Medizinische Universität Graz

COMPREHENSIVE CANCER CENTER Krebszentrum GRAZ

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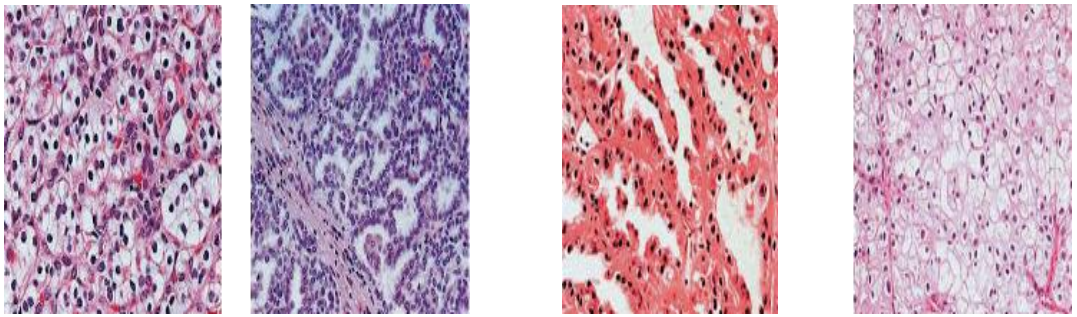
Immunonkologie: Aktuelle Datenlage in der Erstlinientherapie des metastasierten Nierenzellkarzinoms

JAN 2019

G.C. Hutterer
Universitätsklinik für Urologie

Histologische Klassifikation humaner renaler epithelialer Neoplasien

RCC



Typ	klarzellig	pap. Typ I	pap. Typ II	chromophob
Inzidenz (%)	*75%*	*5%*	*10%*	*5%*
assoziierte Mutationen	***VHL***	***c-Met***	***FH***	***BHD***

VHL = von Hippel-Lindau; FH = Fumarathydratase; BHD = Birt-Hogg-Dubé

Modifiziert n. Linehan WM *et al.* J Urol 2003

Rationale für Immuntherapie (RCC):

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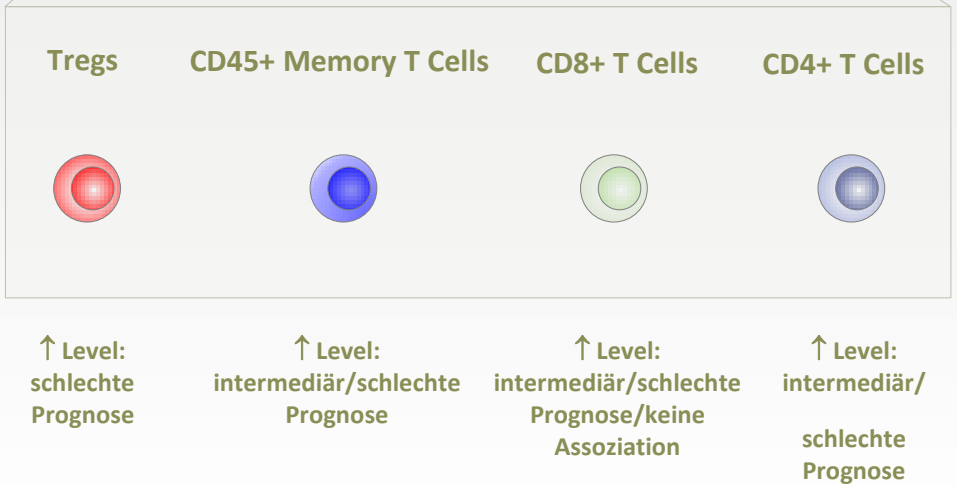
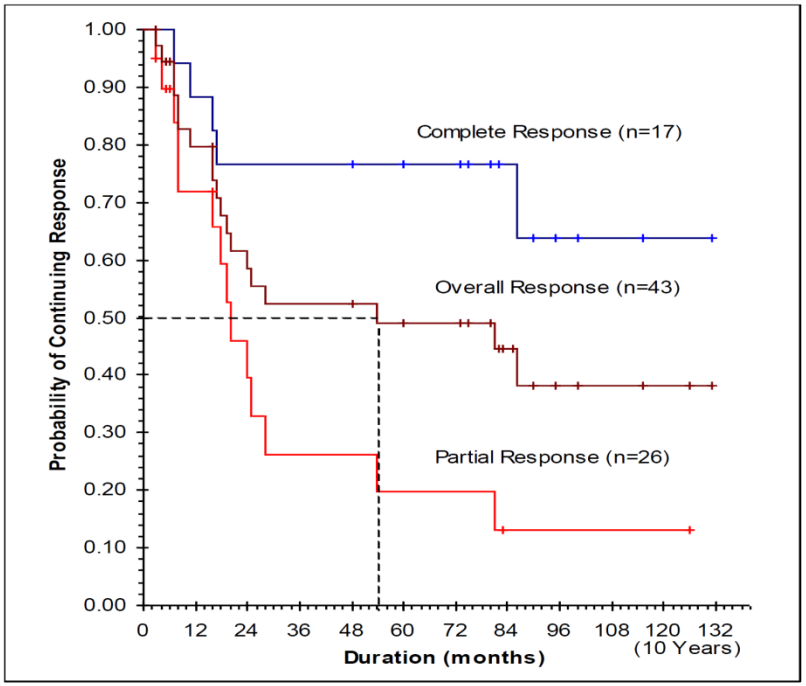
- RCC-Spontanremissionen im fortgeschrittenen Stadium (Immunsystem-mediiert)[1]
- RCC-Immunzellinfiltrate und Immun-Escape-Mechanismen[2,3]
- historisch → mRCC: Immuntherapie mit IL-2 od. IFN-α
- 'Immuno-Oncology is an evolving treatment modality encompassing agents designed to directly harness the patient's own immune system to fight cancer'[7,8]

→ dokumentierte Alterationen verschiedener Immunzelltypen (RCC)[3-6]:



[1]Escudier B *et al.* Ann Oncol 2012
[2]Noessner E *et al.* Oncoimmunol 2012
[3]Bockorny B *et al.* Expert Opin Biol Ther 2013
[4]Hotta K *et al.* Br J Cancer 2011
[5]Nakano O *et al.* Cancer Res 2001
[6]Igarashi T *et al.* Urol Int 2002
[7]Ascierto PA *et al.* J Trans Med 2014
[8]Eggermont A *et al.* Oncoimmunol 2014

High-Dose IV Bolus IL-2 Therapy: (n=255; 7 clinical trials)



FDA Approval 1992

15% RR with durable responses in a small % of patients

MDR - 54 months

But:
Significant toxicity and cost!

Limited to selected patients treated at a few centers

6 PR with response durations of 43+ to 85+ mos. Median survival 15.8 mos

Fyfe GA et al, J Clin Oncol 1995 Mar;13(3):688-96
Fyfe GA et al, J Clin Oncol 1996 Aug;14(8):2410-1

Mutational heterogeneity

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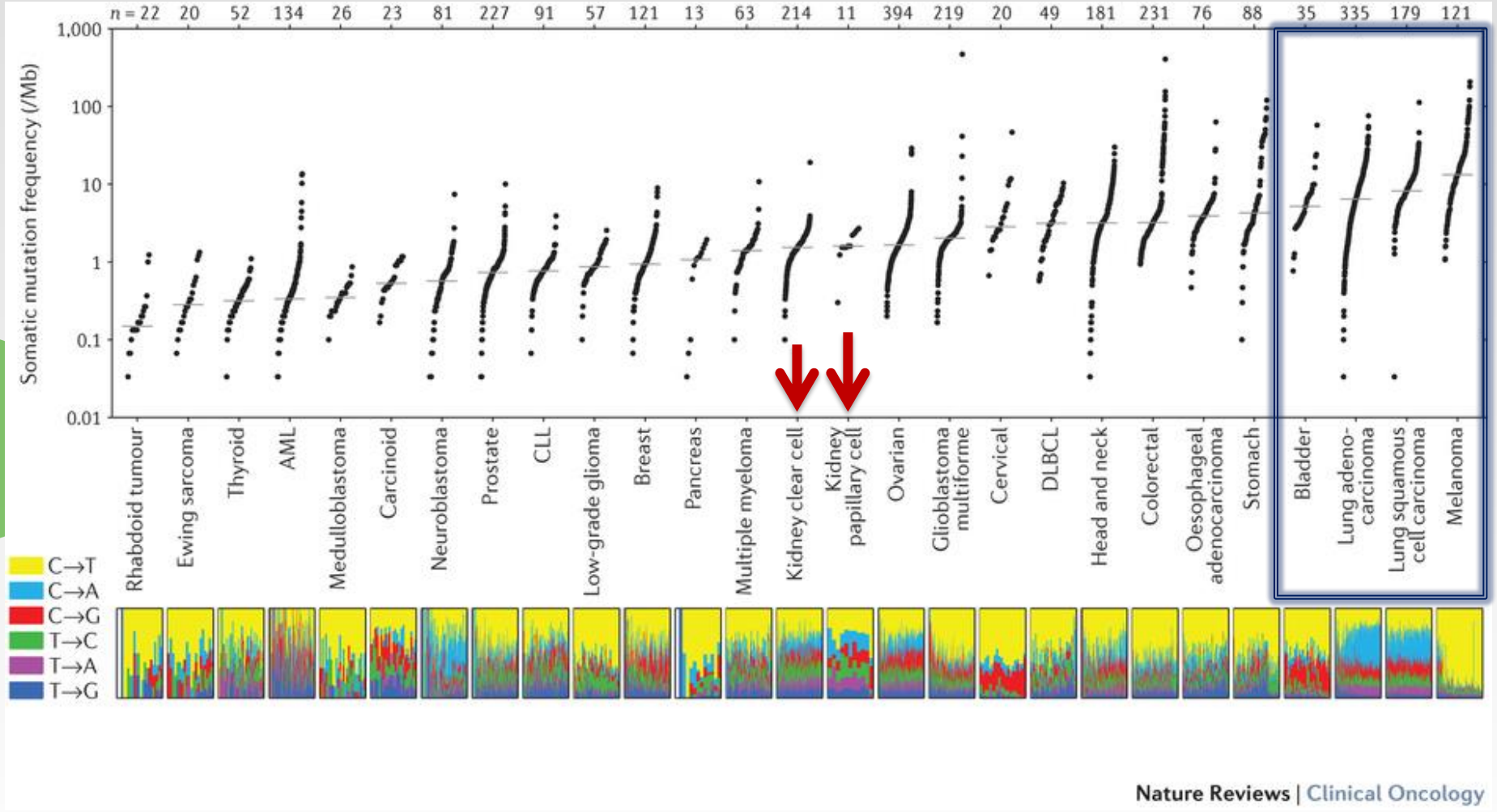

Lordick F *et al.* Nat Rev Clin Oncol 2016

Treatment Landscape

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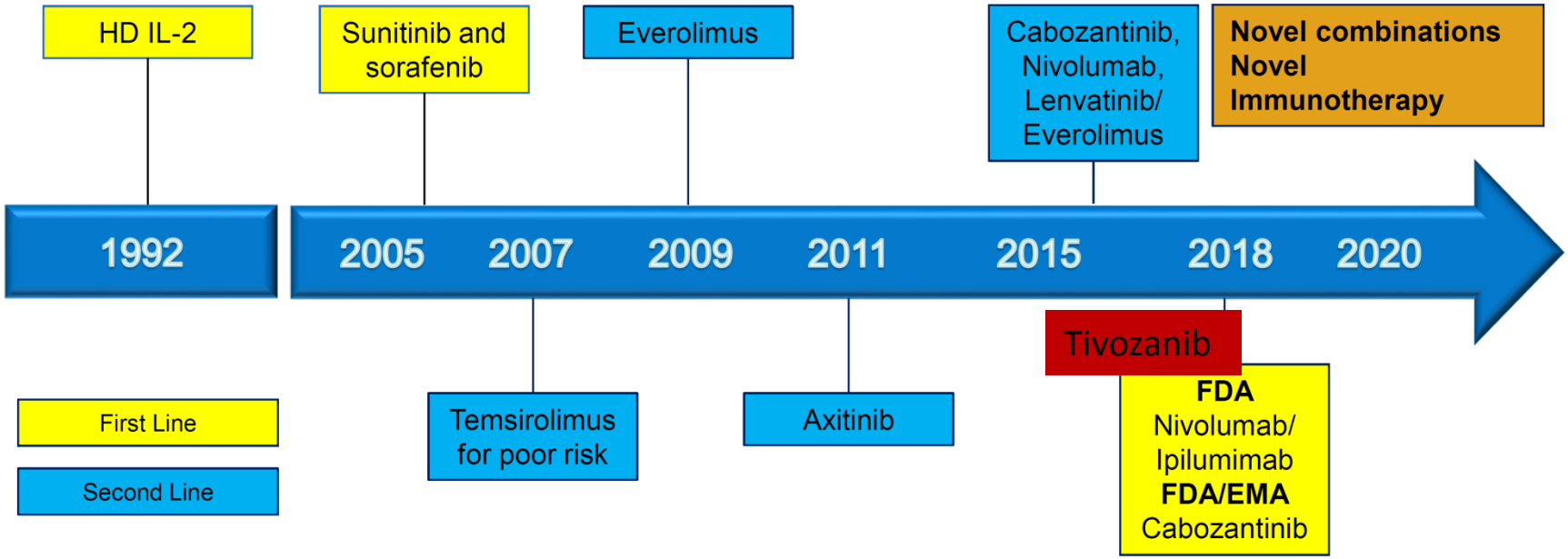
From cytokines to targeted therapies to immunotherapy: 10 drugs approved in the last 10 years in advanced RCC



Modified from S. Pal, ASCO GU 2018

Treatment Landscape

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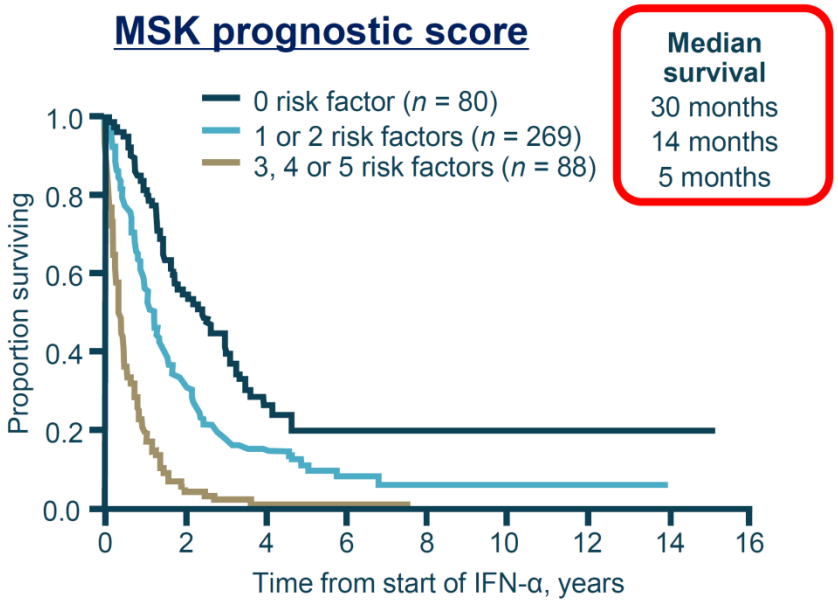
Targeted therapies have improved OS in mRCC

➔ **Before VEGF-targeted therapies**

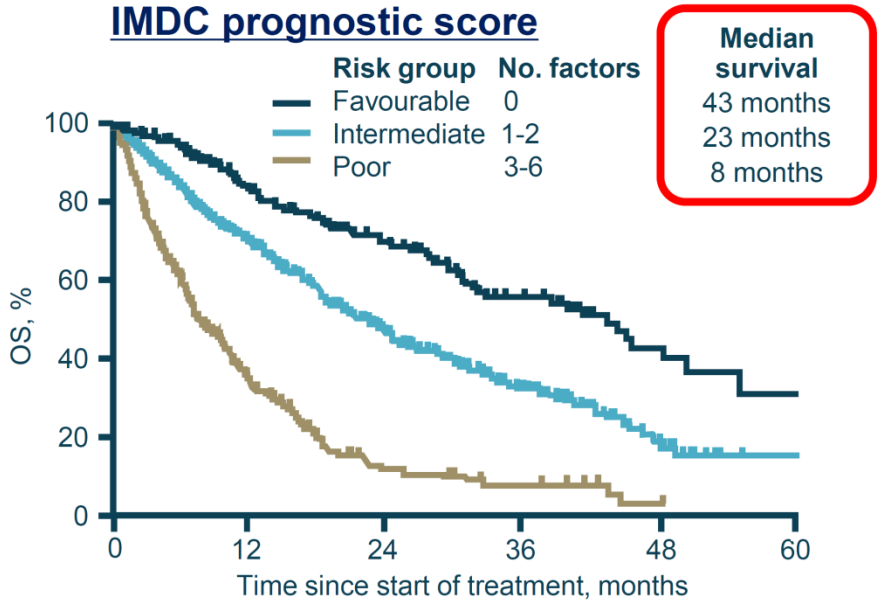
MSK prognostic score



Motzer RJ et al. J Clin Oncol. 2002;20:289-296.

➔ **VEGF-targeted therapies**

IMDC prognostic score



*Risk factors for survival included anemia, thrombocytosis, neutrophilia, hypercalcaemia, KPS <80%, and <1 year from diagnosis to treatment.

Heng DY et al. Lancet Oncol 2013;14:141-148.

