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REVIEW

First-line immunotherapy in advanced non-small-cell lung cancer patients with ECOG performance status 2: results of an International Expert Panel Meeting by the Italian Association of Thoracic Oncology

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Background: Immunotherapy represents the standard of care in the first-line treatment of advanced non-small-cell lung cancer (NSCLC), either as monotherapy in high programmed death-ligand 1 (PD-L1)-positive tumors (≥50%) or in combination with platinum-based chemotherapy regardless of PD-L1 status. However, most pivotal clinical trials of immune checkpoint inhibitors (ICIs) did not include patients with Eastern Cooperative Oncology Group (ECOG) performance status (PS) 2. Hence, a consensus is lacking on the safety and efficacy of ICIs in this specific subgroup of patients.

Materials and methods: A virtual International Expert Panel took place in July 2021 with the aim of reviewing the available evidence on the use of ICIs in NSCLC patients with ECOG PS 2, both in clinical practice and in a research setting.

Results: All panelists expressed concern about the applicability of currently available PS scales to evaluate patients for ICI treatment. The panelists agreed that, though limited, the available data support the safety of single-agent immunotherapy in PS 2 NSCLC patients, whereas concern was raised on the safety of ICI combinations, mainly related to chemotherapy and/or anti-cytotoxic T-lymphocyte-associated antigen 4 toxicity. On the basis of reviewed data, ICI efficacy may be speculated in PS 2 NSCLC patients; however, PS 2 remains a negative prognostic category as compared to PS 0-1 in patients treated with ICI, as it is for chemotherapy. The panelists defined high, medium and low priorities in clinical research. High priority was attributed to the inclusion of PS 2 patients in prospective clinical trials and the specific evaluation of combined ICI treatments with attenuated chemotherapy doses.

Conclusions: Based on the current evidence, the panelists outlined the major limitations affecting PS 2 patients with 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, performance status 2, NSCLC, consensus

INTRODUCTION

The evaluation of performance status (PS) is part of the general assessment of cancer patients in clinical practice. Indeed, PS is roughly a measure of a patient's functional status in daily living, which may be impaired by tumor-related symptoms and pre-existing comorbidities.

The most commonly adopted PS scales are the Karnofsky scale[1] and the Eastern Cooperative Oncology Group (ECOG).[2] The ECOG PS scale is based on five progressive points (0-5), with higher numbers representing greater disability, and represents the benchmark for cancer patients' evaluation in clinical trials and in clinical practice. According to ECOG classification, PS 2 patients are defined as those restricted in their physical activity, resting in bed <50% of waking hours and still capable of self-care.[2] Unfortunately, this particular category, though still potentially outpatient, represents a population subgroup with a negative prognosis compared to PS 0-1 patients. Indeed, PS 2 has emerged as an independent prognostic factor in advanced lung cancer patients from several retrospective and prospective studies.[3,4] Non-small-cell lung cancer (NSCLC) patients with PS 2 receiving chemotherapy have a

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reduced overall survival (OS), progression-free survival (PFS) and lower objective response rates compared to PS 0-1 counterparts, with additional risk for severe treatment toxicity.[5,6] This knowledge generated in the past years the need for a consensus on chemotherapy use in PS 2 patients affected by NSCLC, defining single-agent chemotherapy or carboplatin/cisplatin doublets with attenuated doses as valid options for this special population.[7]

In recent years, the use of immune checkpoint inhibitors (ICIs) radically changed the clinical practice and treatment paradigms in locally advanced and metastatic NSCLC patients. Following the initial positive results in terms of prolonged OS compared to standard docetaxel in platinum-pretreated patients,[8-11] the use of ICIs rapidly moved to the first-line setting of NSCLC treatment.

