Incontri
di aggiornamento
del Dipartimento
Oncologico

Responsabile Scientifico:
DOTT.SSA STEFANIA GORI

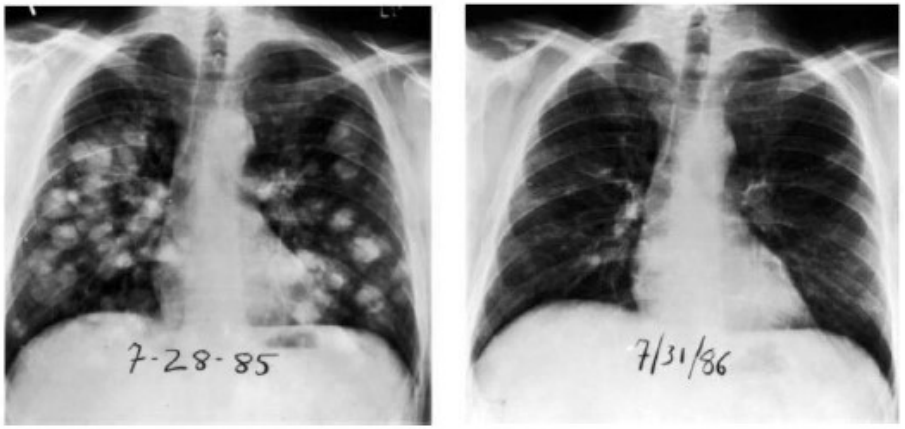
Meccanismo d'azione e indicazioni terapeutiche

Immunoterapia nel carcinoma renale

Michele Milella
Università di Verona/AOUI Verona

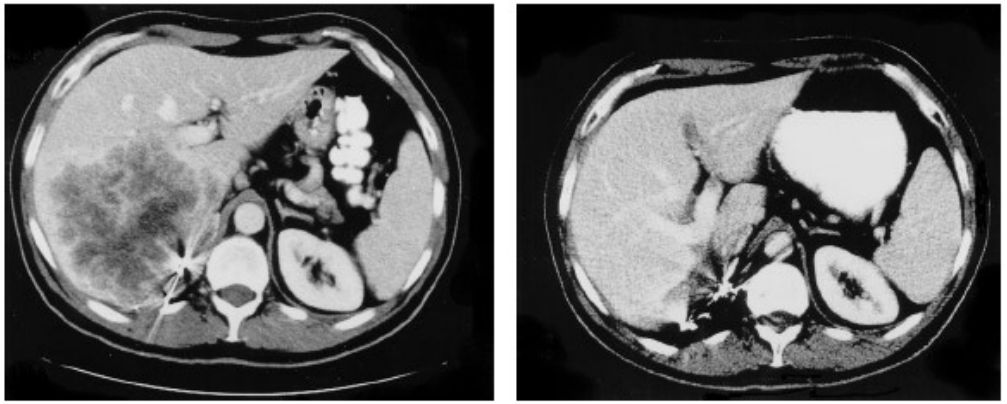
Martedì 18 giugno 2019

Immunotherapy in RCC: back where it all started…



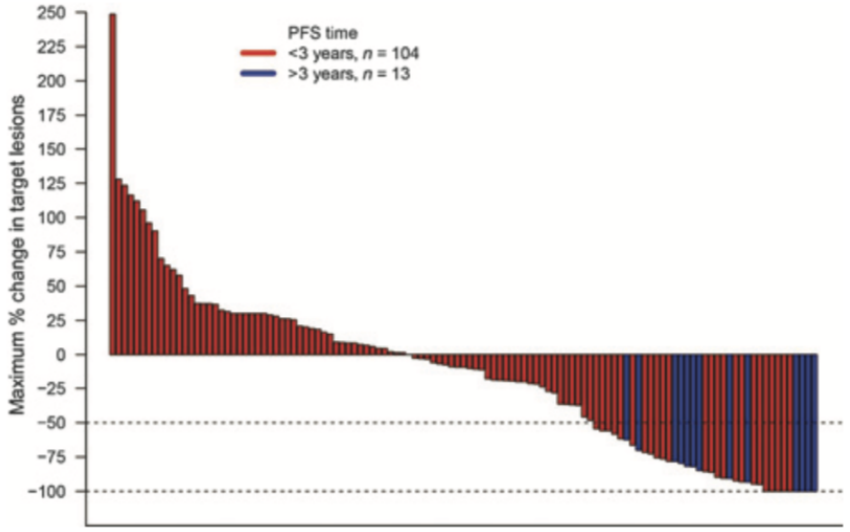
Complete regression of a lung metastasis from melanoma in a patient treated with IL-2

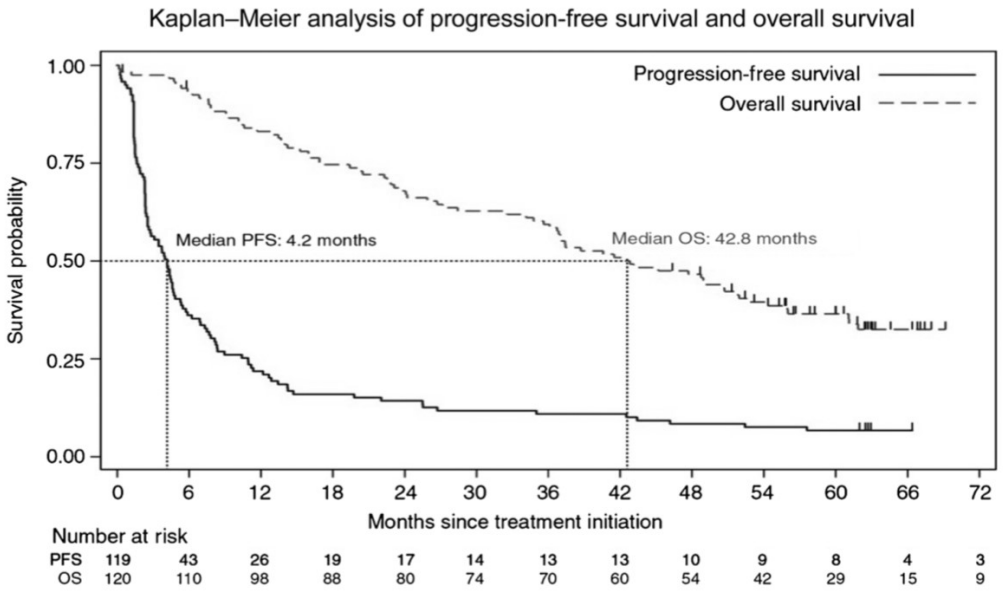
Complete regression of a large liver metastasis from kidney cancer in a patient treated with IL-2



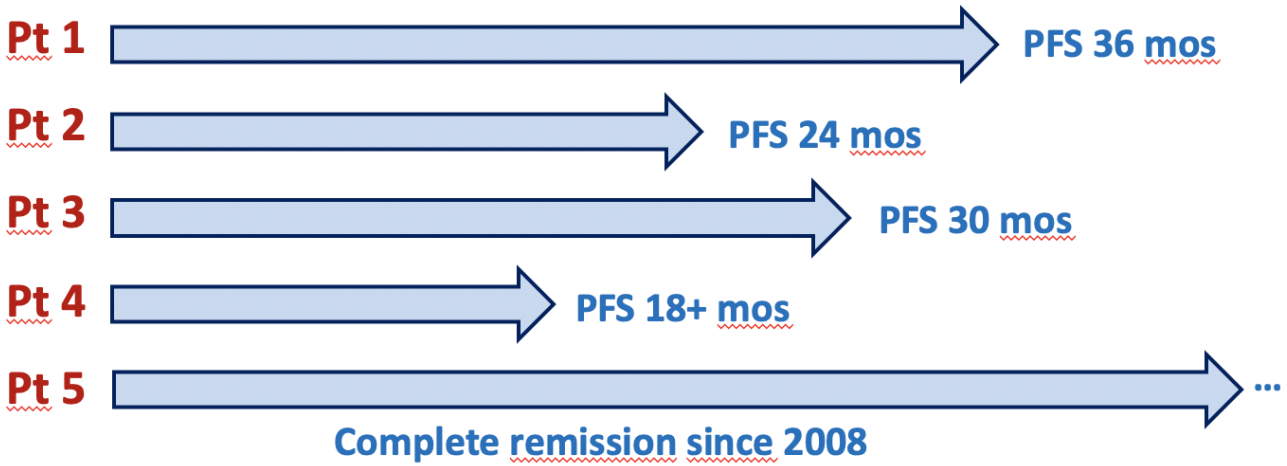
Rosenberg et al, IJC 2001

Immunotherapy in RCC: we know it works!

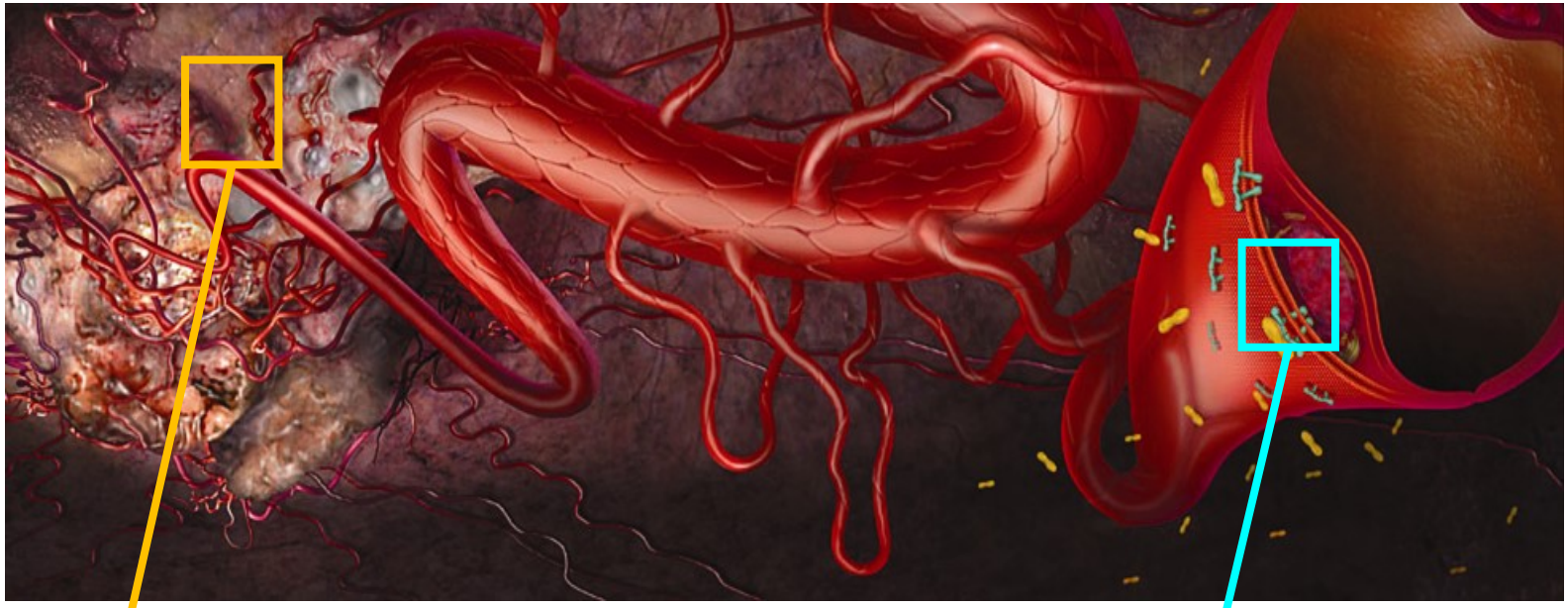




Clin Cancer Res; 21(3) February 1, 2015



A simplified model of cancerogenesis (histotype-independent)



The proliferative compartment

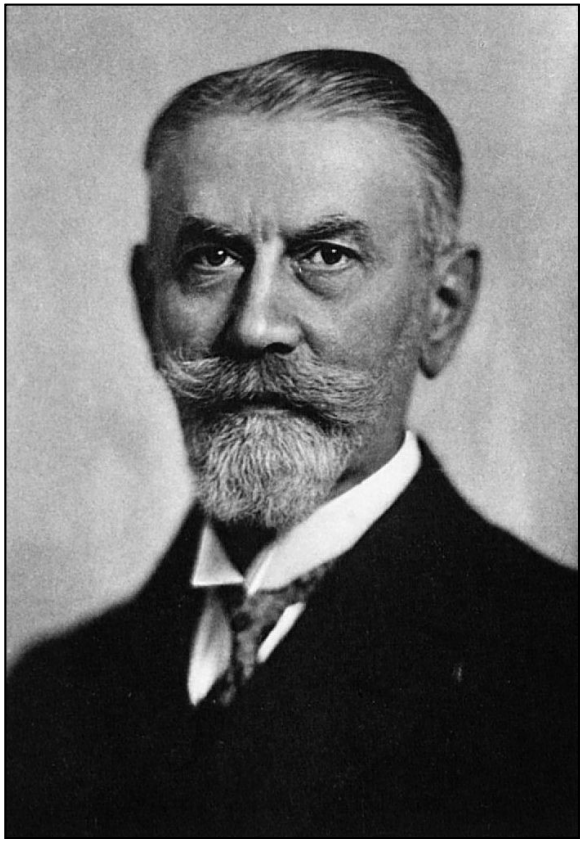
Autocrine and paracrine growth factors activate surface receptors, leading to proliferative signal transduction to the nucleus through complex pathways

The vascular compartment

To grow beyond 1-2 mm, the tumor needs to initiate the recruitment of its own blood vessels; this complex process, driven by autocrine and paracrine growth factors (the most important of which is **VEGF**), is known as 'angiogenic switch'

Courtesy of C. Porta

Everything started with these two gentlemen …



Eugen Von Hippel (1867-1939)

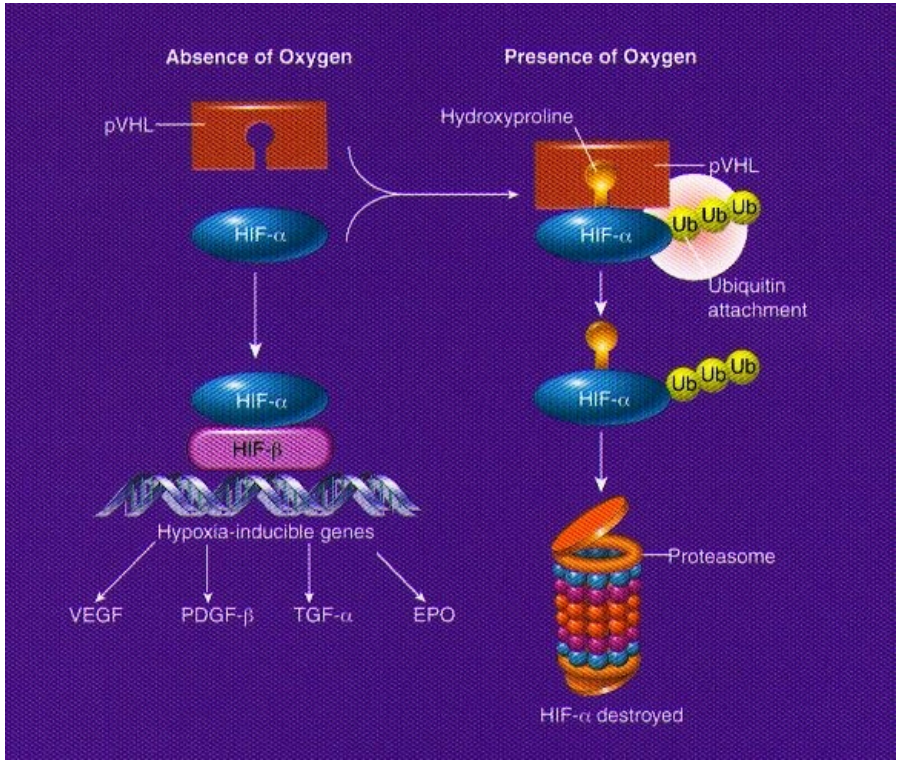
Arvid Lindau (1892-1958)

Autosomal dominant disorder, characterized the association of ccRCC, retinal/chranial hemangioblastomas, pheochromocytomas, pancreatic NETs or cysts, broad ligament/epidydimal cystadenoma.

