Editorial Commentary

The opportunities and challenges of perioperative therapy of localized non-small cell lung cancer—thoughts from the KEYNOTE-671 trial

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The unprecedented success of immune checkpoint inhibitors (ICIs) in the treatment of advanced stage non-small cell lung cancer (NSCLC) has stimulated the interest of testing ICIs in early-stage diseases (1-4) and have significantly revolutionized the therapeutic landscape for localized NSCLC in the peri-operative setting. Results from the phase II trial (NADIM II) evaluating the effect of perioperative nivolumab and chemotherapy have demonstrated significantly increased pathological complete response (pCR) in patients who received combination therapy compared to chemotherapy alone (5). IMpower010 (4) and KEYNOTE-091 (2) led to the approval of ICIs atezolizumab (stage IB–IIIA) and pembrolizumab (stage II–IIIA) for the treatment of NSCLC in the adjuvant setting, respectively, and CheckMate-816 (1,6) established the role of ICI in the neoadjuvant setting and led to the approval of nivolumab in combination with chemotherapy as a neoadjuvant option for stage IB–IIIA NSCLC. However, there remains equipoise whether a combination of neoadjuvant with adjuvant ICI-based therapy would drive additional benefits for patients with localized NSCLC compared to neoadjuvant or adjuvant ICI-based therapy alone. The recently published KEYNOTE-671 (KN671) (2) clinical trial addressed this very question by evaluating the use of perioperative pembrolizumab for stage II–IIIB NSCLC. Along with other recently completed or ongoing trials (7-10), KN671 evaluated whether the use of perioperative therapy had an impact on a range of outcomes.

In KN671, patients with stage II–IIIB NSCLC underwent randomization to receive neoadjuvant pembrolizumab or placebo, with chemotherapy for 3 cycles, prior to surgery, followed by up to 13 cycles of adjuvant pembrolizumab or placebo. At the landmark timepoint of 24 months, patients in the pembrolizumab group exhibited a significantly higher rate (P<0.001) of event-free survival (EFS), with 62.4% of patients remaining free from recurrence compared to 40.6% in the placebo group. These findings highlight the favorable EFS observed with pembrolizumab treatment, and are consistent with the observations from most of perioperative trials including CheckMate-816, IMpower010, and KEYNOTE-091 (1,3,4) confirming the efficacy of ICIs in reducing disease recurrence or progression. The KN671 trial demonstrated clear EFS benefit across various subgroups with the exception of never smokers and patients with programmed cell death ligand 1 (PD-L1) <1%, who may not achieve as durable of a response compared to current or former smokers, and patients with positive PD-L1 expression, in line with previous findings (11,12). Regarding overall survival (OS), the estimated OS at 24 months was 80.9% in the pembrolizumab group and 77.6% in the placebo group with a P=0.02, which did not meet the significance criterion

based on predetermined statistical thresholds. The trend toward better OS in ICI group was also observed in multiple perioperative trials, but none of these has reached statistical significance, which could be due to immature follow up. While KN671 offers crucial insights into perioperative systemic therapy, ongoing research is necessary to address patient selection for neoadjuvant single- or double-agent immunotherapy, as well as chemo-immunotherapy with multiple agents. In this regard, the phase II trial NEOSTAR has provided valuable information, investigating outcomes in patients who received single- or double-agent immunotherapy *vs.* those treated with single- or double-agent immunotherapy in combination with chemotherapy (13,14). Continued investigations in this area are imperative to further elucidate the optimal treatment approaches and enhance patient-centered care for individuals with NSCLC. In the context of the diverse library of protocols available for neoadjuvant, adjuvant, or perioperative therapies, several factors will undoubtedly influence therapeutic decision-making.

