Comprehensive HemOnc Review: Renal Cell Carcinoma

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Disclosures

- **Research Funding**

  AVEO, Bristol-Myers Squibb, Exelixis, HiberCell, Iovance Biotherapeutics, Merck, Nektar Therapeutics, Pfizer, Xencor

- **Honoraria**

  FirstWord Pharma, Targeted Oncology, Cancer Network, Topline Bio

- **Consulting**

  Bristol-Myers Squibb, AVEO Oncology, Exelixis

RCC Learning Objectives

- Epidemiology
- Staging and Histologic Subtypes
- Hereditary RCC cancer syndromes
- Systemic Treatments
  - Overview
  - Local RCC - Adjuvant therapy
  - Metastatic RCC
    - First line – clear cell
    - First line – non clear cell
    - Salvage – clear cell

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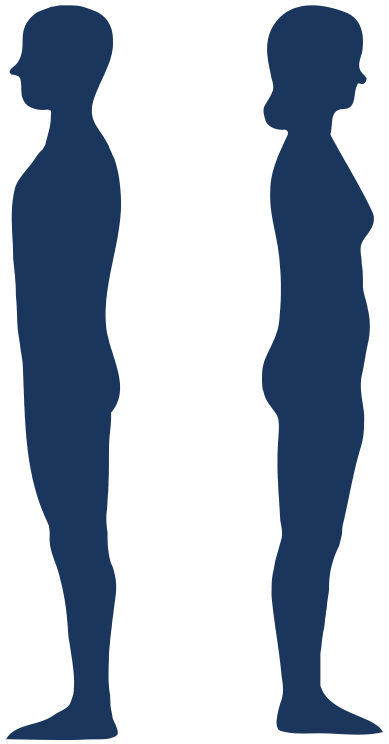
2024 - Estimated US New Cancer Cases

2024 US Estimates:

- **81,610 new cases**
- **14,390 deaths**

Men			Women	
Prostate	29%		32%	Breast
Lung & bronchus	11%		12%	Lung & bronchus
Colon & rectum	8%		7%	Colon & rectum
Urinary bladder	6%		7%	Uterine corpus
Melanoma of skin	6%		4%	Melanoma of skin
Kidney & renal pelvis	5%		4%	Lymphoma
Lymphoma	5%		3%	Pancreas
Oral cavity & pharynx	4%		3%	Thyroid
Leukemia	4%		3%	Kidney & renal pelvis
Pancreas	3%		3%	Leukemia
All Other Sites	19%		22%	All Other Sites



American Cancer Society, Cancer Facts & Figures 2024

Why Me?
Associations and Risk Factors for RCC

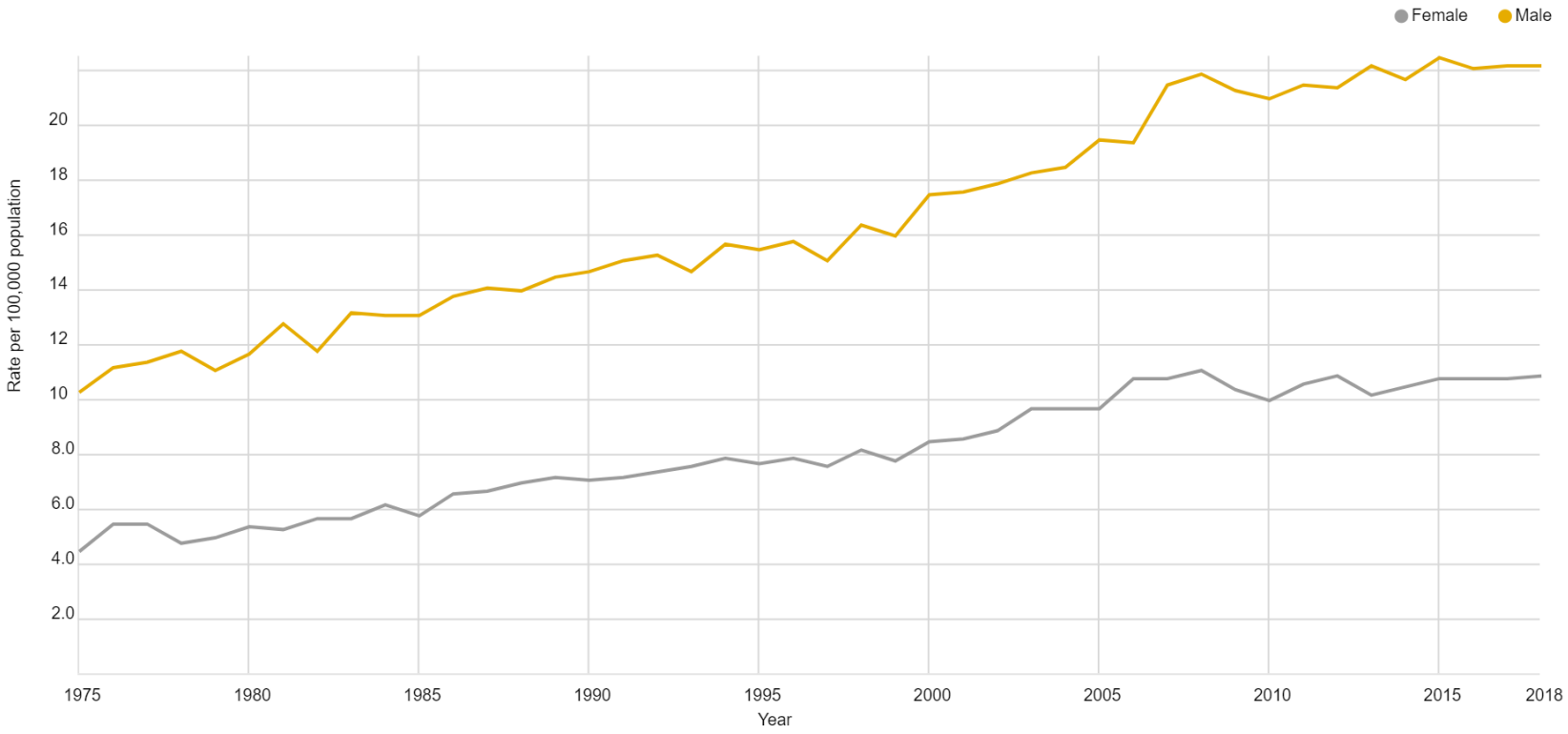
- **Male > female 2:1**
- **Age – median 64**
- **Genetic predisposition**
- **Smoking**
- **Obesity**
- **Uncontrolled hypertension**

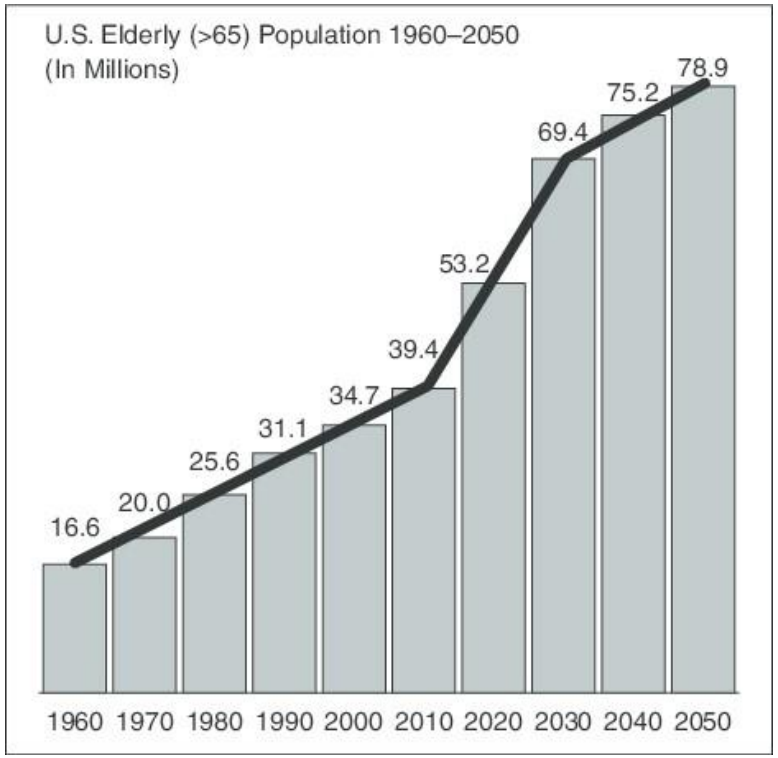
3 modifiable RF's associated with 49% of cases

- Disease associations: **Sickle cell anemia (medullary carcinoma of the kidney)**
  Solid organ transplant recipient
  Polycystic kidney disease
  Chronic Hepatitis C
- Occupational exposure to toxins: Organic solvents (trichloroethylene)
  cadmium
  asbestos
- Drug associations: Prior cytotoxic chemotherapy (translocation RCC)

Trends in incidence rates, 1975-2018

by sex, kidney and renal pelvis





American Cancer Society: www.cancer.org.
ResearchGate: www.researchgate.net

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Staging system for RCC

AJCC 8th ed., 2017

Stage I
Tumor < 7 cm in greatest dimension and limited to kidney

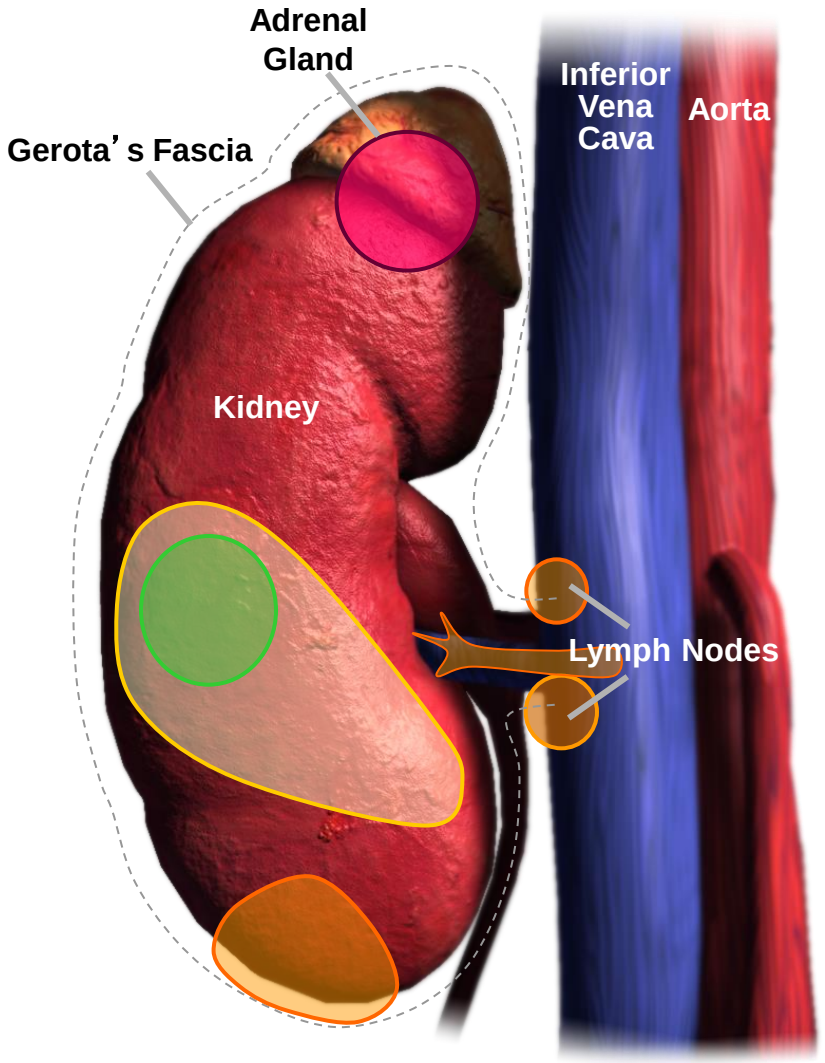
- **Ia** < 4 cm
- **Ib** > 4 to < 7 cm

Stage II
Tumor > 7 cm in greatest dimension and limited to kidney

- **IIa** > 7 to < 10 cm
- **IIb** > 10 cm

Stage III
Tumor major veins, tumor within Gerota's fascia, or regional lymph node involved

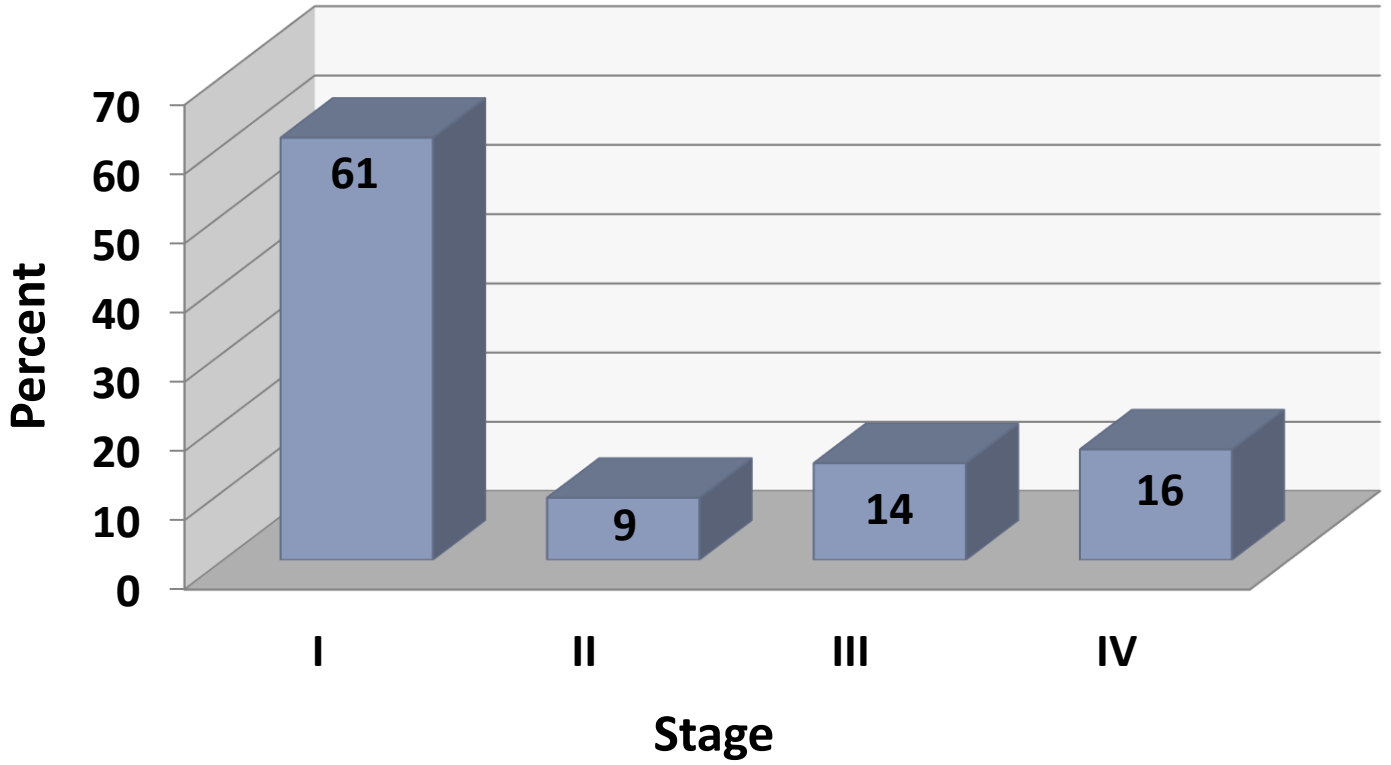
Stage IV
Tumor invasion beyond Gerota's fascia, adrenal or distant metastases



AJCC Cancer Staging Manual, 8th edition. New York: Springer; 2017.

RCC Stage at Diagnosis, 2004-2014

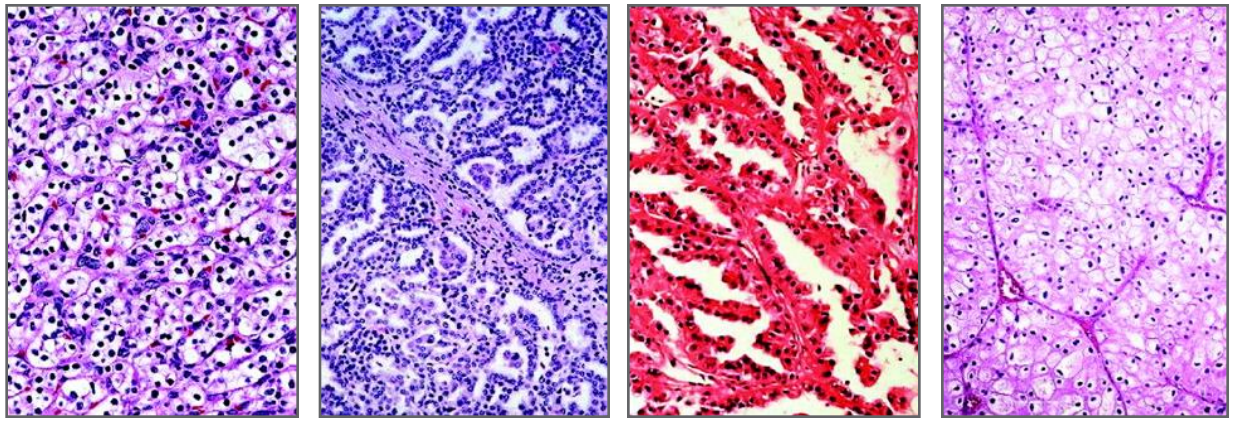
National Cancer Database (NCDB),
1442 hospitals; N=371,851



https://oliver.facs.org/BMPub/Docs/

Common histologic subtypes of RCC

RCC



Type	Clear cell	Papillary type 1	Papillary type 2	Chromophobe	*Unclassified*
Incidence	75%	5%	10%	5%	2-6%
Associated Germline Mutations	*VHL* *SDH* *BAP1* *TSC1/2*	*Met*	*FH*	*FLCN* *TSC1/2* *PTEN*	

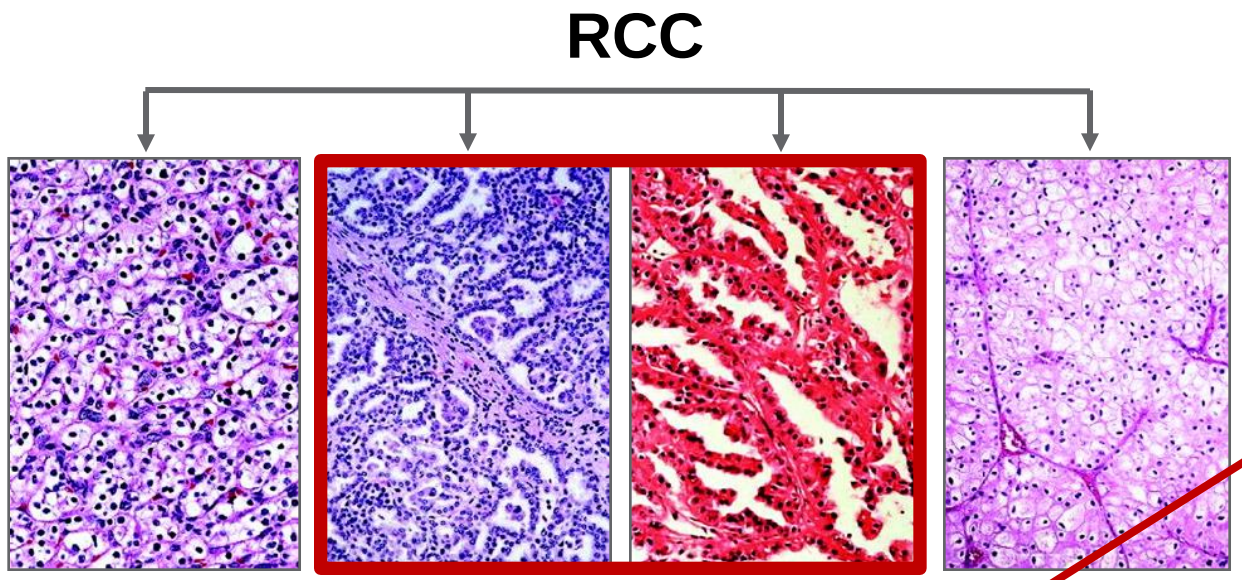
Plus

- Translocation RCC
- Medullary
- Collecting Duct

VHL = von Hippel-Lindau;
SDH = succinate dehydrogenase;
FH = fumarate hydratase;
FLCN = folliculin;
TSC = tuberous sclerosis complex

Modified from Linehan *et al*. J Urol. (2003) 170:2163-2172.
Ho and Jonasch. JNCCN. (2014) 12:1347.