Rationale für Immuntherapie (RCC): Anti-PD-1/Anti-CTLA-4 Immun-Checkpoint-Inhibition

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- **Nivolumab**: vollhumaner IgG4 'programmed death 1' (PD-1) Immun-Checkpoint-Inhibitor-Antikörper

→ selektive Blockade der Interaktion zw. PD-1 (exprimiert auf aktivierten T-Lymphozyten) und PD-1 Ligand 1 (PD-L1) und 2 (PD-L2), exprimiert auf Immunzellen und Tumorzellen[1,2]

→ PD-L1 Expression assoziiert mit schlechter RCC-Prognose (immunosuppressive Funktion)[3,4]

→ Phase 2 Dosis-Findungs-Studie: vortherapiertes mRCC-Kollektiv (n=168), Nivolumab → ORR: 20-22% und OS: 18,2-25,5Mo.[5]

[1]Hamid O *et al.* Expert Opin Biol Ther 2013; [2]Nurieva RI *et al.* Immunol Rev 2011; [3]Thompson RH *et al.* Cancer Res 2006; [4]Choueiri T *et al.* J Clin Oncol 2015; [5]Motzer RJ *et al.* J Clin Oncol 2015

Nivolumab: Wirkmechanismus

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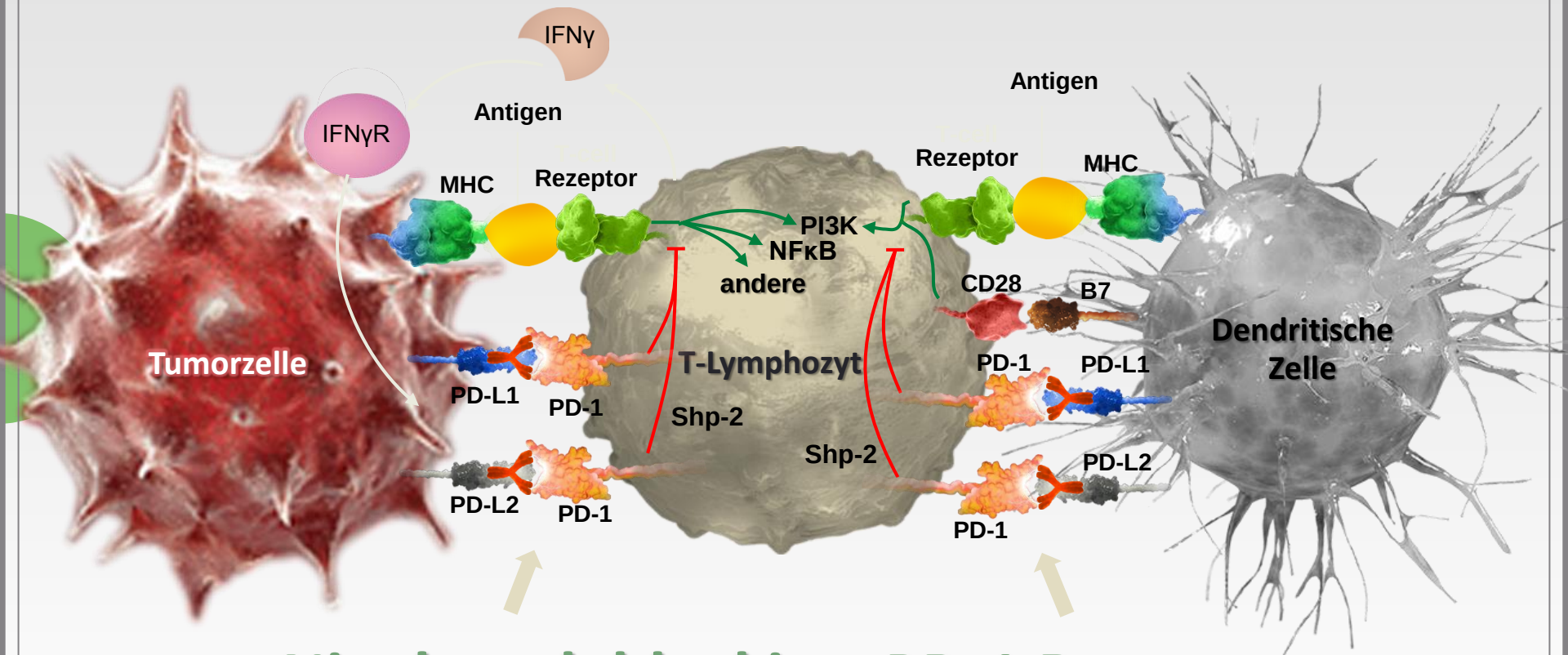
TU-Zellerkennung durch T-Lymphozyten (MHC/AG/TCR-Interaktion mediiert IFN-γ Freisetzung und tumoröse PD-L1/2-Up-Regulation)

Priming und T-Lymphozyten-Aktivierung (MHC/AG/TCR- und CD28/B7-Interaktionen mit AG-präsentierenden Zellen)



Nivolumab blockiert PD-1 Rezeptoren

Modifiziert n. Pardoll DM *et al.* Nat Rev Cancer 2012

➢ Rationale für Anti-PD-1-Inhibition:

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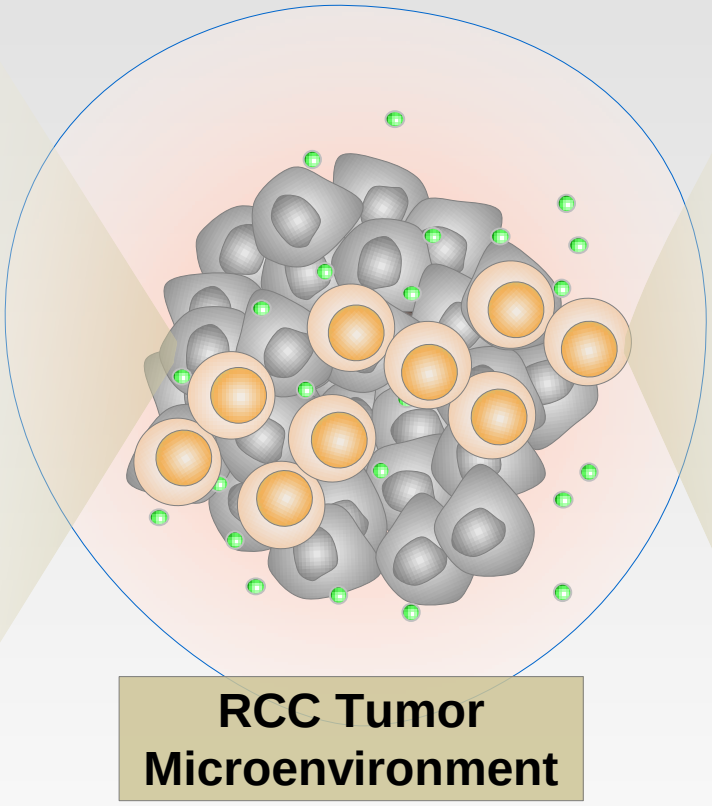
Tumorzellen

- 24% von ccRCC-Samples exprimieren PD-L1[1a]
- PD-L1 Expression korrelierte signifikant mit CSM[1]



RCC Tumor Microenvironment

TILs

- >50% von RCC-TILs exprimieren PD-L1+[2]
- ↑ PD-1 Expression auf TILs assoziiert mit Fernmetastasierung und schlechtem Überleben[3,4]

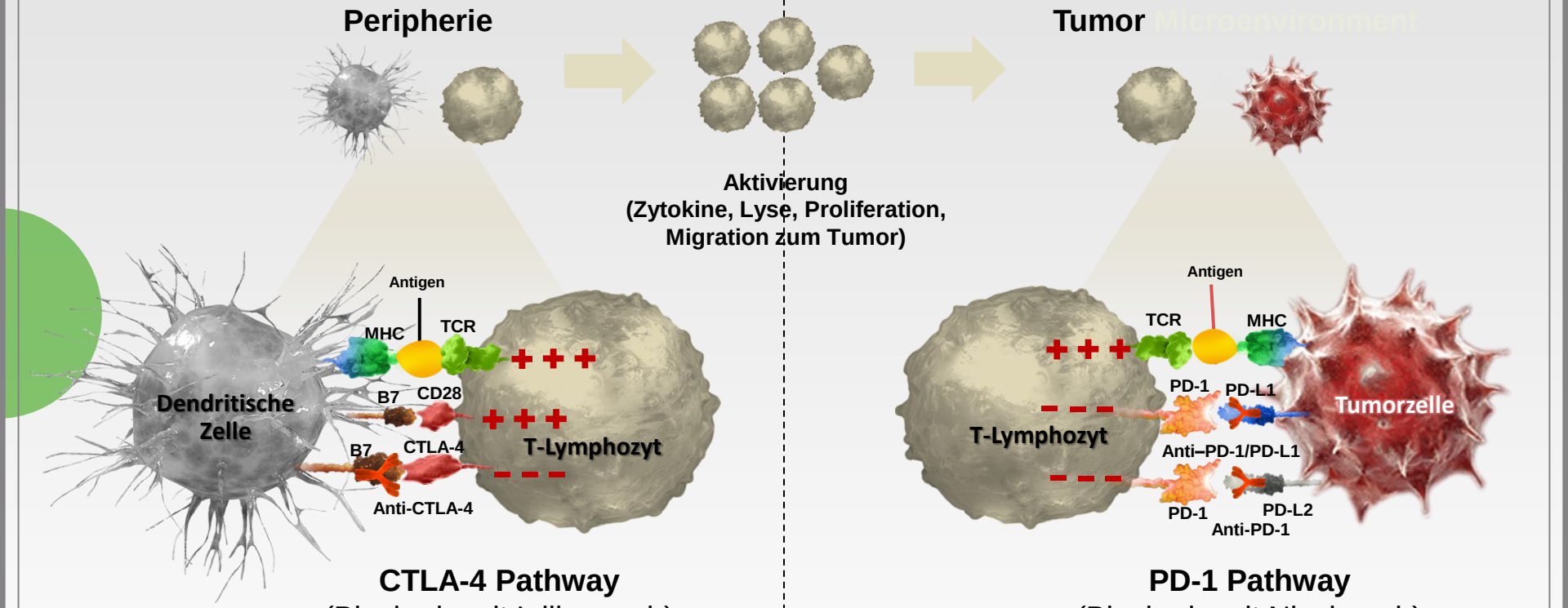
[a]306 Samples mittels IHC analysiert; threshold: ≥5% TU-Zellen mit membranösem Staining

[1]Thompson RH *et al.* Cancer Res 2006; [2]Thompson RH *et al.* Proc Natl Acad Sci USA 2004; [3]Thompson RH *et al.* Clin Cancer Res 2007; [4]Kang MJ *et al.* Transl Oncol 2013

Immun-Checkpoint-Inhibitoren:

→ Potential als Teil von Kombinations-Tx

bestimmte Kombinationen könnten Limitationen der Monotherapie durchbrechen[1,2]



CTLA-4 Pathway
(Blockade mit Ipilimumab)

PD-1 Pathway
(Blockade mit Nivolumab)

[1]Pardoll DM Nat Rev Cancer 2012
[2]Sharma P *et al.* Science 2015

Modifiziert n. Pardoll DM *et al.* Nat Rev Cancer 2012

CheckMate 025 Study

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Phase 3, randomized, open-label study of nivolumab *vs.* everolimus in patients with advanced or metastatic clear cell RCC who have received prior anti-angiogenic therapy[1]

Key Inclusion Criteria[1]

- Advanced/metastatic clear cell RCC
- ≤3 total prior regimens
- 1 or 2 prior anti-angiogenic therapies
- Progression <6 months before enrollment
- KPS ≥70
- No CNS metastases
- No prior therapy with mTOR inhibitor
- No condition requiring glucocorticoids

R 1:1

n=821

Nivolumab
3 mg/kg IV q2w

Everolimus
10 mg PO qd

Until progression,[a] unacceptable toxicity, withdrawal of consent, or end of study

Start Date: 09/2012[2]
Estimated Trial Completion Date: 09/2018[2]
Primary Completion Date: 05/2015[2]
Status: Ongoing but not recruiting[2]
Trial Director: Bristol-Myers Squibb[2]

Primary Endpoint: OS
Secondary Endpoints: ORR, PFS, OS by PD-L1 expression, AEs

[a]Patients were allowed to continue treatment beyond progression if investigator-assessed clinical benefit was achieved and treatment had an acceptable side-effect profile.

[1]Motzer RJ *et al.* N Engl J Med 2015 [2]Clinicaltrials.gov. NCT01668784

CheckMate 025

- clinically relevant reduction ↓ in the risk of death (27%) [nivolumab]

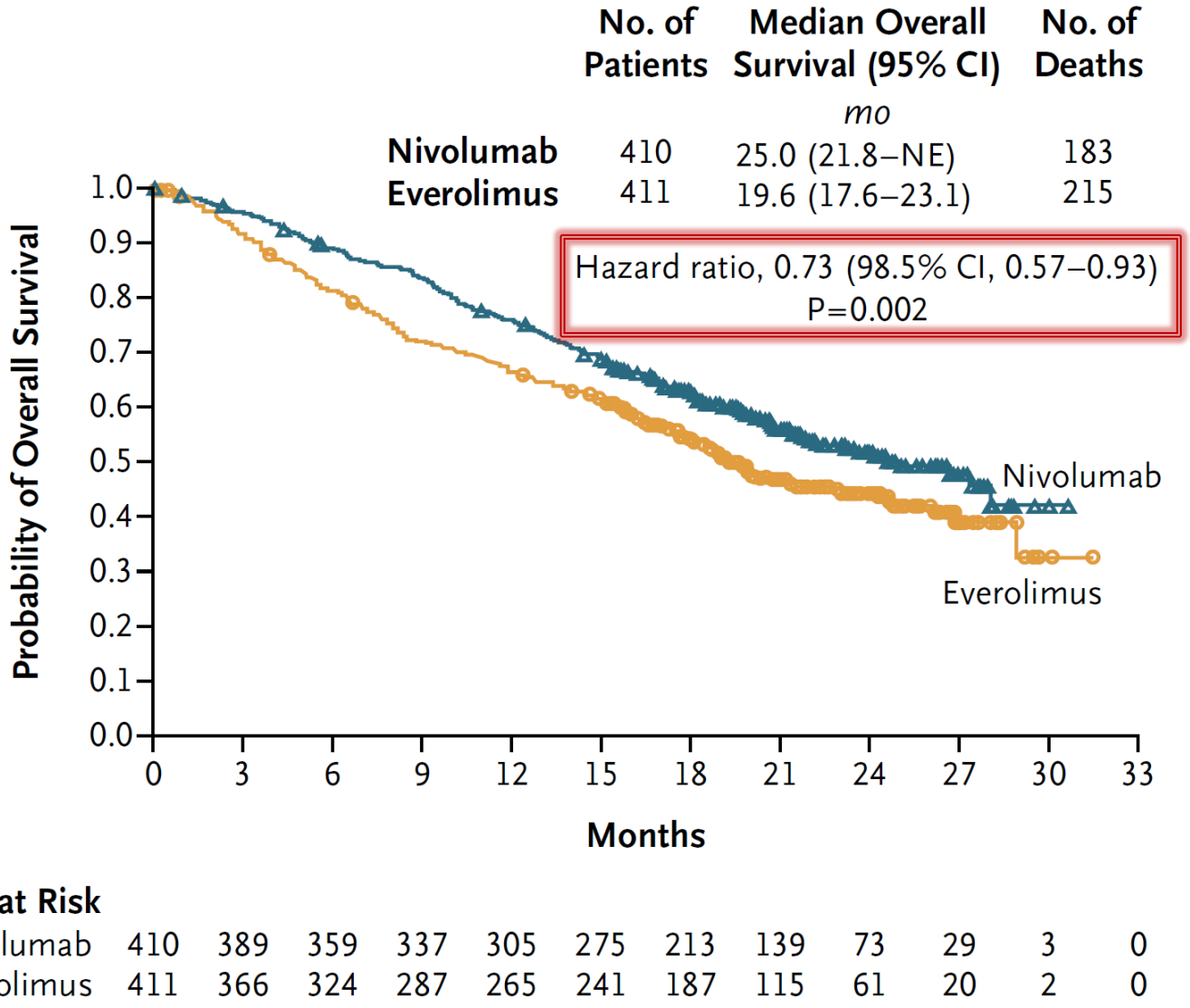

Figure 1. Kaplan–Meier Curve for Overall Survival.

CI denotes confidence interval, and NE not estimable.

Motzer RJ *et al.*
N Engl J Med 2015

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OS: 3-Year Follow-up

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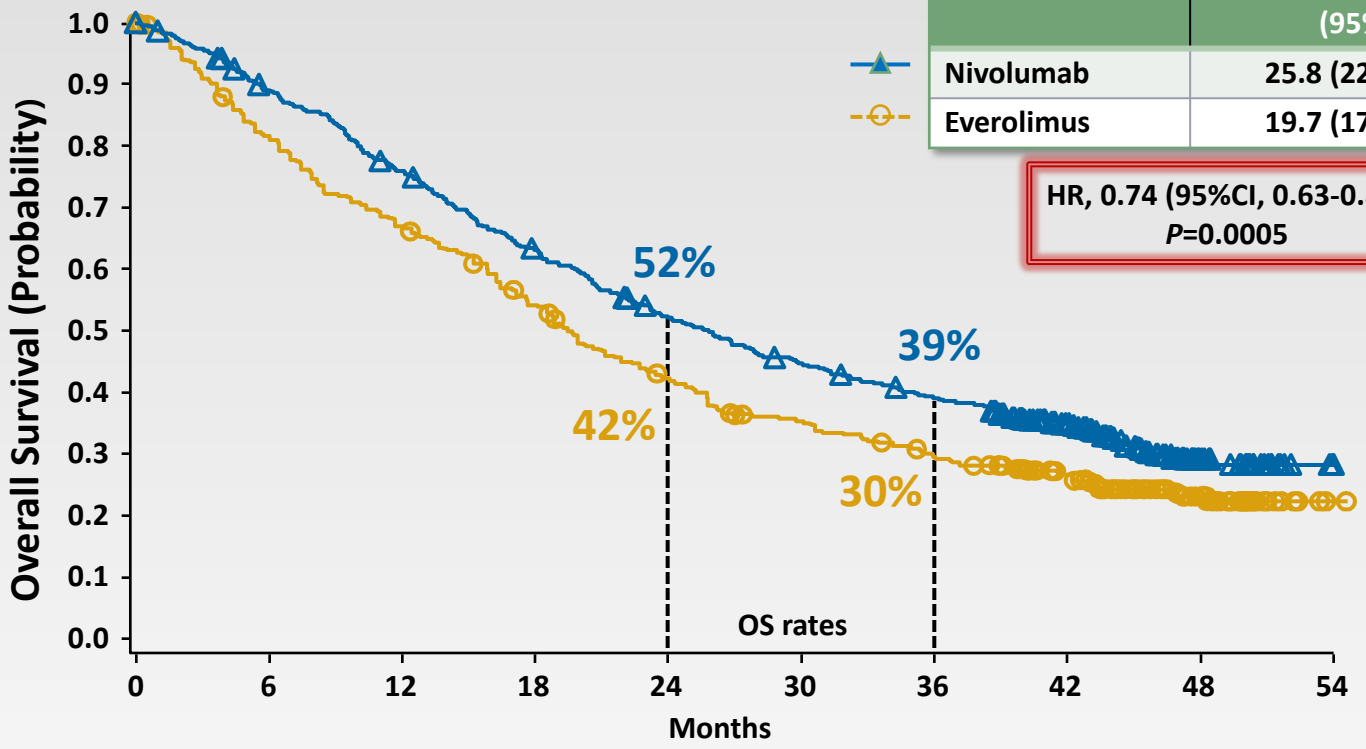
	Median OS, Mo. (95%CI)
Nivolumab	25.8 (22.2-29.8)
Everolimus	19.7 (17.6-22.1)

HR, 0.74 (95%CI, 0.63-0.88)
P=0.0005



No. of patients at risk										
Nivolumab	410	359	305	252	205	175	151	109	31	0
Everolimus	411	325	268	214	163	133	110	85	32	1

Minimum follow-up: ~38 months
Reported as of June 2017
Included with permission from Sharma P *et al.* Poster presentation at KCS 2017.

