Title

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ORIGINAL REPORT

Disease Control Rate at 8 Weeks Predicts Clinical Benefit in Advanced Non–Small-Cell Lung Cancer: Results From Southwest Oncology Group Randomized Trials

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ABSTRACT

Purpose
Tumor shrinkage categorized as complete response (CR) or partial response (PR) is a fundamental efficacy measure for new cancer treatments and often considered a surrogate for overall survival. However, for any given treatment, many more patients typically achieve stable disease (SD) or have progressive disease (PD) than achieve response. We hypothesized that PD (or its converse, disease control rate [DCR], consisting of CR, PR, SD) is a stronger predictor of survival than response alone in advanced non–small-cell lung cancer (NSCLC), and that this determination might be assessable early on during therapy.

Patients and Methods
Data from 984 NSCLC patients entered onto three randomized Southwest Oncology Group trials of platinum-based chemotherapy were pooled and subjected to Landmark survival analysis. Patients were categorized according to proportions alive at weeks 8, 14, and 20 after registration, as well as response status. Elements were fitted into a Cox proportional hazards model.

Results
Tumor response (CR, PR) was seen in 260 patients (27%). Median time to response, time to progression, and survival time were 2.0, 4.3 and 8.9 months, respectively. Median survival times among patients with CR/PR, SD, or PD were 13.5, 8.4, and 3.1 months, respectively. Of 892 patients alive at week 8, DCR was 62%. Although CR/PR at week 8 was associated with longer survival (hazard ratio [HR] = 0.61; $P < .001$), DCR was superior in predicting survival (HR = 0.45; $P < .0001$).

Conclusion
DCR at week 8 is a more powerful predictor of subsequent survival than is the traditional tumor response rate in advanced NSCLC and provides an early assessment of subsequent outcome.

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INTRODUCTION

In advanced non–small-cell lung cancer (NSCLC), tumor shrinkage or "response" has typically been equated with clinical benefit from systemic therapy. Traditionally, physicians and patients have assumed that response results in prolonged survival.[1] Conversely, tumor growth has been associated with worse outcomes and early death. Disease stabilization, wherein tumor size fails to meet criteria for response or progression, has often been viewed as an equivocal result and is therefore of unclear clinical value. In clinical trials, such "stable disease" (SD) is often discounted in favor of tumor response, which in turn is widely used as a screen for drug activity.

In reality, only a minority of patients with advanced NSCLC experience tumor shrinkage after standard platinum-based chemotherapy. Many more patients experience either SD or progressive disease (PD). Moreover, in some phase III trials, improved response rate of one regimen over another has failed to result in improved survival.[2-4] Thus, a clear correlation between response and long-term benefit has not yet been established.[5]

Methods defining tumor response have evolved during the last few decades. In 1960, it was suggested that systemic therapy had a positive outcome if the total tumor mass decreased in size, with no lesions increasing in size and no new lesions appearing.[6] In 1979, the WHO codified this philosophy by establishing bidimensional tumor measurement as a standard.[7] A partial response (PR) was arbitrarily defined as a 50% or greater decrease in tumor size, whereas progression was defined as a

Table 1. Patient Characteristics

Characteristic	S9509 (n = 415) No.	S9509 (n = 415) %	S9806 (n = 193) No.	S9806 (n = 193) %	S0003 (n = 376) No.	S0003 (n = 376) %	Overall (N = 984) No.	Overall (N = 984) %
Age, median	62		61		63		62	
Age ≥ 65, years	179	43	63	33	164	44	406	41
Male sex	285	69	124	64	238	63	647	66
Stage IV disease*	367	88	145	75	314	84	826	84
Weight loss ≥ 5%†	202	49	74	41	128	34	404	42
Performance status‡								
0	144	35	77	40	119	34	340	36
1	259	64	112	59	227	65	598	63
2	5	1	1	1	2	1	8	1

*Zero, 15 (8%), and 11 (3%) patients from S9509, S9806, and S0003, respectively, are missing staging information.
†Zero, 11 (6%), and four (1%) patients from S9509, S9806, and S0003, respectively, are missing weight loss information.
‡Seven (2%), three (2%), and 28 (7%) patients from S9509, S9806, and S0003, respectively, are missing performance status information.

