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Immune checkpoint inhibitors in non-small-cell lung cancer: key to long-term survival?



Since the first approval of immune checkpoint inhibitors (ICIs) for non-small-cell lung cancer in 2015, the treatment landscape of metastatic non-small-cell lung cancer has changed completely. At this point, three programmed death-ligand 1 (PD-[L]1) inhibitors are approved for stage 4 non-small-cell lung cancer, in first line (pembrolizumab) and beyond (nivolumab, pembrolizumab, atezolizumab). All trials showed significantly improved overall survival compared with chemotherapy; the plateau in survival curves suggests long-term benefit. This resulted in rapid implementation of ICIs in daily practice. However, not all patients benefit from ICI because in several trials survival curves crossed and, although grade greater than or equal to 3 toxicity is lower for monotherapy ICI than chemotherapy, ICI can cause diverse and late toxicity, even after discontinuation.¹

As long-term data on overall survival and toxicity are largely lacking, results of the single arm phase 1 KEYNOTE-001 study by Natasha Leighl and colleagues,² accompanying this Comment, are of interest: they could help to improve selection of patients for ICI treatment.

Pembrolizumab (different doses and schedules) was investigated in 550 patients with non-small-cell lung cancer (101 previously untreated, 449 previously treated). Most (82%) had a PD-L1 tumour proportion score (TPS) greater than or equal to 1%: TPS was less than 1% in 12 (12%) of patients who were previously untreated and 90 (20%) of patients who were previously treated. The study was first published in 2015,³ and the authors are to be applauded for providing the long-term overall survival data. With an updated median (minimum) follow-up of 34.5 (25.7) months, the estimated 3-year survival was 26.4% in previously untreated patients and 19.0% in previously treated patients, it was highest in those with a PD-L1 TPS of greater than or equal to 50% (25.2% in previously untreated and 29.7% in previously treated patients). 12% experienced grade 3–5 treatment related adverse events (TRAE), mostly within the first year of treatment and no late (ie, between years 2 and 3) grade 3–5 TRAEs were observed.

How do these data compare with other non-small-cell lung cancer ICI studies with long-term follow-up available? Other data come from the phase 2–3

KEYNOTE-010 (pembrolizumab versus docetaxel),⁴ the phase 1 CA209-003 (nivolumab),⁵ a pooled analysis of the phase 3 CheckMate-017 and CheckMate-057 (nivolumab vs docetaxel),⁶ and the phase 2 POPLAR trial (atezolizumab vs docetaxel).⁷ A difference between the KEYNOTE-001 and the others is that only the KEYNOTE-001 trial also included previously untreated patients.

All these trials show that approximately one-fifth (17–23%) of the patients treated with ICI have long-term benefit. Who are they and is it possible to select these patients beforehand? Nearly all long-term survivors had at least a partial response to ICI, with most responses occurring in the first months of treatment. Those with a high PD-L1 expression had the highest survival prevalence, but also some patients with low or negative PD-L1 levels survived 3 years or more. Data regarding the effect of tumour histology on survival in previously treated patients are conflicting, as in the KEYNOTE-001 trial, those with squamous histology had the longest survival, whereas in the POPLAR study the opposite was found. In KEYNOTE-010, CA209-003, and CheckMate-017–CheckMate-057, no differences were found. In contrast to the previously reported subgroup analysis of the KEYNOTE-001 trial (single institution, n=98),⁸ in this updated analysis, previous radiotherapy was not associated with improved survival. In general, those with an *EGFR*-mutation or *ALK*-rearrangement benefit less from ICI than those without.⁹ As is clear from the KEYNOTE-001 and the other trials, additional predictive factors for long-term ICI benefit should be evaluated.

Regarding toxicity in all the trials above, percentage TRAE grade 3–5 was similar (10–19%) and most of the grade 3–5 toxicity occurred in the first year or even the first months of treatment. This is an important finding for physicians, and underlines why especially in the first months of ICI treatment, close monitoring is advised. However, patients and physicians should be aware that, although rare, toxicity can occur late or even after discontinuation of ICI.

Another important question is the duration of ICI treatment. In the KEYNOTE-001 trial, patients with a complete response could discontinue treatment



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after 6 months, and those with a partial response or stable disease could discontinue after 24 months. Interestingly, 35 (73%) of 48 patients chose to continue pembrolizumab. Information on subsequent progression or rechallenge pembrolizumab was not provided. In the KEYNOTE-010 trial, 79 (12%) of 682 patients completed 2 years of pembrolizumab. 25 (32%) of 79 progressed off-pembrolizumab, 13 were retreated, and 6 (46%) of 13 responded. These results suggest that most responding patients completing 2 years of ICI can safely discontinue ICI. Is it possible to discontinue earlier? On the basis of the CheckMate-153 trial, discontinuing treatment on completion of 1-year nivolumab (regardless of response) is inferior compared with continuing nivolumab.¹⁰ The question remains whether a shorter treatment time is possible in those with a complete response. Furthermore, the role of discontinuing ICI on PET metabolic response,¹¹ or a lower ICI dose or longer interval between cycles in responding patients is unclear and should be evaluated further.

In conclusion, monotherapy with ICI provides promising 3-year overall survival data in both previously untreated and previously treated patients with locally advanced or metastatic non-small-cell lung cancer, being most prevalent in responders and patients with a high PD-L1 TPS score.

*A-M C Dingemans, L E L Hendriks

Department of Pulmonary Diseases, GROW School for Oncology and Developmental Biology, Maastricht University Medical Centre, Maastricht, Netherlands
a.dingemans@mumc.nl

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Burnout in women intensivists: a hidden epidemic?



Although the number of women entering medical training worldwide has largely reached parity with that of men, gender disparities remain, and fewer women than men are employed as intensivists worldwide. Inadequate gender parity in the intensive care workforce might adversely affect organisational diversity and can have unintended ramifications on collaboration and collective intelligence.¹ Efforts to attract and retain a more balanced workforce of women and men intensivists could pay large dividends by impacting important metrics such as quality of care, career satisfaction, and physician retention. These metrics are all adversely affected by burnout syndrome.²

The effects of burnout might be magnified in the intensive care unit (ICU) context, where attrition of the clinical workforce can pose a serious financial burden to health-care systems.³

Burnout develops insidiously. Although symptoms are generally not present early in employment, over time, affected individuals gradually develop emotional stress, disillusionment in their roles, increasing inability to adapt, and excessively negative work-related attitudes. Burnout syndrome is characterised by emotional exhaustion, being unable to find meaning in work, feelings of ineffectiveness, depersonalisation, and a

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