ESCOLA DE MEDICINA

PUCRS

Immunotherapy in Renal Cell Carcinoma

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DANA-FARBER CANCER INSTITUTE

HARVARD MEDICAL SCHOOL

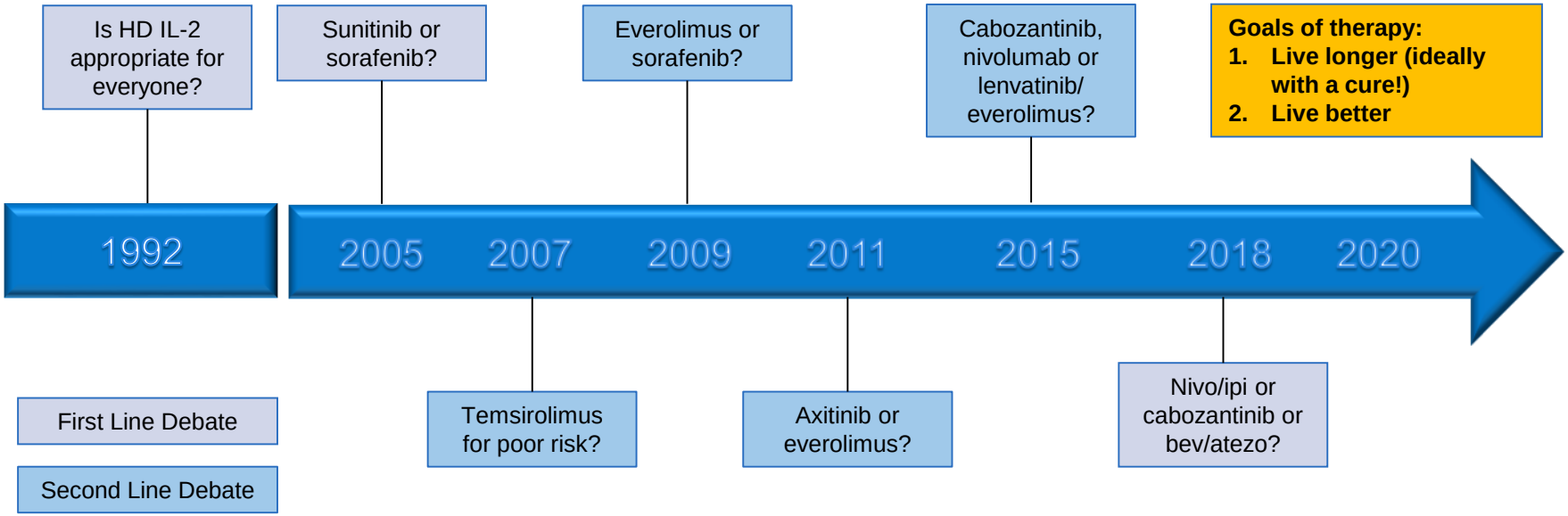
Disclosure

- Honoraria: Pfizer, BMS, Novartis, Roche, AstraZeneca, MSD
- Scientific Advisory Board: Janssen, Novartis, Roche, Pfizer
- Research Grant: CAPES – CNPq, BMS, AstraZeneca, MSD, Roche, Pfizer

Ten FDA-Approved Drugs for RCC Since 2005

Approval	Agent	FDA Indication
2005	**Sorafenib**	Advanced
2006	**Sunitinib**	Advanced
2007	Temsirolimus	Advanced
2009	Bevacizumab + IFN-α	Metastatic
2009	Everolimus	After failure of sunitinib or sorafenib
2009	**Pazopanib**	Advanced
2012	**Axitinib**	Failure of prior systemic therapy
2015	Nivolumab	After failure of anti-angiogenic drug(s)
2016	**Cabozantinib**	Prior anti-angiogenic therapy
2016	**Lenvatinib** (+ everolimus)	Following 1 prior anti-angiogenic therapy

Debates in RCC Therapy



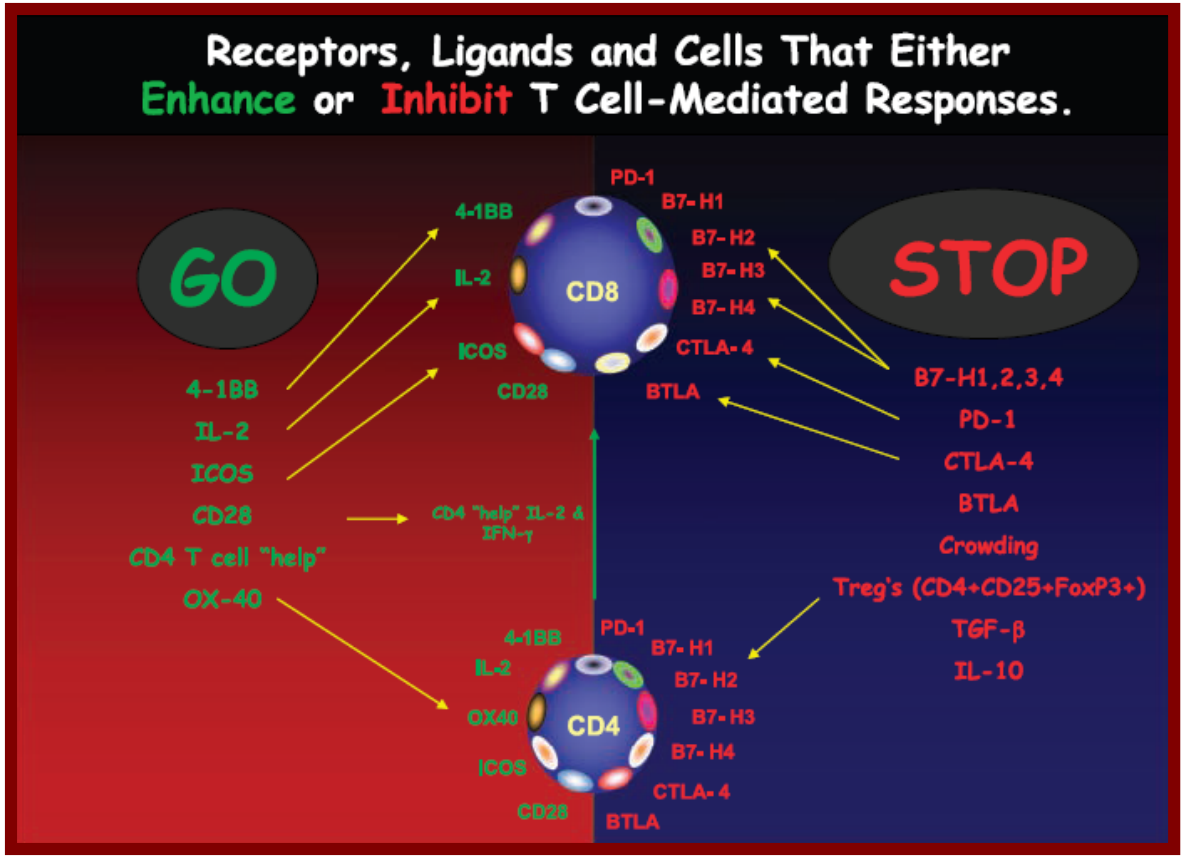
2013


Science
Breakthrough of the Year
Cancer Immunotherapy
AAAS

2014


OUTLOOK
Haemophilia
nature
THE INTERNATIONAL WEEKLY JOURNAL OF SCIENCE
Antitumour immunity enhanced by inhibiting PD-L1/PD-1 and identifying mutant neo-antigens
IMMUNE-CHECKPOINT BLOCKADE IN CANCER
PEER REVIEW
ACCEPT YOUR OWN PAPER
How some scientists are duping the system
PAGE 480
MICROSCOPY
THE CASE FOR AIMING HIGHER
Atomic resolution is there for the taking
PAGE 487
ENERGY
'NIGHT-TIME' COOLING BY DAY
New materials enable radiative cooling in sunlight
PAGE 540
NATURE.COM/NATURE
27 November 2014 £10
Vol. 515, No. 7528

Regulators of Immunity = Immune Checkpoints



Thompson ,Clin Cancer Res 2007;13:709s-715s

The NEW ENGLAND JOURNAL of MEDICINE

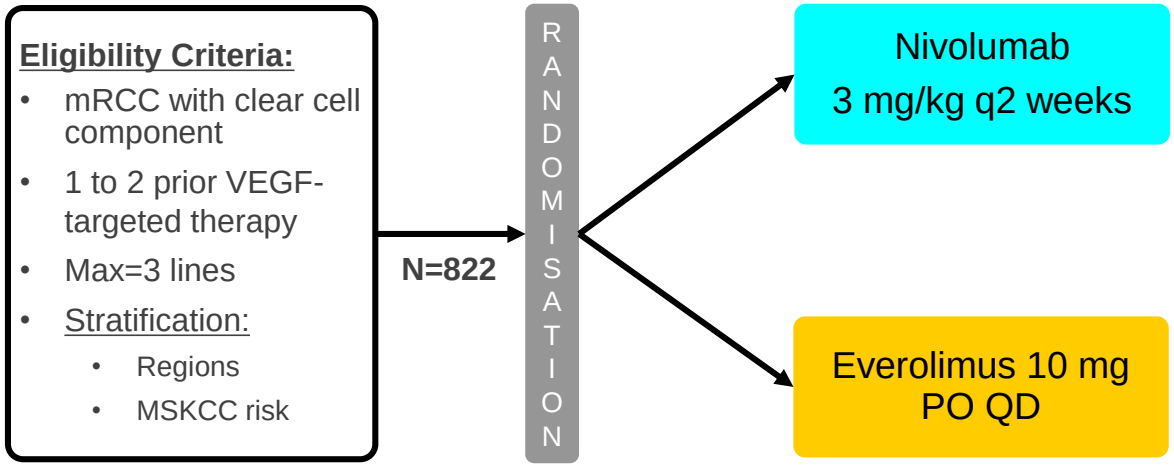
ORIGINAL ARTICLE

Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma

R.J. Motzer, B. Escudier, D.F. McDermott, S. George, H.J. Hammers, S. Srinivas, S.S. Tykodi, J.A. Sosman, G. Procopio, E.R. Plimack, D. Castellano, T.K. Choueiri, H. Gurney, F. Donskov, P. Bono, J. Wagstaff, T.C. Gauler, T. Ueda, Y. Tomita, F.A. Schutz, C. Kollmannsberger, J. Larkin, A. Ravaud, J.S. Simon, L.-A. Xu, I.M. Waxman, and P. Sharma, for the CheckMate 025 Investigators*