25% or greater increase in size or new lesions. The Southwest Oncology Group further modified this system in 1992, employing a volumetric definition for progression.[8] In 2000, the Response Evaluation Criteria in Solid Tumors (RECIST) was introduced after a multinational effort to standardize tumor response assessment. RECIST established unidimensional tumor measurement, utilizing the longest diameter as a reproducible and simpler standard, and defined PR as a 30% or greater decrease in the sum of the measurable lesions and PD as a 20% or greater increase or appearance of new lesions.[9] At the present time, RECIST is the most widely used method of assessing response to anticancer therapy.

There are several limitations in tumor size assessment that restrict the broad applicability of standardized objective criteria. For instance, some patients will have no measurable disease, such as those with a malignant pleural effusion or ill-defined pulmonary densities. There is also high inter- and intraobserver variability in the measurement of NSCLC lesions.[10] Importantly, some lesions may radiographically change in appearance under the influence of systemic therapy, but not necessarily regress in size. For example, lesions can "fade" or cavitate, in neither case meeting criteria for response. These changes are coded as SD, implying no benefit of therapy, although in some cases SD has been associated with prolonged survival.[11]

In light of the reality that many more tumors achieve nonprogression than response, we hypothesized that the rate of nonprogression, also termed the disease control rate (DCR) is a stronger predictor of clinical benefit than traditional tumor response rate (the sum of complete response [CR] and PR) after platinum-based chemotherapy in patients with advanced NSCLC.

PATIENTS AND METHODS

Data from 984 patients with stage IV (metastatic) or IIIB (malignant pleural effusion) NSCLC accrued onto three randomized Southwest Oncology Group (SWOG) trials (S9509, S9806, and S0003) of platinum-based chemotherapy were pooled. S9509 randomly assigned 415 patients to either carboplatin/paclitaxel or cisplatin/vinorelbine.[12] S9806 randomly assigned 193 patients to either cisplatin/vinorelbine followed by docetaxel or carboplatin/gemcitabine followed by paclitaxel.[13] S0003 randomly assigned 376 patients to carboplatin/paclitaxel with or without tirapazamine.[14] S9509 and S9806 employed the SWOG (modified WHO) tumor response criteria, whereas S0003 used RECIST. In S9509 and S0003, patients underwent disease assessments after cycle 2 (approximately week 6) and every two cycles thereafter during receipt of protocol treatment until disease progression and/or completion of protocol treatment. In S9806, reassessment occurred after the third (approximately week 8) and sixth cycles of therapy. None of the trials showed superiority of one treatment arm over the other.

Landmark analyses were performed to assess the association of the intermediate outcomes with overall survival.[15] Three separate analyses were performed at weeks 8, 14, and 20 after registration. Each analysis included only patients alive at each of the time points. Disease control status at each time point was defined as the "best status to date," specifically if patients had CR, PR, or SD. The association of clinical prognostic factors with response, disease control, and survival status at the three time points was assessed using logistic regression. A Cox proportional hazards model was used to assess the associations between disease status at the landmark times and to adjust for prognostic factors. The data analysis for this article was generated using SAS/STAT software, Version 9.2 of the SAS System for PC (SAS Inc, Cary, NC).

