# *Effect of second-line chemotherapy agent TFD725 on patient outcomes in Non-Small Cell Lung Cancer*


## Abstract

*Background:* Receptor tyrosine kinases are known to be overexpressed in non-small cell lung cancer (NSCLC) cases. TFD725, an agent that blocks tyrosine kinase receptors, has been shown to inhibit tumor growth and may be useful as a chemotherapy agent in patients with progression of disease after first-line treatment with platinum-based chemotherapy. Building upon data gathered in phase I and IIa studies, this phase IIb clinical trial evaluated the effectiveness of TFD725 as a second-line chemotherapy agent.
*Objective and Methods:* This study's primary objective was to examine whether or not docetaxel and TFD725 together prolong the survival of NSCLC patients compared to docetaxel alone. The primary outcome of interest was risk of death due to any cause. Kaplan-Meier survival probability estimates were used to compare the overall survival between groups while the Cox proportional hazards regression was used to assess if there was a difference in risk of death between the TFD725 plus docetaxel group (experimental arm) and the docetaxel only group (control arm). A total of 188 subjects were randomized in a 1:1 ratio to either the control arm or experimental arm for the duration of the study. Randomization was stratified by clinical site and stage of cancer. The median time of follow-up for the study was 548 days, which was not largely different from the median time of follow-up for the experimental and control arms separately (546 and 551 respectively).
*Results:* The two treatment groups were generally comparable at baseline though their lactase dehydrogenase (LDH) levels (8.6% difference, P=0.083), alkaline phosphate levels (12.8% difference, *P*=0.044), and performance status at randomization (*P* =0.175) differed. In all cases, the docetaxel only group seemed to have subjects with poorer initial health status. The Kaplan-Meier survival curves showed that median survival is 43 days longer in the TFD725 plus docetaxel group (413 days) than the docetaxel only group (370 days). The survival estimates demonstrated that 75% of subjects were still surviving at 305 days post-randomization in the control arm and 311 days post-randomization in the experimental arm of the study. Similarly, 25% were still surviving at 501 days and 579 days, between the control and experimental arms, respectively. By the Cox proportional hazards regression, the relative risk of death in the docetaxel plus TFD725 group tends to be 0.746 times that in the docetaxel only group (CI: 0.536 to 1.040; *P*=0.084). Though there tended to be an improvement in survival in the experimental arm over the control arm, these results were not statistically significant.
*Conclusions*: From the results of this study, we cannot conclude that use of the candidate second-line chemotherapy agent TFD725 in conjunction with the known second-line drug docetaxel, produces an increase in survival over docetaxel use alone.


**Comment [A1]:** could consider brief description of age, sex, stage

**Comment [A2]:** p values are irrelevant here, though the trends are important to note (lack of stat signif does not preclude problematic differences between the groups that would cause the trial to lose face validity

**Comment [A3]:** stage, LDH, alk phos, and ECOG are relatively correlated observations

**Comment [A4]:** months might be a better unit here

## Background

Lung cancer is the most common cancer worldwide, contributing over 1.2 million new cases annually.[6] The two main types of lung cancer are small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), with NSCLC being the leading cause of cancer death in the US.[2] Though the classification difference in lung cancer is based on the histology of the affected cells, it is also important to differentiate between the two because the treatments differ. SCLC treatment usually involves radiation and chemotherapy, and has a poor prognosis. However, NSCLC treatment depends on the stage of the cancer at diagnosis, and can include surgical procedures with or without chemotherapy. Treatment of early stage NSCLC is best done with surgery, yet less than 50% are cured despite aggressive staging and complete resection.[2] Additionally, in other studies looking at NSCLC and survival, performance status, patient's tumor response to first line therapy, abnormal LDH levels, and abnormal alkaline phosphatase levels were parameters that were investigated.[1,3,4] In particular, abnormal LDH and alkaline phosphatase have been reported to be predictive of poor patient outcome. In late stage NSCLC, treatment begins with a first line

chemotherapy regimen, which is often platinum based. If after the first line chemotherapy the patient's cancer progresses, then a second line chemotherapy regimen is initiated. So far only docetaxel has been demonstrated to lead to improved clinical outcomes in patients whose cancer had progressed after first line chemotherapy with a platinum based regimen. Active research is being conducted to identify more possible chemotherapy agents.

