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

Daniel George1, Michelle Casey2, Evgeny Degtyarev3, Mariajose Lechuga4, Paola Aimone3, Alain Ravaud5, Susan Halabi6, Robert J Motzer7

1Duke Cancer Center, Durham, NC, USA; 2Pfizer Inc, Collegeville, PA, USA; 3Novartis Pharma AG, Basel, Switzerland; 4Pfizer Srl, Milan, Italy; 5Barcelona University Hospital, Barcelona, France; 6Duke University, Durham, NC, USA; 7Almirall Sloan Kettering Cancer Center, New York, NY, USA

BACKGROUND
• Annually, ~338,000 persons are diagnosed with renal cell carcinoma (RCC), resulting in ~146,000 deaths1.
• Patients at high risk of disease recurrence following nephrectomy need adjuvant treatment2.
• A particular issue in clinical trials are “intercurrent events”, in 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 Harmonization Effort guideline3 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 effects and changing the definition of the endpoint or handling intercurrent events differentially targets different scientific questions.

OBJECTIVE
• To explore the impact of estimand selection on the analyses and interpretation of clinical 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?”

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

- Each row of the table provides the design and results for each trial.
- The “Primary estimand” column indicates whether the trial was designed to assess the primary endpoint.
- The “Supplemental estimand” column indicates whether the trial was designed to assess additional endpoints.
- The “Protocol-specified (primary) analysis” column indicates whether the trial was designed to assess the primary endpoint.
- The “Investigator vs BICR DFS” column indicates whether the trial was designed to assess the primary endpoint.

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

CONCLUSIONS
• The estimand framework seeks increased transparency on the treatment effect assessed.
• 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 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.

REFERENCES
4. E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials.
6. 1.
7. ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials.
8. EMA Committee for Human Medicinal Products. ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials.
10. E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials.
14. 1.

Figure 1: Primary and Sensitivity Analyses in S-TRAC(©)

- The table provides an overview of the primary and sensitivity analyses in S-TRAC.
- Each row of the table provides the design and results for each trial.
- The “Primary estimand” column indicates whether the trial was designed to assess the primary endpoint.
- The “Supplemental estimand” column indicates whether the trial was designed to assess additional endpoints.
- The “Protocol-specified (primary) analysis” column indicates whether the trial was designed to assess the primary endpoint.
- The “Investigator vs BICR DFS” column indicates whether the trial was designed to assess the primary endpoint.

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

- Each row of the table provides the design and results for each trial.
- The “Primary estimand” column indicates whether the trial was designed to assess the primary endpoint.
- The “Supplemental estimand” column indicates whether the trial was designed to assess additional endpoints.
- The “Protocol-specified (primary) analysis” column indicates whether the trial was designed to assess the primary endpoint.
- The “Investigator vs BICR DFS” column indicates whether the trial was designed to assess the primary endpoint.

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

- Each row of the table provides the design and results for each trial.
- The “Primary estimand” column indicates whether the trial was designed to assess the primary endpoint.
- The “Supplemental estimand” column indicates whether the trial was designed to assess additional endpoints.
- The “Protocol-specified (primary) analysis” column indicates whether the trial was designed to assess the primary endpoint.
- The “Investigator vs BICR DFS” column indicates whether the trial was designed to assess the primary endpoint.

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

- Each row of the table provides the design and results for each trial.
- The “Primary estimand” column indicates whether the trial was designed to assess the primary endpoint.
- The “Supplemental estimand” column indicates whether the trial was designed to assess additional endpoints.
- The “Protocol-specified (primary) analysis” column indicates whether the trial was designed to assess the primary endpoint.
- The “Investigator vs BICR DFS” column indicates whether the trial was designed to assess the primary endpoint.

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

- Each row of the table provides the design and results for each trial.
- The “Primary estimand” column indicates whether the trial was designed to assess the primary endpoint.
- The “Supplemental estimand” column indicates whether the trial was designed to assess additional endpoints.
- The “Protocol-specified (primary) analysis” column indicates whether the trial was designed to assess the primary endpoint.
- The “Investigator vs BICR DFS” column indicates whether the trial was designed to assess the primary endpoint.

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

- Each row of the table provides the design and results for each trial.
- The “Primary estimand” column indicates whether the trial was designed to assess the primary endpoint.
- The “Supplemental estimand” column indicates whether the trial was designed to assess additional endpoints.
- The “Protocol-specified (primary) analysis” column indicates whether the trial was designed to assess the primary endpoint.
- The “Investigator vs BICR DFS” column indicates whether the trial was designed to assess the primary endpoint.

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

- Each row of the table provides the design and results for each trial.
- The “Primary estimand” column indicates whether the trial was designed to assess the primary endpoint.
- The “Supplemental estimand” column indicates whether the trial was designed to assess additional endpoints.
- The “Protocol-specified (primary) analysis” column indicates whether the trial was designed to assess the primary endpoint.
- The “Investigator vs BICR DFS” column indicates whether the trial was designed to assess the primary endpoint.

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

- Each row of the table provides the design and results for each trial.
- The “Primary estimand” column indicates whether the trial was designed to assess the primary endpoint.
- The “Supplemental estimand” column indicates whether the trial was designed to assess additional endpoints.
- The “Protocol-specified (primary) analysis” column indicates whether the trial was designed to assess the primary endpoint.
- The “Investigator vs BICR DFS” column indicates whether the trial was designed to assess the primary endpoint.

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

- Each row of the table provides the design and results for each trial.
- The “Primary estimand” column indicates whether the trial was designed to assess the primary endpoint.
- The “Supplemental estimand” column indicates whether the trial was designed to assess additional endpoints.
- The “Protocol-specified (primary) analysis” column indicates whether the trial was designed to assess the primary endpoint.
- The “Investigator vs BICR DFS” column indicates whether the trial was designed to assess the primary endpoint.