Metastatic Renal Cell Carcinoma Treatment

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Disclosures

- Consultant for Deka Biosciences, EMD Serono, Exelixis, and Pfizer.
- Grant/Research Support from Aravive, Inc., and EMD Serono.

This presentation and/or comments will be free of any bias toward or promotion of the above referenced companies or their products and/or other business interests.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

This presentation has been peer-reviewed and no conflicts were noted.

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:

The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

EXEMPTION:

Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

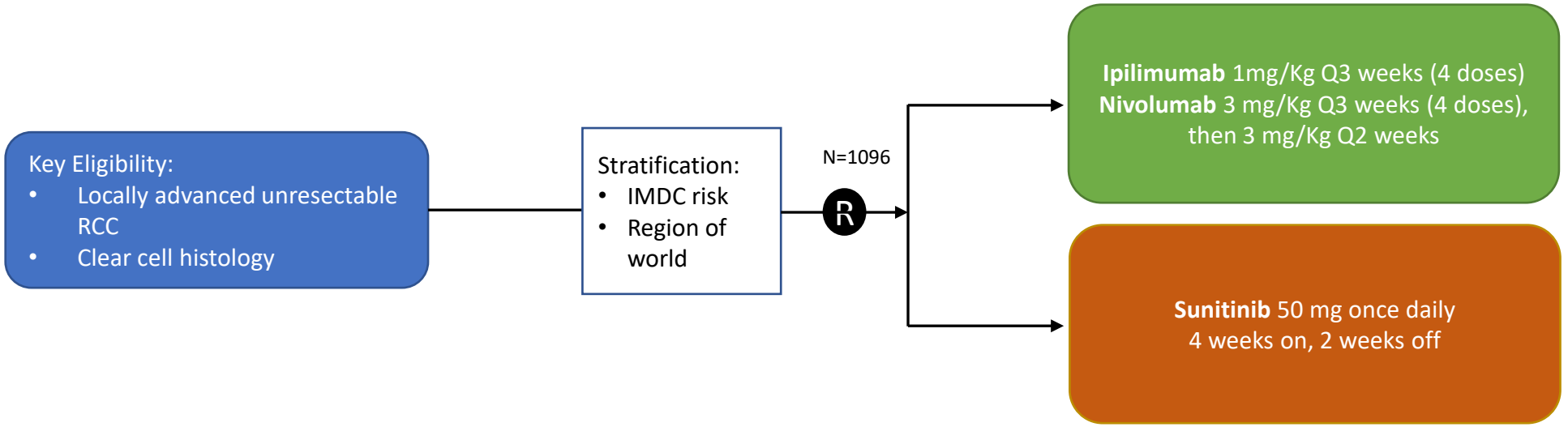
The following CLC & IB components will be addressed in this presentation:

- *Commonalities and differences in patient population*
- *Health disparities*

Outline

- Frontline treatment landscape of advanced clear cell RCC
- Treatment in the second or subsequent lines of therapy
- Emerging data with novel agents

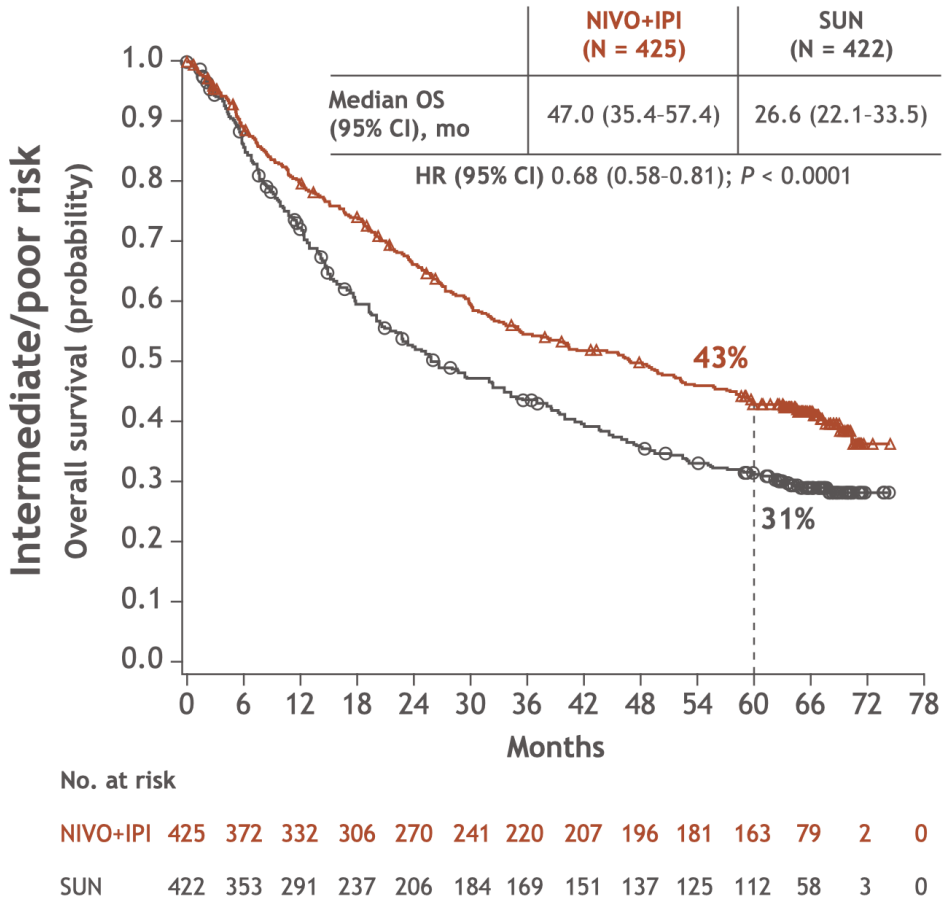
Checkmate 214: ipilimumab + nivolumab in untreated RCC

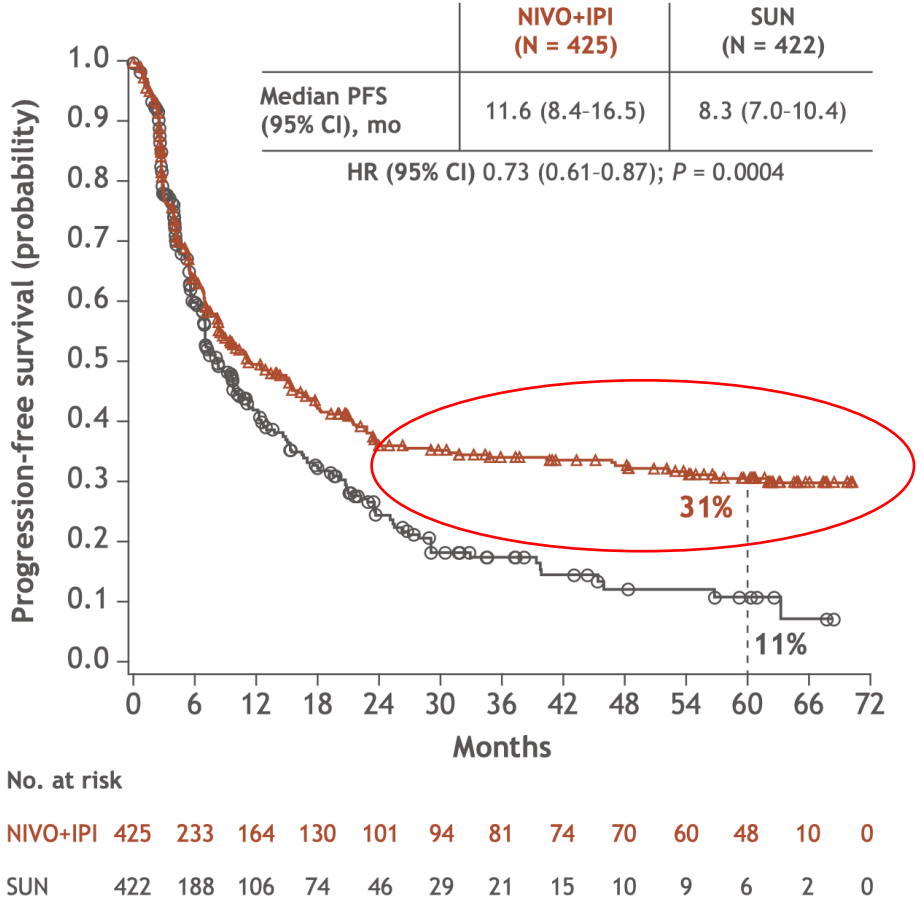


Endpoints:
- Co-primary: PFS, OS and ORR (int/poor risk)
- Secondary: PFS, OS, ORR (ITT)
- Exploratory: PFS, OS, ORR (fav risk)

Intermediate/poor risk patients			
Follow up (months)	**Hazard Ratio (OS)**	**Median OS (months)**	
		Ipi + Nivo	Sunitinib
25 (median)	0.63 (0.44-0.89)	NR	26
42 (min)	0.66 (0.55-0.80)	47	26.6

Checkmate 214: ipilimumab + nivolumab in untreated RCC





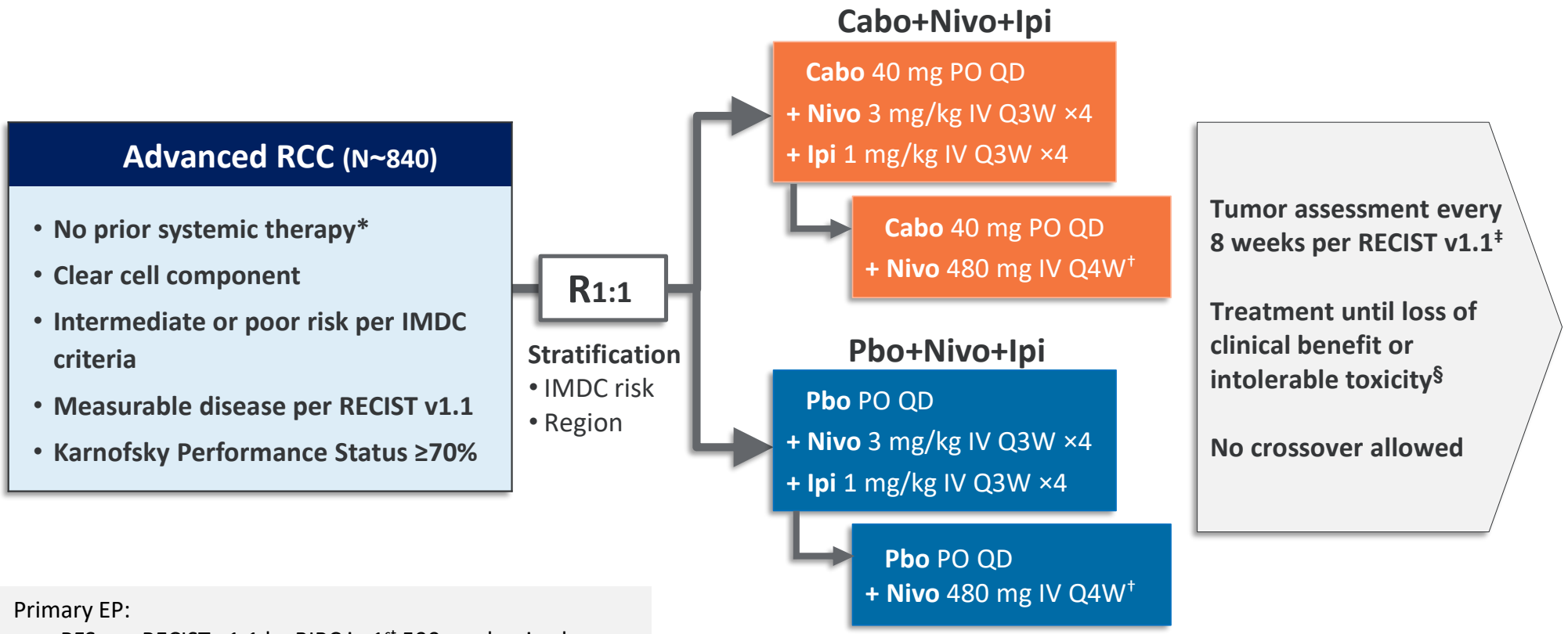
Median Follow up: 66.7 months (min: 5 years)

