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Adjuvant Vascular Endothelial Growth Factor-targeted Therapy in Renal Cell Carcinoma: A Systematic Review and Pooled Analysis

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.eururo.2018.05.002>.

Abstract

Context: Contradictory data exist with regard to adjuvant vascular endothelial growth factor receptor (VEGFR)-targeted therapy in surgically managed patients for localized renal cell carcinoma (RCC).

Objective: To systematically evaluate the current evidence regarding the therapeutic benefit (disease-free survival [DFS] and overall survival [OS]) and grade 3–4 adverse events (AEs) for adjuvant VEGFR-targeted therapy for resected localized RCC.

Evidence acquisition: A critical review of PubMed/Medline, Embase, and the Cochrane Library in January 2018 according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement was performed. We identified reports and reviewed them according to the Consolidated Standards of Reporting Trials and Standards for the Reporting of Diagnostic Accuracy Studies criteria. Of eight full-text articles that were eligible for inclusion, five studies (two of five were updated analyses) were retained in the final synthesis. Study characteristics were abstracted and the number needed to treat (NNT) per trial was estimated.

Evidence synthesis: The three randomized controlled phase III trials included the following comparisons: sunitinib versus placebo or sorafenib versus placebo (Adjuvant Sorafenib or Sunitinib for Unfavorable Renal Carcinoma [ASSURE] study, $n = 1943$), sunitinib versus placebo (S-TRAC, $n = 615$), and pazopanib versus placebo (Pazopanib As Adjuvant Therapy in Localized/ Locally Advanced RCC After Nephrectomy study, $n = 1135$). The NNT ranged from 10 (S-TRAC) to 137 (ASSURE study). The pooled analysis showed that VEGFR-targeted therapy was not statistically significantly associated with improved DFS (hazard ratio [HR_{random}]: 0.92, 95% confidence interval [CI]: 0.82–1.03, $p = 0.16$) or OS (HR_{random} : 0.98, 95% CI: 0.84–1.15, $p = 0.84$) compared with the control group. The adjuvant therapy group experienced significantly higher odds of grade 3–4 AEs (OR_{random} : 5.89, 95% CI: 4.85–7.15, $p < 0.001$). In exploratory analyses focusing on patients who started on the full-dose regimen, DFS was improved in patients who received adjuvant therapy (HR_{random} : 0.83, 95% CI: 0.73–0.95, $p = 0.005$).

Conclusions: This pooled analysis of reported randomized trials did not reveal a statistically significant effect between adjuvant VEGFR-targeted therapy and improved DFS or OS in patients with intermediate/high-risk local or regional fully resected RCC. Improvement in DFS may be more likely with the use of full-dose regimens, pending further results. However, adjuvant treatment was associated with high-grade AEs.

Patient summary: Vascular endothelial growth factor receptor-targeted therapy after nephrectomy for localized kidney cancer is not associated with consistent improvements in delaying cancer recurrence or prolonging life and comes at the expense of potentially significant side effects.

Keywords

Metastatic renal cell carcinoma; Targeted therapy; Adjuvant therapy; Systemic therapy; Meta-analysis

1. Introduction

Kidney cancer is the 12th most common cancer in the world, with 338 000 new cases diagnosed in 2012. The highest incidence of kidney cancer is in North America and Europe, and the lowest in Africa and Asia [1]. Depending on tumor and patient characteristics at diagnosis, up to 40% of patients with locoregional renal cell carcinoma (RCC) recur after surgery and develop metastasis [2]. Given the increased incidence of patients with locoregional RCC, there is an immediate need to optimize treatment strategies for such patients.

Advances in our understanding of the pathogenesis of clear cell RCC, the most common subtype, such as alterations in the *VHL* gene driving the upregulation of the hypoxia inducible pathway including vascular endothelial growth factor receptor (VEGFR), prompted the development of targeted therapies against this frequent driver [3]. Since their debut, VEGFR-targeting drugs, such as the tyrosine kinase inhibitors sunitinib, pazopanib, and sorafenib, have demonstrated improved clinical outcomes in the metastatic setting for RCC [3].

Subsequently, studies have been undertaken to evaluate the efficacy of VEGF-directed therapies in patients with locoregional RCC at a high risk of relapse following nephrectomy. To date, three phase III randomized controlled trials (RCTs) [4–6] examining the effect of VEGFR-targeted therapies on disease-free survival (DFS) in patients with resected RCC tumors have been reported. As results of these studies have been inconsistent, we performed a pooled analysis of these studies to better understand the potential impact of adjuvant VEGFR-targeted therapy on patient outcomes and adverse events (AEs).

2. Evidence acquisition

2.1. Search strategy

A systematic PubMed/Medline, Embase, and Cochrane Library search was conducted in January 2018. The complete free-text search terms and the search strategy are detailed in Figure 1. Three studies were retained for the purpose of our pooled analysis [4–6]. Two additional published subset analyses from these studies were also included in the analyses [7,8]. Searches were limited to studies published from 2010 onward. No language restrictions were imposed. The search was complemented by additional sources, including relevant systematic reviews, and cited references from selected studies were also reviewed.

2.2. Inclusion criteria

The review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines [9]. The search strategy was conducted in accordance with the principles outlined in the Cochrane Handbook for Systematic Reviews of Interventions [10]. Risk of bias (RoB) was performed using the Cochrane Collaboration RoB tool for RCTs [11]. Two coauthors (L.M. and A.B.) screened all abstracts and full-text articles independently. The final list of included studies fulfilled the PICO (problem/patient/population, intervention/indicator, comparison, outcome and optional, time element or type of study) criteria.

