DATA ARCHITECTURE AND MODELS

Adjuvant Tyrosine Kinase Inhibitors in Renal Cell Carcinoma: A Concluded Living Systematic Review and Meta-Analysis

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abstract

PURPOSE Multiple large clinical trials have investigated adjuvant tyrosine kinase inhibitors (TKIs) to reduce the risk of cancer recurrence and progression to metastasis in high-risk renal cell carcinoma. We sought to maintain living and interactive evidence on this topic, until a high level of certainty is reached for key clinical outcomes such that further updates become unnecessary and unlikely to change clinical practice.

METHODS We created a living interactive evidence synthesis platform to maintain a continuously updated meta-analysis on TKI monotherapy in adjuvant renal cell carcinoma. We implemented an automated search strategy with weekly updates to identify randomized phase 2 and 3 clinical trials. Study selection, appraisal, and data extraction were done in duplicate. Cumulative meta-analysis was performed using Analyzer Module in Living Interactive Evidence platform. For each outcome (overall survival [OS], disease-free survival [DFS], and all-cause and treatment-related adverse events), we assessed certainty of evidence using GRADE approach and conducted trial sequential analysis.

RESULTS This final update includes five randomized trials including recently updated data from PROTECT trial. Meta-analysis shows that adjuvant TKI monotherapy offers no benefit in OS (hazard ratio, 1.01; 95% CI, 0.91 to 1.12, high certainty) or DFS (hazard ratio, 0.92; 95% CI, 0.86 to 1.00, high certainty) and significantly increases adverse event risk. Lack of benefit was consistent across subgroups including highest-risk patients (test for subgroup differences: $P = .32$). Optimal information size criteria were met, and there was high certainty of evidence for lack of DFS and OS benefit for adjuvant TKIs.

CONCLUSION There is no guidance on when to stop maintaining a living review. In this example, we used trial sequential analysis and high certainty of evidence (future clinical trials unlikely to change current conclusions) as a benchmark to conclude a living review in view of convincing evidence.

JCO Clin Cancer Inform 5:588-599. © 2021 by American Society of Clinical Oncology

INTRODUCTION

Renal cell carcinoma (RCC) is a common malignancy, with approximately 400,000 new cases annually. It causes significant mortality, with 175,000 reported deaths in 2018 globally.[1] Survival is highly dependent on the stage at diagnosis. The estimated 5-year survival rate for localized disease is 93%, 73% with local lymph node involvement, and only 12% survival for metastatic disease.[2] Although two thirds of all patients with newly diagnosed RCC present with local or locally advanced disease that is amenable to local resection, unfortunately, the risk of cancer recurrence and progression to metastatic disease after surgical resection can be up to 40% in high-risk patients.[3] Thus, several adjuvant treatments—most notably tyrosine kinase inhibitors (TKIs)—have been tested in clinical trials in hopes of decreasing mortality in patients with high-risk RCC.[4] The S-TRAC trial showed a modest disease-free survival (DFS) benefit with the use of 1 year of sunitinib over placebo, which led to US Food and Drug Administration approval for sunitinib in the adjuvant treatment for RCC.[5] Subsequent trials failed to demonstrate any DFS or overall survival (OS) benefit and underscored toxicity concerns with these agents.[6-9]

We initiated a living systematic review (LSR) and cumulative meta-analysis in 2018, and the first report incorporated results from S-TRAC,[5] ASSURE,[8] and PROTECT.[9] LSR allows for incorporating relevant new evidence as soon as it becomes available.[10] Since the presentation of our initial review,[11] we have updated the LSR and meta-analysis every time new evidence became available. In this final update of the LSR, we describe how we addressed key issues pertinent to concluding an LSR. We also demonstrate that the certainty in the evidence is sufficiently high, and conclusive data indicate that no future meta-analyses are needed. Therefore, this final update on TKIs in

ASSOCIATED CONTENT

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on April 5, 2021 and published at ascopubs.org/journal/cci on May 27, 2021: DOI https://doi.org/10.1200/CCI.21.00035

CONTEXT

Key Objective

To illustrate how living systematic reviews (LSRs) can be maintained and reasonably concluded once high certainty in evidence has been achieved, using an example of adjuvant tyrosine kinase inhibitors in renal cell carcinoma.

Knowledge Generated

Living meta-analysis of five randomized clinical trials has shown that adjuvant tyrosine kinase inhibitor has no overall or disease-free survival benefit in resected renal cell carcinoma and has significantly greater toxicity compared with placebo. These findings have remained consistent across all updates of this LSR and have increased in terms of certainty from moderate to high over the course of this LSR (2018-2021).

Relevance

Our semiautomated approach makes the resource-intense process of maintaining LSRs feasible. Trial sequential analysis and certainty of evidence assessments may be used to guide the decision to formally conclude an LSR.

adjuvant RCC can serve as an example of when to conclude a living review.

METHODS

Study Selection and Data Extraction

The search strategy, study selection, and data abstraction methods have been previously described.[12] After the initial search, an automated search strategy was developed to monitor weekly updates. Conference proceedings and abstracts from ASCO, European Society of Medical Oncology, American Association for Cancer Research (AACR), and American Urological Association (AUA) are searched to identify any updated reports of previously included trials (date of last search: February 2021). Study screening, selection, and data extraction processes are conducted in duplicate by two reviewers (M.I. and R.S.) independently. When available, trial reports with the longest follow-up are included.

Study Outcomes

Prespecified outcomes of this meta-analysis include OS, DFS, treatment-related adverse events (trAEs) of any grade and grade $\geq$ 3, and all-cause adverse event (AE) of any grade and grade $\geq$ 3. We expanded our original study outcomes to include quality-of-life (QoL) assessments and patient-reported outcomes for this final update. Subgroup analysis by risk category was performed. The trial definitions of highest risk are given in Table 1.

