The Effects of Study Drug TFD725 on Survival in Non-Small Cell Lung Cancer

Group 21

Summary

Background: Non-small cell lung cancer (NSCLC) is the most common type of lung cancer, worldwide. Most NSCLC cases are diagnosed at an advanced stage (stage IIIb or stage IV). These advanced stages are generally treated first with a combination platinum-based chemotherapy followed by a second line treatment of docetaxel. New treatments that block the epidermal growth factor receptor, such as TFD725, show promise as an additional second line of treatment.

Objectives: This study is primarily interested in whether treatment with a combination of TFD725 and docetaxel has an effect on survival compared to patients receiving docetaxel alone. This study also examines whether treatment with the study drug has an effect on survival compared to the control within groups defined by sex and stage of cancer at initial diagnosis.

Methods: Patients were randomized to receive docetaxel plus TFD725 (98 patients) or docetaxel alone (90 patients) in this multi-center, double blind, placebo-controlled trial. Demographic and clinical information was collected at the start of the study, and patients were monitored until death (74% of subjects) or the end of the study (26% of subjects). Patients were followed for a median time of 394 days (after adjusting for censoring). Kaplan-Meier survival probability estimates were obtained for each treatment group at 12 months. The risk of death averaged across time was compared between the groups using a Cox proportional hazard regression. The ratio of the hazard for death was also estimated for groups defined by sex, as women have been reported to respond better to NSCLC treatment (3), and disease stage, as previous treatments have proven effective for only particular tumor stages (5).

Results: The 12 month survival probability was 0.612 (95% CI: 0.508 – 0.701) for patients in the treatment group and 0.544 (95% CI: 0.436 – 0.640) for patients in the control group. No significant difference was found in survival between the groups treated with TFD725 plus docetaxel and docetaxel alone, as the treatment group had a hazard for death of 0.748 (95% CI: 0.536 – 1.04; p = 0.084) times that of the control group. When compared across disease stage, subjects with stage IIIB disease without malignant pleural effusion (MPE) who were in the treatment group had a hazard for death 0.53 times (95% CI: 0.284 – 0.989; p = 0.046) that of those in the control group. Patients diagnosed with stage IIIb with MPE or stage IV NSCLC in the treatment group had no increased survival advantage (HR = 0.988; 95% CI: 0.668 – 1.46; p = 0.95) over those in the control group.

Discussion: This study suggests that treatment with TFD725 plus docetaxel does not improve survival in patients with advanced NSCLC over treatment with docetaxel alone. Improvement was noted in the subgroup diagnosed with stage IIIB disease without MPE following treatment with TFD725 plus docetaxel. Although correcting for multiple testing rendered such results non-significant, it may be worthwhile to investigate this observation in future studies.

Comment [A1]: You might consider giving a little age, sex, stage info

Comment [A2]: This is incorrect. The median time of follow-up is about 540 days.

Comment [A3]: good to motivate this way

Comment [A4]: very nicely stated

Background

Lung cancer is one of the deadliest diseases worldwide, responsible for over 150,000 deaths in the United States each year (1). The majority of these cases fall into the histological category of non-small cell lung cancer (NSCLC) (2). The primary cause of NSCLC is tobacco smoking, accounting for approximately 75% of all cases. In addition to smoking status, gender and genetic ancestry may also contribute to the

risk of developing lung cancer, as well as the overall survival advantage and response to treatment after diagnosis (3).

If detected early (clinical stages I or II), complete surgical resection of NSCLC provides the greatest survival advantage to patients (4). Unfortunately, over 70% of NSCLC cases present with advanced (clinical stages III or IV) disease where complete resection is impossible (2). The course of treatment in these cases is usually a first line combination chemotherapy containing a platinum-based drug, which cross-links DNA strands together and triggers apoptosis of mitotically dividing cells (5). The addition of chemical agents such as gemcitabine, vinorelbine, paclitaxel and docetaxel has increased the effectiveness of platinum-based chemotherapy alone and has become standard first line therapy (2, 6). Many patients benefit from this initial treatment with combination chemotherapy, but disease progression is inevitable and a second line of treatment is often used. Currently, docetaxel, a cytotoxic agent that irreversibly binds to microtubules to inhibit mitosis, is the only drug approved in second line therapy (2).

