

Aiom
Associazione Italiana di Oncologia Medica
SEZIONE REGIONE LAZIO

The Best of the Year 2018

The Best in Kidney Cancer

Roberto Iacovelli

Gemelli



Fondazione Policlinico Universitario Agostino Gemelli IRCCS
Università Cattolica del Sacro Cuore

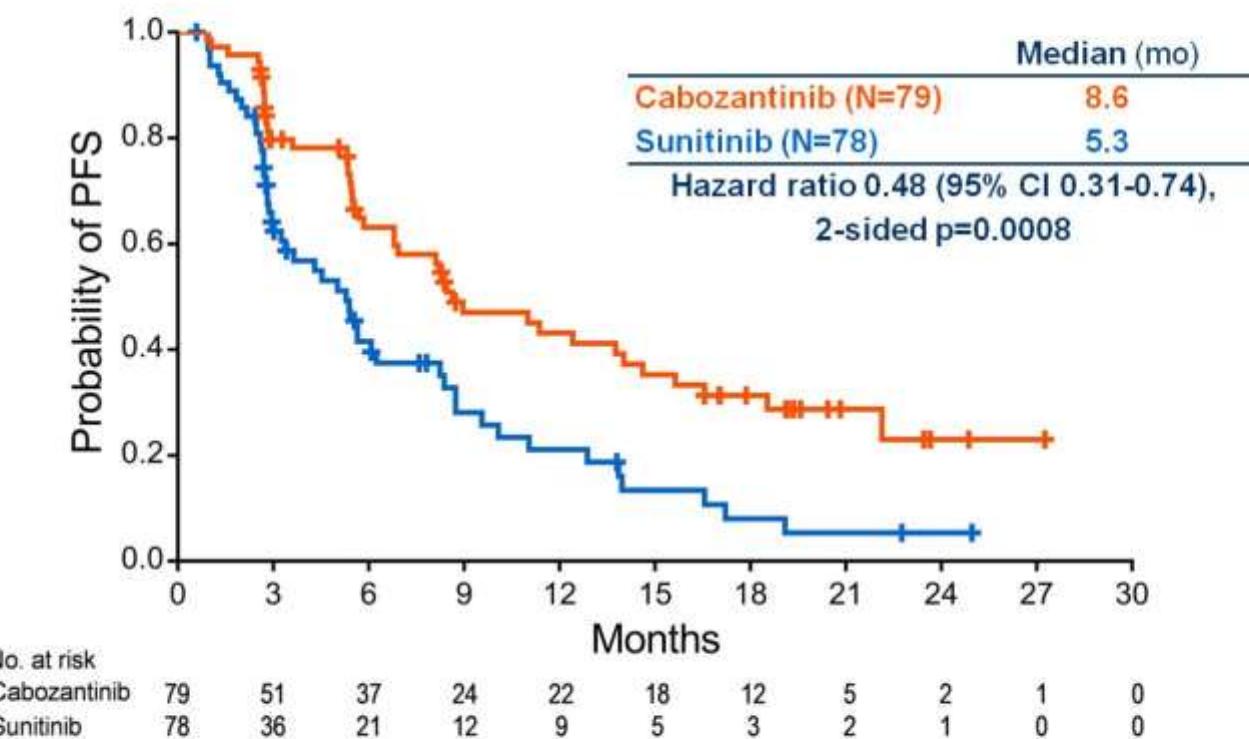
Agenda:

- Cabosun trial, IRC analysis
- IMmotion 151 trial
- Carmena trial
- ATLAS trial
- Molecular correlate to response to Atezo-Bev in mRCC
- Javelin Renal 101 trial

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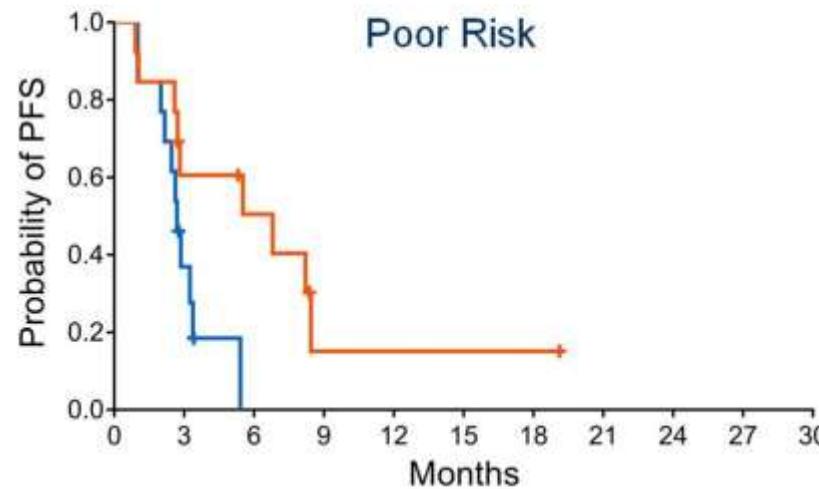
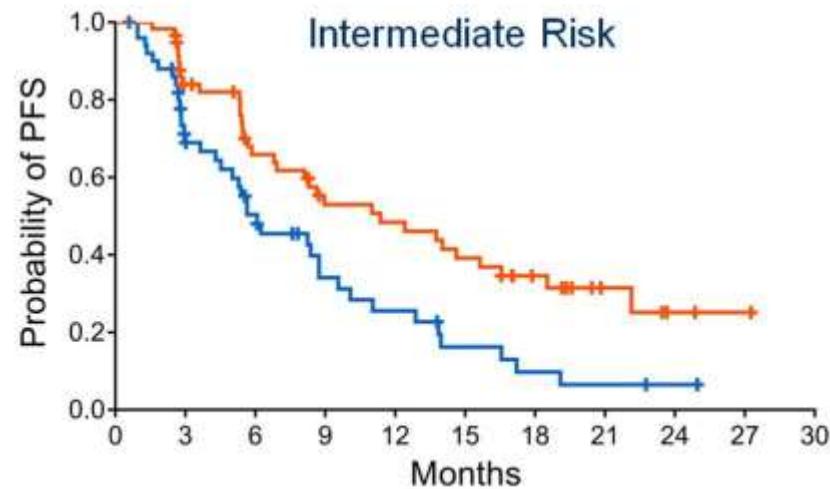
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PFS per IRC in All Randomized Patients



PRESENTED AT: 2018 Genitourinary Cancers Symposium | #GU18
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Progression-Free Survival by IMDC Risk Group



PFS assessed by IRC

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Presented by: Daniel George

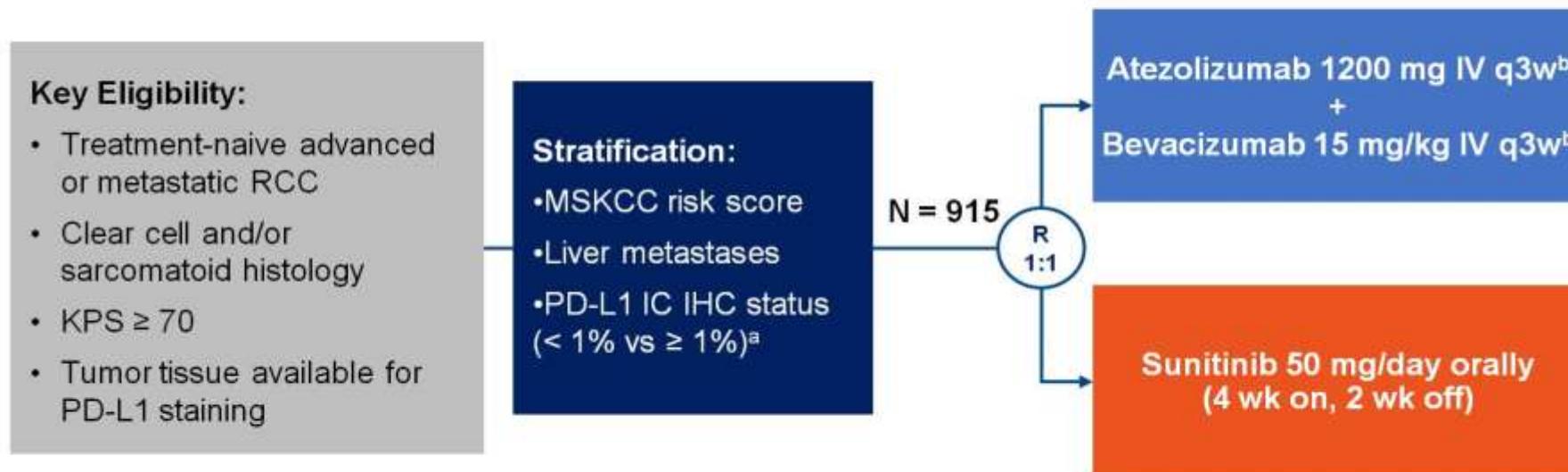
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La prima linea:

The IMmotion151 trial

Study Design



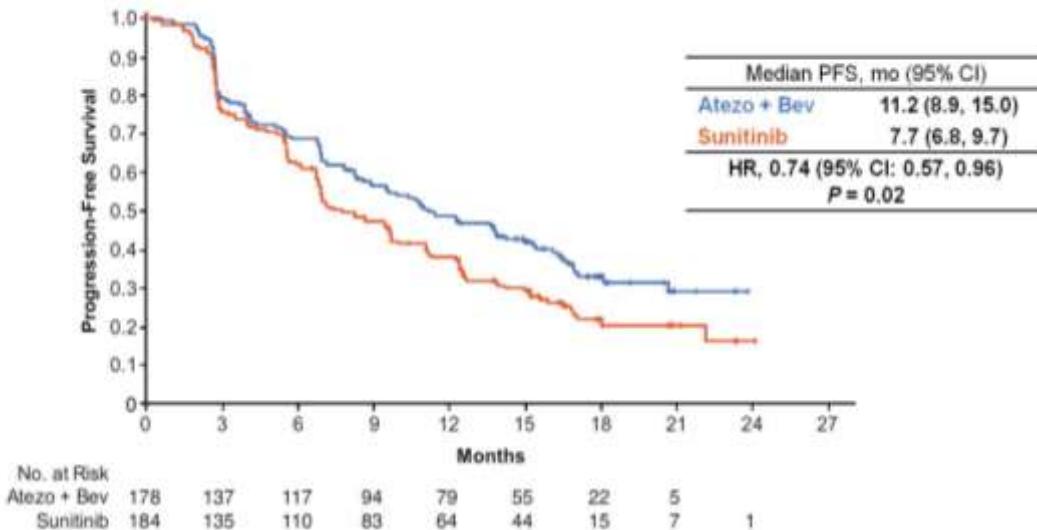
^a $\geq 1\%$ IC: 40% prevalence using SP142 IHC assay; ^b No dose reduction for atezolizumab or bevacizumab.

