Overall Survival with Adjuvant Pembrolizumab in Renal-Cell Carcinoma

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Overall Survival Results From the Phase 3 KEYNOTE-564 Study of Adjuvant Pembrolizumab Versus Placebo for the Treatment of Clear Cell Renal Cell Carcinoma

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The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 18, 2024 VOL. 390 NO. 15

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ABSTRACT

BACKGROUND

Adjuvant pembrolizumab therapy after surgery for renal-cell carcinoma was approved on the basis of a significant improvement in disease-free survival in the KEYNOTE-564 trial. Whether the results regarding overall survival from the third prespecified interim analysis of the trial would also favor pembrolizumab was uncertain.

METHODS

In this phase 3, double-blind, placebo-controlled trial, we randomly assigned (in a 1:1 ratio) participants with clear-cell renal-cell carcinoma who had an increased risk of recurrence after surgery to receive pembrolizumab (at a dose of 200 mg) or placebo every 3 weeks for up to 17 cycles (approximately 1 year) or until recurrence, the occurrence of unacceptable toxic effects, or withdrawal of consent. A significant improvement in disease-free survival according to investigator assessment (the primary end point) was shown previously. Overall survival was the key secondary end point. Safety was a secondary end point.

RESULTS

A total of 496 participants were assigned to receive pembrolizumab and 498 to receive placebo. As of September 15, 2023, the median follow-up was 57.2 months. The disease-free survival benefit was consistent with that in previous analyses (hazard ratio for recurrence or death, 0.72; 95% confidence interval [CI], 0.59 to

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Choueiri can be contacted at toni_choueiri@dfci.harvard.edu or at Dana–Farber Cancer Institute, 450 Brookline Ave., Boston, MA 02215.

*A full list of the KEYNOTE-564 Investigators is provided in the Supplementary Appendix, available at NEJM.org.

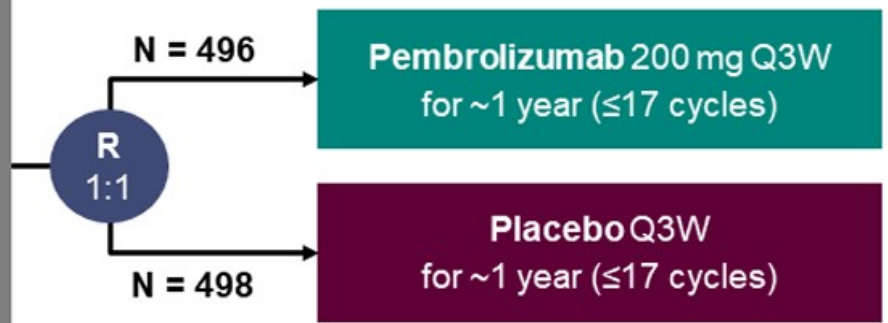
N Engl J Med 2024;390:1359-71.
DOI: 10.1056/NEJMoa2312695

CME

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.

KEYNOTE-564: Prespecified Disease Risk Categories[1,2]

Intermediate-High Risk	High Risk	M1 NED
pT2 with Grade 4 or sarcomatoid, N0, M0	pT4, any grade, N0, M0	M1 No Evidence of Disease
pT3, any grade, N0, M0	Any pT, any grade with node positive, M0	

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1. Keytruda Prescribing Information, MSDIN 06/23 2. Choueiri TK et al. *N Engl J Med*. 2021;385(8):683–694.

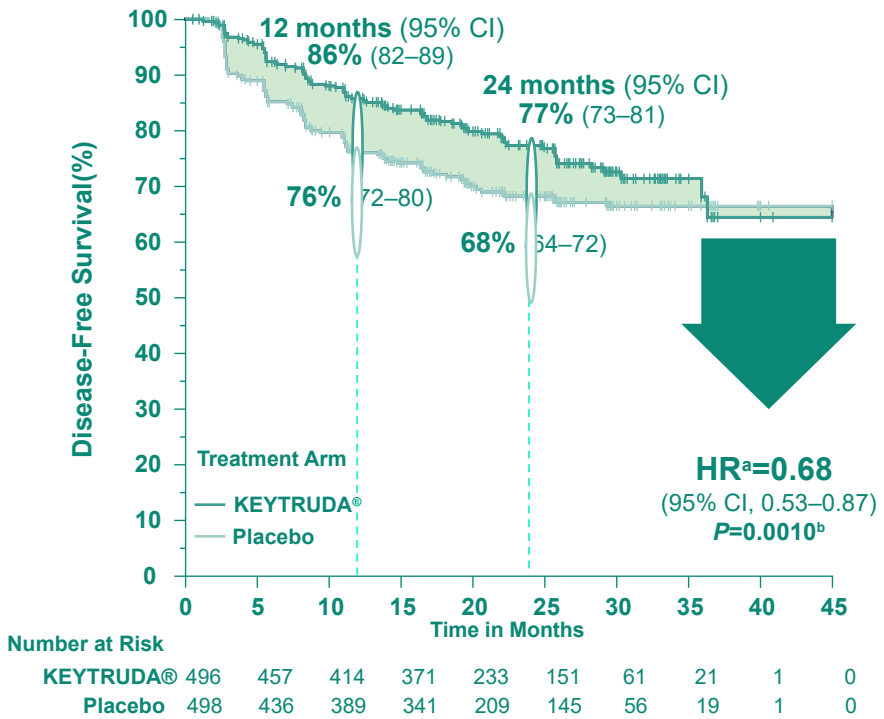
M1: Distant metastasis; M0: Distant metastases; NED: No evidence of disease; N0: Nodal involvement; pT: Pathological stage.

