Dana-Farber Cancer Institute

BRIGHAM HEALTH
BRIGHAM AND WOMEN'S HOSPITAL

HARVARD MEDICAL SCHOOL

@DrChoueiri

Kidney Cancer: Novel Developments in Targeted Therapy and Immunotherapy

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What is “new” in 15 minutes?

- 1L mRCC combination PD-1+CTLA-4 and PD-1+VEGF inhibitors continue to dominate:
  - Updates from JR101 and CM-214 (2024)
- 2L/3L mRCC:
  - PD1/L1 post PD1 does not work (CONTACT-3)
  - HIF2 inhibitor Belzutifan (LITESPARK-005)
- Adjuvant Pembrolizumab has an OS benefit!
  - 1st adjuvant trial in RCC with OS (KYN-564)
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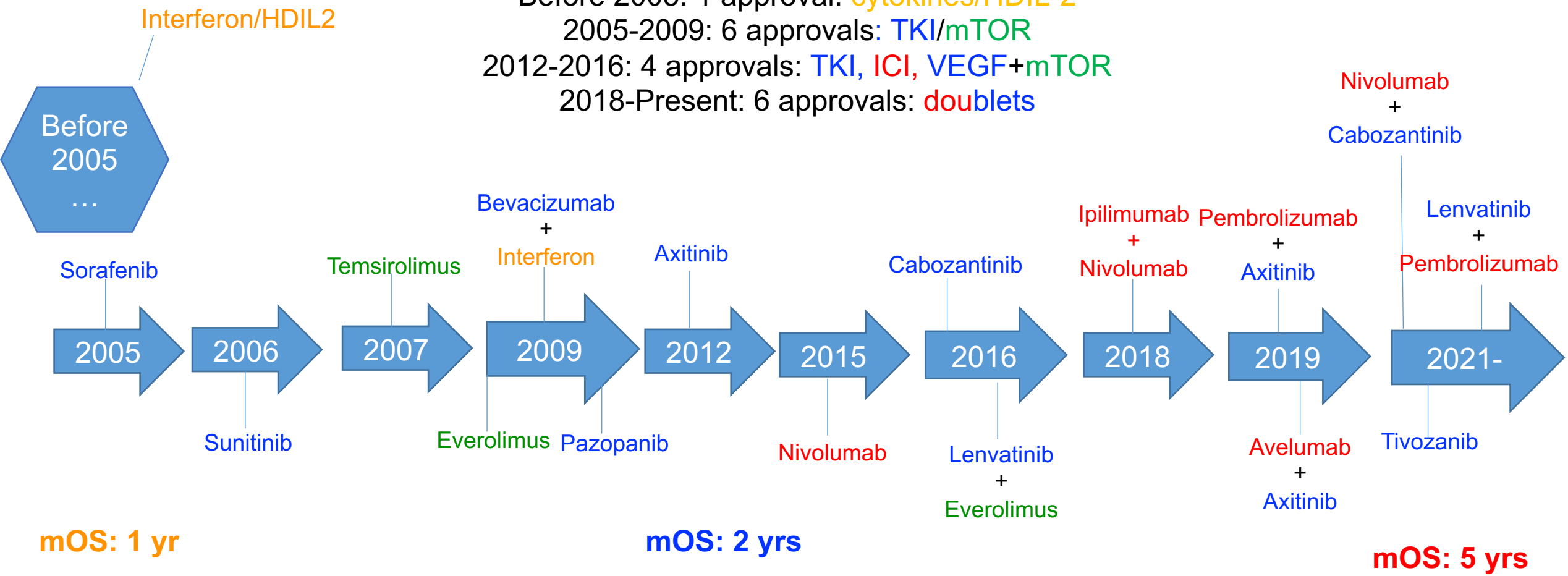
Cytokines
mTOR inhibitors
VEGF/TKI
ICI

2024 landscape of IO and VEGF agents in advanced RCC

Before 2005: 1 approval: cytokines/HDIL-2
2005-2009: 6 approvals: TKI/mTOR
2012-2016: 4 approvals: TKI, ICI, VEGF+mTOR
2018-Present: 6 approvals: doublets



mOS: 1 yr

mOS: 2 yrs

mOS: 5 yrs

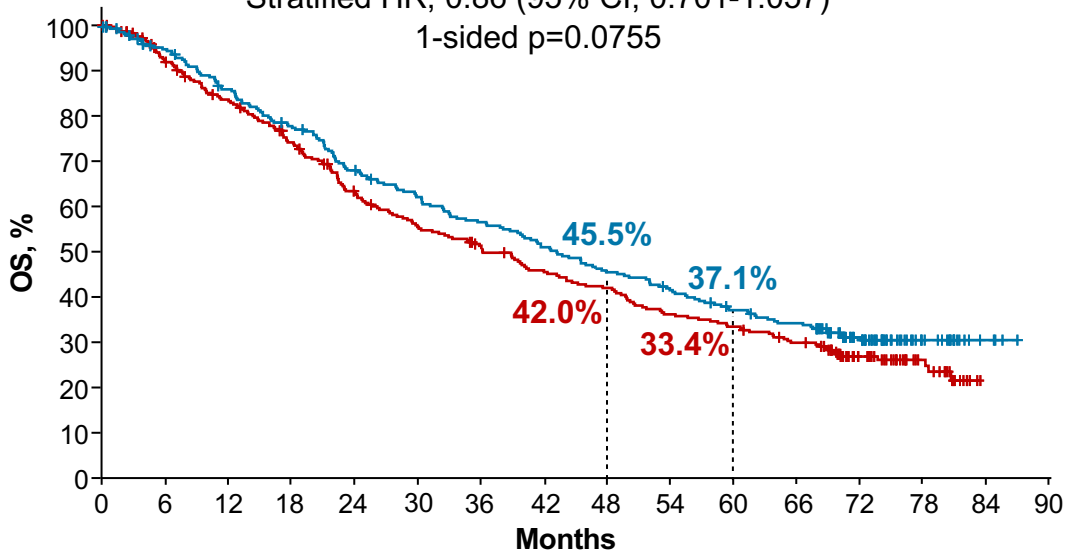
1. Motzer et al., ASCO, 2002. PMID: 11773181. 2. Motzer at al., J Clin Oncol, 2008. 3. Motzer et al., Cancer, 2022. PMID: 35383908. McKay et al., J Clin Oncol, 2018. PMID: 30372392. Choueiri, ESMO, 2022; U.S. Food and Drug Administration

Final analysis of overall survival from JR101 (axitinib+avelumab)

PD-L1+ population*
(Primary endpoint)

Median OS (95% CI), months	
Avelumab + Axitinib (n=270)	**43.2** (36.5-51.7)
Sunitinib (n=290)	**36.2** (29.8-44.2)

Stratified HR, 0.86 (95% CI, 0.701-1.057)
1-sided p=0.0755

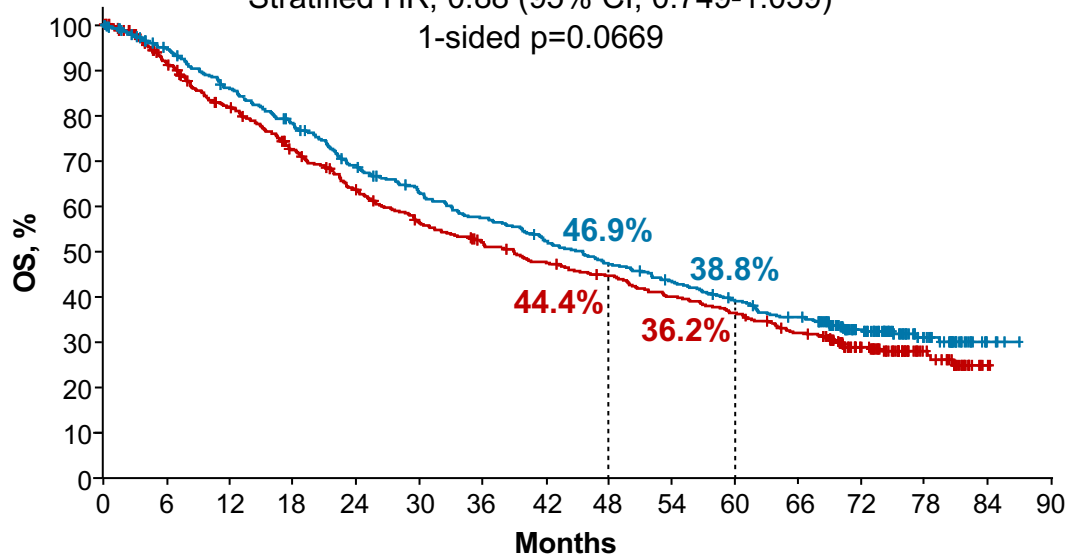


No. at risk																
Avelumab + Axitinib	270	247	222	200	174	157	143	129	115	104	91	83	51	19	4	0
Sunitinib	290	259	231	202	169	147	133	118	108	93	86	75	42	20	0	0

Overall population
(Secondary endpoint)

Median OS (95% CI), months	
Avelumab + Axitinib (N=442)	**44.8** (39.7-51.1)
Sunitinib (N=444)	**38.9** (31.4-45.2)

