Kidney Cancer Research Network of Canada consensus statement on the role of adjuvant therapy after nephrectomy for high-risk, non-metastatic renal cell carcinoma: A comprehensive analysis of the literature and meta-analysis of randomized controlled trials

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Abstract

Introduction: The Kidney Cancer Research Network of Canada (KCRNC) collaborated to prepare this consensus statement about the use of target agents as adjuvant therapy in patients with non-metastatic renal cell carcinoma (nmRCC) after nephrectomy. We reviewed the published data and performed a meta-analysis of studies that focused on vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitors (TKIs).
Methods: A systematic literature search identified seven trials on adjuvant target therapy in nmRCC. Three trials, the ASSURE, S-TRAC, and PROTECT, focused on VEGFR TKIs and represented the focus of the study, including a meta-analysis combining their data on disease-free survival (DFS) and overall survival (OS).
Results: The ASSURE trial showed no DFS or OS benefit of TKIs over placebo after one year of adjuvant sorafenib or sunitinib. In contrast, the S-TRAC trial showed improved DFS after one year of adjuvant sunitinib using central review process, but not using investigator review process. No OS benefit was recorded in either study. Recently, the PROTECT trial also showed no DFS or OS benefit when one year of adjuvant pazopanib was compared to placebo. Meta-analyses of the pooled DFS and OS estimates from all three trials resulted in DFS and OS hazard ratios of 0.87 (95% confidence interval [CI] 0.73–1.04) and 1.04 (95% CI 0.89–1.22), respectively.
Conclusions: Data from three available clinical trials of adjuvant VEGFR TKIs vs. placebo do not currently support the use of adjuvant TKI therapy as standard of care after nephrectomy for nmRCC. At this time, adjuvant TKI-based adjuvant therapy is not recommended for routine use after nephrectomy for high-risk nmRCC, but highly motivated patients may benefit from a discussion with their oncologist regarding the risks and benefits of adjuvant TKI.

Introduction

Several trials were designed to evaluate the effect of adjuvant therapy in patients with non-metastatic renal cell carcinoma (nmRCC) treated with either partial or radical nephrectomy.

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In this report, we review the current evidence regarding adjuvant targeted agent therapy after nephrectomy for nmRCC and provide a meta-analysis of the three published vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitors (TKIs)-based adjuvant trials,[1-3] as discussed at the 2017 Canadian Kidney Cancer Forum (CKCF)[4] and endorsed by the Kidney Cancer Research Network of Canada (KCRNC).[5]

Evidence acquisition

Eligibility criteria

A review of the literature was performed in November 2017 to identify relevant randomized controlled studies evaluating the effect of adjuvant therapy in surgically treated nmRCC using PubMed, Embase, Medline, and Cochrane library, as well as *ClinicalTrials.gov* registry. The following key words were used alone or in combination: renal cell carcinoma, adjuvant therapy, antiangiogenic therapy TKI, nephrectomy, target agents, treatments, and prognosis. Only English language original articles were considered.

Study selection

The search yielded seven prospective randomized trials of adjuvant targeted agents after nephrectomy for patients with high-risk nmRCC: ASSURE,[1] S-TRAC,[2] PROTECT,[3] SORCE,[6] EVEREST,[7] ATLAS,[8] and ARISER[9] (Table 1). The ARISER trial examined a carbonic anhydrase IX inhibitor (girentuximab). It reported negative findings and was not considered in this review due to its different mechanism of action and treatment molecule unavailability in Canada. The EVEREST trial focused at mammalian target of rapamycin (m-TOR) inhibitor (everolimus) and was not included due to lack of reported findings. Of five trials that focused on adjuvant TKI therapy, three published their findings: ASSURE (sorafenib and sunitinib), S-TRAC (sunitinib), and PROTECT (pazopanib), and represent the focus of this report and of the meta-analysis.

Statistical analyses

A quantitative synthesis (i.e., meta-analysis) was performed on the ASSURE, S-TRAC, and PROTECT trials. For disease-free survival (DFS) and overall survival (OS) data, hazard ratios (HR) and 95% confidence intervals (CI) obtained directly from studies were pooled to compare results.

