MLS Seattle
Renal Cell Carcinoma Updates

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Overview

- **Adjuvant**

  KeyNote 564 update for OS (ASCO GU24)

- **Metastatic Front Line**

  CheckMate 214 – good risk cohort with 99-month FU (ASCO GU24)

- **Salvage Therapy**

  Sustained PD1/PDL1 blockade in PD1/PDL1 refractory patients (CONTACT-03 and TiNivo-2)

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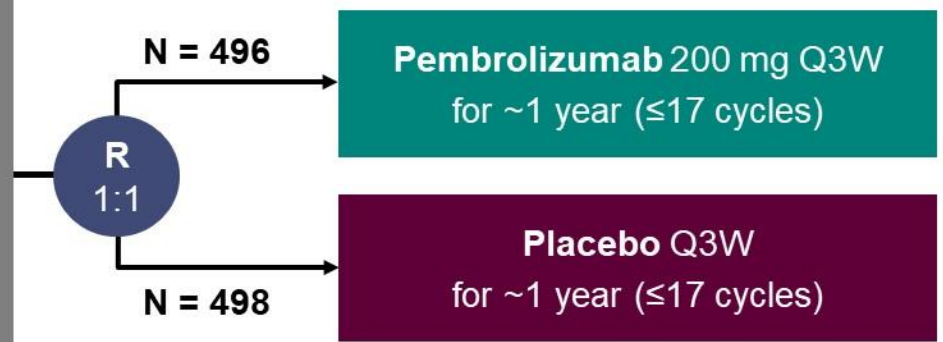
KEYNOTE-564 Study (NCT03142334)

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

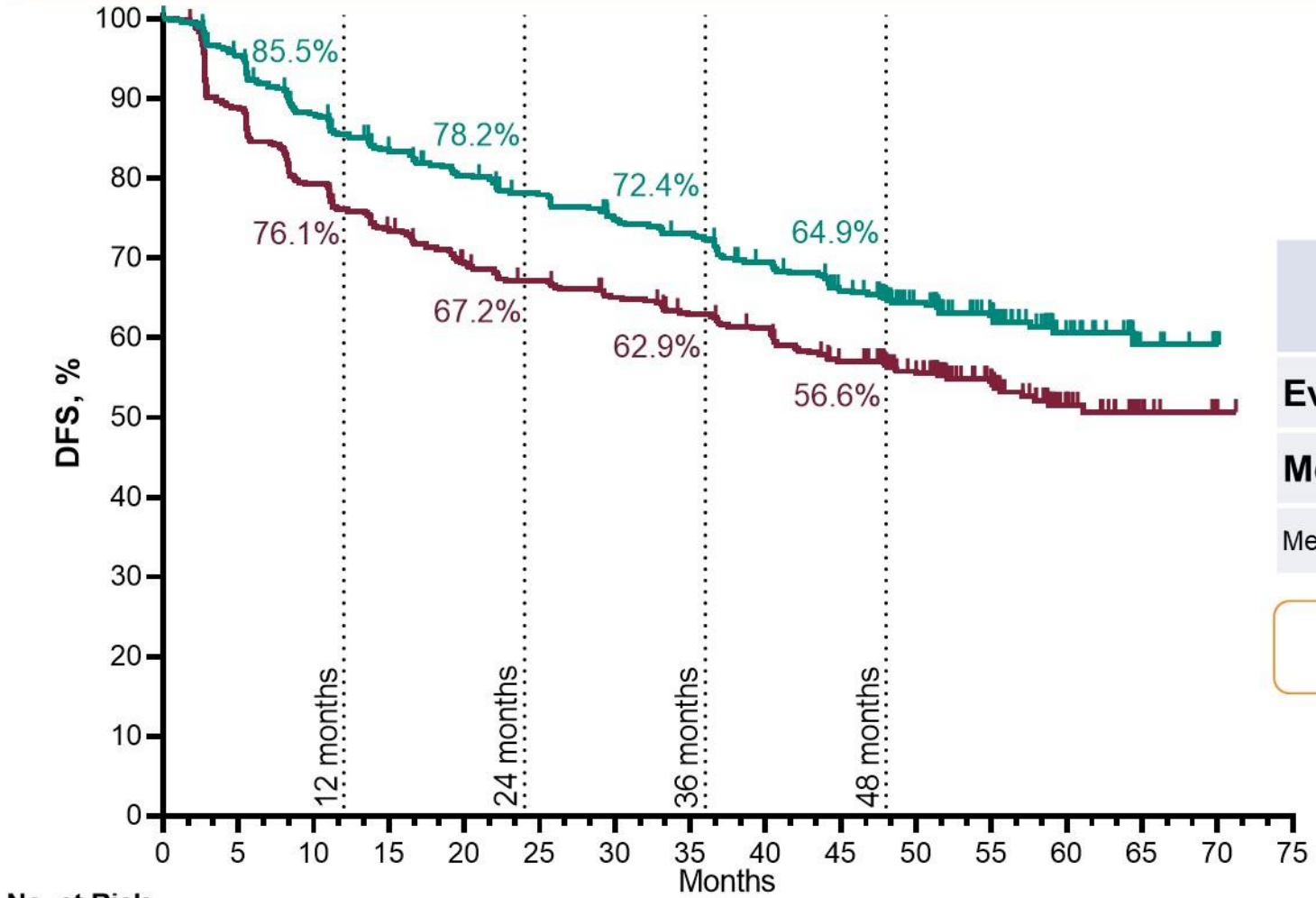
- Overall survival

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)