RESULTS

Patient Characteristics

Table 1 summarizes the characteristics of patients included in this analysis. Overall, the median age of patients was 62 years, with 41% over the age of 65 years. There were 647 males (66%). The vast majority of patients (84%) had stage IV disease. Four hundred four patients (42%) reported weight loss of at least 5% or more. Zubrod

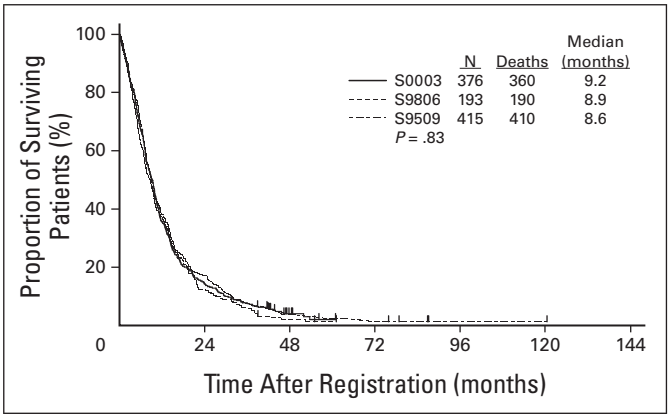

Fig 1. Overall survival for S9509, S9806, and S0003.

Table 2. Response, Stable Disease, Progression, and Survival Data

Criterion	S9509 (n = 415) No.	S9509 (n = 415) %	S9806 (n = 193) No.	S9806 (n = 193) %	S0003 (n = 376) No.	S0003 (n = 376) %	Overall (N = 984) No.	Overall (N = 984) %
Response (complete or partial)	112	27	45	23	107	28	264	27
Median time, months	1.9		2.0		1.5		2.0	
IQR	1.7 to 2.9		1.9 to 2.2		1.3 to 2.8		1.4 to 2.8	
Stable disease	123	30	55	28	121	32	299	30
Progression	377	91	161	83	327	87	865	88
Median survival, months	4.1		4.4		4.3		4.3	
IQR	1.8 to 7.4		2.3 to 7.1		2.0 to 7.4		2.0 to 7.4	
Deaths	410	99	190	98	356	94	956	97
Median survival, months	8.6		8.9		9.2		8.9	
IQR	4.3 to 16.8		5.4 to 15.8		4.8 to 15.5		4.6 to 15.9	

Abbreviation: IQR, interquartile range.

performance status (PS): 36% had PS = 0 whereas 63% had PS = 1. There was no difference in the overall survival across the three trials (Fig 1). In the pooled data set, overall response rate was 27% with a median time to response among responders of 2 months. This time point corresponded to the initial tumor response assessment after two or three cycles of platinum-based chemotherapy. Median time to progression was 4.3 months, whereas median overall survival time was 8.9 months. These data are summarized in Table 2.

Prognostic Factors

The association between survival and potential prognostic factors such as sex, age, weight loss, PS, and stage was assessed. Performance status and weight loss of 5% or greater were significantly associated with worse survival times ($P < .0001$ for both) whereas male sex, age, and stage of disease were not significantly associated with survival time ($P = .07$, 0.36, and 0.13, respectively). These clinical factors were then analyzed with respect to response and PD at weeks 8, 14, and 20. Response by week 8 was not associated with any of the prognostic factors ($P > .05$, for all) while a performance status more than 0 and stage IV disease were associated with a reduced odds of disease control by week 8 (odds ratio [OR] = 0.60; 95% CI, 0.45 to 0.79; and OR = 0.63; 95% CI, 0.42 to 0.95, respectively). Response by week 14 was not significantly associated with any of the clinical factors, whereas performance status and stage IV disease remained negatively associated with DCR at weeks 14 and 20. Performance status of more than 0 was also associated with a reduced chance of response and by week 20. Male sex, age, and weight loss were not associated with response or DCR at any of the time points.

Table 3. Comparison of Best and Worst Outcomes by Study Time

Best/Worst Outcome	Nonprogression	Primary Progression	Death	Total
Week 8				
Response	109	2	0	111
Stable disease*	445	3	4	452
Other	—	333	88	421
Week 14				
Response	214	11	3	228
Stable disease*	274	47	14	335
Other	—	268	153	421
Week 20				
Response	198	51	9	258
Stable disease*	178	93	34	305
Other	—	219	202	421

*Patients who eventually had a response but not by the time-point were classified as having stable disease.

