

ORIGINAL RESEARCH

Correlation between treatment effects on response rate and progression-free survival and overall survival in trials of targeted therapies in molecularly enriched populations

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Background: The number of randomized trials of agents targeting oncogene-addicted tumors has surged in the past 10 years. Using a meta-analysis, we explored whether improvements in objective response rate (ORR) in comparative trials using targeted agents could serve as a potential surrogate endpoint for improvements in progression-free survival (PFS) or overall survival (OS) in populations with oncogene-addicted cancer.

Patients and methods: Using commercial text mining software I2E, we searched [ClinicalTrials.gov](https://clinicaltrials.gov) and MEDLINE databases for randomized, phase III trials based on prospectively defined criteria, including (i) use of agents targeting EGFR activating mutations, ALK rearrangements, BRAF V600E or V600K mutations, and BCR-ABL fusion protein; (ii) molecularly enriched trial population or subpopulation; (iii) control arm only randomized to chemo/cytotoxic therapy. Correlative analyses were performed using ORR, OS, and PFS data from trials that met these criteria.

Results: A total of 62 trials were identified; 15 met all of the prespecified criteria. The ORR effect size (both the difference in ORR between arms and the log odds ratio) and log PFS hazard ratio were strongly correlated: -0.78 ($P = 0.0007$) for the ORR difference model; -0.74 ($P = 0.0017$) for the log odds ratio model. ORR effect size was positively correlated with the log OS hazard ratio, but more weakly: -0.67 ($P = 0.013$) for the ORR difference model and -0.58 ($P = 0.036$) for the log odds ratio model. Analysis of the treatment effects between OS and PFS found no correlation.

Conclusions: These analyses identified a strong correlation between treatment effects on ORR and PFS in randomized clinical trials investigating agents targeting oncogene-driven cancers. A weaker correlation was observed between ORR and OS. These meta-analysis results support the use of a high ORR forming the basis of an initial regulatory approval in biomarker-driven studies.

Key words: meta-analysis, targeted therapy, correlation, objective response rate, progression-free survival, overall survival

INTRODUCTION

Over the past two decades, advances in drug development and sequencing technologies have greatly expanded the field of genomically driven personalized medicine. Large-scale cancer genomic research efforts have enabled the systematic identification of a growing number of genomic alterations directly involved in cancer growth and

proliferation. Oncology research efforts have reflected the growing interest in personalized medicine, driven by the robust clinical outcomes observed with selectively targeted therapies when compared with nonselective treatment options such as chemotherapy.¹⁻⁶

Regular regulatory approval can be granted based on clinically meaningful improvement in patient symptoms, function, or progression-free survival (PFS) in a randomized, controlled phase III study. However, overall survival (OS) continues to be the regulatory gold standard as it is the most widely accepted efficacy endpoint for comparative studies and the one least affected by researcher bias. As the interpretability of OS may be confounded by multiple factors such as postprogression follow-up, treatment

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crossover, and subsequent therapies, the use of PFS has been adopted as a valid and clinically meaningful primary endpoint in late-phase cancer research. More recently, trials testing targeted therapeutic agents have been utilizing objective response rate (ORR) as the primary trial endpoint in single-arm studies. A high ORR, as a surrogate endpoint in oncology, is thought to reasonably predict treatment-related clinical benefit since spontaneous tumor regression is extremely rare in the absence of a therapeutic intervention.⁷

The validity of using clinical response rates as a surrogate endpoint for PFS or OS was previously explored through a meta-analysis of 14 advanced non-small-cell lung cancer (NSCLC) clinical trials, 3 of which focused on targeted therapy.⁷ The analyses presented herein build on this work by focusing exclusively on trials of targeted agents. Specifically, we perform a meta-analysis of comparative trials using targeted agents to examine whether improvements in ORR could serve as a surrogate endpoint for improvements in PFS or OS in populations with oncogene addicted cancers.