Stratified HR, 0.88 (95% CI, 0.749-1.039)
1-sided p=0.0669



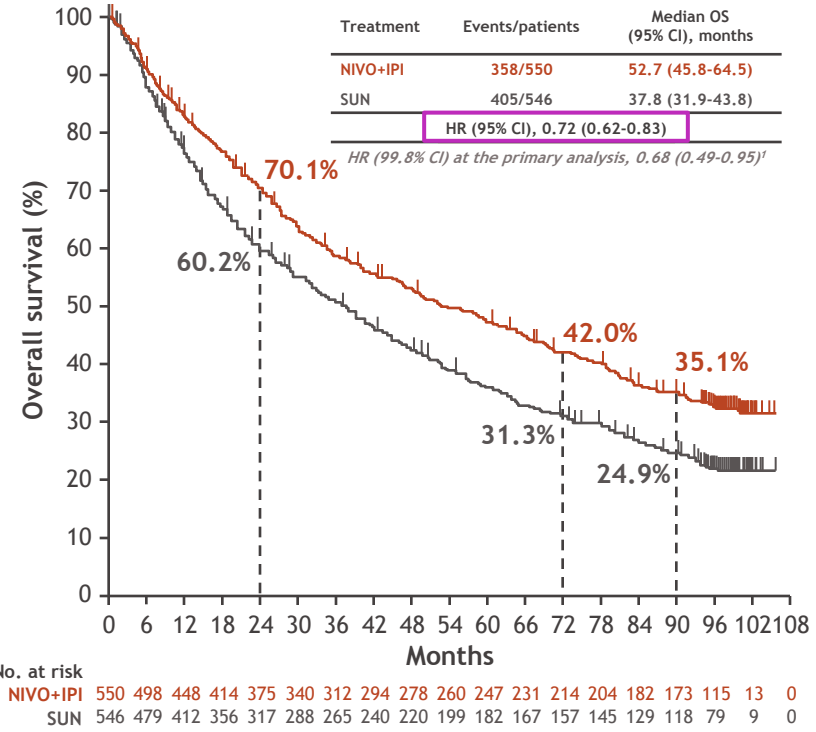
Avelumab + Axitinib	442	403	363	328	287	258	235	213	192	174	155	139	86	36	4	0
Sunitinib	444	391	344	298	258	226	205	187	173	155	141	121	74	30	2	0

At data cutoff (August 31, 2023), median follow-up was 73.7 months in the avelumab + axitinib arm and 73.6 months in the sunitinib arm (≥68 months in all patients).
HR, hazard ratio; **OS**, overall survival.
*PD-L1+ was defined as ≥1% of immune cells staining positive in the tumor area using the Ventana PD-L1 (SP263) assay.

OS from Checkmate-214: Nivo+Ipi vs sunitinib

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

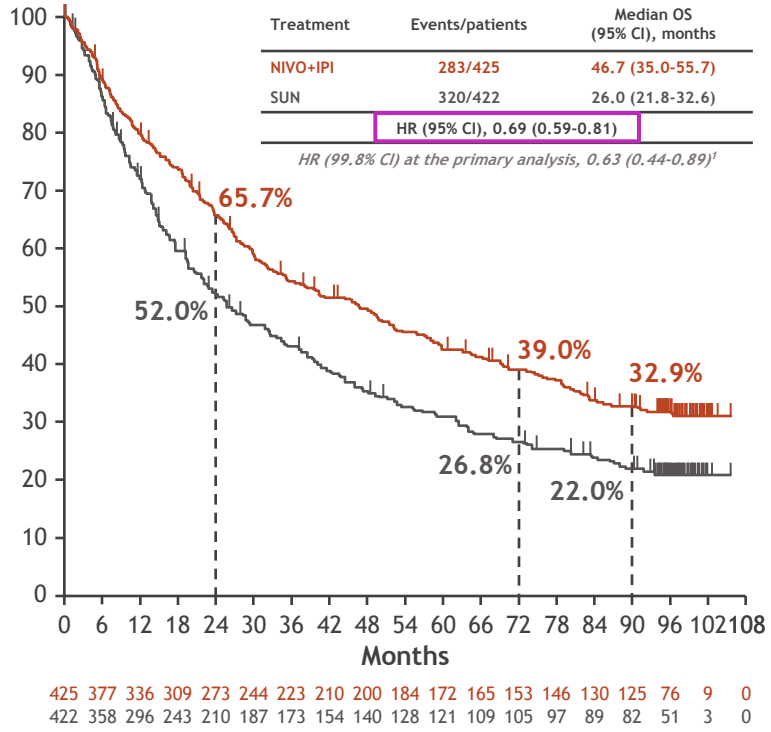
ITT



Treatment	Events/patients	Median OS (95% CI), months
NIVO+IPI	358/550	52.7 (45.8-64.5)
SUN	405/546	37.8 (31.9-43.8)
HR (95% CI), 0.72 (0.62-0.83)		

HR (99.8% CI) at the primary analysis, 0.68 (0.49-0.95)[1]

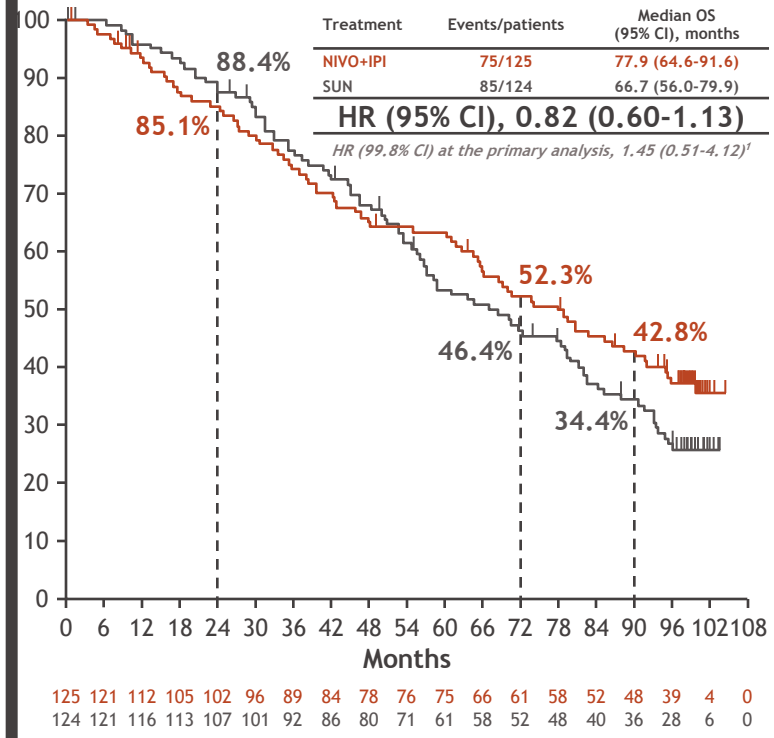
Intermediate/poor risk



Treatment	Events/patients	Median OS (95% CI), months
NIVO+IPI	283/425	46.7 (35.0-55.7)
SUN	320/422	26.0 (21.8-32.6)
HR (95% CI), 0.69 (0.59-0.81)		

HR (99.8% CI) at the primary analysis, 0.63 (0.44-0.89)[1]

Favorable risk



Treatment	Events/patients	Median OS (95% CI), months
NIVO+IPI	75/125	77.9 (64.6-91.6)
SUN	85/124	66.7 (56.0-79.9)
HR (95% CI), 0.82 (0.60-1.13)		

HR (99.8% CI) at the primary analysis, 1.45 (0.51-4.12)[1]

CR in FAV Risk: 12 vs 3%

Tannir et al, GU-ASCO 2024.

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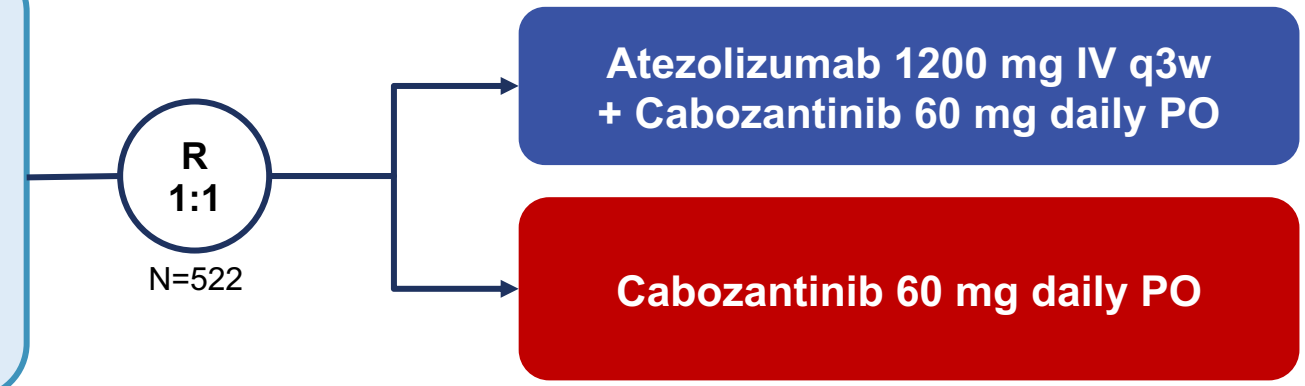
Phase III CONTACT-03 study