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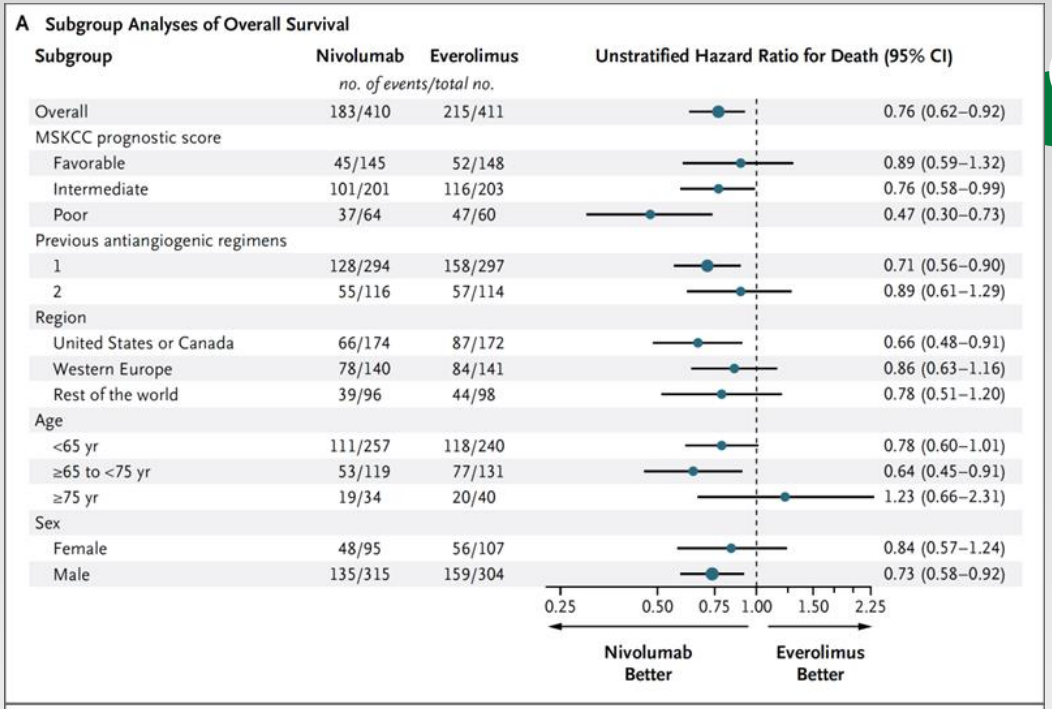

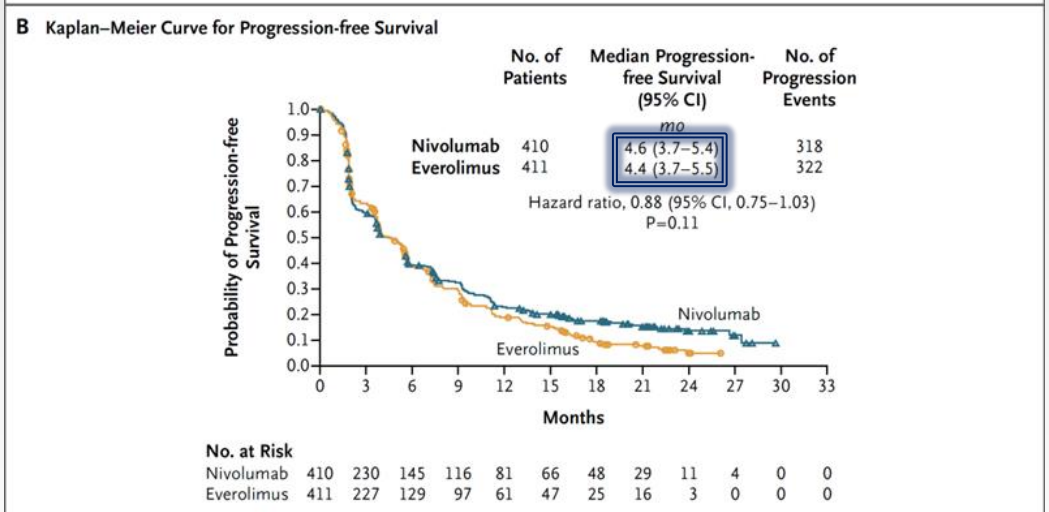

Figure 2. Overall Survival in Subgroup Analyses and Kaplan–Meier Curve for Progression-free Survival.

The Memorial Sloan Kettering Cancer Center (MSKCC) prognostic risk groups are based on the presence of 0 (favorable), 1 or 2 (intermediate), or 3 (poor) of the following prognostic factors: anemia, hypercalcemia, and poor performance status. The analyses in Panel A are based on data collected with the use of an interactive voice response system.

Motzer RJ *et al.*
N Engl J Med 2015

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PFS: 3-Year Follow-up

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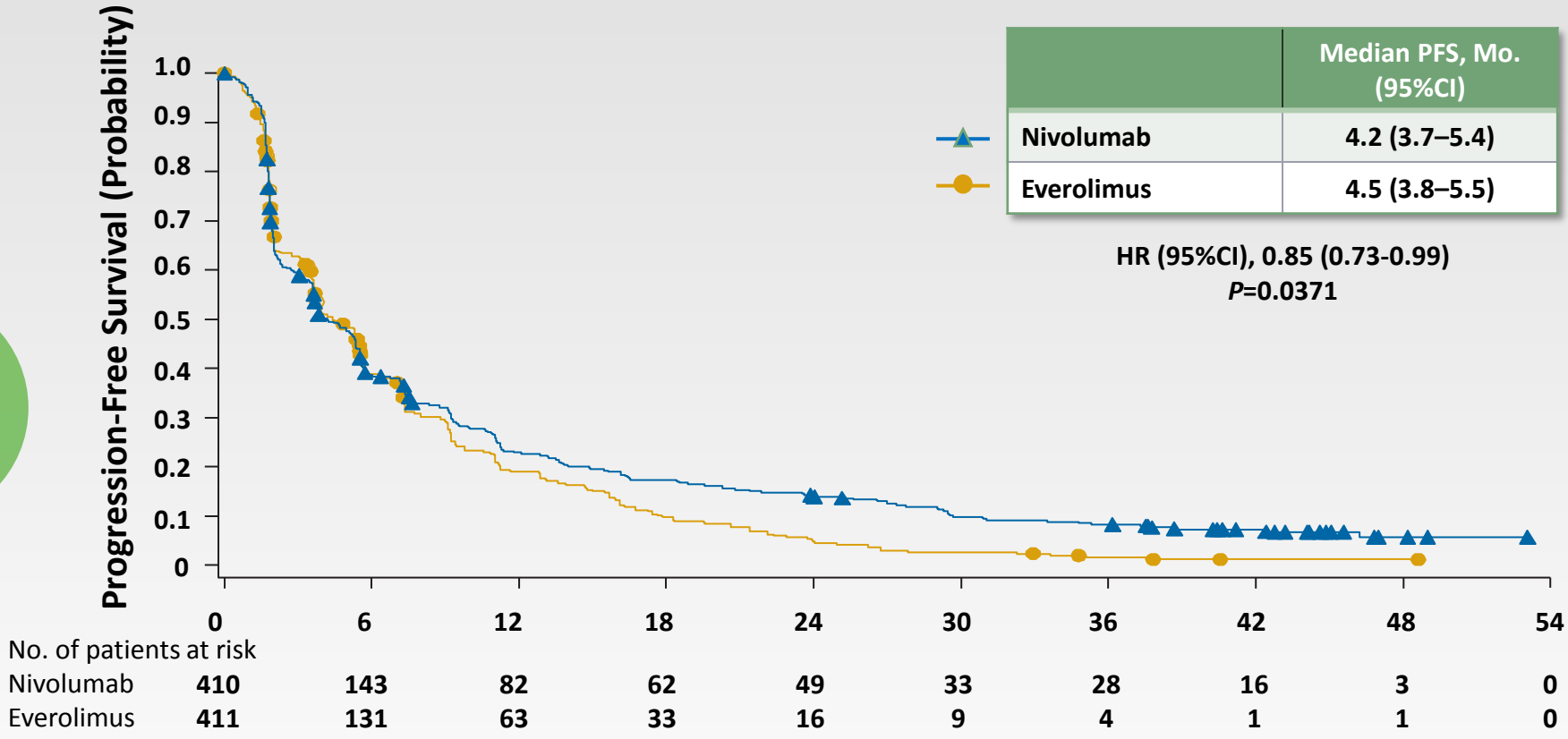
→ a delayed benefit with nivolumab *vs.* everolimus was seen in PFS



	Median PFS, Mo. (95%CI)
Nivolumab	4.2 (3.7–5.4)
Everolimus	4.5 (3.8–5.5)

HR (95%CI), 0.85 (0.73-0.99)
P=0.0371

Minimum follow-up: ~38 months
Reported as of June 2017
Included with permission from Sharma P *et al.* Poster presentation at KCS 2017.

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Antitumor activity

	Nivolumab N = 410	Everolimus N = 411
Objective response rate, %	25	5
Odds ratio (95% CI)	5.98 (3.68–9.72)	
P value	<0.0001	
Best overall response, %		
Complete response	1	1
Partial response	24	5
Stable disease	34	55
Progressive disease	35	28
Not evaluated	6	12
Median time to response, months (range)	3.5 (1.4–24.8)	3.7 (1.5–11.2)
Median duration of response, months (range)*	12.0 (0–27.6)	12.0 (0–22.2)
Ongoing response, n/N (%)	49/103 (48)	10/22 (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.

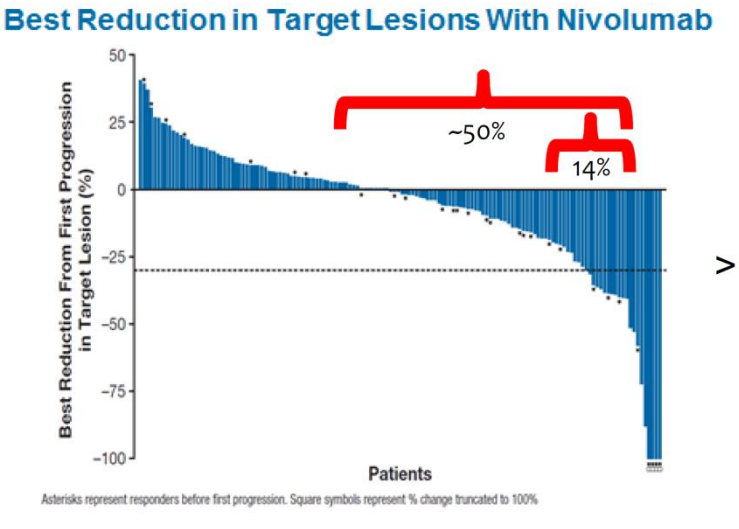
Motzer RJ, et al. N Engl J Med 2015;373:1803-13

Treatment beyond progression

Tumor Burden change post-PD

A total of 142/153 pts treated with nivolumab beyond PD had tumor measurements pre- and post-PD

50% had a reduction in tumor burden post-progression and **14%** (n = 20) had a ≥30% reduction in tumor burden



> 30% reduction

Escudier B et al. Eur Urol. 2017 Sep;72(3):368-376

1st-Linien-Kombinations-Trials: beendet

PD-1 + CTLA-4 Inhibition	PD-L1 + VEGFR Inhibition	personalisierte IT + VEGFR Inhibition

CheckMate 214[1]

Phase III

R → **Sunitinib** 50 mg/d 4/2 (n=1070)

R → **Nivolumab + Ipilimumab** 3 mg/kg IV q3w für 4 Dosen, dann q2w + 1 mg/kg IV q3w für 4 Dosen

Ko-primäre Endpunkte: PFS, OS

IMmotion151[2]

Phase III

R → **Sunitinib** 50 mg/d 4/2 (n=830)

R → **Atezolizumab + Bevazizumab** 1200 mg IV + 15 mg/kg IV q3w

Ko-primäre Endpunkte: PFS, OS

ADAPT[3]

Phase III

R → **Sunitinib** (n=450)

R → **AGS-003 + Sunitinib** 8 Inj./12Mo. + Boosters + Sunitinib

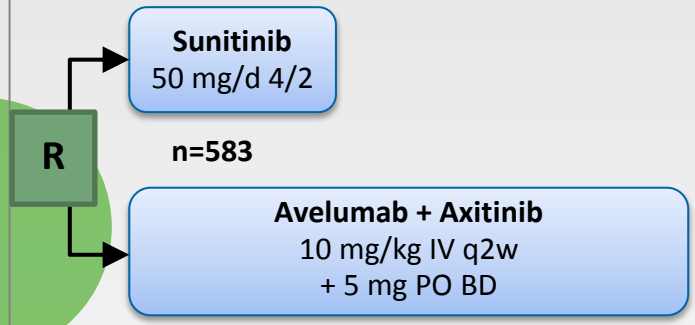
primärer Endpunkt: OS

[1]NCT02231749
[2]NCT02420821
[3]NCT01582672

1st-Linien-Kombinations-Trials: laufend

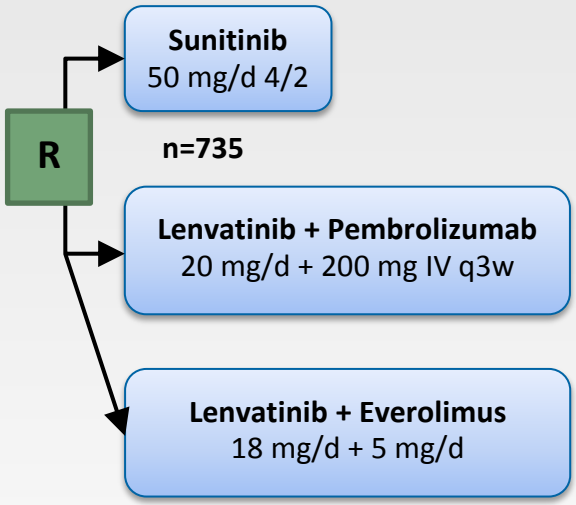
PD-L1 + VEGFR TK Inhibition	VEGFR + mTOR/PD-1 Inhibition	PD-1 + VEGFR TK Inhibition

Javelin renal 101[1]
Phase III



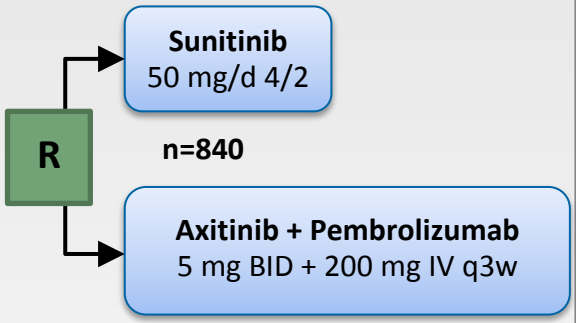
primärer Endpunkt: PFS

Lenvatinib + Everolimus od. Pembrolizumab[2] Phase III



primärer Endpunkt: PFS

KEYNOTE 426[3]
Phase III



Ko-primäre Endpunkte: PFS, OS

Press release 18.10.2018

[1]NCT02684006
[2]NCT02811861
[3]NCT02853331

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 5, 2018 VOL. 378 NO. 14

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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n=1096

CheckMate 214: Study design

Patients

- **Treatment-naïve advanced or metastatic clear-cell RCC**
- **Measurable disease**
- **KPS ≥70%**
- **Tumor tissue available for PD-L1 testing**

Randomize 1:1

Stratified by
- **IMDC prognostic score (0 vs 1–2 vs 3–6)**
- Region (US vs Canada/Europe vs Rest of World)

Treatment

Arm A
3 mg/kg nivolumab IV +
1 mg/kg ipilimumab IV Q3W for **four doses**, then
3 mg/kg nivolumab IV Q2W

Arm B
50 mg sunitinib orally once daily for 4 weeks
(6-week cycles)

Treatment until progression or unacceptable toxicity

Escudier B et al LBA5, ESMO 2017
Motzer RJ et al, N Engl J Med 2018; 378:1277-1290

