J Surg Res 2019; 2 (4): 205-216 *DOI: 10.26502/jsr.10020040*

Research Article

High-Risk Locoregional Renal Cell Cancer: S-TRAC Criteria for the Selection of Adjuvant Treatment Candidates

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Received: 05 September 2019;

Accepted: 20 September 2019;

Published: 24 October 2019

Abstract

Introduction and objective: Clear-cell renal-cell carcinoma (RCCcc) is the genitourinary neoplasm with the highest mortality rate despite primary surgical treatment, which highlights the necessity for adjuvant treatment. To date, only the use of sunitinib in the S-TRAC study (Adjuvant Sunitinib in High-Risk Renal-Cell Carcinoma after Nephrectomy) has shown improvement of disease-free survival (DFS). The aim of the present study is to identify, using a single-center sample of patients with locally advanced RCC, potential candidates for adjuvant treatment by the application of the S-TRAC criteria.

Material and methods: We enrolled patients undergoing oncological nephrectomy from 2009 to 2014. We selected and stratified the patients according to the S-TRAC criteria. DFS and overall survival (OS) were analyzed.

Results: Forty-eight patients out of the 153 (31.4%) previously selected patients met the S-TRAC inclusion criteria. DFS and OS at 5 years were 73.0% and 71.4%, respectively. According to the UISS prognostic model, 85.4%, 4.1% and 6.2% of our patients were assigned to groups A2, B and C, respectively. DFS in these groups was 73%, 100% and 100%, respectively. OS was 76% in group A2 and 67% in group C. No deaths were observed in group B.

Conclusions: At 5 years, a higher proportion of patients in the present study were disease-free (73.0%) compared to the placebo group of the S-TRAC clinical trial (51.3%). Efforts should be focused on the identification of precise prognostic models in order to identify high-risk candidates to receive adjuvant treatment.

Keywords: Renal cancer; Adjuvant treatment; Sunitinib; Risk prognostic models

1. Introduction

Renal cell carcinoma (RCC) accounts for 2-3% of all neoplasms [1]. An increase in incidence has been seen during the last decade because of a greater incidental diagnosis in imaging tests performed for another reason [2]. Risk factors have been identified, which include smoking, hypertension and obesity [3]. The three main types of RCC are clear cell (RCCcc), papillary type I and II (RCCp) and chromophobe (RCCch) [4]. RCCcc is the most frequent type and has the worst prognosis [5]. According to the TNM classification, the specific cancer survival rates for RCCcc are 91%, 74%, 67% and 32% for stages I, II, III and IV, respectively [6]. Thus, locally advanced RCCcc is one of the most lethal genitourinary malignancies, and surgery is its only curative treatment [7]. However, the risk of recurrence after nephrectomy reaches 40%, with OS at 5 years of 30% at stage T4 and 50% in the case of lymphatic involvement [3, 8].

To improve these results, the role of adjuvant treatments after surgery is being investigated to eliminate possible foci of clinically undetectable micrometastases [7]. Several adjuvant strategies, including cytokine therapy, radiotherapy, and hormone therapy, have been explored to decrease the rate of relapse, but none have been successful. The proven efficacy of antiangiogenic therapies, including the vascular endothelial growth factor (VEGF) pathway inhibitors in patients with metastatic renal-cell carcinoma (mRCC) supports the evaluation of these drugs as adjuvant therapy [7].

Citation: Brasero-Burgos J, Gómez-Dos-Santos V, Álvarez-Rodríguez S, Gajate-Borau P, Díaz-Pérez DE, Lorca-Álvaro J, Santiago-González M, Díez-Nicolás V, Hevia-Palacios V, Burgos-Revilla FJ. High-Risk Locoregional Renal Cell Cancer: S-TRAC Criteria for the Selection of Adjuvant Treatment Candidates. Journal of Surgery and Research 2 (2019): 205-216.

In 2016, the S-TRAC study demonstrated an improvement in DFS in patients with locally advanced RCCcc who were treated with adjuvant sunitinib compared to those treated with placebo for 1 year after nephrectomy. This study observed only a moderate worsening in the quality of life in the patients who received sunitinib [9]. However, the other studies with VEGF inhibitors have obtained negative results, so the use of sunitinib continues to be controversial. The aim of the present study was to identify patients at high risk of recurrence according to S-TRAC criteria and select potential candidates with locally advanced RCC for adjuvant treatment in a single-center sample.