Evidence synthesis

The ASSURE trial

The ASSURE trial[1] randomized 1943 patients with completely resected stage pT1b or greater nmRCC. Patients were randomly assigned (1:1:1) to initially receive 54 weeks of sunitinib (n=647) 50 mg once per day orally throughout the first four weeks of each six-week (four weeks on/two weeks off) cycle continuous, sorafenib (n=649) 400 mg twice per day orally, or placebo (n=647). Treatment was discontinued due to toxicity by 193 of 438 (44%) patients on sunitinib, 199 of 441 (45%) patients on sorafenib, and 47 of 444 (11%) patients on placebo. Upon review of this data, the starting dose of each drug was subsequently reduced and then individually titrated up to the original full doses if possible. The most common grade 3 or worse adverse events were hypertension (17% sunitinib patients, 16% sorafenib patients), hand-foot syndrome (15% sunitinib patients, 33% sorafenib patients), rash (2% sunitinib patients, 15% sorafenib patients), and fatigue (18% sunitinib patients, 7% sorafenib patients). The primary analysis showed no significant differences in DFS between study arms: median of 5.8 years (interquartile range [IQR] 1.6–8.2) for sunitinib (HR 1.02; 95% CI 0.85–1.23; p = 0.8), 6.1 years (IQR 1.7–not estimable [NE]) for sorafenib (HR 0.97; 95% CI 0.80-1.17; p=0·7184), and 6.6 years (IQR 1.5–NE) for placebo. In post-hoc subgroup analyses of pathological stage T3 or T4 patients, American Joint Committee on Cancer (AJCC) stage III–IV patients, as well as patients with Fuhrman grade 3 or 4, sunitinib adjuvant therapy failed to demonstrate either DFS or OS benefit compared to placebo. There were six deaths related to treatment: four in sunitinib group vs. one in sorafenib group and one in placebo group. The ASSURE trial investigators concluded that adjuvant treatment with the VEGFR TKI sorafenib or sunitinib did not improve survival relative to placebo. Furthermore, substantial treatment discontinuation occurred in the treatment arm because of excessive toxicity, despite dose reduction strategies. These results provided an important rationale against the use of these drugs for high-risk nmRCC patients in the adjuvant setting after nephrectomy for nmRCC.

The S-TRAC trial

The S-TRAC trial[2] randomized 615 patients with loco-regional, high-risk clear-cell nmRCC to receive either sunitinib (50 mg per day) or placebo on a four-weeks-on, two-weeks-off schedule for one year or until disease recurrence, unacceptable toxicity, or consent withdrawal. The primary endpoint of the study was DFS. Using central radiological review, the median duration of DFS was 6.8 years (95% CI 5.8–

Table 1. Descriptive table of the 7 randomized controlled trials that focused on adjuvant target agent in non-metastatic renal cell carcinoma (RCC)

