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Perspective

Neoadjuvant checkpoint inhibition in non-small cell lung cancer: Is earlier unquestionably better than later?

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A B S T R A C T

On March 4th 2022, nivolumab received regular US Food and Drug Administration approval, based on the CheckMate 816 trial results, for use "with platinum-doublet chemotherapy for adult patients with resectable NSCLC in the neoadjuvant setting". This is the first neoadjuvant approval of a checkpoint inhibitor, a unique event in the history of lung cancer treatment. However, open questions remains. First, the co-primary endpoints of the CheckMate 816 trial (event-free survival and pathological complete response) are not yet validated surrogate endpoints in this setting. Second, the control arm was not reflecting the most common approach, being upfront surgery followed by adjuvant chemotherapy. Third, protocol changes were not plainly justified, questioning the analytic plan of the trial. Fourth and last, a subpar access to checkpoint inhibitor for patients upon progression may weaken overall survival results. Neoadjuvant strategies allow to study initial response under treatment, and constitute an encouraging therapeutic avenue. However, the best sequence of treatment is the key question in the neoadjuvant or adjuvant settings: is treating everyone upfront better than treating only patients that will eventually recur?Investigating optimal sequence strategy is even more critical within the checkpoint-inhibitor era, where patients with advanced or metastatic disease may present long-term advantage. Trials with optimal post-progression treatment are needed to help optimize our treatment algorithm, and spare toxicity for patients who don't derive benefit.

On March 4 2022, nivolumab received US Food and Drug Administration (FDA) regular approval, based on the CheckMate 816 trial results, for use "with platinum-doublet chemotherapy for adult patients with resectable non-small cell lung cancer (NSCLC) in the neoadjuvant setting". This approval is occurring in a changing landscape in the adjuvant setting of lung cancer with more options available. Atezolizumab was FDA approved in 2021 "following resection and platinum-based chemotherapy in patients with stage II to IIIA NSCLC whose tumors have PD-L1 expression on $\geq$ 1% of tumor cells" based on the IMPower010 trial [1]. Osimertinib was FDA approved in 2020 as an adjuvant therapy after tumor resection in patients with EGFR mutations based on the ADAURA trial [2]. However, the CheckMate 816 trial led to the first neoadjuvant approval of an immune checkpoint-inhibitor (ICI) in lung cancer.

CheckMate 816 was a phase 3, open label trial, that randomized 358 patients with resectable, stage IB ($\geq$4 cm) to IIIA NSCLC (according to 7th edition of the American Joint Committee on Cancer), to receive platinum-based chemotherapy with or without nivolumab. A tumor sample was required to assess for PD-L1 expression before treatment, and patients with tumors harboring EGFR or ALK alterations were excluded. Event-free survival (EFS) and pathological complete response (pCR), assessed by blinded evaluation, were co-primary endpoints. The nivolumab arm achieved a 31.6 months median EFS, compared to 20.8 months median EFS in the control arm (HR = 0.63; 97.38% CI: 0.43-0.91; P = 0.005). Pathologic complete response (pCR) was found in 24.0% in the chemo-immunotherapy arm vs 2.2% in the chemotherapy group ($P < 0.001$), with a benefit seen in all key subgroups [3]. Despite understandable enthusiasm, open questions remain. Here we highlight four.

First, whether EFS and pCR are faithful surrogates for overall survival (OS) or quality of life (QoL) with neoadjuvant checkpoint inhibitors in lung cancer remains unknown [4,5]. Per their own statutory language, in order to grant regular approval to nivolumab based on a surrogate, the FDA must feel that EFS and pCR are "reasonably likely to predict" an advantage in direct patient-centered outcome (being OS and QoL). Surrogate validation is conducted in a specific tumor type, a specific setting, under a specific class of treatment [4]. High correlation under some circumstances may vanish in others. In the neoadjuvant setting, data supporting correlation between pCR and OS are derived from patients treated with chemotherapy, such correlation is still lacking after neoadjuvant checkpoint inhibitors [6]. An association have been suggested between pCR and EFS in a post-hoc analysis of the CheckMate 816 trial [7]. However, these are two surrogates endpoints, and EFS may not predict OS. Given this fact, the FDA should have

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utilized the accelerated approval pathway, requiring the company to confirm an OS benefit before conversion into regular approval, providing an important safeguard to patients.

