

Impact of Estimand Selection on Adjuvant Treatment Outcomes in Renal Cell Carcinoma

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BACKGROUND

- Annually, ~338,000 persons are diagnosed with renal cell carcinoma (RCC), resulting in ~144,000 deaths.¹
- Patients at high risk of disease recurrence following nephrectomy need adjuvant treatment options.²⁻⁸
- A particular issue in clinical trials are “intercurrent events”, ie, events that occur after randomization and either preclude the observation of the endpoints of interest or affect their interpretation.
- A draft addendum of the International Conference on Harmonisation E9 guideline⁹ on Statistical Principles for Clinical Trials was released in August 2017 and introduced an estimand framework that recognizes there are multiple ways to quantify the treatment effect and that changing the derivation of the endpoint or handling intercurrent events differently targets different scientific questions.

OBJECTIVE

- To explore the impact of estimand selection on the analysis and interpretation of clinical trial outcomes in the adjuvant treatment of RCC.

METHODS

- A cross-industry collaboration of statisticians and clinicians worked on connecting estimand framework concepts to different applications, including adjuvant treatment of RCC.
- Different estimands require different methods for handling intercurrent events.
 - eg, “Does the drug improve DFS [disease-free survival] if no patient had received new therapy?” vs “Does the drug improve DFS and delay the start of new therapy?”

- Possible intercurrent events in this setting could include:
 - Drop-out due to tolerability.
 - Treatment not initiated.
 - Initiation of systemic therapy prior to an event.
 - Extended lost-to-follow-up (ie, ≥2 missed assessments just before an event).
 - Death or second primary malignancy, if only considering time to recurrence.
- Data are from the phase 3, placebo-controlled trials of adjuvant treatment with sunitinib (S-TRAC; NCT00375674),² pazopanib (PROTECT; NCT01235962),³ and axitinib (ATLAS; NCT01599754).⁴

RESULTS

- Common analyses that have been implemented in trials of adjuvant treatment, using S-TRAC as the example, are shown in **Figure 1**.
 - In addition to the primary endpoint (primary estimand; row 1), some of the analyses consider alternative scientific questions of interest (rows 4–6), whereas others (rows 2, 3, 7, and 8) assess variations in the timing of relapse.
- Table 1** defines the different clinical questions for the primary and supplemental estimands identified for rows 1 and 4–6 in **Figure 1**.
 - Some of these questions were also considered in PROTECT and ATLAS; these results are shown for comparison.
- For S-TRAC, PROTECT, and ATLAS, treatment outcomes were similar to the prespecified primary analysis, irrespective of the clinical question asked.
- A summary of differences between S-TRAC, PROTECT, and ATLAS is shown in **Table 2**.
 - Although at first glance the clinical questions asked are similar among the studies, differences in patient population and the handling of second primary malignancies lead to differences in the primary estimand.

Table 1: Comparison of Clinical Questions of Interest in S-TRAC, PROTECT, and ATLAS

Clinical Question of Interest	S-TRAC (N=615)		PROTECT (N=1538)		ATLAS (N=724)	
	No. Events	HR (95% CI)	No. Events	HR (95% CI)	No. Events	HR (95% CI)
Primary estimand						
Does the drug improve DFS if no patient received new therapy?	257	0.76 (0.59–0.98)	513	0.80 (0.68–0.95)	203	0.87 (0.66–1.15)
Supplemental estimands						
Does the drug improve DFS regardless of whether the patient had received new therapy?	289	0.81 (0.65–1.02)	519	0.81 (0.68–0.96)	216	0.82 (0.63–1.08)
Does the drug improve DFS and delay the start of new therapy?	282	0.77 (0.61–0.97)	N/A	N/A	N/A	N/A
Does the drug improve RFS if no patient had received new therapy?	233	0.78 (0.60–1.01)	N/A	N/A	194	0.95 (0.71–1.25)

