Estimating Correlations between Relative Efficacy of Immuno-oncology Monotherapies across Four Oncology Indications

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Introduction

- As overall survival (OS) is a key outcome in health technology assessments (HTAs), high uncertainty around OS estimates caused by immature data may postpone evaluation of new treatments until more mature data become available, resulting in a high unmet need for patients who could potentially benefit from highly efficacious treatment options.
- To provide results faster, many clinical trials in oncology evaluate response-based outcomes such as progression-free survival [PFS] or overall response rate [ORR] as the primary outcome of the study. It is envisaged that a large treatment effect on such intermediary outcomes may indicate a potentially large treatment effect on long-term outcomes, such as OS, and can provide an early indication of an OS benefit.

Objective

- We conducted a systematic literature review (SLR) and Bayesian bivariate meta-analysis to explore whether PFS and ORR of immuno-oncology (IO) monotherapies are reliable surrogate endpoints of OS across four solid tumour indications: head-and-neck cancer (HNC), melanoma, non-small-cell lung cancer (NSCLC), urothelial cancer (UC).

Conclusions

- Although our analysis indicated patterns of potential association between treatment effects on OS and treatment effects on PFS or ORR, there was no sufficient evidence to suggest that PFS or ORR can be considered strong surrogate endpoints for OS in the IO monotherapy space. Instead, there were indications that the strength of surrogacy between PFS and OS may be indication-specific.
  - This may have implications in regulatory and reimbursement assessments, where statistically significant treatment effects on response outcomes are frequently resulting in positive recommendations.
- This work is subject to limitations that should be acknowledged:
  - The analysis was restricted to only trials including an IO monotherapy arm because these trials were older and thus more likely to report OS result.
  - The analysis was sometimes limited by the lack of OS and PFS/ORR data from the same trial.
  - The inclusion of trials evaluating IO combinations or other treatment classes (e.g., chemotherapies or other targeted therapies) may provide additional evidence to investigate the strength of surrogacy correlations.
- There is an urgent need for further research to evaluate whether correlations of treatment effects on surrogate endpoints and patient-relevant, final endpoints exist across different treatment classes and indications.

Methods

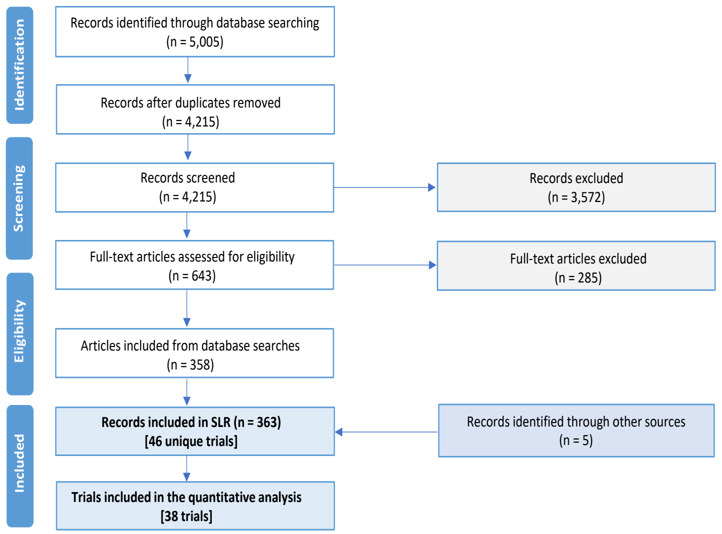
Systematic Literature Review

Criteria	Inclusion Criteria
Population	Adults with HNC, melanoma, NSCLC, or UC*
Interventions / Comparisons	• IO monotherapies (atezolizumab, avelumab, durvalumab, nivolumab, and pembrolizumab)** • Any comparator, including placebo or IO combination therapies
Outcomes	OS and PFS (hazard ratios [HR] and 95% confidence interval [CI]), ORR (%)
Study Design	RCTs (published as full-text articles or conference abstracts)
Data sources	• Embase and MEDLINE (2014 - 29 March 2021) • Citation quality check using the bibliographies of relevant previously published SLRs and references listed on clinicaltrials.gov

* Small-cell lung cancer, triple-negative breast cancer, oesophageal cancer, and renal cell cancer were originally also included in the SLR but not considered for the analysis due to a lack of data for both OS and PFS/ORR.

** The SLR and surrogacy endpoint validation was restricted to trials evaluating IO monotherapies given that these trials were older and thus more likely to report HR for OS.

