Front-line Therapy in Renal Cell Carcinoma

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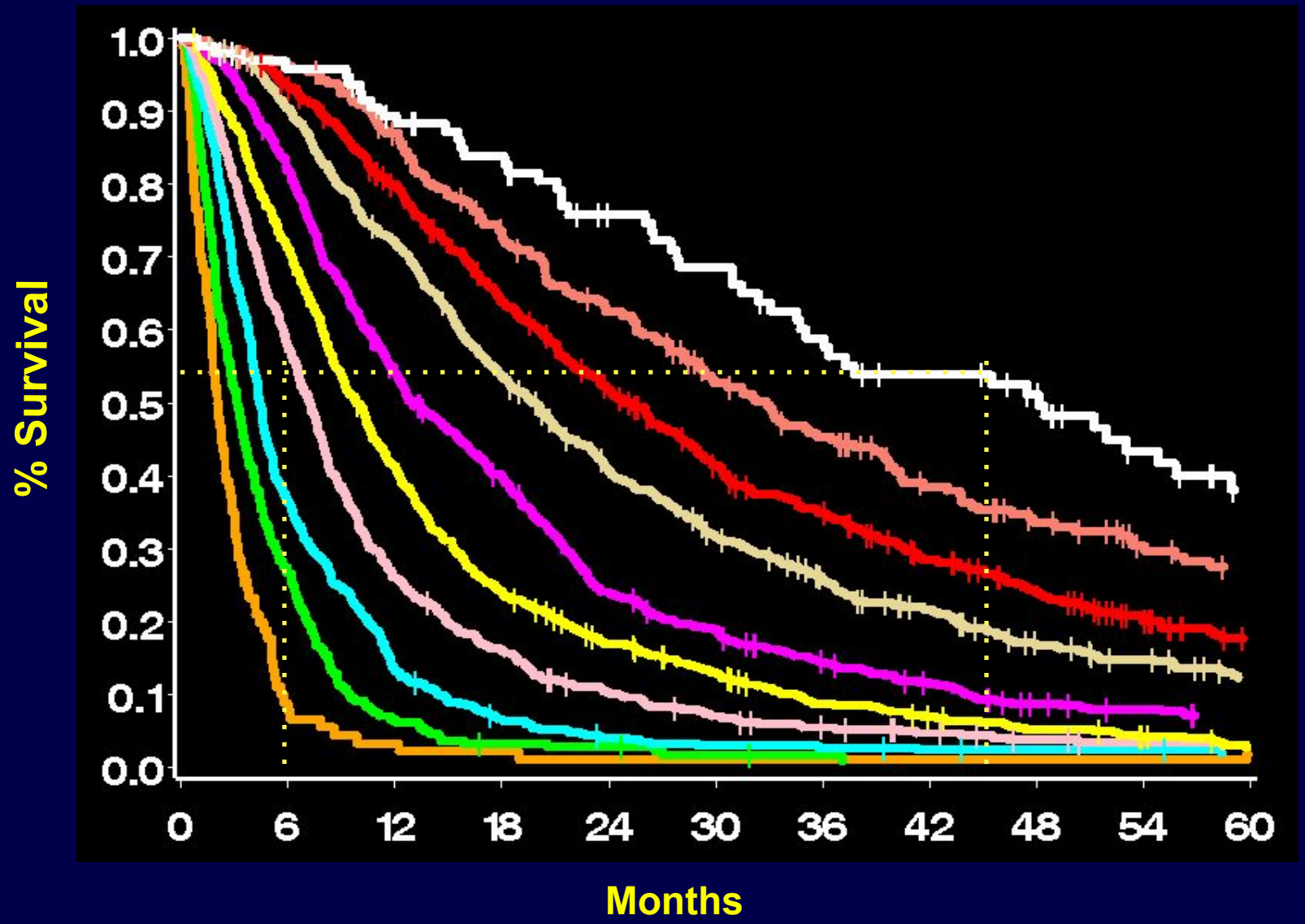
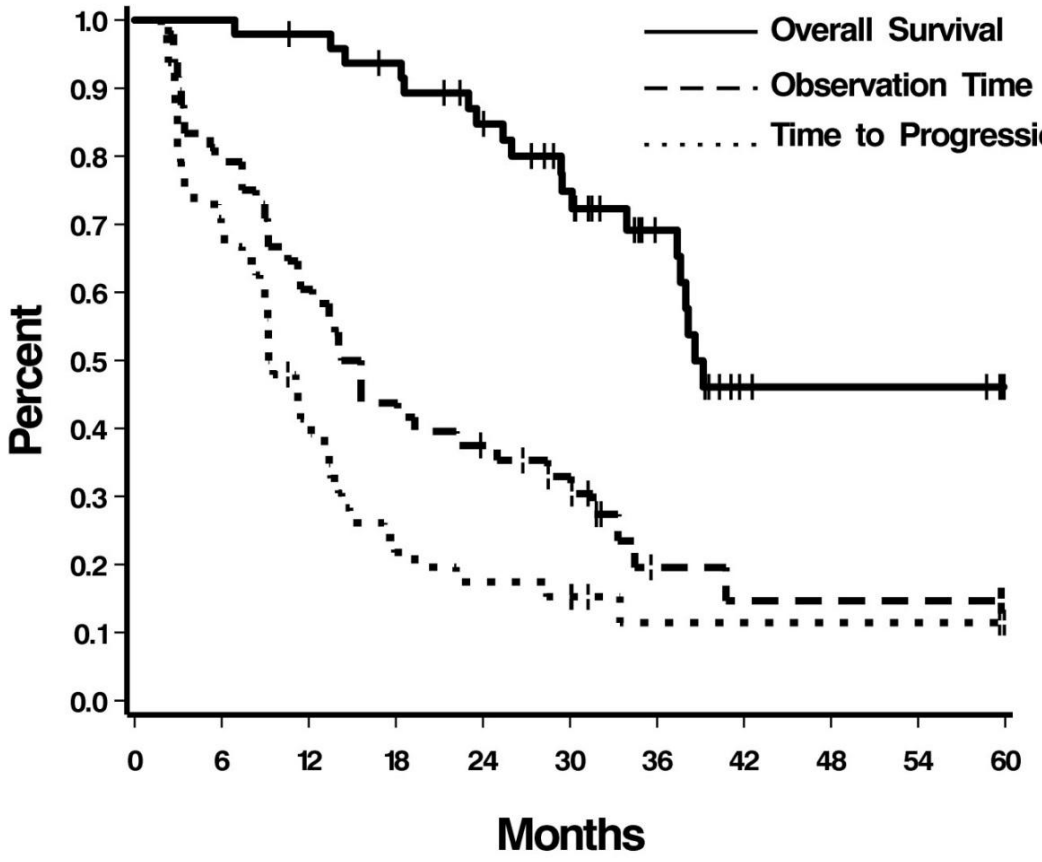
RCC is an inherently diverse disease



Prospective Trial of mRCC Patients on Active Surveillance



OS: 38.6 months
Obs: 14.9 months
PFS: 9.4 months

In the 42 patients who did not undergo resection during the surveillance period:

- Median absolute change in tumor burden during surveillance was 1.3 cm
- Relative change 31%
- **Median growth rate of 0.09 cm per month**

- 8 patients underwent resection informed by the observation period

- 0-1 IMDC risk factors and < 2 organ sites of metastases were associated with longer observation

Rini et al. *Lancet Oncology 2016*

CAIX Detection with ^{89}Zr-DFO-girentuximab

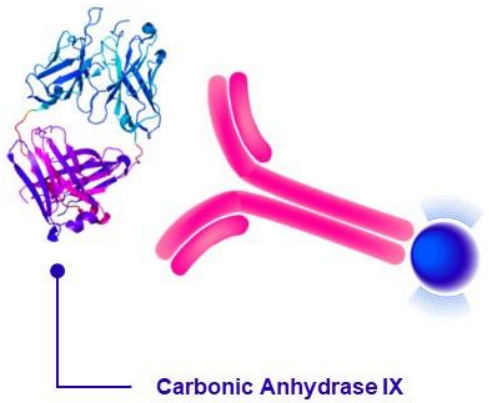
Antibody-based PET imaging agent targeting CAIX

Girentuximab

- IgG1 kappa light chain chimeric monoclonal antibody
- Girentuximab binds with high specificity to CAIX and is internalized
- Extensive safety experience with girentuximab in prior imaging and therapeutic studies
- Hepato-biliary excretion allows optimal renal visualisation

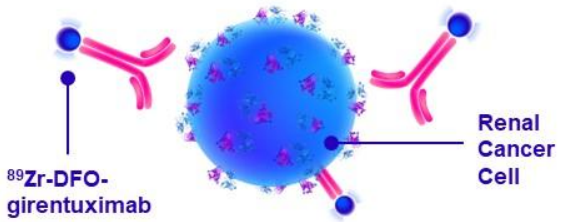
Payload: ^{89}Zr

- Positron emitter
- $T_{1/2}$ 3.3 days
- Suited for antibody-based imaging
- Hepatically cleared



