Use of Circulating Tumor DNA for Early-Stage Solid Tumor Drug Development

Guidance for Industry

DRAFT GUIDANCE

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Guidance for Industry[1]

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I. INTRODUCTION

This guidance is intended to help sponsors planning to use circulating cell-free plasma derived tumor DNA (ctDNA) as a biomarker in cancer clinical trials conducted under an investigational new drug application (IND) and/or to support marketing approval of drugs and biological products[2] for treating solid tumor malignancies in the early-stage setting. This guidance reflects FDA's current thinking regarding drug[2] development and clinical trial design issues related to the use of ctDNA as a biomarker in clinical trials for solid tumor malignancies in the early stage (curative intent) setting. This guidance does not address the use of ctDNA for the early detection of cancer or cancer screening (e.g. situations where cancer has not yet been diagnosed), or in the metastatic cancer setting. Additional information on the related topic on use of minimal residual disease in hematologic malignancies can be found in guidance for industry *Hematologic Malignancies: Regulatory Considerations for Use of Minimal Residual Disease in Development of Drug and Biological Products for Treatment* (December 2020).[3]

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law. FDA guidance documents, including this guidance, should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

[1] This guidance has been prepared by the Oncology Center of Excellence in collaboration with the Center for Drug Evaluation and Research (CDER), the Center for Biologics Evaluation and Research (CBER), and the Center for Devices and Radiological Health (CDRH) at the Food and Drug Administration.

[2] For the purposes of this guidance, all references to *drugs* include both human drugs and therapeutic biological products unless otherwise specified.

[3] We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

II. BACKGROUND

Drug development for solid tumors in the early stage, non-metastatic setting, typically involves large trials and multiple years of conduct and follow-up with time-to-event endpoints. Certain patients with early-stage solid tumors can be cured with local therapy alone (e.g., surgery, radiation or chemoradiation), other patients require (neo)adjuvant systemic therapy in order to be cured, and others may progress to metastatic disease despite surgery and/or systemic therapy. ctDNA is tumor-derived fragmented DNA shed into a patient's bloodstream that is not associated with cells. ctDNA quantity can vary among individuals and depends on the type of tumor, location, stage, tumor burden, and response to therapy. ctDNA as a biomarker has a number of potential regulatory and clinical uses in the early stage setting that may assist and expedite drug development. In the early-stage cancer setting, ctDNA may be used to detect a certain targetable alteration, to enrich a high- or low-risk population for study in a trial, to reflect a patient's response to treatment, or potentially as an early marker of efficacy. We will discuss each of these potential uses below.

The evidence to support the clinical validity or clinical utility of ctDNA varies across solid tumor malignancies, patient populations, and testing modalities. However, multiple small studies have suggested that residual ctDNA detecting molecular residual disease (MRD) after surgery or completion of standard systemic therapy confers a poor prognosis and selects a population at high risk of relapse.[4]

ctDNA assessments can vary among laboratories and technologies used to detect ctDNA which can result in discrepant results. Many clinical laboratories develop their own protocols that can impact ctDNA measurements and detection. Further standardization of assays will allow for better use of ctDNA in a regulatory setting and will allow for analyses across studies to validate the use of ctDNA.

III. DEVELOPMENT OF CTDNA AS A BIOMARKER FOR REGULATORY USE IN EARLY-STAGE SOLID TUMOR CLINICAL TRIALS

Sponsors should consult the FDA if they plan to incorporate ctDNA for patient selection or as an endpoint in early-stage solid tumor clinical trials. The following are potential uses for ctDNA:

A. ctDNA for Patient Selection based on Molecular Alteration:

In the adjuvant treatment setting, patients typically receive curative local therapy followed by systemic treatment to prevent disease recurrence. In this situation, sampling a patient's plasma can allow for detection of ctDNA and for potential

[4] Powles, T., Assaf, Z.J., Davarpanah, N. et al. ctDNA guiding adjuvant immunotherapy in urothelial carcinoma. Nature (2021); Tie J, et al. Sci Transl Med. 2016; 8(346); Garcia-Murillas et al. JAMA Oncol. 2019; 5(10): 1473-1478; Chaudhuri et al. Cancer Discovery 2017; 7: 1394 – 1403; Christensen et al. J Clin Oncol 2019; 37: 1547 – 1557; Reinert, Henriksen et al. Analysis of Plasma Cell-Free DNA by Ultradeep Sequencing in Patients with Stages 1 to III Colorectal Cancer. *JAMA Oncol*. 20195(8): 1124-1131; Coombes, Page et al. Personalized Detection of Circulating Tumor DNA Antedates Breast Cancer Metastatic Recurrence. *Clin Cancer Res* 2019. Jul 15; 25(14): 4255-4263; Abbosh Birkbak et al. Phylogenetic ctDNA analysis depicts early-stage lung cancer evolution. *Nature 2017*.

selection of a patient population harboring genetic or epigenetic alterations that could be targetable by a given drug under study.

