Effect of TFD725, a Tyrosine Kinase Inhibitor, in Combination with Docetaxel vs. Docetaxel on Overall Survival in Advanced Non-Small Cell Lung Cancer

Group 19

SUMMARY

Rationale: Lung cancer is the leading cause of cancer-related deaths in both men and women, with non-small cell lung cancer (NSCLC) comprising 84% of all lung tumors. Current first and second-line chemotherapy result in only modest survival benefits. TFD725, a tyrosine kinase receptor inhibitor, has been shown to impair angiogenesis leading to decreased tumor growth in vitro and in animal experiments.

Methods: A multi-center, randomized, double-blind Phase IIb clinical trial was performed to determine if TFD725 combined with docetaxel prolongs survival compared to docetaxel alone. One hundred eighty-eight patients, age < 80 with performance status 2 or better with stage IIIB/stage IV non-small cell lung cancer were eligible for inclusion in the study after previous treatment with first-line platinum-based chemotherapy. Patients underwent randomization in a 1:1 fashion, stratified by disease stage and center site to receive either docetaxel (75 mg/m^2 every 3 weeks) or docetaxel (50 mg/m^2 every 3 weeks) plus TFD725 (50 mg/day). The primary endpoint was all-cause mortality. Secondary endpoints were median survival times and 1-year survival probabilities between the two groups. Cox proportional hazard regression and Kaplan-Meier estimates were used to obtain hazard ratios and compare overall survival between the two treatment groups.

Results: Baseline demographic and prognostic factors were well balanced. Overall median follow-up time was 18.3 months. Compared to docetaxel alone, the overall risk of death was 25% lower in the group treated with TFD725 combined with docetaxel, but this was not statistically significant (HR 0.75 [95% CI 0.53-1.04], two-sided p-value 0.084). TFD725 with docetaxel resulted in longer median survival times (13.8 months (SE 0.48) vs. 12.3 months (SE 0.36)), and increased one-year survival probability (0.62 [95% CI 0.52-0.71] vs. 0.54 [95% CI 0.44-0.64], two-sided p-value 0.279). A stratified analysis demonstrated that stage IIIB patients treated with TFD725 and docetaxel had a risk of death that was 47% lower compared to docetaxel alone (HR 0.53 [95% CI 0.28-0.98], two-sided p-value 0.046). Although not statistically significant, they also had improved median survival times compared to stage IV patients (16.5 months (SE-) vs. 12.5 months (SE 0.85)) and better one-year survival probabilities (0.72 [95% CI 0.55-0.83] vs. 0.52 [95% CI 0.33-0.67], two-sided p-value 0.079). Similar results were not observed in stage IV disease patients (HR 0.99 [95% CI 0.67-1.46], two-sided p-value 0.954).

Conclusion: TFD725 in combination with docetaxel does not improve overall survival in all patients diagnosed with advanced NSCLC, but does suggest a trend of improved overall survival in patients with specifically stage IIIB disease. In stage IV disease patients, further studies would need to evaluate whether TFD725 was associated with life-threatening toxicities.

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

Comment [A2]: was this prespecified? were other subgroups considered?

Comment [A3]: Your wording tends to suggest that you think the subgroup analysis in stage IIIb patients is conclusive. It is not. There is a multiple comparison problem. However, it might be indicated to restrict Phase III studies just to this group, while planning on a HR of 0.75

BACKGROUND

In the United States in 2005, an estimated 172,570 new cases of lung cancer are expected, with an estimated 163,510 deaths from the disease, making it the leading cause of cancer-related deaths among men and women (1). Among the various histologic types of lung cancer, non-small cell lung cancer (NSCLC) comprises 84% of all lung tumors (2). Despite efforts to identify and develop tools for screening and early detection, approximately 30% of NSCLC patients present with unresectable stage IIIB disease, and 45% present with metastatic disease at the time of diagnosis, with subsequent 5-year survival rates ranging from 5-15% and <5%, respectively (3).

