Sequencing of Therapies and Novel Agents in Metastatic Renal Cell Cancer

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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, Neoleukin, Sanofi, COTA, Idera, Apexigen, Iovance

Advisory Boards:

Eisai, Novartis, Pfizer, Genentech/Roche, Merck, BMS, Pyxis Oncology, Werewolf, Fathom, Pneuma, Leads, X4 Pharma, ValoHealth, Surface, Simcha, Takeda, ScholarRock, Elpis, SAB Bio, OncoRena

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

Stock Options: Werewolf, Pyxis Oncology, Elpis

Other: UpToDate: Melanoma Section Editor

Case - 64 yo man with RCC: History (1)

- 12/06 - Presented in with L sided back pain
  - CT scan showed 8.5 cm left renal mass
  - 1/2007- laparoscopic radical Nx- path RCC Fuhrman Grade 3.
- 1/18 – Surveillance CT showed 4.5 cm mass in left renal bed
  - metastasectomy, distal pancreatectomy and splenectomy
  - Path RCC with + resection margins
- 7/19 - CT showed new hepatic metastases- Largest 5.9cm.
  - RP nodes;
  - Omental mass 16.3 x 5.2 cm;
  - pelvic mass-6.3 cm

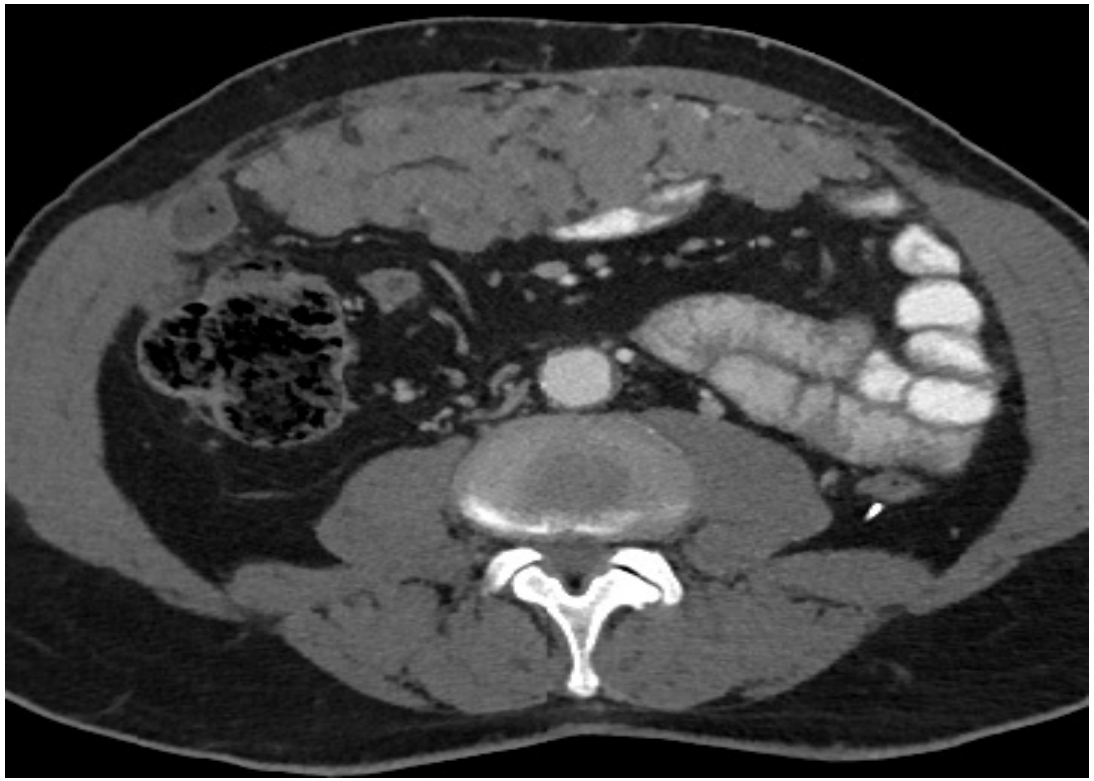
Despite the large extent of disease, patient is IMDC Favorable Risk

History (2)

- 9/19- Treated with axitinib + pembro
- Treatment associated with
  - > 50% reduction in tumor volume
  - HTN, diarrhea, dry cough
- 1/21 Presented with headaches and visual problems.

