# PHASE IIB CLINICAL TRIAL: DIFFERENCES IN SURVIVAL BETWEEN PATIENTS WITH LATE STAGE NON-SMALL CELL LUNG CANCER TREATED WITH DOXETAXEL AND DOCETAXEL PLUS TFD725


## SUMMARY

### *Background and Study Question*

Lung cancer is the leading cause of cancer deaths in the United States claiming more lives than colon, prostate and breast cancer combined. Chemotherapy is the main stay for treatment for late stage lung cancer. The overall goal of this study was to assess whether patients with late stage non-small cell lung cancer (NSCLC) that progressed after treatment with first line chemotherapy had a longer period of survival when their second line chemotherapy used docetaxel and TFD725 compared to similar patients whose second line chemotherapy used docetaxel alone.

### *Methods*

One hundred eighty eight volunteers with stage IIIb or IV NSCLC who had received first line (platinum based) chemotherapy were randomized to receive either docetaxel and TFD725 or docetaxel alone as part of a multicenter Phase II clinical trial. Surviving subjects were followed for a median time of 550 days.

We based our primary statistical inference on hazard ratio, which we used to estimate the risk of death at any given time in the docetaxel and TFD725 treatment group compared to the docetaxel treatment group. We also made secondary inferences on the difference between Kaplan-Meier survival probabilities at 6, 12 and 18 months. We did further comparison of hazard ratios within strata pertaining to age, advanced disease stage and abnormal liver function. All analysis was done using Stata IC version 10.

### *Results*

The hazard ratio of 0.746 (95% CI: 0.536 to 1.040, p=0.084) did not show a significant difference in survival between docetaxel plus TFD725 (treatment) and docetaxel alone (control). There was an improved survival for the treatment group in patients with stage IIIb NSCLC (hazard ratio 0.530; 95% CI: 0.284 to 0.989; p=.046) but not stage IV (hazard ratio 0.988; 95% CI: 0.668 to 1.460; p=0.954).

### *Conclusion*

We found that the combination of docetaxel plus TFD725 compared to docetaxel alone did not improve survival in patients with late-stage non-small cell lung cancer. Our tertiary analysis found improved survival on docetaxel plus TFD725 compared to docetaxel alone in patients with stage IIIb NSCLC and recommend further studies of the use of docetaxel plus TFD725 in stage IIIb NSCLC lung cancer that follows a larger group of patients for a longer period of time.


**Comment [A1]:** 1:1 ratio

**Comment [A2]:** months probably a better unit

**Comment [A3]:** adjustment or looking for effect modification?

**Comment [A4]:** treatment:control

**Comment [A5]:** pre-specified analysis? adjusted for multiple comparisons?

**Comment [A6]:** you might comment that it therefore will require confirmation (even though that should be obvious)

## BACKGROUND

Lung cancer remains the leading cause of cancer death in both men and woman with only approximately 1 in 10 surviving 5 years after diagnosis (Fossela, 1994). The greatest hope for decreasing mortality lies in prevention, as treatment remains challenging. Lung cancer is classified according to the histologic make-up of the malignant cells. Treatment, including surgical, radiation and oncologic, depend on the histiologic classification of the disease as the response to each is variable. Non-small cell lung cancer (NSCLC) is comprised of squamous cells (squamous or neuroendocrine cells) or glandular cells (adenocarcinoma). Small cell lung cancer is derived from neuroendocrine cells.

Staging of cancer is important to determine both treatment and prognosis for patients. Staging is based on size of the tumor, spread to lymph nodes, and distant metastasis. Surgical therapy is reserved for early

stage disease with local involvement. Treatment of unresectable stage III NSCLC remains challenging with a poor prognosis overall for patients. The mainstay therapy for these patients is chemotherapy. Often, the overall goal of therapy in advanced NSCLC is prolonging quality and quantity of life. Advances in terms of survival prolongation have been made primarily with improvement in chemotherapy regimens.

