Renal Cell Carcinoma Updates

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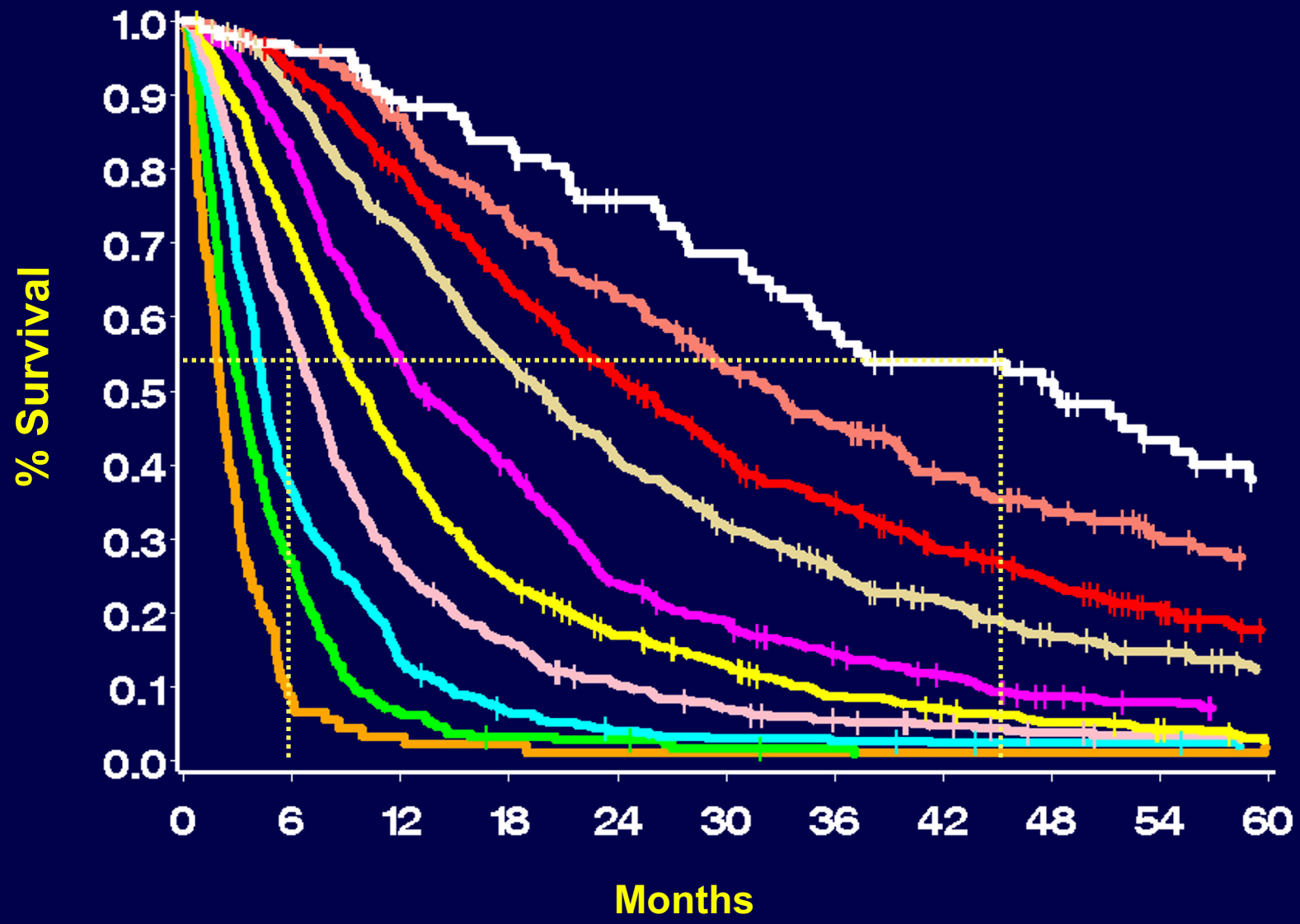
Brian Rini, MD: Conflict of Interest

- Research Funding to Institution: Pfizer, Hoffman-LaRoche, Incyte, AstraZeneca, Seattle Genetics, Arrowhead Pharmaceuticals, Immunomedics, BMS, Mirati Therapeutics, Merck, Surface Oncology, Aravive, Exelixis, Jannsen, Pionyr

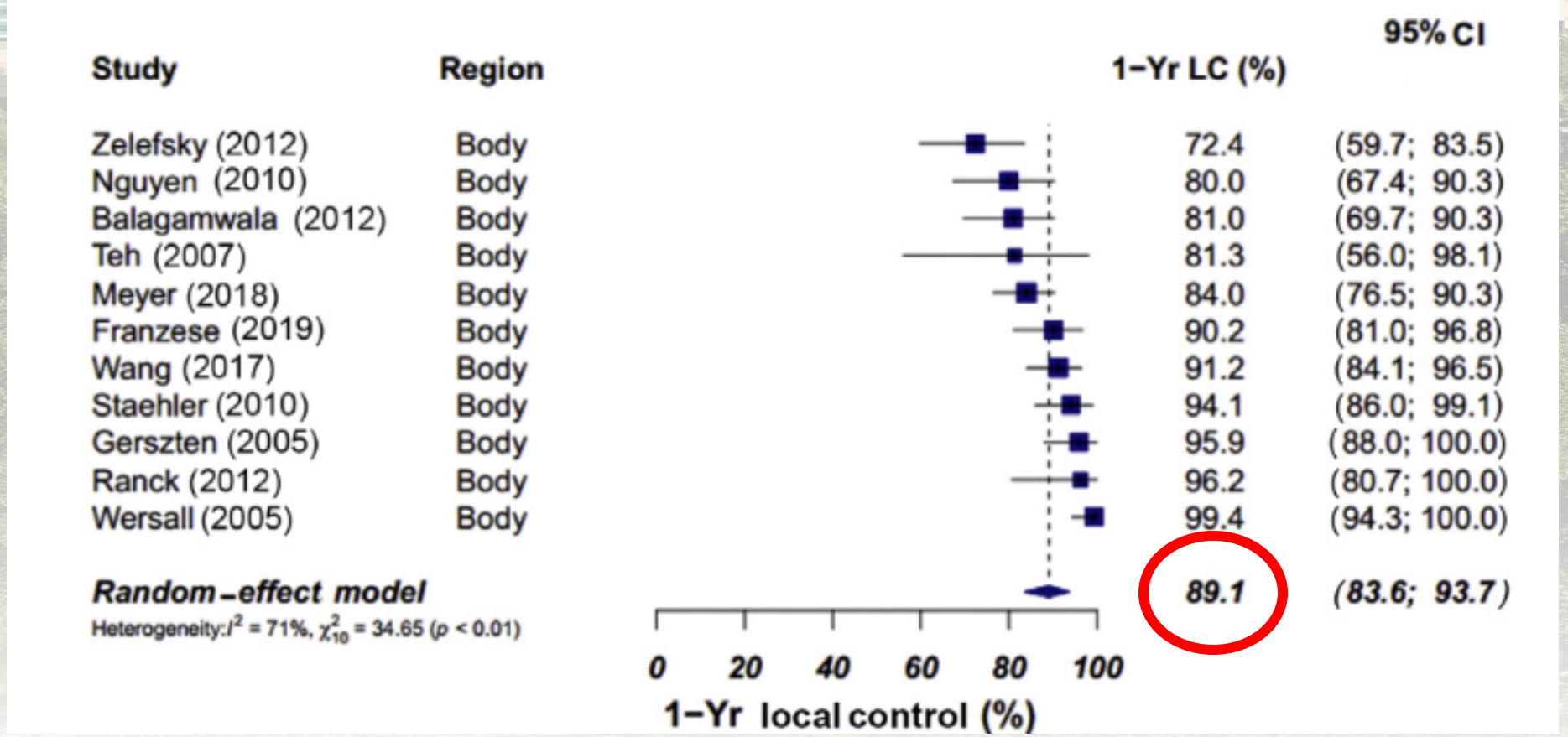
- Consulting: BMS, Pfizer, GNE/Roche, Aveo, Synthorx, Merck, Corvus, Surface Oncology, Aravive, Alkermes, Arrowhead, Shionogi, Eisai, Nikang Therapeutics, EUSA, Athenex, Allogene Therapeutics, Debiopharm

- Stock: PTC therapeutics

RCC is an inherently diverse disease



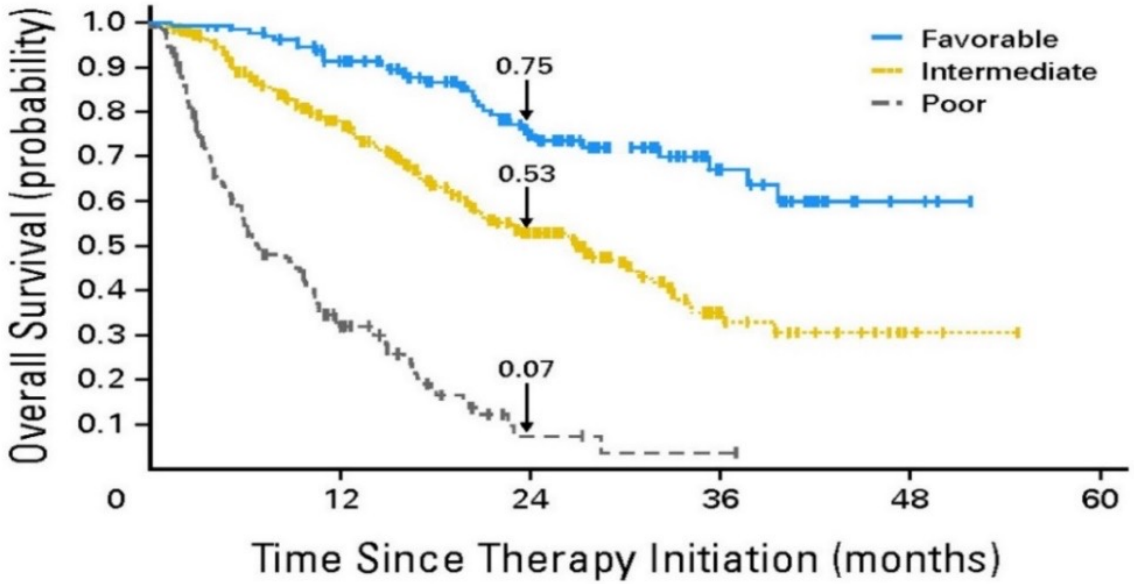
SBRT for RCC oligometastases



Zaorsky et al. *EAU* 2019

IMDC Prognostic Criteria

- **Clinical**
  - KPS < 80%
  - Time from diagnosis to treatment < 1 year
- **Laboratory**
  - Hemoglobin < LLN
  - Calcium > ULN
  - Neutrophil count > ULN
  - Platelet count > ULN

