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Real-World Primary Resistance to First-Line Immune-Based Combinations in Patients with Advanced Renal Cell Carcinoma (ARON-1)

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Abstract

Background: Therapeutic advancements based on immuno-oncology combinations have revolutionized the management of patients with renal cell carcinoma. However, patients who have progressive disease as the best response, "primary refractory" (P_{ref}), face dismal outcomes.

Objective: Our multicenter retrospective real-world study aims to assess the prevalence and clinicopathological characteristics of P_{ref} patients.

Methods: This study collected data from 72 centers across 22 countries (1709 patients), involving patients aged ≥18 years with metastatic clear cell renal cell carcinoma. All patients were treated with first-line immune-oncology combinations. Data included patient demographics, histology, metastatic sites, and treatment responses. Radiological assessments followed Response Evaluation Criteria in Solid Tumors version 1.1. Statistical analyses employed Kaplan-Meier method, Cox proportional hazard models, logistic regression, and the receiver operating characteristic curve.

Results: In our study, the P_{ref} rate was 19%. Nivolumab/ipilimumab showed the highest P_{ref} rate (27%), while pembrolizumab/lenvatinib exhibited the lowest (10%). Primary refactory patients demonstrated significantly lower median overall survival (7.6 months) compared with non-P_{ref} patients (55.7 months), $p < 0.001$. At the multivariate analysis, nephrectomy, sarcomatoid de-differentiation, intermediate/poor International Metastatic RCC Database Consortium risk, and bone and brain metastases emerged as significant predictors of overall survival for P_{ref} patients with renal cell carcinoma. Logistic regression showed a significant relationship between liver metastases, intermediate/poor International Metastatic RCC Database Consortium risk, and no surgery and an increased risk of P_{ref}. This study presents limitations, mainly because of its retrospective design.

Conclusions: The ARON-1 study provides valuable insights into P_{ref} patients, emphasizing the challenges of this precociously resistant subgroup. Identified predictors could guide risk stratification, aiding clinicians in tailored therapeutic approaches.

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