New Developments in Metastatic RCC: A Reassessment for IO/TKI Combos

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Disclosures/ Potential Conflicts

Last 36 Mos

Consultant:

BMS, Merck, Novartis, Genentech/Roche, Pfizer, Exelixis, Aveo, Agenus, SeaGen, AstraZeneca, Calithera, Asher Bio, COTA, Idera, Iovance, Alkermes, GSK

Advisory Boards:

Eisai, Novartis, Pfizer, Genentech/Roche, Merck, BMS, Pyxis Oncology, Werewolf, X4 Pharma, ValoHealth, Surface, Simcha, Takeda, Sanofi, ScholarRock, Elpis, SAB Bio, OncoRena, Sanofi, Pliant Therapeutics, Atreca

Research Support (to institution): BMS, Merck, Pfizer

Stock Options: Werewolf, Pyxis Oncology, Elpis

Other: UpToDate: Melanoma Section Editor

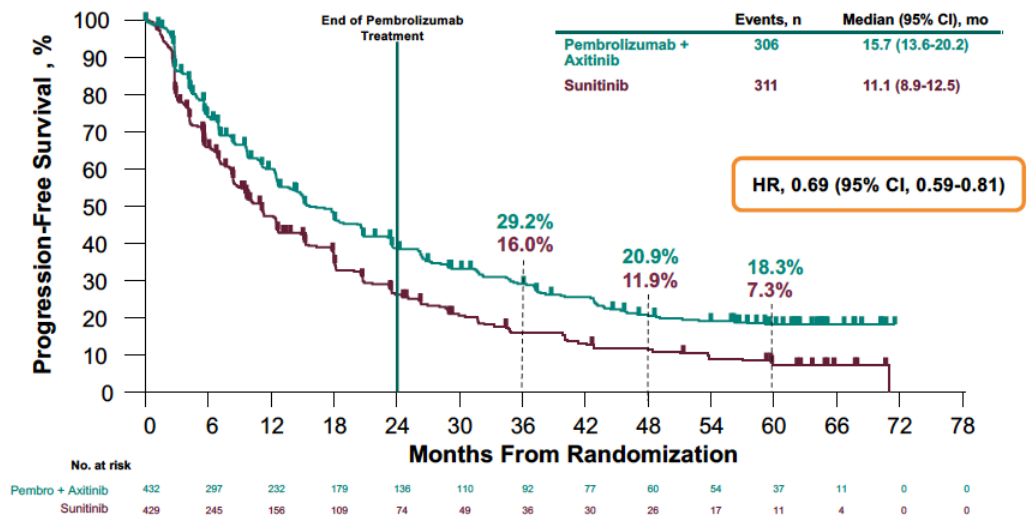
Off Label Usage: Discuss Dab/tram/spartalizumab triplet; fianlimab/cemiplimab results

Presentation Outline

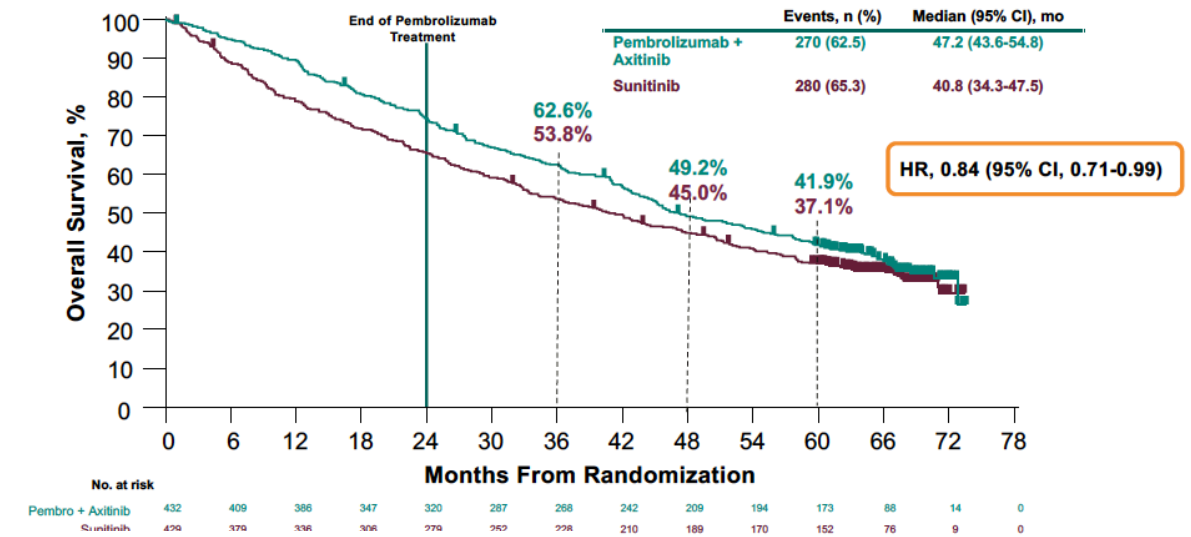
- Anti-PD1 + Anti-VEGF Combos (update)
  - Updated Data (KN-426, CLEAR, COSMIC 313)
- Advantages of Pure IO regimens
  - Duration of Response
  - Stopping therapy/TFS
  - Potential in “good” risk patients
- Second line IO/TKI
- Commentary/Next steps
  - First line Algorithm
  - Biomarkers
  - New Trial

KN 426: 5-year Data

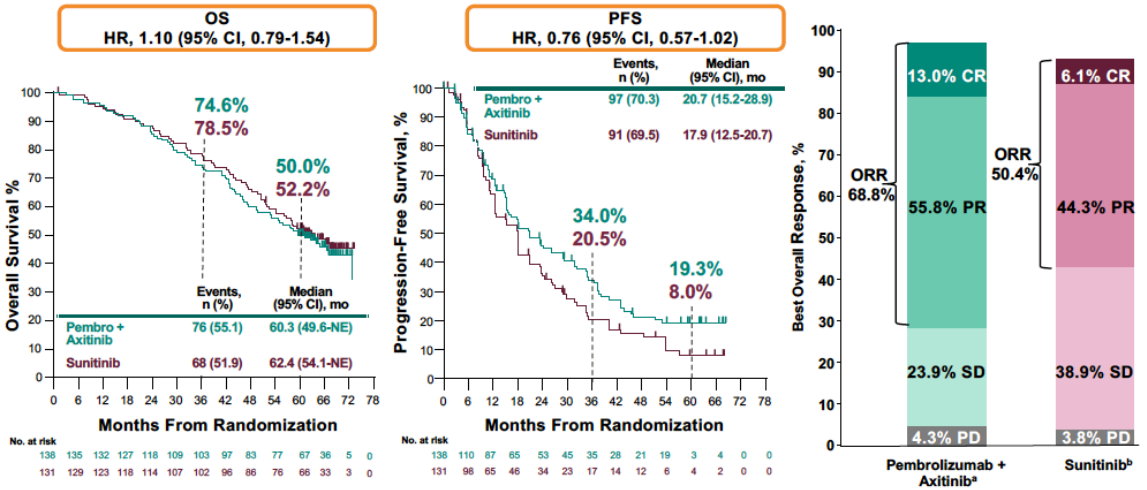
Progression-Free Survival in the ITT Population



Overall Survival in the ITT Population



IMDC Favorable Risk: OS, PFS, ORR

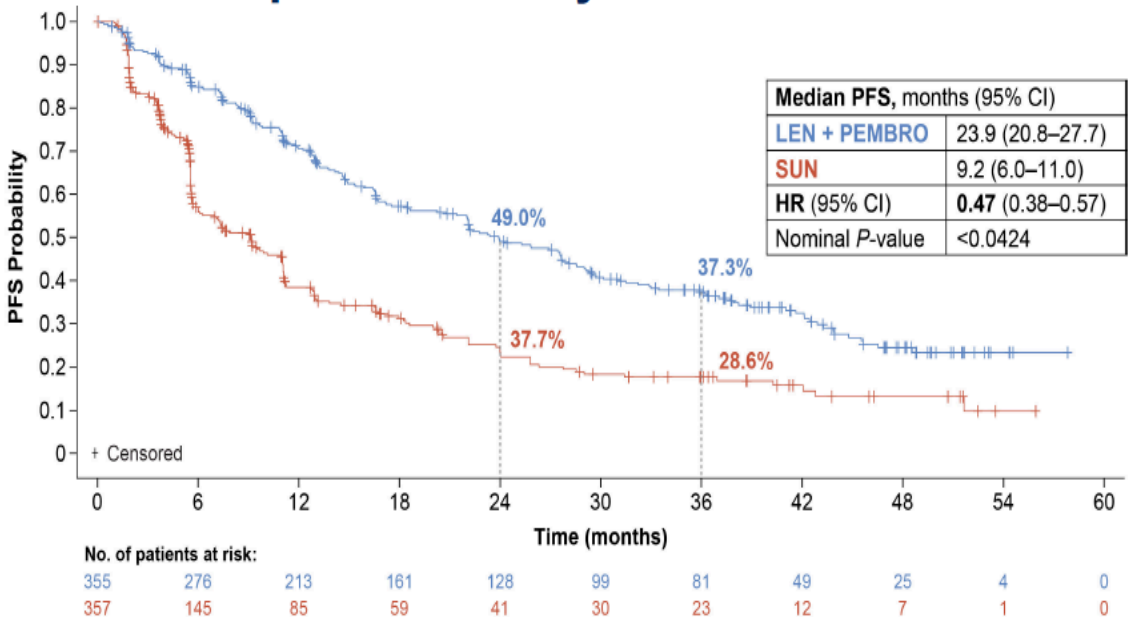


[a]Includes 0.7% NE and 2.2% NA. [b]Includes 1.5% NE and 5.3% NA. Data cutoff: January 23, 2023.

Rini et al ASCO 2023

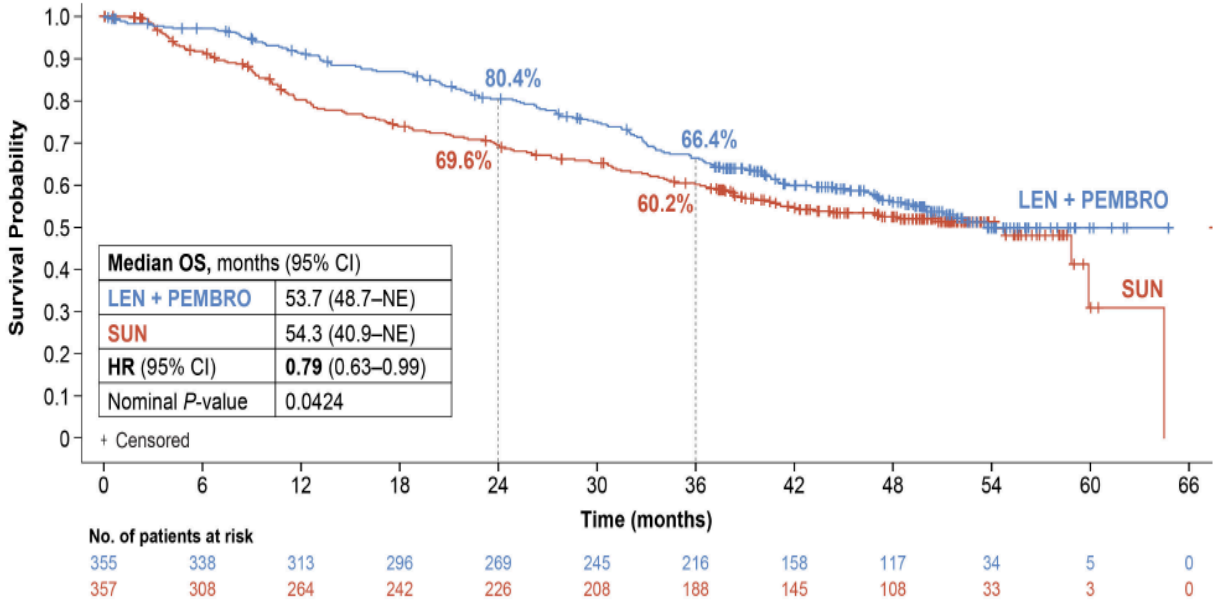
CLEAR Trial: 4-yr Data

Continued PFS benefit of LEN+PEMBRO vs SUN with follow-up extended by over 23 months



Median PFS, months (95% CI)	
LEN + PEMBRO	23.9 (20.8–27.7)
SUN	9.2 (6.0–11.0)
HR (95% CI)	**0.47** (0.38–0.57)
Nominal *P*-value	<0.0424

Final OS analysis (with median follow-up of 4 years)



Median OS, months (95% CI)	
LEN + PEMBRO	53.7 (48.7–NE)
SUN	54.3 (40.9–NE)
HR (95% CI)	**0.79** (0.63–0.99)
Nominal *P*-value	0.0424

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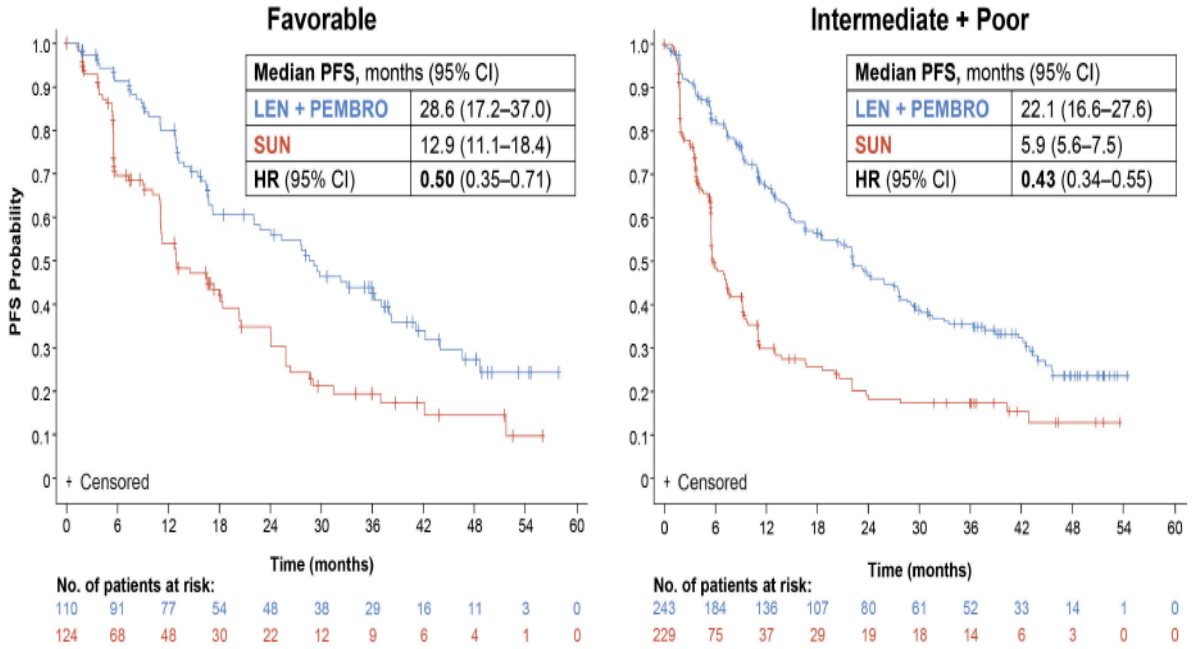
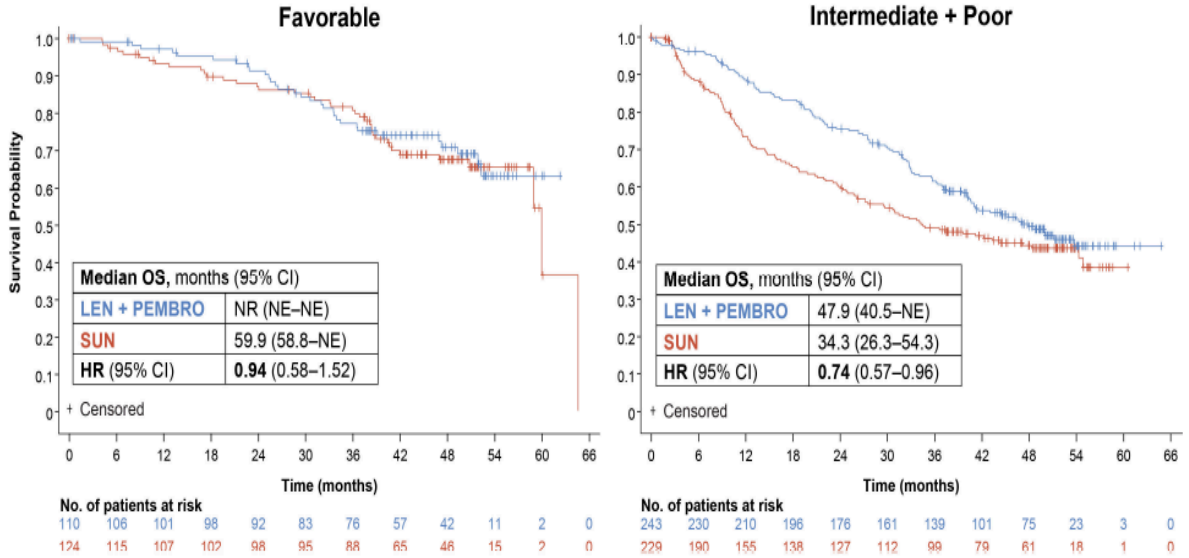
CLEAR Trial: 4-yr Data

