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Progression-Free Survival as a Surrogate Endpoint for Median Overall Survival in Metastatic Colorectal Cancer: Literature-Based Analysis from 50 Randomized First-Line Trials

Clemens Giessen[1], Ruediger Paul Laubender[2], Donna Pauler Ankerst[3], Sebastian Stintzing[1], Dominik Paul Modest[1], Ulrich Mansmann[2], and Volker Heinemann[1]

Abstract

Purpose: To evaluate progression-free survival (PFS) as a potential surrogate endpoint (SEP) for overall survival (OS) in metastatic colorectal cancer (mCRC) with a focus on applicability to trials containing targeted therapy with anti-VEGF- or anti-EGF receptor (EGFR)–directed monoclonal antibodies.

Experimental Design: A systematic literature search of randomized trials of first-line chemotherapy for mCRC reported from January 2000 to January 2012 was conducted. Adjusted weighted linear regression was used to calculate correlations within PFS and OS (endpoints; R_{EP}) and between treatment effects on PFS and on OS (treatment effects; R_{TE}).

Results: Fifty trials reflecting 22,736 patients met the inclusion criteria. Correlation between treatment effects on PFS and OS and between the endpoints PFS and OS was high across all studies ($R_{TE} = 0.87$, $R_{EP} = 0.86$). This was also observed in chemotherapy-only trials ($R_{TE} = 0.93$, $R_{EP} = 0.81$) but less so for trials containing monoclonal antibodies ($R_{TE} = 0.47$; $R_{EP} = 0.52$). Limiting the analysis to bevacizumab-based studies (11 trials, 3,310 patients) again yielded high correlations between treatment effects on PFS and on OS ($R_{TE} = 0.84$), whereas correlation within PFS and OS was low ($R_{EP} = 0.45$). In 7 trials (1,335 patients) investigating cetuximab- or panitumumab-based studies, contrasting correlations with very wide confidence intervals were observed ($R_{TE} = 0.28$; $R_{EP} = 0.96$).

Conclusions: PFS showed consistently high correlation with OS of an order that would justify its use as an SEP in chemotherapy regimens. For validation of surrogacy in anti-VEGF and anti-EGFR–directed therapies, further research and a larger set of trials is needed. *Clin Cancer Res; 19(1); 225–35. ©2012 AACR.*

Introduction

With the widespread use of monoclonal antibodies in the treatment of metastatic colorectal cancer (mCRC) and median survival times in excess of 20 months, surrogate endpoints (SEP) for treatment activity have become a popular and timely topic (1–9). This is not only because the historically favored hard endpoint of overall survival (OS) now takes longer to measure, but also because it is prone to be influenced by subsequent lines of therapies and cross-over designs more commonly encountered in contemporary trials (9, 10).

SEPs that are reached in shorter duration and can be agreed on by consensus as replacements for OS provide a solution to some of the difficulties surrounding the feasibility of OS for trials; among these, progression-free survival (PFS) has taken center stage (3, 4, 11–14). Piedbois and Croswell proposed the definition that "a surrogate endpoint is an endpoint that can be used as a substitute for the true endpoint" (4). The U.S. Food and Drug Administration states that "an acceptable SEP should be able reasonably likely (...) to predict the clinical benefit on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity" (12, 15). However, validation of SEPs has encountered controversy among statisticians, so that to date no formal universally agreed-upon empirical criteria for SEPs exist (3–6, 11, 13, 16–19).

For years, overall response rate (ORR) and PFS have been widely used as primary endpoints in mCRC and in other cancer entities because of earlier assessments showing independence to further-line therapies (1, 5, 6). PFS is currently used in most mCRC-trials as the primary endpoint but has not yet been validated as a surrogate for OS for studies involving monoclonal antibodies, such

Authors' Affiliations: [1]Department of Medical Oncology, Klinikum Grosshadern and Comprehensive Cancer Center; [2]Institute of Medical Informatics, Biometry, and Epidemiology (IBE), Faculty of Medicine, Ludwig Maximilian University of Munich; and [3]Department of Mathematics, Technical University of Munich, Munich, Germany

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Corresponding Author: Clemens Giessen, Department of Medical Oncology, Klinikum Grosshadern and Comprehensive Cancer Center, Ludwig Maximilian University of Munich, Marchioninistrasse 15, Munich 81377, Germany. Phone: 49-89-7095-2208; Fax: 49-89-7095-5256; E-mail: clemens.giessen@med.uni-muenchen.de

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Translational Relevance

Progression-free survival (PFS) is widely adopted as the primary endpoint in clinical trials for metastatic colorectal cancer (mCRC) but has neither been investigated nor validated as a surrogate endpoint (SEP) for overall survival (OS) in treatments incorporating anti-VEGF and anti-EGF receptor–directed monoclonal antibodies. This literature-based analysis of 50 first-line trials for mCRC explored the applicability of PFS as a SEP for OS in the era of targeted chemotherapy regimens. We confirmed previous literature-based and individual patient–based analyses indicating PFS as an applicable SEP for OS in chemotherapy-only trials. Analysis of published trials containing bevacizumab further suggested PFS to be a suitable SEP for chemotherapy- and bevacizumab-trials. On the basis of the present study, we encourage the investigation of additional endpoints incorporating tumor- or patient-related biomarkers and the confirmation at the individual patient level.

as bevacizumab, cetuximab, and panitumumab. The purpose of this study was to conduct a comprehensive literature-based quantitative review to determine whether PFS is correlated with OS in first-line chemotherapy trials for mCRC in the era of VEGF- and EGF receptor (EGFR)–targeting drugs, thus increasing its scope as a SEP for OS in mCRC.

