LY231514 (MTA) End of Phase 2 Meeting with the FDA
Clinical Issues – Friday, September 25, 1998 at FDA

FDA Participants: Division of Oncology Drug Products
Rachel Behrman, M.D., Deputy Office Director, ODEI
Julie Beitz, M.D., Deputy Division Director
Gang Chen, Ph.D., Statistics Team Leader
John Johnson, M.D., Medical Team Leader
Robert Justice, M.D., Oncology Division Director
Robert White, M.D., Medical Reviewer
Liang Zhou, Ph.D., Chemistry Team Leader
Linda McCollum, Consumer Safety Officer

Lilly Participants:
Greg Brophy, Ph.D., U.S. Regulatory Affairs
Steven Hamburger, Ph.D., U.S. Regulatory Affairs
Robert D Johnson, Ph.D., Pharmacokineticist
Astra Liepa, Health Outcomes
Clet Niyikiza, Ph.D., Statistician
David Seitz, M.D., Ph.D., Medical Advisor
Gerald Thompson, Ph.D., MTA Product Team Leader
Jackie Walling, Ph.D., Director of Science, MTA Team
John Worzalla, U.S. Regulatory Affairs

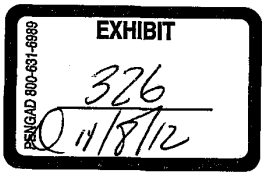
Lilly Consultants:
Ned Patz, M.D., Duke University
Nicholas Vogelzang, M.D., University of Chicago

Meeting Request Submission Date: July 13, 1998
Briefing Document Submission Date: July 29, 1998
Additional Submission Dates: Sept. 8, 1998

Meeting Minutes:

Schedule and Dose: The FDA showed the following acetate:

1. DOSE and SCHEDULE -- Do you agree with the proposed dosing schedule for single agent MTA studies – specifically the registration studies involving NSCLC?
   A. Our agreement is limited to the proposed dosing schedule for single agent MTA. There does not appear to be sufficient efficacy advantage with the 600 mg/m^2 dose of MTA over the 500 mg/m^2 dose. Also there is a trend for hematologic toxicity to be greater for the 600 mg/m^2 dose of MTA than for the 500 mg/m^2 dose. Therefore, the 500 mg/m^2 dose is



recommended unless a dose response for overall response has been shown. Alternatively, patients can start at 500 mg/m^2 and the dose can be escalated to 600 mg/m^2 if tolerated.

The FDA agreed with the proposed 21 day dosing cycle. There was a discussion on the safety profile of the 500 mg/m^2 and 600 mg/m^2 MTA doses between Dr. Walling, Dr. White, Dr. Johnson and Dr. Vogelzang. The FDA recommended an MTA starting dose of 500 mg/m^2 for single agent studies with dose escalation to 600 mg/m^2 allowed. Dr. Walling pointed out that there was no significant increase in Grades 3 and 4 neutropenia seen at the 600 mg/m^2 dose (48% versus 41% at the 500 mg/m^2 dose, but the increase was not statistically significant). Also no excess of toxic deaths has been seen with the 600 mg/m^2 dose. There is not enough data yet to examine the dose response with respect to efficacy, but Lilly agreed to the 500 mg/m^2 starting dose.

The following addition to 1A was provided.

FDA recommendation to use 500 mg/m^2 is advice and not a requirement.

Mesothelioma: The FDA showed the following acetate:

1. MTA in Mesothelioma – The indication being pursued is "MTA Injection is indicated for the treatment of pleural mesothelioma."

   FDA Preliminary comment: Usually, lead indications are approved with two studies. Mesothelioma is a rare disease. Depending on the quality of the mesothelioma trial design and data, further discussions may convince the Agency to accept one mesothelioma study and confirmatory evidence from a closely related disease.

   2a Do you agree this is an acceptable registration strategy (i.e., patient population, patient numbers, endpoints) for accelerated approval for this indication?
   - A. NO. Serial measurement of disease are difficult and inaccurate in mesothelioma. Confirmation of responses by FDA is likely to be impossible and the clinical benefit of response in mesothelioma is uncertain.
   - B. Accelerated approval based on response rate is unlikely. In order to gain accelerated approval with the combination of MTA + cisplatin, you would have to provide evidence that MTA + cisplatin is better than any other combination in response and response duration.
   - C. Survival should be the primary endpoint. Since survival is short in this population, it should not take long to reach the endpoint.
   - D. Tumor related symptoms could also be addressed in a blinded trial.

A lengthy discussion took place on the issues of response rate and unidimensional measurements for mesothelioma. These discussions were led by Drs. Vogelzang and Patz. Dr. Vogelzang explained that unidimensional measurements can be easily obtained, the number of responders is always low and a high correlation was shown in a recent paper between clinical benefit and response. Dr. Patz explained how the CT scans can have resolution down to 1 mm, and that the scans would be digitized and blinded and then read only by Dr. Patz and a colleague in France. Dr. Patz showed an acetate (#1) with W.H.O. guidance on the use of unidimensional measurements and another acetate (#2) with a table showing good concordance between uni and bi-dimensional tumor measurements. Dr. White noted that there were no mesothelioma studies which correlated these measurements. A number of slides with several mesothelioma scans were shown and the technique for using unidimensional measurements was discussed. A discussion suggesting several ways in which unidimensional measurements could be taken at different locations and what changes in these measurements would qualify for a response did not sway the FDA concerning response rate as the primary endpoint. It was restated by the FDA that survival should be the primary endpoint, but response rate might be considered for inclusion in the label.

