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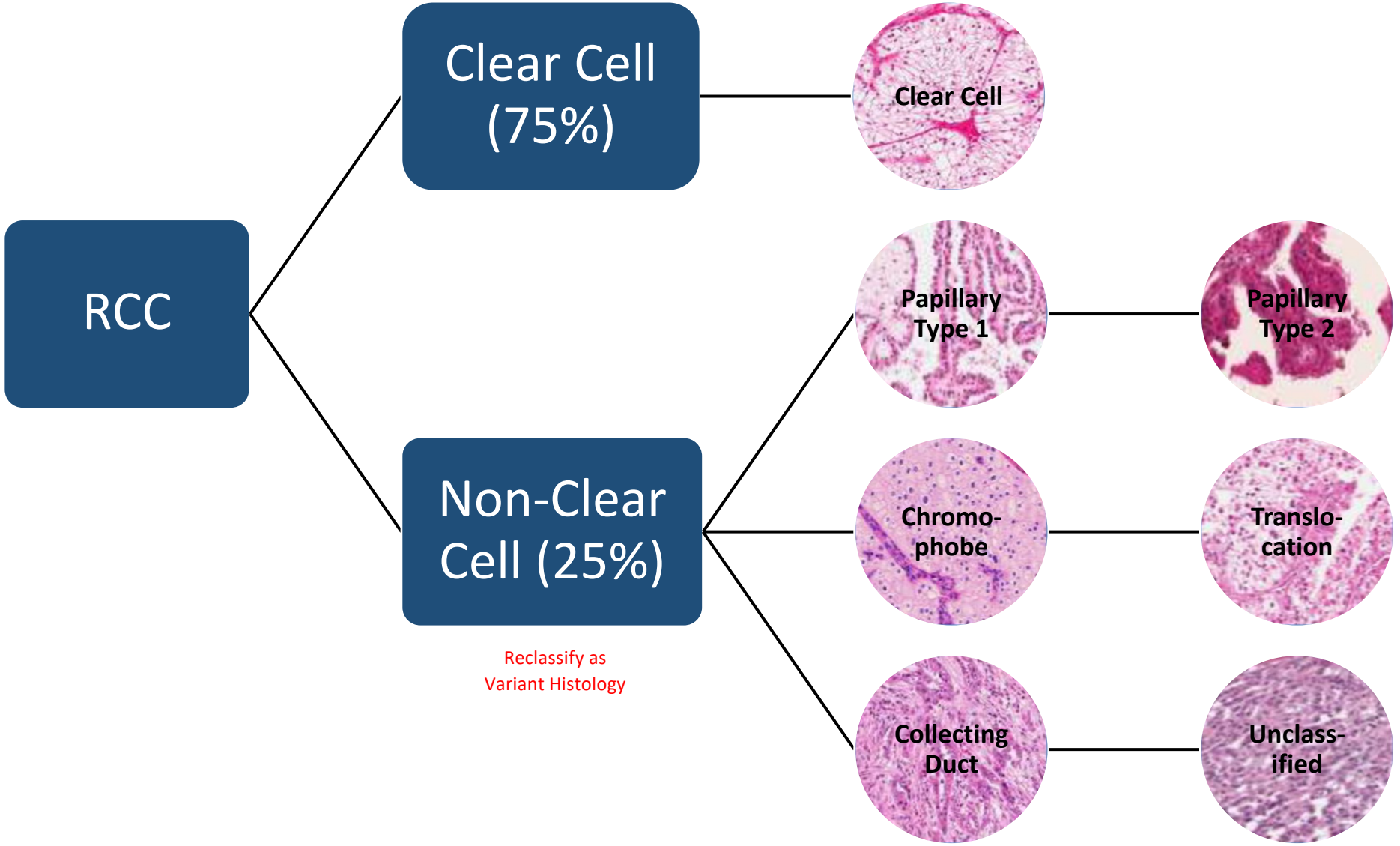
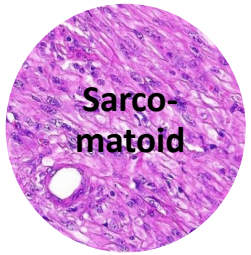
Updates in Renal Cell Carcinoma

RCC is Not Just One Disease



- Sarcomatoid dedifferentiation can occur in all RCC histologies
- 20% of stage IV renal cell carcinoma



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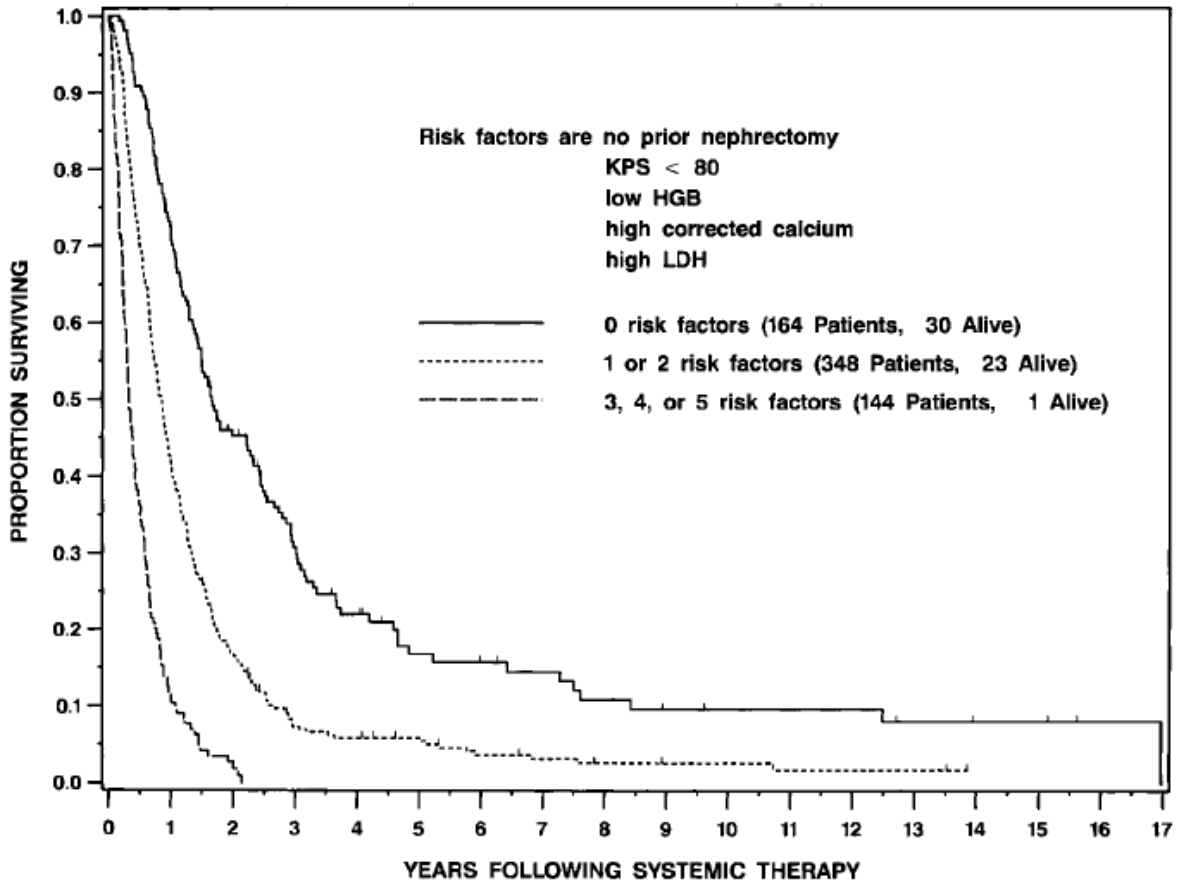
Prognostic Models in Metastatic RCC – MSKCC Model

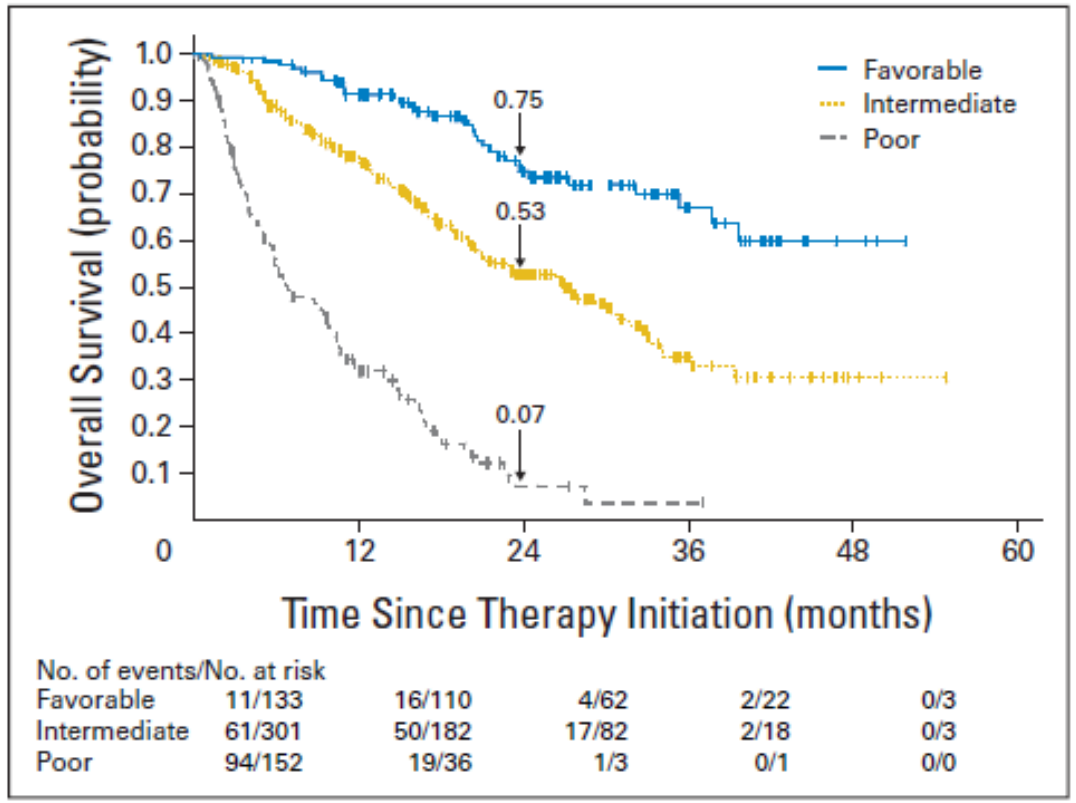


Initial model developed in treatment naïve patients initiating cytokine therapy.