Survival As a Function of Tumor Response

Median survival times among patients with CR/PR, SD, or PD were 13.5, 8.4, and 3.1 months, respectively. Table 3 presents a comparison of the best versus worst outcomes (eg, progression or death) at weeks 8, 14, and 20 after registration. Disease control differs from progression-free survival at a given time point for patients who achieved either a response or SD by that time point, but subsequently progressed or died before that time point.

Response and Survival: weeks 8, 14, and 20

Eight hundred ninety-two patients (91%) enrolled were alive at 8 weeks after registration. Of these patients, 111 (12%) had a response, 448 (50%) had SD, and 333 (37%) had neither a response nor SD by week 8. Therefore, the DCR among patients alive at 8 weeks was 62%. The median survival from registration was 14.7, 12.0, and 6.4 months among responders, those with SD, and those without a response or SD, respectively.

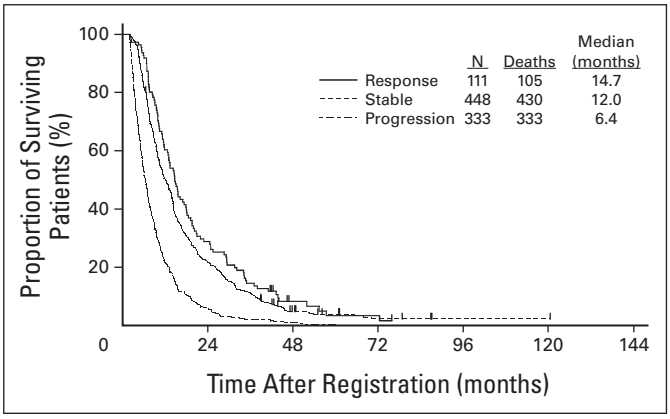

Fig 2. Survival by response status at week 8.

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Table 4. Landmark Analysis at Weeks 8, 14, and 20

	Week 8		Week 14		Week 20	
Best Response	Hazard Ratio	95% CI	Hazard Ratio	95% CI	Hazard Ratio	95% CI
Response	0.61	0.50 to 0.76	0.57	0.48 to 0.67	0.56	0.47 to 0.66
Disease control	0.45	0.39 to 0.52	0.51	0.44 to 0.60	0.56	0.47 to 0.66

Both response and SD at 8 weeks were associated with longer survival times by comparison with patients who never achieved a response or SD. Response (*v* nonresponse) at week 8 was associated with longer survival times with an estimated hazard ratio equal to 0.61 (95% CI, 0.50 to 0.76; $P < .001$). Additionally, disease control at week 8 was also associated with longer survival, with an HR of 0.45 (95% CI, 0.39 to 0.52; $P < .0001$). There was a survival advantage among patients who had achieved a response compared with those with SD, and this difference was statistically significant ($P = .03$). However, patients with SD had significantly longer survival times than did those with PD ($P < .0001$). Figure 2 presents Kaplan-Meier survival curves as a function of tumor response at week 8 of protocol therapy, demonstrating how survival after SD tracks closer to response than to PD. Finally, performance status and weight loss were also found to be significantly associated with survival, with HR of 1.34 for PS greater than 0 and HR of 1.27 for weight loss of 5% or greater.

A similar analysis was performed for weeks 14 and 20 of protocol therapy. In general, no substantial new findings were seen compared with week 8 of therapy, as summarized in Tables 4 and 5. In all analyses, the survival outcomes for those patients with SD were significantly different from those of patients who never achieved a response or SD. Although there was also a significant difference between responders and achievement of SD, for the earlier time points, survival outcomes for those with SD were more similar to those of responders than to those who never achieved a response or SD.

DISCUSSION

In this Landmark survival analysis of a large SWOG database of patients with advanced NSCLC, we found that DCR is a stronger predictor of subsequent outcome after platinum-based chemotherapy than is the traditional response rate of CR + PR. The reduction in the risk of death was substantially more significant for DCR ($P < .0001$) than it was for standard CR + PR rate alone. Thus, DCR may serve as a surrogate for survival after systemic therapy in this disease.

