DDTBMQ000011

February 19, 2019

Foundation for the National Institute of Health
11400 Rockville Pike
Suite 600
North Bethesda, MD 20852

Dear Dr. Doody:

We are issuing this 507 Summary Response Letter to the Foundation for the National Institutes of Health and Quantitative Imaging Biomarker Alliance on your proposed qualification project submitted to the Center for Drug Evaluation and Research (CDER) Biomarker Qualification Program (BQP). We have completed our review of your transition summary submission of October 2, 2018. We support and encourage your ongoing study for tumor volume measured by computed tomography as an imaging biomarker of response to cancer therapy for oncologic drug development.

You have proposed qualification of this imaging biomarker as a primary endpoint for evaluating oncologic drug treatment response. As this biomarker development effort is refined in subsequent submissions, the submitted data, the specifics of your context of use (including the target patient population), and the design of study(ies) used in the clinical validation of the biomarker will ultimately determine which of the recommendations below are most applicable.

Based on our review of the transition summary, we agree there is an unmet need and agree that development of the proposed biomarker would potentially demonstrate a measurable response to investigational oncologic drug treatments for solid tumors.

For the 507 DDT qualification process, please prepare a Qualification Plan (QP) submission that addresses the scientific issues and the recommendations outlined below. A QP contains details of the analytical validation of the biomarker measurement method, detailed summaries of existing data that will support the biomarker and its context of use (COU), and descriptions of knowledge gaps and how you propose they will be mitigated. If future studies are planned, please include detailed study protocols and the statistical analysis plan for each study as part of your QP submission.

In addition to the qualification effort, we encourage further study of your biomarker including collection of specified exploratory information from the proposed clinical trials. When evaluating biomarkers prospectively in clinical trials, sponsors are encouraged to submit study data using Clinical Data

Interchange Consortium (CDISC) standards to facilitate review and utilization of data. Data sharing and the capability to integrate data across trials can enhance biomarker development and utilization.

If sponsors intend to include analyses of these biomarkers to support regulatory decision making for a specific Investigational New Drug (IND) development program, they should prospectively discuss the approach with the appropriate CDER division. Any groups (academia, industry, government) that would like to join in this effort or have information or data that may be useful can contact Dr. Tania Kamphaus, Ph.D. (tkamphaus@fnih.org) the point of contact for this project or view the Foundation for the National Institute of Health website.

Biomarker Considerations

Requestor's Description: **Tumor Volume Change as an Imaging Biomarker of Response to Cancer Therapy**

Type of Biomarker: Imaging
Short Name: *CT volumetry*

FDA's questions for continued development of the biomarker description: We recommend that the biomarker description be changed to "tumor volume change as measured by CT."

Context of Use (COU) Considerations

> *Requestor's COU: Radiologic measurements of whole tumor volume are more precise (reproducible) than unidimensional measurements of tumor diameter. Therefore, longitudinal or serial changes in whole tumor volume during therapy can identify response earlier than corresponding unidimensional measurements, resulting in smaller, more efficient clinical trials. Tumor response or progression as determined by tumor volume can serve as the primary endpoint in well-controlled phase 2 and 3 efficacy studies of cytotoxic, targeted, or immunotherapeutic agents in clinical trials of solid tumors.*

FDA's suggested COU for continued biomarker development: "*Pharmacodynamic/Response biomarker to assess tumor volume change for new oncologic drug clinical trial therapy of solid tumors.***"**

1. Your COU does not indicate whether the CT volumetry biomarker is single lesion-specific (i.e., applies only to single lesions) or is a more general assessment of tumor burden across multiple lesions. RECIST 1.1 is defined as a measure of tumor burden across multiple lesions. You should clarify within the COU whether your CT volumetry biomarker is a single- or multi-lesion measurement and any conditions on applying this biomarker (e.g., conditions on number/location of lesions).

