First-Line Immunotherapy in the management of RCC

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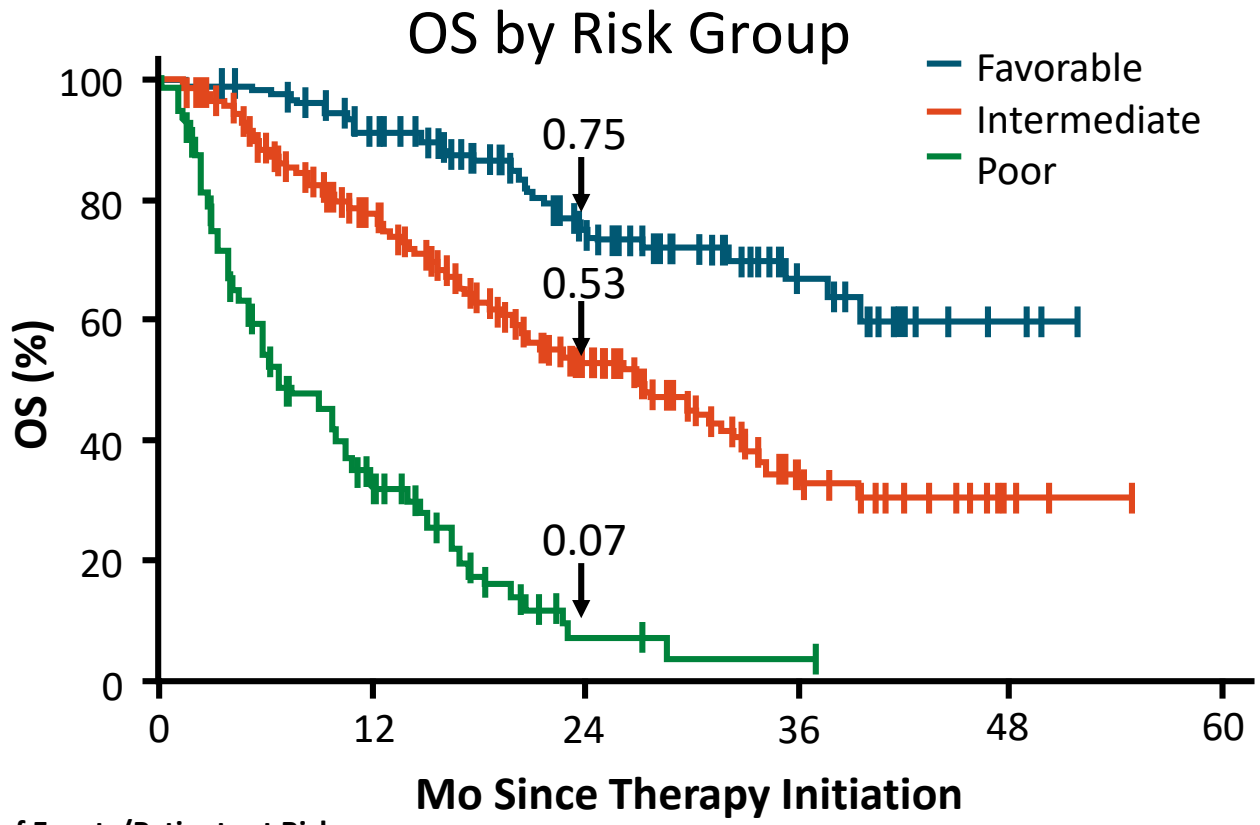
Medanta, Patna

Understanding the Role of Risk in the Treatment of Metastatic RCC

IMDC Criteria for Metastatic RCC
Karnofsky performance score <80%
Time from initial diagnosis to targeted Tx <1 yr
Hemoglobin < LLN
Calcium > ULN
Platelet count > ULN
Neutrophil count > ULN

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

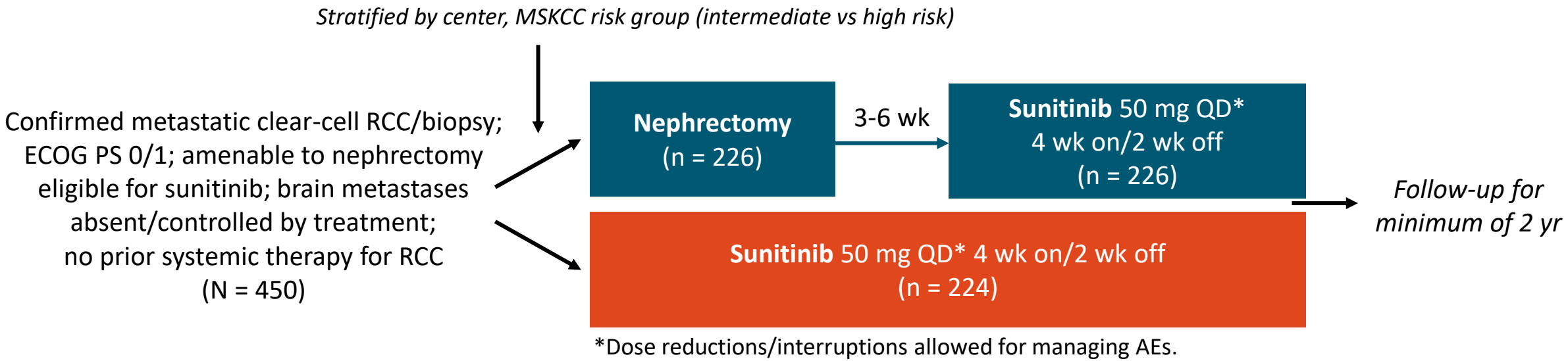
75% to 80% of patients with metastatic RCC are poor or intermediate risk



Heng. J Clin Oncol. 2009;27:5794.

CARMENA: Prospective, Multicenter, Open-Label, Randomized Phase III Noninferiority Study

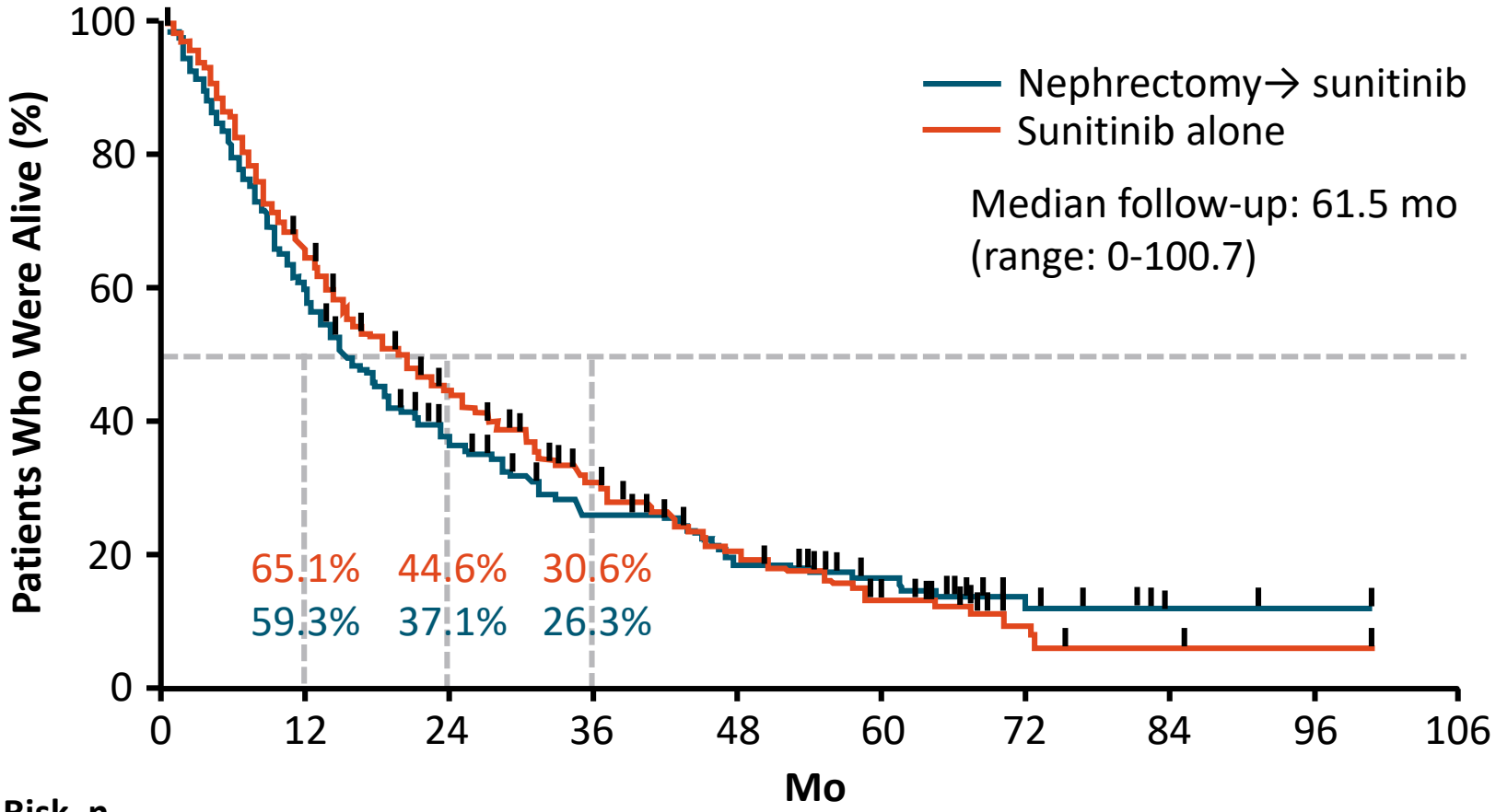
- Multicenter, randomized, open-label noninferiority phase III trial



- Primary endpoint: OS
- Secondary endpoints: PFS, ORR (RECIST v1.1), clinical benefit, safety

Méjean. ASCO 2018. Abstr LBA3. Méjean. NEJM. 2018;379:417.

CARMENA: Overall Survival (ITT)

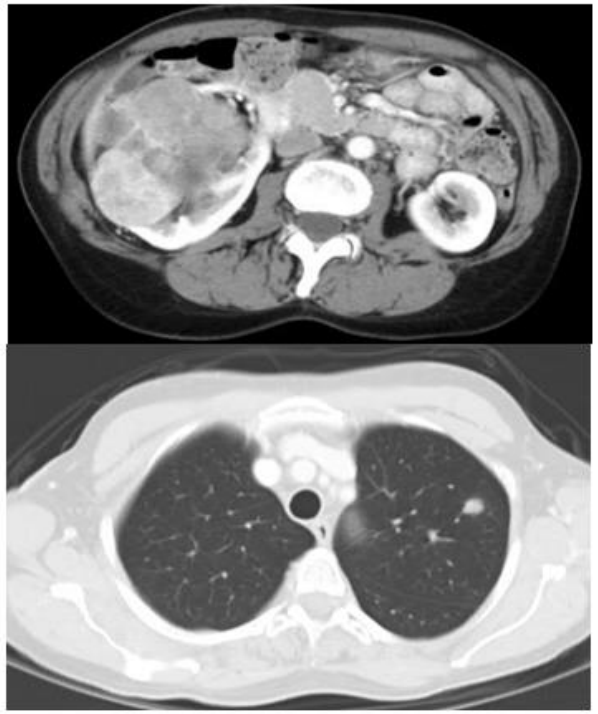


Patients at Risk, n										
Nephrectomy→ sunitinib	226	132	74	47	30	18	8	2	1	0
Sunitinib alone	224	144	90	51	29	16	5	2	1	0

Méjean. ASCO 2019. Abstr 4508.

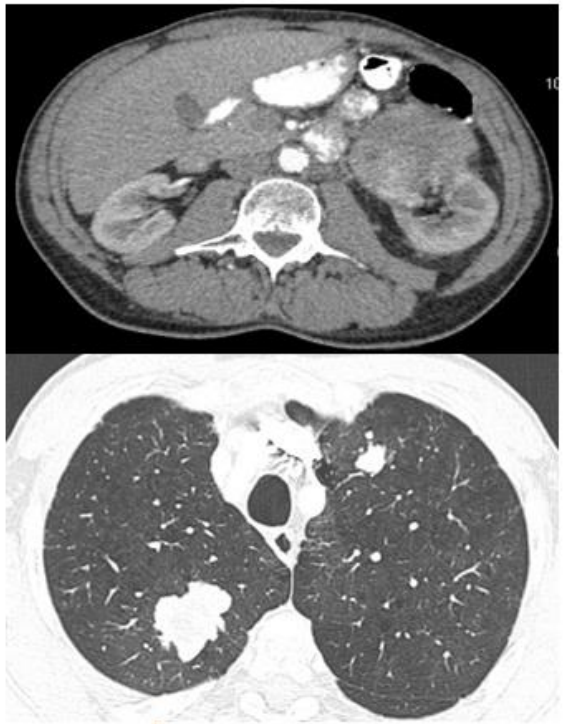
Considerations for Nephrectomy

PS 0
Minimal extrarenal disease



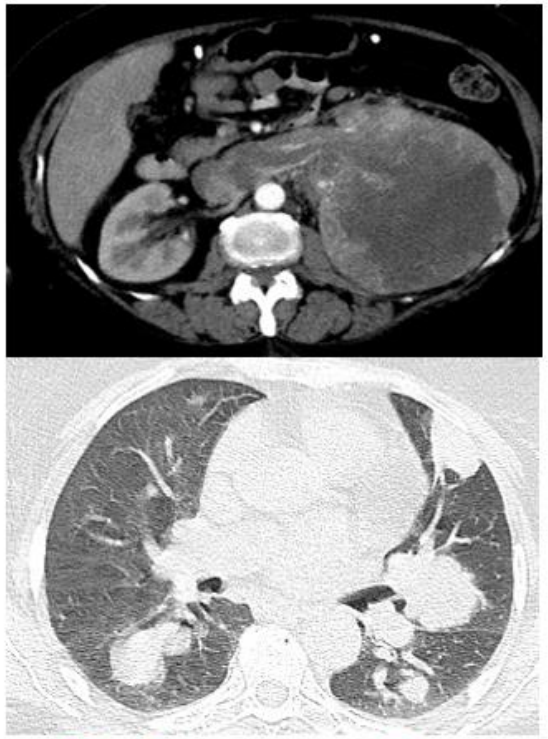
Nephrectomy makes sense

PS 0/1
Intermediate risk
Moderate extrarenal disease



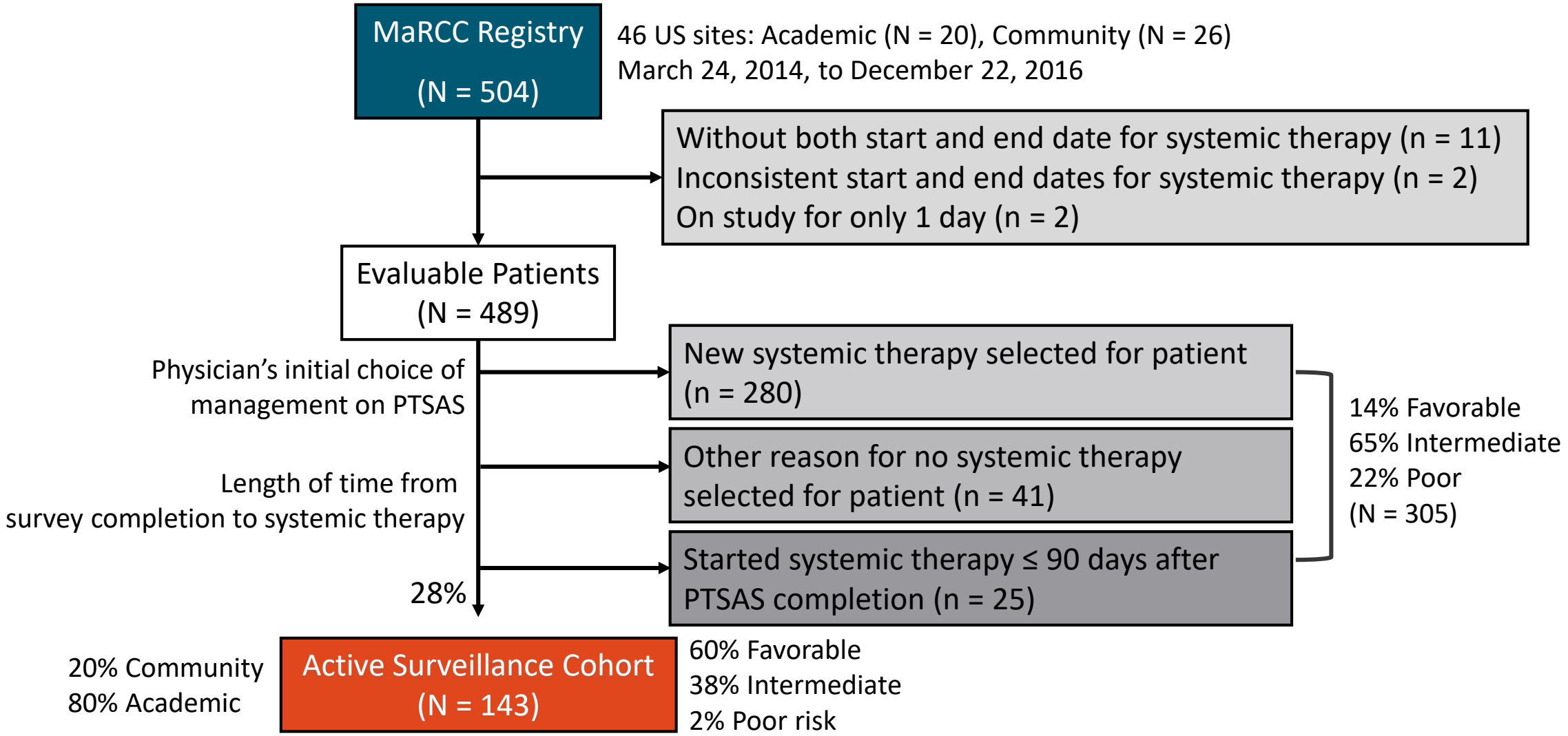
Nephrectomy may or may not be indicated

Poor PS, poor risk
Large primary
Extensive extrarenal disease



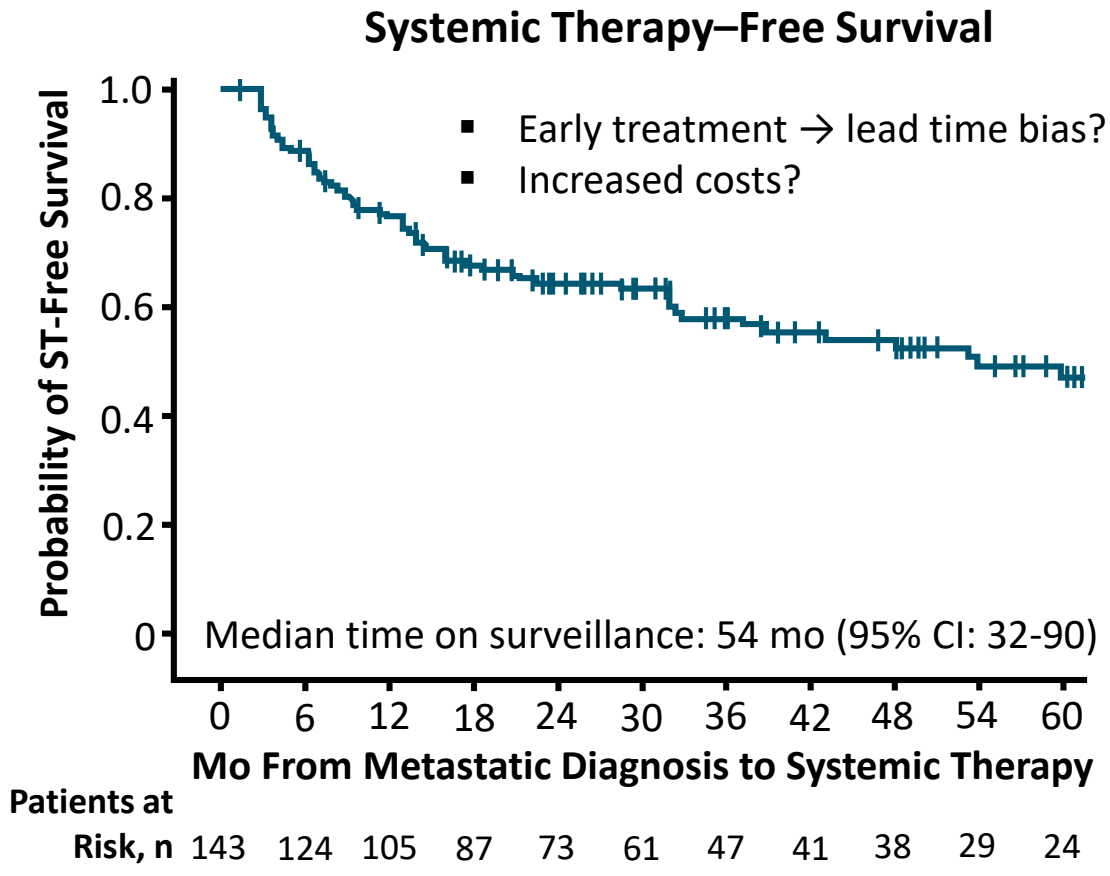
Nephrectomy does not make sense

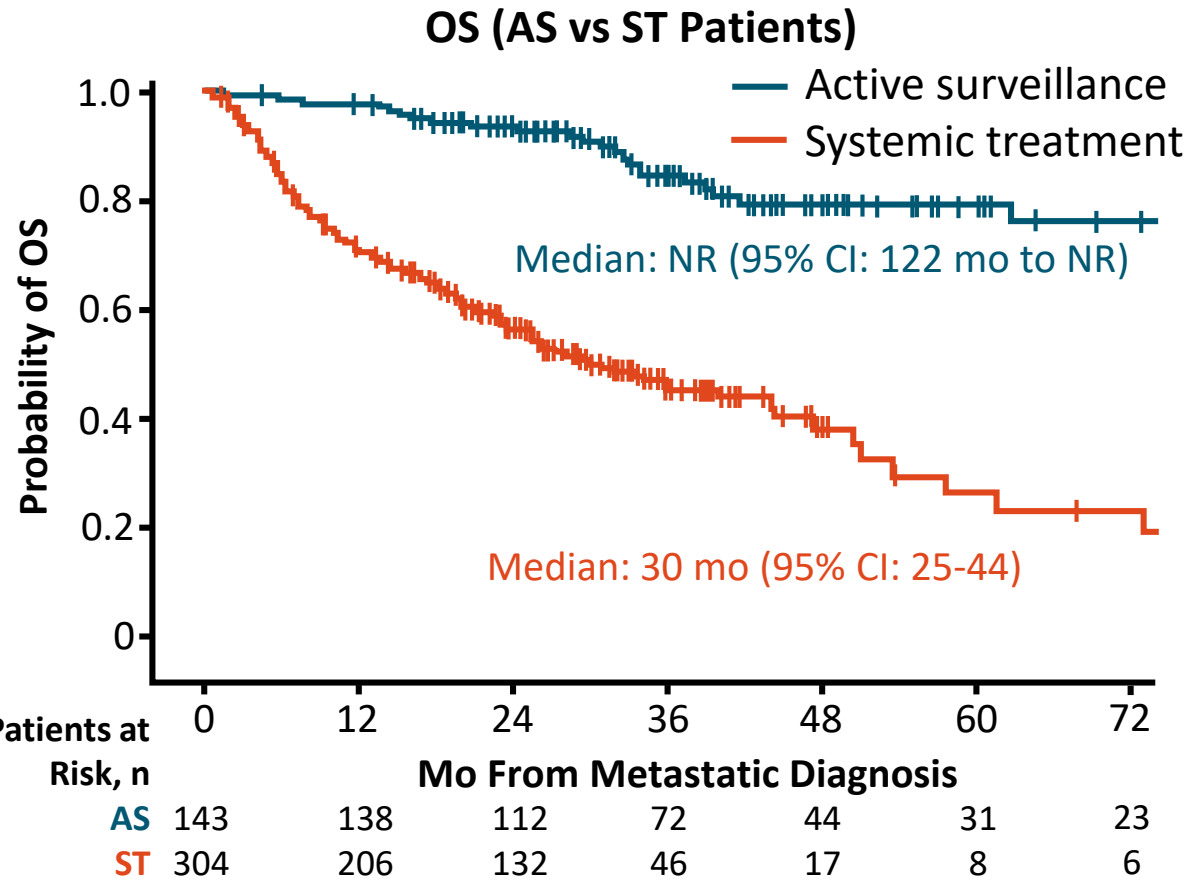
MaRCC Registry: Prospective Observational Registry Data



Harrison. Cancer. 2021;127:2204.

