Immune checkpoint inhibitors (ICIs), including pembrolizumab and nivolumab, both monoclonal antibodies against programmed cell death-1 (PD-1), and antibodies targeting the programmed cell death receptor ligand-1 (PD-L1) such as atezolizumab or durvalumab, have heralded impressive therapeutic advances in previously treated advanced non-small cell lung cancer (NSCLC). Several studies have compared ICI with standard chemotherapy, and reported an unprecedented 5-year overall survival (OS) of 15% with ICIs (1). This breakthrough was followed by a further report of a survival benefit when ICIs were administered in the first-line setting in an unselected population, both as single agents and in combination with chemotherapy or ipilimumab, compared with platinum-based chemotherapy (2).

Nonetheless, due to concerns regarding the risk-benefit ratio, patients with an ECOG performance status (PS) ≥2 are excluded or underrepresented in the contributing phase III clinical trials, despite the fact that they represent up to 25% of newly diagnosed or recurrent patients with NSCLC (3). Several studies have compared ICI with standard chemotherapy, and reported an unprecedented 5-year overall survival (OS) of 15% with ICIs (1). This breakthrough was followed by a further report of a survival benefit when ICIs were administered in the first-line setting in an unselected population, both as single agents and in combination with chemotherapy or ipilimumab, compared with platinum-based chemotherapy (2).

Nonetheless, due to concerns regarding the risk-benefit ratio, patients with an ECOG performance status (PS) ≥2 are excluded or underrepresented in the contributing phase III clinical trials, despite the fact that they represent up to 25% of newly diagnosed or recurrent patients with NSCLC (3). Similarly, although median age at diagnosis is over 70 in almost 50% of cases, with 15% of the population being more than 85 years (4), this older population is also not represented in clinical trials. Additionally, 50% of elderly patients in daily clinical practice have an ECOG PS of 2 (5). Two key points arising from this bias in “over-selecting” the eligible population for phase III trials evaluating ICIs are firstly that it may explain the outcome discrepancies with the real-world population treated with ICIs (6), and secondly, the efficacy of ICIs in the elderly population and in patients with ECOG PS 2 (elderly or not) is unknown.

Various clinical trials in pre-treated NSCLC patients, such as the CheckMate 171 (7), CheckMate 169 (8), TAIL (9) and PeP2 trials (10), as well as pooled analyses (11,12) and retrospective evaluations (5,13-16) have shed light on the outcomes with ICIs in these frail populations. The phase IIIB/IV CheckMate 153 study reported by Spigel et al. (17) describes as a primary endpoint the safety [incidence of grade 3 to 5 selected treatment-related adverse events (TRAEs)] and outcome of nivolumab in 1,426 advanced unselected previously treated NSCLC patients. Importantly, the subgroups of frail patients were large, and included both elderly patients (≥70 years, N=556, 39%) and patients with ECOG PS ≥2 (N=128, 9%). Of note, PD-L1 expression <1% and ≥50% was reported in the same proportion in the overall population as well as in both subgroups, reaching 40% and 20%, respectively. Similar incidence of selected grade 3 to 5 TRAEs (6–9%) and grade 3 or 4 TRAEs (12–14%) were reported between subgroups and the overall population. The median OS in the overall population was of 9.1 and 10.3 months in patients aged
≥70 years. Patients with an ECOG PS of 2 or more presented a shorter median OS (4.0 months). In the global population, OS was longer in PD-L1 positive tumours, however, OS according to PD-L1 expression in the frail populations is not reported. The most common reason for treatment discontinuation was disease progression, with a 50% progression rate in the overall population and in both subgroups.

These CheckMate 153 survival and safety data mirror those reported in a pooled analysis of pivotal phase III clinical trials with nivolumab (CheckMate 017 and CheckMate 057) (18), however in the latter trials, the proportion of patients aged ≥75 years was below 10% and ECOG PS ≥2 patients were excluded. In contrast with the overall population, nivolumab was not associated with an increased OS benefit in 72 elderly patients (≥75 years) compared with chemotherapy (HR =1.19) (1). This is of relevance as some studies have reported that elderly patients (≥70 years) had shorter PFS and OS than younger individuals, without a difference in immune related adverse events, but without reported stratification according to ECOG PS (19).