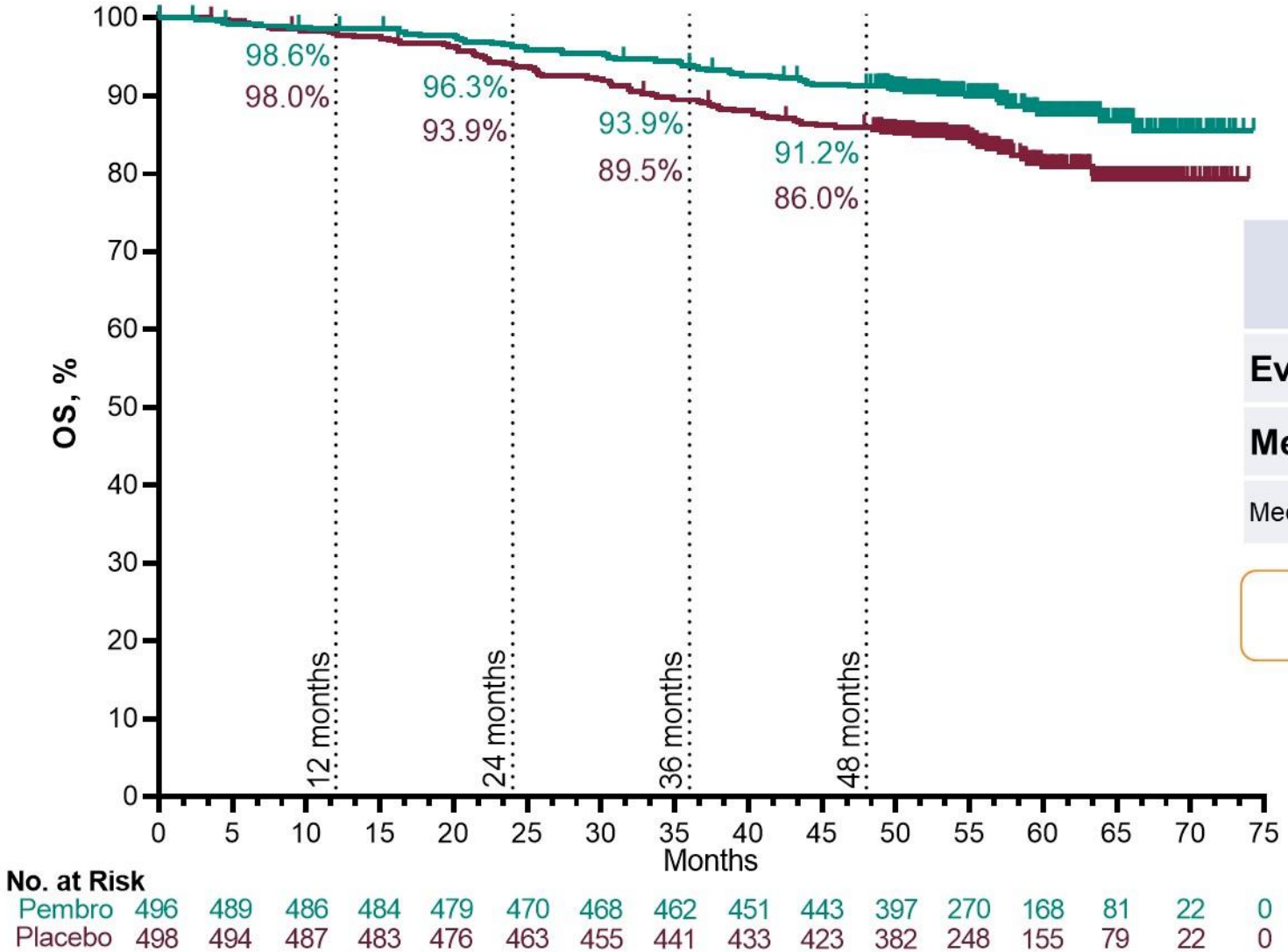
HR 0.72 (95% CI 0.59–0.87)

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

Data cutoff date: September 15, 2023.