At the time of this research, stage IIIb and stage IV cancer is primarily treated with chemotherapy. First line includes platinum based therapy (including cisplatin or carboplatin) combined with a taxane (paclitaxel or docetaxel), gemcitabine, or vinorelbine (Bellani). If a patient fails to have improvement in tumor size or advanced disease, providers often progress to second line therapy. Second line therapy at the time of study includes docetaxel which is a drug that attacks a cells' ability to divide through impairment of microtubule formation. This is the only chemotherapy option that shows clinical improvement after failed first line therapy.

Advances in cancer treatment have expanded to include agents that block tyrosine kinase receptors and their ligands as these have been implicated in angiogenesis (Kim, 2004). The proposed mechanism limits the tumors' ability to continue to grow as well as limits their spread to distant sites. TFD725 has the ability to block tyrosine kinase in vivo and within animal experiments. Phase I and IIa clinical trials have shown favorable initial safety and efficacy data.

## QUESTION OF INTEREST

The primary scientific question of interest in this clinical trial was whether second-line chemotherapy with TFD725 and docetaxel resulted in improved survival compared to second-line chemotherapy with docetaxel alone in patients with late stage non-small cell lung cancer whose cancer had progressed with a first line platinum based chemotherapy regime.

Due to practical study limitations not all patients could be followed until death. We therefore compared the distribution of Kaplan-Meier estimates of survival probabilities between the treatment arms. Our primary analysis consisted of calculating the hazard ratio for the two treatment arms. Secondary analysis examined the difference in survival probabilities at 6, 12 and 18 months. Tertiary analysis examined hazard ratios between various subgroups. While none of our methods estimate the survival time, which was the scientific aim of the study, comparing instantaneous risk of death and survival probabilities serve as an appropriate proxies for survival between groups.

**Comment [A7]:** what about adjustment for baseline factors? And which factors were of interest?

## SOURCES OF DATA

One hundred eighty eight patients were screened and enrolled in a randomized double-blinded, placebo controlled clinical trial. The data for this analysis was collected at multiple centers in North America and Europe as part of a Phase IIB clinical trial. To be included in the trial, patients needed to have had stage IIIb (70 patients) or stage IV (118 patients) NSCLC and must have already received first line chemotherapy. Patients in the treatment group (98 patients) were administered docetaxel (50 mg/m$^2$) every three weeks and TFD725 (50 mg) daily; those in the non-treatment group (90 patients) were administered docetaxel alone (75 mg/m$^2$) once every three weeks. Patients were ineligible for the study if their first-line therapy included docetaxel, they were over age 80 years at the time of randomization, were unwilling to use adequate contraception, or had a performance status that corresponded to ECOG level three or worse at the time of randomization. Patients were randomized by site and stage of disease at initial diagnosis (stage IIIb or IV).

The 188 patients enrolled in this clinical trial had multiple demographic and clinical data collected. Demographic data was collected on a patient's sex, age, and country of residence. Data was also

**Comment [A8]:** treatment

collected on a patient's history of disease including, classification of disease by stage at diagnosis, tumor shrinkage in response to "first line" chemotherapy and the amount of time from their initial diagnosis to randomization. Additionally, laboratory measurements of lactate dehydrogenase and alkaline phosphatase were collected as potential indicators of disease severity at baseline. ECOG performance status was used as a qualitative measurement of a patient's condition at baseline. All patients, regardless of whether they stopped the study treatment early, were followed until the earlier event of death or the end of the treatment period and were included in the analysis. At the planned end of the study, some subjects were still alive. There were no missing observations in any of the variables of interest used in this analysis.

