4 Study CA139-103

4.1 Description of CA139-103

Study objective: To compare the efficacy and the tolerability of Taxol/cisplatin versus teniposide/cisplatin in patients with advanced previously untreated NSCLC.

Study Enrollment Period: August 1993 - February 1994

Study Design: Open label, multicenter, randomized EORTC comparative Phase II/III. Stratification factors were performance status and disease extent (locally advanced vs. metastatic).

The study began as a two-stage Phase II study to determine whether there was sufficient activity to further study Taxol in a Phase III trial. In the first stage, 26 patients were enrolled in each arm. If at least 4 tumor responses were observed, then 7 additional patients were to be added to each arm. By the end of the second stage, if at least 6 responses were observed in each arm, then these regimens would be examined in a Phase III trial.

A protocol amendment dated January 1995 expanded the study to a Phase III trial. Patients who were treated in the Phase II trial were incorporated in the statistical analyses of the Phase III trial.

Sample size: 332 patients

The sponsor based Phase III sample size requirements on survival assumptions. A total of at least 288 patients were to be enrolled in the Phase III stage of the study based on the ability to detect a three-month increase in survival for the Taxol/cisplatin group with 80% power at a two-sided Type I error level of 0.05.

Dose: The Taxol/cisplatin treatment group received 175 mg/m^2 of Taxol as a 3 hour infusion, followed by 80 mg/m^2 of cisplatin. This was repeated every 21 days.

The teniposide/cisplatin group received 100 mg/m^2 of teniposide on days 1, 3, and 5 and 80 mg/m^2/day of cisplatin on day 1. This was repeated every 21 days.

Treatment duration: Treatment was administered for at least 1 course and discontinued for disease progression or severe toxicity. Patients who were randomized to the Taxol/cisplatin arm and received 6 courses could receive an additional four

courses of single-agent Taxol.

Criteria for Evaluation: The primary endpoint for comparison was survival; this was tested with a stratified log-rank test. Standard WHO response criteria were used (complete / partial response / stable disease) and common toxicity criteria (CTC) were used for toxicity. Other secondary endpoints included Cox regression on survival, objective response, time to progression, and QOL.

4.2 Efficacy Endpoints and Results of CA139-103

Survival Analyses

Table 12 shows the median survival estimates and hazard ratio for comparing the two arms. The median survival was 9.5 months (95% CI 8.2-11.7 months) for Taxol/cisplatin and was 9.9 months (95% CI 8.2-12.0 months) for teniposide/cisplatin. One year survival was 41% (95% CI 33 to 49%) for the Taxol/cisplatin arm and 41% (95% CI 33% to 49%) for the teniposide/cisplatin arm. The Taxol arm was not statistically significantly different from the teniposide/cisplatin arm with respect to overall survival (stratified log-rank $p = 0.802$). The stratification factors were performance status and disease extent.

Cox Regression Analysis on Survival Data

The sponsor performed a Cox regression on survival time, pre-specifying the following covariates in the protocol: gender, hemoglobin at baseline, prior radiotherapy (yes/no), weight loss last 3 months, and histology. Table 13 shows the results of the Cox model on the survival data.

Note that treatment arm is not a statistically significant term in the Cox regression model for survival ($p = 0.789$).

Time to Progression Analysis

Tables 14 and 15 show the frequencies of progression and time to progression (TTP) across the treatments. Overall tests for equality between arms gave $p = 0.608$ in a stratified log-rank test. The median time to progression for Taxol/cisplatin was

5.1 months (95% 4.3-5.9 months) and the median time to progression for cisplatin/teniposide was 5.0 months (95% 3.7-5.8 months).

The sponsor performed a stratified Cox regression for time to progression. The stratification factors were clinic, performance status, and disease extent (locally advanced vs. metastatic). The results of this analysis appear in Table 16. Treatment arm as a prognostic factor was not statistically significant ($p = 0.767$). Histology and baseline hemoglobin were statistically significant terms in the Cox regression.