- ctDNA can be used as patient selection for detection of alterations for eligibility criteria for a clinical trial.
- ctDNA can also be used as a stratification factor if a trial enrolls both a marker-positive and marker-negative population. Hierarchical testing procedures with the control of Type-I error rate may allow testing of multiple ordered endpoints in both the intent-to-treat population and biomarker-selected (ctDNA-positive) subgroup.
- The sensitivity of the ctDNA assay for detecting all variants of clinical interest contained within tumor tissue (i.e. discordance between ctDNA and tumor assays) should be evaluated. If no variants are detected in ctDNA, tumor testing may need to be performed to confirm the negative result.

B. ctDNA Molecular Residual Disease for Patient Enrichment:

ctDNA can be used as a marker of MRD after definitive surgery and/or after (neo)adjuvant therapy to enrich a trial for patients with higher risk disease and increased events of disease recurrence or death.

- ctDNA testing after surgery or (neo)adjuvant therapy could determine study eligibility of a biomarker positive population.
- ctDNA status at baseline could alternatively be used as a stratification factor in a study enrolling both ctDNA negative and positive patients. Hierarchical testing procedures could be performed to test both the intent-to-treat population (including both the ctDNA positive and negative group) as well as just the ctDNA positive group.
- Design options could include an escalation design of adding an experimental therapy to standard of care compared to standard of care alone for patients with ctDNA positive status (higher-risk) or a de-escalation design based on ctDNA negative status (lower risk population). The clinical trial should be randomized.
- Primary endpoint should be Disease-free survival (DFS) if only adjuvant therapy is given or Event-free survival (EFS) if neoadjuvant therapy is given (with or without adjuvant therapy), or OS (Overall Survival).[5]
- There should not be any early interim analyses of the primary endpoints due to limited events. Later interim analyses may be considered however these should be pre-specified near the start of the trial, adjusted for the multiple testing and set at a reasonable point with robust data maturity. For example, it would be expected that most

[5] See guidance for industry *Clinical Trials Endpoints for the Approval of Cancer Drugs and Biologics* (December 2018).

patients should have completed treatment prior to any interim analyses being conducted.

C. ctDNA as a Measure of Response

- ctDNA could be used in early phase clinical trials to aid in signal finding of drug activity and to potentially aid sponsors in their drug development plans.
- FDA encourages Sponsors to develop evidence regarding the usefulness of ctDNA response in addition to or supporting pathologic complete response information after neoadjuvant therapy.

D. ctDNA as an Early Endpoint in Clinical Trials:

Although not currently validated for use, changes in ctDNA in response to a drug may have the potential to be used as an early endpoint to support drug approval in the early-stage cancer setting.

- Further data are required to support the use of ctDNA as an endpoint reasonably likely to predict long term outcome (DFS/EFS/OS).
- Trials that collect ctDNA data before and after drug treatment should also collect long term outcome data to characterize the association between ctDNA clearance and outcome.
- Various statistical criteria have been proposed for validating an endpoint and often meta-analytical approaches have been used. [6] An appropriate meta-analysis to validate ctDNA at a trial level association should include only randomized trials. Sponsors should discuss and provide details of any proposed meta-analysis plan to validate use of ctDNA in a particular context of use with the FDA.
    - The plan should include details of trial designs, inclusion and exclusion criteria, ctDNA assessment methods, and disease setting. A justification for the suitability of pooling the studies should be provided.
    - Trials should include a patient population representative of the population in which the endpoint ultimately will be used.
    - An adequate number of randomized trials with sufficient follow-up time should be included and justified.
    - Analysis based on individual patient-level data should allow an assessment of individual-level association.
    - Prespecified criteria for concluding association based on both trial-level and individual -level association measures, including prespecified timing and window of ctDNA assessment should be provided.

[6] For additional information on meta-analyses, see the draft guidance for industry *Meta-analyses of Randomized Controlled Clinical Trials to Evaluate the Safety of Human Drugs or Biological Products (*November 2018). When final, this guidance will represent FDA's current thinking on this topic.

- Long-term clinical endpoints, such as EFS/DFS and OS that have been clearly and consistently defined across studies should be included.
- Sponsors should explore the effects of missing data on trial results.

IV. ASSAY CONSIDERATIONS

A. Types of Molecular Residual Disease Panels

MRD panels can utilize tumor-informed methods, tumor-naïve methods, or a smaller panel of candidate genes each with its own strengths and limitations as summarized below:

- Tumor-informed panels are constructed by sequencing the tumor and then selecting a set of variants to follow.
  - Limitations of this approach include lag time between tumor testing and ctDNA panel creation, and sensitivity and specificity may depend on clinical cutoffs and analytical sensitivity of the device as well as the number of tumor informed targets assayed.
- Tumor-naïve or "tumor-agnostic" panels are those that are not informed by sequencing or by mutations of the primary tumor. This approach uses panel-based next generation Sequencing (NGS) to ascertain MRD.
  - Limitations include tumor markers not covered by the ctDNA panel and additional characterization of panels would be needed to understand what percentage of patients are trackable with such techniques.
  - Whole genome sequencing (WGS) could potentially be used in a tumor-naïve fashion. This would allow the use of other biomarkers besides mutations, epigenetic alterations (e.g. methylation) or fragmentomic analysis of ctDNA to capture tumor derived ctDNA signals.