2022 WHO Classification of Renal Tumors



Plus

- Translocation RCC
- Medullary
- Collecting Duct
- Fumarate Hydratase Deficient
- Others

Type	Clear cell	Papillary		Chromophobe	*Unclassified*
Incidence	75%	5%	10%	5%	2-6%
Associated Germline Mutations	*VHL* *SDH* *BAP1* *TSC1/2*	*Met*	*FH*	*FLCN* *TSC1/2* *PTEN*	

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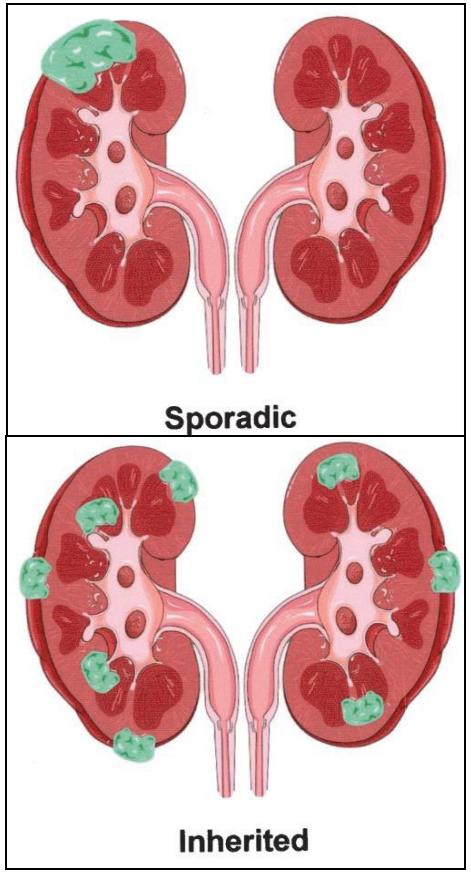
Referral criteria for genetic counseling

- All common histologic subtypes of RCC can be associated with a hereditary syndrome
- Kidney cancer **age of onset ≤ 46 years** (mean 37 years)
- **Bilateral/multifocal** kidney tumors
- **Family history** of kidney cancer
- Association with other clinical features of a recognized cancer syndrome

- Germline mutation incidence in unselected RCC patients with advanced disease – 16%



NCCN Kidney Cancer v1.2024.
Carlo, MI *et al*. JAMA Oncol. (2018) 4:1228-1235.

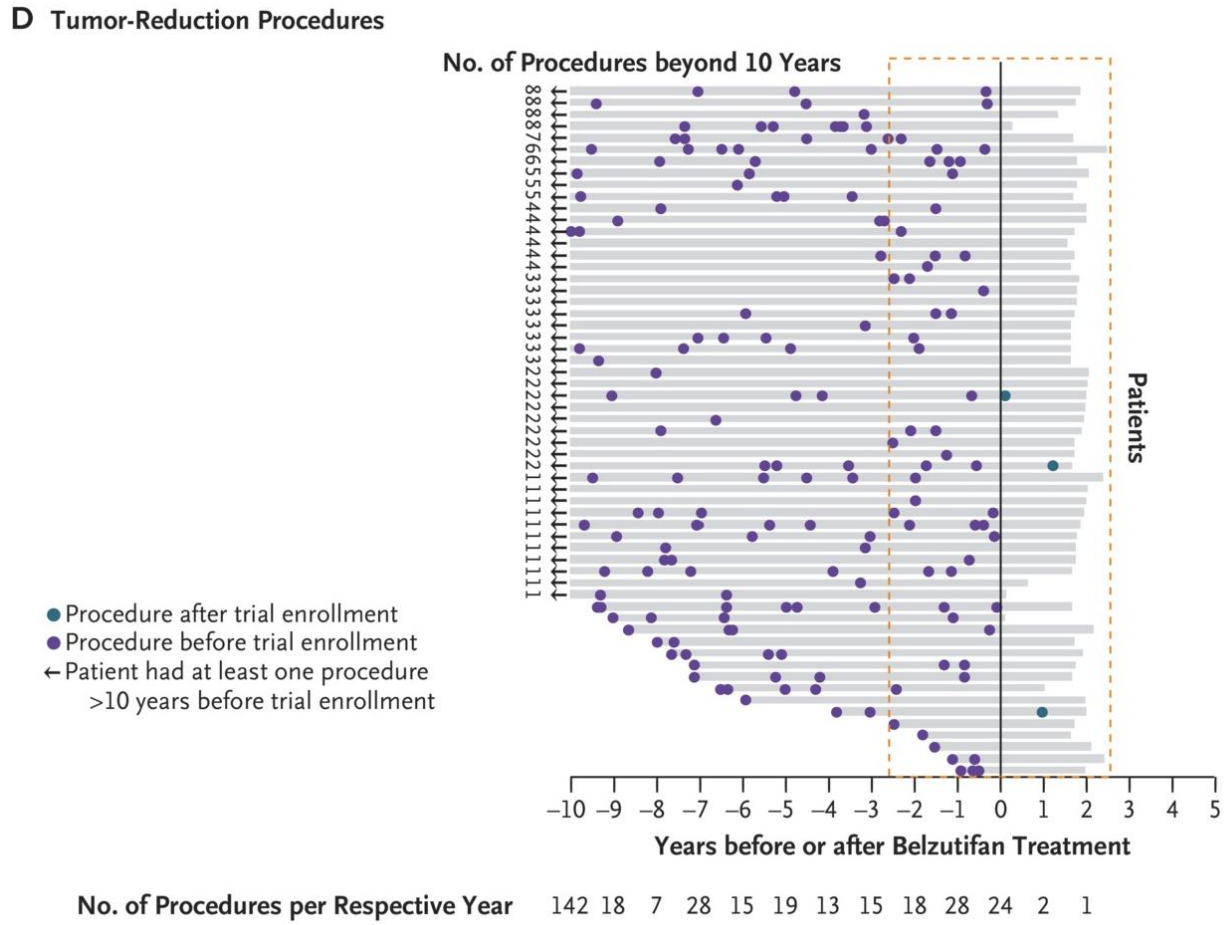
Syndrome-specific systemic therapies

Syndrome	Gene	RCC Histology	Systemic Therapy
von Hippel-Lindau (VHL)	*VHL*	Clear cell	Belzutifan
Tuberous sclerosis complex (TSC)	*TSC1/TSC2*	Angiomyolipoma	Everolimus
Hereditary leiomyomatosis and RCC (HLRCC)	*FH*	FH Deficient RCC	Erlotinib plus bevacizumab

Adapted from NCCN Kidney Cancer v1.2024

Belzutifan for VHL Disease Patients

Target Lesion	ORR	CR
Renal Cell Carcinoma	49%	0%
Pancreatic Lesions	77%	10%
Pancreatic Neuroendocrine Tumors	91%	14%
CNS Hemangioblastoma	30%	6%
Retinal Lesions	100%	N/A



Jonasch, E *et al*. NEJM (2021) 385:2036-46

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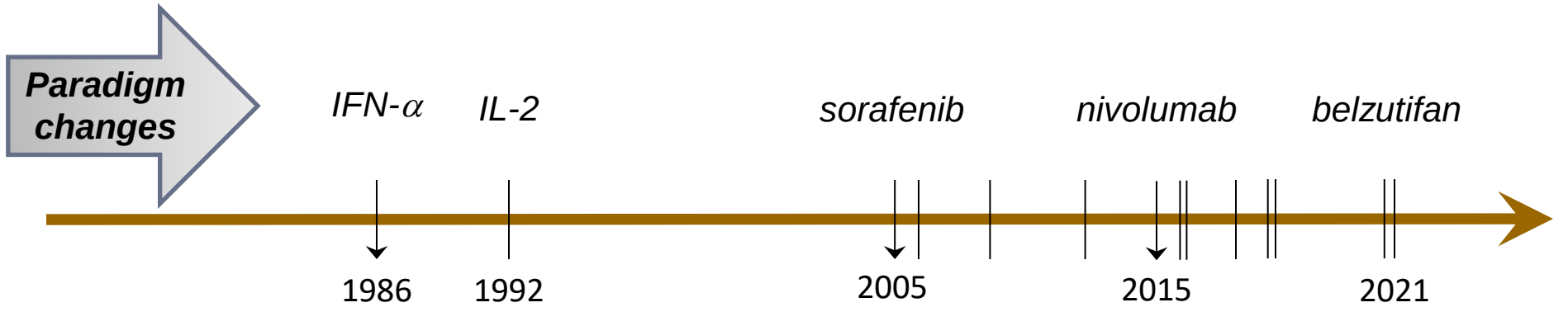
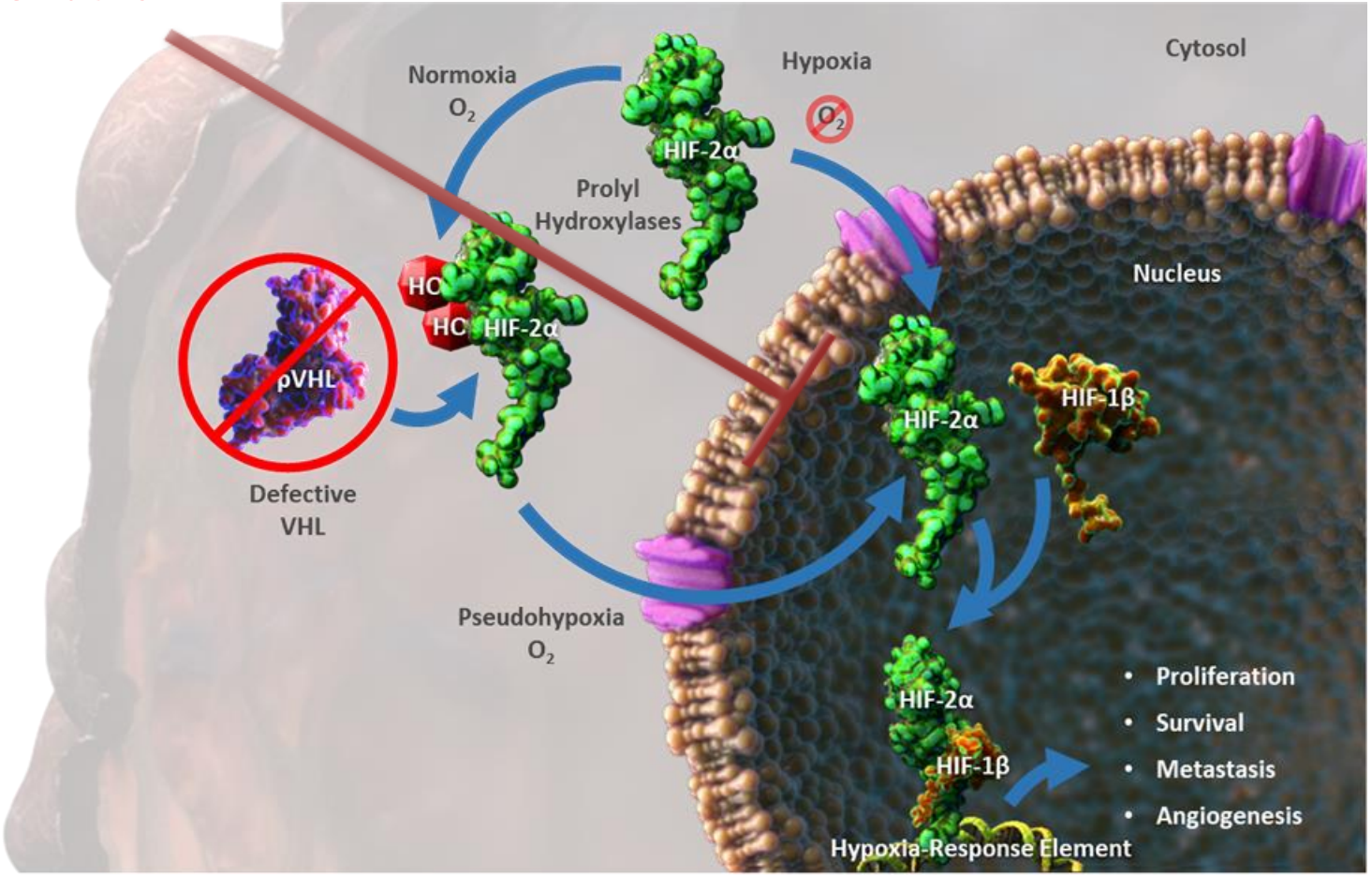
Timeline of Systemic RCC Therapies



No Standard Therapy	Cytokine Immunotherapy	Targeted Therapy	Checkpoint Immunotherapy
cytotoxics	Interferon alfa Interleukin-2	VEGFR-TKI's Sorafenib (2005) Sunitinib (2006) Pazopanib (2009) Axitinib (2012) Cabozantinib (2016) Lenvatinib (2016) Tivozanib (2021) Bevacizumab mTOR- Inhibitors HIF2- inhibitor	Immune Checkpoint-Blocking Abs Nivolumab (2015) Ipilimumab (2018) Pembrolizumab (2019) Avelumab (2019)

Role of HIF-2 in Clear Cell Renal Cell Carcinoma

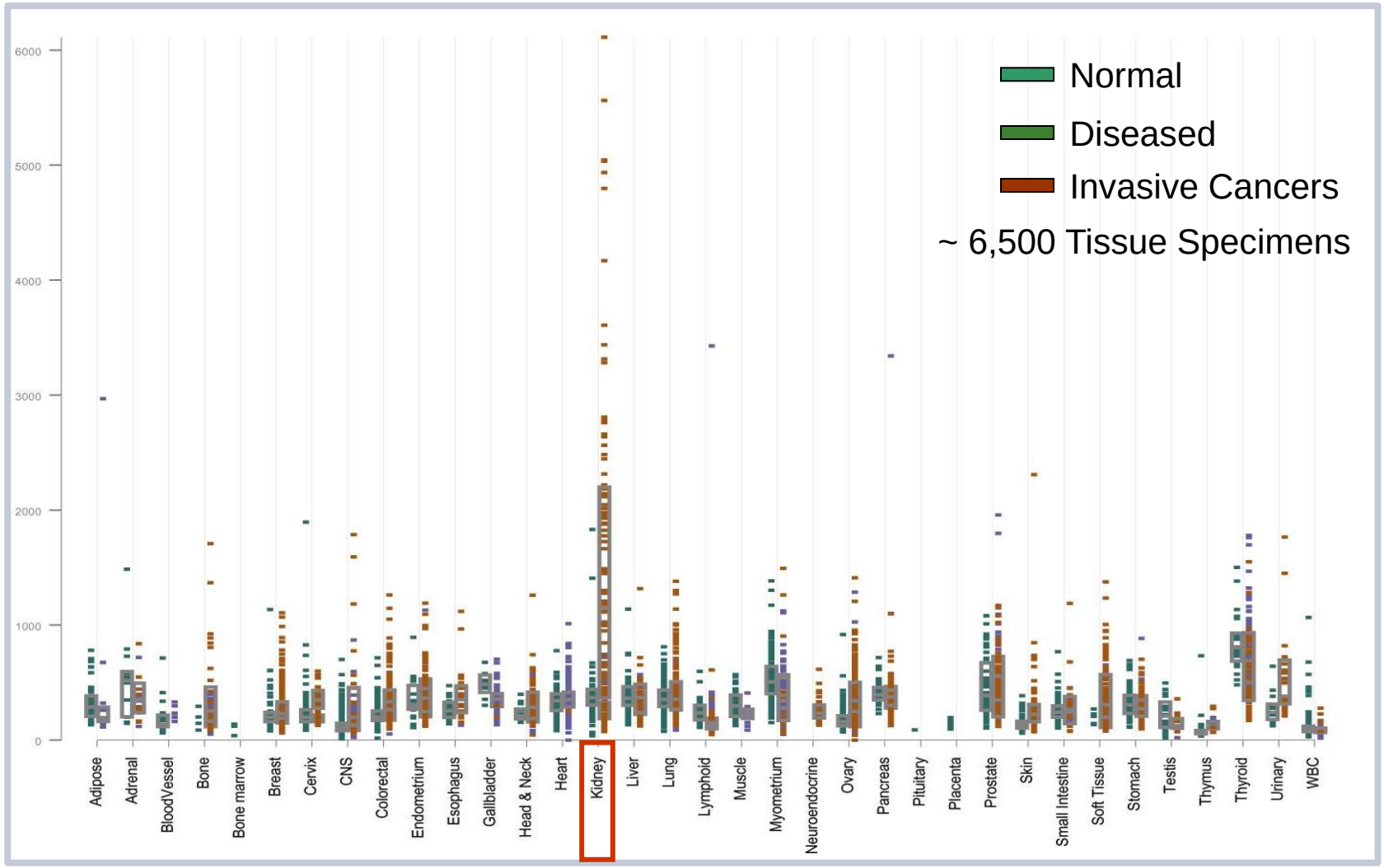
Belzutifan



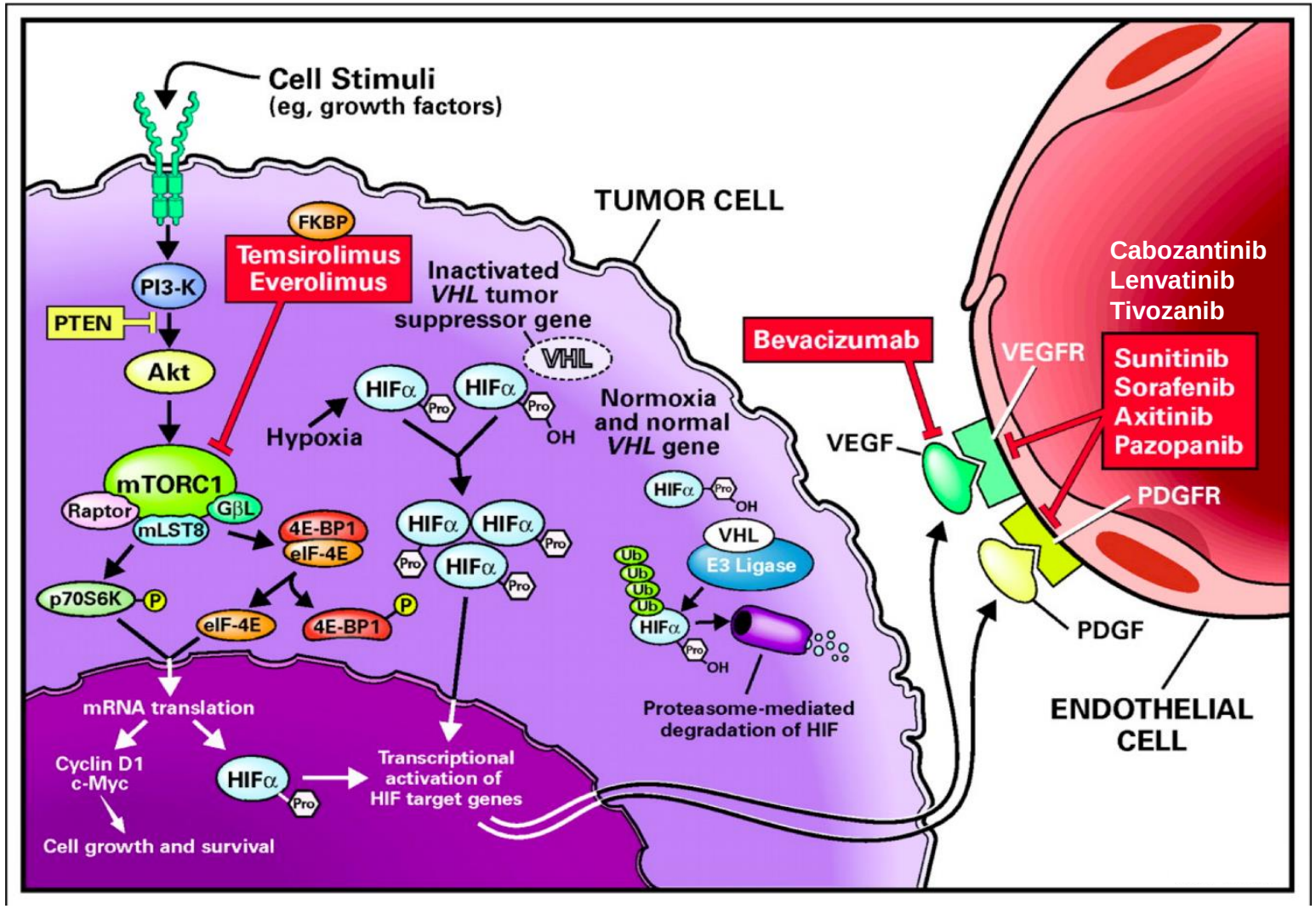
- **90% of patients with sporadic ccRCC have defective pVHL[1,2]**
- **HIF-2α is involved in the activation of genes associated with angiogenesis (*VEGFA, PDGFB),* proliferation *(CDK),* metabolism *(GLUT1),* and growth *(TGFα)*[3]**
- **Belzutifan is a potent, selective, small molecule HIF-2α inhibitor**

[1]Shen C, Kaelin WG Jr. *Semin Cancer Biol.* 2013;23:18-25. [2]Sato Y et al. *Nat Genet.* 2013;45:860-867. [3]Choueiri TK, Kaelin WG Jr. *Nat Med*. 2020;26:1519-1530.