Primary endpoint: PFS in PDL1+ by investigators

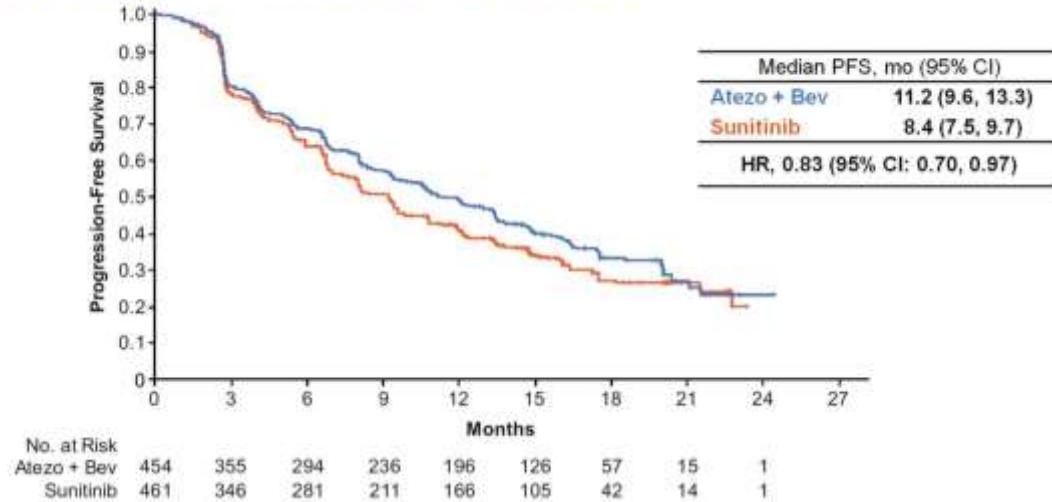
La prima linea:

Progression-Free Survival in PD-L1+

En



Progression-Free Survival in ITT



PFS and ORR by **IRC**

	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)	
Confirmed ORR, % (95% CI)	36% (29, 44)	33% (26, 40)	32% (26, 37)	30% (25, 36)	33% (29, 38)	31% (27, 36)
CR rate	15%	8%	8%	6%	11%	7%

- IRC and investigator assessment of PFS benefit was generally consistent in the ITT population; however, results differed from investigator 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.

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CARMENA: Prospective, multicenter, open-label, randomized, phase 3 non-inferiority study

- Confirmed metastatic clear cell RCC / Biopsy
- ECOG-PS 0-1
- Amenable to nephrectomy
- Eligible for sunitinib
- Brain metastases absent/controlled by treatment
- No prior systemic therapy for RCC



Primary endpoint:
Overall survival

Secondary endpoints:
Progression-free survival, objective response rate, clinical benefit, safety

LPI, last patient included; MSKCC, Memorial Sloan Kettering Cancer Center; QD, once daily; R, randomization; RCC, renal cell carcinoma

PRESENTED AT: **2018 ASCO[®]**
ANNUAL MEETING

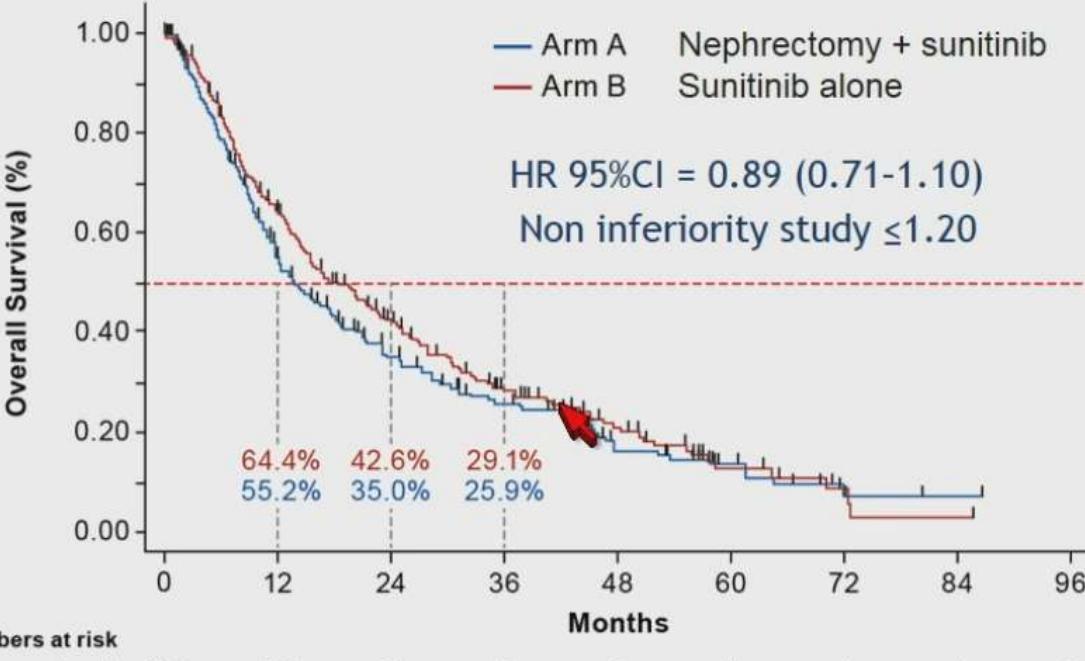
#ASCO18
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PRESENTED BY: Arnaud Méjean

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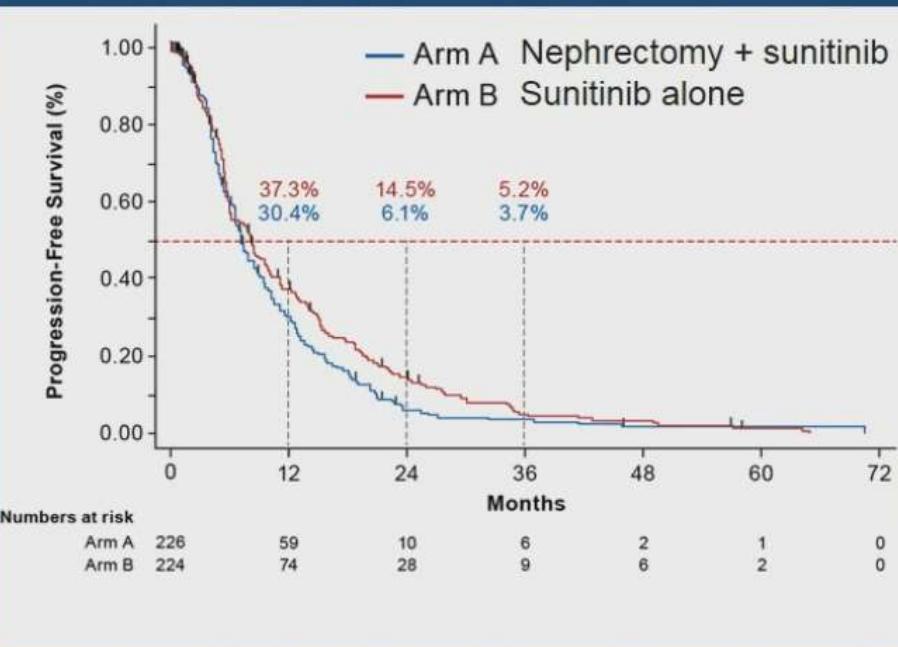
Patients with good-prognosis based on MSKCC were excluded.