Indeed, single-agent immunotherapy with the anti-programmed cell death protein 1 (anti-PD-1) pembrolizumab and cemiplimab, and the anti-programmed death-ligand 1 (anti-PD-L1) atezolizumab, demonstrated survival benefit as compared to platinum-based chemotherapy in either squamous or non-squamous NSCLC, with high PD-L1 expression (defined as PD-L1 tumor proportion score $\geq$50% for pembrolizumab/cemiplimab and PD-L1 on tumor cells $\geq$50% or on immune cells $\geq$10% for atezolizumab) and wild-type (WT) epidermal growth factor receptor (EGFR)/anaplastic lymphoma kinase status.[12-15]

In PD-L1 unselected NSCLC population, WT for EGFR and anaplastic lymphoma kinase, the combination of histology-based platinum doublet chemotherapy and an anti-PD-1 or anti-PD-L1 showed long-term survival benefit with respect to chemotherapy alone, reaching 31.3% and 29.7% OS rate at 3 years with the combination of chemotherapy and pembrolizumab in adenocarcinoma and squamous cell carcinoma histology, respectively.[16-19] Recently, the combination of anti-PD-1/PD-L1 and anti-cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) (nivolumab plus ipilimumab and durvalumab plus tremelimumab) in association with platinum-based chemotherapy demonstrated positive survival results in the same setting.[20,21]

Despite eligibility for all pivotal clinical trials of ICIs being limited to patients with an ECOG PS of 0 or 1, the ICI regimens have been approved by regulatory authorities regardless of PS assessment in NSCLC patients. This aspect has generated concern as PS 2 represents up to 30%-40% of advanced NSCLC (A-NSCLC) patients in clinical practice.[22-24]

In the absence of data from randomized phase III trials on the safety and efficacy of immunotherapy in NSCLC patients with PS 2, mainly real-world evidence studies were conducted trying to address this issue.[25] However, no consensus is available on the opportunity to use ICI-based regimens (monotherapy or combination treatments) in ECOG PS 2 patients, considering safety and expected efficacy in the context of a well-defined poor prognosis NSCLC population.

METHODS

The 13th International Experts Panel Meeting by Associazione Italiana di Oncologia Toracica (AIOT) was held virtually on 7 July 2021 to discuss the topic 'Immunotherapy in the first-line treatment of A-NSCLC patients with PS 2'. The scientific panel of the meeting was made up of six medical oncologists from different countries (China, Germany, 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 ECOG PS 2 patients was formally reviewed to initiate discussion. The second part of the meeting consisted of panelists' discussion aimed at reaching common conclusions 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 'PS 2'. Only articles written in English were considered for the discussion. Abstracts presented between 2000 and 2021 at the main international meetings [by American Society of Clinical Oncology (ASCO), European Society for Medical Oncology (ESMO), International Association for the Study of Lung Cancer] also were searched. The search has been updated for this article with the proceedings of the 2021 ASCO and ESMO meeting. Relevant references from selected articles also were included, and other articles were selected from the personal collections of the panelists.

For the clinical practice, 11 questions, previously agreed by the panelists, were posed to all members and widely discussed. 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 European Medicines Agency. As such, the first-line single-agent pembrolizumab and the combination of nivolumab and ipilimumab in PD-L1 $\geq$1% NSCLC patients (KEYNOTE-042 and CheckMate 227 schedule, respectively) were not considered for panelists' discussion.

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

A summary report was compiled in the form of live-shared minutes during the meeting and agreed by all panelists to serve as the basis to generate the current manuscript. All panelists reviewed the shared statements for each question and approved the final manuscript.

EVIDENCE ON THE USE OF FIRST-LINE IMMUNOTHERAPY IN PS 2 NSCLC PATIENTS

Prospective evidence on the use of immunotherapy in advanced or metastatic NSCLC patients with ECOG PS 2 is very limited.[26] To date, the only prospective data available in the first-line setting derive from the PePS2 trial, selectively evaluating the safety of pembrolizumab monotherapy in PS 2 patients with NSCLC. This phase II study included 60 patients, of whom only 24 received pembrolizumab as first-line treatment. Overall toxicity incidence was 28% [15% grade (G) $\geq$3], and median OS was 7.9 months in the

first-line setting, reaching 14.6 months in those patients ($n = 15$) with PD-L1 $\geq$50%.[27]

Two additional prospective studies, CheckMate 153 and CheckMate 171 trials, were conducted in the pretreated setting and included PS 0-2 patients receiving nivolumab monotherapy.[28,29] The phase II CheckMate 171, limited to squamous cell lung cancer, included 103 patients with PS 2 out of 811 treated patients (12.7%). Nivolumab monotherapy was confirmed to be well tolerated in PS 2 patients, with only 5.9% of patients experiencing G $\geq$3 adverse events. Conversely, OS was halved in PS 2 compared to PS 0-1 population.[28] PS 2 represented 8.9% of study participants in the phase IIIb/IV CheckMate 153 trial with nivolumab in pretreated NSCLC. Of note, despite inferior OS, the tolerability was confirmed (12% G3-4 adverse events) and improvement in symptoms was observed in PS 2 patients.[29]

Several retrospective reports evaluated the outcomes of immunotherapy regimens in the real-world population including those with poor PS.

