The current plan execution is satisfactory and all necessary information has been collected. The next step is to synthesize all gathered data into a comprehensive academic review covering landscape overview, mechanisms of action, development pipeline, comparative efficacy and safety, and emerging trends and research gaps in RCC immunotherapy, while acknowledging data limitations.

An Academic Review of the Renal Cell Carcinoma (RCC) Immunotherapy Landscape in the US and EU: Cytokine Therapies and Bispecific Antibodies

**Current Date: 2025-10-02**

**1. Landscape Overview**

The treatment paradigm for renal cell carcinoma (RCC) has been revolutionized by immunotherapy, primarily through the success of immune checkpoint inhibitors (ICIs). However, as the field matures, there is a renewed focus on established modalities like cytokine therapy and a burgeoning interest in novel platforms such as bispecific antibodies to address unmet needs, including primary and acquired resistance to ICIs. This review provides a comprehensive analysis of the cytokine and bispecific antibody landscape for RCC in the United States (US) and the European Union (EU), covering approved therapies, development pipelines, and emerging trends.

A critical finding of this review is the significant limitation in publicly accessible drug pipeline databases. Despite extensive searches for "renal cell carcinoma," "RCC," and "kidney cancer," these tools consistently failed to identify dedicated cytokine or bispecific antibody development programs specifically for RCC, instead returning results for other renal conditions like "end stage renal disease" or "acute kidney injury" [[1](https://www.noahai.co/tool/drug-compete/?search_param=%7B%22indication_name%22%3A%20%5B%22End%20stage%20renal%20disease%22%2C%20%22Acute%20kidney%20injury%22%5D%2C%20%22drug_modality%22%3A%20%7B%22data%22%3A%20%5B%22Bi-specific%20Antibodies%22%5D%2C%20%22logic%22%3A%20%22or%22%7D%2C%20%22location%22%3A%20%5B%22USA%22%2C%20%22European%20Union%22%2C%20%22EU%22%2C%20%22Germany%22%2C%20%22France%22%2C%20%22Italy%22%2C%20%22Spain%22%2C%20%22UK%22%5D%2C%20%22top_n%22%3A%201000%7D)][[12](https://www.noahai.co/tool/drug-compete/?search_param=%7B%22indication_name%22%3A%20%5B%22End%20stage%20renal%20disease%22%2C%20%22Acute%20kidney%20injury%22%5D%2C%20%22phase%22%3A%20%5B%22Preclinical%22%2C%20%22IND%22%2C%20%22I%22%2C%20%22II%22%2C%20%22III%22%2C%20%22BLA%2FNDA%22%2C%20%22Approved%22%5D%2C%20%22drug_modality%22%3A%20%7B%22data%22%3A%20%5B%22Bi-specific%20Antibodies%22%2C%20%22Monoclonal%20Antibodies%22%5D%2C%20%22logic%22%3A%20%22or%22%7D%2C%20%22location%22%3A%20%5B%22USA%22%2C%20%22China%22%2C%20%22Japan%22%2C%20%22UK%22%2C%20%22France%22%2C%20%22Germany%22%2C%20%22Italy%22%2C%20%22Spain%22%5D%2C%20%22top_n%22%3A%201000%7D)][[23](https://www.noahai.co/tool/drug-compete/?search_param=%7B%22indication_name%22%3A%20%5B%22End%20stage%20renal%20disease%22%2C%20%22Basal%20cell%20carcinoma%22%2C%20%22Acute%20kidney%20injury%22%5D%2C%20%22drug_modality%22%3A%20%7B%22data%22%3A%20%5B%22Polypeptide%22%2C%20%22Monoclonal%20Antibodies%22%2C%20%22Bi-specific%20Antibodies%22%5D%2C%20%22logic%22%3A%20%22or%22%7D%2C%20%22location%22%3A%20%5B%22USA%22%2C%20%22China%22%2C%20%22Japan%22%2C%20%22UK%22%2C%20%22France%22%2C%20%22Germany%22%2C%20%22Italy%22%2C%20%22Spain%22%5D%2C%20%22top_n%22%3A%201000%7D)][[30](https://www.noahai.co/tool/drug-compete/?search_param=%7B%22indication_name%22%3A%20%5B%22End%20stage%20renal%20disease%22%2C%20%22Basal%20cell%20carcinoma%22%2C%20%22Gastrointestinal%20cancer%20metastatic%22%2C%20%22Acute%20kidney%20injury%22%5D%2C%20%22drug_modality%22%3A%20%7B%22data%22%3A%20%5B%22Bi-specific%20Antibodies%22%5D%2C%20%22logic%22%3A%20%22or%22%7D%2C%20%22location%22%3A%20%5B%22USA%22%2C%20%22Germany%22%2C%20%22France%22%2C%20%22Italy%22%2C%20%22Spain%22%2C%20%22Netherlands%22%2C%20%22Belgium%22%2C%20%22Switzerland%22%2C%20%22United%20Kingdom%22%5D%2C%20%22top_n%22%3A%201000%7D)]. Therefore, the development pipeline detailed in this review is constructed from clinical trial registries, patent filings, and recent academic publications rather than commercial pipeline databases.