Baseline Characteristics

	Pembrolizumab (N = 496)	Placebo (N = 498)
Age, median (range), yrs	60 (27–81)	60 (25–84)
Male	70.0%	72.1%
ECOG performance status of 0	84.9%	85.5%
Region		
United States (US)	23.0%	23.5%
Outside US	77.0%	76.5%
M stage		
M0	94.2%	94.4%
M1	5.8%	5.6%
Disease risk category[a]		
M0 intermediate-high risk	85.1%	86.9%
M0 high risk	8.1%	7.4%
M1 NED	5.8%	5.6%
Sarcomatoid features		
Present	10.5%	11.8%
Absent	83.5%	83.3%
Unknown	6.0%	4.8%
PD-L1 status[b]		
CPS <1	25.0%	22.7%
CPS ≥1	73.6%	76.9%
Missing	1.4%	0.4%

KEYNOTE-564: Superior DFS With KEYTRUDA® vs. Placebo (Primary End Point)[1,2]

Kaplan-Meier Estimates for DFS[2]



Superior DFS vs. Placebo[1,2]

- KEYTRUDA® reduced the risk of disease recurrence or death by 32% compared with placebo.
- The events observed were 109/496 (22%) with KEYTRUDA® vs. 151/498 (30%) with placebo.
- The median DFS had not been reached for either treatment group.
- The median follow-up time was 23.9 months (range: 2.5 to 41.5 months).
- At the time of analysis, OS results were not yet mature, with 18 deaths out of 496 patients in the KEYTRUDA® arm and 33 deaths out of 498 patients in the placebo arm.

[a]Based on the stratified Cox proportional hazard model.[1] [b]Based on stratified log-rank test.[1]

KEY-01063 18/09/2023 02/08/2025

1. Keytruda Prescribing Information, MSDIN 06/23. 2. Choueiri TK et al. *N Engl J Med*. 2021;385(8):683–694.

CI: Confidence interval; DFS: Disease-free survival; HR: Hazard ratio; OS: Overall survival.

KEYNOTE-564: Superior DFS With KEYTRUDA® vs. Placebo (Primary End-Point)

	KEYTRUDA® Q3W n=496	**Placebo Q3W** n=498
DFS		
Number (%) of patients with event	109 (22%)	151 (30%)
Median in months (95% CI)	NR	NR
Hazard ratio[a] (95% CI)	0.68 (0.53–0.87)	
P value	0.0010[b]	
Estimated 12 months DFS rate (95% CI)	86% (82–89)	76% (72–80)
Estimated 18 months DFS rate (95% CI)	82% (78–85)	72% (68–76)
Estimated 24 months DFS rate (95% CI)	77% (73–81)	68% (64–72)

a. Based on the stratified Cox proportional hazard model. b. Based on stratified log-rank test.

The median follow-up time was 23.9 months (range 2.5 to 41.5 months).

CI: Confidence interval; DFS: Disease-free survival; NR: Not reached; Q3W: Every 3 weeks.

