A Phase IIb Trial of Supplementation of Docetaxel with TRF725 for the Treatment of Advanced Stage Non-Small Cell Lung Cancer

Group 15

Summary

Background: Non-small cell lung cancer (NSCLC) has one of the poorest prognoses of all cancers due to the tendency for diagnosis to occur at an advanced stage, a low response rate to first-line chemotherapy, and a high rate of progression on or after initial therapy. The current gold-standard for second-line treatment, docetaxel, has a very low response rate and only offers patients a modest extension in survival time. Prior research suggests that angiogenesis, and thus potentially disease progression, can be inhibited by epidermal growth factor receptor tyrosine kinase inhibitors.

Objective: To evaluate whether the addition of TFD725, a novel receptor tyrosine kinase inhibitor, to a regimen of docetaxel modifies the risk of death in patients undergoing second-line treatment for stage IIIb/IV NSCLC.

Methods: One hundred and eighty-eight advanced-stage NSCLC patients who had progressed on first-line platinum therapy were randomly assigned in a 1:1 ratio to receive docetaxel alone (75 mg/m^2 every 3 weeks) or docetaxel (50 mg/m^2 every 3 weeks) plus TFD725 (50 mg / day), and were followed until the first of death or study closure. Baseline data on demographics and markers of disease severity that could impact prognosis were collected. The comparability of treatment arms with respect to baseline characteristics and length of follow-up was assessed descriptively. Kaplan-Meier survival curves and survival probability estimates at 6, 12 and 18 months were also obtained by treatment arm for descriptive purposes. Cox proportional hazards regression was used to compare the groups on ratio of instantaneous risk of death from any cause at any given time. In the secondary analysis, the distribution of survival probabilities by disease stage and treatment arm was considered descriptively by Kaplan-Meier survival curves.

Results: The TFD725 treatment arm appeared have been healthier at baseline. The censoring distributions of the two arms appeared sufficiently similar: median follow-up time was 12.2 months in the placebo arm and 13.6 months in the TFD725 arm. The probability of survival was slightly higher in the TFD725 arm at each of the three time points assessed; the greatest difference was observed at 18 months. In the primary analysis, it was found that the instantaneous risk of death in patients in the placebo group averaged 1.339 times that of patients in TFG925 group (95%CI: 0.96-1.86), but this difference was not statistically significant (p=0.084). In the secondary analyses, inspection of the survival curves for each combination of treatment arm and disease stage suggested improved survival probability in stage IIIb patients treated with the combined docetaxel/TFD725 regimen, relative to other patients.

Conclusions: The combination of TFD725 (50 mg/day) with docetaxel (50 mg/m2 every 3 weeks) did not significantly impact the instantaneous risk of death compared to docetaxel (75 mg/m2 every 3 weeks) alone among patients with stage IIIb/IV NSCLC who have failed first line chemotherapy. Future directions for research aimed at improving survival for this patient population in the second-line setting include using the same docetaxel dose in comparison groups and focusing on effects in patients with stage IIIb disease or better.

Comment [A1]: This is not correct. It was closer to 18 months of follow-up. You instead reported statistics for a mixture of time of follow-up and time until death

Comment [A2]: numbers would be indicated here

Comment [A3]: quantify, and also talk about the other subgroup

Background

In the United States, lung cancer accounts for at least 25% of all cancer deaths.(1) Despite some advances in the past 20 years, long-term survival for patients with non-small cell lung cancer (NSCLC) is dismal.(2, 3) At the time of diagnosis the majority of patients already have stage III or IV disease.(1) Currently, platinum-based combination therapy remains the gold standard in first-line chemotherapy for unresectable NSCLC.(4) First-line response rate is around 25%, with a median overall survival of 8.5 months and one year overall survival <40% among responders. (5, 6) Progression-free survival (PFS) is also very poor among responders.(7)

When progression occurs, median survival without intervention is less than 5 months.(5) Currently, the gold-standard second line therapy for NSCLC is docetaxel, which has a partial response rate of 6% and a median duration of response of 6 months.(7) Patients initiated on docetaxel 75mg/m^2 in the second-line setting experience a median overall survival time of 7.5 months. (7) These poor outcomes have prompted the search for other second line agents to add to our armamentarium against NSCLC.