N. Engl J Med, Sep 2015

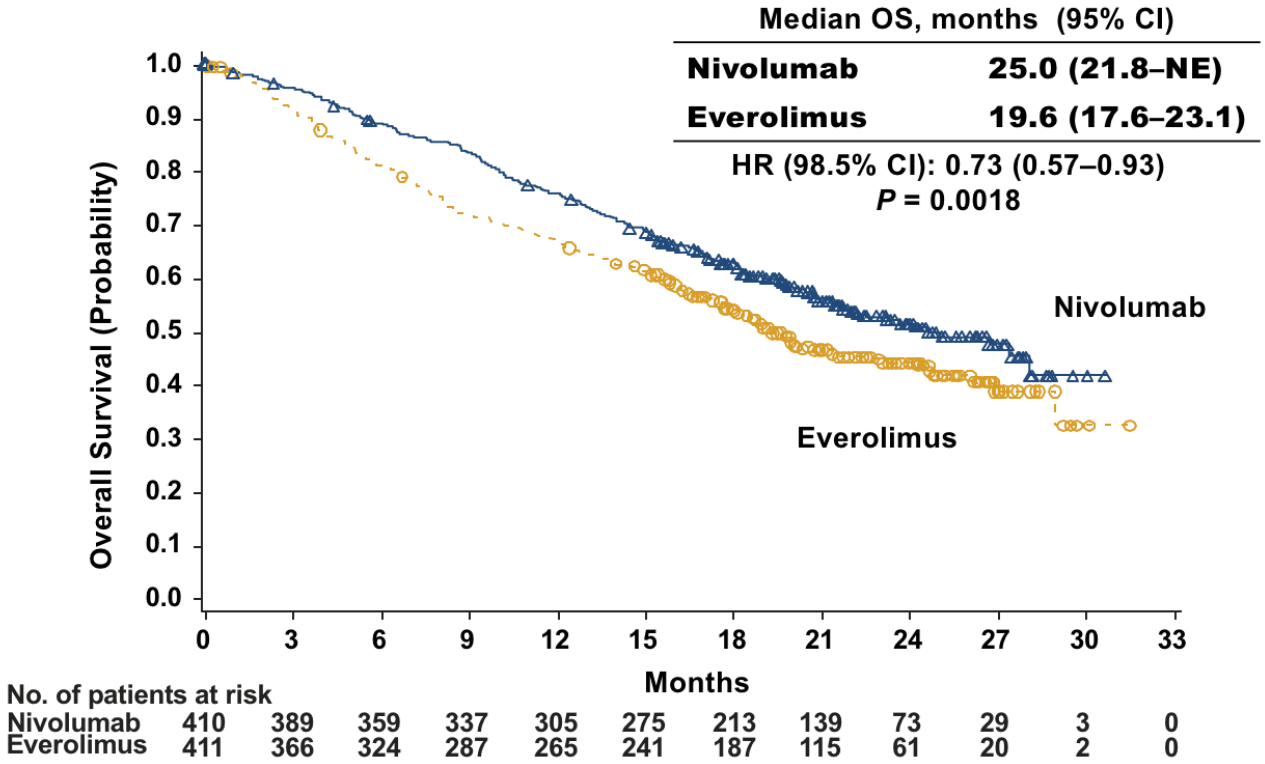
Phase III Nivolumab vs. Everolimus: Checkmate 025



- Primary endpoint: OS
- Secondary endpoints: PFS, ORR, duration of response, OS in relation to PDL-1 status, safety, patients-reported outcomes

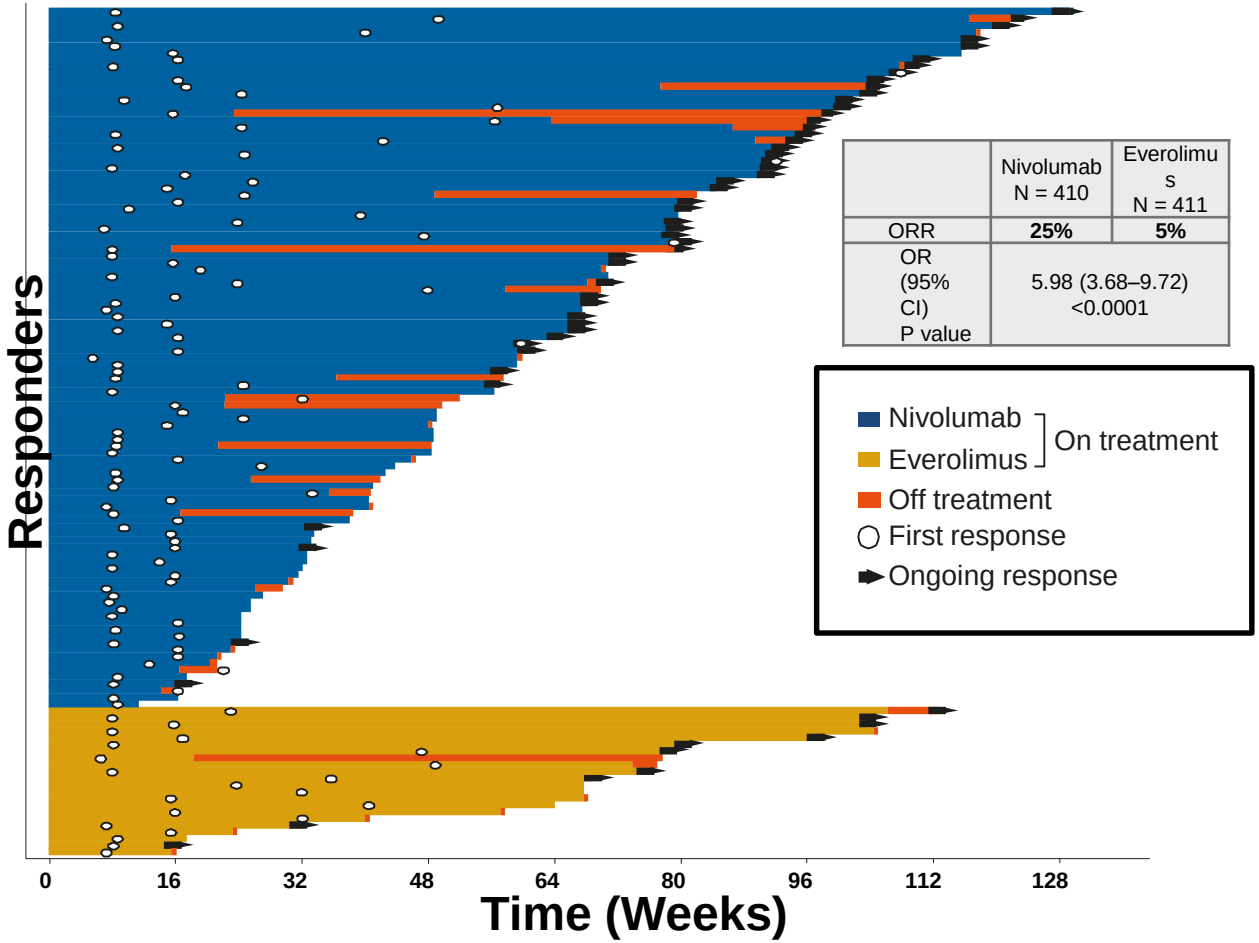
www.clinicaltrials.gov (NCT01668784)

Overall survival



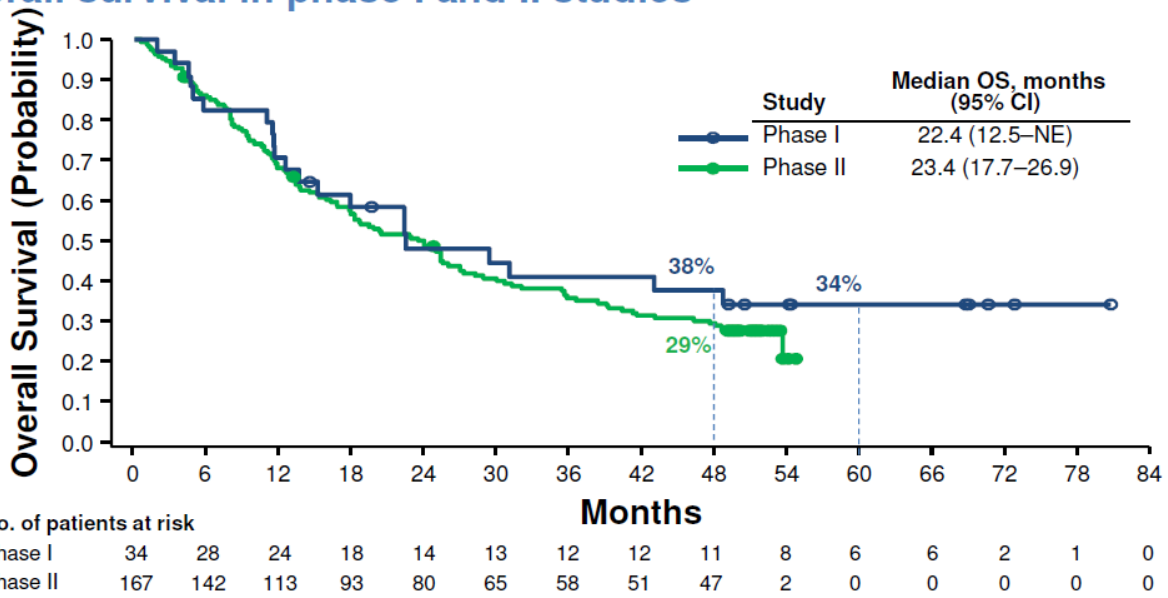
Minimum follow-up was 14 months.

NE, not estimable.