Approved TKI + IO combinations in RCC

JAVELIN 101 Renal	Treatment naïve ccRCC	Axitinib 5 mg twice daily Avelumab 10 mg/Kg every 2 weeks	PFS/OS in PD-L1 positive patients
		Sunitinib 50 mg daily 4 weeks on, 2 weeks off	
Keynote 426	Treatment naïve ccRCC	Axitinib 5 mg twice daily Pembrolizumab 200 mg every 3 weeks	PFS and OS in ITT
		Sunitinib 50 mg daily 4 weeks on, 2 weeks off	
CheckMate 9ER	Treatment naïve ccRCC	Cabozantinib 40 mg daily Nivolumab 240 mg every 2 weeks	PFS in ITT
		Sunitinib 50 mg daily 4 weeks on, 2 weeks off	
CLEAR	Treatment naïve ccRCC	Lenvatinib 20 mg daily Pembrolizumab 200 mg every 3 weeks	PFS/OS in ITT
		Lenvatinib 18 mg daily Everolimus 5 mg daily	
		Sunitinib 50 mg daily 4 weeks on, 2 weeks off	

Motzer et al. *NEJM* 2019; Rini et al. *NEJM* 2019; Choueiri et al. *NEJM* 2021; Motzer et al, *NEJM* 2021

Triplet therapy in RCC: COSMIC-313



Primary EP:
- PFS per RECIST v1.1 by BIRC in 1st 500 randomized patients (PITT)

Secondary EP:
- OS, ORR, DOR in ITT

Triplet therapy in RCC: COSMIC-313

Characteristic	Cabo+Nivo+Ipi (N=428)	Pbo+Nivo+Ipi (N=427)
Median age, years (range)	61 (19–85)	60 (28–87)
Male, %	76	73
Enrollment region, %		
US, Canada, Europe, Australia, New Zealand	65	65
Latin America or Asia	35	35
IMDC risk group, %		
Intermediate / poor	75 / 25	75 / 25
Tumor PD-L1 status, %		
<1% / ≥1%	64 / 20	62 / 22
Indeterminate or missing	17	16
Karnofsky Performance Status, %		
100 or 90 / 70 or 80	59 / 41	63 / 37
Prior nephrectomy, %	65	65
No. of sites with target/non-target lesions per BIRC, %		
1 / ≥2	19 / 80	19 / 80
Most common target/non-target metastatic sites per BIRC, %		
Lung	68	71
Lymph node	54	50
Liver	20	19
Bone	17	21

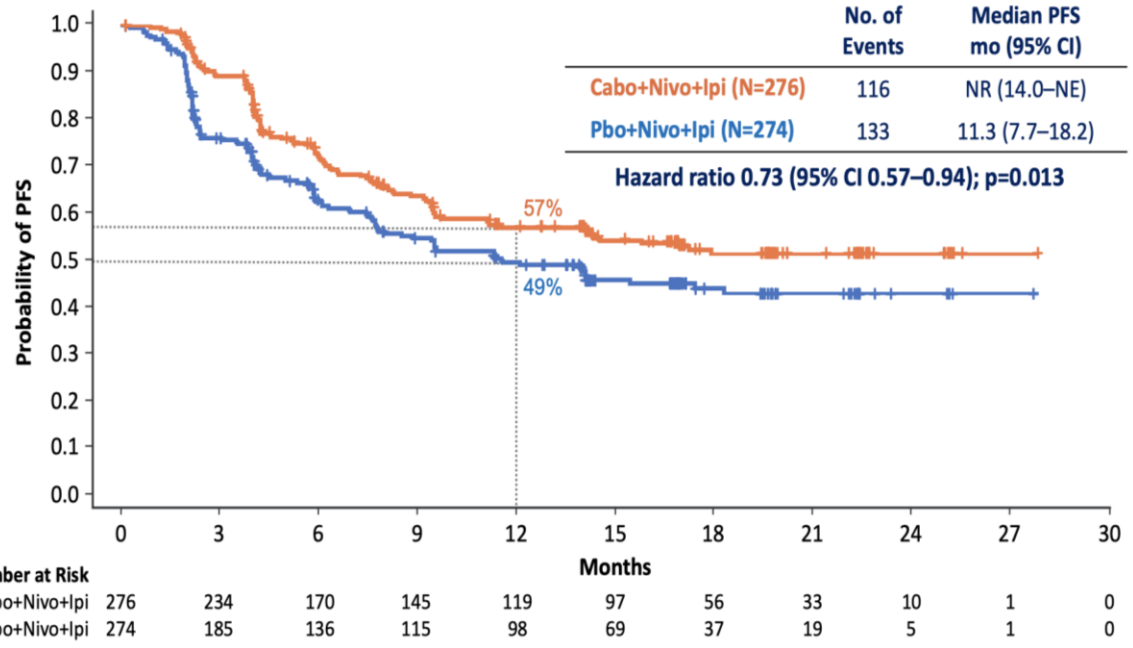
Enrollment region and IMDC risk group are per interactive voice/web response system (IxRS); PD-L1 status is per central assessment using the Dako PD-L1 IHC 28-8 pharmDx test.

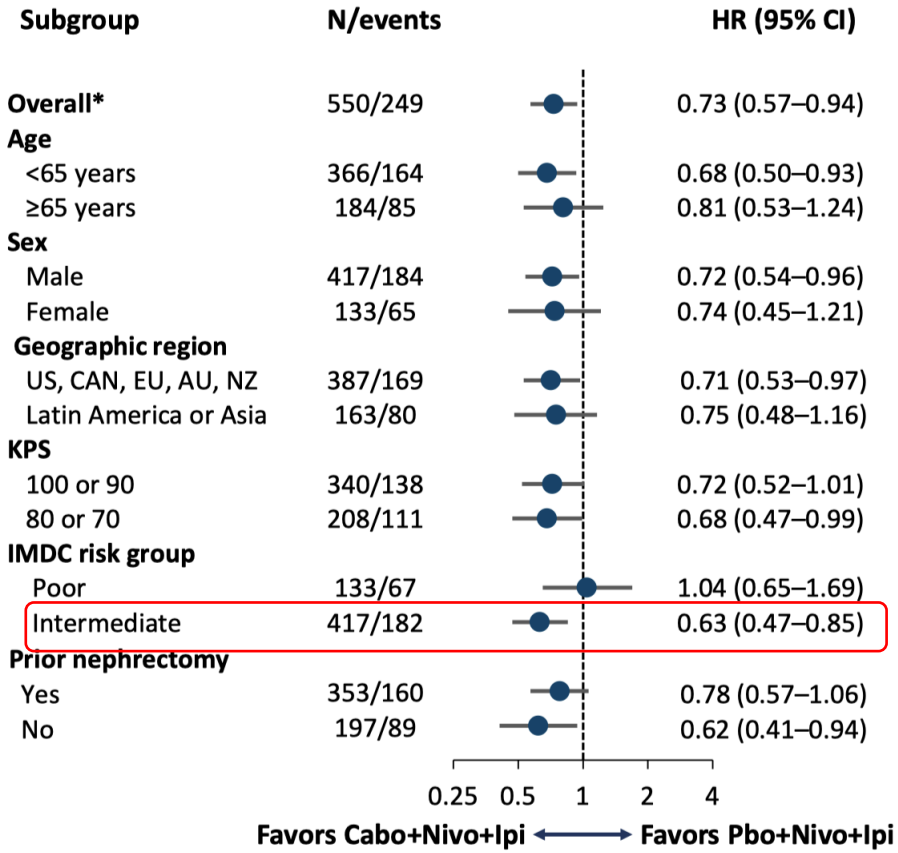
PARIS 2022 ESMO congress

Toni K. Choueiri

Triplet therapy in RCC: COSMIC-313

PFS in PITT population (all risk groups)





Triplet therapy in RCC: COSMIC-313

	Cabo+Nivo+Ipi (N=276)	Pbo+Nivo+Ipi (N=274)
Objective response rate (95% CI), %	43 (37.2–49.2)	36 (30.1–41.8)
Best overall response, n (%)		
Complete response	7 (3)	9 (3)
Partial response	112 (41)	89 (32)
Stable disease	119 (43)	100 (36)
Progressive disease	23 (8)	55 (20)
Not evaluable	15 (5)	21 (8)
Disease control rate, %	86	72
Median time to objective response (range), mo	2.4 (1.5–17.1)	2.3 (1.9–16.8)
Median duration of response (95% CI), mo	NR (20.2–NE)	NR (NE–NE)

IMDC risk group	Objective response rate (%)	
	Cabo + Ipi + Nivo	Pbo + Ipi + Nivo
Intermediate risk	45	35
Poor risk	37	38

Triplet therapy in RCC: COSMIC-313

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

Summary of frontline RCC landscape

	CheckMate 214 (Ipi + Nivo)	Keynote-426 (Axitinib + Pembro)	Checkmate 9ER (Cabo + Nivo)	CLEAR (Lenvatinib + Pembro)	COSMIC 313 (Cabozantinib + Ipi +Nivo)
Comparator	Sunitinib	Sunitinib	Sunitinib	Sunitinib	**Ipi + Nivo**
Favorable risk, %	23	**32**	23	**31**	-
Prior nephrectomy	**82***	83	69	**74**	**65**
Median f/u (months)	**67.7***	42.8	32.9	33.7	20.2
ORR, %	42*	60	55	71	43
CR, %	12*	10	12	16	3
PD, %	18*	11	6	5	8
Median PFS (months)	11.6*	15.7	16.6	23.3	NR
Median OS	47*	45.7	37.7	NR	NR
OS HR (95% CI)	0.68 (0.58-0.81) *	0.73 (0.60-0.88)	0.70 (0.55-0.90)	0.72 (0.55-0.93)	NR
*(int/poor risk)					

Motzer et al. ESMO 2021; Rini et al. ASCO 2021; Powles et al. *Lancet Oncol*. 2020; Motzer et al. *Lancet Oncol 2022; Porta et al.* ESMO *2022;* Choueiri et al. ESMO 2022

Summary of frontline RCC landscape

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Com					
Favo					
Prior					
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*(int/poor risk)					

Doublets (PD-1 + CTLA-4 or IO+ TKI) continue to be treatment of choice for untreated ccRCC

Motzer et al. ESMO 2021; Rini et al. ASCO 2021; Powles et al. *Lancet Oncol*. 2020; Motzer et al. *Lancet Oncol 2022; Porta et al.* ESMO *2022;* Choueiri et al. ESMO 2022