Prospective Observational Registry Data





- Suggests clinicians were able to select patients for active surveillance with very good results based on their clinical judgment and/or intuitive sense

Harrison. Cancer. 2021;127:2204.

NCCN Guidelines Version 4.2022
Kidney Cancer

PRINCIPLES OF SYSTEMIC THERAPY FOR RELAPSE OR STAGE IV DISEASE

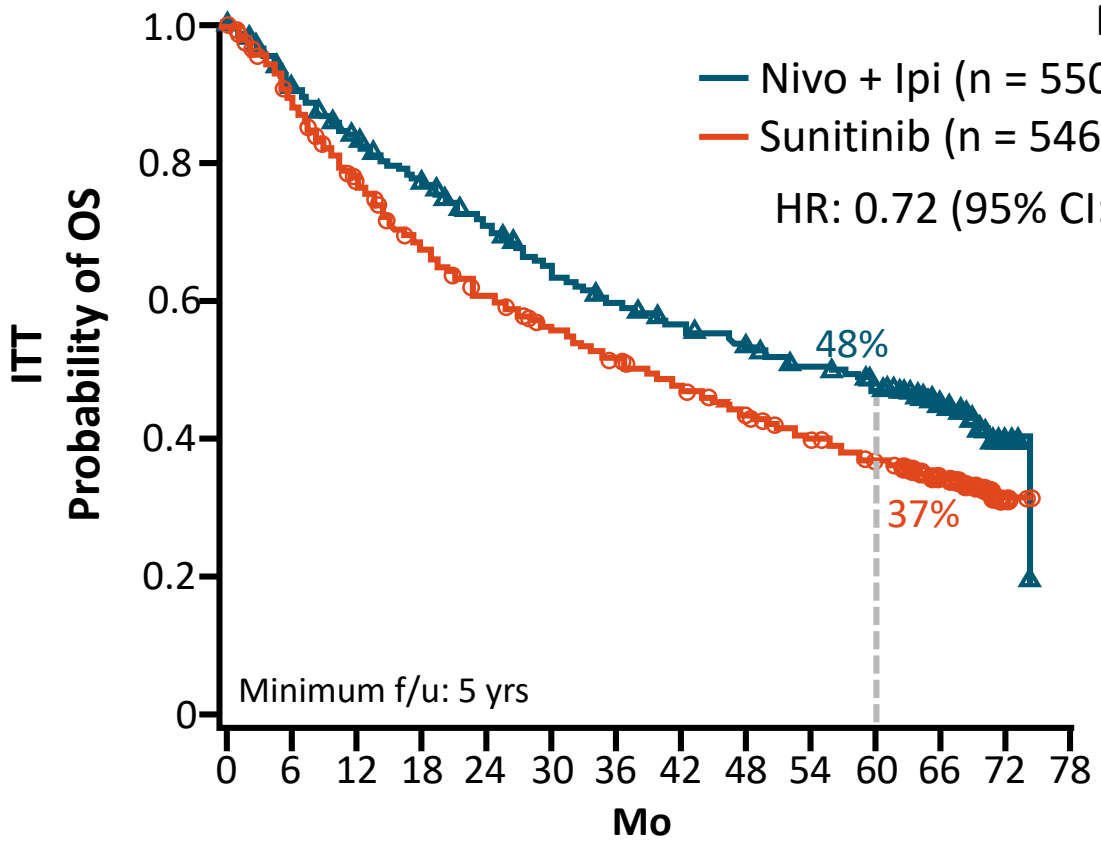
FIRST-LINE THERAPY FOR CLEAR CELL HISTOLOGY

Risk	Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
Favorable[a]	• Axitinib + pembrolizumab[b] (category 1) • Cabozantinib + nivolumab[b] (category 1) • Lenvatinib + pembrolizumab[b] (category 1)	• Axitinib + avelumab[b] • Cabozantinib (category 2B) • Ipilimumab + nivolumab[b] • Pazopanib • Sunitinib	• Active surveillance[c] • Axitinib (category 2B) • High-dose IL-2[d] (category 2B)
Poor/ intermediate[a]	• Axitinib + pembrolizumab[b] (category 1) • Cabozantinib + nivolumab[b] (category 1) • Ipilimumab + nivolumab[b] (category 1) • Lenvatinib + pembrolizumab[b] (category 1) • Cabozantinib	• Axitinib + avelumab[b] • Pazopanib • Sunitinib	• Axitinib (category 2B) • High-dose IL-2[d] (category 3) • Temsirolimus[e] (category 3)

SUBSEQUENT THERAPY FOR CLEAR CELL HISTOLOGY

Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
• Cabozantinib (category 1) • Lenvatinib + everolimus (category 1) • Nivolumab[b] (category 1)	• Axitinib (category 1) • Axitinib + pembrolizumab[b] • Cabozantinib + nivolumab[b] • Ipilimumab + nivolumab[b] • Lenvatinib + pembrolizumab[b] • Pazopanib • Sunitinib • Tivozanib[g] • Axitinib + avelumab[b] (category 3)	• Everolimus • Bevacizumab[f] (category 2B) • High-dose IL-2 for selected patients[d] (category 2B) • Sorafenib (category 3) • Temsirolimus[e] (category 2B)

CheckMate 214: Nivolumab + Ipilimumab vs Sunitinib for Untreated Advanced RCC



Median OS, Mo (95% CI)

Nivo + Ipi (n = 550) 55.7 (46.3-64.6)

Sunitinib (n = 546) 38.4 (32.0-45.0)

HR: 0.72 (95% CI: 0.62-0.85; *P* <.0001)

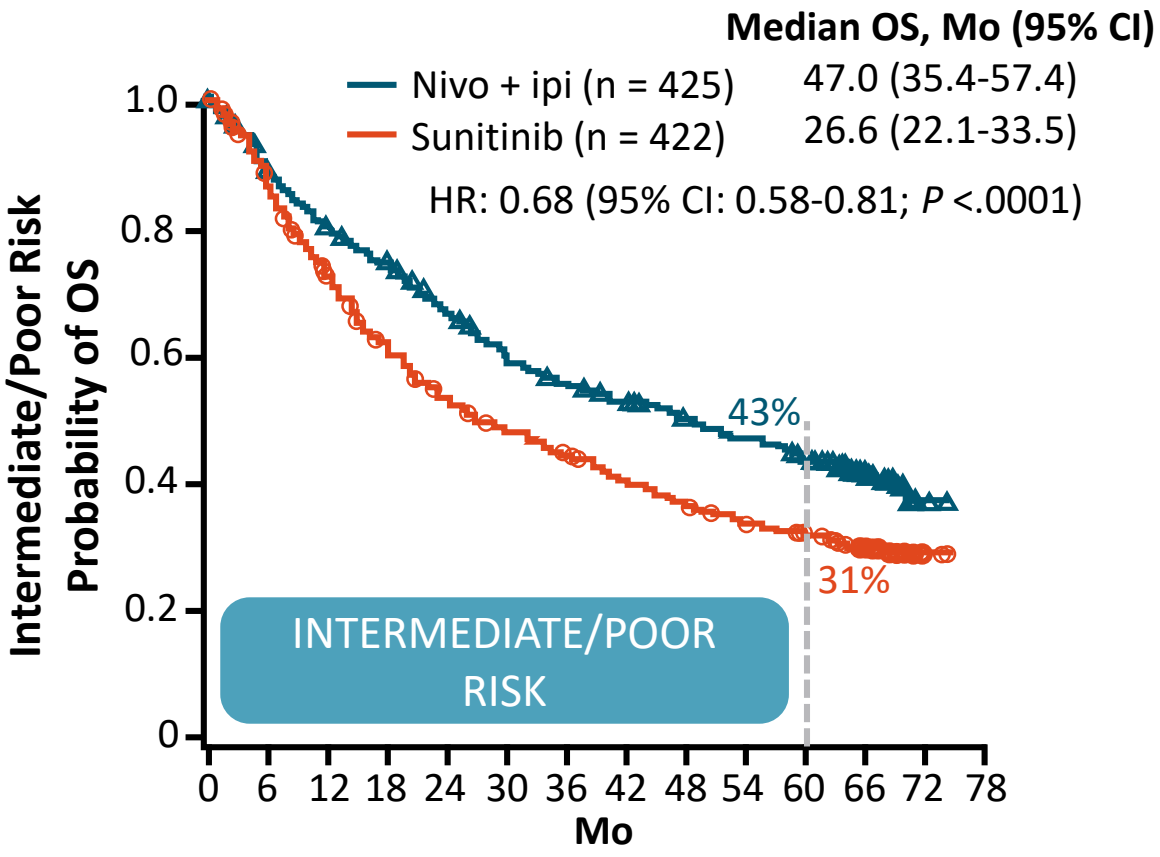
ALL RISK
INTENTION TO TREAT

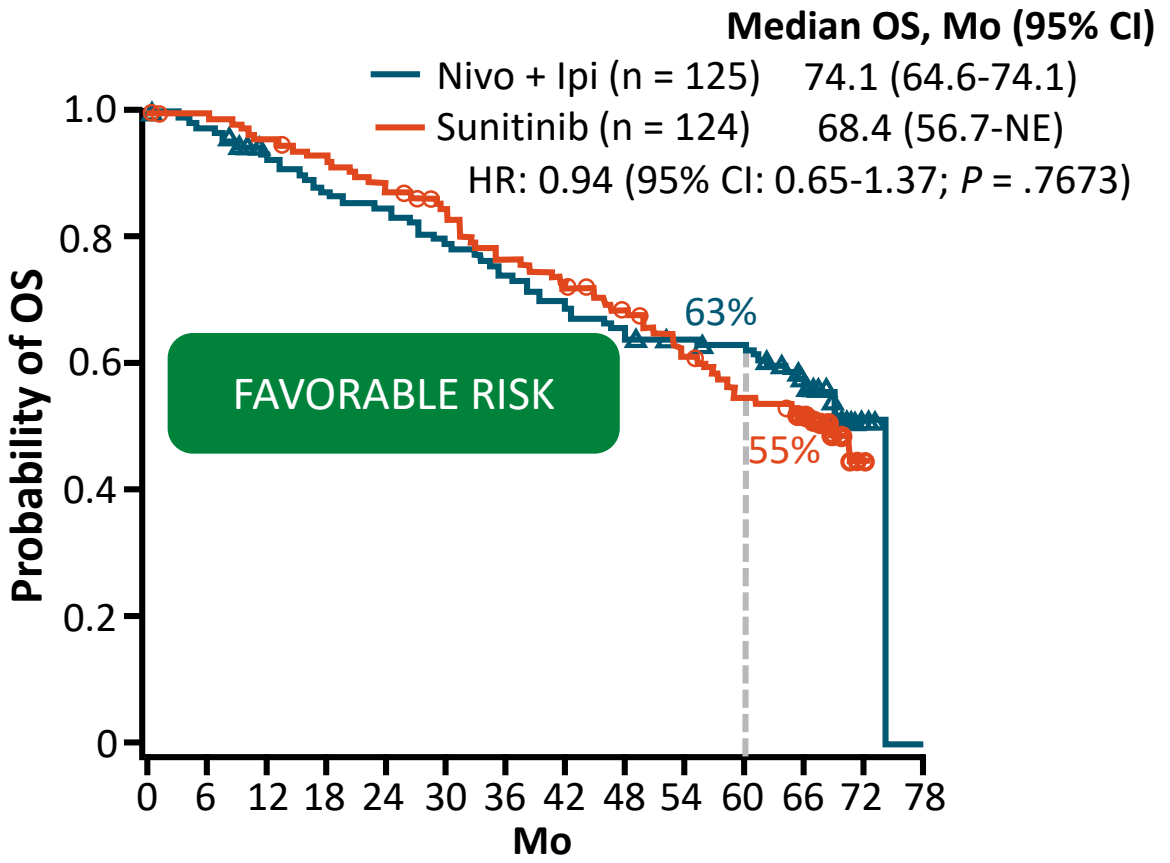
Patients at Risk, n

Nivo + Ipi	550	493	444	411	372	337	309	291	274	256	236	138	5	0
Sunitinib	546	472	405	347	310	281	257	234	213	192	171	108	6	0

Motzer. ESMO 2021. Abstr 661P.

CheckMate 214: Nivolumab + Ipilimumab vs Sunitinib for Untreated Advanced RCC





Patients at Risk, n

Nivo + Ipi	425	372	332	306	270	241	220	207	196	181	163	79	2	0
Sunitinib	422	353	291	237	206	184	169	151	137	125	112	58	3	0

Patients at Risk, n

Nivo + Ipi	125	121	112	105	102	96	89	84	78	75	73	59	3	0
Sunitinib	124	119	114	110	104	97	88	83	76	67	59	50	3	0

Minimum f/u: 5 yrs

Motzer. ESMO 2021. Abstr 661P.

Study Design and Endpoints

TITAN

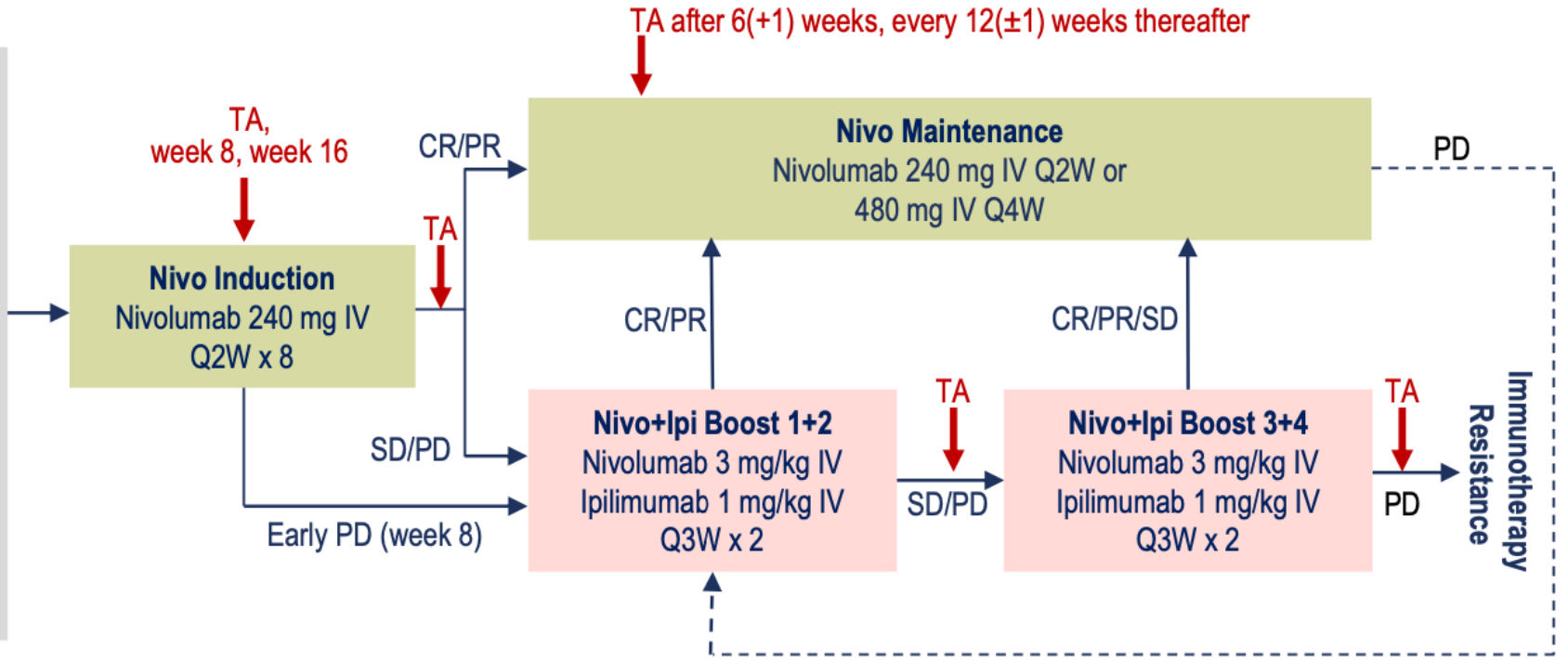
Tailored ImmunoTherapy Approach with Nivolumab in RCC (TITAN-RCC)

n=207

Key Inclusion Criteria

- Metastatic/locally advanced RCC, histologically confirmed
- Clear cell component
- Intermediate/high risk by IMDC
- Untreated or pretreated with 1 prior TKI (⇨ 1st or 2nd line*)
- Measurable disease as per RECIST v1.1
- KPS ≥ 70
- Evaluable tumor sample for PD-L1 expression (Dako PD-L1 IHC 28-8 pharmDx antibody, central lab)

* Statistically independent cohorts



EudraCT number: 2016-002307-26

Primary endpoint: Overall Response Rate (ORR)

Secondary endpoints: PFS, OS, RR after Nivo+Ipi "Boosts"; Safety (TRAE), QoL (FKSI-19)

Efficacy – Antitumor Activity

TITAN

Median follow-up time: 27.6 months

	1L (n=109)		2L (n=98)		Total (n=207)	
	N_{alone} [a]	N ± N+I [b]	N_{alone} [a]	N ± N+I [b]	N_{alone} [a]	N ± N+I [b]
ORR (BOR), n (%)	31 (**28**)	39 (**36**)*	18 (**18**)	31 (**32**)	49 (**24**)	70 (**34**)
Complete response, n (%)	2 (**2**)	8 (**7**)	-	6 (**6**)	2 (**1**)	14 (**7**)
Partial response, n (%)	29 (**27**)	31 (**28**)	18 (**18**)	25 (**26**)	47 (**23**)	56 (**27**)
Stable disease, n (%)	29 (**27**)	30 (**28**)	23 (**23**)	23 (**23**)	52 (**25**)	53 (**26**)
Progressive disease, n (%)	13 (**12**)	38 (**35**)	18 (**18**)	42 (**43**)	31 (**15**)	80 (**39**)
Early Progressive disease / 'Boost' Week 8, n (%)	22 (**20**)	-	27 (**28**)	-	49 (**24**)	-
Not evaluable [c], n (%)	14 (**13**)	2 (**2**)	12 (**12**)	2 (**2**)	26 (**13**)	4 (**2**)

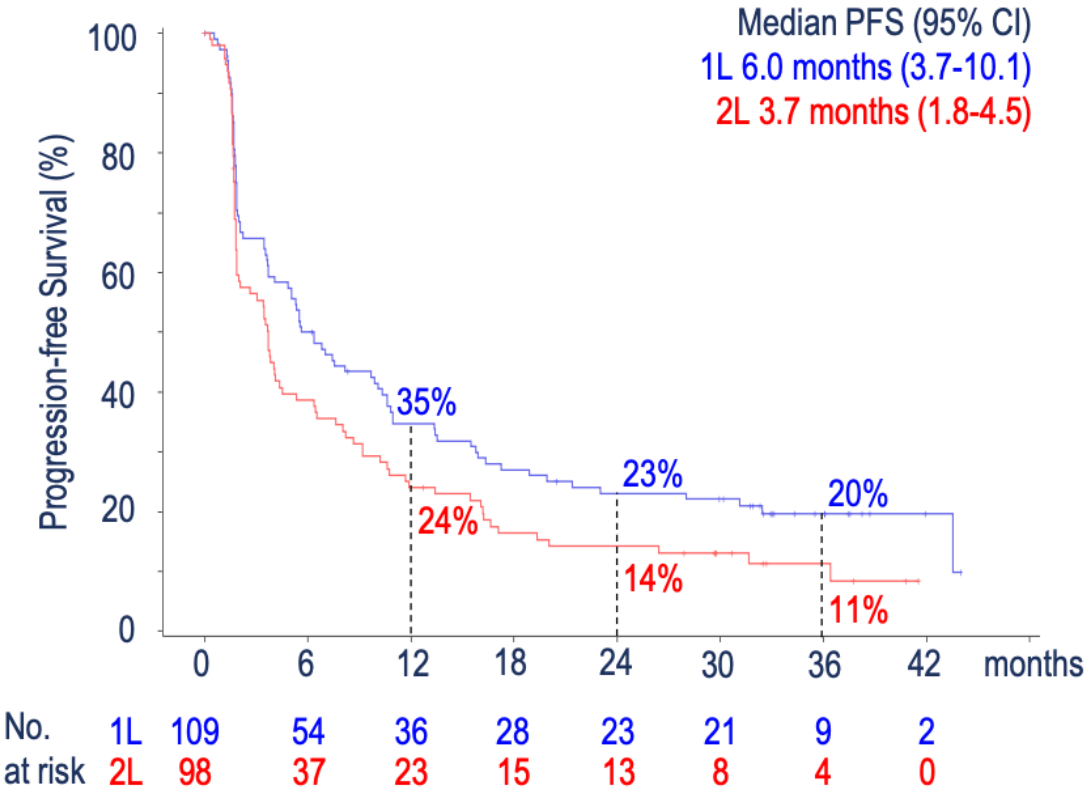
- 67% of all patients (139/207) received at least one ‚boost' cycle

N, Nivolumab; I, Ipilimumab; [a] confirmed overall assessment at week 16; [b] BOR, Best Overall Response; [c] i.e. including patients with early end of study, e.g. due to death or due to treatment-related adverse event (trAE); * significantly better than pre-specified (ORR >25%): *P*=.008 (one-sided).