An important area of chemotherapy research involves agents that block receptor tyrosine kinases. One target that has been well studied is the epidermal-growth-factor receptor (EGFR). In NSCLC this receptor is over expressed 80% of the time and leads to downstream effects related to dysregulation of proliferation, invasion, metastasis and apoptosis.[2] Additionally, this dysregulation has been associated with shorter survival, higher stage and cellular grade, poor cell differentiation, high rates of metastasis and cell proliferation, and poor tumor responses to radiotherapy.[5] A current thought is that by blocking tyrosine kinases, the ability of the tumor to grow and spread would be disrupted.

One agent in particular, TFD725, has shown promise by exhibiting activity against several receptor tyrosine kinases in vitro and in animal experiments. It is thought that by blocking tyrosine kinases, the ability of the tumor to grow and spread will be disrupted. Initial Phase I and IIa clinical trials were conducted generating safety and preliminary efficacy data. The purpose of this phase IIb study was to further investigate TFD725 as an anticancer agent. In this analysis, we report the results of a multicenter, randomized trial looking at the effectiveness of TFD725 as a second line chemotherapy agent in conjunction with docetaxel.

**Question of Interest**

The primary question of interest is whether or not TFD725 plus docetaxel prolongs the survival of NSCLC patients compared to docetaxel alone. In addition, we compared baseline demographics between the two groups to assess the randomization of patients between treatment groups.

**Comment [A5]:** This should not be hypothesis testing, though.

**Sources of the Data**

In 2003, a multicenter Phase IIb clinical trial was conducted to assess the effect of TFD725 on survival amongst NSCLC patients whose cancer progressed despite prior first-line platinum therapy. Subjects (n=188) were studied in a double-blind fashion, under standard protocol, and randomized between two treatment arms, receiving either docetaxel alone (75 mg/m$^2$ every 3 weeks) or docetaxel (50 mg/m$^2$ every 3 weeks) plus TFD725 (50 mg/day). The inclusion criteria were that the patient had been initially diagnosed with stage IIIb or stage IV NSCLC and treated with a standard, platinum based first line chemotherapy regimen. The exclusion criteria included any patient that received docetaxel in their first line chemotherapy regimen, a performance status at the time of randomization corresponding to ECOG level 3 or worse, the patient being over age 80 at time of randomization, or an unwillingness by the patient to use adequate contraception during the trial.

In addition to the two treatment arms, randomization was stratified by clinical site and stage of cancer at initial diagnosis. The treatment period for most subjects was until time of death, but no subject was followed for more than 21 months. An assessment was performed on subjects every 3 weeks to look for adverse events and every 6 weeks to account for clinical or subclinical progression of the disease. Baseline demographic data concerning sex, age, and country of residence were obtained. Other baseline data included classification of stage of cancer at diagnosis and response to prior first-line platinum therapy. Three indicators for disease severity were measured at time of randomization: lactate dehydrogenase and alkaline phopsphatase levels, along with an evaluation of patient condition using the ECOG scale of performance status. Some patients were still alive at the start of data analysis, which leaves some measurements as censored observations.

**Comment [A6]:** Better wording: "randomization to the two treatment arms was randomized in a 1:1 fashion within strata defined by clinical site and stage"

**Statistical Methods**

Baseline descriptive statistics, stratified by the two treatment arms, are provided in Table 1. None of the subjects had missing measurements. The mean, standard deviation, minimum and maximum of the continuous quantitative variables, age and time since initial diagnosis, are provided. For the binary and ordered categorical variables the appropriate percentage or frequency was used for analysis.

**Comment [A7]:** no missing baseline measurements (we did have censoring)

The baseline characteristics where examined for obvious disparities and three variables – abnormal LDH, abnormal alkaline phosphate, and performance status – were further analyzed to determine comparability of the treatment groups. For comparison, a chi-square test was used for the binary variables pertaining to abnormal LDH and abnormal alkaline phosphate levels, yielding point estimates and corresponding two-sided p-values. For the ordered categorical variable concerning performance score, a t-test was performed to ascertain a tendency towards worse performance status in a particular treatment group at the time of randomization. This test gave point estimates used only for comparative, not quantitative, purposes but produced a reliable two-sided p-value.

Since our question of interest is to assess whether administering TFD725 with docetaxel as a second-line chemotherapy agent prolongs the survival of NSCLC patients compared to docetaxel alone, we used Kaplan-Meier survival probability estimates to analyze the right-censored data. The two outcome variables used for the survival analysis were time under observation, either to death or to the end of the study, and a binary event indicator variable to signify whether or not the time under observation corresponds to a death. We computed the Kaplan-Meier survival curves and estimates in order to report the quartiles of surviving subjects and the survival probabilities in 6-month intervals. As the primary analysis for our question of interest, we used the Cox proportional hazards regression in order to obtain a hazard ratio estimate to assess whether the relative risk of death differs between treatment arms. Obtaining a hazard ratio less than 1.00 will mean that treatment with TFD725 plus docetaxel prolongs survival in comparison to docetaxel alone. Confidence intervals were always reflective of an alpha value of 0.05 (95%), thus two-sided p values of less than 0.05 are considered statistically significant for the purposes of these analyses. Data analyses were performed using Stata 9.1 (IC) for Linux64 and Stata 10 (IC) for Windows XP.

