Novel Therapies in Metastatic Kidney Cancer

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Metastatic RCC: Treatment Principles

- The best treatment is one that results in cure
- In the absence of cure, goals are palliative
  - Disease control and prolongation of life are achievable
- Angiogenesis is active throughout natural history of mRCC

Metastatic RCC: Treatment Principles

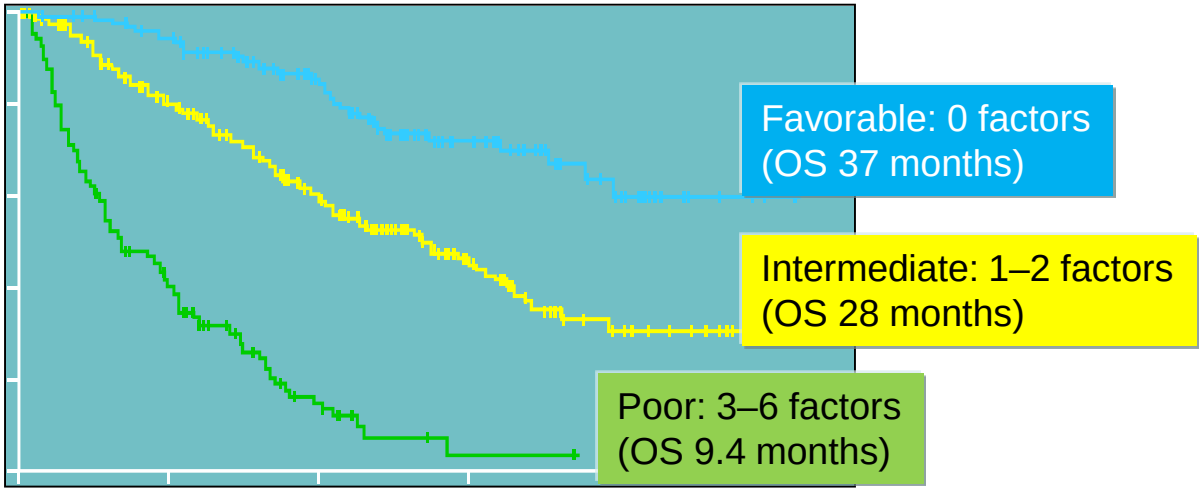
- Current standard of care:
  - Risk stratification
  - Frontline use of immunotherapy-based therapy or angiogenesis inhibitors, dependent on risk group
  - New systemic treatment initiated at time of progression or unacceptable toxicity
  - Whenever possible, clinical trials remain the optimal choice

Risk Stratification in mRCC

- **N = 645 patients with mRCC treated with VEGF-targeted therapy**
  - **Sunitinib (61%); Sorafenib (31%); Bevacizumab (8%)**

- **Predictors for OS:**
  - **Time from diagnosis to treatment***
  - **Hemoglobin***
  - **Calcium***
  - **Performance status***
  - **Neutrophil count**
  - **Platelet count**

* Components of MSKCC prognostic criteria



Risk Group	Number of Risk Factors	Median Survival Time
Favorable Risk (n=133)	**0**	**37 months**
Intermediate Risk (n=292)	**1-2**	**28.5 months**
Poor Risk (n=139)	**>2**	**9.4 months**

Heng DY, et al. *J Clin Oncol* 2009

Efficacy Scorecard: Frontline RCC

Pivotal Trial	N	Response Rate (%)	Median PFS (months)	Median OS (months)
Sunitinib vs. IFN-α	750	47 vs. 12	11 vs. 5	26.4 vs. 21.8
Bevacizumab + IFN-α vs. IFN-α	649	31 vs. 12	10.4 vs. 5.5	23.3 vs. 21.3
	732	25.5 vs. 13.1	8.4 vs. 4.9	18.3 vs. 17.4
Pazopanib vs. placebo	233	30 vs. 3	11.1 vs. 2.8	22.9 vs. 20.5
Pazopanib vs. Sunitinib	1,110	31 vs. 25	8.4 vs. 9.5	28.4 vs. 29.3
Cabozantinib vs. Sunitinib (poor and intermediate risk)*	157	46 vs. 18	8.2 vs. 5.6	30 vs. 21.8
Temsirolimus vs. IFN-α (poor risk)	626	8.6 vs. 4.8	5.5 vs. 3.1	10.9 vs. 7.3
Nivo/Ipi vs. Sunitinib (poor and intermediate risk)	1,070	41.6 vs. 26.5	11.5 vs. 8.4	NR vs 26
Atezo/Bev vs Sunitinib (PDL1+ group)	915 (ITT); 362 (PDL1+)	43 vs 35	11.2 vs. 7.7 (Inv Review) 8.9 vs 7.2 (Ind Review)	NR vs 23.3

* Phase II trial

Established role of angiogenesis inhibitors

Established role of mTOR inhibition

Established role of IO-based therapy

Temsirolimus Phase 3 Trial in Poor-risk RCC*

Eligibility Criteria:

- Locally advanced RCC or mRCC
- Predominant clear cell histology
- 3/6 Poor Risk Features
- LDH >1.5 x ULN
- Hgb < LLN
- Corrected Ca^{++} >10
- KPS <70%
- DFI <1 year
- Multiple sites of metastases)

RANDOMIZATION†

- IFN 3 MU-18 MU (n = 207)
- TEM 25 mg QW (n = 209)
- IFN 6 MU + TEM 15 mg QW (n = 210)

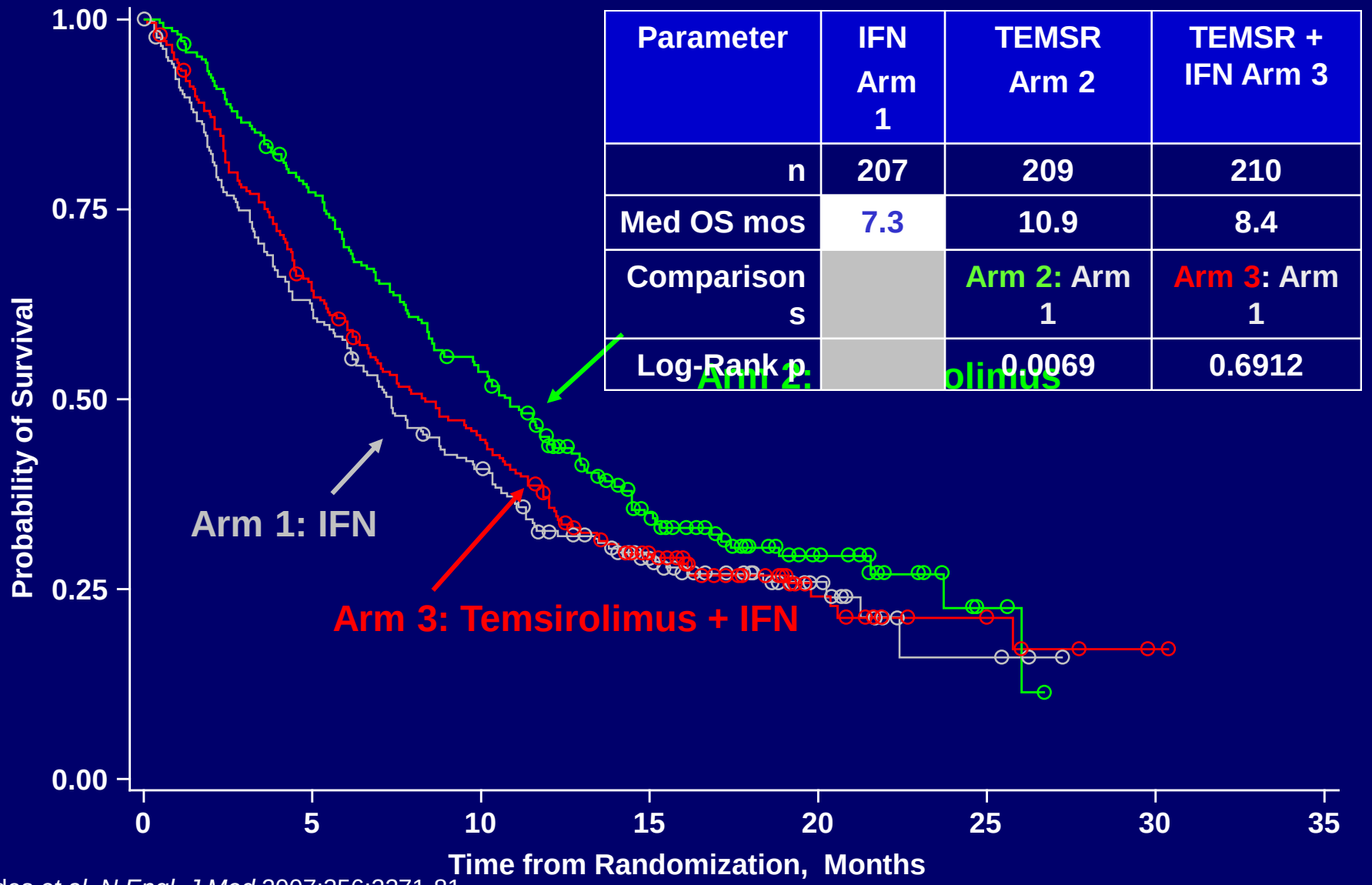
Primary Endpoint: PFS

*Modified MSKCC poor risk; †Stratification by country and nephrectomy status.
DFI = disease-free interval.

Hudes G et al. *N Engl J Med*. 2007;356:2271–2281.

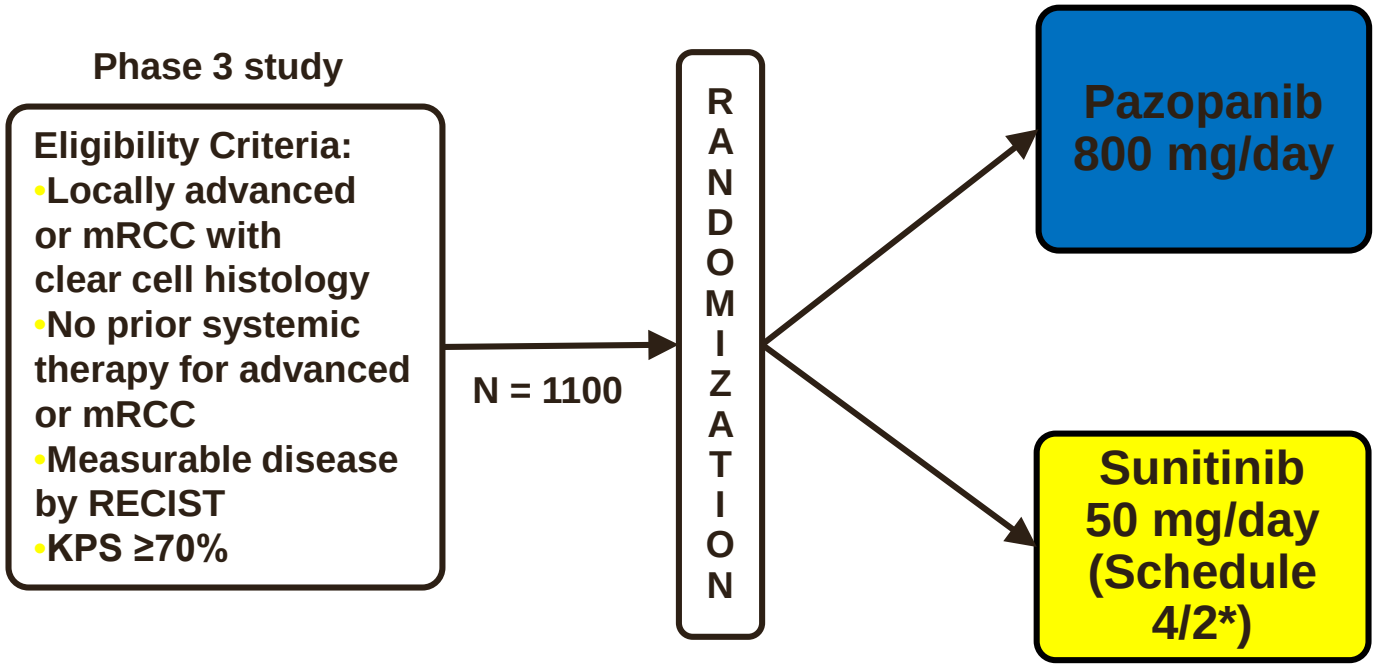
Temsirolimus vs IFN-α: Overall Survival

Parameter	IFN Arm 1	TEMSR Arm 2	TEMSR + IFN Arm 3
n	207	209	210
Med OS mos	7.3	10.9	8.4
Comparisons		Arm 2: Arm 1	Arm 3: Arm 1
Log-Rank p		0.0069	0.6912



Hudes *et al. N Engl J Med* 2007;356:2271-81

Pazopanib vs. Sunitinib for First-line Treatment of Clear Cell mRCC (COMPARZ)



- **Primary Endpoint: PFS (non-inferiority – upper bound of 95% CI for HR < 1.25)**

*Schedule 4/2 = 4 weeks on treatment/ 2 weeks off.
Available at: http://www.clinicaltrials.gov. NCT00720941.

COMPARZ: Summary of Results

Efficacy	Pazopanib (n=557)	Sunitinib (n=553)	HR (95% CI); P Value
Median PFS, mos (95% CI) Independent Review	8.4 (8.3, 10.9)	9.5 (8.3, 11.1)	1.047 (0.898, 1.220)
Interim OS, mos (95% CI)	28.4 (26.2, 35.6)	29.3 (25.3, 32.5)	0.908 (0.762, 1.082) P=0.275
Objective Response Rate (CR+ PR), %	31 (26.9, 34.5)	25 (21.2, 28.4)	P=0.032

Dose modifications	Pazopanib (n=554)	Sunitinib (n=548)
Dose interruptions, %*	60	63
Dose reductions, %	44	51
Discontinuations due to AE, %	24	19

Motzer RJ, et al. Presented at ESMO. 2012 (abstr LBA8_PR).

* Eisen ESMO 2012 (Discussant for abstr 2325).

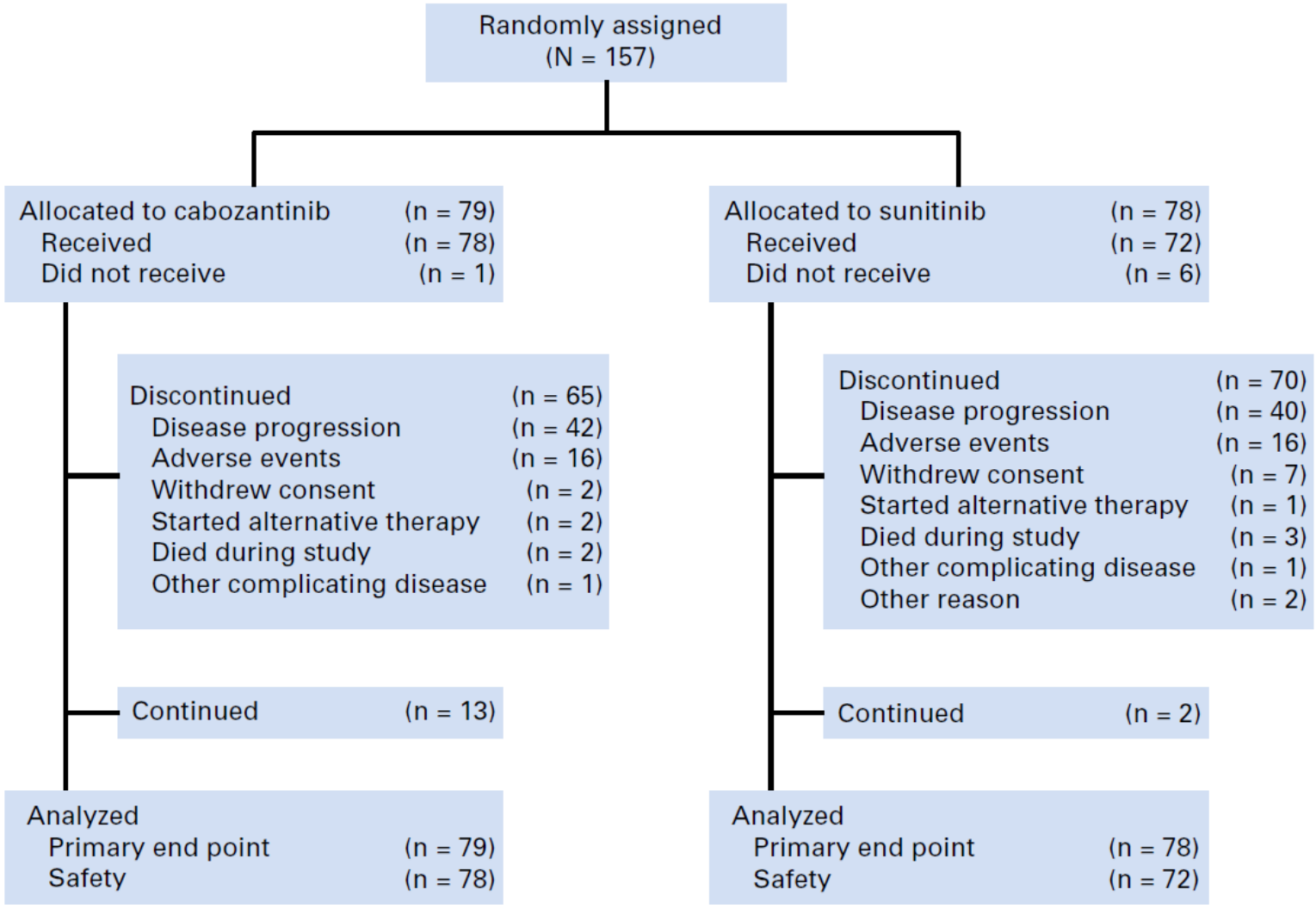
COMPARZ: Most Common Adverse Events (Treatment-emergent)