Due to the mutation of a tumor suppressor gene localized at 3p25-26

Courtesy of C. Porta

… linking clear cell RCC to *VHL*, HIFs, and VEGF



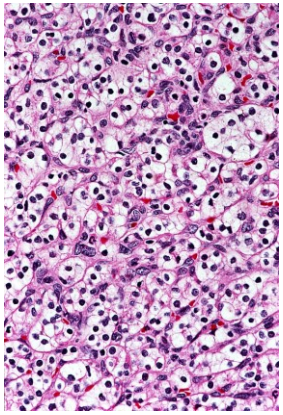
In the presence of a mutated/deleted or hypermethylated *VHL* gene, HIF-1α is not destroyed via the proteasome/ubiquitin pathway, and thus accumulates, leading to the transcription of hypoxia inducible genes

This results in the production of a series of growth factors, including VEGF and PDGF-β, ultimately leading to increased angiogenesis

Courtesy of C. Porta

A more modern and complex view on RCC pathogenesis

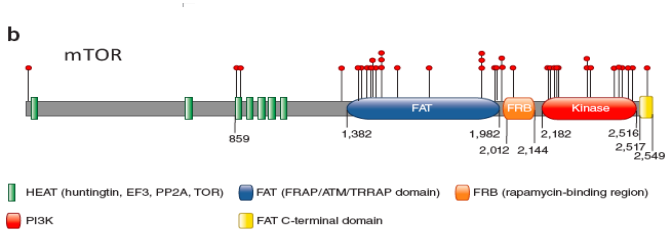
mTOR



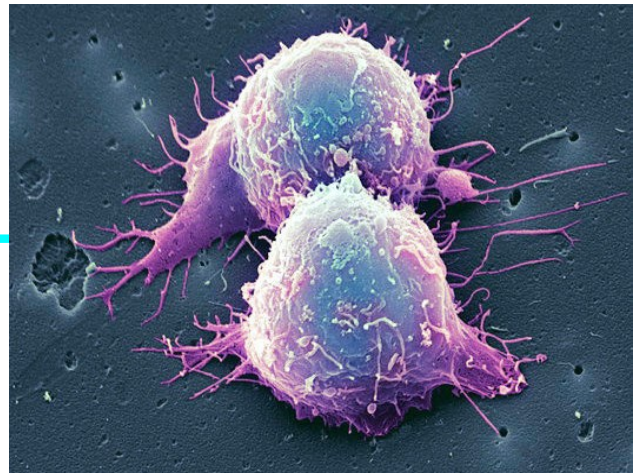
clear cell RCC (75-85%)

VHL

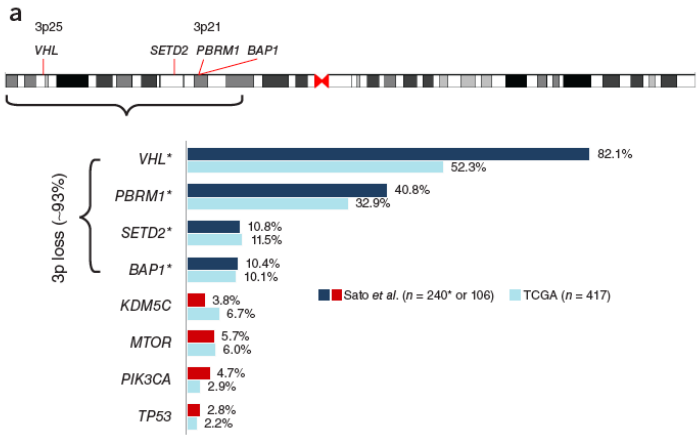
mutated



Increased tumor cell survival and resistance to apoptosis



Immunogenicity



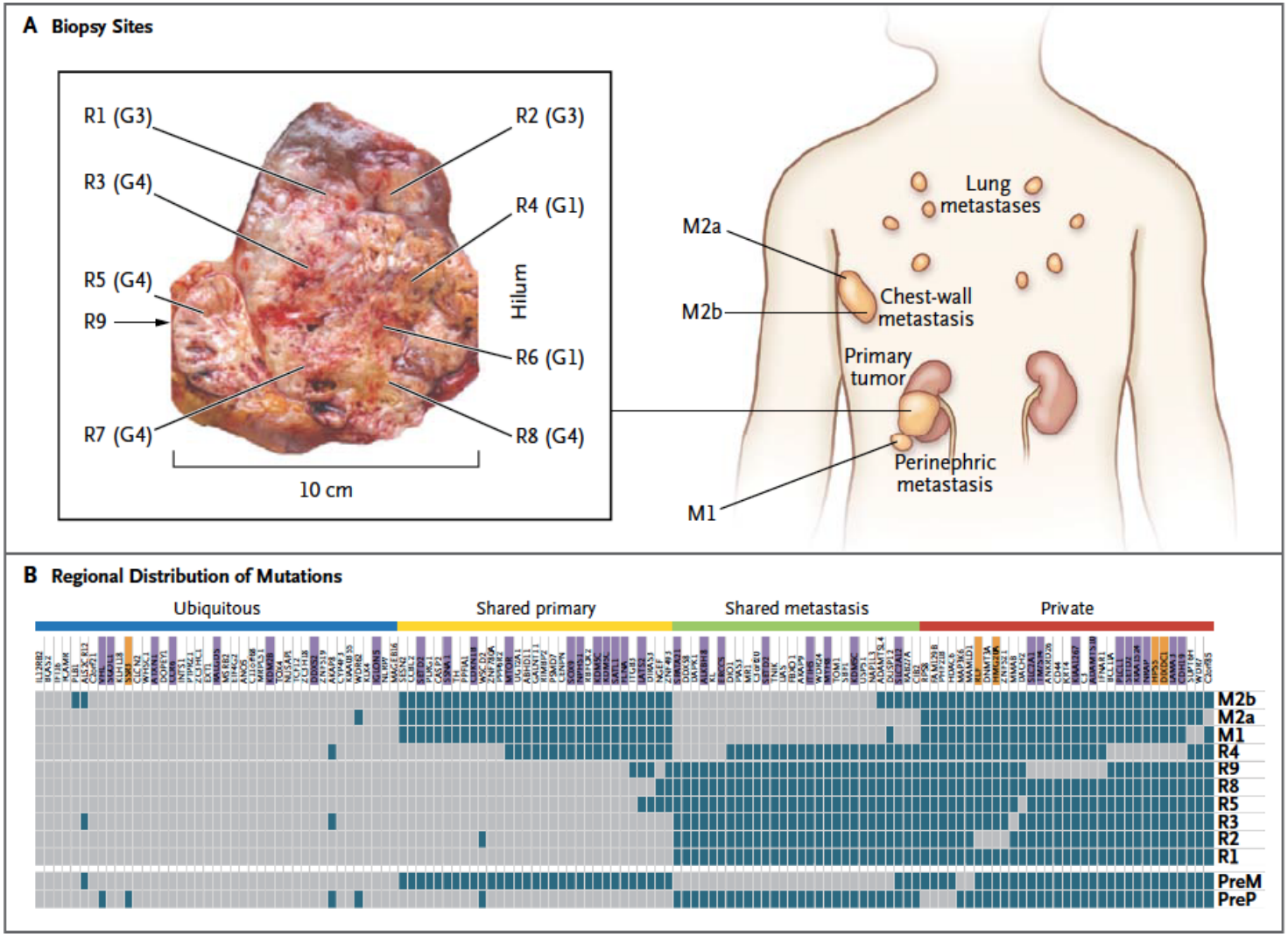
mutated, deleted or hyper-methylated

Hyperproduction of VEGF and other pro-angiogenic cytokines

Exasperated angiogenesis

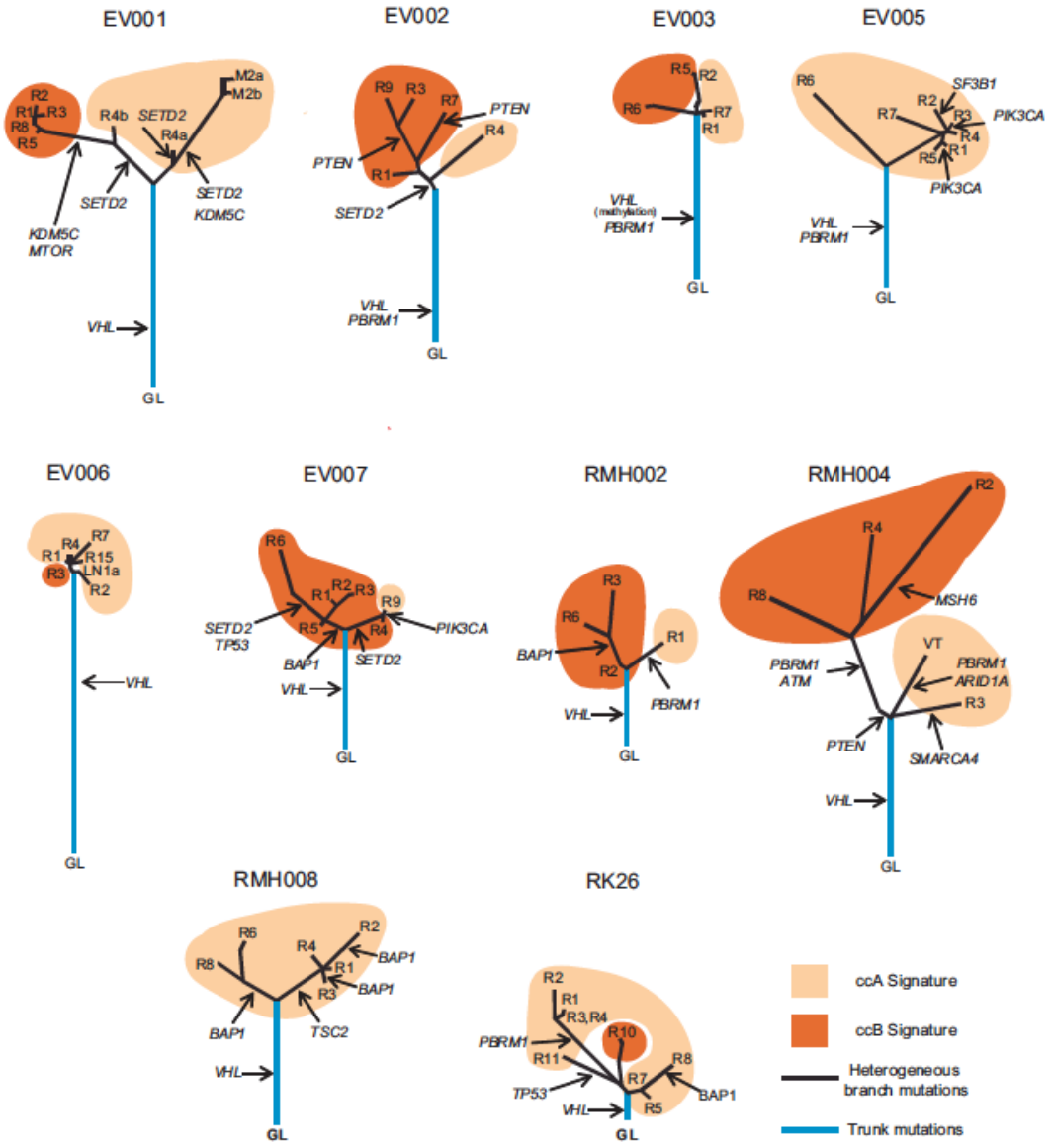
Courtesy of C. Porta

Tumor heterogeneity might constitute a therapeutic obstacle…



N Engl J Med 2012;366:883-92.

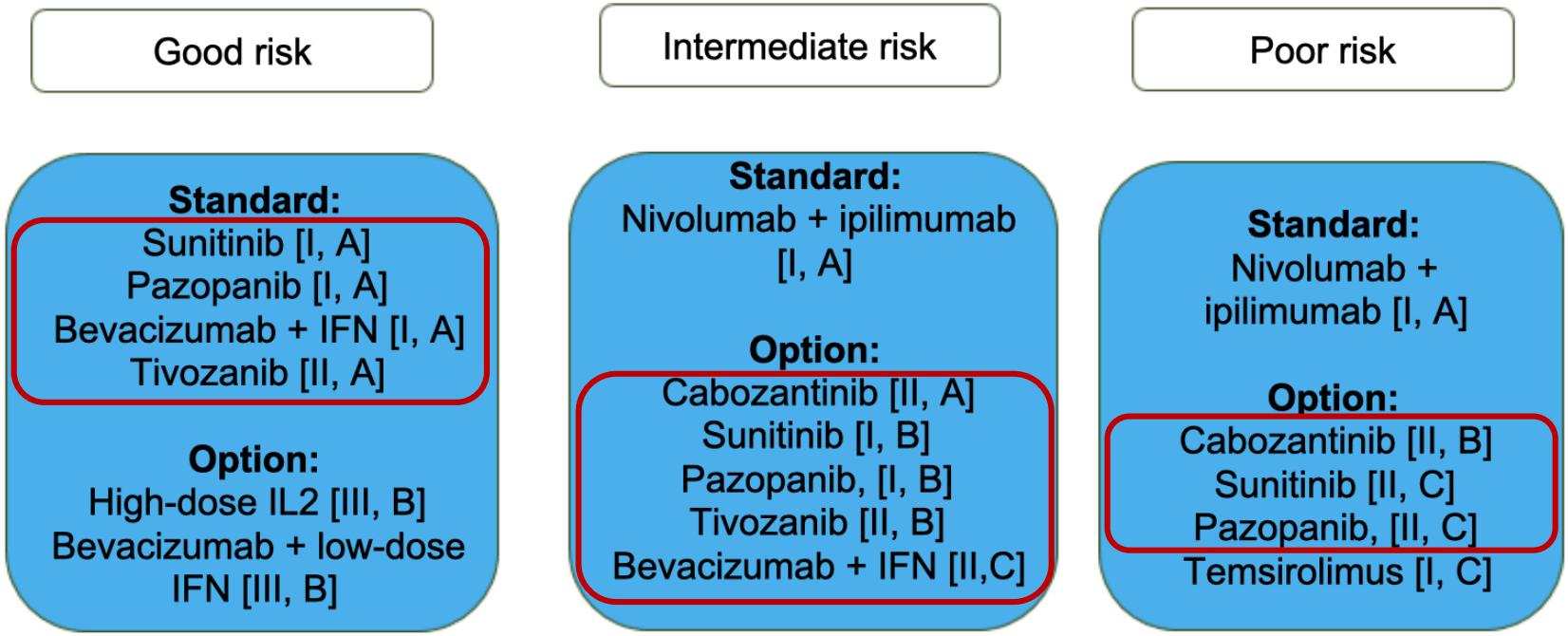
…But HIF/VEGF axis alterations remain one of the main targets!



EUROPEAN UROLOGY 66 (2014) 936–948

Which explains the therapeutic positioning of anti-angiogenic agents...

Systemic first-line treatment of ccRCC



Courtesy of Escudier B et al, ESMO RCC Guidelines 2018 update

...and why they keep working one after the other!

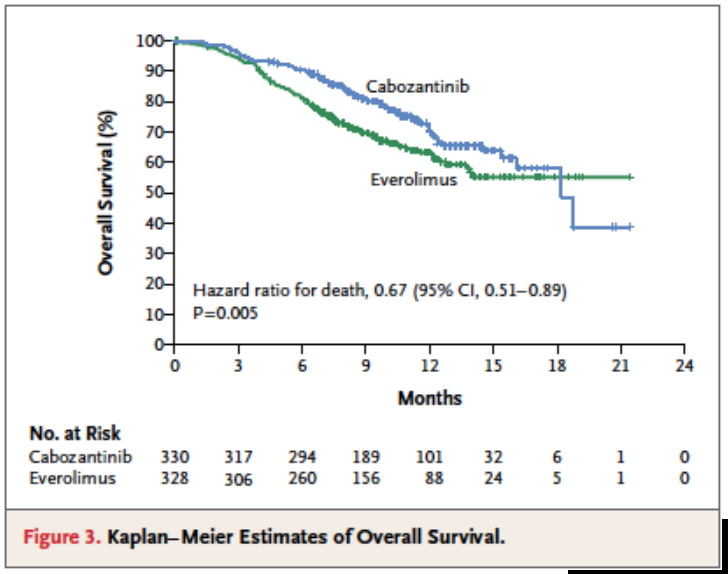
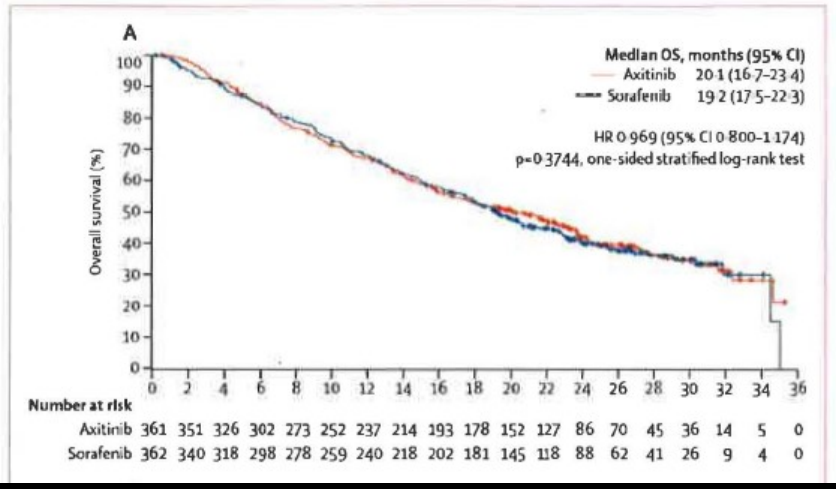
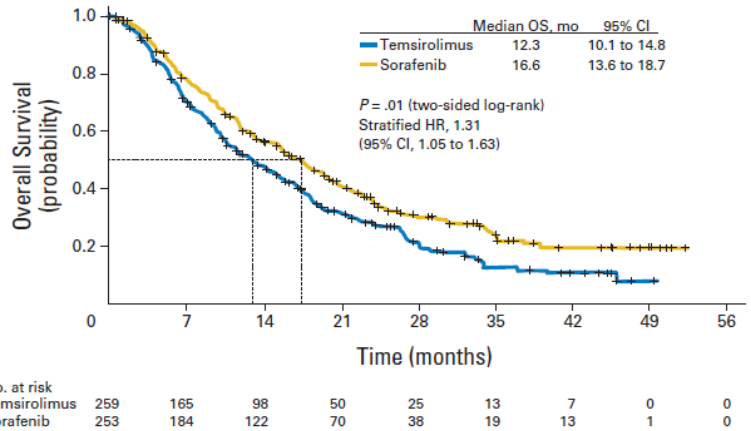
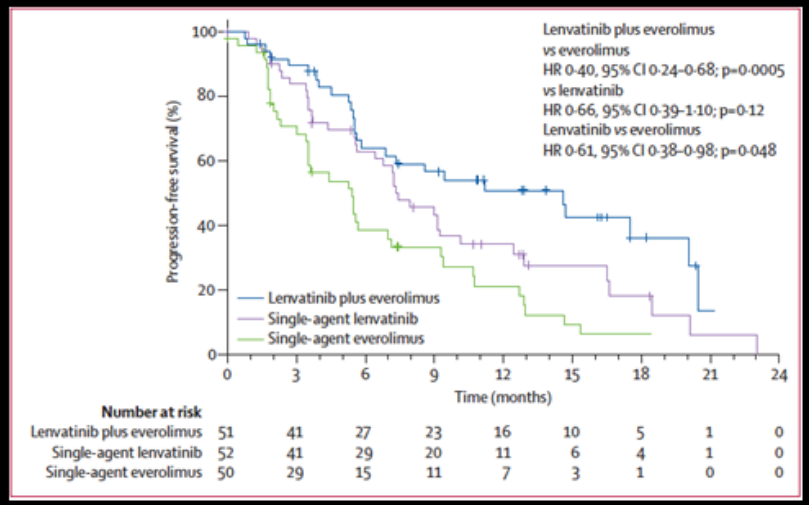


Figure 3. Kaplan–Meier Estimates of Overall Survival.