Progression-free and Overall Survival

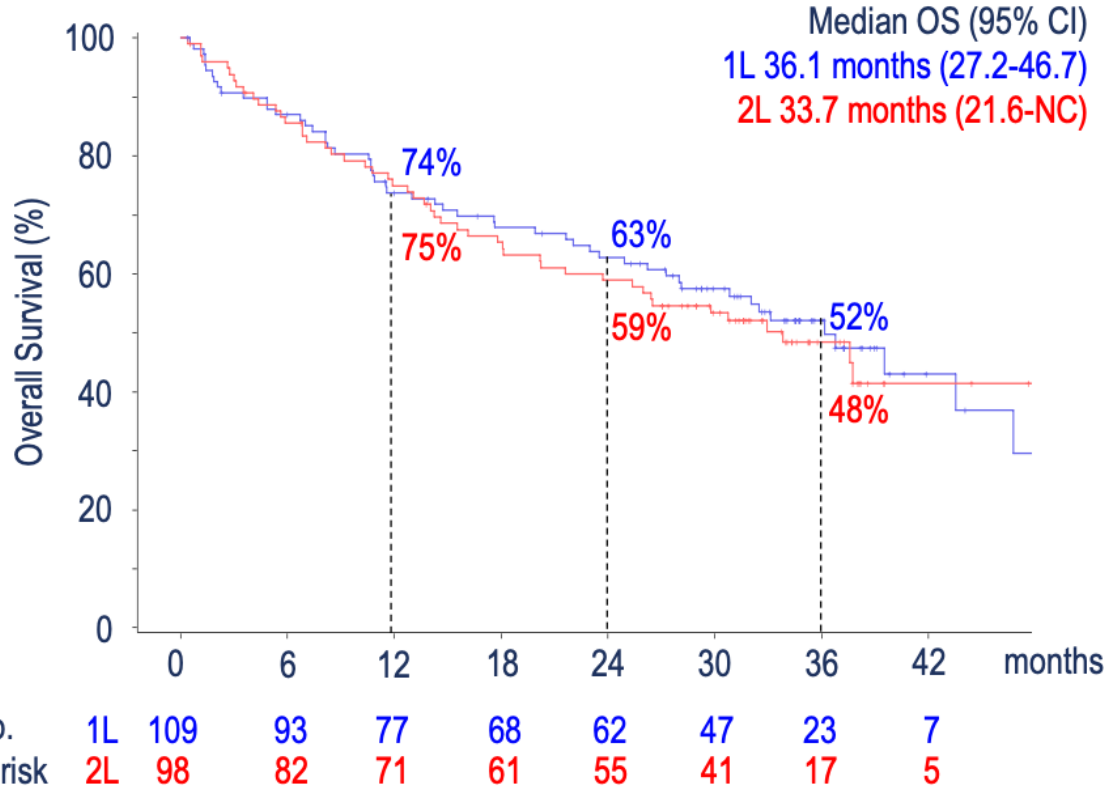
TITAN

PFS [a)]



No. at risk									
1L	109	54	36	28	23	21	9	2
2L	98	37	23	15	13	8	4	0

OS



No. at risk									
1L	109	93	77	68	62	47	23	7
2L	98	82	71	61	55	41	17	5

[a)] PFS refers to the first progression event during the course of the study. Several progression events were possible per individual subject, due to the tailored approach of TITAN-RCC.

TITAN

- TITAN-RCC provides further evidence to the added value of ipilimumab in combination with nivolumab in advanced RCC

1L

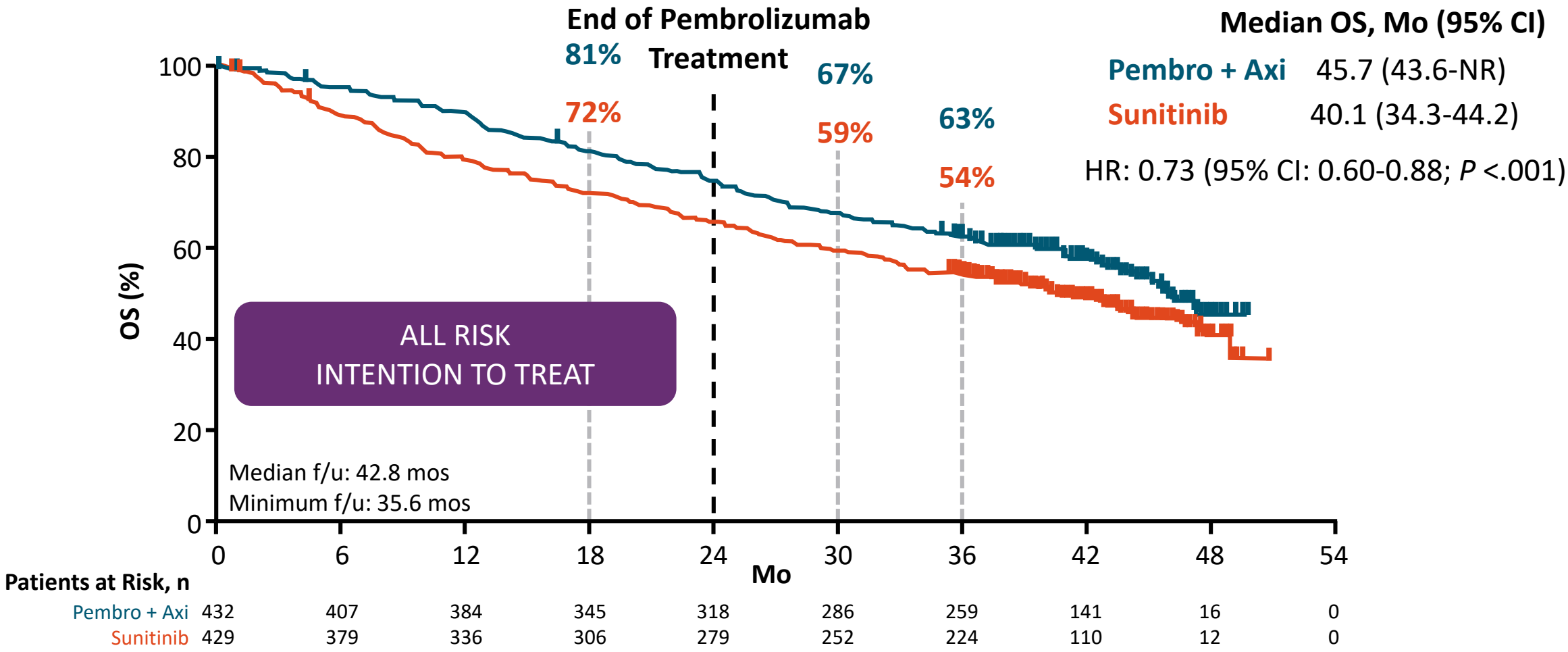
- **Boosting significantly improved ORR**
- Effectivity parameters incl. ORR, OS and PFS **suggest inferiority** of the TITAN-RCC regimen **vs.** a direct start with **nivolumab+ipilimumab (as approved)**

2L

- **Boosting numerically improved ORR**
- Effectivity parameters incl. ORR, OS and PFS **suggest superiority** of the adaptive approach of TITAN-RCC **vs. nivolumab monotherapy (as approved)**
- Upon progression after 2L nivolumab, nivolumab+ipilimumab might be considered as a rescue strategy

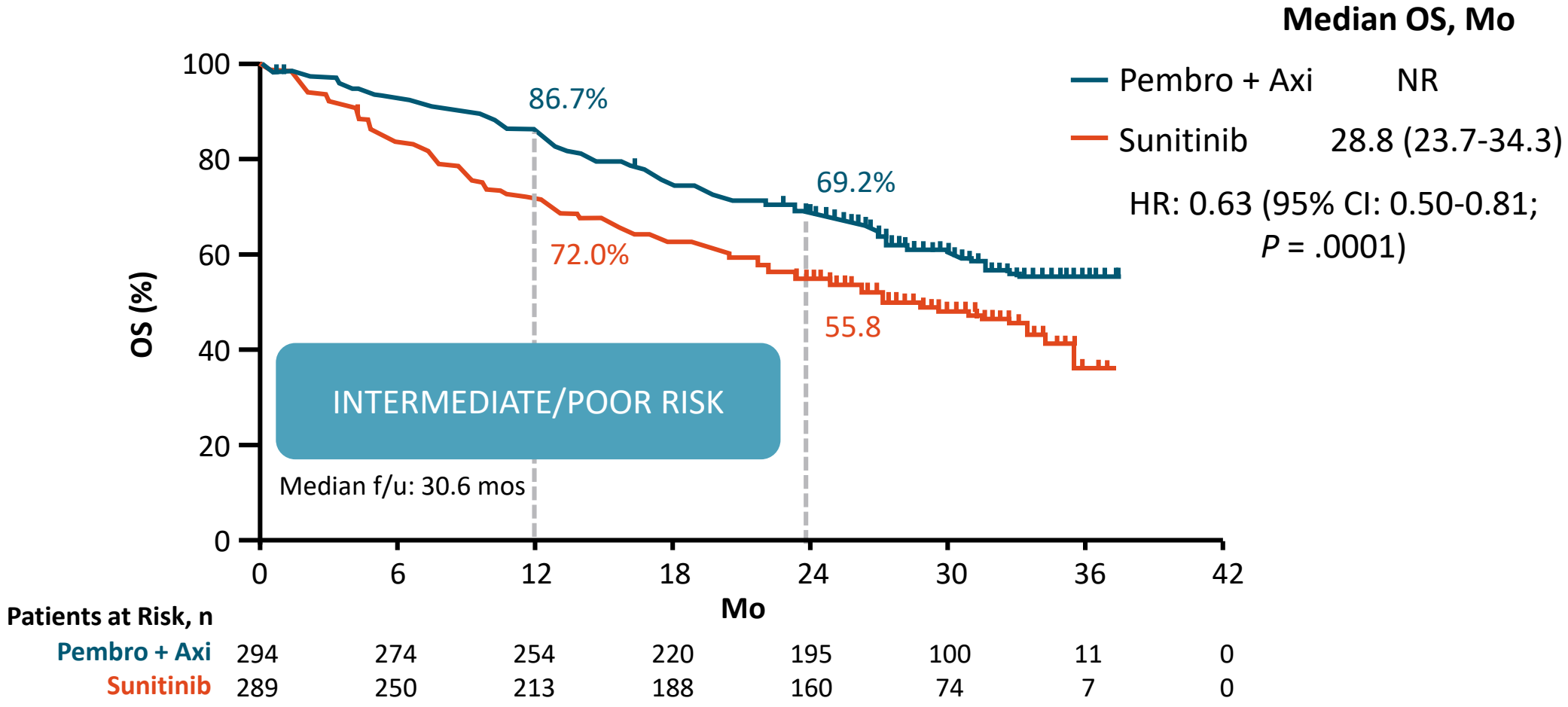
- No new safety signals were identified

KEYNOTE-426: First-line Pembrolizumab + Axitinib vs Sunitinib in Advanced or Metastatic RCC



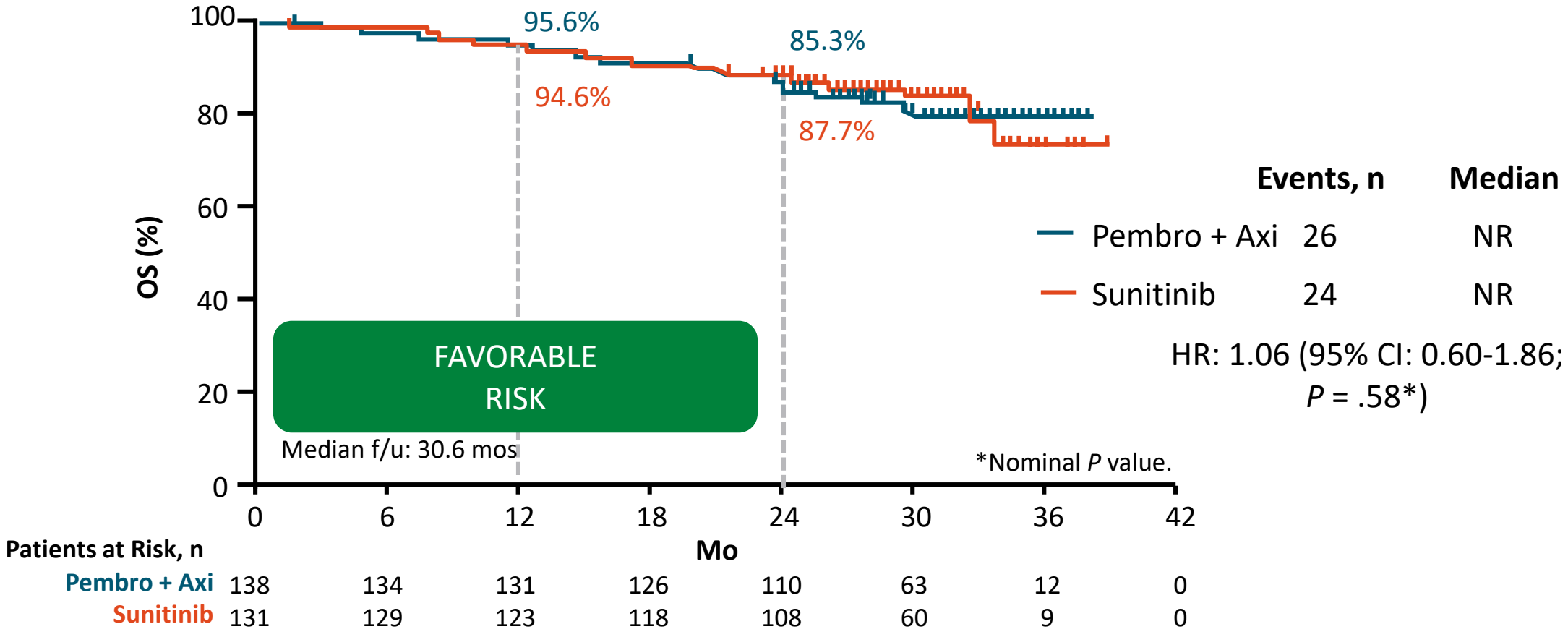
Rini. ASCO 2021. Abstr 4500.

KEYNOTE-426: First-line Pembrolizumab + Axitinib vs Sunitinib in Advanced or Metastatic RCC



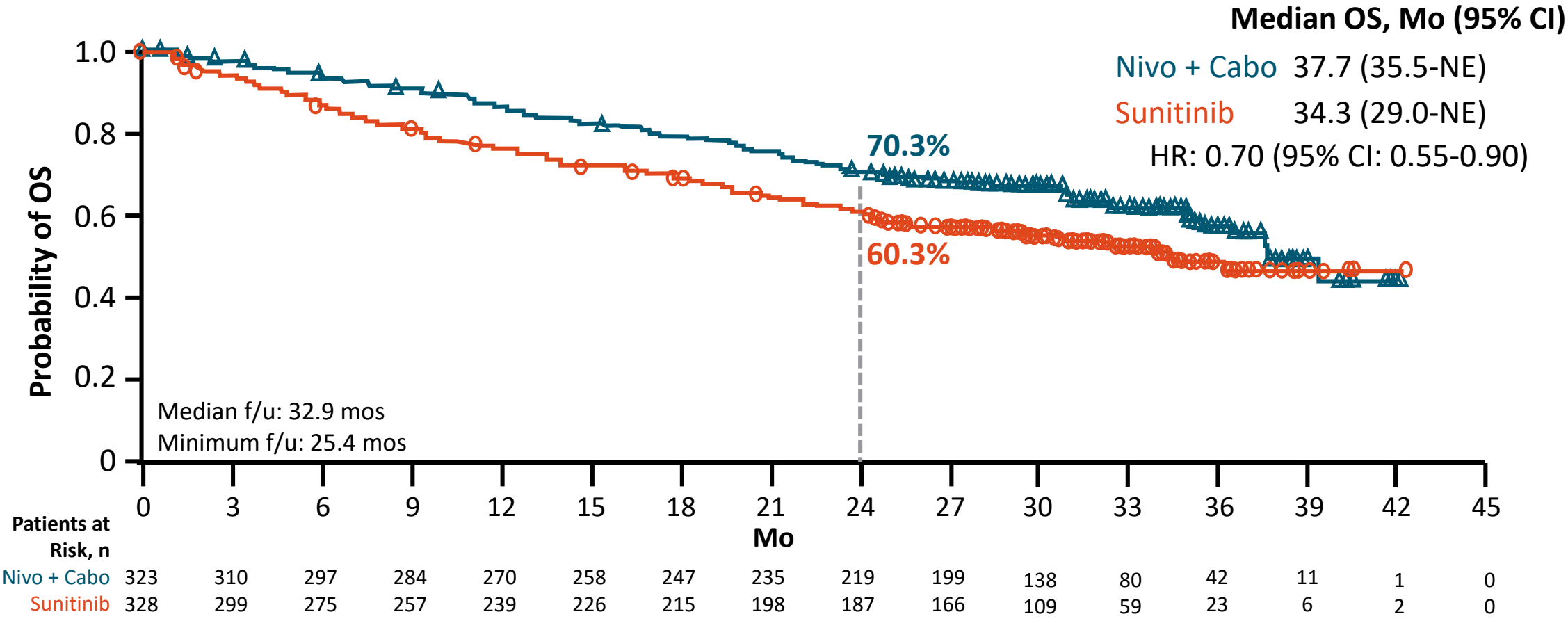
Powles. Lancet Oncol. 2020;21:1563.

KEYNOTE-426: First-line Pembrolizumab + Axitinib vs Sunitinib in Advanced or Metastatic RCC



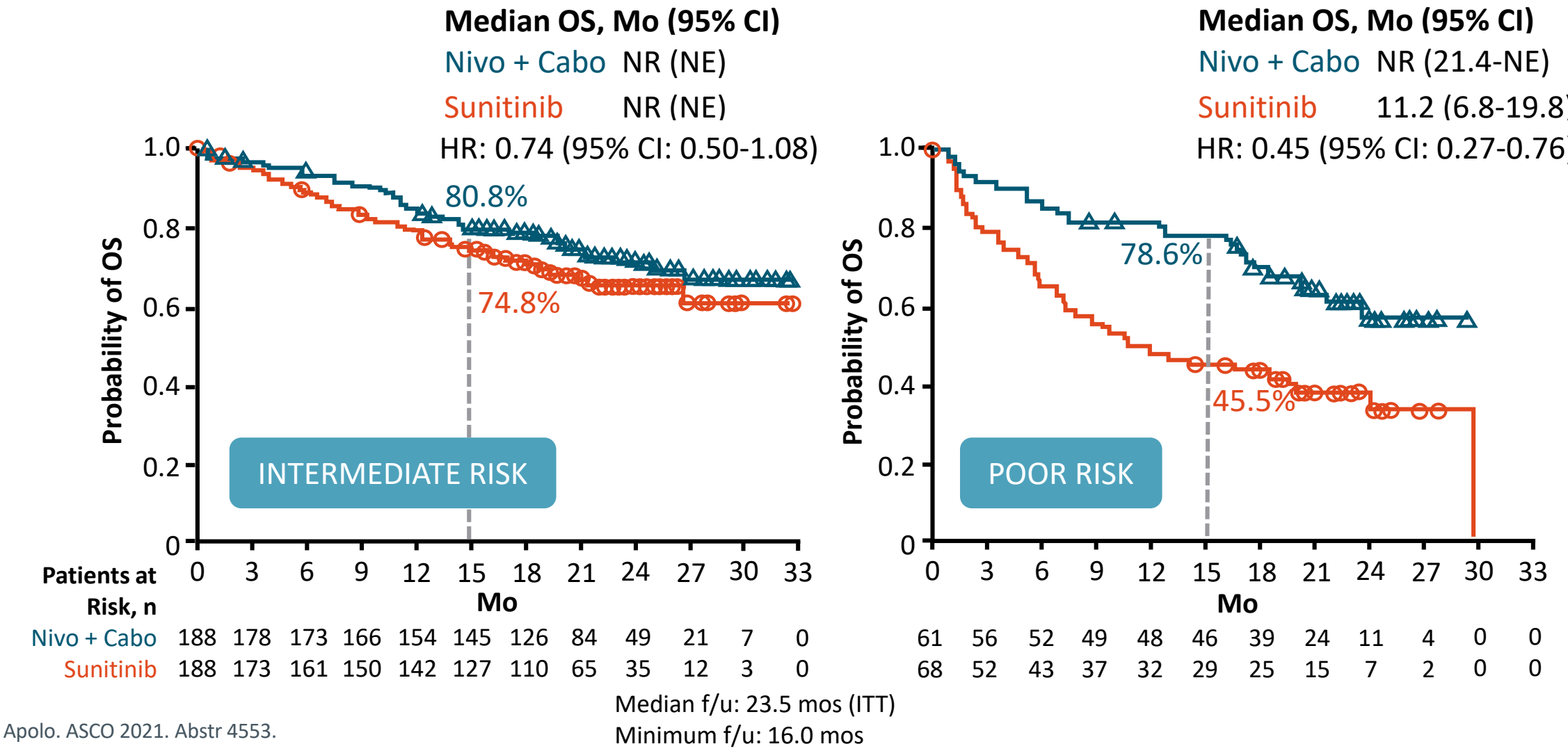
Powles. Lancet Oncol. 2020;21:1563.

