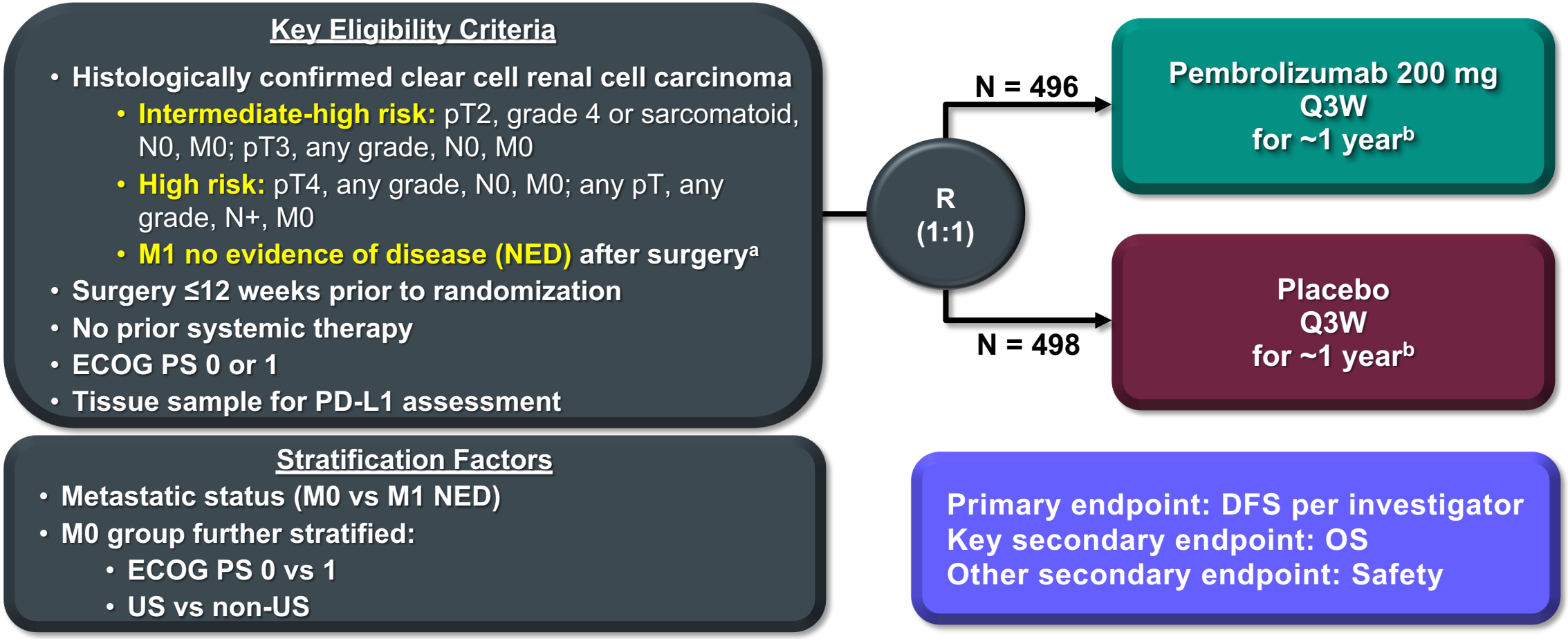
Post-ASCO GU Webcast on Renal Cell Carcinoma

Dr Brian Rini

KEYNOTE-564 (NCT03142334) Study Design

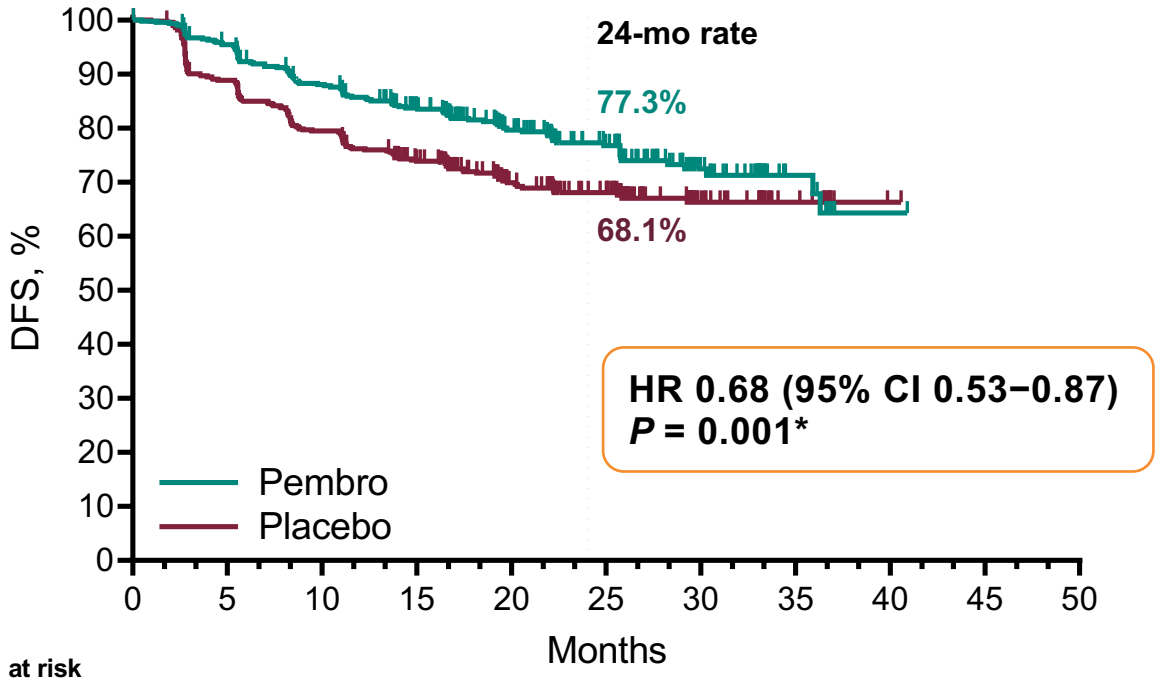


- Median (range) time from randomization to cutoff: 30.1 (20.8−47.5) months

Q3W, every 3 weeks.
[a]M1 NED: no evidence of disease after primary tumor + soft tissue metastases completely resected ≤1 year from nephrectomy; [b]≤17 cycles of treatment were equivalent to ~1 year.
Data cutoff date: June 14, 2021.

Primary Endpoint: DFS, ITT Population

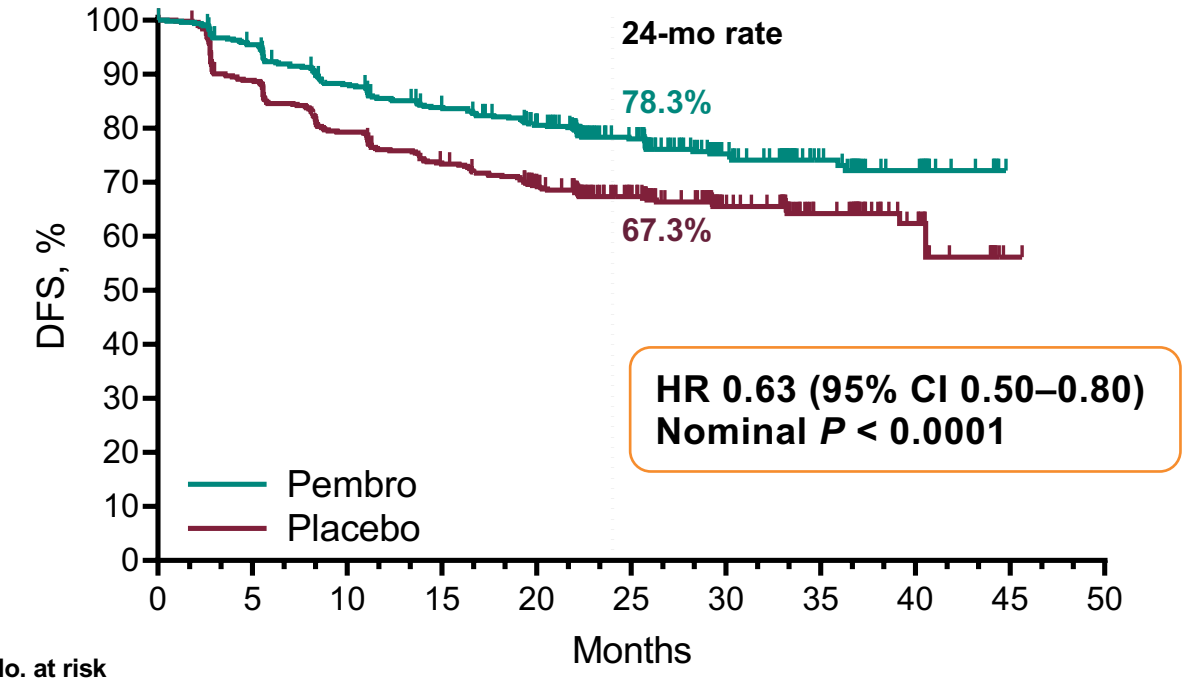
Primary Analysis: 24.1 mo Follow-Up



No. at risk											
Pembro	496	457	414	371	233	151	61	21	1	0	0
Placebo	498	436	389	341	209	145	56	19	1	0	0

	Pts w/ Event	Median, mo (95% CI)
Pembro	109	NR (NR–NR)
Placebo	151	NR (NR–NR)

Updated Analysis: 30.1 mo Follow-Up



No. at risk											
Pembro	496	458	416	389	361	255	135	77	37	0	0
Placebo	498	437	389	356	325	230	125	74	33	1	0

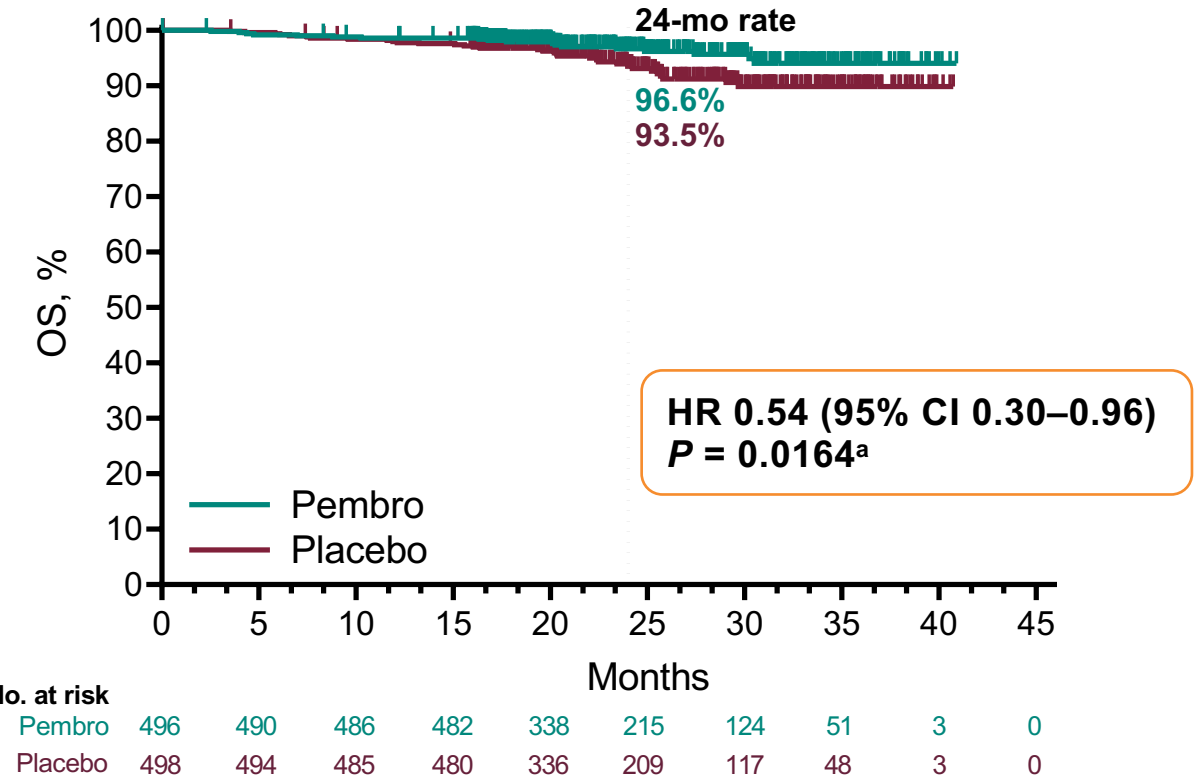
	Pts w/ Event	Median, mo (95% CI)
Pembro	114	NR (NR–NR)
Placebo	169	NR (40.5–NR)

* denotes statistical significance.

ITT population included all randomized participants. DFS, disease-free survival; NR, not reached. Primary analysis data cutoff date: December 14, 2020. Updated analysis data cutoff date: June 14, 2021.

