IO-based Doublets in Metastatic RCC

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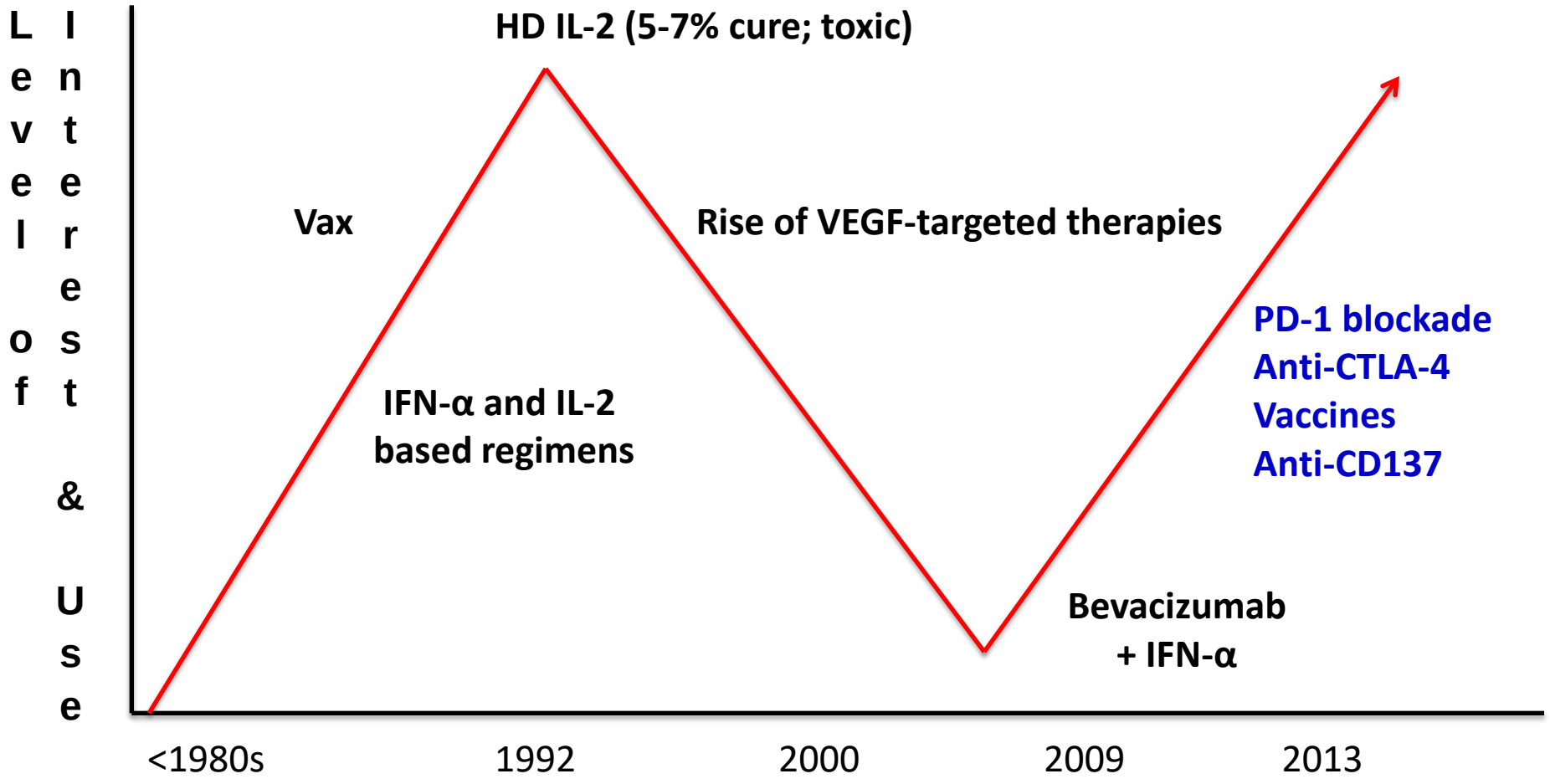
Disclosures*

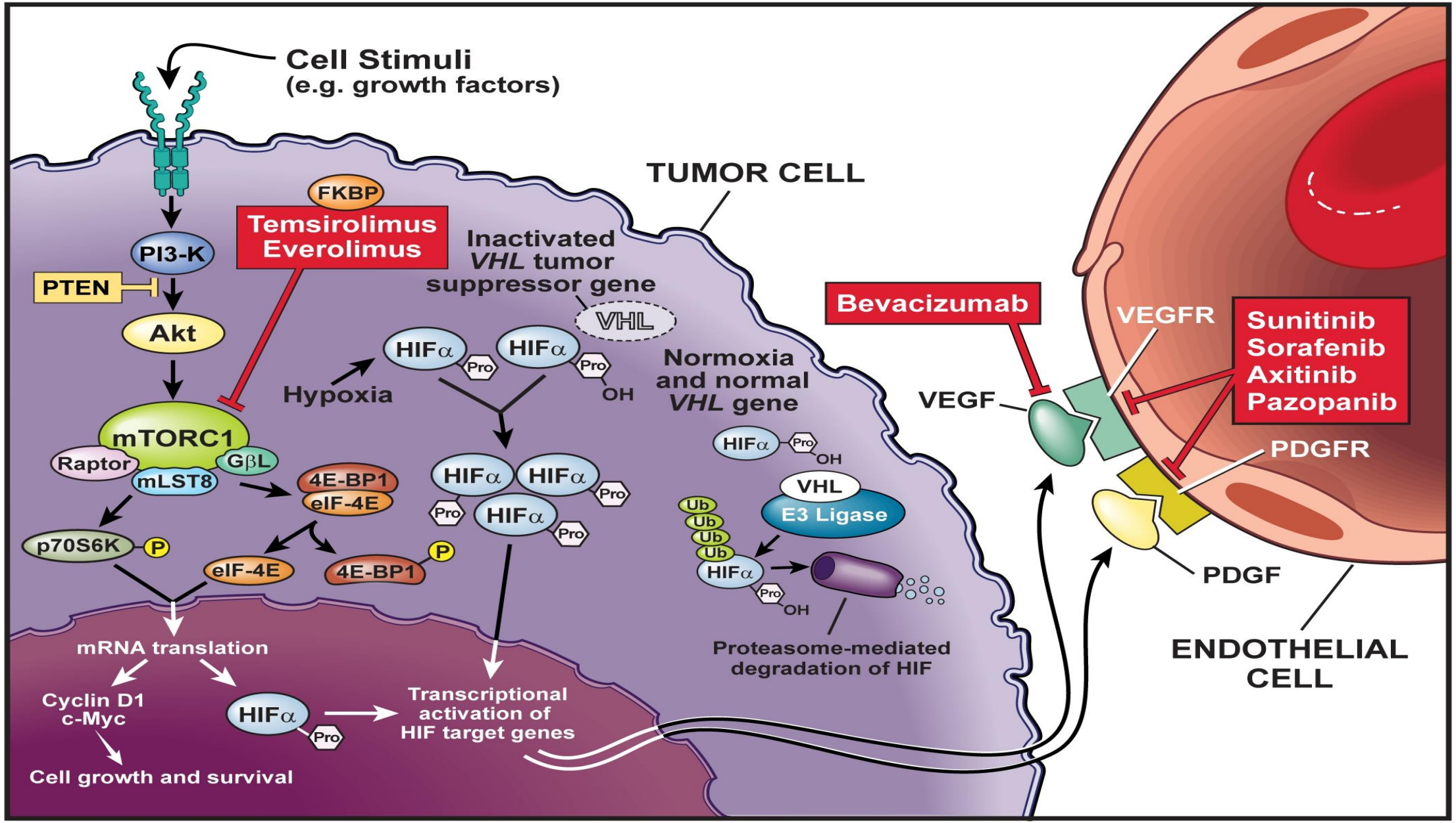
- **Research Funding to Institution: Pfizer, Merck, GNE/Roche, Peloton, Aveo, Astra-Zeneca, BMS**
- **Consulting: BMS, Pfizer, GNE/Roche, Aveo, Novartis, Synthorx, Peloton, Compugen, Merck, Corvus, Exelixis**
- **Stock: PTC therapeutics**

*Last 36 months

Ebb and Flow of Immunotherapy in RCC



HD IL-2: high dose interleukin-2; IFN: interferon


Cell Stimuli
(e.g. growth factors)
TUMOR CELL
FKBP
Temsirolimus
Everolimus
PI3-K
PTEN
Akt
mTORC1
Raptor
GβL
mLST8
4E-BP1
eIF-4E
p70S6K
P
eIF-4E
4E-BP1
P
mRNA translation
Cyclin D1
c-Myc
Cell growth and survival
HIFα
Pro
Transcriptional
activation of
HIF target genes
Inactivated
VHL tumor
suppressor gene
VHL
Hypoxia
HIFα
Pro
OH
Normoxia
and normal
VHL gene
VHL
E3 Ligase
Ub
Proteasome-mediated
degradation of HIF
Bevacizumab
VEGF
VEGFR
Sunitinib
Sorafenib
Axitinib
Pazopanib
PDGFR
PDGF
ENDOTHELIAL
CELL

CCF
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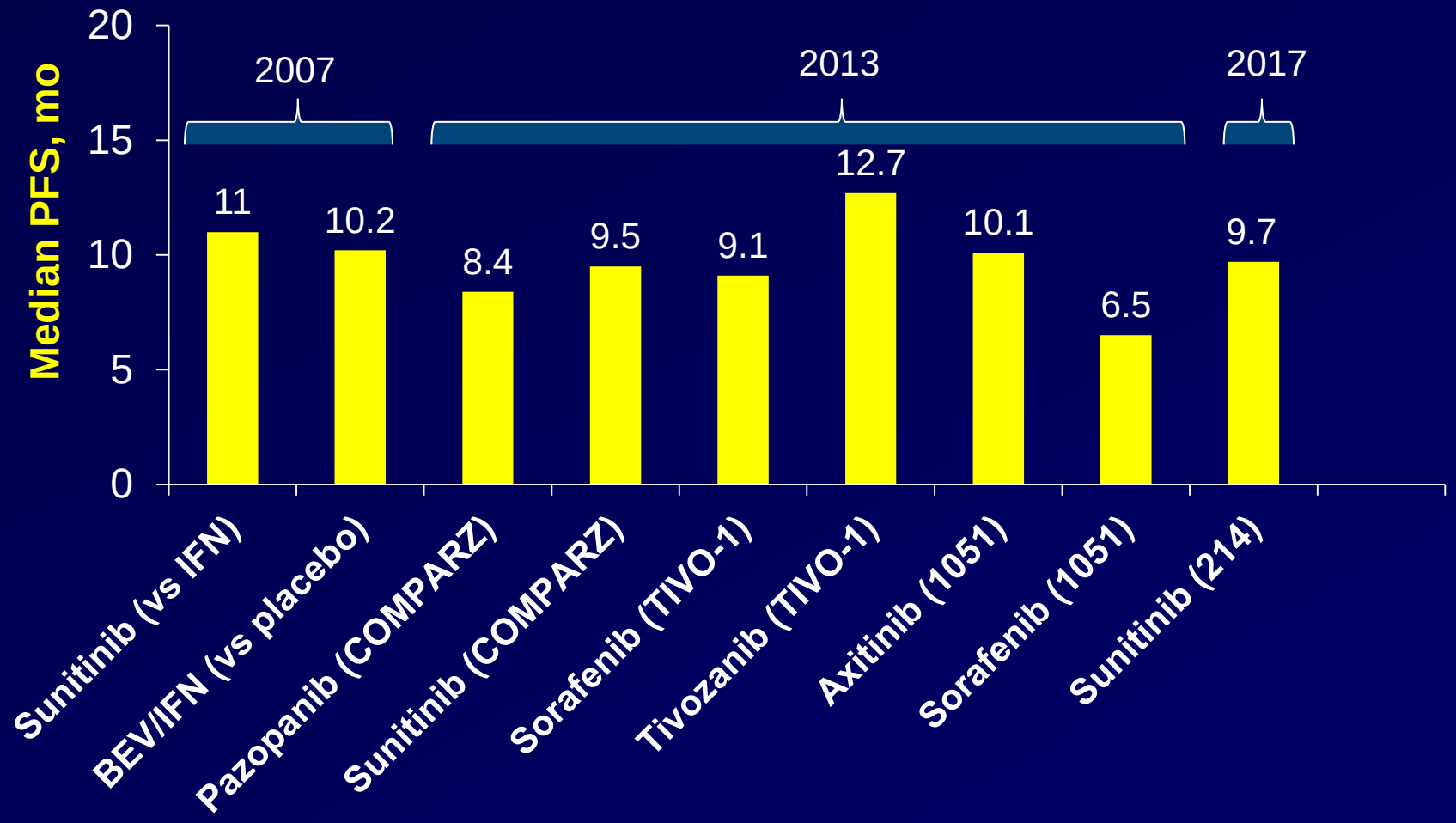
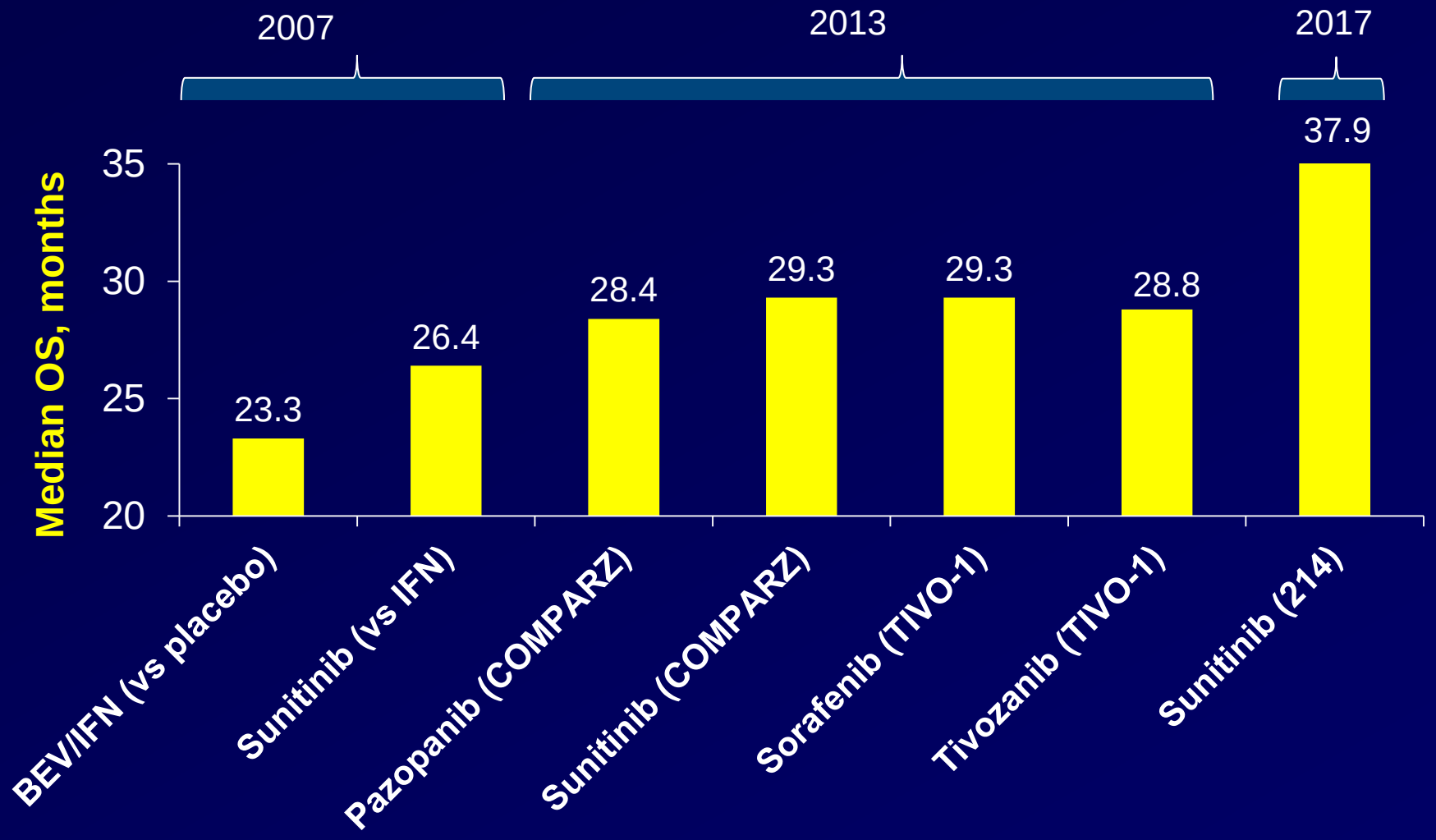
Median PFS With VEGFR-TKIs in Front-Line Phase 3 Studies[1-6]



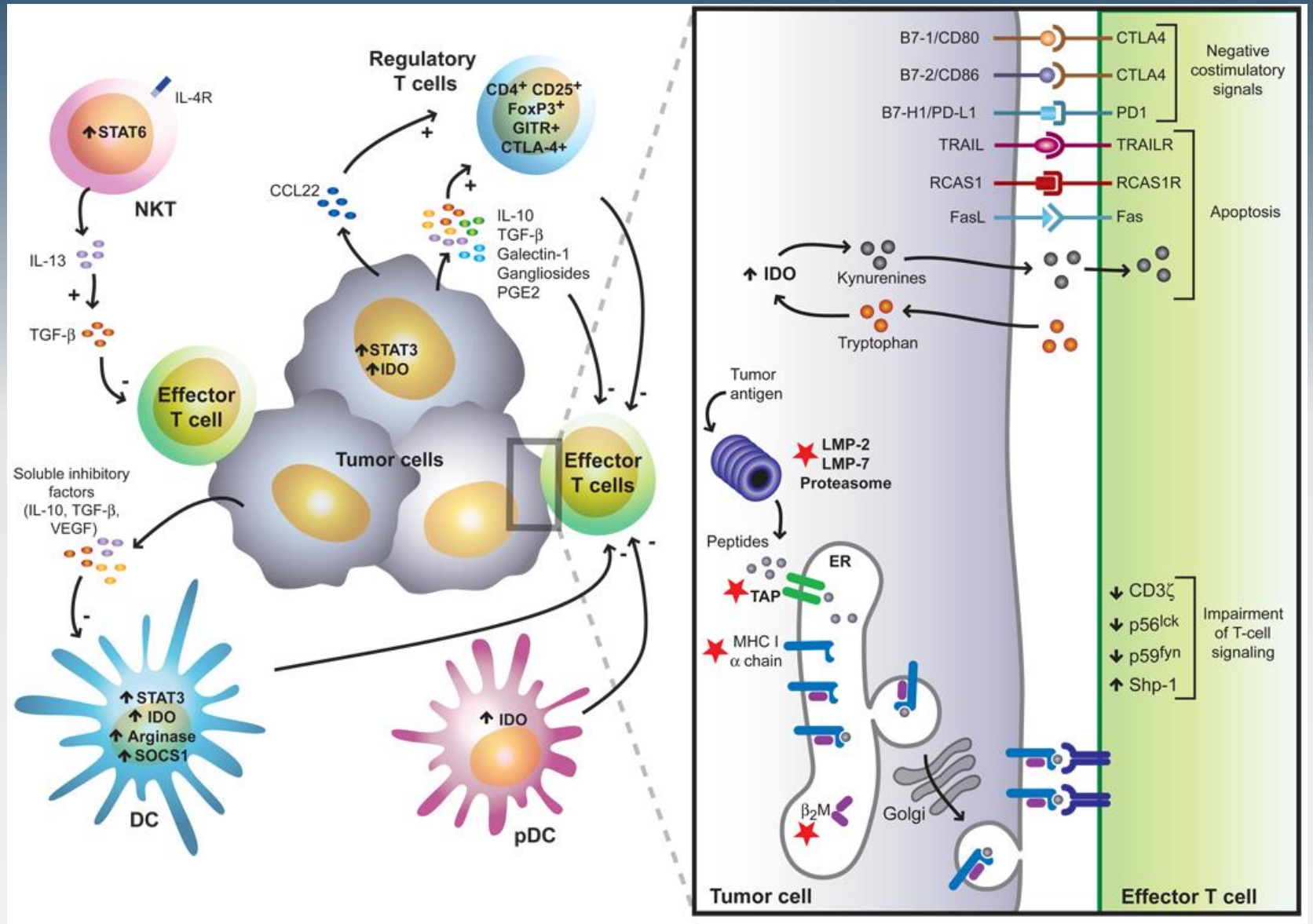
1. Motzer RJ. *N Engl J Med*. 2013;356:115-124. 2. Escudier B et al. *Lancet*. 2007;370:2103-2111. 3. Motzer RJ et al. *N Engl J Med.* 2013;369:722-731. 4. Motzer RJ et al. *J Clin Oncol*. 2013;31:3791-3799. 5. Hutson TE at al. *Lancet Oncol*. 2013;14:1287-1294. 6. Rini BI et al. *J Clin Oncol*. 2014;32:752-759.

