Immunotherapy in older patients with non-small cell lung cancer: Young International Society of Geriatric Oncology position paper.

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Abstract

Immunotherapy with checkpoint inhibitors against programmed cell death receptor (PD1) and programmed cell death ligand (PD-L1) has been implemented in the treatment pathway of non-small cell lung cancer (NSCLC) from locally advanced disease to the metastatic setting. This resulted in improved survival and a more favourable toxicity profile, when compared with chemotherapy. Following the introduction of single-agent immunotherapy agents, ongoing clinical trials are focusing on combinations with chemotherapy and radiotherapy. However, most of the data available from clinical trials is limited to younger and fitter patients rather than older and often frail lung cancer real-world patients. This article provides a detailed review of these agents with a focus on the data available regarding older NSCLC patients.

Keywords

Immunotherapy; lung cancer; NSCLC; elderly; older; SIOG

1. Introduction

More than half of non-small cell lung cancer (NSCLC) patients are aged above 70 and almost 10% are 80 years and older [1]. The incidence of NSCLC in older adults is expected to increase in the context of an ageing general population. The management of NSCLC in older adults is complex since they are a heterogeneous population. The physiologic age-related decline of organ function involving liver, kidney, bone marrow, heart and muscle underlies loss of functional reserve that can alter drug pharmacokinetics and increase the risk of complications of locoregional and systemic treatments in this age group [2, 3]. This risk is also influenced by the increasing burden of comorbidities in older cancer patients, which is associated with worse survival [4]. Polypharmacy can also enhance the risk of drug interactions and adverse events and affect treatment compliance in this cohort [5]. Moreover, quality of life (QOL) and functional endpoints are not well represented in clinical trials and should be considered at least as relevant as overall survival (OS) [6, 7].

Chronologic age alone provides relatively little information regarding older patients' tolerance to cancer treatments. A comprehensive geriatric assessment (CGA) can fill this gap of knowledge and inform treatment decisions (Table 1). CGA is a multidisciplinary diagnostic and treatment process able to identify medical, psychosocial and functional limitations of older adults and facilitate a coordinated plan to maximize overall health in the context of aging [8]. In older cancer patients, the use of CGA is associated with a number of benefits [9, 10]: prediction of complications and side effects from treatment; estimation of survival; aiding patients, clinicians and family members in treatment decisions; detection of problems neglected by routine history and physical examination in the initial evaluation and new problems during follow-up care; improvement of mental health, well-being and pain control; and highlighting areas for potential intervention. Geriatric assessments have also been found to show prognostic value specifically in NSCLC patients [11, 12]. Furthermore, models based upon geriatric assessments have been developed to predict the risk of chemotherapy toxicity in older adults

and better inform decision making [13, 14]. However, these assessment may be time consuming and not practical for all patients and therefore screening tools have been validated to identify those requiring a CGA [15].

Appropriately selected older NSCLC patients derive similar survival benefit compared to their younger counterparts in the curative setting [16, 17]. Nonetheless, the underrepresentation of older adults in clinical trials defining the current standard of care limits the applicability of evidence to the population seen in routine practice [7, 18]. In the palliative setting, if chemotherapy is indicated decision-making should not rely on age alone [19-21]. Single-agent chemotherapy can improve OS without adversely impacting QOL compared to best supportive care alone [22-24]. However, data are controversial regarding the benefit of combination chemotherapy in this age group, particularly those that are more frail [21, 25]. The administration of tyrosine kinase inhibitors (e.g., epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK) and ROS-1) is the treatment of choice in oncogene-addicted NSCLC for their superiority in survival outcomes and the mild toxicity profile. Although these agents are often a good match for older patients, this is a small subset of NSCLC and older patients may still be at higher risk of toxicity.

Immune checkpoint inhibitors targeting either programmed death receptor 1 (PD-1) or programmed death receptor-ligand 1 (PD-L1) have recently revolutionised the management of NSCLC and represent a potentially appropriate treatment option also for older adults. Here we review the data supporting the use of immunotherapy in NSCLC with a particular focus on the evidence for older patients, and the potential impact of the ageing process on efficacy. Immunotherapy is associated with a unique spectrum of treatment-related adverse events (TRAEs) also known as immune-related adverse events. They include dermatologic, gastrointestinal, hepatic, endocrine and other less common inflammatory events arising from general immunologic enhancement [26].

2. Immunotherapy in older cancer patients

2.1. Mechanism of action and immunosenescence

A strict regulation of the immune system is crucial in allowing it to coordinate the clearance of infected or malignant cells and to spare normal cells. In addition, mechanisms to down-regulate immune response are important to prevent immune over-reactivity once a pathogenic insult has been cleared and where cells different from self are encountered in a physiological setting such as gamete formation or the foetus during pregnancy [27].