Responders
Time (Weeks)
0
16
32
48
64
80
96
112
128
Nivolumab N = 410
Everolimus N = 411
ORR
25%
5%
OR (95% CI) P value
5.98 (3.68–9.72) <0.0001
Nivolumab
Everolimus
On treatment
Off treatment
First response
Ongoing response

Update from ASCO 2016

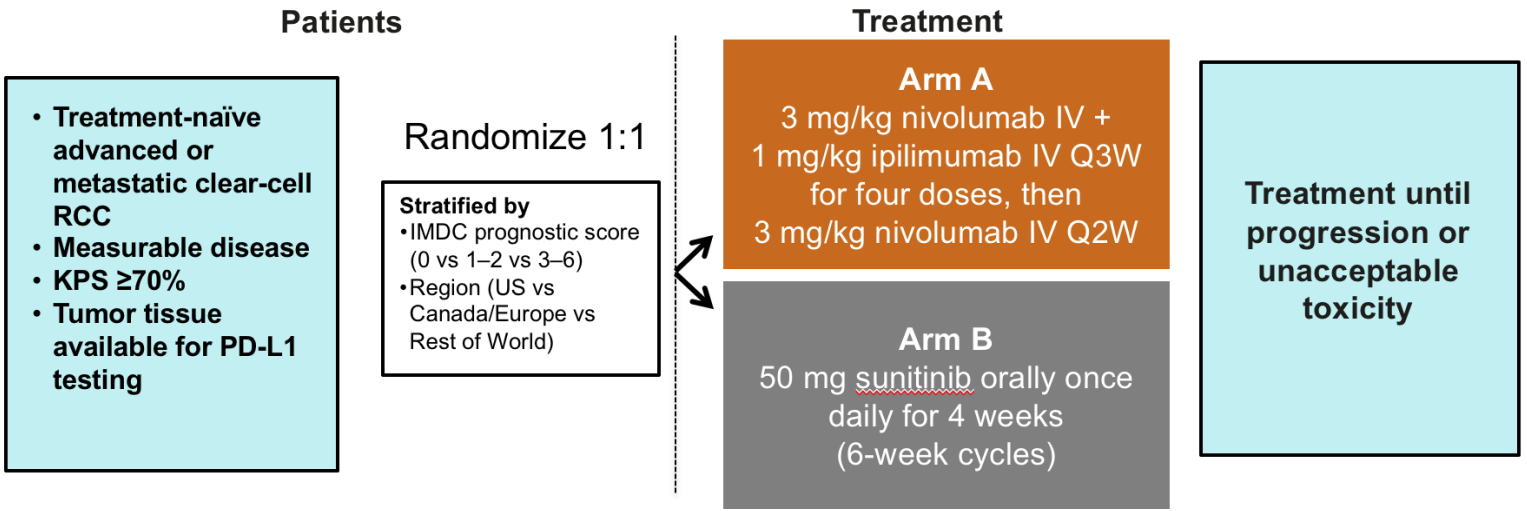
Overall survival in phase I and II studies



- In phase I and II studies, minimum follow-up was 50.5 months and 49.2 months, respectively

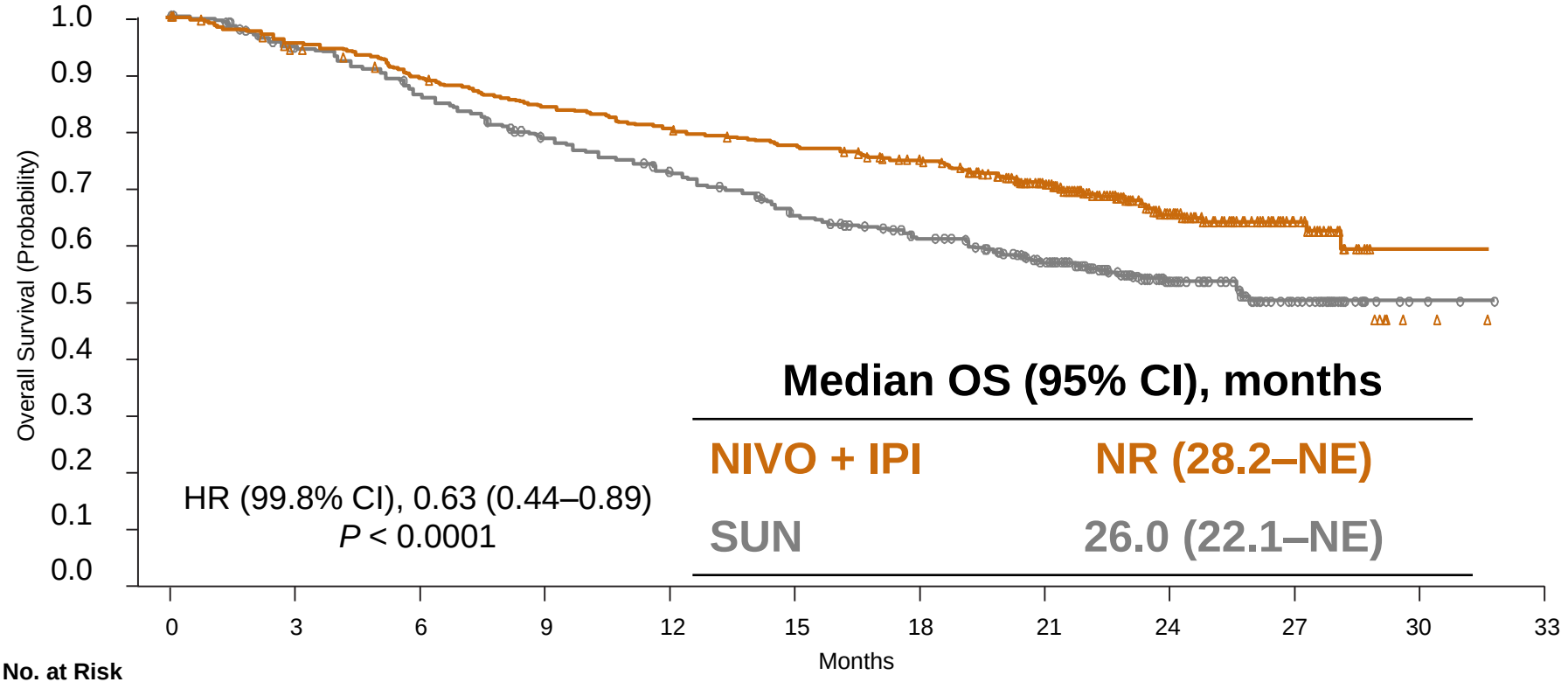
NE, not estimable.

CheckMate 214: Study design



Escudier et al ESMO 2017

Nivo/IPI vs Sunitinib OS: IMDC intermediate/poor risk



No. at Risk												
NIVO + IPI	425	399	372	348	332	318	300	241	119	44	2	0
SUN	422	387	352	315	288	253	225	179	89	34	2	0

ESMO 2017

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

Escudier et al ESMO 2017

Patient disposition: All treated patients

	NIVO + IPI N = 547	SUN N = 535
Treatment discontinuation, %	77	82
Reasons for treatment discontinuation, %		
Disease progression	42	55
Study drug toxicity	**24**	**12**
Adverse event unrelated to study drug	6	6
Other	4	9
Median duration of therapy (95% CI), months	7.9 (6.5–8.4)	7.8 (6.4–8.5)
Median doses received (range), no.		
Nivolumab	14 (1–63)	NA
Ipilimumab	4 (1–4)	NA
Median daily dose (range), mg/day	NA	31 (14–50)

- In the NIVO + IPI arm, 79% of patients received all four doses of IPI
- Median follow-up was 25.2 months

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
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]**	

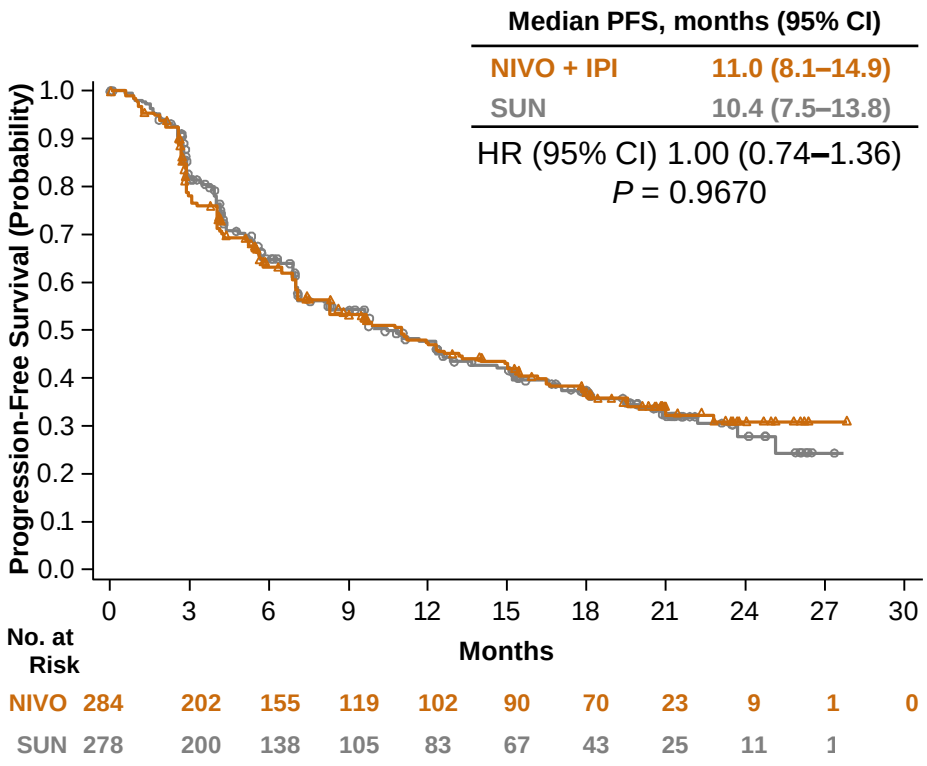
60% of patients treated with NIVO + IPI required systemic corticosteroids for an adverse event

[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

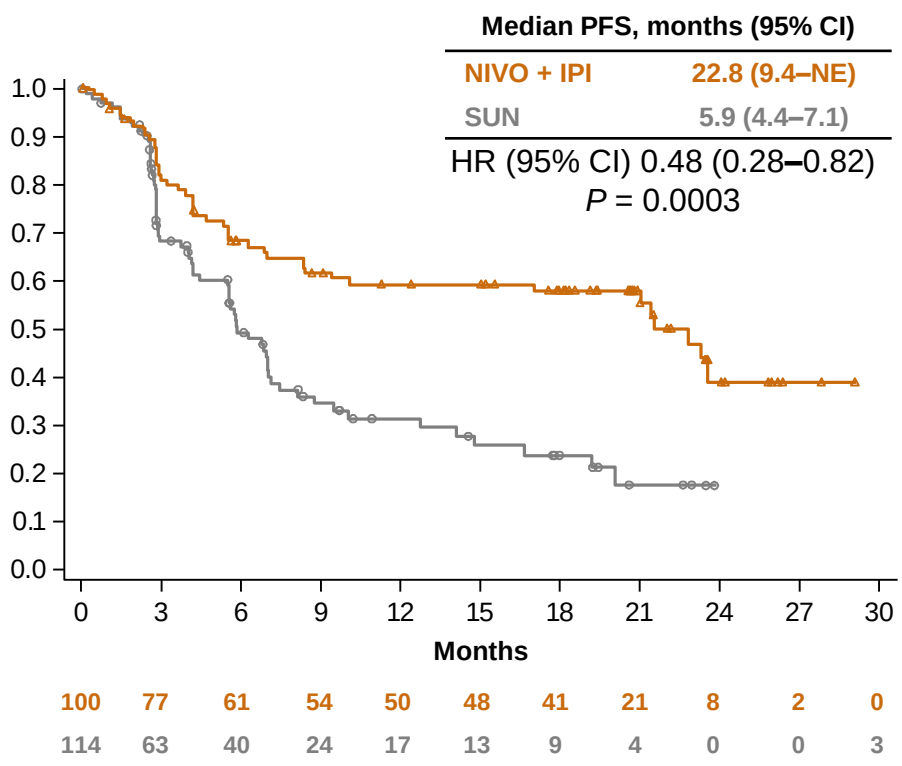
Exploratory endpoint

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

PD-L1 <1% (n = 562)



