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ORIGINAL REPORT

Individual Patient Data Analysis of Progression-Free Survival Versus Overall Survival As a First-Line End Point for Metastatic Colorectal Cancer in Modern Randomized Trials: Findings From the Analysis and Research in Cancers of the Digestive System Database

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See accompanying editorial on page 4 and article on page 36

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Terms in blue are defined in the glossary, found at the end of this article and online at www.jco.org.

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ABSTRACT

Purpose
Progression-free survival (PFS) has previously been established as a surrogate for overall survival (OS) for first-line metastatic colorectal cancer (mCRC). Because mCRC treatment has advanced in the last decade with extended OS, this surrogacy requires re-examination.

Methods
Individual patient data from 16,762 patients were available from 22 first-line mCRC studies conducted from 1997 to 2006; 12 of those studies tested antiangiogenic and/or anti–epidermal growth factor receptor agents. The relationship between PFS (first event of progression or death) and OS was evaluated by using R^2 statistics (the closer the value is to 1, the stronger the correlation) from weighted least squares regression of trial-specific hazard ratios estimated by using Cox and Copula models.

Results
Forty-four percent of patients received a regimen that included biologic agents. Median first-line PFS was 8.3 months, and median OS was 18.2 months. The correlation between PFS and OS was modest (R^2, 0.45 to 0.69). Analyses limited to trials that tested treatments with biologic agents, nonstrategy trials, or superiority trials did not improve surrogacy.

Conclusion
In modern mCRC trials, in which survival after the first progression exceeds time to first progression, a positive but modest correlation was observed between OS and PFS at both the patient and trial levels. This finding demonstrates the substantial variability in OS introduced by the number of lines of therapy and types of effective subsequent treatments and the associated challenge to the use of OS as an end point to assess the benefit attributable to a single line of therapy. PFS remains an appropriate primary end point for first-line mCRC trials to detect the direct treatment effect of new agents.

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INTRODUCTION

Overall survival (OS) has historically been the standard clinical primary end point for most phase III trials in oncology. OS has been preferred because it is a clinical landmark that reflects the ultimate goal of cancer treatment, to prolong patients' survival, and because it is easily defined with almost no subjectivity or measurement bias. However, the substantial progress made over the last few decades in colorectal cancer has challenged the relevance of OS as a primary end point for two reasons. First, with a median survival of approximate 2 years in first-line trials, studies with an OS end point require an extended time to complete. Second, as postprogression survival increases and multiple effective lines of therapy are used, the ability for any single line of the therapy to have an impact on OS is challenged.[1] These

obstacles to the use of OS as a primary end point motivate the search for a surrogate end point.

The Biomarker Definitions Working Group defines a surrogate end point as "a biomarker that is intended to substitute for a clinical end point, and is expected to predict clinical benefit or harm (or lack of benefit or harm) based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence."[2] Formal validation at both the patient and trial level is required.[3,4] In advanced colorectal cancer (CRC), tumor response, progression-free survival (PFS), and time-to-progression have each been evaluated as potential surrogates for OS.[5,6] In these analyses, response rate has consistently been demonstrated to be an unreliable surrogate for OS.[3,5] Conversely, PFS has been demonstrated to achieve strong surrogacy for OS in advanced CRC in trials published before 1999.[5,6]

Treatments with new mechanisms of action, advances in patient care, and the evolution of clinical trial conduct could place a previously validated surrogate end point in question. One of the main goals of the independent academic collaboration of the Analysis and Research in Cancers of the Digestive System (ARCAD) group was to evaluate the surrogacy of PFS for OS on the basis of newer first-line studies conducted from 1997 to 2006 and evaluate the impact of the shift from nonbiologic to biologic treatment agents.

METHODS

Trial Selection and Comparison Definition

As of June 2013, a total of 24 studies[7-30] that met the inclusion criteria (randomized first-line trials in metastatic CRC [mCRC]) were included in the ARCAD database, with 11 studies[8,10,12,15,18,20,21,24,25,27,28] that tested multiple experimental regimens. Five studies[14,15,17-19] evaluated anti–epidermal growth factor receptor agents with *KRAS* status available for four of them. Because *KRAS* is a predictive biomarker in CRC,[31-33] patients with *KRAS* wild-type and mutant tumors were considered as separate cohorts for testing treatment effects of anti–epidermal growth factor receptor agents. In six studies,[13,16,20,26,29,30] additional treatment beyond the first per-protocol regimen (ie, different treatment sequences or crossover after progressive disease [PD]) were prespecified in the protocol. Because the first documented PD defines the PFS end point, comparisons in which two treatment arms started with the same regimen before first PD were not suitable for surrogacy evaluation and were excluded.

On the basis of these considerations, the meta-analytic unit for surrogacy estimation was predefined as the comparison between two arms (experimental *v* control) nested within trials. Throughout the manuscript, we will use the terms "nontargeted" to indicate the comparisons that included only nonbiologic agents in both arms and "targeted" to indicate the comparisons that included biologic agents in at least one of the arms. A total of 22 studies (13 of which tested biologic agents) published from 2003 to 2012 with 43 specific treatment comparisons were included. Appendix Table A1 (online only) provides details regarding the comparison definitions and several key trial-level characteristics.