For patients with adequate performance status, first-line platinum-based chemotherapy results in modest improvements in survival and enhances quality of life (4-6). A randomized phase III trial comparing three

platinum-based doublet chemotherapy regimens (carboplatin/paclitaxel, cisplatin/gemcitabine, cisplatin/docetaxel) to a reference regimen of cisplatin/paclitaxel found similar median survival times of approximately 8 months and a 1-year survival probability of approximately 35% (7).

Most patients will fail to respond or relapse after first-line chemotherapy, and docetaxel is currently the only second-line agent that has established a survival benefit versus best supportive care in two randomized studies. The median survival on docetaxel was 7.0 months (95% confidence interval 5.5 to 9.0 months) vs. 4.6 months (95% confidence interval 3.7 to 6.0 months) on best supportive care (log rank p = 0.047), with 1-year survival rates of 37% vs. 12% in the two groups, respectively (chi square test p = 0.003) (8). After adjustment for other variables that could contribute to improved survival such as performance status, number of organs involved, and number of prior chemotherapy regimens, treatment with docetaxel was found to have a statistically significant impact on survival (HR 0.484, two-sided p-value 0.004) (8). A subsequent study suggested that after second-line treatment with docetaxel, stage IIIB patients had statistically significant longer overall survival time than those with stage IV disease (26.5 months vs. 16.0 months, p=0.02) (9). Similar to first-line chemotherapy, however, these outcomes are modest at best.

Given the limitations of current chemotherapy and with advances in tumor biology, there is growing interest in seeking new molecular targets for lung cancer treatment. Receptor tyrosine kinases are commonly found in normal cells. These receptors have a general structure consisting of an extracellular site for ligand binding, a transmembrane region, and a cytoplasmic or intracellular domain that contains a tyrosine kinase region (10). When a ligand, such as a growth factor, binds to the receptor, the tyrosine kinase part of the receptor is activated, leading to receptor dimerization, autophosphorylation, and subsequent initiation of several signaling pathways that can involve cell proliferation, inhibition of apoptosis, and angiogenesis (11). As a result of mutation, certain tyrosine kinase receptors associated with growth factors (e.g. epidermal growth factor receptor (EGFR), vascular endothelial growth factor (VEGF)) can be over expressed or have abnormally increased function which can lead to cell transformation, unchecked growth, and enhanced survival of resulting cancerous cells (10). Novel agents are being developed that target specific receptor tyrosine kinases involved in lung cancer in either of two ways: by inhibiting ligand binding in the extracellular domain via a monoclonal antibody, or inhibiting intracellular tyrosine kinase activity via a tyrosine kinase inhibitor (12). The overall goal of this study is to determine if a tyrosine kinase inhibitor, TFD725, when given with docetaxel as second-line chemotherapy is associated with increased survival compared to docetaxel alone.

QUESTIONS OF INTEREST

Client question:

> Is second-line chemotherapy using TFD725 in combination with docetaxel associated with decreased all-cause mortality compared to docetaxel alone?

Our questions:

- Is TFD725 in combination with docetaxel associated with improved median survival time?

- Is TFD725 in combination with docetaxel associated with better 1-year survival probability?

- Given findings from a previous study, is the association between treatment with TFD725 and docetaxel and survival modified by disease stage?

Comment [A4]: What is your primary endpoint. In your summary you seemed to focus on HR, not median or 1 year survival.

SOURCE OF THE DATA

This is a multi-center, phase IIb, randomized, double-blind clinical trial of TFD725 combined with docetaxel vs. docetaxel alone after first-line, platinum-based chemotherapy. Patients were stratified by site of treatment (North America vs. Europe) and stage of disease (stage IIIB without malignant pleural effusion vs. stage IV including patients with malignant pleural effusion) and then randomly assigned in a 1:1 ratio to receive either docetaxel (75 mg/m^2 every 3 weeks) or docetaxel (50 mg/m^2 every 3 weeks) plus TFD725 (50 mg / day). Patients were eligible for the study if they were diagnosed with stage IIIB or IV NSCLC and had been treated with a first-line, platinum based chemotherapy regimen. Exclusion criteria included any of the following: 1) docetaxel use during first line chemotherapy, 2) performance status, as measured by the Eastern Cooperative Oncology Group (ECOG) scale, of 3 or worse at randomization, 3) age greater than 80 years at randomization, or 4) unwillingness to use adequate contraception during the trial.

