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Original research

First-line durvalumab in patients with PD-L1 positive, advanced non-small cell lung cancer (NSCLC) with a performance status of 2 (PS2). Primary analysis of the multicenter, single-arm phase II trial SAKK 19/17☆

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ABSTRACT

Introduction: The safety and efficacy of first-line durvalumab in PS2 patients with advanced NSCLC is unknown. Here, we present the primary analysis of first-line durvalumab in PS2 patients, unsuitable for combination chemotherapy.

Methods: In this single-arm, multicenter, phase II trial patients with PD-L1 positive (tumor proportional score ≥25%), advanced NSCLC with PS2, received four-weekly durvalumab 1500 mg. The primary endpoint was overall survival (OS) at 6 months.

Results: Forty-eight patients were included. Median follow-up was 23.3 months (95% CI: 14.3–28.6). OS at 6 months was 60% (95% CI: 45–74%). Median OS was 8.5 months (95%CI: 4.4–16.7). Objective response rate and median progression free survival were 17% (95% CI: 8–30%) and 2.5 months (95% CI: 1.8–7.1), respectively. Thirty-three deaths were observed at the time point of the analysis. Seven early fatal events considered not treatment-related occurred during the first 5 weeks of treatment. Four out of the first 7 early fatal events (4/7; 57%) were respiratory failure in patients with advanced symptomatic primary lung tumors. Three more early fatal events occurred after exclusion of patients with grade ≥ 3 dyspnea. Treatment-related AEs ≥G3 were reported in 9 patients (19%) and included colonic perforation in one patient (grade 5), colitis in 4 patients (8%), increased lipase in 3 patients (6%), and hepatitis in 2 patients (4%).

Conclusions: First-line durvalumab in PS2 patients with advanced PD-L1 positive NSCLC results in a high number of early fatal events. When patients with grade ≥ 3 dyspnea are excluded a promising 6-month OS with an acceptable toxicity profile can be observed. Durvalumab could be an option instead of single agent chemotherapy for PS2 patients who are not candidates for platinum doublet chemotherapy provided they are well selected.

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Introduction

Based on the proven superiority of immune checkpoint inhibitors (ICIs), such as pembrolizumab, atezolizumab, cemiplimab and camrelizumab over standard chemotherapy as first-line treatment of patients (pts) with advanced NSCLC with PD-L1 expression in $\geq$ 50% tumor cells and a good performance status (PS) these drugs have been approved and are now standard of care [1–3].

An estimated 30 to 40% of pts diagnosed with NSCLC have a poor PS defined as a score of 2 or higher on the Eastern Cooperative Oncology Group (ECOG) scale [4]. PS is the most powerful independent prognostic factor in advanced NSCLC and it is a reliable measure of functional independence, ability to perform daily activities and work, and a strong predictor of survival and adverse events (AEs) [5]. Therefore, registration trials have excluded a relevant proportion of NSCLC pts by allowing PS 0–1 pts only.

Although data have shown improved survival with platinum doublets compared to single agent chemotherapy in PS 2 NSCLC pts and are preferred in the first-line setting according to international guidelines [3], toxicity remains a concern [6–8]. Single-agent chemotherapy represents therefore an alternative treatment option for pts with PS 2 deemed unsuitable for platinum-based doublet chemotherapy [3]. However, efficacy of single agent chemotherapy is very limited and the overall outcome of PS2 pts with advanced NSCLC is poor.

Several phase 2 trials have investigated the effect of immune checkpoint blockade in pts with advanced NSCLC and PS2 demonstrating encouraging survival data with a manageable safety profile [9,10]. Nevertheless, these trials were neither restricted to high PD-L1 expression nor specifically designed for pts in the first-line setting. The CheckMate 817 trial enrolled treatment-naïve pts with advanced NSCLC in different cohorts also including PS2 pts independent of PD-L1 expression to evaluate the efficacy and safety of the combination of ipilimumab and nivolumab [11]. The recent IPSOS trial was the first randomized phase 3 trial showing improved overall survival (OS) with frontline atezolizumab compared to single-agent chemotherapy in pts independent of PD-L1 expression with stage IIIB/IV NSCLC who were ineligible for platinum-based therapies [12].

Durvalumab is a selective human IgG1 monoclonal antibody that blocks PD-L1 binding to PD-1 [13,14] and is an integral part of standard of care in the first -line treatment in extensive stage small-cell lung cancer and as a maintenance regimen in irresectable stage III NSCLC after definitive radiochemotherapy [15,16]. Objective response rates (ORRs) with durvalumab were higher in pts with PD-L1-positive tumors ($\geq$25% tumor cells stained) [13]. Important safety data leading to exclusion of pts with relevant respiratory symptoms have been published as an interim report of this trial [17]. Here we present the primary analysis of first-line durvalumab in PS2 pts, unsuitable for combination chemotherapy and PD-L1 expression in $\geq$ 25% of tumor cells.