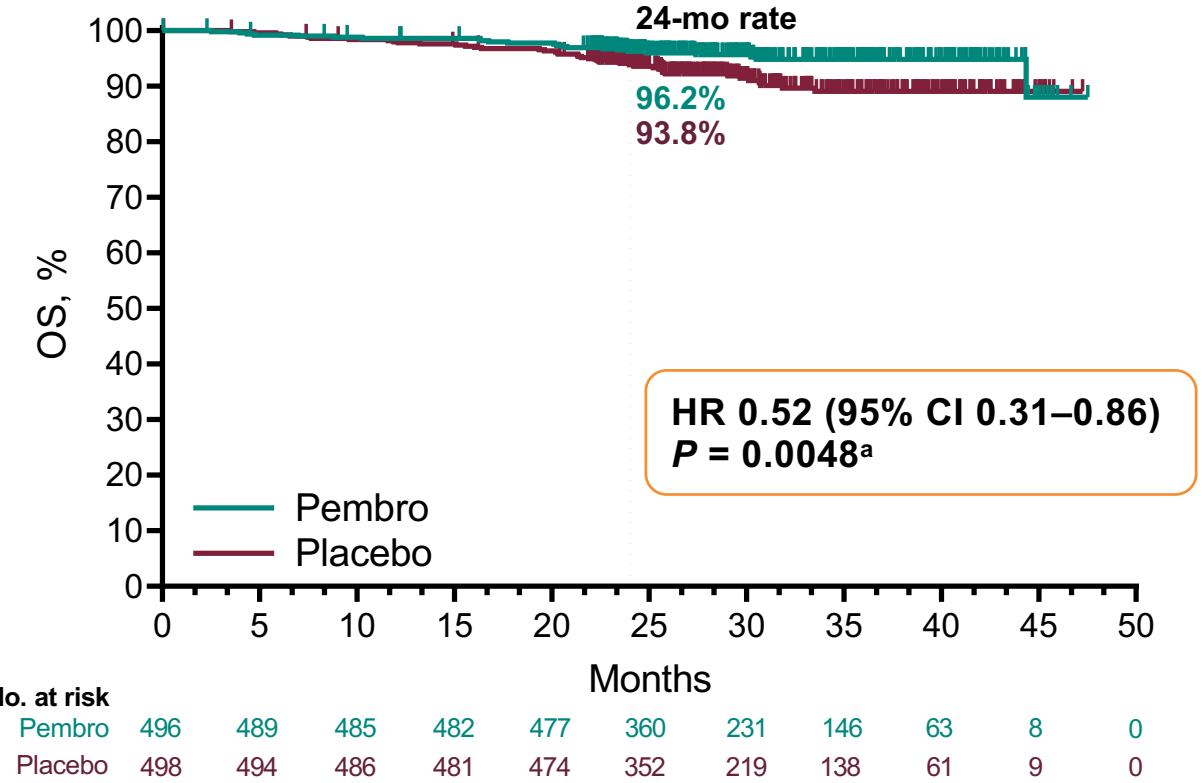
Key Secondary Endpoint: OS, ITT Population

Primary Analysis: 24.1 mo Follow-Up



	Pts w/ Event	Median, mo (95% CI)
Pembro	18	NR (NR–NR)
Placebo	33	NR (NR–NR)

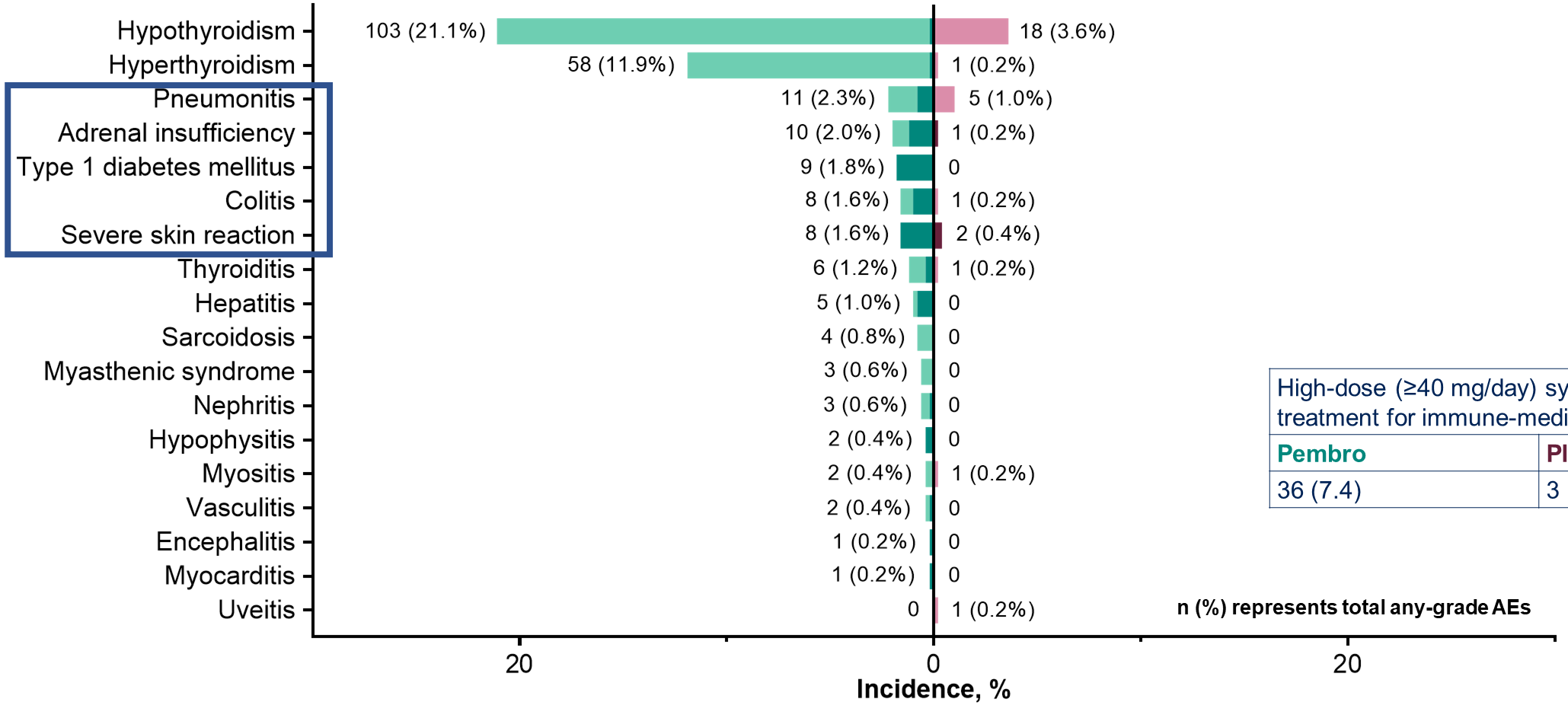
Updated Analysis: 30.1 mo Follow-Up



	Pts w/ Event	Median, mo (95% CI)
Pembro	23	NR (NR–NR)
Placebo	43	NR (NR–NR)

[a]Did not cross prespecified p-value boundary for statistical significance.
ITT population included all randomized participants. NR, not reached. Primary analysis data cutoff date: December 14, 2020. Updated analysis data cutoff date: June 14, 2021.

Immune-Mediated AEs[a], As-Treated Population



High-dose (≥40 mg/day) systemic corticosteroid treatment for immune-mediated AEs, n (%)	
Pembro	**Placebo**
36 (7.4)	3 (0.6)

[a]Based on a prespecified list of terms included regardless of attribution to study treatment by investigator.
Infusion reactions, pembro: any grade in 7 participants (1.4%), grade 3 in 2 participants (0.4%). Infusion reactions, placebo: any grade in 5 participants (1.0%), grade 3-4 in no participants. No deaths due to immune-mediated events occurred. As-treated population included all participants who received ≥1 dose of study treatment. Data cutoff date: December 14, 2020.

Studies of Adjuvant IO in RCC

Trial	Sample Size	Inclusion Criteria	Treatment	Primary Endpoint	Expected Results
Keynote-564[1]	994	pT2G4, pT3aG3-4, pT3b-T4Gx, pTxN1, pTxNxM1 (resected to NED within 1 year); clear cell	Pembrolizumab vs placebo	DFS	**ASCO 2021**
IMmotion010[2]	778	pT2G4, pT3aG3-4, pT3b-T4Gx, pTxN1, pTxNxM1 (resected to NED*); clear cell	Atezolizumab vs placebo	DFS	1/2022
CheckMate-914[3]	1600	pT2aG3-4N0, pT2b-T4GxN0, pTxGxN1; clear cell	Nivolumab + ipilimumab vs. nivolumab + placebo vs placebo *(6 months)*	DFS	1/2023
PROSPER RCC[4]	766	T2Nx, TxN1, TxNxM1 (resected to NED); any RCC histology	Nivolumab vs observation	EFS	11/2023
RAMPART[5]	1750	Leibovich score 3-11; any RCC histology	Durvalumab + tremelimumab vs durvalumab vs observation	DFS, OS	7/2024

*Metachronous pulmonary, lymph node, or soft tissue recurrence >12 months from nephrectomy.

DFS, disease-free survival; EFS, event-free survival; NED, no evidence of disease; RCC, renal cell carcinoma; OS, overall survival.

1. Choueiri TK et al. *N Engl J Med*. 2021;385:683-694. 2. NCT03024996. 3. NCT03138512. 4. NCT03055013. 5. NCT03288532.

IO + IO: CheckMate 214[1,2]

Patients

- **Treatment-naïve advanced or metastatic clear-cell RCC**
- **Measurable disease**
- **KPS ≥70%**
- **Tumor tissue available for PD-L1 testing**

Randomize 1:1

Stratified by
- IMDC prognostic score (favorable vs intermediate vs poor risk)
- Region (US vs Canada/ Europe vs rest of world)

Treatment

Arm A
3 mg/kg nivolumab IV + 1 mg/kg ipilimumab Q3W for four doses, then 3 mg/kg nivolumab Q2W

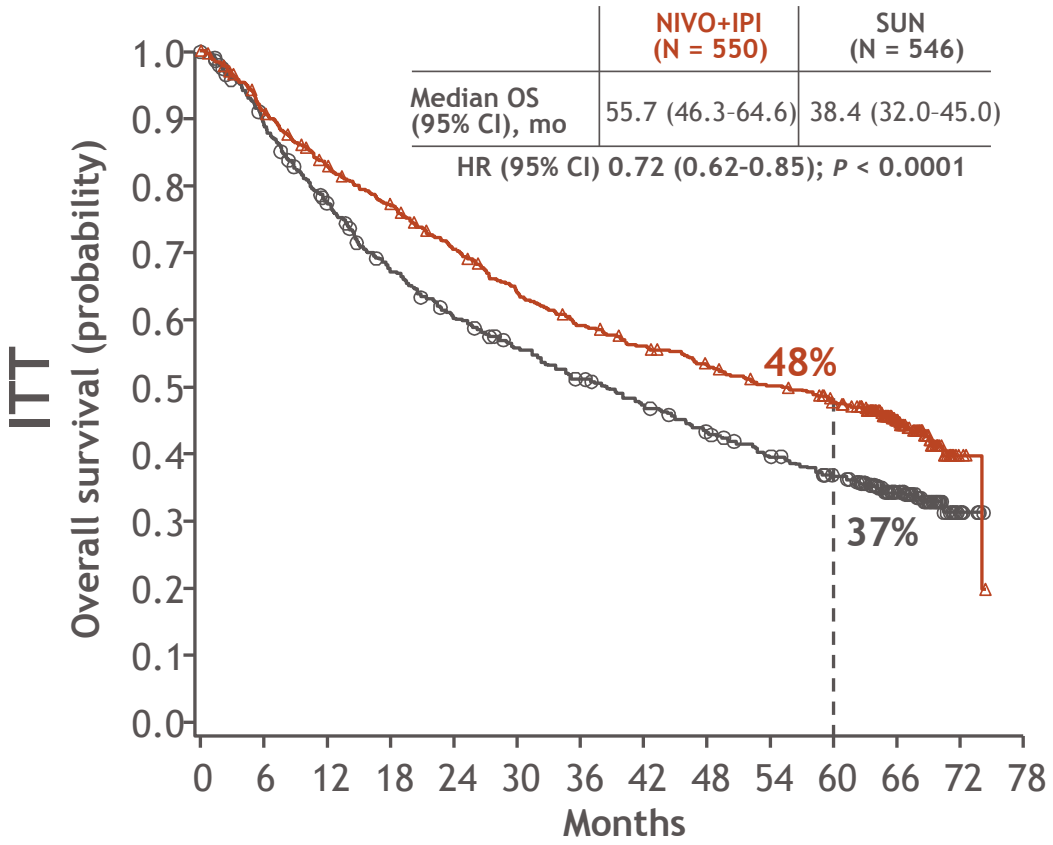
Arm B
50 mg sunitinib orally once daily for 4 weeks (6-week cycles)

