MEMORANDUM

DATE: January 19, 2007

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SUBJECT: Review Issues (I060557)

DEVICE Duke Institute for Genome Science & Policy Lung Metagene Prediction (LMP) Score

RECEIVED: November 01, 2006

Dear Dr. Nevins:

Thank you for submitting pre-IDE on Duke Institute for Genome Science & Policy's Lung Metagene Prediction (LMP) Score for Non-Small Cell Lung Cancer for our review. The purpose of the review of study protocol by FDA staff is to give manufacturers an idea of the types of questions the agency is likely to express during review of a submission. As a rule, FDA review of pre-IDE protocols leads to better prepared submissions and shorter review time.

This is an informal communication that represents the best judgments of the Immunology staff and consultants who reviewed the protocol. It does not constitute an advisory opinion and does not bind or otherwise obligate or commit the agency to the views expressed, as per 21 CFR 10.85 (k).

With the understanding that the study for which you have submitted this protocol for review has **not** yet started, we have provided following statistical comments from FDA

CDER biostatistician on your proposed protocol. Additional analytical and clinical comments from CDRH/Office of in vitro Diagnostics will be sent to you separately next week.

Reviewer comments

- *Appropriateness of the study designs for the proposed study for validating the intended use and indications for use and clinical performance of LMS*

Study Design

The proposed randomized study appears to be an open-label study if the genomic status of LMS is known to patients. If this is the case, in the randomized comparison of chemotherapy (arm B) vs. Observation only (arm C), formal registered patients will know whether they receive chemotherapy or Observation only, and enrolling physicians will make the decision on which chemotherapy patients will take. For the prognostic comparison (arm A vs. arm C), both patients and physicians will know whether patients are assigned to Observation only arm. In the setting described above, due to the open-label nature in the randomized portion of the study, those patients who are in the randomized set who do not receive chemotherapy will have the opportunity to know their LMS prediction status if the patient consent form used in Stage I discloses the result of the LMS assessment that will be used in Stage II randomization. In such cases, 'Observation' patients whose LMS prediction status is LMS ≥ 0.5 may choose not to consent to Stage II randomization. This scheme not only discourages patients' participation in the randomized trial setting that helps assess if there is survival advantage for chemotherapy in patients who are classified as LMS ≥ 0.5, but also confounds the assessment of LMP's prognostic value.

In order to ensure an unbiased validation of LMP's clinical validity on providing individualized prediction of risk recurrence in stage 1a NSCLC patients for prognostic indicator evaluation, the patient consent form should not disclose the LMS prediction status (LMS < 0.5 vs. LMS ≥ 0.5).

The clinical validity of LMP (P1) should also be shown to be a superior classification method than classification based on clinical-pathology prediction model and be considered as the co-primary endpoint of (P1) hypothesis, call it (P1'). If hypothesis tests for both (P1) and (P1') are shown statistically significant, not only the clinical validity of LMP is validated, also the added value of LMP's clinical validity is demonstrated. This reviewer would request the prediction status based on clinical-pathology prediction model be available at the time of randomization. This information can be used as an additional stratification factor for stratified randomization in the randomized portion of the study if such classification provides different information than stratification factor stage (T1N0 vs. T2N0). The Applicant needs to clearly define the clinical-pathology prediction model in the protocol for future review.

Four chemotherapy regimens

Are the proposed four chemotherapies approved regimens? The Applicant should provide references on the effect of these chemotherapy regimens.

To demonstrate the clinical utility of LMP with a survival advantage in adjuvant chemotherapy relative to Observation only (P2), the comparison can be one chemotherapy regimen vs. Observation only. The advantage of such design allows head to head comparison of the particular chemotherapy that addresses a specific chemotherapy effect and not mixed with the effect of other chemotherapies. It also allows easier administration if double-blinded design is considered. That is, the confidentiality of the LMS prediction status is kept and not disclosed to physician or patient, e.g., a masked Observation arm uses the same chemotherapy schedule without the chemo agent and a chemotherapy arm avoiding enrolling physician's subjectivity in deciding on a specific chemotherapy among the four as originally proposed.

The proposed design considering four chemotherapy regimens seeks the clinical utility of LMP with a survival advantage in adjuvant chemotherapy relative to Observation only (P2) as the average effect of the four chemotherapy regimens relative to Observation only. Such design is likely to end up with an underpowered study for individual chemotherapy effect and making it harder administratively for a double-blind design consideration.

If the four chemotherapy regimens design is accepted, the estimated effect of individual chemotherapy relative to Observation only can only be post-hoc assessed and will be a review issue. Given the enrolling physician will decide on the particular chemotherapy among four regimens, unless the treating physician and the enrolling physician can be different, the blinding of treatment assignment to physician is not possible. This reviewer highly recommends that at the minimum, a single-blinded randomization be used. That is, the patient consent form does not disclose the LMS prediction status to patients.