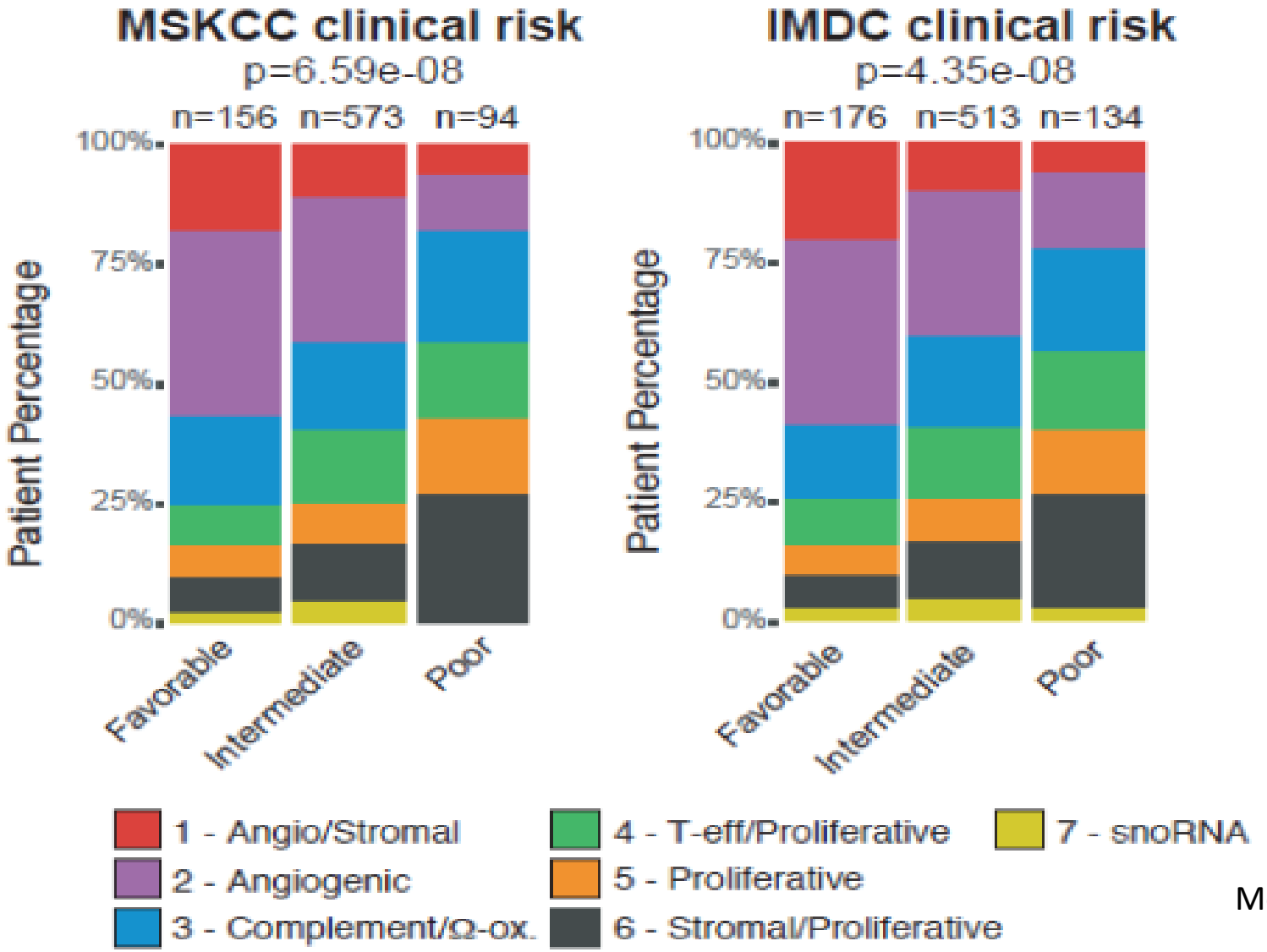


No. of events/No. at risk					
Favorable	11/133	16/110	4/62	2/22	0/3
Intermediate	61/301	50/182	17/82	2/18	0/3
Poor	94/152	19/36	1/3	0/1	0/0

- Favorable: 0 risk factors ⟶ means slow-growing and/or VEGF-responsive (**mostly**)
- Intermediate: 1-2 risk factors ⟶ medium growth rate and somewhat VEGF-responsive
- Poor: 3-6 risk factors ⟶ fast-growing and VEGF-unresponsive

Heng DYC, et al. J Clin Oncol. 2009;

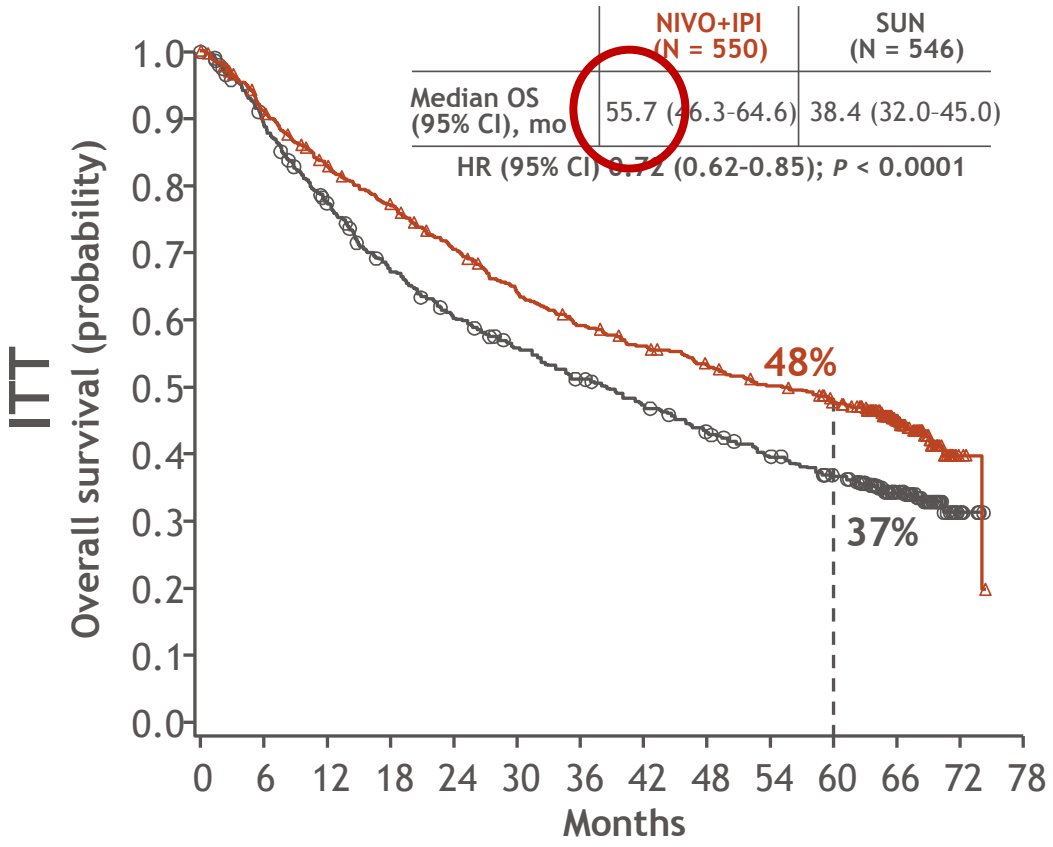
Patient groups defined by clinical characteristics display heterogeneous biology



