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October 16, 1995

Ms. Sharon Risso
Director
DARP (HFM-585)
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike
Rockville, MD 20852-1448

Subject: BB-IND 4517 recombinant humanized Anti-p185^{HER2} Monoclonal Antibody (rhuMAb HER2)
Information Amendment: Clinical
Serial No. 052

Dear Ms. Risso:

Reference is made to Genentech's Investigational New Drug Application, BB-IND No. 4517, recombinant humanized Anti-p185^{HER2} Monoclonal Antibody (rhuMAb HER2), for treating cancer patients with tumors that overexpress the HER2 proto-oncogene (submitted on April 20, 1992, Serial No. 000).

The purpose of this letter is to request a teleconference with the Agency to follow up an important issue initially discussed at our Prepivotal Trial meeting on December 22, 1994. Specifically, the difficulty in enrolling the pivotal comparative protocol H0648g, "A Phase III Multinational, Double-Blind Study Comparing Recombinant Humanized Anti-p185^{HER2} Monoclonal Antibody (rhuMAb HER2) Plus Cyclophosphamide and Doxorubicin with Placebo Plus Cyclophosphamide and Doxorubicin in Patients with HER2/*neu* Overexpression Who Have Not Received Prior Cytotoxic Chemotherapy for Metastatic Breast Cancer" (submitted March 7, 1995/Serial No. 033).

EXHIBIT
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Background

Protocol H0648g has a planned enrollment of 450 patients. The first patient enrolled on June 12, 1995, and only 11 patients have been treated to date. Although the reasons for lack of accrual are multifactorial in this complex trial, one factor appears to stand out in our discussions with oncologists: increasing use of doxorubicin in the adjuvant setting has made finding doxorubicin-naive patients presenting with first recurrence of metastatic disease difficult in most geographic areas. Since only patients with HER2 overexpression are eligible for this study, 70 - 75% of patients are already excluded. It has become clear to us that the eligibility criteria should be modified with respect to patients who have seen prior anthracycline chemotherapy.

We propose the addition of paclitaxel to a strata of patients who have received an anthracycline in the adjuvant setting. Although not approved for first-line therapy, we recognize the off-label use of paclitaxel by American clinical oncologists and the clinical trend in the use of taxanes as therapeutic agents in this fatal disease area. Since only a portion of patients receiving paclitaxel will have relapsed within 6 months of adjuvant therapy with doxorubicin, paclitaxel use in this present protocol will be outside the labeled indication in a significant number of patients. In effect, some patients will receive paclitaxel off-label while some patients will receive paclitaxel within the label.

Proposal

As per our original protocol, doxorubicin-naive patients will be treated with six cycles of cyclophosphamide and doxorubicin coadministered with rhuMAb HER2 or placebo.

We propose to enroll patients who have seen prior doxorubicin. Patients who have been treated with doxorubicin in the adjuvant setting will receive paclitaxel 175 mg/m^2 every three weeks coadministered with rhuMAb HER2 or placebo. Paclitaxel will be given for six cycles and if neither disease progression nor dose limiting neurotoxicity has been reached, the investigator will be permitted to give additional cycles until either of those events occur.

As per the original protocol, the primary endpoint for this study remains the same: time to disease progression. The objective will be to demonstrate a 50% increase in time to progression in the group receiving chemotherapy (AC or paclitaxel) plus rhuMAb HER2 as compared to the group receiving chemotherapy alone.

In terms of the analysis of the study, we propose the following:

- patients will be randomized to rhuMAb HER2 or placebo
- the randomization will be stratified by prior exposure to doxorubicin (yes/no) and by type of metastatic disease (visceral/superficial)
  - patients who received doxorubicin in adjuvant setting will receive paclitaxel alone
  - patients who never received doxorubicin will receive a combination of doxorubicin and cyclophosphamide (AC) as per the original protocol

The primary analysis will be based on the pooled data: all patients receiving rhuMAb HER2 versus all patients receiving placebo. Subgroup analysis will be of an exploratory nature only.

The sample size of 450 patients remains unchanged and will reflect the following assumptions (unchanged):

- 50% increase in time to disease progression
- time to progression on chemotherapy only is eight months
- the primary analysis is based on the pooled data
- follow-up time one year
- loss to follow-up 20%
- two-tail test Logrank test
- level of significance $p < .05$, power 90%

Because of the sample size (450 patients), we acknowledge that an increase in progression must be seen in both strata (AC or paclitaxel); however, within none of the strata will a statistical significance of 0.05 be achieved due to the lack of power in subgroup analysis.

We propose that patients enrolled to the current study will contribute to the total sample size (as part of the "no prior doxorubicin" strata) and will be included in the final analysis.

Summary

We would like to discuss with the Agency the following issues:

- Does the Agency agree with the proposal to use paclitaxel off-label in the pivotal comparator trial H0648g?
- Does the Agency agree with the proposed changes of the analysis plan for H0648g?
- Does the Agency agree that the patients currently enrolled in H0648g will be included as part of the sample size and will be included the final analysis?

We would like to discuss our proposal with the Agency as soon as possible. Therefore, we would like to request a teleconference within the next week. If scheduling will not a permit a teleconference within the next week we ask that the Agency identify a day and time that would be convenient to discuss our proposal. Karl G. Trass of my office will be in contact with you to follow up on this request.

If you have any questions or comments concerning this submission, please contact Karl G. Trass, Senior Associate, Regulatory Affairs, of my staff at (415) 225-5892.

Sincerely,

M. David MacFarlane, Ph.D.
Vice President
Regulatory Affairs

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