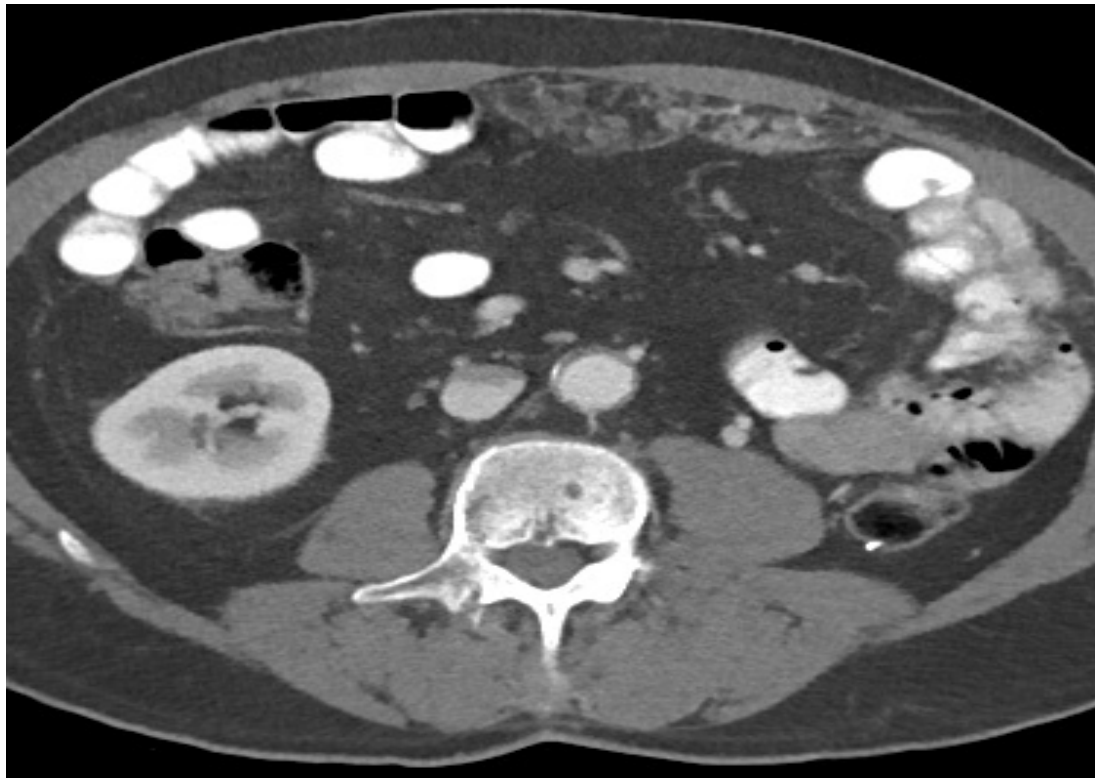
Omental Mass

Baseline Sept 2019



16.3 x 5.2cm

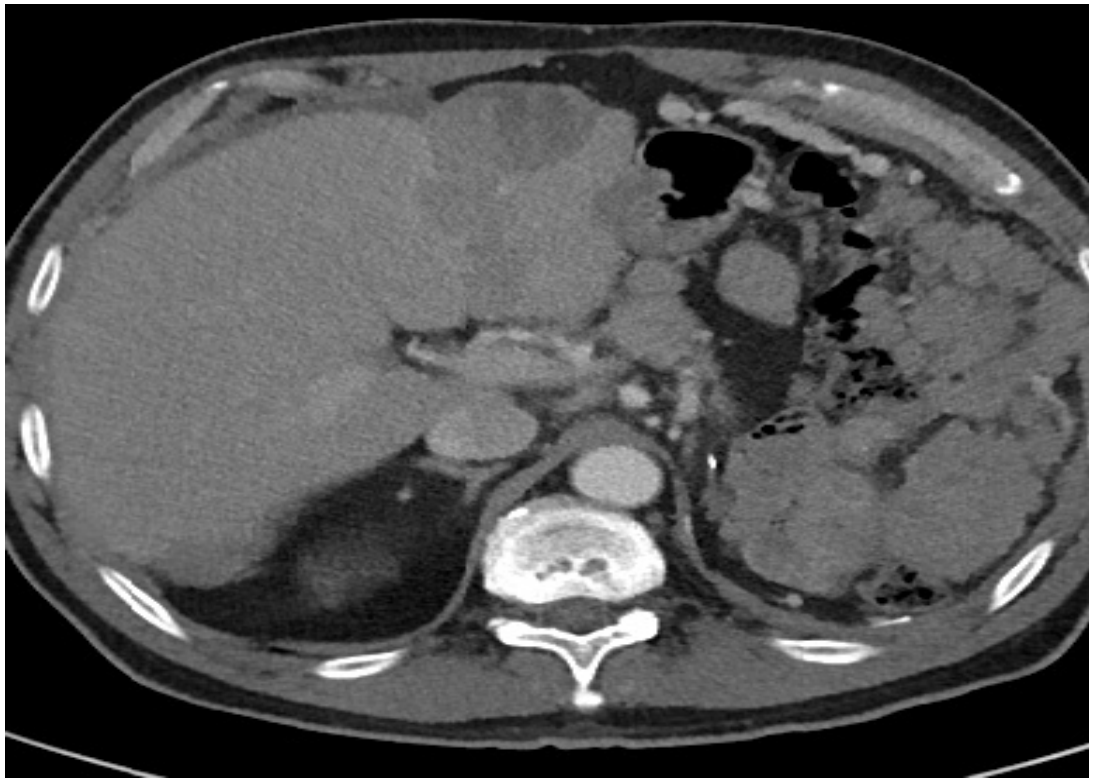
Best Response Dec 2020



8.4 x 2.5cm

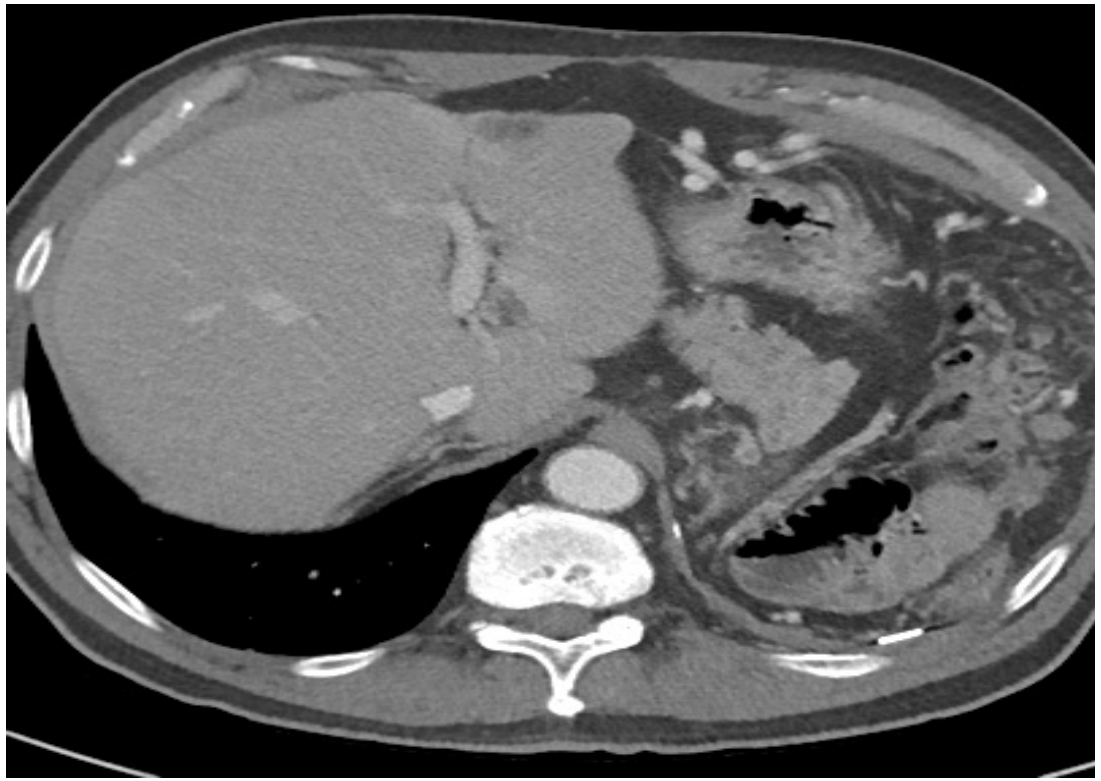
Subcapsular lesion/ LUQ Mass

September 2019



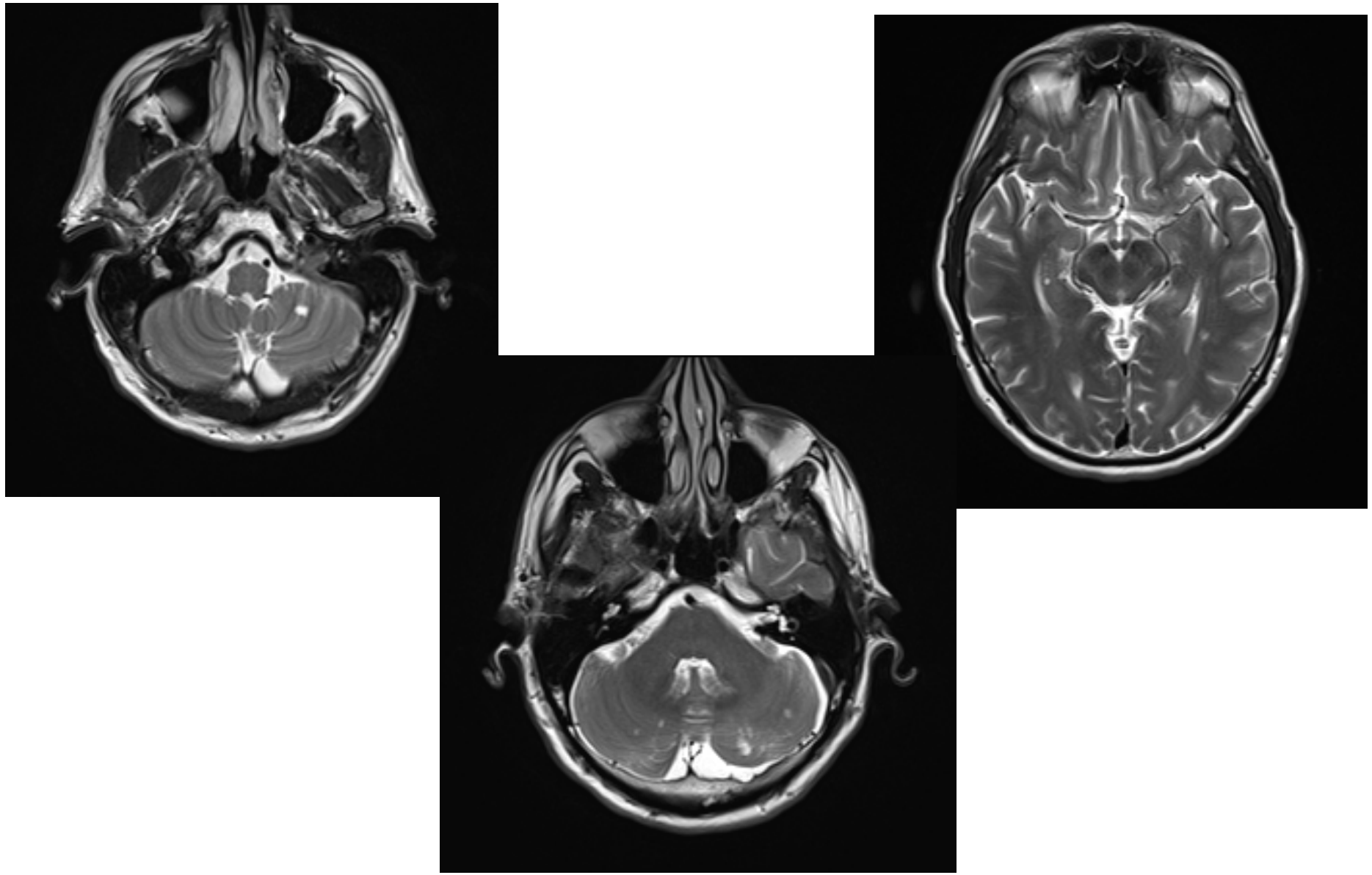
Subcapsular lesion 4.9 x 3.3cm
LUQ mass 5.9 x 3.9cm

December 2020



Segment 3 lesion 1.9 x 1.2cm
LUQ mass 2.4 x 1.5cm

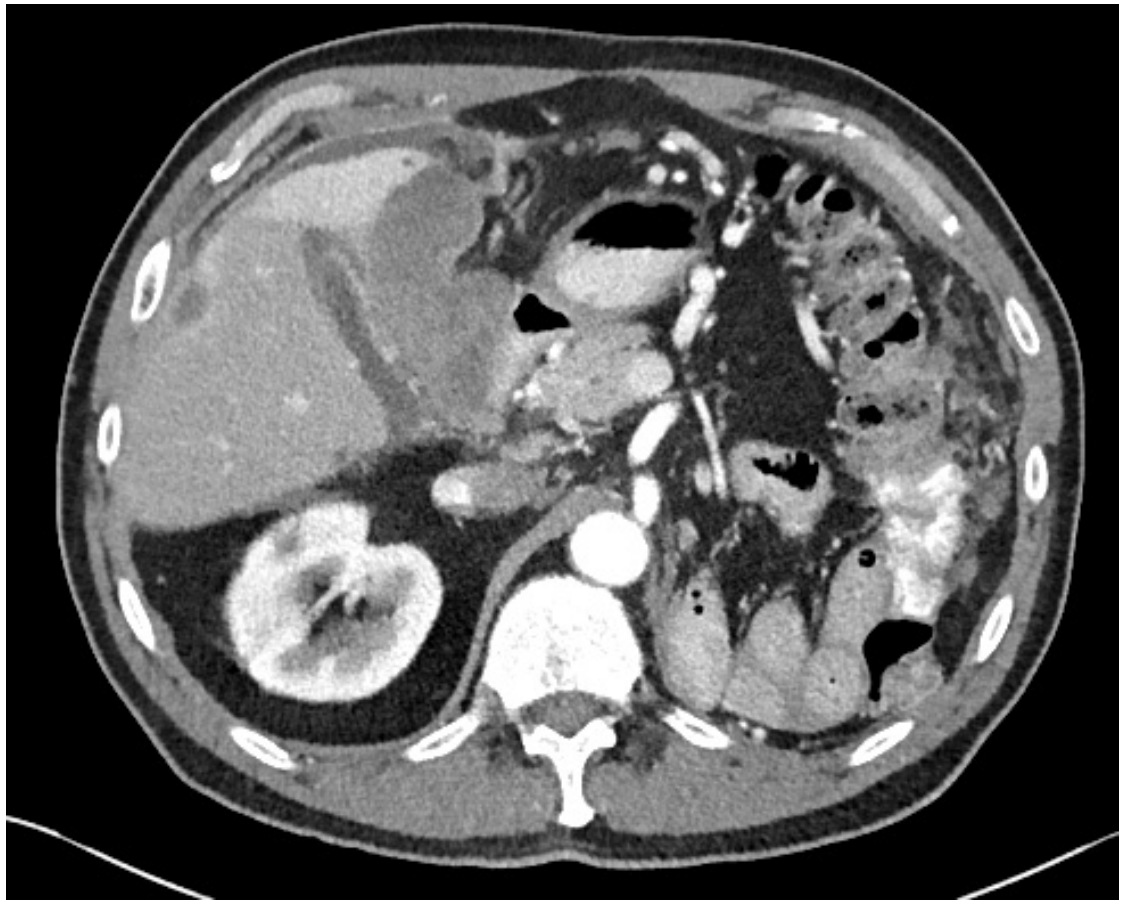
CVA 1/4/21



History (3)

- 1/5/21: Axitinib was held and patient started on Xarelto
- 1/19/21: CT scans showed rapid progression of liver metastases with new lesions and peritoneal carcinomatosis.

New Liver lesions Jan 2021



Segment 4 lesion 8.7 x 4.7cm

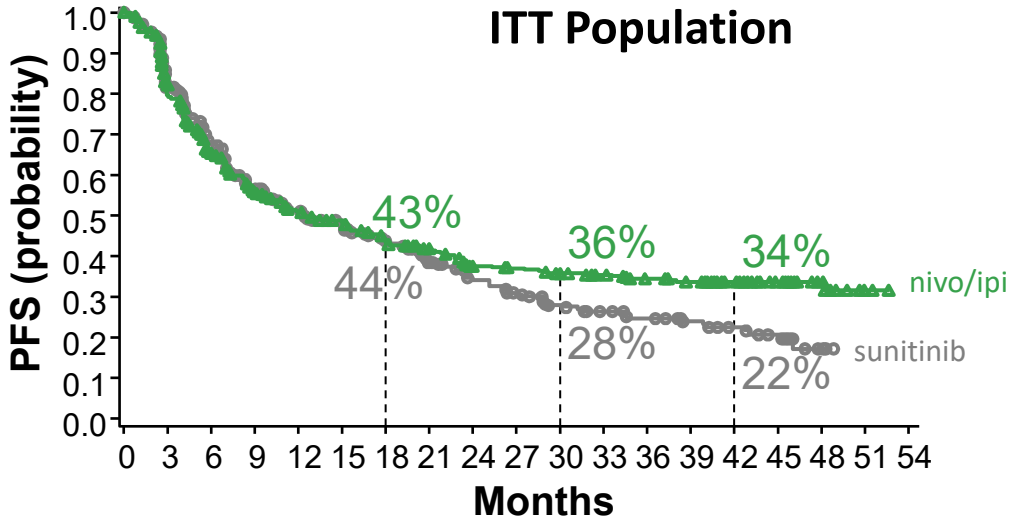
How would you manage this?

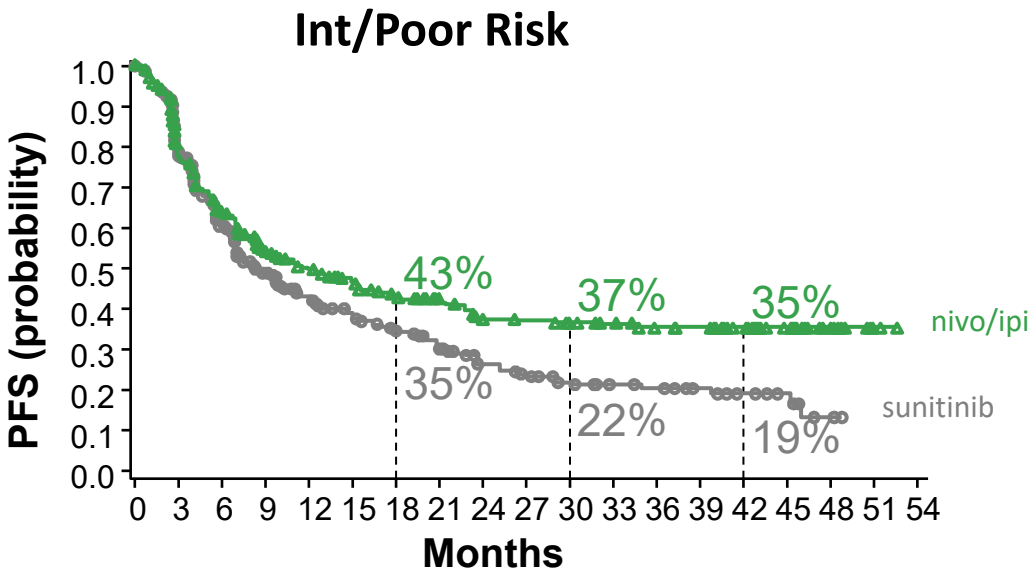
1. sunitinib/pazopanib
2. cabozantinib
3. lenvatinib/everolimus
4. tivozanib
5. resume axitinib
6. nivo monotherapy
7. nivo/ipi