Materials and Methods

Literature search and data extraction

Randomized controlled trials for previously untreated patients who underwent first-line chemotherapy for mCRC published between January 2000 and January 2012 were identified through a systematic search in the National Library of Medicine medical literature database via PubMed gateway, Excerpta Medica Database (EMBASE), and the Cochrane Library using the keywords "metastatic colorectal cancer" and "first-line randomized trials." In addition, abstracts presented at the annual meetings of the American Society of Clinical Oncology and the European Society for Medical Oncology between January 2000 and January 2012 and bibliographies of published overviews were examined (6, 20). Only publications in English were included. Further inclusion criteria were a sample size of at least 100 patients per trial and reports of either PFS or time to progression (TTP) along with OS.

Exclusion criteria were trials containing patients with locally advanced, unresectable disease or with previous chemotherapy for metastatic disease, trials investigating surgical resection of resectable/unresectable metastatic

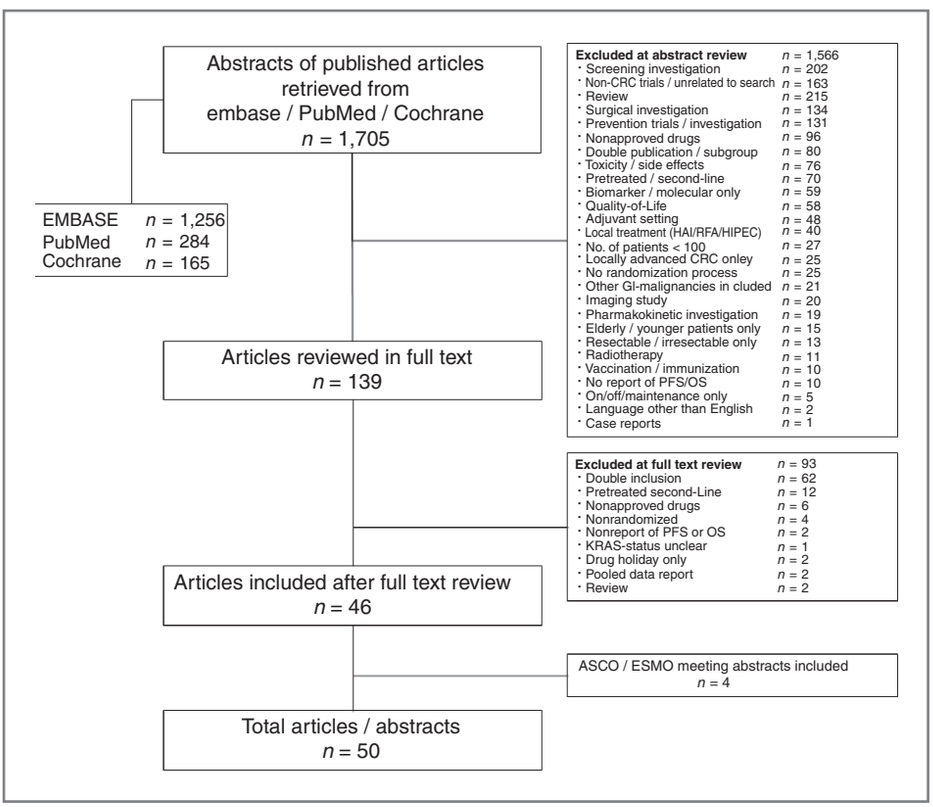

Figure 1. Literature search and selection of articles. PubMed, National Library of Medicine, NLM database; Cochrane, The Cochrane Library from The Cochrane Collaboration; HAI, hepatic arterial infusion; RFA, radio frequency ablation; HIPEC, hyperthermic intraperitoneal chemotherapy; ASCO, American Society of Clinical Oncology; ESMO, European Society of Medical Oncology.

