A RANDOMIZED TRIAL OF TYROSINE KINASE INHIBITOR TFD725 AS SECOND LINE CHEMOTHERAPY IN ADVANCED NON SMALL CELL LUNG CANCER

Summary:

This research study was a randomized, double blinded, placebo controlled trial in patients (N=188) with stage IIIb or IV Non Small Cell Lung Cancer (NSCLC) who had tumor progression on first line platinum based therapy. TFD725 is an experimental molecule, in the class of tyrosine kinase inhibitors; it is thought to block the effects of cellular growth factors and may inhibit the growth of tumors. The primary aim was to investigate whether there was a survival benefit from the addition of TFD725 to a chemotherapy regimen containing a taxane (docetaxel) versus docetaxel alone plus placebo. Patients were followed for a median of 548 days and the primary outcome was time to death from any cause. The primary comparison measure was risk of death as estimated by Cox proportional hazards regression. Kaplan-Meier estimates of survival probability at 12 and 18 months were also compared. Patients were randomized to: the treatment arm (N=98), receiving TFD725 (50mg/day) plus docetaxel (50mg/m^2 every three weeks); or the placebo arm (N=90), receiving docetaxel (75 mg/m^2 every 3 weeks) plus placebo. There was a decrease in overall risk of death of 25% percent in the treatment arm compared to placebo (Hazard Ratio (HR) 0.75; 95%CI: 0.54 to 1.04; P value 0.0824), although these results did not meet statistical significance. There was an overall survival benefit of 6.8% at 12 months in the treatment arm compared to the placebo arm (61.2% vs. 54.4%; 95% CI for difference: -7.3% to 20.9%; P value 0.3460). At 18 months there was a 12.5% overall survival benefit in the treatment arm compared to the placebo arm (32.0% vs. 19.5%; 95%CI for difference: -0.6% to 25.7%; P value 0.0615). Exploratory, stratified analyses revealed a 47% decrease in the risk of death following TFD725 treatment in patients with stage IIIb disease (HR 0.53; 95%CI: 0.28 to 0.99; P value 0.043) but not in those with stage IV disease (HR 0.99; 95%CI: 0.67 to 1.46; P value 0.953). These findings suggest the need to further investigate the potential benefit of adding TFD725, as adjuvant to second-line docetaxel chemotherapy, in the treatment of NSCLC in patients with different stages of advanced disease.

Comment [A1]: Nice summary

Comment [A2]: mulitcenter

Comment [A3]: months would be a better unit

Background:

The leading cause of cancer-related death in the United States is lung cancer, of which NSCLC represents approximately 85% of new cases yearly.[i] More advanced NSCLC, as represented by stages IIIb or IV, has a poor prognosis and few effective treatment options. Overall five-year survival in NSCLC is highly associated with the stage of disease at the time of diagnosis, with five-year survival rates as low as five (5)% for stage IIIb disease[ii] and approximately one (1)% for stage IV disease.[iii] Historically, untreated stage IV disease has a documented median survival of four (4) to five (5) months, and small, but real, differences have been seen in one-, three- and five-year survivals between stage IIIb and stage IV disease.[iv] Even for stage I NSCLC, the five-year survival rate was only estimated at 60-70%.[v] Until now, current treatment has only made small gains, with patients on cisplatin-based chemotherapy for advanced NSCLC having a documented median survival of 7.5 months.[vi] The 1995 NSCLC Collaborative Group meta-analysis showed a 5-year survival benefit of about 5% after first-line cisplatin-based chemotherapy treatment in resectable NSCLC.[vii] However, this modest survival benefit was tempered by the toxicity of platinum-based chemotherapies. Recently, this first-line platinum treatment was complimented by the introduction of effective second-line chemotherapeutic agents, such as docetaxel, and the introduction of promising experimental agents, such as the tyrosine-kinase inhibitor class of drugs. There is a great need to identify novel chemotherapeutic agents to effectively treat more advanced stages of NSCLC disease, increase five-year survivability, and decrease all cause mortality for NSCLC.

