Metastasiertes Nierenzellkarzinom

Aktuelle Therapieoptionen

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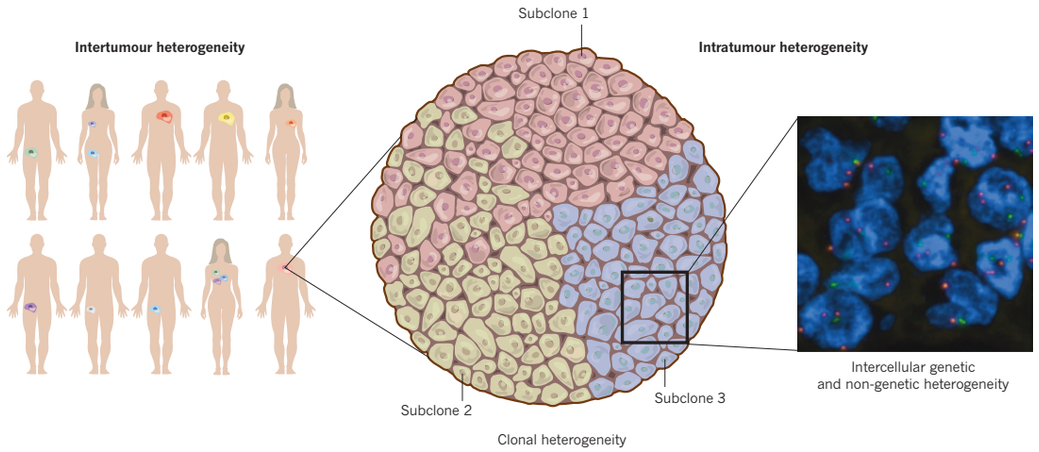
Österreichischen Gesellschaft für Urologie und Andrologie

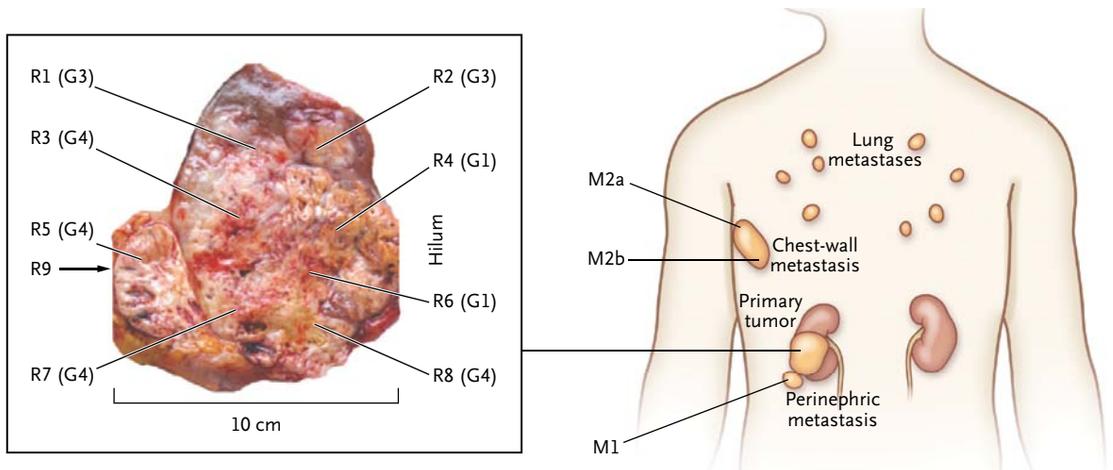
EVOLUTION
einer Tumorerkrankung

The causes and consequences of genetic heterogeneity in cancer evolution

Rebecca A. Burrell[1]*, Nicholas McGranahan[1,2]*, Jiri Bartek[3,4] & Charles Swanton[1,5]

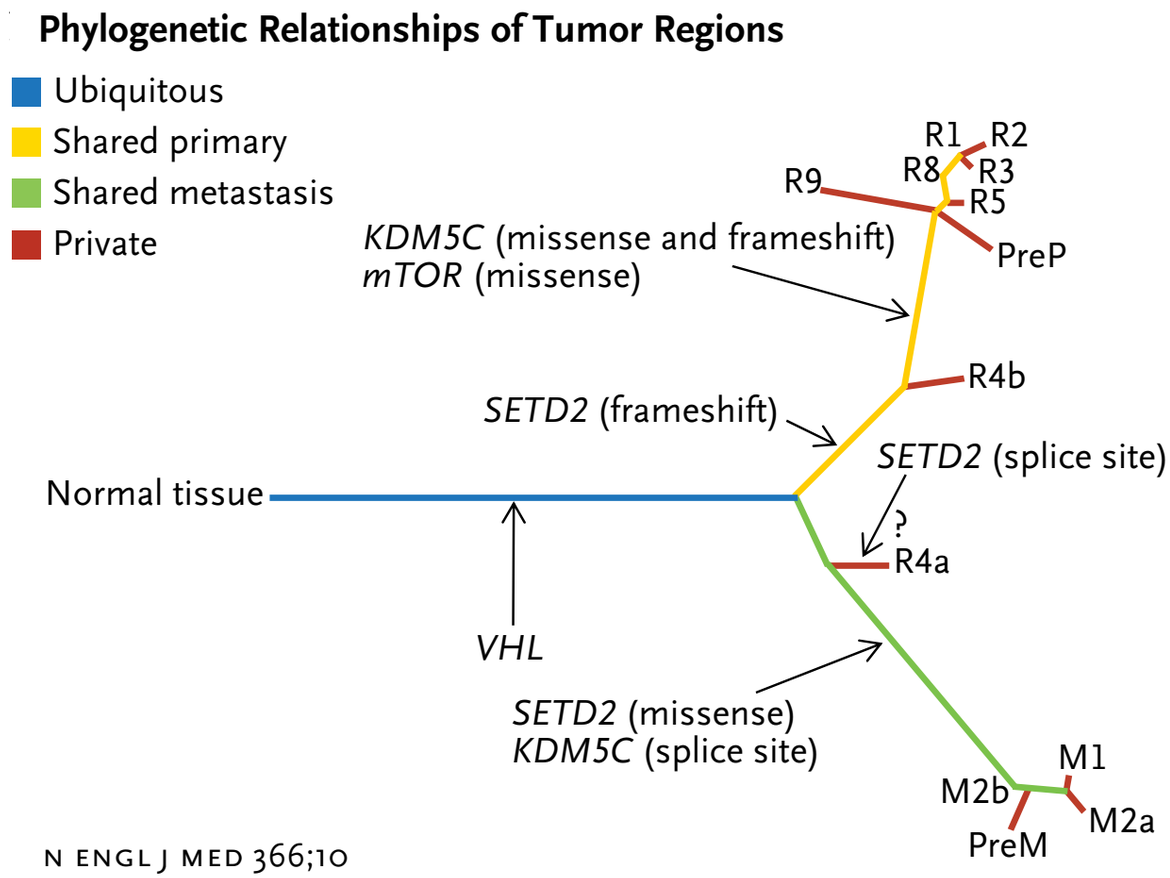
338 | NATURE | VOL 501 | 19 SEPTEMBER 2013





Intratumor Heterogeneity and Branched Evolution Revealed by Multiregion Sequencing

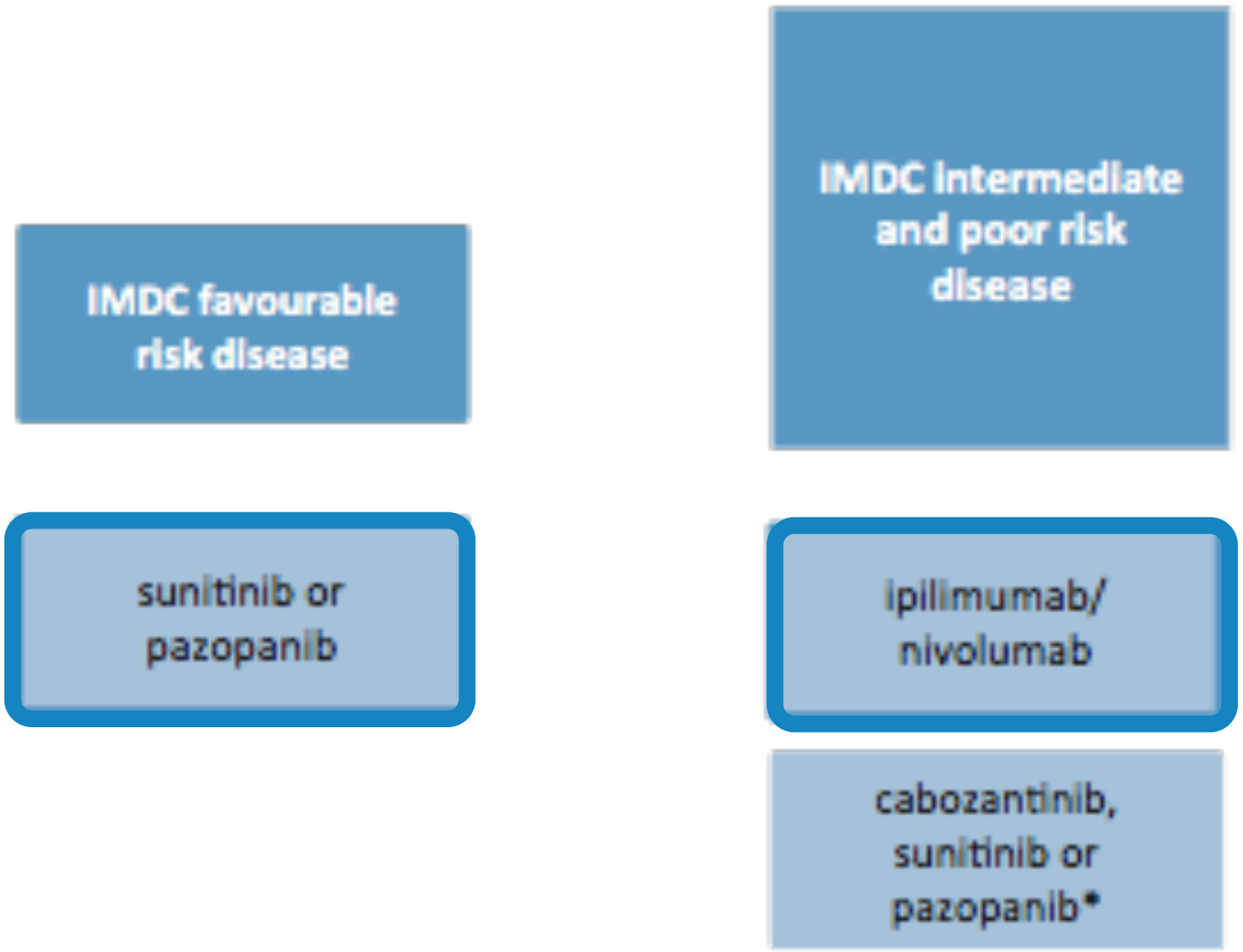
Marco Gerlinger, M.D., Andrew J. Rowan, B.Sc., Stuart Horswell, M.Math., James Larkin, M.D., Ph.D., David Endesfelder, Dip.Math., Eva Gronroos, Ph.D., Pierre Martinez, Ph.D., Nicholas Matthews, B.Sc., Aengus Stewart, M.Sc., Patrick Tarpey, Ph.D., Ignacio Varela, Ph.D., Benjamin Phillimore, B.Sc., Sharmin Begum, M.Sc., Neil Q. McDonald, Ph.D., Adam Butler, B.Sc., David Jones, M.Sc., Keiran Raine, M.Sc., Calli Latimer, B.Sc., Claudio R. Santos, Ph.D., Mahrokh Nohadani, H.N.C., Aron C. Eklund, Ph.D., Bradley Spencer-Dene, Ph.D., Graham Clark, B.Sc., Lisa Pickering, M.D., Ph.D., Gordon Stamp, M.D., Martin Gore, M.D., Ph.D., Zoltan Szallasi, M.D., Julian Downward, Ph.D., P. Andrew Futreal, Ph.D., and Charles Swanton, M.D., Ph.D.