2. Materials and Methods

We retrospectively reviewed hospital surgical and clinical records from January 2009 to December 2014. The study was approved by the hospital ethics committee and was conducted in accordance with International Conference on Harmonisation Good Clinical Practice guidelines and applicable local regulatory requirements and laws. Eligible patients were at least 18 years of age and had received a diagnosis of locoregional RCC (tumor stage 3 or higher, regional lymph-node metastasis, or both). Other eligibility criteria included histologic confirmation of RCCcc, no previous systemic treatment and a score of no more than 2 on the Eastern Cooperative Oncology Group (ECOG) scale before nephrectomy. Patients were stratified into risk groups according to the 2002 UCLA Integrated System (UISS) prognostic model:

- Group A: Stage 3 (T3), no or undetermined nodal involvement (N0/Nx), no metastasis (M0).
    - A1: Low risk. Includes any Fuhrman grade and an ECOG score of 0 or Fuhrman grade 1 and an ECOG ≥ 1.
    - A2: High risk. Includes Fuhrman grade 2 or higher and an ECOG score ≥ 1
- Group B: Stage 4 tumor (T4), N0/Nx, M0.
- Group C: Any tumor stage, locoregional nodal involvement (N1), M0.

Follow-up after nephrectomy was performed in accordance with the European Clinical Guidelines on RCC and included thoracoabdominal-pelvic CT with a periodicity according to the risk group. In the case of high-risk RCC, CT was performed at 6 months after surgery and then annually for up to 5 years. After 5 years, CT was performed every 2 years. A descriptive study of patients' baseline and oncological characteristics was performed. Continuous variables were expressed as the mean and confidence interval or median and range, as required, and categorical variables as the number and percentage. DFS and OS were assessed using the Kaplan-Meir method.

3. Results

We collected data about 153 patients subjected to nephrectomy for RCC between 2009 and 2014. 48 patients out of 153 (31.4%) met S-TRAC eligibility criteria and were subsequently selected and classified according to UISS categories. Two patients were not classifiable due to lack of complete data. Radical surgery was performed in 40 patients (81.6%) while partial nephrectomy was performed in the remaining 8 patients (16.3%). Table 1 shows study patients' baseline and oncological characteristics and their risk stratification according to the UISS classification. Additionally, Table 1 includes placebo- and sunitinib-treated patients' characteristics from the S-TRAC clinical trial.

Our present study includes patients older than S-TRAC, with a similar sex distribution and with an

ECOG score that includes a higher percentage of the ≥ 2 group. Regarding risk profile, the percentage of patients assigned to the highest risk group (Group C) was slightly lower than in that in the placebo- and sunitinib-treated populations in the S-TRAC trial. The mean time of follow-up was 4.6 (SD 2.42) years, which was shorter than the median duration of DFS in the sunitinib and placebo groups (6.8 years and 5.6 years, respectively) in the S-TRAC clinical trial. The median time of follow-up for DFS and OS were not reached in the present study (Figure 1 and 2).

Characteristics n (%)	**Sample of our center (n=48)**	**S-TRAC**	
		Placebo (n=306)	**Sunitinib (n=309)**
Age			
Mean (min-max)	64 (30-89)	58 (21-82)	57 (25-83)
18-64 (%)	23 (47.9)	224 (73.2)	233 (75.4)
≥ 65 (%)	25 (52)	82 (26.8)	76 (24.6)
Sex (%)			
Male	38 (77.6)	229 (74.8)	222 (71.8)
Female	10 (20.4)	77 (25.2)	87 (28.2)
ECOG (%)			
0	30 (62.5)	220 (71.9)	228 (73.8)
1	13 (27.1)	84 (27.5)	79 (25.6)
≥2	2 (4.2)	0	1 (0.3)
Unknown	3 (6.2)	2 (0.7)	1 (0.3)
UISS Classification (%)			
A	41 (85.4)	278 (90.8)	280 (90.6)
. A1	. 0	. 112 (36.6)	. 115 (37.2)
. A2	. 41 (85.4)*	. 166 (54.2)	. 165 (53.4)
B	2 (4.1)**	4 (1.3)	4 (1.3)
C	3 (6.2)***	24 (7.8)	25 (8.1)
Not classifiable	2 (4.1)	0	0

*Consisting of 34 (83%) patients pT3aN0, 5 (12%) pT3bN0 and 2 (5%) pT3c according to the TNM classification; **Consisting of 2 (100%) T4N0 patients according to the TNM classification; *** Consisting of 2 (67%) patients pT1aN1 and 1 (33%) pT3bN2 according to the TNM classification

Table 1: Baseline characteristics.

