Vogl U. Writing History in the Adjuvant Treatment of Clear Cell Renal Cell Carcinoma (ccRCC): The Magic Goal of an Overall Survival Benefit Was Reached as Reported at ASCO GU 2024. *healthbook TIMES Onco Hema.* 2024;19(1):12-14.
doi:10.36000/HBT.OH.2024.19.133

EDITORIAL

Writing History in the Adjuvant Treatment of Clear Cell Renal Cell Carcinoma (ccRCC): The Magic Goal of an Overall Survival Benefit Was Reached as Reported at ASCO GU 2024

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https://doi.org/10.36000/HBT.OH.2024.19.133

healthbook TIMES Oncology Hematology

Vol. 19, Issue 1, 2024

Dear Colleagues,

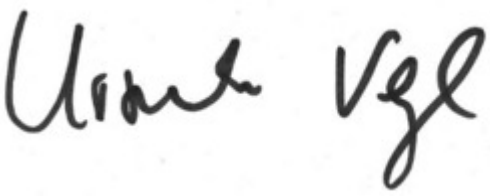
The road was rough for trials investigating adjuvant treatments in clear cell renal cell carcinoma (ccRCC). A total of 17 randomized controlled trials enrolling a total of approximately 12,000 patients that contributed to finding a treatment to help reduce the risk of recurrence and significantly prolong overall survival (OS) have failed, as the principal investigator Prof. Toni Choueiri announced introducing the oral presentation of late-breaking abstract 359 at the annual Genitourinary Cancers Symposium of the American Society of Clinical Oncology (ASCO GU 2024).[1] Interferon-alpha, three multikinase inhibitors (axitinib, pazopanib and sorafenib) and one mTOR inhibitor failed to succeed over placebo.[2-6] Only sunitinib in the phase III STRAC trial reached its primary endpoint of disease-free survival (DFS), but not OS and the rate of treatment discontinuation was excessively high, so sunitinib, although approved by the U.S. Food and Drug Administration (FDA), has never been nominated a standard of care.[7] At the end of 2023 a press release has arrived that the phase III KEYNOTE-564 trial, randomizing patients to one year of adjuvant treatment with the programmed cell death protein 1 (PD-1) inhibitor pembrolizumab versus placebo, was positive for OS.[8] The primary endpoint of DFS was already reached in 2021. Since then, we have critically discussed with patients the possibility of receiving adjuvant treatment with pembrolizumab. So far, until ASCO GU 2024, the guidelines provided a weak recommendation underlining that patients must be informed about missing OS data and conflicting data on three other negative adjuvant trials with checkpoint inhibitors (atezolizumab, nivolumab [Nivo] and ipilimumab [Ipi] plus Nivo) in ccRCC.[9-11] Contemporarily at ASCO GU 2024, also part A of the CheckMate 914 study with six months of Nivo versus placebo was reported to be negative.[12] In summary, the KEYNOTE-564 trial is the only adjuvant trial in ccRCC that has proven DFS and recently an OS benefit.[1] The relative risk for death or progression was reduced by 38% by administering 1-year pembrolizumab compared to placebo.

Are the OS data finally convincing to recommend one year of a three-weekly, very costly intravenous treatment with potential life-changing side effects to all patients with ccRCC with a significant risk of relapse after nephrectomy? I would personally support the recommendation to all patients eligible for adjuvant pembrolizumab. I think this is also the general perception of the RCC expert community, reflecting after ASCO GU 2024. The study has statistically reached the boundary for DFS and OS positivity, the curves continue to separate and all subgroups benefit. Patients must be well informed though that pembrolizumab has known (but well manageable by experienced oncologists) toxicity, which led to treatment discontinuation in approximately 18% and administration of high-dose corticosteroids in approximately 8% of patients. Health-related quality of life data have shown no deterioration when receiving pembrolizumab compared to placebo.[13]

Nevertheless, there are some critical points to mention on the KEYNOTE-564 trial, particularly the subsequent treatments in the placebo arm, which have led to comments and editorials.[14] Only 36% of patients in the placebo arm received immunotherapy as active treatments after progression, which is most likely to be explained by locoregional differences in access to modern and expensive drugs. The trial investigators replied by arguing that many patients received also local treatment by radiotherapy or surgery for metastases or could be closely observed after metastatic recurrence.[15] Indeed, many patients might have had an International Metastatic RCC Database Consortium (IMDC) favorable risk when relapsing, where after all a tyrosine kinase inhibitor (TKI) is the recommended treatment since all immuno-oncology (IO)/TKI trials and Ipi/Nivo did not show a benefit over sunitinib in the subgroup analyses. Another question remains as to why KEYNOTE-564 is the only positive trial in both endpoints with a checkpoint inhibitor? Why did the other three trials with IO drugs fail to do so? Different trial designs, different populations, different length of treatment (CheckMate-914 administered adjuvant Ipi/Nivo or Nivo for only six months) and finally different checkpoint inhibitors, which are different drugs and might work differently in terms of efficacy, may have contributed to the variation in outcomes.

In summary, KEYNOTE-564 is a positive trial that merits regulatory approval also by Swissmedic, since authorities in Switzerland have not yet considered DFS sufficient for approval. However, the magic goal has been hit: an OS benefit of 1-year adjuvant pembrolizumab, for the first time in a randomized clinical trial history of adjuvant RCC treatments. This should therefore obligate even the most critical oncologist concerning adjuvant oncological treatments to inform and discuss with every eligible patient this new standard-of-care treatment with 1-year adjuvant pembrolizumab.