METHODS

Selection criteria

Using the commercial text mining software I2E (Linguamatics), the clinicaltrials.gov and MEDLINE databases were searched for randomized, phase III clinical trials that were investigating targeted therapy. Search terms included terms derived from these key criteria: (i) the trial tested an agent targeting EGFR activating mutations, ALK rearrangements, BRAF V600E or V600K mutations, or BCR-ABL fusion protein; (ii) the trial population (or a ≥ 20 patient subgroup of the population) was molecularly enriched; (iii) the control arm(s) did not include targeted agents directed toward the molecularly enriched population; (iv) the study was a randomized phase III trial reporting ORR and PFS; and (v) trial results were published from 2000 to present in English.

Outcome measures

ORR was defined as the proportion of patients who exhibited a complete or partial response as defined by the response criteria used in the study. All studies included in this meta-analysis used RECIST version 1.1, except one study that used RECIST⁸ and one study for which formal response criteria were not listed.⁹ PFS was defined as the time from random assignment to progression or death from any cause. Patients who had not progressed at data cut-off were censored at the date of the final disease assessment. All trials used PFS as the primary efficacy outcome except one study that used OS.¹⁰ OS was defined as the period from randomization to death from any cause. Patients who were alive on the day of data cut-off were censored at the last day of follow-up. All analyses used the intent-to-treat population.

Statistical analyses

ORR, OS, and PFS data were manually extracted from the [ClinicalTrials.gov](https://clinicaltrials.gov) site for each trial meeting the criteria. Data absent from the [ClinicalTrials.gov](https://clinicaltrials.gov) site were obtained from the associated reference. Weighted linear regression models were used to investigate the association between treatment effects on ORR, PFS, and OS. Weighted Pearson correlation analyses (with associated *P* values) were performed under logarithmic transformation (except for the ORR difference), with weights equal to the precision (back-solved from reported 95% confidence intervals) associated with the log PFS hazard ratios (for the ORR/PFS analyses) and the log OS hazard ratios (for the ORR/OS and PFS/OS analyses). Logistic regression models were used to derive ORR odds ratios where not directly reported in the source reference. Hazard ratios estimated from Cox proportional hazards regression models were used to express the treatment effects on PFS and OS. An odds ratio of >1 (experimental versus control) and a hazard ratio of <1 (experimental versus control) signified the experimental group resulted in a favorable result over the control group.

RESULTS

A schematic of the search strategy is shown in [Figure 1](#). Database mining initially identified 61 publications meeting the search criteria. Thirteen publications were removed as duplicate reports of the same trial; thus 48 unique trials were reviewed. Further review excluded 17 publications because the trial included the targeted therapy in both treatment arms. An additional two trials were removed because the therapies were ineligible. Of the remaining 29 trials, after review of the study results as reported in [ClinicalTrials.gov](https://clinicaltrials.gov) or the primary manuscript, 13 additional trials were excluded due to missing ORR or PFS results ($n = 3$) or an ineligible (unselected) population, that is, one that was not selected for the driver alteration of interest ($n = 10$). One other trial was excluded due to inadequate sample size. Fifteen trials met all of the inclusion criteria and were included in the meta-analysis.^{5-6,8-20}

Results from the 15 trials were published from 2003 to 2020. Data from each of the trials are summarized in [Table 1](#). Thirteen of the 15 trials tested a treatment of NSCLC; one each studied melanoma and chronic myeloid leukemia. Population size, treatment therapy, ORR, median PFS, median OS were extracted for each treatment arm, as well as the PFS hazard ratio and OS hazard ratio comparing the arms, where available. When subgroup results for the appropriate biomarker population (associated with the target of the experimental regimen) were available for studies that enrolled more broadly, the subgroup results were used in lieu of the intent-to-treat results.

