GROUP SEVEN

The Effects of the Combination Therapy of Docetaxel and TFD725 on Survival in the Second-Line Treatment of Non-small Cell Lung Cancer (NSCLC)

Summary:

Background: Current salvage therapies for patients with previously treated stage IIIb and IV non-small cell lung cancer (NSCLC) are quite limited. There is emerging evidence that a new class of drug, the tyrosine kinase inhibitors, may prove to be important adjunctive agents in the treatment of patients with locally advanced or metastatic NSCLC. Our objective was to investigate whether the addition of compound TFD725, a novel tyrosine kinase inhibitor, to a standard docetaxel regimen afforded any additional survival benefit beyond docetaxel monotherapy in patients with stage IIIb and IV NSCLC previously treated with platinum-based chemotherapy. ***Study Design/patient selection***: We conducted a multicenter double blind randomized control trial of 188 patients treated with either docetaxel or docetaxel and TFD725 to assess the effect of treatment regimen on the primary endpoint of death. All patients were younger than 80 years of age, in good functional status, and had been previously treated with a first line chemotherapy regimen that did not include docetaxel. ***Results***: We detected no statistically significant differences in the survival outcomes for those in the docetaxel and TFD725 combination therapy arm compared to those in the docetaxel monotherapy arm. The Cox proportional hazards ratio demonstrated that patients on combined therapy had on average 0.747 times the instantaneous risk of death of those taking only docetaxel at any given time (95% CI = 0.536 to 1.04, p = 0.082). Similarly, the estimated survival probability for the TFD725/docetaxel group was 2.3% higher than that for docetaxel monotherapy group at 180 days (95% CI = 4.2% lower to 8.8 % higher, p = 0.483); 7.8% higher at 360 days (95% CI = 6.4% lower to 22.1% higher, p = 0.280); and12.5% higher at 540 days (95% CI = 0.6% lower to 25.7% higher, p = 0.061), but none of these results are statistically significant. Exploratory stratified analyses based on markers of disease severity (LDH, alkaline phosphatase, and ECOG) were performed but did not show any significant effects in survival trends. ***Conclusion***: Treatment with TFD725 and docetaxel compared to docetaxel monotherapy was not associated with decreased risk of death in this population of 188 patients with advanced, previously-treated NSCLC.

Comment [A1]: randomized in 1:1 ratio, how long were they followed?

Comment [A2]: This is a Phase II study. Were these results at all promising for future trials?

Background: Lung cancer is responsible for more cancer deaths than breast, prostate and colon cancer combined (1). Non-small cell lung cancer (NSCLC) is the most common subtype of lung cancer and accounts for over 75% of all lung cancer. Treatment decisions for patients with NSCLC are determined by a variety of factors including: disease stage, performance status (as quantified by the ECOG score), and other co-morbidities (2). While early stage disease is potentially curable with multimodal therapy including cytotoxic chemotherapy, radiation, and surgical resection, locally advanced and/or metastatic NSCLC is an incurable and uniformly fatal disease. Existing treatment options, which include radiation and chemotherapy, have substantial toxicities and offer only modest benefits in terms of symptom reduction, survival prolongation, and improvements in quality of life (3)**.** First-line treatment of advanced NSCLC includes combination chemotherapy with platinum-based agents like carboplatin or cisplatin and

the addition of vinorelbine, gemcitabine, paclitaxel, or docetaxel (2-4). Even those patients that experience an initially favorable response to one of these regimens will eventually demonstrate disease progression, at which time second-line chemotherapy is employed. In these patients, second-line therapy with docetaxel has been demonstrated to be superior to best supportive care with respect to median survival and tumor response (6).

