

European Association of Urology

# Pembrolizumab outperforms tyrosine kinase inhibitors as adjuvant treatment in patients with high-risk renal cell carcinoma after nephrectomy

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## Article info

### Article history:

Received 15 October 2021  
Received in revised form  
18 November 2021  
Accepted December 17, 2021

### Associate Editor:

Gianluca Giannarini

### Keywords:

Adjuvant therapy  
Immune checkpoint inhibitor  
Tyrosine kinase inhibitor  
Renal cell carcinoma

## Abstract

We determined the oncologic outcomes and safety profiles of adjuvant immune checkpoint inhibitors (ICIs) compared to adjuvant tyrosine kinase inhibitors (TKIs) in patients at high risk after nephrectomy for clinically nonmetastatic renal cell carcinoma (RCC). Network meta-analyses were conducted for disease-free survival (DFS), overall survival (OS), and adverse events (AEs) with placebo as the common comparator arm. Six trials (KEYNOTE-564, S-TRAC, ASSURE, PROTECT, ATLAS, and SORCE) were included in our analysis. Compared to placebo, both pembrolizumab (hazard ratio [HR] 0.68, 95% confidence interval [CI] 0.51–0.92) and pazopanib 800 mg (HR 0.69, 95% CI 0.49–0.97) were significantly associated with better DFS. Adjuvant pembrolizumab (HR 0.54, 95% CI 0.30–0.97) was significantly associated with better OS compared to TKIs (HR 0.93, 95% CI 0.83–1.04). Analysis of treatment ranking revealed that pembrolizumab was the best treatment with regard to both DFS and OS and had the lowest likelihood of any-grade and high-grade AEs in comparison to TKIs. The superior oncologic benefit of pembrolizumab and its better toxicity profile support it as the new standard of care in the adjuvant setting for nephrectomy patients at high risk of RCC relapse.

**Patient summary:** For patients with kidney cancer at high risk of relapse after surgical removal of their kidney, postoperative therapy with the immune checkpoint inhibitor pembrolizumab offers the best risk/benefit ratio.

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The lack of significant survival benefits along with the significant side-effect profile of tyrosine kinase inhibitors (TKIs) poses a challenge to their use in the adjuvant setting for patients who remain at high risk of disease recurrence after nephrectomy for clinically nonmetastatic renal cell carcinoma (RCC) [1,2]. Adjuvant pembrolizumab has recently been assessed in patients at higher risk of relapse after nephrectomy (KEYNOTE-564) in the first phase 3 randomized controlled trial (RCT) of an immune checkpoint inhibitor (ICI) in this setting [3].

Given the lack of data on risk/benefit comparison of ICIs and TKIs in the adjuvant RCC setting, the primary aim of this systematic review and network meta-analysis (NMA) was to determine the oncologic and toxicity outcomes of adjuvant pembrolizumab and compare them to those of adjuvant TKIs in the postnephrectomy setting for patients with nonmetastatic RCC.

The MEDLINE and EMBASE databases were searched to identify phase 3 RCTs reporting on oncologic and toxicity outcomes of adjuvant ICIs and TKIs in postnephrectomy RCC patients. The primary outcomes of interest were disease-free survival (DFS) and overall (OS) survival, and the secondary outcomes were adverse events (AEs). NMAs were conducted for different therapy regimens with placebo as the common comparator arm. Detailed information on the study protocol, literature search, inclusion and exclusion criteria, and statistical analyses are reported in the [Supplementary material](#).

Six trials (KEYNOTE-564, S-TRAC, ASSURE, PROTECT, ATLAS, and SORCE) involving 7525 patients met our inclusion criteria ([Supplementary Fig. 1](#)) [3–10]. [Supplementary Table 1](#) summarizes the characteristics of these trials. For quantitative synthesis within NMA, treatment approaches from six studies were categorized into groups as follows: (1) pembrolizumab; (2) TKIs; and (3) placebo. We also performed an analysis of individual regimens that were categorized into groups as follows: (1) pembrolizumab; (2) sunitinib; (3) axitinib; (4) sorafenib; (5) sorafenib for 1 yr; (6) sorafenib for 3 yr; (7) pazopanib 600 mg; (8) pazopanib 800 mg; and (9) placebo. Networks of eligible comparisons were graphically represented in network plots. Analyses of treatment ranking using the P-score value are presented in [Supplementary Table 2](#).