Multiple markers on a candidate gene panel could help assure that the MRD assay will serve its function, even with the development of additional cytogenetic changes.

B. Sampling Considerations

There are several sampling considerations related to the clinical trial design and the intended use patient population that should be taken into account.

- The shedding of ctDNA is affected by histology, grade, stage, and size of the tumor thus timing of ctDNA testing should be discussed with the FDA and should be supported by performance characteristics of the test, disease characteristics and tumor biology.

- A set time point should be chosen for enrollment into the study and pre-specified.
- If a sponsor wishes to use multiple ctDNA time points to determine eligibility (e.g. screening paradigm evaluating if intervention at early detection of recurrence would influence outcome) this should be supported by scientific data/rationale. Sensitivity analyses based on different time windows could be explored (but should be predetermined and discussed in advance).
- The timing of ctDNA testing should be the same across study arms.
- A baseline pre-treatment sample should be collected to allow for consideration of the impact of variation in tumor shedding rates on assay performance. In addition, this sample will allow for interpretation of the post-treatment sample for study enrollment.
- All sites in the study should follow standardized protocols for sample collection, storage, and processing and handling.

C. Assay analytical validation considerations for marketing applications

Analytical validation ensures that the assay measures the analyte or analytes that it is intended to measure in the intended tumor type. Analytical validation should be conducted to establish the performance characteristics of the assay. Validation studies should be acceptable in terms of the assay's sensitivity, specificity, accuracy, precision, and other relevant performance characteristics using a specified technical protocol, which may include specimen collection, handling, and storage procedures.[7] The acceptance criteria for the validation studies should be adequately justified to support clinical use.

- MRD assay validation should encompass the entire assay system from sample collection (e.g., blood collection in the specific collection tube that will be used with the final market ready assay) to the output of the assay including the detection threshold (cut-off) that determines positive vs negative patients. The cutoff should be established appropriately (e.g., both in terms of allelic frequencies or mutant molecules of the variants per ml of plasma and number of variants that are required to be positive in personalized panels for MRD positivity).
- The assay cutoff should be established to optimize assay sensitivity and specificity for the clinical use. Analytical performance should be robust to detect MRD positivity accurately and reproducibly.
- The assay should have high sensitivity and negative predictive value (NPV) for supporting de-escalation of treatment and high specificity and positive predictive value (PPV) for supporting escalation of treatment.
- The validation approach of an MRD test will depend on the type of MRD testing modality. As noted in section IV A., there are different

[7] Summary of Safety and Effectiveness Data (SSED) for the Guardant360 CDx PMA P200010: https://www.accessdata.fda.gov/cdrh_docs/pdf20/P200010B.pdf

types of MRD testing approaches that are currently under development. For tumor-naïve NGS-based MRD panels, panel-based validation of fixed panel content will be needed; however, for tumor-informed NGS-based personalized panels, the panel content will vary for each patient and therefore the assay validation will be based on each personalized assay. The validation strategy to support the device marketing application should be discussed with CDRH/FDA.

- Samples from clinical trials (clinical specimens) are recommended to be used for key assay validation studies such as confirmation of the assay limit of detection (LoD), assay precision, analytical accuracy, assay input studies. In some analytical validation studies since a large volume of sample will be needed, clinical samples may be supplemented by contrived samples. In general, when using contrived samples in assay validation studies, the functional equivalency between the contrived and clinical samples should be demonstrated and rationale should be provided if contrived samples are used to substitute or supplement clinical samples in certain studies.
- For fixed panels, cell lines carrying the specific alterations (i.e., cell line DNA spiked into an appropriate matrix) may be used as contrived samples. For personalized assays, cell lines that represent a distribution of the number and type of variants based on early clinical study data should be developed.
- Assay precision should be demonstrated using samples across the detection range of the assay including samples at the assay cutoff and samples with the minimum analyte requirements.
- An appropriate set of reference materials should be developed to allow for comparability across multiple MRD assays.

V. INVESTIGATIONAL DEVICE CONSIDERATIONS

- The investigational ctDNA device used in the trial is subject to FDA's investigational device exemption (IDE) regulations as well as 21 CFR parts 50 and 56.[8]
- Whether the sponsor needs to submit an IDE application is dependent on whether the device used in the trial is considered significant risk (SR), non-significant risk (NSR), or exempt.[9]
- Sponsors can submit a Study Risk Determination pre-submission through CDRH's Q-submission program.[10]

[8] See 21 CFR 812.

[9] See guidance for industry *Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors. Significant Risk and Nonsignificant Risk Medical Device Studies* (January 2006).

[10] See guidance for industry and FDA staff *Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program* (January 2021).

- The sponsor may also seek a risk determination through the optional streamlined submission process for investigational devices in oncology trials for new INDs.[11]

[11] See guidance for industry *Investigational In Vitro Diagnostics in Oncology Trials: Streamlined Submission Process for Study Risk Determination* (October 2019).