Renal Cancer
Clinical Breakthrough with Immunotherapy

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CONFLICT OF INTEREST STATEMENT

That I do not conduct activities that would involve a conflict of interest with CME-accreditable training, but that in the past 2 (two) years I have received the funding for advisory boards / speakers bureau from the following sources:

- AZ
- BMS
- Immunocore
- Ipsen
- Incyte
- MSD
- Merck
- Novartis
- Pfizer
- Pierre Fabre
- Roche

Changing Standards of Care for RCC

- Interferon & IL-2
- TKIs – sunitinib, pazopanib, cabozantinib, tivozanib, sorafenib, levantinib, (everolimus)

- Nivolumab (2nd line)
- Ipilimumab + Nivolumab (1st line) – Intermediate + poor risk

- IO – TKI
- Adjuvant

Limitations of TKIs

- Purely palliative
- Secondary resistance inevitable

- Most patients have some benefit
- Early palliative benefit
- Sequential responses

Immunotherapy expectation

- Long term durable benefit
- What is the evidence?

CheckMate 214: study design

Phase III, open-label, randomised study comparing NIVO + IPI vs sunitinib monotherapy in patients with previously untreated aRCC with a clear-cell component[1,2]

Key eligibility criteria
- Aged ≥18 years
- Treatment-naive advanced RCC with a clear-cell component
- Measurable disease per RECIST v1.1
- KPS score ≥70

Key exclusion criteria
- CNS metastases
- Autoimmune disease
- Glucocorticoid or immunosuppressant use

R 1:1

NIVO + IPI
NIVO 3 mg/kg + IPI 1 mg/kg IV Q3W for four doses, then NIVO 3 mg/kg Q2W

n = 550 (ITT)

Sunitinib
50 mg PO QD
(4 weeks on, 2 weeks off)

n = 546 (ITT)

Follow-up analysis[1]

Efficacy outcomes*
- Overall survival
- Investigator-assessed PFS and ORR/best overall response per RECIST v1.1

Safety outcomes†
- Treatment-related AEs
- Treatment related AEs leading to discontinuation
- Grade 3–4 treatment-related AEs

*Assessed in the ITT population, and in intermediate-/poor-risk and in favourable-risk patients (classified using International Metastatic Renal Cell Carcinoma Database Consortium criteria).
†Assessed in all treated patients.
AE, adverse event; CNS, central nervous system; IPI, ipilimumab; ITT, intention-to-treat; IV, intravenous; KPS, Karnofsky performance status; NIVO, nivolumab; ORR, objective response rate; PFS, progression-free survival; PO, orally; QD, once daily; Q2W, every 2 weeks; Q3W, every 3 weeks; R, randomisation; (a)RCC, (advanced) renal cell carcinoma; RECIST, response evaluation criteria in solid tumours.
1. Tannir et al. Presented at 2019 Genitourinary Cancers Symposium; February 14–16, 2019; San Francisco, CA, USA; Abstract 547. 2. Motzer et al. N Engl J Med 2018;378:1277–90.

30-Month Follow-Up of the Phase 3 CheckMate 214 Trial of First-Line Nivolumab Plus Ipilimumab or Sunitinib in Patients With Advanced Renal Cell Carcinoma

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Presented at the 2019 Genitourinary Cancers Symposium; February 14–16, 2019; San Francisco, CA, USA

CheckMate 214

Table 2. Baseline characteristics: ITT, intermediate/poor-risk, and favorable-risk patients[5]

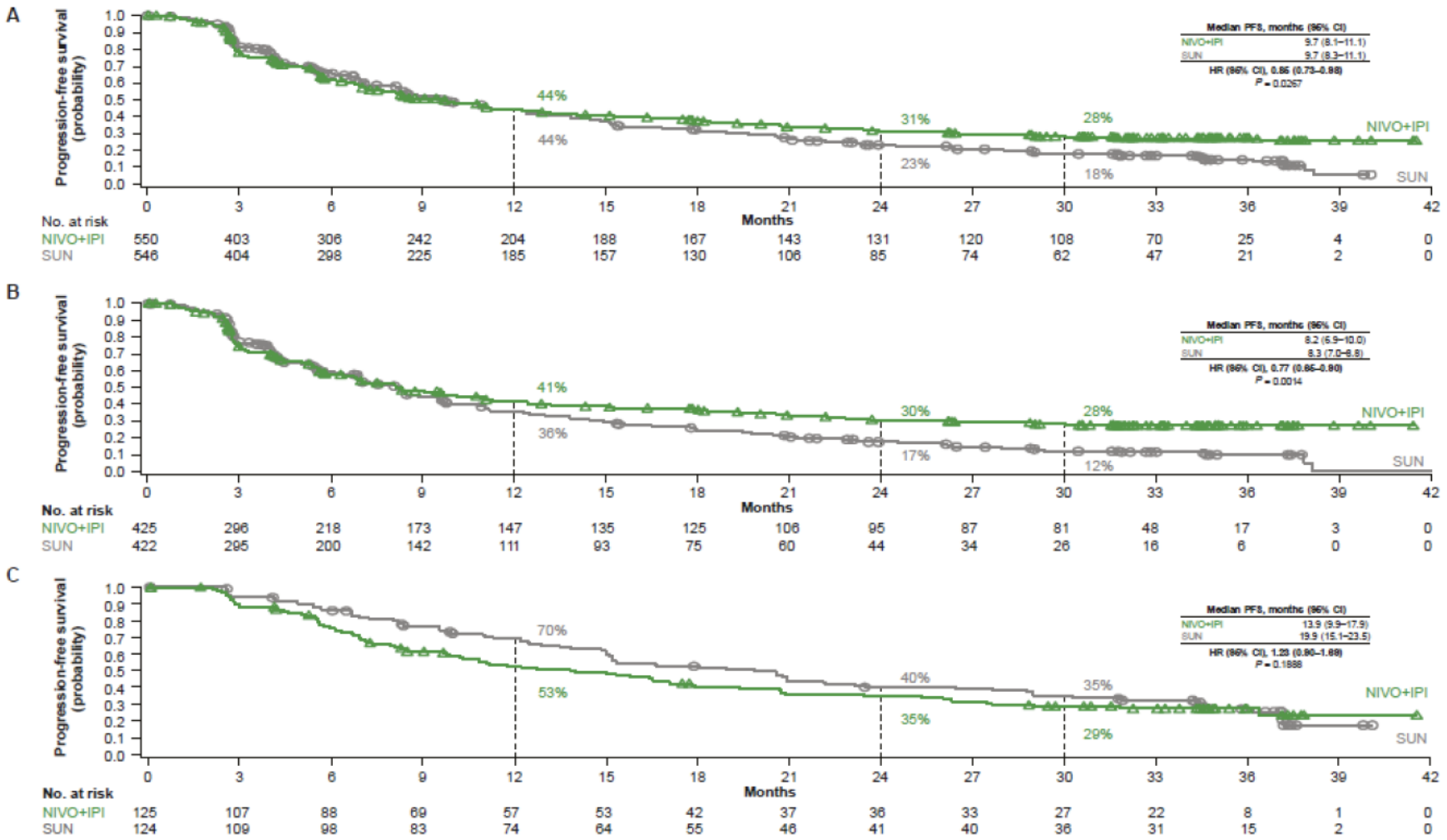
Characteristic[a]	ITT population		Intermediate/poor risk		Favorable risk	
	NIVO+IPI (N = 550)	SUN (N = 546)	NIVO+IPI (N = 425)	SUN (N = 422)	NIVO+IPI (N = 125)	SUN (N = 124)
Median age, years (range)	62 (26–85)	62 (21–85)	62 (26–85)	61 (21–85)	62 (36–85)	63 (38–83)
Male, %	75	72	74	71	79	76
IMDC risk, %						
Favorable (0)	23	23	0	0	100	100
Intermediate (1–2)	61	61	79	79	0	0
Poor (3–6)	17	16	21	21	0	0
Region, %						
United States	28	28	26	26	34	34
Canada and Europe	37	36	35	35	42	43
Rest of the world	35	36	39	39	24	23
No. of sites with target/non-target lesions, %						
1	22	22	21	20	26	27
≥2	78	78	79	80	74	73
Common sites of target/non-target lesions, %[b]						
Lung	69	68	69	70	70	62
Lymph	45	49	45	51	45	42
Bone[c]	20	22	22	23	14	18
Liver	18	20	21	21	9	15
Tumor PD-L1 expression (evaluable patients), %	N = 499	N = 503	N = 384	N = 392	N = 115	N = 111
≥1%	23	25	26	29	11	12

[a]Information shown in the table is based on data collected with the use of an interactive voice-response system. Percentages may not total 100 because of rounding. [b]The number of target or non-target lesions at baseline was not reported for 1 patient in the SUN group. Among favorable-risk patients, 21 (17%) patients in each arm had baseline pancreas lesions. [c]Shown are patients who had bone metastases with or without a soft-tissue component.