The primary endpoint was all-cause mortality. Patients were followed while on therapy, and in the event they discontinued medication for the primary endpoint, data were analyzed according to an intention to treat principle.

Comment [A5]: what summary measure? HR?

One hundred eighty-eight patients met eligibility criteria and were enrolled in the study. Baseline data were obtained, which included information on: age, gender, center/site of treatment (North America vs. Europe), stage of disease at diagnosis, whether there was a tumor response to first line treatment, duration of disease (time from diagnosis to randomization), ECOG performance status, serum lactate dehydrogenase (LDH), and alkaline phosphatase levels. With the exception of center/site of treatment, all of these variables have been associated with survival. Because of randomization, we will not consider these variables as potential confounders. Because a previous study showed differential survival by disease stage, we are interested in whether stage of the disease at diagnosis could potentially modify an association between TFD725 and survival (i.e. effect modification). Patients were followed for a maximum of 615 days and assessed every 3 weeks for adverse events and every 6 weeks for clinical progression. Data on time until death or end of the study were right censored, but otherwise, there were no missing data.

Comment [A6]: Good to provide this justification. how did you handle multiple comparisons?

Comment [A7]: Is this true? Did the first patient accrued die, or was he/she censored. You need to report on the censoring distribution, not the obstime variable (that is a combination of follow-up time (for censored patients) and time to death (for uncensored patients).

STATISTICAL METHODS

We tabulated standard descriptive statistics for the baseline variables across treatment groups. For the right-censored data, we created a new variable for follow-up time by dividing the observed time by 30, so that our analysis could be interpreted based on months instead of days. Kaplan-Meier estimates were obtained to analyze the censoring distribution of follow-up time to assess for any differences in follow-up time between the two groups. For the primary endpoint, the hazard ratios across treatments groups were obtained using the Cox hazard proportional regression with "robust" option to eliminate the need for proportional hazards. Point estimates for the hazard ratio, 95% confidence intervals, and p values are reported. The significance level of hypothesis testing is 0.05. For the secondary endpoints, Kaplan-Meier estimates were obtained to analyze median survival time and 1-year survival probabilities for both treatment groups. We also did stratified analyses with the hypothesis that disease stage at baseline may be an effect modifier. In addition, whether the other baseline prognostic variables are also effect modifiers will be addressed in exploratory analyses obtained by stratifying by the variable in question. We reported the estimated hazard ratios, 95% confidence intervals, and p values stratified by groups defined by these variables. The significance level of hypothesis testing is 0.05. All statistical analysis was performed using Stata 11.0 (StataCorp, College Station, TX).

Comment [A8]: Good to do. (I use 30.4 days/ month).

Comment [A9]: This is Stata terminology. General description would be "the Huber-White sandwich estimator".

Comment [A10]: presumably you are reporting two-sided p values then.

Comment [A11]: you really liked this sentence

RESULTS

In 2003, 188 patients were enrolled in the study and randomly assigned to TFD725 combined with docetaxel (N=98) and docetaxel alone (N=90). 154 (82%) were enrolled and treated in Europe and 34 (18%) in North America. Baseline patient characteristics for the total cohort and by treatment group are summarized in Table 1. No significant baseline differences were observed between the group receiving TFD725 combined with docetaxel and the group receiving docetaxel alone. There was no missing data, and follow-up was obtained on all 188 patients regardless of whether they stopped treatment early. Patients were followed for a maximum time period of 615 days. Median follow-up was similar between the TFD725 + docetaxel group (18.4 months) and docetaxel group (18.2 months) (Table 2).

The primary endpoint was all-cause mortality risk between the two treatment groups. Based on Cox proportional hazards regression, the risk of dying from any cause was 25% lower in the TFD725 + docetaxel group compare to the group treated with docetaxel alone, although this result was not statistically significant (95% CI 0.54 to 1.04, p=0.084) (Table 2).

