RCC 2024 ASCO Updates: From Adjuvant to Refractory

Katy Beckermann, MD, PhD

Assistant Professor of Medicine

Vanderbilt University School of Medicine

Summary of Adjuvant IO Trials in RCC

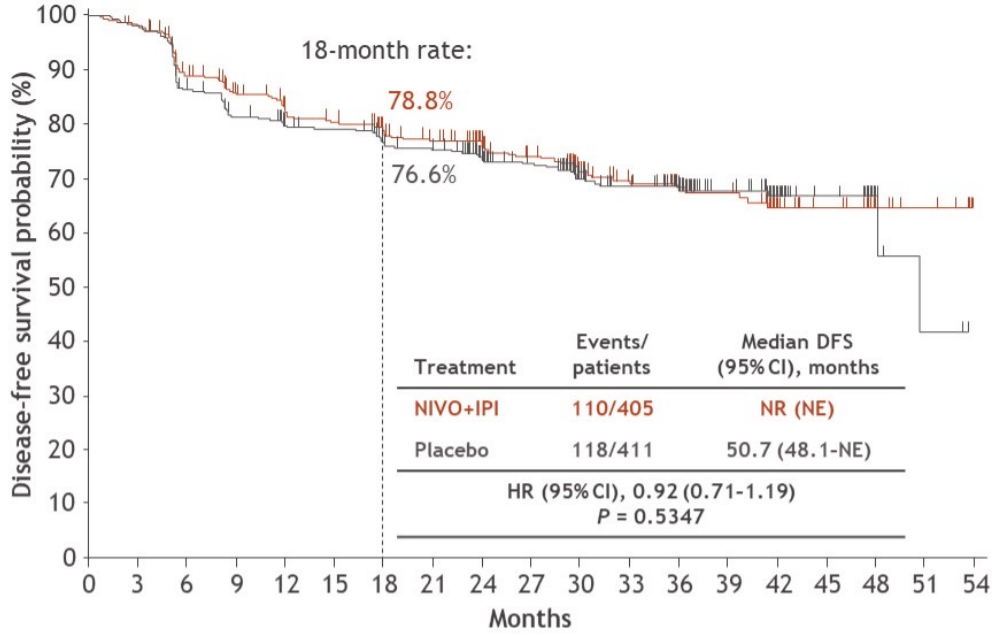
Trial	Enrolled patients	Inclusion Criteria	Treatment	Primary Endpoint	Secondary Endpoint
Keynote-564[1]	994	pT2G4, pT3aG3-4, pT3b-T4Gx, pTxN1, pTxNxM1 (resected to NED within 1 year); clear cell	Pembrolizumab vs placebo 1 year	DFS	**ASCO GU 2024** **HR 0.63; p < 0.0001**
IMmotion010[2]	778	pT2G4, pT3aG3-4, pT3b-T4Gx, pTxN1, pTxNxM1 (resected to NED*); clear cell	Atezolizumab vs placebo 1 year	DFS	**ASCO GU 2024** **NS DFS** **HR 0.93; P=0.4950**
CheckMate-914[3]	1600	pT2aG3-4N0, pT2b-T4GxN0, pTxGxN1; clear cell	Nivolumab + ipilimumab vs. nivolumab 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 perioperative	EFS	**ESMO 2022** **NS DFS** **HR, 0.97; P=0.43** **Trial stopped for futility**

Nivolumab monotherapy and ipi/nivo do not improve DFS

CheckMate 914

DFS per BICR: Parts A and B

Part A: NIVO+IPI vs placebo[1]

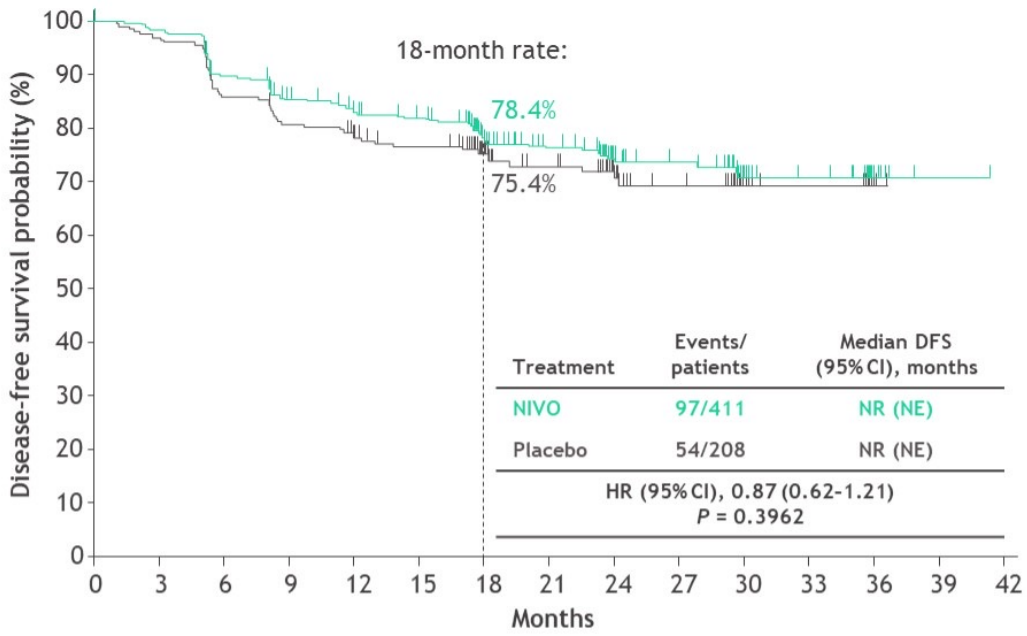


Treatment	Events/ patients	Median DFS (95% CI), months
NIVO+IPI	110/405	NR (NE)
Placebo	118/411	50.7 (48.1-NE)

HR (95% CI), 0.92 (0.71-1.19)
P = 0.5347

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

Part B: NIVO vs placebo



Treatment	Events/ patients	Median DFS (95% CI), months
NIVO	97/411	NR (NE)
Placebo	54/208	NR (NE)

HR (95% CI), 0.87 (0.62-1.21)
P = 0.3962

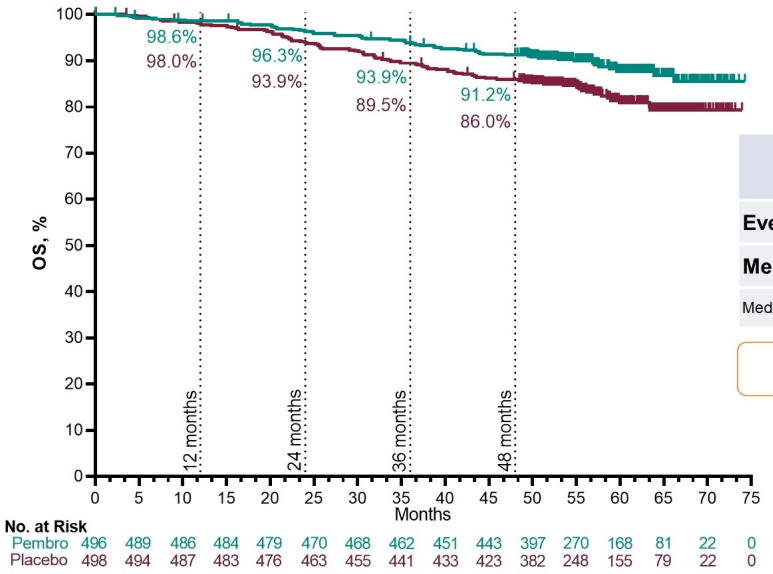
No. at risk														
NIVO	411	393	356	332	317	307	232	189	110	88	32	20	7	1	0
Placebo	208	193	169	158	150	143	105	86	57	46	14	8	2	0	0

- Due to the outcomes of CheckMate 914, a contribution of components analysis is no longer relevant

(Motzer et al., 2024)

A year of adjuvant pembrolizumab improves DFS and OS in ccRCC

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)

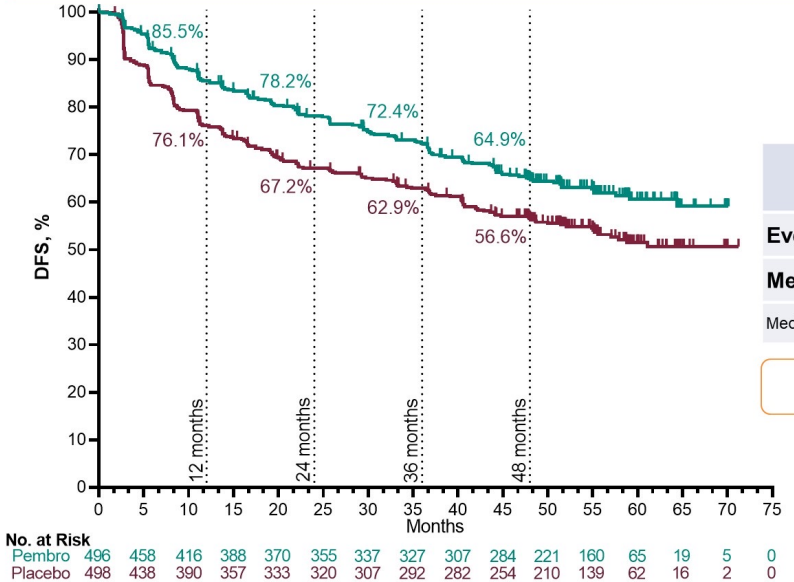
Median follow-up was 57.2 months (range, 47.9–74.5)

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.