Summary of frontline RCC landscape

	CheckMate 214 (Ipi + Nivo)	Keynote-426 (Axitinib + Pembro)	Checkmate 9ER (Cabo + Nivo)	CLEAR (Lenvatinib + Pembro)	COSMIC 313 (Cabozantinib + Ipi +Nivo)
Com					
Favo					
Prior					
Median f/u (months)	67.7*	42.8	32.9	33.7	20.2
ORR					
CR, %					
PD, %	18	11	6	5	8
Median PFS (months)	11.6*	15.7	16.6	23.3	NR
Median OS	47*	45.7	37.7	NR	NR
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*(int/poor risk)					

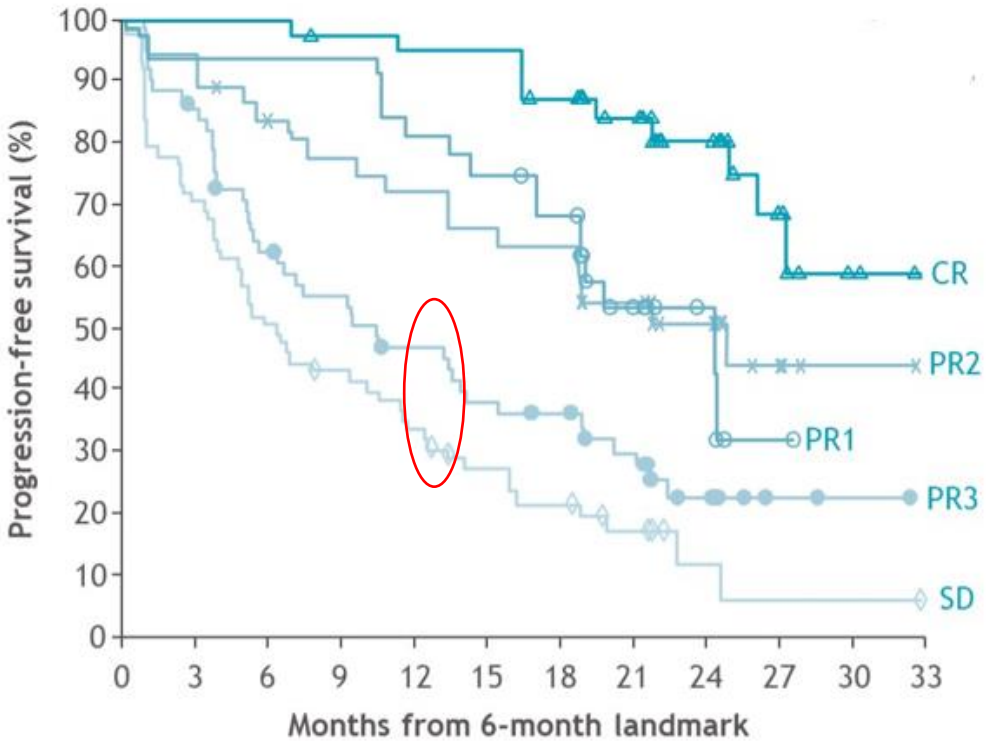
Doublets (PD-1 + CTLA-4 or IO+ TKI) continue to be treatment of choice for untreated ccRCC

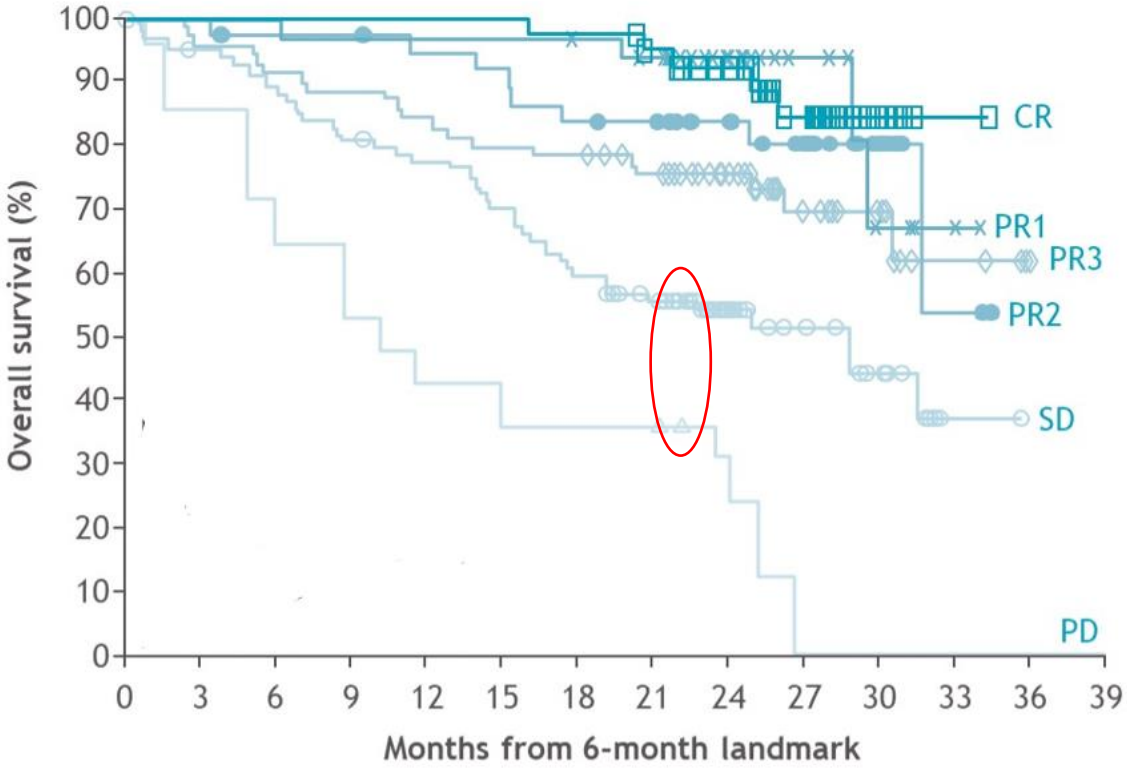
How do we better integrate VEGF targeted therapy with PD-1 + CTLA-4 inhibition?

Motzer et al. ESMO 2021; Rini et al. ASCO 2021; Powles et al. *Lancet Oncol*. 2020; Motzer et al. *Lancet Oncol 2022; Porta et al.* ESMO *2022;* Choueiri et al. ESMO 2022

Depth of response as an on-therapy marker

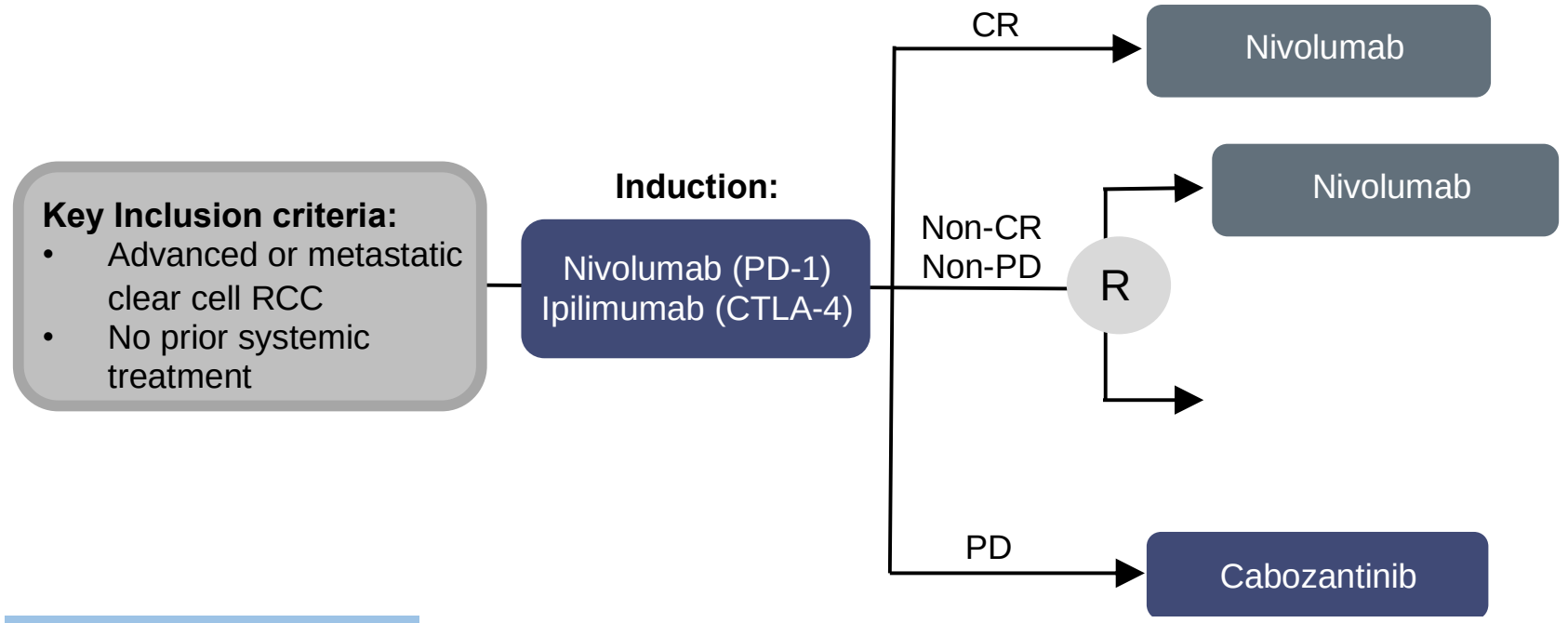
PD	SD	<60% (PR3)	60-80% (PR2)	≥80% (PR3)	CR