PFS analyses in IMDC risk subgroups



Final OS analyses in IMDC risk subgroups (with median follow-up of 4 years)



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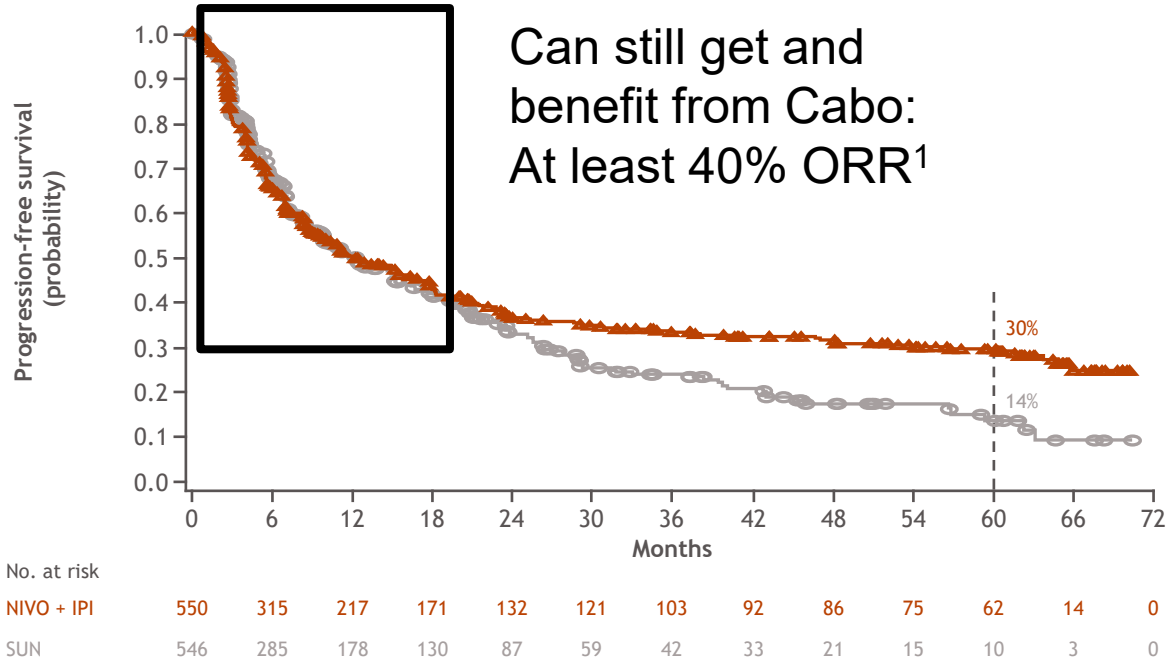
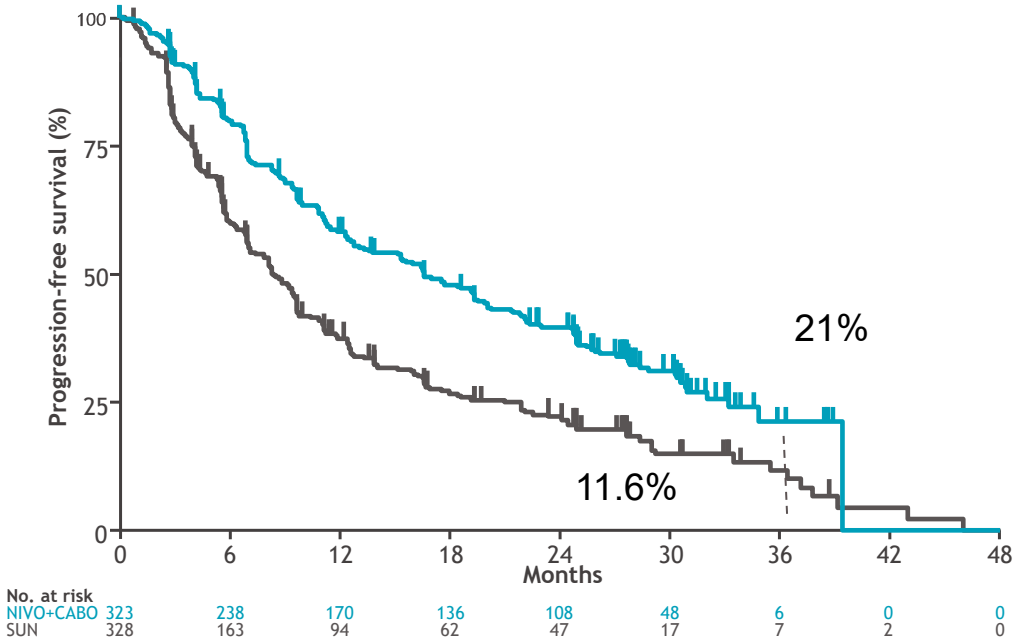
IO/IO vs IO/TKI: PFS in the ITT Population

CM-214: Nivo/ipi vs Sunitinib



Motzer Cancer 2021

CM9ER Cabo/Nivo vs Sunitinib



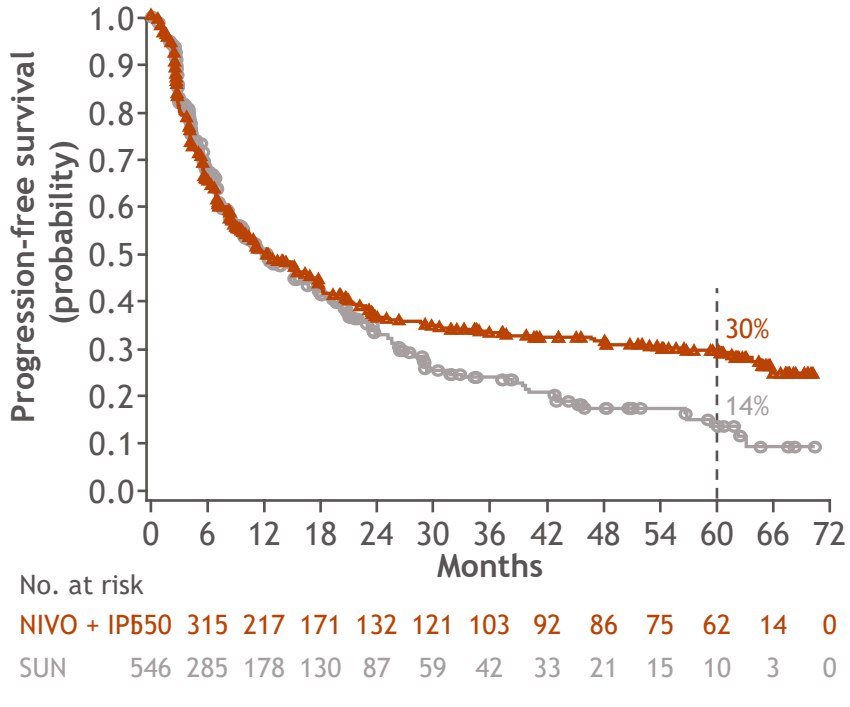
Borotto ASCO GU 2023

[1]Albiges Cabopoint ASCO GU23

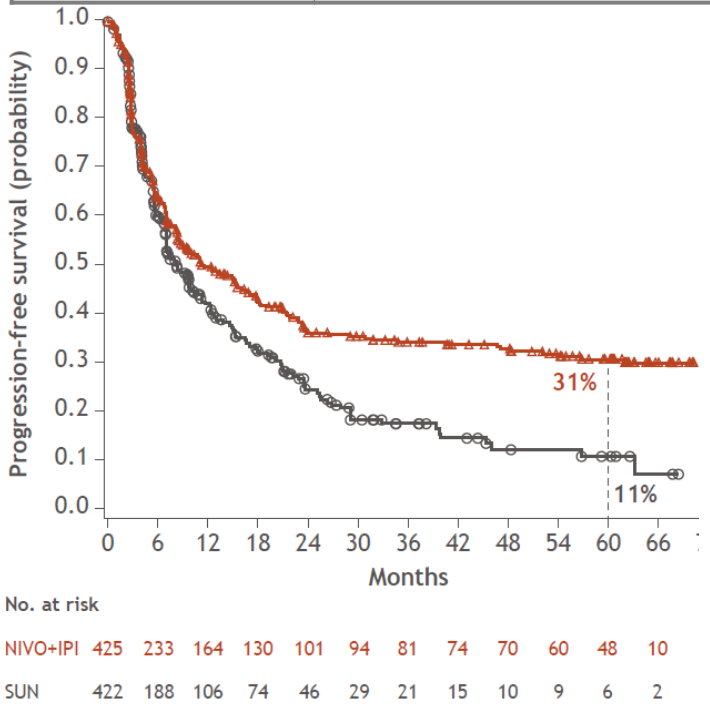
CM 214 minimum follow-up: 60.0 months

PFS in ITT Population and Across IMDC Risk Groups

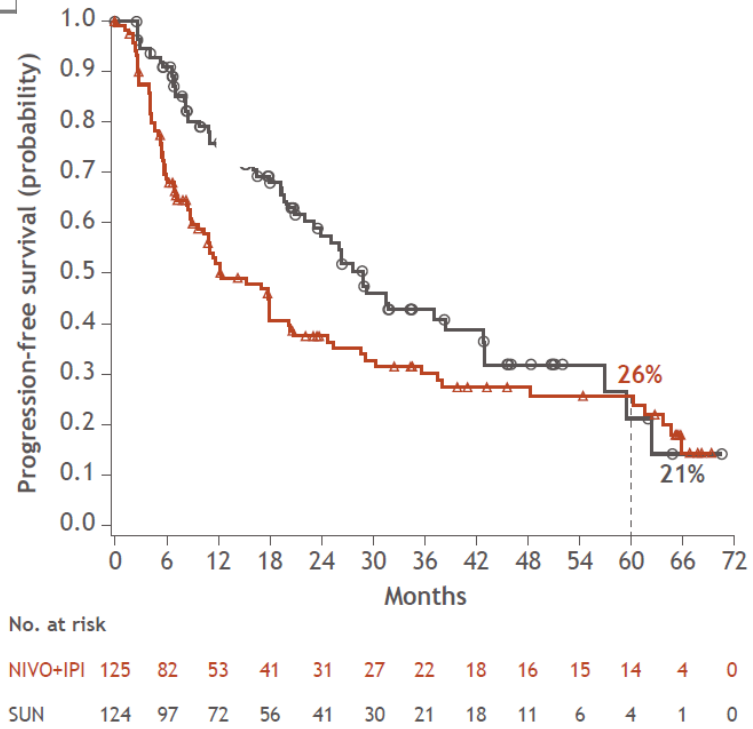
PFS in ITT	NIVO + IPI n=550	SUN n=546
mPFS (95% CI), mos	12.3 (9.7–16.5)	12.3 (9.8–15.2)
HR (95% CI)	0.86 (0.73–1.01), *P*=0.0628	



PFS in intermediate/poor risk	NIVO + IPI n=425	SUN n=422
mPFS (95% CI), mos	11.6 (8.4–16.5)	8.3 (7.0–10.4)
HR (95% CI)	0.73 (0.61–0.87), *P*=0.0004	

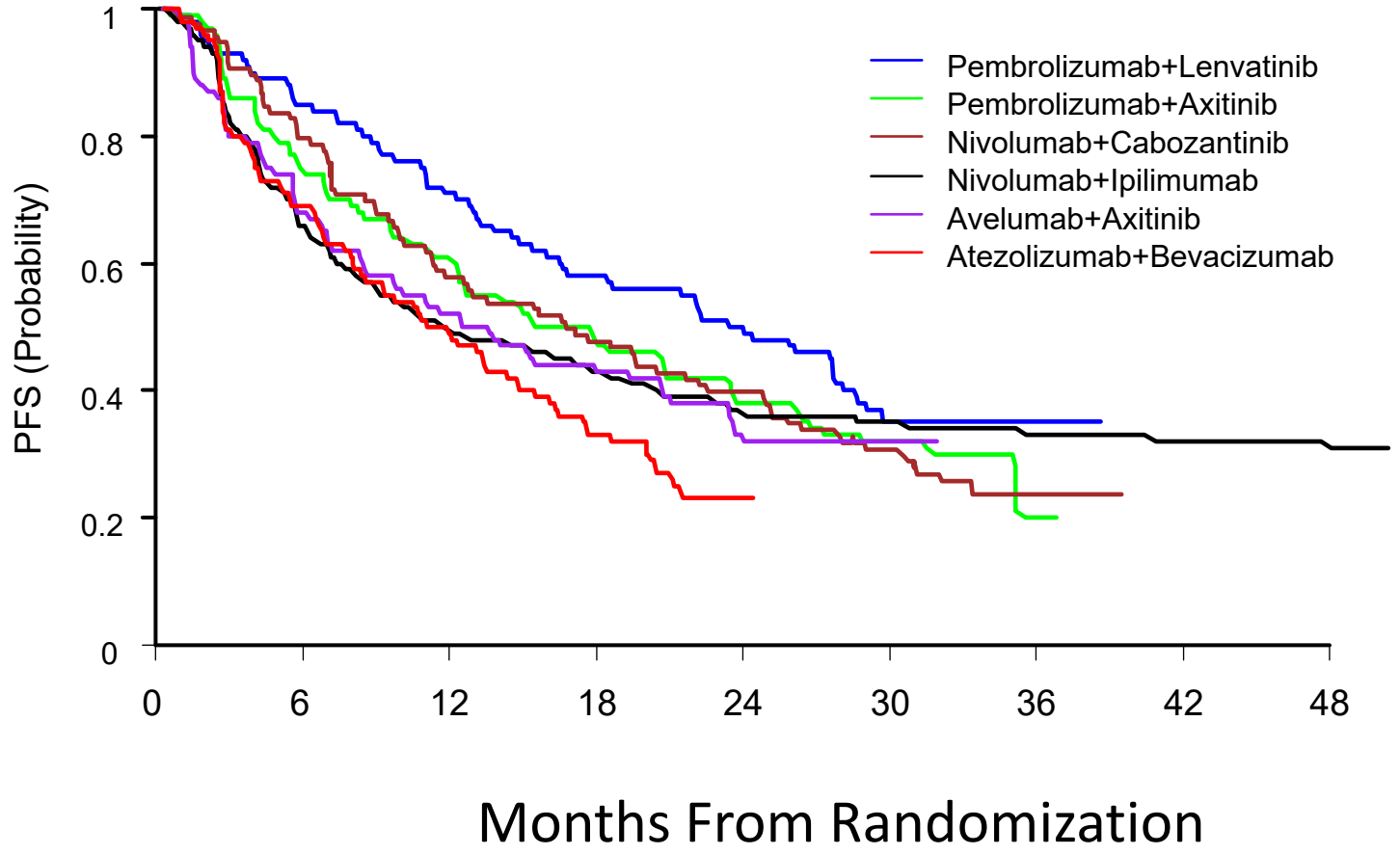


PFS in favorable risk	NIVO + IPI n=125	SUN n=124
mPFS (95% CI), mos	12.4 (9.7–18.0)	28.9 (22.1–38.4)
HR (95% CI)	1.60 (1.13–2.26), *P*=0.0073	



Motzer R J, et al. Cancer 2021.