CheckMate 9ER: First-line Nivolumab + Cabozantinib vs Sunitinib in Advanced or Metastatic RCC



Powles. ASCO GU 2022. Abstr 350.

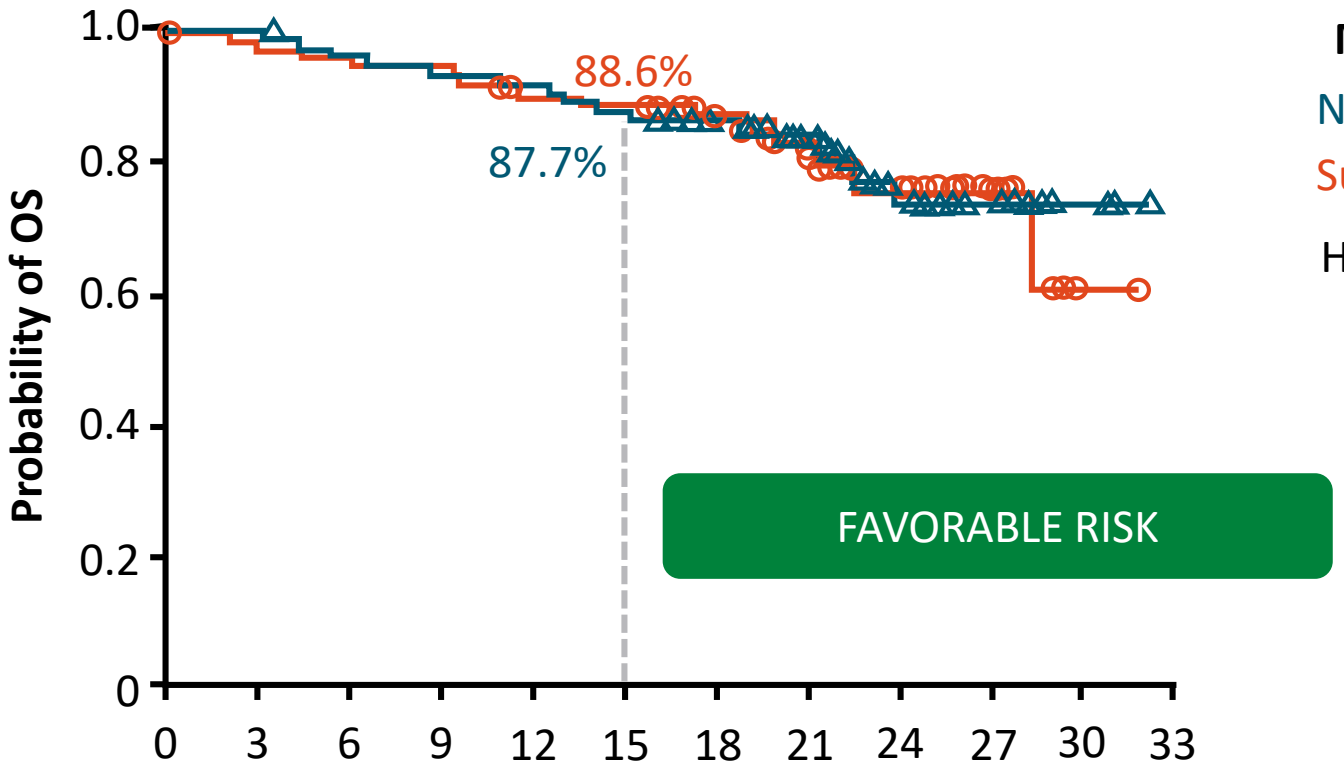
CheckMate 9ER: First-line Nivolumab + Cabozantinib vs Sunitinib in Advanced or Metastatic RCC



Median f/u: 23.5 mos (ITT)
Minimum f/u: 16.0 mos

Apolo. ASCO 2021. Abstr 4553.

CheckMate 9ER: First-line Nivolumab + Cabozantinib vs Sunitinib in Advanced or Metastatic RCC



Median OS, Mo (95% CI)

Nivo + Cabo NR (NE)

Sunitinib NR (28.4-NE)

HR: 0.94 (95% CI: 0.46-1.92)

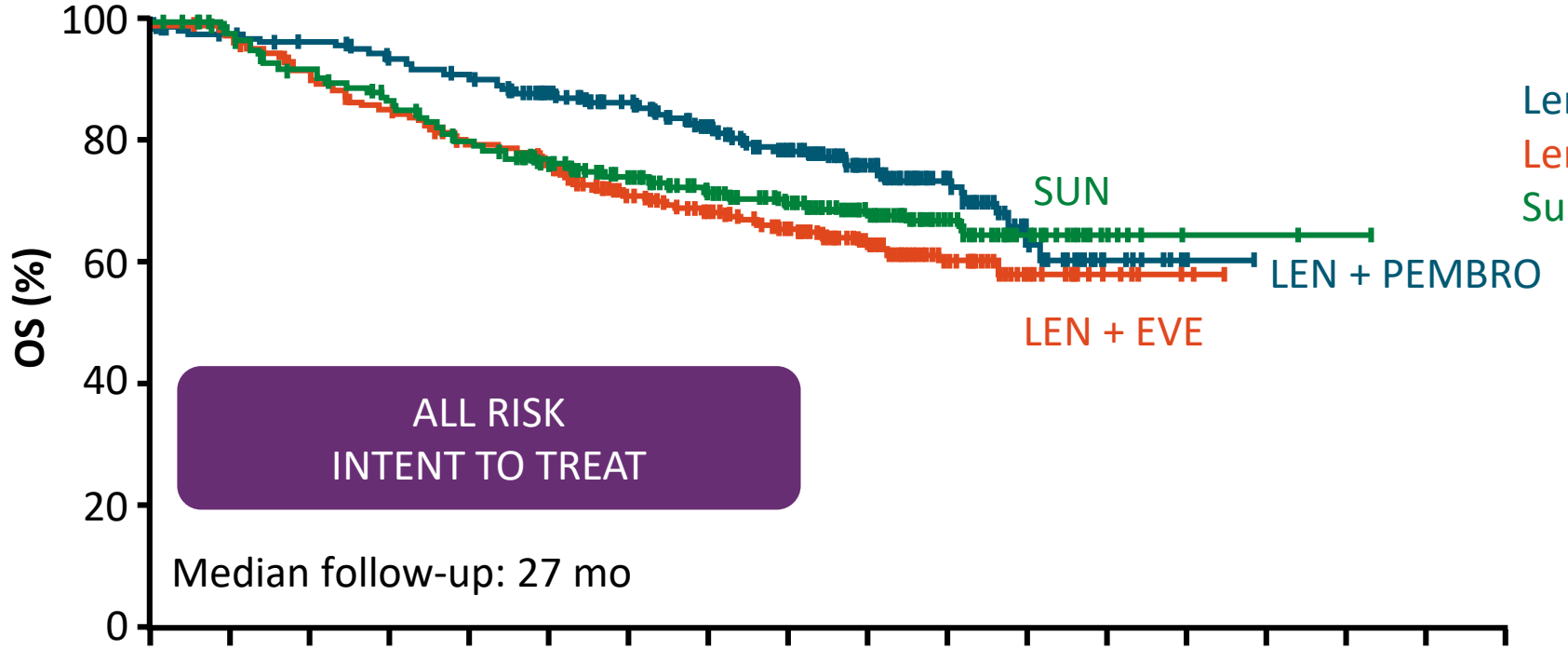
Patients at Risk, n

Nivo + Cabo	74	74	70	68	67	64	55	39	24	15	3	0
Sunitinib	72	70	68	67	62	61	54	38	20	8	1	0

Median f/u: 23.5 mos (ITT)
Minimum f/u: 16.0 mos

Apolo. ASCO 2021. Abstr 4553.

CLEAR: First-line Lenvatinib + Pembrolizumab or Everolimus vs Sunitinib in Advanced RCC



Median OS, Mo (95% CI)

Len + Pembro	NR (33.6-NE)
Len + Eve	NR (NE)
Sunitinib	NR (NE)

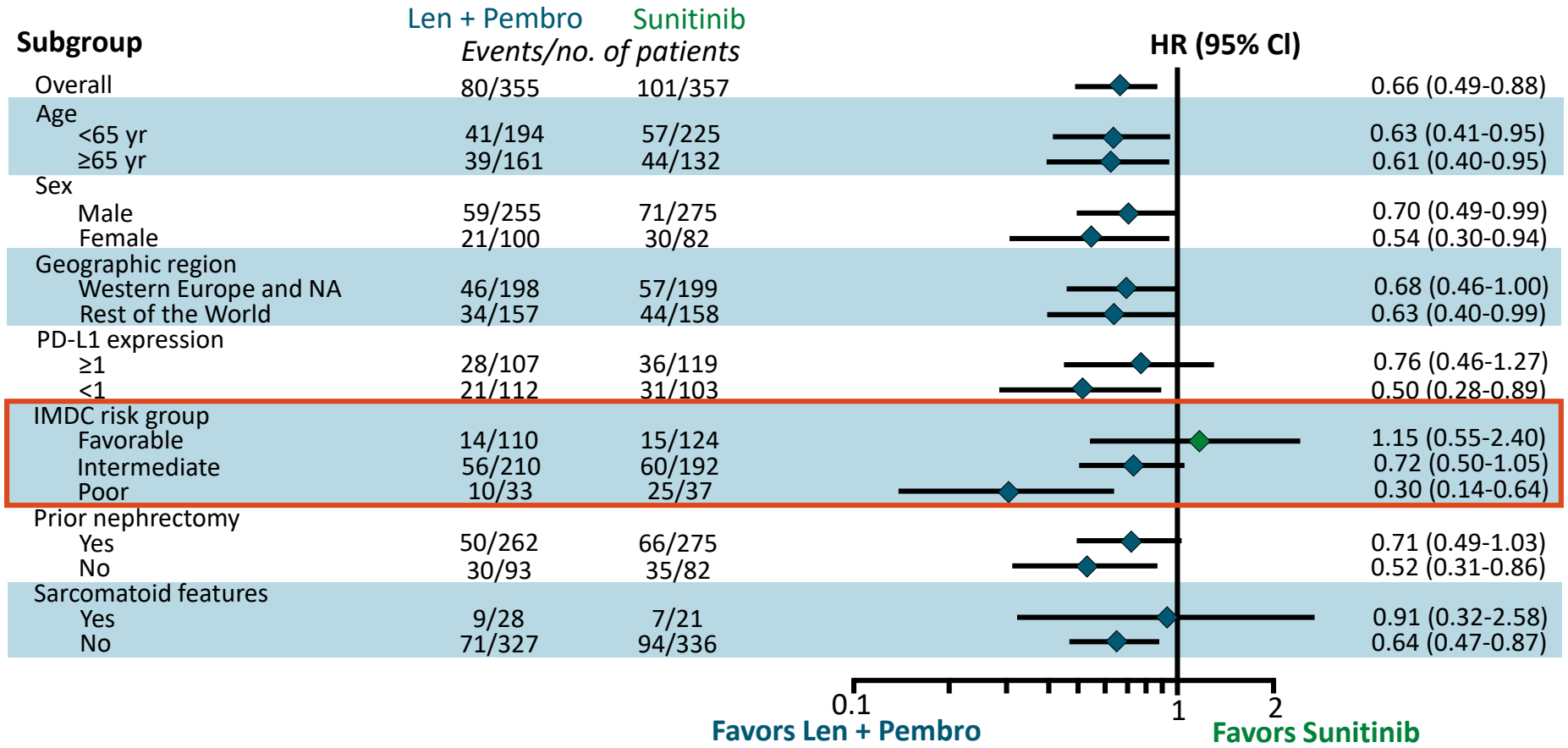
Len + Pembro vs Sunitinib:
HR: 0.66 (95% CI: 0.49-0.88; *P* = .005)

Len + Eve vs Sunitinib:
HR: 1.15 (95% CI: 0.88-1.50; *P* = .3)

Patients at Risk, n	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51
	Mo																	
Len + Pembro	355	342	338	327	313	280	253	222	188	129	66	26	10	2	0			
Len + Eve	357	346	321	299	277	246	205	183	154	109	46	22	8	2	0			
Sunitinib	357	332	307	289	264	236	207	186	169	112	60	25	7	2	2	1	0	

Motzer. ASCO GU 2021. Abstr 269. Motzer. NEJM. 2021;384:1289.

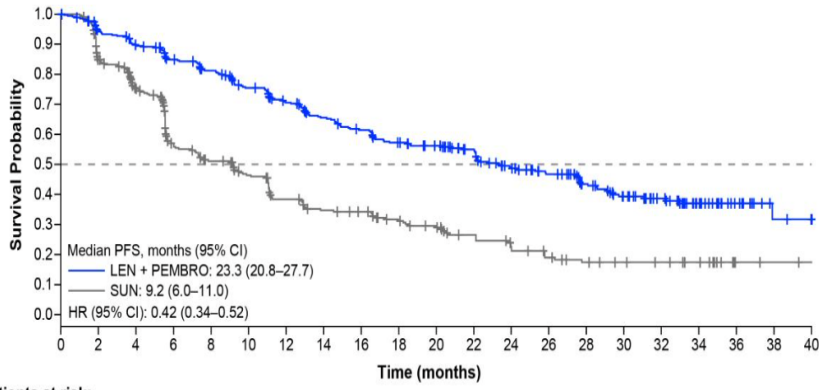
CLEAR: OS in Patient Subgroups



- The OS benefit favored Len + Pembro vs sunitinib across key subgroups except for IMDC favorable risk (HR: 1.15; 95% CI: 0.55-2.40)

Motzer. ASCO GU 2021. Abstr 269.

Continued improvement in PFS (by IIR per RECIST v1.1) with LEN + PEMBRO vs SUN

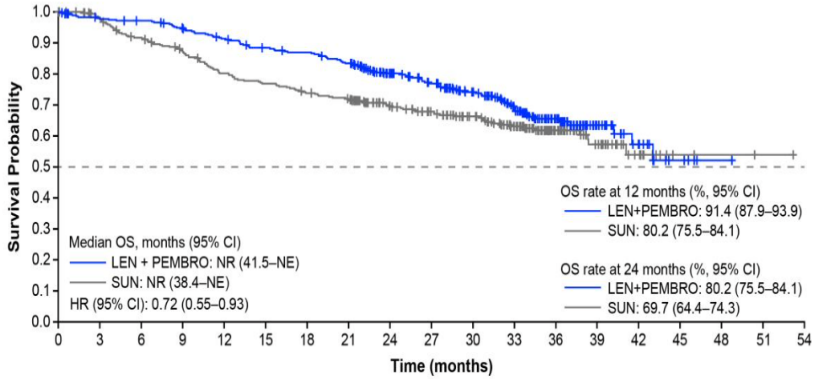


Number of patients at risk:

LEN + PEMBRO	355	321	300	276	259	235	213	193	178	161	151	134	109	95	77	62	50	30	15	6	4
SUN	357	262	218	145	124	107	85	74	70	58	52	41	33	26	21	18	16	12	3	2	1

	MSKCC			IMDC		
	Poor risk	Intermediate risk	Favorable risk	Poor risk	Intermediate risk	Favorable risk
LEN +PEMBRO vs SUN HR (95% CI)	0.18 (0.08–0.42)	0.46 (0.35–0.60)	0.43 (0.29–0.64)	0.30 (0.14–0.62)	0.41 (0.30–0.54)	0.47 (0.32–0.69)

Continued improvement in OS with LEN + PEMBRO vs SUN



Number of patients at risk:

LEN + PEMBRO	355	342	338	327	313	300	294	280	232	207	174	133	75	31	15	5	1	0		
SUN	357	332	307	289	264	253	242	234	195	177	153	116	66	34	14	3	2	1	0	

Beyond the median duration of follow-up, there was a high rate of censoring

	MSKCC			IMDC		
	Poor risk	Intermediate risk	Favorable risk*	Poor risk	Intermediate risk	Favorable risk*
LEN +PEMBRO vs SUN HR (95% CI)	0.50 (0.25–1.02)	0.71 (0.52–0.97)	1.00 (0.51–1.96)	0.39 (0.20–0.77)	0.72 (0.52–1.00)	1.22 (0.66–2.26)*

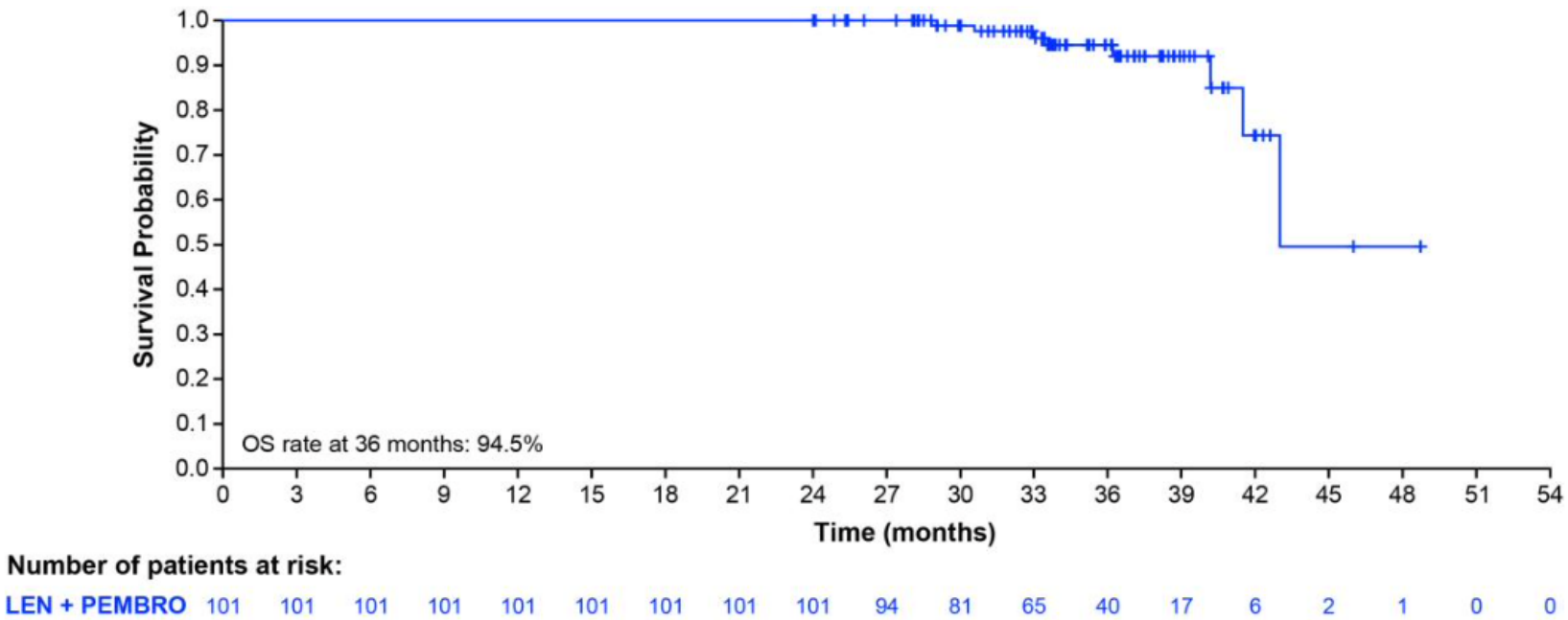
*Median OS was not reached for either arm, and few events were observed for patients in these risk groups.