1. Keytruda Prescribing Information, MSDIN 06/23

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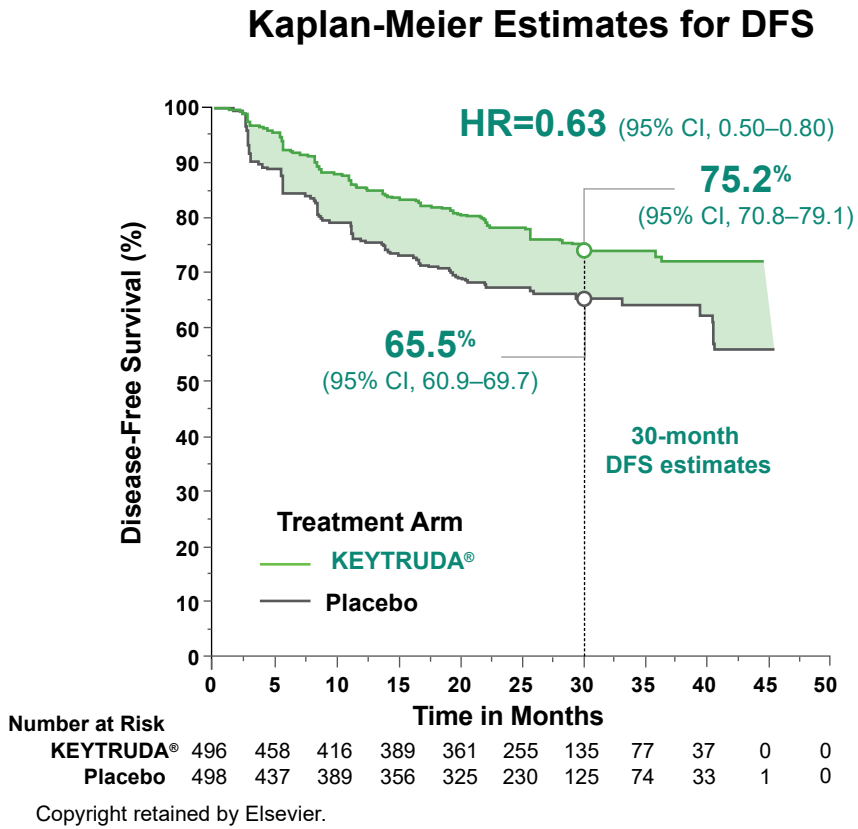
KEYNOTE-564: Follow-Up Exploratory Analysis – Median 30-Month Kaplan-Meier Estimates of DFS with KEYTRUDA® vs. Placebo[1]



DFS: KEYTRUDA® vs. Placebo

The HR for DFS was 0.63 (95% CI, 0.50–0.80) in favor of KEYTRUDA®.

The events observed were 114/496 (23%) with KEYTRUDA® vs. 169/498 (34%) with placebo

The estimated 30-month DFS rates were 75.2% with KEYTRUDA® and 65.5% with placebo.

The median DFS was not reached for either treatment group.

Median time from randomization to data cutoff was 30.1 months (IQR: 25.7–36.7 months).