Best wishes,



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Conflict of interest

The author received advisory board and speaker honoraria from Astellas, Roche, Janssen, Sanofi, Bayer, Merck, MSD, BMS, Pfizer, Novartis AAA and healthbook.

Funding

The author has declared that no financial support was received from any organization for the submitted work.

Author contributions

The author has created and approved the final manuscript.

REFERENCES

1. Choueiri TK, Tomczak P, Park SH, et al. Overall survival results from the phase 3 KEYNOTE-564 study of adjuvant pembrolizumab versus placebo for the treatment of clear cell renal cell carcinoma (ccRCC). *J Clin Oncol*. 2024;42(suppl_4):LBA359. doi:10.1200/JCO.2024.42.4_suppl.LBA359

2. Gross-Goupil M, Kwon TG, Eto M, et al. Axitinib versus placebo as an adjuvant treatment of renal cell carcinoma: results from the phase III, randomized ATLAS trial. *Ann oncol*. 2018;29(12):2371-2378. doi:10.1093/annonc/mdy454

3. Motzer RJ, Haas NB, Donskov F, et al. Randomized Phase III Trial of Adjuvant Pazopanib Versus Placebo After Nephrectomy in Patients With Localized or Locally Advanced Renal Cell Carcinoma. *J Clin Oncol*. 2017;35(35):3916-3923. doi:10.1200/jco.2017.73.5324

4. Eisen T, Frangou E, Oza B, et al. Adjuvant Sorafenib for Renal Cell Carcinoma at Intermediate or High Risk of Relapse: Results From the SORCE Randomized Phase III Intergroup Trial. *J Clin Oncol*. 2020;38(34):4064-4075. doi:10.1200/jco.20.01800

5. Haas NB, Manola J, Uzzo RG, et al. Adjuvant sunitinib or sorafenib for high-risk, non-metastatic renal-cell carcinoma (ECOG-ACRIN E2805): a double-blind, placebo-controlled, randomised, phase 3 trial. *Lancet*. 2016;387(10032):2008-2016. doi:10.1016/s0140-6736(16)00559-6

6. Ryan CW, Tangen CM, Heath EI, et al. Adjuvant everolimus after surgery for renal cell carcinoma (EVEREST): a double-blind, placebo-controlled, randomised, phase 3 trial. *Lancet*. 2023;402(10407):1043-1051. doi:10.1016/s0140-6736(23)00913-3

7. Ravaud A, Motzer RJ, Pandha HS, et al. Adjuvant Sunitinib in High-Risk Renal-Cell Carcinoma after Nephrectomy. *N Engl J Med*. 2016;375(23):2246-2254. doi:10.1056/NEJMoa1611406

8. KEYTRUDA® (pembrolizumab) Signicantly Improved Overall Survival (OS) Versus Placebo as Adjuvant Therapy for Certain Patients With Renal Cell Carcinoma (RCC) Following Nephrectomy. MERCK. Accessed February 2024. https://s2.q4cdn.com/584635680/files/doc_news/KEYTRUDA-pembrolizumab-Significantly-Improved-Overall-Survival-OS-Versus-Placebo-as-Adjuvant-Therapy-for-Certain-Patients-With-Renal--WL8CC.pdf

9. Allaf M, Kim SE, Harshman LC, et al. LBA67 Phase III randomized study comparing perioperative nivolumab (nivo) versus observation in patients (Pts) with renal cell carcinoma (RCC) undergoing nephrectomy (PROSPER, ECOG-ACRIN EA8143), a National Clinical Trials Network trial. *Ann Oncol*. 2022;33(suppl_7):S1432-S1433. doi:10.1016/j.annonc.2022.08.072

10. Motzer RJ, Russo P, Grünwald V, et al. Adjuvant nivolumab plus ipilimumab versus placebo for localised renal cell carcinoma after nephrectomy (CheckMate 914): a double-blind, randomised, phase 3 trial. *Lancet*. 2023;401(10379):821-832. doi:10.1016/s0140-6736(22)02574-0

11. Pal SK, Uzzo R, Karam JA, et al. Adjuvant atezolizumab versus placebo for patients with renal cell carcinoma at increased risk of recurrence following resection (IMmotion010): a multicentre, randomised, double-blind, phase 3 trial. *Lancet*. 2022;400(10358):1103-1116. doi:10.1016/S0140-6736(22)01658-0

12. Motzer RJ, Russo P, Grünwald V, et al. Adjuvant nivolumab plus ipilimumab vs placebo for patients with localized renal cell carcinoma at high risk of relapse after nephrectomy: Subgroup analyses from the phase 3 CheckMate 914 (part A) trial. *J Clin Oncol*. 2023;41(suppl_16):4506. doi:10.1200/JCO.2023.41.16_suppl.4506

13. Choueiri TK, Tomczak P, Park SH, et al. Patient-Reported Outcomes in KEYNOTE-564: Adjuvant Pembrolizumab Versus Placebo for Renal Cell Carcinoma. *Oncologist*. 2024;29(2):142-150. doi:10.1093/oncolo/oyad231

14. Meirson T, Neiman V, Sternschuss M, Markel G, Tannock IF. Clarification needed for pembrolizumab as adjuvant therapy in clear cell renal cell carcinoma. *Lancet Oncol*. 2022;23(11):e489. doi:10.1016/s1470-2045(22)00629-5

15. Powles T, Burgents JE, Xu L, Choueiri TK, KEYNOTE-564 Investigators. Clarification needed for pembrolizumab as adjuvant therapy in clear cell renal cell carcinoma - Authors' reply. *Lancet Oncol*. 2023;24(1):e1-e2. doi:10.1016/S1470-2045(22)00740-9