Alpha-Spending for Interim Analyses

The proposed group sequential design in the randomized comparison plans for at least 358 patients with at least 238 events, and a known total number of death events at the time of each interim analysis. The alpha-spending function with its spending rule should be clearly pre-specified. The sentence "the first interim analysis for survival efficacy of arm B over arm C will occur 2 years after the first enrollment, or when 36 deaths have been observed on arm B and arm C combined" should be modified to add the following text "whichever one occurs first".

Although the overall type I error rate can be controlled by offsetting the inflated alpha for superiority test with the reduced alpha for futility test, we prefer that the alpha-spending for superiority test be followed without the use of the reduced alpha in the futility test because of the futility rule is usually not strictly followed.

The sample size adaptation considers prospective planning for ensuring at least 358 patients in the randomized comparison when there are significantly more than the assumed 64% patients with a LMS < 0.5 after the first 100 patients have been registered to the study. For a time to event analysis on the overall survival, the adaptation consideration makes more sense to ensure total events of 238 events, which may result in total number of patients that is more or less than 358. The fixed total events allow clear pre-specification of the alpha-spending rule for group sequential design. The sample size adjustment, in this case, would be changes in arm A (LMS < 0.5 Observation) making the ratio between LMS < 0.5 versus LMS ≥ 0.5 larger or smaller than the originally planned (3.55 = 636/179). The sample size adaptation should state whether the originally planned ratio is fixed. If it is fixed, the later accrued patients that have an LMS < 0.5 would not be included for the primary statistical analysis in the comparison of arm A vs. arm C.

- *Study endpoints proposed for the clinical validation such as doses and safety concerns*

The proposed study primary endpoint is overall survival, an efficacy endpoint and a safety endpoint in cancer trials. Overall survival is a clinical endpoint that is generally measured without ambiguity. Since all eligible patients will be followed after the last enrollment for at least 3 years, the clinical truth is the death status after at least 3 years of follow-up in the proposed randomized clinical trial or long-term follow-up with timing of mortality assessment pre-specified. Five interim analyses plus final analysis are planned spanned over 7 years. At each interim analysis, there is a possibility of terminating the study for superiority (adjuvant chemotherapy prolongs overall survival over Observation only) or for futility (no overall survival improvement or inferior overall survival with adjuvant chemotherapy over Observation only), Thus potential safety concern on all-cause mortality in patients taking any of the four adjuvant chemotherapies along with their dosing regimens will be monitored using the interim analysis scheme. Specifically, the Applicant proposes that each interim analysis be performed annually after the first interim analysis that will be performed after two years of first enrollment. And, the DSMB will consider the results at each interim analysis and use its discretion in weighing the combined impact of treatment-related morbidity, disease recurrence and overall survival.

In addition, one of the secondary objectives is to characterize the rate of chemotherapy toxicity for the chemotherapy treatment arm. Thus, the adverse events related to adjuvant chemotherapies will be characterized. Such information should be available and be incorporated by DSMB at each of the interim analyses assessment.

- *Statistical plan and acceptance criteria for determining the effectiveness and safety*

Primary statistical analysis method

The statistical plan for determining the effectiveness of the primary endpoint stated in p.50 of the submitted document is “the comparisons of treatment arms on overall survival

will be done using the log ranked or its stratified version (Kalbfleisch 2002). Secondary multivariate survival analysis for the effect of chemotherapy will be performed using a Cox's proportional hazard model (Cox 1972) with the significant prognostic factors as initial model covariates, such as age, gender, smoking status, tumor size, and histological type. A step-down procedure that consists of dropping the least significant covariates, one at a time, will be used to obtain a more parsimonious model. The probabilities of death due to different causes will be estimated and modeled for three treatment arms using the methodology developed by Gray (Gray 1988, Fine 1999)."

The Applicant needs to pre-specify which statistical analysis method will be considered primary for overall survival, the primary endpoint. This reviewer recommends a stratified log-rank analysis stratifying on the stage (T1N0 vs. T2N0) and/or clinical-pathology prediction status (good vs. poor). Note that secondary survival analyses are considered exploratory.