Motzer et al. *Cancer Cell* 2020

OS and PFS in ITT: 5-year Update

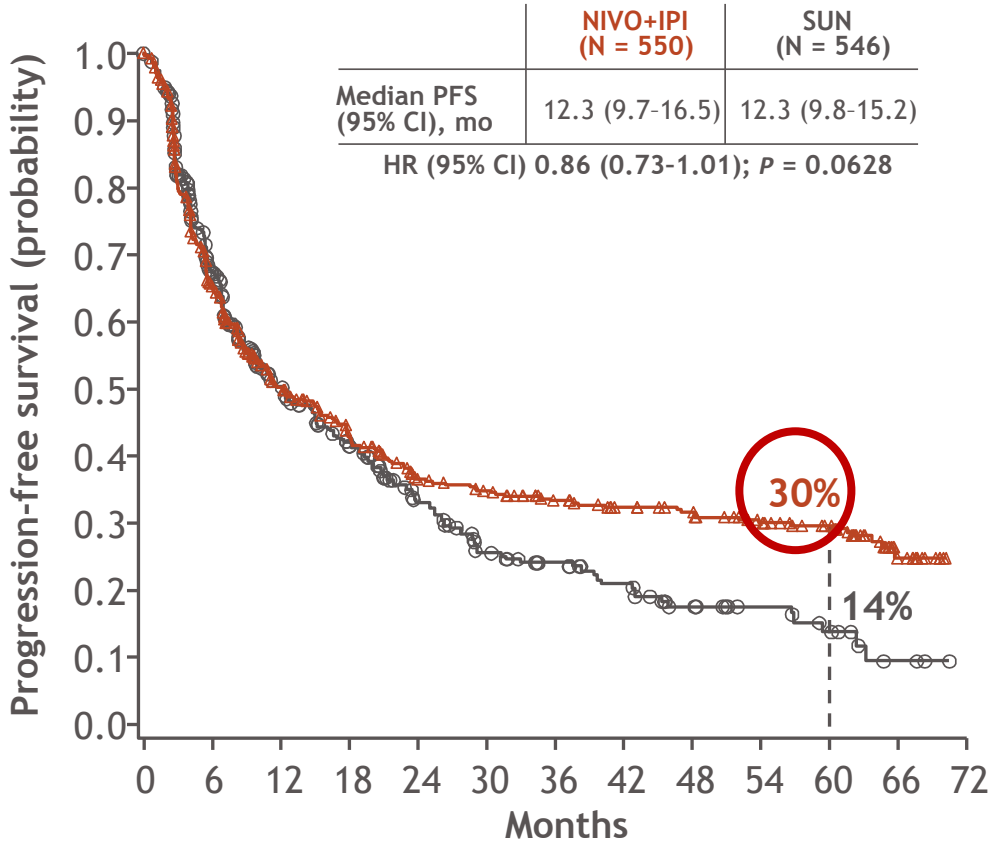
Overall survival



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

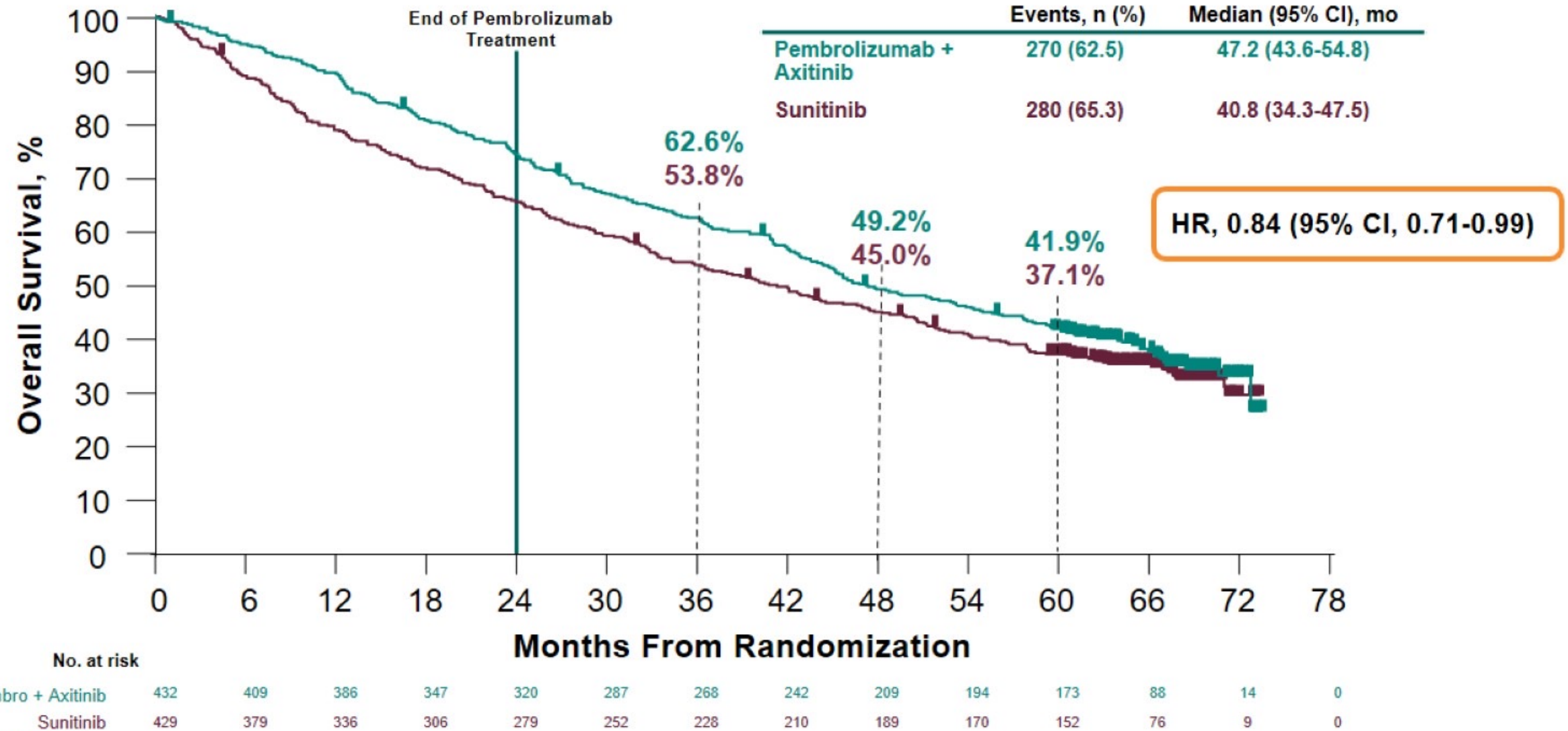


No. at risk

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	

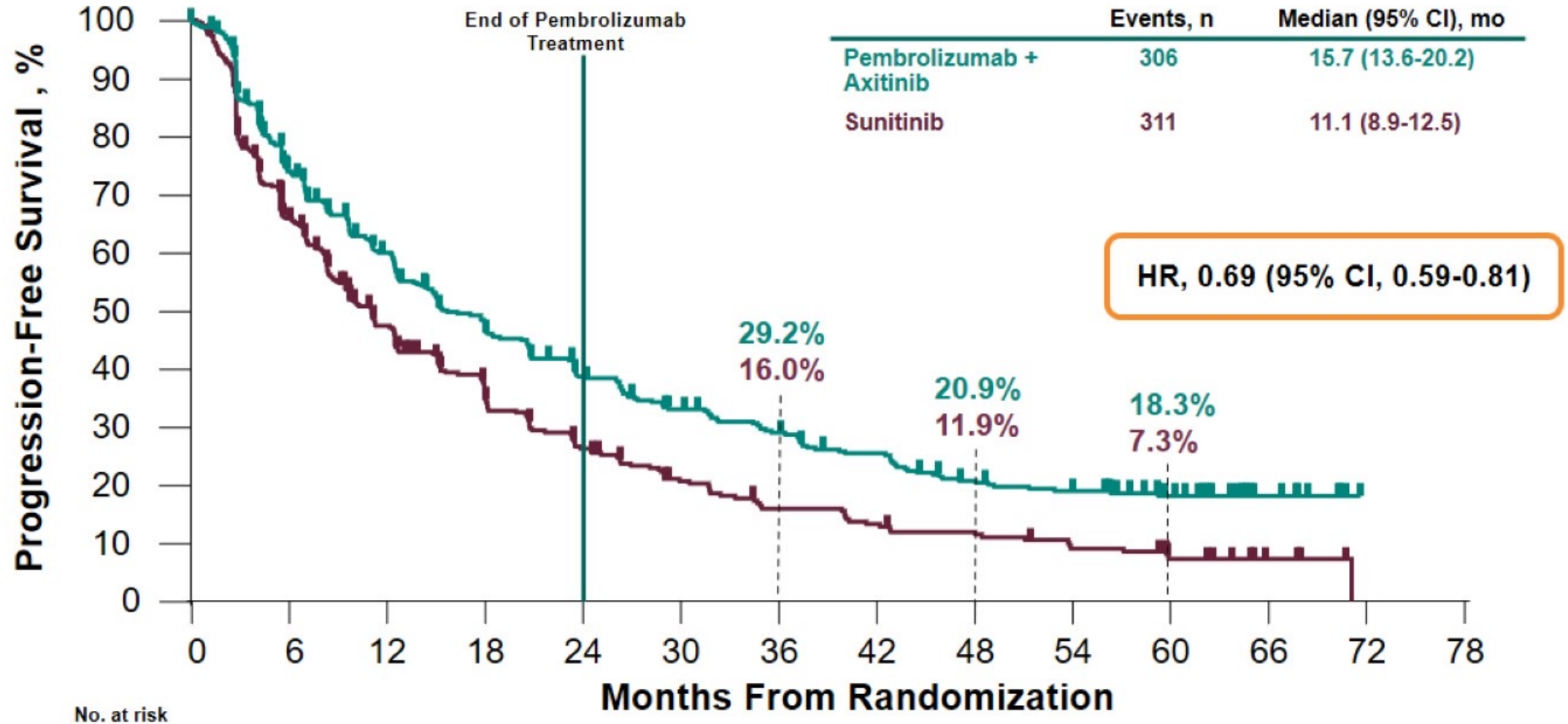
Motzer RJ et al. ESMO 2021. Abstract 661P.

Overall Survival in the ITT Population



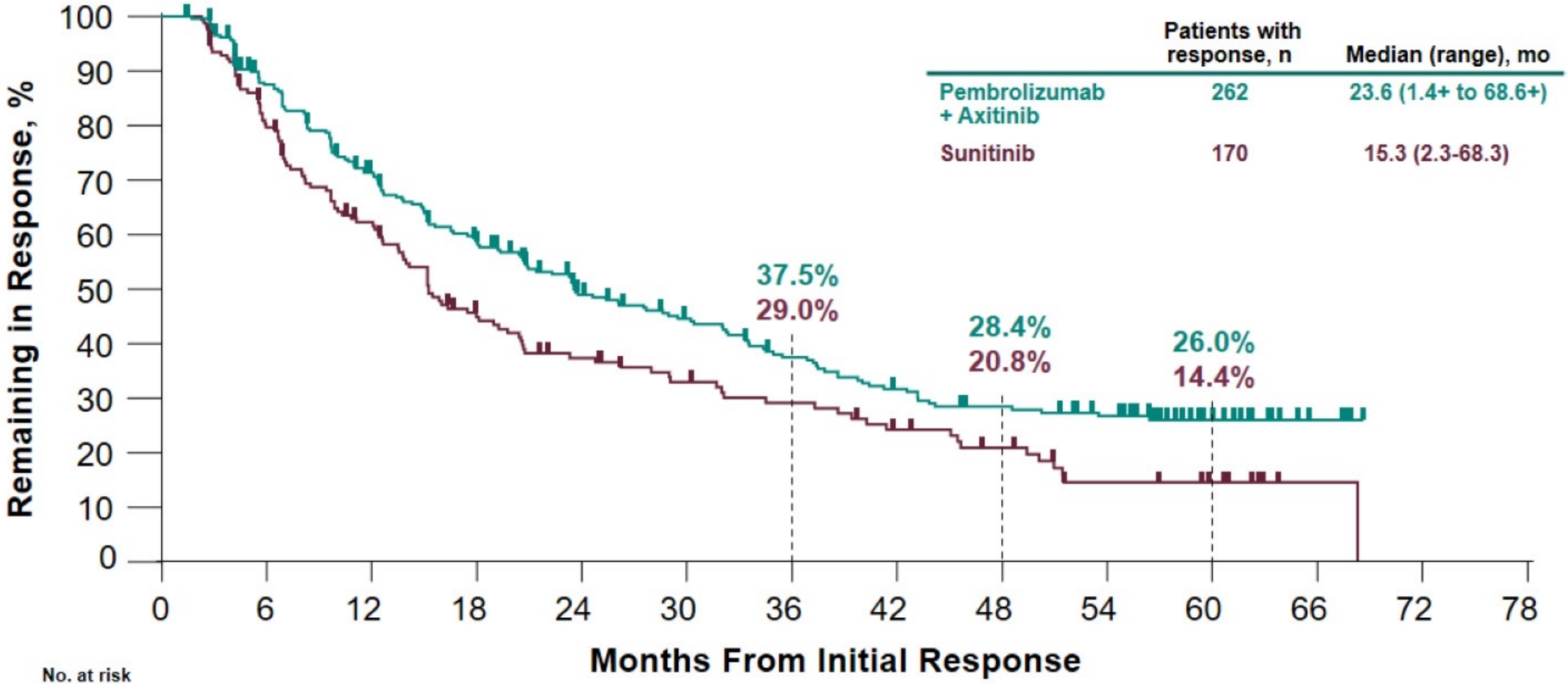
Data cutoff: January 23, 2023.