With respect to DFS, pembrolizumab (hazard ratio [HR] 0.68, 95% confidence interval [CI] 0.53–0.87;  $p = 0.002$ ) and TKIs (HR 0.88, 95% CI 0.49–0.97;  $p = 0.004$ ) were significantly associated with better DFS compared to placebo ([Fig. 1](#)). Subgroup analysis results for patients with clear cell histology did not differ from those for the main analyses ([Supplementary Fig. 3](#)). In the analyses of individual treatment regimens, pembrolizumab (HR 0.68, 95% CI 0.51–0.92) and pazopanib 800 mg (HR 0.69, 95% CI 0.49–0.97) were significantly associated with better DFS compared to placebo; the other TKIs were not. According to the analysis of treatment ranking, adjuvant pembrolizumab provided the highest likelihood of better DFS for postnephrectomy patients.

According to NMA for OS, pembrolizumab (HR 0.54, 95% CI 0.30–0.97) was significantly associated with better OS compared to placebo; none of the TKIs was associated with

an improvement in OS (HR 0.93, 95% CI 0.83–1.04; [Supplementary Fig. 4](#)). According to the analysis of treatment ranking, adjuvant pembrolizumab provided the highest likelihood of better OS in postnephrectomy RCC patients.

In terms of AEs, TKIs were associated with a significant risk of any-grade AEs (odds ratio [OR] 8.83, 95% CI 3.79–20.56) compared to placebo; pembrolizumab did not (OR 1.91, 95% CI 0.62–5.89; [Fig. 2](#)). In the analyses of individual treatment regimens, pazopanib 600 mg (OR 5.40, 95% CI 2.94–9.92) pazopanib 800 mg (OR 35.10, 95% CI 4.74–259.79), pembrolizumab (OR 1.91, 95% CI 1.16–3.17), and sunitinib (OR 10.49, 95% CI 3.69–29.81) resulted in significantly higher rates of any-grade AEs compared to placebo. According to analysis of the treatment ranking, pazopanib 800 mg had the highest likelihood of any-grade AEs.

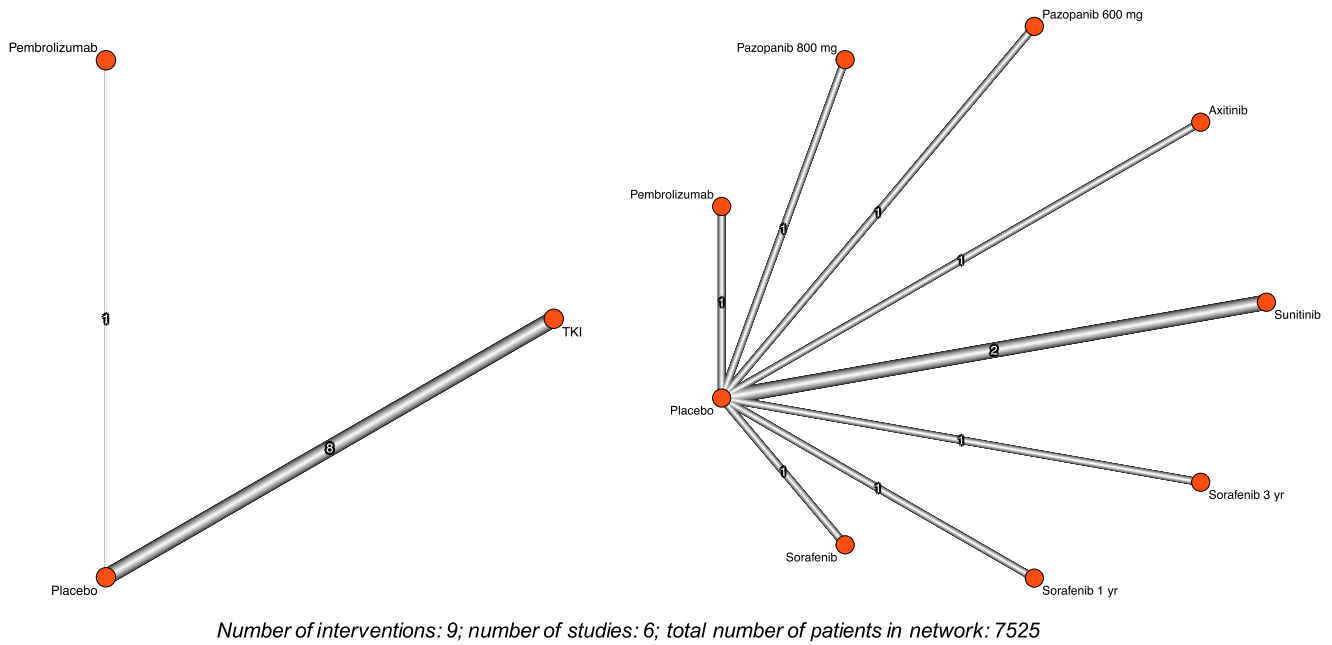
With respect to high-grade AEs, TKIs (OR 6.00, 95% CI 4.95–7.27) and pembrolizumab (OR 2.18, 95% CI 1.62–2.94) were associated with a significant risk of high-grade AEs compared to placebo ([Supplementary Fig. 5](#)). According to analysis of the treatment ranking, pembrolizumab had the lowest likelihood of high-grade AEs among the agents studied.