One promising area of research has been into the epidermal growth factor receptor (EFGR), which is known to be overexpressed in NSCLC; EFGR tyrosine kinase inhibitor agents studied to date have exhibited a favorable toxicity profile.(3) Agents that block receptor tyrosine kinases inhibit angiogenesis and may be able to impact disease progression. In the present investigation we sought to determine whether a novel agent, TFD725, active against tyrosine kinases in vitro and in animal experiments, would show promise as a second line agent in NSCLC. A Phase II, multicenter, randomized, double-blind, placebo-controlled trial was carried out to determine if docetaxel augmented by TFD725 affected survival compared to docetaxel employed as a single agent.

Questions of Interest

The analysis team was presented with the task of determining whether the addition of TFD725 to docetaxel extends survival in patients receiving second-line treatment for NSCLC. In our primary analysis we address this question in terms of a difference between treatment arms in the risk of death. Since TFD725 is still a novel investigative agent, we did not know whether it would be associated with better or worse outcome, so our hypothesis was that it would change survival, rather than specifically improve it. In the secondary analyses, we attempted to determine if one of the strongest *a priori* predictors of survival - disease stage at diagnosis - would also predict a tendency to respond differently to the addition of TFD725 to the docetaxel regimen. Our hypothesis was that people with earlier stage disease (IIIb) at diagnosis might have different tumor biology than those diagnosed at stage IV, and that they might thus respond differently to TFD725. Our goal was only to determine if further studies focusing on patients with stage IIIb disease would be warranted, as this study was not designed to fully answer this question.

Comment [A4]: It is not usually ethical to do a RCT to establish that some new, unapproved therapy is harmful. We are very much interested in improving survival

Source of the Data

The data for this study were collected from a randomized, double-blinded, placebo-controlled, Phase IIb clinical trial conducted at various sites in North America and Europe. Study

participants had stage IIIb or IV NSCLC at initial diagnosis and had experienced disease progression on or after standard first-line platinum-based chemotherapy. Patients were also only eligible if they were docetaxel-naïve, at ECOG performance status 2 or better, under 80 years of age, and pledged to use an acceptable form of contraception during the trial. A total of 188 participants were stratified by clinical site and disease stage at initial diagnosis and randomized in a 1:1 ratio into two treatment groups: 90 received docetaxel alone (75 mg/m2 every 3 weeks) and 98 received docetaxel (50 mg/m2 every 3 weeks) plus TFD725 (50 mg / day). Participants were assessed every three weeks (some measures taken every six weeks) and were to continue therapy until the first of administrative study closure, irresolvable drug toxicity or death. However, the only outcome data the analysis team was given was the length of follow-up for each patient and whether the end of follow-up could be attributed to death or study closure (i.e., censoring).

Baseline data collected that could be used to specify subgroups salient to treatment outcome were patient demographics, disease stage and first-line treatment response, and relevant biochemical and subjective markers of disease severity. There was no missing data.

Statistical Methods

Potential differences between the arms in geographic site, age, sex, disease stage, first line response, LDH and alkaline phosphatase levels at randomization, ECOG performance status, and time from initial diagnosis to randomization were assessed descriptively.

Potential differences between censoring distributions by treatment arm were also assessed descriptively via Kaplan-Meier estimates of length of follow-up.

Comment [A5]: but this is not what you presented in your abstract

Descriptive statistics for survival probability by treatment arm were calculated at 6, 12, and 18 months post-randomization, using the Kaplan-Meier method in order to account for censored data.

In our primary analysis we sought to determine if there was an association between second line chemotherapy using docetaxel and TFD725 and risk of death. Since the clinical trial data are right-censored, with a subset of patients not observed until death, we could not simply compare mean survival times between the arms. Rather, we employed Cox proportional hazards regression to assess differences in instantaneous risk of death between the treatment arms, averaged over all observation times. We chose to restrict primary analysis significance testing to Cox proportional hazards regression in order to avoid the problem of inflated Type I error associated with the performance of multiple comparisons. The resulting parameter estimate indicates how many times as likely patients in one treatment arm are to die compared to patients in the other arm, at any given time. The 95% confidence interval suggests the parameter estimate would be typical given a true population risk within the interval, with an interval including the value of 1.0 indicating no significant difference between treatment arms in risk of death.

The primary analysis was conducted using a two-sided test, with a p-value less than 0.05 considered sufficient grounds for rejection of the null hypothesis. The test was two-sided

because, prior to running the analyses, we did not know whether the addition of TFD725 to the docetaxel regimen would increase or decrease survival.