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

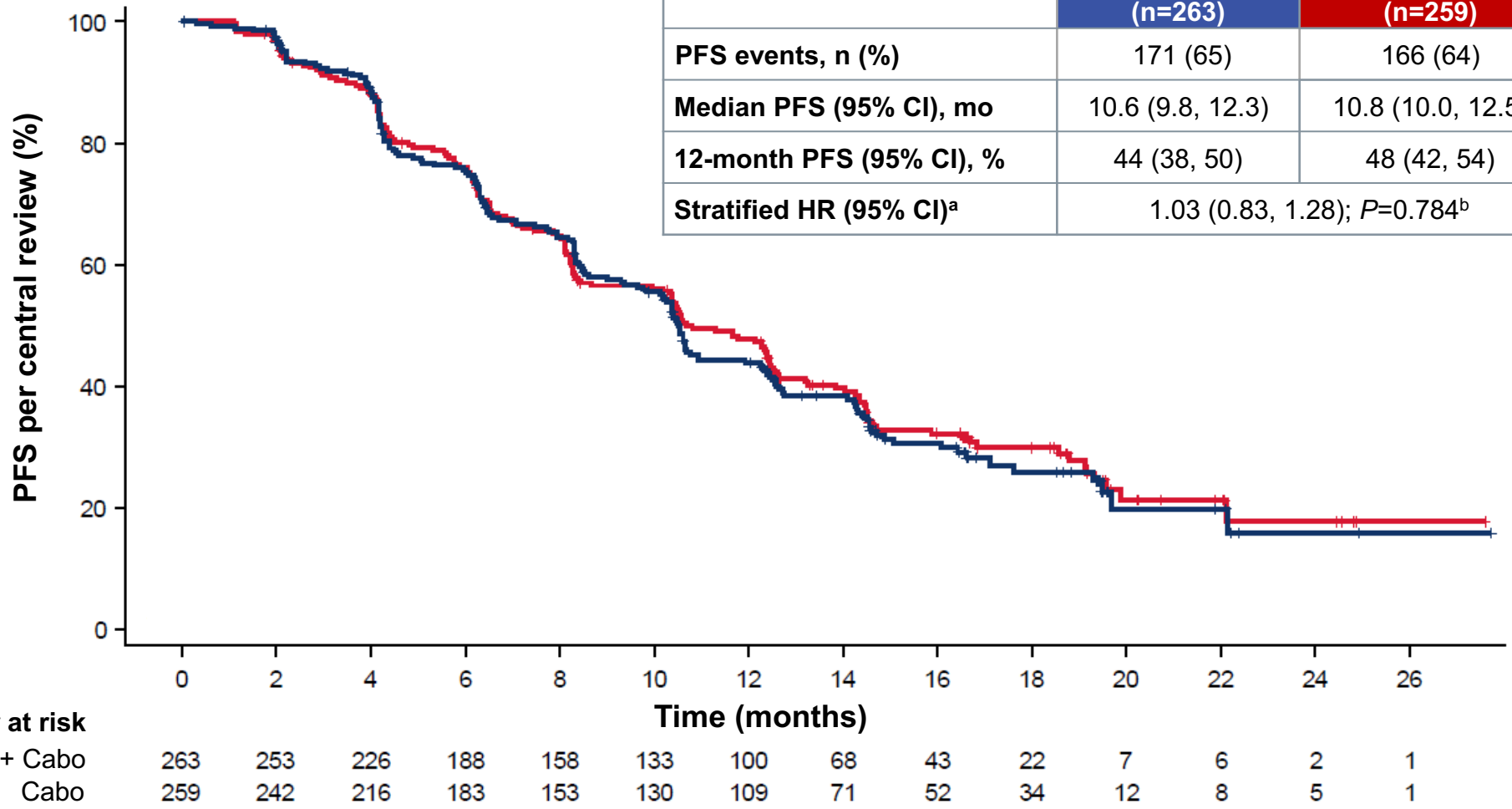
Key secondary endpoints

- 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.

Primary analysis of centrally reviewed PFS

	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]	

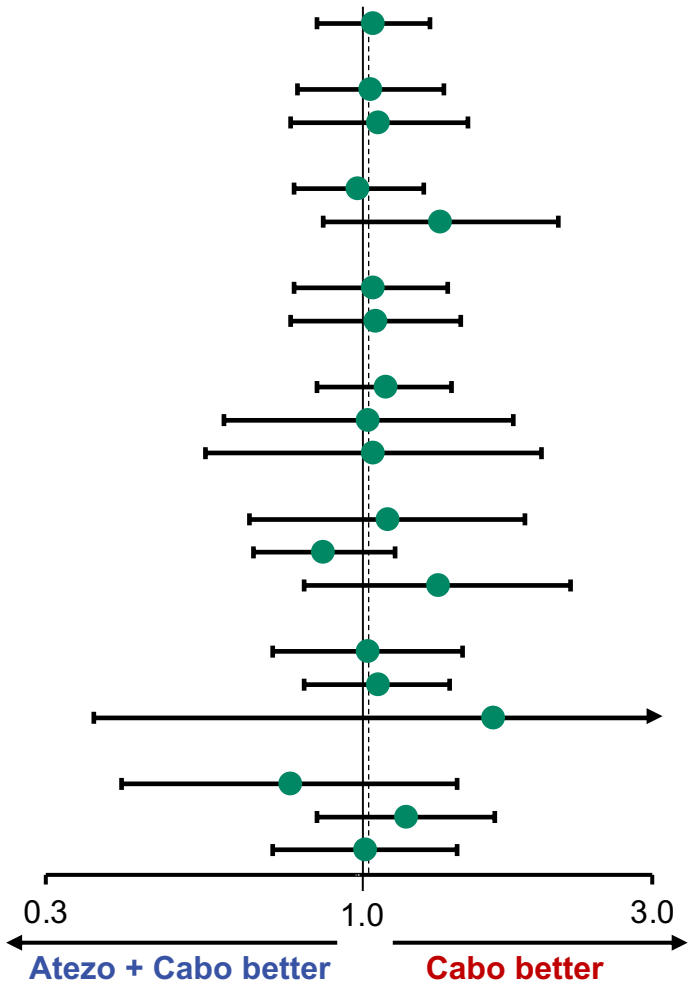


[a] Stratified for IMDC risk group. [b] Not significant at α=0.02.

Choueiri, et al, ASCO 23
Pal et al, Lancet 2023

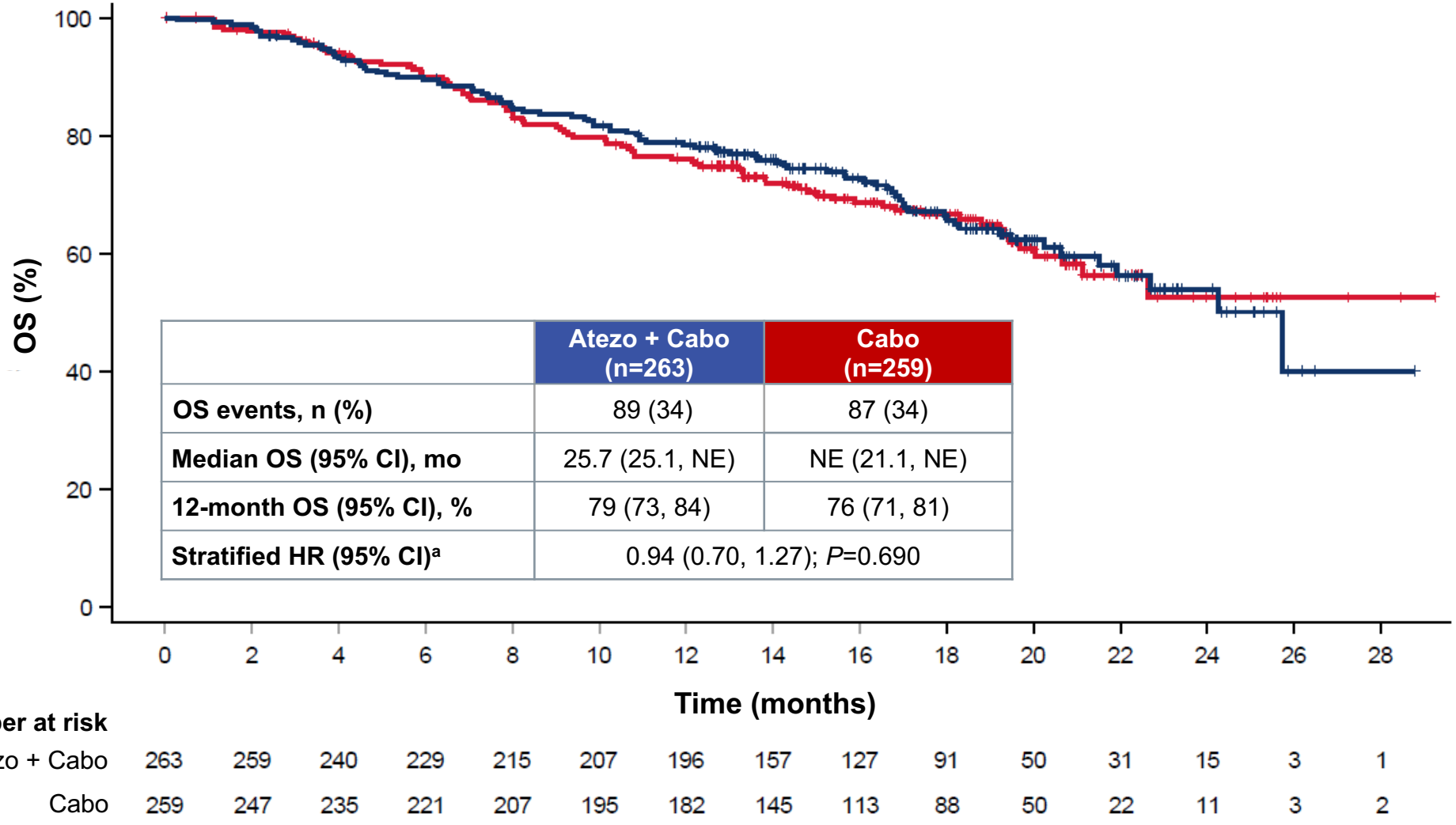
Centrally reviewed PFS by subgroup

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.

