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EDITORIAL

Adjuvant Pazopanib Does Not PROTECT Against Recurrence of High-Risk, Initially Localized Renal Cell Cancer but Does Provide Novel Insights

Grant D. Stewart, *University of Cambridge, Cambridge, United Kingdom*
Bradley C. Leibovich, *Mayo Clinic, Rochester, MN*
Sylvie Negrier, *University of Lyon, Lyon, France*
Robert A. Figlin, *Cedars-Sinai Medical Center, Los Angeles, CA*

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Improved postsurgical management to prevent subsequent progression among the 70% of patients with renal cell cancer (RCC) who present to urologic surgeons with initially localized RCC is an area of great need in urologic oncology. When considering all comers, 50% of patients with initially localized RCC will develop recurrent disease in the 10 years after nephrectomy.[1] This rate of recurrence rises to > 75% for patients deemed at high risk for recurrence,[2] at which point the disease is rarely curable. Postsurgery, patients with RCC are often surprised to hear that, unlike in other cancers, there is no evidence that adjuvant therapy improves survival. As such, the urologic oncology clinical and patient communities have been closely following the rapidly emerging evidence around use of targeted therapy as an adjuvant strategy for initially localized RCC. The assumption that agents that have proven successful in treating metastatic RCC will also be efficacious in micrometastatic RCC led to the development of a series of RCC adjuvant tyrosine kinase inhibitor (TKI) trials, recruitment for which started in 2007.[3] The results of the PROTECT (Pazopanib As Adjuvant Therapy in Localized/Locally Advanced RCC After Nephrectomy) trial,[4] published in the article that accompanies this editorial, represent the third report of a double-blind, placebo-controlled, randomized phase III trial of adjuvant vascular endothelial growth factor receptor (VEGFR) TKIs. PROTECT is reported at a fascinating juncture with our existing evidence base consisting of one large negative study of adjuvant sunitinib or sorafinib (ASSURE [Adjuvant Sorafenib or Sunitinib for Unfavorable Renal Carcinoma])[5] and one smaller positive study of adjuvant sunitinib (S-TRAC [Sunitinib as Adjuvant Treatment for Patients at High Risk of Recurrence of Renal Cell Carcinoma Following Nephrectomy]) demonstrating a hazard ratio (HR) of 0.76 ($P = .03$), providing a 1.2-year delay in disease-free survival (DFS) versus placebo.[6]

In the PROTECT trial, patients with Karnofsky Performance Status of ≥ 80% and pT2, G3-G4, N0; pT3, Gany, N0; pT4, Gany, N0; or pTany, Gany, N1 disease were randomly assigned at a one-to-one ratio to placebo or pazopanib for 1 year. Initially, patients were treated with a starting dose of pazopanib 800 mg once daily (403 randomly assigned patients). However, because of a higher-than-expected trial discontinuation rate, a decision was made by the sponsor and study steering committee (rather than being mandated by the independent data monitoring committee) to reduce this starting dose to 600 mg once daily (1,135 randomly assigned patients). Critically, the primary analysis, which originally included all patients, was also altered, to analysis of DFS only in those patients receiving the 600-mg starting dose of pazopanib, effectively restarting the study. Methodologically, this would seem to be the purest way in which to assess the outcome of PROTECT. However, it is interesting to note that trial-level starting-dose reductions are common in adjuvant trials. In ASSURE, the starting dose of sunitinib was reduced from 50 to 37.5 mg and of sorafenib from 400 mg twice per day to once daily, with the aim of dose escalation; however, the primary analysis remained DFS of the entire cohort.[5] The intended benefit in PROTECT of reducing the pazopanib starting dose was to reduce toxicity and trial discontinuation. However, despite a comparable toxicity profile of pazopanib in this localized RCC cohort relative to metastatic RCC studies, this aim did not come to fruition, with the discontinuation rate remaining similar after the dose reduction (39% of intention-to-treat (ITT) patients receiving 800 mg discontinued pazopanib *v* 35% of ITT patients receiving 600 mg, compared with a maximum of 24% in metastatic RCC pazopanib trials[7]). In retrospect, had the PROTECT trial management group followed the lead of previous RCC adjuvant studies and analyzed the DFS of the entire cohort, PROTECT may well have been a positive study. One of the key learning points from PROTECT is how different patient tolerance of toxicity is among patients with non-metastatic disease versus those with metastatic disease, for whom drug therapy is usually the sole treatment. Thus, successful direct translation of drug dosing and administration schedules from the metastatic setting is not guaranteed. However, a related finding from PROTECT was that quality of life returned to baseline levels as soon as treatment was stopped; indeed, the only clinically relevant reduction in quality of life was at 8 weeks after starting the drug, suggesting that good counseling, especially early in the study, may be essential in preventing patient discontinuation of the study drug.