2.3. Study eligibility

We defined study eligibility using the patient population, intervention, comparator, outcome, and study design approach [12]. We restricted our inclusion to RCT designs only. Case reports and nonrandomized designs were not permitted. The study population consisted of patients diagnosed with nonmetastatic RCC who received adjuvant VEGFR-targeted therapy or placebo after nephrectomy. Studies with ≤ 10 participants were not included. Those without a control group were also not considered. We excluded trials in which patients underwent cytoreductive nephrectomy or metastasectomy. Only trials that examined tyrosine kinase inhibitors were included (sunitinib, sorafenib, axitinib, pazopanib, dovitinib, cabozantinib, tivantinib, and erlotinib). Valid eligible comparators included any of the prespecified systemic therapy agents, placebo, or active surveillance.

2.4. Endpoints

The primary endpoints assessed within the current pooled analysis were DFS and overall survival (OS). DFS definitions differed per trial, as noted in the Supplementary material. As a secondary endpoint, we assessed all high-grade (3–4) AEs, which were graded using the National Cancer Institute Common Toxicity Criteria version 3.0 per clinical trial.

2.5. Statistical analysis

Study characteristics were abstracted and the number needed to treat (NNT) per trial was estimated using a previously reported method [13]. The pooled analysis and forest plots were produced using comprehensive meta-analysis. The overall effect was tested using Z scores, with the significance level set at $p < 0.05$. In the pooled analysis, both random-effect and fixed-effect models are presented. Statistical heterogeneity was quantified using the I^2 statistic, and its significance evaluated based on the accompanying Cochran Q test p value ($p < 0.10$). Given the absence of individual patient data for these trials, we relied on additional methods to obtain the hazard ratio (HR) and associated statistics. Specifically, the log rank of observed minus expected events and the log-rank variance were derived from the number of events and the individual times to event on the intervention arm of each trial. In the case that this was not readily available, the inverse variance approach was used, which may be estimated given the upper and lower bounds of the HRs' confidence intervals. These details have previously been detailed [14].

Within one study (Adjuvant Sorafenib or Sunitinib for Unfavorable Renal Carcinoma [ASSURE] study) [4], the same control group (placebo) was compared with different experimental groups (sorafenib and sunitinib), which produced two different HRs. In the overall analyses, we treated the two comparisons from that study as two independent studies, with a two-sided significance level of 2.5% as significant for comparisons between groups and a 5% level for two-way comparisons. However, we also performed sensitivity analyses by inflating the standard error by 20% in the pooled HR estimate [15]. In those analyses, the results did not change (data not shown). Finally, we calculated the statistical power for random-effects pooled analysis [16]. The statistical power was estimated to be adequate for the overall analysis and subanalyses at $>90\%$.

2.6. Exploratory analyses

Additional analyses were performed by repeating the pooled analysis focusing on DFS in two subpopulations. The first comprised patients who started on full dose at trial initiation (ie, 50 mg/d of sunitinib for the ASSURE and S-TRAC studies, 400 mg twice per day of sorafenib for the ASSURE study, and 800 mg/d of pazopanib for the Pazopanib As Adjuvant Therapy in Localized/Locally Advanced RCC After Nephrectomy [PROTECT] study). The second comprised patients who were considered to be at a higher risk of recurrence, which varied according to trial. Specifically, in the ASSURE study, patients were at a higher risk if they had UCLA Integrated Staging System T3 without or with undetermined nodal involvement (pN0 or pNx), Fuhrman grade 2, Eastern Cooperative Oncology Group (ECOG) performance status 1, T4 tumor or any T stage with nodal involvement, any Fuhrman grade, any ECOG performance status within the S-TRAC study, pT3 or pT4, or node-positive disease. We did not include the PROTECT study in the subanalysis that focused exclusively on higher-risk patients, as the effect of adjuvant therapy in higher-risk populations was not specifically reported, not to mention the contamination of patients with full and reduced doses.

3. Evidence synthesis

3.1. Quantity and quality of evidence

A total of eight eligible full-text manuscripts were identified as of January 1, 2018. Of those, three were excluded because they did not fulfill at least one of the PICO criteria (Supplementary material). The included studies involved the VEGFR-targeted agents sorafenib, sunitinib, or pazopanib, and were placebo controlled [4–6]. In addition, two other studies that published additional analyses were also included in our current review [7,8]. Details of study characteristics and outcomes observed for DFS, OS, and serious AEs are described in Table 1. The estimated NNT ranged from 10 (S-TRAC) to 137 (ASSURE study with sunitinib; Supplementary material). This resulted in the selection of a total of 3693 patients for the meta-analysis. The RoB was considered low across all included studies (Supplementary material).

3.2. DFS and OS

In the overall analysis, VEGFR-targeted therapy was not statistically significantly associated with improved DFS compared with the control group (HR_{random} : 0.92, 95% confidence interval [CI]: 0.82–1.03, $p = 0.16$, Fig. 2A). Heterogeneity was present ($I^2 = 33\%$, $p = 0.22$). VEGFR-targeted therapy was not statistically significantly associated with improved OS compared with the control group (HR_{random} : 0.98, 95% CI: 0.84–1.15, $p = 0.84$, Fig. 2B). Heterogeneity was absent ($I^2 = 21\%$, $p = 0.28$).

