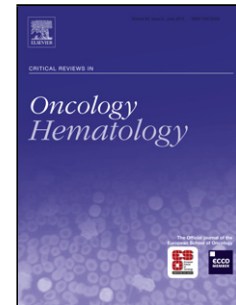# Accepted Manuscript

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Title page

Second-line cabozantinib versus nivolumab in advanced renal cell carcinoma: systematic review and indirect treatment comparison

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Conflict of interest statement

Abstract

Background: Nivolumab and cabozantinib, two new treatment options for previously-treated advanced/metastatic renal cell carcinoma (aRCC), have recently been approved.

Methods: Two independent reviewers performed study selection, data extraction, and risk of bias assessment. Indirect treatment comparisons were carried out by directly assessing HR differences and statistical modeling of Kaplan-Meier curves from these two trials.

Results: Publications identified showed that no head-to-head comparisons had been carried out. Two indirect treatment comparisons used agreed that there was no significant difference in OS between cabozantinib and nivolumab and that cabozantinib significantly improved PFS compared to nivolumab.

Conclusions: The field of aRCC treatments is evolving rapidly, creating opportunities for individualized treatments and challenges for clinicians to keep up with the evidence. In lieu of availability of direct comparisons of all options, advanced modeling results presented herein can help to inform and improve personalized treatments.

Keywords: individualized cancer therapy, treatment algorithm, advanced modeling

1. Introduction

Each year, 4.4 out of every 100,000 people worldwide are diagnosed with renal cell carcinoma (RCC) [1]. Curative surgery is an option for those patients who are diagnosed with localized early stage tumors. First-line treatment of advanced/metastatic disease includes sunitinib, pazopanib, bevacizumab in combination with interferon, and temsirolimus for those patients with poor prognosis. Second-line treatment options had been quite limited until recently and included agents such as axitinib, everolimus and sorafenib. The anti-PD1 monoclonal antibody nivolumab and cabozantinib, which targets vascular endothelial growth factor receptor (VEGFR) and the MET and AXL receptor tyrosine kinases along with other potentially relevant targets in RCC, have recently been approved for second-line use [2,3].

Healthcare decision-makers require comparisons of all relevant treatments, including those that may not have undergone head-to-head comparison in pivotal trials. With increasing amounts of data at hand, these decisions become more and more evidence based. Clinicians must have a deep understanding of all relevant factors and make decisions taking the best evidence, patient preferences, and other specific circumstances into account, a task that needs to be acknowledged to be still more of an art than science.

Concrete questions in clinical practice include identification of the best fast antitumor activity and best strategy for ideal long-term outcomes. If, for example, a given patient requires a quick response, then an agent with a faster response pattern may be a better choice compared to slow-responding, long-acting treatments. On the contrary, if it is possible to wait for the occurrence of a long-term response, the choice of a slower-acting treatment may be justified. Medical oncologists have already faced this dilemma in the field of *BRAF* wild type melanomas, and the empirical conclusion drawn to date is that a combination of targeted agents is felt as preferable in patients needing substantial and quick tumor shrinkage, whilst in other patients, the long-term efficacy of immunotherapy treatments suggests the use of immunotherapies [4].

If the available evidence consists of multiple randomized controlled trials (RCTs), assessments of relative efficacy can be made by pairwise indirect treatment comparison (ITC) or network meta-analysis (NMA). Survival data-based ITCs are often limited to comparisons of hazard ratios (HRs), a method that does not require assumptions regarding the distribution of data. However, the use of HRs for comparing different treatments assumes that the underlying hazards always remain proportional to each other. This assumption can be tested statistically, and Amzal *et al.* [5] showed that using direct comparison of HRs as a method for summarizing survival from the CheckMate025 study is not ideal, because the HRs vary over time.

An alternative comparison method is to compare full Kaplan-Meier survival curves after fitting them to parametric functions. The study by Amzal et al. compared cabozantinib and nivolumab as part of a wider

network of comparators, using five parametric survival functions (lognormal, loglogistic, Weibull, Gompertz and exponential distributions). To further improve the fit of the model to the data at hand, additional parametric models can be explored [6]. In this study, we assessed whether fractional polynomial distributions more closely fit the underlying study data and used this method to compare the cabozantinib and nivolumab progression-free survival (PFS) and overall survival (OS) data.