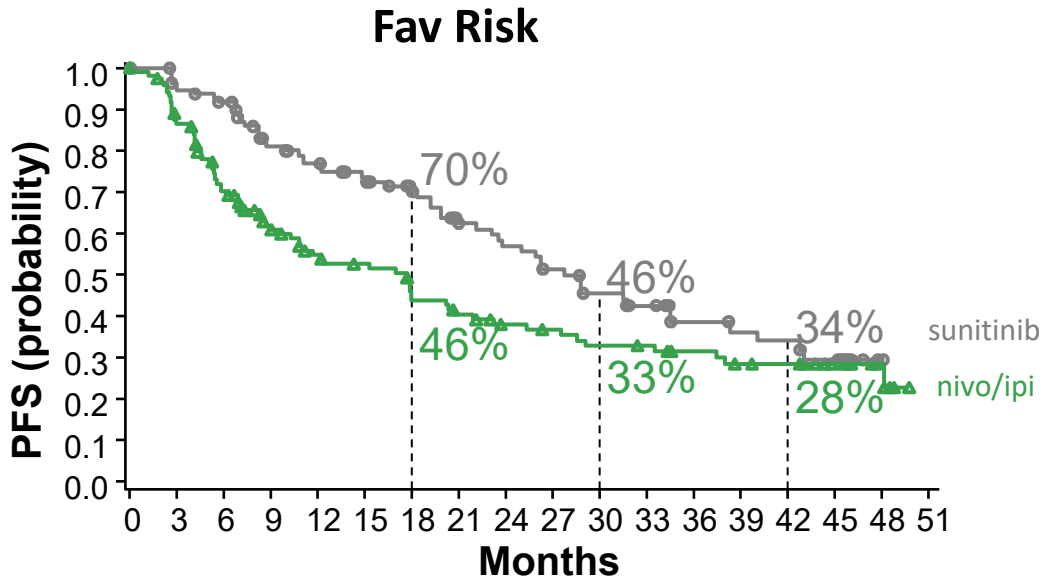
Outline

- Firstline Therapy
  - Options (IO/IO and IO/TKI)
  - Algorithm
- Second Line options after Nivo/ipi
  - Axi, Tivo, Cabo, Lenvatinib/everolimus
  - IO/TKI Studies
  - Principles/Approach
  - Novel Agents
    - Belzutifan
    - Axl Inhibitor

CM 214: PFS @ 42 Months Follow-up Data

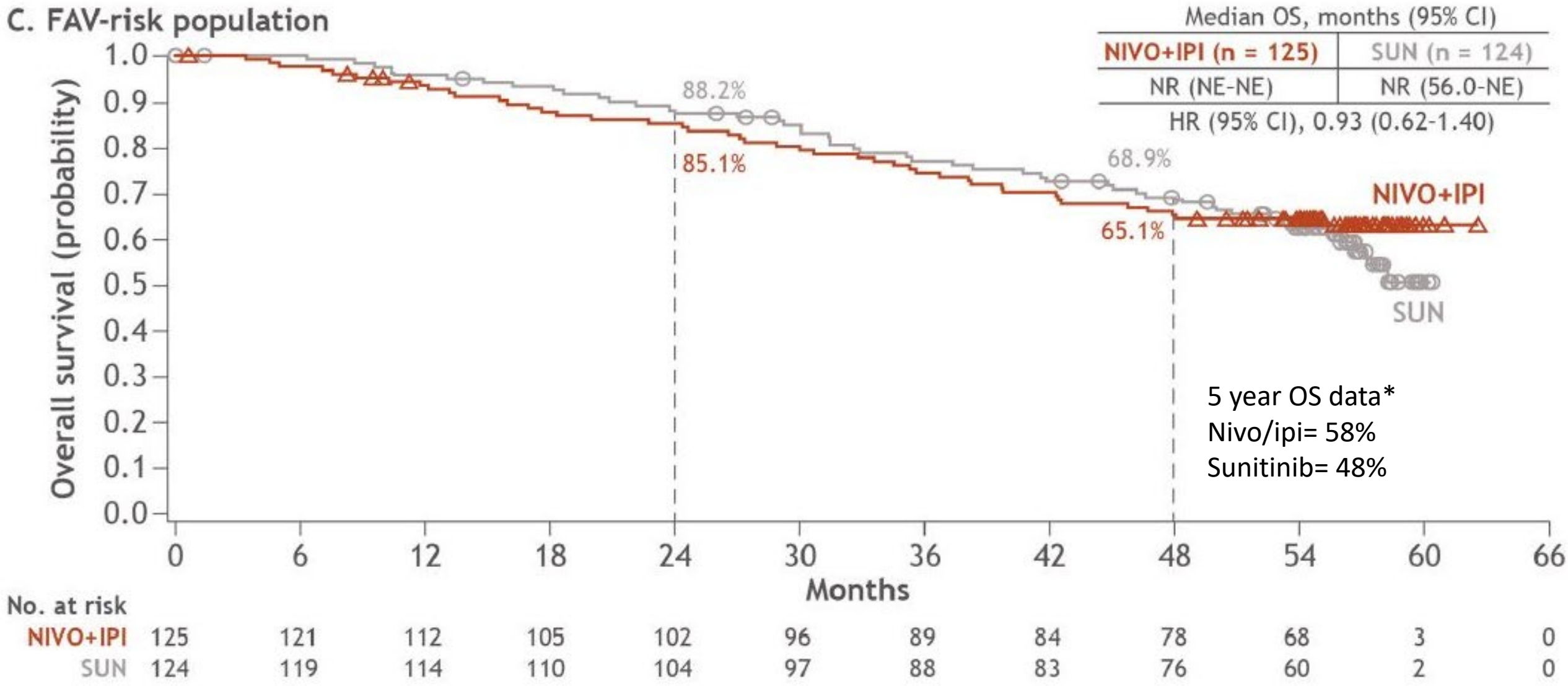






Tannir N et al. Presented at: ASCO GU 2020; February 13-15, 2020; San Francisco, CA. Abstract 609.

OS in Favorable Risk @ 4+ years



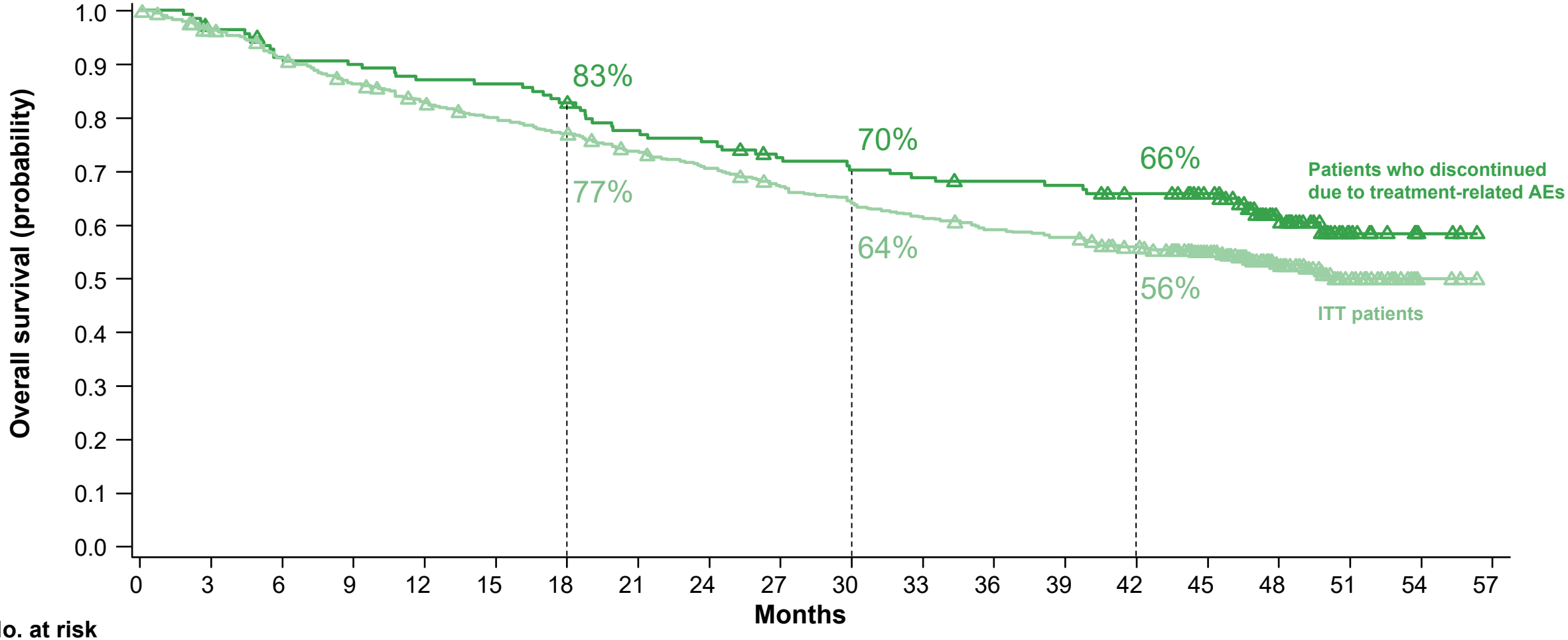
5 year OS data*
Nivo/ipi= 58%
Sunitinib= 48%

Albiges et al ESMO Open 2020

*Tannir et al IKCA 2021

OS in Patients Who Discontinued Due to Treatment-Related AEs

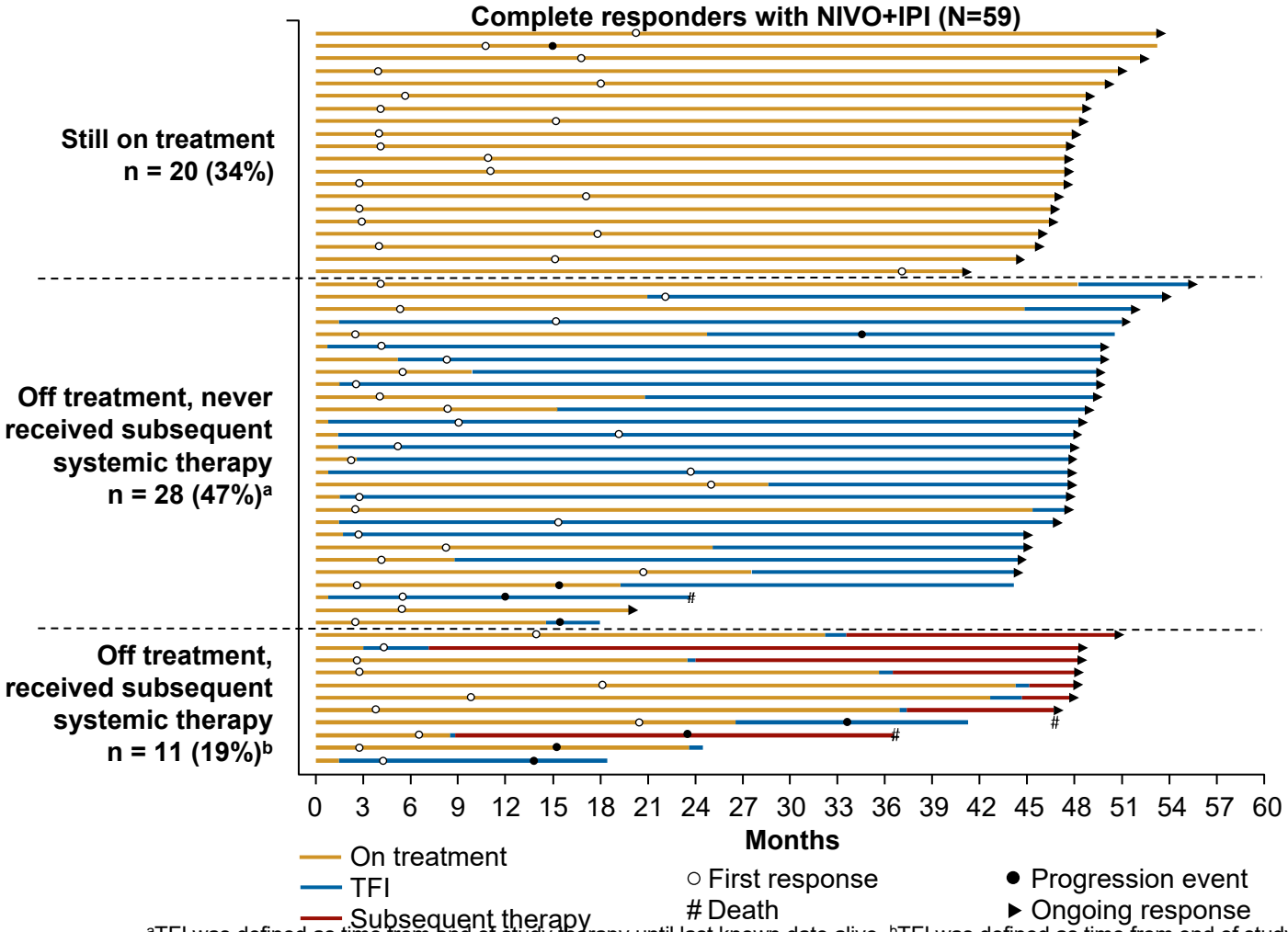
Post hoc analyses in the NIVO+IPI arm



No. at risk																			
Pts who discontinued	141	135	127	125	121	120	115	107	104	98	95	93	91	90	85	74	46	13	3	0
ITT Pts	550	523	493	465	444	426	411	390	372	353	337	323	309	302	286	241	135	49	3	0

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)

[a]TFI was defined as time from end of study therapy until last known date alive. [b]TFI was defined as time from end of study therapy until subsequent systemic therapy initiation. [c]75% of all responses occurred within 2.9 months among complete responders. [d]One additional patient was included in the calculation of ongoing response due to censoring (had not progressed per IRRC at the time of subsequent systemic therapy initiation).
Bar indicates time on treatment/TFI. Time zero corresponds to first treatment date.
TFI, treatment-free interval in patients who are off study treatment.