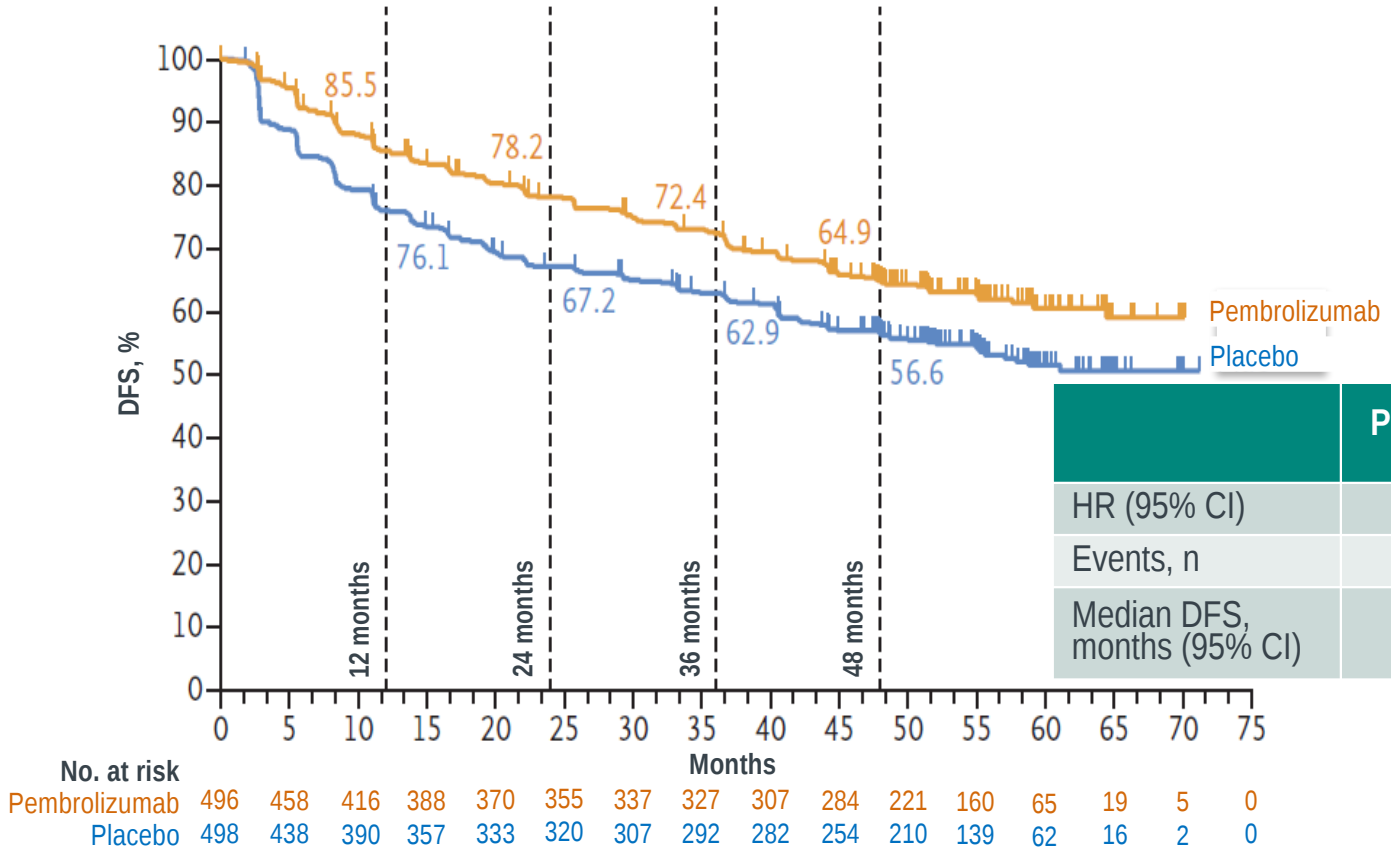
LIMITATION: No formal statistical testing was performed for the updated analysis and, therefore, no conclusions can be drawn.

1. Powles T et al. *Lancet Oncol.* 2022;23(9):1133–1144.

CI: Confidence interval; DFS: Disease-free survival; HR: Hazard ratio; IQR: Interquartile range; OS: Overall survival.

KEYNOTE-564: DFS in the ITT Population by Investigator Assessment

Median follow-up: 57.2 months



	Pembrolizumab n=496	Placebo n=498
HR (95% CI)	0.72 (0.59–0.87)	
Events, n	174	224
Median DFS, months (95% CI)	NR (NR–NR)	NR (54.9–NR)