PD-L1 ≥1% (n = 214)

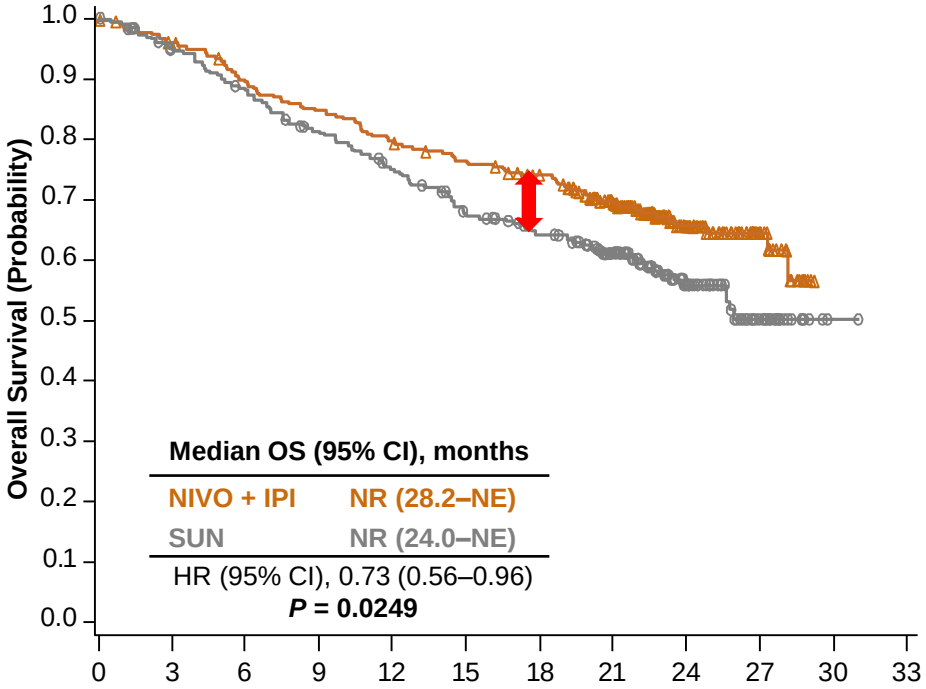


OS by tumor PD-L1 expression:

IMDC intermediate/poor risk

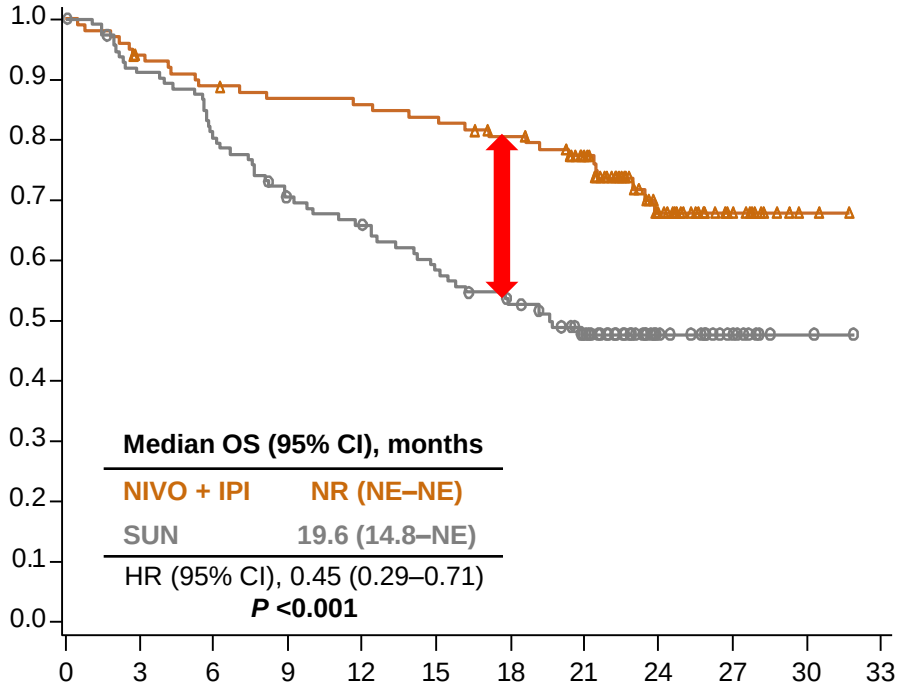
Motzer et al SITC 2017

PD-L1 <1% (n = 562)



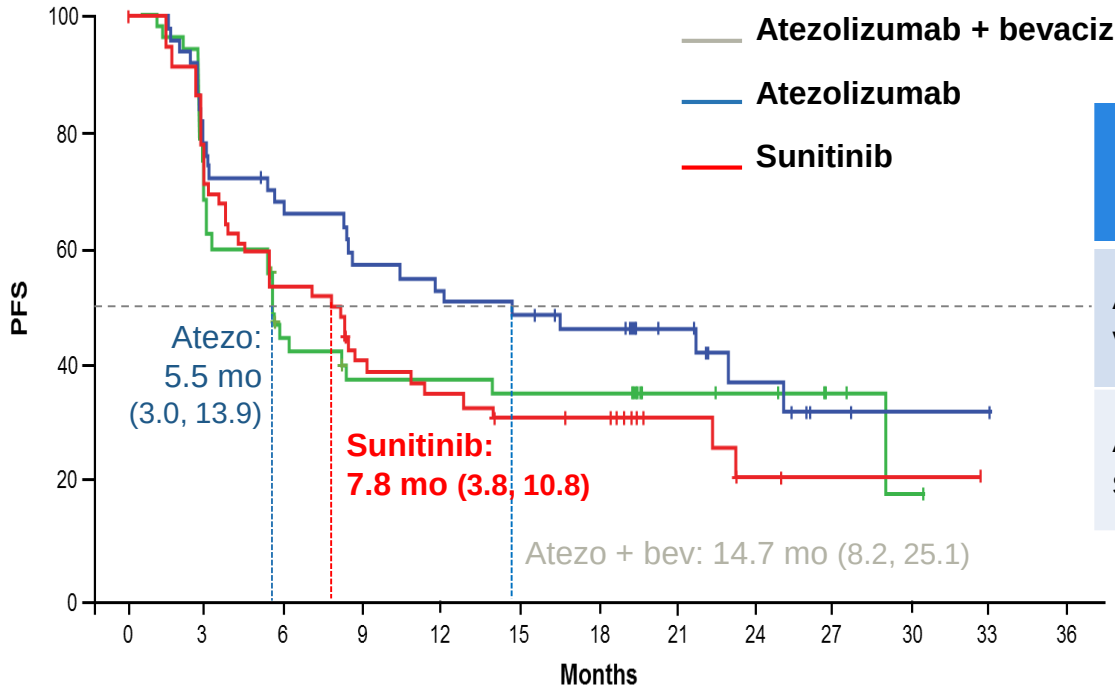
No. at Risk	Months					
NIVO + IPI	284	251	223	200	76	0
SUN	278	239	198	157	61	1

PD-L1 ≥1% (n = 214)



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

Phase 2 Trial of Atezo/Bev vs Sunitinib: PFS ≥ *1% of IC Expressing PD-L1*



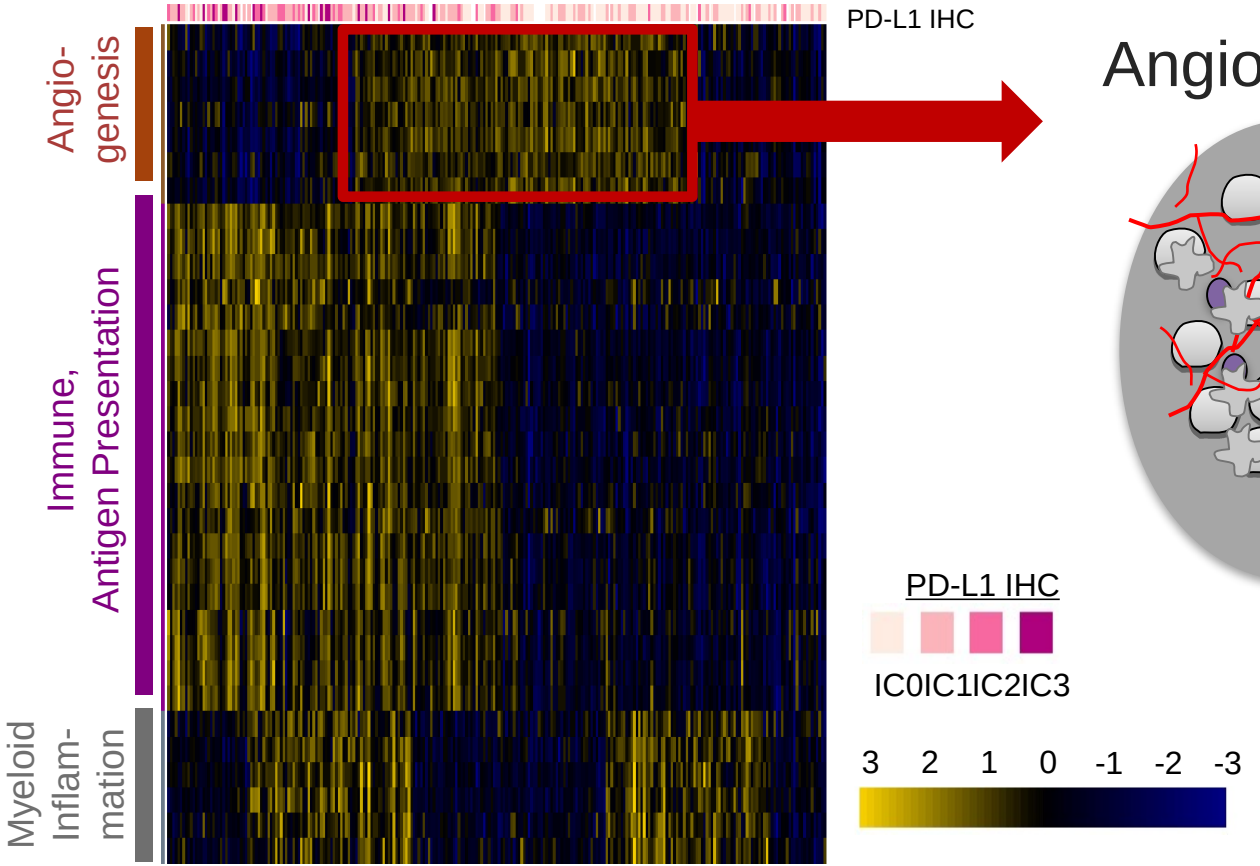
	Stratified HR (95% CI)	*P* Value[a]
Atezo + bev vs sunitinib	**0.64 (0.38, 1.08)**	0.095
Atezo vs sunitinib	**1.03 (0.63, 1.67)**	0.917

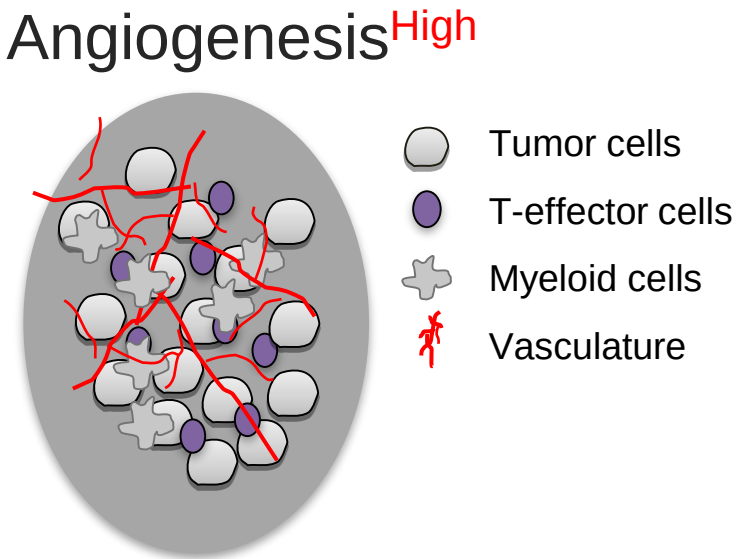
[a] *P* values are for descriptive purposes only and not adjusted for multiple comparisons.