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

1. Motzer et al. Lancet Oncology 2019. **2.** Motzer RJ, et al. N Engl J Med. 2018; 378:1277-1290.

OS and PFS in ITT: 5-year Update

Overall survival



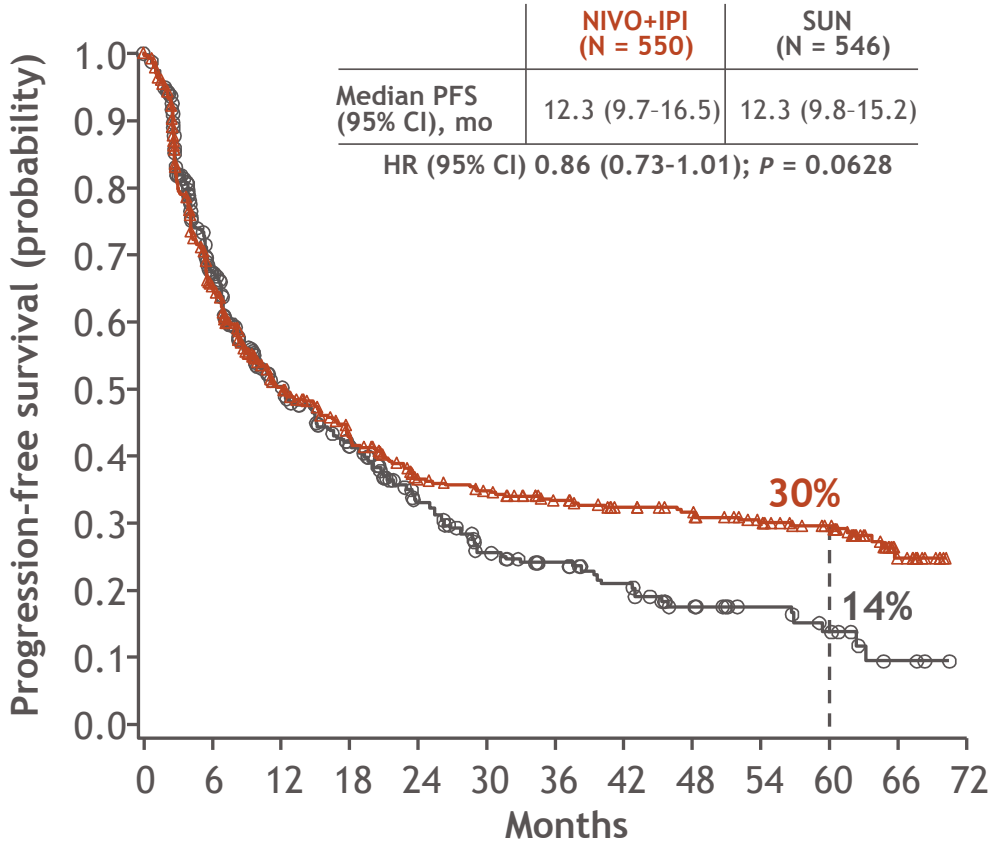
	NIVO+IPI (N = 550)	SUN (N = 546)
Median OS (95% CI), mo	55.7 (46.3-64.6)	38.4 (32.0-45.0)

HR (95% CI) 0.72 (0.62-0.85); *P* < 0.0001

No. at risk

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

Progression-free survival



	NIVO+IPI (N = 550)	SUN (N = 546)
Median PFS (95% CI), mo	12.3 (9.7-16.5)	12.3 (9.8-15.2)

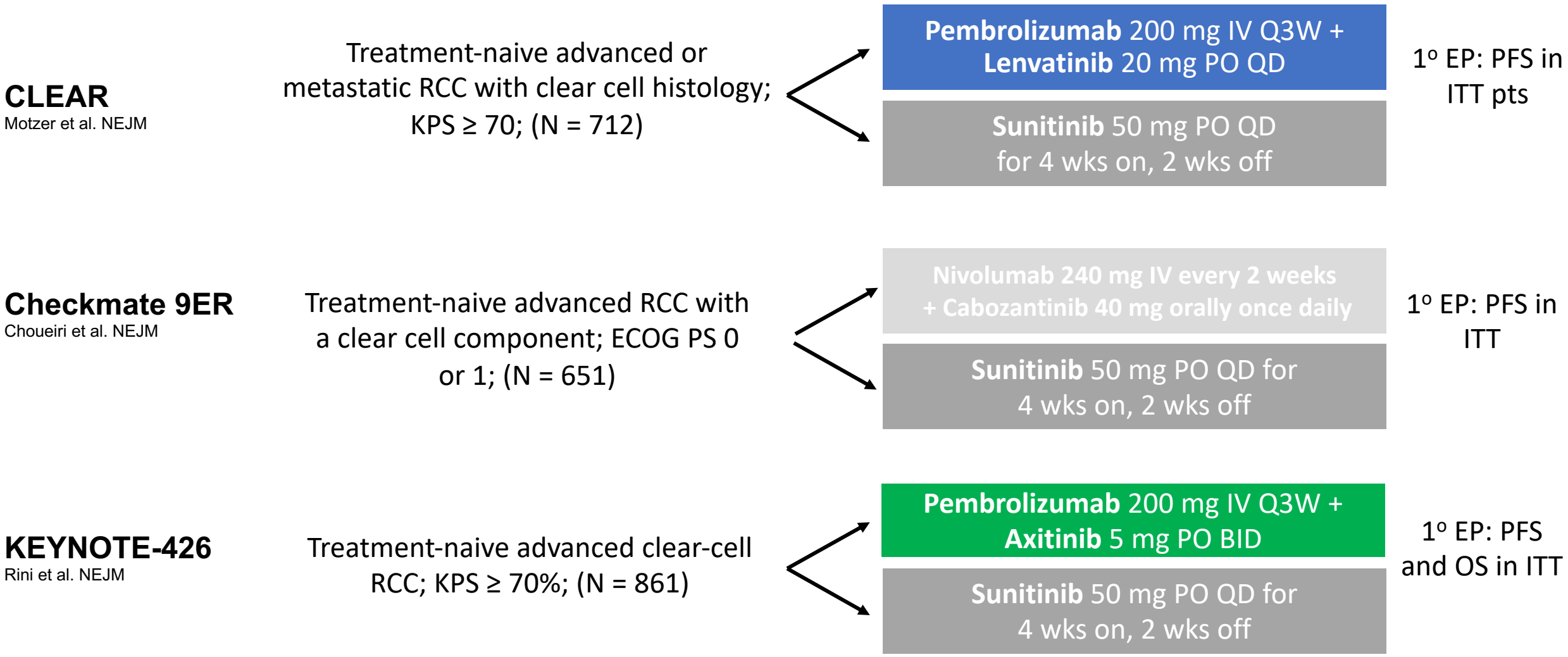
HR (95% CI) 0.86 (0.73-1.01); *P* = 0.0628

No. at risk

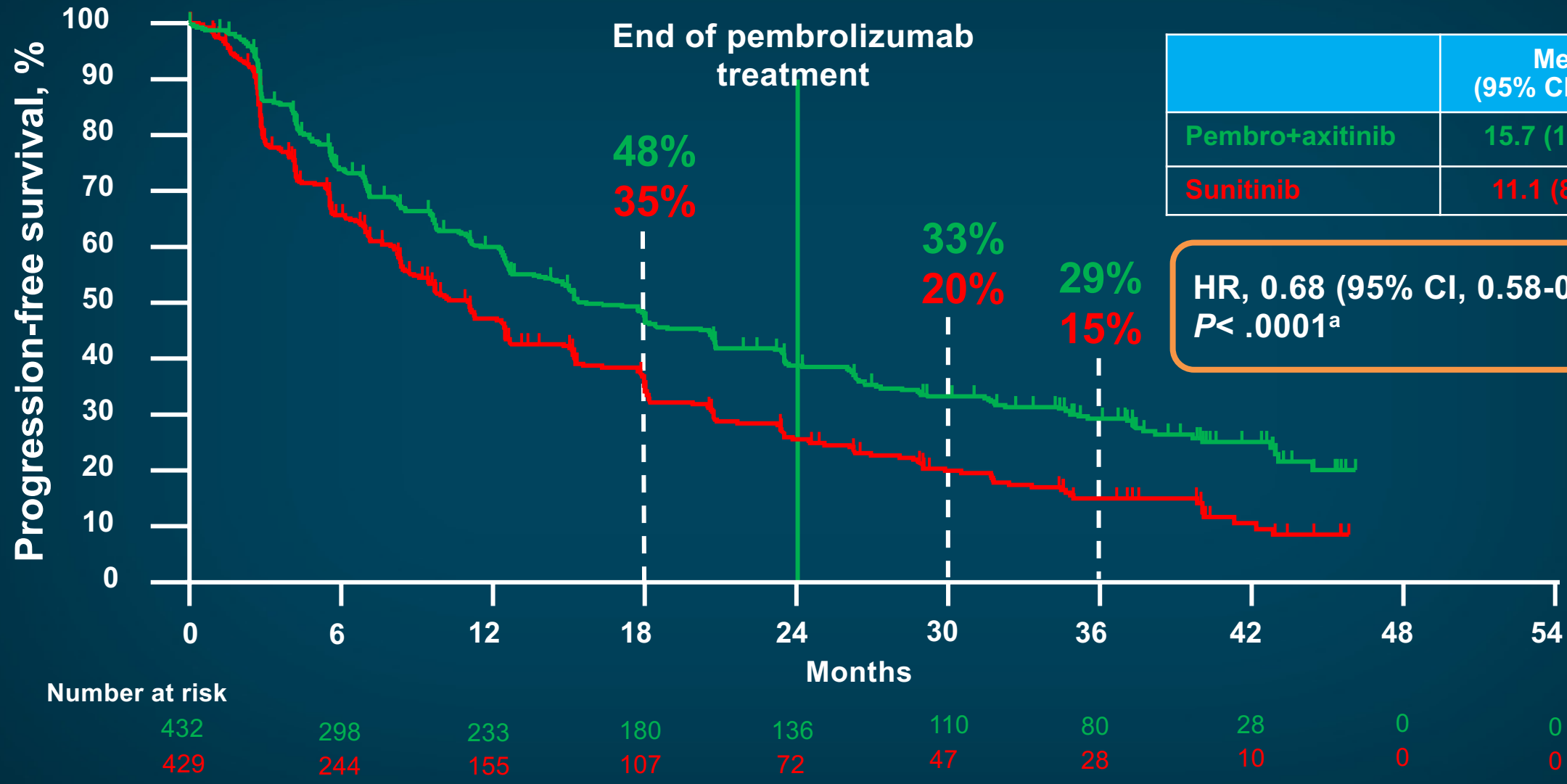
NIVO+IPI	550	315	217	171	132	121	103	92	86	75	62	14	0	
SUN	546	285	178	130	87	59	42	33	21	15	10	3	0	

Motzer RJ et al. ESMO 2021. Abstract 661P.

Randomized Phase III Study Designs for IO + VEGF TKI



KEYNOTE-426: PFS in the ITT Population



	Median (95% CI), months
Pembro+axitinib	15.7 (13.6-20.2)
Sunitinib	11.1 (8.9-12.5)

HR, 0.68 (95% CI, 0.58-0.80)
P< .0001[a]

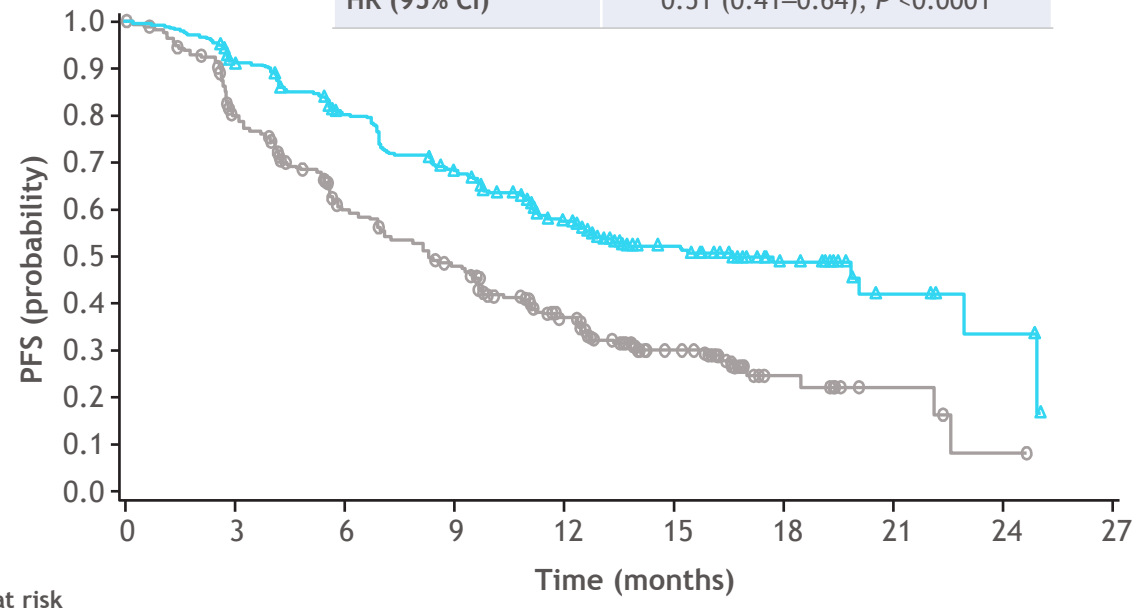
[a]Because superiority of pembrolizumab + axitinib was shown at the first interim analysis, no alpha was allocated to OS; only nominal *P* values are reported. Data cutoff: January 11, 2021.

Rini BI, et al. ASCO 2021; Abstract 4500. Powles T, et al. *Lancet Oncol.* 2020;21:1563-1573.

