Evaluation of Progression-Free Survival as a Surrogate Endpoint for Survival in Chemotherapy and Targeted Agent Metastatic Colorectal Cancer Trials

Roger Sidhu\textsuperscript{1}, Alan Rong\textsuperscript{2}, and Steve Dahlberg\textsuperscript{3}

Abstract

Pooled analyses of chemotherapy trials in metastatic colorectal cancer (mCRC) have suggested that progression-free survival (PFS) is a surrogate endpoint for overall survival (OS). However, this has not been evaluated under current standard-of-care regimens of chemotherapy in combination with targeted therapies. We conducted an analysis of published mCRC trials of chemotherapy and targeted therapies from 2000 to evaluate the surrogacy of PFS and response rate (RR) for OS. Study-level data was pooled from 24 randomized mCRC trials that evaluated fluoropyrimidine-based regimens and included trials conducted with targeted agents (panitumumab, cetuximab, bevacizumab, and aflibercept). A total of 69 treatment arms with a sample size of 20,438 patients was included. Linear regression analysis was carried out to estimate the correlation of PFS and RR with OS. The correlation coefficient between PFS HRs and OS HRs was 0.86 for all trials, 0.89 for 12 phase III trials of targeted agents in combination with chemotherapy, 0.95 for 8 first-line phase III trials of targeted agents, and 0.83 for 9 trials of anti-EGFR-targeted agents. In all cases, correlation coefficients between RR and OS HRs were lower than those between PFS HRs and OS HRs (range, 0.42–0.81). In this study-level analysis of randomized mCRC trials of chemotherapy and targeted agents, improvements in PFS are strongly correlated with improvements in OS. This suggests that PFS remains a valid surrogate endpoint for OS with current treatment regimens in the mCRC setting.

Introduction

Overall survival (OS), the time from randomization/first treatment to death from any cause, is often used as the primary endpoint for phase III trials and for regulatory approval. OS as an endpoint is clinically meaningful and objectively assessed. However, trials using OS endpoints often require large patient numbers and protracted long-term follow-up, which may delay decisions about the effectiveness of new treatments. In addition, given the growing number of efficacious treatments in later lines of therapy and crossover between therapies, improvements in OS for earlier lines of treatments may become increasingly confounded by effective poststudy therapies. OS as an endpoint may also become less relevant in clinical trials as the standard of care may change by the time OS data are mature. Identifying surrogate endpoints that not only measure clinical efficacy and benefit in a timely fashion but also predict OS benefit in randomized trials may help aid the approval of new drugs.

Progression-free survival (PFS) measures the time to the initial progression or to death by any cause. Progression events include a substantial increase in tumor size and/or the development of new tumors according to standardized criteria such as Response Evaluation Criteria in Solid Tumors (RECIST; ref. 1). Therefore, the use of PFS as an endpoint not only incorporates survival, but also the reduction in cancer burden and delays in cancer progression. For these reasons, PFS alone is a clinically relevant endpoint and, compared with OS, can be assessed earlier with potentially smaller patient numbers and a lower likelihood of confounding by subsequent therapies. In advanced breast cancer, the surrogacy between PFS and OS has been examined but remains unclear as studies have only reported a moderate correlation between PFS and OS (2–5). However, in the mCRC disease setting, pooled analyses of chemotherapeutic trials have shown a consistently robust correlation between PFS and OS, have indicated improvements in PFS predict improvements in OS, and have suggested PFS is a valid surrogate endpoint for OS (6, 7).

Response rates in mCRC have also been examined for a correlation with OS (7, 8). By using standardized criteria to...
objectively measure evidence of tumor shrinkage, response rates are commonly used endpoints. However, the results from several pooled analyses have suggested that there is only moderate correlation with OS in chemotherapeutic trials of patients with mCRC (7, 8).

