Renal Cell Carcinoma: Current Approach to First Line Therapy & Beyond

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Bladder Cancer Advocacy Network BCAN Leading the way to awareness and a cure

Seattle Cancer Care Alliance
Fred Hutch · Seattle Children's · UW Medicine

UNIVERSITY of WASHINGTON

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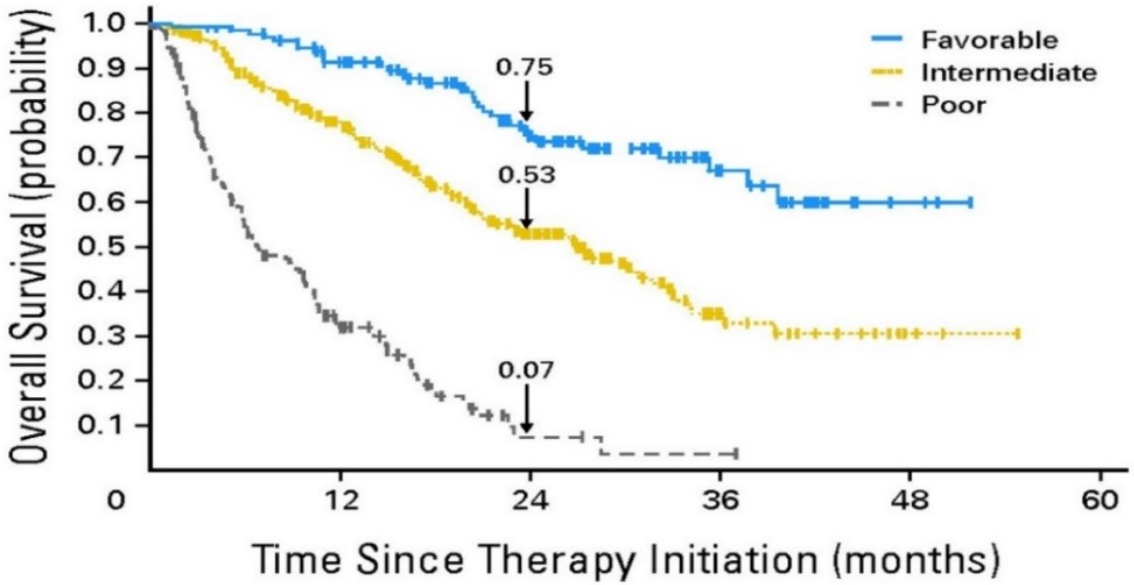
IMDC Prognostic Criteria

- 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

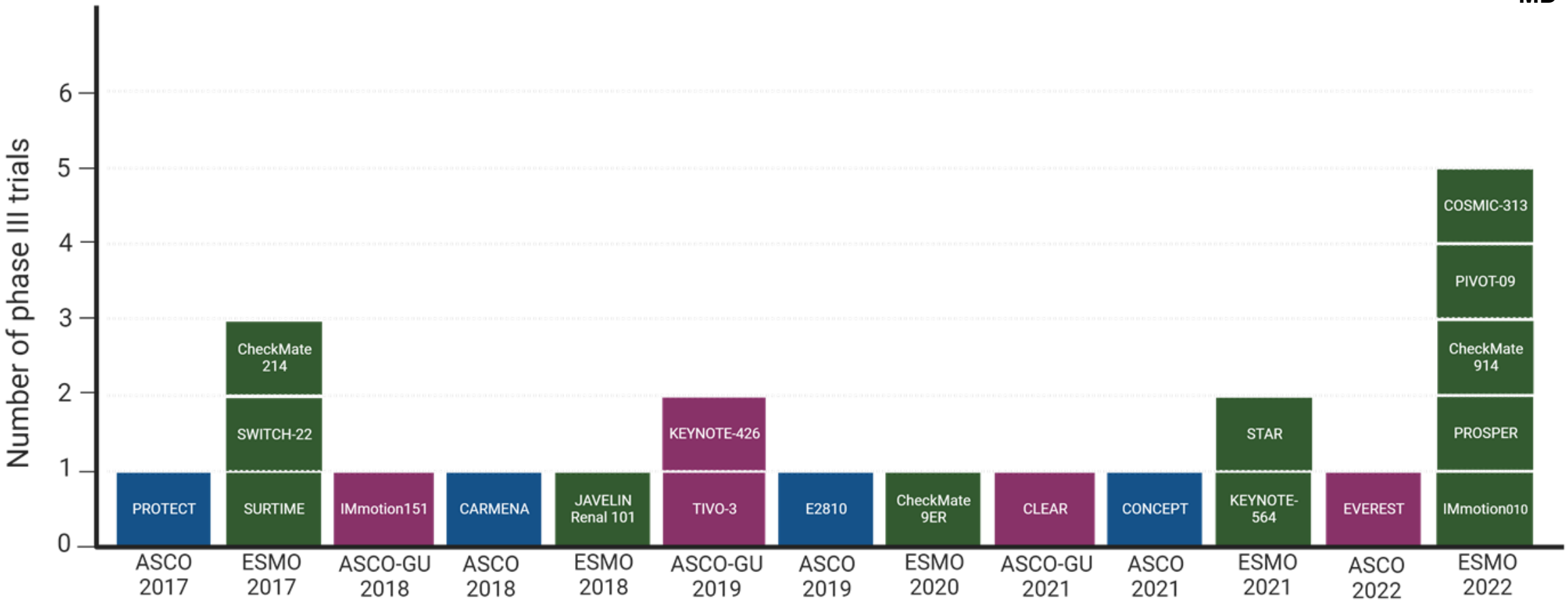
- Favorable: 0 risk factors ⟶ means slow-growing and/or VEGF-responsive (**mostly**)
- Intermediate: 1-2 risk factors ⟶ medium growth rate & somewhat VEGF-responsive
- Poor: 3-6 risk factors ⟶ fast-growing & VEGF-unresponsive

Heng DYC, et al. J Clin Oncol. 2009;27:5794-9

Pivotal Trials in Renal Cell Carcinoma

A meeting-by-meeting synopsis

Courtesy of Z.Zengin, MD



PARIS 2022 ESMO congress

Sumanta K. Pal, MD, FASCO

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. Motzer et al. ASCO GU 2022
4. Motzer et al. ASCO GU 2021.

@brian_rini and @Uromigos

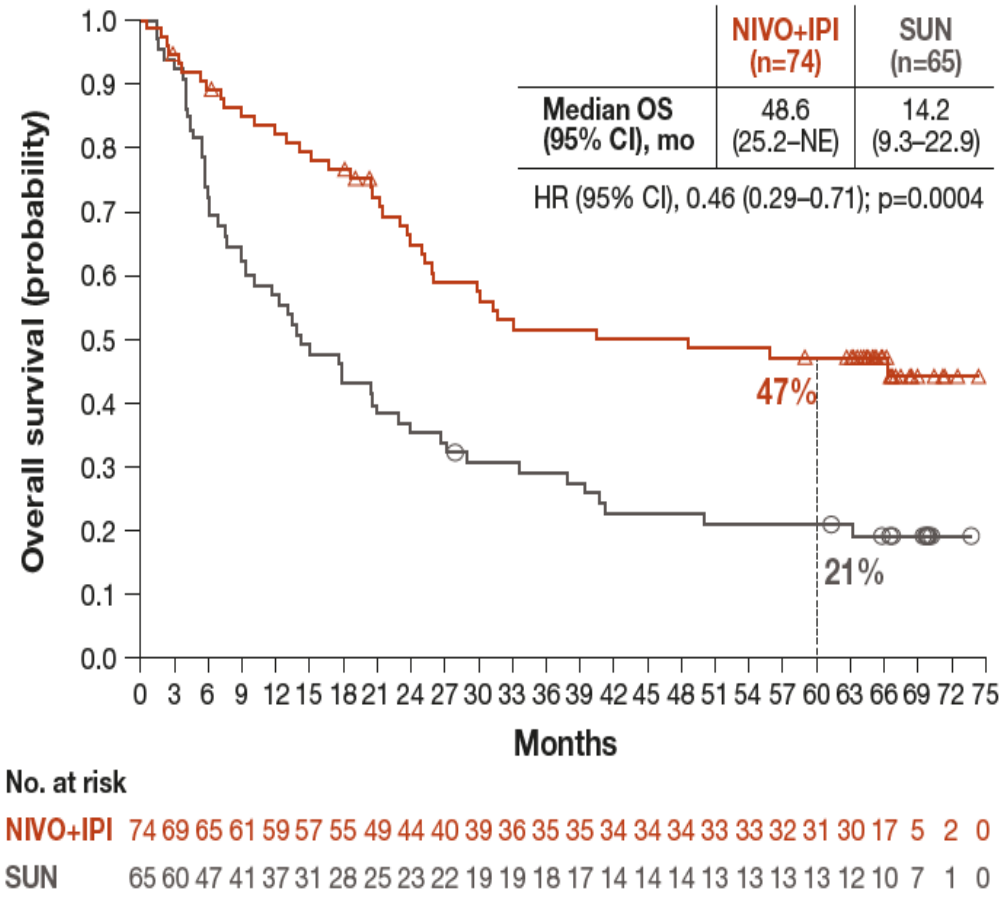
Front-line IO-based Trials in mRCC: IMDC Favorable Risk