Despite the advances over the last 10 years, the benefits of conventional chemotherapy appear to have plateaued. Recent research into pathways of tumorgenesis has identified potential targets for novel pharmacotherapies that show promise in treating advanced lung cancer. Lung cancer cells may exhibit derangements via gene mutation or overexpression in various cell signaling pathways. The epidermal growth factor receptor (EGFR) is a cellular transmembrane receptor with tyrosine kinase enzymatic activity which plays a key role in many of these deranged cell-signaling pathways including: apoptosis, angiogenesis, invasion, and metastasis (7). Gefitinib (Iressa) is the first of these agents to be approved for NSCLC patients. Numerous other anti-EGFR drugs, like TFD725, are in Phase III clinical development as single agents or in combination with other anticancer modalities. While these targeted therapies have demonstrated promise of reduced toxicity and potential synergy with conventional chemotherapy, much remains to be learned about their true place in multidisciplinary treatment of patients with NSCLC. More clinical trials will be required to address which type of chemotherapy regimens should include these tyrosine kinase inhibitors and which patients should be targeted.

Question of Interest: Our objective was to investigate whether the addition of compound TFD725 to a standard docetaxel regimen afforded any additional survival benefit beyond docetaxel monotherapy, as measured by the hazard ratio, in patients with stage IIIb and IV NSCLC previously treated with platinum based chemotherapy. We also explored whether any of the disease severity variables defined at randomization, specifically LDH, alkaline phosphatase, and ECOG, altered the apparent association between treatment arm and survival. These variables, in particular LDH and alkaline phosphatase, are surrogates of disease stage.

Study Design/Source of Data: We conducted a multicenter double-blind randomized control trial comparing docetaxel monotherapy to a regimen of combination chemotherapy that included both docetaxel and the study drug, TFD725. A total of 188 patients with locally advanced or metastatic NSCLC were randomized in a 1:1 ratio to receive docetaxel alone (75 mg/m^2 every 3 weeks) or docetaxel (50 mg/m^2 every 3 weeks) plus TFD725 (50 mg/day). All patients were followed until death or completion of study protocol (for a maximum of 615 days). All patients had been diagnosed with stage IIIb or IV NSCLC and previously treated with a standard platinum-based chemotherapy regimen. Exclusion criteria included age over 80, an ECOG level of 3 or worse at randomization, or prior exposure to docetaxel. Baseline demographic characteristics including age, gender, and site where therapy was provided were obtained at study entry. Other baseline characteristics, such as disease stage, performance status (ECOG), and other objective measurements of disease severity like serum lactate dehydrogenase (LDH) and alkaline phosphatase, were also obtained at the time patients enrolled in the study. Though patients were assessed for adverse events every 3 weeks,

Comment [A3]: was the first person accrued censored or not? Why not give other descriptive statistics? And months are probably a better unit to use here

results regarding adverse events and potential toxicity of TFD725 are not presented in this manuscript.

Statistical Methods and Analysis: Descriptive statistics were calculated for the variables of interest including the demographic and disease characteristics to check for potential errors or outliers; these are presented in Table 1. There were no missing values in any of the data. Survival probabilities according to treatment group were analyzed and reported in Table 2 using the Kaplan-Meier method. A Cox proportional hazard model was used to estimate the relative instantaneous risk of death in the docetaxel plus TFD725 group compared to the docetaxel monotherapy group. In addition, differences in survival probabilities between the two treatment arms were calculated at 180, 360, and 540 days. The effect of disease severity surrogates (LDH, alkaline phosphatase, and ECOG) on overall survival by treatment arm was explored with stratified analyses depicted in Table 3 (ECOG analysis is unpublished). Within each subgroup, a Cox proportional hazard model was fit to estimate the relative risk of death in combined therapy to monotherapy, and differences in survival probabilities between the two treatment arms were again calculated at 180, 360, and 540 days. All statistical analyses were performed using statistical software (R 2.10.0 and STATA 10.0; StataCorp; College Station, TX). Differences in survival probabilities, hazard ratio estimates, 95 percent confidence intervals, and p-values are reported. All statistical tests were two-tailed, and p values < 0.05 were considered statistically significant.