Comment [A4]: a word or two about hypothesized mechanism of action

Questions of interest:

The primary question was to determine if second-line chemotherapy using docetaxel and TFD 725 was associated with a decreased risk of dying compared to docetaxel alone in advanced stage NSCLC. This primary measure was chosen given the demonstrated short survival in advanced NSCLC[viii] and the concern that accurate 3 or 5 year survival estimates would not be obtained in a study of this size. 12 month and 18 month survival estimates will also be calculated. Finally, exploratory analysis will be made of the effect of TFD725 on survival with respect to stage (IIIb versus IIIb with malignant effusion/IV), ECOG performance status (0 being the best), geographic location (Europe vs. North America), age, initial response to platinum chemotherapy, duration of disease prior to randomization, or baseline laboratory values for alkaline phosphatase (AP) and Lactate Dehydrogenase (LDH).

Comment [A5]: Do you also consider adjusted analyses?

Sources of the Data:

Data was collected during a multicenter, international Phase IIb double-blind randomized, controlled trial of 188 patients whose advanced NSLC had progressed on first line platinum based chemotherapy. Patients were randomized to receive docetaxel (50mg/m^2 every three weeks) plus TFD 725 (50mg/day) or docetaxel alone (75 mg/m^2 every 3 weeks) with placebo. Inclusion criteria were: initial diagnosis of stage IIIb or stage IV NSCLC and prior treatment with standard platinum based chemotherapy regimen. Exclusion criteria were: inclusion of docetaxel in first line chemotherapy, poor performance status demonstrated by ECOG level 3 or higher at time of randomization, age > 80 at time of randomization, and unwillingness to use adequate contraception during the trial. Randomization occurred in a 1:1 ratio with stratification by clinical site and stage at initial diagnosis (IIIb versus IIIb with malignant effusion/IV). If patients experienced toxicity, they were continued on the drugs with protocol specified dose modifications. If the toxicity was unacceptable following these modifications, therapy was discontinued. Any patients who discontinued the study medication for any reason were followed for clinical events and death. Patients were monitored for any adverse events every three weeks and every 6 weeks were assessed for clinical or subclinical cancer progression.

Statistical Methods:

Baseline characteristics were compared between the two treatment arms to assess for the effectiveness of the randomization process and the presence of potential confounders. Arithmetic mean, standard deviation, minimum, and maximum were used to compare continuous variables across the two treatment arms. Missing data were not present in this dataset. All analyses were conducted using Stata version 10 (StataCorp, College Station, Texas).

Comment [A6]: OK as stated, but censored data are of course missing

Kaplan-Meier (KM) survival estimates were used to evaluate whether survival differed between the treatment and placebo arms. KM survival curves were displayed for a graphical comparison of survival probabilities between the treatment arms. Cox proportional hazard regression was applied to assess for the average difference in survival distributions over time between the treatment arms. The standard errors of hazard ratios (HR) were calculated using the Huber-White sandwich estimator, which allows for adequate estimation even if the proportional hazards assumption was not satisfied. Statistical significance for the difference in the risk of death as measured by hazard ratios was reported with two-sided P values obtained using the Logrank test. Differences in survival probabilities and corresponding standard errors were estimated using Greenwood's formula, and statistical significance was determined by computing CIs and P values assuming this difference between the treatment arms follows a normal distribution. Similar analyses were performed to explore whether hazard ratios or survival at 12 or 18 months differed across subgroups defined by age, sex, location, months between diagnosis and randomization, degree of advanced disease, tumor response to first line therapy, LDH levels, alkaline phosphatase levels, and performance status on the ECOG scale, using the methods described above.

The results were only presented by subgroups of disease stage, which was found to be a potential source for effect modification.

