A Randomized Multicenter Phase IIb Trial of Docetaxel vs. Docetaxel and TFD725 in the Treatment of Recurrent and Resistant Stage IIIb/IV Non-Small Cell Lung Cancer:

Summary

Background

Non-small cell lung cancer (NSCLC) is associated with very low rates of survival and poor responsiveness to primary treatment. Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKI) have emerged as a promising approach to second-line treatment, and this study evaluates the combination of docetaxel and a novel EGFR-TKI:TFD-725 in the second line treatment of advanced NSCLC.

Objectives

The current study was designed to assess the impact of combined TFD-725 and docetaxel on patient survival in the treatment of recurrent/refractory stage IIIB/IV NSCLC in a multicenter randomized double blind placebo-controlled trial.

Methods

188 patients with recurrent or resistant stage IIIb or IV NSCLC were randomly assigned to receive either docetaxel (n = 90) or combined docetaxel and TFD-725 (n = 98). Patients were followed up for a median of 18 months. The primary outcome of interest was patient survival during the study period, which was assessed using Kaplan-Meier survival probability estimates and compared between groups using univariate Cox proportional hazard regression analysis. Exploratory subgroup analyses were conducted in order to assess the presence of effect modification by stage of disease.

Results

Median survival was 12.2 months in the docetaxel group and 13.6 months in the combined docetaxel and TFD-725 group. The risk of death in the combined group was 0.746 when compared to the docetaxel alone group (95% CI: 0.536 to 1.040), a difference that did not reach statistical significance (p=0.084). Subgroup analyses by stage revealed a risk of death of 0.530 for patients with stage IIIb disease without malignant pleural effusions in the combination arm compared to treatment with docetaxel monotherapy, (95% CI: 0.284 to 0.989). In contrast patients with more advanced disease had a risk of death of 0.988 (95% CI: 0.668 to 1.463).

Conclusions

The results of the current study did not indicate an improved overall survival when TFD-725 is added to standard docetaxel second line chemotherapy for patients with recurrent or resistant advanced-stage NSCLC. Patients with stage IIIb NSCLC without malignant effusions may have a survival benefit from the combination therapy. These new findings suggest that the combined treatment may be advantageous for patients with less severe disease, but further research is required to replicate the observed effect.

Comment [A1]: You need to make clear that you were not testing TFD + docetaxel against placebo, but instead testing TFD + docetaxel vs placebo + docetaxel

Comment [A2]: you could mention age range, sex

Comment [A3]: Was this the only subgroup you considered? If you looked at any other subgroups, you should be upfront with the number. There is a multiple comparison issue here. It is highly likely that you will find some subgroup that looks exciting, if you look long enough

Comment [A4]: This is a hazard ratio. Your wording does not make this clear. "risk of death" is going to be the hazard or probability of death, while you are comparing hazards between arms

Comment [A5]: tell how many patients were in this subgroup either here or back in the methods

Background

Lung cancer is the leading cause of cancer mortality worldwide with 80% of the cases being non-small cell lung cancer (NSCLC) and the majority of patients presenting with advanced stage disease at the time of diagnosis[1]. Primary treatment of advanced stage IIIb and IV NSCLC currently involves the use of platinum based chemotherapy and has been shown to prolong survival and improve quality of life[2].

Unfortunately the majority of patients will have disease refractory to primary chemotherapy or will experience recurrent disease following an initial response to treatment. Second line chemotherapy is generally administered in the setting of refractory or recurrent advanced NSCLC and a number of agents have been investigated in this context.

The most active agent studied to date is docetaxel. Treatment with 75 mg/m^2 of docetaxel every three weeks versus best supportive care resulted in significantly increased time to progression and median overall survival in the second-line setting [3]. Docetaxel was demonstrated to have increased activity in this setting when compared to vinorelbine or ifosfamide and resulted in improved time to progression and one year survival[4]. Despite the fact that docetaxel is the most active agent studied to date in the second line setting, response rates are poor and generally below 10%. A number of phase II trials have explored the activity of a number of two drug combinations in the second line setting. Results have generally been disappointing and substantial toxicities have been observed with no demonstrated improvement in survival over docetaxel monotherapy[5].