	Pazopanib (n = 554) %		Sunitinib (n = 548) %	
Adverse Event [a]	All Grs	Gr 3/4	All Grs	Gr 3/4
Any event [b]	>99	59/15	>99	57/17
Diarrhea	63	9/0	57	7/<1
Fatigue	55	10/<1	63	17/<1
Hypertension	46	15/<1	41	15/<1
Nausea	45	2/0	46	2/0
Decreased appetite	37	1/0	37	3/0
ALT increased	31	10/2	18	2/<1
Hair color changes	30	0/0	10	<1/0
Hand-foot syndrome	29	6/0	50	11/<1
Taste Alteration	26	<1/0	36	0/0
Thrombocytopenia	10	2/<1	34	12/4

[a] AE ≥30% in either arm

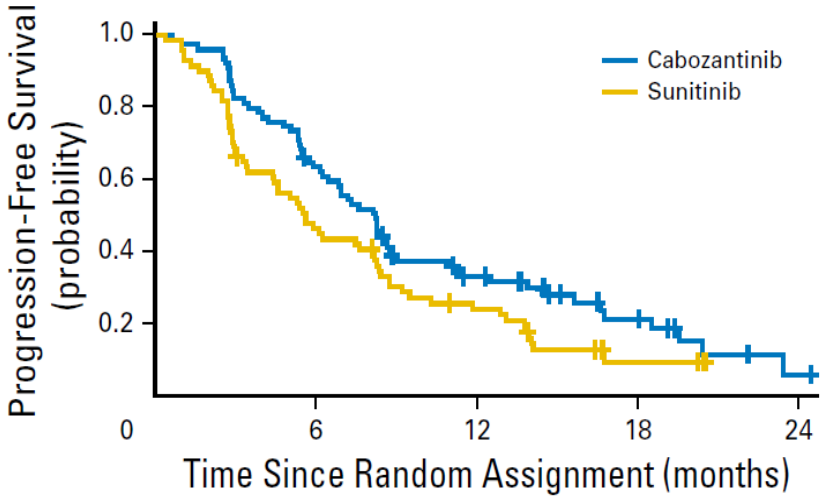
[b] 2% of patients in pazopanib arm and 3% of patients in sunitinib arm had grade 5 adverse events.

Phase II CABOSUN trial

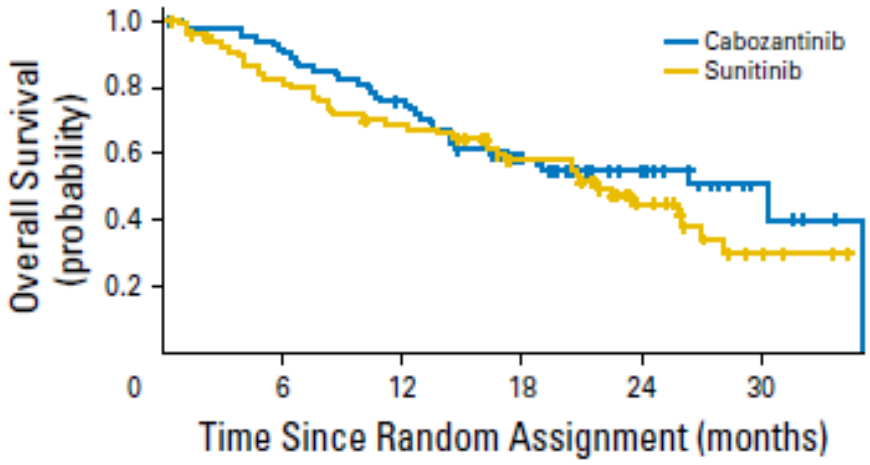


Choueiri, JCO 2016

Phase II CABOSUN trial



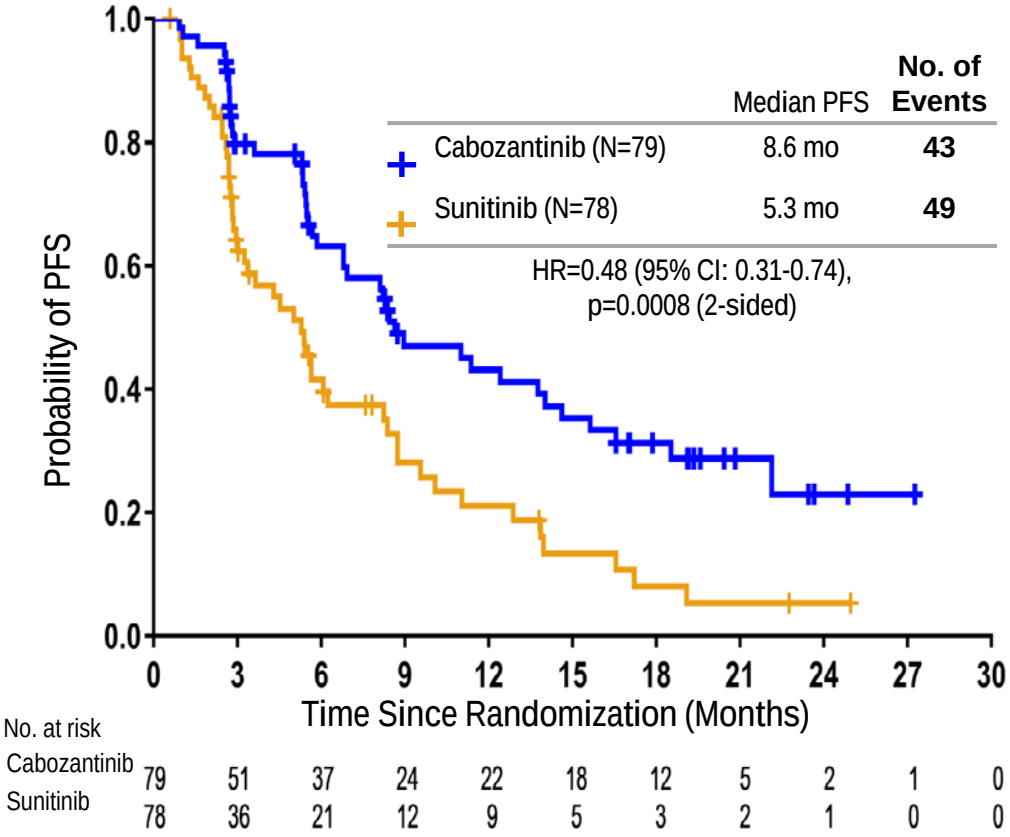
No. at risk					
Cabozantinib	79	49	22	9	1
Sunitinib	78	32	15	3	0

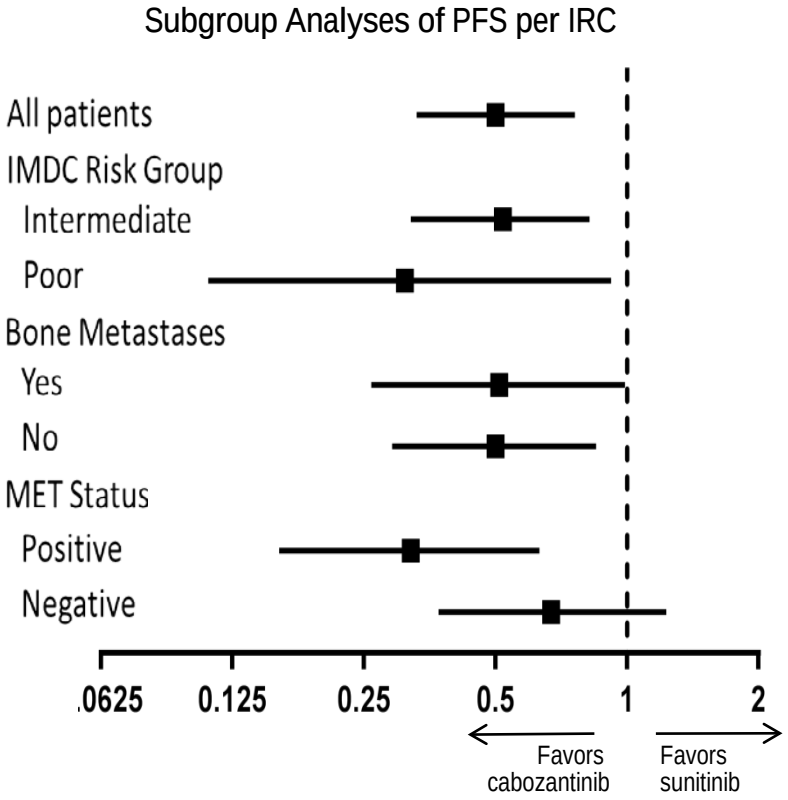


No. at risk						
Cabozantinib	79	71	58	35	16	5
Sunitinib	78	60	49	34	17	4

Response	Cabozantinib (n = 79), No. (%)	Sunitinib (n = 78), No. (%)
ORR, % (95% CI)*	46 (34 to 57)	18 (10 to 28)
Best overall response, No. (%)		
Confirmed CR	1 (1.3)	1 (1.3)
Confirmed PR	35 (44.3)	13 (16.7)
Stable disease	26 (32.9)	28 (35.9)
Progressive disease	14 (17.7)	20 (25.6)
Not evaluable or missing†	3 (3.8)	16 (20.5)

CABOSUN: PFS per IRC and Overall Survival

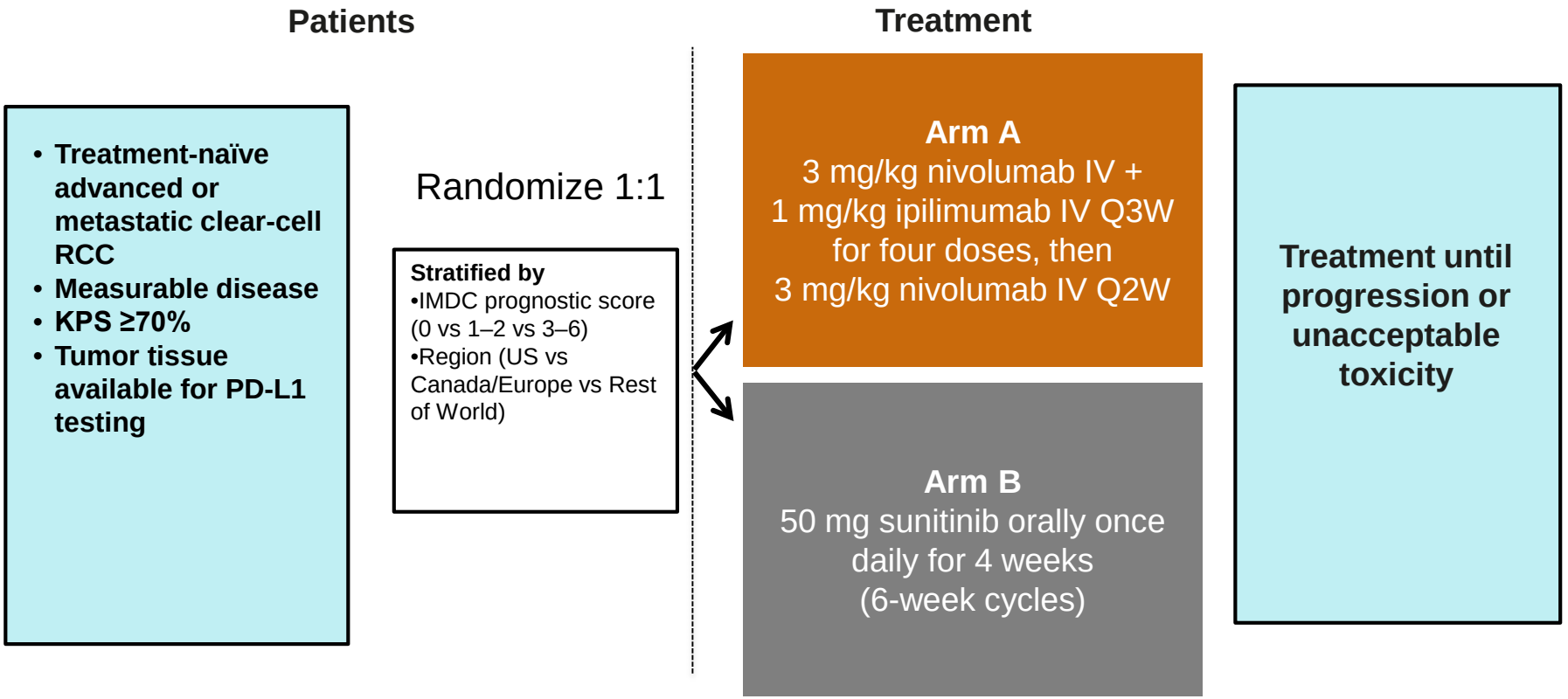




Data cutoff : PFS, Sep 15, 2016; OS, July 1, 2017; IRC, Independent Review Committee; IMDC, International Metastatic RCC Database Consortium.

Overall Survival (OS)
HR=0.80 (95% CI: 0.53-1.21); p=0.29 (2-sided)
Median OS: Cabozantinib 26.6 mo,
Sunitinib 21.2 mo

Nivolumab + Ipilimumab in mRCC: CheckMate 214



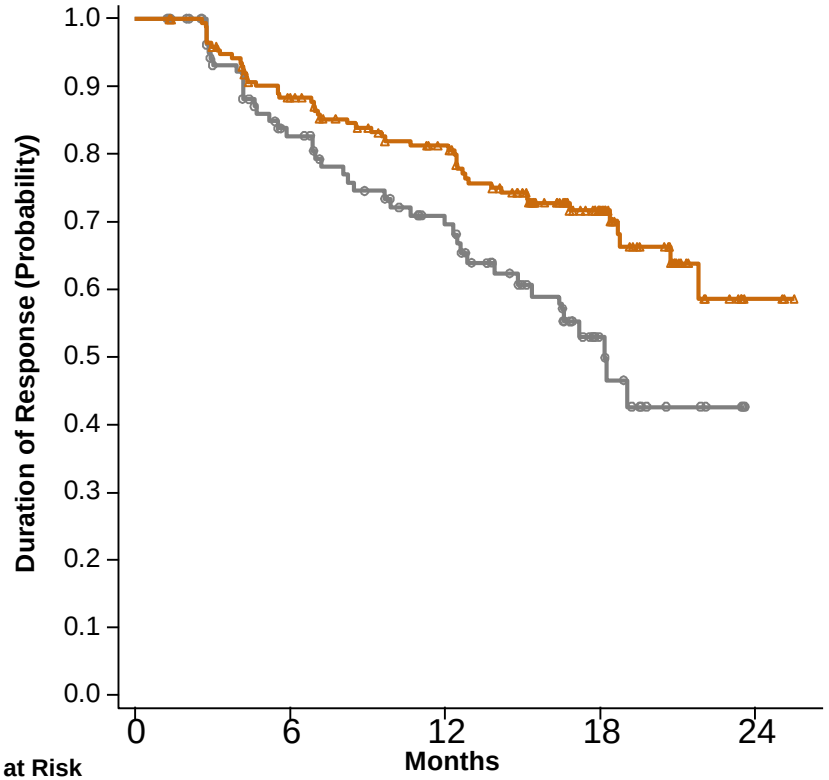
Escudier, ESMO 2017; Motzer NEJM 2018

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

ORR and DOR: IMDC intermediate/poor risk

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

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



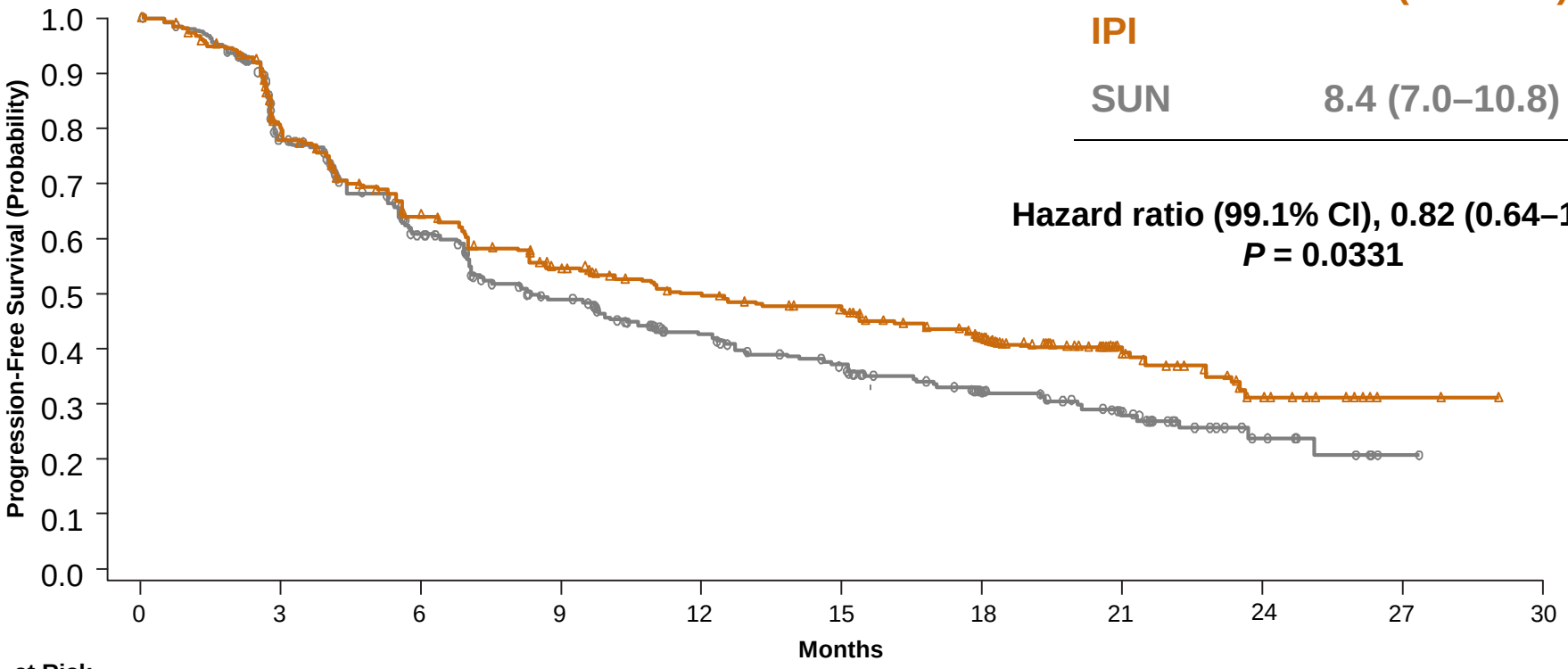
No. at Risk					
NIVO + IPI	177	146	120	55	3
SUN	112	75	52	17	0