**1.1. Approved Therapies and Regulatory Context**

The regulatory landscape for these two modalities in RCC is starkly different, highlighting both historical significance and future opportunity.

**Cytokine Therapies:**  
The only cytokine therapy with formal regulatory approval for RCC in both the US and EU is high-dose aldesleukin (recombinant interleukin-2, IL-2).

* **Aldesleukin (Proleukin®):** Approved by the FDA in 1992 and in multiple EU states since 1990 for metastatic RCC, aldesleukin can induce durable, complete responses in a small subset of carefully selected, physically fit patients [[16](https://pmc.ncbi.nlm.nih.gov/articles/PMC8317793/)]. However, its use is limited by severe, life-threatening toxicities, including vascular leak syndrome [[13](https://www.frontiersin.org/journals/immunology/articles/10.3389/fimmu.2023.1218082/full)]. As of 2024, it remains the sole approved cytokine for this indication, a status unchanged for over three decades [[16](https://pmc.ncbi.nlm.nih.gov/articles/PMC8317793/)][[29](https://www.noahai.co/tool/clinical-result/?search_param=%7B%22indication_name%22%3A%20%5B%22Post-transplant%20acute%20kidney%20injury%22%2C%20%22Renal%20cell%20carcinoma%22%5D%2C%20%22drug_modality%22%3A%20%7B%22data%22%3A%20%5B%22Bi-specific%20Antibodies%22%5D%2C%20%22logic%22%3A%20%22or%22%7D%2C%20%22drug_name%22%3A%20%7B%22data%22%3A%20%5B%22Terns%20Pharmaceuticals%22%5D%2C%20%22logic%22%3A%20%22or%22%7D%2C%20%22top_n%22%3A%20150%7D)].
* **Interferon-α (IFN-α):** Historically used in RCC, IFN-α has been largely supplanted by more effective and better-tolerated agents. It does not carry a specific RCC indication from the FDA, and in the EU, its use is primarily noted in the context of prior therapy failure in the labels of targeted agents like axitinib and sorafenib [[17](https://pmc.ncbi.nlm.nih.gov/articles/PMC10777977/)][[19](https://www.news-medical.net/whitepaper/20220323/The-application-of-cytokines-within-cancer-immunotherapy.aspx)][[24](https://www.ema.europa.eu/en/medicines/human/EPAR/axitinib-accord)][[25](https://www.ema.europa.eu/en/medicines/human/EPAR/sorafenib-accord)].

**Bispecific Antibodies:**  
As of late 2024, **no bispecific antibody has received regulatory approval from the FDA or the European Medicines Agency (EMA) for the treatment of renal cell carcinoma** [[18](https://ascopubs.org/doi/10.1200/EDBK-25-473148)][[26](https://www.sciencedirect.com/science/article/abs/pii/S1470204523002188)]. All approvals for this class of drugs have been in other indications, primarily hematologic malignancies and, more recently, HER2-positive biliary tract cancer [[18](https://ascopubs.org/doi/10.1200/EDBK-25-473148)]. This represents a major unmet need and a significant opportunity for first-in-class development.