Novel agents have focused on the development of molecular targeted therapies in an effort to decrease side effects and improve efficacy. Epidermal growth factor receptor (EGFR) is a receptor tyrosine kinase that has been demonstrated to be expressed in the majority of NSCLC[6]. Several EGFR tyrosine kinase inhibitors (EGFR-TKI) have shown promising results in pre-clinical lung cancer models[7]. The inhibition of EGFR is thought to limit tumor growth by interfering with angiogenesis and cellular growth. A recently published large placebo controlled phase II trial of over 700 patients with recurrent advanced NSCLC treated with ertlotinib demonstrated an improvement in overall and progression free survival with minimal toxicity[8].

The observed activity and favorable side effect profiles of EGFR agents has lead to the proposed benefit of combination chemotherapy with standard cytotoxic chemotherapy. TFD-725 is a novel EGFR-TKI that has been demonstrated to have activity in pre-clinical models. Initial phase I and IIa clinical trials have demonstrated activity and acceptable safety profiles[9]. This study aims to investigate the benefit of combining standard treatment with docetaxel with TFD725 in the treatment of recurrent/refractory stage IIIB/IV NSCLC.

Questions of Interest

The primary question of interest in this analysis is whether the addition of TFD725 to docetaxel in the treatment of advanced recurrent NSCLC results in a prolonged survival when compared to docetaxel alone. For our secondary question, we conducted exploratory subgroup analyses on age, sex, stage of disease, clinic location, response to primary treatment, abnormalities in baseline LDH and Alkaline Phosphates, and baseline performance between the treatment arms to assess possible effect modifiers for prolonged survival.

Comment [A6]: So your abstract was indeed misleading in that it only mentioned the one subgroup that had interesting results

Source of the Data

Patients

Patients with stage IIIb or IV NSCLC initially who experienced progression of disease while being treated with standard first line platinum based chemotherapy were eligible for this study. Patients were eligible if they were either refractory to first line therapy or experienced recurrent disease following an initial response to treatment. Patients were ineligible if their initial chemotherapeutic regimen included docetaxel. Patients were required to have an ECOG performance status of 0-2 and were excluded if they were older than 80 years at the time of randomization or were unwilling to use adequate contraception for the duration of the trial.

Randomization and Treatment

Enrolled patients were then randomized in a 1:1 double blind fashion to treatment with either docetaxel alone at a dose of 75 mg/m^2 every 3 weeks or docetaxel 50 mg/m^2 every 3 weeks plus TFD725 at a dose of 50 mg/m^2 daily. Randomization was stratified by treatment center and stage of disease (IIIb without malignant effusions vs. more advanced disease). Dose modifications were made per protocol and treatment was continued until unacceptable toxicity occurred. A slightly reduced docetaxel dose was used in the combination arm to account for a possible increase in toxicity of the dual agent combination.

Data Collected

Baseline data were collected on each patient including medical history, physical exam with evaluation of performance status and routine laboratory analysis. Patients were monitored for toxicity every 3 weeks and were evaluated for clinical and subclinical evidence of progression every 6 weeks. Primary outcome was death from any cause. Data was available on all patients randomized and there were no missing values in our dataset. For this analysis variables are available on patient demographics including age, sex and country of treatment, all of which may represent potential confounders that should be balanced with randomization between the treatment groups. Furthermore, variables indicating the stage at diagnosis, observed response to primary therapy, and time to progression were also available. The baseline status of the patients by performance status and laboratory measurements of disease severity (as measured by lactate dehydrogenase [LDH] and alkaline phosphatase) were also available for analysis.

Statistical Methods

Descriptive statistics were used to summarize the available data and to assess the adequacy of the randomization procedures. There were no missing observations in the dataset and thus no observations were excluded from the analyses. Arithmetic means, standard deviations, and ranges were calculated for all relevant pre-treatment variables for each treatment arm. In the case of dichotomous data (e.g., sex, clinical site, abnormal LDH), only proportions were calculated as the primary summary statistic. Outcome data (i.e., time of observation in the study and patient death) were summarized similarly for the study period.