Overall survival (ITT)



Median follow-up was 50.9 months (range 0.0-86.6)

Progression free survival (ITT)



	Median PFS, months (95% CI)	HR (95% CI)
Arm A: Nephrectomy + Sunitinib (n = 226)	7.2 (6.5-8.5)	0.82 (0.67-1.00)
Arm B: Sunitinib alone (n = 224)	8.3 (6.2-9.9)	

CN, cytoreductive nephrectomy; PFS, progression-free survival

Intermediate prognosis, a new area of interest

Case 2: RCC

PS 2

High metastatic tumor burden

Nephrectomy does not make sense



RCC, renal cell carcinoma PS, performance status

PRESENTED AT: 2018 ASCO ANNUAL MEETING

RECORDED BY: ARTHUR DEJOURS

Case 3: RCC

PS 0 - 1

Limited metastatic tumor burden

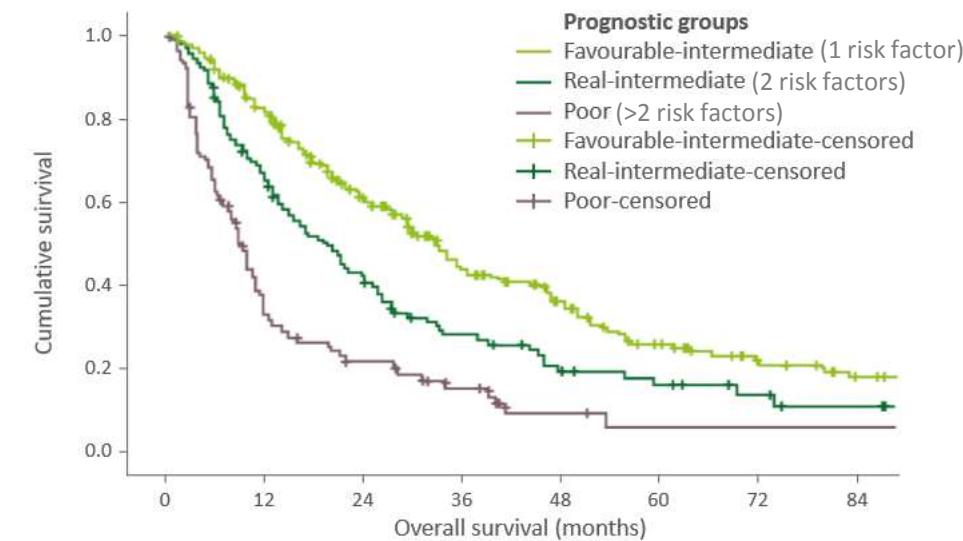
Who knows if nephrectomy is useful ?



RCC, renal cell carcinoma PS, performance status

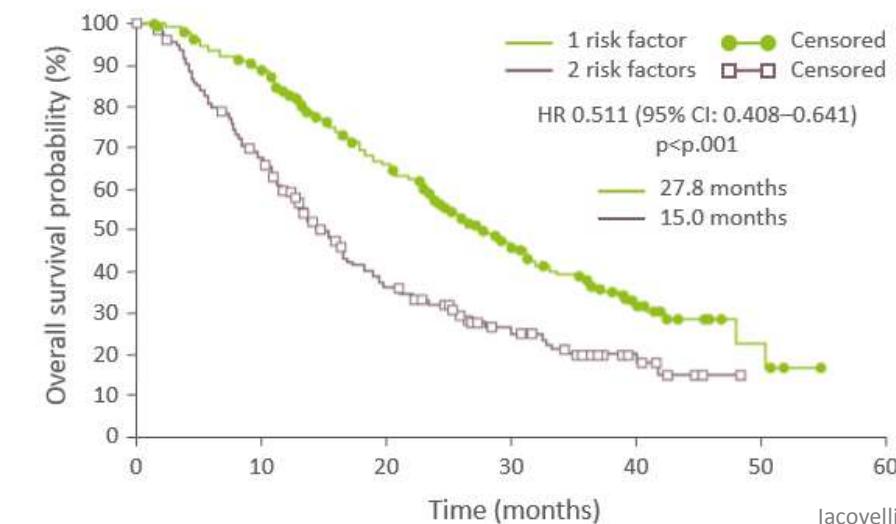
PRESENTED AT: 2018 ASCO ANNUAL MEETING

RECORDED BY: ARTHUR DEJOURS



IMDC

Intermediate prognosis



Secondary nephrectomy in Arm B (sunitinib alone)

- 38 patients required secondary nephrectomy
 - For emergency treatment of the primary tumor
 - For CR or near CR in metastatic sites (> 6 months)
- Median 11.1 months (range 0.7-85.4) from randomisation to surgery
- 31.3% of patients with secondary nephrectomy restarted sunitinib

	Arm B: Sunitinib alone (N = 224)
Secondary nephrectomy, n (%)	
No	185 (83.0)
Yes	38 (17.0)
Missing	1
Emergency	
Yes	7 (18.9)
No	30 (81.1)
Missing	1

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Study Design

- Clear-cell RCC (>50%)
(\geq pT2 and/or N+), any Fuhrman grade
- Prior nephrectomy
- Systemic treatment-naïve
- No evidence of macroscopic residual or metastatic disease (confirmed by IRC)

Stratified by AJCC TNM risk groups and country

N=700 (planned)
N=724 (accrued)

RANDOMIZATION
(1:1)*

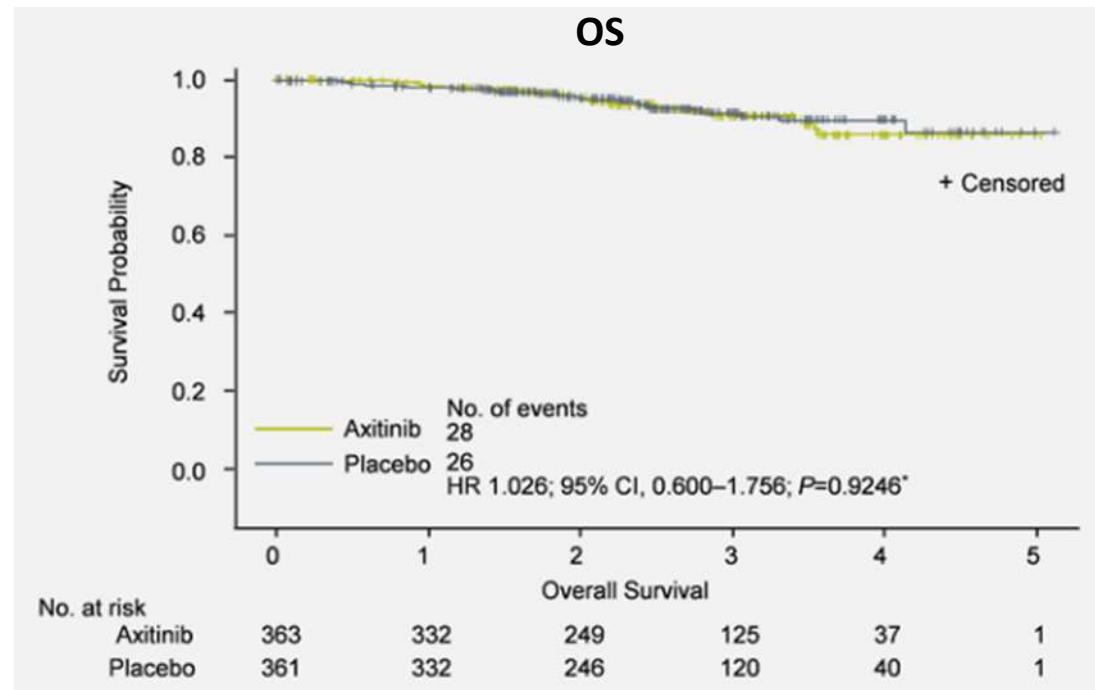
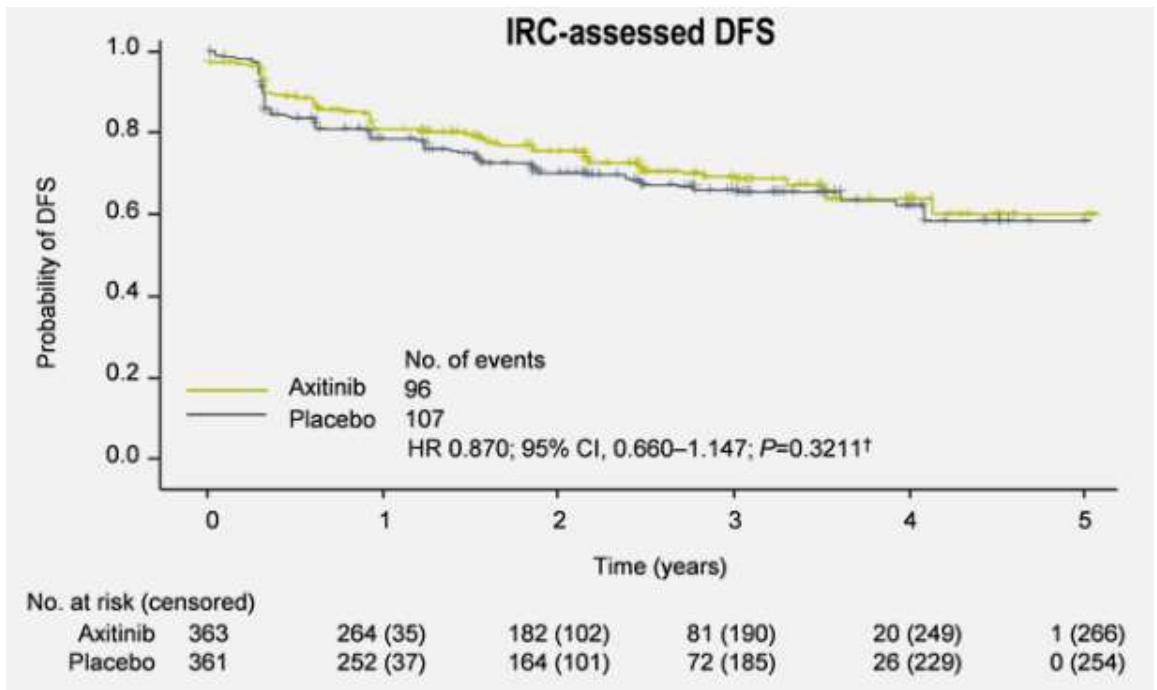
Arm A:
oral axitinib
5 mg BID

