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Improved survival for patients with lung cancer treated with perioperative immunotherapy

Published **Online** September 14, 2024 https://doi.org/10.1016/S0140-6736(24)01920-2

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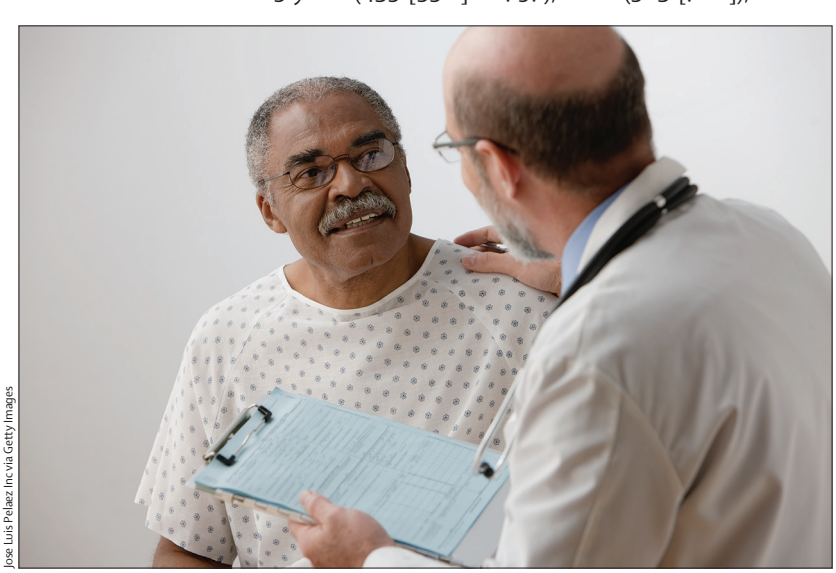
Neoadjuvant and perioperative immune checkpoint inhibitor (ICI) therapy combined with chemotherapy has led to improvement in pathological response rates and event-free survival for patients with resectable non-small cell lung cancer (NSCLC).[1–3] In October, 2023, perioperative pembrolizumab in combination with platinum-containing chemotherapy as neoadjuvant treatment followed by adjuvant pembrolizumab was approved by the US Food and Drug Administration (FDA) for patients with resectable stage II–III NSCLC based on the KEYNOTE-671 trial.[3] Until now, the impact of surrogate endpoints on overall survival was uncertain. In *The Lancet*, Jonathan D Spicer and colleagues[4] report the results of a pre-planned second interim analysis from KEYNOTE-671, which was a global, phase 3 randomised trial of patients with stage II, IIIA, or IIIB (N2) NSCLC of neoadjuvant chemotherapy plus pembrolizumab followed by surgery and adjuvant pembrolizumab compared with placebo-controlled neoadjuvant chemotherapy. As previously reported,[3] the majority of participants were younger than 65 years (435 [55%] of 797), male (563 [71%]), current or former smokers (696 [87%]), and had stage III disease (558 [70%]). In this second interim analysis, Spicer and colleagues found that perioperative pembrolizumab led to improved overall survival in addition to event-free survival without a significant change in patient-reported health-related quality of life (HRQoL). The median estimated 3-year overall survival was 71% (95% CI 66–76) in the perioperative pembrolizumab group compared with 64% (58–69) in the placebo-controlled neoadjuvant chemotherapy-only group (hazard ratio [HR] 0·72 [95% CI 0·56–0·93]; p=0·0052). The median overall survival was not reached in the pembrolizumab-treated patients compared with 52·4 months in the placebo group (95% CI 45·7 to not reached). This study builds on previous practice-changing phase 3 trials demonstrating the benefit of adjuvant, neoadjuvant, and perioperative ICI therapy compared with chemotherapy-only approaches, and the improvement in overall survival reported here is a landmark in the long journey of curing more patients with NSCLC.



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With multiple approved regimens of neoadjuvant-only, adjuvant-only, and perioperative ICI therapy, oncologists now face the challenge of patient selection and treatment personalisation. Importantly, there are no direct head-to-head trials comparing these approaches, and so the contribution of each phase of treatment is impossible to discern, an issue recently raised by the FDA[5] in its review of other perioperative trials. The data presented by Spicer and colleagues are helpful in identifying those patients who benefited in terms of overall survival and, just as importantly, those who did not. In prespecified subgroup analyses, overall survival was significantly longer in patients who were younger (<65 years; HR 0·57 [95% CI 0·40–0·80]) and White (0·66 [0·49–0·90]) and in patients with stage III tumours (0·74 [0·55–0·98]) with PD-L1 expression of 50% or higher (0·55 [0·33–0·92]). Patients without improvement in overall survival included

patients aged 65 years or older (HR 0·96 [0·67–1·38]), patients without a smoking history (1·00 [0·41–2·46]), and patients with PD-L1-negative (expression <1%) tumours (0·91 [0·63–1·32]). In a post-hoc analysis, clinical nodal stage (N0 *vs* N1 *vs* N2) did not identify a specific subset with differential outcomes in overall survival.

