

REVIEW

# Immunotherapy in the first-line treatment of elderly patients with advanced non-small-cell lung cancer: results of an International Experts Panel Meeting by the Italian Association of Thoracic Oncology (AIOT)

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**Background:** The use of immune checkpoint inhibitors (ICIs) in the front-line treatment of advanced non-small-cell lung cancer (NSCLC) is currently the standard of care. However, as clinical trials include a very limited number of elderly patients, evidence on the safety and efficacy of using ICI-based regimens is still limited.

**Methods:** A virtual International Expert Panel took place in July 2022 to review the available evidence on the use of ICI-based regimens in the first-line setting in elderly patients with NSCLC and provide a position paper on the field both in clinical practice and in a research setting.

**Results:** All panelists agreed that age *per se* is not a limitation for ICI treatments, as the elderly should be considered only as a surrogate for other clinical factors of frailty. Overall, ICI efficacy in the elderly population is supported by reviewed data. In addition, the panelists were confident that available data support the safety of single-agent immunotherapy in elderly patients with NSCLC. Conversely, concerns were expressed on the safety of chemo + ICI-based combination, which were considered mainly related to the toxicities of chemotherapy components. Therefore, suggestions were proposed to tailor combined approaches in the elderly patients with NSCLC. The panelists defined high, medium, and low priorities in clinical research. High priority was attributed to implementing the real-world assessment of elderly patients treated with ICIs, who are mostly underrepresented in pivotal clinical trials.

**Conclusions:** Based on the current evidence, the panelists outlined the significant limitations affecting the clinical practice in elderly patients affected by NSCLC, and reached common considerations on the feasibility, safety, and effectiveness of ICI monotherapy and ICI combinations in the first-line setting.

**Key words:** immune checkpoint inhibitors, elderly, NSCLC, consensus

## INTRODUCTION

The definition of the elderly population was statically set at an age cut-off of 65 years, and more than half of new diagnoses of non-small-cell lung cancer (NSCLC) are above this age cut-off.<sup>1</sup> However, the concept of the elderly evolved into a more complex evaluation, taking into account not only chronological age but also biological age, including individuals' functional and social status. Hence, several scales and tools<sup>2</sup> have been developed to assess specific aspects, including function (i.e. activities of daily living—ADL, instrumental ADL), comorbidities (i.e. Charlson

Comorbidity Score), quality of life (QoL) (disease-specific questionnaires), cognition (Folstein Mini-Mental State), and emotions (Geriatric Depression Scale). However, although the geriatric assessment is feasible in cancer patients,<sup>3</sup> the impact of comprehensive geriatric assessment on decision making and treatment allocation did not impact survival but slightly reduced toxicity in patients with advanced NSCLC (A-NSCLC) in a phase III trial.<sup>4</sup>

Indeed, elderly age might better be intended as an indirect measure of potential patient's functional status, which may be impaired by clinical features commonly acquired by increasing age, including progressive organ function reserve failure (mainly renal, cardiovascular, hepatic, bone marrow function), and acquired chronic comorbidities, also linked to tobacco smoking.<sup>5-9</sup> Because of this, in the past years, the concepts of elderly and poor performance status (PS) frequently overlapped, and studies have been conducted to investigate the best chemotherapy

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approach in the front-line treatment of elderly patients with NSCLC. The main clinical trials in this field showed that the addition of platinum chemotherapy did not improve survival. In contrast, added toxicities were observed as compared to single-agent chemotherapy,<sup>10,11</sup> and single-agent chemotherapy was considered as a valid treatment option in the elderly unfit patients.<sup>12</sup>

The introduction of immune checkpoint inhibitors (ICIs) in the front-line treatment of A-NSCLC led to reconsidering the treatment paradigm in elderly patients.

Indeed, single-agent anti-programmed cell death protein 1 (anti-PD-1) and anti-programmed cell death-ligand 1 (anti-PD-L1) demonstrated prolonged overall survival (OS) and long-term survival in platinum-pretreated patients over standard docetaxel,<sup>13-16</sup> and therefore were firmly established as further-line treatment also in the elderly population.

