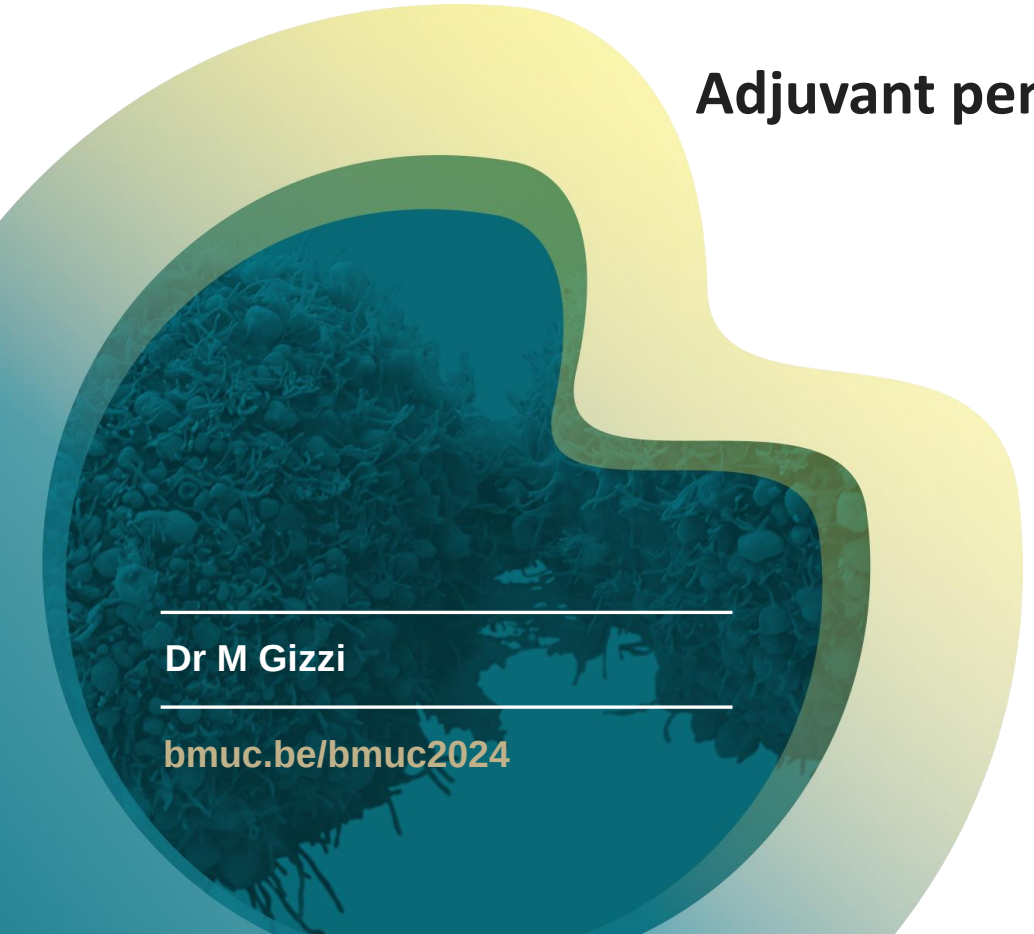
Medical Oncology
Late breaking abstract session

Adjuvant pembrolizumab in ccRCC: results from the Keynote 564 trial

Marco Gizzi



Dr M Gizzi

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Conflicts of interest

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- I have the following potential conflict(s) of interest to report

Type of affiliation / financial interest	Name of commercial company
Receipt of grants/research supports:	/
Receipt of honoraria or consultation fees:	Merck, MSD, Pfizer, Novartis, BMS, Ipsen
Participation in a company sponsored speaker's bureau:	Merck, MSD, Pfizer, Novartis, BMS, Ipsen
Stock shareholder:	/
Spouse/partner:	/
Travel fees	MSD, BMS, Pfizer, Ipsen

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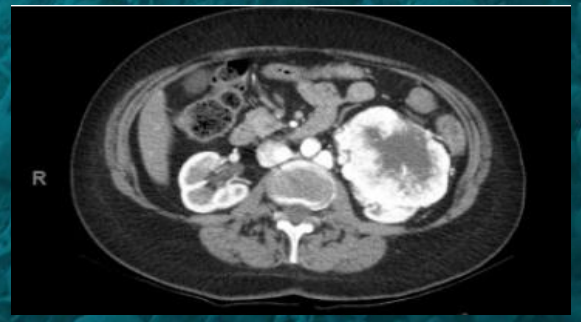
Clinical case question



- Mr X. 53y old.
- HTA, hematuria, fatigue, weight loss.
- Left Renal mass 10,6cm on CT scan.
- Left Nephrectomy: pT2 pN1(1/5) cM0 grade 3 clear cell RCC, with 20% of sarcomatoid component.