New second line treatments for NSCLC are currently being developed to block the epidermal growth factor receptor (EGFR) pathway. EGFR, a receptor tyrosine kinase, is mutated or overexpressed in about 40-80% of NSCLCs leading to increased EGFR signaling. In normal cells, EGFR signaling activates several important biological processes like cell proliferation, differentiation and survival. The overexpression of EGFR is thought to increase signaling to these pathways, thus leading to the development and progression of NSCLC. It is anticipated that these new EGFR targeted treatments, in combination with current cytotoxic treatments, will decrease NSCLC tumor progression over current methods alone (7). TFD725 is a small molecule that specifically inhibits the tyrosine kinase activity of the EGF receptor. This phase IIb clinical trial aims to assess the survival rate of individuals treated with or without TFD725 in combination with current therapies for advanced stage NSCLC.

Questions of Interest

Our primary question of interest is whether treatment of patients with a combination of TFD725 and docetaxel has any effect on survival rates compared to patients receiving docetaxel alone in the second line treatment of NSCLC.

We are also interested in whether the survival outcome in each treatment group differs by sex, as other studies have reported that women generally respond better to NSCLC treatment (3); or stage of cancer (stage IIIb without malignant pleural effusion (MPE) vs. stage IV or stage IIIb with MPE), as previous treatments have proven to be effective only for particular tumor stages (5).

Source of the Data

This study was a randomized, multi-center, double blind, placebo-controlled trial assessing the effect of a combination of TFD725 and docetaxel versus docetaxel alone in second line treatment of patients with advanced NSCLC. 188 patients with advanced NSCLC met our inclusion criteria and were enrolled in the trial. Advanced stage NSCLC was defined as either stage IIIb or IV disease. Patients were excluded from the trial if they had received docetaxel treatment in their first line therapy, had an ECOG performance status of 3 or worse or were over 80 years of age*.

* ECOG performance status is a metric developed by the Eastern Cooperative Oncology Group to classify the impact of a disease on a patient's daily activities. It ranges from 0 (fully active) to 5 (dead). An ECOG status of 3 is defined as "capable of only limited selfcare, confined to bed or chair more than 50% of waking hours (8)."

Patients were randomly assigned in a 1:1 ratio, controlling for clinical site and tumor stage at diagnosis, to one of the following treatment groups: a control group receiving docetaxel alone or a treatment group receiving TFD725 in addition to docetaxel. Demographic information was collected at time of randomization for age, sex and location of residence. In addition, clinical measures of tumor stage, tumor response to first line therapy, abnormality of lactate dehydrogenase (LDH) and alkaline phosphatase levels, and ECOG performance status were collected. Abnormal levels of either LDH or alkaline phosphatase are associated with poor patient outcomes. This demographic and clinical information was used to compare the similarity of patient baseline characteristics across treatment groups. The endpoint of the study was overall survival measured by death. Time to death was measured as the earlier of time from randomization to death or time from randomization to the end of the trial.

Comment [A5]: we would generally mention dose

There were no missing data in the study and 74% of participants were followed until death. The remaining 26% were still alive at the end of the study. If patients discontinued their treatment during the course of the study, they were still followed until the study endpoint and included in the analysis.

Statistical Methods

Since there were no missing measurements in the dataset, measurements from each patient were represented in the descriptive statistics as well as our statistical analyses. Each patient ID was unique, so multiple measurements were not a problem with the dataset. We used the Kaplan-Meier method to estimate survival probabilities for each treatment group. The difference in the probability of surviving 12 months between the two groups was compared using a two-sided Z-test. The estimated survival probabilities and 95% confidence intervals for each group are reported in Table 2. We also fit a Cox proportional hazard regression, using robust standard errors, to each group to estimate the risk of death averaged over time (measured by the hazard ratio). The hazard ratio of treatment to control was tested for statistical significance using a Wald test. The estimated hazard ratio from the Cox regression, as well as the 95% confidence interval and p-value, is also reported in Table 2.