DFS was met at the first prespecified interim analysis and was not formally statistically tested thereafter.
Data cutoff date: September 15, 2023.
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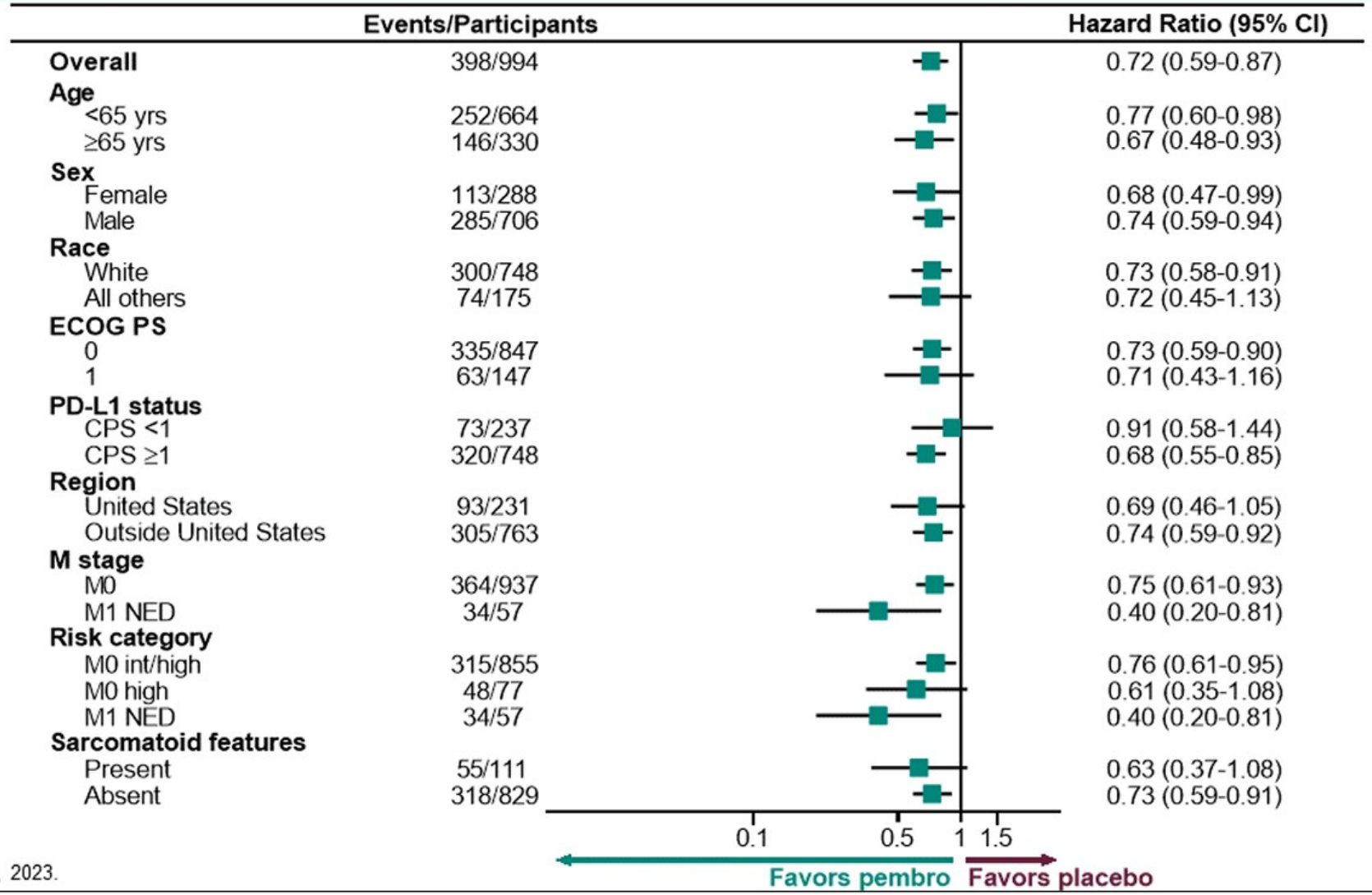
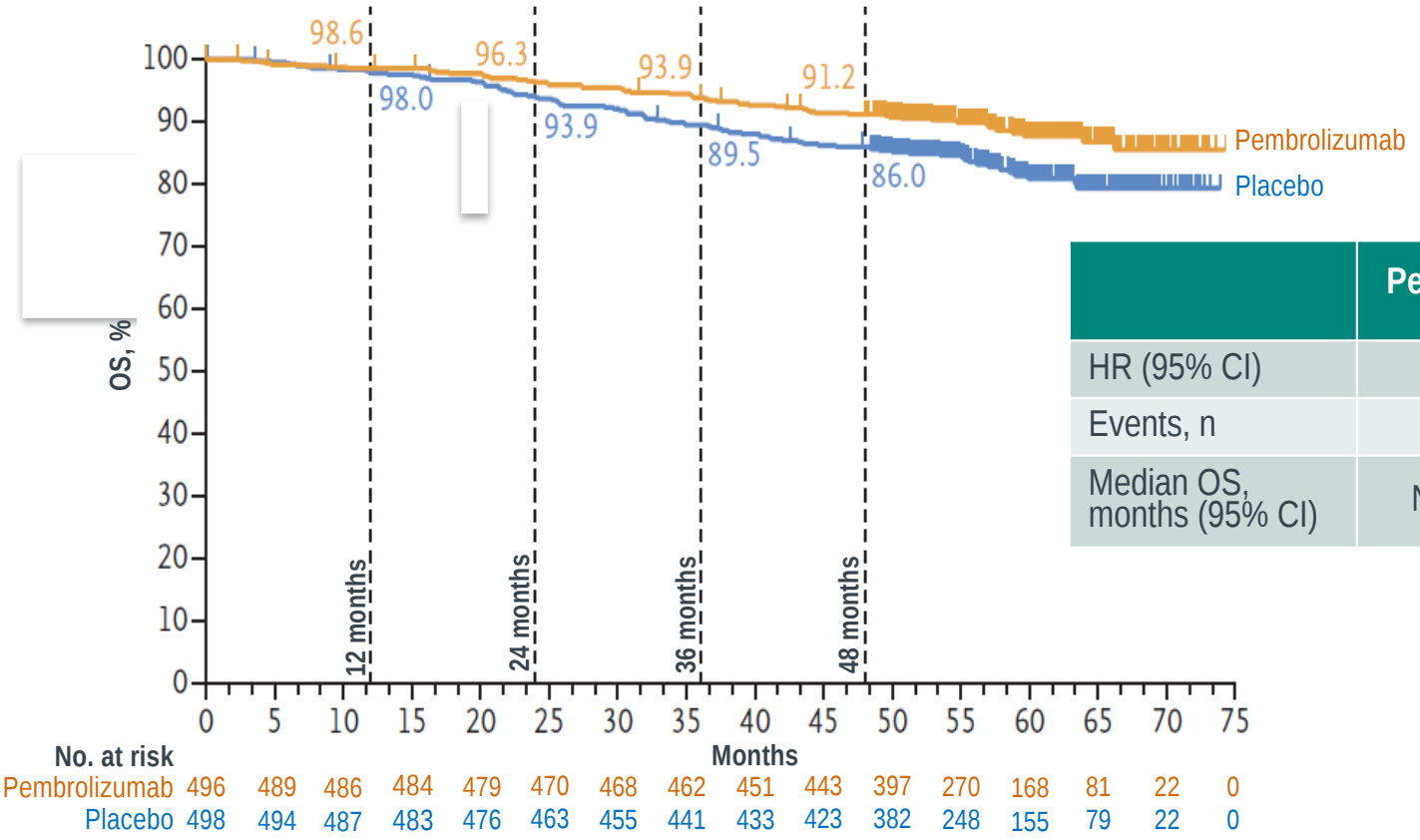
Disease-Free Survival by Subgroups



