A randomized multicenter Phase IIb Clinical Trial of TFD725 plus docetaxel versus docetaxel for second-line treatment of stage IIIb/IV Non-Small Cell Lung Cancer that has progressed on first-line platinum-based therapy
Biostat 517, Autumn 2009 - Group 17 – 16 December 2009 - FINAL

Summary

Non Small Cell Lung Cancer (NSCLC) is the leading cause of cancer deaths in the United States. Docetaxel is a taxane that hyper-stabilizes microtubules, limiting cellular replication and, consequently, the uncontrolled cellular growth typical of cancer cells. TFD725 is a multi-receptor tyrosine kinase (RTK) inhibitor. Selective inhibition of RTKs has been explored actively as a way to limit tumor cell growth both directly and indirectly. In this study, stage IIIB and stage IV NSCLC patients were treated either with a combination of TFD725 and docetaxel or the current standard treatment of docetaxel alone to assess the efficacy and tolerability of TFD725.

A randomized, double-blind, placebo-controlled, Phase IIb clinical trial was conducted at centers in Europe and the United States. Study participants (n=188) were randomized into a placebo group (n=90) to receive docetaxel alone (75 mg/m^2 every 3 weeks) or to the study treatment arm (n=98), receiving docetaxel (50 mg/m^2 every 3 weeks) plus TFD725 (50 mg/day). No data were missing for any patients at study conclusion and there was no differential censoring between treatment group and placebo group over the observed study period. The median age of the sample was 60.5 years and composed of 104 (55%) males and 84 (45%) females. Thirty-four (18%) patients came from European study sites with the remaining 154 (82%) patients coming from North American study sites. One-hundred eighteen (63%) study participants had stage IV cancer, more advanced disease, at time of randomization and from the overall sample, 107 (57%) patients had achieved tumor response to first line therapy. The median survival time for all study participants was 13.0 months (12.2 months in the placebo group, 13.6 months in the treatment group). The primary endpoint for the study was risk of death as measured by hazards. Analysis indicated that patients in the treatment arm had an estimated risk of death 0.75 times that of patients on placebo (95% CI: 0.54 to 1.04); however, this finding was not statistically significant (p=0.0835). The treatment group fared better in survival than the placebo group among those patients who did not have advanced disease, specifically, those patients who were at stage IIIb cancer at randomization; of these stage IIIb cancer patients, those in the treatment group had a risk of death 0.53 times that of those on placebo (95% CI: 0.28 to 0.99; p=0.0460). Among patients with more advanced disease (stage IV cancer) at randomization, there was no observed significant effect of treatment on survival; these advanced disease stage patients in the treatment arm were estimated to have a risk of death 0.99 times that of advanced disease stage patients on placebo (95% CI: 0.67 to 1.46; p=0.9536). There also was no statistically significant outcome in difference of survival probability between treatment groups at 6, 12, or 15-months (respectively, p=0.4331; 0.3460; 0.0615).

Comment [A1]: how long was the follow-up?

Comment [A2]: I would put this up where you were first talking about median survival overall

Background

Lung cancer is one of the most commonly diagnosed cancers and the leading cause of cancer-related mortality, accounting for almost one-third of all cancer deaths (1). Smoking has been identified as the main risk factor for lung cancer, followed by environmental exposures including asbestos and air pollution (1). Lung cancer is classified into small cell lung cancer and non-small cell lung cancer (NSCLC) based on histology. These two types of lung cancer differ in their prognosis and treatments. NSCLC accounts for approximately 80-85% of all diagnosed lung cancer (2). The majority of NSCLC cases present with advanced stage or metastasized cancer at time of diagnosis (designated stage III, IIIb or stage IV) (1). Early stage NSCLC is usually treated with surgery, followed by adjuvant chemotherapy. In contrast, late stage NSCLC (stage III/IIIb and IV) is usually treated with chemotherapy (3,4). Approximately 50% of the patients with NSCLC are more than 70 years old at the time of diagnosis. Thus, management of treatment for these patients strives to balance prolonging survival without compromising quality of life.