3.3. Safety

Safety analyses were based on high-grade (grade 3–4) AEs reported within the three trials. Compared with placebo, adjuvant VEGFR-targeted therapy patients experienced higher odds of high-grade AEs (OR_{random} : 5.89, 95% CI: 4.85–7.15, $p < 0.001$, Fig. 2C). Heterogeneity was present ($I^2 = 50\%$, $p = 0.11$). Specific kinds of AEs expected with this class of agents

occurred more frequently with adjuvant VEGFR-targeted therapy compared with placebo (Table 2).

3.4. Exploratory analyses

We repeated our pooled analysis focusing on (1) DFS in patients who started on the full-dose regimen in all three trials and (2) in patients who were considered at a higher risk of recurrent RCC. In the first set of analyses, patients who started on the full-dose regimen during any of the three trials experienced improved DFS compared with those who received placebo (HR_{random} : 0.83, 95% CI: 0.73–0.95, $p = 0.005$, Fig. 3A). In the second set focusing on patients at a higher risk of recurrent RCC, our analyses did not find a statistically significant difference between adjuvant therapy and placebo (HR_{random} : 0.88, 95% CI: 0.77–1.00, $p = 0.06$, Fig. 3B).

3.5. Discussion

On November 16, 2017, the Food and Drug Administration (FDA) approved sunitinib for the adjuvant treatment of adult patients at a high risk of recurrent RCC following nephrectomy. This approval was based on a multicenter international double-blind placebo-controlled trial (S-TRAC) in 615 patients with high-risk recurrent RCC following nephrectomy. Individuals were randomized 1:1 to 50 mg sunitinib once daily, 4 wk on treatment followed by 2 wk off, or placebo. Median DFS for sunitinib and placebo was 6.8 versus 5.6 yr (HR : 0.76, 95% CI: 0.59–0.98, $p = 0.03$).

DFS benefit was not found in the other two studies of adjuvant VEGFR-targeted therapy reported to date. The ASSURE study of 1943 patients with RCC at intermediate or high risk of relapse did not demonstrate improvement in DFS or OS with 1 yr of adjuvant sunitinib or sorafenib compared with placebo [4,7]. The PROTECT study evaluated the efficacy of pazopanib as an adjuvant therapy for patients with locally advanced RCC at a high risk of relapse after surgery [6]. Initially, the study was designed with pazopanib 800 mg once daily as the starting dose. The primary objective of the study had to be amended to examine DFS in a cohort that received a reduced dose of pazopanib (600 mg) due to toxicity attrition. In the 600 mg cohort, a DFS benefit for pazopanib over placebo was not observed. Although a DFS benefit was observed in the sustained 800 mg dose cohort, it was not considered tolerable. Three other ongoing RCTs are evaluating the clinical benefit of adjuvant targeted therapies including SORCE (adjuvant sorafenib vs placebo; [NCT00492258](#)), EVEREST (adjuvant everolimus vs placebo; [NCT01120249](#)), and ATLAS (adjuvant axitinib vs placebo; [NCT01599754](#)).

Numerous reports have sought to characterize potential reasons why the S-TRAC study found a benefit, whereas the other two did not [17–19]. In an effort to consolidate the inconsistent findings of the studies reported thus far, we performed a pooled analysis of the three completed RCTs focusing on DFS and OS as the primary endpoints, as well as high-grade AEs as a secondary endpoint. The pooled analysis did not detect a statistically significant improvement in DFS or OS with adjuvant VEGFR-targeted therapy. Not unexpectedly, high-grade AEs were more frequent in those treated with adjuvant VEGFR-targeted therapy than controls.

Earlier generation trials of adjuvant therapy in RCC have studied cytokines, combined cytokines and chemotherapy, adoptive immunotherapy, vaccines, and monoclonal antibodies, none of which has demonstrated improvement in patient outcome compared with surgery alone [20]. While these results are not surprising given the minimal effectiveness of older therapies in treating metastatic disease, it was hoped that the significant benefit of VEGFR-targeted therapy in the metastatic setting would translate into meaningful clinical benefit when administered in the adjuvant setting. The lack of dramatic effect of VEGFR-targeted therapy in the context of nonmetastatic RCC may align with the classical angiogenic switch model [21]. Blood-vessel formation will begin and continue as long as the tumor grows to a certain size, and only large tumor nodules may contain topological areas that are dependent on neoangiogenesis and confer sensitivity to VEGF-targeting agents. Consequently, the microscopic disease being targeted in the adjuvant setting may not be as susceptible or it may be simply that the mechanism of these drugs leads to disease stabilization or slowing of growth (cytostatic effect) rather than elimination (cytotoxic effect). When used in the adjuvant setting for a finite time period, this mechanism could result in a delay in radiographic progression.

Our exploratory pooled analysis evaluating the effects of dose intensity revealed that patients who started at full doses could experience improved DFS compared with placebo. This result could be interpreted as an argument in favor of adjuvant therapy for localized RCC, as it suggests that by sustaining the full-dose regimen, there is the possibility that this treatment strategy prolongs DFS. That interpretation, however, is not fully well understood as a recent post hoc analysis showed that within the PROTECT study, those achieving early (pazopanib exposure steady-state blood trough concentrations at week 3 or 5) or late C_{trough} (at week 16 or 20) of $>20.5 \mu\text{g/ml}$ had significantly longer DFS (not estimable) versus 29.5 mo, and not estimable versus 29.9 mo (both $p = 0.008$), respectively [22]. Yet, dose was not correlated with higher C_{trough} . This implies that potential benefit of adjuvant therapy is not completely driven by the starting dose of the drug but rather by blood concentration levels. A future pooled analysis with data on exposure as opposed to dosing and pharmacodynamics may be worthwhile.