VEGF-TKIs help patients live longer at a cost of chronic toxicity and ongoing therapy, with little to no cure rate

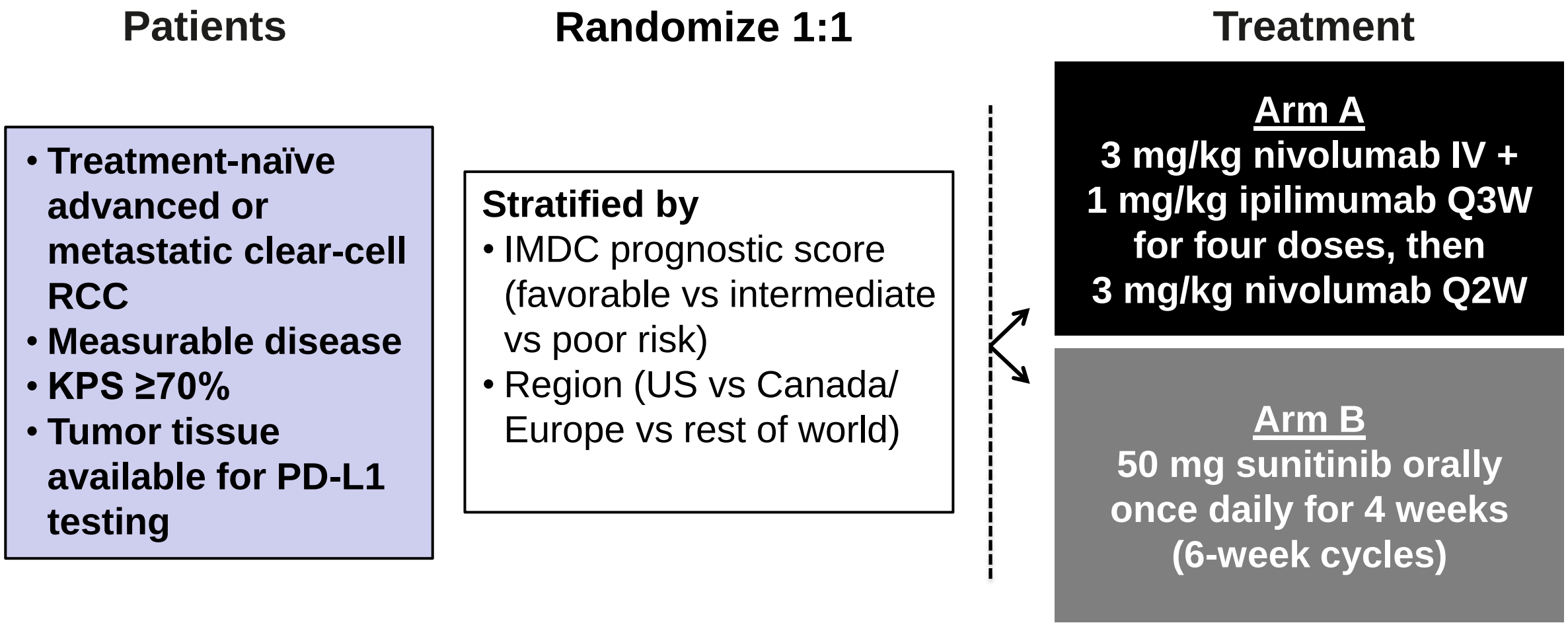


1. Motzer RJ. *N Engl J Med*. 2013;356:115-124. 2. Escudier B et al. *Lancet*. 2007;370:2103-2111. 3. Motzer RJ et al. *N Engl J Med.* 2013;369:722-731.
4. Motzer RJ et al. *J Clin Oncol*. 2013;31:3791-3799. 5. Hutson TE at al. *Lancet Oncol*. 2013;14:1287-1294.
6. Rini BI et al. *J Clin Oncol*. 2014;32:752-759.

Immune recognition



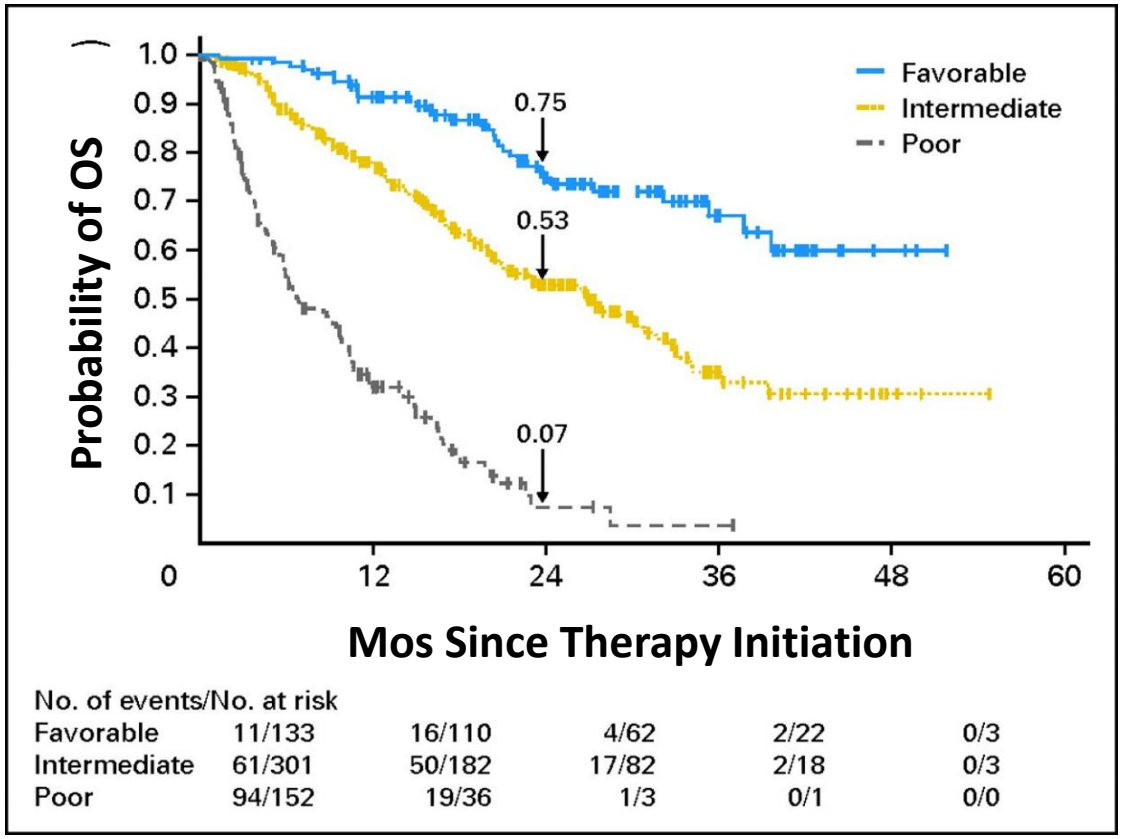
CheckMate 214: Study design



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

IMDC Prognostic Criteria

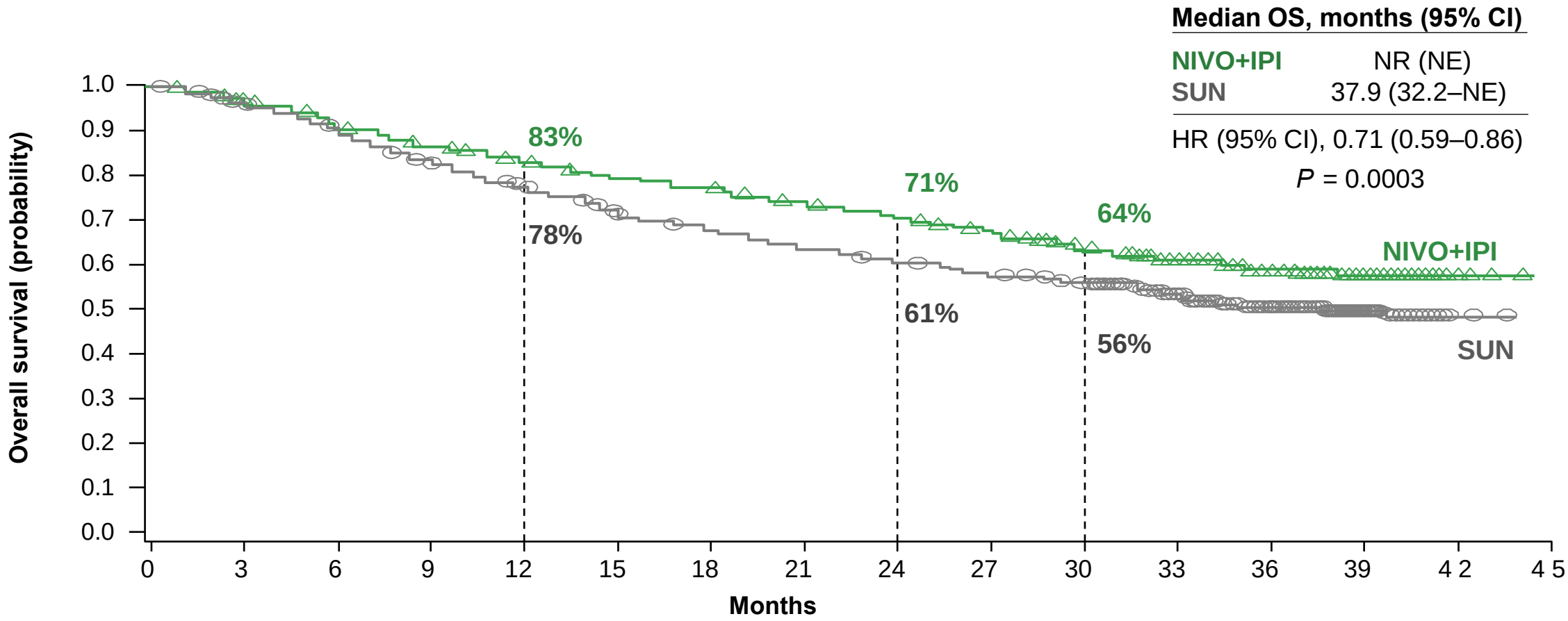
- Clinical
  - KPS < 80%
  - Time from diagnosis to tx < 1 yr
- Laboratory
  - Hemoglobin < LLN
  - Calcium > ULN
  - Neutrophil count > ULN
  - Platelet count > ULN



Favorable: 0 risk factors
Intermediate: 1-2 risk factors
Poor: 3-6 risk factors

Heng. JCO. 2009;27:5794.

Overall Survival: ITT Patients



No. at risk

NIVO+IPI	550	523	492	464	443	425	410	389	371	351	327	271	161	58	4	0
SUN	546	507	472	435	404	367	345	325	310	295	275	232	145	55	5	0

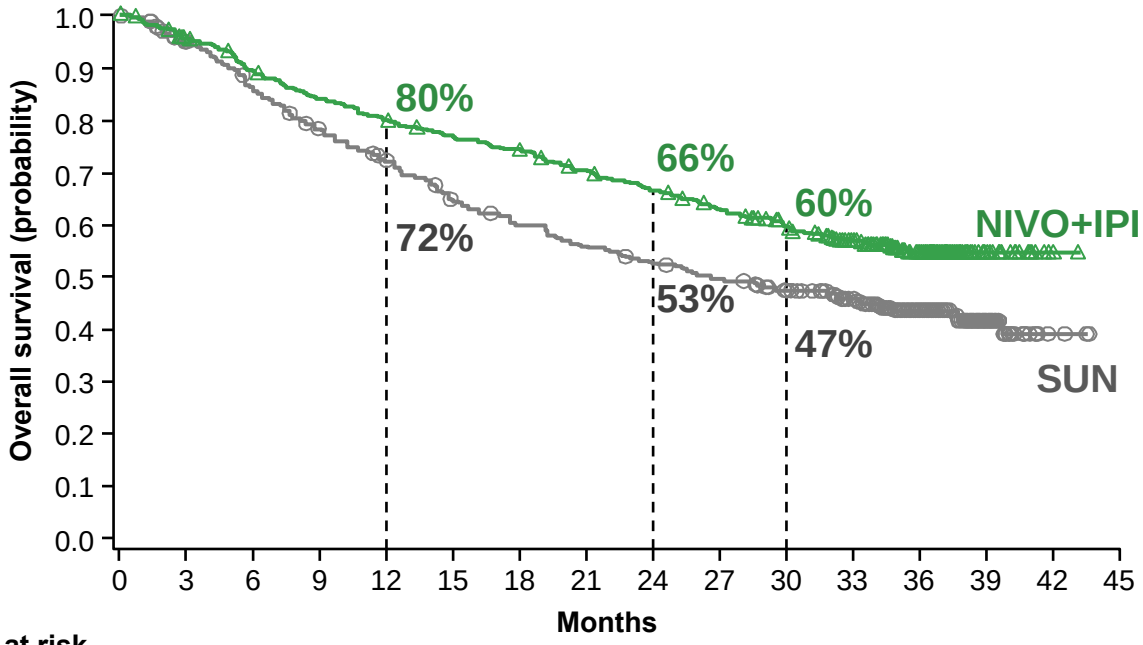
CI, confidence interval; NE, not estimable; NR, not reached.

Overall Survival: by IMDC Risk

Intermediate/poor risk

Median OS, months (95% CI)	
NIVO+IPI	NR (35.6–NE)
SUN	26.6 (22.1–33.4)

HR (95% CI), 0.66 (0.54–0.80)
P < 0.0001



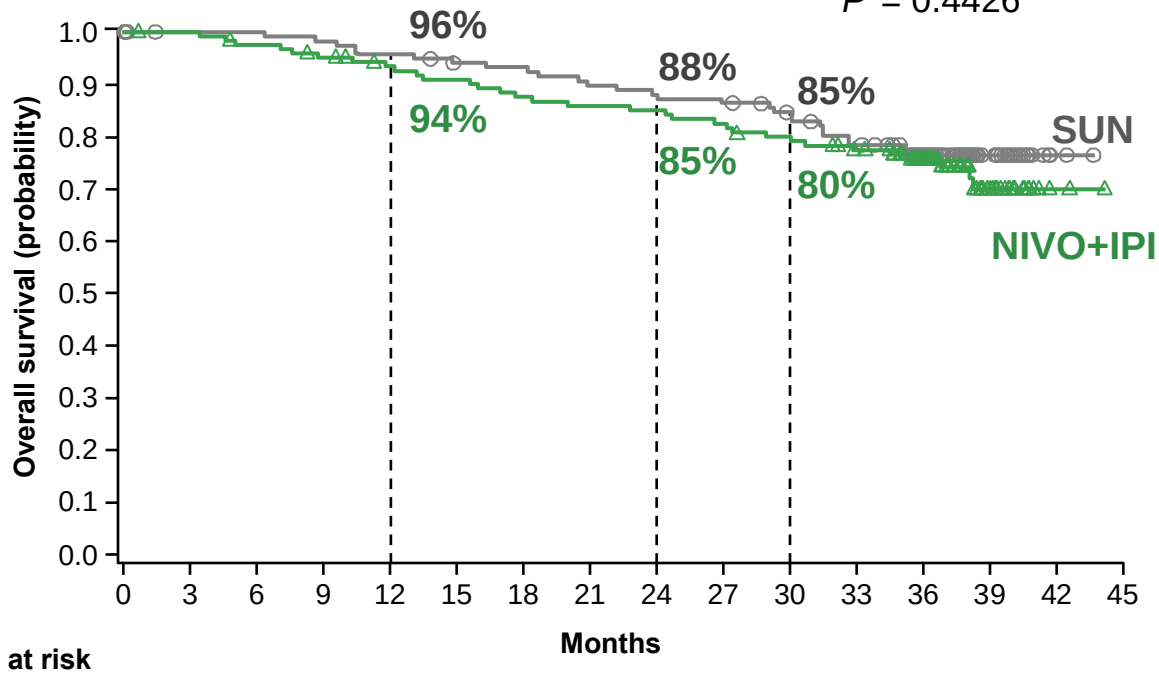
No. at risk

NIVO+IPI	425	399	372	348	332	317	306	287	270	253	233	183	90	34	2	0
SUN	422	388	353	318	290	257	236	220	207	194	179	144	75	29	3	0

Favorable risk

Median OS, months (95% CI)	
NIVO+IPI	NR (NE)
SUN	NR (NE)

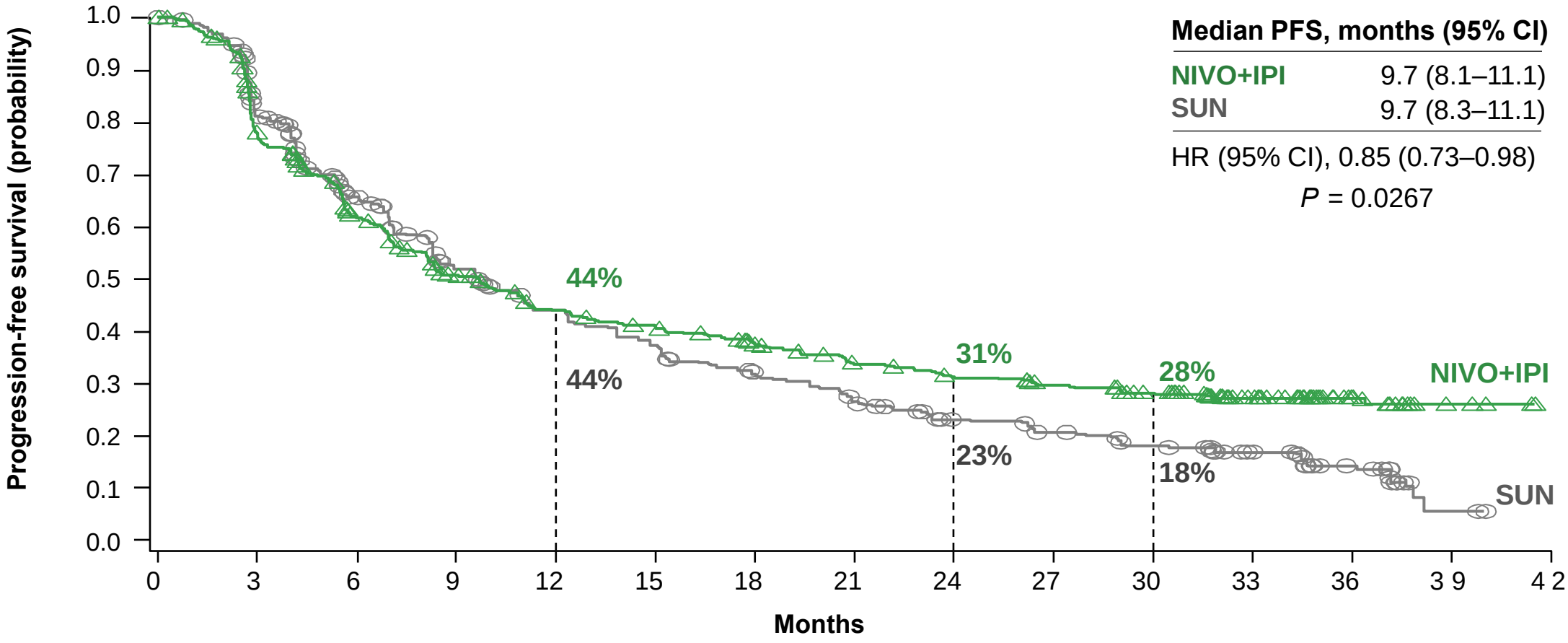
HR (95% CI), 1.22 (0.73–2.04)
P = 0.4426