Statistical Analysis

A generic inverse variance–weighted DerSimonian and Laird random effects model was used to derive estimates for DFS, OS, and AE.[13] Cumulative effect sizes were estimated as hazard ratios (HRs) and 95% CI for OS and DFS and as relative risks (RRs) with 95% CI for AE outcomes. Heterogeneity was assessed using the Cochran Q statistic and quantified using I^2 statistic.[14] All statistical analyses were conducted in the Analyzer Module of the LSR platform, and functions from R Foundation for Statistical Computing package meta (version 4.11.0) were used for this analysis.[15]

Risk of Bias and Certainty of Evidence

Risk of bias was assessed by two reviewers (M.I. and R.S.) for DFS using the Cochrane Risk of Bias tool version 2.0.[16] Certainty of evidence was assessed for each outcome using GRADE approach.[17] For imprecision rating,[18] we calculated optimal information size (OIS) using an online sample size calculator.[19] The expected RR reduction or increase threshold was set at 15%[20]; control event rate was taken as the event rate in control arm of included trials: α = .05 and β = .20. Summary of findings table was generated using the MAGICapp[21]—an online tool developed to facilitate collaborative evidence synthesis.[21]

Trial Sequential Analysis

Trial sequential analysis (TSA) was conducted for each outcome using the TSA software, Copenhagen Trial Unit. The type I error rate was maintained at 5% (α = .05), and required information sizes were calculated with 80% power (β = .20) using user-defined OIS estimates and assuming 15% RR for TKI therapy.

Automating the LSR Process

We have described our approach to automating living reviews (details of automation are accessible at ref. 22). The Watcher Module of living interactive systematic review framework was used to automate the search process and the Analyzer Module to conduct the analyses.[15]

RESULTS

Study Selection and Characteristics

The living PRISMA (Fig 1) shows the process of study selection. The current update includes four new publications: full publication of SORCE trial, updated results and quality-of-life report of the S-TRAC trial, and updated results for PROTECT trial.[6,23-25] An interactive PRISMA flow sheet can be viewed on the companion website. Patient

TABLE 1. Summary Characteristics of Included Studies

Trial	No. of Patients (ITT population)	Median Age (years)	Sex (% male)	Histology (% clear cell)	Risk Scoring System	Risk Category Included	Definition of Highest-Risk Group	Treatment Arm	Control Arm	Planned Treatment Duration (years)	Median Actual Treatment Duration (months)	Median Follow-Up (months)	Rate of Treatment Discontinuation at 1 Year (%)
S-TRAC	615	58	74	100	UISS	High	pT3, G ≥ 2, N0 or pNx, M0, ECOG ≥ 1; or pT4, G any, N0 or pNx, M0; or pT any, G any, N1, M0	Sunitinib 50 mg once daily	Placebo	1	12.4	65 (for OS, 75)	Control: 30 Treatment: 44
ASSURE	1,943	56	67	79	UISS	Intermediate-high; very high	pT3, G any, N any, M0; or pT4, G any, N any, M0; or pT any, G any, N1, M0	Arm 1: Sunitinib 50 mg once daily Arm 2: Sorafenib 400 mg twice daily	Placebo	1	approximately 12	70	Control: 29 Arm 1: 52 Arm 2: 50
PROTECT	1,538	59	72	94	SSIGN	Intermediate; high	NA	Pazopanib 800 mg (amended to 600 mg) once daily	Placebo	1	10.4	77	Control: 27 Treatment: 51
ATLAS	724	58	73	100	TNM and Fuhrman grade	High	pT3, G ≥ 3; or pT4, G any, N any, M0; or pT any, G any, N1, M0	Axitinib 5 mg twice daily	Placebo	3	NA	NA	Control: 28 Treatment: 31
SORCE	1,711	58	71	84	Leibovich model	Intermediate; high	Leibovich score ≥ 6	Arm 1: Sorafenib 400 mg twice daily[a] for 1 year, followed by placebo for 2 years Arm 2: Sorafenib 400 mg twice daily[a] for 3 years	Placebo	3	Arm 1: 11.7 Arm 2: 10.6	78	Control: 26 Arm 1: 49 Arm 2: 50

NOTE. An interactive summary characteristics table can be accessed on the website.

Abbreviations: ECOG, Eastern Cooperative Oncology Group; G, grade; ITT, intention-to-treat; M0, no distant metastasis; N, regional lymph nodes; N0, no regional node metastasis; N1, metastasis in a single regional lymph node; NA, not available; OS, overall survival; SSIGN, stage, size, grade, and necrosis score; TNM, tumor, node, and metastases; UISS, University of California Los Angeles Integrated Staging System.

[a]Amended to 400 mg once daily.

