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Disease Control Rate at 8 Weeks Predicts Subsequent Survival in Platinum-Treated Extensive Stage Small-Cell Lung Cancer: Results From the Southwest Oncology Group (SWOG) Database

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Abstract

In phase 2 trials of investigational agents in relapsed/refractory small-cell lung cancer (SCLC), response rate is often used as an efficacy measure. In this Southwest Oncology Group (SWOG) database of SCLC patients enrolled onto phase 2 trials of targeted therapies, disease control rate at 8 weeks was a better predictor of subsequent survival than tumor response.

Background: Overall response rate is frequently used as an end point in phase 2 trials of platinum-treated extensive stage (ES) small-cell lung cancer (SCLC). We hypothesized that disease control rate (DCR) would be a superior surrogate for subsequent survival outcomes. **Methods:** Updated patient-level data from Southwest Oncology Group (SWOG) trials in second- and/or third-line ES-SCLC patients were pooled. Landmark analysis was performed among patients alive at 8 weeks for overall survival (OS) measured from the 8-week landmark. Association of clinical prognostic factors with DCR was assessed using logistic regression. A Cox proportional hazard model was used to assess the associations between DCR at the landmark time and subsequent OS, adjusted for prognostic factors. **Results:** Of the 319 ES-SCLC patients, 263 were alive at the 8-week landmark and constituted the pooled study population. Only 8 patients had a response. Disease control at 8 weeks was seen in 98 patients. Bivariate analysis of OS from the 8-week landmark revealed that DCR (hazard ratio [HR], 0.47; $P < .0001$) and elevated lactate dehydrogenase (HR, 1.70; $P = .0004$) were significantly associated with OS. In multivariable analysis, DCR remained an independent predictor of subsequent survival from the 8-week landmark (HR, 0.50; $P < .0001$). **Conclusion:** In this large second- and third-line ES-SCLC database, DCR at 8 weeks was found to be a significant predictor of subsequent survival in patients receiving investigational therapy. These results have critical implications in the selection of surrogate end points in future prospective ES-SCLC trials.

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Introduction

Small-cell lung cancer (SCLC) is a highly aggressive and virulent malignancy. Patients typically present with incurable systemic disease (ie, extensive stage) at the time of initial diagnosis. The lethal phenotype of extensive stage (ES) SCLC is perhaps best exemplified

by its high rate of initial sensitivity to treatment with DNA-damaging agents such as platinum-based chemotherapy; however, this is generally followed by the rapid development of drug resistance and subsequent disease progression.¹ Most recently, our group reported that platinum-sensitivity status may no longer be strongly associated

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with survival outcomes in ES-SCLC patients receiving investigational noncytotoxic therapy in the salvage setting.^{2,3} Ultimately, the result is that the estimated median survival time for patients with ES-SCLC is typically less than a year. The treatment approach to SCLC has not significantly advanced over the last quarter century, highlighting the importance of continued attention to the early development of novel agents for this aggressive disease.

The optimal metric to define the efficacy of an agent in phase 2 clinical trials of patients with previously treated SCLC has not yet been clearly defined. The traditional measures of efficacy have included tumor response rate (now commonly assessed using Response Evaluation Criteria in Solid Tumors [RECIST]) and progression-free survival (PFS). However, neither efficacy measure has yet been shown to be significantly associated with overall survival (OS) in this context. In the frontline setting, a pooled analysis of data from over 3000 patients enrolled onto 12 trials failed to demonstrate surrogacy of PFS for OS in ES-SCLC, despite earlier work that suggested otherwise.^{4,5}

In clinical practice, physicians and patients intuitively equate tumor response from systemic therapy with subsequent OS benefit. Similarly, investigators commonly use response rate as a metric for vetting new agents in the phase 2 context, advancing a “promising treatment” into further phases of drug development. However, several features of SCLC suggest that response rate may not be the ideal end point to predict survival outcomes. After frontline platinum-based chemotherapy, response to any subsequent agent tends to be extraordinarily transient and insufficiently durable to result in a survival benefit. Moreover, only a minority of patients with previously treated SCLC experience tumor shrinkage with any subsequent systemic therapy, including investigational agents. For example, in 3 Southwest Oncology Group (SWOG) phase 2 trials of investigational regimens in platinum-treated SCLC (S0802, S0435, and S0327; Table 1), responses were rare, with many more patients having progressive or stable disease.⁶⁻⁷

In 2008, our group reported that in advanced non-SCLC, disease control rate (DCR)—defined as the sum of partial response, complete response, and stable disease—was the strongest predictor of subsequent survival after platinum-based chemotherapy.⁸ In the present study, we hypothesized that DCR at 8 weeks would be a superior predictor of clinical benefit than tumor response rate in patients with ES-SCLC receiving investigational therapy in SWOG clinical trials.