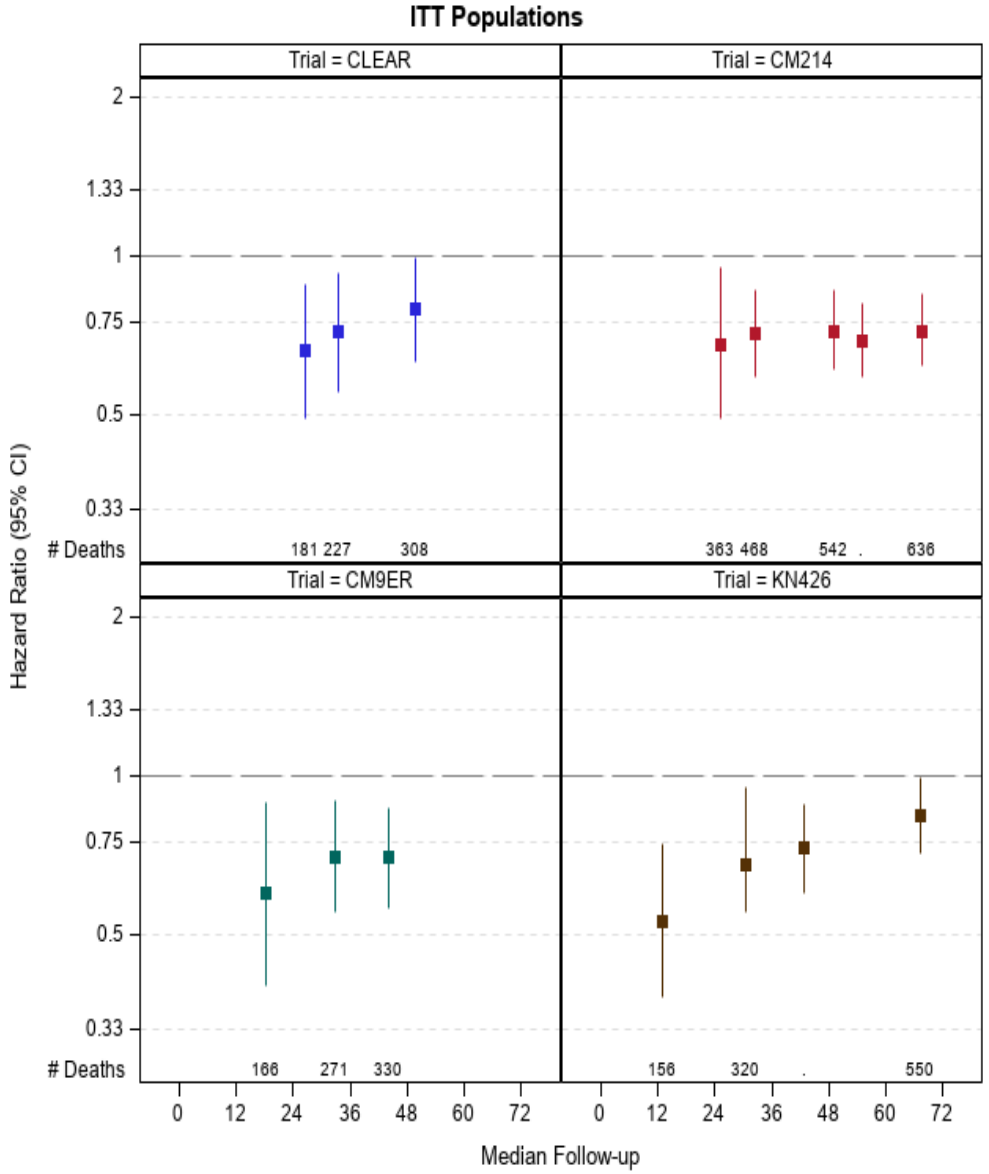
1L mRCC PFS: Phase III Data

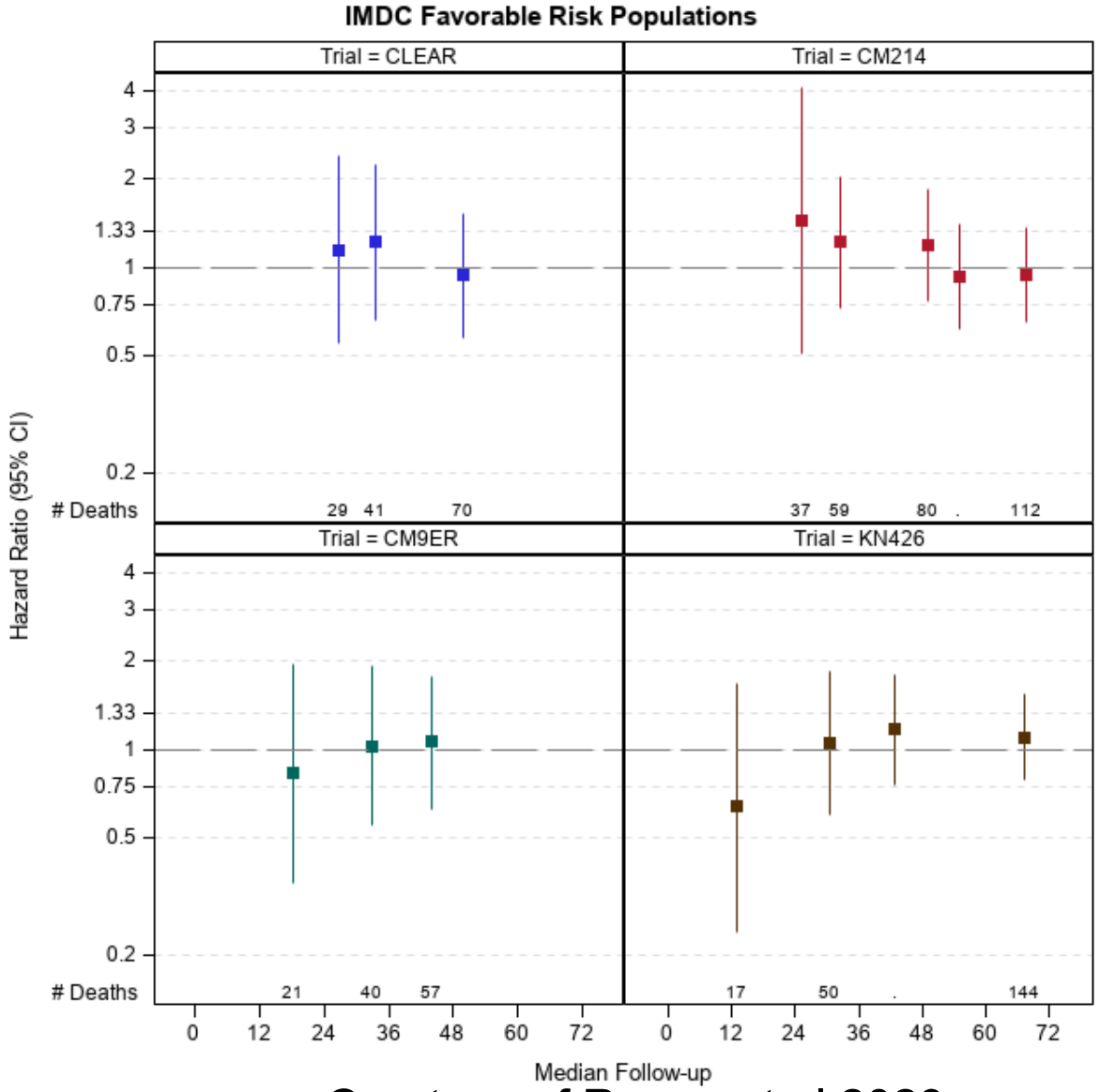


Still TKI Naive

W. Xie
R.M. Saliby
T.K. Choueiri

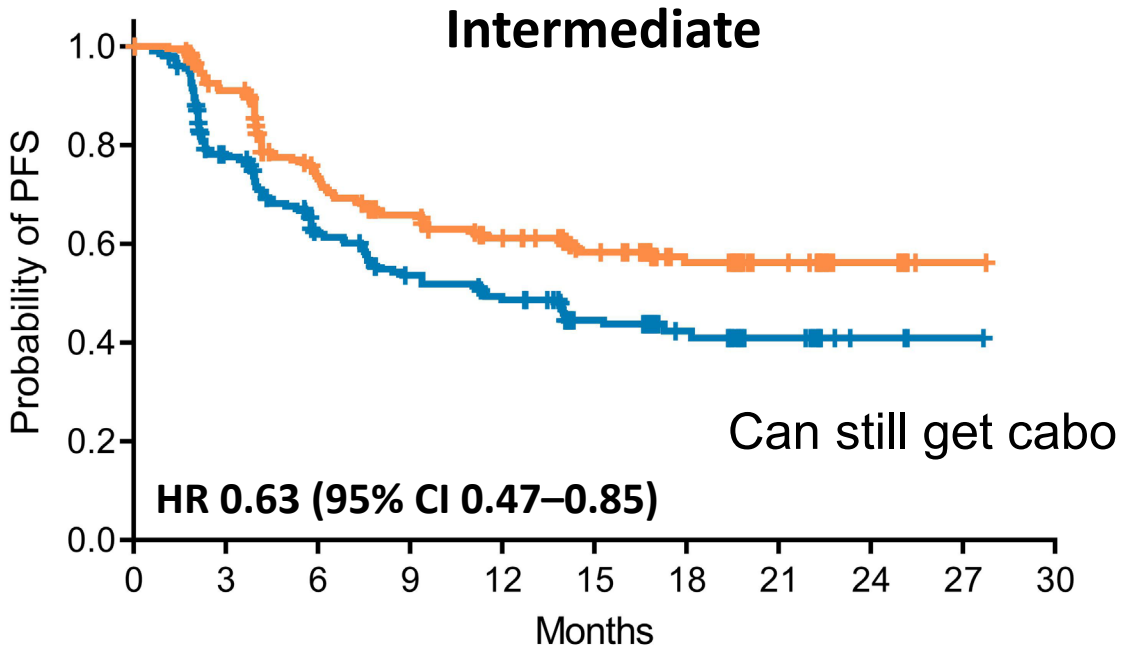
Comparison of First line Trial OS HRs Overtime

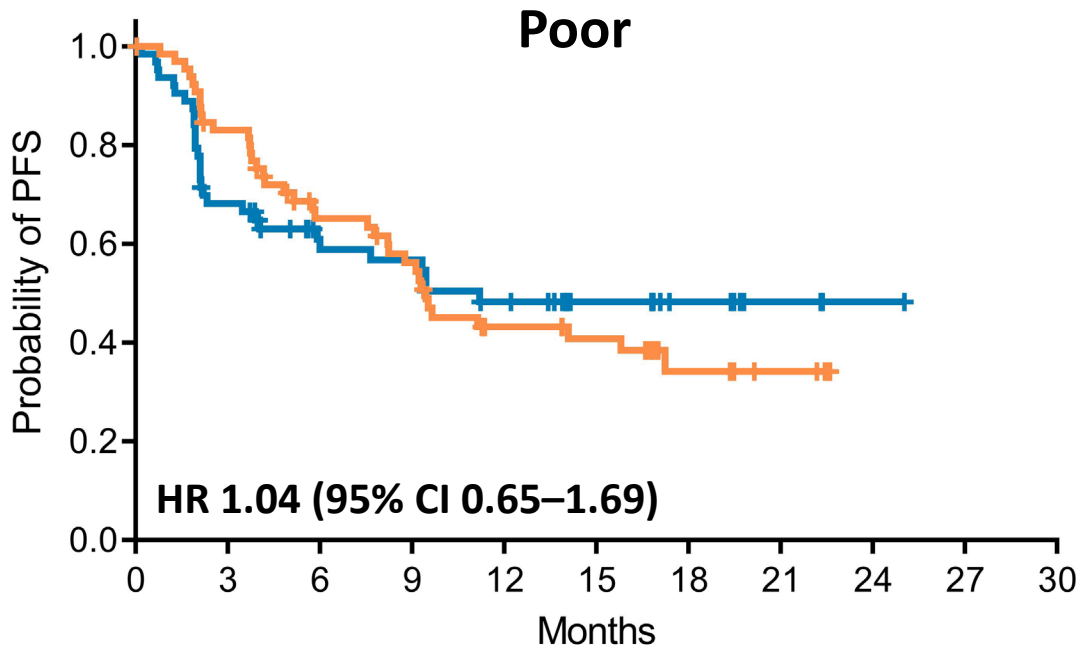




Courtesy of Regan et al 2023

COSMIC 313 PFS and ORR by IMDC Risk Group





	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)

ORR: 45% (95% CI, 38.1–52.0) for Cabo+Nivo+Ipi vs
35% (95% CI, 28.6–42.0) for Pbo+Nivo+Ipi

	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)