What would you propose?

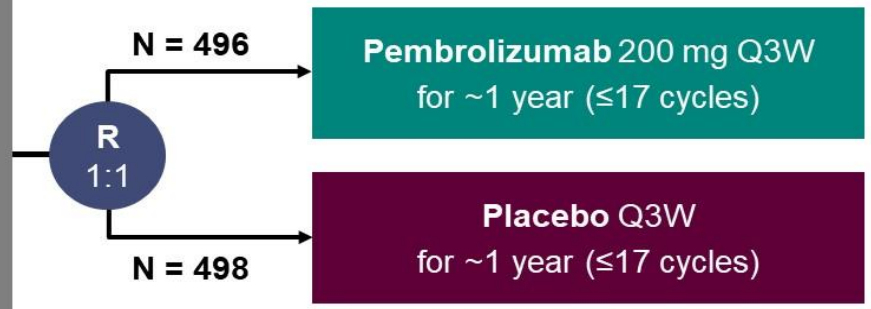
1) Observation

2) Adjuvant Pembrolizumab

Keynote 564 study

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 patient population

Intermediate-High Risk		High Risk		M1 NED
pT2	pT3	pT4	Any pT	NED after resection of oligometastatic sites ≤1 year from nephrectomy
Grade 4 or sarcomatoid	Any grade	Any grade	Any grade	
N0	N0	N0	N+	
M0	M0	M0	M0	

Failure of TKI trials

Brain & bones mets excluded

Characteristic, n (%)	Pembro N = 496	Placebo N = 498
Age, median (range), yrs	60 (27–81)	60 (25–84)
Male	347 (70.0)	359 (72.1)
ECOG PS		
0	421 (84.9)	426 (85.5)
1	75 (15.1)	72 (14.5)
Disease risk category		
M0 intermediate-high risk	427 (86.1)[a]	433 (86.9)
M0 high risk	40 (8.1)	36 (7.2)
M1 NED	29 (5.8)	29 (5.8)

Characteristic, n (%)	Pembro N = 496	Placebo N = 498
Geographic location		
North America	113 (26.8)	125 (25.1)
European Union	188 (37.9)	187 (37.6)
Rest of the world	175 (35.3)	186 (37.3)
PD-L1 status[b]		
CPS <1	124 (25.0)	113 (22.7)
CPS ≥1	365 (73.6)	383 (76.9)
Missing	7 (1.4)	2 (0.4)
Sarcomatoid features		
Present	52 (10.5)	59 (11.8)
Absent	417 (84.1)	415 (83.3)
Unknown	27 (5.4)	24 (4.8)

Intermediate-high risk: pT2, grade 4 or sarcomatoid, N0 M0; or pT3, any grade, N0 M0
High risk: pT4, any grade, N0 M0; or pT any stage, any grade, N+ M0
M1 NED: No evidence of disease after primary tumor + soft tissue metastases completely resected ≤1 year from nephrectomy
[a]Included 5 participants with T2, grade ≤3, N0 M0 or T1 N0 M0. [b]Assessed using the PD-L1 IHC 22C3 pharmDx assay. CPS (combined positive score) is the number of PD-L1–staining cells (tumor cells, lymphocytes, and macrophages) divided by the total number of viable tumor cells, multiplied by 100. Data cutoff date: December 14, 2020

Table S2. Sites of Resected Metastasis for Patients with M1 NED at Baseline, Intention-to-Treat Population.