No. at risk

NIVO+IPI	125	124	120	116	111	108	104	102	101	98	94	88	71	24	2	0
SUN	124	119	119	117	114	110	109	105	103	101	96	88	70	26	2	0

Investigator-Assessed Progression-Free Survival per RECIST v1.1: ITT Patients

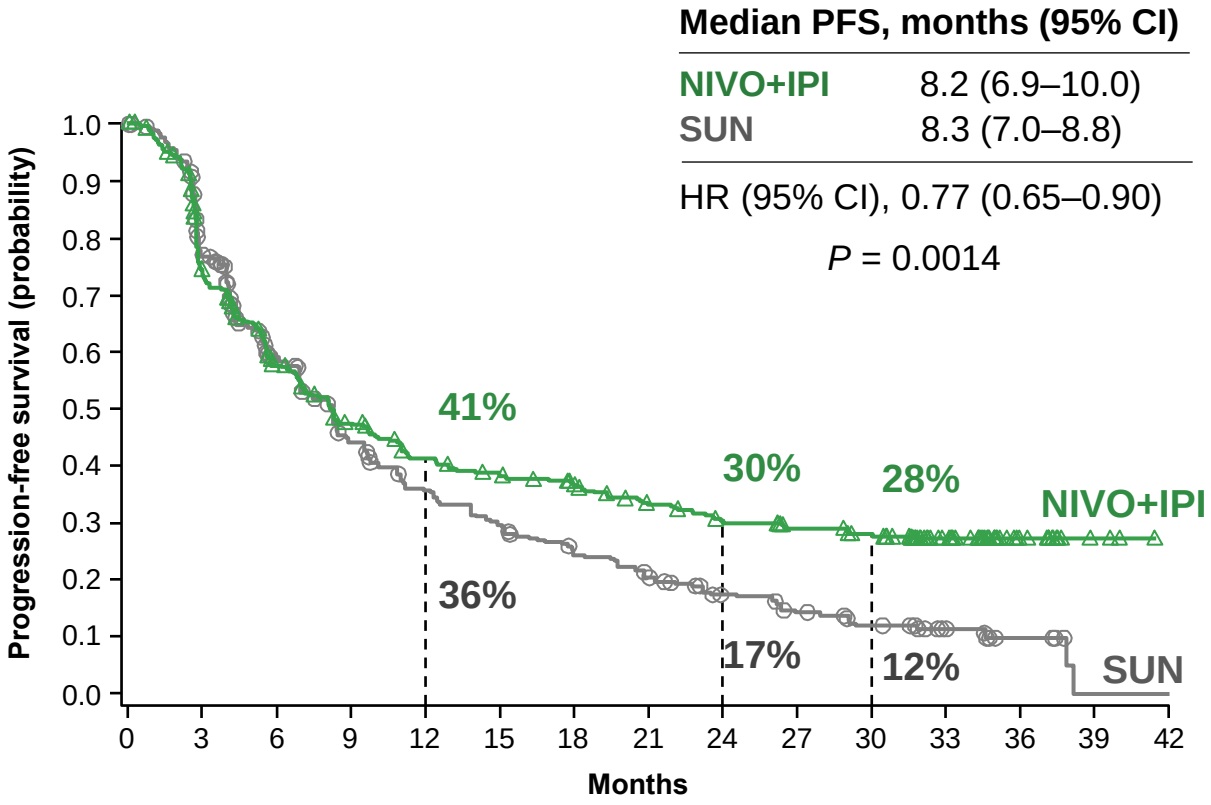


No. at risk

NIVO+IPI	550	403	306	242	204	188	167	143	131	120	108	70	25	4	0
SUN	546	404	298	225	185	157	130	106	85	74	62	47	21	2	0

Investigator-Assessed Progression-Free Survival per RECIST v1.1: by IMDC risk

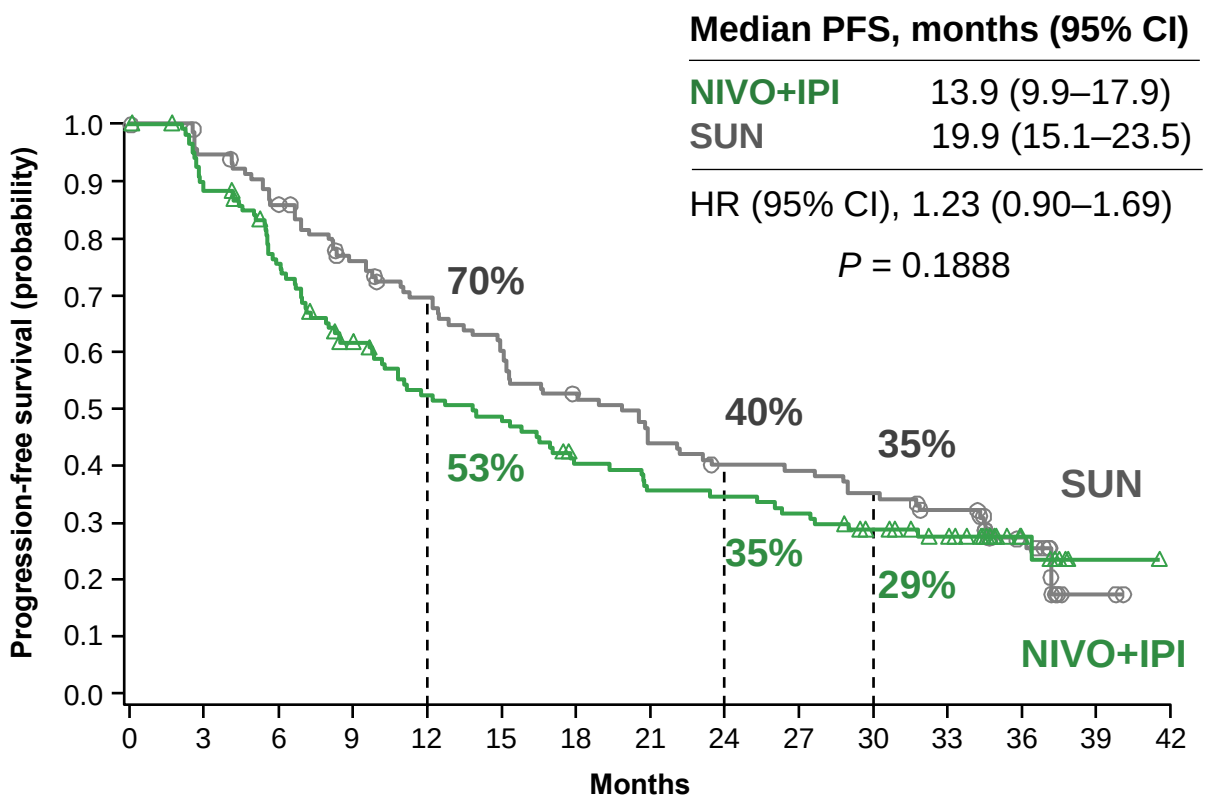
Intermediate/poor risk



No. at risk

NIVO+IPI	425	296	218	173	147	135	125	106	95	87	81	48	17	3	0
SUN	422	295	200	142	111	93	75	60	44	34	26	16	6	0	0

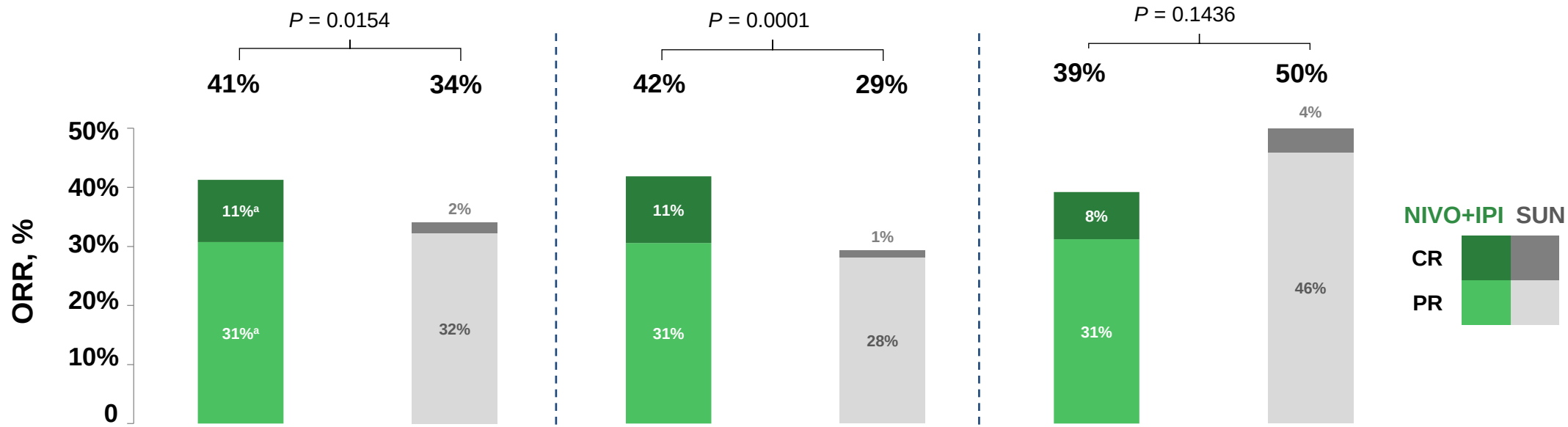
Favorable risk



No. at risk

NIVO+IPI	125	107	88	69	57	53	42	37	36	33	27	22	8	1	0
SUN	124	109	98	83	74	64	55	46	41	40	36	31	15	2	0

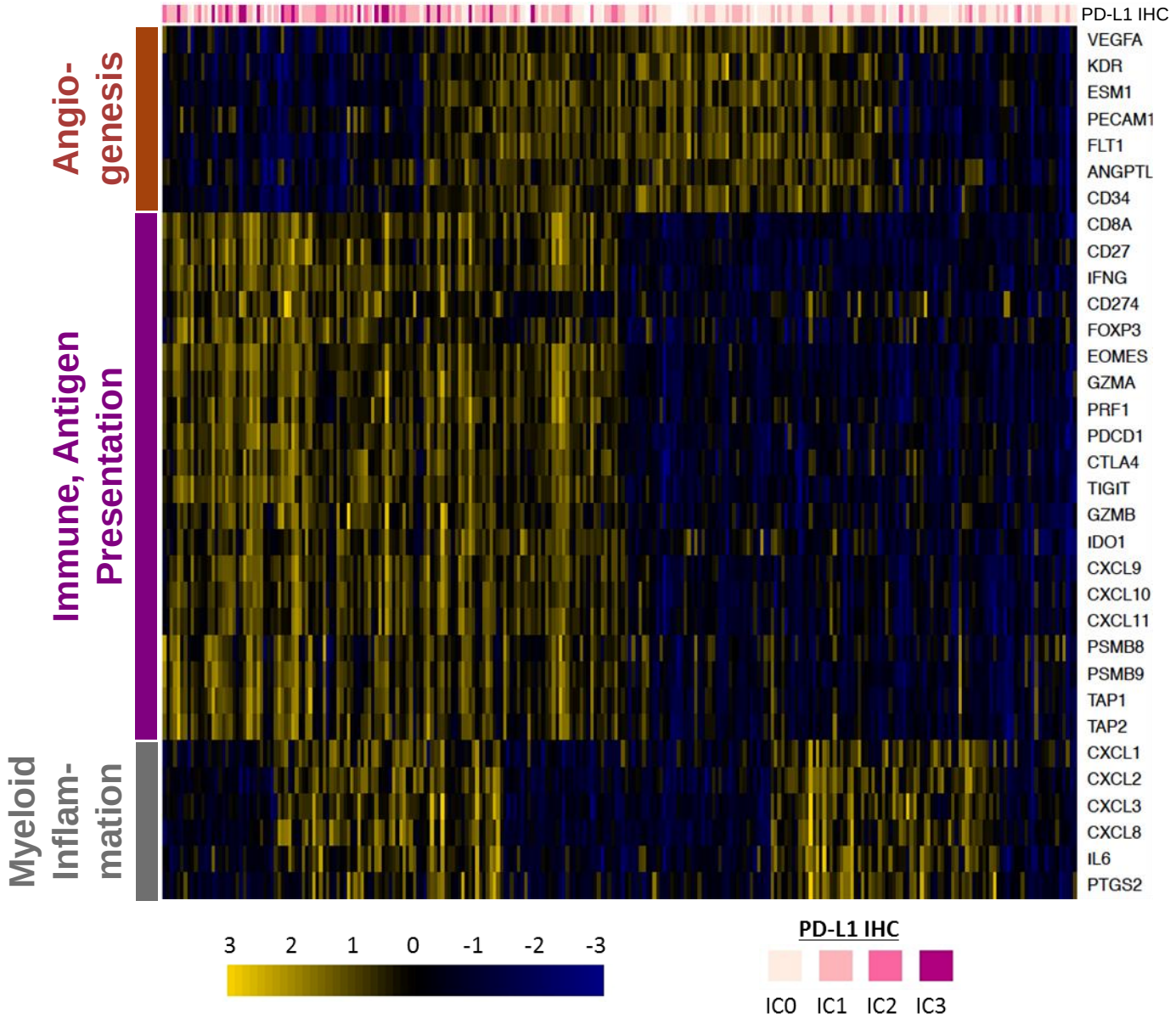
Investigator-Assessed Response per RECIST v1.1



	ITT population		Intermediate/poor risk[1]		Favorable risk	
	NIVO+IPI N = 550	SUN N = 546	NIVO+IPI N = 425	SUN N = 422	NIVO+IPI N = 125	SUN N = 124
DOR ≥18 months, %	53[b]	39	52[b]	28	57	60
Ongoing CR	88% (51/58)	60% (6/10)	88% (42/48)	80% (4/5)	90% (9/10)	40% (2/5)

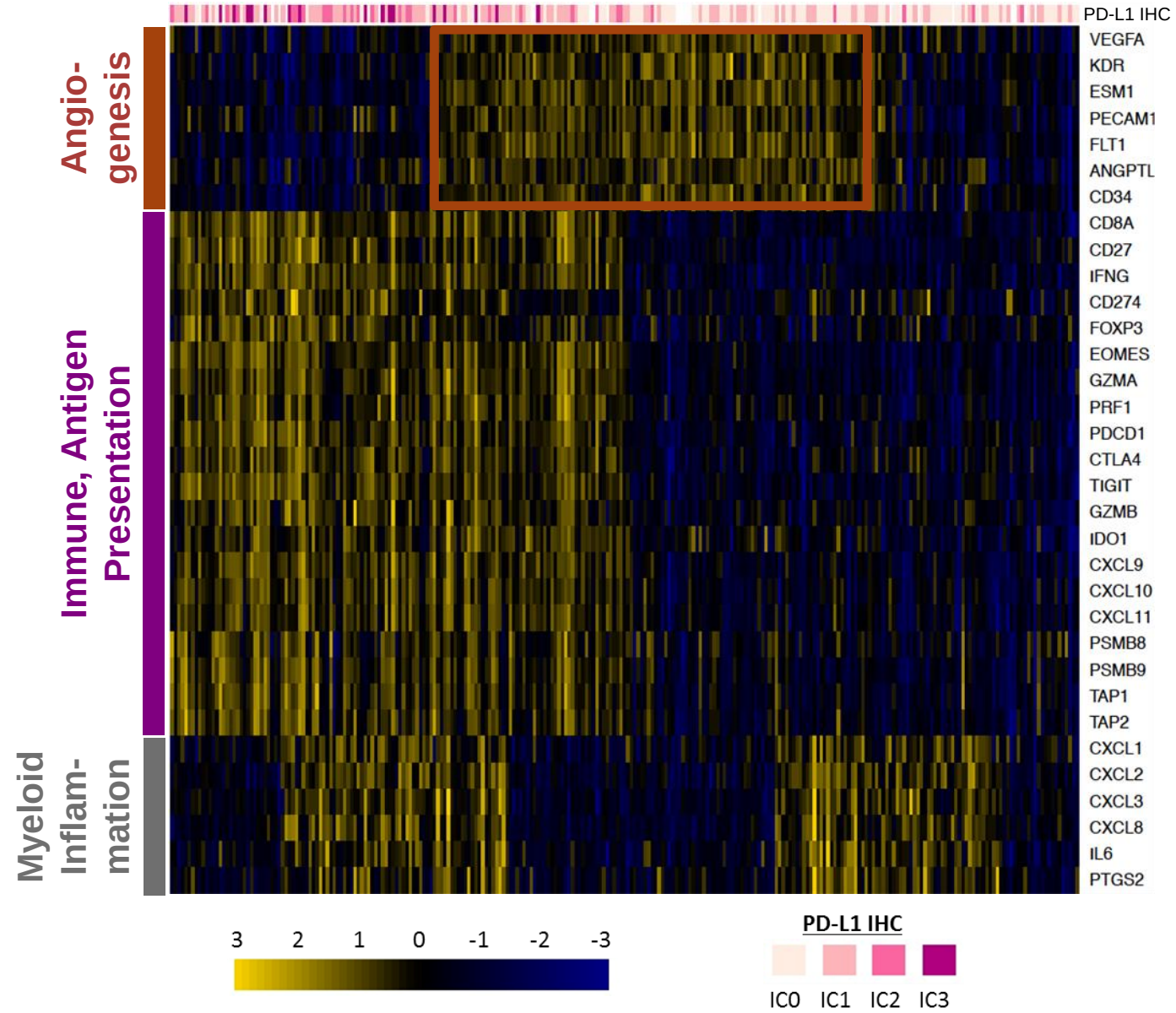
[a]Does not total 42% due to rounding (CR=10.5% and PR = 30.7%) [b]Duration of response could not be calculated for two intermediate/poor-risk partial responders to NIVO+IPI due to missing date of partial response.
CR, complete response; DOR, duration of response; PR partial response.
1. Rini BI, et al. Poster presentation at the European Society for Medical Oncology (ESMO) Congress; October 19–23, 2018; Munich, Germany. Poster 875P.