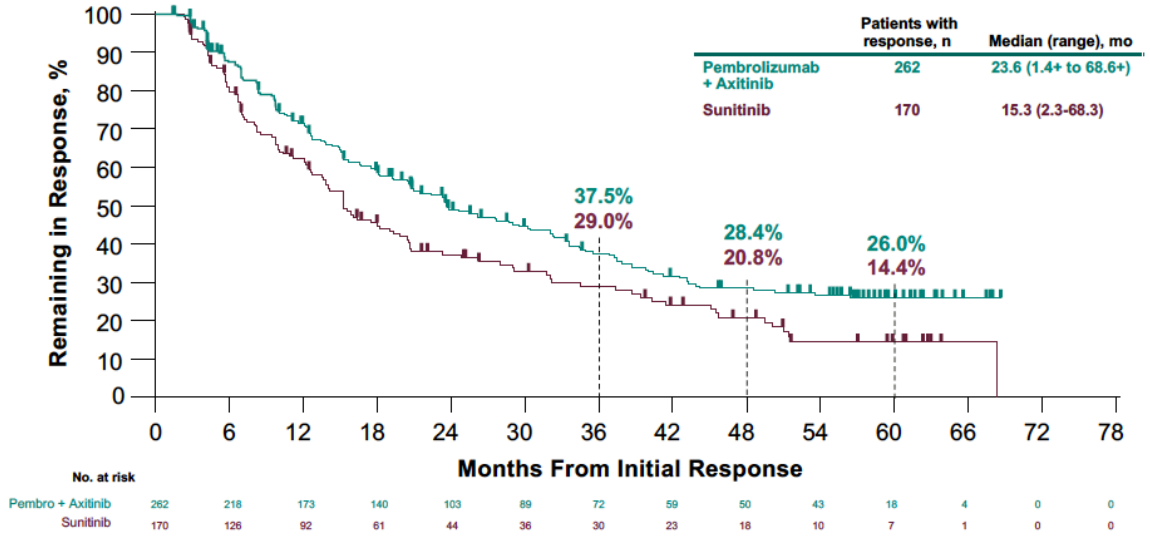
ORR: 37% (95% CI, 25.8–50.0) for Cabo+Nivo+Ipi vs
38% (95% CI, 26.2–50.7) for Pbo+Nivo+Ipi

Date of the 249th PFS event: Aug 23, 2021
Data cut-off for ORR: Jan 31, 2022

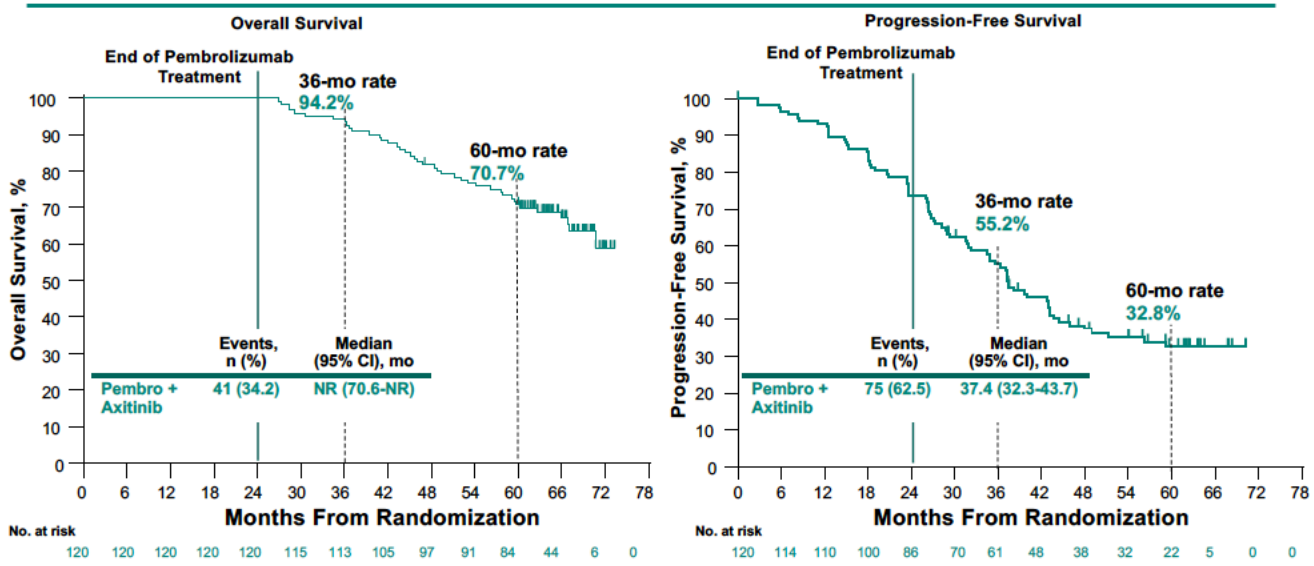
PFS and ORR per RECIST v1.1 by BIRC. IMDC risk group is per IxRS.

KN 426: 5-year DOR Data

Duration of Response in the ITT Population



Patients Who Completed 35 Cycles of Pembrolizumab: PFS and OS



Rini et al ASCO 2023

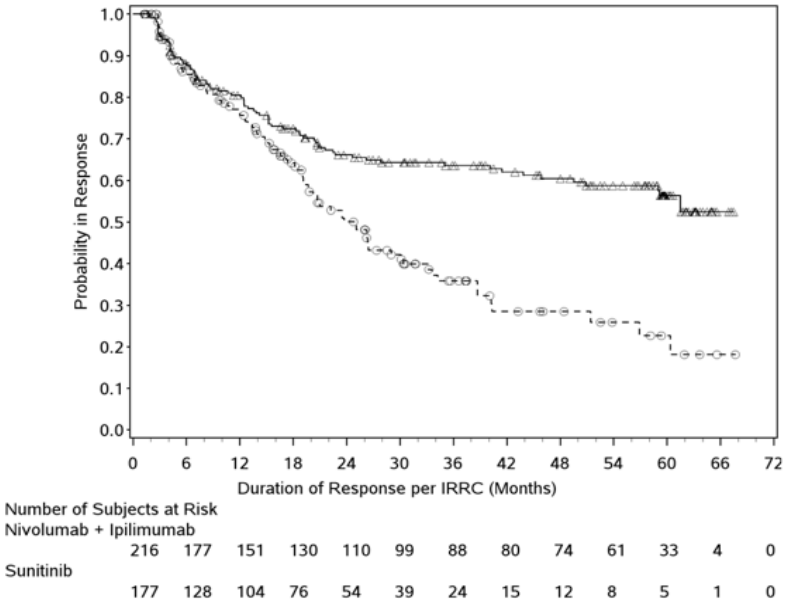
CM 214 minimum follow-up: 60.0 months

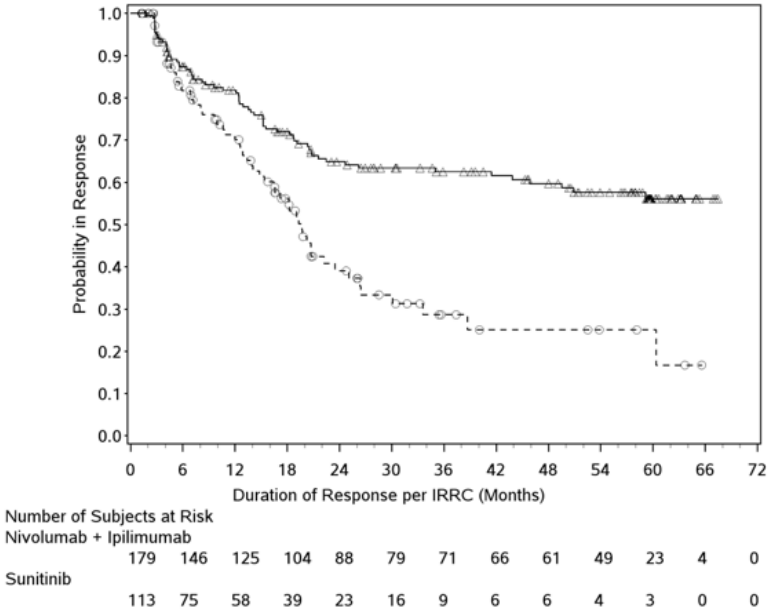
ORR and DOR Across IMDC Risk Groups

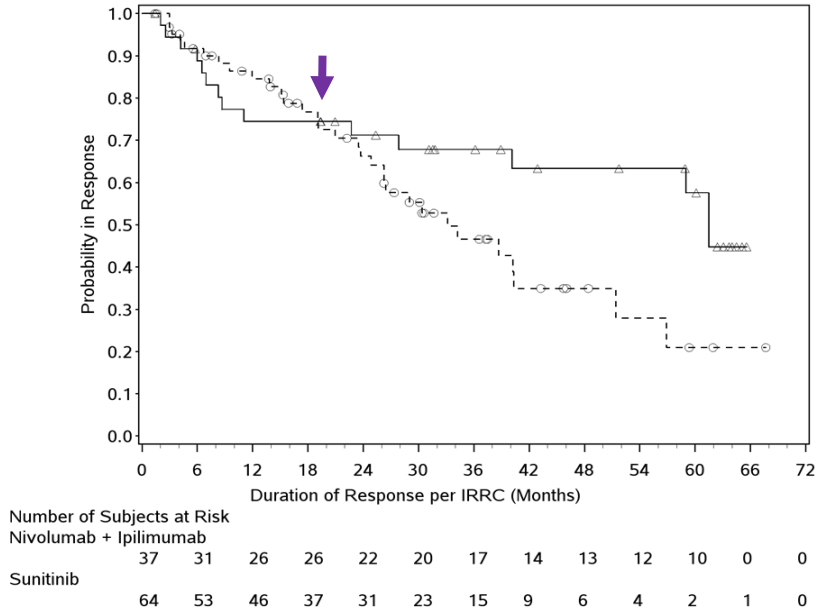
ITT	NIVO mono n=550	SUN n=546
ORR, %	39	32
CR, %	12	3
mDOR, mos	NR	24.8
Pts with ongoing responses, %	63	50

Intermediate/poor risk	NIVO mono n=425	SUN n=422
ORR, %	42	27
CR, %	11	2
mDOR, mos	NR	19.7
Pts with ongoing responses, %	64	50

Favorable risk	NIVO mono n=125	SUN n=124
ORR, %	30	52
CR, %	13	6
mDOR, mos	61.5	33.2
Pts with ongoing responses, %	59	52



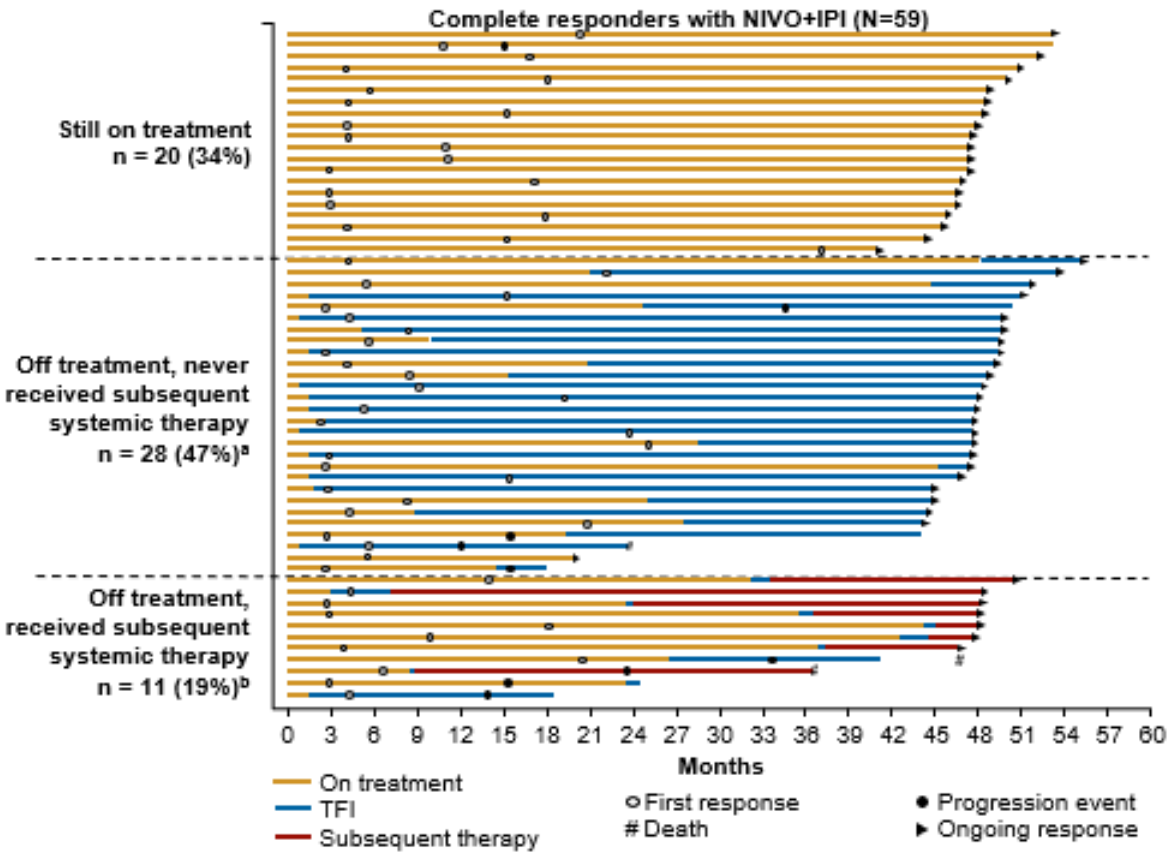




.Motzer et al Cancer 2021

Durability of Complete Response per IRRC

Post hoc analysis in the NIVO+IPI arm: ITT population



NIVO+IPI	Complete responders N = 59
Median time to response in complete responders, months (range)[c]	2.8 (0.9–9.8)
Median duration of response in complete responders, months (95% CI)	NR (NE)
Complete responders with ongoing response, n (%)[d]	51 (86)
Median duration of TFI in patients with complete response with no subsequent systemic therapy, months (range)[a]	**N = 28** 34.6 (0.5–49.7)

In partial responders, ongoing response was observed in 95/156 (61%) patients with NIVO+IPI and median (95% CI) duration of response was not reached (21.6 months–NE)

CM 214: Mean TFS and Survival States by IMDC Risk Score with Minimum 60 Months of Follow-up

Survival state	Mean time, months					
	IMDC favorable risk			IMDC intermediate/poor risk		
	NIVO+IPI (n = 125)	SUN (n = 124)	Difference (95% CI)	NIVO+IPI (n = 425)	SUN (n = 422)	Difference (95% CI)
Overall survival	47.9	49.2	–	38.6	32.2	–
Time on protocol therapy	15.1	21.6	−6.5 (−10.5 to −2.4)	16.2	11.2	5.0 (2.8–7.1)
Time on protocol therapy with grade 2+ TRAEs	4.9	13.6	−8.8 (−11.9 to −2.4)	4.6	6.4	−1.8 (−3.1 to −0.6)
TFS	14.4	5.5	8.9 (4.9–12.8)	10.1	4.1	6.1 (4.2–7.9)
TFS with grade 2+ TRAEs	5.0	2.1	2.9 (0.5–5.4)	4.0	2.0	2.0 (0.9–3.2)
TFS with grade 3+ TRAEs	1.2	0.3	1.0 (−0.2 to 2.1)	0.6	0.3	0.3 (0.0–0.7)

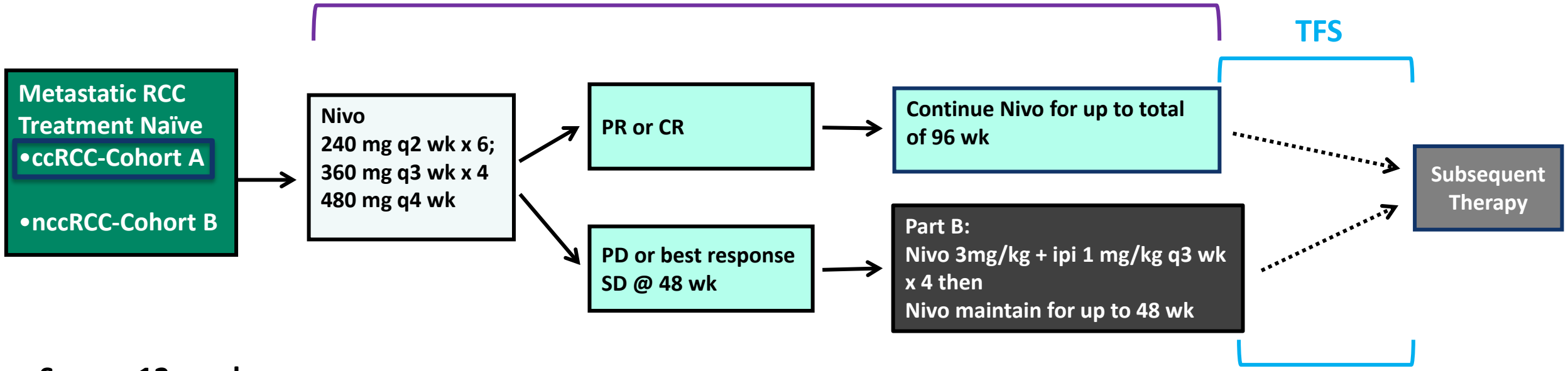
CI, confidence interval.