Escaping the immune system is one of the hallmarks of cancer. Cancer hijacks the key regulatory mechanisms of the immune system which allows its survival [28]. The importance of inhibitory checkpoint signals on T-cells in immune evasion led to the development of monoclonal antibodies blocking: 1) the interaction between cytotoxic T-lymphocyte associated protein 4 (CTLA4) on the tumour and B7 on the T-cell that inhibits T-cell priming activation; and 2) the interaction between PD-L1 on the tumour and PD-1 on the T-cell that inhibits recognition of the tumour cells by T-cell and subsequent tumour cell lysis [29].

Monoclonal antibodies anti-PD-1/PD-L1 are now standard treatment options for a number of malignancies including NSCLC. Ongoing research is investigating the role of multiple targets in thoracic malignancies including other stimulatory/inhibitory receptors at the T-cell checkpoint and the use of novel agents in combination with currently licensed agents [27, 30].

Older age correlates with organ function decline [31]. This involves also the composition and function of the immune system, including its cells, the microenvironment where they operate and the cytokines modulating their proliferation and activity [32], which in principle may result in an altered efficacy and safety profile of immunotherapy agents in the older cancer patient. The remodelling of the immune system associated with the ageing process

is called immunosenescence [32]. This represents a number of changes that can be associated with a decrease in immune surveillance both in the adaptive and innate immune system. This manifests clinically in the older patient with an increased risk of viral and bacterial infections and reactivation of latent infections such as Varicella Zoster Virus and Cytomegalovirus (CMV) [33, 34].

In older individuals, chemotaxis, phagocytosis and cytotoxicity are impaired, including the mechanisms of antigen presentation by macrophages and dendritic cell [35]. The responsiveness of T-cells to pathogens decreases with age and involves reduced ability to move to lymph nodes, lower proliferation in response to antigens and cytokines and reduced cytokine release. These changes result in the loss of the co-stimulatory protein CD28 particularly in CD8 lymphocytes throughout life [36]. CD8+ CD28- lymphocytes down-regulate responses via CD4+ cells and dendritic cells and are often clonally expanded, reducing the numbers of both naïve and central memory T-cells. The impact of recurrent infections, in particular CMV infections, on naïve T-cells is deemed to be a key contributor to these changes [37]. Interestingly, CD8+ CD28- lymphocytes gain other functions, with increased cytotoxicity effects through enzymes usually found in NK cells [38]. Although higher levels of auto-antibodies are seen in the older patient, it is still unclear whether these changes translate into increased risk of side effects on immunotherapy agents [39]. Additionally, it has been suggested that older adults have also higher levels of myeloid derived suppressor cells and T-regulatory (T_{reg}) cells [40, 41] which are key mediators of immune evasion and resistance to checkpoint inhibitors. Older age is associated with higher levels of systemic inflammation with higher levels of pro-inflammatory cytokines such as interleukin-6 (IL-6) and acute phase proteins such as C-Reactive Protein, a phenomenon often called “inflammaging” [42]. Whilst high levels of IL-6 in the tumour micro-environment are associated with resistance to checkpoint inhibitors [27, 43], more research is needed on the implications of inflammaging

on outcomes of immunotherapy [32]. Lastly, age also influences the interaction between microbiome and immune system. Animal models and clinical series suggest that microbiome changes influence the efficacy of checkpoint inhibition [44] and therefore the decline in microbiota diversity associated with ageing may have a negative impact [45].

2.2. Single-agent immunotherapy

Pembrolizumab. This anti-PD1 monoclonal antibody was the first checkpoint inhibitor agent investigated in the management of advanced NSCLC. The phase 3, randomized KEYNOTE-010 trial investigated the use of pembrolizumab in pre-treated patients with PD-L1 ≥1% versus docetaxel [46]. The median OS was 10.4 versus 8.5 months, favouring pembrolizumab (HR 0.71, 95%CI 0.58-0.88; p=0.0008) and a higher PD-L1 expression was associated with better outcomes (HR 0.54, 95% 0.38-0.77; p=0.0002 in the PD-L1 ≥50% sub-group). In this setting, the median OS improvement was 13% inferior for patients aged ≥65 years (Table 2). However, this trial recruited a small proportion of older patients resulting in wide confidence intervals. In the first-line setting, the phase 3 KEYNOTE-024 randomized NSCLC patients with tumour PD-L1 expression of ≥50% to pembrolizumab versus standard-of-care first-line platinum-based chemotherapy [47]. The median overall survival (OS) was 30 versus 14.2 months, favouring pembrolizumab (death HR 0.49; 95% CI, 0.34-0.69, adjusted for crossover). The OS benefit was consistent across sub-groups (Table 2). The 3-year survival update confirmed the durable survival benefit of pembrolizumab with 43.7% of patients alive versus 24.9% on the chemotherapy arm (death HR 0.65; 95% CI, 0.50-0.86; p<0.01) [48]. The phase 3 randomized KEYNOTE-042 had a similar design and treatment arms but randomised patients with PD-L1 expression ≥1% [49]. The median OS was consistently superior for the pembrolizumab arm regardless of PD-L1 expression (≥1%, ≥20% and ≥50%), although the magnitude of benefit was smaller in case of lower PD-L1 expression (HR 0.81, 95% CI 0.71-