**Market and Regulatory Context:**  
The current first-line standard of care for most patients with advanced RCC consists of ICI-based combinations, either with another ICI (e.g., nivolumab plus ipilimumab) or a tyrosine kinase inhibitor (TKI) (e.g., pembrolizumab plus axitinib) [[7](https://www.fda.gov/drugs/resources-information-approved-drugs/oncology-cancerhematologic-malignancies-approval-notifications)][[8](https://www.fda.gov/media/172555/download)]. Any new cytokine or bispecific antibody will face a high regulatory bar, needing to demonstrate significant benefit over these established, effective regimens. The regulatory environment in the EU appears to lag behind the US in driving pivotal studies for these specific modalities in RCC, with most major trials being US-led [[27](https://www.sciencedirect.com/science/article/pii/S104346661630134X)]. This creates a conspicuous gap and an opportunity for innovators to pursue EU-centric development, potentially leveraging orphan designation and PRIME pathways at the EMA [[27](https://www.sciencedirect.com/science/article/pii/S104346661630134X)][[28](https://www.nature.com/articles/s41392-025-02269-w)].

**2. Mechanisms of Action**

**2.1. Immunological Basis of Cytokine Therapies**

Cytokine therapies aim to nonspecifically boost the host immune response against cancer cells.

* **Interleukin-2 (IL-2):** Aldesleukin acts as a powerful T-cell growth factor. At supraphysiologic doses, it promotes the proliferation and activation of cytotoxic T lymphocytes (CTLs) and Natural Killer (NK) cells, which are critical for tumor cell lysis [[3](https://www.nature.com/articles/s41392-024-01823-2)]. However, classical IL-2 also binds with high affinity to the α-chain (CD25) of the IL-2 receptor, which is highly expressed on regulatory T cells (Tregs), leading to the expansion of this immunosuppressive population and contributing to toxicity [[13](https://www.frontiersin.org/journals/immunology/articles/10.3389/fimmu.2023.1218082/full)].
* **Next-Generation Cytokines:** To overcome the limitations of aldesleukin, engineered cytokines are being developed. These include:
  + **"Not-alpha" or "IL-2v" variants (e.g., THOR-707):** These are designed with mutations that abolish or reduce binding to CD25, thereby preferentially activating CD8+ effector T cells and NK cells (which primarily use the IL-2Rβγ intermediate-affinity receptor) over immunosuppressive Tregs [[13](https://www.frontiersin.org/journals/immunology/articles/10.3389/fimmu.2023.1218082/full)].
  + **Pegylated IL-2 (e.g., bempegaldesleukin):** Pegylation extends the drug's half-life and was designed to bias signaling toward the IL-2Rβγ pathway [[13](https://www.frontiersin.org/journals/immunology/articles/10.3389/fimmu.2023.1218082/full)].
  + **Immunocytokines:** These are fusion proteins that link an IL-2 or IL-15 variant to an antibody (e.g., an anti-PD-1), aiming to deliver the cytokine payload directly to the tumor microenvironment (TME) and activate tumor-resident T cells [[14](https://www.sciencedirect.com/science/article/pii/S2211383524003149)].
* **Interleukin-18 (IL-18):** A pro-inflammatory cytokine that enhances NK cell activity and promotes Th1 responses. Its activity is naturally regulated by a decoy receptor, IL-18 binding protein (IL-18BP). Engineered "decoy-resistant" IL-18 variants are designed to bypass this inhibitory mechanism [[15](https://www.preprints.org/manuscript/202411.0864/v1/download)].

**2.2. Immunological Basis of Bispecific Antibodies**

Bispecific antibodies are engineered proteins that can simultaneously bind to two different targets. In oncology, the most common format is a T-cell engager, which acts as a bridge between a tumor cell and a T cell.

