TRATAMENTO ATUAL DO CÂNCER RENAL METASTÁTICO

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Declaração sobre Potenciais Conflitos de Interesse

De acordo com a Resolução 1931/2009 do Conselho Federal de Medicina e com a RDC 96 / 2008 da ANVISA, declaro que:

- *Apresentações*: como palestrante convidado, participo dos eventos de: Janssen, Pfizer, Bayer, Novartis, Astra Zeneca, Astellas, Pierre-Fabre, Merck-Serono, Sanofi, Roche.
- *Consultoria*: como membro de *advisory boards*, participo de reuniões com: Astellas, Janssen, Roche, Bayer, Lilly, Astra Zeneca, Novartis, MSD, BMS.

Não possuo ações de quaisquer destas companhias farmacêuticas.

Os meus pré-requisitos para participar destas atividades são a autonomia do pensamento científico, a independência de opiniões e a liberdade de expressão, aspectos que esta empresa respeita.

Câncer Renal: Epidemiologia

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- 3 a 4% das neoplasias
- 80 a 85% das neoplasias renais são carcinoma de células claras
- 4170 casos novos no Brasil em 2008
- Incidência dos tumores renais vem aumentando
- Idade média de diagnóstico – 65 anos.
- No Brasil 45% dos pacientes apresentam-se com
- doença localizada, 25% com doença localmente
- avançada e 30% com doença metastática
- Até 40% desenvolve metástase após nefrectomia

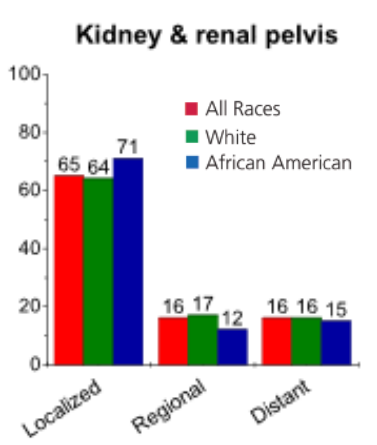

TABLE 1. Estimated New Cancer Cases and Deaths by Sex, United States, 2017*

	ESTIMATED NEW CASES			ESTIMATED DEATHS		
	BOTH SEXES	MALE	FEMALE	BOTH SEXES	MALE	FEMALE
Urinary system	**146,650**	**103,480**	**43,170**	**32,190**	**22,260**	**9,930**
Urinary bladder	79,030	60,490	18,540	16,870	12,240	4,630
Kidney & renal pelvis	63,990	40,610	23,380	14,400	9,470	4,930
Ureter & other urinary organs	3,630	2,380	1,250	920	550	370

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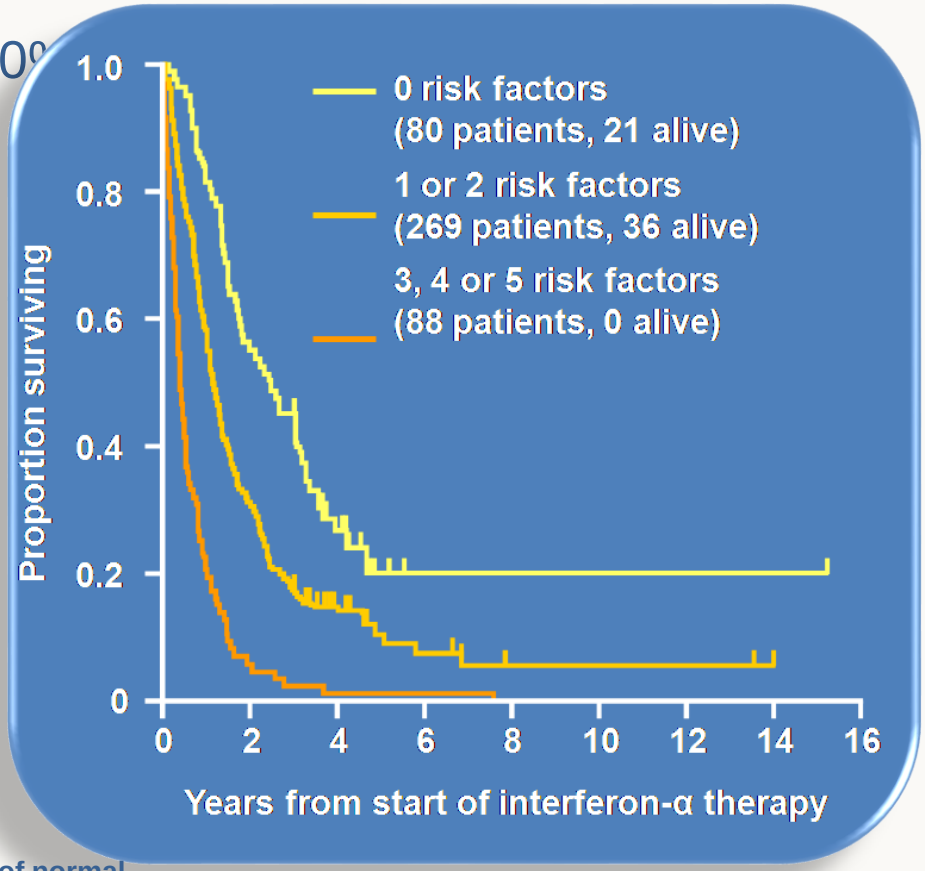
What Clinical Prognostic Factors Influence Patient Outcome?

- ✓ **MSKCC Prognostic Factors**
- ✓ Karnofsky performance status (<80%
- ✓ LDH >1.5 × ULN
- ✓ Low hemoglobin (<LLN)
- ✓ High calcium (>10 mg/dL)
- ✓ Time from diagnosis to treatment (<1 year)

Prognostic Groups	
Favorable risk:	0 risk factors
Intermediate risk:	1–2 risk factors
Poor risk:	≥3 risk factors



LDH, lactate dehydrogenase; ULN, upper limit of normal; LLN, lower limit of normal.

Motzer RJ, et al. *J Clin Oncol*. 2002;20:289–296.

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IL-2

Table 2. Summary of Efficacy

Response	Response Rate No.	Response Rate %	Response Duration (months) Median	Response Duration (months) Range†
CR	12	5	NR	5+-62+
PR*	24	9	19	3-57+
PR + CR	36	14	20.3	3-62+

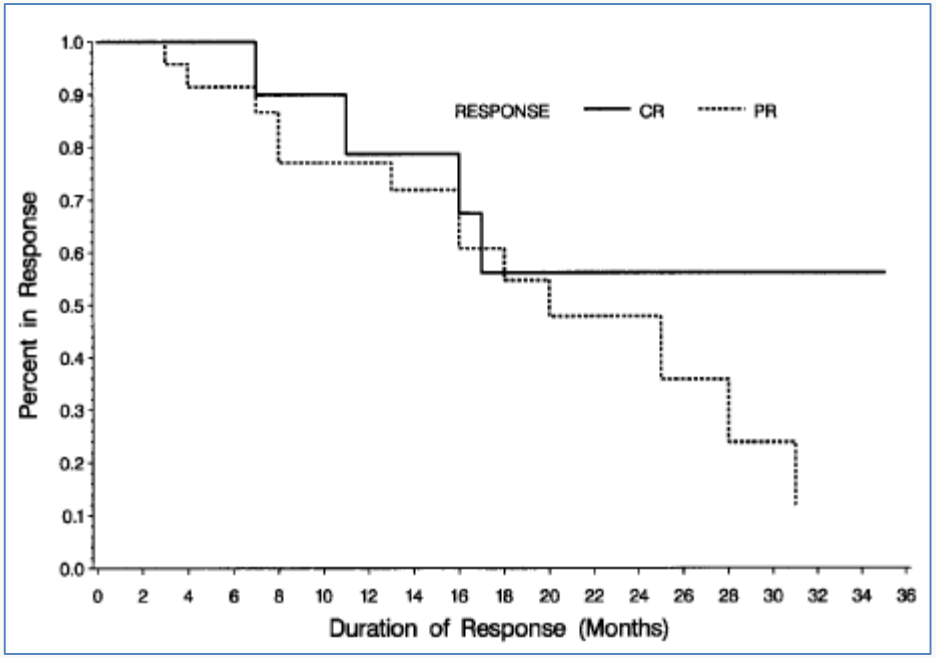

Table 7. Incidence of Most Common and Most Severe Adverse Events (N = 255)

Event by Body System	Grade (%) All	3	4
Cardiovascular			
Hypotension	96	59	15
Arrhythmias	14	2	0
Supraventricular	5	2	1
Ventricular	1	0	0
Myocardial ischemia	2	1	<1
Myocardial infarction	2	0	2
Cardiac arrest	2	<1	2
Myocarditis	1	1	0
Gastrointestinal			
Nausea and vomiting	89	24	1
Diarrhea	81	20	2
Stomatitis	32	4	0
Gastrointestinal bleeding	15	3	1
Intestinal perforation	1	0	<1
Neurologic			
Mental status changes	82	23	5
Coma	2	0	2
Seizure (grand mal)	2	1	1
Pulmonary			
Dyspnea	57	16	1
Adult respiratory distress syndrome	1	<1	<1
Respiratory failure	3	<1	2
Hepatic			
Elevated bilirubin level	85	13	8
Elevated transaminase level	72	7	3
Elevated alkaline phosphatase level	77	8	<1
Renal			
Acidosis	19	4	2
Elevated BUN level	85	12	2
Oliguria/anuria	81	40	6
Serum creatinine elevation	81	11	3
General			
Fever and/or chills	97	19	5
Asthenia	39	4	0
Edema	55	2	0
Sepsis	8	4	2
Hematologic			
Thrombocytopenia	83	16	5
Anemia	99	15	3
Other			
Pruritus	53	4	0
Rash	25	1	0
Arthralgia	7	1	0
Myalgia	7	1	0

Fyfe G, et al. J Clin Oncol. 1995 Mar;13(3):688-96.

Phase III Trial of Sunitinib vs IFN-α as First-line Treatment in Pts With mRCC: PFS

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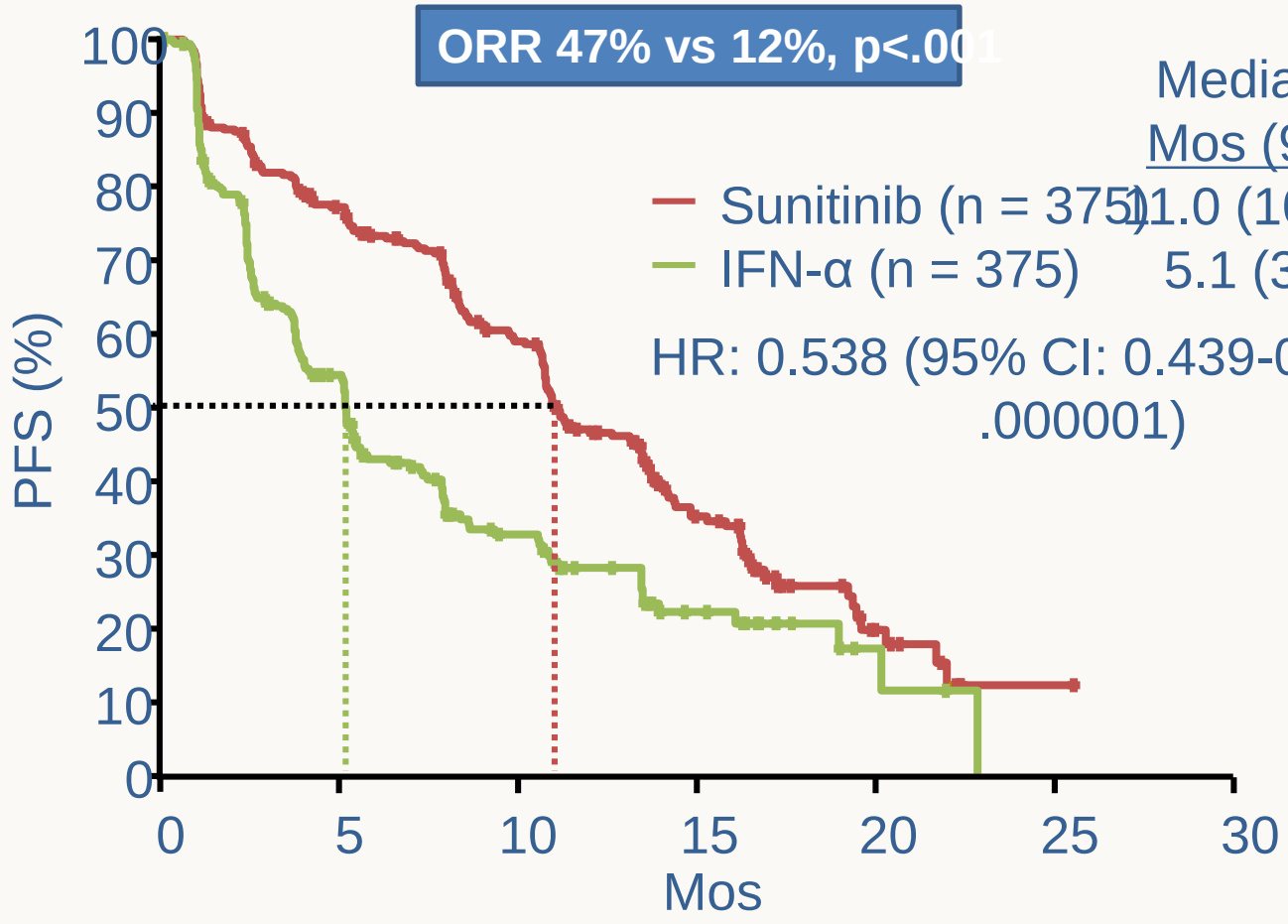
- A randomized phase III trial in previously untreated metastatic RCC with clear cell component



J Clin Oncol. 2009;27:3584–3590

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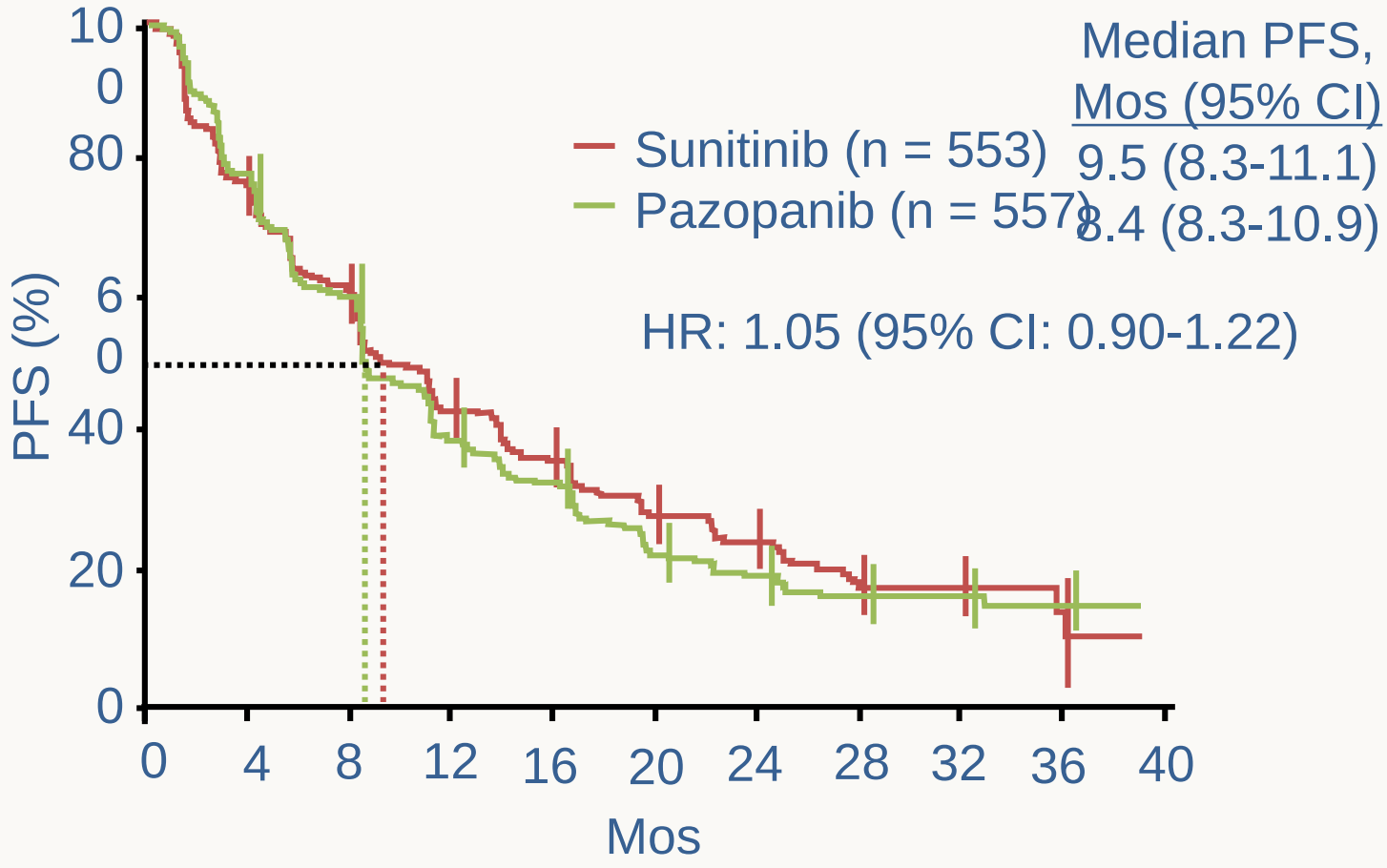
Phase III COMPARZ Trial: No Difference in PFS With First-line Sunitinib vs Pazopanib in mRCC

A randomized phase III trial in patients with previously untreated clear-cell, metastatic RCC



Motzer RJ, et al. N Engl J Med. 2013;369:722-731.

