Group Twenty-Three:
A Randomized Phase IIb Trial of Docetaxel vs. Docetaxel plus TFD725 as Second Line Therapy for Patients with Non-Small Cell Lung Cancer

SUMMARY

Background:
Non-small cell lung cancer (NSCLC) is a leading cause of cancer death in the United States. Traditional chemotherapies have focused on arresting dividing cells, however newer treatments are being developed to target cancer specific enzymes. Our hypothesis was that patients with NSCLC, receiving standard second-line treatment plus a receptor kinase inhibitor, would have improved survival.

Objective:
Data from a multi-center, phase IIb randomized controlled trial where analyzed to examine the effect of TFD725, a receptor kinase inhibitor, on survival in patients with NSCLC receiving docetaxel (traditional second-line treatment). A second objective was to analyze the efficacy of this treatment within the subgroups; by response to first-line treatment, stage of cancer at initial diagnosis (IIIb vs. IV), age (<65 vs. >=65), and gender.

Methods:
A total of 188 patients with advanced stage non-small cell lung cancer were randomized to receive docetaxel alone (n=90, 75 mg/m² every 3 weeks) or docetaxel (75 mg/m² every 3 weeks) plus TFD725 (n=98, 50 mg/day). Death from any cause was ascertained through routine follow-up. Patients were followed for a median time of 551 days for docetaxel alone, and 546 days for docetaxel plus TFD725. Kaplan-Meier survival probability estimates were used to compare survival by treatment group for both overall and subgroups. Cox proportional hazard regression was used to generate estimated overall risk of death, hazard ratios, by treatment for overall and subgroups.

Results:
The hazard ratio for overall relative risk of death was 0.746 (95% CI: 0.536 - 1.040, p=0.084), indicating nearly 25% lower risk of death in the docetaxel plus TFD725 group. However, none of the results obtained demonstrated statistical significance, thus suggesting that treatment with TDF725 added to second-line treatment did not increase overall survival. According to the Kaplan-Meier analyses overall and by subgroups, there were no statistically significant differences in the probability of survival at 6, 12, and 18 months between treatment groups. At 12 months, the docetaxel plus TFD725 group had a survival probability of 0.068 higher than the docetaxel group (95% CI: -0.073 to 0.209, p=0.346). The relative risk of death for stage IIIb patients, by treatment group, was 0.53 (95% CI: 0.284 to 0.99, p=0.046,) while for stage IV patients, by treatment group, it was 0.988 (95% CI: 0.668 to 1.463, p=0.988). These findings suggest that patients with stage IIIB cancer assigned to docetaxel plus TFD724 had a lower relative risk of death than patients with stage IIIB cancer assigned to docetaxel alone.

Conclusions:
Overall, the addition of TFD725 to second-line therapy for the treatment of non-small cell lung cancer did not markedly improve survival. For patients who were initially diagnosed with stage IIIb cancer, docetaxel plus TFD725 appeared to yield a survival benefit compared to docetaxel alone.

Comment [A1]: you might consider brief description of age, sex, stage

Comment [A2]: 1:1

Comment [A3]: which was primary?

Comment [A4]: Give these descriptive statistics first, then give the HR (perhaps using the word "primary")

Comment [A5]: Careful. You have a huge multiple comparison issue here. Soften your wording. The subgroups are exploratory and will need to be confirmed in another study.

Comment [A6]: again, soften wording

BACKGROUND:

Lung cancer is the leading cause of cancer death in the United States. In 2004, more than 160,000 adults in the US died from lung cancer (1). Over the last decade this epidemic has become increasingly more deadly among women; lung cancer is now responsible for more deaths than breast cancer and all other gynecological cancers combined (2-3). Non-small cell lung cancer (NSCLC) accounts for 85 percent of all types of lung cancer (4). Three quarters of patients with lung cancer have metastatic spread to regional or distant sites at the time of diagnosis, leading to a 5-year survival rate of only 15 percent (5). In patients who had unsuccessful treatment with first-line chemotherapy prognosis is especially poor.