2. Material and methods

2.1. Literature search

This literature review was conducted according to the methods outlined in the Cochrane Handbook for Systematic Reviews of Interventions [7]. MEDLINE [8], EMBASE [9], and Cochrane Central Registry of Controlled Trials (CENTRAL) [10] were searched on 12 June 2017. No time or language restrictions were imposed. The search protocols, which were registered in the PROSPERO register of systematic reviews (CRD4201706885) [11], are shown in the supplementary information. Search terms included extensive controlled vocabulary (MeSH and EMTREE) in various combinations, supplemented with keywords including renal cell carcinoma, cabozantinib, and nivolumab. We limited our search to RCTs by applying a Cochrane Highly Sensitive Search Strategy filter for identifying randomized trials in MEDLINE: sensitivity-and precision-maximizing version [12]. We screened systematic literature reviews and health technology assessment (HTA) report reference lists manually for any additional studies, carried out additional searches of gray literature (e.g., manufacturer websites, materials provided during HTA assessments) to complement and update the findings.

2.2. Study Selection

RCTs were included that met the following criteria: 1. Patients with previously treated advanced or metastatic RCC; 2. at least one of the interventions was cabozantinib or nivolumab; and 3. the study reported PFS, OS or both. It is very difficult to design a search algorithm that is both sensitive and specific for second-line use, given the many terminologies used to indicate such use and the possibility of trials with mixed total populations and sub-group analyses. We therefore did not attempt to restrict our computer search algorithm to second-line trials. Instead, we included all trials in the first screening and assigned the task to remove first-line trials to the human reviewers (Figure 1). After duplicates were removed, two reviewers independently screened titles and abstracts and determined eligibility from the full texts. All discrepancies were resolved by consensus or with a third reviewer if required.

2.3. Data Extraction and Risk of Bias Assessment

Data were independently extracted by two reviewers from each eligible study. For multiple publications or data sources of the same study, we used the longest reported follow-up data reporting results and confidence intervals (CI) for analysis. This included unpublished METEOR trial data based on the final, October 2, 2016, data cut made available by the trial sponsor [13]. Subgroup analyses from the same study were not considered (e.g., subgroup of Japanese patients from CheckMate025). Study inclusion and exclusion criteria, baseline population characteristics, OS, and PFS outcomes were extracted. We extracted point estimate of median survival and HRs and corresponding CI. Risk of bias of individual studies was assessed by the two reviewers independently using the Cochrane risk of bias tool [14], with disagreements being solved by consensus.

2.4. Published studies

Our systematic literature search identified 460 citations, of which 97 were duplicates. A further 296 records were excluded after title and abstract screening, leaving 67 citations for full text review (Figure

1). We found 29 eligible publications, referring to two studies: METEOR (NCT01865747) and CheckMate025 (NCT01668784), and additional U.S. Food and Drug Administration approval reports presenting data from these two studies. The underlying trials were the same for the PFS and OS endpoints (Supplementary Figure 1). The main publication for CheckMate025 is Motzer *et al.* [15], which reports OS results after a minimum of 14 months of follow-up. A publication by Plimack et al. 2016 [16] reports OS results after a minimum of 26 months of follow-up, however the OS HR had not changed, and no CIs or Kaplan-Meier data were reported. For this reason, we used the Motzer et al. 2015 publication for these analyses. Baseline patient characteristics are summarized in Supplementary Table 1. For the METEOR trial, we used the final, unpublished data cut (as of October 2, 2016) for overall survival data, which was made available directly by the sponsor and has been used during the UK appraisal process [13]. The PFS data for METEOR were taken from the final published RCT report [17]. The PFS [17] and OS [13] results reported in METEOR and CheckMate025 [15] studies are shown in Table 1.

2.5. Data Synthesis and Analysis

We analyzed evidence for two outcomes: PFS and OS. We performed indirect comparison with the traditionally used method described by Bucher *et al.* [18], which assumes transitivity and proportionality of hazards. It requires only mean HRs and their standard error from the two studies to make an indirect comparison. We report mean HR and its 95% CI. We used the method published by Guyot et al [19]. to estimate the number of deaths and the number of patients censored every month from the published Kaplan-Meier curves. We compared survival curves using parametric methods [20] and fractional polynomials [6]. While these methods do not rely on the proportional hazard assumption, they are based on the general assumptions common to all indirect comparison methods of similarity, homogeneity, and consistency of the underlying trials [21]. Possible violations of these assumptions are discussed further below. For comparison of survival curves, we performed a Bayesian ITC using a

Markov Chain Monte Carlo method on WinBUGs [22]. The analysis used a fixed-effects model, because only one trial provided direct evidence for each comparison. Model fits were compared using the deviance information criterion (DIC). Relative treatment effects are reported using adjusted survival curves for PFS and OS outcomes, along with corresponding 95% credible intervals, which are the Bayesian equivalent of CIs [23].