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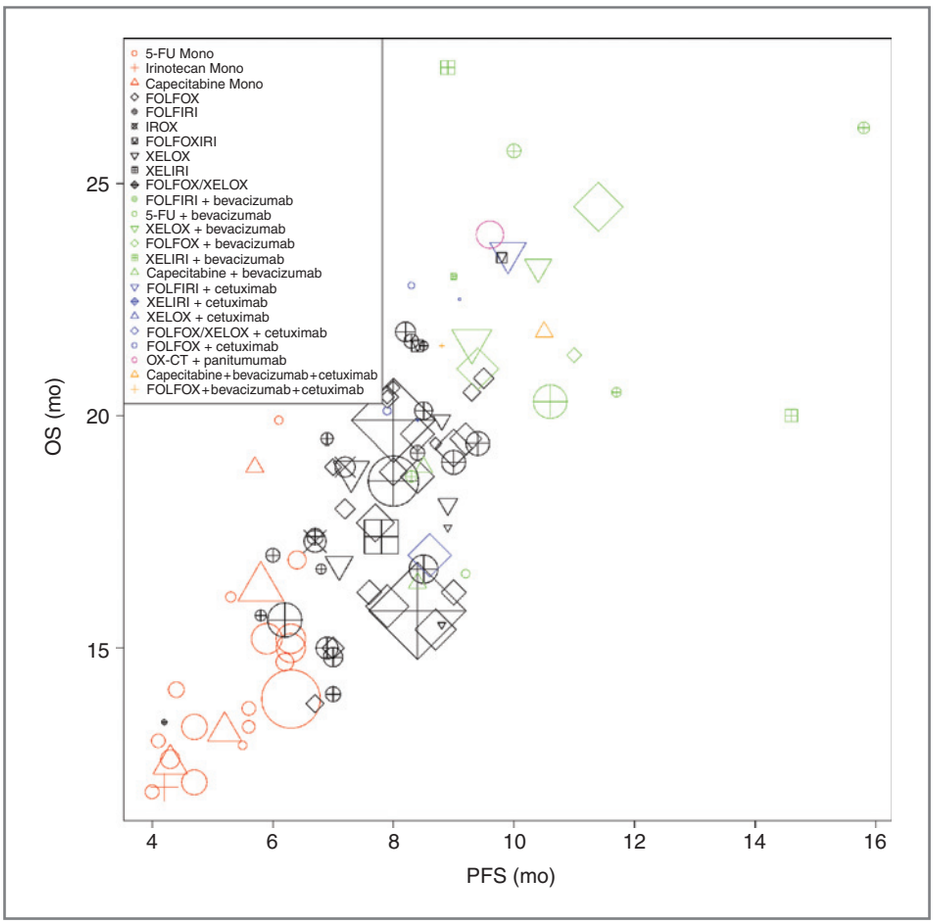

Figure 2. PFS (months) versus OS (months) classified by treatment. Symbol size is proportional to number of patients.

disease, trials limited to elderly/younger patients, pooled data reports or noninterventional trials (registry data), and trials using additional hepatic chemotherapy infusion. Trials involving nonapproved drugs for mCRC by the European Medical Association (EMA), such as raltitrexed, pemetrexed, and trimetrexate or containing patients with gastrointestinal cancers other than colorectal cancer were not considered. From trials comparing maintenance, stop-and-go-strategies (including fluoropyrimidine maintenance treatment), or intermittent chemotherapy versus continuous chemotherapy, only results from the latter treatment arms were included.

Because at present time the anti-EGFR antibodies cetuximab and panitumumab are only registered for patients with KRAS wild-type tumors (KRAS-wt), trials containing 1 of 2 drugs and that did not report KRAS-mutation status were excluded (1 trial excluded). Results from KRAS-mutant patients (KRAS-mut) who underwent chemotherapy with anti-EGFR–directed monoclonal antibodies were not included in the analysis (9 trial arms excluded). With KRAS

Table 1. Correlation between treatment effects on PFS and treatment effects on OS (R_{TE}) and between PFS and OS (R_{EP})

	No. pts	No. trials/ trial arms	R_{TE}	95% CI	R_{EP}	95% CI
All treatments	22,736	50/102	0.87	0.67–0.93	0.86	0.79–0.91
Chemotherapy-only	17,887	40/74	0.93	0.49–0.97	0.81	0.71–0.88
Oxaliplatin-based	10,060	31/44	0.68	0.41–0.85	0.69	0.36–0.87
Irinotecan-based	7,301	24/36	0.82	0.52–0.95	0.74	0.59–0.86
Chemotherapy and antibody	4,849	19/28	0.47	0.05–0.72	0.52	0.09–0.88
Chemotherapy and bevacizumab	3,310	11/17	0.84	0.05–0.94	0.45	0.00–0.84
Chemotherapy and cetuximab or panitumumab	1,335	7/9	0.28	−0.87–0.92	0.96	−0.76–1.00