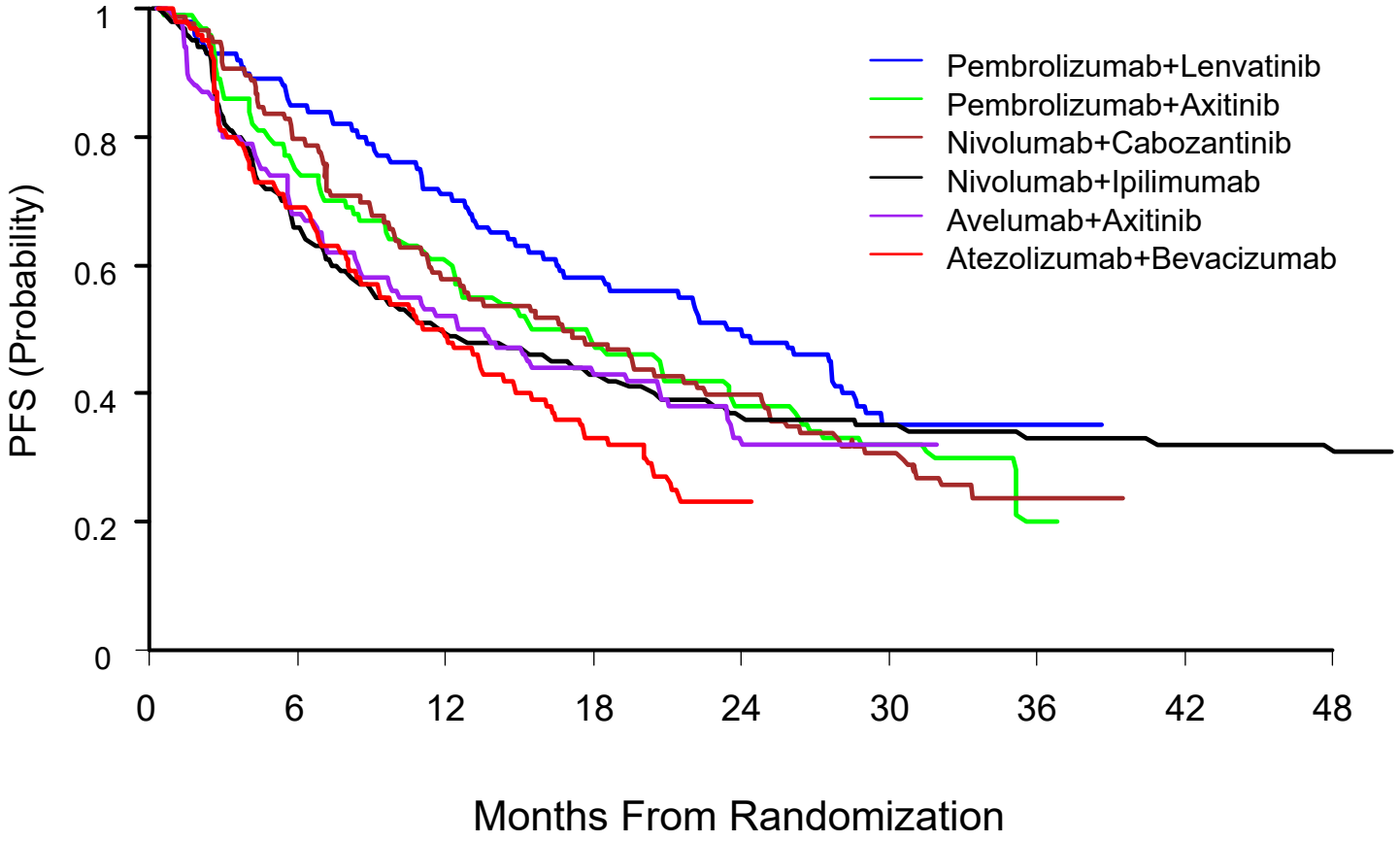
Tannir N et al. Presented at: ASCO GU 2020; February 13-15, 2020; San Francisco, CA. Abstract 609.

Phase III TKI/IO-based Combinations in RCC-Current Status

Control	Comparator(s)	Median Follow-up	PFS (HR)	OS (HR)
Sunitinib	Axitinib + Pembrolizumab[1,2*]	12.8 mo	Yes (0.69)	Yes (0.53)
		27.0 mo	Yes (0.71)	Yes (0.68)
Sunitinib	Bevacizumab + Atezolizumab[3]	15 mo	Yes (0.88)	No (0.93)*
Sunitinib	Axitinib + Avelumab[4]	10.8 mo	Yes (0.69)*	TE (0.78)*
Sunitinib	Cabozantinib + Nivolumab[5]	18.1 mo	Yes (0.51)	Yes (0.60)
Sunitinib	(Lenvatinib + Eve) vs *(*Len + Pembro)[6]	24 mo	Yes (0.39)	Yes (0.66)