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

PFS per IRRC: IMDC intermediate/poor risk

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

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



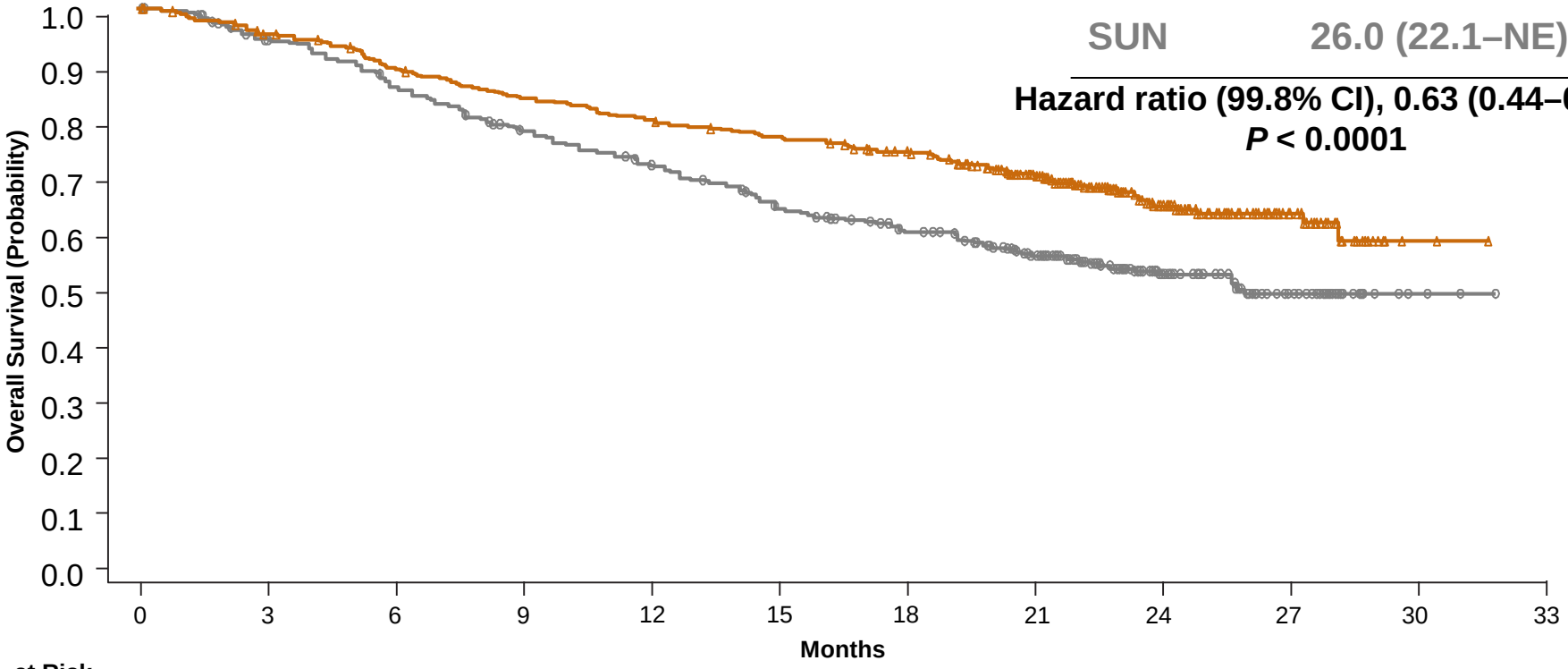
No. at Risk											
NIVO + IPI	425	304	233	187	163	149	118	46	17	3	0
SUN	422	282	191	139	107	86	57	33	11	1	0

Co-primary endpoint

OS: IMDC intermediate/poor risk

Median OS, months (95% CI)	
NIVO + IPI	NR (28.2–NE)
SUN	26.0 (22.1–NE)

Hazard ratio (99.8% CI), 0.63 (0.44–0.89)
***P* < 0.0001**



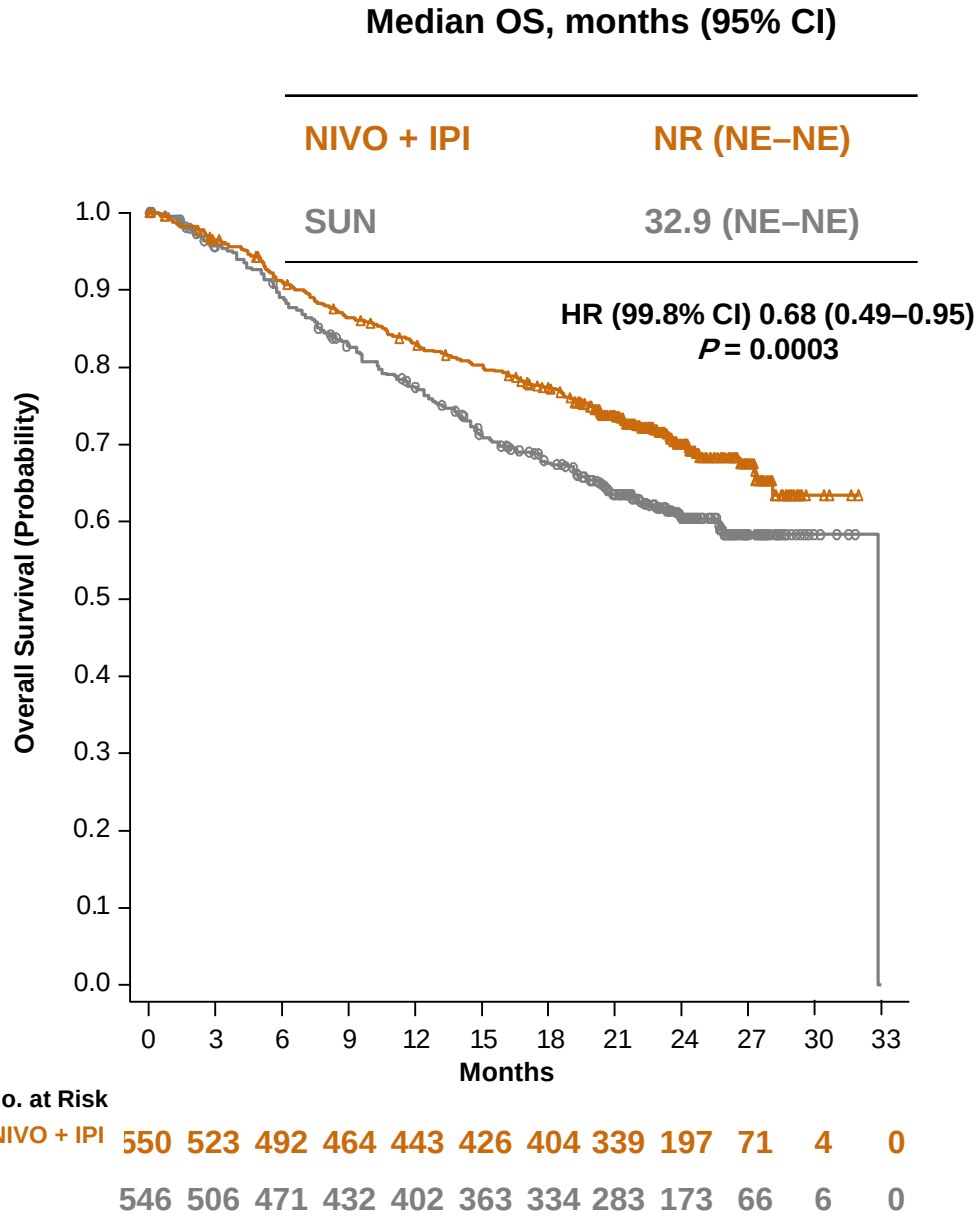
No. at Risk												
NIVO + IPI	425	399	372	348	332	318	300	241	119	44	2	0
SUN	422	387	352	315	288	253	225	179	89	34	3	0

Secondary endpoint

ORR, PFS, and OS: Intention to treat

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

[b]IRRC-assessed by RECIST v1.1
[c]IRRC-assessed



MADRID 2017 ESMO congress

Exploratory endpoint

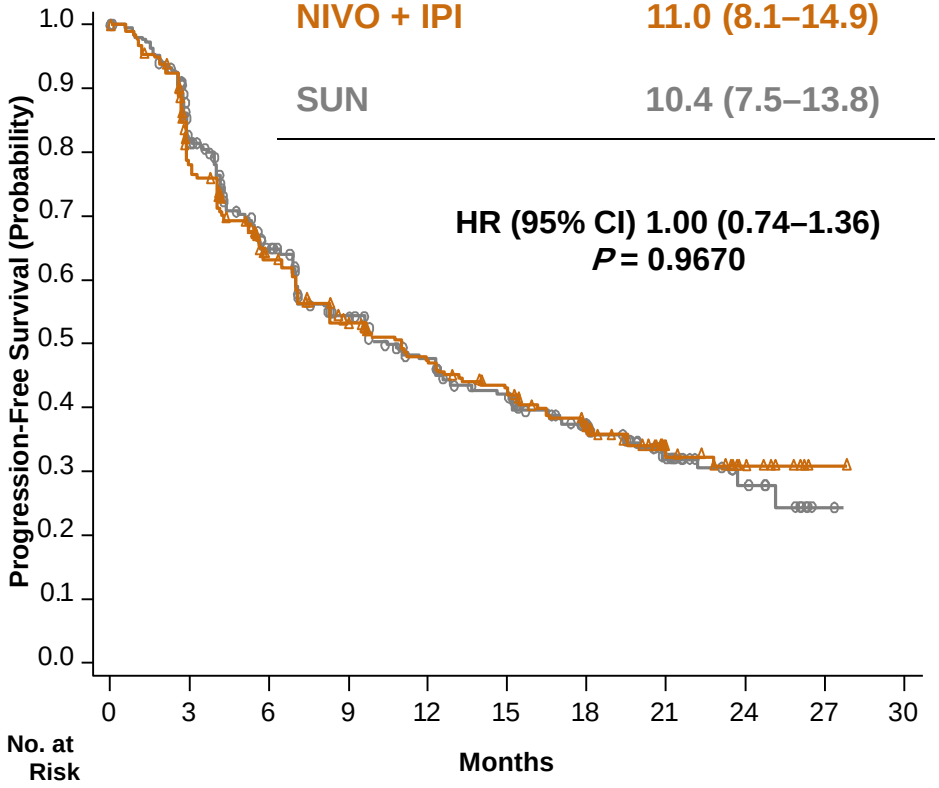
PFS by PD-L1 expression: IMDC intermediate/poor risk

PD-L1 <1% (n = 562)

Median PFS, months (95% CI)

NIVO + IPI	11.0 (8.1–14.9)
SUN	10.4 (7.5–13.8)

HR (95% CI) 1.00 (0.74–1.36)
P = 0.9670



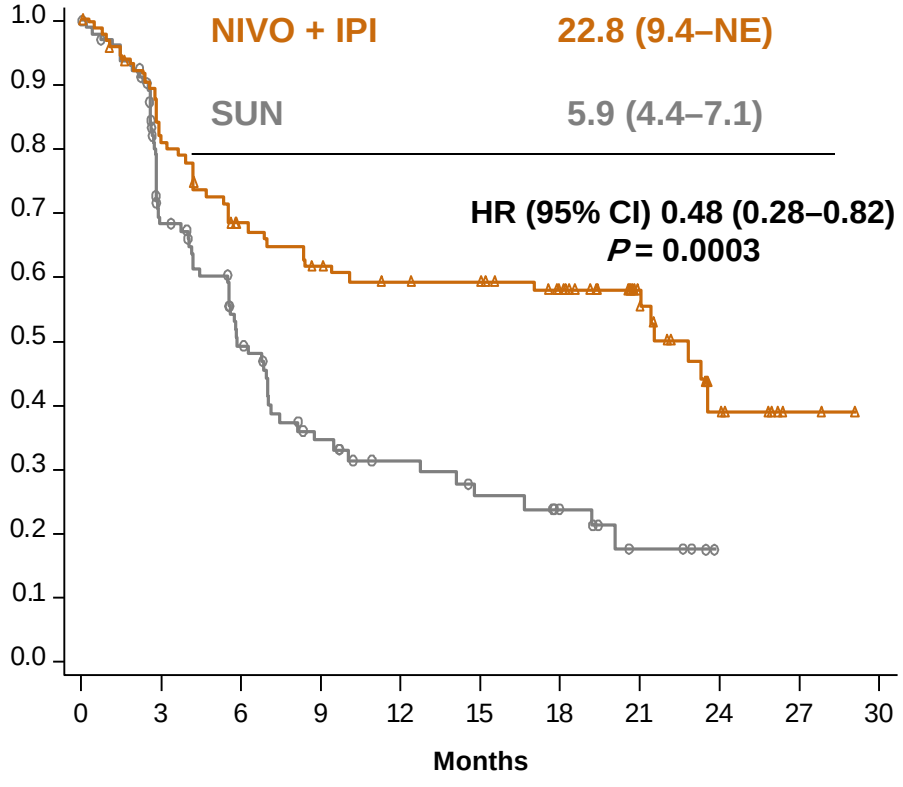
No. at Risk											
NIVO	284	202	155	119	102	90	70	23	9	1	0
SUN	278	200	138	105	83	67	43	25	11	1	

PD-L1 ≥1% (n = 214)

Median PFS, months (95% CI)

NIVO + IPI	22.8 (9.4–NE)
SUN	5.9 (4.4–7.1)