ta cutoff date: September 15, 2023.

KEYNOTE-564: OS in the ITT Population

Median follow-up: 57.2 months



	Pembrolizumab n=496	Placebo n=498
HR (95% CI)	0.62 (0.44–0.87); *P*=0.005[a]	
Events, n	55	86
Median OS, months (95% CI)	NR (NR–NR)	NR (NR–NR)

[a]*P* value boundary for significant OS improvement at the third prespecified interim analysis was 0.0144 (2-sided) reported in accordance with the journal policy, despite the study protocol specification to report 1-sided *P* values.
Data cutoff date: September 15, 2023.

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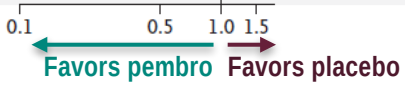
KEYNOTE-564: OS in Subgroups

Median follow-up: 57.2 months

Subgroup	Pembrolizumab	Placebo	Hazard Ratio for Death (95% CI)
	no. of deaths/no. of participants		
Overall	55/496	86/498	0.62 (0.44–0.87)
Age			
<65 yr	25/338	46/326	0.51 (0.31–0.83)
≥65 yr	30/158	40/172	0.77 (0.48–1.23)
Sex			
Female	20/149	18/139	1.08 (0.57–2.04)
Male	35/347	68/359	0.50 (0.33–0.75)
Race			
White	46/372	67/376	0.67 (0.46–0.98)
Other	6/88	13/87	0.45 (0.17–1.20)
ECOG performance-status score			
0	38/421	67/426	0.55 (0.37–0.82)
1	17/75	19/72	0.84 (0.44–1.63)
PD-L1 combined positive score			
<1	12/124	16/113	0.65 (0.31–1.38)
≥1	42/365	69/383	0.62 (0.42–0.91)
Geographic region			
United States	11/114	16/117	0.68 (0.32–1.47)
Other	44/382	70/381	0.61 (0.42–0.88)
Metastatic staging			
M0	51/467	79/470	0.63 (0.44–0.90)
M1 NED	4/29	7/28	0.51 (0.15–1.75)
Disease risk category			
M0 intermediate-to-high risk	41/422	69/433	0.59 (0.40–0.87)
M0 high risk	9/40	10/37	0.78 (0.32–1.93)
M1 NED	4/29	7/28	0.51 (0.15–1.75)
Sarcomatoid features			
Present	8/52	12/59	0.69 (0.28–1.70)
Absent	41/414	70/415	0.57 (0.39–0.84)



Data cutoff date: September 15, 2023.