Protein tyrosine kinases (TK) are enzymes that are important in the regulation of cellular proliferation, survival, differentiation, and function (6). These enzymes are dysregulated in several types of cancers including both hematologic malignancies (leukemia/lymphoma) and solid tumor (lung/breast) cancers. The development of cancer therapies that can target specific enzymes can create therapies that are less toxic than conventional chemotherapy.

In NSCLC, epidermal growth factor receptor (EGFR) is over-expressed in 40-80% of cells (7). EGFR, a sub-class of receptor tyrosine kinase family, is a cell-surface receptor. A small deletion or point mutation in the kinase domain of

EGFR can increase the sensitivity of the receptor. This alteration can lead to an over-expression of EGFR (8). Recent trials have identified drugs such as Gefitinib, (ZD1839), which block EGFR tyrosine kinases and prevent epidermal growth factor-induced proliferation in cell culture (9). However in clinical trials, while this drug has minimal adverse effects, its efficacy was limited. Only 10 to 19 percent of patients with chemotherapy-refractory advanced NSCLC had a tumor response (10). One study has demonstrated that the subgroup of patients that benefited from treatment had a specific mutation in EGFR gene (11).

Similar to Gefitinib, TDF725 is an experimental molecule that inhibits several receptor tyrosine kinases *in vitro* and animal experiments. Initial safety data and preliminary efficacy data are available from Phase I and Phase IIa clinical trials. In this Phase IIb double-blind randomized study, we will analyze the survival benefit of adding TDF725 to standard second-line treatment for patients who have advanced NSCLC.

QUESTIONS OF INTEREST

The primary question of interest is whether TDF725, a receptor tyrosine kinase inhibitor, added to traditional second-line treatment, in patients with NSCLC, improves overall survival. Additionally, we are interested in whether overall survival, related to treatment, differed with respect to age, gender, response to first-line treatment, and stage of cancer at initial diagnosis.

Comment [A7]: Make clear that the subgroup analyses are exploratory, or people might expect you to adjust everything for multiple comparisons.

MATERIALS AND METHODS

Study design:

Starting in 2003, a multi-center Phase IIB double-blind clinical trial in North America and Europe randomized 188 patients with advanced stage non-small cell lung cancer to receive docetaxel alone (75 mg/m² every 3 weeks) or docetaxel (75 mg/m² every 3 weeks) plus TFD725 (50 mg/day). The primary endpoint was death from any cause during the trial period. Patients were monitored for adverse events every 3 weeks and signs of clinical or subclinical progression every 6 weeks. If patients experienced toxicity, their doses were modified according to protocol and treatment was discontinued with continued toxicity.

Comment [A8]: 1:1

Comment [A9]: But, importantly, all patients were followed for outcome regardless of whether they continued on therapy.

Subjects:

Patients were randomized to treatment based on stage of disease at initial diagnosis (stage IIIb without malignant pleural effusion vs. more advance disease) and clinical site. Eligibility criteria included initial diagnosis with stage IIIb or stage IV non-small cell lung cancer and treatment with a standard platinum based chemotherapy. Patients with a history of treatment with docetaxel, performance status on the Eastern Cooperative Oncology Group (ECOG) scale of ambulatory status 3 or worse, over the age of 80, or unwilling to use contraception were excluded. The sample included 104 males (55.3%) and 84 females (44.7%) from North America and Europe between the ages of 46 and 75 at time of randomization. All patients met the inclusion criteria, and were randomized 3 to 31 months after initial diagnosis of disease.