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.

(Chouieri et al., 2024 GU ASCO)

2024 ASCO® ANNUAL MEETING

Circulating kidney injury molecule-1 (KIM-1) biomarker analysis in IMmotion010, a randomized Phase 3 study of adjuvant atezolizumab vs placebo in patients with renal cell carcinoma at increased risk of recurrence after resection

Laurence Albiges,[1] Axel Bex,[2] Cristina Suarez,[3] Robert Uzzo,[4] Xiaobin Tang,[5] Zoe June Assaf,[5] Sarita Dubey,[5] Erik Goluboff,[5] Corey Carter,[5] Romain Banchereau,[5] Mahrukh Huseni,[5] Sumanta Pal,[6] Brian Rini[7]

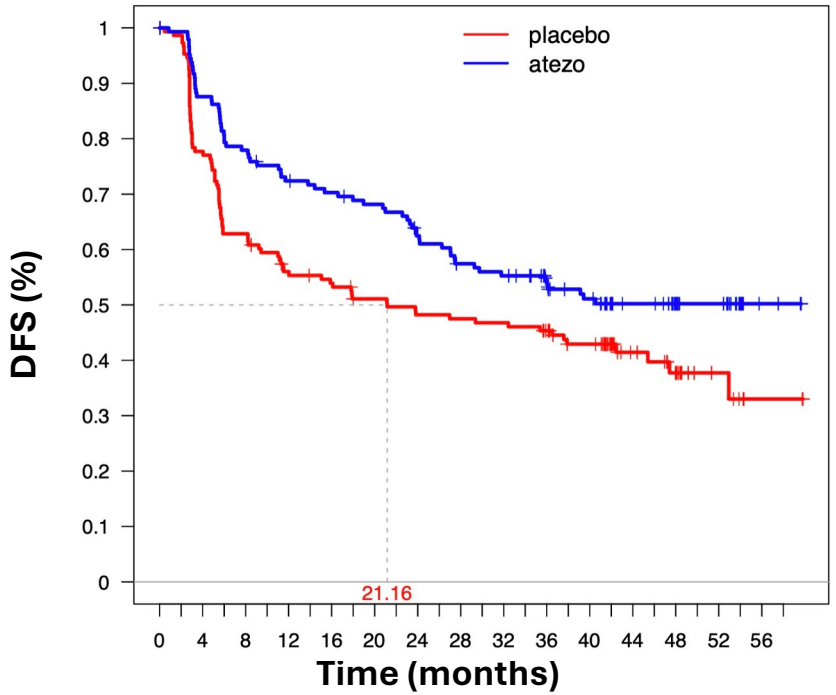
[1]Department of Cancer Medicine, Gustave Roussy, Université Paris-Saclay, Villejuif, France. [2]Department of Urology, The Royal Free London NHS Foundation Trust, University College London Division of Surgery and Interventional Science, London, UK & The Netherlands Cancer Institute, Amsterdam, Netherlands. [3]Medical Oncology Department, Vall d´Hebron Institute of Oncology (VHIO), Hospital Universitari Vall d´Hebron, Vall d´Hebron Barcelona Hospital Campus, Barcelona, Spain. [4]Department of Urology, Fox Chase Cancer Center, Philadelphia, PA, USA. [5]Genentech, South San Francisco, CA, USA. [6]Medical Oncology and Therapeutics Research, City of Hope Comprehensive Cancer Center, Duarte, CA, USA. [7]Division of Hematology Oncology, Vanderbilt University Medical Center, Nashville, TN, USA.

(ESMO, 2023)

Atezolizumab improved DFS vs Placebo in the baseline KIM-1^{High} subgroup

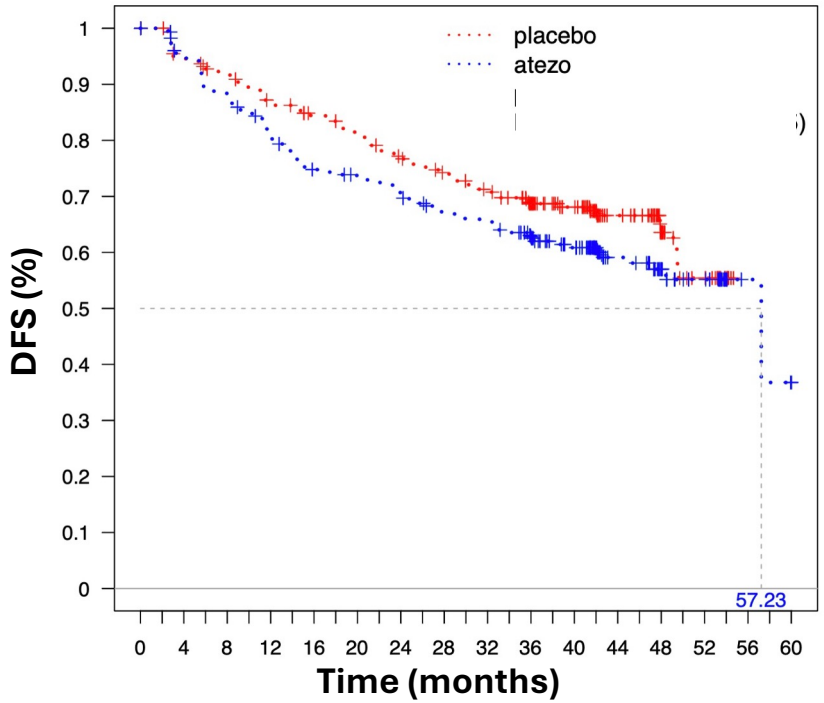
Baseline

KIM-1^{High} subgroup



	n	Median DFS	HR* (95% CI)
Atezolizumab	151	NE	0.72 (0.52, 0.99)
Placebo	149	21.2	

KIM-1^{Low} subgroup



	n	Median DFS	HR* (95% CI)
Atezolizumab	229	57.2	1.12 (0.88, 1.63)
Placebo	223	NE	

HR adjusted for disease stage and geographical location. NE, not estimable.