9ER: Progression-free survival and overall survival

Progression-free survival by BICR

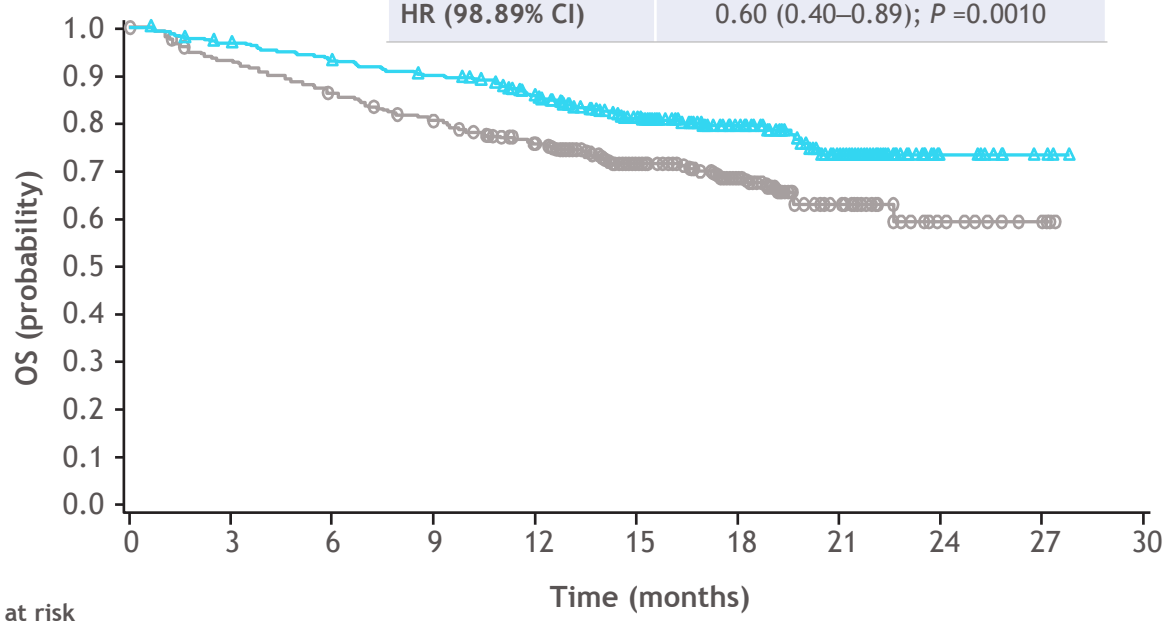
	NIVO + CABO n=323	SUN n=328
mPFS, mo (95% CI)	16.6 (12.5–24.9)	8.3 (7.0–9.7)
HR (95% CI)	0.51 (0.41–0.64); *P* <0.0001	



No. at risk										
NIVO + CABO	323	279	234	196	144	77	35	11	4	0
SUN	328	228	159	122	79	31	10	4	1	0

Overall survival

	NIVO + CABO n=323	SUN n=328
mOS, mo (95% CI)	NR (NE)	NR (22.6–NE)
HR (98.89% CI)	0.60 (0.40–0.89); *P* =0.0010	



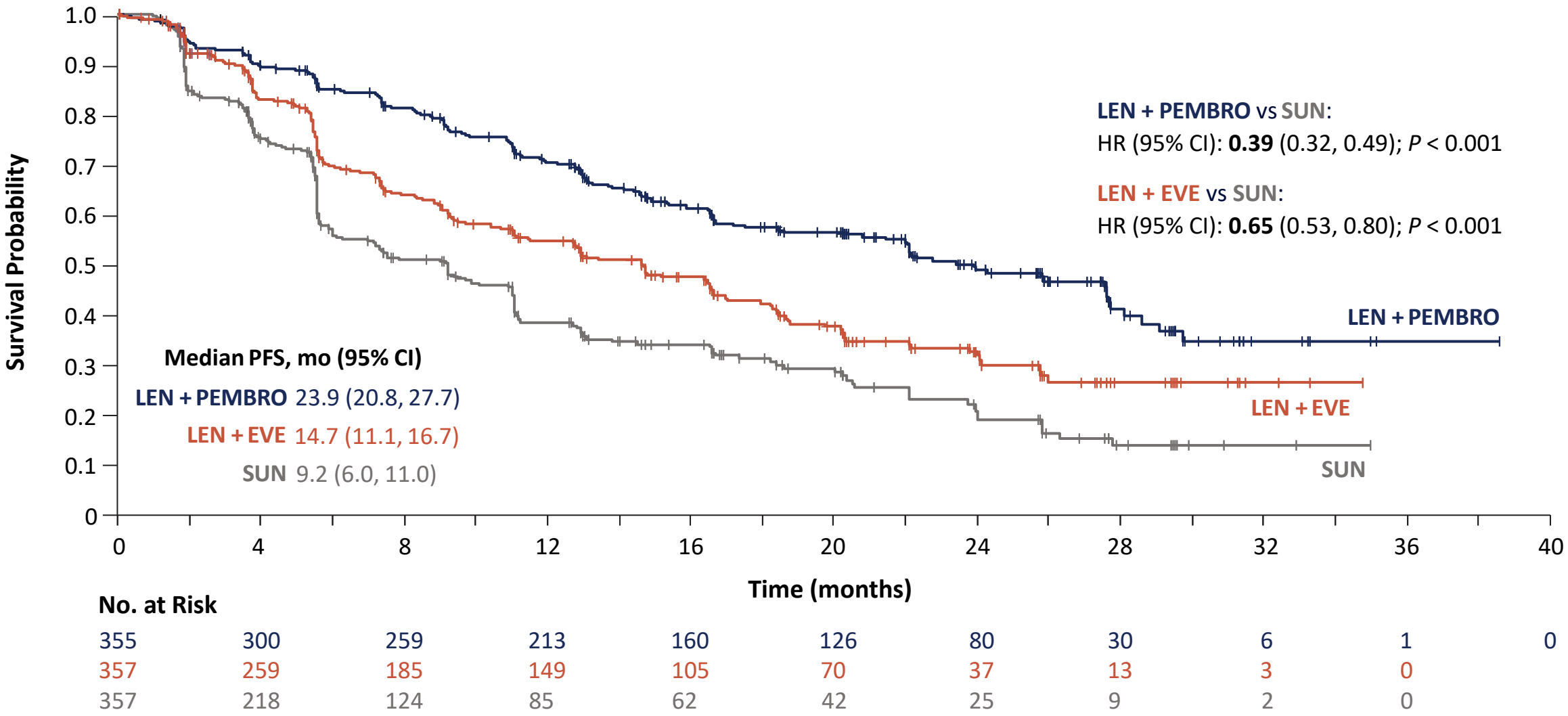
No. at risk												
NIVO + CABO	323	308	295	283	259	184	106	55	11	3	0
SUN	328	296	273	253	223	154	83	36	10	3	0

BICR=blinded independent central review; CABO=cabozantinib; CI=confidence interval; HR=hazard ratio; mo=month; mOS=median OS; mPFS=median PFS; NIVO=nivolumab; OS=overall survival; PFS=progression-free survival; SUN=sunitinib.

Choueiri TK et al. Oral presentation at ESMO 2020. Abstract 696O.

Motzer RJ et al. ASCO GU 2021;Abstract 269.

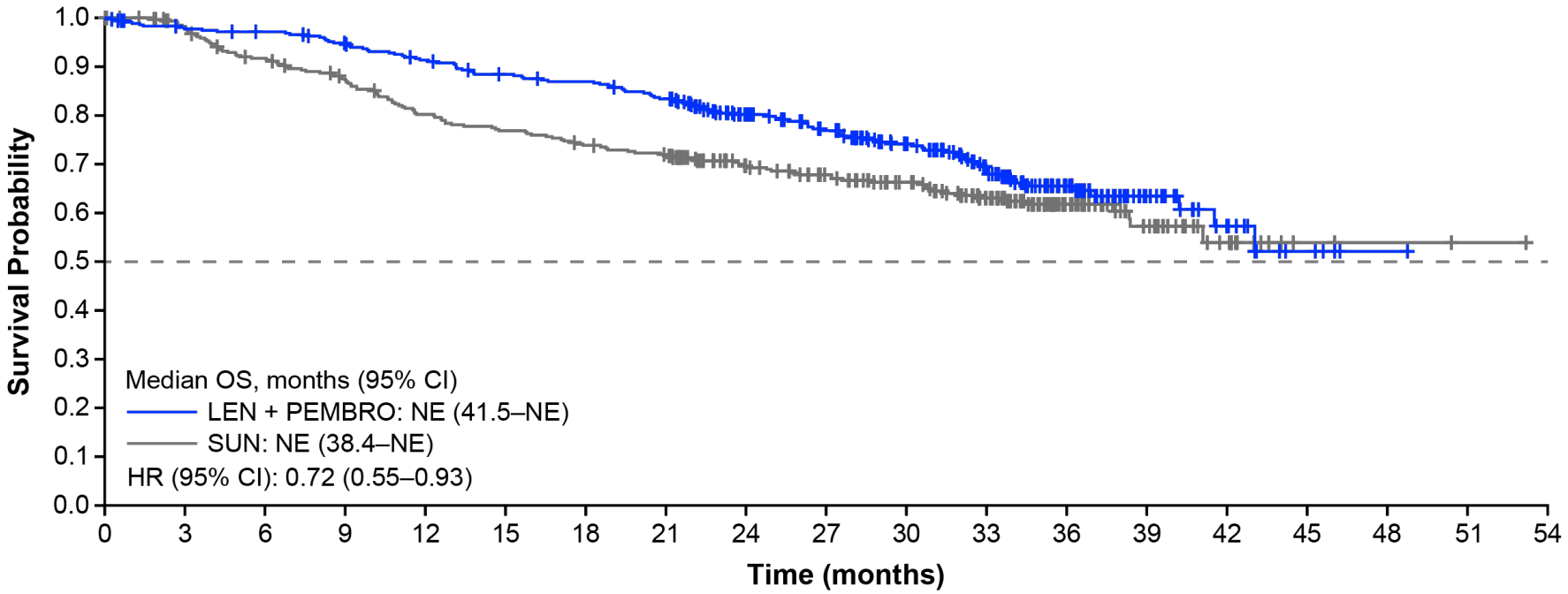
Len/Pembro CLEAR trial: Progression-free Survival*



*By Independent Review Committee per RECIST v1.1.

PRESENTED BY: Dr. Robert Motzer

Len/Pembro CLEAR trial: Overall Survival[a]



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

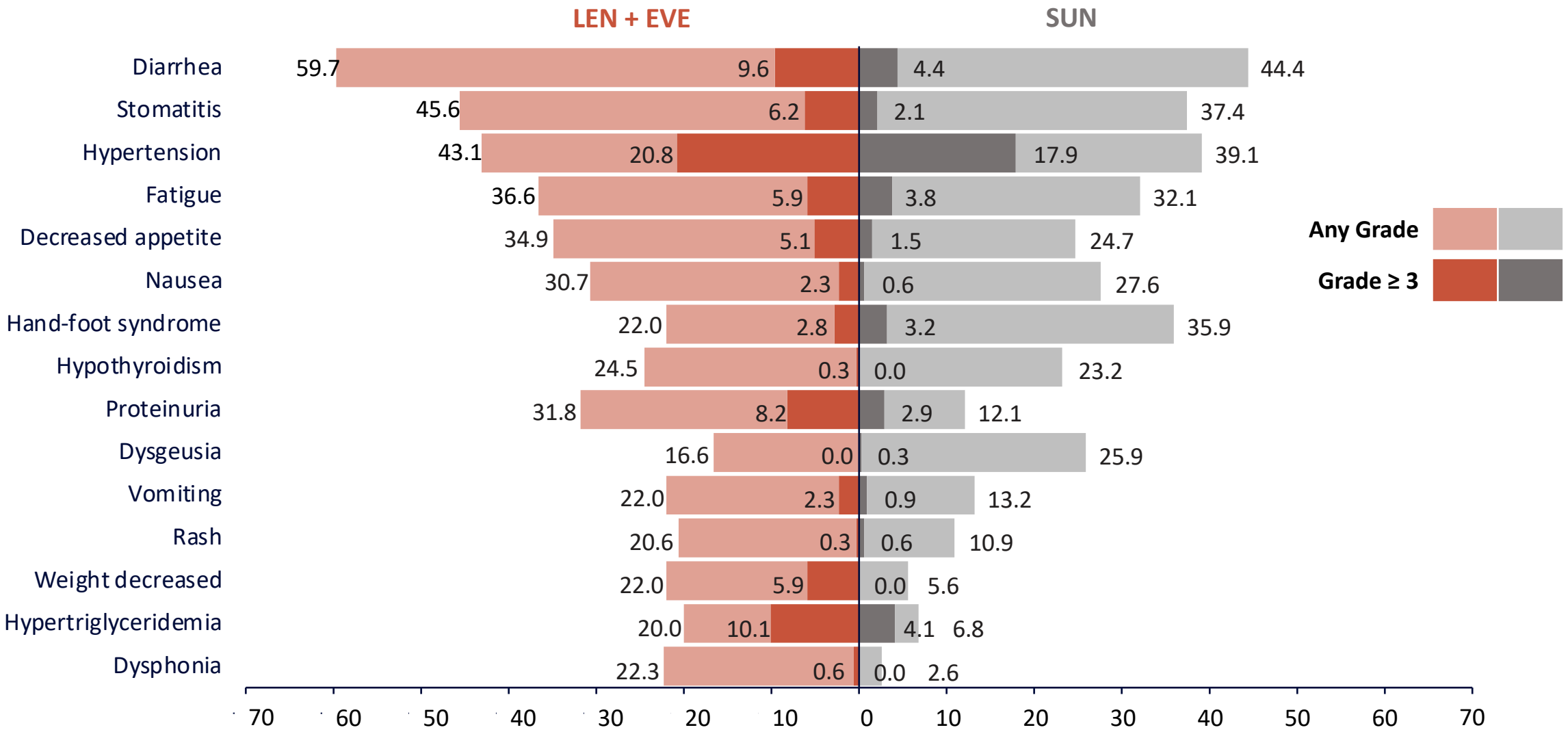
- Median duration of follow-up for OS was 33.7 months (95% CI, 32.8–34.4) in the LEN + PEMBRO arm and 33.4 months (95% CI, 32.5–34.1) in the SUN arm
- 250 (70.4%) and 235 (65.8%) patients in the LEN + PEMBRO and SUN arms were censored, respectively

[a]Data cutoff occurred on March 31, 2021.

CI, confidence interval; HR, hazard ratio; NE, not estimable; OS, overall survival.

Motzer RJ et al. ASCO GU 2021;Abstract 269.