Data sources:

At baseline, a complete medical history, physical examination, and evaluation of ambulatory status were conducted on each patient to assess the stage of cancer at initial diagnosis, tumor response to first line chemotherapy, time of initial diagnosis, levels of biochemical markers, and performance status on ECOG scale (12). Stage of cancer at initial diagnosis, tumor response to first line chemotherapy, and time of initial diagnosis were obtained from patients' medical history. A physical examination measured levels of lactate dehydrogenase (LDH) and alkaline phoshatase, biochemical markers of disease severity. A subjective evaluation of patients' ambulatory status at baseline was performed using the ECOG scale (ranging from 0-2, with 0 being the best score). There are no missing data on demographic information, disease history, and baseline biomarkers at time of randomization.

Comment [A10]: from 0-5, but 3 or greater are ineligible

The primary endpoint, death from any cause during the study period, was ascertained through routine follow-up. Patients were followed up for a maximum of 615 days for death. Patients who discontinued therapy for any reason were followed for clinical events or death. Data are not available on cause of death, amount of time on study drug, toxicity, and other health outcomes such as disease progression post-randomization.

Comment [A11]: This is only true if the earliest ransomized subject was still alive at end of study.

Statistical analysis:

Descriptive statistics by treatment group were found for all baseline variables. We created a variable for patients equal to or over the age of 65, because based on previous study results, we were interested in a subgroup analysis of this characteristic. Summary statistics were given in the form of mean, standard deviation, minimum, median and

Comment [A12]: put this down where you describe your subgroup analyses (or omit it altogether)

maximum for continuous variables and as a count and percentage for binary and categorical data. There were no missing observations. For the primary analysis, Kaplan-Meier estimates were used to handle the censored data for time to death or last follow-up. In this study, censoring occurred when we did not know when a patient died (ie they survived longer than our study period) or they were lost to follow-up. Estimates of survival probabilities at 6 months, 12 months, and 18 months by treatment group were calculated using the Kaplan-Meier method. Kaplan-Meier curves were given by treatment and stratified by subgroups. These Kaplan-Meier estimates were used to estimate the difference between the docetaxel plus TFD725 and the docetaxel group. A 95% confidence intervals and two-sided p-values at the level of 0.05 were calculated, using a z-score statistic to assess the differences in survival by treatment arm. The cox proportional hazard regression was used in examining the relative risk of death for docetaxel plus TFD725 compared to docetaxel alone using the Wald p-value for testing significance. A hazard less than 1.0 indicated higher risk of death for the docetaxel arm. Exploratory analyses of subgroups based on patients 65 years and older, gender, patient response to first line treatment, and advanced stage of disease at initial diagnosis were performed to examine effect modification. Subgroup analysis was done in the same way as the combined group except for stratifying by subgroup. Estimates were then compared to look at effect modification. All subgroups were chosen due to an effect being found in previous studies. In all analyses intent-to-treat was assumed. All of the statistical analyses were accessed using STATA version 10.1 for Windows (13).

Comment [A13]: standard errors from Greenwood's formula

Comment [A14]: "docetaxel alone arm" for clarity

Comment [A15]: explicitly mention how you handle multiple comparisons (I usually just state that I do not adjust for them, and then use caution when describing my results)

RESULTS

From a total of 188 patients, 90 were randomized to receive docetaxel and 98 were randomized to receive docetaxel plus TFD725 (Table 1). The two groups were similar across age, sex, region of clinical site, and disease history. At baseline, patients in both study arms had an average age of 60, with patients in the placebo arm ranging in age from 50 to 75 and patients in the treatment arm ranging in age from 46 to 71. There were slightly more males in the treatment arm (58.16% vs. 52.22%). The majority of patients were from North American clinical sites, 81.11% of those in the docetaxel arm and 82.65% of those in the docetaxel plus TFD725 arm. On average, patients in both arms had been initially diagnosed with non-small cell lung cancer 10 months prior to study randomization. A little over one-third of patients in both treatment groups (docetaxel 34.4% vs. docetaxel plus TFD725 39.8%) were initially diagnosed with stage IIIb disease, while the remaining were diagnosed with stage IV cancer. Approximately 43% of patients in both arms did not achieve tumor response to first line therapy.

