Simultaneous radiation and immunotherapy found to be beneficial for a subset of lung cancer patients

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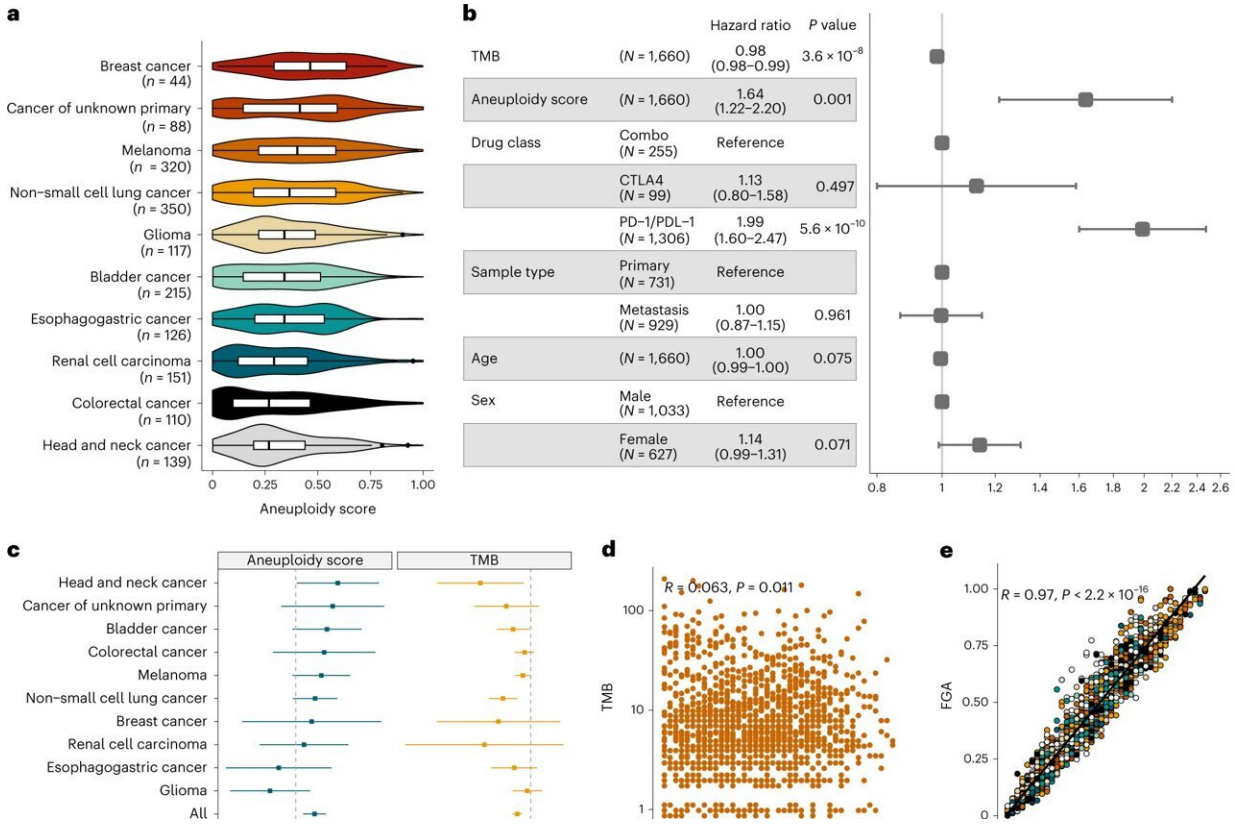

Aneuploidy and TMB are synergistic predictors of survival following immunotherapy. Credit: *Nature Genetics* (2022). DOI: 10.1038/s41588-022-01235-4

In many cancer types, cancer cells try to survive by escaping attack from the immune system. These cancer cells hijack mechanisms called immune checkpoints to trick the immune system into thinking they are healthy cells. Recent advances in cancer treatment have focused on developing immune checkpoint blockers, which have revolutionized treatment approaches for many cancer patients, including those with metastatic non-small-cell lung cancer (mNSCLC).

Unfortunately, only a fraction of patients have benefited, and a large percent of cancer patients are still in need of better treatment. A number of studies in animals have shown that adding radiation therapy (RT) to immune checkpoint blockade (ICB) has yielded positive outcomes; however, this combination therapy has not been proven in humans. Now, the big clinical question is whether and how RT and ICB can be combined to yield positive outcomes in mNSCLC patients.