N ENGL J MED 366;10

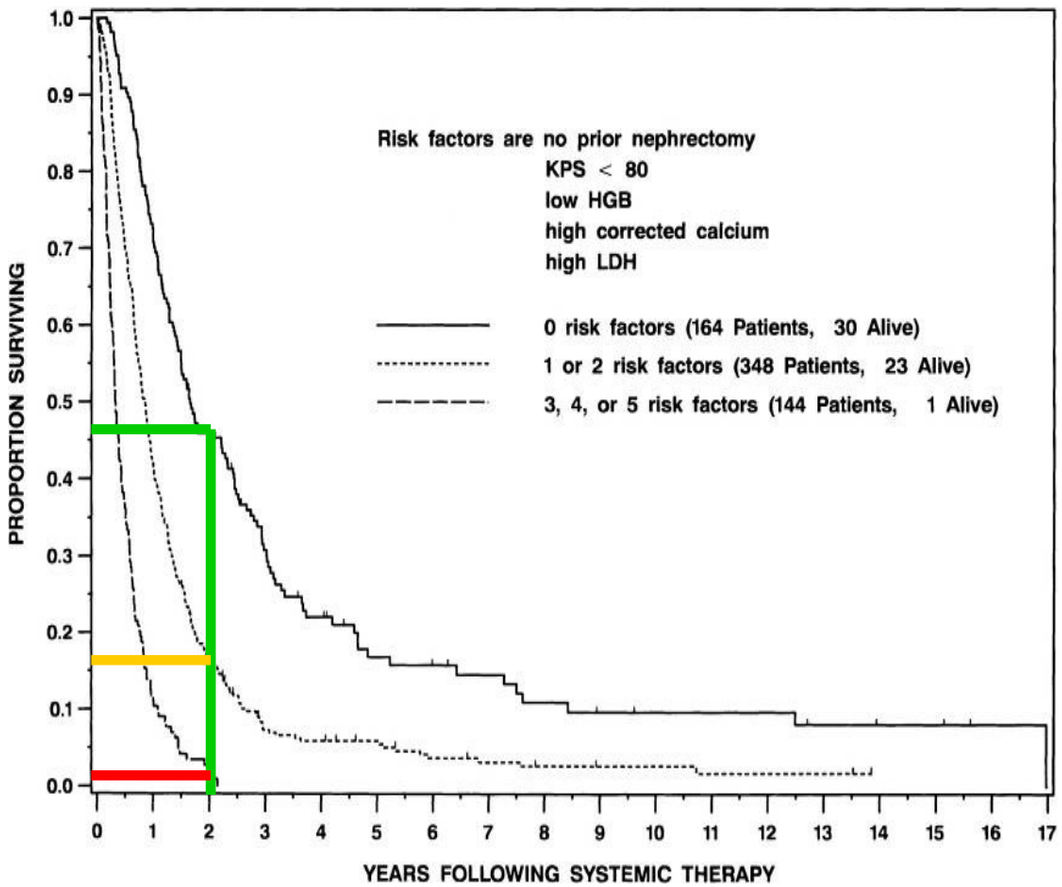
EAU Recommendation

Updated European Association of Urology Guidelines: Recommendations for the Treatment of First-line Metastatic Clear Cell Renal Cancer



Cytokintherapie - historisch

Overall survival: Cytokin - Ära



Motzer et al., J Clin Oncol 1999

IL2+Ifn

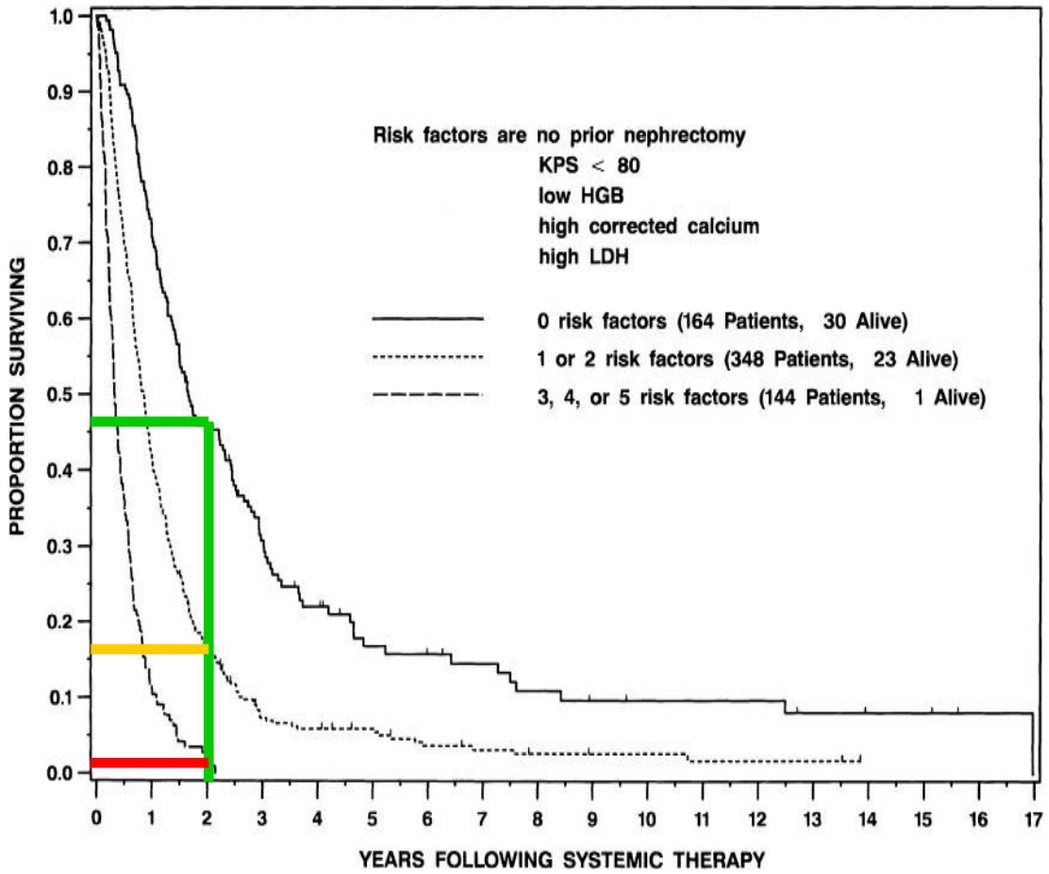
Efficacy

	IL-2 (*n* = 138)	IFN-α (*n* = 147)	IL-2 + IFN-α (*n* = 140)
CR, %	1.4	0	0.7
PR, %	5.1	7.5	17.9
ORR, %	**6.5**	**7.5**	**18.6***
mOS, months	12	13	17

Negrier S et al. *N Engl J Med*. 1998;338:1272-1278.