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First-line treatment landscape

Study	N	ORR (%)	Median PFS (months)	Final Median OS (months)
Phase III				
Sunitinib vs. IFN-α[1]	750	47 vs. 12	11 vs. 5; p<0.001	26.4 vs. 21.8; p=0.051
Bev + IFN-α vs. IFN-α[2]	649	31 vs. 12	10.4 vs. 5.5; p<.001	23.3 vs. 21.3; p=0.1291
Bev + IFN-α vs. IFN-α[3]	732	25.5 vs. 13.1	8.4 vs. 4.9; p<0.0001	18.3 vs. 17.4; p=0.069
Pazopanib vs. placebo[4]	233	32 vs. 3	11.1 vs. 2.8; p<0.0000001	22.9 vs. 23.5[5]; p=0.525
Temsirolimus vs. IFN-α[5]	626	8.6 vs. 4.8	5.5 vs. 3.1; p<0.001	10.9 vs. 7.3; p=0.0069
Pazopanib vs. sunitinib[6]	1110	31 vs. 25	8.4 vs. 9.5; Non-inferior	28.4 vs. 29.3; Non-inferior
Phase II				
Sorafenib vs. IFN-α[7]	189	5.2 vs. 8.7	5.7 vs. 5.6; p=0.504	NA

1. Motzer RJ, et al. J Clin Oncol. 2009;27:3584–3590; 2. Escudier B, et al. J Clin Oncol. 2009;27(Suppl 15S):5020 (Abstract);
3. Rini B, et al. J Clin Oncol. 2009;27(Suppl 15S):LBA5019 (Abstract); 4. Sternberg C, et al. J Clin Oncol. 2010;28:1061–1068;
5. Hudes G, et al. N Engl J Med. 2007;356:2271–2281;
6. Motzer RJ et al. N Engl J Med. 2013;369:722–731; 7. Escudier B, et al. J Clin Oncol. 2009;27:1280–1289;

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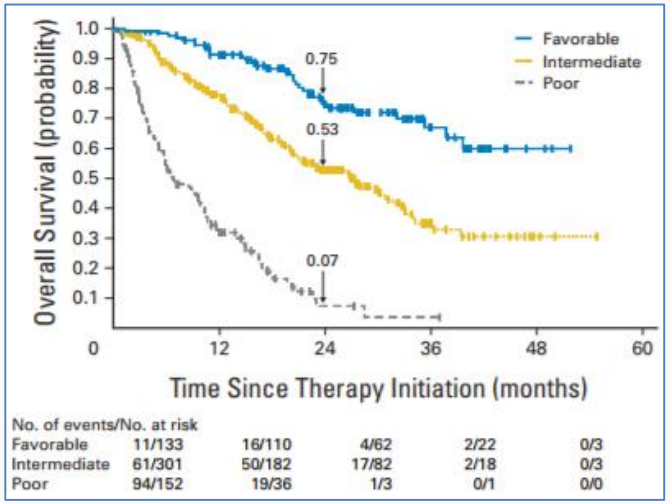
Improving Median OS in mRCC Patients

Historically, Motzer et al 19991 (n=656)

- ✓ mOS: 10 months
- ✓ Favorable risk: 20 months
- ✓ Intermediate risk: 10.3 months
- ✓ Poor risk: 3.9 months

Current Survival in TKI era, Heng et al 20092 (n=645)

- ✓ mOS: 13 months
- ✓ Favorable risk: 37 months
- ✓ Intermediate risk: 27 months
- ✓ Poor risk: 8.8 months



1. Motzer RJ, et al. *J Clin Oncol*. 1999;17:2530–2540. 2. Heng DYC, et al. *J Clin Oncol.* 2009; 27:5794–5799.

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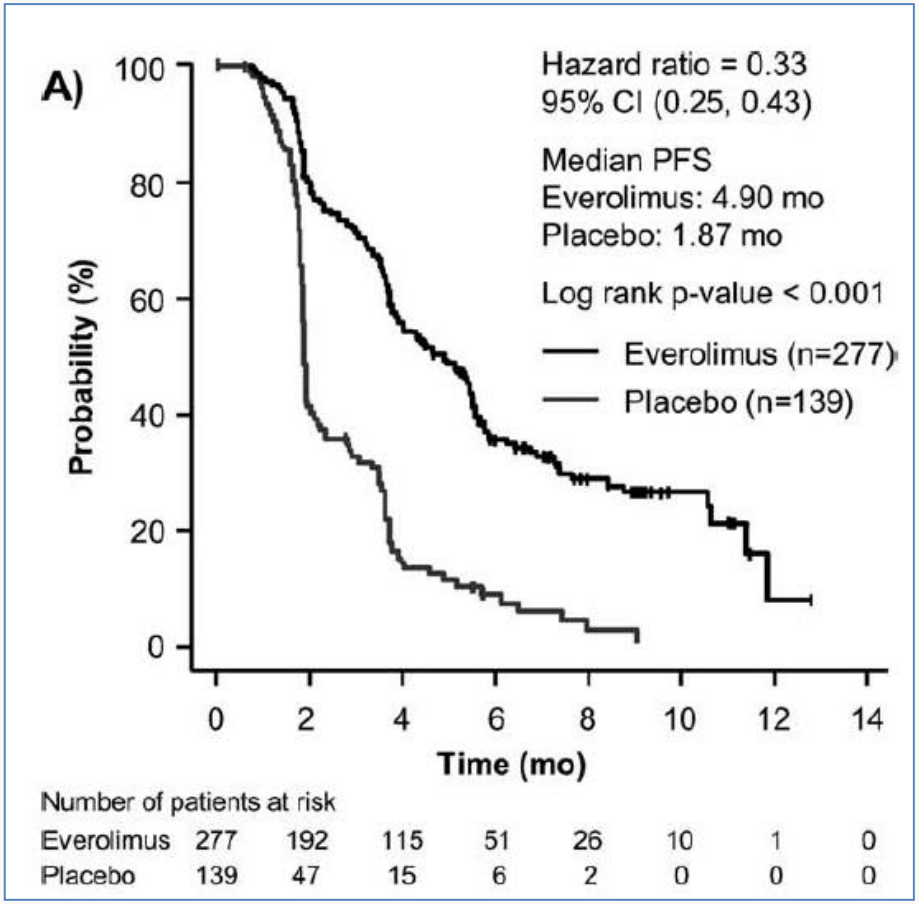
Phase III Trial of Everolimus for mRCC

A randomized phase III trial of second-line therapy in patients with metastatic RCC



Lancet 372;449-456. 2008

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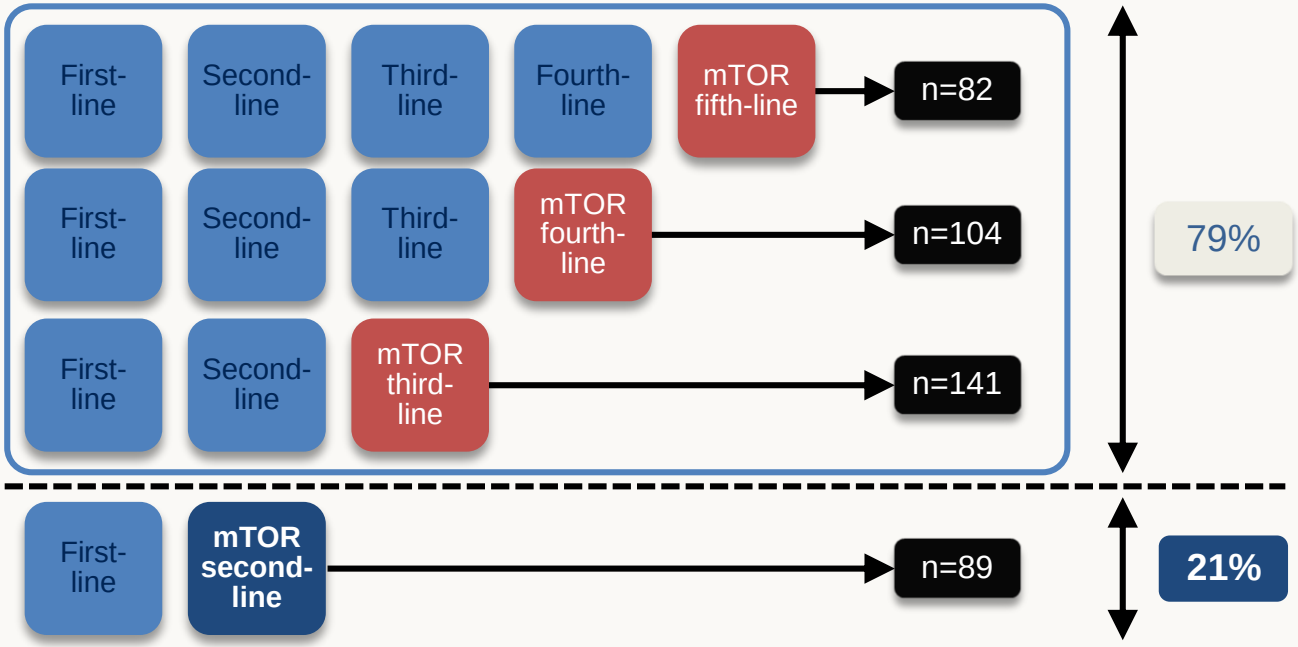
RECORD-1: Overview of patient populations

- In RECORD-1, only 21% of patients were treated with everolimus in second-line[1,2]



1. Zustovich F, et al. Crit Rev Oncol Hematol. 2012;
Motzer RJ, et al. Cancer. 2010;116:4256–4265.

Phase III AXIS Trial: Second-line Axitinib Superior to Sorafenib in Pts With mRCC

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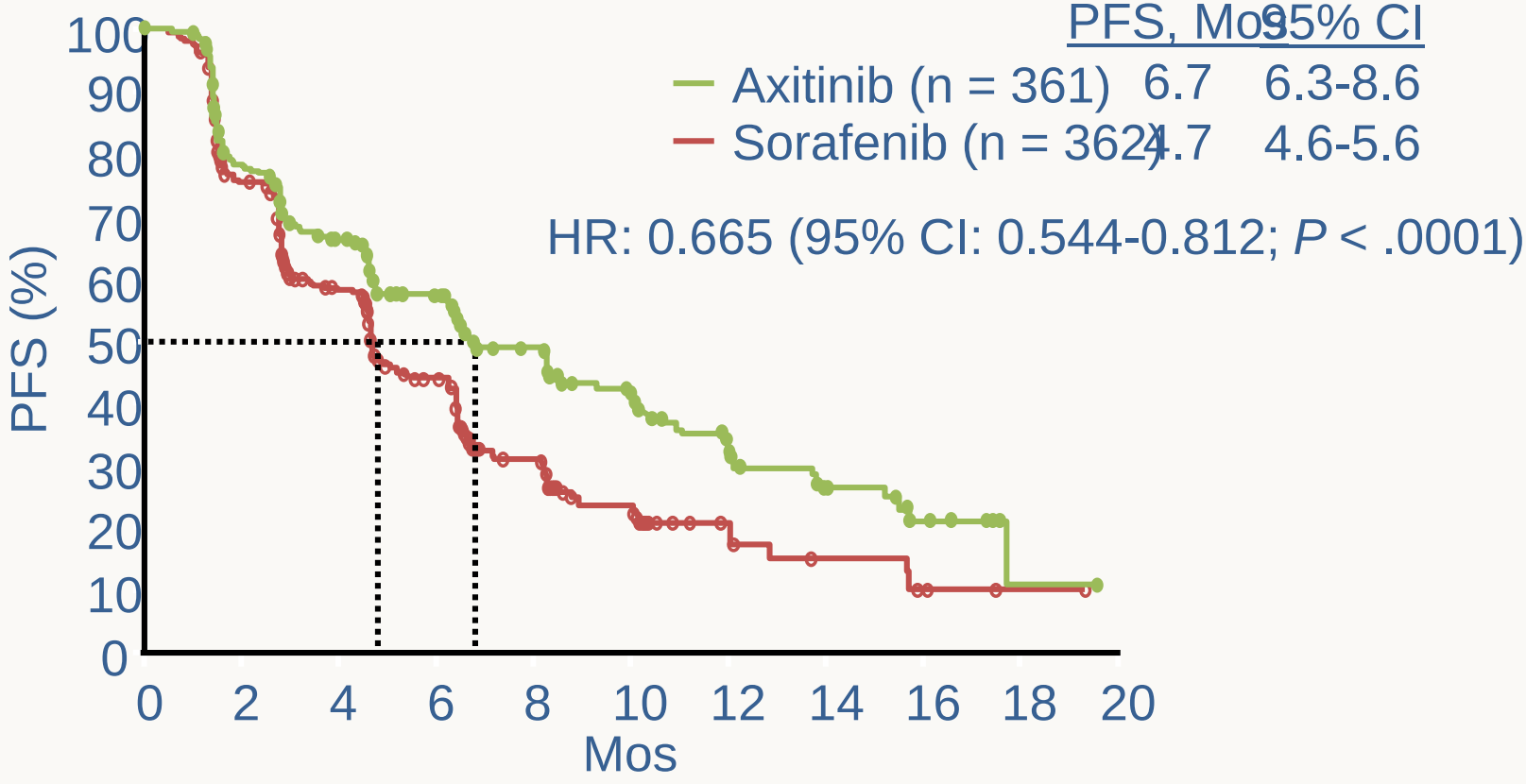
A randomized phase III trial of second-line therapy in patients with metastatic RCC



Rini BI, et al. Lancet. 2011;378:1931-1939.

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Mortalidade

Improved OS with targeted agents

Overall Survival in Swedish RCC Patients treated 2000–2012: Update of the RENCOMP study

Year	# Patients	OS RCC	OS mRCC
2000 – 2012	12171	76m	14m
2000 – 2005	5234	46m	10m
2006 – 2008	2957	86m	13m
2009 – 2012	3980	Not reached	18m

Magnus Lindskog. Abstract Number 413. 2015 Genitourinary Cancer Symposium. Board #B20.

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Switch to mTOR or continue TKI?

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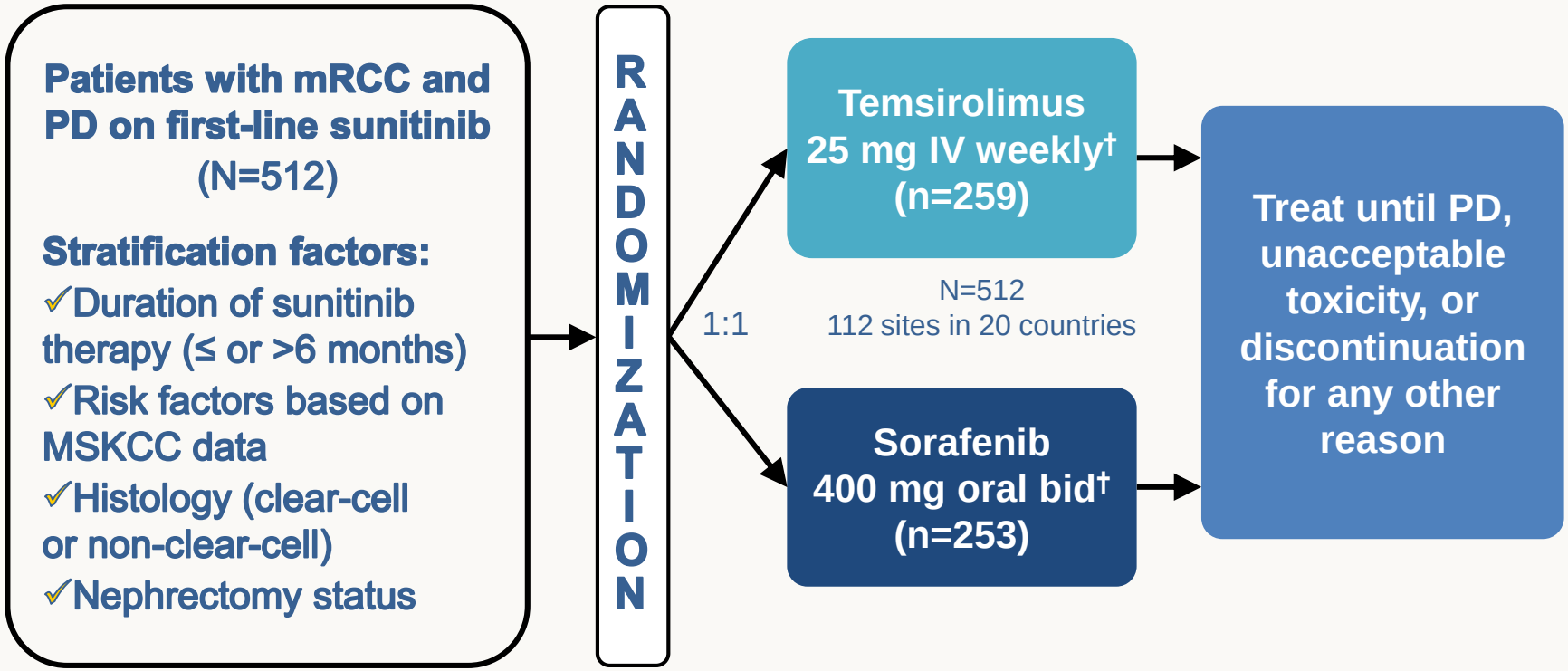
INTORSECT:* Phase III TKI vs. mTOR inhibitor study in second-line mRCC after first-line sunitinib



First patient randomized: 25 September 2007; last patient randomized: 31 January 2012. Data cutoff: 4 May 2012. At present, two patients are on study. *NCT00474786; †Dose reductions were allowed: temsirolimus (to 20 mg then 15 mg); sorafenib (to 400 mg/day then every other day); MSKCC = Memorial Sloan-Kettering Cancer Center; PD = progressive disease.