Based on an *a priori* hypothesis of different biological response in stage IIIb versus stage IV patients (by definition, only the latter have distant metastases) we performed a secondary analysis by comparing the four survival curves representing each treatment arm and disease stage combination. This analysis was conducted purely for descriptive and exploratory purposes.

All analyses were performed using R version 2.9.2. (8)

Results:

A total of 188 patients were randomized to receive docetaxel alone (placebo group) or docetaxel plus TFD725 (TFG725 group), stratified by clinical site and stage of disease at initial diagnosis. Table 1 shows the baseline descriptive statistics, by treatment arm. The study sample was 55.3% male and the mean age of participants was 60.4 years. The distribution of sex and age was similar in each treatment arm. The TFD725 group appeared to be more healthy overall at baseline, with slightly higher proportions of patients with ECOG performance status 0 (34.7% vs. 25.6%), and lower proportions of patients with abnormal LDH (9.2% vs. 17.8%) and alkaline phosphatase (19.4% vs. 32.2%) than the placebo group (these latter two markers are highly predictive of poor outcome) (see Table 1).

The median duration of follow up for the entire study sample was 13.0 months (Interquartile range (IQR): 10.2-16.1), with a median in the placebo arm of 12.2 months (IQR: 10.1-15.8) and a median in the TFD725 arm of 13.6 months (IQR: 10.3-16.3). Visually, there did not appear to be a meaningful difference in censoring distributions between the placebo and TFD725 arms (Figure 1a), so we were not concerned about differential duration of follow-up between treatment arms in this sample biasing the results.

The Kaplan-Meier estimates of survival probabilities of patients in each treatment arm at 6, 12 and 18 months post-randomization are presented in Figure 1b and Table 2. Judging from visual comparison of the survival curves, survival in the TFD725 group was slightly better, particularly between months 11 and 18. Patients in the TFD725 group had a 2.6%, 6.8%, and 12.5% higher probability of survival than the placebo group 6, 12, and 18 months after randomization, respectively. The estimates for median survival duration were 12.2 months (IQR: 10.0-16.4) in the placebo arm and 13.6 months (IQR: 10.2-18.1) in the TFD725 group.

Results of the Cox proportional hazard analysis comparing treatment arms on instantaneous risk of death are shown in Table 3. We estimated that, at any given time, the risk of death in patients in the placebo group tended to be 1.339 times (95%CI: 0.96- 1.86, p=0.084) that of patients in TFD725 group. This estimate would not be unusual if the true hazard ratio was as low as 0.96 or as high as 1.86. Since this confidence interval includes the possibility of a true hazard ratio of 1.0, and the p-value is greater than our significance level threshold of 0.05, we cannot reject the null hypothesis of no effect of TFD725 treatment on instantaneous risk of death.

Comment [A6]: It is perfectly okay to report two-sided p values. But we are only interested in the one-sided hypothesis here. Nowadays, we would usually report a one-sided p value in this case and compare it to 0.025.

Comment [A7]: This is incorrect

The survival curves presented in Figure 1c depict the results of the secondary analysis. It appears that, while the survival distributions for placebo and TFD725 are similar among stage IV patients, they may be different among stage IIIb patients. Patients in stage IIIb treated with TFD725 and docetaxel appeared to have prolonged survival compared with stage IIIb patients treated with docetaxel alone (the latter evidenced a similar survival distribution to that seen in both arms in stage IV patients). The comparison of survival distributions by treatment arm within subgroups defined by disease stage was not subjected to significance testing in this study due to the risk of inflated Type I error associated with multiple comparisons.

Comment [A8]: Your concern about multiple comparisons is well-placed However, we do usually analyze the data and use the p values very cautiously

Discussion

Based on the data provided by this clinical trial, patients in the docetaxel plus TFD725 group had an improved probability of survival as evidenced by a higher proportion surviving to 18 months and a lower instantaneous risk of death, as compared with the group of patients treated with docetaxel alone. However, the difference in instantaneous risk of death between these treatment arms did not reach statistical significance, and we did not perform statistical tests to assess the significance of the difference in probability of survival at specific time points.