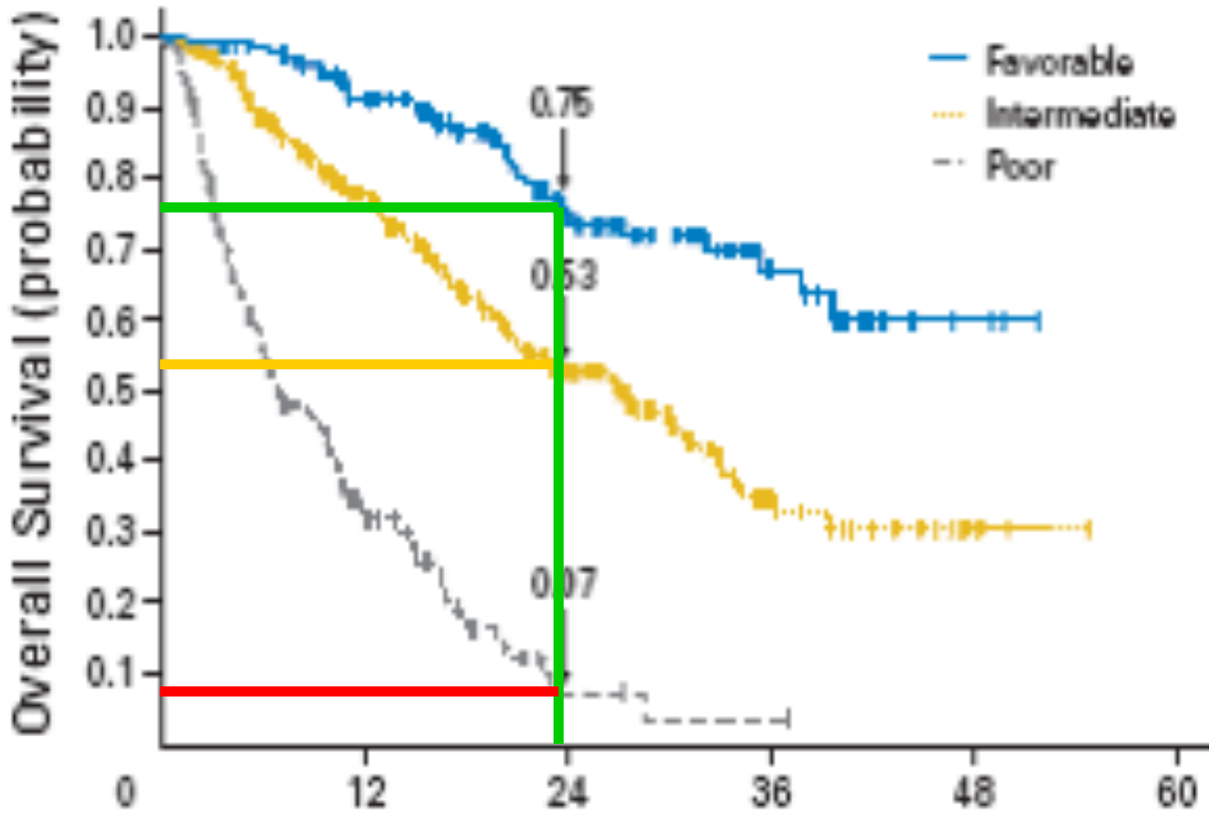
Cytokine vs. VEGF Inhibition

Overall survival: Cytokin - Ära



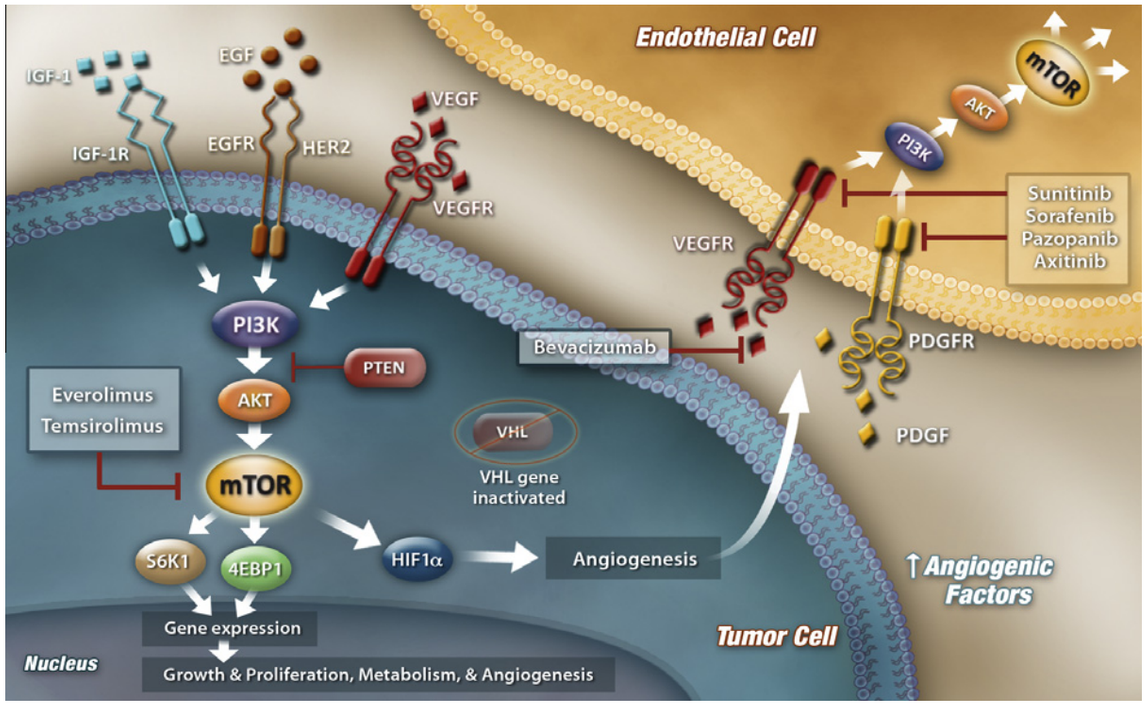
Motzer et al., J Clin Oncol 1999

Overall survival: TKI - Ära



Heng et al., J Clin Oncol 2009

VEGF Inhibition



S. Oudard, R.-T. Elaidi / Cancer Treatment Reviews 38 (2012) 981–987

Hd IL2

IL2+Ifn

Sorafenib

Sunitinib

Temsirolimus

Everolimus

Bevacizumab + Ifn

Pazopanib

Axitinib

Nivolumab

Cabozantinib

Lenvatinib

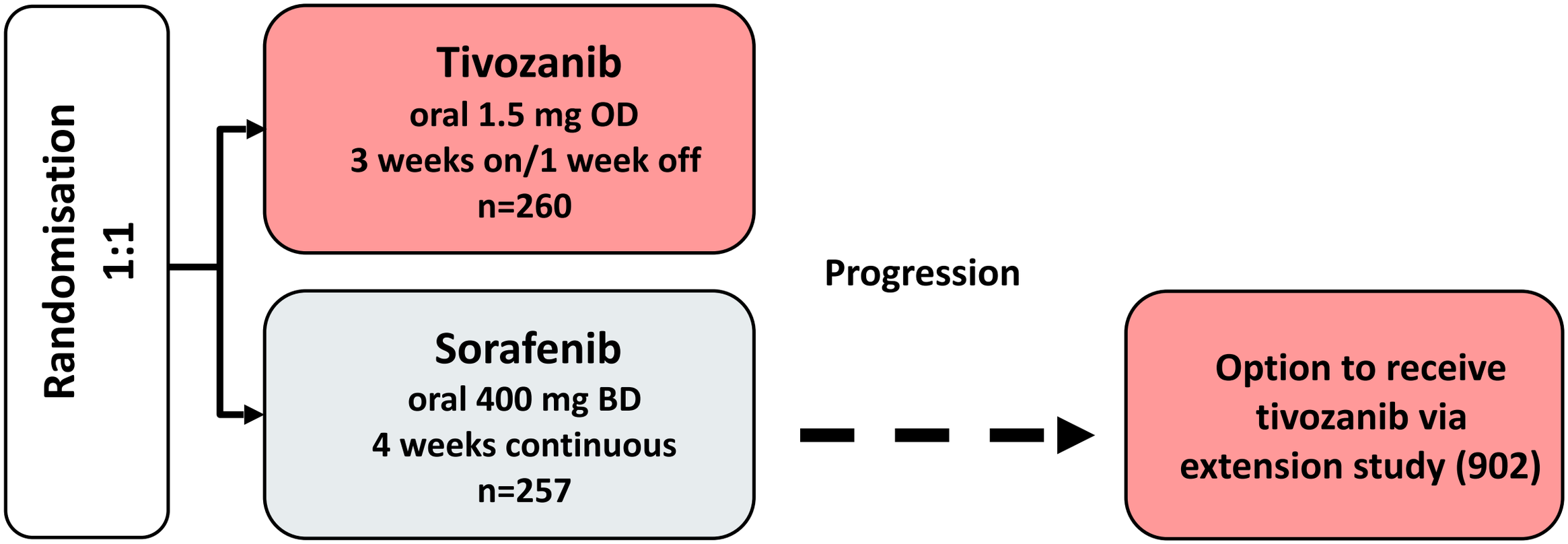
Avelumab + Axitinib

Atezolizumab + Bevacizumab

1992-2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 2016 | 2017 | 2018

Zytokine | **VEGF / mTOR** | **VEGF / Immun/mTor**

TIVO-1 Studiendesign



Eligibility criteria

Advanced RCC
Clear-cell type
Prior nephrectomy
No prior VEGF treatment
ECOG performance score 0-1

Primary end-point

Progression free survival

Secondary end-points

Overall survival
Objective response rate
Quality of life

Motzer RJ, Nosov D, Eisen T et al. J Clin Oncol 2013;31(30):3791-9.
RCC: Renal cell carcinoma; VEGF: Vascular endothelial growth factor; ECOG: Eastern Cooperative Oncology Group;; OD.: once daily; BD.: twice daily

TIVO-1 (patient characteristics)

Characteristic	Tivozanib (n=260) No.	%	Sorafenib (n= 257) No.	%
ECOG performance score				
0	116	45%	139	54%
1	144	55%	118	46%
MSKCC prognostic group				
Favourable	70	27%	87	34%
Intermediate	173	67%	160	62%
Poor	17	7%	10	4%
Prior systemic therapy for metastatic RCC				
0	181	70%	181	70%
1	78	30%	76	30%
Prior systemic therapy by setting				
Metastatic	49	19%	55	21%
Adjuvant	23	9%	22	9%
Other	13	5%	9	4%

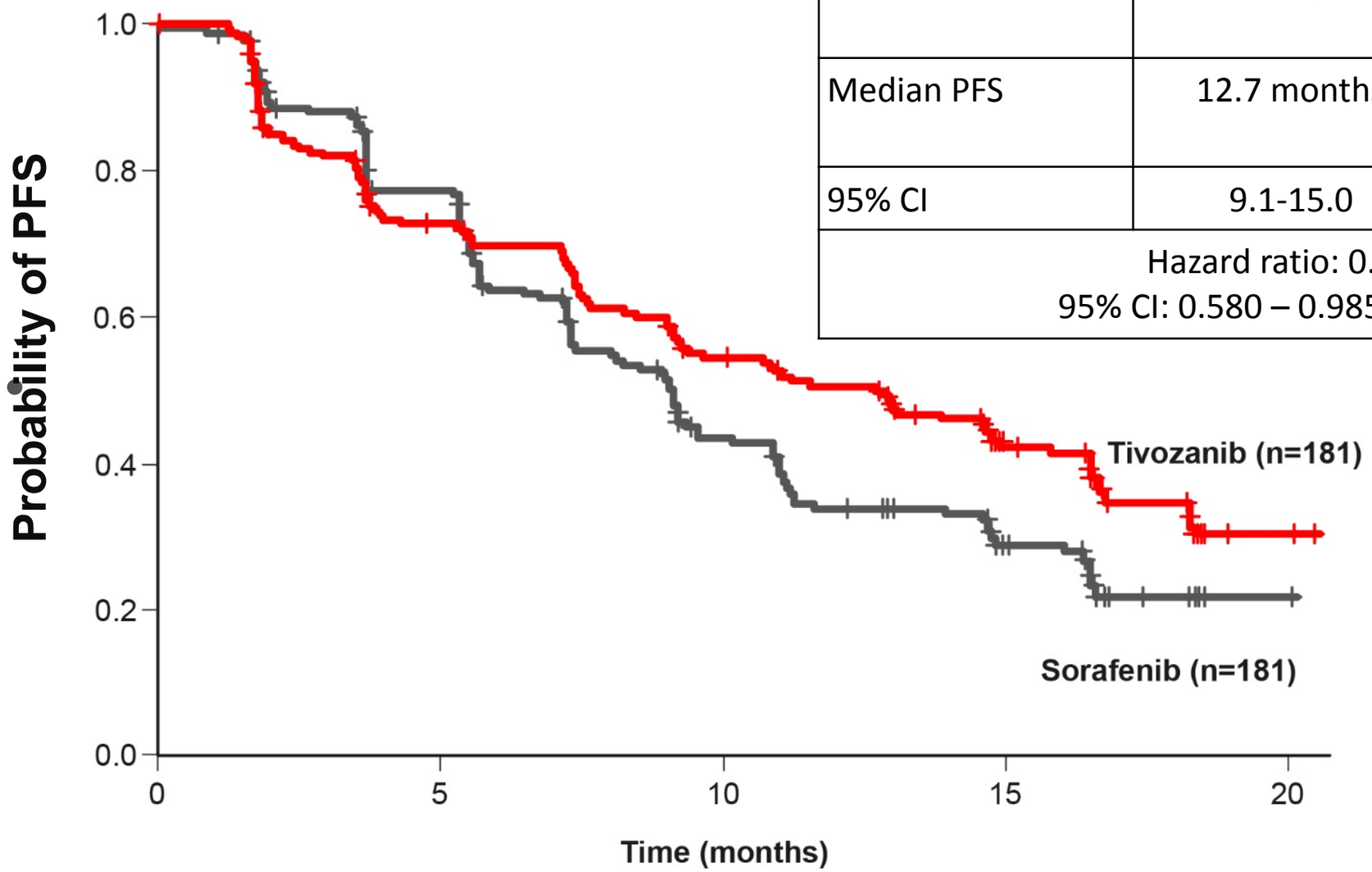
Motzer RJ, Nosov D, Eisen T et al. J Clin Oncol 2013;31(30):3791-9.

ECOG: Eastern Cooperative Oncology Group; MSKCC: Memorial Sloan-Kettering Cancer Center; RCC: Renal cell carcinoma

TIVO-1 PFS (treatment naive patients)

Intention to treat population, PFS by independent radiology review

	Tivozanib (n=181)	Sorafenib (n=181)
Median PFS	12.7 months	9.1 months
95% CI	9.1-15.0	7.3-10.8
Hazard ratio: 0.756 95% CI: 0.580 – 0.985, p=0.037		



TIVO-1 met the end-point of improved PFS versus sorafenib in patients with no prior treatment for metastatic disease

1. Motzer RJ, Nosov D, Eisen T, *et al. J Clin Oncol* 2013;31(30):3791–9.

TIVO-1 Response

	Tivozanib (n=260)		Sorafenib (n=257)	
	n	**%**	**n**	**%**
CR	3	1.2%	2	0.8%
PR	83	31.9%	58	22.6%
SD	134	51.5%	168	65.4%
PD	34	13.1%	19	7.4%
Not evaluable	6	2.3%	10	3.9%
ORR	86	33.1%	60	23.3%

ORR was significantly higher with tivozanib compared with sorafenib

33.1% versus 23.3%, p=0.014

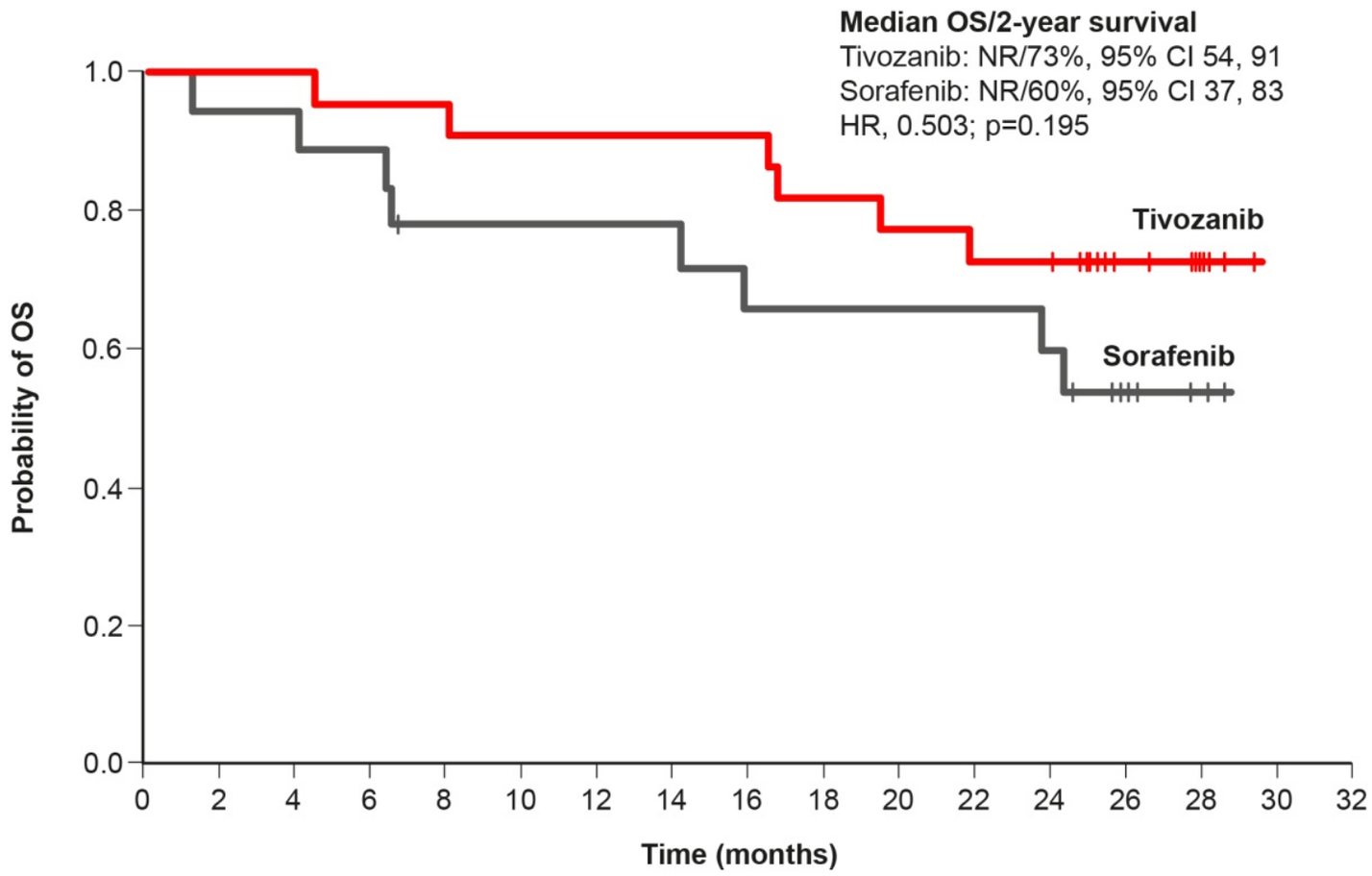
Consistent outcomes across secondary end-points support for efficacy of tivozanib

Motzer RJ, Nosov D, Eisen T et al. J Clin Oncol 2013;31(30):3791-9.

CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease; ORR: Overall response rate

TIVO-1 OS

TIVO-1: If next line treatment balanced, OS trend favours tivozanib
North America and Western Europe cohort (n=40)

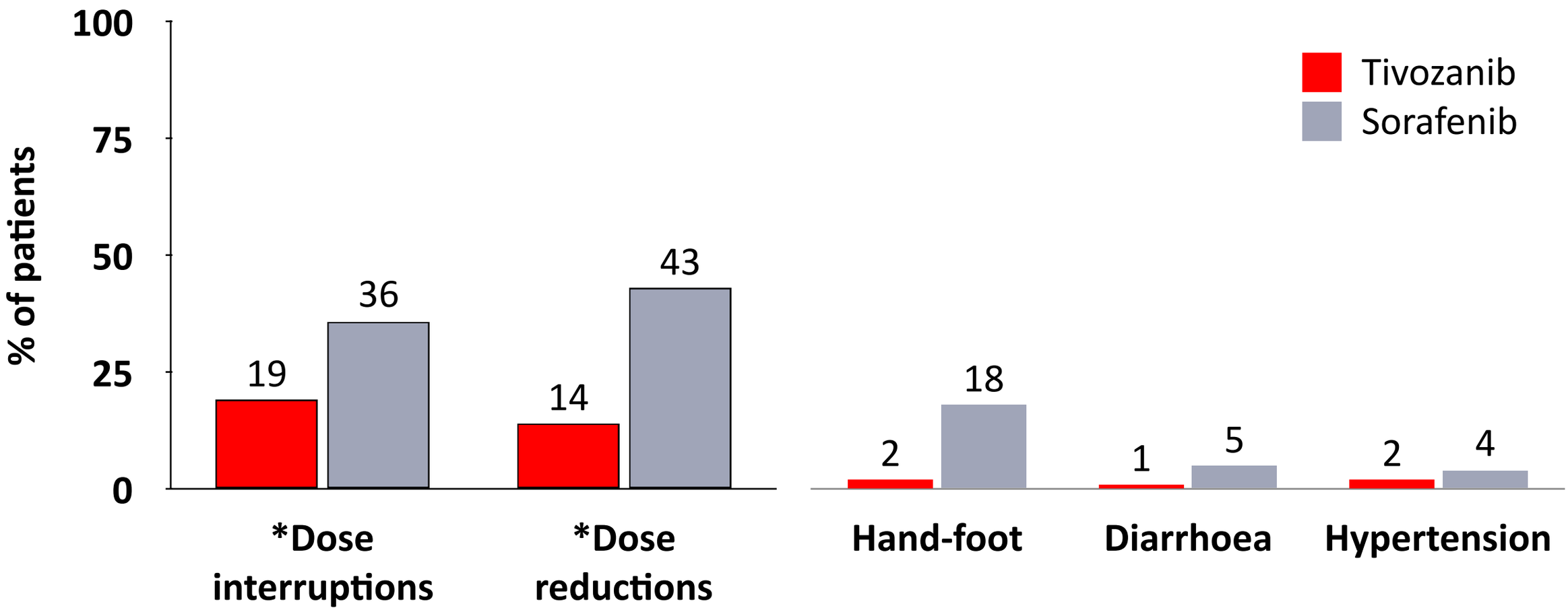


Median OS was not reached

Two-year survival was 73% in the tivozanib arm and 60% in the sorafenib arm, with a trend towards improved OS in the tivozanib arm (HR: 0.503, p=0.195)

1. Motzer R, Eisen T, Hutson TE et al. Poster presented at American Society of Clinical Oncology Genitourinary Symposium 2013; Orlando, Florida

TIVO-1 adverse events

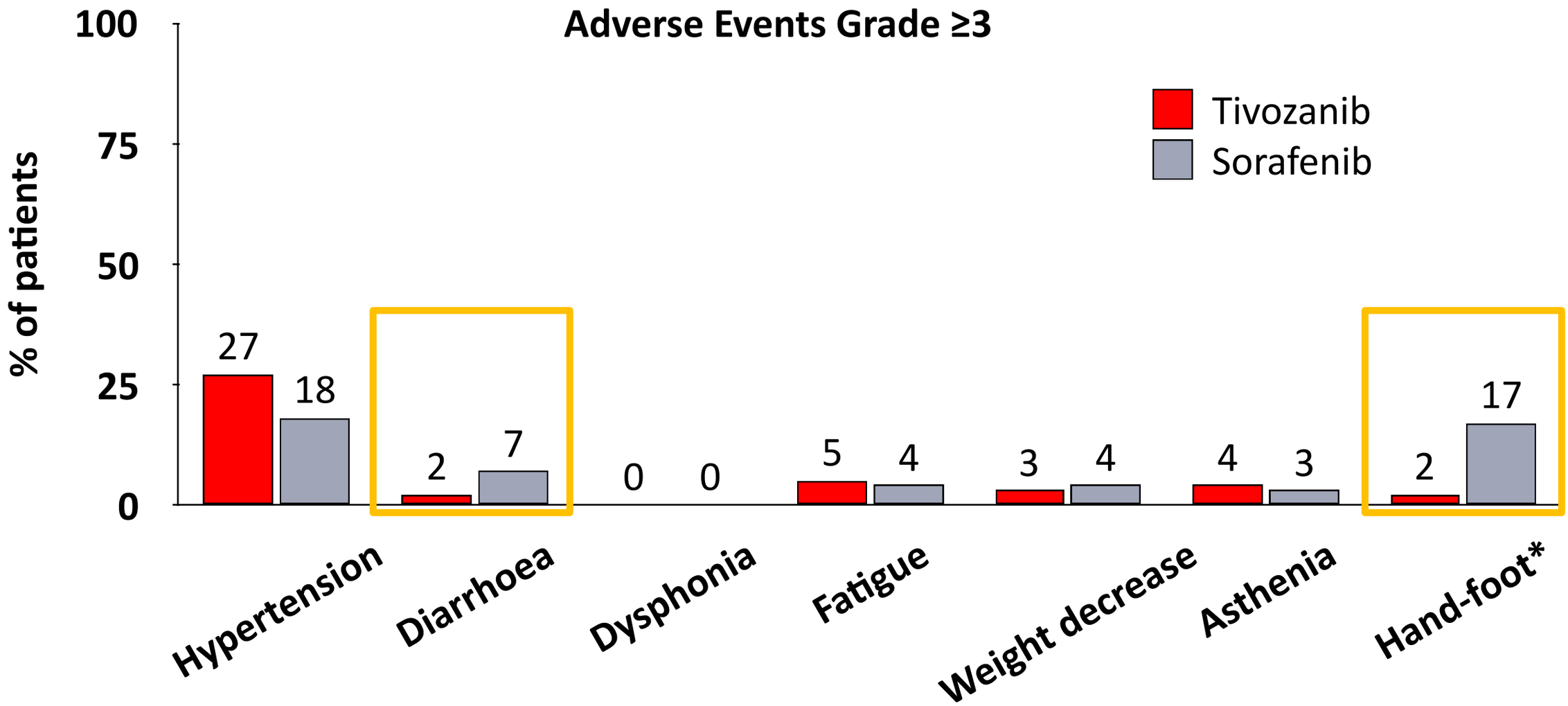


*** Due to treatment-related AEs**

Reasons for dose reductions (All causalities)

Motzer RJ, Nosov D, Eisen T et al. J Clin Oncol 2013;31(30):3791-9

TIVO-1 adverse events

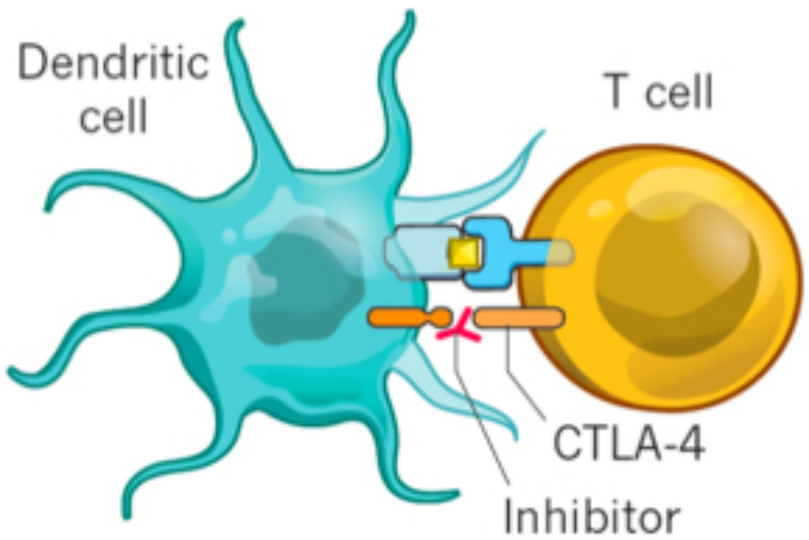


* Also known as PPE (palmar-plantar erythrodysaesthesia syndrome). Hand-foot syndrome is a condition marked by pain, swelling, numbness, tingling, or redness of the hands or feet (National Cancer Institute, 2010).

1. Motzer RJ, Nosov D, Eisen T et al. J Clin Oncol 2013;31(30):3791-9

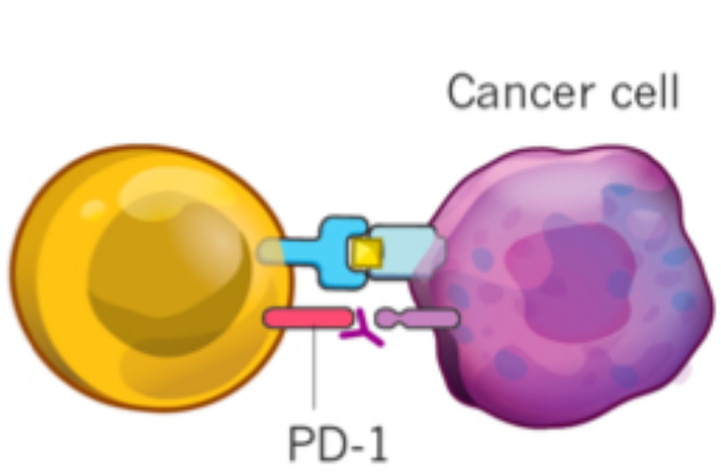
Rationale für I/O Kombination

Ipilimumab



The CTLA-4 checkpoint protein prevents dendritic cells from priming T cells to recognize tumours. Inhibitor drugs block the checkpoint.

Nivolumab



The PD-1 checkpoint protein prevents T cells from attacking cancer cells. The inhibitor drug allows T cells to act.

Beide Mechanismen aktivieren antitumorale T-Zell Aktivität.[1,2]

Möglicherweise unbeeinflusst von Tumorheterogenität[2]

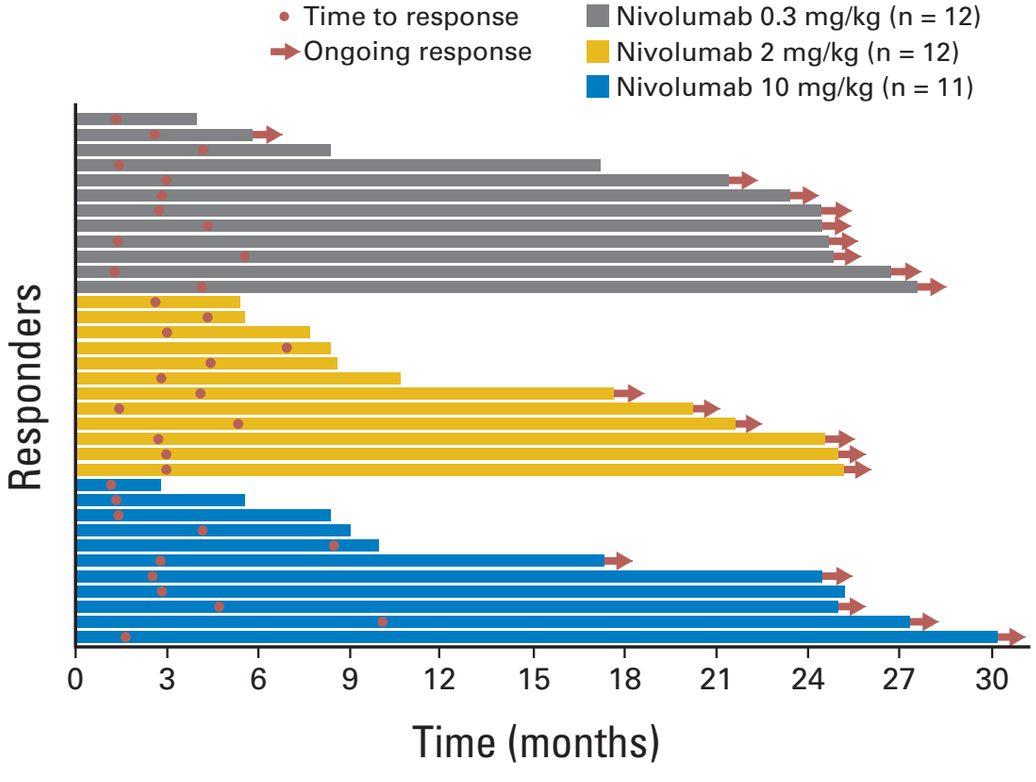
1. Fellner C. *P&T* 2012;37(9):503–30. 2. Raedler LA, *et al. Am Health Drug Benefits* 2015;8:180–3.

