Editorial Commentary

Global implementation of individualized lung cancer care requires wide adoption of molecular tumor profiling

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The utilization of immune-checkpoint inhibitor (ICI) in conjunction with chemotherapy has excitingly and consistently demonstrated a survival advantage in individuals with resectable non-small cell lung cancer (NSCLC). These findings stem from various recently completed randomized clinical trials (1-4), which have not only established the efficacy of such combined therapeutic approaches but have also contributed to a deeper understanding of factors associated with potentially more pronounced responses to systemic therapy. Notably, the presence of targetable oncogenic drivers in NSCLC, such as mutations in the epidermal growth factor receptor (EGFR) gene or translocations in the anaplastic lymphoma kinase (ALK) gene, have been identified as such factors. Understanding these relationships can optimize therapy for a substantial number of patients, as the former aberration can be detected in up to 17% of early-stage NSCLC cases (5).

Targeted therapy for oncogene-positive disease has demonstrated a survival benefit, as evidenced by studies like ADAURA (6). However, the use of immunotherapy in patients with mutations has not been extensively explored (7). For instance, the KEYNOTE-671 trial encompassed patients with stage II to IIIB resectable NSCLC, with or without oncogene-positive disease, managed with perioperative pembrolizumab *vs.* placebo; only 33 patients (4.1%) with known EGFR mutations and 21 patients (2.6%) with known ALK translocations were included (2). Notably, patients with known EGFR mutations exhibited a more substantial benefit from receiving pembrolizumab [hazard ratio (HR) for event-free survival: 0.09, 95% confidence interval (CI): 0.01–0.74]. Conversely, adjuvant ICI was more beneficial in patients lacking ALK translocations (HR: 0.41, 95% CI: 0.26–0.62).

In the PEARLS/KEYNOTE-091 trial, patients with IB to IIIA resectable NSCLC were randomized to receive pembrolizumab *vs.* placebo in the adjuvant setting, among whom 73 patients (6.2%) had known EGFR mutations and 14 patients (1.2%) had known ALK translocations (8). Once again, patients with known EGFR mutations responded positively (HR for disease-free survival: 0.44, 95% CI: 0.23–0.84) to pembrolizumab in the adjuvant setting compared to patients without a mutation (HR: 0.78, 95% CI: 0.59–1.05) or those with an unknown mutation status (HR: 0.82, 95% CI: 0.63–1.05).

The utilization of immunotherapy in patients with stage IV NSCLC and targetable mutations has been scrutinized, revealing an association with elevated adverse events and a lack of meaningful survival benefit. In the TATTON study, a multi-arm phase IB trial, patients with advanced NSCLC and EGFR mutations were randomized to receive various combination therapies, including osimertinib [tyrosine kinase inhibitor (TKI)] with durvalumab (immune-checkpoint blockade) (9). Within this treatment group, 5 out of 23 (21.7%) patients developed interstitial lung disease. The sequential administration of ICI in patients with advanced oncogene-positive NSCLC has

traditionally been linked to severe immune-related adverse events, leading to the current recommendation against this therapeutic approach (10,11), rather, encouraging the use of biomarker testing and targeted agents as first line (12).

Despite the available data regarding adjuvant ICI use in patients with resectable early-stage NSCLC and oncogene-positive disease or in patients with metastatic disease, there is a deficiency in level 1 evidence regarding its application in this population in the neoadjuvant setting. For instance, the pivotal Checkmate-816 trial enrolled patients with IB to IIIA resectable NSCLC but excluded those with known ALK translocations or EGFR mutations (1).