Overall, first-line pembrolizumab showed good tolerability in PS 2 patients, comparable to that obtained in PS 0-1 population.[30,31] Unfortunately, the treatment outcomes were found to be inferior in PS 2 compared to good PS patients in terms of response rate, PFS and OS.[24,31,32] Across different studies, ECOG PS $\geq$2 was confirmed to be an independent prognostic factor and predictor of response to pembrolizumab.[24,31,33,34] A retrospective study selectively evaluating PS 2 patients receiving first-line pembrolizumab showed that both PFS and OS were impaired by the determinants of PS 2. Specifically, comorbidity-related PS 2 had better outcomes as compared to tumor-related PS 2 [median OS 11.8 versus 2.8 months, hazard ratio (HR) = 0.5, $P = 0.001$; median PFS 5.6 versus 1.8 months, HR = 0.5, $P = 0.001$].[30]

A few retrospective reports included a poor PS population receiving chemotherapy plus immunotherapy combination; these confirmed the negative prognostic outcome of PS 2, in the absence of safety data evaluated.[35,36]

Few clinical trials are ongoing specifically evaluating ICIs in PS 2 NSCLC patients. A phase II prospective trial (NCT02581943) randomized advanced or metastatic NSCLC patients, mostly treatment-naïve, to receive either pembrolizumab or the combination of pembrolizumab plus weekly low dose of carboplatin and paclitaxel. First results presented on 20 patients showed increased overall response rate (ORR) with the combination compared to pembrolizumab alone (70% versus 20%), and no G $\geq$3 toxicities were observed.[37] Durvalumab monotherapy is also evaluated in a prospective phase II trial (NCT02879617) in the first-line setting on PS 2 NSCLC patients, currently ongoing. To date, the only phase III trials with first-line immunotherapy dedicated to poor PS patients with NSCLC are the IPSOS study (NCT03191786) and the eNERGY study (NCT03351361). The IPSOS trial was designed to compare atezolizumab monotherapy with single-agent chemotherapy in platinum unfit patients, whereas the eNERGY study compared the combination of nivolumab and ipilimumab with carboplatin doublet chemotherapy. However, both studies were not limited to poor PS, but also elderly patients were included, thereby potentially limiting the interpretation of the awaited results.

DISCUSSION ON CLINICAL PRACTICE

PS 2 assessment

The first issue for panel discussion was related to the validity of the PS scales used in clinical practice for patient's assessment (Table 1, questions Q1-Q2). Because of worldwide use in clinical trials, the panelists focused on ECOG PS scale for their debate. All panelists expressed concern regarding the applicability and reproducibility of the PS 2 definition, which does not consider distinctions by comorbidities, tumor burden or other factors potentially affecting functional state. Indeed, evidence is available that physician-reported PS may differ from that reported by patients, confirming the presence of subjective factors influencing PS evaluation.[38] The panelists agreed that PS 2 category should be clearly distinct from age. Indeed, clinical trials enrolling PS 2 patients usually summarize PS with elderly and frail. However, age is not *per se* a limiting factor for any NSCLC treatment and should not affect PS evaluation.[39]

The panel discussion was based on the observation that PS scale was developed for chemotherapy, as it is predictive for chemotherapy-related toxicity.[5,6] However, the impact of PS 2 on selecting chemotherapy regimen was mitigated by the observation that the addition of platinum to single-agent chemotherapy improved survival as first-line treatment also in PS 2 patients with A-NSCLC.[40,41] As for immunotherapy, PS 2 is not expected to be predictive for additional immune-related toxicity (immune-related adverse events).[27,31] Hence, the determinants of PS 2 (tumor-related or comorbidity-related) are mainly considered as relevant in selecting chemotherapy agents rather than immunotherapy alone. In particular, the panelists agreed that new or amended PS scales are needed to specifically assess immune status evaluation (defining it as an issue for clinical research) and specific comorbidities that limit the use of immunotherapy due to synergistic safety concerns (i.e. pulmonary fibrosis, oxygen support).