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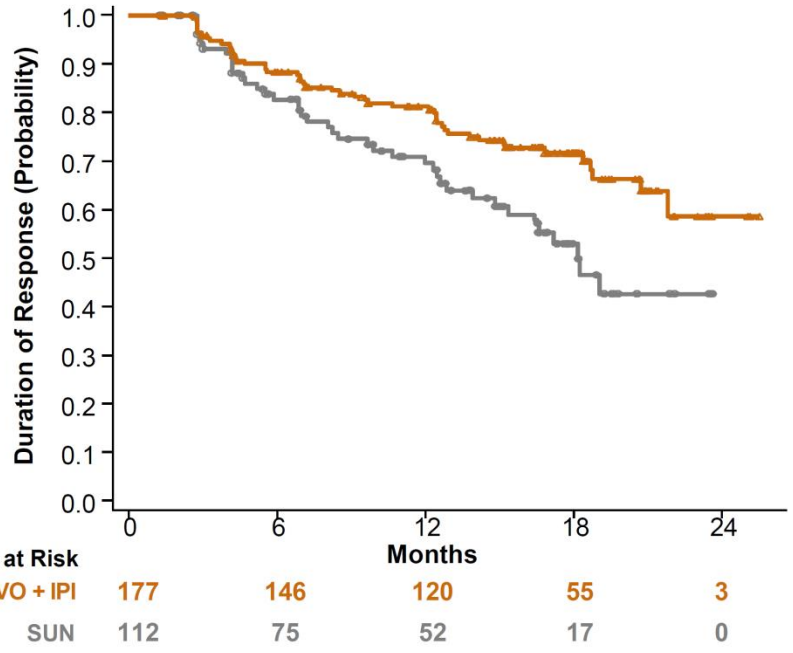
Co-primary endpoint: ORR

ORR and DOR: IMDC intermediate/poor risk

(77%)

Outcome	N = 847	
	NIVO + IPI N = 425	SUN N = 422
Confirmed ORR,[a] % (95% CI)	**42 (37–47)**	**27 (22–31)**
	P < 0.0001	
Confirmed BOR,[a] %		
Complete response	**9[b]**	**1[b]**
Partial response	32	25
Stable disease	31	45
Progressive disease	20	17
Unable to determine/not reported	8	12

	Median duration of response, months (95% CI)	Patients with ongoing response, %
NIVO + IPI	NR (21.8–NE)	72
SUN	18.2 (14.8–NE)	63



MADRID 2017 ESMO congress

[a]IRRC-assessed ORR and BOR by RECIST v1.1; [b]*P* < 0.0001

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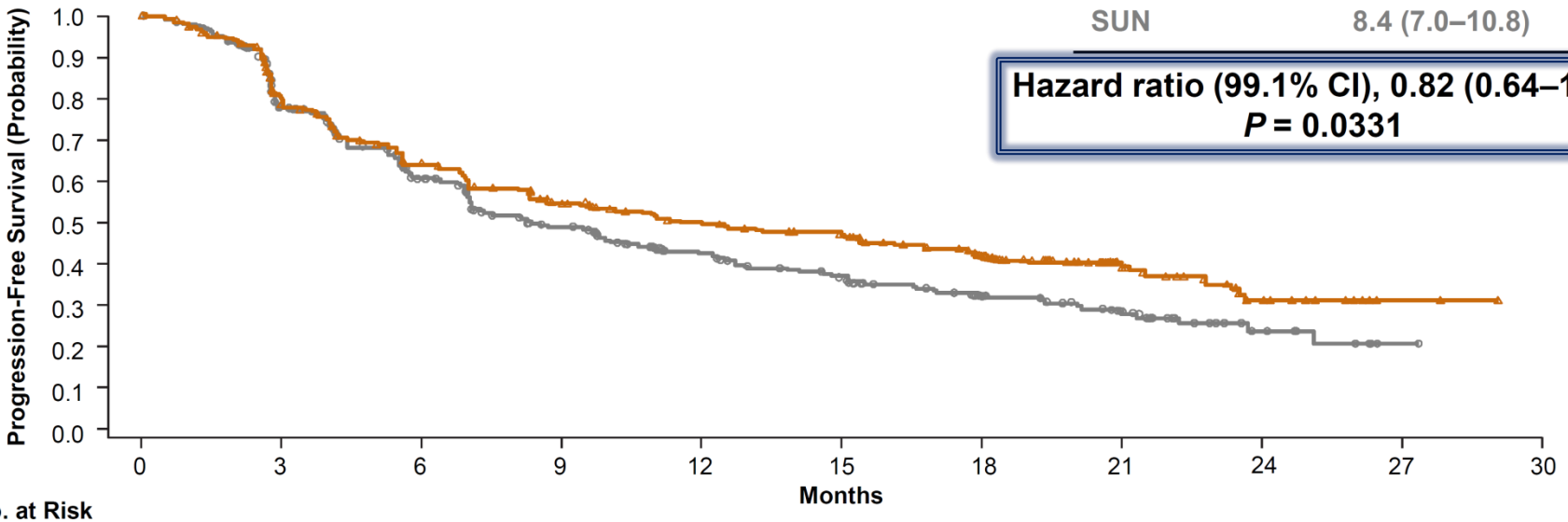
Co-primary endpoint

PFS per IRRC: IMDC intermediate/poor risk

Median PFS, months (95% CI)	
NIVO + IPI	11.6 (8.7–15.5)
SUN	8.4 (7.0–10.8)

Hazard ratio (99.1% CI), 0.82 (0.64–1.05)
P **= 0.0331**



No. at Risk											
NIVO + IPI	425	304	233	187	163	149	118	46	17	3	0
SUN	422	282	191	139	107	86	57	33	11	1	0

Escudier B et al LBA5, ESMO 2017
Motzer RJ et al, N Engl J Med 2018; 378:1277-1290

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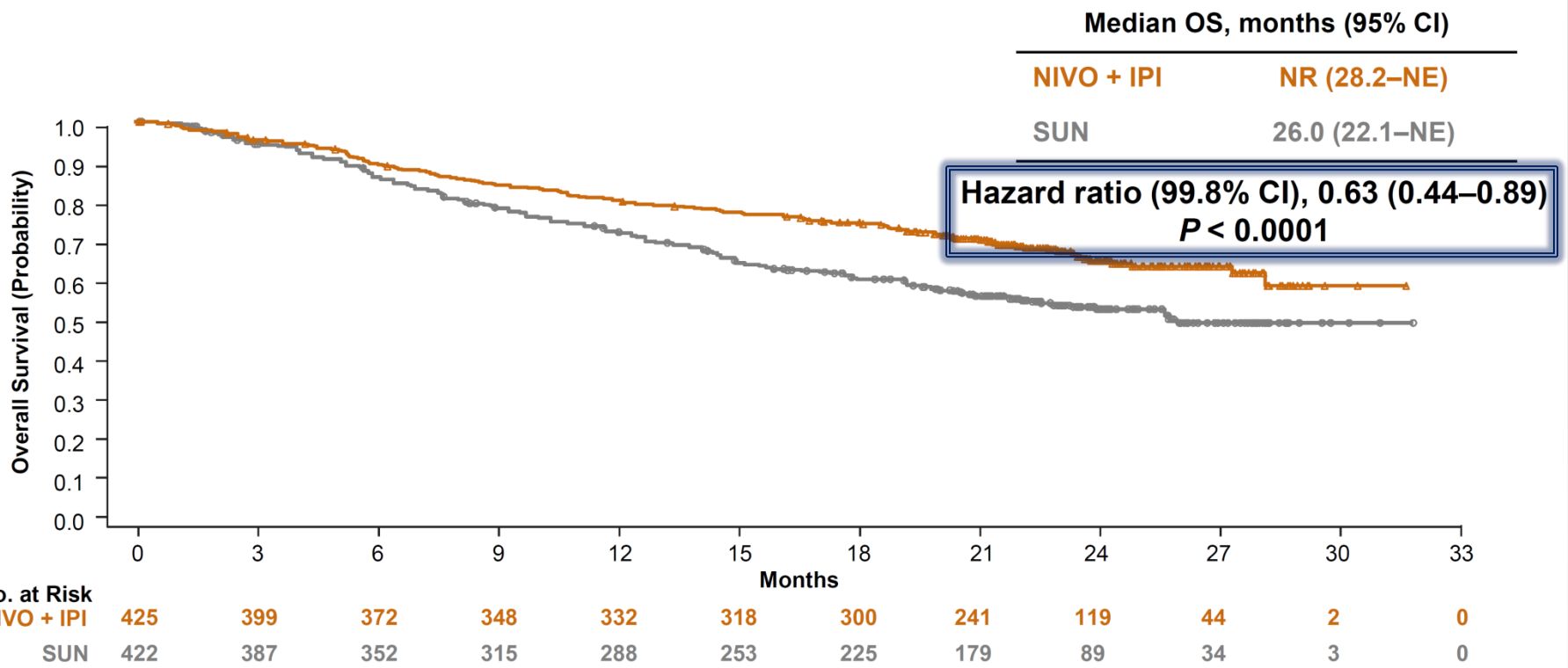
Co-primary endpoint

OS: IMDC intermediate/poor risk



Escudier B et al LBA5, ESMO 2017
Motzer RJ et al, N Engl J Med 2018; 378:1277-1290

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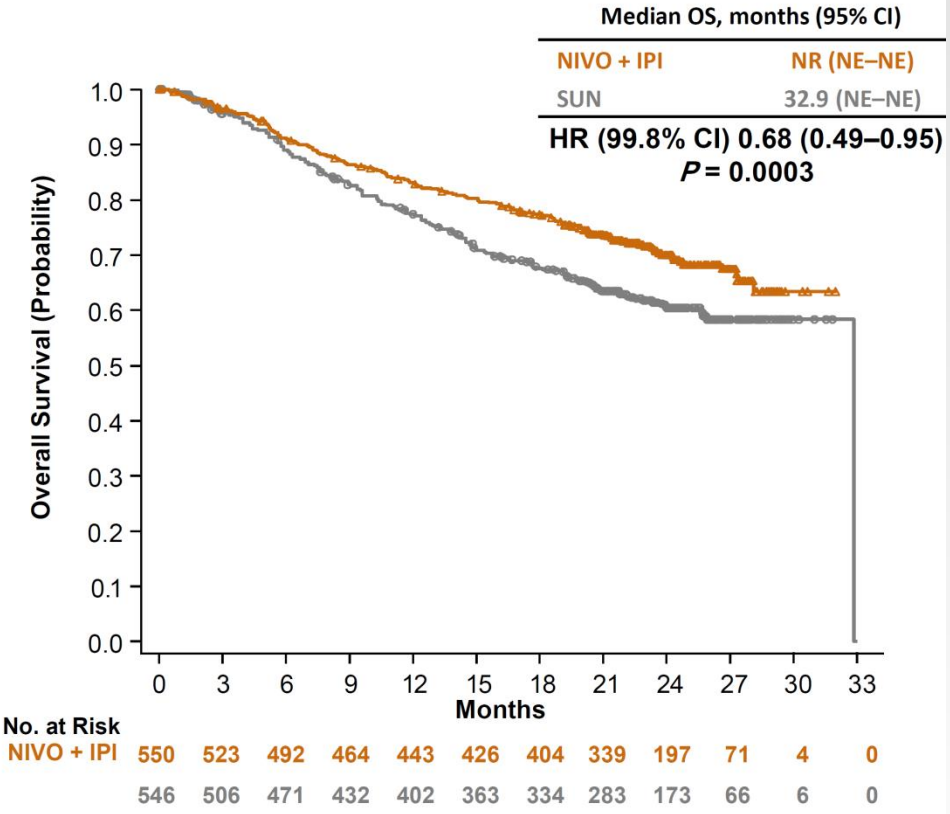
Secondary endpoint

ORR, PFS, and OS: Intention to treat

Outcome	N = 1,096[a]	
	NIVO + IPI N = 550	SUN N = 546
Confirmed ORR,[b] % (95% CI)	**39 (35–43)**	**32 (28–36)**
	P = 0.0191	
PFS,[c] median (95% CI), months	12.4 (9.9–16.5)	12.3 (9.8–15.2)
	HR (99.1% CI) 0.98 (0.79–1.23) ***P* = 0.8498**	

[a]23% of patients in the NIVO + IPI arm and 25% of patients in the SUN arm had tumor PD-L1 expression ≥1%
[b]IRRC-assessed by RECIST v1.1
[c]IRRC-assessed



MADRID 2017 ESMO congress

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Exploratory endpoint

ORR and PFS: IMDC favorable risk (23%)

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**	

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

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Secondary endpoint

Treatment-related adverse events: All treated patients

	NIVO + IPI N = 547		SUN N = 535	
Event, %	Any grade	Grade 3–5	Any grade	Grade 3–5[a]
Treatment-related adverse events in ≥25% of patients	**93**	**46**	**97**	**63**
Fatigue	37	4	49	9
Pruritus	28	<1	9	0
Diarrhea	27	4	52	5
Nausea	20	2	38	1
Hypothyroidism	16	<1	25	<1
Decreased appetite	14	1	25	1
Dysgeusia	6	0	33	<1
Stomatitis	4	0	28	3
Hypertension	2	<1	40	16
Mucosal inflammation	2	0	28	3
Palmar-plantar erythrodysesthesia syndrome	1	0	43	9
Treatment-related AEs leading to discontinuation, %	**22**	**15**	**12**	**7**
Treatment-related deaths	**n = 7[b]**		**n = 4[c]**	

[a]Two patients had grade 5 cardiac arrest. [b]Pneumonitis, immune mediated bronchitis, lower GI hemorrhage, hemophagocytic syndrome, sudden death, liver toxicity, lung infection. [c]Cardiac arrest (n = 2), heart failure, multiple organ failure.

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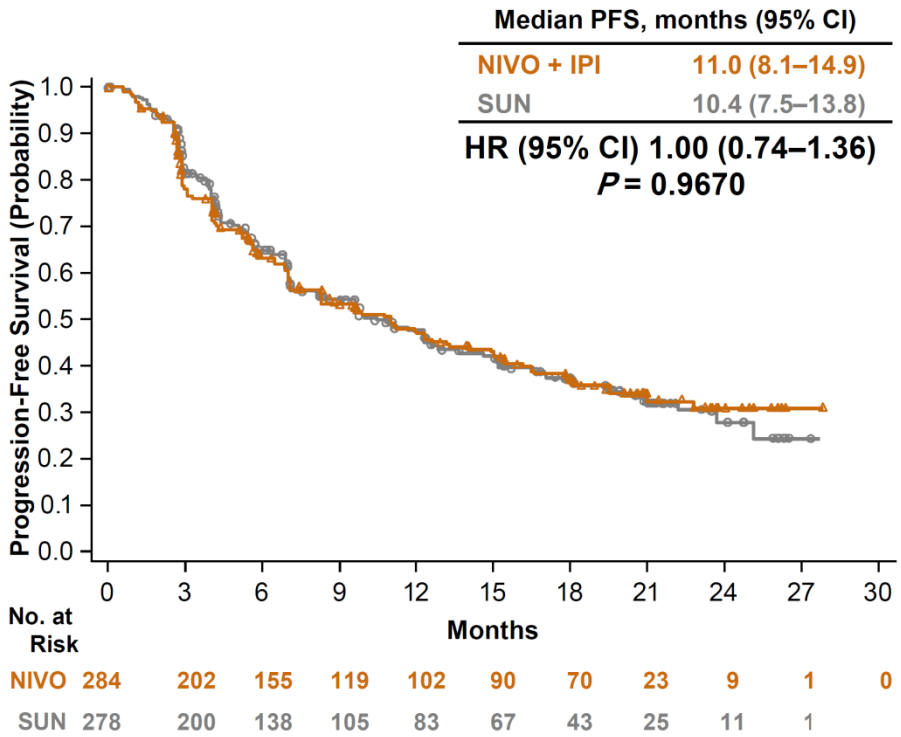
Exploratory endpoint

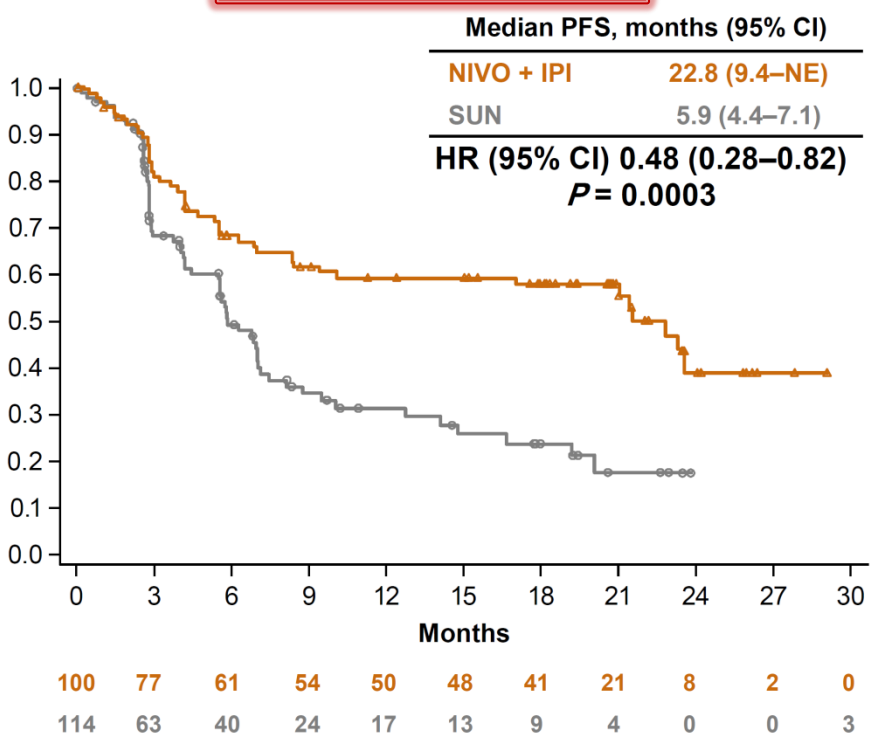
PFS by PD-L1 expression: IMDC intermediate/poor risk

PD-L1 <1% (n = 562)



No. at Risk											
NIVO	284	202	155	119	102	90	70	23	9	1	0
SUN	278	200	138	105	83	67	43	25	11	1	

PD-L1 ≥1% (n = 214)