0.93, p=0.0018, for ≥1% expression versus HR 0.69, 0.56-0.85, p=0.0003 for ≥50% expression). However, there was no benefit with pembrolizumab when explored in the sub-group of PD-L1 1-49%. In regard to older patients, the OS benefit was similar across sub-groups (Table 2).

No age-specific data on toxicity are available from these 3 trials but the overall incidence of TRAEs grade 3-5 varied between 13-31% with pembrolizumab versus 35-53% with chemotherapy [46, 47, 49].

A recent pooled analysis of the above-mentioned phase 3 trials focused on the efficacy and safety for patients with 75 years or above and confirmed an OS benefit on pembrolizumab (either PD-L1 ≥1% or ≥50%) versus chemotherapy, with a favourable toxicity profile similar to their younger counterparts [50, 51].

Nivolumab. The anti-PD1 monoclonal antibody Nivolumab was first evaluated in patients who had previously been treated with platinum doublet chemotherapy within two phase 3 trials. The CHECKMATE-017 and CHECKMATE-057 trials randomized patients regardless of PD-L1 expression to nivolumab versus docetaxel for squamous and non-squamous NSCLC subtypes, respectively [52, 53]. Several pooled analyses of both trials with increasing follow-up periods have been published and the 5-year pooled analysis represents the longest survival follow-up with immunotherapy for randomized phase 3 trials in advanced NSCLC [54-57]. This latest analysis confirmed the long-term OS benefit of nivolumab (HR 0.68; 95%CI 0.59-0.78) with an OS rate at 5 years of 13% versus 3% with docetaxel [56]. In the sub-group analysis, the benefit for patients aged 75 years or above was not clearly established considering the small number of patients within this age group in both trials (Table 2). The use of nivolumab in monotherapy had an incidence of TRAEs grade 3-5 of 10% in the nivolumab pooled analysis compared with 55% for docetaxel. The anti-PD1 monoclonal antibody nivolumab was

compared with the standard of care 1st line platinum-based chemotherapy in the CHECKMATE-026 trial for patients with PD-L1 expression ≥1% [58]. This trial was negative regarding progression free survival (PFS), which was its primary endpoint. The phase 2 CHECKMATE-171 trial evaluated the safety of nivolumab in an European population of pre-treated squamous NSCLC patients [59] and reported toxicity in 35% of participants aged ≥70 years. The incidence of TRAEs grade 3-4 AEs in this cohort was 14% compared with 12% across the study population. Similarly, the phase 3b/4 CHECKMATE-153 trial assess its safety profile in North America and reported an incidence of grade 3-4 TRAEs of 12% for those aged ≥70 years compared to 11% for younger patients [60].

Atezolizumab. This anti-PD-L1 monoclonal antibody was explored in monotherapy versus docetaxel in the phase 3 OAK trial in pre-treated NSCLC patients regardless of PD-L1 expression [61]. The median OS was 13.8 months on atezolizumab compared with 9.6 months on docetaxel (HR 0.73, 95% CI 0.62-0.87; p=0.0003). In the subgroup analysis, older patients (≥65 years) had an additional improvement in the risk of death by 14% compared with younger patients (Table 2). No age-specific safety data are available although the incidence of grade 3-5 TRAEs was 15% for atezolizumab versus 43% with docetaxel. Moreover, the use of atezolizumab delayed the time to deterioration in physical function in the study population (HR 0.75; 95% CI 0.58 – 0.98) [62]. Considering that the lung cancer population is predominantly elderly, a benefit on physical function is of great clinical significance. Data on the use of single-agent atezolizumab in the first line setting from IMPOWER-110 (NCT02409342) and IMPOWER-111 (NCT02409355) trials are awaited. x