Arm B:
oral placebo BID

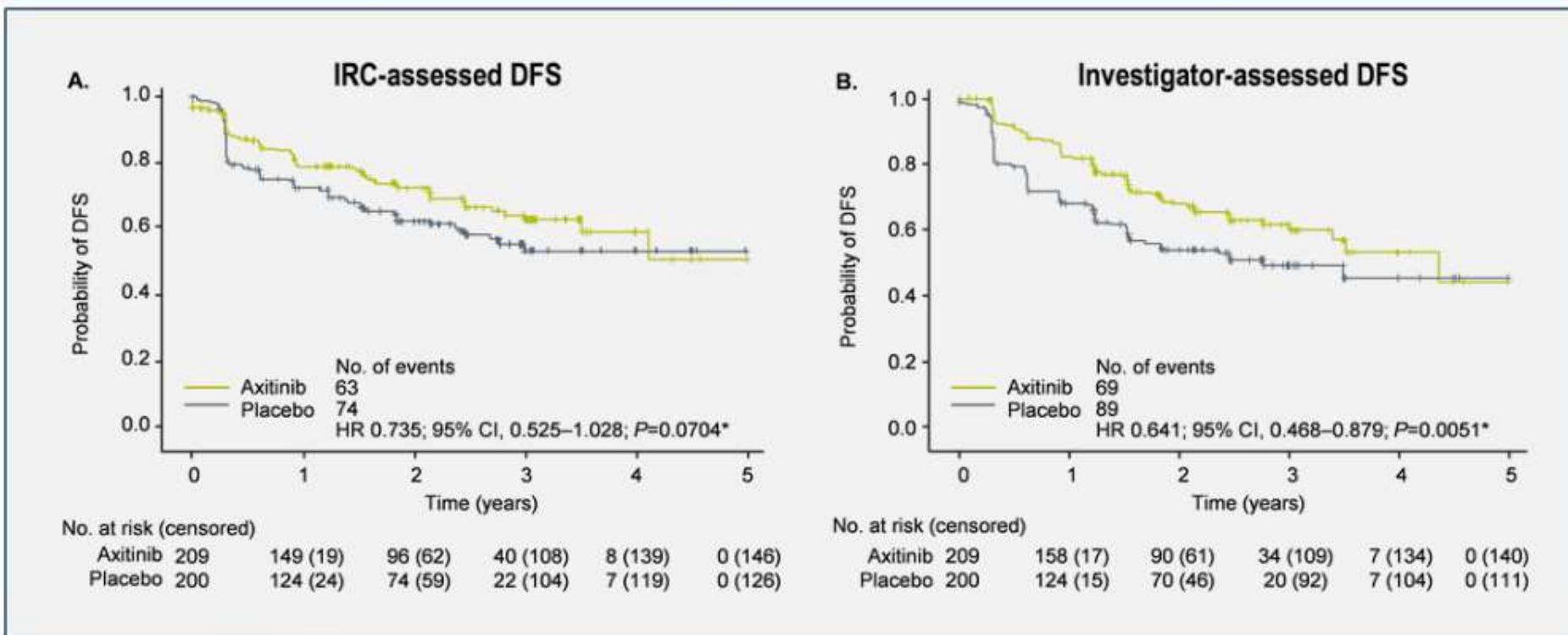
Patients were treated for a minimum of 1 year and up to 3 years unless recurrence, occurrence of a second primary malignancy, significant toxicity, or withdrawal of consent

- Dose interruptions and stepwise reductions to a minimum of 1 mg BID were allowed
- Stepwise dose increases up to 10 mg BID were allowed

* Randomized 4–12 weeks after nephrectomy



Subgroup Analysis: DFS — Highest-Risk Subpopulation



* Two-sided P value from log-rank test.

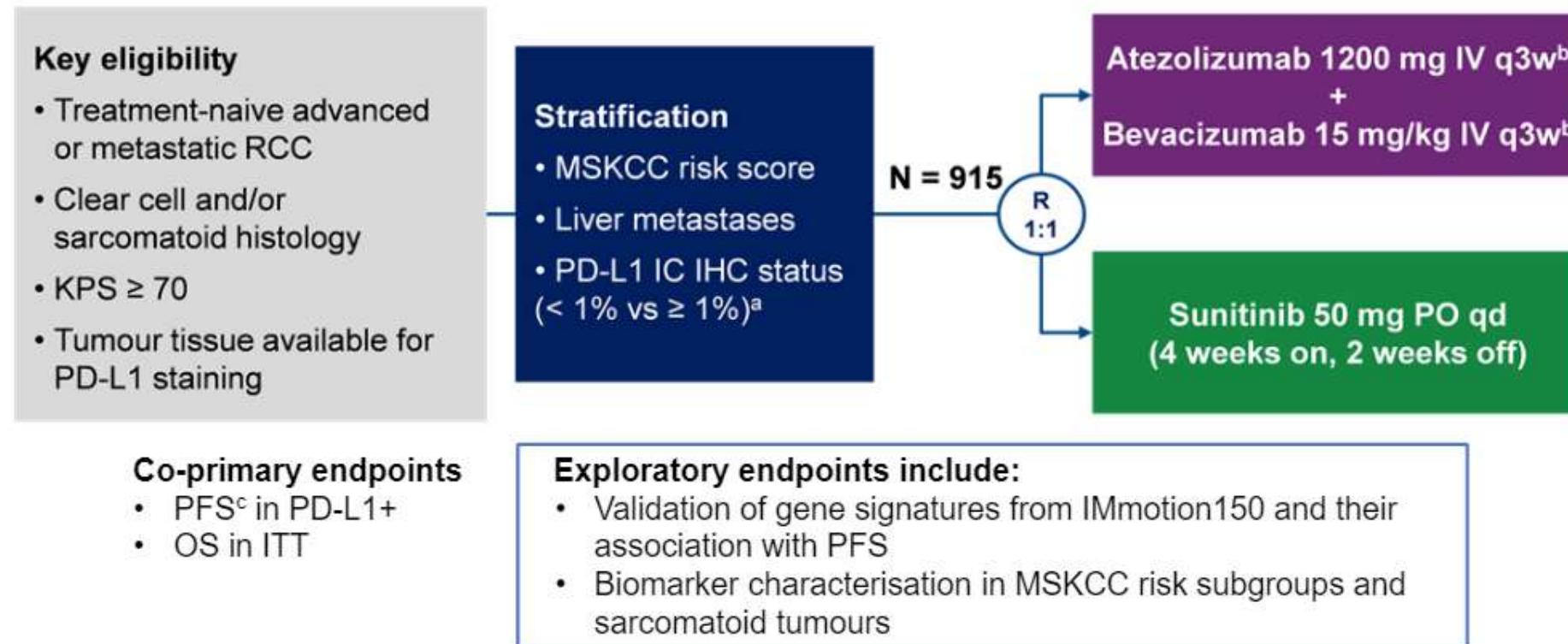
Highest-risk subpopulation: pT3 with Fuhrman grade ≥ 3 or pT4 and/or N+, any T, any Fuhrman grade

CI=confidence interval; DFS=disease-free survival; HR=hazard ratio; IRC=independent review committee

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IMmotion151: Study Design



IC, tumour-infiltrating immune cell; IHC, immunohistochemistry; ITT, intent-to-treat; IV, intravenous; KPS, Karnofsky performance status;
MSKCC, Memorial Sloan Kettering Cancer Center; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival;

PO, by mouth; q3w, every 3 weeks; QD, once a day; R, randomised; RCC, renal cell carcinoma; TME, tumour microenvironment.

^a $\geq 1\%$ IC: 40% prevalence using SP142 IHC assay. ^b No dose reduction for atezolizumab or bevacizumab. ^c Investigator assessed PFS per RECIST v1.1.

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

IMmotion151: Gene Signature Analysis Scheme

IMmotion150 (n = 263)

Identification of gene signatures based on association with clinical outcome

- T_{eff} : *CD8a, IFNG, PRF1, EOMES, CD274*
- Angio: *VEGFA, KDR, ESM1, PECAM1, CD34, ANGPTL4*



Absolute cutoff selection based on PFS HR

- T_{eff} cutoffs: 2.93 (40% prevalence)
- Angio cutoff: 5.82 (50% prevalence)