Methods

Updated patient-level data from S0802, S0435, and S0327 were pooled. S0802 randomized patients to either topotecan alone or topotecan plus the angiogenesis inhibitor aflibercept (VEGF-Trap). S0435 was a single-arm trial of the vascular endothelial growth factor (VEGF) receptor tyrosine kinase inhibitor sorafenib. S0327 was a single-arm trial of the proteasome inhibitor PS-341 (bortezomib). The primary results for each of these trials have been published previously. Each of the trials required progression on at least 1 line of platinum-based chemotherapy, had consistent eligibility criteria, and collected the same baseline demographic variables. Disease assessments were performed every 6 weeks in S0802 and S0327, and every 8

Table 1 Recent SWOG Trials in Previously Treated Extensive Stage SCLC

SWOG Study	Regimen	No. of Patients	Performance Status Allowed	No. of Prior Regimens Allowed
S0327	Bortezomib	57	0-1	≥1
S0435	Sorafenib	83	0-1	≥1 ^a
S0802	Topotecan with or without aflibercept	189	0-1	1

Abbreviation: SWOG = Southwest Oncology Group.

^aS0435 allowed patients with 1 or more prior chemotherapy regimens until February 1, 2006, when it was amended to allow only patients with exactly 1 prior regimen.

weeks in S0435. Response was assessed using RECIST by the site investigators. Although the primary end point was response rate for S0327 and S0435, the primary end point for S0802 was 3-month PFS and thus was the only one of the 3 trials that did not require measurable disease at baseline. Response was assessed in the subset of patients with measurable disease using RECIST and was defined as achieving a best response of either a confirmed or unconfirmed partial or complete response. Disease control was assessed in all patients and was defined as the absence of evidence of progression at the first follow-up disease assessment. Patients with no follow-up disease assessment due to symptomatic deterioration were included in the denominator as not having experienced disease control.

Because there were differences in cycle length and disease assessment times across the 3 protocols, we selected the longest of these (ie, 8 weeks for S0435) as the landmark time point. Response and DCR at 8 weeks were evaluated as intermediate end points for OS using a landmark analysis among patients still alive at 8 weeks. In addition, response at 8 weeks was evaluated as an intermediate end point for PFS.

OS and PFS estimates were calculated by the Kaplan-Meier method. Confidence intervals for the median were constructed by the Brookmeyer-Crowley method. OS was defined as the duration from the date of the 8-week landmark to the date of death due to any cause. Patients last known to be alive were censored at the date of last contact. Progression-free survival was defined as the duration from the date of the 8-week landmark to the date of first documentation of disease progression, as defined by RECIST, symptomatic deterioration without documented disease progression, or death due to any cause. Patients last known to be alive and without evidence of disease progression or symptomatic deterioration were censored at the date of last contact.

Multivariate Cox models were fit to evaluate the association of DCR and response with OS controlling for clinical prognostic factors (including age, sex, platinum sensitivity status, number of prior chemotherapy regimens, weight loss, and lactate dehydrogenase). Platinum sensitivity was defined as follows: platinum sensitive (progression ≥ 90 days from last platinum dose) or refractory (progression < 90 days). Missing values were not replaced or imputed in any way.

Before performing any data analysis, it was decided to adjust for multiple comparisons by only considering *P* values of ≤ .001 as statistically significant. Statistical analysis was performed by SAS (SAS

Table 2 Characteristics of Patients Included in Landmark Analysis (n = 263)

