European Journal of Clinical Pharmacy

Print ISSN: 2385-409X **Online ISSN**: Applied
Website: https://farmclin.es/

Original Research Article

Pembrolizumab-Axitinib for First-Line Treatment of Advanced Renal-Cell Carcinoma

Article History:

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How to cite this article:
Carmen Lucia M.C., *et al.* Pembrolizumab-Axitinib for First-Line Treatment of Advanced Renal-Cell Carcinoma. *Eur J Clin Pharm.* 2021;3(1);1-4

Received: 02-01-2021
Revised: 22-01-2021
Accepted: 11-02-2021
Published: 09-03-2021

Abstract: Advanced renal-cell carcinoma (RCC) poses significant therapeutic challenges, especially for patients with metastatic or unresectable disease. Combination immunotherapy with pembrolizumab (a PD-1 inhibitor) and axitinib (a VEGFR tyrosine kinase inhibitor) has become standard of care for first-line treatment in this setting. This article provides an in-depth review of clinical data, long-term outcomes, safety, real-world application, and the evolving role of pembrolizumab-axitinib based on pivotal studies and updated 5-year analyses. Graphical data illustrate survival and progression-free outcomes compared to previous standards.

Keywords: Advanced renal-cell carcinoma (RCC), Pembrolizumab, Axitinib, Combination immunotherapy, First-line treatment.

INTRODUCTION

Renal-cell carcinoma accounts for approximately 2–3% of adult cancers worldwide. Prognosis is poor for advanced stages. Historically, VEGF-targeted therapies such as sunitinib were the backbone of systemic treatment, with only modest survival benefit. The fusion of immunotherapy and targeted therapy has reshaped the landscape, with the pembrolizumab-axitinib combination now recognized as a highly effective frontline regimen for advanced RCC[1][2].

MECHANISM OF ACTION

- **Pembrolizumab:** A monoclonal antibody targeting the programmed cell death-1 (PD-1) pathway, releasing immune suppression and augmenting T-cell antitumor activity.
- **Axitinib:** An oral tyrosine kinase inhibitor with high specificity for VEGF receptors, impeding angiogenesis required for tumor growth.

Synergy arises by combining immune system activation and angiogenesis blockade, improving both direct tumor cell killing and immune infiltration of the tumor microenvironment[2][3].

Clinical Trial Evidence
KEYNOTE-426: The Pivotal Phase III Trial

- **Design:** 861 patients with advanced or metastatic clear-cell RCC, randomized to pembrolizumab (200mg IV every 3 weeks, up to 2 years) plus axitinib (5mg PO twice daily) vs sunitinib (50mg PO daily, 4 weeks on/2 off)[2].
- **Population:** Treatment-naïve, IMDC risk stratified.

Outcomes at 12–18 Months

- **Overall Survival (OS) at 12 Months:** 89.9% (pembrolizumab-axitinib) vs 78.3% (sunitinib)
- **Progression-Free Survival (PFS) Median:** 15.1 vs 11.1 months
- **Objective Response Rate (ORR):** 59.3% vs 35.7%
- Statistically significant improvements were seen across all IMDC risk subgroups and PD-L1 levels[2][4].

Five-Year Follow-up

- **60-Month OS:** 41.9% (pembrolizumab-axitinib) vs 37.1% (sunitinib)
- **60-Month PFS:** 18.3% vs 7.3%
- **Median Duration of Response:** 23.6 vs 15.3 months
- **ORR at 5 Years:** 60.6% vs 39.6%
- **Hazard Ratio for Death:** 0.84 (pembrolizumab-axitinib reduces risk by 16%)
- These benefits persisted regardless of risk stratification, with durable responses and manageable toxicity[3][5].

Real-World Outcomes

Retrospective studies from the US, Japan, and global cohorts confirm the effectiveness observed in clinical trials:

- **Survival rates and PFS** closely mirror clinical trial metrics.
- **Real-World Progression-Free Survival (rwPFS):** 39.3% at 1 year.
- **Best Overall Response:** Consistently >55%.
- **Patient eligibility and benefit** extends to varied clinical populations, including those with poor-risk disease[6][7][8].

