Dual immunotherapy plus chemotherapy before surgery improves patient outcomes in operable lung cancer

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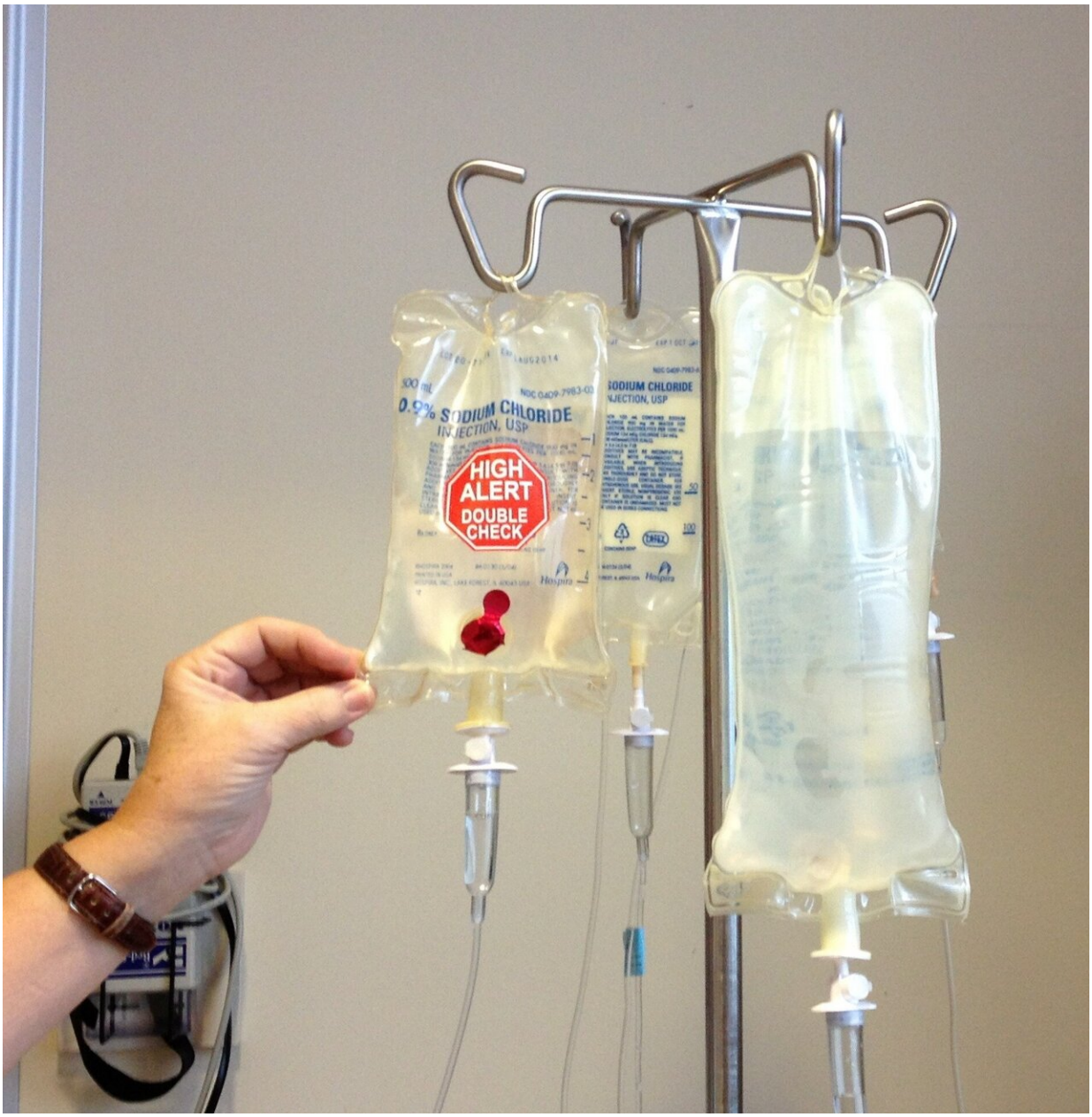

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In a Phase II trial led by researchers from The University of Texas MD Anderson Cancer Center, adding ipilimumab to a neoadjuvant, or pre-surgical, combination of nivolumab plus platinum-based chemotherapy,

resulted in a major pathologic response (MPR) in half of all treated patients with early-stage, resectable non-small cell lung cancer (NSCLC).

New findings from the NEOSTAR trial, published today in *Nature Medicine*, provide further support for neoadjuvant immunotherapy-based treatment as an approach to reduce viable tumor at surgery and to improve outcomes in NSCLC. The combination also was associated with an increase in immune cell infiltration and a favorable gut microbiome composition.