J Clin Oncol. 2014 Mar 10;32(8):760-7

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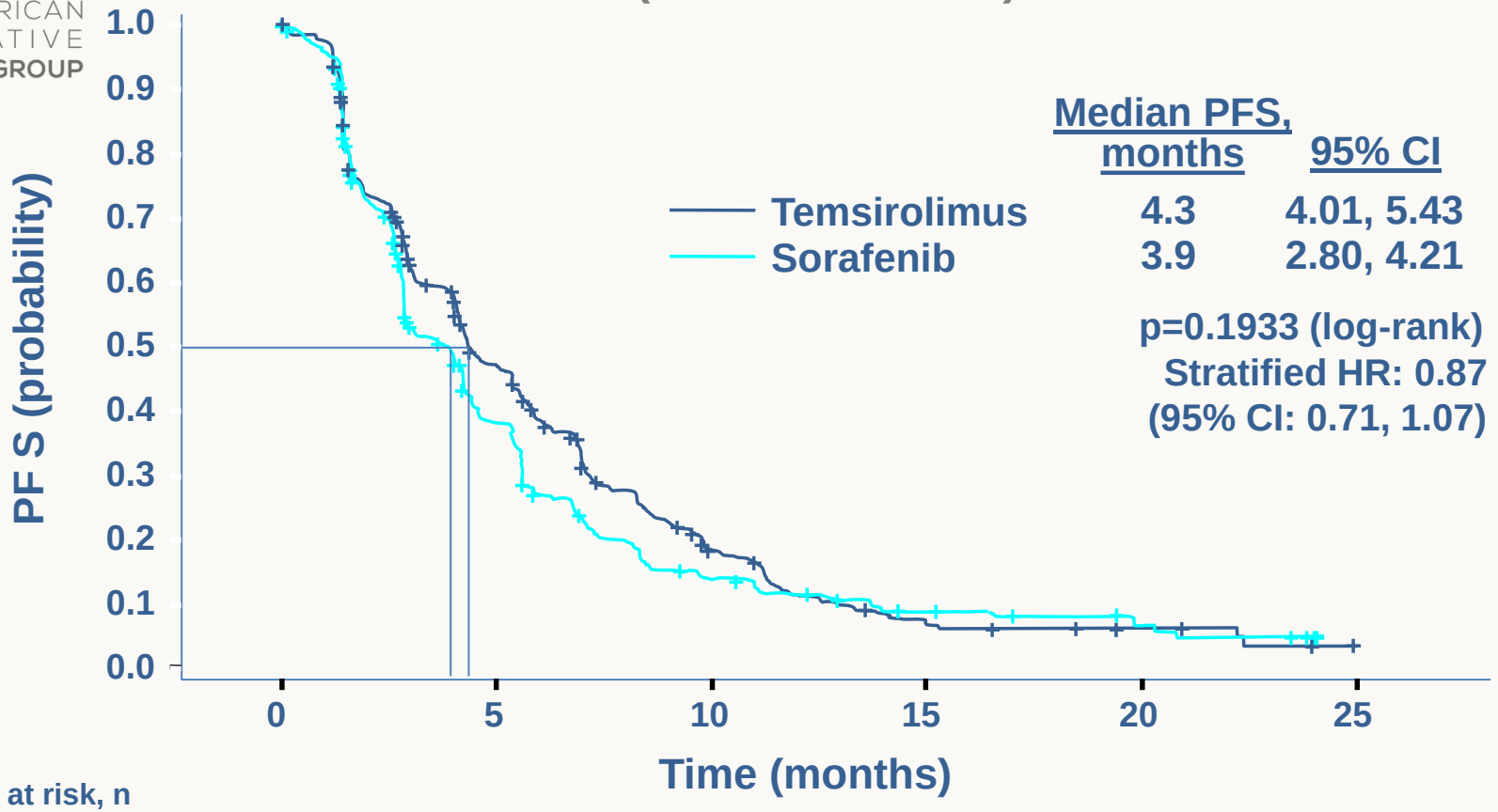
INTORSECT: Progression-free survival

(IRC Assessment)



	Median PFS, months	95% CI
Temsirolimus	4.3	4.01, 5.43
Sorafenib	3.9	2.80, 4.21

p=0.1933 (log-rank)
Stratified HR: 0.87
(95% CI: 0.71, 1.07)

Patients at risk, n

Sorafenib	252	72	22	11	6	0
Temsirolimus	259	96	28	9	5	0

CI = confidence interval; HR = hazard ratio; IRC = Independent Review Committee; PFS = progression-free survival.

Hutson, et al. ESMO 2012; Abstract LBA22;
Hutson TE et al. J Clin Oncol. 2013 [Epub ahead of print].

INTORSE-01 trial: OS significantly longer with sorafenib than with temsirolimus

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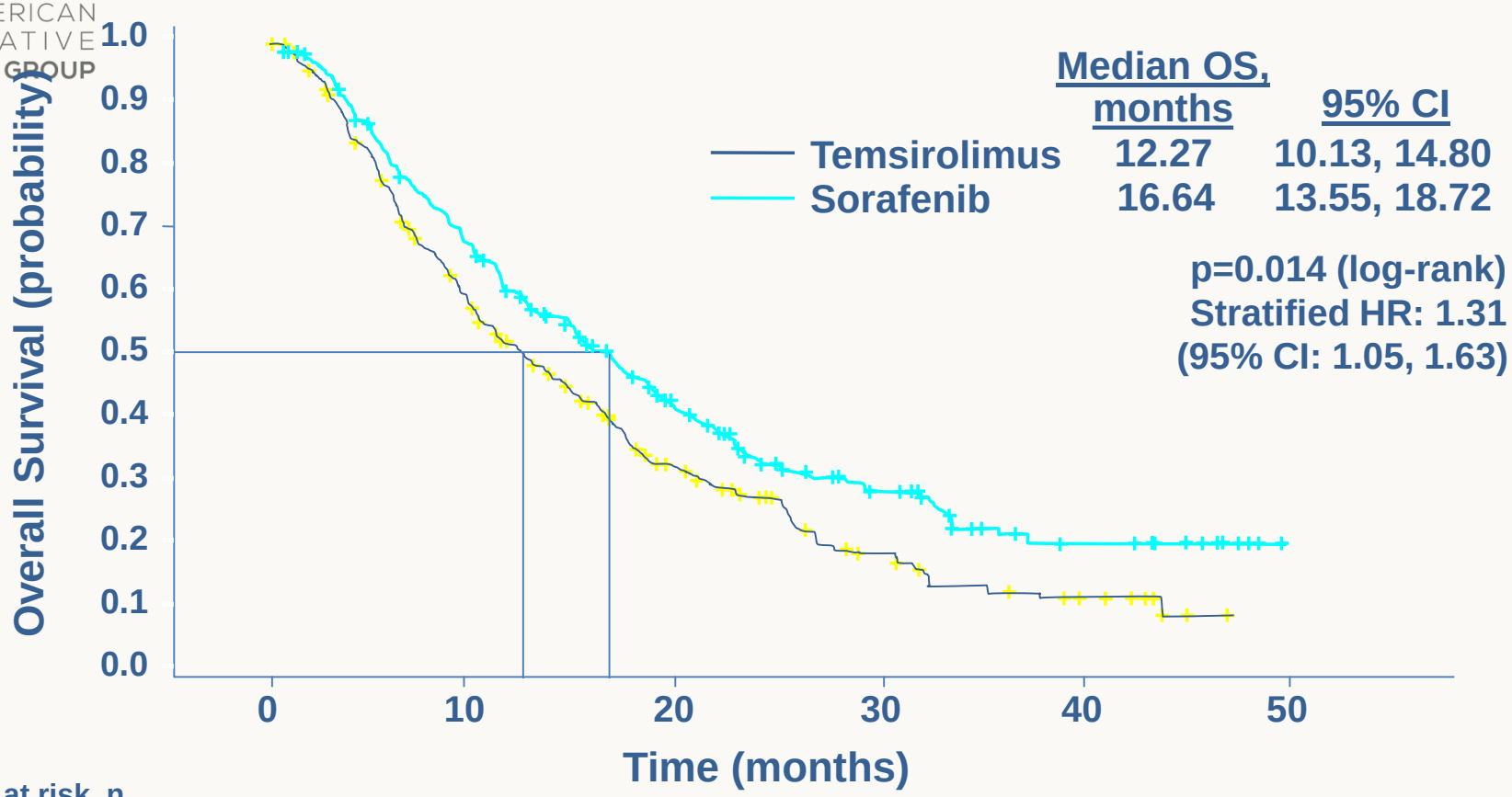

Patients at risk, n

Sorafenib	253	158	74	34	13	0
Temsirolimus	259	132	54	22	8	0

CI = confidence interval; HR = hazard ratio; OS = overall survival.

Hutson, et al. ESMO 2012; Abstract LBA22;
Hutson TE et al. J Clin Oncol. 2013 [Epub ahead of print].

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Sequencing

RECORD-3: Study design

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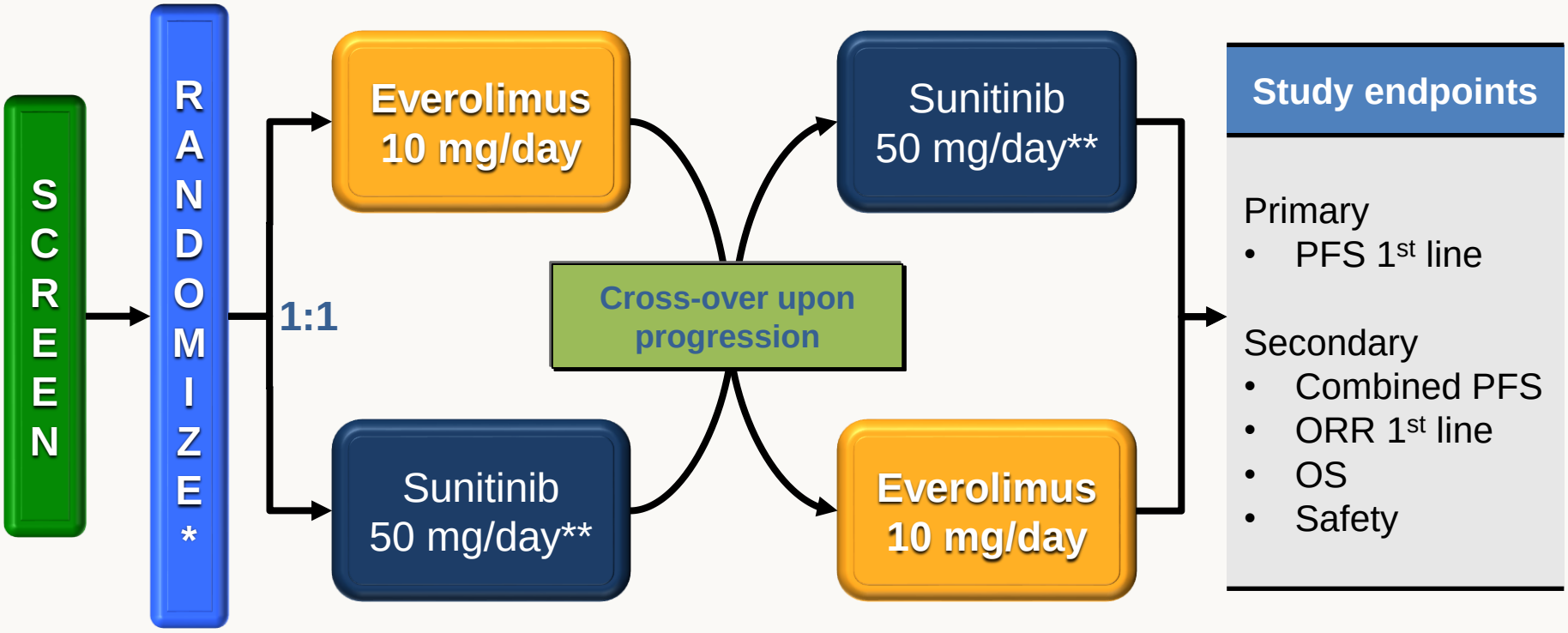

Study endpoints

Primary
- PFS 1st line

Secondary
- Combined PFS
- ORR 1st line
- OS
- Safety

Median follow-up 22.7 months

***stratified by MSKCC prognostic factors. **4 weeks on, 2 weeks off.**

Motzer RJ et al. ASCO 2013 Abstract 4504

Ann Oncol. 2017 Jun 1;28(6):1339-1345

Primary endpoint: First-line PFS

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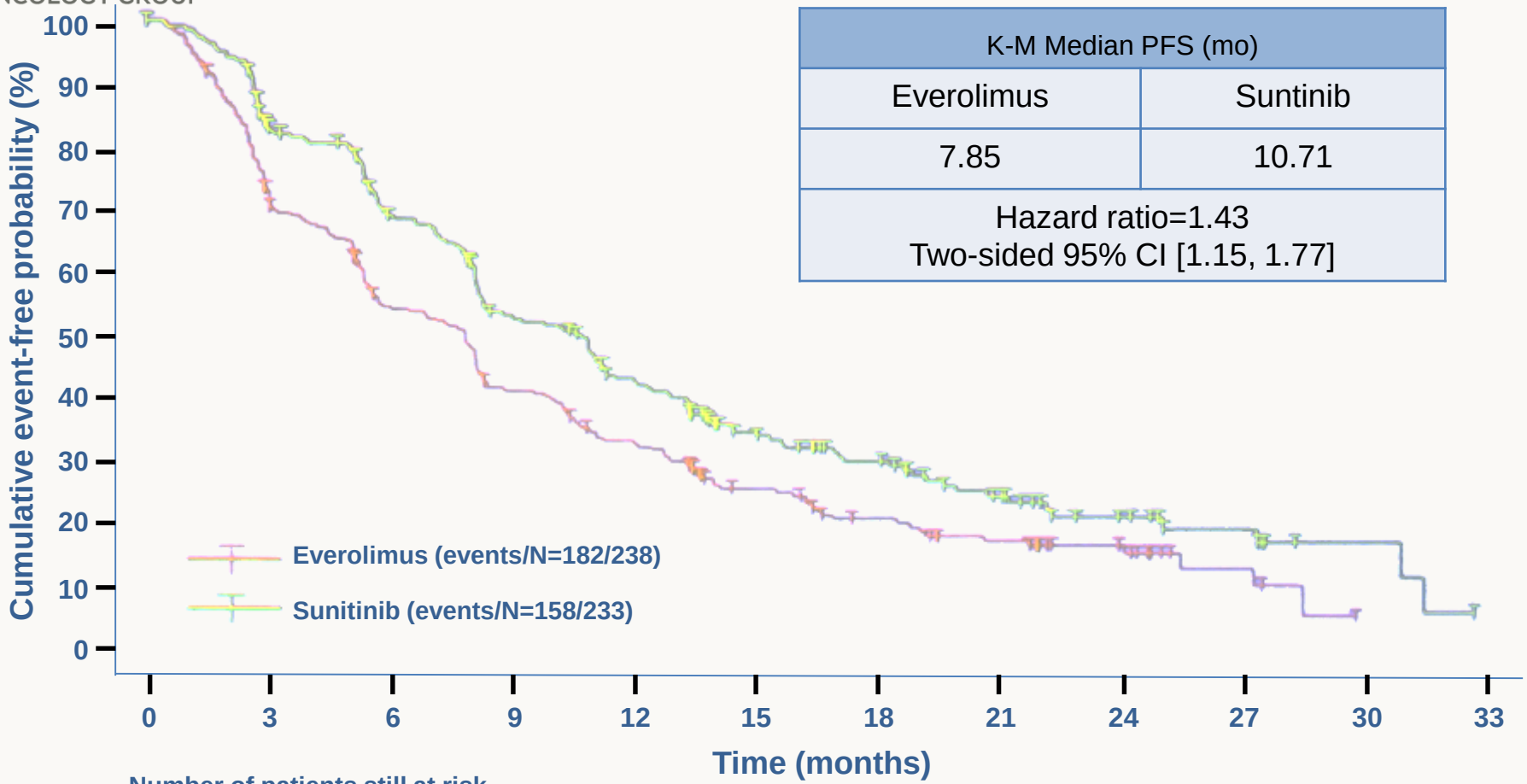
K-M Median PFS (mo)	
Everolimus	Suntinib
7.85	10.71
Hazard ratio=1.43 Two-sided 95% CI [1.15, 1.77]	