^{89}Zr-DFO-girentuximab in CAIX expressing tumors

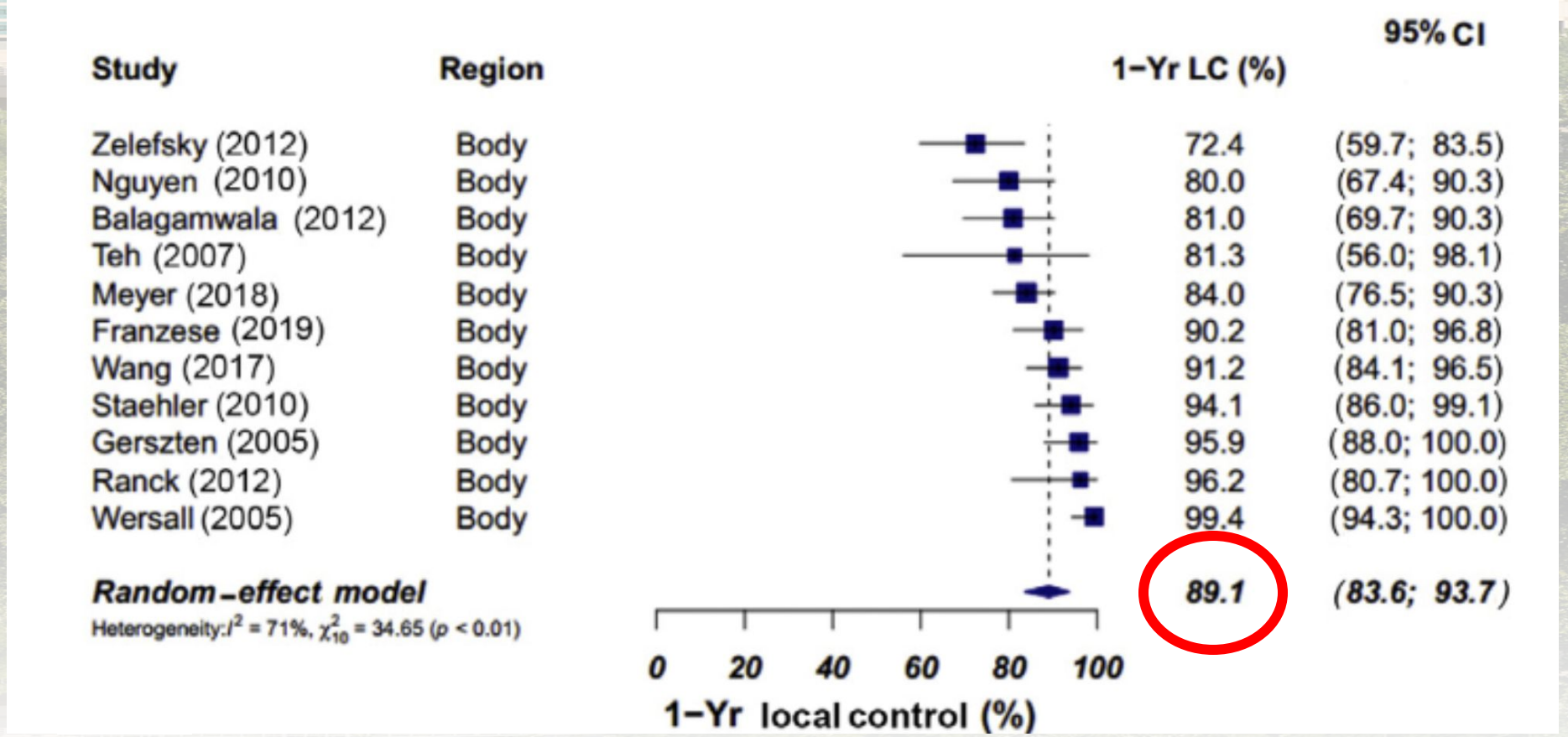
- Previous studies show feasibility imaging CAIX positive tumors (SPECT & PET)[1,2]
- ^{89}Zr-DFO-girentuximab (37 MBq [1 mCi] / 10 mg) was previously shown safe and allowed PET/CT imaging of ccRCC at 4-7 days after administration[3]



1. Oosterwijk-Wakka et al. *Int J Mol Sci.* 2013;14(6):11402-23.
2. Kulterer et al. *J Nucl Med.* 2021;62(3):360-5.
3. Merkx et al. *Eur J Nucl Med Mol Imaging.* 2021;48(10)3277-85.

Shuch et al. ASCO GU 2023

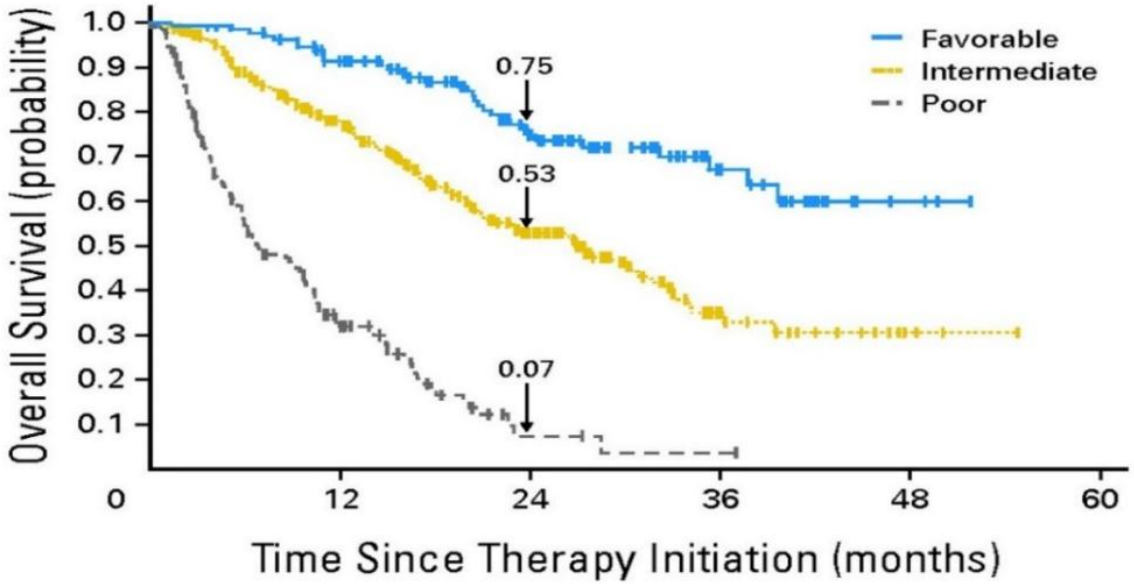
SBRT for RCC oligometastases



Zaorsky et al. *EAU* 2019

IMDC Prognostic Criteria

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

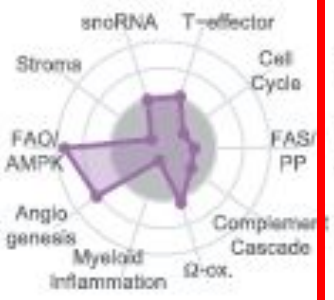
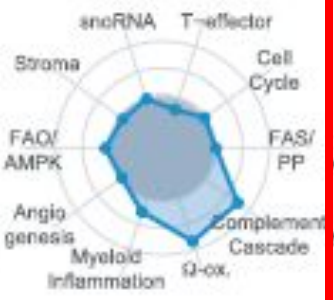
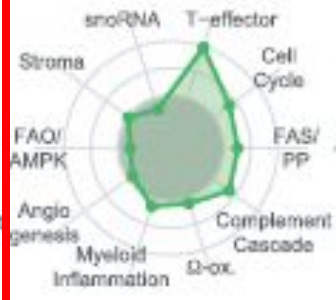
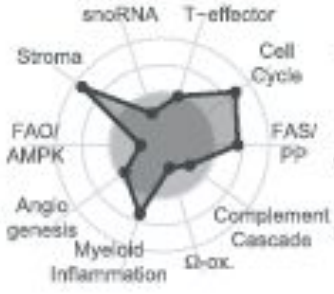


No. of events/No. at risk					
Favorable	11/133	16/110	4/62	2/22	0/3
Intermediate	61/301	50/182	17/82	2/18	0/3
Poor	94/152	19/36	1/3	0/1	0/0

- 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;

RCC is driven primarily (although not exclusively) driven by angiogenic and inflammatory pathways

	Cluster 1	Cluster 2	Cluster 3	Cluster 4	Cluster 5	Cluster 6	Cluster 7
	98/823 (12%)	245/823 (30%)	156/823 (19%)	116/823 (14%)	74/823 (9%)	106/823 (13%)	28/823 (3%)
Pathways	Angiogenesis Stroma	Angiogenesis Fatty acid oxidation	Complement cascade Ω-oxidation	T-effector Cell Cycle Fatty acid synthesis	Cell Cycle Fatty acid synthesis	Stroma Cell Cycle	snoRNA
RNA profile							
DNA alts	VHL PBRM1 KDM5C PTEN	VHL PBRM1 KDM5C	VHL PBRM1 KDM5C PTEN BAP1	VHL CDKN2A/B BAP1	CDKN2A/B TP53	VHL CDKN2A/B TP53	VHL SETD2 PTEN