Characteristic	Characteristic	SWOG Study						Overall (N = 263)
		S0327 (n = 35)		S0435 (n = 74)		S0802 (n = 154) ^a		
Age, years, median (range)	65	(22-85)	62	(44-85)	63	(40-85)	63	(22-85)
Age ≥65 years	17	49%	30	41%	60	39%	107	41%
Male sex	21	60%	41	55%	65	42%	127	48%
Performance Status								
0	12	34%	29	39%	55	36%	96	37%
1	23	66%	43	58%	99	64%	165	63%
Not reported	0	0%	2	3%	0	0%	2	1%
Smoking Status								
Never	0	0%	0	0%	3	2%	3	1%
Former	0	0%	37	50%	96	62%	133	51%
Current	0	0%	36	49%	55	36%	91	35%
Not reported	35	100%	1	1%	0	0%	36	14%
Weight Loss								
≥5%	6	17%	15	20%	36	23%	57	22%
<5%	29	83%	53	72%	112	73%	194	74%
Not reported	0	0%	6	8%	6	4%	12	5%
Elevated LDH								
Yes	7	20%	22	30%	51	33%	80	30%
No	18	51%	38	51%	93	60%	149	57%
Not reported	10	29%	14	19%	10	6%	34	13%
Prior Chemotherapy Regimens								
2 or more	18	51%	6	8%	0	0%	24	9%
0-1	16	46%	67	91%	154	100%	237	90%
Not reported	1	3%	1	1%	0	0%	2	1%
Prior radiotherapy	30	86%	61	82%	108	70%	199	76%

Abbreviations: LDH = lactate dehydrogenase; SWOG = Southwest Oncology Group.
^aS0802 includes only the subset of patients with measurable disease at baseline.

Institute, Cary, NC). The study was registered at [ClinicalTrials.gov](https://clinicaltrials.gov) (NCT00068289, NCT00182689, and NCT00828139).

Results

Of the 319 ES-SCLC patients, 263 were alive at the 8-week landmark and constituted the pooled study population. Patient characteristics were similar among the 3 trials and are summarized in Table 2. Overall, median age was 61 years. Males comprised 48% of the group, while those with a performance status of 1 constituted 63%. There were 57 patients (22%) with clinically significant weight loss of 5% or more within the preceding 3 months. Elevated lactate dehydrogenase was seen in 80 patients (30%).

Overall, 263 patients were alive at the 8-week landmark and were evaluable for analysis of association of disease control with OS. Comparing patients with disease control versus no disease control, hazard ratio (HR) for OS was 0.42, with a statistically significant 2-sided *P* value of < .0001 (Table 3).

Two hundred fifty-six patients who had measurable disease at baseline were alive at 8 weeks and thus were evaluable for OS from the 8-week landmark. There were 8 patients whose disease responded to therapy. In the OS comparison of those with response versus those without, the HR was 0.74, with a 2-sided *P* value of .43.

Kaplan-Meier curves for OS from the 8-week landmark categorized according to response or disease control status are shown in Figure 1. Median OS (8-week landmark) was 8.2 months for those with disease that responded to therapy versus 4.1 months for disease that did not respond to therapy (*P* = .43), while median OS (8-week landmark) was 8.4 months for those with disease control versus 3.1 months for those without disease control (*P* < .0001).

Bivariate analysis of baseline clinical and demographic variables and their association with subsequent OS is summarized in Table 4. As shown, DCR (HR 0.47, *P* < .0001) and elevated lactate dehydrogenase (HR 1.70, *P* = .004) were significantly associated with subsequent OS.

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Table 3 Overall Survival (8-Week Landmark) Categorized According to Response or Disease Control

Category	No. Alive at Week 8	No. of Deaths	Median	95% CI	HR	95% CI	P
Response					0.74	0.35-1.57	.43
Yes	8	7	8.2	0.5-13.3			
No	248	222	4.1	3.3-4.6			
Disease Control					0.47	0.36-0.62	<.0001
Yes	98	79	8.6	6.1-10.5			
No	165	155	2.8	2.5-3.5			

Abbreviations: CI = confidence interval; HR = hazard ratio.

Multivariate analysis for OS accounting for all relevant baseline variables, including only those patients with complete data ($n = 191$), showed that only DCR was independently associated with subsequent survival (Table 5). All other variables, including baseline platinum-refractory status, performance status, and sex, were not significantly associated with OS. DCR at 8 weeks was an independent predictor of subsequent OS, with an estimated HR of 0.50 (95% confidence interval, 0.36-0.70; $P = .0001$), representing a 50% reduction in the risk of death.

In the subset of patients with measurable disease at baseline, 98 patients were alive and free of progression at the 8-week landmark and therefore evaluable for assessment of PFS from the 8-week landmark (Supplemental Table 1 in the online version). Of these, only 8 patients met the criteria for partial response (9.1%). In the PFS comparison of patients whose disease responded therapy versus those whose disease did not respond to therapy, the HR was 0.77, with a 2-sided P value of .51. Kaplan-Meier curves for PFS from the 8-week landmark categorized according to response status are shown in Supplemental Figure 1 in the online version. Median PFS (8-week landmark) was 2.1 months for those with response versus 1.8 months for those without response.

