Disease Control as a Predictor of Survival with Gefitinib and Docetaxel in a Phase III Study (V-15-32) in Advanced Non-small Cell Lung Cancer Patients

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Introduction: This post hoc analysis investigated the relationship between tumor response and overall survival (OS) in pretreated advanced non-small cell lung cancer (NSCLC).

Methods: We conducted landmark survival analyses of V-15-32, a phase III study comparing gefitinib with docetaxel in pretreated advanced NSCLC. Best response at weeks 8, 12, 16, and 20, and visit response at week 4, were evaluated.

Results: Disease control (DC; complete response [CR], partial response [PR], or stable disease) was a better predictor of OS than CR/PR at all time points. The strongest predictor of OS for both gefitinib and docetaxel was DC at week 8 (hazard ratio [HR] DC versus non-DC: 0.30, 95% confidence interval [CI] 0.20–0.45, $p < 0.001$ for both treatments). DC at week 4 was also associated with longer survival compared with non-DC for both treatments (HR 0.33, 95% CI 0.23–0.49, $p < 0.001$ for gefitinib; HR 0.30, 95% CI 0.19–0.47, $p < 0.001$ for docetaxel).

Discussion: DC is a better predictor of OS with gefitinib and docetaxel than CR/PR in advanced pretreated NSCLC, with a best response of DC at week 8 the strongest predictor.

Key Words: Docetaxel, Epidermal growth factor receptor tyrosine kinase inhibitors, Gefitinib, Landmark analysis, NSCLC.

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Patients with advanced/metastatic non-small cell lung cancer (NSCLC) have a poor prognosis, with less than 10% of patients experiencing tumor shrinkage equating to a complete response or partial response (CR or PR) with standard second-/third-line chemotherapy.[1–4] However, many patients do achieve nonprogression or disease control (DC; the sum of CR, PR, and stable disease [SD]), with approximately 35 to 45% of patients achieving SD in clinical trials.[1–4] In the setting of advanced NSCLC, SD may be a positive therapeutic outcome, with potential benefits including improved quality of life and prolonged survival.[5,6] In a prospective, randomized study of erlotinib in advanced NSCLC after first-/second-line chemotherapy, there was significant prolongation of survival with erlotinib compared with placebo (6.7 versus 4.7 months, respectively; hazard ratio [HR] 0.61, $p < 0.001$), despite a response rate of <10%; one possible explanation for this is that a high proportion of patients had SD during therapy and this may have contributed to the prolongation in survival.[4] In clinical trials, response based on the Response Evaluation Criteria in Solid Tumors (RECIST) is widely used to identify and quantify the antitumor activity of new agents, providing a relatively quick assessment of efficacy; however, its value as a predictor of a survival benefit remains unclear.[7]

Based on the fact that many more patients initially achieve nonprogression than CR or PR, Lara et al.[8] first hypothesized that the rate of nonprogression, or DC, is a stronger predictor of clinical benefit than CR/PR after platinum-based chemotherapy in patients with advanced NSCLC. In a pooled analysis of data from 984 patients with advanced NSCLC who entered into three randomized trials of first-line platinum-based chemotherapy, landmark survival analysis showed that DC versus non-DC at week 8 was a stronger predictor of longer survival (HR 0.45, $p < 0.0001$) than the traditional CR/PR versus non-CR/PR (HR 0.61, $p < 0.001$). A study conducted using landmark analysis also found that a decrease or no change in tumor size at week 8 was significantly associated with longer survival ($p = 0.043$) in patients with advanced NSCLC who received first-line chemotherapy in the Four-Arm Cooperative Study or pemetrexed as salvage therapy for previously treated disease.[9] A meta-analysis of the published literature that included 28 phase II/III trials in 6171 patients with advanced NSCLC receiving gefitinib or

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erlotinib found a significant correlation between both response rate and DC with survival ($p < 0.0001$ and $p = 0.003$, respectively).[10]

Gefitinib is an orally bioavailable, epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor and was the first molecular-targeted drug approved for NSCLC. A recent large international phase III study (IRESSA NSCLC Trial Evaluating REsponse and Survival versus Taxotere) comparing gefitinib and docetaxel in 1466 patients with pretreated (at least one platinum-based regimen) advanced NSCLC established noninferior survival of gefitinib compared with docetaxel (HR 1.02, 96% confidence interval [CI] 0.91–1.15; noninferiority margin 1.154).[11] A similar phase III study, V-15-32, compared gefitinib with docetaxel in 489 patients in Japan with advanced NSCLC who had failed one or two chemotherapy regimens.[12] Noninferiority in overall survival (OS) was not proven (HR 1.12, 95.24% CI 0.89–1.40; noninferiority margin 1.25), although there was no significant difference in OS ($p = 0.330$) or in progression-free survival between treatments. The objective response rate was 22.5% in the gefitinib group and 12.8% in the docetaxel group (odds ratio 2.14, 95% CI 1.21–3.78, $p = 0.009$). Gefitinib also significantly improved quality of life versus docetaxel and was associated with a lower incidence of grade 3/4 adverse events (40.6% versus 81.6%, respectively).