Durvalumab. This anti-PD-L1 monoclonal antibody was explored in monotherapy in pre-treated patients in the phase 3 randomized ARTIC trial. This trial explored durvalumab versus

standard-of-care (erlotinib, gemcitabine or vinorelbine) versus the combination of durvalumab and tremelimumab in third line and beyond for patients with advanced NSCLC [63]. The study closed early due to poor enrollment and could not compare outcomes in the overall population. Nonetheless, the sub-group with PD-L1 ≥25% had a median OS of 11.7 months versus 6.8 months, favoring durvalumab (HR 0.63; 95%CI 0.42-0.93). The incidence of TRAEs grade 3-5 was 10% for durvalumab. However, no age-specific data are available. In the first-line setting, the phase 3 MYSTIC trial investigated durvalumab versus platinum-based chemotherapy versus the combination of durvalumab and tremelimumab [64]. In the sub-group of patients with PD-L1 expression ≥25% (primary analysis sub-group), the median OS for durvalumab versus chemotherapy was 16.3 vs 12.9 months, respectively (HR 0.76; 97.5%CI 0.56-1.02; p=0.036). While statistical significance was not achieved, a clinically meaningful improvement in OS was observed for durvalumab versus chemotherapy. A sub-group analysis found a more meaningful benefit for older patients (65 years or older) with HR 0.66 (97.5%CI 0.45-0.95) favoring durvalumab over chemotherapy [65]. When comparing durvalumab plus tremelimumab versus chemotherapy the median OS was 11.9 vs 12.9 months (HR 0.85; 98.8%CI 0.61-1.17; p=0.202) with no benefit in any age groups [64, 65]. A more recent exploratory analysis highlighted that a markedly higher proportion of patients in the chemotherapy arm received subsequent immunotherapy, which may have confounded the primary OS outcome [66]. Therefore, after adjusting for the effect of subsequent immunotherapy on OS for durvalumab versus chemotherapy the median OS was 16.2 vs 11.5 months (HR 0.66; 97.5%CI 0.49-0.90; p=0.002), in favor of durvalumab. In regard to safety, the incidence of TRAEs grade 3-5 was 15% with durvalumab versus 35% with chemotherapy.

Lastly, the efficacy of durvalumab in the setting of stage III NSCLC following chemoradiotherapy was explored in the PACIFIC trial [67]. Durvalumab significantly

prolonged median OS compared with placebo (HR 0.68; 99.7%CI, 0.47-0.997; p=0.0025). Nevertheless, the OS benefit was less clear for older patients (Table 2). The incidence of AEs during treatment was similar between those patients on durvalumab and those on placebo.

2.3. Combination chemo-immunotherapy

Chemotherapy co-administered with immunotherapy is a more recent development in the management of advanced NSCLC. Reasons for better outcomes on a combination may include: 1) exposure of additional antigens due to cytotoxic cell death [68]; 2) reduction in suppressive cells such as MDSC and Treg [69]; and 3) reduced tumour bulk to allow T-lymphocytes to infiltrate the tumour and recovery of an exhausted immune system [70].

Pembrolizumab. In KEYNOTE-189 [71], a phase 3 double-blind randomized placebo-controlled trial of patients with metastatic non-squamous NSCLC and any PD-L1 expression, first-line pembrolizumab plus platinum-based chemotherapy (cisplatin or carboplatin) with pemetrexed was superior to platinum with pemetrexed in OS (overall HR 0.49, 95% CI 0.38-0.64) and PFS (overall HR 0.52, 95% CI 0.43-0.64). Median OS in the chemoimmunotherapy arm was 22.0 months versus 10.7 months for the standard chemotherapy arm (HR 0.56; 95% CI 0.45-0.70); p<0.01) [72]. In subgroup analyses by age (Table 3), the OS benefit extended to older adults (age ≥65 HR 0.64, 95% CI 0.43-0.95) [71]. No subgroup analyses by age were conducted for PFS or any toxicity outcomes. In the chemoimmunotherapy arm, 67.2% of patients of all ages developed grade ≥3 AEs, most commonly anaemia (16.3%) and neutropenia (15.8%). The most common severe TRAEs in the chemoimmunotherapy arm were pneumonitis (2.7%) and skin reaction (2.0%). Results from KEYNOTE-189 [71] and the phase 2 trial KEYNOTE-021 [73, 74] led to the widespread approval of pembrolizumab in combination

with platinum and pemetrexed for first-line treatment of metastatic non-squamous NSCLC in patients without EGFR or ALK genomic tumour aberrations regardless of PD-L1 expression.

For patients with metastatic squamous NSCLC, only one landmark trial to date has demonstrated an OS benefit for chemoimmunotherapy compared to chemotherapy. In KEYNOTE-407 [75, 76], a phase 3 double-blind randomized placebo-controlled trial of patients with metastatic squamous NSCLC and any PD-L1 expression, first-line pembrolizumab plus carboplatin and either paclitaxel or nab-paclitaxel was superior to carboplatin and taxane alone for OS (17.1 versus 11.6 months; HR 0.71, 95% CI 0.58-0.88) and PFS (8.0 versus 5.1 months; HR 0.57, 95% CI 0.47-0.69). In subgroup analyses by age, the PFS benefit extended to older adults (age ≥65 HR 0.63, 95% CI 0.47-0.84). However, when OS was examined among older adults only, there was no longer a statistically significant benefit in OS (age ≥65 HR 0.74, 95% CI 0.51-1.07). Overall, grade ≥3 AEs were similar in both arms affecting 69.8% of patients receiving chemoimmunotherapy arm and 68.2% of patients receiving chemotherapy. No age-specific data on toxicity are available.