Discussion

In this modern SWOG database analysis of ES-SCLC patients receiving investigational therapy, DCR at 8 weeks was found to be the strongest independent predictor of subsequent OS. This finding parallels observations seen in advanced non-SCLC patients receiving platinum-based therapy and has critical implications for the design of future prospective trials in ES-SCLC.

An ideal surrogate end point ought to be strongly associated with OS. In addition, such an end point is expected to fully capture the net effect of a treatment on OS.⁹ In the past, PFS had been proposed as a metric for phase 2 trials in ES-SCLC because of its reported surrogacy with OS.⁵ Unfortunately, this surrogacy was not confirmed by a subsequent larger pooled analysis of cooperative group trials.⁴ In the absence of an accessible database from a randomized trial that shows the OS benefit of a new agent over an existing control in the second- and/or third-line ES-SCLC setting, the landmark analysis we present here provides a reasonable, albeit less robust, alternative to true surrogacy. Furthermore, in contrast to non-SCLC, there is a paucity of highly active second-line treatments against SCLC; thus, the lack of correlation between PFS and OS means that PFS may not be a good measure of clinical benefit with a new therapy in SCLC.⁴ Finally, because the likelihood of a RECIST

response is quite low in this pretreated context (eg, only 8 patients in our database had an objective tumor response), DCR may be a more practical measure for efficacy screening, as it is seen in more patients. Finally, our analysis suggests that DCR at 8 weeks is significantly associated with OS and therefore could be a more appropriate indicator of clinical benefit with a new therapy.