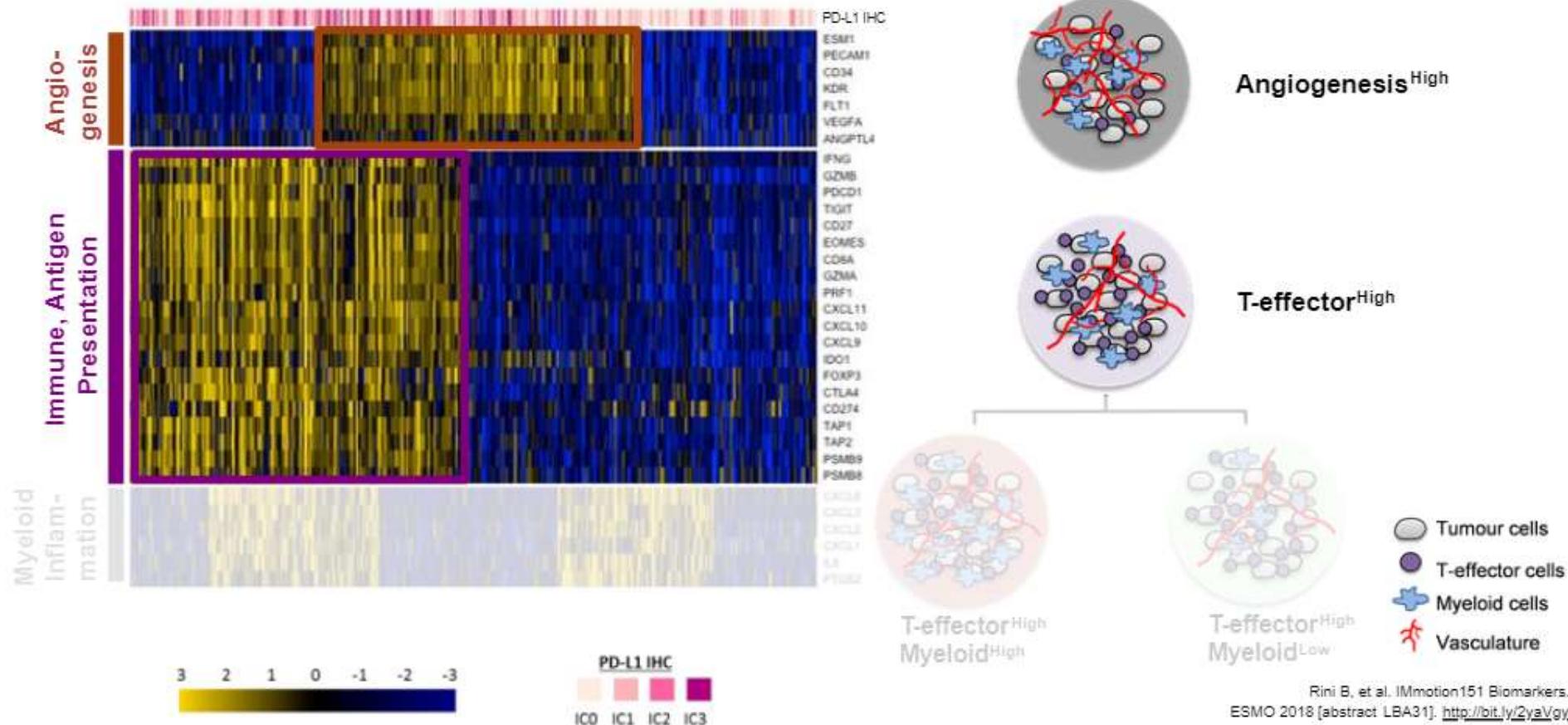


IMmotion151 (n = 823)

Pre-specified analysis of association with PFS

- Unstratified HR and log-rank tests were used for PFS analyses in biomarker-evaluable patients

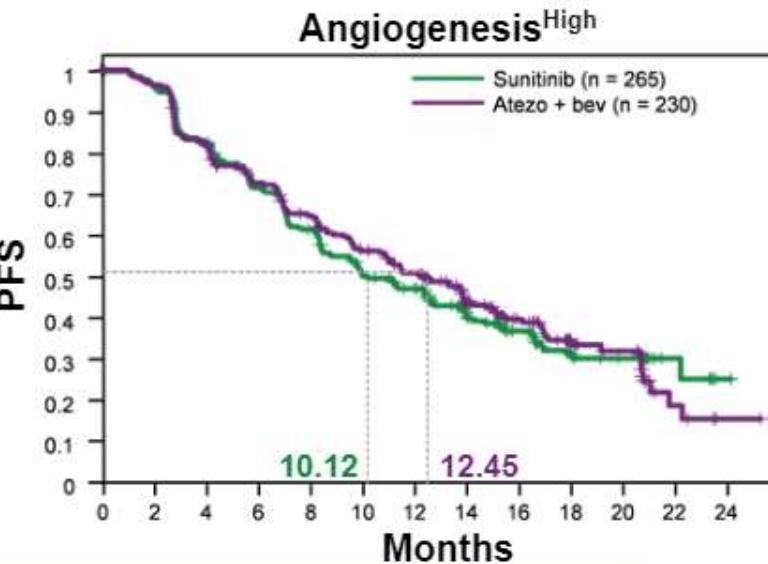
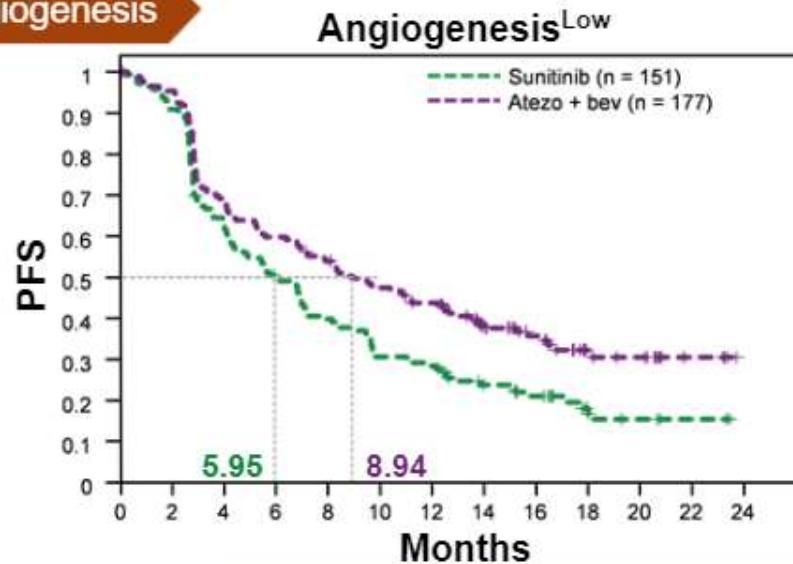
IMmotion151: Transcriptome Map Confirms Biological Subgroups Identified in IMmotion150



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

Atezolizumab + Bevacizumab Improved PFS vs Sunitinib in the Angiogenesis^{Low} Subset

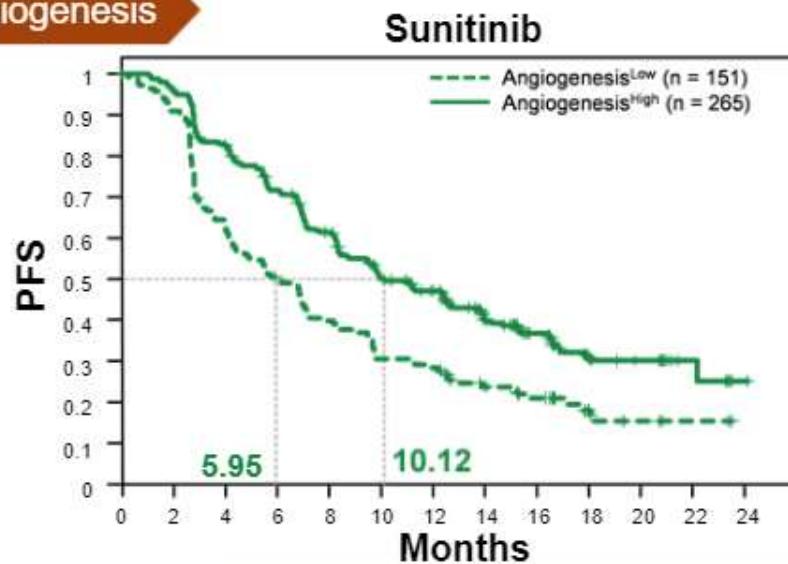
Angiogenesis



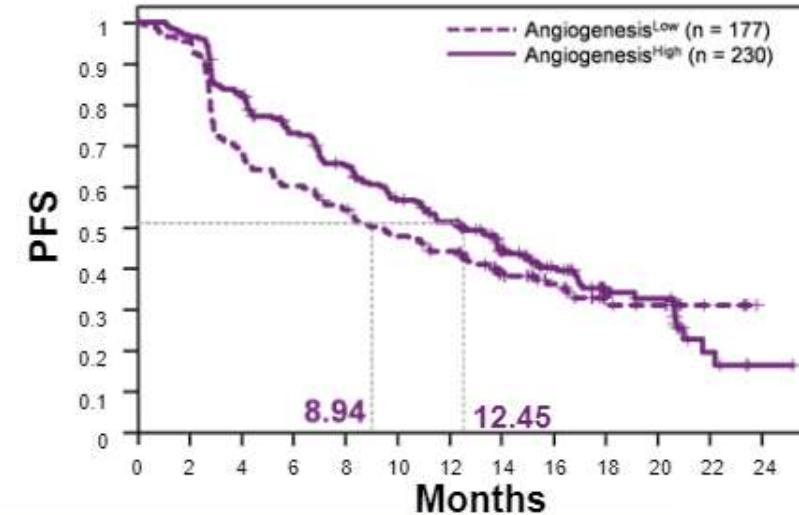
	HR (95% CI)	
	Angiogenesis ^{Low}	Angiogenesis ^{High}
Atezo + bev vs sunitinib	0.68 (0.52, 0.88)	0.95 (0.76, 1.19)

