

EDITORIAL



## Immune checkpoint inhibitors in cancer treatment and potential effect modification by age

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Immune checkpoint inhibitors (ICIs) have revolutionized the treatment of several advanced cancer forms and were rewarded the Nobel Prize in 2018 [1]. The introduction of this new class of monoclonal antibodies has brought major improvements particularly in the treatment of metastatic melanoma and non-small cell lung cancer (NSCLC) and a few other cancer forms. The anti-cytotoxic T-lymphocyte-associated protein 4 (anti-CTLA-4) inhibitor ipilimumab was the first drug ever showing an effect on overall survival (OS) in advanced melanoma in 2011 [2,3]. Some patients achieved long-term survival with ipilimumab but the response rates were still relatively low, approximately 20%. Anti-programmed death-1 (anti-PD-1) treatment has shown superiority compared to anti-CTLA-4 in advanced melanoma [4,5]. For example, among patients receiving pembrolizumab as first line therapy, the median OS was 38.7 versus 17.1 months for ipilimumab (hazard ratio (HR) = 0.73,  $p = .0036$ ) [4]. By combining anti-CTLA-4 (ipilimumab) and anti-PD-1 (nivolumab), objective response rates (ORRs) and OS have increased further [5]. Recently, immune checkpoint inhibitors were also introduced as standard of care in the adjuvant setting of completely resected III–IV melanoma patients at high risk for recurrence [6,7]. In NSCLC, the introduction of ICIs has also resulted in clear survival benefits. Here the programmed death-ligand-1 (PD-L1) expression status (high vs. low) and tumor histology (squamous vs. non-squamous) have an impact on the management. ICIs, including antibodies against PD-L1 (anti-PD-L1), are used alone or combined with chemotherapy or targeted drugs also in NSCLC patients having progressed on platinum-based chemotherapy [8]. For example, in a pivotal study in chemotherapy-naïve NSCLC patients with high PD-L1 expression ( $\geq 50\%$ ), median progression-free survival (PFS) with pembrolizumab was 10.3 months and ORR was 44.8% [9].

The clinical trials that led to the approval of these agents represent only a small and selected proportion of the patient population where older patients are underrepresented [10]. Although individuals aged 65 years and above represent an increasing majority of patients diagnosed with cancer, the effect of ICIs has not been evaluated specifically in older

adult populations. Both cutaneous melanoma and NSCLC are cancers with high tumor mutation burden and thus a high neoantigen load which are positively linked to treatment response to ICIs [11]. The age-related dysregulation of the immune system (i.e., immunosenescence) affects both the innate and the adaptive immune responses including the function of dendritic cells, CD4<sup>+</sup> T cells, CD8<sup>+</sup> T cells, and regulatory T cells [12]. Lower levels of tumor infiltrating lymphocytes in older melanoma patients receiving immune-based therapies have been related to worse PFS and disease-free survival [13]. Old age could thus in theory decrease the response to ICIs because of immunosenescence.

In the current issue of *Acta Oncologica*, Ninomiya and coauthors address potential differences in efficacy of ICIs (CTLA-4, PD-1, and PDL-1 inhibitors) in advanced cancer by age younger or older than 65 years in a large meta-analysis [14]. The study encompasses 6104 cancer patients 65 years or older when treated with ICIs and 8157 patients younger than 65 years from 25 previously published phase 2 or 3 randomized trials where a non-ICI arm was used as standard therapy for comparison. The patients were diagnosed with metastatic melanoma or NSCLC (15 of 25 trials), but also gastric cancer, renal cell carcinoma and squamous-cell lung cancer (two trials each), mesothelioma, head and neck cancer and urothelial carcinoma (one trial each). Overall, ICIs were associated with a statistically significantly improved survival compared to standard treatment of similar magnitude (20–25%) in younger and older patients. In sub-analyses by type of ICI, there was an indication of a differential effect by age with use of CTLA-4 inhibitor treatment with less improvement among the elderly, although this potential effect modification was not statistically significant. Results for anti-PD-1 and anti-PD-L1 were similar by age. Further stratifications by cancer type, trial design and line of treatment yielded consistent results. However, since this is a meta-analysis of previously conducted clinical trials, the preference of inclusion of younger fit individuals is conserved. Hence, the need for further evaluation in elderly patients above 70 and even higher ages remains.

A few other studies have also evaluated potential age differences in effect of ICIs in previously conducted trials with similar results. For example, a smaller meta-analysis including nine randomized clinical trials of PD-1 and PD-L1 inhibitors in solid tumors, showed an overall random-effects HR of death of 0.64 (95% confidence interval (CI), 0.54–0.76) in patients 65 years or older, and an HR of 0.68 (95% CI, 0.61–0.75) in younger patients [15]. Still, in view of multi-morbidities and impaired functional status, the effect of ICIs among older patients could be different in a real-world setting. Interestingly, in a recent publication from the Danish national real-world cohort of metastatic melanoma patients, OS and PFS were particularly favorable when using anti-PD-1 therapy in metastatic melanoma patients in the ages 70 and 80 years, which is encouraging [16].

In conclusion, several lines of data show that ICIs are effective in older patients with advanced cancers such as melanoma and NSCLC. However, the functional status and multi-morbidities of the patients and the risk of therapy-related toxicity must be carefully considered before treatment start. A future focus could be to further investigate the biological differences between age groups aiming at improving therapy outcome of ICIs in both younger and older cancer patients.

### Disclosure statement

No potential conflict of interest was reported by the author(s).

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