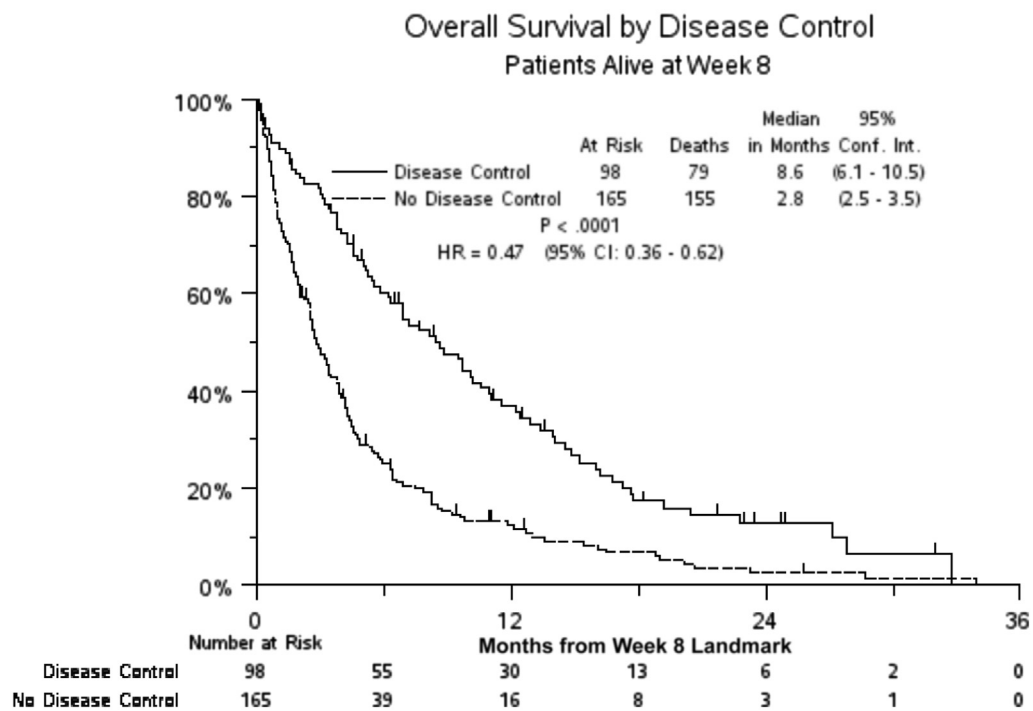
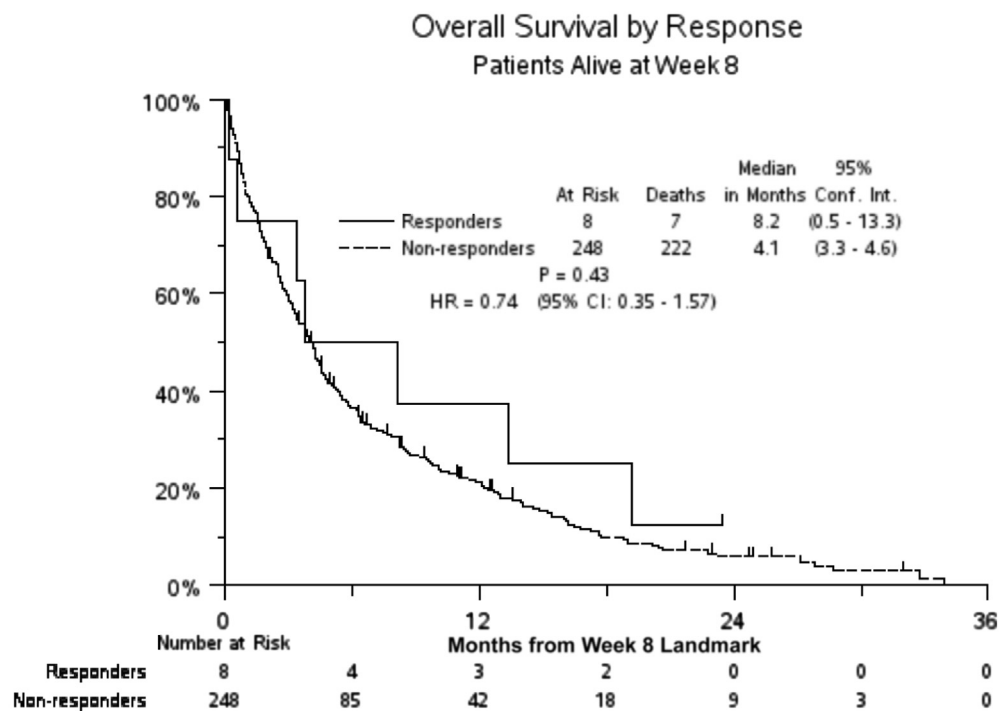
This pooled study is limited by its retrospective nature, the heterogeneity of investigational therapies used in the individual trials, and the lack of molecular phenotype information that may influence prognosis independently. Our observation is certainly influenced by the much smaller proportion of patients who actually had tumor response to investigational therapy at 8 weeks (ie, only 8 individuals out of the entire cohort). Given the size of this cohort, we have limited power to accurately assess the true survival of this group. This is in contrast to the much larger group of 98 patients who exhibited disease control at the 8-week time point. Thus, the rarity of tumor response to investigational agents in the phase 2 clinical trial contributes to its reduced ability to predict subsequent survival outcomes. However, consistent collection of relevant baseline variables and the relative homogeneity of protocol design inherent in SWOG trials greatly facilitate the reliability of the pooled analysis performed here.

If these results are validated in an independent data set, they ought to be considered in future phase 2 clinical trials in ES-SCLC. For instance, the further development of a new anti-cancer agent that does not appreciably result in a RECIST response could be prematurely terminated even when substantial disease control is observed. Our current analysis suggests that in patient cohorts that have not been molecularly enriched, overall response may not be the ideal clinical trial metric to screen for disease activity, given its rarity in that setting. Pending further confirmation, DCR at 8 weeks might be considered as a superior clinical trial metric to screen new agents in an “all-comers” population of ES-SCLC patients.

Conclusion

We found that DCR at 8 weeks was a strong predictor of subsequent survival in platinum-pretreated patients receiving investigational therapy for ES-SCLC. We propose that this metric be considered as a clinical trial end point to screen for drug activity of novel agents targeting this challenging disease. This metric has the potential to allow for a smaller sample size in a phase 2 trial than if OS were used as the primary end point while still providing a meaningful measure of drug activity.