	Survival (months)	1-Year Overall Survival	3-Year Overall Survival
Favorable	20	71%	31%
Intermediate	10	42%	7%
Poor	4	12%	0%

Motzer et al, JCO, 1999

Prognostic Models in Metastatic RCC – IMDC Model



- KPS <80
- Time from original diagnosis to initiation of targeted therapy <1 year
- Hemoglobin less than the lower limit of normal
- Serum calcium, neutrophil count, or platelet count greater than the upper limit of normal

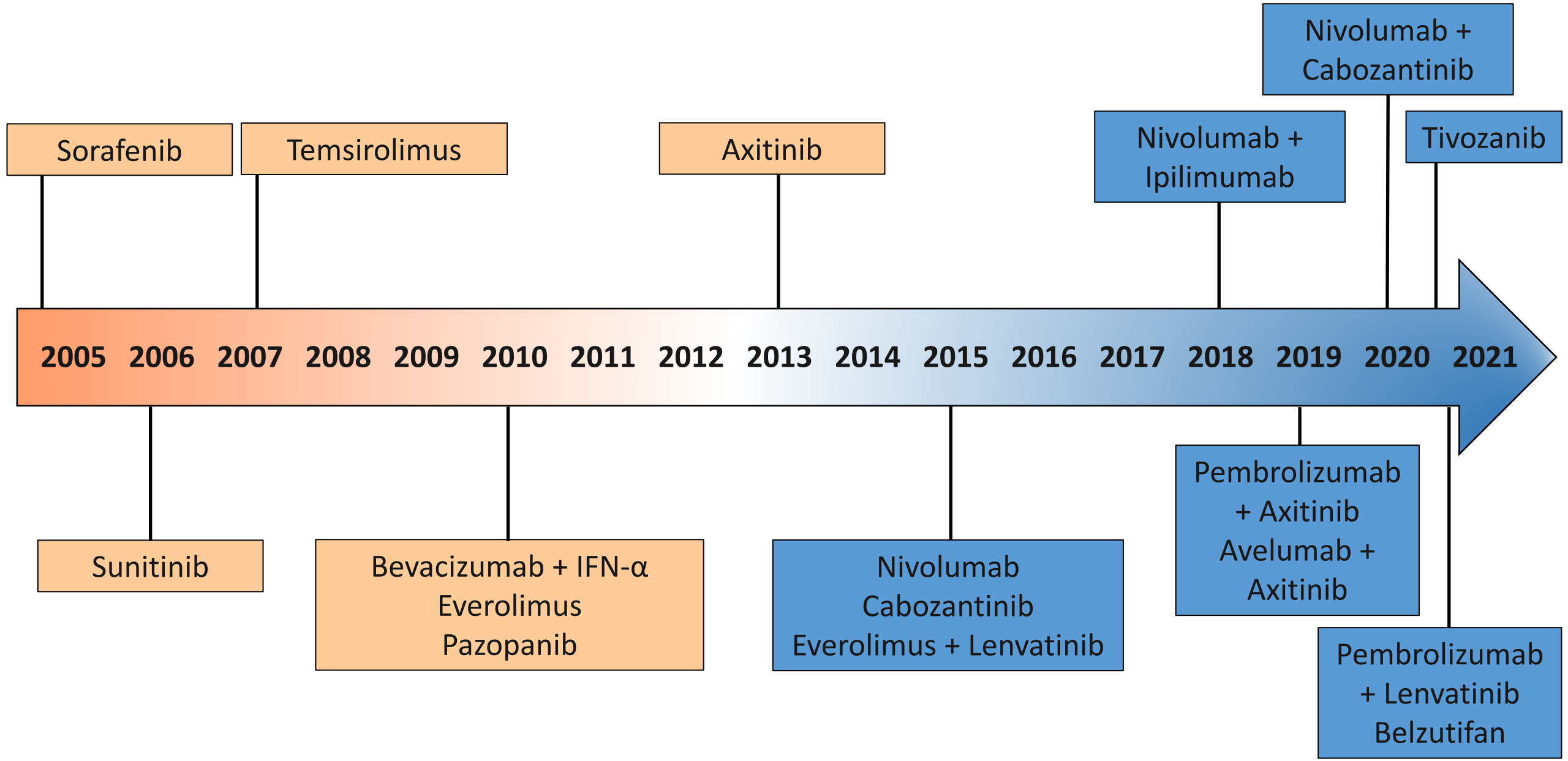
	Median Survival (months)	2-Year Overall Survival
Favorable (0)	NR	75%
Intermediate (1-2)	27	53%
Poor (3-6)	8.8	7%

Initial model developed in treatment naïve patients initiating targeted therapy
Validated in patients previously treated with targeted therapy

KPS=Karnofsky performance status.

Heng et al, JCO, 2009

Treatment Landscape of Metastatic RCC



Front line Systemic Therapy

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Front Line Treatment Options in Metastatic RCC

IO-IO

- Nivolumab + Ipilimumab

IO-VEGF

- Pembrolizumab + Axitinib
- Avelumab + Axitinib
- Nivolumab + Cabozantinib
- Pembrolizumab + Lenvatinib

VEGF

- Cabozantinib
- Sunitinib
- Pazopanib

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Historic Role of VEGF TKI for Frontline RCC

Eligibility
-Advanced/metastatic RCC
-No prior therapy
-Clear cell histology

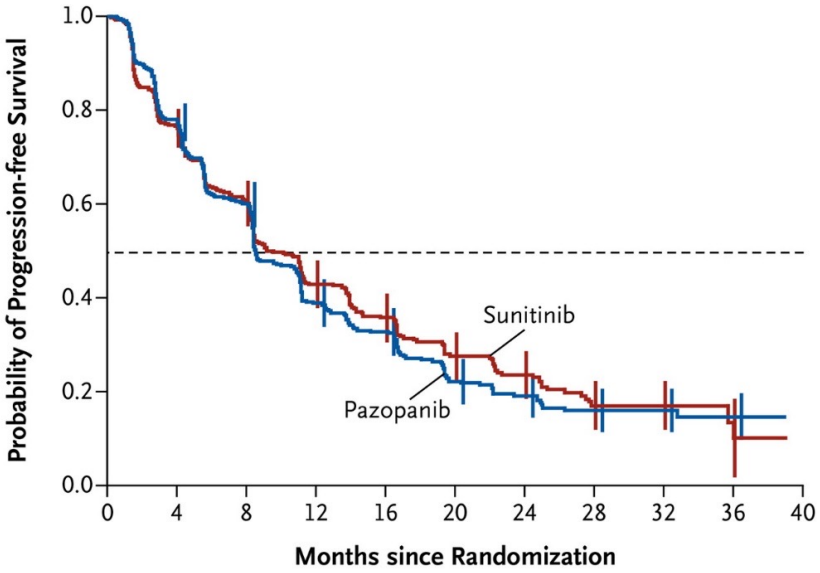
R
1:1

Pazopanib 800 mg PO daily

Sunitinib 50 mg PO daily
(4 weeks on/2 weeks off)

Co-Primary Endpoints: PFS
Open-Label
Non-Inferiority Design
N=890

	Pazopanib	Sunitinib
Median, months	8.4	9.5
HR (95% CI)	1.05 (0.90-1.22)	



No. at Risk

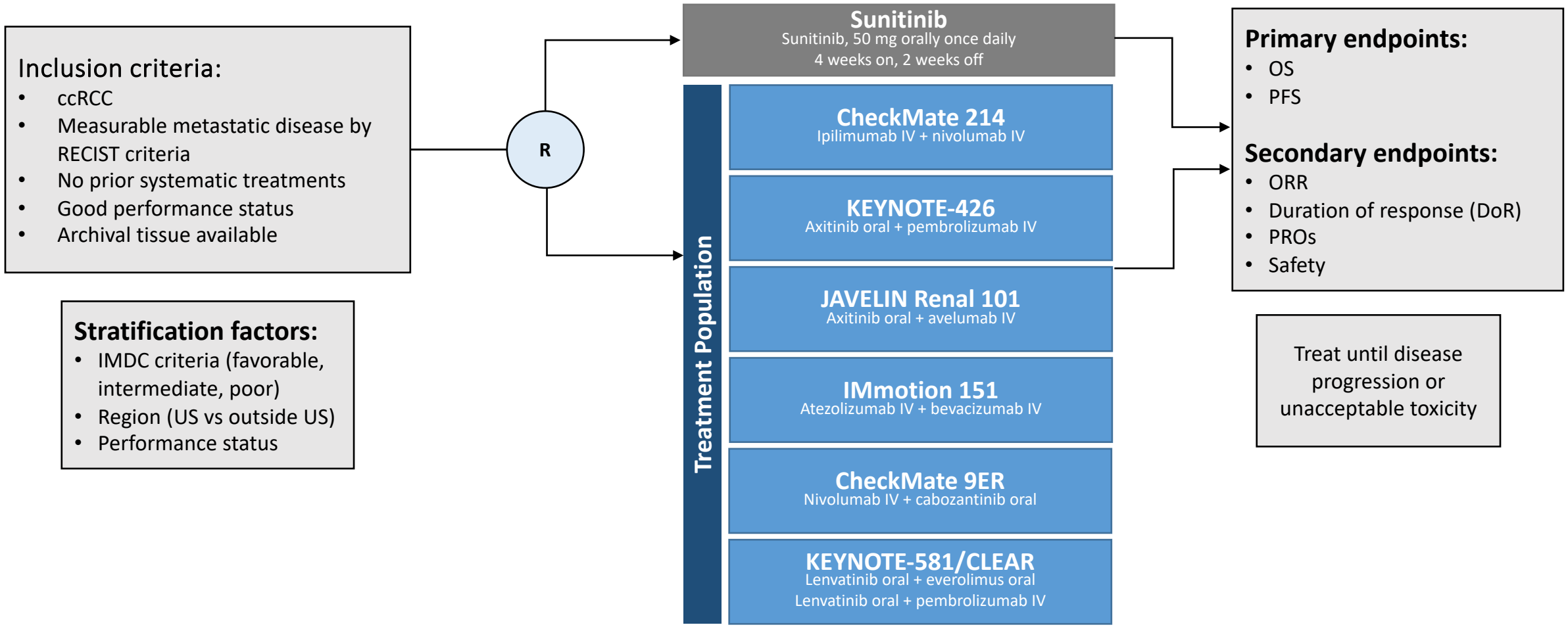
Pazopanib	557	361	245	136	105	61	46	19	13	1
Sunitinib	553	351	249	147	111	69	48	18	10	3

ORR 31% with pazopanib and 24% with sunitinib
Median OS 28.4 with pazopanib and 29.3 months with sunitinib

VEGF TKI=Vascular Endothelial Growth Factor Receptor Tyrosine Kinase Inhibitor; RCC=Renal cell carcinoma; PO=Orally.; PFS=Progression-free survival; HR=Hazard ratio; CI=Confidence interval; ORR=Objective response rate; OS=Overall survival.

