

The Adjuvant Reckoning: Belzutifan, Toxicity, and the Next Phase of RCC Care

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Dear Colleagues,

This has been an unusually productive stretch for renal cell carcinoma (RCC) research, and the Third Quarter 2026 issue of *Kidney Cancer Journal* reflects that momentum. Between the follow-through from ASCO's Genitourinary Cancers Symposium earlier this year and the full publication of several pivotal trials over the summer, our field is refining not just what works, but for whom, and at what cost in toxicity and quality of life. I want to use this space to walk through the developments I consider most consequential for practicing clinicians, and to explain how they shaped the content you will find in the pages that follow.

The Adjuvant Landscape Continues to Mature

Adjuvant therapy for high-risk resected clear cell RCC remains one of the most actively contested areas in our field. KEYNOTE-564 established single-agent pembrolizumab as a standard of

care in the intermediate- to high-risk post-nephrectomy setting, and most of us have now accumulated several years of real-world experience applying it. That benefit has now been improved upon; the open question is for whom, and at what price.

LITESPARK-022, presented at ASCO GU 2026, led to FDA approval on June 12, 2026 of belzutifan plus pembrolizumab as adjuvant therapy for clear cell RCC at increased risk of recurrence after nephrectomy, the first approved PD-1 plus HIF-2 α inhibitor combination. The disease-free survival advantage over pembrolizumab alone, a 28% reduction in the risk of recurrence or death, is real, but so is the added burden of anemia, hypoxia, and other class-related adverse events. I have asked our contributors to address a question I hear constantly from colleagues in community practice: how do we counsel a patient who is already anxious about recurrence, when the incremental benefit must be weighed against

a more demanding toxicity and monitoring profile? The Fox Chase Nomogram and other risk-stratification tools deserve more consistent use in this conversation, and you will see that argument made explicitly in this issue's commentary.

LITESPARK-011: From Publication to Approval

On September 24, the FDA approved belzutifan plus lenvatinib for adults with advanced RCC with a clear cell component after a PD-1 or PD-L1 inhibitor. The approval rests on the phase 3 LITESPARK-011 trial, published in full in *The Lancet* this quarter. It is the first regimen to outperform cabozantinib in a phase 3 trial in this setting. Notably, the new indication does not require prior VEGF-TKI therapy, placing the combination directly in the second-line position cabozantinib has occupied. In the *Lancet* report, median progression-free survival improved from 10.7 to 14.8 months (HR 0.70), and the objective response rate from 40% to 53%. Overall survival favored the combination but did not reach statistical significance at the final analysis (median 33.7 vs 28.6 months; HR 0.85); full results will be presented at ESMO in Madrid, October 23–27. The toxicity profile also changes character rather than lightening: anemia and hypoxia replace hand-foot syndrome and diarrhea as the dominant concerns. I regard this as a meaningful, practice-changing advance, since it gives us a genuinely new option after immunotherapy. But with no significant survival benefit at the final analysis, it enters practice as one of two reasonable second-line choices rather than an automatic default. Patient selection will matter: fitness, baseline hemoglobin, cardiopulmonary reserve and patient preference among different toxicity profiles. More broadly, with an adjuvant approval in June and a second-line approval in September, belzutifan has moved from a niche VHL-disease agent to a central role across multiple lines of RCC therapy.

Biology Catching Up With the Clinic

It is easy, in a quarter dominated by large randomized trials, to overlook the basic and