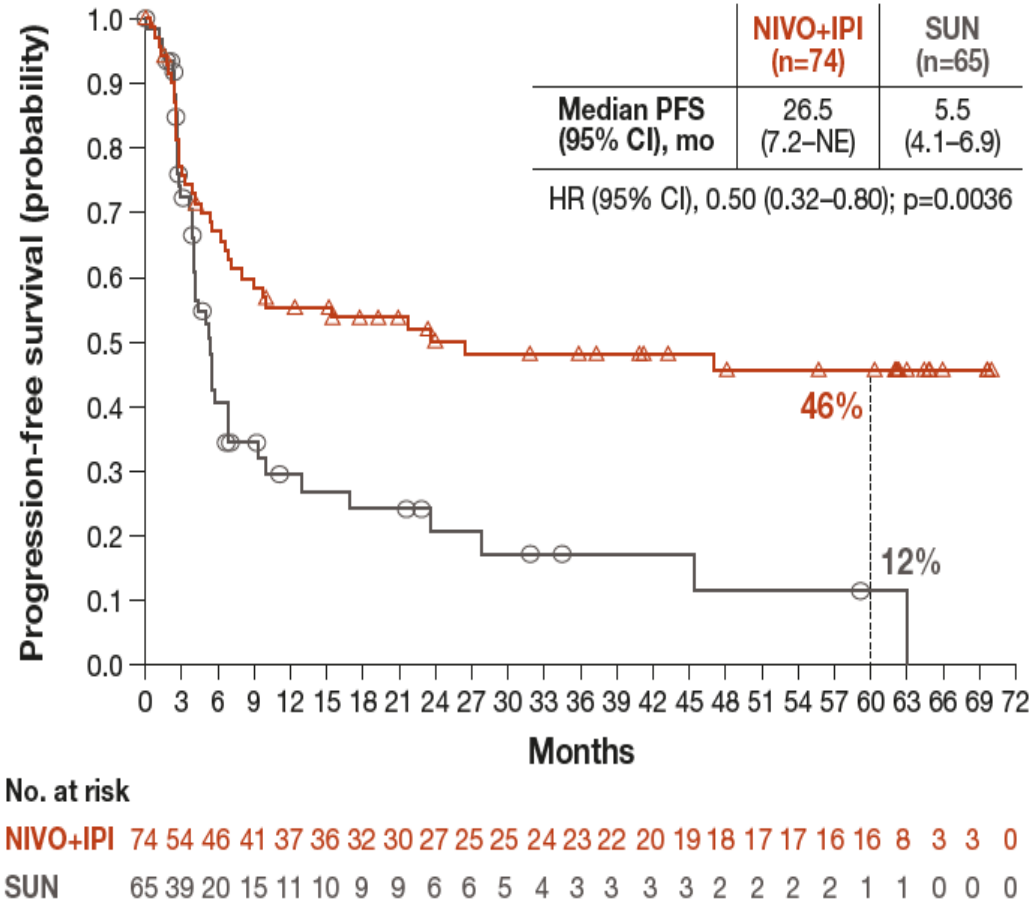
@brian_rini

	CheckMate 214 (Ipi/Nivo)[1] (n=125 vs n=124)	KEYNOTE-426 (Axi/Pembro)[2] (n=138 vs n=131)	CheckMate 9ER (Cabo/Nivo)[3] (n=74 vs n=72)	CLEAR (Len/Pembro)[4] (N=110 vs n=124)	HCRN[5] (Nivo) (N=35)	KEYNOTE-427[6] (Pembro) (N=42)
OS HR	**0.94**	**1.17**	**0.94**	**1.22**	Inconsistent OS effects	
Landmark OS	**63%** vs 55% at 5 years	**72%** vs 73% at 3.5 years	**89%** vs 88% at 15 months	**95%** vs 92% (est.) at 15 months		**88%**
PFS HR	**1.60**	**0.76**	**0.58**	**0.41**	Enhanced tumor shrinkage endpoints	
mPFS, mos	**12.4** vs 28.9	**20.7** vs 17.8	**24.7** vs 12.8	**28.1** vs 12.9	**32.5**	**9.7**
Landmark PFS	**26%** vs 21% at 5 years		**57%** vs 43% at 15 months	**58%** vs 35% (est.) at 2 years	**58%** (est.) at 2 years	**19%** at 2 years
ORR	**30%** vs 52%	**69%** vs 50%	**66%** vs 44%	**68%** vs 51%	**57%**	**31%**
CR	**13%** vs 6%	A subset of favorable risk RCC is immune-responsive		**21%** vs 5%	**11%**	**2%**
Med f/u, months	**67.7**			**33.7**	**27.7**	**35.9**
Duration of response, mos	**61.5** vs 33.2		**Not Reached** vs 13.3	**26.3** vs 14.7	Monotherapy data inconsistent	

1. Motzer et al. ESMO 2021
2. Rini et al. ASCO 2021
3. Apollo et al. ASCO 2021
4. Motzer et al. NEJM 2021, Grunwald et al ASCO 2021 and Choueiri et al. KCRS 2021.
5. Atkins et al. ASCO GU 2022
6. McDermott et al. JCO 2021

Sarcomatoid histology is the best biomarker for Ipi/Nivo

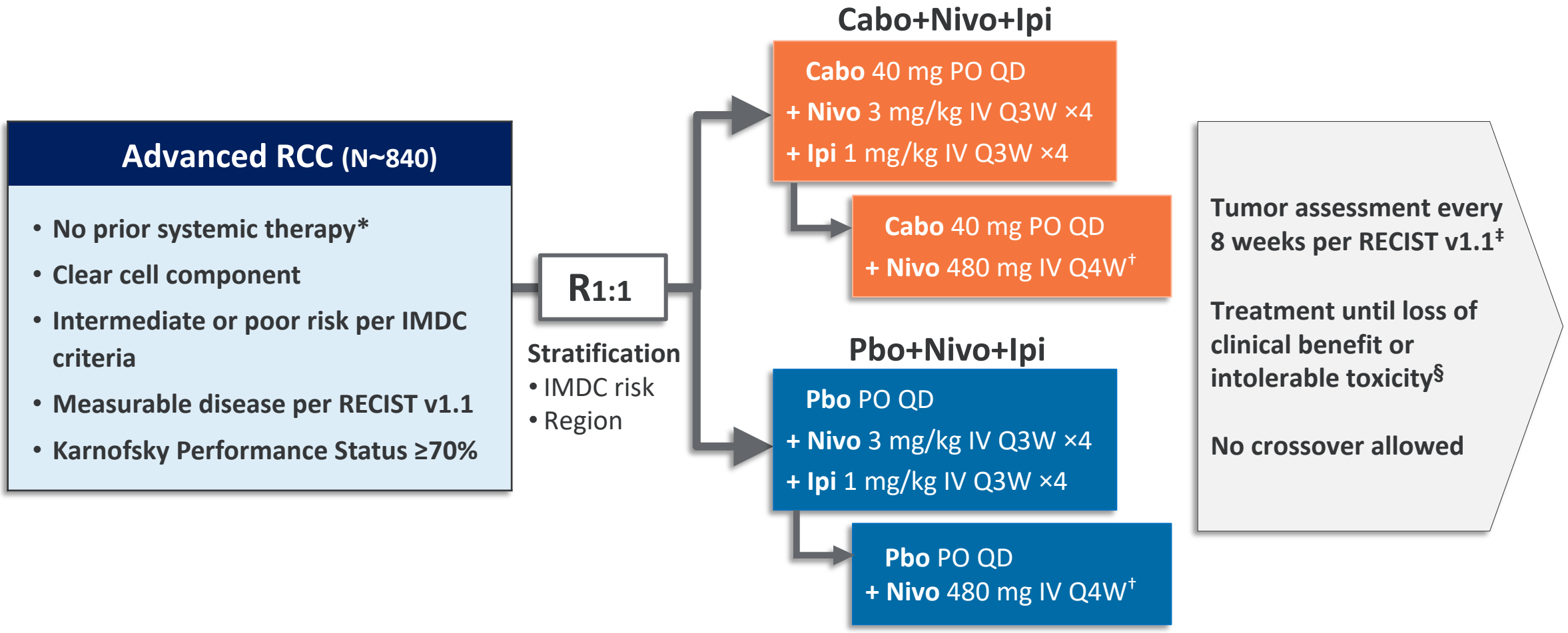




- **ORR 61% / 23% CR**

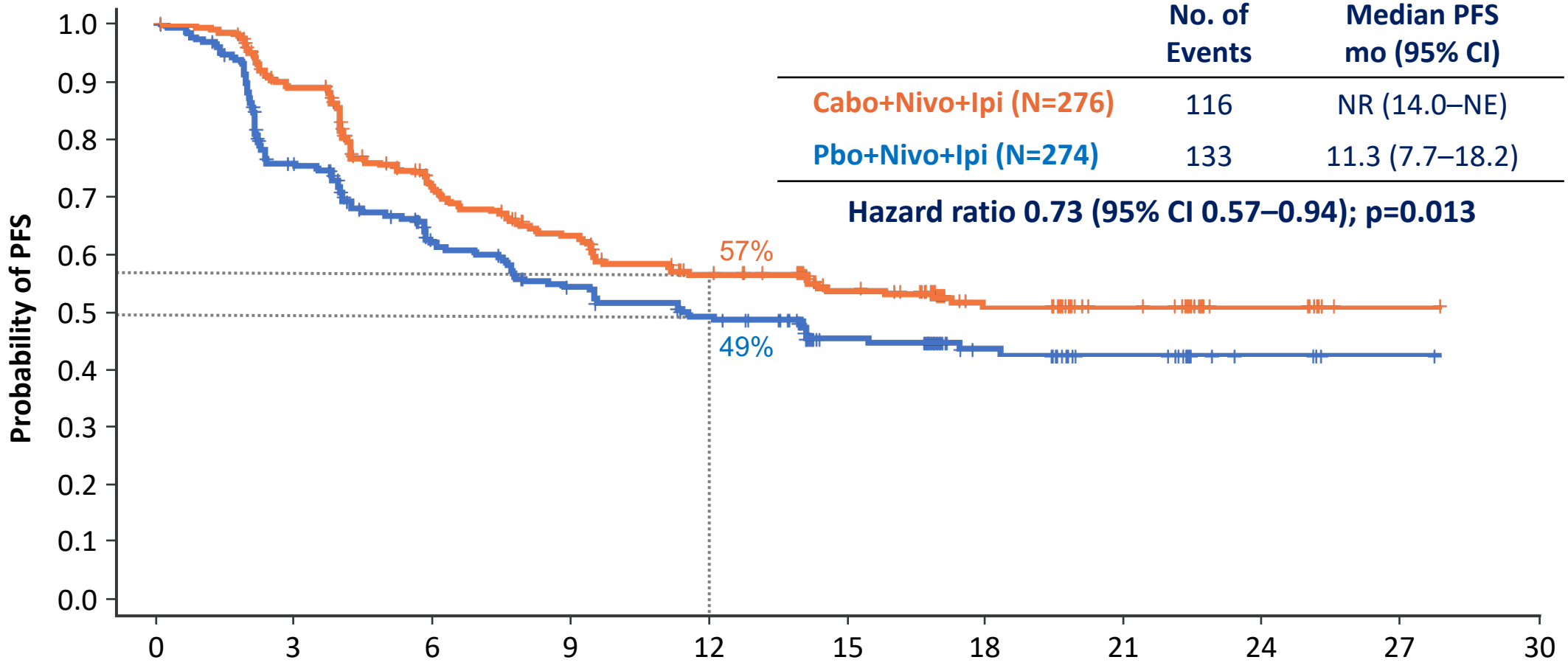
Rini et al. JITC (in press)