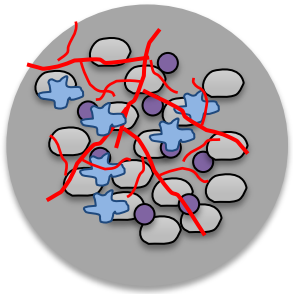
IMmotion150: Transcriptome Map of Angiogenesis and Immune-Associated Genes in RCC Tumours



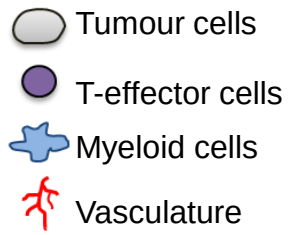
Rini B, et al. IMmotion151 Biomarkers. ESMO 2018 [abstract LBA31]. http://bit.ly/2yaVgyl

IMmotion150: Transcriptome Map of Angiogenesis and Immune-Associated Genes in RCC Tumours





Angiogenesis^{High}



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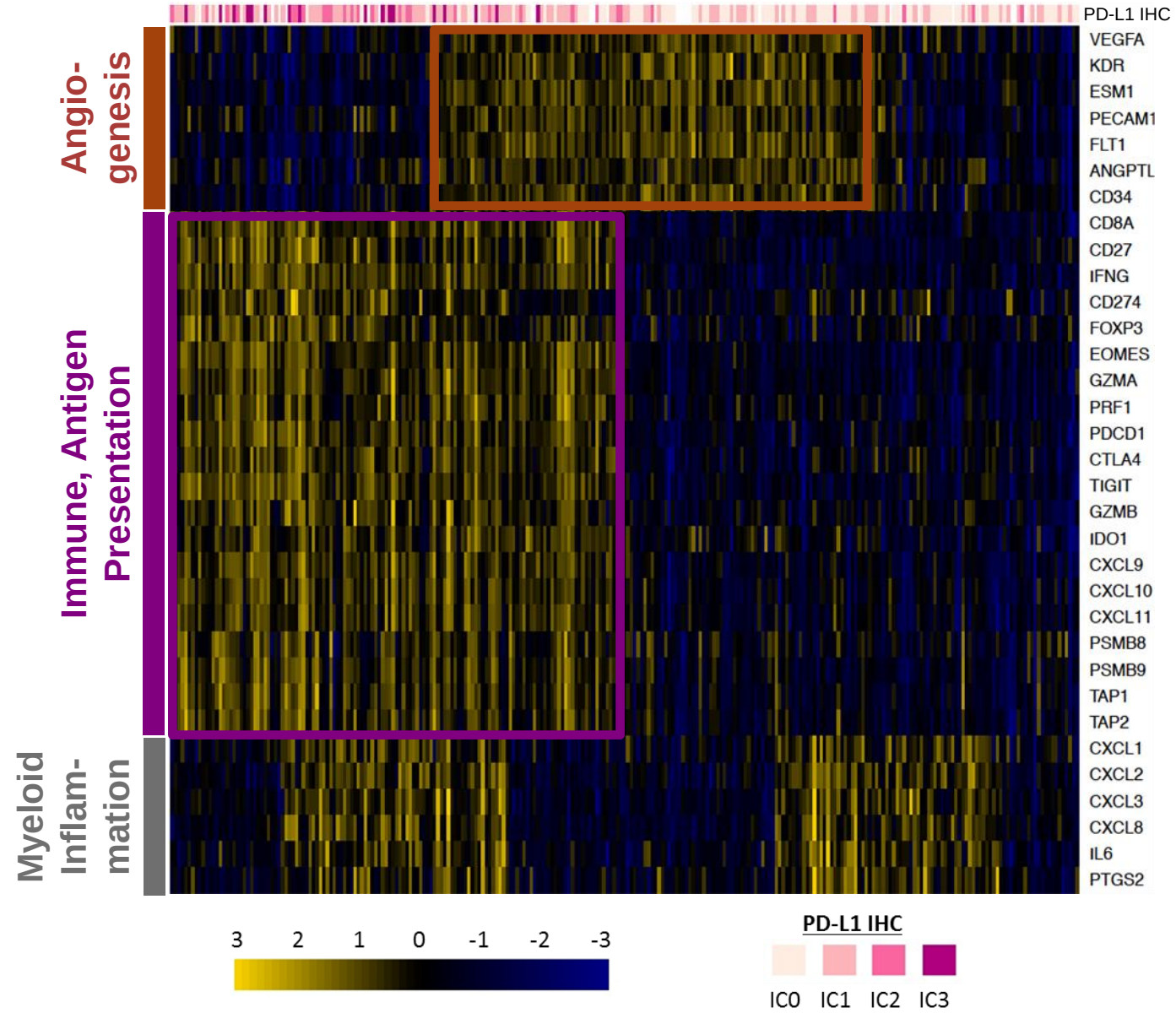
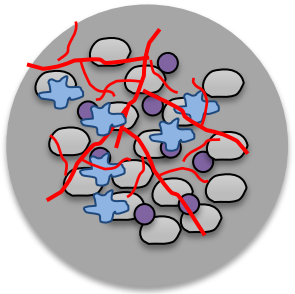
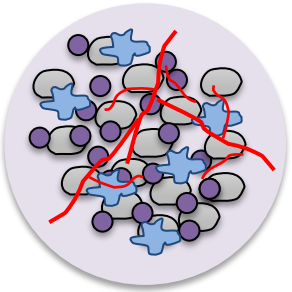
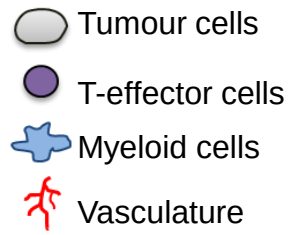




Angiogenesis^{High}

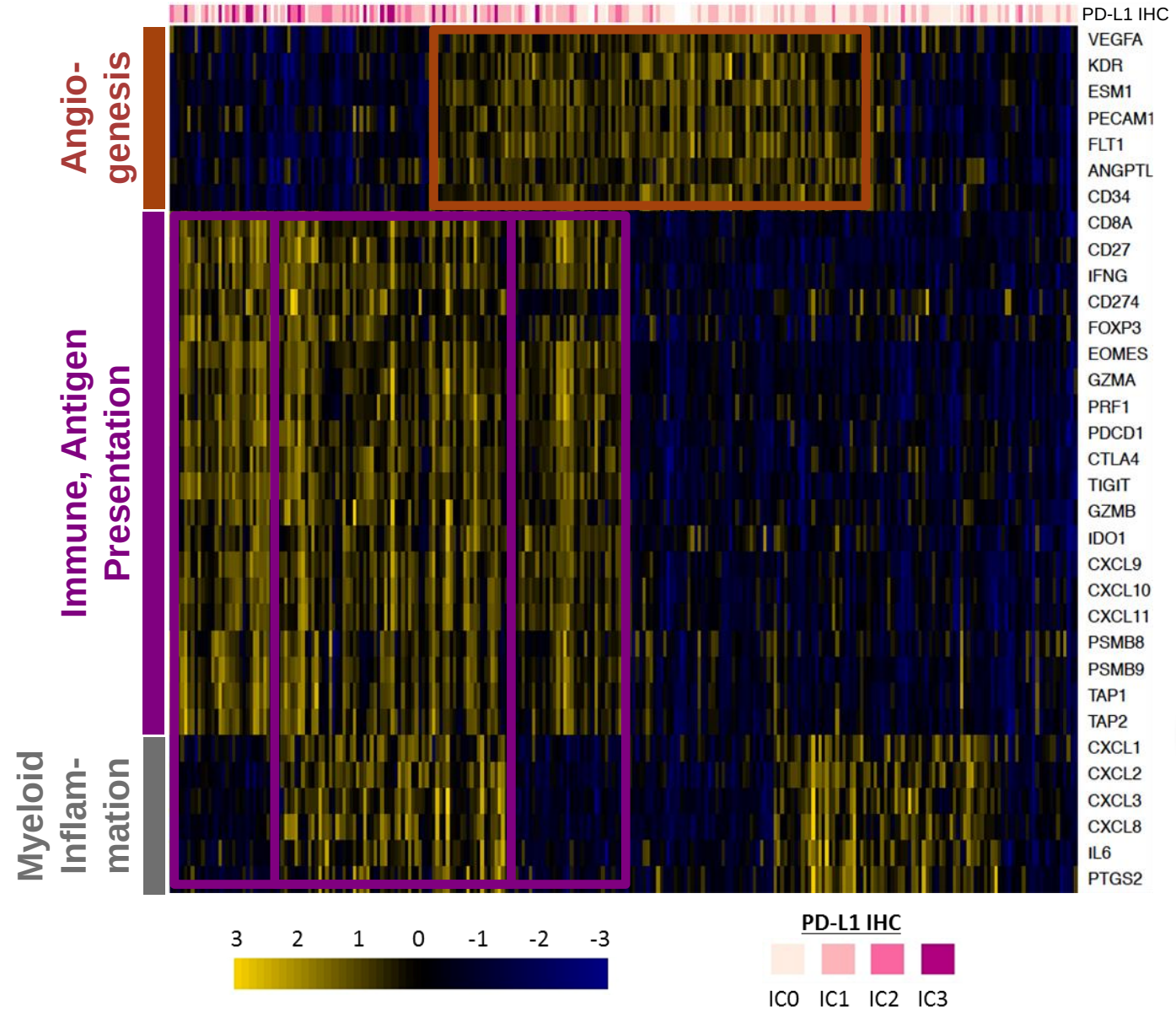


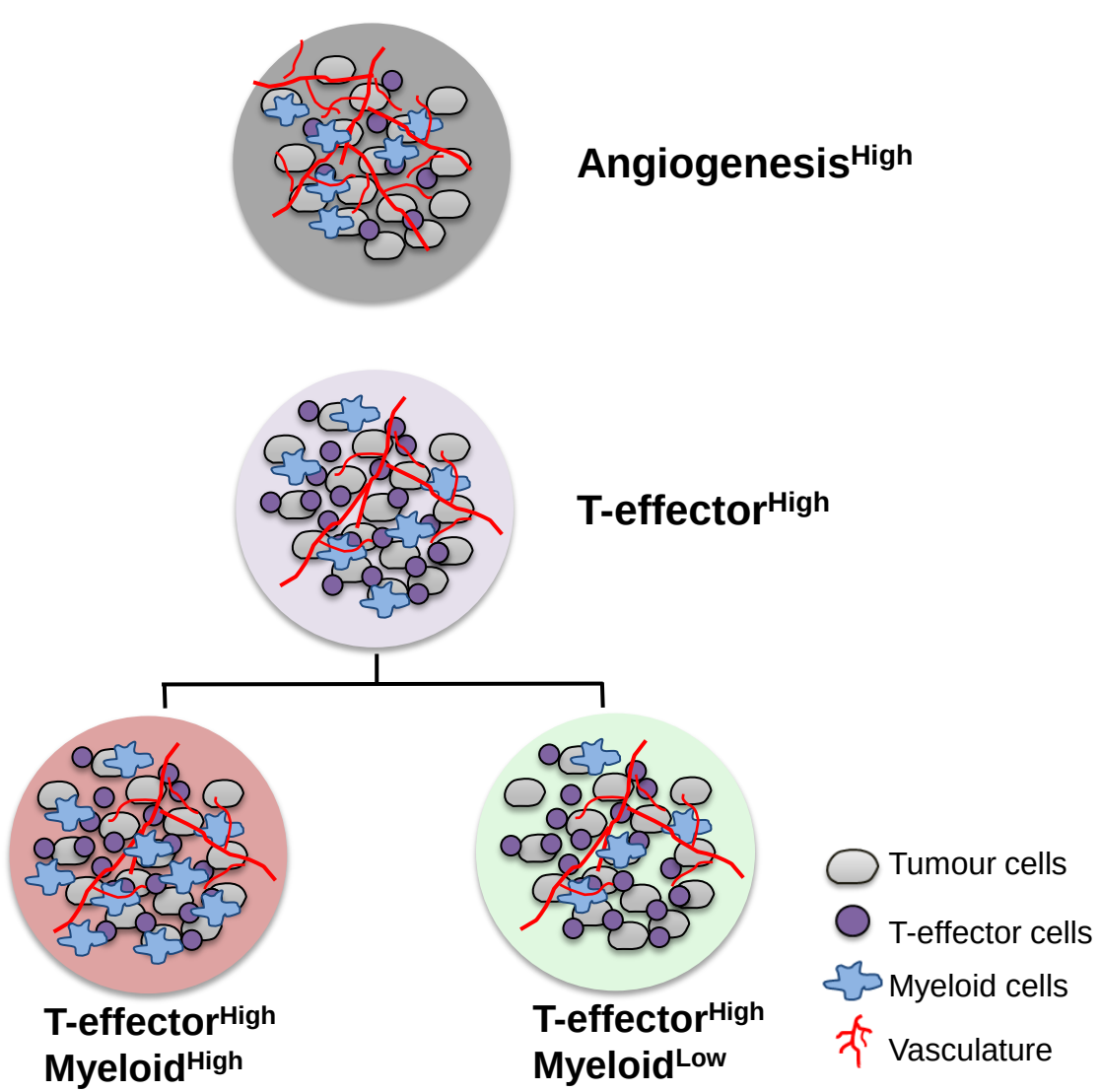
T-effector^{High}



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

IMmotion150: Transcriptome Map of Angiogenesis and Immune-Associated Genes in RCC Tumours





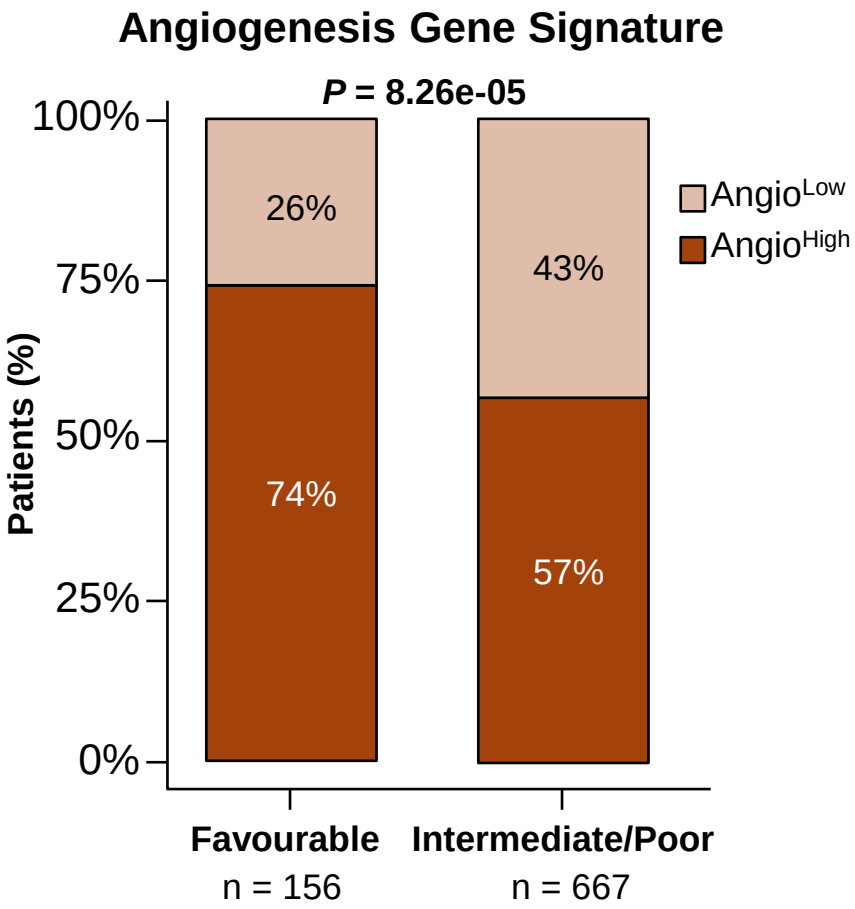
Rini B, et al. IMmotion151 Biomarkers. ESMO 2018 [abstract LBA31]. http://bit.ly/2yaVgyl

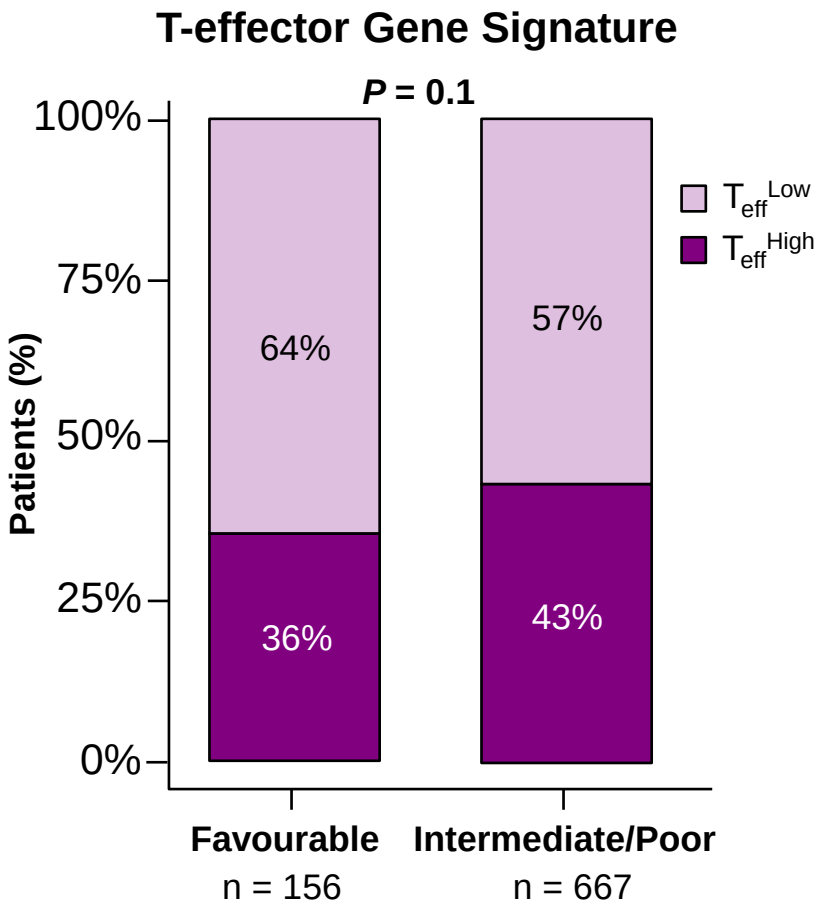
IMmotion150: Molecular Correlates of Differential Response to Atezolizumab ± Bevacizumab vs Sunitinib