In any case, an important clinical consideration is whether in the real-world setting full doses are unlikely to be tolerable and whether the majority of patients will receive a sustained full-dose adjuvant VEGFR-targeted therapy following nephrectomy. Notably, starting dose reductions were required for two of the three trials to address toxicity issues, and all three studies demonstrated marked amounts of drug discontinuations for drug-related toxicity (28–45%, regardless of dosing). Within the PROTECT study, the study protocol had to be amended from 800 to 600 mg of pazopanib due to intolerance and toxicity attrition. While full dosing of drug (800 mg of pazopanib) was associated with improved DFS efficacy, only 198 patients were included in that subanalysis, representing approximately one-third of the overall study group. Similarly, in the ASSURE study, the treatment regimen had to be amended to address toxicity issues for both sunitinib (from 50 to 37.5 mg) and sorafenib (from 400 mg twice per day to 200 mg twice per day). Although the reduction in starting dose ameliorated the toxicities, the proportion of patients who suffered a high-grade AE among those who started at a reduced dosage still exceeded 55% with both sunitinib and sorafenib. Contrary to positive DFS findings in the PROTECT full-dose cohort, post hoc

subset analyses evaluating dose intensity in the ASSURE study did not reveal differences in DFS or OS outcomes [7].

While the mid-trial dose reductions may have obscured the efficacy of adjuvant therapy in delaying radiographic progression, it may also be that any DFS efficacy may be too costly in terms of toxicity in the majority of patients. Using the S-TRAC results as an example, we determine here that, in the best-case scenario, the estimated number of patients needed to receive adjuvant therapy for one patient to experience a benefit in DFS is 10. Thus, we would need to subject nine individuals to the toxicity of VEGFR-targeted therapy for a single patient to benefit from a gain in DFS and without a definite OS benefit. Such quantitative observations are imperative to consider in the real-world clinical setting, potentially causing more harm than benefit and decreased quality of life. The balance between potential therapeutic benefit and associated toxicity and effects on quality of life with adjuvant VEGFR-targeted therapy is complex. The question remains whether clinicians and patients are willing to accept the toxicity while sustaining the full-dose effect, or continue treatment at a lower dose, but without the proven efficacy.

Another point of consideration is the relevancy of DFS as a primary endpoint in adjuvant studies, and whether an increase in DFS without a corresponding OS benefit should contribute to the decision to use these agents. This issue of whether DFS is a good surrogate for OS was recently investigated in a meta-analysis of 13 RCTs of adjuvant therapies in RCC, where only a moderate correlation between 5-yr DFS and OS rates was found [23]. Our pooled analysis currently failed to show superiority for OS in any of the studies, either individually or together. Although the follow-up time may be immature, some have argued that it will unlikely change in the future [18].

The results of this pooled analysis put into question whether routine use of adjuvant VEGFR-targeted therapy should be considered in fully resected RCC. Indeed, while the FDA has approved the use of adjuvant sunitinib for RCC, the European Medical Agency has recommended against such practice. Going forward, there are three important points to consider: (1) there remains the remote possibility that a longer follow-up will result in an effect on OS with adjuvant targeted therapy; (2) in addition to adjuvant VEGFR-targeted therapy studies, the role of mTOR pathway inhibition and immune checkpoint inhibition in the adjuvant setting is being evaluated; (3) the efficacy of immune checkpoint inhibition with anti-PD-1, PD-L1, and CTLA4 in metastatic RCC has generated enthusiasm for the potential utility of such therapies in the adjuvant setting [24]. Currently, five phase III RCTs examining the effect of immunotherapy in the adjuvant setting for locoregional high-risk RCC are ongoing (EA8143 PROSPER: [NCT03055013](#); IMmotion 010: [NCT03024996](#); KEYNOTE-564: [NCT03142334](#); RAMPART: [NCT03142334](#); and Check-Mate 914: [NCT03138512](#)).

The current report is not without limitations. First, there were only three studies to base our pooled analysis on, thereby reducing the generalizability of the results. Second, the studies contained a certain degree of heterogeneity. Heterogeneity across studies can be problematic for pooled analyses, beyond statistical interpretation. For example, the ASSURE study [4,7] included 21% non-clear cell RCC and the definition of high-risk patients differed across all

three trials. Furthermore, the ASSURE study included lower stage (pT1b) albeit high-grade disease, which may have compromised the ability to detect a benefit of adjuvant therapy, as such tumors are less likely to recur. However, our exploratory analysis focusing on patients with higher-risk recurrent RCC failed to detect a difference for adjuvant therapy relative to placebo. In relation to that, it would have been noteworthy to compare adjuvant treatment with controls in patients with higher-risk RCC and/or sustained full dose. However, not all the three trials reported their results for this subgroup. Third, the ASSURE study includes two comparisons with the same control group (ie, the placebo group was the same for both sunitinib and sorafenib). From the statistical standpoint, the two estimates are presumed to be independent of each other, and therefore the point estimate computed across comparisons will likely be small, and the confidence intervals too narrow. To account for this, we have performed sensitivity analyses by artificially inflating the standard error by 20% to see how point estimates vary. The results did not change, and lack of statistical significance for adjuvant targeted therapy versus placebo remained in place despite this adjustment. Fourth, while the random-effect model was preferred, caution should be warranted given the small number of studies included in the meta-analysis ($k = 3$). Indeed when the number of studies is very small, it may be impossible to estimate the between-studies variance (tau square) with precision [15]. To address this, we also included results obtained by adopting a fixed-effect model. The results did not differ between these two approaches. Finally, the current study was not an individual patient data-based meta-analysis.