Mantia et al IKCS 2022

TFS: IO/TKI = sunitinib- Chang et al ASCO 2023

HCRN GU16-260: Study Design

IIT* at 12 sites conducted through the HCRN GU Group
Support provided by BMS (CA209-669)



Scans q12 weeks

TFS begins when treatment stops for either TRAE, PD or treatment completion

- Part A: Up to 96 weeks
- Part A to B: usually up to 108 weeks

TFS ends with start of subsequent therapy or death

* IIT = investigator-initiated trial

Atkins et al ASCO GU 2023

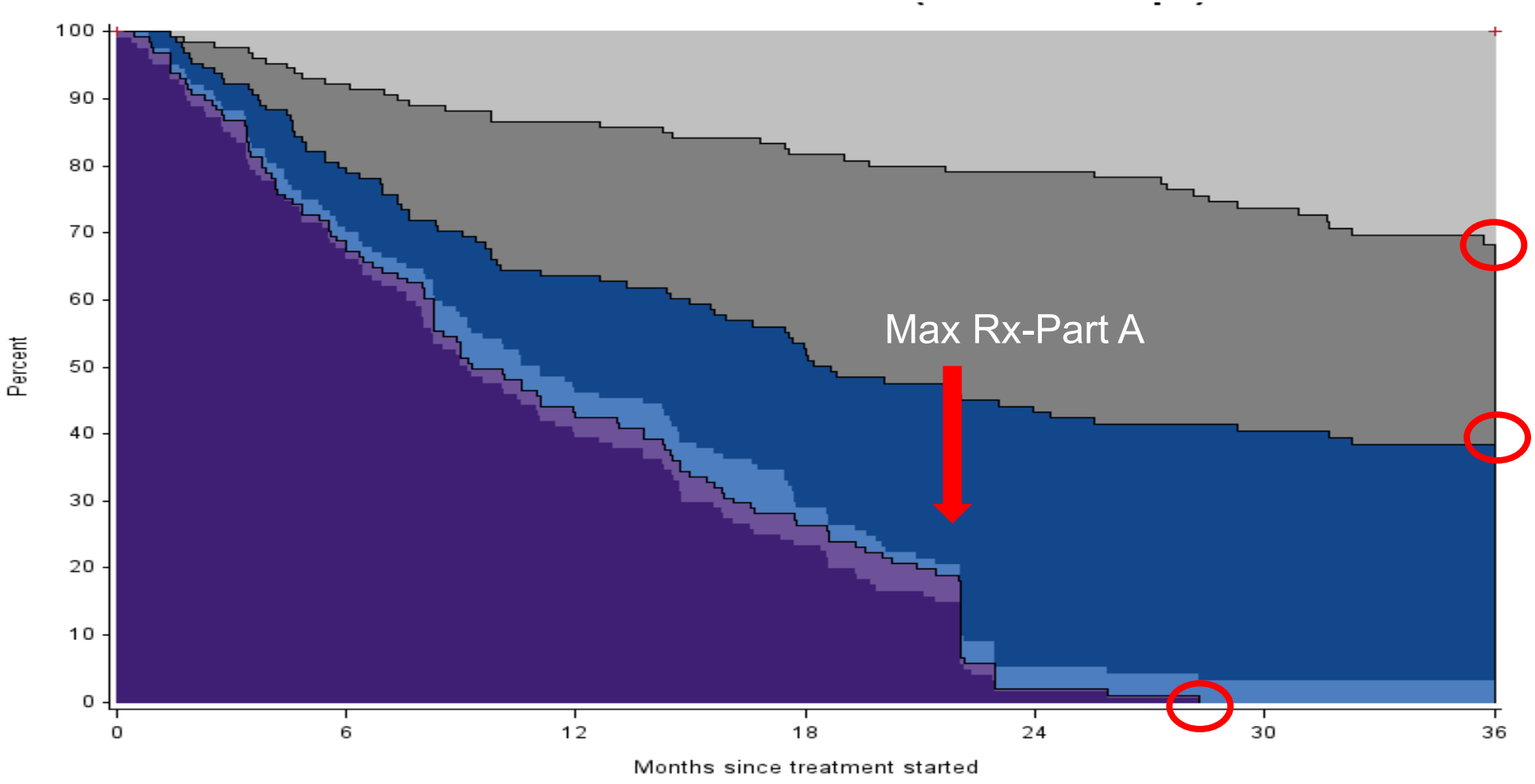
Efficacy Results: By IMDC Category

Best Response	IMDC Risk Category			Overall (N=128)
	Favorable (N=38)	Intermediate (N=78)	Poor (N=12)	
ORR, N (%)*	22 (57.9)	20 (25.6)	4 (33.3)	46 (35.9)
(95% CI) %	(40.8-73.7)	(17.9-37.0)		(27.7-44.9)
SD	15 (39.5)	27 (34.6)	4 (33.3)	46 (35.9)
PD	1 (2.6)	31 (39.7)	4 (33.3)	36 (28.1)
3-yr Endpoints				
PFS	31.2%	7.2%		14.6%
OS	96.8%	56.6%		68.3%
Alive & subseq Rx free	65.6%	27.1%		38.5%
On protocol Rx	0%	0%		0%

* Parts A and B, N=37 proceeded to Part B

Atkins et al GU ASCO 2023
Atkins et JCO 2022

Survival State Endpoints (All Risk Groups)



KM est. at 36 mo:

OS, 68.3% of pts

Alive & subseq Rx-free, 38.5% pts

Protocol Rx, 0% pts

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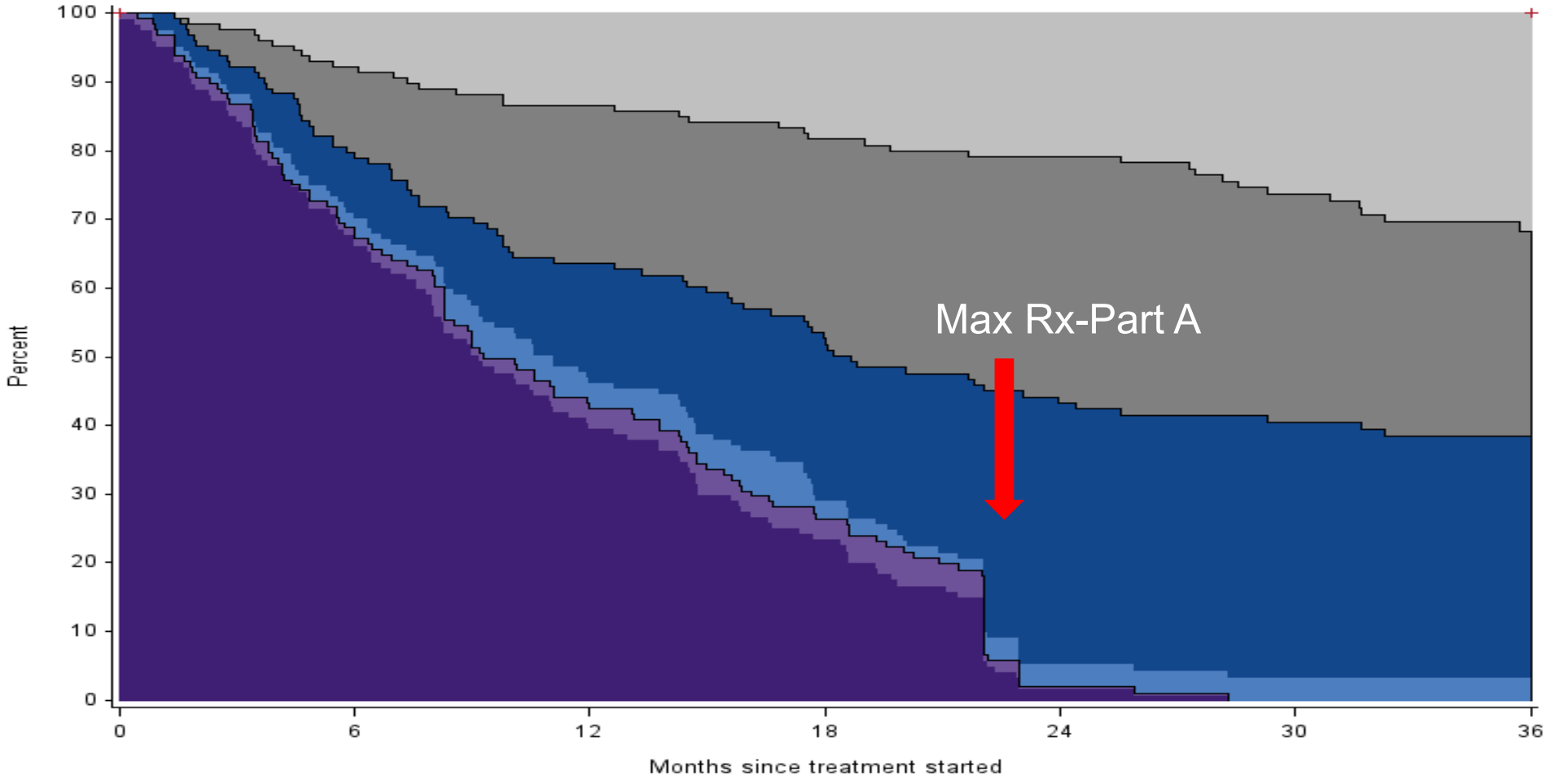
Survival States (All Risk Groups)



Mean mo., area under or between KM curves (% of 36 mo period):

OS 29.9 mo (83%)

Survival after subseq Rx, 8.9 mo (25%)

TFS, 9.4 mo (26%)

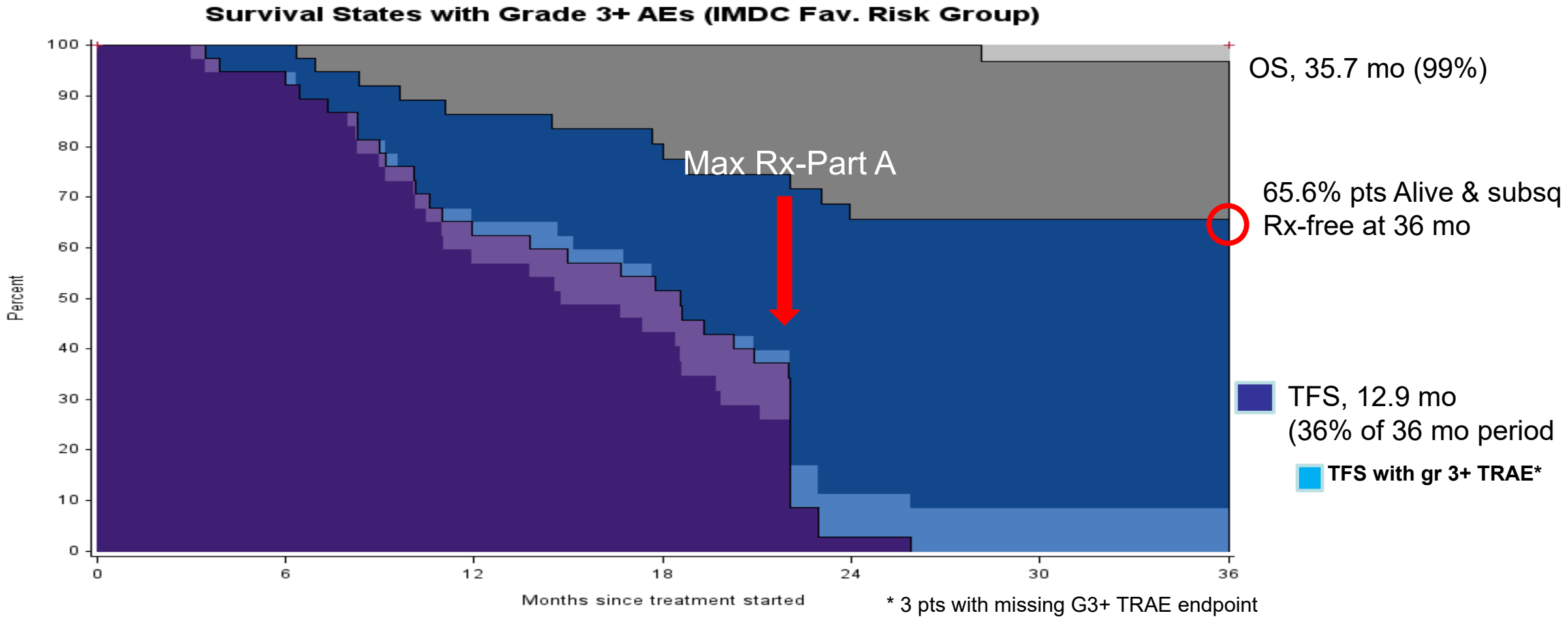
TFS with gr 3+ TRAE

Protocol Rx, 11.5 mo (32%)

Protocol Rx with gr 3+ TRAE

Atkins et al ASCO GU 2023

Survival States (Favorable Risk)



* 3 pts with missing G3+ TRAE endpoint

Atkins et ASCO GU 2023

Second-Line IO/TKI

Phase III CONTACT-03 study

Key eligibility criteria

- Advanced/metastatic clear cell or non–clear cell[a] RCC with or without a sarcomatoid component
- Radiographic progression on or after prior ICI treatment
  - ICI as adjuvant, 1L or 2L (single agent or in combination with another permitted agent)
  - ICI in the immediately preceding line of therapy

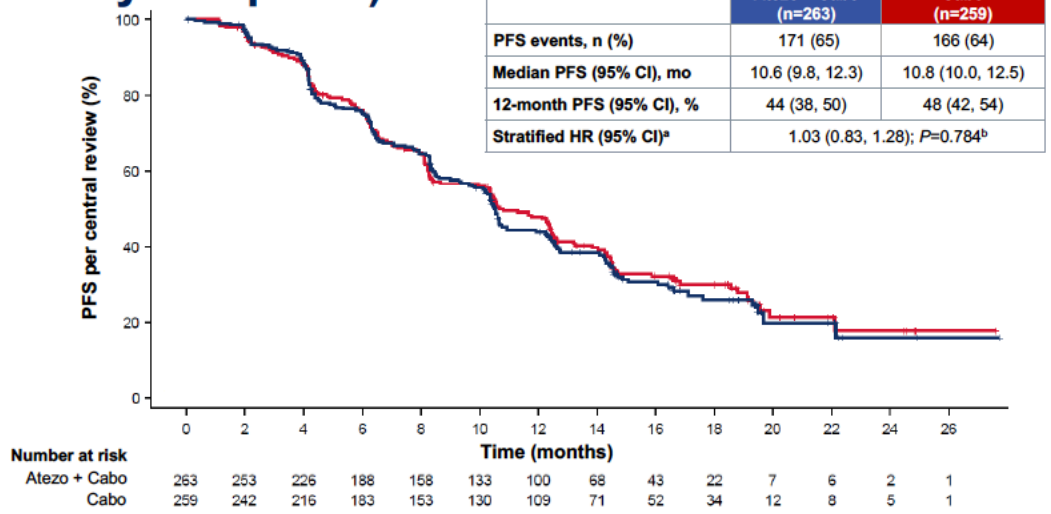
R 1:1

N=522

- Atezolizumab 1200 mg IV q3w + Cabozantinib 60 mg daily PO
- Cabozantinib 60 mg daily PO

