ANTIFOLATE ADVISORY PANEL
Minutes of Meeting
March 16, 1998
Ixtapa, Mexico

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Panel Participants

Carmel Allegra
Robert Allen
Joseph Bertino
Hilary Calvert
James Carmichael
Karin Mattson
Enrico Mini
Jean Louis Misset
Herbie Newell
Peter O'Dwyer
Louis Paz-Ares
Hans Schmoll

Panel Discussion Leader

Jackie Walling (Lilly)

Investigator Participants

Stephen Clarke

Lilly Attendees

Marilyn Arnett, Johannes Blatter, Victor Chen, Stephen Clarke, Dawn Gardner, Steve Hamburger, Kim Hartsock, Constanza Ilardi, Robert Johnson, Louis Kayitalire, Diana Kelley, Sean McCarthy, Mark Miller, Katrina Nelson, Robin Nelson-Rice, Steve Nicol, Clet Niyikiza, Angela Panadero, Angela Ribecco, Michael Scott, Julia Stickland, Adrian Thomas, Jerry Thompson, Don Thornton, Donna Watts

cc of minutes: Rick Schilsky, Dan Von Hoff, meeting participants, MTA Product Team

MINUTES OF MEETING:

The primary objectives of this meeting were to obtain input from the Panel on the fastest route to MTA registration, and to consider the prioritization of the ongoing and planned clinical trials. These objectives were related to the mission/vision/strategic intent statements for the project. These statements include speed to market as the initial registration objective with parallel development of several indications in different clinical settings as a means of accomplishing this objective, and maximizing the value of MTA in the treatment of cancer. Activity of MTA has been demonstrated in a number of areas, and there are insufficient resources to bring all of the possibilities forward to registration at this time.

Discussion focused on NSCLC, breast cancer, mesothelioma, cervical cancer, head and neck cancer, bladder cancer, renal cancer, and pancreatic cancer. Generally, discussion for each indication was initiated with a marketing overview, followed by clinical data, clinical plans and development/registration strategies.

Non-Small cell lung cancer (NSCLC)

Marketing

Market research data from the U.S. Redacted Redacted on the incidence and treatment of 1st and 2nd line NSCLC were provided by Lilly. These data were approximately one year old and involved a data base of 60 physicians (20 patients per physician) in each country.

Redacted

Redacted Other drugs that may be used at the time of an MTA launch could be capecitabine and CPT-11. Taxotere is available in Europe and is being used in NSCLC, although not currently approved for this indication.

NSCLC 2nd line - Clinical Studies/Plans

An approach that is being considered by Lilly to achieve rapid registration involves Phase 2/3 studies in 2nd line NSCLC. If this option does not accomplish a speed-to-market objective, these studies may not be pursued at this time.

A Phase 2 study (JMBR) in patients who have received one prior chemotherapy regime with or without platinum has been initiated (Europe), but it is too early to provide response data. Another proposed study (JMBQ, U.S.) in platinum/taxane failures is planned. This latter study is designed as a pivotal U.S. registration study, with the objective of determining MTA activity in a 2nd line setting, gaining speed to registration

through a single Phase 2/3 study, and asking if vitamin supplementation has an effect on the toxicity of MTA in this group of patients.

Panel input to this study design was requested. The following summarizes recommendations from that discussion:

1. The suggested Phase 2/3 study design compares MTA, MTA + vitamins (vitamins are 1 mg folic acid, 25 mg B6, and 2 mg B12), and Navelbine. In the initial phase II portion of the study response rate will be used as the hurdle and TTP will be the primary endpoint of the study. There was considerable debate about the design of the study, and Jim Carmichael felt that it might be premature, given our understanding of the toxicity of the compound. Peter O' Dwyer felt that the interim hurdle should be based on TTP also.
2. The MTA dose of 600 mg/m2, decreasing if necessary, rather than starting with the 500 mg/m2 was recommended. To date, there is no evidence of a clinical dose-response relationship between the 500 mg/m2 and 600 mg/m2 dosage levels. However, it also is too early to conclude that there is no clinical difference between the two dosages.
3. Pharmacokinetic studies (real time) were suggested to expand our knowledge of MTA's toxicity profile.
4. If a minimum response rate is achieved in the MTA- and MTA/vitamin-treated patients (a 10% response rate in the 2 arms combined), a decision of which of the two MTA arms to carry forward into a standard Phase 3 study will be determined on the basis of the relative toxicity profiles between the two arms. The decision making criteria need to be defined up front in the protocol.
5. There will be balancing of patients in this study for prognostic factors (e.g. performance status, homocysteine levels, investigator sites) so that the treatment effect can be evaluated. Approximately 540 patients will be enrolled in the Phase 2/3 study.
6. Navelbine was the recommended comparator, although there was considerable concern about obtaining signed informed consents/IRB approvals in a study involving Navelbine since this drug is not approved for 2nd line NSCLC and has been shown to be inactive in 2nd line in terms of response rates. It was pointed out, however, that no chemotherapeutic agent currently is approved in 2nd line, and that Navelbine is used routinely at some stage of a patient's disease (U.S. mentioned specifically), with a substantial number of patients deriving benefit (e.g. improvement of symptoms). It will be important to utilize a comparator that offers effective treatment, even if is this comparator is not approved. The choice of the comparator as well as other protocol parameters will be discussed with the FDA when the Phase 2/3 development plans are reviewed.
7. The endpoints agreed to by the Panel were time to progression as the primary endpoint, with an index of palliation (e.g. clinical benefit, quality of life) and median duration of survival as secondary endpoints. Response rates were not considered critical, nor a good surrogate for palliation.

