Updates in Treatment of Metastatic Kidney Cancer

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Disclosures/ Potential Conflicts

Consultant:

BMS, Merck, Novartis, Genentech/Roche, Exelixis, Eisai, SeaGen, AstraZeneca, Abbvie, Syncona

Advisory Boards:

Novartis, Pfizer, Merck, BMS, Pyxis Oncology, Werewolf, Genentech/Roche, Asher Bio, OncoRena, Agenus, SAB Bio, Sanofi, PliantRx, Simcha,

Research Support (to institution):

BMS, Merck, Moderna, Agenus

Stock: Werewolf and Pyxis Oncology

Other: UpToDate: Melanoma, RCC and Immunotherapy Sections Editor

Last 36 Mos

Outline for Talk

- IO/IO vs IO/TKI
- Favorable Risk patients
- Design of Biomarker studies
- New studies toward improved immunotherapy
- Second-line Therapy

mRCC: 2020+: SOC = Front-Line Combination Therapy

Setting	NCCN TREATMENT APPROACH	
Favorable Risk	**IO + TKI**	
Intermediate and Poor Risk	**PD-1 + CTLA-4 vs IO/TKI**	

Cancer Immunotherapy Principles

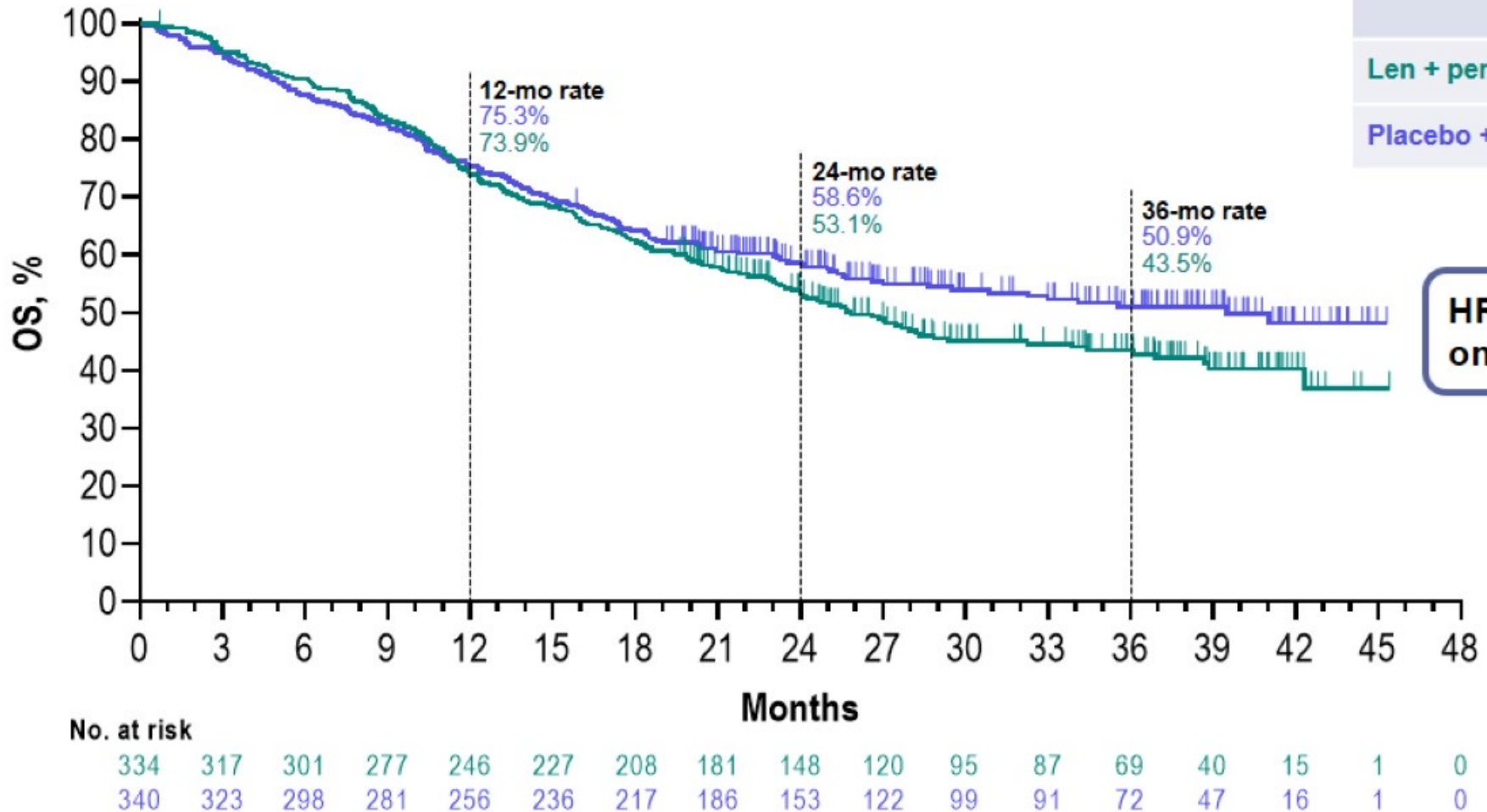
- “Treating the immune system so that it can treat the cancer” Jedd Wolchok

- Because the activated immune system can target many tumor antigens simultaneously, and deepen and broaden over time, IT can cure patients with metastatic cancer

- The hallmark of effective immunotherapy is plateaus on the KM curves (that continue after treatment stops)

Overall Survival, Final Analysis

	Pts w/ Event	Median (95% CI), mo
Len + pembro	54.5%	25.8 (23.0-33.9)
Placebo + pembro	46.2%	39.5 (26.6-NR)

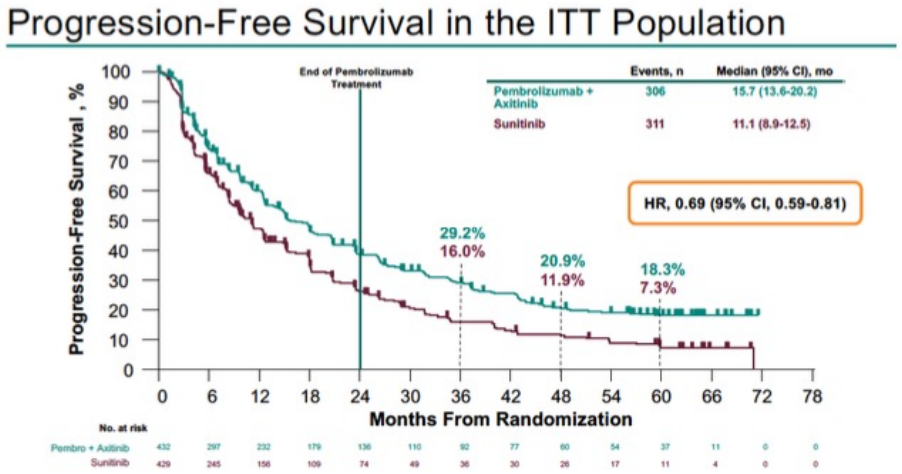


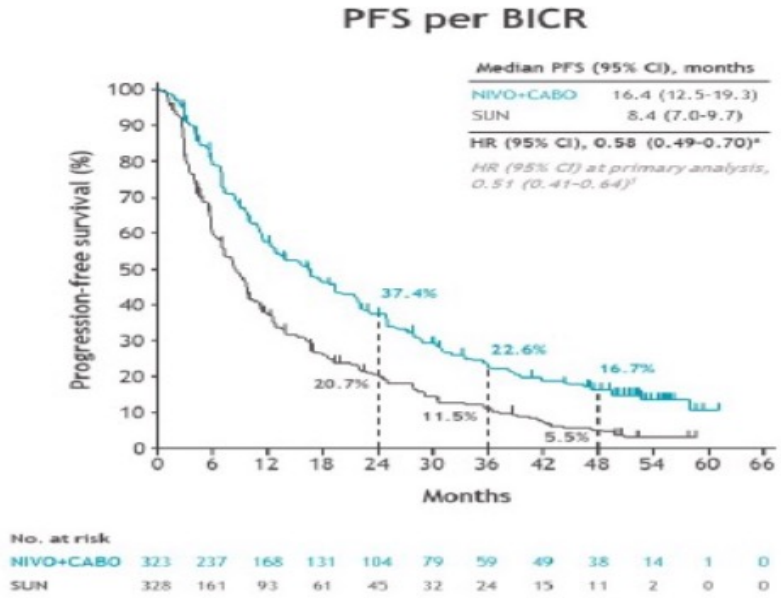
HR 1.20 (95% CI, 0.97-1.48)
one-sided *P* = 0.9521[a]

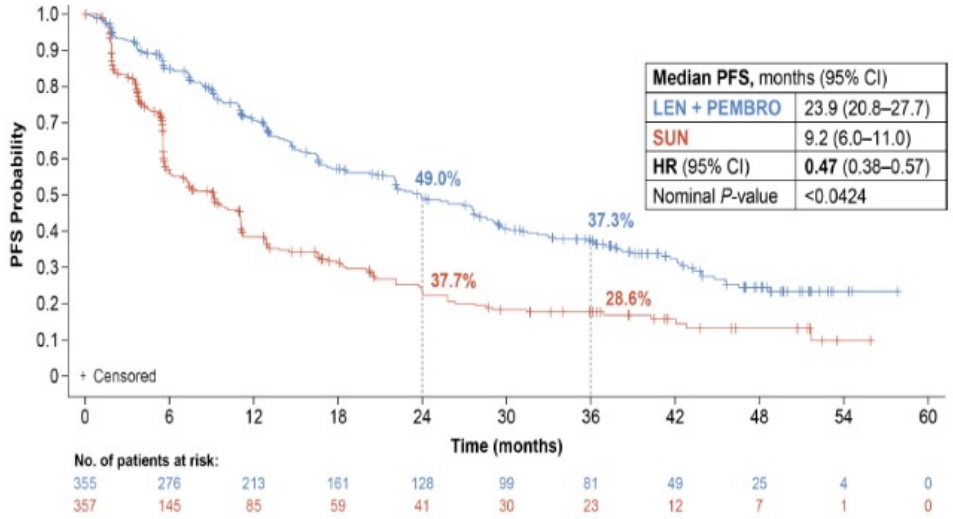
Similar findings with LEAP Program in NSCLC, HNSC, CRC and Endometrial Ca

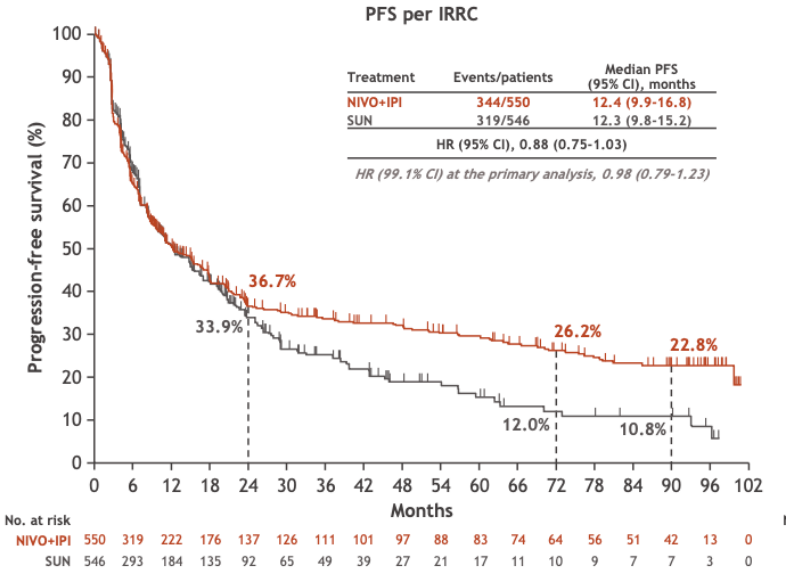
[a]Superiority boundary, one-sided *P* =0.0106.
Data cutoff date for FA: January 18, 2023 (median follow-up, 34.0 months [range, 19.6-45.8]).