Progression-Free Survival in the ITT Population



Data cutoff: January 23, 2023.

Duration of Response in the ITT Population



	Patients with response, n	Median (range), mo
Pembrolizumab + Axitinib	262	23.6 (1.4+ to 68.6+)
Sunitinib	170	15.3 (2.3-68.3)

No. at risk

Pembro + Axitinib	262	218	173	140	103	89	72	59	50	43	18	4	0	0
Sunitinib	170	126	92	61	44	36	30	23	18	10	7	1	0	0

Data cutoff: January 23, 2023.

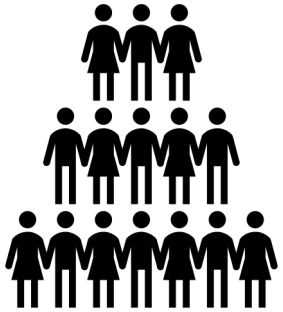
First-line IO Combination Trials in mRCC (ITT)

	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)
OS HR mOS, months	**0.72** 55.7 vs 38.4	**0.84** 47.2 vs 40.8	**0.70** 49.5 vs 35.5	**0.79** 53.7 v. 54.3
Landmark OS	**60%** at 3 years (est.) **48%** at 5 years	**63%** at 3 years **42%** at 5 years	**59%** at 3 years	**66%** at 3 years
PFS HR mPFS, months	**0.86** **12.3** vs 12.3	**0.69** **15.7** vs 11.1	**0.59** **16.6** vs 8.4	**0.47** **23.9** vs 9.2
Landmark PFS	32% (3 years; est.) 30% (5 years)	29% (3 years) 18% (5 years)	23% (3 years)	37% (3 years)
ORR, %	**39** vs 32	**61** vs 40	**56** vs 28	**71** vs 37
CR, %	**12** vs 3	**12** vs 4	**13** vs 5	**18** vs 4
Med f/u, months	**68**	**67**	**44**	**48**
Primary PD, %	**18**	**12**	**7**	**5**

1. Motzer et al. Cancer 2022
2. Rini et al. ASCO 2023
3. Bottaro et al. CITM 2023
4. Motzer et al. ASCO 2023

Which Type of Regimen Leads to the Most Durable Responders?

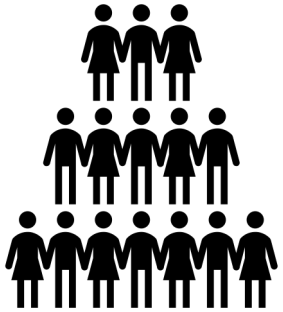
IO/IO



100
patients

100 x 40% ORR x 56% durable responders at 5 years = **22.4 patients**

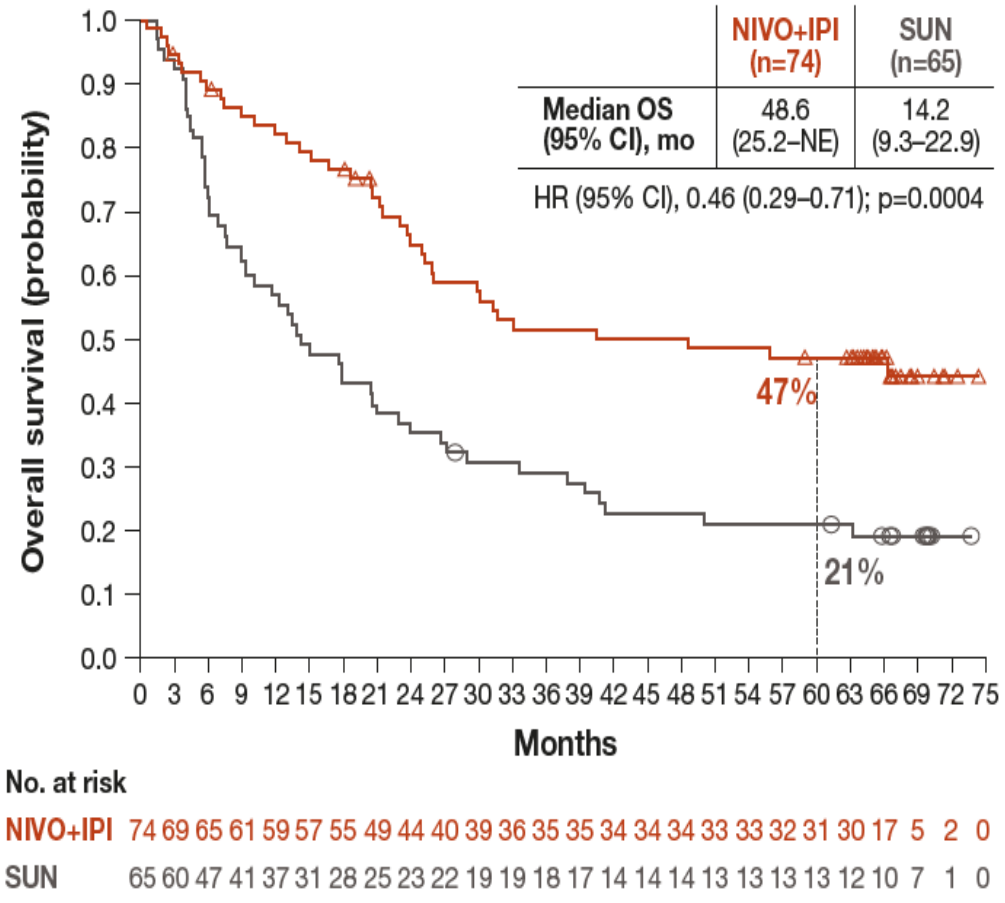
IO/TKI

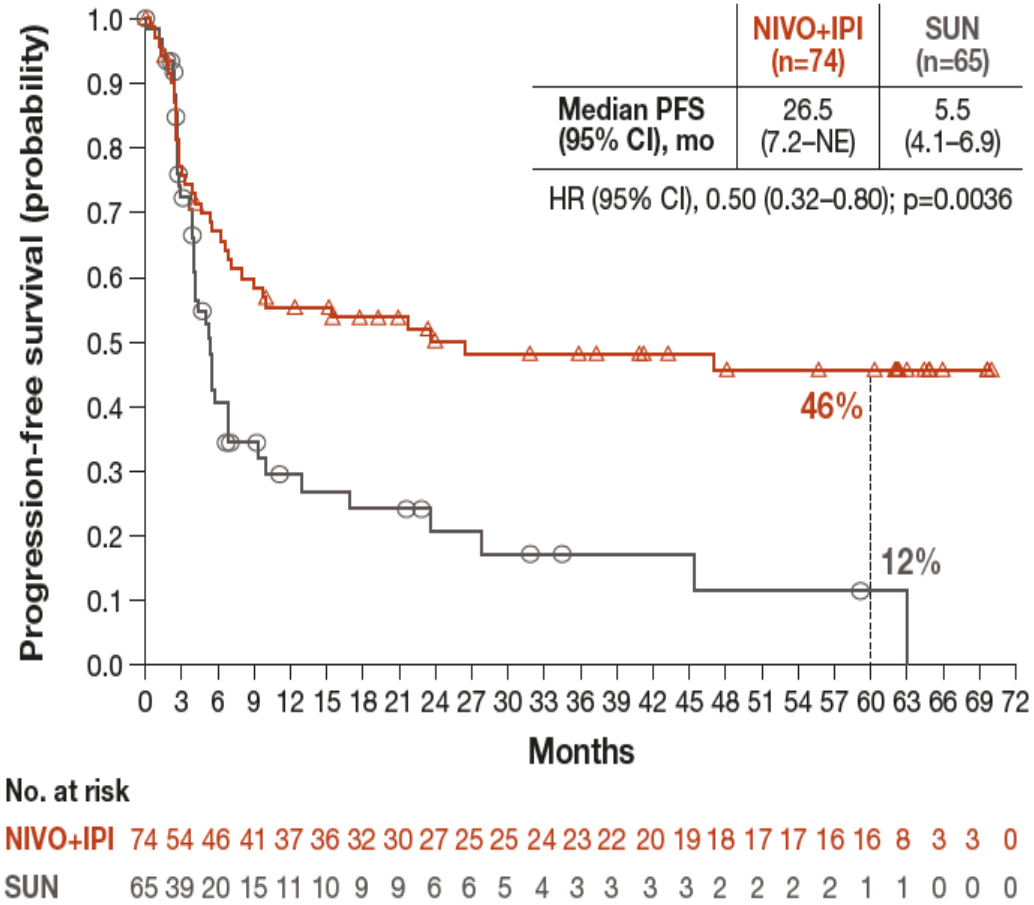


100 x 71% ORR x 41% durable responders at 3 years = **29.1 patients**

100 x 71% ORR x 30% durable responders at 5 years = **21.3 patients**

Sarcomatoid histology is the best biomarker for Ipi/Nivo





- ORR 61% / 23% CR

Rini et al. JITC 2023

IO Doublets in Sarcomatoid RCC

	CheckMate 214 (Ipi/Nivo)[1] (n=74 vs. 65)	KEYNOTE-426 (Axi/Pembro)[2] (n=51 vs. 54)	CheckMate 9ER (Cabo/Nivo)[3] (n=34 vs. 41)	Immotion 151 (Bev/Atezo)[4] (n=68 vs. 74)	JAVELIN101 (Axi/Avelumab)[5] (n=47 vs. 61)
OS HR (95% CI) mOS, months	**0.46** (0.29-0.71) 48.6 vs. 14.2	**0.58** (0.21-1.59) NR vs. NR	**0.36** (0.17–0.79) NR vs. 19.7	**0.64** (0.41-1.01) 21.7 vs. 15.4	**0.78** (0.36-1.72) Medians not reported
Landmark OS	**47%** vs. 21% at 5 years	**83%** vs. 80% at 1 year	**80%** vs. 55% (est) at 1 year	**56%** vs. 45% at 18 months	**83%** vs. 67% at 1 year
PFS HR mPFS, months	**0.50** **26.5** vs. 5.5	**0.54** **NR** vs. 8.4	**0.42** **10.3** vs. 4.2	**0.52** **8.3** vs. 5.3	**0.57** **7.0** vs. 4.0
Landmark PFS	**46%** vs. 12% at 5 years	**57%** vs. 26% at 1 year	**40%** vs. 20% at 1 year	**39%** vs. 22% at 1 year	**35%** vs. 20% at 1 year
ORR, %	**61** vs. 23	**59** vs. 32	**56** vs. 22	**49** vs. 14	**47** vs. 21
CR, %	**23** vs. 6	**12** vs. 0	**9** vs. 2	**10** vs. 3	**4** vs. 0
Med f/u, months	**67**	**13**	**16 month min.**	**17**	**6 month min.**
Primary PD, %	**20**	**NR**	**12**	**NR**	**15**