Among the 15 trials, the ORR ranged from 0.015 to 0.555 (1.5%-55.5%) for the control arm and from 0.114 to 0.953 (11.4%-95.3%) for the experimental arm. The PFS hazard ratio ranged from 0.20 to 0.86. The relationship between ORR and PFS was studied by plotting the PFS hazard ratio (*y*-axis) against two common transformations of the ORR results: the

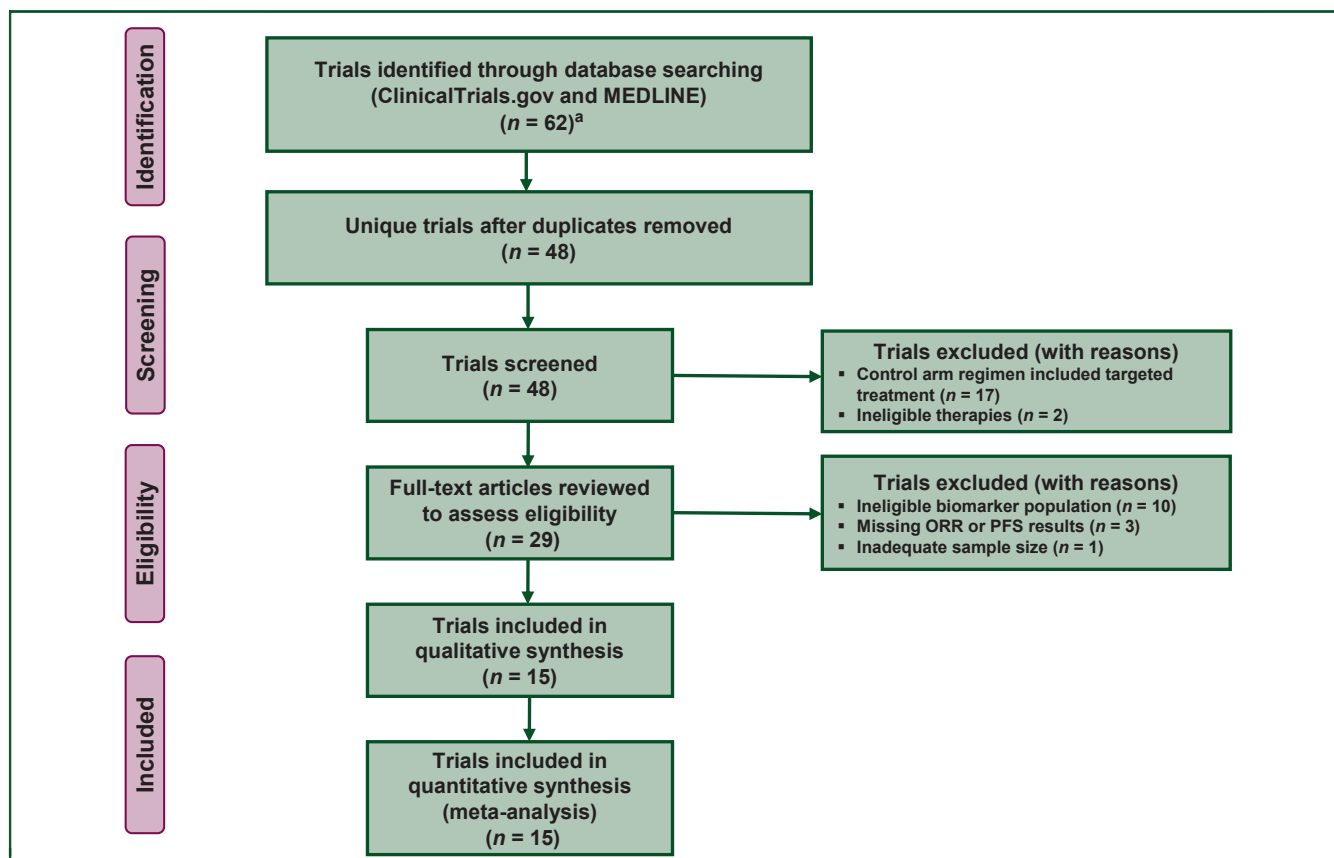


Figure 1. Flow chart detailing trial selection for meta-analysis.

The schematic details the steps taken to identify phase III clinical trials that met the predefined criteria to be included in the meta-analysis.

ORR, objective response rate; PFS, progression-free survival.

^aOne of the 62 trials (IRIS trial of imatinib) was not identified by the search criteria due to the use of hematologic response rather than objective (RECIST) response. This trial was added to the list of trials identified by the search. Later analysis found it to have little impact on numeric results or conclusions.