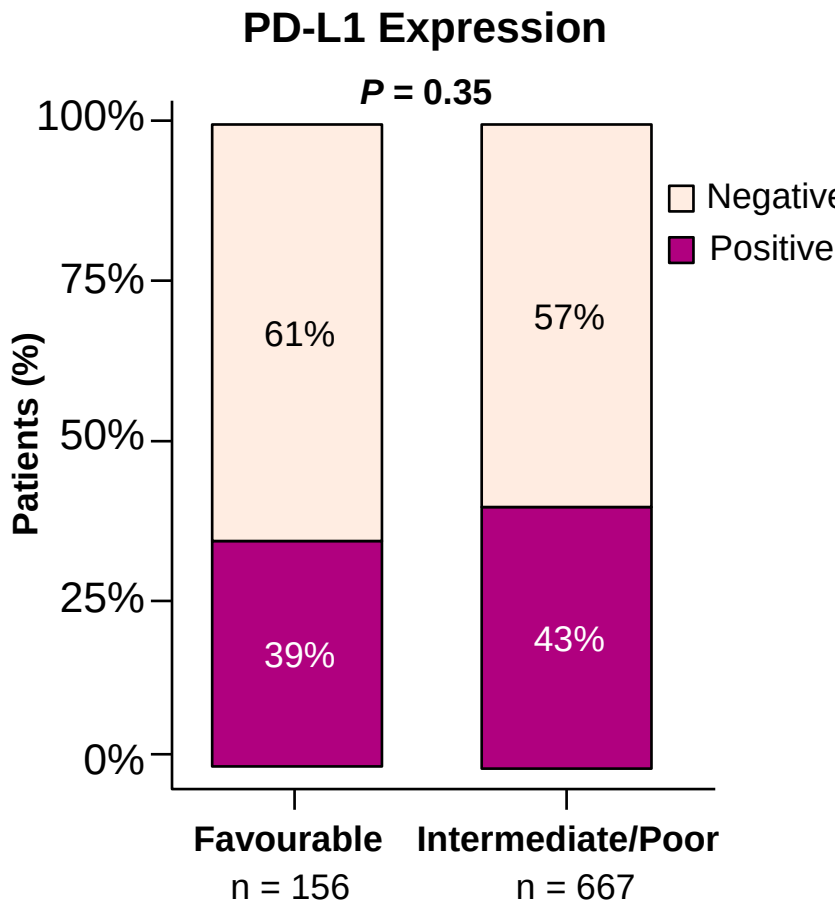
- Relative expression of Angiogenesis and T-effector gene signatures identified differential PFS benefits for atezolizumab ± bevacizumab vs sunitinib
  - Sunitinib showed improved PFS in Angiogenesis^{High} vs Angiogenesis^{Low} subsets
  - Atezolizumab + bevacizumab improved PFS vs sunitinib in T-effector^{High} and Angiogenesis^{Low} tumours
  - Atezolizumab + bevacizumab improved PFS vs atezolizumab in T-effector^{High} Myeloid^{High} tumours

McDermott DM, et al. *Nat Med.* 2018

Angiogenesis Gene Expression Is Higher in Favourable MSKCC Risk Group







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

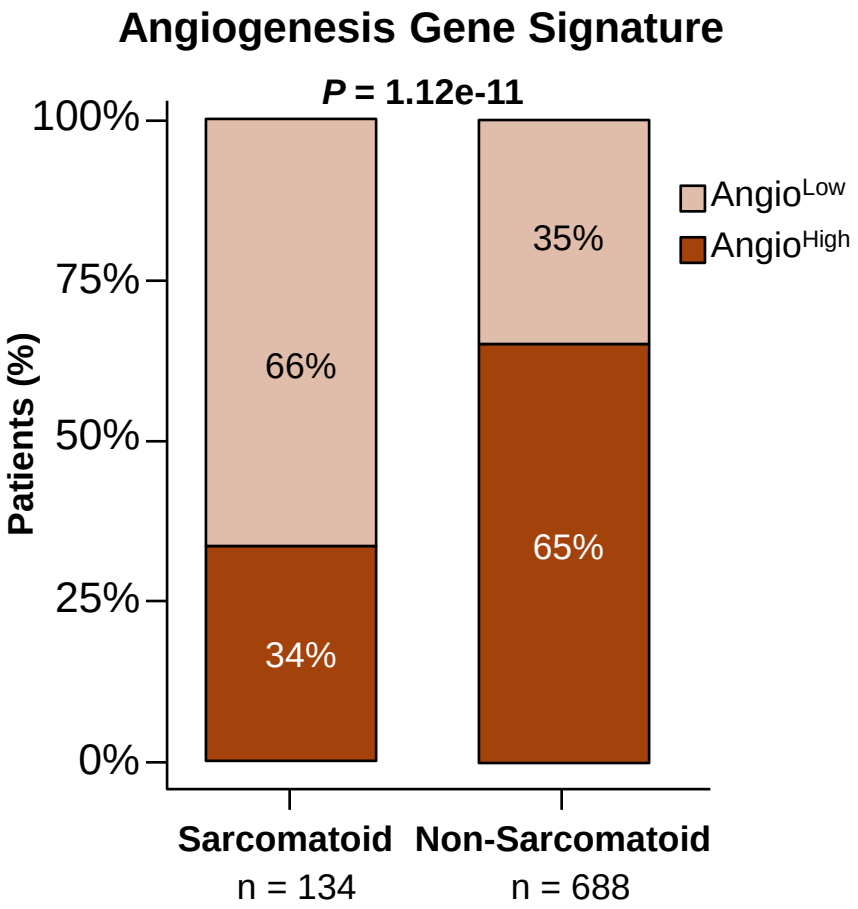
Investigator-Assessed Best Overall Response per RECIST v1.1: All Randomized and Sarcomatoid Intermediate/Poor-Risk Patients

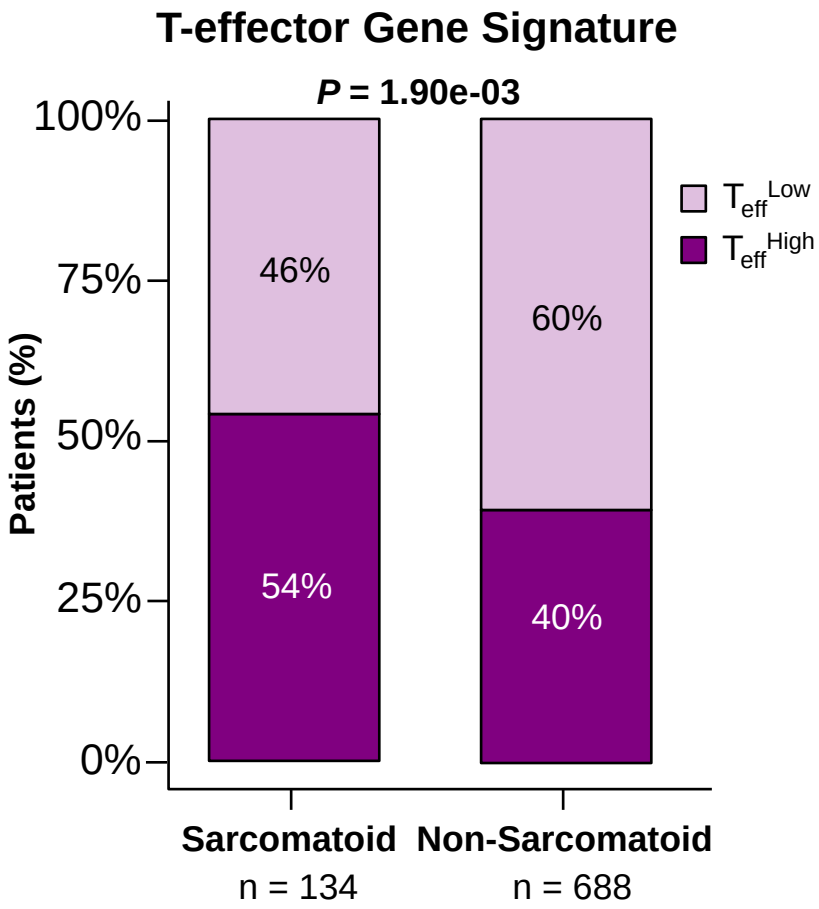
	Sarcomatoid intermediate/poor risk		All intermediate/poor risk[1]	
	NIVO + IPI N = 60	SUN N = 52	NIVO + IPI N = 425	SUN N = 422
Confirmed ORR (95% CI), %	**56.7 (43.2–69.4)**	**19.2 (9.6–32.5)**	**41.9 (37.1–46.7)**	**29.4 (25.1–34.0)**
P value	<0.0001		0.0001	
Confirmed BOR, %				
Complete response	**18.3**	**0**	11.3	1.2
Partial response	**38.3**	**19.2**	30.6	28.2
Stable disease	8.3	42.3	25.9	41.2
Progressive disease	25.0	28.8	24.9	19.0
Unable to determine/not reported	10.0	9.6	7.3	10.4

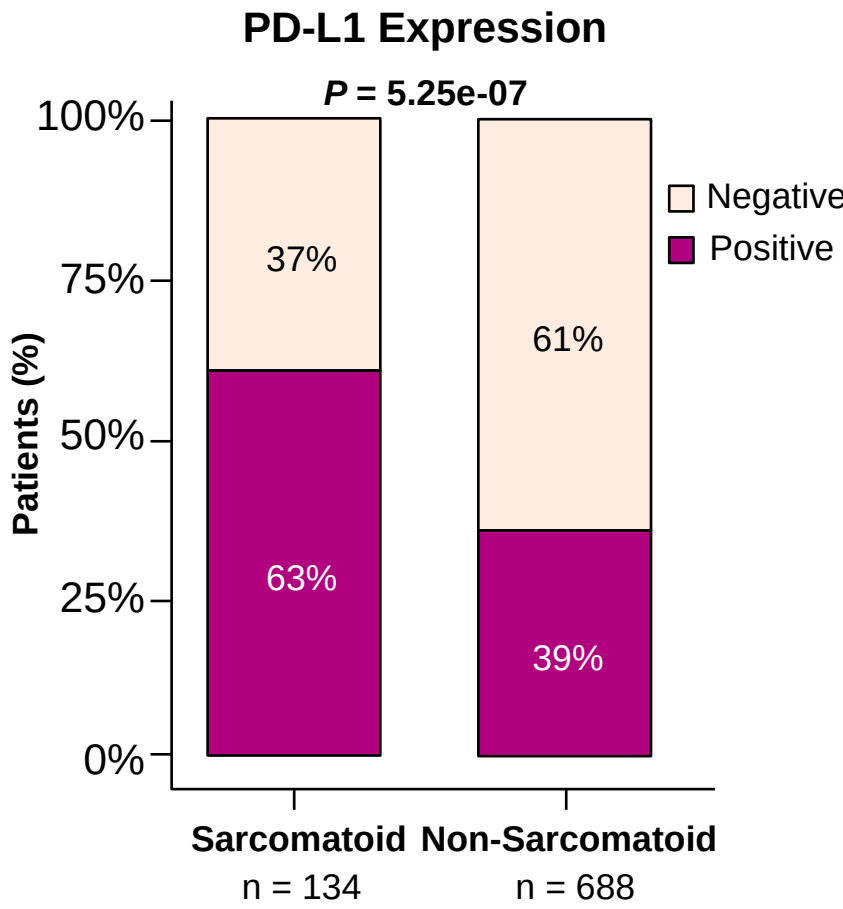
RECIST v1.1, Response Evaluation Criteria in Solid Tumors, version 1.1

1. Rini BI, et al. Poster presentation at the European Society for Medical Oncology (ESMO) Congress; October 19–23, 2018; Munich, Germany. Poster 875P.

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





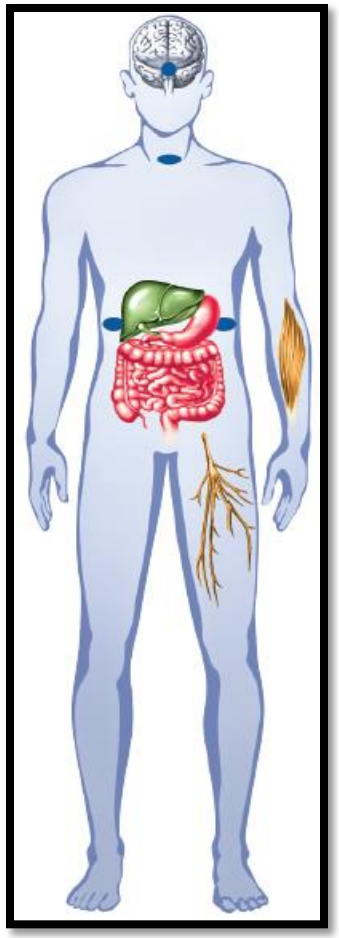


Rini B, et al. IMmotion151 Biomarkers. ESMO 2018 [abstract LBA31]. http://bit.ly/2yaVgyl

Toxicity with immunotherapy agents

Activation of the immune system against tumors can result in a novel spectrum of irAEs[1]

- May be due to cytokine release by activated T cells[1]
- May be unfamiliar to clinicians
- Requires a multidisciplinary approach
- Can be serious[2]
- Requires prompt recognition and treatment[2]
- Requires patient and HCP education[3]



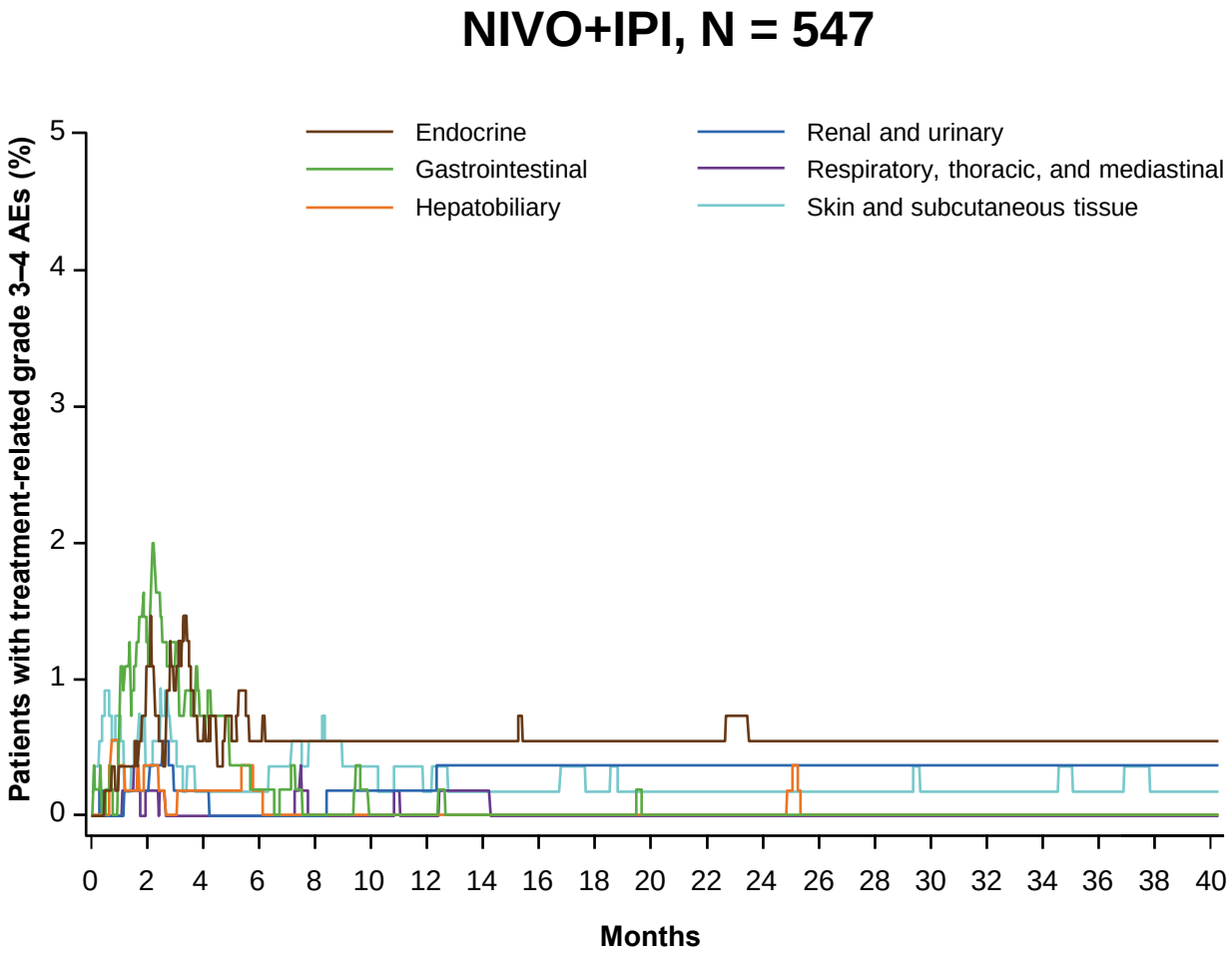
irAEs occur in certain organ systems:[1]

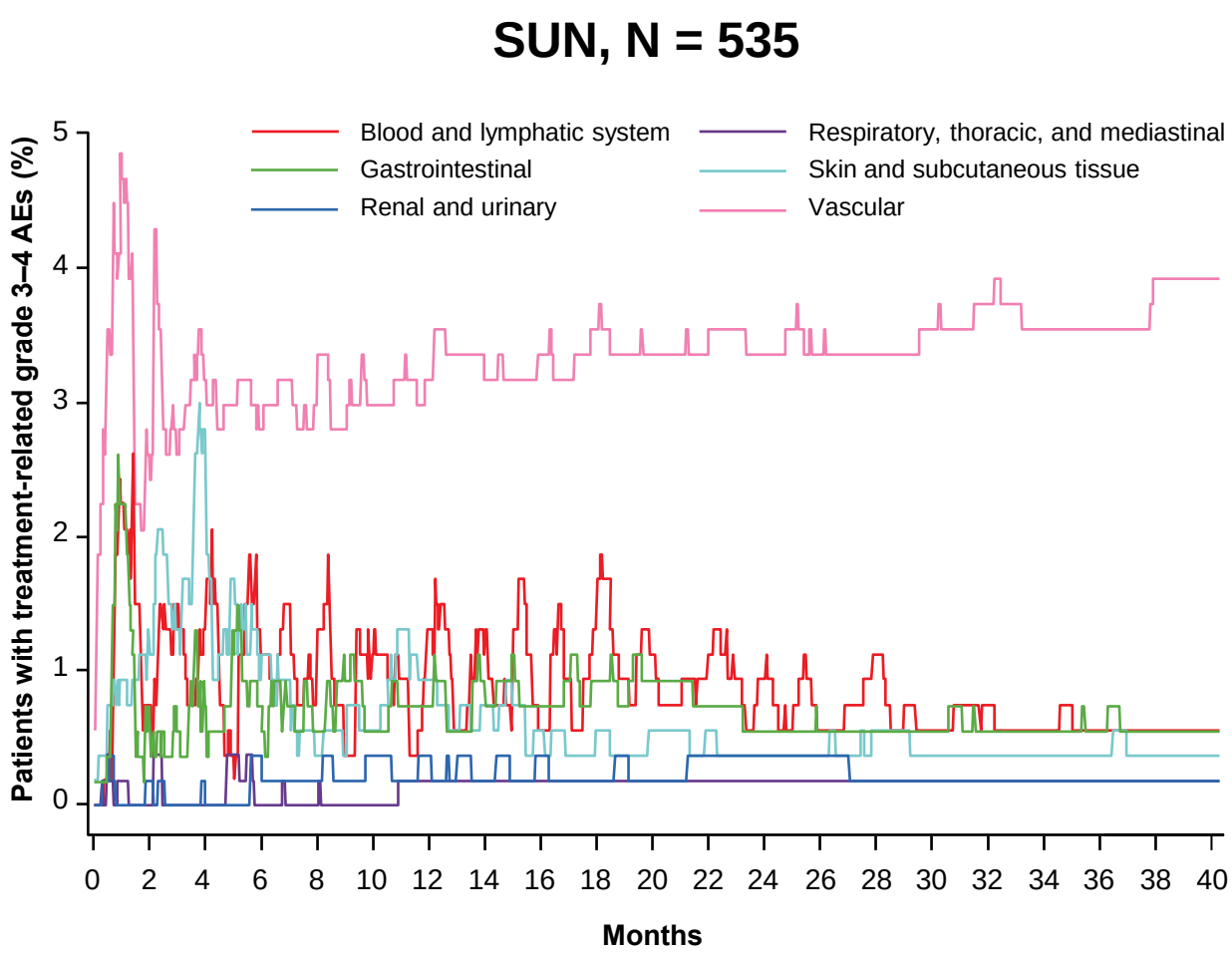
- Skin
- Endocrine system
- Liver
- Gastrointestinal tract
- Nervous system
- Eyes
- Respiratory system
- Hematopoietic cells

irAE = immune-related adverse event.