Although this was a large, global study, there are some considerations about generalisability, especially regarding the exclusive use of cisplatin in KEYNOTE-671. For older adults, or any adult with kidney or hearing impairment, cisplatin is not indicated; in these cases, many oncologists in the USA use carboplatin. Also, the inclusion of patients with driver alterations in *EGFR* in this study—albeit a small number of patients—raises some concern. National guidelines[6] recommend that these patients receive adjuvant therapy with osimertinib,[7] since ICI therapy in these patients is generally not effective alone[8] or with chemotherapy.[9] Furthermore, sequential ICI therapy followed by tyrosine kinase inhibitor therapy might put patients at higher risk of toxicities.[10] The study consisted predominantly of White and Asian patients (>90% in both cohorts), and so under-representation of demographic groups limits interpretation for broader populations. Finally, it is also important to highlight access to post-progression ICI therapies for patients. In KEYNOTE-671, subsequent therapy uptake after disease progression was high overall (80% for pembrolizumab and 86% for placebo cohorts, respectively). However, subsequent ICI therapy was only used in 50% of patients in the placebo group, and the lack of ICI treatment at the time of progression might have substantially affected overall survival. Lastly, no information is provided regarding patient risk assessment for surgery[11] other than Eastern Cooperative Oncology Group performance status, which can under-recognise frail and pre-frail patients as compared with validated frailty assessments.

Given the lack of head-to-head trials, how should oncologists put the data together? We now know that there are groups of patients who benefit from neoadjuvant chemoimmunotherapy (with or without adjuvant ICI therapy) in terms of event-free survival and overall survival consistently across multiple studies,[1,2,4] and that for some patients, perioperative treatment will not significantly worsen their HRQoL.

To guide treatment selection, it is imperative that all patients receive appropriate biomarker testing (at least for PD-L1 by immunohistochemistry, and for mutations in *EGFR* and *ALK*, but ideally with broad-based genomic testing) and undergo multidisciplinary evaluation and risk stratification beyond disease characteristics at the time of diagnosis before starting treatment. Patients with a pathological complete response at the time of surgery seem to have the best outcomes, although how to incorporate this observation into treatment decisions remains unclear. Furthermore, since adjuvant ICI therapy might be associated with higher rates of treatment-related deaths and grade 3–4 adverse events compared with neoadjuvant ICI therapy,[12] it is still not clear which patients might benefit from the addition of adjuvant ICI therapy after neoadjuvant chemoimmunotherapy—or which patients might be harmed by it. Future studies must continue to include HRQoL to best inform patients of potential harms of treatment not captured by event-free survival or overall survival. In addition, some patients might benefit from chemotherapy-sparing immunotherapy-only approaches, although no phase 3 trial has evaluated this strategy.[13,14] Unfortunately, additional slicing and dicing of data from completed trials of perioperative ICI therapy will not be able to answer this question given the inherent design limitations of all studies done to date, particularly among a growing number of older adults with NSCLC. Pending cooperative studies in the National Clinical Trials Network will hopefully address these and other important questions, but for now this remains a critical area of ongoing uncertainty.

CJP reports honoraria from BMS, Regeneron, and Jazz Pharmaceuticals, and research funding from the BMS Foundation and Rising Tide Foundation. DHO reports support from AstraZeneca, Amgen, and Genentech for travel and research funding to institution from BMS, Merck, Palobiofarma, Genetech, AbbVie, Nuvalent, and Onc.AI. The views expressed are those of the authors only, and not representative of the National Comprehensive Cancer Network or the American Society of Clinical Oncology guidelines.

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Long-term ill health in sepsis survivors: an ignored health-care challenge?

Published **Online** September 11, 2024 https://doi.org/10.1016/S0140-6736(24)01754-9

Initiated by the Global Sepsis Alliance in 2012, World Sepsis Day falls on Sept 13 each year. Sepsis remains a global health-care problem that affects all age groups. The extrapolated annual incidence of approximately 49 million cases (with ~20 million cases in children younger than 5 years) and 11 million deaths generates approximately 38 million sepsis survivors per year.[1] There is tacit acknowledgment that sepsis survivorship is a major cause of health loss globally. However, currently no health-care system globally can claim to have a structured approach to improving sepsis survivorship in all individuals who recover from an index sepsis episode. It is in this context that we provide an overview of domains of long-term ill health in sepsis survivors, highlight illustrative knowledge gaps, and emphasise the need for a structured approach to improve sepsis survivorship.

The domains of long-term ill health in sepsis survivors can be grouped into physical and functional disability, swallowing difficulties, cognitive or mental impairment, comorbid conditions, and risk of adverse long-term outcomes.[2] These issues are thought to persist in sepsis survivors for at least 5 years after the index sepsis admission (panel). On average, adult sepsis survivors acquire one or more new functional limitations within activities of daily living.[2,4] Compared with their pre-sepsis health, sepsis survivors have a greater prevalence of cognitive impairment, mental health diagnoses (such as anxiety, depression, and post-traumatic stress disorder),[2,4] and physical frailty.[9] Further, sepsis survivors can also acquire new comorbidities, and some have worsening severity of their existing conditions. Compared with non-sepsis hospitalisations, sepsis survivors have a greater long-term risk of cardiovascular events (such as myocardial infarction, stroke, and congestive heart failure),[6] alongside worsening of chronic respiratory and kidney diseases.[2] In the year following hospital discharge, nearly 50% of sepsis survivors have one or more rehospitalisation events,[7] and one in six adult sepsis survivors die.[2,8,9]

Reasons for long-term ill health after sepsis are not well understood, which is an important consideration in designing structured approaches to improving sepsis survivorship. There seems to be a bidirectional relationship where deteriorating health is associated with increased risk for sepsis, followed by steeper subsequent health deterioration. Although one could argue that several of these issues are not unique to sepsis survivors,[10,11] the pathobiology that causes such long-term ill health might be different in sepsis survivors.

Currently there is no agreement on the definition, spectrum of clinical features, criteria, duration, or what the modifiable features and potential treatment targets are for post-sepsis chronic ill health. There is an urgent need to agree on a common terminology and clinical definition for this acquired chronic ill-health state in sepsis survivors. The current absence of an accepted definition makes it challenging to identify a trial population, which potentially explains the limited number of randomised clinical trials specifically involving the sepsis survivor population with post-sepsis ill-health.