ORR effect size, that is, the difference between the ORR of the two treatment arms (Figure 2A) and the natural logarithm of the ORR odds ratio (Figure 2B). To reflect differences in sample size, the size of each circle was made proportional to the precision associated with the estimate of the log PFS hazard ratio. A strong linear relationship between ORR effect size and associated PFS effect size was apparent in the data. To quantify the strength of this relationship, linear regression models were fit, and weighted Pearson correlation coefficients calculated. The weighted Pearson correlation between the ORR difference and the log PFS hazard ratio was equal to -0.78 . Similarly, the weighted correlation between the log ORR odds ratio and the log PFS hazard ratio was -0.74 , demonstrating the robustness of the correlation. For both ORR transformations, the slope parameter in the linear regression was strongly statistically significant; the two-sided P value for the ORR difference model was 0.0007 and the corresponding P value for the ORR log odds ratio model was 0.0017 .

Thirteen of the 15 trials used for this meta-analysis also had published OS data. Median OS values (months) and the OS hazard ratio were recorded in Table 1 for each of the trials. To examine the relationship between the treatment effect on ORR and OS, the difference between the ORR of the two treatment arms was plotted against log OS hazard

ratio (Figure 3A). Like the corresponding PFS data, the resultant scatter plot showed a positive correlation. The weighted Pearson correlation was -0.67 , and the weighted linear regression P value was 0.013 . Likewise, log OS HR correlated with the ORR odds ratio (Figure 3B). The weighted Pearson correlation was -0.58 , and the weighted linear regression P value was 0.036 . It is important to note, however, that study 01 544 179¹⁸ (a second-line NSCLC trial which evaluated the addition of gefitinib to chemotherapy versus chemotherapy alone) carries high leverage within the correlative analyses of ORR/OS. Indeed, removal of this study (which appears in the upper-left corner of both Figure 3 plots) from the ORR/OS analyses results in a substantial decrease in the magnitude of correlation and a loss of statistical significance (weighted correlation between log OS HR and ORR difference is -0.37 , $P = 0.2355$; weighted correlation between log OS HR and log odds ratio is -0.07 , $P = 0.8247$). By contrast, removal of this study from the ORR/PFS analyses does not result in a loss of statistical significance for the correlative analyses of ORR/PFS significance (weighted correlation between log PFS HR and ORR difference is -0.58 , $P = 0.0292$; weighted correlation between log PFS HR and log odds ratio is -0.53 , $P = 0.0497$).

To explore the relationship between PFS and OS, a scatter plot was constructed of PFS HR versus OS HR displayed on