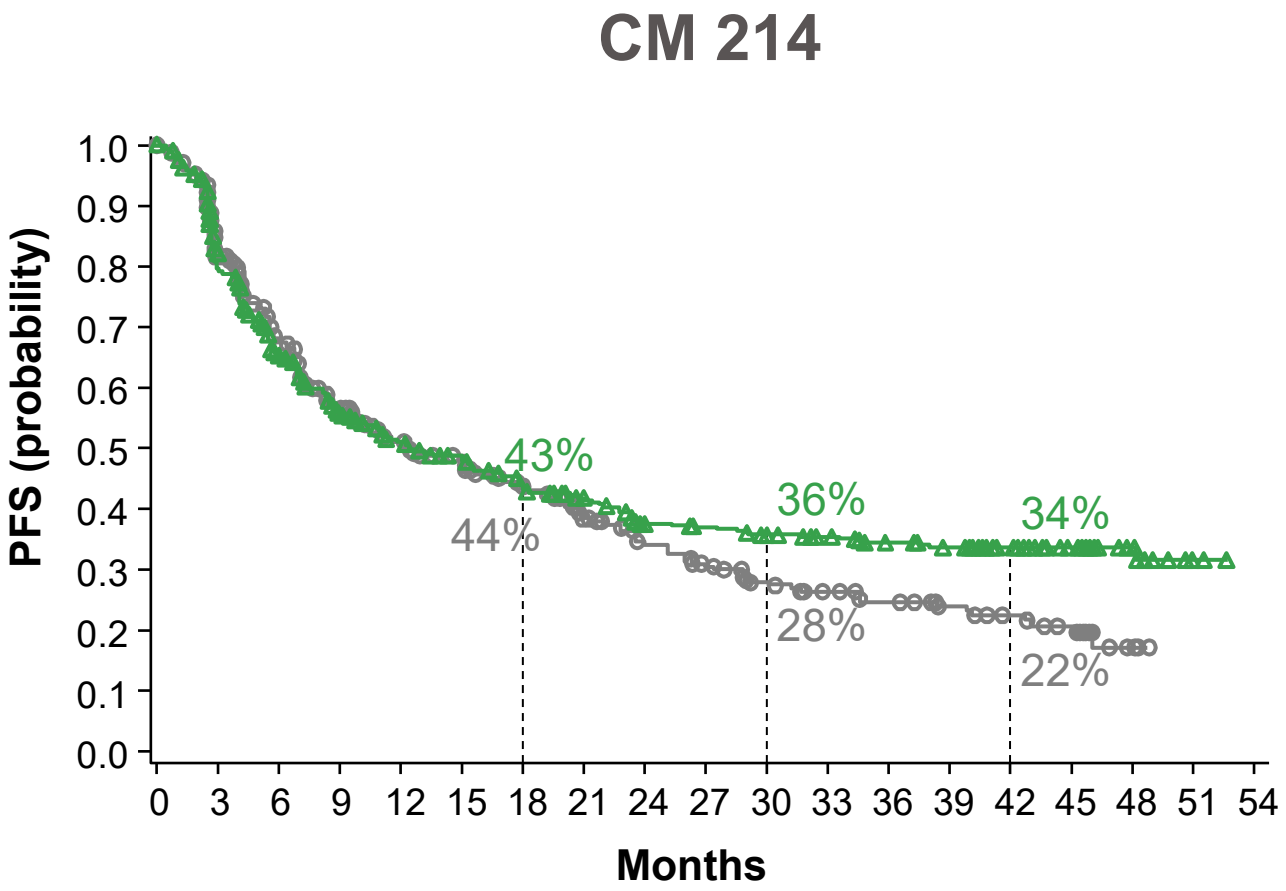
* ITT populations

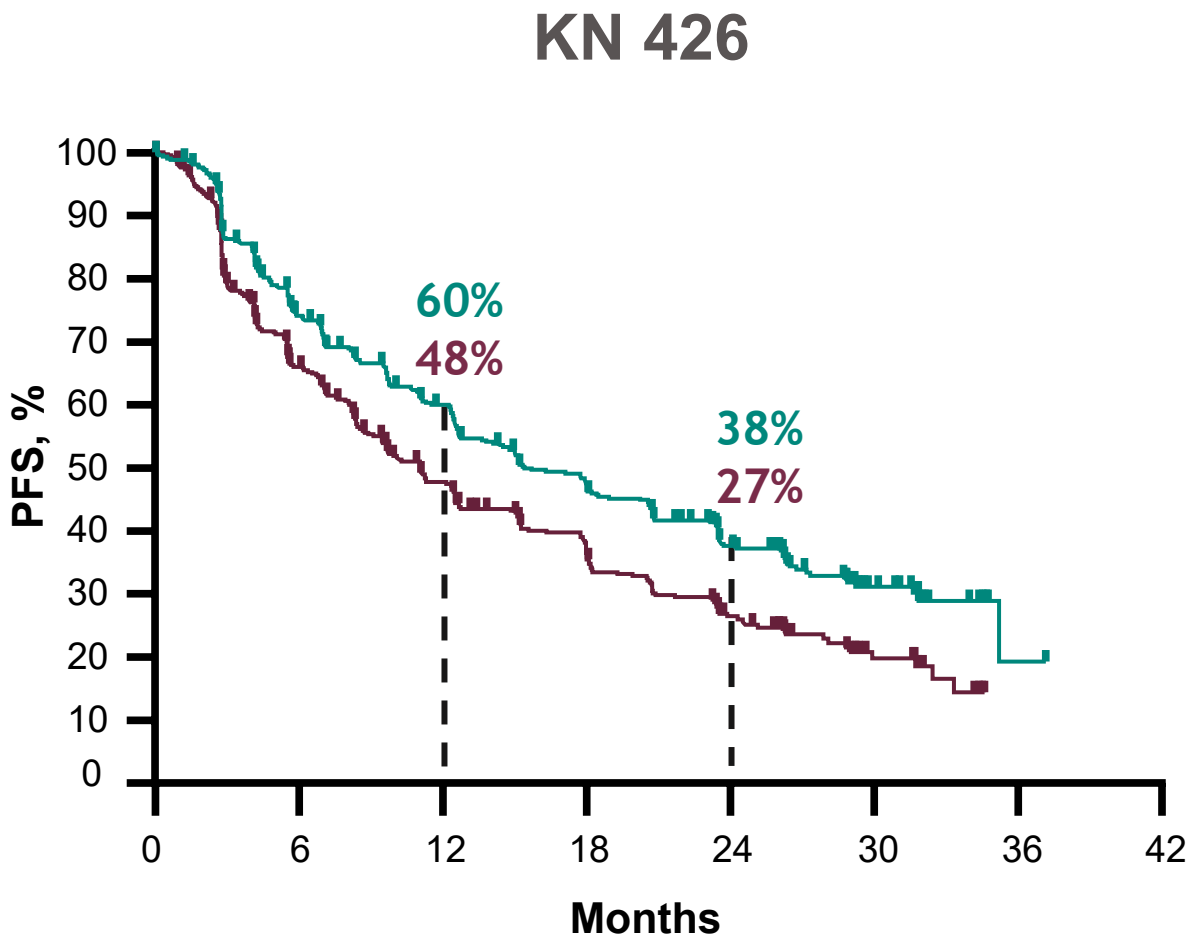
1L mRCC PFS: Phase III data



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

PFS Comparison: ITT Populations

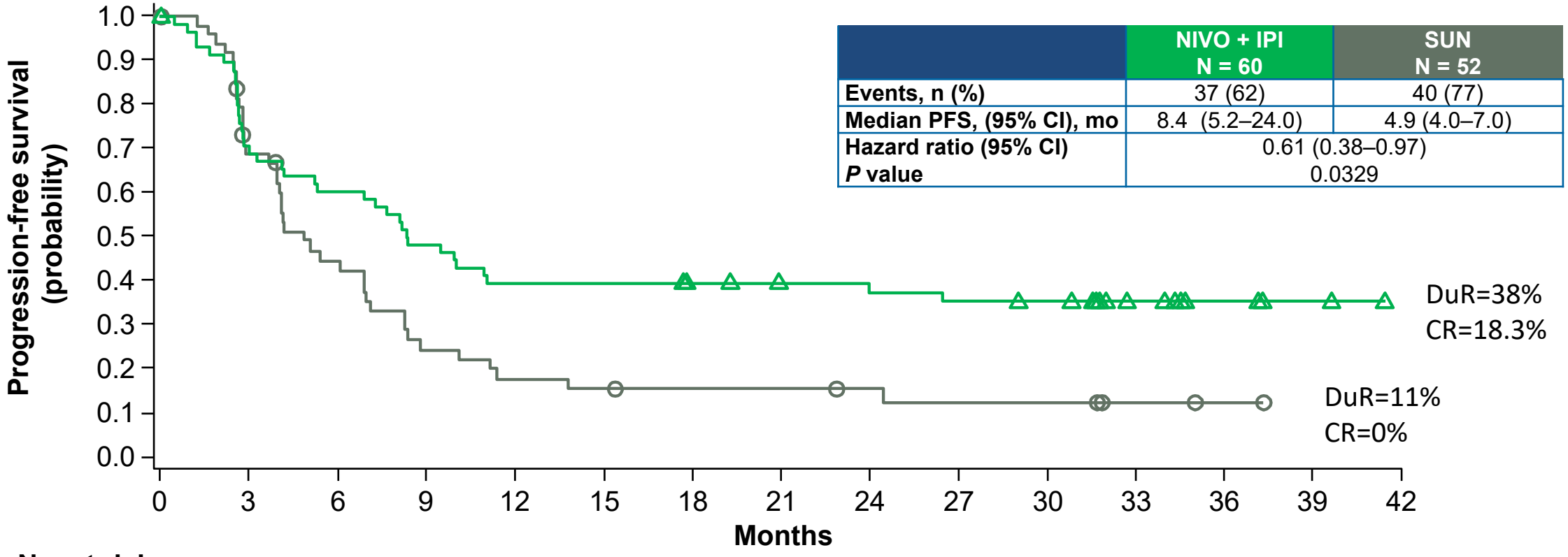




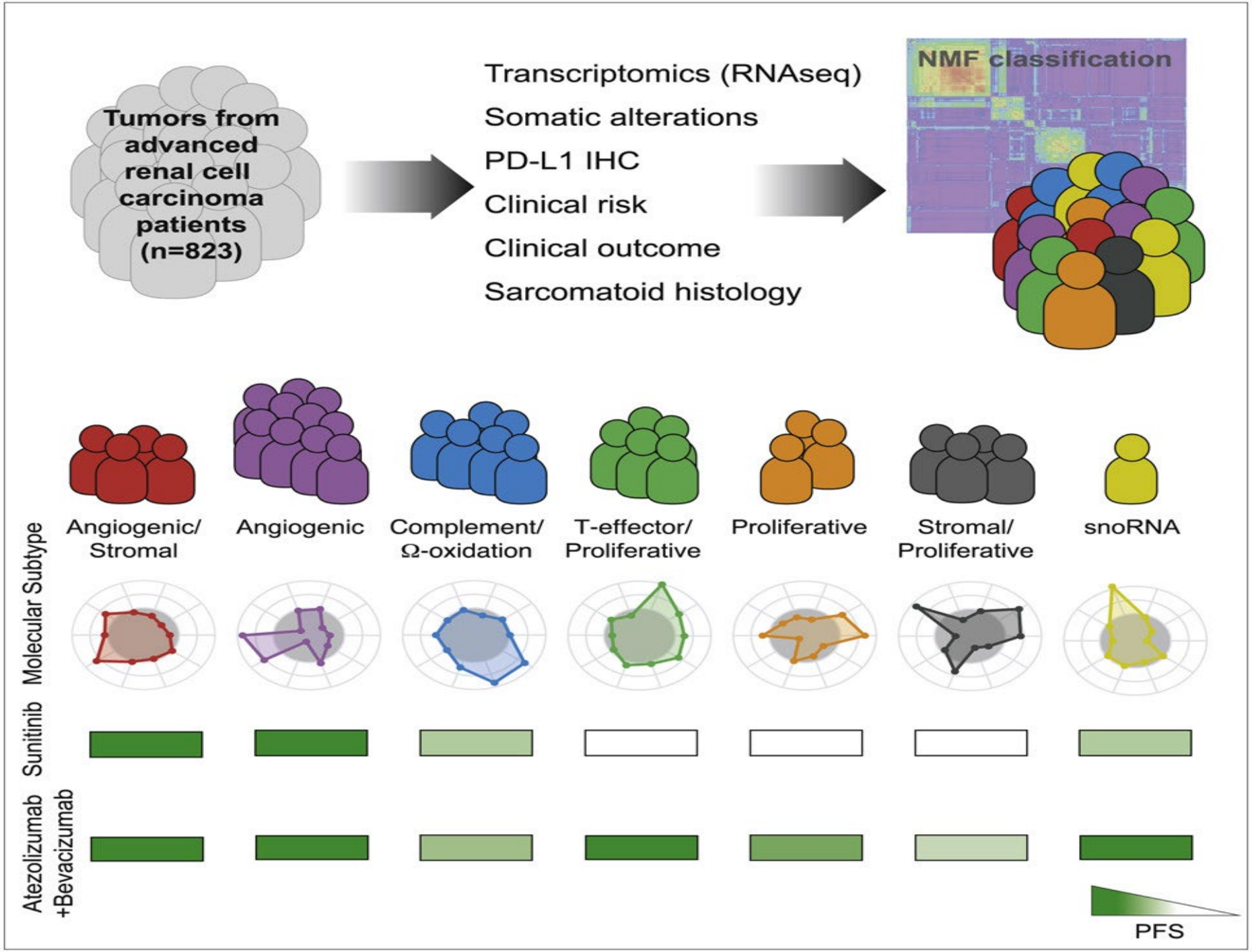
Tannir N et al. Presented at: ASCO GU 2020; February 13-15, 2020; San Francisco, CA. Abstract 609.
Plimack E et al. Presented at: ASCO 2020; May 29-31, 2020; Virtual Meeting. Abstract 5001.

PFS per Investigator: Intermediate/Poor-Risk Sarcomatoid Patients

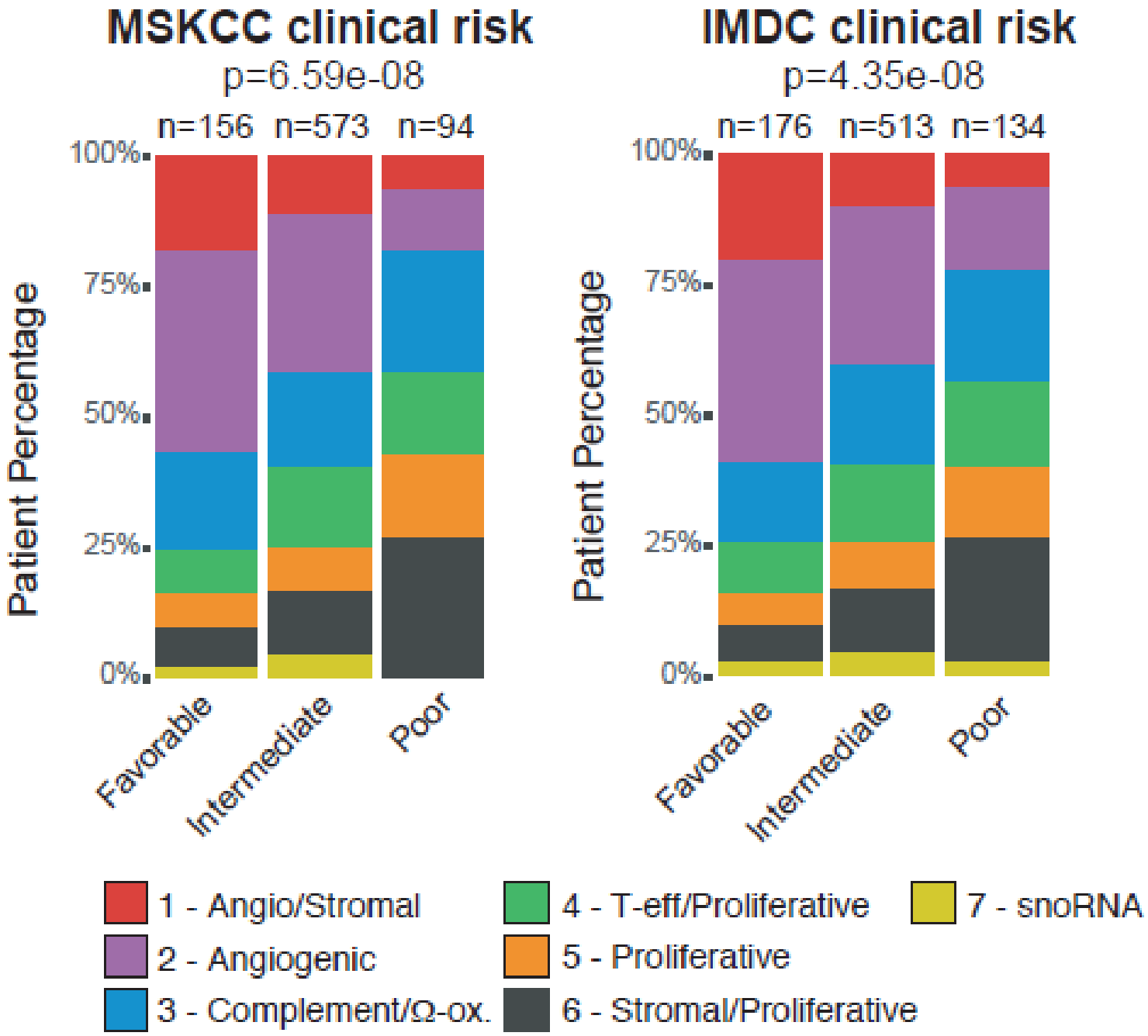
	NIVO + IPI N = 60	SUN N = 52
Events, n (%)	37 (62)	40 (77)
Median PFS, (95% CI), mo	8.4 (5.2–24.0)	4.9 (4.0–7.0)
Hazard ratio (95% CI)	0.61 (0.38–0.97)	
***P* value**	0.0329	



No. at risk														
NIVO+IPI	60	41	35	28	23	23	21	19	19	17	16	10	4	2	0
SUN	52	32	20	11	8	7	6	6	5	4	4	2	1	0	0