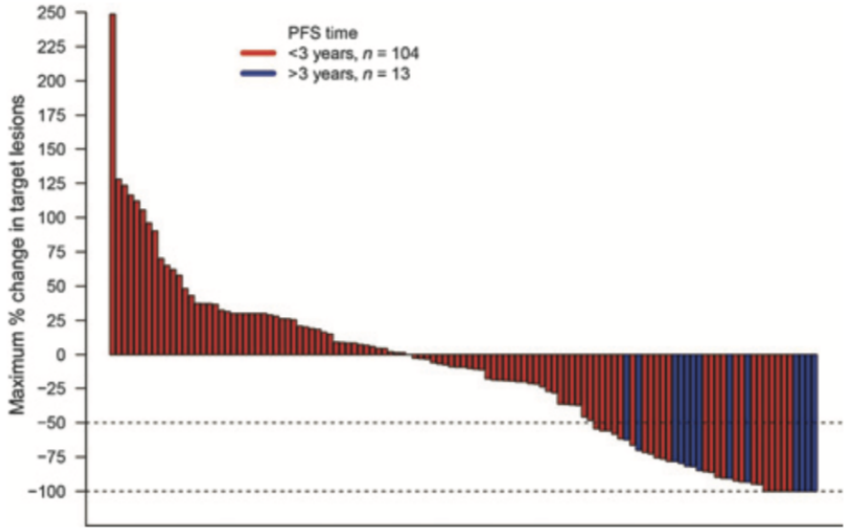


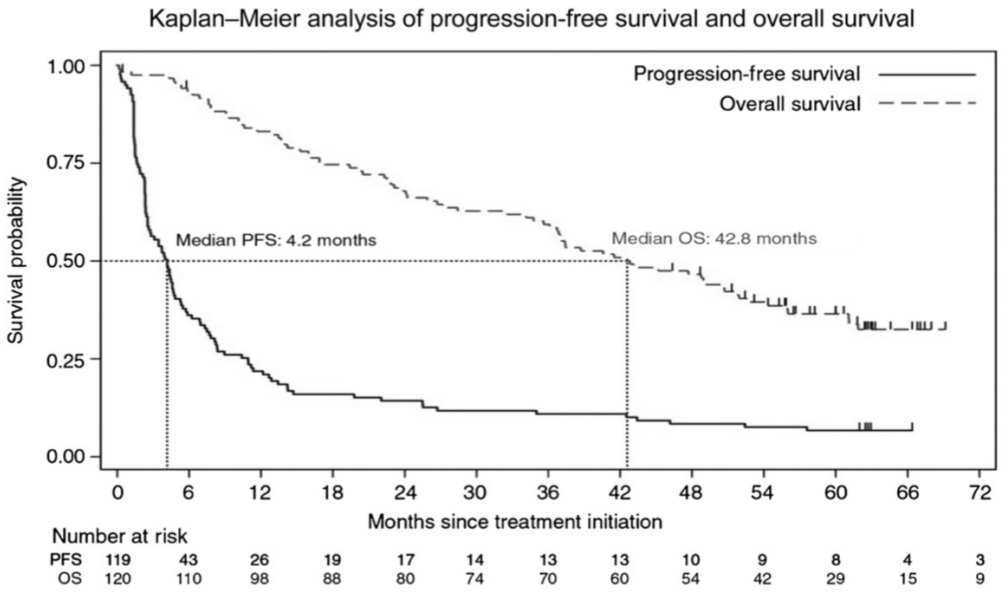




Lancet Oncol 2015; 16: 1473–82

Immunotherapy in RCC: we know it works!





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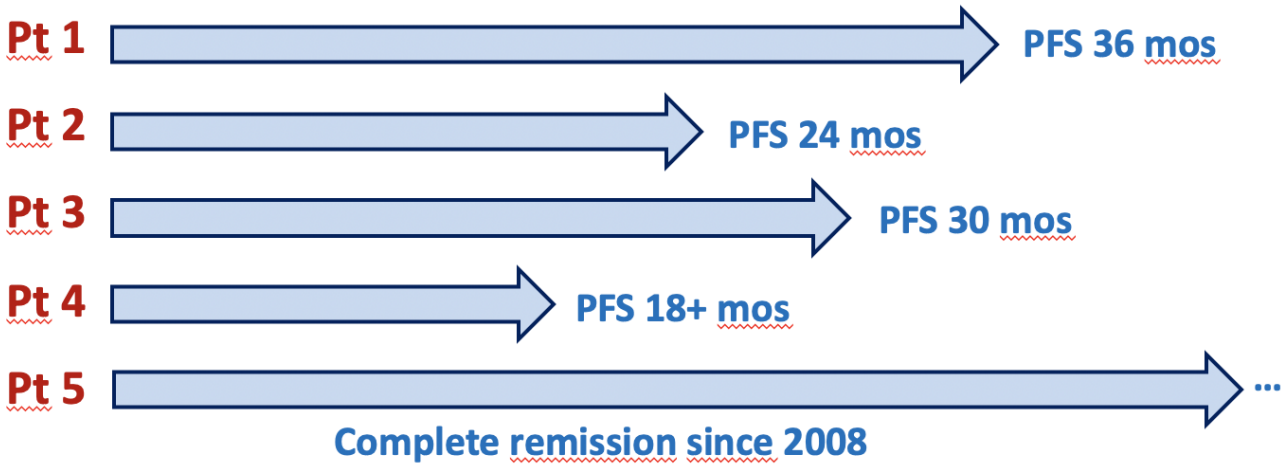
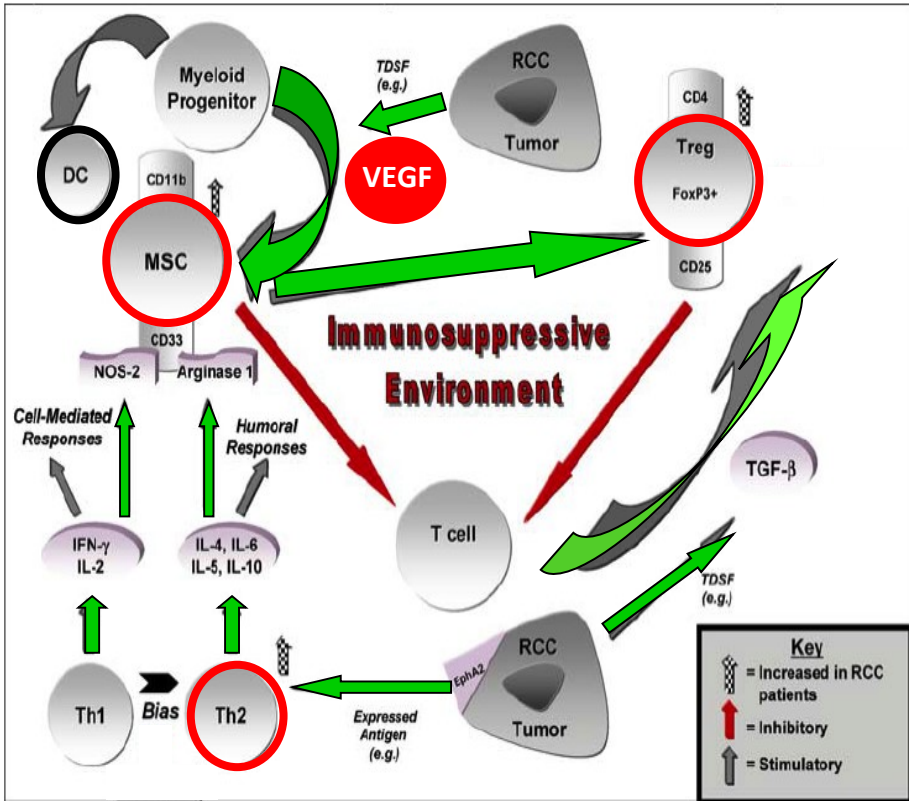
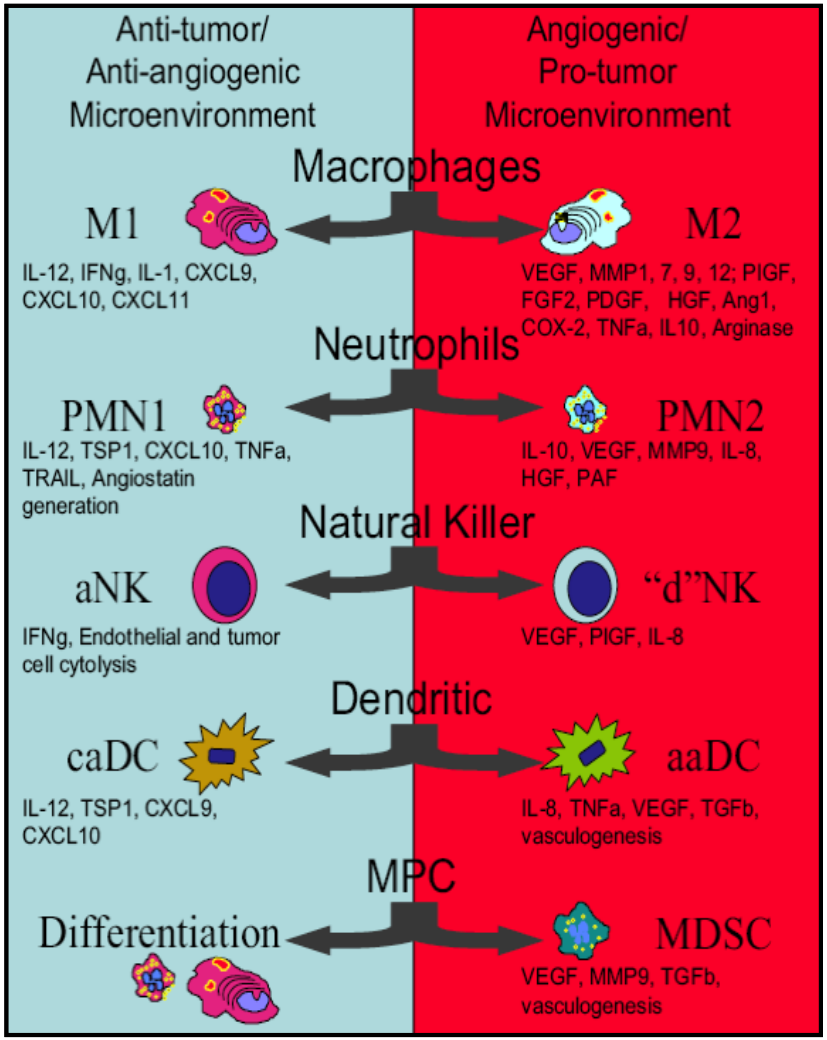


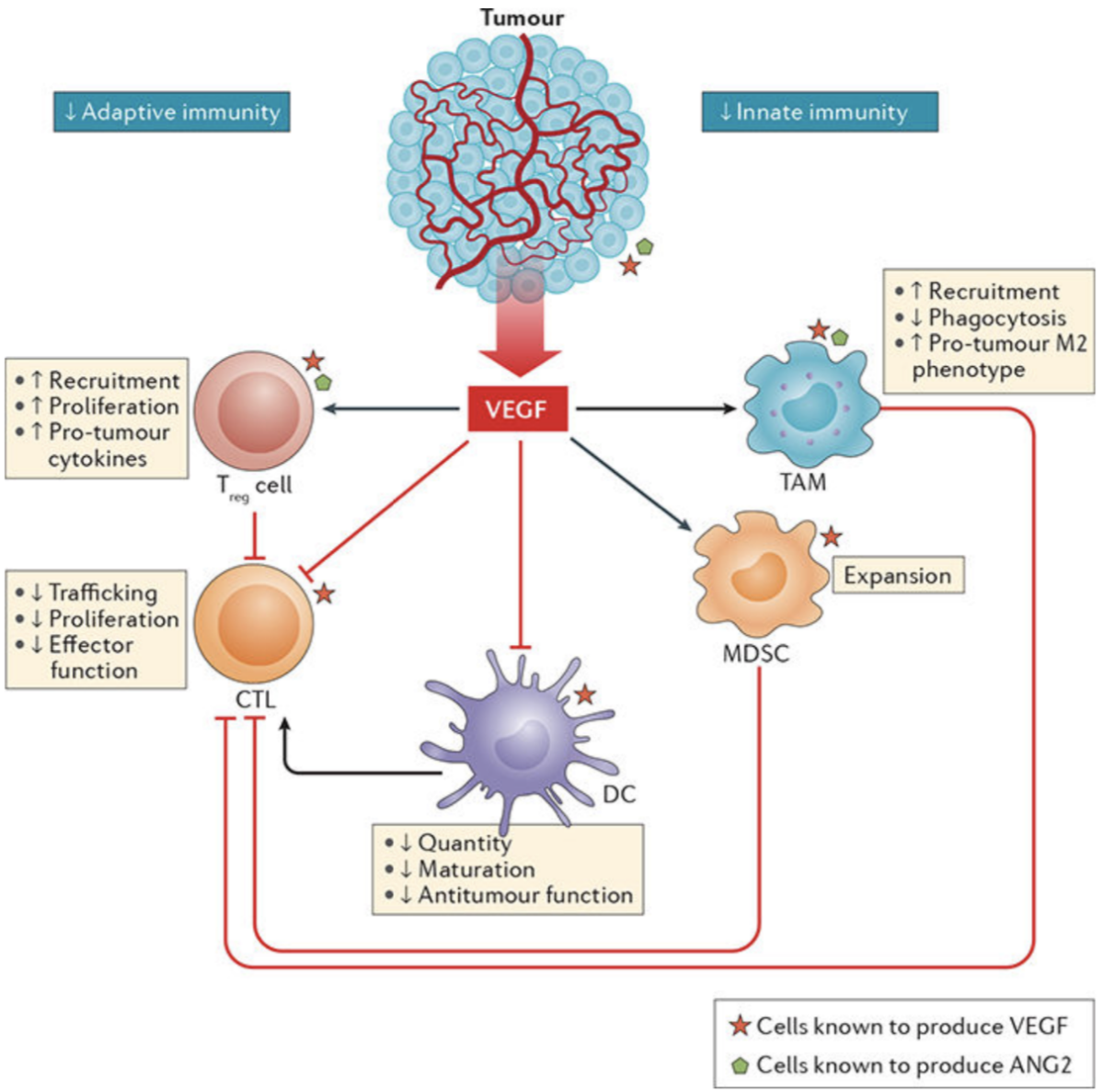
Remember that tumor cells do not exist in isolation…





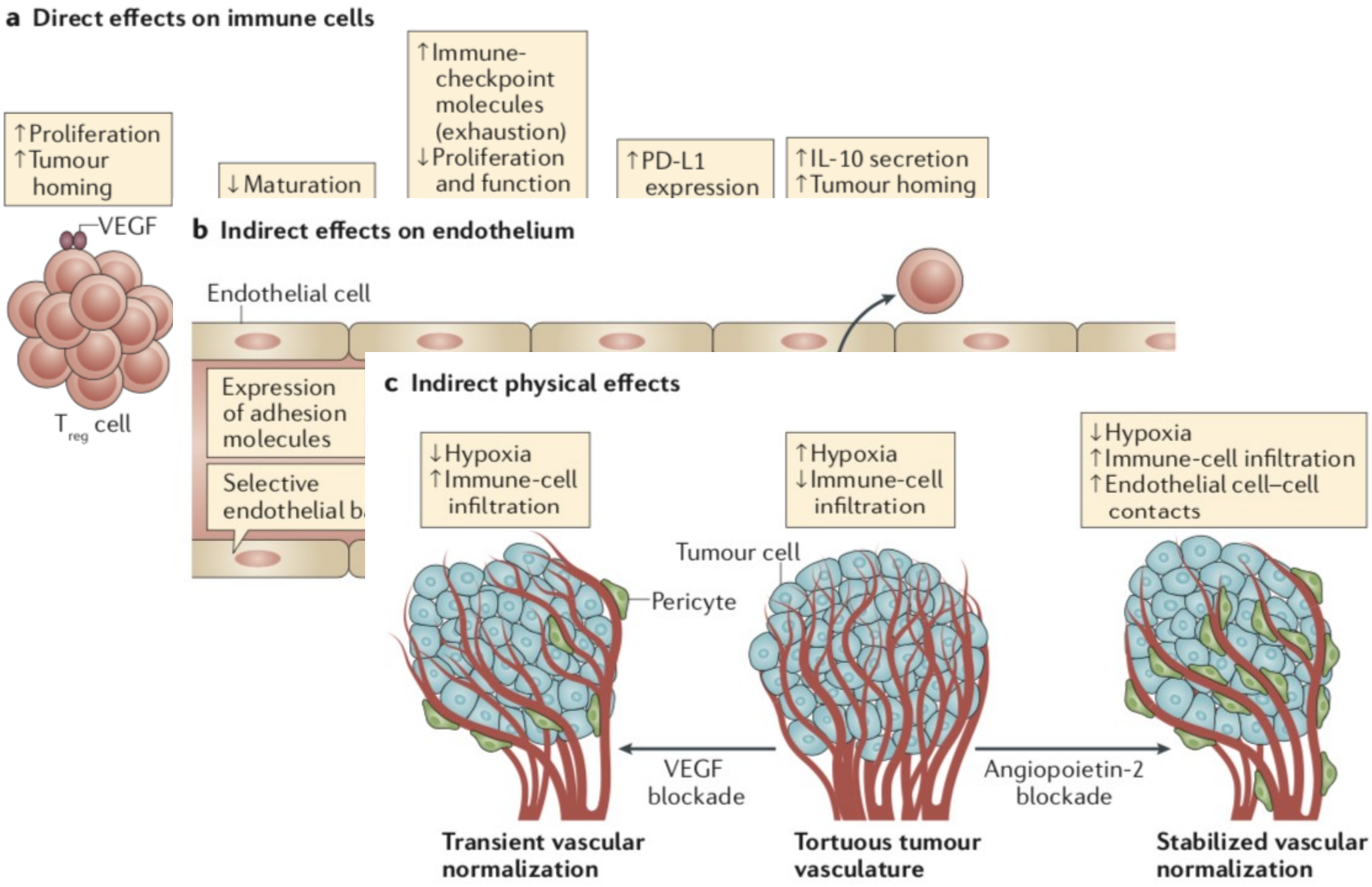
Modified from: Tortora et al, Curr Pharm Des. 2004;10(1):11-26.