NIVO	100	77	61	54	50	48	41	21	8	2	0
SUN	114	63	40	24	17	13	9	4	0	0	3

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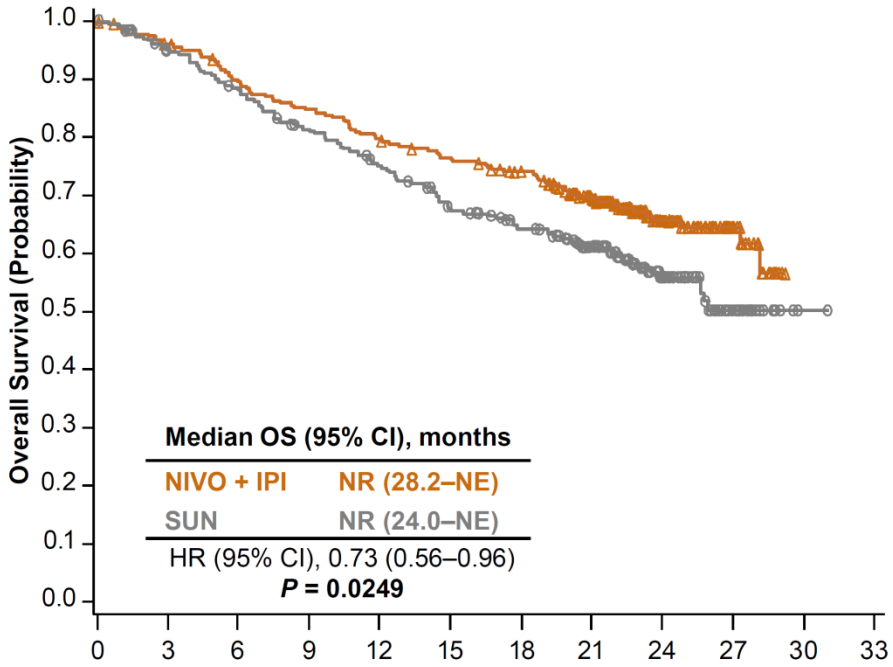
Motzer et al SITC 2017

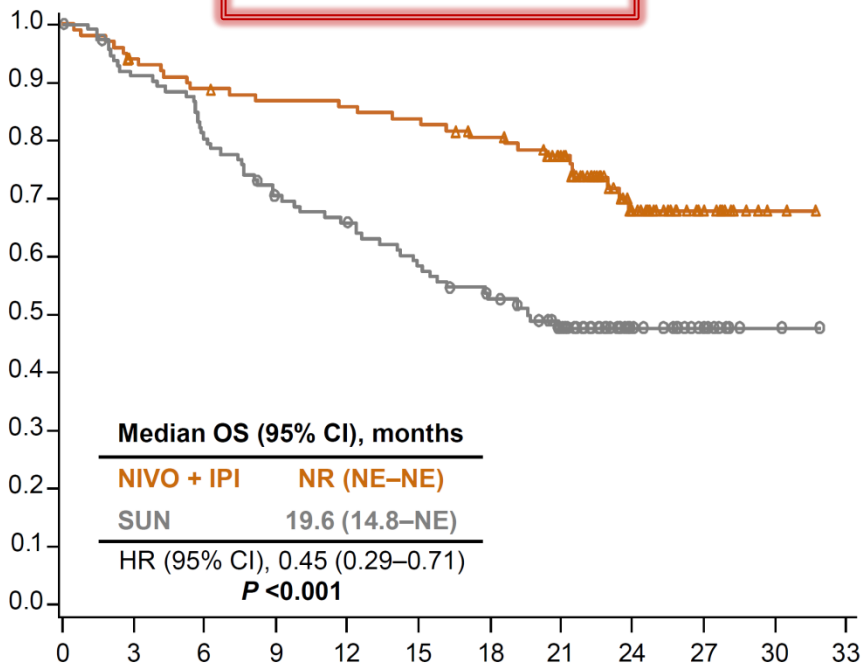
OS by tumor PD-L1 expression: IMDC intermediate/poor risk

PD-L1 <1% (n = 562)



No. at Risk	Months					
NIVO + IPI	284	251	223	200	76	0
SUN	278	239	198	157	61	1

PD-L1 ≥1% (n = 214)



Months					
100	87	83	76	33	2
114	90	72	55	21	2

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 5, 2018 VOL. 378 NO. 14

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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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

15.11.2018

Positive EMA opinion for the ipilimumab/nivolumab combination for the 1st-line treatment of adult patients with intermediate/poor-risk advanced RCC

What were the conclusions of the CHMP following the re-examination?

The CHMP considered that the results from the main study comparing Opdivo and Yervoy with sunitinib showed a clinically important increase in patients' survival with the combination, and side effects were considered acceptable. Although the precise contribution of Yervoy was not clear, the CHMP re-assessed data from other non-clinical and clinical studies, including studies with the combination in relevant other cancer types, and considered that the benefit of Yervoy in the combination has been sufficiently demonstrated. The CHMP was of the opinion that the benefits of the combination largely outweigh its risks and therefore recommended granting the change to the marketing authorisation. However, the company must conduct a study to determine the precise contribution of Yervoy in the combination and if the risks could be further minimised.

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IMmotion151: A Randomized Phase III Study of Atezolizumab Plus Bevacizumab vs Sunitinib in Untreated Metastatic Renal Cell Carcinoma

Robert Motzer,[1] Thomas Powles,[2] Michael Atkins,[3] Bernard Escudier,[4] David McDermott,[5] Cristina Suarez,[6] Sergio Bracarda,[7] Walter M. Stadler,[8] Frede Donskov,[9] Jae Lyun Lee,[10] Robert Hawkins,[11] Alain Ravaud,[12] Boris Alekseev,[13] Michael Staehler,[14] Motohide Uemura,[15] Francis Donaldson,[16] Shi Li,[17] Mahrukh Huseni,[17] Christina Schiff,[17] Brian Rini[18]

[1]Memorial Sloan Kettering Cancer Center, New York, NY; [2]Barts Health NHS Trust – St Bartholomew's Hospital, London, UK; [3]Georgetown Lombardi Comprehensive Cancer Center, Washington, DC; [4]Gustave Roussy, Villejuif, France; [5]Beth Israel Deaconess Medical Center, Boston, MA; [6]Vall d'Hebron Institute of Oncology, Vall d'Hebron University Hospital, Universitat Autònoma de Barcelona, Barcelona, Spain; [7]Ospedale San Donato, Arezzo, Italy; [8]The University of Chicago Medicine, Chicago, IL; [9]Department of Oncology, Aarhus University Hospital, Denmark; [10]Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea; [11]The Christie NHS Foundation Trust, Manchester, UK; [12]CHU Hopitaux de Bordeaux – Hôpital Saint-André, Bordeaux, France; [13]P. Herzen Oncology Research Institute, Moscow, Russia; [14]Klinikum der Universität München, Campus Großhadern, München, Germany; [15]Department of Urology, Osaka University Graduate School of Medicine, Osaka, Japan; [16]Roche Products Ltd, Welwyn Garden City, UK; [17]Genentech, Inc., South San Francisco, CA; [18]Cleveland Clinic Taussig Cancer Institute, Cleveland, OH

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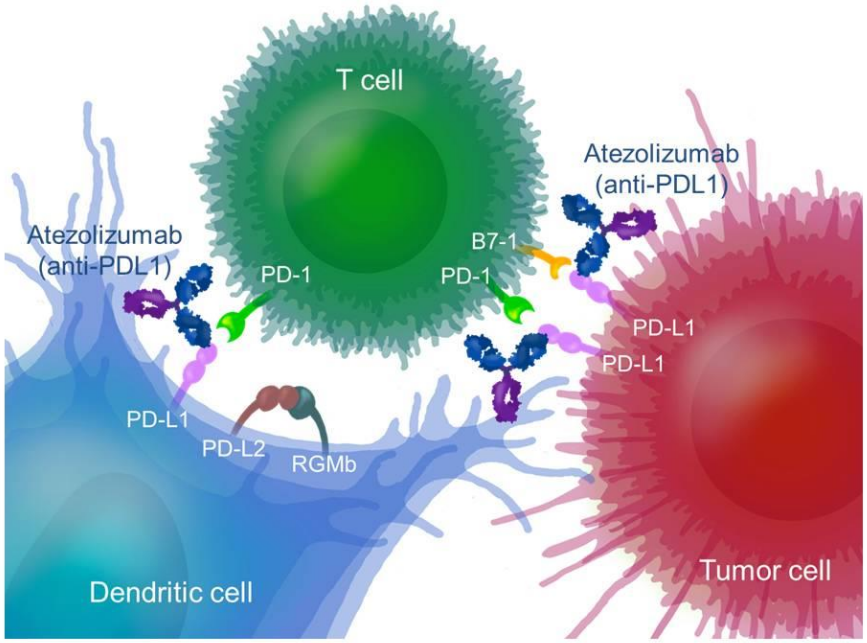
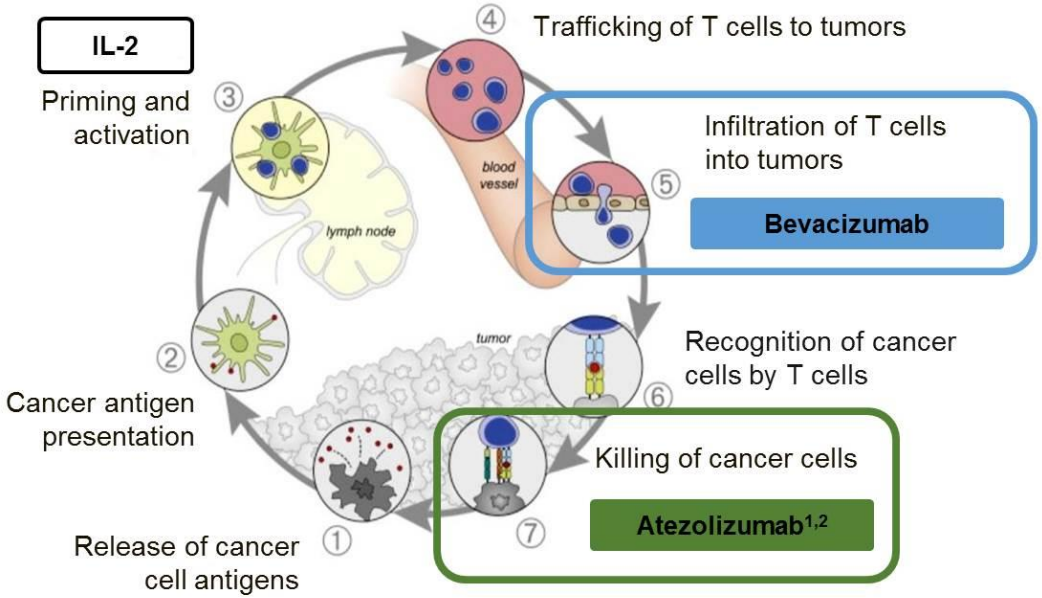
PD-L1 and Atezolizumab



- Atezolizumab is a humanized engineered mAb that selectively targets PD-L1
  - By inhibiting interactions with receptors PD-1 and B7.1, anti-cancer immunity can be reinvigorated and enhanced[1,2]
- Atezolizumab has demonstrated efficacy and safety in a broad range of cancer types, including mUC, NSCLC and RCC[1,3,4]
- PD-L1 expression on immune cells (IC) was evaluated (VENTANA SP142 IHC assay) based on 3 scoring levels: IC2/3 (≥ 5%), IC1 (≥ 1% but < 5%), IC0 (< 1%)

1. Herbst *Nature* 2014. 2 Chen *Immunity* 2013. 3. Powles *Nature* 2014. 4. Rosenberg *Lancet* 2016.

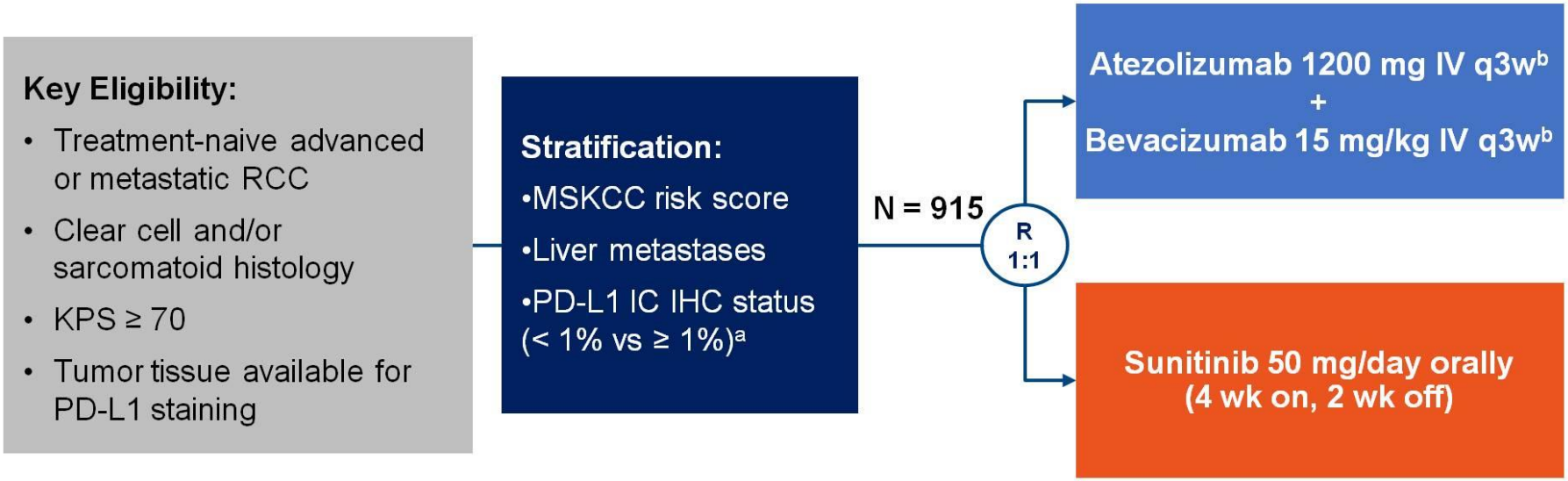
Cancer Immunity Cycle



- Immune therapy (high dose IL-2) is associated with long-term durable responses in patients with mRCC[3]
- Atezolizumab (anti–PD-L1) monotherapy has demonstrated anti-tumor activity and tolerable safety in mRCC[1,4]
- Bevacizumab (VEGF inhibitor) + IFN-α-2a is approved for use in first-line mRCC

1. Herbst *Nature* 2014. 2 Chen *Immunity* 2013. 3. Yan *JCO* 2003. 4. McDermott *JCO* 2016.
IL-2, interleukin-2. mRCC, metastatic renal cell carcinoma.
Figure adapted from Chen *Immunity* 2013.

Study Design



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

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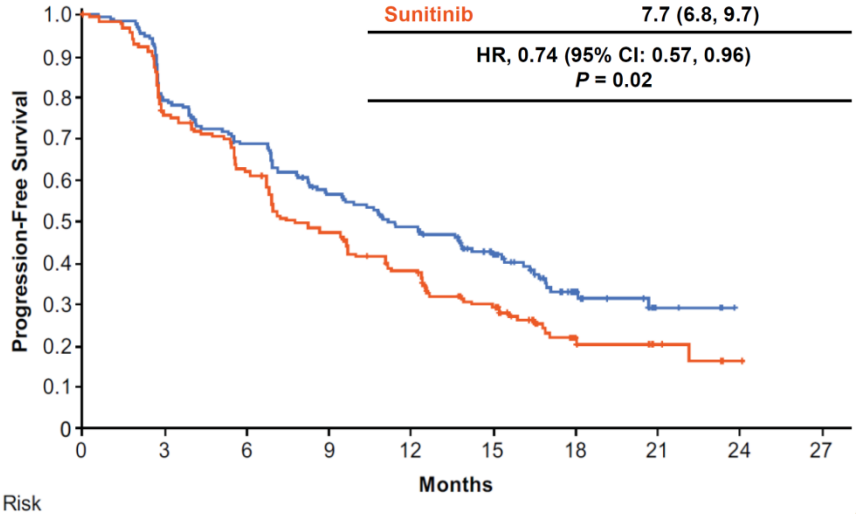
Co-Primary Endpoint

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

PD-L1+

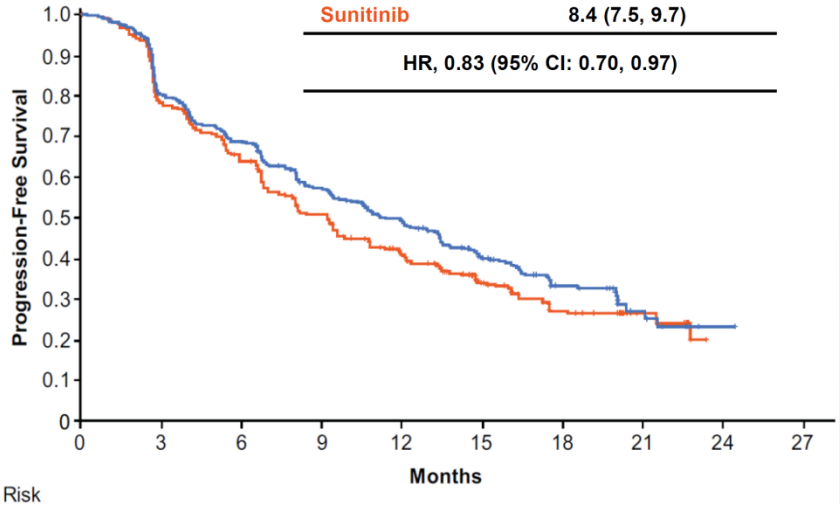
Median PFS, mo (95% CI)	
Atezo + Bev	11.2 (8.9, 15.0)
Sunitinib	7.7 (6.8, 9.7)
HR, 0.74 (95% CI: 0.57, 0.96) *P* = 0.02	



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.