Can triplets be 'optimal' therapy?: 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

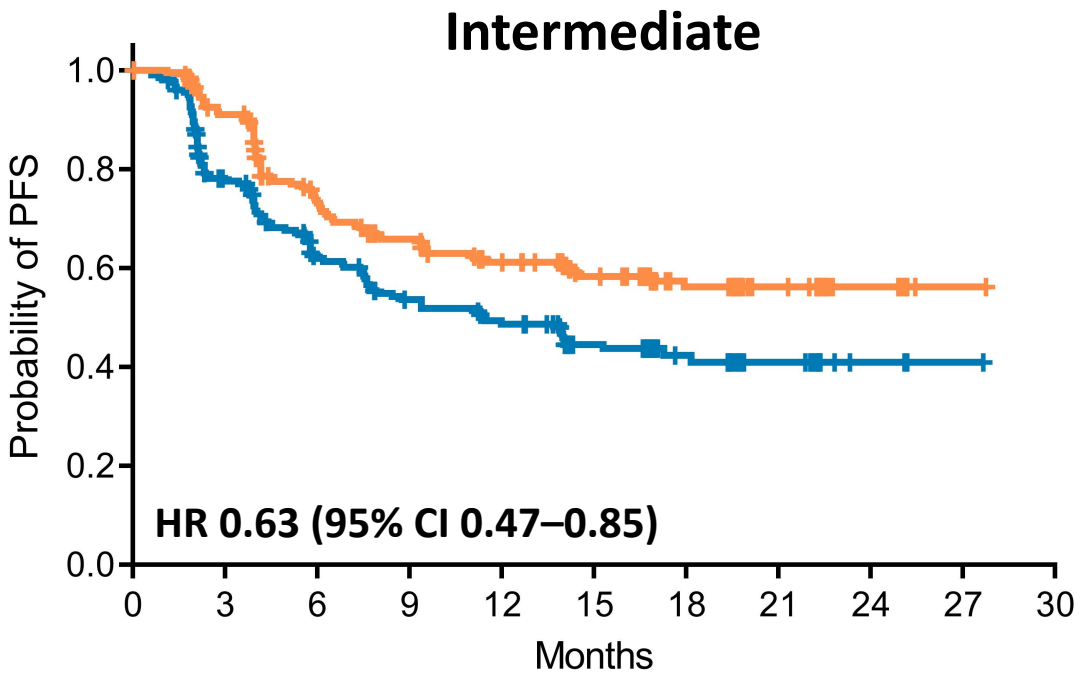
Number at Risk

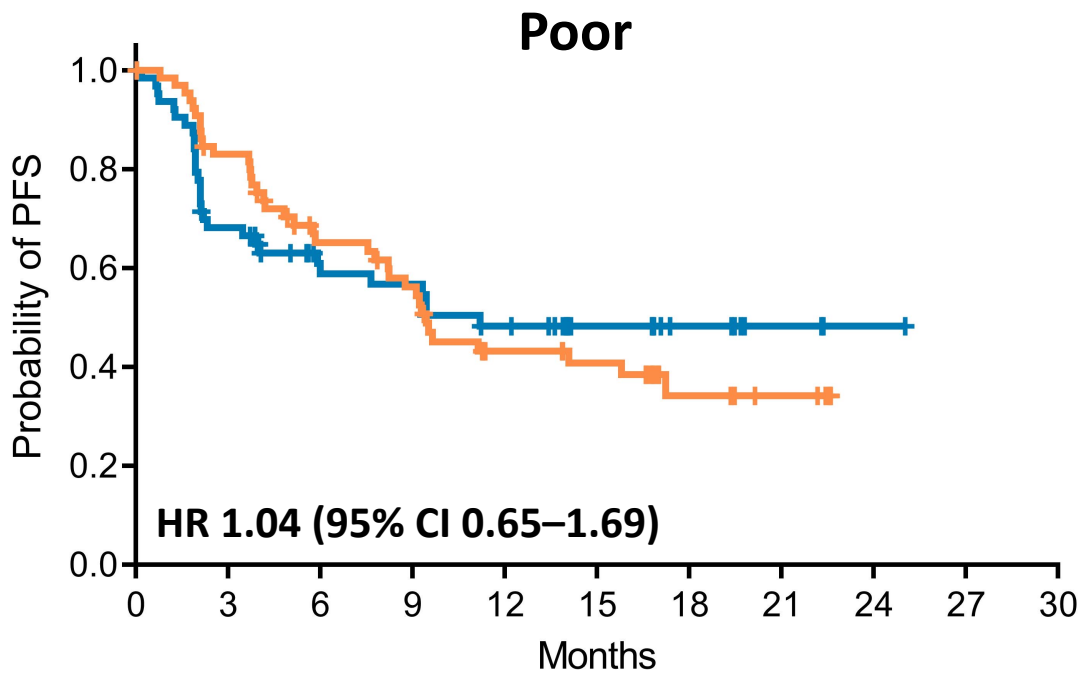
Cabo+Nivo+Ipi	276	234	170	145	119	97	56	33	10	1	0
Pbo+Nivo+Ipi	274	185	136	115	98	69	37	19	5	1	0

PFS per RECIST v1.1 by BIRC.

Data cut-off: Aug 23, 2021

COSMIC313: PFS by IMDC Risk Group (PITT Population)





	No. of Events	Median PFS mo (95% CI)
Cabo+Nivo+Ipi (N=209)	79	NR (16.9–NE)
Pbo+Nivo+Ipi (N=208)	103	11.4 (7.6–17.3)

	No. of Events	Median PFS mo (95% CI)
Cabo+Nivo+Ipi (N=67)	37	9.5 (7.8–17.3)
Pbo+Nivo+Ipi (N=66)	30	11.2 (4.0–NE)

PFS per RECIST v1.1 by BIRC. IMDC risk group is per IxRS.

Data cut-off: Aug 23, 2021

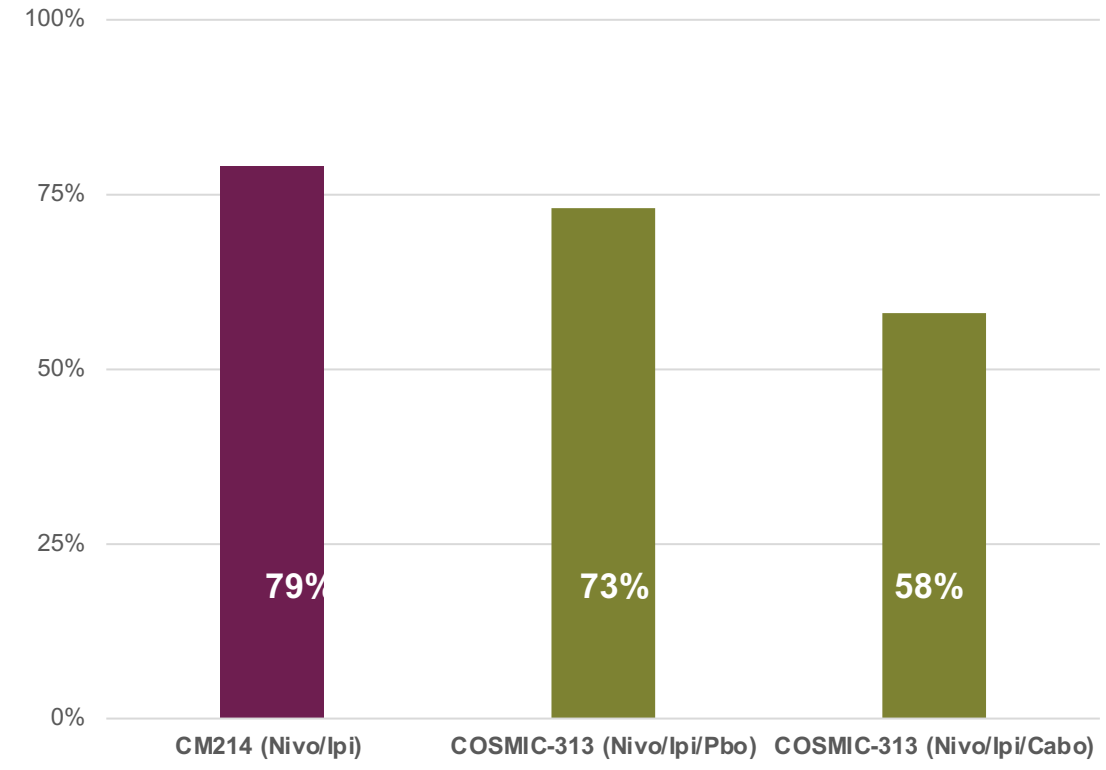
Treatment Exposure and Discontinuation (Safety Population)

	Cabo+Nivo+Ipi (N=426)	Pbo+Nivo+Ipi (N=424)
Median duration of exposure of study treatment (range), mo	10.9 (0.2–28.5)	10.3 (0.1–28.1)
Median average daily dose (range) of Cabo or Pbo, mg	23.2 (3.6–40.0)	36.1 (0.8–40.0)
Median Nivo infusions (range) received, no	10 (1–27)	9 (1–27)
Doses of Ipi received, %		
4	58	73
3	13	14
2	22	7
1	7	6
Any dose hold due to an AE, %	90	70
Any dose reduction of Cabo or Pbo due to an 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 the same AE)	12	5