Response

Nivolumab for Metastatic Renal Cell Carcinoma: Results of a Randomized Phase II Trial

Robert J. Motzer, Brian I. Rini, David F. McDermott, Bruce G. Redman, Timothy M. Kuzel, Michael R. Harrison, Ulka N. Vaishampayan, Harry A. Drabkin, Saby George, Theodore F. Logan, Kim A. Margolin, Elizabeth R. Plimack, Alexandre M. Lambert, Ian M. Waxman, and Hans J. Hammers

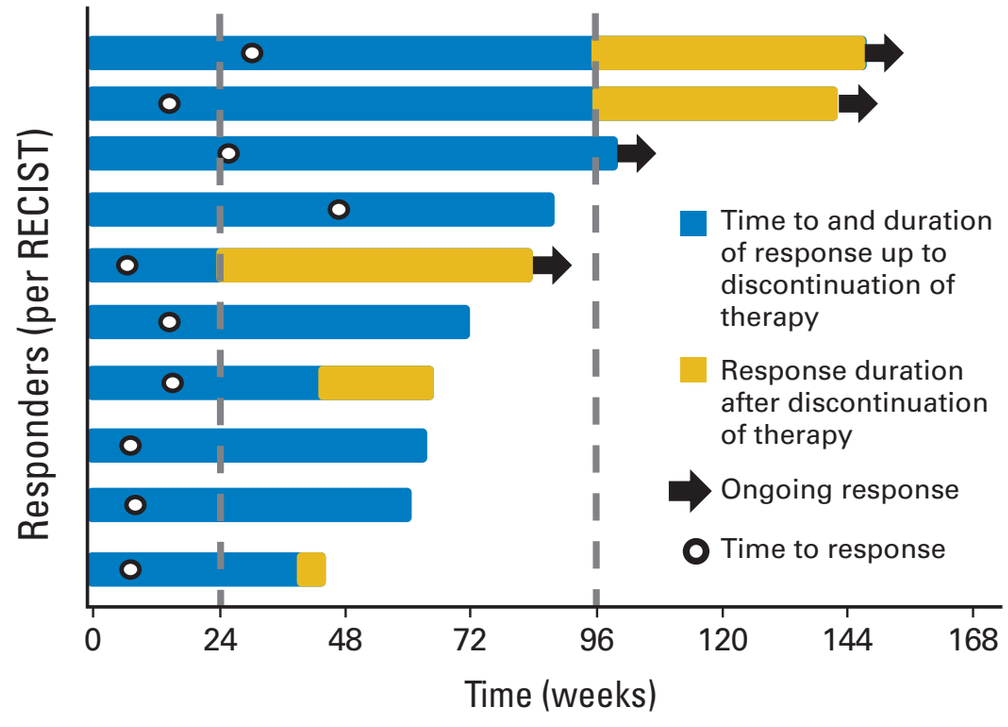
J Clin Oncol 33:1430-1437. © 2014



Survival, Durable Response, and Long-Term Safety in Patients With Previously Treated Advanced Renal Cell Carcinoma Receiving Nivolumab

David F. McDermott, Charles G. Drake, Mario Sznol, Toni K. Choueiri, John D. Powderly, David C. Smith, Julie R. Brahmer, Richard D. Carvajal, Hans J. Hammers, Igor Puzanov, F. Stephen Hodi, Harriet M. Kluger, Suzanne L. Topalian, Drew M. Pardoll, Jon M. Wigginton, Georgia D. Kollia, Ashok Gupta, Dan McDonald, Vindira Sankar, Jeffrey A. Sosman, and Michael B. Atkins

J Clin Oncol 33:2013-2020. © 2015



Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma

R.J. Motzer, N.M. Tannir, D.F. McDermott, O. Arén Frontera, B. Melichar, T.K. Choueiri, E.R. Plimack, P. Barthélémy, C. Porta, S. George, T. Powles, F. Donskov, V. Neiman, C.K. Kollmannsberger, P. Salman, H. Gurney, R. Hawkins, A. Ravaud, M.-O. Grimm, S. Bracarda, C.H. Barrios, Y. Tomita, D. Castellano, B.I. Rini, A.C. Chen, S. Mekan, M.B. McHenry, M. Wind-Rotolo, J. Doan, P. Sharma, H.J. Hammers, and B. Escudier, for the CheckMate 214 Investigators*

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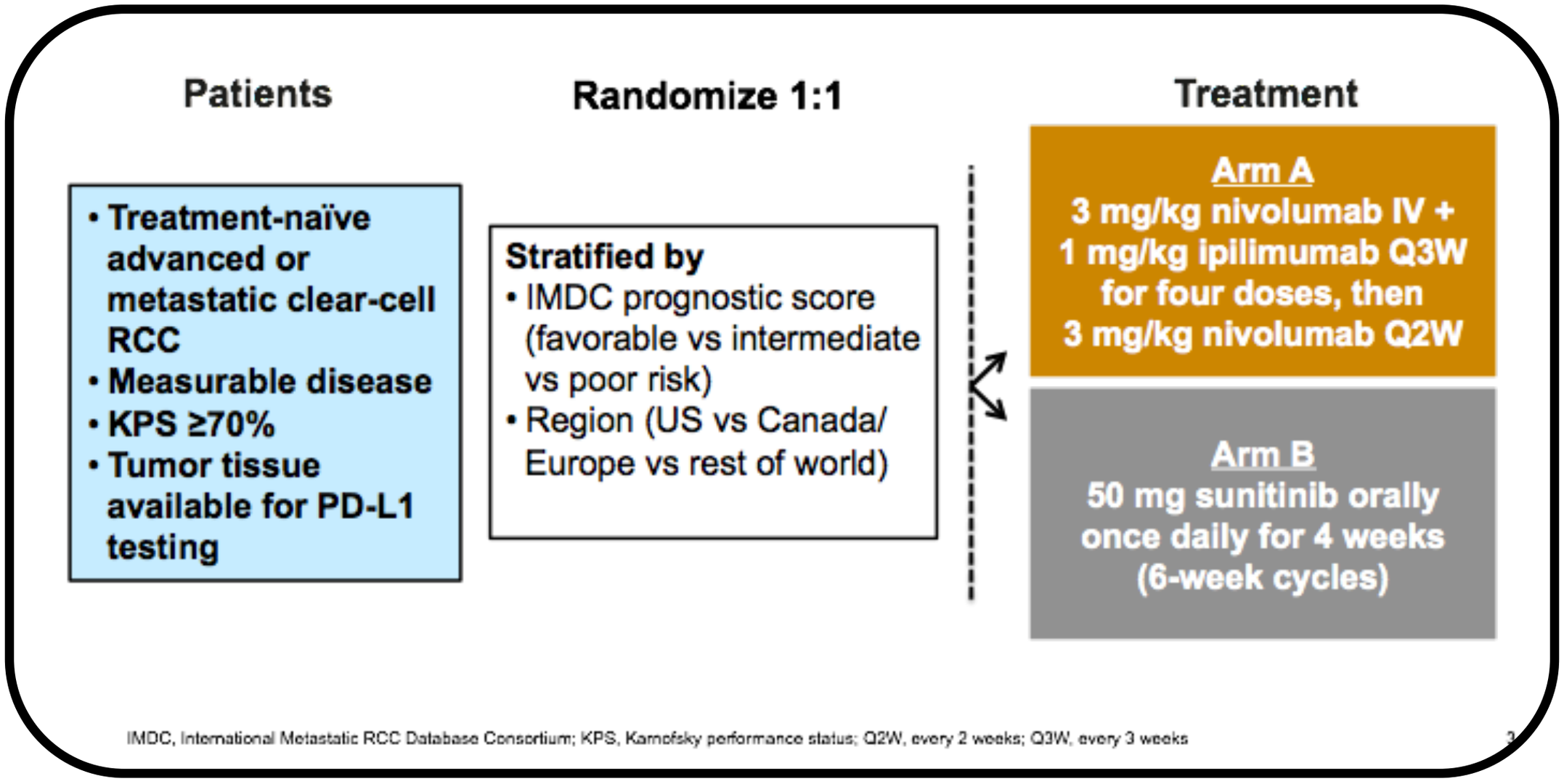

IMDC, International Metastatic RCC Database Consortium; KPS, Karnofsky performance status; Q2W, every 2 weeks; Q3W, every 3 weeks

Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma

R.J. Motzer, N.M. Tannir, D.F. McDermott, O. Arén Frontera, B. Melichar, T.K. Choueiri, E.R. Plimack, P. Barthélémy, C. Porta, S. George, T. Powles, F. Donskov, V. Neiman, C.K. Kollmannsberger, P. Salman, H. Gurney, R. Hawkins, A. Ravaud, M.-O. Grimm, S. Bracarda, C.H. Barrios, Y. Tomita, D. Castellano, B.I. Rini, A.C. Chen, S. Mekan, M.B. McHenry, M. Wind-Rotolo, J. Doan, P. Sharma, H.J. Hammers, and B. Escudier, for the CheckMate 214 Investigators*

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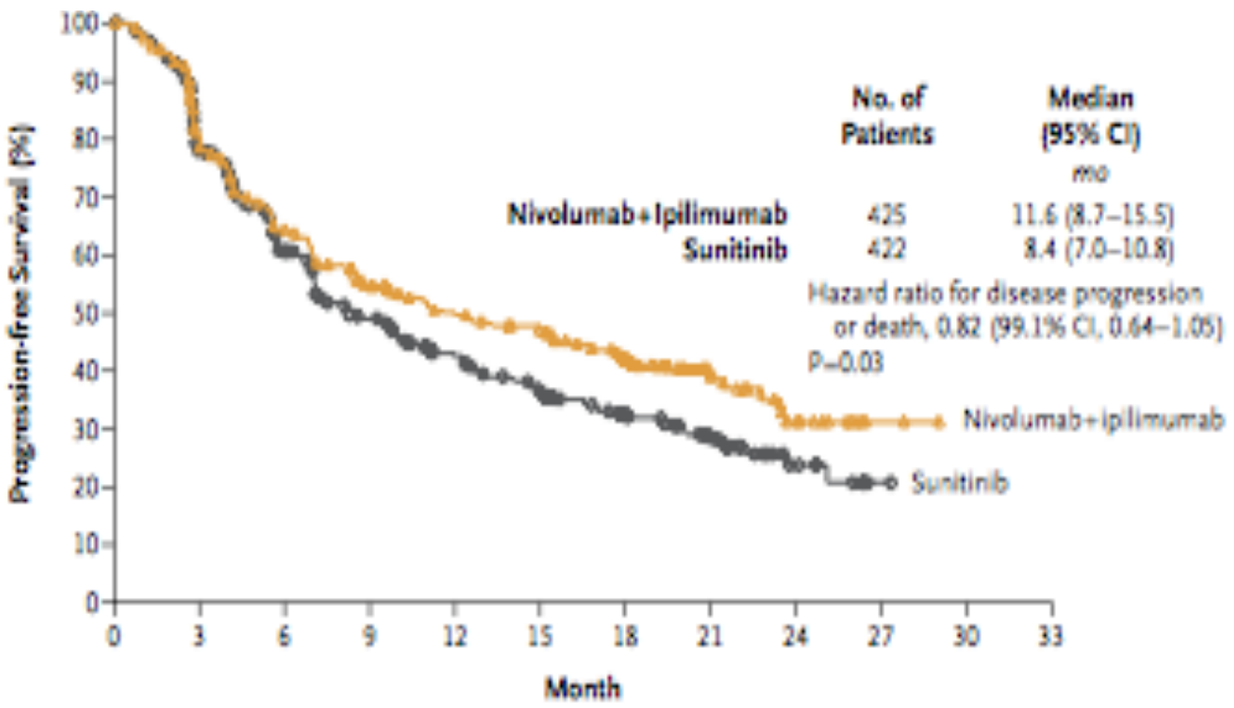
PFS