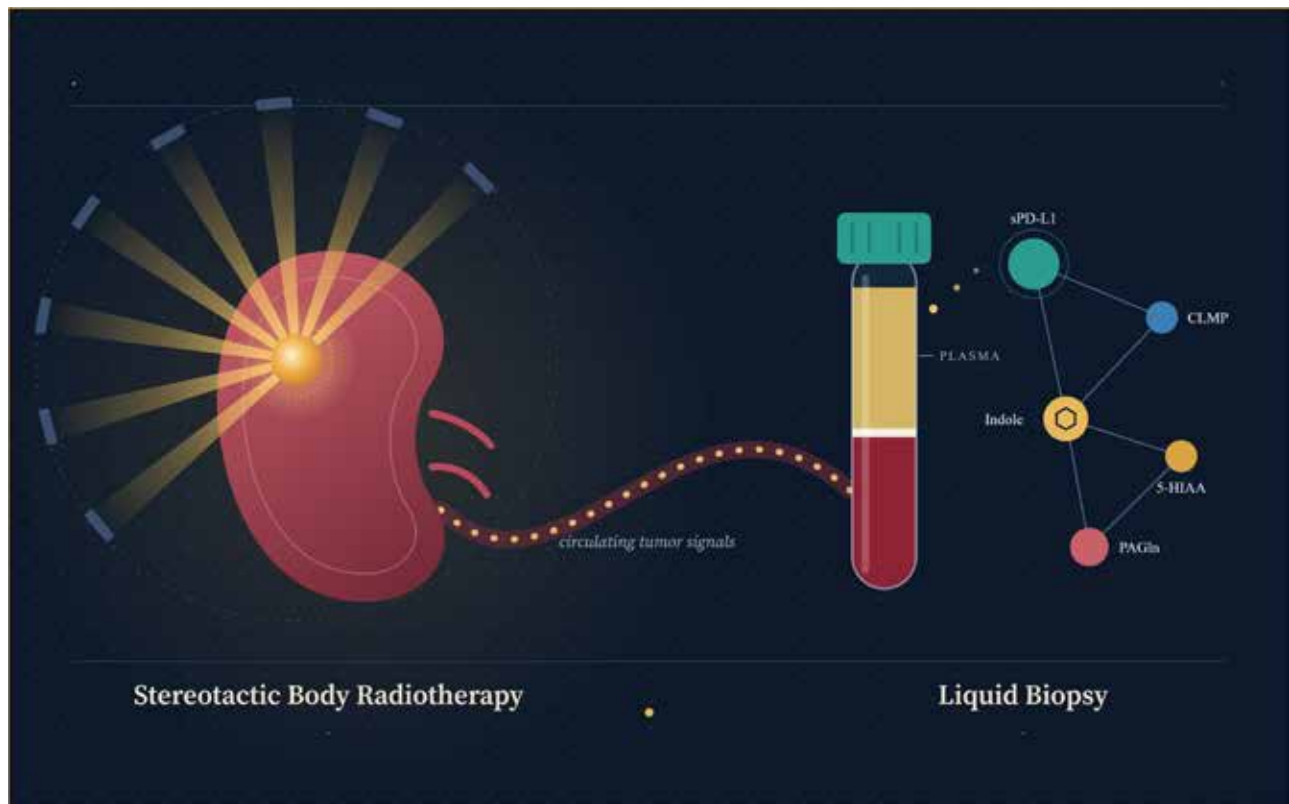
translational science that will define our next decade of therapy. Several papers this quarter caught my attention. Work characterizing tertiary lymphoid structures in RCC tumors has strengthened the case that these structures are not incidental findings but active reservoirs of stem-like, tumor-specific CD8+ T cells, a finding with direct relevance to how we think about immunotherapy response and resistance. Separately, mechanistic work on mTOR inhibitor resistance, tied to ZMYND8 ubiquitination and phase-separation biology, adds another piece to the long-standing puzzle of why mTOR-targeted agents lose efficacy over time in clear cell disease. And a new integrative multi-omic analysis of RCC subtypes offers a broader map of the transcription factors and regulatory circuits driving tumor biology, work that will take years to translate but that our field needs if we are going to move past a treatment paradigm built primarily on VEGF and immune checkpoint blockade.

Novel Agents and Combinations in the Pipeline

This year's ASCO GU meeting continues to reverberate through the abstracts and correspondence crossing my desk. Among the approaches I am watching most closely: the phase 2 IVORY trial of ivonescimab, a bispecific PD-1/VEGF antibody, in patients previously treated with checkpoint inhibitors; early combination work pairing radiolabeled girentuximab with cabozantinib and nivolumab in treatment-naïve advanced clear cell RCC; and cellular approaches such as TANKeR-70, using TGF- β receptor knockout allogeneic NK cells against CD70-expressing tumors. None of these is close to changing standard practice today, but each represents a distinct mechanistic bet on how to extend benefit beyond our current checkpoint-inhibitor and TKI backbone, and our *Journal* is committed to tracking them through to maturity rather than covering them once and moving on.

A Note on Real-World Evidence

I also want to flag the continued output of real-world



and health-related quality-of-life analyses building on CheckMate 9ER, including new work identifying which symptoms most affect patients on nivolumab plus cabozantinib relative to sunitinib. As adjuvant and combination regimens multiply, our obligation to patients extends beyond progression-free and overall survival curves. Quality-of-life data deserves the same editorial rigor we apply to efficacy data, and you will continue to see it represented in these pages.

In This Issue

Beyond the research summaries described above, this issue features two original manuscripts that I believe merit your attention. The first is a review of stereotactic body radiotherapy (SBRT) for localized RCC, which challenges the long-held view of RCC as a radioresistant tumor. The authors argue that the poor outcomes of conventionally fractionated radiotherapy reflected delivery limitations rather than tumor biology, and that modern SBRT now offers high local control with minimal severe

toxicity. For elderly or frail patients, those with chronic kidney disease or a solitary kidney, and those whose tumors are unsuitable for ablation, SBRT is emerging as a credible nephron-sparing alternative, pending prospective comparative data. The second is an original research study that combines high-throughput plasma proteomics with gut microbiome-focused metabolomics in 56 patients to identify non-invasive biomarkers that distinguish metastatic from localized RCC. Soluble PD-L1, indole derivatives, and phenylacetylglutamine emerged as leading candidates, with plausible links to immune regulation and renal integrity. This is early, hypothesis-generating work, but it addresses a genuine gap in our diagnostic and prognostic toolkit. This issue also features our regular "Around the Corner" column, which highlights recent updates in the non-renal genitourinary cancer space. As always, I am grateful to our reviewers and contributing authors for the care they bring to this work, often on a fast turnaround and without much public recognition.