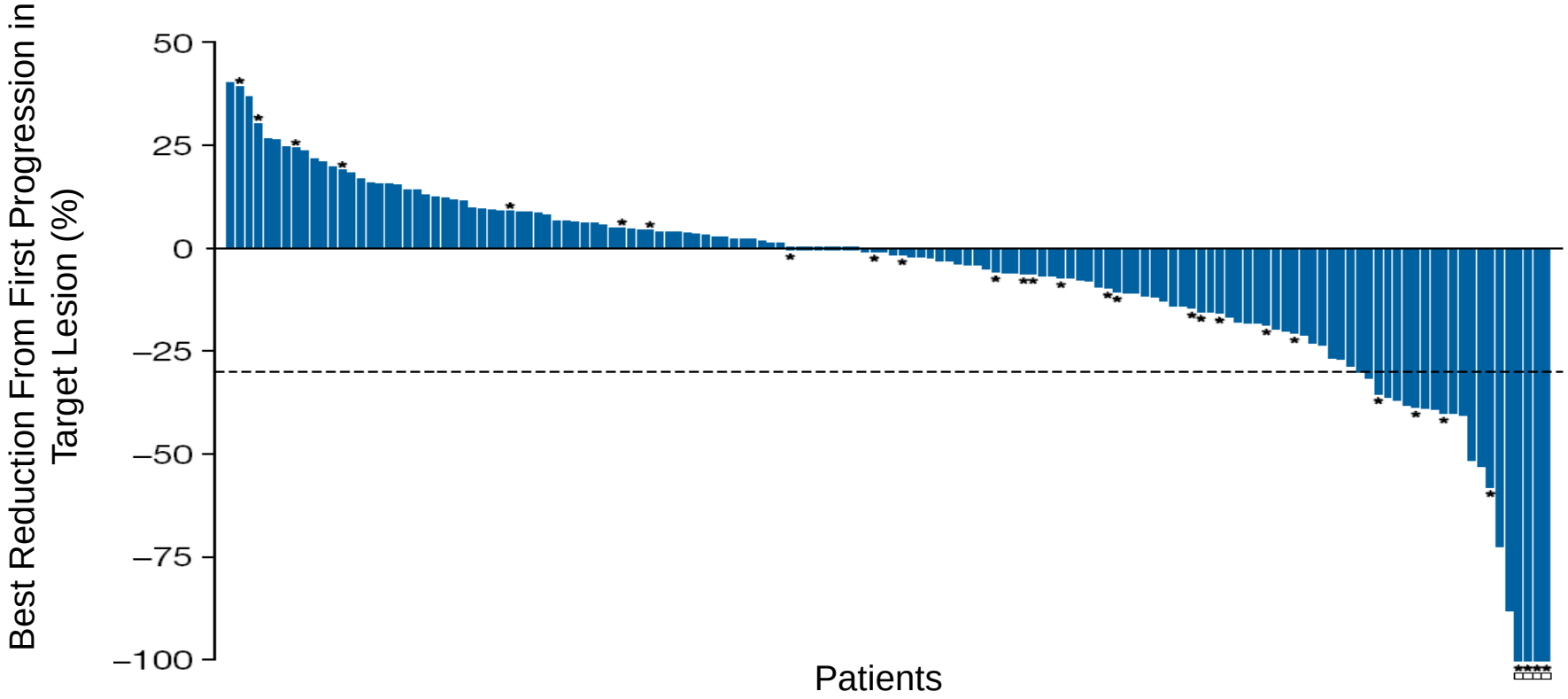
1. Treatment can be stopped:
   - Especially in case of CR
   - In case of severe toxicity
   - Ongoing discontinuation trials are needed

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 ≥30% reduction in tumor burden post-progression