First-line treatment for late stage NSCLC patients with a good performance status score on the Eastern Cooperative Oncology Group (ECOG) Performance Status Scale involves the use of platinum-based DNA-alkylating agent (cisplatin or carboplatin) (5). First-line treatment drugs have been observed to have high levels of toxic side effects; further, it has been observed that cancers become resistant to these drugs. Consequently, second-line anti-cancer drugs are almost always used for treatment of cancer patients. Options for second-line drugs include microtubule hyper-stabilizing drugs (e.g. taxanes such as docetaxel) that limit cellular replication, and therefore the uncontrolled cellular growth typical of cancer cells, or other drugs that affect DNA synthesis (6). Docetaxel is the only agent approved for both first- (7,8) and second-line (9) therapy in advanced NSCLC. Multiple randomized clinical trials have established the efficacy of combined platinum with or followed by docetaxel (7,8,10). Docetaxel has dose-dependent severe toxic side effects and has been observed to cause death at doses of 100 mg/m^2; consequently, docetaxel is usually dosed at 75 mg/m^2 (9). When used in combination with other drugs, docetaxel has been observed, sometimes, to be more toxic than when used on its own; thus, when docetaxel is used in combined drug treatment regimens, its dosing levels are decreased to 50 mg/m^2 to minimize potential toxic effects in patients (11,12). Presently, there are no studies that have evaluated whether or not docetaxel is equally, more, or less effective at 50 mg/m^2 than the medical standard dose of 75 mg/m^2.

In recent years, agents that target receptor tyrosine kinases (RTKs), such as the epidermal growth factor (EGF), which is involved in cellular survival and proliferation, and the anti-vascular endothelial growth factor (VEGF), which is involved in angiogenesis, have been pursued actively as treatment for NSCLC. Unlike most chemotherapeutic drugs that affect all dividing cells (both normal and cancer cells), many of these RTKs are expressed or over expressed only in malignant cells and have rather limited roles in normal non-embryonic tissues. These features make RTKs attractive targets as they have the potential for considerably reduced cytotoxicity (13).

Bevacizumab, a monoclonal antibody that targets VEGF, is the first targeted therapy that prolongs survival in combination with chemotherapy in advanced NSCLC (14). In a randomized phase III clinical trial conducted by the Eastern Cooperative Oncology Group (E4599), paclitaxel-carboplatin doublet therapy was compared to paclitaxel-carboplatin plus bevacizumab (15 mg/kg every 3 weeks) in 855 patients with advanced or recurrent NSCLC. The addition of bevacizumab, did increase median survival times by 2 months (12.5 vs. 10.2 months, p=0.007) and response rates (27% vs. 10%, $p < 0.0001$) were significantly higher in the treatment arm receiving bevacizumab. However, it is important to recognize that only patients meeting specific criteria were included in this Eastern Cooperative Oncology Group clinical trial described above; most notably, patients with hemoptysis at baseline; patients with squamous cell histology; patients with brain metastases; or patients with inadequate (poor) ECOG performance status were excluded from this trial. The addition of bevacizumab to paclitaxel-carboplatin chemotherapy only extends survival in selected group of patients with non-squamous cell NSCLC. In fact, previous clinical trials showed that patients with squamous cell carcinoma treated with bevacizumab exhibited increased toxicity (14,15).

Two other drugs that target EGF pathway, gefinitib and erlonitib, also have been tested for potential cancer treatment use in clinical trials. Only about 10% of NSCLC patients responded to gefinitib treatment. By analyzing the difference between patients that responded to gefinitib or not, somatic mutations in the tyrosine kinase domains of the EGFR gene were found in 8 out of 9 patients with gefinitib-responsive lung cancer, as compared with none of the seven patients with no response ($p<0.001$) (16). Similar results were also found in another study conducted in both Japan and the United States (17). With respect to erlotinib, survival was longer in erlotinib treated patients with NSCLC than in the placebo group when EGFR was expressed (hazard ratio for death, 0.68; p=0.02) or when there was a high number of copies of EGFR (hazard ratio, 0.44; p=0.008). In addition, adenocarcinoma (p=0.01) and never having smoked ($p<0.001$) were associated with an objective response (18). In a separate study, erlotinib was found to prolong survival in patients with non-small-cell lung cancer after first-line or second-line chemotherapy (19).