…and angiogenesis and immunity crosstalk to each other



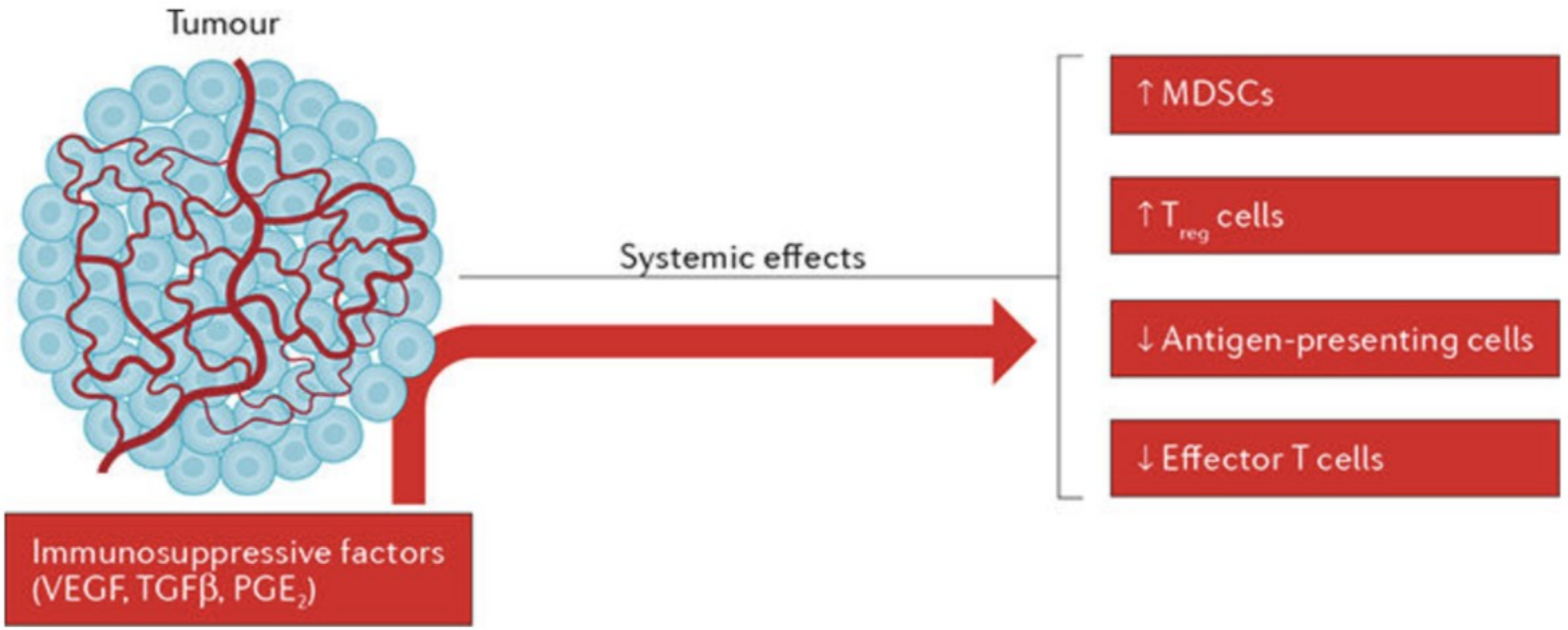
Nat Rev Clin Oncol. 2018 May ; 15(5): 325–340

…through direct and indirect mechanisms



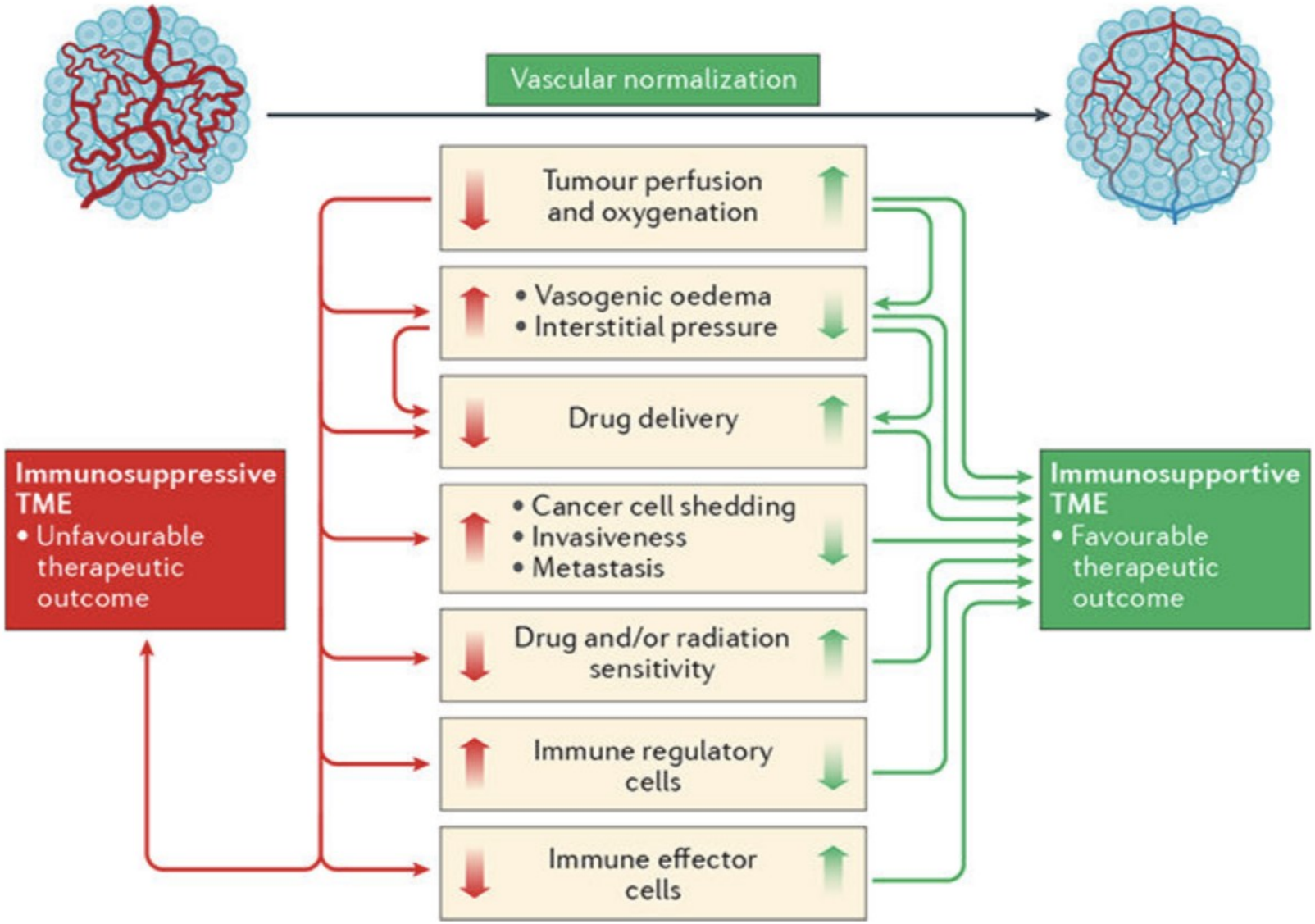
doi:10.1038/nrclinonc.2018.9

Aberrant angiogenesis suppresses immune response…



Nat Rev Clin Oncol. 2018 May ; 15(5): 325–340

And its inhibition activates a *"virtuous"* cycle…



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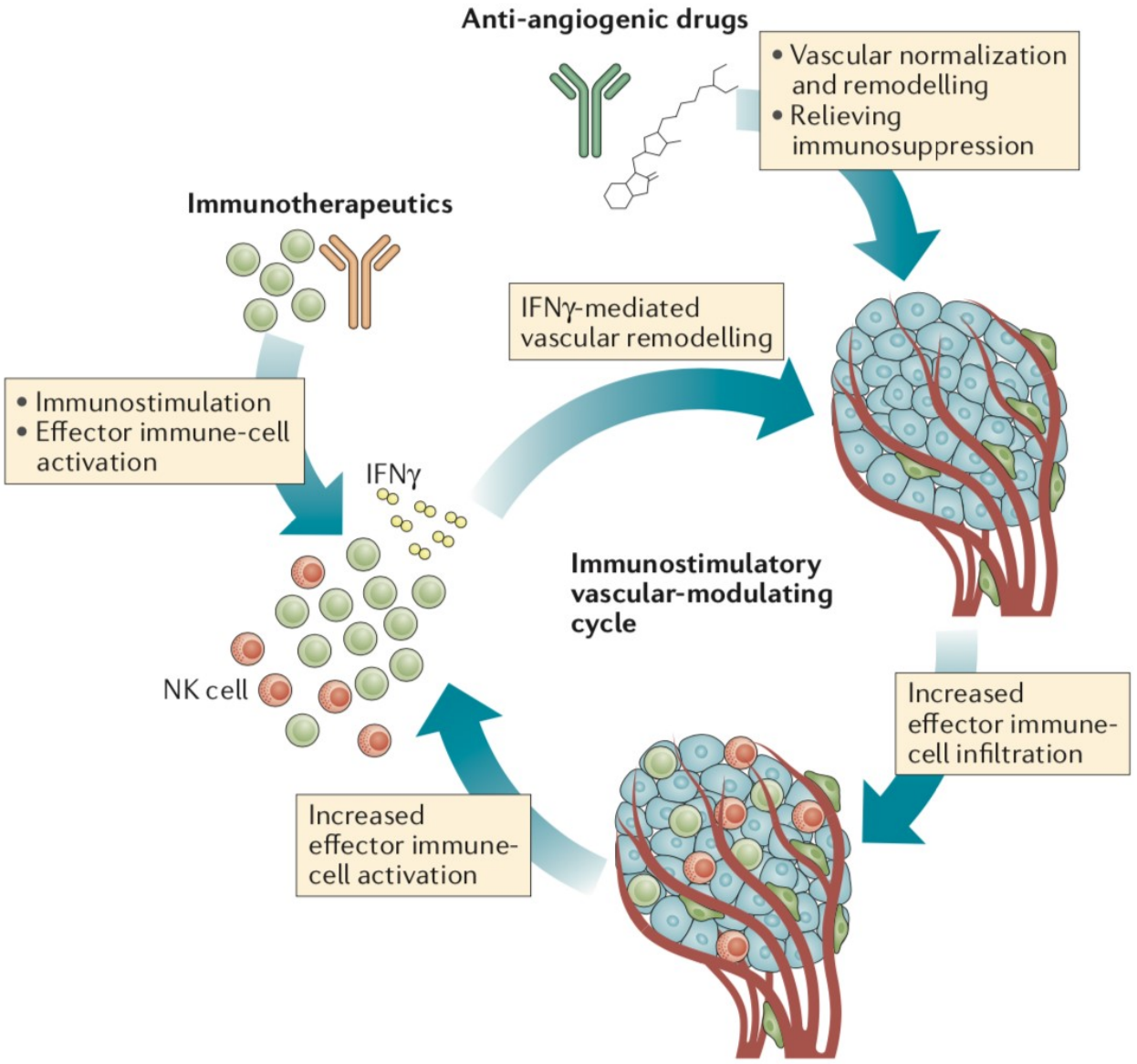
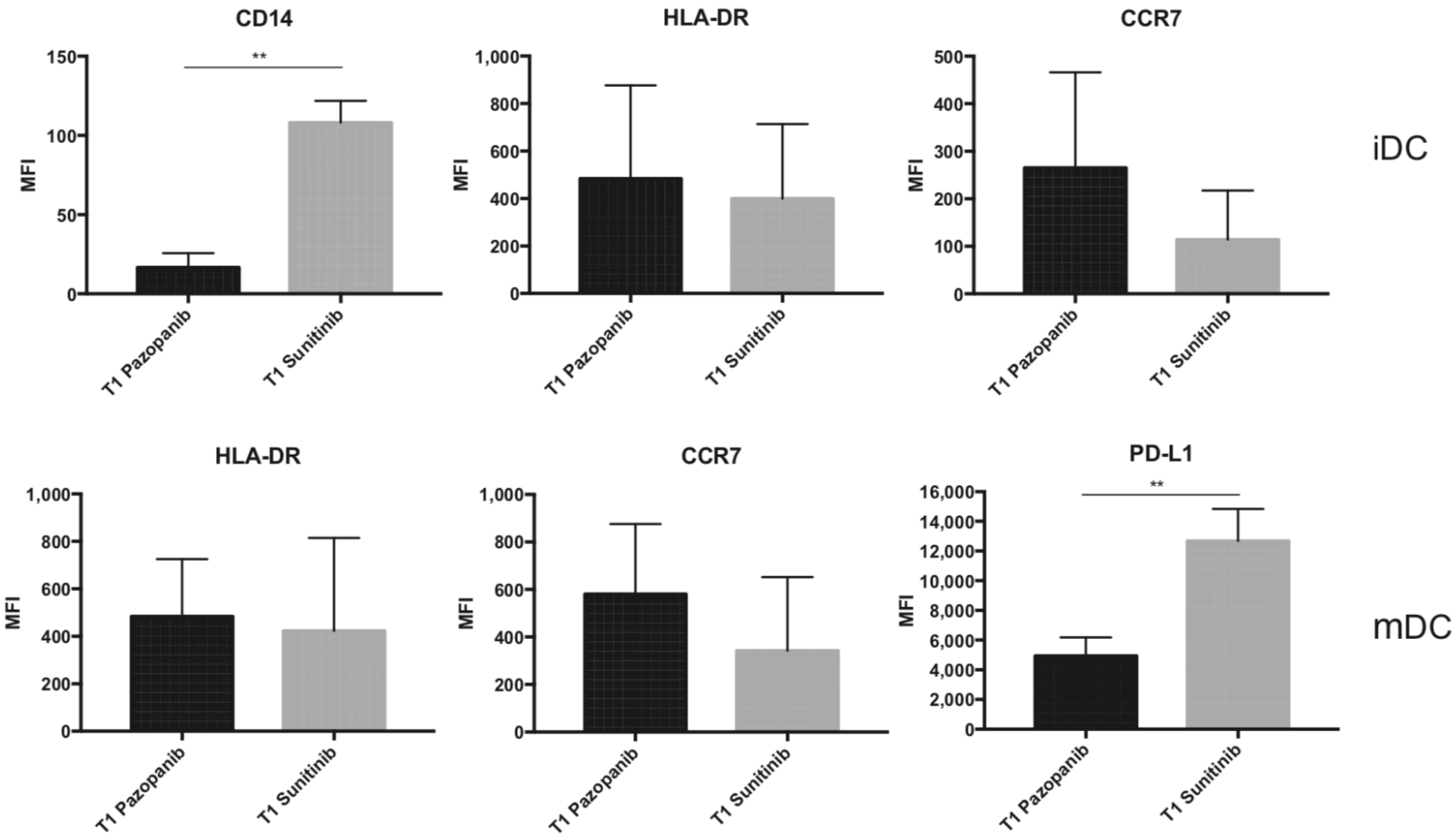


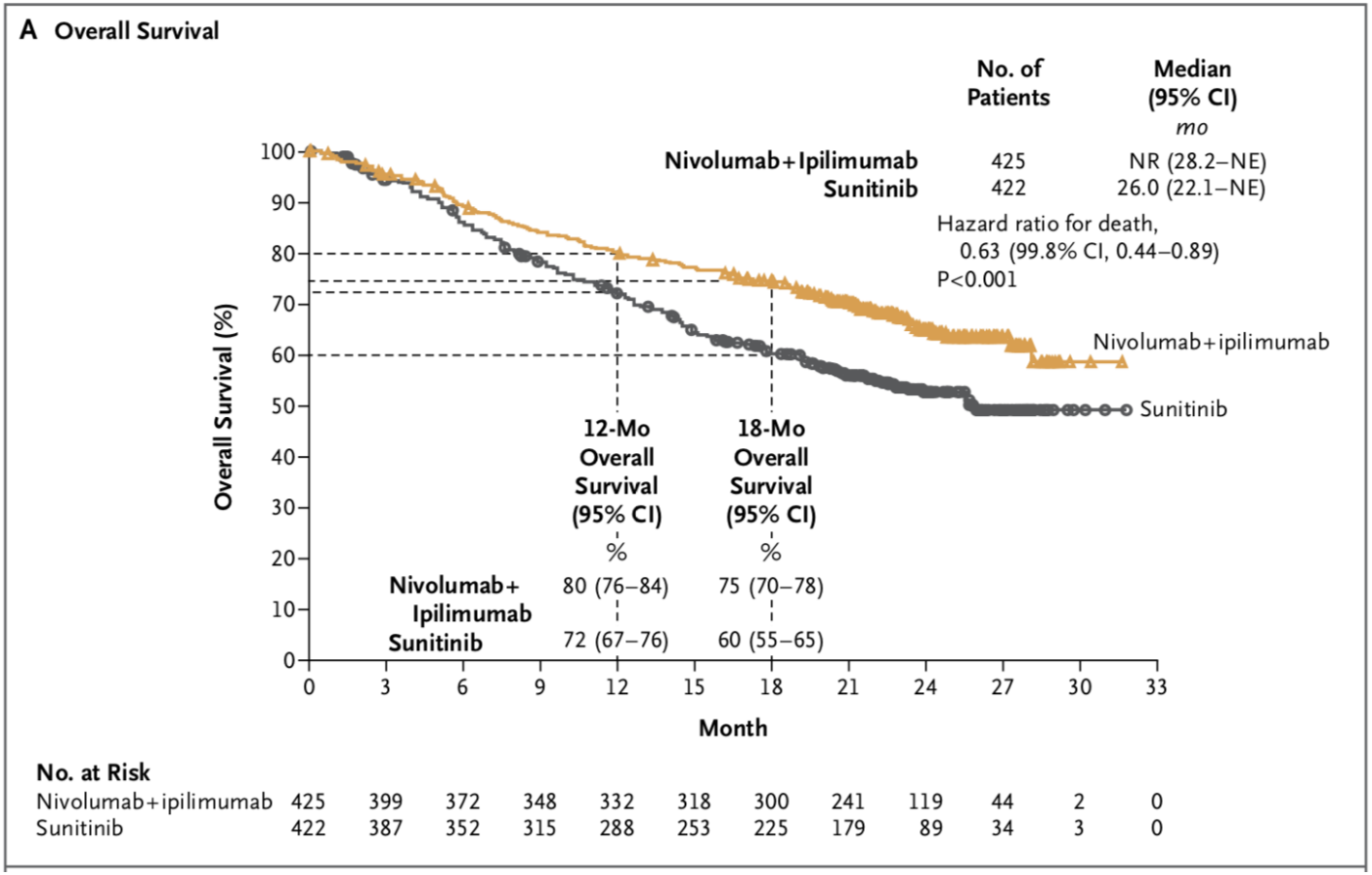
doi:10.1038/nrclinonc.2018.9

…that becomes operational in patients treated with TKIs



Cancer Immunol Res; 6(6) June 2018

Immunotherapy is a new treatment option in first line…



N Engl J Med 2018;378:1277-90.
DOI: 10.1056/NEJMoa1712126

...but maybe not for every patient!

Exploratory endpoint

ORR and PFS: IMDC favorable risk

Outcome	N = 249[a]	
	NIVO + IPI N = 125	SUN N = 124
Confirmed ORR,[b] % (95% CI)	**29 (21–38)**	**52 (43–61)**
	P = 0.0002	
PFS,[c] median (95% CI), months	15.3 (9.7–20.3)	25.1 (20.9–NE)
	HR (99.1% CI) 2.18 (1.29–3.68) ***P* < 0.0001**	

MADRID 2017 ESMO congress

[a]11% of patients in both arms had tumor PD-L1 expression ≥1%
[b]IRRC-assessed by RECIST v1.1
[c]IRRC-assessed

With a possibility for... cure???