It is worth noting that an ideal surrogate end point must be associated with clinical outcome (such as survival) and fully capture the net effect of a treatment on that outcome. In the absence of a large data set from randomized controlled trials that shows a statistically significant effect of treatment on survival, we believe that the approach taken in this analysis serves as a reasonable alternative. In the era of biologic "targeted" therapies that may increase the proportion of SD, a DCR metric more closely mirrors treatment effect than the traditional response rate. If prospectively validated, application of the concept of DCR at 8 weeks might also provide clinical investigators an early-look clinical tool to assess the value of systemic therapy in this setting, allowing in-progress alterations in study design or sample size.

Table 5. Best Tumor Response at Weeks 8, 14, and 20 and Overall Survival

			Best Response					
	Alive		Response		Stable		Progression	
Time Point	No.	%	No.	%	No.	%	No.	%
Week 8								
Patients	892	91	111	12	448	50	333	37
Median survival time	9.7		14.7		12.0		6.4	
HR			0.38		0.48		1.0	Ref
95% CI			0.30 to 0.48		0.41 to 0.56			
Week 14								
Patients	814	83	225	28	321	39	268	33
Median survival time	10.7		15.1		10.7		7.7	
HR			0.43		0.60		1.0	Ref
95% CI			0.36 to 0.52		0.50 to 0.71			
Week 20								
Patients	739	75	249	34	271	37	219	30
Median survival time	11.6		15.5		10.9		9.3	
HR			0.46		0.70		1.0	Ref
95% CI			0.38 to 0.55		0.58 to 0.84			

Abbreviation: HR, hazard ratio.

These data also support the relative value of disease stabilization as a "positive outcome" for advanced NSCLC. Recent prospective data have shown that SD is clinically relevant. Specifically, in a randomized placebo-controlled trial of erlotinib in the second- and third-line settings, patients with SD seemed to have derived clinical benefit from the then-experimental epidermal growth factor receptor–targeted therapy.[11]

Our results can potentially guide clinical practice in that oncologists can appropriately counsel NSCLC patients who are receiving platinum-based chemotherapy about the relative value of tumor shrinkage, SD, and PD using evidence-based data rather than anecdotal experience. Clinicians would thus have such data on which to base the logical conclusion that patients with nonprogression at the first radiographic assessment have a survival benefit over those with PD.

Employing DCR has practical implications for clinical investigations in which the assessment of PD is, in some cases, less equivocal than assessment of response. For example, the development of new lesions on physical examination or radiographic studies is less equivocal than measuring gradations of tumor shrinkage. If DCR were selected as a primary trial end point rather than response (which is often used in phase II efficacy assessment), then measurable disease would not be required at baseline. This change would broaden eligibility for phase II trials, increasing general applicability, and may speed trial completion.

In conclusion, our data suggest that DCR is a more powerful predictor of subsequent survival than is the traditional response rate (CR + PR) in patients receiving platinum-based chemotherapy for advanced stage NSCLC. Employing DCR instead of response rate may enhance clinical trial interpretation and guide clinical practice. If validated, an early-look measure such as DCR at week 8 could also enhance trial design and conduct in advanced NSCLC. These findings may have broad implications for future trial design and will be prospectively tested in SWOG.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Primo N. Lara Jr, Mary W. Redman
Administrative support: Mary W. Redman, John J. Crowley
Provision of study materials or patients: Primo N. Lara Jr, Karen Kelly, Martin J. Edelman, Stephen K. Williamson, David R. Gandara
Collection and assembly of data: Primo N. Lara Jr, Mary W. Redman, John J. Crowley
Data analysis and interpretation: Primo N. Lara Jr, Mary W. Redman, Karen Kelly, Martin J. Edelman, Stephen K. Williamson, John J. Crowley, David R. Gandara
Manuscript writing: Primo N. Lara Jr, Mary W. Redman, David R. Gandara
Final approval of manuscript: Primo N. Lara Jr, Mary W. Redman, Karen Kelly, Martin J. Edelman, Stephen K. Williamson, John J. Crowley, David R. Gandara

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