In addition, a phase II clinical evaluation in NSCLC is currently underway for ZD6474, a dual kinase inhibitor that selectively targets both the VEGF and EGF pathways. A phase I clinical trial has shown that it is well tolerated at a daily oral dose of ≤300mg, and EGFR mutations known to increase the sensitivity of EGFR to gefitinib and erlotinib also increased sensitivity to ZD6474 (20).

Although most RTK inhibitors have demonstrated acceptable cytotoxicity profiles, as found by the studies described above, RTK inhibitors have had rather limited success with respect to efficacy. However, when patients were selected based on factors such as genetic characteristics of their tumor, the efficacy of RTK-based drugs has been observed to improve. In this study, we assessed the efficacy of TFD725, another multi-RTK inhibitor, in prolonging patient survival in combination with docetaxel in advanced NSCLC.

Questions of Interest

Primary Question:

(1) Is second line chemotherapy using docetaxel and TFD725 associated with decreased risk of death compared to docetaxel alone as measured by hazard ratios?

Secondary Questions:

(1) Is there an observed association between treatment (50 mg/m^2 every 3 weeks of docetaxel and 50 mg/day of TFD725), when compared with placebo (75 mg/m^2 every 3 weeks of docetaxel alone), and prolonged survival at 6, 12, and 15 months in this study as measured by Kaplan-Meier estimates of survival probabilities?

(2) Is there an observed association between treatment (50 mg/m^2 every 3 weeks of docetaxel and 50 mg/day of TFD725), when compared with placebo (75 mg/m^2 every 3 weeks of docetaxel alone), and risk of death as measured by hazard ratios, when stratifying for the individual patient characteristics (abnormal LDH levels, abnormal alkaline phosphatase levels, advanced disease status (stage IIIb or stage IV cancer) at diagnosis, or response to first line therapy) that were measured at randomization?

Comment [A3]: It is unclear from this wording whether you are looking at adjustment for baseline covariates, or you are looking within subgroups.

Source of the Data

This study was a multi-center, randomized double-blind placebo-controlled Phase IIb Clinical trial assessing the efficacy of TFD725 in combination with docetaxel versus docetaxel alone in treating NSCLC in advanced disease patients. Patients were eligible for the study only if their first-line therapy did not include docetaxel; if they were under the age of 80 at time of randomization; and if they were willing to use adequate contraception during the trial. Additionally, patients were required to have a performance status score corresponding to an ECOG level less than 3 (0 is the best performance score that can be achieved) and have been diagnosed initially with either stage IIIb or stage IV NSCLC and treated with a standard platinum-based chemotherapy regimen.

One-hundred eighty-eight patients were randomly assigned to receive either 75 mg/m^2 every 3 weeks of docetaxel alone or in conjunction with TFD725 (50 mg/m^2 every 3 weeks of docetaxel and 50 mg/day of TFD725). Patients were randomized to either treatment (n=98) or placebo group (n=90), stratified by clinic site and stage of disease at initial diagnosis. Information for selected demographic characteristics and health-related measures were collected at randomization for all 188 patients in the study. Comparison of these variables allows for assessment of the homogeneity of patients between the study drug treatment group and placebo group. Demographics collected include age, sex, and continent of origin. Data concerning disease progression up to randomization include stage of disease, time from diagnosis to randomization, ECOG score, and whether or not the patient had a positive response to first-line therapy. Baseline information also was collected for general health comparisons of abnormal LDH cholesterol levels and abnormal alkaline phosphatase levels, both of which are reported in literature to be predictive of poor patient outcomes. Data were not available, however, for measures such as individual, quantitative, continuous LDH levels or alkaline phosphatase levels; these variables were only reported as binary indicators of patient status with regard to the variable. Other data that may have been useful to determine influence on a possible association between treatment and survival that were unavailable from this study include patient smoking history and patient environmental exposure to asbestos and air pollution, that may help define subgroups within the NSCLC (1). Patients were assessed for adverse events every 3 weeks and for signs of clinical or subclinical progression every 6 weeks. Patients who experienced toxicity at levels unexplained by the specified dosages were allowed to discontinue therapy; they were, however, still followed within the study. The primary outcome for the study was risk of death as defined by Cox proportional hazards.