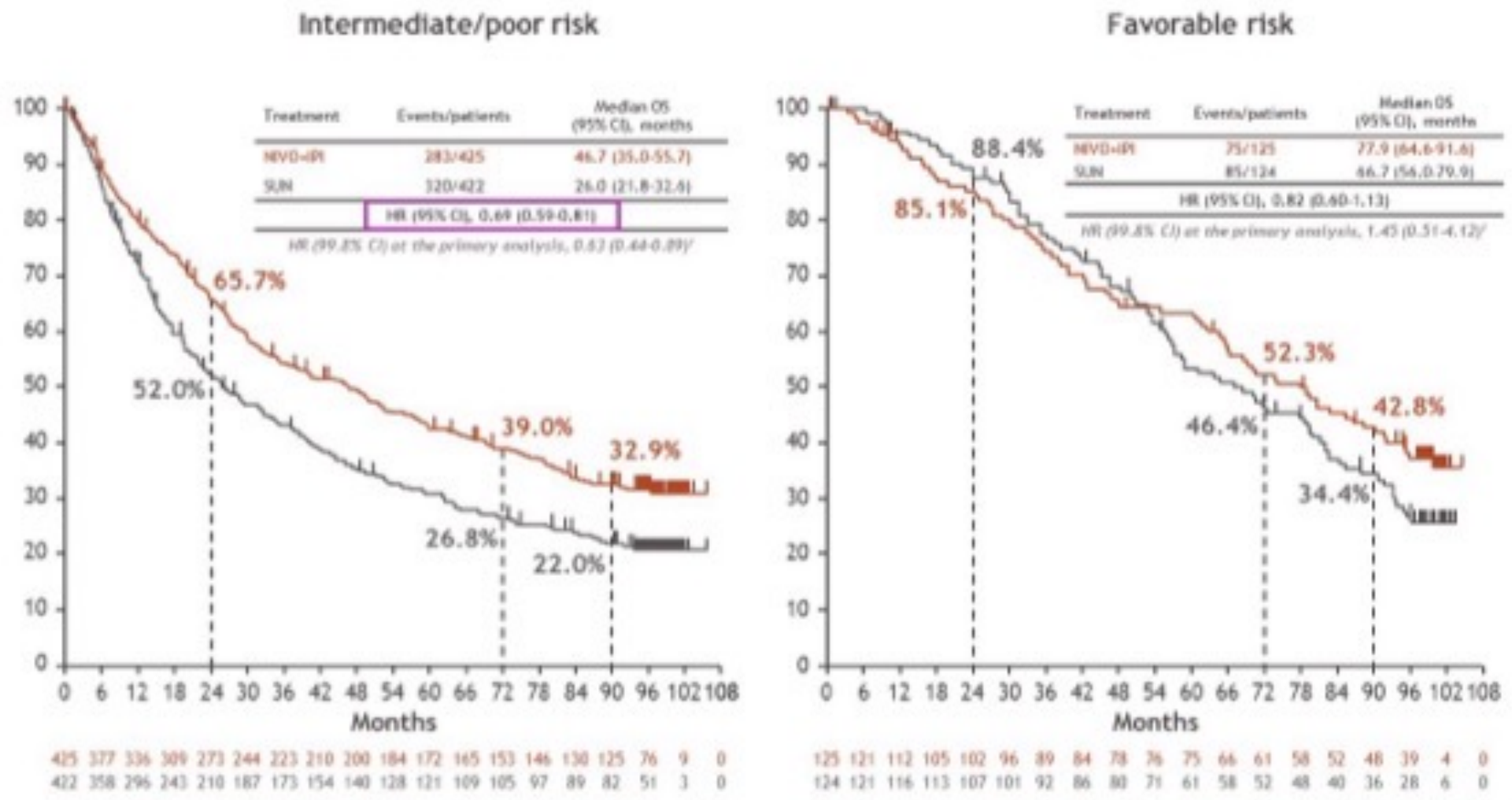
(Albiges et al., ASCO 2024)

First-line IO Combination Trials in mRCC (ITT)

	CheckMate 214 (Ipi/Nivo)[1] (n=550 vs n=546)	KEYNOTE-426 (Axi/Pembro)[2] (n=432 vs n=429)	CheckMate 9ER (Cabo/Nivo)[3] (n=323 vs n=328)	CLEAR (Len/Pembro)[4] (N=355 vs n=357)
OS HR mOS, months	**0.72** 52.7 vs 37.8	**0.84** 47.2 vs 40.8	**0.77** 46.5 vs 36.0	**0.79** 53.7 v. 54.3
Landmark OS	**35%** at 7.5 years	**63%** at 3 years **42%** at 5 years	**49%** at 4 years	**66%** at 3 years
PFS HR mPFS, months	**0.88** **12.4** vs 12.3	**0.69** **15.7** vs 11.1	**0.58** **16.4** vs 8.4	**0.47** **23.9** vs 9.2
Landmark PFS	**23%** at 7.5 years (IRC) **16%** at 7.5 years (investigator)	**18%** (5 years)	**17%** (4 years)	**37%** (3 years)
ORR, %	**39** vs 33	**61** vs 40	**56** vs 28	**71** vs 37
CR, %	**12** vs 3	**12** vs 4	**14** vs 5	**18** vs 4
Med f/u, months	**96**	**67**	**56**	**48**
Primary PD, %	**18**	**12**	**7**	**5**

1. Tannir et al. ASCO GU 2024
2. Rini et al. ASCO 2023
3. Bourlon et al. ASO GU 2024
4. Motzer et al. ASCO 2023

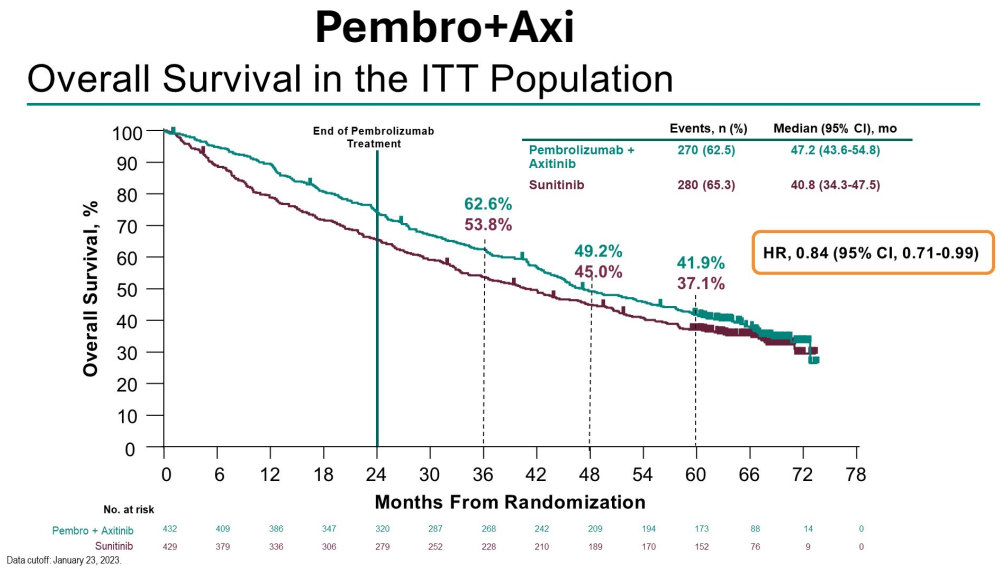
Continued 8 year overall survival benefit with ipilimumab and nivolumab



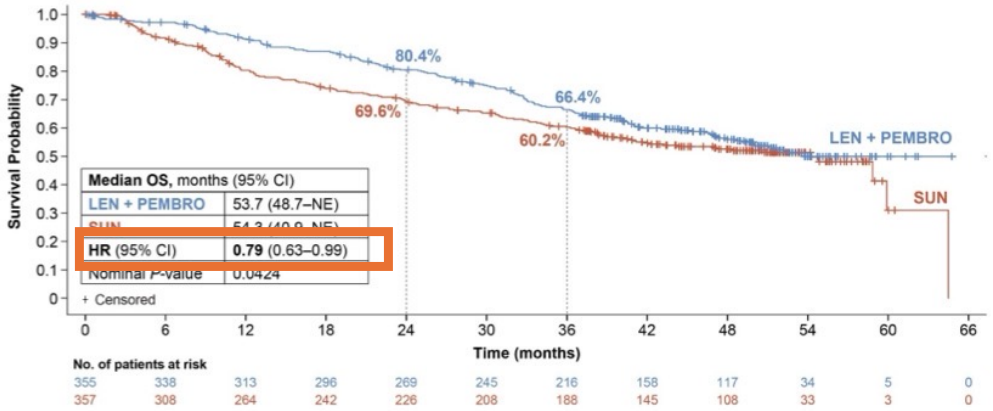
(Tannir et al., GU ASCO 2024)

All IO/ TKI combinations show decline in Kaplan-Meier Curve

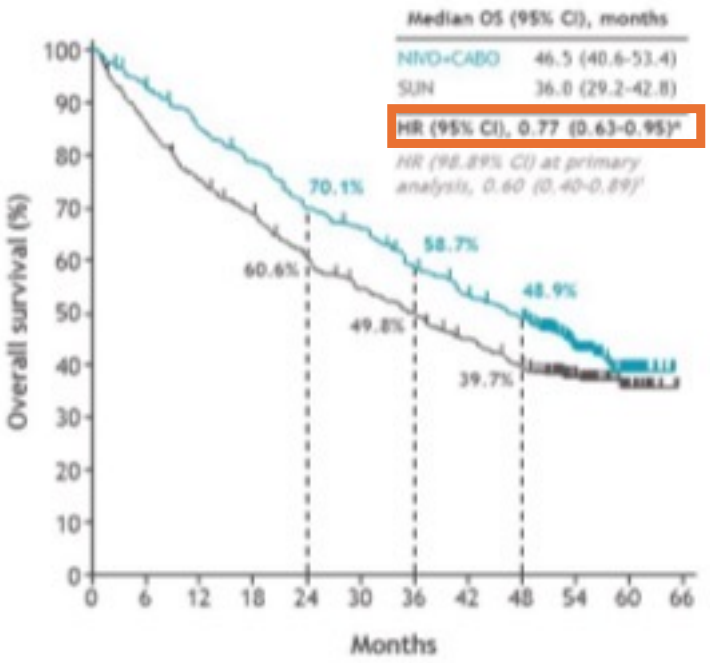
Pembro+Axi



Pembro+Lenva



Nivo+Cabo



(Rini et al., ASCO 2023; Motzer et al., ASCO 2023, Bourlon et al., GU ASCO 2024)