Atezolizumab. In IMpower150 [77], an open-label phase 3 randomized trial of patients with metastatic non-squamous NSCLC and any PD-L1 expression (included patients with EGFR or ALK genetic alterations), carboplatin, paclitaxel, bevacizumab, plus atezolizumab was superior to carboplatin, paclitaxel, and bevacizumab for OS (overall HR 0.78, 95% CI 0.64-0.96) and PFS (overall HR 0.62, 95% CI 0.52-0.74). In the supplemental appendix, PFS was compared by age groups and favoured the chemoimmunotherapy arm among patients age <65 (HR 0.65) and 65-74 (HR 0.52). Among patients age 75-84 (9% of patients), the HR for PFS was 0.78 but was not statistically significant. Results comparing an additional third arm with carboplatin, paclitaxel, plus atezolizumab have not yet been reported. Overall, grade ≥3 TRAEs

were reported in 58.5% of patients in the chemoimmunotherapy arm and 50% in the chemotherapy arm.

In addition, for patients with metastatic non-squamous NSCLC, atezolizumab was also studied in combination with carboplatin and nab-paclitaxel in IMpower130 compared to chemotherapy alone [78]. PFS (HR 0.65, 95% CI 0.54-0.77) and OS (HR 0.80, 95% CI 0.65-0.99) were improved in the chemoimmunotherapy arm in the intention-to-treat population. When analysed by age group, the PFS benefit of the chemoimmunotherapy arm remained and were similar among younger and older patients (age <65 PFS HR 0.64, 95% CI 0.50-0.82; age ≥65 PFS HR 0.64, 95% CI 0.50-0.82). In contrast, the OS benefit of the chemoimmunotherapy arm was no longer statistically significant when stratified by age group (age <65 OS HR 0.79, 95% CI 0.58-1.08; age ≥65 OS HR 0.78, 95% CI 0.58-1.05). Grade ≥3 TRAEs occurred in 75% of patients in the chemoimmunotherapy arm and 60% in the chemotherapy arm.

Furthermore, for patients with metastatic non-squamous NSCLC, atezolizumab was studied in combination with carboplatin or cisplatin plus pemetrexed in IMpower132 compared to chemotherapy [79]. PFS (HR 0.60, 95% CI 0.49-0.72) was improved in the chemoimmunotherapy arm, which was confirmed in age group analyses as well. Among older patients age ≥65, HR for PFS was 0.55 (95% CI 0.42-0.73) compared to HR 0.63 (95% CI 0.49-0.80) for younger patients. Among the oldest old (age 75-84), PFS HR was 0.63 (95% 0.35-1.13). The interim OS analysis did not demonstrate a benefit at this time (HR 0.81, 95% CI 0.64-1.03), which was not impacted by age group (age <65 OS HR 0.89, 95% CI 0.65-1.21; age ≥65 OS HR 0.71, 95% CI 0.50-1.01).

For patients with metastatic squamous NSCLC, the open-label phase 3 randomized trial IMpower131 [80] demonstrated a PFS benefit for first-line atezolizumab plus carboplatin and nab-paclitaxel versus carboplatin and nab-paclitaxel alone (HR 0.71, 95% CI 0.60-0.85). The final OS data was presented more recently with no benefit for the intent-to-treat population

(HR 0.88; 95%CI 0.73-1.05; p=0.158), but on secondary analysis for those with high PD-L1 expression (TC3 or IC3) there was an apparent benefit (HR 0.48; 95%CI 0.29-0.81) [81]. In subgroup analyses by age, only available for PFS, there was a benefit to all three age groups (age <65 HR 0.77, 95% CI 0.61-0.99; age 65-74 HR 0.66, 95% CI 0.51-0.87; age 75-84 HR 0.51, 95% CI 0.30-0.84). Grade ≥3 TRAEs occurred in 69% of patients in the chemoimmunotherapy arm compared with 58% in the chemotherapy arm.