To better understand the benefits of the identified biomarker as a DDT, and to continue to refine the COU, please provide the following information;

Analytical Considerations

2. You stated in Section IV. A, "Measurement of the tumor volume on CT images should follow the consensus guidelines as described in the QIBA Profile: CT Tumor Volume Change for Advanced Disease (CTV< AD). There are a variety of software packages available that are QIBA compliant, and people using this (CT volumetry) biomarker could use any of those packages." It is unclear if your Qualification Package will be based on data solely from the software developed by Dr. Schwartz and Dr. Zhao and if that is intended to be extrapolated across all QIBA-compliant software. We recommend that choose one or two imaging analyses software approaches to provide information to support the overall approach to tumor volume assessment and its interpretation.

3. The role of any manual selection of tumor boundaries with the proposed software is unclear. Please provide a description of how tumor boundaries are determined. If radiologists initiate the selection or determination of tumor boundaries, please explain how inter-reader variability affects tumor volume measurements.

4. You have provided reader studies and repeatability testing to show that similar types of software can produce consistent volume measurements. It is unknown how volume measurements for QIBA-compliant software packages are verified for accuracy. Please provide more detail on the accuracy of measuring the tumor volume in a phantom, in clinical trials, and outside of the research setting. The goal is less to compare/contrast multiple software packages and more to evaluate the measurement approach.

5. In Section IV. D., you state "The acquisition conditions are assumed to meet the industry and regulatory standards." Please describe how the images in each of the phase 3 trials were acquired, i.e., the range of acquisition techniques that would still meet industry and regulatory standards. If the difference in procedures used to acquire the images is significant, include a discussion of how these different procedures would affect the image quality and tumor volume calculations.

Clinical Considerations

6. Most of the data you submitted is supportive of the use of CT volumetry a) in lung nodules that are round, and b) untreated lesions. If you consider your biomarker to be valid for a broad range of clinical contexts, you should submit data that demonstrates that CT volumetry can be used reliably across different

   a. shapes of tumor (spiculated, poorly marginated, plaque-like);
   b. types of therapy (in the 10 trials you submitted, approximately 2800 patients received cytotoxic chemotherapy; 1400 received a VEGF or EGFR monoclonal antibody; 2400 received a small molecule targeted therapy; and 1200 received immunotherapy, which were all for melanoma);

For example, consider including subgroup analyses and additional data for immuno-oncology trials in cancers other than melanoma.

7. We recommend you focus your Qualification Plan on demonstrating that CT volumetry is a more accurate and precise measure of radiographic response than RECIST 1.1. Data demonstrating that radiographic response is correlated with clinical outcomes will be helpful to individual oncology divisions, but the clinical acceptability of using your biomarker as the primary endpoint would need to be adjudicated separately for each tumor type (see page 9 of the recent FDA guidance at https://www.fda.gov/downloads/Drugs/Guidances/ucm071590.pdf: "Treatment effect measured by ORR can be a surrogate endpoint to support accelerated approval, a surrogate endpoint to support traditional approval, or it can represent direct clinical benefit based on the specific disease, context of use, magnitude of the effect, the number of CRs, the durability of response, the disease setting, the location of the tumors, available therapy, and the risk-benefit relationship"). Radiographic response as a predictor of clinical outcomes does not need to be demonstrated for this biomarker qualification.

Statistical Considerations

8. From your data package, it appears that the variance associated with CT measurement of smaller tumors (< 10 mm) is relatively large. Your qualification package should state (a) the minimum amount of tumor change that can be accurately detected by CT volumetry, (b) the minimum baseline lesion volume, and the coefficient of variation for (a) and (b). These quantit1ative measurements will facilitate assessment of CT volumetry precision.

9. You noted that you have obtained access to imaging data and associated patient outcomes data from 10 large and completed landmark phase 3 trials in several measurable solid tumors. If you will focus your efforts on demonstrating that CT volumetry is a more accurate and precise measure of radiographic response than RECIST 1.1, please provide accuracy comparisons and precision comparisons between CT volumetry and RECIST 1.1 using these 10 studies in the statistical analysis plan of your Qualification Plan. This should include inter-reader variability/discordance rates.

If you have questions, please contact Chris Leptak (christopher.leptak@fda.hhs.gov) through email. We look forward to working with you on this beneficial project.

Sincerely,

Christopher L. Leptak -S

Christopher Leptak, M.D., Ph.D.
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Gideon Blumenthal -S

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