Expression of VEGF-A in human tissues: GeneLogic/Affymetrix

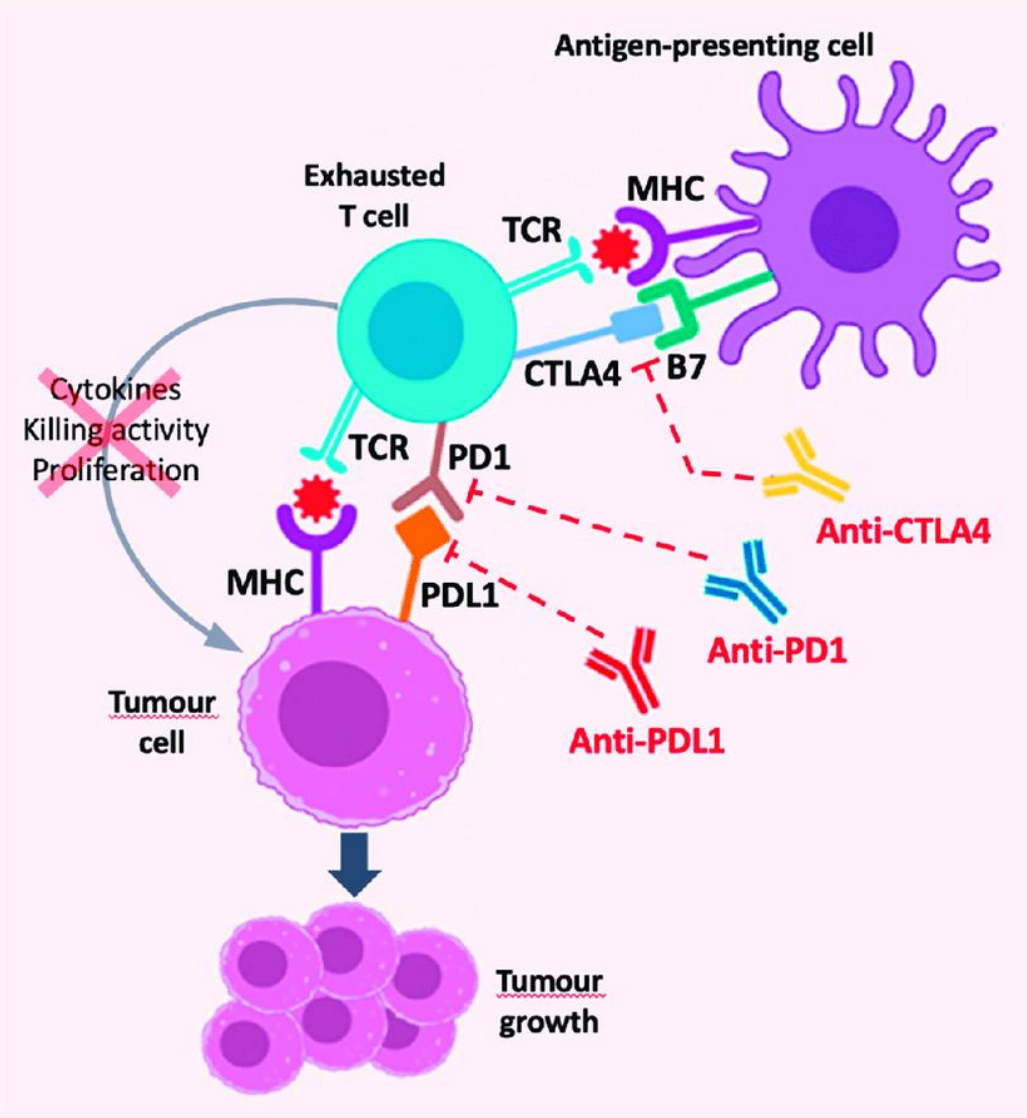


Anti-angiogenic Targeted Therapies for RCC



Vasudev, NS *et al*. BMC Medicine (2012) 10:112

Immune Checkpoint Inhibitors mechanism of action and bio markers



RCC Patient Selection for ICI Therapy

- RCC is TMB low
  - No association of response with neoantigen density
- Tumor PD-L1 is prognostic (~25%)
- Both PD-L1+ and PD-L1- tumors have better outcomes with ICI

- No current role for ICI companion diagnostics in RCC

ResearchGate: www.researchgate.net

Common Toxicities by Drug Class

	VEGF-TKI	mTORi	HIF2i	ICI
Clinical	• Oral symptoms • Anorexia • Nausea • Diarrhea • Hand-Foot • Hypertension • Fatigue • Dysphonia	• Oral symptoms • Rash • GI symptoms • Fatigue • Edema • Pulmonary Sx / pneumonitis • Infections	• Fatigue • Hypoxia	• Fatigue • Skin sx • Diarrhea • Arthritis
Lab Data	• LFT elevation • Low blood cts • Nephrotic renal changes • Hypothyroid	• Elevated lipids • Low blood cts / anemia • Changes in renal function	• Anemia	• LFT elevation • Elevated Cr • Elevated pancreatic enzymes • Endocrinopathy

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Summary of Primary Outcomes for Adjuvant Targeted Therapy for RCC

Trial	Arms	Years	N	Primary Endpoint	Clear Cell Only	Eligibility	Hazard Ratio Confidence Interval
ASSURE (Haas, 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, NEJM, 2016)	Sunitinib vs. Placebo	1	615	DFS	Yes	pT3-4GxN0-x, TxGxN1-2	0.76 (95% CI 0.59-0.98)
PROTECT (Motzer, JCO, 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	0.870 (95% CI 0.66-1.147)
SORCE (Eisen, JCO, 2020)	Sorafenib vs. Placebo)*	1-3	1711	DFS	No	Leibovich score 3-11	1.01 (95% CI 0.83-1.23)
EVEREST	Everolimus vs. Placebo	1	1545	RFS	No	pT1bG3-4N0, pT2-4N1	HR, 0.85 (95% CI, 0.72-1.00)

→ FDA approval 2017

NCCN Category C

*Starting dose change during study; CI, confidence interval; DFS, disease-free survival; RFS, recurrence-free survival

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. ASCO 2022. LBA4500.

Summary of Primary Outcomes for Adjuvant IO Therapy for RCC

Trial	Sample Size	Inclusion Criteria	Clear Cell Only	Treatment	Primary Endpoint	Hazard Ratio Confidence Interval
Keynote-564[1]	994	pT2G4, pT3aG3-4, pT3b-T4Gx, pTxN1, pTxNxM1 (resected to NED within 1 year);	Yes	Pembrolizumab vs placebo	DFS	**0.63 (95% CI 0.50-0.80)**
IMmotion010[2]	778	pT2G4, pT3aG3-4, pT3b-T4Gx, pTxN1, pTxNxM1 (resected to NED*);	Yes	Atezolizumab vs placebo	DFS	**0.93 (95% CI 0.75-1.15)**
CheckMate-914[3]	1600	pT2aG3-4N0, pT2b-T4GxN0, pTxGxN1;	Yes	Nivolumab + ipilimumab vs. nivolumab + placebo vs placebo *(6 months)*	DFS	**Part A (Nivo+Ipi) 0.92 (95% CI 0.71-1.19) Part B (Nivo) 0.87 (95% CI 0.62-1.21)**
PROSPER RCC[4]	766	T2Nx, TxN1, TxNxM1 (resected to NED);	No	Nivolumab vs observation	RFS	**0.97 (95% CI 0.74-1.28)**
RAMPART[5]	1750	Leibovich score 3-11;	No	Durvalumab + tremelimumab vs durvalumab vs observation	DFS, OS	Recruitment closed 6/2023

*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.

1. Choueiri TK, et al. ASCO GU 2022. Abstract 290.
2. Bex A, et al. ESMO 2022. Abstract LBA66.
3. Allaf, M et al. ESMO 2022. Abstract LBA67. Motzer, RJ et al. ASCO GU 2024. Abstract LBA358.
4. Motzer, RJ et al. ESMO 2022. Abstract LBA4.
5. NCT03288532.

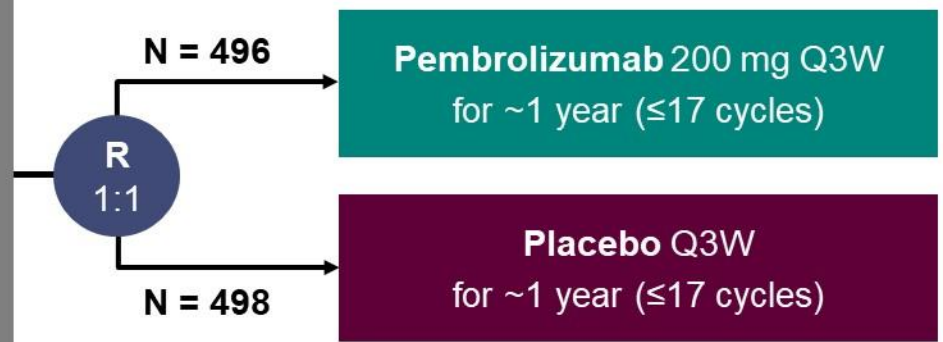
FDA approves pembrolizumab for adjuvant treatment of renal cell carcinoma

On November 17, 2021, the Food and Drug Administration approved pembrolizumab (Keytruda, Merck) for the adjuvant treatment of patients with renal cell carcinoma (RCC) at intermediate-high or high risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions.

KEYNOTE-564 Study (NCT03142334)

Key Eligibility Criteria

- Histologically confirmed clear cell RCC with no prior systemic therapy
- Surgery ≤12 weeks prior to randomization
- Postnephrectomy intermediate-high risk of recurrence (M0):
  - pT2, grade 4 or sarcomatoid, N0
  - pT3, any grade, N0
- Postnephrectomy high risk of recurrence (M0):
  - pT4, any grade, N0
  - Any pT, any grade, N+
- Postnephrectomy + complete resection of metastasis (M1 NED)
- ECOG PS 0 or 1



Stratification Factors

- M stage (M0 vs. M1 NED)
- M0 group further stratified:
  - ECOG PS 0 vs. 1
  - US vs. non-US

Primary Endpoint

- Disease-free survival by investigator

Key Secondary Endpoint

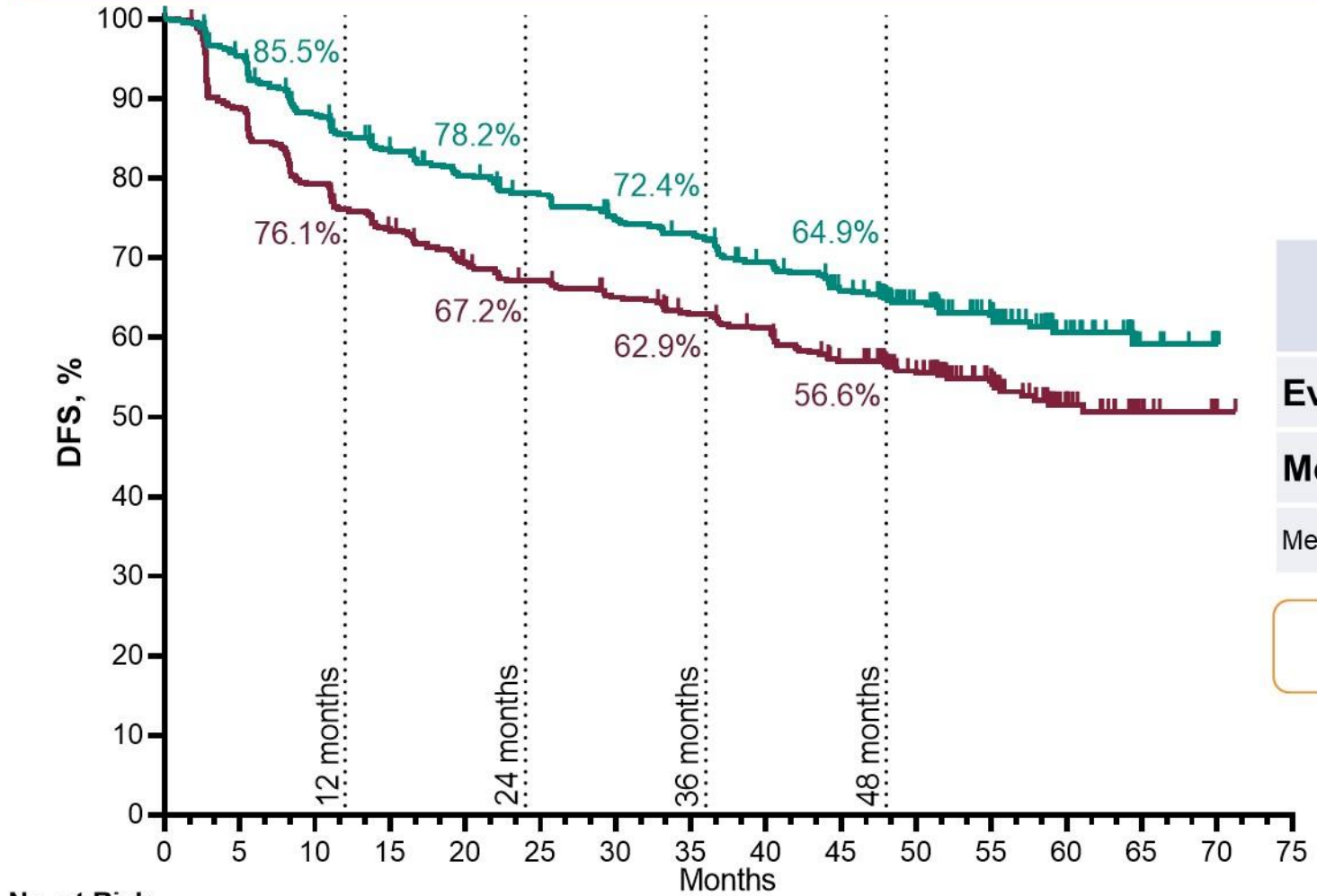
- Overall survival

Other Secondary Endpoints

- Safety

NED, no evidence of disease.

Updated Disease-Free Survival by Investigator, Intention-to-Treat Population



	Pembro (N = 496)	Placebo (N = 498)
Events, n	174	224
Median, mo (95% CI)	NR (NR–NR)	NR (54.9–NR)

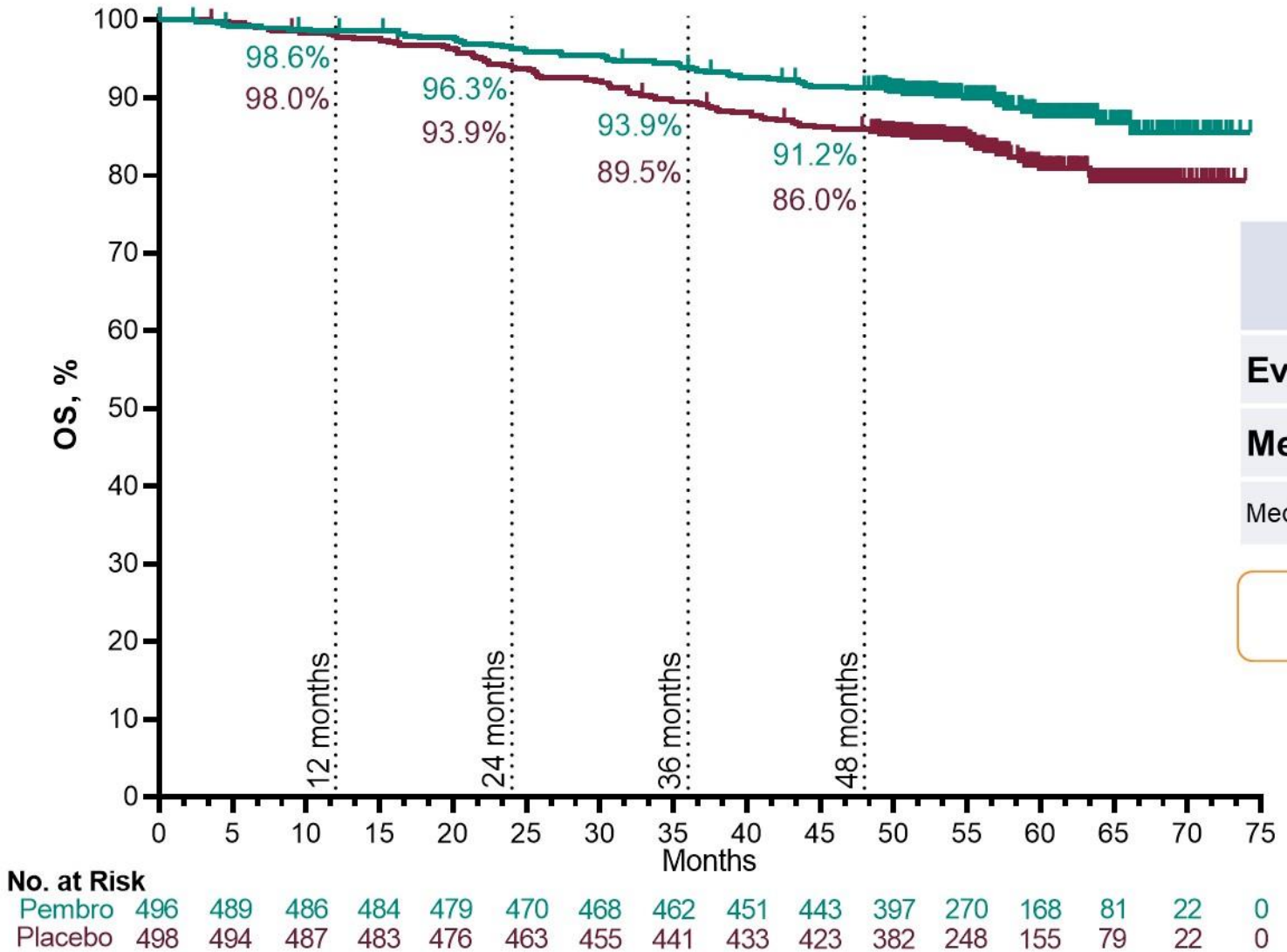
Median follow-up was 57.2 months (range, 47.9–74.5)

HR 0.72 (95% CI 0.59–0.87)

Primary DFS endpoint was met at IA1 and was not formally statistically tested thereafter.

Data cutoff date: September 15, 2023.