Non-informative data censoring occurs when some of the values for a variable of interest are unavailable, but are known to exceed a particular threshold. In the current study, the primary outcome of interest was patient survival following randomization to treatment. Data indicating the duration of time between randomization to death were unavailable for patients who survived beyond the conclusion of the study period (i.e., "right" censoring). Therefore, the main effect of the treatment arms on survival were assessed using Kaplan-Meier (KM) analyses on six month intervals. KM estimates allow for the computation of the conditional probability of survival within a particular interval when there are censored observations.

Stratified KM analyses were then performed on subgroup variables to look for effect modification. Age was dichotomized depending on whether an individual was above 60 or not based on previous studies. Stage was recorded as a binary variable with stage IIIb(without malignant pleural effusions) being compared to more advanced disease (IIIb with malignant pleural effusions or stage IV disease). The duration of disease was examined by observing patients who relapsed within 12 months of primary diagnosis compared to those who relapsed later and were dichotmized accordingly as a possible predictor for the study treatment. Abnormal baseline labs were examined by generating a binary variable that indicated whether a patient had either elevated LDH or Alkaline Phosphatase at the beginning of the study. Finally differences in survival probabilities and their respective 95% confidence intervals were calculated at six month intervals for the treatment arms in general and by their subgroups. P-values were also generated for each of these differences using standard t-tests for the purpose of examining significance alongside the confidence intervals.

Comment [A7]: This makes it seem that your primary endpoint was truly a multiple endpoint based on KM. But in your abstract you only report the HR. It is very important to know the pre-specified primary endpoint in a clinical trial.

Comment [A8]: Conditional on what? It is true that the KM estimates use the hazard, which is some sense conditional. But the KM estimates are based on the cumulative distribution. So your estimates are conditional on treatment group, but we would not usually use the term "conditional probability of survival" here. The "conditional probability of survival within a particular interval" seems to be trying to describe the hazard estimates, which are a means to the end of estimating the survival probability

Comment [A9]: A more typical approach would look at adjusted analyses prior to looking for effect modification

Comment [A10]: There is a HUGE multiple comparison issue here. You are looking at 30 P values here. We expect to see significance. If you really want to look for significance, you need to adjust for multiple comparisons

Since you did not adjust, you should explicitly mention that you did not adjust P values for multiple comparisons (and that is my usual approach—do not adjust in reporting, and discuss that aspect when relevant)

Also, you did not use the t test. Instead you compared KM survival estimates using a Z test of sorts along with Greenwood's formula.

Univariate Cox proportional hazard regression analyses were then used to quantify the relationships between the treatment groups (and their subgroups) and survival. The resulting hazard estimates provide the probability of risk of death over time. Both our primary and secondary analyses consisted of evaluating comparisons of hazard distributions over time for each treatment group with the null hypothesis that there was no association between risk of death and treatment group.

Hazard rations with a value less than 1 indicates better survival in the experimental group. The resulting hazard ratios and two-sided 95% confidence interval estimates were calculated to provide information about the magnitude of the relationship in risk of death between the groups and the range of true values that might be expected from the entire population. Two-sided p-values were interpreted at the 95% level, relative to a cutoff of $p<0.05$.

All analyses in the current study were conducted using either the Stata Statistical Software package, Release 11 [10] or R, release 2.9.2[11].

Comment [A11]: So here you explicitly state your primary endpoint. Change your wording up above

Comment [A12]: R was not developed by Bell Laboratories, but S was. R was modeled after S.

Results

A total of 188 patients were randomized to receive either docetaxel (n = 90) or docetaxel plus TFD725 (n = 98). Results from descriptive analyses of patient characteristics demonstrate that patients are relatively well matched on baseline characteristics between the treatment arms (Table 1). There is a slight imbalance in the distribution of patients with abnormal baseline laboratory results. In the docetaxel alone group, 18% of patients had abnormal baseline LDH and 32% had abnormal alkaline phosphatase compared to 9% and 19% of patients in the docetaxel plus TFD725 group. There is also a slight imbalance in the distribution of stage, with slightly fewer patients in the docetaxel arm having less advanced stage IIIb disease (34% vs.40%). Lastly there is a slight trend towards lower performance status in the docetaxel group.