Figure 1. PRISMA flow diagram



Surrogacy endpoint validation methods

- For each surrogate endpoint (PFS or ORR) and treatment indication (UC, NSCLC, melanoma, HNC), separate analyses were conducted comparing IO monotherapies versus chemotherapy or IO combination therapies.
- The relationship between the treatment effect on OS and each surrogate endpoint was described by the following formulas:

$$\begin{pmatrix} \log RE_{surrogate_i} \\ \log HR_{OS_i} \end{pmatrix} \sim N\left(\begin{pmatrix} \delta_{surrogate_i} \\ \delta_{OS_i} \end{pmatrix}, \begin{pmatrix} \sigma^2_{surrogate_i} & \sigma_{surrogate_i}\sigma_{OS_i}\rho_{wi} \\ \sigma_{surrogate_i}\sigma_{OS_i}\rho_{wi} & \sigma^2_{OS_i} \end{pmatrix} \right)$$

$$\delta_{OS_i} | \delta_{surroagte_i} \sim N(\lambda_0 + \lambda_1 \delta_{surrogate_i}, \psi^2_{OS})$$

$$\delta_{surrogate_i} \sim N(\eta_{surrogate}, \psi^2_{surrogate_i})$$

where OS_i and $RE_{surrogate_i}$ are the correlated relative treatment effects on OS and the surrogate endpoint (i.e. HR for PFS and odds ratio [OR] for ORR) reported in study i, and δ_{OS_i} and $\delta_{surrogate_i}$ are the true effects in the population which are correlated and are assumed exchangeable, and therefore are modelled as random effects with a linear relationship. Finally, ψ^2_{OS} is the conditional variance, which measures the strength of association and ρ_{wi} is the within-study correlation of OS and the surrogate endpoint.

- Prior distributions: $1/\sigma_{OS_i}$, $1/\sigma_{surrogate_i} \sim Unif(0,20)$; $\rho \sim Unif(-1,1)$; and vague normal priors for $\lambda_0, \eta_{surrogate}$; $\rho_{wi} \sim Unif(0,1)$ for PFS; $\rho_{wi} \sim Unif(-1,0)$ for ORR.
- A surrogate relationship is strong if:
  - $\lambda_0 = 0$ (no treatment effect on the surrogate endpoint results in no treatment effect on OS)
  - $\lambda_1 \neq 0$ (describes the relationship between the treatment effect on the surrogate endpoint and the treatment effect on OS)
  - ψ^2_{OS} is small (measures how much of the variability in OS effects is explained by the surrogate —so small variance means more variability explained; 0 for a perfect surrogate relationship)
  - A high between-studies correlation (e.g., ρ≥0.70) is required for surrogacy argument (ρ= ±1 for a perfect relationship)

Results

- 38 trials reported OS and either PFS or ORR and were eligible for analysis (Figure 1).
- No significant correlations between PFS and OS, and ORR and OS were found in any indication.
- Across all four indications, the estimated correlations of OS-PFS were numerically positive, ranging from 0.01 to 0.70 (Figure 2).
- All estimated correlations of OS-ORR were numerically negative, ranging from -0.66 to -0.07 (Figure 3), except for melanoma when comparing chemotherapy vs IO monotherapies (ρ=0.04).
- The largely positive 95% CrI for λ_1 along with the small ψ^2_{OS} may indicate signals for of potential surrogacy relationships in the cases shown in Figure 4.

Results (cont.)

Figure 2. Bivariate meta-analysis results for the surrogacy relationship between PFS and OS

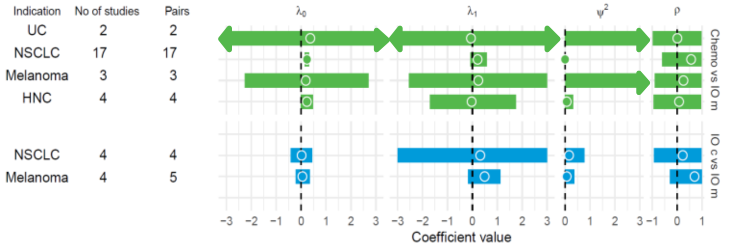


Figure 3. Bivariate meta-analysis results for the surrogacy relationship between ORR and OS

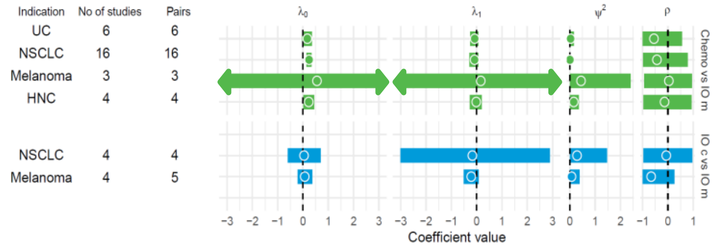
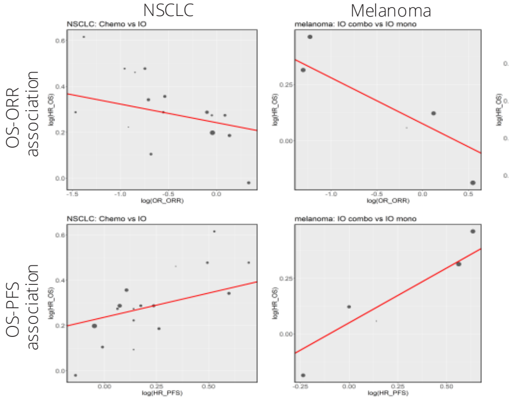


Figure 4. Scatterplot of observed treatment effects on OS and surrogate endpoints, and fitted regression line of estimated association



Scatter plot points weighted by $\frac{1}{Var(\log HR_{OS_i}) + Var(\log RE_{surrogate_i})}$. The red line indicates the regression line of estimated association (i.e. $\lambda_0 + \lambda_1 \delta_{surrogate_i}$)

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