Trial	n	Inclusion criteria		Treatment arms	Study accrual period	Status of the trial
		Stage of disease	RCC histology subtype			
S-TRAC (NCT00375674)	615 (309 sunitinib vs. 306 placebo)	High-risk according to modified UISS[15]00 (tumour stage 3 or higher, regional lymph-node metastasis, or both)	Confirmed RCC	Oral sunitinib (50 mg per day) or placebo on a 4-weeks-on/2-weeks-off schedule for 1 year	August 2007 to April 2011	Complete
ASSURE (NCT00326898)	1943 (647 sunitinib, 649 sorafenib, 647 placebo)	pT1b G3–4 N0 (or pNX where clinically N0) M0 to T (any) G (any) N + (fully resected) M0	Confirmed clear-cell RCC	54 weeks of either sunitinib taken orally at 50 mg per day for the first 28 days of each 6-week cycle, or sorafenib taken orally at 400 mg twice per day throughout all cycles, or placebo	April 2006 to September 2010	Completed
SORCE (NCT00492258)	1656	Intermediate- and high-risk according to Leibovich score[16]00 3–11	Confirmed RCC	Arm I: Oral placebo twice daily for 3 years Arm II: Oral sorafenib tosylate twice daily for 1 year and oral placebo twice daily for 2 years Arm III: Oral sorafenib tosylate twice daily for 3 years	June 2007 to August 2012	Study completed Last update August 2013
EVEREST (NCT01120249)	1218	Pathologically intermediate-high or very-high-risk of recurrence, microvascular invasion of the renal vein of any grade or stage, R0, M0	Confirmed RCC	Oral everolimus once daily on days 1–42. Treatment repeats every 6 weeks for 9 courses in the absence of disease progression or unacceptable toxicity	April 2011 to Estimated October 2021	Ongoing, not recruiting Last update October 2016
PROTECT (NCT01235962)	1538 (198 pazopanib 800 mg vs. 205 placebo, amended to 571 pazopanib 600 mg vs. 564 placebo)	pT2G3–4N0, pT3–T4 $G_{any}N0$, or $pT_{any}G_{any}N1$	Clear-cell or predominant clear-cell RCC histology	Pazopanib 800 mg daily vs. placebo, amended to pazopanib 600 mg daily vs. placebo, for 1 year	December 2010 to September 2013	The final data cutoff for OS analysis is planned for April 15, 2019
ATLAS (NCT01599754)	700	pT2–4, N0 or Nx, M0 or Any pT, N1, M0	Clear-cell RCC or predominantly (>50&) clear-cell RCC	Axitinib starting at 5 mg twice daily given 3 years vs. placebo	April 2012 to Estimated May 2019	Ongoing, not recruiting Last update May 2016
ARIZER (NCT00087022)	864 (433 girentuximab vs. 431 placebo)	pT3/pT4Nx/N0M0 or pTanyN+M0 or pT1b/pT2Nx/N0M0 with nuclear grade 3 or greater	Clear-cell RCC	Intravenous 50 mg girentuximab (week 1) followed by weekly 15-minute intravenous infusions of 20 mg (weeks 2–24). Those randomized to placebo received an infusion of phosphate-buffered saline with polysorbate 20 diluted in 100 mL of normal saline on an identical schedule	July 2004 to August 2008	Completed

not reached) in the sunitinib group and 5.6 years (95% CI 3.8–6.6) in the placebo group (HR 0.76; 95% CI 0.59–0.98; p=0.03). The statistical significance was not confirmed using investigator radiological review (HR 0.81; 95% CI 0.64–1.02; p=0.08). OS data were not mature at data cutoff. Nonetheless, the reported HR for OS failed to reveal an improvement: 1.01 (95% CI 0.72–1.44; p=0.94).

As in the ASSURE trial, S-TRAC required dose reductions. Adverse events were more frequent with sunitinib than placebo (34.3 vs. 2%), as were dose interruptions (46.4 vs. 13.2%) and discontinuations (28.1 vs. 5.6%). Grade 3 or 4 adverse events were more frequent in the sunitinib group (48.4% for Grade 3 events and 12.1% for Grade 4 events) than in the placebo group (15.8% and 3.6%, respectively). The incidence of serious adverse events was similar in both groups (21.9% for sunitinib vs. 17.1% for placebo) and no deaths were attributed to toxicity. Contrary to the ASSURE trial, these observations indicated that among patients with high-risk clear-cell nmRCC after nephrectomy, the median DFS duration was significantly longer in the sunitinib group than in the placebo group: 6.8 years (95% CI 5.8–not reached) vs. 5.6 years (95% CI 3.8–6.6).