IO/TKI vs I0/IO PFS Curves



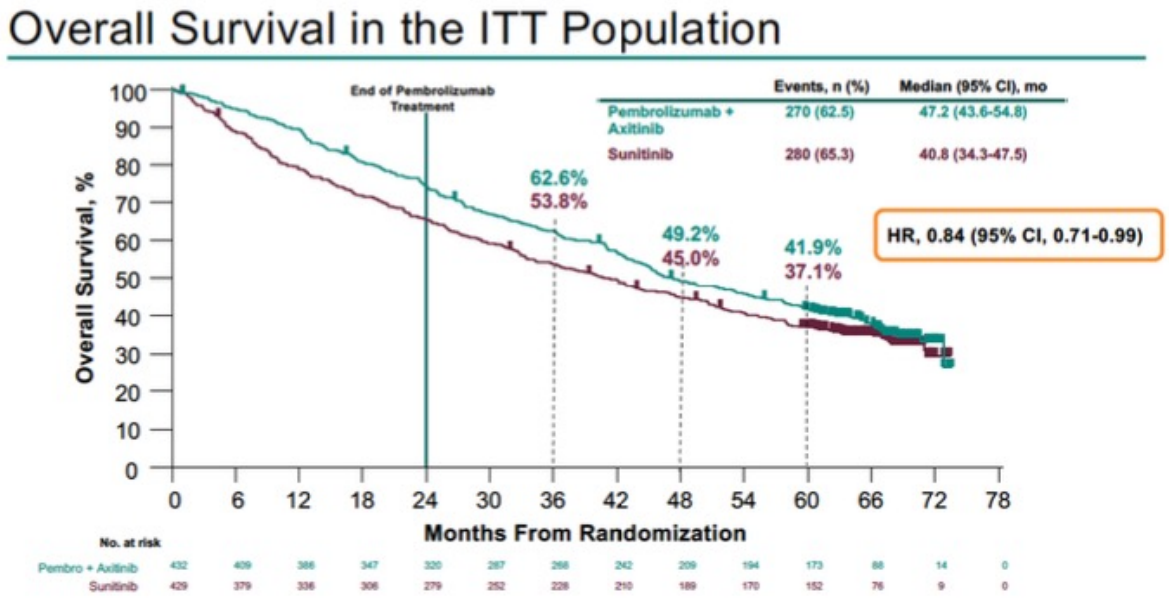


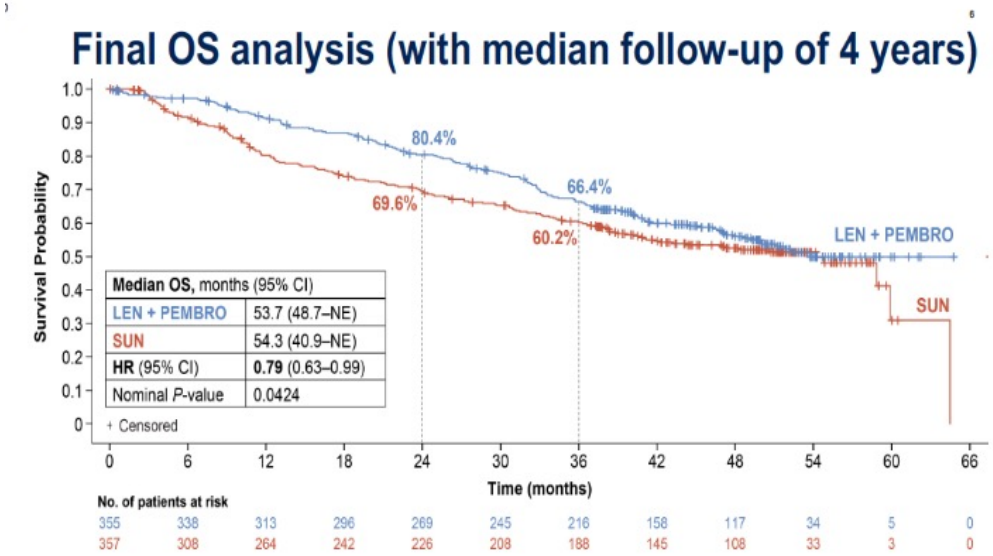




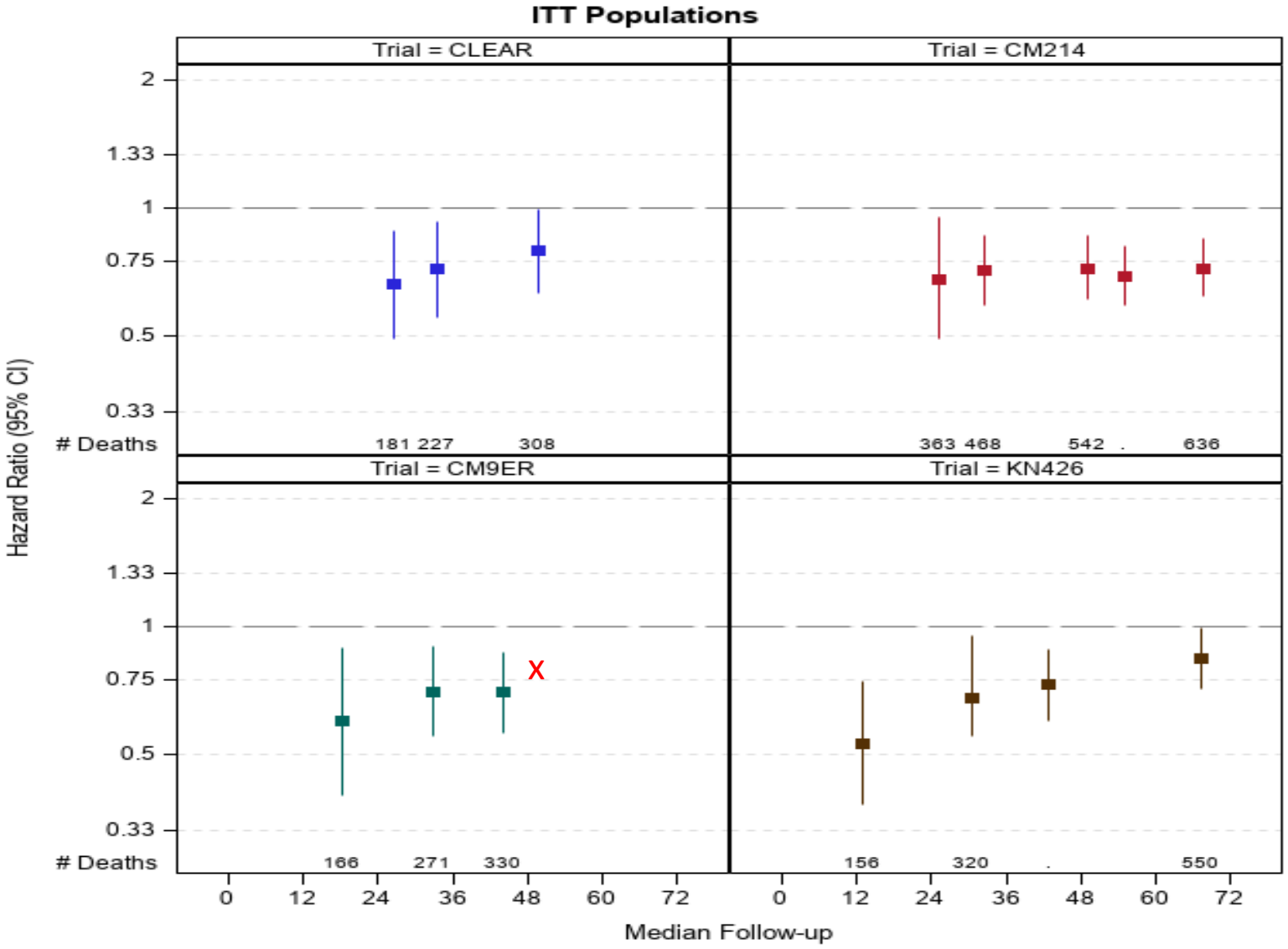
Can still get TKI (40% ORR)

OS for IO/TKIs





Comparison of First line Trial OS HRs Overtime



CM-214 HR for OS at median 8yr f/up = 0.72[1]