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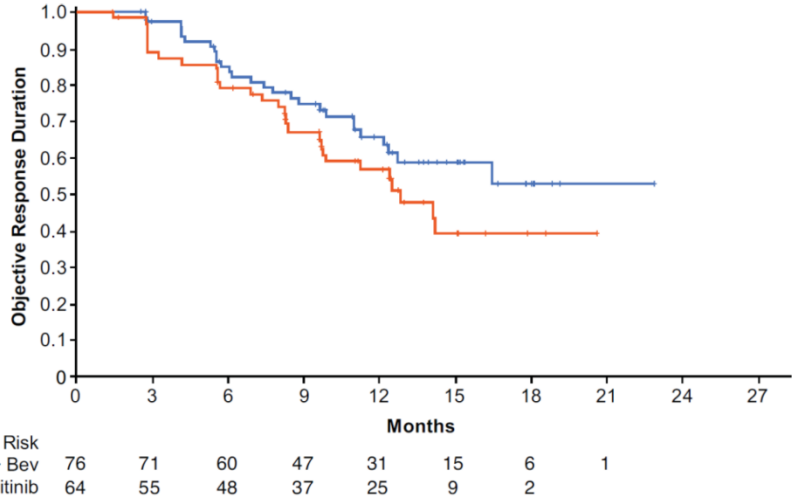
Secondary Endpoint

Objective Response Rate

	PD-L1+	
	Atezo + Bev n = 178	Sunitinib n = 184
Confirmed ORR, % 95% CI	43% (35, 50)	35% (28, 42)
Complete response	9%	4%
Partial response	34%	30%
Stable disease	32%	35%
Progressive disease	19%	21%
Not evaluable[a]	7%	10%

PD-L1+	Median DOR, mo (95% CI)	Ongoing Responders, n (%)
Atezo + Bev	NR (12.4, NR)	49 (65%)
Sunitinib	12.9 (9.8, NR)	34 (53%)



NR, not reached. [a] Including patients with no post-baseline tumor assessment. ORR assessed by investigators in patients with measurable disease at baseline. Minimum follow-up, 12 mo. Median follow-up, 15 mo.

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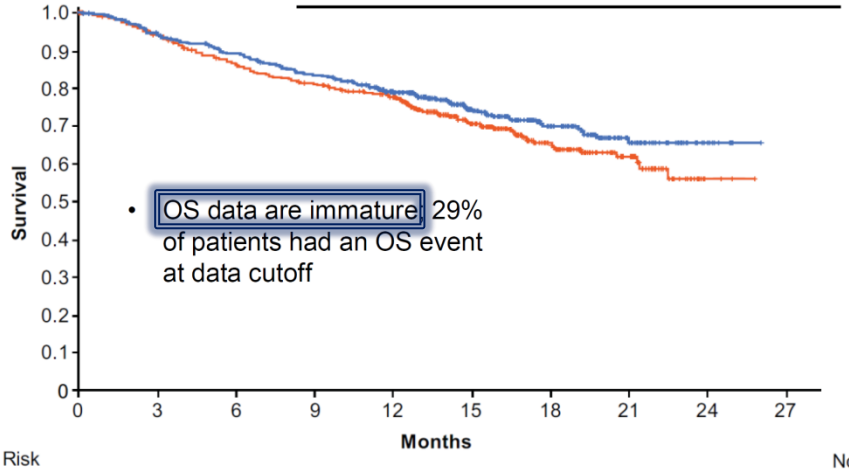
Co-Primary Endpoint

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	

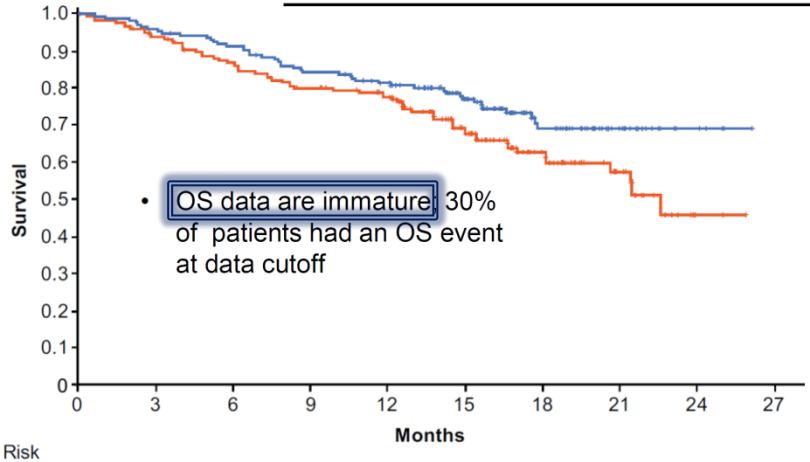


- OS data are immature; 29% of patients had an OS event at data cutoff

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)	



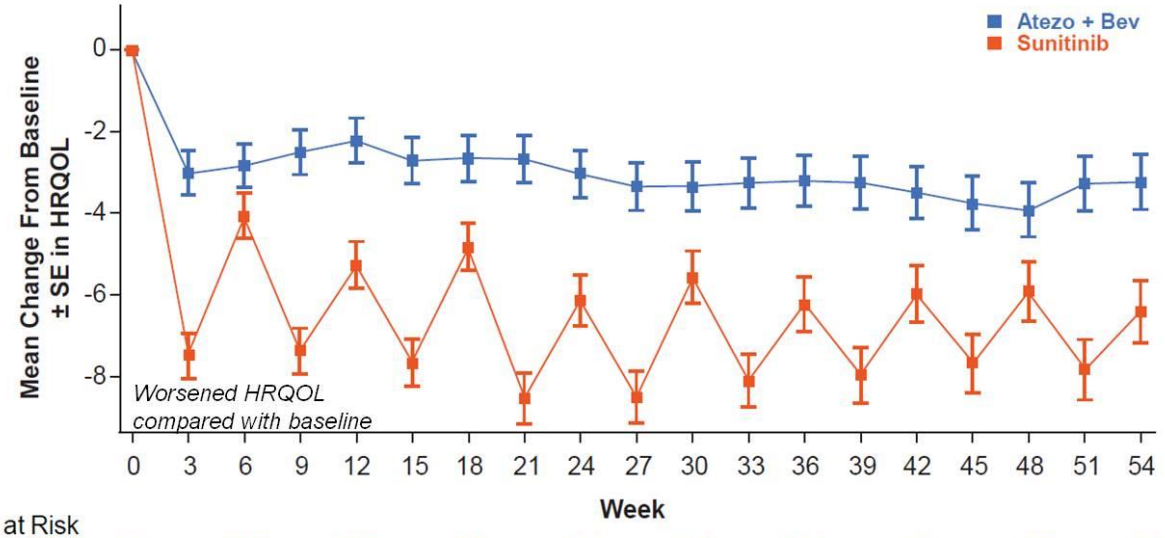
- OS data are immature; 30% of patients had an OS event at data cutoff

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.

HRQOL (FKSI-19)

Change in Health-Related Quality of Life Over Time



No. at Risk

Atezo + Bev	364	305	297	266	238	223	200	191	185	169
Sunitinib	345	276	253	230	210	198	173	161	146	131

- Baseline HRQOL[a] in both arms suggests minimal impairment and scores were comparable to the US general adult population[1]
- Patients treated with atezolizumab + bevacizumab reported less worsening in HRQOL[b,c] compared with patients treated with sunitinib

SE, standardized error. Score range, 0-76. Effect size ≥ 0.20 suggests a clinically important difference between arms.
[a] Mean baseline total scores (SD): atezo + bev, 59.8 (9.8) vs sunitinib, 59.5 (9.4). Mean normative FKSI-19 total score for the US general adult population, 59.8.
[b] $P < 0.05$ from repeated-measures model for atezo + bev vs sunitinib at visits until week 72; exception was at week 6.
[c] Average difference in least-squares mean estimates of score changes for atezo + bev vs sunitinib at visits through week 54 was 3.67; mean effect size, 0.42 (range, 0.16, 0.67).
$P < 0.0001$ from linear mixed model of change from baseline to end of treatment; effect size, 0.35. 1. Butt et al. *Cancer*. 2013;119:429-437.

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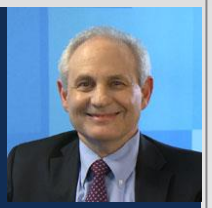
Abstract 579



Safety and efficacy of axitinib in combination with pembrolizumab in patients with advanced renal cell cancer

Michael B Atkins, MD[1], Elizabeth R Plimack, MD[2], Igor Puzanov, MD[3,4], Mayer N Fishman, MD[5], David F McDermott, MD[6], Daniel C Cho, MD[7], Ulka Vaishampayan, MD[8], Saby George, MD[4], Thomas E Olencki, DO[9], Jamal C Tarazi, MD[10], Brad Rosbrook, MS[10], Kathrine C Fernandez, MPH[11], Mariajose Lechuga, MD[12], and Toni K Choueiri, MD[13]

[1]Georgetown-Lombardi Comprehensive Cancer Center, Washington, DC, USA; [2]Fox Chase Cancer Center, Philadelphia, PA, USA; [3]Vanderbilt University Medical Center, Nashville, TN, USA; [4]Roswell Park Cancer Institute, Buffalo, NY, USA; [5]Moffitt Cancer Center, Tampa, FL, USA; [6]Beth Israel Deaconess Medical Center, Boston, MA, USA; [7]NYU Langone Medical Center, New York, NY, USA; [8]Karmanos Cancer Institute, Wayne State University, Detroit, MI, USA; [9]The Ohio State University, Wexner Medical Center, Columbus, OH, USA; [10]Pfizer Oncology, San Diego, CA, USA; [11]Pfizer Oncology, Cambridge, MA, USA; [12]Pfizer S.r.L, Milan, Italy; [13]Dana-Farber Cancer Institute, Boston, MA, USA

PRESENTED AT: **2018 Genitourinary Cancers Symposium | #GU18**

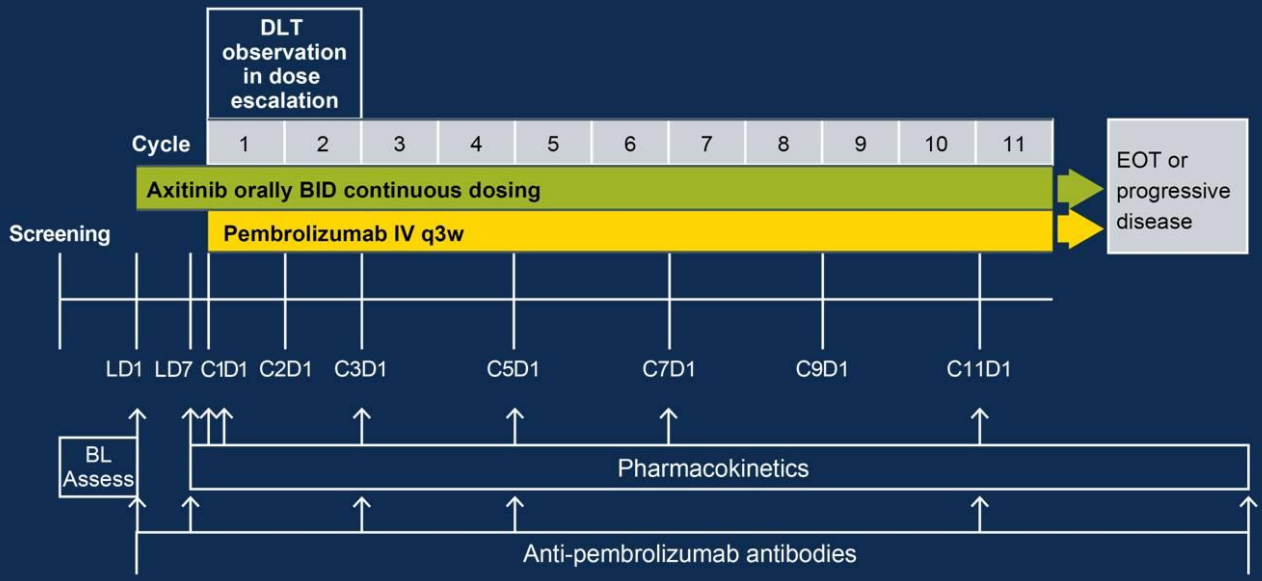
Study Design

Key inclusion criteria

- Clear-cell advanced RCC with primary tumor resected
- Mandatory archival tumor biospecimen
- ≥1 measureable lesion, as defined by RECIST v1.1
- ECOG PS 0 or 1
- Controlled hypertension

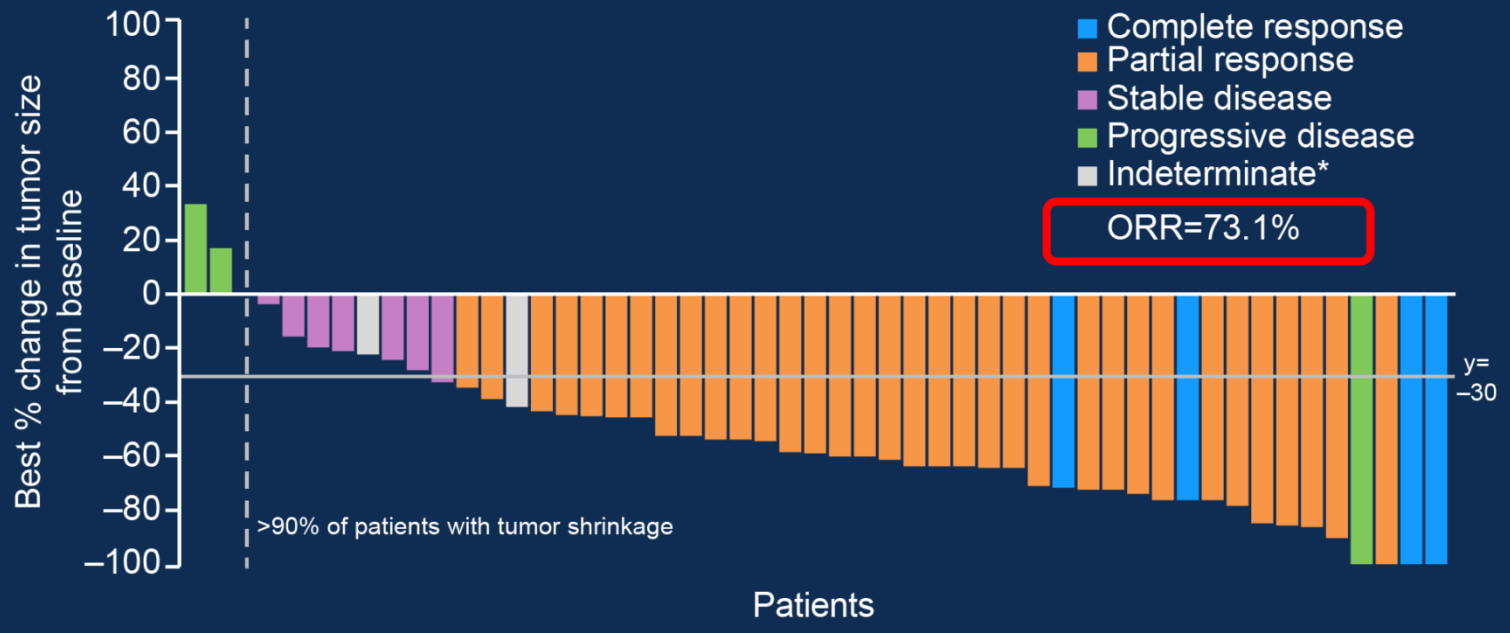
Key exclusion criteria

- Prior systemic therapy for advanced RCC



Arrows indicate dosing.
BID=twice daily; BL assess=baseline assessment; C=cycle; D=day; DLT=dose-limiting toxicity; ECOG PS=Eastern Cooperative Oncology Group performance status; EOT=end of treatment; IV=intravenous; LD1=lead-in Day 1; LD7=lead-in Day 7; q3w=every 3 weeks; RCC=renal cell carcinoma; RECIST=Response Evaluation Criteria in Solid Tumors

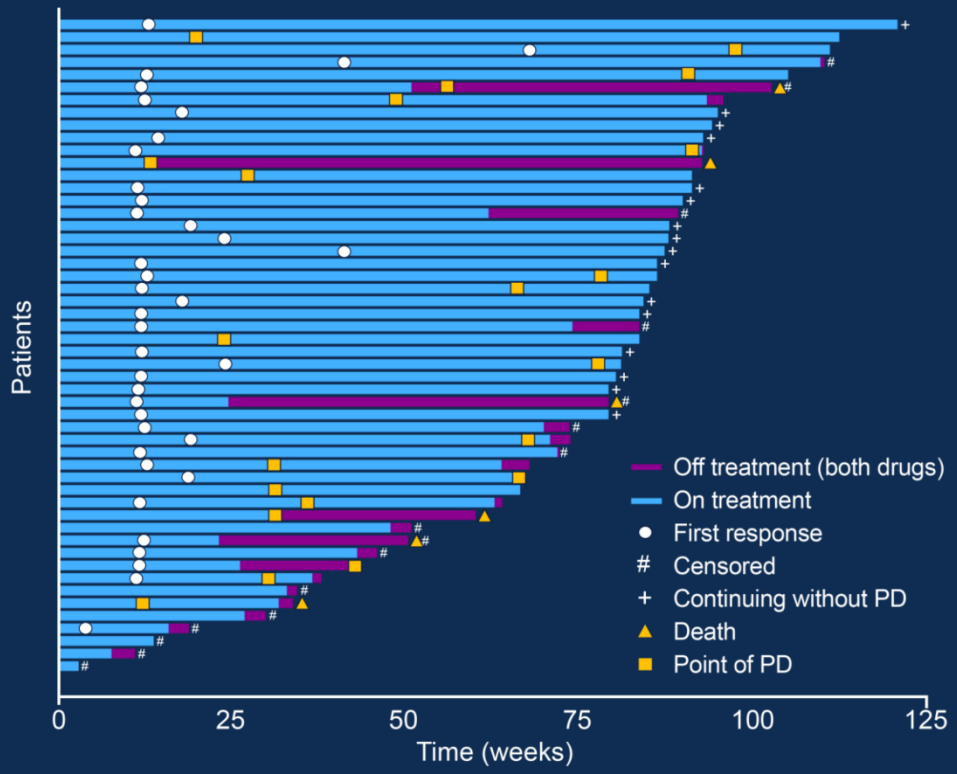
Axitinib + Pembrolizumab



* Stable disease or partial response not confirmed, or no follow-up scans available.
ORR=objective response rate

Axitinib + Pembrolizumab

- Median time to response was 2.8 months (range 0.7–15.2)
- Median duration of tumor response was 18.6 months (95% CI 15.1–not reached)
- Median PFS 20.9 months (95% CI 15.4 – NE)
- Median OS NR