Prognostic groups based on depth of response in Checkmate 9ER a study

Response adapted VEGF inhibition : PDIGREE study

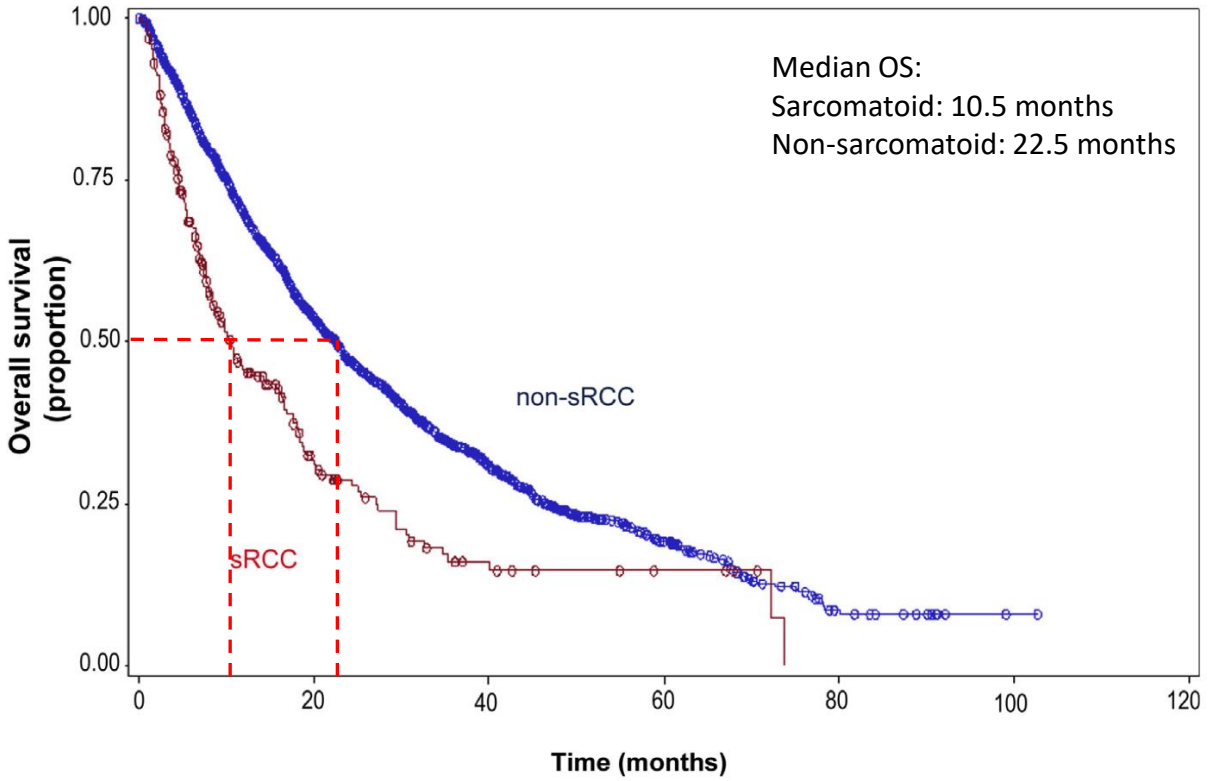


Primary EP: OS
Secondary EP: PFS, ORR, Safety

NCT03793166 ; PI: Tian Zhang MD; Toni Choueiri MD

Sarcomatoid RCC

Characteristic	Nonsarcomatoid, n = 2056[a]	Sarcomatoid, n = 230[a]
Mean Age at Onset of Metastatic Disease, Years	59	58
Heng Prognostic Score		
Favorable	336 (19%)	20 (11%)
Intermediate	995 (57%)	88 (49%)
Poor	417 (24%)	73 (40%)
Greater Than 1 Metastatic Site		
Yes	1494 (73%)	167 (73%)
No	557 (27%)	62 (27%)
Brain Metastases		
Yes	165 (8%)	14 (6%)
No	1878 (92%)	214 (94%)
Underlying Clear Cell Histology		
Yes	1766 (88%)	195 (87%)
No	239 (12%)	30 (13%)
Fuhrman Nuclear Grade		
1	53 (4%)	3 (2%)
2	430 (30%)	9 (5%)
3	661 (46%)	33 (17%)
4	302 (21%)	145 (76%)



Can be seen with or without clear cell
Presented with advanced disease, higher nuclear grade

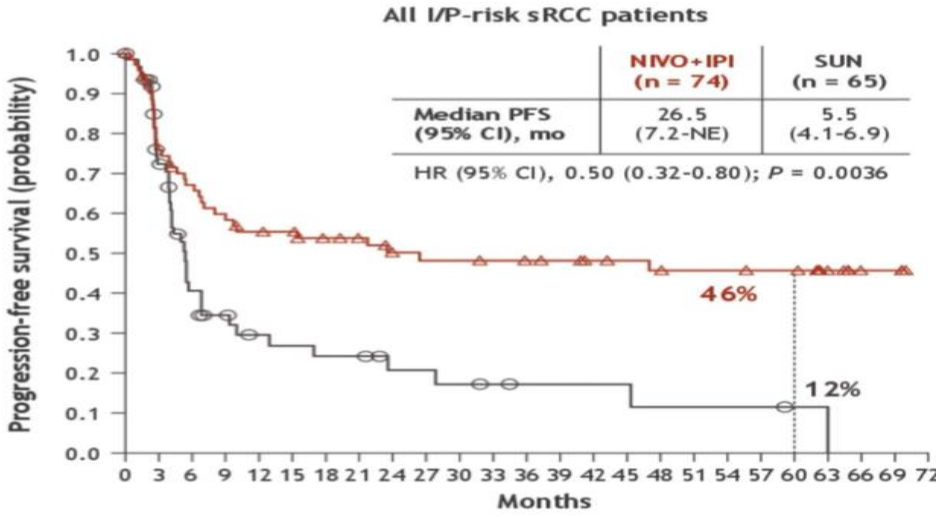
Significantly worse prognosis in the VEGFR-TKI monotherapy era

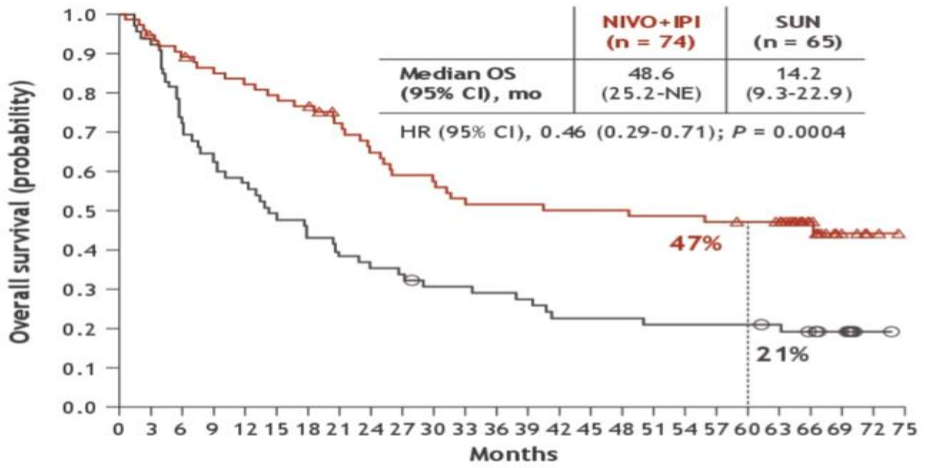
IO combinations in sarcomatoid RCC

- Paradigm shift in outcomes in sarcomatoid RCC
- More likely to develop CR/durable CR
- Plateau in OS curves suggests durability of these responses

	CheckMate 214 (N=139)	Keynote-426 (N=105)	Checkmate 9ER (N=75)
ORR (%)	61	58	56
CR rate (%)	23	11.8	8.8
PFS (months)	26.5	NR	11
OS (months)	48.6	12-month rate: 84%	NR

ORR: Objective response rate; CR: complete response; PFS: Progression-free survival;
OS: Overall survival





Tannir et al. ASCO GU 2022; Rini et al. ASCO 2019; Motzer GU ASCO 2021; Heng ESMO 2022

Implications for second line therapy

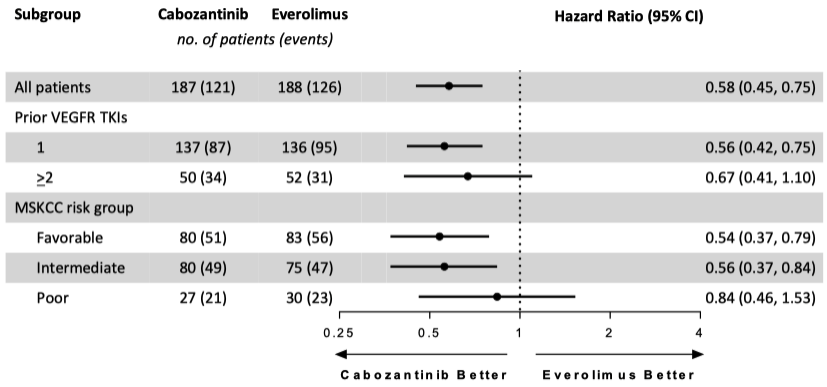
- Increasing proportion of patients refractory to IO +/- VEGF agents in front line setting
- Limited prospective data on optimal sequencing
- IO rechallenge/continuation remains attractive, but unproven strategy
- Agents with novel MOA likely to disrupt this landscape

Cabozantinib in VEGF Refractory RCC

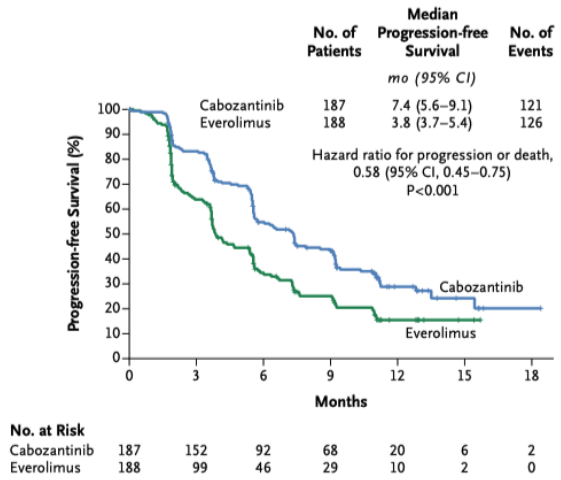
ORIGINAL ARTICLE

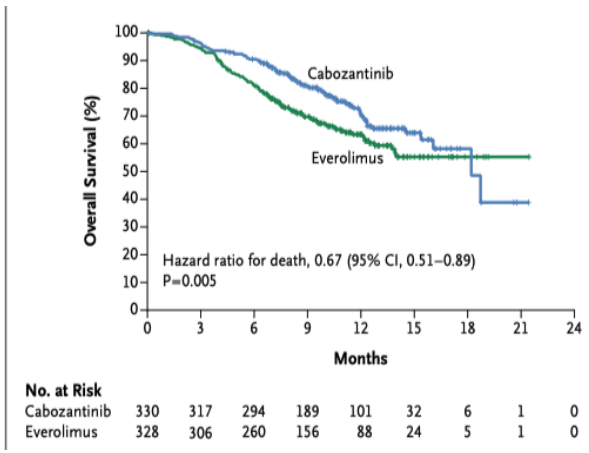
Cabozantinib versus Everolimus in Advanced Renal-Cell Carcinoma

T.K. Choueiri, B. Escudier, T. Powles, P.N. Mainwaring, B.I. Rini, F. Donskov, H. Hammers, T.E. Hutson, J.-L. Lee, K. Peltola, B.J. Roth, G.A. Bjarnason, L. Géczi, B. Keam, P. Maroto, D.Y.C. Heng, M. Schmidinger, P.W. Kantoff, A. Borgman-Hagey, C. Hessel, C. Scheffold, G.M. Schwab, N.M. Tannir, and R.J. Motzer, for the METEOR Investigators*



Characteristic	Progression-free–Survival Population		Overall-Survival Population	
	Cabozantinib (N=187)	Everolimus (N=188)	Cabozantinib (N=330)	Everolimus (N=328)
Previous systemic therapy — no. (%)				
Sunitinib	114 (61)	113 (60)	210 (64)	205 (62)
Pazopanib	87 (47)	78 (41)	144 (44)	136 (41)
Axitinib	28 (15)	28 (15)	52 (16)	55 (17)
Sorafenib	11 (6)	19 (10)	21 (6)	31 (9)
Bevacizumab	1 (<1)	7 (4)	5 (2)	11 (3)
Interleukin-2	11 (6)	13 (7)	20 (6)	29 (9)
Interferon alfa	6 (3)	13 (7)	19 (6)	24 (7)
Nivolumab	9 (5)	11 (6)	17 (5)	14 (4)
Radiotherapy — no. (%)	56 (30)	61 (32)	110 (33)	108 (33)
Nephrectomy — no. (%)	156 (83)	153 (81)	282 (85)	279 (85)