End Points Definition

The primary clinical end point (ie, true end point) of OS and the putative surrogate end point of PFS were calculated by using individual patient data consistently across trials. OS was defined as time from the date of random assignment to death as a result of any cause. When death was not observed, OS was censored at the later of the last disease assessment or last contact date.

Among 22 studies, nine, eight, and five supplied progression only, calculated PFS only, or both raw progression and calculated PFS, respectively. Seven of 13 studies that supplied calculated PFS data stated in the primary manuscript or in supplemental documentation (eg, statistical analysis plan) specific censoring rules for calculating PFS. These definitions varied by study. Detailed censoring rules were not available for the other six studies. Because additional data (eg, curative surgery dates) were not available for most studies, we adopted the following definitions to ensure consistency in calculating PFS across studies. The PFS end point is defined as the time from random assignment to the date of first documented PD or death as a result of any cause, whichever occurred first. When a patient was alive and without progression, PFS was censored at the date of the last disease assessment. When a patient was recorded to have died without documented progression, PFS was considered as an event occurring on the death date. In addition, we defined PFS with an alternative censoring rule to examine the robustness of the surrogacy estimation. In that sensitivity analysis, PFS was coded as censored on the date of last disease assessment if the time between that assessment and death date was greater than 6 months. All 22 studies had primary PFS and 13 studies had PFS sensitivity data available.

General Statistical Methods

The distributions of PFS and OS were estimated by using the Kaplan-Meier method. The effect of treatment (and 95% CIs) for PFS and OS was quantified through hazard ratios (HRs: HR_{PFS} and HR_{OS}) estimated by the Cox proportional hazard model[34] or Copula bivariate survival model.[35]

Surrogacy Evaluation

The validity of PFS as a surrogate for OS was assessed at both the patient and trial levels. At the patient level, the prognostic value of PFS status at 6 months and at 1 year was assessed by the Cox model (stratified by unique treatment arms nested within trials) by using a landmark approach. The rank correlation coefficient ρ between PFS and OS was estimated through a bivariate Copula distribution of the two end points over the entire time range.[35] ρ values approaching 1 indicate a strong correlation between PFS and OS at the patient level.

Within each treatment arm, the short-term PFS rates (at 6 months) and long-term OS rates (at 12 and 18 months, based on proximity to median time points) were estimated from Kaplan-Meier curves. The correlation between PFS and OS rates at these time points was assessed by the weighted least squares coefficient of determination (r^2_{WLS}) through a weighted linear regression model, with weights equal to study arm sample size. Values of r^2_{WLS} close to 1 indicate a strong correlation between the two end points at the treatment arm level.

At the trial level, HR_{PFS} and HR_{OS} were estimated through Cox models comparing the two treatments for each comparison. R^2_{WLS} was estimated on the basis of HR_{PFS} and HR_{OS} to determine the degree of correlation between the treatment effects on the two end points. Trial-level R^2 (R^2_{Copula})[35] was also estimated. Bootstrapping was used to estimate the 95% CIs of the R^2 surrogacy measures. The surrogate threshold effect,[36] the minimum treatment effect on PFS required to predict a nonzero treatment effect on OS in a future trial, was estimated on the basis of the linear regression model between treatment effects.

Leave-one-out cross validation (internal validation) was used to assess the prediction of HR_{OS} based on the estimated regression model at the trial level. External validation was performed by using two additional studies,[37-39] which became available to ARCAD after June 2013.

RESULTS

Patient Characteristics

A total of 16,762 patients were included with a median age of 62 years (range, 19 to 90 years), 61.5% were male, and 53.4% had Eastern Cooperative Oncology Group (ECOG) performance score (PS) of 0 at baseline. Patients were included according to the intention-to-treat principle whenever possible. Overall, age, sex, and ECOG PS were well balanced between experimental and control arms (Appendix Table A2, online only).

Table 1. Patient-Level Prognostic Value of PFS for OS

Variable	Landmark Analysis of PFS						Rank Correlation Coefficient	
	At 6 Months			At 12 Months				
	HR	95% CI	*P*	HR	95% CI	*P*	ρ	95% CI
Overall	3.87	3.72 to 4.03	< .0001	3.81	3.61 to 4.02	< .0001	0.514	0.505 to 0.523
Patients treated with nonbiologic agents only	3.51	3.34 to 3.69	< .0001	3.54	3.31 to 3.79	< .0001	0.472	0.458 to 0.486
Patients treated with biologic agents	4.67	4.36 to 5.00	< .0001	4.25	3.90 to 4.64	< .0001	0.549	0.537 to 0.561

Abbreviations: HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

Median follow-up time was 17.6 months among patients alive at the time of data cutoff. Two- and 3-year data were available for 77% and 71% of patients, respectively. In all, 7,323 patients (43.7%) received targeted agents in combination with chemotherapy.