OS

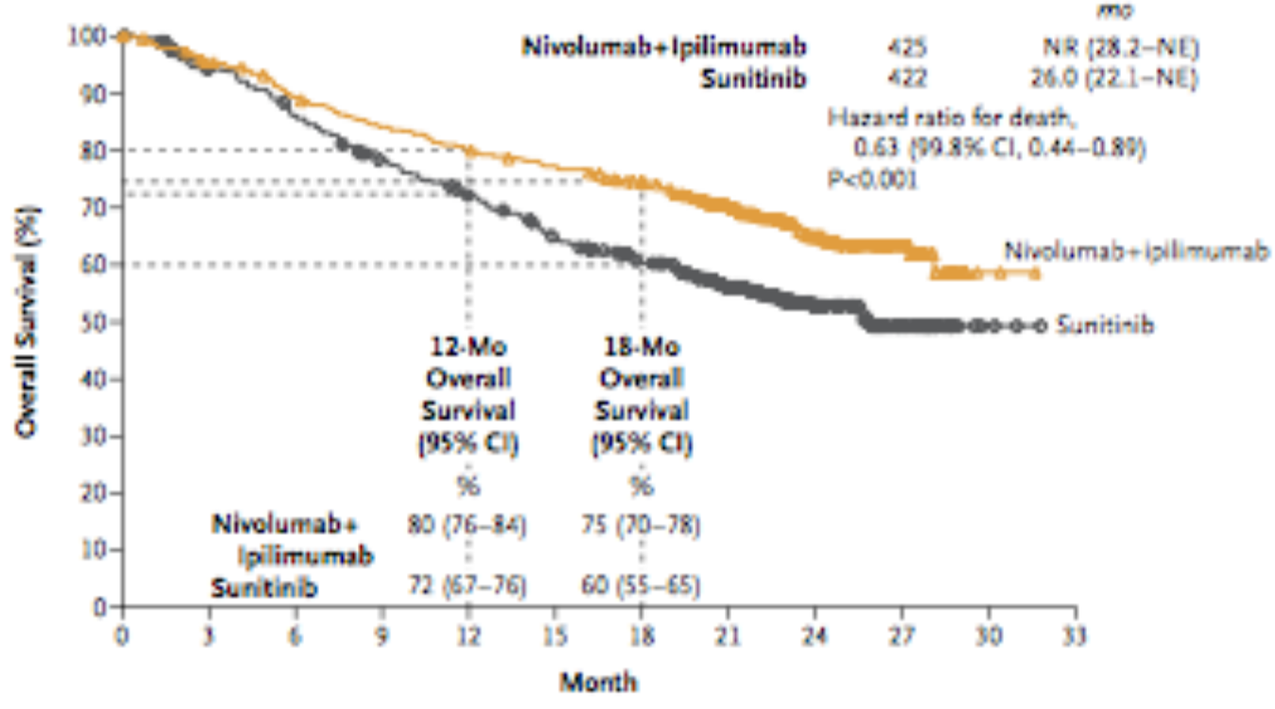


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Table 2. Antitumor Activity in IMDC Intermediate- and Poor-Risk Patients.*

Variable	Nivolumab plus Ipilimumab (N = 425)	Sunitinib (N = 422)
Confirmed objective response rate — % (95% CI)†	42 (37–47)‡	27 (22–31)‡
Confirmed best overall response — no. (%)†		
Complete response	40 (9)‡§	5 (1)‡§
Partial response	137 (32)	107 (25)
Stable disease	133 (31)	188 (45)
Progressive disease	83 (20)	72 (17)
Unable to determine or not reported	32 (8)	50 (12)
Median time to response (range) — mo	2.8 (0.9–11.3)	3.0 (0.6–15.0)
Median duration of response (95% CI) — mo	NR (21.8–NE)	18.2 (14.8–NE)
Patients with ongoing response — no./total no. (%)	128/177 (72)	71/112 (63)

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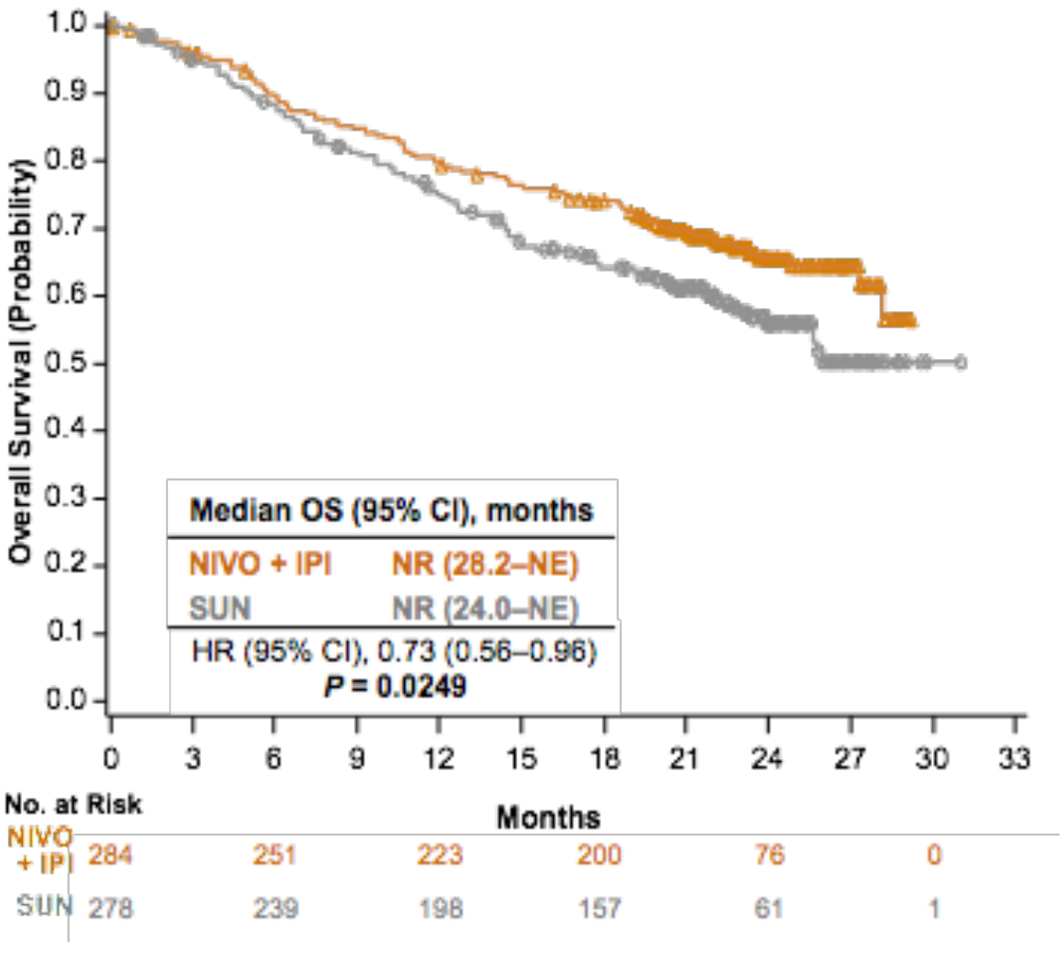
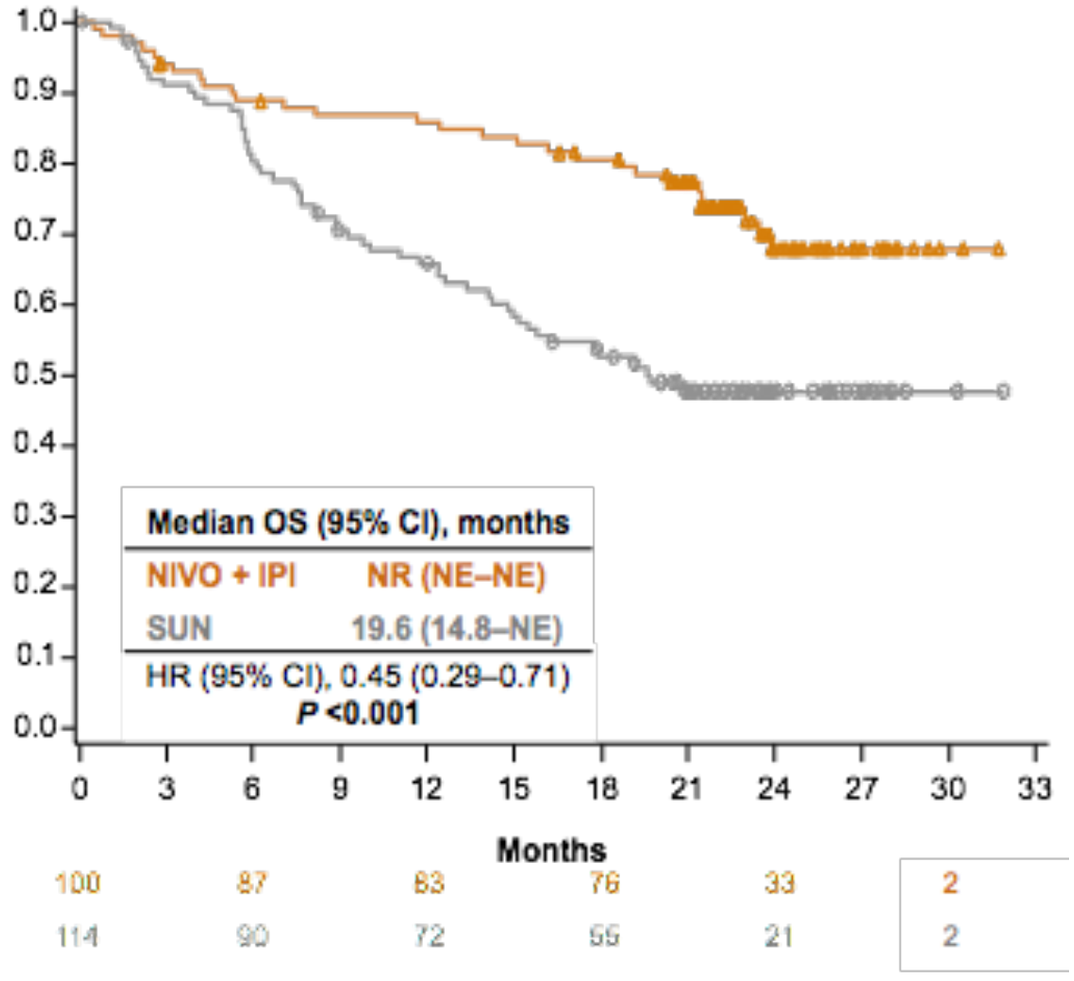
OS by tumor PD-L1 expression: IMDC intermediate/poor risk

PD-L1 <1% (n = 562)



PD-L1 ≥1% (n = 214)



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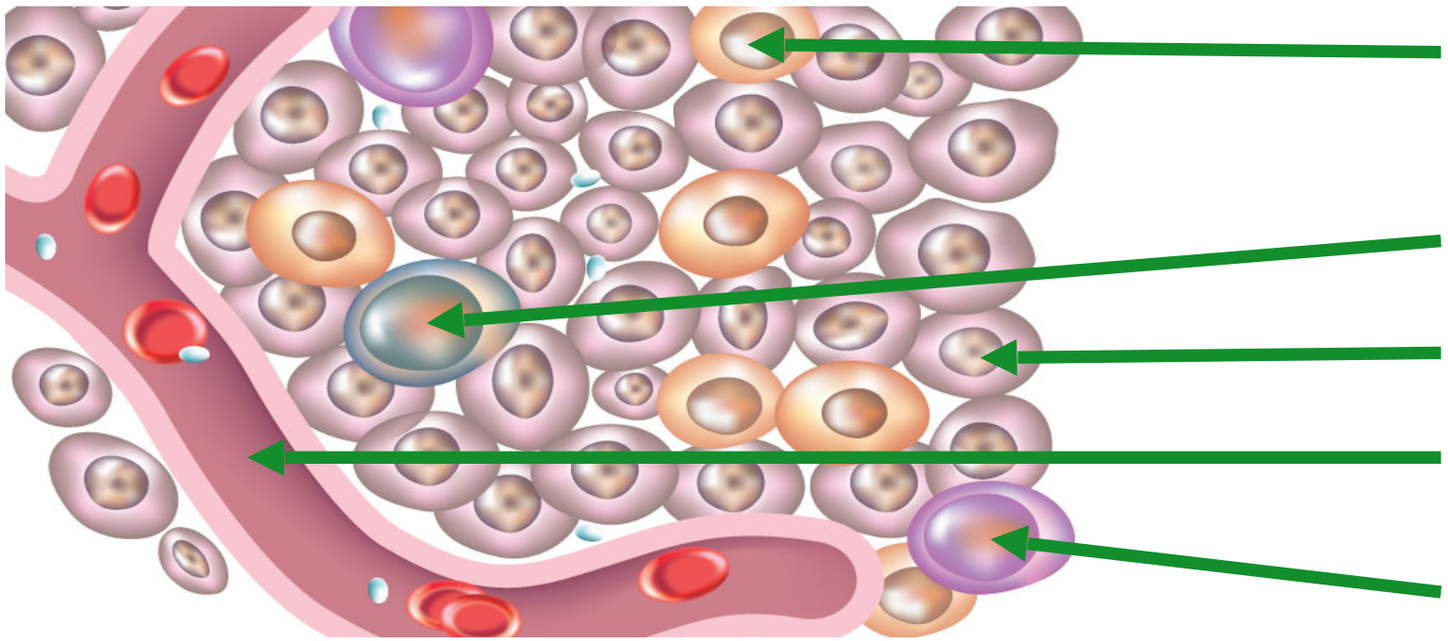
Responserate und PFS in der Favorable Risk Group