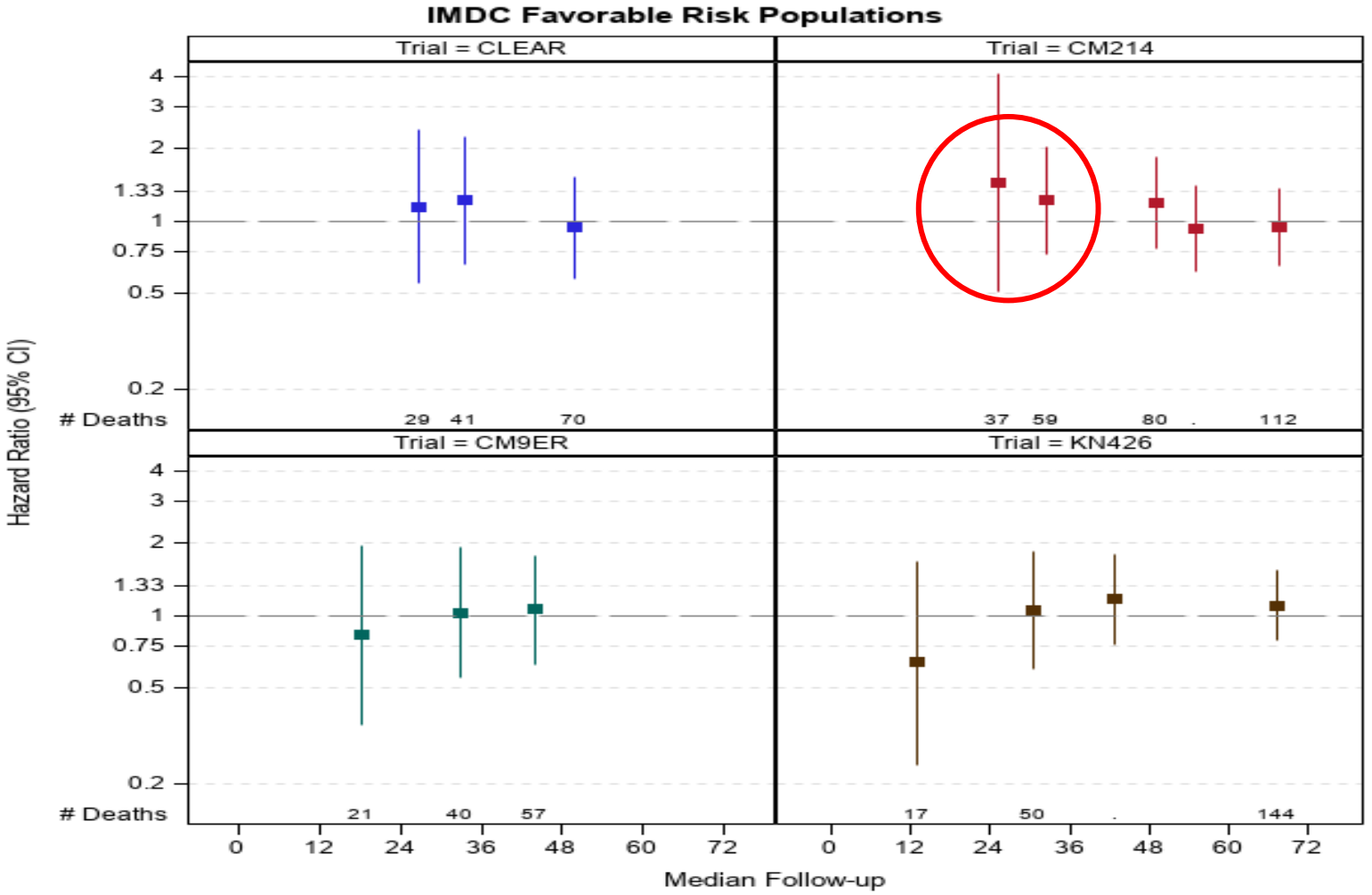
CM-9ER HR for OS at median 4yr f/up = 0.77 (95% CI 0.63-0.95)[2]

[1]Tannir et al ASCO GU 2024, [2]Bourlon et al ASCO GU 2024

Courtesy of Regan et al 2023

What to do with the IMDC favorable Risk Population?

Comparison of First line Trial OS HRs Overtime: FR Group



CM-214 HR for OS in FR at 8yr f/up = 0.82[1]

ESMO and NCCN Guidelines modified to enable Nivo/Ipi for FR patients

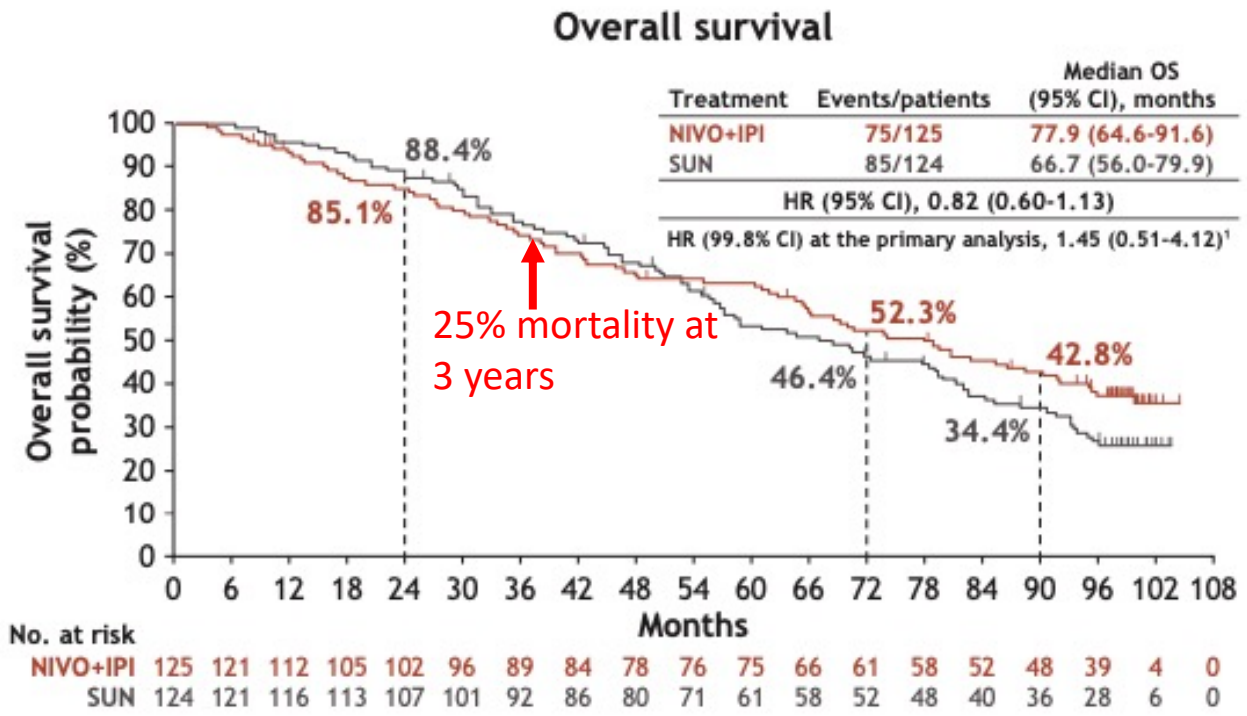
CM-9ER HR for OS in FR at 4yr f/up = 1.1[2]

[1]Tannir et al ASCO GU 2024, [2]Bourlon et al ASCO GU 2024

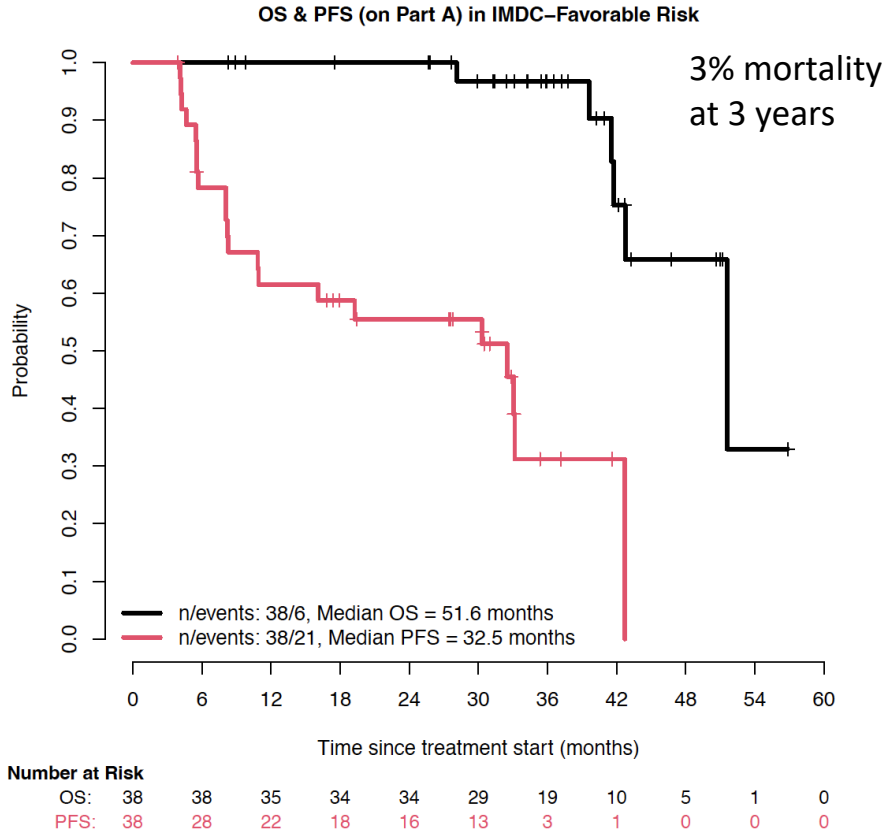
Courtesy of Regan et al 2023

OS for frontline pure IO regimens in Favorable-Risk populations

CM 214 OS-Favorable Risk



HCRN GU 16-260



What did patients on CM-214 die from?
Why weren't they salvaged with other therapies?
Are these data still relevant in 2024?