2.4. Combinations of immunotherapy

Combination between different immunotherapy agents targeting different checkpoint in the T cells is the most recent development in the field of advanced NSCLC. The CHECKMATE-227 is a complex randomized phase 3 trial divided into 2 parts for the first line treatment of advanced NSCLC exploring primarily the combination nivolumab plus ipilimumab versus standard platinum-based chemotherapy. The part 1 was published and had two independent primary endpoints: PFS with nivolumab plus ipilimumab, as compared with chemotherapy, in patients with a high tumour mutational burden (≥10 mutations per megabase) [82]; and OS with nivolumab plus ipilimumab, as compared with chemotherapy, in patients with a tumour PD-L1 expression of 1% or more [83]. For other hierarchical endpoints the trial included a group with PD-L1 expression bellow 1% and also treatment arms with nivolumab or nivolumab plus chemotherapy. Focusing on the published data for the primary OS endpoint in PD-L1≥1%, the combination nivolumab plus ipilimumab was superior to the chemotherapy arm (17.1 vs 14.9 months; HR 0.79; 95%CI 0.65-0.96; p=0.007). In the sub-group analysis, the benefit for the group aged 65-74 years was not clear when compared with younger patients with a HR of 0.91 (0.70-1.19) versus HR 0.70 (0.55-0.89), respectively. Similarly, the group aged 75 years or more did not seem to benefit, yet this was a small group of only 81 patients. Of note, in an exploratory analysis for the smaller group with PD-L1 <1% included in this multi-part trial,

the combination of nivolumab/ipilimumab also showed improved OS compared with chemotherapy (HR 0.62; 95%CI 0.48-0.78). In regard to toxicity, grade ≥3 TRAEs were reported in 32.8% of patients in the nivolumab/ipilimumab arm and 36% in the chemotherapy arm with more serious AEs occurring in the immunotherapy arm (24.5% vs 13.9%). The CHECKMATE-817 is a phase 3b/4 trial primarily exploring the safety (grade 3-5 TRAEs) of a flat dose of nivolumab combined with ipilimumab (standard weight-based dose) in the first line treatment of advanced NSCLC. The trial included 2 cohorts, a standard cohort for patients with PS 0-1 and a smaller special populations cohort for those with PS-2 or PS 0-1 with other factors that might have excluded them from other clinical studies of immunotherapy agents (asymptomatic untreated brain metastasis or hepatic impairment or renal impairment or human immunodeficiency virus) [84, 85]. The main cohort of 391 PS 0-1 patients had 15% aged 75 years or above, while the PS-2 group within the special populations' cohort had 22% of its 139 patients aged 75 years or above. The incidence of grade 3-4 TRAEs was 35% and 26%, favouring the older and frail group, with no difference in treatment-related death and an overall safety data identical to the weight-based dosing of nivolumab. The Lung-MAP is a biomarker-target study with multiple sub-studies with one in particular for those patients with no biomarker-target match using immunotherapy. The sub-study S1400I is a randomized phase 3 for pre-treated patients with advanced squamous NSCLC which explored the addition of ipilimumab to the standard nivolumab in this setting [86]. This was a negative study for its primary endpoint (OS) with HR 0.97 (95%CI 0.71-1.31; p=0.82). Lastly, the phase 3 MYSTIC trial on the combination of durvalumab and tremelimumab was discussed previously.

2.5. Combination radio-immunotherapy

Between 30-50% of patients diagnosed with NSCLC receive radiotherapy (RT) in the early- or late-stage disease setting and as such, RT is a valuable treatment modality. RT is known to

induce immune and inflammatory changes that can prime the tumour microenvironment to initiate an immune response. This initial immune priming can be augmented systemically by combining RT with immunotherapies to relay an abscopal response. Radiation-induced immunogenic cell death includes release of tumour antigens, dendritic cell maturation, augmentation of T-cell priming, upregulation of MHC-I and PD-L1, and upregulation of cytokines and chemokines [87-91]. Hence, there has been interest in combining RT with immunotherapy agents to improve anti-tumour immunity and responses.

Preclinical immunocompetent mouse models serve as useful tools to investigate these treatment combinations, given the ability to study RT dose and fractionation, as well as scheduling of RT and immunotherapies. Furthermore, they allow investigation of the tumour immune microenvironment which cannot be similarly performed in patients through serial repeat biopsies. RT has been shown to improve response to anti-PD-1/PD-L1 preclinically; in a KRAS-mutant lung model RT upregulated PD-L1 expression on tumour cells and when combined with anti-PD-1, $CD8^+$:Treg ratios and survival improved [92]. Additionally, anti-PD-L1 in combination with RT can reduce tumour growth, myeloid derived suppressor cells and Treg cells, as well as increase infiltration of $CD8^+$ T-cells [93]. RT can also upregulate major histocompatibility complex class I (MHC-I) expression on anti-PD-1-resistant tumour cells and restore responsiveness to anti-PD-1 [88]. There is also rationale for combining RT with immunostimulatory receptor agonists to help sustain anti-tumour T-cell responses. For example, anti-OX40 agonist administered with RT has demonstrated improved survival in an otherwise anti-PD-1 resistant lung model [94]. However, the anti-OX40 only improved survival when administered in the adjuvant setting (versus induction or concurrent regimens). This highlights how essential the sequencing of therapies may be. Scheduling has also made notable impacts in colorectal cancer (adjuvant versus concurrent anti-PD-1 with RT was

detrimental) and breast cancer models (concurrent versus adjuvant anti-OX40 with anti-PD-1 was detrimental) [89, 95].