Clinical Response

In an intent-to-treat (ITT) analysis, the proportion of objective response (CR+PR) for the teniposide/cisplatin arm was 25% (95% CI 18-32%), compared with 35% (95% CI 28-43%) in the Taxol/cisplatin arm. The test for a difference in objective response yielded a p-value of 0.046.

Out of the 320 patients with evaluable responses, there were 2 out of 159 (1%) with complete responses in the Taxol/cisplatin arm, and 0 out of 161 with a complete response in the teniposide/cisplatin arm. Table 17 shows the tumor response rates between treatment groups.

The sponsor performed a logistic regression to compare response rates while adjusting for several prognostic factors. In this logistic regression on all measurable patients, the three factors which had a statistically significant impact on objective response were baseline hemoglobin level, gender, and treatment arm. Patients who had an increased likelihood of response were those with a normal baseline hemoglobin level ($p = 0.022$), those who were female ($p = 0.044$) and those who were assigned to the Taxol/cisplatin arm ($p = 0.0496$).

Duration of Response

Duration of response was calculated for all responders (CR+PR) and was defined as the period between the day of the first treatment administration until the date progressive disease was first noticed. Sixty-one percent (25/41) of cisplatin/teniposide responders experienced disease recurrence. The median duration of response was 8.1 months with range 3.4 to 18.7+ months. Sixty-nine percent (40/58) of the Taxol/cisplatin arm progressed and the median duration of response was 8.1 months with a range of 3.3 to 23.1 months.

There was no statistically significant difference between cisplatin/etoposide and Taxol/cisplatin (log-rank p = 0.520) with respect to duration of response.

Quality of Life

The sponsor administered the EORTC QOL questionnaire (QLQ-C30) and the lung module (LC-30) to patients in each treatment arm, beginning at baseline and again approximately every 6 weeks. The number of patients with completed questionnaires appears in Table 18. The sponsor used the Wei-Johnson test to compare QOL subscales.

The sponsor examined 6 functional scales, including global health status, and 18 symptom scales. To compare the QOL of Taxol versus teniposide/cisplatin, the sponsor tested the differences in medians of each subscale and at each period with the baseline medians. Using this strategy, the sponsor found statistically significant differences in 6 QOL endpoints. Using this strategy, the Taxol arm resulted in improvement to baseline in Physical Functioning, Role Functioning, Social Functioning, Global Health Status, and Fatigue. Teniposide/cisplatin patients had less discomfort on the Peripheral Neuropathy subscale than those patients on the Taxol arm.

Graphs of the means of all 24 QOL subscales appear in Figure 4. Note that for the five "functioning" subscales and the global health status subscale, 100 on the scale is interpreted as "high level of functioning." For the remaining 18 symptom scales, 0 on these scales is interpreted as "minimal discomfort" while 100 on these scales means "intense discomfort."

This reviewer had some concerns about the time between followup visits. Follow up of QOL for the QLQ30 QOL Core Questionnaire ranged between 21 and 77 days between consecutive visits. It was not uncommon to see ranges over 70 days and under 25 days among patient followups between consecutive visits.

This reviewer instead considered a GEE approach coupled with the idea of "working correlation," using M-estimation theory for a robust variance estimate. A fuller description of this technique, as well as its justification, appears in Section 3.2.

The following QOL subscales were deemed relevant by this reviewer and the medical reviewer: Physical Functioning, Global Health Status, Peripheral Neuropathy, and Pain. This reviewer also considered Role Functioning and Social Functioning, QOL subscales that were statistically significant in the sponsor's analysis.

Table 19 shows the results of fitting the models described above to this study's QOL data. There was no non-ignorable dropout among the QOL subscales that this reviewer considered; this was determined by the methods due to Diggle and Kenward (1994). It is apparent that the sponsor's analysis underestimated the standard errors of the QOL trends. Considering the small proportion of patients who completed questionnaires and high proportion of patients who eventually dropped out of the study, it is not surprising that the variances of the QOL subscales were quite large. Any QOL trend must overcome this variability to be detectable given the small sample size.