Statistical Methods

Descriptive statistics of patients at baseline were compared across treatment groups to evaluate the effectiveness of randomization. Additionally, the censoring distribution was analyzed using Cox proportional hazards to assess any informative or non-informative censoring. Then, Kaplan-Meier survival estimates and Cox proportional hazards regression were used to analyze survival and instantaneous risk of death, respectively, associated with treatment versus placebo. Null hypotheses for all tests conducted were equality between groups being compared.

Comment [A4]: Technically, you can never tell whether there is informative censoring. But if we saw differential censoring we would worry.

There were no missing measurements in this data; consequently, all patients were included in the primary analysis. Kaplan-Meier methods were used to estimate survival probabilities defined for treatment groups and also stratified by stage of disease, abnormal LDH levels, and abnormal alkaline phosphatase levels. We chose to stratify based on these variables because each of these are known to be very strong indicators of patient outcomes. Cumulative survival probability estimates as well as 95% confidence intervals are given for 6, 12, and 15 months after study initiation. Cox proportional hazards regression was utilized to determine the instantaneous risk of death for treatment arms both overall and stratified by disease stage, abnormal LDH, abnormal alkaline phosphatase, and response to first line therapy. Estimated hazards ratios as well as 95% confidence intervals and two-sided p-values are reported from the likelihood ratio test. All tests were conducted at alpha-level 0.05; that is, two-sided p-values were considered significant only if they were less than 0.05. Analyses were conducted in both R version 2.10.0 and STATA version 10 for Windows (StataCorp LP, College Station, TX, USA).

Comment [A5]: Again, unclear. Did we do strata specific (subgroup) analyses, or just adjust for these variables in a stratified analysis.

Results

Descriptive results. There were no data missing for any of the subjects in this study sample. Table 1 presents characteristics of the study sample at baseline. The study sample was composed of 188 patients, 104 (55%) men and 84 (45%) women, with a mean age of 60.4 years (range: 46.0 -75.0 years) at baseline. Additionally, the study sample consisted of 34 (18%) patients from European study sites, while the other 154 (82%) patients were from North American study sites. Randomization into treatment arms resulted in 98 patients in the treatment group and 90 patients in the placebo group. The demographic traits of sex, continent of origin, and age were distributed evenly among the treatment group and the placebo group. Also, the mean time from initial diagnosis to randomization was approximately 10 months both in the overall study sample and within both treatment groups, ranging from 3 months to 31 months in the total sample. At randomization, an ECOG test to quantify patients' performance status was conducted, where a higher numeric score corresponded to a poorer performance. Patients with a level 3 score or worse were excluded from the study at the time of randomization. Of those patients with an ECOG score of 0, 23 (40%) were in the placebo group and 34 (60%) were in the treatment group; sixty-two (51%) patients with an ECOG score

Comment [A6]: not really a "test", just a characterization

Comment [A7]: OK to say this way, but usually we talk about what percent of tx group is ECOG=0, etc.

equal to 1 were randomized to the placebo group and 60 (49%) to the treatment group; and of those patients receiving a performance status score of 2, 5 (56%) were in the placebo group and 4 (44%) received treatment.

Additional information about patients collected at baseline includes variables that were dichotomized to describe patient LDL levels, alkaline phosphatase levels, stage of non-small cell lung cancer at initial disease diagnosis, and whether or not a patient had achieved tumor response to first line therapy. Study participants who had achieved tumor response to first line therapy, which did not include docetaxel as part of the treatment regimen, composed 57% of both the placebo group and the treatment group. After randomization into treatment arms 66% of the placebo group and 60% of the treatment group were classified as having more advanced disease. Sixteen (18%) study participants in the placebo group had abnormal LDH levels at randomization, as compared to 9 (9%) of patients randomized into the treatment group. Abnormal alkaline phosphatase levels were measured at baseline in 29 (32%) of patients randomized into the placebo group and 19 (19%) of patients randomized into the treatment arm.