Number of patients still at risk

Everolimus	238	164	118	88	68	44	31	23	12	5	0	0
Sunitinib	233	181	145	108	84	55	42	28	15	9	3	0

Ann Oncol. 2017 Jun 1;28(6):1339-13

METEOR: PFS and OS With Cabozantinib

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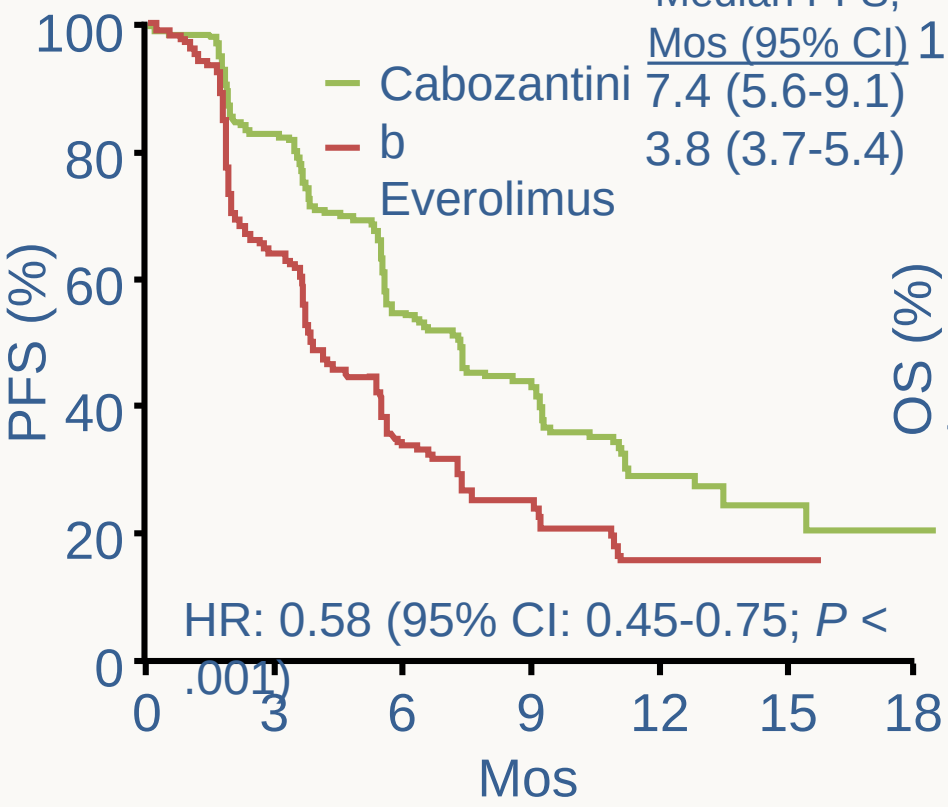
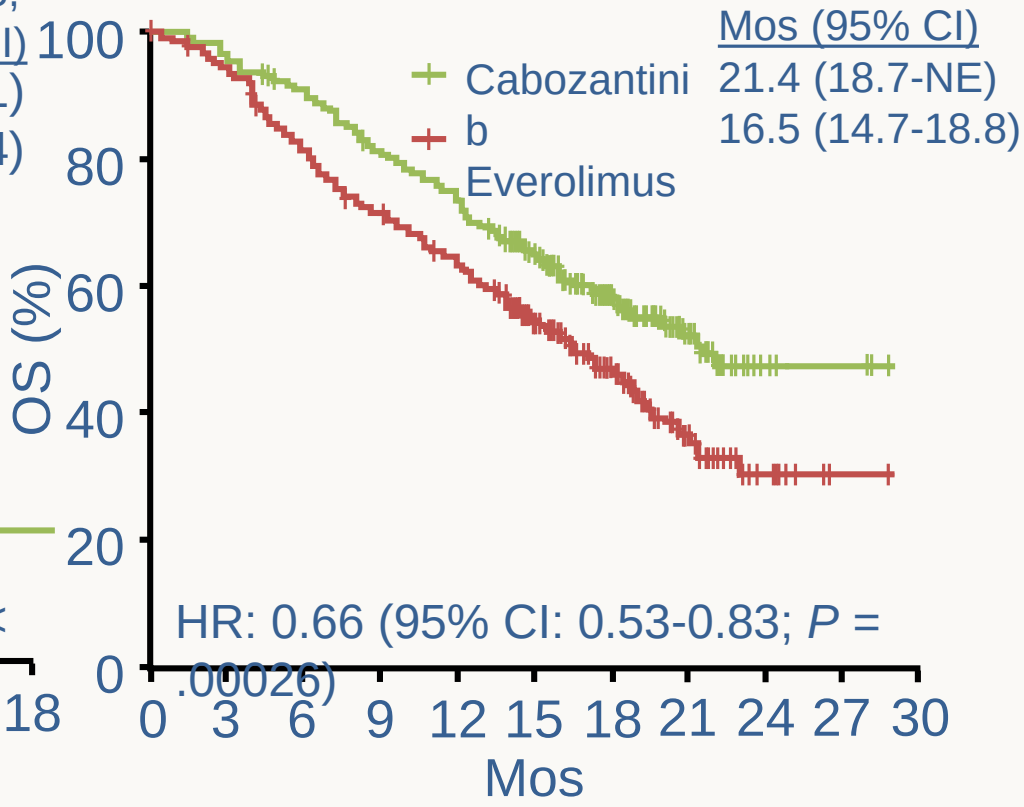
Randomized, open-label phase III trial in pts with CC mRCC after ≥ 1 prior VEGF TKI

PFS[1]



OS[2]



Choueiri TK, et al. N Engl J Med. 2015;373:1814-1823. Choueiri TK, et al. Lancet Oncol. 2016;17:917-927.

Lenvatinib ± Everolimus in mRCC: PFS (Primary Endpoint) and Updated OS

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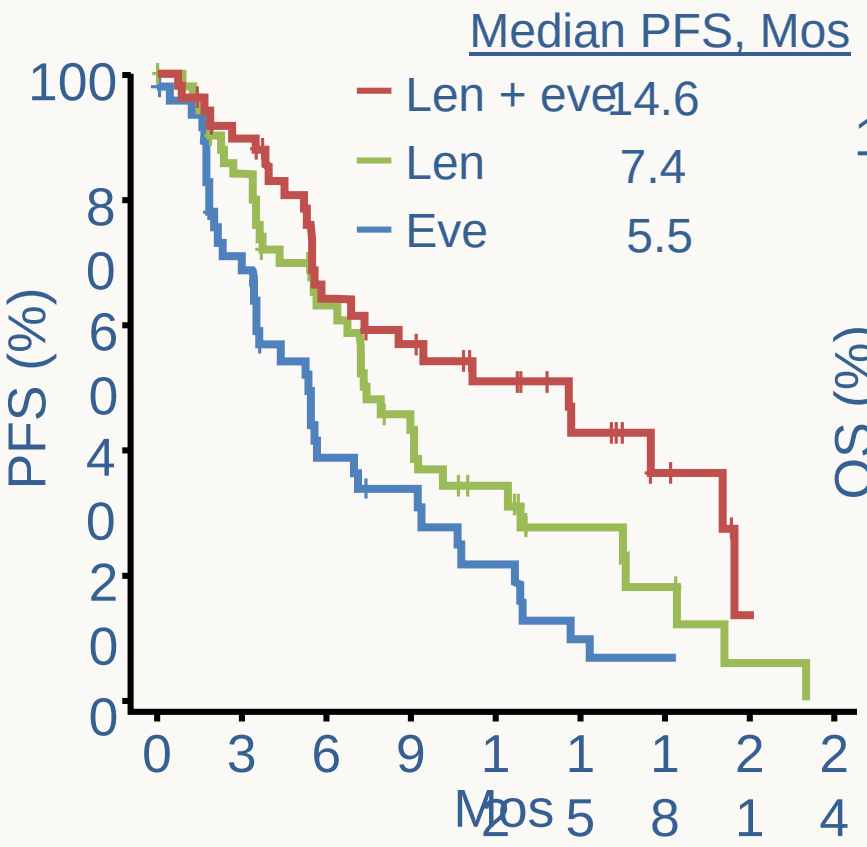
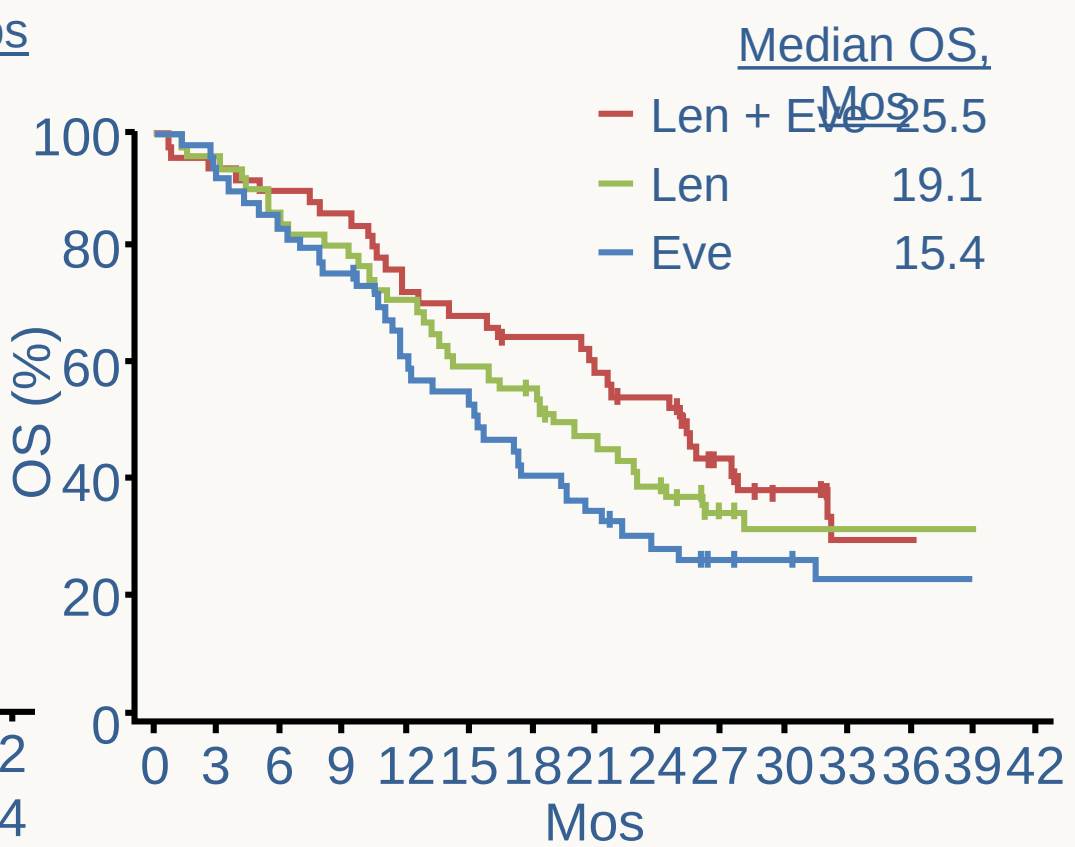
Randomized, open-label registrational trial in pts with CC mRCC after ≥ 1 prior VEGF TKI



Len + eve vs eve: HR: 0.40 (95% CI: 0.24-0.68; *P* = .0005) Len vs eve: HR: 0.61 (95% CI: 0.38-0.98; *P* = .048)



Len + Eve vs Eve: HR: 0.59 (95% CI: 0.36-0.97; *P* = .065)
Len vs Eve: HR: 0.75 (95% CI: 0.47-1.20; *P* = .130)
Len + Eve vs Len: HR: 0.79 (95% CI: 0.48-1.30; *P* = .309)

Motzer R, et al. Lancet Oncol. 2015;16:1473-1482.

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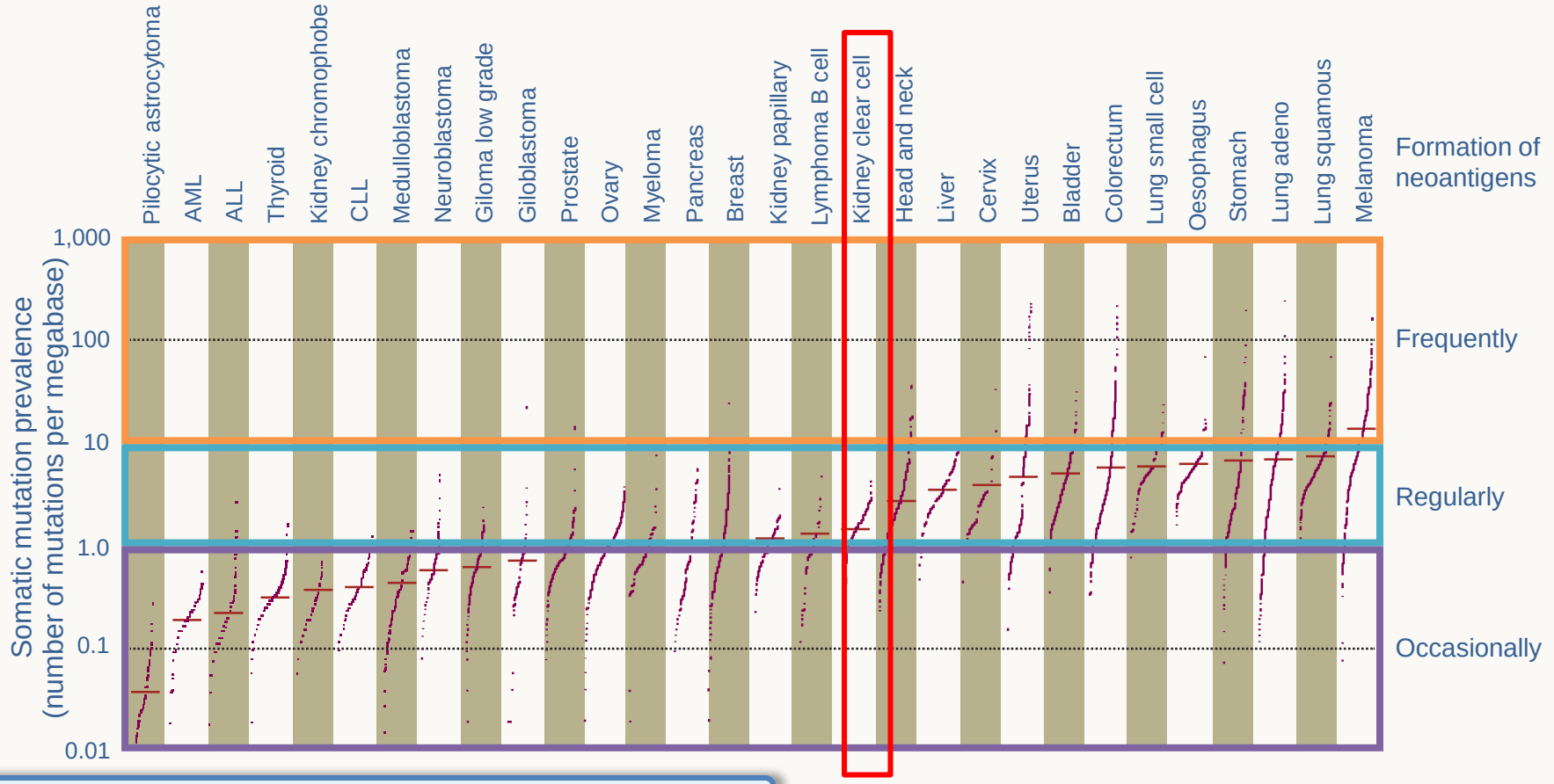
Kidney cancer is considered to be a moderate immunogenic tumour[1]

Estimate of the neoantigen repertoire in human cancer[2]



Bladder cancer is highly immunogenic,[1] and has been estimated to regularly form neoantigens[2]