Considerations such as the stage of disease and genomic characteristics are paramount in tailoring treatment approaches. For instance, patients with stage IIIB or IIIC NSCLC are not believed to be surgical candidates in the pre-ICI era. Given the robust response to neoadjuvant chemo-ICI treatment in at least a subset of patients, the question arises now whether some of these patients should be offered the option of neoadjuvant chemo-ICI treatment and surgical resection to achieve the best chance of cure. A robust neoadjuvant protocol incorporating dual systemic therapy (chemotherapy plus immunotherapy) may be a viable option aiming to optimize tumor response before proceeding to surgery (15) although the optimal duration of treatment remains as an open question. In KN671, patients who were found to have pathologic stage III disease benefited from this perioperative protocol [hazard ratio (HR): 0.54; 95% confidence interval (CI): 0.42–0.70]. While all patients included had resectable disease, one can imagine that a neoadjuvant protocol may potentially translate unresectable disease into disease that might be amenable to resection. In a recently published retrospective study (16) that included stage IIIB and IIIC diseases, patients managed with neoadjuvant of chemo-ICI safely underwent resection. Of note, in this retrospective series, there were 60% of patients with N2 disease who achieved complete pathological nodal response, and 56% of patients with stage IIIA-B-C disease achieving major pathological response. These results indicate that with neoadjuvant chemo-ICI and surgical resection could be revisited as a new option for patients who are not traditionally treated by surgical resection. Of course, this option has to be compared in randomized trials to the current standard of care concurrent chemoradiation followed by adjuvant durvalumab established in the PACIFIC trial (17). Importantly, this concept of resection in advanced disease is being tested even in the metastatic setting in clinical trials such as LONESTAR (NCT03391869). Furthermore, for patients with advanced local disease, neoadjuvant therapy may offer the opportunity for a less invasive surgical intervention. As such, the comparison between neoadjuvant and adjuvant approaches becomes important, as each approach confers distinct benefits that may vary based on individual patient characteristics.

Conversely, in patients with early-stage disease, systemic therapy-related morbidity may heighten the risk of subsequent surgical procedures. The CheckMate-816 clinical trial demonstrated significant survival benefits associated with neoadjuvant chemotherapy combined with immunotherapy (1). Nevertheless, it is noteworthy that 15.6% of patients who had resectable disease at trial inclusion, and received neoadjuvant therapy did not undergo surgery due to disease progression, adverse events, or other reasons. This considerable subset of patients represents a potential cohort that could have potentially benefitted from upfront surgical management followed by adjuvant therapy. In the IMpower010 trial, investigators evaluated the efficacy of atezolizumab plus chemotherapy in patients with resected stage II and IIIA NSCLC, and showed a significant survival benefit associated with dual therapy, compared to chemotherapy alone (74.6% *vs.* 61.0% 2-year disease-free survival, P=0.0039) (4). In light of this observation, exploring optimal treatment strategies for this specific group of patients who may not benefit most from neoadjuvant therapy is warranted. The consideration of upfront surgery followed by adjuvant therapy may potentially yield meaningful survival outcomes in this subgroup. Such an approach would optimize therapeutic sequencing, mitigate the risk of disease progression, and enhance OS. Ultimately, the selection between neoadjuvant and adjuvant therapy, or both, may be individualized. While KN671 confirmed the efficacy of ICI in the perioperative setting and may provide another perioperative regimen, without clear OS benefit being observed yet, the central question remains as how to choose neoadjuvant, adjuvant *vs.* neoadjuvant plus adjuvant ICI-based therapy for patients with localized NSCLC. The rate of return to intended oncologic therapy (RIOT)

following surgery is a crucial aspect of perioperative therapy in thoracic oncology (18,19). In the intervention group of KN671, it was observed that a significant proportion of patients did not start adjuvant therapy (26.8%, n=106). Furthermore, 22.2% (n=88) of patients discontinued therapy, and only 40.4% (n=160) completed the full course of adjuvant pembrolizumab at the time of data analysis. It is important to consider that the limitations in RIOT observed in the study can be attributed, at least in part, to the receipt of surgical intervention. In the placebo group, only two-thirds of patients (66.9%, n=267) initiated adjuvant therapy. Of these patients, 20.3% (n=81) discontinued therapy, and 35.3% (n=141) completed the full course of treatment at the time of data lock. In KEYNOTE-091, 48.3% of patients assigned to receive pembrolizumab in the adjuvant setting did not receive more than 1 dose of therapy, compared to 34.5% of patients in the placebo group. In IMpower010, 34.7% of patients randomized to receive atezolizumab following resection did not complete treatment, compared to 24.2% in the placebo group. These findings highlight the challenges associated with the resumption of intended oncology therapy following surgical procedures, which is even present in groups randomized to receive placebo. In addition to disease progression, other factors that may have impacted this metric included adverse effects from systemic treatment, logistic reasons such as lodging and travel to receive these treatments, and patient preference. However, details of these factors are difficult to capture.

