A randomized, controlled trial of combined TFD725 / docetaxel for the treatment of relapsed non small-cell lung cancer.

BIOST517, Group #9

Summary

Lung cancer is the leading cause of death in the developed world. Treatment of relapsed non-small cell lung cancer (NSCLC) poses a particular challenge, as the current survival is less than 10%. This study investigated whether combination therapy using docetaxel plus an experimental receptor tyrosine kinase inhibitor, TFD725, leads to longer survival time than chemotherapy with docetaxel alone. We report here on the findings of a phase IIb randomized controlled clinical trial that enrolled 188 patients with stage IIIb or IV NSCLC who had failed first line chemotherapy. Patients were followed for a median of 13.2 months. The primary outcome of the study was time to death. Statistical analysis included Kaplan-Meier survival curves and Cox proportional hazards. In this study of docetaxel plus TFD725 versus docetaxel alone as second-line chemotherapy for relapsed NSCLC, we observed 4.1% greater survival (95% CI [-11.5, 19.7], p = 0.06) in the treatment group. Unadjusted Cox regression analysis revealed a hazard ratio estimate of 0.75 for the experimental group, (95% CI [0.54-1.04], p = 0.08). Multiple instances of multivariate Cox regression using treatment and each baseline covariate did not significantly alter the estimated hazard ratio of treatment. We were unable to conclude that combined TFD725/docetaxel treatment significantly improved survival compared to docetaxel alone.

Comment [A1]: Actually, the 1 day survival is on the order of 100% and the 100 year survival is on the order of 0%. So I cannot understand this comment without a timeframe.

Comment [A2]: Wrong. It was on the order of 18 months.

Comment [A3]: what timeframe

Comment [A4]: treatment to control

Background

Lung cancer is the leading cause of death in the developed world, accounting for 159,217 deaths in 2005* in the United States alone (*1*). Furthermore, although lung cancer rates are declining in wealthy nations, the incidence of lung cancer is expected to increase worldwide until 2030 (*2*). Lung cancer is difficult to treat; the average five-year survival rate for persons diagnosed with lung cancer is 15% (*3*). Because lung cancer remains such a threat to public health, it is imperative that investigators devise improved methods of diagnosing and treating the disease.

Small cell lung carcinoma (SCLC) is an aggressive subtype of lung cancer. Treatment options for SCLC are limited, and as a result prognosis for SCLC is generally poor—five-year survival for SCLC is between 5-10% (*3*). Non-small cell lung carcinoma (NSCLC) is a broader category encompassing multiple cell types. NSCLC is staged according to a four-level series defined by tumor size and degree of metastasis. If identified in stages I or II, surgical resection can be employed and prognosis improves drastically—five-year survival for NSCLC is as high as 40% in stage I, but drops precipitously to 10% by stage IIIB or IV when it can only be treated by chemo- or radiotherapy (*3*). Because most patients with NSCLC present with more advanced metastatic stages (i.e. stages III and IV), and because NSCLC typically does not respond well to established chemotherapies, better drug therapies are needed to treat them (*4*).

Because they are implicated in the regulation of cell growth, migration, and death, tyrosine kinase receptors (RTKs) are attractive targets for novel chemotherapeutic compounds. The epidermal growth factor receptor (EGFR) is a member of the RTK family; it has garnered particular interest in NSCLC therapy because of several lines of evidence implicating it in the onset of the disease. Many EGFR mutations are associated with NSCLC; these are generally gain-of-function mutations in the tyrosine kinase domain of EGFR that obviate the requirement of ligand binding for receptor activation (*5, 6*).

Another member of the RTK family implicated in NSCLC etiology is the vascular endothelial growth factor receptor (VEGFR). Interactions between VEGF and its cognate receptor promote vascular growth, a requisite step for large tumor formation (*7*). Indeed, VEGF is expressed in many NSCLCs, and it appears to be at least a modest prognostic risk factor (*7*). Bevacizumab, a monoclonal antibody directed against VEGF, has been shown to improve survival in NSCLC patients when administered in combination with carboplatin (*7*).