Soon after, the use of ICIs rapidly moved to the first-line setting of NSCLC treatment. Single-agent anti-PD-1 (pembrolizumab and cemiplimab) and anti-PD-L1 (atezolizumab) are current standard of care in the first-line treatment of patients with either squamous or non-squamous NSCLC whose tumors have PD-L1 expression  $\geq 50\%$  and are wild type (WT) for epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) status.<sup>17-20</sup> Front-line combination of single-agent pembrolizumab or atezolizumab or cemiplimab, as well as dual-agent anti-PD-1/PD-L1 and anti-cytotoxic T-lymphocyte-associated antigen (CTLA-4) (nivolumab plus ipilimumab and durvalumab plus tremelimumab), with histology-based platinum-doublet chemotherapy, showed survival benefit over chemotherapy alone regardless of PD-L1 expression levels in EGFR/ALK WT tumors, and are standard treatment options in this setting.<sup>21-27</sup>

Since eligibility for pivotal clinical trials of first-line ICIs in NSCLC was conditioned by platinum eligibility, the elderly population is not well represented here, with patients  $\geq 75$  years of age being almost 10% of the overall population. In addition, the age cut-offs used were different among clinical trials and no information is available on specific subsets of elderly patients included. These aspects are crucial considering that  $>40\%$  of patients with lung cancer are aged  $\geq 70$  years in clinical practice, and therefore represent a significant proportion of potential applicability of ICI-based treatments (monotherapy or combination) in the first-line setting. The main concerns raised on using ICIs in the elderly population were first related to potential toxicity, based on previous studies demonstrating a high prevalence of autoantibodies in the elderly population.<sup>28</sup> In addition, immune senescence, meaning the modifications in the immune system activity related to aging, including decreased pro-inflammatory activity (i.e. cytokine production, signal transduction, chemotaxis) of the adaptive and innate immune cells,<sup>29</sup> raised doubts on potential ICI efficacy in this special population.

In light of the few prospective data specifically addressing the elderly population, an updated consensus is needed to refocus on the first-line approaches for elderly patients affected by NSCLC in the immunotherapy era.

## METHODS

The 14th International Experts Panel Meeting by Associazione Italiana di Oncologia Toracica (AIOT) was held virtually on 7 July 2022 to discuss the topic 'Immunotherapy in the first-line treatment of elderly patients with advanced NSCLC'. The scientific panel of the meeting was made up of five medical oncologists from different countries (Italy, Switzerland, and the United States) with clinical and research expertise in NSCLC treatment. During the first part of the meeting, the available evidence on the use of first-line immunotherapy in elderly patients was formally reviewed to initiate discussion. The second part of the meeting consisted of panelists' discussion to reach common conclusions to include in a position paper on the field on clinical practice and clinical research.

Published data useful for panel discussion were identified using a PubMed search, carried out with combinations of the following search terms: 'non-small-cell lung cancer' and 'elderly'. Only articles written in English were considered for the discussion. Abstracts presented between 2000 and 2022 at the main international meetings were also searched. The search has been updated for this article with the proceedings of the 2022 American Society of Clinical Oncology and European Society of Medical Oncology meeting. Relevant references from selected articles and other articles selected from the personal collections of the panelists were also included.

For the clinical practice, 11 questions, previously agreed upon by the panelists, were proposed and widely discussed during the meeting. As reported previously,<sup>30</sup> due to the intended international applicability of the Expert Panel Consensus, the discussion was limited to the approved ICI treatment regimens by both the Food and Drug Administration (FDA) and the European Medicines Agency (EMA), so that the first-line single-agent pembrolizumab and the combination of nivolumab and ipilimumab in PD-L1  $\geq 1\%$  NSCLC patients were not considered for panelists' discussion.

For discussion on clinical research, issues were proposed by each panelist and attributed priorities in the form of high-medium-low according to panel voting.

As in the previous AIOT meeting, live-shared minutes were used to produce a summary report of the meeting, which was agreed by all panelists to serve as the basis to generate the current manuscript. All panelists reviewed the shared statements and approved the final manuscript.