Minimum follow up (time to first censoring) for surviving patients was 14 months in both treatment arms. Median survival was 12.2 months in the docetaxel arm and 13.6 months in the docetaxel/TFD-725 arm (Table 2). There were 72 and 68 deaths in the control and treatment arms respectively. Kaplan-Meier estimates for survival probability at 6, 12, and 18 months are also found in Table 2. The two groups demonstrate very similar survival probabilities at 6 months, but these values became increasingly divergent at 12 and 18 months.

KM survival curves are shown in Figure 1 and Table 2 presents survival probabilities for each of the treatment arms at 6 month intervals. The hazard ratio for death is 0.746 when comparing the TFD725 arm to the standard treatment arm (p=0.084). The 95% confidence interval for this hazard ratio is 0.536 to 1.040, which leads us to conclude that there is no significant difference between the treatment arms Exploratory subgroup analysis did not reveal significant differences in the risk of death by treatment group with respect to sex age, clinical location, baseline laboratory values, performance status or response to primary treatment (data not shown). However, stratification by stage did reveal a reduction in the risk of death for patients with less advanced disease in the Doectaxel/TFD725 arm over the Doectaxel arm. Patients with stage IIIb disease without malignant effusions had a hazard ratio of death 0.530 with a 95% confidence interval of 0.284 and 0.989 which was statically significant (p=0.046). In contrast patients with more advanced disease (IIIb with malignant effusions and stage IV) had a hazard ratio of risk of death of 0.988 (95% CI: 0.668 to 1.463).

Comment [A13]: I would have abstracted this a bit more and said there was a tendency toward more serious disease in the placebo group as evidenced by imbalances in LDH, alkphos, ECOG status, and stage.

Comment [A14]: Both arms received docetaxel. Better to say "docetaxel alone" every time, or to call it the placebo or control arm.

Comment [A15]: You gave the median censoring time in the abstract, so give it here as well, alongside the minimum observed censoring time.

Comment [A16]: Usually I give this sentence before the survival probabilities. With censored data, the number of events is giving an idea of the sample size (statistical information)

Comment [A17]: It is highly misleading to go cherry picking. Why not include all of the subgroups you examined in the same table as the one subgroup you found interesting. That will make clear to the reader the level to which we were data dredging

Comment [A18]: Do not use the term "statistically significant" here, and do acknowledge that the P value has not been adjusted for multiple comparisons. I would have said: "with a p value of 0.046 that was unadjusted for the multiple comparisons involved in the exploration of subgroups"

Discussion

Docetaxel is the only currently FDA approved agent for use in the second line treatment of advanced recurrent NSCLC. This trial is the first multi-center randomized controlled trial to compare the addition of a novel EGFR-TKI, TFD-725 to standard docetaxel therapy in this setting. The primary outcome of this study was death from any cause. We did not identify a statistically significant difference

in the overall risk of death during the study period of 20 months between the two treatment arms (HR 0.746, p=0.084)

Our ability to detect a difference in overall risk of death between the two groups may have been limited by an underpowered study to detect a clinically significant difference in survival. Examination of the survival curves suggest that there may be a subgroup of patients that survive beyond 1 year that might benefit from the addition of TFD-725 to second line chemotherapy. While not part of the original study design, an exploratory analysis was conducted to identify subgroups of patients that might demonstrate an improved response to combination treatment to guide further investigations. The subgroup of patients in this study with stage IIIb disease without malignant pleural effusions in the experimental arm had a statistically significantly lower risk of death when compared to those in the standard Docetaxel group. (Figure 1b). Thus patients with stage IIIb NSCLC without malignant pleural effusions may have prolonged survival with the addition of TFD-725 to standard docetaxel second line chemotherapy. In this group of patients the hazard ratio for death on the active treatment arm was 0.530, which was statistically significant (p=0.046, 95%CI: 0.284-0.989). However, these results need to be interpreted with caution due to multiple comparison issues since we did not adjust the p value to account for an overall study type I error (i.e. the more tests we conduct, the more likely we will eventually find something significant when it is not).