To put the primary endpoint into perspective, we evaluated secondary endpoints of median survival time and 1-year survival probabilities using Kaplan-Meier survival curves to compare the TFD725 + docetaxel treatment group to docetaxel alone (see Figure 1). The survival curves show a generally higher survival probability for the TFD725 + docetaxel compared with the docetaxel group. The separation between the two survival curves is greater over longer observation time (roughly 12 months after randomization). Specifically, the estimated 1-year survival was 62% for patients treated with TFD725 compared to 54% for patients treated with docetaxel alone, for a difference in survival probability of 8% (95% CI 6.3% lower to 2.19% higher, two-sided p-value 0.279). The median survival time for group treated with TFD725 is 13.8 months (SE 0.48) compared to 12.3 months (SE 0.36) for the group treated with docetaxel alone, a statistically significant difference of 1.5 months (two-sided p-value 0.0124). These results are summarized in Table 3.

Given our concern for effect modification by disease stage, a stratified analysis was performed. Disease stage was found to modify the association between TFD725 treatment and survival. At any given point in time, patients with stage IIIB disease were 47% less likely to die from any cause when treated with TFD725 compared to docetaxel alone (95% CI 0.28-0.98, two-sided p-value = 0.046), a statistically significant difference. Patients diagnosed with stage IIIb disease who were treated with TFD725 + docetaxel had an increased median survival time of 16.5 months compared to 12.5 months for a difference of 4 months. Although we cannot calculate an exact p-value given that there is no standard error in the TFD725+docetaxel group (i.e. after 16.5 months, survival probability remains linear at 0.5 throughout the rest of the study), this is likely a statistically significant difference, given that the overall median survival time is different between treatment groups, but there was no statistically significant difference in the stage IV disease stratum. When comparing 1-year survival probabilities, there was an increased survival probability of 20% when TFD725 was added to the regimen ([95% CI 2.4% lower to 42.8% higher], two-sided p-value = 0.079), although these results were not statistically significant. Similar results were not seen in patients diagnosed with stage IV disease. In this group, the risk of dying from any cause was 1% lower in the TFD725 + docetaxel group compared to the group treated with docetaxel alone ([95% CI 33% lower to 46% higher, two-sided p-value 0.954). In stage IV disease patients, there was not a statistically significant difference between treatment with TFD725 + docetaxel vs. docetaxel with regard to median survival time (12.8 months (SE 1.32) vs. 12.3 (SE 0.38), two-sided p-value 0.716) or 1-year survival probability (difference 0.00, [95% CI 17.9% lower to 17.9% higher], two-sided p-value 0.852). In the exploratory analyses, no other baseline prognostic variables modified the association between treatment with TFD725 and survival (Table 3).

Comment [A12]: Statistical significance is irrelevant. There was a somewhat troubling tendency for the placebo patients to have more serious disease (advanced stage, abnormal LDH and alk phos, worse ECOG)

Comment [A13]: these are the better descriptions to use for the censoring

Comment [A14]: I typically give the descriptive KM estimates first, and then give the inferential HR analysis

Comment [A15]: This is not your primary endpoint and it is not adjusted for multiple comparisons. Avoid using “stat signif”. Just report on the inference (incl p values) and maybe explicitly state that it is not adjusted for multiple comparisons.

Comment [A16]: This is not stat signif once you consider you had two subgroups (and you looked at overall HR, overall KM, etc.)

DISCUSSION

The primary objective of this trial was to judge the efficacy of TFD725 when added to second-line therapy with docetaxel with regard to overall survival in advanced stage NSCLC. We did observe that patients treated with TFD725 combined with docetaxel had a median survival time that was higher by 1.5 months. This was a statistically significant difference, although whether this is a clinically relevant difference depends on other factors not measured in this trial including tumor response and quality of life as well as the individual patient. In addition, there was not a statistically significant difference in 1-year survival probabilities between treatment groups or risk of death from any cause.