Although the relationships between PFS, response rate, and OS have been examined for classical cytotoxic chemotherapy (6, 7), the correlation of these relationships with current treatment regimens that employ targeted agents is not clear and previous analyses may have become less relevant with the addition of new standard-of-care treatments for mCRC. With the introduction of targeted therapies (panitumumab, cetuximab, and bevacizumab; refs. 9–12) and improved chemotherapeutic regimens for patients with mCRC (13, 14), understanding the correlations among PFS, response rate, and OS remains an important issue for treatment selection. Here, we conduct a comprehensive literature-based analysis to determine whether PFS and/or response rate are correlated with OS in trials using current standard-of-care treatment regimens in patients with mCRC. This study-level analysis evaluates these relationships in all recent randomized trials, first-line trials, targeted therapy trials, and anti-EGF receptor (EGFR) therapy trials.

Methods

Literature search and selection of studies

A study-level analysis of randomized controlled trials published between 2000 and 2011 was conducted to evaluate whether PFS and/or response rate are correlated with OS in mCRC trials. These included historical trials with fluoropyrimidine alone, all reported mCRC trials conducted with the targeted agents in combination with oxaliplatin- or irinotecan-based regimens that matched the search criteria, and trials with anti-EGFR therapies in patients with wild-type (WT) and mutant KRAS mCRC (analyzed as separate treatment arms when KRAS status was reported).

The inclusion criteria for these published trials included at least 100 patients enrolled, fluoropyrimidine-based regimens, and data available on PFS, response rate, and OS. A systematic MEDLINE literature search was conducted using the keywords ‘colorectal neoplasm’ and ‘neoplasm metastasis.’ Results were limited to “randomized controlled trial,” “clinical trial phase II,” and “clinical trial phase III.” A manual search (matching the MEDLINE search criteria) was done for abstracts presented at the European Society for Medical Oncology and the American Society of Clinical Oncology. Bibliographies of published overviews were also checked for additional citations.

Statistical analysis

This analysis used OS, PFS, and response-rate endpoints as defined in the respective published trials. For each trial, data on treatment regimen, sample size, response rate, PFS and OS HRs, and medians were extracted. The reported definition of surrogacy has varied (15–17), but the criterion has remained focused on the ability of the treatment’s effect on the surrogate to predict its effect on OS. Therefore, the surrogacy of PFS and response rate with OS (i.e., the prediction of OS) is dependent on the correlation between the treatment’s effect on the surrogate endpoint and its effect on OS with a strong correlation indicating a better precision of the prediction (3). In this analysis, the correlation between effects of PFS and response rate with OS characterized by $R^2$ (i.e., the percentage of OS variability explained by PFS or response rate) and the corresponding correlation coefficient were evaluated using linear regression weighted by study sample sizes. HRs were used to summarize treatment effects for PFS and OS. Odds ratios (OR), response-rate differences, and response-rate ratios were used to summarize treatment effects for response rate. Additional supportive analyses including linear regression unweighted by study sample sizes and error-in-variable linear regression were carried out to further confirm the findings.

Results

Trials included in the analysis

A total of 28 published studies were identified. Four of these studies did not report OS HRs and were excluded from the analysis (18–21). Therefore, 24 randomized, controlled trials were included (Table 1). Eighteen phase III trials evaluated first-line treatment of patients with mCRC. Five phase III trials evaluated later lines of therapy, and 1 study was a phase II trial. Thirteen of the 24 trials had targeted therapies in at least 1 arm with 9 of these trials evaluating anti-EGFR therapies in combination with chemotherapy (2 trials also combined anti-EGFR therapies with bevacizumab).

In total, 20,438 patients in 69 treatment arms were included in the analysis with 66 of the treatment arms containing an FU/capecitabine regimen and 53 containing either oxaliplatin or irinotecan. All of the control arms contained a chemotherapy regimen. When KRAS status was reported, patients with WT or mutant KRAS mCRC were analyzed as separate treatment arms as the efficacy of anti-EGFR therapies is limited to patients with WT KRAS mCRC (22).