Interim analysis of OS (co-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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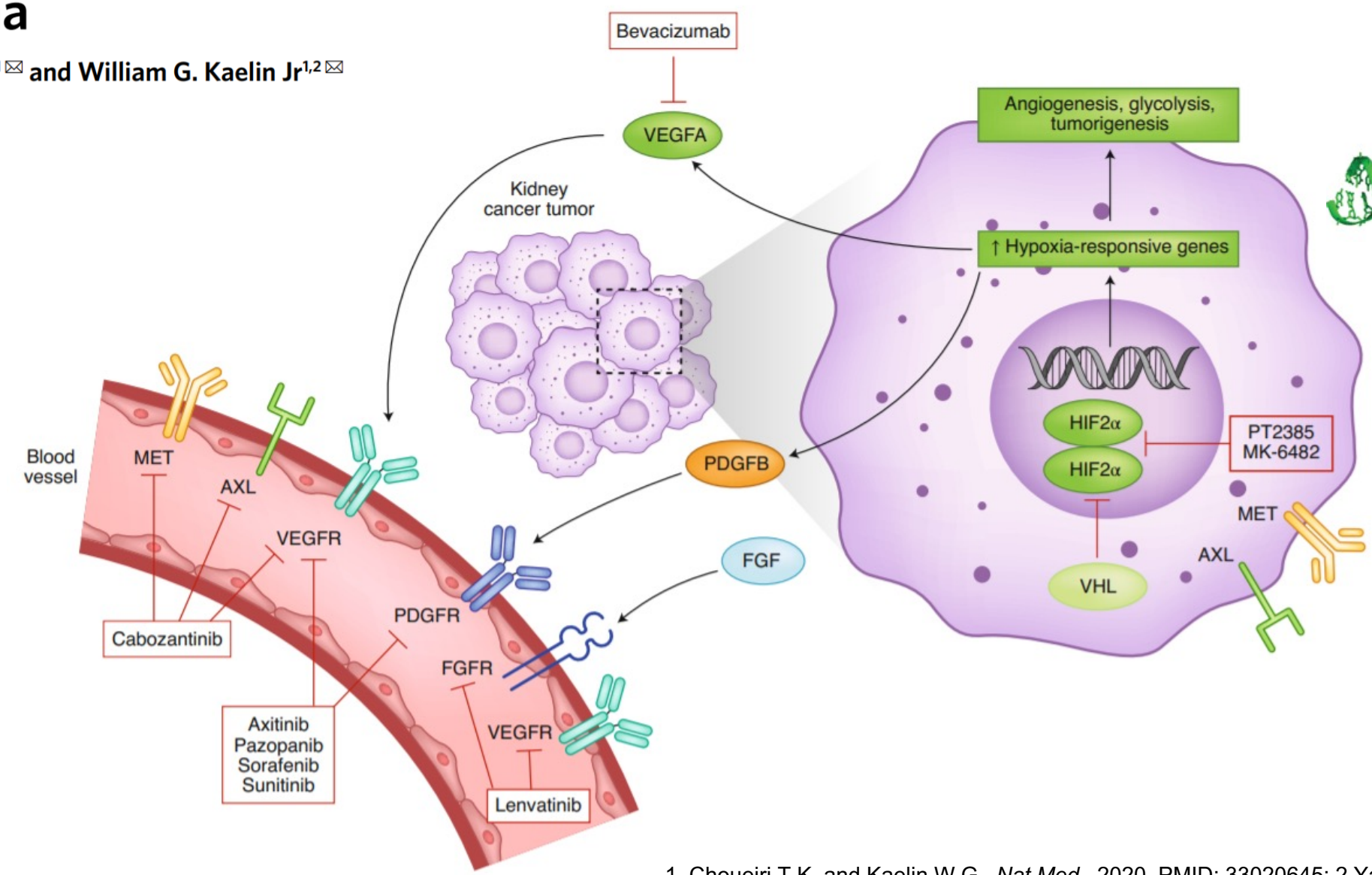
nature medicine

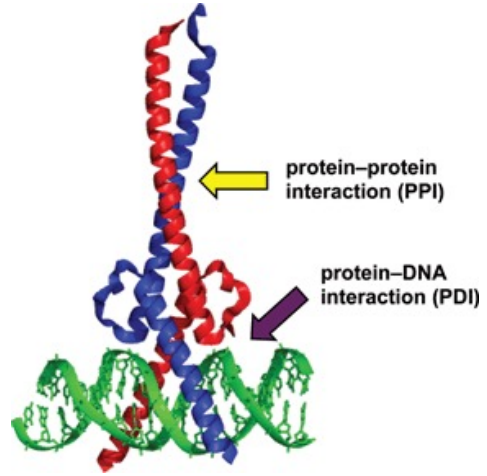
PERSPECTIVE

https://doi.org/10.1038/s41591-020-1093-z

Targeting the HIF2–VEGF axis in renal cell carcinoma

Toni K. Choueiri[1]✉ and William G. Kaelin Jr[1,2]✉





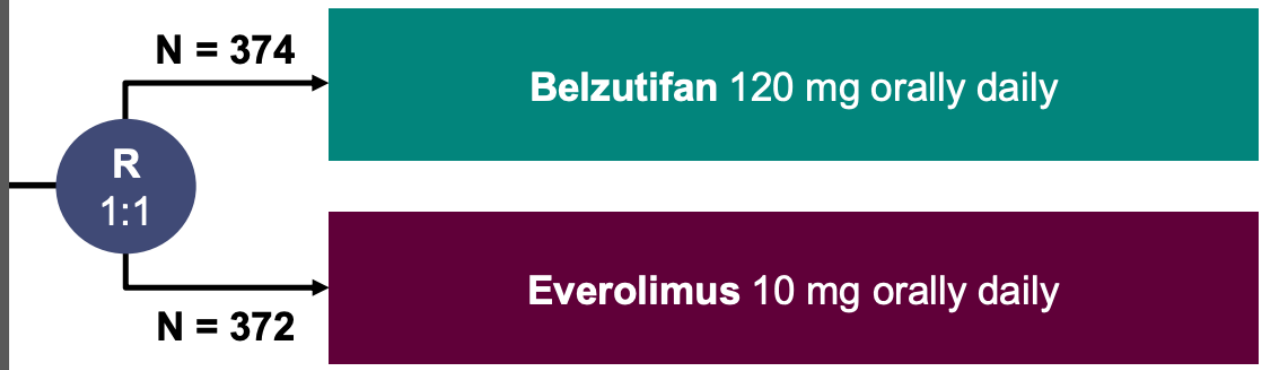
1. Choueiri T.K. and Kaelin W.G., *Nat Med*., 2020. PMID: 33020645; 2.Yap et al, *Med Chem Comm*, 2012

LITESPARK-005 Study Design

LITESPARK-005 (Phase 3 trial)

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 VEGF/VEGFR-targeted therapies: 1 vs 2-3

Dual Primary Endpoints:

- PFS per RECIST 1.1 by BICR
- OS

Key Secondary Endpoint:

- ORR per RECIST 1.1 by BICR

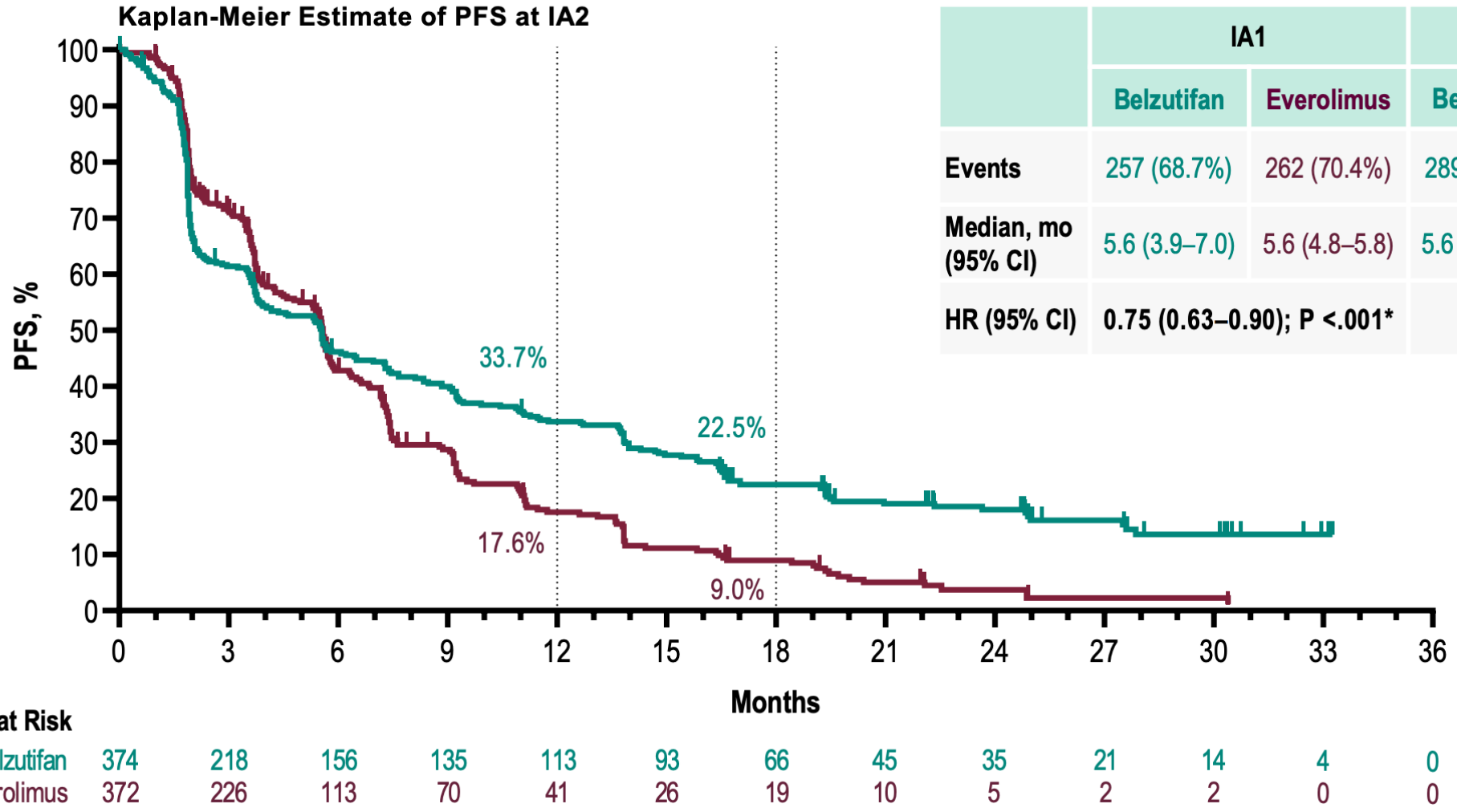
Other Secondary Endpoints Include:

- DOR per RECIST 1.1 by BICR
- Safety
- Time to deterioration in FKSI-DRS and EORTC QLQ-C30 GHS/QoL

Albiges et al., ESMO 2023

LITESPARK-005 Results

Primary Endpoint: PFS per RECIST 1.1 by BICR

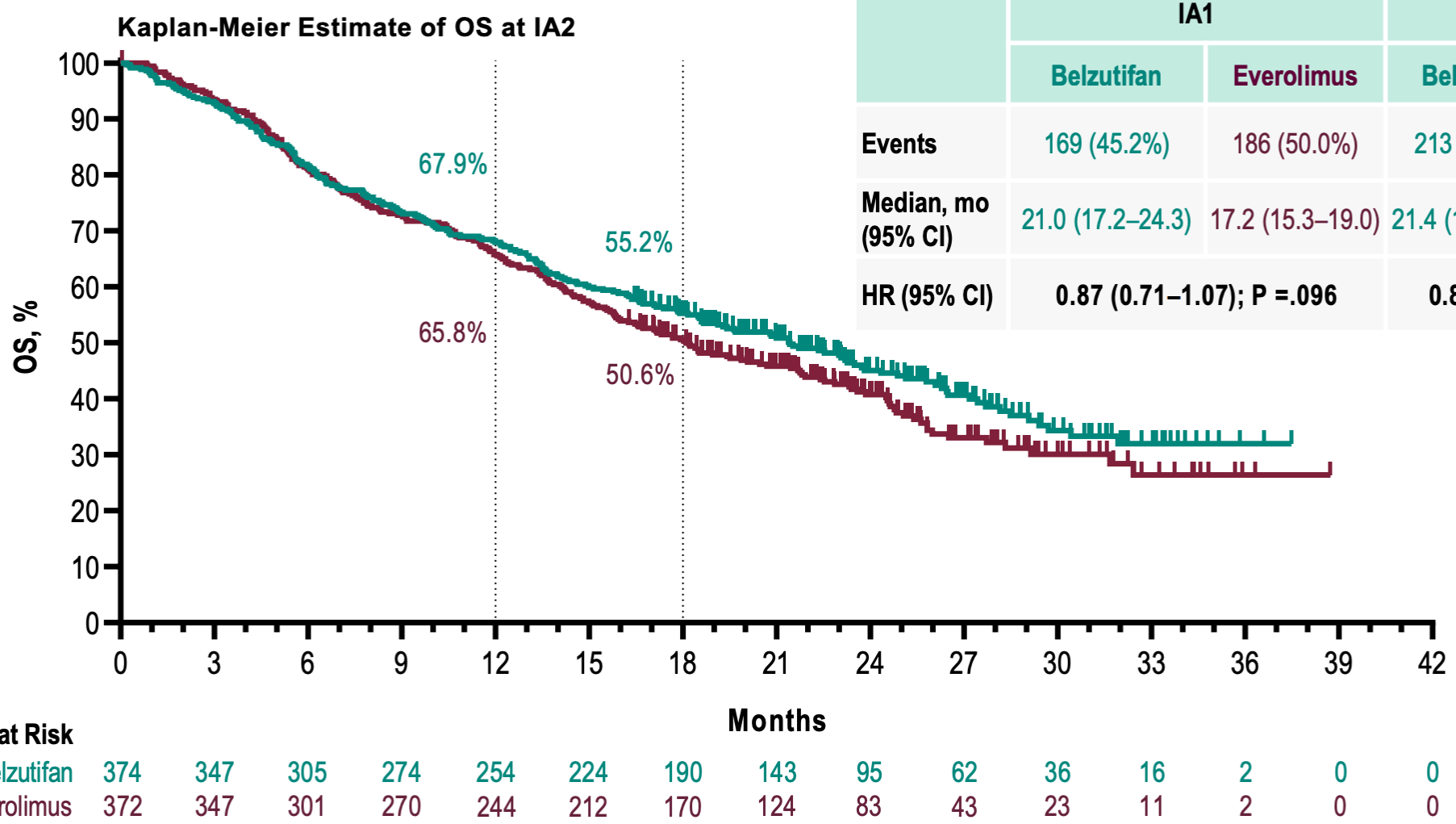


	IA1		IA2	
	Belzutifan	Everolimus	Belzutifan	Everolimus
Events	257 (68.7%)	262 (70.4%)	289 (77.3%)	276 (74.2%)
Median, mo (95% CI)	5.6 (3.9–7.0)	5.6 (4.8–5.8)	5.6 (3.8–6.5)	5.6 (4.8–5.8)
HR (95% CI)	0.75 (0.63–0.90); P <.001*		0.74 (0.63–0.88)	

Albiges et al., ESMO 2023

LITESPARK-005 Results

Primary Endpoint: OS



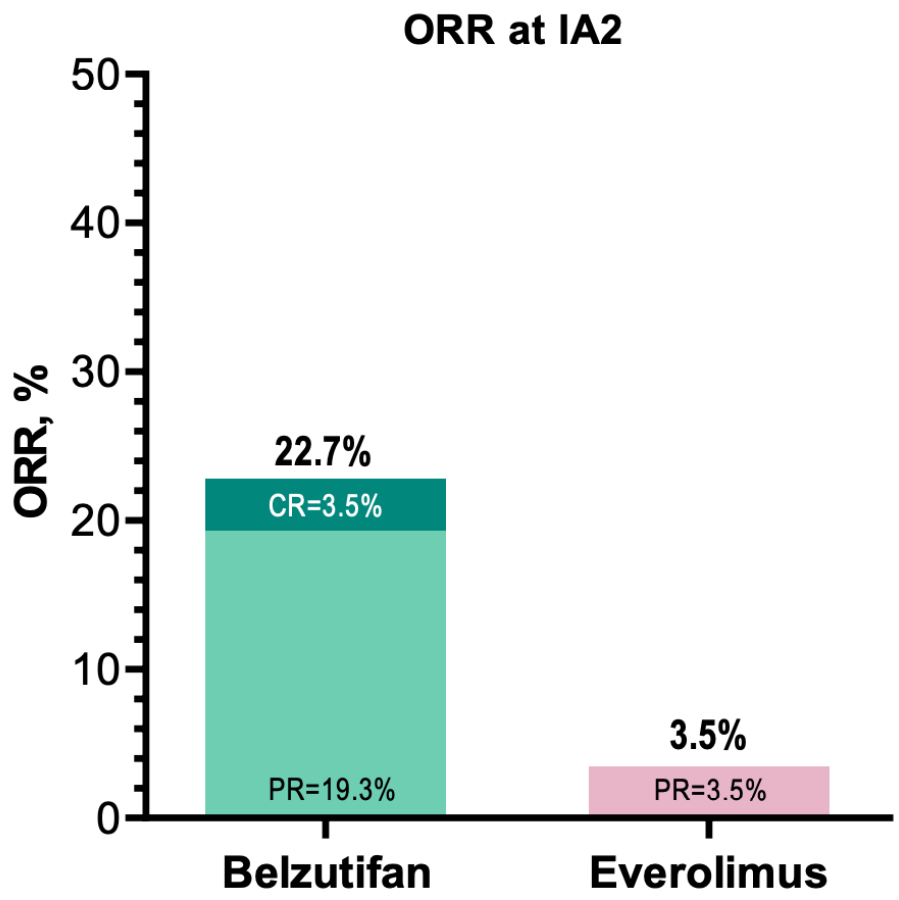
	IA1		IA2	
	Belzutifan	Everolimus	Belzutifan	Everolimus
Events	169 (45.2%)	186 (50.0%)	213 (57.0%)	228 (61.3%)
Median, mo (95% CI)	21.0 (17.2–24.3)	17.2 (15.3–19.0)	21.4 (18.2–24.3)	18.1 (15.8–21.8)
HR (95% CI)	0.87 (0.71–1.07); P =.096		0.88 (0.73–1.07); *P* =.099	

Albiges et al., ESMO 2023

LITESPARK-005 Results

Key Secondary Endpoint: ORR by BICR per RECIST 1.1

	Belzutifan (N = 374)	Everolimus (N = 372)
	IA1	
ORR, % (95% CI)	**21.9% (17.8–26.5)**	**3.5% (1.9–5.9)**
Estimated difference in % (95% CI)	**18.4 (14.0–23.2); P <.00001***	
CR	2.7%	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 in % (95% CI)	**19.2 (14.8–24.0)**	