1. Smith SG, Zaharoff DA. Immunotherapy 2016;8:351-365
2. Schumacher TN, Schreiber RD. Science 2015;348:69-74

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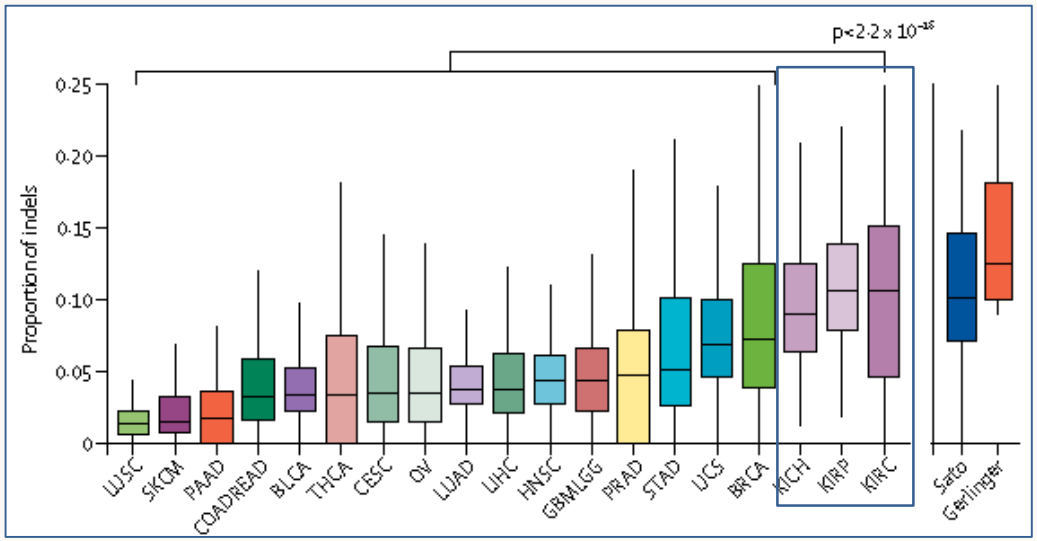
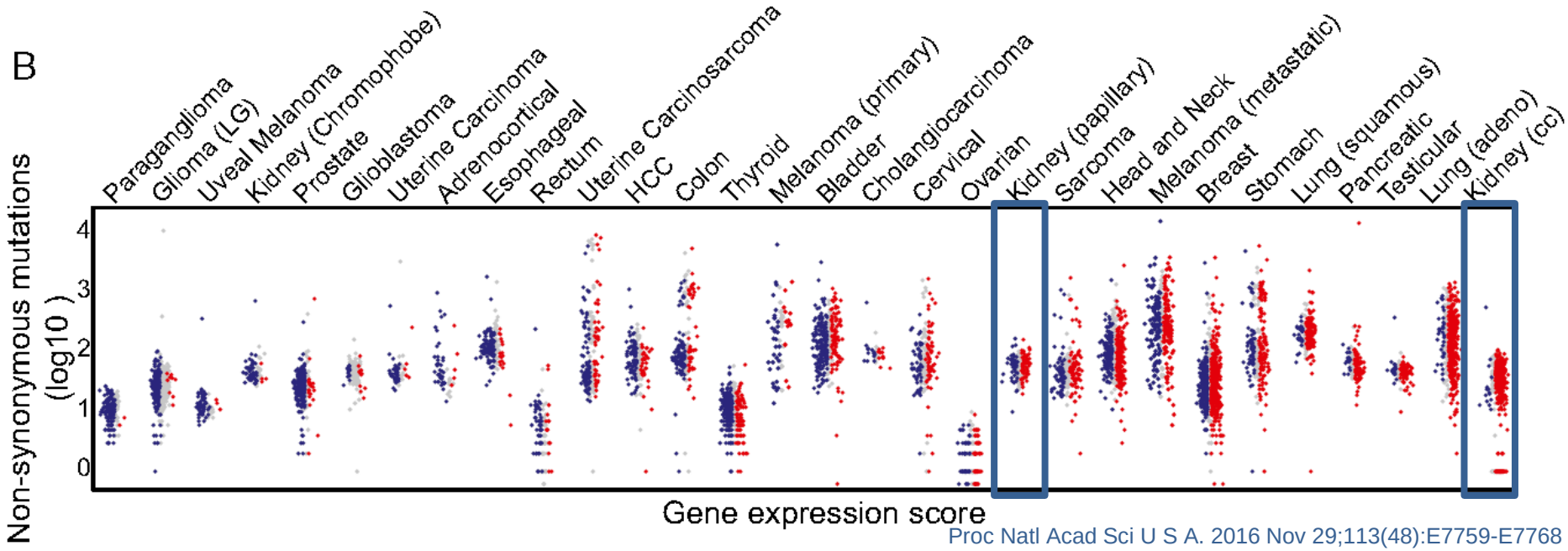
Inflamed tumor x TMB





Proc Natl Acad Sci U S A. 2016 Nov 29;113(48):E7759-E7768
Lancet Oncol. 2017 Aug;18(8):1009-1021

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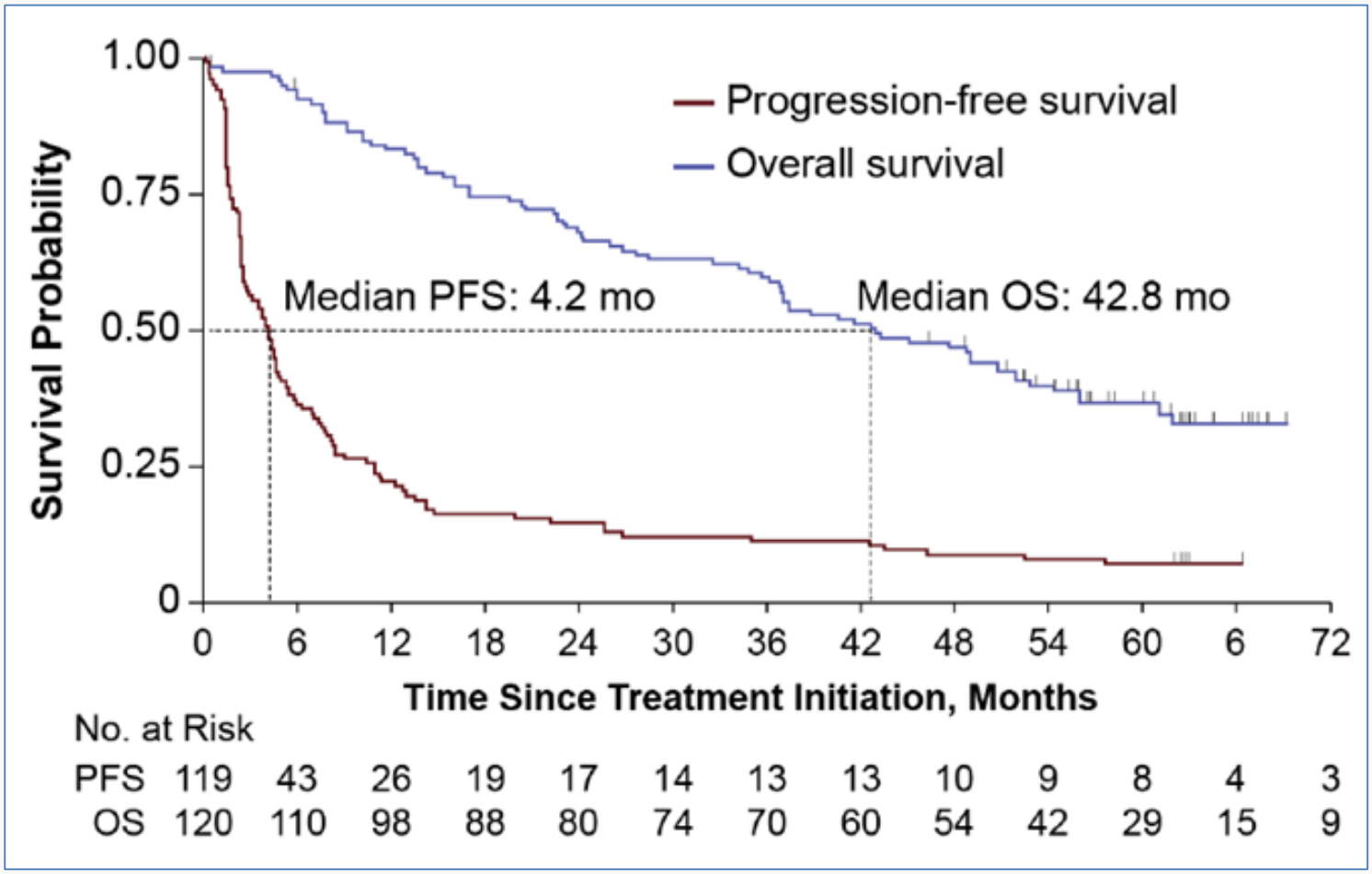
High Dose IL-2 = Accepting Short PFS



Clin Cancer Res. 2015;21:561–568

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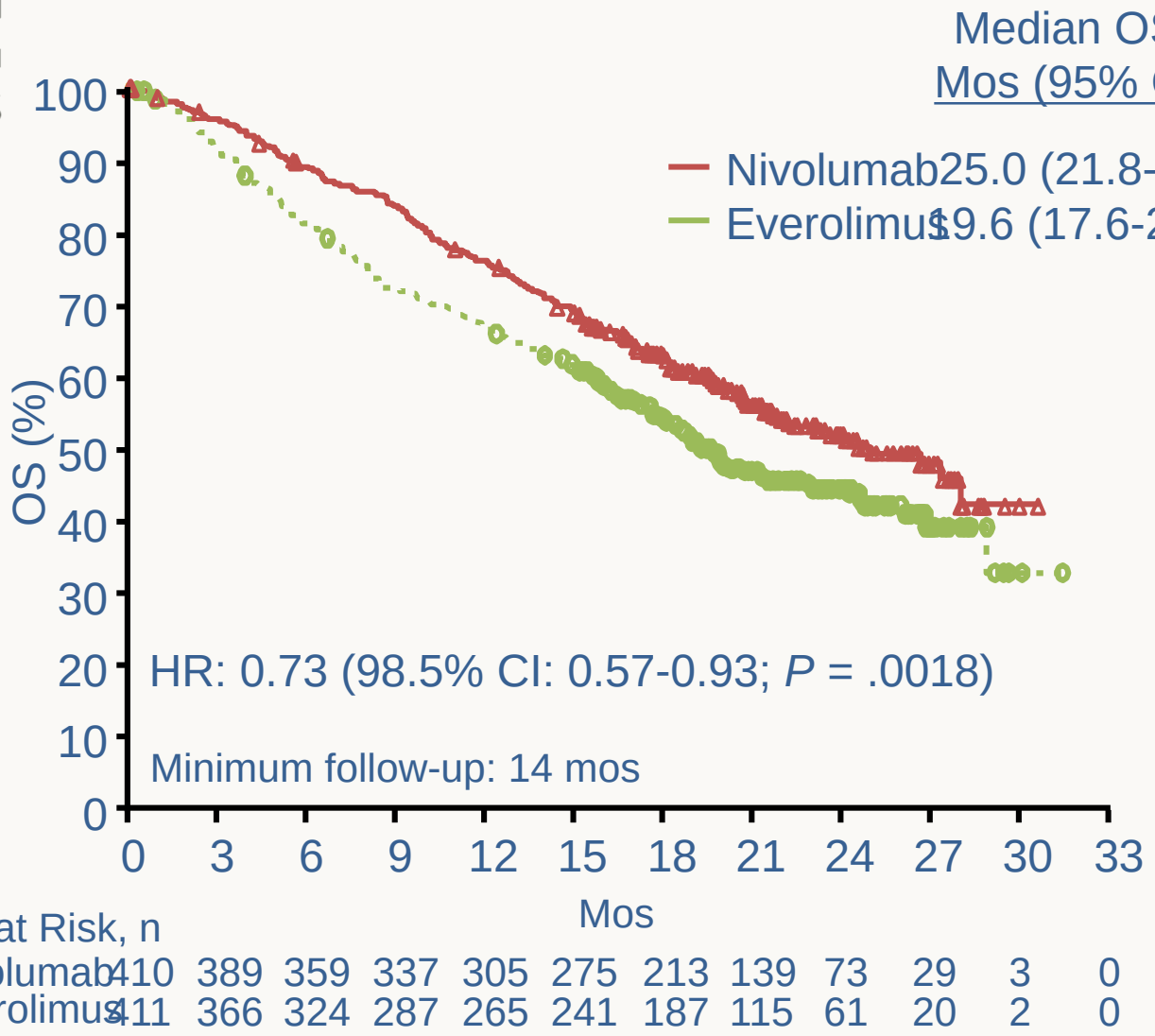
CheckMate 025: OS



Motzer RJ, et al. N Engl J Med. 2015;373:1803-1813.

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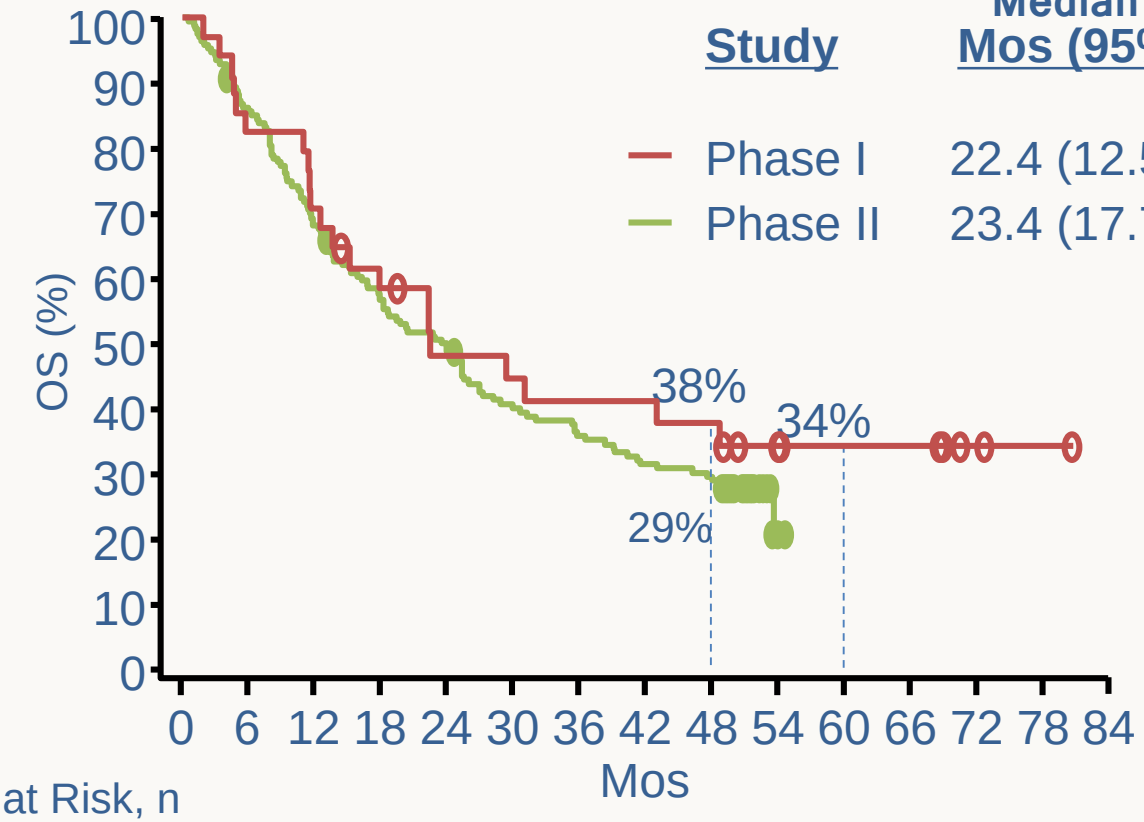
Phase I and II Studies of Nivo in Previously Treated Pts With Advanced RCC: Long-term OS

Study	Median OS, Mos (95% CI)	Minimum Follow-up, Mos
Phase I	22.4 (12.5-NE)	50.5
Phase II	23.4 (17.7-26.9)	49.2



Pts at Risk, n

Phase I	34	28	24	18	14	13	12	12	11	8	6	6	2	1
Phase II	167	142	113	93	80	65	58	51	47	2	0	0	0	0

0

0

McDermott DF, et al. ASCO 2016. Abstract 4507.

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Second line

	RECORD-1[23]	AXIS[7]	CheckMate-025[4]	METEOR[15]	Randomized Phase II[11,24]
Agent	Everolimus	Axitinib	Nivolumab	Cabozantinib	Lenvatinib + everolimus
Comparator	Placebo	Sorafenib	Everolimus	Everolimus	Lenvatinib or everolimus
Patients	416	389	821	658	153
D/C Due to AE	13%	7%	8%	9%	29%
PD as Best Response	31.4%	22%	35%	9%	4%
Median PFS (mos)	4.9 vs. 1.87 HR 0.33 $p < 0.001$	6.7 vs. 4.7 HR 0.665 $p < 0.0001$	4.6 vs. 4.4 HR 0.88 $p = 0.11$	7.4 vs. 3.8 HR 0.58 $p < 0.001$	12.8 vs. 9.0 vs. 5.6 HR 0.40/$p = 0.0005$ to EVE HR 0.66/$p = 0.12$ to LEN
Median OS (mos)	14.8 vs. 14.4 HR 0.87 $p = 0.162$	20.1 vs. 19.2 HR 0.969 $p = 0.3744$	25.0 vs. 19.6 HR 0.73 $p = 0.002$	21.4 vs. 16.5 HR 0.66 $p = 0.00026$	25.5 vs. 19.1 vs. 15.4 HR 0.59 to EVE $p = 0.065$ to EVE

Abbreviations: D/C, discontinue; AE, adverse event; PD, progressive disease; mos, months, PFS, progression-free survival; HR, hazard ratio; EVE, everolimus; LEN, lenvatinib; OS, overall survival.