Motzer et al, NEJM, 2013

Recent Clinical Trials In Frist Line RCC



Frontline Immunotherapy Combination Studies

Baseline Characteristics

Variable		Nivolumab + Ipilimumab CheckMate-214 n=1096	Pembrolizumab + Axitinib Keynote 426 n=861	Avelumab + Axitinib Javelin 101 n=886	Nivolumab + Cabozantinib CheckMate-9ER n=651	Pembrolizumab + Lenvatinib CLEAR n=1096
Follow-up, mo		67.7 (median)	42.8 (median)	34.1 (median)	44.0 (median)	49.8 (median)
IMDC Risk Group	Favorable	23%	33%	21%	23%	32%
	Intermediate	61%	56%	62%	58%	54%
	Poor	17%	13%	16%	19%	10%
Previous Nephrectomy		81%	83%	80%	69%	73%
PD-L1 Expression ≥1%		24% (Dako PD-L1 28-8; Tumor)	60% (Agilent Tech PD-L1 22C3; CPS)	63% (Ventana PD-L1 SP263; Immune)	25% (Dako PD-L1 28-8; Tumor)	31% (Agilent Tech PD-L1 22C3; CPS)
Primary Endpoint		ORR, PFS, OS in Int/Poor (IRC)	OS, PFS (IRC)	OS, PFS in PD-L1+ (IRC)	PFS (IRC)	PFS (IRC)

IMDC=International Metastatic RCC Database Consortium; PD-L1=Programmed Death Ligand 1; CPS=Combined positive score (TC+IC positive/TC all); ORR=Objective response rate; PFS=Progression-free survival; OS=Overall survival; Int=Intermediate; IRC=Independent review committee.

Motzer et al, NEJM, 2018; Rini et al, NEJM, 2019; Motzer et al, NEJM, 2019; Choueiri et al, NEJM, 2021; Motzer et al, NEJM, 2021.

Summary of Select Immunotherapy Combination Trials

	Nivolumab + Ipilimumab CheckMate-214 n=1096	Pembrolizumab + Axitinib Keynote 426 n=861	Nivolumab + Cabozantinib CheckMate-9ER n=651	Pembrolizumab + Lenvatinib Clear n=1096
Follow-up, mo	67.7 (median)	42.8 (median)	44.0 (median)	49.8 (median)
Median PFS, mo	12.3	15.7	16.6	23.9
PFS HR	0.86	0.69	0.58	0.47
Median OS, mo	55.7	47.2	49.5	53.7
24-month OS, %	71	78	76	80
36-month OS, %	58	63	59	66
OS HR	0.72	0.84	0.70	0.79
ORR, %	39	61	56	71
CR, %	12	12	12	18
PD, %	18	12	6	5

Mo=months; PFS=Progression-free survival; HR=Hazard ratio; ORR=Objective response rate; CR=Complete response rate; PD=Progressive disease rate; TTR=Time to response; DOR=Duration of response.

What about Toxicity?

	Nivolumab + Ipilimumab CheckMate-214 n=1096 Median Follow-Up 67.7 mo	Pembrolizumab + Axitinib Keynote 426 n=861 Median Follow-Up 42.8 mo	Nivolumab + Cabozantinib CheckMate-9ER n=651 Median Follow-Up 44.0 mo	Pembrolizumab + Lenvatinib Clear n=1096 Median Follow-Up 49.8 mo
TRAE Grade 3-5	48%	68%	67%	74%
TRAE leading to D/C (either/both drugs)	22.1%*	33.3/NR	27.5%/6.6%	29% pembrolizumab 26% lenvatinib 13% both
HD Corticosteroid	29%	27%	13%	Not reported
TR deaths, n (%)	1.5%	1.2%	0%	1.1%

*From minimum 42 month follow-up. #From median 16.6 month follow-up.
Mo=Months; TRAE=Treatment-related adverse events; D/C=Discontinue; HD=high dose; TR=Treatment-related.

What about Quality of Life?

	CheckMate-214		Keynote-426		Checkmate-9ER		Clear		
	Nivolumab + Ipilimumab	Sunitinib	Pembrolizumab + Axitinib	Sunitinib	Nivolumab + Cabozantinib	Sunitinib	Pembrolizumab + Lenvatinib	Lenvatinib + Everolimus	Sunitinib
	Intermediate/Poor		All Risk		All Risk		All Risk		
FKSI-19	↑				↑				
FKSI-DRS			=		↑		=/↑	=/↓	
EQ-5D-3L	↑		=		↑		=/↑	=/↓	
EORTC QLQ-C30			=				=/↑	=/↓	
FACT-G	↑								

FKSI-19=Functional Assessment of Cancer Therapy—Kidney Symptom Index; FKSI-DRS=Functional Assessment of Cancer Therapy-Disease related symptoms; EPRTC QLQ-C30=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire—Core 30; FACT-G=Functional Assessment of Cancer Therapy—General.

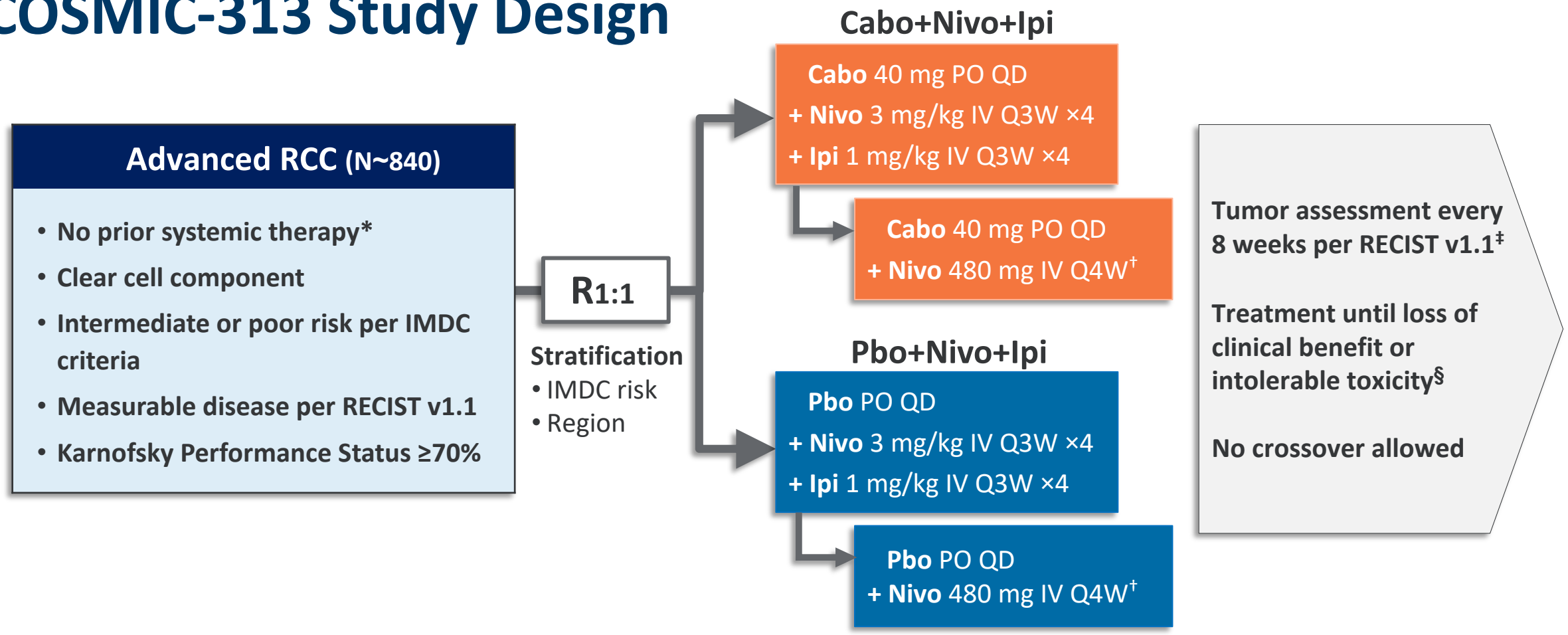
PRINCIPLES OF SYSTEMIC THERAPY FOR RELAPSE OR STAGE IV DISEASE

FIRST-LINE THERAPY FOR CLEAR CELL HISTOLOGY			
Risk	**Preferred Regimens**	**Other Recommended Regimens**	**Useful in Certain Circumstances**
Favorable[a]	• Axitinib + pembrolizumab[b] (category 1) • Cabozantinib + nivolumab[b] (category 1) • Lenvatinib + pembrolizumab[b] (category 1)	• Axitinib + avelumab[b] • Cabozantinib (category 2B) • Ipilimumab + nivolumab[b] • Pazopanib • Sunitinib	• Active surveillance[c] • Axitinib (category 2B) • High-dose IL-2[d] (category 2B)
Poor/ intermediate[a]	• Axitinib + pembrolizumab[b] (category 1) • Cabozantinib + nivolumab[b] (category 1) • Ipilimumab + nivolumab[b] (category 1) • Lenvatinib + pembrolizumab[b] (category 1) • Cabozantinib	• Axitinib + avelumab[b] • Pazopanib • Sunitinib	• Axitinib (category 2B) • High-dose IL-2[d] (category 3) • Temsirolimus[e] (category 3)

SUBSEQUENT THERAPY FOR CLEAR CELL HISTOLOGY (IN ALPHABETICAL ORDER BY CATEGORY)			
Immuno-oncology (IO) Therapy History Status	**Preferred Regimens**	**Other Recommended Regimens**	**Useful in Certain Circumstances**
IO Therapy Naïve	• None	• Axitinib + pembrolizumab[b] • Cabozantinib • Cabozantinib + nivolumab[b] • Ipilimumab + nivolumab[b] • Lenvatinib + everolimus • Lenvatinib + pembrolizumab[b] • Nivolumab[b]	• Axitinib • Everolimus • Pazopanib • Sunitinib • Tivozanib[f] • Belzutifan (category 2B) • Bevacizumab[g] (category 2B) • High-dose IL-2 for selected patients[d] (category 2B) • Temsirolimus[e] (category 2B) • Axitinib + avelumab[b] (category 3)
Prior IO Therapy	• None	• Axitinib • Cabozantinib • Lenvatinib + everolimus • Tivozanib[f]	• Axitinib + pembrolizumab[b] • Cabozantinib + nivolumab[b] • Everolimus • Ipilimumab + nivolumab[b] • Lenvatinib + pembrolizumab[b] • Pazopanib • Sunitinib • Belzutifan (category 2B) • Bevacizumab[g] (category 2B) • High-dose IL-2 for selected patients[d] (category 2B) • Temsirolimus[e] (category 2B) • Axitinib + avelumab[b] (category 3)