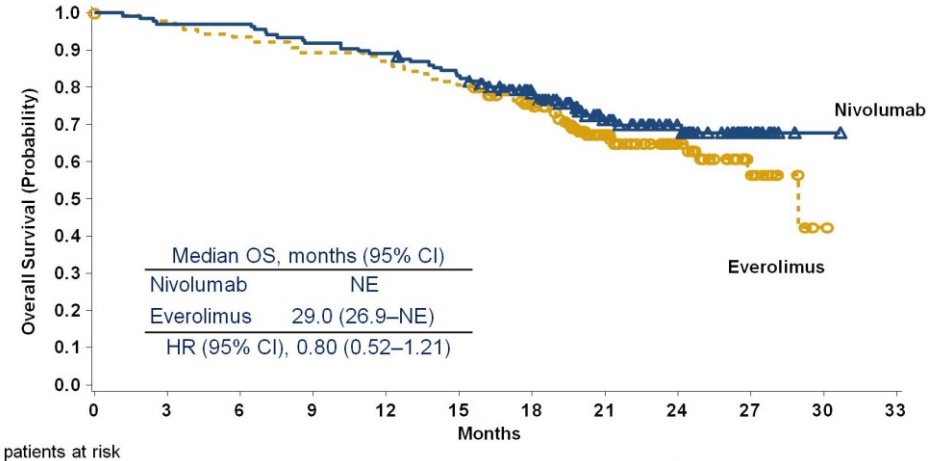
	Intermediate/poor risk		Favourable risk		Overall (ITT)	
	Nivo + Ipi N=425	SUN N=422	Nivo + Ipi N=125	SUN N=124	Nivo + Ipi N=550	SUN N=546
ORR*, % (95% CI)	42 (37–47)	27 (22–31)	29 (21–38)	52 (43–61)	39 (35–43)	32 (28–36)
P value	0.0001		0.0002		0.0191	
CR rate, %	9	1	10.4	3	9.3	1.6
Median PFS (95% CI)	11.6 (8.7–15.5)	8.4 (7.0–10.8)	15.3 (9.7–20.3)	25.1 (20.9–NE)	12.4 (9.9–16.5)	12.3 (9.8–1.23)
HR	0.82 (0.64–1.05) P=0.03		2.18 (1.29–3.68) P<0.0001		0.98 (0.79–1.23) P=0.85	
Median OS (95% CI)	NR (28.2–NE)	26.0 (22.1–NE)	TE	TE	NR (NE–NE)	32.9 (NE–NE)
HR	0.63 (0.44–0.89) P<0.0001		NA		0.68 (0.49–0.95) P=0.0003	

*Best overall response according to RECIST v1.1 per IRC

Motzer NEJM 2018

Same line of reasoning might apply to second-line treatment...

OS: Favorable MSKCC risk



No. of patients at risk

Nivolumab	137	133	122	88	35	1
Everolimus	145	132	123	98	35	1

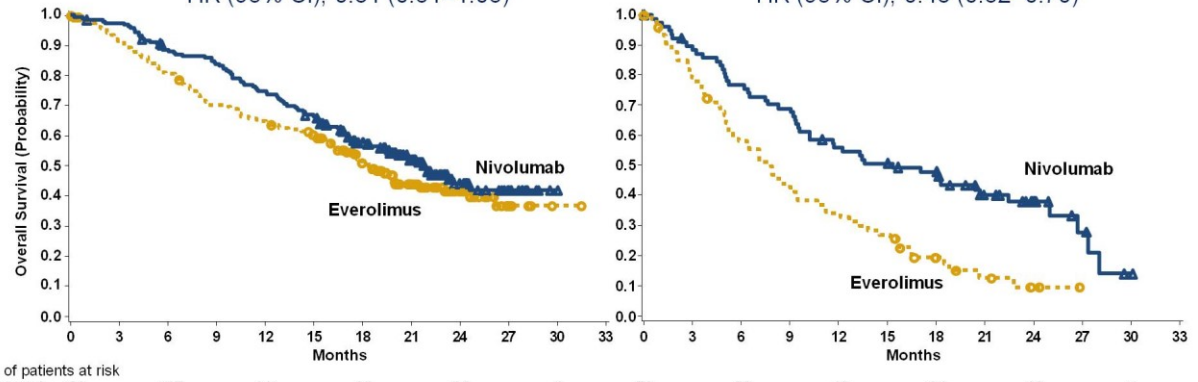
OS: Intermediate and poor MSKCC risk

Intermediate

Median OS, months (95% CI)	
Nivolumab	21.8 (18.3–NE)
Everolimus	18.4 (16.1–23.1)
HR (95% CI), 0.81 (0.61–1.06)	

Poor

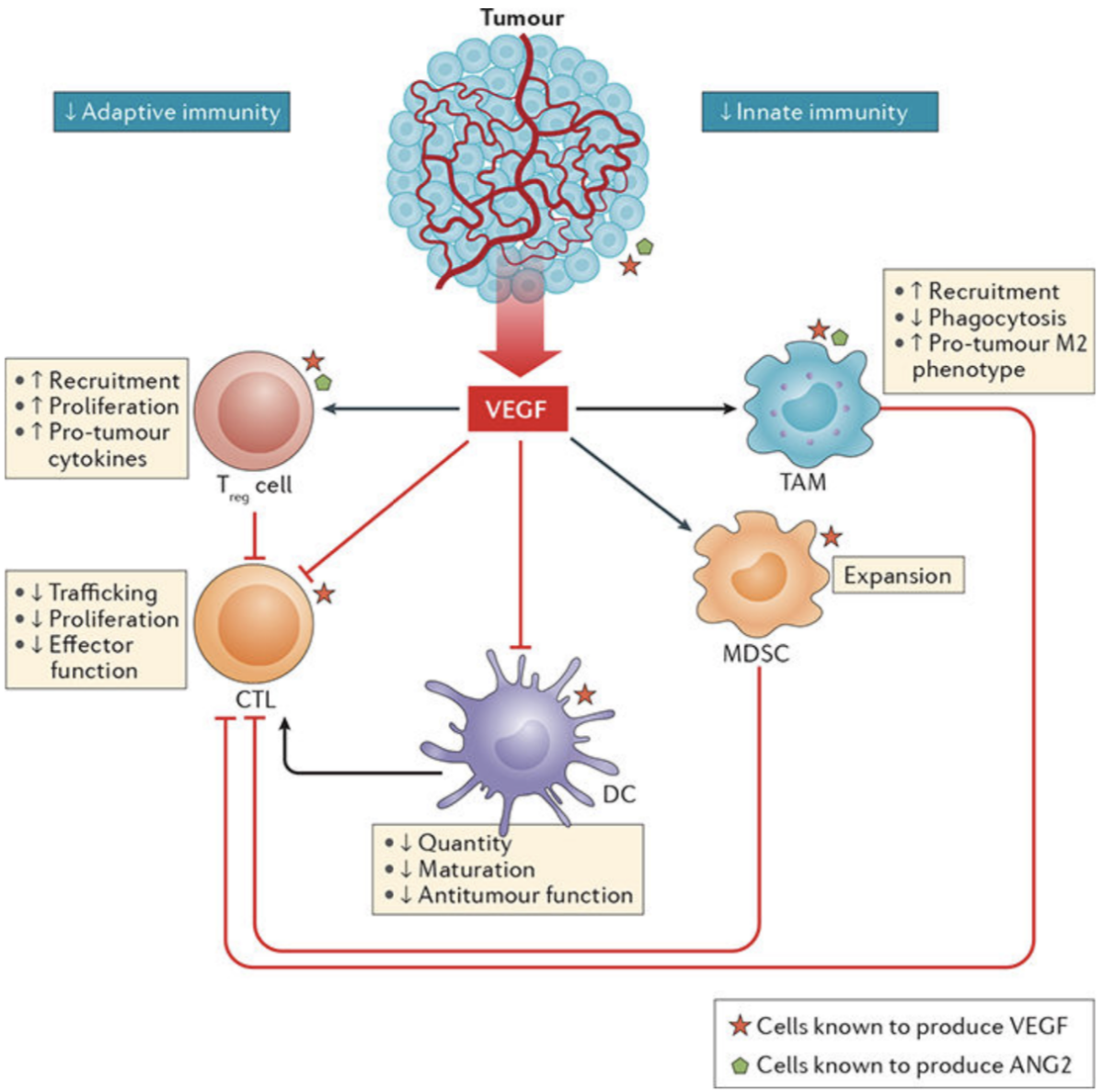
Median OS, months (95% CI)	
Nivolumab	15.3 (9.6–22.4)
Everolimus	7.9 (5.4–9.7)
HR (95% CI), 0.48 (0.32–0.70)	



No. of patients at risk

Nivolumab	193	167	141	91	26	1	79	59	42	34	12	1
Everolimus	192	151	118	80	24	1	74	41	24	9	2	0

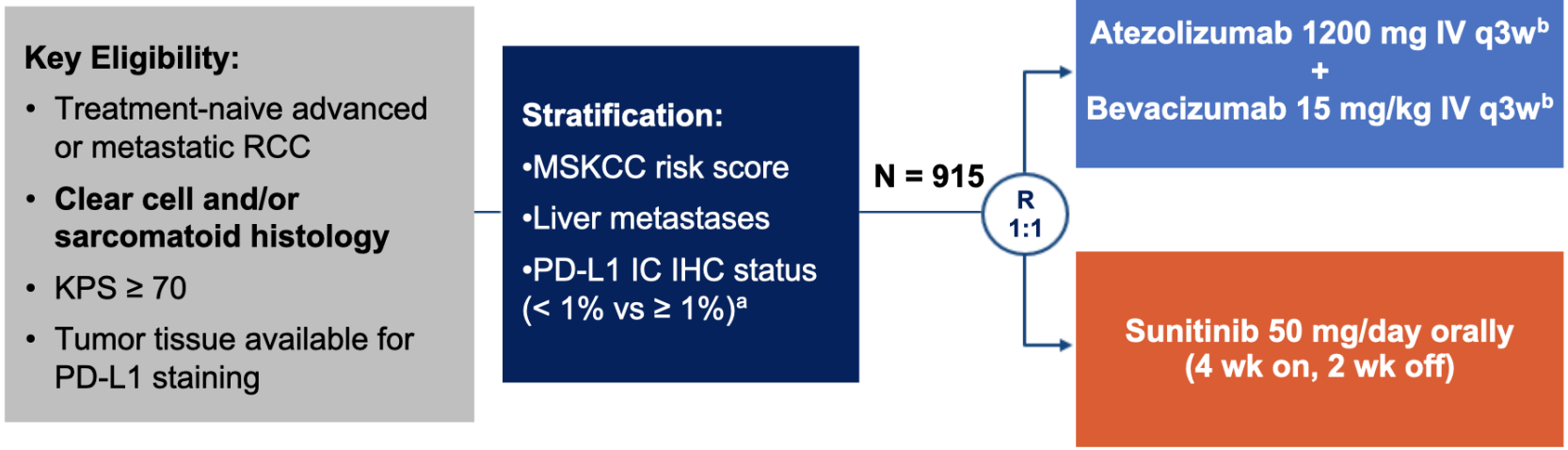
Angiogenesis and immunity crosstalk to each other



Nat Rev Clin Oncol. 2018 May ; 15(5): 325–340

Then… it makes sense to *"combine"*!!!

IMmotion 151: Study Design



[a] ≥ 1% IC: 40% prevalence using SP142 IHC assay; [b] No dose reduction for atezolizumab or bevacizumab.

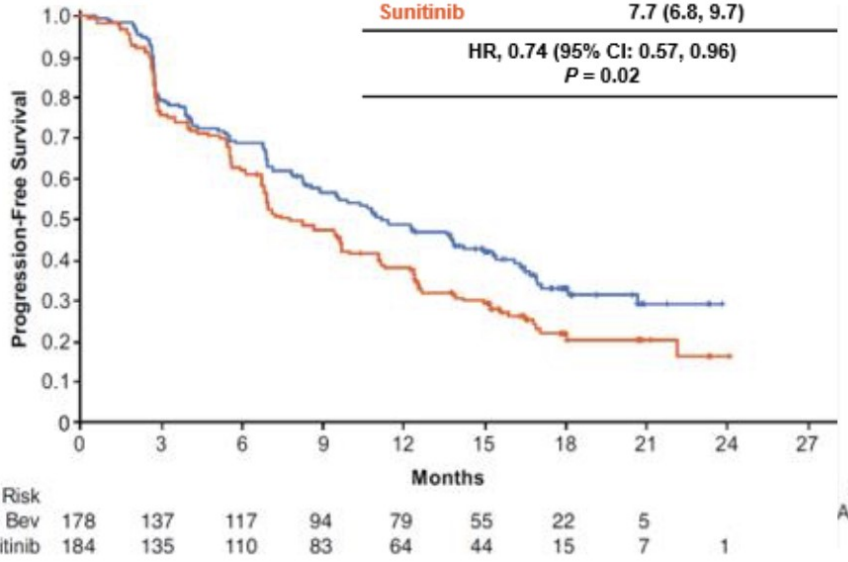
Then… it makes sense to *"combine"*!!!

Co-Primary Endpoint

Consistent PFS (PD-L1+ & ITT) by Investigator

PD-L1+

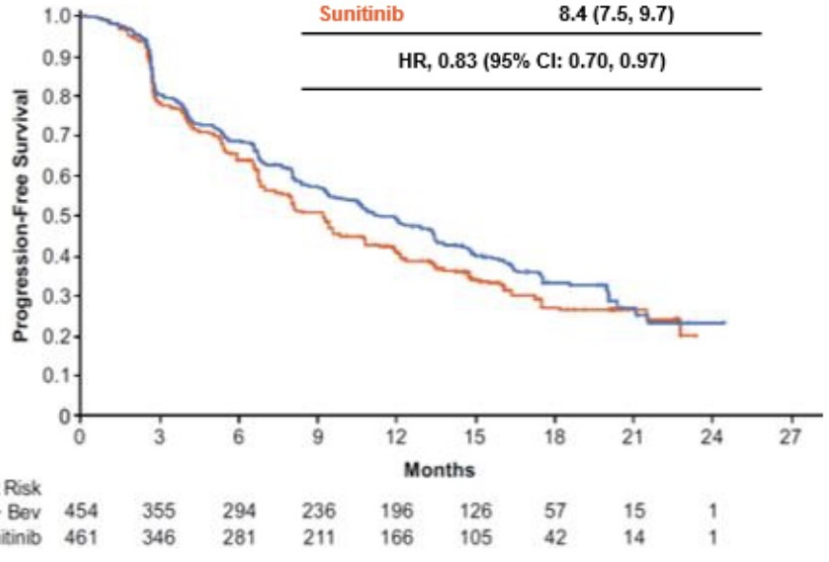
Median PFS, mo (95% CI)	
Atezo + Bev	11.2 (8.9, 15.0)
Sunitinib	7.7 (6.8, 9.7)
HR, 0.74 (95% CI: 0.57, 0.96) *P* = 0.02	



No. at Risk								
Atezo + Bev	178	137	117	94	79	55	22	5
Sunitinib	184	135	110	83	64	44	15	7	1

ITT

Median PFS, mo (95% CI)	
Atezo + Bev	11.2 (9.6, 13.3)
Sunitinib	8.4 (7.5, 9.7)
HR, 0.83 (95% CI: 0.70, 0.97)	



No. at Risk								
Atezo + Bev	454	355	294	236	196	126	57	15	1
Sunitinib	461	346	281	211	166	105	42	14	1

PFS assessed by investigators. Minimum follow-up, 12 mo. Median follow-up, 15 mo.

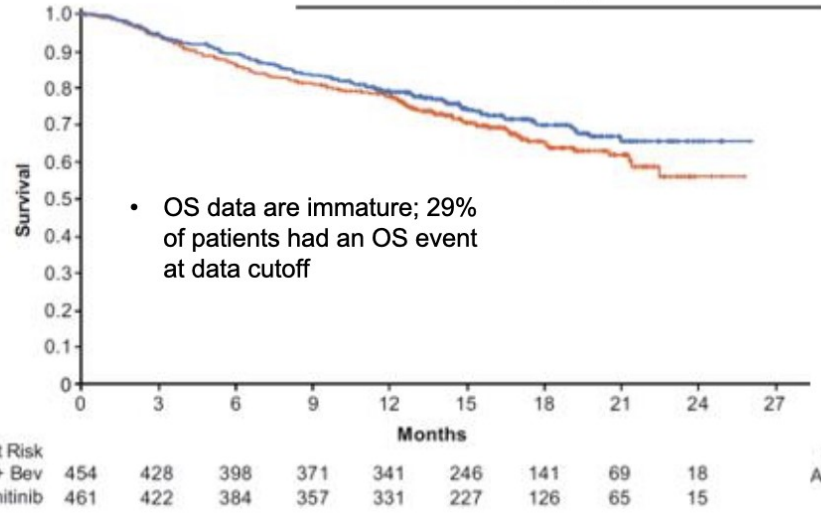
Then… it makes sense to *"combine"*!!!