Patient-Level Correlation Between PFS and OS

Overall, 5,565 and 11,613 patients had progressed or died at 6 and 12 months, respectively. Of those, 5,063 patients had died at 12 months and 9,240 patients had died at 24 months. The results of landmark analyses assessing the patient-level association between PFS at 6 and 12 months and OS are presented in Table 1. Overall, as expected, experiencing a PFS event before or at 6 months after random assignment is strongly associated with worse survival (HR, 3.87; 95% CI, 3.72 to 4.03; $P < .0001$). This correlation remains when PFS rate was evaluated at 12 months. Compared with patients who received nonbiologic agents, the difference in the long-term mortality risk between patients who had progressed and/or died and patients without PFS events at 6 months seems larger among patients who received biologic agents (HR of 4.67 for biologic agents *v* HR of 3.51 for nonbiologic agents). Adjusting for age, sex, and ECOG PS, all associations remain highly significant. However, despite the strong prediction of long-term OS by early progression or death for individual patients, the magnitude of the patient-level correlation between the two end points considering the entire duration of follow-up was only moderate. The rank correlation coefficient ρ estimated by a bivariate survival distribution was 0.51 (95% CI, 0.50 to 0.52) overall, 0.47 (95% CI, 0.46 to 0.49) among nontargeted, and 0.55 (95% CI, 0.54 to 0.56) among targeted comparisons (Table 1).

Treatment Arm–Level Correlation Between PFS and OS

Figure 1A presents the association between treatment arm–specific PFS rates at an early time point (6 months) and the OS rate at later time points. The estimated r^2_{WLS} is listed in Table 2. Overall, the association at the treatment arm level is relatively strong (r^2_{WLS}, 0.69; 95% CI, 0.58 to 0.79) when year 1 survival rates are considered. The correlation decreases to moderate (r^2_{WLS}, 0.51; 95% CI, 0.35 to 0.67) at 18 months at which the median follow-up is reached. The correlation is slightly stronger among treatment arms with biologic agents (r^2_{WLS}, 0.70) than among arms without biologic agents (r^2_{WLS}, 0.59).

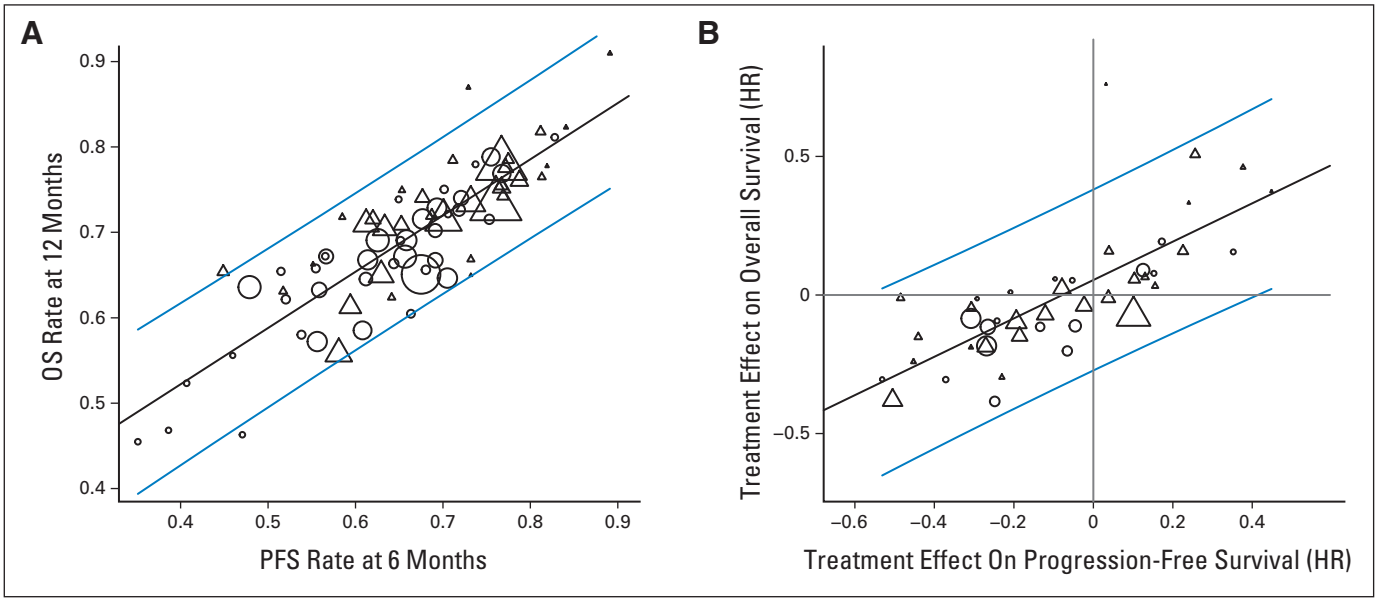

Fig 1. (A) Correlation between progression-free survival (PFS) at 6 months and overall survival (OS) at 12 months at the treatment arm level. (B) Correlation between treatment effects on PFS and OS. (A, B) Circles indicate treatment arm with nonbiologic agents only; triangles indicate treatment arm with biologic agents; blue lines indicate 95% prediction limits. (B) Log scale was used for x- and y-axes. Horizontal line corresponds to the hazard ratio (HR) for OS of 1. The vertical line corresponds to the HR for PFS of 1.

Table 2. Treatment Arm–Level Correlation Between PFS and OS

Variable	PFS6 *v* OS12		PFS6 *v* OS18	
	r^2_{WLS}	95% CI	r^2_{WLS}	95% CI
Overall	0.685	0.576 to 0.794	0.511	0.349 to 0.672
Patients treated with nonbiologic agents only	0.589	0.393 to 0.786	0.409	0.169 to 0.650
Patients treated with biologic agents	0.695	0.478 to 0.912	0.419	0.111 to 0.727

Abbreviations: OS, overall survival; OS12, OS rate at 12 months after random assignment; OS18, OS rate at 18 months after random assignment; PFS, progression-free survival; PFS6, PFS rate at 6 months after random assignment; WLS, weighted least squares.