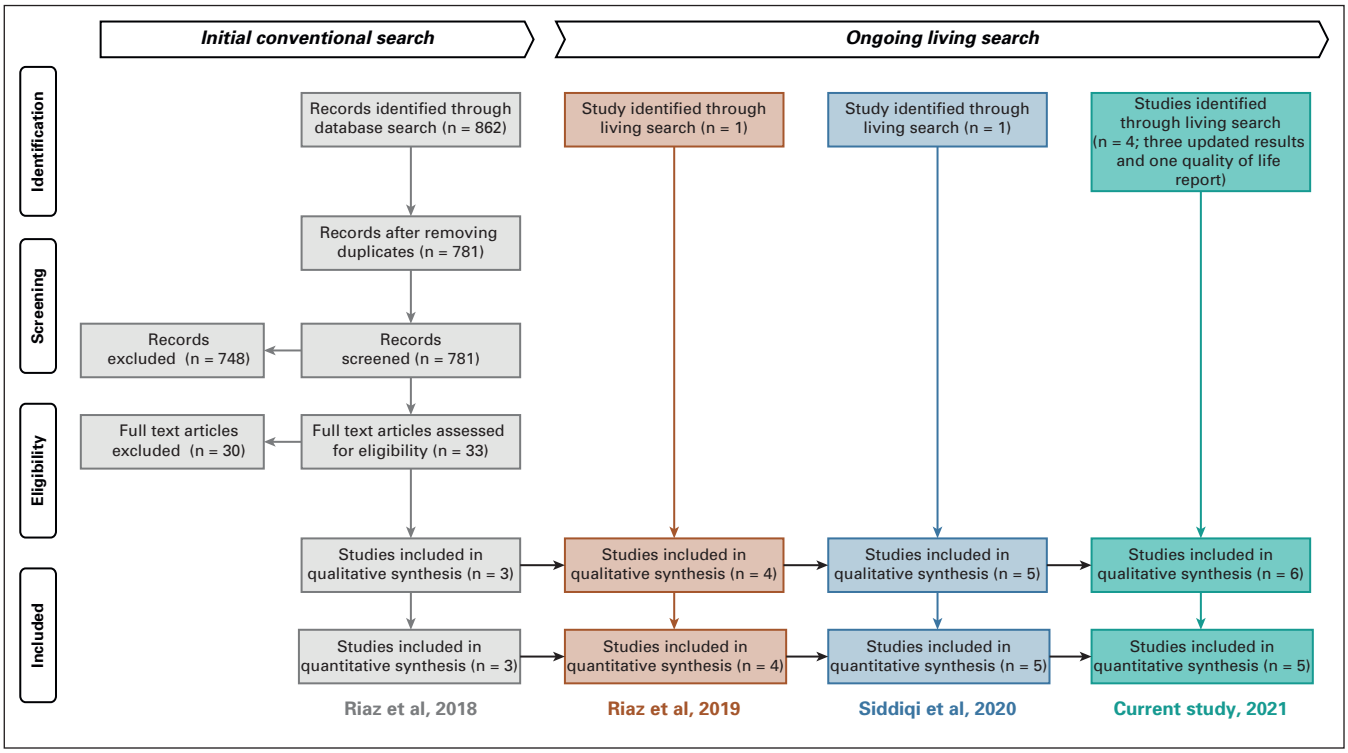


FIG 1. Living PRISMA, showing how study selection is a continuous ongoing process in the living systematic review model. An interactive PRISMA flow sheet can be accessed on the website.

and study characteristics of the five phase III trials are summarized in Table 1. The median age of included patients was 58 years in all trials except ASSURE where it was 56 years of age. The proportion of male patients ranged from 67% to 74%. ATLAS and ASSURE studies exclusively enrolled patients of clear cell histology. Although risk scoring systems differed across trials, all enrolled high-risk patients; additionally, but the PROTECT and SORCE also included some intermediate-risk patients, as defined by SSIGN (stage, size, grade, and necrosis) and Leibovich categories, respectively.[26] The median duration of treatment was approximately 1 year, and the median follow-up duration ranged from 65 to 78 months. The treatment discontinuation rate at 1 year was 31%-52% for patients on TKI treatment and 26%-30% for those on placebo. Study characteristics can also be viewed in an Interactive Table on the website.

Efficacy Outcomes: DFS and OS

Cumulative meta-analysis shows that adjuvant TKIs offer no OS or DFS benefit. The pooled HR for OS was 1.01 (95% CI, 0.91 to 1.12), with no significant heterogeneity (I^2 = 0; P = .90; Fig 2A and Data Supplement). Likewise, the pooled HR for DFS was 0.92 (95% CI, 0.86 to 1.00), with no significant heterogeneity (I^2 = 0%; P = .44; Fig 2B and Data Supplement). Absolute effect estimates are presented in Table 2. Sensitivity analyses excluding ATLAS because of longer median treatment duration and the 800 mg dosage group of PROTECT were consistent with the primary analysis (Data Supplement).

Subgroup analysis of the highest-risk patients demonstrated no benefit in DFS in either risk category, although notably, the definition of highest risk varied across trials (Table 1). For highest-risk patients, the HR was 0.91 (95% CI, 0.82 to 1.02), whereas for lower-risk patients, it was 1.02 (95% CI, 0.84 to 1.24), with a statistically nonsignificant P value of interaction (P = .32; Data Supplement).

Interactive results for the primary analysis, sensitivity analysis, and subgroup analysis can be viewed on the website.

Safety Outcomes: All-Cause AE (All Grade and Grade ≥ 3) and Treatment-Related AE (All Grade and Grade ≥ 3)

TKI therapy was associated with significantly higher risk of all-grade and grade ≥ 3 AEs, compared with placebo. All-cause all-grade AEs were reported in all trials except ASSURE—the pooled RR was 1.07 (95% CI, 1.03 to 1.11; I^2 = 92%; P < .01; Fig 2C and Data Supplement). All-cause grade ≥ 3 AEs were reported in all five trials, and the pooled RR was 2.44 (95% CI, 2.17 to 2.76) with statistically significant heterogeneity (I^2 = 74%; P < .01; Fig 2D and Data Supplement).

The RR for all-grade trAE was 1.45 (95% CI, 1.16 to 1.80; I^2 = 93%; P < .01; Fig 2E and Data Supplement), based on data from only two studies (S-TRAC and ATLAS). The