Tannir et al

CheckMate 214

Figure 2. Investigator-assessed progression-free survival per RECIST v1.1: ITT (A), intermediate/poor-risk (B), and favorable-risk (C) patients



Tannir et al

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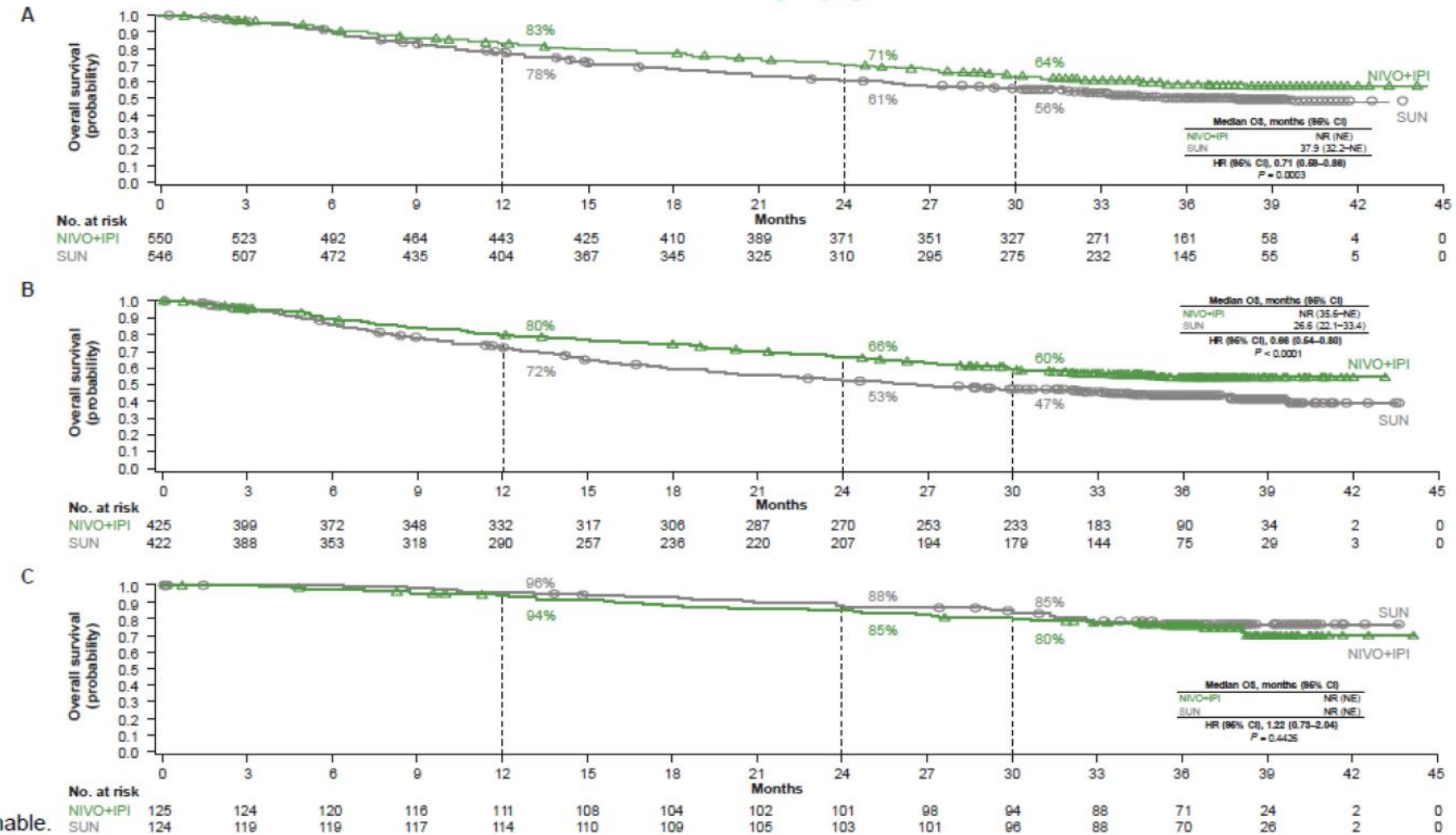
Figure 1. Overall survival: ITT (A), intermediate/poor-risk (B), and favorable-risk (C) patients



NE, not estimable.

Tannir et al

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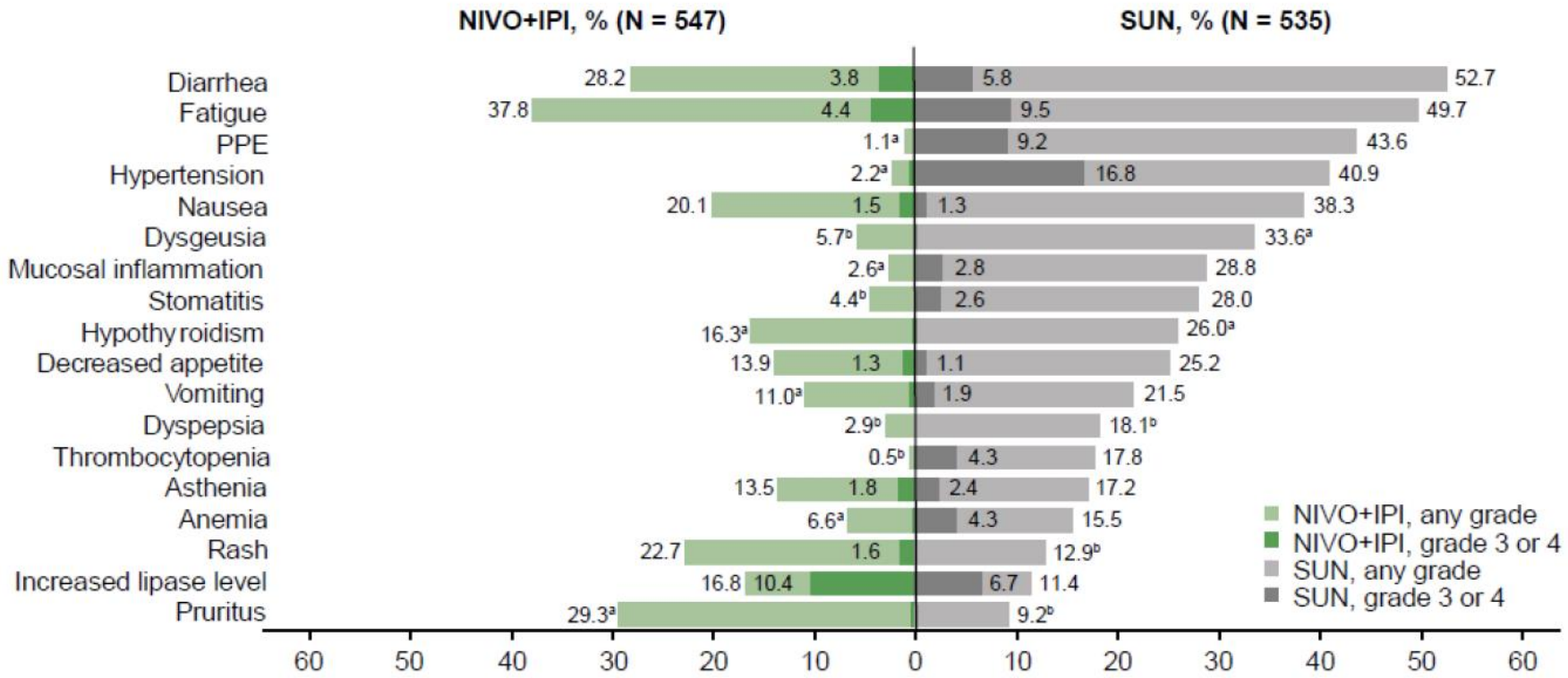
Figure 3. Any-grade treatment-related AEs occurring in >15% of patients in either arm: all treated patients

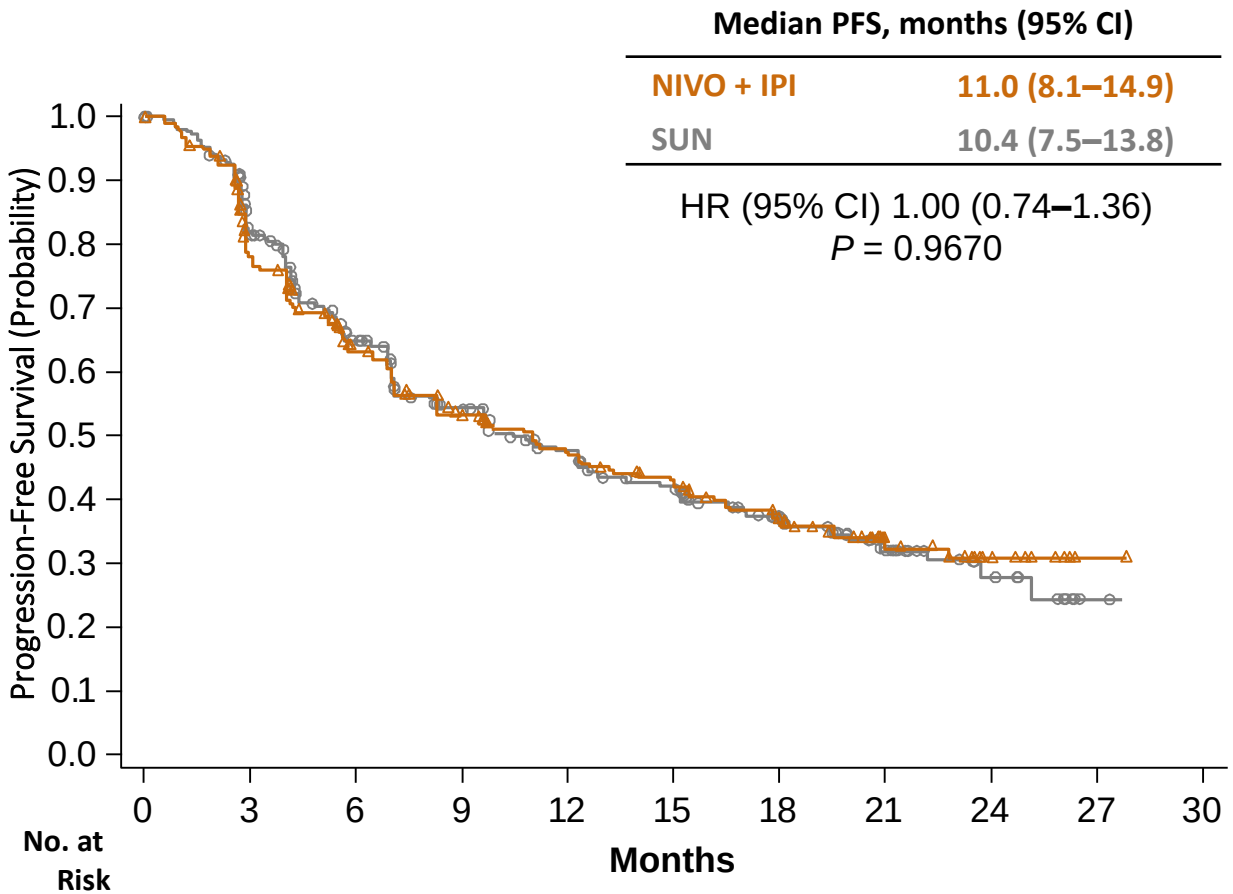


[a]<1% reported grade 3-4 treatment-related AE; [b]No patients reported a grade 3-4 treatment-related AE.
PPE, palmoplantar erythrodysesthesia.