Trial-Level Correlation Between PFS and OS

Figure 1B and Table 3 summarize the correlation between treatment effects on PFS and OS at the trial level. The results are consistent with the treatment arm–level correlation, with surrogacy overall in the moderate range (R^2_{WLS}, 0.54; 95% CI, 0.33 to 0.75; R^2_{Copula}, 0.46; 95% CI, 0.24 to 0.68). By using the R^2_{Copula} measure, the association was greater among comparisons involving targeted agents (R^2_{Copula}, 0.45; 95% CI, 0.16 to 0.75) than comparisons involving nontargeted agents (R^2_{Copula}, 0.35; 95% CI, 0.0 to 0.71). However, R^2_{WLS} demonstrated a slightly higher surrogacy (R^2_{WLS}, 0.59; 95% CI, 0.32 to 0.87) among nontargeted compared with targeted comparisons (R^2_{WLS}, 0.52; 95% CI, 0.24 to 0.80). Overall, 20 treatment comparisons demonstrated that the experimental treatment was significantly different from the control treatment based on PFS, whereas only eight comparisons were significant for OS.

Internal and External Validation

Leave-one-out cross-validation results showed large differences between observed and predicted OS treatment effects based on PFS treatment effects, reflecting the moderate trial-level correlation(Fig 2). Table 4 compares the predicted HRs for OS by using the regression models based on all studies and studies testing targeted regimens only, with the actual observed HRs for OS for the two validation studies.[37,39] Because the observed correlation between treatment effects on PFS and OS was only moderate, the prediction intervals are much wider than the observed CIs. The surrogate threshold effect (Table 3) indicates that an HR of at most 0.57 (or at least 1.75) would need to be ascertained in a future trial to predict a nonzero treatment effect on OS.

Sensitivity Analyses

Table 3 also presents the trial-level surrogacy assessments when excluding comparisons that compared treatment strategies and comparisons designed as noninferiority tests. The magnitude of the various surrogacy measures remains in the moderate range. Some additional sensitivity analyses excluded one outlier by using PFS as originally calculated by the original study and by using the sensitivity PFS definition as defined in the "Methods" section. The trial-level surrogacy estimates based on these analyses were consistent with the primary analyses.

DISCUSSION

The choice of a primary end point is one of the most vexing challenges facing the design of clinical trials in oncology. In the setting of metastatic disease, several authors have proposed that OS remains the preferred choice because of its unambiguous interpretation, ease of measurement, and ultimate importance.[40,41] However, the use of this end point comes at a high cost in terms of required trial duration, sample size, and financial cost, which when taken as a whole, ultimately has the potential to slow the introduction of beneficial therapies to patients. Thus, the search continues for validated surrogate end points that would allow for reliable prediction of the impact of OS on treatment based on an early end point.

Previous analyses, primarily using mCRC trials conducted before 2000, concluded that there is a strong surrogate relationship between PFS and OS.[6] This conclusion was well accepted because it was consistent with the treatment and course of the disease at that time—specifically, there were few effective regimens, and survival after initial progression was short. It also critically provided a biologic proof of principle that delaying progression predicts ultimate patient benefit. In current practice and in most modern trials, however, median survival now exceeds 2 years, and there are multiple effective agents not only as initial treatment but also in second-line and later-line settings. Given that any validation of a surrogate end point is relevant only within the context in which the validation occurred, these factors prompted a re-examination of the association between PFS and OS in more recent trials.

Our analysis demonstrates consistently, on the basis of all measures considered, an existent but reduced relationship between PFS and OS in this large set of recent first-line mCRC trials. This was true for trials that tested treatments with and without biologic agents. The modest surrogacy was also demonstrated in the sensitivity analyses when excluding noninferiority and strategy trials, respectively. In

Table 3. Trial-Level Correlations Between Treatment Effects on PFS and OS

Variable	r^2_{WLS}	95% CI	r^2_{Copula}	95% CI	No. of Significant Results (PFS *v* OS)	STE
Overall	0.536	0.328 to 0.745	0.461	0.240 to 0.683	20 *v* 8	0.571
Nontargeted comparison	0.594	0.315 to 0.874	0.348	0.0 to 0.714	8 *v* 5	0.590
Targeted comparison	0.521	0.241 to 0.801	0.453	0.159 to 0.748	12 *v* 3	0.484
Without strategy comparisons	0.538	0.315 to 0.761	0.477	0.244 to 0.709	17 *v* 7	0.571
Without noninferiority design comparisons	0.505	0.241 to 0.770	0.542	0.305 to 0.780	18 *v* 8	0.587

NOTE. Nontargeted comparison indicates that there were only nonbiologic agents in both treatment arms; targeted comparison indicates that there were biologic agents in at least one of the treatment arms.
Abbreviations: OS, overall survival; PFS, progression-free survival; STE, surrogacy threshold effect; WLS, weighted least squares.