1. Amos SM, et al. *Blood*. 2011;118:499–509; 2. YERVOY immune-related adverse reactions management guide. October 2012. Available at https://www.yervoy.co.uk/Images/6682_IrAR%20management%20guide%20731EMEA12PM014.pdf. Accessed September 2014;
3. Chin K, et al. Poster presented at ESMO 2008 (abstr. 787P).

Treatment-Related AEs Over Time by Most Common System Organ Class (All Treated Patients)



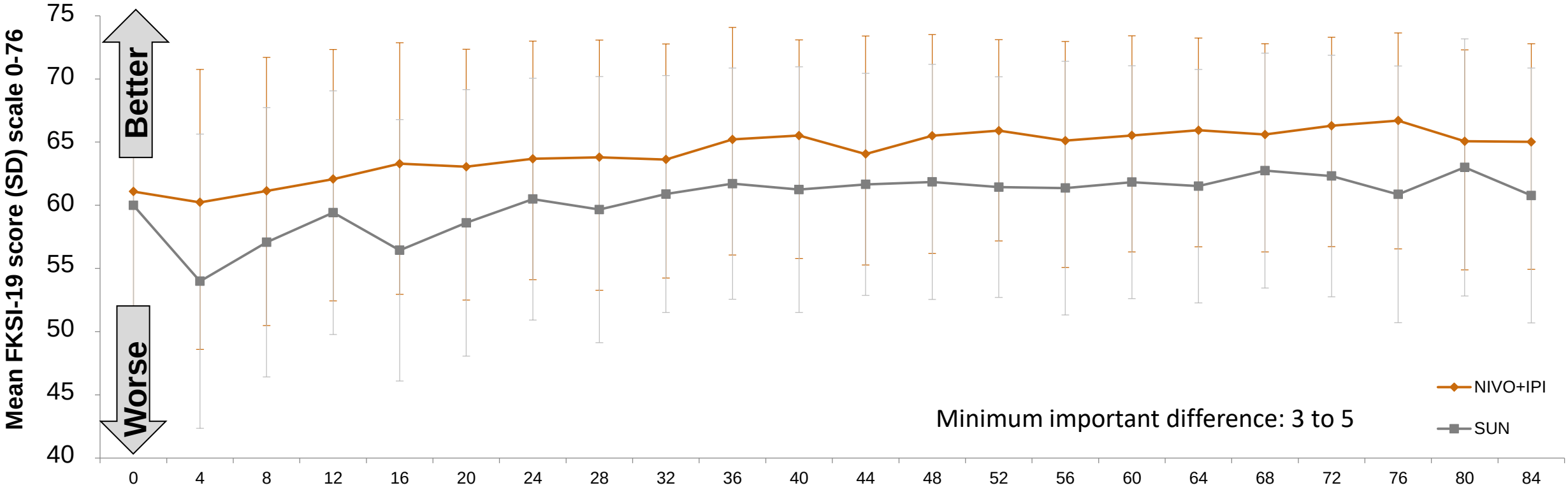


Treatment-related adverse events: Ipi/Nivo

	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

Ipi/Nivo with better QOL and tolerated although a subset with severe toxicity



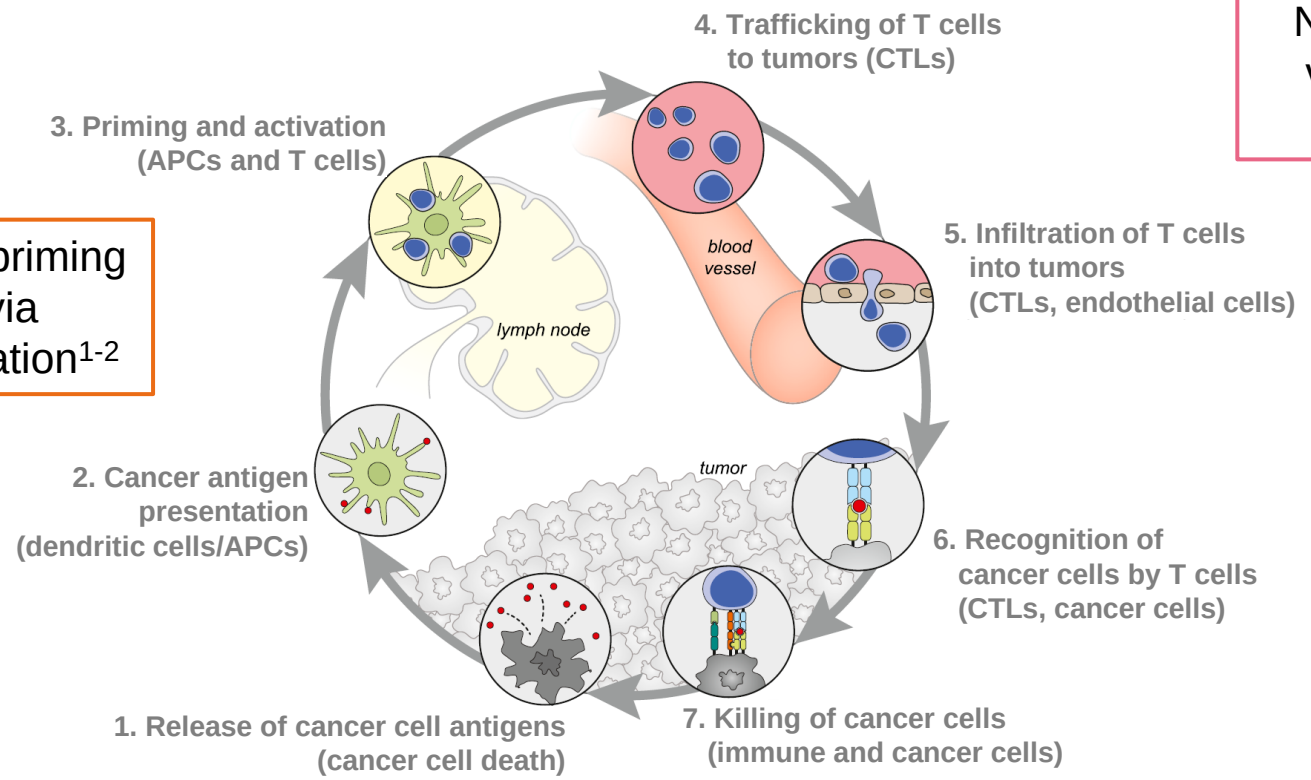
No. at Risk

NIVO	532	502	399	350	323	298	288	188	142	190	126	118	154	118	103	114	108	104	119	89	90	103
SUN	515	502	460	402	383	294	311	169	111	215	134	98	173	103	92	156	91	71	132	82	64	106

MADRID 2017 ESMO congress

Rationale for Combining Immunotherapy with VEGF-targeted Therapy

Promotion of T-cell priming and activation via dendritic cell maturation[1-2]



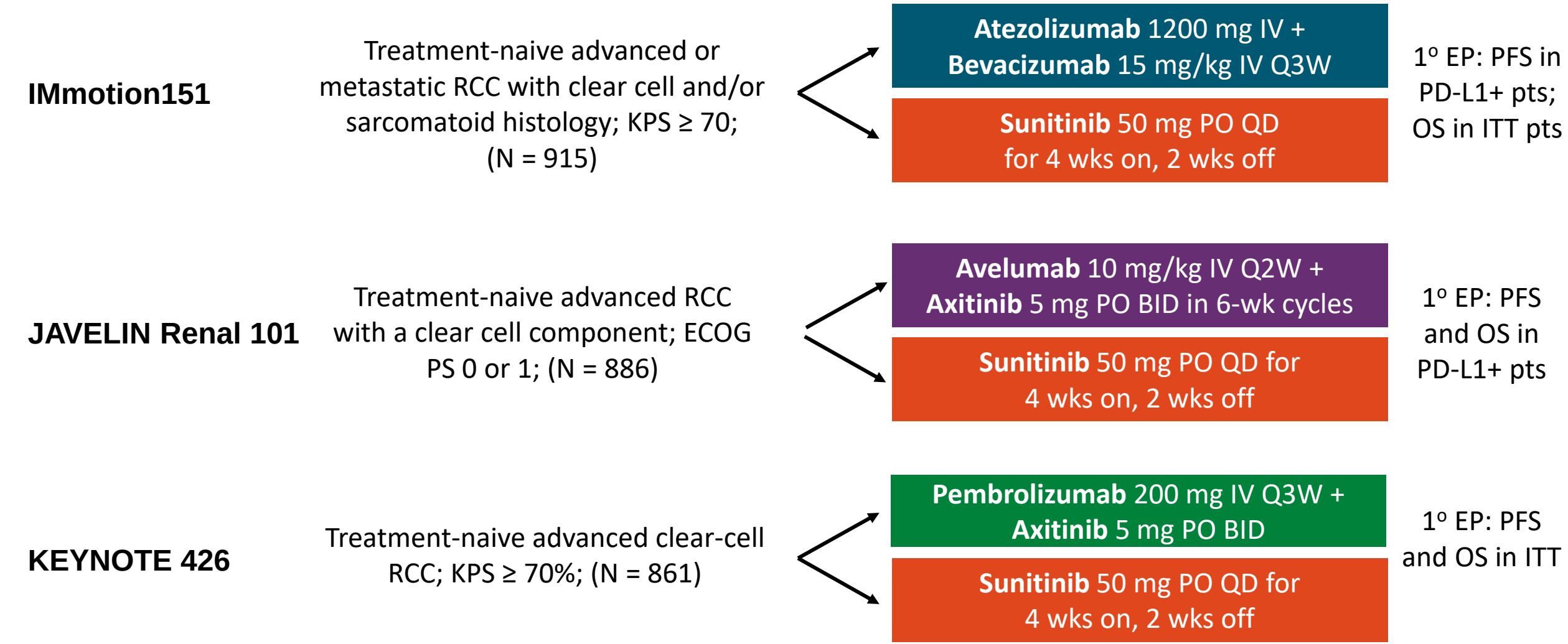
Normalization of the tumor vasculature for increased T-cell tumor infiltration[3-6]

Establishing an immune-permissive tumor microenvironment by decreasing MDSC and Treg populations[6-10]

- T-cell mediated cancer cell killing may be enhanced through reversal of VEGF-mediated immunosuppression

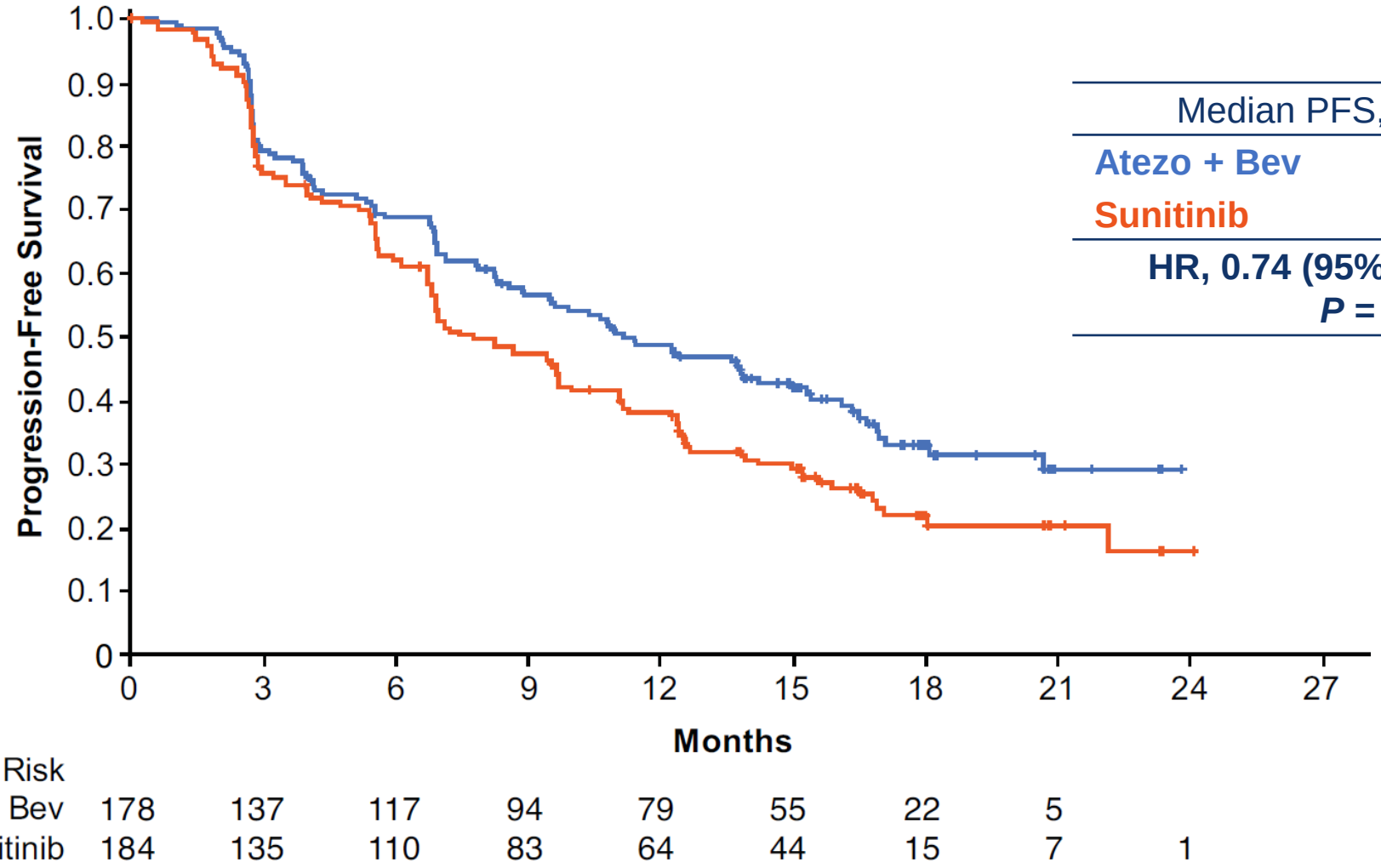
1. Gabrilovich DI, et al. *Nat Med*, 1996. 2. Oyama T, et al. *J Immunol*, 1998. 3. Goel S, et al. *Physiol Rev*, 2011. 4. Motz GT, et al. *Nat Med*, 2014. 5. Hodi FS, et al. *Cancer Immunol Res*, 2014.
6. Wallin JJ, et al. *Nat Commun*, 2016. 7. Gabrilovich DI, Nagaraj S. *Nat Rev Immunol*, 2009. 8. Roland CL, et al. *PLoS One*, 2009. 9. Facciabene A, et al. *Nature*, 2011. 10. Voron T, et al. *J Exp Med*, 2015.
Figure adapted from Chen DS, Mellman I. *Immunity*, 2013.

Randomized Phase III Study Designs for IO + VEGF



Progression-Free Survival in PD-L1+: Atezo/Bev vs Sunitinib

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**

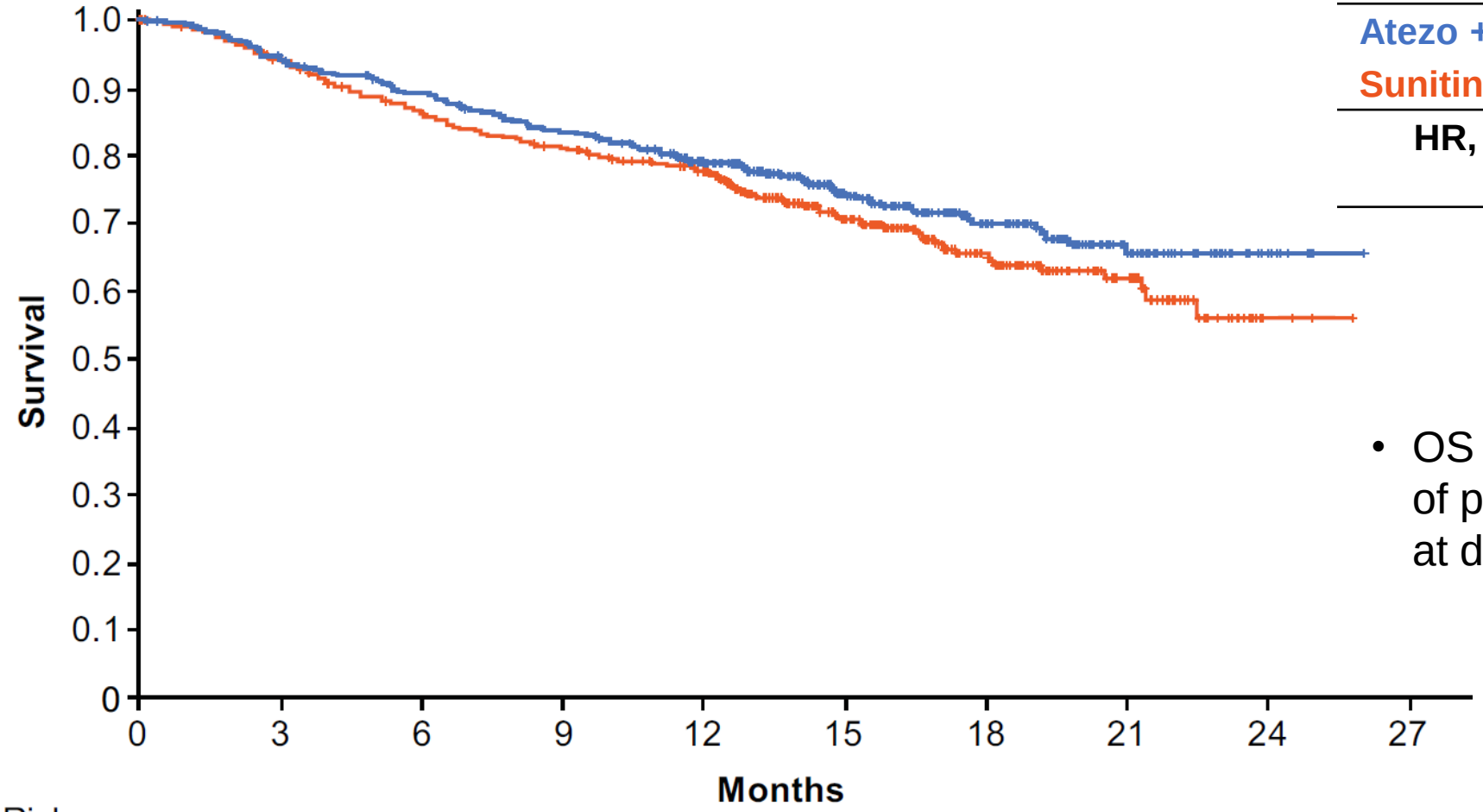
PFS assessed by investigators. Minimum follow-up, 12 mo. Median follow-up, 15 mo.
The PFS analysis passed the pre-specified *P* value boundary of alpha = 0.04.