4. Conclusions

This pooled analysis of reported randomized trials did not reveal a statistically significant effect between adjuvant VEGFR-targeted therapy and improved DFS or OS in patients with intermediate/high-risk local or regional fully resected RCC. Improvement in DFS may be more likely with the use of full-dose regimens, pending further results. However, adjuvant treatment was associated with high-grade AEs. Our recommendation is that the existing randomized data do not collectively justify the use of routine adjuvant VEGFR-targeted therapy in resected RCC, pending the results of ongoing trials. Shared decision making between the patient and the physician should always be undertaken in considering adjuvant VEGFR-targeted therapy for patients with high-risk disease. The best potential treatment option continues to include a clinical trial in this setting.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Financial disclosures:

Maxine Sun certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: Bernard Escudier receives honoraria from Pfizer, Novartis, Bayer, Bristol-Myers Squibb, Ipsen, Exelixis, and Genentech; holds a consulting or advisory role for Bayer, Novartis, Pfizer, Exelixis, Bristol-Myers Squibb, and Ipsen; and has received travel and accommodation expenses from Novartis, Bristol-Myers Squibb, and Pfizer. Naomi B. Haas holds a consulting or advisory role for Cerulean Pharma, Exelixis, Pfizer, and Novartis; has been an expert testimony for Eli Lilly (I); and possesses stock or other ownership in Tetralogic. Lauren C. Harshman is the principal investigator/study chair of the National Clinical Trials Network

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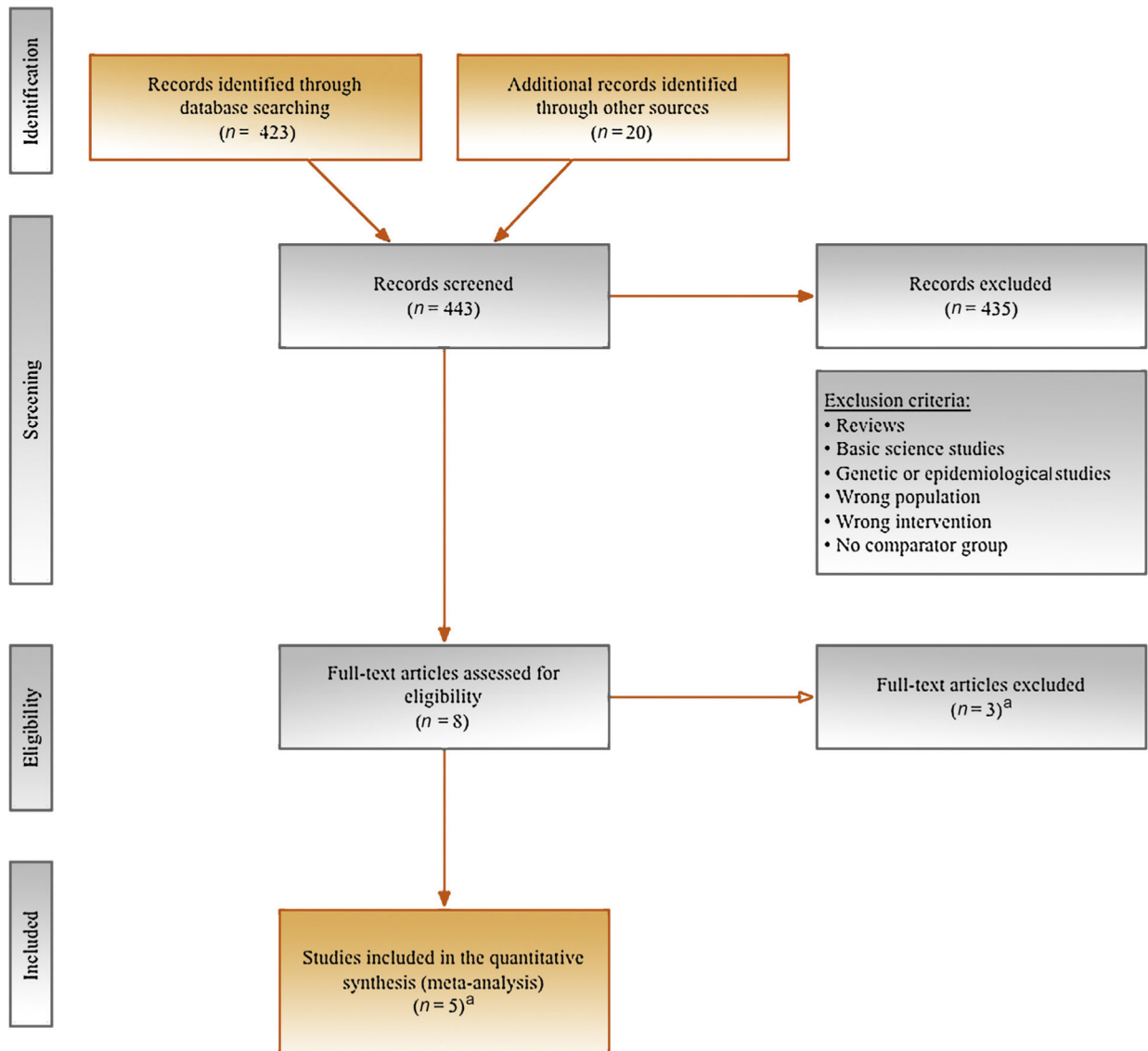


Fig. 1 - PRISMA flow diagram outlining search strategy and final included and excluded studies. PRISMA = Preferred Reporting Items for Systematic Review and Meta-Analysis. ^a Reasons for the three full-text articles that were excluded and the five full-text articles that were included are described in the Supplementary material.