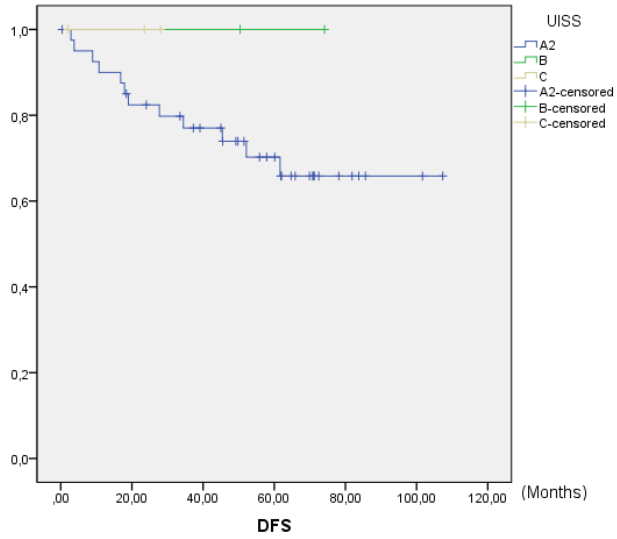

Figure 1: Disease-free survival.

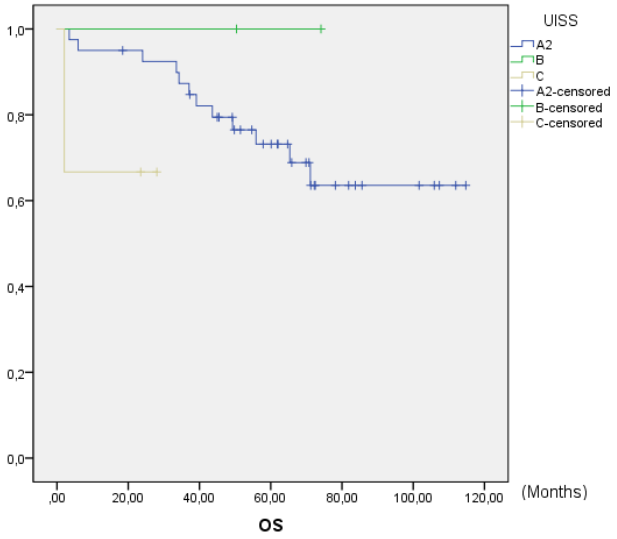

Figure 2: Overall survival.

DFS at 5 years was 73.0% (Figure 1). In the global series, 27% (13/48) of patient relapses were observed. Of the relapses, 23.1% (3/13) were local relapses, 61.5% (8/13) were distance relapses and finally, 15.4% (2/13) presented both local and distance recurrences. DFS in UISS groups A2, B and C were 73%, 100% and 100%, respectively. Global OS at 5 years was 71.4%. OS was 76% in group A2 and 67% in group C. No deaths were observed in group B. No statistically significant differences were observed among the UISS groups (Figure 2). A total of 28.6% (14/48) of patients died during follow-up, and 35.7% (5/14) of the deaths were due to recurrence and progression of the RCC. The remaining 64.3% (9/14) deaths were due to other non-oncological causes. Both oncological and non-oncological deaths were similarly distributed over time. The median cancer-specific survival (CSS) was 3.25 (SD 0.67) years.