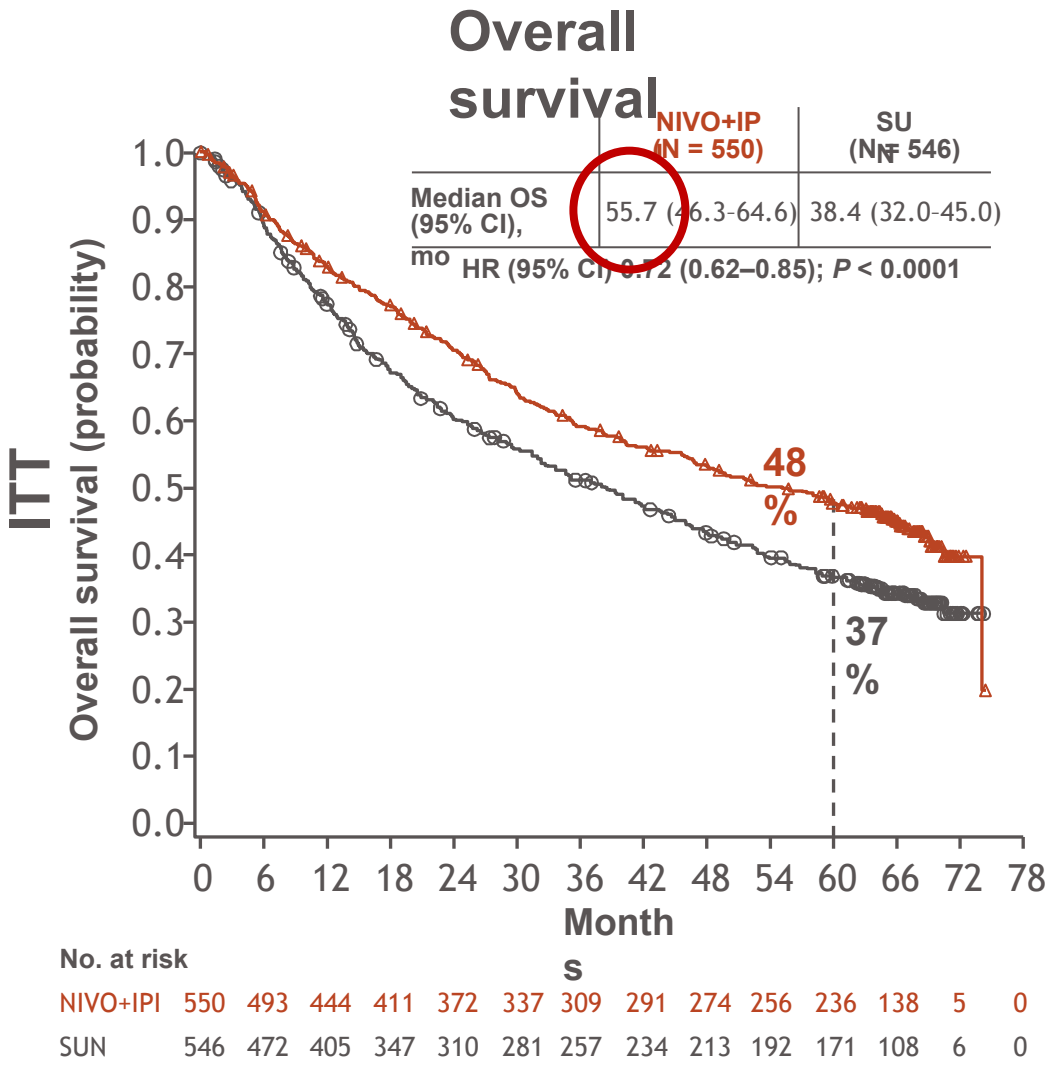
Motzer et al. *Cancer Cell* 2020

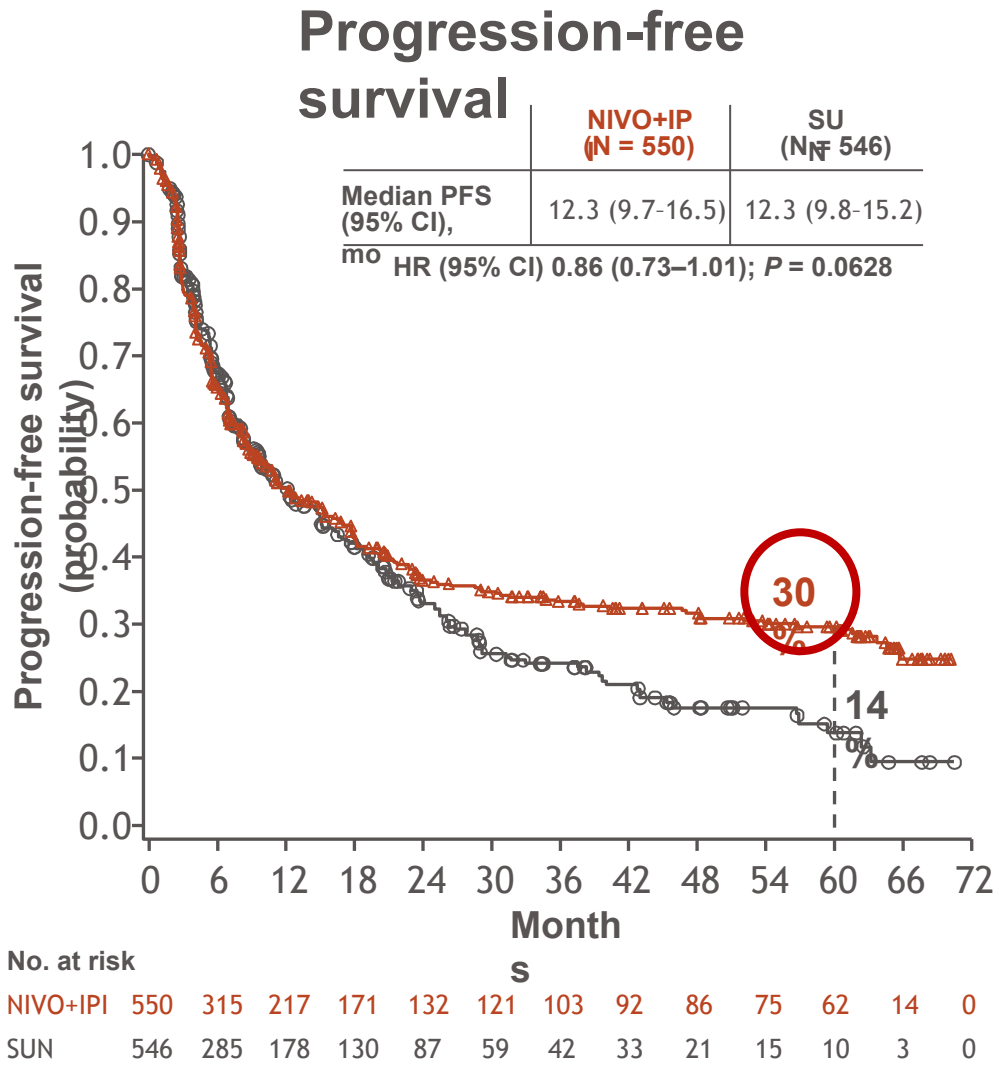
First-line IO Combination Trials in mRCC (ITT)

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

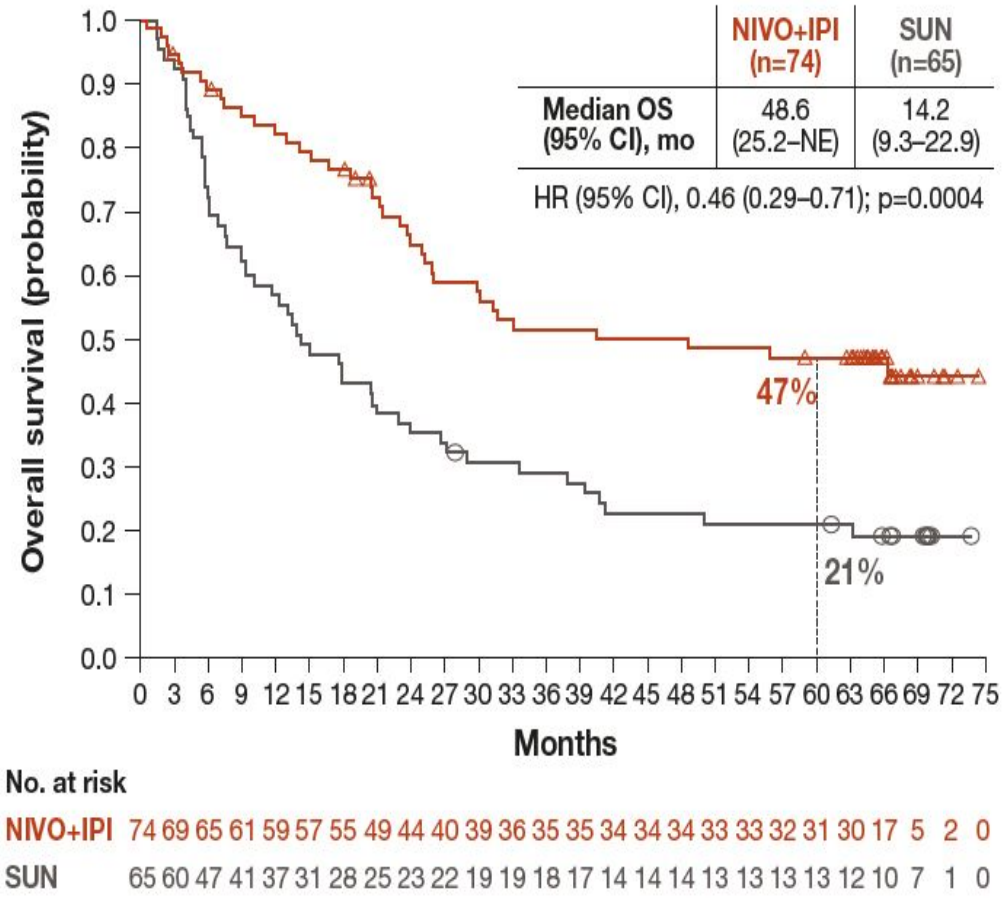
OS and PFS in ITT: 5-year Update

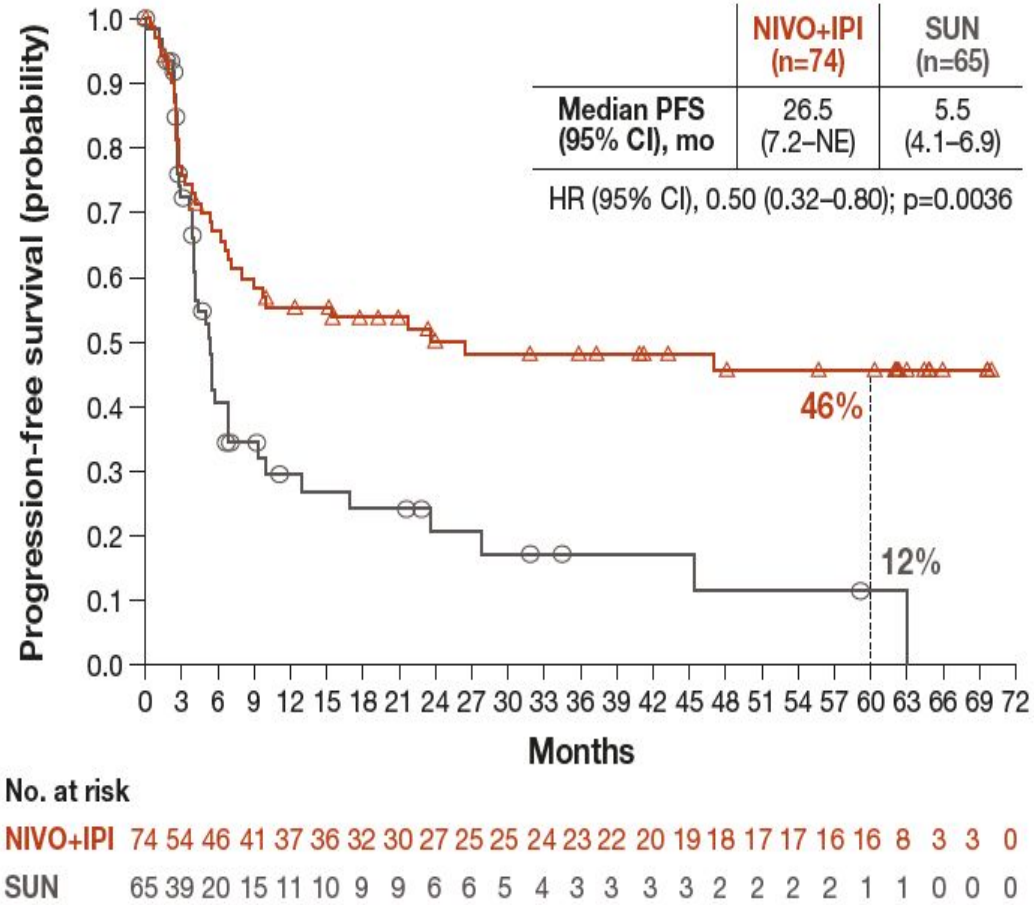




Motzer RJ et al. ESMO 2021. Abstract 661P.