The aim of this post hoc landmark analysis was to assess the relationship between tumor response and OS in Japanese patients with advanced, previously treated NSCLC who received gefitinib or docetaxel in the V-15-32 study.

PATIENTS AND METHODS

The methodology and overall study results for V-15-32 (clinicaltrials.gov identifier NCT00252707) have been reported in full previously.[12] Tumor responses were assessed by RECIST[13] at baseline, every 4 weeks for the first 24 weeks, and every 8 weeks thereafter.

Two types of objective tumor response were assessed: visit response (CR/PR, SD, or progressive disease [PD]) at week 4 and best overall response (CR/PR, SD, or PD) up to weeks 8, 12, 16, and 20. In the analysis of best response, patients who eventually had a CR/PR but not by the time point were classified as having SD; patients who eventually had SD but not by the time point (because of missing values or being not evaluable [NE]) were classified as NE. PD included "symptomatic deterioration." For the purposes of the analyses reported here, DC was defined as CR/PR/SD where SD is defined as SD lasting ≥6 weeks after randomization, instead of ≥12 weeks used in the previous report.[12] In the analysis of visit response at week 4, CR/PR/SD were

TABLE 1. Landmark Analysis of Overall Survival by Best Response up to Weeks 8, 12, 16, and 20, and Visit Response at Week 4 (Evaluable for Response Population)

							Comparison	
				Best Response[a]			Survival HR (95% CI), *p*	
Treatment	Week	Statistics	Evaluable for Response	CR/PR	SD	PD	CR/PR vs. non-CR/PR	DC vs. non-DC
Best response analysis								
Gefitinib	8	No. of patients (%)	182 (91.0)	28 (14.0)	52 (26.0)	102 (51.0)	0.55 (0.31–0.96)	0.30 (0.20–0.45)
		No. of deaths	119	14	23	82	0.034	<0.001
	12	No. of patients (%)	173 (86.5)	40 (20.0)	42 (21.0)	91 (45.5)	0.44 (0.26–0.73)	0.32 (0.22–0.48)
		No. of deaths	109	17	20	72	0.002	<0.001
	16	No. of patients (%)	160 (80.0)	42 (21.0)	40 (20.0)	78 (39.0)	0.47 (0.28–0.80)	0.36 (0.23–0.54)
		No. of deaths	95	17	19	59	0.005	<0.001
	20	No. of patients (%)	151 (75.5)	45 (22.5)	37 (18.5)	69 (34.5)	0.46 (0.27–0.78)	0.40 (0.26–0.62)
		No. of deaths	86	17	19	50	0.004	<0.001
Docetaxel	8	No. of patients (%)	173 (92.5)	8 (4.3)	71 (38.0)	94 (50.3)	0.64 (0.24–1.75)	0.30 (0.20–0.45)
		No. of deaths	107	4	29	74	0.386	<0.001
	12	No. of patients (%)	170 (90.9)	18 (9.6)	64 (34.2)	88 (47.1)	0.35 (0.15–0.79)	0.33 (0.22–0.50)
		No. of deaths	104	6	30	68	0.012	<0.001
	16	No. of patients (%)	160 (85.6)	21 (11.2)	61 (32.6)	78 (41.7)	0.49 (0.25–0.98)	0.37 (0.25–0.57)
		No. of deaths	94	9	27	58	0.044	<0.001
	20	No. of patients (%)	150 (80.2)	24 (12.8)	57 (30.5)	69 (36.9)	0.54 (0.28–1.05)	0.41 (0.27–0.63)
		No. of deaths	84	10	25	49	0.070	<0.001
Visit response analysis								
Gefitinib	4	No. of patients (%)	172 (86.0)	33 (16.5)	83 (41.5)	56 (28.0)	0.44 (0.26–0.76)	0.33 (0.23–0.49)
		No. of deaths	114	15	52	47	0.003	<0.001
Docetaxel	4	No. of patients (%)	156 (83.4)	11 (5.9)	105 (56.1)	40 (21.4)	0.85 (0.37–1.94)	0.30 (0.19–0.47)
		No. of deaths	92	6	54	32	0.695	<0.001

HR <1 implies a lower risk of death for those patients with CR/PR vs. non-CR/PR or DC vs. non-DC.
[a]Visit response for week 4.
CI, confidence interval; CR, complete response; DC, disease control (CR, PR, or SD); HR, hazard ratio; PD, progressive disease; PR, partial response; SD, stable disease.