Overall Survival, Intention-to-Treat Population



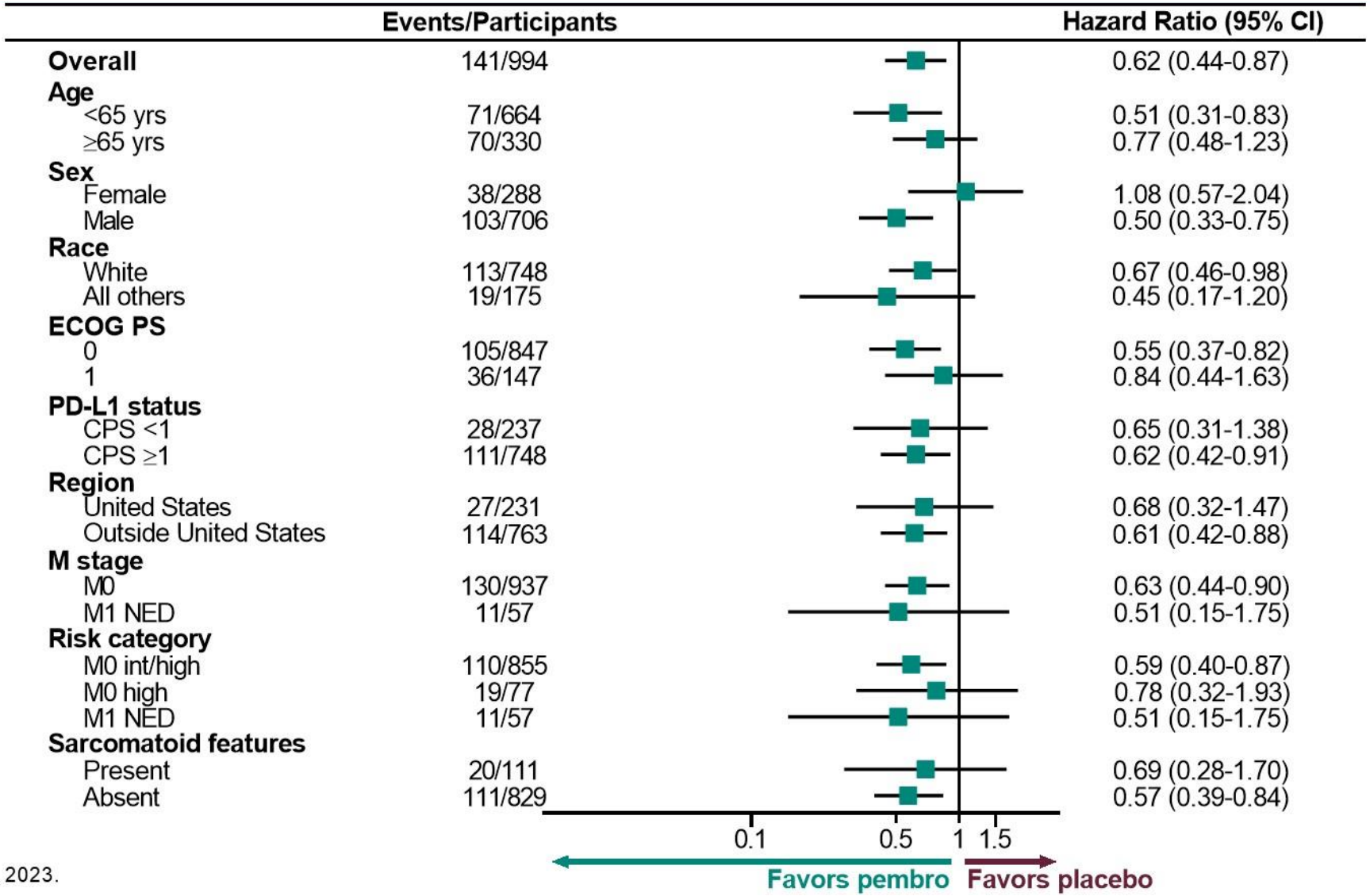
	Pembro (N = 496)	Placebo (N = 498)
Events, n	55	86
Median, mo (95% CI)	NR (NR–NR)	NR (NR–NR)
Median follow-up was 57.2 months (range, 47.9–74.5)		

HR 0.62 (95% CI 0.44–0.87); *P* =.002*

*** denotes statistical significance**. P-value boundary for OS at IA3 was 0.0072 (1-sided) per Lan-DeMets O'Brien-Fleming spending approximation α-spending function. As this key secondary endpoint was formally met, any future OS analyses will be descriptive only.

Data cutoff date: September 15, 2023.

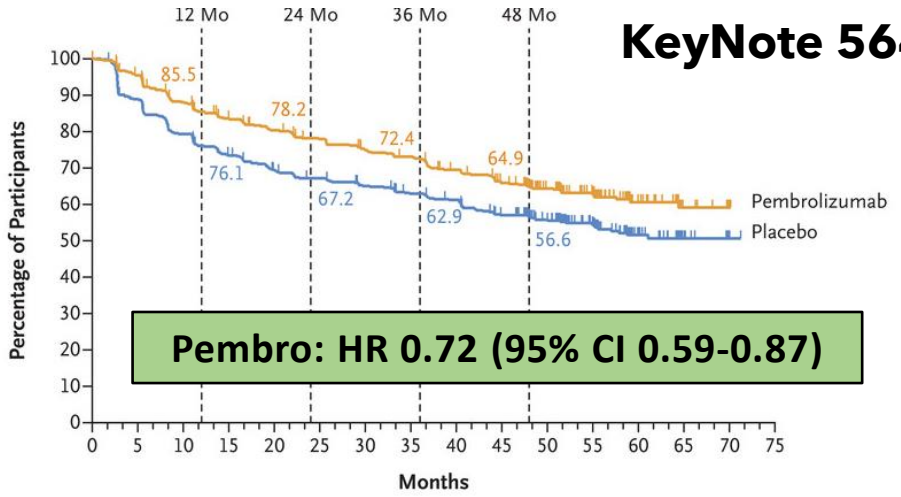
Overall Survival by Subgroups



Data cutoff date: September 15, 2023.

Adjuvant IO Therapy in RCC: 1 positive followed by 3 negative trials

KeyNote 564

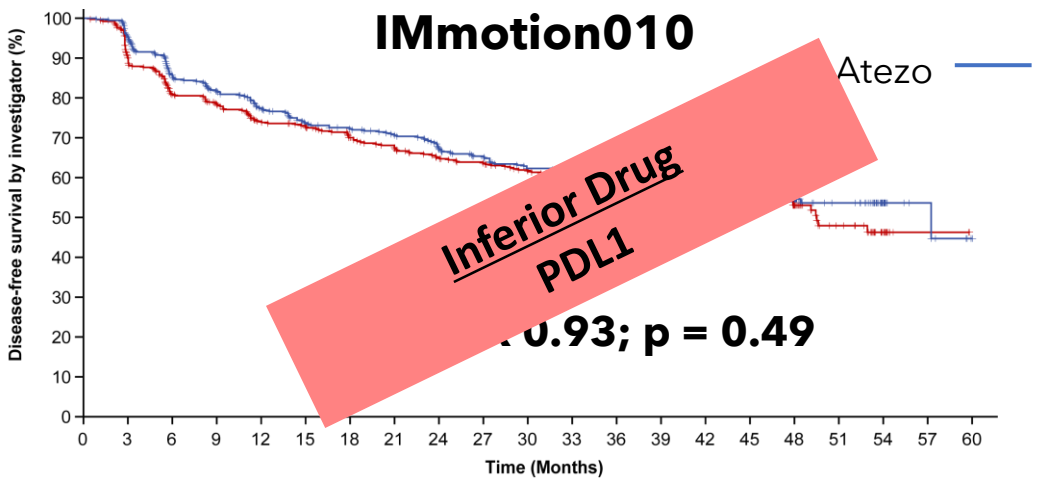


Pembro: HR 0.72 (95% CI 0.59-0.87)

No. at Risk

Pembrolizumab	496	458	416	388	370	355	337	327	307	284	221	160	65	19	5	0
Placebo	498	438	390	357	333	320	307	292	282	254	210	139	62	16	2	0

IMmotion010



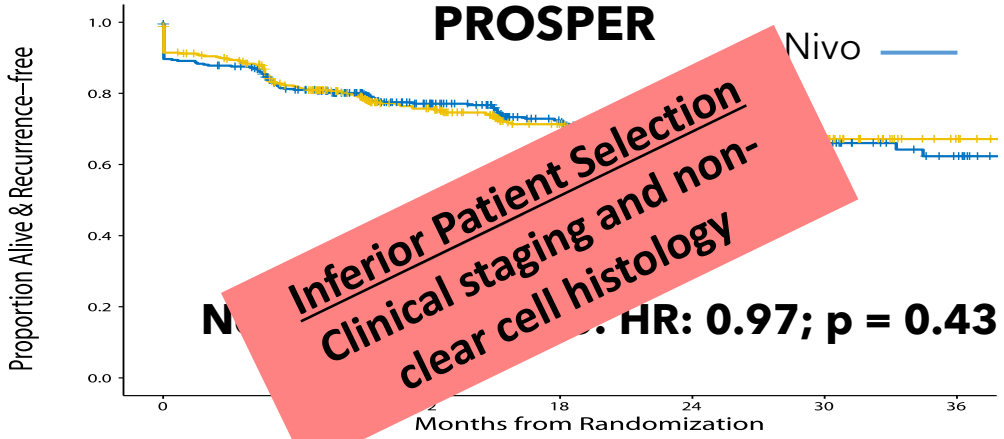
Inferior Drug
PDL1

0.93; p = 0.49

Number at risk

Atezolizumab	390	360	322	306	288	272	265	257	244	234	222	218	194	171	124	100	75	48	22	6	1
Placebo	388	343	305	294	275	268	254	243	232	226	216	209	187	161	121	91	56	33	15	3	NE

PROSPER



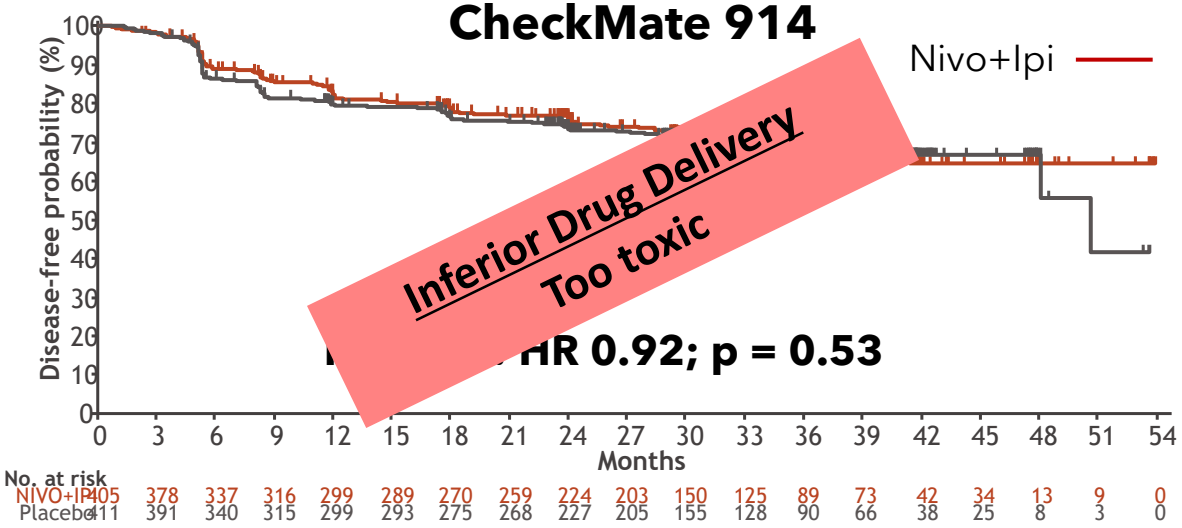
Inferior Patient Selection
Clinical staging and non-clear cell histology

N . HR: 0.97; p = 0.43

Number at risk

Nivo arm	379	291	208	151	99	50	30
bservation arm	400	300	214	161	100	47	22

CheckMate 914



Inferior Drug Delivery
Too toxic

HR 0.92; p = 0.53

No. at risk

NIVO+IPI	405	378	337	316	299	289	270	259	224	203	150	125	89	73	42	34	13	9	0
Placebo	411	391	340	315	299	293	275	268	227	205	155	128	90	66	38	25	8	3	0

Choueiri NEJM (2024) 390:1359; Bex ESMO 2022; Allaf ESMO 2022; Motzer ESMO 2022

Adjuvant IO for RCC: Summary

- Continued disease-free survival benefit vs placebo was observed with further follow-up
- FDA-approval of adjuvant pembrolizumab November 17, 2021
- Discordant phase III trials of adjuvant IO therapy created uncertainty for best practice
- Adjuvant pembrolizumab significantly prolonged OS versus placebo
  - 38% reduction in risk of death with adjuvant pembrolizumab versus placebo
  - Survival benefit seen across key clinical subgroups
- KeyNote 564 is the first study to show a statistically significant and clinically meaningful survival benefit with adjuvant therapy in RCC
- See Choueiri, TK *et al*. NEJM (2024) Apr 18; 390(15): 1359-1371.

Can We Develop A More Potent Immunotherapy-Based Adjuvant Treatment Regimen Based on the Success of Pembrolizumab?

Study Name	Phase	Treatment	Status
LITESPARK-002	III	Pembrolizumab plus Belzutifan vs Pembrolizumab plus placebo	Completed accrual April 2024
V940-004	II	Pembrolizumab plus V940 (personalized mRNA cancer vaccine) vs Pembrolizumab plus placebo	Will open at FHCC ~ 4 months

RCC Learning Objectives

- Epidemiology
- Staging and Histologic Subtypes
- Hereditary RCC cancer syndromes
- **Systemic Treatments**
  - Overview
  - Local RCC - Adjuvant therapy
  - **Metastatic RCC**
    - **First line – clear cell**
    - First line – non clear cell
    - Salvage – clear cell

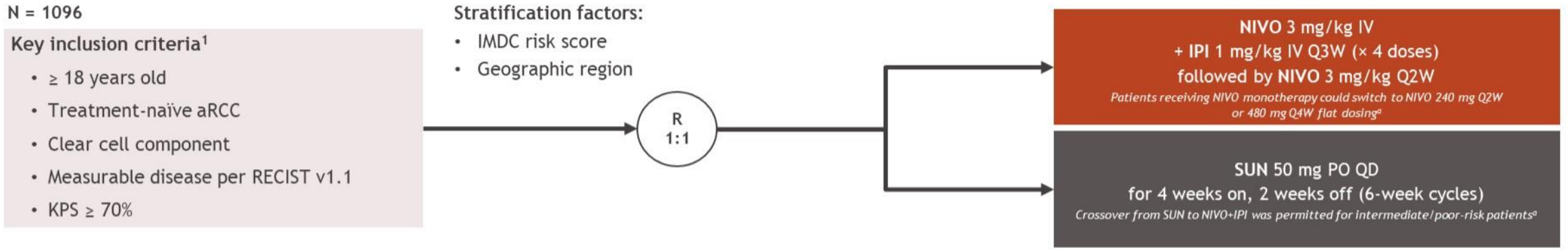
Front-line phase 3 trials with IO agents (efficacy summary)

	CheckMate 214[1]	KEYNOTE-426[2]	CheckMate 9ER[3]	CLEAR[4]
Intervention	Nivolumab + Ipilimumab N=550	Pembrolizumab + Axitinib N=432	Nivolumab + Cabozantinib N=323	Pembrolizumab + Lenvatinib N=355
Fav/Int/Poor %	23/61/17	32/55/13	23/58/19	31/58/9
Comparator	Sunitinib	Sunitinib	Sunitinib	Sunitinib
Primary Endpoint	OS, PFS, ORR in int/poor risk	OS, PFS	PFS	PFS
mOS (ITT), months	(median 67.7 mo FU) 55.7 vs 38.4 HR 0.72	(median 42.8 mo FU) 45.7 vs 40.1 HR 0.73	(median 44 mo FU) 49.5 vs 35.5 HR 0.70	(median 49.8 mo FU) 53.7 vs 54.3 HR 0.79
PFS (ITT), months	12.3 vs 12.3 HR 0.86	15.7 vs 11.1 HR 0.68	16.6 vs 8.4 HR 0.58	23.3 vs 9.2 HR 0.47
ORR (ITT), %	39% vs 33%	60% vs 40%	56% vs 28%	71% vs 37%
CR rate (ITT)	12% vs 3%	10% vs 4%	12% vs 5%	18% vs 5%
Primary PD	18% vs 14%	11% vs 17%	6% vs 14%	5% vs 14%

[1]Motzer et al. ESMO 2021. Abstract 661P; Albiges et al. ESMO Open 2020; [2]Rini et al. ASCO 2021 abstract 4500; Powles et al. *Lancet Oncol*. 2020;21:P1563-1573.
[3]Choueiri et al. *N Engl J Med.* 2021;384:829-41. Apolo et al. ASCO 2021 abstract 4553; Burotto et al. GU Ca Symp 2023 Abstract 603; [4]Porta et al.ESMO 2022 abstract 1449MO; Motzer et al. *N Engl J Med*. 2021;384:1289-1300; Motzer, RJ et al. ASCO GU 2023, abstract 4502.

Background and study design (CheckMate 214)

- NIVO+IPI is approved for first-line treatment of IMDC intermediate/poor-risk aRCC, based on superior OS and ORR over SUN in the randomized, phase 3 CheckMate 214 trial[1-3]
- NIVO+IPI has demonstrated durable survival and response benefits versus SUN across a broad range of patients, providing the opportunity to conduct long-term survival analyses[4-6]
- With a median follow-up of 8 years in the CheckMate 214 trial, we present updated efficacy and safety outcomes, and exploratory subgroup analyses in patients by organ sites of metastasis at baseline



Median (range) follow-up for OS, 99.1 (91.0-107.3) months

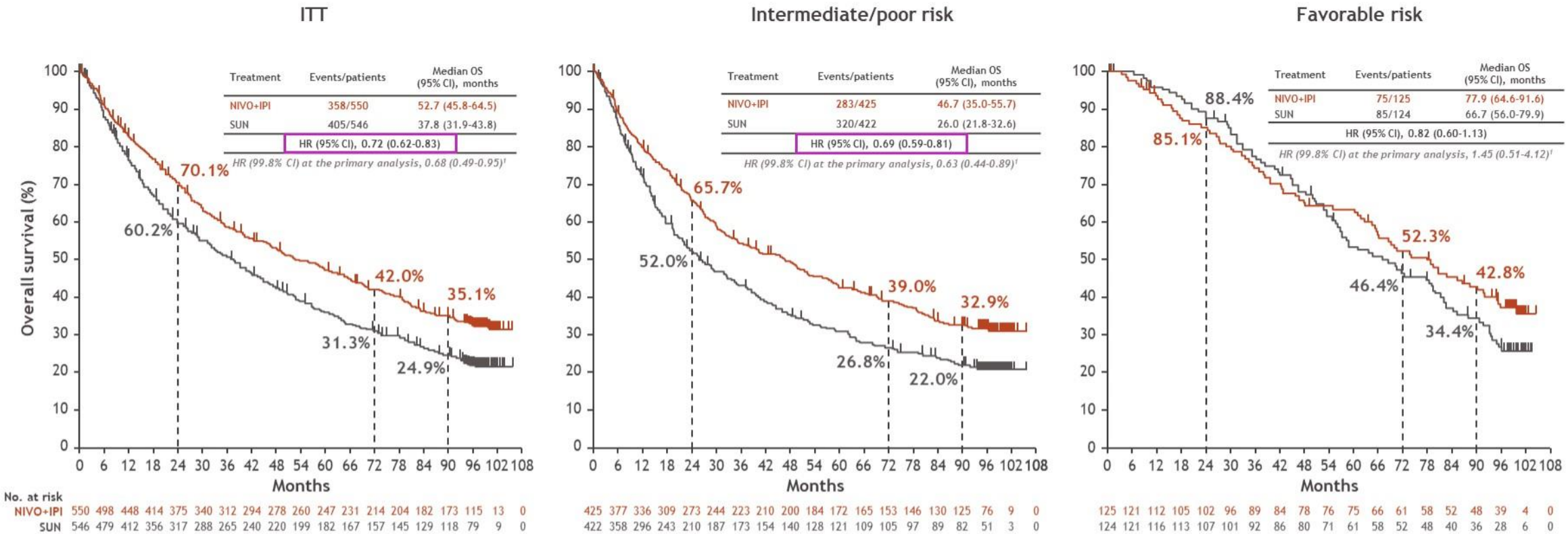
Primary endpoints: OS, PFS and ORR (both per IRRC) in IMDC intermediate/poor-risk patients
Secondary endpoints: OS, PFS and ORR (both per IRRC) in ITT patients; safety in all treated patients
Exploratory endpoints: OS, PFS and ORR (both per IRRC) in IMDC favorable-risk patients

Response was assessed using RECIST v1.1. [a]As of a November 2017 protocol amendment and protocol revision 04.

1. Motzer RJ, et al. *N Engl J Med* 2018;378:1277-1290. 2. OPDIVO (nivolumab) [package insert]. Princeton, NJ: Bristol Myers Squibb; 2023. 3. YERVOY (ipilimumab) [package insert]. Princeton, NJ: Bristol Myers Squibb; 2023. 4. Motzer RJ, et al. *Cancer* 2022;128:2085-2097. 5. Albiges L, et al. *Eur Urol* 2022; 81:266-271. 6. Tannir NM, et al. Poster presentation at the International Kidney Cancer Symposium (IKCS); November 5-6, 2021; Austin, TX. Abstract CTR11.