**Results**

Analysis was performed on data from a total of 188 subjects, 90 of which received docetaxel alone and 98 of which received docetaxel and the experimental drug, TFD725. At baseline, the two treatment groups were comparable on age, gender, stage at initial diagnosis, response to first line-therapy, and time past since initial diagnosis. The mean (± SD) age of those in the experimental group was 60.5± 4.8 years while for the control group mean (± SD) age was 60.4±5.4 years. The experimental group was composed of 52.2% men compared to the control group which was 58.8% men. Additionally, in the experimental group 81% were from North America compared to 83% in the control group.

Baseline statistics of possible interest were the difference in abnormal lactose dehydrogenase (LDH), alkaline phosphate levels, and performance status. Within the experimental arm 9.2% of subjects had abnormal levels of LDH at randomization, compared to 17.8% in the control arm, resulting in a difference of 8.6%. Similarly, 19.4% of subjects in the experimental arm had abnormal alkaline phosphate levels at randomization, in contrast to 32.2% in the control arm, yielding a difference of 12.8%. The difference in LDH was not statistically significant (CI: 1.2%-18.3%, *P*=0.083,), while the alkaline phosphate difference was statistically significant (CI: 0.4%-25.2%, P=0.044). Finally, performance scores tended to be higher in the control arm than the experimental arm of the study, which is indicative of a worse initial condition. However, the performance score distribution between treatment groups was not statistically significant (P=0.175). Descriptive statistics for all of the variables are presented in table 1.

**Comment [A8]:** stat signif is irrelevant. All the info is in the descriptive statistics and our prior knowledge about the importance of the variables

The median follow-up time was 546 days (CI: 505-552) for the experimental group compared to 551 days (CI: 499-575) days for the control group. This 5-day difference is not clinically significant (*P*=0.7263).

**Comment [A9]:** again stat signif is not important here—we would generally not perform a hypothesis test

The Kaplan-Meier survival curves for each treatment group are shown in Figure 1. The Kaplan-Meier survival curves for each treatment group are shown in Figure 1. Additionally, Table 2 stratifies the survival estimates by treatment group and presents estimated quartiles of survival (expressed for the times at which 75%, 50%, and 25% of the patients would still be alive), as well as the estimated probabilities of surviving from 6 to 18 months at 6-month intervals.

From Figure 1, there is a noticeable separation between the treatment groups, with the experimental arm showing greater survival starting at approximately 320 days post-randomization. The Kaplan-Meier survival curves showed that median survival is 43 days longer in the TFD725 plus docetaxel group (413 days) compared to the docetaxel alone group (370 days). As shown in Table 2, seventy-five percent of subjects were still surviving at 305 days post-randomization in the control arm and 311 days post-randomization in the experimental arm of the study – a difference of 6 days. This result was exaggerated later on in the study. Twenty-five percent of patients still alive in the experimental arm were still alive at 579 days, rather than 501 days in the control arm, demonstrating a 78-day difference in survival between the treatment groups. As shown in Table 2, the difference in survival probability at 18 months is 12.5% greater among patients in the TFD725 plus docetaxel group compared to the docetaxel only group.

From the Cox proportional hazards regression, we estimate that the relative risk of death in the TFD725 plus docetaxel group tends to be 0.746 times that in the docetaxel only group (CI: 0.536-1.040; P=0.084). Despite the notable findings highlighted from the Kaplan-Meier estimates, the estimate of relative risk of death is not statistically significant. Therefore, we cannot support the hypothesis that survival is prolonged by treatment with TFD725 plus docetaxel over docetaxel alone.

**Discussion**

The primary question of interest in this analysis was whether second line chemotherapy using docetaxel and TFD 725 (treatment) prolonged survival compared to docetaxel alone (control). As noted previously, the better survival in the treatment group did not reach a level of statistical significance compared to the control group.