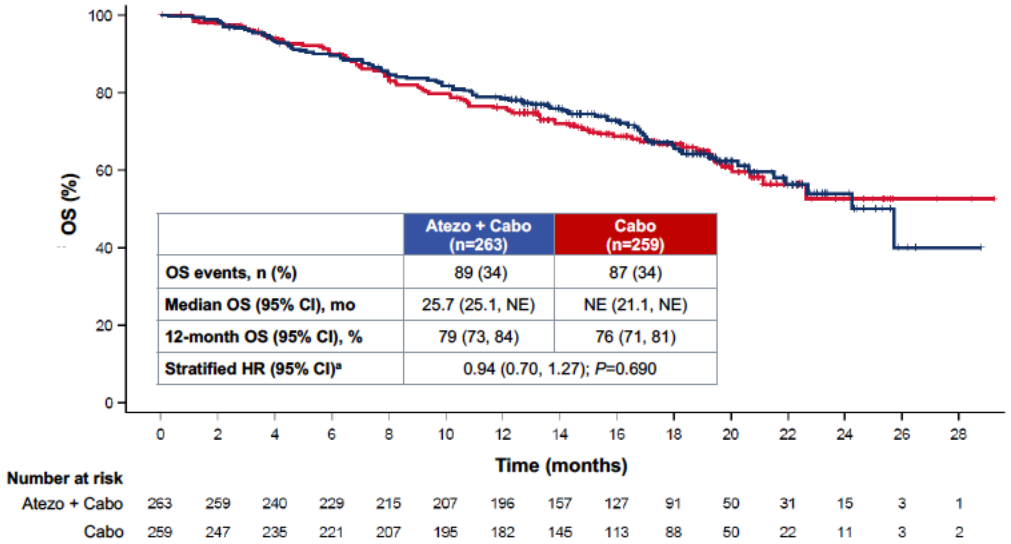
Primary analysis of centrally reviewed PFS (primary endpoint)

	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]	



Interim analysis of OS (primary endpoint)

	Atezo + Cabo (n=263)	Cabo (n=259)
OS events, n (%)	89 (34)	87 (34)
Median OS (95% CI), mo	25.7 (25.1, NE)	NE (21.1, NE)
12-month OS (95% CI), %	79 (73, 84)	76 (71, 81)
Stratified HR (95% CI)[a]	0.94 (0.70, 1.27); *P*=0.690	



Choueiri et al ASCO 2023

Lessons from BRAFm Melanoma

- Nivo/ipi followed by TKI is associated with greater landmark OS than the converse sequence
  - Nivo/ipi results in more durable responses and TFS than TKI in the frontline
  - TKI works as well in 2nd line as first line (Cosmic 313 vs CaboSun), while IO does not (HCRN-GU-260 vs CM-025)
- IO/TKI combinations are less effective for OS and TFS than the approaches given in sequence

- Principle: To maximize OS, (?cure) the best IO followed by the best non-IO (if necessary) is the preferred approach

1 Choueiri et al; 2. Albiges L, et al. *ASCO GU* 2023; Atkins MB, et al. *J Clin Oncol* 2022; Motzer et al

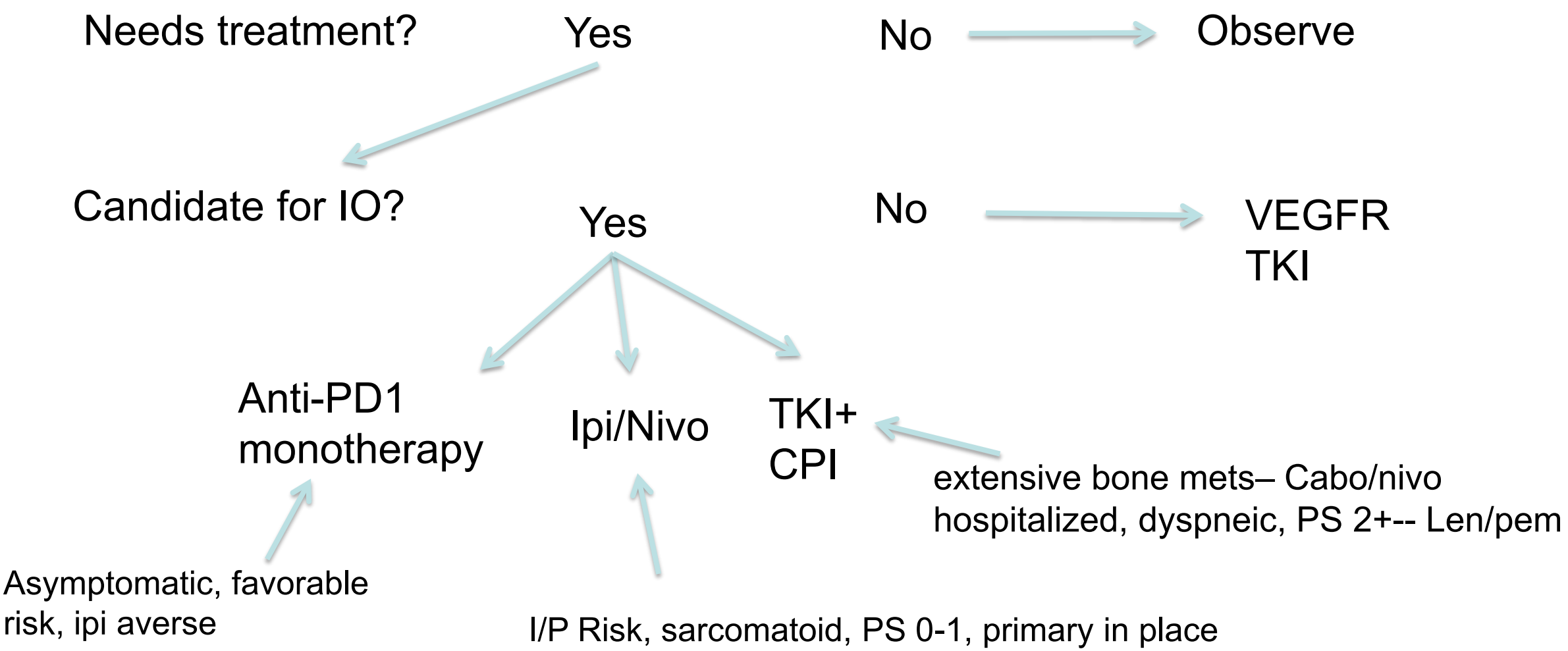
Application to RCC

“It is time to concede that IO/TKI combinations are not in the long-term best interest of the majority of patients with metastatic ccRCC.

If we want to improve cure rates for patients with metastatic ccRCC we need to build on a pure IO backbone”

Atkins – ASCO 2023 RCC Oral Session

Algorithm for Front-line RCC Rx- Atkins 2023

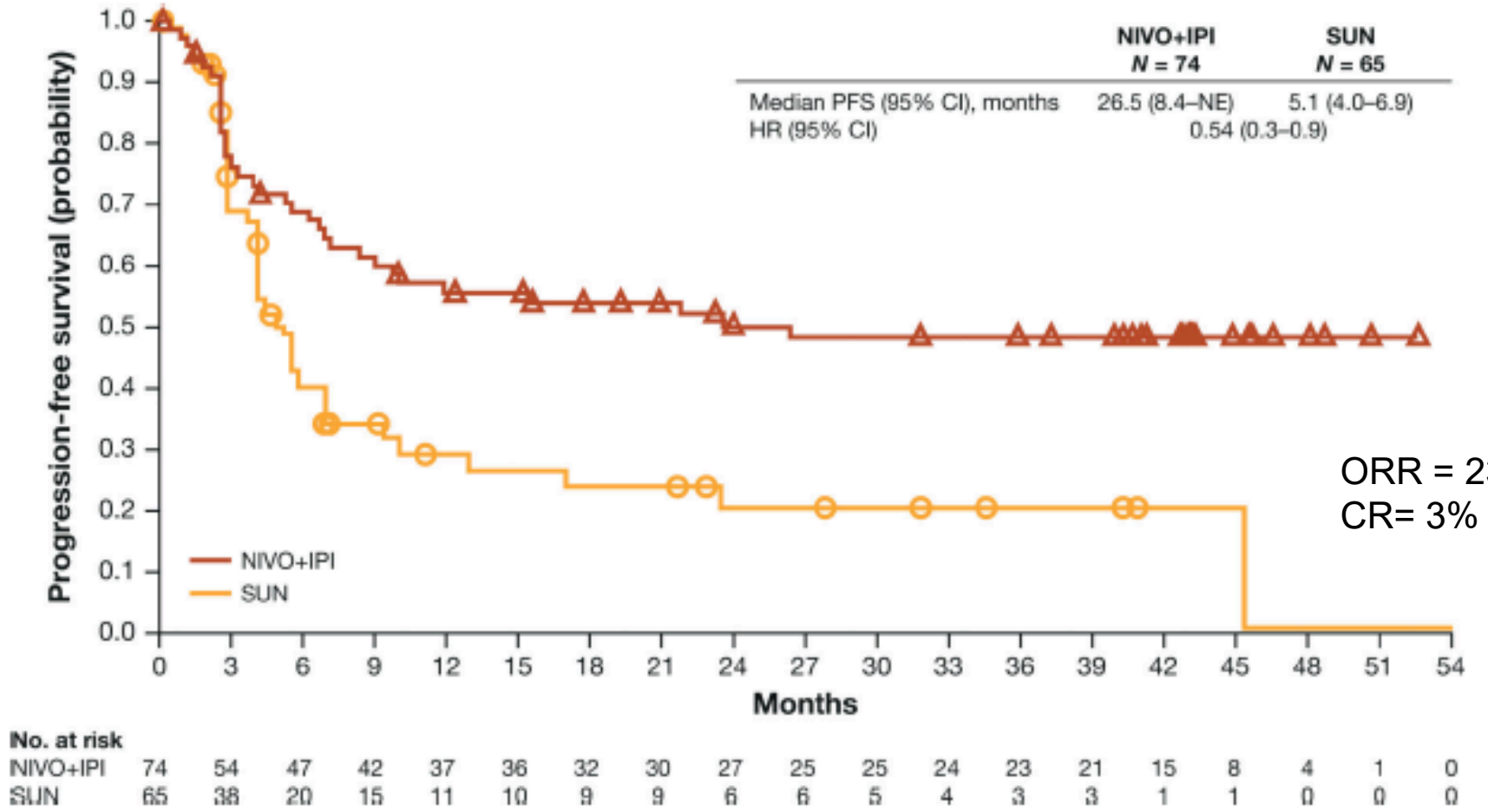


How to Move Forward?

- Predictive biomarkers for IO therapy
- Develop regimens to overcome IO resistance mechanisms
- Focus on IO endpoints
  - Landmark PFS, OS, Durable response, TFS