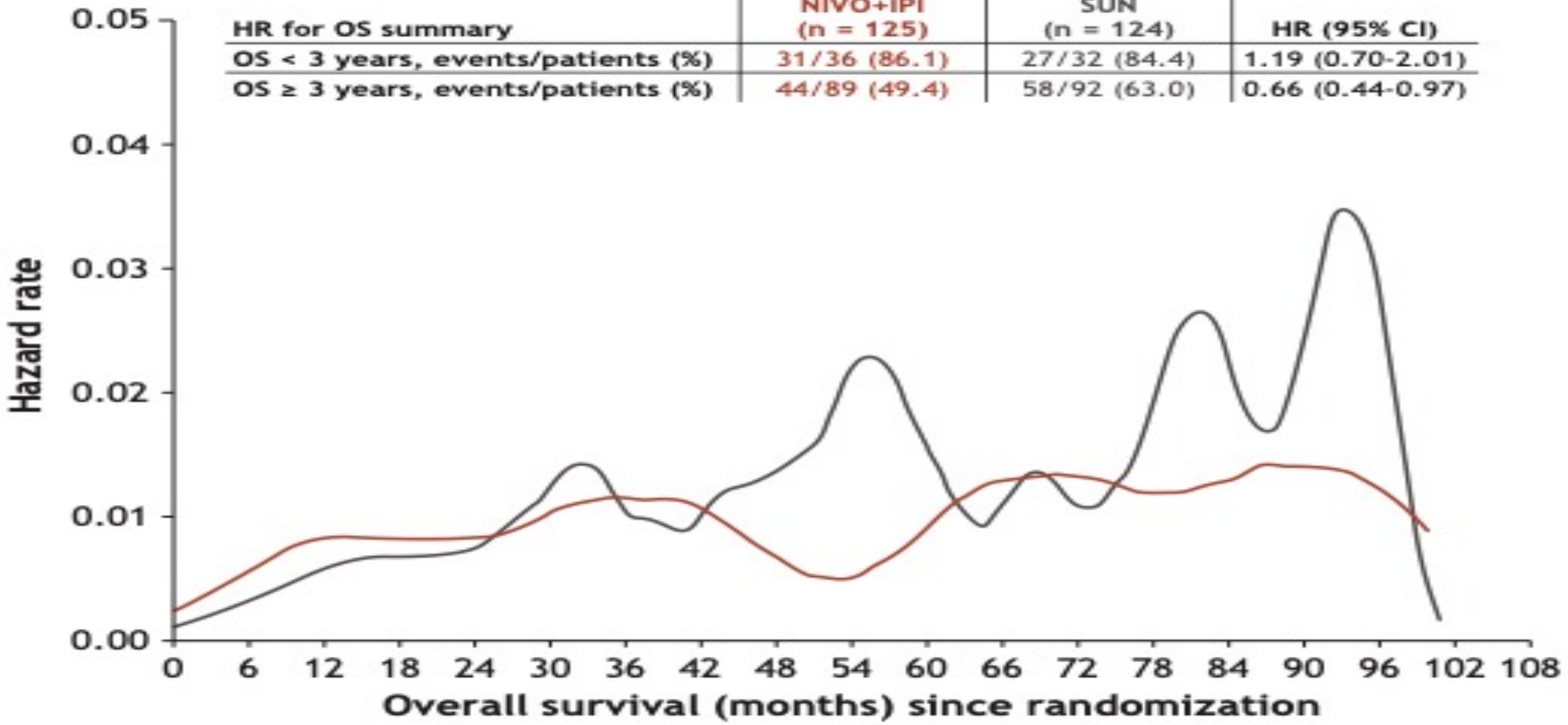
Motzer R J, et al. Cancer 2021., Atkins MB, Jegede YA et al; JITC 2024

CM 214: Subsequent Therapy in Fav Risk Pts

- 31/75 (41%) deaths in Fav-Risk pts on NIVO/IPI occurred within 3 years of randomization
- 12/27 (44%) FAV-risk pts in the NIVO/IPI arm who died after PD within 3 years did not receive 2nd-line systemic Rx vs 2/28 (8%) on SUN
- Beyond 3 years, only 2/44 (5%) pts on NIVO/IPI arm who died after PD did not receive subsequent systemic Rx vs 11/54 (20%) on SUN

Hazard Function by Treatment Group in pts with Fav Risk

HR for OS summary	NIVO+IPI (n = 125)	SUN (n = 124)	HR (95% CI)
OS < 3 years, events/patients (%)	31/36 (86.1)	27/32 (84.4)	1.19 (0.70-2.01)
OS ≥ 3 years, events/patients (%)	44/89 (49.4)	58/92 (63.0)	0.66 (0.44-0.97)



Atkins et al KCRS Meeting Boston 7/12/24

Emerging Understanding in 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.

And if we want to improve cure rates for patients with metastatic ccRCC, we need to build on a pure IO backbone

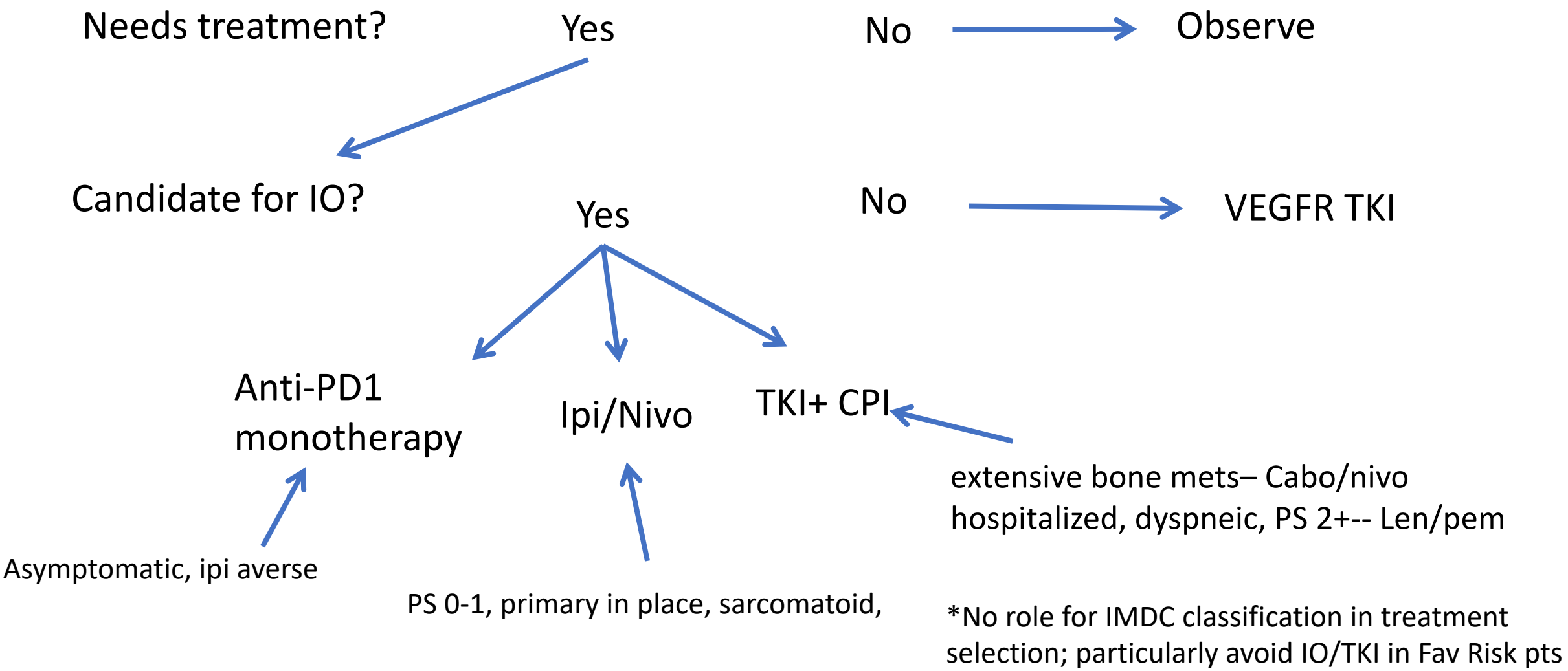
It is time to concede that IMDC categories should not inform immunotherapy treatment recommendations for patients with advanced RCC

We should include FR patients in all trials and only report ITT endpoints

Atkins – ASCO 2023 RCC Oral Session

Atkins – ASCO GU 2024

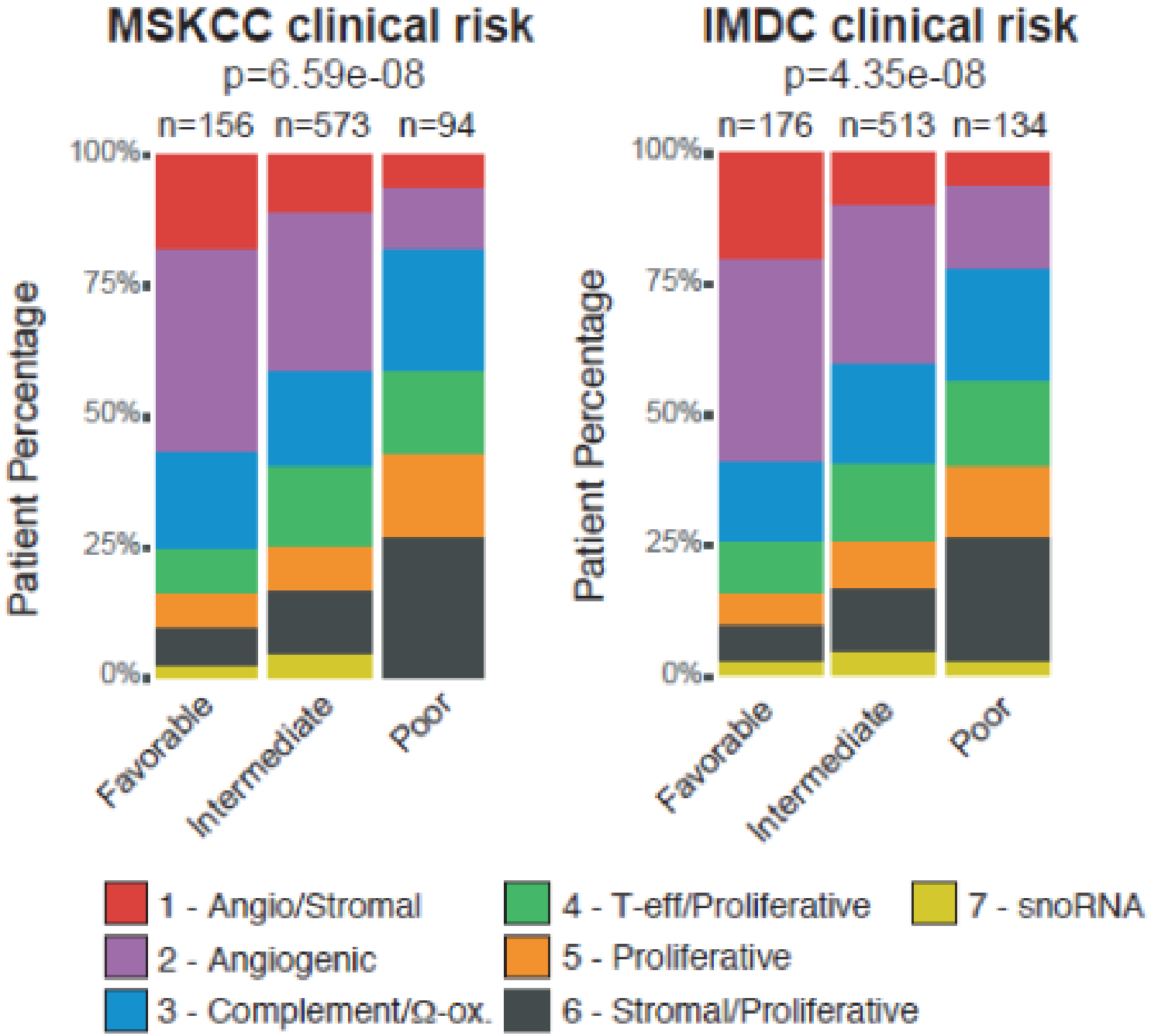
Algorithm for Front-line RCC Rx- Atkins 2024*



*No role for IMDC classification in treatment selection; particularly avoid IO/TKI in Fav Risk pts

How to Move Forward?