Rini B et al. *Lancet* (in press)

Overall Survival in ITT

Co-Primary Endpoint

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



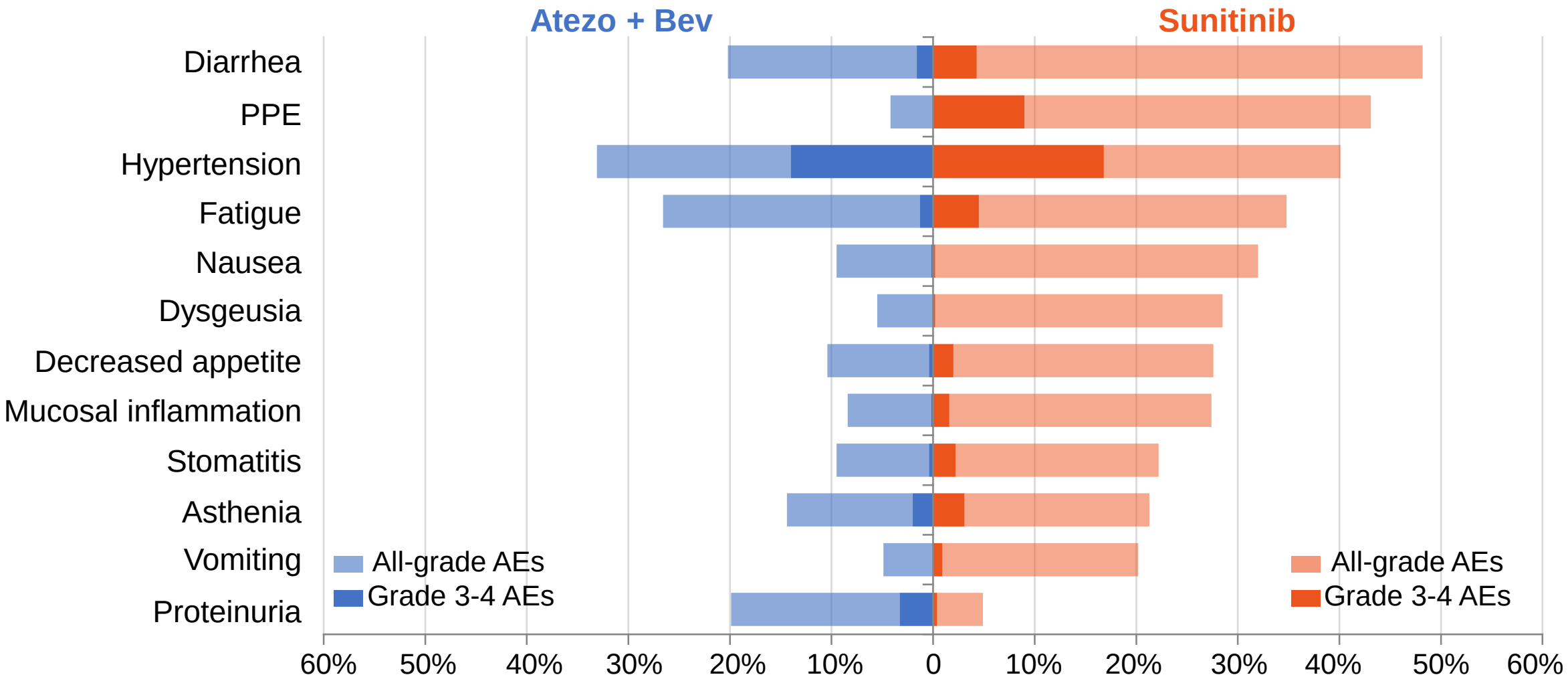
No. at Risk									
Atezo + Bev	454	428	398	371	341	246	141	69	18
Sunitinib	461	422	384	357	331	227	126	65	15

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

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.

Treatment-related AEs: Atezo / Bev

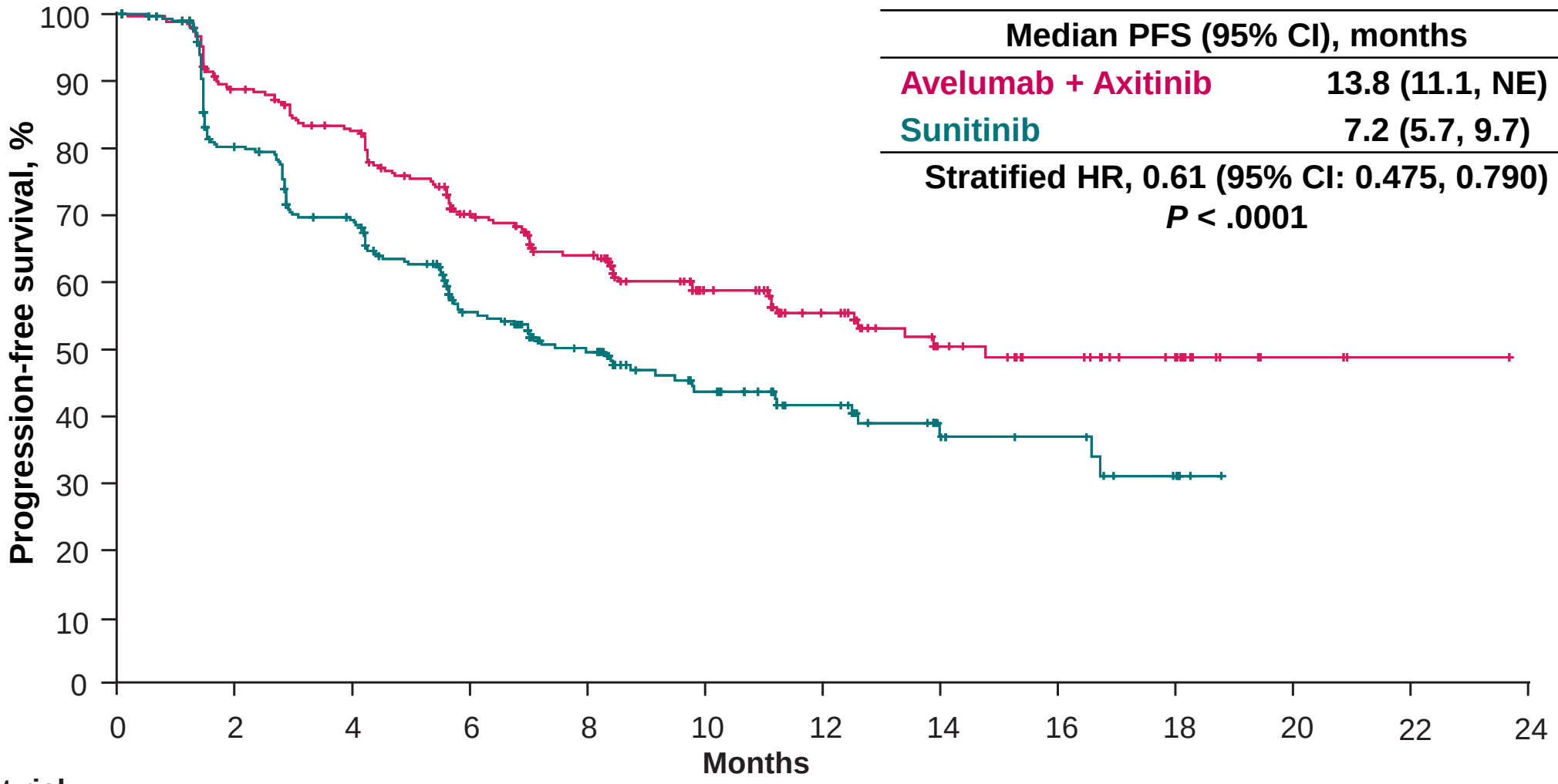
≥ 20% frequency in either arm and > 5% difference between arms



PPE, palmar-plantar erythrodysesthesia.

Axitinib + Avelumab: PFS per IRC in PD-L1+

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		

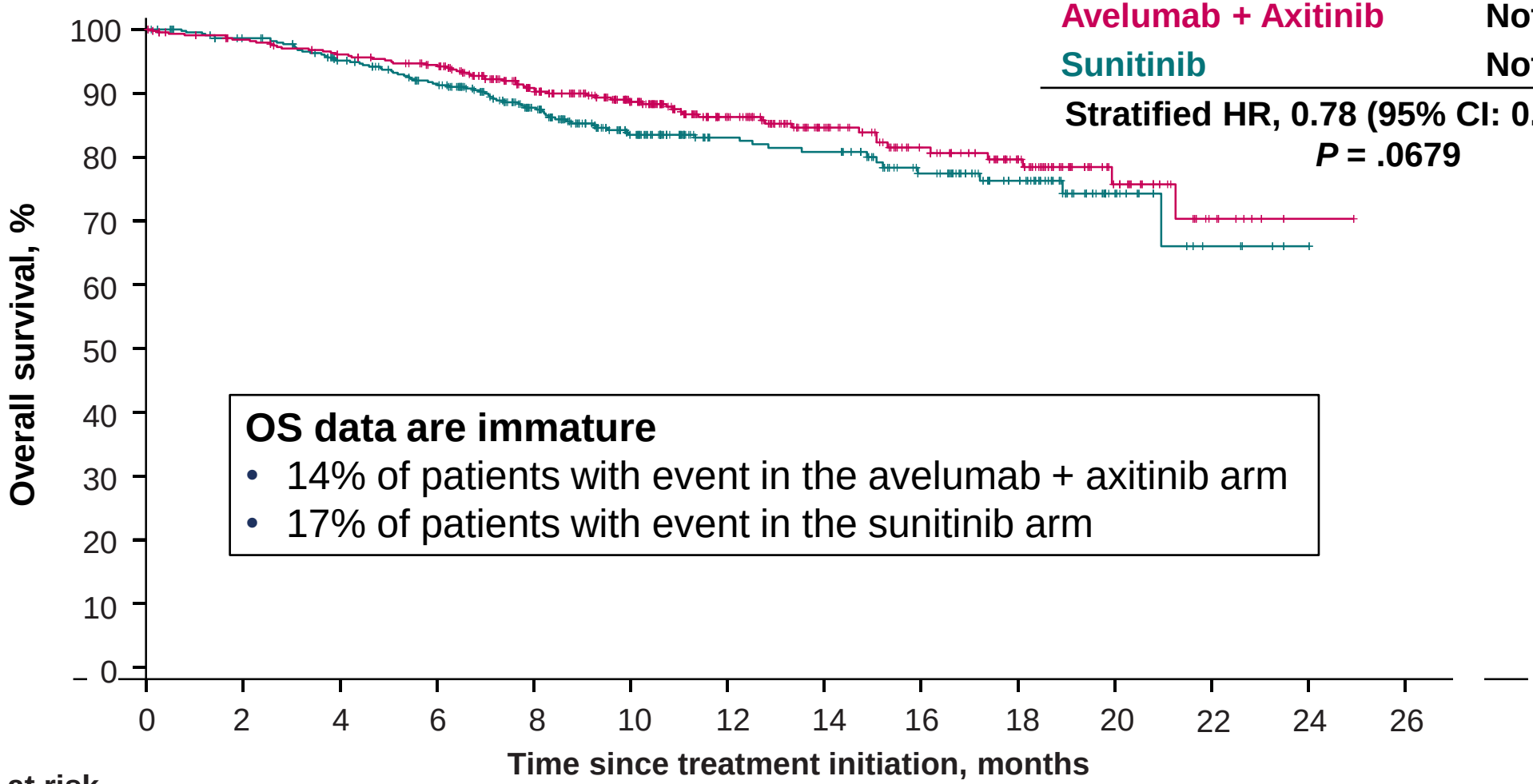
Minimum follow-up, 6 months. Median follow-up, 9.9 months (avelumab + axitinib) and 8.4 months (sunitinib).
The PFS analysis crossed the prespecified efficacy boundary based on the alpha-spending function (*P* = .001).

NE, not estimable.

OS: Axi/Avelumab immature

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

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



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).

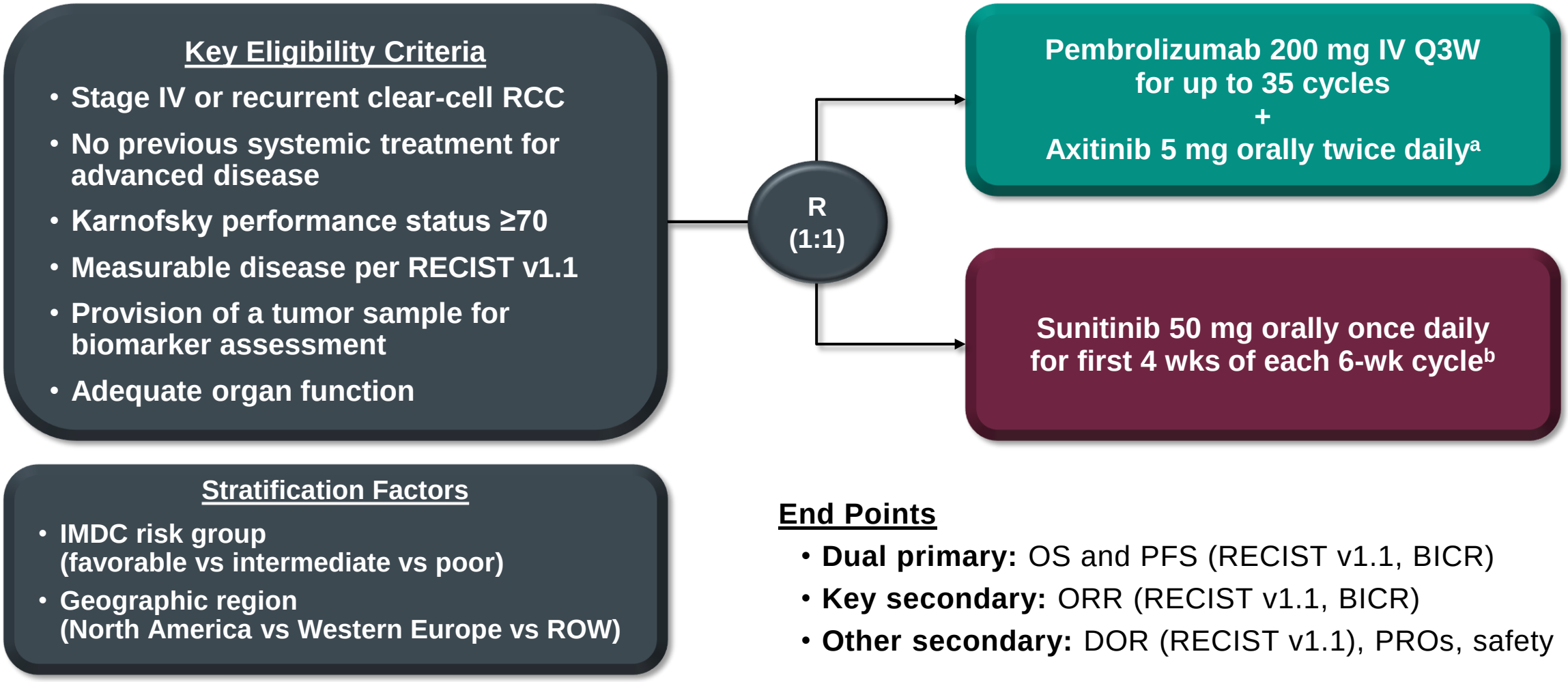
TRAEs: Axi/Avelumab

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**	

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).

KEYNOTE-426 Study Design

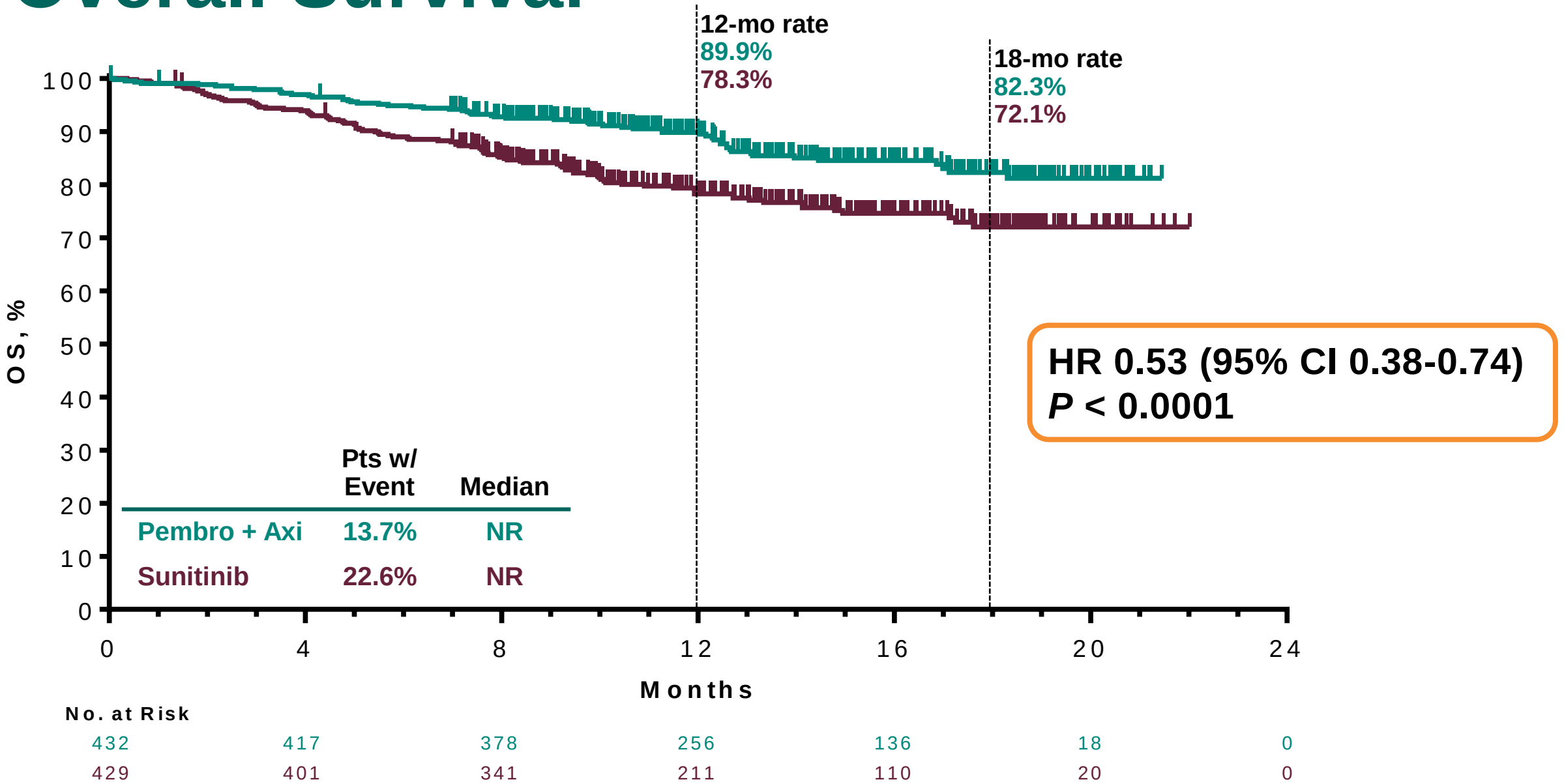


End Points

- **Dual primary:** OS and PFS (RECIST v1.1, BICR)
- **Key secondary:** ORR (RECIST v1.1, BICR)
- **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.
ClinicalTrials.gov identifier NCT02853331.