In a recently published *Nature Cancer* paper, UChicago Medicine researchers have identified the first biomarker that predicts response to the RT and ICB treatment combination. Aneuploidy is a condition where tumor cells exhibit either missing or extra chromosomes. In the current study, mNSCLC patients with high tumor aneuploidy were found to have significantly better survival if RT was added to ICB. By contrast, there was no survival benefit for patients with low aneuploidy when adding RT to ICB treatment.

Moreover, the researchers demonstrated that radiotherapy to metastatic sites concomitant with, but not before or after, ICB improves survival in patients with high aneuploidy tumors, according to Sean Pitroda, MD, Assistant Professor of Radiation and Cellular Oncology at UChicago Medicine and the senior author of the paper.

To evaluate the differences in clinical and genomic parameters between sequential (radiation therapy followed by ICB therapy) and concurrent

(radiation therapy while ICB is on-board) therapies, 37 patients with mNSCLC were enrolled in a randomized phase 1 clinical trial. Tumor tissue samples that were analyzed before and during treatment showed radiation therapy alone is less effective in tumor cell elimination as compared to simultaneous radiation and immunotherapy.

"A key observation was that radiation therapy alone caused depletion of important immune cells within the tumor, however, with concurrent therapy there was enrichment of immune cells and improved elimination of tumor cells that led to positive survival outcomes in mNSCLC patients," Pitroda said.

He described that in concurrent treatment, immunotherapy takes the brakes off of the immune cells that would not normally recognize the cancer because cancer has ways to hide from the immune system. Essentially, immunotherapy is unmasking cancer cells and helping those immune cells hone in on the tumor to fight the cancer.

"By giving immunotherapy with radiation, we believe that radiation becomes more effective at killing tumor cells by helping immune cells find the damaged tumor that's dying off," he said. "Our findings highlight that radiation therapy alone is not enough to trigger a localized immune response in mNSCLC and the timing of radiation and immunotherapy is critical to this process," said Pitroda.

The concept of tumor aneuploidy has been of increasing interest to researchers and other work has shown a connection between aneuploidy and the immune system, but exactly how it can be used to improve cancer treatments had not been identified. Liam Spurr, a current medical student at the University of Chicago Pritzker School of Medicine and first author of these studies, had previously developed an algorithm that quantifies the degree of aneuploidy in patients' tumors when they undergo DNA sequencing. Together, the investigators came up with the

hypothesis that perhaps aneuploidy could be useful in determining which tumors might respond better to immunotherapy.

Based on their findings in the *Nature Cancer* study, the team further tested whether aneuploidy could have utility as a biomarker for predicting survival in another study published in *Nature Genetics*, where a larger cohort consisting of 1,660 patients with a wide range of cancer types who have been treated with immune checkpoint blockers were re-analyzed.

Tumors with a high degree of aneuploidy had a worse prognosis because these patients did not respond to immunotherapy alone. In addition, tumor aneuploidy complemented tumor mutational burden (TMB)—an established biomarker across many cancers for immunotherapy response. Patients with high TMB often respond well to immunotherapy, and patients with low TMB usually do not.

"For low TMB tumors, you look for another biomarker, like aneuploidy, to improve your prediction of immunotherapy response. The ones that have the worst survival after immunotherapy are the ones that have low TMB and high aneuploidy scores and those are probably the patients that need something more than immunotherapy, like radiation, to improve their treatment response and outcomes," Sean Pitroda said.

Immunotherapy has completely revolutionized how we treat many types of cancer. Some cancers are fatal, especially when they become metastatic, but now people can live for a long time and a fraction can even be cured with immunotherapy. Many patients, however, do not respond to immunotherapy and better strategies are required to improve outcomes, potentially by combining immunotherapies with other cancer treatments like radiation or chemotherapy.

The current study identified a completely new way to predicts patients'

response to immunotherapy and proposed that adding radiation to those who do not respond to immunotherapy alone can improve outcomes.

Pitroda said, "We have the first method to personalize therapy—to choose the right therapy for the right patient at the right time—employing radiation and immunotherapy."

More information: Sean Pitroda, Tumor aneuploidy predicts survival following immunotherapy across multiple cancers, *Nature Genetics* (2022). DOI: 10.1038/s41588-022-01235-4. www.nature.com/articles/s41588-022-01235-4

Sean Pitroda, Highly aneuploid non-small cell lung cancer shows enhanced responsiveness to concurrent radiation and immune checkpoint blockade, *Nature Cancer* (2022). DOI: 10.1038/s43018-022-00467-x. www.nature.com/articles/s43018-022-00467-x

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