Overall survival

- The HR for OS has been stable over 8 years of median follow-up in ITT and intermediate/poor-risk patients and has improved over time in favorable risk patients

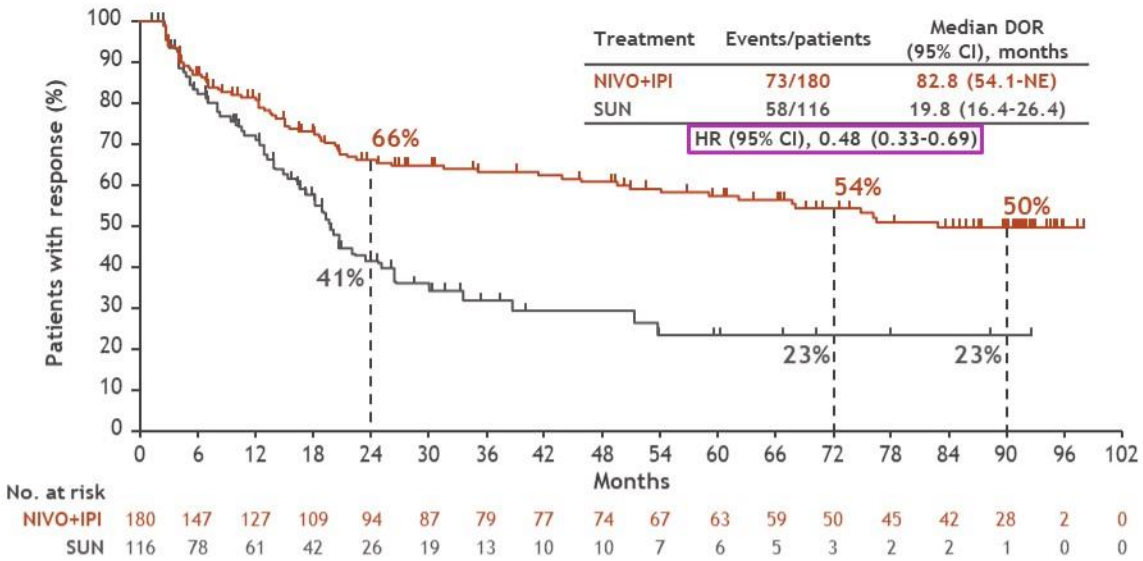


Stratified Cox proportional hazards model.

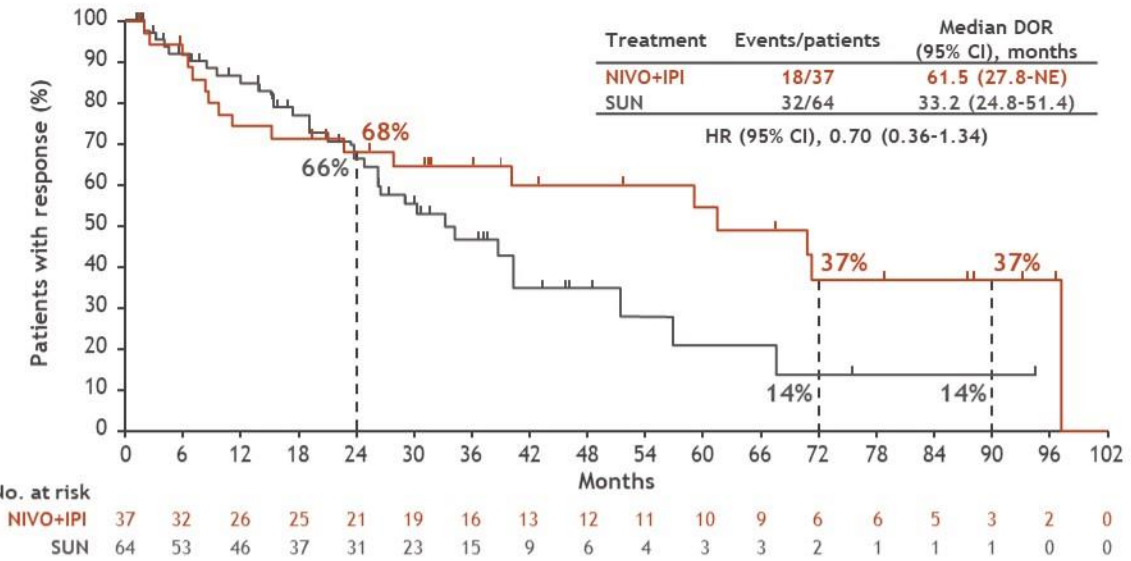
1. Motzer RJ, et al. *N Engl J Med* 2018;378:1277-1290.

DOR, ORR, and BOR (all per IRRC)

Intermediate/poor risk



Favorable risk



	ITT population		Intermediate/poor risk		Favorable risk	
	NIVO+IPI N = 550	SUN N = 546	NIVO+IPI N = 425	SUN N = 422	NIVO+IPI N = 125	SUN N = 124
ORR (95% CI), %	39 (35-44)	33 (29-37)	42 (38-47)	27 (23-32)	30 (22-38)	52 (43-61)
Best overall response, n (%)						
Complete response	66 (12)	19 (3)	50 (12)	11 (3)	16 (13)	8 (6)
Partial response	151 (27)	161 (29)	130 (31)	105 (25)	21 (17)	56 (45)
Stable disease	197 (36)	230 (42)	130 (31)	186 (44)	67 (54)	44 (35)
Progressive disease	97 (18)	77 (14)	82 (19)	71 (17)	15 (12)	6 (5)
UTD/NR	39 (7)	59 (11)	33 (8)	49 (12)	6 (5)	10 (8)
Ongoing response, % (n/N)	58 (126/217)	50 (90/180)	59 (107/180)	50 (58/116)	51 (19/37)	50 (32/64)
Ongoing complete response, % (n/N)	80 (53/66)	89 (17/19)	84 (42/50)	91 (10/11)	69 (11/16)	88 (7/8)

RECIST v1.1 response criteria. Stratified Cox proportional hazards model.
In the ITT population, median (95% CI) DOR was 76.2 (59.1-NE) months with NIVO+IPI and 25.1 (19.8-33.2) months with SUN (HR, 0.52; 95% CI, 0.38-0.72).

Efficacy Outcomes for IMDC Favorable Risk ccRCC With Front-Line IO Regimens

Regimen	Follow Up	ORR	PFS	OS
Nivo + Ipi[1] CheckMate 214	99.1 mo median	30% vs 52%	12.4 vs 28.8 mo HR=1.76	77.9 vs 66.7 mo HR = 0.82
Pembro + Axitinib[2] KeyNote 426	42.8 mo median	69% vs 50%	20.7 vs 17.8 mo HR=0.76	NR vs NR HR=1.17
Nivo + Cabo[3] CheckMate 9ER	55.6 mo median	66% vs 44%	21.4 vs 12.8 mo HR=0.72	52.9 vs 58.9 mo HR = 1.10
Pembro + Len[4] CLEAR	49.8 mo median	N/A	28.6 vs 12.9 HR=0.50	NR vs 59.9 mo HR 0.94

[1]Motzer ASCO GU 2024 abstract 363. [2]Rini et al. ASCO 2021 abstract 4500.
[3]Bourlon, MT et al. GU Ca Symp 2024 Abstract 362; [4]Motzer, RJ et a. ASCO GU 2023, abstract 4502

Kidney Cancer NCCN Guidelines v1.2025

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) • Ipilimumab + nivolumab[b]	• Axitinib + avelumab[b] • Cabozantinib (category 2B) • Pazopanib • Sunitinib	• Active surveillance[1,2,3] • Axitinib (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)

https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1440

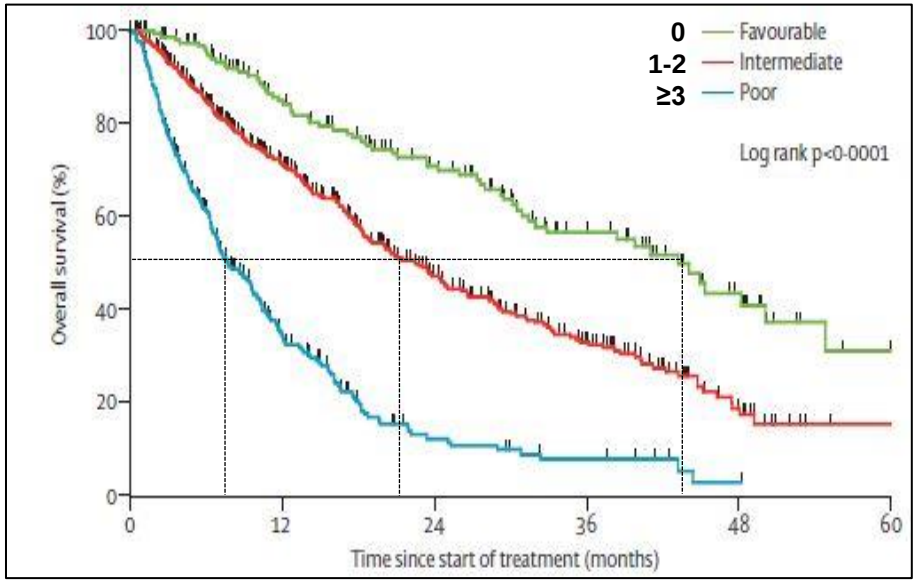
IMDC (Heng) Risk Model for mRCC Treated by Targeted Therapy

International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) Risk Model:

6 Baseline Risk Factors Predict Diminished Overall Survival (OS) in mRCC:

- Diagnosis to systemic treatment < 1 year* (DxTx<1yr)
- Diminished performance status (PS)*
- Elevated corrected calcium*
- Anemia*
- Elevated neutrophils (new)
- Elevated platelets (new)

*Same as MSKCC risk model[3]



Median OS by IMDC risk group:

- Favorable risk: 43 months
- Intermediate risk: 22.5 months
- Poor risk: 7.8 months

1. Heng, D *et al*. JCO (2009) 27:5794
2. Heng, D *et al*. Lancet Oncology. (2013) 14:141
3. Motzer, RJ *et al*. JCO (2002) 20:289-296

CM214 8-yr Follow up: Summary

- CM214 results represent the longest follow-up in a phase 3 trial of a checkpoint inhibitor combination therapy in first-line aRCC
- The hazard ratio for OS with NIVO+IPI vs SUN has improved over time in the favorable risk patients
- Responses to NIVO+IPI were deep and durable in the overall study population; patients had notably improved DOR and more CRs with NIVO+IPI over SUN regardless of risk group.
- Optimal therapy for favorable risk patients based on an OS outcome remains unclear and encourages patient-specific customization.

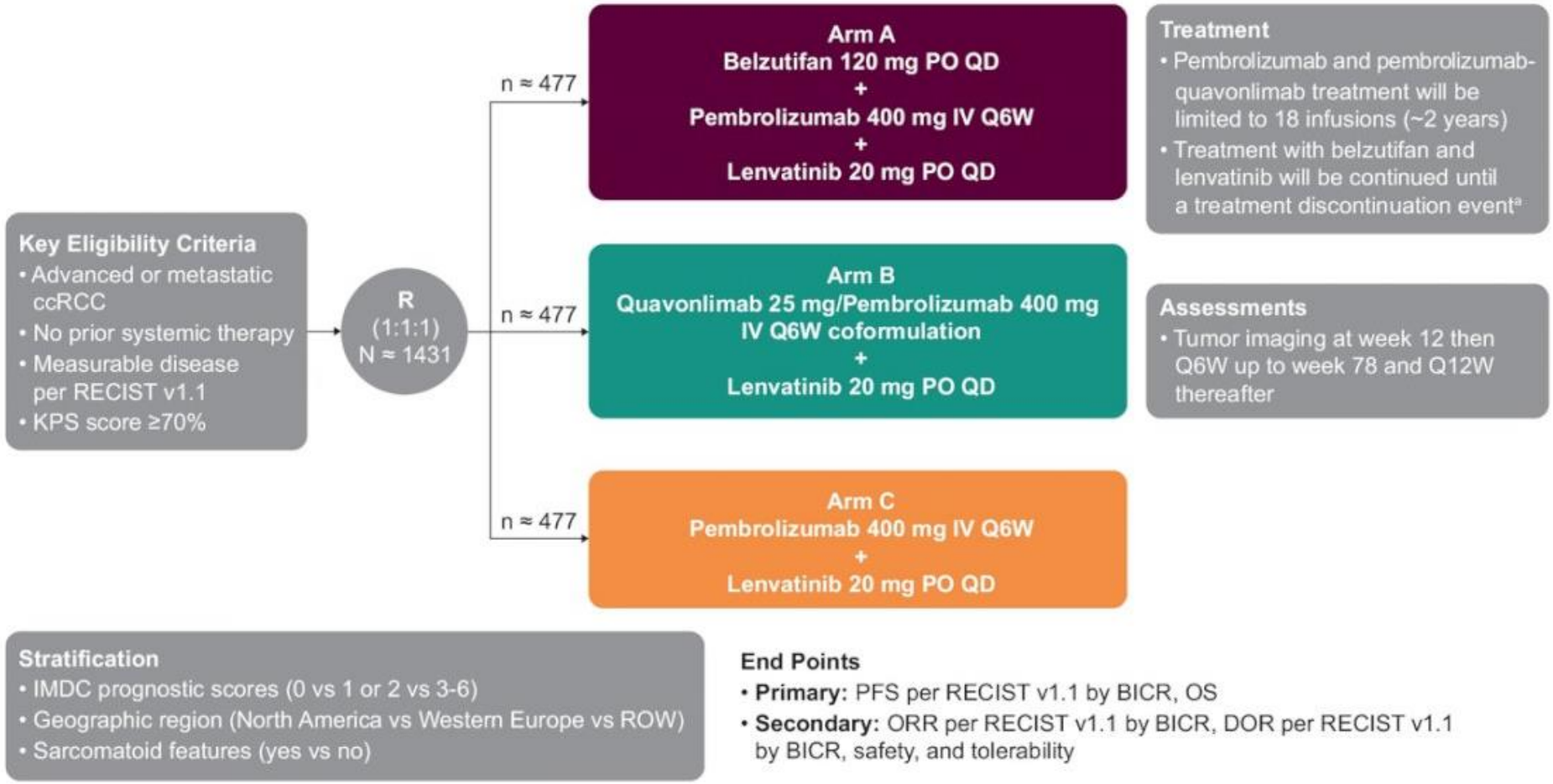
Front-Line Therapy for Advanced Clear Cell RCC

What We Are Using	What We Are Not Using
▪ Ipilimumab + Nivolumab ▪ Pembrolizumab + Axitinib ▪ Nivolumab + Cabozantinib ▪ Pembrolizumab + Lenvatinib	▪ Avelumab + Axitinib (JAVELIN Renal 101) ▪ Ipilimumab + Nivolumab + Cabozantinib (COSMIC 313)

Selecting Between First-Line Checkpoint Containing Regimens

	Favors IO/IO	Favors IO/TKI
Risk Category	IMDC Favorable Risk?	
Disease Phenotype	"Late" efficacy endpoints: • Strong median OS • Treatment-free survival ⇨ Favors small volume / asymptomatic	"Early" efficacy endpoints: • Low primary refractory disease incidence • High ORR • Stronger PFS ⇨ Favors bulky / symptomatic
Toxicity	Patient tolerance	

What's coming? Another front-line phase III triplet study



Choueiri et al. ASCO GU 2022

RCC Learning Objectives

- Epidemiology
- Staging and Histologic Subtypes
- Hereditary RCC cancer syndromes
- **Systemic Treatments**
  - Overview
  - Local RCC - Adjuvant therapy
  - **Metastatic RCC**
    - First line – clear cell
    - **First line – non clear cell**
    - Salvage – clear cell

Efficacy Outcomes for Sarcomatoid ccRCC

	Historical			*Contextual*		
Treatment	**Chemo**	**Targeted Tx**	**Ipi/Nivo vs Sun**	**Other Immunotherapy**		
Regimen (N)	**Dox+Gem[1] 39**	**Sun+Gem[2] 39**	**CM214[3] 74/65**	**Avelumab/Ax[4] 47**	**Pembro/Ax[5] 51**	**Pembro[6] 11**
ORR, %	16	26	**61** vs 23	47	59	64
CR, %	3	3	**23** vs 6	4	12	0
PR, %	13	23	**38** vs 17	43	47	64
Median PFS, mo	3.5	5	**26.5** vs 5.5	7.0	NR	16.3
Median OS, mo	8.8	10	**48.6** vs 14.2 *HR = 0.46*	NR *HR vs SUN 0.78*	NR *HR vs SUN 0.58*	32.2

[1]Haas, NB *et al*. Med Oncol (2012)
[2]Michaelson, MD *et al*. Cancer (2015)
[3]Rini, BI *et al*. JITC (2022)
[4]Chouriri, TK *et al*. ESMO Open (2021)
[5]ASCO 2019, abstr #4500
[6]McDermott, DF *et al*. JCO (2021)

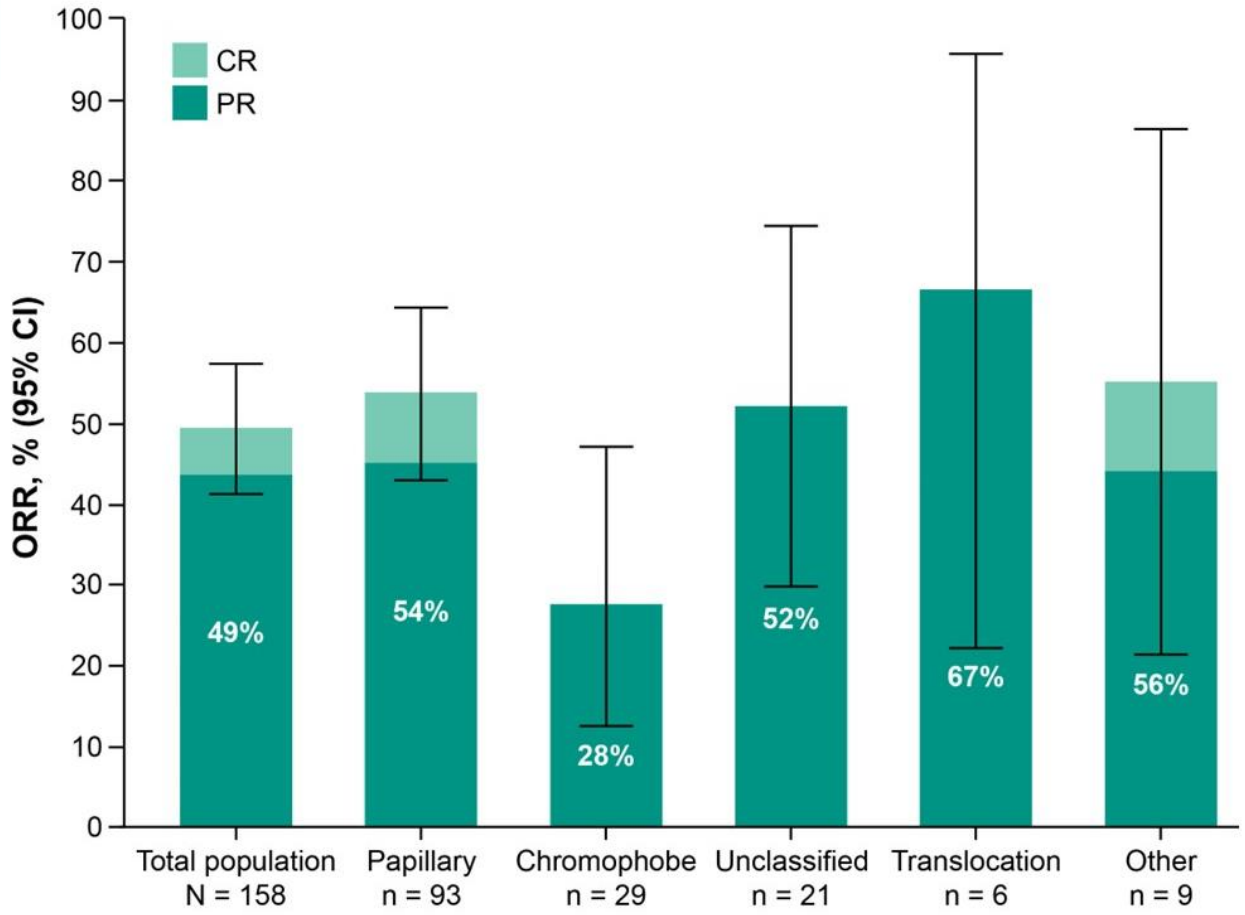
Front-line data for metastatic papillary RCC

	PAPMET[1]	KEYNOTE-427[2]	Nivo + Cabo[3]	KeyNote B61[4]
Intervention	Cabozantinib vs Sunitinib N=44	Pembrolizumab N=118	Nivolumab + Cabozantinib N=32	Pembrolizumab + Lenvatinib N=93
Comparator	Sunitinib	None	None	None
Primary Endpoint	PFS	ORR	ORR	ORR
mOS (ITT), months	20.0 vs 16.4 HR 0.84	(median 31.5 mo FU) 31.5	(median 13.1 mo FU) 28.0	(median 14.9 mo FU) Not reported
PFS (ITT), months	9.0 vs 5.6 HR 0.60	5.5	12.5 (cohort 1)	Not reported (17.9 for all pts)
ORR (ITT), %	23% vs 4%	29%	47%	54%
CR rate (ITT)	5% vs 0%	6%	0%	9%
Primary PD	14% vs 28%	32%	3%	10%

[1]Pal, SK et al. Lancet (2021) 397:695.
[2]McDermnott, DF et al. JCO (2021) 39:1029.
[3]Lee, CH et al. JCO (2022) DOI https://doi.org/10.1200/JCO.21.01944
[4]Lee, C-H et al. ASCO 2023 abstract 4518.