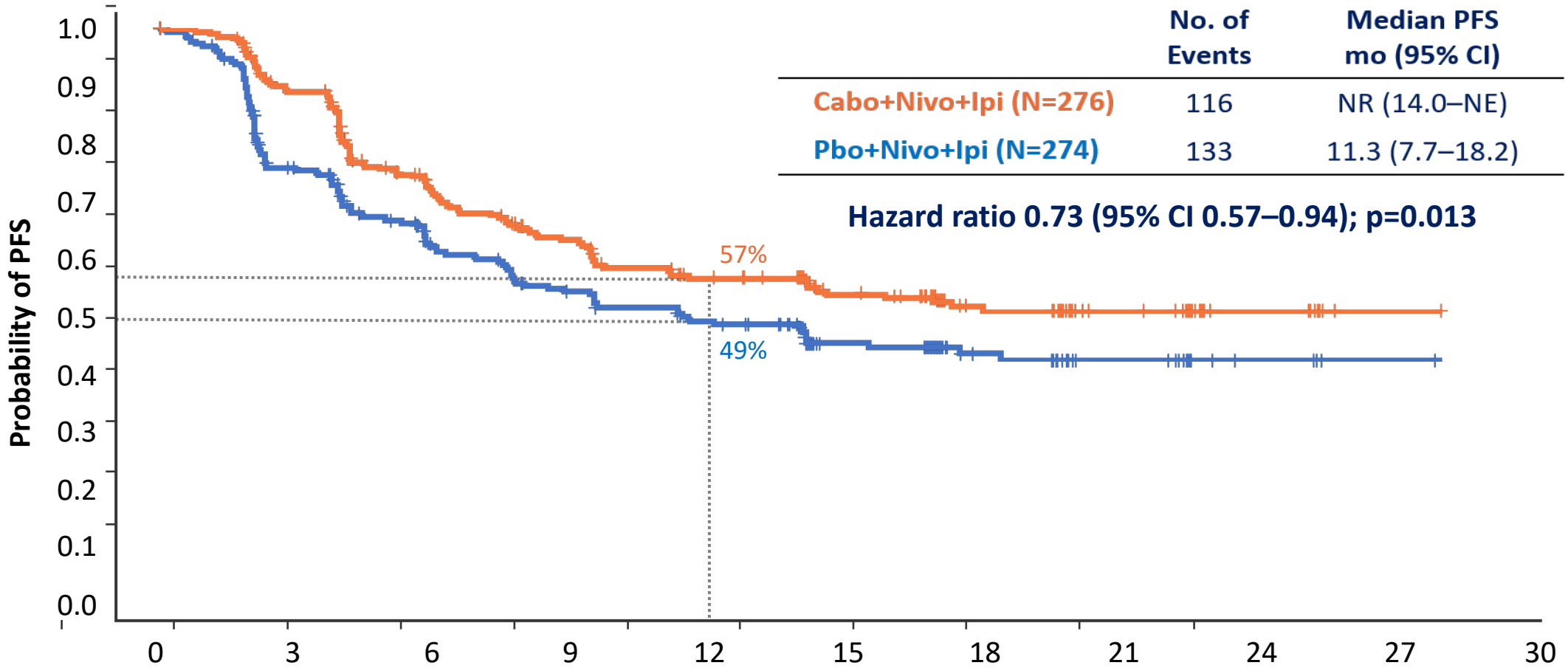
What about triple therapy?

COSMIC-313 Study Design



*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.

Progression-Free Survival: 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.

Date of the 249th event: Aug 23, 2021

Tumor Response (PITT Population)

	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)

Tumor response per RECIST v1.1 by BIRC
Disease control rate = complete response + partial response + stable disease

Data cut-off: Jan 31, 2022

Treatment Exposure and Discontinuation

	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

What about patients not able to receive IO?

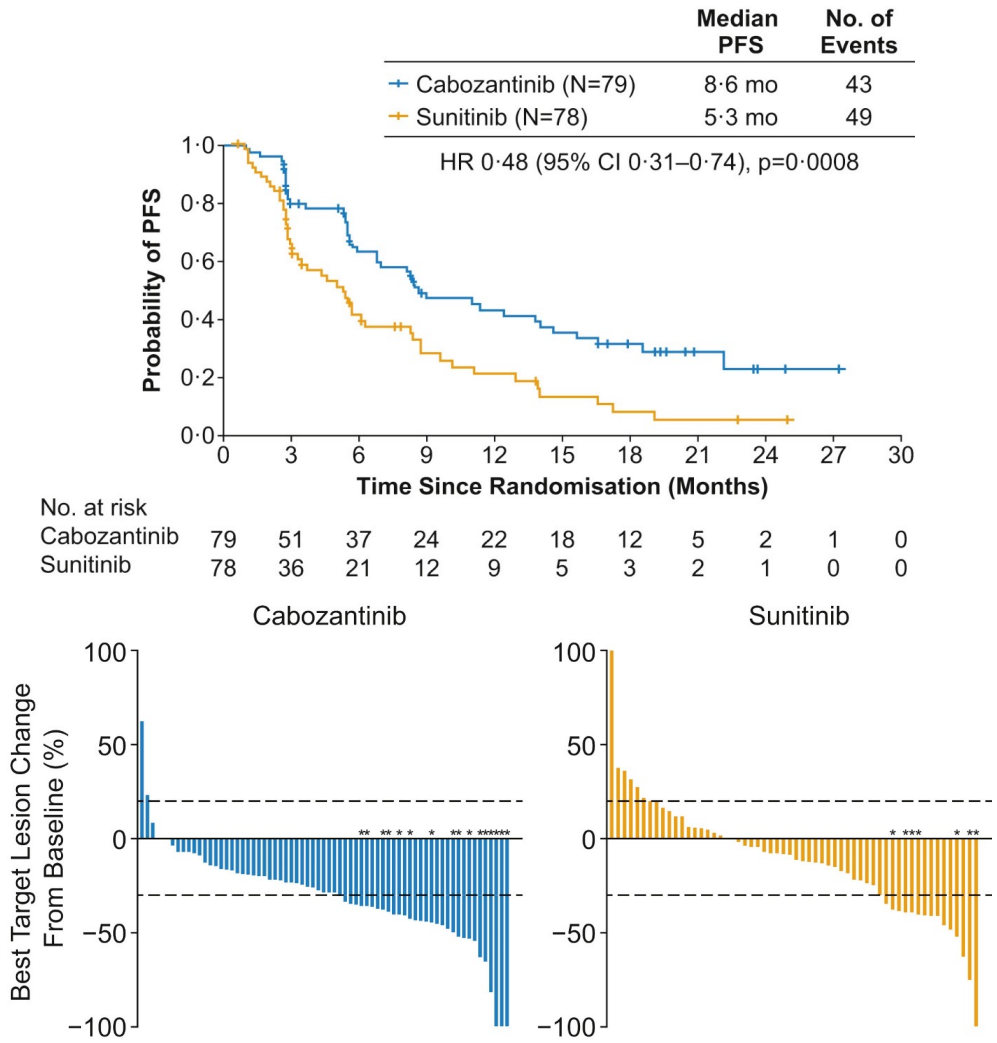
Eligibility
-Advanced/metastatic RCC
-No prior therapy
-Clear cell histology
-IMDC Intermediate/Poor Risk

R
1:1

Cabozantinib 60 mg PO daily
(continuous)

Sunitinib 50 mg PO daily
(4 weeks on/2 weeks off)

Co-Primary Endpoints: PFS
N=157



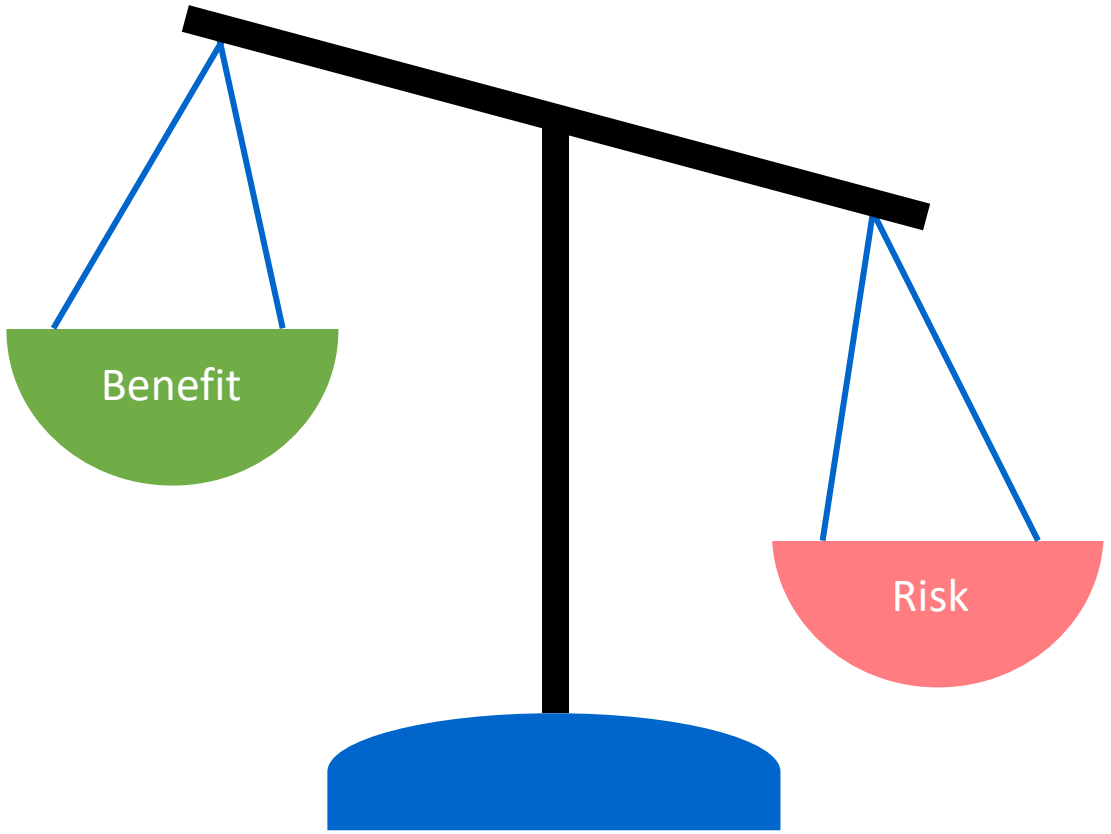
ORR 20% versus 9%*

*Assessed by independent review committee. IO=Immunotherapy; RCC=Renal cell carcinoma; IMDC=International Metastatic RCC Database Consortium; PO=Orally.; PFS=Progression-free survival.