Based on this longitudinal analysis of the QOL data, the only statistically significant difference between the Taxol arm and the teniposide/cisplatin arm occurs in the Physical Functioning subscale ($p = 0.03$). It appears that the time trends found across treatments in the sponsor's QOL analysis are accompanied by a high degree of variability when examined from a longitudinal perspective. Therefore, the sponsor's QOL conclusions must be interpreted with caution.

4.3 Summary and Conclusions for CA139-103

Summary

Overall, CA139-103 was a study that this reviewer considered to be well-designed. However, there seemed to be little evidence as to any increased efficacy of the Taxol/cisplatin arm versus the teniposide/cisplatin arm. While the Taxol/cisplatin arm generally yielded favorable results in a number of endpoints, this Taxol arm only showed an improvement over teniposide/cisplatin in clinical response and in one quality of life endpoint.

The primary endpoint for this study was overall survival. There was no statistical significance found in the primary endpoint of overall survival between the Taxol arm and the teniposide/cisplatin arm (stratified log-rank $p = 0.802$). The median survival was 9.5 months (95% CI 8.2-11.7 months) for Taxol/cisplatin and was 9.9 months (95% CI 8.2-12.0 months) for teniposide/cisplatin.

The median time to progression for Taxol/cisplatin was 5.1 months (95% 4.3-5.9 months) and the median time to progression for cisplatin/teniposide was 5.0 months (95% 3.7-5.8 months). The time to progression was not statistically significantly different for the two arms (stratified log-rank $p = 0.608$), nor was there a difference with respect to treatment in a stratified Cox regression on time to pro-

gression (stratified p = 0.723).

In an ITT analysis, the objective response rate was 35% (95% CI 28-43%) for Taxol/cisplatin and was 25% (95% CI 18-32%) for cisplatin/teniposide. The test for a difference in objective response yielded a p-value of 0.046. In the subset of measurable patients only, there was also a difference between the Taxol arm and the teniposide/cisplatin arm when covariates such as histology, hemoglobin level, and gender were considered as explanatory variables in a logistic regression (hazard ratio 1.64 (95% CI 1.001-2.70), p = 0.0496). There were no statistically significant differences with respect to response duration (stratified log-rank p = 0.520).

The sponsor's QOL analysis concluded that the Taxol/cisplatin arm resulted in improvements for several QOL subscales. However, this reviewer believed that the sponsor's analysis could suffer from bias, based on the fact that there was considerable dropout and correlation within the QOL data set. There was also no Type I error adjustment for the multiplicity of subscales that were considered in the QOL analysis. Therefore, this reviewer performed a longitudinal analysis on the QOL data. This resulting analysis determined that only one relevant QOL subscale, Physical Functioning, showed a statistically significant difference in favor of the Taxol arm (p = 0.03).

Conclusions

There is little evidence to support a claim that Taxol/cisplatin is superior to teniposide/cisplatin in this study. There were no statistical differences found between Taxol/cisplatin and teniposide/cisplatin for survival (p = 0.802) or time to progression (p = 0.608).

The Taxol arm was determined to be statistically significantly better than teniposide/cisplatin with respect to objective response (p = 0.031) and objective response adjusted for covariates (p = 0.0496).

There is little evidence to support a conclusion that there are any differences between the arms in this study with respect to quality of life endpoints in general. This reviewer's longitudinal analysis of the QOL data indicated that there was far too much variability in responses to detect differences in trends, except in one endpoint (Physical Functioning).

5 Study CA139-208

5.1 Description of CA139-208

Study objective: To compare the efficacy and the tolerability of Taxol/cisplatin versus high dose cisplatin (HD cisplatin) in patients with advanced previously untreated NSCLC.

Study Enrollment Period: January 1995 - April 1996

Study Design: Open label, multicenter, randomized comparative Phase III. The stratification factors were Karnofsky Performance Status, disease stage, and study center.

Sample size: 414 patients

The sponsor based sample size requirements on survival assumptions. Assuming a one-year survival rate of 25% (*i.e.*, a median survival of six months) for cisplatin single agent and using a two-sided Type I error level of 0.05, a total of 200 patients per arm will provide at least 85% power to detect a difference of 2.5 months in median survival between the two treatment arms.