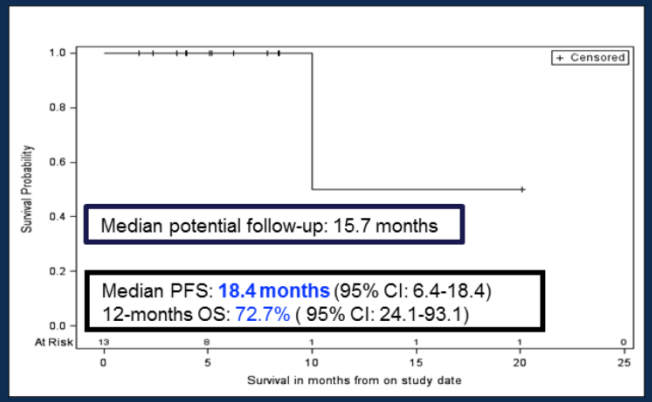
CI=confidence interval; PD=progressive disease

Cabozantinib/Nivolumab +/- Ipilimumab

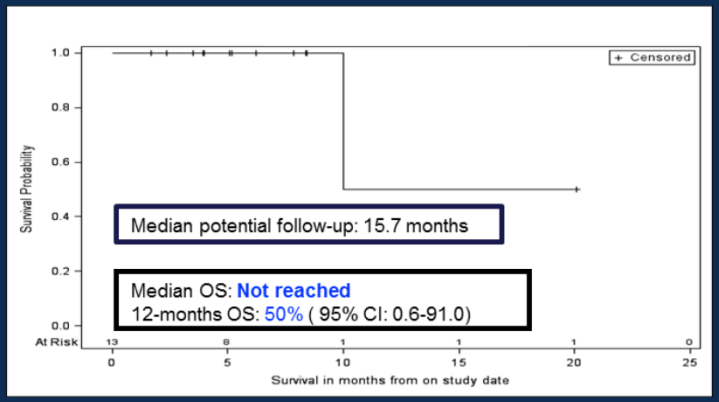
n (%)	Median F/U months	ORR	PR	CR	SD	PR+CR+SD
RCC N=13	5.2	**53.9%** (7/13) (95% CI: 25.1-80.8%)	**53.9%** (7/13) (95% CI: 25.1-80.8%)	0	**46.1%** (6/13) (95% CI: 19.2-74.9%)	**100%** (13/13) (95% CI: 75.3-100.0%)

RCC: Median Duration of Response: 18.4 months (95% CI: 6.4-18.4)

RCC: PFS

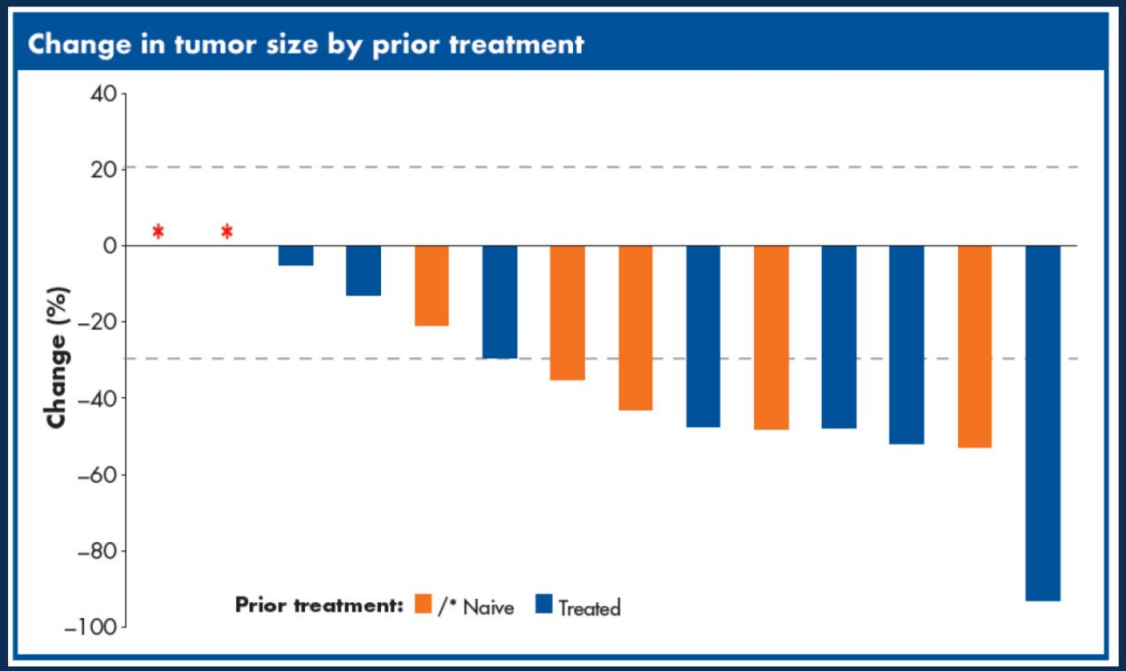


RCC: OS



Nadal R *et al.* ASCO GU 2018

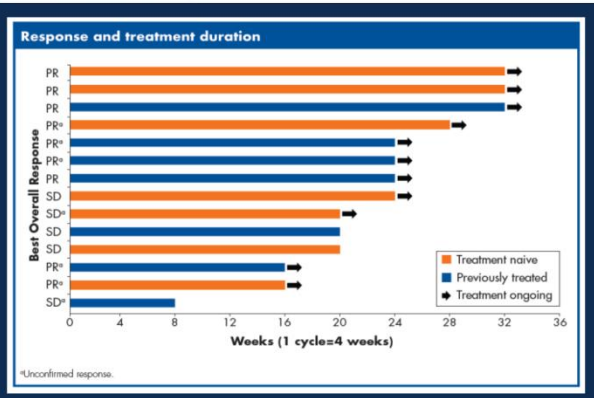
Tivozanib + Nivolumab



Response to treatment in patients receiving the full treatment dose with ≥2 treatment scans

Best overall response, n (%)	Patients (n=14)
CR	0
PR	9 (64.3)[a]
SD	5 (35.7)[b]
Progressive disease	0
Objective response rate (CR + PR)	9/14 (64.3)
Disease control rate (CR + PR + SD)	14/14 (100)

CR, complete response; SD, stable disease.
[a]Includes 5 patients with an unconfirmed response.
[b]Includes 2 patients with an unconfirmed response.



Escudier B *et al.* ASCO GU 2018

JAVELIN Renal 101: Randomized Phase 3 Trial of Avelumab + Axitinib vs Sunitinib as First-Line Treatment of Advanced Renal Cell Carcinoma

Robert J. Motzer,[1] Konstantin Penkov,[2] John Haanen,[3] Brian Rini,[4] Laurence Albiges,[5] Matthew T. Campbell,[6] Christian Kollmannsberger,[7] Sylvie Negrier,[8] Motohide Uemura,[9] Jae Lyun Lee,[10] Howard Gurney,[11] Raanan Berger,[12] Manuela Schmidinger,[13] James Larkin,[14] Michael B. Atkins,[15] Jing Wang,[16] Paul B. Robbins,[17] Aleksander Chudnovsky,[16] Alessandra di Pietro,[18] and Toni K. Choueiri[19]

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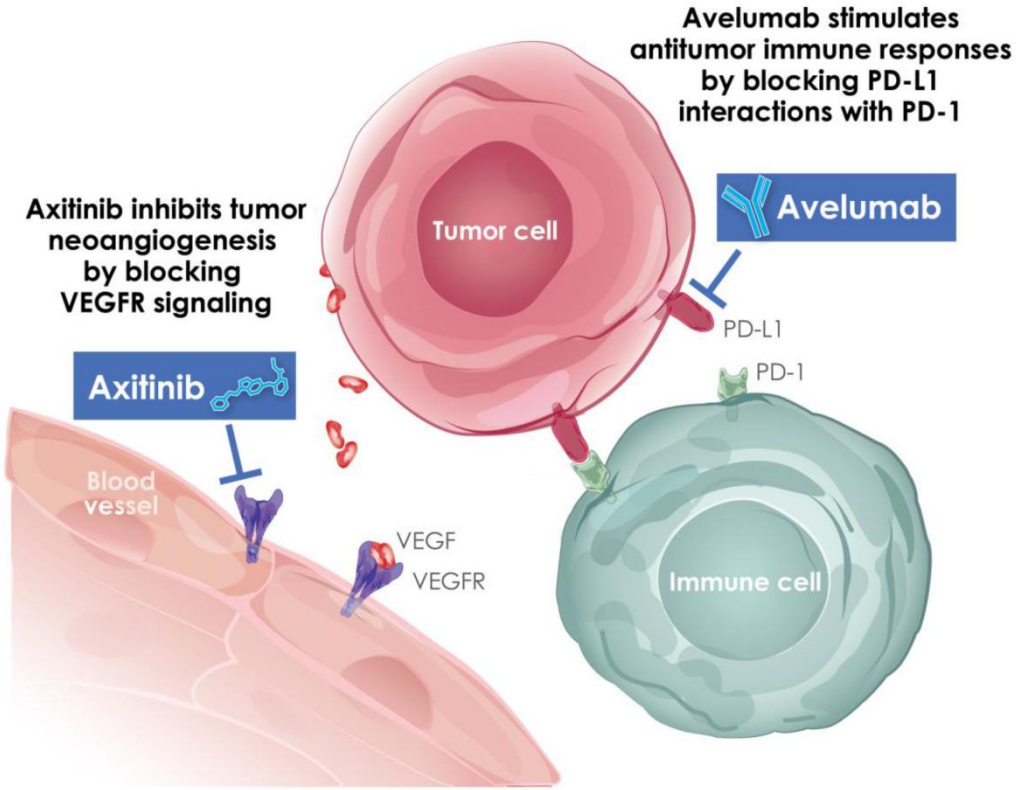
Abstract No. LBA6_PR

esmo.org

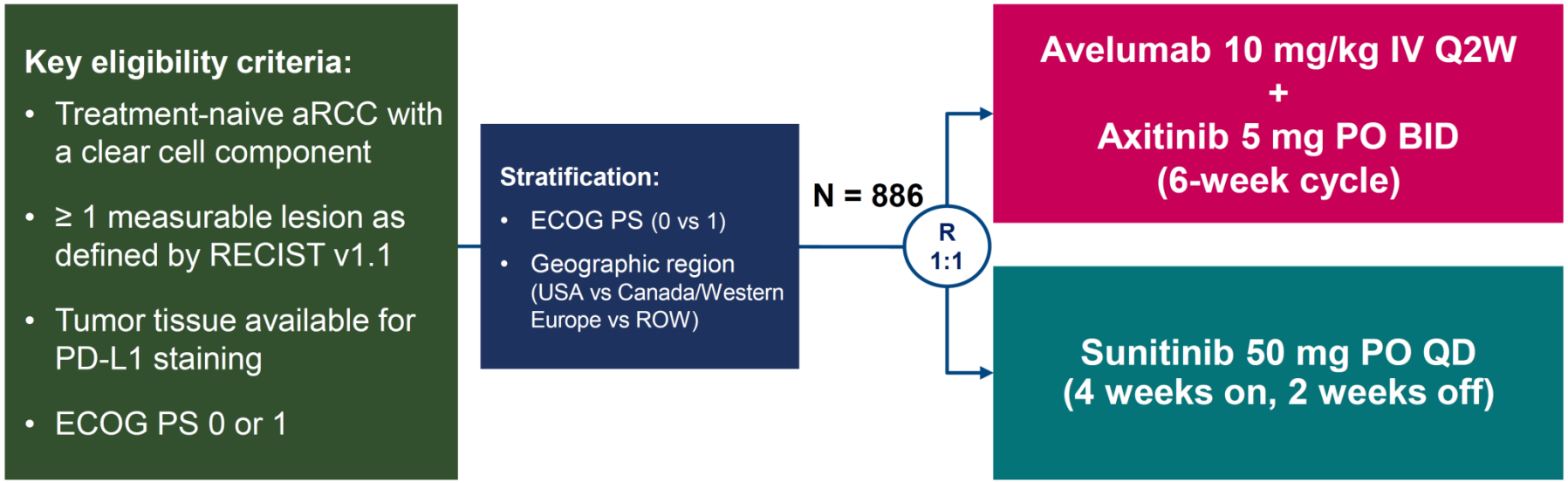
Rationale for combining Avelumab and Axitinib



- In addition to antiangiogenic effects, VEGFR blockade by axitinib has immunomodulatory effects[1]
  - ↑ immune cell tumor infiltration
  - ↓ immune suppressor cells
- Simultaneous inhibition of the PD-1/PD-L1 axis and VEGFR/VEGF had synergistic antitumor effects in preclinical models[2]

1. Roland et al. *PLoS One*. 2009; 2. Yasuda et al. *Clin Exp Immunol*. 2013.

JAVELIN Renal 101: study design



BID, twice per day; **ECOG PS**, Eastern Cooperative Oncology Group performance status; **IV**, intravenous; **PO**, orally; **Q2W**, every 2 weeks; **QD**, once per day; **ROW**, rest of the world.

➢ rel. Risikoreduktion ↓ für Progress/† (39%) [Avelumab + Axitinib]

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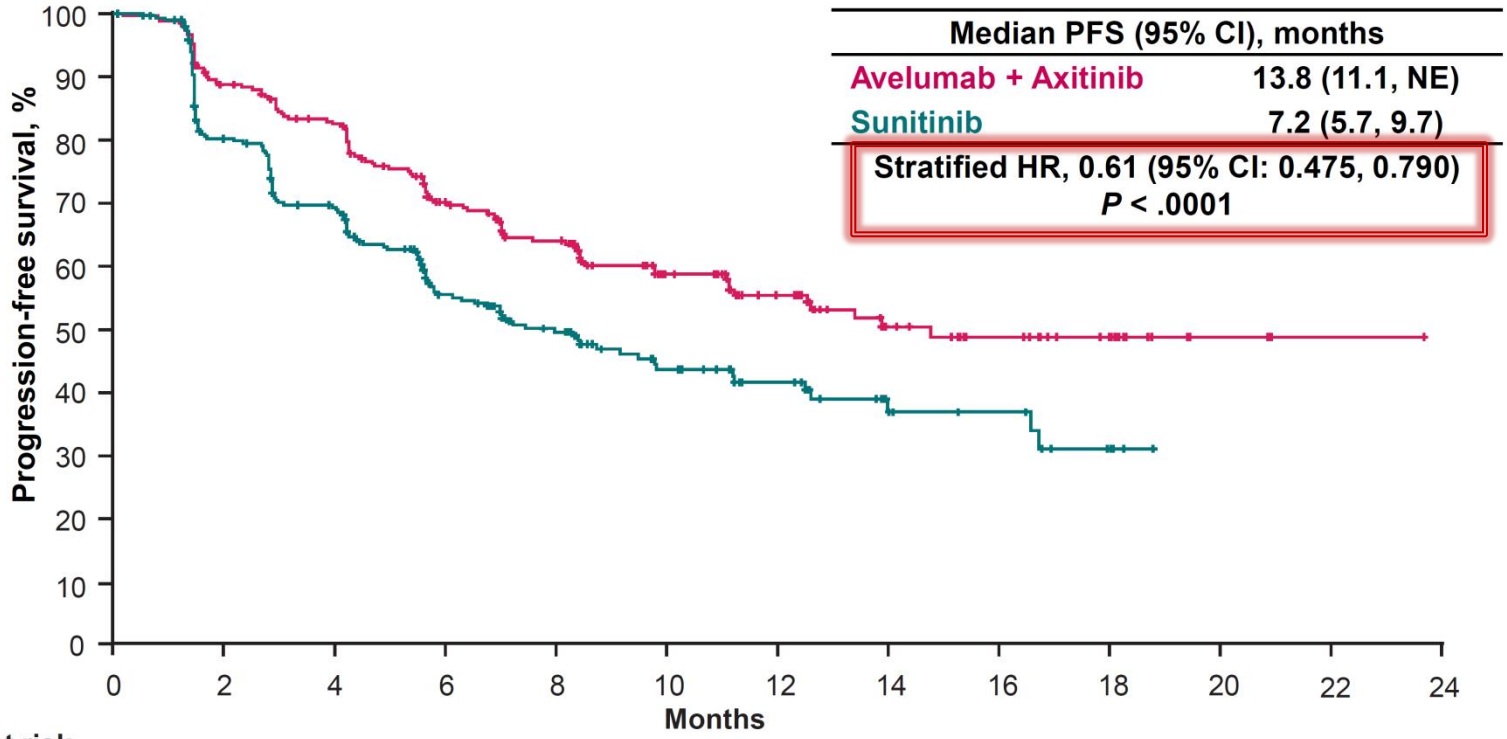
Primary endpoint

PFS per IRC in the PD-L1+ group



Median PFS (95% CI), months	
Avelumab + Axitinib	13.8 (11.1, NE)
Sunitinib	7.2 (5.7, 9.7)

Stratified HR, 0.61 (95% CI: 0.475, 0.790)
P < .0001

Number at risk

Avel + Axit:	270	227	205	154	120	76	53	32	23	13	3	1	0
Sunitinib:	290	210	174	119	85	49	35	16	13	5	0		

Minimum follow-up, 6 months. Median follow-up, 9.9 months (avelumab + axitinib) and 8.4 months (sunitinib).
The PFS analysis crossed the prespecified efficacy boundary based on the alpha-spending function (*P* = .001).

NE, not estimable.