Tannir et al

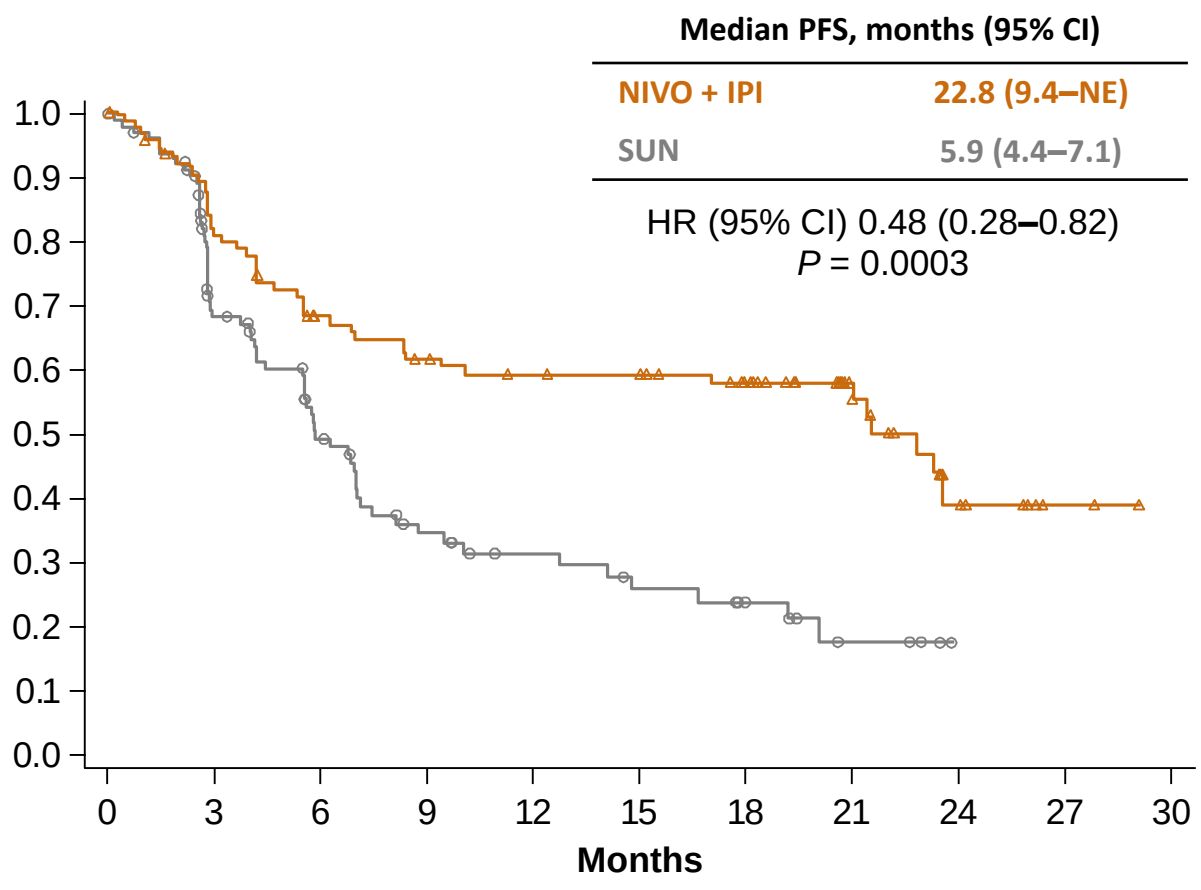
PFS by PD-L1 expression: IMDC intermediate/poor risk

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	

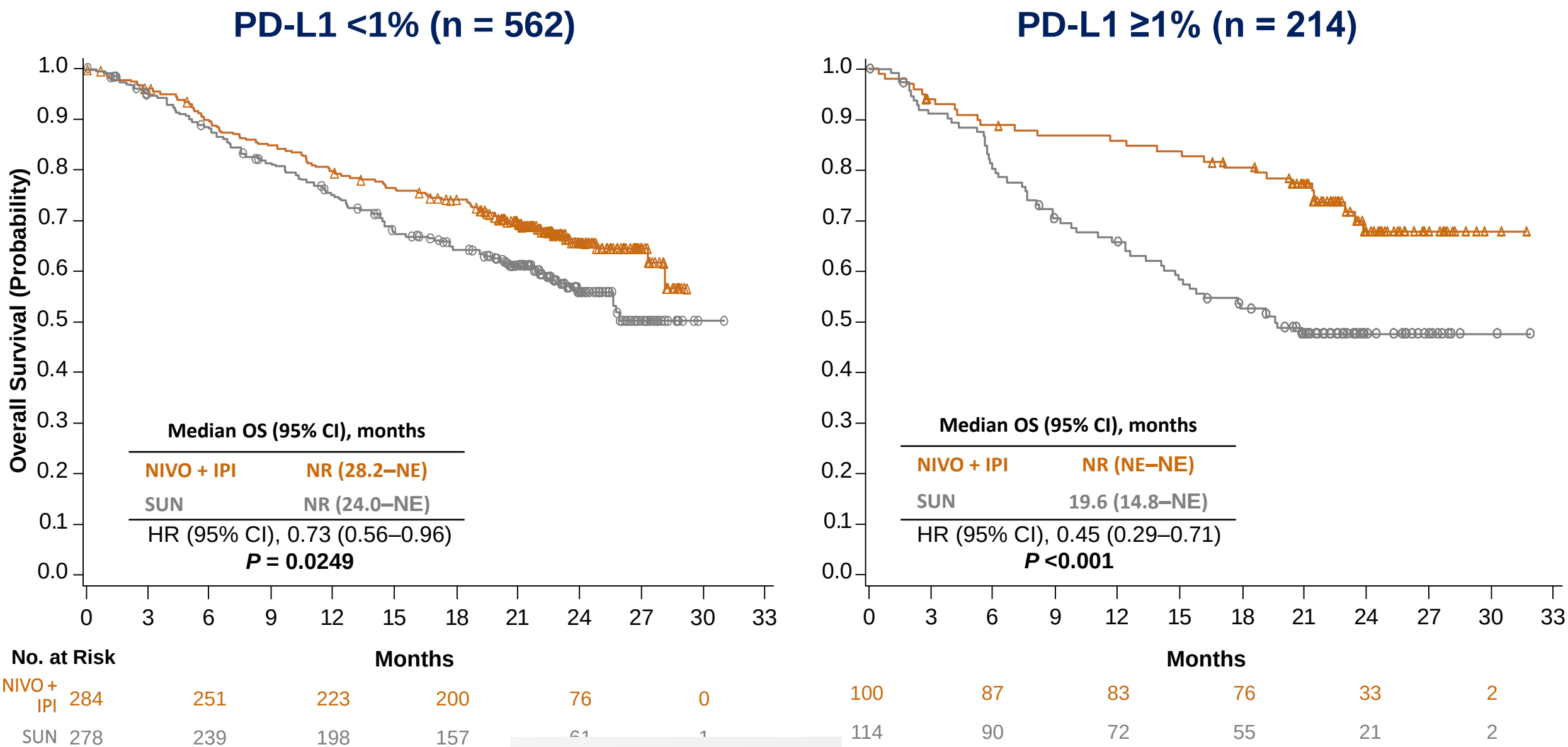
PD-L1 ≥1% (n = 214)



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

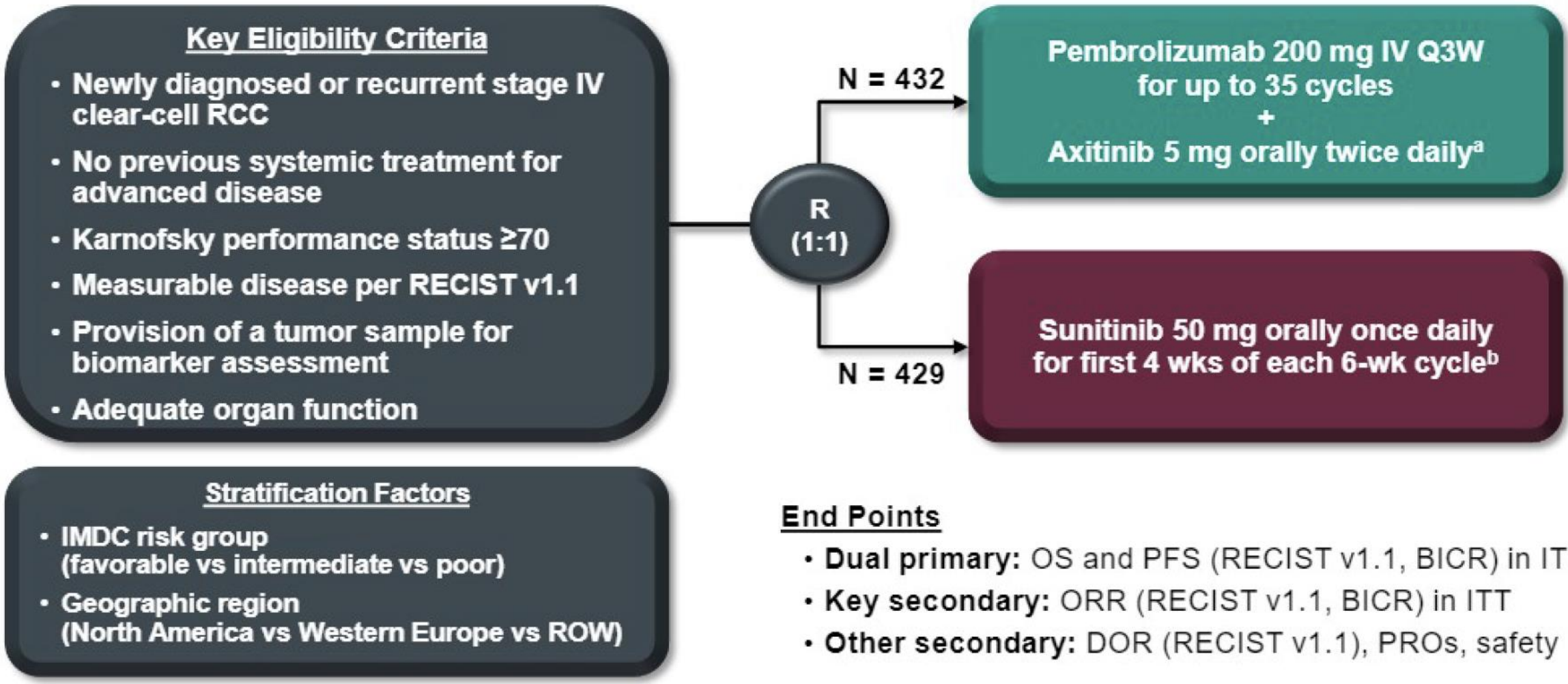
Motzer et al

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



CheckMate 214, Motzer et al.