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Novas estratégias

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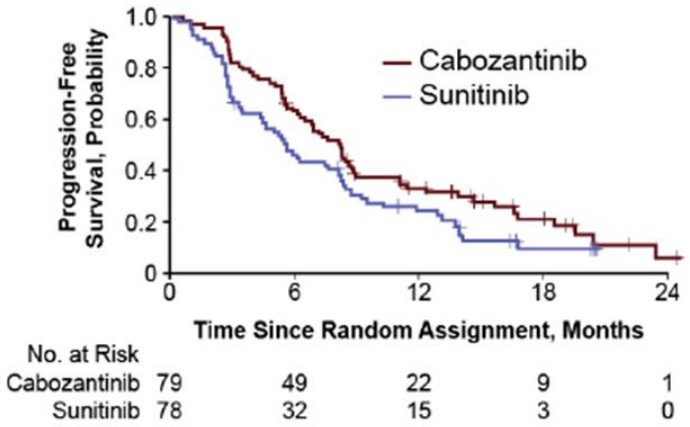
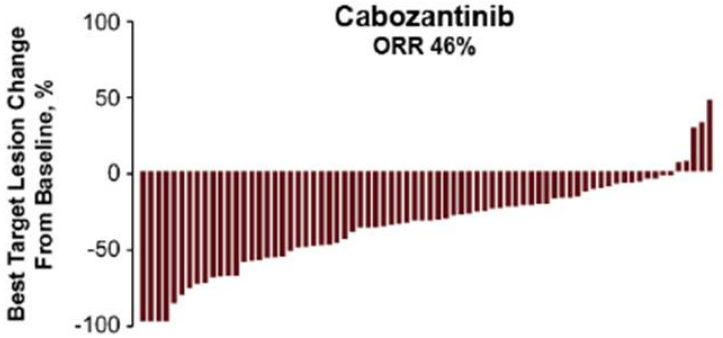
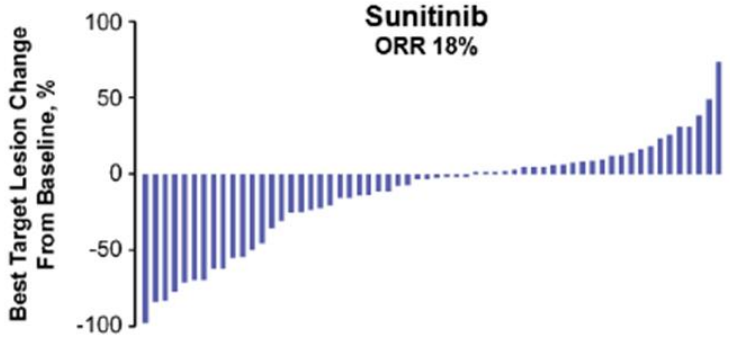
VEGFR-TKI Versus VEGFR-TKI: Intermediate/Poor risk[1]

CABOSUN: Progression-Free Survival



	N	Median PFS
Cabozantinib	79	8.2 months (6.2-8.8)
Sunitinib	78	5.6 months (3.4-8.1)
HR = 0.66 (95% CI 0.46 to 0.95, 1-sided *P* = .012)		





1. Choueiri TK et al. *J Clin Oncol*. 2016;doi:10.1200/JCO.2016.70.7398.

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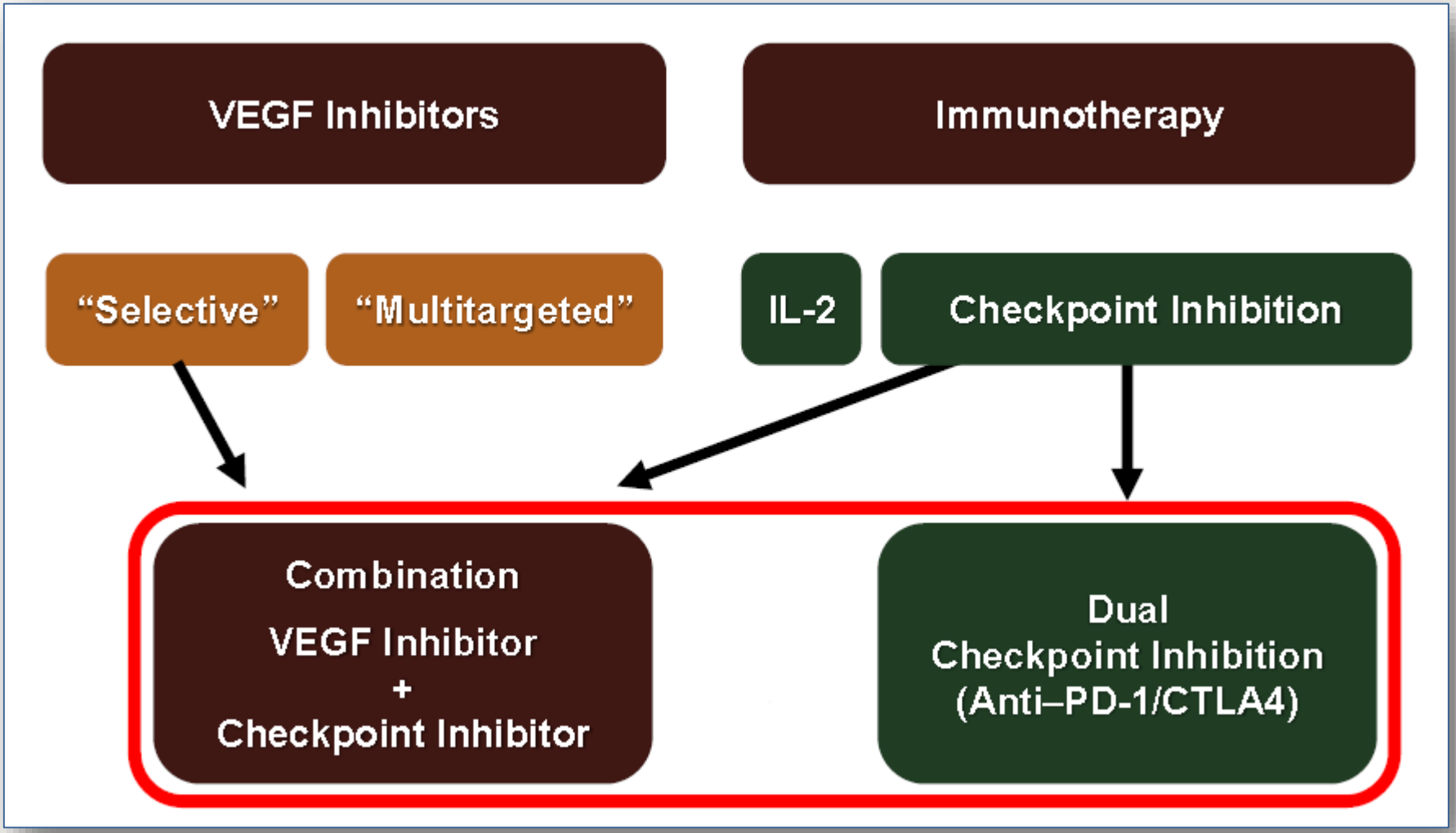
First-Line Therapy: Significant Changes Expected



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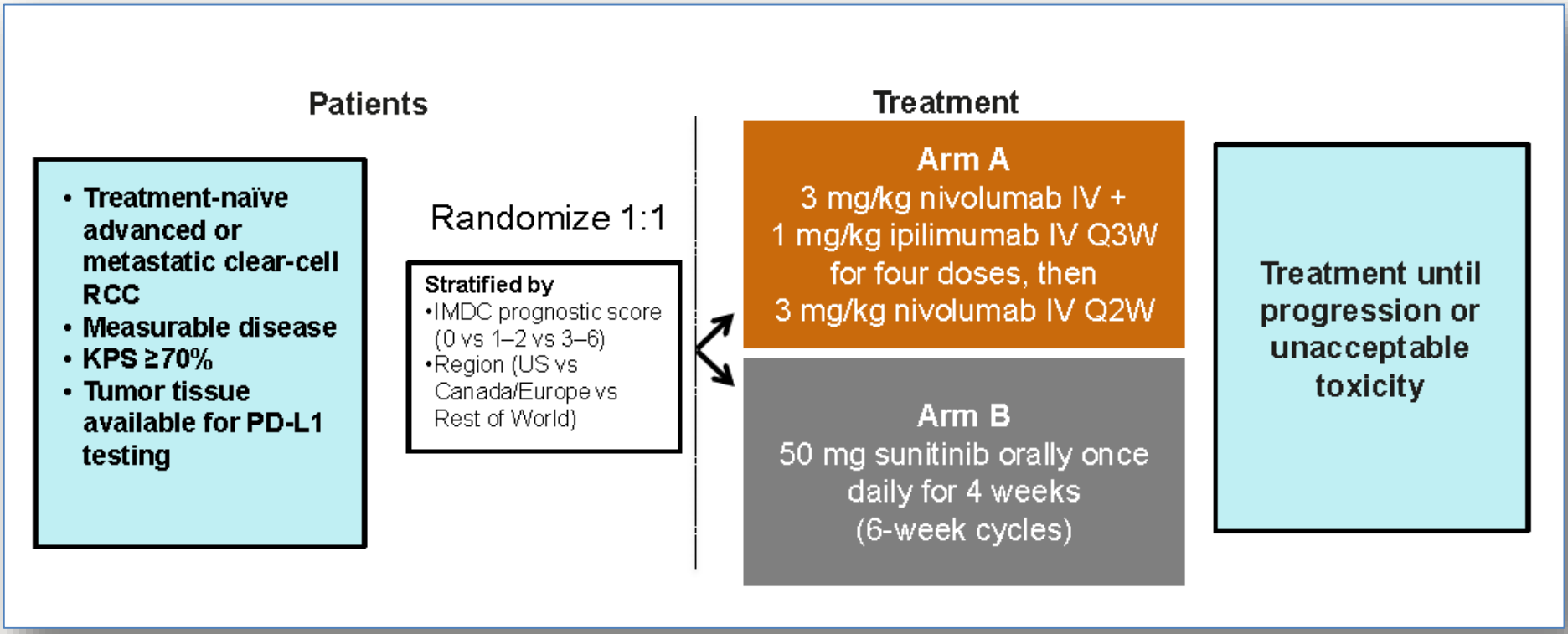
Dual Checkpoint Inhibition: Phase 3 CHECKMATE 214 Trial[1]



Escudier B, et al. ESMO 2017. Abstract LBA5.

CheckMate 214: Response and Survival Outcomes in IDMC Intermediate-/Poor-Risk Pts

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Significantly improved ORR and CR rates (both *P* < .0001) with nivo + ipi vs sun in IDMC intermediate-/poor-risk pts

ORR most improved in pts with tumor PD-L1 ≥ 1% (58% vs 22%; *P* < .0001)

Response per IRRC,* %	Nivo + Ipi (n = 425)	Sun (n = 422)
ORR	42	27
▪ CR	9	1
▪ PR	32	25
▪ SD	31	45
▪ PD	20	17
▪ NR/Unable to determine	8	12

*By RECIST v1.1.

Escudier B, et al. ESMO 2017. Abstract LBA5.

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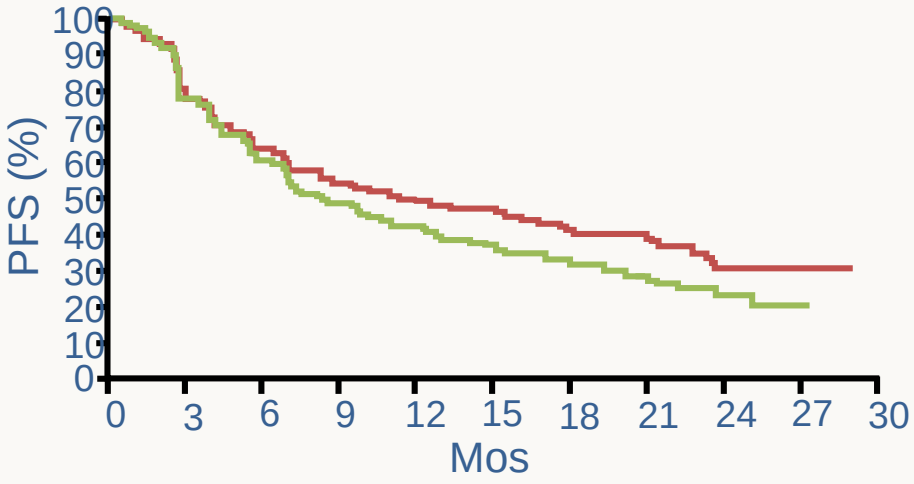
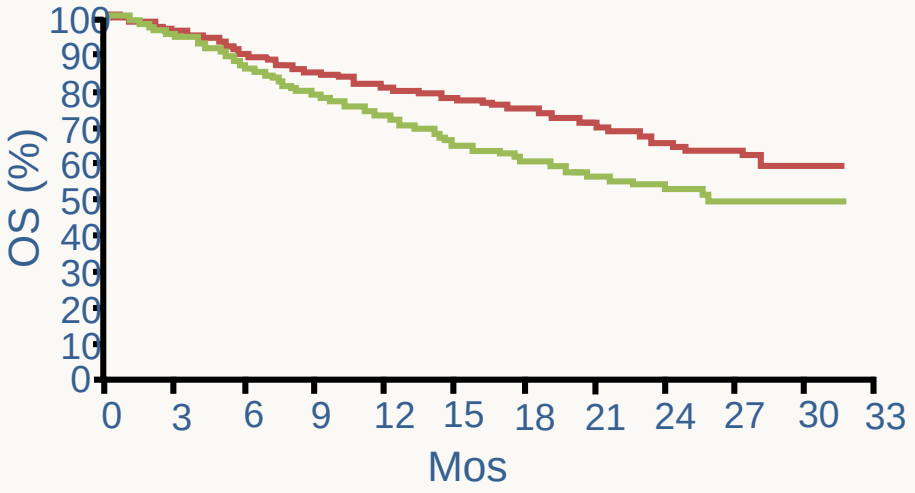
CheckMate 214: Response and Survival Outcomes in IDMC Intermediate-/Poor-Risk Pts

PFS per IRRC



	Nivo + Ipi (n = 425)	Sunitinib (n = 422)
mPFS, mos	11.6	8.4
HR (99.1% CI)	0.82 (0.64-1.05); P = .0331	

OS



	Nivo + Ipi (n = 425)	Sunitinib (n = 422)
mOS, mos	NR	26.0
HR (99.8% CI)	0.63 (0.44-0.89); P < .0001	

Escudier B, et al. ESMO 2017. Abstract LBA5.

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CheckMate 214: Response and Progression Fre Survival Outcomes in IDMC Favorable-Risk Pts

Outcome	N = 249[a]	
	NIVO + IPI N = 125	SUN N = 124
Confirmed ORR,[b] % (95% CI)	**29 (21–38)**	**52 (43–61)**
	P = 0.0002	
PFS,[c] median (95% CI), months	15.3 (9.7–20.3)	25.1 (20.9–NE)
	HR (99.1% CI) 2.18 (1.29–3.68) ***P* < 0.0001**	

[a]11% of patients in both arms had tumor PD-L1 expression ≥1%
[b]IRRC-assessed by RECIST v1.1
[c]IRRC-assessed

Escudier B, et al. ESMO 2017. Abstract LBA5.

CheckMate 214: Safety in All Treated Pts

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Tx-related deaths: nivo + ipi, n = 7; sun, n
TRAE leading to d/c: nivo + ipi, 22%; sun,

irAE,* %	Nivo + Ipi (n = 547)	
	Any	Gr 3-4
Rash	17	3
Diarrhea/colitis	10	5
Hepatitis	7	6
Nephritis & renal dysfunction	5	2
Pneumonitis	4	2
Hypersensitivity/infusion rxn	1	0
Hypothyroidism	19	< 1
Hyperthyroidism	12	< 1
Adrenal insufficiency	8	3

*Additional irAE in ≤ 5% of pts: hypophysitis, thyroiditis, diabetes mellitus.

TRAE, %	Nivo + Ipi (n = 547)		Sun (n = 535)	
	Any	Gr 3-5	Any	Gr 3-5
TRAE in ≥ 25% of pts	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
▪ Hand–foot syndrome	1	0	43	9

Escudier B, et al. ESMO 2017. Abstract LBA5.