Despite the superior outcomes achieved with adjuvant pembrolizumab, these results should be interpreted with caution because of several factors. In contrast to TKI studies, the KEYNOTE-564 trial included patients who developed metastasis within 1 yr after radical nephrectomy and those who underwent metastasectomy, in addition to patients with intermediate- and high-risk disease. Hence, the KEYNOTE-564 patient population is highly heterogeneous with enrichment for patients with the highest risk of recurrence. Furthermore, the ASSURE and SORCE trials enrolled patients with any RCC histologic subtype, whereas the KEYNOTE-564, PROTECT, S-TRAC, and ATLAS trials only enrolled patients with clear cell RCC. To reduce potential bias, we performed subgroup analyses in the clear cell RCC population alone and the results did not differ from those for the main analyses.

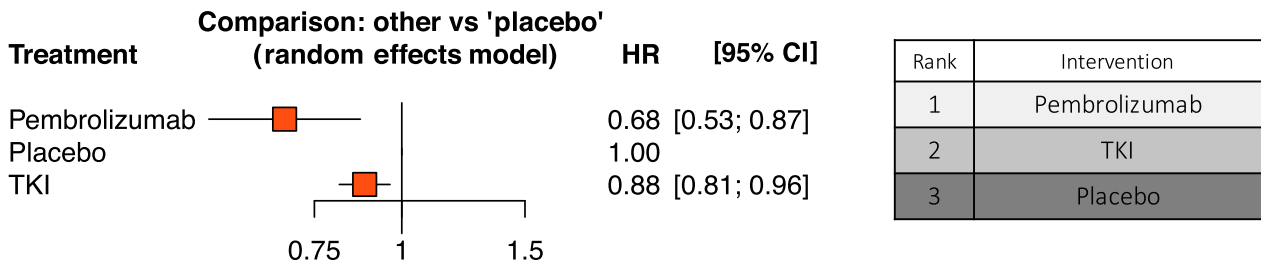
Among the limitations of the present study, the ICI trial included suffers from immature follow-up and OS data; with further follow-up, the data may change. The second limitation is the inconsistencies in intervention regimens across TKI studies; this and the evaluation method for the curative effect for all trials could lead to some potential confounding and bias. To overcome inconsistencies in TKIs, we also performed analyses of each treatment regimen separately. The results confirmed our findings. Third, the discrepancy across the studies in the definition of the risk of disease relapse might lead to attribution bias. This heterogeneity highlights the need for a standardized prediction tool to assess the risk of disease relapse. Fourth, despite an indirect comparison of outcomes in RCTs provided by the NMA, this approach is not equivalent to a head-to-head treatment comparison. Therefore, well-designed comparative trials are required to validate the findings of our study.

Our analyses suggest superior oncologic and safety benefits of adjuvant pembrolizumab compared to adjuvant TKIs in patients treated with nephrectomy for localized or locally advanced RCC. Pembrolizumab should be considered as a potential standard of care in the adjuvant setting for

(A) Network plots of RCTs that assessed disease-free survival (DFS)



(B) Forest plot and network meta-analysis rank chart comparing ICIs and TKIs



(C) Forest plot and network meta-analysis rank chart analyzing individual treatment regimens