In addition to assessing efficacy, the consideration of treatment-associated toxicity is a crucial element in the decision-making process for choosing the appropriate perioperative regimens. In the context of neoadjuvant and adjuvant trials employing agents targeting anti-programmed death 1 (PD-1)/PD-L1, the occurrence of adverse events, particularly immune-mediated, remains consistent across various studies. However, it is essential to highlight that the incidence of grade 3 or above toxicities was notably elevated in the perioperative KN671 trial in comparison to other neoadjuvant or adjuvant trials. Specifically, the percentage of patients in the treatment group experiencing grade 3 or above toxicities was 44.9% compared to 37.3% in the control group in the KN671 trial, while it stood at 35% *vs.* 25% in the KEYNOTE-091 trial, 22% *vs.* 13% in the IMpower010 trial, and 33.5% *vs.* 36.9% in the CheckMate-816 (1-4). It is important to acknowledge that direct comparisons across trials might not be entirely equitable due to variances in patient characteristics among these studies. Nevertheless, the higher rate of toxicities observed in the KN671 trial suggests a correlation between the intensity of treatment and the incidence of adverse effects. This observation underscores the necessity of carefully weighing the balance between treatment efficacy and associated toxicity when making informed decisions regarding cancer treatment strategies.

One question that arises is whether the prescription of adjuvant therapy should be based on the response to neoadjuvant ICIs by pathologic review of resected tumors. In the aforementioned trial, patients who received pembrolizumab and chemotherapy in the neoadjuvant setting achieved a pCR rate of 18.1% (n=72) *vs.* 4.0% (n=16) in the placebo group (chemotherapy alone). Additionally, a major pathologic response was seen in 30.2% (n=120) of patients receiving pembrolizumab and 11.0% (n=44) of patients in the placebo group. In CheckMate-816, pCR was achieved in 24.0% of patients who received nivolumab plus chemotherapy, and only in 2.2% of patients who received chemotherapy alone. In the single-arm NADIM trial, there were 63% of patients receiving nivolumab plus chemotherapy who achieved pCR (20). Further investigation is warranted evaluating whether patients who achieve a pCR would benefit most from active surveillance, adjuvant therapy, or maintenance therapy. One promising avenue for identifying patients who may benefit from additional therapy is the ongoing developments in liquid biomarkers, such as circulating tumor DNA (ctDNA) (21). For example, In the CheckMate-816 trial, it was observed that no patients achieved a pCR if ctDNA remained positive after neoadjuvant therapy (1). Similarly, the NADIM trial also demonstrated that patients with positive baseline ctDNA had a shorter OS, while patients who achieved clearance of ctDNA shedding after neoadjuvant chemoimmunotherapy experienced a remarkably high OS (22). These biomarkers have the potential to provide valuable data to aid in the decision-making process, helping to identify patients who may derive the most benefit from additional therapy while minimizing financial toxicity and unnecessary treatment burden. Other disease markers, such as radiomics, can also help inform the therapeutic response potential of patients prior to the receipt of therapy, as well as longitudinally during the treatment protocol (23,24). Ongoing advancements in this field can offer critical insights into personalized treatment strategies and improve patient outcomes in the context of both clinical efficacy and financial wellbeing. Determining the optimal approach for these patients is essential for tailoring treatment to their specific needs and maximizing outcomes. Within

the context of clinical (25,26) or financial toxicity (27,28) associated with lung cancer care, it remains essential to assess whether patients who have achieved a robust response to neoadjuvant therapy, as evidenced by surgical pathology, should undergo further potentially morbid and costly therapy. This is a significant area of research that can impact patients' quality of survivorship and financial wellbeing. Fast-tracked access to financial advisors, or nurse navigators and social work may mitigate economic complications associated with cancer diagnosis.