GU ASCO, 2017

AACR 2017

Transcriptome Map of Angiogenesis and Immune-Associated Genes in RCC Tumors

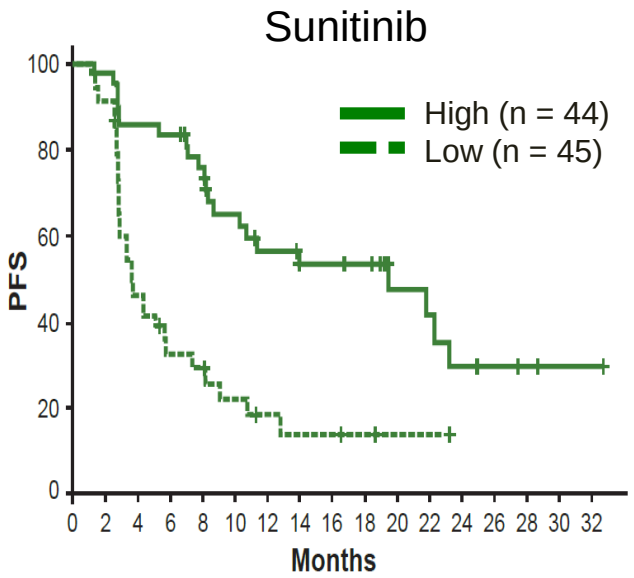


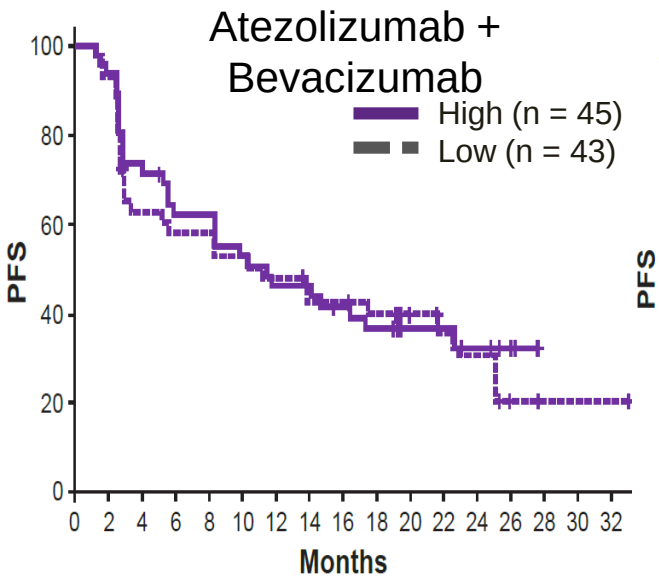


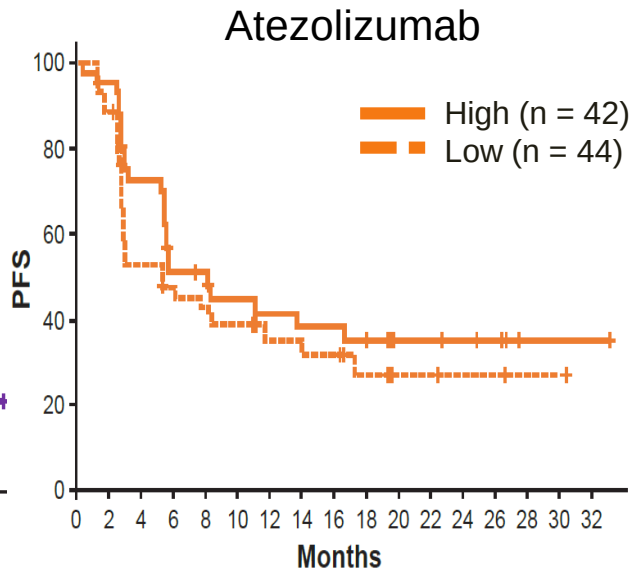
Brauer, *Clin Cancer Res.* 2012; Herbst, *Nature* 2014; Powles, *SITC* 2015; Fehrenbacher, *Lancet* 2016.

AACR 2017

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







Sunitinib		
	HR	95% CI
Angiogenesis (High vs Low)	0.31	(0.18, 0.55)

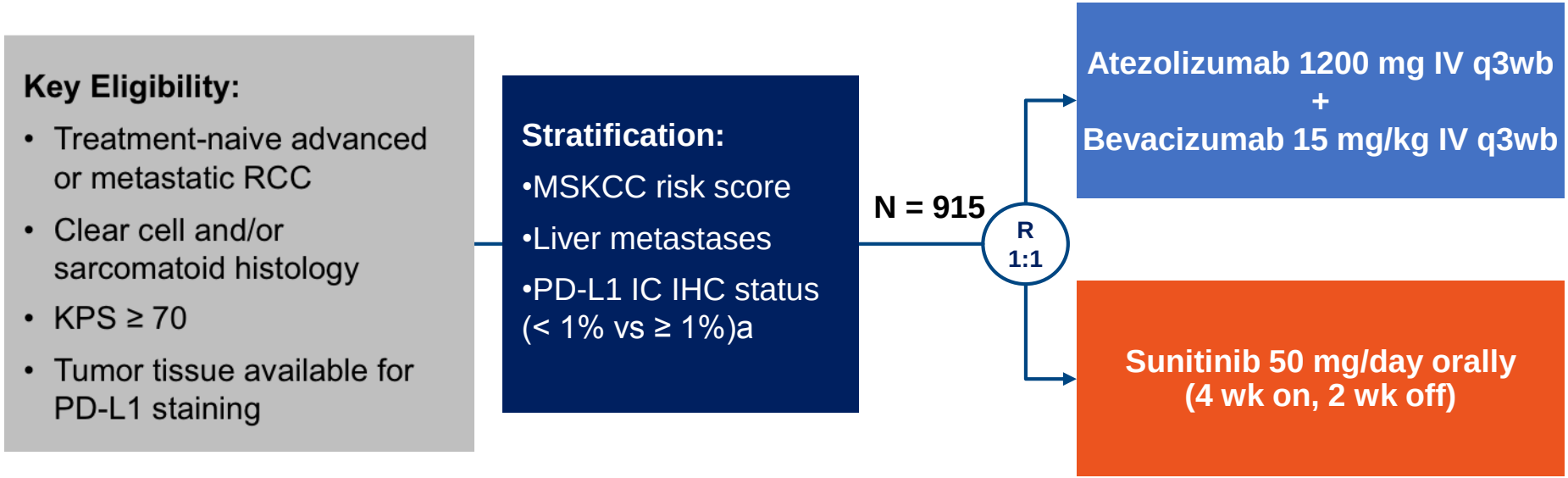
Atezolizumab + Bevacizumab		
	HR	95% CI
Angiogenesis (High vs Low)	0.90	(0.54, 1.51)

Atezolizumab		
	HR	95% CI
Angiogenesis (High vs Low)	0.74	(0.42, 1.28)

- Angiogenesis gene signature: *VEGFA, KDR, ESM1, PECAM1, ANGPTL4, CD34*.
- Angiogenesis High: ≥ median expression, Angiogenesis Low: < median expression.

AACR 2017

Study Design

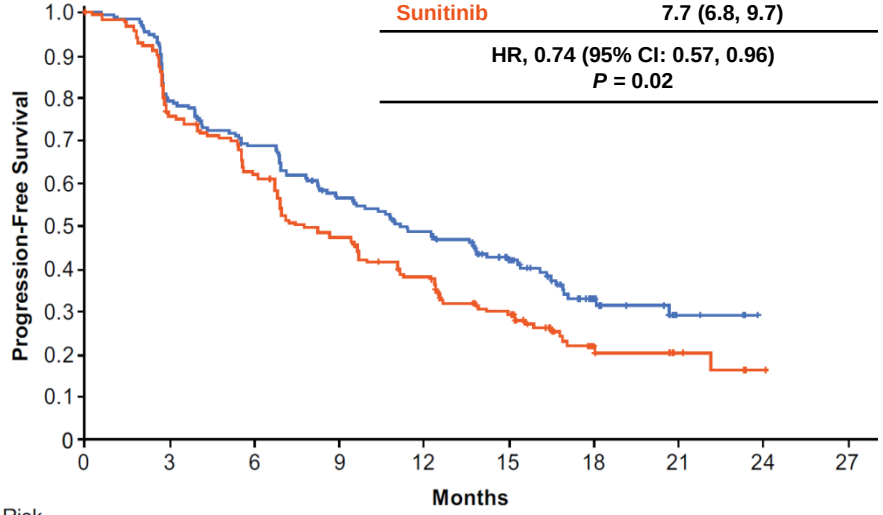


[a] ≥ 1% IC: 40% prevalence using SP142 IHC assay; [b] No dose reduction for atezolizumab or bevacizumab.