Real-world studies in elderly patients (defined as age ≥75 years) have demonstrated no differences in clinical outcomes with nivolumab compared to non-elderly patients, whereas those with a poor ECOG PS (≥2) had inferior outcomes even when adjusting for age (20). Other real-world cohorts (5,6,13) have reported that the benefit with ICIs in previously-treated and elderly NSCLC patients was comparable to younger counterparts, even using different age cut-offs, and some retrospective data have reported efficacy of patients aged ≥80 years, albeit with small sample sizes (5,21). Similarly, among 10,452 French NSCLC patients who initiated nivolumab in 2015 as second-line therapy or beyond, 514 (4.9%) were 80 years or over (median age 82.5 years), and their median OS was similar to non-elderly patients (11.5 months in both age-subgroups). In this cohort, comorbidities were statistically less frequent in the elderly group (P<0.001), which may reflect an over-selection even in the routine setting (22). Octogenarians may get benefit from this ICI, but comorbidities and PS are relevant for making treatment decisions in this subgroup. Importantly, the upper age limit for ICIs, if of value, has not been established. Data coming from a recent meta-analysis enrolling 5,265 cancer patients from nine randomized controlled trials did not observed differential efficacy of ICIs according to age. However, this meta-analysis only included two trials concerning NSCLC. Sixteen percent of all patients, 854 of 5,265 patients, were enrolled. The exploratory subgroup analysis did not report significant OS benefit with anti-PD-1 agents in patients older than 75 years (12). Although the CheckMate 153 trial (17) enrolled patients ≥70 years, the proportion of patients aged ≥75 or ≥80 remains unknown so firm conclusions in these specific subgroups of age cannot be made.

One concern is the potential correlation between the elderly and an immune phenotype of primary resistance through a paradoxically higher concentration of inflammatory cytokines and autoantibodies, a phenomenon probably linked to the progressive and continuous deterioration of the immune system functions with ageing, known as immunosenescence (23,24). In cancer patients, older age (≥65 years) during ICI treatment has been correlated with increased risk of hyper-progressive disease (25), however, this association was not observed in a cohort of NSCLC patients (26) or in the CheckMate 153 study, with a 50% progression rate in the overall population and both subgroups (17). Indeed, immunosenescence defined by a CD28 CD57 ‘KLRG1’ phenotype on peripheral T-lymphocytes, which occurs in one-third of advanced NSCLC patients and correlates with a lower disease control rate for ICIs, is independent of age (27).

Results of the CheckMate 153 trial in ECOG PS ≥2 patients suggest that safety with ICIs is consistent with the overall population, although it is known that tolerance of chemotherapy is worse (17). However, efficacy is limited with a median OS ranging from 3.4 to 5.9 months (5-17), suggesting poor PS is a negative predictive and prognostic factor for ICI treatment. Surprisingly, the PeP2 study assessing the role of pembrolizumab in 60 patients with ECOG PS ≥2 reported a response rate of 25.5% and median progression-free survival and OS of 6.0 and 12.1 months, respectively, with 12% grade ≥3 adverse events. Different factors contribute to patients’ PS scoring such as age, symptoms related to lung cancer and comorbidities. Therefore, discrepancies in any of these characteristics in the PeP2 study for selecting PS 2 patients may have contributed to explain differences in outcome. The predictive role of PD-L1 expression seems controversial in ECOG PS ≥2 patients, as despite that 20% of ECOG PS ≥2 patients in CheckMate 153 (17) and PeP2 (10) having tumors expressing PD-L1 ≥50%, median OS is three times longer in the PeP2 trial (10).

Clearly, besides chronological age, an optimal geriatric assessment, along with validated fragility and comorbidity scales, such as FRAGIL, polypharmacy or the Charlson...
index, may be necessary to obtain a global medical picture with the aim to select elderly patients and ECOG PS ≥2 patients who may obtain most benefit from ICI therapy.

The CheckMate 153 study endorses ICI efficacy in previously-treated elderly patients and suggests ICIs as an alternative treatment strategy in ECOG PS ≥2 patients with their better safety profile than chemotherapy. Stratifying the benefit according to geriatric assessment and PS in elderly patients and defining the optimal ECOG PS ≥2 patients for receiving ICIs, based on age, comorbidities and disease-related factors, are future achievable challenges for defining the optimal ICI therapy in these subgroups.

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Footnote

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