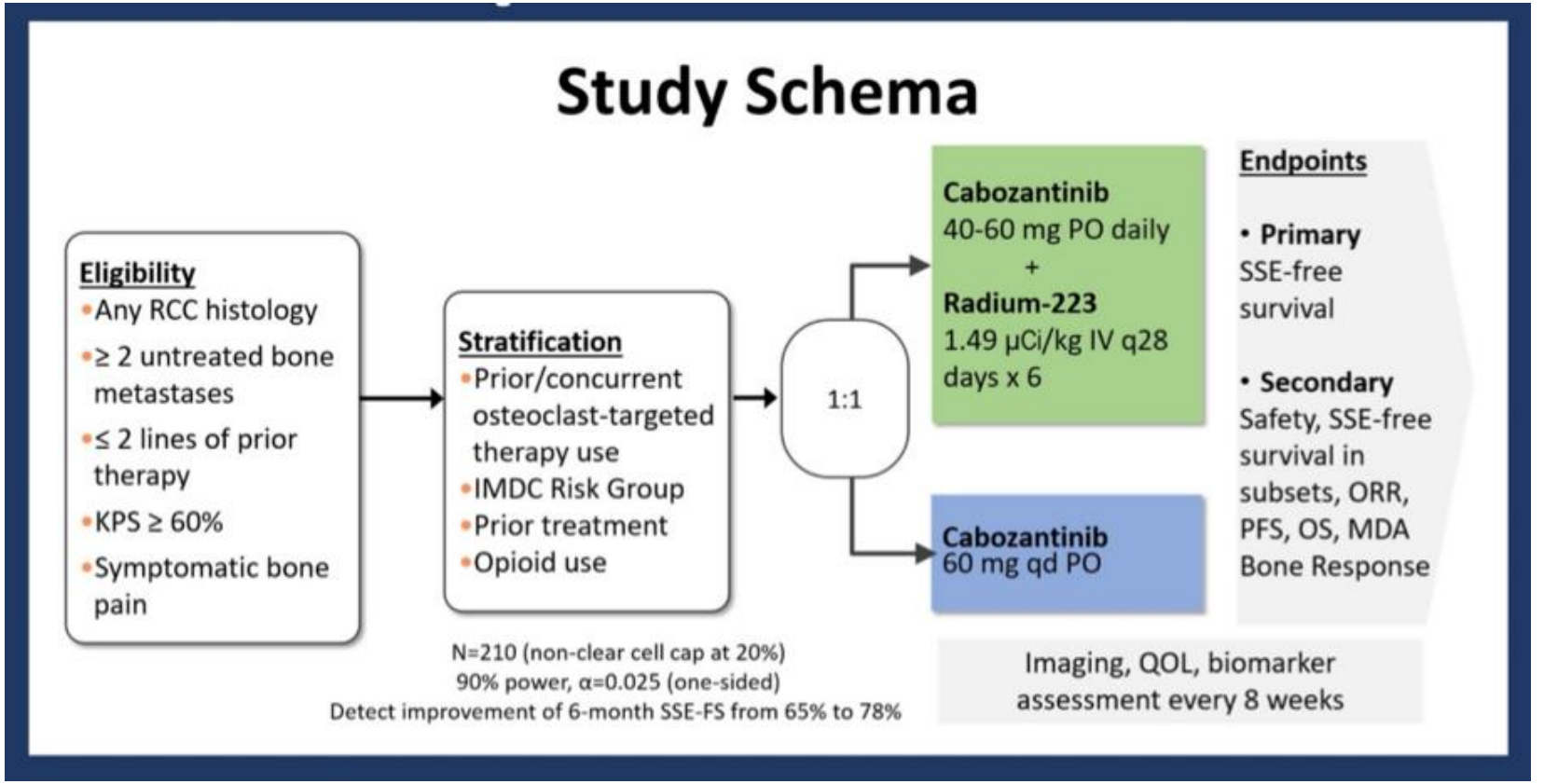
Cabozantinib efficacy in IO-refractory RCC

Table 2 Clinical Outcomes for Patients that Received 2L CABO

	Median TTF months (95% CI)	Median OS months (95% CI)	1 Year Treatment Failure Free	1 Year OS	Objective Response Rate	Progressive Disease
CABO post 1L ALL N = 346	7.59 (6.61 - 8.98)	18.12 (15.42 - 24.10)	34.3%	63.5%	26.2% 70/268	20.1%54/268
CABO post 1L IPI-NIVO N = 78	6.90 (6.05 - NE)	21.44 (12.07 - NE)	34.1%	66.6%	26.4% 14/53 (1.9% CR)	9.4% 5/53
CABO post 1L IOVE N = 46	5.72 (4.41 - NE)	15.68 (9.27 - NE)	26.8%	54.3%	32.5% 13/40 (0% CR)	17.5% 7/40
CABO post 1L PAZ/SUN N = 161	8.22 (7.33 - 10.82)	20.74 (15.58 - 35.64)	36.8%	65.6%	25.2% 37/147 (1.3% CR)	30.6% 45/147
CABO post 1L OTHER N = 61	6.84 (5.03 - 17.92)	14.30 (10.49 - 28.77)	32.1%	56.5%	20.8% 11/53	24.5% 13/53
CABO post 1L VEGFi METEOR[10]		21.4 (18.7 - NE)		73%	17%	14%

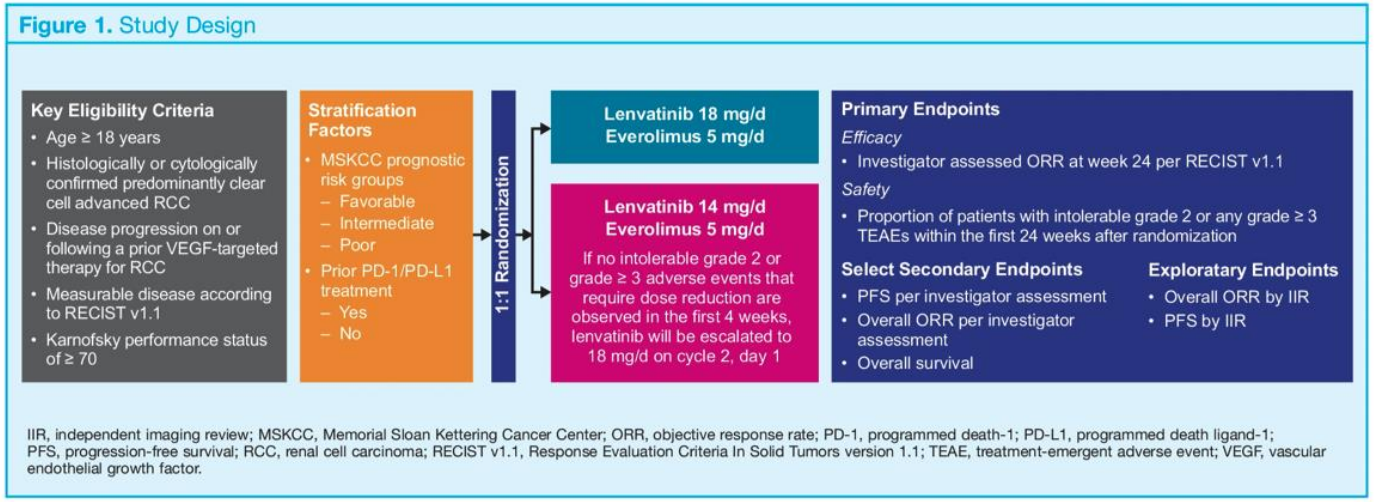
Acronyms – CABO= cabozantinib; VEGFi= Vascular endothelial growth factor receptor inhibitor; TTF= Time to treatment failure; OS= Overall survival; CI= confidence interval; 2L= Second line

Cabozantinib in IO-refractory RCC



Lenvatinib + everolimus in VEGF/IO Refractory RCC

Figure 1. Study Design



IIR, independent imaging review; MSKCC, Memorial Sloan Kettering Cancer Center; ORR, objective response rate; PD-1, programmed death-1; PD-L1, programmed death ligand-1; PFS, progression-free survival; RCC, renal cell carcinoma; RECIST v1.1, Response Evaluation Criteria In Solid Tumors version 1.1; TEAE, treatment-emergent adverse event; VEGF, vascular endothelial growth factor.

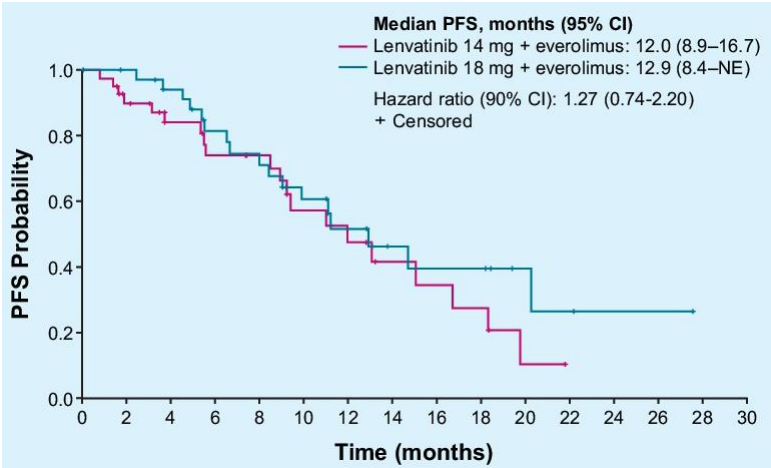


Table 1. Patient Baseline Characteristics

Characteristic	Overall Population		Prior ICI Subgroup[a]	
	Lenvatinib 14 mg + Everolimus (n = 172)	Lenvatinib 18 mg + Everolimus (n = 171)	Lenvatinib 14 mg + Everolimus (n = 49)	Lenvatinib 18 mg + Everolimus (n = 41)
Median age (range), years	61 (28–82)	62 (35–87)	60 (30–77)	65 (35–80)
Sex, male, n (%)	133 (77.3)	129 (75.4)	36 (73.5)	31 (75.6)
MSKCC Prognostic risk group[b], n (%)				
Favorable	49 (28.5)	50 (29.2)	13 (26.5)	13 (31.7)
Intermediate	93 (54.1)	90 (52.6)	25 (51.0)	17 (41.5)
Poor	30 (17.4)	31 (18.1)	11 (22.4)	11 (26.8)
IMDC Prognostic risk group, n (%)				
Favorable	25 (14.5)	38 (22.2)	6 (12.2)	7 (17.1)
Intermediate	107 (62.2)	78 (45.6)	26 (53.1)	17 (41.5)
Poor	40 (23.3)	52 (30.4)	17 (34.7)	16 (39.0)
Missing	0	3 (1.8)	0	1 (2.4)
Sites of metastasis[c], n (%)				
Bone	59 (34.3)	64 (37.4)	17 (34.7)	19 (46.3)
Lung	114 (66.3)	124 (72.5)	30 (61.2)	29 (70.7)
Liver	42 (24.2)	43 (25.1)	12 (24.5)	14 (34.1)
Lymph node	97 (56.4)	99 (57.9)	29 (59.2)	26 (63.4)
Number of prior anticancer therapy regimens, n (%)				
1	129 (75.0)	140 (81.9)	12 (24.5)	16 (39.0)
2	38 (22.1)	29 (17.0)	32 (65.3)	23 (56.1)
≥ 3	5 (2.9)	2 (1.2)	5 (10.2)	2 (4.9)