1. Rini et al. JITC 2022 2. Rini et al. ASCO 2019 3. Motzer et al. ASCO GU 2021
4. Rini et al. Eur Urol 2021 5. Choueiri et al. ESMO Open 2021

@brian_rini and @Uromigos (podcasts: https://podcasters.spotify.com/pod/show/the-uromigos)

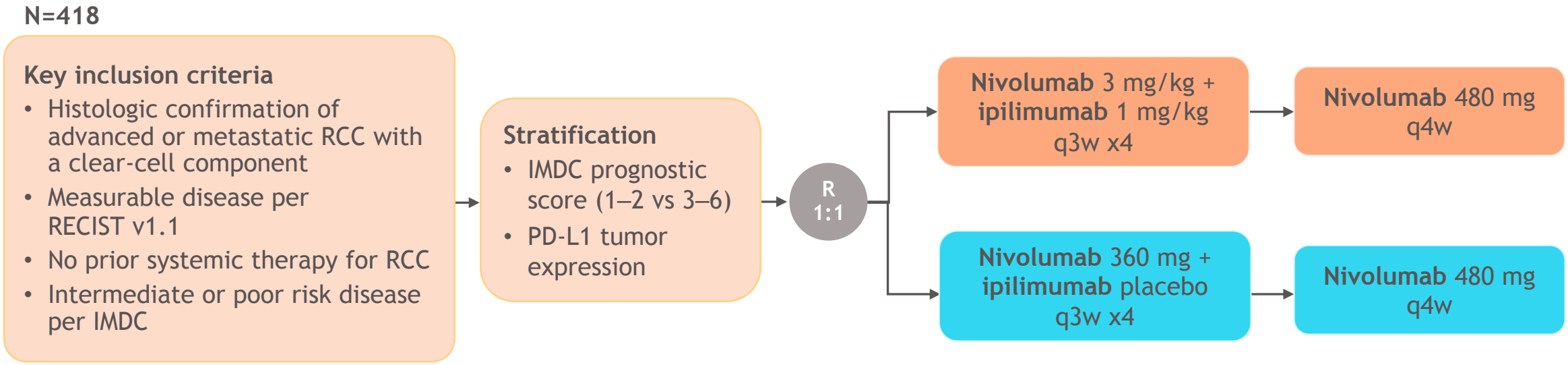
Ipilimumab is not a good salvage agent in RCC

	HCRN[1]	OMNIVORE[2]	TITAN RCC[3]		FRACTION[4]	Salvage Ipi/Nivo[5]
N	35*	57	49		46	45
Prior TKI allowed	No	Yes	No		Yes	Yes
Timing	Nivo→Ipi (SD at 48 weeks or PD)	Nivo→Ipi (SD or PD at ≤ 6 months)	Nivo→Ipi (SD/PD at week 8 or 16)		Nivo+Ipi in IO-refractory	Nivo+Ipi in IO-refractory
Ipi doses	4	2	2-4		4	4
ORR	11%	4%	14%		17%	20%
PD	63%	40%	67%		30%	62%
CR	3%	0%	2%		0%	0%

Nivo+ipi combo untreated ccRCC ORR 39%, PD 19%, CR 12% (Checkmate 214)
* 87% PD-L1 negative

1. Atkins M et al. JCO 2022 2. McKay et al. JCO 2020 3. Grimm et al. ESMO 2022 4. Choueiri et al. JITC 2022 5. Gul et al. JCO 2020

CA209-8Y8 is a phase 3 study to evaluate nivolumab + ipilimumab vs nivolumab mono in aRCC patients[1,2]



Start date: April 2019
Estimated trial completion date: January 2025
Estimated primary completion date: January 2022
Trial sponsor: Bristol Myers Squibb

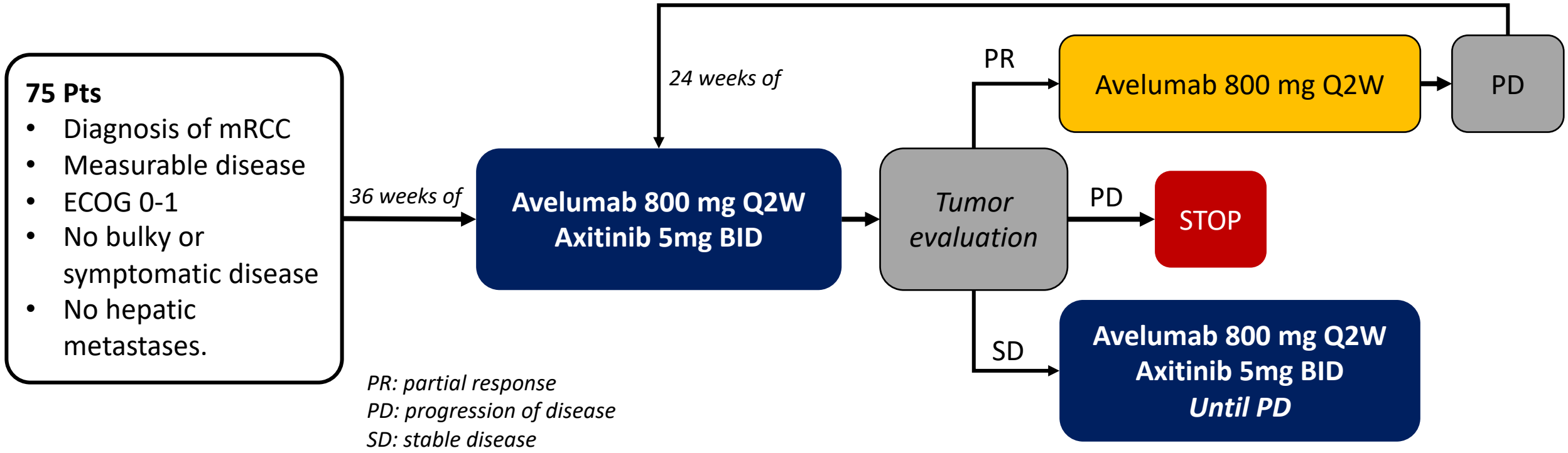
Primary outcome measures: PFS,* ORR*
Select secondary outcome measures†: OS, ORR,*‡ DCR, DOR, TTR, PFS,‡ AEs

*Assessed by BICR per RECIST v1.1.[1] †The time frame for all secondary outcome measures is up to 4 years.[1] ‡Investigator assessed per RECIST v1.1.[1]

AE=adverse event; aRCC=advanced RCC; BICR=blinded independent central review; DCR=disease control rate; DOR=duration of response; IMDC=International Metastatic RCC Database Consortium; mono=monotherapy; ORR=overall response rate; OS=overall survival; PD-L1=programmed death ligand 1; PFS=progression-free survival; q3w=every 3 weeks; q4w=every 4 weeks; R=randomization; RCC=renal cell carcinoma; RECIST=Response Evaluation Criteria In Solid Tumors; TTR=time to response.

1. Clinicaltrials.gov. NCT03873402. Accessed July 30, 2020. 2. Suarez C et al. Proffered paper discussion at ESMO 2019. Invited discussant LBA56 and LBA57.

Can the TKI be discontinued?: Tide A Study design



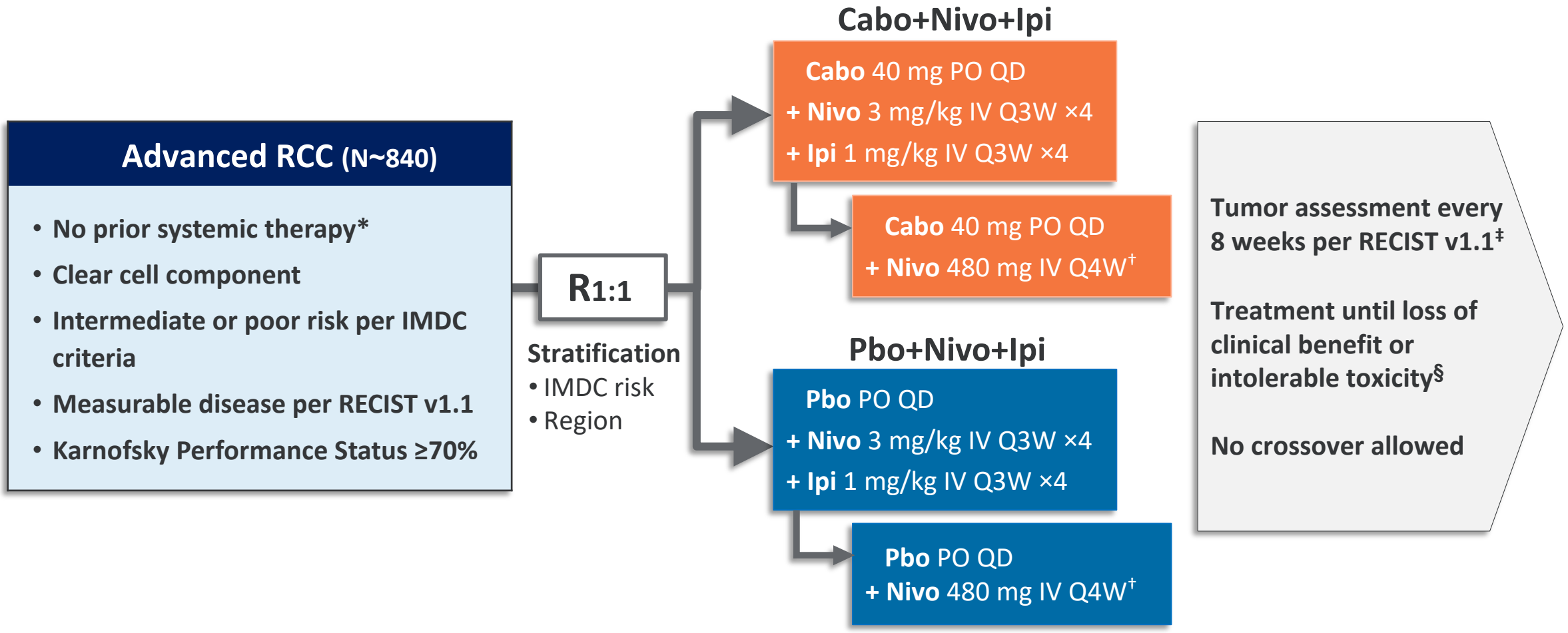
Eudract CT number: 2019-004098-23
ClinicalTrials.gov Identifier: NCT04698213