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

Angiogenesis

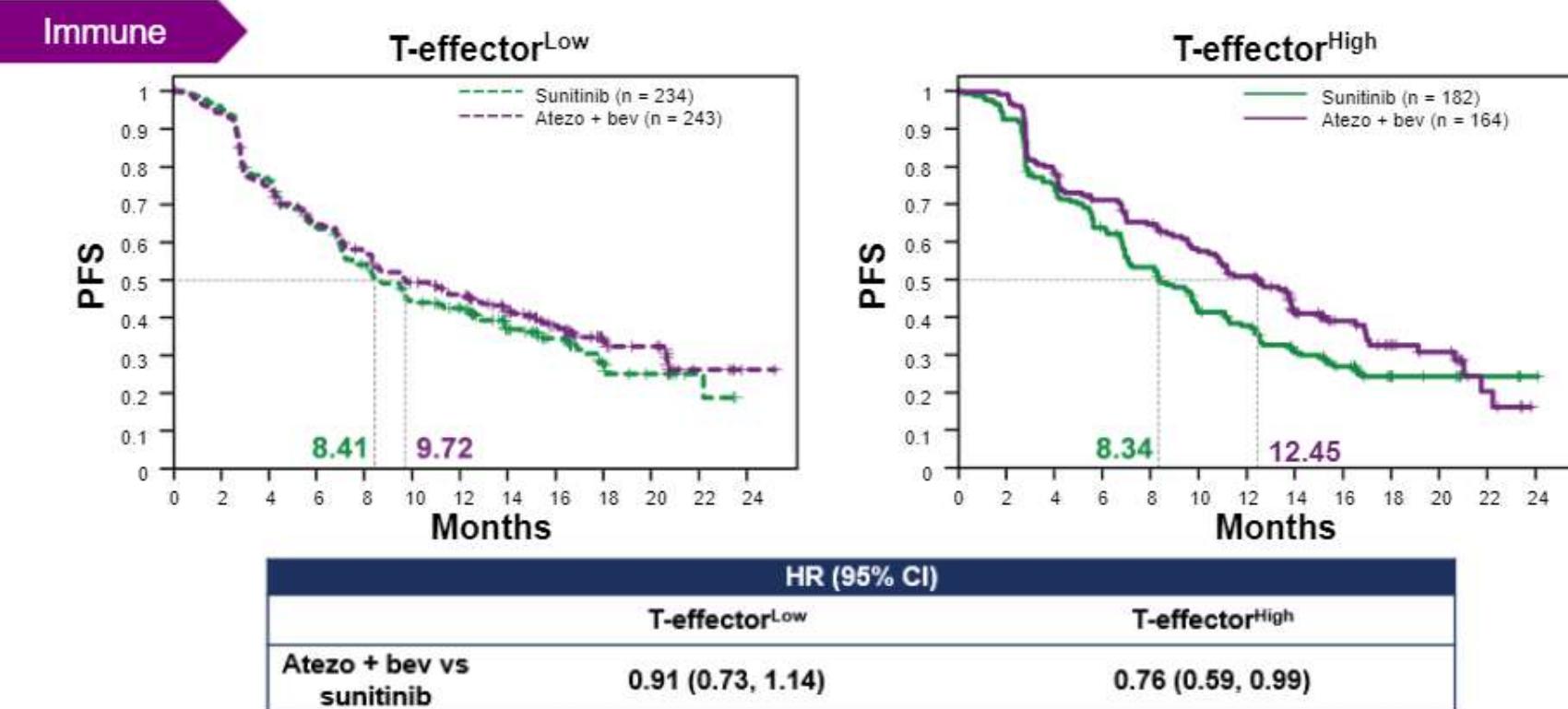


Atezolizumab + Bevacizumab



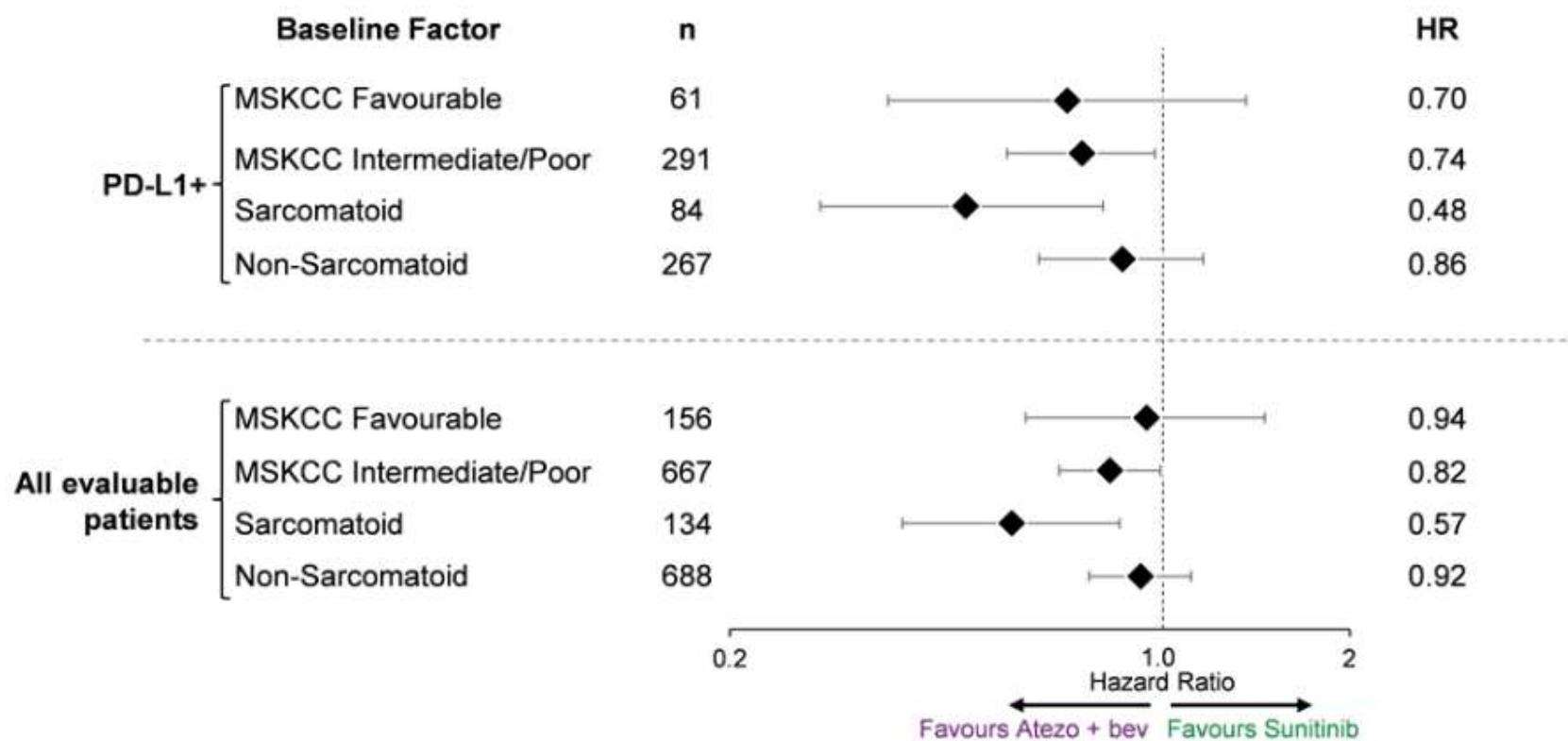
HR (95% CI)		
	Sunitinib	Atezo + Bev
Angiogenesis (High vs Low)	0.59 (0.47, 0.75)	0.86 (0.67, 1.1)

Atezolizumab + Bevacizumab Demonstrated Improved PFS vs Sunitinib in T_{eff}^{High} Subset



- T-effector gene signature did not differentiate PFS within the sunitinib or atezolizumab + bevacizumab treatment arms

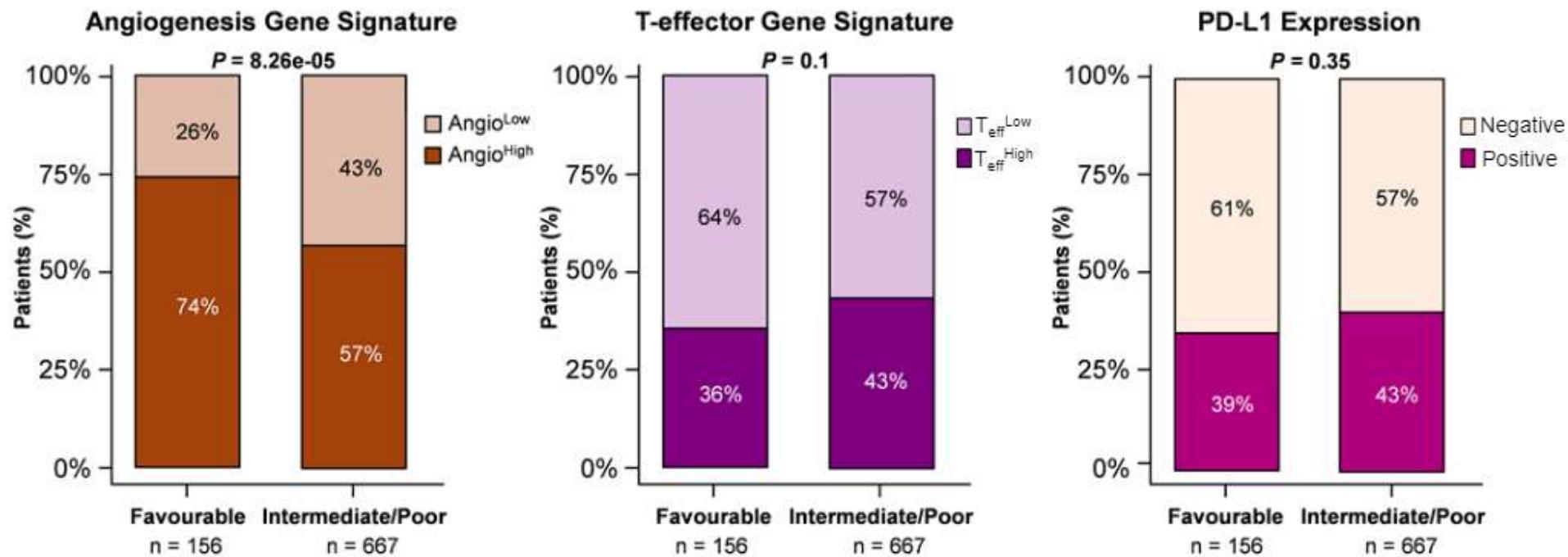
Subgroup PFS Analyses in PD-L1+ and All Evaluable Patients^a