When initially looking at the baseline characteristics of the study arms, there appeared to be a trend of baseline biomarkers of better health in the docetaxel plus TFD725 arm. A higher proportion of patients in the docetaxel arm had abnormal LDL level (17.78% vs. 9.18%) and abnormal alkaline phosphatase level (32.22% vs. 19.39%). A slightly higher proportion of patients in the docetaxel plus TFD725 arm had the highest performance on the ECOG scale of ambulatory status (34.69% vs. 25.56%). The differences were most likely due to random chance.

Comment [A16]: good to note this way

Comment [A17]: Indeed, but it can still cause difficulty with the face validity of the study In real life, we usually specify important secondary analyses adjusting for important baseline variables (sometimes even the primary analysis)

The median follow-up for patients on docetaxel was 551 days. In the docetaxel plus TFD725 group the median follow-up time was 546 days. Overall, 140 of 188 patients died from any cause during the study period, 72 from the docetaxel arm and 68 from the docetaxel plus TFD725 arm. In a comparison of the censoring distributions by treatment group, 48 patients were censored, 18 and 30 from the docetaxel and docetaxel plus TFD725 arms respectively, either due to loss to follow-up or being alive when the study ended.

Comment [A18]: You could omit this sentence, as everyone who did not die wa censored.

Comment [A19]: Actually, everyone who was censored was "administrative censoring" due to still being alive at end of study

Kaplan-Meier estimates of the probabilities of overall survival were presented at 6, 12, and 18 months for each treatment group (Fig 1a & Table 2). The probability of survival was slightly greater at 6, 12, and 18 months among patients in the docetaxel plus TFD725 arm. However, overall, the Kaplan-Meier survival estimates, between treatment groups, demonstrated that at no time interval was there a statistically significant difference in survival. For example, at 6 months the survival probability in the docetaxel plus TFD725 group was 0.026 higher (95% CI: 0.039 to 0.091, p=0.433). Similarly at 12 months, the docetaxel plus TFD725 group had a survival probability of 0.068 higher (95% CI: -0.073 to 0.209, p=0.346) and at 18 months 0.125 higher (95% CI: -0.006 to 0.257, p=0.061). The hazard ratio for the relative risk of death was 0.746 (95% CI: 0.536 - 1.040, p=0.084). Based on this ratio there was approximately 25% lower risk of death in the docetaxel plus TFD725 group. However, none of the results obtained demonstrated statistical significance, thus suggesting that treatment with TDF725 added to second-line treatment did not increase overall survival.

Comment [A20]: Present the descriptive estimates, plus or minus CI and p values. But avoid using the word "stat signif" with secondary and exploratory analyses, or else you need to adjust for multiple comparisons

Comment [A21]: If the primary endpoint was HR, use "not stat signif" to describe that result alond

In the subgroup analysis by age (<65 vs. >=65), the Kaplan-Meier survival estimates showed that the docetaxel plus TFD725 group had a higher survival probability in both the older and younger age group (Table 3). Of note the older age group had a higher overall survival probability at 12 months (docetaxel plus TFD725 71% vs. docetaxel 63%)

when compared to the younger age group (56% vs. 53%). The estimated relative risk of death among the older age group by treatment arm was 0.672 (95% CI: 0.31 to 1.47, p=0.32), while the relative risk of death for the younger age group was 0.778 (95% CI: 0.54 to 1.12, =0.181).

In the subgroup analysis by gender, the Kaplan-Meier survival estimates demonstrated that within both males and females the survival probabilities are higher in the docetaxel plus TFD725 arm (Table 3). In males at 12 months the survival probability was lower in the docetaxel group (docetaxel 45% vs. docetaxel plus TFD725 71%) and in females (docetaxel 65% vs. docetaxel plus TFD725 73%). As seen in Table 3, the estimated relative risk of death for males by treatment group was 0.782 (95% CI: 0.51 to 1.22, p=0.277) with the relative risk of death for females being 0.632 (95% CI: 0.38 to 1.06, p=0.082).