Discussion on single-agent immunotherapy

Besides the consensus obtained on PS 2 assessment, the panel focused on treatments available in the first-line setting. The first addressed topic was related to the use of single-agent immunotherapy in PS 2 patients with A-NSCLC and high PD-L1 ($\geq$50%) expression. Two aspects were separately faced: safety and efficacy (Table 1, Q3-Q4).

To all panelists, there is no particular concern on the safety of mono-immunotherapy in this setting. Indeed, the only available prospective data from the phase II PePS 2 trial, although limited by the small sample size ($n = 60$ patients), showed relatively low rate (15%) of G $\geq$3 treatment-related adverse events (TRAEs), with only 10% pembrolizumab discontinuation rate across treatment lines.[27] In addition, a recent meta-analysis evaluating the

Table 1. Expert panel statements on the use of first-line immunotherapy in A-NSCLC patients with PS 2

Panel questions	Expert conclusions
PS 2 assessment	
Q1. Is ECOG PS scale still adequate for clinical condition assessment in the immunotherapy era?	At all panelists, ECOG PS scale is considered not adequate and needs subclassifications according to the determinants of PS impairment (tumor-related versus comorbidities).
Q2. In A-NSCLC patients with PS 2 does the determinant of poor PS (tumor-related or comorbidity) affect your treatment choice?	Yes, with particular concern regarding chemotherapy agents rather than immunotherapy *per se*.
Single-agent immunotherapy	
Q3. In A-NSCLC patients with PS 2 and PD-L1 ≥50% is single-agent immunotherapy feasible and safe?	Yes, based on data available from real life only, to date in the absence of prospective phase III trials including PS 2 patients.
Q4. In A-NSCLC patients with PS 2 and PD-L1 ≥50% is single-agent immunotherapy effective?	Probably yes, based on data available from real life only, to date in the absence of prospective phase III trials including PS 2 patients. However, PS 2 is a strong negative prognostic factor and results are, as with any treatment, inferior compared to PS 0-1 patients.
Combined chemotherapy and immunotherapy	
Q5. In A-NSCLC patients with squamous histology and PS 2 is combined chemotherapy plus single-agent immunotherapy feasible and safe?	Probably no, unless further data supporting safety become available. Based on data available from real life only, to date in the absence of prospective phase III trials including PS 2 patients, concerns are mainly related to platinum-based doublet tolerability.
Q6. In A-NSCLC patients with squamous histology and PS 2 is combined chemotherapy plus single-agent immunotherapy effective?	Probably yes, based on data available from real life only, to date in the absence of prospective phase III trials including PS 2 patients.
Q7. In A-NSCLC patients with non-squamous histology and PS 2 is combined chemotherapy plus single-agent immunotherapy feasible and safe?	Probably no, unless further data supporting safety become available. Based on data available from real life only, to date in the absence of prospective phase III trials including PS 2 patients, concerns are mainly related to platinum-based doublet tolerability. However, pemetrexed-based doublets are generally better tolerated as compared to chemotherapy regimens used in squamous histology.
Q8. In A-NSCLC patients with non-squamous histology and PS 2 is combined chemotherapy plus single-agent immunotherapy effective?	Probably yes, based on data available from real life only, to date in the absence of prospective phase III trials including PS 2 patients.
Q9. In A-NSCLC patients with PS 2 is combined chemotherapy plus double immunotherapy feasible and safe?	Probably no, unless further data supporting safety become available. Based on data available from real life only, to date in the absence of prospective phase III trials including PS 2 patients, concerns are mainly related to additional toxicity from anti-CTLA-4.
Q10. In A-NSCLC patients with PS 2 is combined chemotherapy plus double immunotherapy effective?	Probably yes, to date in the absence of prospective phase III trials including PS 2 patients.
Preferred treatments	
Q11. In A-NSCLC patients with PS 2 and PD-L1 ≥50%, does the PD-L1 value affect your choice between single-agent immunotherapy and combined chemo–immunotherapy?	No