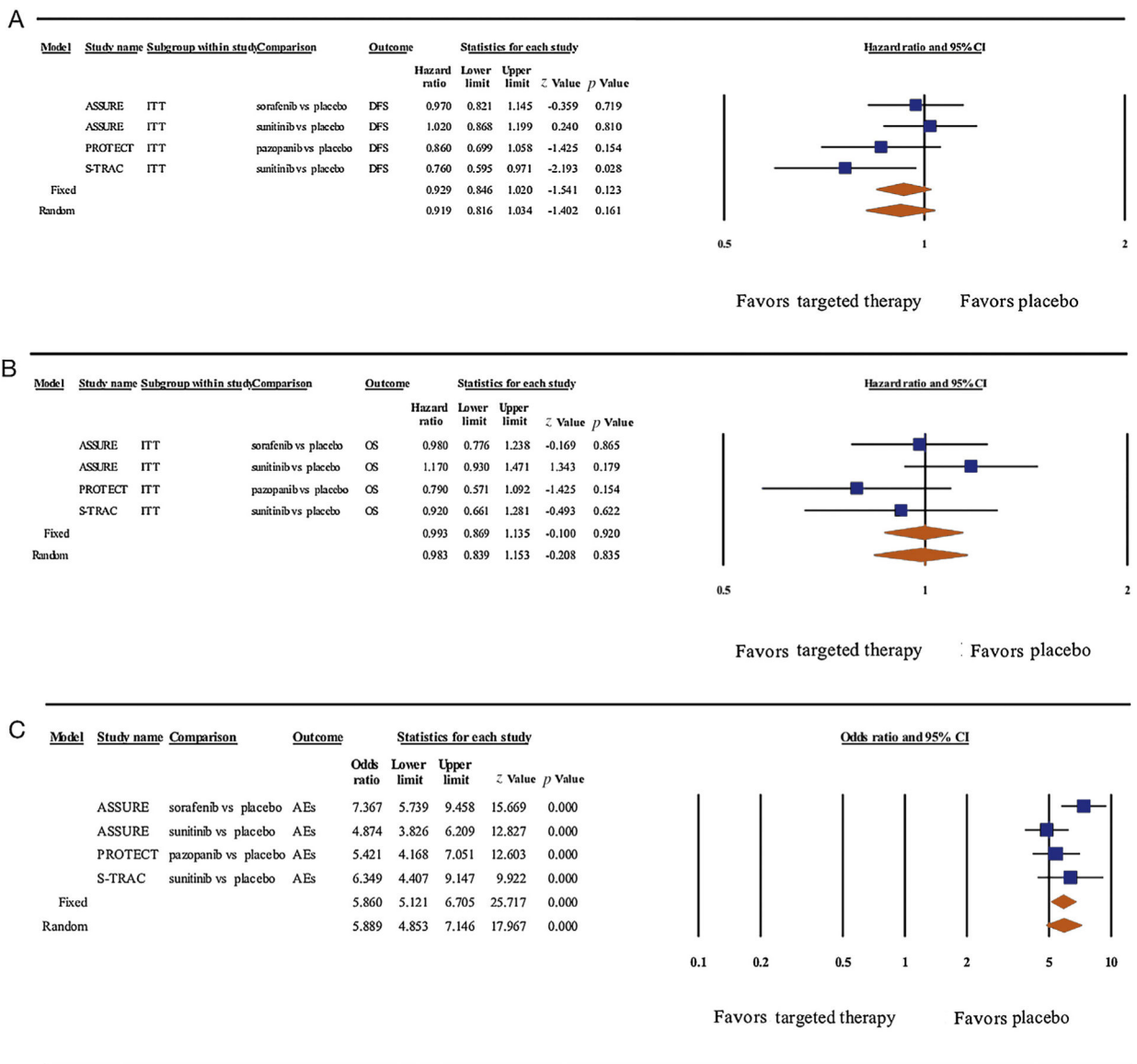


Fig. 2 - Forest plots for (A) meta-analyses of the adjusted effects between adjuvant vascular endothelial growth factor receptor (VEGFR)-targeted therapy and disease-free survival (DFS), (B) overall survival (OS), and (C) high-grade adverse effects (AEs; grade 3–4) in surgically managed patients for localized renal cell carcinoma. All data were pooled using both a fixed- and a random-effect model. CI = confidence interval; ITT = intention to treat.