Several variables potentially confound true differences in the survival probability between treatment groups. Abnormal LDH and alkaline phosphatase may be associated with the way a patient responds to treatment as abnormal lab values may indicate liver disease and therefore may affect drug metabolism. In addition, abnormal LDH and alkaline phoshatase levels may also be associated with poor survival. Similarly, the stage of disease at the initial diagnosis and ECOG measurement at randomization may be associated with a healthier patient who may be able to tolerate chemotherapy better and in whom chemotherapy may be more effective than a sicker patient. The stage of disease and performance measured by ECOG may also be associated with prolonged survival since patients with further spread of disease or lower performance status are more likely to have a shorter survival time

**Comment [A9]:** so this would suggest adjustment for covariates in an analysis. Where do you motivate subgroup analyses such as you reported in the abstract?

Response to first line therapy could also confound survival probabilities since a failure in response to first line treatment may be associated with failure in response to second line treatment. Response to first line treatment could also be associated with survival since people who made progress during the first line treatment may be healthier and more likely to have a longer survival time.

## STATISTICAL METHODS

We assessed whether randomization of the docetaxel plus TFD725 group and docetaxel group resulted in similar descriptive statistics between the groups.

In our primary analysis to assess whether the combination of docetaxel and TFD725 was associated with improved survival over docetaxel alone, we compared survival probabilities between the two treatment groups using the proportional hazard ratio. Because the observations were right censored we used Kaplan-Meier estimates of survival probability. Cox proportional hazard regression was used to compare the risk of death (as measured by the hazard) between treatment arms. The hazard ratio compares the instantaneous risk of death of the treatment (docetaxel plus TFD 725) to the control (docetaxel alone). We report the hazard ratio, 95% confidence intervals and the two-sided p-value indicating whether we can reject the null hypothesis of no treatment effect (a hazard ratio of 1).

In order to examine survival at clinically relevant benchmark times we used Kaplan-Meier estimates of survival probabilities and 95% confidence intervals at 6, 12 and 18 months for our secondary analsysis. Since patients with NSCLC have a poor prognosis of survival, benchmark times of 6, 12 and 18 months were chosen to assess survival at frequent intervals and at time points where treatment might have an effect on prolonged survival. Inference on the difference in survival probabilities was made at each of the benchmark times by calculating confidence intervals and two-sided p-values.

In order to better understand where the treatment might have been effective and to inform Phase III trials, we further analyzed survival probabilities stratified by various factors. Because treatment might be different based on age, we dichotomized the group at 60 years. Other studies have dichotomized between ages 60 to 65 years. We looked at disease stage as we anticipated that those patients who had stage IIIb disease may have a different treatment outcome than patients with malignant pleural effusion (stage IV). This might be due to cancer biology or disease progression. Because impaired liver function could affect drug metabolism, we also stratified for patients with abnormal levels of alkaline phosphatase and lactate

**Comment [A10]:** again, not clear whether you were just doing adjusted analyses or whether you were looking at subgroup analyses.

dehydogenase. Last, expecting that patients whose cancer had responded to first line therapy might influence treatment outcomes, we stratified by response to first line therapy. All analysis was done using Stata IC version 10.

**Comment [A11]:** adjustment for multiple comparisons? (I usually explicitly state that I did not do so.)

## RESULTS

Overall, the treatment and control groups were similar (Table 1) with respect to patient demographics and characteristics. There was a slightly higher proportion of men than women in both groups (treatment group 58% and control group 52%). The mean age was similar in both groups with a mean age of 60.5 ± 4.8 years in the control group and 60.4 ± 5.4 years in the treatment group. Approximately 65% (control group) vs 60% (treatment group) had Stage IV NSCLC (malignant pleural effusion or metastatic disease). In both groups, 57% responded to first line therapy indicating that the cancer biology was similar for response to chemotherapy. Similarly both groups were similar in the time from diagnosis to randomization. More patients in the docetaxel (control) group had abnormal values for lactate dehydrogenase (18% control vs 9% treatment) and alkaline phosphatase levels (32% control vs 19% treatment) at the time of randomization. The median Kaplan-Meier estimates for the follow up time were 555 days for the control group and 550 days for the treatment group.