4. Discussion

Despite progress in the systemic treatment of advanced RCC over the last decade, it remains one of the most lethal genitourinary malignancies. OS rates at 5 years for patients with locally advanced or lymph-node positive disease remain at 53%, and this OS rate drops to 8% for those with T4 stage disease or with distant metastases. Surgery is the primary treatment for locally advanced RCC. To improve on these outcomes, effective adjuvant therapy is needed for high-risk RCC [7, 10]. In our series, only 27% of the patients with nonmetastatic RCC, considered at high risk according to the UISS prognostic model, presented local or distant recurrence. This percentage was clearly lower than the recurrence rate in the placebo populations in published TKIs clinical trials on advanced RCC. The therapeutic landscape for RCC has changed dramatically with the introduction of targeted molecular therapies. Much of this progress is attributed to characterization of the von Hippel-Lindau (VHL) tumor suppressor and its role in the carcinogenesis of ccRCC. Bi-allelic loss of VHL leads to unmitigated activation of hypoxia-inducible factor (HIF)-1α, which serves as a transcription factor for pro-angiogenic genes in a tumor cell, including for VEGF and platelet-derived growth factor. This sequence promotes angiogenesis to facilitate tumor growth and progression. Overproduction of HIF-1α can also occur due to hyperactive signaling via the mammalian target of rapamycin (mTOR) pathway, which may occur independently of VHL loss [7].

Drugs exploiting these two mechanistically unique pathways, referred to as targeted therapy, are available and have been successfully used in treating mRCC. Targeted agents that are currently Food and Drug Administration (FDA)-approved for mRCC include six inhibitors of the VEGF receptor (sunitinib, sorafenib, pazopinib, axitinib, cabozantinib and lenvatinib), two mTOR inhibitors (everolimus and temsirolimus), and one VEGF inhibitor (bevacizumab, in combination with interferon-α [IFN-a]). Several clinical trials have been conducted to test most of these drugs in the context of loco-regional advanced RCC after surgery [7]. The identification of patients who are at increased risk of relapse is key for the development of rational adjuvant strategies. A number of predictive models have been developed to accomplish this goal. These models all incorporate widely available, easily obtainable, clinicopathological variables that are associated with prognosis following surgery (Table 2) [11, 12]. Variables that showed the greatest predictive capacity in DFS and CSS were TNM stage, Furhman nuclear grade and tumor size. We selected the UISS model because it has been one of the most commonly used models, and more specifically, in the S-TRAC clinical trial the UISS model was unique with a positive result regarding DFS for adjuvant treatment.

The UISS model includes two tumor-specific features, namely, TNM stage and Fuhrman grade, together with a patient specific feature, namely, the ECOG performance status. This combination of features stratifies patients into low-risk, intermediate-risk and high-risk prognostic categories. In patients with non-metastatic disease, the application of the UISS model correctly predicted 2-year and 5-year survival values regardless of tumor histology in 76.5-86.3% of patients [13]. In recent years, several trials utilizing different VEGF TKIs have been completed and reported conflicting results regarding clinical benefit and patient safety. Table 3 summarizes the main characteristics of these trials [9, 14, 15].

Postoperative prognostic models in localized RCC	Event	Variable										c-index
		Histological subtype	TNM stage	ECOG PS	Related symptoms RCC	Incidental diagnosis	Furhman grade	Tumor necrosis	Vascular invasion	Tumor size	Surgical margin	
Kattan/MSKCC (2001)	DFS	CCRcc-p-ch	x	-	x	-	-	-	-	x	-	Internal: 0.74
Zisman/UISS (modified) (2002)	OS, CSS, DFS	CCRcc	x	x	-	-	x	-	-	-	-	External: 0.64-0.86
Frank/ SSIGN (2002)	DFS	CCRc	x	-	-	-	x	x	-	x	-	Internal: 0.84
Frank (2003)	DFS	CCRc	x	-	-	-	x	x	-	x	x	Internal: 0.8-0.82*
Leibovich (2003)	DFS	CCRcc	x	-	-	-	x	x	-	x	-	Internal: 0.82
Modified Kattan/Sorbellini (2005)	DFS	CCRcc	x	-	x	-	x	x	x	x	-	Internal: 0.82
Karakiewicz (2007)	CSS	CCRcc-p-ch	x	-	x	-	x	-	-	x	-	Internal: 0.86
Klatte (2010)	CSS	CCRp	x	-	-	x	-	x	x	-	-	Internal: 0.93

*0.8 abdominal and bone metastases; 0.82 thoracic metastases

Table 2: Postoperative predictive nomograms of recurrence in nonmetastatic RCC.