Figure 1 Kaplan-Meier Curves for Overall Survival According to Response or Disease Control



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Table 4 Bivariate Analysis: Baseline Variables and Overall Survival From 8-Week Landmark for 191 Patients With Complete Data at Baseline

Parameter	HR	95% CI	P
Response	0.74	0.35-1.57	.43
Disease control rate	0.47	0.36-0.62	<.0001
Platinum refractory	1.25	0.96-1.62	.10
Age \geq 65 years	1.02	0.78-1.32	.90
Performance status = 1	1.36	1.04-1.78	.03
Current smoker vs. former or never	1.05	0.79-1.40	.75
Male sex	1.12	0.86-1.45	.40
Elevated LDH	1.70	1.27-2.28	.0004
2 or more prior chemotherapy regimens vs. only 1	0.64	0.41-1.00	.05
Weight loss \geq 5%	0.98	0.72-1.34	.91
Prior radiotherapy	0.98	0.72-1.32	.88
SWOG S0802 vs. SWOG S0435 or S0327	1.21	0.93-1.58	.16

Abbreviations: CI = confidence interval; HR = hazard ratio; LDH = lactate dehydrogenase; SWOG = Southwest Oncology Group.

Table 5 Multivariate Analysis: Baseline Variables and Overall Survival From 8-Week Landmark for 191 Patients With Complete Data at Baseline

Parameter	HR	95% CI	P
Disease control rate	0.50	0.36-0.70	<.0001
Platinum refractory	1.33	0.96-1.84	.09
Age \geq 65 years	0.99	0.71-1.38	.94
Performance status = 1	1.39	1.00-1.94	.05
Current smoker vs. former or never	1.00	0.71-1.40	.98
Male sex	1.16	0.83-1.61	.38
Elevated LDH	1.38	0.98-1.94	.06
2 or more prior chemotherapy regimens vs. only 1	0.58	0.29-1.17	.13
Weight loss \geq 5%	1.11	0.75-1.63	.61
Prior radiotherapy	0.78	0.54-1.13	.18
SWOG S0802 vs. SWOG S0435 or S0327	1.03	0.71-1.50	.88

Abbreviations: CI = confidence interval; HR = hazard ratio; LDH = lactate dehydrogenase; SWOG = Southwest Oncology Group.

Clinical Practice Points

- The optimal intermediate end point that best predicts subsequent survival in SCLC patients receiving investigational therapy has not yet been clearly defined.
- Traditionally, response rate and progression-free survival end points have been used to assess the efficacy of an investigational agent; however, these end points have not been shown to be associated with OS in SCLC.
- DCR has not yet been formally assessed in this setting.
- In a multivariate analysis for OS, DCR at 8 weeks was an independent predictor of subsequent OS, with an estimated HR of 0.50 ($P < .0001$), representing a 50% reduction in the risk of death.
- If validated in an independent dataset, DCR ought to be considered as a clinical trial end point to screen for drug activity of novel agents in relapsed SCLC.
- DCR has the potential to allow for a smaller sample size in a phase 2 trial than if OS were used as the primary end point while still providing a meaningful measure of drug activity.

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Disclosure

The authors have stated that they have no conflicts of interest.