3. Results

3.1. Quality of Evidence

Due to the small size of the network and its geometry, with one study per comparison, a quantitative heterogeneity assessment, such as the one using the local and global Higgins coefficients, was not possible. We therefore performed a qualitative heterogeneity assessment based on a side-by-side comparison of patient inclusion and exclusion criteria, baseline characteristics, and of the risk of bias of the two studies included in the network. The overall risk of bias of using the identified studies for an indirect comparison was low according to our assessment (Supplementary Figure 2).

3.2. Progression-Free Survival

The comparison of PFS curves produced consistent results until approximately month 20 (Figure 2). The model that provided the best statistical fit (i.e. the lowest DIC) to METEOR and Checkmate 025 study PFS data was the second order fractional polynomial model (with the parameters P1=-1, P2=0), followed by a lognormal distribution. The DIC for the lognormal model was 3284, with two degrees of freedom, while the DIC for the fractional polynomial model was 3197, with one degree of freedom. A visual check was also conducted of the overlaid curves, see Supplementary eFigure 3, to verify that the selected distributions provided a good fit all throughout the period when trial data were available. ~~The results of the ITC showed a significant difference in cabozantinib PFS compared with nivolumab (HR 0.58, 95% CIs~~

~~0.34 – 0.98), see last column in Table 1.~~ The best-fitting fractional polynomial model further showed that while cabozantinib is associated with favorable PFS until month 20, after this time point PFS gain with nivolumab is predicted to be greater than that of cabozantinib (Figure 2). As indicated earlier, a direct comparison of the HRs with each other is problematic, because the underlying assumption of proportional hazards is violated. However, because these comparisons are used commonly in the field, we checked the outcomes for such comparisons for our data and found that they would have agreed: cabozantinib was associated with longer PFS compared to nivolumab (HR 0.58 95% CIs 0.34 – 0.98), see final column in Table 1.

3.3. Overall Survival

An analysis of the survival curves showed that the best statistical fit (i.e., lowest DIC) was provided by fractional polynomial model (with parameter P=-1; Figure 3). The second-best statistical fit was provided by a lognormal model (see Supplementary Figure 4). The DIC for the log-normal model was 2375, with two degrees of freedom, while the DIC for the fractional polynomial model was 2367, also with two degrees of freedom. The higher proportion of patients surviving at a given time point with cabozantinib over nivolumab was not statistically significant, as seen by the overlapping credible intervals in Figure 3 (HR 0.96, 95% CIs 0.57 – 1.62). OS results were consistent across all the different statistical models tested. In addition to statistical fits, a visual check was also conducted to ensure the goodness of fit all throughout the period of the source clinical trials, see Supplementary Figure 4. Again, because direct comparisons of HRs are widely used, we checked the outcome of such a test against our results and found agreement: no statistically significant difference for OS was found~~, while the HR of such direct comparison nominally favored cabozantinib~~ (HR 0.96, 95% CIs 0.57 – 1.62).

4. Discussion

Until recently, second-line treatment options for patients with aRCC were limited to axitinib, everolimus and sorafenib. These treatments provided median gains in clinical trials in the range of 1.9 – 6.8 months and 14.4 – 20.1 months for PFS and OS, respectively [24–30]. Cabozantinib and nivolumab are more recently approved and recommended treatment options associated with prolonged OS, with different mechanisms of action. While cabozantinib is a small molecule tyrosine kinase inhibitor (TKI) with VEGF, MET, and AXL inhibition properties, nivolumab is an antibody against programmed cell death protein 1 (anti-PD-1).