* **T-Cell Engagers:** These molecules typically bind to CD3 on the T-cell surface and a tumor-associated antigen (TAA) on the cancer cell. This forced synapse triggers T-cell activation, proliferation, and potent, targeted killing of the tumor cell, independent of traditional T-cell receptor (TCR)-MHC interactions [[5](https://jhoonline.biomedcentral.com/articles/10.1186/s13045-025-01704-3)][[17](https://pmc.ncbi.nlm.nih.gov/articles/PMC10777977/)].
* **Key Targets in RCC:** The selection of an appropriate TAA is crucial. In RCC, promising targets include:
  + **Carbonic Anhydrase IX (CAIX):** A cell surface enzyme highly and almost universally expressed in clear cell RCC (ccRCC), the most common subtype, particularly under hypoxic conditions. Its expression is low in normal tissues, making it an attractive target [[5](https://jhoonline.biomedcentral.com/articles/10.1186/s13045-025-01704-3)][[10](https://www.nature.com/articles/s41598-025-04990-6)].
  + **CD70:** A member of the tumor necrosis factor (TNF) receptor superfamily, expressed on a subset of ccRCC tumors and associated with poor prognosis. It is also the target of an investigational CAR-T therapy [[17](https://pmc.ncbi.nlm.nih.gov/articles/PMC10777977/)].
  + **ENPP3:** A cell surface protein that is another emerging target for T-cell engagers in ccRCC [[17](https://pmc.ncbi.nlm.nih.gov/articles/PMC10777977/)][[36](https://www.cancernetwork.com/view/xmab819-targets-highly-expressed-protein-in-clear-cell-renal-cell-carcinoma)].
* **Other Formats:** Beyond T-cell engagers, other bispecific concepts include dual checkpoint blockade (e.g., targeting PD-1 and CTLA-4 simultaneously) and conditional agonists (e.g., a PD-L1 x 4-1BB antibody that only activates the costimulatory 4-1BB pathway within the PD-L1-positive TME to limit systemic toxicity) [[5](https://jhoonline.biomedcentral.com/articles/10.1186/s13045-025-01704-3)][[18](https://ascopubs.org/doi/10.1200/EDBK-25-473148)].

**3. Development Pipeline**

As noted, the pipeline below is constructed from clinical trial data and publications due to the limitations of drug pipeline databases.

**3.1. Cytokine Therapy Pipeline**

| Modality | Representative Asset(s) | Stage in RCC | Key Details |
| --- | --- | --- | --- |
| **Approved** | Aldesleukin (Proleukin®) | Approved | Legacy therapy for metastatic RCC, used in select patients [[16](https://pmc.ncbi.nlm.nih.gov/articles/PMC8317793/)]. |
| **Phase III** | Bempegaldesleukin (NKTR-214) | Completed | The PIVOT-09 trial in combination with nivolumab for first-line RCC **failed to meet its primary endpoints**, a major setback for this class [[13](https://www.frontiersin.org/journals/immunology/articles/10.3389/fimmu.2023.1218082/full)]. |
| **Phase III** | Bevacizumab + Interferon Alfa-2a | Ongoing | An EU-registered trial evaluating the combination of a VEGF inhibitor with IFN-α in RCC [[32](https://www.clinicaltrialsregister.eu/ctr-search/search?query=Renal+Cell+Carcinoma)]. |
| **Phase II/III** | Low-dose IL-2 + Interferon-α | Completed/Ongoing | An adjuvant therapy trial for operable RCC, with results pending [[34](https://pubmed.ncbi.nlm.nih.gov/25304727/)]. |
| **Phase I/II** | Pegilodecakin (IL-10 agonist) | Completed | In a Phase I study, combination with an anti-PD-1 agent showed a 40% ORR in RCC patients [[2](https://www.noahai.co/tool/clinical-result/?search_param=%7B%22indication_name%22%3A%20%5B%22Post-transplant%20acute%20kidney%20injury%22%2C%20%22Renal%20cell%20carcinoma%22%5D%2C%20%22phase%22%3A%20%5B%22I%22%2C%20%22II%22%2C%20%22III%22%5D%2C%20%22top_n%22%3A%20150%7D)]. |
| **Phase I** | THOR-707 (IL-2v) | Early Clinical | A "not-alpha" IL-2 variant designed to spare Tregs; being evaluated in solid tumors [[13](https://www.frontiersin.org/journals/immunology/articles/10.3389/fimmu.2023.1218082/full)]. |
| **Preclinical** | Anti-PD-1-IL-2v Immunocytokines | Preclinical | Murine models showed complete tumor regression in RCC by selectively activating tumor-resident CD8+ T cells [[14](https://www.sciencedirect.com/science/article/pii/S2211383524003149)]. |
| **Preclinical** | Decoy-Resistant IL-18 (DR-18) | Preclinical | Showed restored antitumor immunity in solid tumor models, including RCC xenografts [[15](https://www.preprints.org/manuscript/202411.0864/v1/download)]. |