Len/Pembro CLEAR trial: TRAEs With Frequency ≥ 20%



Alanine aminotransferase/aspartate aminotransferase increased in 10.4/11.5% (grade 3: 2.0/1.4%) of patients in the LEN + EVE arm and 8.8/8.8% of patients (grade 3: 1.8/0.6%) in the SUN arm.

First-line IO Combination Trials in mRCC

	CheckMate 214 (Ipi/Nivo)[1] (n=550 vs n=546)	KEYNOTE-426 (Axi/Pembro)[2] (n=432 vs n=429)	CheckMate 9ER (Cabo/Nivo)[3] (n=323 vs n=328)	CLEAR (Len/Pembro)[4] (N=355 vs n=357)
HR mOS, months	**0.72** 55.7 v	**0.73**	**0.70**	**0.72** NR vs NR
Landmark OS 12 mo Landmark OS 24 mo	**83%** vs. 78% **71%** vs. 61%	**90%** vs. 79% **74%** vs. 66%	**86%** vs. 76% **70%** vs 60%	**90%** vs 79% (est.) **79%** vs. 70%
HR mPFS, months	**0.86** **12.3** vs 12.3	**0.68**	**0.56**	**0.39**
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
Med f/u, months	**67.7**	**42.8**	**32.9**	**33.7**
Primary PD, %	**18**	**11**	**6**	**5**
Landmark PFS	30% (5 years)			

Consistent OS benefit vs VEGF TKI

More tumor shrinkage with TKI-containing regimens

Less early PD with TKI-containing regimens

CTLA-4 containing regimen perhaps with higher tail of the curve

1. Motzer et al. ESMO 2021
2. Rini et al. ASCO 2021
3. Powles et al. ASCO GU 2022
4. Motzer et al. ASCO GU 2021.

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

The role of NIVO + IPI (salvage/rescue)

	HCRN ASCO GU 2022	OMNIVORE ASCO 2020	FRACTION ASCO 2020	TITAN RCC ESMO 2019	Salvage Ipi/Nivo (JCO 2020)
N	35	83	46	207	45
Prior TKI	No	Yes	Yes	Yes	Yes
Timing	Nivo→Ipi	Nivo→Ipi	Nivo+Ipi	Nivo→Ipi	Nivo+Ipi after prior IO
Ipi doses	4	2	4	4	4
ORR	11%	14%	15%	33%	20%
CR	3%	0%	0%	3%	0%

Nivo+ipi combo untreated ccRCC ORR 39%, CR 12% (Checkmate 214)[1]

Lenvatinib + Pembro in IO-refractory RCC

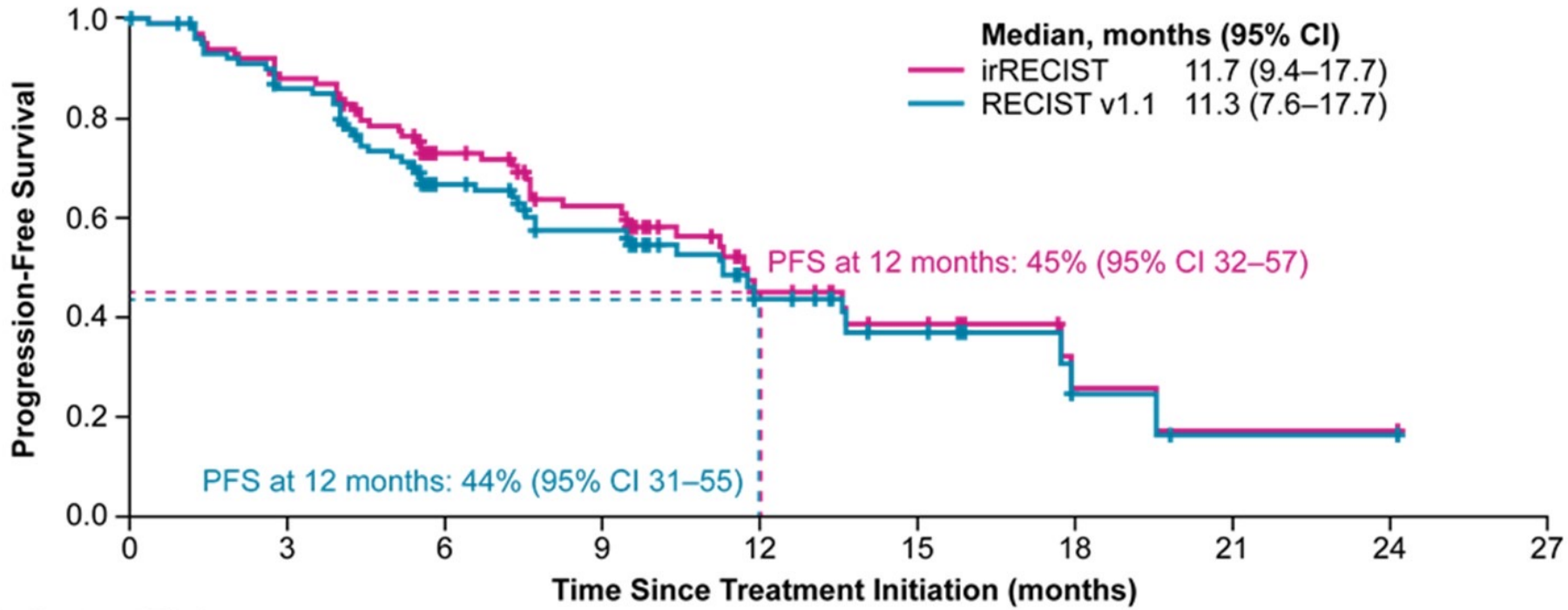
Tumor Response by Investigator Assessment

Parameter	irRECIST N = 104	RECIST v1.1[a] N = 104
ORR at week 24, % (95% CI)	51 (41–61)	–
ORR, % (95% CI)	55 (45–65)	52 (42–62)
Best objective response, %		
Partial response	55	52
Stable disease	36	38
Progressive disease	5	6
Not evaluable	5	5
Median DOR, months (95% CI)	12 (9–18)	12 (9–18)

[a] Up to 10 target lesions could be selected (up to 5 per organ).

DOR, duration of response.

PFS Kaplan–Meier Curves by irRECIST[a] and RECIST v1.1[a,b]



Number of Patients at Risk:

irRECIST	104	86	58	45	18	11	3	1	1	0
RECIST v1.1	104	84	53	41	17	10	3	1	1	0

[a] Per investigator assessment; [b] up to 10 target lesions could be selected (up to 5 per organ).

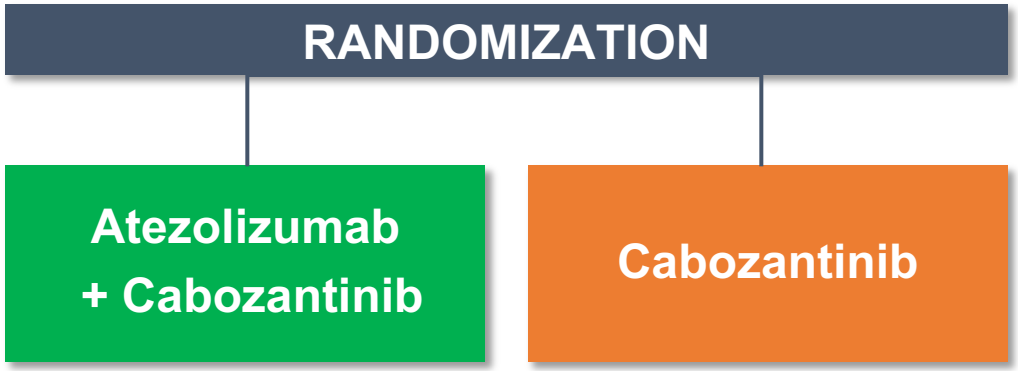
Randomized PD-1/VEGF Blockade Salvage Trial

CONTACT-03 (NCT04338269)

mRCC 2/3L (clear cell, papillary, unclassified)

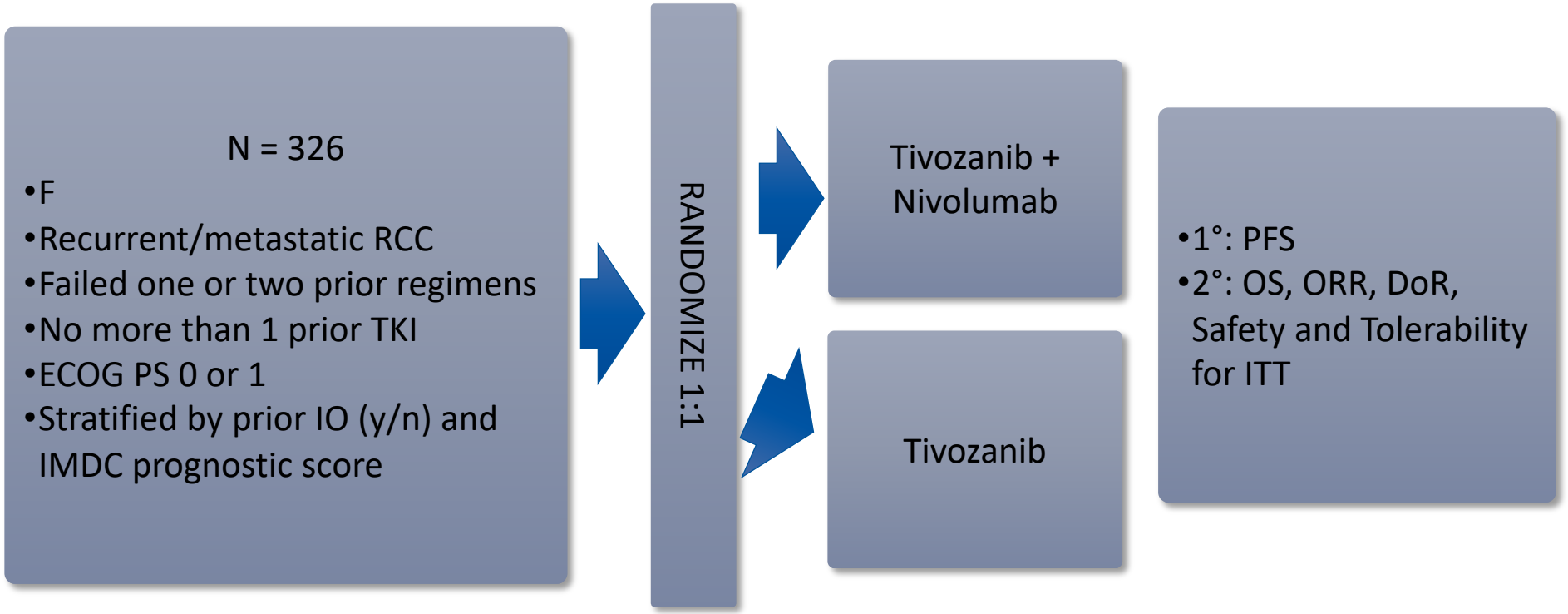
VEGFRTKI ± PD-L1 inhibition

Phase 3 (N = 500)
Primary endpoint: PFS, OS



TiNivo-2: Tivozanib + Nivolumab Combination in RCC – Ph3

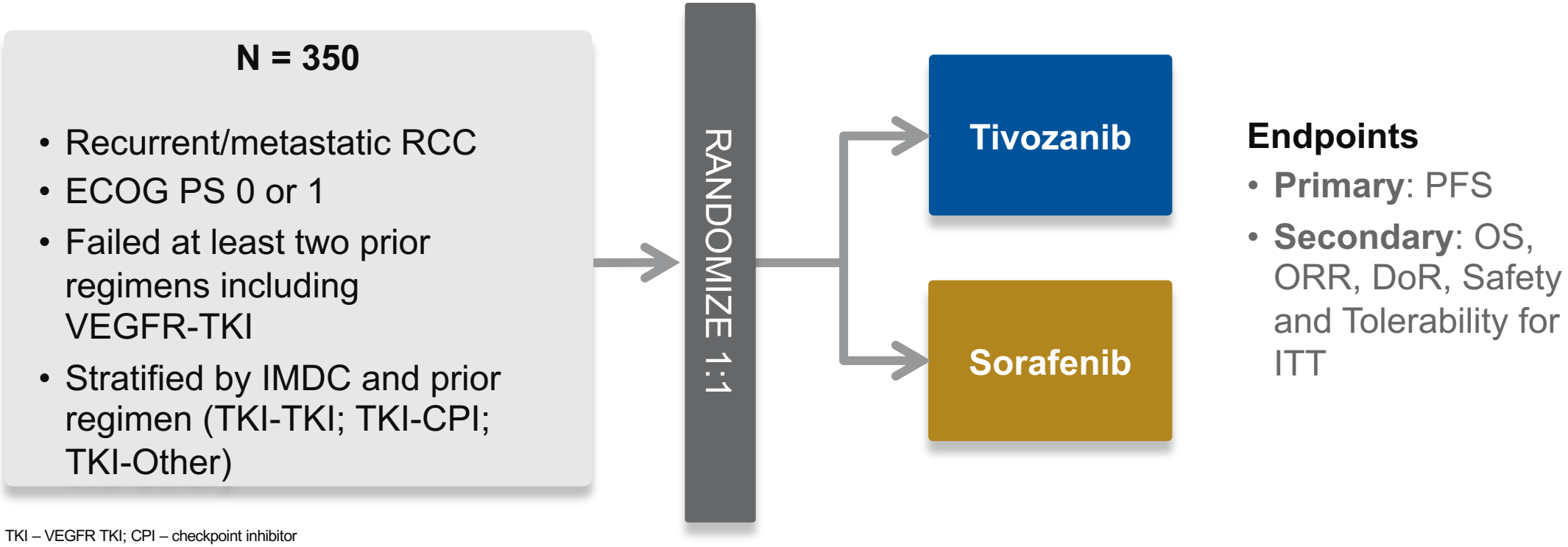
Phase 3, Randomized, Controlled, Multi-Center, Open-Label Study to Compare Tivozanib + Nivolumab to Tivozanib in Subjects With 2nd and 3rd Line Advanced RCC