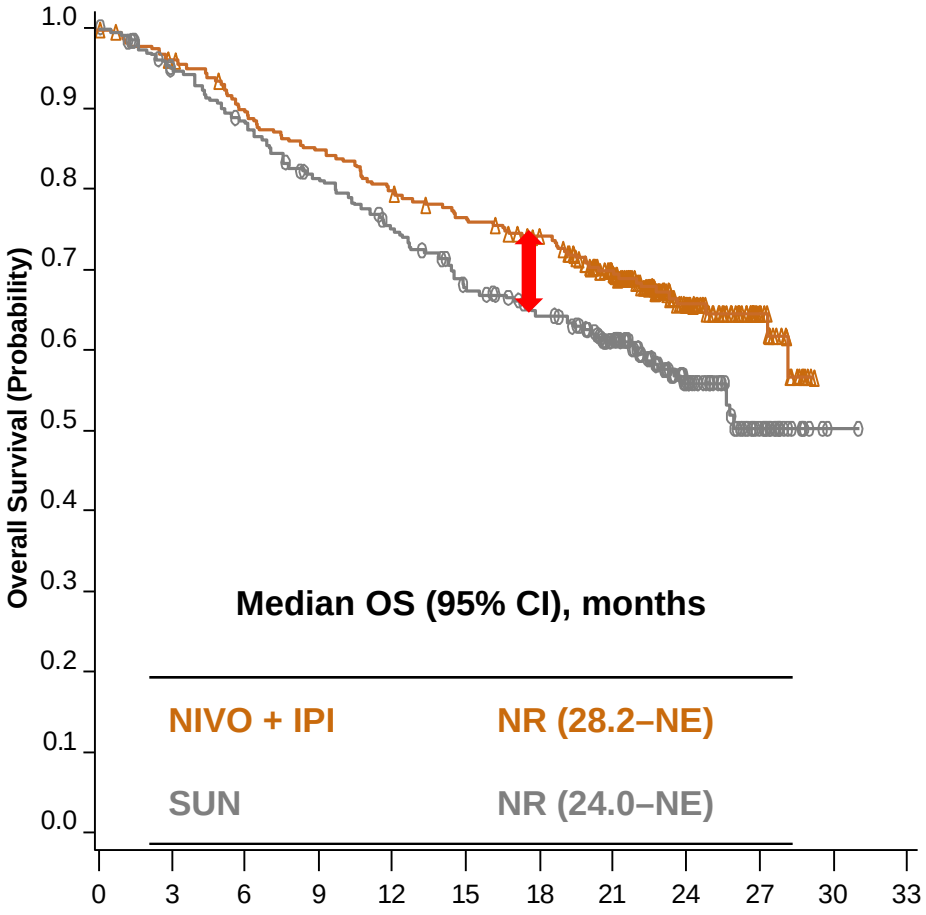
HR (95% CI) 0.48 (0.28–0.82)
P = 0.0003



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

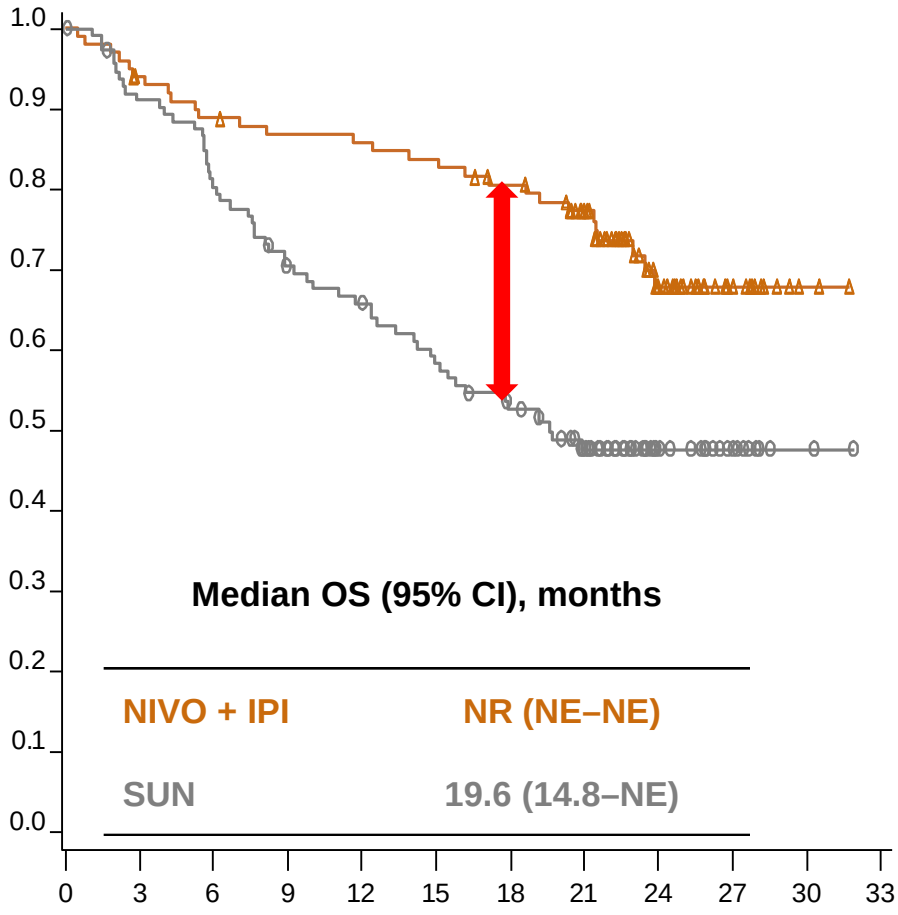
OS by tumor PD-L1 expression: IMDC intermediate/poor risk

PD-L1 <1% (n = 562)



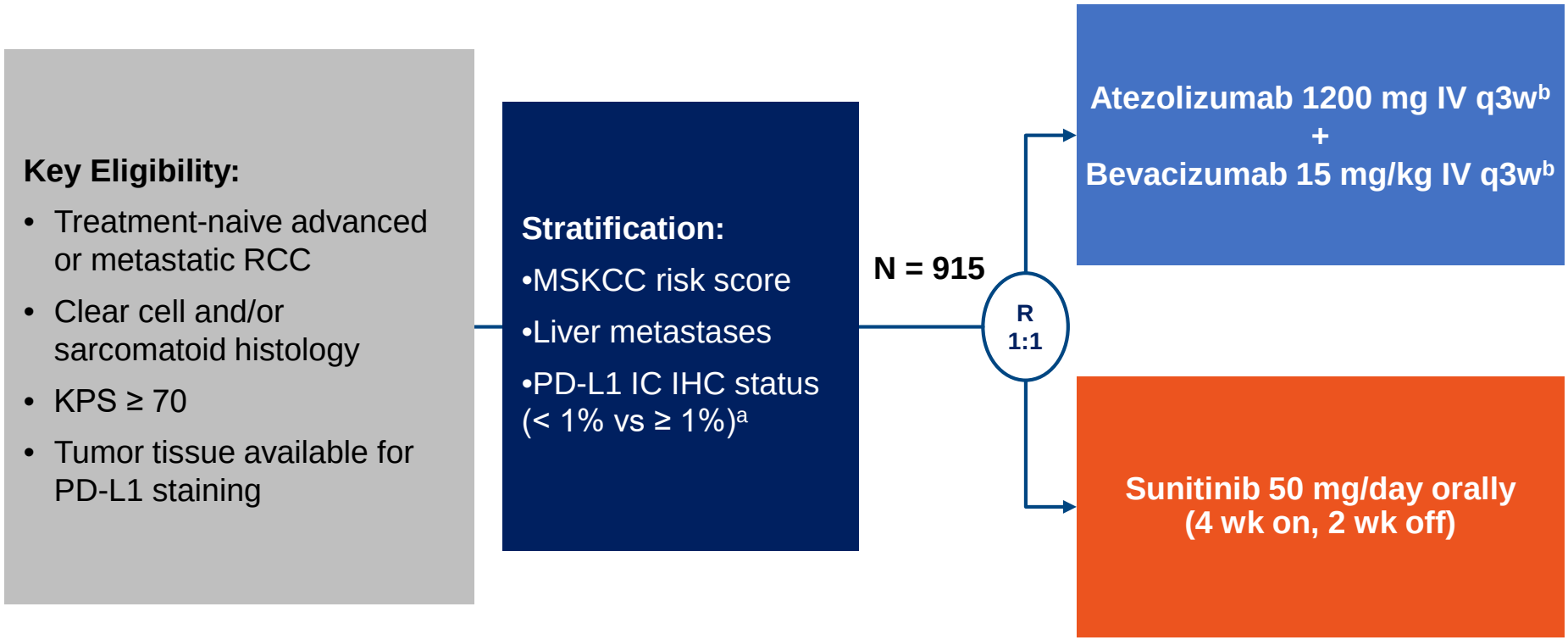
No. at Risk	Months					
NIVO + IPI	284	251	223	200	76	0
SUN	278	239	198	157	61	1

PD-L1 ≥1% (n = 214)



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

IMMotion 151 Study Design

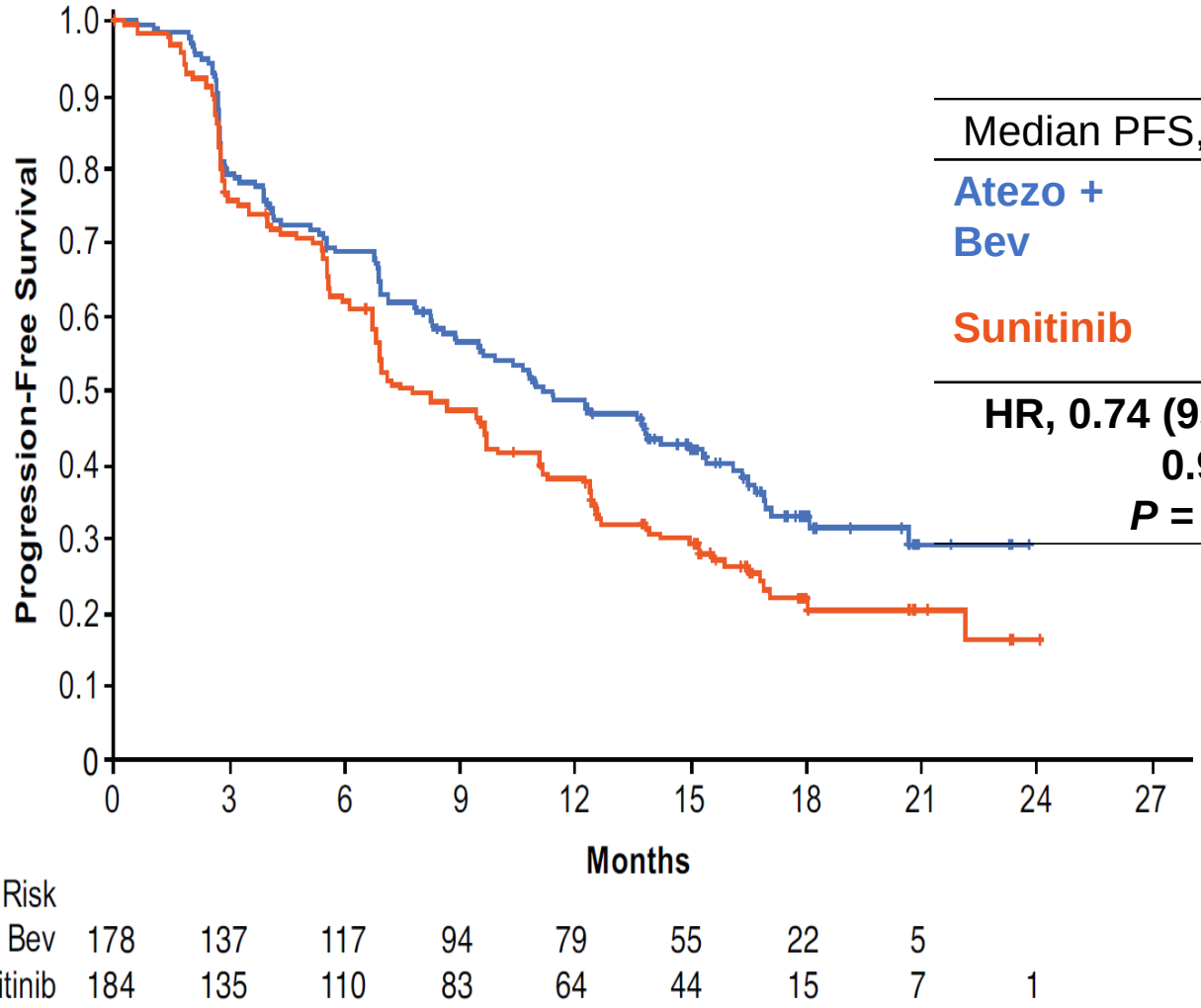


[a] ≥ 1% IC: 40% prevalence using SP142 IHC assay; [b] No dose reduction for atezolizumab or bevacizumab.

Statistical Design and Conduct

- IMmotion151 enrolled 915 randomized patients, 362 (40%) of whom had PD-L1 IC IHC status ≥ 1% (PD-L1+)
- Primary analysis of PFS in the PD-L1+ subgroup was triggered by 236 PFS events (65% event-to-patient ratio) at the data cutoff date of September 29, 2017
- First OS interim analysis was also conducted with the same cutoff date
- Stratified HR and log-rank test were used for primary analyses
- 5% alpha was split: 4% for PFS in PD-L1+ and 1% for OS in ITT populations
  - The *P* value boundary at the first OS interim analysis was alpha = 0.0009

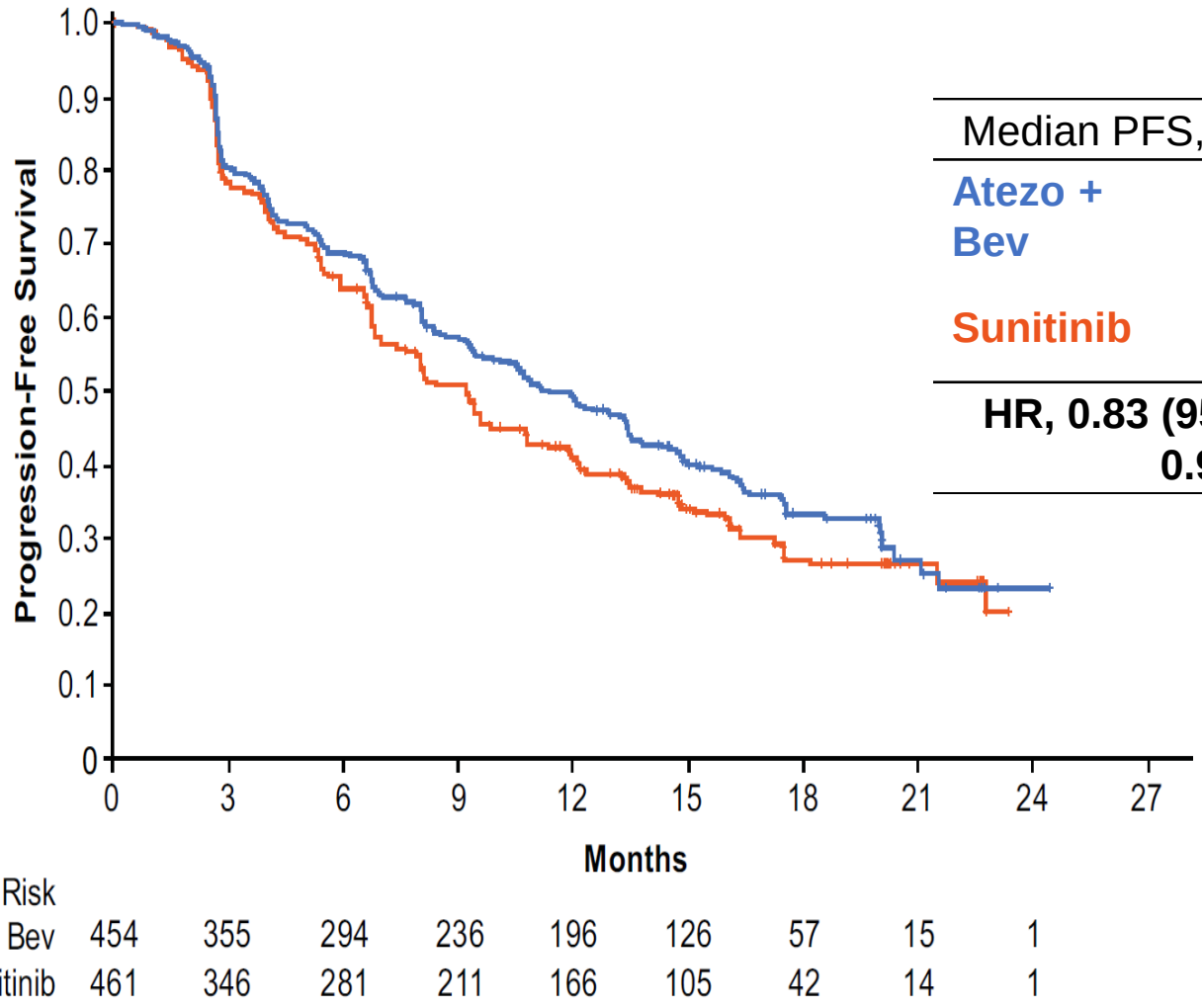
Progression-Free Survival in PD-L1+



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

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.

Progression-Free Survival in ITT



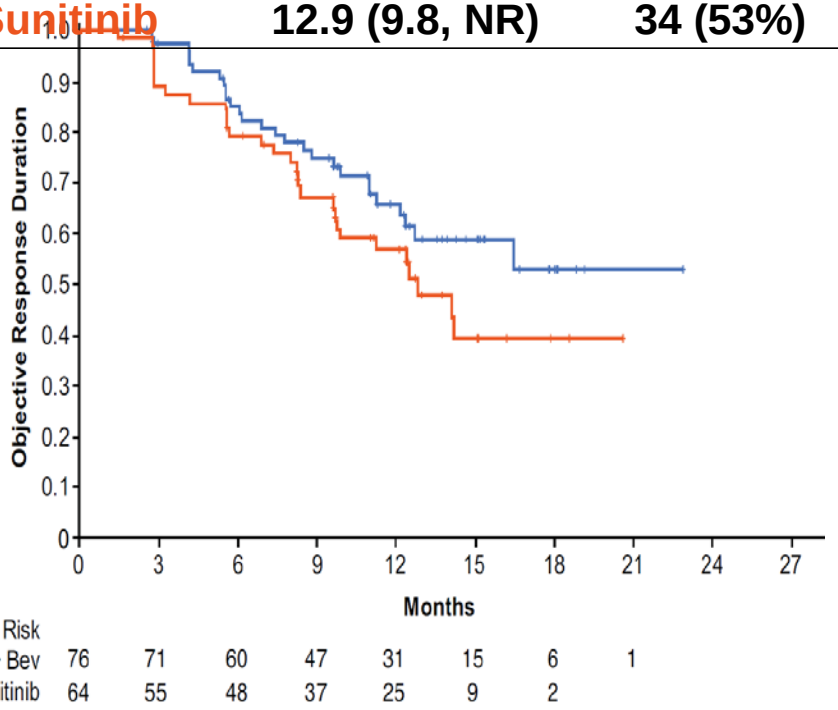
Median PFS, mo (95% CI)	
Atezo + Bev	**11.2 (9.6, 13.3)**
Sunitinib	**8.4 (7.5, 9.7)**
HR, 0.83 (95% CI: 0.70, 0.97)	

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

Objective Response Rate

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

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



N essed by investigators in patients with measurable disease at baseline.
Minimum follow-up, 12 mo. Median follow-up, 15 mo.