Comment [A4]: Probably OK as you wrote it, but censoring is a type of missing data

Comment [A5]: did you also consider adjusted analyses? We would usually consider that before effect modification.

Comment [A6]: why?

Comment [A7]: An awful lot of analyses (but appropriate). What did you do about adjusting for multiple comparisons?

Results: The descriptive statistics in Table 1 show that subjects in the two treatment arms, docetaxel alone (n=90) and docetaxel in combination with TFD725 (n=98), were demographically similar. The average age of patients in this study was 60 and did not differ between treatment arms. Approximately half of the subjects in each treatment were male (docetaxel 52.2%, docetaxel/TFD725 58.2%). Variables measuring the history and classification of NSCLC were also similar across both treatment arms. Of the patients taking docetaxel, 65.6% were classified as having stage IV disease compared with 60.2% of patients in the combination therapy arm of the study. While most variables were similar, indicators of advanced disease were observed with higher frequency in the docetaxel treatment group than in the combination therapy group: abnormal alkaline phosphatase level (observed in 32.2% of docetaxel patients vs. 19.4% of combination patients) and abnormal LDH (17.8% vs. 9.2%). ECOG scores of 0, 1, and 2 measure the performance status of patients, with 0 being the best possible performance and 2 the worst. The distributions of these scores were similar in the two treatment groups.

Comment [A8]: all of this suggests more severe disease in placebo group

The censoring distributions for the two treatment arms were compared using Kaplan-Meier estimates. The restricted mean length of observation for the monotherapy group was 539.0 days (95% CI = 521.3 to 556.6) compared to 535.7 days (95% CI = 520.6 to 550.8) for the combination treatment arm. The similarity in the mean length of observations suggest that the two treatment arms did not significantly differ with respect to loss to follow-up.

Comment [A9]: hypothesis tests of little interest here. Just comment that censoring was similar

The Cox proportional hazards model estimates that, on average, the instantaneous risk of death at any given time in patients taking combination therapy is 0.747 times that of patients taking only docetaxel (95% CI = 0.536 to 1.04, p = 0.082). Based on this result there is no statistically significant association between treatment arms and death.

Kaplan-Meier estimates for the survival of patients in each treatment group were obtained, and the survival curves are shown in Figure 1 (Panel A). Table 2 provides the survival estimates for the treatment groups, and Table 3 provides the differences in these survival estimates as well as the hazard ratio estimates. Although the point estimates for survival are lower for the docetaxel alone group than for the combined treatment group at 180, 360 and 540 days, none of these differences are statistically significant, as shown in Table 2. At 180 days of observation, the combination group had an estimated 2.3% higher survival probability than the docetaxel alone group (95% CI = 4.2% lower to 8.8% higher, p = 0.483). At 360 days of observation, the combination group had an estimated 7.8% higher survival probability than the docetaxel alone group (95% CI = 6.4% lower to 22.1% higher, p = 0.280). By 540 days, the difference in survival probability had increased to 12.5% higher in the combination therapy arm (95% CI = 0.6% lower to 25.7% higher, p = 0.062).

For exploratory purposes, Kaplan-Meier survival curves for the groups stratified by indicators of disease status [abnormal LDH (Figure 1, Panel B), abnormal alkaline phosphatase (Figure 1, Panel C), and ECOG (figure omitted)] were also obtained. In each treatment arm, patients with abnormal LDH or alkaline phosphatase levels had decreased survival probabilities compared to patients with normal levels. Tests performed in the same way as those described above still showed no significant differences in survival probabilities or hazard ratios between treatment groups when stratified by these variables (Table 3). Though there was a statistically significant difference between the two treatment groups in patients with abnormal LDH at 180 days, this result is unlikely to be true of the population and is most likely a type I error due to multiple comparisons.