Our analysis was based on high quality primary studies, with a low risk of bias. While the inclusion criteria in the two retained trials were similar, the included populations differed in several ways. The METEOR study contained a higher percentage of patients with favorable prognosis (45.6% in METEOR vs. 36% in Checkmate 025; p=0.0006; Chi-squared test). Both studies included patients who failed prior VEGFR-therapy, although in CheckMate025 patients with one or two previous treatments were included whereas METEOR did not limit the maximum number of prior therapies. In the CheckMate 025 study, 72% of patients had received one and 28% had received two prior regimens. The study protocol did not allow for inclusion of patients with three or more prior therapies. In the METEOR study, 70.5% of patients had received one and 29.5% had received two or more prior regimens. While the everolimus control curves in both studies had similar slopes (see supplementary eFigures 3 and 4), and our methodology can account for differences between trials by using the respective control group from each trial for the comparison, it is still possible that the observed differences in study populations could affect our results due to a possible violation of the assumption of similarity. Since we did not have access to individual-level data for both trials, we could not account for these differences in the statistical analysis. Ultimately, a randomized direct comparison trial of cabozantinib and nivolumab would be able to provide an answer that would be free of such possible bias.

OS is improved over everolimus with both cabozantinib and nivolumab, complicating the decision making for clinicians and patients in circumstances when both new treatments are available. In this systematic literature review and ITC, we found that OS is similar between cabozantinib and nivolumab. Our study provides the first comparison of cabozantinib and nivolumab using the final cut of METEOR OS data and including the use of fractional polynomial models to compare PFS and OS for these two therapies. Our ITC analysis found that PFS was significantly longer with cabozantinib under the best-performing statistical models.

It had already previously been established that using HRs may not be an appropriate method for summarizing survival from the CheckMate-025 study [5,31,32]. However, because such comparisons are intuitive to interpret and used widely in the field, we included a comparison of HRs. The results agreed with the fractional polynomial model: there was no significant difference in OS between the two treatments, and PFS was significantly superior for cabozantinib.

Wiecek and Karcher [33] recently performed an ITC of parametric survival curves for cabozantinib and nivolumab. The probability of cabozantinib having superior OS was above 50% until month 24, and after that time point the probability of nivolumab having superior OS was higher. The authors concluded that numerical differences in OS estimates between the two treatments were small. Their analysis was based on published METEOR data from 2015 [31], whereas our analysis is based on longer term survival data up until October 2, 2016 [13].

Our analysis is limited by the sparse network of two studies for both PFS and OS. Evidence for cabozantinib and nivolumab was based on two studies. Indirect evidence was derived from the common comparator everolimus, for which the dose and frequency was similar in both trials, suggesting that it was reasonable to assume transitivity. Publication bias could not be assessed because only two studies were available.

In addition to the efficacy data analyzed herein, clinicians will have to take the different biological properties and safety profiles of the two treatments into account, the severity, temporal patterns, and management of which show very substantial differences that are beyond the scope of our current work.

Furthermore, clinicians will set treatment goals and choose regimens based on individual patient expectations and needs regarding quality of life, as well as practical concerns of disease management.

A recent indirect comparison study in the first-line setting concluded that "cabozantinib and nivolumab plus ipilimumab are likely to be the preferred first-line agents for treating mRCC; however, direct comparative studies are warranted" [34]. Because the nivolumab/ipilimumab combination, approved by the FDA and available in the USA, has not yet been approved by the EMA for first-line use in Europe [35], this option remains presently hypothetical for European oncologists.

5. Conclusions

After decades of slow progress, the field of aRCC treatments is now evolving at a rapid and unprecedented pace that makes it difficult for statisticians and clinicians to keep up with the latest evidence and derive the best recommendations and decisions. Our work contributes to the analytic side of this arms race by exploring new and improved ways to compare results indirectly. The findings of our study are based on the latest available complete data and add to the continuous learning about the comparative benefits of cabozantinib and nivolumab. Using the latest available data may have introduced some bias due to the different data cut-offs for the analyses. As more evidence becomes available, including long-term follow-up data and real-world evidence, our analysis can be updated to continuously learn more about the efficacy of these treatments.

Ultimately, identification of biomarkers of response for one or the other treatment may allow prediction ahead of the commencement of treatment and allow additional stratification of patient populations and further optimization of clinical results.