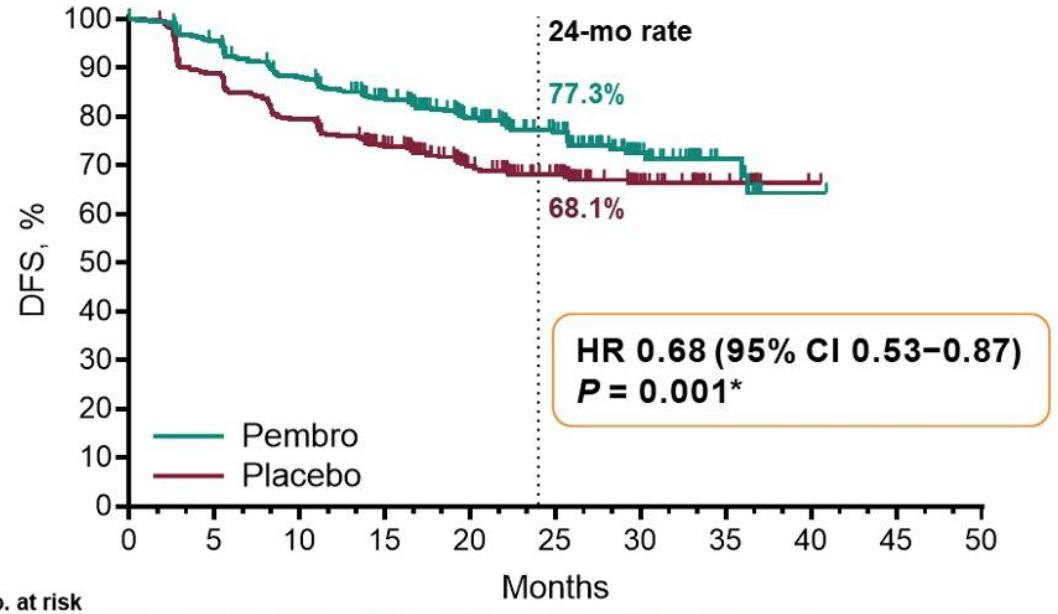
Site of metastasis—no.	Pembrolizumab N = 29*	Placebo N = 29*
Abdominal cavity	0	2
Adrenal gland	9	13
Bone†	2	0
Brain†	0	1
Contralateral kidney	1	2
Liver	1	1
Lung	8	3
Lymph node	2	5
Oral/buccal lesion	2	0
Pancreas	2	2
Retroperitoneum	1	1
Subcutaneous lesion	1	0
Testicle	1	0

*Columns may add up to more than 29 because some patients had multiple sites of metastasis.
†Brain and bone metastasis were considered protocol violations.
NED=no evidence of disease.