**Comment [A12]:** Note that stage, LDH, alk phos all suggest more severe disease in placebo group

In our primary analysis we found that the proportional hazard ratio for the treatment arms (treatment to control) is 0.746 (95% CI: 0.536 to 1.040, two-sided p-value=0.084, Table 2). Proportional hazards analysis suggests that the instantaneous risk of death in the treatment group was 0.746 times that of the control group. Though the estimate is not statistically significant (p=0.084) the confidence interval suggests that such an observation would not be unusual if the true hazard ratio were between 0.536 and 1.040.

In our secondary analysis, survival probabilities between the treatment and control groups did not differ at each benchmark time of 6, 12 and 18 months (table 2). Although not significantly different, the survival probability in the treatment group at 18 months was 0.125 higher than that of the control group (95% CI: 0.006 lower to 0.257 higher, p-value=0.062).

The hazard ratio between the various strata (age, liver function, first line response) did not differ significantly between the treatment and control groups (Table 3). The only improved survival, as measured by the hazard ratio, (treatment to control) was for patients with stage IIIb disease (hazard ratio: 0.53; 95% CI: 0.284 to 0.989; two-sided p-value=0.046). Patients with stage IV disease did not show improved survival (hazard ratio 0.988; 95% CI: 0.668 to 1.460; p=0.954).

**Comment [A13]:** I do not see any tests of effect modification that this wording seems to suggest.

**Comment [A14]:** Huge multiple comparison problem here, soften your wording.

## DISCUSSION

In evaluating the effect of both the treatment and the control group, it was necessary to consider subpopulations of patients that may show a survival benefit with the second line chemotherapy. The demographics (age, sex, response to first line therapy) were similar across groups. However, the control group (docetaxel alone) had more abnormal values of LDH and alkaline phosphatase at the time of randomization indicating a potential worse baseline liver function. Therefore, it is possible that the control (docetaxel alone) group had more severe liver disease at the time of randomization. This may affect the control group's ability to metabolize chemotherapy and other drugs leading to confounding of our outcomes. Due to the complexity of liver metabolism of chemotherapy it would be difficult to say if this would under or over estimate our results for survival for this group.

In the overall study population, 40% of patients had failed first line therapy. The tumor in these patients had continued to progress despite possible treatment with possible combined therapy with a taxane. This is the same class of drug as docetaxel (however, patients previously administered docetaxel were exempt). Docetaxel is shown to improve clinical outcomes in patients that fail platinum based therapy, but it is

unclear if patients were included who underwent first line therapy with both platinum and a non-docetaxel taxane. TFD725 blocks angiogenesis with a goal of stopping tumor growth by limiting blood supply and hematologic spread of disease and therefore takes a different pathway in slowing the destruction of this late stage cancer. Given that late stage NSCLC has such an overall relatively short life expectancy and a significant number of patients in the study had failed first line therapy, our study may be underpowered to show a survival difference due to severity of disease and short predicted survival. To improve our ability to show a survival benefit using TFD725, it may be beneficial in future studies to evaluate a larger number of patients at earlier stage disease.

This study evaluated patients with advanced stage NSCLC for second line chemotherapy. Treatment options are poor at for this stage of disease with an oncologic emphasis on increasing survival and palliation for symptoms. Curative therapy including surgery is often not an option due to metastatic disease. One limitation with interpretation of this data is lack of information on the number of patients who discontinued therapy due to factors like voluntary withdrawal, toxicity problems and lost to follow-up. Chemotherapy is often poorly tolerated and the number of patients who discontinued treatment has the potential to play a significant role in effecting clinical outcomes. For instance, if a majority of patients experience significant side effects from TFD725 and discontinue therapy, this could potentially have a significant impact on our survival analysis. Additional data on early termination of treatment would be helpful for addressing this issue but we do not have information on this data.