Recently, Zhao and colleagues conducted a multicenter study aiming to explore the neoadjuvant immunotherapeutic benefits in patients with resectable oncogene-positive NSCLC (13). The authors retrospectively reviewed four institutions, identifying 137 patients with stage IIA to IIIB resectable NSCLC who received neoadjuvant ICI or combination chemotherapy-ICI. Stratification was performed based on oncogene status, encompassing EGFR mutations, ALK translocations or mutations, KRAS mutations, MET amplifications or mutations, BRAF mutations, ROS1 rearrangements or mutations, and RET fusions. PD-1 blockade monotherapy (nivolumab or pembrolizumab) or combination therapy (PD-1 blockade or PD-L1 blockade with platinum-based doublet therapy) was administered. Surgery followed 4 to 6 weeks after completing neoadjuvant therapy. Among participants, 22 (16.1%) had oncogene-driven tumors, all of whom received combination therapy, while 4/115 (3.5%) oncogene-negative patients received ICI monotherapy. Most patients (81.8% oncogene-positive, 62.6% oncogene-negative) received three or more cycles of neoadjuvant therapy. Oncogene-positive patients exhibited non-squamous histology, more frequent N2 involvement, a lower smoking history, and underwent invasive mediastinal staging more often. Oncogene-positive patients were less likely to achieve complete nodal downstaging and major pathological response (<10% viable residual tumor) at lower rates (odds ratio: 0.13, 95% CI: 0.03–0.64). The authors emphasize the essential role of molecular testing for appropriate neoadjuvant treatment.

Recent trials have included a substantial number of patients with unknown oncogene status, highlighting the importance of acquiring comprehensive pre-therapy clinicopathologic data to identify those who will benefit most from specific regimens. For instance, in KEYNOTE-671, 238 (66.0%) patients had unknown EGFR mutational status, and in KEYNOTE-091, 670 (56.9%) lacked EGFR mutation testing, with 747 (63.5%) having unknown ALK translocations (8). And so despite robust evidence originating from these trials, important questions relating to the use of ICI in patients with targetable mutations remains, specifically in patients with early disease, who have historically otherwise not be offered molecular testing. Despite the meticulous propensity-score matching conducted by Zhao and colleagues in their study, a crucial question persists: whether the presence of an oncogene influences the response to immunotherapy. Ideally, a direct comparison of outcomes between immunotherapy and targeted therapy in patients with positive oncogenes and early-stage disease would provide valuable insights. However, conducting such a study would be overwhelmingly limited due to the low incidence of molecular testing in early-stage disease outside of the realm of clinical trials, again, reaffirming the urgent need of its adoption. Clinical trials currently recruiting aim to evaluate the use of neoadjuvant TKI combination therapy or monotherapy in the neoadjuvant setting for patients with early-stage resectable EGFR-mutated NSCLC (14,15).

Moreover, in the distinction between early- and advanced-stage disease, it is crucial to assess appropriate endpoints. For early-stage disease, evaluating pathologic response may be pertinent, while for more advanced disease, event-free survival is more frequently tracked. Importantly, a comprehensive discussion is warranted regarding patient-reported outcomes and whether clinical trials and the selection of systemic therapies should incorporate these critical endpoints (16-18). This consideration becomes particularly relevant in the context of the potential risks of adverse immune reactions associated with immunotherapy and/or combination therapies (19,20). Ensuring transparent discussions with patients before initiating systemic therapy is imperative to genuinely assess the significance of quality versus length of survivorship in the personalized decision-making process.

Despite robust sponsorship of international trials, the potential clinical implications of the genetic epidemiology differences between East Asia and the West, particularly with respect to the high EGFR mutation rates in the Asian population must be further researched (21). The mutMapII study evaluated the incidence of EGFR mutations in patients with lung adenocarcinoma and observed a frequency of mutation of nearly 50% in the Asia-Pacific region, compared to 15% in Europe, and 22% in North America (22). This large review of available EGFR data also revealed a substantial variation in mutation frequency

between studies, even when grouped by geographic region and country.

Ultimately, the work by Zhao and colleagues should be commended, as it fills a void in available evidence regarding to the safety and efficacy of neoadjuvant ICI in patients with early-stage oncogene-positive NSCLC. While this work is a great first step, important questions remain, such as whether combination therapy may offer a more pronounced therapeutic benefit in patients with positive mutational status. Unfortunately, this data is often lacking, as highlighted in this commentary. Thus, when tasked with providing lung cancer care across currently genetically different populations, clinical trials must obtain all available clinicopathologic data, such as mutational status, in order to implement individualized cancer care globally.

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