Second, we question the study design, and the choice of neo-adjuvant chemotherapy as the control arm.[8] Systemic therapy before surgery may be appealing to avoid any delay in the initiation of adjuvant treatment. The median lengths of stay (LOS) after lung cancer surgery, however, is reported to be around 5 to 7 days, yet with wide variations according to patient characteristics [9,10]. Nonetheless, neoadjuvant chemotherapy is not the most usual standard-of-care in NSCLC: this strategy in resectable NSCLC was tested in few trials. Conversely, surgery followed by adjuvant chemotherapy remains the most common approach. The LACE meta-analysis supported the adjuvant approach by follow-up of 4584 randomized patients [11]. In this meta-analysis, the benefit of cisplatin-based doublet chemotherapy was established, with a 5-year absolute benefit of 5.4% after adjuvant chemotherapy. Critically, no randomized trial compared neoadjuvant to adjuvant approaches [5]. We worry that neoadjuvant therapy may be inferior to a surgery-first strategy, yet the availability of a new drug will incentivize this paradigm shift, despite limited empirical data supporting it.

Third, CheckMate 816 reports eight amendments and versions. The nivolumab plus chemotherapy arm was added midstream, an initial arm (ipilimumab plus nivolumab) was closed, and primary endpoints were changed.[] [3]. While investigators should be commended to assessing novel external data to modify an ongoing trial, the numerous changes in CheckMate 816, including in the ultimate versions, are concerning (eg "Removed the first of 2 interim analyses of EFS and updated alpha spending on the remaining interim and final analyses of EFS" in revision 6 and "Include one additional EFS interim analysis at 90% information fraction" in amendment 7). These changes raise the question of whether *p-hacking* - the idea that investigators may modify analytic plans with preliminary knowledge of results until a desired result, a nominally significant *p*-value ($p < 0.05$), is achieved – occurred [12] (some parts of the amendments, which may help clarify, are redacted).

Fourth, use of ICI for metastatic recurrence, which is the indisputable global standard, was absolutely subpar. Among patient receiving systemic therapy at progression, only 65% received an immune checkpoint inhibitor (ICI) in the control arm. When companies aim to move into earlier settings drugs that already benefited patients in latter lines, the question is whether early administration (to everybody) is better than treatment only to those progressing. In CheckMate 816, every patient, initially thought to be eligible for the ICI-containing experimental arm, should have had access to this class of treatment at progression. Poor access to post-progression ICI therapy - 35% of patients receiving another treatment - is not acceptable. The most likely explanation is that the trial was run globally, including in countries with limited access to optimal treatment after the trial ended. However, this explanation raises two issues. First, a trial run globally is more likely to result in subpar post-progression treatment which may drive part of the positive results. However, those results may erode in places with optimal treatment upon progression, like in the US or Europe where companies are seeking approvals. Second, after the trial ends, low- and middle-income countries have very limited access to these cutting-edge treatments, therefore deepening global inequities in healthcare access.

The first and fourth point share a commonality. Relationships between EFS and OS were derived from cytotoxic drugs, which are capable of eradicating microscopic tumor (in the adjuvant setting), but when given in the metastatic setting do not result in cure. Yet, immunotherapy has resulted in durable remissions even when disease burden is high [13]. Thus, the surrogacy of EFS must be questioned and it is vital to know if OS benefits still persist when post-progression treatment includes ICI. If the same survival can be achieved, why subject many more patients to unnecessary side effects, therapeutic burden, and cost?

The CheckMate 816 trial has decisive limitations: protocol changes were not plainly justified, primary endpoints are lacking validated surrogacy, and post-progression treatment was inferior to the usual care. NSCLC carries a poor prognosis, with high rates of relapse even after curative intended treatment. Neoadjuvant strategies have strengths, unlocking the understanding of pathologic and molecular initial response, which is precluded with upfront surgery. The key question in a neoadjuvant trial is about sequence of treatment, this is even more important in the immunotherapy era, with patients with metastatic disease having long-term benefits. Trials studying the best sequence of a drug, like a neoadjuvant trial of a drug already proven to be beneficial in the metastatic setting, should provide the standard-of-care to those who progress. This is needed to help refine our treatment algorithms, and spare toxicity to patients who do not derive benefit.

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Authors contribution statement

Authors' contributions: VP and TO contributed to the conception. TO wrote first draft of manuscript and all authors reviewed and revised the manuscript. All authors provided final approval of the manuscript.

Declaration of Competing Interest

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