Co-Primary Endpoint

Overall Survival in ITT & PD-L1+

ITT

ITT Median OS, mo (95% CI)	
Atezo + Bev	Not reached
Sunitinib	Not reached
HR, 0.81 (95% CI: 0.63, 1.03) *P* = 0.09	

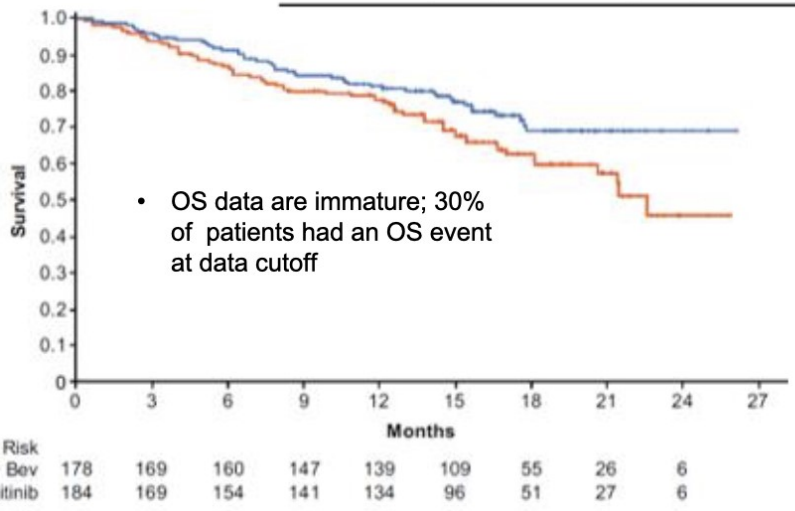


- OS data are immature; 29% of patients had an OS event at data cutoff

No. at Risk									
Atezo + Bev	454	428	398	371	341	246	141	69	18
Sunitinib	461	422	384	357	331	227	126	65	15

PD-L1+

PD-L1+ Median OS, mo (95% CI)	
Atezo + Bev	Not reached
Sunitinib	23.3 (21.3, NR)
HR, 0.68 (95% CI: 0.46, 1.00)	

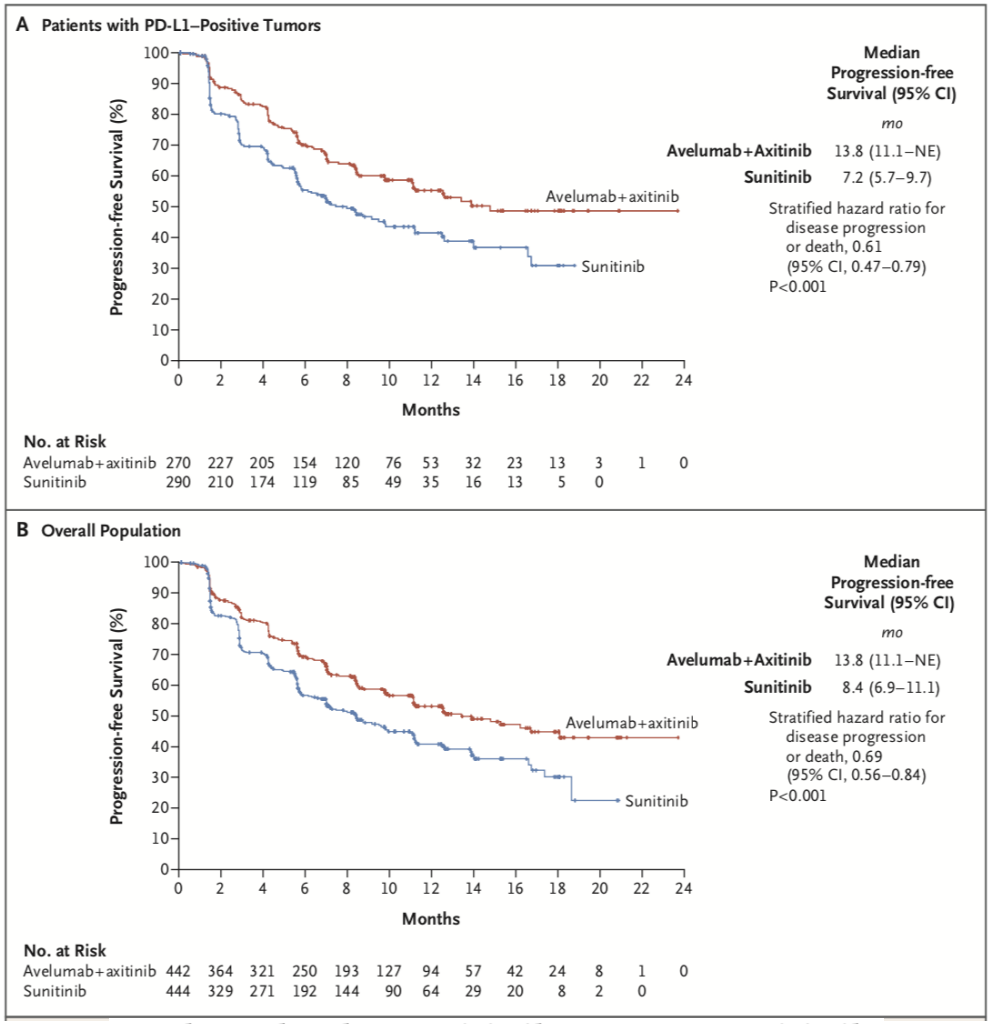


- OS data are immature; 30% of patients had an OS event at data cutoff

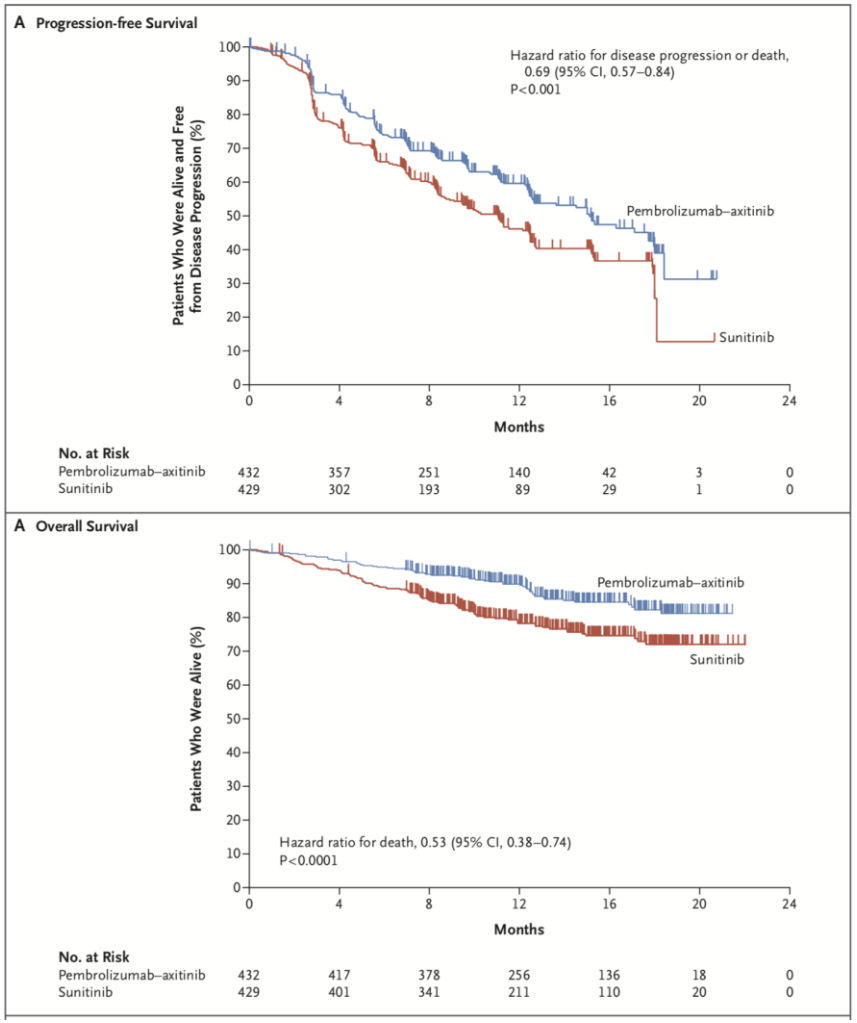
No. at Risk									
Atezo + Bev	178	169	160	147	139	109	55	26	6
Sunitinib	184	169	154	141	134	96	51	27	6

Minimum follow-up, 12 mo. Median of follow-up, 15 mo. Event/patient ratio: 27% for atezo + bev, 31% for sunitinib.
The OS analysis did not pass the *P* value boundary of alpha = 0.0009 at the first interim analysis.

Then… it makes sense to *"combine"*!!!

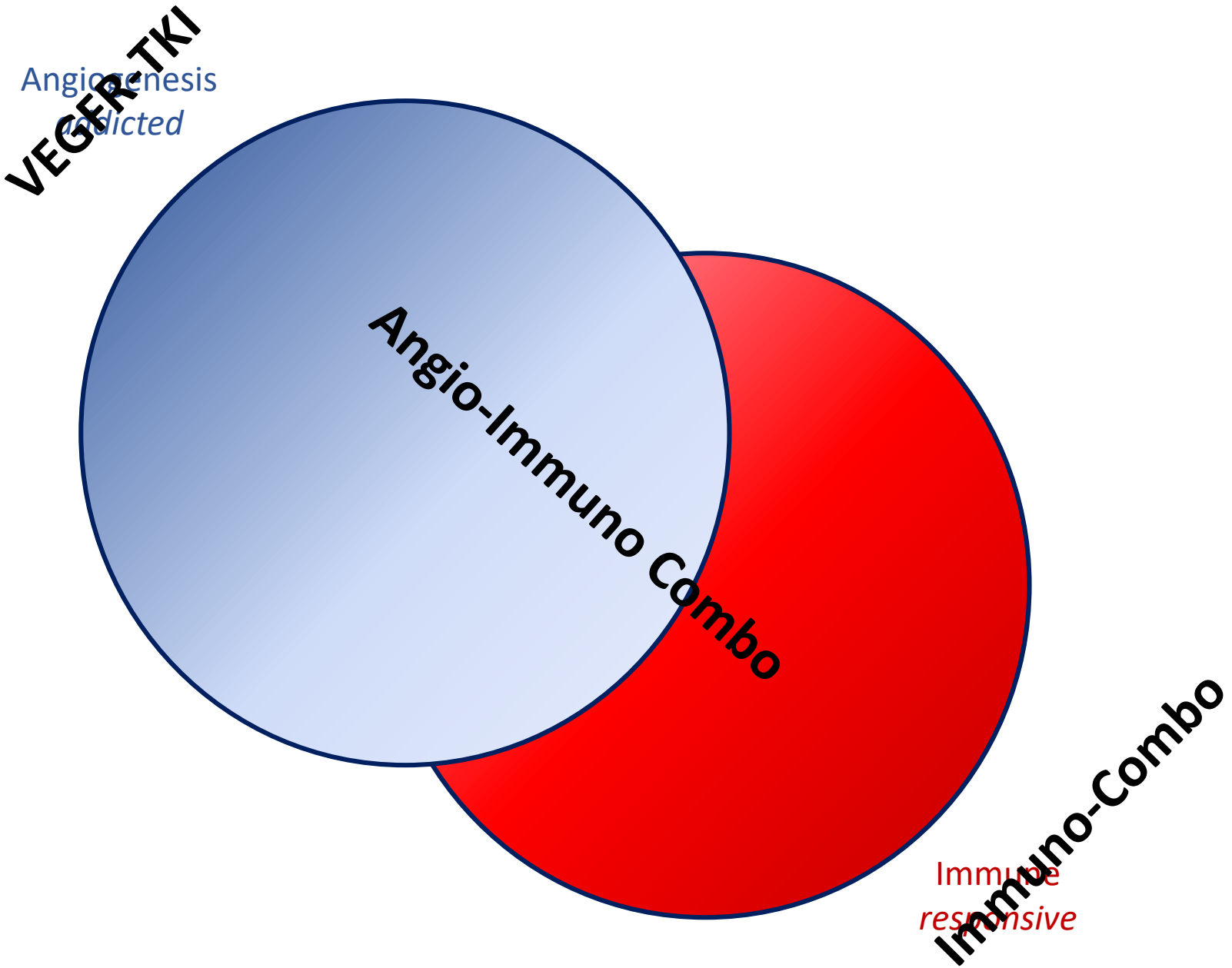


Avelumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma

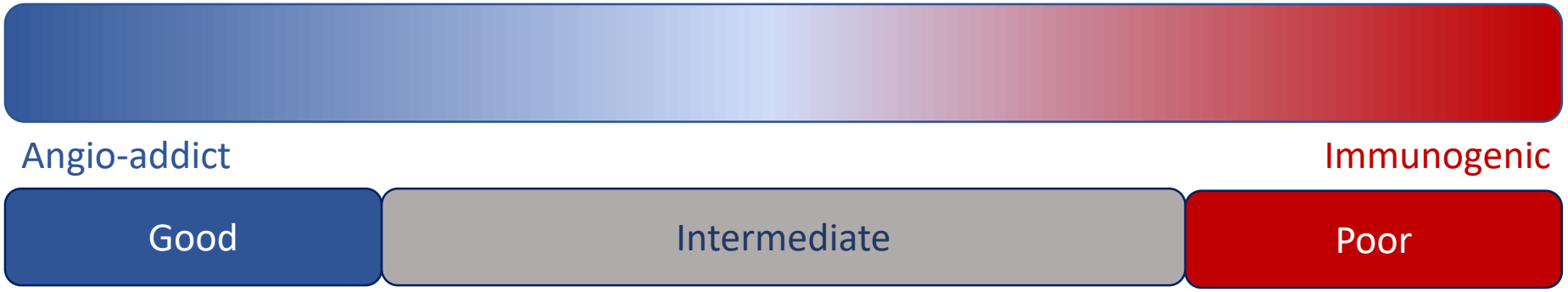


Pembrolizumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma

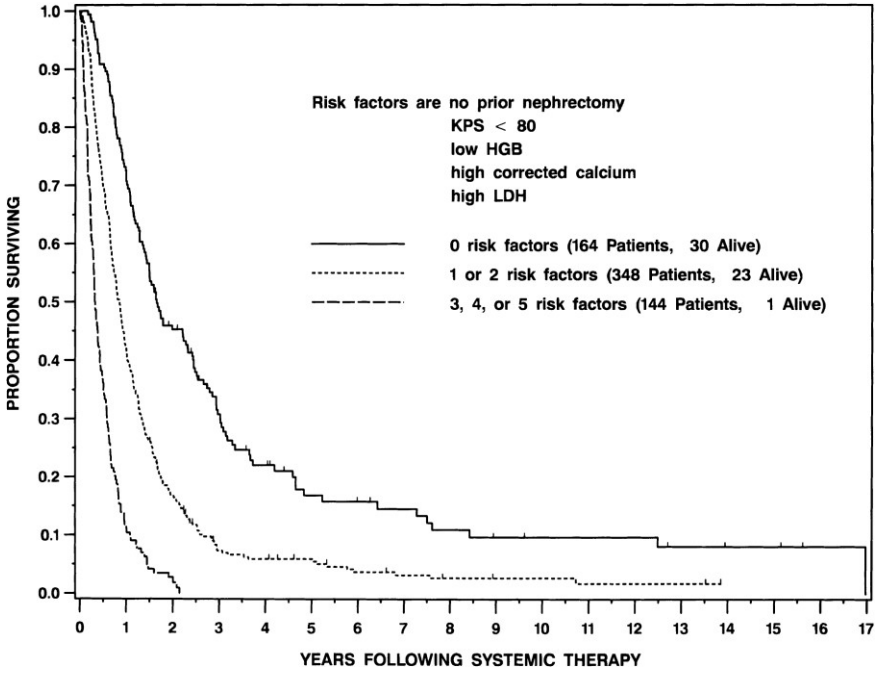
My (very personal) view…



Too easy maybe…



But remember risk classes are PROGNOSTIC... Not PREDICTIVE!!!



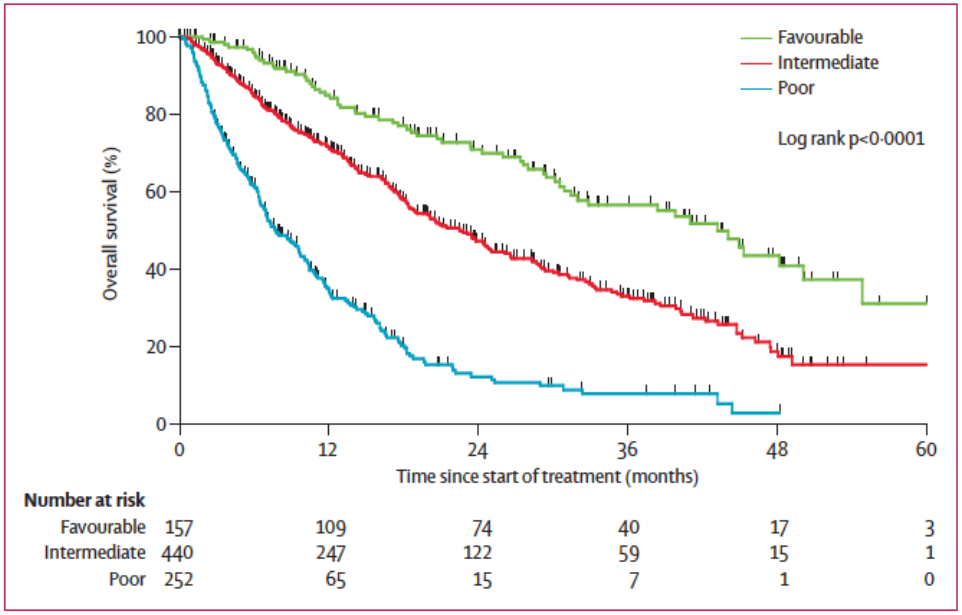
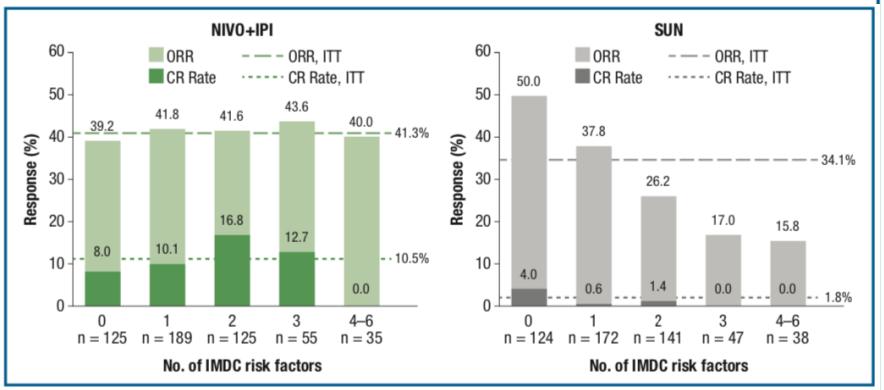


Figure 1: Results of Kaplan-Meier analysis of overall survival for the Database Consortium model

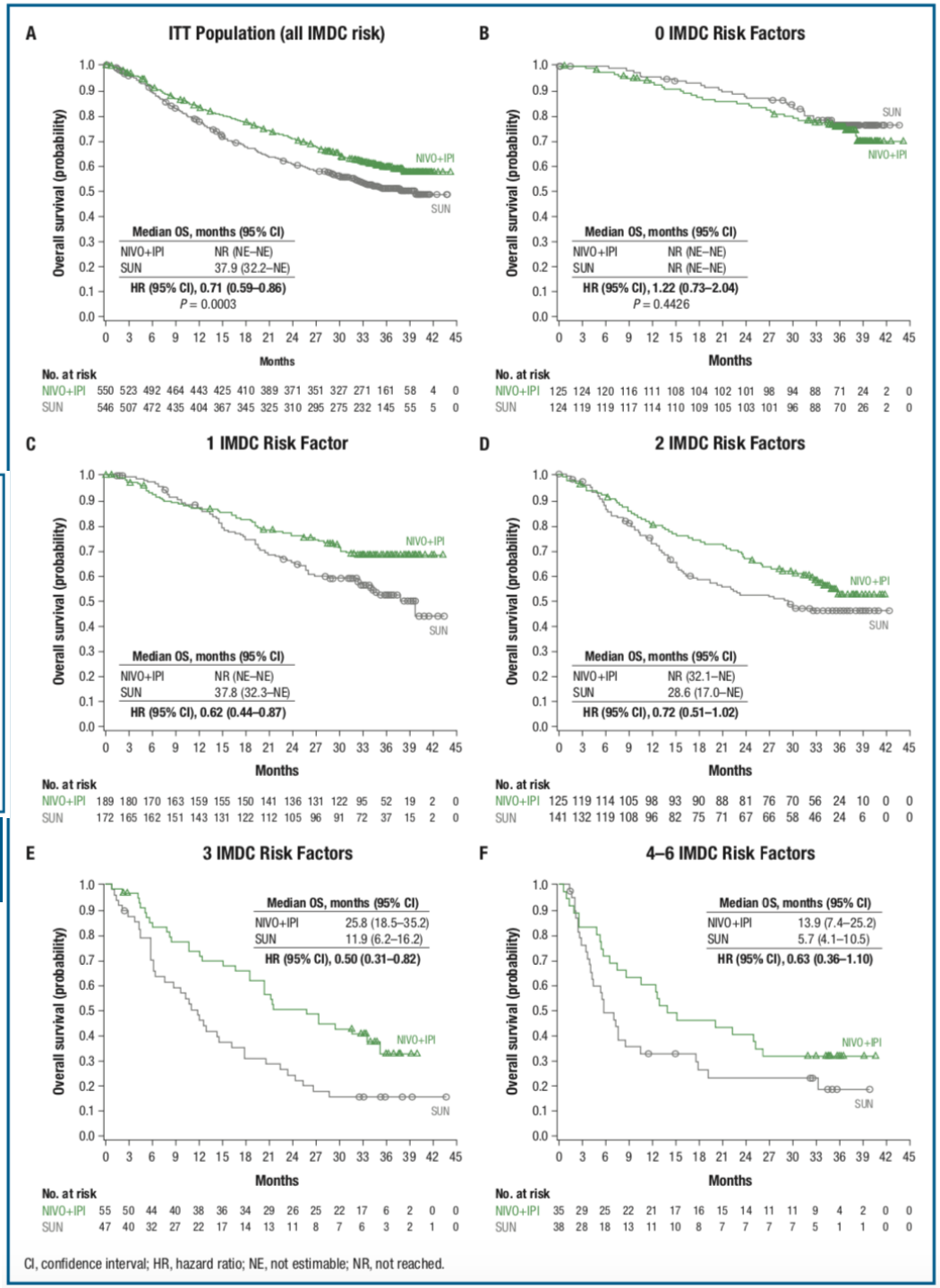
	Immunotherapy era[1]	Targeted agents era[2]
Median OS of good risk patients	20 months	43.2 months (95% CI: 31.4–50.1)
Median OS of intermediate risk patients	10 months	22.5 months (95% CI: 18.7–25.1)
Median OS of poor risk patients	4 months	7.8 months (95% CI: 6.5–9.7)