**3.2. Bispecific Antibody Pipeline**

| Modality | Representative Asset(s) | Stage in RCC | Key Details |
| --- | --- | --- | --- |
| **Approved** | *None* | N/A | No bispecific antibody is approved for RCC in the US or EU [[18](https://ascopubs.org/doi/10.1200/EDBK-25-473148)]. |
| **Phase I** | XmAb819 (ENPP3 x CD3) | Ongoing | A first-in-human trial (NCT05433142) evaluating this T-cell engager in patients with relapsed/refractory clear cell RCC [[36](https://www.cancernetwork.com/view/xmab819-targets-highly-expressed-protein-in-clear-cell-renal-cell-carcinoma)]. |
| **Early Phase** | CAIX x CD3 | Early Clinical | Dose-escalation studies have shown early signals of efficacy (ORR ~20%) with manageable CRS [[5](https://jhoonline.biomedcentral.com/articles/10.1186/s13045-025-01704-3)]. |
| **Preclinical** | CD70 x CD3 | Preclinical | Preclinical models demonstrated potent tumor eradication, supporting first-in-human trial designs [[17](https://pmc.ncbi.nlm.nih.gov/articles/PMC10777977/)]. |
| **Preclinical** | PD-L1 x 4-1BB | Preclinical | A conditional agonist format designed to mitigate hepatotoxicity seen with systemic 4-1BB agonists [[5](https://jhoonline.biomedcentral.com/articles/10.1186/s13045-025-01704-3)]. |

A related and highly relevant development is in cellular therapy. The Phase I trial of **CTX130**, an allogeneic CAR-T cell therapy targeting CD70, showed an 81.3% disease control rate in RCC patients and yielded the first documented complete response in a solid tumor with an allogeneic CAR-T, lasting over 36 months [[2](https://www.noahai.co/tool/clinical-result/?search_param=%7B%22indication_name%22%3A%20%5B%22Post-transplant%20acute%20kidney%20injury%22%2C%20%22Renal%20cell%20carcinoma%22%5D%2C%20%22phase%22%3A%20%5B%22I%22%2C%20%22II%22%2C%20%22III%22%5D%2C%20%22top_n%22%3A%20150%7D)]. This provides strong proof-of-concept for CD70 as a viable target for T-cell-based immunotherapies in RCC.

**4. Efficacy and Safety Data**

Comparing efficacy and safety across these diverse modalities reveals a clear trade-off between potent activity and toxicity, which next-generation engineering aims to solve.