Choueiri et al, NEJM 2021

Keynote 564: what we knew before ASCO GU 24

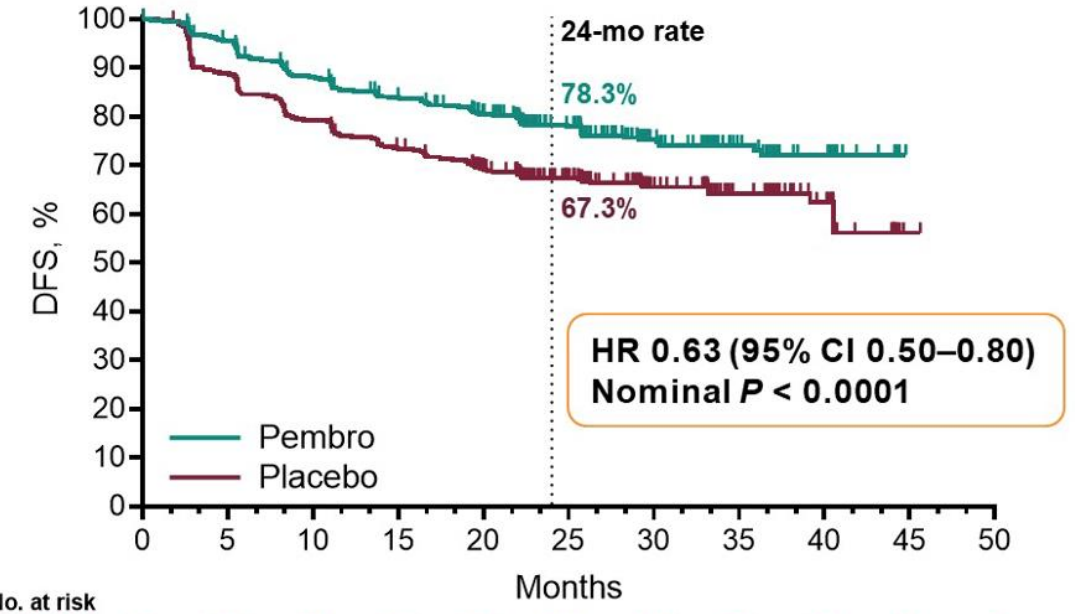
Primary Analysis: 24.1 mo Follow-Up



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

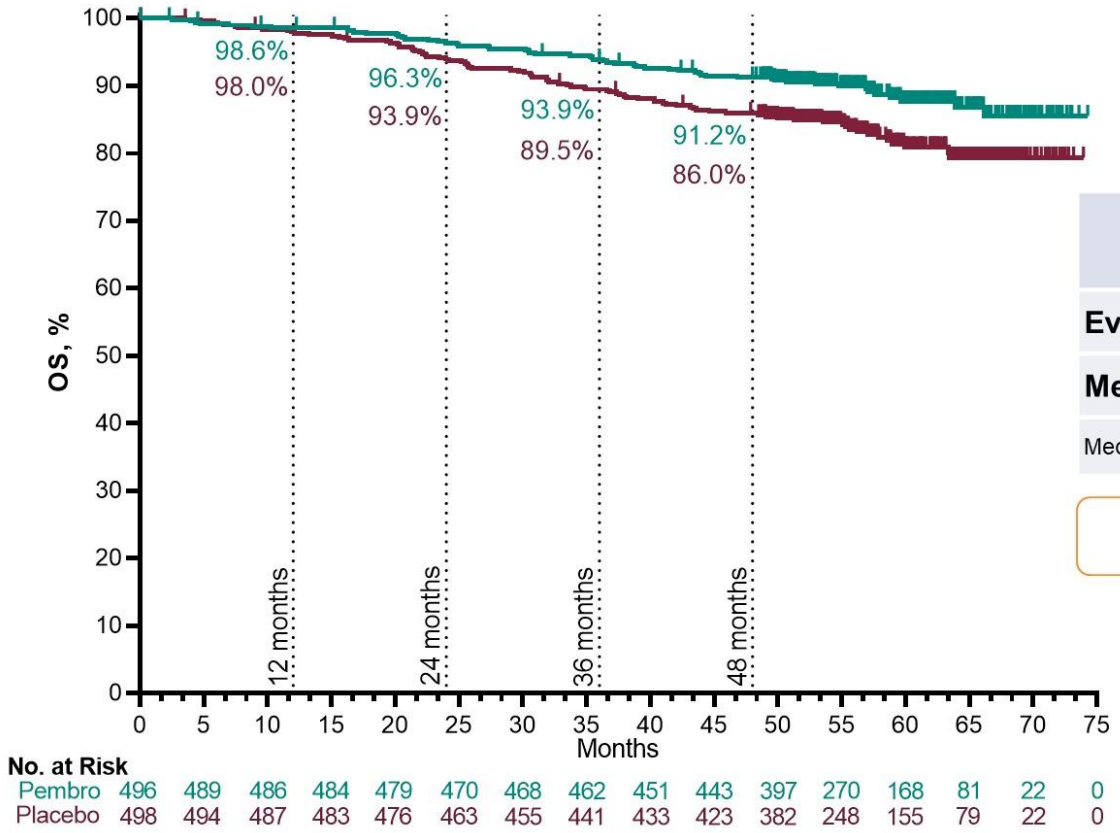
	Pts w/ Event	Median, mo (95% CI)
Pembro	114	NR (NR–NR)
Placebo	169	NR (40.5–NR)

denotes statistical significance.
TT 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.