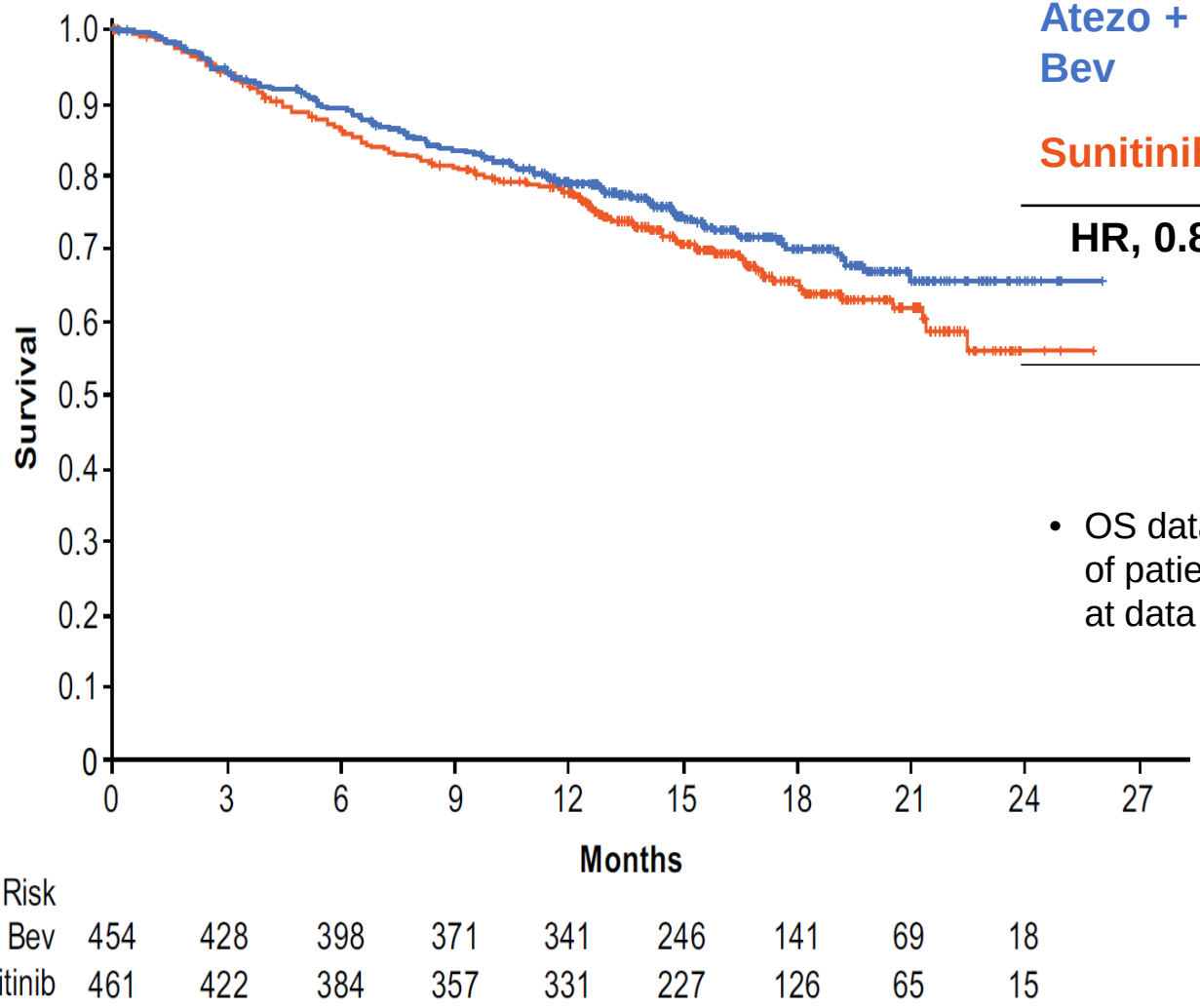
PFS and ORR by IRC

	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 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.

Overall Survival in ITT



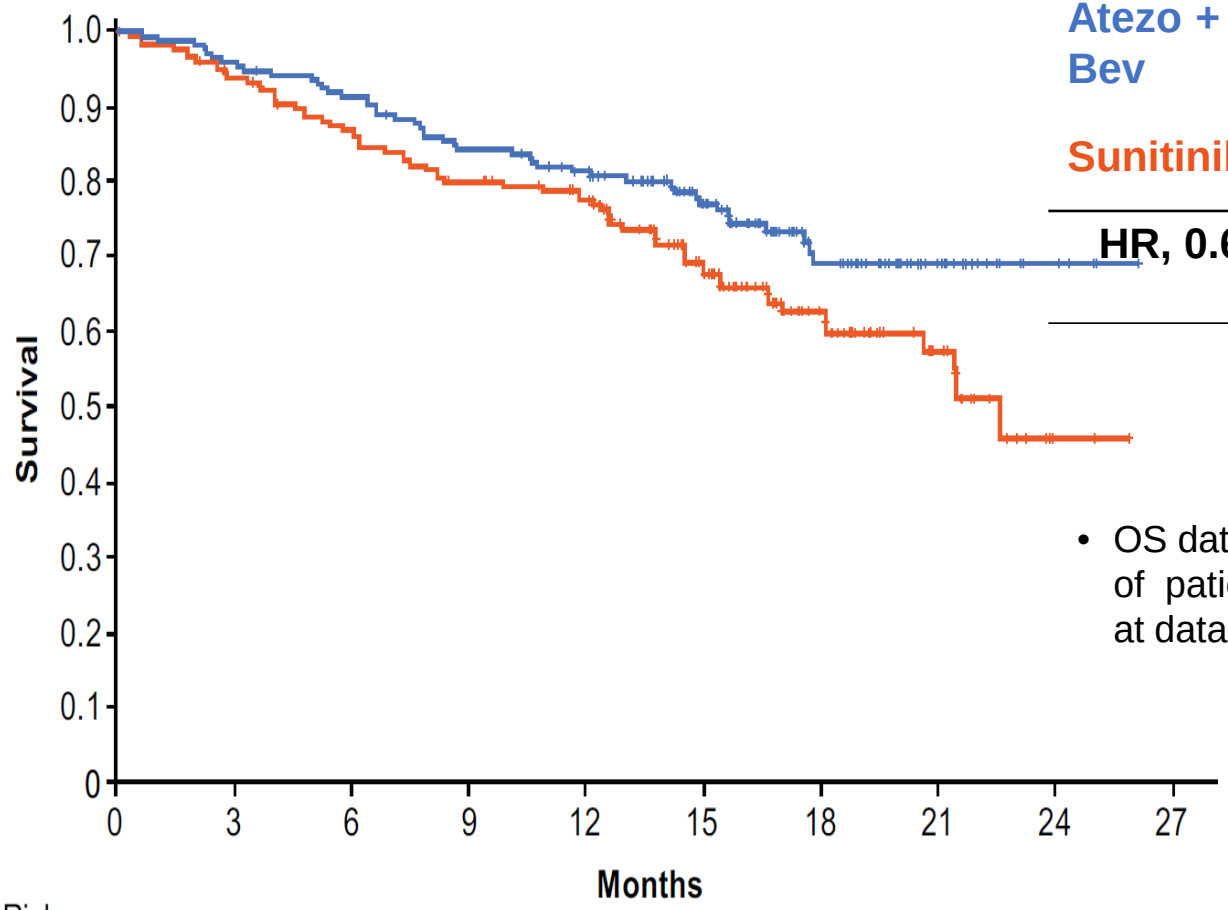
Median OS, mo (95% CI)	
Atezo + Bev	Not reached
Sunitinib	Not reached
HR, 0.81 (95% CI: 0.63, 1.03)	
***P* = 0.09**	

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

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.

Overall Survival in PD-L1+

Median OS, mo (95% CI)	
Atezo + Bev	Not reached
Sunitinib	23.3 (21.3, NR)
HR, 0.68 (95% CI: 0.46, 1.00)	



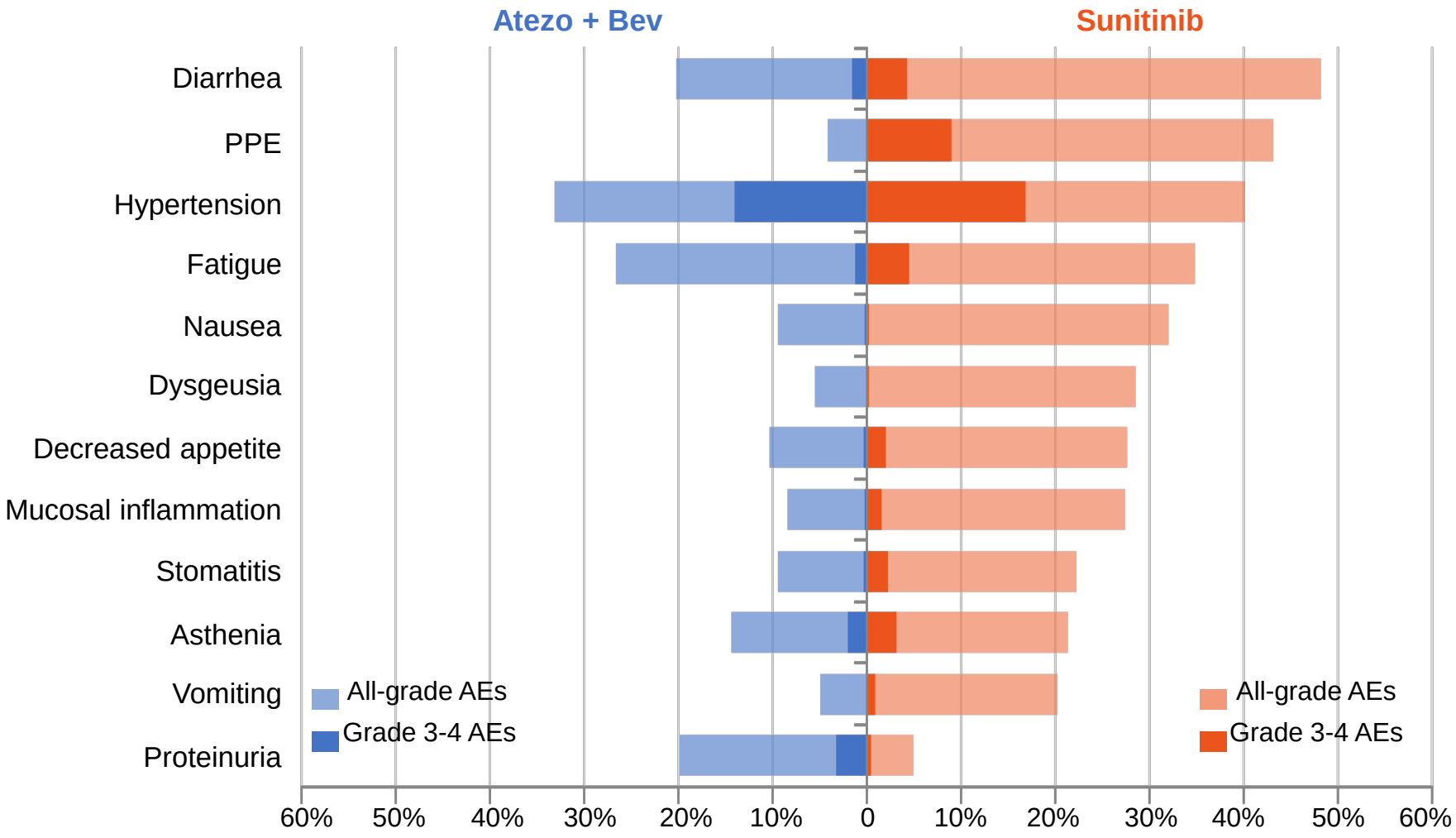
No. at Risk									
Atezo + Bev	178	169	160	147	139	109	55	26	6
Sunitinib	184	169	154	141	134	96	51	27	6

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

NR, not reached. Minimum follow-up, 12 mo. Median follow-up, 15 mo. Event/patient ratio: 25% for atezo + bev, 35% for sunitinib.

Treatment-related AEs

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

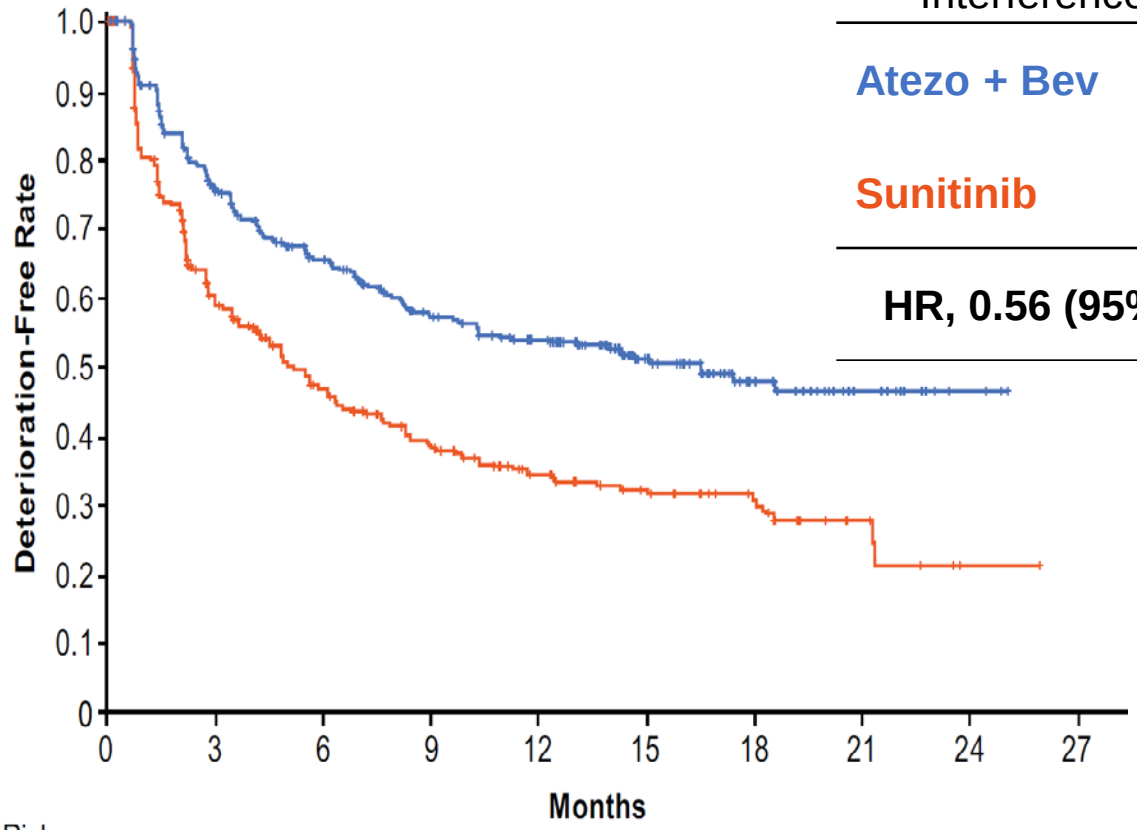


PPE, palmar-plantar erythrodysesthesia.

Time to Symptom Interference With Activities of Daily Living in ITT

Secondary Endpoint

Median Time to Symptom Interference, mo (95% CI)	
Atezo + Bev	**11.3 (8.3, 17.5)**
Sunitinib	**4.3 (3.1, 5.6)**
HR, 0.56 (95% CI: 0.46, 0.68)	



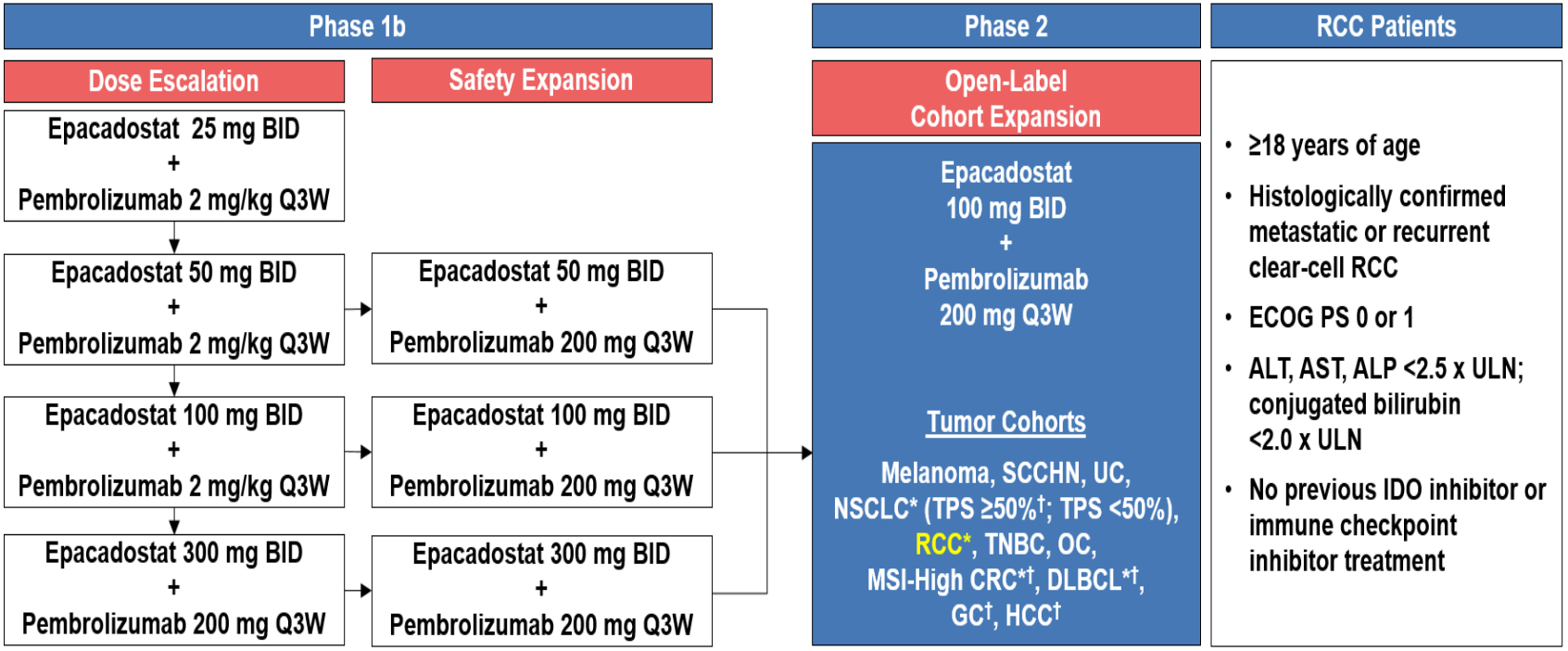
Per the MD Anderson Symptom Interference Scale, event defined as a ≥ 2-point score increase (on a 10-point scale) from baseline.