A-NSCLC, advanced non-small-cell lung cancer; CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; ECOG, Eastern Cooperative Oncology Group; PD-L1, programmed death-ligand 1; PS, performance status; Q, question.

efficacy and safety of ICIs in NSCLC patients with PS ≥2 revealed no differences in the incidence of adverse events between PS ≥2 ($n = 1339$) and PS ≤1 ($n = 5963$), regardless of treatment line.[31] Such conclusions on good safety profile of single-agent immunotherapy are supported by long-term safety results from randomized, controlled trials (RCTs) and patient-reported outcome data generated for the different trials, although limited to PS 0-1 patients. With the same referral considerations, the panelists observed no differences among the approved agents in this setting. As a general consideration, the panelists agreed that exceptions to the safe use of single-agent ICIs should be related to specific comorbidities (i.e. oxygen need, lung interstitial disease, steroid need), rather than PS 2 itself. Additionally, the discussion pointed out that safety concerns are generally applicable to the PS 2 category regardless of the PD-L1 status, as toxicity from ICIs is not expected to be more than that from chemotherapy. Therefore, although the discussion was focused on high PD-L1 A-NSCLC because of worldwide approvals, they expressed no safety limitations to the use of single-agent ICI also in PD-L1 ≥1% in countries where it is approved according to local authorities.

With regard to efficacy, retrospective data clearly show worse outcomes in PS 2 patients compared to PS 0-1 patients receiving first-line single-agent pembrolizumab. In particular, reduced ORR, shorter PFS and OS were observed in the PS 2 group.[24,30,32,34] These results reflect the already well-known prognostic impact of PS 2, which was confirmed as independent negative prognostic factor also in patients receiving immunotherapy, similarly to chemotherapy.[32,33,42] As a matter of fact, in the absence of a direct comparison with chemotherapy alone, survival results in the PePS 2 trial [median OS 7.9 months, 95% confidence interval (CI) 2.6 months-not reached, in the first-line setting across squamous and non-squamous histology][27] are quite comparable to those with platinum doublet chemotherapy in PS 2 patients (median OS 9.3 months, 95% CI 7.4-11.2 months, with platinum plus pemetrexed in non-squamous histology; median OS 5.9 months, 95% CI 2.8-11.3 months, with platinum plus gemcitabine in mixed squamous and non-squamous).[40,41]

In addition, the observed reduced ORR accounts for an impact of PS 2 as a factor predicting response with first-line single-agent ICIs. However, ORR of 20%-25% was consistently observed across the available studies, including the

21% ORR and 38% durable clinical benefit in the first-line setting in PePS 2 trial ($n = 24$), underlining that a fraction of NSCLC patients with poor PS can derive long-term benefit from ICIs.[27,43] In this field, a recent retrospective paper showed that the determinants of poor PS have indeed an impact on survival outcomes. In fact, among A-NSCLC patients with PS 2 and high PD-L1 receiving first-line pembrolizumab, those with PS 2 determined by comorbidities had significantly better PFS and OS compared to those with PS 2 related to tumor burden.[30] In addition, data from the CheckMate 153 trial of nivolumab in pretreated NSCLC patients suggest that, despite confirmed worse outcomes, PS 2 subgroup reported significant symptom improvements.[29] To summarize the evidence into a consensus, the panelists agreed that one can speculate that single-agent immunotherapy may be effective as first-line treatment in PS 2 A-NSCLC, but there are no substantial data to support that, outside retrospective and small prospective phase II trials (Table 1).