Clinical evidence on the combination of thoracic RT and immunotherapy is lacking.
However, some data are available on their sequential use. A secondary analysis of the phase 1 study, KEYNOTE-001, which included patients with metastatic NSCLC, showed that patients who previously received RT had a significantly longer PFS and OS [96]. However, these patients also experienced more pulmonary toxicity compared to non-irradiated patients. Whilst increasing age was associated with improved PFS in this model on univariate analysis; it no longer reached significance on mult-variate analysis.The previously described PACIFIC trial adds to the evidence of using immunotherapy sequentially after chemo-RT [67]. In this trial, the incidence of any grade pneumonitis was higher in the durvalumab arm versus placebo (34% vs 25%), however with similar grade 3-4 rates (4% vs 3%). An exploratory analysis investigated the efficacy of durvalumab in patients who developed pneumonitis and the survival outcomes were similar to the intent-to-treat population [97]. Radiation pneumonitis does become more common with age, although this does not appear to be the case for immunotherapy pneumonitis

Several clinical trials on the role of concomitant thoracic RT and immunotherapy are ongoing. The European Thoracic Oncology Platform (ETOP) NICOLAS study is a phase 2 trial assessing the safety and efficacy of nivolumab combined with concurrent chemo-RT for unresectable stage III NSCLC. No grade 3 or higher events of pneumonitis were identified in the pre-planned safety interim analysis (3 months follow-up post-RT for the first 21 patients) [98]. The primary efficacy endpoint defined as PFS at 1 year was 54% (95%CI 41-65%) with a median PFS of 12.4 months (95%CI 9-not reached) at an interim analysis. This supports the

use of concurrent immunotherapy and chemo-RT [99]. Nonetheless there are still no data specific for older and/or PS-2 patients. The DETERRED is a phase 2 trial which investigated primarily the safety of combining atezolizumab with concurrent chemo-RT in unresectable stage II-III NSCLC patients. The study was divided in 2 parts, the Part 1 (n=10) included atezolizumab only during the consolidation phase, but the Part 2 (n=30) incorporated it concurrently with chemo-RT. This reported an incidence of grade 2 or above pneumonitis of 16% and a median PFS of 13.2 months [100]. Lastly, the use of pembrolizumab is also being explored and two key trials are ongoing: the KEYNOTE-867 which is combining pembrolizumab with thoracic RT in a phase 3 randomized trial for stage I-IIA inoperable cases; and the KEYNOTE-799 which is a single-arm phase 2 trial looking at the combination of pembrolizumab with chemo-RT for unresectable stage III NSCLC.

3. Discussion

Immune checkpoint inhibition therapy targeting PD-1/PD-L1 has changed the treatment landscape for advanced NSCLC. Theoretical concerns exist that older patients might be at risk of lower efficacy and /or increased side-effects with these agents. Limited sub-group analysis from the pivotal clinical trials suggests that older patients may have the same benefit from immunotherapy as younger patients with an acceptable toxicity profile.

However, methodologically and conceptually results from the pivotal phase 3 trials cannot yet be generalized to older patient populations. These trials only included patients with performance status (PS) of 0-1, consequently the evidence in vulnerable/frail patients remains very limited. The median age at trial enrolment was about 10 years younger than the median age of NSCLC diagnosis in Western countries. The subgroup analyses on older patients were conducted *post hoc* and the trials not powered for age group comparison. There is also a lack

of data on patients >75 years old and the data available are conflicting. The reasons are not clear however this could be due to the small sample size of this elderly cohort, poorer tolerance of therapy and additional comorbidities within this population.

Nonetheless, whether poorer PS and multiple comorbidities predict for more toxicity or less efficacy with immunotherapy is uncertain. In two large cohort studies, PS 2 patients had similar side effects but poorer outcomes in terms of OS [101, 102]. However, this was not reproduced in the recent PePS2 study assessing pembrolizumab in a purely PS 2 population where response and OS appeared similar to previous reports in patients with PS 0-1 [103]. Additionally, the CheckMate-171 trial which included elderly and PS 2 patients found no differences in terms of toxicity and OS between the overall population and the elderly subgroup [59]. Real world data derived from the Italian expanded access program (EAP) for nivolumab in pre-treated patients also suggested a similar OS across age groups and although toxicities were not analysed separately, their overall incidence was similar to data coming from randomized trials [104-106]. More recently, data from an Italian multicenter retrospective study of patients >75 years old treated with anti PD-1 agents (either nivolumab or pembrolizumab) were also consistent with previous registration trials in terms of toxicity profile and efficacy [107]. Therefore at present there is no need to exclude patients on the basis of age from treatment with immunotherapy.