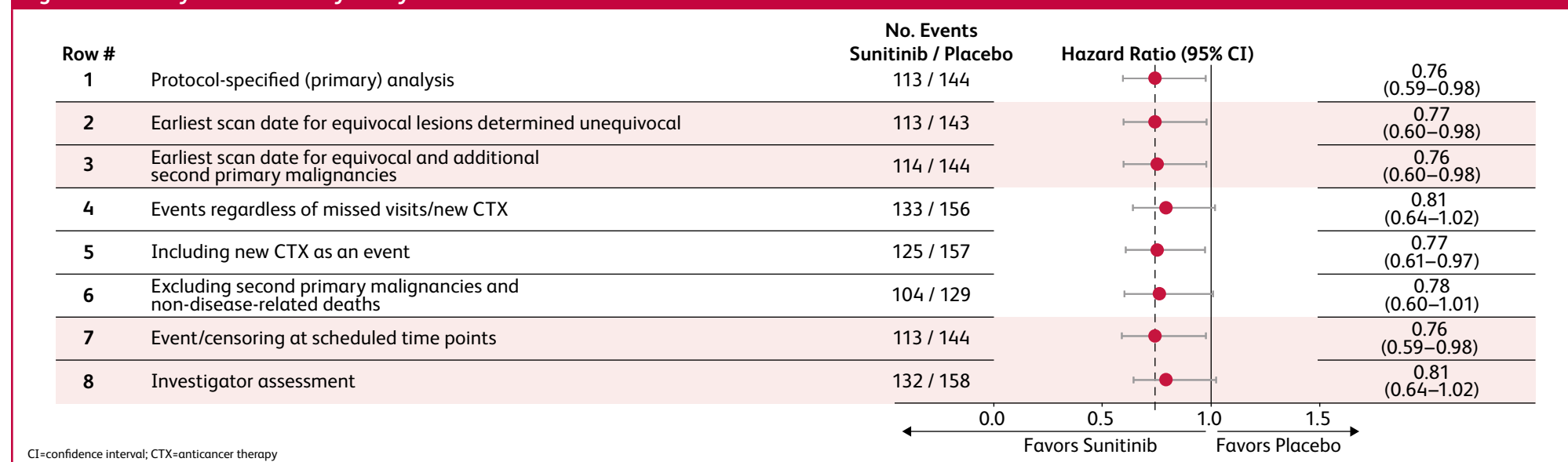
CI=confidence interval; DFS=disease-free survival; HR=hazard ratio; N/A=not applicable; RFS=recurrence-free survival

Table 2: Differences Between S-TRAC, PROTECT, and ATLAS

	S-TRAC	PROTECT	ATLAS
Endpoint definition	Recurrence, second primary cancer, death from any cause	Local recurrence, metastasis, death from any cause	Recurrence, second primary cancer, death from any cause
Population: high risk or recurrence	Stage: ≥T3 and/or N+	Stage: T2, G3 or G4, N0 ≥T3 and/or N+	Stage: ≥T2 and/or N+
Investigator vs BICR DFS	BICR-assessed primary analysis; additional analysis performed using investigator assessment	Investigator-assessed primary analysis; no BICR results	BICR-assessed primary analysis; additional analysis performed using investigator assessment
Earliest vs latest scan date for equivocal lesions later determined to meet criteria for relapse	Latest date used for primary analysis; additional analysis performed using earliest date	Earliest date used for primary analysis	Earliest date used for primary analysis; additional analyses performed using earliest date
Assessment schedule	Tumor imaging at baseline, every 12 wk during first 3 yr, every 6 mo thereafter	Tumor imaging at baseline, Weeks 20, 36, and 52 in Year 1, every 6 mo in Years 2–5, yearly thereafter	Tumor imaging at baseline, every 16 wk during first 3 yr, every 6 mo thereafter

BICR=blinded independent central review; DFS=disease-free survival

Figure 1: Primary and Sensitivity Analyses in S-TRAC¹⁰



CONCLUSIONS

- The estimand framework seeks increased transparency on the treatment effect of interest.
- In S-TRAC, PROTECT, and ATLAS, there were similar treatment effects irrespective of the estimand selected and the resultant clinical question:
 - The studies were not powered to address each of these questions and not all reached statistical significance.
 - However, estimand selection may affect treatment outcomes in other trials.
 - Caution is required when comparing results from different studies as they may ask different scientific questions.
- Consideration should be given to the clinical question of interest during trial design:
 - Dialogue between all stakeholders is required to ensure alignment on the key points such as the definition of the treatment effect, analysis, and interpretation of results.
 - Clinicians will play a key role in such discussions to identify the appropriate estimand.
- The choice of primary estimand may not only impact study design but also have regulatory implications.

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