- Predictive biomarkers for IO therapy
  - Focus on tissue from metastatic lesions in treatment naïve pts using pure IO regimens
- Focus on IO endpoints
  - Landmark PFS, OS, Durable response, TFS
- Develop regimens to overcome IO resistance mechanisms



Rini et al OPTIC RCC Trial

Motzer, Rini Atkins et al Cancer Cell 2020

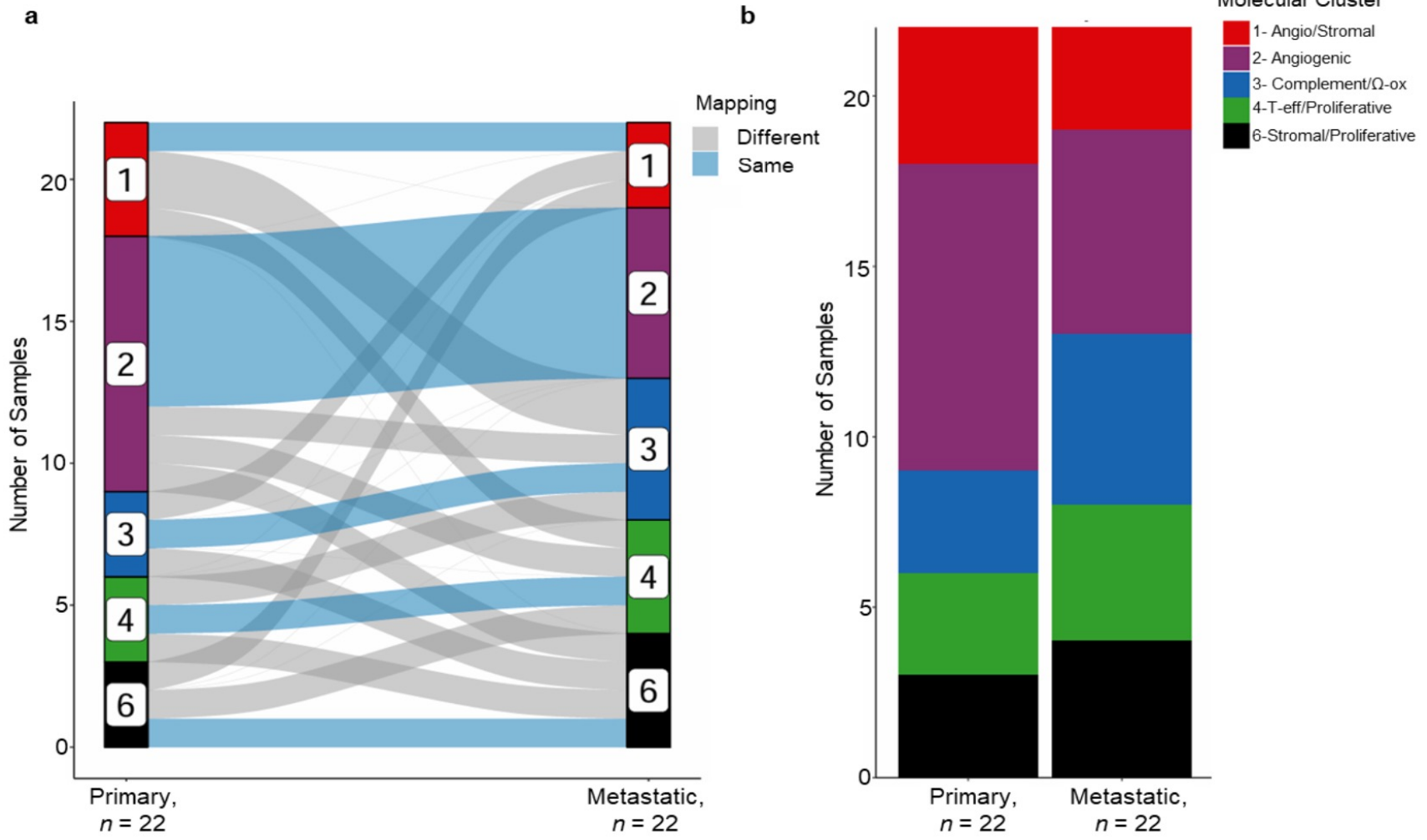
Clusters Applied to HCRN GU 16-260 Data

CL	N	IMDC: Fav (N,%) 21 pts	IMDC, Int (N,%) 44 pts	IMDC Poor (N,%) 5 pts		CR/PR (N,%) 28 pts	SD (N,%) 21 pts	PD (N,%) 21 pts		PFS (median, months)	PFS (1-year, %)
1	9	2 (9.5)	7 (15.9)	0 (0)		6 (66.7)	0 (0)	3 (33.3)		13.7	55.6
2	22	5 (23.8)	16 (36.4)	1 (20.0)		2 (9.1)	15 (68.2)	5 (22.7)		8.6	27.3
3	13	7 (33.3)	6 (13.6)	0 (0)		6 (46.2)	2 (15.4)	5 (38.5)		5.5	38.5
4	11	4 (19.0)	6 (13.6)	1 (20.0)		7 (63.6)	2 (18.2)	2 (18.2)		16.7	63.6
5	3	0 (0)	1 (2.3)	2 (40.0)		1 (33.3)	1 (33.3)	1 (33.3)		4.2	33.3
6	12	3 (14.3)	8 (18.2)	1 (20.0)		6 (50.0)	1 (8.3)	5 (41.7)		12.0	50.0

Clusters can enrich for (e.g Cluster 4), but do not fully predict for pure IO therapy efficacy

Zaemes, Signoretti, Atkins, Braun et al ASCO 2024

Mapping of molecular clusters for individual patients with matched primary and metastatic tumor biopsies



No strong correlation between Cluster Type in primary and met

Mets tend to be less angiogenic than their primaries

Zaemes, Signoretti, Atkins Braun ASCO 2024

Promising Biomarkers - Associated with Response or Resistance

Response:

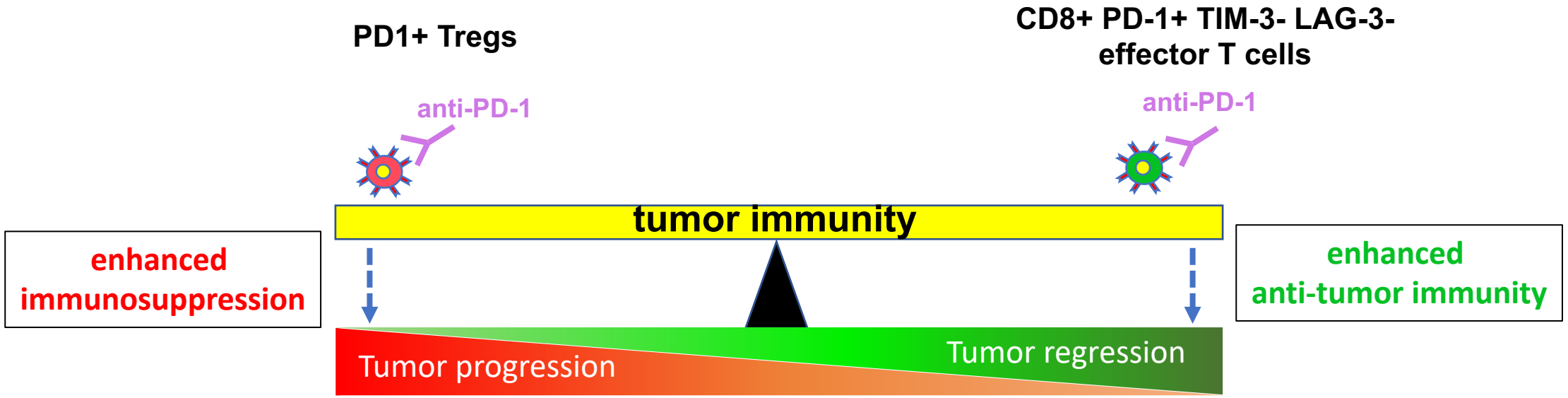
- TLS Signature (Braun, Atkins, Wu et al)
- PD-1^{+} LAG3^{-} Tim3^{-} CD8 T cells (Signoretti)

Resistance:

- *ZNF683*$^{+}$ SLAMF7^{+} CD8 T cells-scRNAseq (Braun et al)
- PD-1^{+} Treg numbers/ratio (Sharpe, Signoretti)

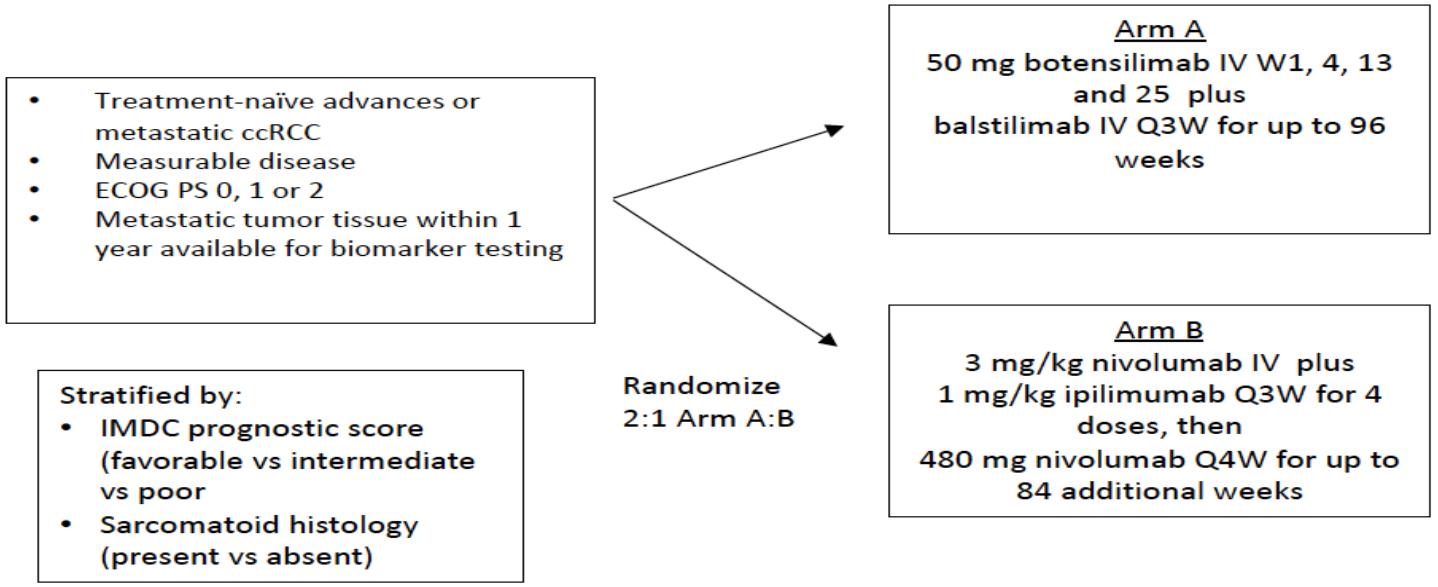
* “SLAMF7 Signaling Reprograms T Cells toward Exhaustion in the Tumor Microenvironment” O’Connell et al J Immunol 2021