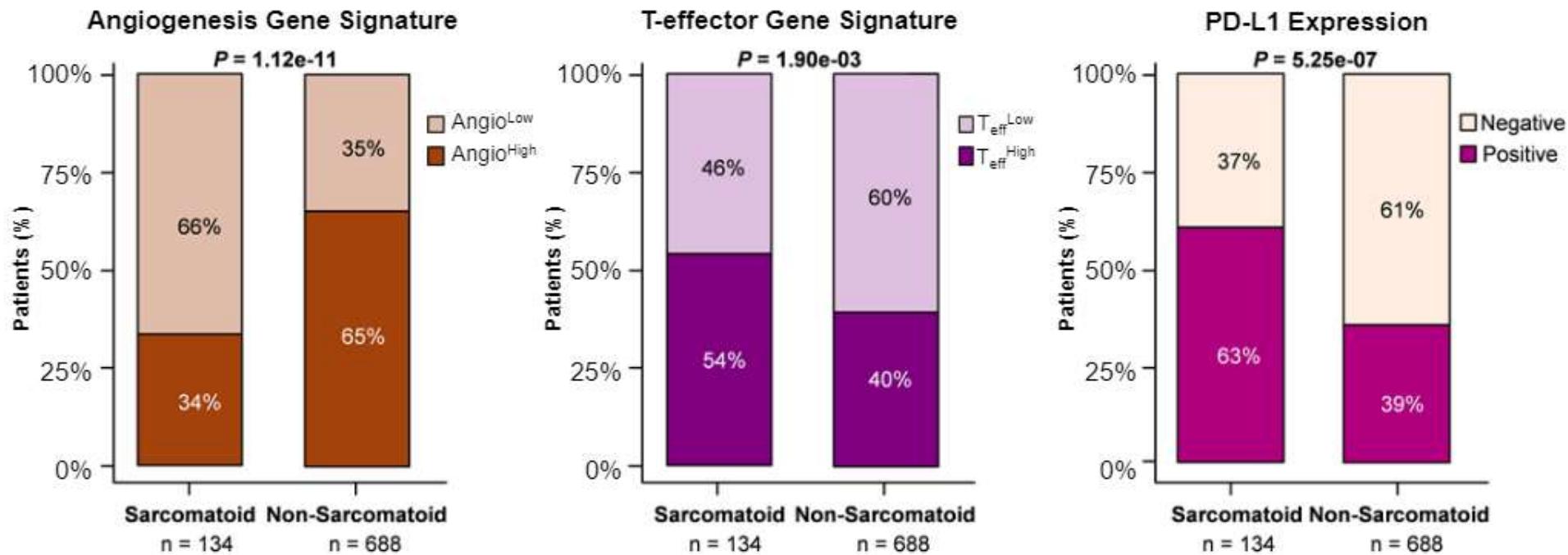
^a Biomarker-evaluable population.

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

Angiogenesis Gene Expression Is Higher in Favourable MSKCC Risk Group



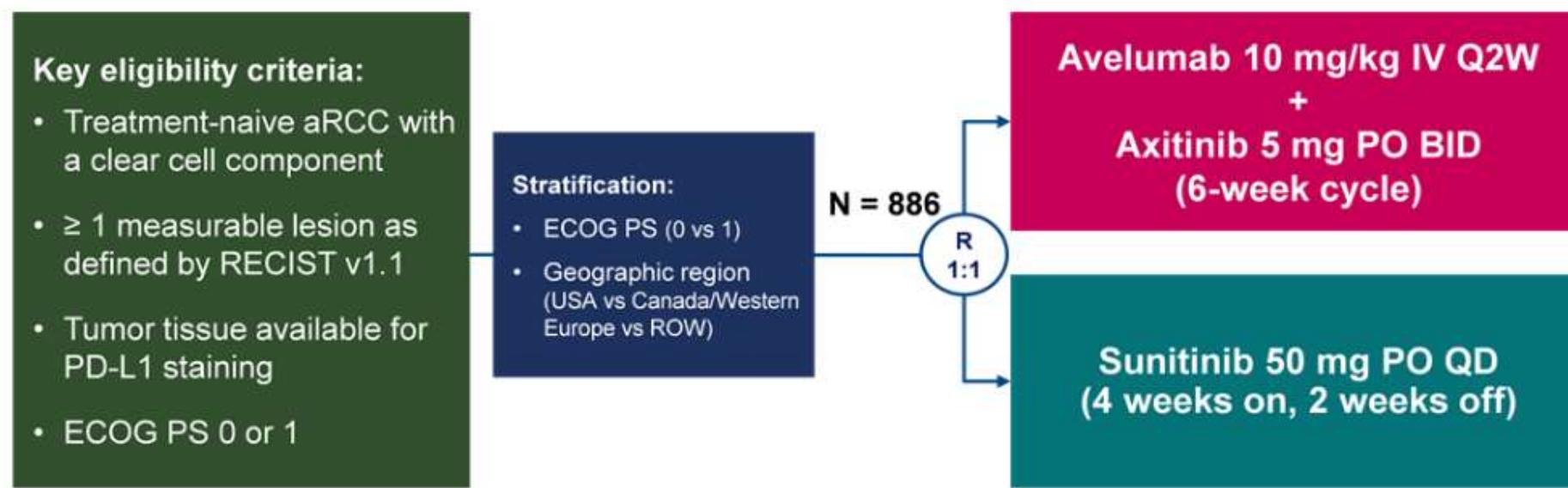
Angiogenesis Gene Expression Is Lower and PD-L1 Expression Is Higher in Sarcomatoid Tumours



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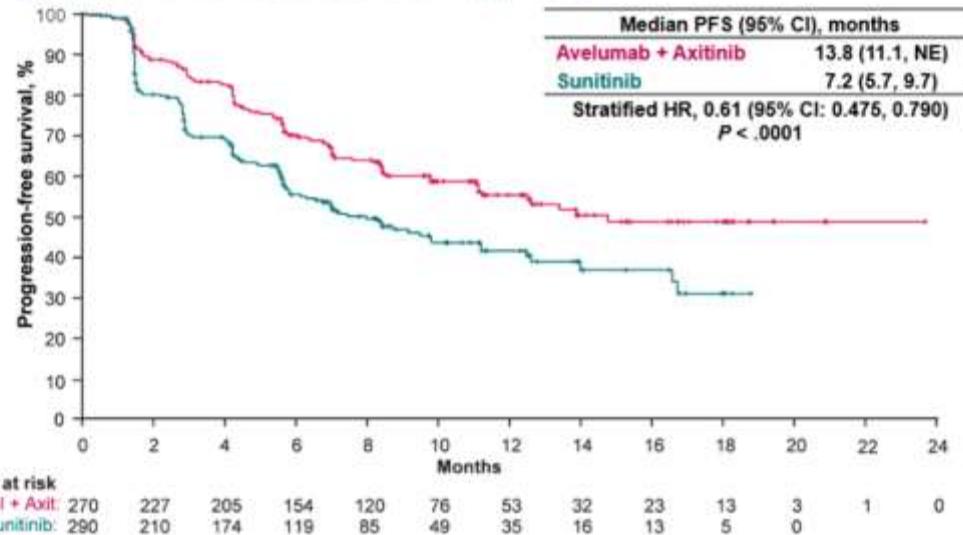
JAVELIN Renal 101: study design



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

PFS per IRC in the PD-L1+ group

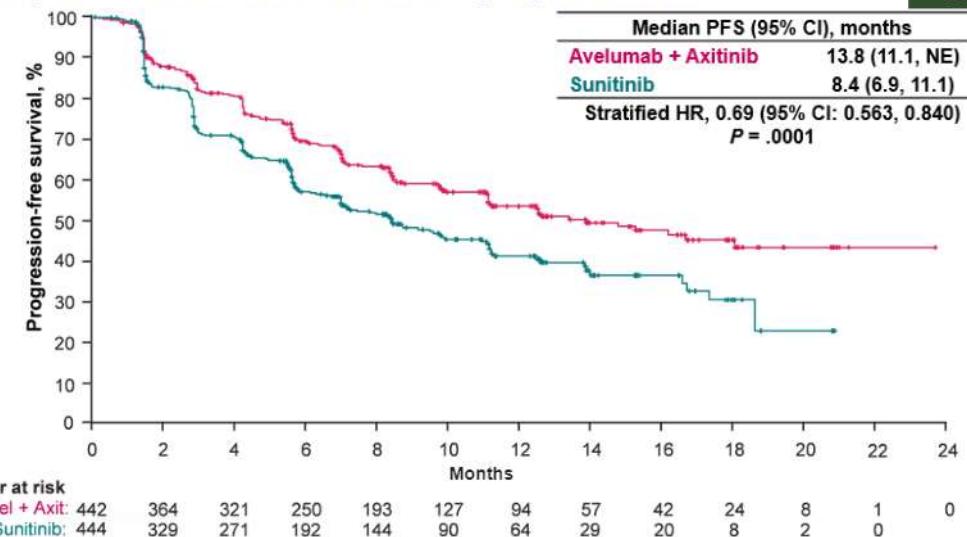


Minimum follow-up, 6 months. Median follow-up, 9.9 months (avelumab + axitinib) and 8.4 months (sunitinib).