Based on a previous study that observed differential survival according to disease stage at the time of diagnosis, we were concerned that any association between TFD725 and decreased mortality may be modified by disease stage at presentation. In stratified analyses, disease stage was observed to modify the effect of treatment with TFD725 on survival. At any given point in time during the study, patients diagnosed with Stage IIIB NSCLC who were treated with TFD725 combined with docetaxel had a risk of dying from any cause that was 47% lower compared to otherwise similar patients treated with docetaxel alone, a statistically significant difference (HR 0.53 [95% CI 0.28-0.98], two-sided p value = 0.046). In addition, median survival time was 4 months longer in the stage IIIB group treated with TFD725 compared to docetaxel alone.

Treatment with TFD725 did not show a statistically significant decrease in all-cause mortality risk in stage IV patients (HR 0.99, [95% CI 0.67-1.46], two-sided p-value 0.954). One concerning aspect of this trial, however, is the possibility that treatment with TFD725 may be harmful in stage IV patients. The upper bound of the 95% confidence interval in this group is up to 1.46, suggesting that the addition of TFD725 may result in a 46% higher risk of death from any cause in patients with stage IV disease.

The study had several limitations. We lose precision when having multiple summary measures. Because of multiple comparisons in this study, we can inflate the type I error. Although the censoring distribution was not significantly different between treatment groups, it is possible that there was informative censoring between treatment groups, especially since the improvement in survival with TFD725 was seen only in stage IIIB patients. In addition, other variables may modify the association observed between TFD725 and survival that were not included in this study such as ethnicity/race and NSCLC histologic subtypes.

Comment [A17]: Also placebo group had more serious disease. In real life we might have prespecified adjusted analyses including the important baseline variables.

Our results require confirmation in future clinical trials with TFD725 that would recruit patients diagnosed with only stage IIIB NSCLC (without malignant pleural effusion). In addition, future studies with other endpoints such as tumor response, adverse side effects and toxicity with TFD725 treatment, relapse-free survival, and quality of life could support the argument that TFD725 is beneficial in advanced NSCLC when added to docetaxel.

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Table 1. Baseline characteristics of patients

Characteristic	Total Cohort (N=188)	Docetaxel (N=90)	Docetaxel + TFD725 (N=98)
Age (years)			
Median	60.5	61	60
Mean (SD)	60.4 (5.11)	60.5 (4.79)	60.3 (5.41)
Range	46-75	50-75	46-71
Sex (%)			
Male	55.3	52.2	58.2
Female	44.7	47.8	41.8
Study center (%)			
North America	81.9	81.1	82.7
Europe	18.1	18.9	17.3
Performance status (%)			
0	30.3	25.5	34.7
1	64.9	68.9	61.2
2	4.8	5.6	4.1
Disease stage (%)			
Stage IIIb	37.2	34.4	39.8
Stage IV*	62.8	65.6	60.2
Response to first-line chemotherapy (%)			
Yes	56.9	56.7	57.1
No	43.1	43.4	42.9
Duration of disease (months)			
Median	10	10	10
Mean (SD)	10.3 (4.56)	10.2 (4.34)	10.4 (4.77)
Range	3-31	3-27	3-31
Lactate dehydrogenase (LDH) level (%)			
Abnormal	13.3	17.8	9.2
Normal	86.7	82.2	90.8
Alkaline phosphatase level (%)			
Abnormal	25.5	32.2	19.4
Normal	74.5	67.8	80.6