Safety and Tolerability

- **Adverse Events:** Almost all patients experienced some treatment-emergent events. Most common included diarrhea, hypertension, fatigue, hypothyroidism, hepatotoxicity, decreased appetite, stomatitis, and palmar-plantar erythrodysesthesia[4].
- **Grade ≥3 Toxicities:** 62.9% (pembrolizumab-axitinib group) vs 58.1% (sunitinib)
- **Immune-Mediated Events:** Usually manageable; permanent discontinuation rates for immune-related toxicity ~13%.
- **Discontinuation Rates:** 10.7% (pembrolizumab-axitinib) vs 13.9% (sunitinib)[2][9].

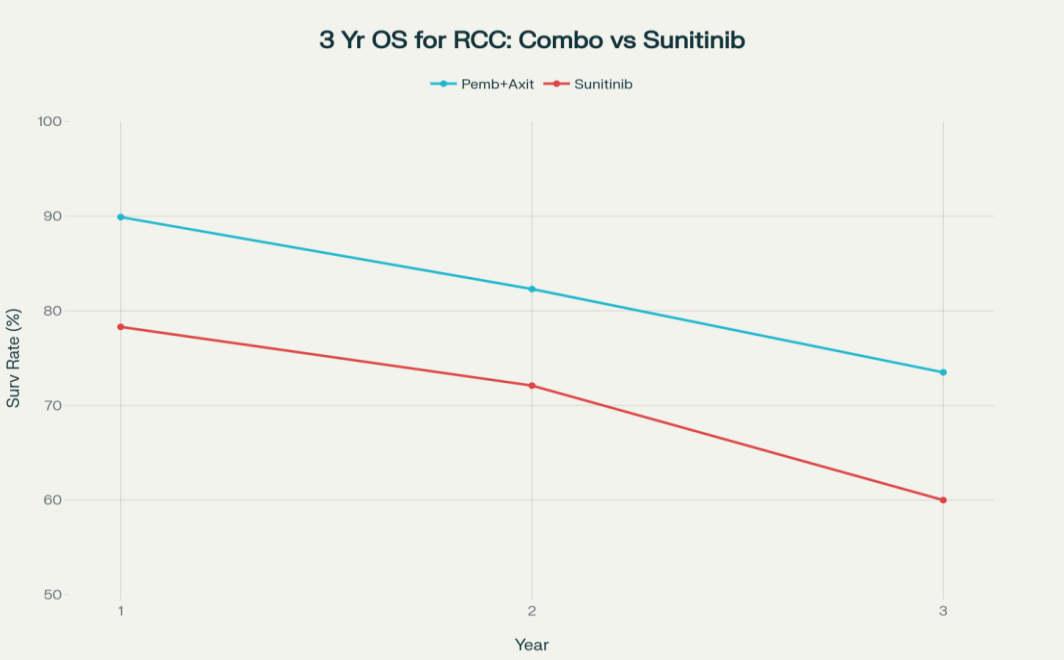
Dosing and Administration

- **Pembrolizumab:** 200mg IV every 3 weeks, maximum 2 years (35 cycles)
- **Axitinib:** 5mg orally twice daily, continued until progression or unacceptable toxicity

Dose modifications and careful monitoring are crucial, especially for hypertension, liver function abnormalities, and immune-mediated toxicities[10][11].

Comparative Survival and Progression Outcomes

Comparison of overall survival and progression-free survival rates between pembrolizumab-axitinib and sunitinib over several years demonstrates durable advantage for the combination regimen.



Comparison of Overall Survival and Progression-Free Survival rates between Pembrolizumab + Axitinib and Sunitinib treatments in advanced renal cell carcinoma over several years.

Chart: Superior overall and progression-free survival rates with pembrolizumab-axitinib versus sunitinib, reflecting results from the KEYNOTE-426 5-year analysis and contemporaneous studies.

DISCUSSION

Pembrolizumab-axitinib has redefined the first-line standard for advanced RCC. Long-term data show a sustained survival benefit and higher response rates than monotherapy with VEGFR TKIs. Real-world data confirm clinical trial results, reinforcing broad utility. The safety profile, while significant, is manageable with experienced multidisciplinary care. Questions remain about sequencing with newer agents, predictors of durable response, and long-term immune-related sequelae, but pembrolizumab-axitinib remains the preferred regimen for most patients.

CONCLUSION

The pembrolizumab-axitinib combination offers substantial improvements in survival, disease control, and response durability for first-line management of advanced RCC. Its integration into guidelines reflects accumulated evidence from randomized trials and real-world use. Ongoing research continues to refine patient selection and determine best practices for toxicity management and therapy personalization.

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