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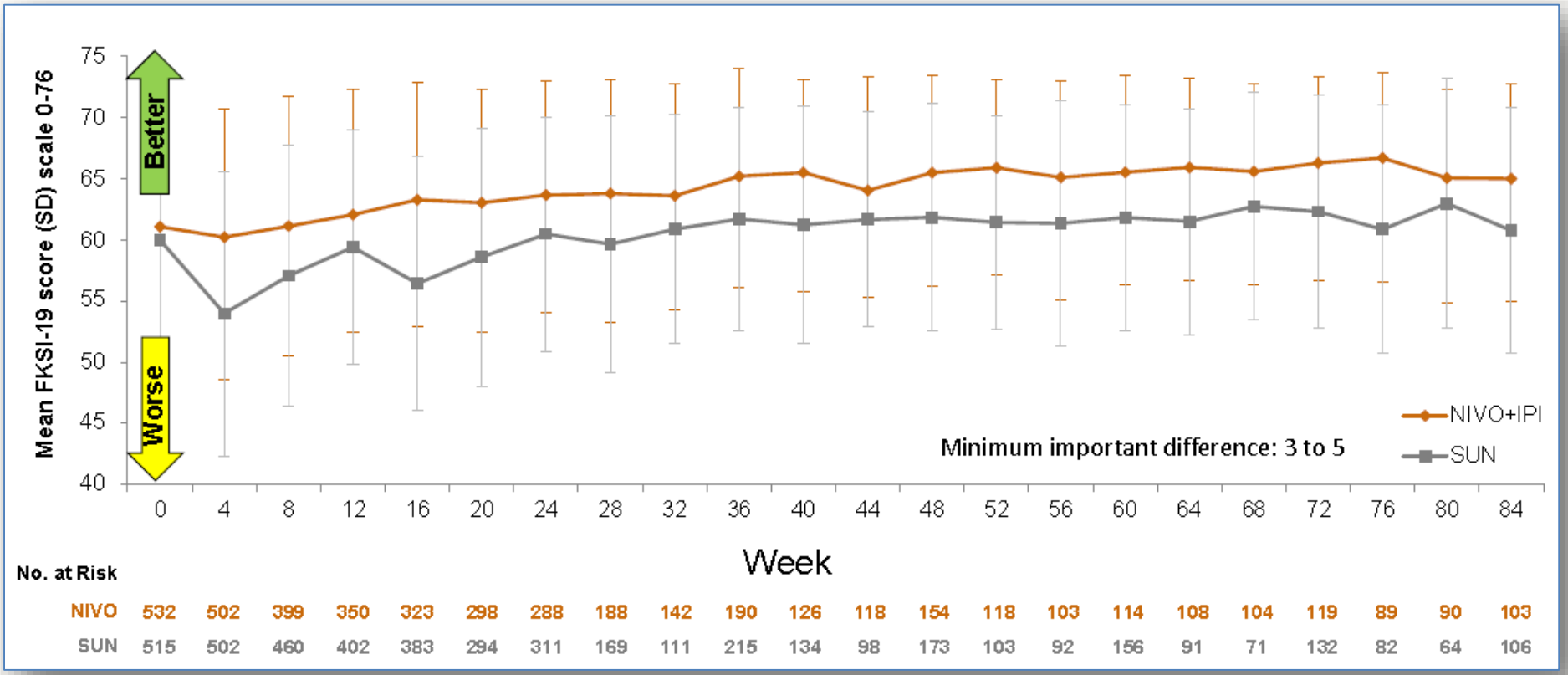
Health-Related Quality of Life: ITT



Escudier B, et al. ESMO 2017. Abstract LBA5.

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VEGFR-TKI + Anti PD-1: Combos with Sunitinib and Pazopanib

Category, %	Sunitinib + Nivolumab (n=33)		Pazopanib + Nivolumab (n=20)		Pazo 800 + Pembrolizumab (n=10)		Pazo 600 + Pembrolizumab (n=10)	
	All	Grade 3-4	All	Grade 3-4	All	Grade 3-4	All	Grade 3-4
ALT increased	39	18	25	20	70	60	60	60
AST increased	36	9	30	20	70	60	50	40
Diarrhea	20	9	60	20	60	0	60	0

Prohibitive hepatic and gastrointesintal toxicity?

Amin A *et al* ASCO Meeting Abstracts 32:5010, 2014; McDermott *et al* Presented at the 2015 ECC Annual Meeting in Vienna [Abstr 2622]

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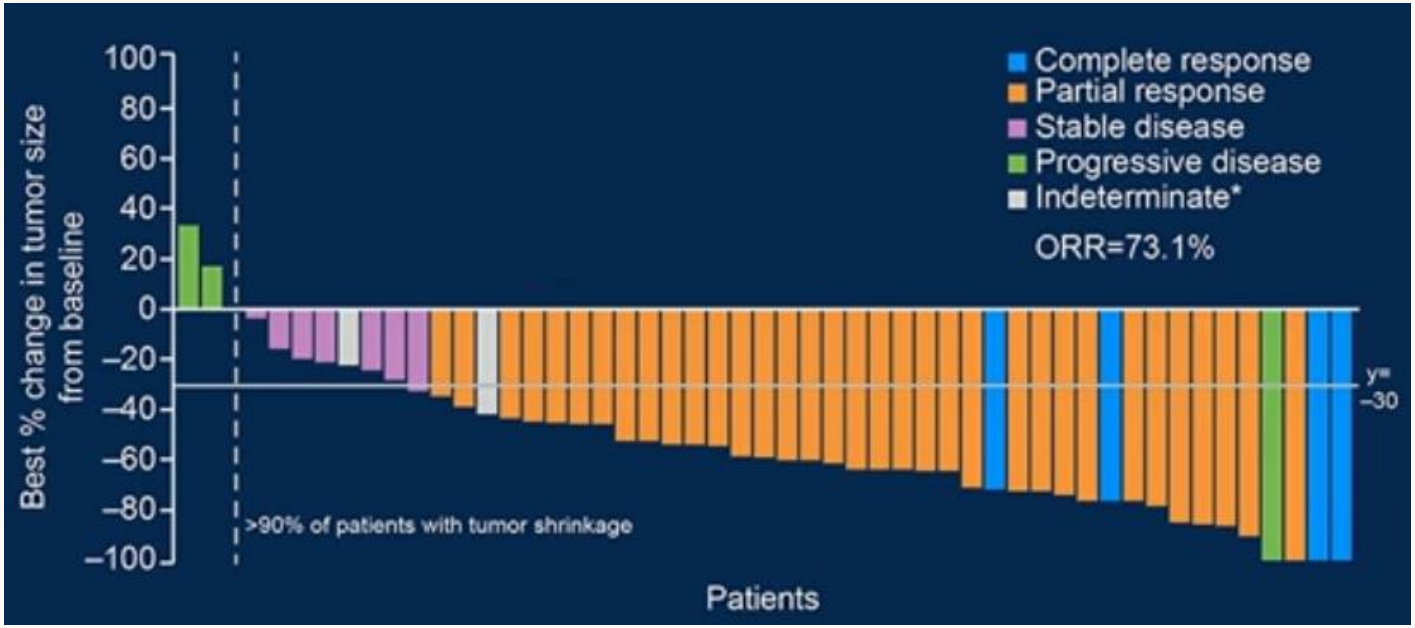
VEGFR-TKI + Anti PD-1: Axitinib + Pembrolizumab: Efficacy[1]

Best Overall Response, n (%)	(N=52)
Complete response (CR)	4 (7.7)
Partial response (PR)	34 (65.4)
Stable disease	8 (15.4)
Progressive disease	3 (5.8)
Indeterminate*	3 (5.8)
ORR (CR+PR)	38 (73.1)
95% Exact CI	59.0–84.4



J Clin Oncol 36, 2018 (suppl 6S; abstr 5

Lenvatinib + Pembrolizumab in Metastatic RCC: Efficacy Outcomes

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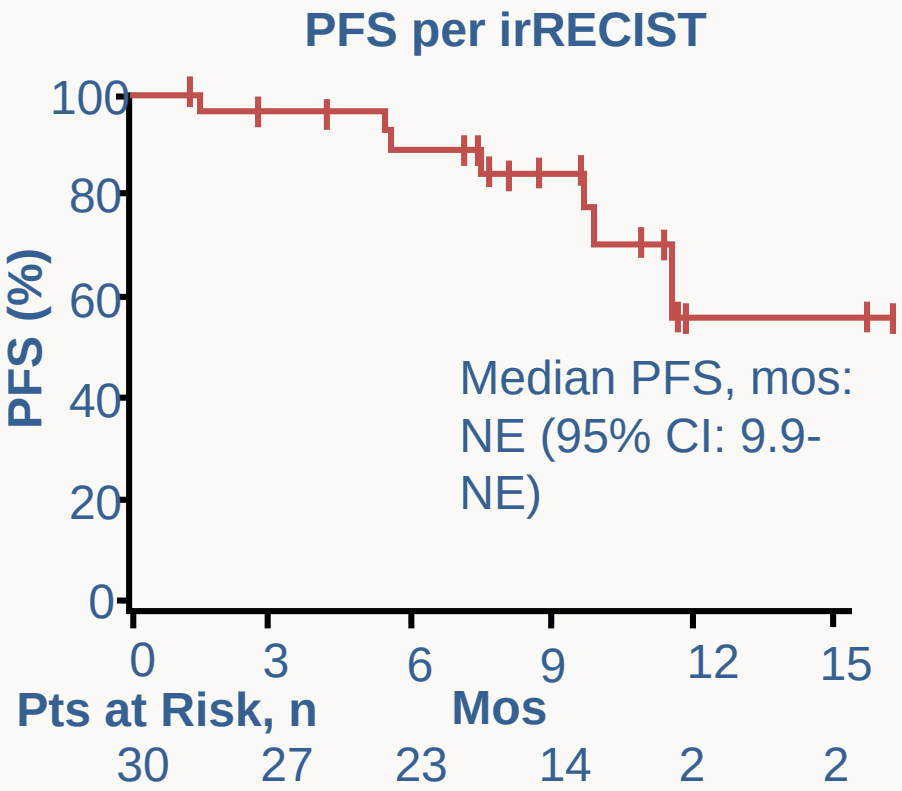
Pts	ORR at Wk 24,* n (%)
All (N = 30)	19 (63)
Treatment naive (n = 12)	10 (83)
Previously treated	
▪ 1 regimen (n = 10)	5 (50)
▪ ≥ 2 regimens (n = 8)	4 (50)
PD-L1 status	
▪ Positive (n = 12)	7 (58)
▪ Negative (n = 14)	10 (71)
▪ Unknown (n = 4)	2 (50)

*All PR per irRECIST.



Lee C, et al. ESMO 2017. Abstract 847O.

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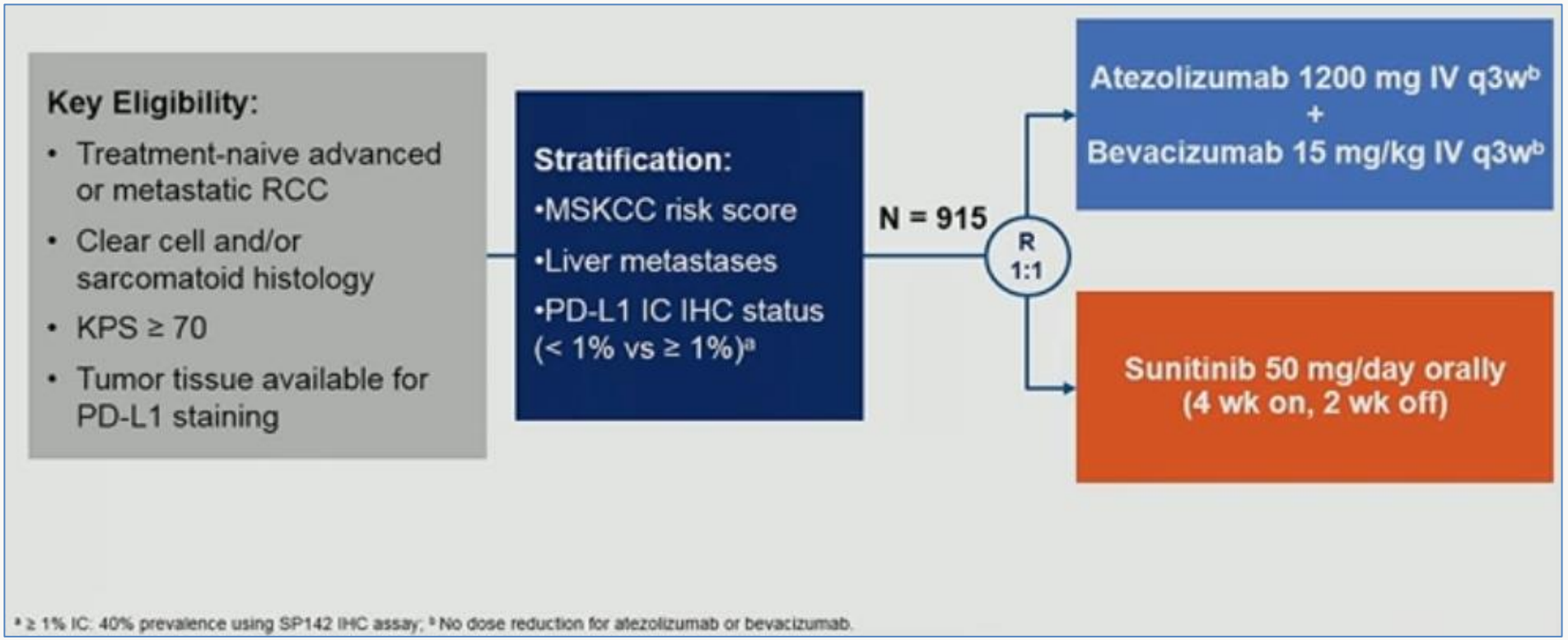
Immotion 151



J Clin Oncol 36, 2018 (suppl 6S; abstr 578

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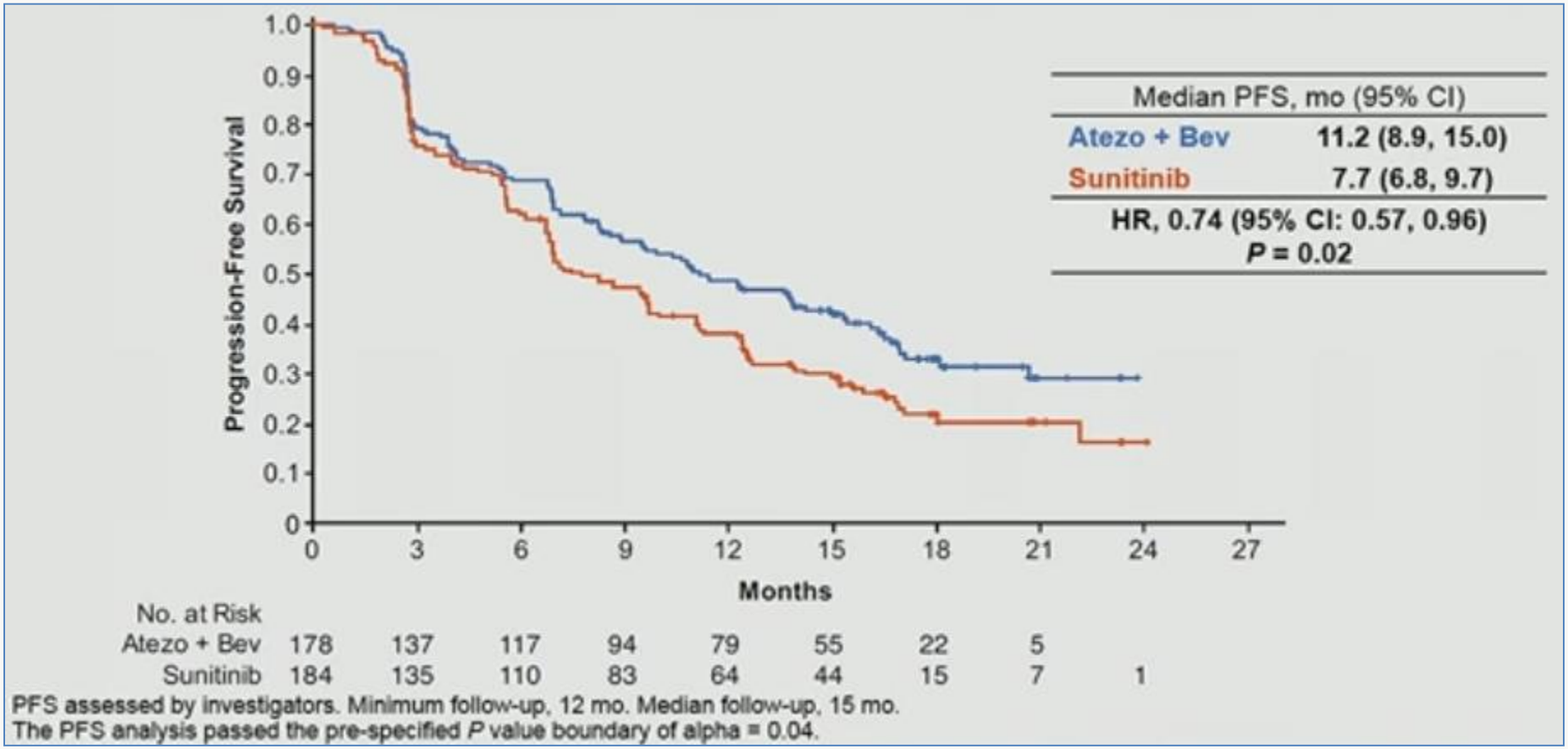
Progression Free Survival in PD-L1 +



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.