Sarcomatoid histology is the best biomarker for Ipi/Nivo





- ORR 61% / 23% CR

Rini et al. JITC 2023

IO Doublets in Sarcomatoid RCC

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)

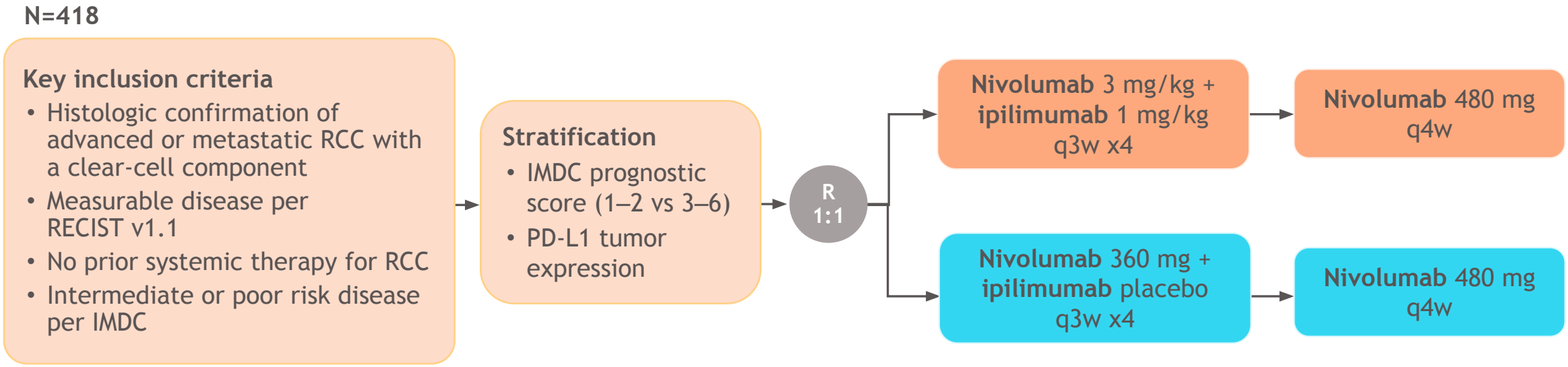
Ipilimumab is not a good salvage agent in RCC

	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

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

Primary outcome measures: PFS,* ORR*

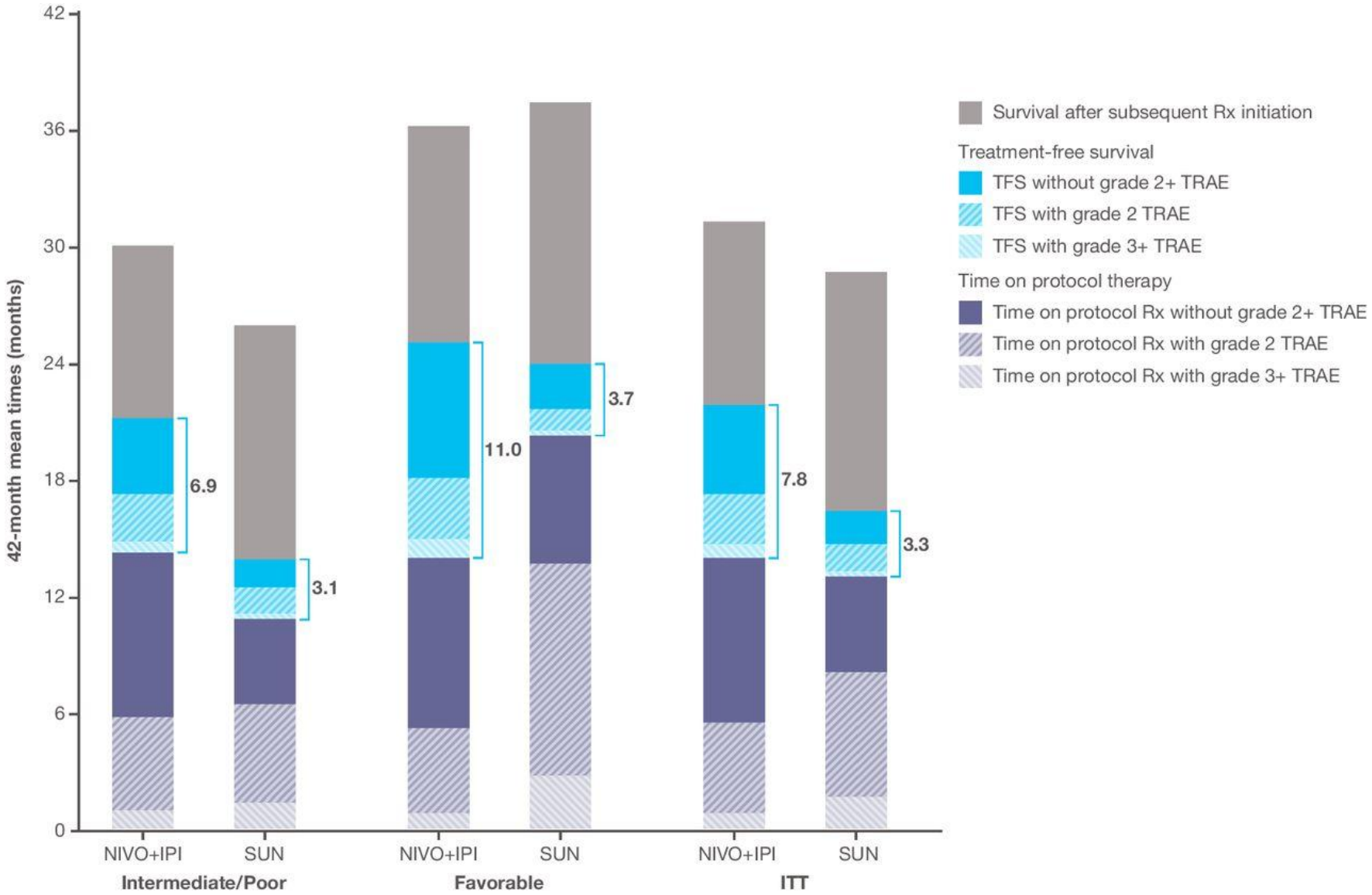
Select secondary outcome measures†: OS, ORR,*‡ DCR, DOR, TTR, PFS,‡ AEs

*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.

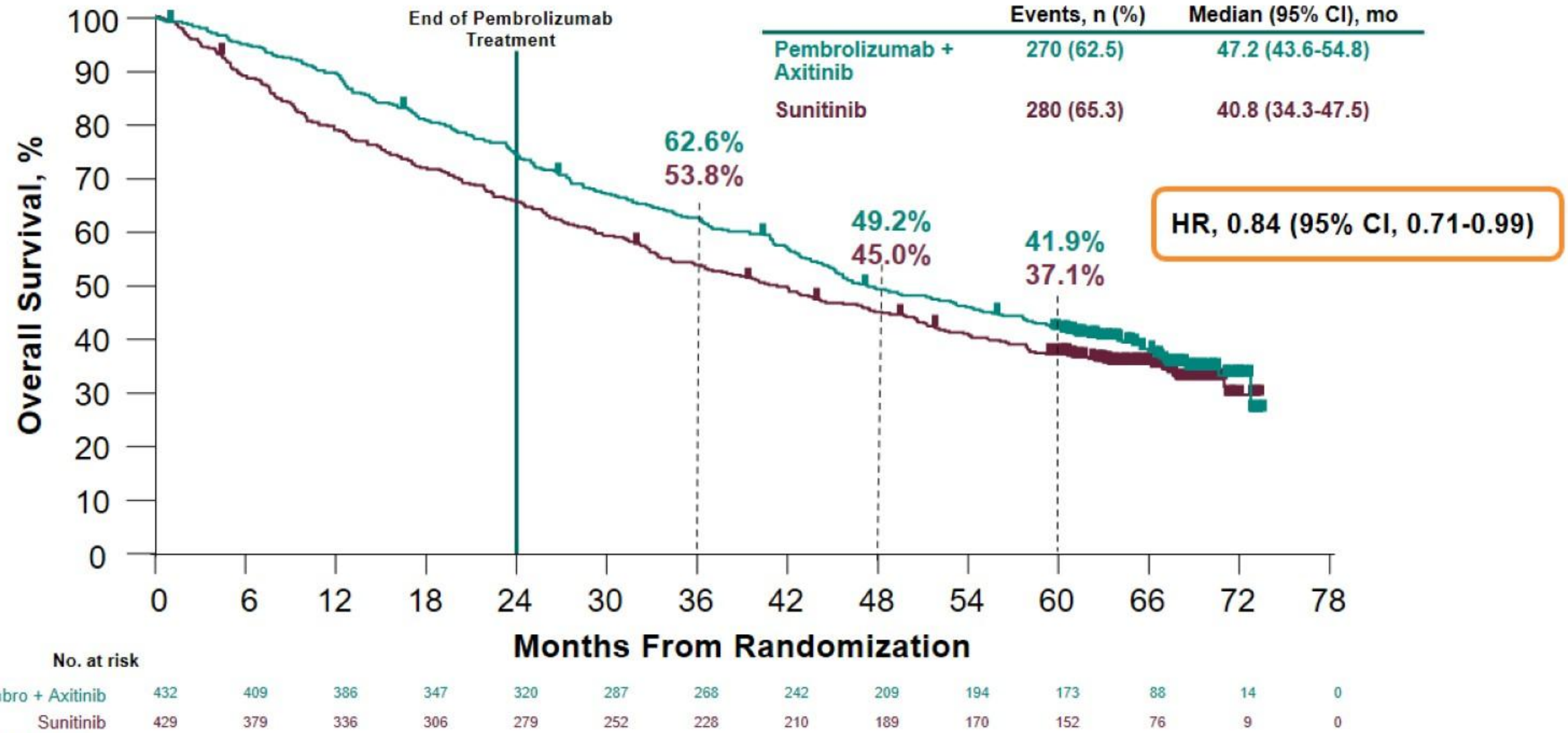
1. Clinicaltrials.gov. NCT03873402. Accessed July 30, 2020. 2. Suarez C et al. Proffered paper discussion at ESMO 2019. Invited discussant LBA56 and LBA57.