KEYNOTE-426 Study Design



End Points

- **Dual primary:** OS and PFS (RECIST v1.1, BICR) in ITT
- **Key secondary:** ORR (RECIST v1.1, BICR) in ITT
- **Other secondary:** DOR (RECIST v1.1), PROs, safety

[a]Axitinib dose could be increased to 7 mg, then 10 mg, twice daily if safety criteria were met; dose could be reduced to 3 mg, then 2 mg, twice daily to manage toxicity.
[b]Sunitinib dose could be decreased to 37.5 mg, then 25 mg, once daily for the first 4 wks of each 6-wk cycle to manage toxicity.
BICR, blinded independent central radiologic review; DOR, duration of response; PROs, patient-reported outcomes; ROW, rest of world.
KEYNOTE-426 is a randomized, open-label, phase 3 study (ClinicalTrials.gov identifier NCT0285333[illegible]

Powles et al , ASCO GU 2019

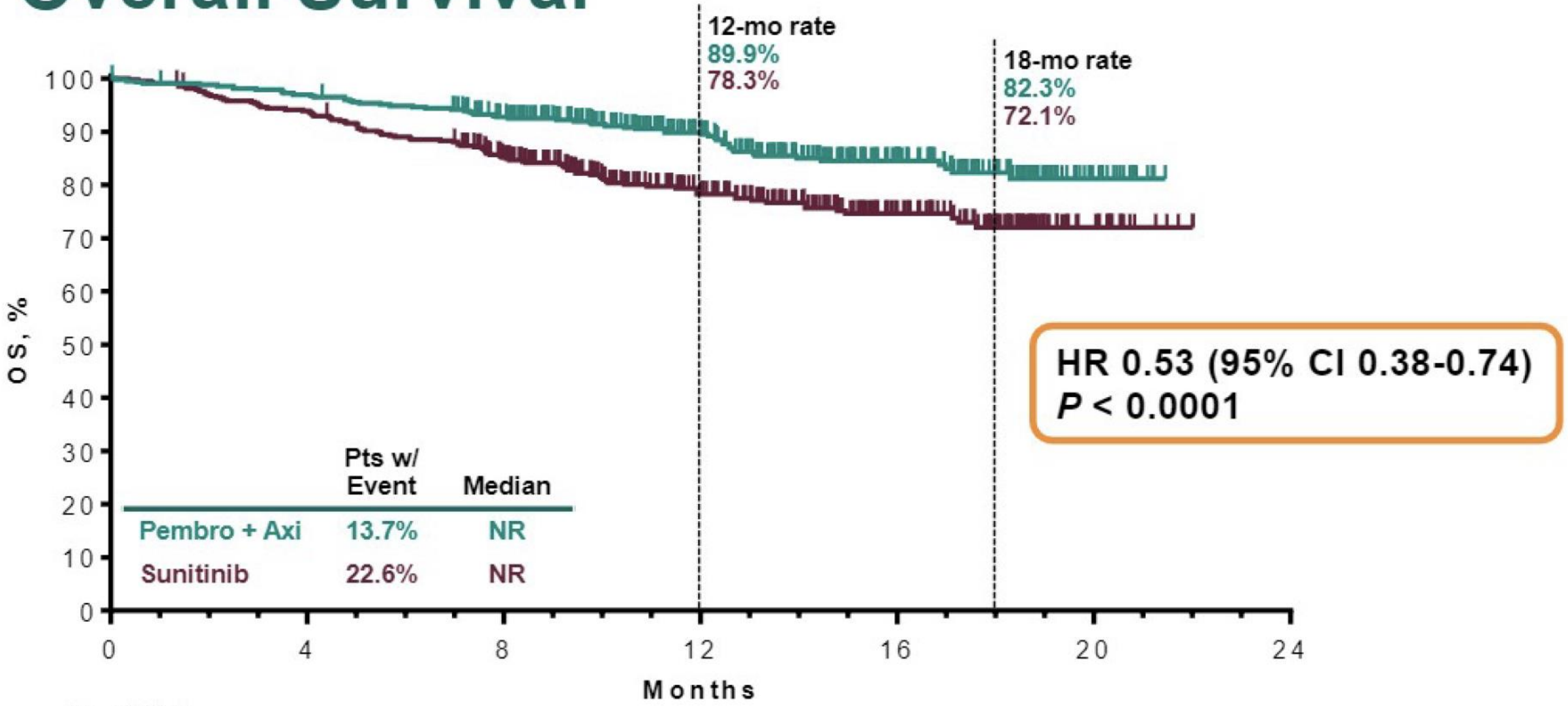
Subsequent Anticancer Therapy Among Patients Who Discontinued Study Therapy

	Pembro + Axi n = 176	Sunitinib n = 242
Any subsequent therapy	88 (50.0%)	147 (60.7%)
Any PD-1 or PD-L1 inhibitor	8 (4.5%)	91 (37.6%)
Any VEGF or VEGFR inhibitor	78 (44.3%)	86 (35.5%)
Any other therapy	21 (11.9%)	26 (10.7%)

Patients may have received more than one subsequent therapy overall or within a category.
Data cutoff date: Aug 24, 2018.

Powles et al , ASCO GU 2019

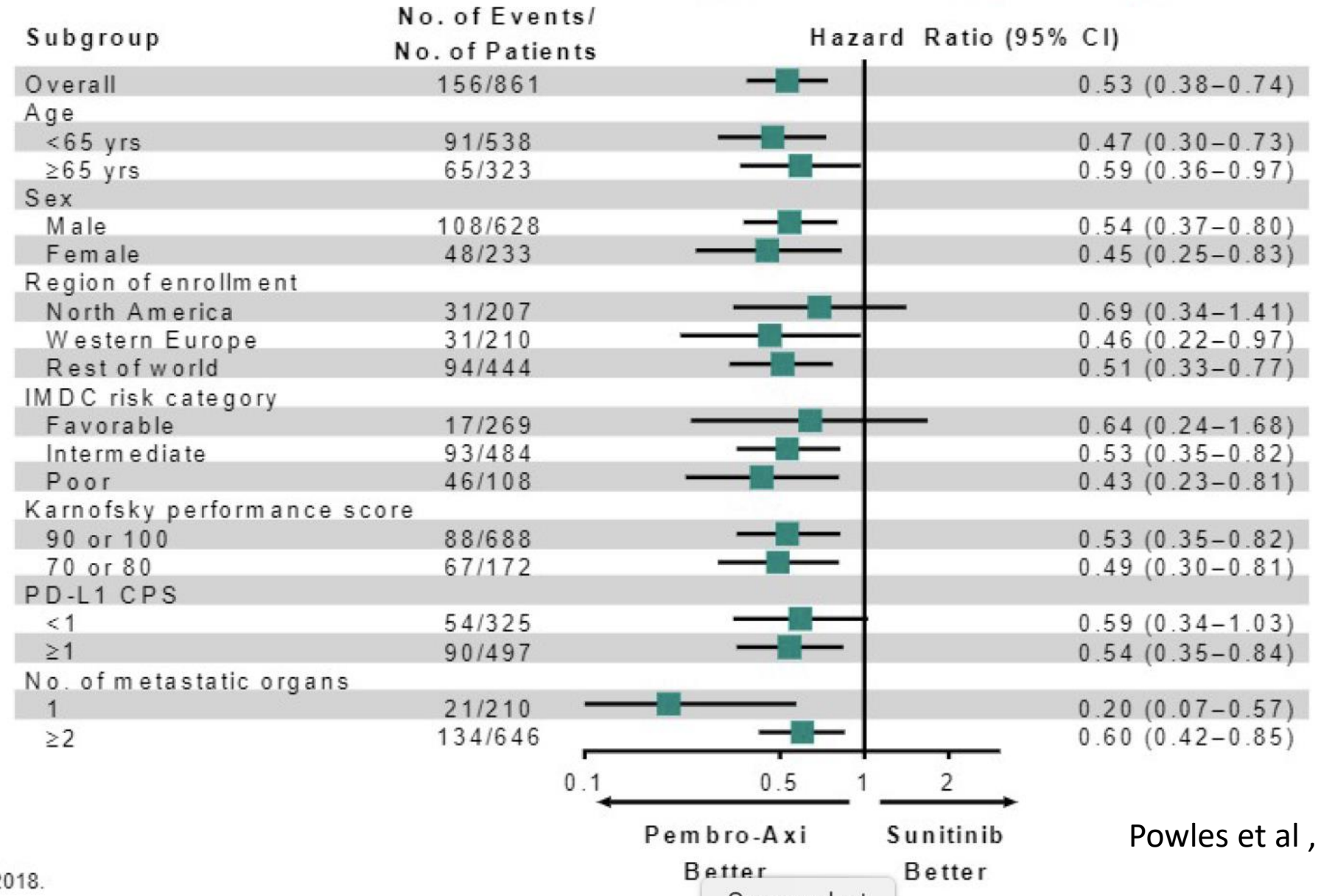
Overall Survival



Data cutoff date: Aug 24, 2018.