Table 1. Reported results of phase III trials included in the meta-analysis

Trial ID (NCT no.)	Experimental arm therapy	Control arm therapy	Cancer target	Oncogene target	Line of therapy	Experimental Arm				Control Arm				PFS HR	OS HR
						N	ORR	mPFS (months)	mOS (months)	N	ORR	mPFS (months)	mOS (months)		
00949650 ⁵	Afatinib	Pemetrexed/cisplatin	NSCLC	EGFR	1	230	0.565	11.17	28.16	115	0.226	6.90	28.22	0.576	0.880
01121393 ¹¹	Afatinib	Gemcitabine/cisplatin	NSCLC	EGFR	1	242	0.678	11.01	23.10	122	0.230	5.59	23.46	0.281	0.904
02604342 ¹²	Alectinib	Pemetrexed or docetaxel	NSCLC	ALK	3	79	0.506	10.9	27.8	40	0.025	1.4	NE	0.20	NE
01154140 ¹³	Crizotinib	Pemetrexed/platinum	NSCLC	ALK	1	172	0.744	10.9	NE	171	0.450	7.0	47.5	0.454	0.76
01639001 ¹⁴	Crizotinib	Pemetrexed/platinum	NSCLC	ALK	1	104	0.875	11.1	28.5	103	0.456	6.8	27.7	0.402	0.897
00932893 ⁶	Crizotinib	Pemetrexed or docetaxel	NSCLC	ALK	2	173	0.653	7.7	21.7	174	0.195	3.0	21.9	0.487	0.854
01227889 ¹⁵	Dabrafenib	Dacarbazine	Melanoma	BRAF	1	187	0.599	6.9	20.0	63	0.238	2.7	15.6	0.40	0.82
01000025 ^{3,10}	Dacomitinib	Placebo	NSCLC	EGFR	2-4	114	0.114	3.52	7.23	68	0.015	0.95	7.52	0.48	0.98
01342965 ¹⁶	Erlotinib	Gemcitabine/cisplatin	NSCLC	EGFR	1	110	0.627	11.0	26.3	107	0.336	5.5	25.5	0.34	0.91
00883779 ^{3,17}	Erlotinib/ gemcitabine/ platinum	Placebo/gemcitabine/ platinum	NSCLC	EGFR	1	49	0.84	16.8	30.3	48	0.15	6.9	20.6	0.25	0.72
00322452 ^{3,8}	Gefitinib	Carboplatin/paclitaxel	NSCLC	EGFR	1	132	0.712	NR	NR	129	0.473	NR	NR	0.48	0.78
01544179 ¹⁸	Gefitinib/ pemetrexed/ cisplatin	Placebo/pemetrexed/ cisplatin	NSCLC	EGFR	2	133	0.316	5.4	14.8	132	0.341	5.4	17.2	0.86	1.62
IRIS ^{6,9}	Imatinib	Interferon/cytarabine	CML	BCR-ABL	1	553	0.953	NR	NR	553	0.555	NR	NR	0.378	NR
02151981 ¹⁹	Osimertinib	Pemetrexed/platinum	NSCLC	EGFR T790M	2	279	0.706	10.1	26.8	140	0.314	4.4	22.5	0.30	0.87
02959749 ²⁰	Osimertinib	Docetaxel/bevacizumab	NSCLC	EGFR T790M	3	74	0.616	10.2	15.65	73	0.083	2.95	15.29	0.23	0.79

Note: Values are provided in this table as reported on [ClinicalTrials.gov](https://clinicaltrials.gov) or in the reference, with no rounding.

CML, chronic myeloid leukemia; HR, hazard ratio; ID, identification; mOS, median overall survival; mPFS, median progression-free survival; NCT, National Clinical Trial; NE, non-estimable; NR, not reported at the time of the analysis; NSCLC, non-small-cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

^aData derived from a trial subgroup.

^bNo NCT number.

