Neoadjuvant PD-1 blockade in lung cancer: we’re not in Kansas anymore

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In the May 24th, 2018 issue of The New England Journal of Medicine, Patrick Forde and colleagues published a pilot study which examined the safety and feasibility of immune therapy to block programmed death 1 (PD-1) proteins by administering neo-adjuvant PD-1 Inhibitor in the setting of resectable non-small cell lung cancer (NSCLC) (1). In addition to demonstrating a lack of serious adverse events or surgical delay, they were also able to reveal a major pathologic response in tumor burden and provide greater insight into the dynamics of any anti-tumor immune response.

The study was carried out at two medical centers among a single group of 22 patients with stage I, II, or IIIA NSCLC which was deemed to be resectable. Forde et al. administered intravenous nivolumab (at 3 mg/kilogram of body weight) every two weeks prior to surgical resection for two doses. The primary endpoint was safety and feasibility. To this end, patients were monitored for adverse events or delay in surgery. All patients underwent clinical staging, diagnostic evaluation, and then surgical resection of their primary tumor and lymph nodes following treatment. Further data was collected using genomic analysis of pretreatment tumors, post-treatment tumors, and peripheral blood samples to further investigate anti-tumor action of PD-1 inhibitor. Patients were followed for recurrence-free and overall survival. Of the 22 patients who were enrolled in the trial, 20 received two doses of nivolumab and underwent surgical resection as planned, with one patient undergoing resection after one dose, and another deemed ineligible due to a diagnosis of small cell lung carcinoma. There were minimal adverse effects and no logistic delay in planned surgery that would have rendered this treatment unfeasible.

Post-treatment imaging showed a partial response in 2 out of 21 patients, stable disease in 18, and progression in one. However, of the 20 patients who underwent resection, nine patients (45%) demonstrated a major pathologic response, with a complete pathologic response in three patients—suggesting that enlargement on preoperative imaging may represent immune-cell activity rather than tumor progression.

Eleven patients provided pretreatment tumor samples for whole-exome gene sequencing and went on to have their tumors resected. Analysis revealed that tumors with a major pathologic response were those with a significantly higher mutational burden. Additionally, the authors were able to demonstrate that nivolumab increased the frequency of T-cell clones, both in the tumor and systemically. They were able to observe the post-treatment maturation of new mutation-associated, neoantigen-specific T-cell clones that were present in the tumor, as well as in lymph nodes both with and without measurable tumor infiltration. This measured immune response may represent the stimulated ability to identify and target new, tumor-specific antigens in vivo after PD-1 inhibitor administration. The involvement of lymphocytes within lymph nodes was an especially encouraging indication that this treatment may provide a durable response, preventing further tumor growth or...
metastasis post-resection.

Forde’s work builds on the understanding that genetic mutations within tumors have the potential to be targeted and destroyed by the immune system. However, this pathway is subject to resistance through the down regulation of the T-cell response (2-5). Other studies have demonstrated the safety and transformational effect of immunotherapy in the treatment of a broad range of cancers, including NSCLC, melanoma, and renal cell carcinoma (6,7). Specifically, in the setting of advanced NSCLC, prior studies have demonstrated an overall survival of 14.9 months, with 1-, 2-, and 3-year survival rates of 56%, 45%, and 27%, respectively. These are remarkable results in patients who had already shown disease progression after undergoing one to five prior systemic treatment regimens (8).

This current study has particular value in presenting response after neoadjuvant immunotherapy. The overall response rate of 45% compares favorably to the maximum objective response rate of 22.2% observed in the setting of adjuvant nivolumab in advanced disease (8), though this comparison should be made with caution given the difference in trial designs and disease burden between groups. The authors cite the work of Liu et al. which compare the therapeutic power of neoadjuvant vs. adjuvant immunotherapy in mice models, concluding that neoadjuvant administration generates a greater tumor-specific immune response (9). Indeed, this study describes a strong correlation between the pathological response and the mutational burden of the pretreatment tumor. The presence of post-treatment tumor-specific T-cells clones in the resected tumor, lymph nodes, and the peripheral blood, further support the notion that neoadjuvant immunotherapy could lead to a sustained response, a hypothesis that has been supported by additional work in mice populations (10,11). A recurrence free survival of 73% at 18 months with this treatment modality show promise and warrant additional study. However, this study was not designed with adequate follow up to speak further to longer-term outcomes.

Ford et al. have cleared an import early hurdle for use of this promising treatment modality. To their primary endpoint, they have shown neoadjuvant nivolumab to be safe and feasible in the setting of this small pilot study. The absence of any new or toxic adverse effects is reassuring, while the ability to administer the treatment preoperatively without delay of planned resection is logistically important for the development and investigation into PD-1 Inhibitors’ role in any new treatment algorithms.

Beyond feasibility, they were also able to glean promising information into the pathologic response and immunologic mechanism of neoadjuvant nivolumab. Though these results warrant cautious interpretation given the small sample size of this single-arm pilot study, this study provides exciting preliminary evidence of the efficacy of this treatment modality. Additionally, their carefully tested hypotheses, though performed on a limited number of patients and tumor samples, provided insight into the mechanism of a durable response that is consistent with known mechanisms and prior animal models, and may signal the important role that neoadjuvant administration of immunotherapy may play in the future.

There is an obvious need for more research and better-defined protocols and expectations for PD-1 inhibitors’ role in future treatment algorithms for NSCLC. This work plays an important role in establishing neoadjuvant immunotherapy administration as a valuable target for future research, and helps to reassure the safety and feasibility of such work.

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Footnote

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References