Refractory RCC Treatment Options

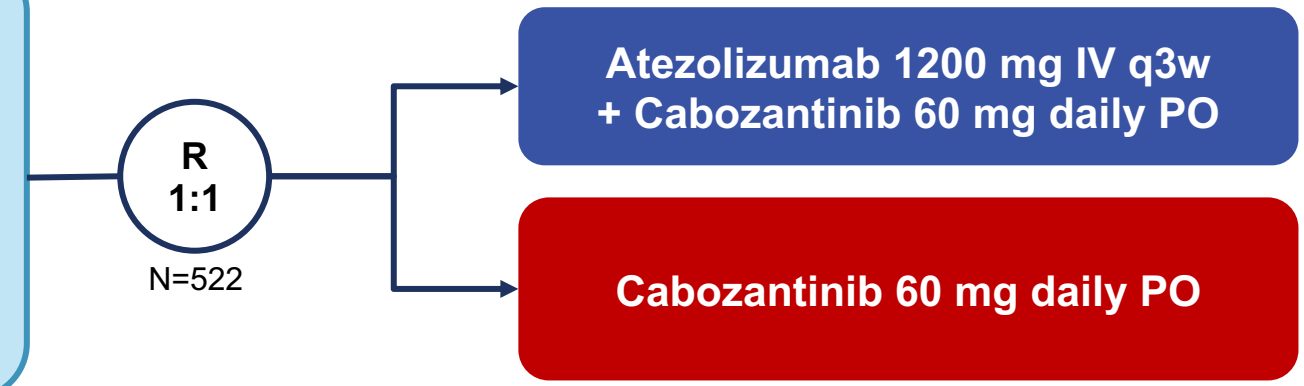
SUBSEQUENT THERAPY FOR CLEAR CELL HISTOLOGY (IN ALPHABETICAL ORDER BY CATEGORY)			
Immuno-oncology (IO) Therapy History Status	**Preferred Regimens**	**Other Recommended Regimens**	**Useful in Certain Circumstances**
IO Therapy Naïve	• None	• Axitinib + pembrolizumab[b] • Cabozantinib • Cabozantinib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

(NCCN, v4 2024)

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



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

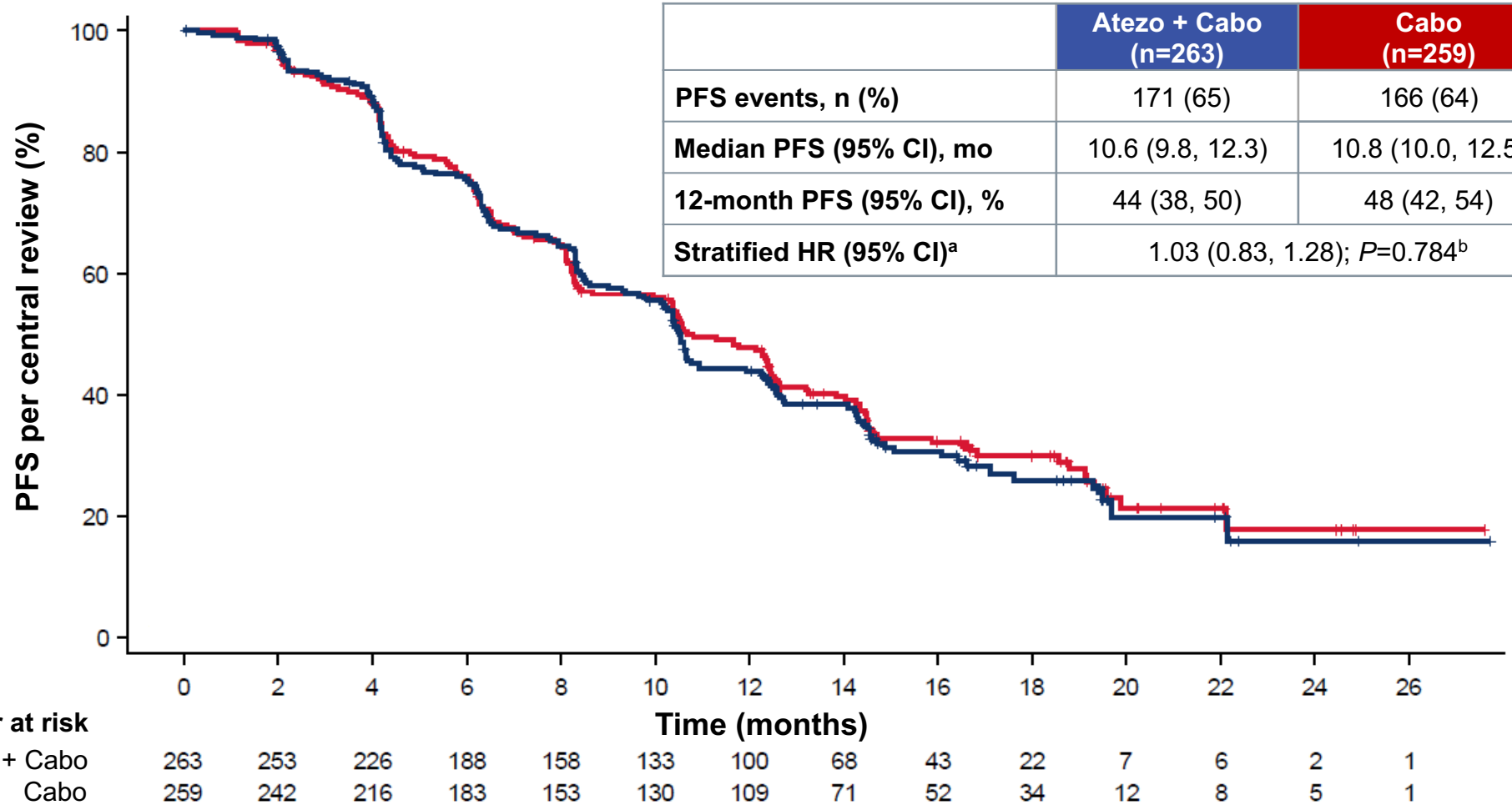
Key secondary endpoints

- 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.

PD-L1 inhibitor not efficacious in PD-1 refractory setting

	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]	



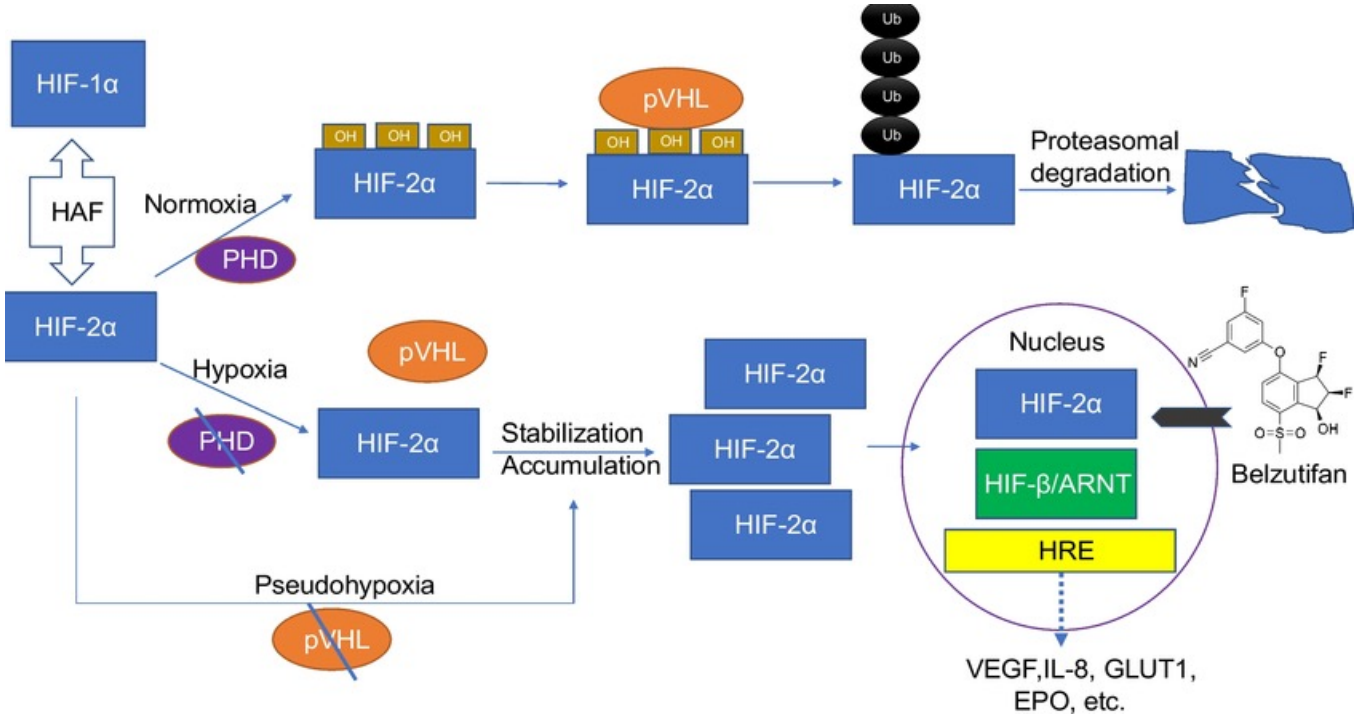
[a] Stratified for IMDC risk group. [b] Not significant at α=0.02.