Summary of mRCC Treatment Strategy: April 2018

- Risk stratification by IMDC criteria (Favorable, Intermediate, Poor); Consider PDL1-testing
- Favorable risk
  - Angiogenesis inhibitor (TKI): Sunitinib, Pazopanib, or Cabozantinib
- Intermediate/Poor risk
  - Immunotherapy: Nivolumab/Ipilumumab
  - Angiogenesis inhibitor (TKI): Cabozantinib
- Poor risk
  - Consider Temsirolimus in selected patients not suitable for above options
- PDL-1 positive
  - Consider Atezolizumab + Bevacizumab

ECHO 201/Keynote 037
(Lara, et al. ASCO 2017)

- ECHO-202/KEYNOTE-037 (NCT02178722) is an ongoing phase 1/2 study evaluating the efficacy, safety, and tolerability of epacadostat plus pembrolizumab across multiple tumor types
- This analysis provided preliminary phase 1/2 efficacy, safety, and tolerability of epacadostat plus pembrolizumab in patients with advanced RCC (data cutoff, February 27, 2017)

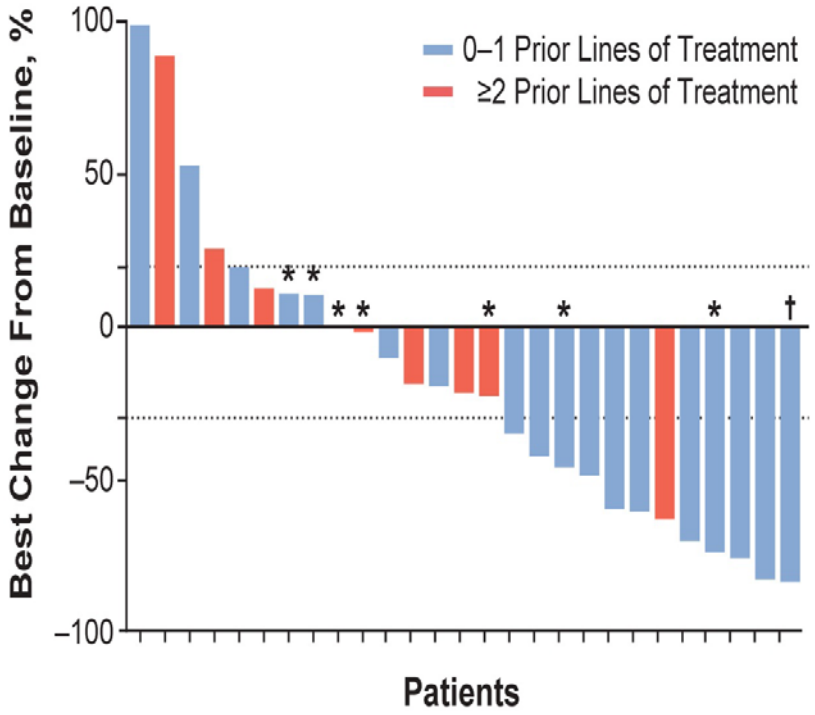


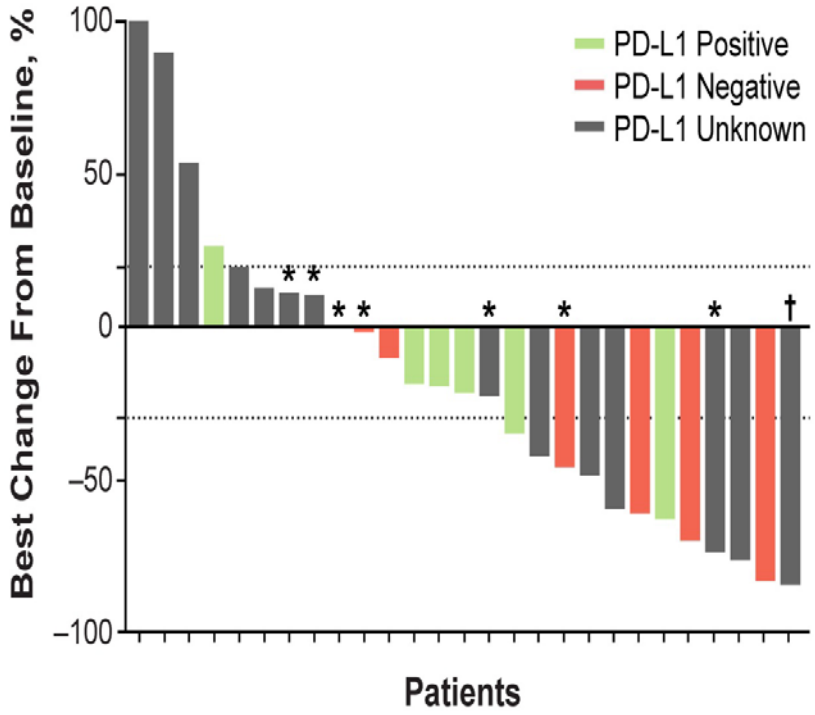
ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BID, twice daily; CRC, colorectal cancer; DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; GC, gastric cancer; HCC, hepatocellular carcinoma; IDO, indoleamine 2,3 dioxygenase; MSI, microsatellite instability; NSCLC, non-small cell lung cancer; OC, ovarian cancer; Q3W, every 3 weeks; RCC, renal cell carcinoma; SCCHN, squamous cell carcinoma of the head and neck; TNBC, triple-negative breast cancer; TPS, tumor proportion score; UC, urothelial carcinoma; ULN, upper limit of normal.
Note: GC and HCC cohorts were not yet open for patient enrollment at data cutoff (February 27, 2017).
* Ongoing patient enrollment at data cutoff (February 27, 2017). † Ongoing patient enrollment at time of ASCO presentation (June 4, 2017).

Best Percentage Change in Target Lesions

Epacadostat Plus Pembrolizumab
Phase 1/2 Advanced RCC

Efficacy-Evaluable Patients: ORR=10/30 (33%); DCR=15/30 (50%) by RECIST v1.1
0–1 Prior Lines of Treatment: ORR=9/19 (47%); DCR=11/19 (58%) by RECIST v1.1



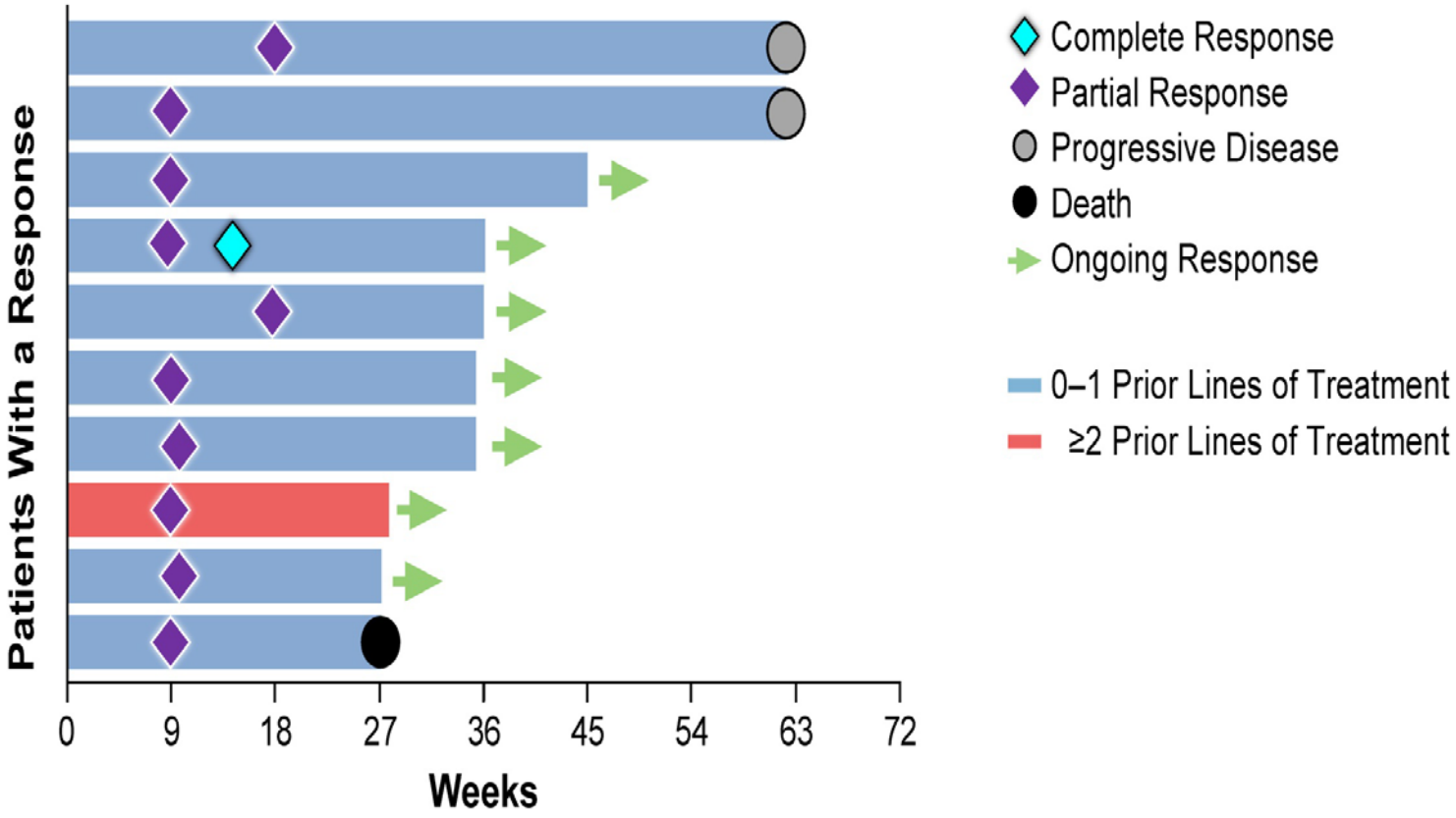


AE, adverse event; CR, complete response; DCR, disease control rate; ORR, objective response rate; PD, progressive disease; PD-L1, programmed death ligand 1; RCC, renal cell carcinoma; RECIST, Response Evaluation Criteria in Solid Tumors.
Horizontal dotted lines indicate the thresholds for progressive disease and response according to RECIST v1.1 criteria.
Of 30 efficacy-evaluable patients, data are shown for the 27 patients with postbaseline scans that included assessment of target lesions. Three patients are not shown in this figure: 1 patient discontinued treatment for clinical progression (target lesions not assessed); 1 patient discontinued treatment for an AE (autoimmune hepatitis) prior to the first postbaseline scan; and 1 patient died prior to the first postbaseline scan.
* Objective response is PD per new lesions. † Objective response is CR (sum of reduction from baseline in both lymph node target lesions met RECIST v1.1 definition of CR).

Time to and Duration of Response (RECIST v1.1)

Epacadostat Plus Pembrolizumab
Phase 1/2 Advanced RCC

7/10 responses were ongoing
Median (range) duration of response, 26.8+ (18.1+ to 53.1) weeks



RCC, renal cell carcinoma; RECIST, Response Evaluation Criteria in Solid Tumors.
Data cutoff: February 27, 2017.

Safety Results

Epacadostat Plus Pembrolizumab
Phase 1/2 Advanced RCC

Treatment-Related AEs ≥10% (N=46)

AE, n (%)	All Grade	Grade 3/4*
Total	**37 (80)**	**8 (17)**
Fatigue	17 (37)	0
Rash†	14 (30)	1 (2)
Diarrhea	6 (13)	0
Decreased appetite	5 (11)	0
Nausea	5 (11)	1 (2)
Pruritus	5 (11)	0
Pyrexia	5 (11)	0

AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities.
* Other grade 3/4 treatment-related AEs not included in the table: lipase increased (n=3); amylase increased, aseptic meningitis, autoimmune hepatitis, headache, hyperglycemia, musculoskeletal pain, and vomiting (n=1 each).
† Rash includes the following MedDRA preferred terms: rash, rash erythematous, rash generalized, rash maculopapular, and rash pruritic.

AEs of Special Interest* (N=46)

AE, n (%)	All Grade	Grade 3/4
Total	**6 (13)**	**2 (4)**
Hypothyroidism	4 (9)	0
Hepatitis†	1 (2)	1 (2)
Severe skin reaction‡	1 (2)	1 (2)

AE, adverse event; RCC, renal cell carcinoma.
* AEs of special interest include AEs with an immune-related cause, regardless of attribution to study treatment by the investigator.
† Includes autoimmune hepatitis.
‡ The severe skin reaction the patient with RCC in this study was grade ≥3 rash maculopapular.

- Treatment-related AEs led to dose interruptions in 8 patients (17%), and dose reductions in 4 patients (9%)
- Treatment-related AEs led to treatment discontinuation in 2 patients (4%); all AEs resolved with standard supportive care
- There were no treatment-related deaths

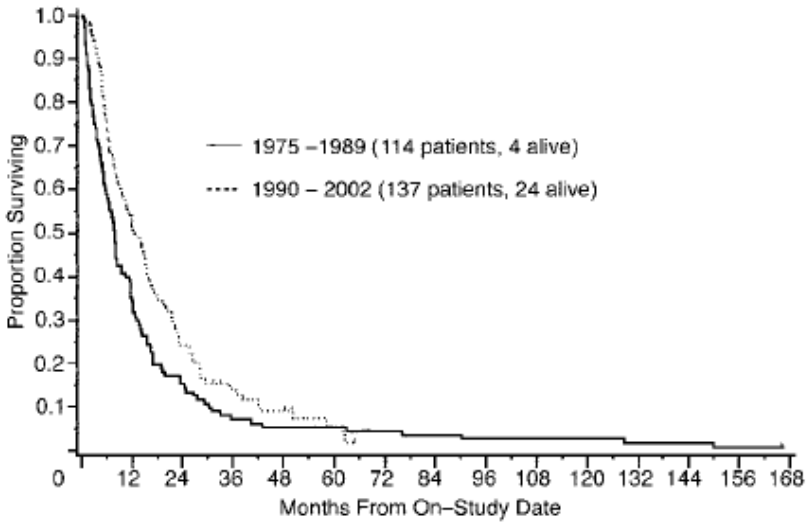
Phase III Trials of Checkpoint Inhibitor-Based Combinations in RCC

Control Arm	Experimental Arm(s)
Sunitinib	Nivolumab/Ipilimumab*
Sunitinib	Bevacizumab + Atezolizumab*
Sunitinib	Axitinib + Pembrolizumab
Sunitinib	Lenvatinib + Everolimus Lenvatinib/Pembrolizumab
Sunitinib	Axitinib + Avelumab
Sunitinib	Cabozantinib/Nivolumab Cabozantinib/Ipi/Nivo
Sunitinib or Pazopanib	Pembrolizumab + Epacadostat

**Completed and reported*

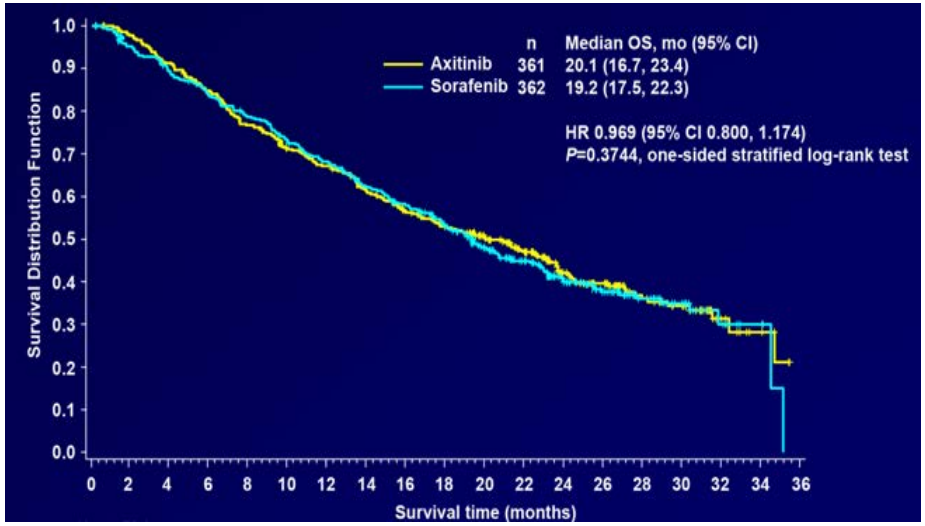
Why second-line treatment in mRCC?