Iacovelli et al. Presented at ASCO GU 2020 TPS762

IO/TKI vs. IO/IO

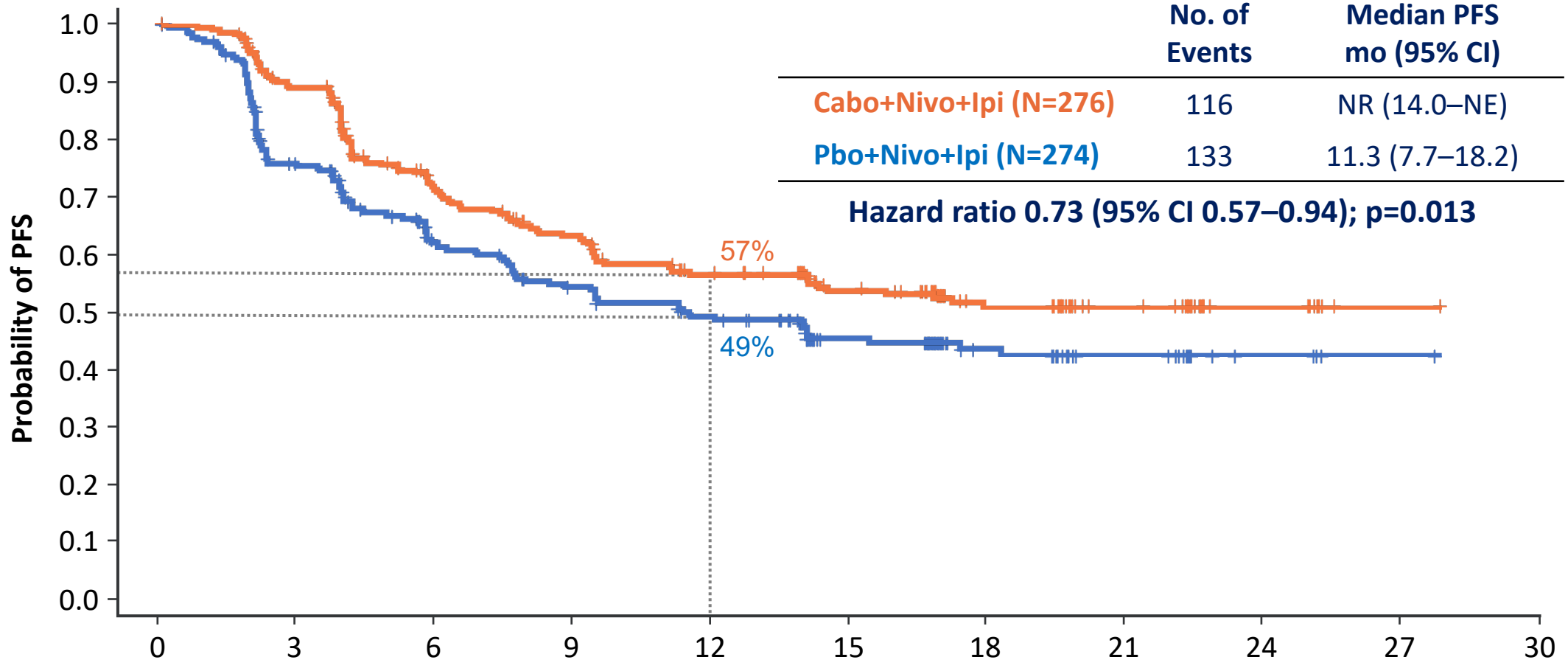
	Pros	Cons
IO/TKI	• Consistent effects on OS, PFS and ORR across IMDC risk groups • Significant tumor burden reduction reflected in high ORR and long PFS • Manageable toxicity • QoL maintained vs TKI	• Long-term durability of response yet to be demonstrated • Potential for acute and chronic TKI toxicity
IO/IO	• OS and ORR advantages over TKI monotherapy • Durability of response / disease-control • Treatment-free interval possible • QoL improved vs TKI	• Sometimes significant initial toxicity • Lower ORR and shorter PFS compared with IO/TKI regimens • Less effect in favorable risk patients

Triplets: COSMIC-313



*One prior systemic adjuvant therapy allowed for completely resected RCC and if recurrence occurred ≥6 months after the last dose of adjuvant therapy; adjuvant PD-1 or PD-L1 inhibitor in combination with a CTLA-4 inhibitor not permitted. †Nivolumab given for a maximum of 2 years. ‡Tumor assessment (RECIST v1.1) at week 10, then every 8 weeks through week 50, then every 12 weeks thereafter. §Discontinuation of one agent did not mandate discontinuation of all agents.

COSMIC313: PFS Final Analysis (PITT Population)



	No. of Events	Median PFS mo (95% CI)
Cabo+Nivo+Ipi (N=276)	116	NR (14.0–NE)
Pbo+Nivo+Ipi (N=274)	133	11.3 (7.7–18.2)

Hazard ratio 0.73 (95% CI 0.57–0.94); p=0.013

Number at Risk

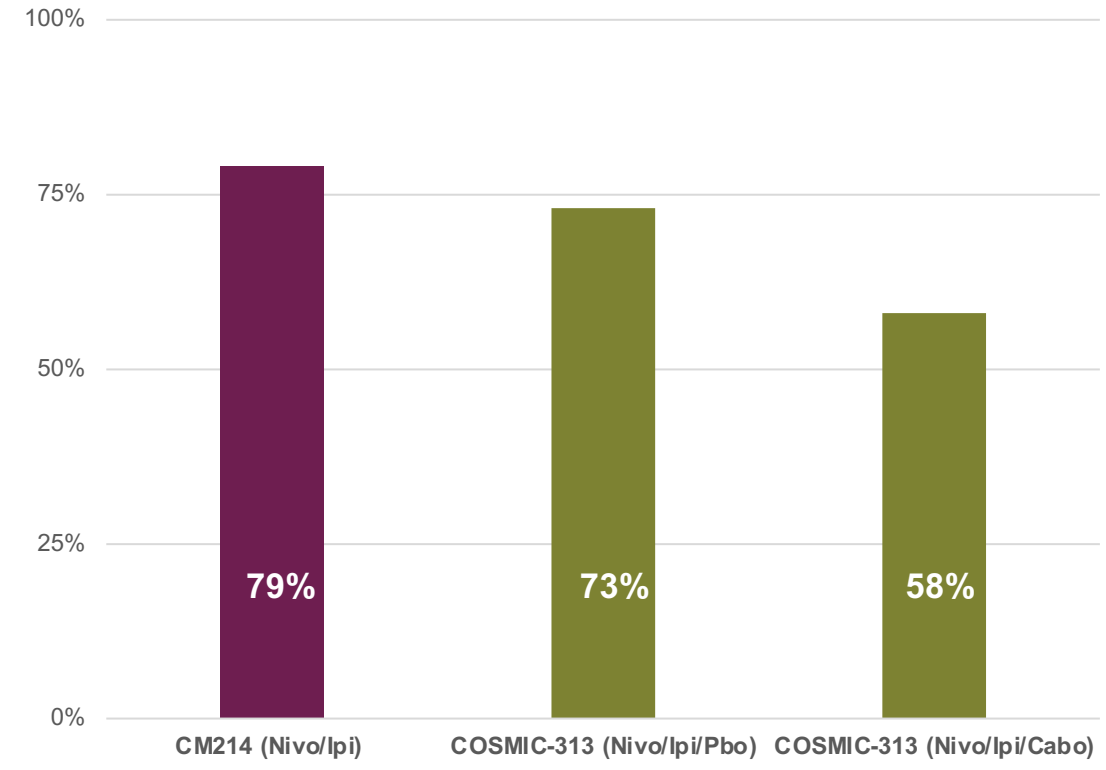
Cabo+Nivo+Ipi	276	234	170	145	119	97	56	33	10	1	0
Pbo+Nivo+Ipi	274	185	136	115	98	69	37	19	5	1	0

PFS per RECIST v1.1 by BIRC.