The absence of the expected association between risk of death and treatment group could be explained by one of four reasons. First, doses of docetaxel were different between treatment and control groups. The control group was given docetaxel for 75 $mg/m^2$ every 3 weeks, while the treatment group was assigned docetaxel only for 50$mg/m^2$ every 3 weeks. Although, it was not unreasonable to think that the effect of TFD725 was compromised by the decreased dose of docetaxel in the treatment arm of the clinical trial.

**Comment [A10]:** The problem was one of dose limiting toxicity. Adding an additional therapy might have made the combined dose too toxic unless DOC were reduced

Second, the randomization was stratified by clinical site and stage of disease at initial diagnosis. However, randomization did not guarantee that the patients in the two groups were similar in every respect. In fact, a careful examination demonstrated that patients in the treatment group were in better condition at the time of randomization, as reflected by the statistical significance of the differences in their alkaline phosphatase level. The higher percentage of patients in the control group with an abnormal alkaline phosphatase suggested that there were more patients in that group with metastatic disease. This discrepancy at randomization limited our ability to detect the true effect of TFD725. In other words, if the severity of the disease were equivalent in both groups at baseline, we might have seen a better survival when they took TFD725.

**Comment [A11]:** This is unlikely to explain lack of effect. If anything, it might explain why we saw better survival in the TFD group—that was the group with the better condition.

**Comment [A12]:** This is the scientifically and clinically important way to do the study. We DO NOT gain any info by doing an analysis among compliers. That ruins our RCT.

Third, patients were followed for the clinical event of death even in the cases when they discontinued the study medication. Our data did not provide any information on the compliance rate of the drugs or drop-off rate because of drug toxicity. Both of these factors could influence the survival probability, thereby

**Comment [A13]:** Or, just as likely, impending death could have affected compliance. You do not know cause and effect except through randomization.

distorting the association. Lastly, the distribution of survival might be truly different between the two groups, however we did not have enough precision to be able to statistically demonstrate that difference.

One limitation of this study design was that the bulk of the measurements are baseline measurements, and we had only one variable "death" as our primary endpoint. Due to the lack of data gathering throughout the trial, we cannot observe the progression or regression of the disease parallel to the treatment. It would have been more helpful to have intermediary measurements such as serum fragment CYFRA 21-1, or carcinoembryonic antigen (CEA)[7] to better assess the effectiveness of TFD725.

Three things could be considered for future studies. First, we observed a higher survival probability in treatment arm after approximately 320 days. We could prolong the treatment period or increase the dose of TFD725 to see whether the effects of the drug change. Second, we could do a separate analysis to estimate whether this drug works better in certain group of subjects, such as older people, females, or subjects with normal/abnormal LDH level. Additionally, in this analysis we saw that the treatment groups differed at baseline in the number of patients with abnormal alkaline phosphatase levels. Moreover, we know these variables are predictive of poor patient outcomes, therefore, future studies or analyses controlling for the difference in these variables across groups could be important in determining a statistically significant difference in survival between the treatment and control groups.

To conclude, we did not observe a statistically significant difference in survival between traditional treatment of docetaxel and TFD725 plus docetaxel among non-small cell lung cancer patients. Future studies need to be done to further evaluate the effect of TFD 725.

**Comment [A14]:** death is the ultimate endpoint

**Comment [A15]:** I never believe such surrogate endpoints. See the wealth of literature warning of the dangers of using such endpoints

**Comment [A16]:** In real life, we would have prespecified secondary analyses adjusting for important baseline variables as well as exploratory analyses looking at effects within subgroups.

Results of such exploratory analyses might affect how we do a phase III study.

**References**

1. Carles J, Rosell R, Ariza A, et al. Neuroendocrine differentiation as a prognostic factor in non-small cell lung cancer. *Lung Cancer*. 1993;10(3-4):209-219.

2. Dowell JE, Minna JD. The impact of epidermal-growth-factor-receptor mutations in response to lung-cancer therapy. *Nat Clin Pract Oncol*. 2004;1(1):2-3.

3. Gomm SA, Keevil BG, Thatcher N, Hasleton PS, Swindell RS. The value of tumour markers in lung cancer. *Br J Cancer*. 1988;58(6):797-804.

4. Muley T, Dienemann H, Ebert W. Increased CYFRA 21-1 and CEA levels are negative predictors of outcome in p-stage I NSCLC. *Anticancer Res*. 2003;23(5b):4085-4093.

5. Toloza EM, D'Amico TA. Targeted therapy for non-small cell lung cancer. *Semin Thorac Cardiovasc Surg*. 2005;17(3):199-204.