TK Choueiri ASCO GU24

Overall Survival, Intention-to-Treat Population



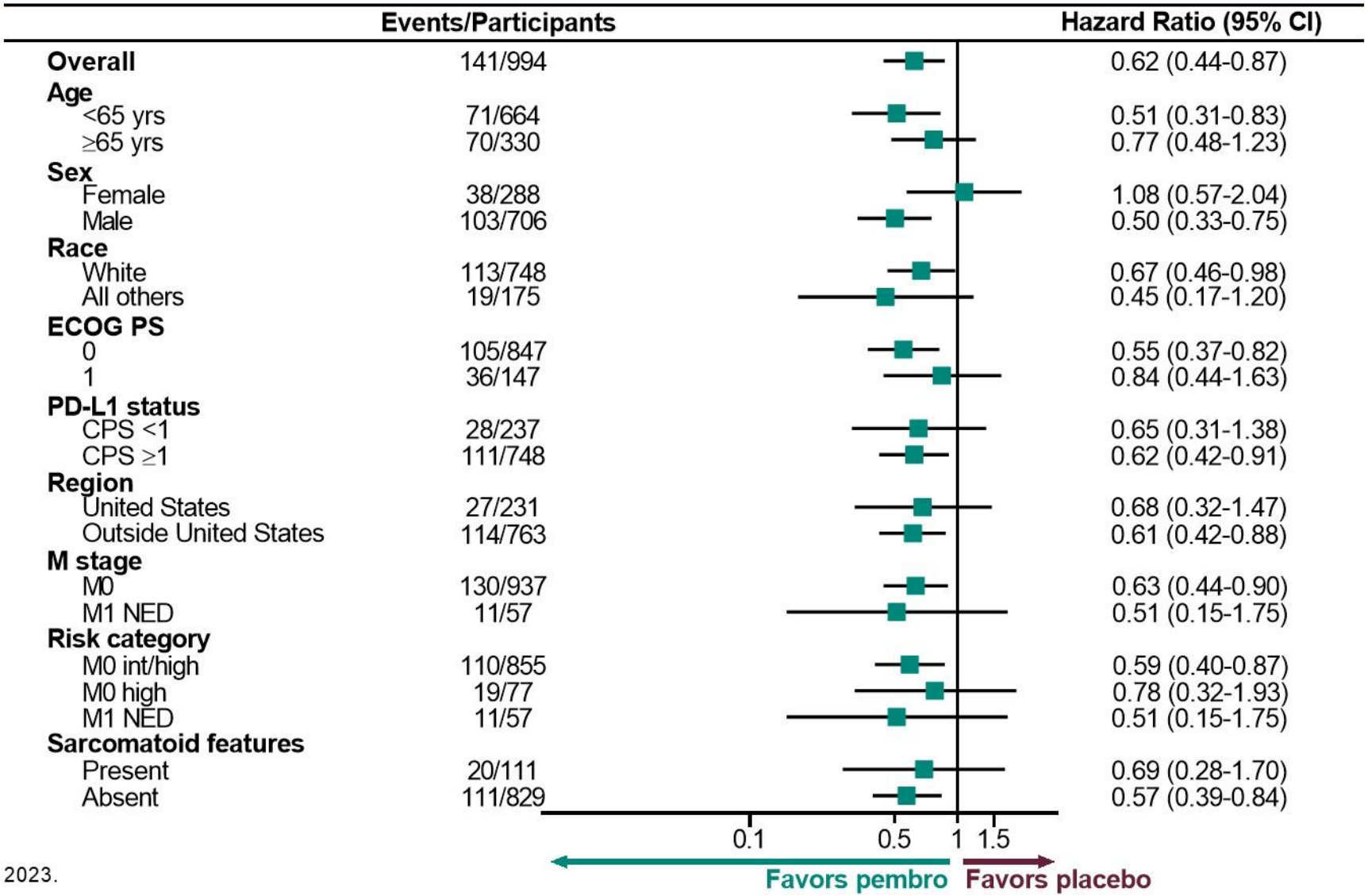
	Pembro (N = 496)	Placebo (N = 498)
Events, n	55	86
Median, mo (95% CI)	NR (NR–NR)	NR (NR–NR)
Median follow-up was 57.2 months (range, 47.9–74.5)		

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.

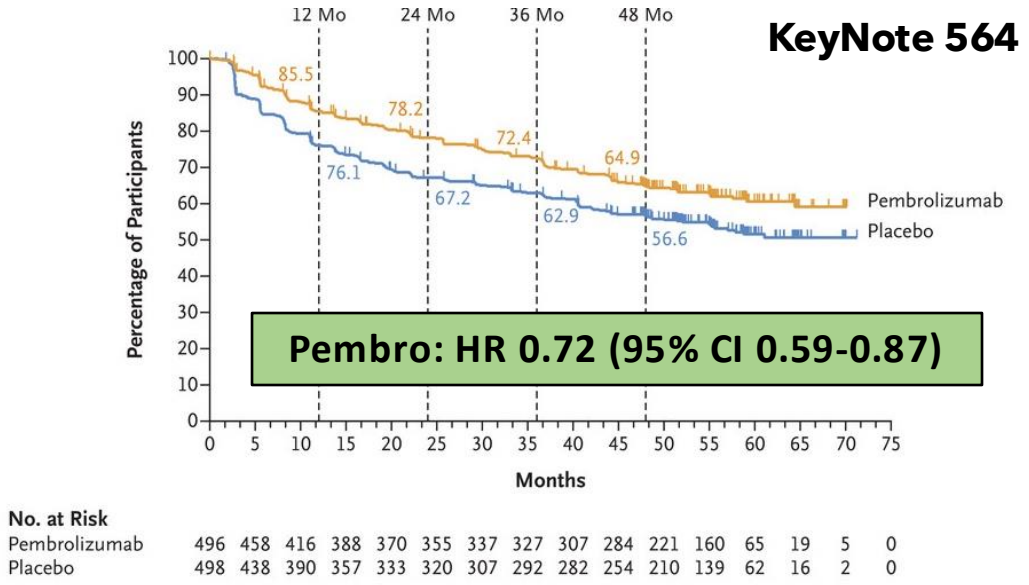
Data cutoff date: September 15, 2023.