The PFS analysis crossed the prespecified efficacy boundary based on the alpha-spending function (P = .001)

Primary
endpoint

PFS per IRC in the overall population



Minimum follow-up, 6 months. Median follow-up, 10.8 months (avelumab + axitinib) and 8.6 months (sunitinib).

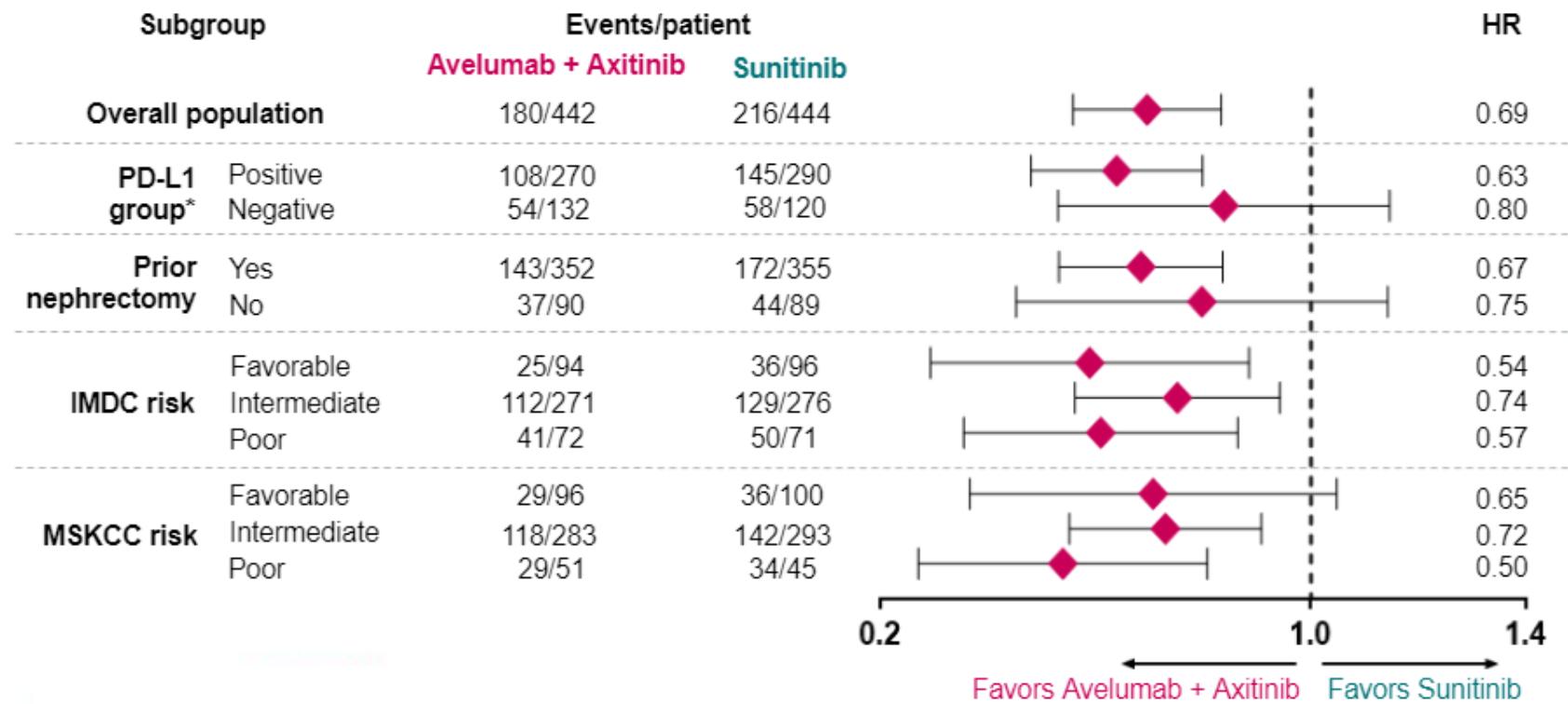
The PFS analysis crossed the prespecified efficacy boundary based on the alpha-spending function (P = .001).

NE, not estimable. 9

10

PFS per IRC in key subgroups

Subgroup analysis



* 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.

Confirmed objective response

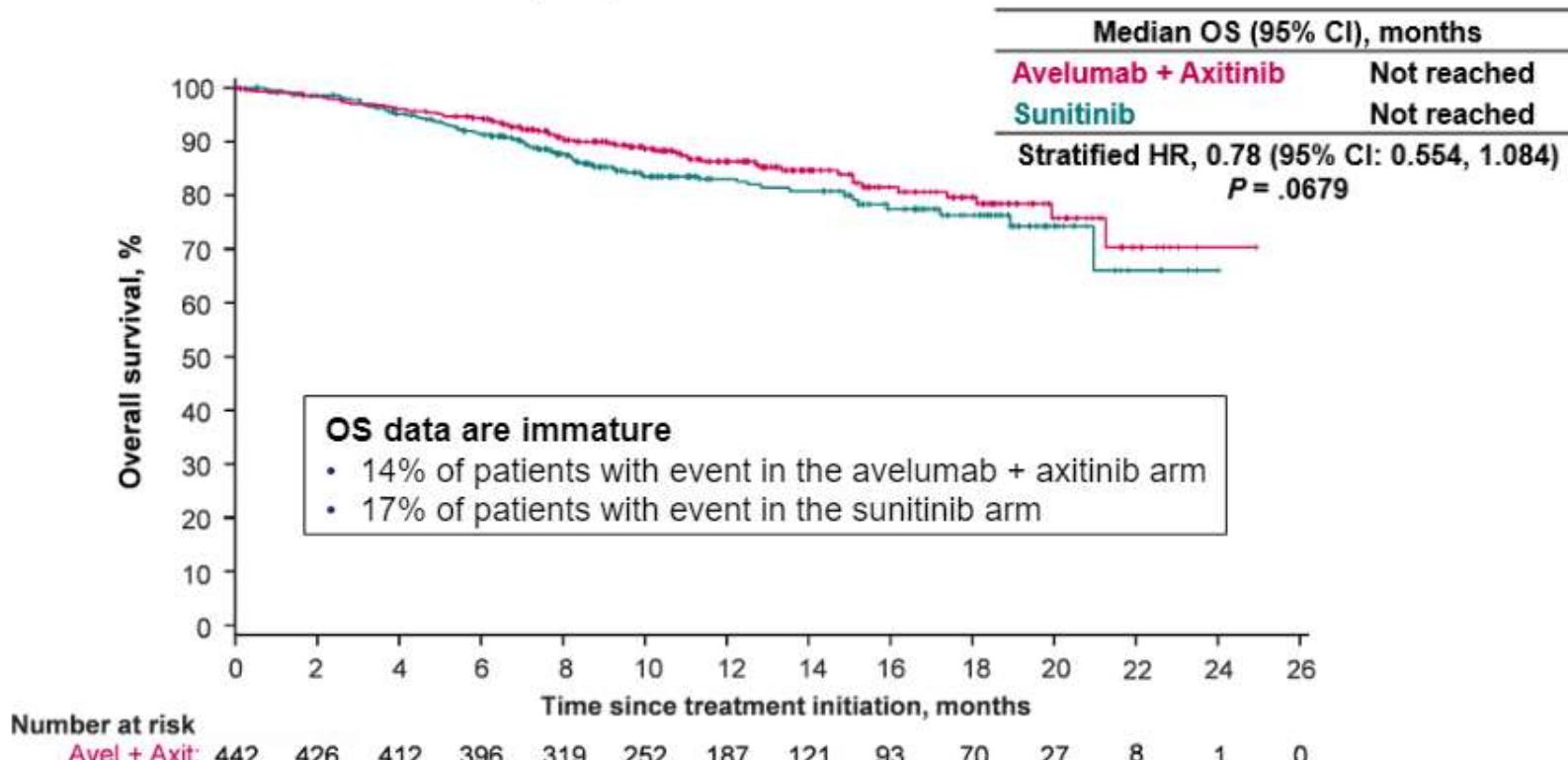
Secondary endpoint

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
<hr/>				
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.

OS in the overall population



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

Riflessioni:

Pazienti a prognosi «intermediate-poor» due standard in prima linea (Cabo vs Nivo+Ipi) nel prossimo futuro.

Atezo+Beva dati poco convincenti...

Nefrectomia NON si fa nei pazienti poor. *Possiamo ancora parlarne nei pazienti a prognosi intermedia?*

Adiuvante, non c'è spazio per i TKI (*al Gemelli attivo protocollo di immunoterapia*).

Il profilo molecolare del tumore una strada da sviluppare per orientare la scelta su basi scientifiche.

Avelumab + Axitinib, l'inizio di un nuovo standard di cura in prima linea (*all'ASCO GU vedremo i dati positivi della combinazione Pembro+Axitinib*).