Discussion: Here we present the results of a randomized clinical trial investigating whether combination chemotherapy with docetaxel and TFD725 prolonged survival compared to docetaxel monotherapy in patients with previously treated Stage IIIb or IV NSCLC. We found that on average the instantaneous risk of death in patients taking combination therapy is 0.747 times that of patients taking only docetaxel. This estimate would be typical if the true risk of death in the population for patients on combination therapy were between 0.536 and 1.04 times that of patients on monotherapy. Thus, we found no statistically significant difference between the two therapies when comparing risk of death.

This analysis was performed after determination that the randomization of study subjects was sufficient for comparison of the treatment effects on survival in both groups. Baseline variables collected at randomization, including demographic characteristics as well as disease stage, duration, and prior treatment response, showed little variation between the two groups. This suggests that the two groups were sufficiently randomized with respect to these characteristics. The censoring distributions were also similar between the two groups, suggesting that there was not differential loss to follow up in one of the treatment arms.

We noted that the indicators of disease severity (LDH level, alkaline phosphatase level, and patient performance on the ECOG scale) were distributed differently between the two treatment arms in our sample. Due to this, as well as biological plausibility, we focused our secondary analyses on determining if the treatments performed differently in

Comment [A10]: I would usually give these descriptive statistics first and then explicitly note that HR was primary analysis

Comment [A11]: I don't see the test of interactions. (But then, I probably would not have bothered and just shown the effects within subgroups that you did show.)

Comment [A12]: Too strong wording. You are suggesting you did a Bayesian analysis. Without telling us the prior, you should avoid this. Instead, just say "results need to be interpreted cautiously due to multiple comparisons that we did not adjust for"

Comment [A13]: But you never considered an adjusted analysis

subgroups defined by these indicators, but we did not detect a statistically significant association between treatment arm and survival within any subgroup. We also note that the number of study subjects with abnormal levels of these two indicators was small in each treatment group, and a larger sample size would provide us with more precise estimates.

Limitations of our analysis include the lack of secondary clinical endpoints such as potential toxicities for TFD725 as well as effects on tumor regression. Our analysis shows the effect of the treatments on survival only; it is possible that the therapies may have had differential effects on disease progression or other physiologic indicators, and examining these effects would require further data collection and analysis.

Our analysis suggests the combination therapy of docetaxel and TFD725 does not improve survival in comparison to the monotherapy of docetaxel alone. Further investigation of other of tyrosine kinase inhibitors may identify therapies with improved effectiveness in the second-line treatment of NSCLC.

Comment [A14]: This is not motivation for subgroup analyses, just motivation for an adjusted analysis. And of course, a unifying aspect of the imbalance in LDH, alk phos, stage is more severe disease. So you could have explored that.

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Table 1. Descriptive Statistics of Baseline Patient Characteristics by Treatment Group

	Docetaxel (n=90)		Docetaxel and TFD725 (n=98)	
	mean ± std dev	*(min, max)*	*mean ± std dev*	*(min, max)*
Demographic characteristics				
Age	60.5 ± 4.8	(50.0, 75.0)	60.4 ± 5.4	(46.0, 71.0)
Ancestry, %				
European	18.9		17.4	
American	81.1		82.7	
Sex, %				
Male	52.2		58.2	
Female	47.8		41.8	
Classification of NSCLC at Diagnosis				
Indicator of Advanced Disease, %				
Stage IV (with Malignant Pleural Effusion)	65.6		60.2	
Stage IIIb (without Malignant Pleural Effusion)	34.4		39.8	
History of NSCLC				
Response to First-Line Therapy, %				
Yes	56.7		57.1	
No	43.3		42.9	
Duration*, months	10.2 ± 4.3	(3.0, 27.0)	10.4 ± 4.8	(3.0, 31.0)
Indicators of NSCLC Severity at Randomization				
LDH level, %				
Abnormal	17.8		9.2	
Normal	82.2		90.8	
Alkaline phosphatase level, %				
Abnormal	32.2		19.4	
Normal	67.8		80.6	
Patient performance on ECOG Scale, %				
Score 0	25.6		34.7	
Score 1	68.9		61.2	
Score 2	5.6		4.1	