Choueiri et al, ASCO GU 2022 Oral presentation

Keynote 564 overall survival (key secondary endpoint)

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)

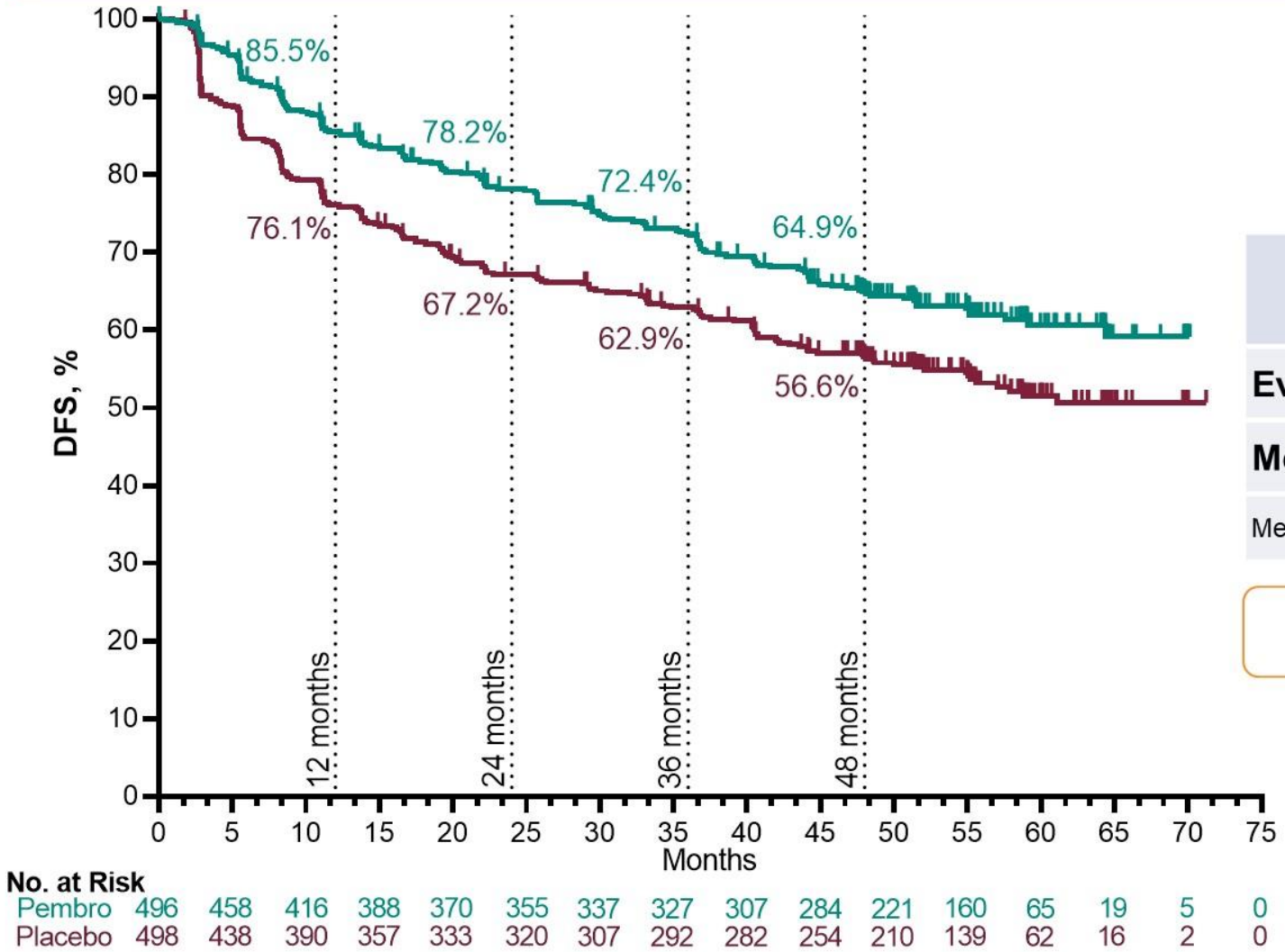
Median follow-up was 57.2 months (range, 47.9–74.5)

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)