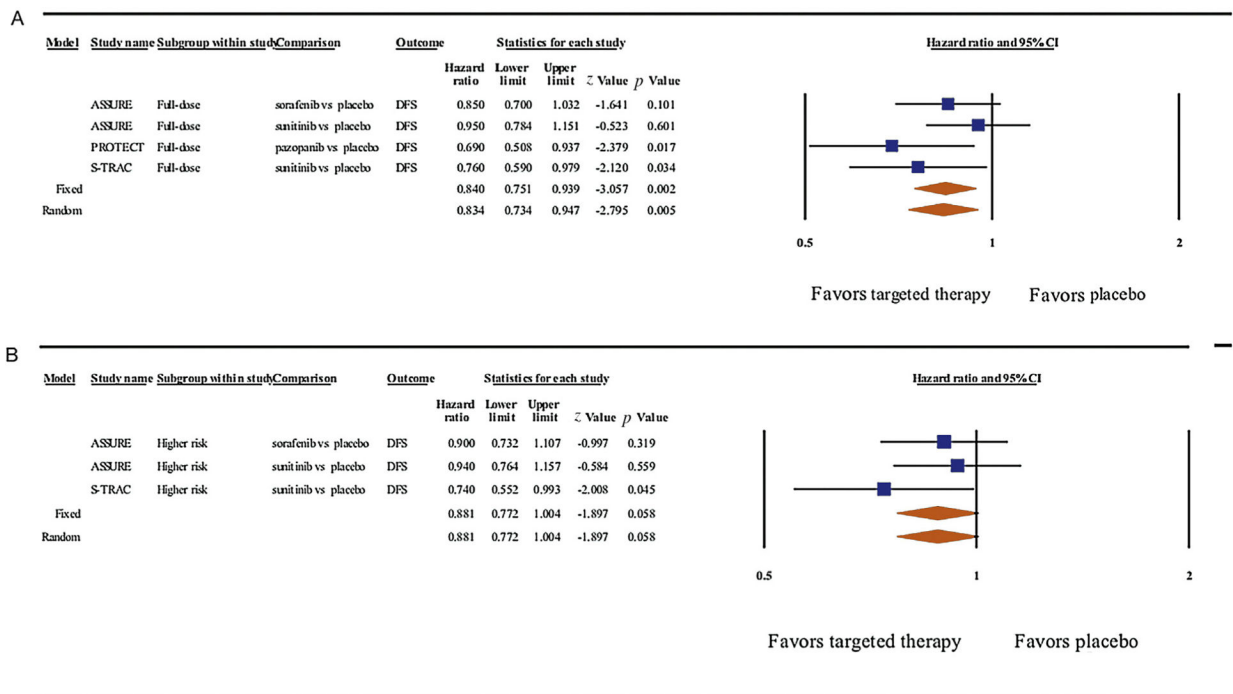


Fig. 3 - Forest plots for meta-analyses of the adjusted effects between adjuvant vascular endothelial growth factor receptor (VEGFR)-targeted therapy and disease-free survival (DFS) in (A) surgically managed patients for localized renal cell carcinoma who received the full-dose regimen during any of the three trials and (B) those with higher-risk disease. Data were pooled using both a fixed- and a random-effect model. Of note, the PROTECT study was not included in the analyses that pertained to higher-risk patients, as the original report did not specifically address this population. CI = confidence interval.

Table 1 -
Detailed data of the three randomized controlled trials included in the pooled analysis

Source	Trial phase	Disease stage	Follow-up (yr)	Additional criteria	Study groups	Treatment design	Dosage ^a	Median time to DFS	No. of patients	DFS	Any death	G3/4 AE
Haas et al [4] (ASSURE)	III	Pt1b high-grade N0M0 or N + M0, clear cell and non-clear cell RCC	4	ECOG 0-1, normal liver and hematological function; creatinine clearance of >30 ml/min	Exp.	Sunitinib/sorafenib	Sunitinib: 50 mg/d for the first 28 d of each 6-wk cycle. Sorafenib: 400 mg twice per day throughout all cycles	5.8/6.1 yr	647/649	284/284	156/138	390/449
Ravaud et al [5] (S-TRAC)	III	Stage III-IV M0 (UISS modified criteria), clear cell RCC	4	ECOG 0-2	Con. Exp.	Placebo Sunitinib	50 mg/d on a 4-wk-on, 2-wk-off schedule for 1 yr	6.6 yr 6.8 yr	647 309	287 113	141 67	159 185
Motzer et al [6] (PROTECT)	III	pT2 high-grade, pT3-4 N0M0 or N + M0, clear cell RCC	5	KPS 80%	Con. Exp.	Placebo Pazopanib	Starting 600 mg/d for 1 yr, with optional dose escalation to 800 mg/d after 8-12 wk	5.6 yr 30.4 mo	306 571	144 188	74 65	59 338
					Con.	Placebo		30.7 mo	564	203	83	119

Con. = control; DFS = disease-free survival; ECOG = Eastern Cooperative Oncology Group; Exp. = experimental; G3/4 AE = grade 3/4 adverse events; KPS = Karnofsky performance status; RCC = renal cell carcinoma; UISS = UCLA Integrated Staging System.

^aDosage: For ASSURE, given that high rates of toxicity-related discontinuation occurred after 1323 patients had enrolled (treatment discontinued by in 44% (193/438) and 45% (199/441) of sunitinib- and sorafenib-treated patients, respectively), the starting doses for each drug was reduced compared with individually titrated up to the original full doses. Specifically, the starting dose was amended to 37.5 mg for sunitinib or 400 mg for sorafenib for the first one to cycles of therapy. For PROTECT, the trial was originally designed with pazopanib 800 mg once daily as the starting dose. An amendment to the protocol was introduced to reduce the starting dose to 600 mg once daily due to a higher than expected treatment discontinuation. This resulted in 568 patients being recruited, which served as the group for primary analysis. Previously, 198 patients received 800 mg as the starting dose, where 53% experienced adverse events and had their dosage reduced, and 51% discontinued treatment. For S-TRAC, dose interruptions occurred in 54% (166/309) of sunitinib patients, while dose reductions (to 37.5 mg/d) occurred in 46% (140/309).