Tumor response by IIR per RECIST v1.1

	Lenvatinib + Pembrolizumab (N = 355)	Sunitinib (N = 357)
Objective response rate, n (%)	252 (71.0)	129 (36.1)
95% CI[a]	(66.3, 75.7)	(31.2, 41.1)
Difference (%) (95% CI)[a]	34.9 (28.0, 41.7)	
Relative risk[b]	1.97 (1.69, 2.29)	
Best overall response, n (%)		
Complete response	61 (17.2)	15 (4.2)
Partial response	191 (53.8)	114 (31.9)
Stable disease[c]	68 (19.2)	136 (38.1)
Progressive disease	19 (5.4)	50 (14.0)
Unknown/Not evaluable	16 (4.5)	42 (11.8)
Median duration of objective response, mo (95% CI)	26.0 (22.2, 41.4)	14.7 (9.4, 16.8)

[a]95% CI is constructed using the method of normal approximation; [b]relative risk is calculated using the Cochran-Mantel-Haenszel method, stratified by IxRS stratification factors; [c]must be ≥ 7 weeks after randomization

Overall survival in patients who completed 2 years of PEMBRO and continued on LEN monotherapy

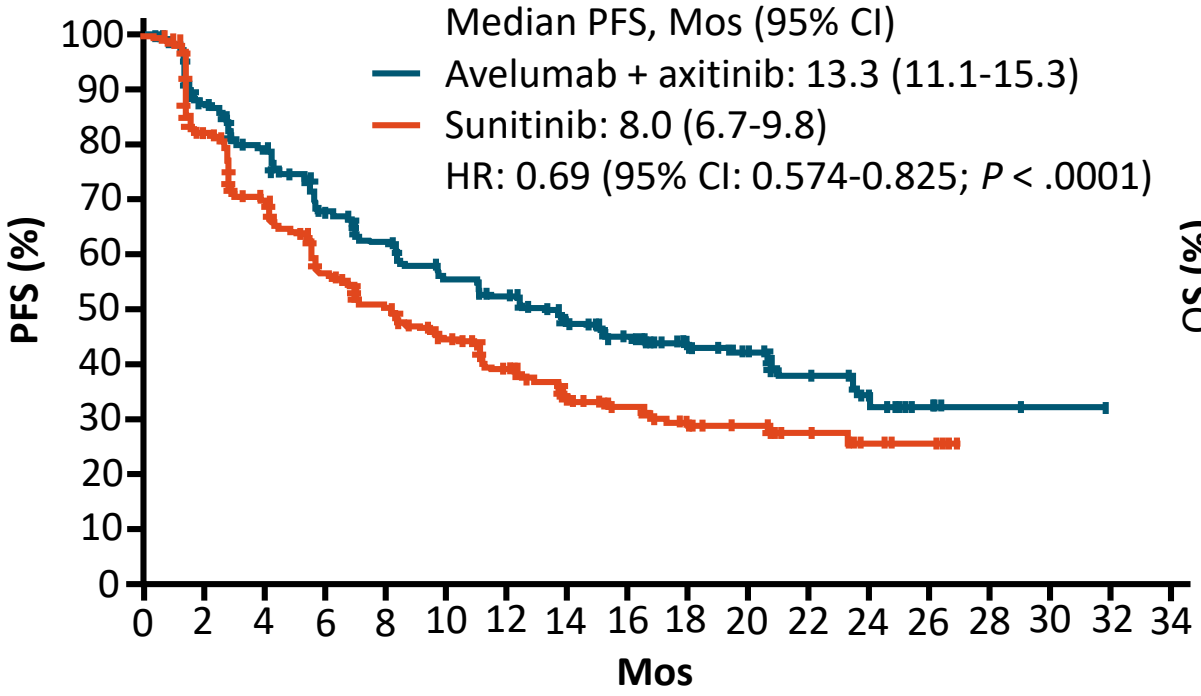


Of pts who completed 2 yrs of PEMBRO (n = 101 of 355 pts), most (n = 65) had IMDC intermediate/ poor risk disease and fewer (n = 36) had favorable risk disease, consistent with the ITT population

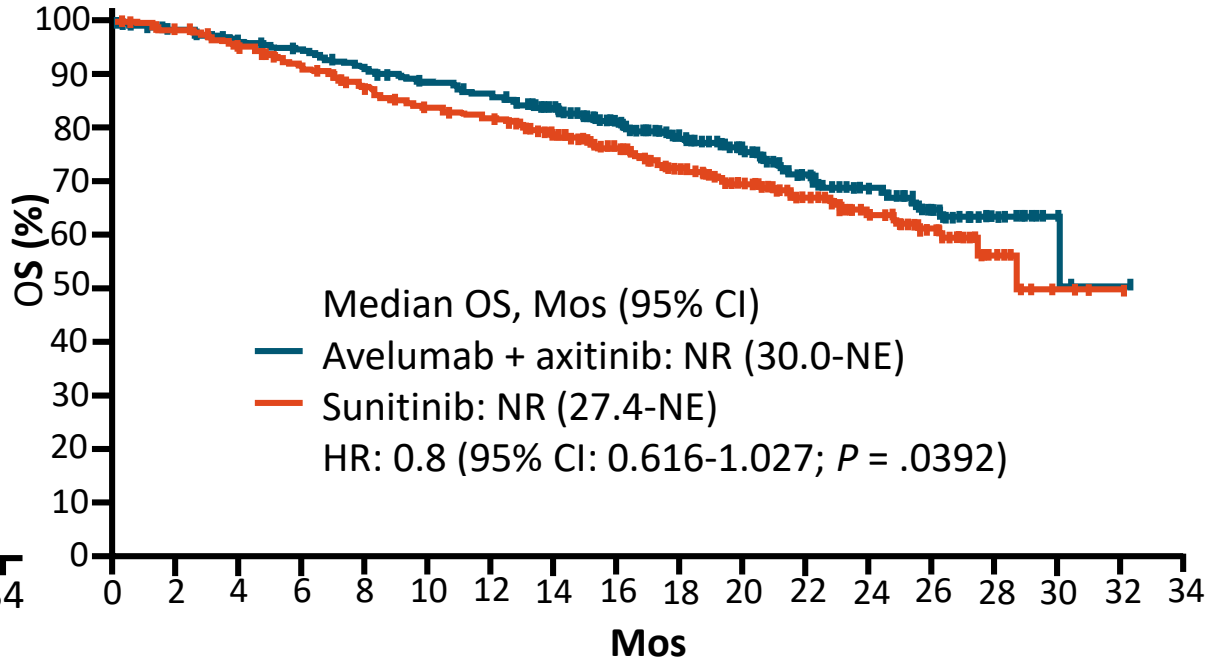
JAVELIN Renal 101: Avelumab + Axitinib in Treatment-Naive Advanced RCC

- Randomized phase III study for patients with untreated advanced RCC were treated with avelumab + axitinib vs sunitinib (N = 886; median follow-up: ~ 19 mos)

PFS in ITT Population



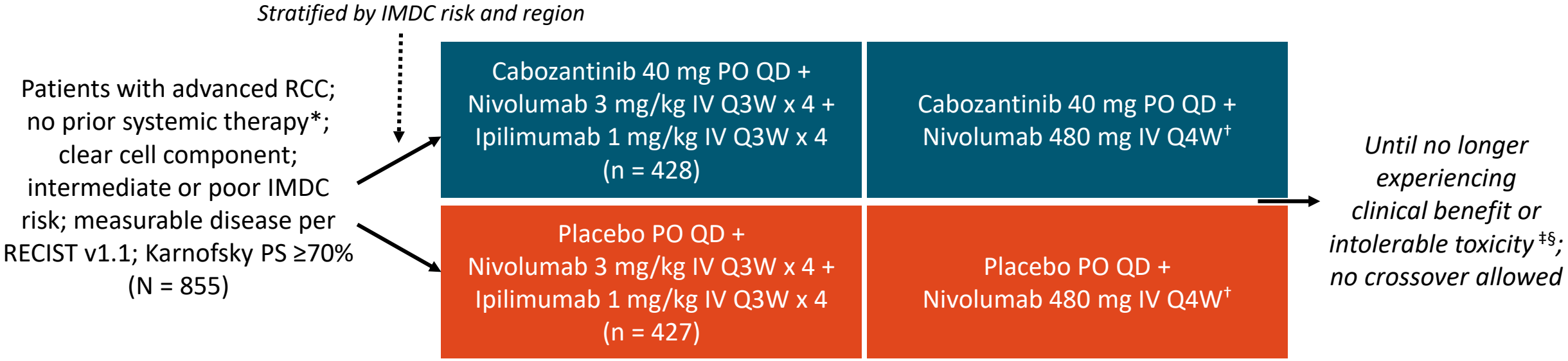
OS in ITT Population



Choueiri. Ann Oncol. 2020;31:1030.

COSMIC-313: Study Design

- Multicenter, randomized, double-blind phase III trial



*One prior systemic adjuvant therapy allowed for completely resected RCC and if recurrence occurred ≥6 mo after last dose of adjuvant therapy; adjuvant PD-1 or PD-L1 inhibitor in combination with CTLA-4 inhibitor not permitted. †Nivolumab given for maximum of 2 yr. ‡Tumor assessment (RECIST v1.1) at Wk 10, then every 8 wk through 50 wk, then every 12 wk. §Discontinuation of 1 agent did not necessitate discontinuing all agents.

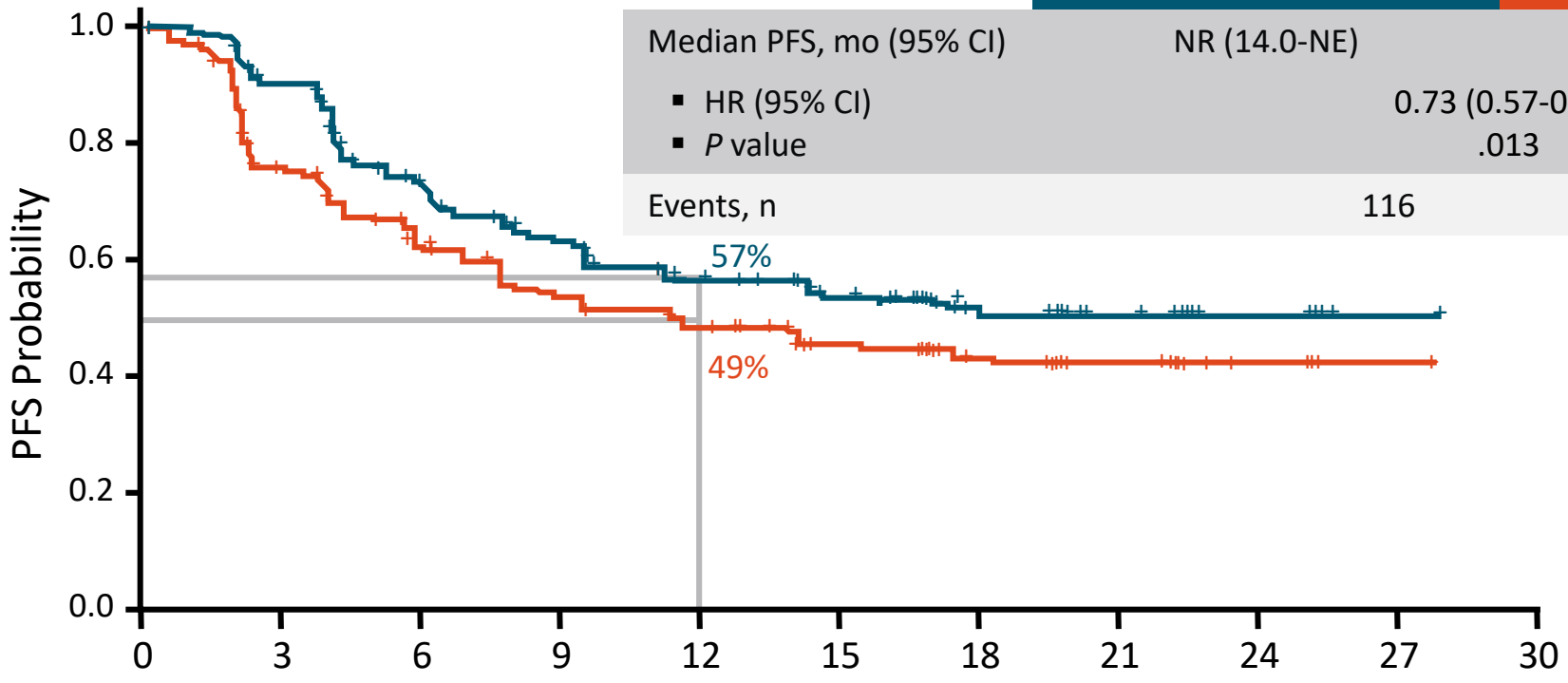
- Primary endpoint: PFS per RECIST v1.1 by BIRC (analyzed after 249 events in PITT population [first 550 patients randomized])
- Secondary endpoint: OS
- Additional endpoints: ORR, DoR, safety

- Median follow-up
  - ITT: 17.7 mo
  - PITT: 20.2 mo

Choueiri. ESMO 2022. Abstr LBA8.

COSMIC-313: PFS (PITT Population)

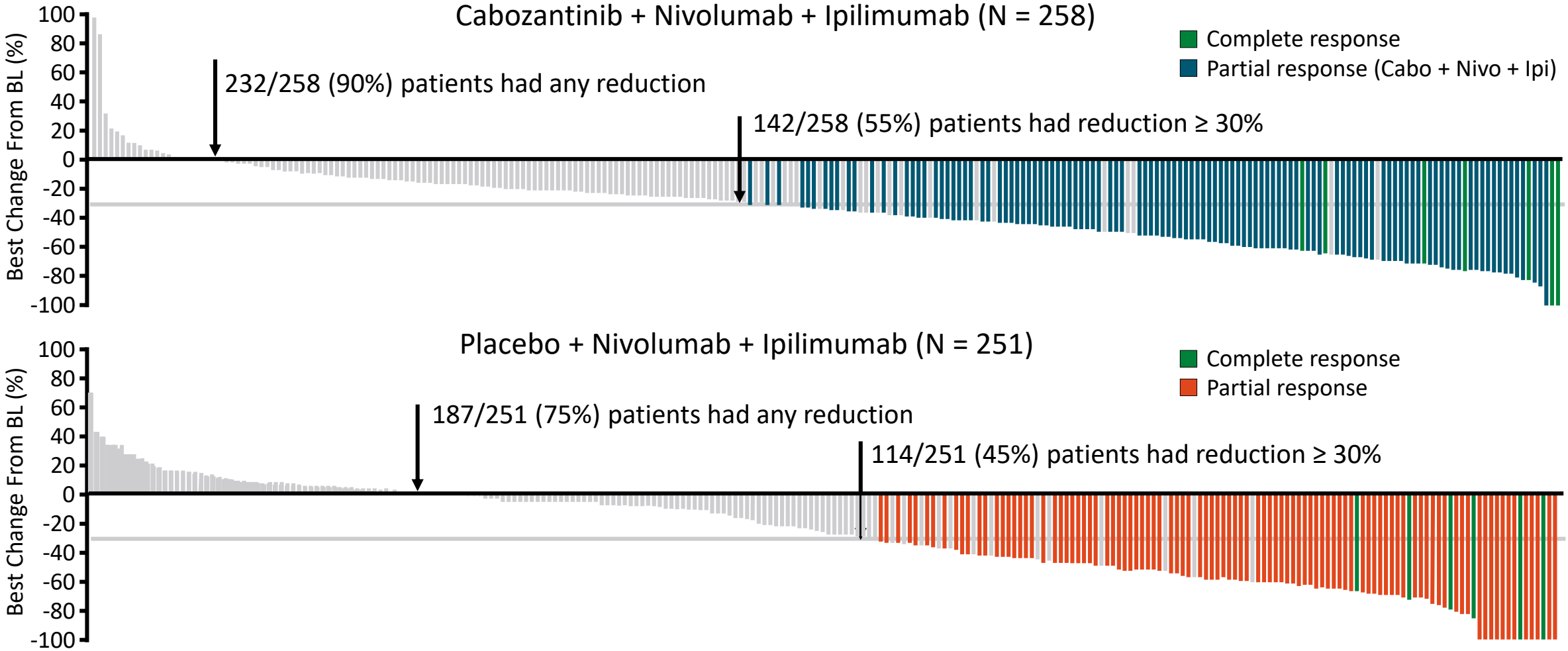
	Cabozantinib + Nivolumab + Ipilimumab (n = 276)	Placebo + Nivolumab + Ipilimumab (n = 274)
Median PFS, mo (95% CI)	NR (14.0-NE)	11.3 (7.7-18.2)
▪ HR (95% CI)	0.73 (0.57-0.94)	
▪ *P* value	.013	
Events, n	116	133



Patients at Risk, n											
Cabo ≠ Nivo Ipi	276	234	170	145	119	97	56	33	10	1	0
Pbo + Nivo + Ipi	274	185	136	115	98	69	37	19	5	1	0

Choueiri. ESMO 2022. Abstr LBA8. Reproduced with permission.

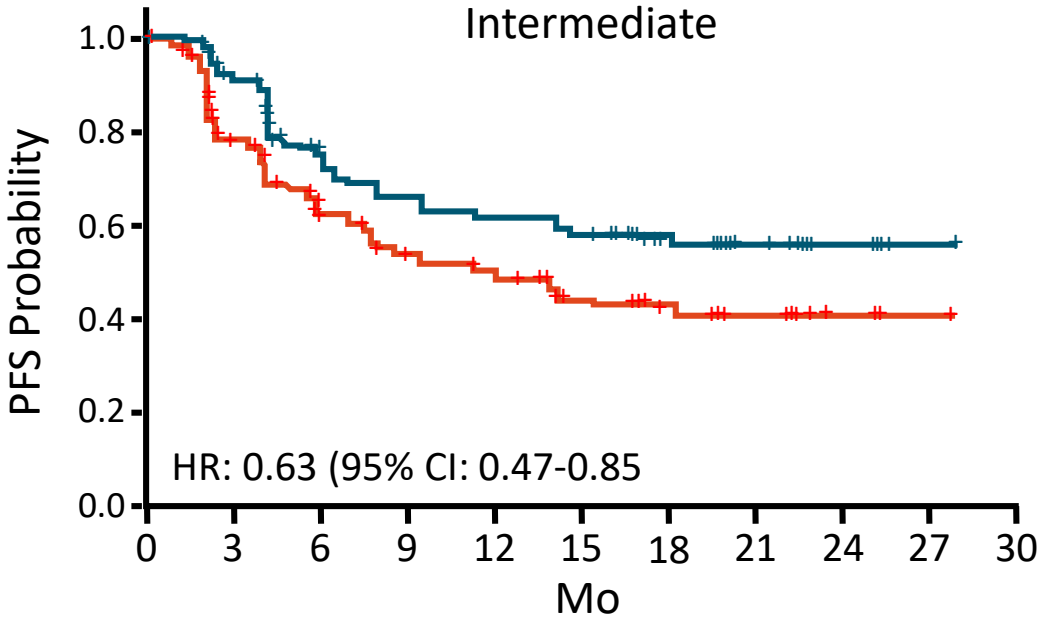
COSMIC-313: Best Change From Baseline in SoD of Target Lesions (PITT Population*)

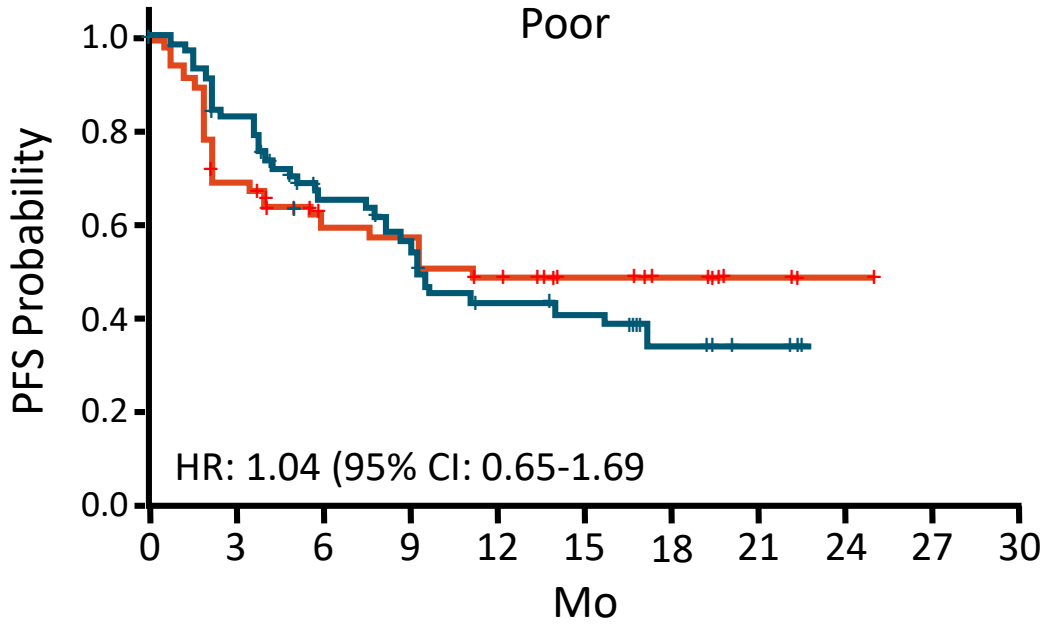


*Patients in PITT population with ≥1 baseline and postbaseline assessment.

Choueiri. ESMO 2022. Abstr LBA8. Reproduced with permission.

COSMIC-313: PFS and ORR by IMDC Risk Group (PITT Population)





	Cabozantinib + Nivolumab + Ipilimumab (n = 209)	Placebo + Nivolumab + Ipilimumab (n = 208)
Median PFS, mo (95% CI)	NR (16.9-NE)	11.4 (7.6-17.3)
ORR, % (95% CI)	45 (38.1-52.0)	35 (28.6-42.0)
Events, n	79	103

	Cabozantinib + Nivolumab + Ipilimumab (n = 209)	Placebo + Nivolumab + Ipilimumab (n = 208)
Median PFS, mo (95% CI)	9.5 (7.8-17.3)	11.2 (4.0-NE)
ORR, % (95% CI)	37 (25.8-50.0)	38 (26.2-50.7)
Events, n	37	30

Choueiri. ESMO 2022. Abstr LBA8. Reproduced with permission.