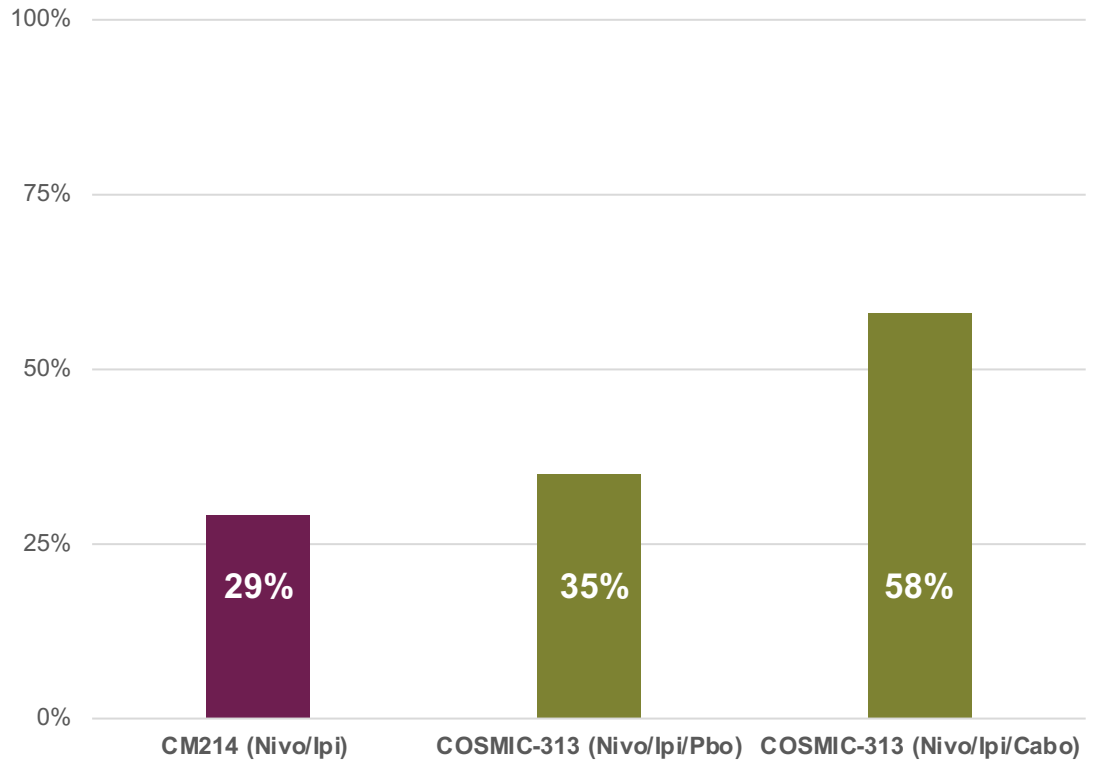
Data cut-off: Aug 23, 2021

Toxicity limited drug delivery

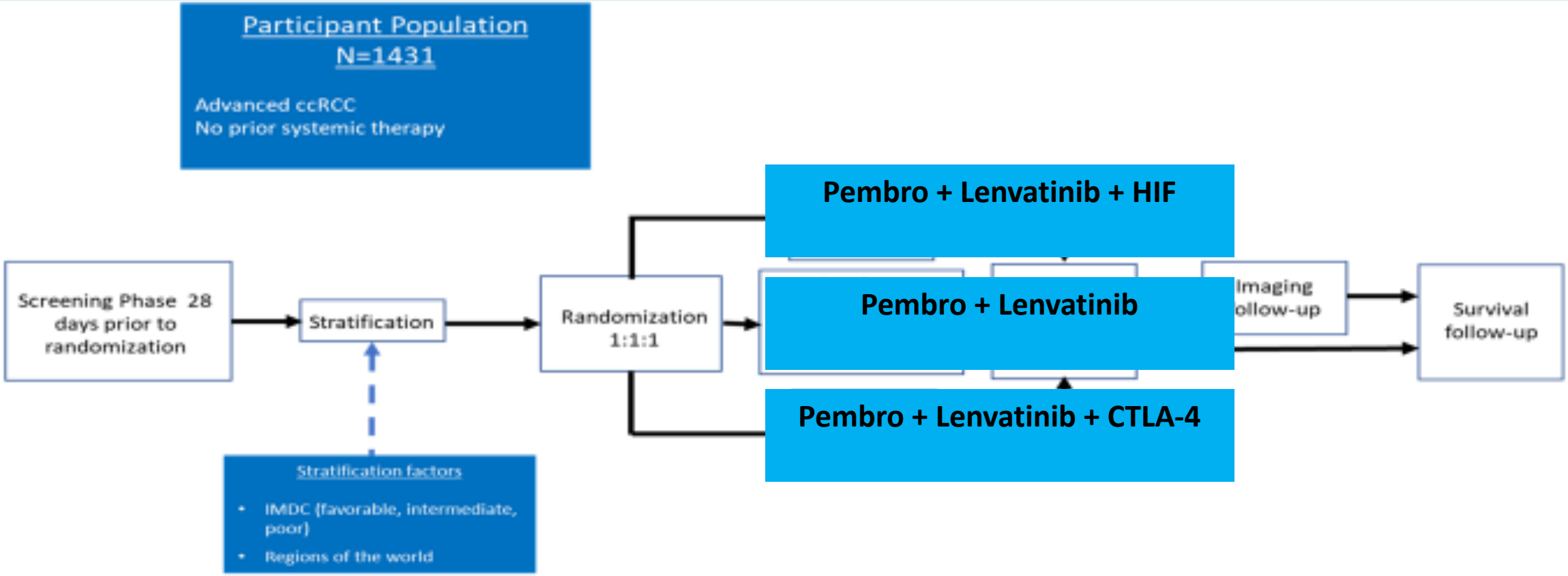
Proportion of patients receiving 4 doses of ipilimumab



Proportion of patients receiving >40 mg of prednisone or equivalent



MK-6482-012 Study Design



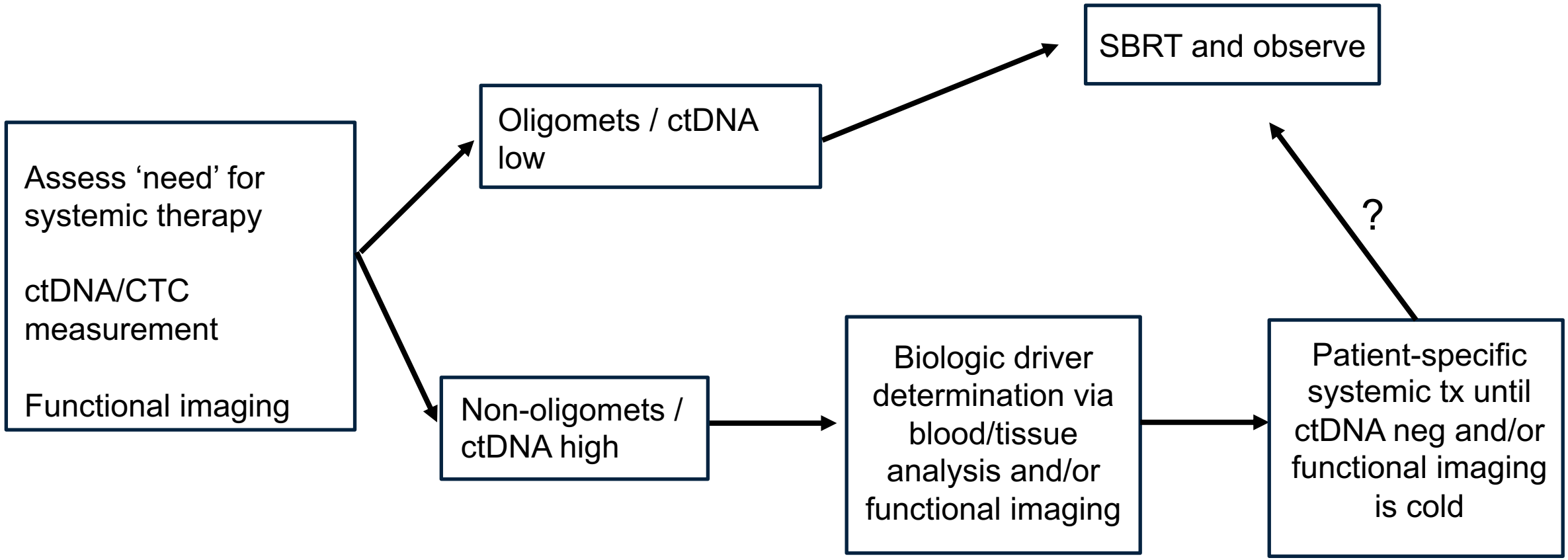
- Abbreviations: IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; ccRCC = clear cell renal cell carcinoma.
- a. The treatment arms are the HIF triplet (MK-6482 + pembrolizumab + lenvatinib), the CTLA4 triplet (MK-1308A + lenvatinib), and the doublet (pembrolizumab + lenvatinib).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

Conclusions: How I Choose Front-line Therapy

- IO/TKI most applicable for all patients but durability of response is likely less. Ipi/Nivo with durable responses but less initial disease control and Ipi-related toxicity
- Tolerability
  - Short half-life of TKIs is relevant to managing toxicity
  - Ipi/nivo more initial inflammatory toxicity, although nivo maintenance generally easy
- I'd like to give IO monotherapy to select patients, but I usually don't because I don't know how to select appropriate patients
- We need biomarkers to select patients who need initial VEGF TKI for disease control and others who need initial Ipi
- Triplets may be effective, but strategies to manage toxicity and de-intensify are needed

@brian_rini and @Uromigos (podcasts on Apple, Spotify, etc.)

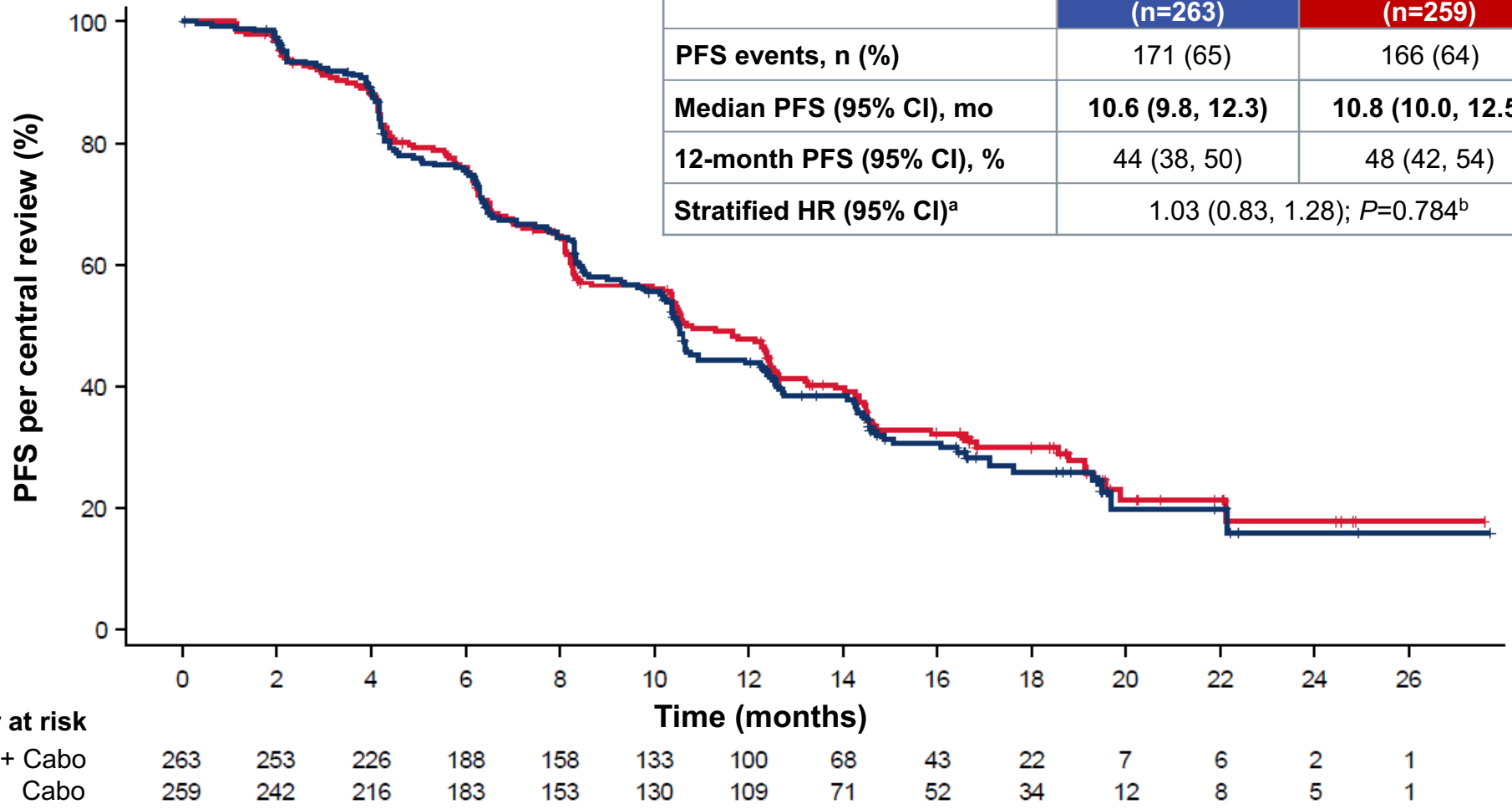
Metastatic Renal Cell Carcinoma in 2028



IO-Refractory RCC

CONTACT-03: Primary analysis of centrally reviewed PFS

	Atezo + Cabo (n=263)	Cabo (n=259)
PFS events, n (%)	171 (65)	166 (64)
Median PFS (95% CI), mo	**10.6 (9.8, 12.3)**	**10.8 (10.0, 12.5)**
12-month PFS (95% CI), %	44 (38, 50)	48 (42, 54)
Stratified HR (95% CI)[a]	1.03 (0.83, 1.28); *P*=0.784[b]	



