Surgery is the preferred treatment for localized renal cell carcinoma (RCC). Although pursued with curative intent, approximately 50% of patients will experience disease recurrence. Pembrolizumab was approved as adjuvant treatment for patients at high risk for recurrence after nephrectomy based on the KEYNOTE-564 trial, and an improvement in overall survival (OS) was seen for the first time with an adjuvant therapy in RCC on further follow-up.¹ However, the KEYNOTE-564 trial enrolled patients with clear-cell RCC, an important caveat when the announcement of approval of adjuvant pembrolizumab by the US Food and Drug Administration designated it for renal cell carcinoma overall. To my knowledge, there are no data to support the use of adjuvant pembrolizumab in non–clear cell RCC, and clinical oncologists are left to make decisions for their patients within an information vacuum. This study by Gulati et al² attempts to decrease this chasm with their subgroup analysis of 109 patients with papillary RCC and 99 patients with chromophobe RCC enrolled in the larger phase 3 EVEREST randomized clinical trial of everolimus vs placebo in patients with RCC at high risk of recurrence after nephrectomy. Adjuvant everolimus did not lead to improvement in recurrence-free survival (papillary RCC: hazard ratio [HR], 1.19; 95% CI, 0.61-2.33; \( P = .61 \); chromophobe RCC: HR, 0.89; 95% CI, 0.37-2.13; \( P = .79 \)) or OS (papillary RCC HR for death, 1.47; 95% CI, 0.67-3.24; \( P = .34 \); chromophobe RCC HR for death, 0.93; 95% CI, 0.33-2.65; \( P = .89 \)) in either subgroup but had a significantly increased rate of grade 3 or higher adverse events compared with placebo (48% vs 9%).

There have been systematic problems with the investigation and implementation of novel therapies in non–clear cell RCC historically. Non–clear cell RCC has been treated like a single entity in trials when in fact, the unique subtypes of RCC contained therein are disparate in terms of the histology, biology, and epidemiology. The amalgamation of chromophobe, papillary, translocation, or unclassified RCC within single studies leads to an output of information of questionable utility, given the extremely small sample sizes of each subtype included. A trial design flaw has been the reflexive application of agents shown to have activity in clear-cell RCC in non–clear cell RCC subtypes without a clear biologic rationale. And in the absence of data altogether, oncologists find themselves treating their patients with non–clear cell RCC outside of clinical trials with agents approved in clear-cell RCC out of sheer necessity. The broad approval of drugs for RCC without subtype specification does not make their job any easier.

While extrapolation is inherently flawed, most data available on treating non–clear cell RCC come from the metastatic setting. Everolimus was previously investigated in the randomized, phase 2 ESPN trial of everolimus vs sunitinib in patients with advanced non–clear cell RCC; the trial was closed early after interim analysis showing significantly worse outcomes with everolimus vs sunitinib.³ A somatic TSC2 variation was noted in 1 of the patients with chromophobe RCC who achieved partial response, suggesting that mammalian target of rapamycin (mTOR) hyperactivation in this patient may have equated to sensitivity to everolimus. The ASPEN trial similarly showed an improvement in PFS with sunitinib over everolimus in all patients with non–clear cell RCC included but highlighted that 2 of 6 patients with chromophobe RCC treated with everolimus achieved a partial response or better, suggesting a role for further investigation of the agent in this histology.⁴ It is worth noting that the total numbers of patients in each trial with papillary RCC and chromophobe RCC were 17 and 12 in ESPN and 70 and 16 in ASPEN, making it difficult to draw any definitive conclusions. Whether adjuvant everolimus in non–clear cell RCC could be improved on by combination with lenvatinib or another anti–vascular endothelial growth factor (VEGF) agent is an open question.