Correlation between treatment effects

Across all 24 trials, a total of 36 pairs of HRs for OS and PFS were identified (Table 1). Linear regression analysis weighted by study sample size to account for differences in trial sizes was conducted. A linear regression line with 95% confidence intervals (CI) was used to predict the treatment effects on OS from the observed treatment effects on PFS (Fig. 1A). The correlation coefficient between log (OS HR) and log (PFS HR) across all trials was 0.86 (95% CI, 0.73–0.92). $R^2$ was 0.73 (95% CI, 0.53–0.85).

In 18 first-line phase III trials (Figure 1B), 28 pairs of HRs for OS and PFS were identified. The correlation coefficient was 0.90 (95% CI, 0.78–0.95) and the $R^2$ was 0.80 (95% CI, 0.60–0.90).
Table 1. Clinical trials included in the analysis

<table>
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<tr>
<th>Trial</th>
<th>Treatment arms (n)</th>
<th>Primary endpoint</th>
<th>No. of patients*</th>
<th>OS HR 95% CI</th>
<th>PFS HR 95% CI</th>
<th>1st-line</th>
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<tr>
<td>Saltz et al, 2000 (32)</td>
<td>FU/LV vs. IFL</td>
<td>PFS</td>
<td>683</td>
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<td>Blanke et al, 2002 (33)</td>
<td>FU/LV vs. FU/LV/TMTX</td>
<td>PFS</td>
<td>382</td>
<td>0.96 0.77-1.20 1.00 0.81-1.25</td>
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<tr>
<td>Pun et al, 2002 (34)</td>
<td>FU/LV vs. FU/LV/TMTX</td>
<td>PFS</td>
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<td>Schilsky et al, 2002 (35)</td>
<td>FU/LV vs. eniluracil/FU</td>
<td>OS</td>
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<td>0.88 0.75-1.03 0.83 0.73-0.95</td>
<td>Yes</td>
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</tr>
<tr>
<td>Kohne et al, 2003 (26)</td>
<td>FU/LV vs. FU</td>
<td>OS</td>
<td>497</td>
<td>0.90 0.68-1.19 0.76 0.59-0.99</td>
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</tr>
<tr>
<td>Kohne et al, 2005 (36)</td>
<td>FU/LV vs. bFU/LV</td>
<td>OS</td>
<td>430</td>
<td>0.95 0.72-1.26 0.78 0.60-1.02</td>
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<tr>
<td>Falcone et al, 2007 (14)</td>
<td>FU/LV vs. FU</td>
<td>OS</td>
<td>598</td>
<td>0.96 0.73-1.27 0.97 0.75-1.26</td>
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<td>Yes</td>
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</table>

Targeted therapy | | | | | | |
| Hurwit et al, 2004 (12) | IFL vs. IFL+Bev | OS | 813 | 0.66 N/A 0.54 N/A | Yes |
| Giantonio et al, 2007 (40) | FOLFOX vs. FOLFIRI+Bev | OS | 829 | 0.75 N/A 0.61 N/A | No |
| Saltz et al, 2008 (27) | Ox vs. Bev+Ox | OS | 1400 | 0.84 0.68-1.04 0.77 0.63-0.94 | Yes |
| Schilsky et al, 2002 (35) | FU/LV vs. FU | OS | 497 | 0.90 0.68-1.19 0.76 0.59-0.99 | Yes |
| Kohne et al, 2003 (26) | FU/LV vs. FU | OS | 497 | 0.90 0.68-1.19 0.76 0.59-0.99 | Yes |
| Kohne et al, 2005 (36) | FU/LV vs. FU | OS | 430 | 0.95 0.72-1.26 0.78 0.60-1.02 | Yes |
| Falcone et al, 2007 (14) | FU/LV vs. FU | OS | 598 | 0.96 0.73-1.27 0.97 0.75-1.26 | Yes |
| Schilsky et al, 2002 (35) | FU/LV vs. eniluracil/FU | OS | 981 | 0.88 0.75-1.03 0.83 0.73-0.95 | Yes |
| Kohne et al, 2003 (26) | FU/LV vs. FU | OS | 497 | 0.90 0.68-1.19 0.76 0.59-0.99 | Yes |
| Kohne et al, 2005 (36) | FU/LV vs. bFU/LV | OS | 430 | 0.95 0.72-1.26 0.78 0.60-1.02 | Yes |