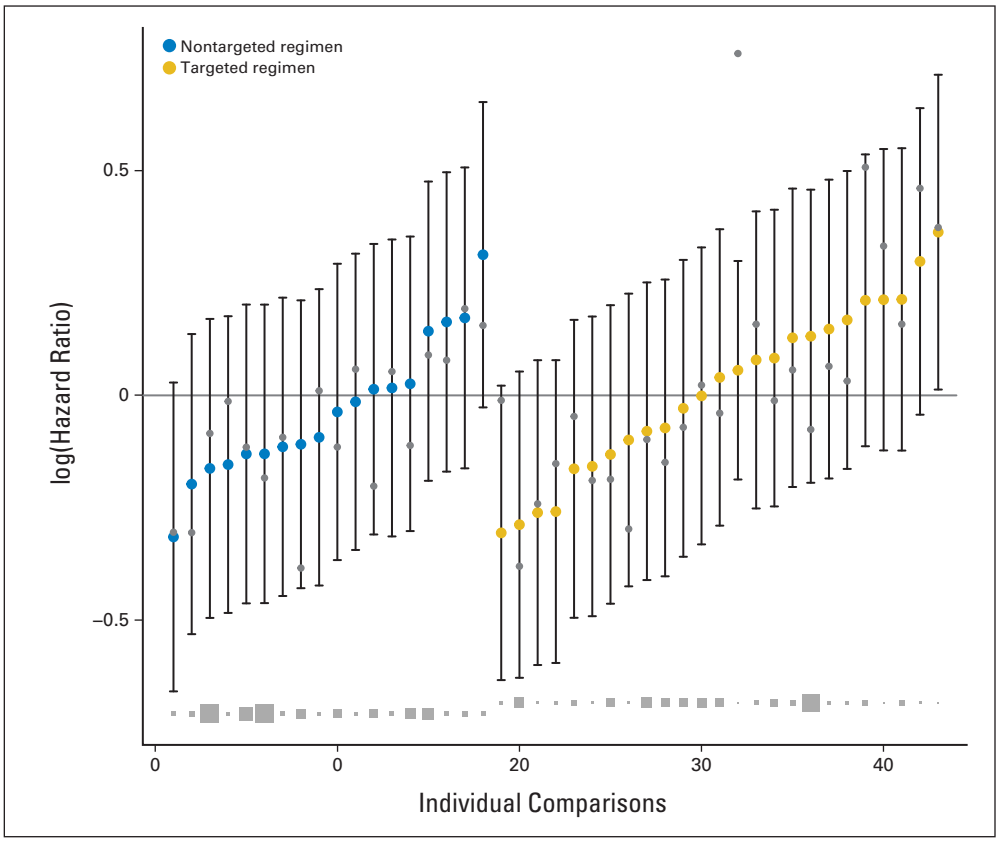

Fig 2. The gray dots are the actual observed overall survival hazard ratios. The colored dots are predicted overall survival hazard ratios based on the fitted regression line. The gray bars are the 95% prediction limits. The plots were grouped by nontargeted (blue circle) and targeted (gold circle) comparisons. The sizes of gray boxes at the bottom of the figure are proportional to the sample size of each of the comparisons.

most of the studies included, more than 50% of patients received subsequent treatment (with or without biologic agents), which likely contributes to the long postprogression survival and diminishes the possibility of formal surrogacy. Median postprogression survival was longer than median first-line PFS (8.3 months) for patients who initially received biologic agents (9.9 months) and for those who did not (9.7 months). Our findings of reduced association of PFS and OS in more recent trials are consistent with the simulations of Broglio and Berry,[1] who showed that even with perfect concordance of true treatment effects between PFS and OS, as median survival postprogression increases, the reliability of the association between PFS and OS within any individual trial diminishes. Clearly, a relationship between the end points does exist. However, the prediction precision (ie, surrogacy) is reduced compared with the prior results based on trials with limited subsequent treatment after first progression. Consequently, on the basis of the surrogate threshold analysis, only large PFS treatment effects (HRs < 0.57) can reliably be expected to translate into OS advantages. Our findings are appropriately considered only within the context we investigated—first-line mCRC; analyses in later-line studies are ongoing.

Table 4. Validation in Two Additional Studies: Observed and Predicted Treatment Effect on OS Based on the Observed Treatment Effect on PFS

						Model Using Data From All Studies*		Model Using Data From Trials With Targeted Regimens Only†	
Validation Trial	Reference	Observed HR_{PFS}‡	95% CI	Observed HR_{OS}‡	95% CI	Predicted HR_{OS}	95% CI	Predicted HR_{OS}	95% CI
CRYSTAL	Van Cutsem et al[37,38]	0.85	0.73 to 1.00	0.88	0.77 to 1.00	0.95	0.53 to 1.37	0.97	0.44 to 1.51
KRAS wild type		0.70	0.56 to 0.87	0.80	0.67 to 0.95	0.83	0.41 to 1.26	0.85	0.30 to 1.39
KRAS mutant		1.17	0.89 to 1.54	1.04	0.83 to 1.28	1.20	0.77 to 1.62	1.24	0.70 to 1.78
OPUS	Bokemeyer et al[39]	0.93	0.71 to 1.23	1.02	0.79 to 1.30	1.01	0.59 to 1.43	1.04	0.50 to 1.58
KRAS wild type		0.57	0.38 to 0.86	0.86	0.60 to 1.22	0.73	0.30 to 1.16	0.74	0.18 to 1.30
KRAS mutant		1.72	1.10 to 2.68	1.29	0.87 to 1.91	1.63	1.16 to 2.09	1.70	1.09 to 2.32

Abbreviations: CRYSTAL, Cetuximab Combined With Irinotecan in First-Line Therapy for Metastatic Colorectal Cancer; HR, hazard ratio; OPUS, Oxaliplatin and Cetuximab in First-Line Treatment of Metastatic Colorectal Cancer; OS, overall survival; PFS, progression-free survival.
*Regression model based on all studies: $0.2828 + 0.7799 \times$ treatment effect.
†Regression model only based on studies that included targeted regimens: $0.2595 + 0.8394 \times$ treatment effect.
‡HRs and CIs were taken from the publications.