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KEYNOTE-564: Subsequent Therapies in the ITT Population

Median follow-up: 57.2 months

n/N (%)	Patients with documented recurrence	
	Pembrolizumab n=161	Placebo n=210
Received any subsequent therapy[a,b]	128/161 (79.5)	171/210 (81.4)
Received systemic anticancer drug therapy	105/132 (79.5)	145/172 (84.3)
Anti–PD-1/PD-L1 therapy[c]	43/105 (41.0)	101/145 (69.7)
VEGF/VEGFR inhibitor[d]	97/105 (92.4)	123/145 (84.8)
Other[e]	32/105 (30.5)	60/145 (41.4)
Received radiation therapy	32/132 (24.2)	34/172 (19.8)
Received surgery	36/132 (27.3)	50/172 (29.1)

[a]An additional 4 and 1 patients in the pembrolizumab and placebo arms, respectively, who were not included in the table received subsequent therapy without documented recurrence. [b]Patients could have received multiple subsequent anticancer therapies for RCC; each patient was counted once in each applicable category. [c]Atezolizumab, avelumab, durvalumab, nivolumab, pembrolizumab. [d]Axitinib, bevacizumab, cabozantinib, lenvatinib, pazopanib, sorafenib, sunitinib, tivozanib. [e]Included but was not limited to belzutifan, everolimus, and ipilimumab.

Data cutoff date: September 15, 2023.

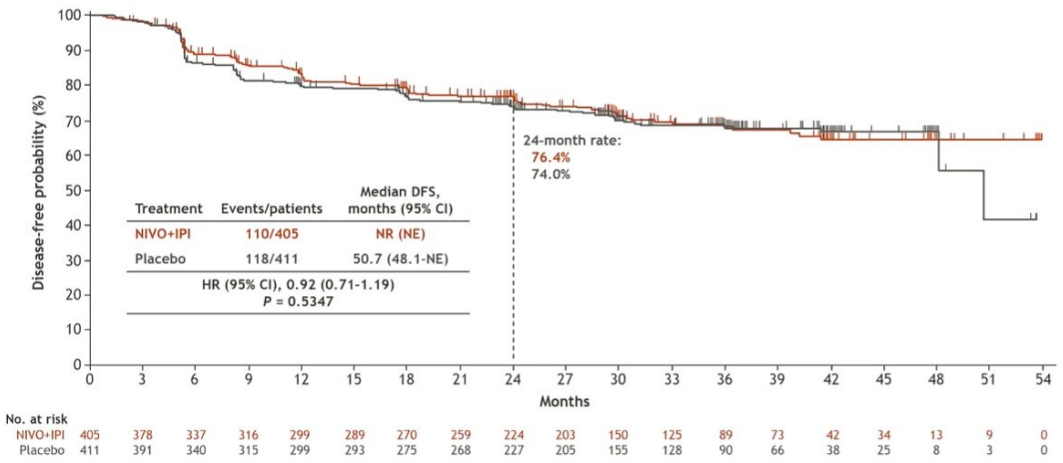
Choueiri TK et al. *N Engl J Med.* 2024;390(15):1359–1371.