Comment [A7]: OK, but it would not be that much more ink to give the other subgroups analyses in a table

KM estimates were used because the observed time-to-death represents right-censored data; the KM method assumes non-informative censoring, which means that the presence of censoring was independent from whether a patient will experience death. Hazard is the instantaneous risk that an event will occur at any point in time. Using Cox proportional hazards regression, we calculated average HR comparing the treatment group to the placebo group. P values were reported to measure statistical significance. Under the null hypothesis, the P value is the probability of getting data as, or more extreme, than the observed. We used alpha (α)=0.05 for testing, which means that we would reject the null hypothesis that survival was not different in the two arms if the P value was less than 0.05.

Comment [A8]: Explicitly mention that you did not adjust exploratory analyses p values for multiple comparisons

Results

Baseline Characteristics: At randomization, 90 patients were assigned to the placebo arm, and 98 were assigned to the treatment arm. Baseline data collected on all patients included age, sex, location of residence (Europe or North America), number of months between diagnosis and randomization, degree of advanced disease (IIIb versus IIIb with malignant effusion/IV), whether their tumors responded to first line therapy, whether they had abnormal LDH levels at randomization, whether they had abnormal alkaline phosphatase levels at randomization, and performance status on the ECOG scale (0=best, 1, or 2). These baseline characteristics are summarized in Table 1. There were no missing data.

Table 1. Baseline characteristics for placebo and treatment arms.

	Placebo (N = 90)			TFD725 (N = 98)		
	Mean	*SD*	*Range*	*Mean*	*SD*	*Range*
Age at randomization (years)	60.51	4.79	50, 75	60.38	5.41	46, 71
Time from diagnosis to randomization (months)	10.23	4.34	3, 27	10.39	4.77	3, 31
	n	*%*		*n*	*%*	
Country of residence						
North America	73	81.11		81	82.65	
Europe	17	18.89		17	17.35	
Male	47	52.22		57	58.16	
Advanced stage at diagnosis	59	65.56		59	60.20	
Response to first line therapy	51	56.67		56	57.14	
Abnormal LDH	16	17.78		9	9.18	
Abnormal alkaline phosphatase	29	32.22		19	19.39	
Performance status by ECOG						
0 (best)	23	25.56		34	34.69	
1	62	68.89		60	61.22	
2	5	5.56		4	4.08	

Baseline characteristics were generally similar between the treatment arms. The percentage of men was slightly higher in the treatment arm (58.16% vs. 52.22%). The placebo arm had slightly higher percentages of patients with: advanced stage at diagnosis (65.56% vs. 60.20%), an indicator of more severe disease; abnormal LDH (17.78% vs. 9.18%); and abnormal alkaline phosphatase (32.22% vs.

19.39%). The treatment arm had a slightly higher percentage of patients with the highest ECOG score (34.69% vs. 25.56%) and a slightly lower percentage of patients with the middle ECOG score (61.22% vs. 68.89%).

Survival Analysis: Patients were followed for a median observation period of 548 days. There were 72 deaths in the placebo arm and 68 deaths in the treatment arm. Kaplan-Meier estimates of survival probability were used to compare survival across treatment groups. The primary comparison was risk of death as estimated by Cox proportional hazards regression. Survival at 12 and 18 months was the secondary comparison. Similar analyses were performed to explore whether hazard ratios or survival at 12 or 18 months differed across subgroups defined by the baseline demographic and disease variables.

Comment [A9]: good to note

Figure 1a: Kaplan-Meier survival estimates for overall survival by treatment

Figure 1b: Kaplan-Meier survival estimates by treatment and stage of advanced disease at randomization