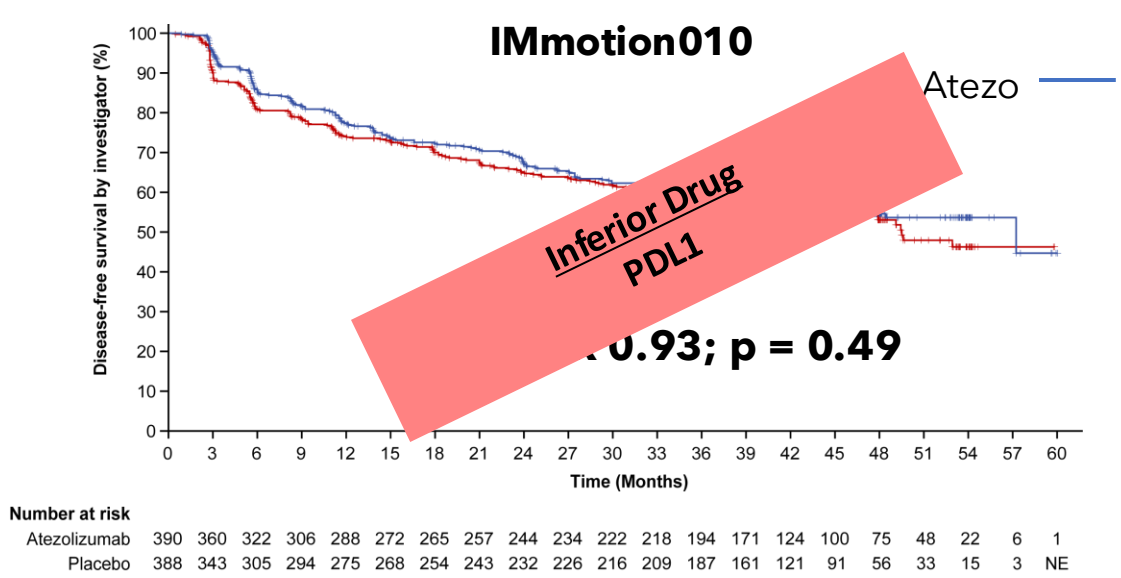
Overall Survival by Subgroups

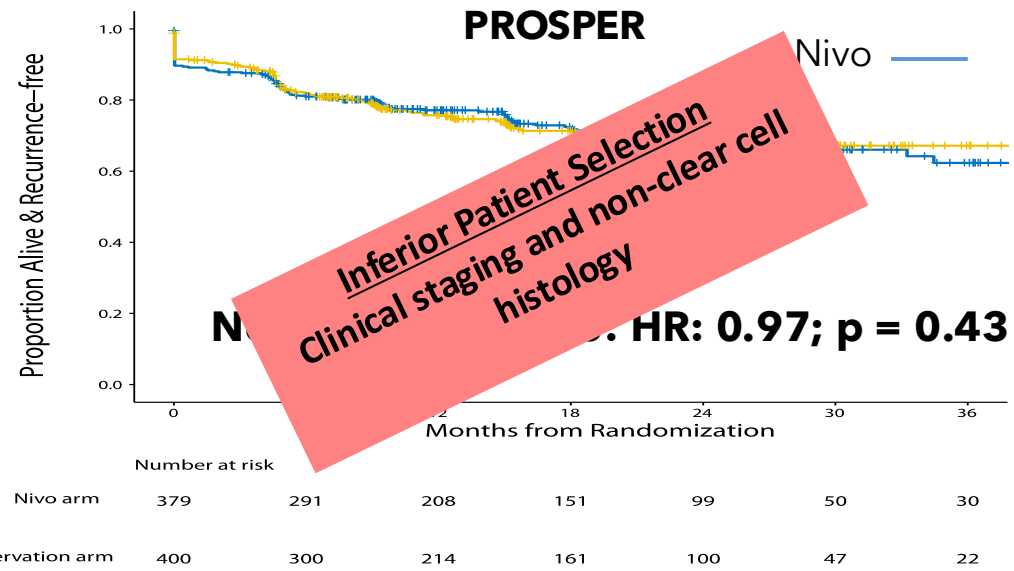


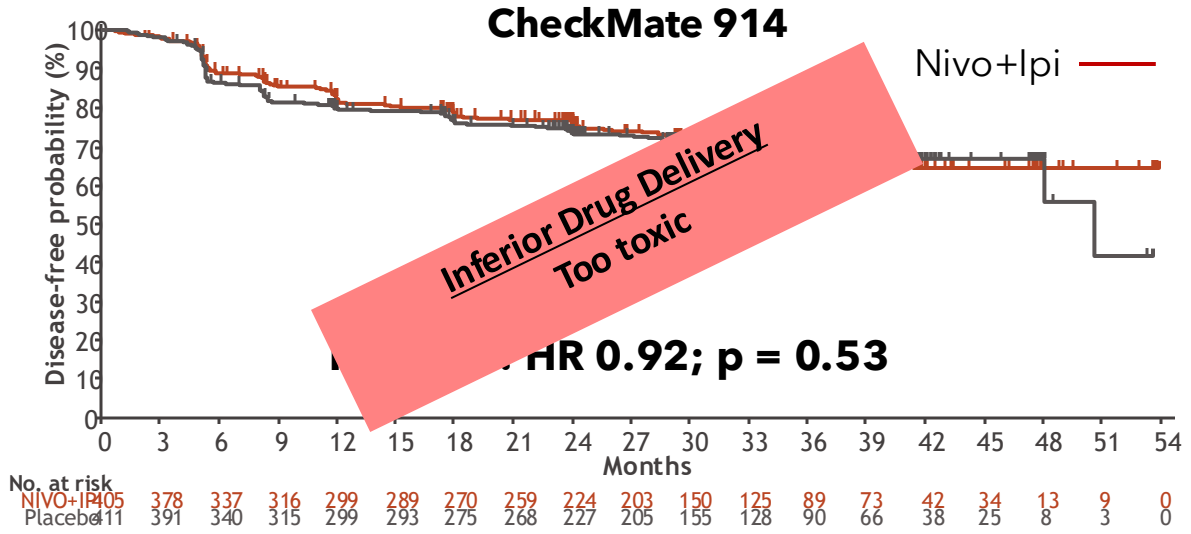
Data cutoff date: September 15, 2023.