Comment [A9]: soften your wording, this is not the primary endpoint

In this study, all patients were followed for clinical events and death even after discontinuation of study medication. We would have preferred to know what proportion of the study patients discontinued the medication in each treatment arm, and whether duration of study drug intake was associated with toxicity or duration of survival.

Comment [A10]: this sort of analysis is extremely problematic

It is notable that patients in the TFD725 arm received lower doses of docetaxel than did those in the placebo arm (50mg/m2 vs. 75 mg/m2, respectively). It is possible that, absent a detrimental effect on safety, boosting docetaxel dosing to 75 mg/m^2 could have improved survival in the TFD725 arm to an even greater extent.

Comment [A11]: this is not an uncommon approach to deal with toxicity: the combination therapy has to have a lower dose of docetaxel

In the descriptive analysis of baseline characteristics, we noticed that the TFD725 group appeared to be slightly healthier than the placebo group as evidenced by to a higher proportion of patients at ECOG performance status 0, more patients having experienced first line tumor response, and fewer patients with abnormal LDH and alkaline phosphatase. Had the treatment arms been more comparable in health status going into the study, we may not have observed the tendency for patients in the TFD725 arm to experience improved survival, as health status may have confounded the association between treatment arm and risk of death.

Comment [A12]: In real life, we likely would have had secondary analyses that adjusted for these baseline characteristics

Augmentation of the docetaxel regimen with TFD725 may have a differential effect on duration of survival in patients diagnosed at stage IIIb versus stage IV. The results of our secondary analysis indicated that patients with relatively less extensive disease at initial diagnosis might respond favorably to the addition of TFD725 to their docetaxel treatment protocol, whereas TFD725 may not impact survival in stage IV patients, who already have distant metastases at diagnosis. Less extensive disease at diagnosis may reflect a different cancer biology that is more responsive to the anti-angiogenic action of TFD725.

In summary, the data from this clinical trial do not provide sufficient evidence to state with high confidence that the addition of TFD725 to docetaxel extends survival in patients receiving

second-line treatment for NSCLC. The exploratory subgroup analysis suggested that TFD725 may have the most beneficial effect on patients who were initially diagnosed at stage IIIb. We suggest that future trials use larger patient samples and focus on whether the addition of TFD725 to the gold-standard docetaxel regimen prolongs survival specifically in patients diagnosed at stage IIIb or earlier.

References

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Table 1. Summary of baseline measurements by treatment group.

	Placebo (N=90)	TFD725 (N=98)
Age		
Mean	60.5	60.4
SD	4.79	5.41
Median	61	60
Min-Max	50 – 75	46 – 71
1st Quartile-3rd Quartile	58 – 63	57 – 64
Gender		
Male	47 (52.2%)	57 (58.2%)
Female	43 (47.8%)	41 (41.8%)
ECOG PS		
0	23 (25.6%)	34 (34.7%)
1	62 (68.9%)	60 (61.2%)
2	5 (5.6%)	4 (4.1%)
Site*		
Europe	17 (18.9%)	17 (17.3%)
North America	73 (81.1%)	81 (82.7%)
Disease Stage*		
Stage IIIb	31 (34.4%)	39 (39.8%)
Stage IV	59 (65.6%)	59 (60.2%)
First Line Tumor Response		
Yes	39 (43.3%)	42 (42.9%)
No	51 (56.7%)	56 (57.1%)
Abnormal LDH at Randomization		
Yes	16 (17.8%)	9 (9.2%)
No	74 (82.2%)	89 (90.8%)
Abnormal Alkaline Phosphatase at Randomization		
Yes	29 (32.2%)	19 (19.4%)
No	61 (67.8%)	79 (80.6%)
Months from initial diagnosis to randomization		
Mean	10.2	10.39
SD	4.3	4.8
Median	10	10
Min-Max	3 – 27	3 – 31
1st Quartile-3rd Quartile	7 – 13	7 – 13

* Stratification factors for randomization

Figure 1a. Censoring Distribution by Treatment Group.