COSMIC-313: Adverse Events (Safety Population)

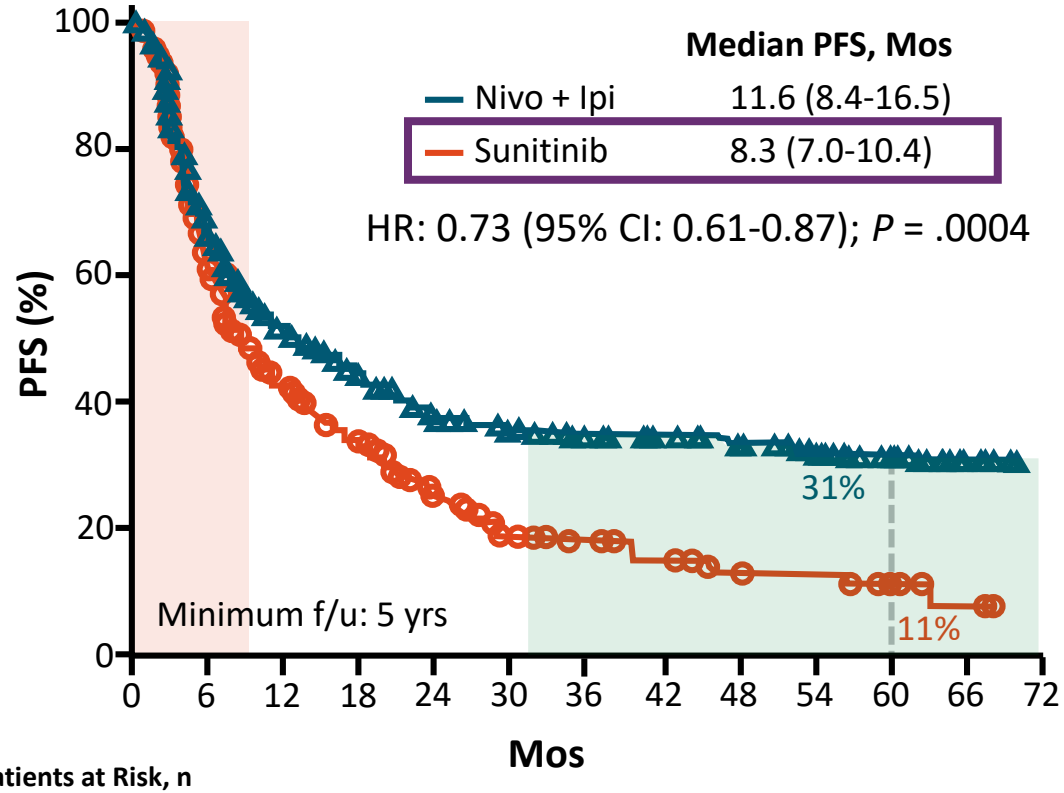
TRAEs, %	Cabozantinib + Nivolumab + Ipilimumab (n = 426)		Placebo + Nivolumab + Ipilimumab (n = 424)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Any event occurring in ≥20% in either group	99	73	91	41
▪ Alanine aminotransferase increased	46	26	17	6
▪ Aspartate aminotransferase increased	44	20	16	5
▪ Diarrhea	41	4	18	3
▪ Palmar–plantar erythrodysesthesia	28	3	4	0
▪ Hypothyroidism	24	<1	15	0
▪ Hypertension	23	8	5	2
▪ Fatigue	22	2	21	1
▪ Lipase increased	22	9	13	6
▪ Amylase increased	20	5	12	2
▪ Rash	20	2	20	1
▪ Pruritis	20	0	26	<1

- Grade 5 TRAEs
  - ≤30 days after last dose: 3 patients (1%) in cabozantinib + nivolumab + ipilimumab arm (gastrointestinal hemorrhage, hepatic failure, respiratory failure) and 3 patients (1%) in placebo + nivolumab + ipilimumab arm (renal failure, myocarditis, sudden death)
  - Through 100 days after last dose: 2 patients in cabozantinib + nivolumab + ipilimumab arm (immune-mediated hepatitis and hepatic failure) and 1 patient in placebo + nivolumab + ipilimumab arm (perforated ulcer)
- 58% and 35% of patients in cabozantinib + nivolumab + ipilimumab vs placebo + nivolumab + ipilimumab arms, respectively, used high-dose corticosteroids (≥40 mg of prednisone or equivalent) for AEs

Choueiri. ESMO 2022. Abstr LBA8.

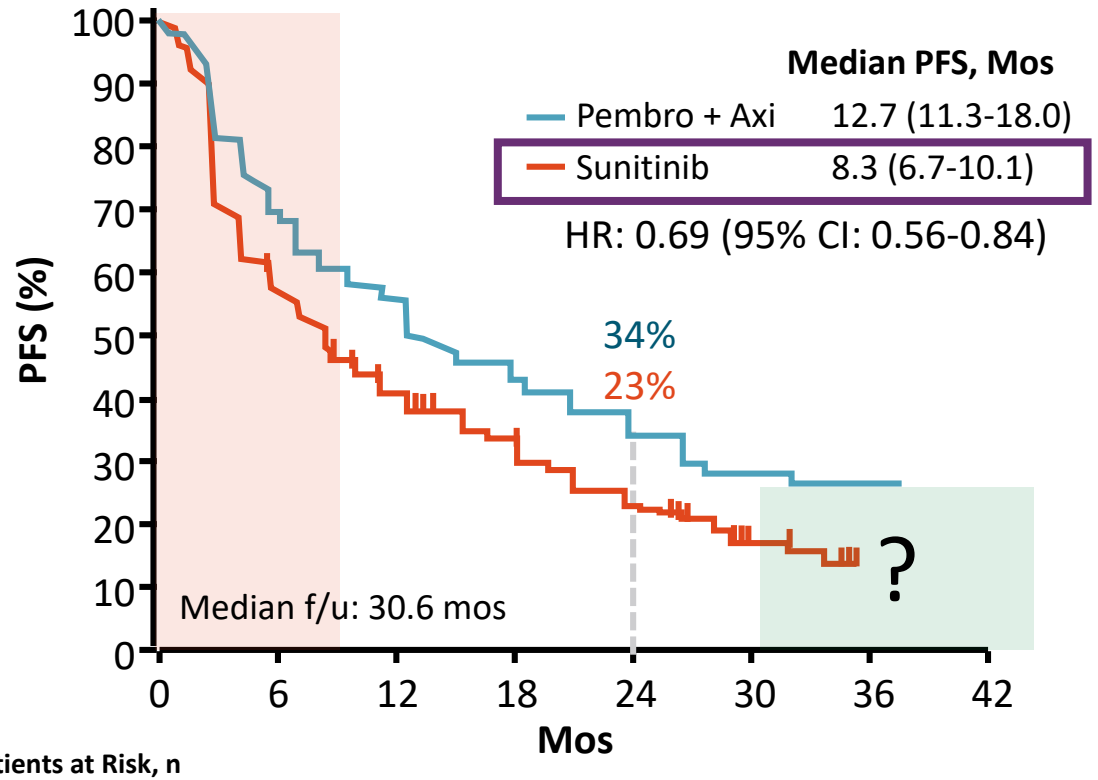
PFS for IMDC Intermediate-/Poor-Risk Disease

CheckMate 214: Nivo + Ipi vs Sunitinib (n = 847)[1]



Patients at Risk, n													
Nivo + Ipi	425	233	164	130	101	94	81	74	70	60	48	10	0
Sunitinib	422	188	106	74	46	29	21	15	10	9	6	2	0

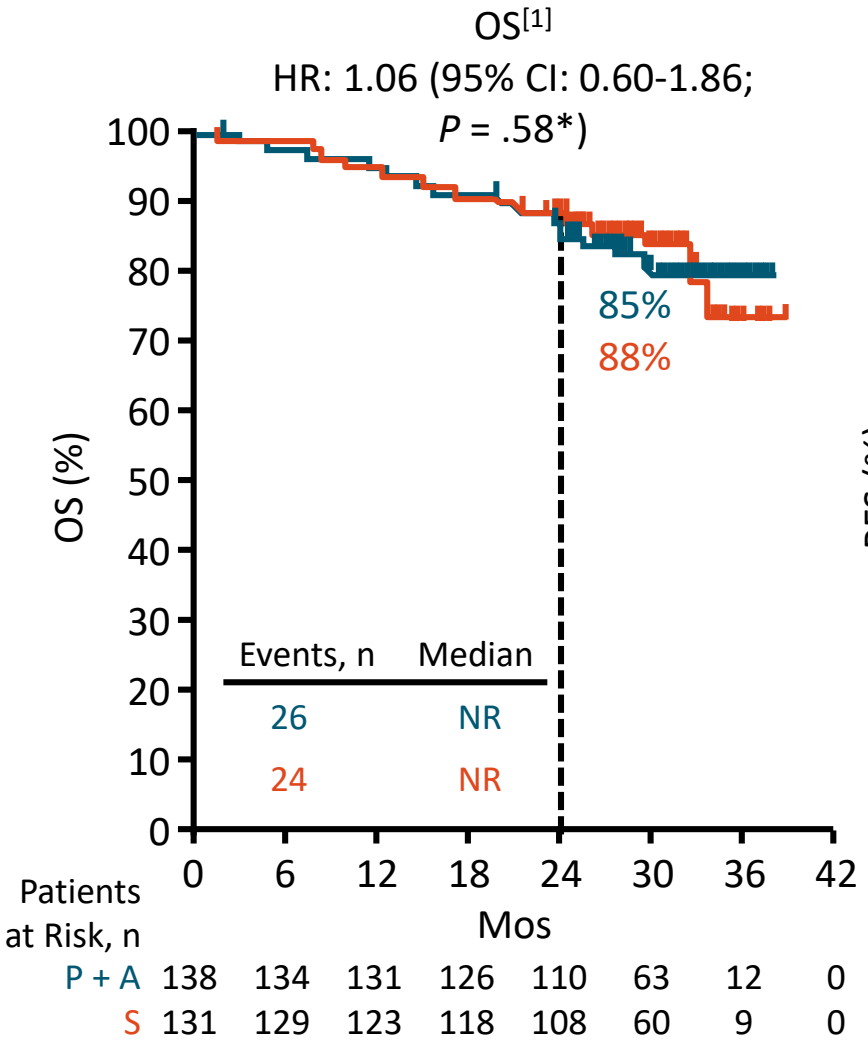
KEYNOTE-426: Axitinib + Pembro vs Sunitinib (n = 592)[2]

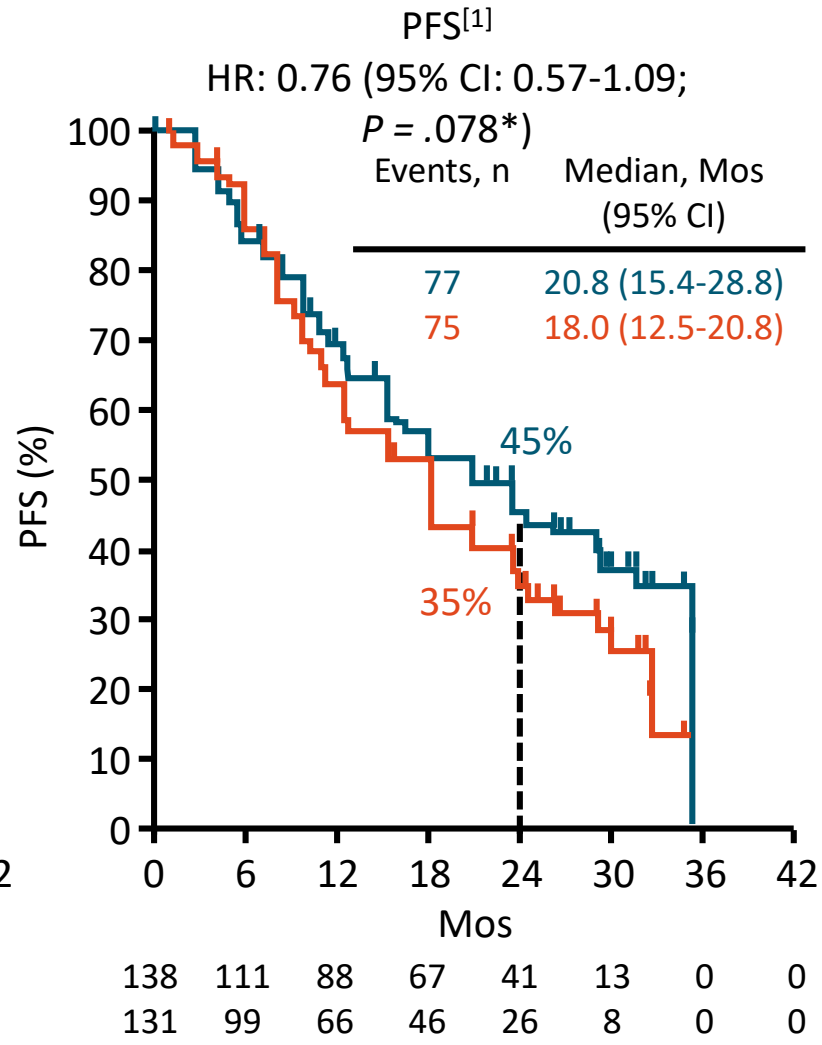


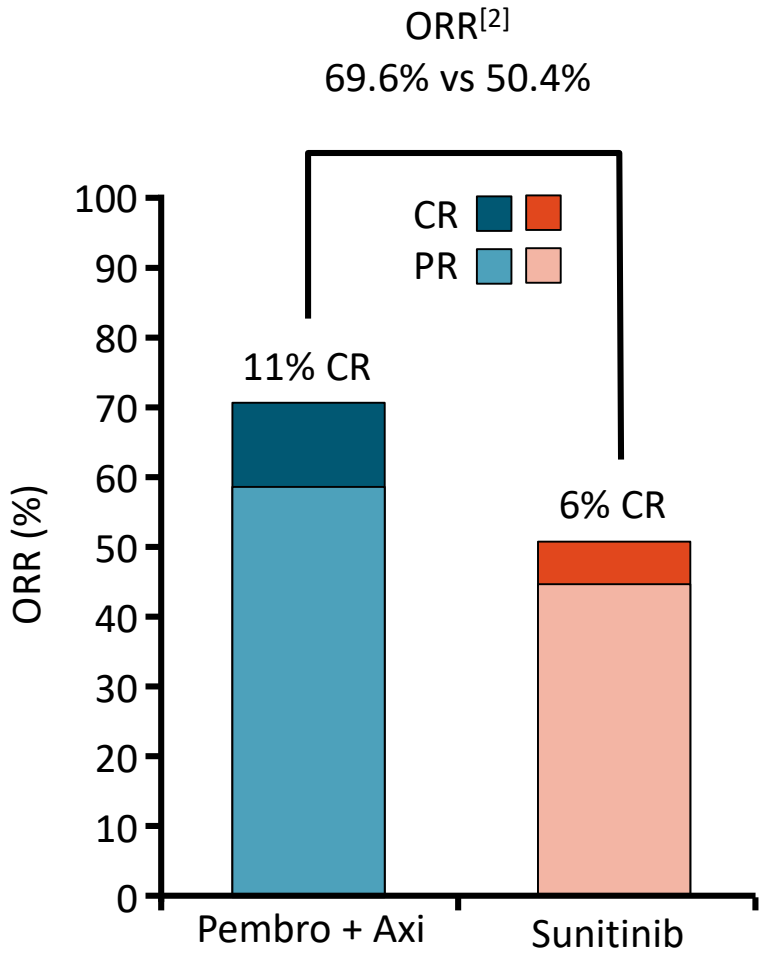
Patients at Risk, n								
Pembro + Axi	294	189	146	113	68	23	2	0
Sunitinib	298	149	93	66	35	11	0	0

1. Motzer. ESMO 2021. Abstr 661P. 2. Powles. Lancet Oncol. 2020;21:1563.

KEYNOTE-426: OS, PFS, and ORR in IMDC Favorable-Risk Group





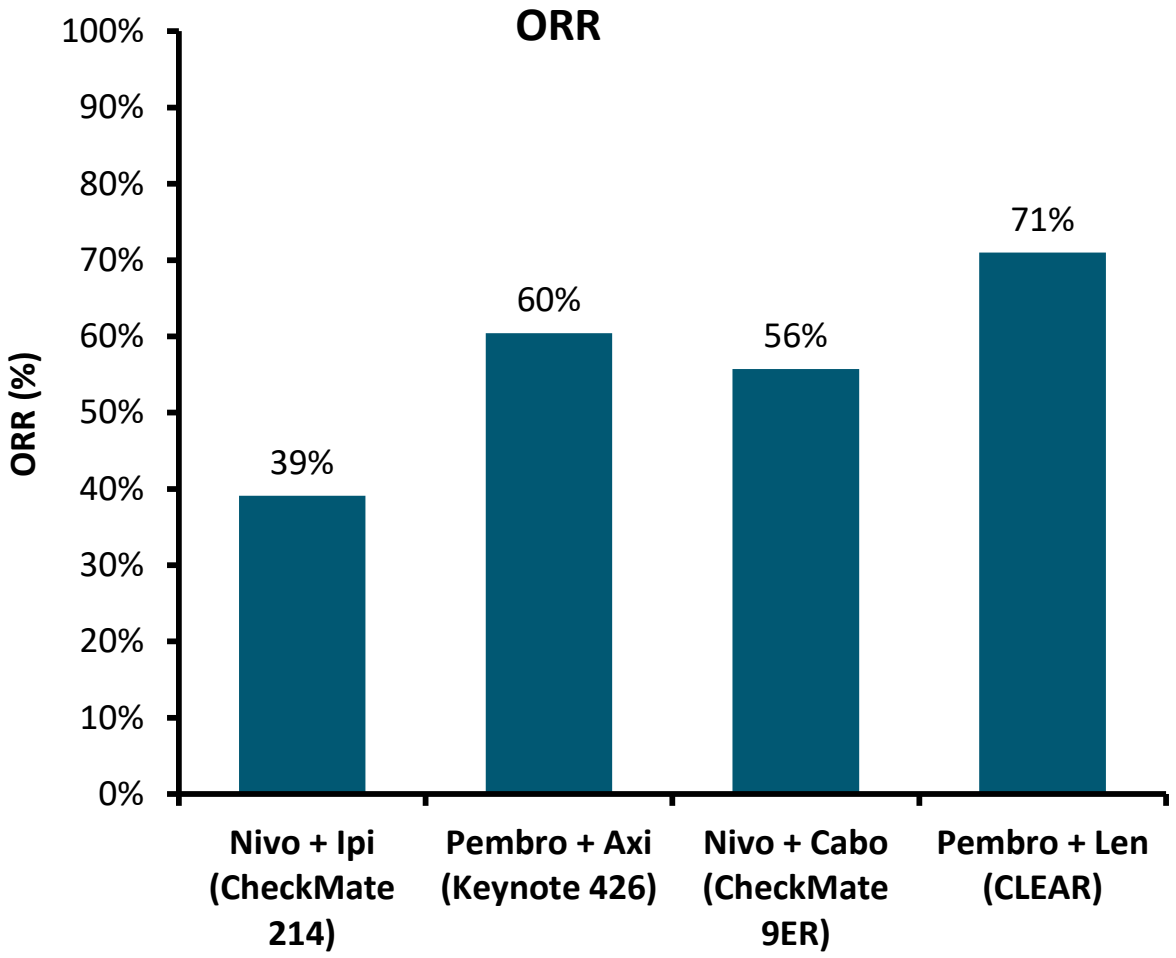


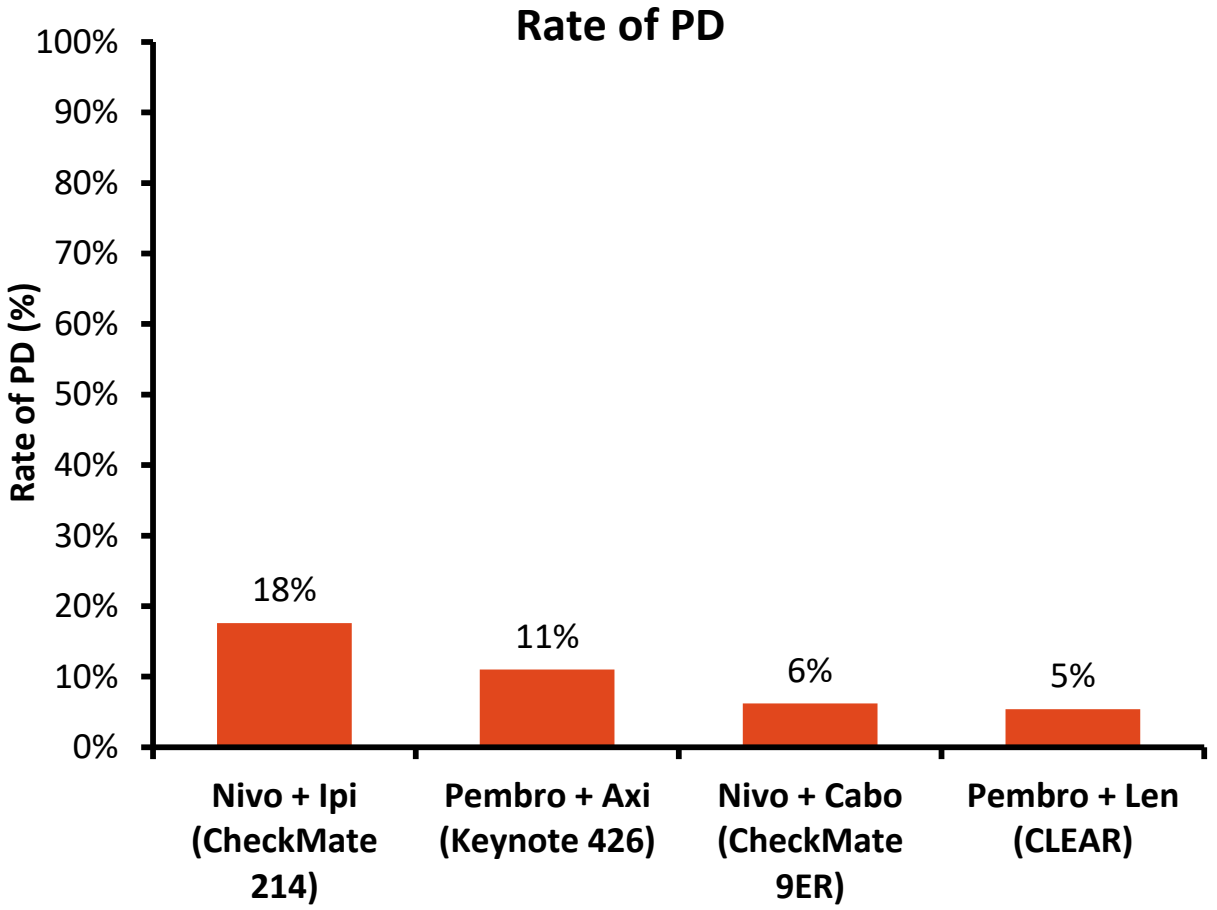
1. Powles. Lancet Oncol. 2020;21:1563. 2. Plimack. ASCO 2020. Abstr 5001.

*Nominal *P* value.

Slide credit: clinicaloptions.com

Cross-Trial Comparison of Response in ITT Population





Motzer. ESMO 2021. Abstr 661P. Rini. ASCO 2021. Abstr 4500.
Motzer. ASCO GU 2022. Abstr 350. Motzer. ASCO GU 2021. Abstr 269.