Table 2. Priority issues in clinical research on first-line immunotherapy in ECOG PS 2 patients with NSCLC

Issue	Priority
Inclusion of PS 2 patients in upcoming clinical trials evaluating immune-oncology agents in NSCLC (PS 2 versus 0-1 as stratification factor in phase III studies or different cohort studies)	High
Studies on single-agent chemotherapy plus ICIs	High
Studies on platinum-based chemotherapy with personalized/attenuated doses plus ICI	High
Studies on dual anti-PD-1/PD-L1 plus anti-CTLA-4 in PS 2	Medium
Studies on duration of ICI treatment	Medium
Studies on alternative schedules/doses of ICI treatment	Medium
Studies on single-agent immunotherapy versus platinum-based doublet chemotherapy plus immunotherapy in PD-L1 $\geq$50%	Medium
Biological and translational studies on blood biomarkers to evaluate immune activation in PS 2 patients receiving immunotherapy	Low

CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; ECOG, Eastern Cooperative Oncology Group; ICI, immune checkpoint inhibitor; NSCLC, non-small-cell lung cancer; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PS, performance status.

Discussion on combined chemotherapy plus single-agent immunotherapy

Following the discussion on single-agent immunotherapy, consensus was sought on the safety and efficacy of the combination of chemotherapy plus single-agent ICIs (Table 1, Q5-Q6-Q7-Q8). In this setting, no prospective data are available, and evidence is limited to few retrospective studies including both squamous and non-squamous histology and mixed populations.[35,36] Results from these studies were mainly limited to efficacy assessment. In the study by Waterhouse et al.,[36] evaluating real-world outcomes of A-NSCLC patients receiving first-line ICIs, poor PS was confirmed as a negative prognostic factor in patients receiving combined chemotherapy plus immunotherapy (PS $\geq$2 patients: 16%; median OS 8 versus 11.6 months in squamous histology; 6.3 versus 14.2 months in non-squamous histology).[36] Similarly, a very recent study investigated the outcomes of trial-eligible and trial-ineligible patients treated with immunotherapy for different tumors.[35] ECOG PS >1 patients represented 61% of the trial-ineligible population within the NSCLC cohort. In this setting, the survival results of trial-ineligible versus trial-eligible patients were disappointing across treatment regimens including ICI monotherapy and ICI combinations (median OS 5.3 versus 20.4 months, $P < 0.0001$),[35] again confirming the negative prognostic impact of PS 2 category.

Safety evaluation was not carried out in these studies; therefore, the panelists' discussion was primarily based on their expert opinion and toxicity data from RCTs not including PS 2 patients. Overall, the panelists expressed concern on toxicity, mainly related to chemotherapy regimens that are administered with single-agent ICIs. This consideration was particularly stressed for the regimens available for squamous histology, as pemetrexed-based doublets are generally better tolerated and already considered an accepted protocol for PS 2 patients.[40] Based on these data, the panelists identified issues for clinical research in this setting, including the evaluation of combination with flexible chemotherapy regimens and doses, that might be proposed in selected PS 2 patients with intensive monitoring for toxicity (Table 2). Of note, the panelists recommended that, in countries where single-agent immunotherapy is approved in PD-L1 $\geq$1%, consideration of combined chemo—immunotherapy be limited to the treatment of PD-L1-negative patients.

Discussion on combined chemotherapy plus double-agent immunotherapy

Moving forward, the panelists considered the option of first-line treatment with chemotherapy plus double-agent immunotherapy, namely anti-PD-1/PD-L1 plus anti-CTLA-4, based on the results of the CheckMate 9LA and POSEIDON trials[20,21] (Table 1, Q9-Q10). In the absence of evidence available in this setting in PS 2 patients, the experts discussed on their safety concern related to these regimens. In particular, considering the increased rate of TRAEs in RCTs with anti-CTLA4 (Table 3), they foresee the consistent risk of potentially adding anti-CTLA4-related toxicity to a potentially high-risk group, despite the reduced chemotherapy exposure (only two cycles of chemotherapy in the CheckMate 9LA with nivolumab and ipilimumab).

Of note, the chemotherapy sparing option of nivolumab plus ipilimumab alone was investigated in PS 2 patients in the cohort A1 of the open-label phase IIIb/IV CheckMate 817 trial.[44] Initial results in ECOG PS 2 patients ($n = 139$) showed an ORR of 20%, with particularly interesting PFS results in the PD-L1-high subgroup (median PFS 8.2 months, 95% CI 1.4-14.18 months).[44] However, the toxicity profile, despite being similar to that obtained in the PS 0-1 population, showed a 24% rate of G3-4 TRAEs, which is highly relevant in a high-risk population. Due to the absence of final data from this trial and the only FDA approval of the nivolumab plus ipilimumab regimen being in PD-L1-positive NSCLC,[45] this option was not discussed more deeply.

