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Clinical Trials Corner: The dreaded IVC thrombus - optimizing management

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Dear Readers,

The Clinical Trials Corner of *Kidney Cancer* highlights planned or ongoing high-impact studies in renal cell carcinoma (RCC). In this issue, we highlight two small early stage trials that address a particularly morbid condition in patients with RCC- the presence of inferior vena cava (IVC) tumor thrombus.

In the future, if you feel that you would like to draw attention to a specific trial, please feel free to email us at mbparikh@ucdavis.edu or kca@iospress.com.

Sincerely,

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Noeadjuvant pembrolizumab and axitinib in renal cell carcinoma with associated inferior vena cava tumor thrombus (NEOPAX)

Status: Recruiting

Clinicaltrials.gov identifier: NCT05969496

Sponsor: University of Colorado, Denver

Enrollment: 17

Rationale: Surgical resection is often indicated for a patient with RCC who also has findings of an inferior vena cava (IVC) tumor thrombus. However, in this setting, surgery is not without risk, with significant perioperative mortality as well as elevated recurrence rates. As a result, neoadjuvant approaches to treatment of patients with RCC with IVC tumor thrombus are of interest, especially as systemic therapy approaches have evolved to include the combination of vascular endothelial growth factor tyrosine kinase inhibitors (VEGF TKIs) and immune checkpoint inhibitors (ICIs).

Study Design: This open label, Phase 2 study enrolls patients with histologically proven RCC with a clear cell component, who are deemed upfront surgical candidates suitable to undergo nephrectomy per the treating

urologist. Patients may have cT3b, cT3c, or cT4, cN0 or cN1, and cM0 or cM1 disease (participants could be suitable for nephrectomy for cytoreductive or curative intent), and must have an IVC tumor thrombus. In terms of other key eligibility criteria, participants cannot have received prior systemic therapy for RCC, cannot have active autoimmune disease requiring immunosuppressive therapy with the exception of vitiligo, Sjogren's syndrome, Type 1 diabetes, hypothyroidism or adrenal/pituitary insufficiency on stable replacement therapy. They also cannot have had active CNS metastases. All participants enrolled to the study will be treated with pembrolizumab and axitinib for a total of 12 weeks, after which they will undergo imaging to assess response and for staging. Patients can then undergo definitive surgery within 2 weeks (+/- 7 days) after end of treatment scan.

Endpoints: The primary endpoint of the study is to evaluate the change in IVC tumor thrombus extent based on Mayo classification, based on MRI imaging obtained at baseline and at 12 weeks of therapy. A co-primary endpoint is to evaluate the change in IVC tumor thrombus size from baseline using anteroposterior and transverse diameter. Secondary endpoints include evaluating surgical complications after neoadjuvant therapy, based on the Clavien-Dindo classification and using a 30-day post-operative timepoint, as well as examining the safety profile of axitinib with pembrolizumab in these patients, and 1 year progression free survival (1-yr-PFS) and overall survival (1-yr-OS).

Safety and efficacy of neoadjuvant lenvatinib and pembrolizumab in patients with renal cell carcinoma and IVC tumor thrombus

Status: recruiting

Clinicaltrials.gov identifier: NCT05319015

Sponsor: University of Texas Southwestern Medical Center

Enrollment: 30

Rationale: The rationale for this study is similar to NEOPAX- namely that, again, there is high risk of perioperative mortality or complications as well as recurrence in patients with RCC with IVC tumor thrombus. Again, the combination of a VEGF TKI and an ICI is of interest to study in the neoadjuvant setting.

Study Design: This open-label Phase 2 study enrolls patients with histologically confirmed cT3-4, N0-1, M0-1 RCC of any subtype with a level II-IV IVC thrombus. The primary tumor and thrombus must be assessed to be resectable or unresectable at the time of enrollment, and disease must be measurable based on RECIST 1.1. Archival tumor tissue must also be available. An Eastern Cooperative Oncology (ECOG) performance status of 0-1 is required. Other key eligibility criteria involves exclusion of participants who have received prior systemic therapy for RCC and of participants with known immunodeficiency or autoimmune disease requiring any form of immunosuppressive therapy except for replacement therapy. Patients with metastatic disease may not have more than three different sites of disease. Those enrolled to the study will receive neoadjuvant lenvatinib (20 mg daily) and pembrolizumab (200 mg every 3 weeks) for a total of 12 weeks, prior to surgical resection of locally advanced RCC with IVC tumor thrombus. Following surgery, patients will continue to receive adjuvant pembrolizumab for up to 13 additional doses.

Endpoints: The co-primary endpoints of the study are disease control rate (DCR), local and metastatic progression rate, and 90-day post-operative complication rate. DCR will be based on evaluating changes in size of primary tumor and size and level of IVC thrombus. Secondary endpoints include estimated blood loss, operative time, length of stay, intra-operative complications, post-operative complications, and survival outcomes (including recurrence-free survival and overall survival at 3 years).

Discussion:
These small but commendable single-center Phase 2 studies are evaluating an important question about the feasibility as well as the benefit of neoadjuvant VEGF TKI and ICI prior to surgical resection in patients with RCC with IVC thrombus. Both studies involve 12 weeks of neoadjuvant treatment, though there are some small differences. NEOPAX enrolls patients to receive neoadjuvant pembrolizumab and axitinib, and there is no specification as to whether adjuvant pembrolizumab is then administered post-operatively. Neoadjuvant lenvatinib and pembrolizumab are administered prior to surgical resection in the UTSW study, but subsequently all patients on the study will be continued on pembrolizumab in the adjuvant setting. This may impact evaluation of recurrence rates, PFS, and OS. However, the most important aspect of these studies is establishing that neoadjuvant systemic treatment is feasible- this requires multidisciplinary coordination with careful evaluation of patients by both Urologic Oncology and Medical Oncology. Moreover, these trials presuppose that IVC tumor thrombus responses will be sufficient that the thrombus will not evolve during the neoadjuvant therapy course. This, of course, carries some risk, as patients on both trials will be receiving VEGF TKIs for 12 weeks in the neoadjuvant setting, which could potentially lead to surgical complications if emergent surgical resection is required. However, presumably, these small studies will carefully select patients for whom surgeons have equipoise regarding administration of neoadjuvant therapy. If these studies are feasible, this may indicate that it is now time to consider a larger, multi-center study evaluating the benefit of neoadjuvant therapy in patients with RCC and IVC tumor thrombus.

CONFLICT OF INTEREST

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Consultant: Bristol-Myers Squibb, Exelixis, Oncocyte, Natera, Pfizer, Sanofi, Seagen