Powles et al , ASCO GU 2019

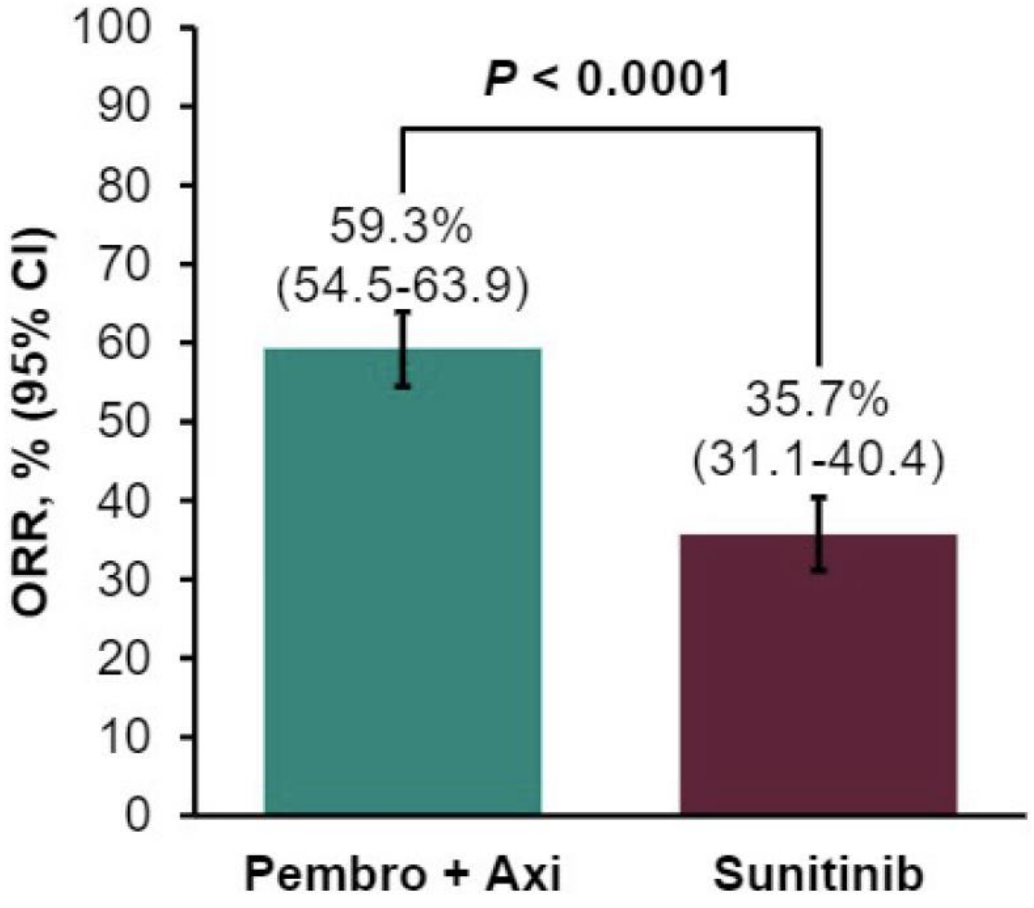
Overall Survival in Key Subgroups



Powles et al , ASCO GU 2019

Data cutoff date: Aug 24, 2018.

Confirmed Objective Response Rate



Best Response	Pembro + Axi N = 432	Sunitinib N = 429
CR	25 (5.8%)	8 (1.9%)
PR	231 (53.5%)	145 (33.8%)
SD	106 (24.5%)	169 (39.4%)
PD	47 (10.9%)	73 (17.0%)
NE[a]	8 (1.9%)	6 (1.4%)
NA[b]	15 (3.5%)	28 (6.5%)
Response Duration	**N = 256**	**N = 153**
Median (range), mo	NR (1.4+ to 18.2+)	15.2 (1.1+ to 15.4+)

Powles et al , ASCO GU 2019

[a]Patients who had ≥1 post-baseline imaging assessment, none of which were evaluable per RECIST v1.1 by BICR. [b]Patients who did not have ≥1 post-baseline imaging assessment.
Data cutoff date: Aug 24, 2018.

Summary of Adverse Events

	All Cause		Treatment Related	
	Pembro + Axi N = 429	Sunitinib N = 425	Pembro + Axi N = 429	Sunitinib N = 425
Any	98.4%	99.5%	96.3%	97.6%
Grade 3-5	75.8%	70.6%	62.9%	58.1%
Led to death	2.6%	3.5%	0.9%[a]	1.6%[b]
Led to discontinuation of any treatment	30.5%	13.9%	25.9%	10.1%
Led to discontinuation of both pembro and axi	10.7%	—	8.2%	—
Led to axi or sunitinib dose reduction	20.3%	30.1%	20.0%	28.5%
Led to interruption of any treatment	69.9%	49.9%	62.2%	40.2%

[a]One patient each from myasthenia gravis, myocarditis, necrotizing fasciitis, and pneumonitis.
[b]One patient each from acute myocardial infarction, cardiac arrest, fulminant hepatitis, gastrointestinal hemorrhage, intracranial hemorrhage, malignant neoplasm progression, and pneumonia.
Data cutoff date: Aug 24, 2018.

Powles et al , ASCO GU 2019

MUNICH 2018 ESMO congress

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

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Abstract No. LBA6_PR

JAVELIN Renal 101: study design

Key eligibility criteria:

- Treatment-naive aRCC with a clear cell component
- ≥ 1 measurable lesion as defined by RECIST v1.1
- Tumor tissue available for PD-L1 staining
- ECOG PS 0 or 1

Stratification:

- ECOG PS (0 vs 1)
- Geographic region (USA vs Canada/Western Europe vs ROW)

N = 886

R 1:1

Avelumab 10 mg/kg IV Q2W + Axitinib 5 mg PO BID (6-week cycle)

Sunitinib 50 mg PO QD (4 weeks on, 2 weeks off)

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.

Study objectives

- **Primary endpoints**
  - PFS by RECIST v1.1 per independent review committee (IRC) in patients with PD-L1+ tumors (PD-L1+ group)*
  - OS in the PD-L1+ group
- **Key secondary endpoints**
  - PFS per IRC in the overall population
  - OS in the overall population
- **Other secondary endpoints**
  - PFS per investigator assessment in the PD-L1+ group and in the overall population
  - Objective response per IRC and investigator assessment in the PD-L1+ group and in the overall population
  - Safety in all treated patients

* Defined as ≥ 1% expression on tumor-infiltrating immune cells using the Ventana PD-L1 (SP263) immunohistochemistry assay.
OS, overall survival; **PFS**, progression-free survival.

Motzer et al, ESMO 2018

Key baseline characteristics

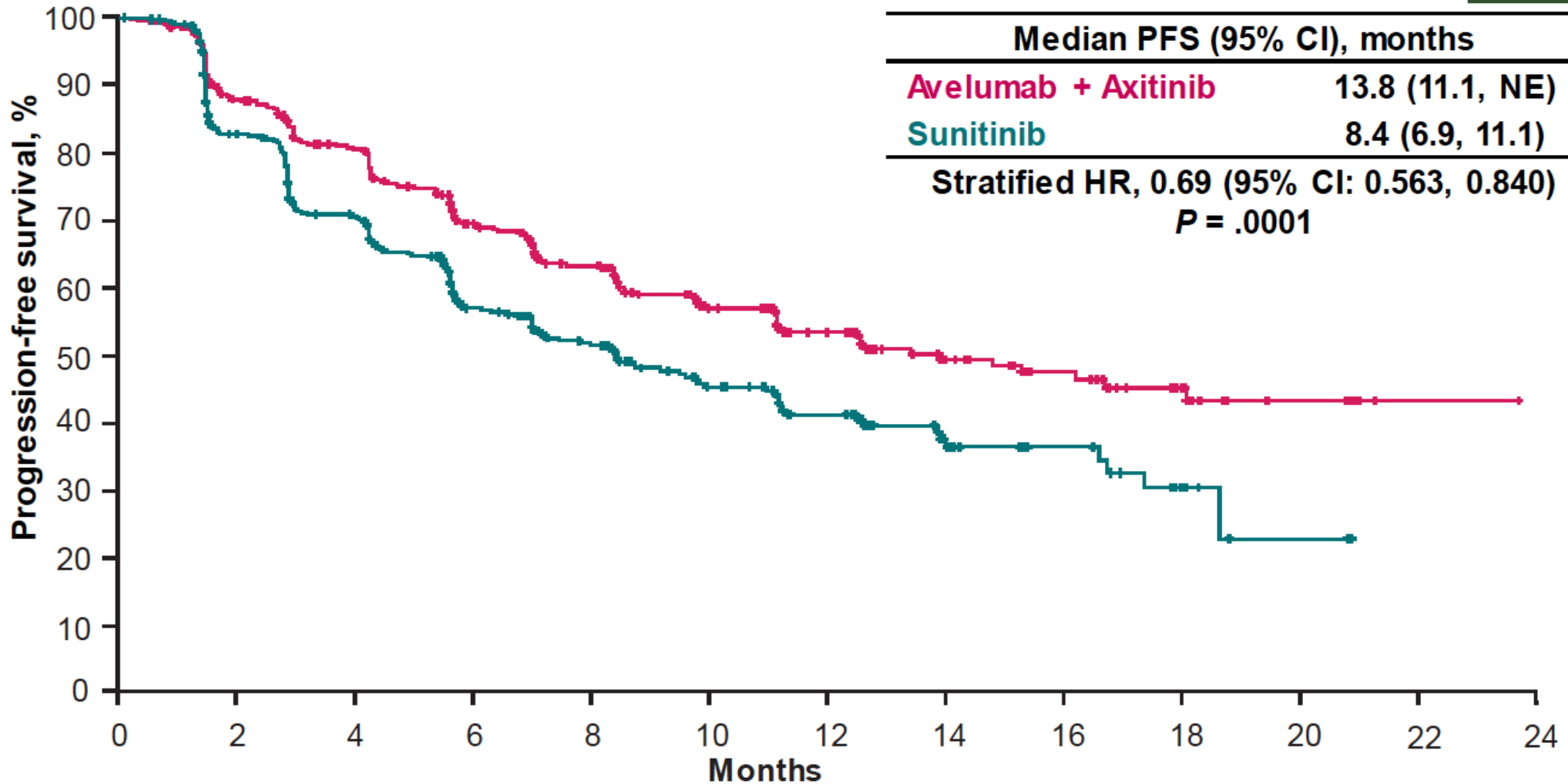
Characteristic	PD-L1+ group (N = 560)		Overall population (N = 886)	
	Avelumab + Axitinib (N = 270)	Sunitinib (N = 290)	Avelumab + Axitinib (N = 442)	Sunitinib (N = 444)
Median age, years	62	61	62	61
Male, %	75	77	72	78
Prior nephrectomy, %	86	87	80	80
ECOG performance status, %				
0/1	62/38	67/33	63/37	63/37
IMDC prognostic risk, %*				
Favorable	19	20	21	22
Intermediate/poor	64/16	66/13	61/16	62/16
MSKCC prognostic risk, %†				
Favorable	19	21	22	23
Intermediate/poor	67/12	69/8	64/12	66/10
Geographic region, %				
United States	28	28	29	30
Canada/Western Europe	30	28	29	29
Rest of the World	43	44	42	42

Values may not sum to 100% due to rounding. * Not reported in < 1% of patients. † Not reported in < 3% of patients.
IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; **MSKCC**, Memorial Sloan Kettering Cancer Center.