Inhibitors of receptor tyrosine kinases (TKIs) have been developed and applied to NSCLC patient populations with mixed results. Although improvements in response and survival are observed with the TKIs erlotinib and gefitinib, these are somewhat modest effects. Notably, these effects are not uniform across all demographic strata—women, patients of Asian descent, and patients naïve to smoking exhibit improved responses to TKIs relative to other groups (*6*). These same patient groups tend to carry mutations in EGFR. Similarly, female NSCLC patients do not receive the survival benefits observed in male patients treated with the VEGF inhibitor bevacizumab. These data have led investigators to question whether a “personalized medicine” approach could be applied to NSCLC patients; however it is not entirely clear whether EGFR mutation status or VEGF expression are general prognostic indicators or predictors of TKI treatment efficacy. Since both pathways are implicated in NSCLC pathology and they may converge on common targets, broad-spectrum inhibition of RTKs is an appealing strategy for controlling NSCLCs.

At the time of this study, the current practice was to administer first line chemotherapy consisting of an alkylating agent, usually cisplatin or carboplatin, in combination with a taxane, usually paclitaxil or docetaxel (*8, 9*). However, failure to achieve remission with these combination regimens is still quite common. This paper reports the results of a

* Most recently available data

Phase IIb clinical trial involving the experimental RTK inhibitor TFD 725. The specific aim of our study was to compare second line therapy regimens of docetaxel alone (currently considered standard of care), and docetaxel plus TFD 725 for use in patients diagnosed with stage IIIb or IV NSCLC. The overall goal was to assess the impact of the experimental drug on survival time in NSCLC patients.

Questions of interest

The specific aim of this statistical analysis was to determine if second line chemotherapy using docetaxel and TFD725 was associated with prolonged survival compared to docetaxel alone. Secondary questions of interest included whether age, sex, advanced disease, baseline LDH and alkaline phosphatase levels, performance status, or response to first line therapy modified the effect of either therapy.

Source of the data

The current study is a phase IIb clinical trial conducted at two sites, one in the United States and one in Europe. Participants were included if initially diagnosed with stage IIIb or worse NSCLC that exhibited disease progression on first line therapy[1]. Prospective participants were excluded from the study if they met any of the following criteria—(A) were subject to treatment that included docetaxel as a first-line therapy, (B) exhibited an Eastern Cooperative Oncology Group (ECOG) performance status[2] of 3 or worse at the time of randomization[3], (C) were unwilling to use adequate contraception throughout the trial, or (D) were older than 80 years of age.

188 patients were randomized to one of two treatment arms. Randomization was stratified according to clinical site and disease stage at time of randomization. Ninety patients were placed on docetaxel alone[4]; ninety-eight patients were placed on docetaxel plus TFD725[5]. Baseline information on demographics and severity of illness were collected; these included sex, age, indicators of advanced disease at time of diagnosis and patient response to first line therapy, the duration of disease at time of entry into the trial, binary indicators of whether levels of serum alkaline phosphatse and LDH were abnormal, and ECOG performance status. Treatment was discontinued in the event of unacceptable toxicity, but data regarding these events was not included in our data set. However, observation for death and clinical effects was maintained for patients that discontinued therapy. Clinicians and study participants were not aware of the treatment administered until the end of the study. Adverse effects were monitored every 3 weeks until study cessation; disease progression was monitored every 6 weeks, however this information was not made available to us. There were no missing data from either group during the period of the trial. At the time of enrollment, basic demographic and baseline disease information was gathered and is shown in Table 1.

Statistical methods

The primary predictor of interest in the present analysis was treatment arm. The primary outcome of interest is time to death regardless of cause. Descriptive statistics were generated to assess whether baseline randomization was effectively achieved and to assess for the presence of outliers (Table 1). Chi-squared analysis was used to determine whether the treatment groups differed significantly in their demographic or disease state characteristics. It should be noted that the main analysis was not contingent on these results, only the confidence in its validity. Kaplan-Meier survival estimates of survival were constructed for both treatment groups. The empirical censoring distribution was examined to check for evidence of differing censoring distributions between the two groups. At three time points of interest, arithmetic differences in survival between treatments were computed and t-tests were performed to determine significance. A Cox proportional hazards analysis was performed for the survival curves and hazard ratios were computed to test for overall differences in distribution of survival.

Subgroup analysis was performed for each covariate and adjusted Cox regression was used to assess the influence on survival of baseline characteristics asymmetrically distributed across treatment groups.