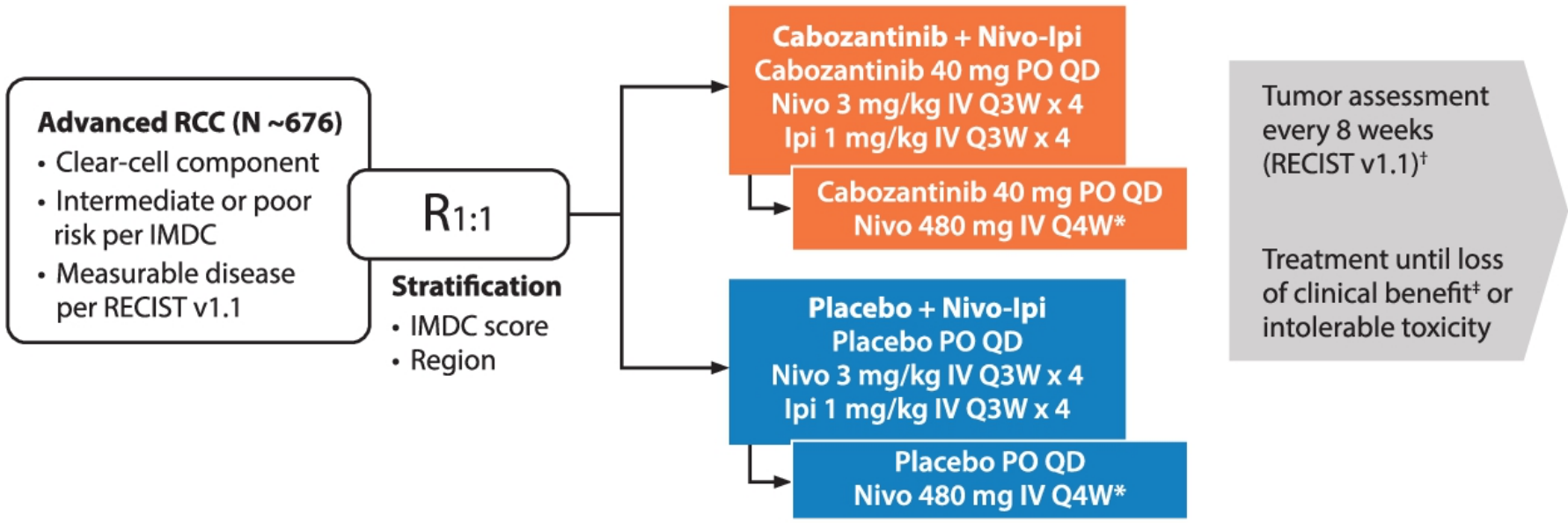
Motzer, Atkins et al Cancer Cell 2020



Motzer, Atkins et al Cancer Cell 2020

Cosmic-313 Trial

Figure 2. Study Design



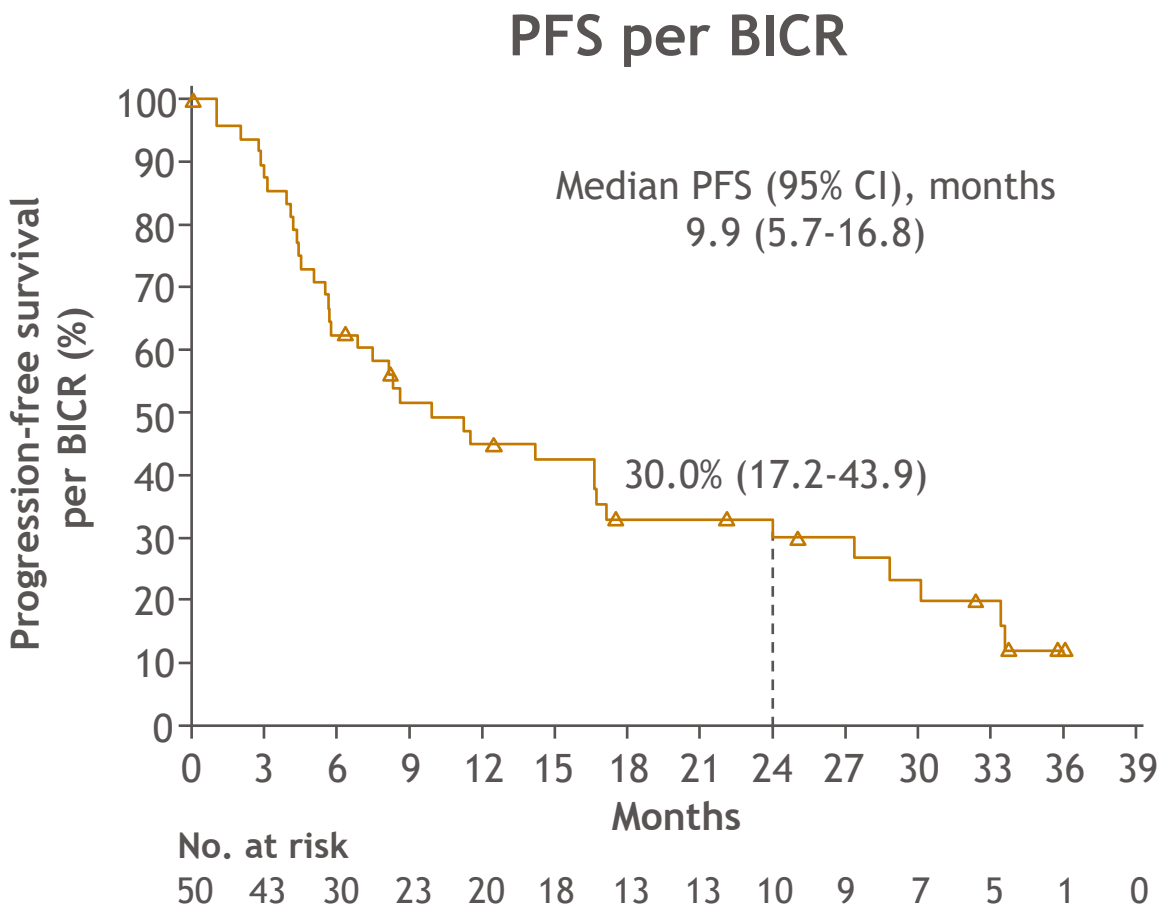
*Nivolumab administered for a maximum of 2 years

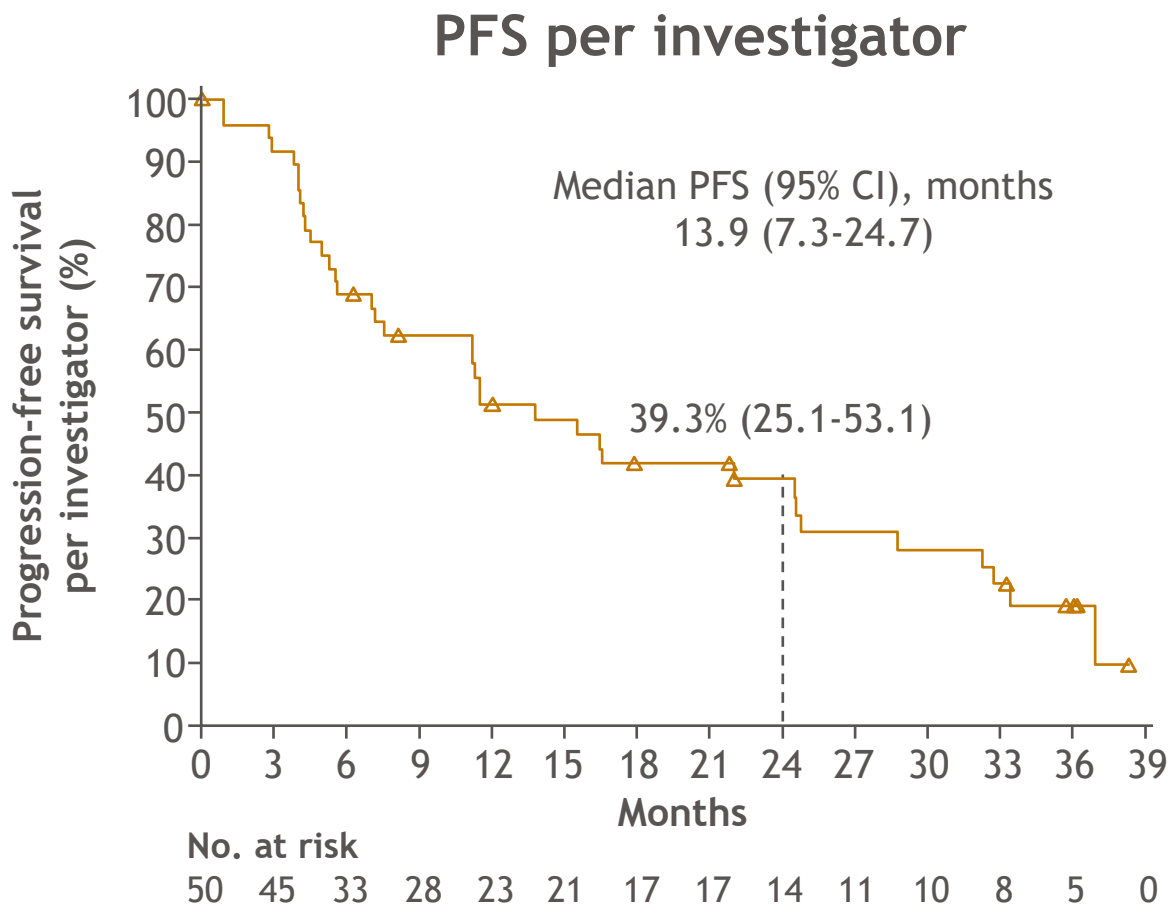
†Tumor assessment (RECIST v1.1) at week 10, then every 8 weeks for the first 50 weeks, then every 12 weeks thereafter

‡Patients may be treated beyond progression if there is clinical benefit in the opinion of the investigator

Press Release 7/11/22: PFS HR 0.73; OS TE

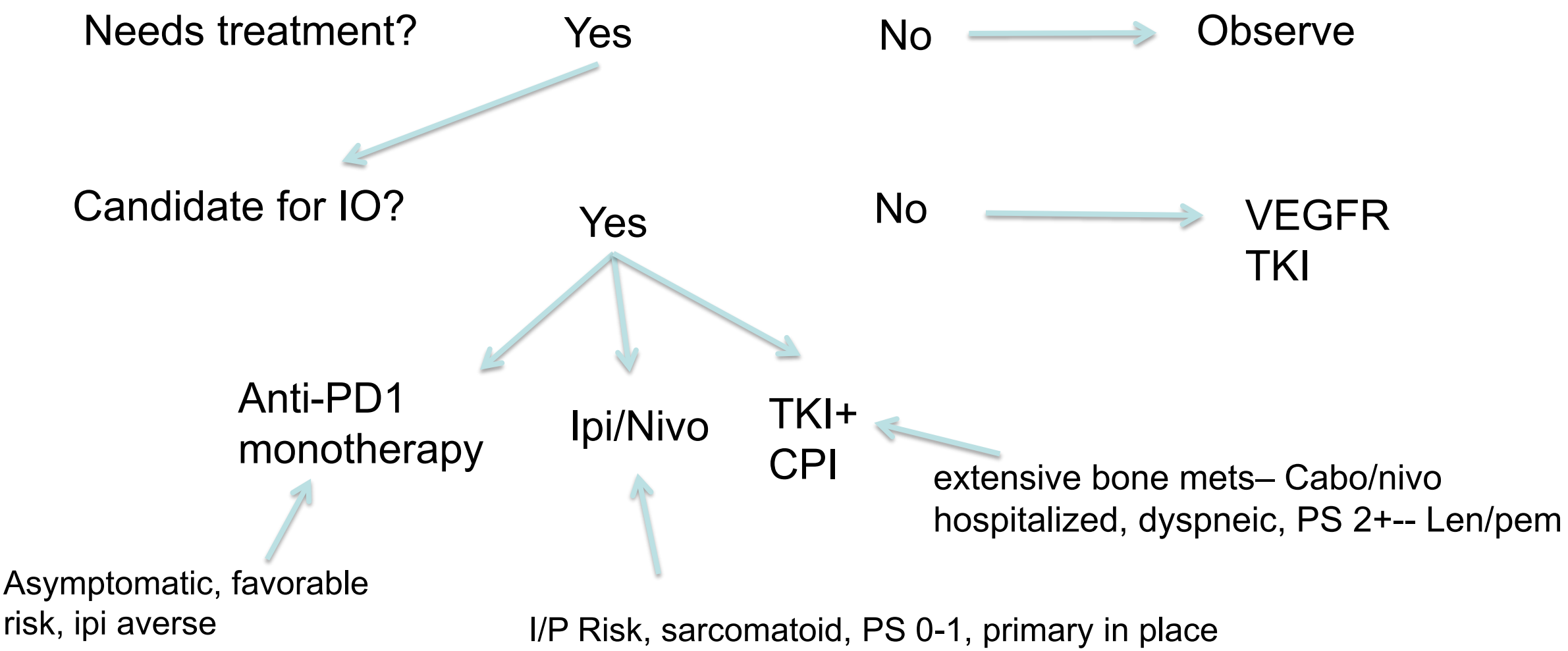
PFS per BICR and investigator (Cohort B: Cabo/nivo/ipi)[a]





[a]Using RECIST v1.1.
Database lock, June 24, 2021; median (range) follow-up for OS, 39.1 (33.4–44.5) months.
CI, confidence interval.