This analysis was limited by the lack of data on other relevant clinical outcomes. Specifically it would have been informative to have information about response rates to treatment, quality of life and toxicity experienced by subjects. Given the modest survival gains exhibited by patients with recurrent advanced stage NSCLC, it is especially relevant to ensure that this is not at the expense of significant treatment toxicity and impaired quality of life. Our study may have been unable to detect an advantage to combination therapy due to the reduced dose of docetaxel used in the combination arm. The availability of toxicity data would have allowed us to assess the impact of dual therapy on toxicity. Were there no increases in toxicity experienced in the combination arm, future trials may consider using a comparable dose of docetaxel with FTD-725 which may improve response rates.

Overall our study failed to demonstrate a significant decrease in the risk of death when FTD-725 is added to standard docetaxel chemotherapy in the second line setting for the treatment of recurrent advanced stage NSCLC. However, it did suggest that patients with stage IIIB disease without malignant pleural effusions do exhibit a survival benefit with the addition of FTD-725 and this group needs to be studied further in future trials.

Comment [A19]: This was a Phase II study. They are never fully powered.

Comment [A20]: Very good to note. (I will state however that it is extremely common that you would have pre-specified some of the exploratory subgroup analyses.)

Comment [A21]: analyses—you did lots of them, and that is an extremely important point. We would ascribe much more importance to the results from one prespecified exploratory analysis, than we would to the most exciting of 100 exploratory analyses.

Comment [A22]: This is not statistically significant owing to the multiple comparisons. The true p value might be somewhere around 0.4 (sort of made that number up—ask me why I think it might be a reasonable guess).

Comment [A23]: Again, I would report the "p value", but we need to recognize that it is not a true p value owing to the multiple comparisons.

Comment [A24]: Very good to note. And in your Methods section you should mention that your approach was to not adjust.

Comment [A25]: Yes, but why? (I look at response as "mechanism of action", but with this class of drugs I do worry about inflammatory response being confused with tumor progression.

Comment [A26]: Absolutely. What were the gains in units that matter to a patient? The mean time alive in the first 18 months post treatment is approximately 16 months for patients on expt arm and 13.4 months for patients on control arm (I did not do a careful analysis to come up with these numbers). So your point is well taken: If we put patients through an additional 2.6 months of aggressive therapy during which time they are extremely sick and in the hospital, they have not really gained anything. We need to be able to assess this

Comment [A27]: And the purpose of a Phase II trial is to gather info to see how you want to proceed in a Phase III study., more than it is to provide the definitive answer to the public health question that is most relevant.

Table 1. Patient characteristics by treatment group*

	Docetaxel arm n(%)	Doectaxel/TFD725 arm n(%)
No. of patients	90	98
Median age in years (range)	61 (50-75)	60 (46-71)
Sex		
Male	47 (52)	57 (58)
Female	43 (48)	41 (42)
ECOG Performance Status		
0	23 (26)	34 (35)
1	62 (69)	60 (61)
2	5 (6)	4 (4)
Clinical Site		
North American	73(81)	81(83)
Europe	17(19)	17(17)
Stage		
IIIb (without malignant effusion)	31 (34)	39 (40)
IIIb (with malignant effusion) or IV	59 (66)	59 (60)
Response to primary chemotherapy		
Complete or partial response	51 (57)	56 (57)
Progressive disease	39 (43)	42 (43)
Median time from initial diagnosis in months (range)	10 (3-27)	10 (3-31)
Baseline abnormal LDH	16 (18)	9(9)
Baseline abnormal alkaline phosphatase	29(32)	19(19)

* Because of rounding , not all percentages add up to 100.
ECOG: Eastern Cooperative Oncology Group