Significance was defined as a p-value lower than 0.05. Confidence intervals were calculated at 95%. All t-tests were two-sided.

Comment [A5]: Actually at multiple sites in each region

Comment [A6]: Hypothesis testing is irrelevant here. Confounding can occur in the absence of statistical significance, and statistical significance does not imply confounding

Comment [A7]: So if you checked this, why not report the median censoring time?

Comment [A8]: Probably better to call this a Z test. and to mention that it compared KM estimates using Greenwood's formula.

Comment [A9]: I would do this before the subgroups, and it should be done based on pre-specification

Comment [A10]: Explicit mention of how you handle the multiple comparisons inherent in the adjustment, subgroups.

Comment [A11]: p values

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1 First line therapy generally includes platinum based chemotherapy (cisplatin or carboplatin) in combination with a taxane (paclitaxel or docetaxel), gemcitabine, or vinorelbine.

2 ECOG is a measure of a disease's impact on patients' activity scored from 0 (fully active) to 5 (dead).

3 This level is defined as follows: "Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours." (CITE)

4 74 mg/m^2 docetaxel every three weeks

5 50 mg/m^2 docetaxel every three weeks, 50 mg/day TFD725

Results

		Docetaxel	TFD725
Subjects		90	98
Demographics			
Age (years)	*Mean*	60.5	60.4
	SD	4.8	5.4
Male (%)		52.2	58.2
European site (%)		18.9	17.3
Disease state			
Advanced disease (%)		65.6	60.2
Responding to first line Tx (%)		56.7	57.1
Time from Dx to randomization	*Mean*	10.2	10.4
	SD	4.3	4.8
Abnormal LDH (%)		17.8	9.2
Abnormal alkaline phosphatase (%)		32.2*	19.4*
ECOG (%)	*0*	25.6	34.7
	1	68.9	61.2
	2	5.6	4.1

Table 1. *Baseline characteristics of each treatment group. * = \ Abnormal alkaline phosphatase is unequally distributed between treatment arms.*

Table 1 describes the baseline characteristics of both treatment groups. Groups were similar with regard to demographics and disease status. A chi-squared test was used to simultaneously test if proportion was independent of treatment group for all of the binary variables (p=0.5082). This suggests that, for at least the binary variables, the difference in distributions are in the range of what one would expect for a trial of this size. . However, we see that the proportion of people with abnormal LDH and abnormal alkaline phosphatase were respectively 8.6% and 12.8% higher in the reference group than in the experimental group. These differences were of note because these factors are known to be associated with worse outcomes. This prompted a more detailed subgroup analysis.

A Cox proportional hazards model of time to censoring regressed on treatment group was constructed to look for evidence of differing censoring distributions. The coefficient for treatment arm was non-significant (e^{β} = 1.057, CI= (0.607, 1.842), p=0.8445). We interpreted this finding as a lack of evidence that the observed censoring distribution differed significantly from what one would expect if censoring was equally likely at all times in each group.

Comment [A12]: simultaneously? This is highly unusual, and could not be done with the usual chi squared test owing to the repeated measurements made on the same subjects.

Comment [A13]: I would argue that the DOC arm had more severe disease as evidenced by the differences in advanced disease, LDH, alkphos, and ECOG status.

Comment [A14]: Usually we anticipate the desire to do some adjustment as secondary analyses and a few secondary or tertiary subgroup analyses.

Comment [A15]: Hypothesis testing is again not too relevant here. We would probably be bothered