Comment [A6]: OK as stated, but censoring is a form of missingness

Comment [A7]: This is Stata terminology. General description would be "the Huber-White sandwich estimator"

Each treatment group was stratified by sex and disease stage (IIIb without MPE vs. IIIb with MPE or IV NSCLC), and a Cox proportional hazard regression (using robust standard errors) was used to estimate the hazard ratio (treatment to control) in each stratum. Estimated hazard ratios with 95% confidence intervals and p-values from corresponding Wald tests are reported in Table 3. We chose to stratify the data by these variables because sex has been reported in the literature to modify the effect of treatment of NSCLC on survival rate (3), and different stages of cancer are typically treated with different courses of therapy. All reported summary measures and estimates were computed via STATA version 10 for Windows (StataCorp LP, College Station, TX, USA).

Results

Patients were demographically similar across treatment groups (Table 1). Fifty-eight percent (58.2%) of patients were males in the treatment group and 52.2% of patients were male in the control group. Patients ranged in age from 46 to 75 years with a mean age of 60 (SD = 5) in the treatment group and 61 (SD = 5) in the control group. Patients with stage IIIb without MPE NSCLC made up 34.4% of the treatment group and 39.4% of the control, while patients with stage IV or IIIb with MPE NSCLC made up 65.6% of the treatment group and 60.6% of the control. Patients with abnormal LDH or alkaline phosphatase levels were overrepresented in the control group with 17.8% (vs. 9.2% in treatment) of patients with abnormal LDH levels and 32.3% (vs. 19.4% in treatment) of patients with abnormal alkaline phosphatase levels. Patients in the treatment group were followed for a median time of 414 days, while patients in the control group were followed for a median time of 372 days. The mean time from initial diagnosis to randomization into the study was 10 months for both treatment groups.

Comment [A8]: So a somewhat disturbing trend toward more serious disease in the placebo group

Comment [A9]: No. They were followed for about 18 months. (Many died before their follow-up was over, but we know they are still dead.)

The Kaplan-Meier survival curves by treatment group are shown in Figure 1a. The 1-year survival probability was 0.612 (95% CI: 0.508 – 0.701) for patients in the treatment group and 0.544 (95% CI: 0.436 – 0.640) for patients in the control group. The overall risk of death, measured by the hazard ratio (HR), in patients in the treatment group compared to the control group was 0.746 (95% CI: 0.536 – 1.04; p = 0.084). Thus, there was not a significant survival advantage for patients in the treatment group.

We stratified treatment groups by sex to investigate the effect modification by sex on survival advantage in treatment and control groups. The Kaplan-Meier curves in Figure 1b shows that, independent of treatment group, women had a greater overall survival advantage than men. The relative risk of death in the treatment group compared to the control group was 0.784 (95% CI: 0.506 – 1.22; p = 0.277) for men and 0.632 (95% CI: 0.376 – 1.06; p = 0.082) for women (Table 3). These results show that women in the treatment group have a greater decreased risk of death than men, but the risk of death for either sex in the treatment group was not significantly different from the risk of death for either in the control group.

We also stratified treatment groups by tumor stage at initial diagnosis (stage IIIb without MPE vs. stage IIIb with MPE or stage IV) to determine the effect of tumor stage on survival advantage in treatment and control groups. The relative risk of death for treatment versus control groups between tumor stages was significantly different (Table 3). Patients diagnosed with stage IIIb NSCLC in the treatment group showed a significantly decreased risk of death (HR = 0.53; 95% CI: 0.284 – 0.989; p = 0.046) than those in the control group, though this result is not significant after correcting for multiple tests. Patients diagnosed with stage IV NSCLC in the treatment group had no increased survival advantage (HR = 0.988; 95% CI: 0.668 – 1.46; p = 0.95) than those in the control group. The Kaplan-Meier curves stratified by tumor stage are shown in Figure 1c.

Comment [A10]: very good to note

Discussion

The main objective of this study was to assess the effectiveness of a new experimental drug, TFD725, in combination with docetaxel on overall survival in second line treatment of patients with advanced stage NSCLC. We found no statistical evidence for a difference in survival between patients treated with TFD725 with docetaxel and patients treated with docetaxel alone.