[a] Stratified for IMDC risk group. [b] Not significant at α=0.02.

The Main Reason CONTACT-03 was negative was…

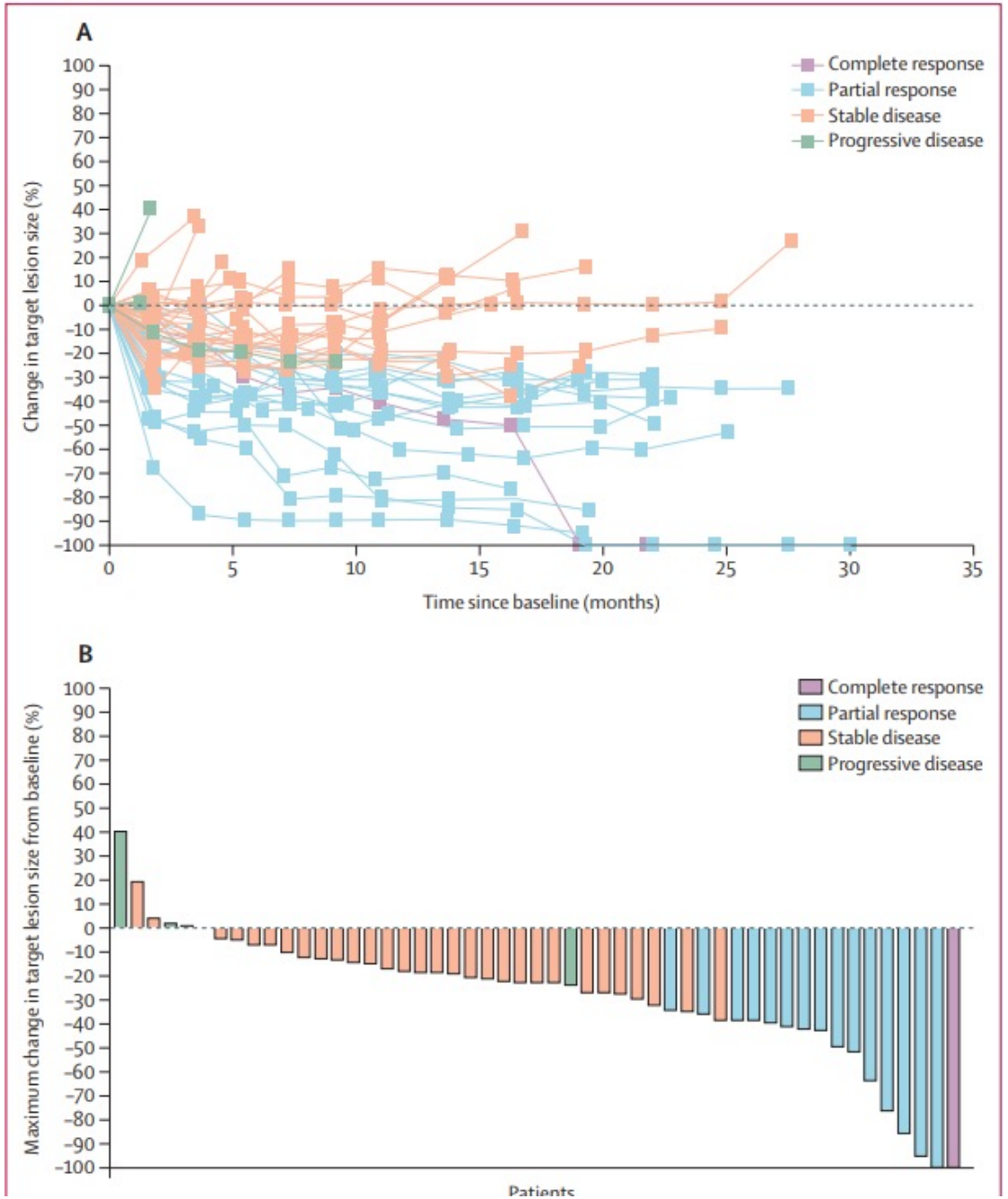
1. PD-L1 inhibitor used and not PD-1 inhibitor
2. Previous IO persisted (either drug and/or T cells) so arms were not that different
3. IO-refractory patients are selected for an angiogenic phenotype

LITESPARK-003: **Belzutifan+Cabo in IO-refractory RCC**

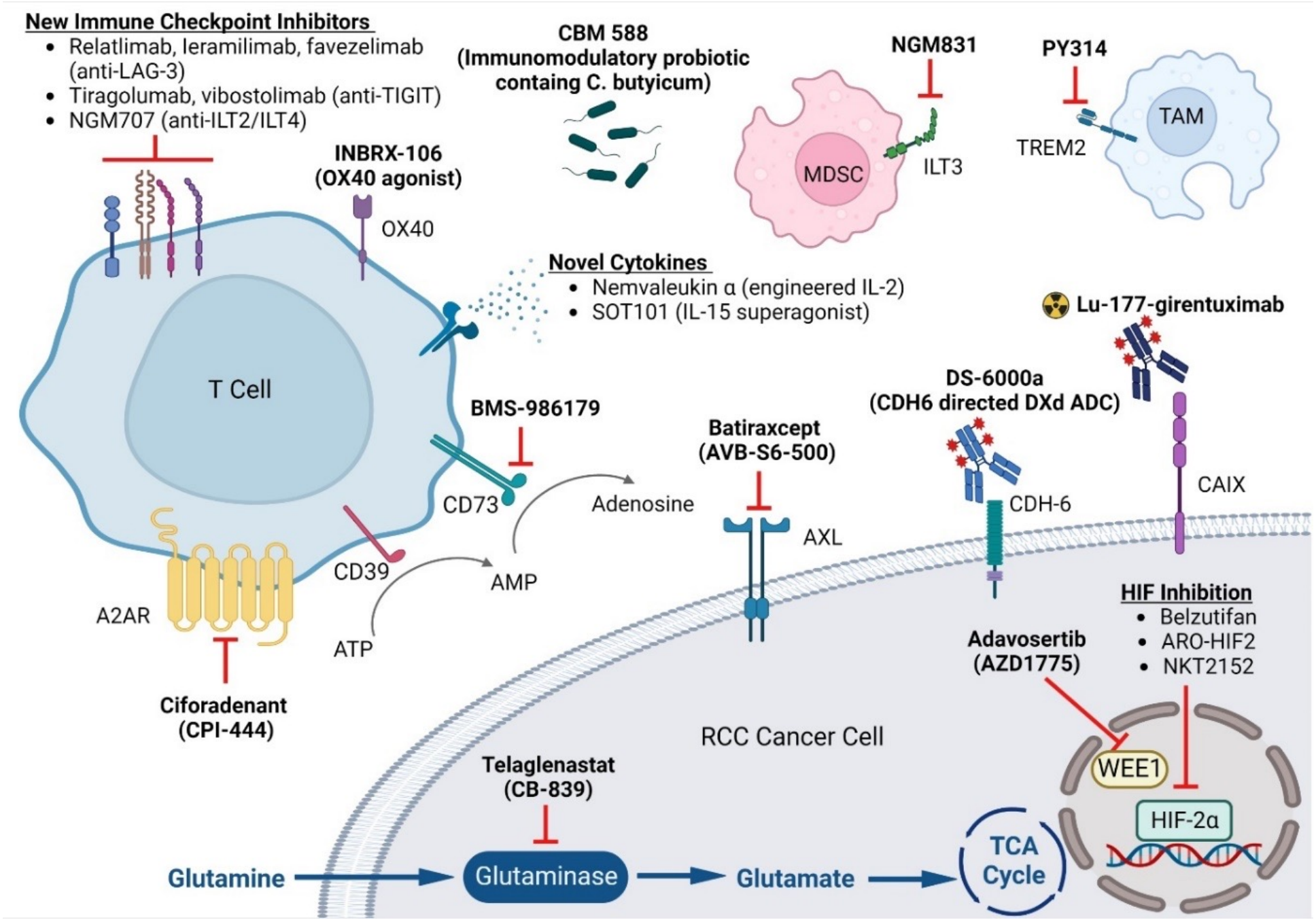
	Patients (N=52)
Proportion of patients with confirmed objective response*	16 (30·8%; 18·7–45·1)
Best overall response	
Complete response	1 (2%)
Partial response	15 (29%)
Stable disease	32 (62%)
Progressive disease	3 (6%)
Not available	1 (2%)

Data are n (%; 95% CI) or n (%). *95% CI based on binomial exact method for binomial data.

Table 2: **Best overall response per Response Evaluation Criteria in Solid Tumours version 1.1 criteria, as assessed by the investigators**



Choueiri et al. Lancet Onc 2023



Chen, Rini, and Beckermann; 2022

Conclusions for Refractory RCC

- Checkpoint inhibitor after checkpoint inhibitor is not active and can cause harm and should not be done pending additional data
- Single agent VEGF inhibitor is the very unexciting standard of care for now
- Belzutifan (HIF inhibitor) has activity in refractory RCC and is more active than everolimus (which isn't very active…)
- Novel targets and drugs are needed