	N = 249[a]	
Outcome	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	

Escudier, ESMO 2017

Rationale für I/O-TKI Kombination



Myeloid-derived suppressor cell (MDSC)

CD8+ T Zelle

Tumorzelle

Abnormale Angiogenese durch VEGF

Regulatorische T Zelle (Treg)

verminderte Akkumulation von MDSC

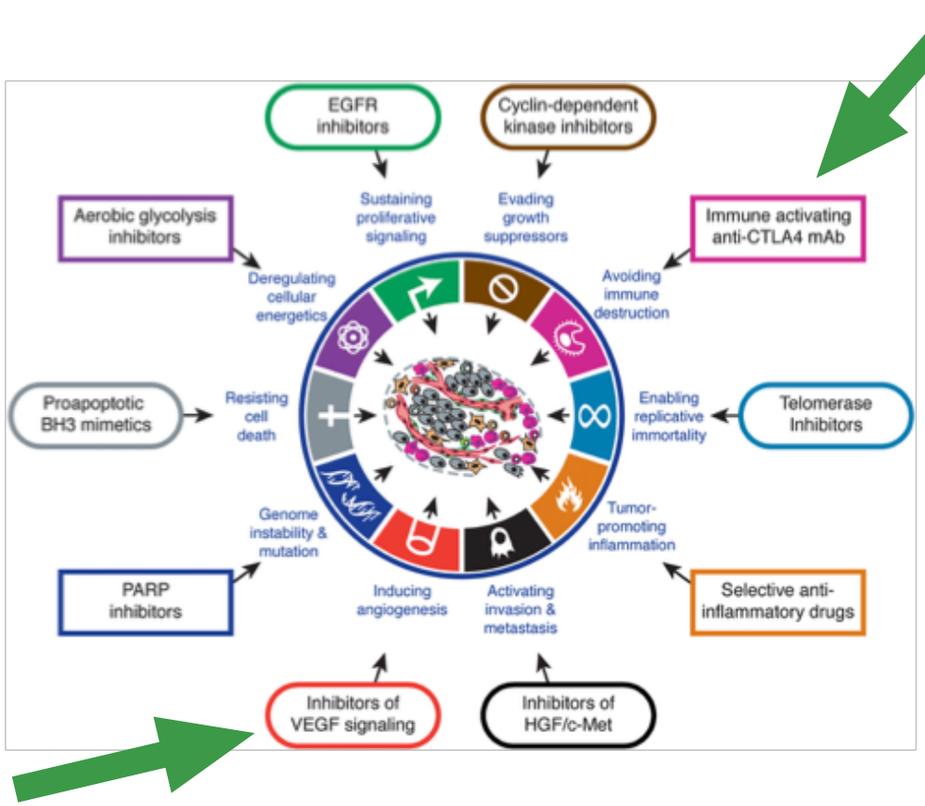
Reduktion inflammatorischer Signale

gesteigerte Immunaktivität / Antigenpräsentation (CD8+ / CD45+)

verminderte Angiogenese und Metastasierung

Figure adapted from: Kerkar S, Restifo N. *Cancer Res*. 2012;72(13):3125-3130.
References: 1. Facciabene A, et al. *Cancer Res*. 2012;72(9):2162-2171.

Rationale für I/O-TKI Kombination



CPI + TKI:

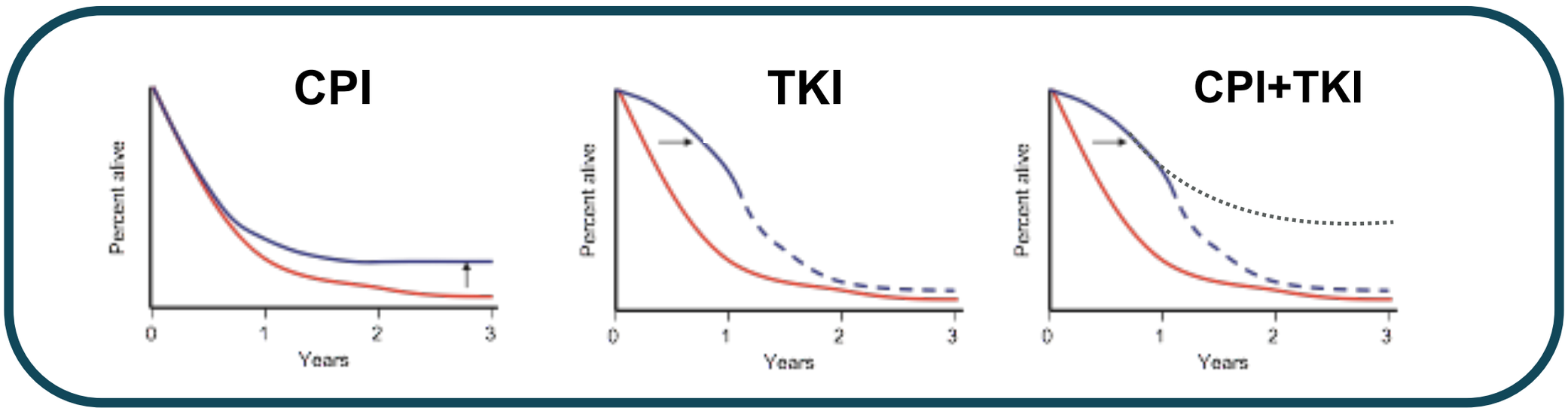
additiv oder synergistisch?

ORR / PFS: vielversprechend

dauerhaft?

substanzieller OS Effekt?

Rezidivfreiheit? CR?

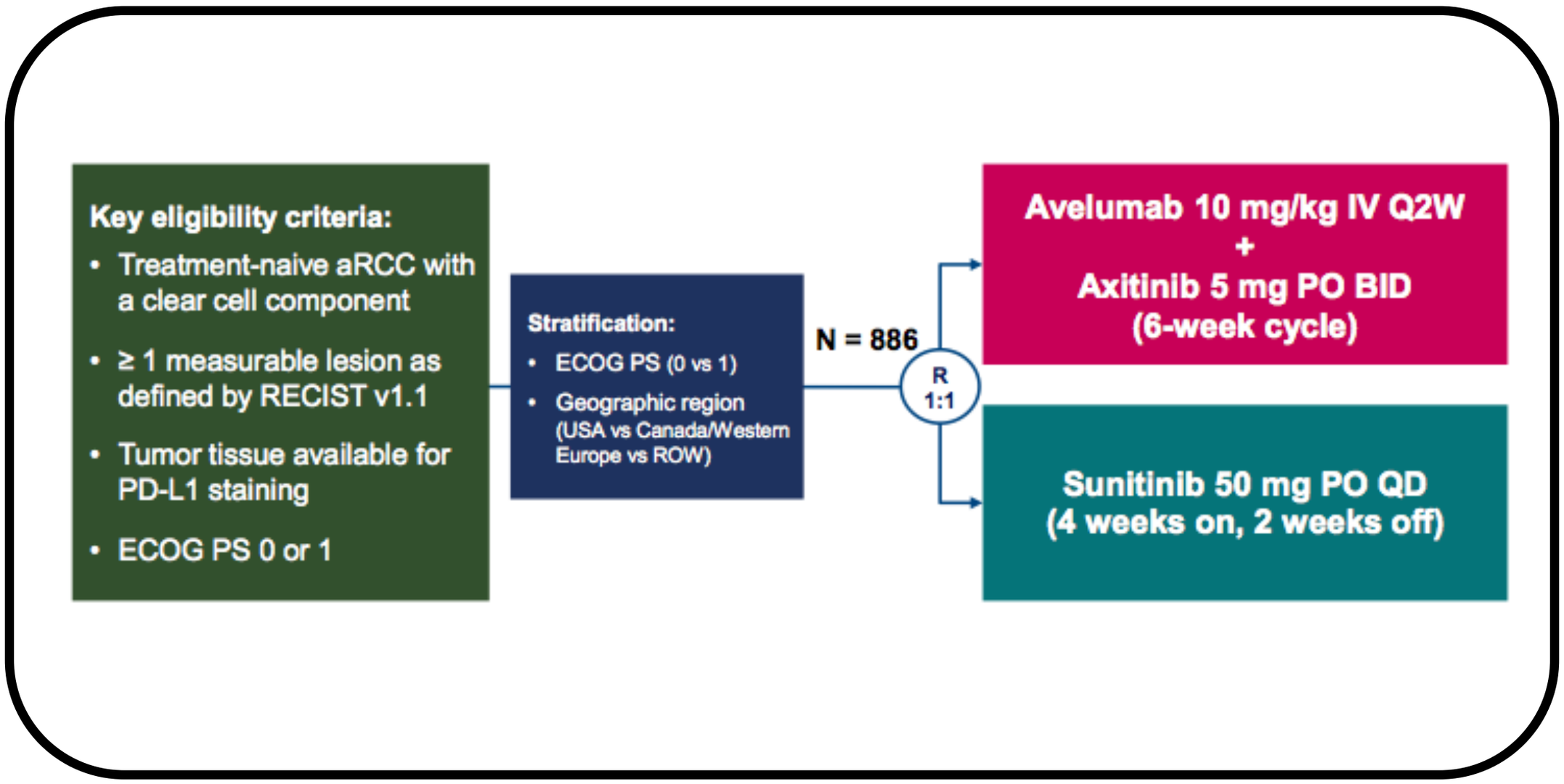


Ribas et al, Clin Cancer Res 2012; Hanahan et al, Cell 2011

Avelumab + Axitinib vs. Sunitinib
First line in advanced RCC

JAVELIN Renal 101

Avelumab: anti PD-L1
Avelumab + Axitinib: Phase 1b: ORR 58%



presented by R. Motzer @ ESMO 2018;

Avelumab + Axitinib vs. Sunitinib
First line in advanced RCC

JAVELIN Renal 101

per investigator	**PD-L1 + Group** (n=560)		**Overall Population** (N=886)	
	Avelumab + Axitinib (n=270)	**Sunitinib** (n=290)	**Avelumab + Axitinib** (n=442)	**Sunitinib** (n=444)
median PFS	**13.3 mon**	8.2 mon	**12.5 mon**	8.4 mon
HR	**0.51** (95%CI: 0.39,0.65)	p<.0001	**0.64** (95%CI: 0.52,0.77)	p<.0001

presented by R. Motzer @ ESMO 2018;

