Commentary: Another win for immunotherapy

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In this issue of the Journal, authors Hashimoto and colleagues1 from the Japanese Cancer Institute Hospital group report their experience in postresection recurrence in non–small cell lung cancer (NSCLC), with data encompassing the pretargeted and immunotherapy era as well as the current era, including tyrosine kinase inhibitors (TKIs) against epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) fusions, and immunotherapy targeting the programmed cell death protein 1/programmed cell death ligand 1 (PD-1/PD-L1) pathways. The authors included 2254 patients at their institution with NSCLC who underwent R0 resection via lobectomy or pneumonectomy between 2008 and 2018. Of these greater than 2000 patients, 19.7% of patients had a postresection recurrence. Postresection recurrence is an issue faced by thoracic surgeons and medical oncologists in their daily practice, and yet there is no standard accepted treatment. Treatment being offered is often extrapolated from the treatment of stage IV lung cancer, which does not necessarily represent the same entity as a postresection recurrence.

During the study, TKIs against EGFR were available at the beginning of the time course, with ALK-TKIs becoming commercially available in 2012 and then the first immunotherapy drug (nivolumab, a PD-1 inhibitor) for NSCLC becoming available in 2015. The authors conducted regular surveillance of their postresection patients with routine imaging, including at least annual computed tomography scans. The average time to recurrence was just over a year. Both the initial resection specimens and the postresection recurrence specimens were tested for EGFR and ALK mutation status. EGFR mutations (EGFR+ group) and ALK rearrangements (ALK+ group) were detected in (43.1%) and (2.9%) of patients with recurrence. In the rest of the 239 patients with recurrence (54.0%), mutations were not detected or unknown. Patients who were discovered to have postresection recurrence received a variety of therapies, including resection of the recurrence, radiation, chemoradiation, and systemic therapy. Throughout the postrecurrence course, 36% of patients received EGFR-TKIs, 2.9% received ALK-TKIs, and 15.3% received immunotherapy.

Overall, patients with EGFR and ALK mutations had significantly improved postrecurrence survival as compared with those without targetable mutations in these pathways, with a median survival of 4.7 years in the EGFR+/ALK+ group and 2.1 years in patients without driver mutations. When the study data were analyzed including all patients regardless of mutation status, the 2-year survival after recurrence improved significantly over the study period. However, when broken down by mutation status, the EGFR+ and ALK+ patients had stable 2-year survival postrecurrence over the decade whereas the nonmutant group made significant gains in 2-year postrecurrence survival over time; this was also associated with the utilization of immunotherapy in the same group of patients. Thus, the authors posit that improvement in

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postrecurrence survival in patients with NSCLC, especially those without targetable mutations in EGFR or ALK, was positively influenced by the adoption of immunotherapy in the treatment of postresection patients experiencing recurrence.

PD-1/PD-L1–based regimens have shown a survival benefit in patients with metastatic NSCLC.2-4 Recently, the CheckMate 816 trial also demonstrated a benefit of immunotherapy in patients with resectable Stage Ib-IIIa NSCLC.5 In fact, the addition of neoadjuvant immunotherapy with nivolumab decreased the rate of postresection recurrence, progression, and death in this group. Hashimoto and colleagues6 did not include the PD-L1 status of the tumor in their analysis for this paper, but other studies have shown an increase in the benefit of immunotherapy in tumors with high PD-L1 expression.5 Interestingly, CheckMate 816 demonstrated both a benefit with nivolumab plus chemotherapy in all PD-L1 subgroups, with a greater event-free survival benefit in patients with a high tumor PD-L1 expression level of (>1%) but yet still an advantage in the group with low PD-L1–expressing tumors.

As the authors state within their limitations and also as noted in the title of the article, the results described by this study may be specific to Asian populations, as prevalence of driver mutations differ between different racial and ethnic groups. For example, in this study, 43% of patients had an EGFR mutation, compared with a reported incidence of only 15% in Western populations. However, one could interpret this situation that in Western populations without a prevalence of driver mutations in EGFR/ALK, there is the potential to gain even larger societal benefit from immunotherapy in postresection recurrences.

Previously published work on postresection recurrence has shown that the number of lesions and sites at the time of recurrence is an important prognostic factor.7 This important issue is not explored in this study by Hashimoto and colleagues.1 These authors previously showed that local ablative treatment (surgery or radiation therapy) without systemic treatment may result in favorable survival if the recurrence pattern is that of oligorecurrence.8 Further research into the merits of immunotherapy in combination with local ablative therapies for recurrent NSCLC is needed. Given the overwhelming positive trials with the inclusion of immunotherapy in nearly every phase of lung cancer treatment,2-6 it seems likely to be beneficial. Overall, immunotherapy clearly has changed the way we treat NSCLC. It likely provides a benefit to patients with postresection recurrence. It’s an incredible tool in our armamentarium for treating advanced-stage or recurrent lung cancer, as evidenced by this study.

References