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Randomized Phase II Study of Carboplatin and Etoposide With or Without the *bcl-2* Antisense Oligonucleotide Oblimersen for Extensive-Stage Small-Cell Lung Cancer: CALGB 30103

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Abstract

Purpose—To assess the efficacy and toxicity of carboplatin, etoposide, and the *bcl-2* antisense oligonucleotide oblimersen as initial therapy for extensive-stage small-cell lung cancer (ES-SCLC). *bcl-2* has been implicated as a key factor in SCLC oncogenesis and chemotherapeutic resistance.

Patients and Methods—A 3:1 randomized phase II study was performed to evaluate carboplatin and etoposide with (arm A) or without oblimersen (arm B) in 56 assessable patients with chemotherapy-naïve ES-SCLC. Outcome measures including toxicity, objective response rate, complete response rate, failure-free survival, overall survival, and 1-year survival rate.

Results—Oblimersen was associated with slightly more grade 3 to 4 hematologic toxicity (88% v 60%; $P = .05$). Response rates were 61% (95% CI, 45% to 76%) for arm A and 60% (95% CI, 32% to 84%) for arm B. The percentage of patients alive at 1 year was 24% (95% CI, 12% to 40%) with oblimersen, and 47% (95% CI, 21% to 73%) without oblimersen. Hazard ratios for failure-free survival (1.79; $P = .07$) and overall survival (2.13; $P = .02$) suggested worse outcome

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for patients receiving oblimersen. These results hold when adjusted for other prognostic factors, such as weight loss, in multivariate regression analysis.

Conclusion—Despite extensive data supporting a critical role for Bcl-2 in chemoresistance in SCLC, addition of oblimersen to a standard regimen for this disease did not improve any clinical outcome measure. Emerging data from several groups suggest that this lack of efficacy may be due to insufficient suppression of Bcl-2 in vivo. Additional evaluation of this agent in SCLC is not warranted.

INTRODUCTION

Lung cancer is the leading cause of cancer deaths in the United States.¹ Small-cell lung cancer (SCLC) represents approximately 15% of lung cancer. The majority of patients have extensive-stage disease at the time of diagnosis. First-line platinum-based chemotherapy for extensive-stage SCLC has been associated with response rates as high as 65% to 75%, but responses observed are typically of short duration, evidenced by a median survival of approximately 9 to 10 months with currently available therapies.² Five-year survival with extensive-stage SCLC is less than 1%. There is a critical need for new approaches, and new targeted agents, for this disease.³

Bcl-2 is a central apoptotic inhibitor, overexpressed by many tumors including the majority of SCLCs.^{4–7} Analyses by many groups have demonstrated that chemotherapeutic agents, including platinum compounds and topoisomerase II inhibitors, kill cancer cells by induction of the intrinsic apoptotic pathway regulated by Bcl-2.^{8–12} Bcl-2 overexpression (or elevation of the ratio of Bcl-2 to proapoptotic Bcl-2 family members) increases resistance to chemotherapy in both in vitro and in vivo models.^{13–17} An antisense oligonucleotide directed against the *bcl-2* mRNA increased the efficacy of cisplatin and etoposide against human SCLC lines in tissue culture and as murine xenografts.¹⁸ Taken together, these data suggest that suppression of *bcl-2* may significantly increase the antitumor efficacy of standard cytotoxic chemotherapy.

Oblimersen (G3139) is an antisense oligonucleotide complementary to the first six codons of the *bcl-2* mRNA, and represents the first targeted Bcl-2 inhibitor available for clinical use.¹⁹ Oblimersen is an artificial oligonucleotide in which the phosphodiester linkages of natural DNA have been replaced by phosphorothioate linkages to increase stability.²⁰ Preclinical studies have suggested that intravenous administration of oblimersen can result in cellular uptake and *bcl-2* mRNA degradation, resulting in reduction of Bcl-2 protein levels in tumor cells.²¹ Oblimersen demonstrates evident synergy with chemotherapeutic agents in multiple preclinical models.^{22–24}

We previously completed two phase I studies of oblimersen in combination with chemotherapy for SCLC.^{25,26} The first of these evaluated oblimersen with paclitaxel in patients with chemotherapy-refractory SCLC, a cohort with particularly poor prognosis and lack of response to standard therapies.²⁶ Oblimersen was administered at 3 mg/kg/d continuous intravenous infusion days 1 through 8, with paclitaxel given on day 6 of a 21-day cycle. Because of hematologic dose-limiting toxicities in two of the first three patients treated, paclitaxel dose was reduced from an initial dose of 175 mg/m² to 150 mg/m² in all subsequent patients. No objective responses were seen. Two patients had stable disease for six cycles, one of whom discontinued therapy with stable disease after a total of 10 cycles of therapy and remained without evident progression for more than 6 months.