For our secondary analysis, we first examined the effect of treatment with TFD725 and docetaxel compared to treatment with docetaxel alone on survival within subgroups defined by sex. This analysis was of interest because women have a greater survival advantage than men (3), and so we were interested in determining if treatment with the experimental drug impacted women differently than men. Neither sex showed any significant improvement in survival associated with the experimental treatment. In our study sample, we noticed that there were slightly more males (55%) than females (45%) across treatment groups. In the United States, approximately 53% of new lung cancer cases are male (1), so our study sample is representative of the overall population.

We then analyzed the effect of treatment with the study drug compared to the control on survival within subgroups defined by tumor stage at initial diagnosis. Interestingly, patients with stage IIIb NSCLC without MPE had an increase in survival when treated with TFD725 plus docetaxel, while patients with stage IV or stage IIIb with MPE NSCLC had no survival advantage in the treatment group. These results, however, were not significant after correcting for multiple testing.

Cancer stage was determined at a patient's initial diagnosis for NSCLC and the time from initial diagnosis to entrance into this study varied greatly among participants. Time up to randomization ranged between 3 and 31 months, with a median of 10 months. As a result, some patients may have progressed from stage IIIb without MPE to stage IV or stage IIIb with MPE NSCLC during the time up to

randomization. This may have caused the effect of TFD725 with docetaxel for the treatment of stage IV or stage IIIb with MPE NSCLC to be underestimated in our analysis.

One limitation of this study is a lack of information regarding if and when patients discontinued their study medication. Patients who discontinued treatment were still followed until one of the endpoints of the study (death or end of study), so it is possible that patients who discontinued their study medication had worse outcomes than those who stayed on their study medication. Without this information, we cannot generalize how long patients received the study treatments or how frequently they discontinued their study medication. This limits our ability to analyze the relationship between survival and the length of time a subject was receiving the treatment. Future studies should provide information regarding if and when patients discontinue study medication.

We were also concerned about possible confounding in the study sample. Two baseline measurements - abnormal LDH and alkaline phoshatase levels - were collected, which have been previously reported to be highly predictive of poor patient outcomes. Although this was a randomized trial, the distribution of patients with abnormal LDH and alkaline phosphatase levels was not uniform between the two treatment groups. The control group contained almost twice as many patients with abnormal levels of either enzyme as the treatment group. As a result, it must be noted that the relatively poor survival in the control group compared to the treatment group may have partially been the result of this imbalance.

In this study, no significant difference in survival was detected between patients treated with docetaxel alone and patients treated with docetaxel plus TFD725. However, in the analysis of our secondary question of interest, it did appear that treatment with docetaxel plus TFD725 improved survival over treatment with docetaxel alone in the subgroup of subjects classified as having stage IIIb disease without MPE, while no improvement was observed in those with stage IV/stage IIIb with MPE NSCLC. These results, however, were not statistically significant after correcting for multiple testing. This classification by disease stage was complicated by the large range of times between diagnosis and time to enrollment in the study which might have lead to further progression of disease stage after classification. However, these findings might warrant further study into whether docetaxel plus TFD725 might be an effective treatment in prolonging survival in patients who were diagnosed with stage IIIb disease without MPE.

Comment [A11]: We care about what they were at randomization. (Maybe the treatment halts metastasis, so the progression to stage IV might be different across treatment groups)

Comment [A12]: This is a strength of the study. It is VERY VERY VERY BAD to do an analysis only in patients who take their drugs. That is a post randomization variable, and may be affected by treatment.

Comment [A13]: We generally do not care about this.