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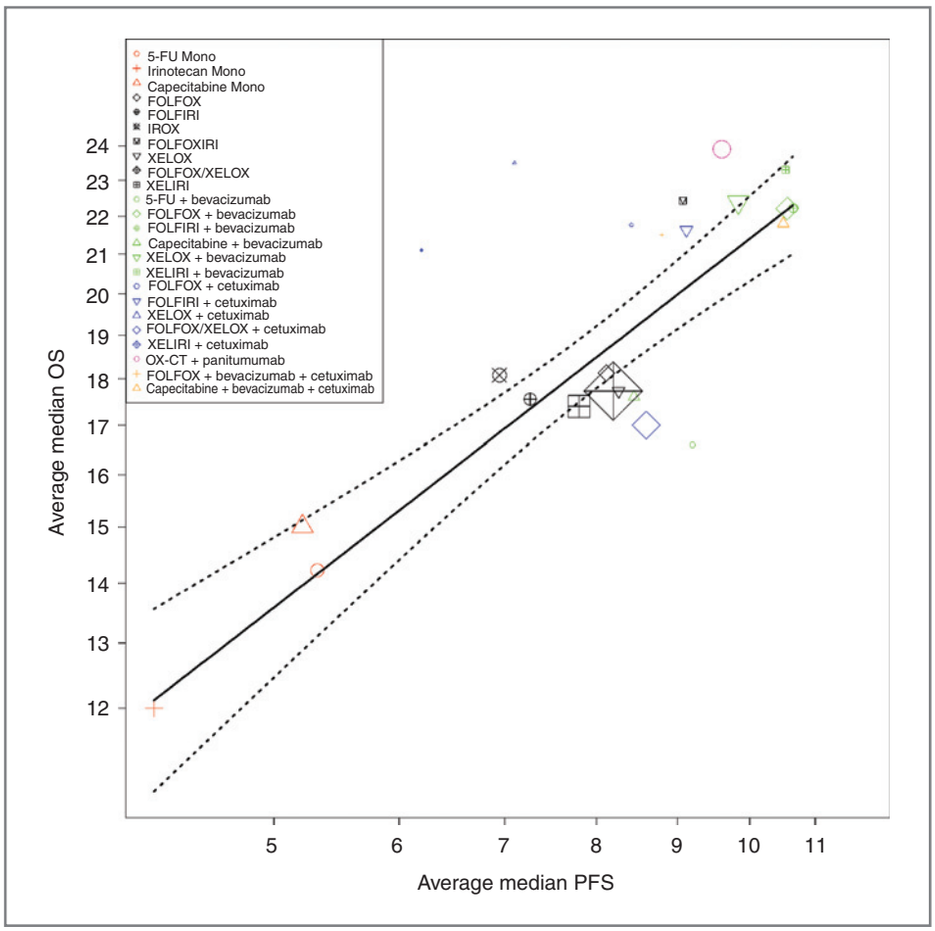

Figure 3. Treatment effects (log ORs) on PFS versus OS according to treatment type. The solid line is the regression line; dotted lines indicate pointwise 95% CIs. Symbol size is proportional to number of patients. Trial arms using comparable treatment regimens were summarized.

mutational status also currently undergoing discussion as a prognostic factor for OS in chemotherapy-only treatment, control was needed to avoid selection-bias resulting from KRAS-wt and/or KRAS-mut patients included in control arms not containing cetuximab and panitumumab. Therefore, KRAS-independent results were used for analyses of within treatment surrogacy (R_{EP}) in chemotherapy-only trial arms. For at the trial level surrogacy (R_{TE}) analyses, results according to KRAS-status were used in studies investigating anti-EGFR–directed agents. Four investigators (C. Giessen, S. Stintzing, D.P. Modest, and V. Heinemann) reviewed data for inclusion and exclusion, following the review process in Fig. 1 according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (21).

For each trial, reported data on sample size, chemotherapy regimens, median PFS (months), and median OS (months) were extracted for all treatment arms using published data. A total of 7 trials used TTP as the primary endpoint. In contrast to PFS, TTP uses disease progression as the only event of interest and disregards death from any cause. Because both endpoints, TTP and PFS, are unaffected by subsequent therapies, they were used exchangeably for this analysis and were referred to as PFS as previously conducted in similar meta-analyses of colorectal and metastatic breast cancer (19, 22, 23).

Statistical methods

Two correlations were calculated between summary statistics to assess surrogacy based on aggregated data (6, 23–25). Correlations were conducted according to treatment class, defined as comparable chemotherapy regimens using the same cytotoxic drugs or monoclonal antibodies, using weighted linear regression with log transformation of all endpoints and weights proportional to the sample sizes.

The first approach, termed within treatment surrogacy, computed the correlation between median PFS, the potential SEP, and median OS, and the relevant endpoint reported for the same study arm (arm by arm analysis). The correlation is evaluated over all treatment arms within a specific treatment class and is called the R_{EP} (endpoint). A strong positive correlation indicates that median PFS calibrates with median OS and is considered one form of evidence for PFS as a surrogate measure for OS (26).

The second approach, termed trial level surrogacy, computed the correlation (R_{TE}) between the reported treatment effects on PFS, the potential SEP, with the reported treatment effects on OS, and the relevant endpoint. It was similarly computed among regimens from specific treatment classes with strong positive correlation indicating the treatment effects on PFS are well calibrated to treatment