Table 2 -

Pooled odds ratio estimates of serious adverse events (grade III–IV) within three randomized controlled trials of adjuvant targeted therapy for localized renal cell carcinoma

Study	TKI	OR (95% CI)	p value
Decreased appetite			
ASSURE	Sorafenib	11.05 (0.61–200.312)	0.104
ASSURE	Sunitinib	25.53 (1.51–432.13)	0.025
PROTECT	Pazopanib	1.97 (0.18–21.77)	0.581
S-TRAC	Sunitinib	5.00 (0.24–104.58)	0.300
Pooled OR _{fixed} (95% CI)		6.49 (1.63–25.78)	0.008
Pooled OR _{random} (95% CI)		6.49 (1.63–25.78)	0.008
Diarrhea			
ASSURE	Sorafenib	21.13 (6.58–67.81)	<0.001
ASSURE	Sunitinib	22.87 (7.14–73.26)	<0.001
S-TRAC	Sunitinib	12.37(1.60–95.71)	0.016
PROTECT	Pazopanib	9.93 (3.52–28.01)	<0.001
S-TRAC	Sunitinib	12.37 (1.60–95.71)	0.016
Pooled OR _{fixed} (95% CI)		15.79 (8.53–29.19)	<0.001
Pooled OR _{random} (95% CI)		15.79 (8.53–29.19)	<0.001
Dyspepsia			
ASSURE	Sorafenib	6.03 (0.72–50.22)	0.097
ASSURE	Sunitinib	15.37 (2.02–116.71)	0.008
PROTECT	Pazopanib	NR	-
S-TRAC	Sunitinib	9.06 (0.49–168.99)	0.140
Pooled OR _{fixed} (95% CI)		9.67 (2.61–35.84)	0.001
Pooled OR _{random} (95% CI)		9.67 (2.61–35.84)	0.001
Fatigue			
ASSURE	Sorafenib	2.41 (1.39–4.17)	0.002
ASSURE	Sunitinib	6.82 (4.14–11.26)	<0.001
PROTECT	Pazopanib	3.24 (1.05–10.01)	0.041
S-TRAC	Sunitinib	3.87 (1.27–11.79)	0.017
Pooled OR _{fixed} (95% CI)		4.12 (2.94–5.76)	<0.001
Pooled OR _{random} (95% CI)		3.90 (2.14–4.44)	<0.001
Headache			
ASSURE	Sorafenib	6.03 (0.72–50.22)	0.097
ASSURE	Sunitinib	8.10 (1.01–64.99)	0.049
PROTECT	Pazopanib	1.97 (0.18–21.77)	0.581
S-TRAC	Sunitinib	5.00 (0.24–104.58)	0.300
Pooled OR _{fixed} (95% CI)		4.94 (1.54–15.88)	0.007
Pooled OR _{random} (95% CI)		4.94 (1.54–15.88)	0.007
Hand-food syndrome			

Study	TKI	OR (95% CI)	p value
ASSURE	Sorafenib	43.79 (20.41–93.95)	<0.001
ASSURE	Sunitinib	15.65 (7.20–34.03)	<0.001
PROTECT	Pazopanib	NR	-
S-TRAC	Sunitinib	57.77 (7.92–421.28)	<0.001
Pooled OR _{fixed} (95% CI)		27.90 (16.50–47.17)	<0.001
Pooled OR _{random} (95% CI)		29.27 (12.87–66.57)	<0.001
Hypertension			
ASSURE	Sorafenib	4.48 (2.86–6.99)	<0.001
ASSURE	Sunitinib	4.66 (2.99–7.27)	<0.001
PROTECT	Pazopanib	4.65 (3.17–6.83)	<0.001
S-TRAC	Sunitinib	2.13 (0.72–6.28)	0.172
Pooled OR _{fixed} (95% CI)		4.43 (3.50–5.62)	<0.001
Pooled OR _{random} (95% CI)		4.43 (3.50–5.62)	<0.001
Mucositis/stomatitis			
ASSURE	Sorafenib	14.25 (1.87–108.70)	0.010
ASSURE	Sunitinib	26.04 (3.52–192.79)	0.001
PROTECT	Pazopanib	4.93 (0.24–102.91)	0.304
S-TRAC	Sunitinib	45.86 (2.77–760.62)	0.008
Pooled OR _{fixed} (95% CI)		18.35 (5.68–59.29)	<0.001
Pooled OR _{random} (95% CI)		18.35 (5.68–59.29)	<0.001
Nausea			
ASSURE	Sorafenib	8.07 (1.01–64.67)	0.049
ASSURE	Sunitinib	23.88 (3.22–177.37)	0.002
PROTECT	Pazopanib	4.93 (0.24–102.91)	0.304
S-TRAC	Sunitinib	13.17 (0.74–234.87)	0.079
Pooled OR _{fixed} (95% CI)		11.904 (3.63–39.06)	<0.001
Pooled OR _{random} (95% CI)		11.904 (3.63–39.06)	<0.001
Neutropenia/infection			
ASSURE	Sorafenib	2.39 (1.20–4.74)	0.013
ASSURE	Sunitinib	1.52 (0.73–3.18)	0.269
PROTECT	Pazopanib	NR	NR
S-TRAC	Sunitinib	57.54 (3.49–948.54)	0.005
Pooled OR _{fixed} (95% CI)		2.15 (1.31–3.53)	0.002
Pooled OR _{random} (95% CI)		2.80 (0.98–7.97)	0.054
Vomiting			
ASSURE	Sorafenib	3.52 (0.73–17.00)	0.118
ASSURE	Sunitinib	7.15 (1.62–31.59)	0.009
PROTECT	Pazopanib	0.98 (0.06–15.74)	0.990
S-TRAC	Sunitinib	15.25 (0.87–268.21)	0.063
Pooled OR _{fixed} (95% CI)		4.76 (1.84–12.30)	0.001
Pooled OR _{random} (95% CI)		4.76 (1.842–12.30)	0.001

CI = confidence interval; NR = not reported; OR = odds ratio; TKI = tyrosine kinase inhibitors.

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