The PROTECT trial

Results from the randomized, double-blind, phase 3 PROTECT trial were recently published. It assessed the effect of pazopanib 800 mg vs. placebo in high-risk nmRCC after nephrectomy. It is noteworthy that one year after study initiation, the primary objective (DFS for pazopanib 800 mg) was amended based on a high treatment discontinuation rate secondary to adverse events. The primary study objective became DFS for pazopanib 600 mg vs. placebo. Secondary objectives were DFS for pazopanib 800 mg vs. placebo, as well as DFS for pazopanib at either 800 mg or 600 mg vs. placebo. The PROTECT trial also examined OS for both treatment doses, relative to placebo. Overall, the PROTECT trial enrolled 1538 patients: 571 received pazopanib 600 mg, 198 received pazopanib 800 mg, and 769 received placebo. The study did not meet its primary endpoint in the intention-to-treat (ITT) pazopanib 600 mg group, as evidenced by DFS HR of 0.86 (95% CI 0.70–1.06) relative to placebo. Conversely, the results of the secondary endpoint analyses demonstrated a DFS benefit in the ITT pazopanib 800 mg group (HR 0.69; 95% CI 0.51–0.94) and in the combined ITT pazopanib 800 mg and ITT pazopanib 600 mg groups (HR 0.80; 95% CI 0.68–0.95) relative to placebo. The DFS results for the pazopanib 800 mg and the pazopanib 600 mg were conflicting. The OS results are not yet mature and for now are inconclusive. To date, the reported HR for OS failed to reveal an improvement either for pazopanib 600 mg (HR 0.79; 95% CI 0.57–1.09; p=0.16) or for pazopanib 800 mg (HR 0.9; 95% CI 0.55–1.46; p=0.66). The final data cutoff for OS analyses is planned for April 2019.

Reported adverse event data showed that nearly all (558/568, 98%) 600 mg pazopanib patients and (501/558, 90%) placebo patients experienced treatment-related adverse events. Of those in the ITT 600 mg pazopanib group, 60% experienced greater than Grade 3/4 adverse events vs. 21% in the placebo arm. Taken together, pazopanib showed no OS benefit, but improved DFS at the 800 mg doses. On the other hand, pazopanib 800 mg and pazopanib 600 mg also contributed to an elevated proportion of side effects.

Meta-analysis

To examine the combined findings of all three VEGFR TKI-based adjuvant studies, including the most recent PROTECT trial, we performed a meta-analysis of the S-TRAC, ASSURE, and PROTECT results using DFS and OS data from their original reports.[1-3] Median DFS estimates for sunitinib vs. placebo group were 81.6 vs. 67.2 months (HR 0.76; 95% CI 0.59–0.98; p=0.03) in the S-TRAC and 70 vs. 79.6 months (HR 1.02; 95% CI 0.85–1.23; p=0.7) in the ASSURE trial. Median DFS estimate for sorafenib vs. placebo was 73.4 vs. 79.6 months (HR 0.97; 95% CI 0.80–1.17; p=0.7) in the ASSURE trial. Median recurrence-free survival data were not mature in the PROTECT trial. Nonetheless, after three years of followup, the DFS rates for pazopanib 800 mg vs. placebo were respectively 66 vs. 56% (HR 0.69; 95% CI 0.51–0.94; p=0.02) and 67 vs. 64% (HR 0.86; 95% CI 0.69–1.06; p=0.16) for pazopanib 600 mg vs. placebo. The pooled DFS estimates derived from S-TRAC, ASSURE, and PROTECT (800 mg) resulted in a HR of 0.87 (95% CI 0.73–1.04) (Fig. 1). The pooled DFS estimates derived from the S-TRAC, ASSURE, and PROTECT (600 mg) resulted in a HR of 0.92 (95% CI 0.82–1.03) (Fig. 2). Regarding OS outcomes, no study had mature OS data and none reported a statistically significant OS benefit favouring TKI-based treatment. OS rates for sunitinib vs. placebo were 79.3 vs. 79.1% (HR 1.01; 95% CI 0.71–1.44) in the S-TRAC and 77.9 vs. 80.3% (HR1.17; 95% CI 0.90–1.52; p=0.17) in the ASSURE trial. OS rates for sorafenib vs. placebo were 80.5 vs. 80.3% (HR 0.98; 95% CI 0.75–1.28; p=0.85) in the ASSURE trial. The reported OS rate for pazopanib 800 mg vs. placebo after three years of followup were 85.4 vs. 82.9% (HR 0.90; 95% CI 0.55–1.46; p=0.66) and 88.6 vs. 85.3% (HR 0.79; 95% CI 0.57–1.09; p=0.16) for pazopanib 600 mg vs. placebo in the PROTECT trial. The pooled OS estimates derived from S-TRAC, ASSURE, and PROTECT (800 mg) trials resulted in a HR of 1.04 (95% CI 0.89–1.22) (Fig. 3). The pooled OS estimates derived from S-TRAC, ASSURE, and PROTECT (600 mg) trials resulted in a HR of 0.99 (95% CI 0.85–1.17) (Fig. 4). Taken together, the meta-analysis results failed to show any statistically significant DFS or OS benefit of adjuvant VEGFR TKI therapy in patients with high-risk nmRCC when all three trials were considered.