Contrary to chemotherapy, the treatment duration with immunotherapy is long and although its target duration is still debated, many patients receive treatment for many months or years. However, the impact of long-term treatment on patients' fitness and comorbidities is unclear. In patients experiencing immune-related AEs, steroids are recommended, often at high doses and for prolonged courses [110]. The impact of managing these toxicities on the older patient

is not clear but may be as problematic as immunotherapy treatment itself since long-term steroid use may influence muscle bulk, bone strength, glucose tolerance and immune function.

The combination of immunotherapy and chemotherapy is rapidly becoming the standard of care in the first-line treatment setting of NSCLC. Although such combinations result in improved response rates, PFS and OS (regardless of PD-L1 status), the toxicity rates are higher in almost all studies. Whilst monotherapy may seem a better match for many older patients, combination strategies may be a better option in appropriately selected older patients. It is therefore of even higher importance to adequately assess older patients within this treatment scenario for a frailty or pre-frailty status in order to avoid over- or under-treatment. Determining which patients will be able to tolerate the combination and determining the underlying cause of a given toxicity can be more challenging when combining chemotherapy and immunotherapy. Older patients are more prone to get chemotherapy toxicity and to discontinue chemotherapy as a result [111]. The major concern is that events could produce a functional decline that results in a loss of independence and a poorer quality of life.

Similarly, immunotherapy is increasingly given with RT both thoracic and to other sites. In the real-world setting pneumonitis rates are higher than in clinical trials and in particular in patients receiving curative doses of radiotherapy [112]. Nonetheless, data on thoracic radiotherapy and immunotherapy in older patients are still limited.

Other important considerations in regard to the pivotal trials´ design and selection criteria are the limited number and severity of comorbidities, which do not reflect real-world population. Moreover, these trials did not include CGA, nor geriatric screening at baseline, as suggested by current guidelines [108]. The ELDERS study is the first prospective study with a real-world population incorporating geriatric assessments in its design. This observational cohort study with 150 patients (NSCLC and melanoma) was designed with the primary aim to investigate

the safety and secondarily the efficacy and quality of life with immunotherapy between younger and older (≥70 years) patients. PS was not part of the selection criteria and the study integrated geriatric screening and assessments for subsequent exploratory analysis. An interim analysis of the first 32 patients with NSCLC reported no significant differences in the toxicity between age groups despite 30% of PS-2 patients and 46% of the elderly failing the geriatric screening (G8 tool) [109]. The final results of this study are expected in 2020.

In conclusion, there is a primary need to generate data to address the use of immunotherapy in the older population as a whole, including vulnerable and pre frail patients [113]. These should include functional measures of frailty such as a G8 with a formal CGA in patients identified as vulnerable. End-points should not only be based around response on imaging or survival but should include patient reported outcomes as maintaining QOL which may be a more relevant goal in older patients. In addition, a further consideration is the potential impact of immunosenescence on immunotherapy. Biological markers and markers of immunosenescence could be incorporated in clinical trials to help determine whether the changes in the immune system with ageing have any impact on treatment efficacy and/or toxicity. These could include: 1) assessment of T-cell phenotype including the presence of circulating T_{regs} and CD8+/CD28-ve T-cells and function to antigen challenge using EliSpot; 2) Presence of autoantibodies; 3) Markers of inflammation including neutrophil to lymphocyte ratio, C-Reactive Protein and IL6; and 4) Assessment of the stool microbiome for Firmicutes and Bacteroides species.

Conducting such trials, however, may be difficult due to the heterogeneity of this population and the complex clinical variables. In addition, pharmaceutical companies may be less interested in focussing their studies in older patients or those with co-morbidities where higher rates of adverse events may be encountered. In this regard, a good methodological compromise might be to design phase II studies focusing on such patient populations, or to include specific

pre-planned subgroup analysis on older patients in pivotal randomized trials. Additionally, functional endpoints and patient-reported outcomes for older individuals could be included as exploratory or secondary end points in registration trials. Lastly, real-world data are an invaluable resource readily available and should be collected and shared to help inform decision making when discussing treatment in these patient groups.

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Conflicts of interest

Dr. Wong has reported a conflict of interest outside of the submitted work (immediate family member is an employee of Genentech with stock ownership). Dr. Battisti has reported a conflict of interest outside of the submitted work (speaker fees from Pfizer, travel grants from Genomic Health). The other authors have no relevant conflicts of interest to declare.

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