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open question, although the single-group study of 20 patients with advanced papillary RCC and 9 patients with chromophobe RCC treated with lenvatinib and everolimus yielded an overall response rate (ORR) of 15% and 44%, respectively, a surprisingly low number for papillary RCC but a high one for chromophobe RCC, albeit based on responses in 4 patients.5

Since there are patients with resected non–clear cell RCC being treated with adjuvant pembrolizumab in clinical practice, what data exist for checkpoint inhibitor (CPI) monotherapy in advanced non–clear cell RCC? In the non–clear cell, single-group cohort of the KEYNOTE-427 trial, 118 patients with papillary RCC and 21 with chromophobe RCC were treated with pembrolizumab and experienced an ORR of 28.8% and 9.5%, respectively. Regarding additional data on VEGF inhibitors applied to papillary RCC and chromophobe RCC, there has been particular interest in cabozantinib in papillary RCC, given its concurrent VEGF and MET targeting, with alterations in MET playing a significant role in the pathogenesis of type I papillary RCC. Cabozantinib outperformed sunitinib in advanced papillary RCC in the phase 2 PAPMET/SWOG1500 trial; the crizotinib and savolitinib groups were closed early following a prespecified futility analysis.6 Cabozantinib achieved a PFS of 9.0 months vs 5.6 months with sunitinib (HR, 0.60; 95% CI, 0.37-0.97; P = .02) and ORR of 23% vs 4% (P = .01) and took the crown for the preferred anti-VEGF (and anti-MET) tyrosine kinase inhibitor (TKI) in papillary RCC. It is important to temper enthusiasm with the paucity of data to support adjuvant application of anti-VEGF agents in non–clear cell RCC, let alone clear-cell RCC; one must remember the S-TRAC trial in which adjuvant sunitinib improved disease-free survival but not OS in clear-cell RCC.

Dual VEGF and CPI in advanced non–clear cell RCC has been investigated most recently with the application of 2 of the most well-established combinations in clear-cell RCC. First, cabozantinib plus nivolumab was studied in a single-group trial of 32 patients with papillary RCC and 7 patients with chromophobe RCC. While the ORR was 47% in patients with papillary RCC, there were no responses in the patients with chromophobe RCC.7 Lenvatinib and pembrolizumab were studied in the single-group KEYNOTE-B61 trial.8 Among 93 patients with papillary RCC, the ORR was 52.9%, and perhaps even more notable was the ORR of 28% in 29 patients with chromophobe RCC, setting a new benchmark for clinical activity in this difficult-to-treat population.

Perhaps investigation of adjuvant therapeutic combinations is the new frontier in non–clear cell RCC. The RAMPART study will provide important information on adjuvant CPI and is recruiting across RCC subtypes, with groups testing durvalumab with or without tremelimumab (NCT03288532). An adjuvant trial of a CPI with an anti-VEGF TKI is overdue and desperately needed. With doublet therapy outperforming single-agent anti-VEGF TKIs across trials in the metastatic setting for non–clear cell RCC, recognizing the folly of cross-trial comparisons and such small sample sizes, it seems likely that the sun has set on adjuvant TKI monotherapy trials in non–clear cell RCC. A real strength of this analysis by Gulati et al2 is presentation of some of the largest numbers of patients to date with papillary RCC and chromophobe RCC. While everolimus did not show a significant response, there are lessons to be learned. While randomized trials are great, their impact dwindles if the numbers of patients being randomized in each disease type are in the low double-digits. Acruing to trials of rare cancers, like chromophobe RCC, is challenging, but we do our patients a disservice by perpetuating the artificial label of non–clear cell RCC for wildly different diseases. Studies like PAPMET2 (NCT05410081) and SAMETA (NCT05043090) represent our evolution as a field with focus on advanced papillary RCC and MET-driven papillary RCC, respectively. Cooperative groups will undoubtedly play a predominant role in conducting practical trials in rare non–clear cell RCC subtypes, but collaboration with industry colleagues will also be an essential part of advancing the field via development of agents with biologic rationale or biomarker selection specific for non–clear cell RCC. Trial designs based on areas where success has been achieved in clear-cell RCC will not suffice if we are to make real progress in treating resected or metastatic non–clear cell RCC.
ARTICLE INFORMATION
Published: August 6, 2024. doi:10.1001/jamanetworkopen.2024.25251
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Corresponding Author: Jacqueline T. Brown, MD, Winship Cancer Institute of Emory University, 1365B Clifton Rd NE, Ste B400, Office 4213, Atlanta, GA 30322 (jacqueline.theresa.brown@emory.edu).
Author Affiliation: Winship Cancer Institute of Emory University, Atlanta, Georgia.
Conflict of Interest Disclosures: Dr Brown reported grants from Exelixis, Xencor, Merck, Medicenna, Surface Oncology, Plant Therapeutics, Macrogenics, and Duality Bio (paid to institution) and personal fees from Exelixis, Xencor, and Gilead outside the submitted work.

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