Algorithm for Front-line RCC Rx- Atkins 2022



Post-IO Therapy

Agent	ORR*	Reference
Axitinib	39.5%	Orenstein ASCO 2018
Cabozantinib	42%	McGregor ASCO 2018
Levatinib/Pembro*		Lee ASCO 2020
- Post IO/IO	47%	
- Post IO/anti-VEGF	59%	

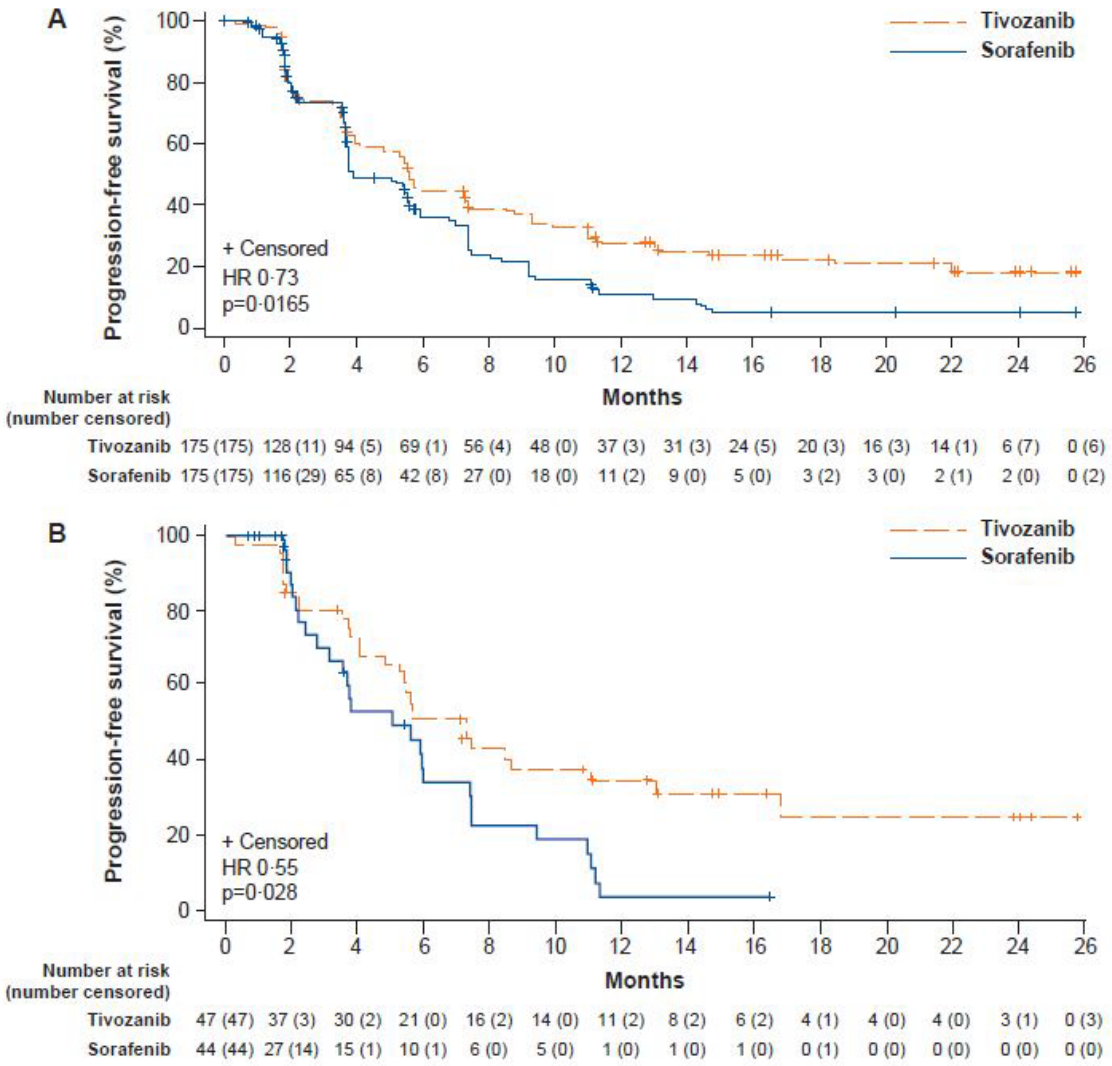
*All PRs

Efficacy Results by Prior Anticancer Therapy Subgroup[a]

Parameter	Anti-PD-1/ PD-L1[b] (N = 104)	Anti-PD-1/PD-L1 and Anti-VEGF[c] (n = 68)	Nivolumab + Ipilimumab (n = 38)
ORR, %	55	59	47
(95% CI)	(45–65)	(46–71)	(31–64)
Best objective response, %			
Partial response	55	59	47
Stable disease	36	31	42
Progressive disease	5	6	8
Not evaluable	5	4	3
Median duration of response, months	12	9	NR
(95% CI)	(9–18)	(7–17)	(7–NR)

[a] By irRECIST per investigator assessment. Patients can belong to > 1 category; [b] in combination or as monotherapy; [c] in combination or sequentially.

TIVO 3 PFS Data



ITT Population n=350
Median PFS
Tivo 5.6 (5.29-7.33) mos
Sor 3.9 (3.71-5.55) mos

Prior CPI Therapy n=91
Median PFS
Tivo 7.3 (4.8-11.1) mos
Sor 5.1 (3.2-7.4) mos

Rini et al Lancet Oncol 2019
NCT02627963

RCC Sequencing Recommendations-2022

General Principles:

1. Give the regimen with the most curative potential first
2. TKI containing regimens are largely non-curative
3. For non-curative therapies, proceed based on ther index and pt symptoms and first line Rx
4. TKI strength- Axi=Tivo, < Cabo < Len/Eve

1st line therapy	2nd line	3rd line	4th line
Nivo/ipi - Slow growing - Fast growing	 Axitinib or Tivo Cabo	 Cabo Len/eve	 Len/eve ????
Axi/Pembro	Cabo	Len/eve	????
Cabo/Nivo	Len/eve	???	????
Lev/Pemb	???	???	????

Second-Line Studies

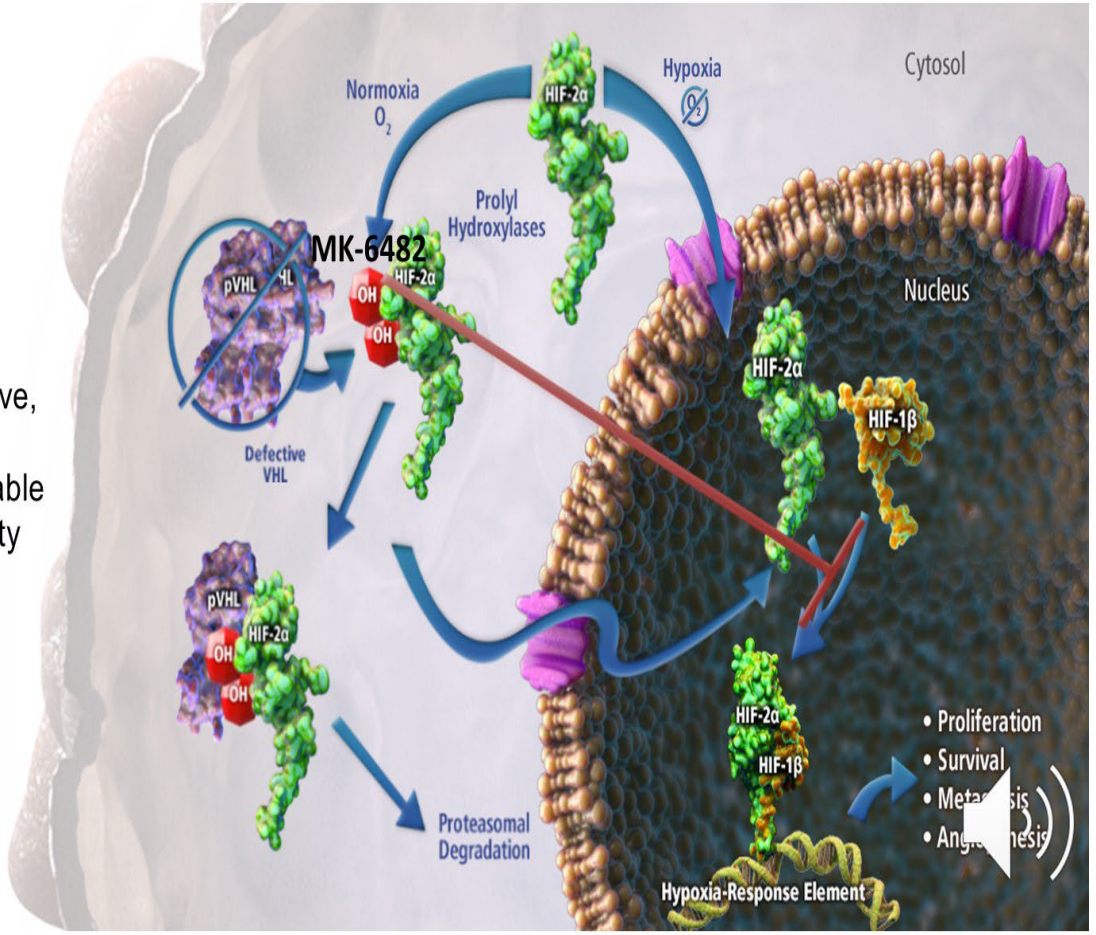
- PD1GREE: Cabo/Nivo vs Nivo in pts with PR/SD on ipi/nivo
- Contact-3: Cabo/Atezo vs Cabo following frontline doublet
- Tivo/Nivo vs Tivo following frontline IO doublet
- Novel Agents
  - HIF-2 Alpha Inhibitors (belzutifan etc)
  - Axl inhibitor (batiaxcept)

VHL Loss and HIF2α Upregulation in RCC

2019 Nobel Laureate

HIF-2α Drives Tumor Growth in VHL-RCC

- *VHL* inactivation results in aberrant stabilization and accumulation of HIF-2α[1-3]
  - Subsequent constitutive activation of genes that drive tumor growth
- MK-6482, a potent, selective, small molecule HIF-2α inhibitor, has shown favorable safety and antitumor activity in advanced RCC[4]



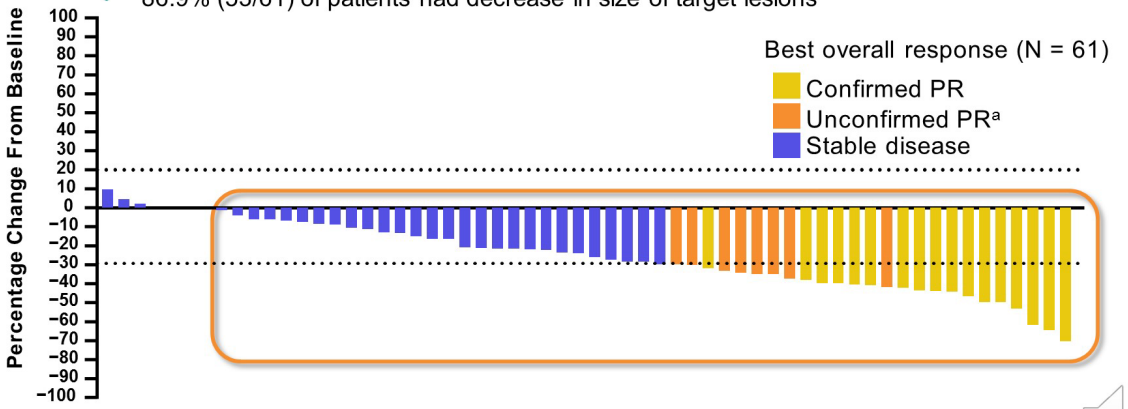
1. Kaelin WG Jr. *Trans Am Clin Climatol Assoc.* 2017;128:298-307. 2. Kondo K et al. *Cancer Cell* 2002;1:237-246. 3. Xu R et al. *J Med Chem.* 2019;62:6876-6893. 4. Choueiri TK et al. *J Clin Oncol.* 2020;38(suppl 6). Abstract 611.