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









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

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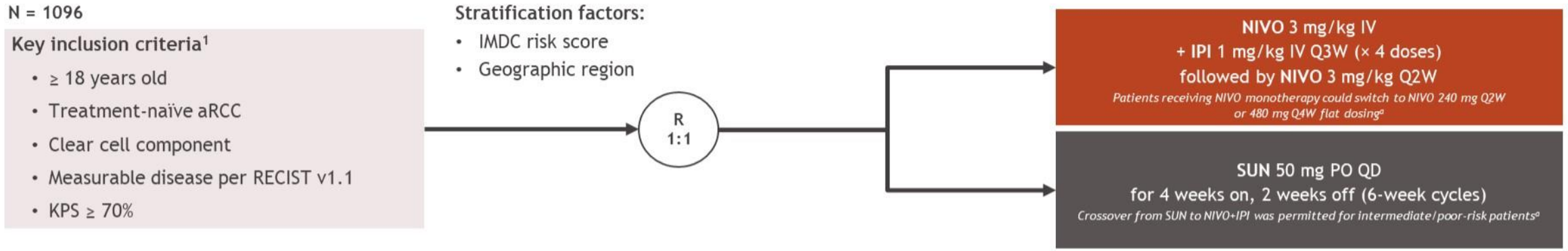
  Sustained PD1/PDL1 blockade in PD1/PDL1 refractory patients (CONTACT-03 and TiNivo-2)

Background and study design

- 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

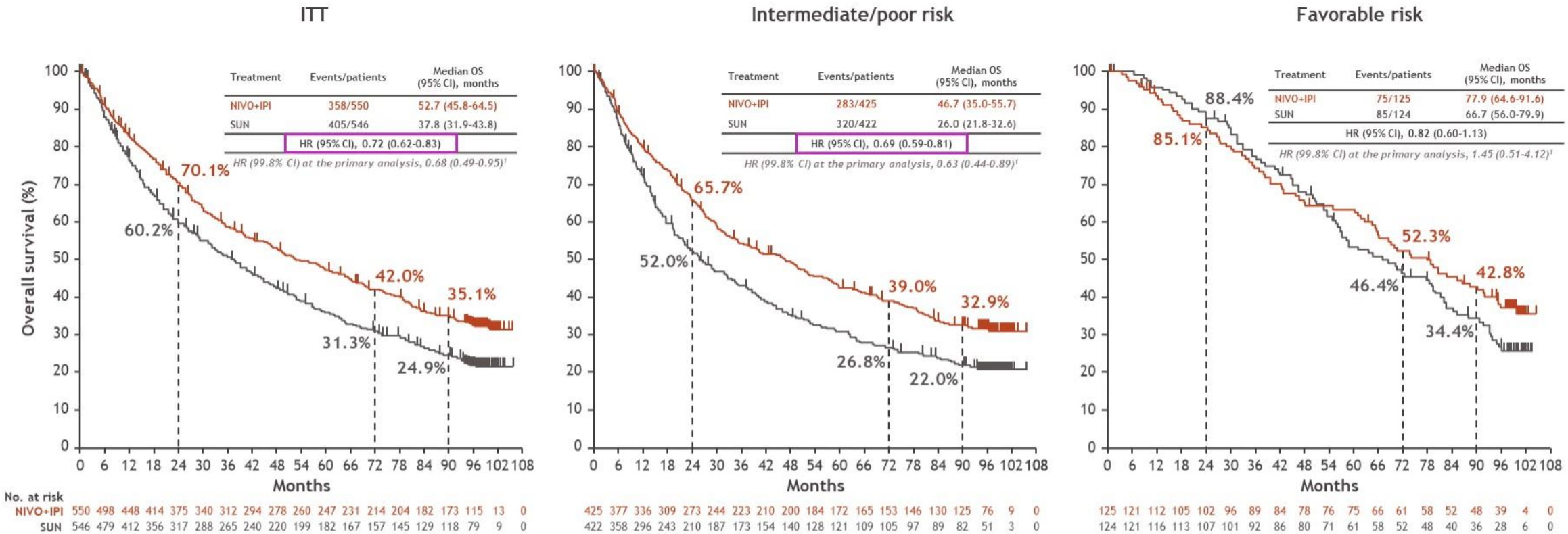
Primary endpoints: OS, PFS and ORR (both per IRRC) in IMDC intermediate/poor-risk patients
Secondary endpoints: OS, PFS and ORR (both per IRRC) in ITT patients; safety in all treated patients
Exploratory endpoints: OS, PFS and ORR (both per IRRC) in IMDC favorable-risk patients

