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ASO PERSPECTIVES

Neoadjuvant Immunotherapy for Resectable Non-small Cell Lung Cancer: Exciting New Horizon in Early-Stage Lung Cancer Care

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Immune checkpoint inhibitors (ICIs) are revolutionizing non-small cell lung cancer (NSCLC) treatment. Initial reports describe their use in the metastatic setting.[1] The PACIFIC trial (NCT02125461) was the first to demonstrate a survival benefit of ICI for non-metastatic patients, with improved overall survival (OS) at 5 years (42.9% vs 33.4%) using durvalumab versus placebo after concurrent chemo-radiation for unresectable stage III patients.[2]

In the spring of 2021 two large phase 3 trials combining ICI with surgical resection for NSCLC reported results and ushered in the next big breakthrough in resectable NSCLC care. The results of Impower 010 (NCT02486718) were reported at multiple conferences in 2021.[3] Impower 010 showed superior disease-free survival (DFS) with atezolizumab administered for 1 year after adjuvant chemotherapy for patients with completely resected stages II to IIIA NSCLC and tumor PD-L1 expression greater than 1%. The Food and Drug Administration (FDA) granted approval for this cohort in the fall of 2021.

The CheckMate 816 trial (NCT02998528) evaluated ICI in the neoadjuvant setting. Patients with resectable stages IB to IIIA NSCLC were randomized to nivolumab plus chemotherapy or chemotherapy alone for three cycles before resection. The primary pathologic end point of this trial was reported at the American Association for Cancer Research (AACR) in 2021, and in 2022, the primary survival end point was reported at AACR, the manuscript was published,[4] and FDA approval was granted for this treatment approach. A robust enthusiasm for this approach stems from three main points.

First, pathologic complete response (pCR) improved dramatically with the addition of nivolumab (24% vs 2%; odds ratio [OR], 13.94; $p < 0.001$). This corresponded with impressive improvement in median event-free survival (EFS): 31.6 months with nivolumab plus chemotherapy versus 20.8 months with chemotherapy alone (hazard ratio [HR], 0.63). The 2-year EFS rates were respectively 63.8% and 45.3%, favoring the addition of nivolumab across most subgroups. The magnitude of benefit was greater for the patients with stage IIIA (HR 0.54) than for those with stages IB to II (HR 0.87) disease, and for patients with tumor PD-L1 expression of 1% or greater (HR 0.41) than for those with PD-L1 expression lower than 1% (HR 0.85).

There is growing enthusiasm for pathologic end points as surrogates for survival in neoadjuvant NSCLC trials. Pathologic end points are validated survival surrogates in breast cancer but have yet to be used for regulatory approval in NSCLC. In the initial analysis from Checkmate 816, patients with a pCR appeared to have a longer median EFS (not reached) than those with residual disease in both the experimental and chemotherapy arms of the study (26.6 and 18.4 months, respectively). These data could go a long way toward validating pCR as a survival surrogate for neoadjuvant NSCLC trials going forward.

Second, the ultimate goal of neoadjuvant treatment in NSCLC is the eradication micro-metastatic disease. Scientifically, the ability of cytotoxic chemotherapy to do that should differ little before and after resection, but the same may not be true for ICIs. These agents leverage the patient's immune system to destroy cancer cells, and immune cell-priming appears to be enhanced when ICI is given with the primary tumor in place. Melanoma data demonstrate greater expansion of tumor-targeted T cell

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clones for neoadjuvant versus adjuvant ICI.[5,6] Analysis of T cell clones from CheckMate 159 (NCT02259621) showed robust cross-pollination of T cell clones between the tumor and circulating blood and larger and more diverse clonal populations associated with deeper pathologic response.[7]

The third reason for excitement relates to the short-term surgical data presented at the American Association of Clinical Oncology (ASCO) in 2021.[8] Short-term surgical outcomes were pre-specified as key exploratory end points, and the results are encouraging. Attrition, operative approach, extent of resection, operative time, blood loss, and postoperative complications all were statistically similar between the treatment groups, but the overall picture trended toward favoring the nivolumab arm, with subtle improvements in all the reported outcomes except time to resection, suggesting at least equivocal and possibly less challenging resections due to the depth of response with the addition of nivolumab to chemotherapy. Further data on these points are needed, but results are in line with reports from multiple phase 2 trials.[9–11] These data are extremely important for surgical acceptance of novel neoadjuvant treatments.

Some clinicians have hesitancy about integrating this therapy as standard of care in resectable NSCLC until an OS benefit is reported. Overall survival is the treatment goal in curable populations, but OS is being used less frequently as a clinical trial end point in curable NSCLC cohorts due to time, costs, and its accuracy as an efficacy measure. Ideal trial end points are clinically relevant, easily measured, low in cost, reproducible, and sensitive and specific to the intervention.[12] Overall survival carries obvious clinical relevance but falls short on other criteria. Sensitivity to the intervention is declining due to increasing effectiveness of subsequent therapies after recurrence, but the greatest challenge to OS end points for adjuvant NSCLC relates to cost and ease of measurement. Following curable patients until death to determine efficacy is time-consuming, requires a large sample, is expensive, and results in slow adoption of novel agents. The median time from trial initiation to publication for adjuvant platinum chemotherapy trials in NSCLC was longer than 10 years.[13] For these reasons, EFS and DFS are frequent surrogates for OS in recent adjuvant and neoadjuvant trials.

The current cure rates for stage III NSCLC are dismal, and the EFS benefit for stage IIIA patients with the addition of nivolumab in CheckMate 816 was impressive (HR 0.54). Adding nivolumab to chemotherapy does not represent a dramatic change in treatment. When identified preoperatively, stage IIIA patients are treated with induction therapy, which is simply a modification to that regimen. The perioperative data from ASCO and the tolerability data for stage IV disease allows us to do that without significant concern for increased toxicity, so there is little reason to delay integration of this approach for these patients. For stages IB and II disease, a greater number of patients were cured with surgery alone, and the added benefit of nivolumab to chemotherapy was more modest (HR 0.87). Routine neoadjuvant treatment is a significant shift from the current standard of care, which is resection and adjuvant chemotherapy. Therefore, some caution may be warranted before a large change in treatment approach is made without further survival data from this trial or other ongoing trials. These patients have the options for ICI in the adjuvant setting, as reported in Impower 010, and overall survivals may be quite similar between approaches.

It has been longer than 15 years since the introduction of novel therapies into resectable NSCLC care. The surgical approach and techniques evolved considerably during that time, and personalized care currently is ushered in with ICI and targeted therapies with NSCLC resection. Although long-term data are still pending, the early evidence for ICI with resection is impressive. These therapies place increased onus on the surgeons to educate their patients, perform appropriate molecular tissue analysis, and provide rapid return to intended oncologic care to allow maximal integration and benefit.

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