Circulating tumor DNA levels predict outcomes for gastroesophageal cancer treated with immunotherapy

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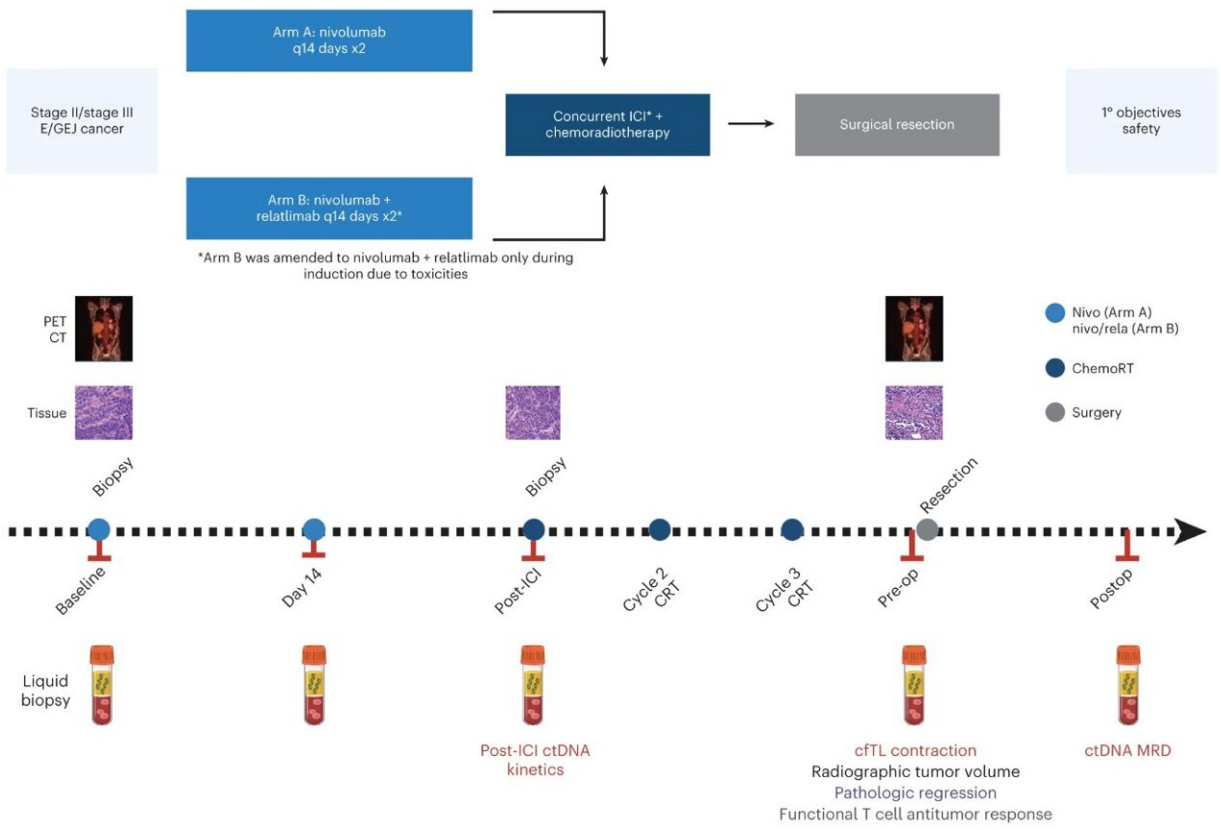

Clinical trial schema, CONSORT flow diagram and patient characteristics.
Credit: *Nature Medicine* (2024). DOI: 10.1038/s41591-024-02877-z

Monitoring levels of DNA shed by tumors and circulating in the

bloodstream could help doctors accurately assess how gastroesophageal cancers are responding to treatment, and potentially predict future prognosis, suggests a new study led by researchers at the Johns Hopkins Kimmel Cancer Center and its Bloomberg–Kimmel Institute for Cancer Immunotherapy.