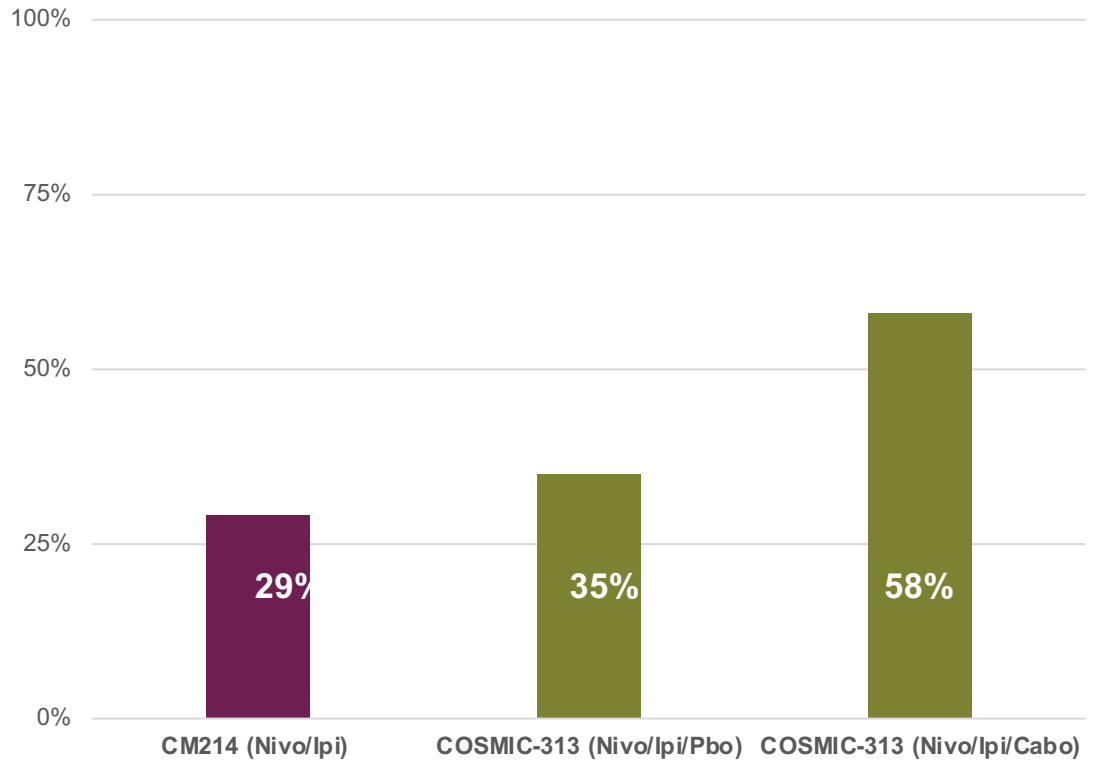
Data cut-off: Jan 31, 2022

Toxicity limited drug delivery

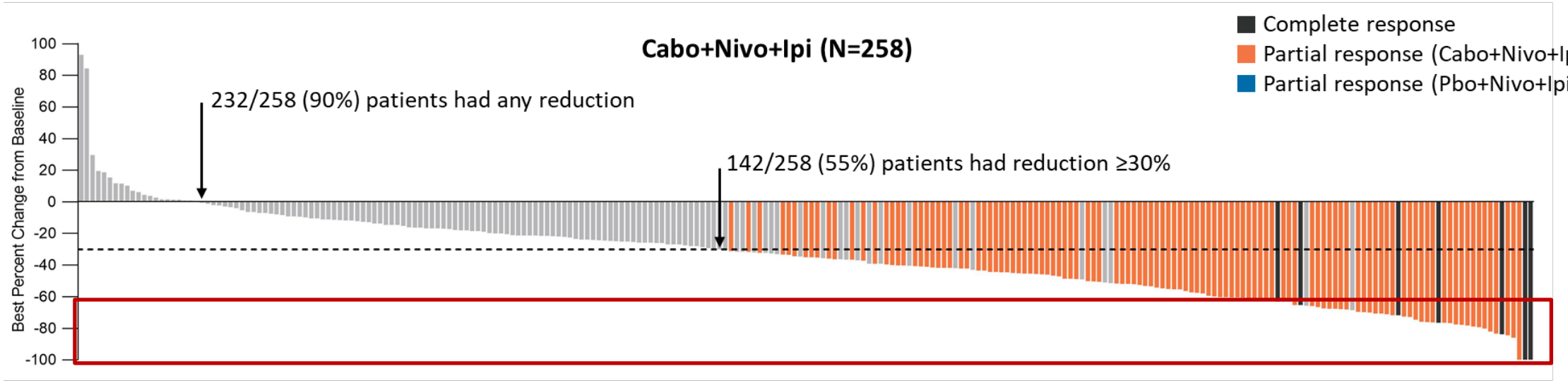
Proportion of patients receiving 4 doses of ipilimumab

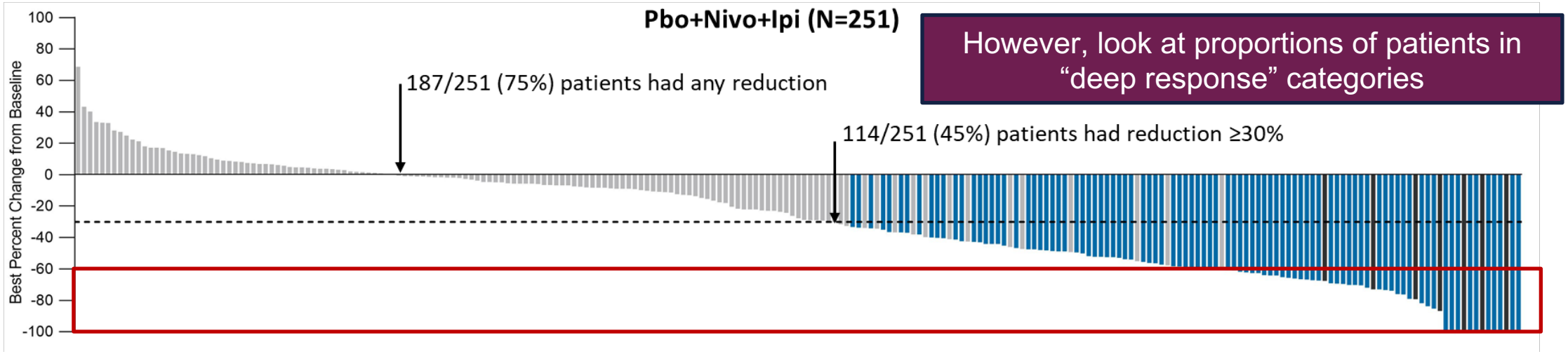


Proportion of patients receiving >40 mg of prednisone or equivalent



More shrinkage with triplet but less deep responses





However, look at proportions of patients in "deep response" categories

Sumanta K. Pal, MD, FASCO

Thoughts

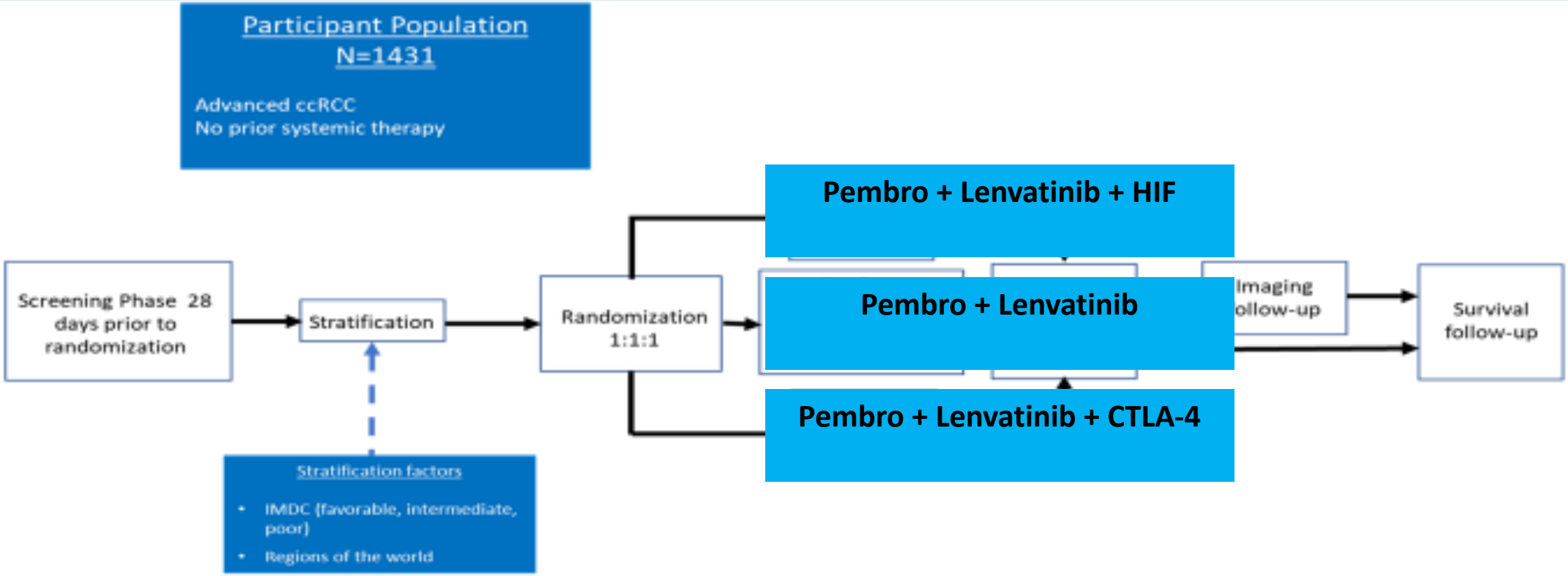
COSMIC-313 is a trial of firsts in RCC
- First results of a phase 3 clinical trial using a contemporary control arm (nivolumab/ipilimumab)
- First results of a phase 3 clinical trial comparing triplet therapy to doublet therapy
- First results of a phase 3 clinical trial (with the above) meeting its primary endpoint

Questions remain …
- What will analysis of overall survival show?
- Does the toxicity of with triplet therapy challenge delivery of individual agents (e.g., ipilimumab)?

Looking into the future …
- Can a risk-adapted approach allow for optimal delivery of “triplet therapy”?
- Can we invest in biomarker studies for contemporary regimens & pivot rapidly to prospective assessment?
- Can we shift towards adding agents with novel MOA that may not yield overlapping toxicities?