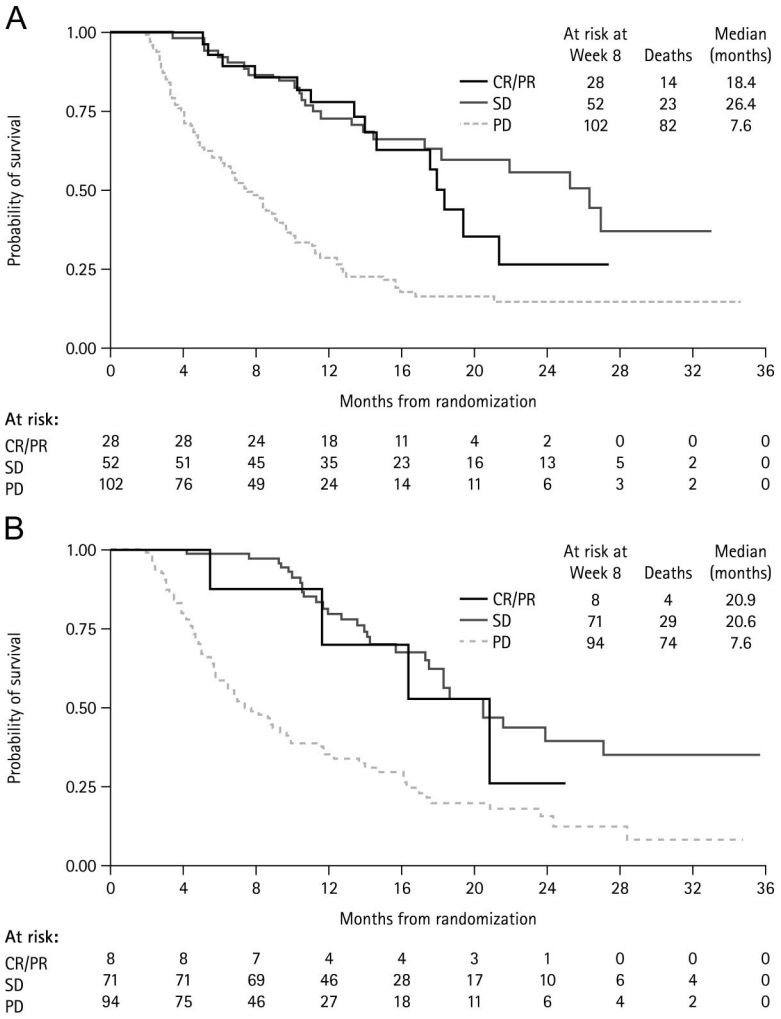


FIGURE 1. Overall survival by best response up to week 8 after treatment with (*A*) gefitinib or (*B*) docetaxel (evaluable for response population).

CR, complete response; PD, progresssive disease; PR, partial response; SD, stable disease