Choueiri, et al. CONTACT-03 (LBA4500)

@DrChoueiri

HIF-2α Inhibition in Renal Cell Carcinoma

- The HIF pathway is central to the pathophysiology of clear cell renal cell carcinoma (ccRCC) and von Hippel-Lindau (VHL) disease
- Belzutifan is a first-in-class oral HIF-2α inhibitor that blocks heterodimerization with HIF-2β and downstream oncogenic pathways[1,2]
  - Approved in the US for certain VHL disease-associated RCC, pNET and CNS-HB
  - Demonstrated clinical activity in pretreated advanced ccRCC[2-5]

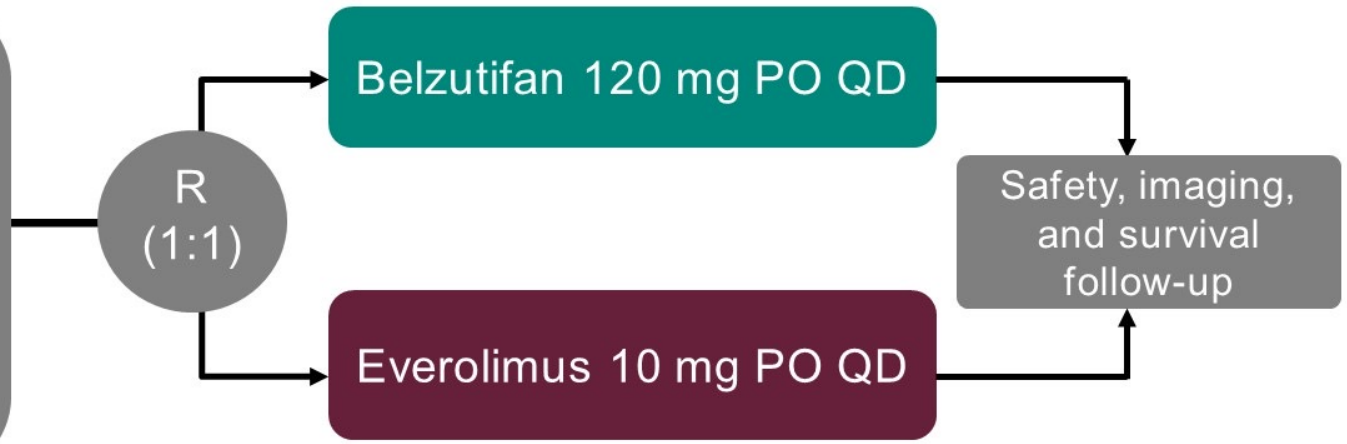


(Choi et al., 2023)

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-1/L1 agent and ≥1 VEGFR-TKI
- Karnofsky Performance Status score ≥70%



Stratification Factors

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

Primary End Points: PFS per RECIST v1.1 by BICR; OS

Key Secondary End Point: ORR per RECIST v1.1 by BICR

Other Secondary End Points: Safety; PROs

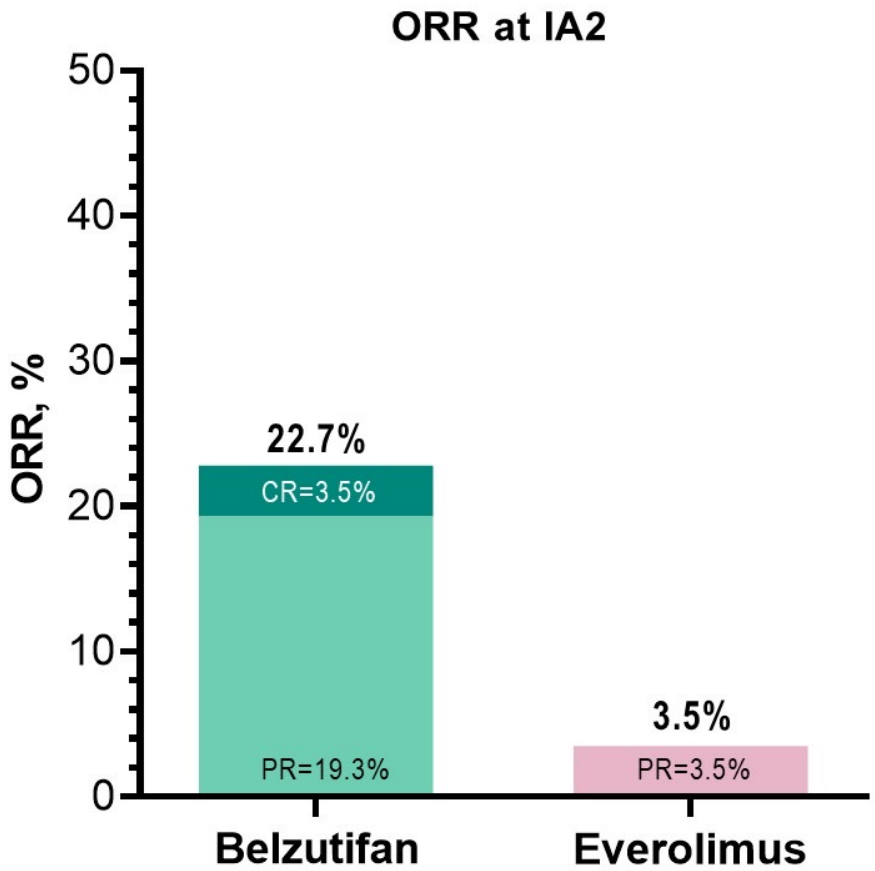
- **Median follow-up[b] at IA2: 25.7 months (range, 16.8-39.1)**

[a]Based on the number of present risk factors according to the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC). [b]Follow-up is the time from randomization to the data cutoff date (June 13, 2023).
BICR, blinded independent central review; IA2, interim analysis 2.

(Albiges et al., 2023 ESMO)

Key Secondary End Point: ORR per RECIST v1.1 by BICR[1]

	Belzutifan n = 374	Everolimus n = 372
	IA1	
ORR, % (95% CI)	21.9 (17.8-26.5)	3.5 (1.9-5.9)
Estimated difference, % (95% CI)	18.4 (14.0-23.2); *P* <0.00001*	
BOR, %		
CR	2.7	0.0
PR	19.3	3.5
SD	39.3	65.9
PD	33.7	21.5
Non-evaluable[a]	1.3	2.2
No assessment[b]	3.7	7.0
	IA2	
ORR, % (95% CI)	22.7 (18.6-27.3)	3.5 (1.9-5.9)
Estimated difference, % (95% CI)	19.2 (14.8-24.0)	