Supplemental Data

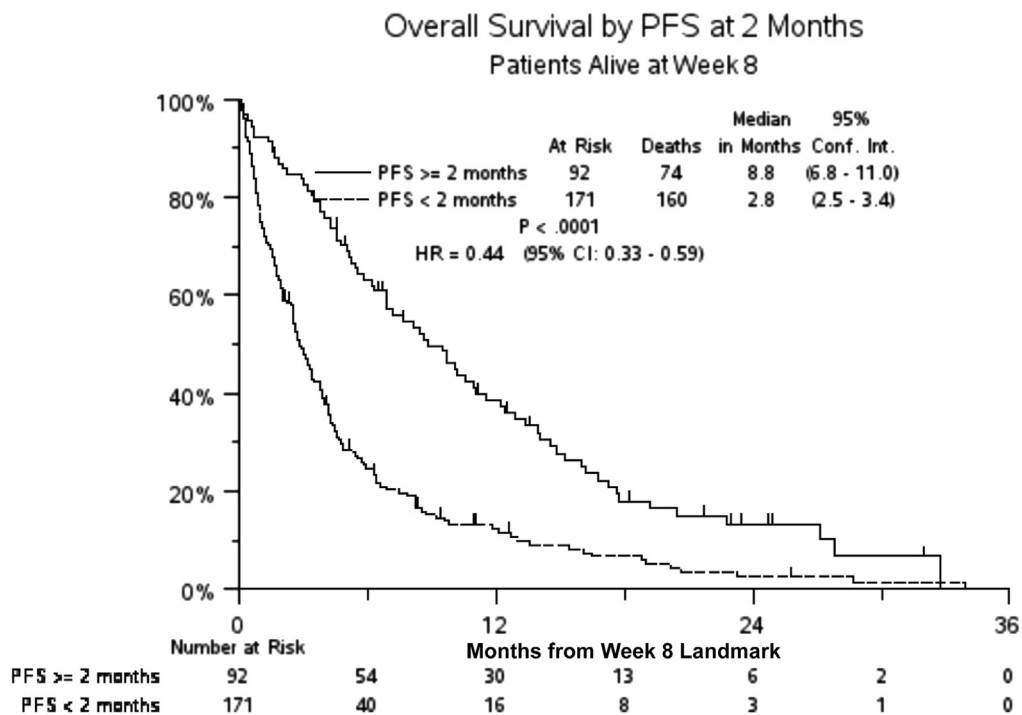
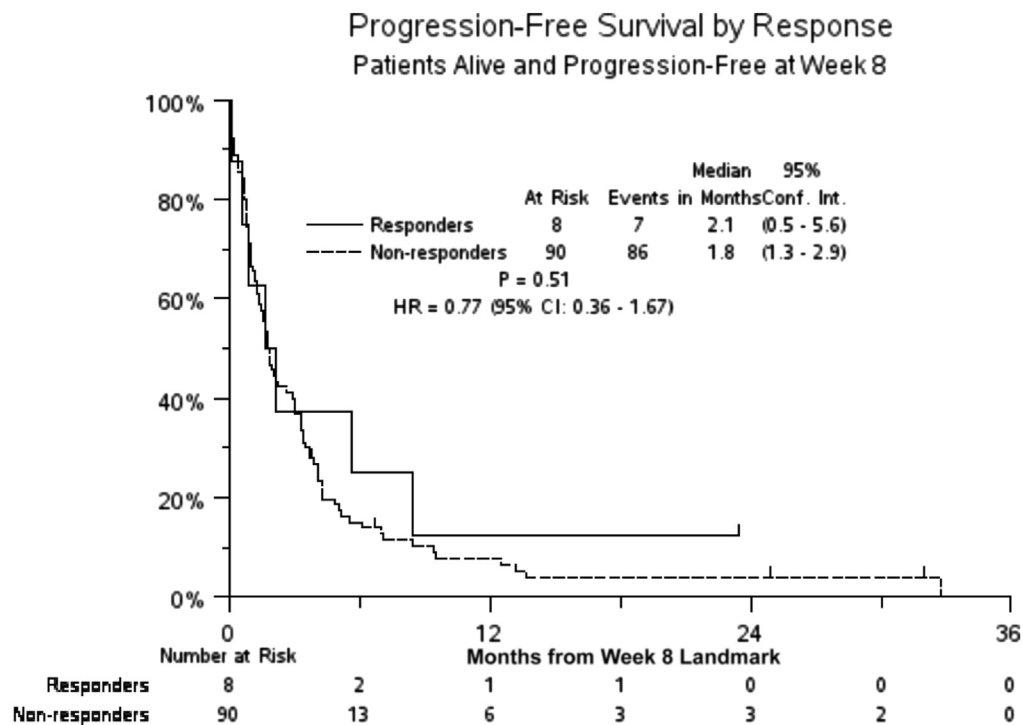
Supplemental table and figure accompanying this article can be found in the online version at <http://dx.doi.org/10.1016/j.clc.2015.09.003>.

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Supplemental Figure 1

Kaplan-Meier Curves for PFS According to Response. (A) PFS by Response, With Patients Alive at Week 8. (B) Overall Survival by PFS at 2 Months, With Patients Alive at Week 8. This Alternative Analysis Used 2-Month PFS Instead of DCR. Six Patients Qualified for DCR by Having Best Response of Stable Disease but Had a PFS of < 2 Months. If We Change These to Failures, Then Essentially 2-Month PFS Is Used in Place of DCR. Results Are Virtually Identical



Abbreviations: DCR = disease control rate; PFS = progression-free survival.

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Supplemental Table 1 Progression-Free Survival (8-Week Landmark) Categorized by Response or Disease Control							
Category	N ^a	Events	Median	95% CI	HR	95% CI	P
Response					1.30	0.60-2.82	.51
Yes	90	86	1.8	1.3-2.9			
No	8	7	2.1	0.5-5.6			
Disease Control					0.83	0.53-1.29	.41
Yes	68	64	2.0	1.4-3.0			
No	30	29	1.5	0.3-2.9			

Abbreviations: CI = confidence interval; HR = hazard ratio.

^aPatients alive and free of progression at week 8.