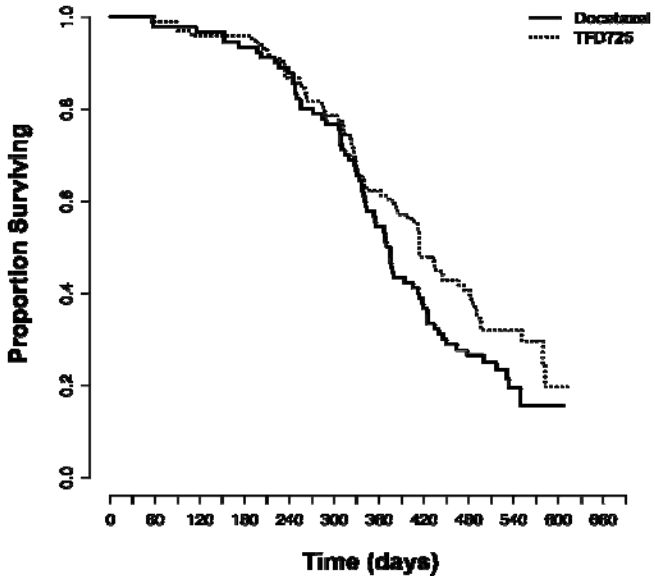

Figure 1. *Kaplan-Meier survival estimates for each treatment group.*

Months	Tx	Patients surviving (count)	Patients surviving (%)	Standard error	95% confidence interval of		p-value
6	*TFD725*	95	95.9	2.0	[99.9	92.1]	0.430
	Docetaxel	85	93.3	2.6	[98.6	88.3]	
	Difference	10	2.6	3.3	[9.1	-3.9]	
12	*TFD725*	62	62.2	4.9	[72.6	53.4]	0.279
	Docetaxel	50	54.4	5.3	[65.8	45.1]	
	Difference	12	7.8	7.2	[21.9	-6.3]	
18	*TFD725*	27	32.0	4.9	[43.2	23.7]	0.062
	Docetaxel	11	19.5	4.6	[30.9	12.2]	
	Difference	16	12.5	6.7	[25.6	-0.6]	

Table 2. *Proportion of patients surviving in each treatment condition at 6, 12, and 18 months of treatment.*

Figure 1 illustrates an unadjusted Kaplan-Meier survival curve based on treatment group. At the conclusion of the trial, difference in survival was 4.1% greater in the experimental group (95%CI: [-11.5, 19.7], p-value: 0.0607). Differences in survival between the two groups at selected time points are further described in Table 2. We examined survival at 6, 12, and 18 months; at these time points, survival did not differ under pre-specified levels of significance.

	Hazard ratio	95% confidence interval of hazard ratio			p-value
TFD725 + docetaxel	0.7467	[0.5359	,	1.04]	0.082
TFD725 + docetaxel / LDH	0.7788	[0.5544	,	1.094]	0.150
TFD725 + docetaxel / AlkPhos	0.8377	[0.5995	,	1.171]	0.300
TFD725 + docetaxel / Gender	0.7343	[0.524	,	1.029]	0.072
TFD725 + docetaxel / Age	0.7469	[0.5365	,	1.04]	0.084
TFD725 + docetaxel / Advanced Disease	0.8116	[0.5828	,	1.2565]	0.217
TFD725 + docetaxel / Response to Prior Tx	0.7374	[0.5266	,	1.033]	0.076
TFD725 + docetaxel / Duration of Disease	0.7462	[0.5356	,	1.04]	0.084
TFD725 + docetaxel / ECOG=1	0.7504	[0.539	,	1.045]	0.089
TFD725 + docetaxel / ECOG=2	0.7499	[0.5383	,	1.045]	0.089
TFD725 + docetaxel / ECOG=3	0.7469	[0.5359	,	1.04]	0.084

Comment [A16]: This is unusual to fit three models adjusting for ECOG. Generally we would either use stratified adjustment or just a continuous variable in a single model

Table 3. *Proportional hazard analysis, adjusted for abnormal LDH and abnormal alkaline phosphatase. Hazard ratios are expressed as comparisons of experimental treatment (TFD725 + docetaxel) relative to control treatment (docetaxel alone).*