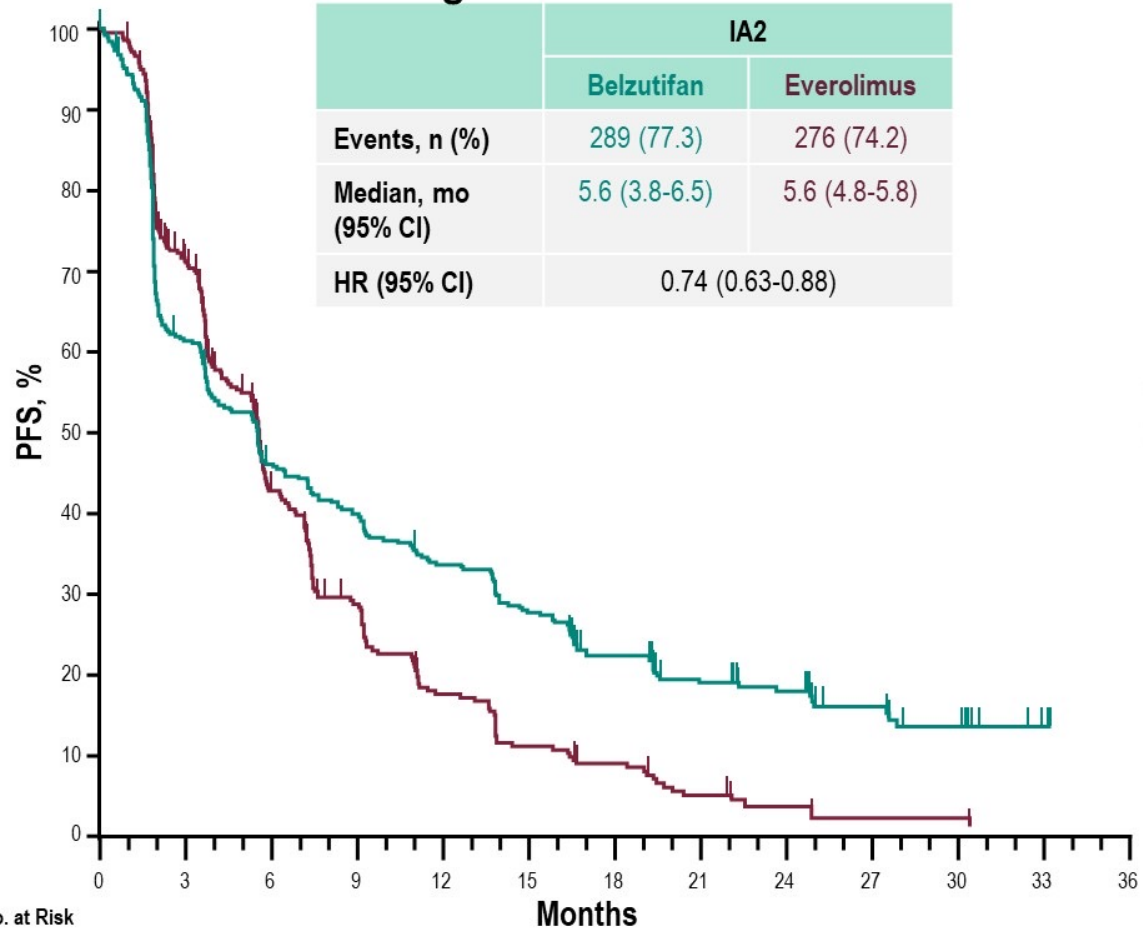
*Denotes statistical significance. [a]Insufficient data for response assessment per RECIST v1.1. [b]No post-baseline assessment available. 1. Albiges L et al. *Ann Oncol*. 2023;34:S1329-S1330. Data cutoff date for IA1: November 1, 2022. Data cutoff date for IA2: June 13, 2023.

(Albiges et al., 2023 ESMO)

Primary End Points: PFS per RECIST v1.1 by BICR and OS[1]

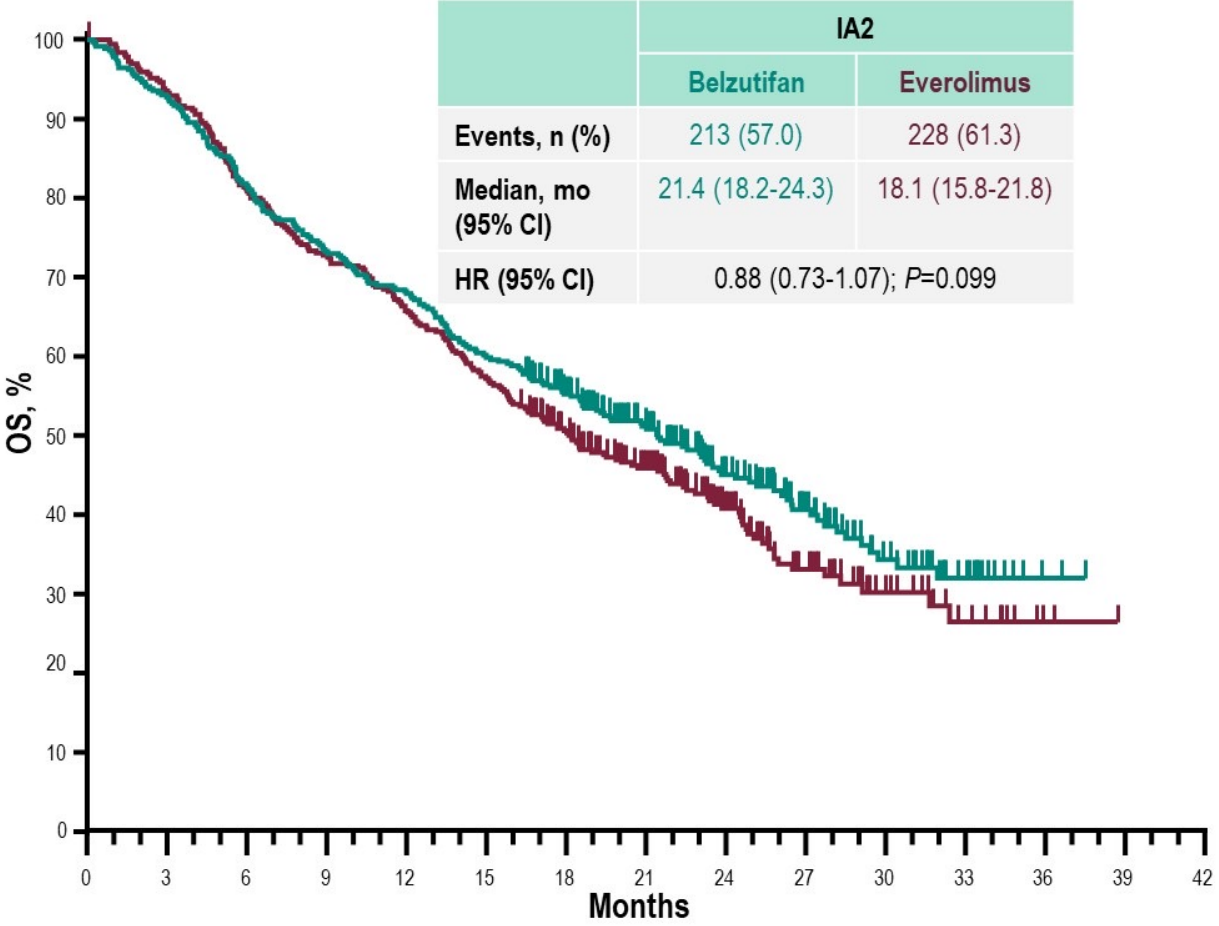
Progression-Free Survival

	IA2	
	Belzutifan	Everolimus
Events, n (%)	289 (77.3)	276 (74.2)
Median, mo (95% CI)	5.6 (3.8-6.5)	5.6 (4.8-5.8)
HR (95% CI)	0.74 (0.63-0.88)	



Overall Survival

	IA2	
	Belzutifan	Everolimus
Events, n (%)	213 (57.0)	228 (61.3)
Median, mo (95% CI)	21.4 (18.2-24.3)	18.1 (15.8-21.8)
HR (95% CI)	0.88 (0.73-1.07); *P*=0.099	

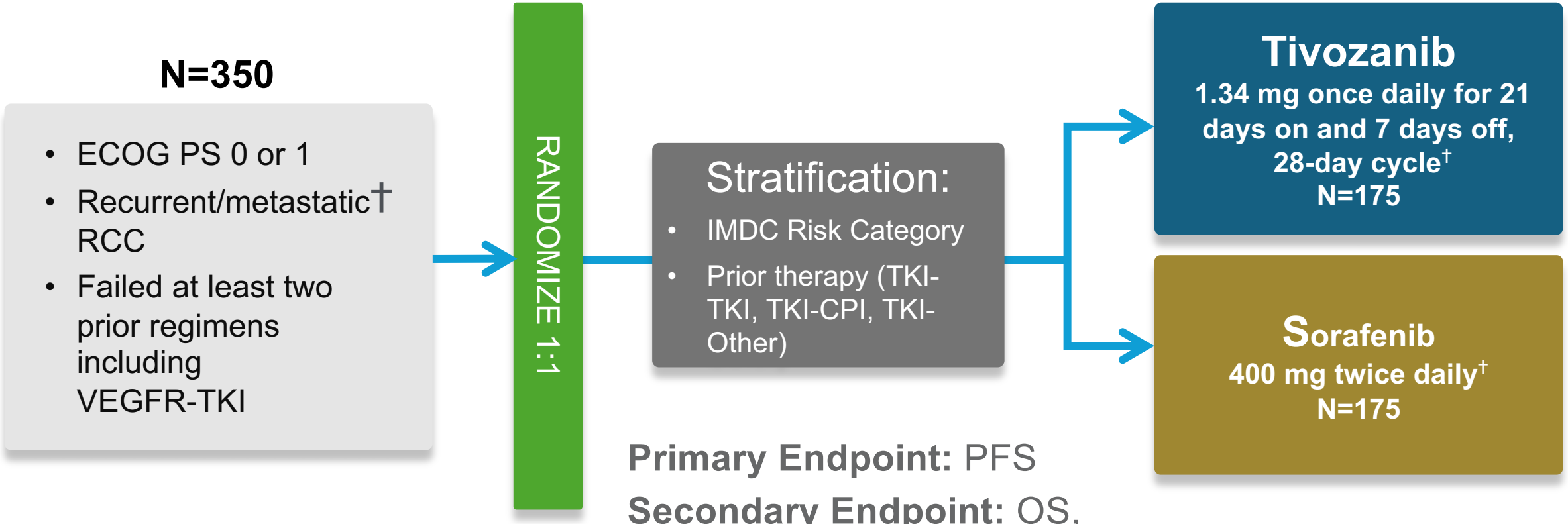


No. at Risk																												
Belzutifan	374	218	156	135	113	93	66	45	35	21	14	4	0	374	347	305	274	254	224	190	143	95	62	36	16	2	0	0
Everolimus	372	226	113	70	41	26	19	10	5	2	2	0	0	372	347	301	270	244	212	170	124	83	43	23	11	2	0	0

*Denotes statistical significance. Primary PFS was met at IA1 and was not formally statistically tested at IA2. 1. Albiges L et al. *Ann Oncol*. 2023;34:S1329-S1330. Data cutoff date for IA1: November 1, 2022. Data cutoff date for IA2: June 13, 2023.