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

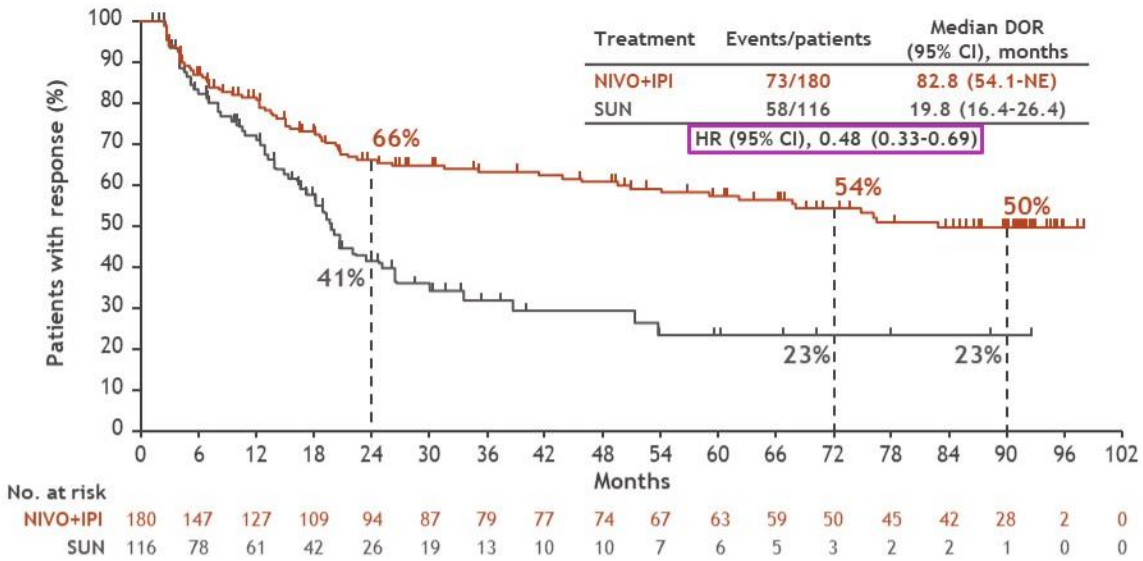


Stratified Cox proportional hazards model.

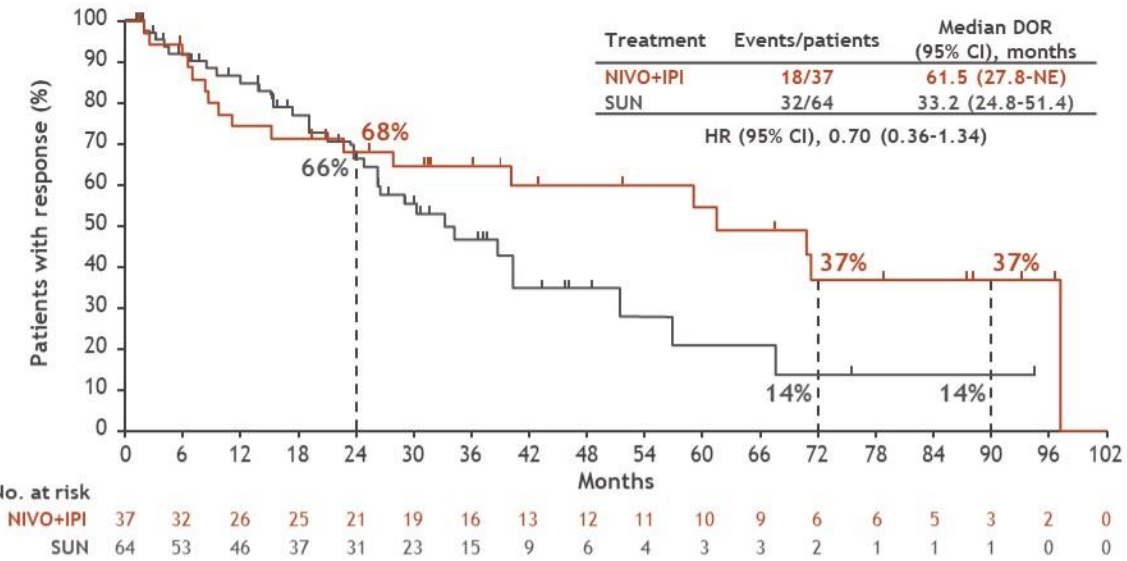
1. Motzer RJ, et al. *N Engl J Med* 2018;378:1277-1290.

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

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.

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  CheckMate 214 – good risk cohort with 99-month FU (ASCO GU24)

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  Sustained PD1/PDL1 blockade in PD1/PDL1 refractory patients (CONTACT-03 and TiNivo-2)

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

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.

Choueiri et al. ASCO 2023

Baseline demographics and characteristics

Characteristic	Atezo + Cabo (n=263)	Cabo (n=259)
Age, median (range), y	62 (20-85)	63 (18-89)
Male sex, n (%)	204 (77.6)	197 (76.1)
Race, n (%)		
White	219 (83.3)	213 (82.2)
Asian	33 (12.5)	23 (8.9)
Other	11 (4.2)	23 (8.9)
Most recent line of immune checkpoint inhibitor therapy, n (%)[a]		
Adjuvant	1 (0.4)	1 (0.4)
Locally advanced or metastatic; first line	144 (54.8)	132 (51.0)
Locally advanced or metastatic; second line	118 (44.9)	124 (47.9)
Histology, n (%)[b]		
Dominant clear cell without sarcomatoid	207 (78.7)	200 (77.2)
Dominant non-clear cell without sarcomatoid	30 (11.4)	31 (12.0)
Any sarcomatoid	25 (9.5)	28 (10.8)
IMDC score, n (%)[c]		
0	49 (18.6)	69 (26.6)
1-2	172 (65.4)	153 (59.1)
≥3	41 (15.6)	36 (13.9)
Prior VEGFR-TKI use, n (%)		
0	93 (35.4)	95 (36.7)
1	166 (63.1)	159 (61.4)
2	4 (1.5)	5 (1.9)