## EVIDENCE ON THE USE OF FIRST-LINE IMMUNOTHERAPY IN ELDERLY PATIENTS WITH NSCLC

Prospective evidence on the use of immunotherapy in elderly patients with advanced or metastatic NSCLC is limited. The pivotal first-line clinical trials used different age cut-offs to define subgroups. In particular, the atezolizumab trials (IMpower110, IMpower150, IMpower130)<sup>18,22,23</sup> and the chemotherapy plus nivolumab and ipilimumab (Check-Mate 9LA)<sup>25</sup> evaluated age subgroups using 75 years cut-off. Conversely, the KEYNOTE series of studies with

pembrolizumab (KEYNOTE-024, 042, 189),<sup>17,31,32</sup> cemiplimab studies,<sup>20,27</sup> and the POSEIDON trial<sup>26</sup> with chemotherapy plus durvalumab and tremelimumab limited their analysis to 65 years cut-off. Overall, no impact on treatment outcomes was observed when using a 65-year age cut-off through trials. Conversely, the OS benefit of ICI-based treatments was not confirmed in the  $\geq 75$ -year age subgroup, when evaluated, either as monotherapy or as combination,<sup>18,25</sup> but the small proportion ( $\sim 10\%$ ) of patients in this subgroup makes it impossible to try conclusions on these data from clinical trials.

Of note, the FDA recently presented a pooled analysis of randomized clinical trials (RCTs) with pembrolizumab or atezolizumab monotherapy and combinations, investigating outcomes between single-agent ICI and chemotherapy in PD-L1  $\geq 50\%$  NSCLC. Comparable outcomes with the two approaches were observed in the overall population, but single-agent immunotherapy showed favorable OS in patients aged  $\geq 75$  years.<sup>33</sup>

To overcome the intrinsic limitations of clinical trials, meta-analyses have been conducted to assess the safety and efficacy of ICIs in elderly patients with NSCLC. Overall, in the pretreated setting, comparable efficacy was observed in older and younger adults treated with ICI monotherapy using a cut-off of 65 years.<sup>34-37</sup> In a meta-analysis of 12 RCTs, OS benefit with mono-immunotherapy was not observed when considering a cut-off of 75 years.<sup>36</sup> Of interest, patients aged  $\geq 75$  years were reporting lower incidence of grade 3 or higher ( $G \geq 3$ ) adverse events (AEs) compared to those  $< 65$  years in a pooled analysis of four RCTs with single-agent ICI by FDA.<sup>35</sup>

Two prospective studies with nivolumab monotherapy, CheckMate 153 and CheckMate 171 trials, were conducted in the pretreated setting and included patients aged 70 years or older (278 out of 811 in the squamous histology population in CheckMate 171; 99 out of 252 in CheckMate 153).<sup>38,39</sup> The incidence of AEs was similar between older and overall patients in both trials (56% versus 50%, and 64% versus 62%, respectively). Comparable survival outcomes were also observed between the older and the overall population.

A small phase II prospective study conducted in Japan enrolled 26 patients aged  $\geq 75$  years affected by A-NSCLC with PD-L1  $\geq 50\%$  and EGFR/ALK WT, who received front-line pembrolizumab.<sup>40</sup> Median progression-free survival (PFS) was 9.6 months, median OS was 21.6 months, overall response rate (ORR) was 41.7%, and  $G \geq 3$  AEs were 15.4%, comparable with pivotal clinical trial results. No changes in patients' QoL were observed during treatment. Another small prospective phase II trial was conducted in Spain, enrolling 75 patients aged  $\geq 70$  years, with PD-L1  $\geq 1\%$  and EGFR/ALK WT, treated with pembrolizumab. This study provides a comprehensive geriatric description of the treated population, confirming the safety and efficacy of pembrolizumab monotherapy.<sup>41</sup>

A pooled analysis was carried out on 264 patients aged  $\geq 75$  years included in the KEYNOTE-010 (pretreated), KEYNOTE-024, and KEYNOTE-042 (front-line) trials.<sup>42</sup>