The second phase I study evaluated oblimersen together with carboplatin and etoposide in patients with newly diagnosed extensive-stage SCLC.²⁵ The combination of carboplatin and etoposide comprise a commonly used regimen for patients with untreated SCLC and

represents a standard of care for this disease. Phase II studies of the combination of carboplatin and etoposide for untreated SCLC were initially reported in 1987.^{27,28} The efficacy of carboplatin and etoposide combination therapy for untreated SCLC is indistinguishable from that of cisplatin and etoposide, with equivalent response rates and survival duration in randomized comparisons.^{29,30}

Oblimersen dose levels evaluated in the phase I study included 5 and 7 mg/kg/d.²⁵ This study defined a recommended phase II dose for the three-drug combination of oblimersen 7 mg/kg/d on days 1 through 8, carboplatin area under the concentration curve (AUC) 5 on day 6, and etoposide 80 mg/m²/d on days 6 through 8, on a 21-day cycle. Dose-limiting toxicities were again hematologic, with two of four patients experiencing cycle 1 grade 4 neutropenia and one experiencing cycle 1 grade 3 thrombocytopenia when carboplatin was increased to AUC 6.

Objective response rate on this phase I study was 83% (10 of 12 assessable patients). However, Western blotting of total protein extracts from serial sampling of peripheral-blood mononuclear cells (PBMCs) of patients treated on this study failed to demonstrate significant change of Bcl-2 protein levels with oblimersen administration.²⁵ There may be significant differences between antisense uptake and effect on tumor and nonmalignant cells. Nonetheless this result called into question whether adequate target suppression was being achieved, and whether this somewhat encouraging response rate was in fact indicative of an enhancement of chemotherapeutic efficacy by oblimersen.

Cancer and Leukemia Group B (CALGB) 30103 is a randomized phase II study designed to evaluate toxicity and efficacy of the combination of oblimersen, carboplatin, and etoposide for the treatment of chemotherapy-naïve extensive-stage SCLC. Patients were assigned to cohorts receiving carboplatin and etoposide with or without oblimersen using a 3:1 randomization schema. The primary efficacy measure for this study, and primary statistical end point, is 1-year survival in arm A.

PATIENTS AND METHODS

Patients

Enrollment onto this study was limited to adults (≥ 18 years of age) with Eastern Cooperative Oncology Group performance status 0 to 2, histologically or cytologically documented extensive-stage SCLC, and no prior chemotherapy. Prior radiation, including CNS radiation for brain metastases, was allowed after an interval of ≥ 1 week, and after clinical recovery from the toxicity of radiotherapy. Patients with currently active second malignancies other than nonmelanoma skin cancers were excluded. Key laboratory parameters for study enrollment included adequate hematologic status (granulocytes ≥ 1,500/μL, platelets ≥ 100,000/μL) liver function (bilirubin within normal limits, AST ≤ 2.5× upper limit of normal, prothrombin time and partial thromboplastin time ≤ 1.5× upper limit of normal), and kidney function (creatinine ≤ 2 mg/dL or creatinine clearance ≥ 60 mL/min).

Enrollment and Random Assignment

Enrollment onto this study was coordinated by the CALGB Statistical Center through an on-line patient registration system. Randomization and assignment to a study arm was performed centrally by the CALGB Statistical Center. The study was reviewed and approved by the institutional review boards of all participating institutions, and signed informed consent was obtained from all patients.

Therapeutics

Oblimersen (G3139; Genta Inc, Berkeley Heights, NJ) was provided for this study through the Pharmaceutical Management Branch of the National Cancer Institute Cancer Therapy Evaluation Program. Continuous infusion pumps for oblimersen administration were provided by Genta Inc. Commercially available carboplatin (Paraplatin; Bristol-Myers Squibb, Princeton, NJ) and etoposide (VePesid; Bristol-Myers Squibb) were given in accordance with the standard preparation and administration guidelines in their respective package inserts. Antiemetic regimens and other supportive measures were at the discretion of the individual treating physician or institution.