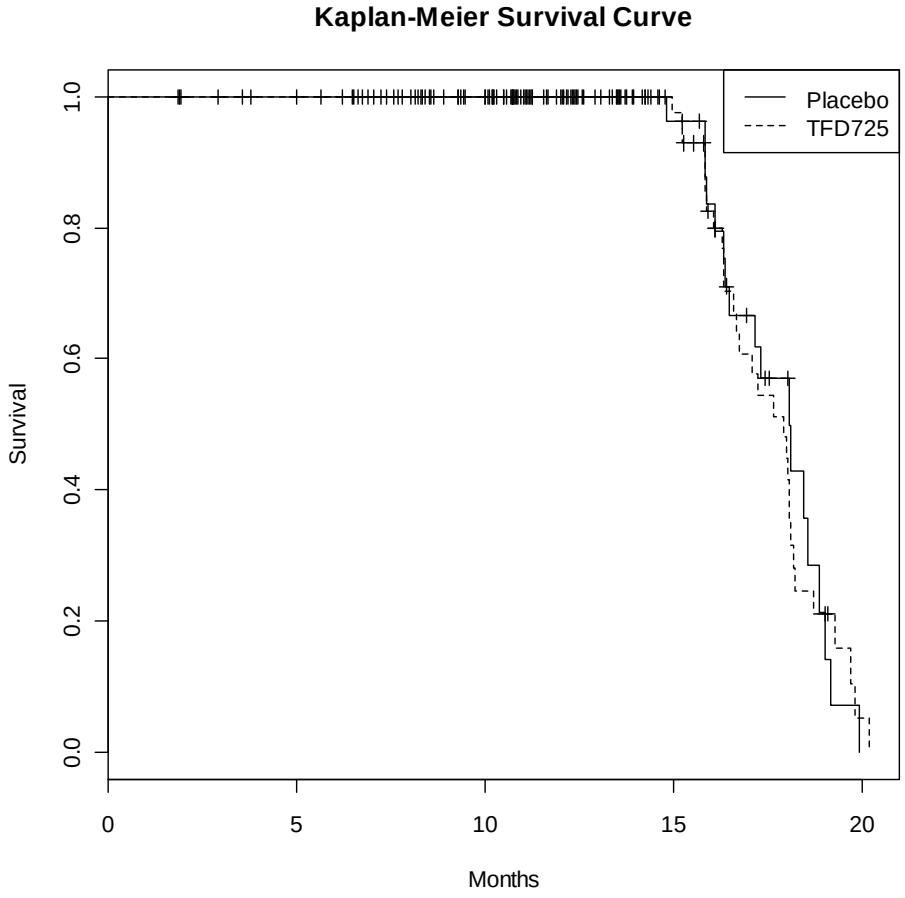

Figure 1b. Time to Death by Treatment Group.