The completion and continuation of perioperative ICI-based therapies have indeed transformed the landscape of lung cancer treatment. However, despite the significant progress, numerous unanswered questions persist, extending beyond those previously discussed. For instance, the optimal duration of neoadjuvant and adjuvant treatments remains uncertain. Additionally, the role of radiation, both with and without immunotherapy, in the neoadjuvant setting needs further clarification. Moreover, there is a pressing need to establish effective methods for selecting patients for perioperative ICI-based therapies, moving beyond the current biomarker-based approaches such as PD-L1 expression and tumor mutation burden. Addressing these inquiries is pivotal to refining and advancing the application of ICI-based therapies in the perioperative context for lung cancer patients. As personalized medicine continues to evolve, comprehensive integration of molecular, clinical, radiomics characteristics and other treatment modalities will undoubtedly aid in refining treatment strategies, allowing for more tailored and effective therapeutic approaches. In-depth analysis of clinical data, along with molecular profiling, will be instrumental in guiding therapeutic decisions and ultimately improving patient outcomes in the management of NSCLC.

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References

1. Forde PM, Spicer J, Lu S, et al. Neoadjuvant Nivolumab plus Chemotherapy in Resectable Lung Cancer. N Engl J Med 2022;386:1973-85.
2. Wakelee H, Liberman M, Kato T, et al. Perioperative Pembrolizumab for Early-Stage Non-Small-Cell Lung