Motzer et al, ESMO 2018

PFS per IRC in the overall population

Key secondary endpoint



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

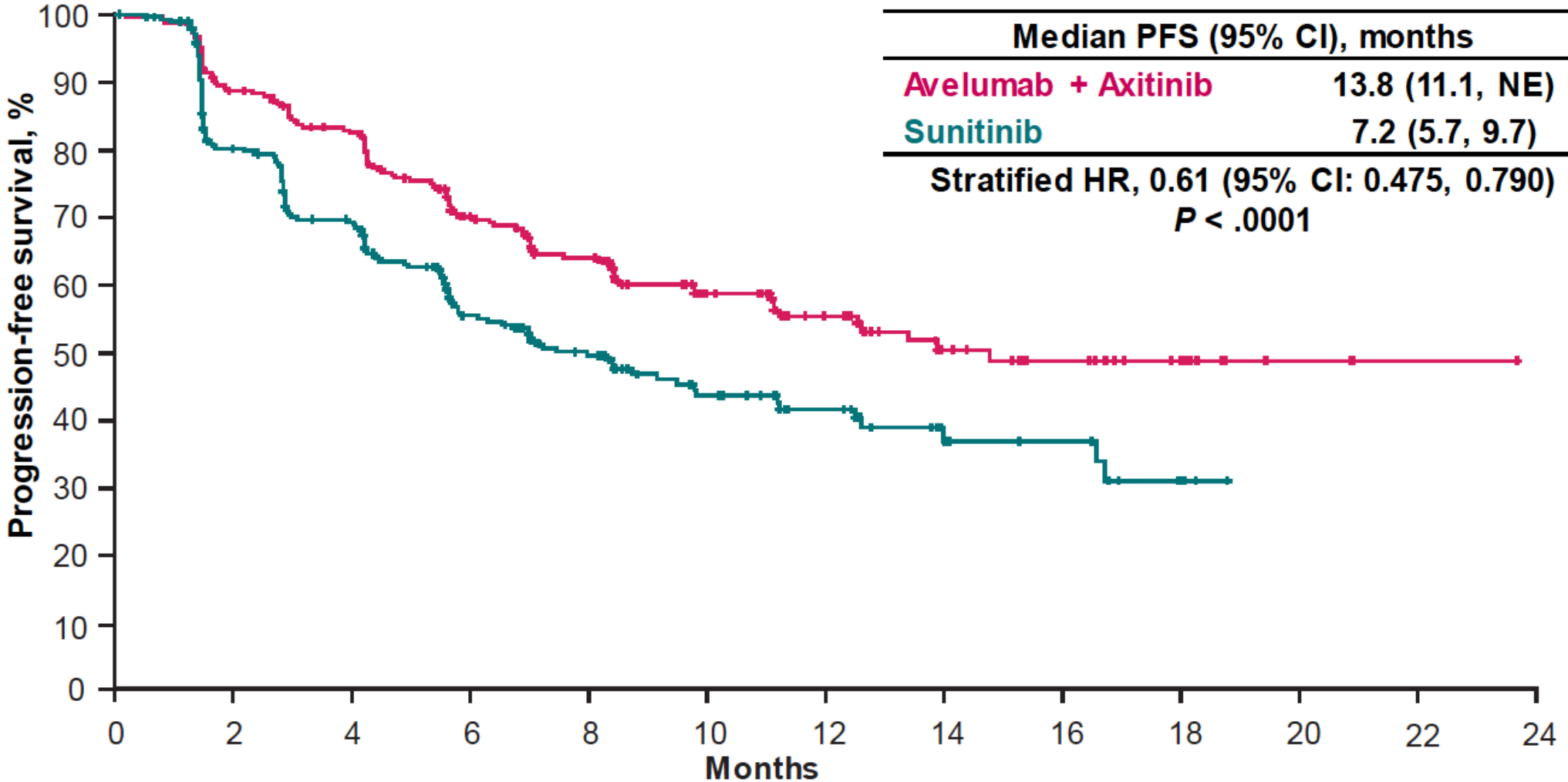
Avel + Axit:	442	364	321	250	193	127	94	57	42	24	8	1	0
Sunitinib:	444	329	271	192	144	90	64	29	20	8	2	0	

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).

Motzer et al, ESMO 2018

PFS per IRC in the PD-L1+ group

Primary endpoint



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		

Motzer et al, ESMO 2018

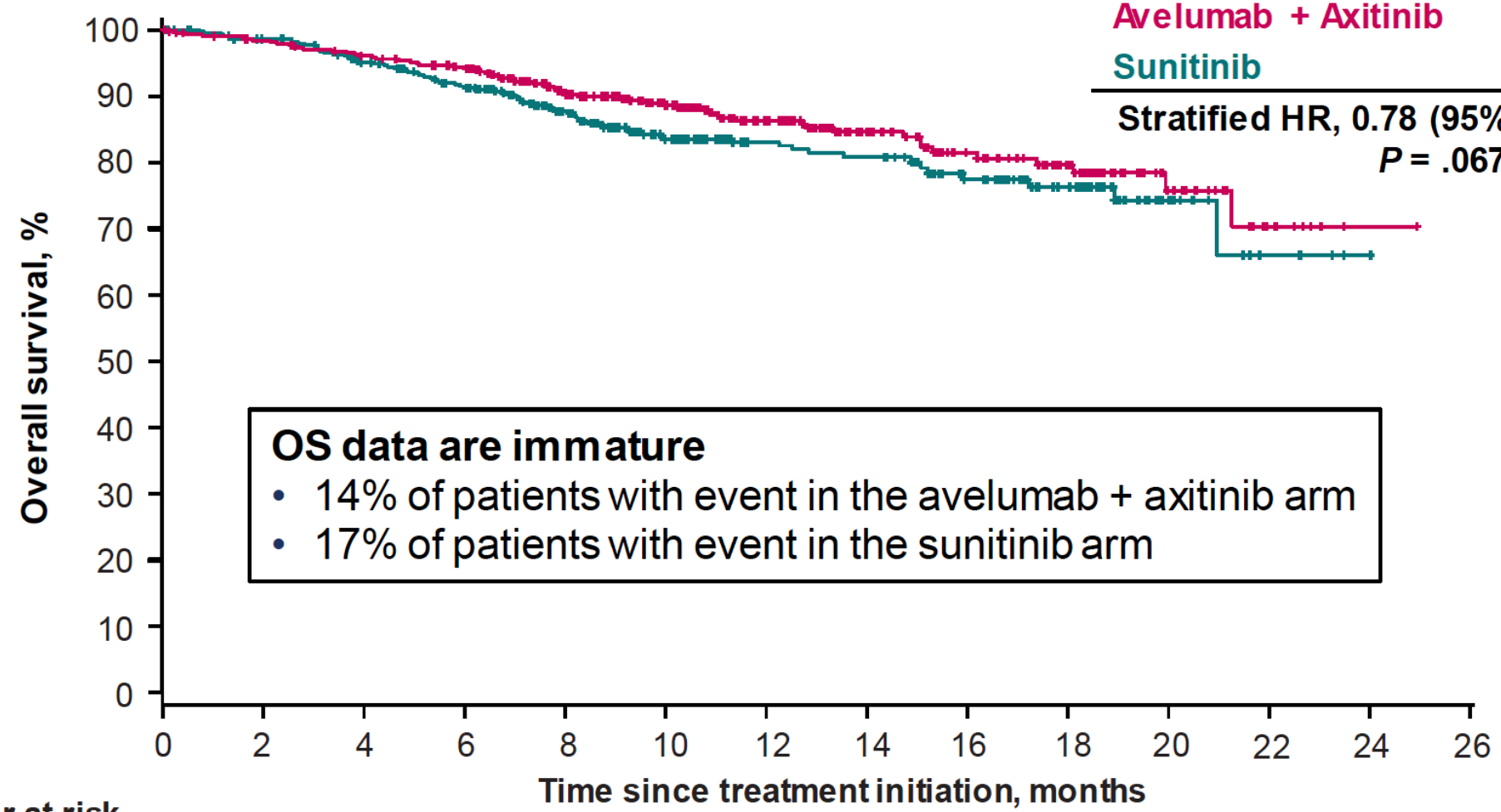
Minimum follow-up, 6 months. Median follow-up, 9.9 months (avelumab + axitinib) and 8.4 months (sunitinib).
The PFS analysis crossed the prespecified efficacy boundary based on the alpha-spending function (*P* = .001).

NE, not estimable.

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).

Motzer et al, ESMO 2018

Confirmed objective response

Secondary endpoint

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.

Motzer et al, ESMO 2018

* 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.