The estimate of enrolling 540 patients in 1 year for the above study was considered reasonable in view of the Panel's and Lilly's experiences. The first patient visit was estimated as June, 1998 with a U.S. submission/approval in Q400/Q301 (assuming that necessary safety data for selection of an MTA arm and efficacy data are available and that enrollment into the Phase 3 portion of the study will not be delayed.)

The Panel felt that there currently was insufficient information to know the activity of MTA in 2nd line NSCLC, and agreed that additional studies in this patient population were warranted.

NSCLC 1st line - Clinical Studies/Plans

Lilly's two Phase 2 studies (chemonaive, Stage 3 and 4) have indicated response rates of 23%, median survival 9.2 months (JMAO, n=30) and 17%, median survival 7.5 months* (JMAL, n=35) (*these data are heavily censored, with several patients remaining on study). Another Phase 2 study in NSCLC (JMAY) involves combination cisplatin (75 mg/m2) and MTA (500 mg/m2) every 21 days. Responses have been reported in this study, but it is too early to determine response rates.

The Panel agreed that MTA had shown activity in 1st line NSCLC, but that additional efficacy and safety data were needed before strategic discussions could be made, given the competition in this indication.

Because the MTA combination Phase 1 studies with cisplatin will be completed prior to combination studies with other possible combination agents, the combination of MTA and cisplatin may offer a means of securing the most rapid route to registration in 1st line NSCLC. The advisors, however, generally did not favor proceeding with this combination. Carboplatin was the favored combination agent, although a number of combinations including carboplatin Taxol, cisplatin Taxol, gemcitabine cisplatin and cisplatin Taxotere are currently being compared in the big ECOG study. Despite the lack of phase III data, carboplatin/Taxol is a broadly accepted regimen (described by some as efficacious and easy to administer). These combinations have response rates of the order of 40 to 60% and hence have established a fairly high hurdle rate for an MTA combination. The advisors felt that the MTA/cisplatin combination would have to have significant safety and/or efficacy advantages to be adopted in the marketplace in preference to these regimes. In Phase 2 studies, it would be critical to demonstrate a reasonable and acceptable safety profile, a comparable response rate to these regimes and a median survival of greater than one year before proceeding to Phase 3. Days of hospitalization due to complications of chemotherapy was suggested as an endpoint (possibly a tertiary endpoint). There was concern expressed regarding possible nephrotoxicity of an MTA/cisplatin combination when administered the same day. The possible renal toxicity of MTA is being investigated further in several studies.

The comparator for 1st line NSCLC studies will depend on the outcome of ODAC's review of Taxol on March 20 (Taxol + cisplatin, NSCLC) and results of the ongoing ECOG study. (Note: Taxol was approved in combination with cisplatin for front line

NSCLC.) MTA + GEMZAR was suggested as a combination for future evaluation, although Jim Carmichael expressed concerns about the dose intensity of the gemcitabine in the MTA plus Gem phase I study. This combination will probably need further evaluation in a phase I setting before taking it into phase II.

Biomarker studies were suggested as a means of stratifying the population and discriminating between patient groups. Particular subgroups could then be selected for MTA treatment to determine if there was a distinct advantage for MTA. Such studies could be conducted in parallel with other evaluations.

From a strategic standpoint, the Panel agreed that 1st line NSCLC studies were not a high priority. There was more enthusiasm for pursuing 2nd line NSCLC as an immediate registration strategy, and for generating additional data in 1st line that would be analyzed for subsequent decision-making.

If one were to proceed in a front-line setting with MTA plus Gem, the accrual assumptions of 1 year to enroll 600 patients were considered reasonable assuming encouraging Phase 1 data. Assuming combination MTA + cisplatin, studies would not begin enrollment until Q1 99, with submission/approval Q401/Q302. This assumes initial submission with interim data (TTP data on one-half of the patients), with remaining TTP and survival data made available to reviewers as it is available.

Breast Cancer

Marketing

Redacted

Breast Cancer - 2nd line

The response rate in a single Phase 2 study (JMAG) that involved a heterogeneous population (i.e. including patients treated in the metastatic setting previously) was 33% (1 CR, 9 PR). Some of the patients in this study had failed an anthracycline or taxane. A second Phase 2 study (JMBP) in anthracycline failures is ongoing. Responses have been

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