Treatment-free Survival after Immune Checkpoint Inhibitor Therapy versus Targeted Therapy for Advanced Renal Cell Carcinoma: 42-Month Results of the CheckMate 214 Trial



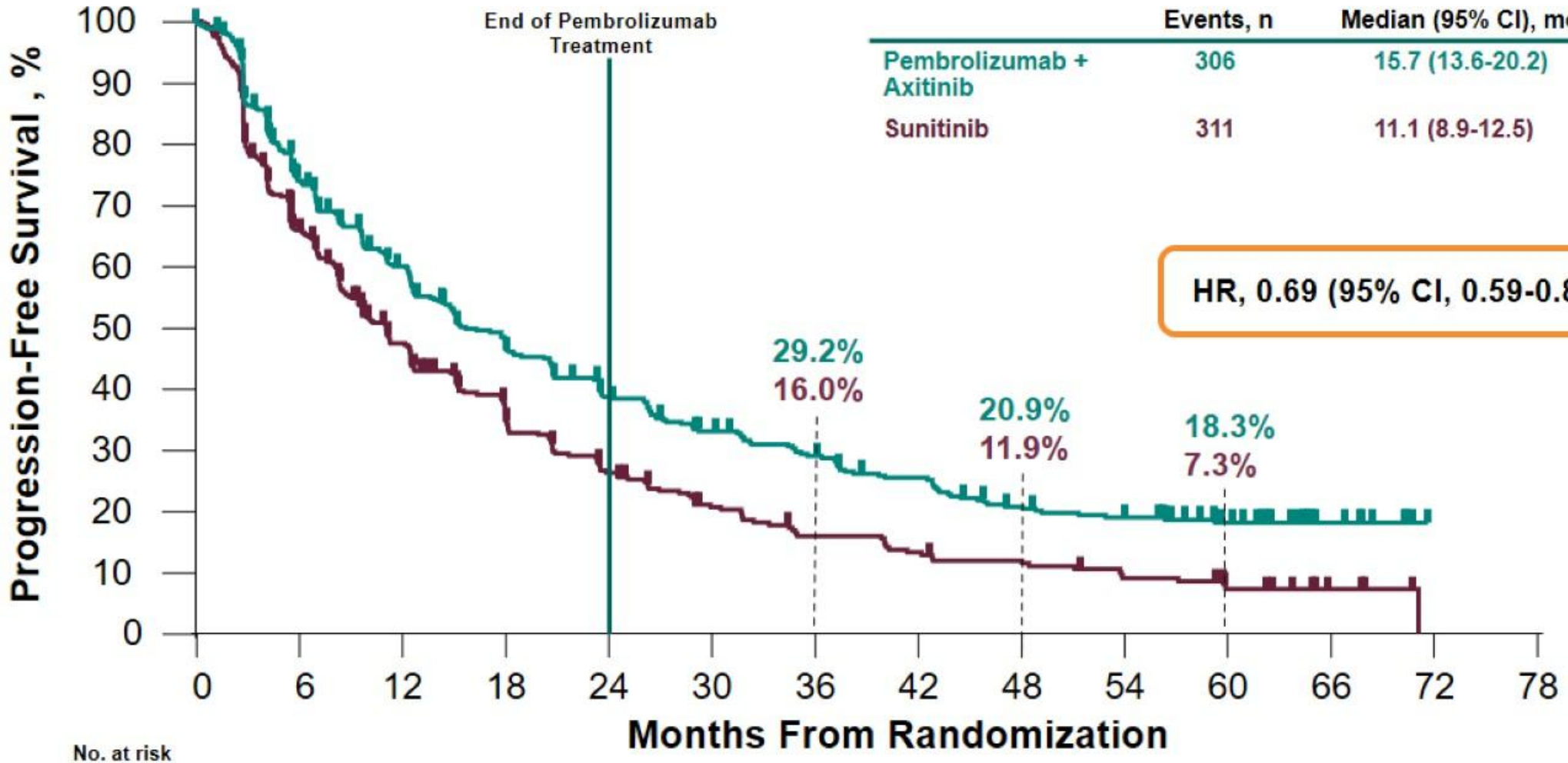
Clin Cancer Res. 2021;27(24):6687-6695

Overall Survival in the ITT Population



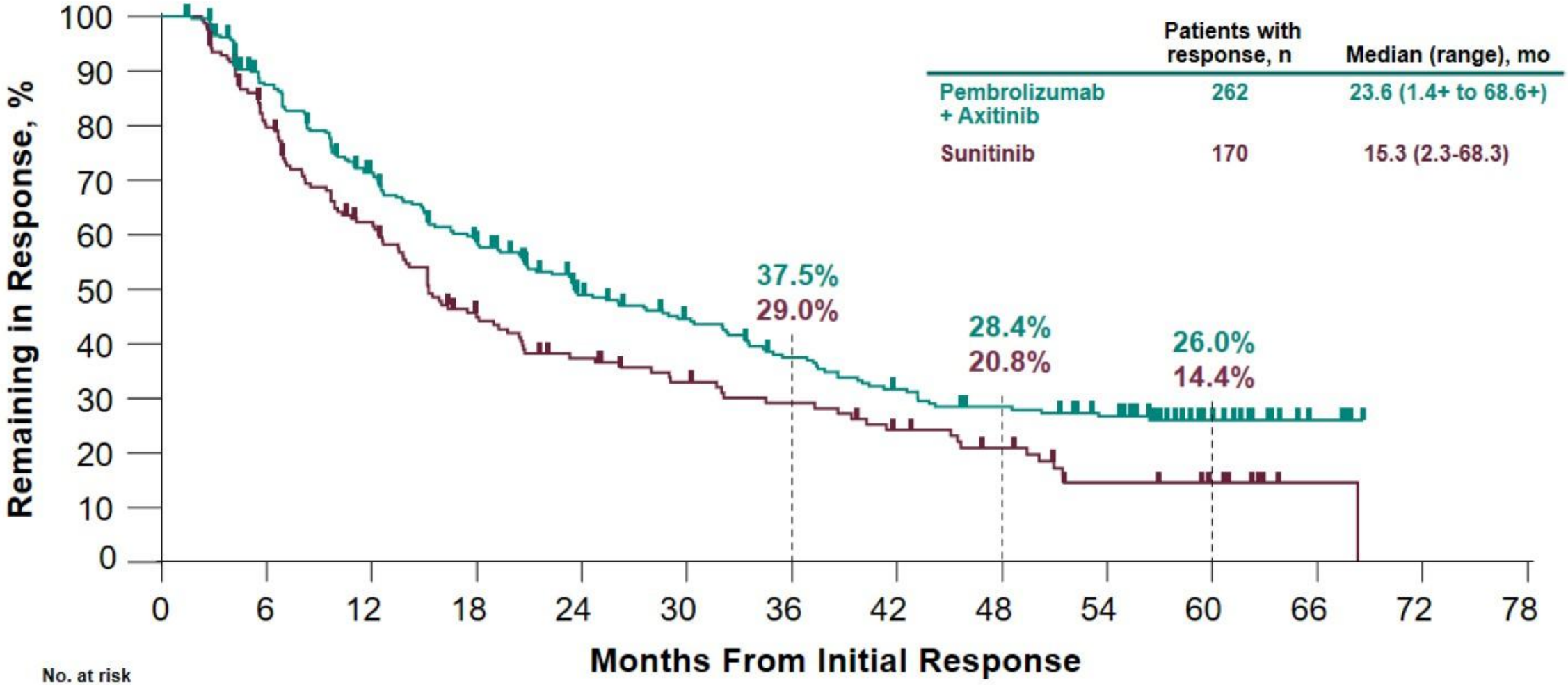
Data cutoff: January 23, 2023.

Progression-Free Survival in the ITT Population



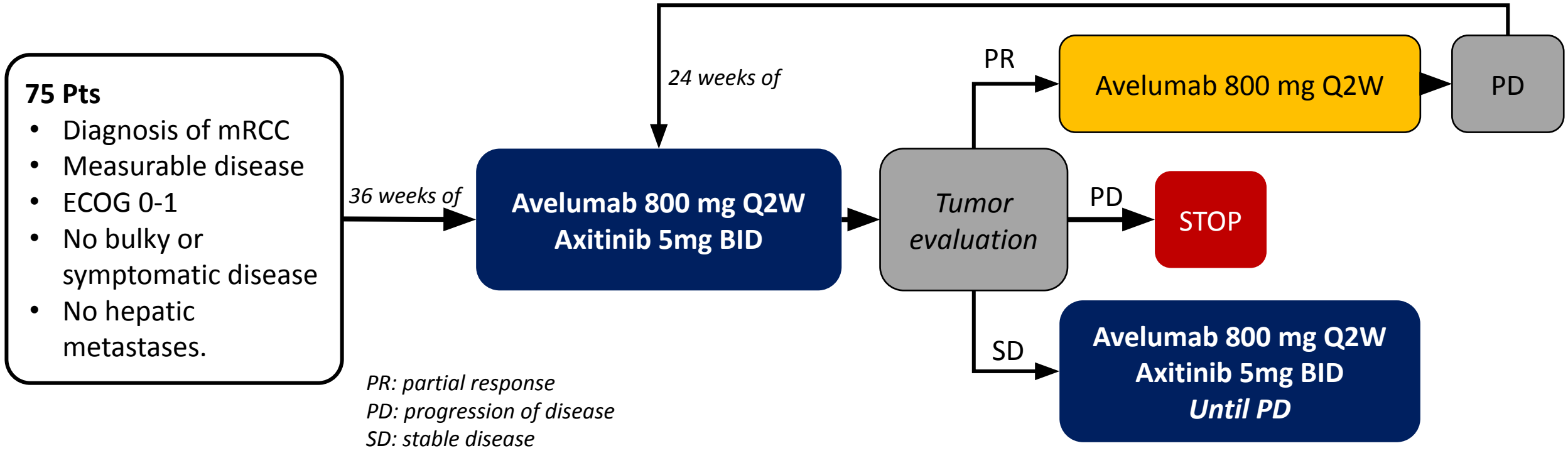
Data cutoff: January 23, 2023.

Duration of Response in the ITT Population



Data cutoff: January 23, 2023.