Study Design

This study is a two-arm, randomized, phase II study using a 3:1 randomization scheme to assign patients to carboplatin and etoposide treatment with (arm A) or without (arm B) oblimersen. For patients in arm A, oblimersen was given at 7 mg/kg/d on days 1 through 8, with carboplatin administered at AUC = 5 on day 6, and etoposide given at 80 mg/m²/d on days 6 through 8 of a 21-day cycle. Identical doses and schedule of carboplatin and etoposide were used in arm B, starting on day 1 of each cycle. The target accrual was 55 patients, with 41 patients randomly assigned to arm A and 14 patients randomly assigned to arm B. Study schema is shown in Figure 1. The primary objective was to assess the overall 1-year survival percentage of patients with extensive-stage SCLC treated with oblimersen, carboplatin, and etoposide. CALGB 9033 was the last phase III study completed by CALGB that involved patients with extensive SCLC. That study reported a median survival of 9 to 10 months, a value similar to that seen in other cooperative group studies involving SCLC. The size of arm A was chosen such that it has approximately 90% power to differentiate a 12-month survival rate of 40% v 60% with a type I error of 0.10. Arm B was included to determine whether the incidence of grade 4 neutropenia or thrombocytopenia in arm A was substantially greater than that seen in arm B.

Data collection was managed by the CALGB Statistical Center. Data quality was ensured by careful review of CALGB Statistical Center staff and by the study chairperson. Statistical analyses were performed by CALGB statisticians. Participants were given a maximum of six cycles of treatment, with response evaluation after every even-numbered cycle. Patients were observed for response, failure-free survival (FFS) and overall survival (OS). Toxicity assessment and adverse event reporting were based on the National Cancer Institute Common Toxicity Criteria version 2.0. Response evaluation was performed by computed tomography scanning using Response Evaluation Criteria in Solid Tumors Group classifications.³² The response rate and its 95% CI were estimated. The difference of response rates between arms were tested by χ^2 test. FFS is defined as the time from random assignment to the date of disease progression or death, whichever comes first. OS is defined as the time from random assignment to the date of death as a result of any cause. Kaplan-Meier curves were used to characterize OS and FFS.³³ Median survival and 1-year survival percentage, as well as their 95% CIs, were computed. Log-rank test was used to test the survival difference between treatment arms.³⁴ Hazard ratio and its CI were estimated using Cox proportional hazards model. Multivariate analysis of the treatment effect on survivals were done using Cox model with other prognostic factors, such as performance status, weight loss, and pleural effusion, subject to forward variable selection.³⁵ All *P* values reported are two sided without adjusting for multiple comparisons.

RESULTS

Patient Demographics

Table 1 lists patient characteristics by treatment arm at study registration. Actual accrual to this study was a total of 63 patients (47 in arm A and 16 in arm B). Of these 63 patients, six patients assigned to arm A and one patient assigned to arm B were registered but did not receive treatment. In two cases, cancellation was due to death before any treatment was received. Except for Table 1, all results presented in this report have excluded the seven patients who were not treated. Treatment arms were well balanced for age, sex, performance status, prior weight loss, prior brain metastases, and other features (Table 1; all P values $>.50$). More than 80% of patients in both study arms were of performance status 0 to 1.

Toxicity

A major reason for inclusion of a control arm on this study was for toxicity comparison, particularly with reference to the hematologic dose-limiting toxicities seen in our prior phase I studies. A total of five patients experienced grade 4+ toxicities in cycle 1: four patients (10%) in arm A and one patient (7%) in arm B. These included grade 4 neutropenia in two patients (5%) in arm A and one patient (7%) in arm B. Two patients in arm A (oblimersen, carboplatin, and etoposide) had fatal events in cycle 1: one death was as a result of renal failure, and one death was as a result of infection with unknown absolute neutrophil count.