PFS (PD-L1+ & ITT)

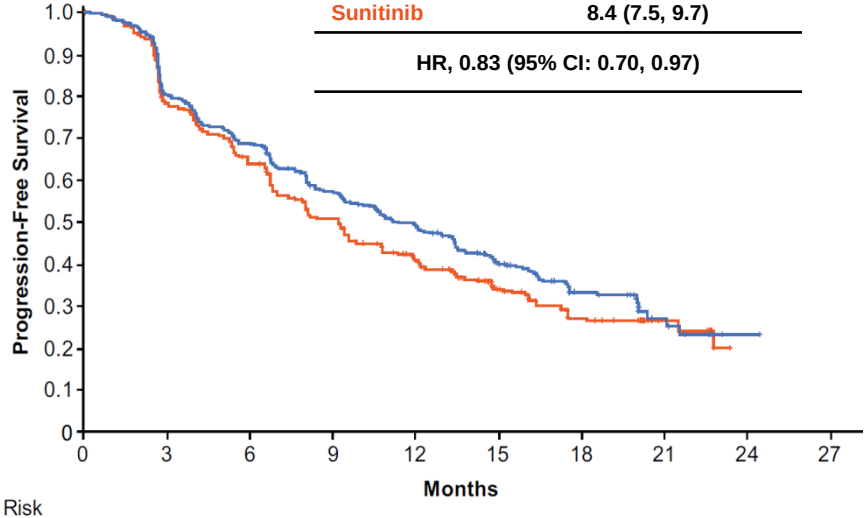
Co-Primary Endpoint

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

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

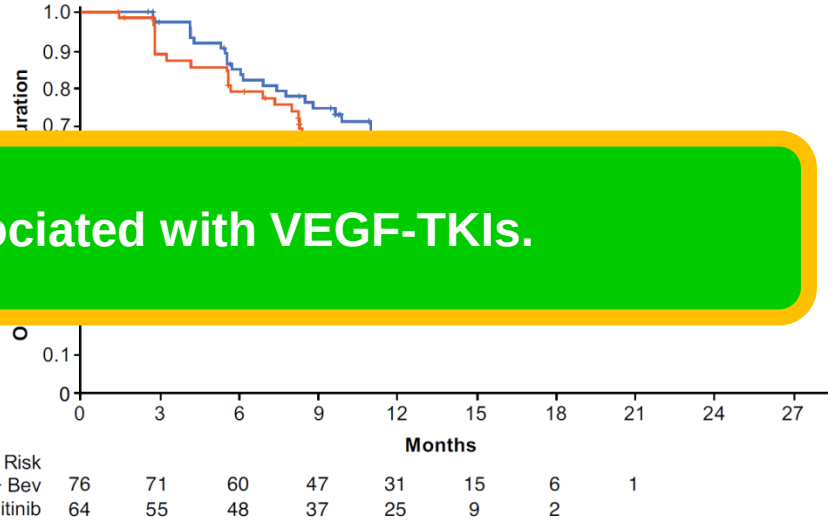
PFS assessed by investigators. Minimum follow-up, 12 mo. Median follow-up, 15 mo.

Objective Response Rate

Secondary Endpoint

	PD-L1+	
	Atezo + Bev n = 178	Sunitinib n = 184
Confirmed ORR, % 95% CI	43% (35, 50)	35% (28, 42)
Complete response	9%	4%
Pa		
St		
Pr		
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%)



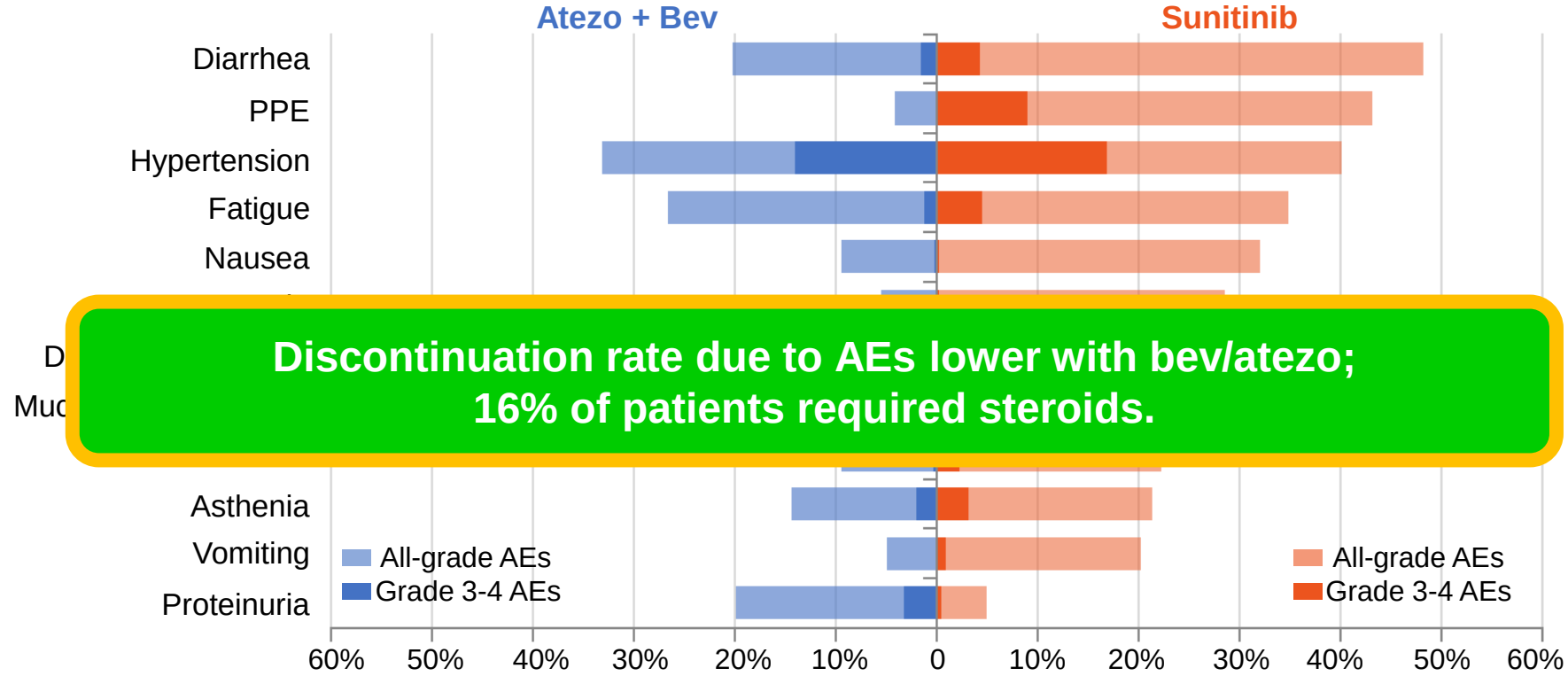
Higher CR rates than associated with VEGF-TKIs.

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.

Secondary Endpoint

Treatment-related AEs

> 5% difference between arms and ≥ 20% frequency in either arm



Discontinuation rate due to AEs lower with bev/atezo; 16% of patients required steroids.

PPE, palmar-plantar erythrodysesthesia.

PFS and ORR by IRC

Secondary Endpoint

	PD-L1+		PD-L1-[a]		ITT	
	Atezo + Bev n = 178	Sunitinib n = 184	Atezo + Bev n = 276	Sunitinib n = 277[b]	Atezo + Bev n = 454	Sunitinib n = 461
Median PFS, mo (95% CI)	8.9 (6.9, 12.5)	7.2 (6.1, 11.1)	11.0 (8.3, 13.3)	8.4 (7.4, 10.1)	9.6 (8.3, 11.5)	8.3 (7.0, 9.7)
Stratified HR (95% CI)	0.93 (0.72, 1.21)		0.84 (0.67, 1.04)		0.88 (0.74, 1.04)	

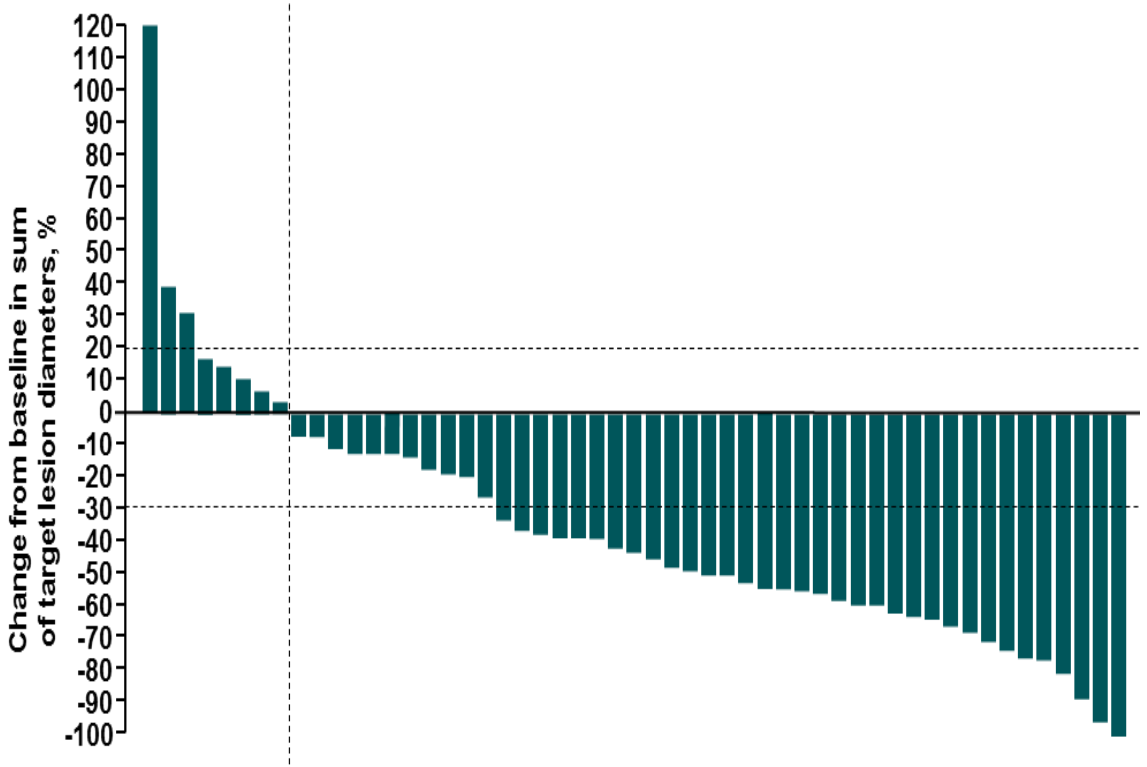
What could drive discordance between investigator and central review?

- IRC and INV assessment of PFS benefit was generally consistent in the ITT population; however, results differed from INV assessment in patients with PD-L1+ disease
- Investigators, IRC reviewers and the sponsor were blinded to PD-L1 status

[a] PD-L1 negative tumors had a PD-L1 IC IHC expression < 1%. [b] n = 276 for ORR.