Avelumab + Axitinib vs. Sunitinib
First line in advanced RCC

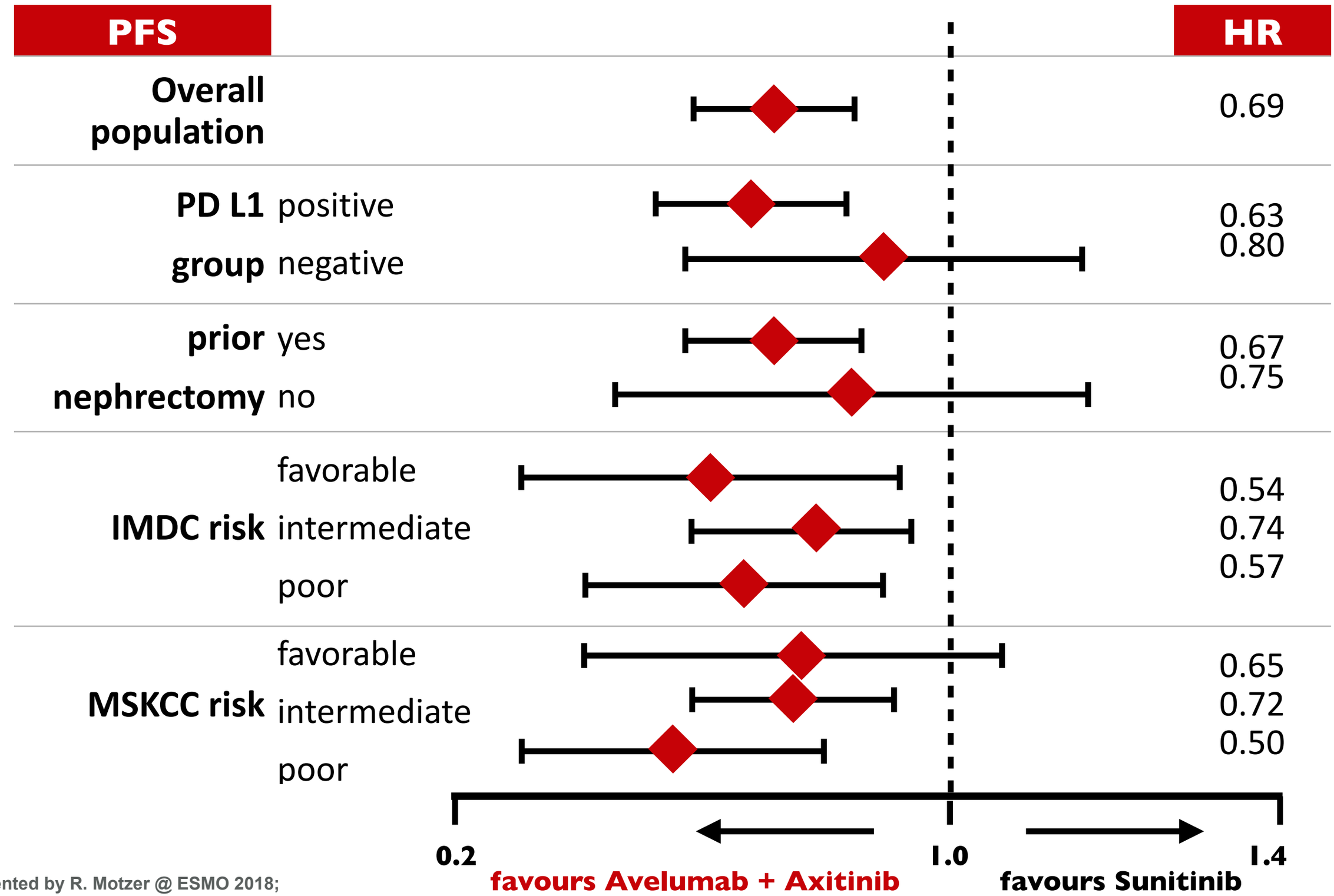
JAVELIN Renal 101

per ICR	**PD-L1 + Group** (n=560)		**Overall Population** (N=886)	
	Avelumab + Axitinib (n=270)	**Sunitinib** (n=290)	**Avelumab + Axitinib** (n=442)	**Sunitinib** (n=444)
ORR %	**55**	26	**51**	26
Best response %				
CR	4	2	3	2
PR	51	23	48	24
SD	27	43	30	46
PD	11	22	12	19
NE	4	7	6	8
ongoing response	73	65	70	71
per investigator				
ORR %	**62**	30	**56**	30
Best response %				
CR	4	3	3	2
PR	58	27	53	28

presented by R. Motzer @ ESMO 2018;

Avelumab + Axitinib vs. Sunitinib
First line in advanced RCC

JAVELIN Renal 101



presented by R. Motzer @ ESMO 2018;

Avelumab + Axitinib vs. Sunitinib
First line in advanced RCC

JAVELIN Renal 101

ADVERSE EVENTS	overall			
	Avelumab + Axitinib (n=434)		Sunitinib (n=439)	
	All Grades	Grade 3 (4)	All Grades	Grade 3 (4)
All TRAE%	**95**	**51(4)**	**96**	**48(7)**
Diarrhea	54	5(0)	45	3(0)
Hypertension	48	24(0)	32	15(0)
Fatigue	36	3(0)	36	4(0)
Discountinuation %	4		8	
Death %	1		<1	

presented by R. Motzer @ ESMO 2018;

Avelumab + Axitinib vs. Sunitinib
First line in advanced RCC

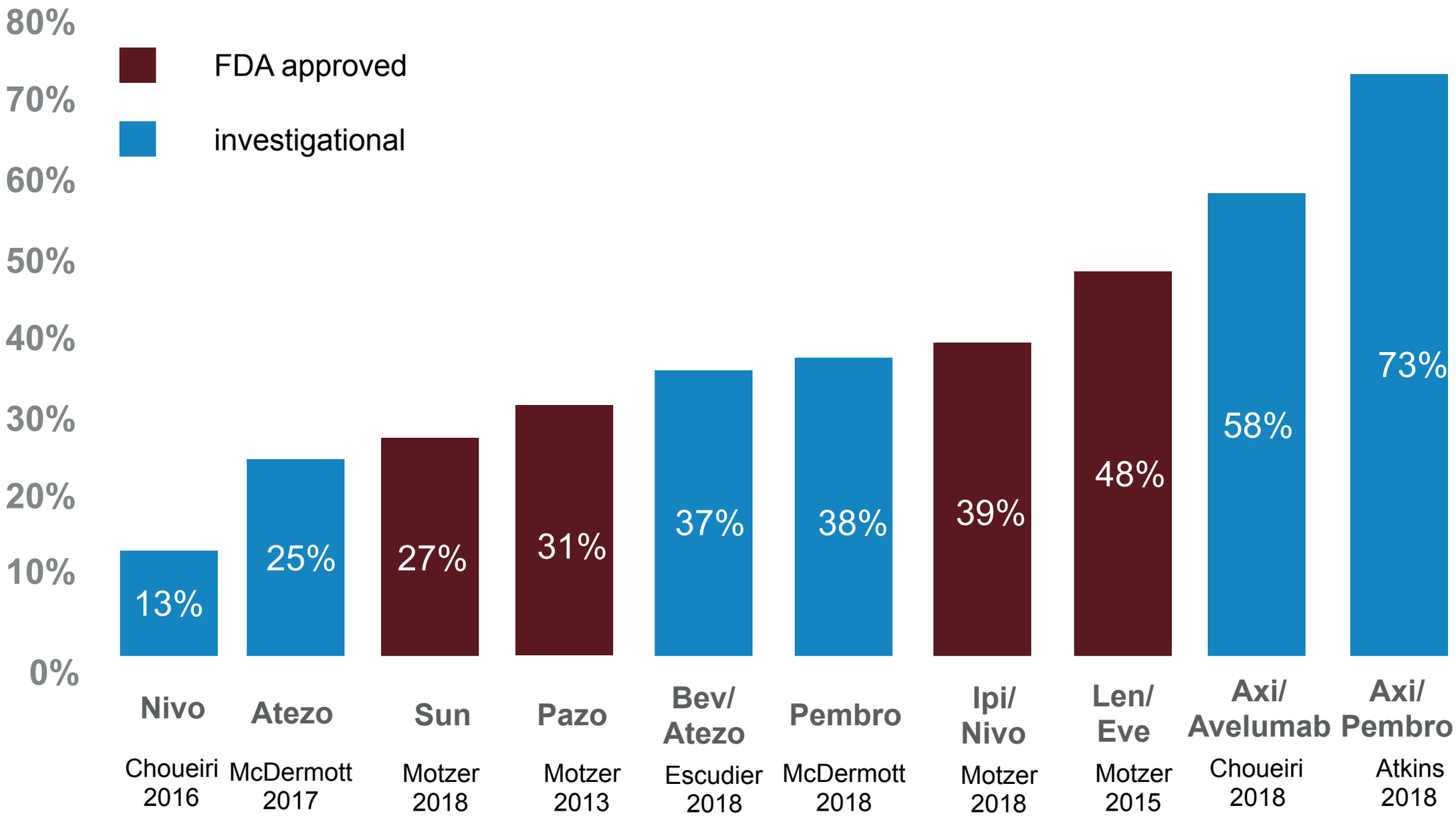
JAVELIN Renal 101

ADVERSE EVENTS		immune related
	All Grades	Grade 3 (4)
All immune TRAE%	36	8(1)
Hypothyroidism	21	<1(0)
Liver function	5	4(<1)
Adrenal insufficiency	2	1(0)
Diarrhea	2	1(0)
Acute kidney injury	1	1(0)
Colitis	1	1(0)
Hepatotoxicity	1	1(0)

presented by R. Motzer @ ESMO 2018;

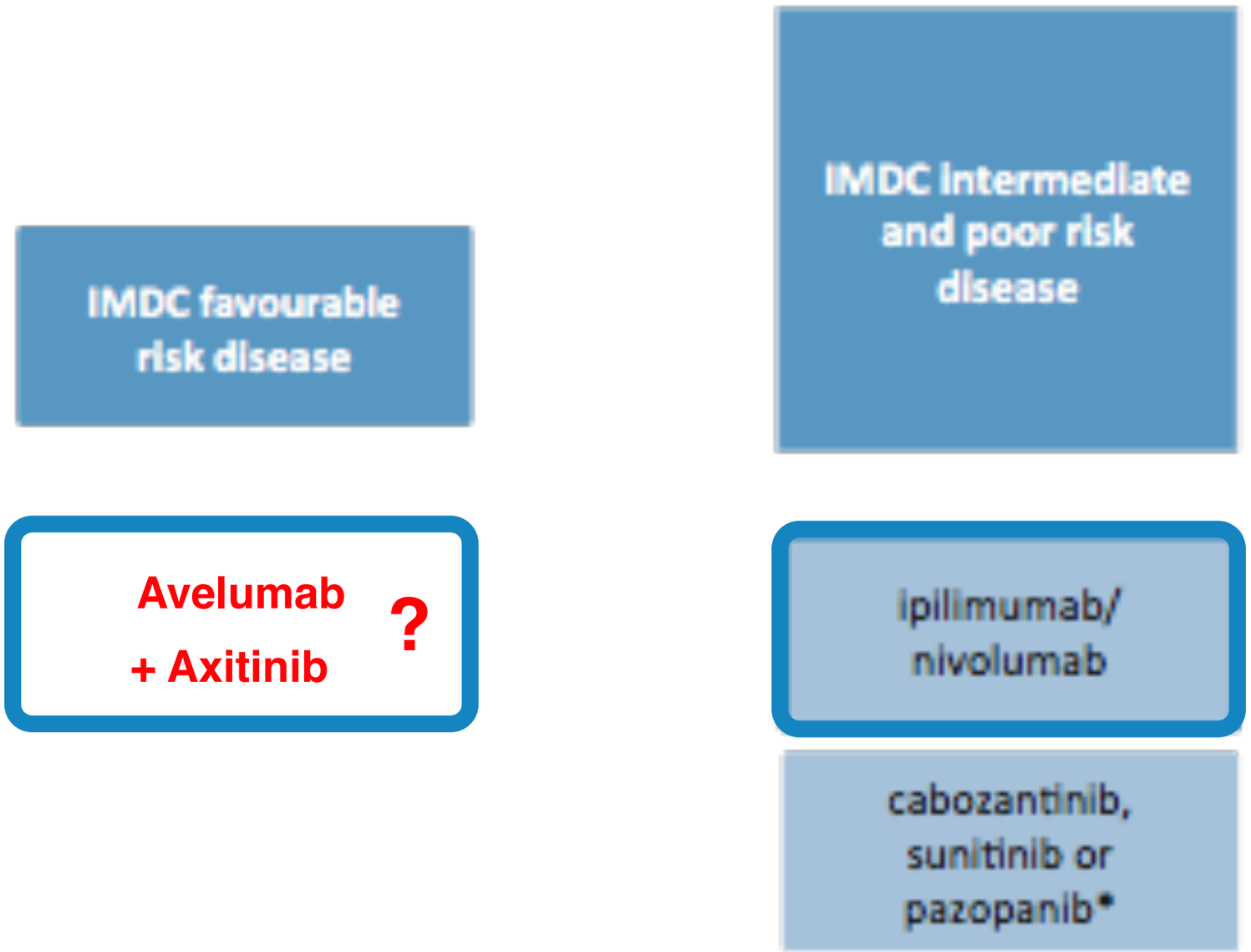
RESPONSE RATEN FIRST LINE THERAPIEOPTIONEN

metastasiertes ccRCC (alle Risikogruppen)



EAU Recommendation

Updated European Association of Urology Guidelines: Recommendations for the Treatment of First-line Metastatic Clear Cell Renal Cancer



Was wir gelernt haben…

Tivozanib: wirksamer VEGF TKI mit günstigem Nebenwirkungsprofil

IPI + NIVO: OS Benefit in der First Line

IPI + NIVO: **Standard of care** bei **intermediate/high risk** mRCC

VEGF TKI: immunmodulatorische Effekte

JAVELIN Renal 101: Avelumab + Axitinib first line
PFS/ORR Benefit (PDL1 / Risiko unabhängig)