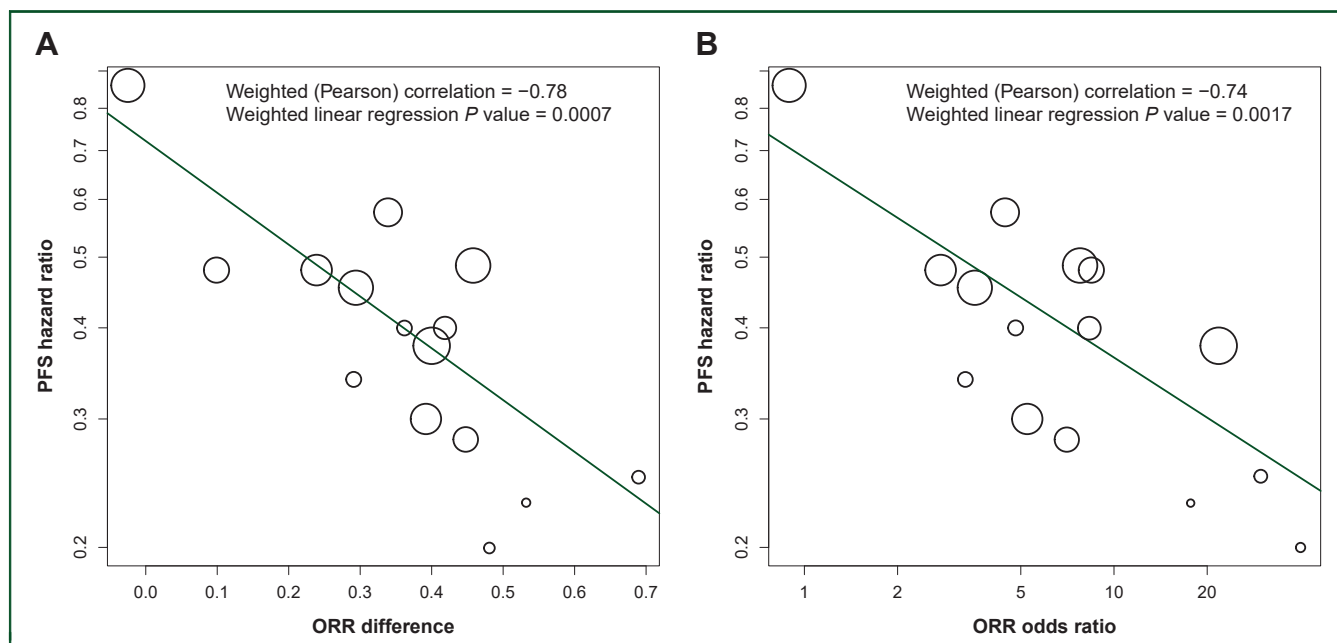


Figure 2. Scatter plot of the relationship of the PFS hazard ratio with ORR difference and ORR odds ratio. For each of 15 trials, (A) the difference of the ORR between the two treatment arms was plotted against the log of the PFS HR, and (B) the log of the ORR odds ratio was plotted against the log of the PFS HR. Each circle represents the ORR/PFS effect sizes for an individual clinical trial. For both plots, the relative size of each circle is based on the standard error associated with the reported hazard ratio. The weighted least squares regression lines (solid blue lines) are plotted in both panels. ORR, objective response rate; PFS, progression-free survival.

the log scale (Figure 4). The weighted Pearson correlation was 0.48 with a weighted linear regression *P* value of 0.095, indicating no statistically significant correlation between the two efficacy measures, although a possible trend in that direction.

DISCUSSION

The meta-analysis results presented here demonstrate a correlation between ORR and PFS effects in randomized clinical trials investigating the comparative efficacy between