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Conflict of interest statement
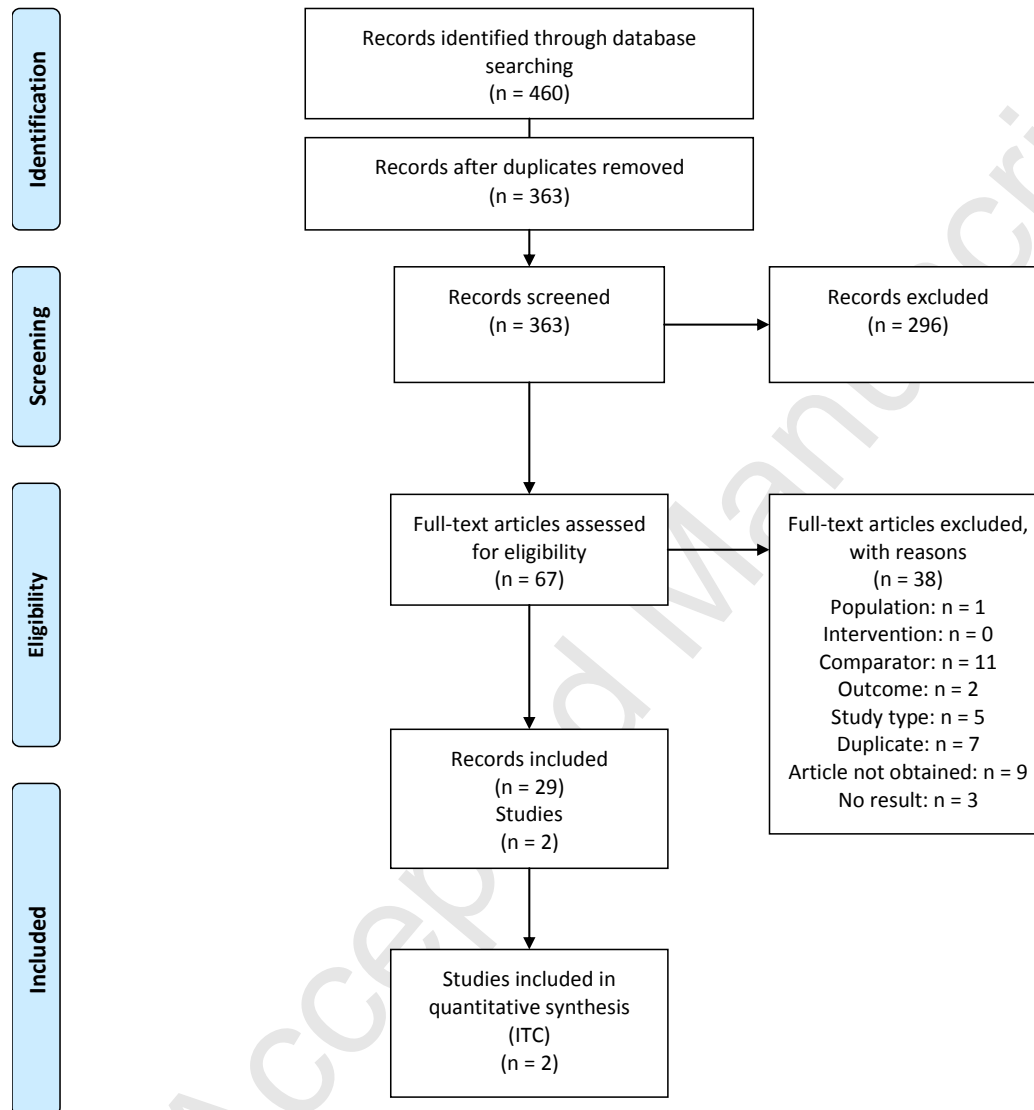