Statistical Inference for Clinical Validation and Clinical Utility

Acceptance criteria for determining the effectiveness is based on Hochberg procedure. The Hochberg decision rule proposed addresses (P1) and (P2) hypotheses without any order of relevance as long as at least one of the alternative hypotheses can be concluded. In other words, the statistical inference can result in one of the four possible scenarios described below:

(i) Median survival is significantly longer in patients with LMS<0.5 than with LMS≥0.5 without chemotherapy (Observation only), but, not so in patients receiving chemotherapy as compared to Observation in patients with LMS ≥ 0.5;

(ii) Median survival is significantly longer in patients receiving chemotherapy as compared to Observation in patients with LMS ≥ 0.5, but, not so in patients with LMS<0.5 than with LMS≥0.5 without chemotherapy (Observation only);

(iii) Median survival is significantly longer in patients with LMS<0.5 than with LMS≥0.5 without chemotherapy (Observation only) and is longer in patients receiving chemotherapy as compared to Observation in patients with LMS ≥ 0.5;

(iv) Median survival is not significantly longer in patients with LMS<0.5 than with LMS≥0.5 without chemotherapy (Observation only), and is not significantly longer in patients receiving chemotherapy as compared to Observation in patients with LMS ≥ 0.5.

However, in the analytical performance section, studies that were used to develop and to validate the LMS score to predict cancer recurrence or death are studies that involved stage I NSCLC patients without adjuvant chemotherapy. Thus, in this proposed study, the prognostic indicator hypothesis, i.e., (P1), should be the primary hypothesis and the predictive hypothesis that addresses the validation of the clinical utility of LMP to guide the use of adjuvant chemotherapy, i.e., (P2), should be the secondary primary hypothesis in the order relevance of the two primary hypotheses. When the order of (P1) and (P2) is

considered, the (P2) hypothesis accounting for 5-interim analyses plus final analysis would only be tested if statistical significance is reached in testing (P1) hypothesis. Note that there is no interim analysis for testing (P1). Thus, the ordered hypotheses approach would be problematic.

On the other hand, the intended use and indications for use that captures the study objective and the two primary objectives seems to indicate that the two hypotheses are both relevant and important. The language used in the **Intended Use** is repeated here: "The Lung Megagene Score will utilize RNA expression levels from a surgical resected tumor sample to generate an individualized prediction of disease recurrence in stage I non-small cell lung cancer (NSCLC) patients. The probability of recurrence, as determined by the Lung Metagene Score, will then be used by the treating physician to inform the administration of adjuvant chemotherapy". Indications for use are in all diagnosed stage I NSCLC patients. In this case, the statistical requirement for controlling the overall type I error rate would require that both (P1) and (P2) be tested at a two-sided 5% level. A positive result of the prospectively planned randomized study can be concluded only when both statistical tests for (P1) and for (P2) establish statistical significance at the required level, where (P2) incorporates interim analyses rules. This reviewer recommends this decision rule for validating the clinical validity (P1) and clinical utility (P2). The co-primary hypothesis (P1') for (P1) proposed earlier if adopted should also demonstrate the same level of statistical significance.

Additional analyses are recommended to assess the robustness of the clinical prediction utility. For instance, 15% of registered patients are assumed to either have incorrect pathological stage or un-usable genomic data. These patients may be classified as LMS ≥ 0.5 in the statistical testing for (P1) as a robustness assessment in comparison to the formal (P1).

- *Additional comments related to the pre-IDE protocol*

Logistic issue

The primary endpoint for both objectives will be overall survival, defined as the time from formal registration to death of all causes. All eligible patients will be followed after the last enrollment for at least 3 years. For the purpose of testing the two primary hypotheses, (P1) and (P2), the study cutoff date for recording the overall survival time and censoring status should be the same for prognostic indicator evaluation and for randomized comparison evaluation.

Inconsistent descriptions in the text

Below are examples of inconsistent descriptions. These need to be corrected.

- Second paragraph in p.48, (P1) and (P2) should be switched.
- Under Sample Size Considerations section in p.48, in one place, it states: the 5-year overall survivals for patients with LMS≥0.5 and LMS<0.5 are 85% and 25%,

respectively, whereas, in the last paragraph assumption (4) the percentages for the two groups are reversed.

- The fourth line from the bottom of p.48, 'with 132 deaths on arm B and 106 deaths on arm C' – arms B and C are reversed.

Additional comments

For overall assessment of the added value of the LMP as compared to conventional clinical-pathological prediction, in addition to the pre-specified secondary objectives, (S1), (S2), (S3), this reviewer recommends the following details be provided.

(i) In the clinical-pathology prediction model shown in p.19 of the submitted document, describe what constitute the clinical-pathology prediction model. Provide the data by individual patients for verification of the reported accuracy of 61%, similarly, for the prediction model of 94% accuracy.

(ii) Provide a summary Table on overall survival comparison and PFS comparison stratifying on the clinical-pathology prediction status for (P1) and for (P2) each.

(iii) Instead of single chemotherapy, if the four chemotherapy regimens are considered in the study design as proposed in the randomized trial, provide summary table of survival analysis and PFS analysis by chemotherapy regimens received vs. Observation only.

Please submit your revised study protocol if you would like further FDA evaluation. Any revision that you submit in response to this memo should be submitted in duplicate to address below and should reference the pre-IDE number above to facilitate processing.

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