6. World Health Organization. Media Center, News Release 2003: Global cancer rates could increase by 50% to 15 million by 2020. .http://www.who.int/mediacentre/news/releases/2003/pr27/en/. Updated 2003. Accessed 12/16, 2009.

7. Nisman B, Lafair J, Heching N, Lyass O, Baras M, Peretz T, et al. (1998). Evaluation of tissue polypeptide specific antigen, CYFRA 21-1, and carcinoembryonic antigen in nonsmall cell lung carcinoma: does the combined use of cytokeratin markers give any additional information? Cancer. 82 (10), 1850-9

**Table 1: Patient Characteristics at Randomization (by treatment group)**

| | Docetaxel Only (n=90) | | | | Docetaxel + TFD725 (n=98) | | | |
|---|---|---|---|---|---|---|---|---|
| | **mean** | **SD** | **min** | **max** | **mean** | **SD** | **min** | **max** |
| ***Demographics*** | | | | | | | | |
| **Age (years)** | **60.5** | **4.8** | **50** | **75** | **60.4** | **5.4** | **46** | **71** |
| **Sex, %** | | | | | | | | |
| **Male** | **52.2** | | | | | | | |
| **Female** | **47.8** | | | | | | | |
| **Site Location** | | | | | | | | |
| **North America, %** | **81** | | | | **83** | | | |
| **Europe, %** | **19** | | | | **17** | | | |
| ***Indicator of lung damage and physical condition*** | | | | | | | | |
| **Malignant or stage IV at Initial Diagnosis, %** | **65.6** | | | | **60.2** | | | |
| **Tumor Responded to First Line Therapy, %** | **56.7** | | | | **57.1** | | | |
| **Abnormal LDH Level , %** | **17.8** | | | | **9.2** | | | |
| **Abnormal Alkaline Phosphatase Level, %** | **32.2** | | | | **19.4** | | | |
| **Performance Status on ECOG Scale, frequency** | | | | | | | | |
| **0 (best)** | **25.6** | | | | **34.7** | | | |
| **1** | **68.9** | | | | **61.2** | | | |
| **2 (worst)** | **5.5** | | | | **4.1** | | | |

**Figure 1. Kaplan-Meier Survival Curves by NSCLC Second-Line Chemotherapy Treatment**

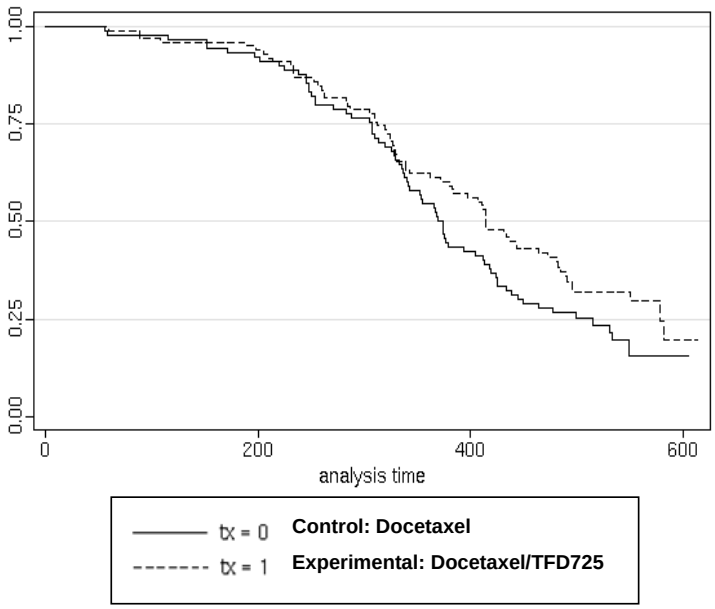

**Table 2. Kaplan-Meier Survival Estimates by NSCLC Second-Line Chemotherapy Treatment**

| Treatment Group | Quartiles for Survival (days) | | | Survival Probability (95% CI) | | |
|---|---|---|---|---|---|---|
| | 75% | 50% | 25% | 6 months (183 days) | 12 months (365 days) | 18 months (547 days) |
| **Docetaxel** | 305 | 370 | 501 | 0.933 (0.8576, 0.9695) | 0.544 (0.4362, 0.6405) | 0.195 (0.1139, 0.2913) |
| **Docetaxel+TFD725** | 311 | 413 | 579 | 0.959 (0.8949, 0.9845) | 0.612 (0.5084, 0.7006) | 0.320 (0.2273, 0.4163) |
| **Difference** | 6 | 43 | 78 | 0.026 (-0.039, 0.091) | 0.068 (0.073, 0.209) | 0.125 (-0.006, 0.257) |