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Assessment of progression-free survival as a surrogate end-point for overall survival in patients with metastatic renal cell carcinoma

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Abstract ***Background:*** To determine suitability of progression-free survival (PFS) as a surrogate end-point for overall survival (OS), we evaluated the relationship between PFS and OS in 750 treatment-naïve metastatic renal cell carcinoma (mRCC) patients who received sunitinib or interferon-alpha (IFN-α) in a phase III study.

Methods: The relationship between PFS and post-progression survival (PPS; the difference between PFS and OS) was studied, which correctly removes inherent dependencies between PFS and OS, to properly estimate whether and to what extent PFS can serve as a surrogate for OS. A Weibull parametric model to failure time data was fit to determine whether longer PFS was significantly and meaningfully predictive of longer PPS. In a sensitivity analysis by Kaplan–Meier non-parametric method, PPS curves for three approximately equal numbered groups of patients categorised by PFS were compared by log-rank test.

Results: In the Weibull parametric model, longer PFS was significantly predictive of longer PPS ($P < 0.001$). The model also allowed prediction of estimated median PPS duration from actual PFS times. In the Kaplan–Meier (non-parametric) analysis, incrementally longer PFS

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was also associated with longer PPS, and the PPS curves for the three PFS groups were significantly different ($P < 0.0001$).

Conclusions: A positive relationship was found between PFS and PPS duration in individual mRCC patients randomised to first-line treatment with sunitinib or IFN-α. These results indicate that PFS can act as a surrogate end-point for OS in the first-line mRCC setting and provide clinical researchers with a potentially useful approach to estimate median PPS based on PFS.

1. Introduction

Overall survival (OS) is the traditional gold standard of clinical end-points in oncology trials. However, powering clinical trials to show treatment-group differences in OS can be challenging given the length of post-progression survival (PPS), patient heterogeneity and variability in use of active treatments after disease progression. These factors can dilute differences in OS, requiring very large sample sizes and increasing the time and cost associated with drug development [1], consequently limiting or delaying treatment options for patients. For example, Di Leo et al. [2] critically assessed the findings of a number of phase III colorectal and breast cancer trials and reported that sample sizes were likely too small to detect realistic survival differences, even in the presence of response rate and time to progression benefits; they concluded that OS may not be a realistic end-point for clinical trials of new drugs in advanced solid tumours, especially for those tumours with a number of post-progression treatment options.

Establishing one or more disease-progression end-points as a valid surrogate for OS in pivotal clinical studies could bring considerable benefit to patients. Among the various end-points proposed as surrogates for OS, progression-free survival (PFS) has increasingly taken the lead [3]. The suitability of PFS as an OS surrogate has been investigated in various tumour types, including cancers of the stomach, lung, breast and colorectum [4–9]. However, equivalent studies in renal cell carcinoma (RCC) are scarce, with only limited evidence available from a retrospective meta-analysis and landmark analysis [10,11].

The introduction of targeted therapies has revolutionised the treatment of metastatic RCC (mRCC), and most of the clinical trials of agents that target the vascular endothelial growth factor (VEGF) and mammalian target of rapamycin (mTOR) pathways have used PFS as the primary end-point. Although, in the past, regulatory agencies have viewed surrogate end-points with caution, sunitinib, sorafenib, pazopanib, everolimus and bevacizumab have all gained regulatory approval on the basis of clinical trials that demonstrated a PFS benefit [12–17]. The majority of these trials did not demonstrate an OS benefit, and crossover and post-study cancer treatment were cited as confounding factors, since patients initially randomised to the control arm were allowed to receive the active agent or similar second- and third-line treatments, which may have diluted any true OS benefit [1].

The availability of subsequent lines of targeted therapies may make it difficult to prove OS benefit in future clinical trials of first-line mRCC treatment. In a recently published retrospective analysis of PFS as a predictor of OS in patients with mRCC, Heng and colleagues concluded that PFS may be the only end-point that is not affected by issues of crossover and contamination in trials of contemporary targeted therapies [11]. They cautioned, however, that prospective evaluation will be required to confirm these findings.

A variety of methodological approaches have been used to assess surrogacy. Although many surrogate-end-point investigations have been relatively simple empirical studies of the built-in inter-dependence of PFS and OS (i.e. OS is a function of PFS), some investigators have developed statistical models to further interpret this inter-dependence after removing or accounting for it [1,3,18]. However, there is a need to develop new methods that will further improve our understanding of the relationship between OS and PFS.

In the current analysis, we fitted parametric models to failure time data to assess the suitability of PFS as a surrogate of OS in patients with treatment-naïve mRCC, applying a novel statistical approach to patient-level data. Our objective was to assess the relationship between PFS and OS in patients with treatment-naïve mRCC treated with sunitinib or interferon-alpha (IFN-α) in a pivotal phase III study [19], in order to determine the suitability of PFS as a surrogate of OS, providing supportive evidence to decision makers in both regulatory and reimbursement authorities, as well as to treating physicians and their patients.

2. Patients and methods

2.1. Study population

The study population was comprised of patients aged 18 years or older with histologically confirmed mRCC with a component of clear-cell histology. Key eligibility criteria included the following: no previous systemic (including adjuvant or neoadjuvant) therapy for RCC; measurable disease; Eastern Cooperative Oncology

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