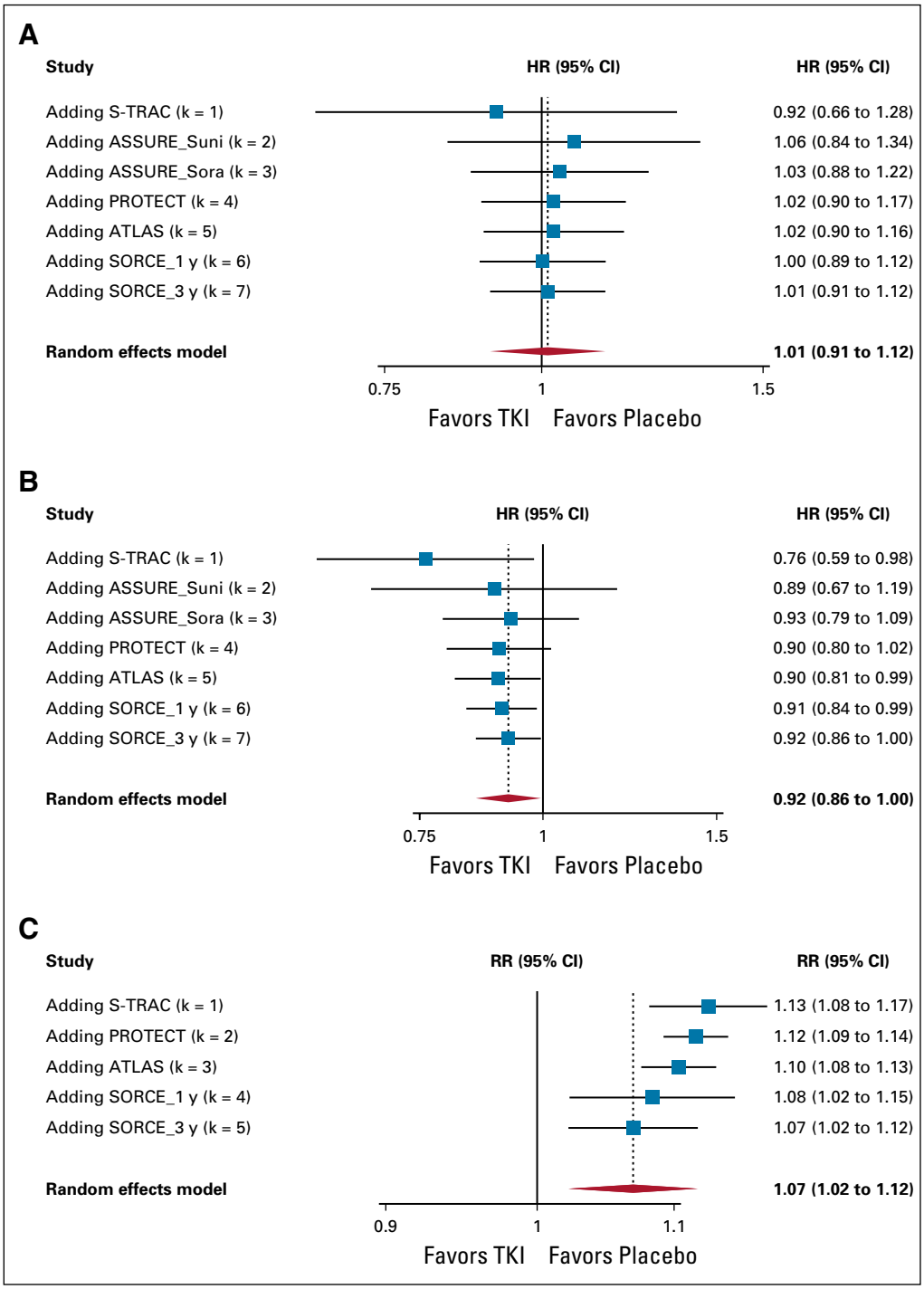


FIG 2. Forest plots showing cumulative meta-analysis results for (A) overall survival, (B) disease-free survival, (C) all-cause all-grade AE, (D) all-cause grade ≥ 3 AE, (E) treatment-related all-grade AE, and (F) treatment-related grade ≥ 3 AE. AE, adverse event; HR, hazard ratio; RR, relative risk; TKI, tyrosine kinase inhibitor.

estimate for grade ≥ 3 trAE was much higher, with an RR of 5.25 (95% CI, 3.12 to 8.84) and significant heterogeneity (I^2 = 78%; P = .03; Fig 2F and Data Supplement).

Risk of Bias and Certainty of Evidence

All trials were judged to carry low risk of bias (Data Supplement). The methods of allocation concealment were not always described. ASSURE, PROTECT, and SORCE did not have DFS assessment by blinded independent central review. Certainty of evidence was high or moderate for most outcomes (summary of findings is presented in Table 2). In our final update, OIS criteria are easily met for all outcomes except grade 3+ trAE. As shown in Fig 3, all three LSR updates have maintained moderate-high certainty in the