TRAEs in all treated patients (N = 873)

Secondary endpoint

	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**	

Motzer et al, ESMO 2019

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).

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

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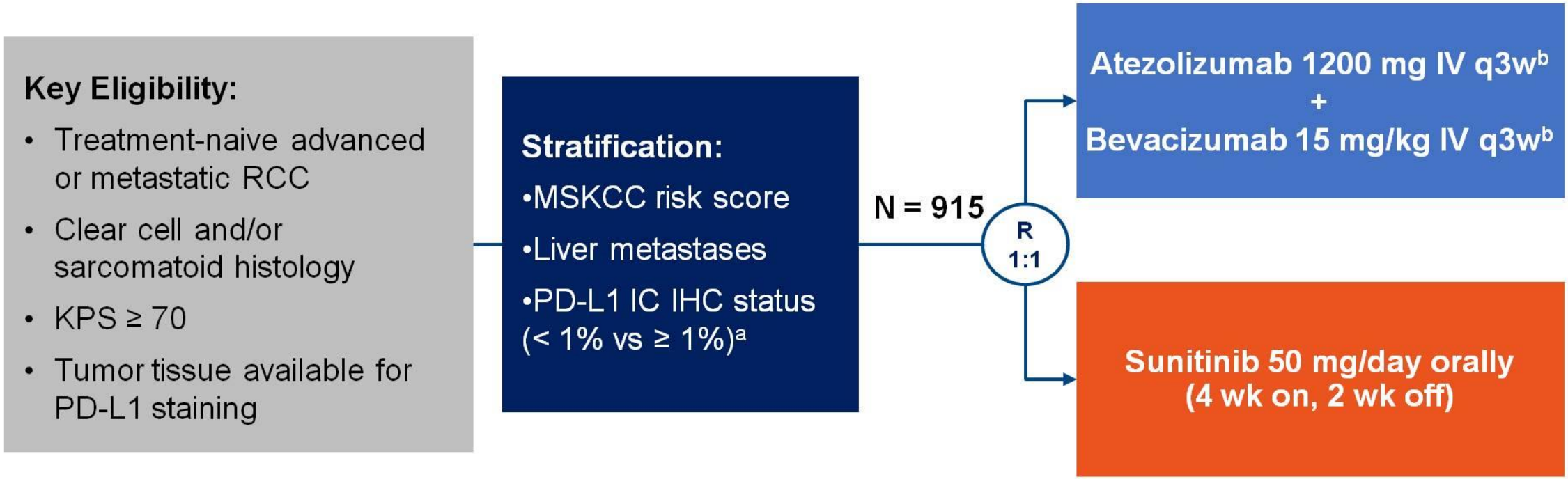
PRESENTED AT: 2018 Genitourinary Cancers Symposium | #GU18

Presented By Robert Motzer at 2018 Genitourinary Cancers Symposium: Translating Evidence to Multidisciplinary Care

Study Design

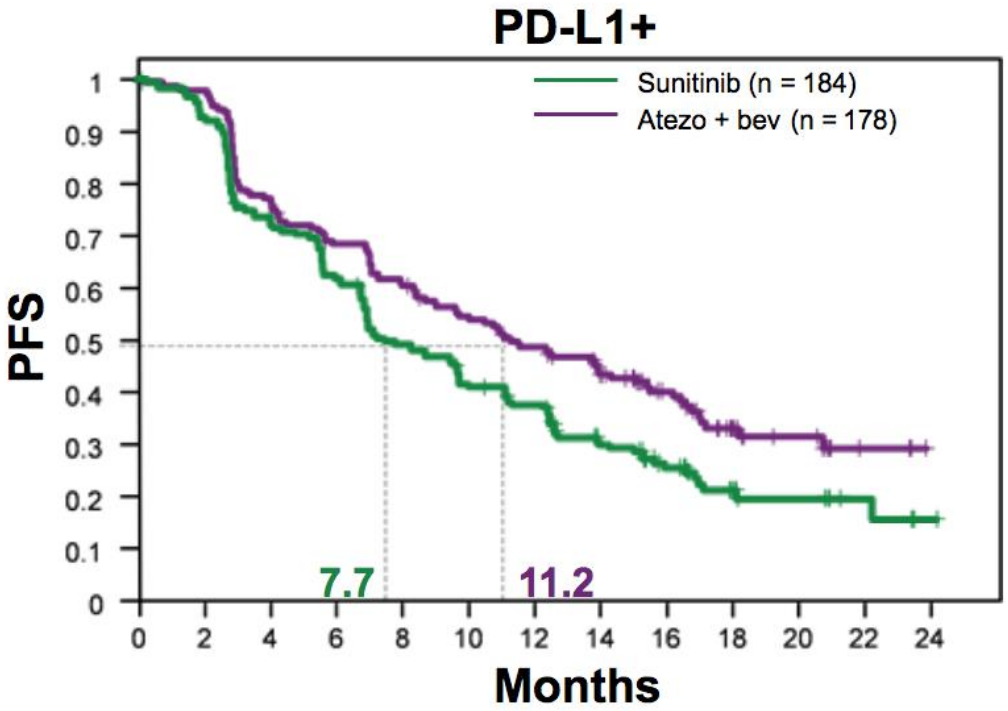


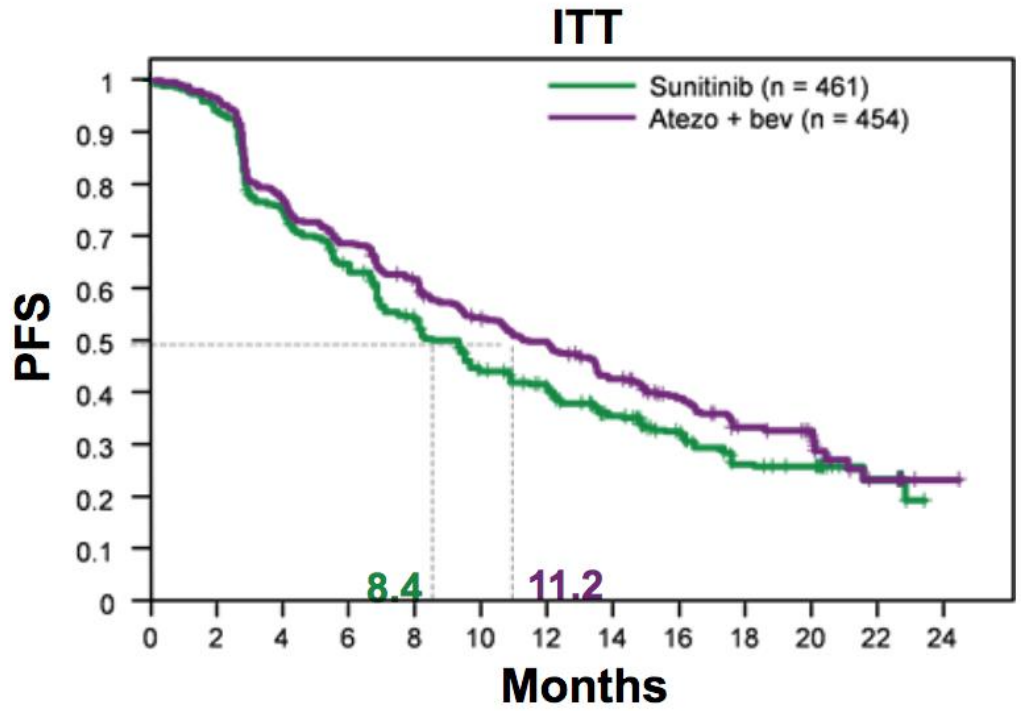
[a] ≥ 1% IC: 40% prevalence using SP142 IHC assay; [b] No dose reduction for atezolizumab or bevacizumab.

Baseline Characteristics

	PD-L1+ (n = 362)		ITT (N = 915)	
Characteristic	Atezo + Bev n = 178	Sunitinib n = 184	Atezo + Bev n = 454	Sunitinib n = 461
Age, median (range)	62 y (33-84)	59 y (23-80)	62 y (24-88)	60 y (18-84)
Male	67%	79%	70%	76%
KPS ≥ 80	95%	95%	91%	92%
Liver metastasis	17%	18%	17%	18%
Prior nephrectomy	84%	83%	74%	72%
Predominant clear cell histology	92%	87%	93%	92%
Sarcomatoid component	20%	27%	15%	16%
≥ 1% of IC expressing PD-L1 (PD-L1+)	-	-	39%	40%
MSKCC risk category				
Favorable (0)	17%	18%	20%	20%
Intermediate (1 or 2)	74%	73%	71%	70%
Poor (≥ 3)	8%	9%	10%	10%

IMmotion151: PFS Summary





HR (95% CI)		
	PD-L1+	ITT
Atezo + bev vs sunitinib	0.74 (0.57, 0.96); *P* = 0.02[a]	0.83 (0.70, 0.97)

PFS assessed by investigators. Minimum follow-up, 12 months. Median follow-up, 16 months (PD-L1+) and 15 months (ITT).
[a] The PFS analysis passed the pre-specified *P* value boundary of α = 0.04.
Motzer RJ, et al. ASCO GU 2018 [abstract 578].

