Editorial

Neoadjuvant immunotherapy for non-small cell lung cancer: can early intervention result in durable clinical benefit?

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Management of patients with locally advanced non-small cell lung cancer (NSCLC) often relies on multimodality treatment that includes surgical resection in appropriate cases and peri-operative chemotherapy with or without radiation therapy. Despite these aggressive measures, the propensity of the disease to relapse has a detrimental effect on survival. The risk of distant relapse following surgical resection increases from 15% in stage IA NSCLC to 60% in stage IIIA disease with a corresponding decrease in 5-year survival from 67% to 25% or less (1). The rationale for the use of peri-operative chemotherapy in potentially resectable NSCLC is to increase the chances of achieving complete surgical resection by reducing tumor size and to eradicate micrometastatic disease and decrease the risk of disease recurrence. However, these measures come at a cost of increased toxicity and add only a modest survival benefit over surgery alone with the absolute risk of death decreasing by approximately 5% at 5 years as a result of adjuvant chemotherapy (2). In view of these limited benefits, there is a pressing need to develop newer approaches for the treatment of locally advanced NSCLC.

Immune checkpoint inhibitors that target programmed death-1 (PD-1) or its ligand (PD-L1) have transformed the treatment of advanced, unresectable NSCLC and are associated with higher response rates and improved overall survival when compared with cytotoxic chemotherapy (3-7). More recently, durvalumab, an anti-PD-L1 antibody, has been shown to improve progression-free survival in unresectable stage III NSCLC when administered as consolidation therapy in patients responding to definitive chemoradiation (8).

The central premise for the use of immune checkpoint inhibitors is to activate a previously suppressed anti-tumor immune response to effect tumor kill. This phenomenon is dependent on interactions between tumor cells and immune cells and results in the generation of a CD8+ T-cell response against tumor antigens. There exists compelling preclinical data to support the use of neoadjuvant immunotherapy as opposed to its use in the adjuvant setting. In a murine model of triple-negative breast cancer (TNBC) it has been shown that neoadjuvant administration of an anti-PD-1/CD137 antibody is associated with the generation of a strong tumor-specific CD8+ T-cell response and results in longer survival as compared with administration of the same drug as adjuvant therapy (9). Plausible explanations for these observations include a greater chance of interaction between tumor cells and immune cells in the presence of a larger tumor before surgery and the presence of a wider repertoire of tumor neoantigens in treatment-naïve tumors resulting in the generation of a strong anti-tumor immune response and early development of immunological memory that could potentially eliminate micrometastatic disease and improve survival. Preliminary data from ongoing phase I trials evaluating immune checkpoint inhibitors in patients with stage III melanoma and locally advanced TNBC has shown high pathological complete response rates and low rates of tumor relapse (10,11).

Neoadjuvant immunotherapy is under active investigation

in patients with potentially resectable NSCLC. In one of the first published studies in this patient population, Forde *et al.* have evaluated the safety and feasibility of pre-operative PD-1 blockade in patients with untreated, resectable, stage I–IIIA NSCLC (12). Twenty-two patients were enrolled in this pilot study and received two preoperative doses of nivolumab, with the second dose administered not more than 29 days prior to surgery. The majority of patients had stage II or IIIA disease (81%) and 86% of patients were current or former smokers. In addition to clinical, radiological and pathological assessment of response, immunologic and genomic studies were performed on blood and tumor samples. Nivolumab was well tolerated and did not result in delayed surgery. Twenty of 21 eligible patients underwent complete surgical resection. A far greater proportion of patients experienced a major pathological response compared with an objective radiological response [9 of 20 (45%) versus 2 of 20 (10%)]. The pathological response rate was more than twice the rate that has been reported previously after administration of neoadjuvant chemotherapy (13). The recurrence-free survival at 18 months was 73%. Two patients with tumor enlargement after receiving nivolumab were found to have a major and a complete pathological response, respectively at the time of surgery. This finding is a vivid example of the phenomenon of radiological "pseudoprogression" and emphasizes the need for refinement of radiological criteria to determine response to immunotherapy. Tumors demonstrating a major pathological response in response to nivolumab were infiltrated with large numbers of lymphocytes and macrophages and these changes were seen in both PD-L1-positive and PD-L1-negative tumors. Since high tumor cell PD-L1 expression is a known determinant of response to immune checkpoint blockade, the demonstration of major pathological responses in PD-L1-negative tumors highlights the limitations of PD-L1 testing as a predictive marker of tumor response. As expected, tumors with a major pathological response had a higher tumor mutational burden. Interestingly, there were no alterations in immune-related genes, including *CD274*, *PDCD1*, *CTLA4*, *B2M*, and *HLA* in patients with or without a major pathological response. Other novel observations in this pilot study include a higher frequency of T-cells clones in the tumor and periphery and a higher clonality of the T-cell population in patients with a major pathological response. Additionally, neoadjuvant PD-1 blockade induced mutation-associated, neoantigen-specific T-cell responses that were not detectable in pre-treatment blood samples. These findings reflect an enhancement of systemic anti-tumor immunity that can potentially eliminate micrometastatic disease and decrease the risk of recurrence, thereby providing a justification for the use of immune checkpoint inhibitors prior to surgery.