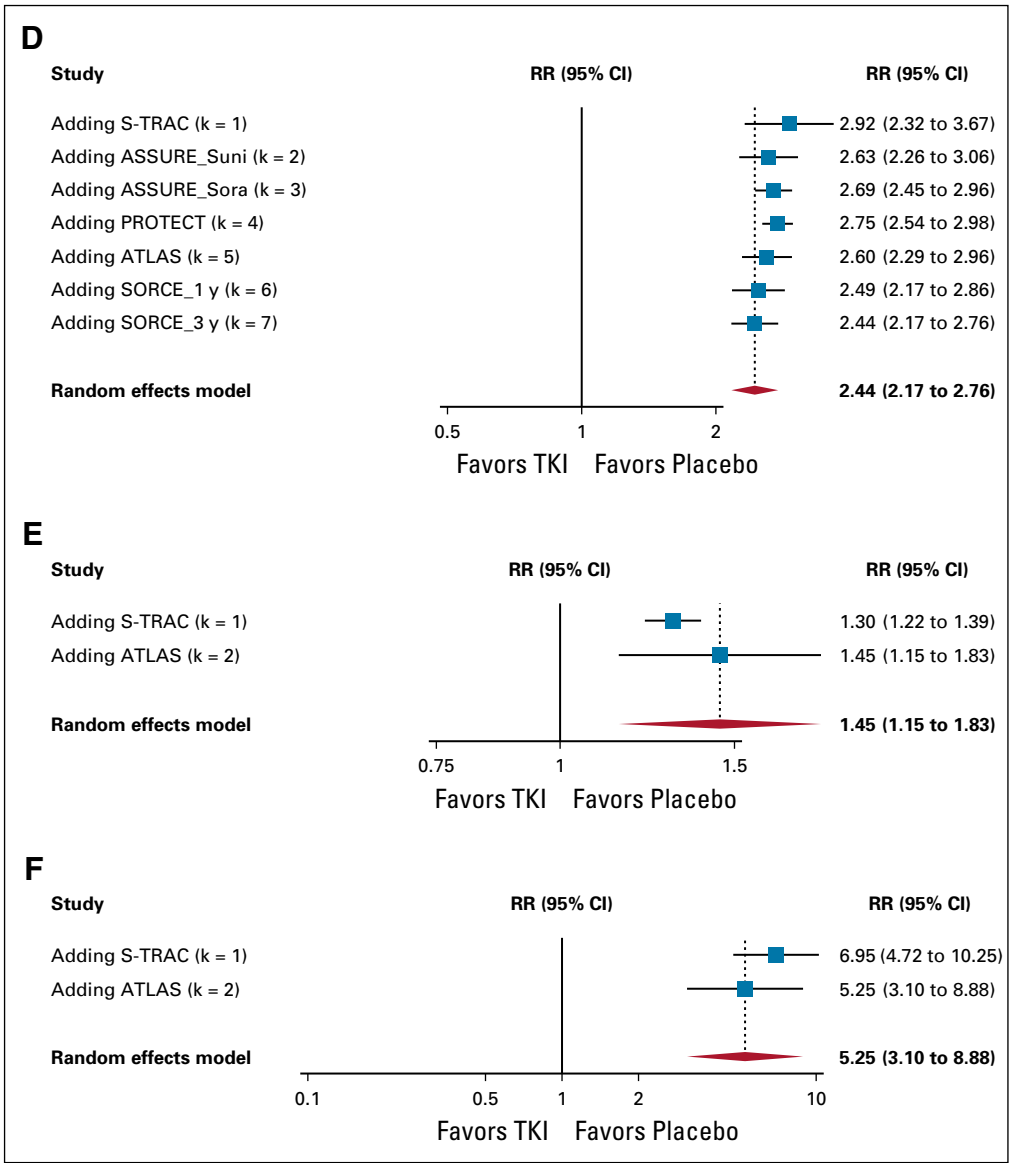


FIG 2. (Continued).

conclusions of no treatment benefit and increased risk of AE with adjuvant TKI therapy. An Interactive Summary of Findings Table can be viewed on the website.

Trial Sequential Analysis

For both OS and DFS, cumulative Z-curves were found to cross futility boundaries and reach the required information size. OS and DFS Z-curves reached neither the traditional boundaries for statistical significance nor the trial sequential monitoring boundaries. In view of the required OIS, this indicates that a statistical significance of $< .05$ is unlikely to be reached even with the inclusion of additional trials (Fig 4).

Quality-of-Life Outcomes

The PROTECT, S-TRAC, and ASSURE trials included some measure of QoL as a study outcome. The PROTECT trial used the Functional Assessment of Cancer Therapy-Kidney Symptom Index 19 (FKSI-19) questionnaire to assess QoL, and although significantly greater deterioration in QoL from baseline was seen in the TKI group compared with placebo (adjusted mean change in total FKSI-19 score at 1 year: –4.49 *v* –0.47, $P < .01$), this was not considered clinically relevant and QoL scores in both groups returned to baseline after treatment cessation.[8] Similarly, in S-TRAC, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) scores favored placebo, but the difference was not clinically meaningful.[23] The ASSURE trial collected patient-reported data on a quality-of-life (QoL) assessment for fatigue, called PROMIS Fatigue-SF1, but these results are yet to be published.

DISCUSSION

In the final update of this LSR, we summarize the totality of evidence for the use of adjuvant TKIs in patients with resected RCC by adding data from SORCE and updated

TABLE 2. Summary of Findings of Final Living Systematic Review Update

Outcome Time Frame	Study Results and Measurements	Trials Included	Absolute Effect Estimates Placebo	 Adjuvant TKI Therapy	Certainty of the Evidence (quality of evidence)	Plain Text Summary
OS 65-78 months	HR: 1.01 (95% CI, 0.91 to 1.12) Based on data from 6,531 patients in five studies[b] Follow-up 65-78 months	S-TRAC, ASSURE, PROTECT, ATLAS, and SORCE	193 per 1,000	195 per 1,000 Difference: two more per 1,000 (95% CI, 16 fewer to 21 more)	High[a]	Adjuvant TKI therapy has little or no difference in OS
Disease-free survival 65-78 months	HR: 0.92 (95% CI, 0.86 to 1.00) Based on data from 6,531 patients in five studies[d] Follow-up 65-78 months	S-TRAC, ASSURE, PROTECT, ATLAS, and SORCE	404 per 1,000	379 per 1,000 Difference: 25 fewer per 1,000 (95% CI, 45 fewer to equal)	High[c]	Adjuvant TKI therapy has little or no difference in disease-free survival
All-cause all-grade AEs 65-78 months	RR: 1.07 (95% CI, 1.03 to 1.11) Based on data from 4,516 patients in four studies[e] Follow-up 65-78 months	S-TRAC, PROTECT, ATLAS, and SORCE	912 per 1,000	976 per 1,000 Difference: 64 more per 1,000 (95% CI, 27 more to 100 more)	Moderate Because of serious inconsistency[f]	Adjuvant TKI therapy probably increases all-cause all-grade AEs slightly
Treatment-related all-grade AEs 65 months	RR: 1.45 (95% CI, 1.16 to 1.8) Based on data from 1,325 patients in two studies[g] Follow-up 65 months	S-TRAC and ATLAS	650 per 1,000	943 per 1,000 Difference: 293 more per 1,000 (95% CI, 104 more to 520 more)	Moderate Because of serious inconsistency[h]	Adjuvant TKI therapy probably increases treatment-related all-grade AEs
All-cause grade 3+ AEs 65-78 months	RR: 2.44 (95% CI, 2.17 to 2.76) Based on data from 6,395 patients in five studies[i] Follow-up 65-78 months	S-TRAC, ASSURE, PROTECT, ATLAS, and SORCE	250 per 1,000	610 per 1,000 Difference: 360 more per 1,000 (95% CI, 293 more to 440 more)	High[j]	Adjuvant TKI therapy increases all-cause grade 3+ AEs
Treatment-related grade 3+ AEs 65 months	RR: 5.25 (95% CI, 3.12 to 8.84) Based on data from 1,325 patients in two studies[k] Follow-up 65 months	S-TRAC and ATLAS	103 per 1,000	541 per 1,000 Difference: 438 more per 1,000 (95% CI, 218 more to 808 more)	Moderate Because of serious imprecision[l]	Adjuvant TKI therapy probably increases treatment-related grade 3+ AEs

NOTE. An interactive summary of findings table can be accessed on the website.