The Kaplan-Meier estimates by treatment and response to first line treatment (Table 3) suggested that, regardless of response to first line treatment, both groups had lower survival probabilities in the docetaxel only arm. Once again looking at 12 month survival those with response to first line treatment had a higher survival probability in the docetaxel plus TFD725 group (docetaxel 59% vs. docetaxel plus TFD725 66%) compared to those in Table 2 and those without response had a slightly higher survival probability in the docetaxel group and a lower survival probability in the docetaxel plus TFD725 arm (docetaxel 49% vs. docetaxel plus TFD725 55%). According to Table 3, the hazard ratio for response to first line treatment was 0.749 (95% CI: 0.481 to 1.168, p=0.202) while for no response the hazard ratio was 0.733 (95% CI: 0.445 to 1.207, p=0.222). Thus the risk of death was lower in the docetaxel group regardless of response to first treatment and the risk of death between these two groups was not that different from each other with those with response having a slightly higher risk of death.

In the subgroup analysis by disease stage, patients initially diagnosed with stage IIIb had higher survival probabilities in the docetaxel plus TFD725 arm, while stage IV patients had higher survival probabilities in the docetaxel arm (Figure 1b & Table 3). Among patients diagnosed with stage IIIb disease, the survival probability at 12 months was lower in the docetaxel group (docetaxel 52% vs. docetaxel plus TFD725 72%). While patients initially diagnosed with stage IV cancer had similar survival probabilities at 12 months (docetaxel 56% vs. docetaxel plus TFD725 54%). As seen in Table 3, the estimated relative risk of death for stage IIIb patients by treatment group was 0.53 (95% CI: 0.284 to 0.99, p=0.046) and the relative risk of death for stage IV patients by treatment was 0.988 (95% CI: 0.668 to 1.463, p=0.988). The effect found in those taking the docetaxel plus TFD725 was most noteworthy. The survival probabilities change from 72% for stage IIIb to only 54% in stage IV. Within patients taking the docetaxel plus TFD725, stage of disease at initial diagnosis was associated with survival, implying that this new combination of second-line therapy was more beneficial in those with stage IIIb cancer.

Comment [A22]: Careful here. You have reported 8 subgroup p values. The probability that one of them might be less than 0.05 could be as high as 40%. These results are intriguing, but will need to be confirmed in additional studies. Use very soft wording.

In the subgroup analyses, there were no statistically significant differences between the treatment arms by age, gender, or response to first line therapy (Table 3.) The relative risk of death within subgroups were notable for differences between age and gender, however none of the p-values demonstrated significance. The main effect seen was in the stratified analysis by stage of disease at initial diagnosis. Patients with stage IIIB cancer assigned to docetaxel plus TFD724 had a higher survival probability than patients with stage IIIB cancer assigned to docetaxel alone. Note that in those taking docetaxel plus TFD725, the survival probability was much lower in stage IV patients causing the docetaxel only to have a higher survival probability. This is the only time docetaxel was seen to have a higher survival than the docetaxel plus TFD725.

Comment [A23]: I would not make much of the differences in the stage IV group.