N = 326 (Assumes 15 vs 10 months PFS)
Data mid 2024

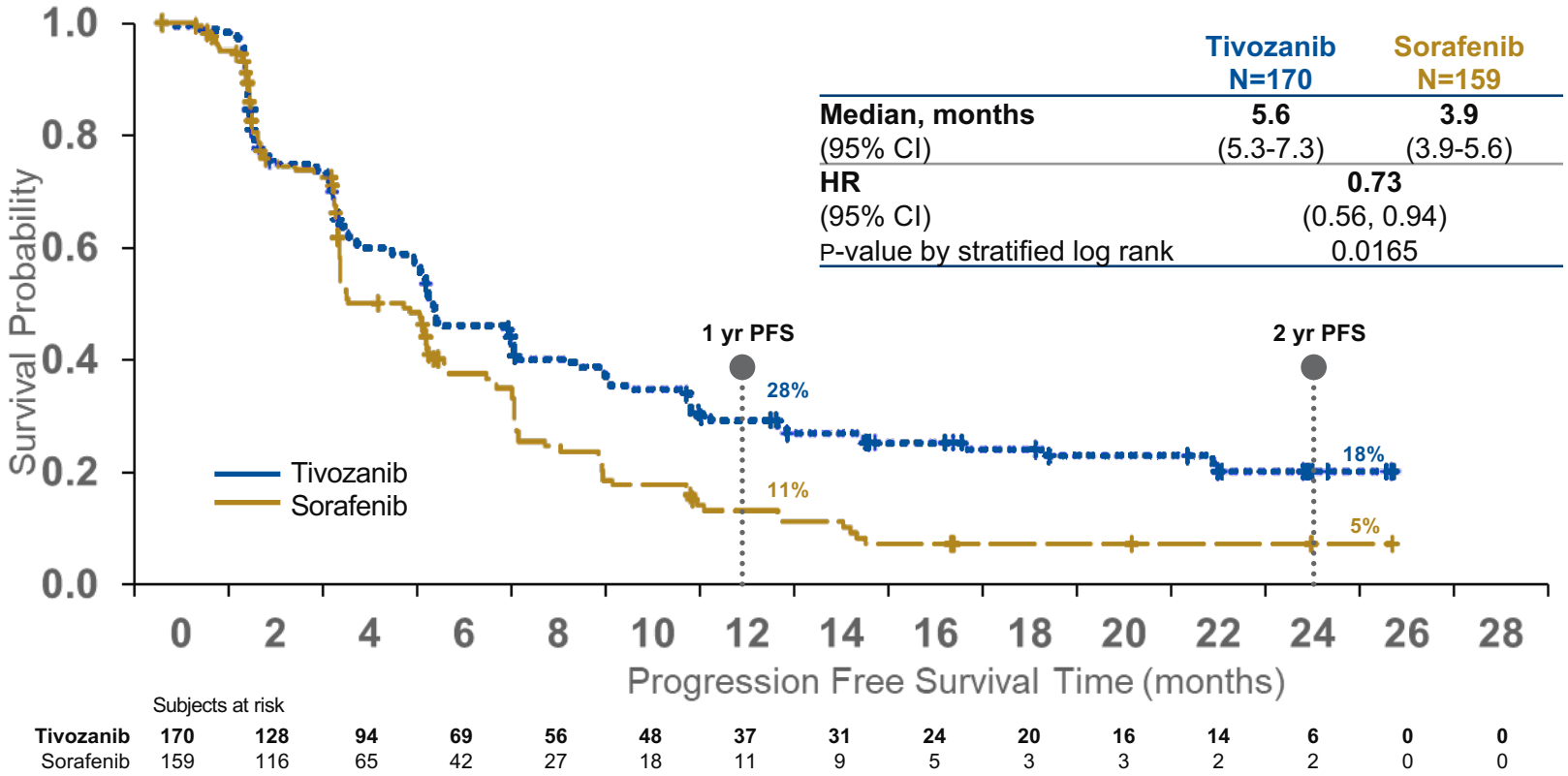
Refractory RCC: TIVO-3 Study Schema

Randomized Trial in Relapsed or Refractory Advanced Renal Cell Carcinoma



TKI – VEGFR TKI; CPI – checkpoint inhibitor

TIVO-3: Primary Endpoint of PFS



	Tivozanib N=170	Sorafenib N=159
Median, months	**5.6**	**3.9**
(95% CI)	(5.3-7.3)	(3.9-5.6)
HR	**0.73**	
(95% CI)	(0.56, 0.94)	
P-value by stratified log rank	0.0165	

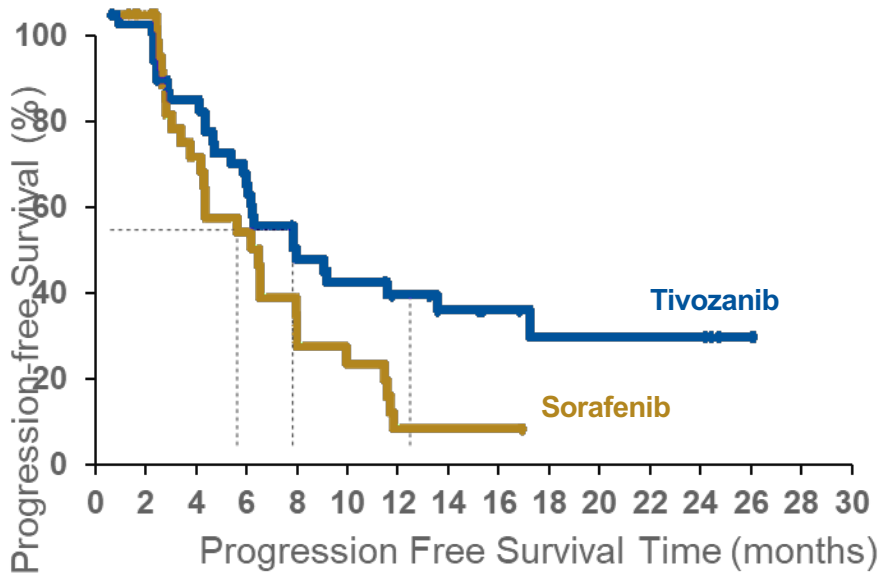
Subjects at risk

Tivozanib	**170**	**128**	**94**	**69**	**56**	**48**	**37**	**31**	**24**	**20**	**16**	**14**	**6**	**0**	**0**
Sorafenib	159	116	65	42	27	18	11	9	5	3	3	2	2	0	0

Primary PFS endpoint final analyses, Oct 4, 2018

Rini B et al. ASCO GU 2021;Abstract 278

TIVO-3: PFS & ORR in Prior IO Subgroup



Porta et al. ASCO 2019

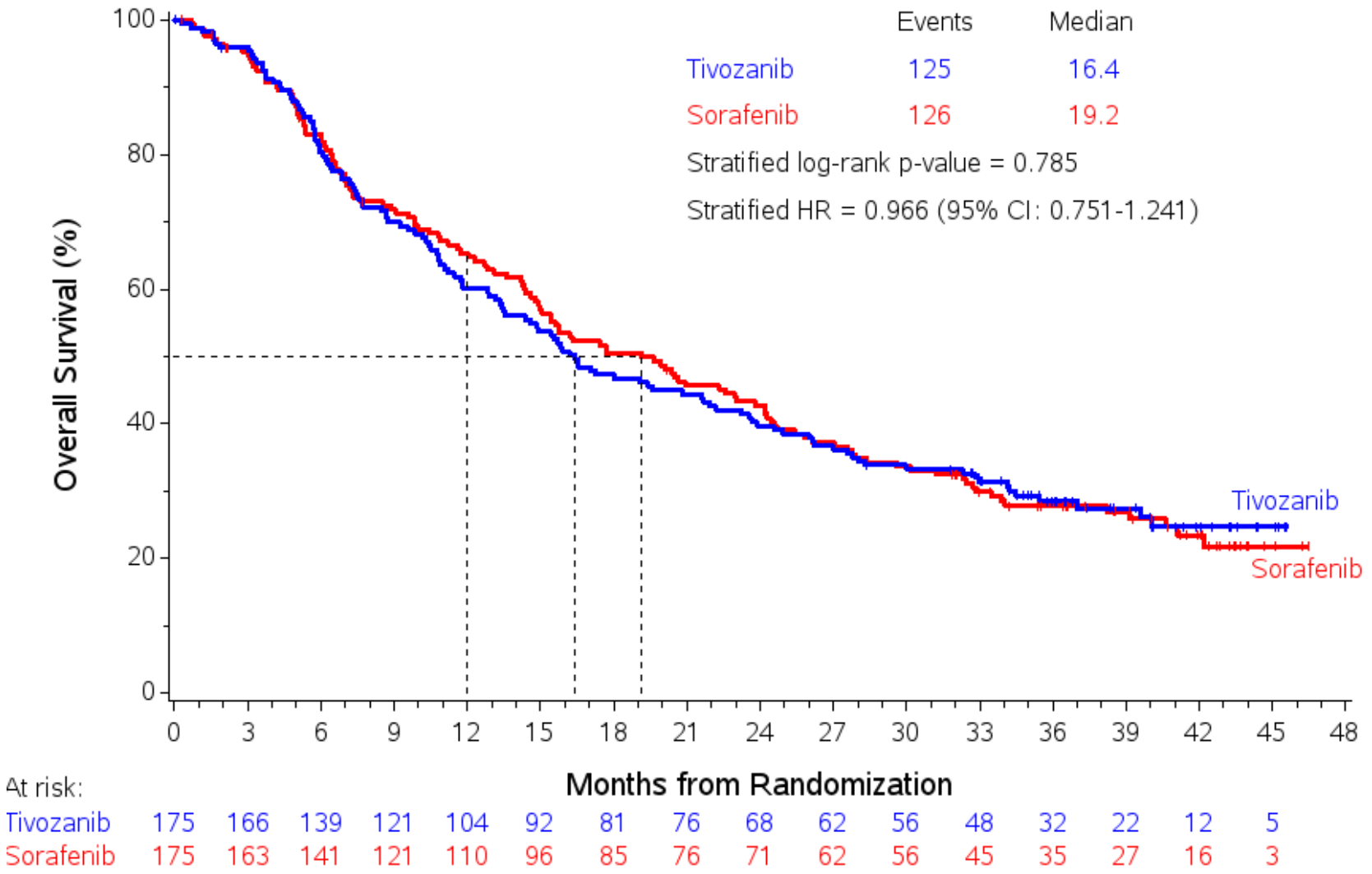
Final analyses, Oct 4, 2018

Prior Checkpoint Inhibitor (CPI) + VEGFR TKI

	Tivozanib (n=47)	Sorafenib (n=44)
Median PFS months (95% CI)	**7.3** (4.8, 11.1)	**5.1** (3.2, 7.4)
HR (95% CI)	**0.55** (0.32, 0.94)	
P-value	0.028	
ORR	24.4%	6.8%

Rini B et al. ASCO GU 2021;Abstract 278

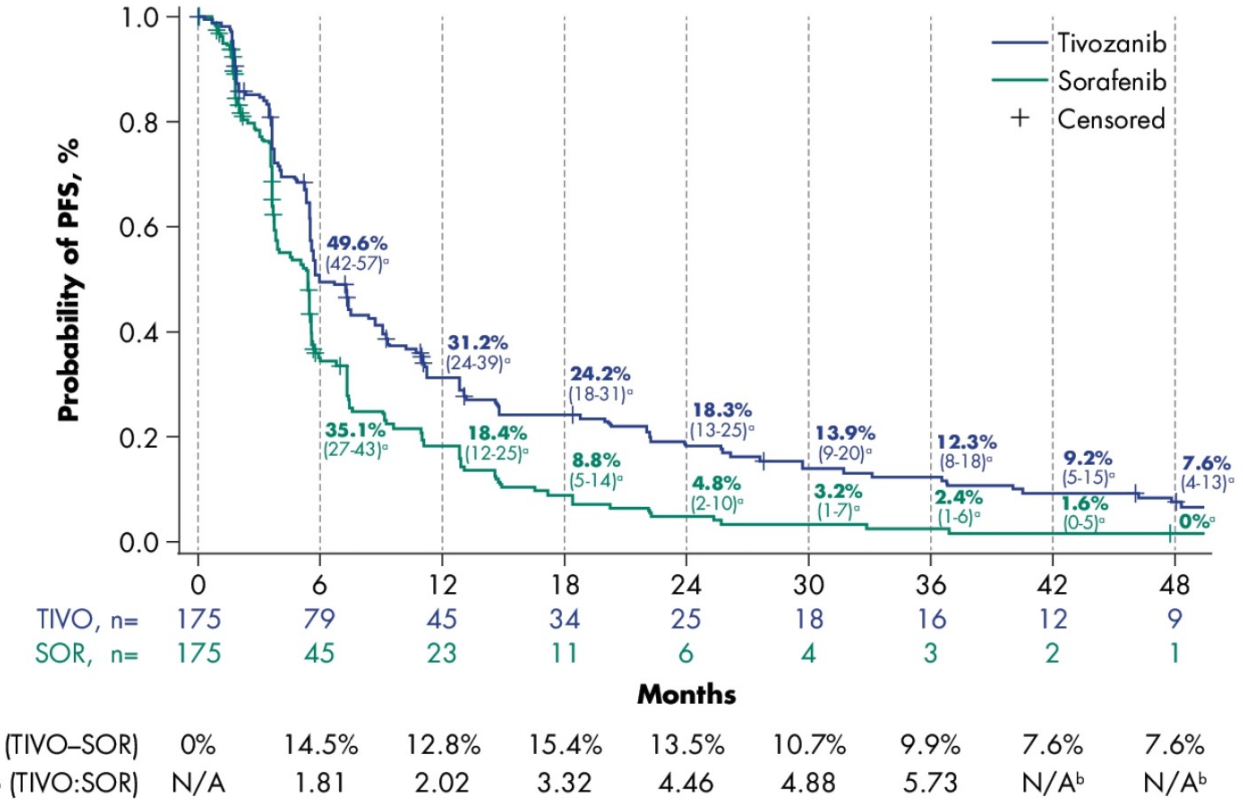
TIVO-3: Final OS



Pal Eur Urol 2020;78(6):P783-5

Long-term PFS from TIVO-3

Figure 2. Landmark Rates (95% CI) of LT-PFS in TIVO-3: TIVO vs SOR



LT-PFS Δ (TIVO–SOR)	0%	14.5%	12.8%	15.4%	13.5%	10.7%	9.9%	7.6%	7.6%
Odds ratio (TIVO:SOR)	N/A	1.81	2.02	3.32	4.46	4.88	5.73	N/A[b]	N/A[b]