On initial inspection of the survival curves and HRs of the ITT 800-mg versus placebo cohorts, it seems there might be benefit in

this adjuvant pazopanib dose, with a significant improvement in DFS (HR, 0.69; $P = .02$), which in turn pushed the ITT all-patient cohort to a significantly improved DFS with pazopanib over placebo (HR, 0.80; $P = .01$). However, the ITT 800-mg cohort was an underpowered and nondefinitive secondary end point, which included only 198 patients receiving pazopanib and 205 receiving placebo versus 571 and 564 patients, respectively, in the primary end point ITT 600-mg cohort. Although one cannot be definitive, there seems to be a marked difference in DFS rate in the placebo group between ITT patients receiving 600 versus 800 mg (3-years DFS rate, 64% *v* 56%, respectively; whereas DFS rates for pazopanib-treated ITT patients were similar at 67% and 66% for 600 *v* 800 mg, respectively). The reason for such a difference in sequentially recruited patients in a randomized controlled trial is unclear; the authors believe it may have resulted from missing demographic data; nonetheless, this difference may account for the significant improvement in DFS at the ITT 800-mg dose.

How should we interpret PROTECT in the context of ASSURE and S-TRAC? The PROTECT authors suggest that all three adjuvant studies reported to date enrolled a similar population of patients. However, the level of interstudy heterogeneity appears to make cross-study comparisons even more invalid than usual. Key eligibility criteria differed across the three studies. First, PROTECT and S-TRAC recruited patients with clear cell or predominantly clear cell RCC, whereas in ASSURE, 20% of patients had non–clear cell RCC. Second, there was limited uniformity in patient prognostic risk inclusion criteria. PROTECT claimed to risk stratify using stage, size, grade and necrosis, but the scores were not tabulated, and necrosis was not included[8]; similarly, S-TRAC and ASSURE inclusion criteria were based on the University of California Los Angeles Integrated Staging System (UISS), but the studies did not adhere rigidly to the defined criteria.[9] When mapped onto the UISS, all three studies included intermediate- and high-risk patients,[9] but of the three trials, ASSURE had the least aggressive profile (setting lower end of inclusion criteria at pT1b, G3/4, N0 disease), followed by PROTECT (including patients with pT2, G3/4, N0 disease) and S-TRAC, with the highest risk profile (including patients with pT3, Gany, N0 disease). S-TRAC also included a modified very high-risk UISS group as a preplanned secondary analysis, where a 2.2-year delay in DFS after sunitinib therapy was seen (HR, 0.74; $P = .04$).[6] In all three studies, $>$ 80% of included patients had pT3 disease, the majority of whom will have had pT3a disease; this is a heterogeneous group of patients when considering sinus fat versus perirenal fat versus renal vein invasion, with markedly different outcomes, also dependent on tumor size.[10,11] These concepts emphasize that more advanced and unified prognostic scores, potentially including molecular stratifiers such as the RNA-based recurrence score,[12,13] are needed for the design of future adjuvant studies. In the meantime, access to patient-level, rather than trial-level, data from the three adjuvant trials is necessary to allow accurate meta-analysis.

Putting aside these issues and the possibility that PROTECT might have been positive using the original planned analysis, PROTECT follows ASSURE in representing another large negative study of an adjuvant VEGFR TKI in initially localized RCC. As in both S-TRAC and ASSURE, overall survival, which would seem to be of key importance to patients in deciding whether to begin adjuvant therapy, was a secondary end point in PROTECT. As in the other studies, PROTECT did not show a significant survival advantage for pazopanib after a median of 30 months of follow-up, although the data are currently immature.