Interim analysis: None

Dose: The Taxol/cisplatin treatment group received 175 mg/m^2 of Taxol as a 3 hour infusion, followed by 80 mg/m^2 of cisplatin. This was repeated every 21 days.

The HD cisplatin group received 100 mg/m^2 of cisplatin as a 30 minute infusion. This was repeated every 21 days.

Treatment duration: Treatment was administered for at least 3 courses and discontinued for disease progression or severe toxicity. Patients who achieved stable disease received up to six courses.

Criteria for Evaluation: The primary endpoint for comparison was survival; this was tested with a log-rank test, stratified by the following factors: Karnofsky performance status (80-100 vs. 60-70) and stage of disease (IIIB vs. IV). Standard WHO response criteria were used (complete / partial remissions / stable disease) and common toxicity criteria (CTC) were used for toxicity. Secondary endpoints included time to progression, objective response, duration of response, and QOL.

The p-values for all time-to-event comparisons were calculated with a stratified log-rank test. The stratification factors were Karnofsky performance status and disease stage.

5.2 Efficacy Endpoints and Results of CA139-208

Survival Analyses

Table 20 shows survival estimates and hazard ratio for comparing the two arms. The median survival was 8.6 months (95% CI (7.1-10.3 months) for HD Cisplatin and 8.1 months (95% CI 7.3-9.2 months) for Taxol/cisplatin. The Taxol arm was not significantly different from the HD cisplatin arm with respect to overall survival (stratified log-rank p = 0.862). The stratification factors for this test were Karnofsky performance status and disease stage.

One year survival was 30% (95% CI 23 to 36%) for the Taxol/cisplatin arm and 36% (95% CI 29 to 42%) for the HD cisplatin arm.

The sponsor performed a stratified Cox regression on survival. The covariates were the same as those that appear in Table 16 except that the sponsor also included Baseline LDH. Out of the the seven factors considered, only Baseline LDH (p = 0.0004) and Weight Loss (p = 0.011) were statistically significant. Treatment arm was not statistically significant with p = 0.958.

Time to Progression Analysis

Table 21 shows the time to progression (TTP) for the two treatments. The median TTP for HD Cisplatin was 3.2 months (2.4-3.9 months) and for Taxol/cisplatin was 4.3 months (3.5-4.6 months). Overall tests for equality between arms gave p = 0.085 for the stratified log-rank test. The hazard ratio for for Taxol/cisplatin over HD cisplatin was 1.21 (0.97, 1.50).

The sponsor performed a stratified Cox regression for time to progression. The results of this analysis appear in Table 22. The p-value was on the margin of statistical significance (p = 0.056), favoring the Taxol/cisplatin arm.

Clinical Response

Out of the 396 patients with measurable disease, 9 patients were not evaluable, 3 out of 196 (2%) had complete responses in the Taxol/cisplatin group, and 1 out of 200 (1%) had a complete response in the Cisplatin group.

In an intent-to-treat analysis, the proportions of objective response (CR+PR) were 16% (95% CI 12-22%) for HD cisplatin and 24% (95% CI 18-31%) for Taxol/cisplatin (Odds ratio 1.65 (95% CI 1.01-2.71) p = 0.047).

Table 23 shows the tumor response rates between treatment groups. A logistic regression on the clinical response of evaluable patients, which included performance status and disease stage as stratification factors, resulted in a statistically significant advantage of Taxol/cisplatin over HD Cisplatin (p = 0.024). The odds ratio in favor of Taxol/cisplatin was 1.80 (95% CI 1.08-2.98).

Duration of Response

Duration of response was calculated for all responders (CR+PR) and was defined as the period between the day of the first treatment administration until the date progressive disease was first noticed. Seventy-one percent (24/34) of confirmed cisplatin responders progressed or experienced disease recurrence. The median duration of response was 7.5 months with a range of 3.2 to 24.9+ months. Seventy-six percent (38/50) of confirmed Taxol/cisplatin responders progressed and the median duration of response was 6.5 months with a range of 3.1+ to 20.2 months.