Abbreviations: AE, adverse event; HR, hazard ratio; OIS, optimal information size; OS, overall survival; RR, relative risk; TKI, tyrosine kinase inhibitor.

[a]Indirectness: Not serious. Different risk scores were used across trials; SORCE and PROTECT trials included intermediate-risk patients as well.

[b]Systematic review with included studies: refs. 6-8, 23, and 25; baseline or comparator control arm of reference used for intervention.

[c]Indirectness: Not serious. Different risk scores were used across trials; SORCE and PROTECT trials included intermediate-risk patients as well.

[d]Systematic review with included studies: refs. 5-9; baseline or comparator control arm of reference used for intervention.

[e]Systematic review with included studies: refs. 5-7 and 9; baseline or comparator control arm of reference used for intervention.

[f]Inconsistency: Serious. The magnitude of statistical heterogeneity was high, with I^2: 92%. Imprecision: Not serious.

[g]Systematic review with included studies: refs. 5 and 7; baseline or comparator control arm of reference used for intervention.

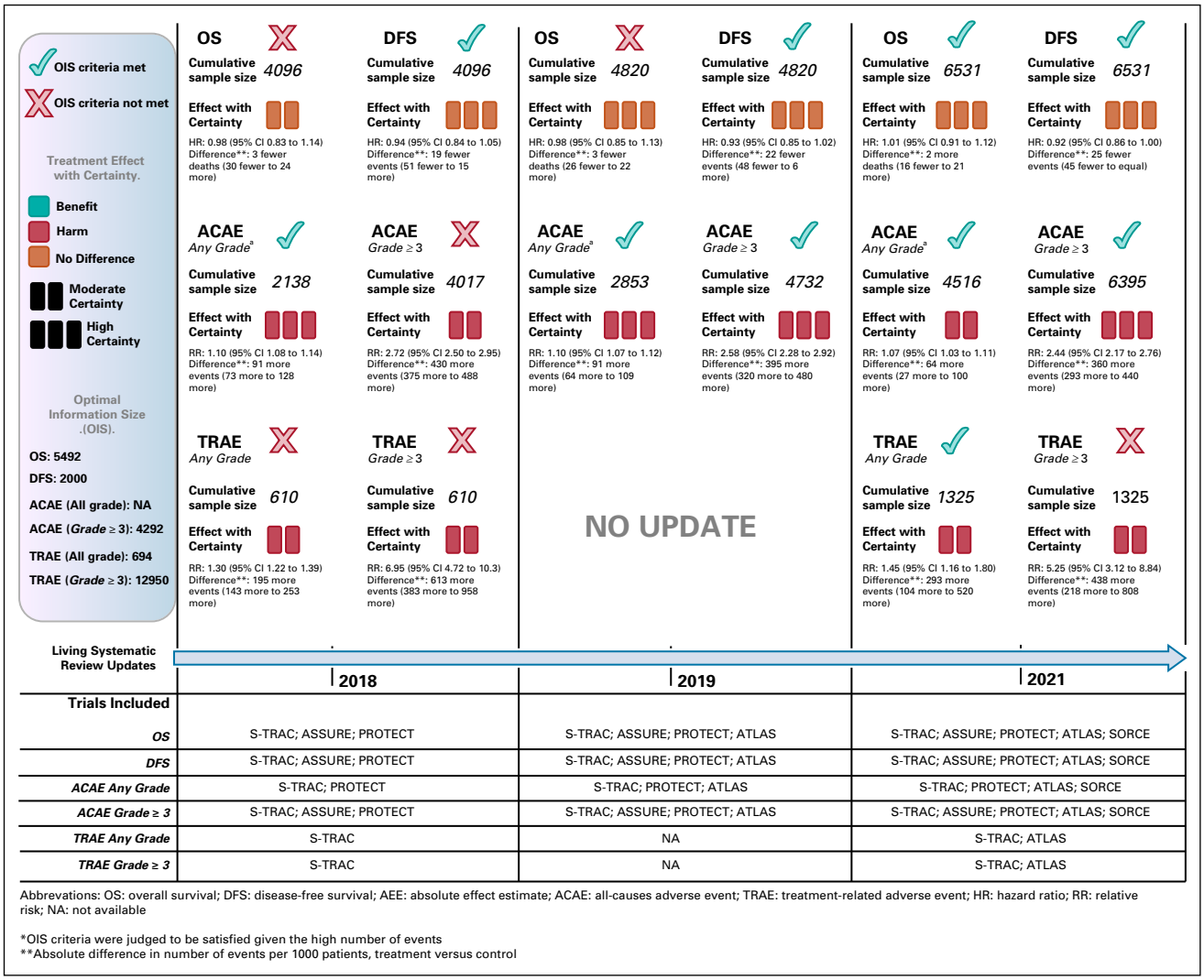
[h]Inconsistency: Serious. The magnitude of statistical heterogeneity was high, with I^2: 93%. The CI of some of the studies do not overlap with those of most included studies or the point estimate of some of the included studies. Imprecision: Not serious. Wide CIs.

[i]Systematic review with included studies: refs. 5-9; baseline or comparator control arm of reference used for intervention.

[j]Inconsistency: Not serious. The magnitude of statistical heterogeneity was high, with I^2: 74%. Imprecision: Not serious. Wide CIs.

[k]Systematic review with included studies: refs. 5 and 7; baseline or comparator control arm of reference used for intervention.

[l]Inconsistency: Not serious. The magnitude of statistical heterogeneity was high, with I^2: 78%. Imprecision: Serious. OIS criteria not met.