DISCUSSION

In this phase IIb randomized control trial, we investigated whether the addition of TDF725, a receptor tyrosine kinase inhibitor, to docetexal, a traditional second-line treatment, improves overall survival of patients with NSCLC. The main analysis found there was not a statistically significant difference between the survival probabilities or risk of death between the treatment groups. The lack of difference in survival could be due to the tumors not having the mutation needed to respond to the receptor kinases in the added treatment TFD725. Both the 18 month survival analysis and hazard ratio analysis were very close to being significant at the 0.05 level. Since most patients were censored in the 70 days after 18 months it was assumed that doing the analysis on the final time point would not have made the difference between the treatment groups significant. However, if the length of the study was increased or the sample size larger a significant difference may have been noticed. Another concern in the main analysis is the censored patients. Of the 48 patients that were censored there is no way to know who was actually lost to follow up or if the study was just ended before they had died. Likewise, there was no way of knowing whether or not patients stopped taking the study drug because they felt well enough to do so. In addition it remains

Comment [A24]: Or it may not have been. I would avoid speculation about whether larger sample sizes will make results significant. With a larger sample size we might get “regression to the mean”. But it is worthwhile to note that in this pilot study there were some results that might be of interest in future studies.

unclear if increasing the dose of the medication would have improved survival. Knowledge and information about toxicities would better inform future studies.

The subgroup analysis explored whether docetaxel plus TFD725 was more effective than docetaxel alone when stratifying by age, gender, treatment history, or stage of disease. Previous studies suggested that older patients and women had better survival. Responsiveness to first-line therapy and stage of disease at initial diagnosis also seemed to be an important predictor of the effectiveness of a different second-line therapy and ultimately survival. Findings from this exploratory analysis suggested that patients with an earlier stage of cancer at initial diagnosis had better survival on docetaxel plus TFD725. There was a trend of slightly higher probability of survival among women and patients who responded to first-line therapy, especially among patients who survived beyond one year. In analyzing the subgroups, there were no significant differences in one year survival probabilities or hazard ratios when treatment groups were stratified by age, gender, and response to first-line therapy. The small sample size in patients 65 years and older could have affected the ability to find a significant difference between treatment groups for survival and risk of death. To look at this more closely future studies should enroll more patients over the age of 65 years to be able to detect a difference in treatment arms. Stage of disease at initial diagnosis may modify the effect of docetaxel plus TFD725 on survival, suggesting that this drug might be beneficial in those with stage IIIb. Further studies limited to patients initially diagnosed with stage IIIb cancer might allow this difference to be detected.

A limitation of this study was not having follow up laboratory data that could have indicated if the patients' tumor was progressing faster than anticipated. Measures of quality of life as well as side effects are measures that were not taken that are important when considering cancer treatments. There were no data on the duration of treatment and whether patients discontinued treatment for any reason, including toxicity. To address this limitation, intent-to-treat analyses were performed on the assumption that there was not differential discontinuation of study drug between treatment groups. Knowing if a patient stopped using the drug would have allowed an analysis showing a difference in those actually taking the treatment. This also would allow the ability to look at issues of toxicity in the treatments. Future studies may explore the quality of life relative to type of second-line chemotherapy and the role of patient characteristics, such as the mutation of the EFGR gene, in the effectiveness of treatment.

In conclusion, these study results suggested that the addition of TFD725 to second-line therapy does not markedly improve overall survival of patients with stage IIIb-IV non-small cell lung cancer. For patients with less advanced stage of disease at initial diagnosis, docetaxel plus TFD725 appeared to yield a survival benefit compared to docetaxel alone.

Comment [A25]: There is never a laboratory measure that really answers the question of how the tumor would have responded on the other therapy. That is why we do an RCT.

Comment [A26]: NO, NO, NO. We do ITT because that is the clinically relevant analysis. This is true even when we do have detailed info on how much drug was taken when. It is true that I like to have compliance info in order to describe tolerability, but the treatment determines the tolerability. We should not force patients to take a toxic (for them) treatment, but we may have lost the window of opportunity for using some other therapy.

Comment [A27]: Such an analysis is largely worthless, though every now and then we do use it to assess mechanism of action: We often do expect to see more effect with higher dose. However, this sort of analysis violates randomization. And many reports have showed that patients who take more placebo do better than those who do not.

REFERENCES

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13. STATA version 10.1. STATA Corps., College Station, TX.

Table 1. Descriptive statistics for patient characteristics, by treatment group.