PFS: Intermediate/Poor-Risk Sarcomatoid Patients

CM 214

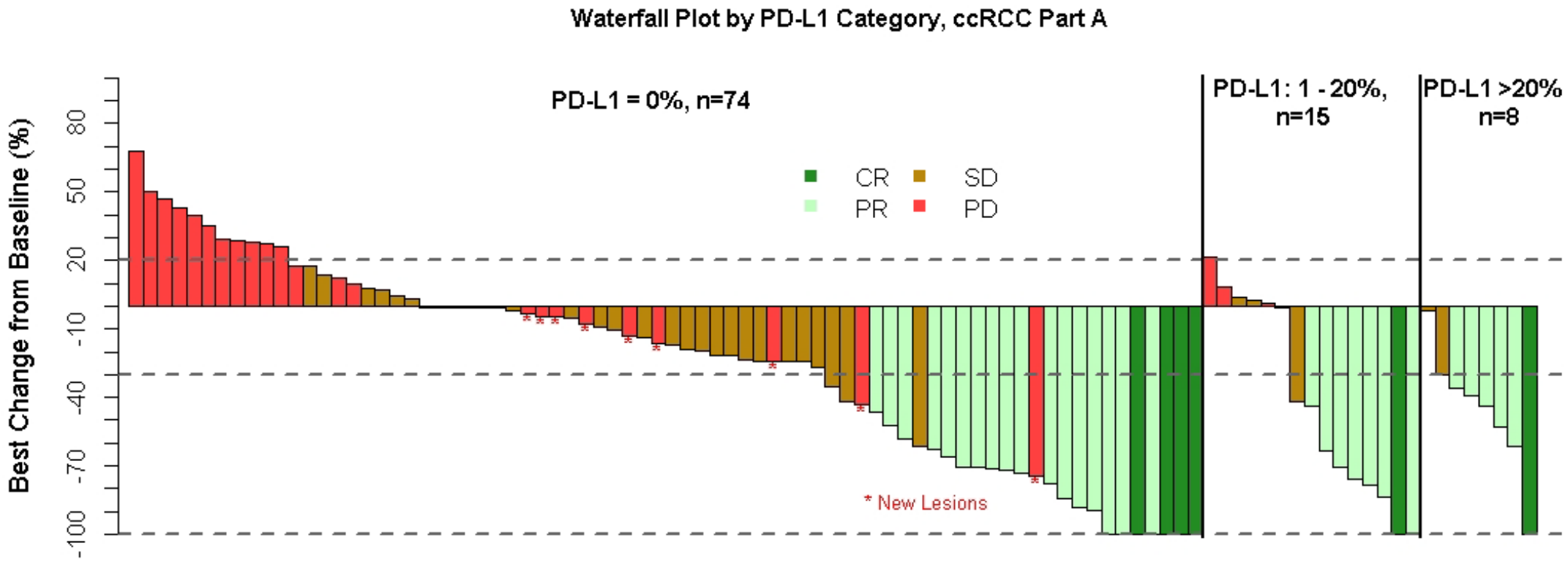


ORR = 61% (49-72)
CR= 19%

ORR = 23% (14-35)
CR= 3%

Tannir et al CCR 2022

Best Tumor Shrinkage by Tumor PD-L1 Status



ORR= 26%

ORR=50%

ORR=75%

Atkins et al JCO 2022

HCRN GU 16-260: PD-L1 Biomarker Conclusions

Tumor PD-L1 associated with better ORR and PFS

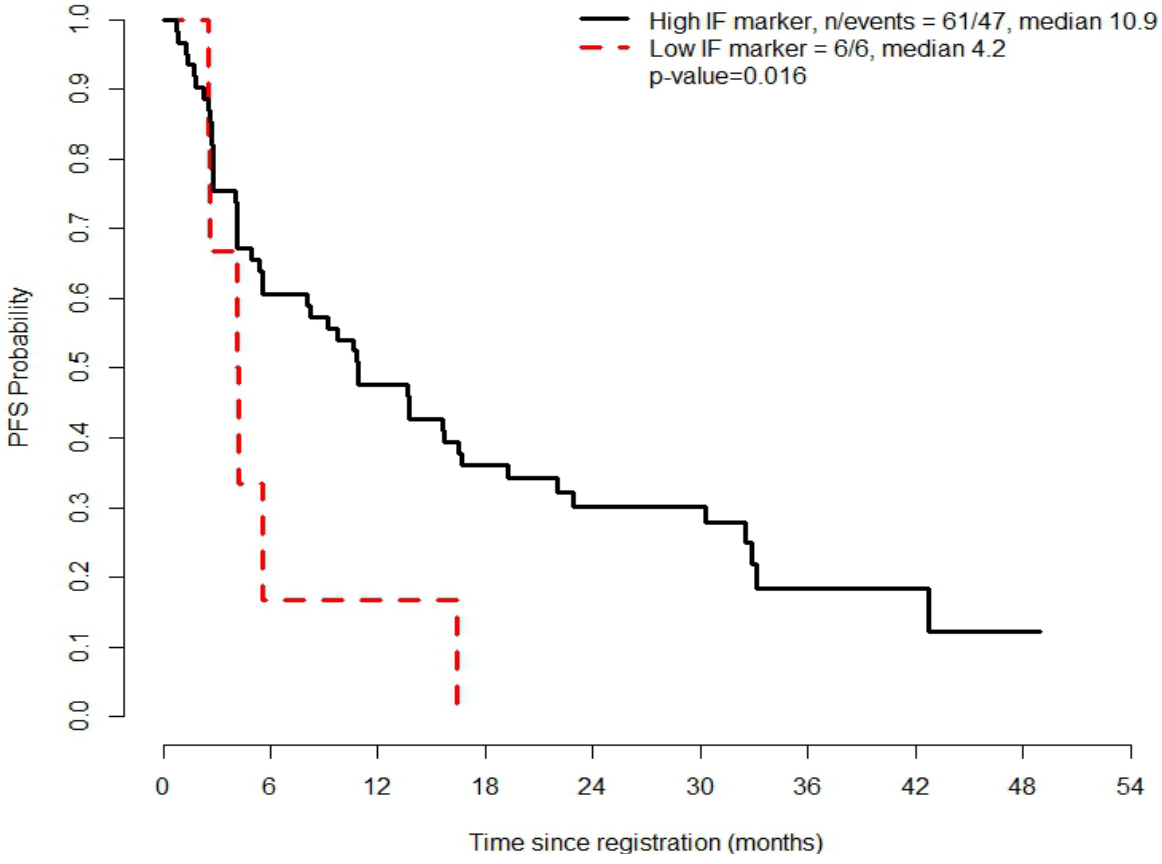
- Too few (24%) tumors PD-L1+; majority of responses in PD-L1 negative tumors

- Can’t use for Rx decisions!!!

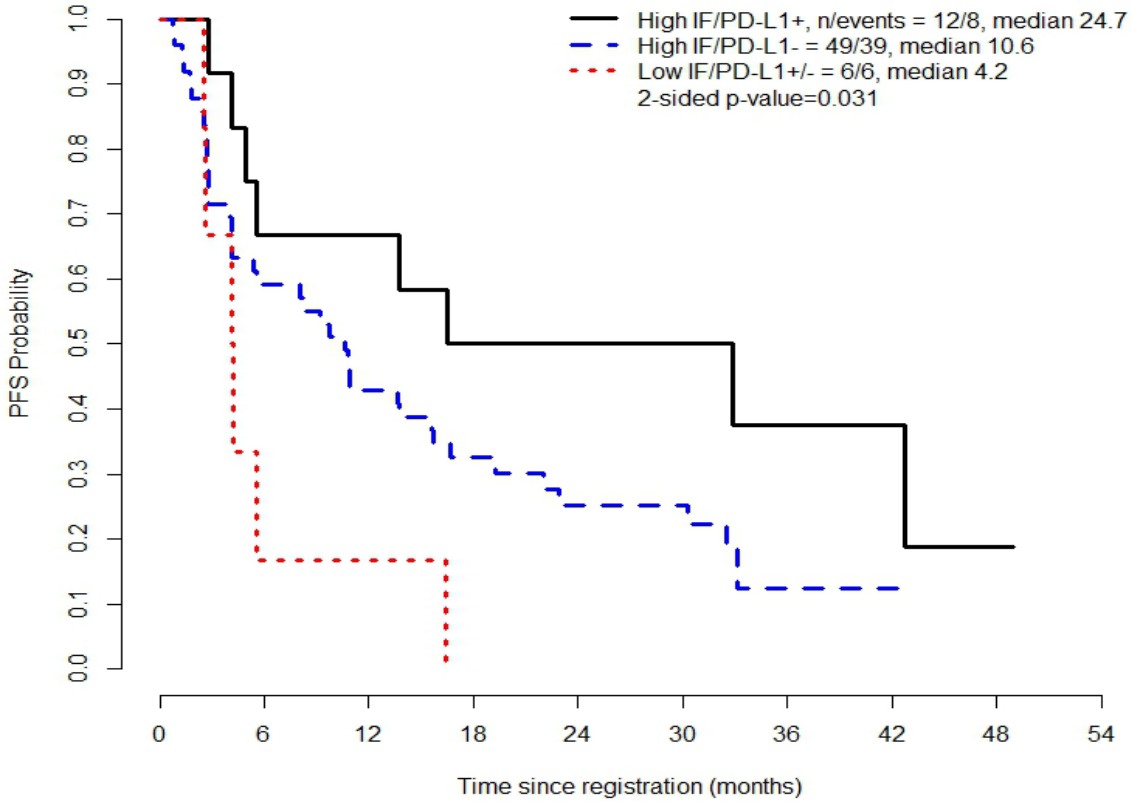
- Could be part of a multi-component predictive biomarker

Biomarker: CD8+ PD-1+LAG3-Tim3- TIL

Biomarker High vs Low



Biomarker +/- PDL1 Expression



Signoretti et al ASCO 2023

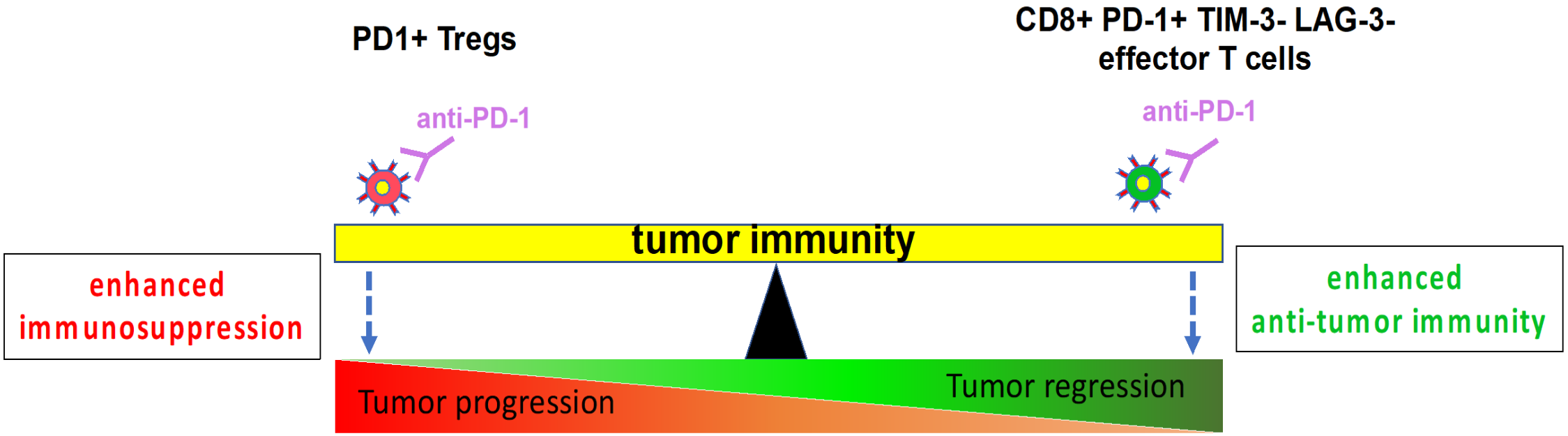
Promising Biomarkers - Associated with Resistance

- PD-1^{+} Treg numbers –
  - Signoretti and Sharpe DFHCC RCC SPORE

- SLAMF7- scRNAseq-
  - Braun et al HCRN GU 16-260-ASCO 2023

"SLAMF7 Signaling Reprograms T Cells toward Exhaustion in the Tumor Microenvironment" O'Connell et al J Immunol 2021

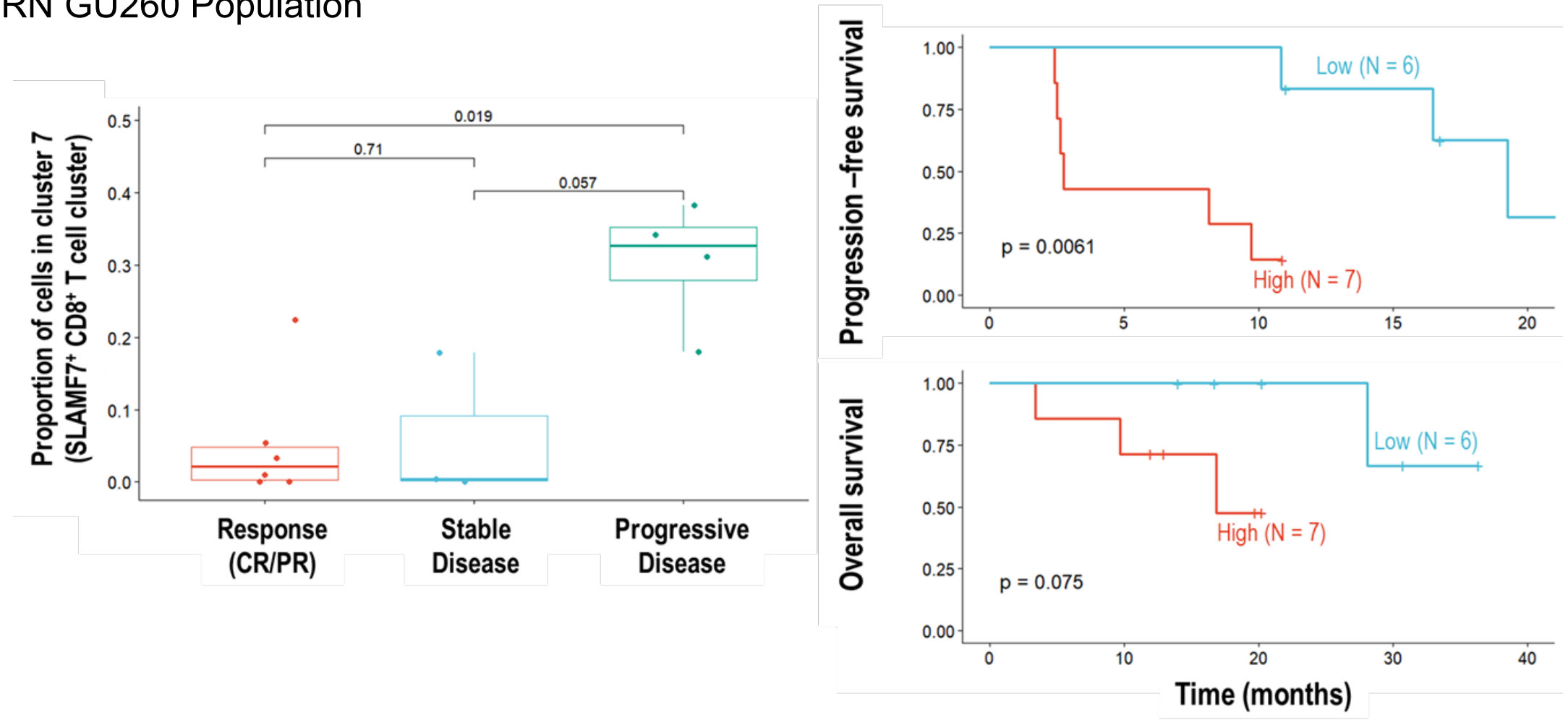
PD1+ T Cell Model



Dineen, Signoretti, Atkins et al (submitted)

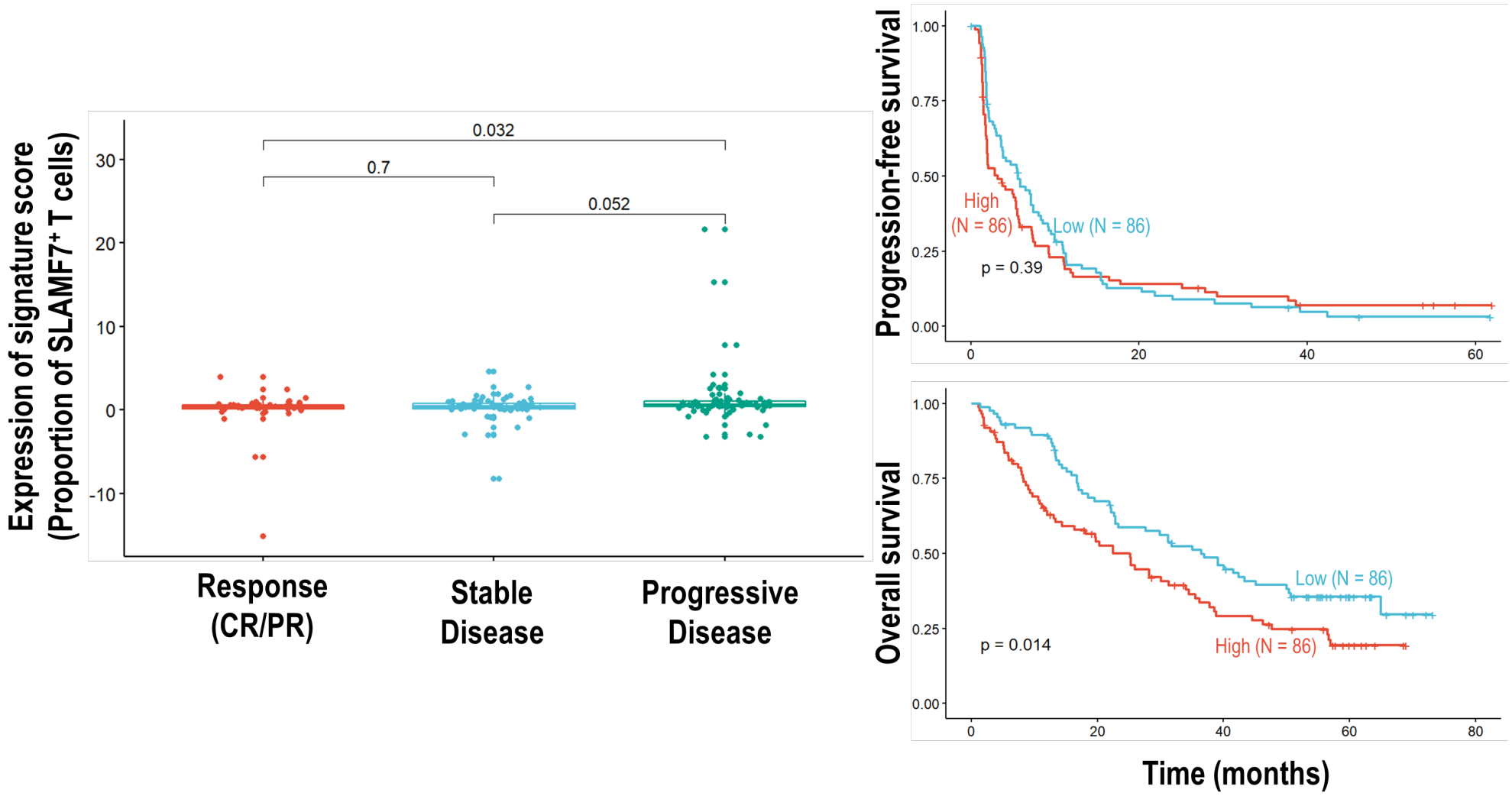
SLAMF7+ CD8+ T cells are enriched in nivo-resistant ccRCC