| Treatment Modality | Efficacy Highlights | Key Safety & Tolerability Profile |
| --- | --- | --- |
| **High-Dose IL-2 (Aldesleukin)** | Durable complete responses in ~5-10% of patients [[16](https://pmc.ncbi.nlm.nih.gov/articles/PMC8317793/)]. | **High Toxicity:** Grade ≥3 AEs in 70-80% of patients. High rates of vascular leak syndrome, hypotension, and cardiac toxicity, requiring intensive care management [[29](https://www.noahai.co/tool/clinical-result/?search_param=%7B%22indication_name%22%3A%20%5B%22Post-transplant%20acute%20kidney%20injury%22%2C%20%22Renal%20cell%20carcinoma%22%5D%2C%20%22drug_modality%22%3A%20%7B%22data%22%3A%20%5B%22Bi-specific%20Antibodies%22%5D%2C%20%22logic%22%3A%20%22or%22%7D%2C%20%22drug_name%22%3A%20%7B%22data%22%3A%20%5B%22Terns%20Pharmaceuticals%22%5D%2C%20%22logic%22%3A%20%22or%22%7D%2C%20%22top_n%22%3A%20150%7D)]. |
| **Engineered Cytokines (e.g., IL-2v)** | **Bempegaldesleukin:** Showed objective responses but failed its pivotal trial [[13](https://www.frontiersin.org/journals/immunology/articles/10.3389/fimmu.2023.1218082/full)]. **Pegilodecakin (IL-10):** 40% ORR with anti-PD-1 in Phase I [[2](https://www.noahai.co/tool/clinical-result/?search_param=%7B%22indication_name%22%3A%20%5B%22Post-transplant%20acute%20kidney%20injury%22%2C%20%22Renal%20cell%20carcinoma%22%5D%2C%20%22phase%22%3A%20%5B%22I%22%2C%20%22II%22%2C%20%22III%22%5D%2C%20%22top_n%22%3A%20150%7D)]. | **Improved but still significant toxicity:** Grade ≥3 AEs in the range of 36-50%. Designed to reduce vascular leak, but other immune-related AEs remain [[13](https://www.frontiersin.org/journals/immunology/articles/10.3389/fimmu.2023.1218082/full)][[29](https://www.noahai.co/tool/clinical-result/?search_param=%7B%22indication_name%22%3A%20%5B%22Post-transplant%20acute%20kidney%20injury%22%2C%20%22Renal%20cell%20carcinoma%22%5D%2C%20%22drug_modality%22%3A%20%7B%22data%22%3A%20%5B%22Bi-specific%20Antibodies%22%5D%2C%20%22logic%22%3A%20%22or%22%7D%2C%20%22drug_name%22%3A%20%7B%22data%22%3A%20%5B%22Terns%20Pharmaceuticals%22%5D%2C%20%22logic%22%3A%20%22or%22%7D%2C%20%22top_n%22%3A%20150%7D)]. |
| **Bispecific T-Cell Engagers** | **CAIX x CD3:** Early data shows ~20% ORR in dose-escalation cohorts [[5](https://jhoonline.biomedcentral.com/articles/10.1186/s13045-025-01704-3)]. **XmAb819 (ENPP3 x CD3):** Efficacy data is immature [[36](https://www.cancernetwork.com/view/xmab819-targets-highly-expressed-protein-in-clear-cell-renal-cell-carcinoma)]. | **Primary concern is Cytokine Release Syndrome (CRS):** Can range from mild (fever, fatigue) to severe (hypotension, hypoxia). Manageable with step-up dosing and IL-6 receptor blockade (tocilizumab) [[5](https://jhoonline.biomedcentral.com/articles/10.1186/s13045-025-01704-3)]. Neurotoxicity is another potential risk. |
| **CD70-Targeting CAR-T (CTX130)** | **81.3% Disease Control Rate.** First documented durable CR in solid tumors with an allogeneic CAR-T [[2](https://www.noahai.co/tool/clinical-result/?search_param=%7B%22indication_name%22%3A%20%5B%22Post-transplant%20acute%20kidney%20injury%22%2C%20%22Renal%20cell%20carcinoma%22%5D%2C%20%22phase%22%3A%20%5B%22I%22%2C%20%22II%22%2C%20%22III%22%5D%2C%20%22top_n%22%3A%20150%7D)]. | **Excellent Safety Profile:** 50% of patients had CRS, but all cases were Grade 1-2. No dose-limiting toxicities, neurotoxicity, or graft-versus-host disease (GVHD) were observed [[2](https://www.noahai.co/tool/clinical-result/?search_param=%7B%22indication_name%22%3A%20%5B%22Post-transplant%20acute%20kidney%20injury%22%2C%20%22Renal%20cell%20carcinoma%22%5D%2C%20%22phase%22%3A%20%5B%22I%22%2C%20%22II%22%2C%20%22III%22%5D%2C%20%22top_n%22%3A%20150%7D)]. |

**5. Emerging Trends and Research Gaps**

**5.1. Novel Targets and Combination Strategies**

The field is moving beyond traditional approaches to embrace novel targets and rational combinations.

* **Novel Targets:** Beyond the bispecific targets (CAIX, CD70, ENPP3), other pathways are being explored. The success of **belzutifan**, a HIF-2α inhibitor, in VHL-associated RCC (70% ORR) and its ongoing Phase III trial in combination with pembrolizumab highlights the importance of the hypoxia pathway [[2](https://www.noahai.co/tool/clinical-result/?search_param=%7B%22indication_name%22%3A%20%5B%22Post-transplant%20acute%20kidney%20injury%22%2C%20%22Renal%20cell%20carcinoma%22%5D%2C%20%22phase%22%3A%20%5B%22I%22%2C%20%22II%22%2C%20%22III%22%5D%2C%20%22top_n%22%3A%20150%7D)][[6](https://www.nature.com/articles/s41392-021-00868-x)]. Other novel targets with early clinical data include HPK1 (NDI-101150) and HLA-G (TTX-080) [[2](https://www.noahai.co/tool/clinical-result/?search_param=%7B%22indication_name%22%3A%20%5B%22Post-transplant%20acute%20kidney%20injury%22%2C%20%22Renal%20cell%20carcinoma%22%5D%2C%20%22phase%22%3A%20%5B%22I%22%2C%20%22II%22%2C%20%22III%22%5D%2C%20%22top_n%22%3A%20150%7D)].
* **Combination Strategies:** The future of RCC therapy lies in combinations. Ongoing trials in the EU are exploring legacy cytokines (IL-2/IFN-α) with the anti-VEGF antibody bevacizumab [[31](https://www.clinicaltrials.gov/study/NCT00003091)][[33](https://clinicaltrials.gov/study/NCT01274273?term=AREA%5BConditionSearch%5D%28%22Renal%20Cell%20Carcinoma%22%29%20AND%20AREA%5BInterventionSearch%5D%28%22interleukin-2%22%29&rank=8)]. The most promising future strategies may involve combining next-generation cytokines or bispecifics with ICIs to overcome resistance, or even combining engineered cytokines with bispecifics to enhance T-cell function and persistence.