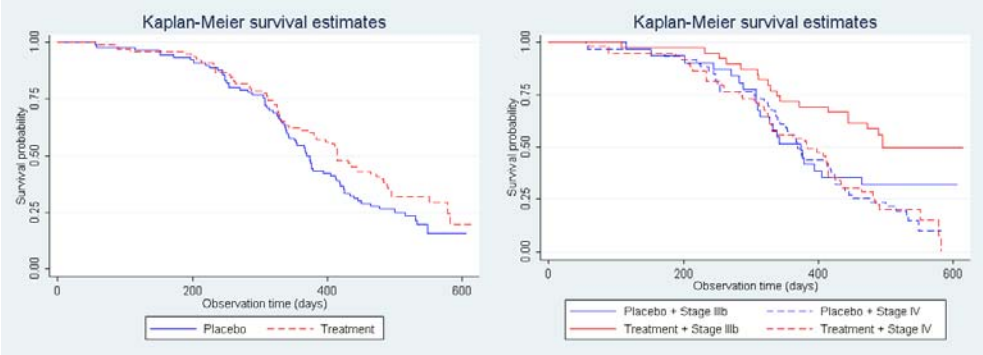

Figure 1a shows Kaplan-Meier survival curves for placebo and treatment arms. There appears to be a slight trend toward a late occurring treatment effect, with higher survival in the treatment arm during the latter half of the study period, as compared to placebo. Figure 1b shows Kaplan-Meier survival curves for subgroup analysis of advanced disease stage (IIIb vs. IIIb with malignant effusion/IV). Survival past 400 days appears to be greater in both of the stage IIIb groups compared to the stage IV groups. There also appears to be a trend toward higher survival in the treatment arm compared to the placebo arm for the stage IIIb group, but not for the stage IV group.

Table 2 shows the estimated hazard ratio as well as survival probabilities by treatment at 12 and 18 months. A proportional hazards regression analysis of the association between treatment and survival found that patients in the treatment arm had an estimated 25% lower risk of death than patients in the placebo arm (95%CI: 46% lower to 4% higher; P value 0.0824). There was an estimated survival benefit in the treatment arm of 6.8% at 12 months (95%CI: -7.3% to 20.9%; P value 0.3460) and 12.5% at 18 months (95%CI: -0.6% to 25.7%; P value 0.0615), respectively. However, none of these results met statistical significance, and we cannot reject the null hypothesis of no difference in survival between the placebo and treatment arms. Thus, although the data suggest that treatment with TFD725 may have been associated with lower risk of death and higher 12 month and 18 month survival, we do not have sufficient evidence to conclude that this was so.

Comment [A10]: I tend to report the descriptive statistics first, then report the primary endpoint analysis.

Table 2: Overall Survival by Treatment Arm

	Hazard Ratio (95% CI)	P value
TFD725 / Placebo	0.75 (0.54, 1.04)	0.0824
	Survival Probability (95%CI)	
	12 months	18 months
Placebo	54.4% (43.6%, 64.1%)	19.5% (11.4%, 29.1%)
TFD725	61.2% (50.8%, 70.1%)	32.0% (22.7%, 41.6%)
Difference (TFD725 – Placebo)	6.8% (-7.3%, 20.9%)	12.5% (-0.6%, 25.7%)
P Value for Difference	P = 0.3460	P = 0.0615

Table 3 shows the estimated hazard ratio as well as survival probabilities by treatment at 12 and 18 months for patients with different stages of disease. A proportional hazards regression analysis of the association between treatment and survival found that for stage IIIb patients, treatment was associated with an estimated 47% lower risk of death relative to placebo (95%CI: 72% lower to 1% lower; P value 0.0427). For patients with stage IIIb disease, there was an estimated survival benefit in the treatment arm of 20.2% at 12 months (95%CI: 2.4% to 42.8%; P value 0.0797) and 17.7% at 18 months (95%CI: 5.4% to 40.9%; two-sided P value 0.1335), respectively, although these results did not meet statistical significance and so we cannot reject the null hypothesis of no difference in 12 month and 18 month survival between the treatment arms.

Comment [A11]: not adjusted for multiple comparisons

For stage IV patients, a proportional hazards regression analysis found that treatment was not associated with a lower risk of death relative to placebo (HR 0.99; 95%CI: 0.67 to 1.46; P value 0.9536). Estimates of 12 month and 18 month survival for stage IV patients were similar across treatment groups, with a 12 month difference of -1.7% (95%CI: -19.6% to 16.3%; P value 0.8536) and an 18 month difference of 5.5% (95%CI: -9.1% to 20.9%; two-sided P value 0.4609).

