

Capturing immunotherapy response in a blood drop

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An impressionist painting of a liquid biopsy. Credit: Valsamo Anagnostou x DALL-E, openAI

Liquid biopsies are blood tests that can serially measure circulating tumor DNA (cell-free DNA that is shed into the bloodstream by dying cancer cells). When used in patients with advanced non-small cell lung cancer undergoing immunotherapy, they may identify patients who could benefit from treatment with additional drugs, according to a phase 2 clinical trial in the U.S. and Canada.

The trial is led by investigators at the Johns Hopkins Kimmel Cancer Center and its Bloomberg~Kimmel Institute for Cancer Immunotherapy, BC Cancer and the Canadian Cancer trials Group (CCTG). The results, [published October 9 in the journal *Nature Medicine*](#), suggest that ctDNA analyses could be used as an early marker of immunotherapy response and may help guide therapy.

Immunotherapies are drugs which unharness the power of the immune system against cancers. Despite their success in improving survival, they pose a challenge to the standard use of imaging to determine [treatment response](#) because changes in imaging may not always reflect how well immunotherapy is working.

Liquid biopsies may help determine which patients are benefiting from available immunotherapies and could be a new endpoint for [clinical trials](#) testing these treatments. Although initial reports are promising, how these approaches can best be used has not been established through a clinical trial.

The BR.36 clinical trial (NCT04093167) is designed to establish the role of ctDNA as an early measurement of immunotherapy response by first,

defining ctDNA response, its timing and how it compares with the gold standard of imaging tests and then by using ctDNA response to guide treatment for patients with advanced non-small cell lung cancer.

The first stage of the BR.36 trial found that by serial testing ctDNA using next-generation sequencing (an advanced technology that can rapidly sequence millions of gene targets), immunotherapy responses were detected early, within an average of eight weeks after treatment started. A ctDNA response (ctDNA no longer detected in the blood) reflected tumor shrinkage by imaging, however, there were notable exceptions that showed that ctDNA response may capture survival more accurately, especially for patients with stable disease on imaging.

Compared to patients who did not have a ctDNA response, patients with a ctDNA response had a longer progression-free survival (the time in which the disease does not worsen), a difference of 2.6 months versus 5.03 months respectively. In addition, patients with a ctDNA response had a longer overall survival, with median survival not reached at the time of analysis.

"There is an unmet clinical need to implement real-time, minimally invasive molecular analyses to understand patients' responses to cancer treatments and guide clinical decision-making," says lead study author Valsamo "Elsa" Anagnostou, M.D., Ph.D., director of the thoracic oncology biorepository at Johns Hopkins, leader of Precision Oncology Analytics, co-leader of the Johns Hopkins Molecular Tumor Board and co-director of the Lung Cancer Precision Medicine Center of Excellence.

"Our study demonstrates that ctDNA response correlated with tumor size seen on imaging, which is the gold standard for monitoring response to cancer treatments and seemed to be better correlated with survival. This suggests ctDNA could be used as a strategy to identify patients at high

risk of disease progression who could benefit from a switch in their therapeutic regimen."

Investigators hypothesized that liquid biopsies would rapidly and accurately predict outcomes for patients. During the first stage of the BR.36 study, investigators enrolled 50 patients with advanced or metastatic non-small cell lung cancer at six medical centers in the U.S. and Canada, between May 2020 and September 2022.

Nearly all patients had been smokers, and 92% received no prior therapies. The group was 82% white, 52% female and 56% age 65 or older. The goals were to identify the optimal timepoint for ctDNA molecular response and to see how well molecular response correlated to response evaluation criteria in solid tumors (RECIST), the standard for measuring response to cancer treatment by monitoring changes in tumor size as seen on imaging.

Patients received the immunotherapy drug pembrolizumab based on standard of care, at a 200 mg or 2 mg/kg infusion every three weeks. After the first three cycles, investigators could switch to a 400 mg or 4 mg/kg infusion every six weeks. Patients remained in the trial until they received 24 months of therapy, had unacceptable drug toxicity, or imaging tests revealed progression of disease.

Investigators performed RECIST response assessments every six weeks until week twelve, and at longer intervals thereafter. They also collected blood samples from patients prior to treatment administration on the first day of the first cycle (baseline), the first day of the second cycle (three weeks into treatment) and the first day of the third cycle (six weeks) of treatment. These were used to conduct a ctDNA response assessment at these timepoints and to define molecular response as ctDNA clearance on the first day of the third cycle of treatment with pembrolizumab.

Analyses of molecular response were assessed using the Personal Genome Diagnostics (PGDx) elio liquid biopsy platform, which "represents an exciting opportunity for tailoring immunotherapy to enhance the interpretation of patterns of tumor response and progression during treatment," states Mark Sausen, Ph.D., executive director and head of technology innovation, PGDx, Labcorp.

"ctDNA response is particularly informative to understand the complexity of stable disease on imaging, which represents a sizable fraction of patients in whom imaging fails to timely and accurately detect the magnitude of therapeutic response," Anagnostou says.

Implementing the results from the first stage of the BR.36 trial, investigators moved forward with the second stage of the trial, in which they will evaluate the potential clinical benefit of tailoring treatment for patients with lung cancer based on their ctDNA responses after two cycles of pembrolizumab treatment. ctDNA response will be used to identify patients with lung cancer at high risk for disease progression, who will be subsequently randomized to treatment intensification with pembrolizumab and chemotherapy versus continuation of pembrolizumab.

"The Cancer Research Institute (CRI) is pleased to invest in Stage 2 of this clinical trial," says Jay Campbell, managing director of the CRI Anna-Maria Kellen Clinical Accelerator.

"This is being designed as a registrational study, meaning if the study meets its primary endpoint, the ctDNA detection assay used in the BR.36 study could be approved. This could lead to molecular assessment by liquid biopsies becoming the standard means of assessing whether first-line patients with non-small cell lung cancer are responding to cancer immunotherapies, compared to conventional radiographical assessment of response."

Janet Dancey, M.D., director of the Canadian Cancer Trials Group, states, "ctDNA has the potential to improve our ability to advise patients on the best treatment options for them. It may be better than traditional imaging in determining changes to treatments or providing assurance that patients should continue their current treatment. Our initial study indicates promising results, and we will move forward with a larger trial to clearly show whether ctDNA monitoring provides useful information based on treatment recommendations."

More information: ctDNA response after pembrolizumab in non-small cell lung cancer: phase 2 adaptive trial results, *Nature Medicine* (2023). [DOI: 10.1038/s41591-023-02598-9](https://doi.org/10.1038/s41591-023-02598-9) , www.nature.com/articles/s41591-023-02598-9

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