First-line IO Combination Trials in mRCC

	CheckMate 214[1] Ipi/Nivo vs Sun (n = 550 vs n = 546)	KEYNOTE-426[2] Axi/Pembro vs Sun (n = 432 vs n = 429)	CheckMate 9ER[3] Cabo/Nivo vs Sun (n = 323 vs n = 328)	CLEAR[4] Len/Pembro vs Sun (n = 355 vs n = 357)
mOS, mo HR (CI)	55.7 vs 38.4 **0.72** (0.62-0.85)	45.7 vs 40.1 **0.73** (0.60-0.88)	37.7 vs 34.3 **0.70** (0.55-0.90)	NR vs NR **0.72** (0.55-0.93)
Landmark OS 12 mo Landmark OS 24 mo	**83%** vs 78% **71%** vs 61%	**90%** vs 79% **74%** vs 66%	**86%** vs 76% (est.) **70.3%** vs 60.3%	**90%** vs 79% (est.) **79%** vs 70%
mPFS, mo HR (CI)	**12.2** vs 12.3 0.86 (0.73-1.01)	**15.7** vs 11.1 0.68 (0.58-0.80)	**16.6** vs 8.3 0.56 (0.46-0.68)	**23.9** vs 9.2 0.39 (0.32-0.49)
ORR, %	**39** vs 32	**60** vs 40	**56** vs 28	**71** vs 36
CR, %	**12** vs 3	**10** vs 4	**12** vs 5	**16** vs 4
Median f/u, mo	**67.7**	**42.8**	**32.9**	**33.7**
Primary PD, %	**18**	**11**	**6**	**5**
Prognostic risk, % ▪ Favorable ▪ Intermediate ▪ Poor	 23 61 17	 32 55 13	 23 58 19	 31 59 9
Prior nephrectomy, %	82	83	69	74
Subsequent systemic tx for Sun arm, %	Overall (68) IO (42)	Overall (69) IO (48)	Overall (40) IO (29)	Overall (71) IO (53)
Tx discontinuation due to AEs, %	23 vs 13	20 vs 18	27 vs 10	18.5 (len) / 25 (pembro) / 9.7 (len + pembro) vs 10

1. Motzer. ESMO 2021. Abstr 661P. 2. Rini. ASCO 2021. Abstr 4500.
3. Motzer. ASCO GU 2022. Abstr 350. 4. Motzer. ASCO GU 2021. Abstr 269.

Adapted from @brian_rini and @Uromigos (podcasts: https://anchor.fm/the-Uromigos)

KEYNOTE B61: Phase II Trial of Lenvatinib and Pembrolizumab in Non-Clear Cell RCC

Patients with histologically confirmed nccRCC and advanced/metastatic disease; no previous systemic therapy; Karnofsky performance score ≥70% (N = 147)

→

Pembrolizumab
400 mg IV 6W
Lenvatinib
20 mg orally daily

Continued up to 18 cycles

- Primary endpoint: confirmed ORR by BICR
  - Confirmed ORR of 47.6% (95% CI: 36.4-58.9)
- At 6 months, PFS rate 72.3% (95% CI: 60.7-81) and OS rate 87.8% (95% CI: 78.5-93.2)

Albiges. ESMO 2022. Abstr 14480.

First-line Combination Therapies for Advanced RCC

- Use of IMDC risk stratification or other risk models may help predict prognosis and guide choice of first-line therapy for patients with advanced RCC
  - Favorable risk: consider treatment with ICI + VEGFR TKI; watch and wait or single agent VEGFR TKI can be considered in select patients
  - Intermediate/poor risk: consider treatment with ICI + VEGFR TKI or ICI + ICI combination
- Consider disease characteristics (e.g. risk category) and patient preferences (e.g. dosage forms) to decide between available treatment options

Thanks

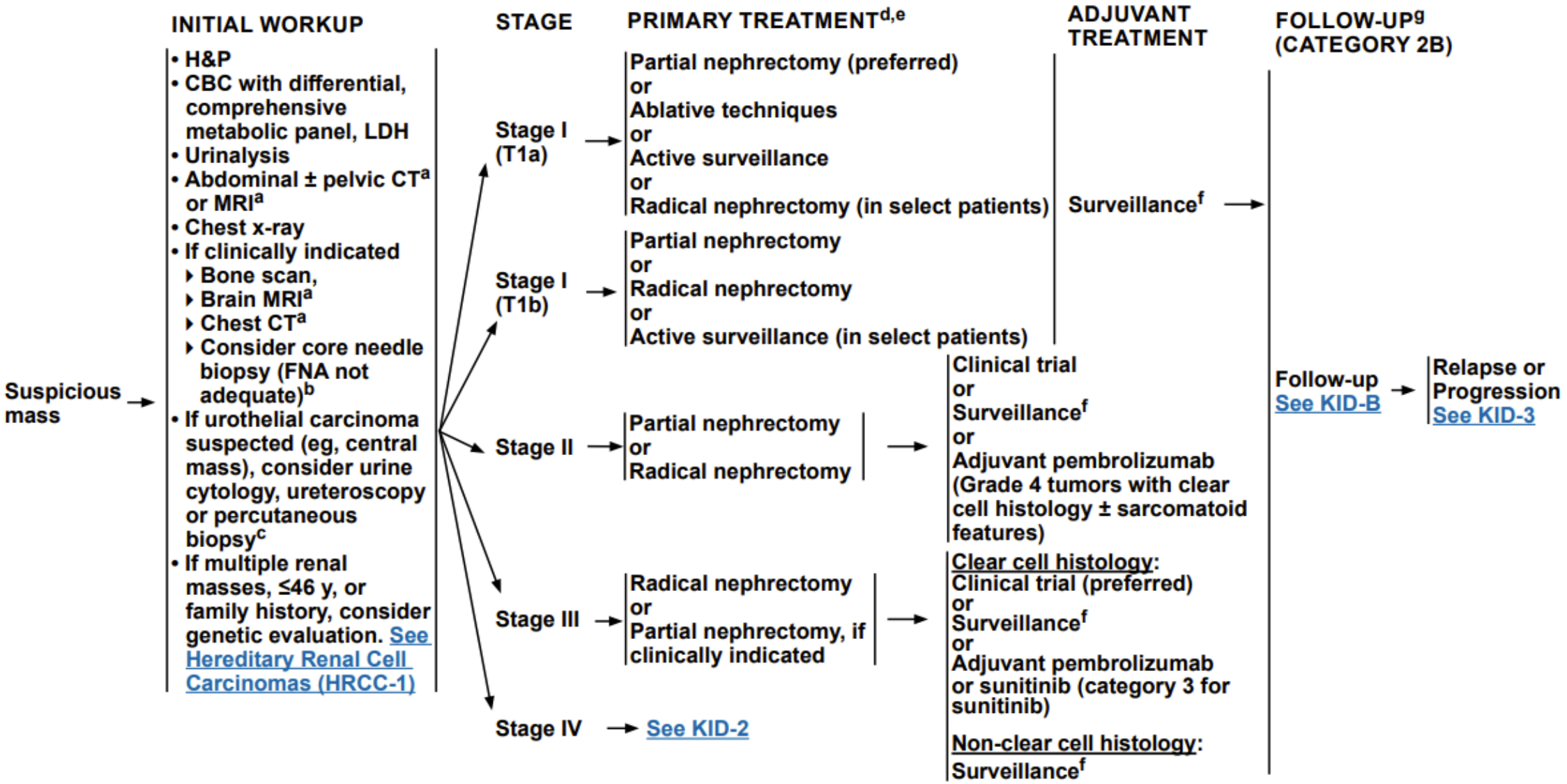
First-line IO Combination Trial Regimens in mRCC

	CheckMate 214[1,2] Ipi/Nivo vs Sun (n = 550 vs n = 546)	KEYNOTE-426[3,4] Axi/Pembro vs Sun (n = 432 vs n = 429)	CheckMate 9ER[2,5] Cabo/Nivo vs Sun (n = 323 vs n = 328)	CLEAR[4,6] Len/Pembro vs Sun (n = 355 vs n = 357)
IO Regimen Induction	Nivolumab 3 mg/kg IV + Ipilimumab 1 mg/kg IV q3W x 4 doses	Pembrolizumab 200 mg IV q3W or 400 mg IV q6W Axitinib 5 mg BID	Nivolumab 240 mg IV q2W or 480 mg IV q4W Cabozantinib 40 mg daily	Pembrolizumab 200 mg IV q3W or 400 mg IVq6W Lenvatinib 20 mg once daily
IO Regimen Maintenance	Nivolumab 240 mg IV q2W or 480 mg IV q4W	NA	NA	NA
Duration	Until disease progression or toxicity	Until disease progression or toxicity; maximum 2 years for pembrolizumab	Until disease progression or toxicity; maximum 2 years for nivolumab	Until disease progression or toxicity; maximum 2 years for pembrolizumab

1. Motzer. NEJM. 2018;278:1277.. 2. Nivolumab PI. 3. Rini. NEJM. 2019;380:1116. 4. Pembrolizumab PI.
5. Motzer. Lancet Oncol. 2022;23:888. 6. Motzer. NEJM. 2021;384:1289.

Perplexities in Nonmetastatic RCC at Initial Diagnosis

NCCN Guidelines Version 4.2022
Kidney Cancer



Published Tyrosine Kinase Inhibitor Adjuvant Trials

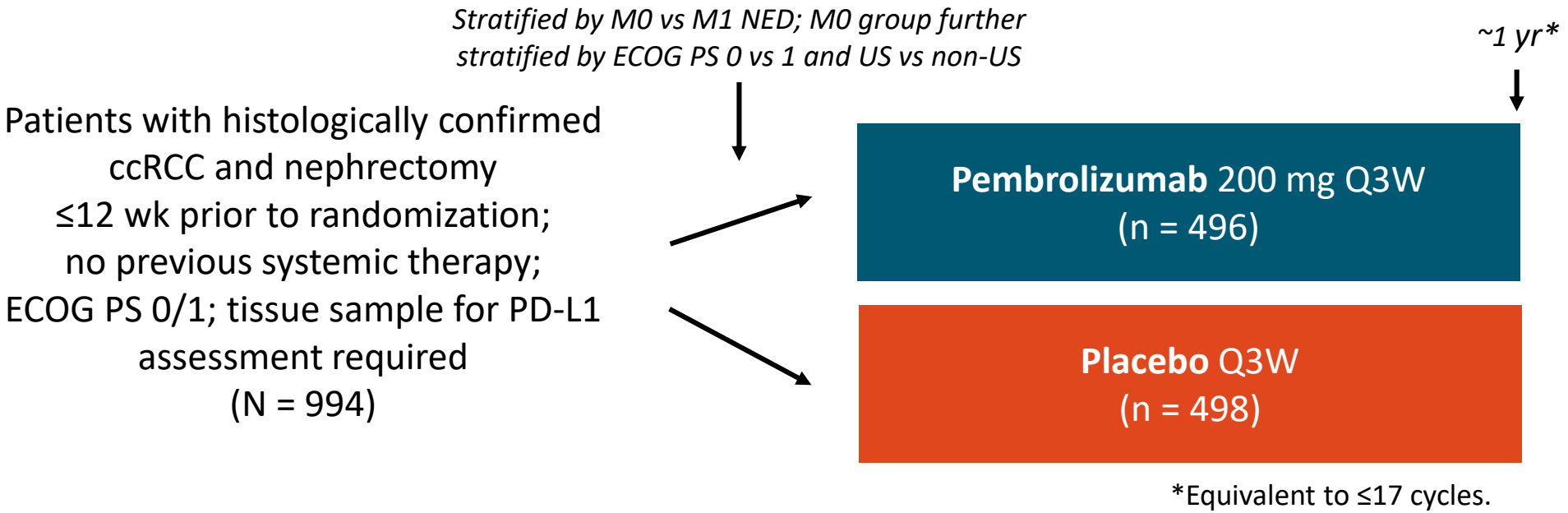
Trial	Therapy	N	Histology	Stage	Starting Dose	Minimum Dose	Significant Difference? DFS	Significant Difference? OS*
ASSURE[1]	Sunitinib Sorafenib Placebo	1943	**79% ccRCC**	> pT1b, G3-4, or N+	50 or 37.5 mg (Su)/ 400 mg (So)	25 mg (Su)/40 mg (So)	No	No
S-TRAC[2,3]	Sunitinib Placebo	615	ccRCC	> pT3b or N+	**50 mg**	**37.5 mg**	Yes	No
PROTECT[4,5]	Pazopanib Placebo	1538	ccRCC or mostly ccRCC	pT2 (G3-4), ≥pT3, or N+	600 mg	400 mg	No	No

*Studies included OS as secondary endpoint and may not be powered to show an improvement.

1. Haas. Lancet. 2016;387:2008. 2. Ravaud. NEJM. 2016;375:2246. 3. Motzer. Eur Urol. 2018;73:62. 4. Motzer. JCO. 2017;35:3916. 5. Motzer. Eur Urol. 2021;79:334.

KEYNOTE-564 30-Mo Follow-up: Adjuvant Pembrolizumab vs Placebo for ccRCC

- Multicenter, randomized, double-blind phase III trial of adjuvant therapy



- Primary endpoint: DFS per investigator
  - Met in first interim analysis
- Secondary endpoints: OS, safety
  - *P* value boundary for OS significance: .0000095

Choueiri. ASCO GU 2022. Abstr 290. NCT03142334.

Slide credit: clinicaloptions.com

KEYNOTE-564: Eligibility Criteria

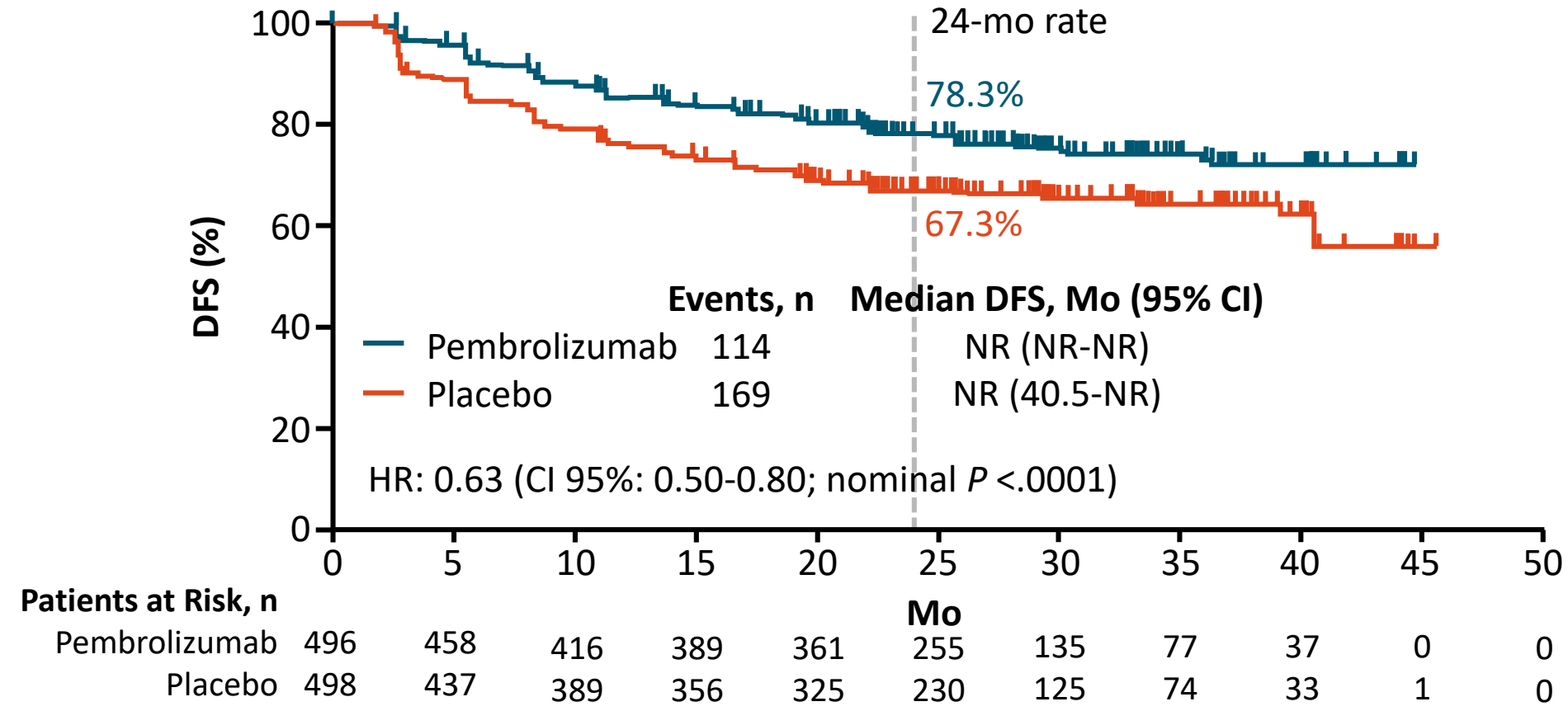
Histologically confirmed clear-cell RCC with:

1. **Intermediate-risk to high-risk disease**
   - pT2, grade 4 or sarcomatoid differentiation with N0, M0
   - pT3, any grade with N0, M0
2. **High risk disease**
   - pT4, any grade with N0, M0
   - Any pT, any grade with N+, M0
3. **M1 no evidence of disease (NED)** with M1 disease in addition to primary tumor at diagnosis, and complete resection at time of nephrectomy or within 1 year after nephrectomy

Choueiri. ASCO GU 2022. Abstr 290. NCT03142334.

Slide credit: clinicaloptions.com

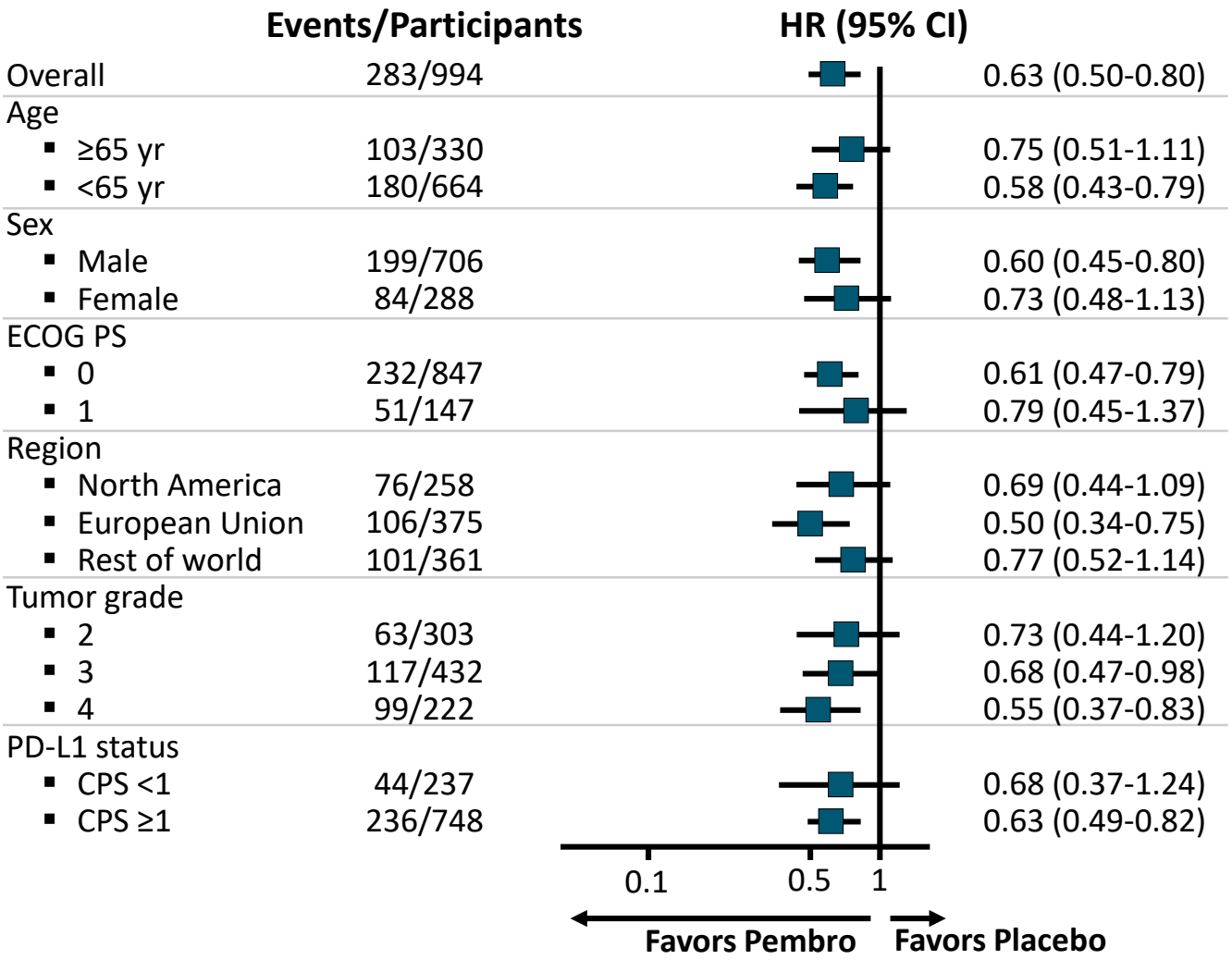
KEYNOTE-564 Updated Analysis: DFS in ITT Population (Primary Endpoint)



Choueiri. ASCO GU 2022. Abstr 290.