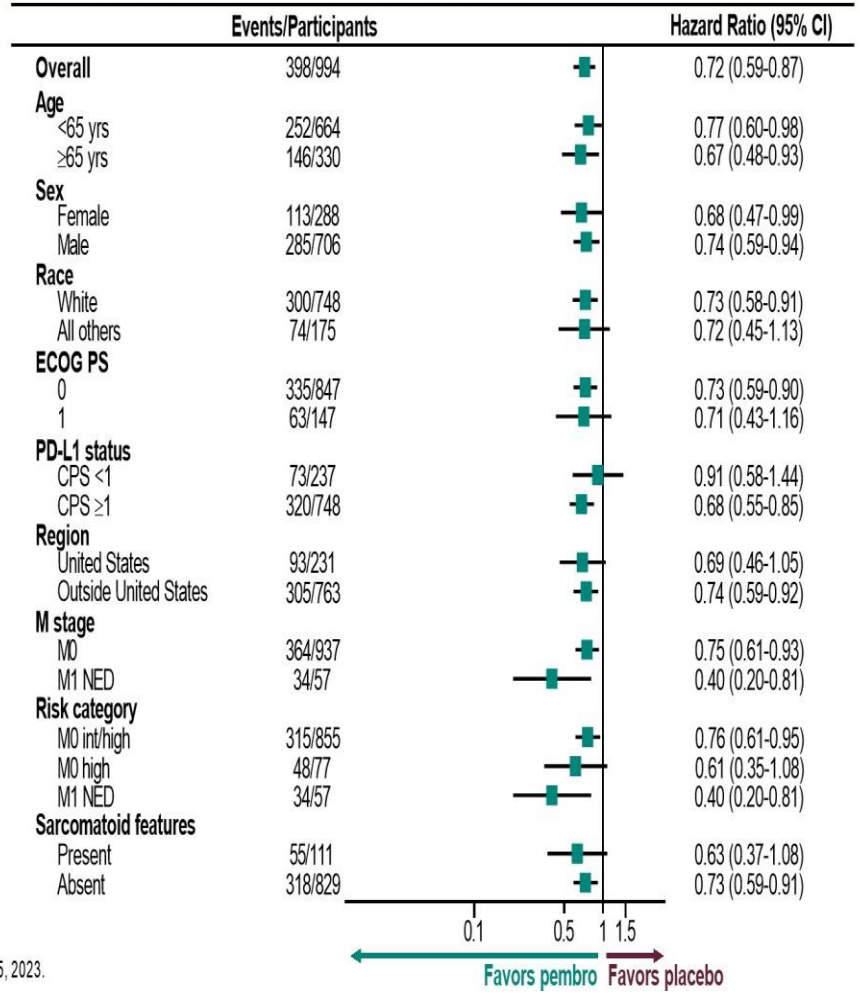
Median follow-up was 57.2 months (range, 47.9–74.5)

HR 0.72 (95% CI 0.59–0.87)

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

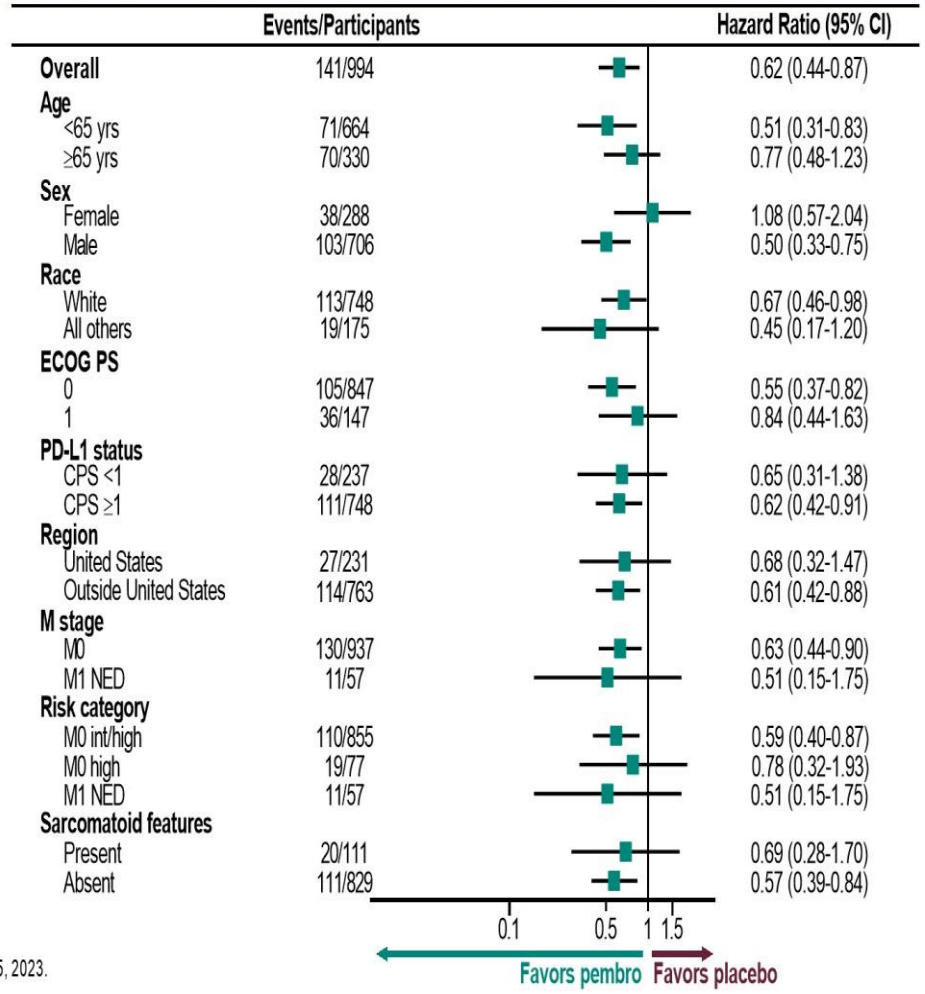
Data cutoff date: September 15, 2023.