(Albiges et al., 2023 ESMO)

Tivo3: Randomized Phase 3 Trial in Refractory RCC



Primary Endpoint: PFS

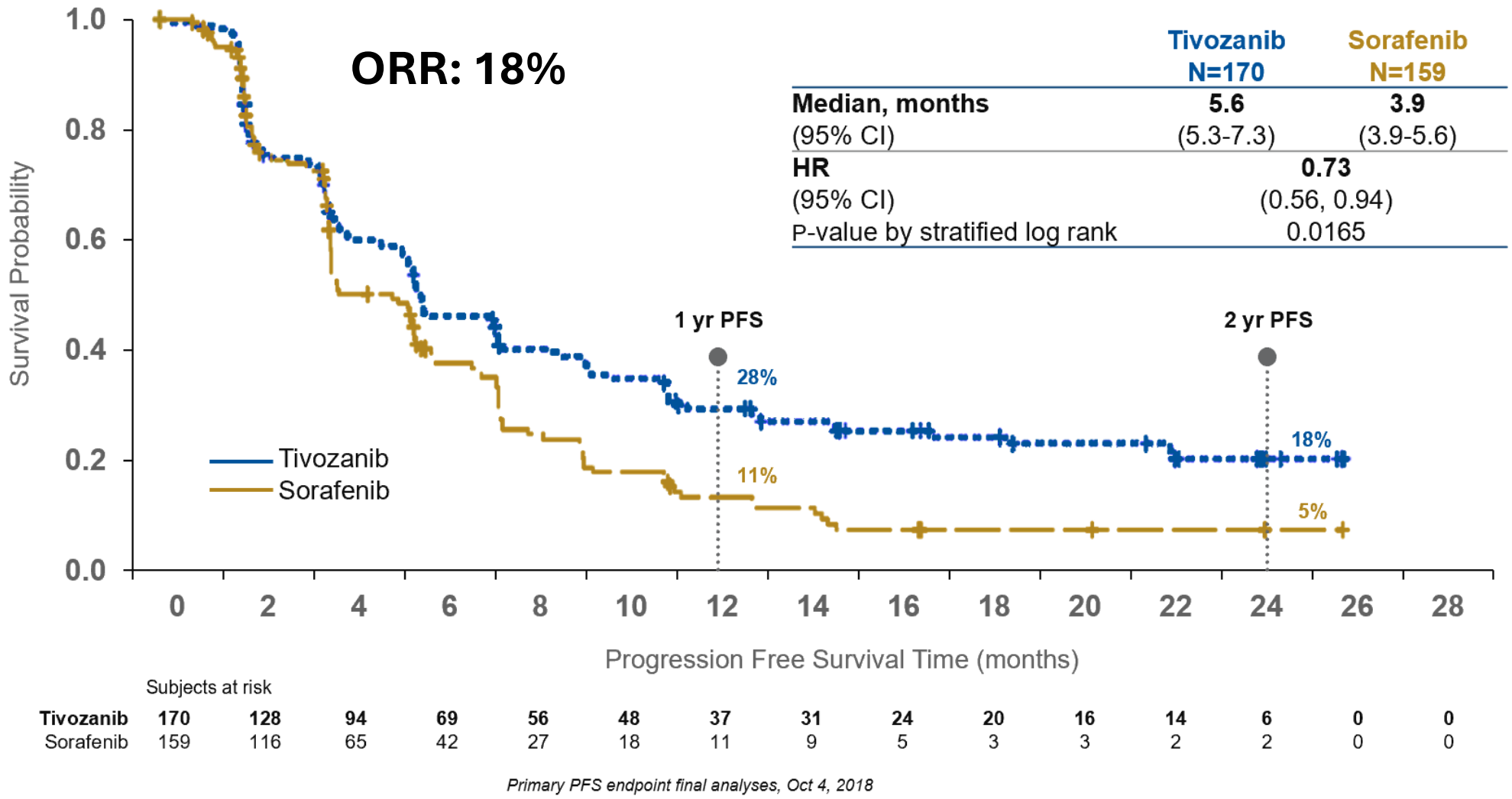
Secondary Endpoint: OS, ORR, DoR, Safety and Tolerability for ITT

† Patients were treated until disease progression or unacceptable toxicity

ECOG, Eastern Cooperative Oncology Group;
TKI, Tyrosine Kinase Inhibitor; CPI, Checkpoint Inhibitor
IMDC, International Metastatic Renal Cell Carcinoma Database Consortium