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

Escudier et al. Eur Urol 2017, in press

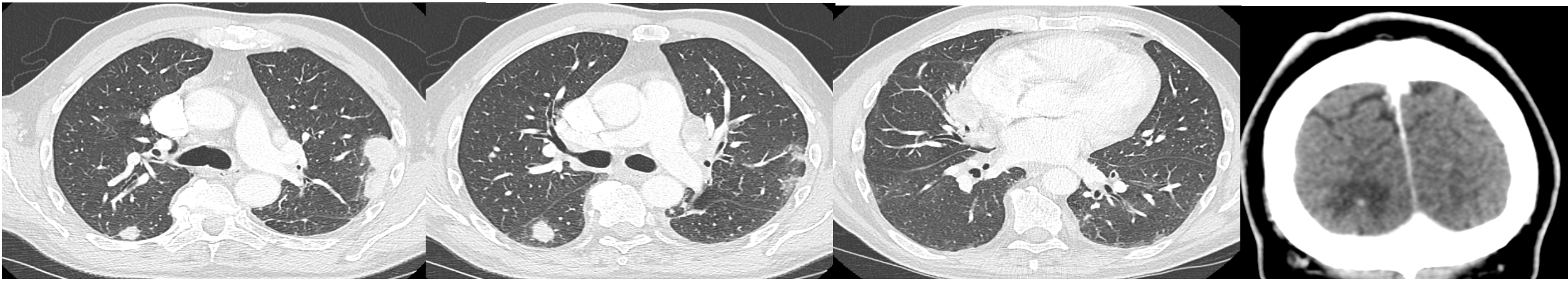
Who should we treat beyond progression?

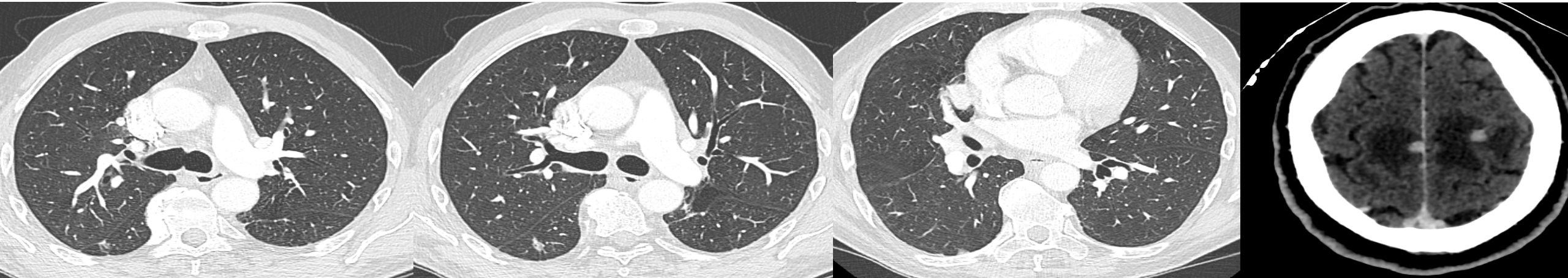
- Patients with good safety profile
- Patients with « clinical benefit »
  - No impairment of general condition
  - No major progression