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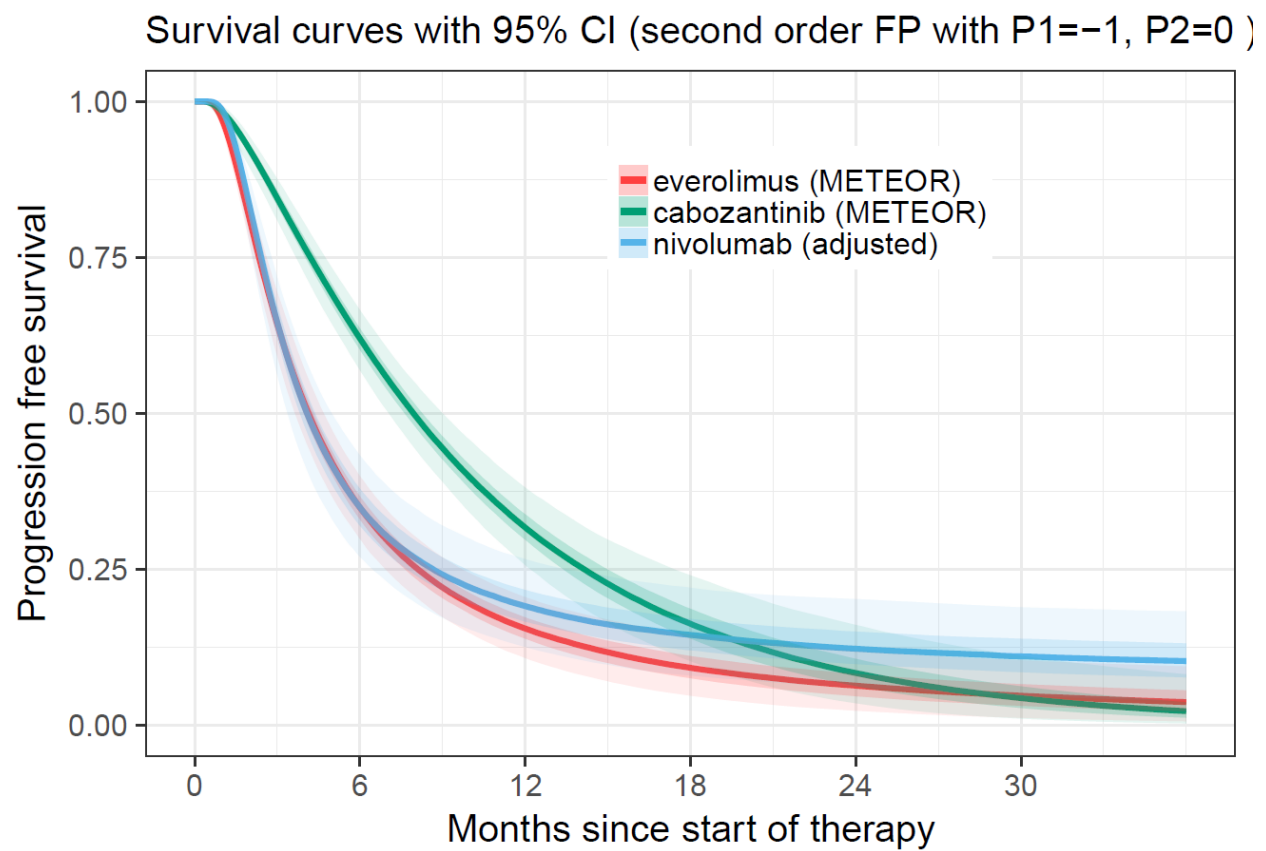
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Figures