The current study reports on the latest two arms of the NEOSTAR trial, evaluating neoadjuvant nivolumab plus chemotherapy (double combination) and neoadjuvant ipilimumab plus nivolumab and chemotherapy (triple combination). Both treatment arms met their prespecified primary endpoint boundaries of six or more patients achieving MPR, defined as 10% or less residual viable tumor (RVT) in the resected tumor specimen at surgery, a candidate surrogate endpoint of improved survival outcomes from prior studies.

In the intention-to-treat population, the triple combination resulted in an MPR rate of 50%, whereas 32.1% of patients achieved MPR after double combination treatment. Both treatment arms also exceeded the historical MPR rates of 15% achieved by neoadjuvant chemotherapy alone.

"The results we see with neoadjuvant dual immunotherapy and chemotherapy are very encouraging," said corresponding author Tina Cascone, M.D., Ph.D., assistant professor of Thoracic/Head & Neck Medical Oncology.

"This is a population of patients that can potentially be cured, but they need more effective treatment strategies to reduce their risk of disease

relapse and improve their outcomes. The NEOSTAR platform provides us with a quick readout of potentially effective regimens and allows us to perform translational analyses and correlative research work before and after treatment."

Among patients diagnosed with NSCLC, roughly 30% have potentially resectable disease, meaning their tumor can be surgically removed. While many of these patients can potentially be cured with surgery, it is estimated that more than half will have a recurrence without additional therapy. Unfortunately, chemotherapy given either before or after surgery provides only a minimal survival benefit.

Previous reports from the NEOSTAR trial demonstrated that neoadjuvant nivolumab plus ipilimumab induced higher MPR rates relative to historical controls of chemotherapy and nivolumab alone and resulted in greater immunological memory relative to nivolumab monotherapy.

Triple combination reduces viable tumor, enhances markers of immune activation

Each arm enrolled 22 patients with surgically resectable stage IB to IIIA NSCLC between December 2018 and December 2020. In the double combination arm, participants were 86% White, 14% Asian, and 45% male; in the triple combination arm, participants were 82% White, 5% Asian, 14% Black, and 68% male.

The NEOSTAR trial was not designed for direct comparisons between arms, but an exploratory analysis of clinical and pathological findings showed that adding a single dose of ipilimumab resulted in an increase in beneficial tumor immune cell infiltration and reduced RVT at surgery.

Patients treated with the triple combination had a median of 4.5% RVT

at surgery, compared to 50.5% RVT in patients treated with the double combination. All patients achieving MPR in the triple combination cohort and 86% of those achieving MPR in the double combination cohort had less than 5% RVT at surgery. All patients treated with the double combination and 91% of those treated with the triple combination underwent surgery. No new safety signals were observed in both treatment arms.

Further analyses showed treatment with the triple combination resulted in an increase in tumor-infiltrating lymphocytes—including subtypes of CD8+ T cells and B cells and in markers of specialized immune cell clusters called tertiary lymphoid structures, as well as reduced infiltration of immunosuppressive cells, all of which can be signs of enhanced anti-tumor response.

Upon analyzing the gut microbiome in patients who achieved MPR, the researchers found an enrichment in beneficial bacteria previously associated with favorable responses to immunotherapy in lung cancer, melanoma and other cancer types, along with reduced abundance of potentially pathogenic microbes.

NEOSTAR platform is an effective strategy to rapidly test neoadjuvant therapies

Interestingly, an exploratory comparison indicates some results from the double combination arm of the NEOSTAR trial are similar overall to those seen in the recent Checkmate-816 trial. This global randomized Phase III study evaluated neoadjuvant nivolumab plus chemotherapy compared to chemotherapy alone in patients with resectable NSCLC, and results from the study led to the first FDA-approved neoadjuvant therapy for NSCLC.

Both Checkmate-816 and NEOSTAR showed similar overall MPR rates

and event-free survival benefits from adding neoadjuvant nivolumab to chemotherapy. The similarity between the two trials suggests that the NEOSTAR platform may offer a viable strategy to rapidly evaluate neoadjuvant therapies.

"The modular platform of the NEOSTAR trial provides an opportunity to test promising regimens and quickly make a 'go' or 'no-go' decision," Cascone said.

"This trial is an incredible testament to the team science environment at MD Anderson. Our clinical and multi-omics analyses were made possible through collaborative efforts from clinicians, surgeons, pathologists, scientists, bioinformaticians and statisticians across several departments looking at many features of these patients and their tumors and other samples. Thanks to their incredible work, we are able to rapidly generate results that could guide the next generation of trials to further improve patient outcomes."

The results of these latest two arms of the study support the addition of neoadjuvant CTLA-4 blockade to nivolumab plus chemotherapy prior to NSCLC resection for improving outcomes and suggest that this combination merits further investigation.

More information: Tina Cascone, Neoadjuvant chemotherapy plus nivolumab with or without ipilimumab in operable non-small cell lung cancer: the phase 2 platform NEOSTAR trial, *Nature Medicine* (2023). DOI: 10.1038/s41591-022-02189-0.
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