Abbreviations: Acept, Afbiccept; Bev, bevacizumab; Cmab, cetuximab; CI, confidence interval; EGFR, EGF receptor; Iri, irinotecan; MT, mutant; N/A, not available; OS, overall survival; Ox, oxaliplatin; PFS, progression-free survival; Pmab, panitumumab; WT, wild-type.

*For trials reporting KRAS status, the total number of patients whose KRAS status was ascertained is displayed.

**Included any fluorouracil, leucovorin, and oxaliplatin-based chemotherapy regimen.

All patients received OxFp (XELOX or OxMdG). Only WT KRAS data was reported for results stratified by XELOX and only MT KRAS data for results stratified by OxMdG.

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Correlation between treatment effects in phase III trials with targeted agents

Twelve phase III trials with targeted agents (panitumumab, cetuximab, bevacizumab, and aflibercept) with 21 pairs of HRs for OS and PFS were used to estimate the treatment effects on OS from the observed treatment effects on PFS (Fig. 2A). The correlation coefficient was 0.89 (95% CI, 0.74–0.95) and the $R^2$ was 0.80 (95% CI, 0.55–0.91). It is recognized that the clinical benefit associated with anti-EGFR antibody therapies in mCRC is restricted to patients with WT KRAS tumors (22). When the analysis excluded treatment arms with mutant KRAS mCRC for trials that reported KRAS status, 11 pairs of HRs were identified (Fig. 3B). The correlation coefficient was 0.85 (95% CI, 0.49–0.95) and the $R^2$ was 0.72 (95% CI, 0.24–0.91).

Correlation between treatment effects in trials with anti-EGFR therapy

When the analysis was limited to trials with anti-EGFR antibody therapies (Fig. 3A), 9 trials (3 panitumumab and 6 cetuximab studies) with 17 pairs of HRs for OS and PFS were identified. Six of the trials were in the first-line treatment setting. The correlation coefficient was 0.83 (95% CI, 0.56–0.93) and the $R^2$ was 0.68 (95% CI, 0.32–0.87). It is recognized that the clinical benefit associated with anti-EGFR antibody therapies in mCRC is restricted to patients with WT KRAS tumors (22). When the analysis excluded treatment arms with mutant KRAS mCRC for trials that reported KRAS status, 11 pairs of HRs were identified (Fig. 3B). The correlation coefficient was 0.85 (95% CI, 0.49–0.95) and the $R^2$ was 0.72 (95% CI, 0.24–0.91).

The magnitude of the PFS prediction on OS

For small HRs, $\log (HR)$ is approximately equal to 1 minus the HR; therefore, $\log (HR)$ can be used as an approximate estimate of the risk reduction (6). From the slope of each regression line, the predicted OS risk reduction associated with a 10% PFS risk reduction can be estimated (Table 2) and ranged from 5.6% (trials with anti-EGFR therapy) to 7.7% (first-line phase III trials). The surrogate threshold effect, derived from a vertical line that transects...
the upper 95% CI and an OS HR equal to 1, represents the minimum PFS effect that predicts a positive OS effect (i.e., OS HR < 1). The surrogate threshold effect ranged from 0.72 (trials with anti-EGFR, WT KRAS subgroup) to 0.91 (first-line phase III trials).