Cancer. N Engl J Med 2023;389:491-503.
3. O'Brien M, Paz-Ares L, Marreaud S, et al. Pembrolizumab versus placebo as adjuvant therapy for completely resected stage IB-IIIA non-small-cell lung cancer (PEARLS/KEYNOTE-091): an interim analysis of a randomised, triple-blind, phase 3 trial. Lancet Oncol 2022;23:1274-86.
4. Felip E, Altorki N, Zhou C, et al. Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB-IIIA non-small-cell lung cancer (IMpower010): a randomised, multicentre, open-label, phase 3 trial. Lancet 2021;398:1344-57.
5. Provencio M, Nadal E, González-Larriba JL, et al. Perioperative Nivolumab and Chemotherapy in Stage III Non-Small-Cell Lung Cancer. N Engl J Med 2023;389:504-13.
6. Spicer J, Wang C, Tanaka F, et al. Surgical outcomes from the phase 3 CheckMate 816 trial: Nivolumab (NIVO)+ platinum-doublet chemotherapy (chemo) vs chemo alone as neoadjuvant treatment for patients with resectable non-small cell lung cancer (NSCLC). J Clin Oncol 2021;39:8503.
7. Heymach JV, Harpole D, Mitsudomi T, et al. Abstract CT005: AEGEAN: A phase 3 trial of neoadjuvant durvalumab+ chemotherapy followed by adjuvant durvalumab in patients with resectable NSCLC. Cancer Res 2023;83:CT005.
8. Cascone T, Provencio M, Sepesi B, et al. Checkmate 77T: A phase III trial of neoadjuvant nivolumab (NIVO) plus chemotherapy (chemo) followed by adjuvant nivo in resectable early-stage NSCLC. J Clin Oncol 2020;38:TPS9076.
9. Genentech, Inc. NAUTIKA1: multicenter, phase ii, neoadjuvant and adjuvant study of alectinib, entrectinib, vemurafenib plus cobimetinib, or pralsetinib in patients with resectable stages II-III non-small cell lung cancer with ALK, ROS1, NTRK, BRAF V600, or RET molecular alterations. NCT04302025. Available online: https://www.cancer.columbia.edu/cancer-types-care/clinical-trials/find-clinical-trial/nautika1-multicenter-phase-ii-neoadjuvant-and-adjuvant-study-alectinib-entrectinib-vemurafenib-plus-cobimetinib-or-pralsetinib-patients-resectable-stages-ii-iii-non-small-cell-lung-cancer-alk-ros1-ntrk
10. Peters S, Kim AW, Solomon B, et al. IMpower030: Phase III study evaluating neoadjuvant treatment of resectable stage II-IIIB non-small cell lung cancer (NSCLC) with atezolizumab (atezo)+ chemotherapy. Ann Oncol 2019;30:ii30.
11. Silver A, Ho C, Ye Q, et al. Prediction of Disease Progression to Upfront Pembrolizumab Monotherapy in Advanced Non-Small-Cell Lung Cancer with High PD-L1 Expression Using Baseline CT Disease Quantification and Smoking Pack Years. Curr Oncol 2023;30:5546-59.
12. Hong L, Aminu M, Li S, et al. Efficacy and clinicogenomic correlates of response to immune checkpoint inhibitors alone or with chemotherapy in non-small cell lung cancer. Nat Commun 2023;14:695.
13. Cascone T, Leung CH, Weissferdt A, et al. Neoadjuvant chemotherapy plus nivolumab with or without ipilimumab in operable non-small cell lung cancer: the phase 2 platform NEOSTAR trial. Nat Med 2023;29:593-604.
14. Cascone T, William WN Jr, Weissferdt A, et al. Neoadjuvant nivolumab or nivolumab plus ipilimumab in operable non-small cell lung cancer: the phase 2 randomized NEOSTAR trial. Nat Med 2021;27:504-14.
15. Deboever N, Zhang J. Neoadjuvant chemo-immunotherapy for lung cancer: how much is too much? Transl Lung Cancer Res 2022;11:2360-3.
16. Deng H, Liang H, Chen J, et al. Preoperative immunochemotherapy for locally advanced non-small cell lung cancer: an analysis of the clinical outcomes, optimal number of cycles, and peripheral immune markers. Transl Lung Cancer Res 2022;11:2364-81.
17. Antonia SJ, Villegas A, Daniel D, et al. Durvalumab after Chemoradiotherapy in Stage III Non-Small-Cell Lung Cancer. N Engl J Med 2017;377:1919-29.
18. Nelson DB, Mehran RJ, Mitchell KG, et al. Enhanced recovery after thoracic surgery is associated with improved adjuvant chemotherapy completion for non-small cell lung cancer. J Thorac Cardiovasc Surg 2019;158:279-286.e1.
19. Nelson DB, Rice DC, Mitchell KG, et al. Return to intended oncologic treatment after surgery for malignant pleural mesothelioma. J Thorac Cardiovasc Surg 2019;158:924-9.
20. Provencio M, Nadal E, Insa A, et al. Neoadjuvant chemotherapy and nivolumab in resectable non-small-cell lung cancer (NADIM): an open-label, multicentre, single-arm, phase 2 trial. Lancet Oncol 2020;21:1413-22.
21. Ostrin EJ, Sidransky D, Spira A, et al. Biomarkers for Lung Cancer Screening and Detection. Cancer Epidemiol Biomarkers Prev 2020;29:2411-5.
22. Provencio M, Serna-Blasco R, Nadal E, et al. Overall Survival and Biomarker Analysis of Neoadjuvant Nivolumab Plus Chemotherapy in Operable Stage IIIA Non-Small-Cell Lung Cancer (NADIM phase II trial). J Clin Oncol 2022;40:2924-33.
23. Saad MB, Hong L, Aminu M, et al. Predicting benefit

from immune checkpoint inhibitors in patients with non-small-cell lung cancer by CT-based ensemble deep learning: a retrospective study. Lancet Digit Health 2023;5:e404-20.
24. Wu J, Li C, Gensheimer M, et al. Radiological tumor classification across imaging modality and histology. Nat Mach Intell 2021;3:787-98.
25. Blidner AG, Choi J, Cooksley T, et al. Cancer immunotherapy-related adverse events: causes and challenges. Support Care Cancer 2020;28:6111-7.
26. Cousin S, Seneschal J, Italiano A. Toxicity profiles of immunotherapy. Pharmacol Ther 2018;181:91-100.
27. Deboever N, Eisenberg MA, Antonoff MB, et al. Perspectives, risk factors, and coping mechanisms in patients with self-reported financial burden following lung cancer surgery. J Thorac Cardiovasc Surg 2023. [Epub ahead of print]. doi: 10.1016/j.jtcvs.2023.05.044.
28. Deboever N, Eisenberg M, Hofstetter WL, et al. Financial Toxicity in Patients With Resected Lung Cancer. Ann Surg 2023;278:1038-44.

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