Figure 1. PRISMA flow diagram for systematic literature review

Identification

Records identified through database searching
(n = 460)

Records after duplicates removed
(n = 363)

Screening

Records screened
(n = 363)

Records excluded
(n = 296)

Eligibility

Full-text articles assessed for eligibility
(n = 67)

Full-text articles excluded, with reasons
(n = 38)
Population: n = 1
Intervention: n = 0
Comparator: n = 11
Outcome: n = 2
Study type: n = 5
Duplicate: n = 7
Article not obtained: n = 9
No result: n = 3

Included

Records included
(n = 29)
Studies
(n = 2)

Studies included in quantitative synthesis
(ITC)
(n = 2)

[to be printed in colour]

Figure 2. Fitted results for PFS, with P1=-1 and P2=0

Survival curves with 95% CI (second order FP with P1=−1, P2=0)

[to be printed in colour]

Figure 3. Fitted results for OS data, with P1=-1

Survival curves with 95% CI (first order FP with P=−1)
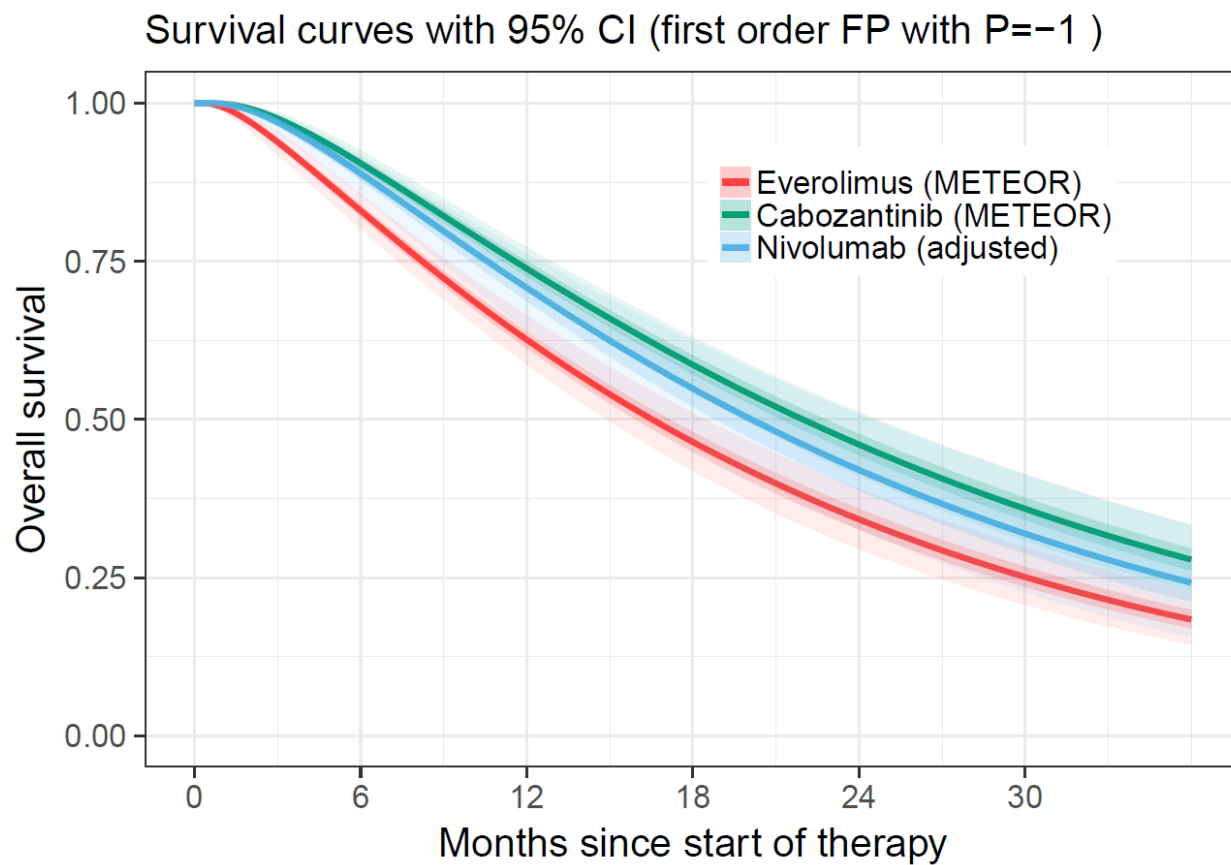
[to be printed in colour]

Tables

Table 1. Reported PFS and OS results from METEOR and CheckMate025 studies: median (months) and HRs

	METEOR, final RCT results [17] and October 2, 2016 data cut [13]			CheckMate025, pivotal trial publication [15]			ITC result (current study)
	Cabo, median (months) [95% CI]	Evero, median (months) [95% CI]	HR [95% CI] p-value	Nivo, median (months) [95% CI]	Evero, median (months) [95% CI]	HR [95% CI] p-value	Cabo vs. Nivo, HR [95% confidence interval] p-value
PFS	7.4 [6.6 - 9.1)	3.9 [3.7-5.1]	0.51 [0.41 - 0.62]; P<0.0001	4.6 [3.7 – 5.4]	4.4 [3.7 – 5.5]	0.88 [0.75-1.03]; P=0.11	HR 0.58 [0.34 – 0.98] p=0.04
OS	21.4 [18.6 - 23.5]	17.1 [14.9 - 18.9]	0.70 [0.58-0.85]; P<0.0002	25.0 [21.8 – n.e.]	19.6 [17.6 – 23.1]	0.73 [98.5% 0.57 – 0.93]; P=0.002	HR 0.96 [0.57 – 1.62] p=0.437

Abbreviations: Cabo – cabozantinib; Evero – everolimus; HR – hazard ratio; CI – Confidence Interval; Nivo – nivolumab; ITC – indirect treatment comparison; PFS – progression-free survival; OS – overall survival ; n.e.   – not estimable.