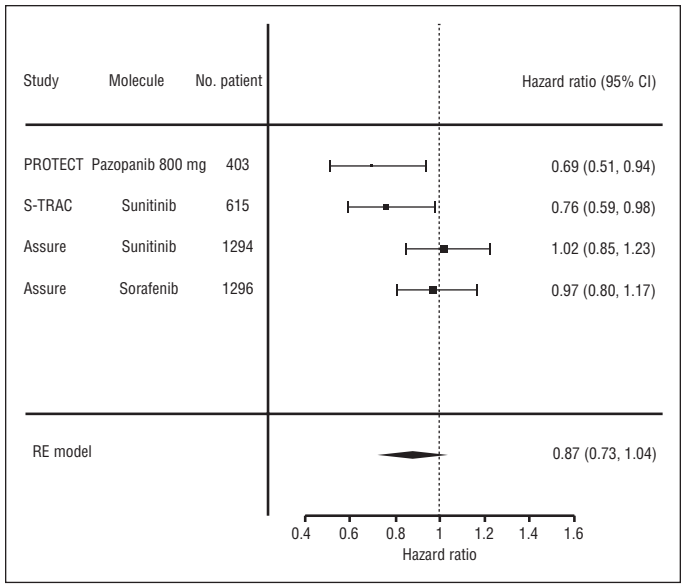

Fig. 1. Forest plot showing disease-free survival (DFS) for sunitinib, sorafenib, and pazopanib 800 mg, as recorded in ASSURE, S-TRAC, and PROTECT trials. The left columns respectively show the study name, the active treatment agent, and the sample size. The right column shows the hazard ratio (HR) and the 95% confidence interval (CI) for each study, as well as for their pooled effect.

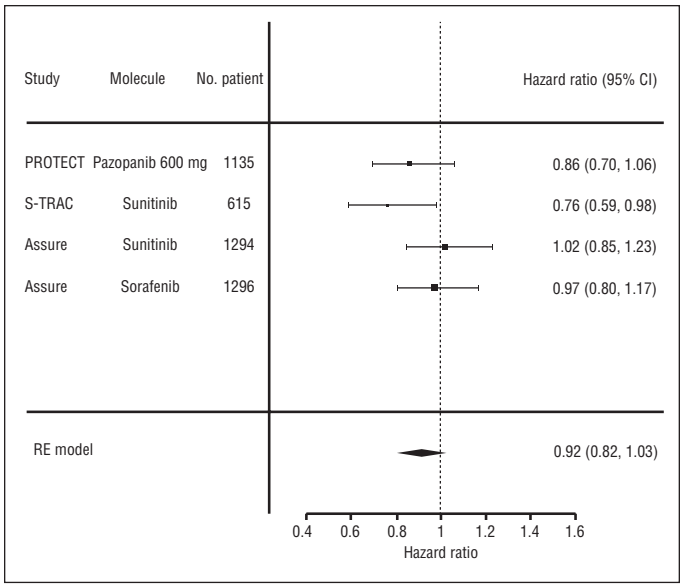

Fig. 2. Forest plot showing disease-free survival (DFS) for sunitinib, sorafenib, and pazopanib 600 mg, as recorded in ASSURE, S-TRAC, and PROTECT trials. The left columns respectively show the study name, the active treatment agent, and the sample size. The right column shows the hazard ratio (HR) and the 95% confidence interval (CI) for each study, as well as for their pooled effect.