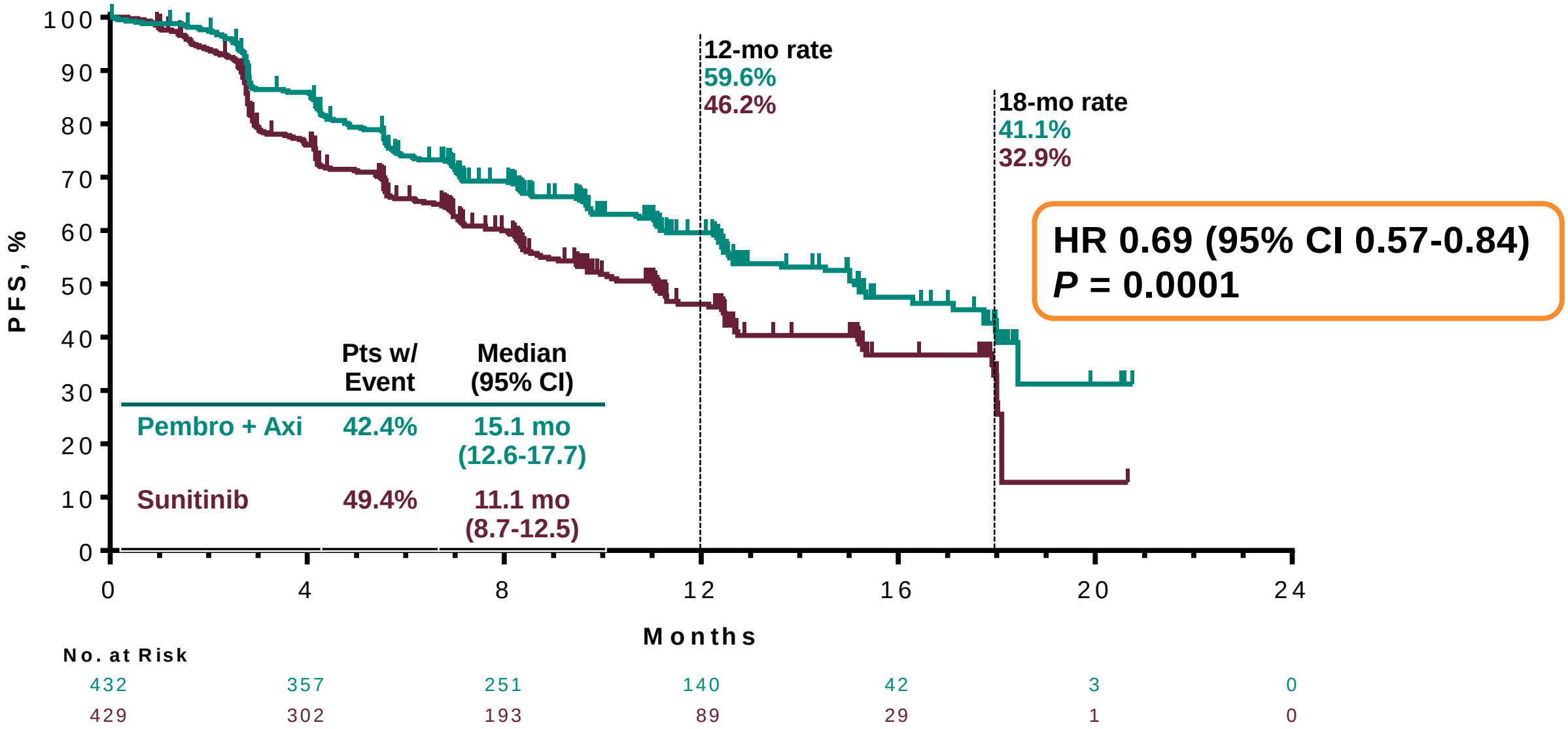
Overall Survival



Data cutoff date: Aug 24, 2018.

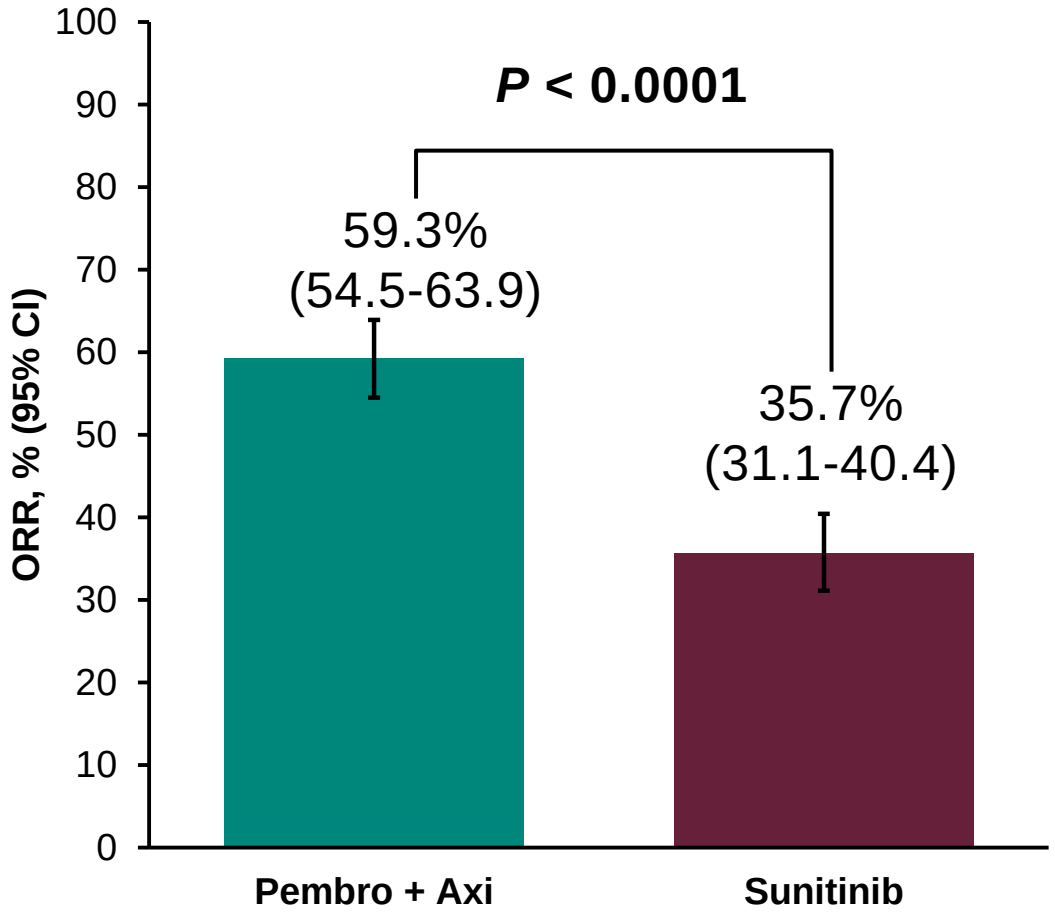
Rini B et al. NEJM 2019

Progression-Free Survival



Data cutoff date: Aug 24, 2018.

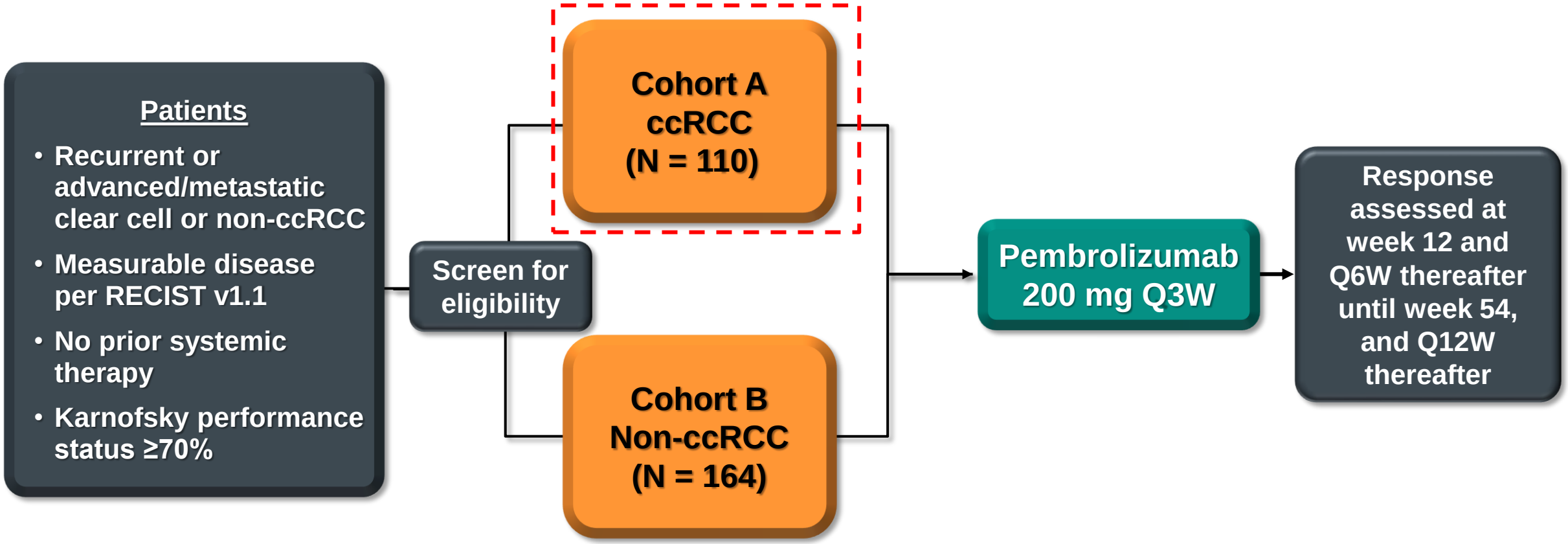
Confirmed Objective Response Rate



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+)

[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.

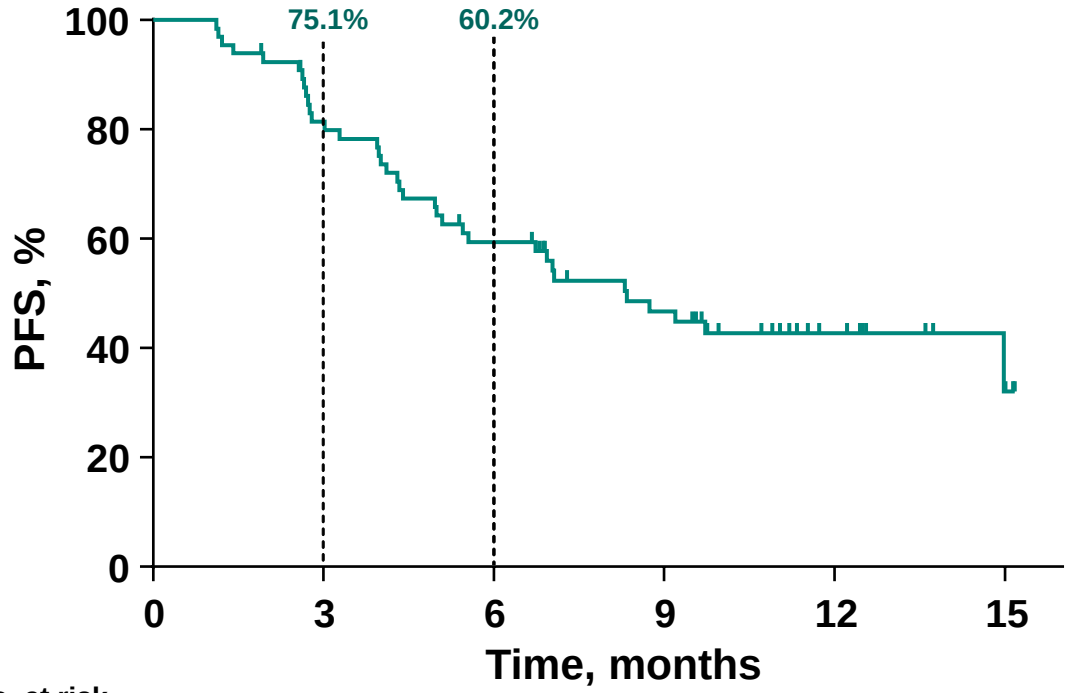
KEYNOTE-427: Pembro monotherapy in mRCC



McDermott et al. ASCO GU 2019

Relative ability for Pembro monotherapy to control disease and live longer not yet defined

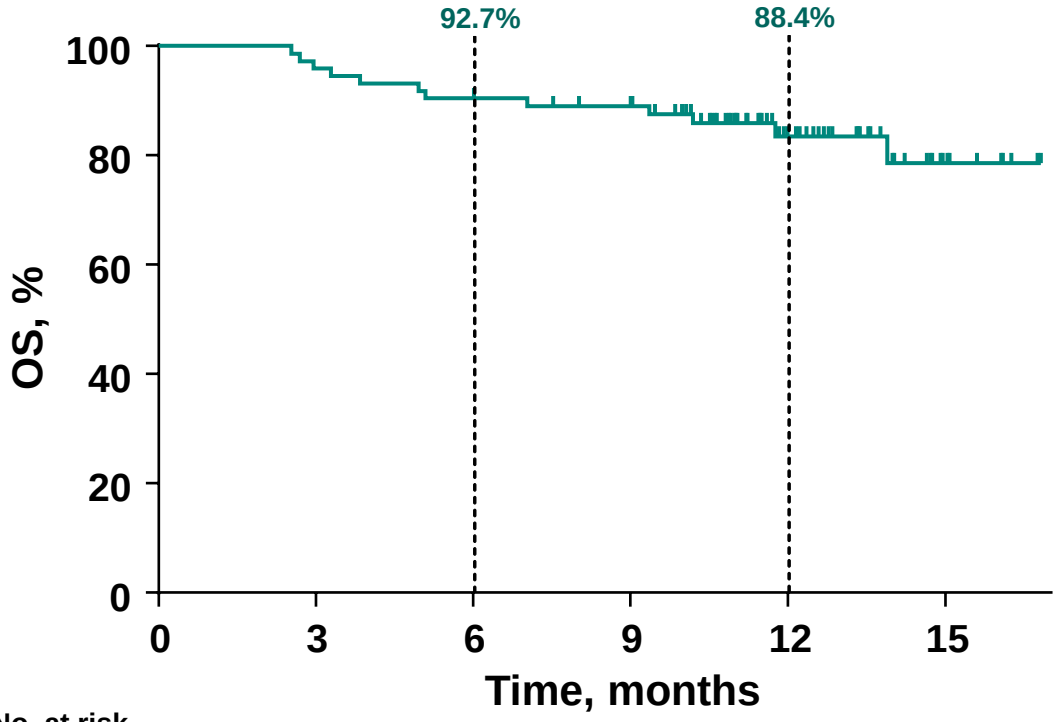
Median PFS
8.7 months (95% CI, 6.7-12.2 months)



No. at risk

Cohort A	110	81	62	47	21	0

Median OS
NR (95% CI, NR)



No. at risk

Cohort A	110	107	102	98	57	0

Database cutoff: March 12, 2018.

First-line IO Combination Trials in mRCC

	CheckMate 214[1,2] ITT (n=550 vs n=546)	KEYNOTE-426[4] ITT (n=432 vs n=429)	JAVELIN Renal 101[3] ITT (n=442 vs n=444)	IMmotion 151[5] ITT (n=454 vs n=461)
mOS, months HR (CI); P-value	NR vs 37.9 **0.71** (0.59–0.86); 0.0003	NR vs NR **0.53** (0.38–0.74); <0.0001	NR vs NR **0.78** (0.554–1.084); 0.0679 (NS)	NR vs NR **0.81** (0.63–1.03) 0.09 (NS)
Landmark OS at 12 months	**83%** vs. 78%	**90%** vs. 78%	**86%** vs. 83% (est)	**80%** vs. 79% (est)
mPFS, months HR (CI); P-value	**9.7** vs 9.7 0.85 (0.73–0.98); 0.0267 (NS)	**15.1** vs 11.1 0.69 (0.57–0.84); 0.0001	**13.8** vs 8.4 0.69 (0.563–0.840); 0.0001	**11.2** vs 8.4 0.83 (0.70–0.97) 0.02
ORR, % P-value	**41** vs 34 0.0154	**59** vs 36 <0.0001	**51** vs 26 NA	**37** vs 33
CR, %	**9** vs 2	**6** vs 2	**3** vs 2	**5** vs. 2
mDOF, months	**32.4**	12.8	12.0 vs 11.5	15
Prognostic risk, % Favorable Intermediate Poor	 23 vs 23 61 vs 61 17 vs 16	 32 vs 31 55 vs 57 13 vs 12	 21 vs 22 61 vs 62 16 vs 16	 20 vs 20 71 vs 70 10 vs 10
Randomization period	Oct 2014 – Feb 2016	Oct 2016 – Jan 2018	March 2016 – Dec 2017	May 2015 – Oct 2016
Subsequent therapies for sunitinib arm, %	Overall (39%) IO (27%)	Overall (34%) IO (21%)	Overall (41%) IO (28%)	NR

NA=not available; NE=not estimable; NR=not reached.

1. Tannir NM, et al. ASCO GU 2019. Abstract 547. **2.** Motzer RJ, et al. N Engl J Med. 2018; 378:1277-1290. **3.** Choueiri et al. ASCO GU 2019. **4.** Rini B, et al. N Engl J Med. 2018; 378:1277-1290. Abstract 543. **5.** Motzer R, et al. ASCO GU 2018. Abstract 578.

The CR Issue in mRCC

- CRs are usually durable to IO (HD IL-2) and thus a measure of a regimen's effectiveness and a patient's goal, however….

- Comparing CR rates across trials has many caveats…
  - Some of the PRs will be durable/cured in my opinion
  - There is inherent subjectivity in calling CR vs. deep PR
  - Differing duration of follow up across trials
  - Differing sites of mets (e.g. bone) and primary in place could affect CR rates

- Work is needed to define a 'functional CR' which ideally could be identified early based on eg tumor shrinkage to aid clinical decision-making and possibly regulatory endpoints

Remission rates for major regimens in mRCC

Regimen	CR (ITT per IRC)	CR in selected pts	PR	Remission Rate
Ipi/Nivo	9%	16% PD-L1+ 18% sarcomatoid	32%	?
Atezo/Bev	5%	9% PD-L1+	31%	?
Axi/Avelumab	3%	4% PD-L1+	48%	?
Axi/Pembro	6%	?	54%	?
Pembro mono	3%	7% CPS >1	35%	?
TKIs	<5%	?	30-40%	~0

Control disease (PFS) rates for major regimens in mRCC

Regimen	PFS (months)	Primary PD rate
Ipi/Nivo	12.4	20%
Atezo/Bev	11.2	18%
Axi/Avelumab	13.8	12%
Axi/Pembro (Ph1)	15.1	11%
Pembro mono	8.7	28%
TKIs	9-12	20%

Open Questions for IO in mRCC

- Ipi/Nivo vs Axi/Pembro?
- Does everyone need combination therapy up front, or can we select patients for monotherapy (via clinical features/strategy or biomarkers)?
- Do we need to continue one or both components of therapy forever?
- Are there endpoints prior to OS that can be used to build on IO-based combination regimens?

Conclusions

- The goal of an newly metastatic RCC patient is to live as long as possible with as much quality as possible, and regimens with the highest chance of survival ideally maximizing cure/durable response balanced against acceptable toxicity/time off treatment should be prioritized

- I/O-based regimens offer the best chance of achieving patient goals
  - Whether I/O + I/O or VEGF + I/O most effectively achieves these goals is as yet undefined