Table 2. Descriptive Statistics for Outcomes by Treatment Group

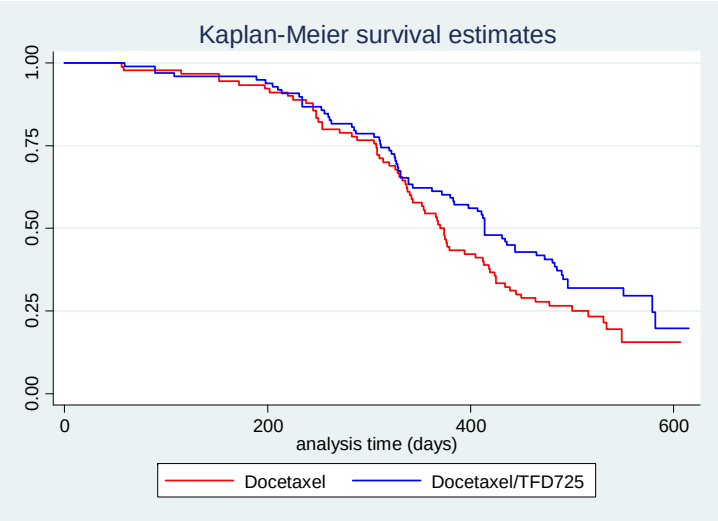
	Docetaxel arm n(%)	Doectaxel/TFD725 arm n(%)
Number of deaths	72 (80)	68 (69)
Median survival in days (range)	370 (56-607)	414 (59-615)
Range of follow up in days	451-607	456-651
Time (Months)	Proportion Surviving (95% CI)	Proportion Surviving (95% CI)
6	0.933 (0.858, 0.969)	0.959 (0.895, 0.985)
12	0.544 (0.436, 0.641)	0.612 (0.508, 0.701)
18	0.195 (0.114, 0.291)	0.320 (0.227, 0.416)

Comment [A28]: It is really more interesting to talk about the censoring distribution, than the distribution of censored observations. If the last patient you accrued died early, this provides a biased estimate of what the true limitations of your follow-up were

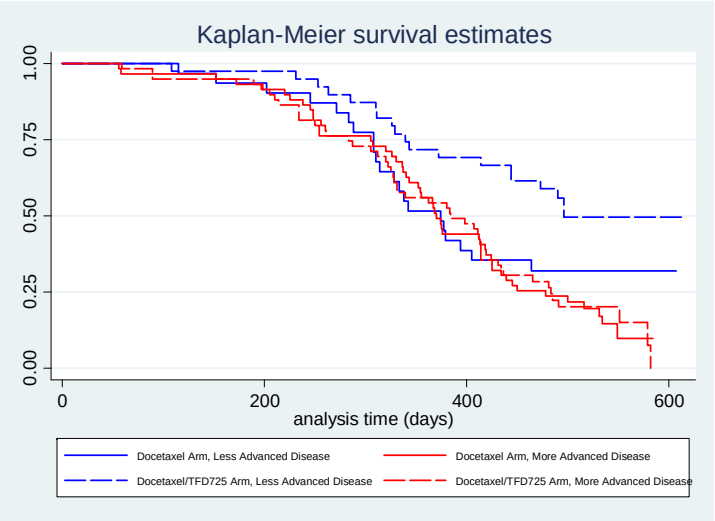
Also, changing everything to months would be more readable.

Figure 1a Kaplan-Meier curves for survival in both treatment arms 1b. Kaplan-Meier curves for survival in both treatment arms stratified by stage of disease*

1a.



1b.



* Less advanced disease = stage IIIb without a malignant pleural effusion and more advanced disease = stage IIIb with a malignant pleural effusion or stage IV.

Table 3. Estimated Differences in Survival Probabilities by Stage across Time and Hazard Ratios

	All patients			Differences Stratified by Stage: IIIb (without malignant effusion)			IIIb (with malignant effusion) or IV		
	Estimate	CI (95 %)	P-Value	Estimate	CI (95%)	P-Value	Estimate	CI (95%)	P-Value
6 months	0.026	-0.039, 0.091	0.433	0.039	-0.061, 0.139	0.444	0.017	-0.068, 0.102	0.696
12 months	0.068	-0.073, 0.209	0.346	0.202	-0.024, 0.428	0.080	-0.017	-0.196, 0.163	0.854
18 months	0.125	-0.006, 0.257	0.061	0.177	-0.054, 0.409	0.133	0.055	-0.091, 0.200	0.461
Hazard Ratio	0.746	0.536, 1.040	0.084	0.530	0.284, 0.989	0.046	0.988	0.668, 1.463	0.954

References

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