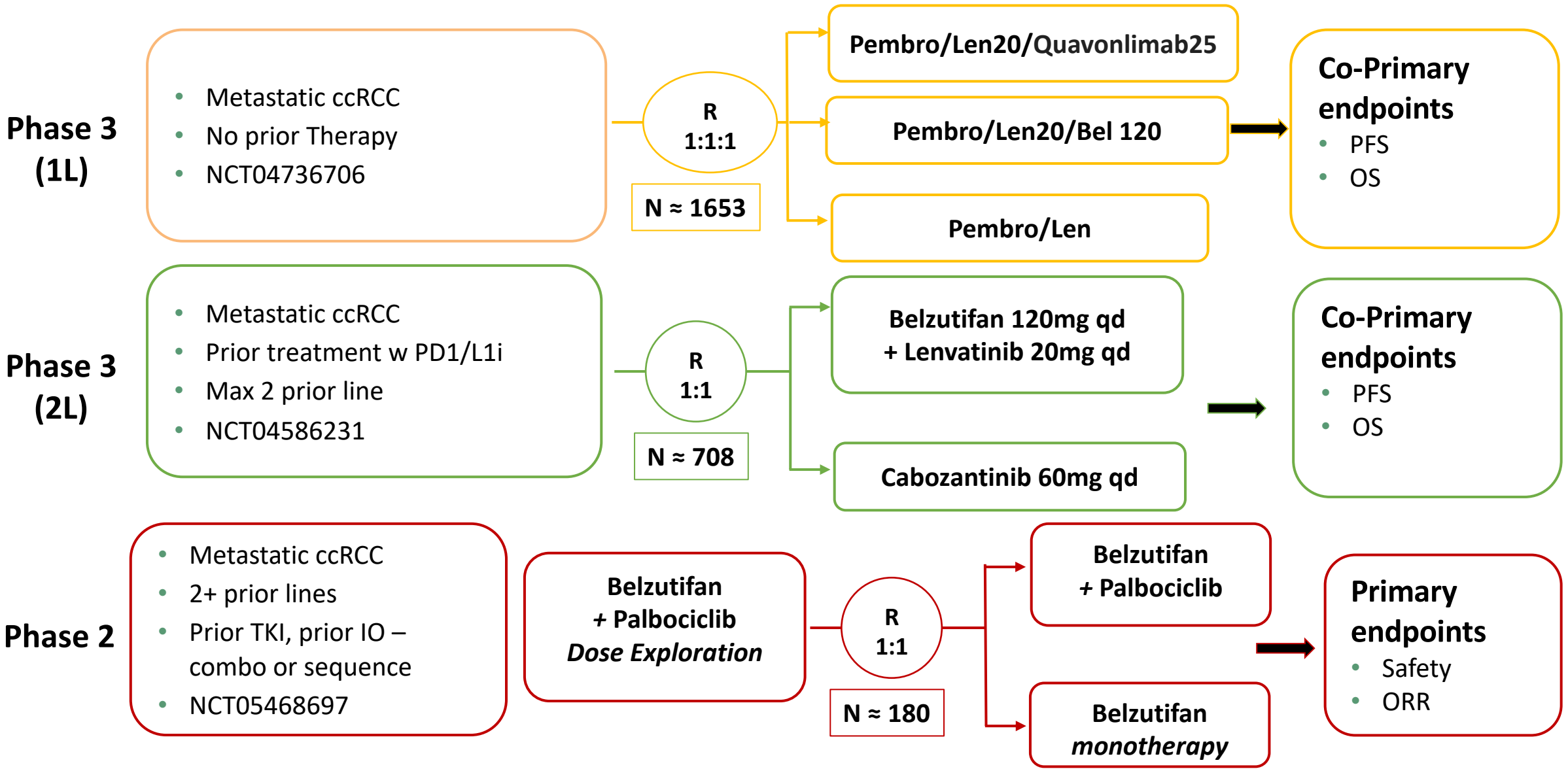
Albiges et al., ESMO 2023

LITESPARK-005

FDA approves belzutifan for advanced renal cell carcinoma

On December 14, 2023, the Food and Drug Administration approved belzutifan [redacted] for patients with advanced renal cell carcinoma (RCC) following a programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor and a vascular endothelial growth factor tyrosine kinase inhibitor (VEGF-TKI).

Belzutifan in ongoing randomized clinical trials



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- Biomarkers in mRCC remain elusive (ASCO 2024), though KIM-1 promising

KEYNOTE-564 Study Design

Key Eligibility Criteria

- Histologically confirmed clear cell renal cell carcinoma
- Nephrectomy ≤12 weeks prior to randomization
- No prior systemic therapy
- ECOG PS 0 or 1
- Tissue sample for PD-L1 assessment

Stratification Factors

- M0 vs M1 NED
- M0 group further stratified:
  - ECOG PS 0 vs 1
  - US vs non-US

R (1:1)

Pembrolizumab 200 mg Q3W for ~1 year[a]

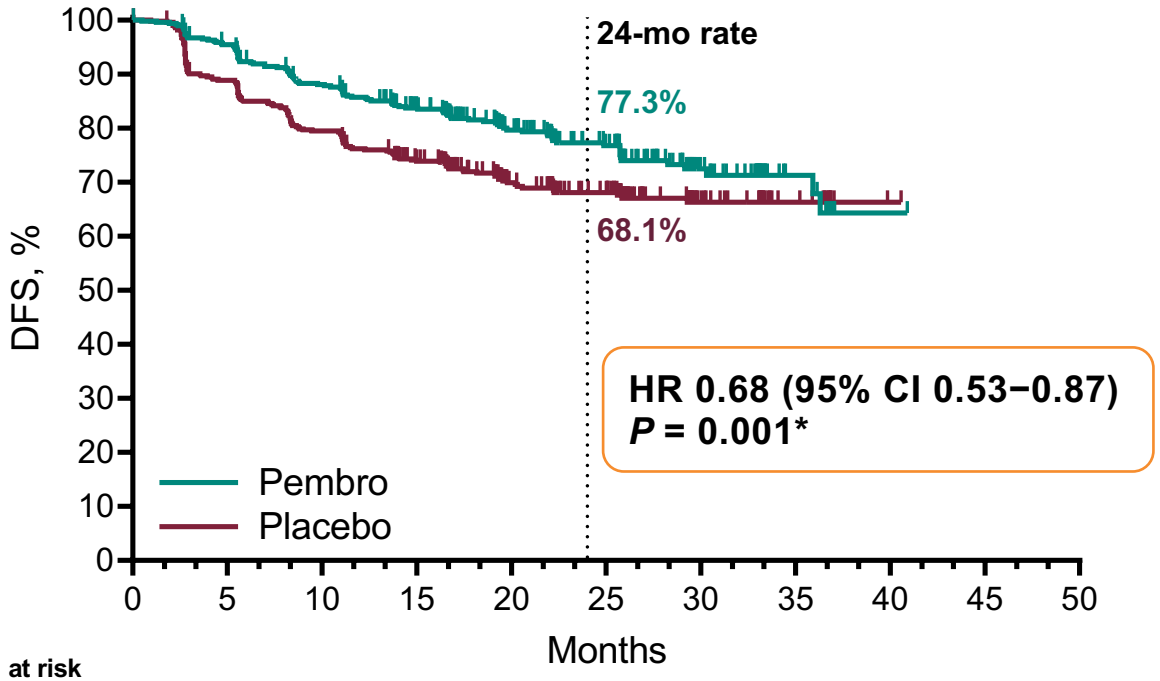
Placebo Q3W for ~1 year[a]

- Primary end point: DFS per investigator
- Key secondary end point: OS
- Other secondary end points: Safety

DFS, disease-free survival; Q3W, every 3 weeks.
[a]≤17 cycles of treatment were equivalent to ~1 year.

Primary Endpoint: DFS, ITT Population

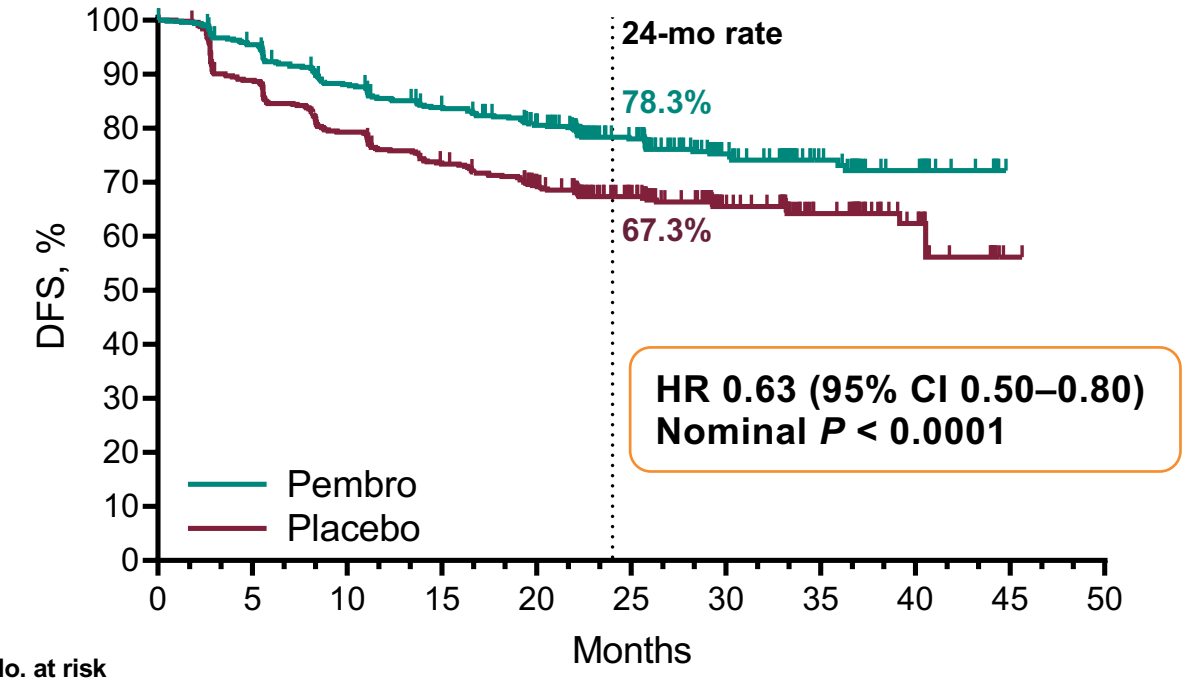
Primary Analysis: 24.1 mo Follow-Up



No. at risk											
Pembro	496	457	414	371	233	151	61	21	1	0	0
Placebo	498	436	389	341	209	145	56	19	1	0	0

	Pts w/ Event	Median, mo (95% CI)
Pembro	109	NR (NR–NR)
Placebo	151	NR (NR–NR)

Updated Analysis: 30.1 mo Follow-Up



No. at risk											
Pembro	496	458	416	389	361	255	135	77	37	0	0
Placebo	498	437	389	356	325	230	125	74	33	1	0