The FDA recommended using Study JMCH as designed except using survival as the primary endpoint with clinical benefit (reduction in pain or dyspnea) as a secondary endpoint to qualify for full approval. Thus, if survival was improved, but fell short of statistical significance, then response rate plus clinical benefit (reduction in pain or dyspnea) might provide additional evidence for approval.

Dr. Walling asked about the censoring rate for the survival study, and the FDA responded that 50% or less censoring rate (50% patients alive in the control arm) is the minimum, but that 25% censoring rate (25% of patients alive) would be better.

The final agreement to points 2a. A and 2a. B above were listed as shown below:

2a A. Lilly has access to the technology (Spiral Hi-Res CT scans), protocol, and dedicated assessment team in place to adequately assess response in mesothelioma

2a B. We recommend that appropriately designed trials demonstrating clinical benefit, i.e., pain reduction breath shortness, etc., (see C & D) be the strategy for gaining full approval if survival benefit can't be shown instead of response rate for accelerated approval. (See previous FDA comments)

The FDA also agreed that evidence of activity against NSCLC might also serve as confirmatory evidence (see FDA preliminary comment above).

A discussion was held on the suggestion of blinding for study JMCH. Dr. Justice said that approval could be given for an unblinded study. However, the FDA also pointed out that it would be easier to get approval with a blinded trial, since improved clinical benefit would be considered more robust in context of a blinded trial. Again, this was advice from the FDA, and it is Lilly's decision as to whether or not to do a blinded study.

The following FDA acetate for issue 2b was shown:

2b Is the design of study (JMCH) adequate and well controlled?
- A. Yes, with reservations. This would be a better study if it were blinded.
- B. A randomized trial of MTA + cisplatin vs. cisplatin alone is an adequate trial. However the addition of the vitamins to the MTA arm without data that efficacy is not reduced is risky. We would like to know the basis for your determination that the addition of vitamins will not affect efficacy.

Dr. Walling answered this with an acetate (#3) with preclinical data from a murine L5178Y/TK-/Hx- lymphoma tumor model showing that folic acid at 15 mg/kg (45 mg/m^2) ameliorates the toxicity of MTA, but it does not affect the efficacy. There still was concern from the FDA that folic acid might reduce efficacy. Dr. Walling again responded that we are using low doses of folic acid that are in a range (350 to 600 µg/day which is similar to the 100% RDA of 400 µg/day) that would give physiologic levels that might be expected from dietary exposure to folate. Thus, if MTA efficacy was negatively impacted by these low levels of folic acid in the multivitamins, then the activity of MTA would be compromised by similar levels of folate that could be ingested with food in a normal diet. The FDA responded that it was Lilly's decision whether or not to use folate.

The following FDA acetates for issues 2c through 2e were shown, but agreement as to these had been reached in the discussions noted above:

2c. Do you agree that the choice of primary and secondary endpoints, and the analysis plan in study JMCH is acceptable?
- A. NO. Response rate is not an acceptable primary endpoint in this disease. Survival should be the primary endpoint and superior survival in the patients on the MTA arm should be the basis for approval.
- B. Secondary endpoints of response rate, duration of response and time to progression could be supportive of the primary endpoint.

2d. Do you agree that allowing the measurement of unidimensional disease will provide sufficient information for determining response rate?

A. NO. It is uncertain that unidimensional disease measurements in mesothelioma will provide sufficient information for determining response rate.

2e. Do you agree that there will be sufficient safety data to support registration, i.e., the studies of MTA and cisplatin in NSCLC may be used to support the safety profile obtained in mesothelioma?
A. YES

Next the discussion turned to MTA for non-small cell lung cancer. The FDA displayed their first acetate for Issue 3:

3. NSCLC – The indication being pursued is: "MTA Injection is indicated for treatment of patients with advanced non-small cell lung cancer (NSCLC) whose disease has recurred or progressed following platin- and taxane-based therapy."
   3a. Do you agree this is an acceptable registration strategy (i.e., patient population, patient numbers, endpoints) for this indication?
      A. NO. Time to progression is not a sufficient surrogate for clinical benefit in NSCLC. Since the interval between disease progression and death is short, the primary endpoint should be survival.
      B. Two randomized, controlled trials will be needed.

Nick Vogelzang began by stating the importance of time to tumor progression for patients. He said that when a tumor begins to grow, this is accepted as time to switch the therapy, and he added that patients are looking for "no growth of tumor – you cannot live with growing tumor". Dr. Justice said that there are problems with assessing progression such as the need for frequent tumor measurements. Dr. White agreed in part, but said that survival is also important. It was mentioned that a 4 week increase in time to tumor progression would be a good result, but the FDA asked how often Lilly was planning on doing tumor measurements. Dr. Walling replied that Lilly would be taking scans every 6 weeks, and Dr. John Johnson pointed out the difficulty in taking measurements only every 6 weeks while trying to demonstrate an increase of 4 weeks in time to tumor progression. Dr. Justice said that the FDA recognizes time to tumor progression, but questioned it as grounds for approval. Dr. Walling said that Lilly will accept survival as the primary endpoint. Dr. John Johnson said that the Agency will look at other things besides survival if the survival trend is there. Thus, he suggested survival as the primary endpoint with time to tumor progression as a secondary endpoint.

Thus, the following was agreed to:

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