*includes patients with malignant pleural effusion

Figure 1. Kaplan-Meier survival estimates

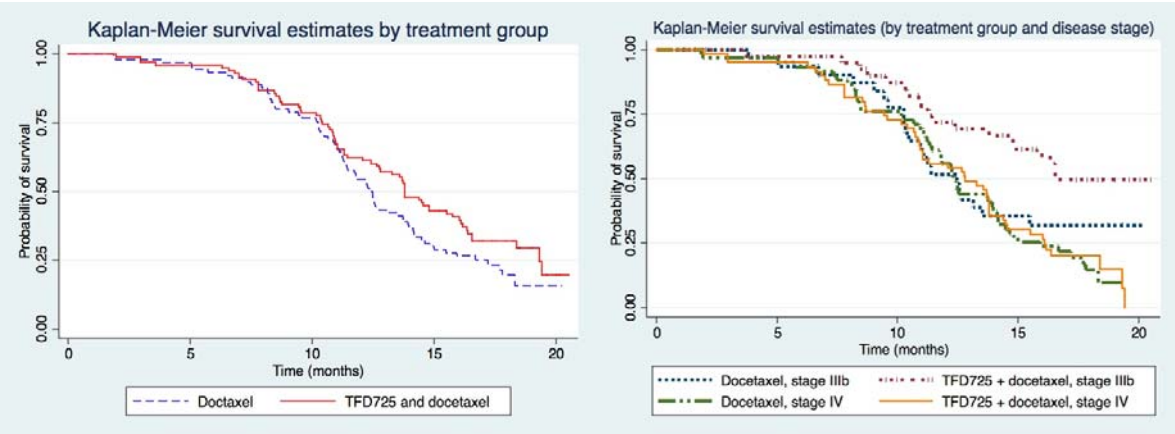

Table 2. Hazard Ratios by Subgroups of Baseline Prognostic Factors

Subgroup	*Hazard Ratio (95% CI)	** P-value
Overall	0.75 [0.53-1.04]	0.084
Center/site		
Europe	0.76 [0.34-1.69]	0.498
North America	0.74 [0.51-1.07]	0.111
Sex		
Female	0.63 [0.38-1.06]	0.082
Male	0.78 [0.50-1.21]	0.277
Disease stage		
Stage IIIB	0.53 [0.28-0.98]	**0.046**
Stage IV	0.99 [0.67-1.46]	0.954
ECOG		
0	0.82 [0.44-1.53]	0.533
1	0.71 [0.47-1.06]	0.093
2	1.06 [0.23-4.80]	0.941
Abnormal LDH		
No	0.79 [0.55-1.14]	0.209
Yes	0.72 [0.31-1.65]	0.438
Abnormal alkaline phosphatase		
No	0.74 [0.49-1.11]	0.141
Yes	1.04 [0.55-1.95]	0.912
Response to first-line chemotherapy?		
No	0.73 [0.44-1.21]	0.222
Yes	0.75 [0.48-1.17]	0.202
Duration of disease		
$\geq$8 months	0.76 [0.51-1.12]	0.168
<8 months	0.73 [0.39-1.36]	0.324

*Hazard ratio compares event rates in docetaxel+TFD725 group to docetaxel alone
**p-values are all two-sided

Table 3. Summary of secondary outcome measures

Outcome measure	N	Docetaxel [95% CI]	N	Docetaxel + TFD725 [95% CI]	**Difference in survival probability	***P-value
Follow-up time (months)	90		98			
25th %ile		16.6 (SE 0.33)		16.6 (SE 0.33)		
Median		18.4 (SE 0.08)		18.2 (SE 0.61)		
75th %ile		19.2 (SE 0.28)		18.5 (SE 0.59)		
Median survival (months)						
Overall	90	12.3 (SE 0.36)	98	13.8 (SE 0.48)		0.0124
Stage IIIB	31	12.5 (SE 0.85)	39	16.5 (SE-)*		-
Stage IV	59	12.3 (SE 0.38)	59	12.8 (SE 1.32)		0.716
Survival probability 1 year						
Overall	90	0.54 [0.44-0.64]	98	0.62 [0.52-0.71]	0.08 [-0.063-0.219]	0.279
Stage IIIB	31	0.52 [0.33-0.67]	39	0.72 [0.55-0.83]	0.20 [-0.024-0.428]	0.079
Stage IV	59	0.56 [0.42-0.67]	59	0.56 [0.42-0.67]	0.00 [-0.179-0.179]	0.852

*after 16.5 months, survival probability remains 0.5 throughout rest of study
**Difference is TFD725+docetaxel group – docetaxel group
***p-values are two-sided