The study tracked minimal residual disease (the amount of cancer left following treatment) by analyzing circulating tumor DNA (ctDNA), showing how these "liquid biopsies" can provide valuable insights into treatment outcomes over time. Absence of ctDNA was seen occurring together with specific activation of T cells that are part of the immune system's defense to recognize and fight cancer.

"We found that the elimination of ctDNA was a good indicator of patients' cancer-free survival," says Valsamo "Elsa" Anagnostou, M.D., Ph.D., senior co-author of the study and associate professor of oncology and director of the thoracic oncology biorepository at Johns Hopkins.

Anagnostou is also 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 at Johns Hopkins. "We were gratified to see tumor shrinkage at a molecular level together with the immune system flaring up and clearing the tumor," she says.

The findings, reported in a paper published March 19 in *Nature Medicine*, emerged from a clinical trial examining the safety and efficacy of two immunotherapy drugs—nivolumab and relatlimab—as part of pre-operative treatment for patients with operable esophageal and gastroesophageal junction cancer.

Patients with gastroesophageal cancer who have successfully completed the standard treatment of chemoradiotherapy followed by surgery unfortunately often see a resurgence of the disease. Therefore,

researchers are looking for new immunotherapy approaches, as well as more accurate ways to assess tumors' response to treatment.

"Immunotherapy has not yet been broadly effective for patients with gastroesophageal cancer," says senior study co-author Vincent Lam, M.D., director of the Esophageal Cancer Research Program and an assistant professor of oncology at Johns Hopkins.

"By testing new treatments in patients prior to surgery, we can make these powerful observations linking treatment-induced molecular changes with survival outcomes, thus accelerating the development of different immunotherapy approaches for our patients."

The trial included 32 patients with operable esophageal or gastroesophageal junction cancer, who received nivolumab either alone or in combination with relatlimab prior to and during their standard treatment of chemotherapy and radiation. The drugs tested are both immune checkpoint inhibitors, which prevent cancer cells from dampening the body's anti-cancer immune response.

Researchers used liquid biopsies—tests that monitor trace levels of tumor DNA shed into the bloodstream—at different timepoints during treatment. They also measured levels of tumor-recognizing T cells and other components of tumor-specific immune responses.

About 40% of those in the nivolumab arm and 21.4% in the combination arm had a pathological complete response, meaning there was no evidence of cancer at the time of surgery. Over half of patients in both arms had a major pathological response, meaning less than 10% of cancer cells were remaining at the time of surgery.

"Historically, about two-thirds of patients treated with standard chemoradiation prior to surgery are alive after two years," Lam says. "In

our study, some 72.5% of participants had no signs of cancer and 82.6% were still living after two years. Notably, patients with undetectable ctDNA at different timepoints following immunotherapy had significantly longer cancer-free survival."

The findings "open the door for more personalized treatment," says lead study author Ronan Kelly, M.D., M.B.A., chief of oncology at Baylor Scott & White Health—North Texas. Kelly was at Johns Hopkins at the time of the study.

"We can either de-escalate or intensify the treatment for patients who have gone through the standard protocol," he says. "If we see ctDNA is still there, and they don't have robust T cell response, these are the patients who may benefit most from additional treatment."

The study adds to a growing collection of evidence showing the value of molecular readouts like ctDNA to assess response to therapy and guide future treatment plans. For example, another recent study from Anagnostou's lab, along with a ctDNA-adaptive clinical trial led by Johns Hopkins investigators, showed that ctDNA clearance can predict the success of immunotherapy treatment in patients with advanced lung cancer.

"You can imagine that liquid biopsies may be used to capture and monitor cancer spread in the body and determine tumor regression across all types of cancers and therapies. There's ever-growing evidence to support the use of ctDNA in the full range of the cancer care continuum," says Anagnostou. "We think it's the future."

More information: Ronan J. Kelly et al, Neoadjuvant nivolumab or nivolumab plus LAG-3 inhibitor relatlimab in resectable

esophageal/gastroesophageal junction cancer: a phase Ib trial and ctDNA analyses, *Nature Medicine* (2024). DOI: 10.1038/s41591-024-02877-z