J Clin Oncol 36, 2018 (suppl 6S; abstr 578

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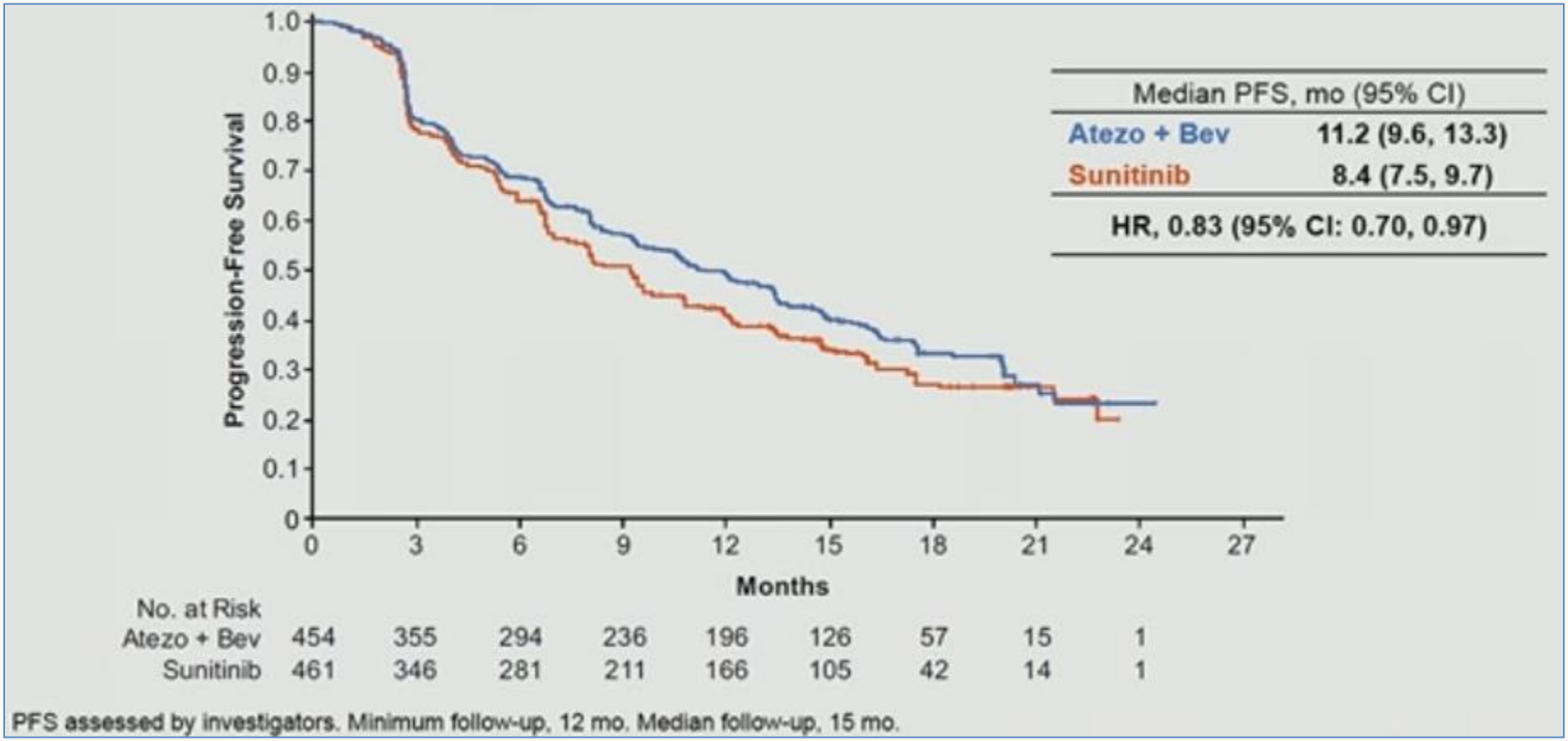
Progression Free Survival in ITT



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

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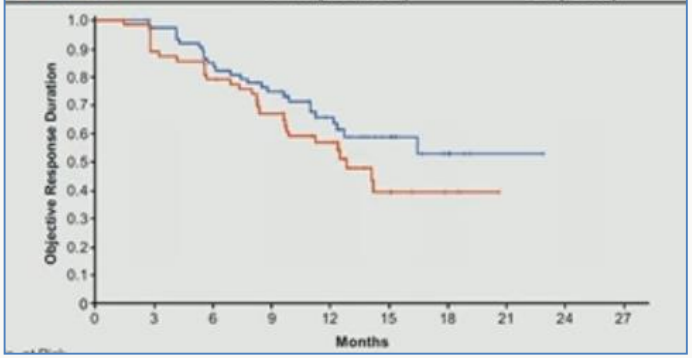
Objective Response Rate and DoR

	PD-L1+		ITT	
	Atezo + Bev n = 178	Sunitinib n = 184	Atezo + Bev n = 454	Sunitinib n = 460
Confirmed ORR, % 95% CI	43% (35, 50)	35% (28, 42)	37% (32, 41)	33% (29, 38)
Complete response	9%	4%	5%	2%
Partial response	34%	30%	31%	31%
Stable disease	32%	35%	39%	39%
Progressive disease	19%	21%	18%	19%
Not evaluable[a]	7%	10%	7%	9%

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%)



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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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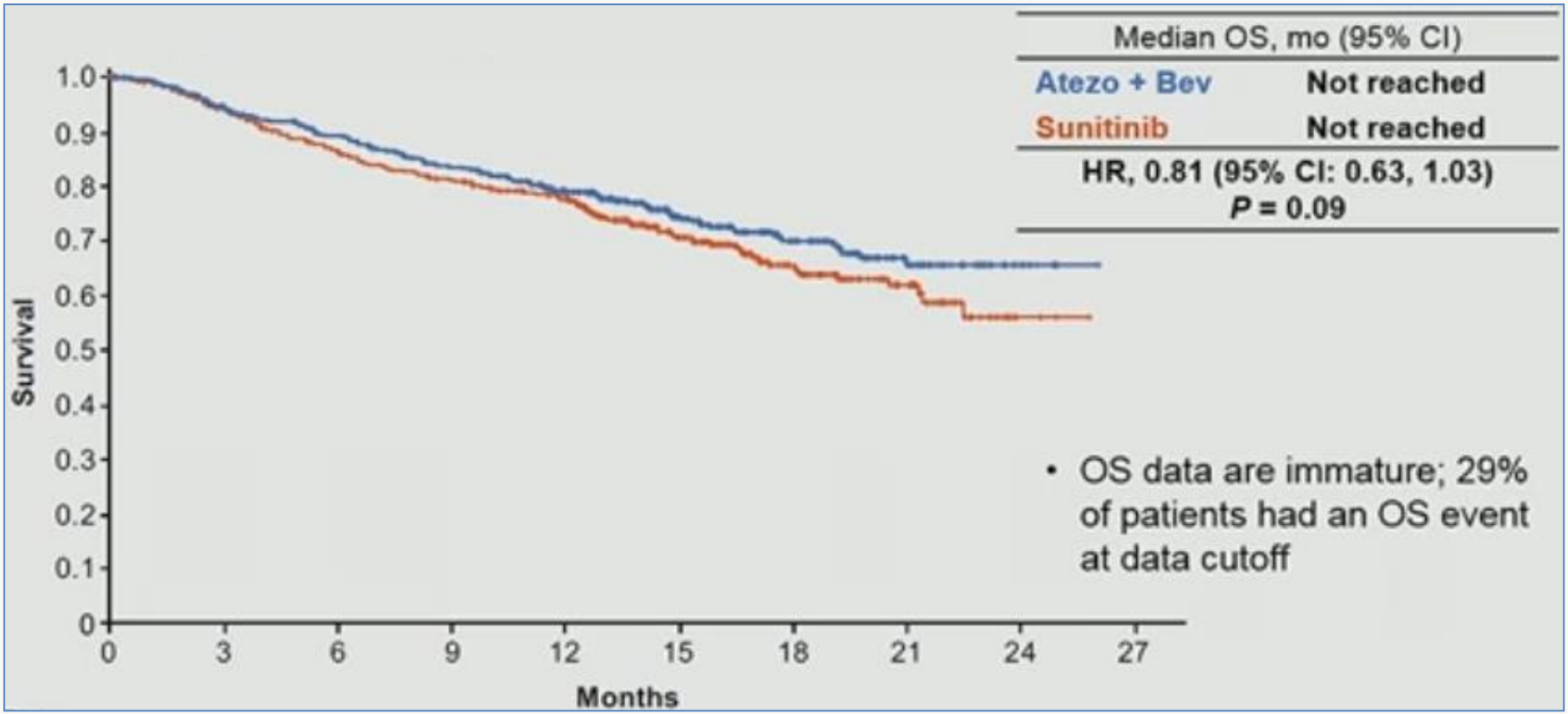
Overall Survival in ITT



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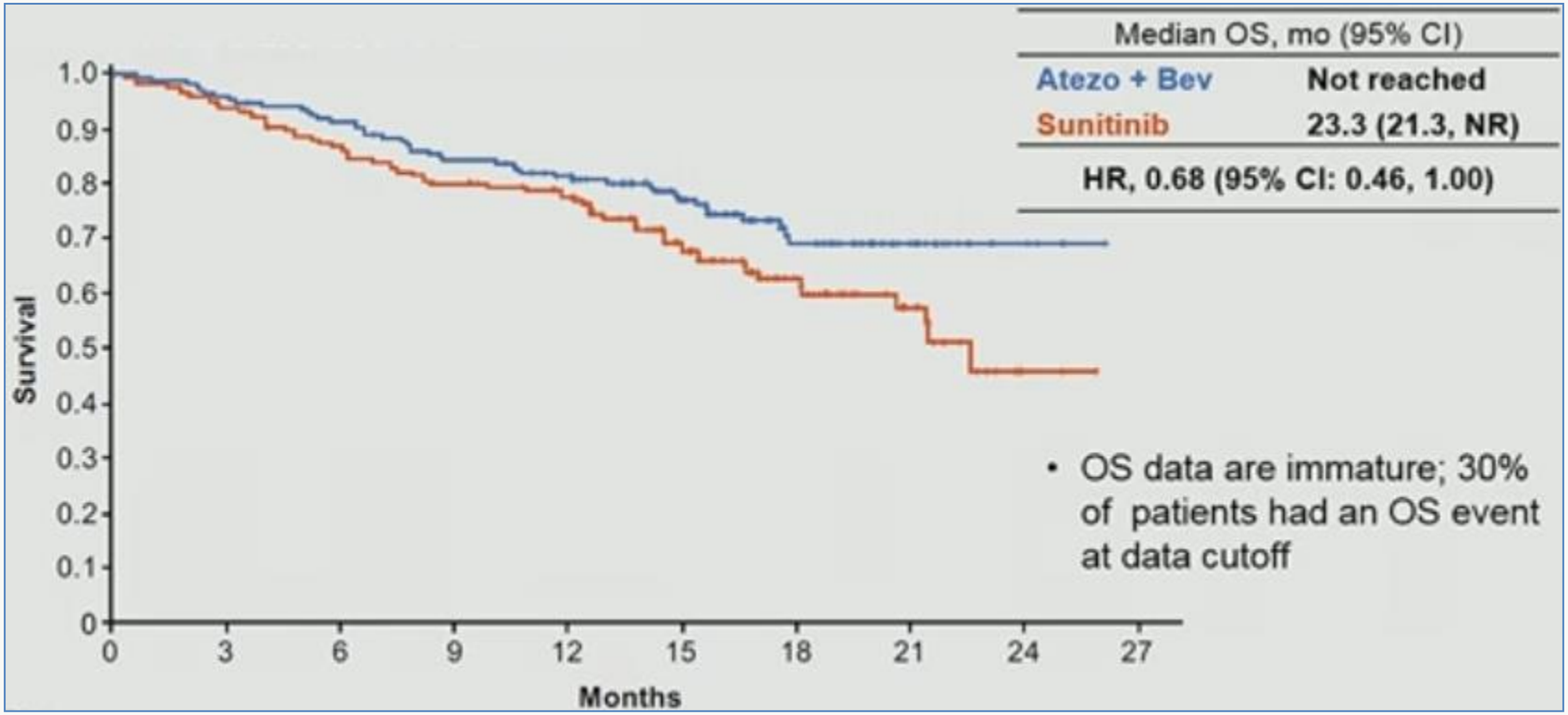
Overall Survival in PD-L1 +



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Safety Profile

All treated	Atezo + Bev n = 451	Sunitinib n = 446
Median treatment duration (range), mo	12.0 (0-26.2)	9.2 (0-26.6)
AEs, % Grade 3-4, %	91% 40%	96% 54%
AEs leading to discontinuation of treatment regimen, %	5%	8%
AEs leading to discontinuation of any treatment component, %[a]	12%	8%
Deaths, n	5[b]	1[c]

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First Line Phase 3 Trials in Advanced RCC[1]

Control Arm	Experimental Arm	Primary Endpoint	Estimated N	Trial	ClinicalTrials.gov No.
Sunitinib	Axitinib + Avelumab	PFS	583	JAVELIN Renal 101	NCT02684006
Sunitinib	Axitinib + Pembrolizumab	PFS, OS	840	KEYNOTE-426	NCT02853331
Sunitinib	Bevacizumab + Atezolizumab	PFS, OS in PD-L1–detectable tumors	900	IMmotion151	NCT02420821
Sunitinib	Nivolumab + Ipilumab	PFS, OS	1,070	CheckMate 214	NCT02231749
Sunitinib	Sunitinib + AGS-003	OS	450	ADAPT	NCT01582672
Sunitinib	Lenvatinib-Pembrolizumab or Lenvatinib-Everolimus	PFS	735	CLEAR	NCT02811861

1. Choueiri TK and Motzer R. *N Engl J Med.* 2017;376:354-366.

THANK YOU

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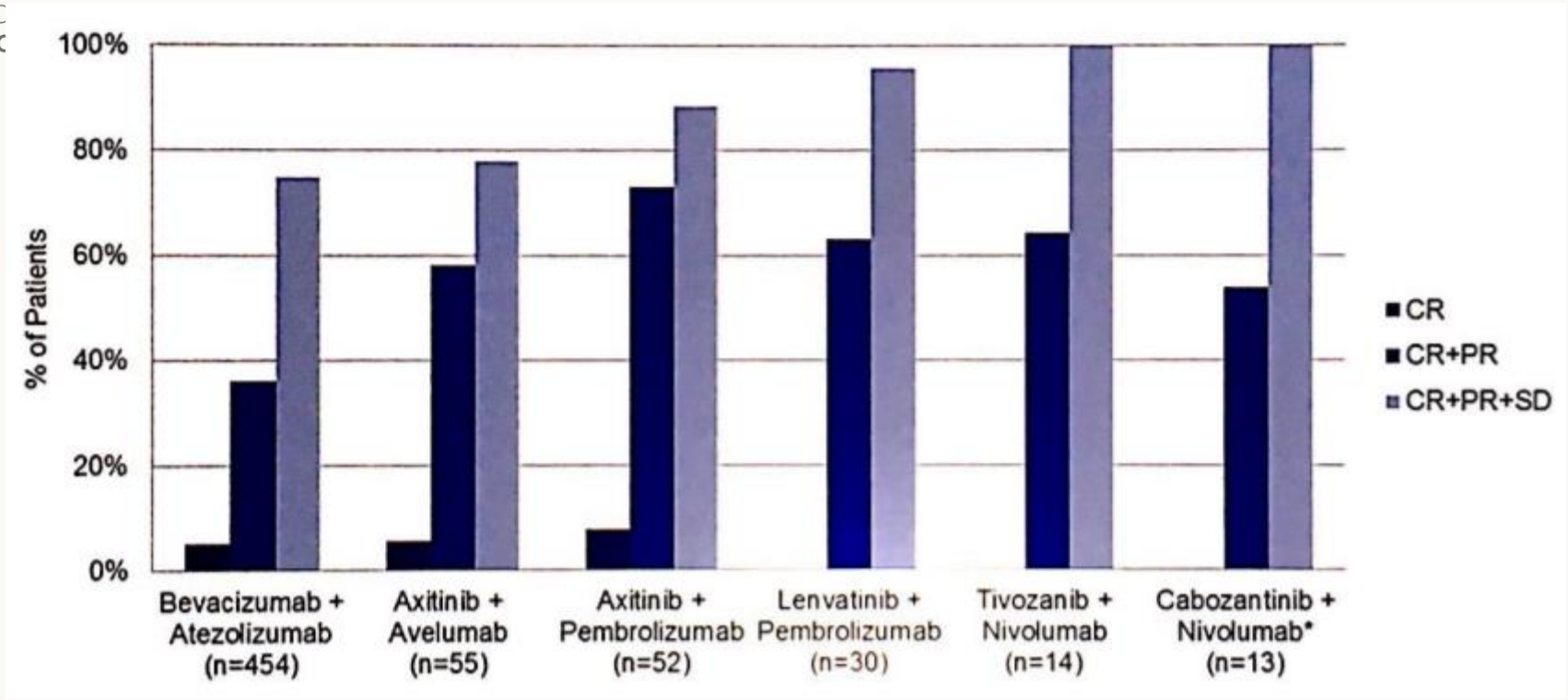

Motzer et al ASCO GU 2018; Lee et al ESMO 2017; Choueiri et al ASCO 2017, Atkins et al ASCO GU 2018, Nadal et al ASCO GU 2018