Non-small cell lung cancer- Phase IIb clinical trial, *Descriptive Statistics*[1]		
	Docetaxel n= 90	**Docetaxel plus TFD725 n=98**
	mean (n)	mean (n)
Demographic Characteristics		
Age at randomization, yrs [std dev]	60.51 [4.79]	60.38 [5.41]
min, median, max	*50, 61, 75*	*46, 60, 71*
>= 65 (n=39) %	17.78 (16)	23.47 (23)
< 65 (n=149) %	82.2 (74)	76.53 (75)
Sex %		
Female (n=84)	47.78 (43)	41.84 (41)
Male (n=104)	52.22 (47)	58.16 (57)
Clinical Site - Region %		
North America (n=154)	81.11 (73)	82.65 (81)
Europe (n=34)	18.89 (17)	17.35 (17)
Disease History		
Advance stage at initial diagnosis %		
Stage IIIb (n=70)	34.44 (31)	39.8 (39)
Stage IV (n=118)	65.56 (59)	60.2 (59)
Response to first line therapy %		
No (n=81)	43.33 (39)	42.86 (42)
Yes (n=107)	56.67 (51)	57.14 (56)
Time to randomization after initial diagnosis, months [std dev]	10.23 [4.34]	10.39 [4.77]
min, median, max	*3, 10, 27*	*3, 10, 31*
Baseline biomarkers		
Abnormal LDL level %		
No (n=163)	82.22 (74)	90.82 (89)
Yes (n=25)	17.78 (16)	9.18 (9)
Abnormal alkaline phosphatase level %		
No (n=140)	67.78 (61)	80.61 (79)
Yes (n=48)	32.22 (29)	19.39 (19)
Patient's performance status on ECOG scale %		
0=Best (n=57)	25.56 (23)	34.69 (34)
1 (n=122)	68.89 (62)	61.22 (60)
2 (n=9)	5.56 (5)	4.08 (4)

[1] *There were no missing data for either treatment groups*

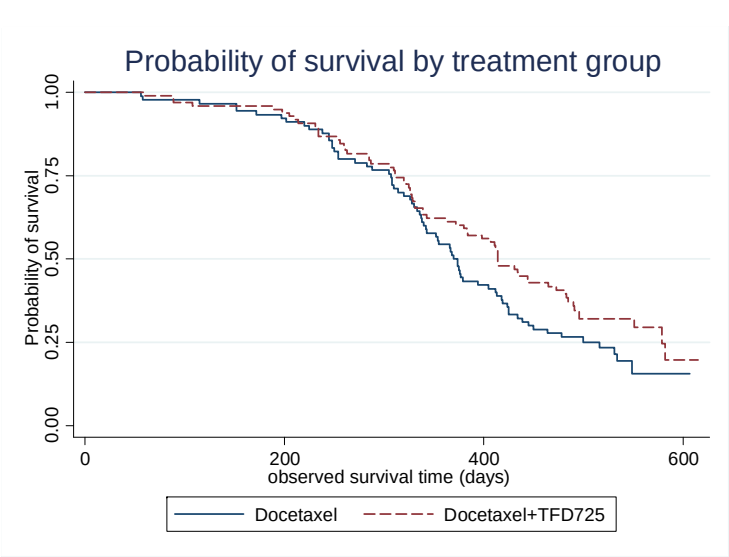
Comment [A28]: good to explicitly note in this manner

Table 2. Survival Probabilities & Differences in Survival Probabilities at 180, 365, and 545 Day Intervals, by Treatment Group.