Inferential statistics. First, as presented in table 2, we determined that at any given time, patients in the treatment group were 1.06 times as likely to be censored as those in the placebo group. This finding, based on a two-sided p-value (0.8458), was not statistically significant (95% CI: 0.61 to 1.83). The median survival time for all study participants was 13.0 months (12.2 months in the placebo group, 13.6 months in the treatment group). Although, data revealed that at any given time, patients in the treatment group had a risk of death 0.75 times that of patients in the placebo group (95% CI: 0.54 to 1.04), the survival probability between treatment groups was not statistically different (p=0.0835) (Graph 1).

Next, survival probability between the study drug group and the placebo group was assessed by individual patient characteristics of scientific interest (table 2, Graph 1). The only observed significant survival probability for patients in the treatment group as compared to patients in the placebo group were for patients with stage IIIb cancer without malignant pleural effusion, less advanced disease. Those patients on the study drug without advanced disease at initial diagnosis had, at any given time, a risk of death 0.53 times those patients without advanced disease at initial diagnosis in the placebo group (95% CI: 0.28 to 0.99; p=0.0460). However, in patients with stage IV cancer, more advanced disease, we did not observe a statistically significant benefit of treatment drug as compared to placebo. Patients with stage IV cancer at initial diagnosis in the treatment group were estimated to have, at any given time, a risk of death 0.99 times a stage IV study participant who was receiving placebo (95% CI: 0.67 to 1.46; p=0.9536).

We also assessed the difference in survival probability between the treatment group and the placebo group at 6, 12, and 15-months to determine if a significant difference in survival would be observed at these time periods. Our findings indicate that at no observed time period was a significant difference in survival probabilities observed between study group arms (table 3). At 15-months, toward the end of the study observation period, the treatment group had a 12.54% higher (absolute difference) survival probability than patients treated with the placebo (95% CI: -38.22% to 63.29%; p = 0.0615).

Discussion

In this study, we did not find that our treatment regimen of 50 mg/m^2 every 3 weeks of docetaxel combined with 50 mg/day of TFD725 significantly improved survival probability as compared to use of the placebo, 75 mg/m^2 docetaxel every 3 weeks. Additionally, we found that there was no significant change in lowered risk of death between treatment group and placebo group over time. Noteworthy is that for patients who began our study drug regimen at stage IIIb cancer, as compared to those patients with more advanced disease (stage IV cancer), treatment was observed to have significantly improved survival outcome. This implies that our study regimen may be effective if patients begin treatment before their disease status progresses. Further evaluation of survival probability for patients with less advanced NSCLC (<stage IV), independent of response to first line therapy, on 50 mg/m^2 every 3 weeks of docetaxel combined with 50 mg/day of TFD725 should be pursued. In addition, different combinations of RTK inhibitors and docetaxel should be used in randomized, double-blinded, placebo-controlled trials, at different dose combinations, to assess whether this type of treatment regimen may improve survival outcome in NSCLC patients over time as compared to the present standard treatment regimens.

Limitations of this study include the absence of variables that are known risk factors for NSCLC and that may have negative effects on survival outcomes, such as smoking and environmental exposures. Through randomization, we hoped to distribute patients with these characteristics in a homogenous manner between our two study group arms. However, we have no way of assessing whether or not these variables may exert an influence on survival outcome when a patient is either receiving our prescribed study regimen or a placebo, or if any potential influence on survival outcome would be systematically different between our treatment arms. It is also possible that by the time a patient has progressed to late-stage NSCLC, risk factors for cancer, such as smoking and environmental exposures, may play a very small, if any, role in survival outcome, making the absence of these variables in our data less relevant to the association we hoped to observe between treatment and survival outcome. Another study limitation is that we cannot be certain that the docetaxel dose quantity used in the drug treatment regimen for this study of 50 mg/m^2, with or without the RTK inhibitor, is equivalent in magnitude of effect or comparable in

Comment [A8]: This is consistent with the ECOG status and stage of disease: The placebo group had worse patients

Comment [A9]: Testing for the censoring distn is irrelevant. We just examine it and form an opinion.