Disease-Free Survival by Subgroups



Data cutoff date: September 15, 2023.

Overall Survival by Subgroups



Data cutoff date: September 15, 2023.

Geographic location		
North America	133 (26.8%)	125 (25.1%)
European Union	188 (37.9%)	187 (37.6%)
Rest of world	175 (35.3%)	186 (37.3%)

Choueiri et al, ASCO GU 2024 OA

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%)	263 (53.0%)
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%)

[a]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 capture known risks of pembro and were considered regardless of attribution to study treatment by the investigator.
Data cutoff date: September 15, 2023.

Subsequent Therapies, Intention-to-Treat Population

Subsequent Therapies, Intention-to-Treat Population

	Participants 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	102/128 (79.7%)	145/171 (84.8%)
Anti–PD-(L)1 therapy[c]	42/102 (41.2%)	101/145 (69.7%)
VEGF/VEGFR inhibitor[d]	94/102 (92.2%)	123/145 (84.8%)
Other[e]	32/102 (31.4%)	60/145 (41.4%)
Received radiation therapy	31/128 (24.2%)	33/171 (19.3%)
Received surgery	35/128 (27.3%)	50/171 (29.2%)
No subsequent therapy	28/161 (17.4%)	28/210 (13.3%)
No subsequent therapy data available	5/161 (3.1%)	11/210 (5.2%)

101/210 (48%) exposed to PD1 in all the trial

[a]An additional 4 and 1 pts respectively in the pembro and placebo arms who are not included in the figure received subsequent therapy without documented recurrence. [b]Pts could have multiple subsequent anticancer therapies for RCC; each pt is 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.

Some caveats about Keynote 564

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Informative censoring?

unequal dropout between the arms of the study during the early follow-up period of PFS
> lack information about recurrence for censored patients (5% vs 1%) might impact the curves [1]

Optimal post progression therapy?

101/210 in the control arm were exposed to ICI at relapse

Bad reason: Drug access availability in some countries discrepancies?

Would be of interest to see the datas of early vs delayed use of Pembrolizumab in the control arm patitents exposed to Pembro in the metastatic setting
(early vs delayed and not early vs never)

Consistency with other studies?

Nivolumab, Ipi/Nivo, Atezolizumab adjuvant trial did not met OS/PFS significant benefit

→ Need to step back and look closer to dataset

[1] Tannock I et al, JCO march 2023 Evaluating Trials of Adjuvant Therapy: Is There Benefit for People With Resected Renal Cancer? Volume 41, Number 15 • https://doi.org/10.1200/JC0.23.00280

Pending questions after Keynote 564

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What about non clear cell RCC?

Pembro vs placebo in st3 papillary RCC(NCT06146777)

No predictive tissue- or blood-based biomarkers to guide therapy selection for patients? Not all patients are benefiting from adjuvant pembrolizumab

ctDNA/Epigenomic profiling/methylated DNA (need further validation)

If disease progression develops following receipt of adjuvant checkpoint blockade, what is the optimal front-line treatment strategy for recurrent disease?

Those trials are needed

Post protocol therapy influence on OS HR ?