Can the TKI be discontinued?: Tide A Study design



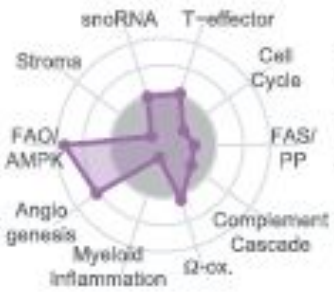
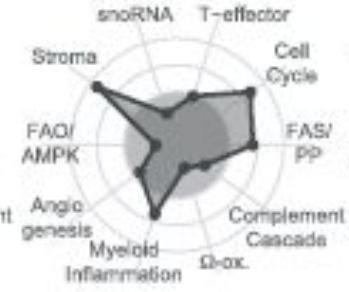
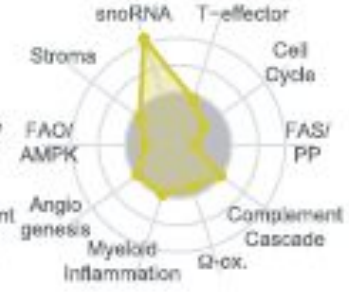
PR: partial response
PD: progression of disease
SD: stable disease

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

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

Using Underlying Biology to Choose Therapy

	Cluster 1	Cluster 2	Cluster 3	Cluster 4	Cluster 5	Cluster 6	Cluster 7
	98/823 (12%)	245/823 (30%)	156/823 (19%)	116/823 (14%)	74/823 (9%)	106/823 (13%)	28/823 (3%)
Pathways	Angiogenesis Stroma	Angiogenesis Fatty acid oxidation	Complement cascade Ω-oxidation	T-effector Cell Cycle Fatty acid synthesis	Cell Cycle Fatty acid synthesis	Stroma Cell Cycle	snoRNA
RNA profile							
DNA alts	VHL PBRM1 KDM5C PTEN	VHL PBRM1 KDM5C	VHL PBRM1 KDM5C PTEN BAP1	VHL CDKN2A/B BAP1	CDKN2A/B TP53	VHL CDKN2A/B TP53	VHL SETD2 PTEN

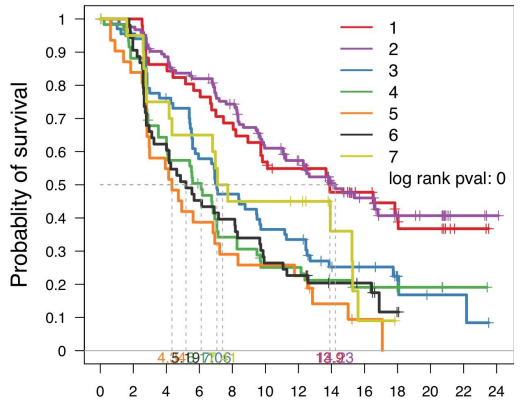
Motzer et al. *Cancer Cell* 2020

NMF subsets associate with differential prognostic and predictive effect

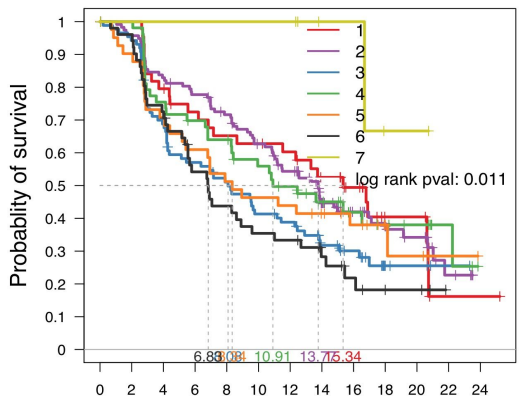
Atezolizumab+Bevacizumab shows improved PFS and a trend of improved OS in T-eff/Proliferative and Proliferative subsets in IMmotion 151

PFS

Sunitinib

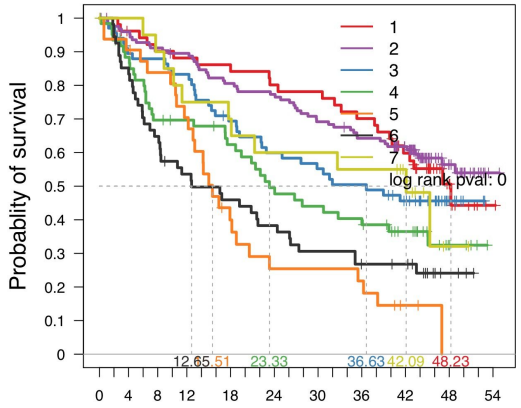


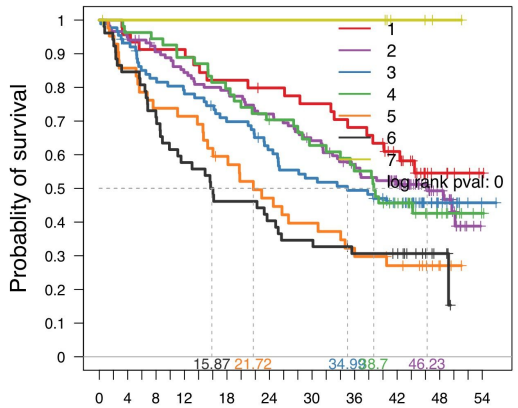
Atezolizumab + Bevacizumab



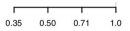
Cluster	HR (95% CI)	Pval	mPFS Atezo+Bev	mPFS Sun
Cluster 1	1.11 (0.65–1.88)	0.708	15.34	13.9
Cluster 2	1.16 (0.82–1.63)	0.397	13.77	14.23
Cluster 3	0.92 (0.63–1.34)	0.666	8.08	7.06
Cluster 4	0.52 (0.33–0.82)	0.005	10.91	6.11
Cluster 5	0.47 (0.27–0.82)	0.007	8.34	4.34
Clusters 4&5	0.52 (0.37–0.74)	<0.001	10.81	5.52
Cluster 6	0.81 (0.52–1.25)	0.331	6.83	5.19
Cluster 7	0.1 (0.01–0.77)	0.028		7.41

OS





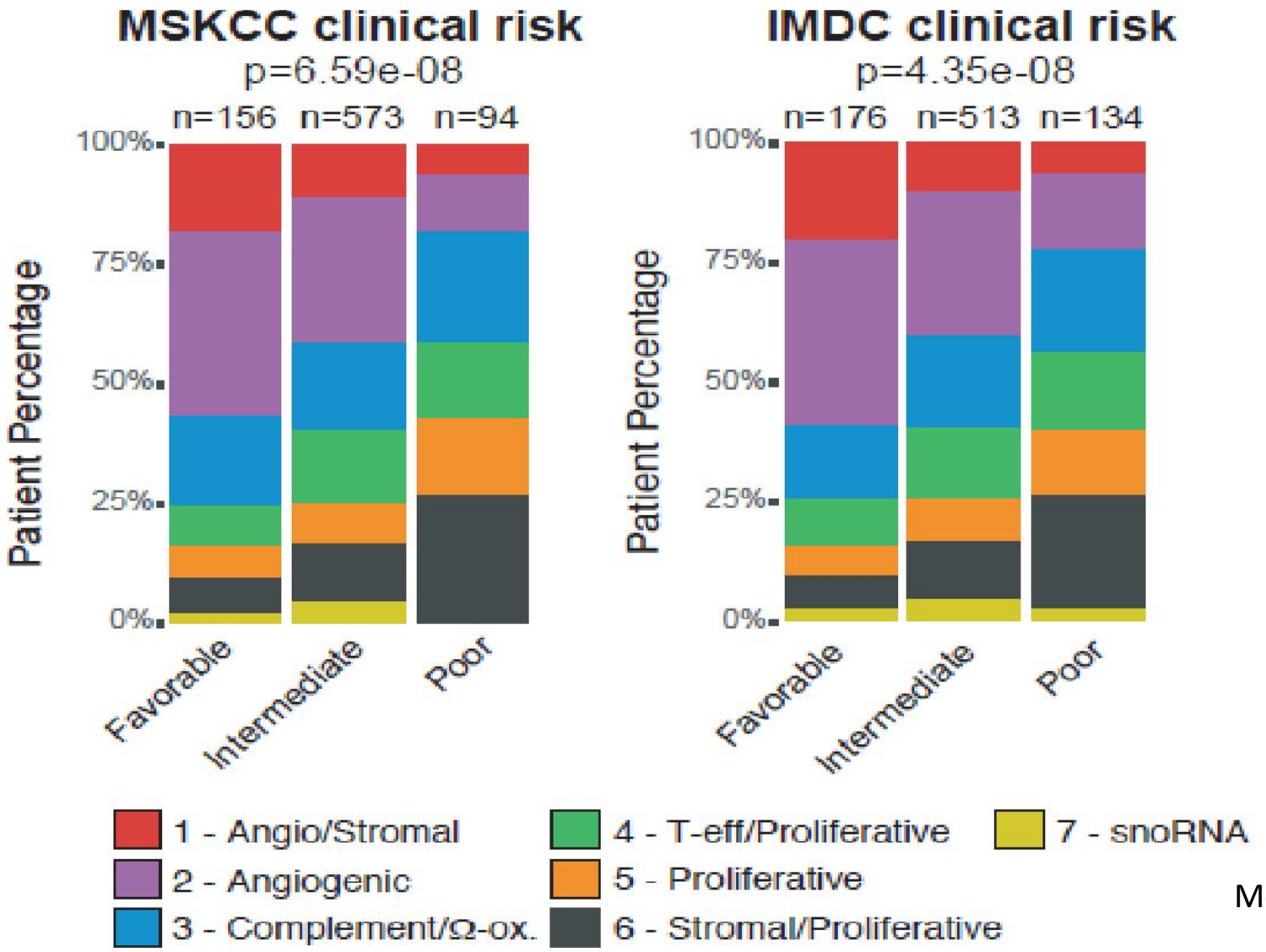
Cluster	HR (95% CI)	Pval	mOS Atezo+Bev	mOS Sun
Cluster 1	0.94 (0.52–1.72)	0.843		48.23
Cluster 2	1.32 (0.91–1.91)	0.148	46.23	
Cluster 3	0.99 (0.64–1.54)	0.979	34.99	36.63
Cluster 4	0.66 (0.41–1.06)	0.088	38.7	23.33
Cluster 5	0.66 (0.39–1.12)	0.122	21.72	15.51
Clusters 4&5	0.69 (0.48–0.98)	0.039	34	19.48
Cluster 6	0.9 (0.57–1.4)	0.635	15.87	12.65
Cluster 7 *				