Studies	Research dates	Follow-up (years)	Histology	Patient stratification nomogram	Stages included	n- evaluated treatment	Treatment duration	Main aim DFS	Toxicity (grade ≥3)
ASSURE	April 2006-September 2010	4	RCC	UISS	pT1b G3-4, pT2-4 NO or $pT_{Any}N+$ (completely resected) M0	1943 (647 sunitinib, 649 sorafenib, 647 placebo)	54 weeks sunitinib at 50 mg per day the first 28 days of each 6-week cycle or sorafenib at 400 mg/12 h or placebo	5.8, 6.1 and 6.6 years; HR 1.02, p=0.80 and HR 0.97, p=0.71	57% sunitinib/68% sorafenib*
S-TRAC	August 2007- April 2011	4	RCCcc	Modified UISS	pT3-4 NO or $pT_{Any}N+$	615 (309 sunitinib, 306 placebo)	Sunitinib 50 mg vs placebo on a 4 weeks-on, 2-weeks-off schedule for 1 year	6.8 vs 5.6 years to sunitinib vs placebo (HR: 0.76; 95% CI 0.59–0.98; p=0.03)	60.5% sunitinib**
PROTECT	December 2010-September 2013	5	RCCcc or predominantly clear cells	SSIGN	pT2G3-4, pT3-4N0 or $pT_{Any}G_{Any}N+$	1538 (198 pazopanib 800 mg vs 205 placebo; toxicity modified to 571 pazopanib 600 mg vs 564 placebo)	Pazopanib 800 mg for 1 year (modified to 600 mg) vs placebo	With 600 mg dose p > 0.05 In secondary analysis with 800 mg dose HR*: 0.69; IC 95%: 0.51-0.94, p=0.02)	60% pazopanib***; 21% placebo

*44% sunitinib group and 45% sorafenib group had to stop treatment because of toxicity; 55% of patients had to reduce doses due to adverse effects grade ≥ 3; ** 28% had to interrupt treatment because of toxicity; 34% of patients had to reduce doses due to adverse effects grade ≥ 3; *** The dose of the study had to be modified to 600 mg due to high toxicity with 800 mg

Table 3: ASSURE, S-TRAC, and PROTECT characteristics.

Overall, antiangiogenics did not improve DFS (HR 0.92, 95% CI 0.78-1.07) or OS (HR 0.99, 95% CI 0.79-1.25) when compared to placebo in postnephrectomy patients with nonmetastatic RCC. Similarly, DFS was comparable between the two groups (HR 0.89, 95% CI 0.78-1.02) when examining the effect of VEGF TKIs in the subsets of patients with the highest risk of relapse as reported by the individual trials PROTECT, ASSURE, or S-TRAC (PROTECT: pT2 G3-4 N0, pT3-T4 G any N0, or pT any G any N1; ASSURE 2017: pT3, pT4 or node-positive disease: and S-TRAC 2017: T3, no or undetermined nodal involvement, Fuhrman grade 2, and ECOG performance score 1 or T4 and/or nodal involvement) [7, 9, 14, 15].

Finally, in 2018, the Axitinib Versus Placebo in Patients at High Risk of Recurrent Renal Cell Carcinoma (ATLAS) study was stopped owing to futility at a preplanned interim analysis. This study included patients with RCCcc ≥ pT2 and/or N+, G_{any} and ECOG 0-1. The available data showed no significant difference in DFS according to the independent review committee (IRC) assessment (HR 0.870, 95% CI 0.660-1.147; p=0.3211). In the highest-risk subpopulation, a 36% and 27% reduction in risk of a DFS event with axitinib was observed in the investigator assessment (HR 0.641, 95% CI 0.468–0.879; p=0.0051) and IRC assessment (HR 0.735, 95% CI 0.525-1.028; p=0.0704), respectively. The incidence of adverse effects was similar in both groups, although the toxicity ≥ 3 degree was greater in the axitinib group (61% vs. 30%). The OS data were not mature [16].