Table 2 summarizes adverse events through all cycles of therapy. Grade 3+ toxicities experienced by more than two study participants are tabulated individually. The summaries (maximum hematologic, maximum nonhematologic, and maximum overall) include all adverse events, regardless of frequency. Overall, patients in arm A had a higher percentage of grade 4+ toxicity (26 of 41; 63%) than those in arm B (seven of 15; 47%), but the difference is not statistically significant (Fisher's exact test, $P=.36$). The numerical difference in grade 4+ toxicity between arms was attributable to a slightly higher rate of hematologic toxicity in arm A (56% v 40%); nonhematologic grade 4+ toxicity in both arms was 20%. The most frequent grade 4 hematologic toxicities were neutropenia, leucopenia, and thrombocytopenia. Considering adverse events grade 3, addition of oblimersen was associated with a small but statistically significant increase in overall hematologic toxicity (88% v 60%; Fisher's exact test, $P=.05$).

Response and FFS

Table 3 summarizes the frequency and percentage of best overall response for patients with follow-up data. The response rate (complete and partial) is 61% (95% CI, 45% to 76%) for arm A and 60% (95% CI, 32% to 84%) for arm B ($P=1.0$; Fisher's exact χ^2 test). Complete responses were observed in one of 41 patients in arm A, and two of 15 patients in arm B. Median FFS was 6.0 months in arm A versus 7.6 months in arm B (Table 4; Fig 2). The hazard ratio for FFS in arm A versus arm B was 1.8 (95% CI, 1.0 to 3.4; score test, $P=.07$), favoring carboplatin and etoposide without oblimersen.

Survival

The primary objective of this study was to assess 1-year survival in patients with extensive-stage SCLC treated with oblimersen, carboplatin, and etoposide. Table 4 summarizes the survival data and Figure 3 provides a Kaplan-Meier curve for overall survival. To date there have been 55 deaths (41 in arm A; 14 in arm B). One patient in arm B remains alive at last follow-up, 23 months after registration. One-year OS in arm A (oblimersen, carboplatin, and etoposide) was 24% v 47% in arm B. The 1-year survival rate for arm A is far less than the prespecified 51% cutoff percentage for a trial success. This was associated with a median survival of 8.6 months for arm A and 10.6 months for arm B. The hazard ratio for death in

arm A versus arm B was 2.1 (95% CI, 1.1 to 4.1; $P = .02$). The findings of significantly worse OS for arm A compared with arm B held in a multivariate analysis using Cox model with baseline patient characteristics eligible to enter the model via a forward selection procedure. Of all potential predictors, weight loss is the most significant ($P = .38$), in addition to treatment arm. Adjusting for weight loss, the hazard ratio of the treatment effect was 2.26 (95% CI, 1.08 to 4.7, $P = .03$).

DISCUSSION

This study was designed to evaluate the hypothesis that addition of oblimersen to a standard first-line regimen for extensive-stage SCLC would improve outcome, as measured by survival at 1 year. Sample size for arm A of this study was calculated to differentiate between 1-year survival of 40% and 60%: if the true success rate of this therapy were 60% in this arm, it would be considered worthy of additional consideration; if the success rate were 40%, the regimen would be considered not worthy of additional consideration. The actual 1-year survival in arm A was 24%, clearly not supporting additional investigation of the three-drug regimen. One-year survival in the control arm was 47%, consistent with previous experience with carboplatin and etoposide.

The results of this randomized phase II study are definitively, and importantly, negative. Toxicity was similar in both arms, with a slightly higher but acceptable rate of hematologic toxicity observed in patients treated with oblimersen. Of primary concern, the addition of oblimersen to carboplatin and etoposide was not associated with improvements in objective response, complete response, FFS, or OS. Although survival comparison between arms was not a prospectively planned study end point, the hazard ratio for death suggests that the addition of oblimersen to standard therapy for this disease may have had a negative impact on survival. A clear caveat is the small sample size of the control arm, which could produce demographic differences that, although not statistically significant, might influence outcome (Table 1; all P values $> .50$).

There are several possible explanations for the lack of evident clinical benefit from the addition of oblimersen to carboplatin and etoposide in patients with SCLC. One possibility is that the target, Bcl-2, although overexpressed, is not in fact relevant in this disease. That conclusion would appear to be contradicted by a large number of preclinical analyses using a variety of approaches in vitro and in vivo consistently demonstrating that Bcl-2 suppression in human SCLC is associated with enhanced chemotherapeutic sensitivity, as well as by clinical data correlating Bcl-2 expression in SCLC with poor therapeutic response and poor clinical outcome. Most notably, more than any other solid tumor tested, SCLC demonstrates remarkable sensitivity to a high-potency, high-specificity small molecule inhibitor of Bcl-2.^{36,37} Taken together, these data support the relevance of Bcl-2 as a therapeutic target in SCLC.

