EVALUATING SURROGATE ENDPOINTS FOR OVERALL SURVIVAL IN RANDOMIZED CLINICAL TRIALS TESTING IMMUNE CHECKPOINT INHIBITORS

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Introduction

Overall survival hazard ratio (HR_{OS}) is the gold-standard endpoint used to demonstrate the clinical efficacy of new cancer drugs in randomized clinical trials (RCTs). A reliable estimation of HR_{OS} requires large RCTs with long follow-up, resulting in increase in costs and time required before a new cancer drug is available to patients. To expedite drug approvals, the evaluation of new treatments in RCTs often relies on the assessment of their effects on surrogate endpoints, such as progression-free survival (PFS), under the assumption that these effects accurately predict those on OS at the final analysis [1].
Immune checkpoint inhibitors' (ICI) novel mechanisms of activating self-immunity against tumors could result in delayed clinical effects and long-term responders, and also in disease progression followed by tumor shrinkage (pseudo-progression), leading to the violation of the proportional hazard (PH) assumption on which the calculation of HR is based [2].
The restricted mean survival time (RMST) was proposed as an alternative measure to account for deviation from PH assumption [3], and the modified PFS (mPFS) as a novel endpoint to omit pseudo-progressions from PFS [4].

Aims

The aim of the present study was to compare the value of PFS and mPFS as surrogate of OS in RCTs testing ICIs, when the treatment effect is measured by the HR for OS, and by the HR and the ratio of RMST (rRMST) for PFS and mPFS.

Methods

We systematically searched for phase II and III RCTs testing ICIs in patients with advanced solid tumors, up to December 2021. Inclusion criteria were: RCTs i) assessing PD-1, PD-L1 and CTLA-4 inhibitors either as monotherapy or in combination with another ICI, and/or targeted therapy, and/or anti-angiogenesis drugs, and/or chemotherapy, in patients with advanced solid tumors; ii) randomizing at least 100 patients; iii) displaying the Kaplan-Meier (KM) survival curves for OS and PFS.
Pseudo individual patient-level data (IPD) for PFS and OS were reconstructed from the published KM curves. We used a web based validated tool (WebPlotDigitizer) to extract data coordinates from published KM curves. Then, pseudo IPD were reconstructed using the validated algorithm proposed by Guyot et al. [5].
To derive mPFS, disjointed PFS and OS pseudo IPD were matched using a simulation-based algorithm, as described in Wang et al. [4]. Briefly, the algorithm matches PFS-OS pseudo IPD under the following conditions: i) for a given patient, the PFS duration should not exceed the OS duration; ii) patients with events in the OS pseudo IPD dataset should be a subgroup of patients with events in the PFS pseudo IPD dataset.

Given that these requirements are insufficient to accurately capture the original matched PFS-OS IPD, we simulated 1000 qualified datasets of matched PFS-OS pseudo IPD for each included treatment arm.
For each treatment comparison we calculated the treatment effect measures of interest (HR_{OS}, HR_{PFS}, HR_{mPFS}, $rRMST_{PFS}$, $rRMST_{mPFS}$) with their 95% confidence intervals.
We assessed the trial-level correlation between (m)PFS treatment effect measures and HR_{OS}, in strata of immunotherapy strategy (i.e., ICI alone, ICI plus chemotherapy, ICI plus ICI or other treatment(s)), using weighted linear regression models.
The coefficient of determination (R^2) was used to quantify the surrogacy value at trial level of each potential surrogate endpoint. According to ReSEEM guidelines [6], R^2 values equal to or higher than 0.7 represent strong correlations (and was therefore suggestive of surrogacy), values between 0.69 and 0.5 represent moderate correlations, and values lower than 0.5 represent weak correlations.
All the analyses were performed using the SAS software v. 9.4 (SAS Institute, Cary, NC) and R software v 3.6.0.

Results
Overall, 61 RCTs (67 treatment comparisons and 36,034 patients) were included in the analysis. In comparisons testing ICI plus chemotherapy, HR_{PFS} and HR_{mPFS} both had a strong surrogacy value (R^2=0.74 and R^2=0.81, respectively). In comparisons testing ICI alone, HR_{PFS} was the best surrogate, although having a moderate correlation (R^2=0.58). In the ICI plus ICI or other treatment(s) strata, the associations were very weak for all the surrogate endpoints and treatment effect measures, with R^2 ranging from 0.01 to 0.22.

Conclusions
In RCTs testing ICIs, the value of potential surrogates for HR_{OS} was strongly affected by the type of treatment(s) tested. Even in the presence of significant deviation from the PH assumption, our results do not support the use of alternative endpoints, such as the mPFS, or treatment effect measures, such as the RMST.

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