Although OS remains a gold standard as a primary end point in oncology trials, it is not perfect in the present era. For example, when an experimental agent is compared with placebo, allowing patients who receive placebo and who subsequently progressed to cross over to active treatment benefits the patients on the study. However, this will reduce the apparent treatment effect differences between the two arms as measured by OS, even when the experimental agent actually has OS benefit. This phenomenon was illustrated by the following example. Both irinotecan and oxaliplatin were tested in the late 1990s in combination with fluorouracil-leucovorin. In the irinotecan trial, no crossover was allowed, and significant differences in both PFS and OS were observed, leading to approval by the US Food and Drug Administration.[42] The oxaliplatin trial allowed crossover as second-line treatment, with treatment efficacy demonstrated for PFS but not for OS,[43] and approval by the US Food and Drug Administration for oxaliplatin was not granted at the time. Later the efficacy of the identical oxaliplatin (plus fluorouracil-leucovorin) over irinotecan (plus fluorouracil-leucovorin) regimen used in those trials was established for both PFS and OS in a concurrent comparison of two the regimens.[27] In modern mCRC first-line trials, a variety of effective treatments are available for patients after progression on first-line therapy. Thus, whether OS measures the pure treatment effect of the first-line treatment is questionable. Insistence on using OS as an end point in this setting risks vastly longer studies, and more importantly, risks discarding an effective treatment whose impact on OS may be obscured by multiple subsequent treatments. It is our expectation that as biomarkers become available to identify specific biologically defined subgroups that may be sensitive to a targeted therapy, robust PFS and resultant OS benefits will be possible.

Our results highlight the continuous need to examine alternative end points. Ongoing ARCAD analyses include the examination of alternative definitions of progression, the use of continuous tumor measurements, and the examination of end point associations in additional subsets. Our analysis suggests that as progress continues in the treatment of mCRC, attaining a significant OS benefit from a single line of treatment will be increasingly challenging because of both increased noise (lengthy postprogression survival times with a greater chance for heterogeneous patient treatment) and decreased signal (ability for patients to obtain protocol treatment postprogression that would dilute the difference between randomly assigned treatment arms). Despite the reduced direct ability to predict OS results in modern trials, we feel that PFS remains an appropriate end point for first-line superiority trials in mCRC and that agents that demonstrate a robust PFS treatment effect with acceptable tolerability and lack of negative OS signal provide a clinically important advantage to patients in this setting. Meanwhile, the identification of more reliable, likely multifactor end points that may predict OS remain urgently needed.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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GLOSSARY TERMS

overall survival: the duration between random assignment and death.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Individual Patient Data Analysis of Progression-Free Survival Versus Overall Survival As a First-Line End Point for Metastatic Colorectal Cancer in Modern Randomized Trials: Findings From the Analysis and Research in Cancers of the Digestive System Database

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Table A1. Studies and Comparisons Included in the Analysis