In this trial comparing survival for advanced stage NSCLC, we found there was no significant difference between treatment with docetaxel alone versus docetaxel plus TFD725 overall. However, in our subgroup analysis we found that in patients with stage IIIb disease, patients in the treatment group showed an improved survival benefit with a hazard ratio of 0.53 (95% CI 0.284 - 0.989, p=0.046). This suggests that this sub-populaton of patients may benefit from TDF725 plus docetaxal as second line therapy. In this trial there were only 30 people in the control group and 39 people in the treatment group with stage IIIb disease. Future trials may include a larger study populations with focus on stage IIIb disease. Following these patients for a longer period of time may give more detailed insight into the potential for of docetaxel plus TFD725 to prolong the median time of survival with NSCLC.

**Comment [A15]:** wording too strong

## REFERENCES


Belani, C Optimizing Chemotherapy for Advanced Non-small Cell Lung Cancer with Focus on Docetaxel *Lung Cancer*; 2005; 50; 53-58

Fossella, et al Phase II Study of Docetaxel for Recurrent of Metastatic Non-small Cell Lung Cancer . *Journal of Clinical Oncology* 1994; 12; 1238-1244

Kim, DW, LU B, Hallahan DE Receptor tyrosine kinase inhibitors as anti-angiogenic agents. Curr Opin Investig Drugs. 2004 Jun 597-604