Need for better clarification on subsequent therapies

Post pembrolizumab adjuvant progression treatment possible algorithm

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Refractory patients
Recurrence during and in the first 3 months

- TKI alone

Early recurrence
Recurrence 3-12months after

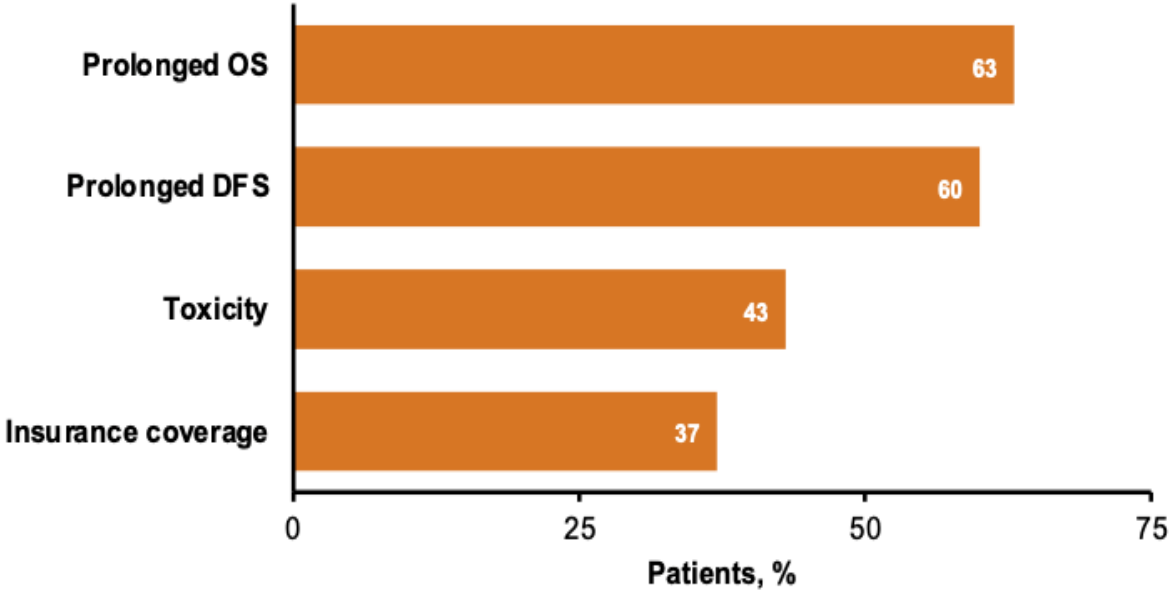
- TKI alone

Late relapse
>12months after

- ICI rechallenge (IO/IO or IO/TKI)
- TKI alone

Patient perspectives

Q. If you were able to get treatment to prevent recurrence of your kidney cancer, what would be important for you?[1,2,a]



- Patient surveys indicate that patients are willing to use adjuvant therapy if the treatment prolongs OS or DFS
- Toxicity of treatment is less important to patients than efficacy endpoints

[a] N = 450 patients with RCC.

1. Battle D et al. *J Clin Oncol.* 2018;36(6_suppl):644. 2. Battle D et al. *J Clin Oncol.* 2018;36(15_suppl):4571.

Conclusions

First trial to demonstrate an OS benefit in adjuvant treatment of ccRCC

Need for better clarification for pembrolizumab as adjuvant therapy in ccRCC
> early pembrolizumab vs delayed (>< early vs never in the control arm)
✓ Informative censoring bias
➢ Might influence the magnitude of benefit on OS HR?

Still need to better identify who really need/benefit from adjuvant Pembro and not take all patients on board (financial and physical toxicity)

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Clinical case question

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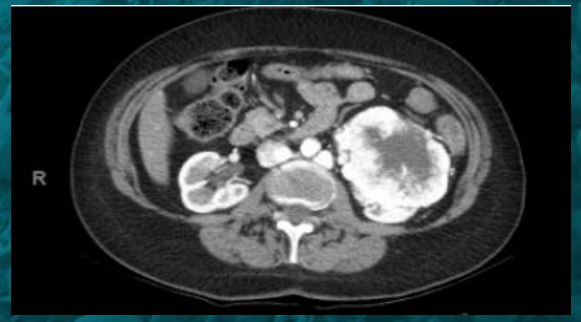

What would you propose?

1) Observation

2) Adjuvant Pembrolizumab