Discussion

The standard of care for nmRCC remains nephrectomy. However, despite complete resection and negative margins, many patients may experience disease recurrence. The latter puts them at risk of death from RCC.[10] Seven randomized studies attempted to evaluate if adjuvant therapy after nephrectomy improves survival. Of those, five examined the use of VEGFR TKI-based therapy. To date, the ASSURE, S-TRAC, and the PROTECT trials have reported their findings. All three studies agreed that toxicity is an important barrier to adjuvant therapy. However, their results regarding

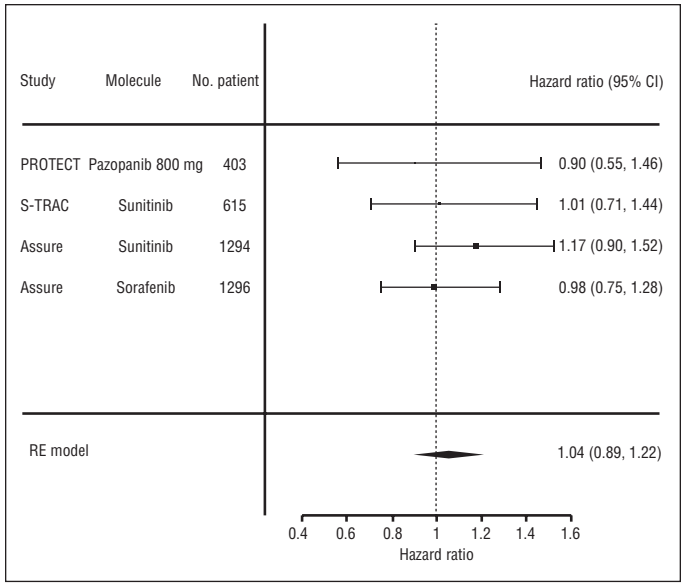

Fig. 3. Forest plot showing overall survival (OS) for sunitinib, sorafenib, and pazopanib 800 mg, as recorded in ASSURE, S-TRAC, and PROTECT trials. The left columns respectively show the study name, the active treatment agent, and the sample size. The right column shows the hazard ratio (HR) and the 95% confidence interval (CI) for each study, as well as for their pooled effect.

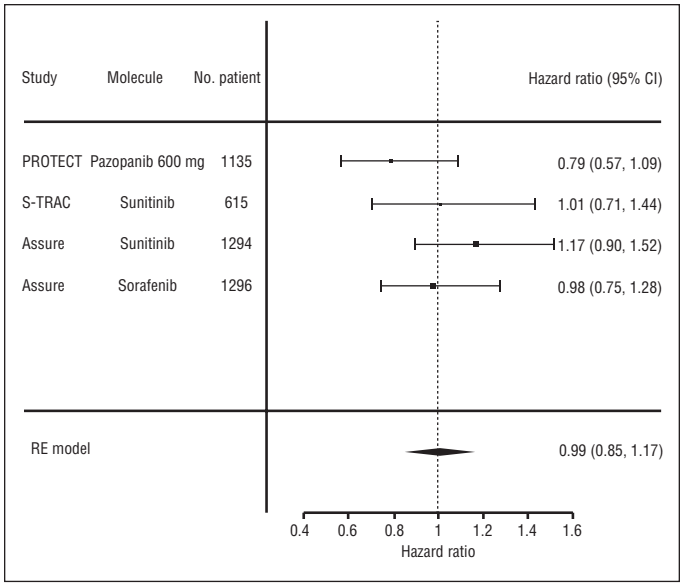

Fig. 4. Forest plot showing overall survival (OS) of sunitinib, sorafenib, and pazopanib 600 mg, as recorded in ASSURE, S-TRAC, and PROTECT trials. The left columns respectively show the study name, the active treatment agent and the sample size. The right column shows the hazard ratio (HR) and the 95% confidence interval (CI) for each study, as well as for their pooled effect.

the protective effect of adjuvant therapy on DFS conflicted. Several comments regarding these findings deserve mention.