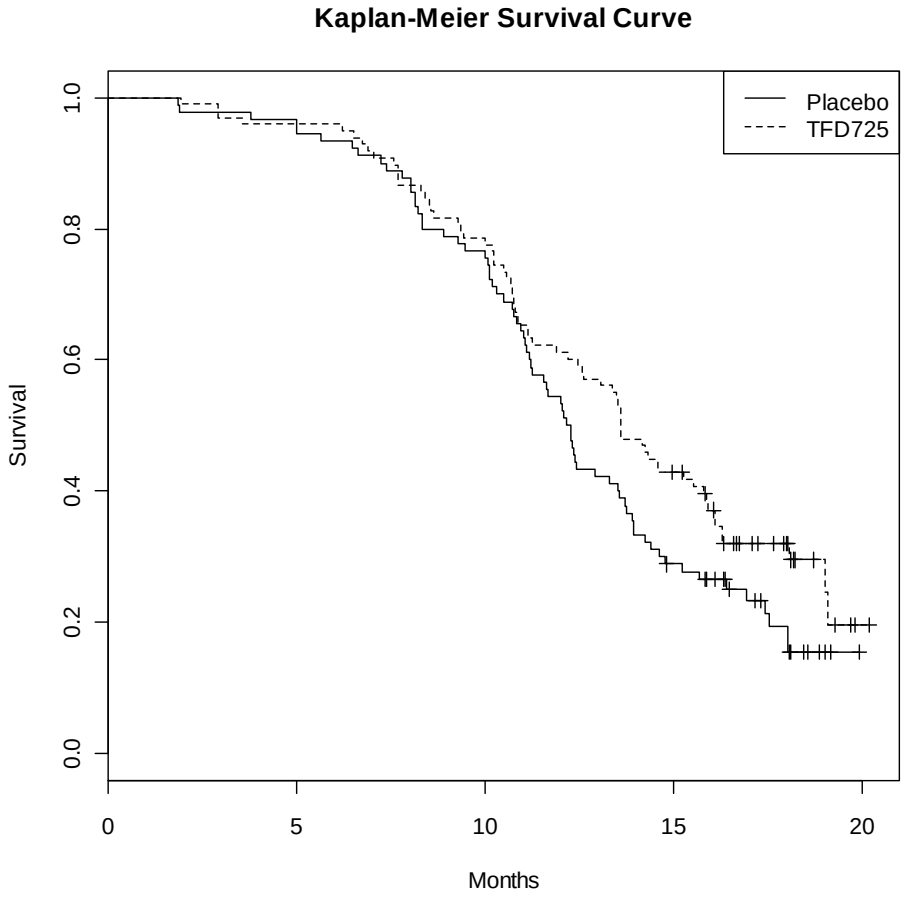

Figure 1c. Time to Death by Treatment Group and Disease Stage.

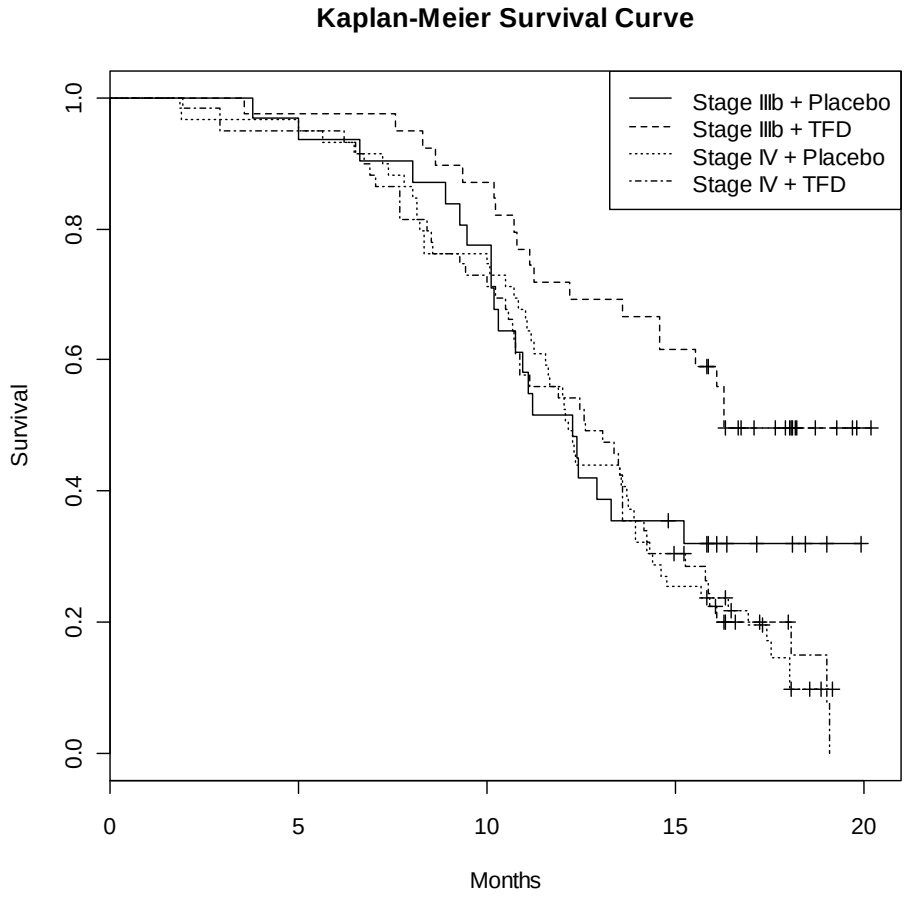

Table 2. Kaplan-Meier survival estimates by treatment group.

Summary of Survival Proportions at 6, 12, and 18 months				
Placebo (N=90)				
Months	Number at Risk	Events	Survival Proportion	Standard Error
6	84	3	0.933	0.0263
12	49	20	0.544	0.0525
18	10	4	0.195	0.046
TFD725 (N=98)				
Months	Number at Risk	Events	Survival Proportion	Standard Error
6	94	0	0.959	0.02
12	60	17	0.612	0.0492
18	15	4	0.32	0.0488

Table 3. Cox Proportional Hazard Ratio by treatment group.

Treatment Arm (Placebo vs. TFD725)	Hazard Ratio	p-value	95% CI
Overall	1.339	0.0843	0.961 – 1.861