Sumanta K. Pal, MD, FASCO

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

Front-line IO-based Trials in mRCC: 1 vs 2 vs 3 drugs in IMDC Int/Poor

	1 (IO)	2 (IO/IO)	2 (IO/TKI)			3 (IO/IO/TKI)
Comparator	None	Sunitinib				Ipi/Nivo
	KEYNOTE-427 (Pembro)[1]	**CheckMate 214 (Ipi/Nivo)[2]**	**KEYNOTE-426 (Axi/Pembro)[3]**	**CheckMate 9ER (Cabo/Nivo)[4]**	**CLEAR (Len/Pembro)[5]**	**COSMIC313 (I/N/C vs I/N)[6]**
OS HR	**NA**	**0.68**	**0.64**	**I: 0.74 P: 0.44**	**I: 0.72 P: 0.39**	NR
PFS HR	**NR**	**0.73**	**0.67**	**I: 0.59 P: 0.36**	**I: 0.41 P: 0.30**	0.73
mPFS, mos.	**6.9**	**11.6**	**13.8**	**I: 17.5 P: 9.9**	**22.1**	Not reached
Landmark PFS	**24%** at 2 years	**31%** at 5 years	NR	**I: 55% P: 44%** at 15 months	**45%** (est.) at 2 years	**57%** at 1 year
ORR	**40%**	**42%**	**57%**	**51%**	**72%**	**43%**
CR	**4%**	**11%**	**9%**	**9%**	**14%**	**3%**
Primary PD	**37%**	**19%**		**7%**	**6%**	**8%**
Med f/u, mos	**35.9**	**67.7**	**42.8**	**32.9**	**33.7**	**20.2**

1. McDermott et al. JCO 2021 2. Motzer et al. ESMO 2021/Cancer 2022 3. Rini et al. ASCO 2021 4. Motzer et al. Lancet Oncology 2022/Apollo et al ASCO 2022 5. Motzer et al. NEJM 2021/Choueiri et al. KCRS 2021/Grunwald et al. ASCO 2021/Porta et al. ESMO 2022. 6. Choueiri et al. ESMO 2022

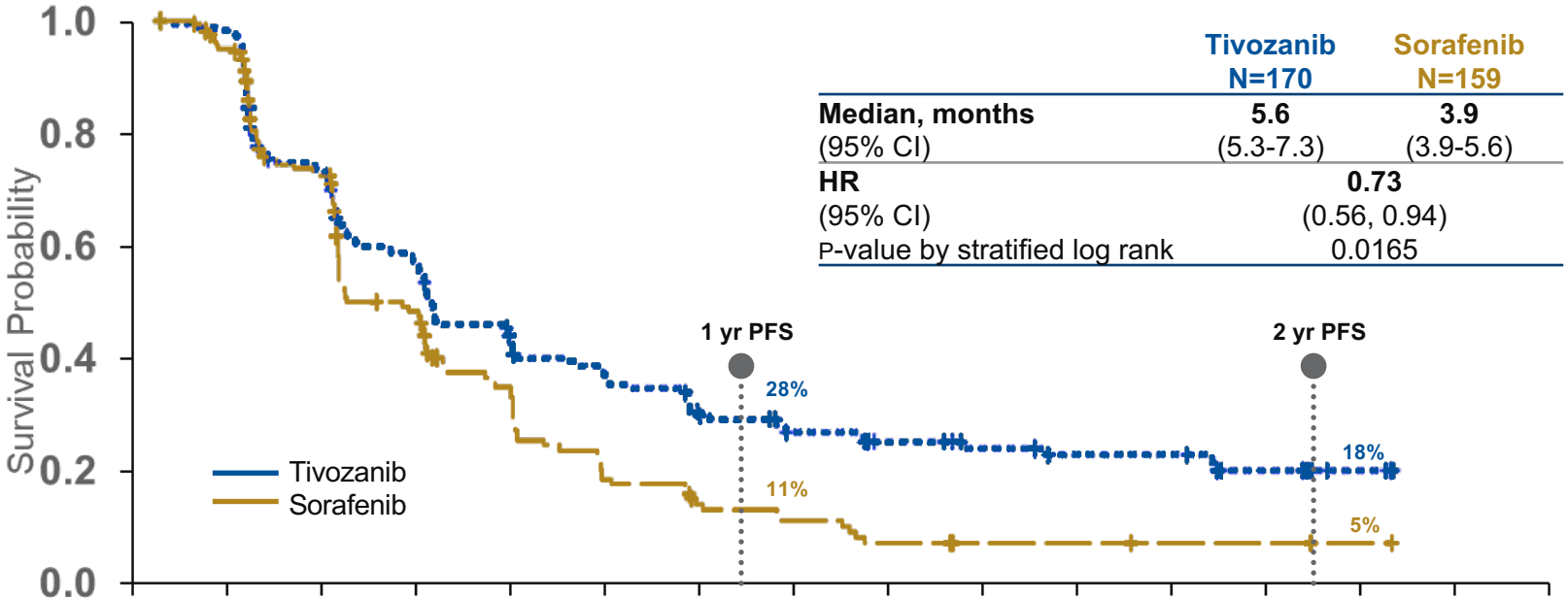
2nd-Line Agents: Post VEGF-TKI

	Axitinib [1,2]	Nivolumab [3]	Cabozantinib [4]	Lenvatinib/Eve (RP2) [5,6]
Patient Population	2nd Line	TKI-refractory (72% 1 prior)	TKI-refractory (71% 1 prior)	TKI-refractory (100% 1 prior)
MSKCC risk: good/int/poor	28/37/33	35/49/16	45/42/12	24/37/39
Comparator	Sorafenib	Everolimus	Everolimus	Everolimus
ORR, % PD, %	19% 22%	22% 35%	17% 12%	35% 4%
PFS, months	4.8	4.6	7.4	12.8
OS, months	20.1	25.0	21.4	25.5
Dose reductions	31% (37% Increase)	n/a	62%	71%
D/C due to AE	4%	8%	12%	24%
Toxicity	Grade 3: 50% Grade 4: 6%	Grade 3 or 4: 19%	Grade 3: 63%* Grade 4: 8%	Grade 3: 57% Grade 4: 14%

* All AEs regardless of attribution to the drugs

[1] Motzer, et al. *Lancet Oncol*. 2013;14:552. [2] Rini, et al. *Lancet* 2011;378:19312. [3] Motzer, et al. *N Engl J Med*. 2015;373:1803. [4] Choueiri, et al. *Lancet Oncol*. 2016.
[5] Motzer, et al. *Lancet* 2015;16:1473. [6] Motzer, et al. *Lancet* 2016;17:E4-45.

TIVO-3: Primary Endpoint of PFS



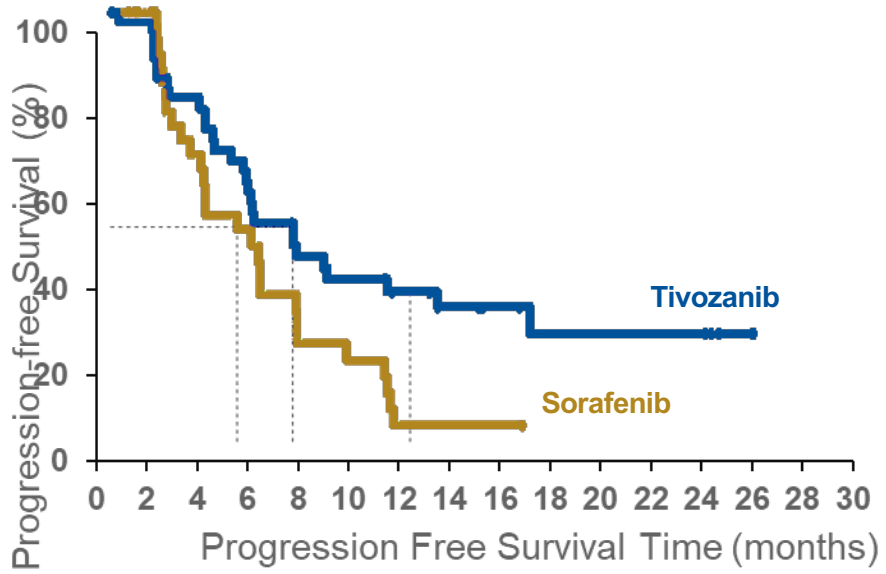
	Tivozanib N=170	Sorafenib N=159
Median, months	**5.6**	**3.9**
(95% CI)	(5.3-7.3)	(3.9-5.6)
HR	**0.73**	
(95% CI)	(0.56, 0.94)	
P-value by stratified log rank	0.0165	

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

TIVO-3: PFS & ORR in Prior IO Subgroup



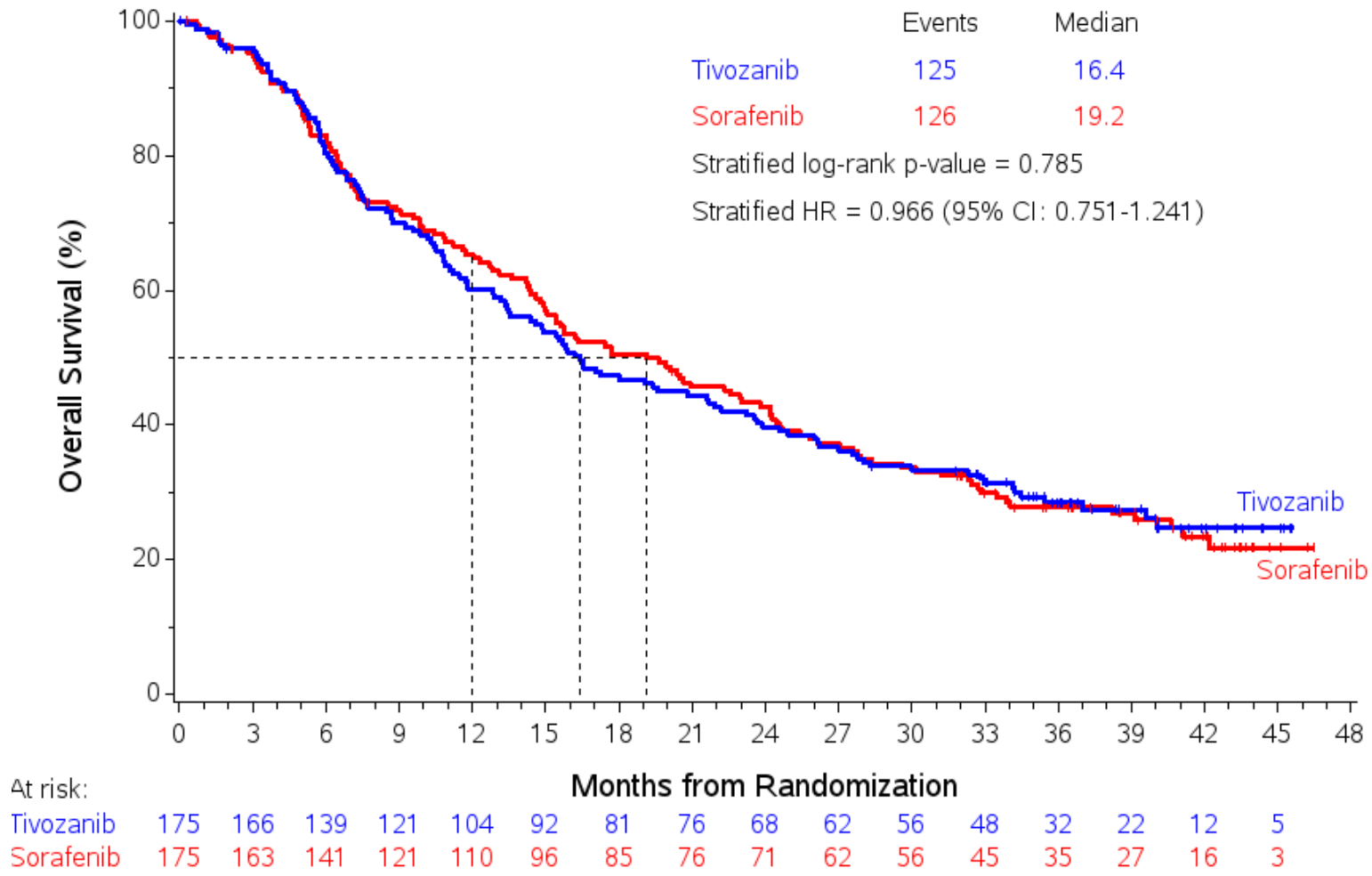
Prior Checkpoint Inhibitor (CPI) + VEGFR TKI