*Time from initial diagnosis to randomization

Table 2: Probabilities of Survival by Treatment Group

	Docetaxel (n=90)		Docetaxel +TFD725 (n=98)	
	estimate	95% CI	estimate	95% CI
180 days	0.933	*0.883, 0.986*	0.959	*0.921, 0.999*
360 days	0.544	*0.451, 0.658*	0.622	*0.534, 0.726*
540 days	0.195	*0.122, 0.309*	0.320	*0.237, 0.432*

**Differences refer to docetaxel +TFD725 related to docetaxel alone.*

Table 3: Differences in Survival and Risk of Death due to Treatment: Overall, by Alkaline Phosphatase Level, and by LDH Level

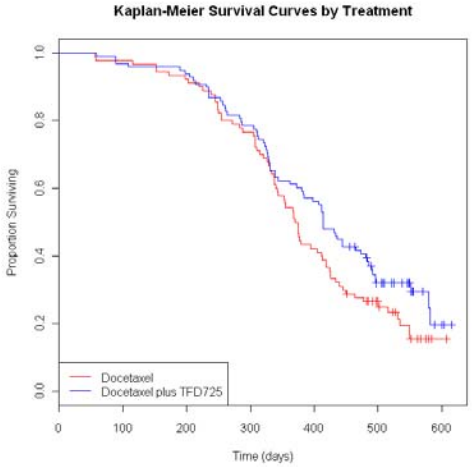
	Overall (n=90, 98)**			**Alkaline Phosphatase**						**LDH**					
				Normal (n=79, 61)			Abnormal (n=19, 29)			Normal (n=89, 74)			Abnormal (n=9, 16)		
	est	95% CI	p	est	95% CI	p	est	95% CI	p	est	95% CI	p	est	95% CI	p
180 days	0.023	*-0.042, 0.088*	0.483	0.044	*-0.037, 0.125*	0.285	-0.018	*-0.139, 0.102*	0.768	-0.031	*-0.082, 0.019*	0.222	0.313	0.085, 0.540	0.007
360 days	0.078	*-0.064, 0.221*	0.280	0.097	*-0.065, 0.259*	0.239	-0.062	*-0.349, 0.225*	0.674	0.030	*-0.118, 0.178*	0.691	0.146	-0.217, 0.508	0.430
540 days	0.125	*-0.006, 0.257*	0.061	0.101	*-0.065, 0.268*	0.233	0.018	*-0.102, 0.139*	0.768	0.122	*-0.025, 0.270*	0.103	0.049	-0.189, 0.286	0.688
risk of death	0.767	*0.536, 1.040*	0.082	0.793	*0.552, 1.139*	0.206	0.716	*0.316, 1.164*	0.431	0.737	*0.491, 1,105*	0.141	1.041	0.557, 1.945	0.900

**Differences refer to docetaxel +TFD725 related to docetaxel alone. Risks of death were estimated with Cox proportional hazards regression.*

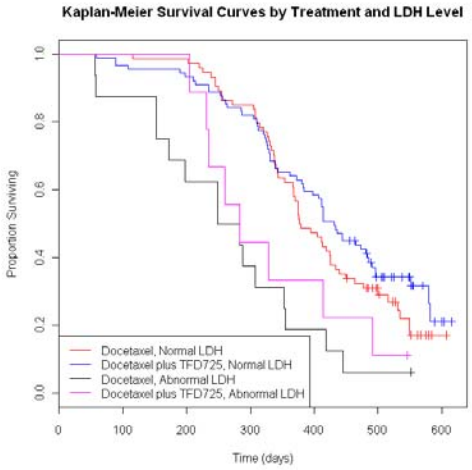
***n=(number of of patients taking combination therapy, number of patients taking docetaxel)*

Figure 1. Kaplan-Meier Estimates of Overall Survival by Treatment, by Treatment and LDH Level, and by Treatment and Alkaline Phosphatase Level.

Panel A.



Panel B.



Panel C.