- Commonly those with dissociated responses

Good patients to treat beyond progression

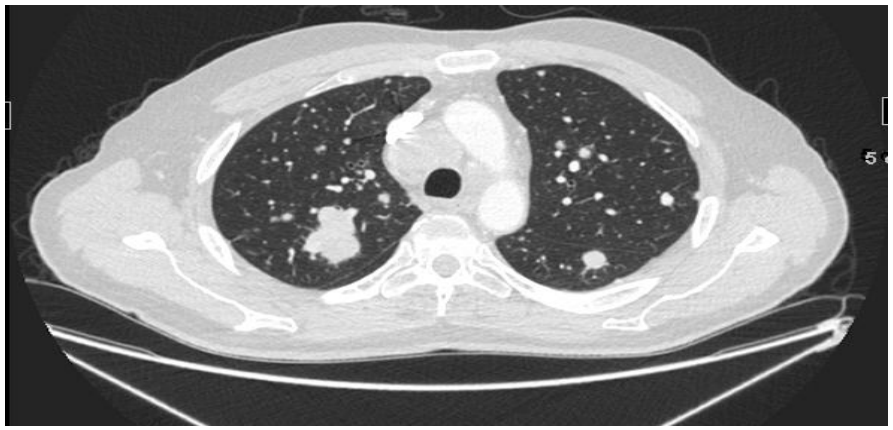
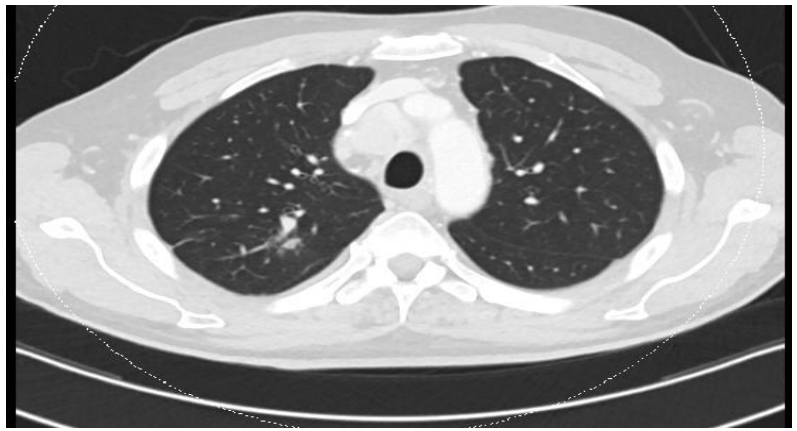