1. Motzer RJ, et al. *J Clin Oncol* 1993;11:1368-75; 2. Heng DY, et al. *Lancet Oncol* 2013;14:141-8.



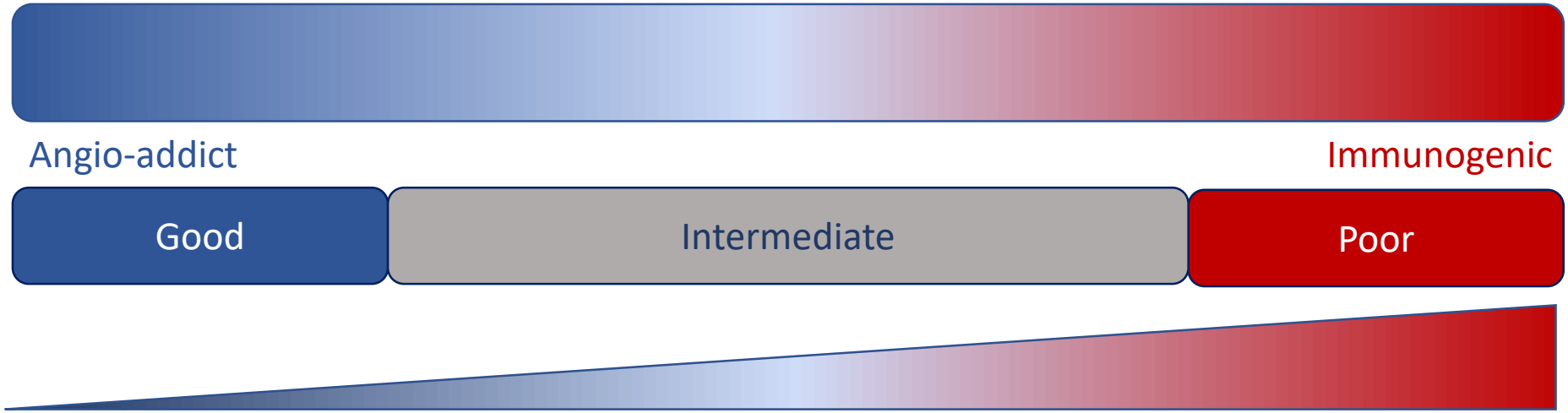
Consistent Efficacy of Nivolumab Plus Ipilimumab Across Number of IMDC Risk Factors in CheckMate 214

Bernard Escudier,[1] Robert J. Motzer,[2] Nizar M. Tannir,[3] Camillo Porta,[4] Yoshihiko Tomita,[5] Sabeen Mekan,*[6] M. Brent McHenry,[6] Brian I. Rini[7]

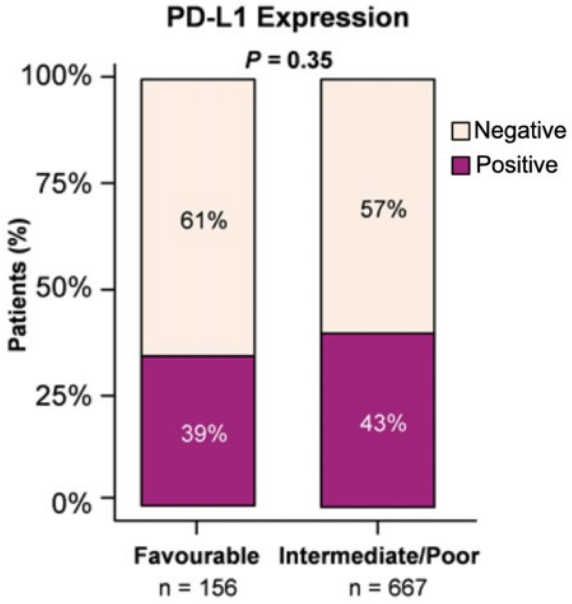


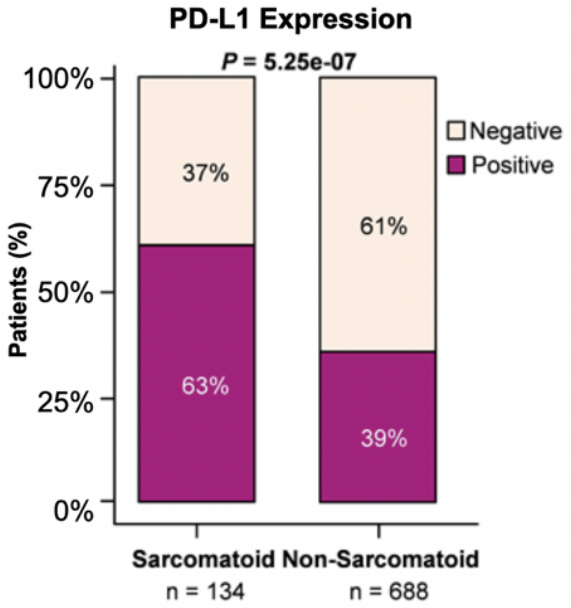
CI, confidence interval; HR, hazard ratio; NE, not estimable; NR, not reached.

Too easy maybe…



Other clinico-pathological features (i.e. sarcomatoid component)???

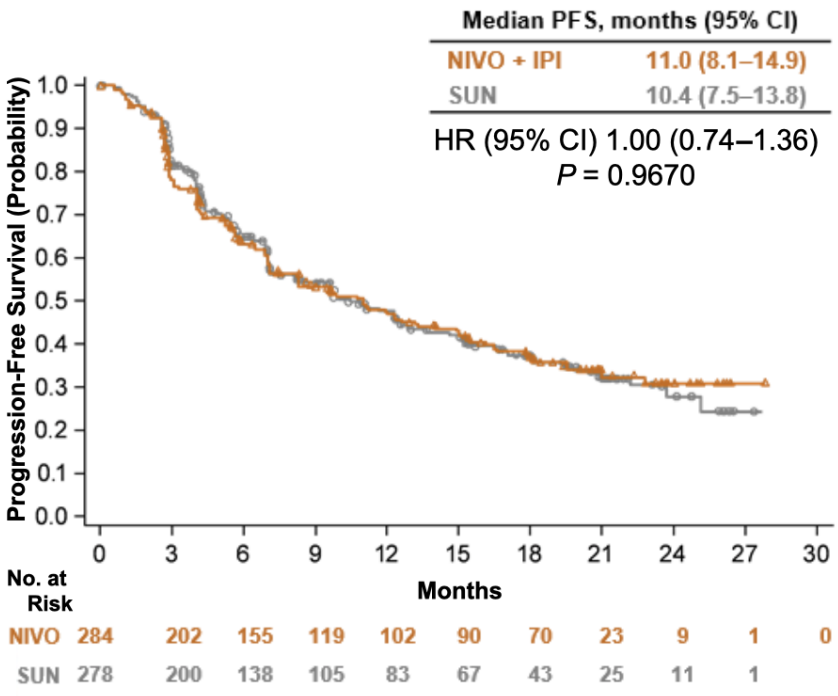




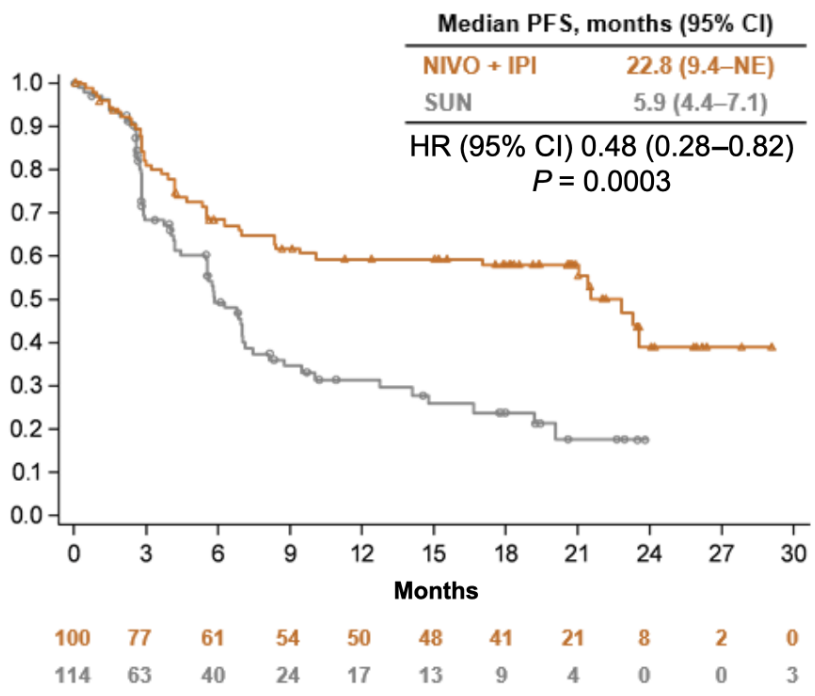
Exploratory endpoint

PFS by PD-L1 expression: IMDC intermediate/poor risk

PD-L1 <1% (n = 562)



PD-L1 ≥1% (n = 214)



Too easy maybe…

Angio-addict

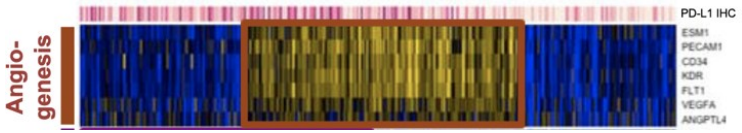
Immunogenic

Good	Intermediate	Poor

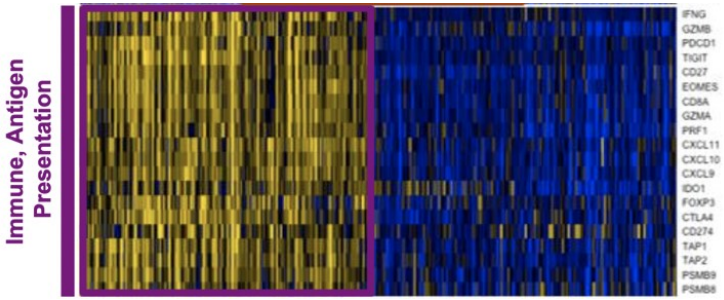
Other clinico-pathological features (i.e. sarcomatoid component)???

PD-L1 expression

Angiogenesis signature

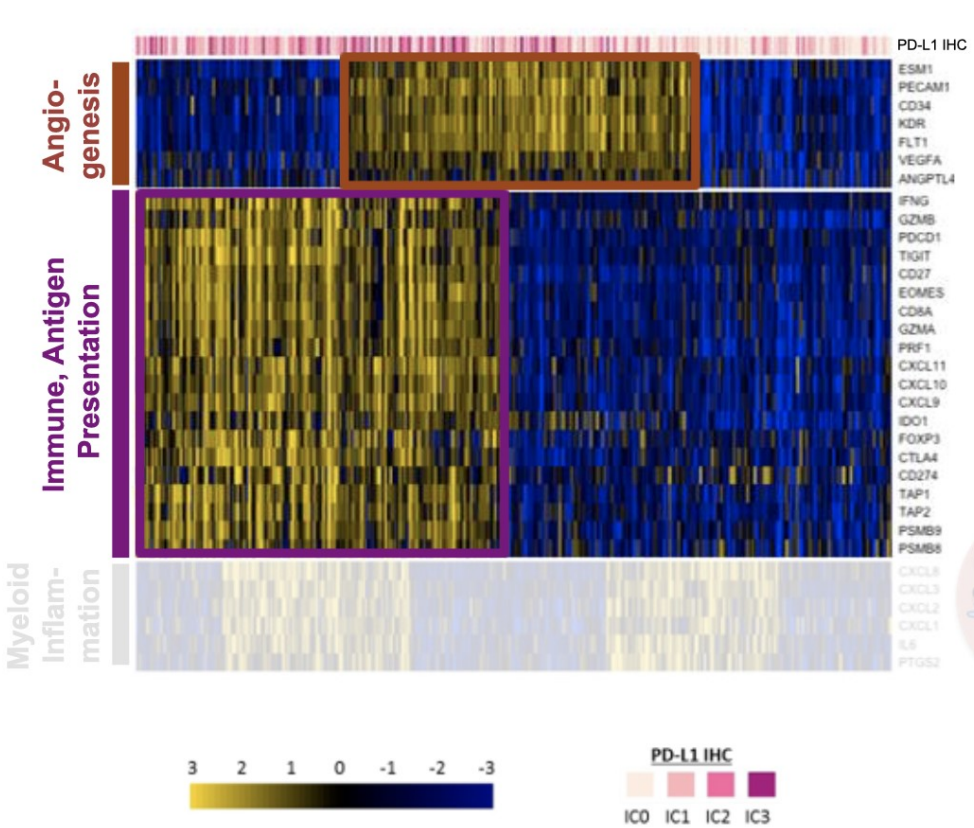


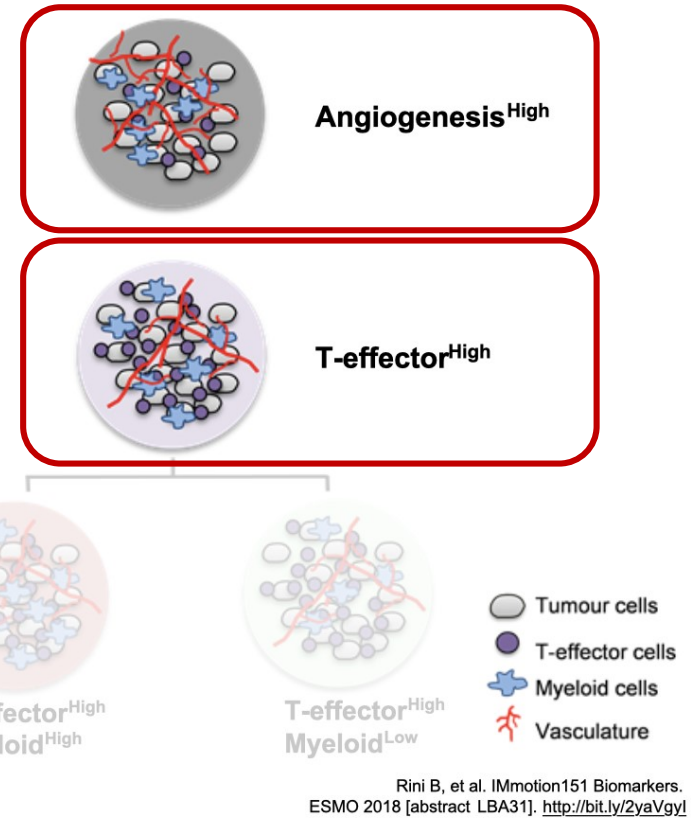
T-effector signature



Molecular signatures might exist…

IMmotion151: Transcriptome Map Confirms Biological Subgroups Identified in IMmotion150





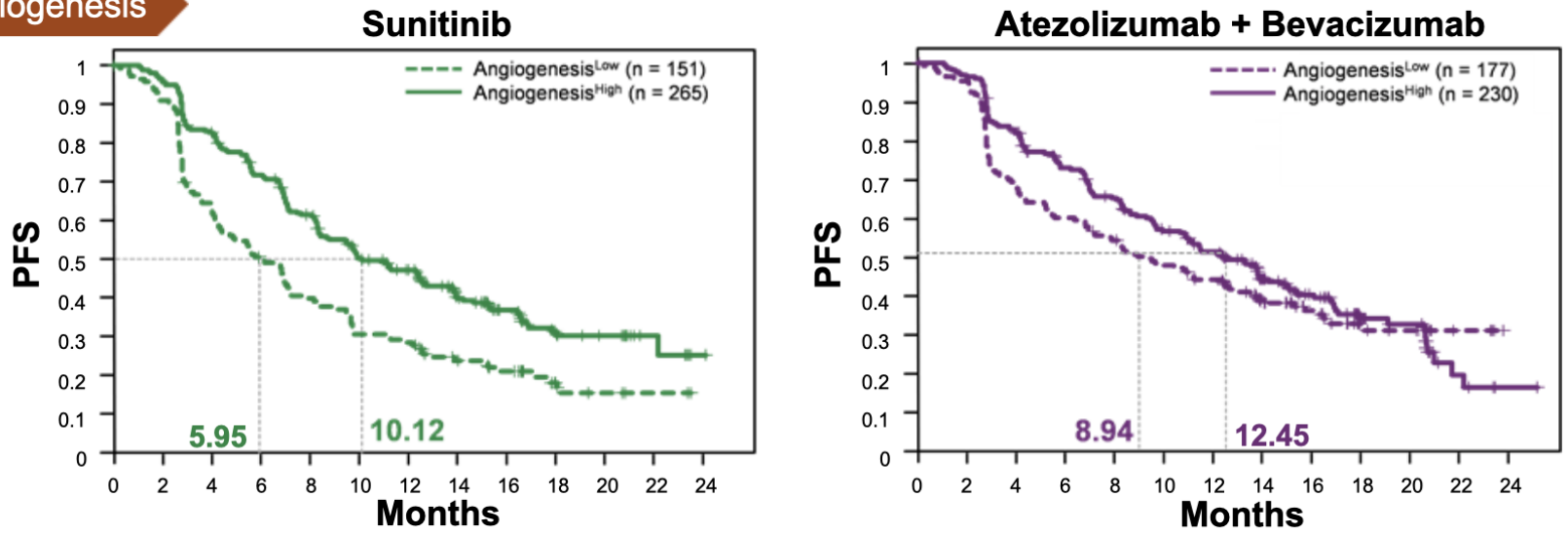
Rini B, et al. IMmotion151 Biomarkers. ESMO 2018 [abstract LBA31]. http://bit.ly/2yaVgyl