"Pre-targeted therapy era"



Median OS: <u>10.2 months</u>
(using several investigational agents)
N=251 pts

"Post-targeted therapy era"



Median OS: <u>20.1 months</u>
(axitinib after SU or IFN-α)
N=361 pts

Motzer et al. JCO 2004; Motzer et al. 2012 ESMO Congress

The NEW ENGLAND JOURNAL of MEDICINE

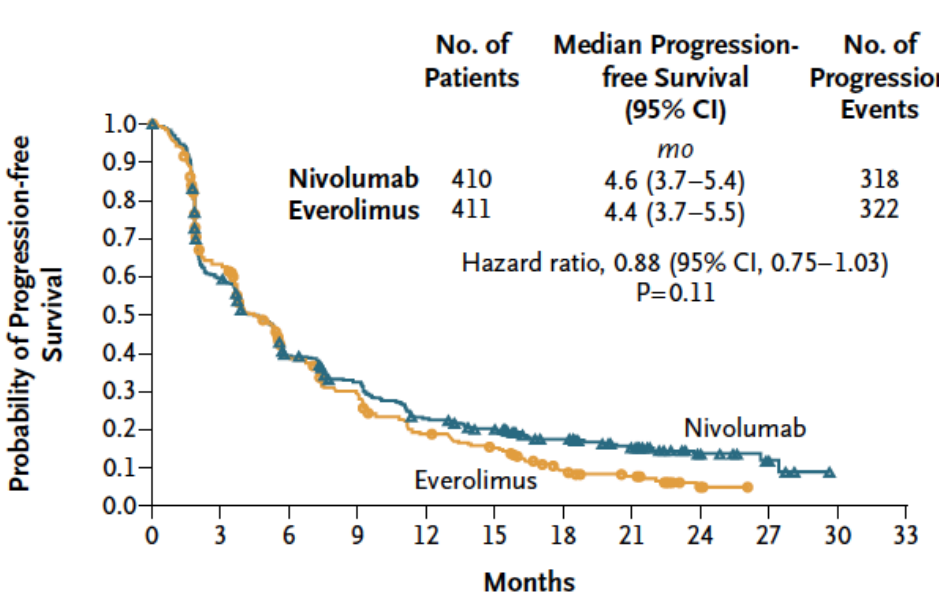
ORIGINAL ARTICLE

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*

Response Rate:

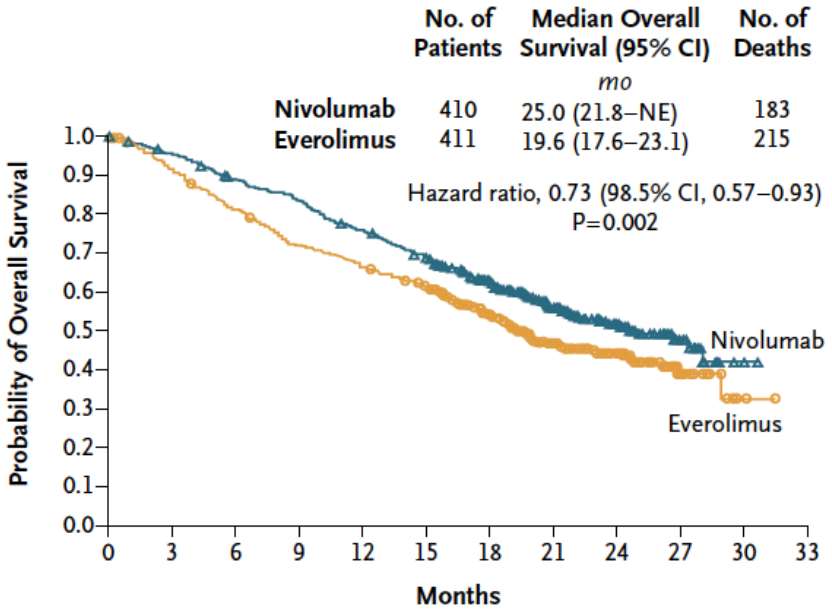
- Nivolumab: 25%
- Everolimus: 5%
- Odds ratio 5.98; P<0.001



No. at Risk

Nivolumab	410	230	145	116	81	66	48	29	11	4	0	0
Everolimus	411	227	129	97	61	47	25	16	3	0	0	0

PFS

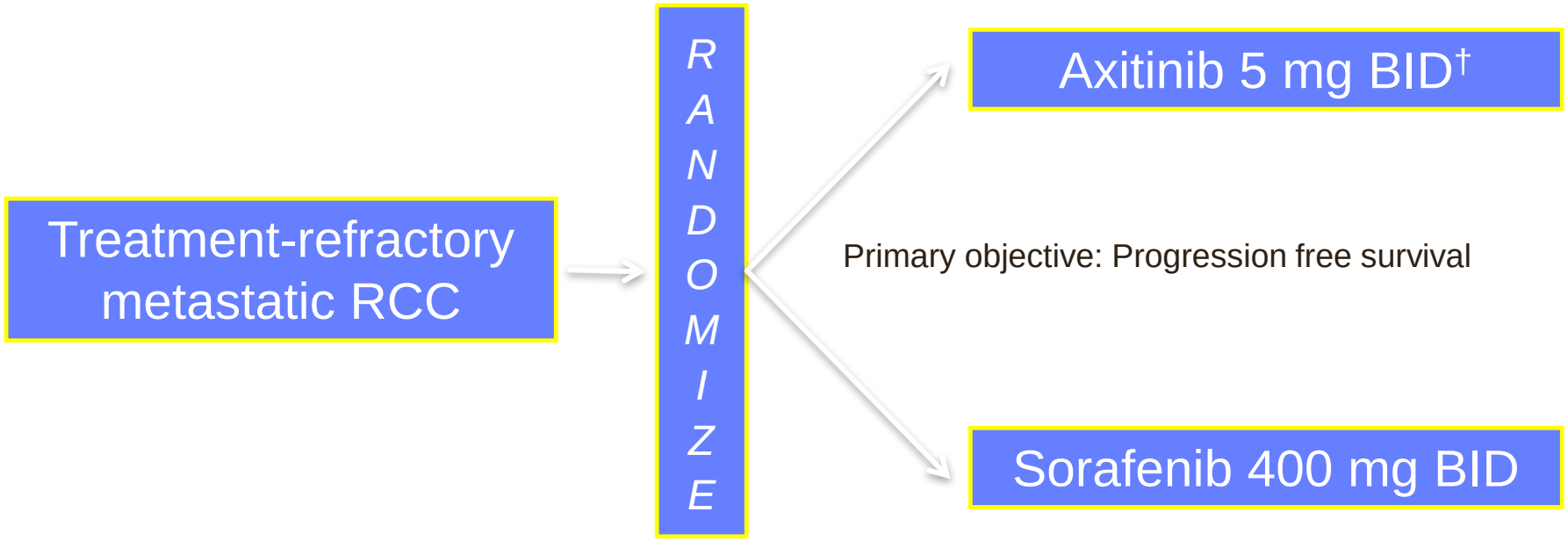


No. at Risk

Nivolumab	410	389	359	337	305	275	213	139	73	29	3	0
Everolimus	411	366	324	287	265	241	187	115	61	20	2	0

OS

AXIS: Study Design



Primary objective: Progression free survival

Eligibility criteria:

- mRCC, clear-cell histology
- Measurable disease
- RECIST defined PD after 1 prior sunitinib-, bev + IFN-α-, temsirolimus-, or cytokine-based regimen
- ECOG 0 or 1
- Adequate lab studies

Randomization stratified by ECOG PS and type of prior treatment

†Starting dose 5 mg BID with option for dose titration to 10 mg BID

Rini B, *et al.* Lancet 2011

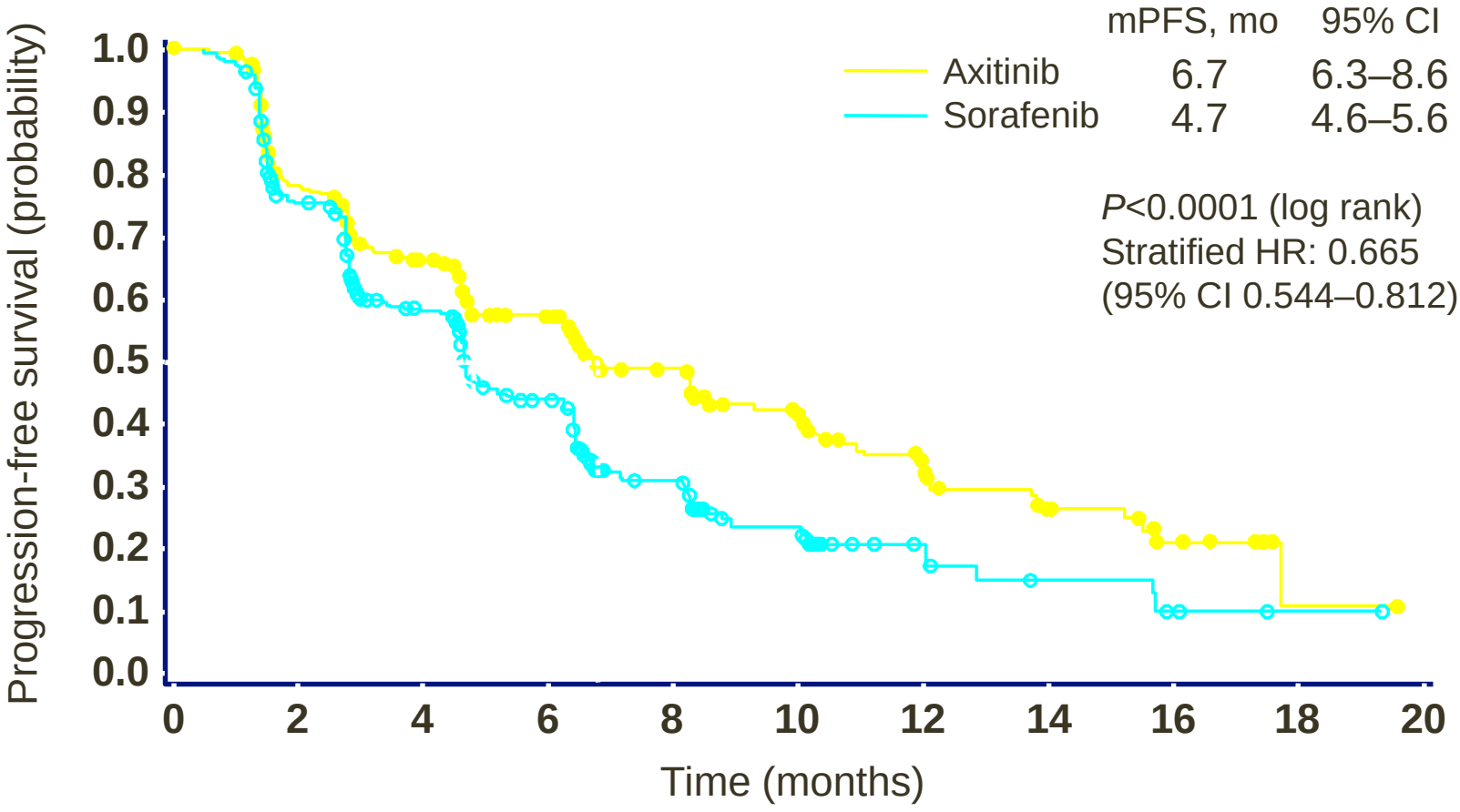
Best Response by RECIST (IRC Assessment)

Best Response (%)	Axitinib	Sorafenib
Partial response*	19.4	9.4
Stable disease	49.9	54.4
Progressive disease	21.6	21.0
Indeterminate	6.1	11.6
Risk ratio (95% CI)	2.1 (1.4–3.0)	

*Axitinib *vs*. sorafenib: P=0.0001

Rini B, *et al.* Lancet 2011

Progression-free Survival (IRC Assessment)

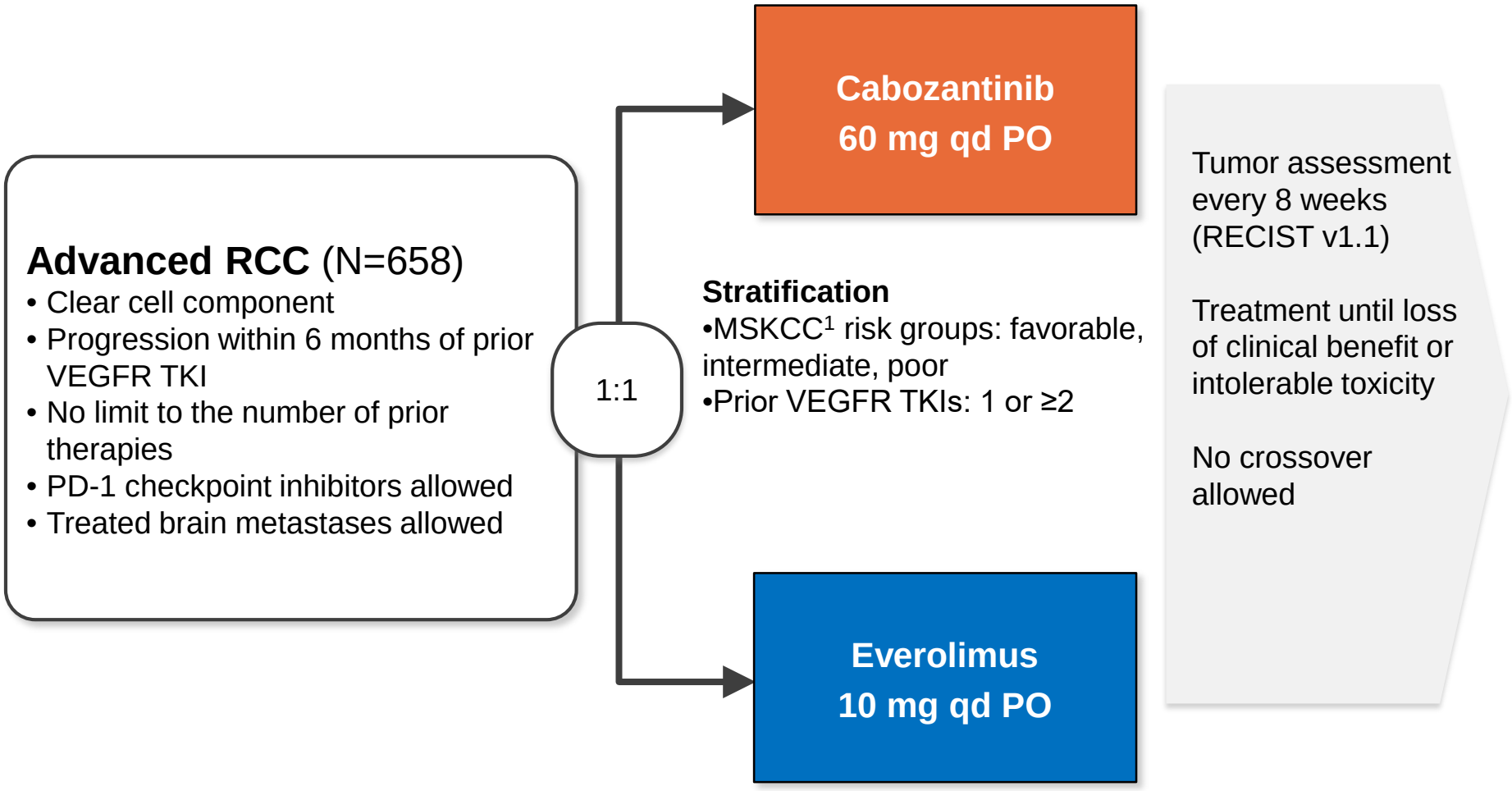


Subjects at risk, n

Axitinib	361	256	202	145	96	64	38	20	10	1	0
Sorafenib	362	224	157	100	51	28	12	6	3	1	0

IRC=Independent Review Committee

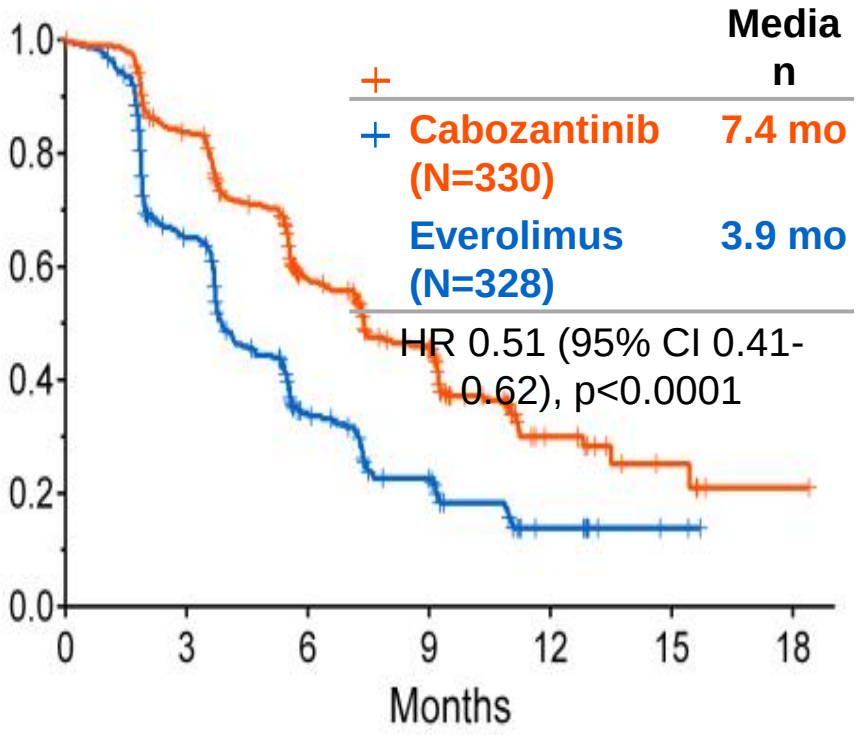
Cabozantinib in mRCC: METEOR Study Design