Table 3. Incidence of treatment-related adverse events with first-line immunotherapy regimens in NSCLC in phase III RCTs with positive OS results

1L approach	RCT	Investigational arm (versus platinum-based chemo)	G ≥3 TRAEs (%)[a]	Treatment discontinuation due to any TRAEs (%)[a]
Single-agent immunotherapy	KEYNOTE 024	Pembrolizumab	26.6% (versus 53.3%)	7.1% (versus 10.7%)
	KEYNOTE 042	Pembrolizumab	18% (versus 41%)	9% (versus 9%)
	IMpower110	Atezolizumab	33.9% (versus 56.7%)	6.3% (versus 16.3%)
	Empower Lung 01	Cemiplimab	14% (versus 39%)	6% (versus 4%)
Chemotherapy plus single-agent immunotherapy	KEYNOTE 189	Pembrolizumab + platinum + pemetrexed	67.2% (versus 65.8%)	25.7% (versus 14.8%)
	KEYNOTE 407	Pembrolizumab + carboplatin + (nab)paclitaxel	69.8% (versus 68.2%)	25.5% (versus 12.8%)
	IMpower150	Atezolizumab + bevacizumab + carboplatin+ paclitaxel[b]	58.5% (versus 50%)	32.6% (versus 24.9%)
	IMpower130	Atezolizumab + carboplatin + nabpaclitaxel	75% (versus 61%)	26% (versus 22%)
Double-agent immunotherapy	CheckMate 227	Nivolumab + ipilimumab	32.8% (versus 36%)	18.1% (versus 9.1%)
Chemotherapy plus single-agent immunotherapy	CheckMate 9LA	Nivolumab + ipilimumab + two cycles of platinum-based chemotherapy	47% (versus 38%)	19% (versus 7%)
	POSEIDON	Durvalumab + tremelimumab + platinum-based chemotherapy	NR	NR

1L, first line; G, grade; NR, not reported; NSCLC, non-small-cell lung cancer; OS, overall survival; RCT, randomized, controlled trial; TRAE, treatment-related adverse event.
[a] Versus comparator arm.
[b] Comparator arm: atezolizumab + carboplatin + paclitaxel.

Discussion on preferred treatments

The final question (Q11) was related to the choice between single-agent immunotherapy and combined chemo–immunotherapy in the first-line setting of NSCLC patients with PS 2 and high PD-L1 (PD-L1 ≥50%) (Table 1). The rationale for this issue is that in principle the mono-immunotherapy would be preferred in PS 2 patients, based on the previously expressed concern regarding chemotherapy-related toxicity in this population.

On the other hand, given the observed poor survival in PS 2 patients, one of the hypotheses is that the addition of chemotherapy could improve symptoms related to tumor burden and survival. However, an analysis of the Flatiron electronic records recently presented showed that PD-L1-high patients receiving chemo–immunotherapy combination have similar outcomes compared to those receiving single-agent pembrolizumab in the first-line treatment in all subgroups but those who are never smokers.[46] Although this analysis only included PS 0-1 patients, to the panelists it supported the absence of selection criteria for whichever of the two treatments, except for never smokers in which the combination with chemotherapy would be preferred if clinically feasible even in PS 2 patients.

In addition, retrospective data were reviewed on the impact of increasing value of PD-L1, within PD-L1-high population, on response and survival. Of note, significantly higher ORR with first-line pembrolizumab was observed in NSCLC patients with PD-L1 ≥90% as compared to PD-L1 50%-89% (ORR 60% versus 32.7%, $P < 0.001$).[47] This analysis also included a total of 187 patients, of whom 34 (18%) were with ECOG PS ≥2. Significantly longer PFS (14.5 versus 4.1 months, $P < 0.01$) and OS (not reached versus 15.9 months, $P = 0.002$) were observed according to the same PD-L1 cut-off distinction.[47] However, the panelists agreed that it is not possible to assume further cut-offs within the PD-L1-high subgroup to definitively select alternative single-agent or combined treatments, unless the evidence of large prospective data.