There was no statistically significant difference between cisplatin/etoposide and Taxol/cisplatin (stratified log-rank p = 0.237) with respect to duration of response.

Quality of Life

The sponsor administered evaluated quality of life (QOL) based on the EORTC core questionnaire (QLQ-30) and the lung cancer module (LC-30). Patients were evaluated at baseline, before each treatment course, and every two weeks until progression. Table 24 shows the questionnaire compliance in the two arms with respect to followup.

The sponsor compared QOL between treatment arms by evaluating changes in

QOL from baseline over all on-study periods. The sponsor found a statistically significant improvement of patients on the Taxol/cisplatin arm versus the Cisplatin arm in the following subscales: Physical Functioning, Nausea and Vomiting, Appetite Loss, and Constipation. The sponsor found a statistically significant improvement of patients on the Cisplatin arm versus the Taxol/cisplatin arm in the following subscales: Hair Loss and Peripheral Neuropathy.

The sponsor analyzed the data with three longitudinal approaches, including a Wei-Johnson model (Wei and Johnson, 1985), a Wei-Lachin analysis (Wei and Lachin, 1984), and a linear mixed effects model with a banded longitudinal covariance matrix and fixed effects of treatment arm and period (categorical). They considered the Wei-Johnson test to be their primary analysis. However, this test is biased in the presence of informative dropout, and so this assumption must be confirmed.

To test the assumption of non-informative dropout, the sponsor compared the results of the Wei-Johnson test on the entire patient population with the results of a Wei-Johnson analysis on just those patients who completed no more than the first four periods. There was little difference between the parameter estimates and p-values between the former subgroup and the latter subgroup, although this was not tested formally. Only in one instance would conclusions about QOL change due to dropout problems in the sponsor's analysis; this occurred in Physical Functioning, where $p = 0.054$ for the former Wei-Johnson analysis and $p = 0.045$ for the latter Wei-Johnson analysis.

Graphs of the means of all 26 QOL subscales appear in Figure 5 and Figure 6. Note that for the five "functioning" variables and the global health status variables, 100 on the scale is interpreted as "high level of functioning." For the remaining 18 symptom scales, 0 on these scales is interpreted as "minimal discomfort" while 100 on these scales means "intense discomfort."

From this set of longitudinal analyses, the subscales that were found to be statistically significant were Physical Functioning, Nausea and Vomiting Symptoms, Appetite Loss, Constipation (all favorable to Taxol/cisplatin), Hair Loss and Peripheral Neuropathy (both favorable to HD Cisplatin). The p-values of the statistically significant QOL subscales appear in Table 25.

5.3 Summary and Conclusions for CA139-208

Summary

The primary endpoint for this study was overall survival. There was no statistical significance found between the primary endpoint of overall survival between the Taxol arm and the HD cisplatin arm; the median survival for Taxol/cisplatin was 8.6 (95% CI 7.1-10.3) months and the median survival for HD cisplatin was 8.1 (95% CI 7.3-9.2) months (stratified log-rank p = 0.862).

Based on an intent-to-treat population, evidence of superiority of the Taxol/cisplatin arm over the cisplatin arm was found in objective response (CR+PR; 16% (95% CI 12-22% for HD cisplatin and 24% (95% CI 18-31% for Taxol/cisplatin; odds ratio 1.65 (95% CI 1.01-2.71) p = 0.047). This was confirmed in a logistic regression with performance status and disease stage as stratification factors and weight loss, age and gender as covariates (p = 0.024).

There was a statistically marginal advantage in a time to progression Cox regression (hazard ratio of 1.24 (95% CI 1.00, 1.54); p = 0.056). However, there was no statistically significant difference between treatment in a stratified log-rank test (p = 0.085). There were no statistically significant differences with respect to response duration (stratified log-rank p = 0.237).

There was also a statistically marginal QOL advantage in favor of Taxol/cisplatin in the Physical Functioning subscale, and statistically significant advantage in Nausea and Vomiting Symptoms, Appetite Loss and Constipation. There was a statistically significant QOL advantage in favor of Cisplatin in Peripheral Neuropathy and Hair Loss subscales. However, no Type I error adjustments were made for the multiplicity of QOL subscales.