An alternative possibility is that the drug has not hit the target. Oblimersen may not sufficiently suppress intratumoral Bcl-2 levels to affect chemotherapeutic sensitivity in patients with SCLC. Repeated tumor biopsies in patients with advanced SCLC, the most definitive way to assess this hypothesis, was not considered feasible in this cooperative group study. In the phase I trial defining dose and schedule for this planned randomized phase II study, repetitive PBMC collection was performed to assess Bcl-2 levels in patients receiving therapy, with the rationale that if the target were not being affected with an intravenous drug in PBMC, it was unlikely to be adequately suppressed in solid tumors.²⁵ The negative result from this simple pharmacodynamic analysis of a surrogate tissue would seem to foreshadow the primary result of this randomized study.

Prior studies have suggested that oblimersen might enhance chemotherapeutic efficacy in other diseases. These include recent phase III trials in advanced melanoma and relapsed or refractory chronic lymphocytic leukemia (CLL).^{38,39} In the 771-patient melanoma study, the addition of oblimersen to dacarbazine resulted in a trend toward improved survival (9.0 v 7.8 months; $P = .077$) and statistically significant improvements in secondary end points including progression-free survival and response.³⁸ The 241-patient CLL trial was designed to evaluate response to fludarabine and cyclophosphamide with or without oblimersen, and did show an improved response rate (17% v 7%; $P = .025$) with oblimersen.³⁹ This was not associated with a difference in OS (33.8 v 32.9 months). Both of these studies reported survival benefits in select patient subsets, including melanoma patients with normal baseline lactate dehydrogenase ($P = .02$), and CLL patients previously responsive to fludarabine ($P = .05$). The mechanistic basis of these associations is not clear. The melanoma study reported increased neutropenia and both studies confirmed increased thrombocytopenia in patients receiving oblimersen.

A final possibility to explain the apparent enhancement of anticancer therapy with oblimersen in one solid tumor (melanoma) and not another (SCLC) may be off-target effects. It has been hypothesized previously that oblimersen, an 18-mer oligonucleotide containing 3 cytosine phosphate guanine dinucleotides, may have significant immunostimulatory activity.^{40–42} Similar cytosine phosphate guanine oligonucleotides are being explored actively as anticancer immuno-therapeutics through stimulation of the Toll-like receptor 9, among other mechanisms.⁴³ In addition, recent work in both prostate and melanoma models suggests strongly that the direct anticancer effects of oblimersen may be independent of Bcl-2.^{44–46} Melanoma is notable as a solid tumor for which immunotherapy has been a primary focus of therapeutic research. Off-target effects of oblimersen, including immunostimulatory effects, could help resolve the apparent dichotomy between enhancement of response in melanoma and our data demonstrating lack of Bcl-2 target suppression, and lack of clinical benefit in patients with SCLC.

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Fig 1.
Protocol schema. AUC, area under the time-concentration curve.

Fig 2.
Failure-free survival.

Fig 3.
Overall survival.

Table 1

Baseline Patient Characteristics

Characteristic	Arm A (n = 41)		Arm B (n = 15)		Overall (N = 56)	
	No. of Patients	%	No. of Patients	%	No. of Patients	%
Age, years						
Median		69		66		68
Range		46–81		41–81		41–81
Sex						
Female	20	49	9	60	29	52
Male	21	51	6	40	27	48
Race						
White	37	90	14	94	51	91
African American	3	7	1	6	4	7
Other	1	2	0	0	1	2
Ethnicity						
Hispanic	1	2	1	7	2	4
Non-Hispanic	37	90	14	93	51	91
Unknown	3	7	0	0	3	5
Performance status						
0	16	39	6	40	22	39
1	20	49	7	47	27	48
2	5	12	2	13	7	13
Weight loss						
0%–5%	25	61	9	60	34	61
5%–10%	7	17	2	13	9	16
10%–20%	6	15	1	7	7	13
> 20%	1	2	0	0	1	2
Missing	2	5	3	20	5	9

Characteristic	Arm A (n = 41)		Arm B (n = 15)		Overall (N = 56)	
	No. of Patients	%	No. of Patients	%	No. of Patients	%
Pleural effusion						
No	26	63	10	67	36	64
Yes	15	37	4	27	19	34
Missing	0	0	1	7	1	2
Brain metastases						
No	39	95	13	87	52	93
Yes	2	5	2	13	4	7

NOTE. The balance of baseline characteristics of patients across treatment arms was tested by Wilcoxon rank sum test for age, and χ^2 test for categorical variables. All P values > .50.