Table 3. Subgroup Survival by Treatment Arm

TFD725 / Placebo	Hazard Ratio (95%CI)	P value
Stage IIIb	0.53 (0.28, 0.99)	0.0427
Stage IV	0.99 (0.67, 1.46)	0.9536
	Survival Probability (95%CI)	
	12 months	18 months
Stage IIIb		
Placebo	51.6% (33.0%, 67.4%)	31.9% (16.6%, 48.4%)
TFD725	71.8% (54.9%, 83.3%)	49.7% (32.8%, 64.5%)
Difference (TFD725 – Placebo)	20.2% (-2.4%, 42.8%)	17.7% (-5.4%, 40.9%)
P Value for Difference	P = 0.0797	P = 0.1335
Stage IV		
Placebo	55.9% (42.4%, 67.5%)	14.7% (6.6%, 25.7%)
TFD725	54.2% (40.8%, 65.9%)	20.1% (10.7%, 31.7%)
Difference (TFD725 – Placebo)	-1.7% (-19.6%, 16.3%)	5.5% (-9.1%, 20.0%)
P Value for Difference	P = 0.8536	P = 0.4609

In similar stratified analyses performed to explore whether hazard ratios or survival at 12 or 18 months differed across subgroups defined by age, sex, location, months between diagnosis and randomization, tumor response to first line therapy, LDH levels, alkaline phosphatase levels, and performance status on the ECOG scale, no large or statistically significant differences were found.

Discussion:

The addition of TFD 725 to docetaxel second-line chemotherapy in advanced NSCLC did not confer a statistically significant survival benefit versus docetaxel plus placebo at 12 months, 18 months or in overall mortality as measured by the hazard ratio. In the exploratory subgroup analysis, there was evidence for effect modification by the stage of disease at the time of enrollment. For patients who had only stage IIIb disease, there was a statistically significant 47% reduction in mortality, as measured by risk of disease, in those receiving TFD725 compared to a negligible effect on survival for those in the stage IV subgroup. However, the treatment associated decrease in all cause mortality did not extend to the stage IIIb/IV NSCLC subgroup. These results can be explained given that stage of disease is recognized as one of the most reliable predictors of survival in NSCLC.[viii] It is likely that the shorter survival seen in more advanced, widespread NSCLC has a smaller window of opportunity, both temporally and clinically, for any demonstrable improvement from chemotherapeutics. These results suggest that it may be of interest to conduct future studies with the primary goal of determining whether TFD725 plus docetaxel treatment has an efficacious chemotherapeutic action above that of docetaxel alone in stage IIIb NSCLC. Future studies could include a larger sample size to facilitate greater precision and to better detect the significance of trends in increased overall survival benefit seen in the treatment arm, compared to placebo.

Comment [A12]: did you do tests of interactions? If so, you did not report them. Instead, you looked at effects within subgroups.

This study has multiple limitations. The ability to detect and draw inferences about the effectiveness of treatment with TFD725 may have been limited by sample sizes, particularly the relatively small number of patients with stage IIIb disease. Also, data on adverse events and dropout rates were not available. An optimal treatment regimen should not only effectively reduce mortality, but have minimal side effects as well. A common goal of using multiple drugs with a modification in dosage is to reduce the occurrence of adverse events related to treatment. This study was unable to address whether or not the treatment (TFD725 and docetaxel) was desirable in this aspect. Any future investigations will thus need to collect information on toxicity, adverse events, and dropout rates.

Citations:

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[i] American Cancer Society. *Cancer Facts and Figures 2004*. Atlanta: ACS, 2004.
[ii] Bonomi PD. Therapeutic Advances in Second-Line Treatment of Advanced Non–Small-Cell Lung Cancer. *Clinical Lung Cancer*. 2004; 6(3):154-161.
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[v] Pisters KM. Adjuvant chemotherapy for non-small-cell lung cancer. *Clin Adv Hematol Oncol*. 2003; Sep;1(9):533-7.
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[viii] Brundage MD, Davies D, and Mackillop WJ. Prognostic Factors in Non-small Cell Lung Cancer. *Chest* 2002; 122: 1037-1057.