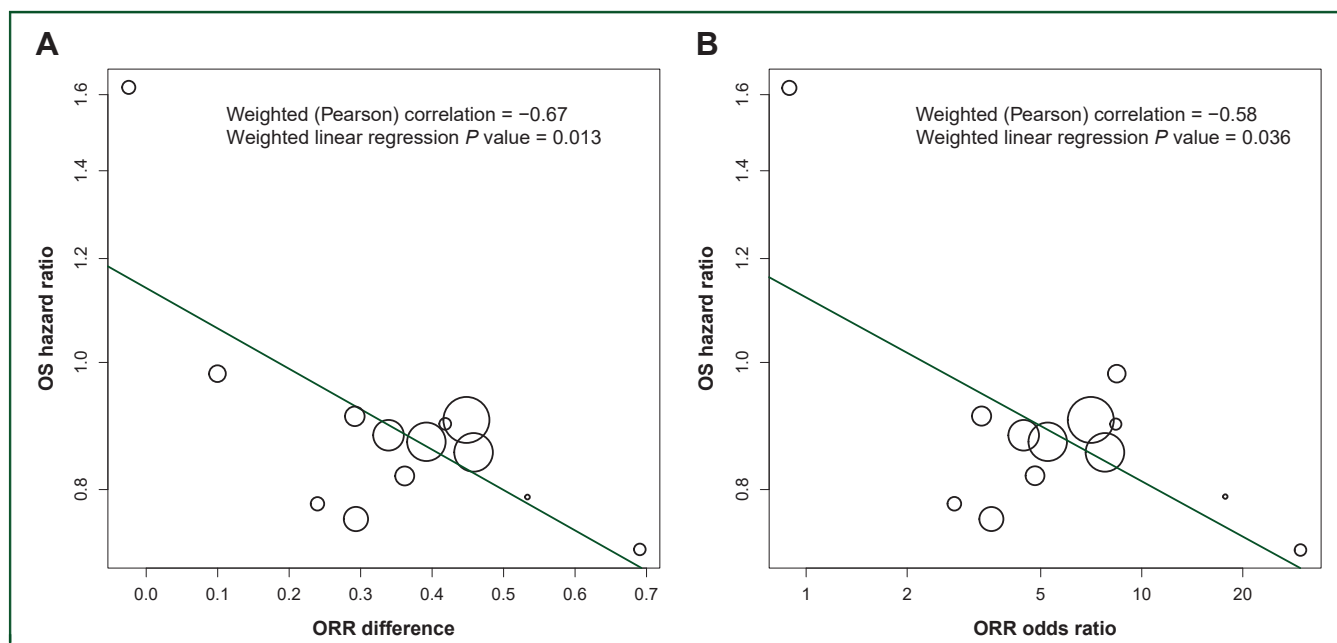


Figure 3. Scatter plot of the relationship of the OS hazard ratio with ORR difference and ORR odds ratio. For the 13 trials with OS data, (A) the difference of the ORR between the two treatment arms was plotted against the log of the OS hazard ratio, and (B) the log of the ORR odds ratio was plotted against the log of the OS hazard ratio. Each circle represents the ORR/OS effect sizes for an individual clinical trial. For both plots, the relative size of each circle is based on the precision associated with the reported PFS hazard ratio. The weighted least squares regression lines (solid blue lines) are plotted in both panels. ORR, objective response rate; OS, overall survival.

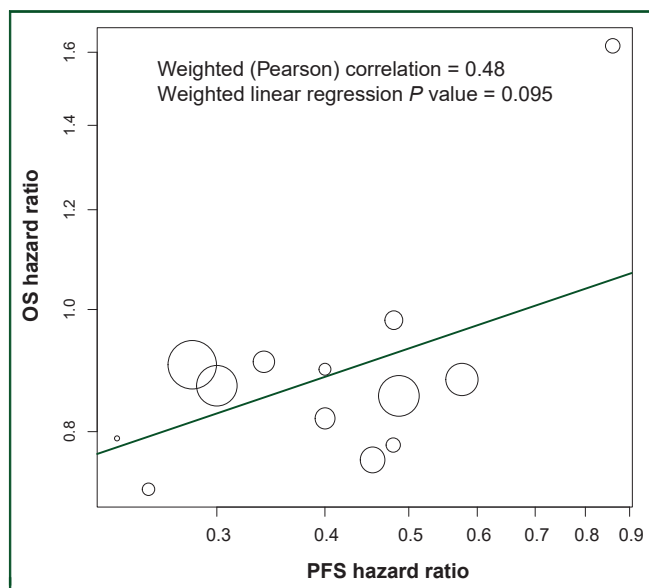


Figure 4. Scatter plot of the relationship of the PFS hazard ratio with OS hazard ratio.

The PFS hazard ratio was plotted against the OS hazard ratio for the 13 trials with both PFS and OS data. The relative size of each circle is based on the precision associated with the reported OS hazard ratios. The weighted least squares regression line (solid blue line) is shown.

OS, overall survival; PFS, progression-free survival.

targeted agents and nontargeted treatment options in molecularly enriched patient populations. The potential selection bias from including in the meta-analysis phase III studies that had already been deemed to be promising (typically based on high response rates in earlier trials) is not expected to be consequential in this setting: scenarios to which the results of this paper are applicable are cases of early-phase studies in which a strong ORR treatment effect is observed, or in which the ORR clearly exceeds a threshold expected under standard of care. Therefore the range of response rate outcomes that one would like to translate to a corresponding range of effects on PFS or OS is confined already to a set of promising outcomes. The linear relationship observed when the ORR effect size (either the difference between ORR of the two treatment arms or the ORR odds ratio) was plotted against the PFS hazard ratio indicates that the magnitude of the treatment effect on ORR was proportional to the treatment effect on PFS. These results may support the use of ORR as an initial efficacy endpoint in trials assessing targeted therapeutic agents. Moreover, a better understanding of the relationship between ORR and PFS could be informative in the planning and design of future trials in a molecularly enriched cancer patient setting by enabling prediction of a potential treatment effect size expected for PFS. For instance, this prediction could be based on an inferred ORR effect calculated as the difference between the response rate observed from an early-phase single-arm study and the putative response rate from an appropriate historical control cohort. Two key limitations of such an approach are (i) the typical challenges inherent in cross-trial comparisons, and (ii) the fact that the only available historical control data may be derived from