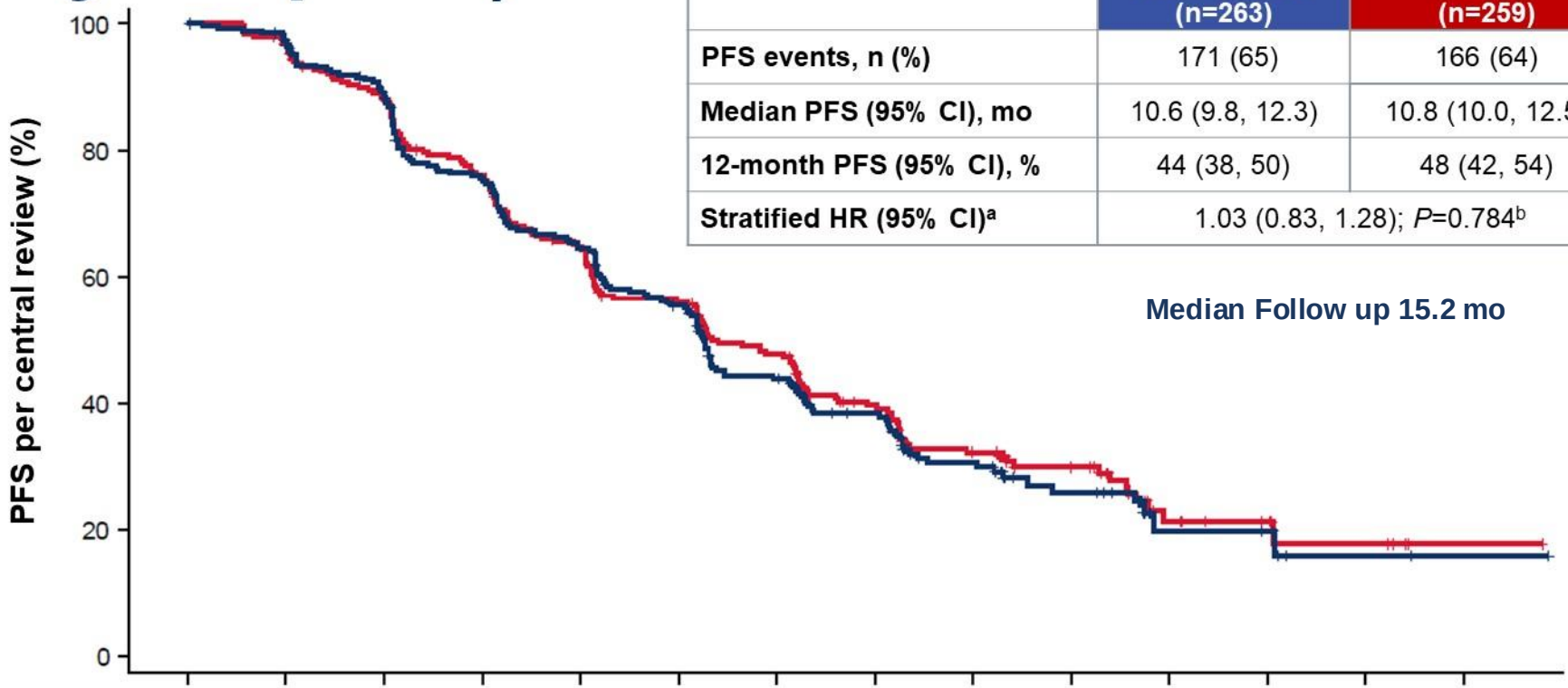
[a] In the Cabo arm, 2 patients had no most recent ICI. [b] In the Atezo + Cabo arm, 1 patient had missing histology. [c] In each arm, there was 1 patient with missing IMDC score.