Comment [A14]: In real life we would generally have prespecified an adjusted analysis using important baseline variables

Literature Cited

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Table 1. Descriptive Statistics by Control (Docetaxel Only) and Treatment (Docetaxel plus TFD725) Groups

	Treatment Group	N	mean	SD	min	p25	p50	p75	max
Age	Control	90	61	5	50	58	61	63	75
	TFD725	98	60	5	46	57	60	64	71
Time from initial diagnosis to randomization (months)	Control	90	10	4	3	7	10	13	27
	TFD725	98	10	5	3	7	10	13	31

	Treatment Group	N	%
Male	Control	90	52.2%
	TFD725	98	58.2%
Region			
North America	Control	90	81.1%
	TFD725	98	82.7%
Europe	Control	90	18.9%
	TFD725	98	17.3%
Advanced Stage at Initial Diagnosis			
Stage IIIb without malignant pleural effusion	Control	90	65.6%
	TFD725	98	60.2%
Malignant pleural effusion or stage IV	Control	90	34.4%
	TFD725	98	39.8%
Tumor response to first line therapy	Control	90	56.7%
	TFD725	98	57.1%
Abnormal LDH level at time of randomization	Control	90	17.8%
	TFD725	98	9.2%
Abnormal alkaline phosphatase level at time of randomization	Control	90	32.2%
	TFD725	98	19.4%
ECOG Score (0=best, 2=worst)			
0	Control	90	25.6%
	TFD725	98	34.7%
1	Control	90	68.9%
	TFD725	98	61.2%
2	Control	90	5.6%
	TFD725	98	4.1%

Table 2. Probability of Survival by Treatment Group at 12 Months and Risk of Death (Hazard Ratio of Treatment to Control)

Treatment Arm	Estimate	95% CI		p-value
Control	0.5444	0.4362	0.6405	
Treatment	0.6122	0.5084	0.7006	
Hazard Ratio of Treatment to Control	0.7462	0.5356	1.0396	0.0840

Table 3. Risk of Death (Hazard Ratio of Treatment to Control) by Treatment Group: By Sex, and by Stage of Disease at Initial Diagnosis

	Time (months)	**Difference between Treatment and Control**			
		Estimate	95% CI		p-value
Male					
Hazard Ratio of Treatment to Control		0.7840	0.5057	1.2155	0.2770
Female					
Hazard Ratio of Treatment to Control		0.6316	0.3763	1.0602	0.0820
Stage IIIb w/o malignant pleural effusion					
Hazard Ratio of Treatment to Control		0.5300	0.2840	0.9889	0.0460
Stage IV or malignant pleural effusion					
Hazard Ratio of Treatment to Control		0.9884	0.6680	1.4625	0.9540

Figure 1a.

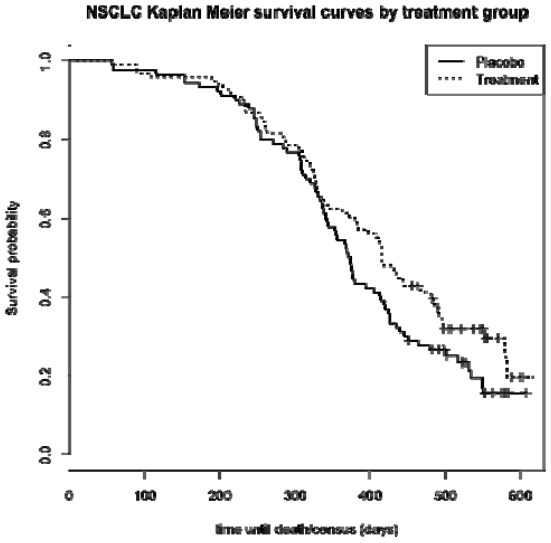

Figure 1b.

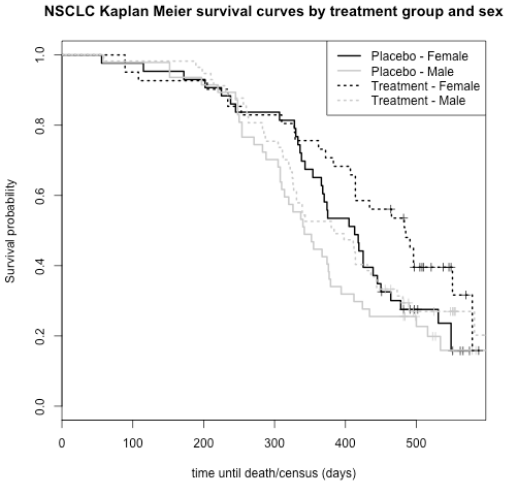

Figure 1c.