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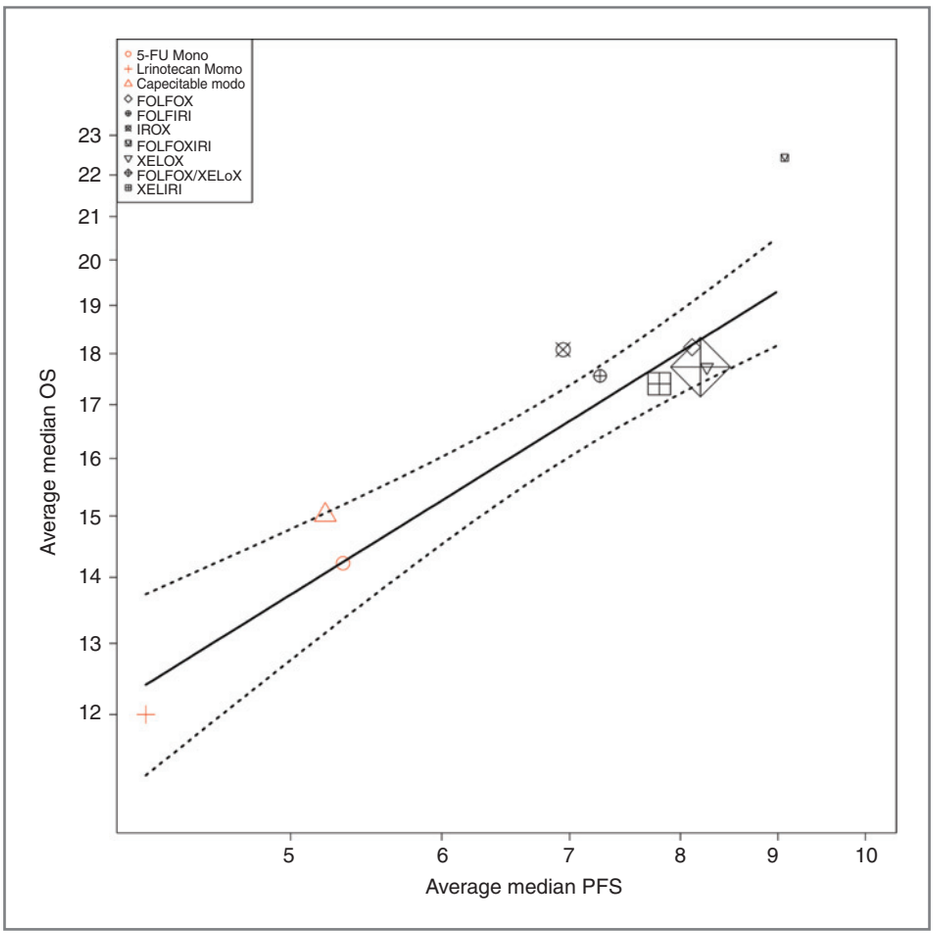

Figure 4. Treatment effects (log ORs) on PFS versus OS (months) in chemotherapy-only trials. The solid line is the regression line; dotted lines indicate pointwise 95% CIs. Symbol size is proportional to number of patients. Trial arms using comparable treatment regimens were summarized

effects on OS, so that PFS could be considered as evidence for surrogacy (27).

The 95% confidence intervals (CI) for R_{EP} and R_{TE} were obtained using the percentile bootstrap. All analyses were conducted using the R version 2.13.2 statistical package and the nlme package (R Development Core Team Vienna, Austria, 2012. Available from: http://www.r-project.org).

Results

All trials

For the PFS analysis, data from 50 trials representing 22,736 patients were included (refs. 28–76; Supplementary Table S1; Fig. 2). When median PFS and OS were plotted against the year of publication, a large variability without an apparent time trend was observed (data not shown). In the analysis of all treatment regimens (chemotherapy and monoclonal antibodies), treatment effects on PFS and OS were strongly correlated ($R_{TE} = 0.87$; 95% CI, 0.67–0.93), and PFS also correlated well with OS ($R_{EP} = 0.86$; 95% CI, 0.79–0.91; Table 1; Fig. 3).

Chemotherapy-only trials

Restricting the analysis to the 40 trials representing 17,887 patients, who received only cytotoxic chemotherapy (monotherapy and combination chemotherapy), a higher correlation among treatment effects was observed, but the smaller sample size resulted in a lower 95% confidence limit ($R_{TE} = 0.93$; 95% CI, 0.49–0.97); correlation among median PFS and OS remained high ($R_{EP} = 0.81$; 95% CI, 0.71–0.88; Table 1, Fig. 4).

Oxaliplatin- and irinotecan-based trials

Among 24 trials using irinotecan-based chemotherapy, a high correlation among the treatment effects on PFS and OS was observed (R_{TE} 0.82; 95% CI, 0.52–0.95) when compared with the 31 oxaliplatin-based trials (R_{TE} 0.68; 95% CI, 0.41–0.85). Correlation between median PFS and OS was also higher in the irinotecan-based trials (R_{EP} 0.74; 95% CI, 0.09–0.88 vs. R_{EP} 0.69; 95% CI, 0.36–0.87; Table 1; figure not shown).

Trials containing monoclonal antibodies

Confinement to antibody-based regimens (4,849 patients from 19 trials) revealed weak correlation between treatment effects on PFS and OS ($R_{TE} = 0.47$; 95% CI, 0.05–0.72) and between the endpoints themselves ($R_{EP} = 0.52$; 95% CI, 0.09–0.88; Table 1; Fig. 5).