	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%

Porta et al. ASCO 2019

Final analyses, Oct 4, 2018

TIVO-3: Final OS



Lenvatinib + Pembrolizumab After Progression on Prior IO Therapy

Phase II KEYNOTE-146/Study 111

(N = 104)
- Metastatic clear-cell RCC with PD after anti–PD-1/ PD-L1 therapy
- ≥1 previous lines of therapy

→

Lenvatinib 20 mg QD PO

Pembrolizumab 200 mg Q3W IV

Primary Endpoint:
ORR at 24 wks

Key Secondary Endpoints:
ORR, PFS, DoR, Safety and tolerability

Baseline Characteristic	Patients (N = 104)
1/≥ 2 prior anticancer regimens, %	39/62
Prior ICI regimen, %[a]	
Anti–PD-L1/anti–PD-1 in combination or as monotherapy	100
Anti–PD-L1/anti–PD-1 and anti-VEGF in combination or sequentially	65
Ipilimumab/nivolumab	37
Median duration of prior ICI therapy, mos (IQR)	7 (3-13)

Lenvatinib + Pembrolizumab After Progression On Prior IO Therapy

Phase II KEYNOTE-146/Study 111: Responses by Previous Therapy

Event	Anti–PD-1/PD-L1 (n = 104)	Anti–PD-1/PD-L1 and Anti-VEGF (n = 68)	Nivo + Ipi (n = 38)
ORR, % (95% CI)	**55** (45-65)	59 (46-71)	47 (31-64)
Best objective response, %			
• PR	55	59	47
• SD	36	31	42
• PD	5	6	8
• NE	5	4	3
Median DoR, mos (95% CI)	12 (9-18)	9 (7-17)	NR (7-NR)

Lee. ASCO 2020. Abstr 5008.

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%	4%	15%	12%	20%
CR	3%	0%	0%	3%	0%

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

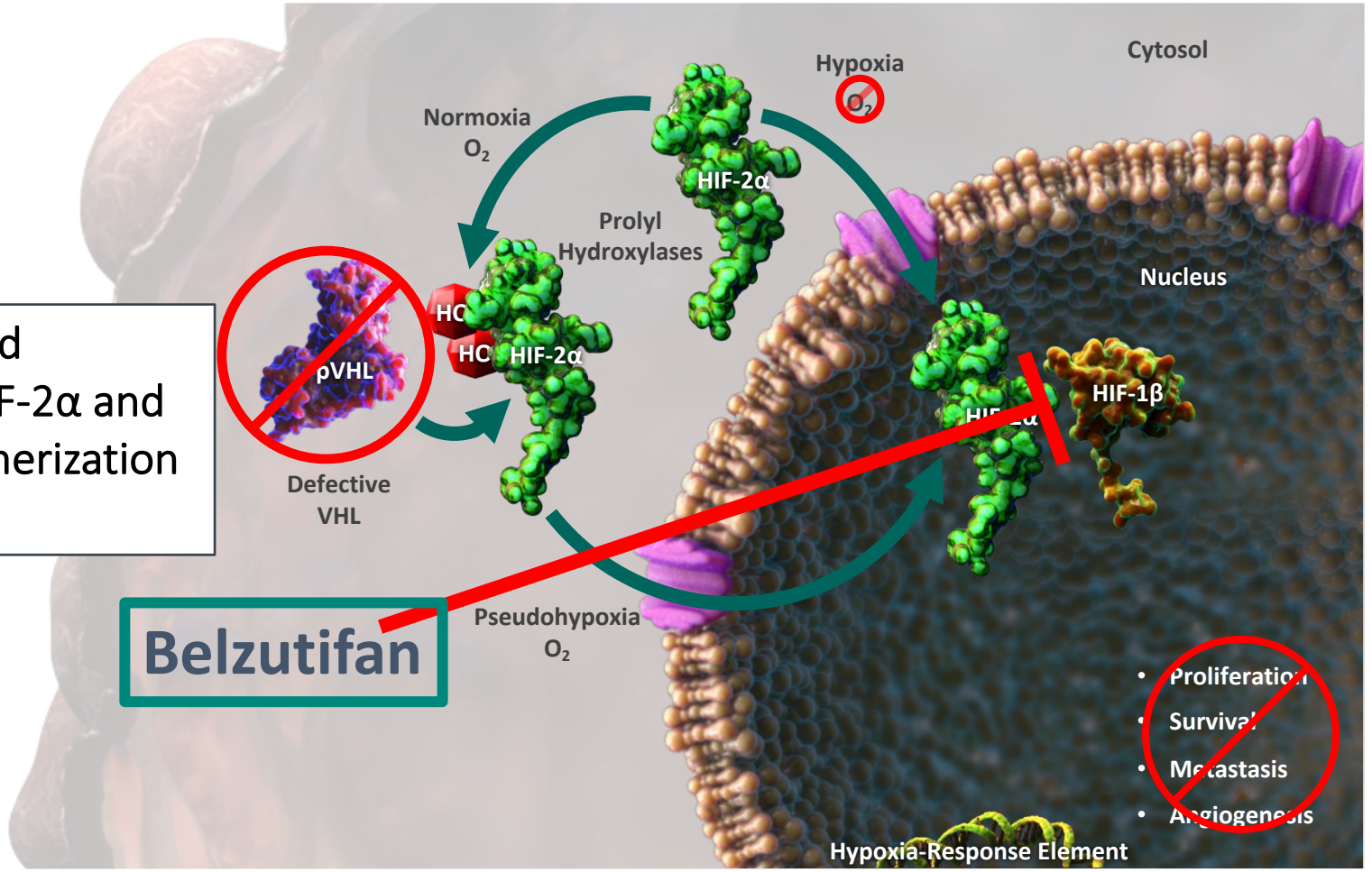
Activity of Batiraxcept (Axl Inhibitor) + Cabozantinib

Efficacy Evaluable	All P1b Patients (N=26)	P1b 15 mg/kg (n=16)	P1b 20 mg/kg (n=10)
Best Response			
Confirmed Partial Response	11 **(42%)**	8 (50%)	3 (30%)
Confirmed Stable Disease	11 (42%)	6 (38%)	5 (50%)
Progressive Disease [2]	4 (15%)	2 (12%)	2 (20%)

	Best Response		
	All P1b Patients (n=25) [1]	**P1b 15 mg/kg (n=16)**	**P1b 20 mg/kg (n=9) [1]**
PR for Patients with low sAXL/GAS6	0/5 **(0%)**	0/4 (0%)	0/1 (0%)
Confirmed PR for Patients with high sAXL/GAS6	11/20 **(55%)**	8/12 (67%) [2]	3/8 (38%)

Belzutifan: HIF-2α Inhibitor

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



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)

ata cutoff: June 1, 2020.