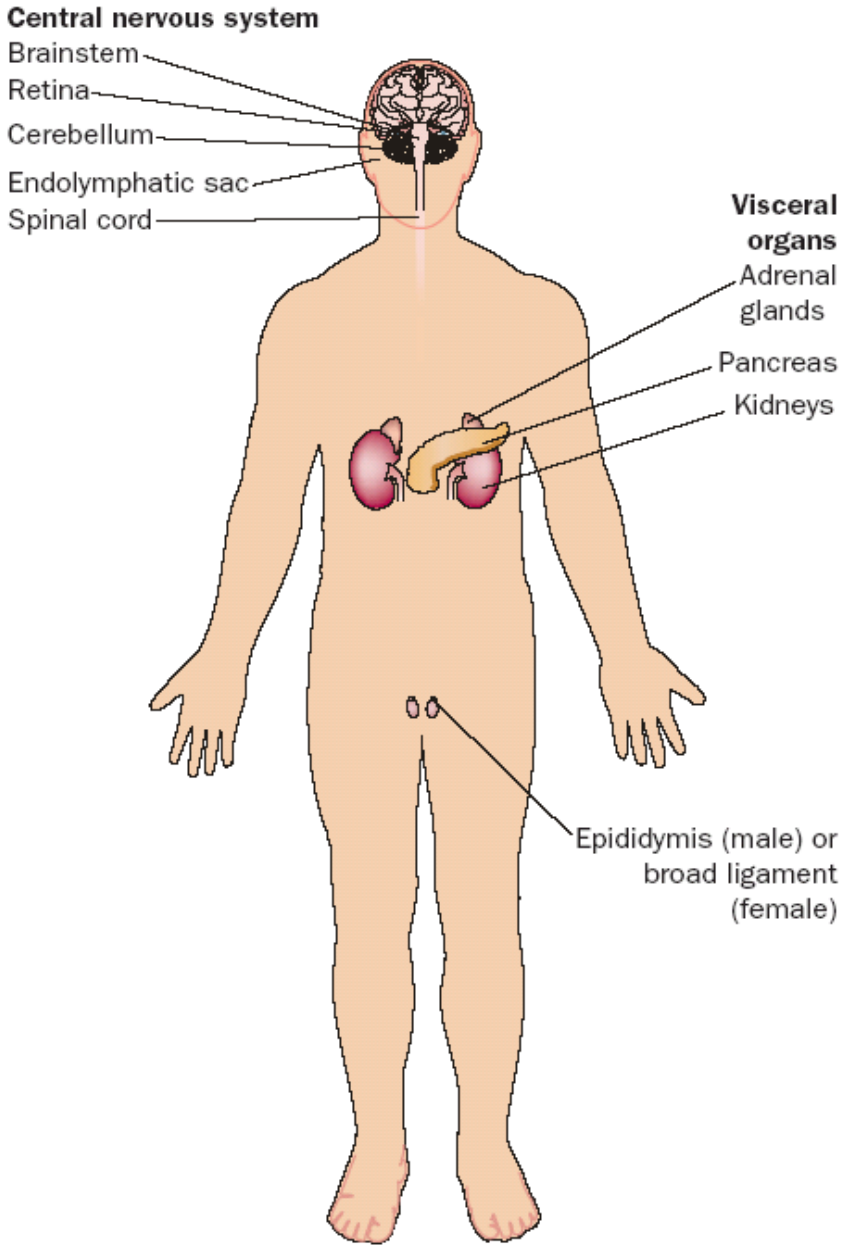
[a]% (95% CI). [b]OR not calculated at months 42 and 48 due to insufficient number at risk.
HR, 0.624 (95% CI, 0.49-0.79); log-rank *P*<.0001

- Mature OS was also analyzed, and a nonsignificant trend favoring TIVO continued to emerge with accumulation of events (HR, 0.89; 95% CI, 0.70-1.14)

Atkins MB et al. ASCO GU 2022;Abstract 362.

VHL disease manifestations

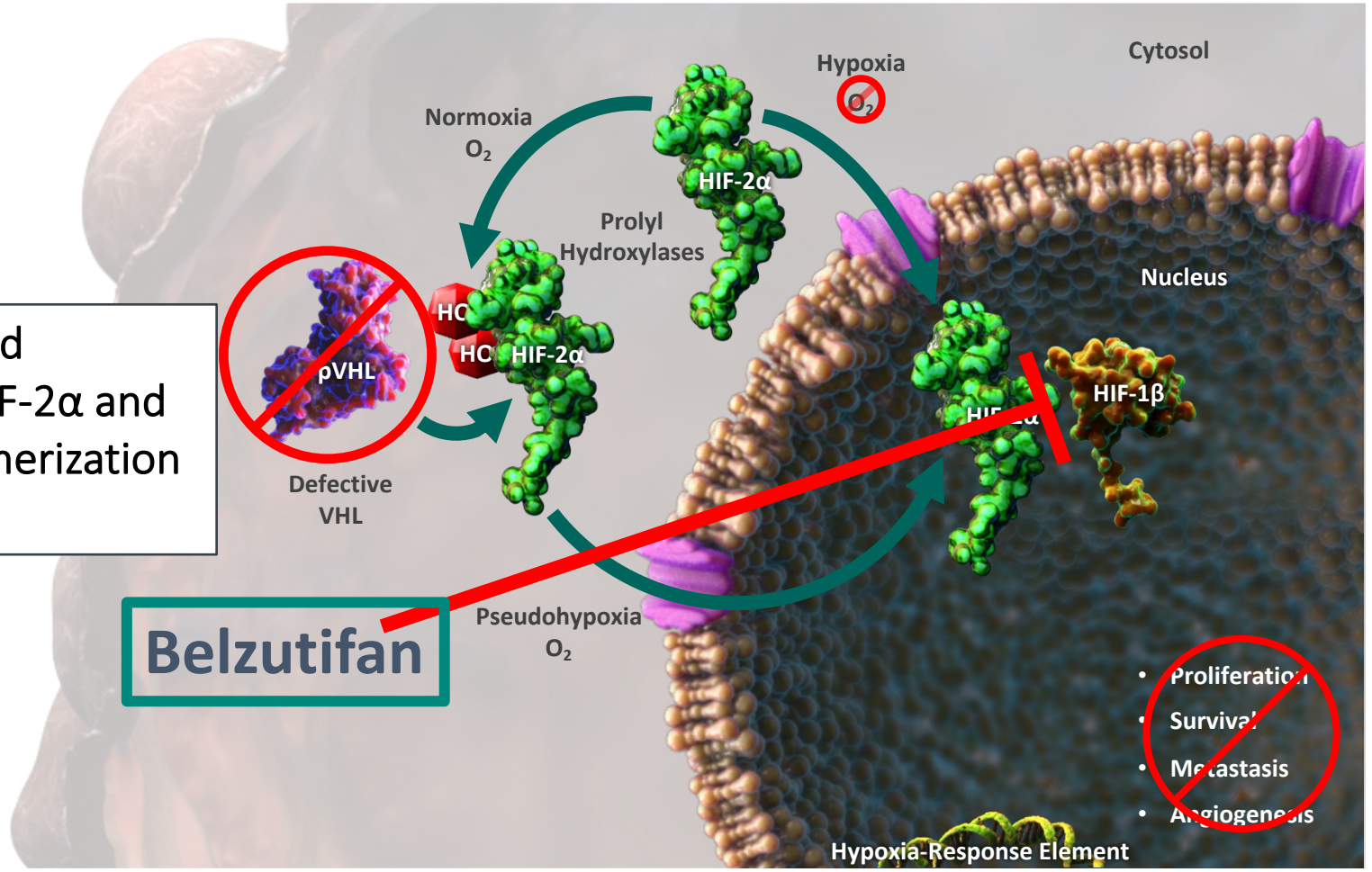
1. Endolymphatic sac tumors
2. Retinal hemangioblastomas
3. Cerebellar and spinal hemangioblastomas
4. Pancreatic cyst and neuroendocrine tumors
5. Kidney cysts and clear cell carcinomas
6. Pheochromocytomas
7. Epididymis/round ligament cysts



Lonser *Lancet* 2003

Belzutifan: HIF-2α Inhibitor

Belzutifan potently and selectively binds to HIF-2α and prevents its heterodimerization with HIF-1β



Kaelin WG Jr. *Trans Am Clin Climatol Assoc*. 2017;128:298-307. Kondo K et al. *Cancer Cell.* 2002;1:237-246. Xu R et al. *J Med Chem.* 2019;62:6876-6893.

Belzutifan for VHL-associated RCC (NCT03401788)

- Diagnosis of VHL disease, based on germline mutation
- ≥1 measurable RCC tumor
- No prior systemic anticancer therapy
- No metastatic disease
- ECOG PS 0 or 1

N = 61

MK-6482
120 mg orally once daily

Tumor evaluation performed at screening and every 12 weeks thereafter

Primary End Point
- ORR in VHL-associated RCC tumors per RECIST v1.1 by independent central review

Secondary End Points
- ORR in non-RCC lesions
- DOR **in RCC and non-RCC lesions**
- Safety

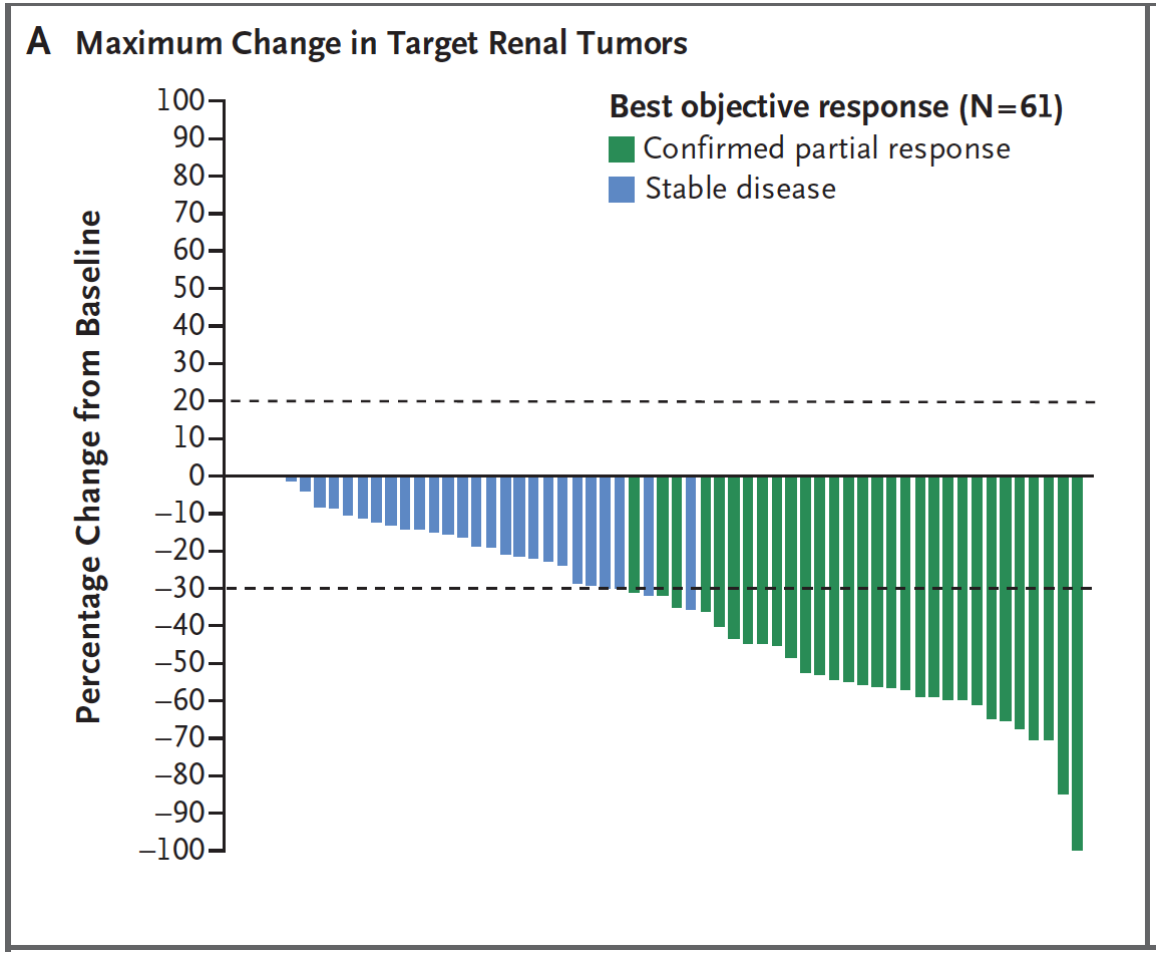
Primary Objective

- To evaluate efficacy of MK-6482 for the treatment of VHL disease–associated RCC