PD-1 blockade on Tregs and non-terminally exhausted CD8+ T cells have opposite effects on tumor growth



Denize T, Signoretti S, Atkins MB (CCR Feb 2024)

Implications PD1+ Treg Data
ARCITeCT Schema- (HCRN GU22-587)



Current Status

- Open and accruing at almost all 13 sites (including Emory)
- Anticipate accrual to complete by 10/2025
- Metastatic tumor (FFPE) for analysis by Signoretti Lab
- Fresh biopsies of mets to be obtained at DFCI and G-LCCC sites for DOD grant and SPORE Project

Arm A: 80 subjects
Arm B: 40 subjects

Atkins, Serzan Co-PIs

Correlative Analyses:
Signoretti and Braun Labs
Supported by DOD Team Science Grant and DF/HCC SPORE Grant

Further Impliations of Data

CD8+PD1+TIM3-LAG3- TIL data creates a rationale for studying anti-LAG3 + anti-PD1 (+/- anti-CTLA-4) in patients with ccRCC

a) Nivo/(Ipi) + Relatlimab vs Nivo/Ipi (KCRS Consortium)

b) Cemiplimab/fianlimab (+/- anti-CTLA-4) vs Nivo/ipi (HCRN)

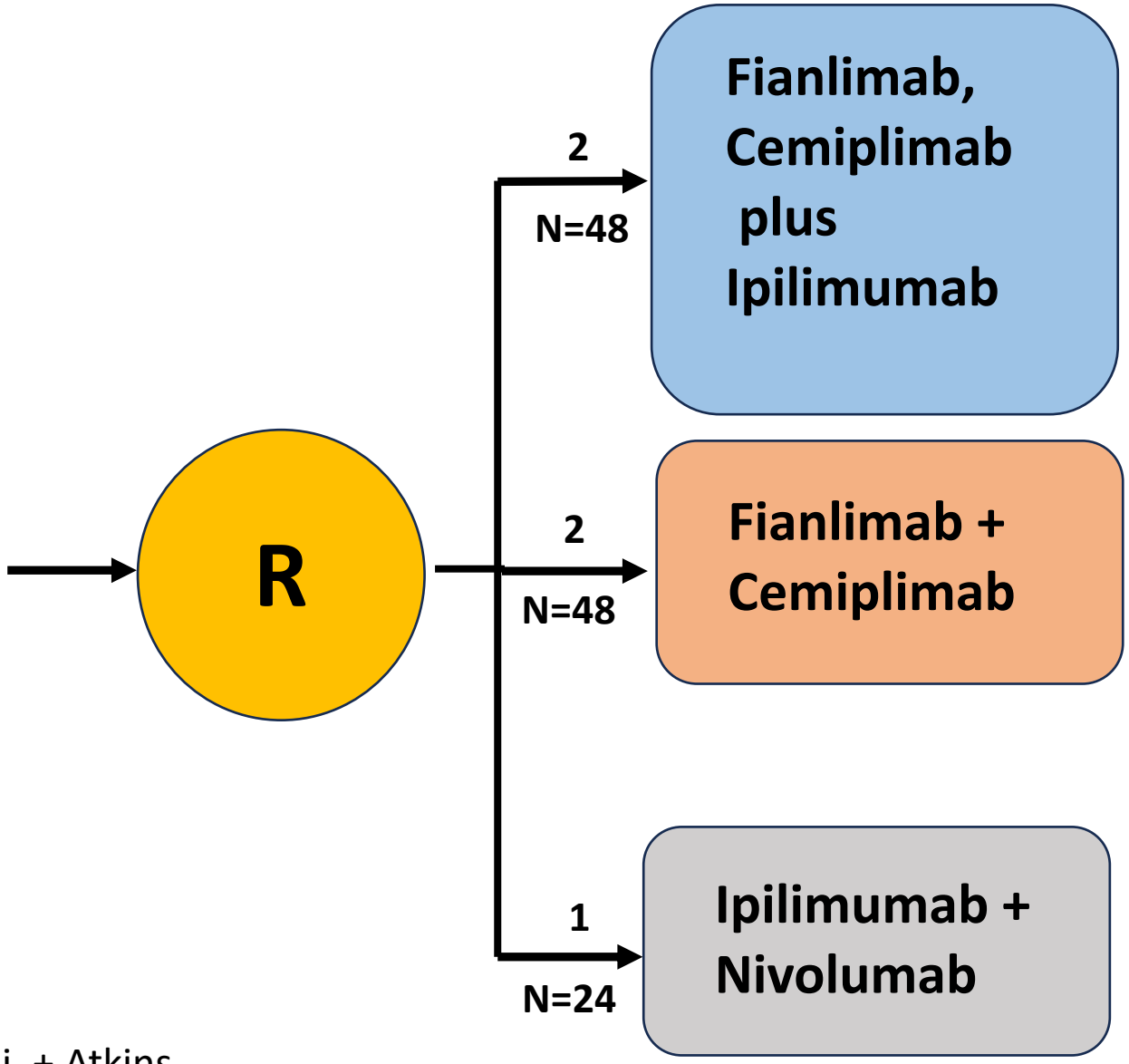
A Randomized Phase 2 Trial of Fianlimab, Cemiplimab plus Ipilimumab and Fianlimab/Cemiplimab vs. Ipilimumab/Nivolumab in first-line advanced RCC

Main inclusion criteria:

- Advanced renal cell carcinoma having a clear cell component
- No prior systemic therapy for renal cell carcinoma
- Karnofsky performance status ≥ 70%
- Measurable disease by RECIST1.1
- Adequate organ function

Main Exclusion Criteria

- Prior systemic therapy in the neo/adjuvant or metastatic setting
- Any autoimmune condition requiring ≥ 10 mg prednisone equivalent/day
- Active CNS metastasis



Primary Endpoint:

Objective Response Rate

HCRN GU23-651: Beckerman, Rini, + Atkins

What to do in patients who don’t respond to front line immunotherapy?

Second-Line IO/TKI

Cabo ORR 40% in pts with no prior 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

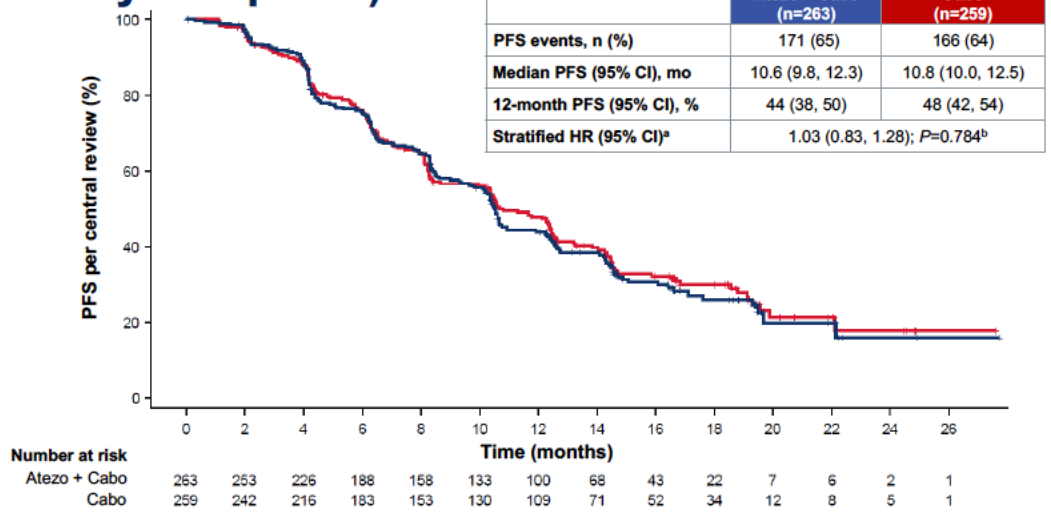
R 1:1

N=522

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

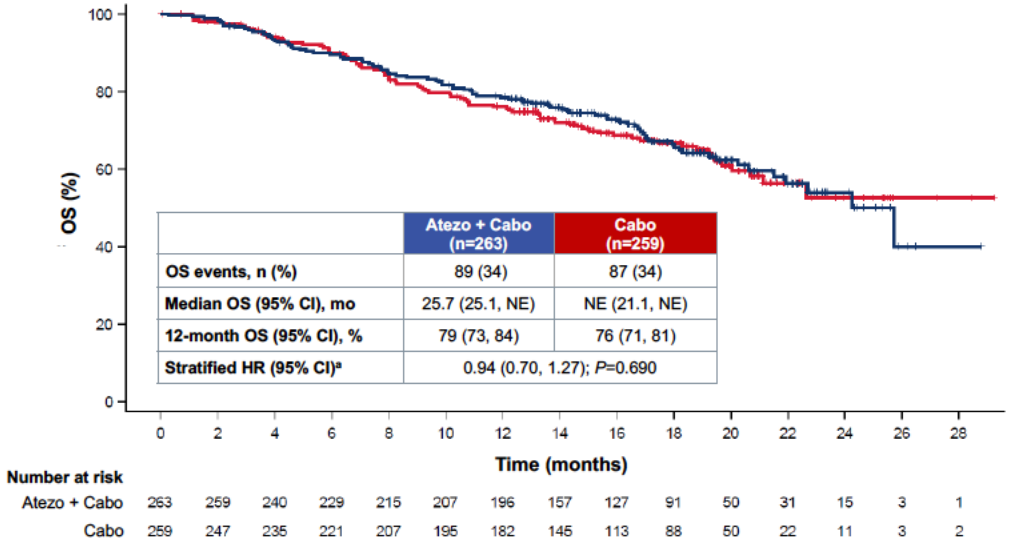
Primary analysis of centrally reviewed PFS (primary endpoint)