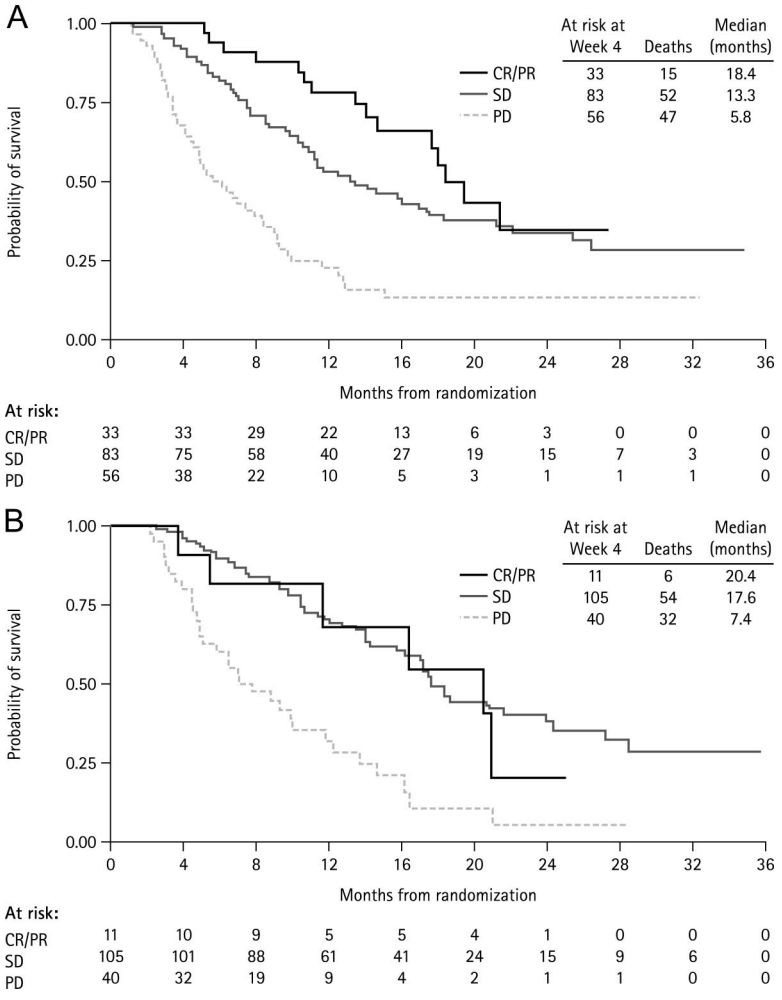
defined according to RECIST (tumor shrinkage) without considering the duration of each status. In the analysis of visit response at week 4, if a patient was judged as "symptomatic deterioration" before the time window of week 4 defined in the protocol (25–31 days), it was assumed to occur at week 4.

Landmark analysis is a valid method of comparing survival by response category[14] and determines each patient's response at a fixed time point, with survival estimates calculated from that time point and associated statistical tests being conditional on patients' landmark responses. Patients who die before the landmark time point are excluded from the analysis. In this study, landmark analysis was performed to assess the associations of best response and visit response outcomes with OS in the evaluable for response population (defined as patients with $\geq$1 measurable lesion at baseline by RECIST), excluding NE patients. Separate Cox regression models for each treatment group and time point in patients in the evaluable for response population who were alive at the response assessment time point were used to determine HRs for comparing response groups (CR/PR versus non-CR/PR, DC versus non-DC).

RESULTS

The evaluable for response population included 200 patients randomized to gefitinib and 187 patients randomized to docetaxel.

At each time point (best response at weeks 8, 12, 16, and 20), and for both treatments, survival was significantly longer among patients with DC compared with non-DC (Table 1). Similarly, survival was longer among patients with CR/PR compared with non-CR/PR. However, DC was a stronger predictor of survival than CR/PR, with smaller HRs for both treatments at all time points. The HR of DC versus non-DC was smallest at week 8 than at later time points in both treatment groups (HR 0.30, 95% CI 0.20–0.45, $p < 0.001$ with both gefitinib and docetaxel). Both CR/PR and SD as best response at week 8 were associated with longer survival times compared with PD for both gefitinib and docetaxel (Figure 1), although the docetaxel data are harder to interpret because of the small number of responders. In the gefitinib group, OS was similar among patients with CR/PR and those with SD as their best response at week 8 (Figure



CR, complete response; PD, progresssive disease; PR, partial response; SD, stable disease

FIGURE 2. Overall survival by visit response at week 4 after treatment with (*A*) gefitinib or (*B*) docetaxel (evaluable for response population).

1*A*). With both treatments, survival in patients with SD by week 8 tracked closer to survival in patients with CR/PR than to those with PD. A similar pattern of results was obtained by best response at weeks 12, 16, and 20 (data not shown).

Consistent with the findings for best response at later time points, at week 4, a visit response of DC was associated with longer survival compared with non-DC for both gefitinib and docetaxel, with smaller HRs than CR/PR versus non-CR/PR (Table 1). The magnitude of effect was similar at week 4 (visit response analysis) to week 8 (best response analysis) (gefitinib HRs of 0.33 [week 4] and 0.30 [week 8]; docetaxel HRs of 0.30 [week 4] and 0.30 [week 8]). In both treatment groups, the Kaplan-Meier survival curves for patients with CR/PR and for those with SD were separated from those with PD by visit response at week 4 (Figure 2). In the gefitinib group, there was also some separation in the survival curves between the CR/PR and SD subgroups at week 4. This was difficult to assess for the docetaxel group because of the small number of responders.

Comparing visit response at week 4 to best response at week 8 shows that most patients with a best response of CR/PR at week 8 also had a visit response of CR/PR at week 4 (27 of 28 [96%] on gefitinib; 8 of 8 [100%] on docetaxel). Similarly most patients with a best response of DC at week 8 also had a visit response of DC at week 4 (75 of 80 [94%] on gefitinib, 78 of 79 [99%] on docetaxel) (Table 2). Of those patients with a visit response of DC at week 4, 75 of 116 (65%) on gefitinib and 78 of 116 (67%) on docetaxel maintained DC at week 8.