…to segregate patients at different chances to respond to TKI…

Sunitinib Demonstrated Improved PFS in Angiogenesis^{High} vs Angiogenesis^{Low} Subsets

MUNICH 2018 ESMO congress 14

Angiogenesis



	HR (95% CI)	
	Sunitinib	Atezo + Bev
Angiogenesis (High vs Low)	0.59 (0.47, 0.75)	0.86 (0.67, 1.1)

Rini B, et al. IMmotion151 Biomarkers. ESMO 2018 [abstract LBA31]. http://bit.ly/2yaVgyl

…to segregate patients at different chances to respond to TKI…

Atezolizumab + Bevacizumab Improved PFS vs Sunitinib in the Angiogenesis^{Low} Subset

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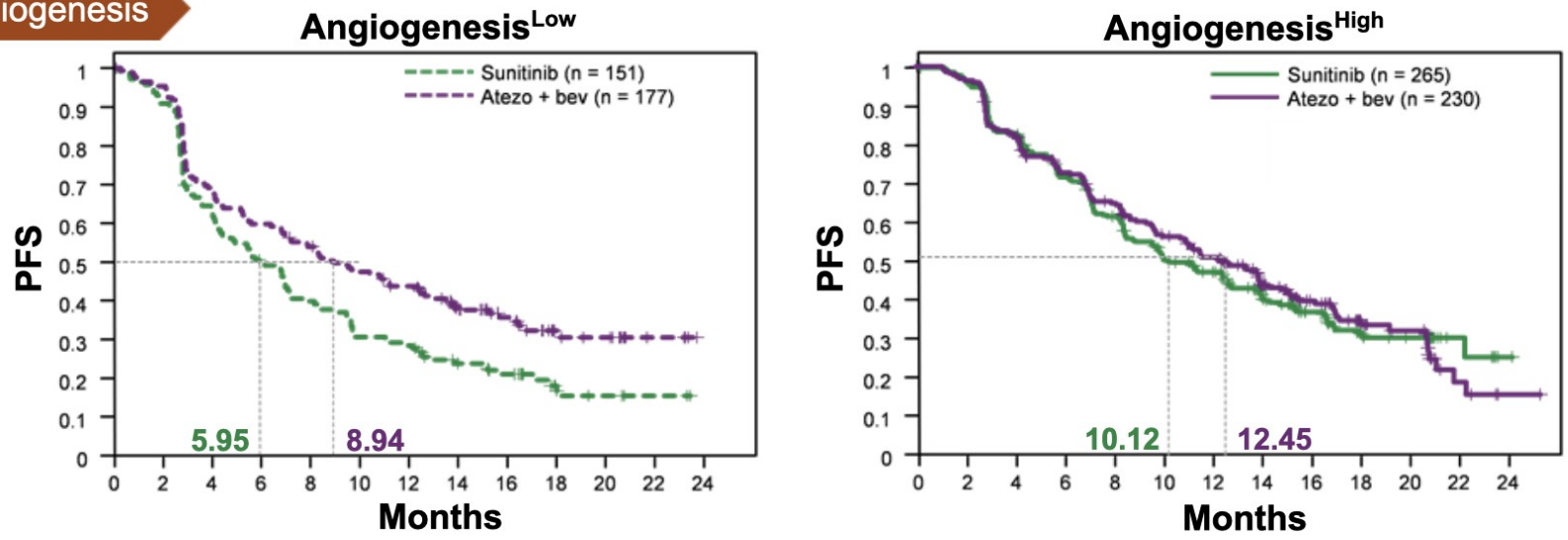
Angiogenesis



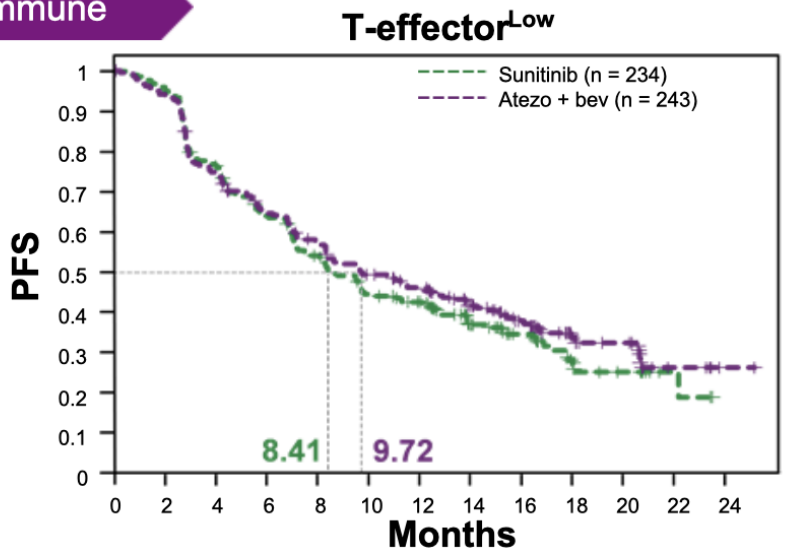
HR (95% CI)		
	Angiogenesis^{Low}	Angiogenesis^{High}
Atezo + bev vs sunitinib	0.68 (0.52, 0.88)	0.95 (0.76, 1.19)

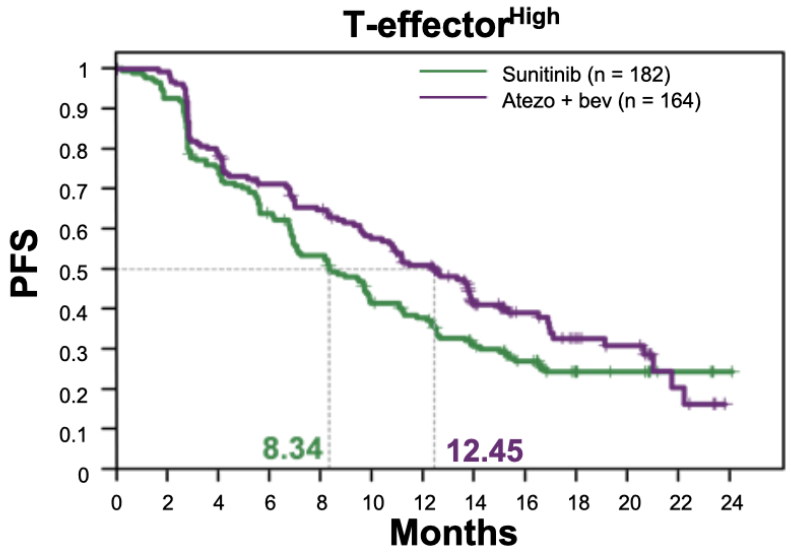
Rini B, et al. IMmotion151 Biomarkers. ESMO 2018 [abstract LBA31]. http://bit.ly/2yaVgyl

…or to Angio-Immuno combos!

Atezolizumab + Bevacizumab Demonstrated Improved PFS vs Sunitinib in T_{eff}^{High} Subset

Immune



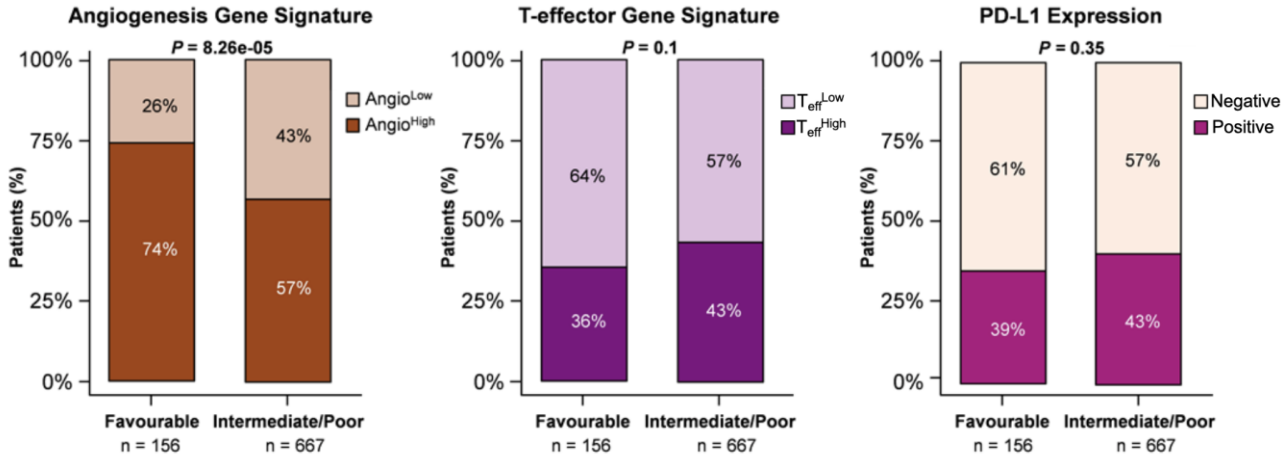


HR (95% CI)		
	T-effector^{Low}	T-effector^{High}
Atezo + bev vs sunitinib	0.91 (0.73, 1.14)	0.76 (0.59, 0.99)

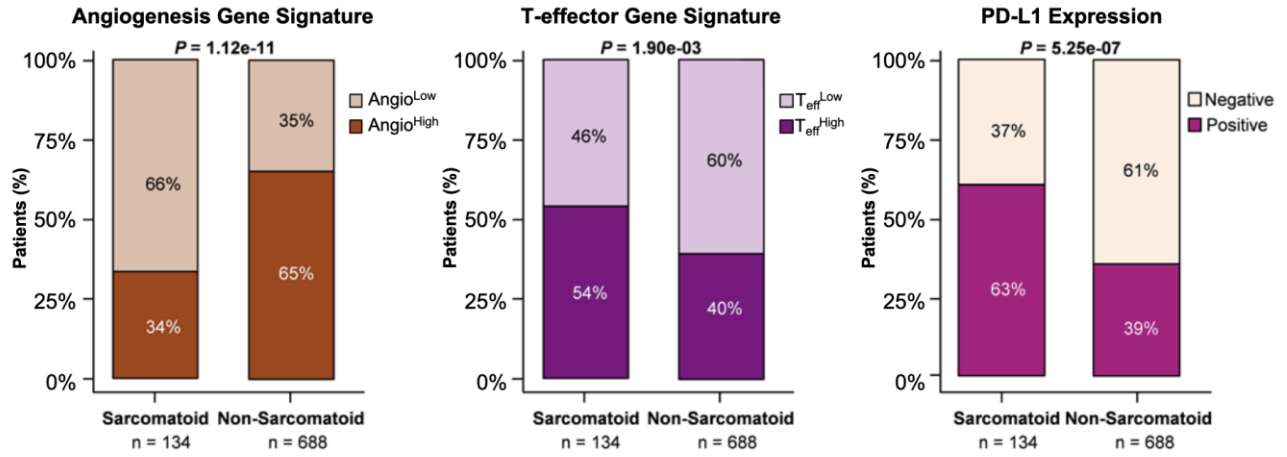
- T-effector gene signature did not differentiate PFS within the sunitinib or atezolizumab + bevacizumab treatment arms

Rini B, et al. IMmotion151 Biomarkers. ESMO 2018 [abstract LBA31]. http://bit.ly/2yaVgyl

Angiogenesis Gene Expression Is Higher in Favourable MSKCC Risk Group



Angiogenesis Gene Expression Is Lower and PD-L1 Expression Is Higher in Sarcomatoid Tumours



Rini B, et al. IMmotion151 Biomarkers. ESMO 2018 [abstract LBA31]. http://bit.ly/2yaVgyI

Too easy maybe…

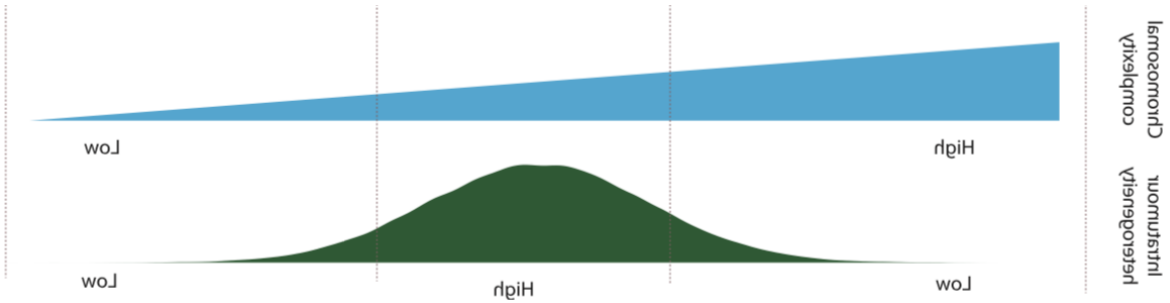
Angio-addict — Immunogenic

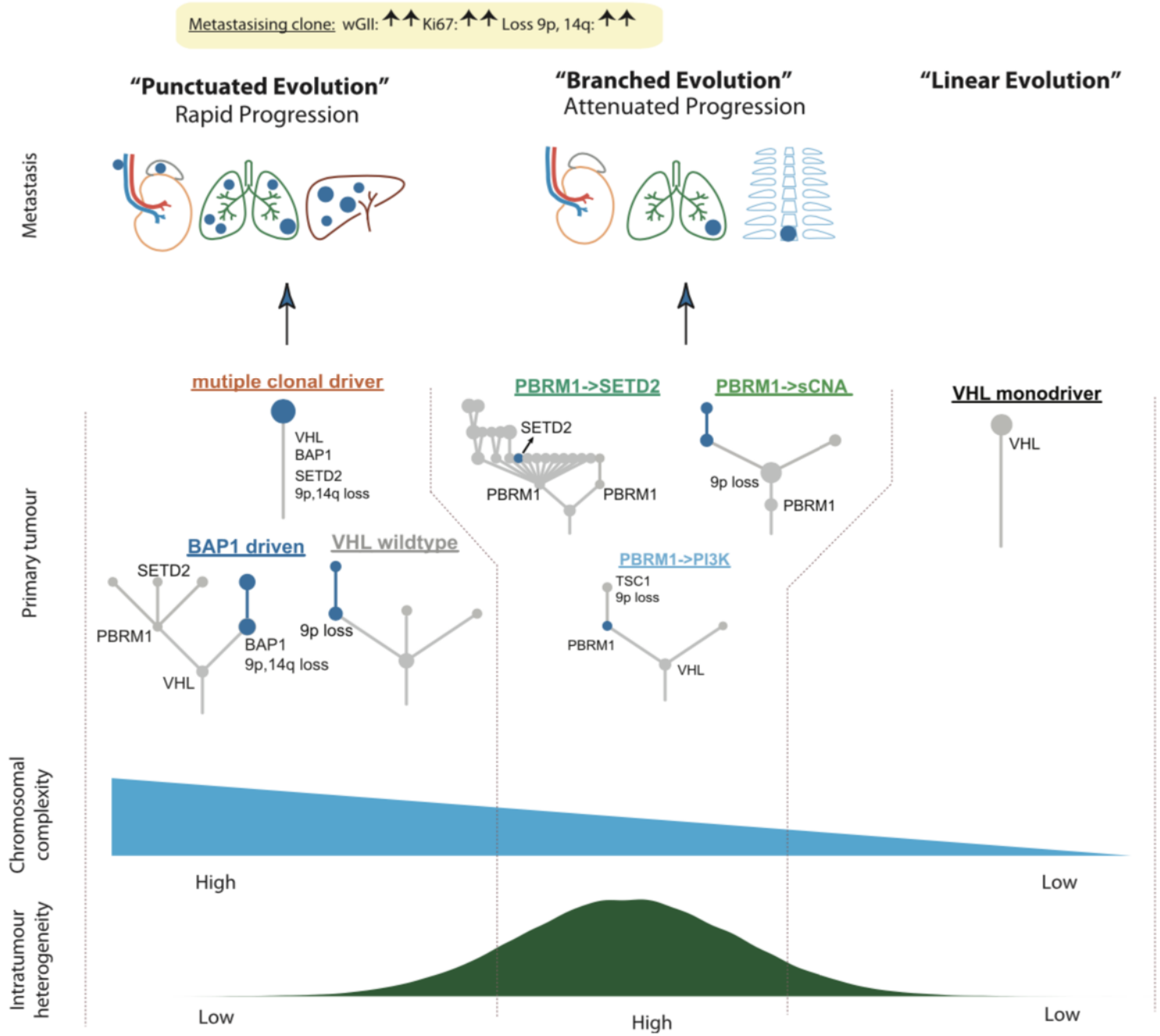
Good	Intermediate	Poor

Other clinico-pathological features (i.e. sarcomatoid component)???

PD-L1 expression

Angiogenesis signature — T-effector signature




Metastasising clone: wGII: ↑↑ Ki67: ↑↑ Loss 9p, 14q: ↑↑
"Punctuated Evolution"
Rapid Progression
"Branched Evolution"
Attenuated Progression
"Linear Evolution"
Metastasis
Primary tumour
mutiple clonal driver
VHL
BAP1
SETD2
9p,14q loss
PBRM1->SETD2
SETD2
PBRM1
PBRM1
PBRM1->sCNA
9p loss
PBRM1
VHL monodriver
VHL
BAP1 driven
SETD2
PBRM1
BAP1
9p,14q loss
VHL
VHL wildtype
9p loss
PBRM1->PI3K
TSC1
9p loss
PBRM1
VHL
Chromosomal complexity
High
Low
Intratumour heterogeneity
Low
High
Low

Conclusions (my personal ones…)

- *Angiogenesis* and *immune response regulation* are both critical to the pathogenesis and clinical evolution of RCC
- Molecular mechanisms regulating *angiogenesis* and *immune response* crosstalk and influence each other
- Molecular mechanisms regulating *angiogenesis* and *immune response* are dynamic and respond to the selective pressure of the applied treatment
- *Angiogenesis* and *immune response* are both highly relevant therapeutic targets that can be exploited clinically with great success
- Some patients will benefit most from targeting *angiogenesis*, some from (combined) *immune checkpoint inhibition*, some will need both for optimal disease control
- I believe time is coming to try and personalize treatment in mRCC, by giving ***the right drug(s), to the right patient, at the right time***

Grazie!!!

michele.milella@univr.it