	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

Second-Line IO/TKI

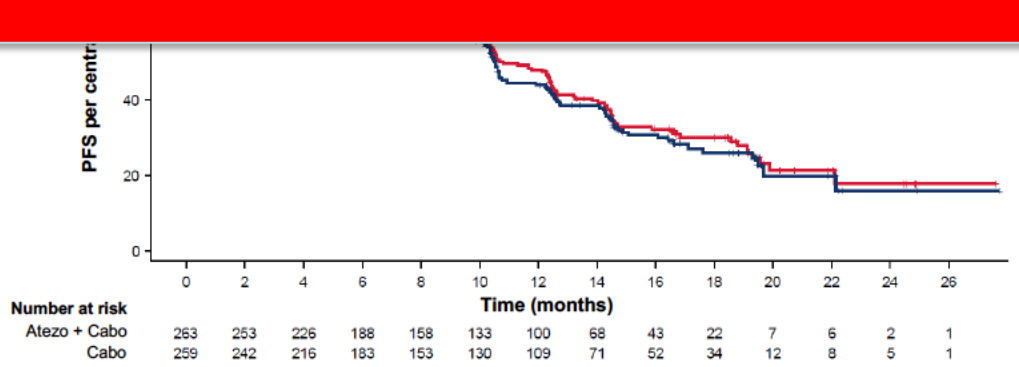
Phase III CONTACT-03 study

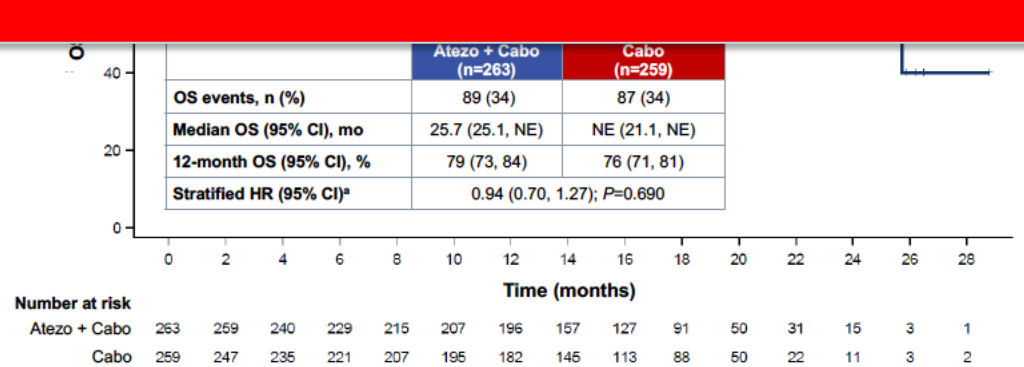
Key eligibility criteria

- Advanced/metastatic clear cell or non–clear cell[a] RCC with or without a sarcomatoid component

Atezolizumab 1200 mg IV q3w + Cabozantinib 60 mg daily PO

Phase III Ti-Nivo2 trial similarly failed to show benefit for IO/TKI vs TKI in previously treated patients with metastatic ccRCC
Aveo Press Release 7/10/24





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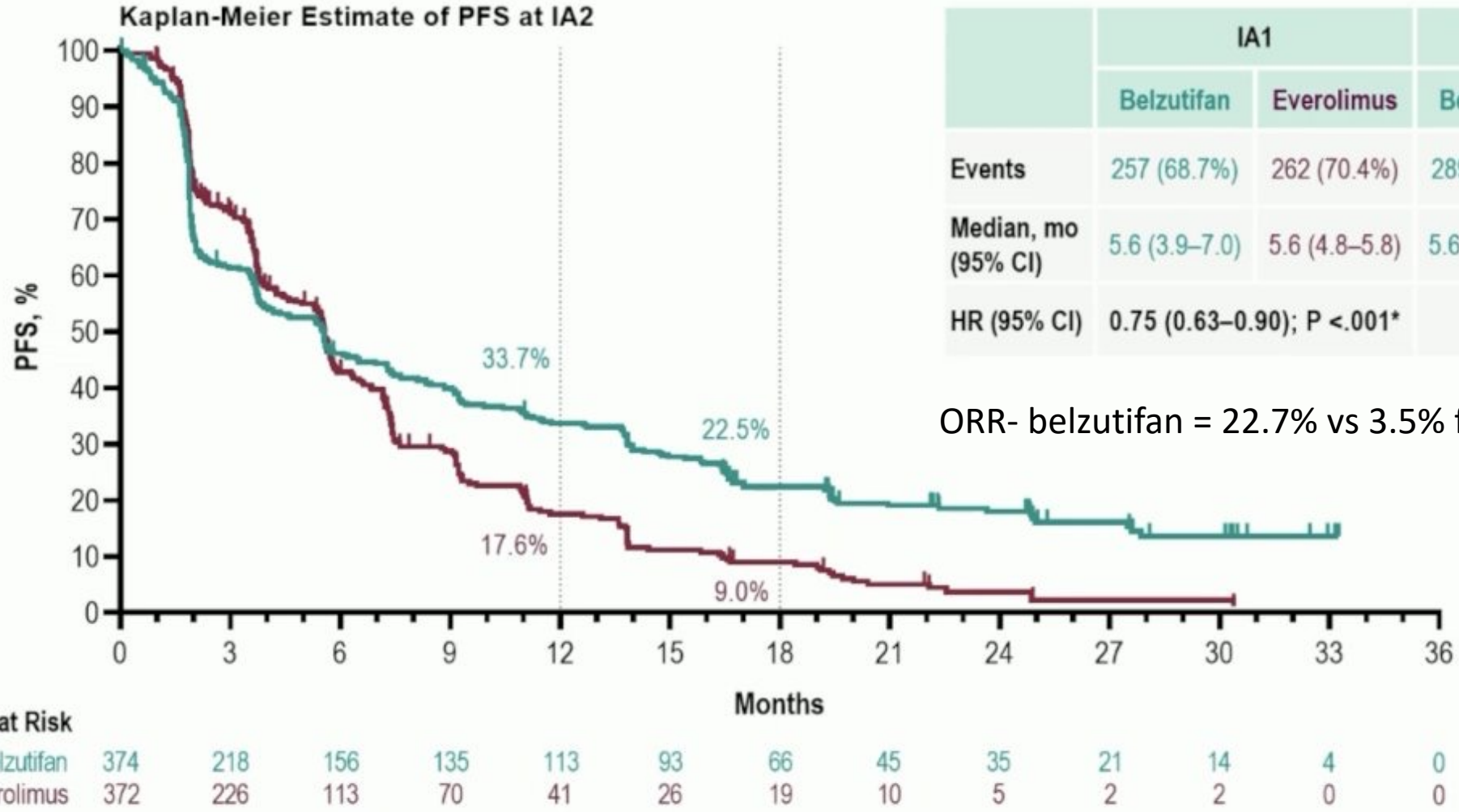
Choueiri et al ASCO 2023

LiteSpark 005: Phase III Trial of belzutifan vs everolimus in IO and TKI resistant metastatic RCC

Primary Endpoint: PFS per RECIST 1.1 by BICR



	IA1		IA2	
	Belzutifan	Everolimus	Belzutifan	Everolimus
Events	257 (68.7%)	262 (70.4%)	289 (77.3%)	276 (74.2%)
Median, mo (95% CI)	5.6 (3.9–7.0)	5.6 (4.8–5.8)	5.6 (3.8–6.5)	5.6 (4.8–5.8)
HR (95% CI)	0.75 (0.63–0.90); P <.001*		0.74 (0.63–0.88)	

ORR- belzutifan = 22.7% vs 3.5% for everolimus

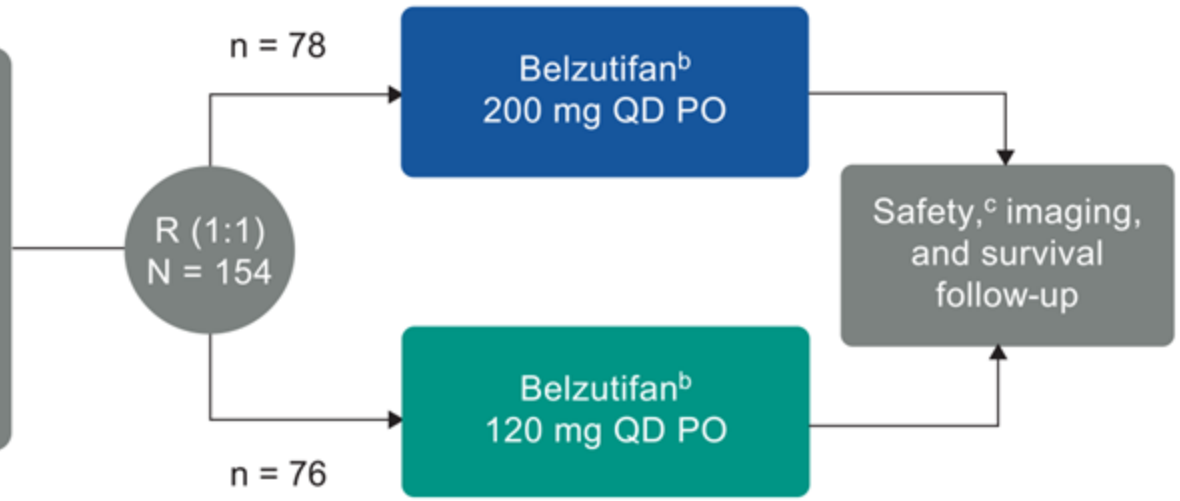
* denotes statistical significance. Primary PFS endpoint was met at IA1 and was not formally statistically tested at IA2. Data cutoff date for IA1: November 1, 2022. Data cutoff date for IA2: June 13, 2023.

Albiges et al ESMO 2023 Annals of Oncology

LITESPARK-013 Study Design

Key Eligibility Criteria

- Histologically confirmed advanced/metastatic RCC with clear cell component
- Measurable disease per RECIST v1.1
- Received ≤3 prior systemic therapies for advanced or metastatic disease
- Received only 1 prior anti−PD-(L)1 therapy[a]