DISCUSSION

In this landmark survival analysis of data from a single randomized phase III study, we found that DC was a better predictor of OS than CR/PR at all time points in previously treated Japanese patients with advanced NSCLC. The strongest predictor of OS for both gefitinib and docetaxel was DC as best response at week 8. Once a patient has PD, survival outcome is predicted to be markedly poorer than for patients without PD at that time. In addition, DC and CR/PR at the week 4 visit were also early predictors of survival for both gefitinib and docetaxel. Consistent with the later findings at week 8, DC at week 4 was a stronger predictor of survival than CR/PR. The strength of the predictive value of DC for

TABLE 2. Relationship Between Visit Response at Week 4 and Best Response at Week 8 (Evaluable for Response Population)

	Best Response at Week 8					
Treatment	**CR/PR**	**SD**	**PD**	**NE**	**Dead**	**Total**
Gefitinib						
Visit response at week 4						
CR/PR	27	6	0	0	0	33
SD	0	42	39	1	1	83
PD	0	0	53	0	3	56
NE	1	4	10	2	9	26
Dead	0	0	0	0	2	2
Total	28	52	102	3	15	200
Docetaxel						
Visit response at week 4						
CR/PR	8	1	1	1	0	11
SD	0	69	34	2	0	105
PD	0	0	40	0	0	40
NE	0	1	19	5	5	30
Dead	0	0	0	0	1	1
Total	8	71	94	8	6	187

CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease; NE, not evaluable.

survival was similar at weeks 4 and 8, suggesting that the visit response at week 4 may potentially be used as an early predictor of survival.

These results are consistent with those of Lara et al.[8] and Yamamoto et al.,[9] supporting the concept that week 8 is a landmark time point for advanced NSCLC patients for systemic therapy regardless of line of therapy. Lara et al.[8] found no substantial new findings from analyses at later time points (weeks 14 and 20), compared with week 8 of therapy. However, although in the current analysis visit response at week 4 was a predictor of survival, as well as best response at week 8, during second- or third-line treatment with either docetaxel or gefitinib, in our previous analysis of other studies employing first-line chemotherapy or pemetrexed as salvage therapy, week 4 was not a landmark time point, with no significant associations found between response and survival.[9]

Lara et al.[8] also found that DC at week 8 was a better predictor of survival than CR/PR after platinum-based chemotherapy in the first-line setting using either Southwest Oncology Group (modified World Health Organization) tumor response criteria or RECIST to define response.[8] In our earlier landmark analysis, tumor shrinkage rate (defined as a decrease or no change in tumor size) at week 8 was significantly associated with longer survival after first-line platinum-based chemotherapy or after salvage therapy with pemetrexed.[9] It has been suggested that because of the mechanism of action, it might be more important to achieve SD with EGFR tyrosine kinase inhibitors such as gefitinib than with cytotoxic chemotherapy[5]; however, the relationship between DC and survival seemed similar for docetaxel and gefitinib in the current analyses.

EGFR mutation is predictive of outcome to gefitinib[15–17] and it would have been interesting to have looked at the impact of EGFR mutation on our analysis. However, in this study, data on EGFR mutation were limited due to the fact that informed consent for tissue collection was obtained at a very late stage of the study and consequently was obtained from patients with relatively longer survival. Thus, biomarker analyses were not performed because analyzing these samples would have introduced considerable bias.

These data suggest that DC could give an early indication of OS time; whether this is a true surrogate for OS benefit is yet to be determined. If proven, DC could be used as a predictor in early phase development and as a possible end point in phase II trials. There are also implications for medical practice, raising the importance of continuing to treat patients who achieve SD because of the potential survival time; patients who achieve SD have a survival outcome similar to those patients with a CR/PR, suggesting that they should remain on the same treatment rather than switch to an alternative therapy because they are considered not to have responded to treatment. Further validation of DC as a predictor or surrogate of survival benefit in a prospective study is required.

In conclusion, our data suggest that DC is a stronger predictor of subsequent survival than the traditional CR/PR in patients receiving second- or third-line gefitinib or docetaxel for advanced NSCLC, as previously shown for patients who received first-line platinum-based chemotherapy. These results suggest that patients with DC should remain on their current treatment rather than switching. The strongest predictor of OS for both gefitinib and docetaxel was DC as best response at week 8.

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