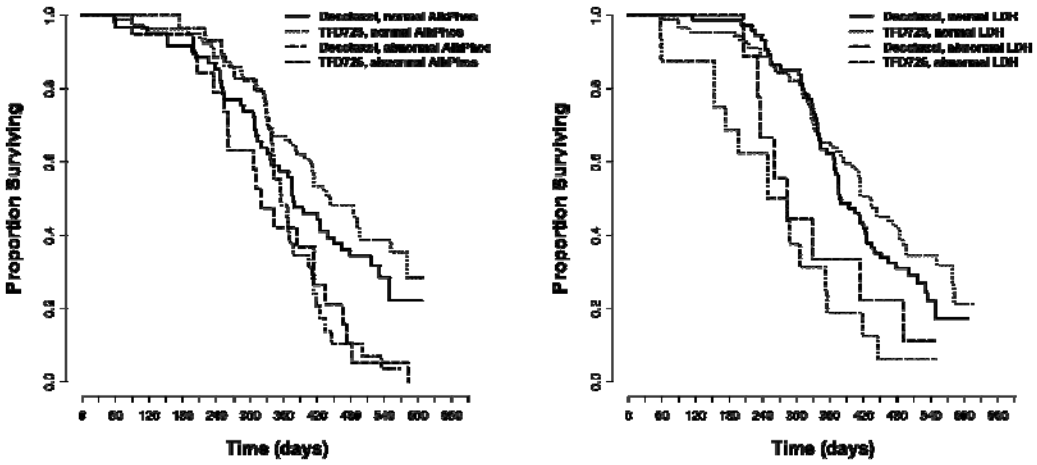

Figure 2. *(A) Kaplan-Meier estimates stratified by treatment group and alkaline phosphatase levels. (B) Kaplan-Meier estimates stratified by treatment group and LDH levels. Abnormal LDH and alkaline phosphatase levels are associated with a survival deficit irrespective of treatment arm.*

A Cox proportional hazards analysis is represented in Table 3. The primary, unadjusted, analysis (shaded) resulted in a point estimate of the hazard ratio for treatment of 0.75 with a p-value of 0.082; this provides inadequate evidence to support a differential effect of the experimental treatment compared to the control treatment. We performed multiple instances of multivariate Cox regression, combining treatment with each baseline characteristic (Table 3) to see if the inclusion of other variables affected our unadjusted estimates. Due to concerns about sample bias for some baseline characteristics, we performed stratified survival analysis on abnormal baseline levels of LDH and alkaline phosphatase (Figure 2) Abnormal LDH, alkaline phosphatase, and advanced disease at the time of diagnosis contributed the greatest increases to our adjusted hazard ratio, suggesting that some of the effect of the experimental treatment in our sample can be accounted for by differing distributions of these covariates across treatment groups.

Discussion

Although we observed a modest improvement in survival for the experimental treatment in our sample, these results are not significantly different from those that we might observe by chance. One possible explanation for these results is that the treatment is not more effective in the population of interest than the conventional treatment. Alternatively, the sample we examined might not be sufficiently large to reveal a treatment effect. The issue of sample size is particularly important because we had to adjust our model to account for an asymmetrical distribution of covariates in treatment groups. A larger sample size would help to mitigate this effect by increasing the similarity of the distributions of covariates across groups and by decreasing the variability of point estimates.

We are also unable to exclude the possibility that unmeasured covariates were randomized properly across groups, which could modify the point estimate of differential survival in either direction. Further, it could be that some of these unmeasured variables are effect modifiers, and could be used to identify subgroups of the population for whom the treatment had clinically significant differences than what was observed in the aggregate response. That is, the population of the study was not necessarily identical to the population that would experience the greatest benefit of the drug.

Previous studies of TKI therapy for NSCLC have illustrated a survival benefit for certain demographic subgroups that exceeds that of the general population. Specifically, women, persons of Asian descent, and subjects that are naïve to smoking derive greater survival benefits from TKI treatment. We may not have observed a general reduction in mortality due to obfuscation of these specific subpopulations. Furthermore, it is possible that there are even more specifically defined subgroups that respond to this therapy. In future studies then, it will be necessary to prospectively collect more demographic data to identify prospective treatment responders.

Comment [A17]: I would avoid "modify", as you are really talking about confounding here, and this might confuse the reader re effect modification

Comment [A18]: A reference is important here, and I would not even mention this without making sure to note whether these are based on post hoc subgroup analyses or are based on pre-specified analyses designed to confirm these specific questions.

1. United States Cancer Statistics. (2009), vol. 2009.
2. World Health Organization. (2009), vol. 2009.

3. J. H. Schiller, *Oncology* **61 Suppl 1**, 3 (Jan 1, 2001).
4. T. Le Chevalier, *Anticancer Drugs* **6 Suppl 4**, 13 (Jul 1, 1995).
5. T. J. Lynch *et al.*, *N Engl J Med* **350**, 2129 (May 20, 2004).
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8. Q. Chu *et al.*, *Lung Cancer* **50**, 355 (Dec 1, 2005).
9. H. Wakelee, C. P. Belani, *Oncologist* **10 Suppl 3**, 1 (Jan 1, 2005).