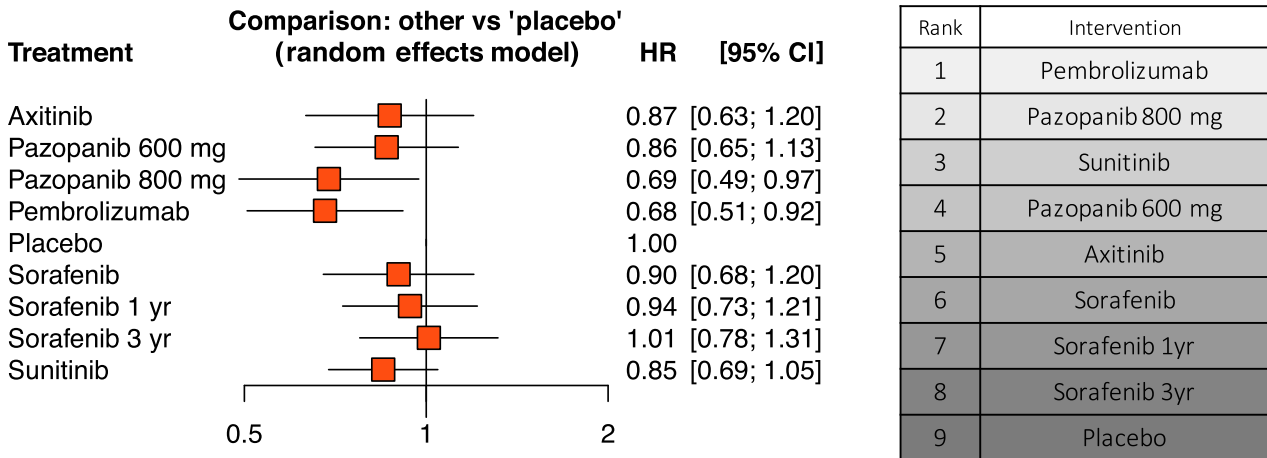
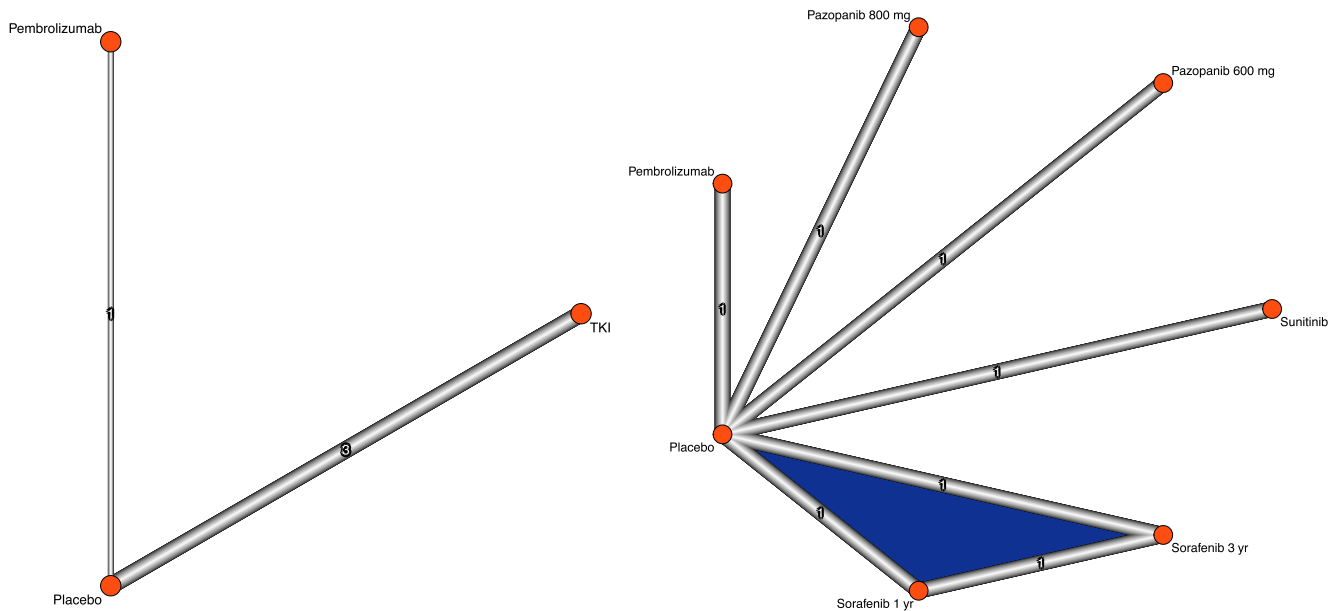