Presented By Eric Jonasch at ASCO 2020 Virtual Meeting

MK6482 in Patients with VHL Syndrome and ccRCC

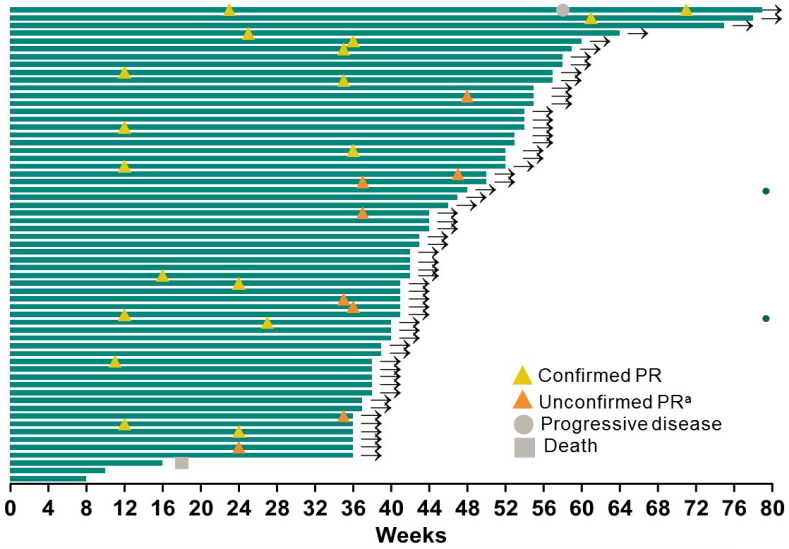
Maximum Change From Baseline in Target RCC Lesions by Independent Central Review

- 86.9% (53/61) of patients had decrease in size of target lesions



[a]Documented at 1 time point and to be confirmed at subsequent time point. Data cutoff: December 6, 2019.

Duration of Treatment by Independent Central Review



[a]Documented at 1 time point and to be confirmed at subsequent time point. Data cutoff: December 6, 2019.

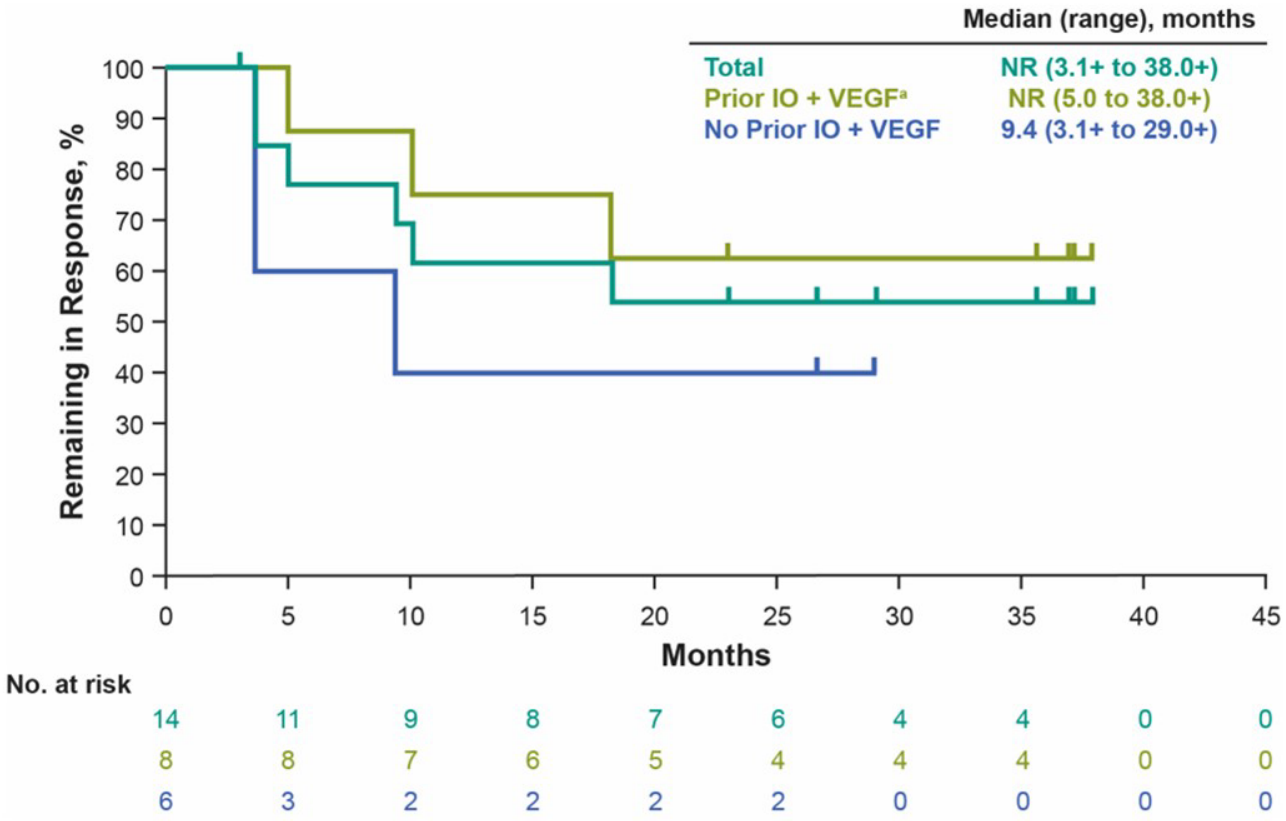
- Time to response, median (range), weeks
  - 23.7 (11.6-61.0)
- Duration of response, median (range), weeks
  - Not reached (9.1-39.0)

Recent FDA Approval

Presented By Eric Jonasch ASCO Virtual 2020

Objective Response Rate and Kaplan-Meier Estimate of Duration of Response Per RECIST v1.1

n (%)	All patients N = 55	Prior IO and VEGF[a] n = 39	Prior IO or VEGF n = 16
ORR	14 (25)	8 (21)	6 (38)
DCR	44 (80)	29 (74)	15 (94)
Best objective response			
CR	1 (2)	1 (3)	0 (0)
PR	13 (24)	7 (18)	6 (38)
SD	30 (55)	21 (54)	9 (56)
PD	8 (15)	7 (18)	1 (6)
NE	3 (5)	3 (8)	0 (0)



[a]In combination or in sequence. Database cutoff date: July 15, 2021.

LiteSpark 001 Trial- ASCO 2022- Jonasch et al

MK6482 Sporadic RCC Trials (2nd or 3rd line)

- MK6482-005: Randomized Phase III of MK6482 vs everolimus
- MK6482-013: Randomized Phase II at 2 different doses
- MK6482-011: Randomized Phase II of MK6482 + Lenvatinib vs Cabo

- Litespark-022 – Pembro +/- MK6482 (adjuvant trial)

Batiraxcept is a fusion protein containing the extracellular region of human AXL linked to a human IgG1 heavy chain (Fc)- Binds GAS6 preventing its binding to AXL (fM activity)

Phase 1b Efficacy Results

- 42% confirmed ORR for batiraxcept + cabozantinib exceeds historical cabozantinib monotherapy ORR of 17-27.8%

Table 5	Efficacy Overall		
Best Overall Response assessed by Investigator per RECIST v1.1	All Patients N = 26 (%)	15 mg/kg N = 16 (%)	20 mg/kg N = 10 (%)
Confirmed Partial Response (PR)	11 (42)	8 (50)	3 (30)
Unconfirmed PR	1 (4)	0	1 (10)
Stable Disease (SD)	11 (42)	6 (38)	5 (50)
Progressive Disease (PD)[2]	3 (12)	2 (12)	1 (10)
PR for Patients in Biomarker Low (sAXL/GAS6)	0/5 (0)	0/4 (0)	0/1 (0)
PR for Patients in Biomarker High (sAXL/GAS6)	12/20 (60)	8/12 (67)	4/8 (50)

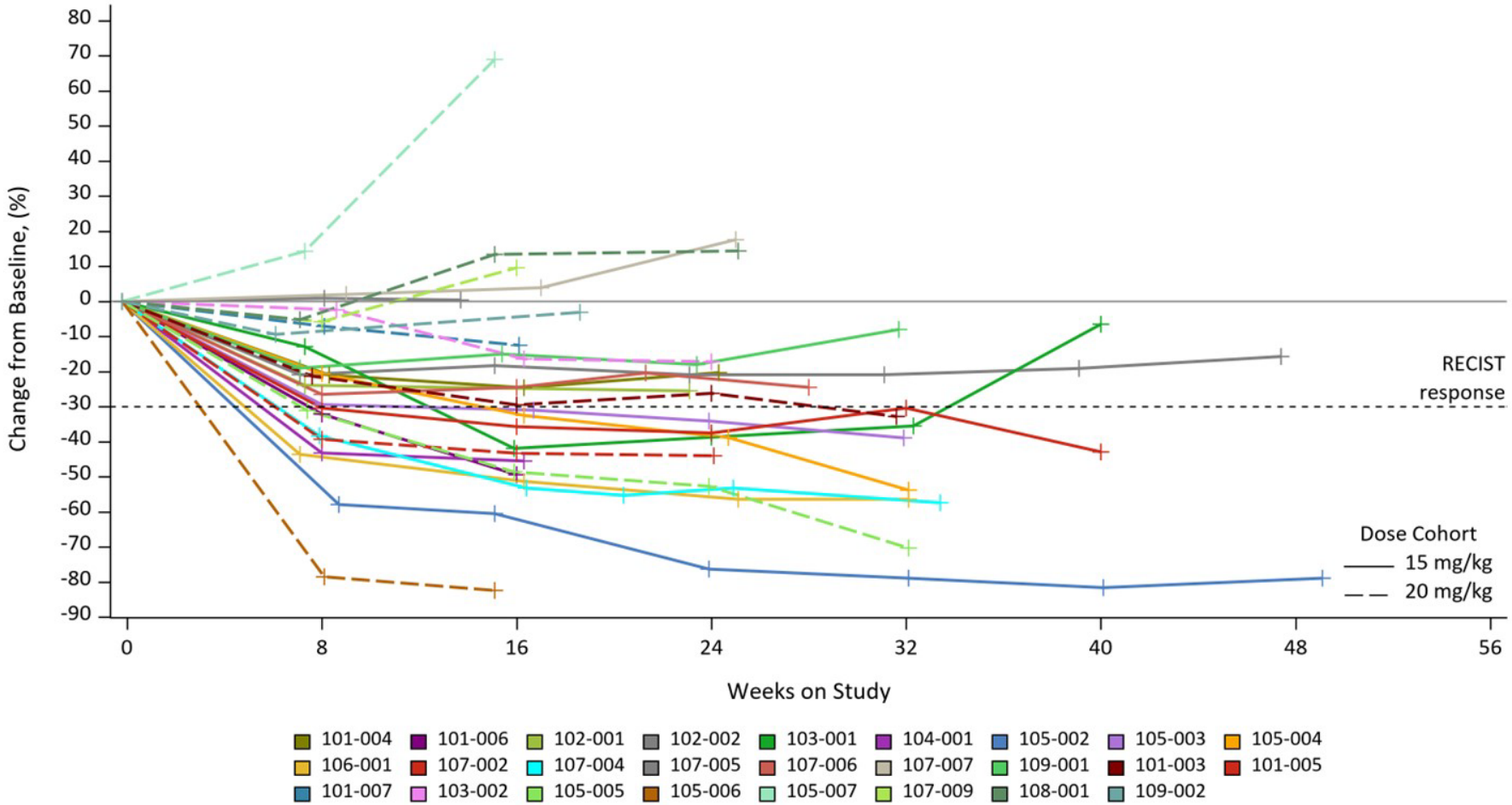
7-month PFS Rate of 71% exceeds that of cabo monotherapy

Data cutoff April 30, 2022

Shah N et al ASCO 2022

Cabo + Batiraxcept Study

Phase 1b Response Data



- Eight patients experienced resolution of one or more target lesions
- All responders were biomarker high
- 14 of 26 patients still on treatment

Data cutoff April 30, 2022

Case: 64 yo man with rapid PD after stopping Axi-Pembro due to CVA

How would you manage this?

1. sunitinib/pazopanib
2. cabozantinib
3. lenvatinib/everolimus
4. tivozanib
5. resume axitinib
6. nivo monotherapy
7. nivo/ipi

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Suthee Rapisuwon
Nancy Dawson
George Philips
Anton Wellstein
Kellie Gardner
Ming Tan
Keith Kowalczyk
Chunling Yi

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HCRN GU Team

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DFHCC Kidney Cancer SPORE
DOD Translational Science Team Award
NCI Provocative Question R01
NCI CCSG Program
William M Scholl Foundation
Stan & Linda Sher Immunotherapy Grant