Comment [A10]: You could also describe survival probs at, say 12 months.

Comment [A11]: Careful here. There is a multiple comparison issue. I would avoid using "stat signif" for exploratory endpoints. I would report the p value and comment on the fact that I did not adjust for multiple comparisons.

Comment [A12]: This should go up above where you talk about the median survival

Comment [A13]: Yes.

effect, to the docetaxel dose of 75 mg/m^2 received by the placebo group. Any increase in survival probability observed in the patients in the treatment group as compared to the placebo group, whether statistically significant or not, may be due to decreased toxicity effects as a result of the lower dose of docetaxel received by the treatment group as compared to the placebo group. Lastly, randomization led to the placebo group being composed of a higher percentage of patients with abnormal LDH levels and abnormal alkaline phosphatase levels as compared to the treatment group. Since randomization of study participants led to a greater percentage of patients with these biomarkers for disease severity in the placebo group as compared to the treatment arm, it may have mitigated some of the observed results between treatment group and placebo group. If this bore an influence on our observed results, then the treatment group patients, after randomization, were a group with an increased chance of survival (less severe disease) as compared to the placebo group after randomization, before beginning the prescribed study treatment. Although our results demonstrated, except in patients with stage IIIb cancer, statistically insignificant findings between treatment and survival probability, a healthier treatment group at randomization may have inflated the observed lowered risk of death, although not statistically significant, between treatment and placebo groups. Further, the statistically significant lowered risk of death observed in patients with stage IIIb cancer on treatment, as compared to the placebo group, may be partially attributed to better health status in the treatment group patients as compared to placebo group patients after randomization. Further exploration of patients' health status as defined by biological measures, and a potential association with both survival outcome and prescribed drug therapies, should be considered.

Comment [A14]: Yes. In real life we would likely have prespecified secondary analyses adjusting for important baseline variables.

Among phase II clinical trials, with respect to treatment drug efficacy, our study findings of minimal, if any, improved survival probability in the treatment arm when compared to placebo are similar to findings observed for other RTK inhibitors in earlier studies (14-16,20). However, this minimal lowered risk of death as found only in one subgroup, patients with stage IIIb cancer, should not be considered discouraging. Multiple earlier studies of RTK inhibitors in NSCLC allude to the importance of identifying subgroups of patients to target based on their tumors' genetic characteristics (such as EGFR mutations), important scientific variables which were absent, unfortunately, in this study. Also, previous studies have shown that RTK inhibitors as a group are in general well-tolerated. The observation of non-informative censoring between the two study arms could speak potentially to an equivalent toxicity effect from both the study drug dose and the placebo drug dose; however, more information including quality of life and various general health measures would be needed to truly assess this. If quality of life is not significantly compromised by the study drug regimen used in this phase II trial, further trials examining its use in the subgroup we found to respond to treatment, patients with less advanced disease status, should be explored. These additional trials may consider closer examination of scientific variables of interest, such as the genetic mutations, gene amplifications and other characteristics of individual tumors, as well as disease risk factors not collected for this study, such as smoking and environmental exposures, and levels of LDH and alkaline phosphate both pre- and post-baseline, for reasons described above.