1 - Angio/Stromal
2 - Angiogenic
3 - Complement/Ω-ox.
4 - T-eff/Proliferative
5 - Proliferative
6 - Stromal/Proliferative
7 - snoRNA

* OS HR not calculated as there were no events in Atezo+Bev treated patients in Cluster 7

Patient groups defined by clinical characteristics display heterogeneous biology



Motzer et al. *Cancer Cell* 2020

OPtimal Treatment by Invoking biologic Clusters in Renal Cell Carcinoma (OPTIC RCC) (NCT 05361720)

Key Eligibility Criteria

- ECOG 0 or 1
- Newly diagnosed mccRCC
- No prior systemic therapy
- Available tumor tissue for RNA-sequencing/cluster prediction
- Clusters 3/6/7 will be excluded

Simon's Minimax Two-Stage Design

Clusters 1/2 → **Nivolumab/Cabozantinib (N=26)**

- H_0: ORR ≤ 55%
- H_A: ORR > 55%
- Primary Endpoint: ORR>75%

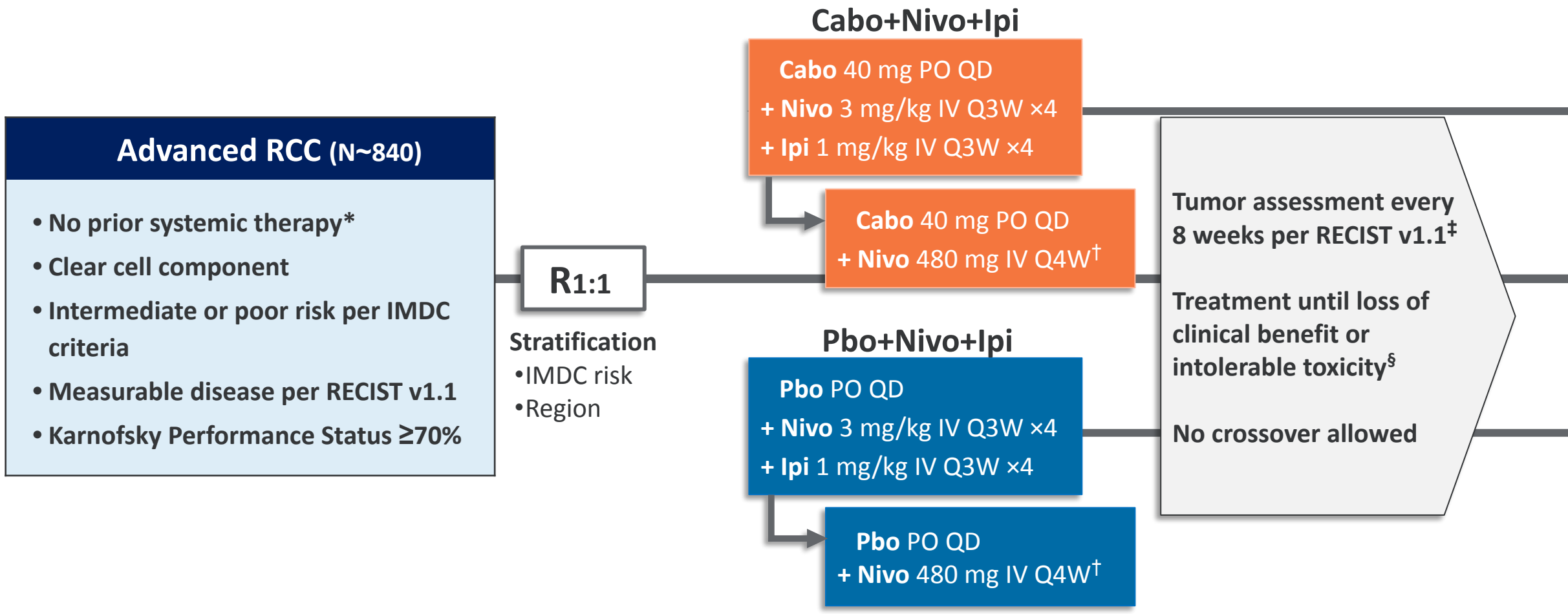
Stage I (N=12)
≥7/12 responders → **Stage II (N=14)**
≥18/26 responders

Clusters 4/5 → **Ipilimumab/Nivolumab (N=28)**

- H_0: ORR ≤ 40%
- H_A: ORR > 40%
- Primary Endpoint: ORR> 60%

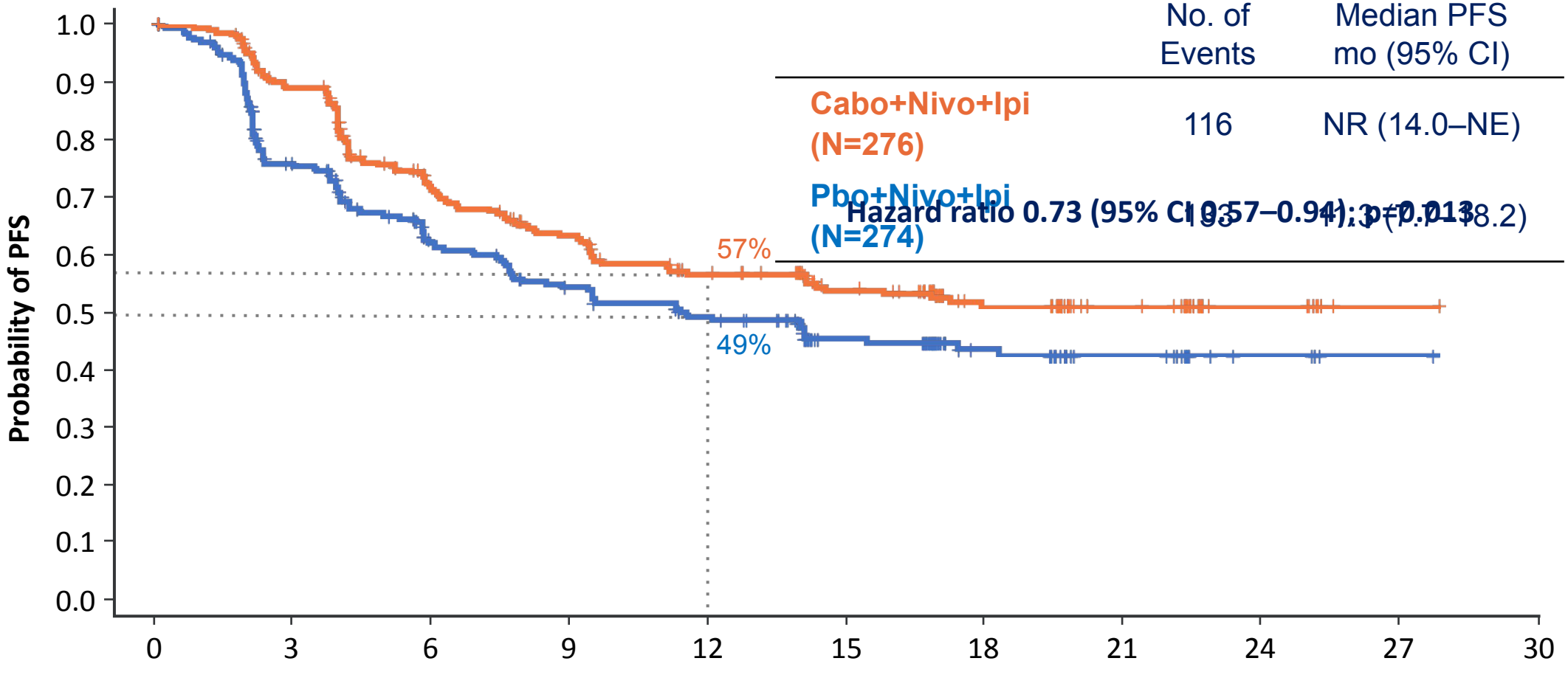
Stage I (N=16)
≥7/16 responders → **Stage II (N=12)**
≥15/28 responders

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)



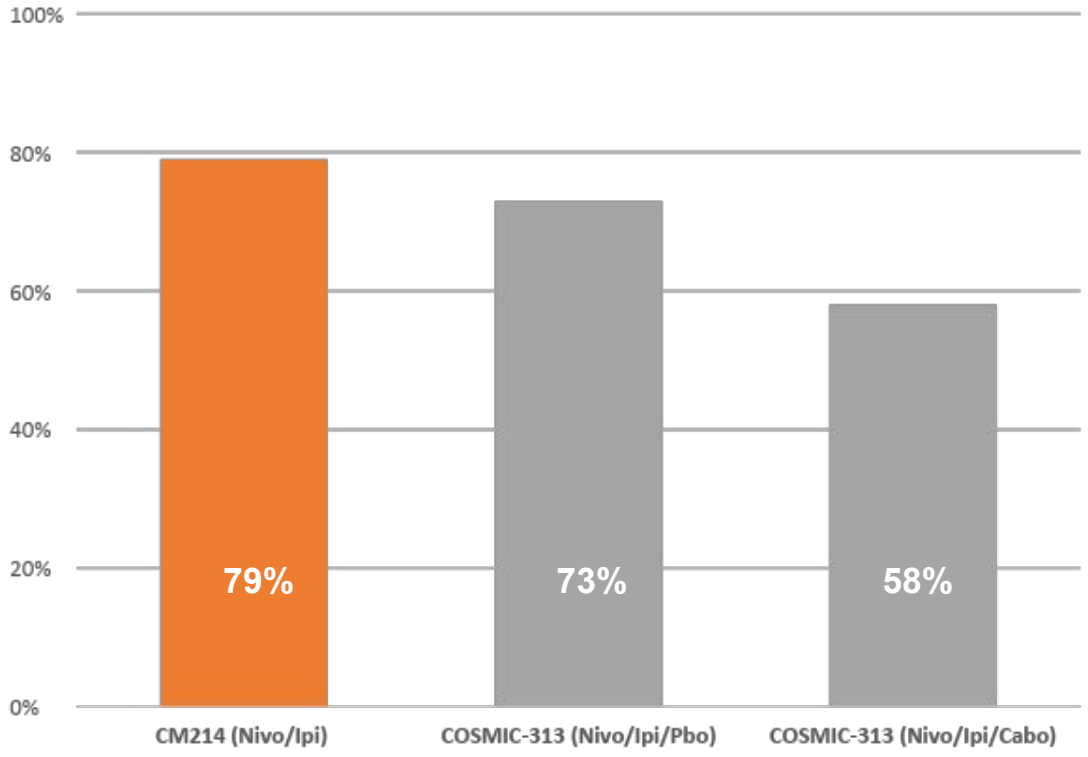
Number at Risk											
Cabo+Nivo+Ipi	276	234	170	145	119	97	56	33	10	1	0
Pbo+Nivo+Ipi	274	185	136	115	98	69	37	19	5	1	0

PFS per RECIST v1.1 by BIRC.