**Correlation between ratios HRs and PFS HRs using unweighted analysis**

The above findings were consistent with analyses unweighted by study sample size (Supplementary Fig. S1). For all selected trials, the correlation coefficient remained at 0.86 (95% CI, 0.74–0.93). For analyses stratified by various study criteria, the correlation coefficients were all greater than or equal to 0.84.

**Correlation between OS HRs and response rates**

Sixty-five of the 69 treatment arms in this analysis reported response rate data. To evaluate the correlation between OS and response rate (Supplementary Table S1), unweighted linear regression analysis was used to estimate the treatment effects on OS HRs from the observed treatment effects on response-rate ORs, response-rate differences, and response-rate ratios. For response-rate ORs, correlation coefficients ranged from 0.50 (phase III trials with targeted agents) to 0.68 (trials with anti-EGFR therapy, WT KRAS subgroup). For response-rate differences, correlation coefficients ranged from 0.58 (phase III trials with targeted therapies) to 0.81 (trials with anti-EGFR therapy, WT KRAS subgroup). In addition, finally, for OS HRs compared with response-rate ratios, correlation coefficients ranged from 0.42 (phase III trials with targeted therapies) to 0.63 (first-line phase III trials with targeted therapies).

**Discussion**

Recent advances in systemic cytotoxic therapies and the introduction of targeted agents into treatment regimens have improved survival for patients with mCRC. The introduction of new regimens, curative metastasectomies, and differences in treatment practice make the interpretation of OS challenging in clinical trials (23). Identifying surrogate endpoints for OS that reach their endpoint faster may aid in more informative comparisons for new therapies. This may lead to earlier treatment decisions and more rapid drug approval and availability of efficacious therapies for metastatic disease.

Currently, there is no consensus on the definition of a valid surrogate endpoint. It has been proposed that a valid surrogate endpoint must have a significant impact on the true endpoint and must fully capture the treatment effect on the true endpoint (15). Other approaches have suggested that for a surrogate endpoint to be valid, the effect of treatment on the surrogate endpoint must predict the effect of treatment on the true endpoint; therefore, high correlations between the treatment effect on the surrogate and the true endpoints are needed in both individual and trial levels for a true surrogacy (16, 17).
Results from Sargent and colleagues (24) suggested that the validity of a surrogate endpoint for OS in CRC trials could be evaluated by examining the correlation between the endpoints and the treatment effects on these endpoints in a series of trials. In an extension of the study by Sargent and colleagues (24) and others (6, 7), we conducted a study-level analysis of 24 fluoropyrimidine-based chemotherapy trials in mCRC over the past decade to evaluate the relationships between PFS, response rate, and OS among current treatment regimens that employ targeted agents.

The observed correlation coefficient between PFS and OS for all 24 trials was 0.86 (95% CI, 0.73–0.92) and for phase III trials with targeted agents was 0.89 (95% CI, 0.74–0.95). This was consistent with previous analyses of chemotherapy trials (6, 7), suggesting that this correlation remains robust for recent treatment advances in cytotoxic chemotherapies and targeted therapies. In a study by Buyse and colleagues (6), individual patient data from 10 historical trials (fluorouracil and leucovorin) and 3 validation trials (fluorouracil and leucovorin ± irinotecan or oxaliplatin) were analyzed. The correlation coefficient between PFS and OS in all trials was 0.99. A study by Tang and colleagues (7) analyzed 39 randomized controlled trials of first-line chemotherapy in mCRC including 12 validation trials and 2 trials with new therapeutic agents. The correlation coefficient between PFS and OS was 0.79. Although the correlation between PFS and OS may be less robust when patients are exposed to subsequent lines of effective therapies (6, 25), a consistently strong correlation between PFS and OS has been reported for all published mCRC analyses and across different statistical methodologies (6, 7). Taken together, this suggests that PFS remains a valid surrogate endpoint for OS in the current mCRC treatment setting of chemotherapy in combination with targeted agents.