Comparison	Study Acronym	Study Name	Year Accrual Started	Reference	Treatment Assignments at Randomization	No. of Patients	Regimen Type	Strategy*	Design†	Subsequent Treatments (%)‡
1	C97-3		1997	Tournigand et al[13]	C: FOLFIRI → FOLFOX6 E: FOLFOX6 → FOLFIRI	220	NT	Yes	NI	50 to 70
2	N9741		1999	Goldberg et al[27]	C: IFL E: FOLFOX	531	NT	No	Sup	> 70
3					C: IFL E: irinotecan + oxaliplatin	528	NT	No	Sup	50 to 70
4§					C: rIFL E: FOLFOX	304	NT	No	Sup	> 70
5§					C: rIFL E: irinotecan + oxaliplatin	269	NT	No	Sup	50 to 70
6	FOCUS		2000	Seymour et al[20]	C: fluorouracil → irinotecan E: fluorouracil + irinotecan	1058	NT	Yes	Sup	50 to 70
7					C: fluorouracil → irinotecan E: fluorouracil + oxaliplatin	1057	NT	Yes	Sup	50 to 70
8	AVF2192g		2000	Kabbinavar et al[11]	C: fluorouracil + leucovorin + placebo E: fluorouracil + leucovorin + bevacizumab	209	Anti-ANG	No	Sup	50 to 70
9	AVF2107g		2000	Hurwitz et al[10]	C: IFL + placebo E: IFL + bevacizumab	813	Anti-ANG	No	Sup	50 to 70
10§					C: IFL + placebo E: fluorouracil + leucovorin + bevacizumab	220	Anti-ANG	No	Sup	50 to 70
11	HORG		2000	Souglakos et al[23]	C: FOLFIRI E: FOLFOXIRI	283	NT	No	Sup	50 to 70
12	GONO		2001	Falcone et al[22]	C: FOLFIRI E: FOLFOXIRI	244	NT	No	Sup	> 70
13	03-TTD-01		2002	Díaz-Rubio et al[7]	C: fluorouracil + oxaliplatin E: capecitabine + oxaliplatin	348	NT	No	NI	50 to 70
14	AIO22		2002	Porschen et al[9]	C: capecitabine + oxaliplatin E: FUFOX	474	NT	No	NI	50 to 70
15	HORIZON II		2005	Hoff et al[24]	C: FOLFOX + capecitabine + oxaliplatin + placebo E: FOLFOX + capecitabine + oxaliplatin + cediranib 20 mg	860	Anti-ANG	No	Sup	50 to 70
16§					C: FOLFOX + capecitabine + oxaliplatin + placebo E: FOLFOX + capecitabine + oxaliplatin + cediranib 30 mg	432	Anti-ANG	No	Sup	50 to 70
17	CAIRO		2003	Koopman et al[16]	C: capecitabine → irinotecan → capecitabine + oxaliplatin E: capecitabine + irinotecan → capecitabine + oxaliplatin	803	NT	Yes	Sup	50 to 70
18	BICC-C		2003	Fuchs et al[12]	C: FOLFIRI E: mIFL	285	NT	No	NI	> 70
19					C: FOLFIRI + bevacizumab E: mIFL + bevacizumab	117	Anti-ANG	No	NI	50 to 70
20					C: FOLFIRI E: capecitabine + irinotecan	289	NT	No	NI	> 70
21	FOCUS2		2004	Seymour et al[21]	C: fluorouracil + leucovorin E: fluorouracil + leucovorin + oxaliplatin	230	NT	No	Sup	< 50
22					C: capecitabine E: capecitabine + oxaliplatin	229	NT	No	Sup	< 50
23§	NO16966		2003	Saltz et al[28]	C: FOLFOX4 E: capecitabine + oxaliplatin	634	NT	No	NI	50 to 70
24					C: FOLFOX4 + placebo E: capecitabine + oxaliplatin + placebo	701	NT	No	NI	50 to 70 -

(continued on following page)

Table A1. Studies and Comparisons Included in the Analysis (continued)

Comparison	Study Acronym	Study Name	Year Accrual Started	Reference	Treatment Assignments at Randomization	No. of Patients	Regimen Type	Strategy*	Design†	Subsequent Treatments (%)‡
25					C: FOLFOX4 + bevacizumab E: capecitabine + oxaliplatin + bevacizumab	699	Anti-ANG	No	NI	< 50
26					C: capecitabine + oxaliplatin + placebo E: capecitabine + oxaliplatin + bevacizumab	700	Anti-ANG	No	Sup	50 to 70
27					C: FOLFOX4 + placebo E: FOLFOX4 + bevacizumab	700	Anti-ANG	No	Sup	50 to 70
28	AIO KRK-0104		2004	Moosmann et al[19]	C: cetuximab + capecitabine + irinotecan E: cetuximab + capecitabine + oxaliplatin	177	Anti-EGFR	No	NI	> 70
29	PACCE		2005	Hecht et al[15]	C: bevacizumab + oxaliplatin (*KRAS* WT) E: bevacizumab + oxaliplatin + panitumumab (*KRAS* WT)	408	Anti-ANG + Anti-EGFR	No	Sup	NR
30					C: bevacizumab + oxaliplatin (*KRAS* MT) E: bevacizumab + oxaliplatin + panitumumab (*KRAS* MT)	262	Anti-ANG + Anti-EGFR	No	Sup	NR
31					C: bevacizumab + irinotecan (*KRAS* WT) E: bevacizumab + irinotecan + panitumumab (*KRAS* WT)	116	Anti-ANG + Anti-EGFR	No	Sup	NR
32					C: bevacizumab + irinotecan (*KRAS* MT) E: bevacizumab + irinotecan + panitumumab (*KRAS* MT)	89	Anti-ANG + Anti-EGFR	No	Sup	NR
33	COIN		2005	Maughan et al[18]	C: fluorouracil + leucovorin + capecitabine + oxaliplatin (*KRAS* WT) E: fluorouracil + leucovorin-capecitabine + oxaliplatin + cetuximab (*KRAS* WT)	729	Anti-EGFR	No	Sup	50 to 70
34					C: fluorouracil + leucovorin + capecitabine + oxaliplatin (*KRAS* MT) E: fluorouracil + leucovorin-capecitabine + oxaliplatin + cetuximab (*KRAS* MT)	565	Anti-EGFR	No	Sup	50 to 70
35	CAIRO		2005	Tol et al[17]	C: capecitabine + oxaliplatin + bevacizumab (*KRAS* WT) E: capecitabine + oxaliplatin + bevacizumab + cetuximab (*KRAS* WT)	316	Anti-ANG + Anti-EGFR	No	Sup	< 50
36					C: capecitabine + oxaliplatin + bevacizumab (*KRAS* MT) E: capecitabine + oxaliplatin + bevacizumab + cetuximab (*KRAS* MT)	204	Anti-ANG + Anti-EGFR	No	Sup	< 50
37	MAX		2005	Tebbutt et al[8]	C: capecitabine E: capecitabine + bevacizumab	313	Anti-ANG	No	Sup	50 to 70
38					C: capecitabine E: capecitabine + bevacizumab + mitomycin	314	Anti-ANG	No	Sup	50 to 70
39	Macro		2006	Díaz-Rubio et al[26]	C: capecitabine + oxaliplatin + bevacizumab → capecitabine + oxaliplatin + bevacizumab E: capecitabine + oxaliplatin + bevacizumab → bevacizumab	480	Anti-ANG	Yes	NI	> 70
40	PRIME		2006	Douillard et al[14]	C: FOLFOX4 (*KRAS* WT) E: FOLFOX4 + panitumumab (*KRAS* WT)	656	Anti-EGFR	No	Sup	< 50
41					C: FOLFOX4 (*KRAS* MT) E: FOLFOX4 + panitumumab (*KRAS* MT)	440	Anti-EGFR	No	Sup	< 50
42	HORIZON III		2006	Schmoll et al[25]	C: mFOLFOX6 + bevacizumab E: mFOLFOX6 + cediranib 20 mg	1409	Anti-ANG	No	Sup	< 50
43§					C: mFOLFOX6 + bevacizumab E: mFOLFOX6 + cediranib 30 mg	380	Anti-ANG	No	Sup	< 50