Response in target RCC lesions by independent central review

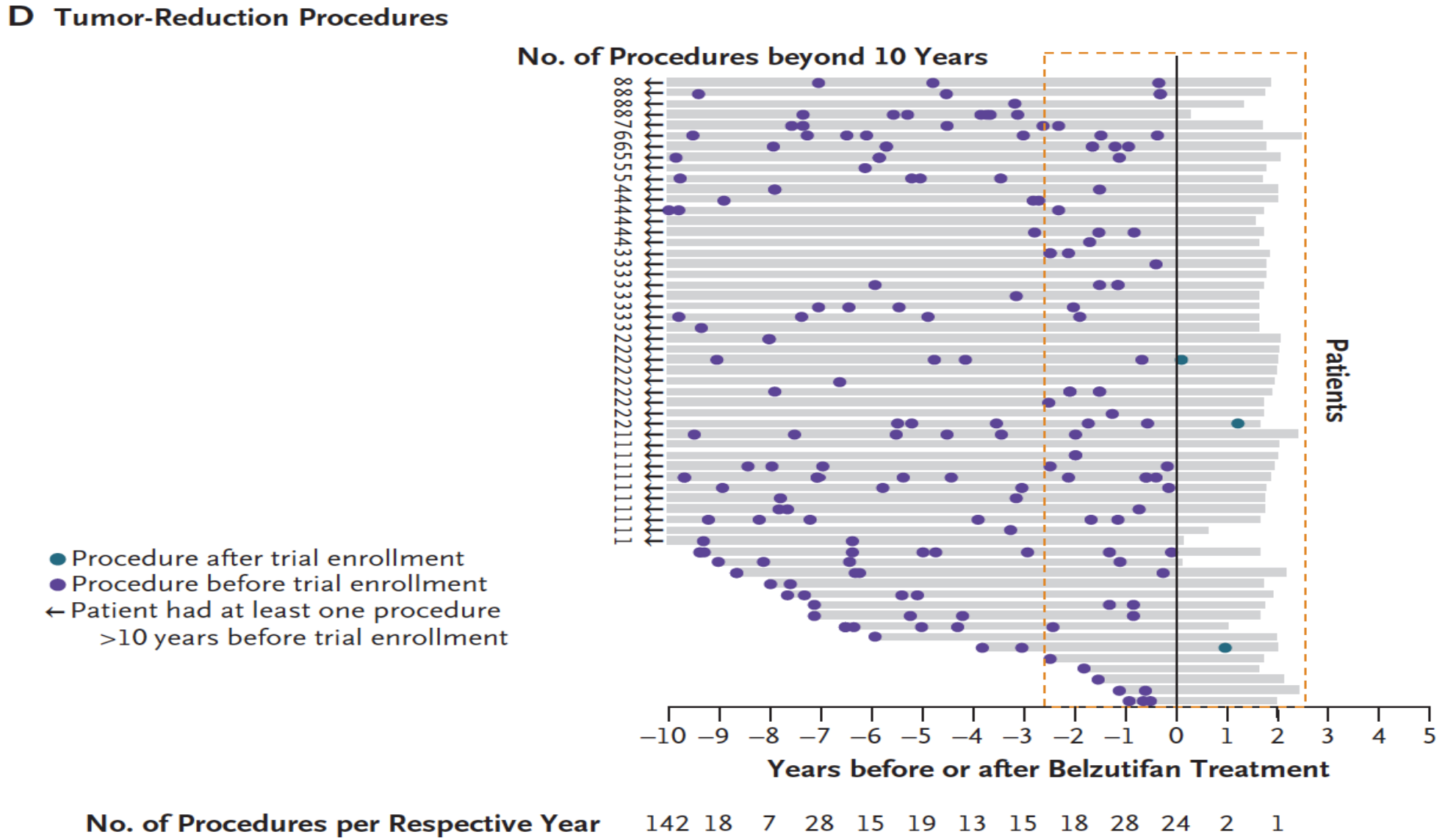
Table 2. Best Objective Response in Renal Cell Carcinoma Associated with VHL Disease.*

Variable	Efficacy Population (N=61)
Objective response — no. (% [95% CI])	30 (49 [36 to 62])
Best response — no. (%)	
Complete response	0
Partial response	30 (49)
Stable disease	30 (49)
Disease progression	0
Unable to be evaluated†	1 (2)
Median time to response (range) — mo	8.2 (2.7 to 19.1)
Median duration of response (range) — mo‡	NR (2.8+ to 22.3+)



Jonasch and Srinivasan *NEJM* 2021

Distribution of all tumor reduction procedures before and after treatment initiation for individual patients



Jonasch and Srinivasan *NEJM* 2021

Confirmed ORR in pancreatic lesions and CNS hemangioblastomas by independent central review

	Pancreatic Lesions[a] N = 61	Pancreatic Neuroendocrine Tumors N = 22	CNS Hemangioblastoma N = 50
ORR, % (95% CI)	77.0 (64.5-86.8)	90.9 (70.8-98.9)	30.0 (17.9-44.6)
Best response, n (%)			
CR	6 (9.8)	3 (13.6)	3 (6.0)
PR	41 (67.2)	17 (77.3)	12 (24.0)
SD	13 (21.3)	2 (9.1)	31 (62.0)
PD	0	0	2 (4.0)
Not evaluable	1 (1.6)	0	2 (4.0)

[a]Includes pancreatic neuroendocrine tumors and serous cystadenomas.

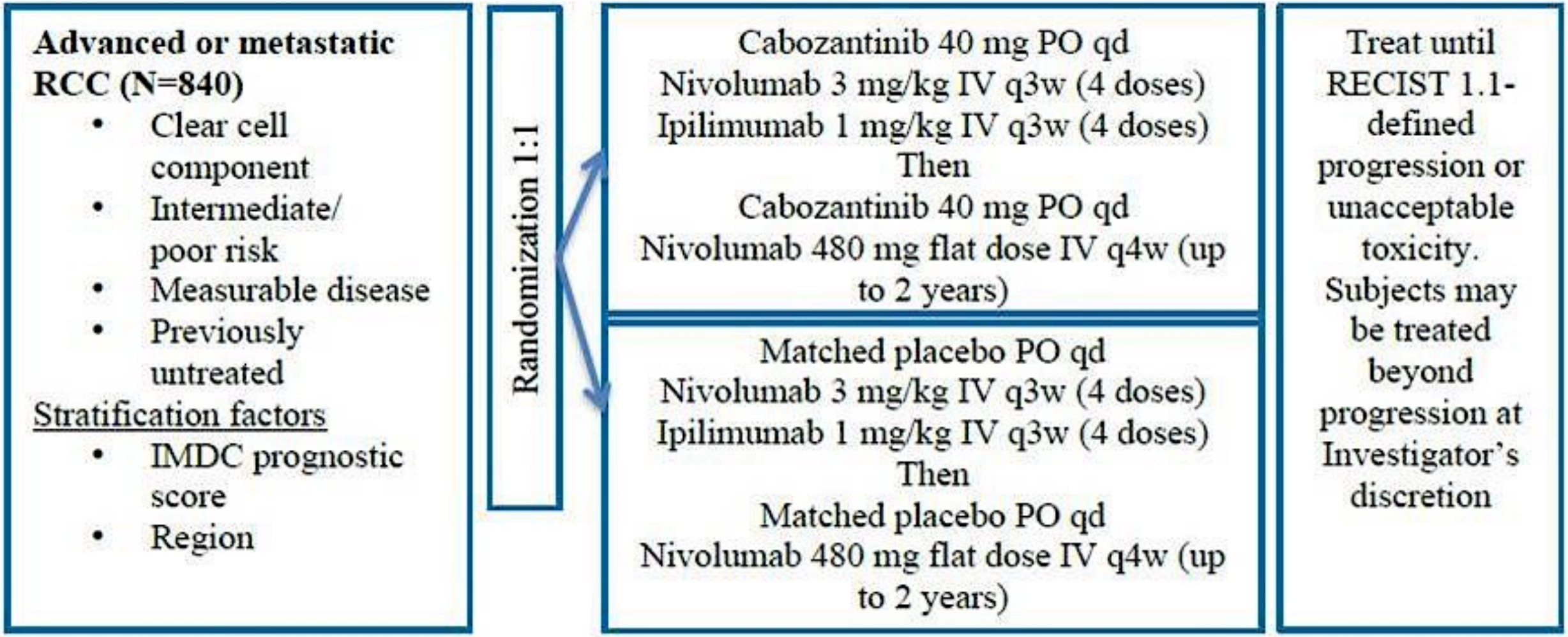
Jonasch and Srinivasan *NEJM* 2021

Sporadic RCC: Best confirmed objective response by RECIST v1.1 per Investigator Assessment (ccRCC cohort)

Efficacy Parameter, n (%) [95%CI]	All Patients N = 55	IMDC Favorable n = 13	IMDC Intermediate/Poor n = 42
Objective Response Rate	14 (25) [15-39]	4 (31) [9-61]	10 (24) [12-40]
Complete Response (CR)	0	0	0
Partial Response (PR)	14 (25)	4 (31)	10 (24)
Stable Disease (SD)	30 (54)	8 (62)	22 (52)
Disease Control Rate (CR + PR + SD)	44 (80) [67-90]	12 (92) [64-100]	32 (76) [61-88]
Progressive Disease	8 (15)	1 (8)	7 (17)
Not Evaluable	3 (5)	0	3 (7)

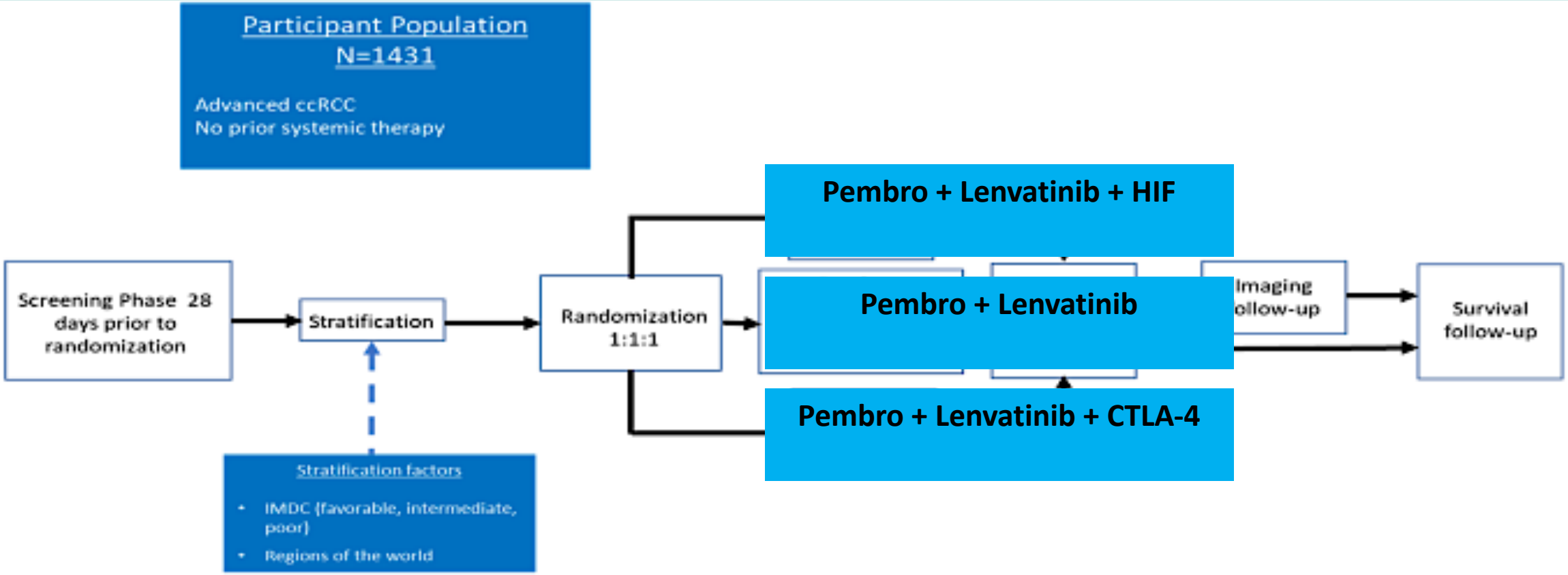
Choueiri TK et al. *Nat Med.* 2021;27:802-805.

COSMIC-313



IMDC, international metastatic renal cell carcinoma database consortium; IV, intravenous; PO, oral administration; qd, once daily; q3(4)w once every 3(4) weeks; RECIST, response evaluation criteria in solid tumors; RCC, renal cell carcinoma

MK-6482-012 Study Design



- Abbreviations: IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; ccRCC = clear cell renal cell carcinoma.
- a. The treatment arms are the HIF triplet (MK-6482 + pembrolizumab + lenvatinib), the CTLA4 triplet (MK-1308A + lenvatinib), and the doublet (pembrolizumab + lenvatinib). Note: MK-1308A is a coformulation of pembrolizumab and MK-1308
- Global Study- ~225 sites, 33 countries

MSD

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