Trials Included	2018	2019	2021
OS	S-TRAC; ASSURE; PROTECT	S-TRAC; ASSURE; PROTECT; ATLAS	S-TRAC; ASSURE; PROTECT; ATLAS; SORCE
DFS	S-TRAC; ASSURE; PROTECT	S-TRAC; ASSURE; PROTECT; ATLAS	S-TRAC; ASSURE; PROTECT; ATLAS; SORCE
ACAE Any Grade	S-TRAC; PROTECT	S-TRAC; PROTECT; ATLAS	S-TRAC; PROTECT; ATLAS; SORCE
ACAE Grade ≥ 3	S-TRAC; ASSURE; PROTECT	S-TRAC; ASSURE; PROTECT; ATLAS	S-TRAC; ASSURE; PROTECT; ATLAS; SORCE
TRAE Any Grade	S-TRAC	NA	S-TRAC; ATLAS
TRAE Grade ≥ 3	S-TRAC	NA	S-TRAC; ATLAS

Abbrevations: OS: overall survival; DFS: disease-free survival; AEE: absolute effect estimate; ACAE: all-causes adverse event; TRAE: treatment-related adverse event; HR: hazard ratio; RR: relative risk; NA: not available

*OIS criteria were judged to be satisfied given the high number of events
**Absolute difference in number of events per 1000 patients, treatment versus control

FIG 3. Summary of OIS and certainty of evidence assessments for all three successive living systematic review updates. [a]OIS criteria were judged to be satisfied given the high number of events. ACAE, all-cause adverse event; DFS, disease-free survival; HR, hazard ratio; NA, not available; OIS, optimal information size; OS, overall survival; RR, relative risk; TRAE, treatment-related adverse event.

results from S-TRAC and PROTECT (Table 1). Meta-analysis results indicate lack of any meaningful clinical improvement in survival and quality-of-life outcomes with the addition of an adjuvant TKI and a significant increase in the risk of high-grade AE with adjuvant TKIs when compared with placebo. Overall, these results are consistent with previous analyses,[11,12,27] TKIs significantly increase toxicity, and now, we have additional data to support that there is neither improvement in quality of life nor a survival advantage with the use of adjuvant TKI monotherapy.

There is some evidence in favor of using TKI in high-risk patients. The modest DFS benefit (HR, 0.76; 95% CI, 0.59 to 0.98) seen in the S-TRAC trial (which did not translate into OS benefit) is often attributed to a larger proportion of high-risk patients in the trial population. Similarly, the subgroup analysis of high-risk patients in the ATLAS trial also indicates a significant improvement in DFS. A previous pooled subgroup analysis[28] also favored the superiority of adjuvant TKIs in prolonging DFS in high-risk patients (ie, with T3-T4 tumors and/or nodal metastasis), leading to the suggestion of selecting patients at highest risk for adjuvant TKI therapy. However, the data for the latter are inconsistent and not practice-changing. It is neither consistent within trials nor across the trials or pooled analyses. DFS benefit in high-risk patients was only seen in independent review committee–assessed DFS[5] and investigator-assessed DFS in S-TRAC and ATLAS, respectively. Similarly, across trials, S-TRAC and ATLAS suggest a DFS benefit in higher-risk patients, but ASSURE and SORCE have identified no such improvement. Again, across meta-analyses, the results of our subgroup analysis do not support this; however, our analysis differs from Massari et al in the inclusion of SORCE, which expands the sample size of this subgroup to 4,993 patients (from 3,282 patients in the subgroup analysis by Massari et al, including the ASSURE, S-TRAC, and ATLAS trials only). Moreover, the