KeyNote B61 (Pem + Len) - Best ORR by Histologic Subtype
A "One Size Fits All" Front-Line Choice?

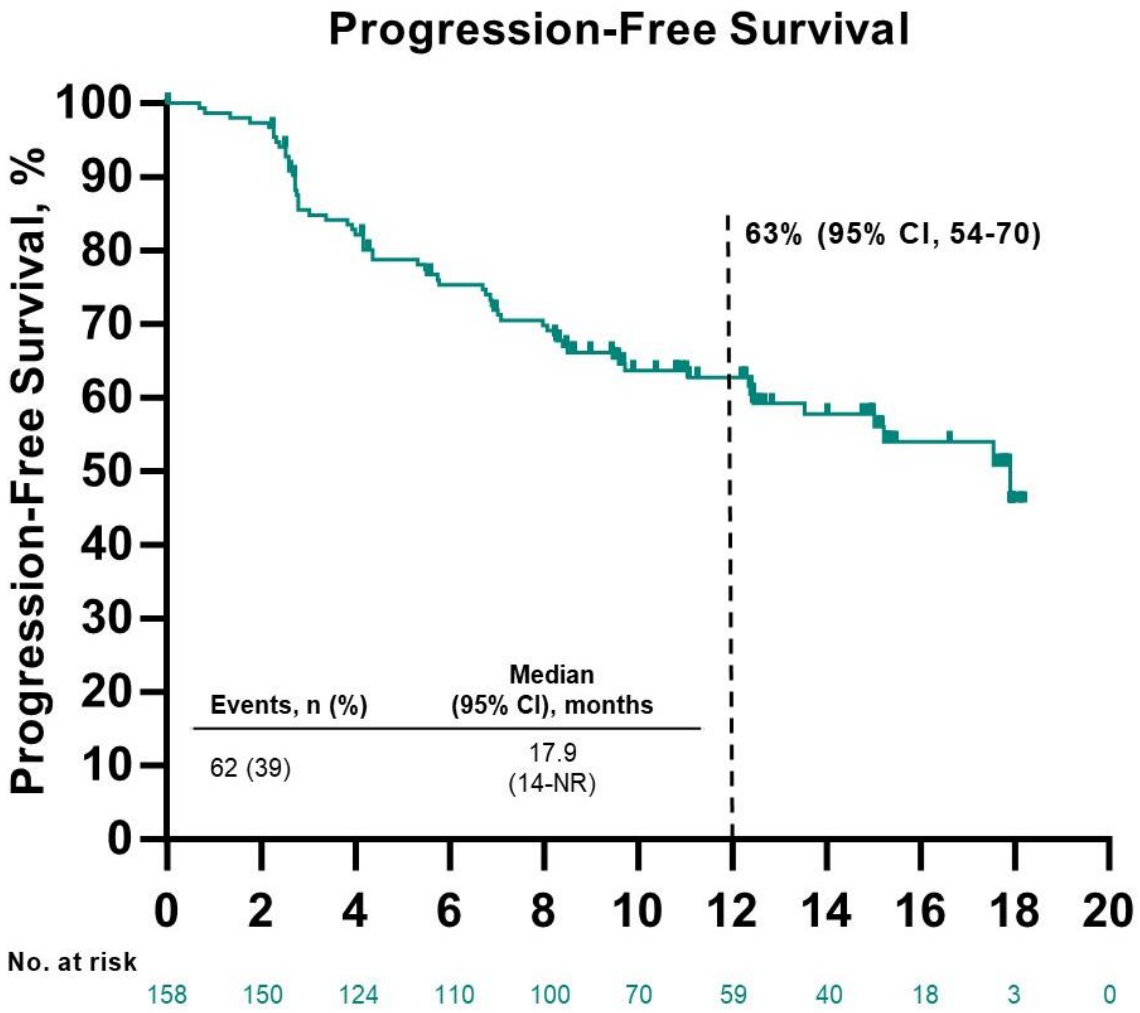
	Pembrolizumab + lenvatinib N = 158
ORR (CR + PR), % (95% CI)	49 (41-57)
DCR (CR + PR + SD), % (95% CI)	82 (75-88)
CBR (CR, PR, or SD for ≥6 months), % (95% CI)	72 (64-78)
Best response, n (%)	
CR	9 (6)
PR	69 (44)
SD	52 (33)
PD	17 (11)
NE[a]	1 (0.6)
NA[b]	10 (6)

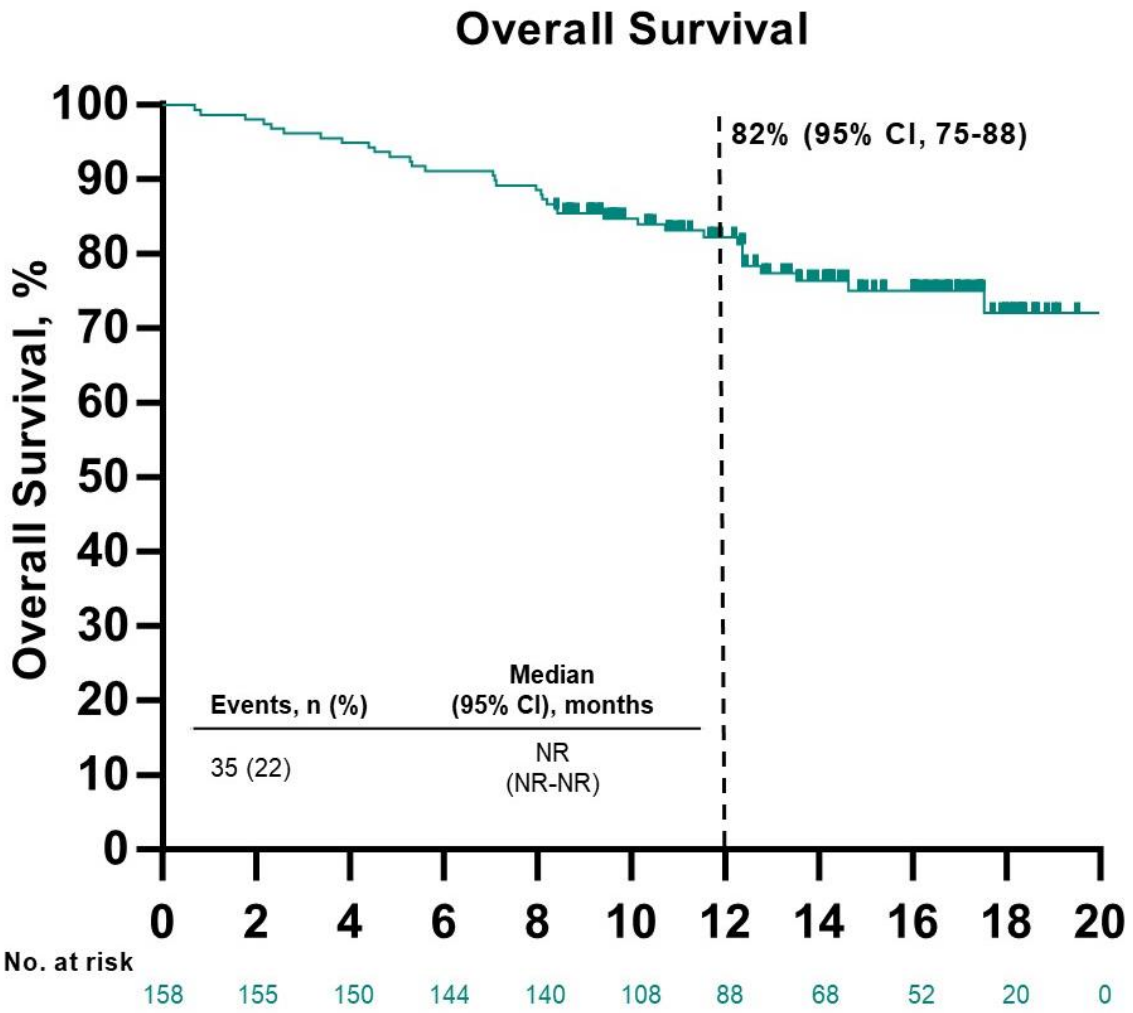


CR, complete response; NA, not applicable; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease. [a]Post-baseline assessment available but not evaluable. [b]No post-baseline assessment available. Data cutoff date: November 7, 2022.

Lee, C-H et al. ASCO 2023 abstract 4518.

KeyNote B61 - PFS and OS





Data cutoff date: November 7, 2022.

Lee, C-H et al. ASCO 2023 abstract 4518.

Conclusions

- Immune checkpoint inhibitors appear to be the drug class of choice for sarcomatoid (cc) RCC tumors
- Cabozantinib had better activity by PFS and ORR versus sunitinib for advanced papillary RCC
- Single agent (cabozantinib, pembrolizumab) or IO/TKI combination regimens are rationale first-line options for metastatic papillary RCC.
- Pembrolizumab plus lenvatinib has good activity across a broad range of RCC histologic subtypes.

RCC Learning Objectives

- Epidemiology
- Staging and Histologic Subtypes
- Hereditary RCC cancer syndromes
- **Systemic Treatments**
  - Overview
  - Local RCC - Adjuvant therapy
  - **Metastatic RCC**
    - First line – clear cell
    - First line – non clear cell
    - **Salvage – clear cell**

Comparison of Current Salvage Treatment Options for RCC from Randomized Trials

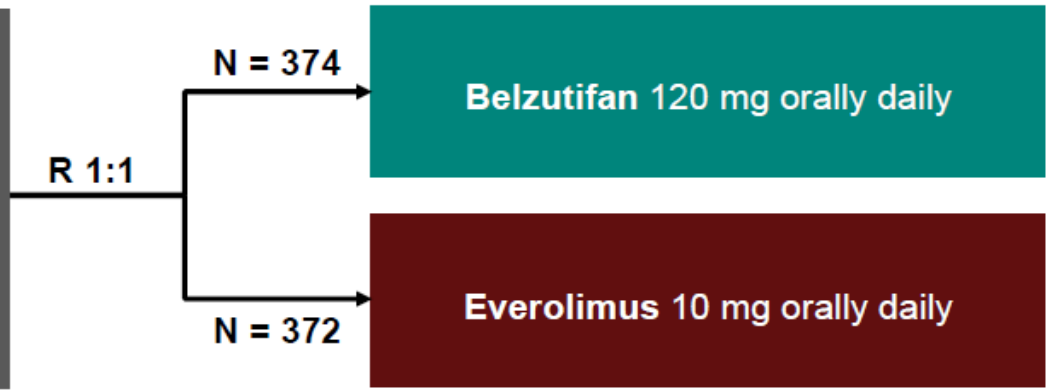
	Axitinib	Nivolumab	Cabozantinib	Lenvatinib/ Everolimus	Tivozanib	Belzutifan
Patient Population	TKI refractory*	TKI refractory	TKI refractory	TKI refractory	TKI refractory	IO / TKI refractory
Comparator	Sorafenib	Everolimus	Everolimus	Everolimus	Sorafenib	Everolimus
ORR	9%*	22%	17%	35%	18%	23%
PFS, months	6.5*	4.6	7.4	12.8	5.6	5.6
OS, months	15.2*	25.0	21.4	25.5	16.4	21.4
Dose reductions	30%	n/a	60%	71%	24%	14%
D/C due to AE	7%	8%	9%	29%	NS	6%
Toxicity	G3 50%	18%	63%	57%	NS	40%
	G4 6%	1%	8%	14%	NS	

Rini, BI *et al*.. Lancet (2011)
Choueiri, TK *et al*. NEJM (2015)
Motzer, RJ *et al*. Lancet Oncol (2015)
Motzer, RJ *et al*. NEJM (2015)
Rini, BI *et al*. Lancet Oncol (2020)
Rini, B *et al*. ESMO (2024)

LITESPARK-005 Study (NCT04195750)

Key Eligibility Criteria

- Unresectable, locally advanced or metastatic clear cell RCC
- Disease progression after 1-3 prior systemic regimens, including ≥1 anti−PD-(L)1 mAb and ≥1 VEGFR-TKI
- Karnofsky Performance Status score ≥70%



Stratification Factors

- IMDC prognostic score[a]: 0 vs 1-2 vs 3-6
- Prior VEGFR-targeted therapies: 1 vs 2-3

Dual Primary Endpoints:

- PFS per RECIST 1.1 by BICR
- OS
- The study was considered positive if either of the dual primary endpoints was met

Key Secondary Endpoint:

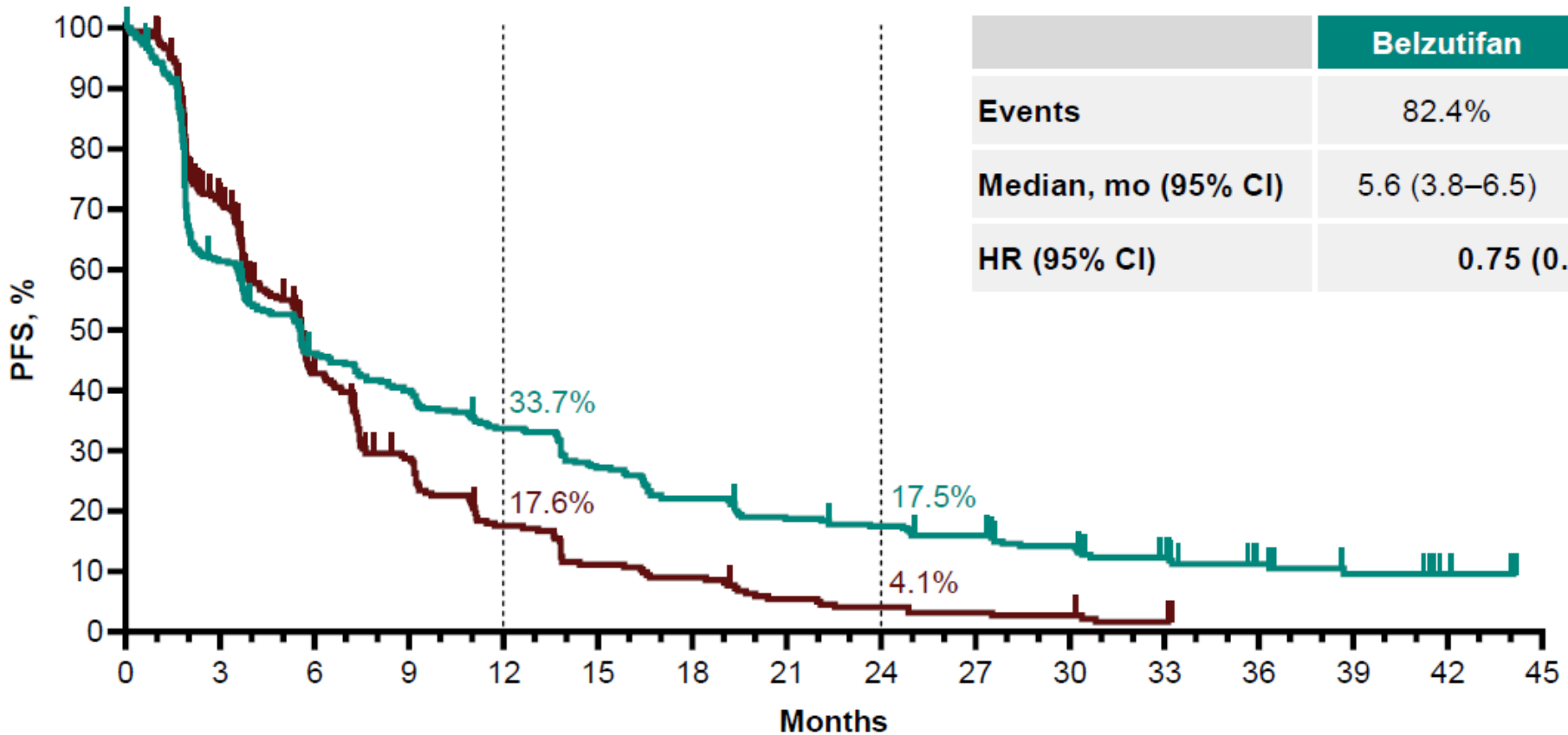
- ORR per RECIST 1.1 by BICR

Other Secondary Endpoints Include:

- DOR per RECIST 1.1 by BICR
- Safety

Rini et al. ESMO 2024

Primary Endpoint: PFS per RECIST 1.1 by BICR



	Belzutifan	Everolimus
Events	82.4%	75.0%
Median, mo (95% CI)	5.6 (3.8–6.5)	5.6 (4.8–5.8)
HR (95% CI)	0.75 (0.63–0.88)	

No. at Risk

Belzutifan	374	218	156	135	113	91	74	61	56	50	39	27	16	10	5	0
Everolimus	372	226	113	70	41	26	21	12	9	7	6	3	0	0	0	0

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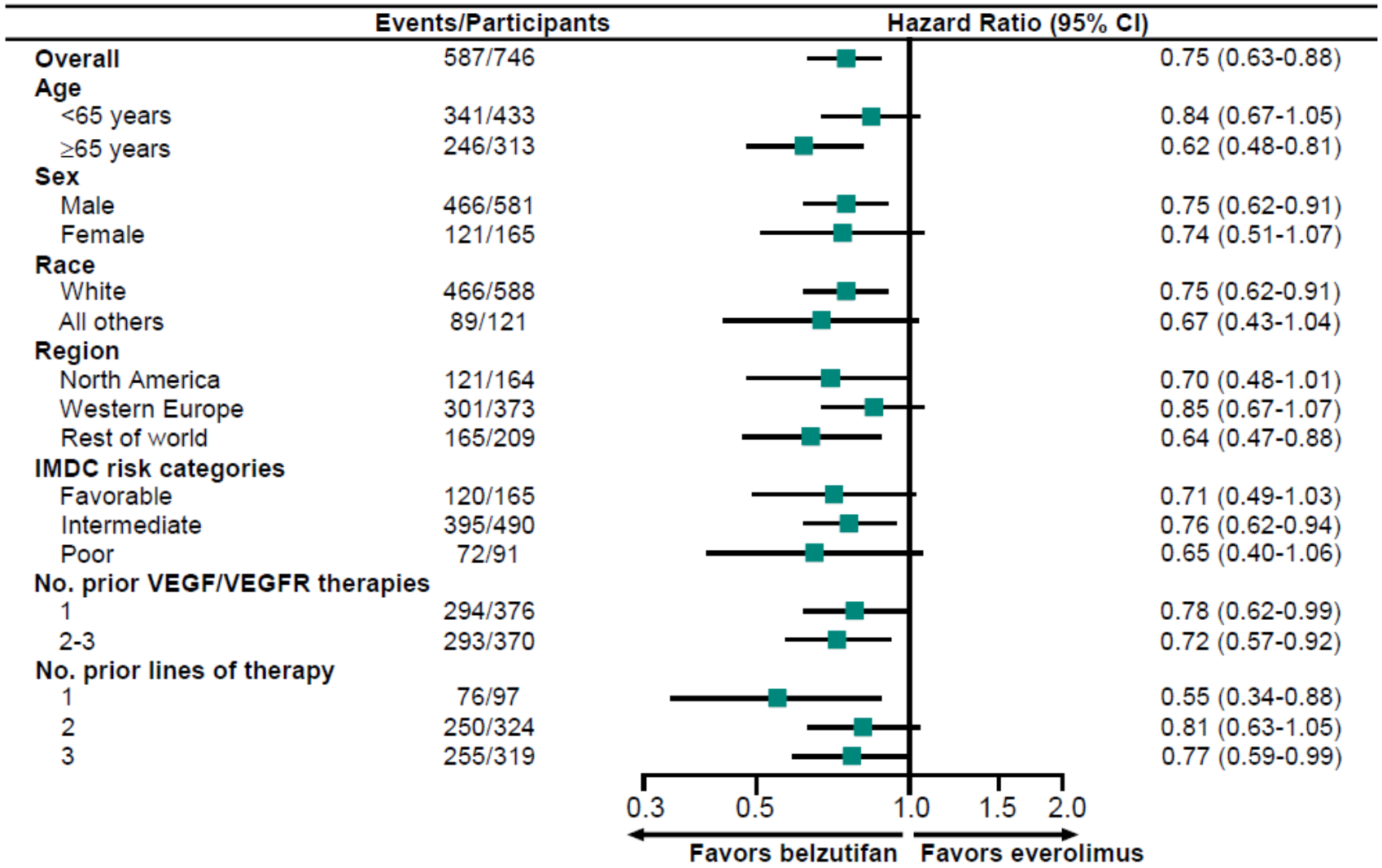
PFS by BICR per RECIST 1.1 in Subgroups