The correlation between response rates and OS HRs was also evaluated. Comparing response-rate ORs, response-rate differences, and response-rate ratios with OS HRs, the correlation coefficients were relatively low with the majority ranging from 0.42 to 0.68. Our results are in general agreement with previous studies (7, 8), which have reported poor to moderate correlations between response rate and OS and suggest response rate may not be a valid surrogate endpoint for OS.

Our study was subject to several limitations. The search strategy may have excluded smaller trials involving targeted agents (other than panitumumab, cetuximab, bevacizumab, and aflibercept) that impacted our analysis. Two studies in this analysis used a treatment arm in more than 1 comparison (26, 27) and the data points may not have been completely independent. We did not include individual patient-level data and were susceptible to publication bias and missing data/events and rates/HRs. Disease assessment times, the definition of progression, the primary endpoint, and the study power also varied by trial. It was not possible to determine if assessment of progression occurred at comparable time points between arms within a trial. The specific definition of the HR and OR may have differed by study which make summary measures of the HR and OR difficult to interpret. Finally, subsequent treatments were not reported in most of the trials and any potential confounding effects were not addressed in our analysis.

To our knowledge, the analysis reported here is the first to examine the correlation between PFS and OS in randomized, controlled trials with targeted agents and encompasses several recent pivotal trials of targeted biologic combination therapies in mCRC. These recently reported trials reflect the current treatment setting of longer survival times due to the increasing number of efficacious therapies and provide evidence of the use of PFS as an endpoint in earlier lines of therapy with targeted agents. Other recently reported endpoints such as duration of disease control and time to failure of strategy may also be correlated with OS (25) but still require further validation in the setting of targeted agents.

There remains debate about using surrogate endpoints in clinical trials and it has been suggested that OS is the most relevant primary endpoint and should be considered the true measure of clinical benefit (28). However, as the approval of new therapies in the treatment of patients with mCRC increases, the confounding effect of later lines of therapies may make interpretation of OS results more difficult especially in trials with crossover designs and where effective subsequent therapies are not balanced across treatment arms. PFS is less sensitive to subsequent therapy effects as patients will have already experienced a progression event. PFS is a direct measure of tumor control and assesses the timing of the event.

As the time between progression and death becomes extended due to improving treatment regimens, the increasing confounding of OS may make establishing PFS surrogacy for OS more difficult in the future. This may already be reflected in our analysis of PFS surrogacy: in the trials that were identified, the PFS HRs were generally lower than those for OS (Table 1) and the slopes of the linear regression lines were all less than 1 (Figs. 1–3).

There are a variety of definitions of surrogacy, all requiring a strong correlation with the surrogate and the final endpoint. Consistent with recent findings (29), our data suggest that in current mCRC treatment regimens, PFS remains strongly correlated with OS. Regardless of this, PFS may reflect clinical benefit on its own, has many intrinsic advantages, and, therefore, should be considered a true primary endpoint in mCRC (30–32). Indeed, our results suggest PFS has been a commonly used primary endpoint in recent mCRC trials as 14 of the 24 studies identified used PFS as the primary or coprimary endpoint (8 studies used OS).

Our analysis in the mCRC disease setting shows a consistently high correlation between PFS and OS among modern chemotherapy trials, first-line trials, targeted therapy trials, and anti-EGFR inhibitor trials. In addition to its role as a primary endpoint in mCRC trials, PFS currently remains an attractive surrogate endpoint for OS as it may help save costs in trials, lead to earlier analysis of...
the data, and ultimately help to speed approval of new therapies.

Disclosure of Potential Conflicts of Interest
All authors are employees of the sponsor, Amgen Inc., and have stock ownership interests in the sponsor.

Authors’ Contributions
Conception and design: R. Sidhu, A. Rong, S. Dahlberg
Development of methodology: R. Sidhu, A. Rong, S. Dahlberg
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): R. Sidhu, S. Dahlberg
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): R. Sidhu, A. Rong, S. Dahlberg

References


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