an unselected population, one not reflecting the genomic alteration of interest. In addition, the studies analyzed were not a systematically chosen set. For feasibility purposes, a select number of oncogenic driver-kinase inhibitor pairs were chosen based on substantial activity (high ORR and durable PFS), maturity of follow-up (e.g. drivers discovered earlier than others like ROS1/RET/NTRK were included here), and relative frequency (i.e. the 1% events like ROS1 were not included).

As a clinical trial endpoint, ORR directly measures the antitumor activity of the intervention, because spontaneous tumor regression is infrequent. The correlation of ORR with PFS, an established trial endpoint, is of interest because ORR can be assessed very rapidly. Targeted agents will typically achieve a tumor response in molecularly selected patients within 2-3 months because the treatment targets the driver of an oncogene-addicted cancer. For example, the LIBRETTO-001 trial that assessed efficacy of selpercatinib in patients with metastatic *RET* fusion-positive NSCLC recorded a median time to response of 1.8 months—timing that corresponded to the first radiological assessment at 8 weeks.²¹

Investigation of the correlation between ORR and OS effects also identified a positive association, but it was weaker and less robust to potential outlying observations. In addition, there was no significant association between treatment effects on OS and PFS, seemingly in accord with the weak ORR/OS association. Other reported analyses have also failed to observe a positive correlation between ORR and OS.^{7,22,23} For example, a meta-analysis of 14 trials (dated 2003-2013) of new treatments for NSCLC by Blumenthal and colleagues⁷ noted that the association between the ORR odds ratio and OS HR was weak ($R^2 = 0.09$, 95% CI 0-0.33).⁷ By contrast, there was a strong correlation between the ORR odds ratio and PFS HR in the same analysis: $R^2 = 0.89$ (95% CI 0.80-0.98). The authors reasoned that the lack of correlation between ORR and OS might be due to confounding factors such as treatment crossover following progression, number of subsequent therapies, long postprogression survival in the first-line setting, and noncancer deaths. Interestingly, the trials upon which our OS meta-analysis were based included 10 of 13 trials with a high degree of crossover (up to 85%) and 8 of 13 trials that tested front-line treatments. Perhaps because our analysis focused exclusively on targeted therapies tested in molecularly enriched populations with corresponding large effect sizes relative to the control, detection of a weak, but positive correlation between ORR and OS efficacy endpoints was possible despite the confounding factors.

The meta-analysis detailed here focused exclusively on assessing ORR (difference and odds ratio) as a surrogate endpoint for PFS and OS, based on randomized phase III trials investigating targeted agents in corresponding molecularly enriched populations. The evolution and phase III trial testing of targeted therapeutics led to our meta-analysis identifying 15 trials, of which 13 focused on lung cancer. A greater number of trials and ones representing a

wider range of cancer types would have provided a more robust analysis. However, we believe it is biologically plausible to extrapolate from these meta-analysis results to other trials investigating targeted agents and selected populations. In particular, ORR and PFS are both tumor-based endpoints, so it is reasonable to believe that the high ORR associated with successful targeted agents would be associated with protracted PFS. The meta-analysis by Blumenthal and colleagues led to a similar conclusion.⁷

As additional targeted agents are developed, a high ORR identified in an early-phase single-arm trial could form the basis of an initial regulatory approval, especially when there are limited patient numbers with the driver alteration of interest. Because ORR can be assessed in single-arm trials and then compared with historic controls, ORR has been used as a surrogate endpoint for accelerated approvals, with the requirement for later confirmation of clinical benefits in randomized trials. Our findings further warrant the use of ORR as an early surrogate for PFS in biomarker-driven studies.

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