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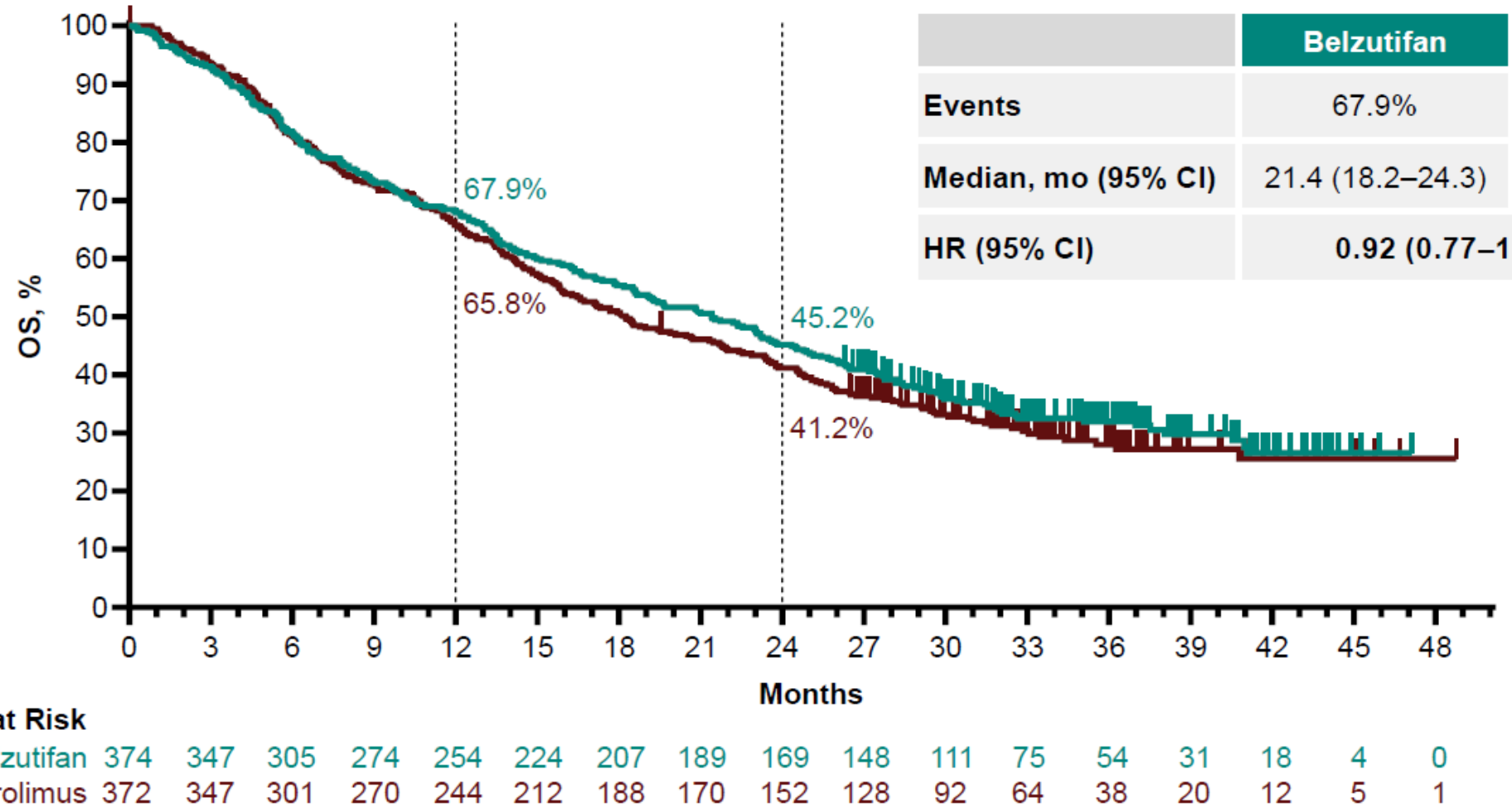
Primary Endpoint: OS



	Belzutifan	Everolimus
Events	67.9%	69.6%
Median, mo (95% CI)	21.4 (18.2–24.3)	18.2 (15.8–21.8)
HR (95% CI)	0.92 (0.77–1.10); *P*=0.18	

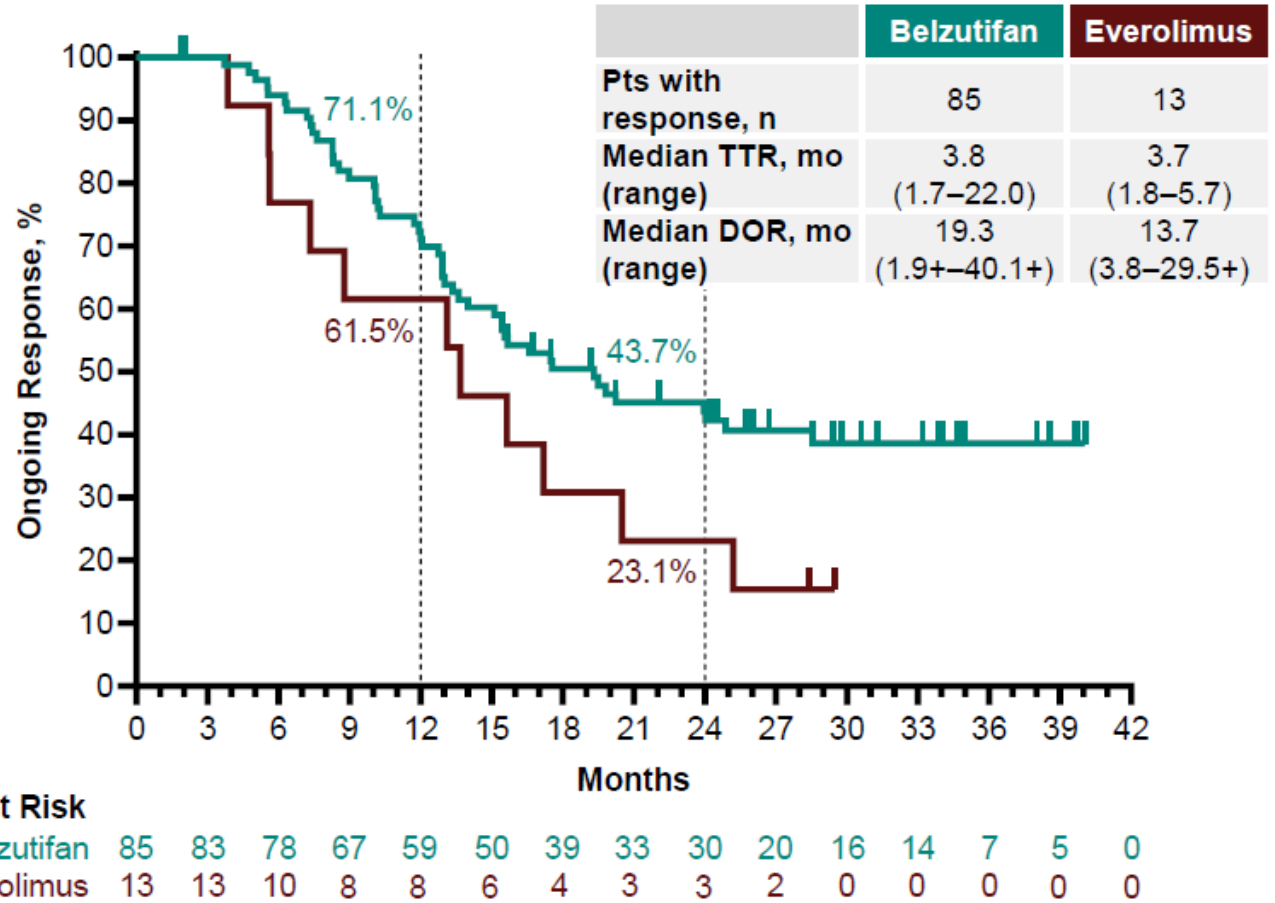
No. at Risk

Belzutifan	374	347	305	274	254	224	207	189	169	148	111	75	54	31	18	4	0
Everolimus	372	347	301	270	244	212	188	170	152	128	92	64	38	20	12	5	1

Rini et al. ESMO 2024

ORR (Key Secondary) and DOR (Secondary Endpoint) by BICR per RECIST 1.1

	Belzutifan (N = 374)	Everolimus (N = 372)
ORR, % (95% CI)	**22.7% (18.6–27.3)**	**3.5% (1.9–5.9)**
Estimated difference in % (95% CI)	**19.2 (14.8–24.1)**	
Confirmed best objective response, %		
CR	3.5%	0
PR	19.3%	3.5%
SD	38.2%	65.9%
PD	34.0%	21.5%
Not evaluable[a]	1.3%	2.4%
No assessment[b]	3.7%	6.7%



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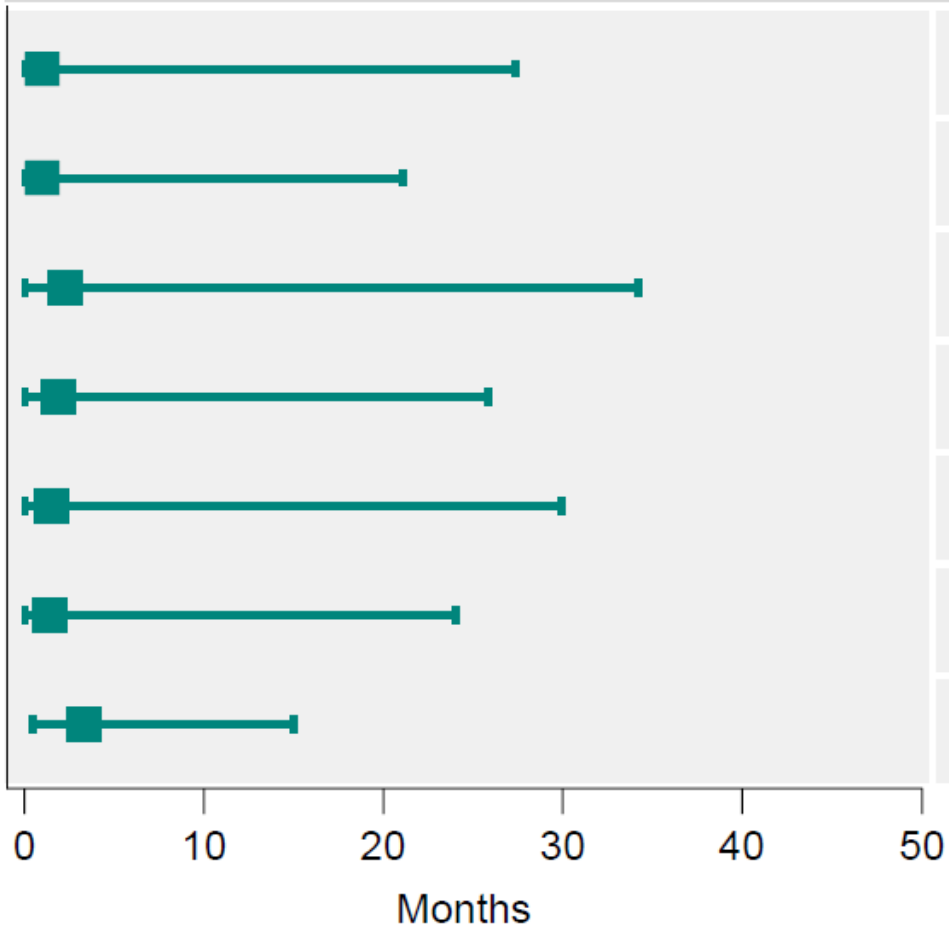
Time to First Onset of Common Any-Grade AEs Attributed to Belzutifan (Adverse Drug Reactions)

ADR	Incidence, n (%)	Time to onset, median (range), mo
Anemia	310 (83.3)	1.0 (0.03–27.4)
Hypoxia	53 (14.2)	1.0 (0.03–21.1)
Dizziness	50 (13.4)	2.3 (0.03–34.2)
Dyspnea	57 (15.3)	1.9 (0.03–25.8)
Fatigue	120 (32.3)	1.5 (0.03–29.9)
Nausea	69 (18.5)	1.4 (0.03–24.0)
Weight increased	22 (5.9)	3.3 (0.5–15.0)



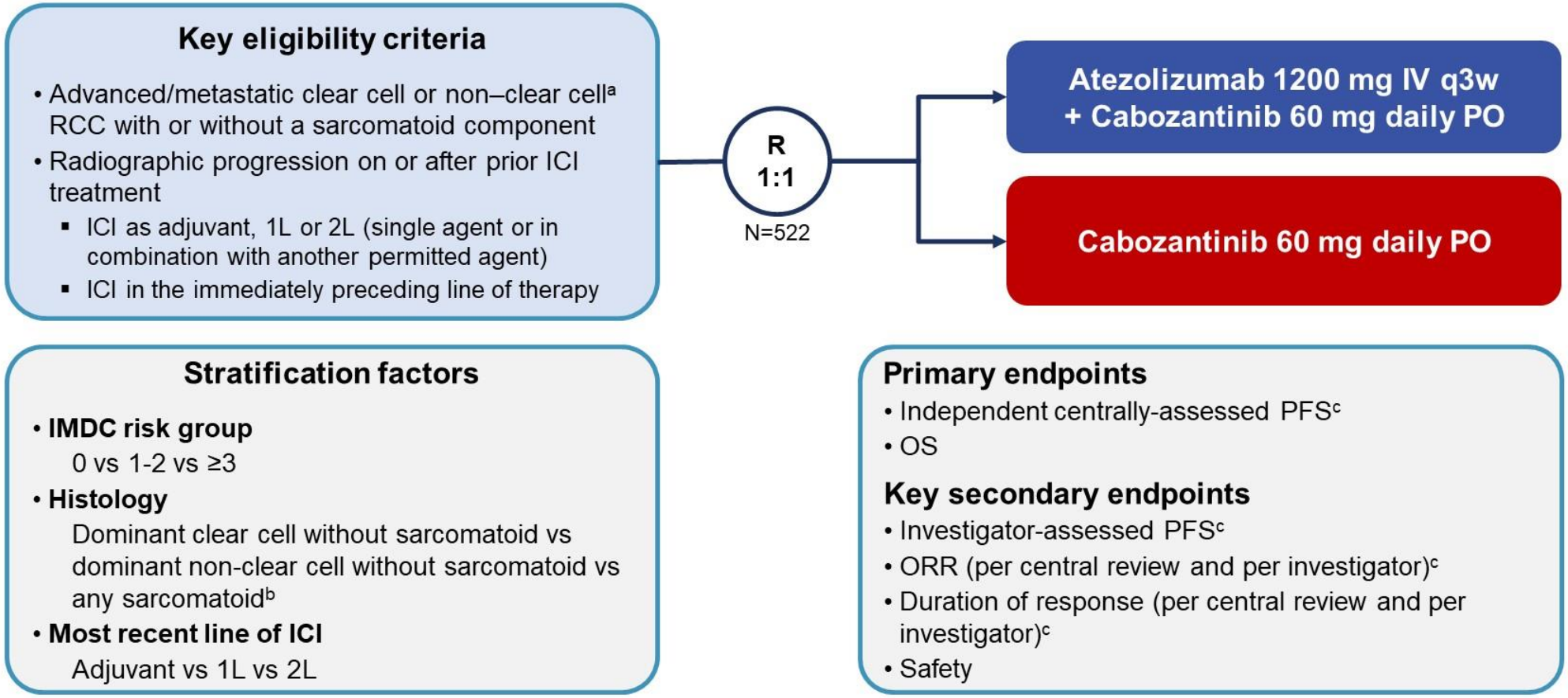
Rini et al. ESMO 2024

Should we continue PD1/PDL1 blockade in the salvage setting?

- Single arm datasets suggest provocative activity for PD1/TKI combinations in PD1 refractory RCC
  - Nivolumab/tivozanib[1]
  - Pembrolizumab/lenvatinib[2]
- Randomized prospective studies evaluating IO/TKI synergy in the IO refractory setting
  - CONTACT-03 (ASCO 2023)
  - TiNivo-2 (ESMO 2024)

[1]Albiges et al. Ann Oncol. 2021; [2]Lee et al. Lancet Oncol. 2021

Phase III CONTACT-03 study



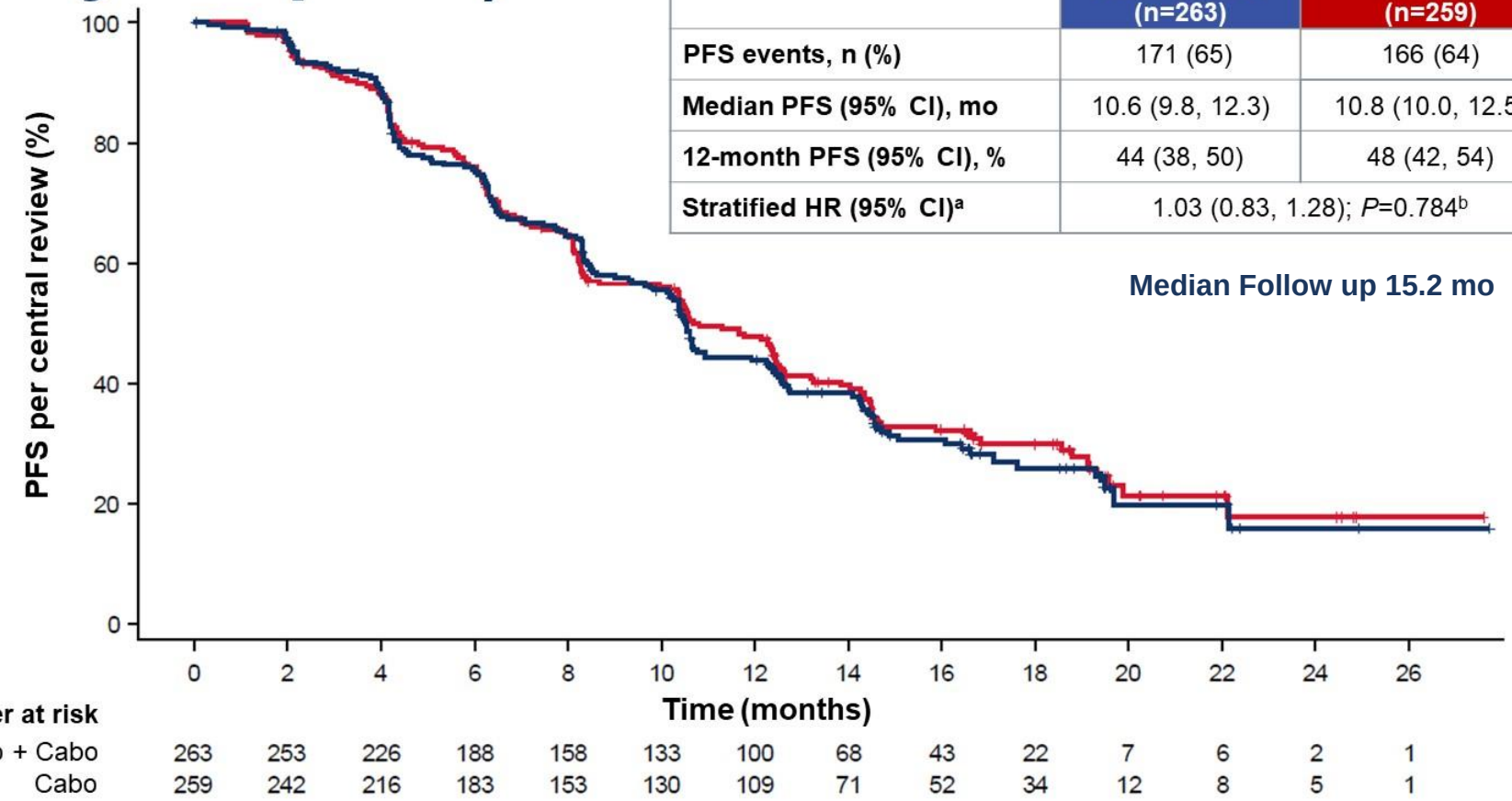
ClinicalTrials.gov ID, NCT04338269. IMDC, International Metastatic RCC Database Consortium. Patients were enrolled between July 28, 2020 and December 27, 2021.
[a] Papillary, chromophobe or unclassified (chromophobe requires sarcomatoid differentiation). [b] Clear cell or non-clear cell. [c] Assessed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