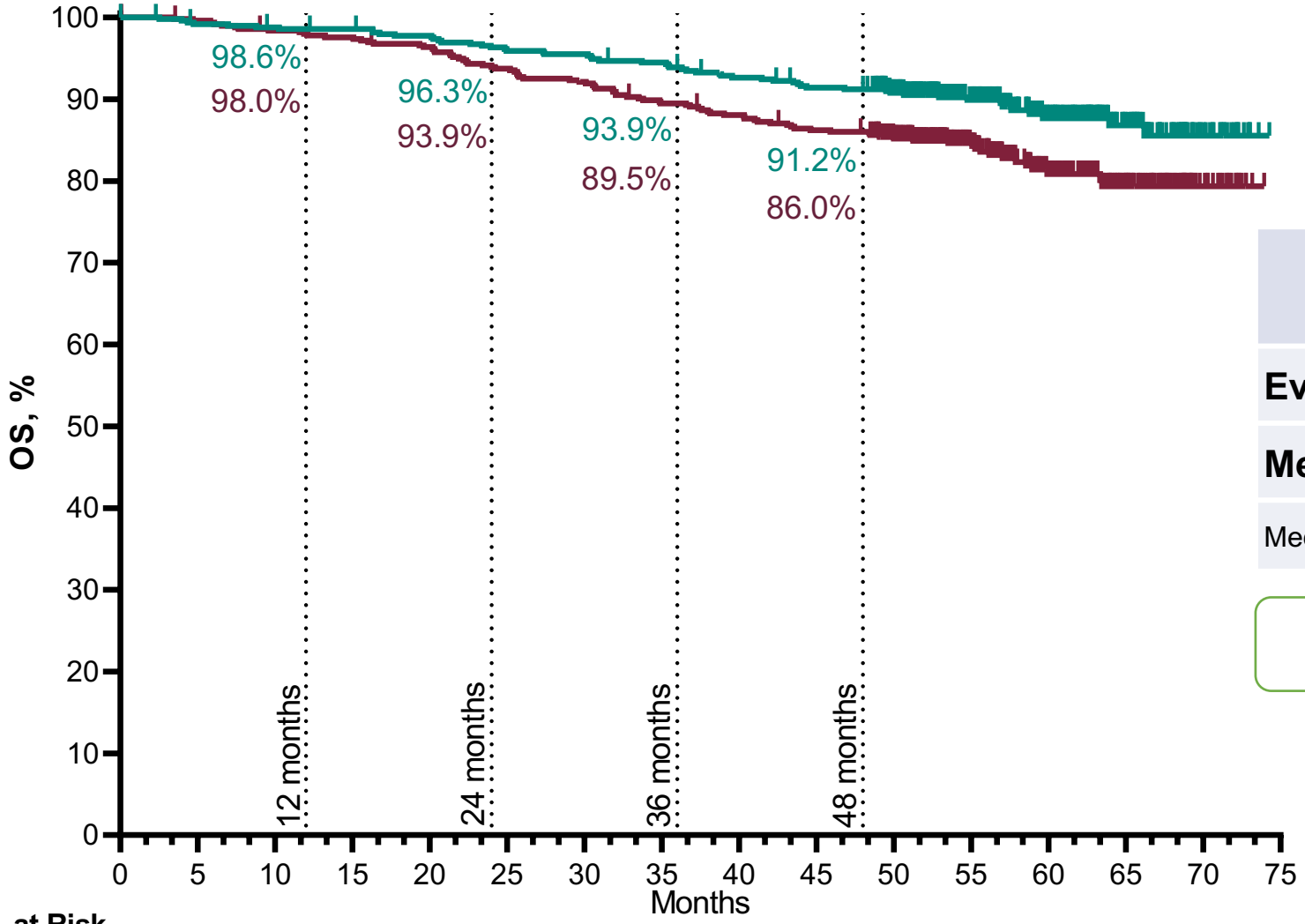
	Pts w/ Event	Median, mo (95% CI)
Pembro	114	NR (NR–NR)
Placebo	169	NR (40.5–NR)

* denotes statistical significance.

ITT population included all randomized participants. DFS, disease-free survival; NR, not reached. Primary analysis data cutoff date: December 14, 2020. Updated analysis data cutoff date: June 14, 2021.

OVERALL SURVIVAL

#GU24 San Fran 1/27/2024 and NEJM 2024



No. at Risk

Pembro	496	489	486	484	479	470	468	462	451	443	397	270	168	81	22	0
Placebo	498	494	487	483	476	463	455	441	433	423	382	248	155	79	22	0

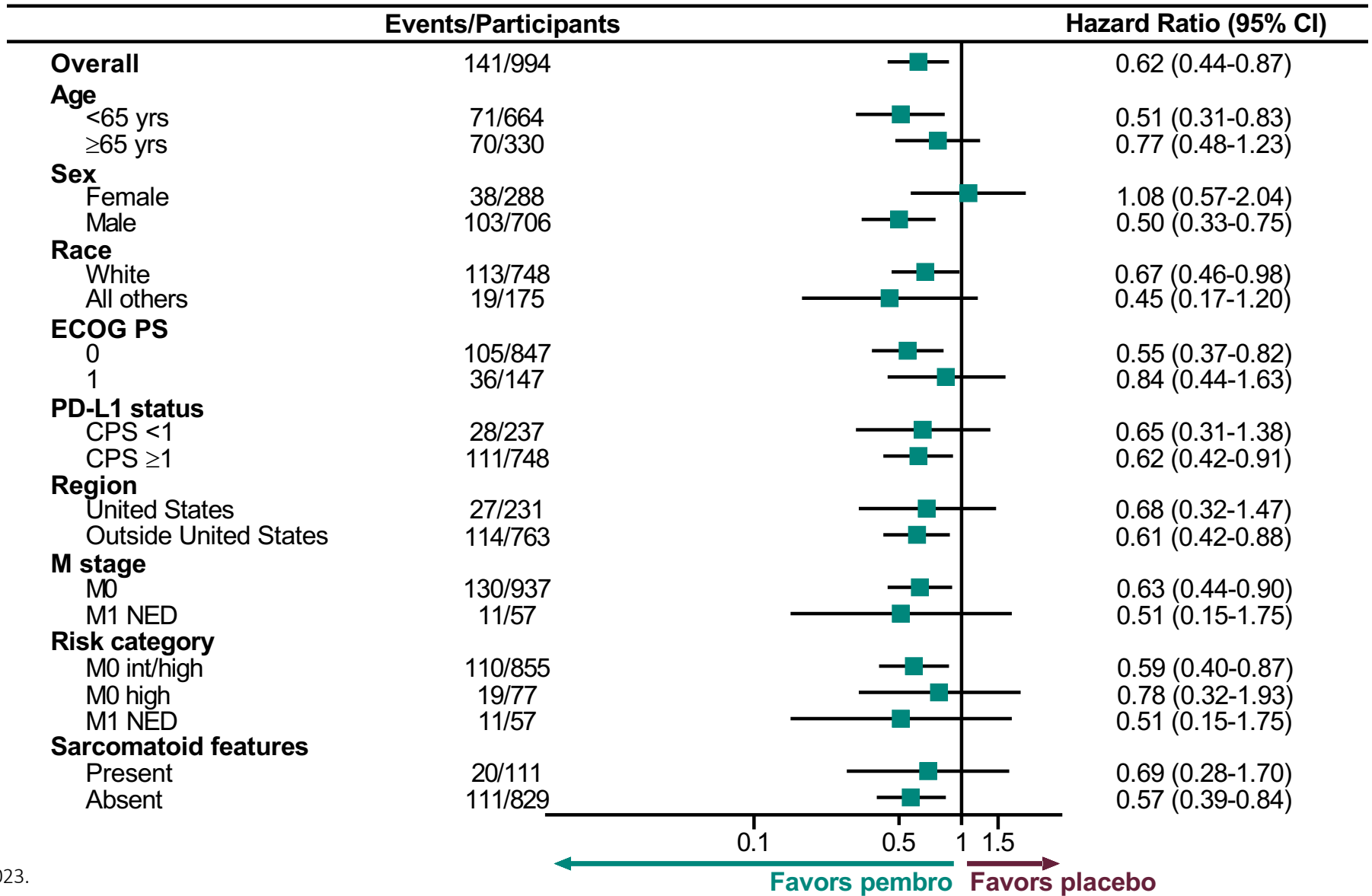
	Pembro (N = 496)	Placebo (N = 498)
Events, n	55	86
Median, mo (95% CI)	NR (NR–NR)	NR (NR–NR)
Median follow-up was 57.2 months (range, 47.9–74.5)		

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.

LITESPARK-022: Belzutifan (HIF-2 inhibitor) + Pembro for Adjuvant RCC (finished accrual)

Key Eligibility Criteria:

- Histologically confirmed diagnosis of ccRCC
  - **Intermediate-high risk:** pT2, Grade 4 or sarcomatoid, N0, M0; pT3, any Grade, N0, M0
  - **High risk:** pT4, any Grade, N0, M0; any pT, any Grade, N+, M0
  - **M1 no evidence of disease (NED)** after surgery (≤ 2 yrs from nephrectomy)
- Complete resection of primary tumor (partial or radical nephrectomy) and metastatic lesions (for M1 NED pts)
- Randomized ≤ 12 wks after surgery
- ECOG PS 0-1
- Positive microscopic margins ok
- No preexisting brain or bone metastatic lesions
- No prior systemic therapy or radiotherapy for RCC

N = 1600
1:1 (blinded)

Belzutifan (120 mg QD ~12 mo) + **Pembrolizumab** (400 mg Q6W x 9 cycles)
N=800

Placebo (QD ~12 mo) + **Pembrolizumab** (400 mg Q6W x 9 cycles)
N=800

Primary endpoint:

- DFS by Investigator

Secondary endpoints:

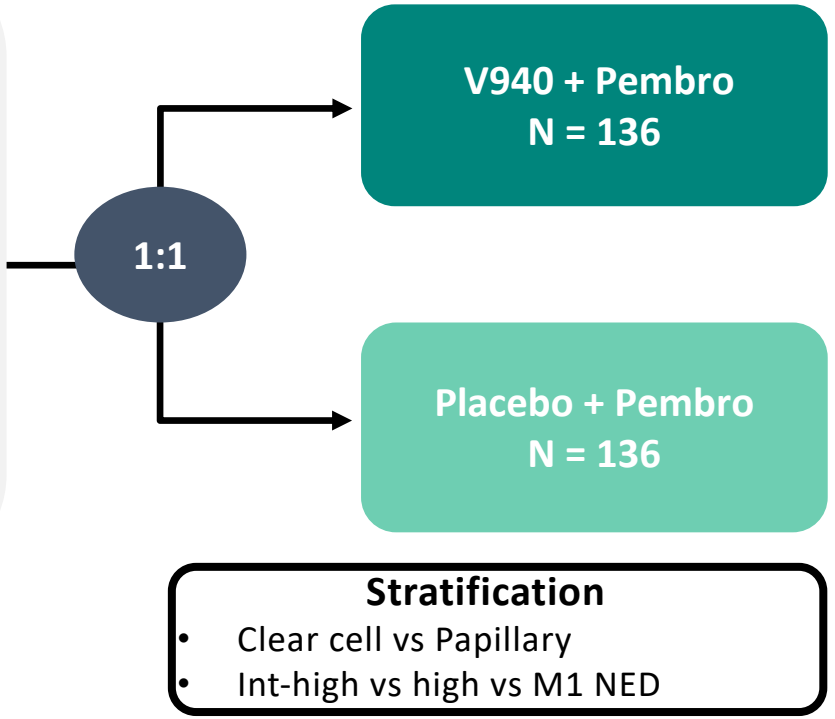
- OS, safety, disease recurrence-specific survival, and PROs

ClinicalTrials.gov Identifier: NCT05239728

A Phase 2, Randomized, Double-blind, Study of V940 (mRNA-4157 + Pembrolizumab vs. Placebo + Pembrolizumab in the Adjuvant Treatment of RCC (ongoing)

Key Eligibility:

- Adjuvant (post nephrectomy) RCC,
- Clear cell and Papillary histology permitted
  - Papillary capped at 15%
- Int-high or high risk of recurrence defined as:
  - pT2 Gr4 or pT3 Gr3/4, N0, M0
  - pT4, N0, M0 or pT any stage, N1, M0
  - M1 NED (post metastasectomy)



Primary Endpoint:

- DFS (by investigator)

Secondary Endpoints:

- DMFS
- OS
- Safety

Exploratory Endpoint:

- DFS MRD+ subgroup
- BICR EFS (collect and hold)

Design Considerations:

- Slightly higher risk pt pop than KN564 in order to accelerate signal generation (excludes T3G1-2)
- Include nccRCC (papillary) which not included in KN564, but MOA of INT should be histology-independent and nccRCC responds to immunotherapy (KN427B pembro mono in advanced papillary RCC, ORR 28.8%, vs 36.4% for ccRCC)

ClinicalTrials.gov Identifier: NCT06307431

What is “new” in 15 minutes?

- 1L mRCC combination PD-1+CTLA-4 and PD-1+VEGF inhibitors continue to dominate:
  - Updates from JR101 and CM-214 (2024)
- 2L/3L mRCC:
  - PD1/L1 post PD1 does not work (CONTACT-3)
  - HIF2 inhibitor Belzutifan (LITESPARK-005)
- Adjuvant Pembrolizumab has an OS benefit!
  - 1st adjuvant trial in RCC with OS (KYN-564)

- Biomarkers in mRCC remain elusive (ASCO 2024), though KIM-1 promising (#ASCO2024)

Abstract 4504 (Choueiri)
Biomarker analyses from the phase 3 CLEAR trial : Pembro+Lenvatinib vs. Sunitinib

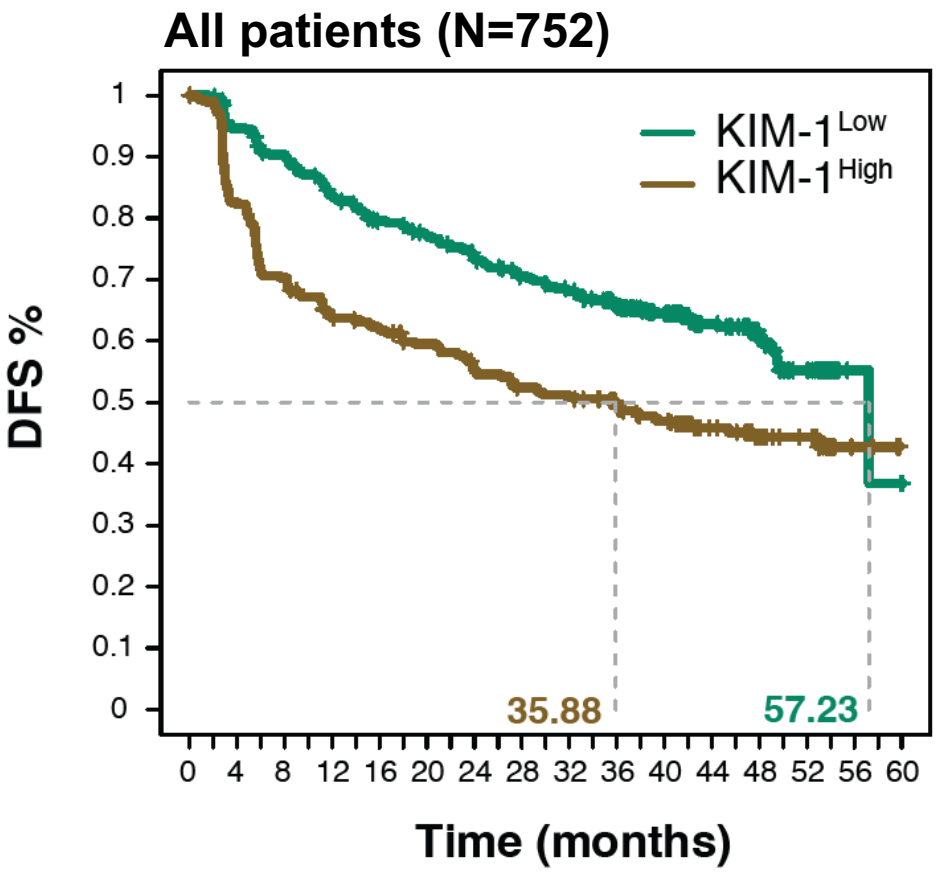
Abstract 4505 (Rini)
Biomarker analysis from the phase 3 KEYNOTE-426: Pembro + Axitinib vs. sunitinib

Can we identify subgroups which benefit more from VEGFR TKI vs PD1+TKI combination therapy?

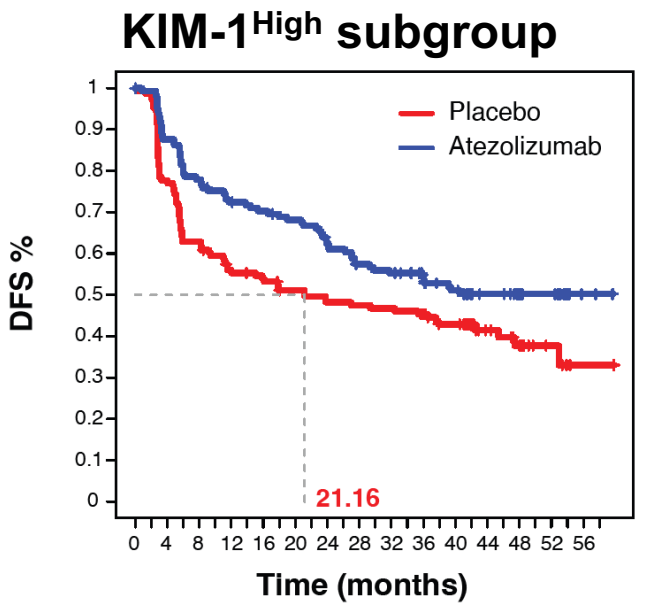
- PD-L1 expression
- Tumor mutations (WES)
- Gene expression changes (RNA-seq)

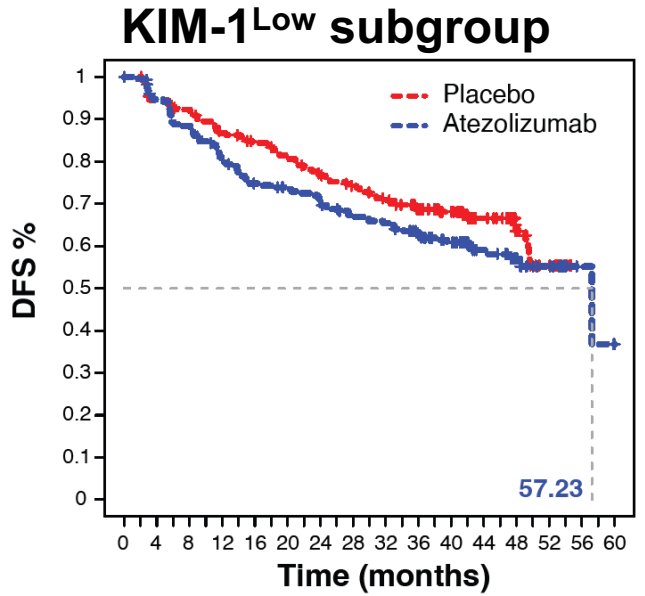
NO

KIM-1 is both prognostic and predictive in IMmotion010 adjuvant trial (atezolizumab vs. placebo)



Reversal of HR suggests an interaction between KIM-1 High and atezolizumab effect on DFS





Albiges et al., *ASCO* 2024 (Abs 4506).

Summary

- 1L mRCC combination PD-1+CTLA-4 and PD-1+VEGF inhibitors continue to dominate.
- 2L/3L mRCC:
  - PD1/L1 post PD1 does not work
  - HIF2 inhibitor Belzutifan is an option post IO and VEGF with ongoing adjuvant/1L/2L combinations
- Adjuvant Pembrolizumab has an OS benefit
  - ccRCC with T2G4/T3/T4/N+/M1NED
- Biomarkers in mRCC are not standard