Efficacy measure*	Lenvatinib 18 mg	Lenvatinib 14 mg
ORR (%)	51.3	30.2
PFS (months)	12.9	12
OS (months)	18	17.1

* Investigator assessed; ORR: Objective response rate; PFS: Progression-free survival; OS: Overall survival

Tivozanib in VEGF-refractory RCC

Tivozanib versus sorafenib in patients with advanced renal cell carcinoma (TIVO-3): a phase 3, multicentre, randomised, controlled, open-label study

Brian I Rini, Sumanta K Pal*, Bernard J Escudier, Michael B Atkins, Thomas E Hutson, Camillo Porta, Elena Verzoni, Michael N Needle, David F McDermott*

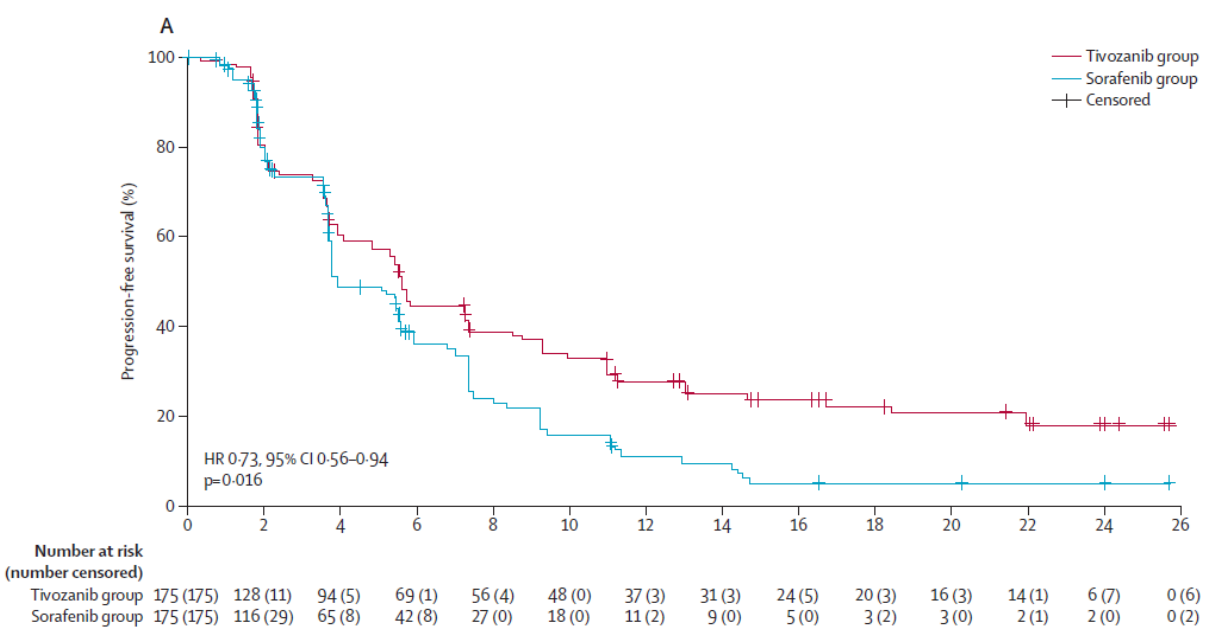
	Tivozanib group (n=175)*	Sorafenib group (n=175)*
Complete response	0	0
Partial response	31 (18%)	14 (8%)
Stable disease	94 (55%)	99 (57%)
Progressive disease	37 (22%)	32 (18%)
Not evaluable	10 (6%)	30 (17%)
Patients achieving an objective response	31 (18%; 12–24)	14 (8%; 4–13)
Duration of response (months)	NR (12·9–NR)	5·7 (5·6–NR)

Data are n (%), n (%; 95% CI), or median (95% CI). RECIST v1.1=Response Evaluation Criteria in Solid Tumors version 1.1. NR=not reached. *Patients with measurable disease at baseline.

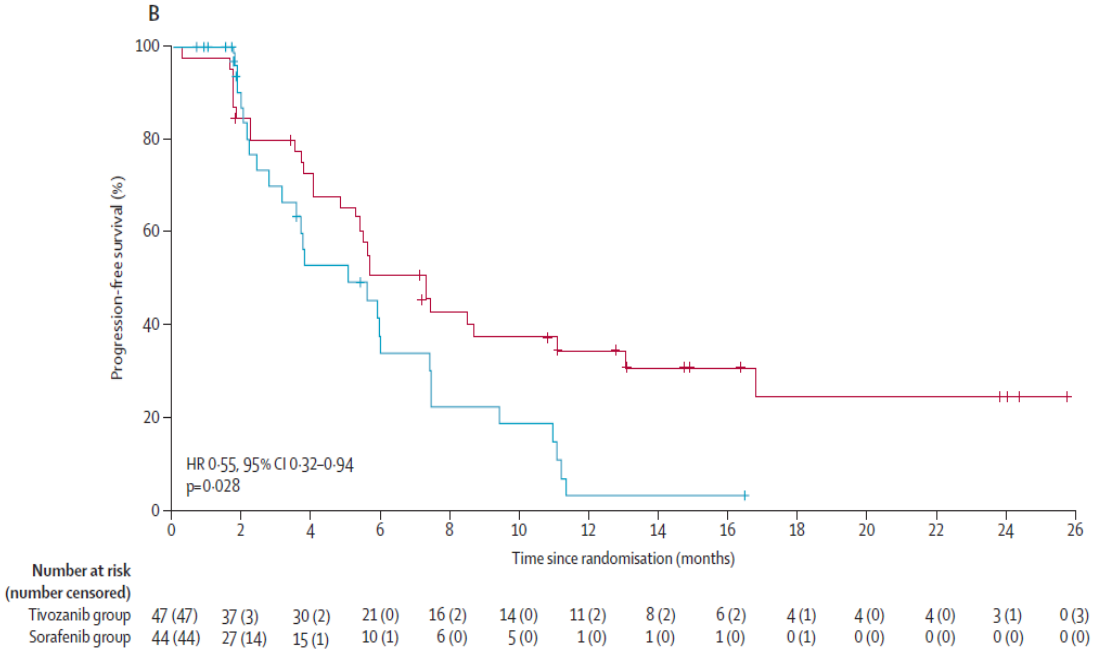
Table 2: **Best overall response, according to RECIST v1.1**

	Tivozanib group (n=175)	Sorafenib group (n=175)
Age (years)	62 (34–88)	63 (30–90)
Sex		
Male	126 (72%)	128 (73%)
Female	49 (28%)	47 (27%)
Race		
White	165 (94%)	167 (95%)
Non-white	10 (6%)	8 (5%)
Pathological diagnosis		
Clear cell	165 (94%)	160 (91%)
Clear cell component	9 (5%)	9 (5%)
Other*	1 (1%)	5 (3%)
IMDC risk category		
Favourable	34 (19%)	36 (21%)
Intermediate	109 (62%)	105 (60%)
Poor	32 (18%)	34 (19%)
Number of previous systemic therapies		
Two	108 (62%)	104 (59%)
Three	67 (38%)	71 (41%)
Previous therapies		
Two VEGFR TKIs	79 (45%)	80 (46%)
Checkpoint inhibitor plus VEGFR TKI	47 (27%)	44 (25%)
VEGFR TKI plus other systemic agent†	49 (28%)	51 (29%)
Time from initial diagnosis (months)	50 (10–347)	50 (9–224)
Time from most recent relapse (months)	1 (<1–121)	1 (<1–87)

Tivozanib in VEGF-refractory RCC



All patients

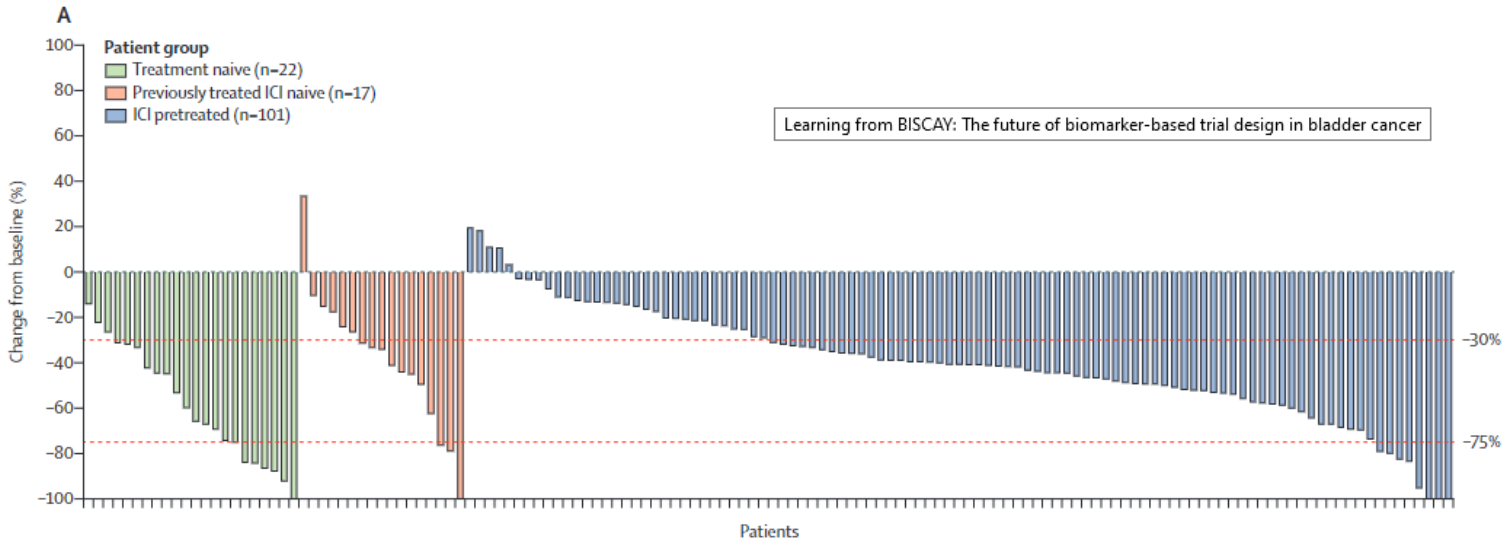


VEGF and IO refractory patients

IO rechallenge in PD-1 refractory setting

Lenvatinib plus pembrolizumab in patients with either treatment-naive or previously treated metastatic renal cell carcinoma (Study 111/KEYNOTE-146): a phase 1b/2 study

Chung-Han Lee, Amishi Yogesh Shah, Drew Rasco, Arpit Rao, Matthew H Taylor, Christopher Di Simone, James J Hsieh, Alvaro Pinto, David R Shaffer, Regina Girones Sarrio, Allen Lee Cohn, Nicholas J Vogelzang, Mehmet Asim Bilen, Sara Gunnestad Ribe, Musaberk Goksel, Øyvind Krohn Tennøe, Donald Richards, Randy F Sweis, Jay Courtright, Daniel Heinrich, Sharad Jain, Jane Wu, Emmett V Schmidt, Rodolfo F Perini, Peter Kubiak, Chinyere E Okpara, Alan D Smith, Robert J Motzer