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

Molecular correlates differentiate response to atezolizumab + bevacizumab vs sunitinib: results from a Phase III study (IMmotion151) in untreated metastatic renal cell carcinoma

Brian I. Rini,[1] Mahrukh Huseni,[2] Michael B. Atkins,[3] David F. McDermott,[4] Thomas Powles,[5] Bernard Escudier,[6] Romain Banchereau,[2] Li-Fen Liu,[2] Ning Leng,[2] Jinzhen Fan,[2] Jennifer Doss,[2] Stefani Nalle,[2] Susheela Carroll,[2] Shi Li,[2] Christina Schiff,[2] Marjorie Green,[2] Robert J. Motzer[7]

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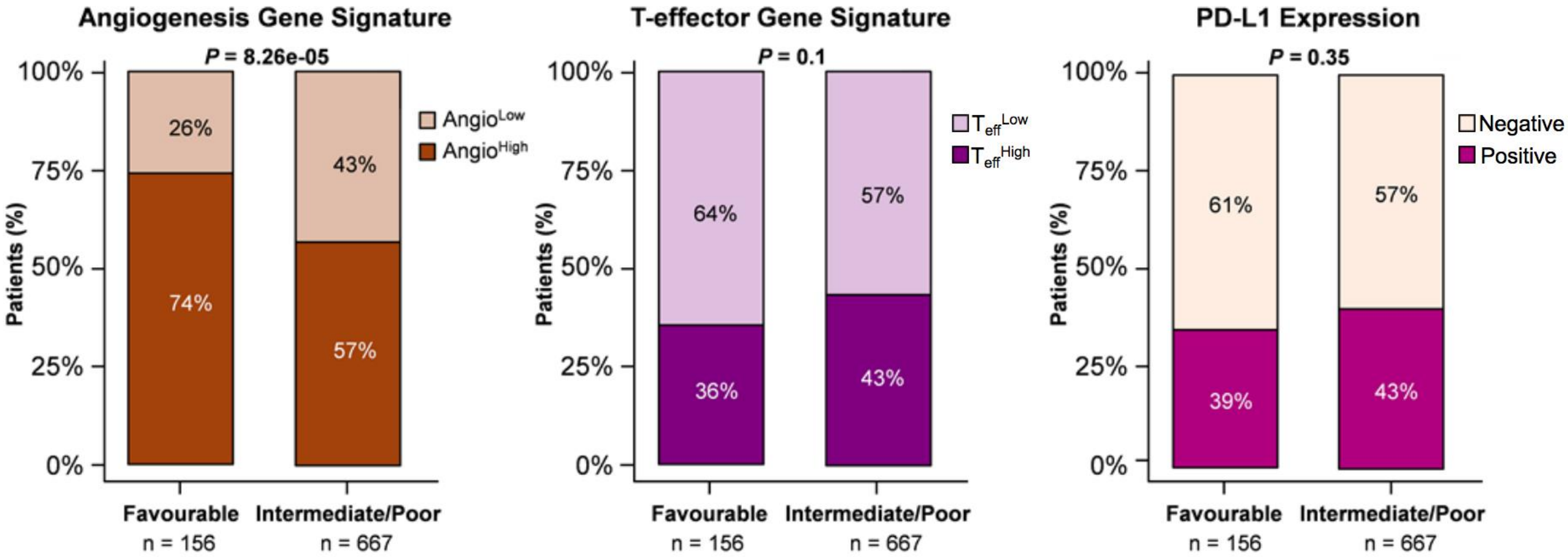
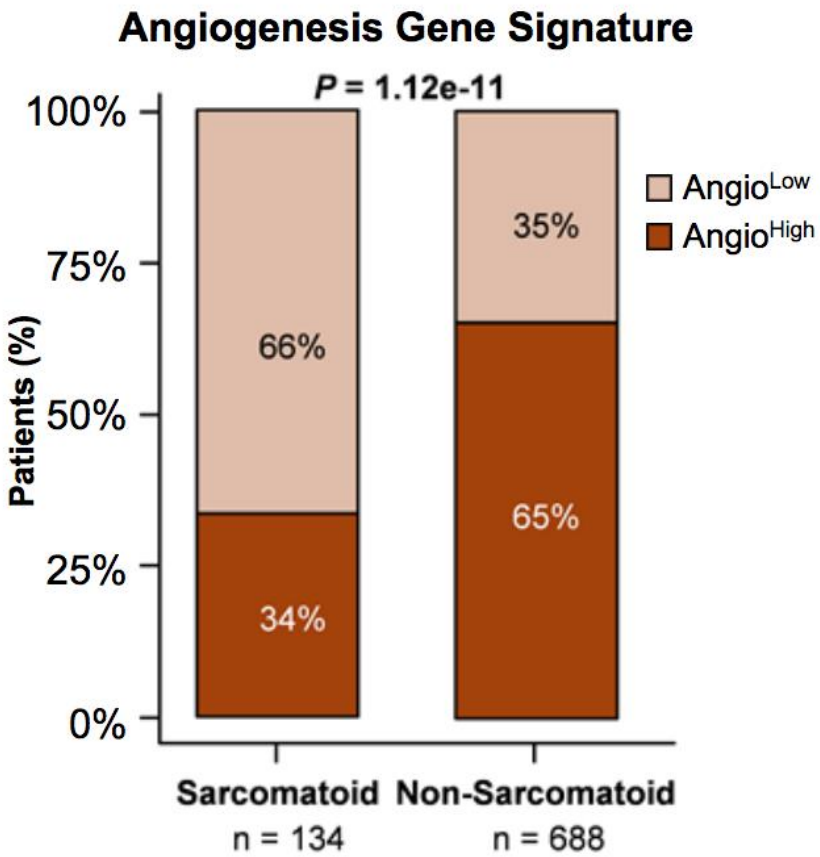
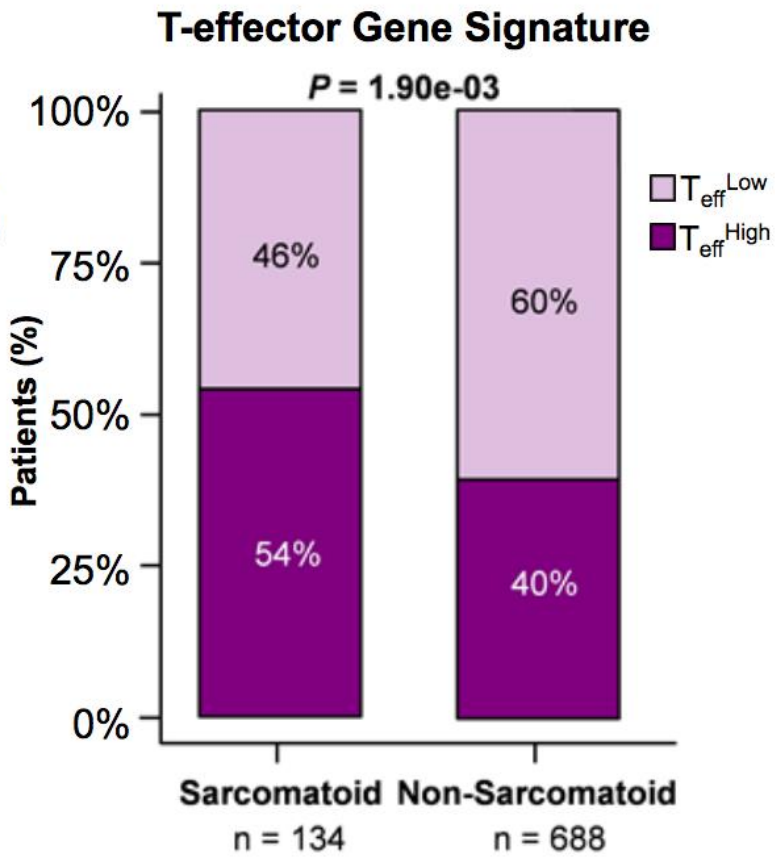
Angiogenesis Gene Expression Is Higher in Favourable MSKCC Risk Group

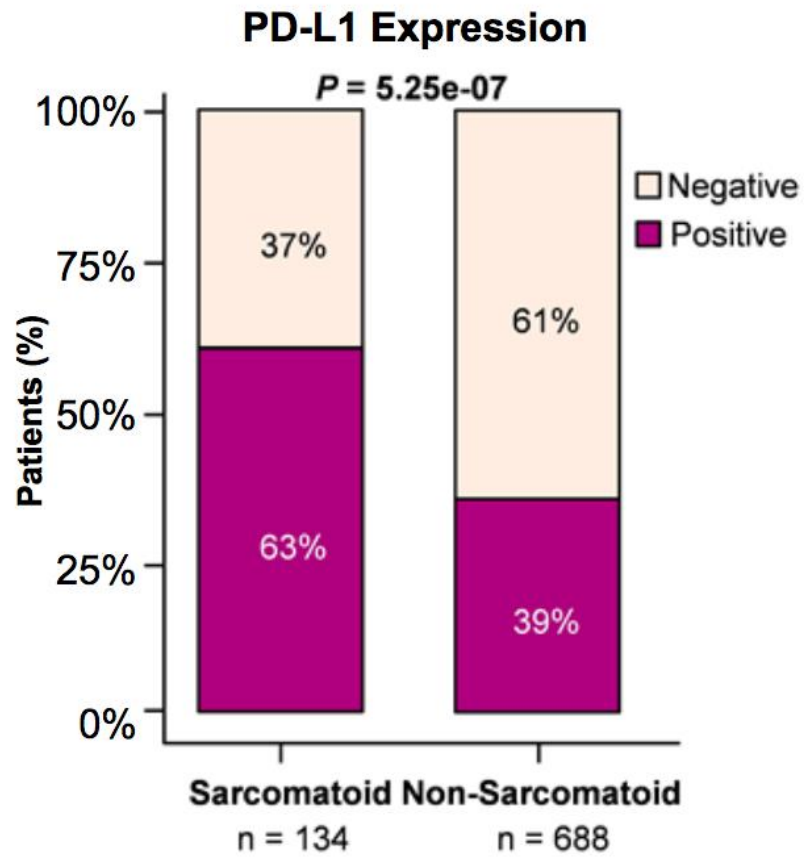


Rini B, et al. IMmotion151 Biomarkers. ESMO 2018 [abstract LBA31]. http://bit.ly/2yaVgyl

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







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Summary

- IO-IO (Ipi – Nivo) Standard of Care for Intermediate & Poor Risk
- Good risk patients – currently TKI
  - IO-TKI combo likely efficacy
  - Ipi-Nivo may demonstrate durability of response with longer follow up vs TKI
- PDL-1 not an adequate predictive biomarker for patient selection

Moving Forward

- Adjuvant IO , IO + IO studies ongoing
  - RAMPART, BMS 914

- Heterogeneity particularly marked in RCC
  - TMB modest, no correlation with activity of atezoluzimab + bev (McDermott Nature Med)
  - High Indel frequency (Turajlic et al)
  - Identification of truncal neo-antigens (Turajlic et al) may provide a target for cellular therapies