The only positive RCC adjuvant study to date, S-TRAC, was also the only one that did not require a protocol amendment for the starting dose. All patients began sunitinib treatment at 50 mg once daily (dose reduction rate, 34%; discontinuation rate, 28%).[6] Taken together with the information from PROTECT (ie, ITT patients receiving 800 mg seemed to have significantly improved DFS), these data indicate that cumulative dose of VEGFR TKI might be key in delaying recurrence.

Another difference in the S-TRAC study was that it was the only study with central imaging review for both baseline and primary end point. There was no central imaging review in ASSURE, and there was only baseline review in PROTECT. It is impossible to conclude that this was a defining factor in the results of ASSURE or PROTECT, but it was a differentiating feature of the S-TRAC design. On the basis of these data, should central imaging review at baseline and primary end point now be standard?

We now have one positive study, one negative study, and one negative study with tantalizing secondary end points. There are a series of other RCC adjuvant TKI studies due to report over the next few years[3]: SORCE (a phase III randomised double-blind study comparing SOrafenib with placebo in patients with Resected primary renal CEll carcinoma at high or intermediate risk of relapse; patients randomly assigned at a three-to-three-to-two ratio to sorafenib for 1 year followed by placebo for 2 years, sorafenib for 3 years, or placebo for 3 years; ClinicalTrials.gov identifier: NCT00492258), EVEREST (EVErolimus for Renal Cancer Ensuing Surgical Therapy; everolimus *v* placebo in nine courses of 6 weeks; ClinicalTrials.gov identifier: NCT01120249), and ATLAS (Adjuvant Axitinib Therapy of Renal Cell Cancer in High Risk Patients; axitinib *v* placebo for 3 years; ClinicalTrials.gov identifier: NCT01599754). On the basis of our now greater understanding of how patients with nonmetastatic disease respond to treatment with targeted therapy, there will be several unique points on which each upcoming trial will provide information. First, we will gain the first data on axitinib and everolimus in the adjuvant setting. In all three published adjuvant trials, there was a perceptible separation of the DFS Kaplan-Meier curve during receipt of therapy; furthermore, the DFS advantage in S-TRAC was 1.2 years, suggesting that the study drug may extend DFS for the duration of treatment. As such, secondly, we will also further define the role of more chronic treatment based on the SORCE and ATLAS trials, where patients receive 3 years of therapy. Third, the strategies of different adjuvant studies for keeping patients on higher doses of drug for longer will be scrutinized in more detail, because cumulative dose seems to be critical in the adjuvant setting. It does seem that the dosing tolerated by metastatic patients is not tolerated in the same proportion of patients postnephrectomy for localized disease. Fourth, a better understanding of how to counsel patients on what they can expect is needed from previous and ongoing adjuvant studies. Finally, and perhaps most importantly, none of the adjuvant studies have shown any overall survival benefit (S-TRAC showed a delay in progression only), placing a focus on what exactly patients would expect to gain from a period of adjuvant therapy with its concomitant toxicity. In particular, is deferment of potentially symptomatic metastases (and for how long), without prolongation of life, desired by patients? It is for reasons such as this that patients must be involved in

the design of clinical trials, especially in a setting where approximately 50% patients will not develop relapse without systemic therapy after surgery but would be exposed to associated drug toxicity.

As we shift focus back to our current clinical practice, adjuvant therapy is not standard of care after surgery for initially localized RCC, and PROTECT does not provide further evidence altering this viewpoint. As such, we are now starting to recruit patients to the next era of adjuvant RCC trials using immunooncology agents.[3] However, PROTECT has provided a greater understanding of the nuances of the effect of VEGFR TKIs in pT2+ clear cell RCC after surgery and, importantly for ongoing immunooncology adjuvant trials, has not provided any suggestion that the control arm of these studies needs to be altered, at least not yet.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Grant D. Stewart
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