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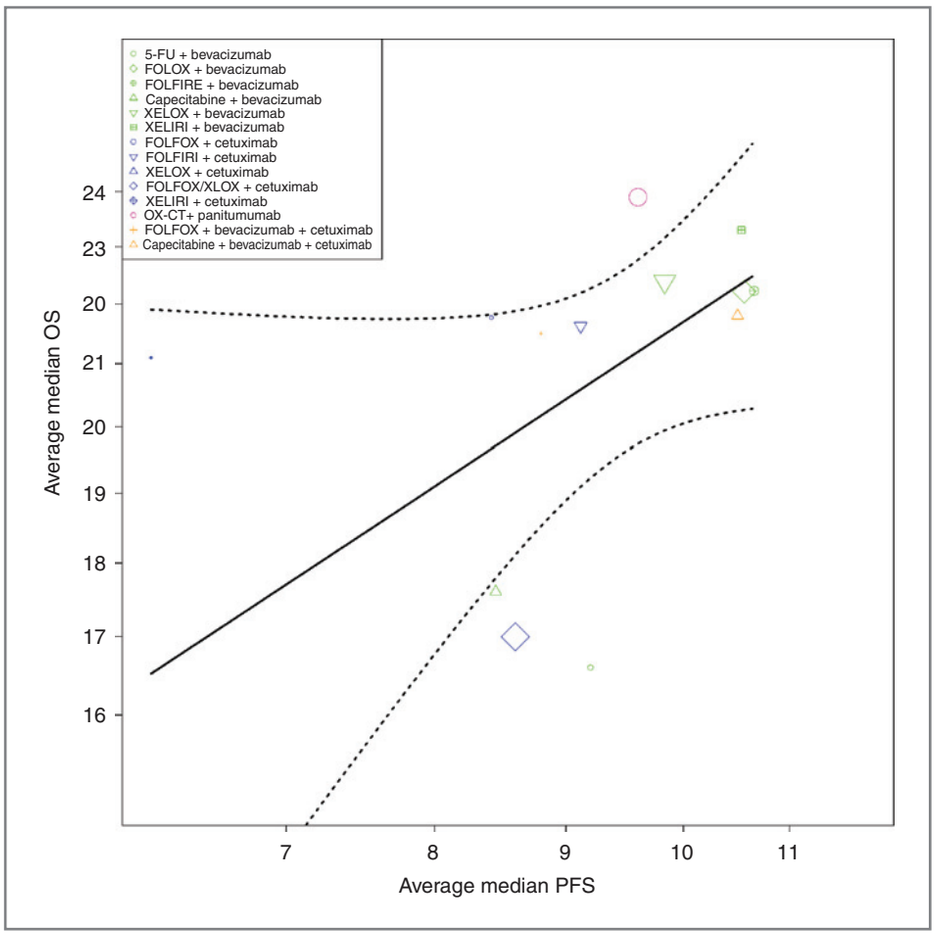

Figure 5. Treatment effects (log ORs) on PFS versus OS (months) in chemotherapy and antibody trials. The solid line is the regression line; dotted lines indicate pointwise 95% CIs. Symbol size is proportional to number of patients. Trial arms using comparable treatment regimens were summarized.

Trials containing bevacizumab

The 11 bevacizumab-based trials representing 3,310 patients exhibited a high correlation between treatment effects on PFS and OS (R_{TE} = 0.84; 95% CI, 0.05–0.94). In contrast, a low correlation was found between PFS and OS within this treatment group (R_{EP} = 0.45; 95% CI, 0.00–0.84; Table 1; Fig. 6).

Trials containing cetuximab or panitumumab

A total of 7 trials representing 1,335 patients were available for analysis. Low correlation between treatment effects on PFS and OS was found (R_{TE} = 0.28; 95% CI, -0.87–0.92). Correlation between PFS and OS within anti-EGFR-based trials was very high (R_{EP} = 0.96; 95% CI, −0.76–1.00; Table 1; Fig. 7).

Discussion

The use of PFS instead of OS as a primary endpoint in clinical trials has accelerated drug development by the earlier reporting of results, thus facilitating the more rapid introduction of new combination regimens and drugs into clinical practice. Other groups have previously investigated and validated PFS as an SEP in mCRC. A combined meta-analysis of individual patient-level data, from 10 randomized trials of first-line chemotherapy for mCRC revealed a strong correlation between PFS and OS (rank correlation coefficient = 0.82; 95% CI, 0.82–0.83; ref. 1). On the basis of that data, PFS was deemed to be an appropriate SEP for mCRC providing a direct measure of activity that is not affected by subsequent lines of therapy. A comprehensive literature-based analysis of 39 randomized trials conducted in 2007 also showed a strong correlation between treatment HRs for PFS and OS and further suggested that PFS could serve as a reliable SEP for OS in mCRC (6). In 2010, a review on surrogacy of PFS in breast and colorectal cancer trials recommended on the basis of evidence that PFS could serve as a validated SEP, but its role in trials with molecular-targeted agents and high rates of effective second-line treatment was questioned (5). Recently, a meta-analysis of association between PFS and OS in first- and second-line chemotherapy for mCRC revealed a robust correlation between PFS and OS across all treatment lines (23). However, the impact of targeted drug combinations on the correlation between PFS and OS, and hence the potential of PFS as a SEP for these regimens remained unanswered.

Currently, the widespread use of SEPs in first-line chemotherapy for mCRC constitutes an ongoing debate among medical oncologists, statisticians, and drug approval