[1] Motzer R et al, J Clin Oncol, 2004

PFS and Response in All 658 Patients

Progression-Free Survival per IRC[1]



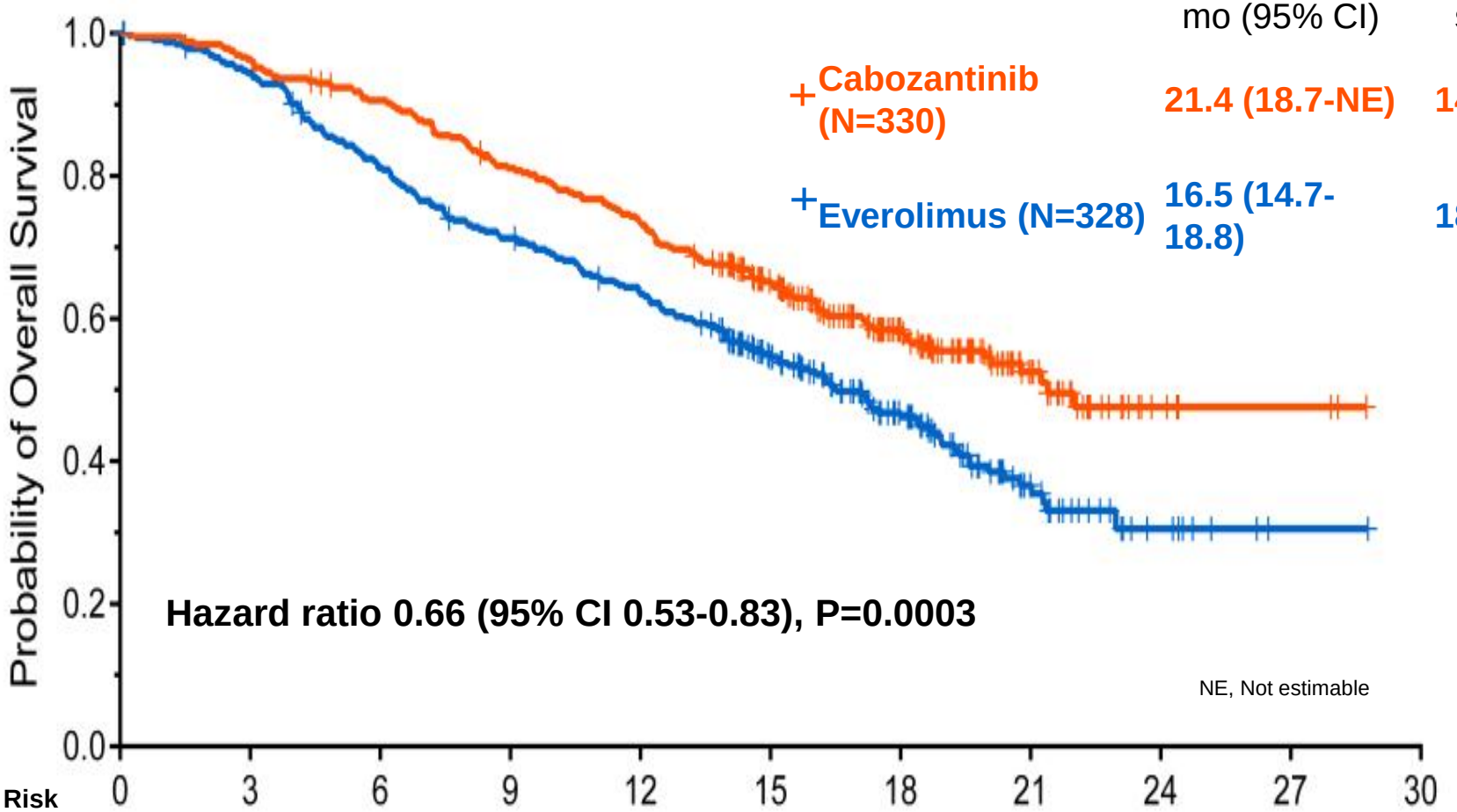
Objective Response Rate[1,2]

	Cabozantinib (N=330), %	Everolimus (N=328), %
ORR per IRC (95% CI)	17 (13, 22)	3 (2, 6)
Stable disease	65	62
Progressive disease	12	27
Unable to determine	5	8
ORR per Investigator (95% CI)	24 (19, 29)	4 (2, 7)
Stable disease	63	63
Progressive disease	9	27
Unable to determine	4	7

Cut-off for PFS and ORR: May 22, 2015

[1] Escudier B et al, J Clin Oncol, 2016; 34(suppl 2S): Abstr 499, [2] Confirmed responses per RECIST version 1.1. All responses were partial responses.

Overall Survival



	Median OS mo (95% CI)	No. of Deaths
+ Cabozantinib (N=330)	21.4 (18.7-NE)	140
+ Everolimus (N=328)	16.5 (14.7-18.8)	180

Hazard ratio 0.66 (95% CI 0.53-0.83), P=0.0003

NE, Not estimable

No. at Risk											
Cabozantinib	330	318	296	264	239	178	105	41	6	3	0
Everolimus	328	307	262	229	202	141	82	32	8	1	0

Cut-off: Dec 31, 2015

Safety/Toxicity

Table 2. Adverse Events.*

Event	Cabozantinib (N=331)		Everolimus (N=322)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients with an event (percent)			
Any adverse event	331 (100)	226 (68)	321 (>99)	187 (58)
Diarrhea	245 (74)	38 (11)	88 (27)	7 (2)
Fatigue	186 (56)	30 (9)	148 (46)	22 (7)
Nausea	165 (50)	13 (4)	90 (28)	1 (<1)
Decreased appetite	152 (46)	8 (2)	108 (34)	3 (<1)
Palmar–plantar erythrodysesthesia syndrome	139 (42)	28 (8)	19 (6)	3 (<1)
Hypertension	122 (37)	49 (15)	23 (7)	10 (3)
Vomiting	106 (32)	7 (2)	45 (14)	3 (<1)
Weight decreased	102 (31)	6 (2)	40 (12)	0
Constipation	83 (25)	1 (<1)	60 (19)	1 (<1)
Dysgeusia	78 (24)	0	30 (9)	0

Choueiri, NEJM 2015

Lenvatinib, everolimus, and the combination in patients with metastatic renal cell carcinoma: a randomised, phase 2, open-label, multicentre trial

Robert J Motzer, Thomas E Hutson, Hilary Glen, M Dror Michaelson, Ana Molina, Timothy Eisen, Jacek Jassem, Jakub Zolnierek, Jose Pablo Maroto, Begoña Mellado, Bohuslav Melichar, Jiri Tomasek, Alton Kremer, Han-Joo Kim, Karen Wood, Corina Dutcus, James Larkin

Lenvatinib: an oral multitargeted TKI against VEGFR1, VEGFR2, VEGFR3, and FGF receptors (FGFR1, FGFR2, FGFR3, and FGFR4), PDGFRα, RET, and KIT.

- Metastatic RCC
- Progression < 9 months after 1 prior VEGF targeted therapy

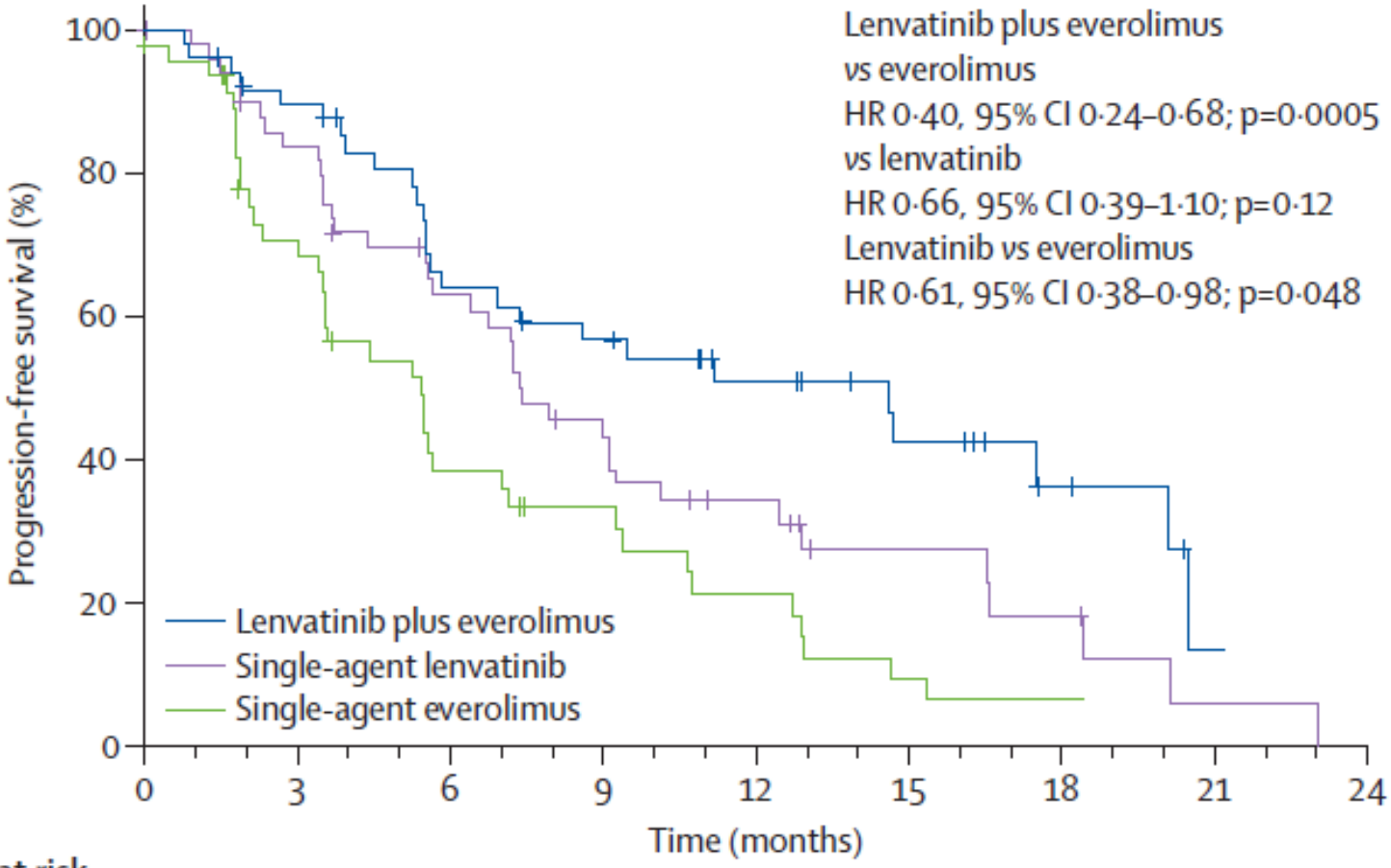
Lenvantinib 18 mg QD + Everolimus 5 mg QD (n=51)

Lenvantinib 24 mg QD (n=52)

Everolimus 10 mg QD (n=50)

Primary endpoint: PFS with Len +/- Eve vs. Eve alone

Phase II trial of Lenvantinib vs Everolimus vs Both



Number at risk									
Lenvatinib plus everolimus	51	41	27	23	16	10	5	1	0
Single-agent lenvatinib	52	41	29	20	11	6	4	1	0
Single-agent everolimus	50	29	15	11	7	3	1	0	0

Efficacy

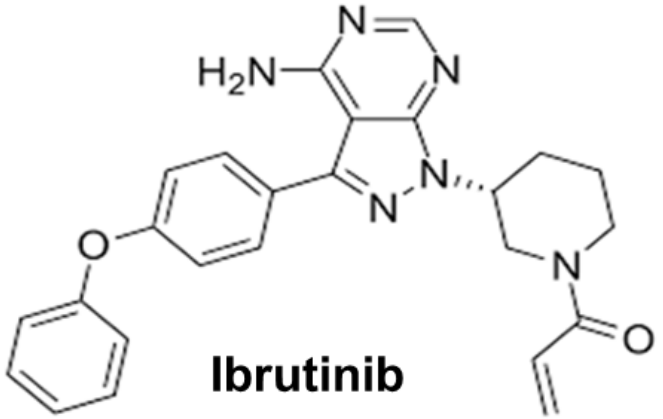
	Lenvatinib plus everolimus (n=51)	Single-agent lenvatinib (n=52)	Single-agent everolimus (n=50)
Progression-free survival			
Events	26 (51%)	38 (73%)	37 (74%)
Median (95% CI) progression-free survival (months)	14·6 (5·9–20·1)	7·4 (5·6–10·2)	5·5 (3·5–7·1)
Progression-free survival (95% CI)			
At 6 months	64% (48–76)	63% (48–75)	39% (24–53)
At 12 months	51% (35–65)	34% (21–48)	21% (10–36)
Objective response			
Events	22 (43%)	14 (27%)	3 (6%)
95% CI	29–58	16–41	1–17
Best overall response			
Complete response	1 (2%)	0	0
Partial response	21 (41%)	14 (27%)	3 (6%)
Stable disease	21 (41%)	27 (52%)	31 (62%)
Progressive disease	2 (4%)	3 (6%)	12 (24%)
Not assessed	6 (12%)	8 (15%)	4 (8%)
Overall survival (at June 13, 2014)			
Events	19 (37%)	26 (50%)	26 (52%)
Median (95% CI) overall survival (months)	25·5 (20·8–25·5)	18·4 (13·3–NE)	17·5 (11·8–NE)
Overall survival (95% CI)			
At 12 months	74% (60–84)	71% (57–82)	62% (47–74)
At 18 months	67% (51–78)	54% (39–67)	47% (31–62)

Safety/Toxicity

	Lenvatinib plus everolimus (n=51)			Lenvatinib (n=52)			Everolimus (n=50)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Any TEAE	14 (28%)	29 (57%)	7 (14%)	8 (15%)	38 (73%)	3 (6%)	23 (46%)	21 (42%)	4 (8%)
Diarrhoea	33 (65%)	10 (20%)	0	31 (60%)	6 (12%)	0	16 (32%)	1 (2%)	0
Decreased appetite	23 (45%)	3 (6%)	0	28 (54%)	2 (4%)	0	9 (18%)	0	0
Fatigue or asthenia	23 (45%)	7 (14%)	0	22 (42%)	4 (8%)	0	18 (36%)	0	1 (2%)
Vomiting	19 (37%)	3 (8%)	0	18 (35%)	2 (4%)	0	5 (10%)	0	0
Nausea	18 (35%)	3 (6%)	0	28 (54%)	4 (8%)	0	8 (16%)	0	0
Cough	19 (37%)	0	0	8 (15%)	1 (2%)	0	15 (30%)	0	0
Hypercholesterolaemia	16 (31%)	1 (2%)	0	5 (10%)	0	1 (2%)	8 (16%)	0	0
Decreased weight	15 (29%)	1 (2%)	0	22 (42%)	3 (6%)	0	4 (8%)	0	0
Stomatitis	15 (29%)	0	0	12 (23%)	1 (2%)	0	20 (40%)	1 (2%)	0
Hypertriglyceridaemia	14 (27%)	4 (8%)	0	5 (10%)	2 (4%)	0	8 (16%)	4 (8%)	0

Pilot trial of ibrutinib plus nivolumab in patients with metastatic renal cell cancer (mRCC): results from a dose-finding cohort

- Myeloid derived suppressor cells (MDSC) express BTK
- Ibrutinib inhibits MDSCs and can potentiate checkpoint inhibitor immunotherapy
- A pilot trial of ibrutinib+nivolumab was initiated
- 12 mRCC patients were enrolled in the dose finding phase



Ibrutinib

- Ibrutinib at a dose of 420 mg orally once daily in combination with nivolumab 240 mg IV q 2 weeks appears feasible and tolerable in mRCC patients.
- No unique immune-related AEs seen
- Anti-tumor activity was confirmed in 2 patients previously exposed to PD1-targeted therapy.
  - 1 PR + 1 CR

Lara, et al. ASCO GU 2018

Conclusions

- New agents (e.g., immune checkpoint inhibitors) have changed the disease course of mRCC
  - Nivolumab/Ipilumumab: a new standard frontline therapy (intermediate/poor risk)
  - Atezolizumab/bevacizumab: an option for PDL1+ mRCC
- Presently, empiric sequencing is considered standard of care in advanced RCC
  - Biomarker enrichment is not yet in place
- Many options for 2nd line (and beyond) therapy
  - VEGFR-targeted (TKI) and checkpoint inhibitor therapy are reasonable options