Choueiri et al, JCO, 2017; Choueiri et al Eur J Cancer, 2018

Balancing Endpoints for Selection of Frontline Therapy

Improved OS
Improved PFS
Improved response rate
Limited PD rate
Durability of response
Depth of response
Complete response
Treatment-free survival
Improved QOL



Immune-mediated AE
Chronic TKI toxicity
Limited durability of response
Primary PD rate
No benefit in QOL

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Subsequent Line Systemic Therapy

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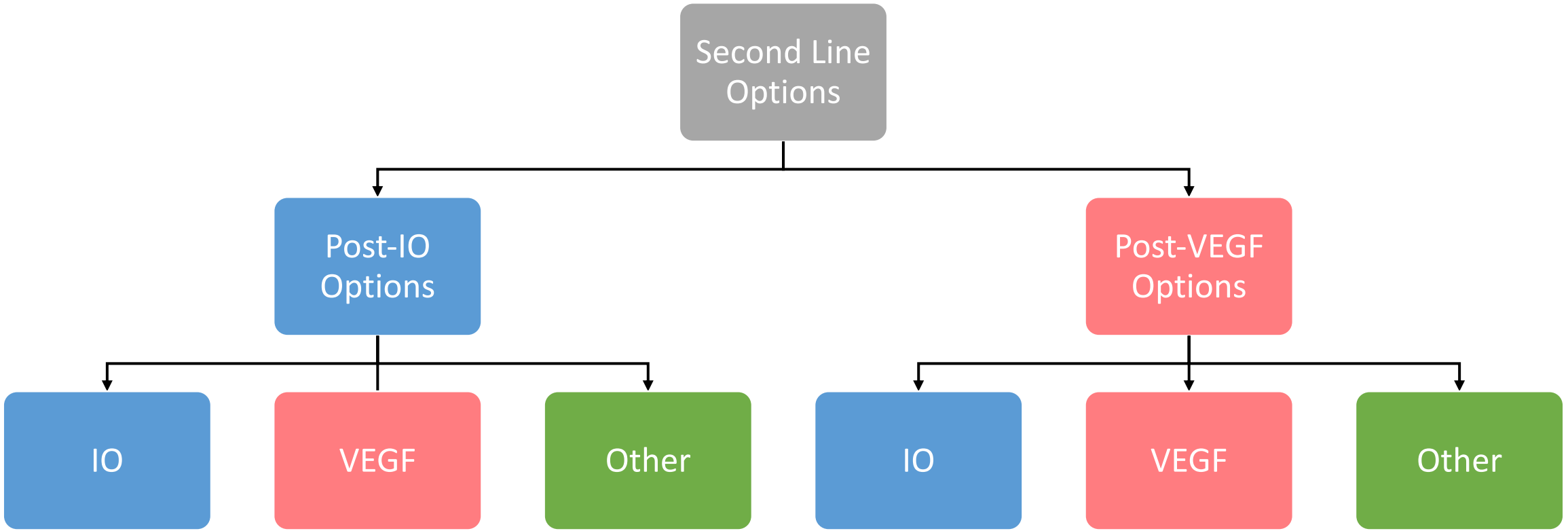
Landscape of Second Line Options



IO=immunotherapy; VEGF=Vascular endothelial growth factor.

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Second Line TKI Therapy

	Axitinib (Phase 3 AXIS)	Cabozantinib (Phase 3 METEOR)	Lenvatinib + Everolimus (Phase 2)
N	723	658	153
Treatment line	2nd	≥2nd	2nd
Comparator(s)	Sorafenib	Everolimus	Lenvatinib vs everolimus
ORR	19% vs 9%	17% vs 3%	
PFS	6.7 vs 4.7 months HR, 0.665; P = .0001	7.4 vs 3.9 months HR, 0.51; P < .0001	14.6 vs 7.4 vs 5.5 HR combination vs everolimus, 0.4; P = .0005
OS	20.1 vs 19.2 months HR, 0.97; P = .3744	21.4 vs 16.5 months HR, 0.66; P = .0003	25.5 vs 19.1 vs 15.4 HR combination vs everolimus, 0.51; P = .024
Approval date	2012	2016	2016

Rini et al, Lancet, 2011; Motzer et al, Lancet Oncol, 2013; Choueiri et al, Lancet Oncol, 2016; Motzer et al, Lancet Oncol, 2015; Alonso-Gordoa et al, Int J Mol Sci, 2019.

Second Line IO

CheckMate 025

	Nivolumab (Phase 3 CheckMate 025)
N	821
Treatment line	2nd or 3rd
Comparator(s)	Everolimus
ORR	23% vs 4%
PFS	4.2 vs 4.5 months HR, 0.84
OS	25.8 vs 19.7 months HR, 0.73
Approval date	2015

Motzer et al, Cancer, 2020

What about IO post IO?

	Titan RCC ESMO 2019	OMNIVORE ASCO 2020	HCRN GU16-260 ASCO 2020
Number of patients	207	83	123
Prior TKI	Yes	Yes	No
Treatment	Nivo→Ipi	Nivo→Ipi	Nivo→Ipi
Ipilimumab doses	4	2	4
ORR	12%	4%	13%
CR	2.7%	0%	0%

Adaptive trials with addition of ipilimumab based on response
In aggregate, demonstrated low rate of conversion to ORR and low CR rate

TKI=Tyrosine kinase inhibitor; ORR=Objective response rate; CR=Complete response; Nivo=nivolumab; Ipi=Ipilimumab.

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Phase 2 Lenvatinib + Pembrolizumab

Eligibility

-Advanced/metastatic RCC

-Clear cell histology

-Disease progression post PD-1/PD-L1 (must have received ≥2 doses)

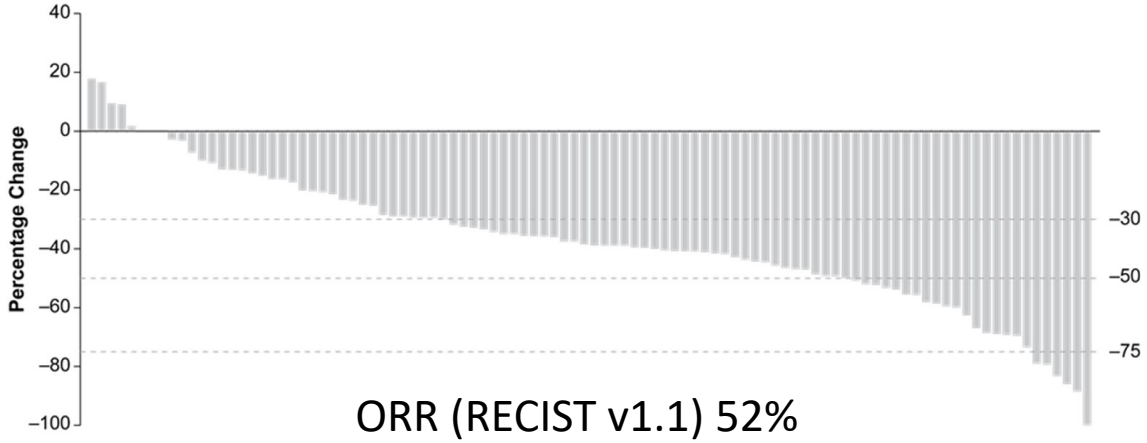
→

Lenvatinib 20 mg PO daily + Pembrolizumab 200 mg IV every three weeks

Primary Endpoint: Objective response rate at 24 weeks

Open-Label

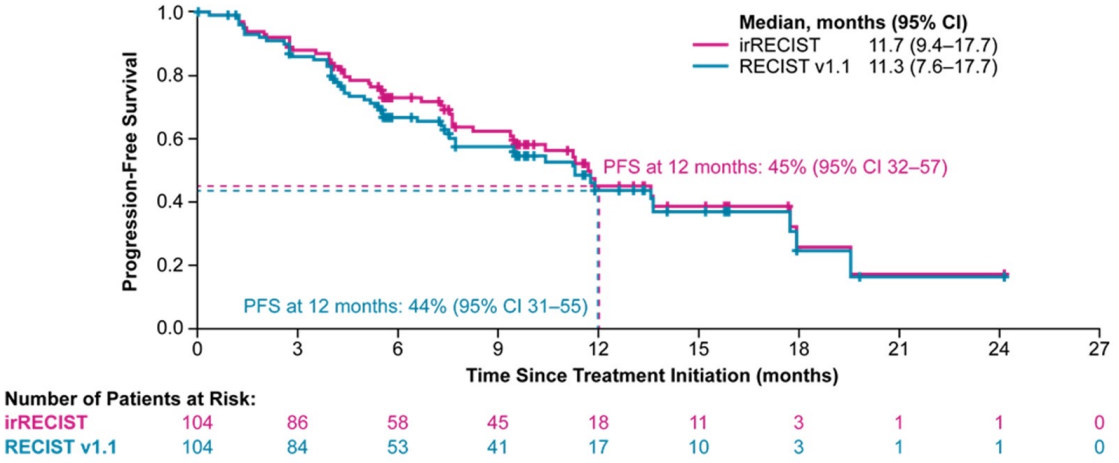
N=104



ORR (RECIST v1.1) 52%

ORR (irRECIST) 55%

CR 0%



RCC=Renal cell carcinoma; PD-1=Programmed death 1; PD-L1=Programmed death ligand 1; PO=By mouth; IV=Intravenous; ORR=Objective response rate; RECIST=Response Evaluation Criteria in Solid Tumours; irRECIST=Immune-related Response Evaluation Criteria in Solid Tumours.

Lee et al, ASCO Virtual Meeting, 2020

What about VEGF Blockade Post IO?

	Study	Agents	N	ORR	PFS/TTF (months)
Albiges (EJC, 2015)	Retro	VEGF TKI/mTOR (axitinib/everolimus)	56	13%	6.6
Nadal (Ann Oncol, 2016)	Retro	VEGF TKI	70	28%	6.4
Derosa (ESMO, 2017)	Retro	VEGF TKI (cabozantinib/axitinib)	56	33%	8.0
McGregor (EJC, 2020)	Retro	Cabozantinib	86	36%	6.5
Auvray (EJC, 2019)	Retro	TKI (post nivolumab/ipilimumab)	33	36%	8.
Shah (EJC, 2019)	Retro	TKI	70	41%	13.2
Powles (BJC, 2018)	Subgroup P3	Cabozantinib/Everolimus	32	22%	4.1
Ornstein (Lancet Oncol, 2019)	Prospective	Axitinib	38	45%	8.8

Single of efficacy of VEGF targeted therapy post immunotherapy treatment

Retro=Retrospective; P3=Phase 3; VEGF=Vascular endothelial growth factor; TKI=Tyrosine kinase inhibitor; mTOR=Mammalian target of rapamycin; N=Number; ORR=Objective response rate; PFS=Progression-free survival; TTF=Time to treatment failure.