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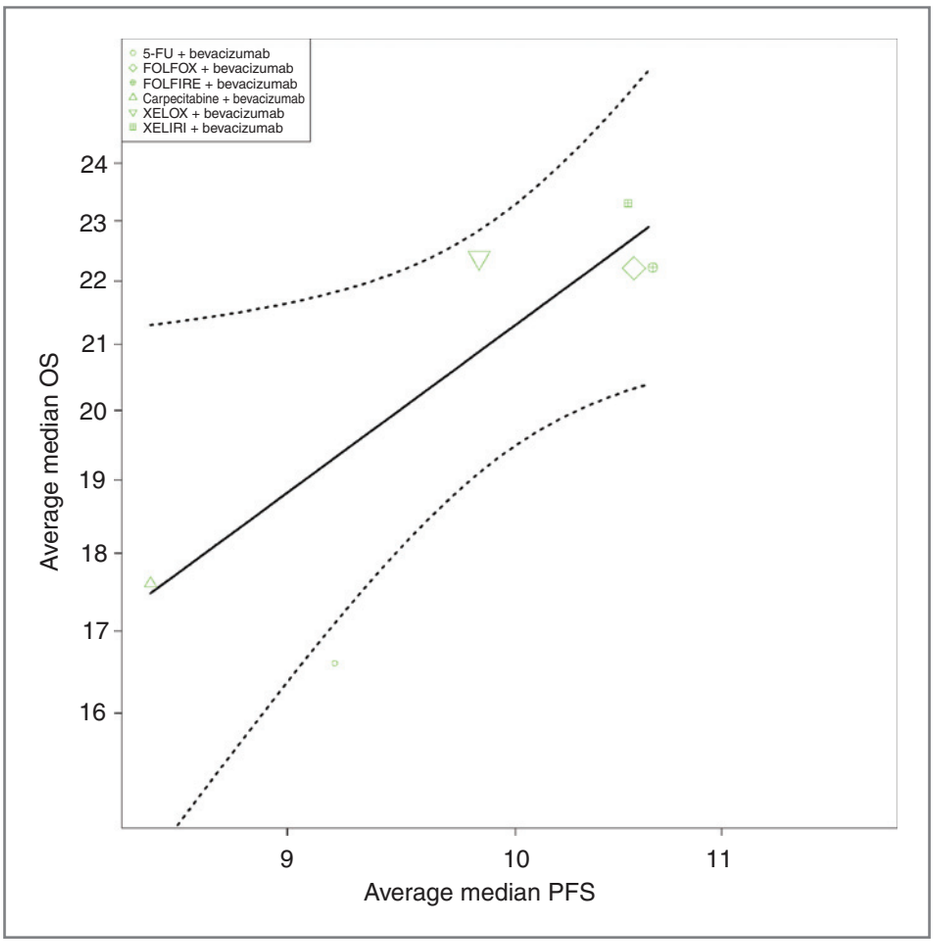

Figure 6. Treatment effects (log ORs) on PFS versus OS (months) in bevacizumab-based trials. The solid line is the regression line; dotted lines indicate pointwise 95% CIs. Symbol size is proportional to number of patients. Trial arms using comparable treatment regimens were summarized.

authorities and SEPs have been validated for cytotoxic agents [5-fluorouracil (5-FU), irinotecan, and oxaliplatin combinations] only (1, 4–6).

To the best of our knowledge, this meta-analysis represents the first analysis of SEPs in mCRC that investigated monoclonal antibody trials separately, thus addressing the question of viable clinical endpoints in the targeted drug era. This quantitative review has confirmed previous findings of PFS as an acceptable SEP for cytotoxic chemotherapy regimens.

As this study focused on applicability of PFS as a potential SEP for OS in trials investigating monoclonal antibodies, all studies containing VEGF- and EGFR-directed drugs were analyzed together and weak correlations between treatment effects, PFS, and OS were found. Analyses of bevacizumab plus chemotherapy suggest that PFS might serve as a suitable SEP for these regimens with strong correlation between the treatment effects on PFS and OS (R_{TE}). Heterogeneous data among these trials yielded weak correlation among the endpoints themselves (R_{EP}) and wide 95% CIs. Of note, confirmation in a larger set of trials and at the individual patient-level is required.

At present time, 2 EGFR-inhibiting drugs, cetuximab and panitumumab, are approved for first-line chemotherapy for mCRC. In our systematic literature search, 7 trials investigating anti-EGFR agents were evaluable. A weak correlation between the treatment effects on PFS and OS (R_{TE}) was found, whereas small sample sizes resulted in a strong correlation within PFS and OS (R_{EP}). Unfortunately, the estimated correlations are not definitive. In view of the rather large CIs, again, surrogacy in anti-EGFR–directed therapies should be further validated once more data are available. Our findings may be explained by divergent results obtained for different fluoropyrimidine backbones. Among the available trials, 4 used infusional 5-FU regimens (77–80), whereas other 3 used either capecitabine or bolus 5-FU as their chemotherapy backbone (81–83). An interaction between anti-EGFR agents and the mode of fluoropyrimidine application (oral vs. infusional) is currently discussed (84).

It is important to note that in our study only aggregated data could be analyzed. The gold standard for investigation of SEPs uses individual patient-level analyses; therefore, the meta-analytic approach used in this study can only be regarded as a first step toward this issue (85). Furthermore, we could not base our meta-analysis on measures of treatment effects, such as HRs, as studies comparing identical treatment classes did not permit the estimation of HRs (86).