Overall, pembrolizumab monotherapy significantly improved survival compared to chemotherapy [median OS 15.7 versus 11.7 months, hazard ratio (HR) 0.76], and the magnitude of benefit was greater in patients with PD-L1  $\geq 50\%$ . In treatment-naïve elderly patients ( $n = 93$ ) with PD-L1  $\geq 50\%$ , median OS with pembrolizumab was 27.4 months, compared to 7.7 months with chemotherapy (HR 0.41). The incidence of AEs appeared lower in the elderly population receiving pembrolizumab than in those treated with chemotherapy ( $G \geq 3$  AEs 24.2% versus 61%).<sup>42</sup>

Several retrospective reports evaluated the outcomes of immunotherapy regimens in the real-world elderly population. In a retrospective study with a small sample size (27 patients out of 98 aged  $\geq 70$  years), worse OS was reported in elderly compared to younger patients treated with immunotherapy (median OS 5.3 versus 13 months).<sup>43</sup> A larger retrospective cohort of 327 patients with NSCLC and PD-L1  $\geq 50\%$  treated with pembrolizumab monotherapy included 169 (51.7%) patients aged  $\geq 70$  years. No difference in clinical outcomes, OS, ORR, and safety was observed between older and younger patients in this study. Of note, multivariate analysis showed poor PS, and not age, as a factor impacting OS.<sup>44</sup>

A few retrospective reports included the elderly population receiving chemotherapy plus immunotherapy combinations. A real-world Japanese study included 299 patients with advanced non-squamous NSCLC receiving first-line chemo-immunotherapy combination with platinum, pemetrexed, and pembrolizumab.<sup>45</sup> Forty-three patients were aged  $\geq 75$  years. Comparable survival results were obtained in older and younger patients (median PFS 8.9 versus 8.5 months, median OS not reached in both groups). Conversely, the rate of AE-related discontinuation of all treatment components was significantly higher in the elderly population (40% versus 21%,  $P = 0.012$ ).<sup>45</sup>

Another real-world study was conducted in the United States in the same setting. Overall, 283 patients were included, 59 (21%) were aged  $\geq 75$  years.<sup>46</sup> The effectiveness and feasibility of platinum plus pemetrexed plus pembrolizumab combination was consistent in the extended cohort of elderly patients in this analysis ( $n = 99$ ). Of note, pemetrexed was sooner discontinued compared to pembrolizumab in the elderly population (32% due to toxicity), with time on treatment for pembrolizumab and pemetrexed of 4.9 (3.8-6.2) and 2.8 (2.2-3.6) months, respectively.<sup>47</sup>

A retrospective trial specifically collected data from 136 elderly ( $\geq 75$  years) patients with A-NSCLC without EGFR/ALK/ROS1 targetable alterations, treated with first-line pembrolizumab plus chemotherapy ( $n = 43$ ) or mono-chemotherapy ( $n = 93$ ). Significant survival benefit was observed with the combination (median PFS 12.5 versus 5.3 months,  $P < 0.001$ ; median OS not reached versus 21.3,  $P = 0.037$ , respectively).<sup>48</sup> As expected, higher treatment discontinuation (26% versus 5%) was observed with chemo-immunotherapy.

To date, two phase III trials with first-line immunotherapy specifically addressed to elderly patients ( $\geq 70$  years) with

NSCLC have data presented: the IPSOS study (NCT03191786)<sup>49</sup> and the eENERGY study (NCT03351361).<sup>50</sup> Both studies were not limited to the elderly population but were extended to poor PS (eENERGY) and more in general platinum-ineligible population (IPSOS). The IPSOS trial was designed to compare atezolizumab monotherapy with single-agent chemotherapy in platinum-unfit patients. Among 453 randomized patients in this trial, 31% were aged  $\geq 80$  years. With a median follow-up of 41 months, atezolizumab significantly improved OS compared to chemotherapy (stratified HR 0.78, 95% confidence interval 0.63-0.97,  $P = 0.028$ ) across key subgroups in this frail population.<sup>49</sup> Of note, lower AEs were observed with atezolizumab compared to chemotherapy (16.3% versus 33.3%), and improvements in chest pain, appetite loss, and cough were observed with atezolizumab from baseline.