Rini BI et al *Lancet Oncol* 2020;21(1):95-104

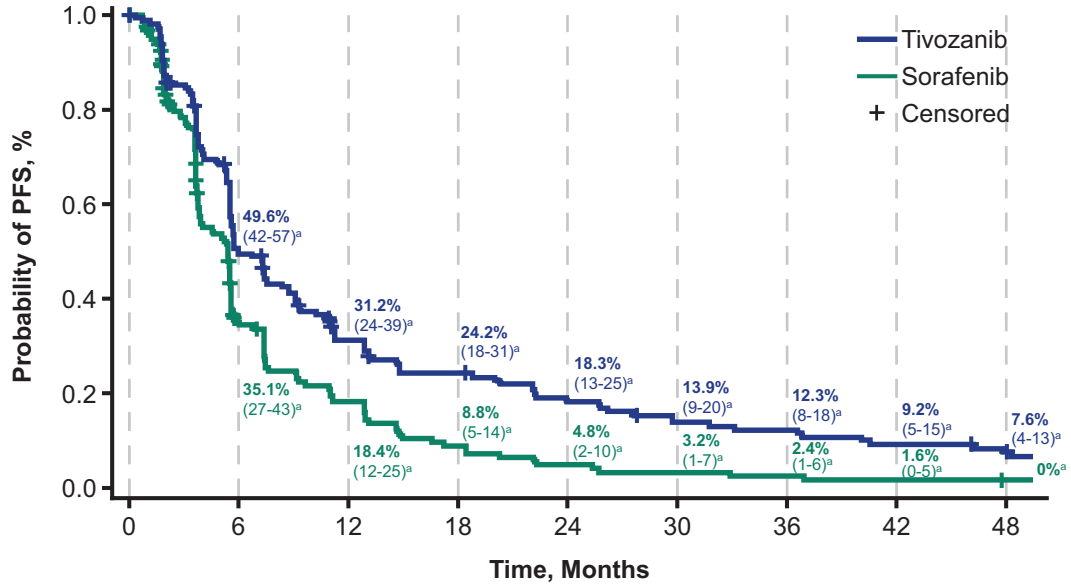
Tivo-3: Primary Endpoint: PFS



Primary PFS endpoint final analyses, Oct 4, 2018

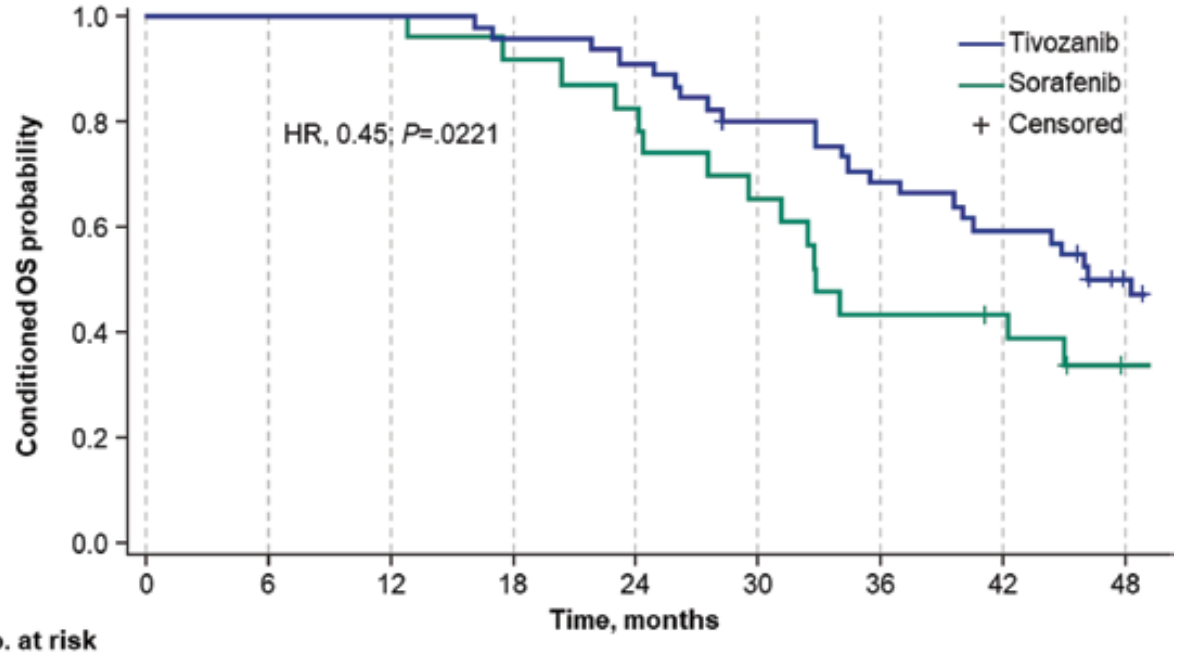
Rini BI et al *Lancet Oncol* 2020;21(1):95-104

Long-term Tivo-3 Follow-up



No. at risk

TIVO,	175	79	45	34	25	18	16	12	9
SOR,	175	45	23	11	6	4	3	2	1
LT-PFS Δ (TIVO–SOR)	0%	14.5%	12.8%	15.4%	13.5%	10.7%	9.9%	7.6%	7.6%
Odds ratio (TIVO:SOR)	N/A	1.81	2.02	3.32	4.46	4.88	5.73	N/A	N/A

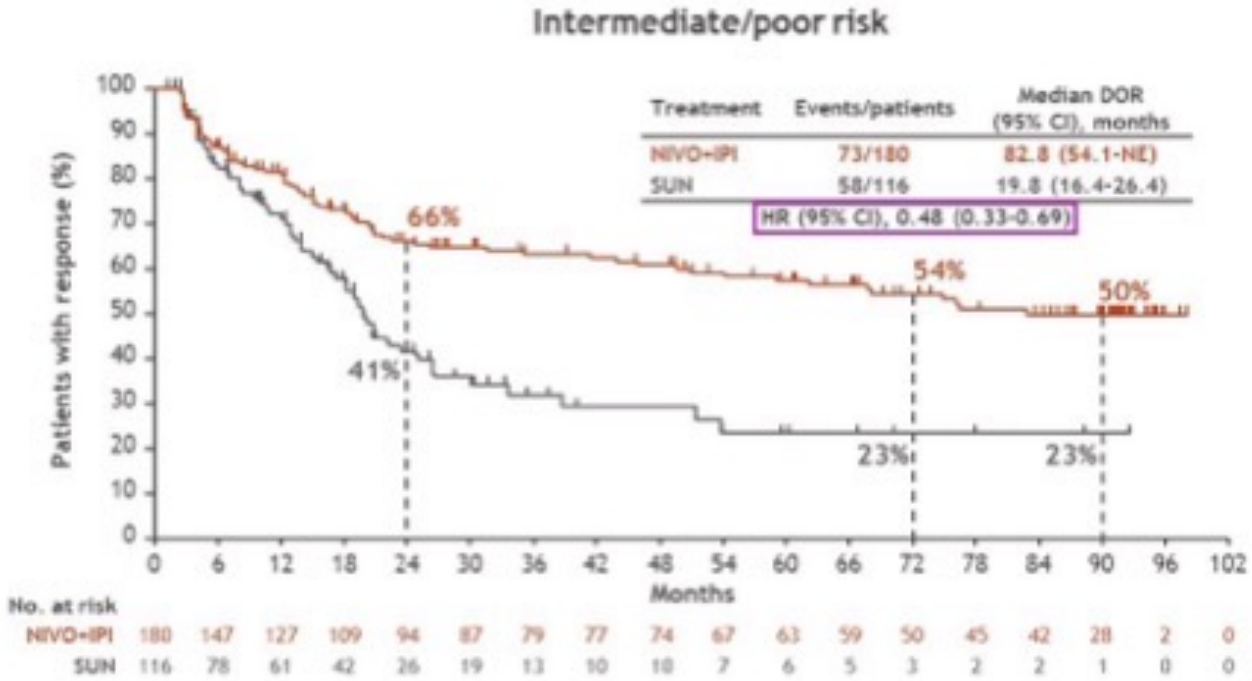


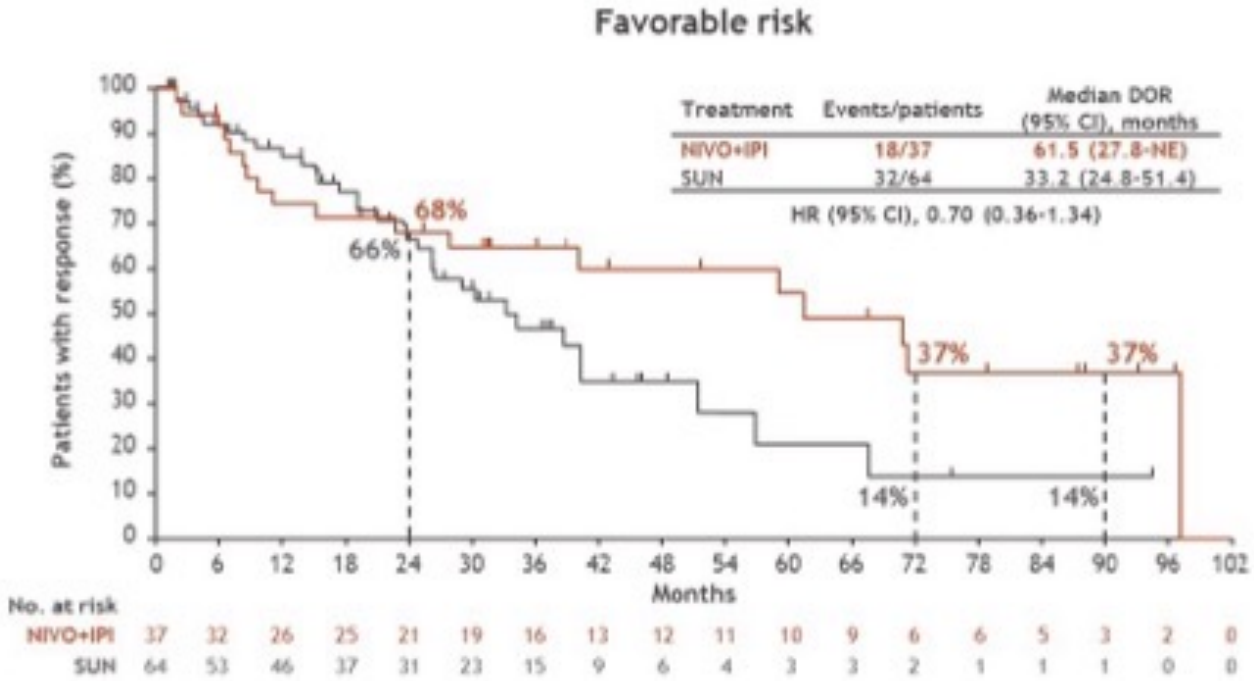
No. at risk

TIVO,	45	45	45	43	41	35	30	26	18
SOR,	23	23	23	21	19	15	10	9	5

(Beckermann et al., 2024)

Thank you!





(Tannir et al., GU ASCO 2024)

Outline

- Adjuvant:
  - GU ASCO: Keynote-564 Overall Survival data for pembrolizumab
  - GU ASCO: CheckMate914, negative nivo or ipi/nivo DFS benefit
  - ASCO: Atezolizumab KIM-1 correlates with recurrence

- First Line Metastatic RCC
  - GU ASCO: 8 years OS data from Checkmate 214
  - GU ASCO: 55 month CheckMate 9ER
  - ASCO: Final OS Javelin Renal 101

- Refractory RCC
  - Belzutifan approval based on LITESPARK-005
  - TIVO-3