	Treatment naive* (n=22)	Previously treated ICI naive† (n=17)	ICI pretreated* (n=104)	All patients‡ (N=145)
Age, years	55 (49–68)	66 (60–68)	60 (54–67)	60 (52–68)
Sex				
Male	18 (82%)	13 (76%)	80 (77%)	113 (78%)
Female	4 (18%)	4 (24%)	24 (23%)	32 (22%)
Previous nephrectomy	18 (82%)	17 (100%)	79 (76%)	115 (79%)
ECOG performance status				
0	13 (59%)	13 (76%)	47 (45%)	74 (51%)
1	9 (41%)	4 (24%)	57 (55%)	71 (49%)
MSKCC risk group§				
Favourable	9 (41%)	9 (53%)	37 (36%)	56 (39%)
Intermediate	10 (45%)	6 (35%)	44 (42%)	60 (41%)
Poor	3 (14%)	2 (12%)	23 (22%)	29 (20%)
IMDC risk group				
Favourable	9 (41%)	5 (29%)	18 (17%)	32 (22%)
Intermediate	10 (45%)	10 (59%)	61 (59%)	83 (57%)
Poor	3 (14%)	2 (12%)	25 (24%)	30 (21%)

IO rechallenge in PD-1 refractory setting

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

ORIGINAL ARTICLE

TiNivo: safety and efficacy of tivozanib-nivolumab combination therapy in patients with metastatic renal cell carcinoma

L. Albiges[1*], P. Barthélémy[2], M. Gross-Goupil[3], S. Negrier[4], M. N. Needle[5] & B. Escudier[1]

[1]Medical Oncology, Gustave Roussy, Villejuif, France; [2]Medical Oncology, Institut de Cancérologie Strasbourg Europe, Strasbourg, France; [3]Medical Oncology, Bordeaux University Hospital, Bordeaux, France; [4]Univ Lyon, Claude Bernard University Lyon 1, Medical Oncology, Léon Bérard Cancer Centre, Lyon, France; [5]AVEO Oncology, Boston, USA

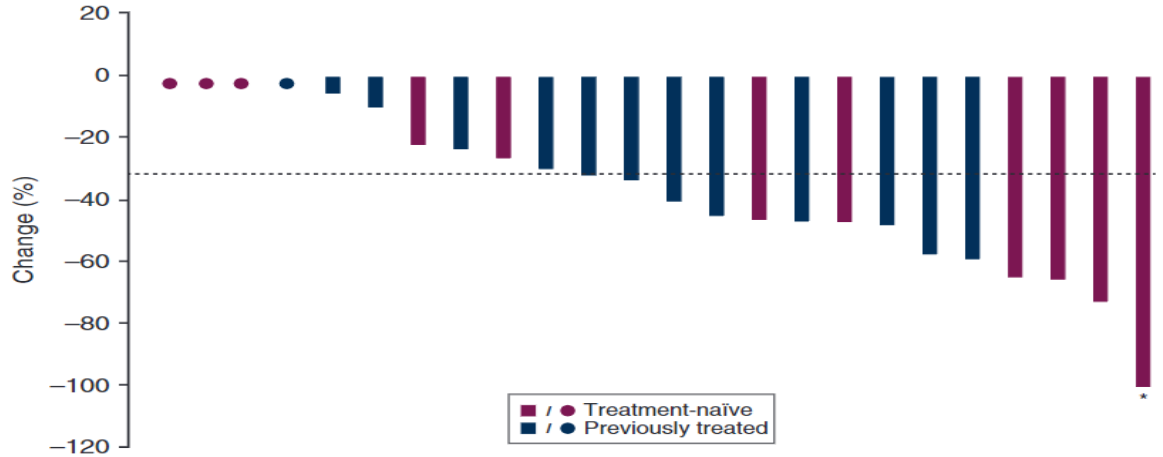


Table 1. Baseline patient characteristics

	Patients (N = 25)
Age, years, median (range)	64 (37–75)
Sex, *n* (%)	
Male	19 (76)
Female	6 (24)
Prior therapy, *n* (%)	
0	12 (48)
1	11 (44)
2+	2 (8)
ECOG PS, *n* (%)	
0	15 (60)
1	10 (40)
IMDC, *n* (%)	
Favorable	7 (28)
Intermediate	17 (68)
Poor	1 (4)

ECOG PS, Eastern Cooperative Oncology Group performance status; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium.

Table 3. Investigator-assessed response

	All patients (N = 25)	Treatment-naïve (n = 12)	Previously treated (n = 13)
Best overall response, *n* (%)			
CR	1 (4)	1 (8)	0
PR[a]	13 (52)	5 (42)	8 (62)
SD	10 (40)	5 (42)	5 (38)
PD	1 (4)	1 (8)	0
ORR (CR + PR)	14 (56)	6 (50)	8 (62)[a]
Disease control rate (CR + PR + SD)	24 (96)	11 (92)	13 (100)

IO rechallenge in in PD-1 refractory setting

ClinicalTrials.gov: NCT04338269

Advanced RCC (N≈500)
- Clear cell or non-clear cell (papillary or unclassified); sarcomatoid component allowed
- 1-2 prior lines of therapy
- 1 prior line of ICI; must be in immediately preceding line of therapy
- Progression on or after prior ICI

1:1

Cabozantinib 60 mg QD PO + Atezolizumab 1200 mg Q3W IV

Cabozantinib 60 mg QD PO

Stratification
- IMDC risk group (0, 1-2, ≥3)
- Clear cell vs non-clear cell (both without sarcomatoid component) vs any sarcomatoid component (clear cell or non-clear cell)
- Most recent ICI therapy (1L vs 2L)

Tumor assessment every 9 weeks for the first 18 months and every 12 weeks thereafter (RECIST v1.1)

Treatment until loss of clinical benefit or intolerable toxicity

No crossover allowed

Primary Endpoints: PFS by Independent Review Facility (IRF), OS

Secondary Endpoints: PFS by Investigator, ORR by Investigator and IRF, DOR by Investigator and IRF

TiNiVo-2

Phase 3, Randomized, Controlled, Multi-Center, Open-Label Study to Compare FOTIVDA® with OPDIVO® to FOTIVDA® Following Immunotherapy in RCC Patients

N = 326
- Histologically / cytologically confirmed recurrent/metastatic RCC
- ECOG PS 0 or 1
- Progressed following immediate prior immunotherapy treatment in first or second line
- Stratified by IMDC and prior TKI

Randomize 1:1

Tivozanib + Nivolumab

Tivozanib

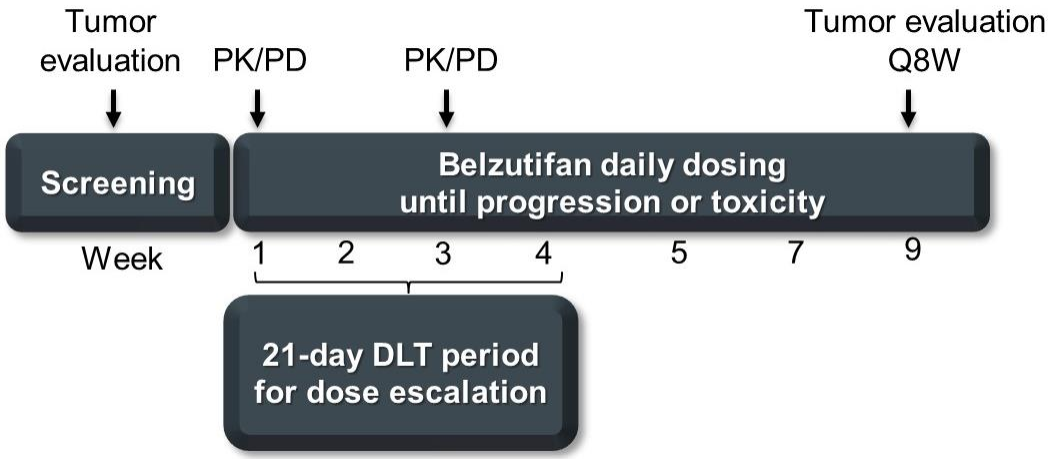
Treatment Until Progression

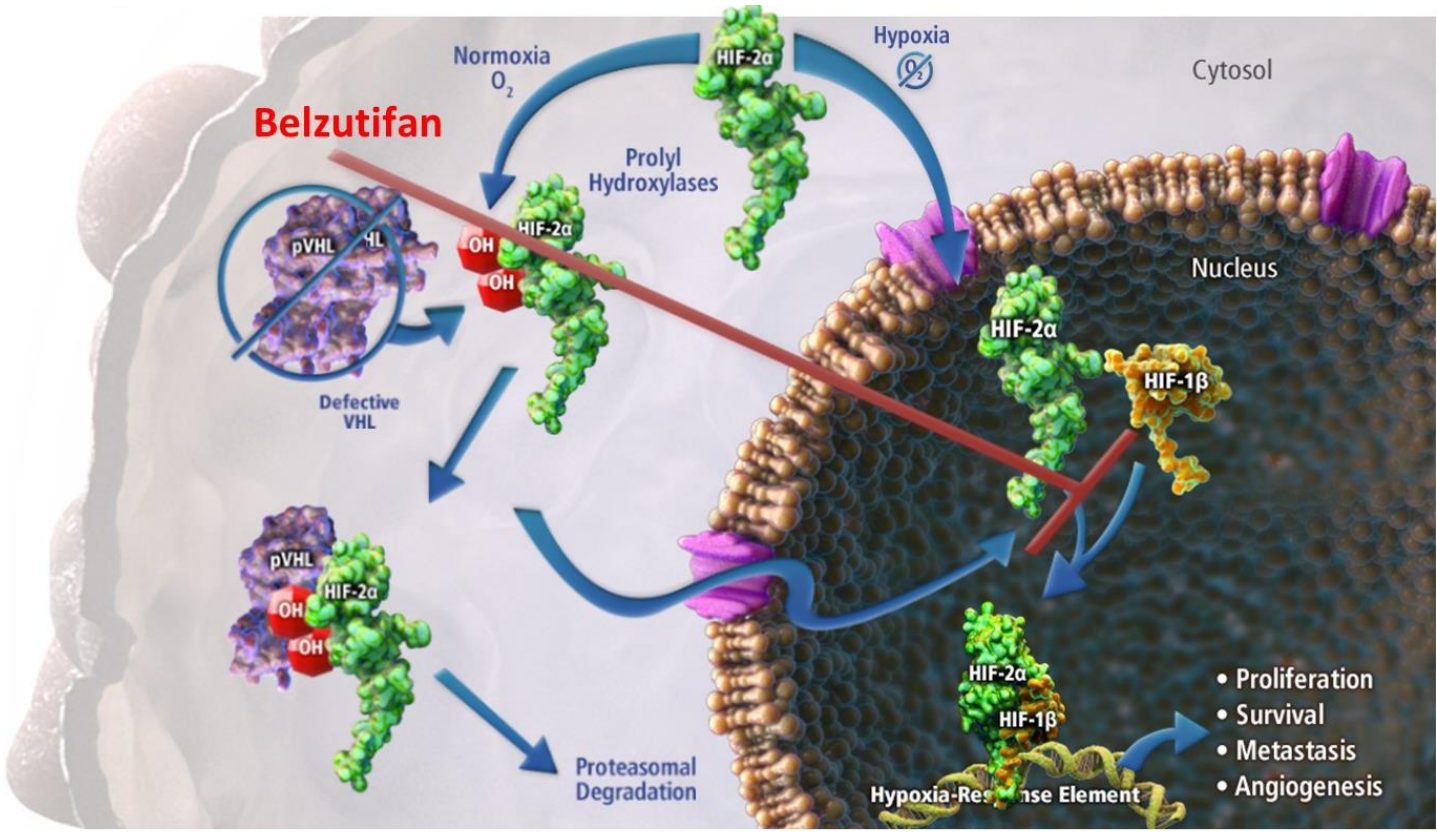
Endpoints
- Primary: PFS
- Secondary: OS, ORR, DoR, Safety and Tolerability