TKI/IO Combination: Axitinib plus Avelumab (n=53)

Confirmed best OR*, n (%)	Overall population (N=55)
Complete response	3 (5.5)
Partial response	29 (52.7)
Stable disease	11 (20.0)
Progressive disease	10 (18.2)
Nonevaluable†	2 (3.6)
ORR, % (95% CI)	58.2 (44.1–71.3)



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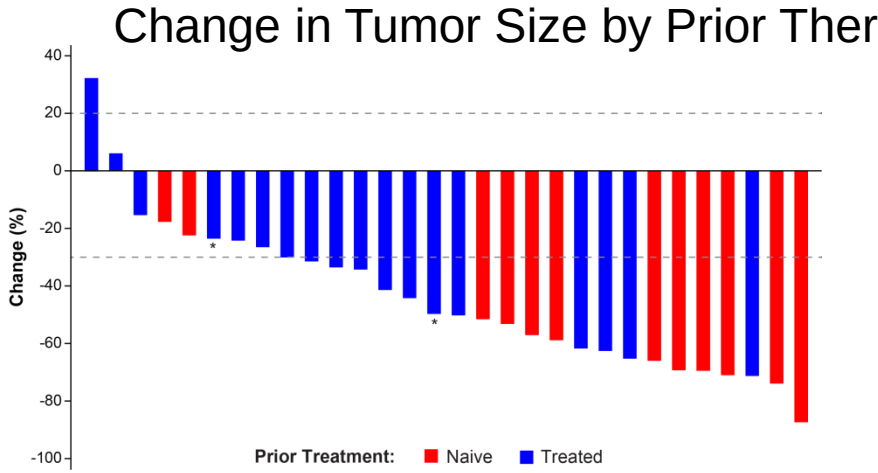
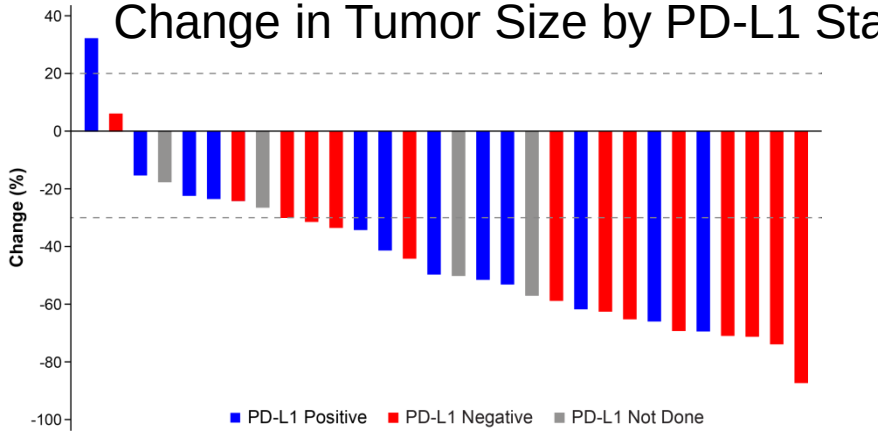
TKI/IO Combinations: Lenvatinib + Pembrolizumab

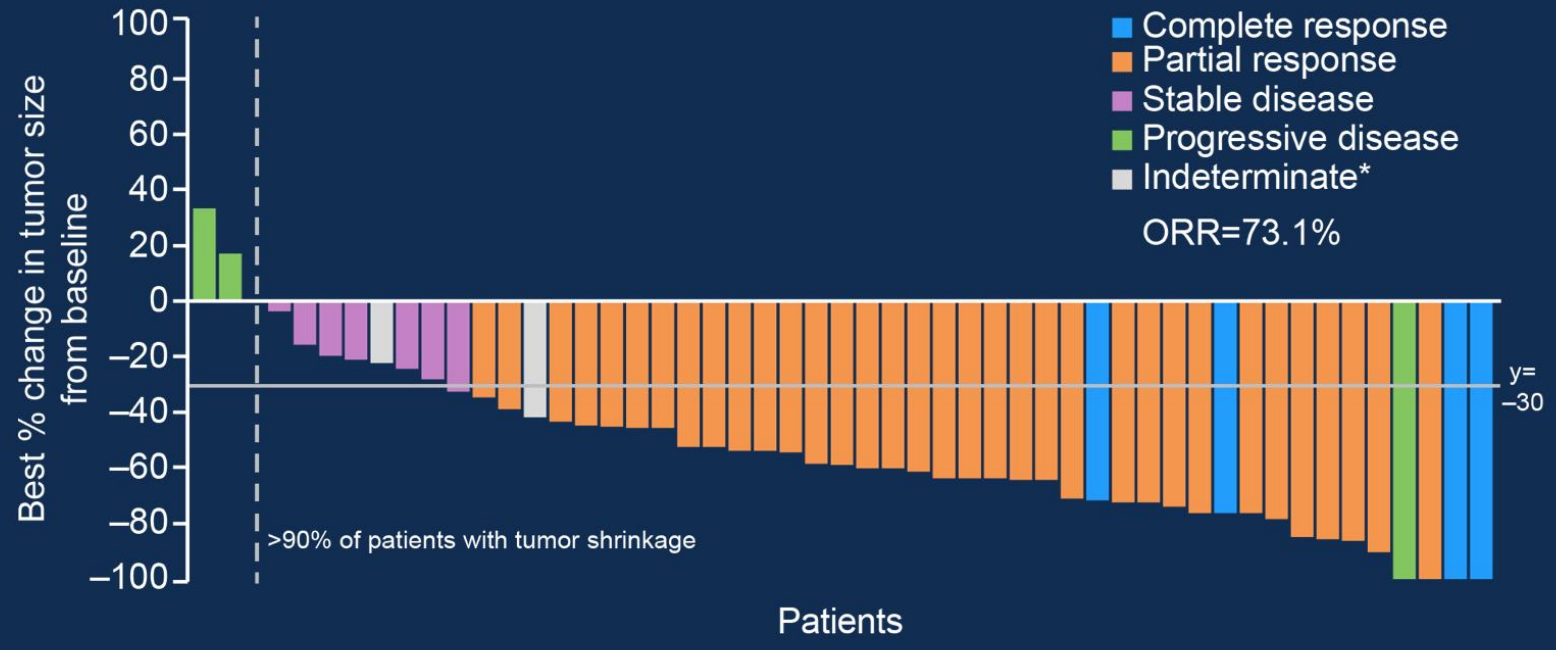
Parameter	Total (n = 30)	Treatment Naïve (n = 12)	Previous Treatments (n=18)
$ORR_{(Week\ 24)}$, n (%)	19 (63)	10 (83)	9 (50)
95% CI	44–80	52–98	26–74
ORR, n (%)	19 (63)	10 (83)	9 (50)
95% CI	44–80	52–98	26–74
BOR, n (%)			
Partial response	19 (63)	10 (83)	9 (50)
Stable disease	10 (33)	2 (17)	8 (44)
Progression	1 (3)	0	1 (6)





ESMO 2017.

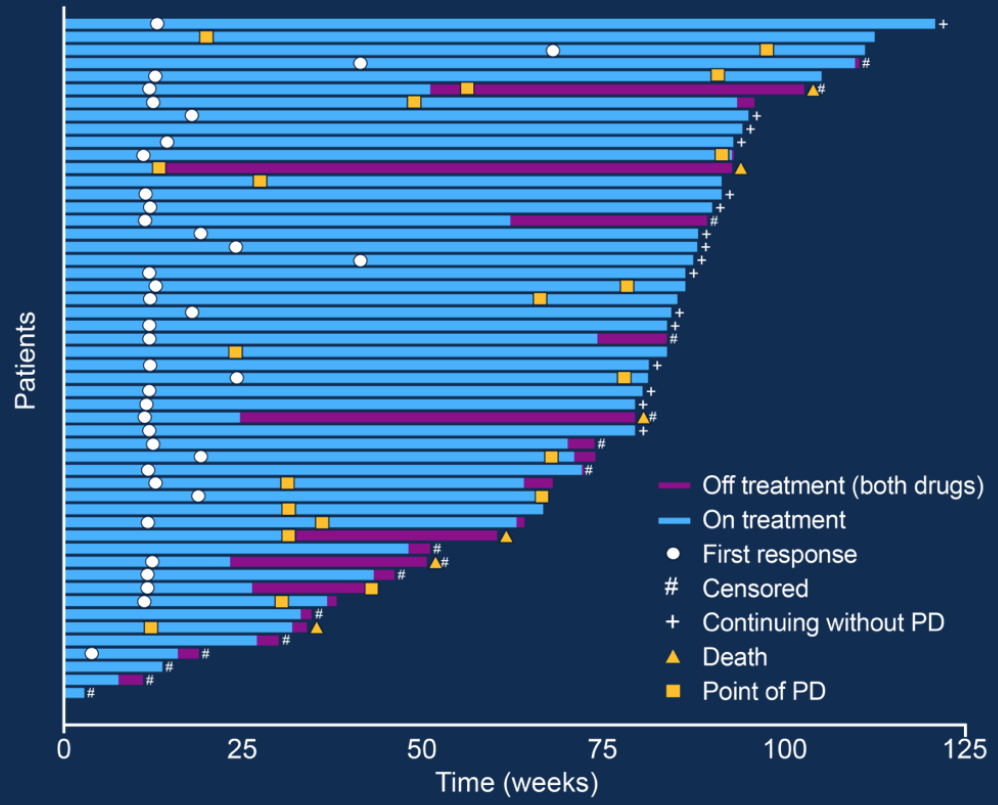
Axitinib + Pembrolizumab



* 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



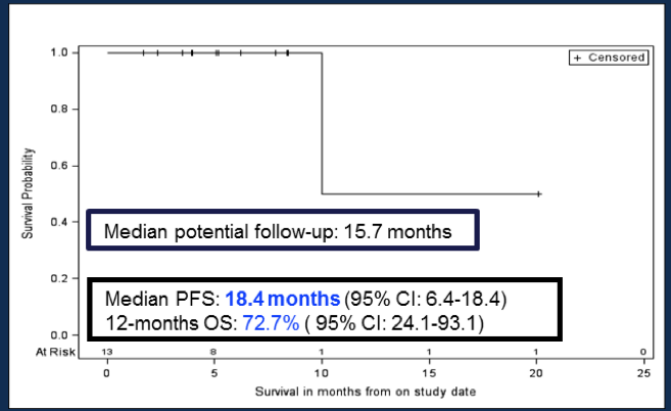
CI=confidence interval; PD=progressive disease

Cabozantinib/Nivolumab +/- Ipilimumab

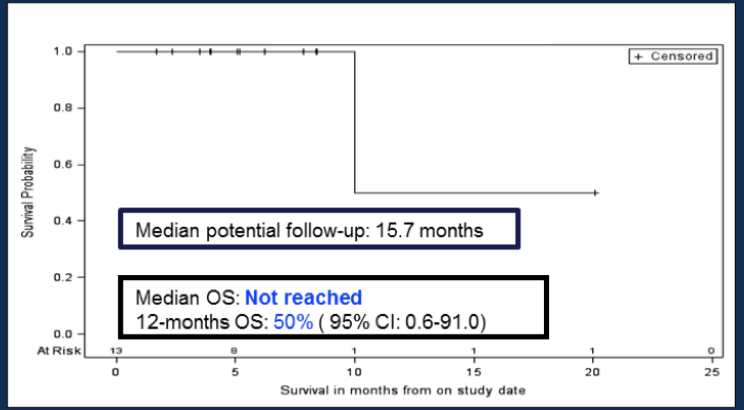
n (%)	Median F/U months	ORR	PR	CR	SD	PR+CR+SD
RCC N=13	5.2	**53.9%** (7/13) (95% CI: 25.1-80.8%)	**53.9%** (7/13) (95% CI: 25.1-80.8%)	0	**46.1%** (6/13) (95% CI: 19.2-74.9%)	**100%** (13/13) (95% CI: 75.3-100.0%)