➢ **rel. Risikoreduktion ↓ für Progress/† (31%) [Avelumab + Axitinib]**

→ Benefit unabhängig vom PD-L1-Status

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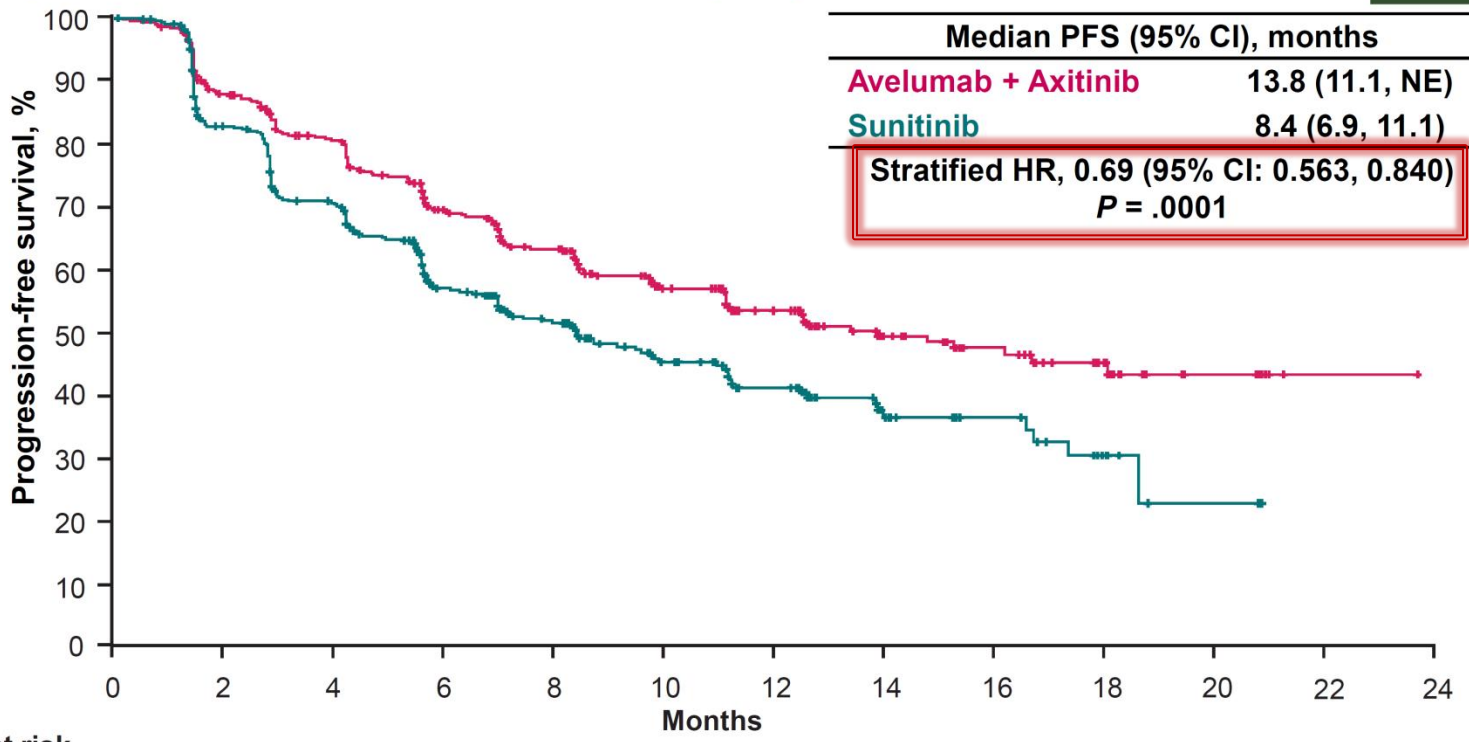
Key secondary endpoint

PFS per IRC in the overall population



Median PFS (95% CI), months	
Avelumab + Axitinib	13.8 (11.1, NE)
Sunitinib	8.4 (6.9, 11.1)

Stratified HR, 0.69 (95% CI: 0.563, 0.840)
P = .0001

Number at risk

Avel + Axit:	442	364	321	250	193	127	94	57	42	24	8	1	0
Sunitinib:	444	329	271	192	144	90	64	29	20	8	2	0	

Minimum follow-up, 6 months. Median follow-up, 10.8 months (avelumab + axitinib) and 8.6 months (sunitinib).
The PFS analysis crossed the prespecified efficacy boundary based on the alpha-spending function (*P* = .001).

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Secondary endpoint

Confirmed objective response

Per IRC	PD-L1+ group (N = 560)		Overall population (N = 886)	
	Avelumab + Axitinib (N = 270)	Sunitinib (N = 290)	Avelumab + Axitinib (N = 442)	Sunitinib (N = 444)
Objective response rate (95% CI), %	**55 (49.0, 61.2)**	**26 (20.6, 30.9)**	**51 (46.6, 56.1)**	**26 (21.7, 30.0)**
Best overall response, %*				
Complete response	4	2	3	2
Partial response	51	23	48	24
Stable disease	27	43	30	46
Progressive disease	11	22	12	19
Not evaluable†	4	7	6	8
Patients with ongoing response, %‡	73	65	70	71
Per investigator assessment				
Objective response rate (95% CI), %	**62 (55.8, 67.7)**	**30 (24.5, 35.3)**	**56 (51.1, 60.6)**	**30 (25.9, 34.7)**
Best overall response, %				
Complete response	4	3	3	2
Partial response	58	27	53	28

Median duration of response was not yet reached in either treatment arm in either population.

* Patients without target lesions at baseline per IRC who achieved non-complete response/non-progressive disease: 3% (avelumab + axitinib) and 2% (sunitinib) in the PD-L1+ group; 2% (avelumab + axitinib) and 2% (sunitinib) in the overall population. † Including patients with no postbaseline assessments. ‡ In patients with confirmed complete or partial response.

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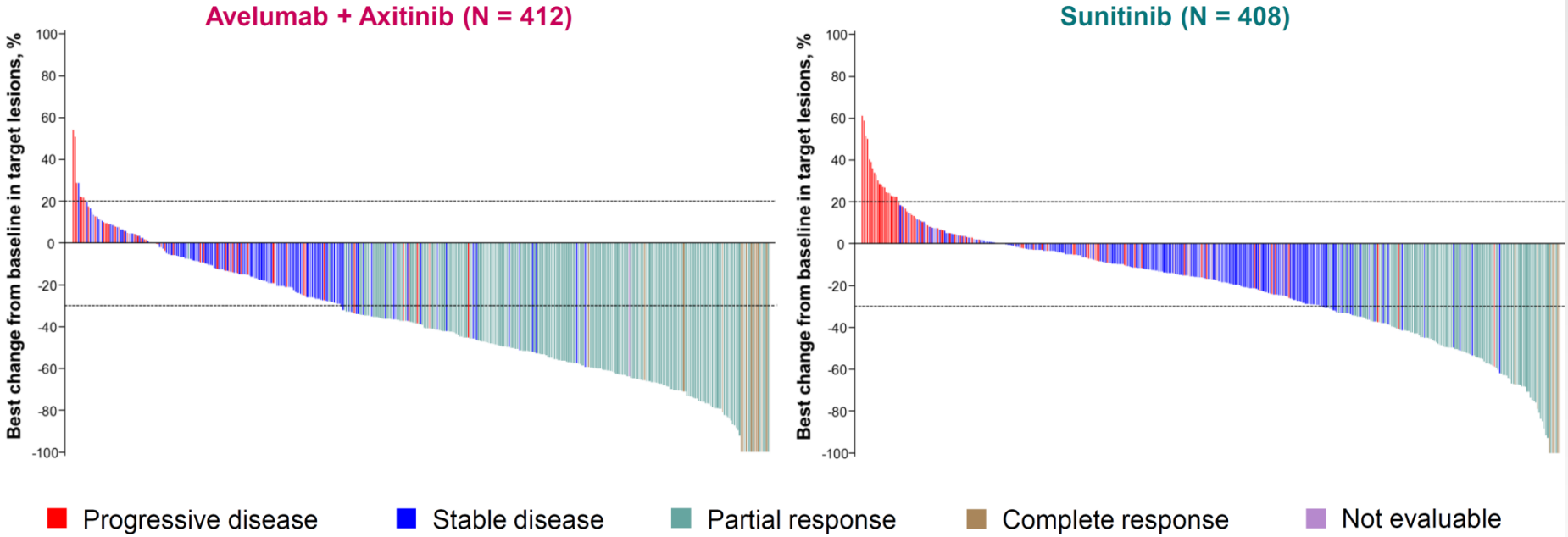
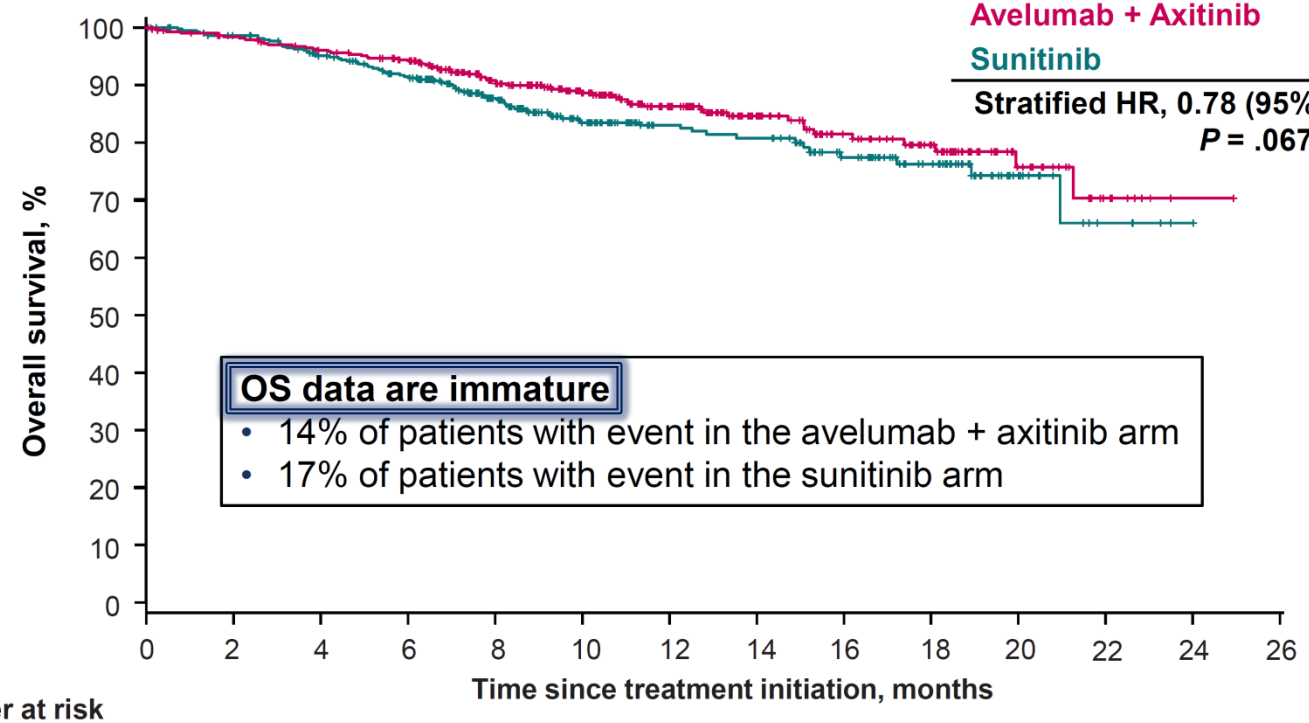
Percent change in target lesions in the overall population



OS in the overall population

Median OS (95% CI), months	
Avelumab + Axitinib	Not reached
Sunitinib	Not reached

Stratified HR, 0.78 (95% CI: 0.554, 1.084)
P = .0679



OS data are immature
- 14% of patients with event in the avelumab + axitinib arm
- 17% of patients with event in the sunitinib arm

Number at risk

Avel + Axit:	442	426	412	396	319	252	187	121	93	70	27	8	1	0
Sunitinib:	444	426	401	373	295	224	175	113	84	59	17	5	1	0

Median follow-up, 12.0 months (avelumab + axitinib) and 11.5 months (sunitinib).

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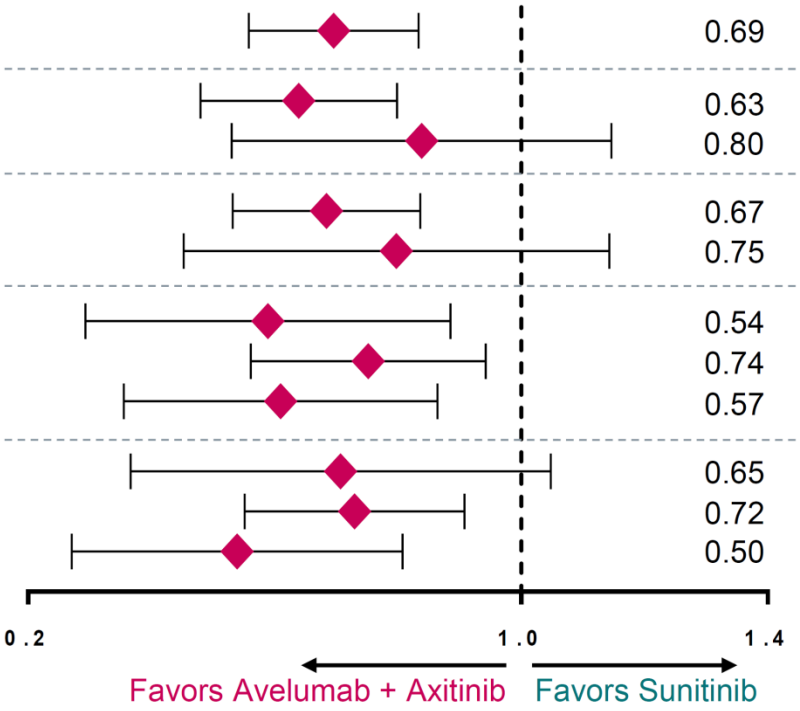
Subgroup analysis

PFS per IRC in key subgroups

Subgroup		Events/patient: Avelumab + Axitinib	Events/patient: Sunitinib	HR
Overall population		180/442	216/444	0.69
PD-L1 group*	Positive	108/270	145/290	0.63
	Negative	54/132	58/120	0.80
Prior nephrectomy	Yes	143/352	172/355	0.67
	No	37/90	44/89	0.75
IMDC risk	Favorable	25/94	36/96	0.54
	Intermediate	112/271	129/276	0.74
	Poor	41/72	50/71	0.57
MSKCC risk	Favorable	29/96	36/100	0.65
	Intermediate	118/283	142/293	0.72
	Poor	29/51	34/45	0.50



* Among patients not evaluable for PD-L1 expression, PFS events occurred in 18/40 patients (avelumab + axitinib) vs 13/34 patients (sunitinib); HR, 0.83; 95% CI: 0.403, 1.699.

Secondary endpoint

TRAEs in all treated patients (N = 873)

	Avelumab + Axitinib (N = 434)		Sunitinib (N = 439)	
	All grades	Grade 3 (4)	All grades	Grade 3 (4)
All TRAEs, %	**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)
Hand-foot syndrome	33	6 (0)	34	4 (0)
Dysphonia	27	1 (0)	3	0 (0)
Nausea	25	1 (0)	34	1 (0)
Hypothyroidism	24	< 1 (0)	13	< 1 (0)
Stomatitis	22	2 (0)	23	1 (0)
Decreased appetite	20	2 (0)	26	1 (0)
Dysgeusia	13	0 (0)	32	0 (0)
Increased alanine aminotransferase	13	4 (1)	10	2 (0)
Thrombocytopenia	3	< 1 (0)	18	5 (1)
Anemia	2	< 1 (0)	17	5 (< 1)
Neutropenia	1	< 1 (0)	18	7 (1)
TRAEs leading to discontinuation of all study drugs, %*	**4**		**8**	
TRAEs leading to death, %†	**1**		**< 1**	

Treatment-related adverse events (**TRAEs**) of any grade occurring in ≥ 20% of patients or grade 3-4 in ≥ 3% of patients are shown. * No events occurred in ≥ 1% of patients. † Grade 5 events occurred in 3 patients in the avelumab + axitinib arm (myocarditis, necrotizing pancreatitis, sudden death; n = 1 each); in 1 patient in the sunitinib arm (intestinal perforation).

➢ **Stand der Dinge 01/2019 (mRCC):**

Systemic first-line treatment of ccRCC

Good risk	Intermediate risk	Poor risk
Standard: Sunitinib [I, A] Pazopanib [I, A] Bevacizumab + IFN [I, A] Tivozanib [II, A] **Option:** High-dose IL2 [III, B] Bevacizumab + low-dose IFN [III, B]	**Standard:** Nivolumab + ipilimumab [I, A] **Option:** Cabozantinib [II, A] Sunitinib [I, B] Pazopanib, [I, B] Tivozanib [II, B] Bevacizumab + IFN [II,C]	**Standard:** Nivolumab + ipilimumab [I, A] **Option:** Cabozantinib [II, B] Sunitinib [II, C] Pazopanib, [II, C] Temsirolimus [I, C]

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

➢ die (nähere) 1.-Linien-Zukunft (mRCC):

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Table 3. Ongoing phase III trials in the first-line treatment setting in patients with advanced or metastatic renal cell carcinoma

Trial (Clinicaltrials.gov Identifier)	MOA	Agents	Comparator arm	Primary data expected	Primary endpoint(s)	Estimated/ actual enrollment (*n*)
KEYNOTE-426 (NCT02853331)	PD-1 inhibitor + TKI	Pembrolizumab + axitinib	Sunitinib	January 2020	PFS and OS	862
CLEAR (NCT02811861)	PD-1 inhibitor + TKI *or* TKI + mTOR inhibitor	Pembrolizumab + lenvatinib or lenvatinib + everolimus	Sunitinib	October 2019	PFS	735
CheckMate 9ER (NCT03141177)	PD-1 inhibitor + TKI	Nivolumab + cabozantinib	Sunitinib	September 2019	PFS	630
IMmotion151 (NCT02420821)	PD-L1 inhibitor + anti-VEGF mAb	Atezolizumab + bevacizumab	Sunitinib	PFS reported February 2018 [87]; OS data awaited	PFS in pts with detectable PD-L1; OS in ITT pts	915
JAVELIN Renal 101 (NCT02684006)	PD-L1 inhibitor + TKI	Avelumab + axitinib	Sunitinib	December 2018	PFS in PD-L1+ pts; OS in PD-L1+ pts	830

Abbreviations: ITT, intention-to-treat; mAb, monoclonal antibody; MOA, mechanism of action; mTOR, mammalian target of rapamycin; OS, overall survival; PD-1, programmed death-1; PD-L1, programmed death-ligand 1; PFS, progression-free survival; pts, patients; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor.

Herzlichen Dank für ihre Aufmerksamkeit!

Calvo E *et al.* The Oncologist 2018