Table 2

Adverse Events (grade 3; possibly, probably or definitely attributed to therapy)

Adverse Event*	Arm	Grade					
		3		4		5	
		No. of Patients	%	No. of Patients	%	No. of Patients	%
Hematologic adverse events							
Hemoglobin	A	6	15	1	2	0	—
	B	1	7	0	-	0	—
Leukocytes (total WBC)	A	14	34	6	15	0	—
	B	3	20	2	13	0	—
Lymphopenia	A	2	5	0	—	0	—
	B	2	13	0	—	0	—
Neutrophils/granulocytes (ANC/AGC)	A	12	29	21	51	0	—
	B	3	20	6	40	0	—
Platelets	A	9	22	5	12	0	—
	B	3	20	0	—	0	—
Transfusion: platelets	A	3	7	0	—	0	—
	B	1	7	0	—	0	—
Transfusion: RBCs	A	4	10	0	—	0	—
	B	1	7	0	—	0	—
Maximum hematologic adverse events	A	13	32	23	56	0	—
	B	3	20	6	40	0	—
Nonhematologic adverse event							
Fatigue (asthenia, lethargy, malaise)	A	6	15	1	2	0	—
	B	1	7	0	—	0	—
Dehydration	A	4	10	0	—	0	—
	B	0	—	0	—	0	—
Nausea	A	5	12	0	—	0	—
	B	1	7	0	—	0	—
Vomiting	A	3	7	0	—	0	—

Adverse Event *	Arm	Grade					
		3		4		5	
		No. of Patients	%	No. of Patients	%	No. of Patients	%
Infection without neutropenia	B	0	—	0	—	0	—
	A	4	10	0	—	0	—
Hyperglycemia	B	1	7	0	—	0	—
	A	3	7	0	—	0	—
Hypokalemia	B	0	—	0	—	0	—
	A	2	5	1	2	0	—
Hyponatremia	B	0	—	0	—	0	—
	A	5	12	1	2	0	—
Maximum nonhematologic adverse events	B	2	13	2	13	0	—
	A	18	44	6	15	2	5
	B	4	27	3	20	0	—
Maximum overall adverse events	A	12	29	24	59	2	5
	B	4	27	7	47	0	—

Abbreviations: ANC, absolute neutrophil count; AGN, absolute granulocyte count.

*Toxicities experienced by two patients on study are not individually listed, but are included in the summaries of maximum adverse events.

Table 3

Best Response by Treatment Arm

Response	Arm A (n = 41)		Arm B (n = 15)		Total (N = 56)	
	No. of Patients	%	No. of Patients	%	No. of Patients	%
Complete response	1	2	2	13	3	5
Partial response	24	59	7	47	31	55
Stable disease	10	24	2	13	12	21
Progressive disease	1	2	1	7	2	4
Not assessable	5	12	1	7	6	11
No data	0	0	2	13	2	4
Response rate (%)	61		60		61	
95% CI (%)	45 to 76		32 to 84		48 to 74	

Survival Data by Treatment Arm

Table 4

Outcome	Arm A (n = 41)				Arm B (n = 15)				Total (n = 56)			
	No. of Patients	%	95% CI	No. of Patients	%	95% CI	No. of Patients	%	95% CI	%	95% CI	
Survival 12 months	10	24	12 to 40	7	47	21 to 73	17	30	19 to 44			
Median survival												
OS (months)		8.6	7.2 to 10.8		10.6	8.4 to 17.0		9.1	7.5 to 10.8			
FFS (months)		6.0	5.4 to 7.2		7.6	6.4 to 9.9		6.4	5.8 to 7.6			
Arm A v Arm B		HR				95% CI						Log-Rank Test <i>P</i>
OS		2.1				1.1 to 4.1						.02
FFS		1.8				1.0 to 3.4						.07

Abbreviations: OS, overall survival; FFS, failure-free survival; HR, hazard ratio.