The eENERGY study compared the combination of nivolumab and ipilimumab with carboplatin doublet chemotherapy. In this trial, despite non-significant OS benefit in the overall population, subgroup analysis showed significant OS benefit in elderly patients with PS 0-1 treated with dual-agent immunotherapy compared to chemotherapy (median OS 22.6 versus 11.8 months,  $P = 0.02$ ), with similar toxicity rates.<sup>50</sup>

## DISCUSSION ON CLINICAL PRACTICE

### Elderly definition

The first issue for panel discussion was related to the validity of the elderly definition in clinical practice to assess patients for immunotherapy treatment (Table 1, questions Q1-Q2).

To all panelists, patients' age does not represent *per se* a limitation for adequate treatment selection in A-NSCLC, whichever the age cut-off selected for elderly definition. Indeed, rising chronological age could be an indirect indicator of increasing risk to develop clinical features of frailty that may impact treatment safety. These include major comorbidities, drug polytherapy, worsening Eastern Cooperative Oncology Group PS, and decreased renal function. As such, panelists agreed that age should be considered mainly as a surrogate for other factors potentially related to age. In this view, the authors discussed the uselessness of an age boundary in a population that is overall getting older, with increasing number of octogenarians. A multifactorial approach is indeed needed to evaluate elderly patients for treatment selection. Overall, panelists considered age not a problem for single-agent anti-PD-1/PD-L1. Conversely, they expressed concerns for combined chemotherapy plus immunotherapy in octogenarians, mainly related to the concerns on toxicities from chemotherapy components (see section 'Discussion on combined chemotherapy plus single-agent immunotherapy', Table 1, Q5-Q7).

### Discussion on single-agent immunotherapy

Besides the consensus on elderly definition, the panelists focused the discussion on treatments available in the first-

