CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-462

Statistical Review(s)

STATISTICAL REVIEW AND EVALUATION

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEDICAL DIVISION: Oncology Drug Products (HFD-150)
BIOMETRICS DIVISION: Division of Biometrics I (HFD-710)

NDA NUMBER: NDA 21-462

DRUG NAME: ALIMTA® (pemetrexed, LY231514) 500 mg Vials

INDICATION: Treatment of Malignant Pleural Mesothelioma

SPONSOR: Eli Lilly and Company

DOCUMENTS REVIEWED:
1. Cover letter and documents (CDER REC'D Dates: 24-OCT-2002, 22-NOV-2002 and 26-NOV-2002) including SAS data base
2. Cover letter (CDER REC'D Dates: 6-DEC-2002) including the pdf file for review's aids, SAS data sets, and SAS programs for the efficacy analyses

STATISTICAL KEY WORDS: Log-rank test, proportional hazard model, Kaplan-Meier estimate, hazard ratio, multiple comparison, Bonferroni adjustment

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1 Executive Summary of Statistical Findings

1.1 Recommendations and Conclusions

Based on the collective evidences and findings, in this statistical reviewer's opinion the data and results of the Phase III Study H3E-MC-JMCH support the sponsor's efficacy claim of ALIMTA® (pemetrexed, LY231514) 500 mg Vials with respect to the survival endpoint for the patients with Malignant Pleural Mesothelioma. The data and results of the study show that the primary endpoint, survival, is statistically significantly improved in new treatment arm as compared to control arm for the randomized and treated (RT) population (p-value=0.021). The secondary endpoints, time to progressive disease, time to treatment failure, and response rate, are also demonstrated statistically significant improvement in new treatment group compared to the control group. In the fully supplemented (FS) subgroup, efficacy results are similar to those findings in the RT population. The hazard ratios for both RT and FS populations showed the consistency of the magnitude of survival benefit.

1.2 Brief Overview of Clinical Studies

This application consists of report of results from the Study H3E-MC-JMCH (referred as Study JMCH here and after) in the patients with Malignant Pleural Mesothelioma (MPM).

The registration Study JMCH was a multi-national, multi-center, single-blind, and parallel-arm Phase III trial with MPM patients randomized to LY231514 plus Cisplatin (LY/cis) and Cisplatin alone treatment arms. A total of 574 patients were entered into the study (that is, signed the Informed Consent Document); 456 of these patients were randomized to a treatment arm; 448 of these patients were treated and constitute the randomized and treated (RT) population.

LY/cis: Total: 226, Male: 184, Female: 42. Fully Supplemented (FS): 168, Partially Supplemented (PS) or Never Supplemented (NS): 58.

Cisplatin alone: Total 222, Male: 181, Female: 41. Fully Supplemented: 163, Partially Supplemented or Never Supplemented: 59.

LY/cis treatment: LY231514 was administrated at the dose of 500 mg/m^2 as a 10-minute intravenous infusion, diluted in approximately 100 mL normal saline. Approximately 30 minutes after the administration of LY231514, Cisplatin was administered at the dose of 75 mg/m^2 over 2 hours. Both drugs were administered on Day 1 of a 21-day period. This 21-day period defined one cycle of therapy.

Cisplatin alone treatment: approximately 100 mL normal saline was given as an intravenous infusion over approximately 10 minutes. Approximately 30 minutes after the administration of normal saline, Cisplatin was administered at 75 mg/m^2 over 2 hours of Day 1 of a 21-day period. This 21-day period defined one cycle of therapy.

Both treatment arms: (1) Dexamethasone, 4mg (or an equivalent corticosteriod), was to be taken by all enrolled patients orally twice a day (BID) 1 day before, on the day of, and 1 day after each dose of LY231514, for primary prophylaxis against rash. (2) Folic acid and vitamin B_{12} for supplementation were a standard component of therapy for all patients participating in the study. Folic acid, 350 µg to 1000 µg, was to be taken orally daily, beginning approximately 1 to 3 weeks before the first dose of therapy and continued daily for 1 to 3 weeks after the patient discontinued treatment. A vitamin B_{12} injection, 1000 µg, was to be administered intramuscularly approximately 1 to 3 weeks before the first dose of therapy and should have been the first dose of therapy and should have been repeated approximately every 9 weeks until the patient discontinued study therapy. (3) Pre- and post-hydration for Cisplatin was administered according to institutional guidelines.

The primary objective of Study JMCH was to compare survival in chemonaive patients with MPM when treated with LY231514 plus Cisplatin combination therapy to survival in the same patient population when treated with Cisplatin alone. The primary efficacy endpoint was the overall survival time.

1.3 Statistical Issues and Findings

Statistical Issues:

- 456 patients were randomized to treatment arms out of which 8 of these patients were died from study disease before any dosing. The sponsor did not follow the statistical reviewer's comments of IND 40061/SN298 that the primary survival analysis should be based on all patients as randomized. The sponsor did primary efficacy analysis based on the randomized and treated population which did not include those 8 patients.
- The sponsor' efficacy claim was based on the RT population and stated that in clinically, folic acid and vitamin B_{12} would improve the clinical outcome regardless of the treatment arm. The results of the FS subgroup also support the efficacy claim.
- There was a heterogeneous distribution for gender in the two treatment arms (male and female with 81.4% vs. 18.6% and 81.5% vs. 18.5% in LY/cis and Cisplatin groups, respectively). The multivariate analysis for the treatment and gender showed that the interaction between treatment and gender had a small p-value (p-value=0.072) for the RT population and was statistically

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