First, ASSURE examined sorafenib and sunitinib in the adjuvant setting after nephrectomy for nmRCC and both agents failed to demonstrate a DFS or OS benefit relative to placebo.[1] The S-TRAC trial showed DFS benefit, without OS benefit.[2] The PROTECT trial failed to show DFS benefit, except for pazopanib 800 mg subgroup, where accrual was interrupted due to adverse effects.[3] In all three reports, data have not reached adequate maturity for final OS analyses. Nonetheless, not even a trend towards OS benefit from adjuvant therapy was observed in any of three studies. Moreover, lack of meaningful trend toward OS benefit questions the reversal of OS findings with longer followup.

Second, DFS data from the ASSURE and S-TRAC trials regarding sunitinib are conflicting. The ASSURE trial showed no DFS benefit in patients treated with sunitinib relative to placebo. Moreover, post-hoc subgroup analyses also failed to show statistically significant DFS benefit in subgroups of patients with more aggressive nmRCC characteristics: pT3–4 (824 patients on sunitinib or placebo), AJCC stages III–IV, as well as in Fuhrman grade 3 and 4 (847 patients on sunitinib or placebo).[1] These observations suggest that these specific tumour characteristics are not the driver of the null DFS effect observed in the ASSURE trial. Therefore, a study design that would exclusively rely on patients with the most aggressive pathological characteristics would unlikely contribute to greater DFS benefit than that reported. In view of these findings, the S-TRAC trial findings that showed a DFS benefit in sunitinib-exposed patients cannot be solely explained by inclusion of patients with more aggressive disease characteristics. Moreover, it is of interest that within the S-TRAC trial, patients with more aggressive disease characteristics failed to demonstrate a stronger DFS benefit (HR 0.74, investigator review) than that observed in all patients (HR 0.76, investigator review). Thus, both trials suggest that inclusion of patients with more aggressive disease characteristics will result in little, if any additional effect on DFS.

Third, important sunitinib dosing characteristics distinguish both studies and may represent the most plausible explanation for the discordant findings regarding the effect on DFS that were recorded in the ASSURE and the S-TRAC trials. In the ASSURE trial, important dose reductions were required due to treatment toxicity that translated into a 44% sunitinib discontinuation rate vs. 28% in the S-TRAC trial. Despite this, in ASSURE, a median of eight six-week sunitinib cycles (of an expected total of nine cycles) were administered to those who completed treatment (56%). Moreover, the proportion of sunitinib patients, who received the intended ASSURE sunitinib dose at cycle three was only 42%. However, at mid-study, the starting dose reduction threshold was reduced from 50 to 37.5 mg to avoid elevated treatment discontinuation rate and this starting dose was administered to 34% of ASSURE patients. In addition, dose reductions to 25 mg were allowed in ASSURE. In post-hoc ASSURE analyses, comparisons of patients who started sunitinib at a reduced dose vs. placebo patients favoured the placebo arm. In consequence, the ASSURE trial data suggest that dose reductions contributed to inferior response rates. Sunitinib dosing also warrants close examination within the S-TRAC trial. Here, the starting dose was 50 mg and dose reductions down to 37.5, but not to 25 mg, were allowed. This observation may, at least in part, explain better DFS benefit of sunitinib in S-TRAC relative to that reported in the ASSURE trial. In consequence, dose escalations, such as described by Bjarnason et al[11,12] might result in better DFS and possibly also in better OS, and dose individualization may warrant consideration if adjuvant sunitinib therapy is considered.