HIF-2α Inhibition in advanced RCC

The Oral HIF-2α Inhibitor Belzutifan (MK-6482) in Patients With Advanced Clear Cell Renal Cell Carcinoma: Updated Follow-up of a Phase 1/2 Study

Todd Michael Bauer,[1] Toni K. Choueiri,[2] Kyriakos P. Papadopoulos,[3] Elizabeth R. Plimack,[4] Jaime R. Merchan,[5] David F. McDermott,[6] M. Dror Michaelson,[7] Leonard Joseph Appleman,[8] Sanjay Thamake,[9] Rodolfo F. Perini,[9] Eric Kristopher Park,[9] Eric Jonasch[10]

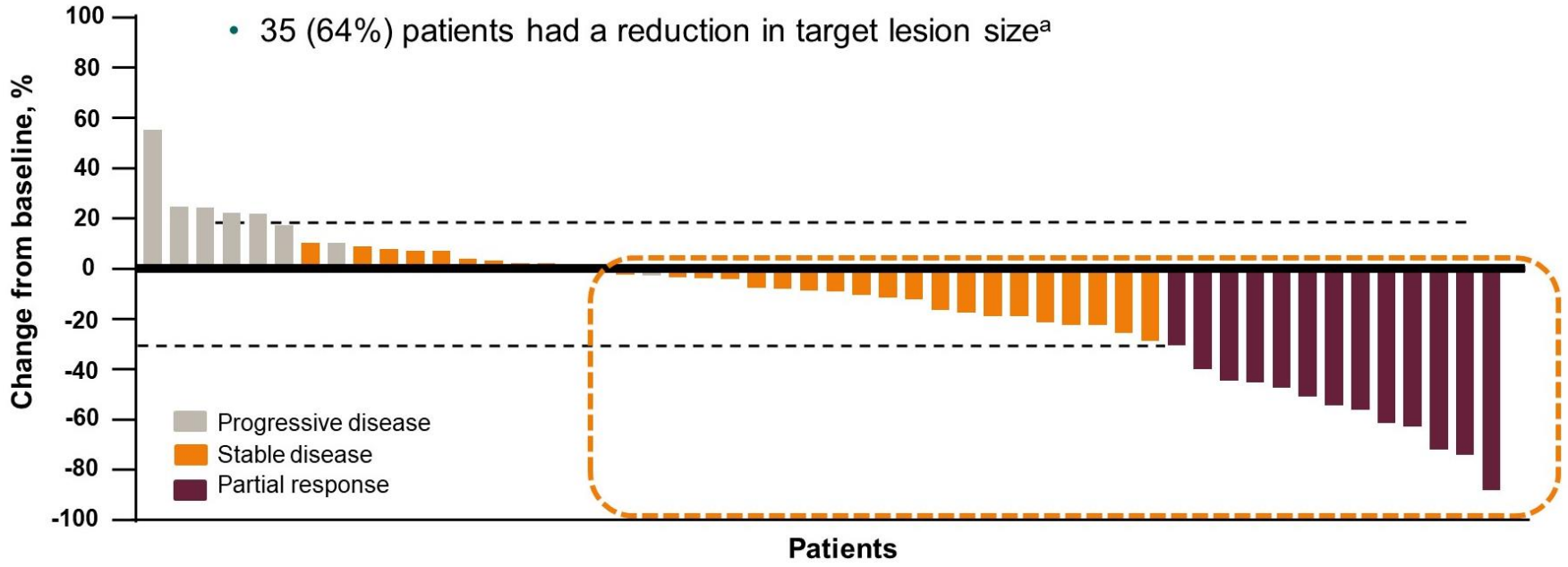




1. Linehan WM, Rickets CJ. *Nat Rev Urol*. 2019;16:539-552. 2. Couvé S et al. *Cancer Res*. 2014;74:6554-6564.

HIF-2α Inhibition in advanced RCC

Characteristics	All Patients N = 55
Prior systemic therapies, median (range), n	3 (1-9)
Prior systemic therapies, n (%)	
1	8 (15)
2	13 (24)
≥3	34 (62)
Prior anticancer therapies, n (%)	
VEGF/VEGFR	50 (91)
Checkpoint inhibitor	44 (80)
Investigational/other	16 (29)
mTOR inhibitor	13 (24)
Cytokine	10 (18)



HIF-2α Inhibition in advanced RCC

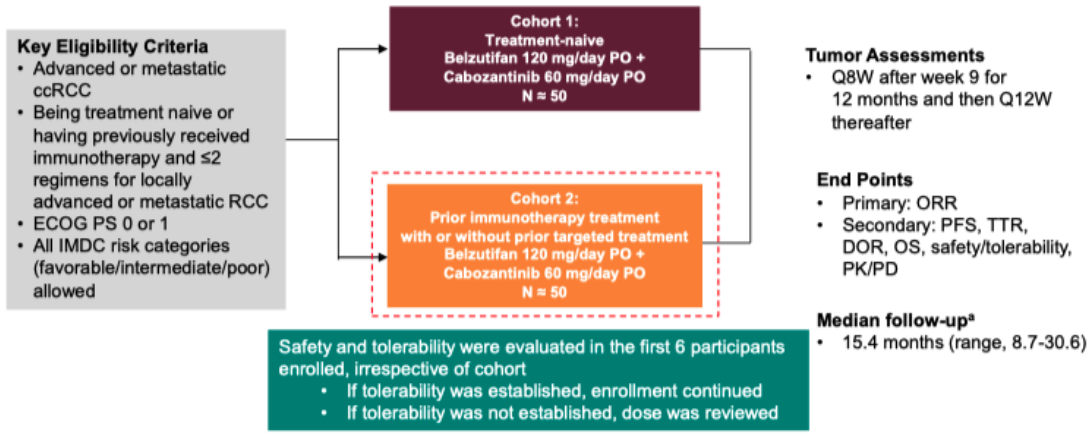
Phase 2 Study of Belzutifan, an Oral Hypoxia-Inducible Factor 2α Inhibitor, Plus Cabozantinib for Treatment of Advanced Clear Cell Renal Cell Carcinoma

David McDermott[1]; Toni Choueiri[2]; Todd Bauer[3]; Jaime Merchan[4]; Edward Arrowsmith[5]; Ananya Roy[6]; Rodolfo Perini[6]; Donna Vickery[6]; Scott Tykodi[7]

Baseline Clinical Characteristics

Characteristics	All Patients N = 52
Age, median (range), years	63 (43-79)
Sex, n (%)	
Male	38 (73.1)
Female	14 (26.9)
ECOG PS, n (%)	
0	23 (44.2)
1	29 (55.8)
IMDC risk group	
Favorable	11 (21.2)
Intermediate/poor	41 (78.8)
No. of previous lines of anticancer therapy, n (%)	
1	29 (55.8)
2	23 (44.2)
Prior anticancer therapy, n (%)	
IO only[a]	28 (53.8)
IO/VEGF[b]	24 (46.2)

Study Design (NCT03634540)



HIF-2α Inhibition in advanced RCC

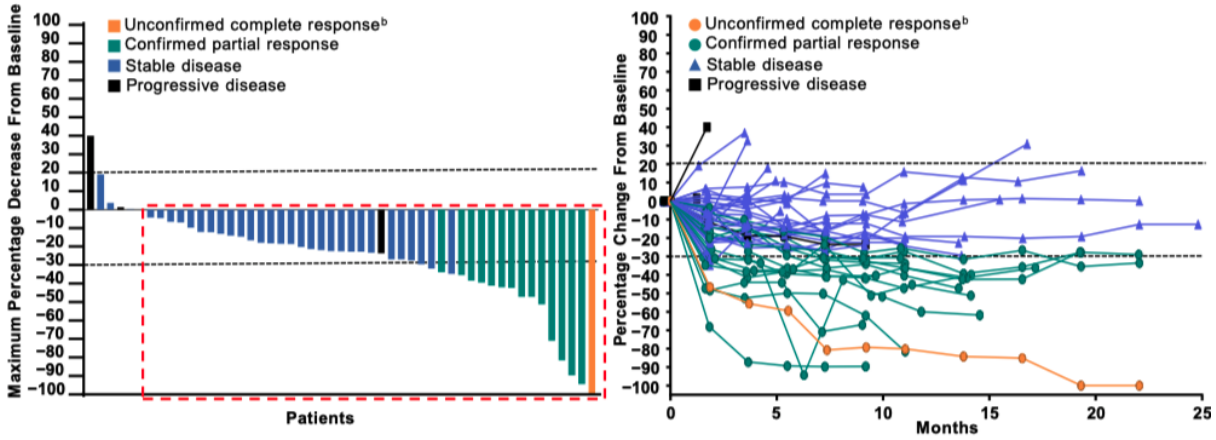
Objective Response Rate and Disease Control Rate

Population	ORR (CR + PR) n/N	ORR (CR + PR) % (95% CI)	DCR (CR + PR + SD) n/N	DCR (CR + PR + SD) % (95% CI)
All patients	15/52	28.8 (17.1-43.1)	48/52	92.3 (81.5-97.9)
IMDC risk category				
Favorable	3/11	27.3 (6.0-61.0)	11/11	100 (71.5-100)
Intermediate/poor	12/41	29.3 (16.1-45.5)	37/41	90.2 (76.9-97.3)
Prior anticancer therapy				
IO only	8/28	28.6 (13.2-48.7)	26/28	92.9 (76.5-99.1)
IO/VEGF	7/24	29.2 (12.6-51.1)	22/24	91.7 (73.0-99.0)

ıta cutoff: May 3, 2021.

Best Tumor Change From Baseline

- 45 of 52 patients (86.5%) experienced a reduction in target lesion size[a]



[a]1 patient had a response of "not available" and was recorded as having no change from baseline value. [b]Documented at a single time point before the data cutoff date; to be confirmed at a subsequent time point. Data cutoff: May 3, 2021.

Conclusions

- Frontline therapy for advanced RCC has undergone a paradigm shift in past 5 years
    - IO-based combination therapy (IO-IO vs. VEGF/IO) considered standard of care for most patients
    - Therapy selection should be individualized to patient goals, comorbidities and adverse event profiles
- Ongoing trials will be crucial for defining the optimal sequence in VEGF and IO refractory setting
- Novel agents (HIF-2a inhibitors) have shown promising early efficacy and will likely affect treatment landscape in relapsed refractory setting