**Table 1. Expert Panel statements on the use of first-line immunotherapy in elderly patients with A-NSCLC**

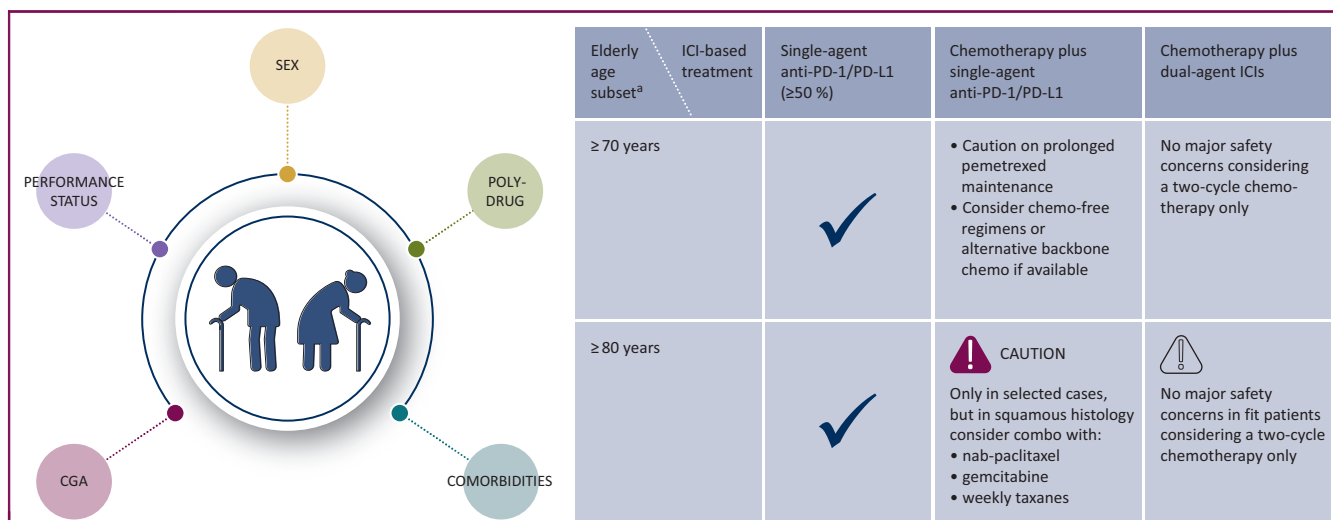
Panel questions	Expert conclusions
<b>Elderly assessment</b>	
<b>Q1. Is 'elderly' definition still adequate in the immunotherapy era?</b>	Age is not <i>per se</i> a limitation for treatment selection but should be considered as a surrogate for other factors potentially related to age (ECOG PS, comorbidities).
<b>Q2. In patients with A-NSCLC, does age affect your treatment choice with ICIs?</b>	<ul style="list-style-type: none"> <li>• No, for single-agent anti-PD-1/PD-L1.</li> <li>• Probably yes, for chemotherapy plus immunotherapy, mainly due to the concerns on toxicities from chemotherapy components.</li> </ul>
<b>Single-agent immunotherapy</b>	
<b>Q3. Is single-agent immunotherapy feasible and safe in elderly patients with A-NSCLC and PD-L1 <math>\geq 50\%</math>?</b>	Yes, with available data.
<b>Q4. Is single-agent immunotherapy effective in elderly patients with A-NSCLC and PD-L1 <math>\geq 50\%</math>?</b>	Yes, with available data.
<b>Combined chemotherapy and immunotherapy</b>	
<b>Q5. In elderly patients with A-NSCLC and squamous histology is combined chemotherapy plus single-agent immunotherapy feasible and safe?</b>	Yes, but concerned about paclitaxel due to neurotoxicity.
<b>Q6. Is combined chemotherapy plus single-agent immunotherapy effective in elderly patients with A-NSCLC and squamous histology?</b>	Probably yes. We only have exploratory analysis from clinical trial KEYNOTE-407, showing no difference with 65 years cut-off.
<b>Q7. In elderly patients with A-NSCLC and non-squamous histology is combined chemotherapy plus single-agent immunotherapy feasible and safe?</b>	Yes, but concerns are expressed for combined chemotherapy plus immunotherapy in octogenarians. Caution on maintenance with pemetrexed.
<b>Q8. Is combined chemotherapy plus single-agent immunotherapy effective in elderly patients with A-NSCLC and non-squamous histology?</b>	Probably yes. We only have exploratory analysis from clinical trial KEYNOTE-189, showing no difference with 65 years cut-off.
<b>Q9. In elderly patients with A-NSCLC is combined chemotherapy plus double immunotherapy feasible and safe?</b>	Yes, considering that the regimen with two cycles of chemo without maintenance pemetrexed could be favorable in the elderly population.
<b>Q10. In elderly patients with A-NSCLC is combined chemotherapy plus double immunotherapy effective?</b>	Probably yes, as we cannot avoid treatment in the elderly based only on a small subgroup analysis on $\geq 75$ years cut-off in the CM9LA.
<b>Preferred treatments</b>	
<b>Q11. In elderly patients with A-NSCLC and PD-L1 <math>\geq 50\%</math>, how do you choose between single-agent immunotherapy and combined chemo-immunotherapy?</b>	Based on FDA pooled analysis and real-world data, it is reasonable to choose single-agent anti-PD-1/PD-L1, excluding never smokers (irrespective of age).

A-NSCLC, advanced non-small-cell lung cancer; ECOG, Eastern Cooperative Oncology Group; FDA, Food and Drug Administration; ICIs, immune checkpoint inhibitors; PD-1, programmed cell death protein 1; PD-L1, programmed cell death-ligand 1; PS, performance status; Q, question.

line setting. As first, the safety and efficacy of single-agent immunotherapy in elderly patients with A-NSCLC and high PD-L1 ( $\geq 50\%$ ) expression were reviewed (Table 1, Q3-Q4).

To all panelists, there is no particular concern on the safety of mono-immunotherapy in this setting (Figure 1).





**Figure 1. Summary of clinical consensus for ICI treatment in elderly patients with advanced NSCLC.**

The figure represents the main factors involved in the evaluation of elderly patients and expert consensus indications for the choice of first-line treatment with ICI-based regimens in the clinical setting.

