Cooley

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On May 3, 2022, the US Food and Drug Administration issued a draft guidance document on the Use of Circulating Tumor DNA for Early-Stage Solid Tumor Drug Development. The guidance is aimed at helping developers use circulating tumor DNA (ctDNA) as a biomarker in early-stage solid tumor clinical trials and in seeking market approval for in vitro diagnostic assays.

What you need to know about ctDNA

As a tumor-derived fragmented DNA circulating in a patient's bloodstream that is not associated with cells, ctDNA originates directly from the tumor or circulating tumor cells, and can reflect part or all of the tumor genome. Its quantity depends on the type of tumor, location, stage, tumor burden and response to therapy. Due to these features, ctDNA is used in "liquid biopsies" to detect tumors, monitor tumor progression and detect molecular residual disease (MRD), which refers to tumor cells that remain in patients in remission during or after treatment (a major cause of cancer relapse). For the same reason, ctDNA also can serve as a valuable biomarker in clinical trials of early-stage solid tumor drugs.

The approaches and technologies used for ctDNA assessment vary among clinical laboratories, and can produce inconsistent results, which can affect the reliability of ctDNA's regulatory uses.

Regulatory uses of ctDNA as a biomarker

In the draft guidance, the FDA has put forward four main uses for ctDNA as a biomarker in early-stage solid tumor clinical trials, involving patient selection, patient enrichment, measure of response and early endpoint. Sponsors are encouraged to consult the FDA if they plan to incorporate ctDNA for patient selection or as an endpoint.

1. **For patient selection based on molecular alteration –** ctDNA can be used to set eligibility criteria for clinical trials to target certain genetic or epigenetic alterations in patients, and as a stratification factor to specify patient subgroups. For these uses, the FDA recommends evaluation of the sensitivity of ctDNA assay for detecting all variants of clinical interest contained within tumor tissue, and confirmatory tumor testing if no variants are detected.
2. **As a marker of MRD for patient enrichment –** ctDNA can be used as a marker of MRD after treatment to enrich a trial with patients who have a higher-risk disease and increased incidents of disease recurrence or death. For such a trial, the primary endpoint should be disease-free survival if only adjuvant therapy is given, event-free survival if neoadjuvant therapy is given, or overall survival, and there should not be any early interim analyses of the primary endpoint due to limited events.
3. **As a measure of response –** ctDNA can be used in early-phase clinical trials to signal drug activity. The FDA encourages sponsors to develop evidence regarding the usefulness of ctDNA response after neoadjuvant therapy.
4. **As an early endpoint in clinical trials –** The FDA recognizes that changes in ctDNA in response to a drug may have the potential to be used as an early endpoint to support drug approval. The agency gives specific guidelines on what type of evidence could be used to validate this use, and requests that sponsors discuss their validation plans with the FDA. Trials should collect ctDNA before and after drug treatment, as well as long-term data.

Assay and investigational device considerations

For assays, the FDA puts forward considerations for types of MRD panels, sampling and assay analytical validation for marketing applications. The draft guidance lists strengths and limitations of MRD panels utilizing tumor-informed methods, tumor-naive methods and a smaller panel of candidate genes. It encourages sponsors to discuss with the FDA the timing of ctDNA testing, which should be supported by performance characteristics of the test, disease characteristics and tumor biology. It also includes detailed instructions for conducting analytical validation to establish the performance characteristics of ctDNA assay.

Sponsors using ctDNA technology for in vitro diagnostic devices that may be used in clinical trials for oncology therapeutics also are invited to take advantage of the FDA's streamlined submission process for investigational devices in oncology trials. This process enables sponsors to submit information about the investigational device in an Investigational New Drug (IND) submission. As part of the IND review, CBER or CDER will consult with CDRH or CBER, as appropriate, to determine the investigational device's risk level and the corresponding requirements applicable for such devices under the FDA's investigational device exemption regulations.

Our recommendations

Manufacturers developing early-stage solid tumor drugs or considering the use of ctDNA in drug development should review the draft guidance closely. The agency is accepting public comments on this guidance through July 5, 2022. If you are contemplating any uses for ctDNA that are not covered by this guidance, consider working with your Cooley team to submit a comment asking the FDA to include your use case, which may potentially reduce your regulatory burden in the future.

Cooley summer associate Sarah Miller also contributed to this alert.

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