Slide credit: clinicaloptions.com

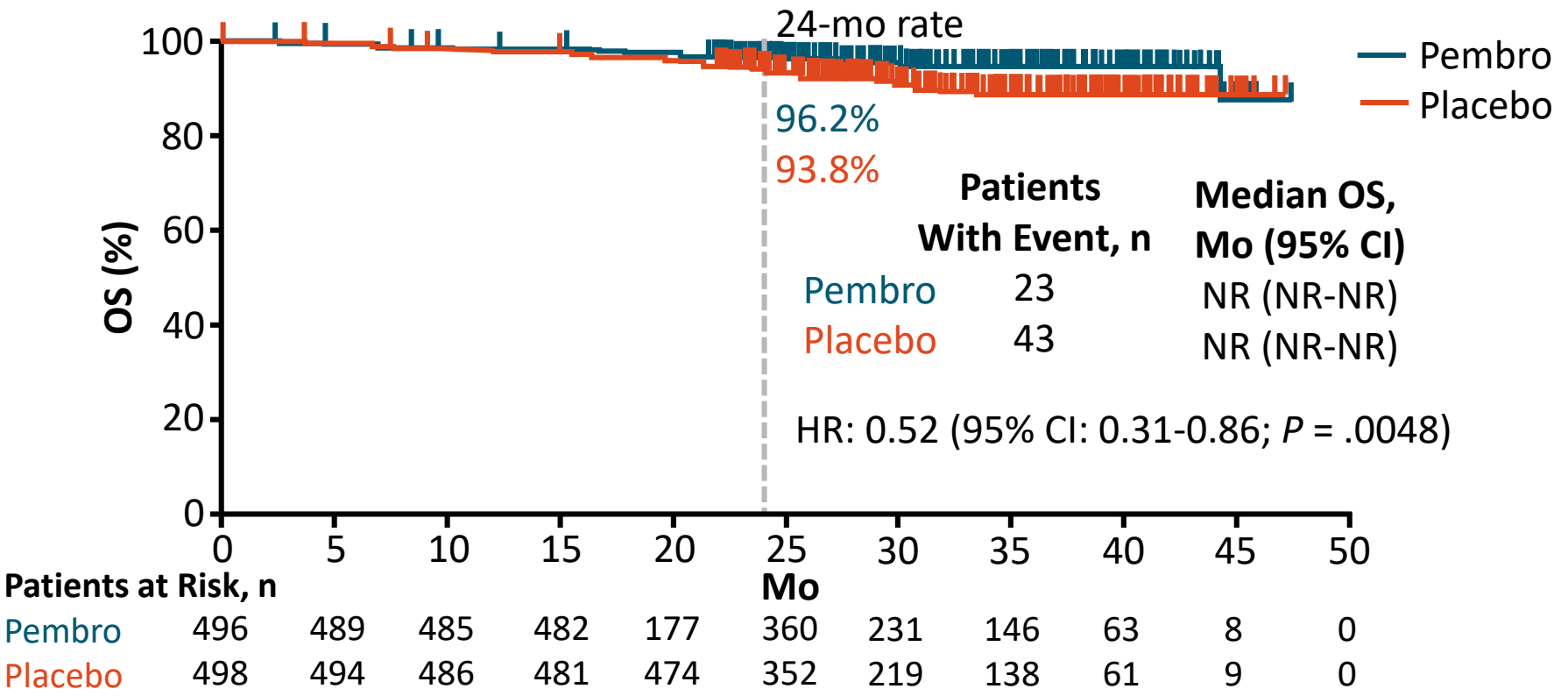
KEYNOTE-564 30-Mo Follow-up: DFS in Key Subgroups



Choueiri. ASCO GU 2022. Abstr 290.

Slide credit: clinicaloptions.com

KEYNOTE-564 30-Mo Follow-up: OS in ITT Population



- Comparison did not meet criteria for statistical significance in this analysis
- Final OS analysis will be conducted after ~200 OS events have occurred

Choueiri. ASCO GU 2022. Abstr 290.

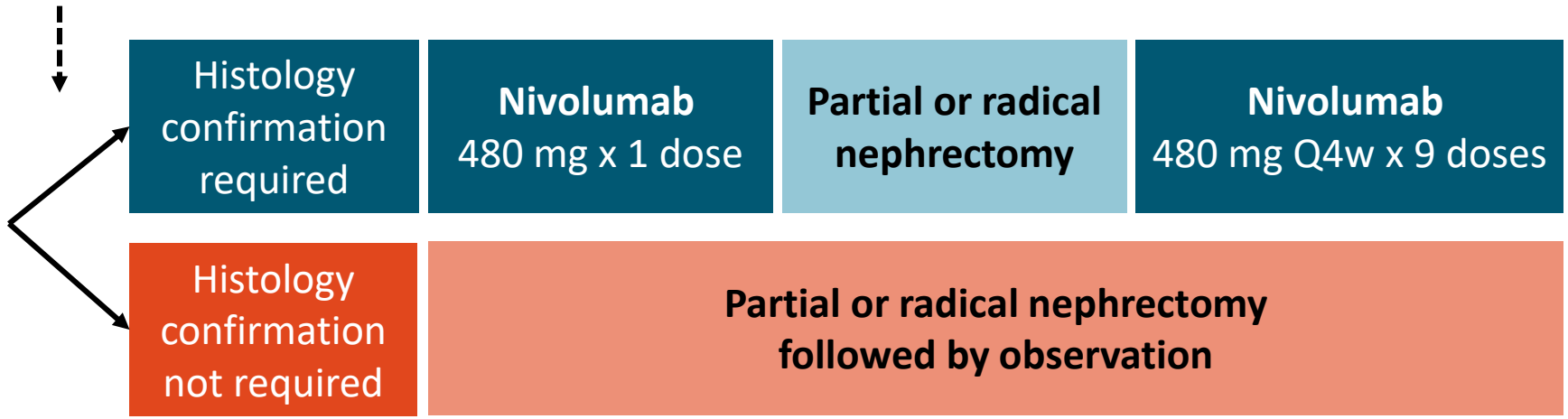
Slide credit: clinicaloptions.com

PROSPER RCC: Perioperative Nivolumab vs Observation for Localized RCC

- Multicenter, randomized, open-label phase III trial

Stratified by clinical T stage (cT1-2 vs cT3-4, N0/1), clinical N stage (cN0 vs cN+), clinical M stage (M0 vs oligometastatic M1 that can be fully resected)

Patients with histologically confirmed clinical T2 or any node positive RCC, M0 or oligometastatic that can be rendered NED; planned nephrectomy with no previous or concurrent systemic therapy; ECOG PS 0/1
(N = 805)



- Primary endpoint: RFS
- Secondary endpoints: OS, safety, tolerability, and QoL

NCT03055013.

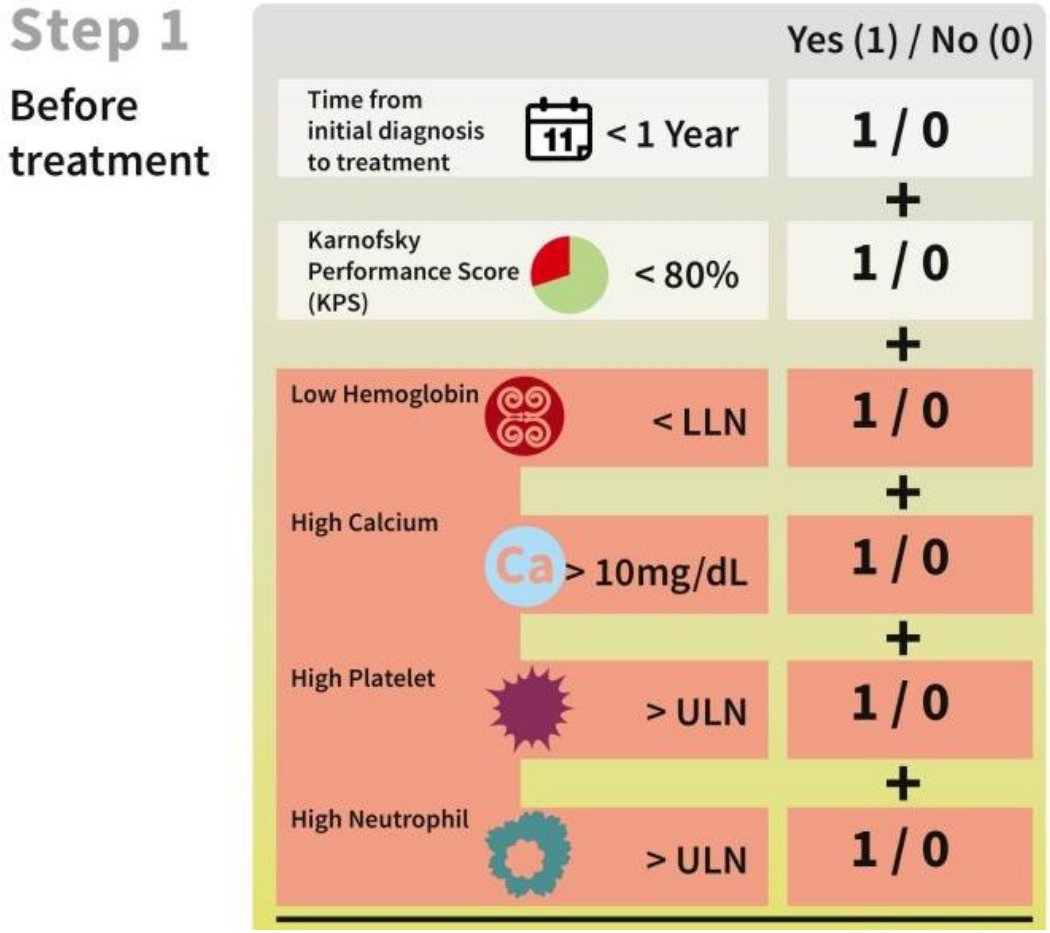
Slide credit: clinicaloptions.com

Planning Optimal First-line Treatment for Patients With Advanced RCC

Case 3: Initial Management

- Patient underwent nephrectomy
  - 9.1 x 8.6–cm mass
  - pT3a clear-cell RCC, Fuhrman grade 4, no sarcomatoid/rhabdoid features
- Chest CT 15 mo post-op with increase in lung nodules, up to 15 mm
- CT-guided lung biopsy consistent with mRCC
- Performance status 0; all labs WNL

International Metastatic Renal Cell Carcinoma Database Consortium Criteria for Metastatic RCC

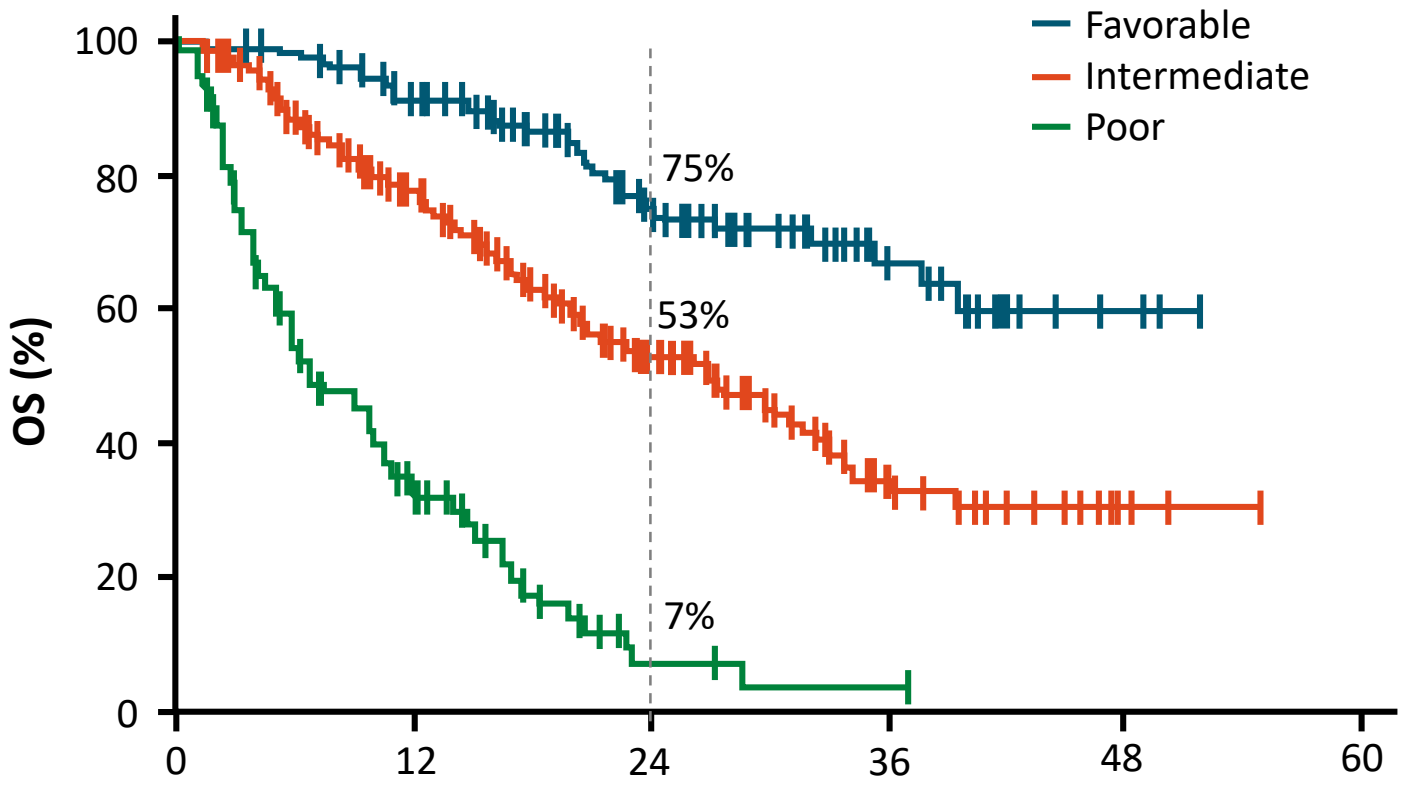


- Prognostic risk groups
  - Favorable-risk group: no prognostic factors
  - Intermediate group: 1 or 2 prognostic factors
  - Poor-risk group: 3-6 prognostic factors
- **75% to 80% of patients with metastatic RCC are poor or intermediate risk**

International Kidney Cancer Coalition. Heng. JCO. 2009;27:5794.

IMDC Prognostic Criteria

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



No. of Events/No. at Risk

Favorable	11/133	16/110	4/62	2/22	0/3
Intermediate	61/301	50/182	17/82	2/18	0/3
Poor	94/152	19/36	1/3	0/1	0/0

Heng. JCO. 2009;27:5794.

COSMIC-313: Background

- For patients with IMDC intermediate- or poor-risk advanced RCC, first-line standard of care is dual checkpoint inhibition with nivolumab + ipilimimab[1]
  - Improved survival and response rate vs sunitinib with durable responses, but progressive disease was best response in 20% of patients
- Multitargeted TKI cabozantinib is standard of care for advanced RCC alone or in combination with nivolumab[2]
- Combination of cabozantinib + nivolumab and ipilimumab was shown to be active with acceptable toxicity in phase I study in genitourinary tumors and in small cohort of patients with previously untreated advanced RCC[3,4]
- Current phase III COSMIC-313 study is investigating addition of cabozantinib to nivolumab + ipilimumab in previously untreated patients with IMDC intermediate- or poor-risk advanced RCC[5]

1. Motzer. NEJM. 2018;378:1277. 2. Choueiri. NEJM. 2021;384:829.
3. Apolo. JCO. 2020;38:3672. 4. Apolo. EIKCS 2022. Abstr 1. 5. Choueiri. ESMO 2022. Abstr LBA8.

COSMIC-313: Baseline Characteristics (ITT Population)

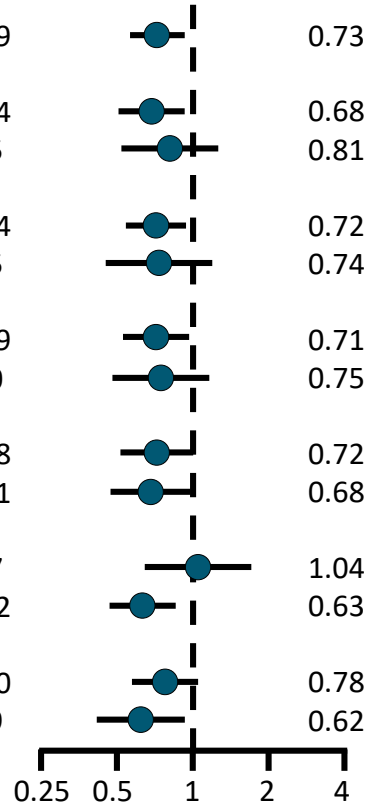
Characteristic	Cabozantinib + Nivolumab + Ipilimumab (n = 428)	Placebo + Nivolumab + Ipilimumab (n = 427)
Median age, yr (range)	61 (19-85)	60 (28-87)
Male, %	76	73
Region, %		
▪ US, Canada, Europe, Australia, New Zealand	65	65
▪ Latin America, Asia	35	35
IMDC intermediate/poor risk, %	75/25	75/25
Tumor PD-L1 status, %		
▪ <1%	64	62
▪ ≥1%	20	22
▪ Indeterminate/missing	17	16

Characteristic	Cabozantinib + Nivolumab + Ipilimumab (n = 428)	Placebo + Nivolumab + Ipilimumab (n = 427)
Karnofsky PS 100 or 90/70 or 80, %	59/41	63/37
Prior nephrectomy, %	65	65
1/≥2 sites with target/nontarget lesions per BIRC, %	19/80	19/80
Most common target/nontarget metastatic sites per BIRC, %		
▪ Lung	68	71
▪ Lymph node	54	50
▪ Liver	20	19
▪ Bone	17	21

Choueiri. ESMO 2022. Abstr LBA8.

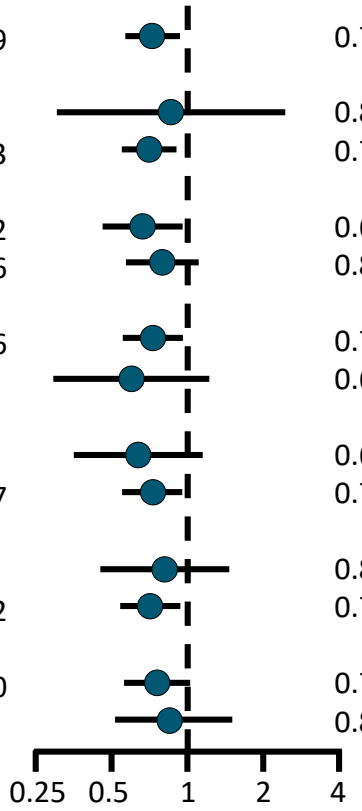
COSMIC-313: PFS Subgroup Analysis

Subgroup	N/events	HR (95% CI)
Overall*	550/249	0.73 (0.57–0.94)
Age		
< 65 yr	366/164	0.68 (0.50–0.93)
≥ 65 yr	184/85	0.81 (0.53–1.24)
Sex		
Male	417/184	0.72 (0.54–0.96)
Female	133/65	0.74 (0.45–1.21)
Geographic		
US, CAN, EU, AU, NZ	387/169	0.71 (0.53–0.97)
Latin America or Asia	163/80	0.75 (0.48–1.16)
KPS		
100 or 90	340/138	0.72 (0.52–1.01)
80 or 70	208/111	0.68 (0.47–0.99)
IMDC risk group		
Poor	133/67	1.04 (0.65–1.69)
Intermediate	417/182	0.63 (0.47–0.85)
Prior nephrectomy		
Yes	353/160	0.78 (0.57–1.06)
No	197/89	0.62 (0.41–0.94)



Favors Cabozantinib + Nivolumab + Ipilimumab ⟷ Favors Pbo + Nivolumab + Ipi

Subgroup	N/events	HR (95% CI)
Overall*	550/249	0.73 (0.57–0.94)
Sarcomatoid		
Yes	35/16	0.87 (0.30–2.52)
No	515/233	0.71 (0.55–0.92)
SoD of target lesions		
< Median	264/112	0.65 (0.45–0.94)
≥ Median	264/126	0.80 (0.57–1.14)
Visceral matastasis		
Yes	481/216	0.73 (0.56–0.96)
No	69/33	0.60 (0.30–1.20)
Liver metastasis		
Yes	86/42	0.64 (0.35–1.17)
No	464/207	0.73 (0.56–0.97)
Bone metastasis		
Yes	90/47	0.82 (0.45–1.49)
No	460/202	0.72 (0.55–0.95)
Tumor PD-L1 status		
< 1%	350/160	0.76 (0.56–1.04)
≥ 1%	112/50	0.87 (0.50–1.53)



Favors Cabozantinib + Nivolumab + Ipi ⟷ Favors Pbo + Nivolumab + Ipi

*Stratified. PFS per RECIST v1.1 by BIRC. Region and IMDC risk group are per IxRS.

COSMIC-313: Treatment Exposure and Discontinuation (Safety Population)

Parameter	Cabozantinib + Nivolumab + Ipilimumab (n = 426)	Cabozantinib + Nivolumab + Ipilimumab (n = 424)
Median exposure to study treatment, mo (range)	10.9 (0.2-28.5)	10.3 (0.1-28.1)
Median average daily dose of Cabo or Pbo, mg (range)	23.2 (3.6-40.0)	36.1 (0.8-40.0)
Median number of Nivo infusions (range)	10 (1-27)	9 (1-27)
Doses of Ipi received, %		
▪ 4	58	73
▪ 3	13	14
▪ 2	22	7
▪ 1	7	6

Parameter	Cabozantinib + Nivolumab + Ipilimumab (n = 426)	Cabozantinib + Nivolumab + Ipilimumab (n = 424)
Any dose hold due to AE, %	90	70
Any dose reduction of cabozantinib or placebo due to AE, %	54	20
Treatment-related AE leading to discontinuation, %		
▪ Any study treatment	45	24
▪ Cabo or Pbo	28	14
▪ Nivo	26	18
▪ Ipi	30	12
▪ All treatment components (due to same AE)	12	5

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COSMIC-313: Tumor Response (PITT Population)

BIRC Analysis	Cabozantinib + Nivolumab + Ipilimumab (n = 276)	Placebo + Nivolumab + Ipilimumab (n = 274)
ORR, % (95% CI)	43 (37.2-49.2)	36 (30.1-41.8)
Best overall response, n (%)		
▪ CR	7 (3)	9 (3)
▪ PR	112 (41)	89 (32)
▪ SD	119 (43)	100 (36)
▪ PD	23 (8)	55 (20)
▪ NE	15 (5)	21 (8)
Disease control rate, %*	86	72
Median time to objective response, mo (range)	2.4 (1.5-17.1)	2.3 (1.9-16.8)
Median DoR, mo (95% CI)	NR (20.2-NE)	NR (NE-NE)

*CR + PR + SD.

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COSMIC-313: Investigators' Conclusions

- In COSMIC-313, PFS was significantly improved with addition of cabozantinib to nivolumab and ipilimumab in previously untreated patients with IMDC intermediate- or poor-risk advanced RCC
  - Results consistent across subgroups examined
  - Benefit generally greater for IMDC intermediate- vs poor-risk groups
- Numerically higher ORR and disease control rate with cabozantinib + nivolumab + ipilimumab vs placebo + nivolumab + ipilimumab
- Manageable safety profile, consistent with individual profiles of different agents
  - Adverse events increased with cabozantinib + nivolumab + ipilimumab vs placebo + nivolumab + ipilimumab: elevated liver transaminases, diarrhea, skin toxicity
- Ongoing follow-up for OS (secondary endpoint)

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