Some of the clinical benefits observed in this pilot trial such as the relatively low rate of disease recurrence appear to be consistent with the results of prior preclinical studies of neoadjuvant immunotherapy (9). Forde and colleagues have also shown that neoadjuvant immunotherapy can be administered safely, does not result in surgical delay and does not appear to increase the risk of complications in the post-operative period. However, definite conclusions about a reduction in the risk of disease recurrence and an improvement in survival cannot be drawn from a small, single-arm trial with a relatively short follow-up period. It should also be borne in mind that recently developed tests to study the dynamics of the immune system such as the assay used to evaluate mutation-associated, neoantigen-specific T-cell clones need to be standardized to ensure the accuracy of results and uniformity across clinical trials.

Larger studies of neoadjuvant and/or adjuvant immunotherapy alone or in combination with chemotherapy are underway in patients with locally advanced NSCLC to address these unanswered questions (14). The NADIM study (NCT03081689) is a single-arm, multicenter phase II trial of three cycles of neoadjuvant nivolumab in combination with carboplatin and paclitaxel in 46 patients with resectable stage IIIA (N2) NSCLC followed by 12 months of nivolumab after surgery. After enrollment of 30 patients, treatment has been found to be well tolerated and has not caused delays in surgery. A pathological response rate of 85% has been observed in 13 patients who have undergone surgery so far, including a complete pathological response in 69% of patients (15). AFT-16 (NCT03102242) is a single-arm, phase II trial of atezolizumab before and after definitive chemoradiotherapy in patients with stage III NSCLC with an accrual goal of 63 patients. Tumor samples and blood will be collected for immune cell subset analysis, T-cell receptor immunophenotyping, and cytokine analyses (16). SAKK 16/14 (NCT02572843) is a single-arm, phase II trial of 2 cycles of neoadjuvant durvalumab administered after 3 cycles of cisplatin and docetaxel in patients with stage IIIA (N2) NSCLC followed by postoperative durvalumab for 12 months. The study accrual ceiling is set at 68 patients and the primary endpoint is event-free survival at 12 months. After the first 25 surgeries, the 30-day postoperative mortality rate is less than 10%.

In addition to biomarkers of PD-L1 blockade, this trial is designed to study the tumor immunome before the start of treatment and at the time of surgery (17). EA5142 (ANVIL; NCT02595944), a part of the ALCHEMIST clinical trial, is a phase III, randomized clinical trial with an estimated enrollment of 714 subjects that will evaluate adjuvant nivolumab versus standard-of-care observation in patients with pathologically confirmed stage IB–IIIA NSCLC. The study is designed to detect a 30% improvement in overall survival and/or a 33% improvement in disease-free survival in favor of nivolumab (18). Checkmate-816 (NCT02998528) is a phase III, randomized trial of nivolumab plus ipilimumab versus platinum-doublet chemotherapy as neoadjuvant therapy in patients with stage IB–IIIA NSCLC. The study has an accrual goal of 326 patients and a primary endpoint of major pathological response rate (19).

Preliminary results from the NADIM and SAKK 16/14 trials confirm the safety and tolerability of peri-operative immune checkpoint blockade. The availability of surgically resected tumor tissue for immune correlative studies will be extremely beneficial in understanding the dynamics of response and resistance to immunotherapy, with potential applications in the setting of advanced NSCLC as well. If ongoing trials demonstrate a decrease in the rate of disease recurrence and an improvement in overall survival after surgical resection, peri-operative immune checkpoint blockade is likely to be established as a necessary systemic therapy for locally advanced NSCLC.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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