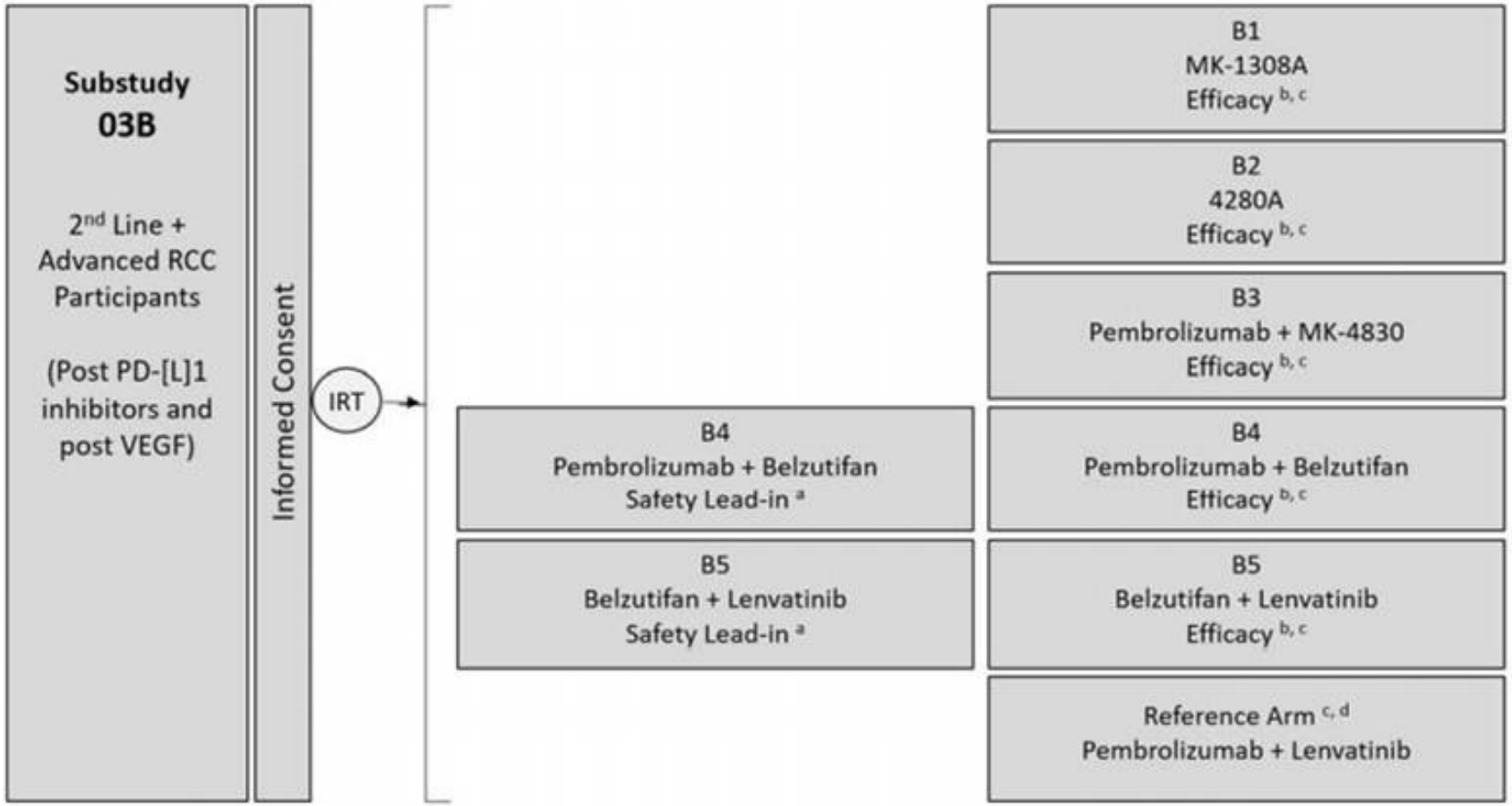
Ongoing Phase III Trials in the Post-IO Setting

Title	Inclusion	Treatment Arms
MK-6482-005: Phase III Trial of Belzutifan vs Everolimus in Advanced RCC After PD-1/PD-L1 and TKI Therapy (n = 736)[1]	▪ Clear-cell RCC ▪ Prior therapy with PD-1/PD-L1 inhibitor and VEGF TKI, as monotherapy or in combination ▪ ≤3 prior therapies	Belzutifan vs Everolimus

1. NCT04195750. 2. NCT04338269. 3. NCT04987203.

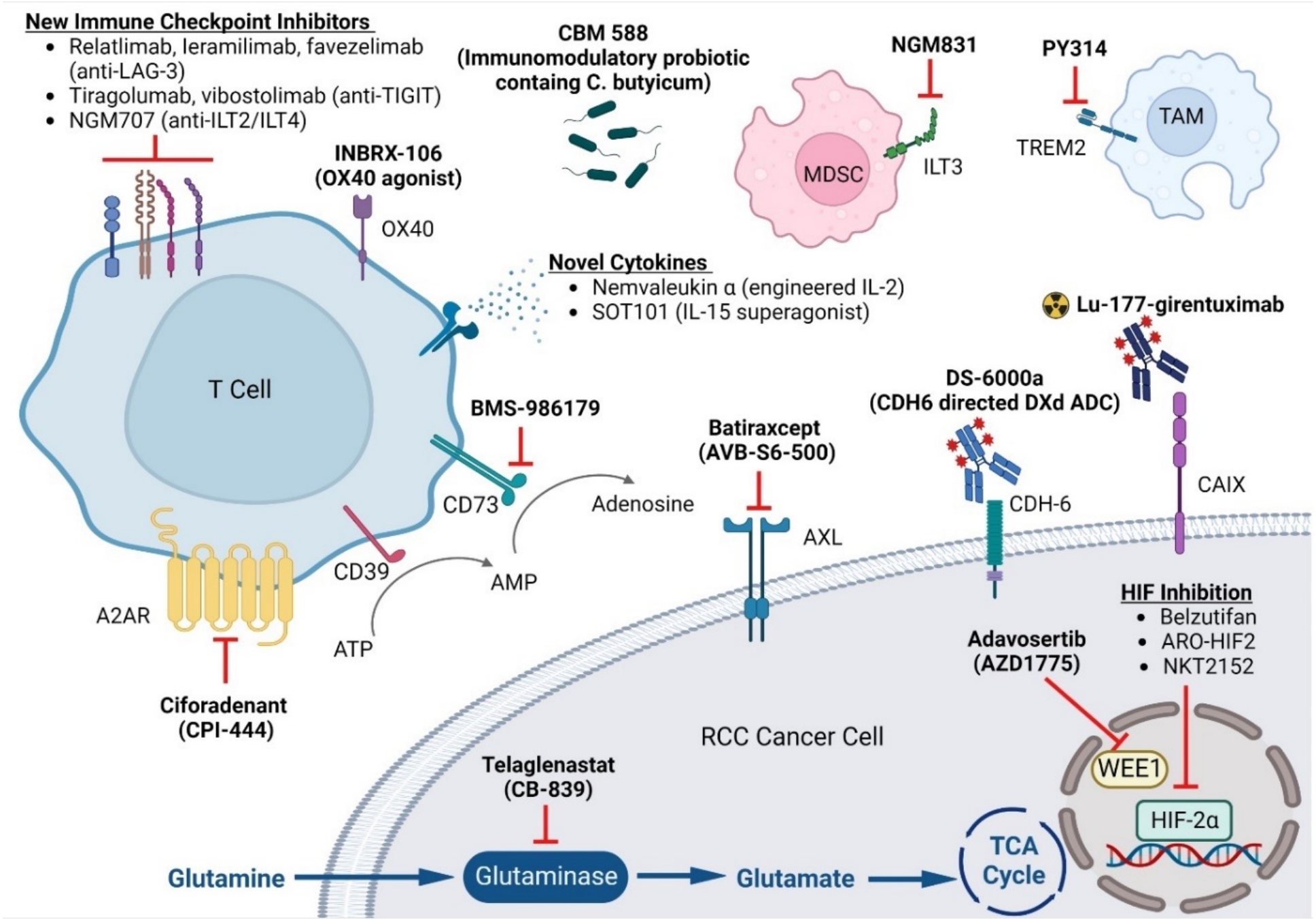
Umbrella trial in post-IO setting

Figure 1 Study Design



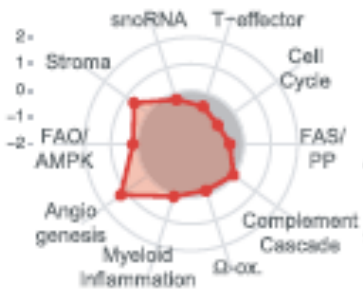
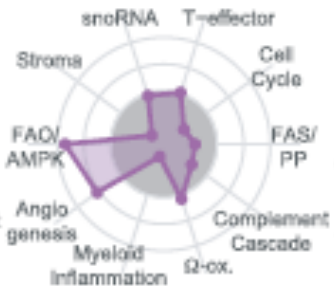
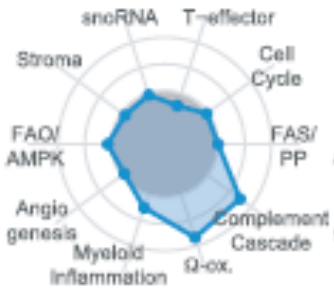
[a] Safety Lead-in: N ≥ 10 per arm. Exact N will depend on number of doses assessed. Lead-in participants are not randomized but are allocated by IRT.
[b] Efficacy Phase: N = 50 per experimental arm.
[c] Randomization Ratio: 1:1 randomization ratio. For 1 participant enrolled in efficacy arm(s), 1 is enrolled *concurrently* into reference arm.
[d] Reference Arm: N ≥ 50. Exact N will depend on enrollment period for the experimental efficacy arms.

IRT=interactive response technology; PD-[L]1=programmed cell death/ programmed cell death ligand 1; RCC=renal cell carcinoma; VEGF=vascular endothelial growth factor.