Choueiri et al. ASCO 2023

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]	

Median Follow up 15.2 mo



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

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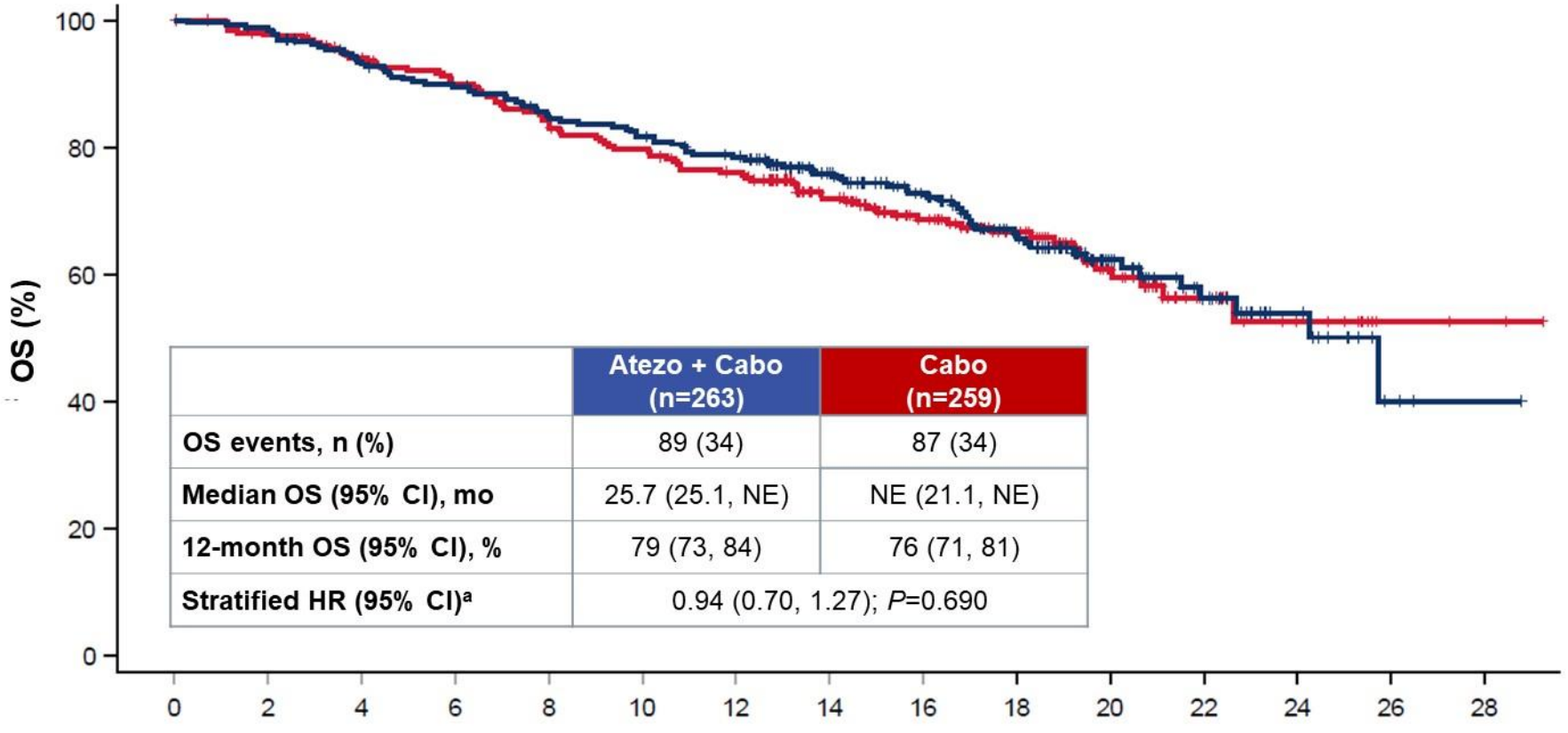
Interim analysis of OS (primary endpoint)



	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	

Number at risk

Atezo + Cabo	263	259	240	229	215	207	196	157	127	91	50	31	15	3	1
Cabo	259	247	235	221	207	195	182	145	113	88	50	22	11	3	2

[a] Stratified for IMDC risk group.

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Key secondary endpoints

	RECIST 1.1 per central review[a]		RECIST 1.1 per investigator[a]	
	Atezo + Cabo (n=259)	Cabo (n=254)	Atezo + Cabo (n=263)	Cabo (n=259)
Confirmed objective response, n, (%) [95% CI]	105 (40.5) [34.5, 46.8]	104 (40.9) [34.8, 47.3]	100 (38.0) [32.1, 44.2]	108 (41.7) [35.6, 48.0]
Complete response, n (%)	0	2 (0.8)	4 (1.5)	2 (0.8)
Partial response, n (%)	105 (40.5)	102 (40.2)	96 (36.5)	106 (40.9)
Stable disease, n (%)	131 (50.6)	121 (47.6)	127 (48.3)	120 (46.3)
Progressive disease, n (%)	11 (4.2)	13 (5.1)	24 (9.1)	17 (6.6)
Not evaluable or missing, n (%)	12 (4.6)	16 (6.3)	12 (4.6)	14 (5.4)
Ongoing response at data cutoff, n/N (%)[b]	53/105 (50.5)	55/104 (52.9)	58/100 (58.0)	48/108 (44.4)
Median duration of response (range), mo	12.7 (2.1+ to 22.9+)	14.8 (2.3+ to 25.6+)	NE (2.1+ to 23.2+)	12.2 (2.1+ to 25.6+)

[a] Included are patients who presented with measurable disease according to RECIST 1.1, as assessed by either a central review facility or by investigators. [b] Patients with complete or partial response who did not experience disease progression or death. The plus sign indicates a censored value.

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TiNivo-2: Phase 3 Study Design

Locally advanced or metastatic clear cell RCC after progression on 1 or 2 lines of therapy, one of which was an ICI:

- Progression during or following ≥6 weeks of treatment with an ICI
- Time from immediate prior line of therapy to randomization ≤6 months
- Measurable disease (RECIST v1.1)
- ECOG PS: 0 or 1

N=343

R
1:1

Tivozanib
0.89 mg PO, D1-21
Nivolumab
480 mg IV, D1
n=171

Tivozanib
1.34 mg PO, D1-21
n=172

28-day cycles[a]

Endpoints

Primary
- PFS by IRR

Secondary
- OS
- PFS by INV
- ORR
- DOR
- Safety/tolerability

Stratification Factors
- IMDC risk category
- Prior therapy (ICI as most recent therapy or not)

Statistical Analysis
- 220 PFS events, statistically powered to detected an improvement of 4 months in PFS (HR=0.67)
- Stratified log-rank test with a two-sided 5% significance level

Key Considerations
- Reduced dose of tivozanib in combination arm was agreed with regulatory authorities due to potential risk of higher rate of grade 3/4 hypertension
- Prior therapy (ICI as most recent therapy or not)
  - Test if ICI break impacts outcome (to resensitize the immune system to ICI therapy)

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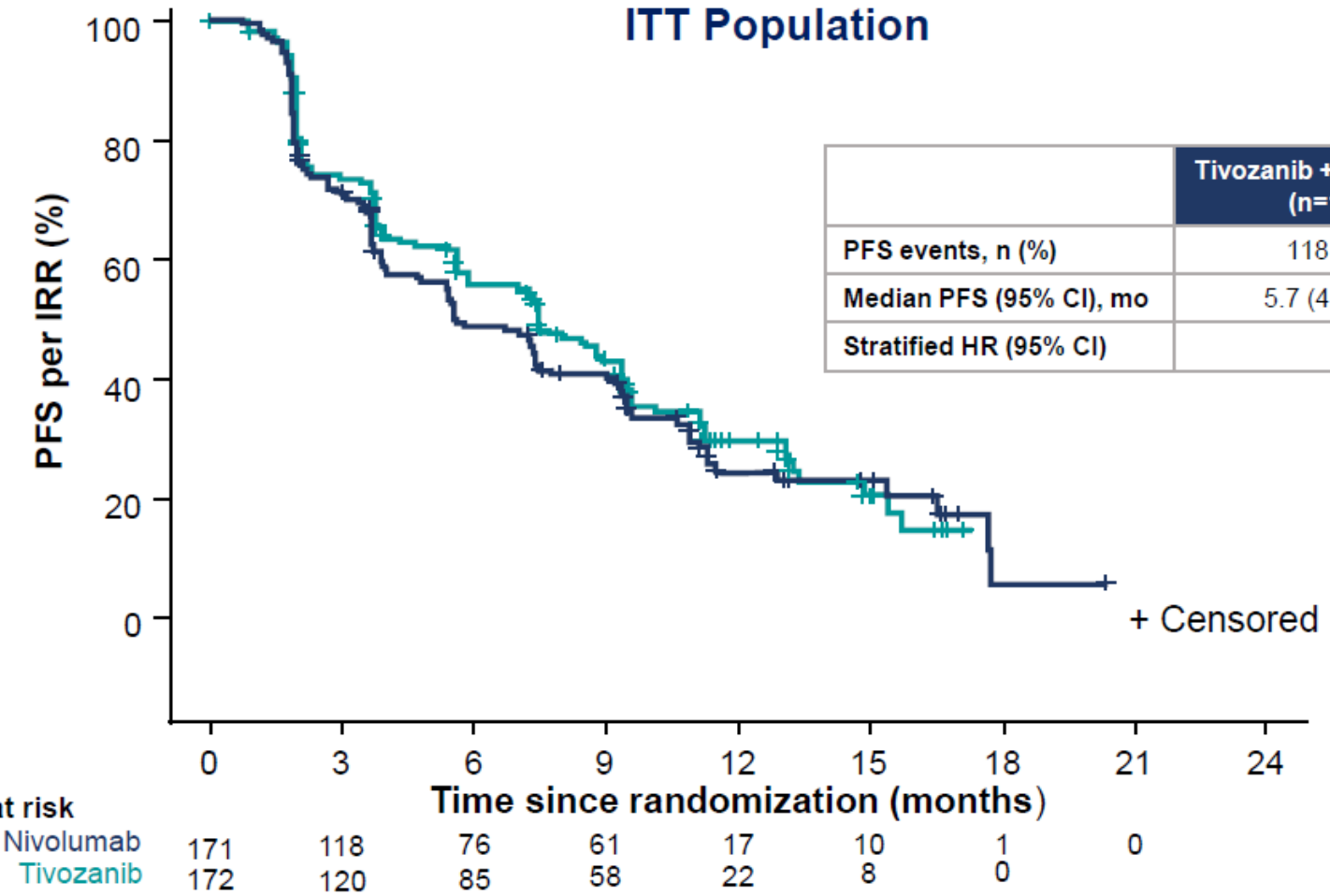
Primary Analysis of Centrally Reviewed PFS (primary endpoint)



	Tivozanib + Nivolumab (n=171)	Tivozanib (n=172)
PFS events, n (%)	118 (69)	112 (65)
Median PFS (95% CI), mo	5.7 (4.0-7.4)	7.4 (5.6-9.2)
Stratified HR (95% CI)	1.10 (0.84-1.43); p=0.49	

Median follow-up was 11.8 months in the tivozanib + nivolumab cohort and 12.5 months in the tivozanib monotherapy arm

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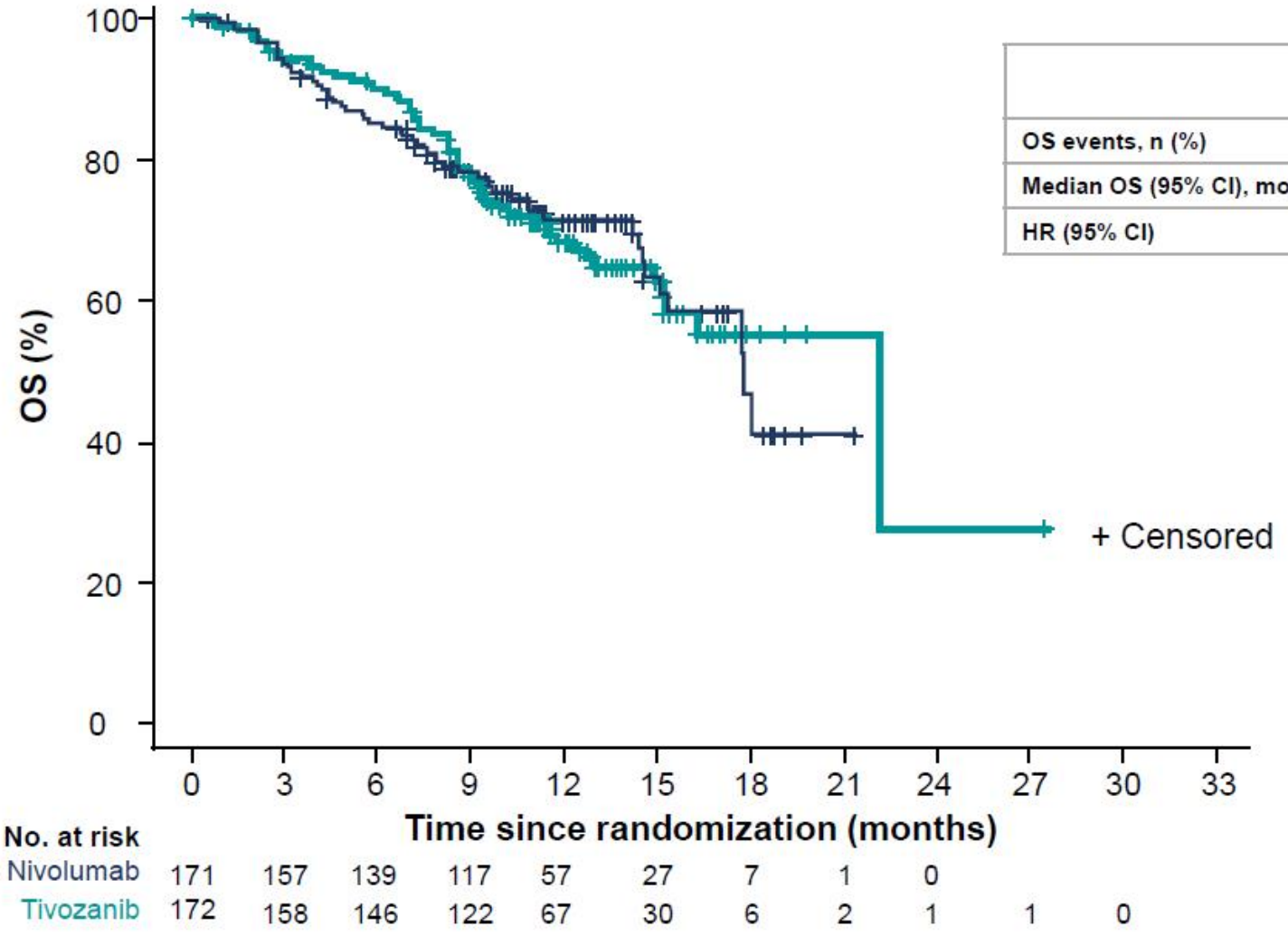
Overall Survival



	Tivozanib + Nivolumab (n=171)	Tivozanib (n=172)
OS events, n (%)	53 (31)	57 (33)
Median OS (95% CI), mo	17.7 (15.1-NR)	22.1 (15.2-NR)
HR (95% CI)	1.00 (0.68-1.46); p=0.9868	

Overall survival data are not mature.
At data cutoff, 32% of events had occurred.

Choueiri et al. ESMO 2024

Best Overall Response per Central Review

	Tivozanib + Nivolumab (n=171)	Tivozanib (n=172)
ORR, n (%) [95% CI]	33 (19.3) [13.7-26.0]	34 (19.8) [14.1-26.5]
CR, n (%)	1 (0.6)	1 (0.6)
PR, n (%)	32 (18.7)	33 (19.2)
SD, n (%)	74 (43.3)	81 (47.1)
PD, n (%)	49 (28.7)	43 (25.0)
NE, n (%)	15 (8.8)	14 (8.1)
mDOR (95% CI), mo	15.77 (5.65-NR)	9.66 (3.71-NR)

Included are patients who presented with measurable disease according to RECIST 1.1, as assessed by central review.
CR, complete response; mDOR, median duration of response; NE, not evaluable; NR, not reached. ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

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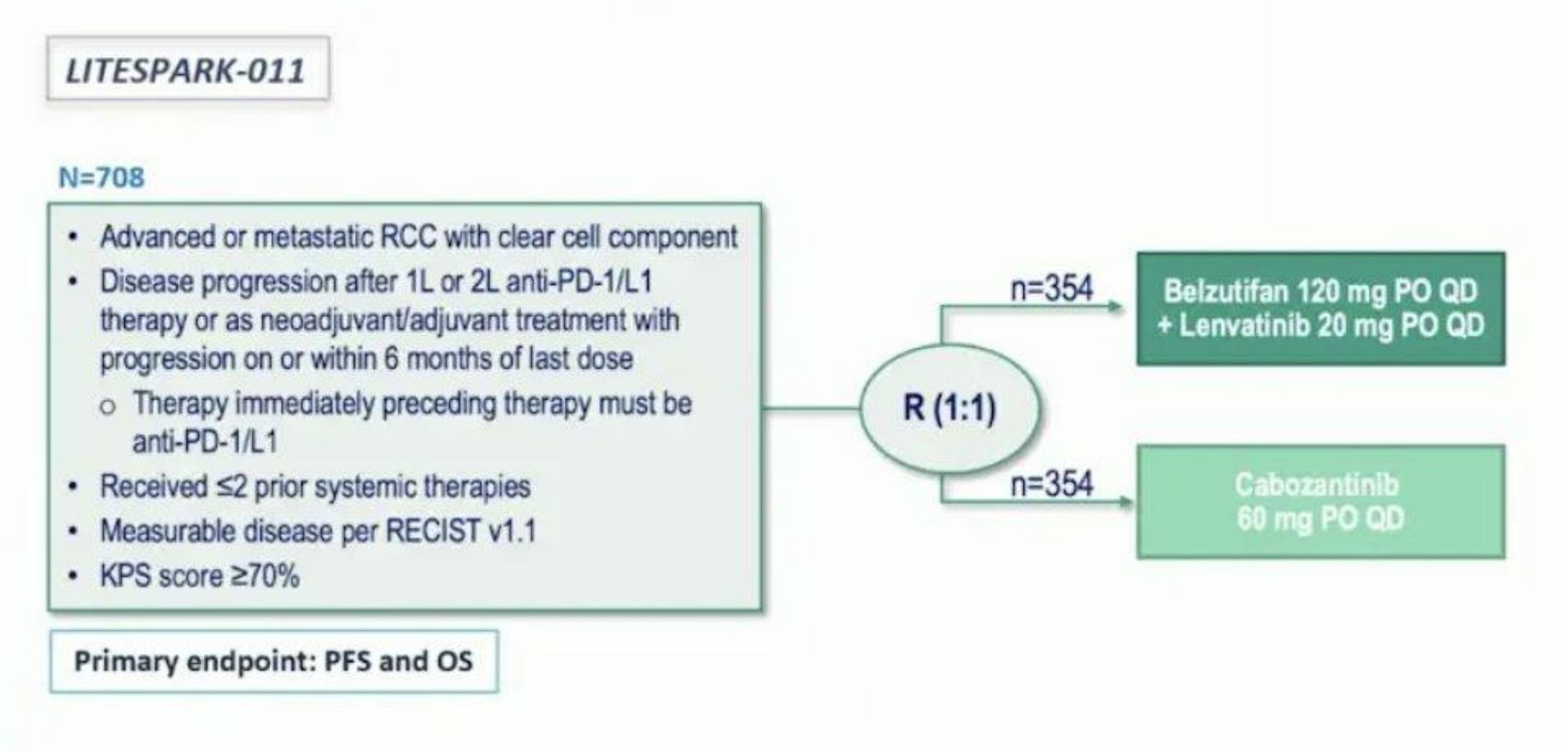
Salvage PD1/PDL1 Blockade for RCC: Summary

- No emerging synergy signal for IO/TKI combinations in PD1/PDL1 refractory disease
- PD1/PDL1 “rechallenge” should be avoided in clinical practice without new positive data
  - Did not improve clinical outcomes
  - Higher toxicity
  - Higher cost
- Recall that CTLA-4 blockade (NIVO + IPI) has clinical activity in the PD1/PDL1 refractory patient population

Beckermann, KE and BI Rini. Lancet (2023) 402:160-1

What Could be Practice Changing for Salvage Therapy on the Horizon?



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Thank you for your attention