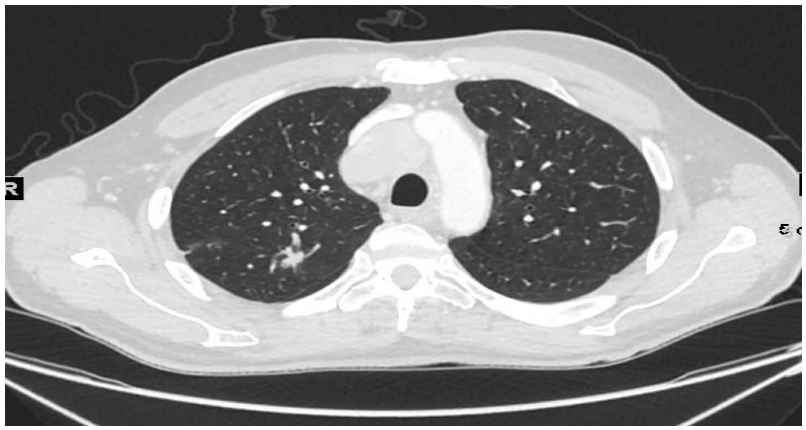
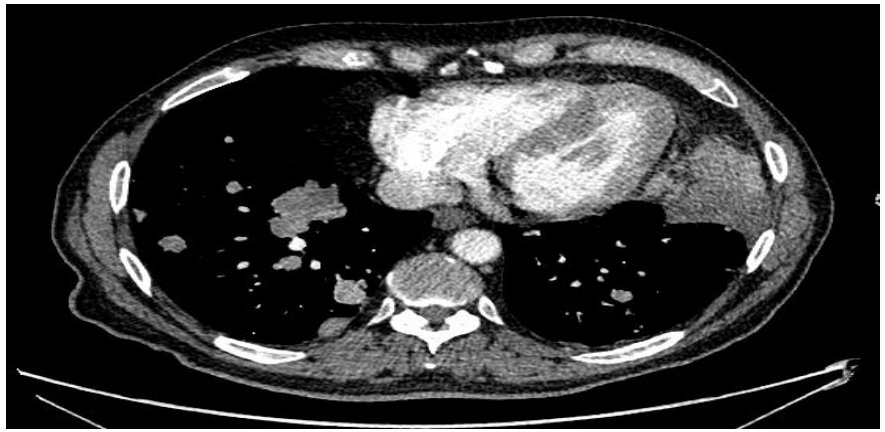
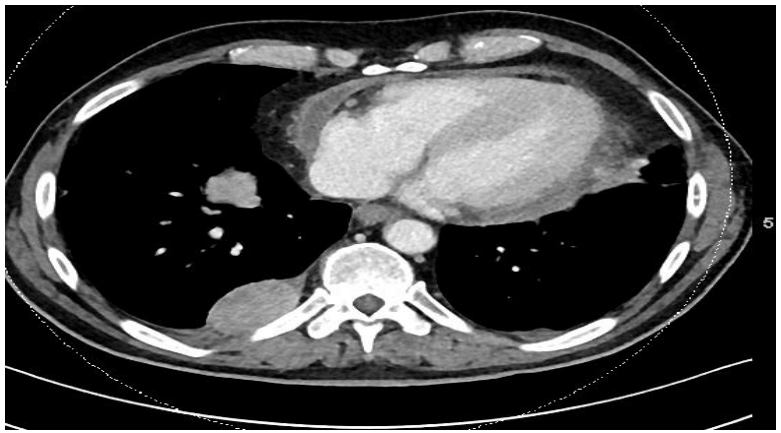
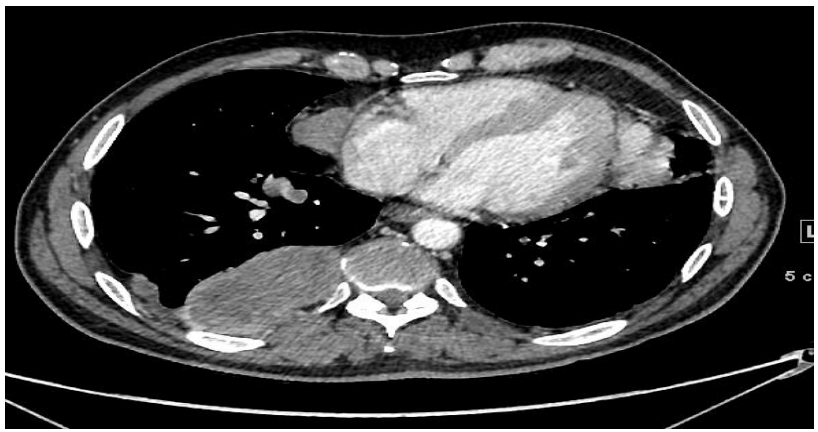
- Case 1