Abbreviations: AIO, Arbeitsgemeinschaft Internistische Onkologie; Anti-ANG, antiangiogenic regimen; Anti-EGFR, anti[en]epidermal growth factor receptor regimen; C, control arm; CAIRO, Capecitabine, Irinotecan, Oxaliplatin; COIN, Continuous or Intermittent; E, experimental arm; FOCUS, Fluorouracil, Oxaliplatin, and CPT11 [irinotecan][em]Use and Sequencing; FOLFIRI, fluorouracil, leucovorin, irinotecan; FOLFOX, infusional fluorouracil, leucovorin, oxaliplatin; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; FOLFOXIRI, folinic acid, fluorouracil, oxaliplatin, and irinotecan; FUFOX, infusional fluorouracil, folinic acid (leucovorin), oxaliplatin; GONO, Gruppo Oncologico Nord Ovest; HORG, Hellenic Oncology Research Group; HORIZON, First-Line Metastatic Colorectal Cancer Therapy in Combination With FOLFOX; IFL, irinotecan and bolus fluorouracil plus leucovorin; MAX, Mitomycin, Avastin, Xeloda; mIFL, modified irinotecan and bolus fluorouracil plus leucovorin; MT, mutated; NI, noninferiority; NR, not reported; NT, nontargeted; PACCE, Panitumumab Advanced Colorectal Cancer Evaluation; PRIME, Panitumumab Randomized Trial in Combination With Chemotherapy for Metastatic Colorectal Cancer to Determine Efficacy; rIFL, irinotecan and bolus fluorouracil plus leucovorin with reduced starting dose; Sup, superiority; WT, wild type.

*In a strategy trial, more treatment was specified by protocol beyond the first per-protocol regimen. For example, a sequence of treatment was specified per protocol (ie, the treatment effect of the whole strategy of the experimental arm was compared with the control arm), or crossover after progressive disease (PD) was specified per protocol. For these studies, the progression-free survival with the first PD occurred during study follow-up; that is, one of the events may not be the appropriate end point if the regimen before the first PD was the same for both the experimental and control arms.

†The design refers to the intended primary comparison between arms (ie, noninferiority or superiority comparison). The statistical sample size and power consideration section may not reflect noninferiority or superiority design.

‡The percentage of patients receiving subsequent treatment was based on numbers reported in the publications.

§There are the cohorts that were not reported in the original main efficacy publications.

Appendix Table A2. Patient Characteristics

Characteristic	Control Arm (n = 7,701) No.	%	Experimental Arm (n = 9,061) No.	%	Total (N = 16,762) No.	%	*P*
Age (continuous), years							.7966*
No. of patients	7,696		9,055		16,751		
Median	62		62		62		
Range	19-90		18-89		18-90		
Age, years (categorical)							.3989†
Missing	5		6		11		
< 50	1,075	14.0	1,264	14.0	2,339	14.0	
50-59	2,029	26.4	2,332	25.8	4,361	26.0	
60-69	2,665	34.6	3,246	35.8	5,911	35.3	
> 70	1,927	25.0	2,213	24.4	4,140	24.7	
Sex							.6191†
Female	2,984	38.7	3,477	38.4	6,461	38.5	
Male	4,717	61.3	5,584	61.6	10,301	61.5	
ECOG PS							.2413†
Missing	100		140		240		
0	4,010	52.8	4,807	53.9	8,817	53.4	
1	3,216	42.3	3,733	41.8	6,949	42.1	
2	372	4.9	379	4.2	751	4.5	
3	2	0.0	1	0.0	3	0.0	
4	1	0.0	1	0.0	2	0.0	
Targeted regimen							< .0001†
Without	5,569	72.3	3,870	42.7	9,439	56.3	
With	2,132	27.7	5,191	57.3	7,323	43.7	

Abbreviation: ECOG PS, Eastern Cooperative Oncology Group performance score.
*Unequal variance two-sample *t* test.
†χ^2 test.