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

Stratification factors

- **IMDC risk group**
  0 vs 1-2 vs ≥3
- **Histology**
  Dominant clear cell without sarcomatoid vs dominant non-clear cell without sarcomatoid vs any sarcomatoid[b]
- **Most recent line of ICI**
  Adjuvant vs 1L vs 2L

Primary endpoints

- Independent centrally-assessed PFS[c]
- OS

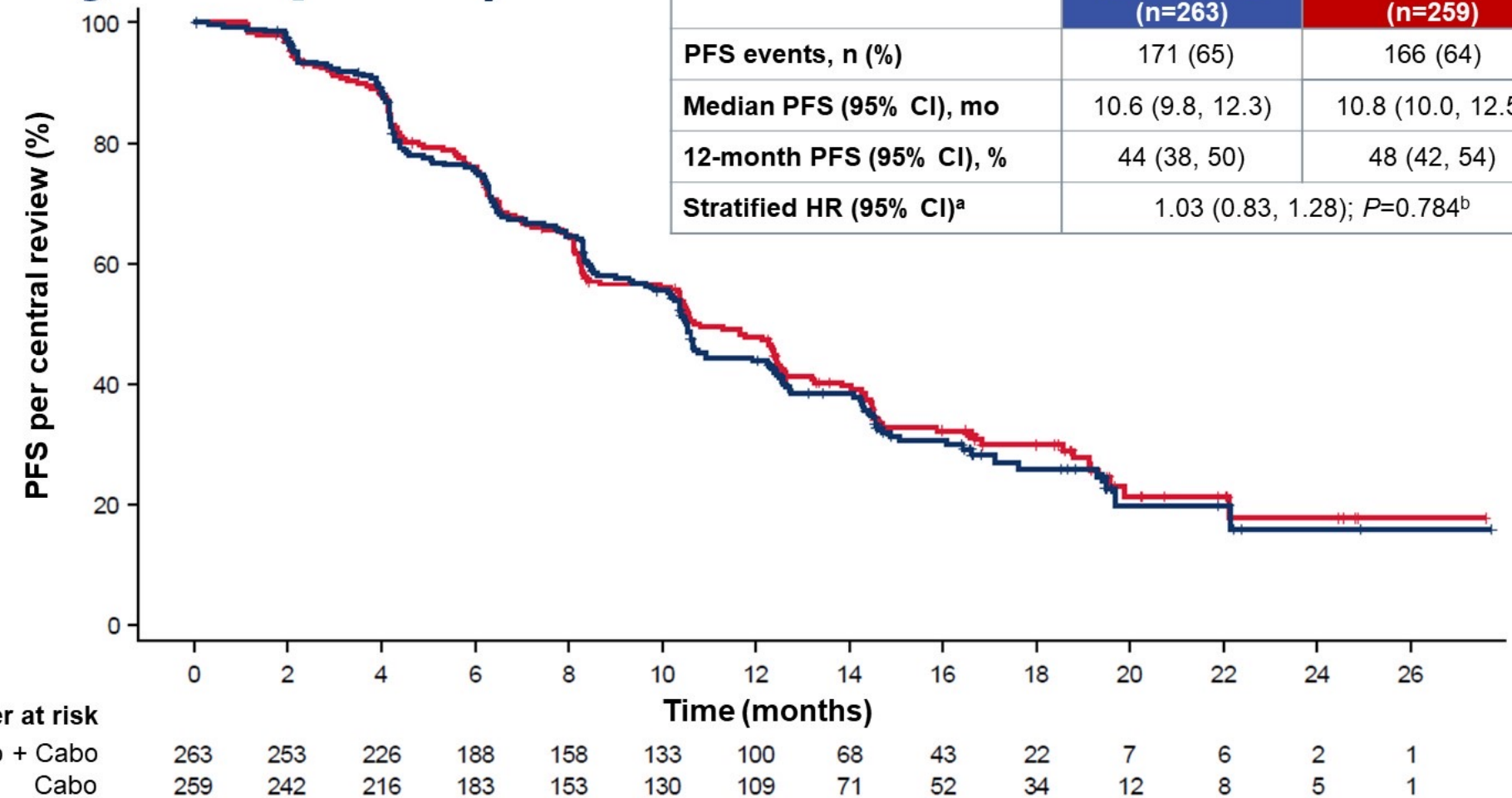
Key secondary endpoints

- Investigator-assessed PFS[c]
- ORR (per central review and per investigator)[c]
- Duration of response (per central review and per investigator)[c]
- Safety

ClinicalTrials.gov ID, NCT04338269. IMDC, International Metastatic RCC Database Consortium. Patients were enrolled between July 28, 2020 and December 27, 2021.
[a] Papillary, chromophobe or unclassified (chromophobe requires sarcomatoid differentiation). [b] Clear cell or non-clear cell. [c] Assessed according to RECIST 1.1.

Primary analysis of centrally reviewed PFS (primary endpoint)

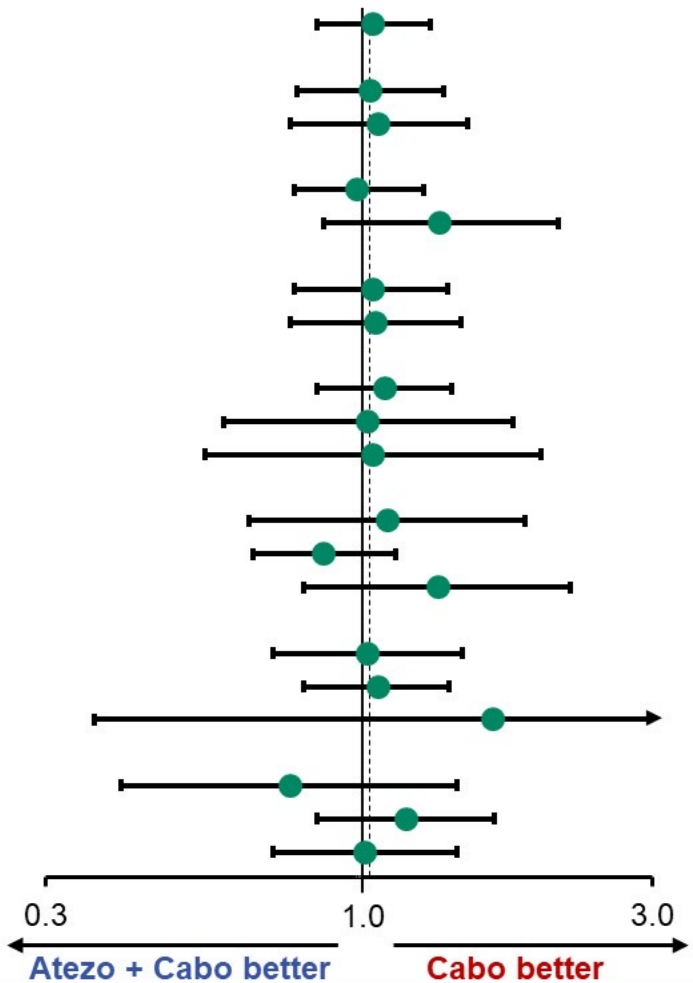
	Atezo + Cabo (n=263)	Cabo (n=259)
PFS events, n (%)	171 (65)	166 (64)
Median PFS (95% CI), mo	10.6 (9.8, 12.3)	10.8 (10.0, 12.5)
12-month PFS (95% CI), %	44 (38, 50)	48 (42, 54)
Stratified HR (95% CI)[a]	1.03 (0.83, 1.28); *P*=0.784[b]	



[a] Stratified for IMDC risk group. [b] Not significant at α=0.02.

Centrally reviewed PFS by subgroup

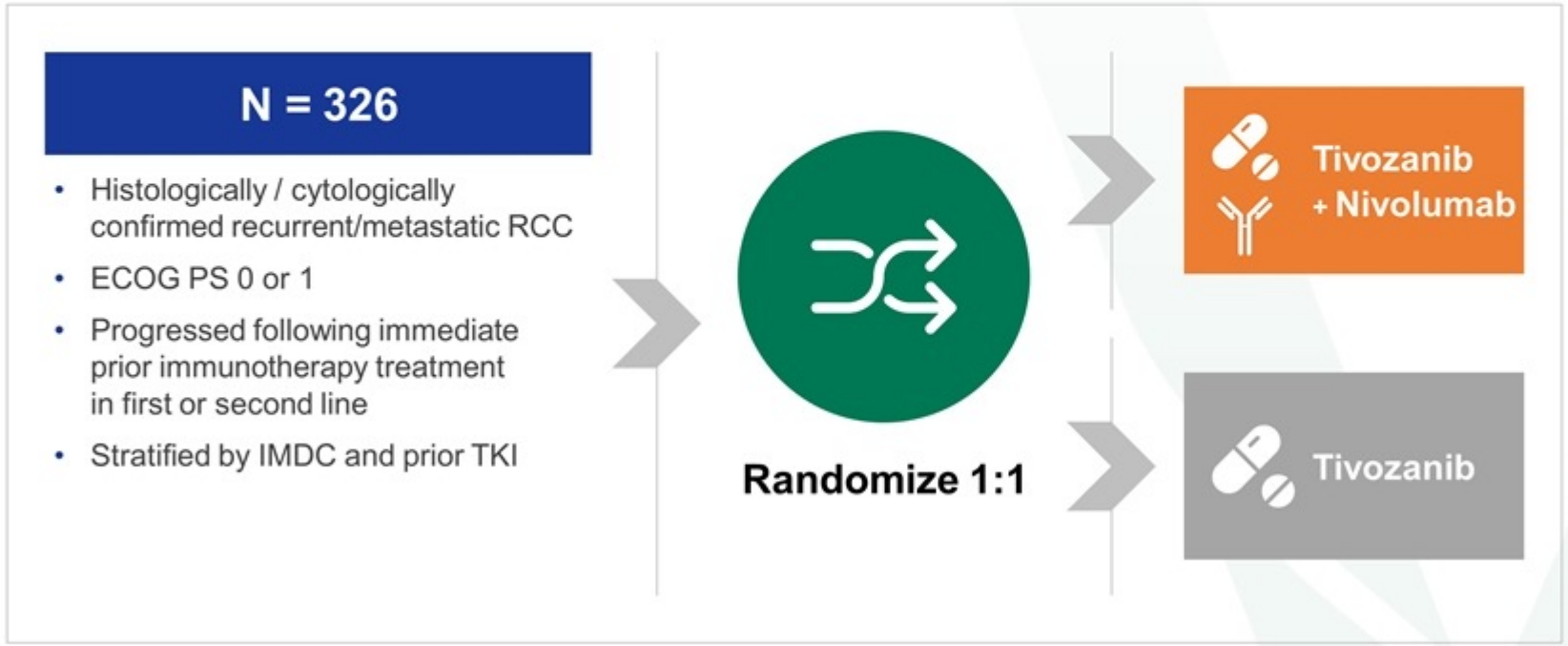
Characteristic[a]	Atezo + Cabo: No. of PFS events/patients	Atezo + Cabo: Median PFS, mo	Cabo: No. of PFS events/patients	Cabo: Median PFS, mo	PFS HR (95% CI)[b]
All patients	171/263	10.5	166/259	10.8	1.04 (0.84, 1.29)
Age					
<65 y	104/153	10.4	96/144	10.6	1.03 (0.78, 1.36)
≥65 y	67/110	10.6	115/225	12.1	1.06 (0.76, 1.49)
Sex					
Male	130/204	10.6	197/401	10.6	0.98 (0.77, 1.26)
Female	41/59	10.1	62/121	12.4	1.34 (0.86, 2.10)
Most recent line of ICI therapy					
First line	98/144	9.9	87/132	10.3	1.04 (0.77, 1.38)
Second line	72/118	12.4	77/124	12.5	1.05 (0.76, 1.45)
Histology					
Dominant clear cell	128/207	10.7	117/200	12.5	1.09 (0.84, 1.40)
Dominant non-clear cell	25/30	6.3	27/31	8.3	1.02 (0.59, 1.77)
Any sarcomatoid component	18/25	8.3	22/28	8.2	1.04 (0.55, 1.97)
IMDC score					
0	25/49	14.3	34/69	14.5	1.10 (0.65, 1.85)
1-2	109/172	10.8	104/153	11.7	0.86 (0.66, 1.13)
3-6	36/41	4.9	28/36	6.0	1.33 (0.80, 2.20)
Prior lines of VEGFR-TKI					
0	61/93	9.7	60/95	10.4	1.02 (0.71, 1.46)
1	107/166	10.6	102/159	11.7	1.06 (0.80, 1.39)
2	3/4	6.7	4/5	11.3	1.64 (0.36, 7.47)
Best response to most recent ICI					
CR/PR	25/47	11.9	16/30	10.4	0.76 (0.40, 1.43)
SD	70/104	10.5	65/97	10.5	1.18 (0.84, 1.65)
PD	63/92	10.4	63/95	10.6	1.01 (0.71, 1.43)



CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.
[a] Categories with ≤2 patients are not shown. [b] Unstratified.

TiNiVo-2

Phase 3, Randomized, Controlled, Multi-Center, Open-Label Study to Compare Tivozanib with Nivolumab to Tivozanib Following Immunotherapy in RCC Patients



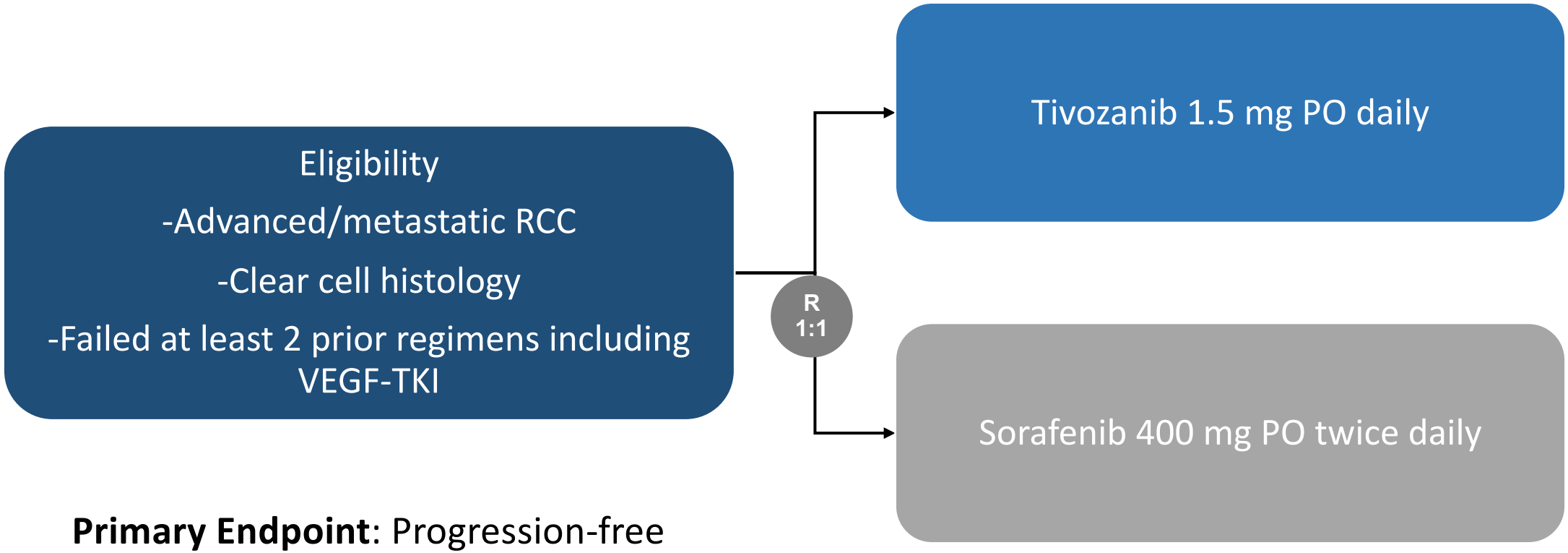
Treatment Until Progression

Endpoints

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

Enrollment Expected to Start Mid-Year

Phase 3 Tivo-3 Trial



Primary Endpoint: Progression-free survival

Open-Label

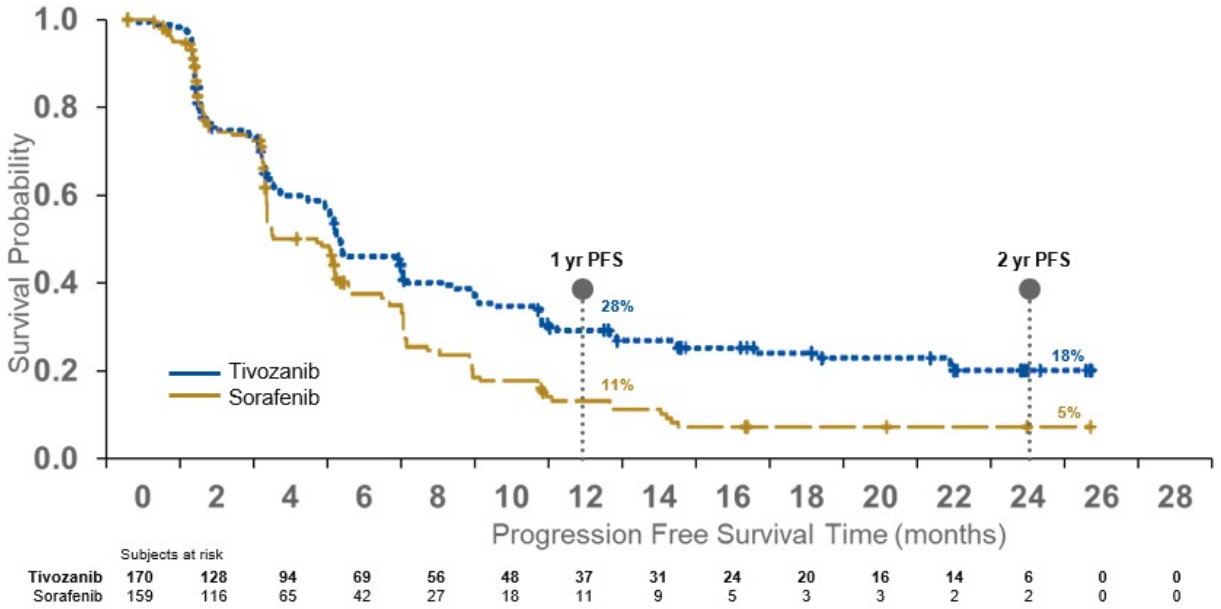
N=350

RCC=Renal cell carcinoma; VEGF-TKI=Vascular endothelial growth factor tyrosine kinase inhibitor; PO=By mouth.

Rini et al, Lancet, 2020

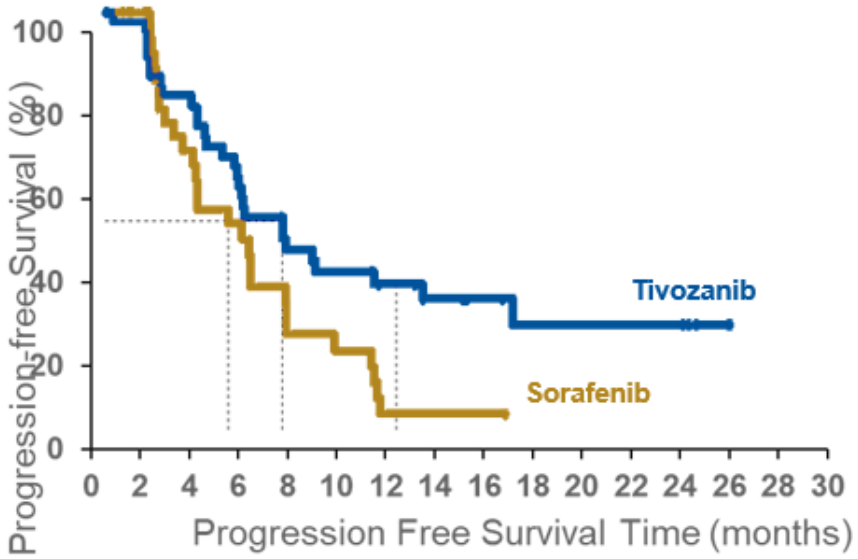
Phase 3 Tivo-3: Efficacy

Overall Population



	Tivozanib N=170	Sorafenib N=159
Median, months	5.6	3.9
HR (95% CI)	0.73 (0.56, 0.94)	
P-value	0.016	

Post IO/VEGF TKI Population



	Tivozanib N=47	Sorafenib N=44
Median, months	7.3	5.1
HR (95% CI)	0.55 (0.32, 0.94)	
P-value	0.028	

Rini et al, Lancet, 2020

Belzutifan in Refractory RCC

Study Population
Advanced RCC
≥1 prior line of therapy (median, 3)
Any risk group (intermediate, 73%)

	Belzutifan (Phase 1/2 Trial)
N	55
Median (range) treatment line	3 (1-9)
Median follow-up	28 months
ORR	25% (14 confirmed PRs)
Disease control rate	80%
Median PFS (overall)	14.5 months
Median DOR	NR
Most common AEs	Anemia (76%) and fatigue (71%)
Most common grade 3 AEs	Anemia (27%) and hypoxia (16%)

