TRIAL SPOTLIGHT: A PHASE 3 RANDOMIZED STUDY COMPARING PERIOPERATIVE NIVOLUMAB VS. OBSERVATION IN PATIENTS WITH RENAL CELL CARCINOMA UNDERGOING NEPHRECTOMY (EA8143/PROSPER RCC)
LAUREN C. HARSHMAN, MD

PROSPER RCC is an innovative phase 3 randomized study poised to transform how we treat advanced high risk renal cell cancer planned for nephrectomy. In 2019, there remains no proven adjuvant systemic therapy that can increase overall survival over surgery alone for non-metastatic renal cell carcinoma (RCC). The checkpoint inhibitors are broadly effective for RCC, proven to increase overall survival in both the first and second line metastatic setting. Nivolumab, the anti-PD-1 antibody, has the longest track record and is generally tolerable.

Despite over 40 years of clinical trials testing various forms of cytokine based immunotherapy, chemotherapy, vaccines, and most recently targeted therapy, we still have no effective regimen that increases survival over surgery alone. To break this losing streak in kidney cancer and by considering the biology of how PD-1 blockade works, i.e., that it requires tumor antigen to work and build the T cell army, PROSPER is shifting from the usual surgery first/adjuvant only paradigm and priming the immune system with one dose of nivolumab prior to nephrectomy. This strategy makes sense when you think about the biology of PD-1 blockade and is backed up from mouse solid tumor models that have revealed a benefit with a short course of neoadjuvant PD-1 blockade compared to adjuvant only therapy. In humans, we have seen encouraging rates of significant pathologic response in several other cancers such as bladder, breast and lung with neoadjuvant PD-1 blockade. Two ongoing phase 2 studies of perioperative nivolumab in RCC patients have shown preliminary feasibility and safety with no surgical delays or complications.

Ultimately, the PROSPER RCC trial strives to test whether the addition of perioperative nivolumab to radical or partial nephrectomy can improve clinical outcomes in patients with high risk localized and oligometastatic disease. Specifically, we aim to increase cures and recurrence-free survival (RFS) rates by executing a three-pronged, multidisciplinary approach of presurgical priming with nivolumab followed by nephrectomy and further engagement of the immune system with 9 months of adjuvant PD-1 blockade. We plan to enroll 805 patients with clinical stage T2 or node positive M0 RCC of any histology (clear cell or non-clear cell) in this global, randomized, unblinded, phase 3 National Clinical Trials Network study. Oligometastatic disease is allowed if <3 metastases (no brain, liver or bone) that can be resected or thermally ablated within a 12 week period. The investigational arm will receive 1 dose of nivolumab 480mg IV prior to surgery followed by adjuvant nivolumab monthly for 9 months. The control arm will undergo the current standard of care: partial or radical nephrectomy followed by observation. Key safety, feasibility, and quality of life endpoints are incorporated. PROSPER RCC exemplifies team science with a host of planned correlative work to investigate the impact of the baseline immune milieu and changes after neoadjuvant priming on clinical outcomes with room for more collaborations.

PROSPER is one-third of the way accrued to our 805 patient goal, so we are calling on all NCTN sites to join us in our fight for the cure in RCC! If interested, learn more on ClinicalTrials.gov or get in touch via email at: EA8143_PROSPER@ecog-acrin.org or LaurenC_Harshman@dfci.harvard.edu.