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Table 1. Select patient characteristics, by treatment group and total

		n (%)	Mean (SD)	Minimum	Median	Maximum
Placebo Group (n=90)						
Age in years		--	60.5 (4.8)	50.0	61.0	75.0
Time from initial diagnosis to randomization (months)		--	10.2 (4.3)	3.0	10.0	27.0
European		17 (19)				
Male		47 (52)				
Tumor response*		51 (57)				
Advanced stage at diagnosis**		59 (66)				
Abnormal LDH levels		16 (18)				
Abnormal Alkaline Phosphatase levels		29 (32)				
ECOG Score†	0	23 (25)				
	1	62 (69)				
	2	5 (6)				
Treatment Group (n=98)						
Age in years		--	60.4 (5.4)	46.0	60.0	71.0
Time from initial diagnosis to randomization (months)		--	10.4 (4.8)	3.0	10.0	31.0
European		17 (17)				
Male		57 (58)				
Tumor response*		56 (57)				
Advanced stage at diagnosis**		59 (60)				
Abnormal LDH levels		9 (9)				
Abnormal Alkaline Phosphatase levels		19 (19)				
ECOG Score†	0	34 (35)				
	1	60 (61)				
	2	4 (4)				
Total (n=188)						
Age in years		--	60.4 (5.1)	46.0	60.5	75.0
Time from initial diagnosis to randomization (months)		--	10.3 (4.6)	3.0	10.0	31.0
European		34 (18)				
Male		104 (55)				
Tumor response*		107 (57)				
Advanced stage at diagnosis**		118 (63)				
Abnormal LDH levels		25 (13)				
Abnormal Alkaline Phosphatase levels		48 (26)				
ECOG Score†	0	57 (30)				
	1	122 (65)				
	2	9 (5)				

*Percent of patients that achieved tumor response to first line therapy

**Advanced stage at diagnosis was defined as malignant pleural effusion or stage IV cancer; non-advanced stage at diagnosis was defined as stage IIIb without malignant pleural effusion

†ECOG: Eastern Cooperative Oncology Group Performance Status Test; 0= Fully active, able to carry on all pre-disease performance without restriction; 1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work; 2= Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours

Table 2. Likelihood Ratio Test Results for Survival Probability, by treatment groups, when stratified by select scientific variables of interest corresponding to patient characteristics at baseline[#]

		Hazard Ratio	95% Confidence Interval	2-sided p-value
Censoring Distribution		1.06	(0.61, 1.83)	0.8458
Survival Probability		0.75	(0.54, 1.04)	0.0835
Advanced Disease Status‡	No	0.53	(0.28, 0.99)	0.0460*
	Yes	0.99	(0.67, 1.46)	0.9536
Alkaline phosphatase levels	Normal alkaline phosphatase	0.74	(0.49, 1.11)	0.1410
	Abnormal alkaline phosphatase	1.04	(0.55, 1.95)	0.9115
LDH levels	Normal LDH	0.79	(0.55, 1.14)	0.2092
	Abnormal LDH	0.72	(0.31, 1.65)	0.4382
Responded to first line therapy†	Yes	0.75	(0.48, 1.17)	0.2020
	No	0.73	(0.44, 1.21)	0.2219

[#]All hazard ratios compare the treatment group with respect to placebo group
*Statistically significant finding based on two-sided p-value <0.05
‡Advanced stage at diagnosis was defined as malignant pleural effusion or stage IV cancer; non- advanced stage at diagnosis was defined as stage IIIb without malignant pleural effusion
†Patients achieved tumor response to first line therapy

Comment [A15]: Omit this from the table. But give descriptives in the text about length of follow-up

Table 3. Kaplan-Meier Estimates: Difference in Survival Probabilities at 6, 12, and 15 months between Treatment Group and Placebo Group

	6 Month Survival Probability (95% CI)	12 Month Survival Probability (95% CI)	15 Month Survival Probability (95% CI)
Treatment Group	95.92% (89.49%, 98.45%)	61.22% (50.84%. 70.06%)	42.86% (32.96%, 52.37%)
Placebo Group	93.33% (85.76%, 96.95%)	54.44% (43.62%, 64.05%)	28.89% (19.95%, 38.43%)
Difference between treatment and placebo groups	2.59% (-33.04%, 8.22%)	6.78% (-45.79%, 59.35%)	12.54% (-38.22%, 63.29%)
Two-sided p-values	0.4331	0.3460	0.0615

Graph 1. Kaplan-Meier Estimates for selected survival probabilities, by treatment group and selected variables of scientific interest