CGA, comprehensive geriatric assessment; ICI, immune checkpoint inhibitor; NSCLC, non-small-cell lung cancer; PD-1, programmed cell death protein 1; PD-L1, programmed cell death-ligand 1.

<sup>a</sup>Absolute value of age boundaries to be considered within a multifactorial approach.

This conclusion is supported by the reviewed evidence derived from FDA pooled analysis, meta-analysis, pooled analysis from the KEYNOTE studies, and real-world studies.

In the same line, the efficacy of single-agent immunotherapy in the elderly population was confirmed across the same available evidence. Moreover, with the same referral considerations, the panelists observed no differences among the approved agents in this setting, neither in terms of toxicities nor in terms of efficacy.

To strengthen the validity of the consensus, the panelists agreed that, due to concerns on chemotherapy toxicity, single-agent anti-PD-1/PD-L1 should be considered as preferred treatment in elderly patients with A-NSCLC and PD-L1 ≥50%, at least in the absence of dedicated prospective trials to evaluate survival benefit between single-agent and combination treatments.

**Discussion on combined chemotherapy plus single-agent immunotherapy**

Following the consensus on single-agent immunotherapy, the discussion was focused on the safety and efficacy of the combination of chemotherapy plus single-agent ICIs (Table 1, Q5-Q6-Q7-Q8).

In this setting, the main concerns were expressed by all panelists on the toxicities of the chemotherapy components, in both squamous and non-squamous histology. General concern was expressed for combined chemotherapy plus immunotherapy in octogenarians. In particular, in squamous histology, the major concern was noticed on paclitaxel due to neurotoxicity. Because of this, panelists agreed to prefer, where available, nab-paclitaxel or gemcitabine, or even weekly paclitaxel schedule to better manage chemotherapy toxicity.

In non-squamous histology, caution was recommended on maintenance with pemetrexed. Indeed, renal function in

elderly is extremely variable, related to organ failure, but also to frequently low water intake and body mass index composition. As such, signals of early discontinuation from real-world data confirm the alert on prolonged pemetrexed maintenance (Figure 1).

To this extent, data from IPSOS and eENERGY trials support the use of chemo-free regimens in the elderly population, regardless of PD-L1 value.<sup>49,50</sup> Furthermore, data about alternative backbone chemotherapy (i.e. for platinum-eligible patients) are recommended topic for research issue (Supplementary Table S1, available at <https://doi.org/10.1016/j.esmooop.2023.101192>).

With respect to efficacy, besides real-world data confirming activity in patients with non-squamous histology aged ≥75 years, the panelists based their opinion on the exploratory analysis available from pivotal RCTs. In particular, data from KEYNOTE-407 and KEYNOTE-189 showed no difference in treatment efficacy with 65-year age cut-off, but only few elderly patients ≥75 years were included in clinical trials.

**Discussion on combined chemotherapy plus double-agent immunotherapy**

The option of first-line treatment with chemotherapy plus double-agent immunotherapy, namely anti-PD-1/PD-L1 plus anti-CTLA-4, was considered for panelists’ discussion, based on the results of the CheckMate 9LA and POSEIDON trials<sup>25,51</sup> (Table 1, Q9-Q10).

In this setting, the panelists agreed that the absence of benefit deriving from a small subgroup analysis on 10% of patients aged ≥75 years in the CheckMate 9LA trial cannot be used as a backbone to avoid this treatment in the elderly (Figure 1).

In addition, no major safety concerns were expressed with this regimen, considering that a regimen with two

**Table 2.** Ongoing clinical trials with ICIs in the front-line setting in elderly patients

Trials ID	Study phase	Treatment arms	PD-L1	Age setting (years)	Primary endpoint
NCT04396457	II	Pembrolizumab plus pemetrexed	<50%	≥75	ORR
NCT03975114 (MILES-5)	II	CTx → at PD: durvalumab or Durvalumab → at PD: CTx or Durvalumab plus tremelimumab → at PD: CTx	Any	≥70	12 months OS
NCT03293680	II	Pembrolizumab	≥1%	≥70	12 months OS
NCT05273814	I	Tislelizumab plus bevacizumab and pemetrexed	Any	≥65	ORR
NCT04533451	II	Pembrolizumab or Pembrolizumab plus carboplatin plus pemetrexed	Any	≥70	AEs
NCT03977194	III	Carboplatin plus paclitaxel or Carboplatin plus paclitaxel plus atezolizumab	Any	≥70-89	OS
NCT05230888	Prospective	CGA and VES-13 questionnaire in patients receiving ICIs	Any	≥70	irAEs