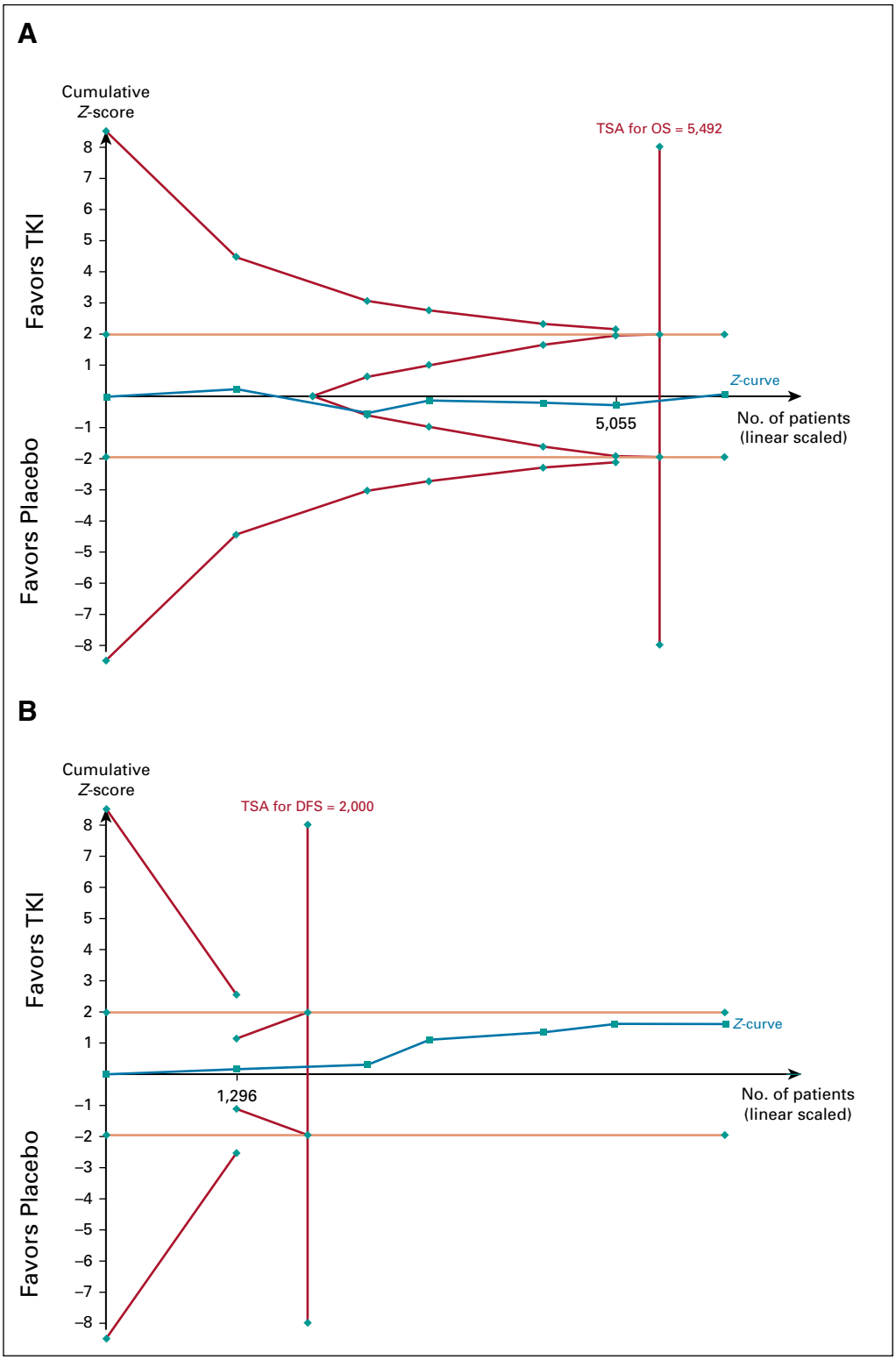


FIG 4. TSA graphs (a two-sided graph) for (A) OS and (B) DFS. DFS, disease-free survival; OS, overall survival; TKI, tyrosine kinase inhibitor; TSA, trial sequential analysis.

use of different scoring systems in randomized controlled trials to define subpopulations and variations in their use of tumor, node, and metastases staging to profile risk is another source of inconsistency.

Although we have not been able to assess the dose-response relationship because of lack of available data, trends favoring TKI benefit may be observed with increased doses of the TKI. A subgroup analysis by starting dose from

the ASSURE trial shows a notable (albeit nonsignificant) trend of improved DFS in patients who received a full starting dose of sunitinib or sorafenib versus patients who received reduced doses. However, any potential gain is offset by the frequent need for dose reductions and discontinuations because of unacceptable toxicity; in both the PROTECT and ASSURE trials, high treatment discontinuation rates and AE necessitated alteration of the dosing protocol midtrial. In SORCE, only 13% of patients received the full starting dose of sorafenib because of patient noncompliance. Ultimately, regardless of any potential survival gain, intolerance severely limits the practicality of using higher TKI doses in most patient populations.

The use of adjuvant TKIs is not recommended in any subset of patients postnephrectomy based on an unfavorable survival and adverse effect profile. Although sunitinib is approved by the US Food and Drug Administration for the adjuvant indication, this approval was not granted by the European Medicines Agency (EMA) and adjuvant therapy is not recommended by the European Society of Medical Oncology guidelines.[29] The National Comprehensive Cancer Network guideline version 2.2021 recommends adjuvant sunitinib as category three evidence: "based upon any level of evidence, there is major National Comprehensive Cancer Network disagreement that the intervention is appropriate." Immune checkpoint inhibitor (ICI)–based options are emerging as a potential option in the management adjuvant RCC. Several ICI-based options are thus moving forward into phase III clinical trials in the neoadjuvant, adjuvant, and perioperative setting. IMmotion010 (atezolizumab; ClinicalTrials.gov identifier: NCT03024996), KEYNOTE-564 (pembrolizumab; ClinicalTrials.gov identifier: NCT03142334), RAMPART (durvalumab or durvalumab and tremelimumab; ClinicalTrials.gov identifier: NCT03288532), PROSPER (nivolumab; ClinicalTrials.gov identifier: NCT03055013), and CheckMate 914 (nivolumab or nivolumab-ipilimumab; ClinicalTrials.gov identifier: NCT03138512) are already underway, and the results are pending (Data Supplement).[30] Given the recent success of TKI + ICI in the metastatic setting, it is likely that this strategy will also be explored in the future in the adjuvant setting.[31-33]

Maintaining LSR is a resource-intense process. Although it is manageable to maintain living updates when the number of studies is small such as in this case, the task quickly becomes daunting if the evidence is rapidly accumulating or if it requires more complex analyses such as network meta-analyses. Thus, it is necessary to work toward automation to sustain the LSR process. With advances in programming and machine learning, several efforts are underway to achieve this automation.[34] Indeed, we have developed a living evidence framework and applied several strategies such as automated searches and analyses successfully in this review. Furthermore, we have introduced several interactive features on the companion website, which allow users to interact with the evidence using living PRISMA, Interactive tables, and forest plots.[15]

After initiating an LSR, it is also important to recognize when to stop conducting new clinical trials and hence no longer update the evidence. Although there is no consensus on the latter, it may be reasonable to stop the update process once high certainty is achieved for key clinical end points on benefits and harms and an OIS is achieved. TSA indicating that current level of evidence is conclusive can further support the decision of formally concluding the living review. The GRADE Working Group has published detailed guidance for adjudicating certainty of evidence, and high certainty is achieved when any additional data are unlikely to significantly change the summary effect estimates. In this case of adjuvant TKI for resected RCC, moderate to high certainty of evidence in key clinical outcomes suggests no decrease in recurrence and increased toxicity. Hence, future clinical trials, if conducted, are unlikely to change our conclusions about the benefit profile of adjuvant TKI treatment.

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EQUAL CONTRIBUTION

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The following represents disclosure information provided by the authors of this manuscript. All relationships are considered compensated unless

otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/cci/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

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Stock and Other Ownership Interests: HemOnc.org
Consulting or Advisory Role: Westat, IBM
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Travel, Accommodations, Expenses: Celgene

No other potential conflicts of interest were reported.

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