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



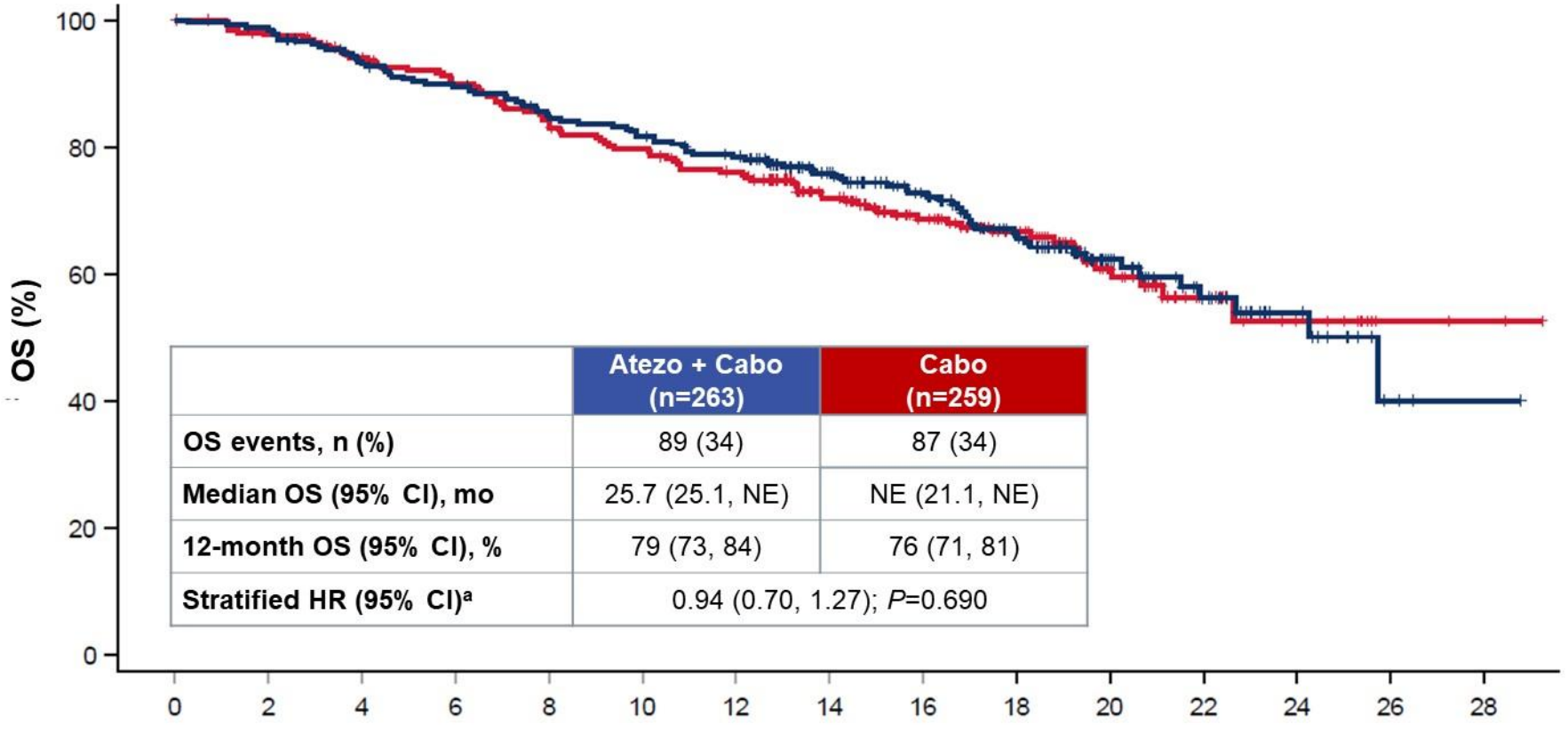
Number at risk

Atezo + Cabo	263	253	226	188	158	133	100	68	43	22	7	6	2	1
Cabo	259	242	216	183	153	130	109	71	52	34	12	8	5	1

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

Choueiri et al. ASCO 2023

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.

Choueiri et al. ASCO 2023

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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Safety Summary

	Atezolizumab plus cabozantinib group (n=262)	Cabozantinib group (n=256)
Any-cause adverse event	262 (100%)	254 (99%)
Any-cause adverse event related to treatment	252 (96%)	249 (97%)
Grade 3 or 4 adverse event	177 (68%)	158 (62%)
Grade 3 or 4 adverse event related to treatment	145 (55%)	121 (47%)
Death due to adverse event	17 (6%)	9 (4%)
Death due to adverse event related to treatment	3 (1%)	0
Serious adverse event	126 (48%)	84 (33%)
Serious adverse event related to treatment	63 (24%)	30 (12%)
Adverse event leading to withdrawal from a trial drug	41 (16%)	10 (4%)
Adverse event leading to withdrawal from atezolizumab	29 (11%)	0
Adverse event leading to withdrawal from cabozantinib	25 (10%)	10 (4%)
Adverse event leading to interruption or reduction of a trial drug	240 (92%)	223 (87%)
Adverse event leading to interruption of atezolizumab	159 (61%)	0
Adverse event leading to interruption or reduction of cabozantinib	234 (89%)*	223 (87%)†

Pal, SK et al. Lancet (2023) 402:185-95

TiNivo-2: Study Scheme

- Subjects with advanced clear cell renal cell carcinoma (RCC) who have had 1 or 2 prior lines of therapy, one of which was an immune checkpoint inhibitor (ICI)
  - Previous nivolumab is allowed
- Stratified by IMDC risk category and prior therapy with ICI in or not in the most recent line

N = 326

RANDOMIZE 1:1

Tivozanib 0.89 mg PO D1-21
No Treatment D22-28
Nivolumab 480 mg IV D1
(N = 163)

Cycles will be 28 days in duration

Tivozanib 1.34 mg PO D1-21
No Treatment D22-28
(N = 163)

Endpoints

- Primary: PFS by IRC
- Secondary: OS, ORR, DOR, Safety and Tolerability
- Exploratory: FKSI-DRS, EORTC QLQ-C30, PK

IRC, Independent Review Committee; FKSI-DRS, Functional Assessment of Cancer Therapy-Kidney Symptom Index-Disease-related Symptoms; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire
www.clinicaltrials.gov/NCT04987203

Treat until progression

Subjects with documented stable disease or an objective response may continue to receive tivozanib therapy at the same dose and schedule until progression.

Nivolumab will be discontinued in all subjects after 2 years.

TiNivo-2 First Look

- Press Release July 18, 2024:
  - The primary endpoint (PFS) was not met
  - Tivozanib monotherapy (control arm) results provide clinically meaningful efficacy and safety data following front-line ICI combinations
  - Safety results reinforce tivozanib is well-tolerated
- Data to be presented at ESMO 2024

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
- Await more complete TiNivo-2 analysis
  - PD1 vs PDL1 blockade
  - IO rechallenge after a delay
- Recall 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

UW Medicine and
Fred Hutchinson Cancer Center

Thank you for your attention