## Figures

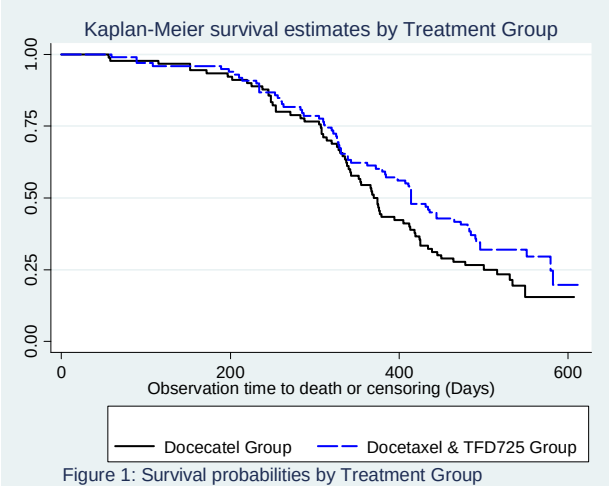


Figure 1: Survival probabilities by Treatment Group

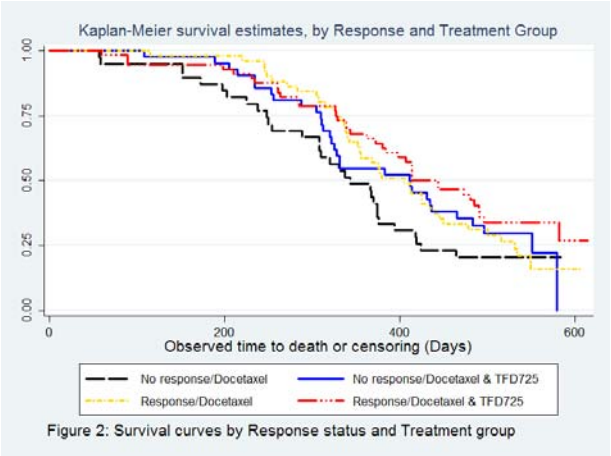


Figure 2: Survival curves by Response status and Treatment group

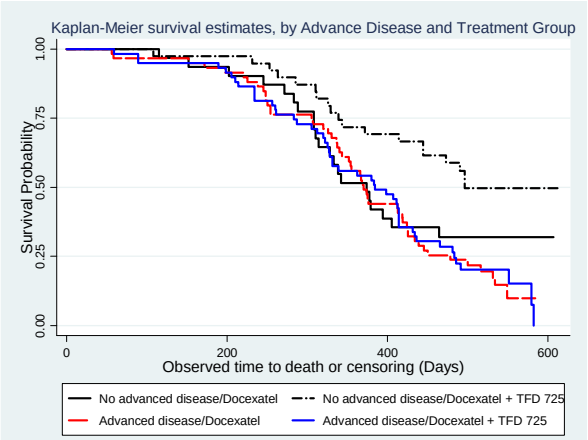


Figure 3: Survival curves by advanced disease and treatment group

**Table 1: Characteristics of study population, by treatment group**

| Variable | Mean (SD) | Min | Median | Max | Mean (SD) | Min | Median | Max |
|---|---|---|---|---|---|---|---|---|
| | Docetaxel Group | | | | Docetaxel and TFD725 Group | | | |
| N | 90 | | | | 98 | | | |
| Male (gender) | 52% | | | | 58% | | | |
| Age (Years) | 60.51 (±4.79) | 50 | 61 | 75 | 60.38 (±5.41) | 46 | 60 | 71 |
| Europe (Site) | 19% | | | | 17% | | | |
| Percent Stage IV NSCLC | 66% | | | | 60% | | | |
| Months from diagnosis to randomization | 10.23 (±4.35) | 3 | 10 | 27 | 10.39 (±4.78) | 3 | 10 | 31 |
| Percent with response to first line chemotherapy | 57% | | | | 57% | | | |
| Percent with abnormal LDH levels | 18% | | | | 9% | | | |
| Percent with abnormal alkaline phosphatase levels | 32% | | | | 19% | | | |
| ECOG stage - performance status | 0.80 (±0.52) | 0 | 1 | 2 | 0.69 (±0.55) | 0 | 1 | 2 |
| Follow Up Time (Estimated with KM) | | | 555 | | | | 550 | |

**Table 2: Difference in Survival Measured by the Hazard Ratio and Probability of Survival at six month intervals**

| | Treatment | Control | Comparison | |
|---|---|---|---|---|
| | Survival prob(95% CI) | Survival prob(95% CI) | Difference ( 95% CI) | Two sided P-Value |
| 6 months | 0.959 (0.895, 0.985) | 0.933 (0.858, 0.970) | 0.026 (-0.039, 0.091) | 0.433 |
| 12 months | 0.612 (0.508, 0.701) | 0.544 (0.436, 0.641) | 0.068 (-0.073, 0.209) | 0.346 |
| 18 months | 0.320 (0.227, 0.4163) | 0.195 (0.114, 0.291) | 0.125 (-0.006, 0.257) | 0.062 |
| Hazard Ratio | | | 0.746 (0.536, 1.040) | 0.084 |

**Table3: Stratified Analysis: Hazard Ratio Comparing Treatment Group to Control Group**

| | Hazard Ratio | 95% Confidence Interval | Two sided p-value |
|---|---|---|---|
| *All patients* | | | |
| | 0.746 | (0.536, 1.040) | 0.084 |
| *Age* | | | |
| **Less than or equal to 60 years old** | 0.738 | (0.461, 1.18) | 0.204 |
| **Greater than 60 years old** | 0.742 | (0.447, 1.231) | 0.248 |
| *Stage of Disease* | | | |
| **Stage IIIb** | 0.530 | (0.284, 0.989) | 0.046 |
| **Stage IV** | 0.988 | (0.668, 1.46) | 0.954 |
| *Response to Firstline Chemotherapy* | | | |
| **Response** | 0.749 | (0.481, 1.168) | 0.202 |
| **No Response** | 0.733 | (0.445, 1.207) | 0.222 |
| *Alkaline Phosphatase Levels* | | | |
| **Normal** | 0.737 | (0.491, 1.106) | 0.141 |
| **Abnormal** | 1.036 | (0.552, 1.946) | 0.912 |
| *LDH Levels* | | | |
| **Normal** | 0.793 | (0.553, 1.139) | 0.209 |
| **Abnormal** | 0.72 | (0.314, 1.65) | 0.438 |