Only the S-TRAC trial showed a clinical and statistically significant reduction of 24% in the occurrence of recurrence events in comparison to placebo [9, 10]. In light of the positive results of S-TRAC, the Food and Drug Administration (FDA) approved sunitinib as adjuvant therapy in high-risk RCC in November 2017 [7]. However, the European Medicines Agency (EMA) did not view the results in the same way [17], and controversy regarding the benefit of sunitinib in the adjuvant setting continues. Two studies evaluated the efficacy of sunitinib versus placebo in RCC patients. In a meta-analysis of these two trials (ASSURE 2016 and S-TRAC 2016), sunitinib did not show any improvement in the overall cohort for either DFS (HR 0.89, 95% CI 0.67-1.19) or OS (HR 1.11, 95% CI 0.90-1.37) [18, 19]. However, it is important to note the high heterogeneity, which is most likely secondary to the differences in design and study populations between ASSURE and S-TRAC, mainly the inclusion of fewer high-risk patients in ASSURE (T1b) compared to S-TRAC (>T3). In addition, approximately 20% of the patients included in ASSURE had non-clear cell histology compared to mainly clear-cell RCC in S-TRAC (Table 3).

To evaluate if S-TRAC results could be applied to our actual RCC population and, consequently, to consider sunitinib adjuvant treatment after surgery for high-risk patients with loco-regional, advanced, nonmetastatic disease, we performed a risk assessment by means of a UISS prognostic model, and DFS and OS were assessed. DFS at 5 years in our series was 73%, which was greater than in the previously described clinical trial where DFS in the placebo population varied from 51.3 to 56.4% and 64.0% in the S-TRAC, ASSURE and PROTECT trials, respectively [9, 14, 15]. One possible explanation could be the smaller number of patients included in the present study. Nevertheless, we are obliged to identify in our RCC population the very high-risk patients who would benefit from adjuvant treatment or inclusion in a clinical trial and who would probably correspond to those with lymph node metastases.

Among the possible reasons for failure of VEGF TKIs in the adjuvant setting, poor tolerability and risk of non-

adherence to treatment or treatment withdrawal are major issues in potentially cured patients that could result in an excess number of dose reductions and treatment pauses and ultimately lead to a suboptimal dose intensity of the adjuvant treatment. A systematic review comparing the ASSURE, S-TRAC and PROTECT data showed an association to a higher risk of grade 3-4 toxicity compared to placebo (64.3% vs. 22.7%, HR 2.74, 95% CI 2.49-3.03). Treatment suspension rates varies among the different clinical trials from 23% (ATLAS) to 45% (ASSURE). The most frequent VEGF TKIs adverse events were hand-foot syndrome, diarrhea, hypertension, increased transaminases and fatigue [21, 22].

Beyond comparing the results of the studies presented and that of our sample, what remains as the main problem in the context of the targeted therapies is the proper selection of patients. It is crucial to identify patients who are truly going to benefit from adjuvant treatment and to achieve balance between clinical benefit and the avoidance of overtreatment and unnecessary adverse effects. This premise has led our center to a policy of action guided by a multidisciplinary team composed of urologists and medical oncologists (with joint consultation and their own agendas) and supported by the clinical trials unit. The strategy of our group, as recommended by the different clinical guidelines, is to prioritize the inclusion of patients in clinical trials and relegate the use of sunitinib to very high-risk patients (groups B and/or C of the UISS) with a comorbidity-favorable profile and in the absence of available trials. Two ongoing post-nephrectomy RCTs are evaluating the efficacy of adjuvant sorafenib therapy (SORCE study) and everolimus therapy (EVEREST). However, given the disappointing findings discussed above, positive results seem unlikely [22].

5. Conclusion

The management of RCCcc, especially in advanced stages, is a challenge because it represents a disease with a high risk of recurrence and mortality. To date, only the use of sunitinib as an adjuvant treatment has been approved by the FDA after the results of the S-TRAC study. In our study, only 27% of the selected patients based on the UISS model had tumor recurrences. Future studies should potentially focus on identifying patients at higher risk of relapse on the basis of clinicopathological and molecular biomarkers that improve classification accuracy of actual prognostic models. Taking into consideration the controversial results of clinical trials and the significant toxicity of VEGF TKIs, there is currently insufficient evidence for the use of VEGF TKIs in the adjuvant setting in patients with advanced RCC after nephrectomy. Novel immune checkpoint inhibitors hold promise for the adjuvant therapy of RCC. However, improved patient selection and stratification, use of active, biology-driven treatments and improved management of therapy are required to prevent failure of these and other novel agents in the future. Finally, multidisciplinary management of all patients with RCC is mandatory.

Acknowledgements

The authors acknowledge the kidney, transplant and research section of our hospital for their help and support.

Conflict of Interests

There is no conflict of interest to declare.

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