**5.2. Unmet Needs and Research Gaps**

Despite progress, significant gaps remain:

1. **Lack of Approved Next-Generation Therapies:** There are no approved engineered cytokines or bispecific antibodies for RCC, representing the largest unmet need.
2. **Non-Clear Cell Histologies:** Most research focuses on ccRCC. Papillary, chromophobe, and other non-clear cell subtypes have distinct biology and lack dedicated, effective immunotherapies [[11](https://www.nature.com/articles/s41392-023-01606-1)].
3. **Post-ICI Resistance:** Treatment options for patients who progress on or after ICI-based combinations are limited. The TiNivo-2 trial, which failed to show a benefit for adding nivolumab to tivozanib in this setting, underscores this challenge [[2](https://www.noahai.co/tool/clinical-result/?search_param=%7B%22indication_name%22%3A%20%5B%22Post-transplant%20acute%20kidney%20injury%22%2C%20%22Renal%20cell%20carcinoma%22%5D%2C%20%22phase%22%3A%20%5B%22I%22%2C%20%22II%22%2C%20%22III%22%5D%2C%20%22top_n%22%3A%20150%7D)].
4. **Predictive Biomarkers:** There is a critical need for biomarkers to select patients most likely to respond to a given therapy. CA9 expression for anti-CAIX therapies is one example, but more robust markers are needed [[10](https://www.nature.com/articles/s41598-025-04990-6)].
5. **Patent and Development Gaps:** A comprehensive patent search from 2020-2024 found **no patents explicitly combining a bispecific antibody with IL-2 or IL-12 for the treatment of RCC** [[20](https://patents.google.com/patent/WO2020247843A2/en)][[21](https://patents.google.com/patent/WO2021258213A1/en)][[22](https://patents.google.com/patent/WO2021202675A1/en)]. This "patent white space" indicates a significant strategic opportunity for innovation. Furthermore, the lack of EU-led pivotal trials for these modalities highlights a geographic development gap that could be filled by European academic and commercial entities, supported by frameworks like HORIZON Europe [[27](https://www.sciencedirect.com/science/article/pii/S104346661630134X)][[39](https://research-and-innovation.ec.europa.eu/document/download/70bfefda-fb4b-4a7a-934a-e80d627e3d5e_en)].

**6. Conclusion**

The immunotherapy landscape for renal cell carcinoma is in a dynamic phase of evolution. While checkpoint inhibitors form the current backbone of treatment, cytokine therapies and bispecific antibodies represent two of the most promising frontiers for future progress.

* **Cytokine therapy**, once a cornerstone of RCC treatment, is being reimagined through sophisticated protein engineering to enhance efficacy and mitigate the severe toxicities that have limited its use. While the failure of bempegaldesleukin was a setback, the lessons learned are fueling the development of more refined IL-2 variants, immunocytokines, and novel cytokine agents.
* **Bispecific antibodies** are poised to become the next major therapeutic class in RCC. With potent preclinical activity and promising early clinical signals against well-validated RCC targets like CAIX and CD70, these agents offer a new mechanism to overcome ICI resistance.

The path forward is not without challenges. The regulatory bar is high, toxicity management remains paramount, and the need for predictive biomarkers is urgent. However, the clear opportunities—highlighted by the lack of approved next-generation agents, the open patent landscape, and the promising science—ensure that cytokine therapies and bispecific antibodies will be central to the next wave of innovation in the fight against renal cell carcinoma. The success of these modalities, likely in rational combination regimens, holds the potential to deliver durable responses to a broader population of patients.