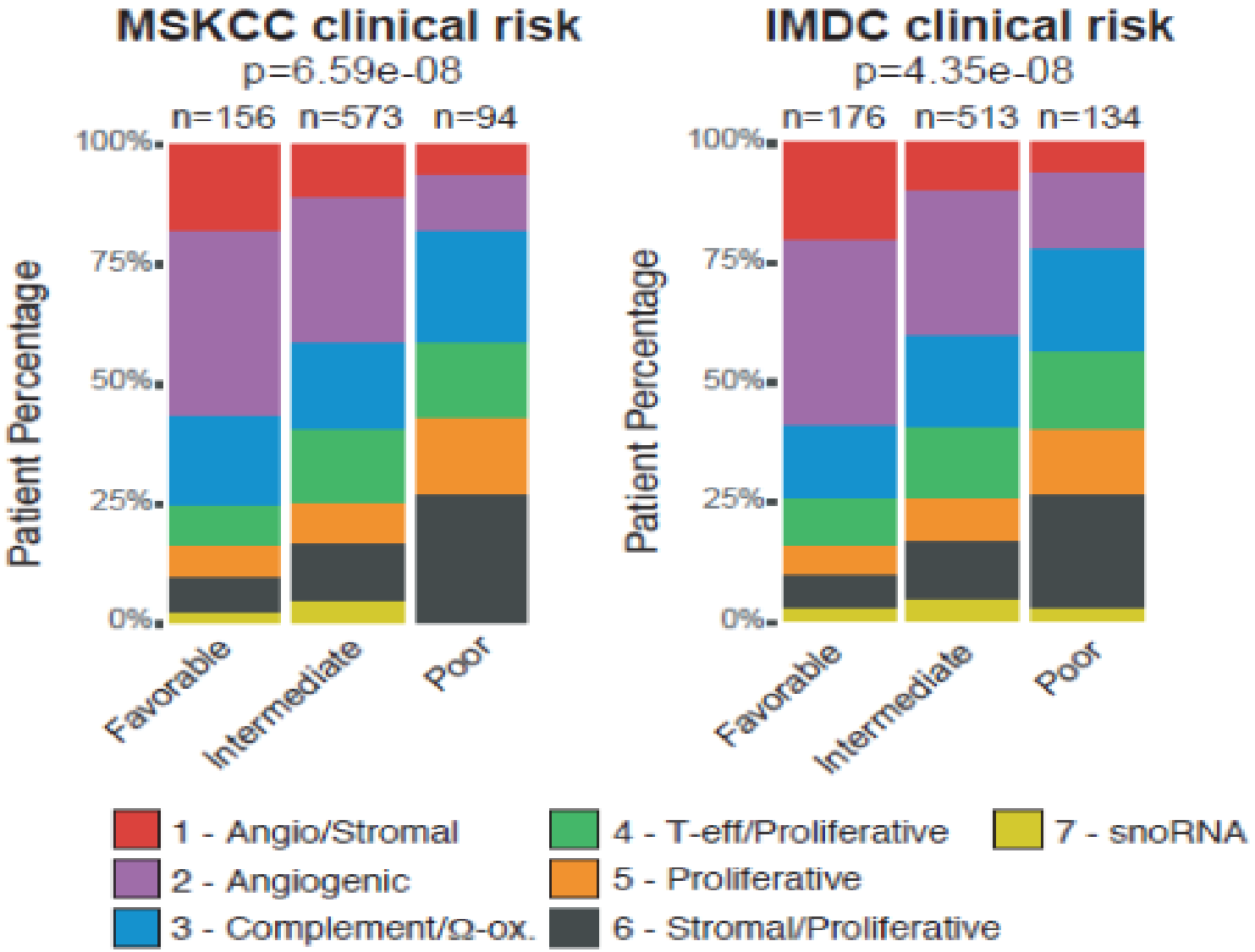
Chen, Rini, and Beckermann; 2022

The biology of 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, Rini et al. *Cancer Cell* 2020

Patient groups defined by clinical characteristics display heterogeneous biology

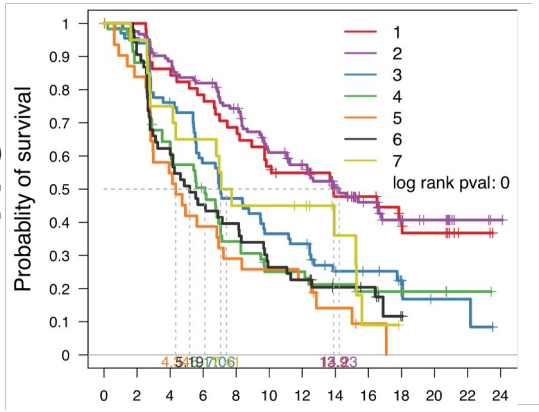


NMF subsets associate with differential prognostic and predictive effect

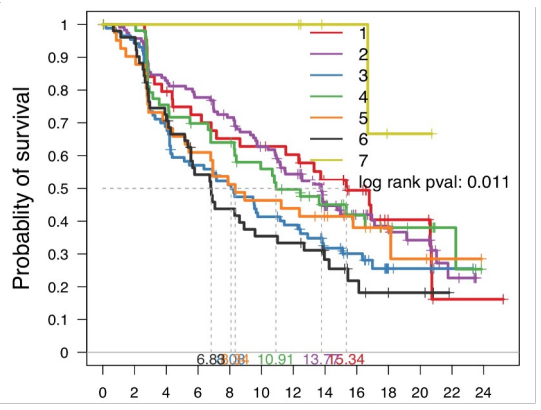
Atezolizumab+Bevacizumab shows improved PFS and a trend of improved OS in T-eff/Proliferative and Proliferative subsets in IMmotion 151

PFS

Sunitinib

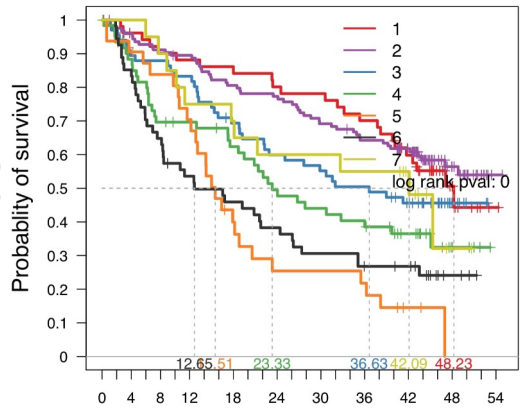


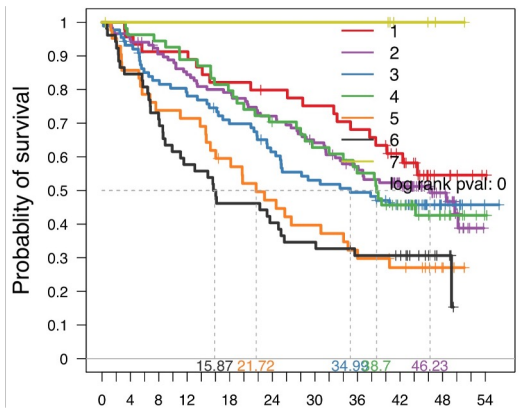
Atezolizumab + Bevacizumab



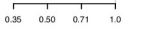
Cluster	HR (95% CI)	Pval	mPFS Atezo+Bev	mPFS Sun
Cluster 1	1.11 (0.65–1.88)	0.708	15.34	13.9
Cluster 2	1.16 (0.82–1.63)	0.397	13.77	14.23
Cluster 3	0.92 (0.63–1.34)	0.666	8.08	7.06
Cluster 4	0.52 (0.33–0.82)	0.005	10.91	6.11
Cluster 5	0.47 (0.27–0.82)	0.007	8.34	4.34
Clusters 4&5	0.52 (0.37–0.74)	<0.001	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





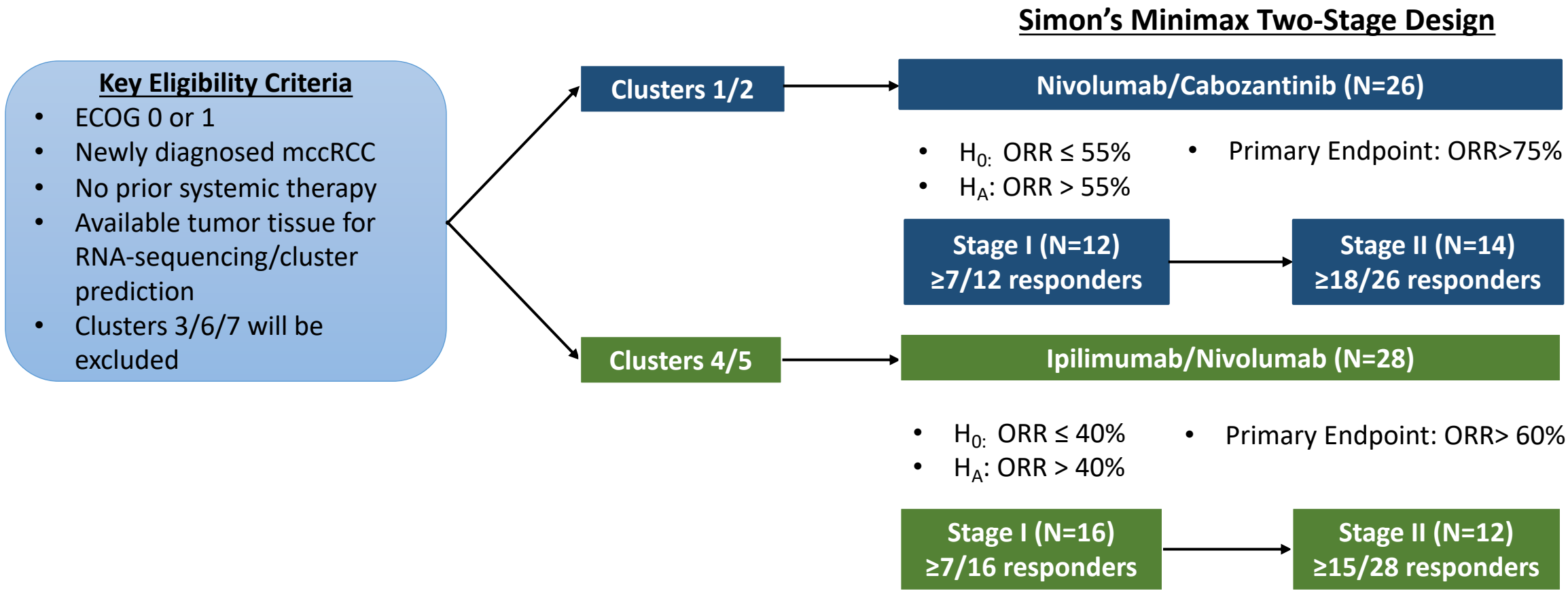
Cluster	HR (95% CI)	Pval	mOS Atezo+Bev	mOS Sun
Cluster 1	0.94 (0.52–1.72)	0.843		48.23
Cluster 2	1.32 (0.91–1.91)	0.148	46.23	
Cluster 3	0.99 (0.64–1.54)	0.979	34.99	36.63
Cluster 4	0.66 (0.41–1.06)	0.088	38.7	23.33
Cluster 5	0.66 (0.39–1.12)	0.122	21.72	15.51
Clusters 4&5	0.69 (0.48–0.98)	0.039	34	19.48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

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



Conclusions (1)

- IO-based doublets are initial standards of care
  - IO and ?TKI monotherapy? in very well-selected pts
  - Duration of TKI/therapy in general is undefined as de-intensification efforts are needed
- We lack clinically useful/validated biomarkers upon which to individualize/optimize therapy
- Triplets are being tested but may be unlikely to be effective in unselected pts if toxicity limits drug delivery

Conclusions (2)

- Multiple options in the refractory RCC space
  - Single-agent VEGF is the (unexciting) SOC for now, with emerging data for novel agents & combinations
- Biomarker-based therapy urgently needed in RCC
  - OPTIC is (hopefully) a small first step

Thank you ☺
Patient & families!

Collaborators, sponsors, institutions, foundations, colleagues, research, admin & clinical staff: TEAMS! ***Dr. Brian Rini*** **@PGrivasMDPhD**