Fourth, additional differences between study designs of the ASSURE and S-TRAC regarding sunitinib need to be considered. Foremost of these is the sample size difference that distinguishes ASSURE from S-TRAC. Specifically, the ASSURE trial randomized 647 patients each to the sunitinib and placebo arms. The S-TRAC trial was smaller, with only 309 and 306 patients randomized to sunitinib or placebo, respectively. The sample size differences invariably weigh on the results of all meta-analyses. Indeed, the European Association of Urology (EAU) RCC guideline panel commented on a meta-analysis[13] of the ASSURE and S-TRAC trials to help reconcile the conflicting DFS data. The pooled ASSURE and S-TRAC-derived DFS and OS estimates showed no differences favouring sunitinib over placebo: pooled DFS estimates resulted in a HR of 0.89 (95% CI 0.67–1.19) and pooled OS estimates resulted in a HR of 1.12 (95% CI 0.92–1.35). The meta-analysis exclusively focused on the sunitinib data of the ASSURE and on the central review for the S-TRAC trial. It is also important to note that the negative ASSURE trial had no central review. Conversely, the positive DFS findings were reported upon central review of the S-TRAC data. Similar to ASSURE, investigator review within the S-TRAC trial showed no statistically significant DFS benefit of adjuvant sunitinib when all patients were analyzed (HR 0.81; 95% CI 0.64–1.02), as well as when only patients with more aggressive characteristics were analyzed (HR 0.76; 95% CI 0.58–1.01). This observation has two implications. Firstly, it shows that central review would have been ideal within the ASSURE study. It is, however, unlikely that central review would have changed the reported DFS from truly insignificant (HR 1.02; 95% CI 0.85–1.23; p=0.8) to statistically significant and clinically relevant findings. Secondly, it is important to note the effect of central vs. investigator review on reported DFS in all patients, as well in the higher-risk subgroup in the S-TRAC study. In both S-TRAC analyses, central review yielded statistically significant results (all patients HR 0.76 [95% CI 0.59–0.98]; higher-risk patients HR 0.74 [95% CI 0.55–0.99]), while investigator review

resulted in loss of statistical significance (all patients HR 0.81 [95% CI 0.64–1.02]; high-risk patients HR 0.76 [95% CI 0.58–1.01]). Such sensitivity to radiological interpretation (central vs. investigator review) questions the robustness of the S-TRAC trial findings, especially given that central review is not feasible in the real-world clinical environment.

Fifth, it is of note that a third prospective, randomized controlled trial of a VEGFR inhibitor, the PROTECT trial that relied on pazopanib, also failed to demonstrate an OS benefit.[1-3] However, its results regarding DFS are equivocal. Specifically, the comparison between pazopanib 800 mg vs. placebo revealed a statistically significant DFS benefit. However, study design modifications towards pazopanib 600 mg dosing scheme did not result in a statistically significant DFS benefit. Differences in followup length might explain the difference: 800 mg pazopanib patients were treated in the early part of the study and those exposed to 600 mg were treated in the later part, with resulting shorter followup at data cutoff. Moreover, higher dose intensity of 800 mg might also add to DFS benefit. Taken together, the contribution of the PROTECT trial corroborates the lack of OS benefit and also does not modify the body of evidence regarding DFS benefit. To integrate the findings of the PROTECT trial to those of the ASSURE and S-TRAC trials, we performed a meta-analysis regarding the pooled three trial DFS and OS. Lack of DFS benefit in the pooled analysis was obtained, even when using the best case-scenario for pazopanib data, namely those recorded with 800 mg dosing.

Lastly, it is of interest to examine opinions of expert clinicians, such as the EAU RCC panellists, regarding their perception of the ASSURE and S-TRAC meta-analysis findings.[14] Here, review of several hypothetical scenarios revealed that the beneficial effects of adjuvant therapy on DFS is not sufficient to be considered as practice-changing. Conversely, a protective effect on OS, quantified with a HR of 0.75 or better, could represent a practice-changing finding. This observation implies that even statistically significant meta-analysis-derived DFS benefits would not be a sufficient substitute for OS benefit.

Conclusion

To date, randomized controlled trials of adjuvant therapy after nephrectomy for nmRCC showed no OS benefit and equivocal DFS benefit. These findings are confirmed by our meta-analysis of three RCTs of adjuvant VEGFR TKI therapy for nmRCC. In consequence, it is the opinion of the KCRNC panelists on TKI adjuvant therapy that such therapy should not be recommended for routine use after nephrectomy for nmRCC (Level 1A evidence). Nonetheless, such an approach may represent an option in highly motivated patients.

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