Good patients to treat beyond progression

- Case 2

BL 8w 16w

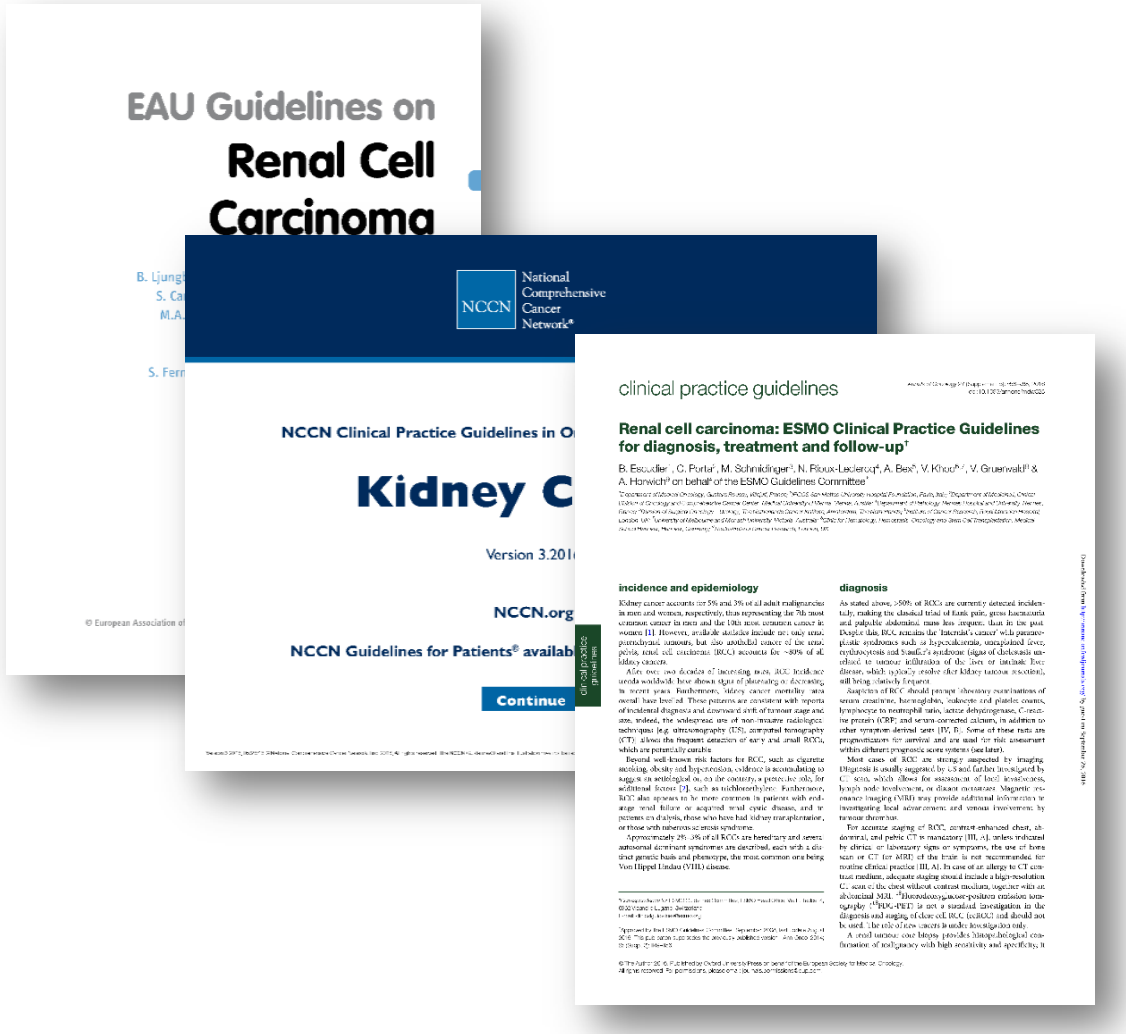
What is the future of immunotherapy in RCC and melanoma?

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?



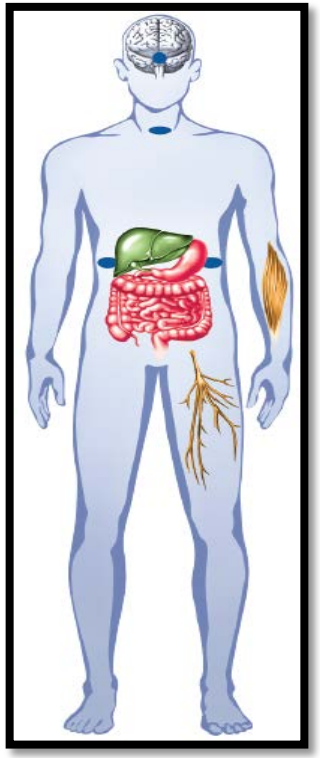
Treatment-Related AEs Occurring in ≥10% of Patients in Either Arm

Event	Nivolumab N=406		Everolimus N=397	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Treatment-related AEs, %	79	**19**	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[1]