AEs, adverse events; CGA, comprehensive geriatric assessment; CTx, chemotherapy; ICIs, immune checkpoint inhibitors; irAEs, immune-related adverse events; ORR, overall response rate; OS, overall survival; PD, progressive disease; PD-L1, programmed cell death-ligand 1; VES, Vulnerable Elders Survey.

cycles of chemotherapy, avoiding maintenance pemetrexed, could be favorable in the elderly population.

As a reminder, they evaluated, based on the results from the eENERGY trial, that the use of dual immunotherapy without chemotherapy in PD-L1 1%-49% could be an option in the United States, where this regimen is approved.

### Discussion on preferred treatments

Moving forward, the panelists discussed on preferred treatments in the PD-L1 ≥50% population of elderly patients. In this setting, as also expressed in the 'Discussion on single-agent immunotherapy' section, the panelists agreed that, based on FDA pooled analysis and real-world data, it is reasonable to choose single-agent anti-PD-1/PD-L1, with the only exception of never-smoker patients, irrespective of age (Table 1, Q11).

### DISCUSSION ON CLINICAL RESEARCH

According to the panelists, the main limitation in the evaluation of the elderly population in NSCLC is related to the lack of consistent data from pivotal clinical trials, including a small proportion of elderly patients, with different age cut-offs and not amenable to be assessed for their functional status. Hence, the panelists prioritized real-world supplementation of data in the elderly population. More in depth, they advocate the adoption of better data quality from real-world databases, to be able to assess all the subsets in the elderly population, including frailty, comorbidities, which may impact tumor response, treatment efficacy, and tolerability with ICI-based regimens (Supplementary Table S1, available at <https://doi.org/10.1016/j.esmooop.2023.101192>).

In line with the recently presented data from the IPSOS trial, and the elderly subpopulation of the eENERGY trial, with OS benefit of single- or dual-agent ICI over chemotherapy, the panelists agreed that medium priority should be given to increase research on chemotherapy-free

regimens (Table 2), or even in clinical trials with combination of single-agent chemotherapy plus immunotherapy. Indeed, single-agent chemotherapy treatments were considered as preferred options for unfit elderly patients in the pre-immunotherapy era.<sup>10</sup>

To better evaluate the impact of senescence on immunotherapy outcomes, medium priority was also attributed to studies evaluating pharmacokinetics and pharmacodynamics of ICIs in the elderly population. In the same line of investigation, the potential role of sex in influencing immunosenescence should be addressed.

In addition, the panelists prompted further relevant aspects related to patients' QoL as they might affect patients' survival. Indeed, as elderly patients are often not self-sustaining, the role of caregiver and its relationship with survival deserves investigation. Moreover, due to the potential multiple needs of the elderly population, and burden for patients and their caregivers to sustain multiple outpatient visits, decentralization of patients' cures should be prioritized, at least for those identified as frail patients.

### CONCLUSIONS

The use of immunotherapy in the first-line treatment of elderly patients with NSCLC was discussed during the 14th International Experts Panel Meeting, and issues for debate were evaluated. The limited prospective evidence is due to an underrepresentation of the elderly population in clinical trials. However, implementation with data from pooled analysis and real-world experiences helped to reach out a consensus on specific statements related to safety and efficacy of ICI-based regimens in this population.

Despite the fact that efficacy was mainly confirmed across data, no safety concerns were expressed with single-agent immunotherapy, whereas some concerns were pointed out with combinations, especially in octogenarians. In this line, the panel experts agreed on the need to expand clinical research with robust real-world studies, and

investigate alternative combination strategies with less toxic potential in the elderly patients with A-NSCLC.

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## DISCLOSURE

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