Summary of Updated Safety Findings, As-Treated Population

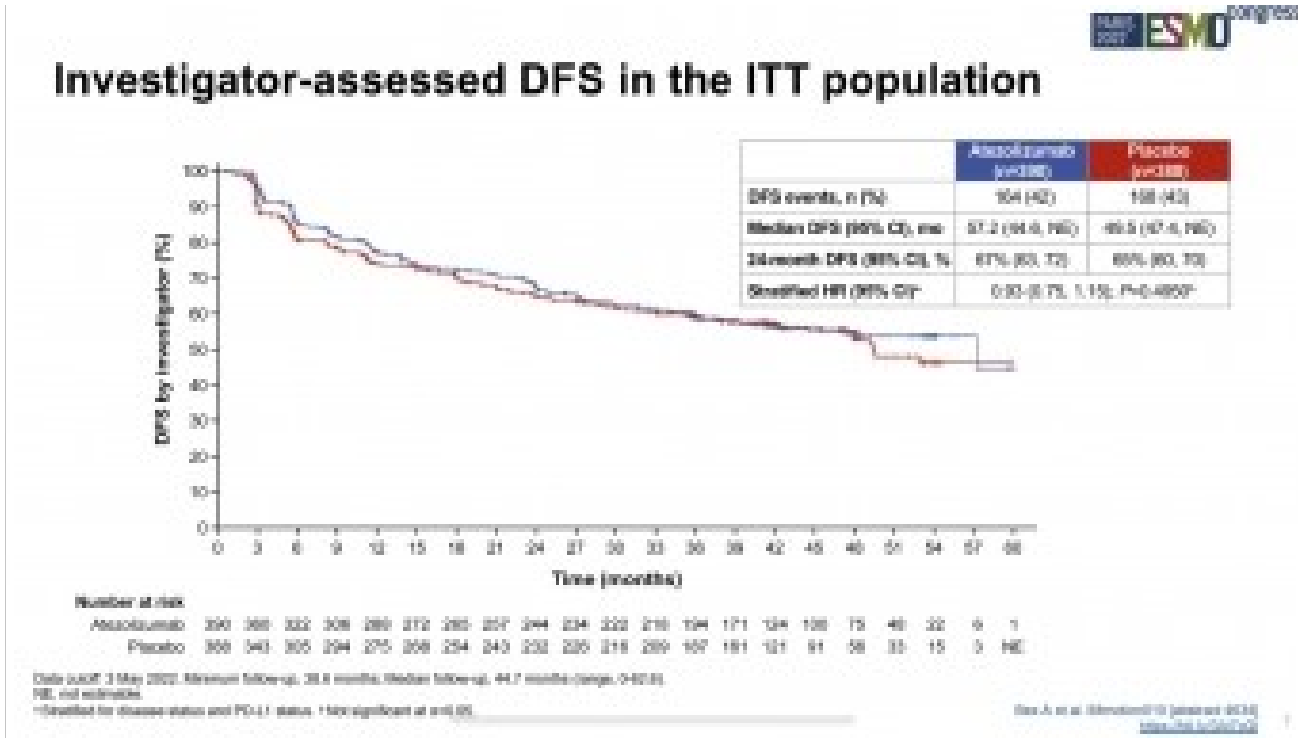
	Prior Analysis (30.1 mo follow-up)		IA3 (57.2 mo follow-up)	
	Pembrolizumab (N = 488)	Placebo (N = 496)	Pembrolizumab (N = 488)	Placebo (N = 496)
Duration of therapy, median (range), months	11.1 (0.03–14.3)	11.1 (0.03–15.4)	11.1 (0.03–14.3)	11.1 (0.03–15.4)
Any-cause AEs[a]	470 (96.3%)	453 (91.3%)	470 (96.3%)	453 (91.3%)
Grade 3 to 5	157 (32.2%)	88 (17.7%)	156 (32.0%)	88 (17.7%)
Led to treatment discontinuation	103 (21.1%)	11 (2.2%)	103 (21.1%)	11 (2.2%)
Led to death	2 (0.4%)	1 (0.2%)	2 (0.4%)	1 (0.2%)
Serious AEs[a]	101 (20.7%)	57 (11.5%)	101 (20.7%)	57 (11.5%)
Led to treatment discontinuation	49 (10.0%)	5 (1.0%)	49 (10.0%)	5 (1.0%)
Treatment-related AEs[a]	386 (79.1%)	265 (53.4%)	386 (79.1%)	265 (53.4%)
Grade 3 to 4	91 (18.6%)	6 (1.2%)	91 (18.6%)	6 (1.2%)
Led to treatment discontinuation	89 (18.2%)	4 (0.8%)	89 (18.2%)	4 (0.8%)
Led to death	0	0	0	0
Immune-mediated AEs and infusion reactions[b]	174 (35.7%)	34 (6.9%)	178 (36.5%)	36 (7.3%)
Grade 3 to 4	45 (9.2%)	3 (0.6%)	46 (9.4%)	3 (0.6%)
Led to death	0	0	0	0
Required high-dose (≥40 mg/day) systemic corticosteroids	37 (7.6%)	3 (0.6%)	37 (7.6%)	3 (0.6%)

AEs were graded per the NCI CTCAE v4.0 and reported from randomization to 30 days (90 days for serious AEs) after study therapy discontinuation. [b]Based on a list of preferred terms intended to

CheckMate 914



IMmotion010



- CheckMate914 trial and IMmotion010 trial.
- Both failed to achieve any DFS benefit
- In CheckMate914 - Adjuvant Nivolumab plus Ipilimumab was for 6 months
- IMmotion010- small number of participants with non–clear-cell re nal-cell carcinoma were enrolled
- Furthermore, the proportion of participants with M1 NED status was higher in the IMmotion010 trial

Conclusions

- Adjuvant pembrolizumab significantly prolonged overall survival versus placebo in participants with clear cell RCC at increased risk of recurrence following surgery
  - 38% reduction in risk of death with adjuvant pembrolizumab versus placebo
  - Survival benefit was seen across key subgroups
- Continued disease-free survival benefit with pembrolizumab versus placebo was observed with further follow-up
- All participants completed or discontinued study therapy by December 2020; safety findings did not change substantially since last analysis
- KEYNOTE-564 is the first study to show a statistically significant and clinically meaningful survival improvement with an adjuvant therapy in RCC
- These results further support adjuvant pembrolizumab as a standard of care after surgery in this disease setting


Thank you