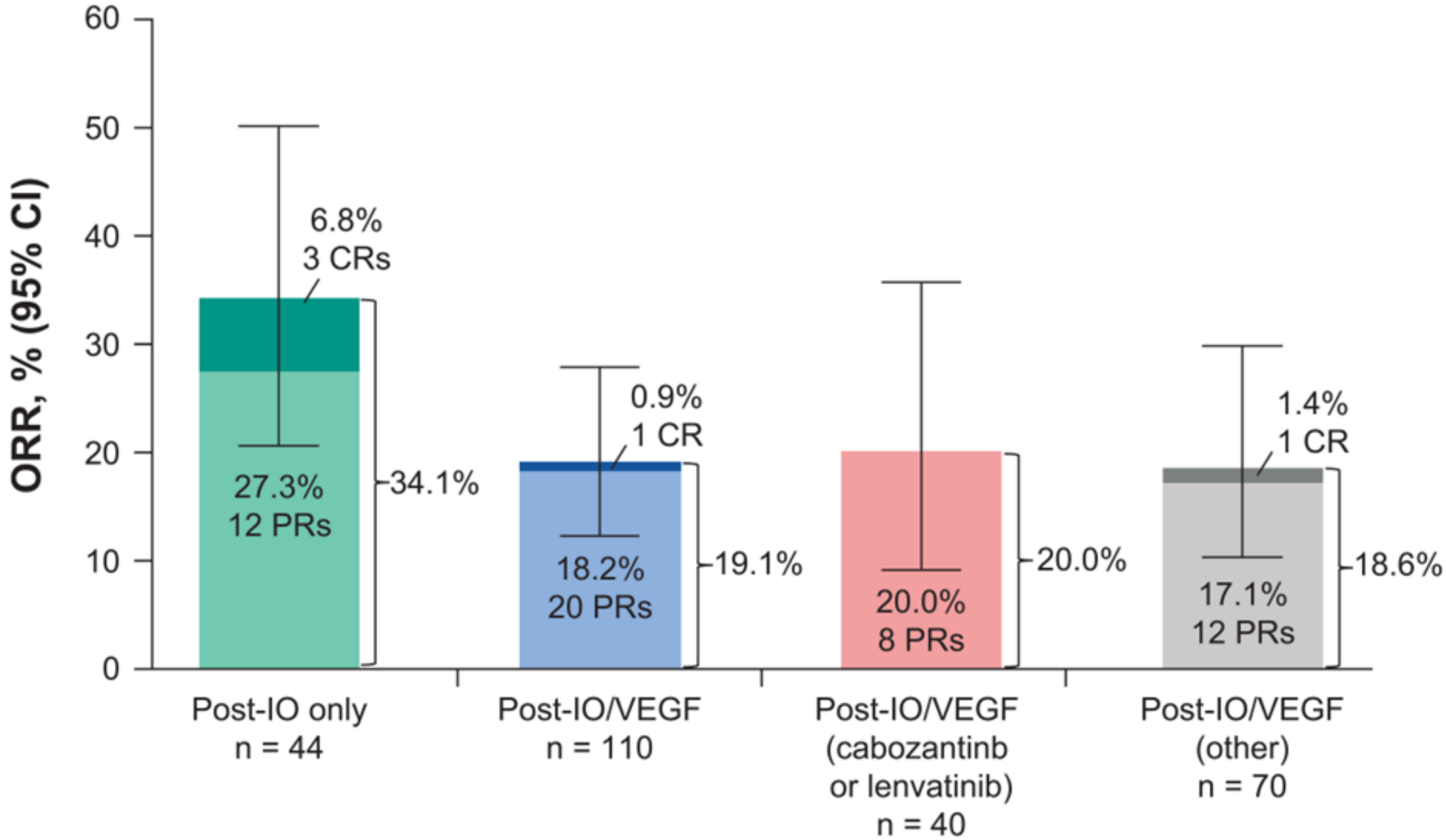


Stratification Factors

- IMDC prognostic scores (0 vs 1 or 2 vs 3-6)
- Number of prior TKI regimens for advanced RCC (0 vs 1 vs 2 or 3)

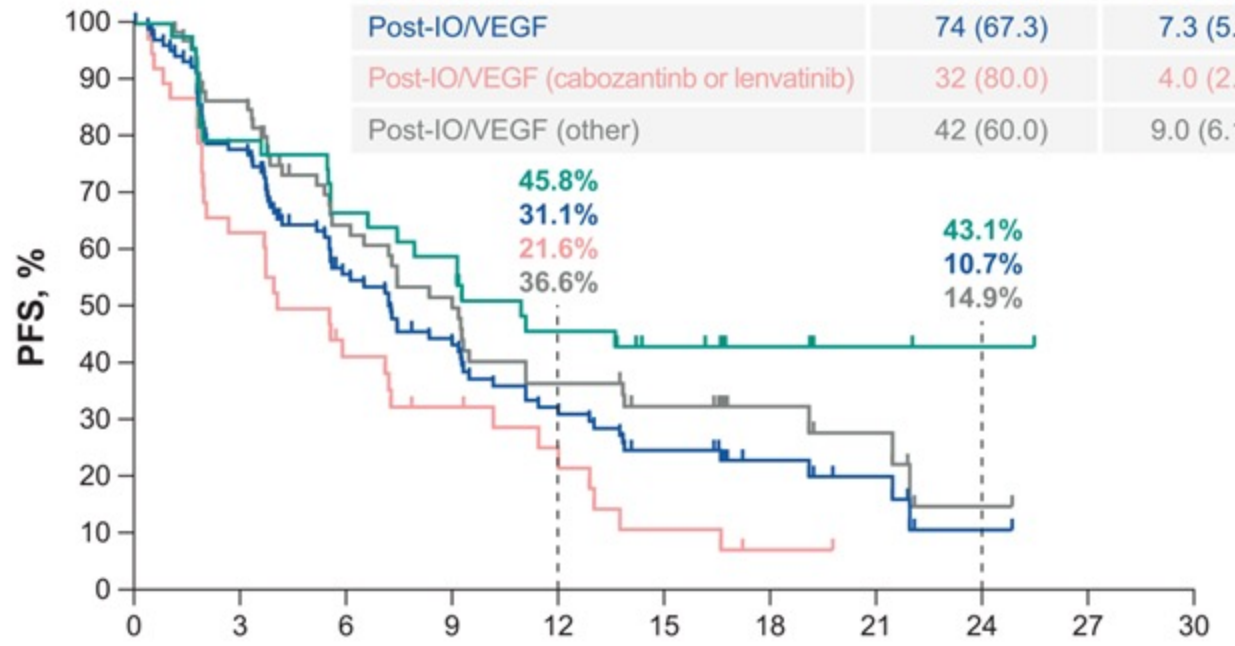
PD, progressive disease; PO, by mouth; R, randomization.
[a]Applicable to patients who were enrolled under protocol amendment 01.
[b]Treatment continued until documented radiographic PD per RECIST v1.1, unacceptable toxicity, or patient withdrawal from the study.
[c]Patients who discontinued study treatment for reasons other than PD continued with imaging assessments per the protocol-defined schedule until PD, initiation of a new anticancer treatment, death, pregnancy, withdrawal of consent, study conclusion, or early termination, whichever occurred first.

Confirmed ORR per RECIST v1.1 by BICR in the Pooled Population by Prior Regimen



Kaplan-Meier Estimates of PFS per RECIST v1.1 by BICR in the Pooled Population by Prior Regimens

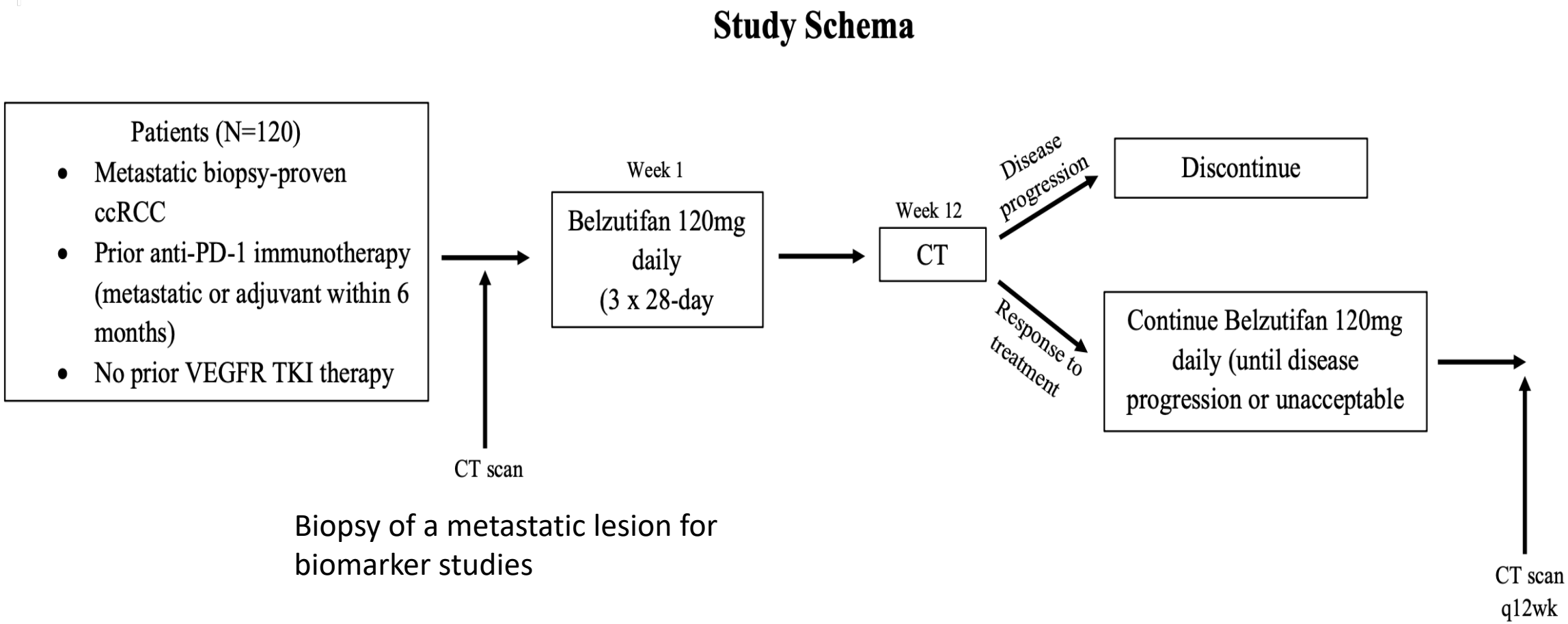
	Progression or death, n (%)	PFS, median (95% CI), months
Post-IO only	23 (52.3)	10.9 (6.6-NR)
Post-IO/VEGF	74 (67.3)	7.3 (5.5-9.3)
Post-IO/VEGF (cabozantinb or lenvatinib)	32 (80.0)	4.0 (2.0-7.3)
Post-IO/VEGF (other)	42 (60.0)	9.0 (6.1-11.1)



No. at risk

44	32	26	23	17	11	5	2	1	0	0
110	78	50	38	25	18	8	5	1	0	0
40	24	14	10	6	3	1	0	0	0	0
70	54	36	28	19	15	7	5	1	0	0

Proposed Belzutifan in TKI Naïve Biomarker Trial- HCRN GU Group



PIs: Atkins and Sackstein

Summary/Conclusions

- No role for IMDC classification in treatment selection
- Improvements in RCC cure rates will require building on an pure IO backbone and adding treatments that enhance tumor specific immune response
- Biomarker studies should use metastatic lesions and link to IO endpoints
- Treatments in IO resistant pts should consider therapeutic index and titrate treatment to patient symptoms

Our goal should not be simply to turn cancer into a chronic disease…

We should strive to make cancer a curable disease

Using agents/combinations as first line treatment that maximize the anti-tumor immune response (and don't compromise the efficacy of subsequent therapy) is critical to achieving that goal

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