HCRN GU260 Population



Braun D, Atkins M et al ASCO GU 2023

Validation of SLAMF7 Signature on CD8+ T cells in CM09 and 025 Cohorts

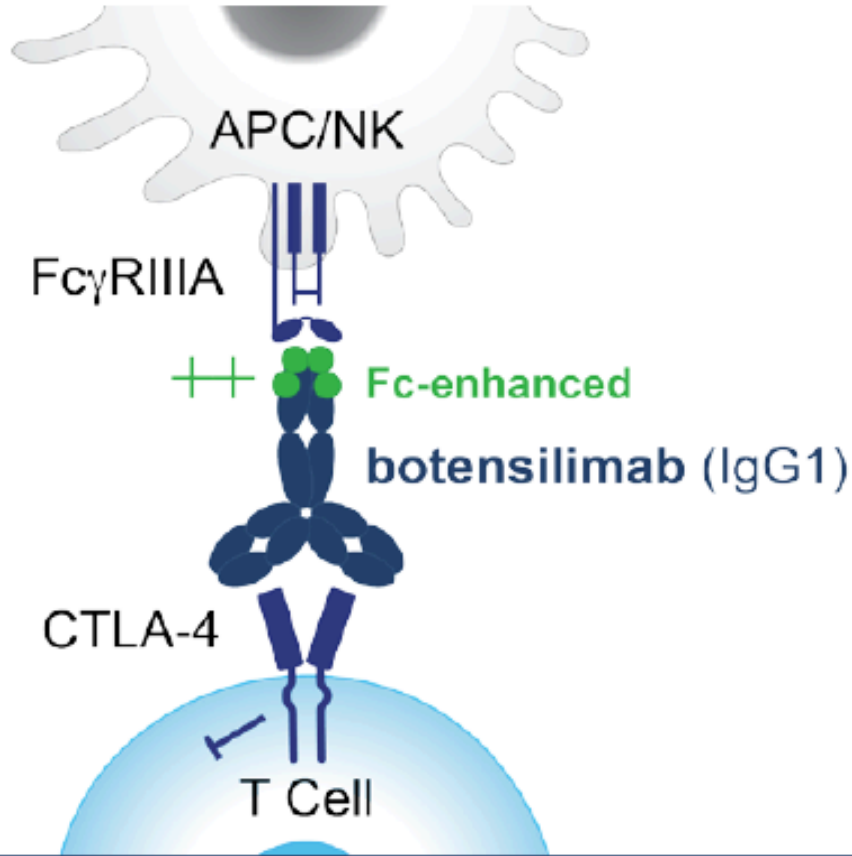


Braun, Atkins et al GU ASCO 2023

Novel Immunotherapy Agents

botensilimab

Fc-enhanced CTLA-4 Inhibitor



Active in cold and IO refractory tumors[1]:

Design:

- Improved binding to activating FcγRs on APCs and NK cells
- Reduced complement binding

Function (relative to first-gen CTLA-4)[2,3]:

- ↑ Frequency of activated DCs
- ↑ T cell priming, expansion, memory
- ↑ Treg depletion
- ↓ Complement mediated toxicity

1. El-Khoueiry AB. SITC 2021 Annual Meeting. Poster #479. 2. Waight et al. *Cancer Cell*. 2018;33(6): 1033-1047. 3. Data on File. Agenus Inc. June 2022.

Novel Immunotherapy Agents

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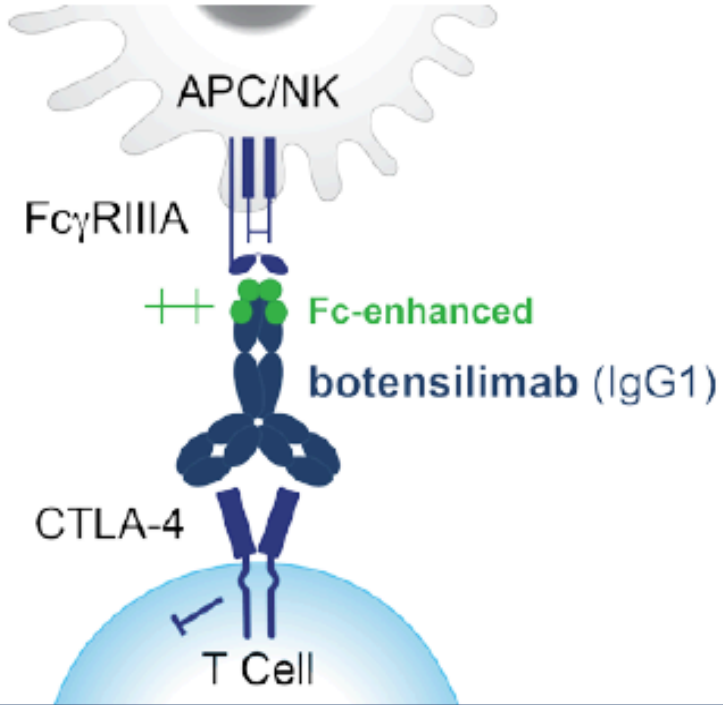
Fc-enhanced CTLA-4 Inhibitor

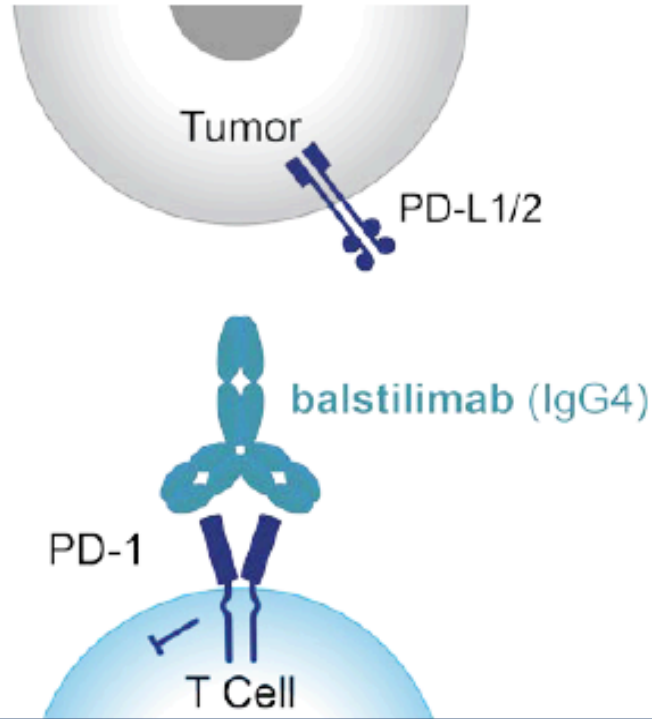


Active in cold and IO refractory tumors[1]:

- ↑ T cell priming, expansion, memory[2]
- ↑ Treg depletion
- ↓ Complement mediated toxicity

balstilimab

PD-1 Inhibitor



Safety and efficacy analogous to approved anti-PD-1 mAbs[3,4]

- > 650 patients treated; 8 ongoing trials / 2 completed
- Complete blocker of PD-1-PD-L1/2 interactions
- Enhanced T cell activation and effector function

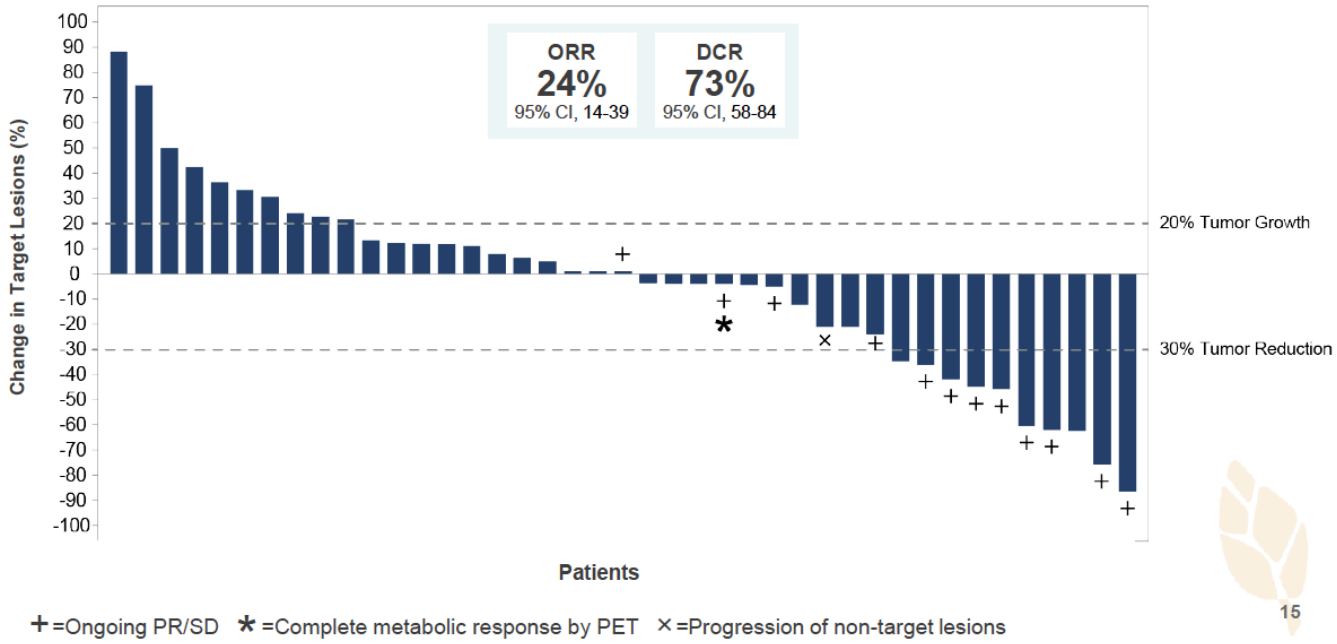
1. El-Khoueiry AB. SITC 2021 Annual Meeting. Poster #479. 2. Waight et al. *Cancer Cell*. 2018;33(6): 1033-1047. 3. O'Malley, et al. *Gynecol Oncol*. 2021; 163: 274-280. 4. O'Malley et al, *J Clin Oncol*. 2022; 40(7): 762-771.

Agenus Bot/Bal Combo- MSS CRC Efficacy Data

MSS CRC treated with Agenus CTLA-4/PD-1 Combo

	Overall (N=41)
ORR, % (95% CI)	**24%** (14-39)
BOR, n (%)	
CR	0 (0)
PR	10 (24)
SD	20 (49)
PD	11 (27)
DCR (PR + SD), % (95% CI)	**73%** (58-84)
Median Follow-up, mo. (range)	5.8 (1.6-24.4)

Waterfall Plot (N=41)



80% of responses ongoing; 3 > 1 year

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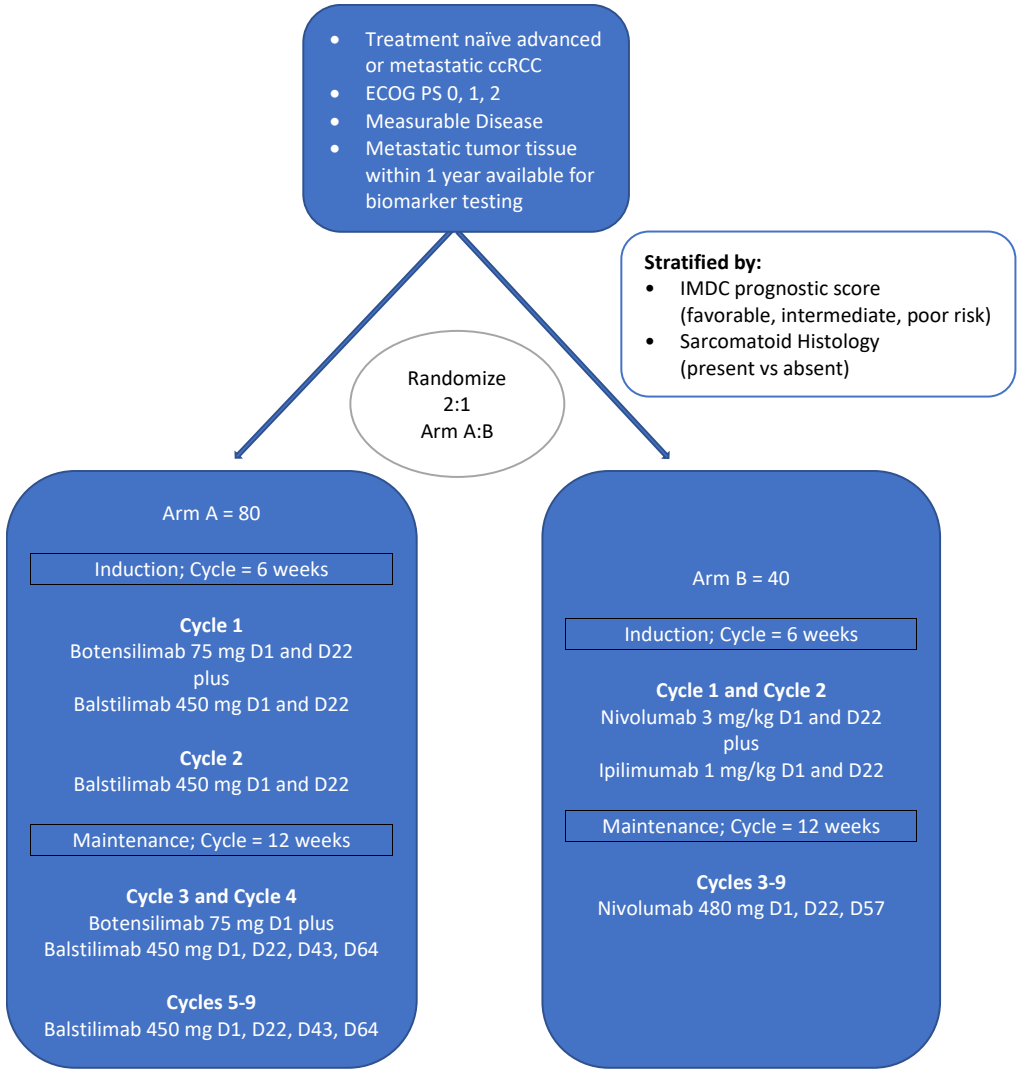
Bullock A et al, ESMO GI 2022

ARCITeCT SCHEMA (N=120)



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RCC 2023: Take Home Messages

Our goal should not be simply to turn RCC into a chronic disease…We should strive to make RCC a curable disease

Using agents/combinations as first-line treatment that maximize the anti-tumor immune response is critical to achieving that goal

Using TKIs in the frontline does not accomplish that goal