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



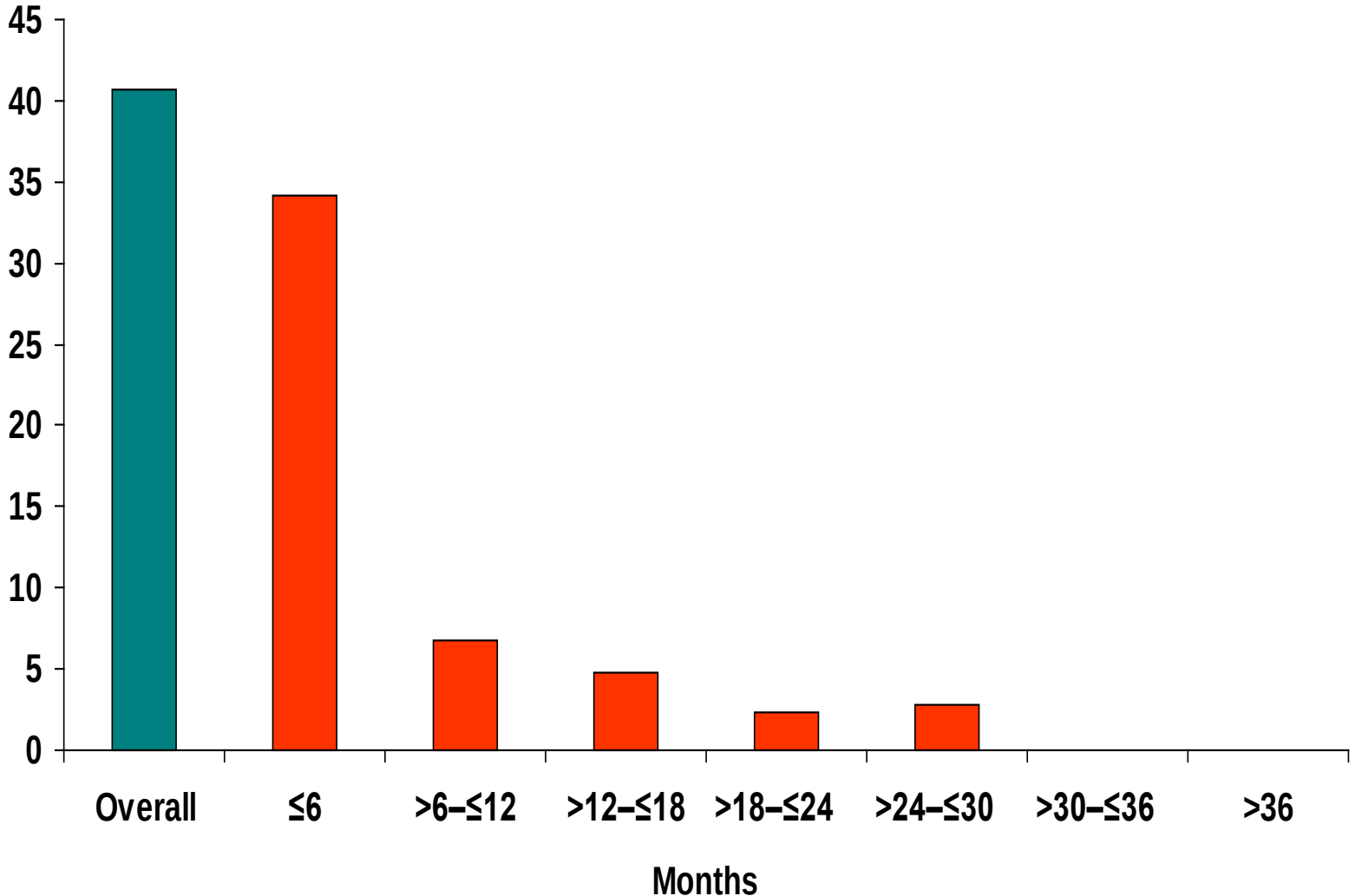
irAEs occur in certain organ systems:[1]

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

1. Amos SM et al. *Blood*. 2011;118:499–509; 2. YERVOY™ (ipilimumab) Immune-Mediated Adverse Reaction Management Guide. October 2012. http://www.accessdata.fda.gov/drugsatfda_docs/rems/Yervoy_2012-02-16_IMMUNE%20MEDIATED%20ADVERSE%20REACTION%20MANAGEMENT%20GUIDE.pdf. March 2011. Accessed May 12, 2016; 3. Association of Community Cancer Centers. Advancing Immuno-Oncology in the Community Setting. http://accc-iclio.org/resources/iclio-white-paper/. Accessed May 12, 2016.

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