Adjuvant Therapy

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Summary of Results from Adjuvant Targeted Therapy for RCC

Trial	Arms	Years	N	Primary Endpoint	Clear Cell Only	Eligibility	Hazard Ratio Confidence Interval
ASSURE (Hass, *Lancet* 2016)	Sunitinib vs Sorafenib vs Placebo*	1	1943	DFS	No	pT1bG3-4N0, pT2-4GxN0, TxGxN+	Sunitinib: 1.02 (97.5% CI, 0.85-1.23) Sorafenib: 0.97 (97.5% CI, 0.80-1.17)
STRAC (Ravaud, *N Engl J Med* 2016)	Sunitinib vs Placebo	1	615	DFS	Yes	pT3-4GxN0-x TxGxN1-2	0.76 (95% CI, 0.59-0.98)
PROTECT (Motzer, *J Clin Oncol* 2017)	Pazopanib vs. Placebo*	1	1538	DFS	Yes	pT2G3-4N0 pT3-4N0 pTxN1	0.86 (95% CI, 0.70-1.06)
ATLAS (Gross-Goupil, *Ann Oncol* 2018)	Axitinib vs Placebo	1-3	724	DFS	Yes	pT2-4GxN0 pTxN1	0.87 (95% CI, 0.66-1.147)
SOURCE (Eisen, *J Clin Oncol* 2020)	Sorafenib vs Placebo*	1-3	1711	DFS	No	Leibovich Score: 3-11	1.01 (95% CI, 0.83-1.23)
EVEREST (Ryan C, *J Clin Oncol* 2022)	Everolimus vs Placebo	1	1545	RFS	No	pT1bG3-4N0 pT2-4N1	HR, 0.85 (95% CI, 0.72-1.00)

Haas NB et al. *Lancet.* 2016;387(10032):2008-2016; Ravaud A et al. *N Engl J Med.* 2016; 375(23):2246-2254;
Motzer RJ et al. *J Clin Oncol*. 2017;35(35):3916-3923; Gross-Goupil M, et al. *Ann Oncol*. 2018;29(12):2371-2378;
Tacconi EMC, et al. *Onco Targets Ther*. 2020;13:12301-12316; Ryan C, et al. *J Clin Oncol. 2022;*40(17_suppl): Abstract LBA4500.

*Starting dose change during study.
CI, confidence interval.
DFS, disease-free survival
RCC, renal cell carcinoma
RFS, recurrence-free survival

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Studies of Adjuvant Immune Oncology in RCC

Trial	Sample Size	Inclusion Criteria	Treatment	Primary Endpoint	Expected Results
Keynote-564[1]	994	pT2G4, pT3aG3-4, pT3b-T4Gx, pTxN1, pTxNxM1 (resected to NED within 1 year); clear cell	Pembrolizumab vs placebo	DFS	**ASCO GU 2022 HR 0.63; p < 0.0001**
IMmotion010[2]	778	pT2G4, pT3aG3-4, pT3b-T4Gx, pTxN1, pTxNxM1 (resected to NED*); clear cell	Atezolizumab vs placebo	DFS	**ESMO 2022 NS DFS HR 0.93; P=0.4950**
CheckMate-914[3]	1600	pT2aG3-4N0, pT2b-T4GxN0, pTxGxN1; clear cell	Nivolumab + ipilimumab vs. nivolumab + placebo vs placebo *(6 months)*	DFS	**ESMO 2022 *Part A (Nivo+Ipi)* NS DFS HR, 0.92; P=0.5347**
PROSPER RCC[4]	766	cT2Nx, cTxN1, cTxNxM1 (resected to NED); any RCC histology	Nivolumab vs observation	EFS	**ESMO 2022 NS DFS HR, 0.97; P=0.43 Trial stopped for futility**
RAMPART[5]	1750	Leibovich score 3-11; any RCC histology	Durvalumab + tremelimumab vs durvalumab vs observation	DFS, OS	July 2024

*Metachronous pulmonary, lymph node, or soft tissue recurrence >12 months from nephrectomy.
DFS, disease-free survival; EFS, event-free survival; NED, no evidence of disease; RCC, renal cell carcinoma; OS, overall survival; NS, non-significant.
Powles T, et al. *Lancet Oncol*. 2022;23;1133-1144.; Choueiri TK, et al. ASCO GU 2022. Abstract 290.; 2. NCT03024996. 3. NCT03138512. 4. NCT03055013. 5. NCT03288532.

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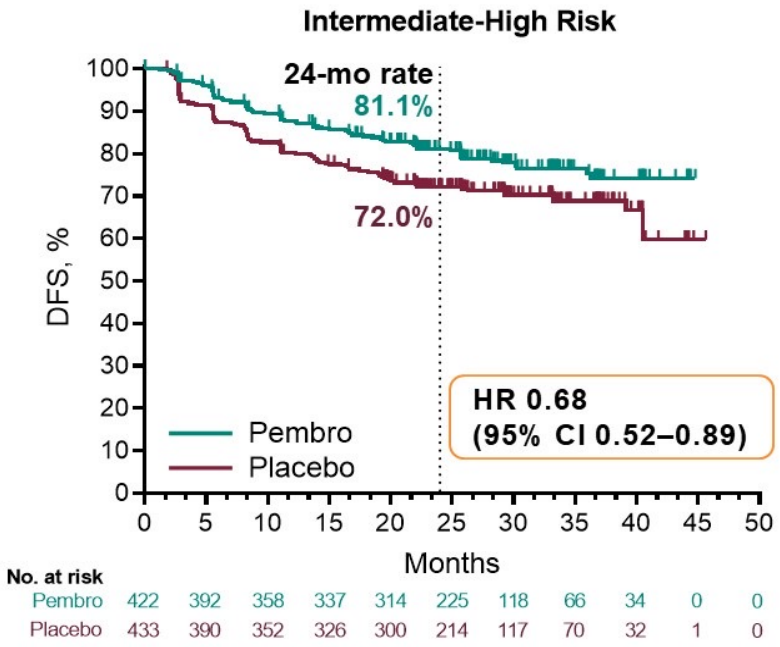
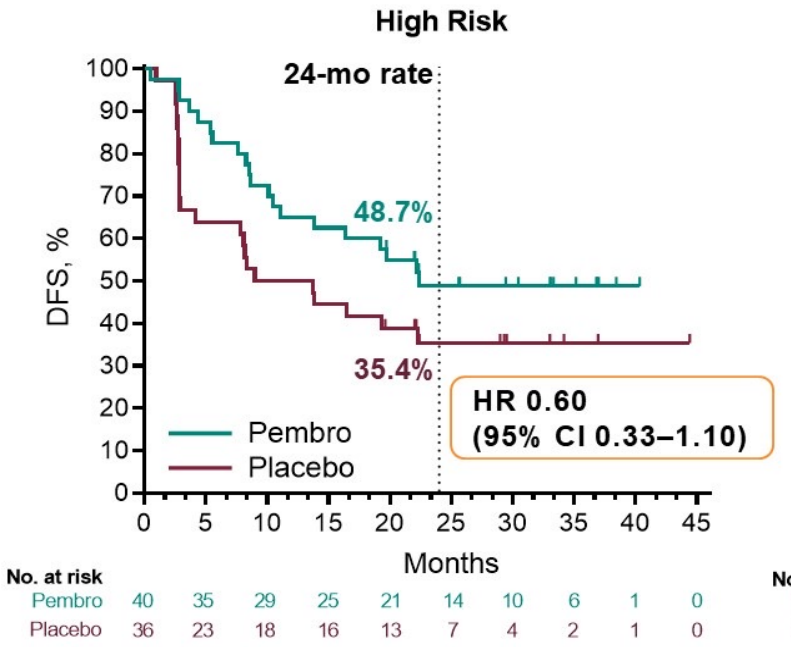
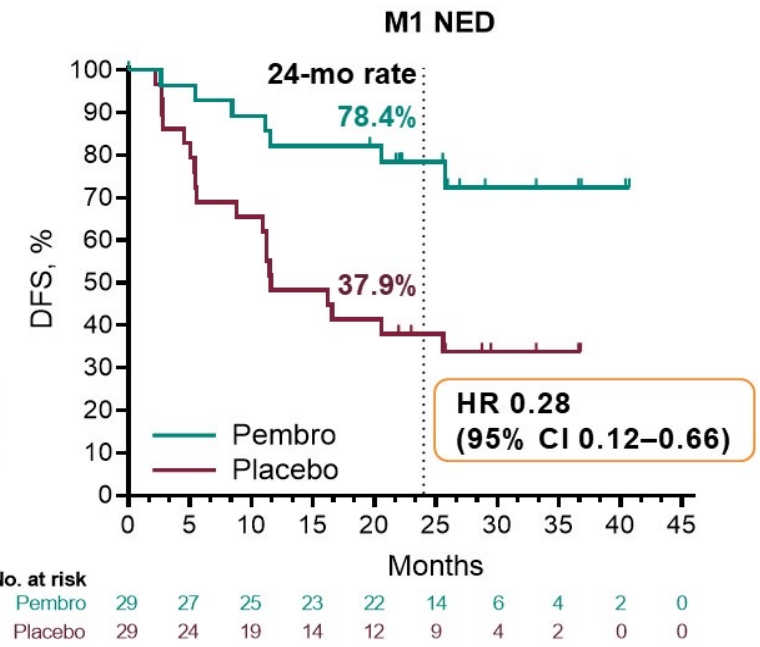
DFS by Recurrence Risk Subgroups







	Pts w/ Event	Median, mo (95% CI)
Pembro	87	NR (NR–NR)
Placebo	127	NR (40.5–NR)

	Pts w/ Event	Median, mo (95% CI)
Pembro	20	22.4 (11.1–NR)
Placebo	23	11.4 (2.9–NR)

	Pts w/ Event	Median, mo (95% CI)
Pembro	7	NR (25.7–NR)
Placebo	19	11.6 (5.6–NR)

Intermediate-high risk: pT2, grade 4 or sarcomatoid, N0, M0; or pT3, any grade, N0, M0;
High risk: pT4, any grade, N0, M0; or pT any stage, any grade, N+, M0;
M1 NED: No evidence of disease after primary tumor + soft tissue metastases completely resected ≤1 year from nephrectomy.
DFS, disease-free survival; NR, not reached. Data cutoff date: June 14, 2021.

Closing Remarks

- The treatment landscape for advanced renal cell carcinoma has been rapidly evolving and patients are living longer and better;
- Both IO/IO and IO/VEGF are suitable frontline treatments for patients;
- Treatment options in the subsequent line space are expanding with the introduction of novel targets in development;
- We're seeing progress in the non-metastatic setting with impact in the management of advanced disease

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