Non-small cell lung cancer- Phase IIb clinical trial										
	Survival Probabilities by Treatment Group						*Differences in Survival Probabilities*			
	Docetaxel n= 90			Docetaxel plus TFD725 n=98			All Patients, by treatment			
Time, days	**Estimate**	**95% Conf. Int.**		**Estimate**	**95% Conf. Int.**		**Estimate**	**95% Conf. Int.**		**p-value**
180 (6 Mo.)	0.933	0.858	0.970	0.959	0.895	0.985	0.026	-0.039	0.091	0.433
365 (12 Mo.)	0.544	0.436	0.641	0.612	0.508	0.701	0.068	-0.073	0.209	0.346
545 (18 Mo.)	0.197	0.114	0.291	0.320	0.227	0.416	0.125	-0.006	0.257	0.061
Risk of Death *							0.746	0.536	1.040	0.084 **

** Cox Proportional Hazard, by treatment group; ** Wald p-value*

Figure 1. Kaplan-Meier Curves of Survival by Treatment and by Treatment and Disease Stage at Initial Diagnosis (IIIb vs. IV).



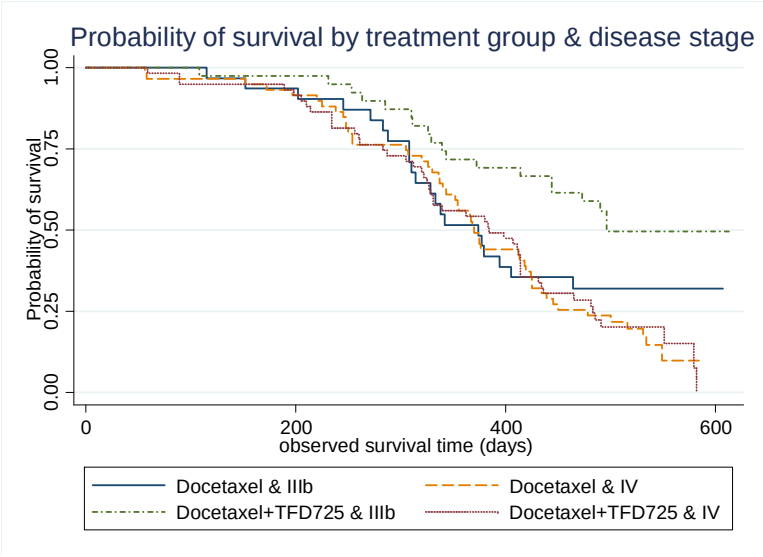


Table 3. Estimated Survival Probabilities and Differences in Survival Probabilities at 12 months, for Subgroups, by Treatment; Hazard Ratios for Subgroups, by Treatment.

Non-small cell lung cancer- Phase IIb clinical trial, by treatment group										
	Survival Probabilities at 12 months		*Differences in Survival Probabilities at 12 months*				*Hazard Ratios **			
	Docetaxel n= 90	Docetaxel plus TFD725 n=98	All Patients, by treatment				All Patients, by treatment			
Subgroups	Estimate	Estimate	Estimate	95% Confidence Interval		p-value	Estimate	95% Confidence Interval		p-value **
Age										
>=65	0.625	0.713	0.158	-0.133	0.449	0.288	0.672	0.307	1.471	0.320
<65	0.527	0.560	0.033	-0.127	0.193	0.686	0.778	0.538	1.124	0.181
Gender										
Male	0.447	0.526	0.080	-0.113	0.272	0.418	0.784	0.506	1.215	0.277
Female	0.651	0.732	0.081	-0.116	0.277	0.423	0.632	0.376	1.060	0.082
Response to initial treatment										
Yes	0.588	0.661	0.073	-0.111	0.256	0.438	0.749	0.481	1.168	0.202
No	0.487	0.548	0.060	-0.157	0.278	0.586	0.733	0.445	1.207	0.222
Advance stage at initial diagnosis										
Stage IIIb	0.516	0.718	0.202	-0.024	0.428	0.080	0.530	0.284	0.989	0.046
Stage IV	0.559	0.542	-0.017	-0.196	0.163	0.854	0.988	0.668	1.463	0.954

** Cox Proportional Hazard, by treatment group; ** Wald p-value*