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

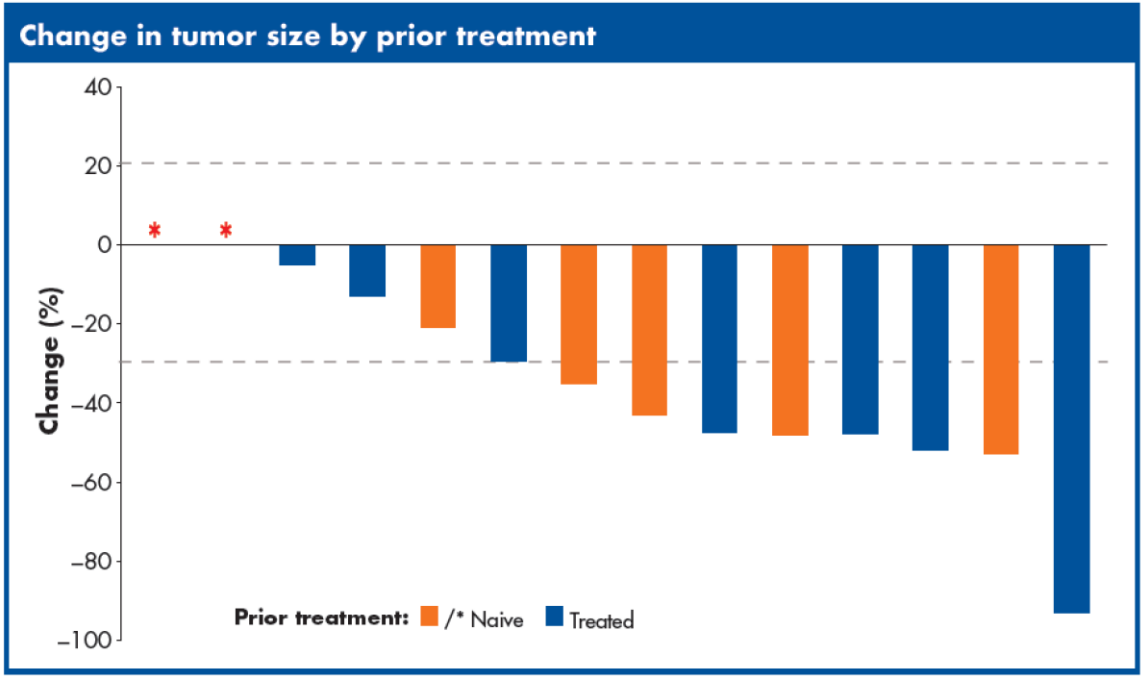
RCC: PFS



RCC: OS



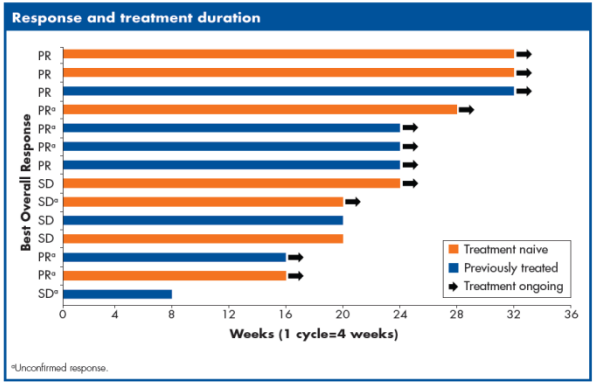
Tivozanib + Nivolumab



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.

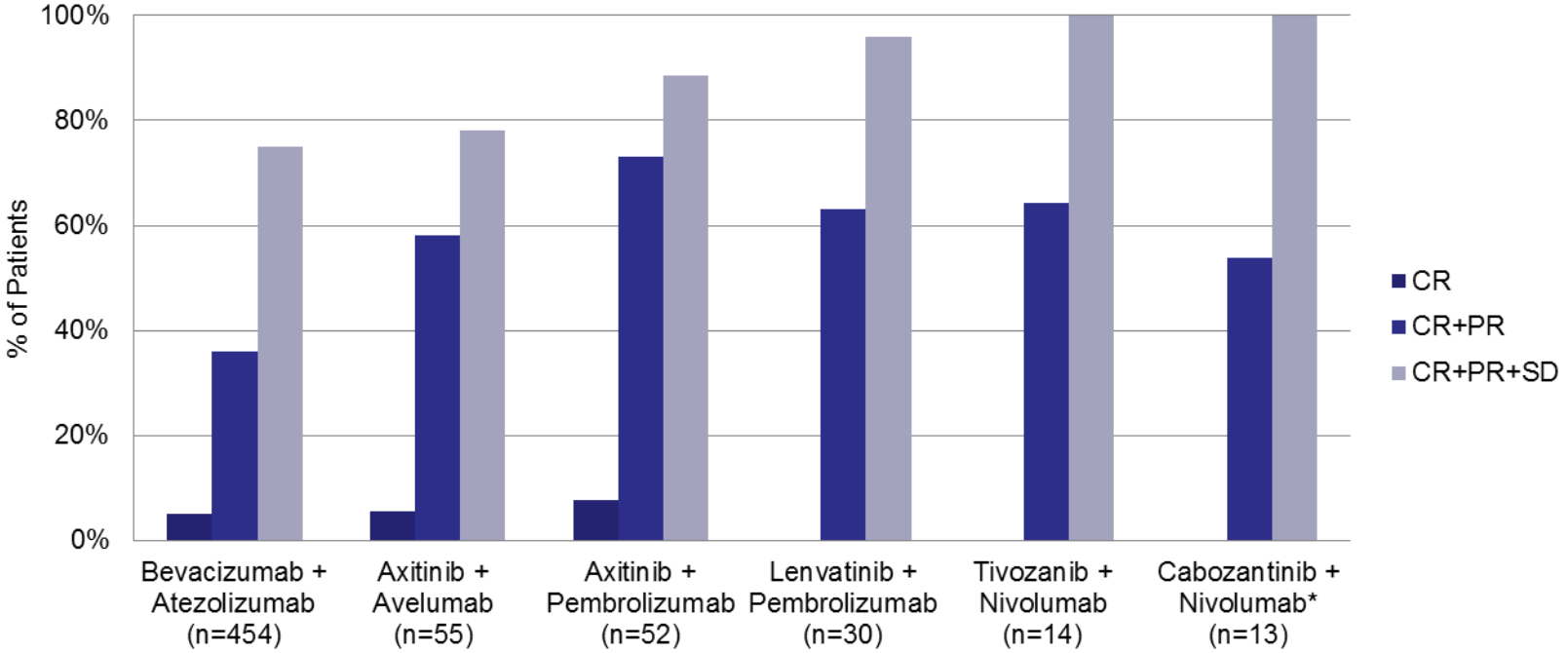


Presented by: Dr. Bernard Escudier - GUCS 2018

Phase 3 VEGF/PD-1 Blockade Combination Studies

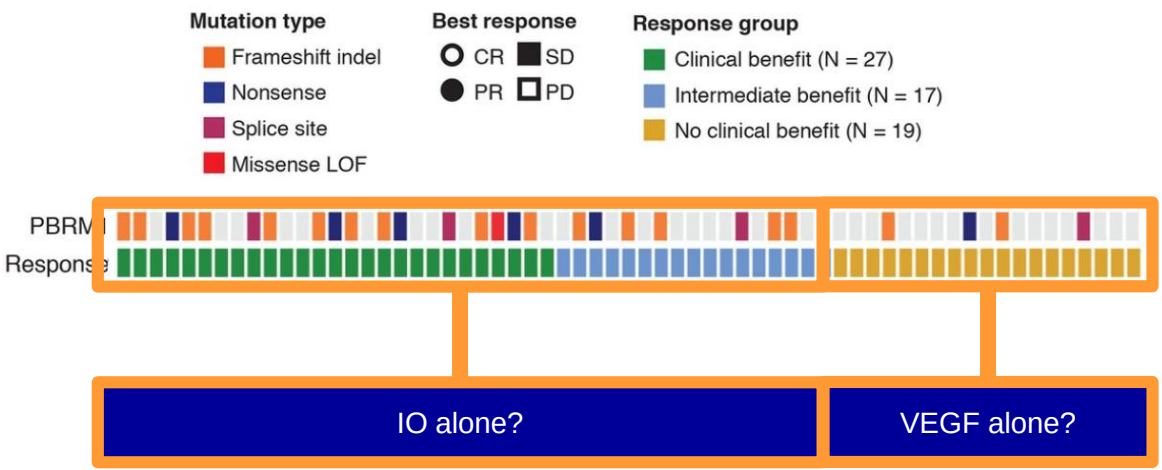
Study	Treatment	Setting	Phase	Status	Patients
Lenvatinib					
NCT02811861 (CLEAR)	LEN + PEM vs SUN vs LEN + EVE	First line	III	Accruing	735
Axitinib					
NCT020684006	AXI + PEM vs SUN	First line	III	Accruing	840
NCT02493751 (JAVELIN 101)	AVELU + AXI vs SUN	First line	III	Completed accrual	583
Bevacizumab					
NCT02420821 IMmotion151	ATEZO + BEV vs SUN	First line	III	**Resulted**	850
Cabozantinib					
NCT03141177 BMS-9ER	CABO + NIVO vs SUN	First line	III	Accruing	500+

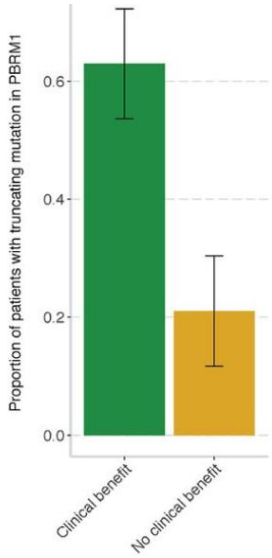
The current landscape …



Motzer et al ASCO GU 2018; Lee et al ESMO 2017; Choueiri et al ASCO 2017; Atkins et al ASCO GU 2018; Nadal et al ASCO GU 2018

Taking a step back from combinations: Role for monotherapy?





Miao D …. Choueiri T, Van Allen E. Science 2018

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Immunotherapy in Renal Cell Carcinoma

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