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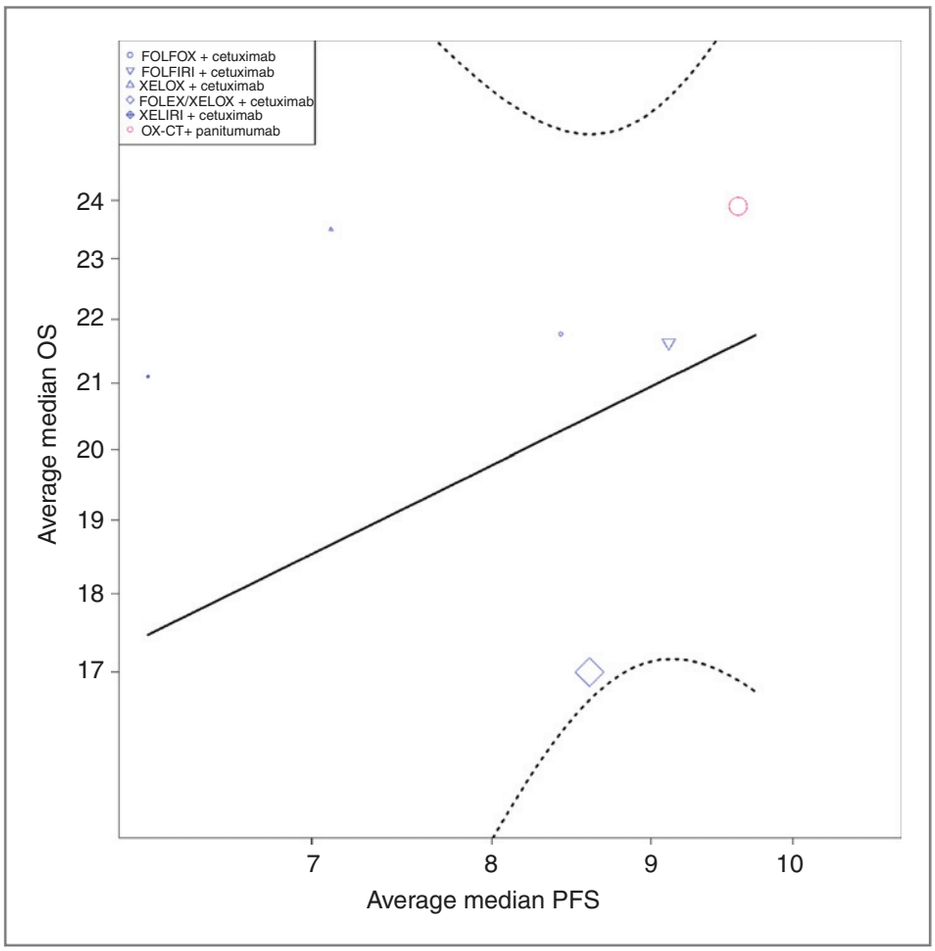

Figure 7. Treatment effects (log ORs) on PFS versus OS (months) in cetuximab or panitumumab-based trials. The solid line is the regression line; dotted lines indicate pointwise 95% confidence intervals. Symbol size is proportional to number of patients. Trial arms using comparable treatment regimens were summarized.

Another limitation of the present study is the variety of disease assessment times and different definitions of disease progression. This remains a common issue when comparing trials using PFS as a clinical endpoint (7). In addition, only few publications reported postprogression treatment or surgical metastasectomy, both of which constitute important determinants of survival (87). Standardized reporting of trial results is essential in the future design of randomized trials.

A recent study reported on different alternative endpoints in advanced colorectal cancer and conducted a pooled analysis of 3 randomized trials at the individual patient-level (86). Composite endpoints, such as duration of disease control and time to failure of strategy showed good correlation with OS, whereas PFS failed to show acceptable correlation. Adding the PFS of second and subsequent lines of therapy can possibly restore the surrogacy between the treatment effects and OS. The discordant findings to the present study emphasize the need for further confirmation at the individual patient-level, once more data from anti-EGFR- and anti-VEGF–based trials are available.

The present analysis of 50 trials has confirmed the use of PFS as an applicable SEP for OS in first-line treatment of mCRC using chemotherapy alone. Results from bevacizumab-based trials seemed to show satisfying surrogacy of PFS. Findings obtained for trials investigating anti-EGFR directed agents have to be confirmed once a larger database is available. Additional endpoints in mCRC including tumor- or patient-related biomarkers, as have been successfully implemented in other diseases, and investigation of these potential SEPs is strongly encouraged.

Disclosure of Potential Conflicts of Interest

C. Giessen has travel support from Roche. S. Stintzing has honoraria from speakers bureau of Merck Serono, Roche AG, and Amgen. D.P. Modest is a consultant/advisory board member of Amgen and has expert testimony from Amgen, Merck, and Roche. V. Heinemann has honoraria from speakers bureau and is a consultant/advisory board member of Merck, Roche, Amgen, and Sanofi. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

Conception and design: C. Giessen, R.P. Laubender, U. Mansmann, V. Heinemann

Development of methodology: C. Giessen, R.P. Laubender, U. Mansmann, V. Heinemann

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): C. Giessen, V. Heinemann

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): C. Giessen, R.P. Laubender, D.P. Ankerst, S. Stintzing, U. Mansmann, V. Heinemann

Writing, review, and/or revision of the manuscript: C. Giessen, R.P. Laubender, D.P. Ankerst, S. Stintzing, D.P. Modest, U. Mansmann, V. Heinemann

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): C. Giessen, V. Heinemann
Study supervision: C. Giessen, V. Heinemann

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Clemens Giessen, Ruediger Paul Laubender, Donna Pauler Ankerst, et al.

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