Fig. 1 - Summary of the network meta-analysis of disease-free survival for patients treated with adjuvant therapy for localized or locally advanced renal cell carcinoma after nephrectomy. RCT = randomized controlled trial; ICI = immune checkpoint inhibitor; TKI = tyrosine kinase inhibitor; HR = hazard ratio; CI = confidence interval.

postnephrectomy patients with RCC who are at very high risk of disease relapse. Identification of the patients most

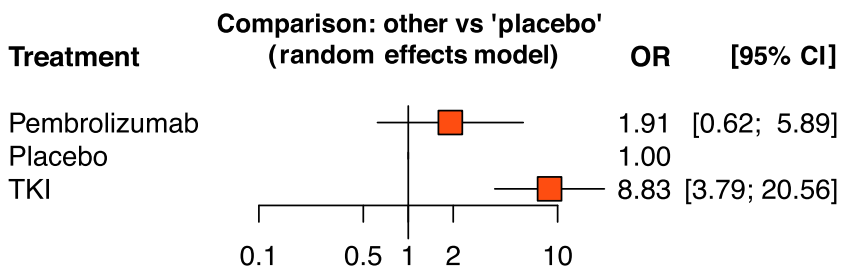
likely to benefit from adjuvant pembrolizumab and the ideal length of this therapy require further investigation.

(A) Network plots of RCTs that assessed any grade AEs



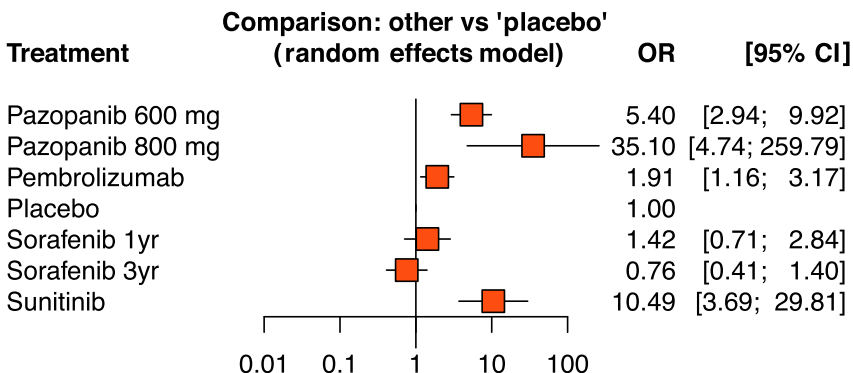
Number of interventions: 7; number of studies: 4; total number of patients in network: 4857

(B) Forest plot and network meta-analysis rank chart comparing ICIs and TKIs



Rank	Intervention
1	Placebo
2	Pembrolizumab
3	TKI

(C) Forest plot and network meta-analysis rank chart analyzing individual treatment regimens



Rank	Intervention
1	Sorafenib 3yr
2	Placebo
3	Sorafenib 1yr
4	Pembrolizumab
5	Pazopanib 600 mg
6	Sunitinib
7	Pazopanib 800 mg

Fig. 2 – Summary of the network meta-analysis of any-grade adverse events (AEs) in patients treated with adjuvant therapy for localized or locally advanced renal cell carcinoma after nephrectomy. RCT = randomized controlled trial; ICI = immune checkpoint inhibitor; TKI = tyrosine kinase inhibitor; OR = odds ratio; CI = confidence interval.

**Author contributions:** Ekaterina Laukhtina had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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**Acquisition of data:** Laukhtina, Quhail.  
**Analysis and interpretation of data:** Laukhtina, Quhail.

*Drafting of the manuscript:* Laukhtina.

*Critical revision of the manuscript for important intellectual content:* Quhal, Mori, Sari Motlagh, Rajwa, Yanagisawa, Mostafaei, König, Aydh, Pradere, Enikeev, Karakiewicz, Schmidinger, Shariat.

*Statistical analysis:* Laukhtina, Quhal.

*Obtaining funding:* None.

*Administrative, technical, or material support:* None.

*Supervision:* Shariat.

*Other:* None.

**Financial disclosures:** Ekaterina Laukhtina certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

**Funding/Support and role of the sponsor:** None.

**Acknowledgments:** Pawel Rajwa is supported by an EUSP scholarship from the European Association of Urology. Keiichiro Mori is supported by the Uehara Memorial Foundation.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.euo.2021.12.007>.

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