Clinical trial shows combination immunotherapy treatment effective before lung cancer surgery

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Combination immunotherapy with the anti-PD-L1 monoclonal antibody durvalumab and other novel agents outperforms durvalumab alone in the

neoadjuvant (pre-surgical) setting for early-stage non-small-cell lung cancer (NSCLC), according to researchers at The University of Texas MD Anderson Cancer Center.

The findings, published in *Cancer Discovery*, were first presented at the American Association for Cancer Research (AACR) Annual Meeting 2022.

The multicenter, randomized Phase II NeoCOAST clinical trial evaluated neoadjuvant durvalumab alone and in combination with each of the following novel immunotherapies: the anti-CD73 monoclonal antibody oleclumab, the anti-NKG2A monoclonal antibody monalizumab, and the anti-STAT3 antisense oligonucleotide danvatirsen. While the study was not statistically powered to compare arms, all combinations resulted in numerically higher major pathological response (MPR) rates than with durvalumab monotherapy.

"This study builds on the growing evidence that combination immunotherapy has a role in the neoadjuvant setting for this patient population," said Tina Cascone, MD., Ph.D., associate professor of Thoracic/Head and Neck Medical Oncology and lead author of the study. "Ultimately, we want to give patients a chance to live longer without their cancer returning."

The NeoCOAST trial adds to recent progress in neoadjuvant treatment for NSCLC, including the Phase II NEOSTAR study results published in *Nature Medicine*, which showed nivolumab and ipilimumab together induced higher responses than nivolumab alone, and the March 2022 approval of nivolumab combined with platinum-based chemotherapy from the Checkmate-816 study. The durvalumab combinations tested previously in the Phase II COAST trial were shown to be effective in unresectable stage III NSCLC, providing rationale for testing in earlier stage disease.

The NeoCOAST study enrolled 84 patients with untreated, resectable (>2cm), stage I-IIIA NSCLC, between March 2019 and September 2020. Most patients were male (59.5%) and had a smoking history (89%). The median age was 67.5, and the racial breakdown was 89% white, 6% Black, 2% Asian and 2% other. Eighty-three patients received one 28-day cycle of neoadjuvant durvalumab alone or combined with another therapy.

The primary endpoint was investigator-assessed MPR, defined as ≤10% residual viable tumor cells in the resected tumor tissue and sampled nodes at surgery. The investigators assessed pathological complete response (pCR), or complete disappearance of viable tumor cells, as a secondary endpoint. Exploratory endpoints included tumor, fecal and blood biomarkers.

All combinations had numerically higher rates of MPR and pCR than monotherapy, and there were no statistically significant differences in responses between the combination arms:

- For the patients who received durvalumab monotherapy, MPR occurred in 11.1% and pCR in 3.7%, which is comparable to results from other monotherapy studies.
- MPR rates for combination therapy ranged from 19% (oleclumab) to 31.3% (danvatirsen), and pCR rates ranged from 9.5% (with oleclumab) to 12.5% (with danvatirsen). For combination therapy with monalizumab, MPR was 30% and pCR was 10%.

The safety profile in the durvalumab monotherapy arm (treatment-related adverse events in 34.6% of patients) was similar to previously published data for anti-PD-1/PD-L1 antibodies. No new safety signals were identified with any of the combination regimens (treatment-related adverse events seen in 43.8% to 57.1% of patients).

MPR was associated with baseline tumor PD-L1 expression of ≥1% in the oleclumab and monalizumab combination arms. In the oleclumab (anti-CD73) combination arm, high baseline CD73 expression was associated with pathological tumor regression, and treatment decreased CD73 expression on tumor cells, as previously observed in other studies.

The oleclumab combination also was associated with greater natural killer (NK) and CD8 T cell density in the tumor center on treatment compared with baseline, suggesting an increased infiltration of effector cells in the tumor microenvironment.

Updated translational studies on tumor tissues and blood samples revealed the impact of neoadjuvant treatment on the immune system. Transcriptome analysis on pre- and post-treatment samples showed an upregulation of genes associated with cytotoxicity, tertiary lymphoid structures and lymphocyte recruitment, all indicators of an activated immune response.

The number of patients with no detected circulating tumor DNA (ctDNA) increased progressively from pre-to post-treatment and post-surgery follow up, highlighting the relationship between decreasing ctDNA levels and improved patient outcomes. Notably, surgery was the most effective intervention to result in clearance of ctDNA. Researchers also found an enrichment of beneficial bacteria in the gut microbiome of patients who achieved MPR. These bacteria were previously associated with a favorable immunotherapy response across several cancer types.

"Our study is a testament to how clinical trials designed with translational findings in mind can support the rapid advancement of novel immune-based combinations to larger scale studies," Cascone said. "I'm encouraged by these early findings as we work toward reducing the risk of recurrence and increasing cure rates for patients with early-stage non-small cell lung cancer."

Limitations of the study include the exploratory nature of the endpoints, small sample sizes and investigator-assessed outcomes without central review.

Based on these results and the recent approval of neoadjuvant nivolumab plus chemotherapy, the team has launched a follow-up randomized clinical trial, NeoCOAST-2, with Cascone serving as the global principal investigator. The trial is now enrolling patients with resectable, stage IIA-IIIA NSCLC to receive neoadjuvant durvalumab combined with chemotherapy and either oleclumab or monalizumab or other novel and promising immuno-oncology (I-O) agents, followed by surgery and adjuvant durvalumab plus oleclumab or monalizumab or other I-O agents.

More information: Tina Cascone et al, *Cancer Discovery* (2023). aacrjournals.org/cancerdiscove … 2159-8290.CD-23-0436

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