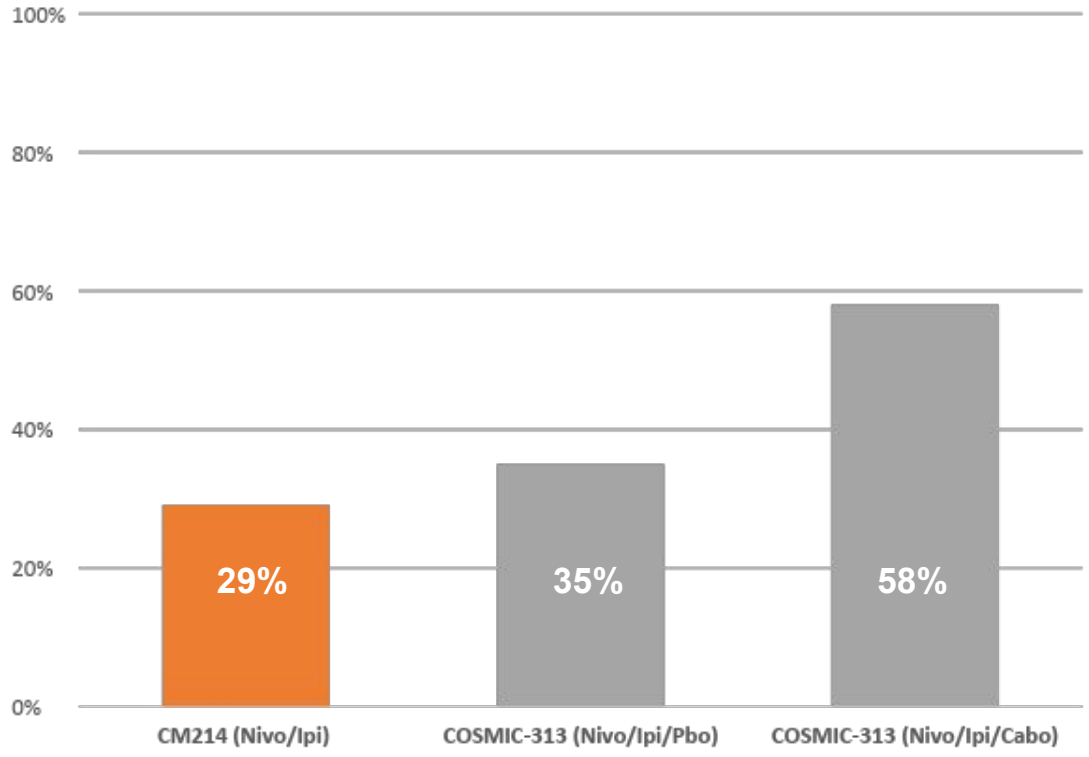
Data cut-off: Aug 23, 2021

Toxicity limited drug delivery

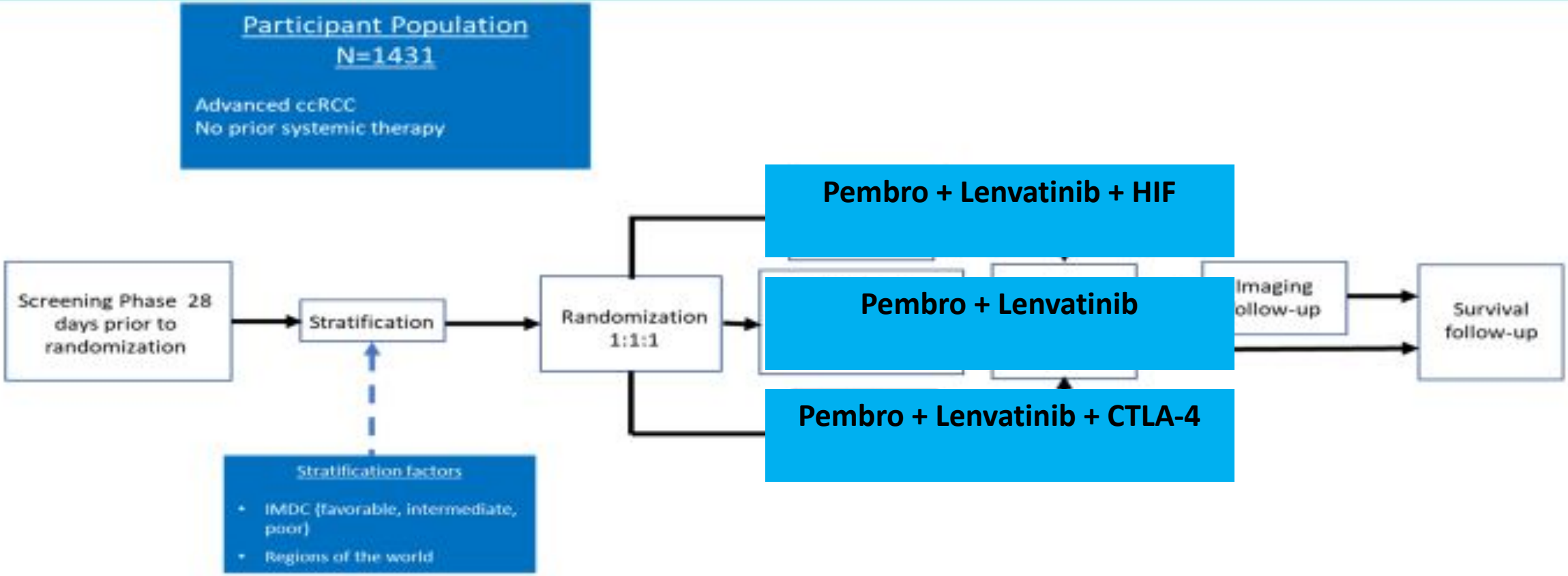
Proportion of patients receiving 4 doses of ipilimumab



Proportion of patients receiving >40 mg of prednisone or equivalent



MK-6482-012 Study Design

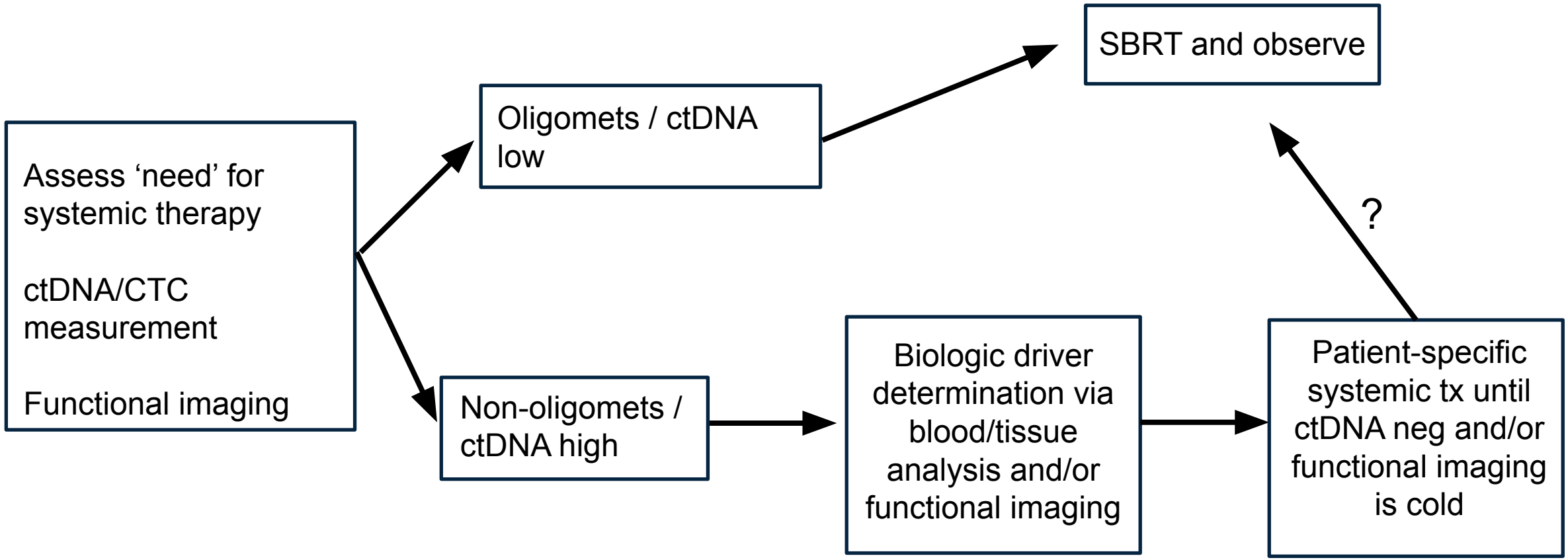


- Abbreviations: IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; ccRCC = clear cell renal cell carcinoma.
- a. The treatment arms are the HIF triplet (MK-6482 + pembrolizumab + lenvatinib), the CTLA4 triplet (MK-1308A + lenvatinib), and the doublet (pembrolizumab + lenvatinib). 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

Metastatic Renal Cell Carcinoma in 2028



Renal Cell Carcinoma in 2028

- There will be thoughtful application of metastasis-directed therapy enabled by more sensitive imaging
- Initial systemic therapy in advanced RCC will be anti-PD-1-based combination IO regimens.
  - Patients are selected for type and intensity of therapy based on ctDNA/CTC and/or metastatic tissue analysis
  - Advanced imaging techniques will enable better therapy selection and assessment of response to allow for cessation of therapy
  - VEGF TKIs will be used initially, intermittently when control of disease bulk is needed, or are replaced altogether with HIF inhibitors or replaced with more tumor-shrinking combination IO regimens
  - Toxic early Ipi is replaced with alternative mechanisms including targeting myeloid cells and alternative CTLA-4 targeting agents