DISCUSSION ON CLINICAL RESEARCH

All panelists agreed that clinical decision making for the use of ICIs in A-NSCLC with PS 2 is strongly impaired by the total absence of data from prospective phase III clinical trials. Hence, to the expert panel, high priority should be set on the inclusion of PS 2 patients in the future clinical trials evaluating immunotherapy in NSCLC. Being aware that PS status may affect study results, the panelists propose either the possibility to plan dedicated cohort studies to PS 2 patients or the disposition of PS status as a stratification criterion (Table 2).

The panelists' discussion on clinical practice in PS 2 patients brought out concern regarding potential toxicity related to chemotherapy regimens evaluated in association with ICIs in clinical trials. To address this issue, all panel members propose that high priority be given to the evaluation of alternative chemotherapy regimens to combine with ICIs, namely single-agent chemotherapy or attenuated doses of platinum doublet. Indeed, such chemotherapy treatments were considered as preferred options for PS 2 patients in the pre-immunotherapy era,[7] and the addition of single-agent immunotherapy does not raise concern on potential additional toxicity. In addition, although not available as a treatment option in Europe, the panelists propose to investigate the safety and efficacy of the dual anti-PD-1/PD-L1 and anti-CTLA-4 without chemotherapy specifically in NSCLC PS 2 population (medium priority). The addition of anti-CTLA-4 to an anti-PD-1 (ipilimumab plus nivolumab) showed a survival advantage in PD-L1-positive (≥1%) NSCLC in the CheckMate 227 trial,[45] but the application of this regimen is limited to the United States.

In the PD-L1-high population, the panel outlined the need to compare single-agent immunotherapy alone or in

combination with chemotherapy. Given the observed poor survival results in PS 2 patients treated with first-line pembrolizumab, one of the research questions is whether the addition of chemotherapy would be beneficial in PD-L1 $\geq$50% to rapidly reduce tumor burden and related symptoms. Conversely, large retrospective data available from the Flatiron registry, limited to PS 0-1 patients, reveal that there are no differences in survival outcomes between these two regimens, with the only exception of never smokers.[46] If these results are confirmed in PS 2 patients with PD-L1 $\geq$50%, potential additional toxicity from chemotherapy combination could be definitively avoided in this subgroup.

Still in connection with toxicity, the study of alternative ICI regimens was assigned medium priority by the panelists (Table 2). In particular, the need for studies on treatment duration was established, as well as the evaluation of different ICI schedules and doses (i.e. prolonged dose interval, considering the duration of anti-PD-1 receptor binding[48]), with the aim of lowering the risk of ICI toxicity, and also reducing the frequency of outpatient visits in patients with limited functional status.

The possibility to perform translational studies is another important issue explored during the panel meeting discussion, though mainly limited to the research field (low priority). In fact, the common concept of functional status influencing the immune system and immune responsiveness in individuals raises concern on the effective role of treatments based on immune activation in cancer patients with a declined PS. The possibility to individuate blood biomarkers of immune activation, immune editing or immune defect during immunotherapy could be helpful to build stronger rationale on the applicability of ICIs in PS 2 NSCLC patients.

CONCLUSIONS

The debate on the use of immunotherapy in the first-line treatment of ECOG PS 2 patients with NSCLC remains controversial within the oncology community, due to the lack of robust data. During the 13th International Experts Panel Meeting, this topic was deeply discussed and issues for debate were evaluated. The absence of prospective evidence revealed to be the major reason for the absence of a clear consensus worldwide.

The discussion pointed out that the concerns related to safety are currently leading the meeting statements. Indeed, the use of single-agent ICI demonstrated a good tolerability over platinum-based chemotherapy regimens, whichever containing ICIs, and could be safely adopted in frail patients as those with PS 2.

However, despite common considerations on clinical practice being reached by the panel experts, the stronger message emerging from this meeting is related to the need for high-level research in the field of PS 2 patients. As such, the experts highly recommend the inclusion of ECOG PS 2 population in randomized clinical trials with ICIs in NSCLC, to finally be able to evaluate efficacy results of these regimens, in addition to a confirmation of safety data.

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