Conclusions

This large, well-designed trial failed to show a statistically significant advantage on the primary endpoint of survival. There was some advantage in the Taxol arm over HD Cisplatin on some QOL endpoints.

The sponsor showed a statistically significant advantage of Taxol/ cisplatin on objective response (p = 0.020). There was also a statistically marginal advantage in a Cox regression on time to progression, but a stratified analysis of time to pro-

gression failed to confirm statistical significance. There was also a QOL advantage favoring Taxol on the Physical Functioning subscale, and statistically significant advantage in Nausea and Vomiting Symptoms, Appetite Loss and Constipation. This was offset by a statistically significant QOL advantage in favor of HD Cisplatin in Peripheral Neuropathy and Hair Loss QOL subscales. However, no Type I error adjustments were made for the multiplicity of subscales that were considered in the QOL analysis and no formal test considered whether dropout was ignorable or nonignorable.

This study provides substantially more information on QOL than the previous studies considered here. The question of whether those patients on a Taxol regimen experience greater patient benefit as determined by the time to progression and clinical response endpoints must be weighed against this arm's toxicity. The Medical Reviewer will include a more detailed discussion regarding the safety data.

6 Overall Conclusions and Recommendations

Although the three Phase III studies that examine the efficacy of Taxol all fail on survival endpoints, one may conclude that are statistically significant advantages of Taxol over other cisplatin-based regimens with respect to objective response. The advantage of Taxol over time to progression endpoints is not consistent within these studies; in study CA139-165 there was a statistically significant increase in time to progression of Taxol/cisplatin/G-CSF over cisplatin/etoposide. However, lower-dose Taxol regimens show no advantage.

Quality of life conclusions about a Taxol advantage are difficult to make, although it is this reviewer's opinion that the QOL analysis of CA139-208 gives the clearest picture of QOL among the three Phase III studies. In CA139-165, there was no QOL advantage to be found among any subscales. However, tests for differences on the Lung Cancer Specific Symptoms subscale yielded $p = 0.026$ for cisp/etop vs. Taxol/cisp and $p = 0.016$ for cisp/etop vs. Taxol/cisp/G-CSF for patients who dropped out within two QOL assessments. For Completers, $p = 0.021$ for cisp/etop vs. Taxol/cisp and $p = 0.154$ for cisp/etop vs. Taxol/cisp/G-CSF. The nominal Type I error for these comparisons is 0.0125 due to the nature of the three-arm design. Conclusions about QOL in CA139-103 must be made with caution.

Only in objective response do Taxol arms consistently show increased efficacy compared to controls. On the other hand, there is no "duration of response" ad-

vantage for patients on the Taxol arms. There is little evidence to support patient benefit outside of objective response, although there seemed to be some patient benefit in quality of life endpoints in study CA139-208. There was no Type I error adjustment for the number of secondary endpoints considered and therefore the p-values of each of these endpoints should be considered to be inflated.

It is this reviewer's opinion that all three trials fail to demonstrate a general improvement in efficacy in favor of Taxol arms compared to controls. The evidence suggests that although the Taxol arms show a slight increase with respect to time to event descriptive statistics over other controls, there is no statistically significant advantage in favor of Taxol.

/S/

David Smith, Ph.D.
Mathematical Statistician

Concur:

Dr. Koutsoukos Antonis Koutsoukos 3/30/98

Dr. Chi 3/30/98

cc: Archival NDA 20-262

HFD-150 / Ms. D. Spillman, Project Manager

HFD-150 / Dr. I. Chico

HFD-150 / Dr. G. Williams

HFD-344 / Dr. B. Barton

HFD-710 / Dr. G. Chi

HFD-710 / Dr. T. Koutsoukos

HFD-710 / Dr. D. Smith

HFD-710 / Chron

Smith / March 27, 1998 / PDF

This review consists of 28 pages of text, one page of references, and 16 pages of tables and figures.

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