Materials and methods

Study design and study population

Eligibility criteria for SAKK 19/17 have been described previously [17]. After an unexpectedly high early number of fatal events due to tumor progression among the first 21 pts we have implemented a protocol amendment designed to exclude pts with grade $\geq$ 3 dyspnea according to the modified Medical Research Council (mMRC) dyspnea scale [18]. In addition, confirmation of PS2 independently by a second physician, taking into account the interobserver variability of ECOG PS assessment, was newly required. Only if the second physician also classified the respective patient as PS2, could the patient be included in the study. All patients provided written informed consent prior to enrollment. The trial was approved by the institutional ethical committees of the respective centers.

Endpoints and assessments

The primary endpoint was OS at 6 months. Secondary endpoints were ORR, duration of response, progression free survival (PFS) according to RECIST 1.1 and iRECIST, OS, safety and quality of life (QoL) including a geriatric assessment (GA). All adverse events (AEs) and severe AEs (SAEs) including AEs/SAEs for dyspnea were classified and graded according to the National Cancer Institute Common Terminology Criteria for AEs (NCI CTCAE), Version 5.0, and monitored from the start of the study, with their relation to study treatment assessed by the investigators. QoL was measured by the European Organisation for Research and Treatment of Cancer (EORTC) Quality-of-life Core Questionnaire (QLQ-C30) and the Lung Cancer Module (QLQ-LC13) [19,20] at baseline, at day 1 of every cycle and at the end of treatment visit, up to 1 year maximum after treatment start. GA at baseline included a screening instrument (G8) to identify frail pts (score of $\leq$ 14; range 0–17) [21]. It was complemented by a measure used in geriatrics to assess functional status, i.e. a patient's ability to perform instrumental activities of daily life (IADL), and comorbidities measured by the Charlson Comorbidity Index (CCI) [22,23].

Statistical analysis

A single stage design based on the binomial distribution was chosen using the software package PASS 11.0, NCSS, Kaysville. The null hypothesis was OS at 6 months $\leq$ 35% (median OS: 4 months) according to the results by Lilenbaum et al [8], comparing single-agent versus combination chemotherapy in advanced NSCLC, the alternative hypothesis was OS at 6 months $\geq$ 53% (median OS: 6.5 months), one-sided type I error 0.05, power 0.8. This leads to a required sample size of 46 pts evaluable for the primary endpoint. To account for ineligible pts, the sample size was increased by 5% to 48 pts. Time-to-event endpoints were summarized by the median and corresponding 95% confidence interval (CI) using the Kaplan-Meier (KM) method. Binary endpoints were presented by the point estimate along with the two-sided 95% CI using the Clopper-Pearson method (except the primary endpoint with 90% CI). An explorative subgroup analysis for OS and PFS was performed with the pts included before and after the amendment (addition of exclusion of pts with initially relevant respiratory symptoms). All efficacy analyses were based on the full analysis set, including all pts who received at least one dose of trial treatment, yet excluding those with major eligibility violations. Tolerability was analyzed based on the safety population, i.e., all pts having received at least one study drug dose. All AEs reported until 28 days after the last administration of the trial treatment were taken into account and summarized by system organ class. The difference of OS between subgroups was assessed by the log-rank test. Changes in QoL scores from baseline (minimally important change $\geq$ 4 points) were analyzed descriptively [24]. The GA screening tool G8 scores were compared between pts who met the primary endpoint and those who did not meet the primary endpoint by calculating the Wilcoxon rank-sum test. All analyses were performed using SAS® 9.4 (SAS Institute Inc., Cary, NC) on a Windows platform and R 4.3.0 (The R Foundation) [25].

Results

Patient characteristics

Between 04/12/2018 and 07/04/2022 48 pts from 10 sites in Switzerland were enrolled into the trial. All 48 pts received at least one dose of durvalumab. The pts baseline characteristics are summarized in Table 1. 41 samples (85.4%) were available for confirmatory central PD-L1 testing proving conformity (PD-L1 $\geq$ 25%) in 35/41 (85%) of the cases. The median follow-up time for the full analysis set was 23.3 months (95% CI: 14.3–28.6). Median treatment duration was 2.8 months (95% CI: 0–28.6), and the median number of cycles was 4 (95%

Table 1
Patient characteristics.

Variable	N = 48 (100%)
Age (years), median (range)	76 (37–87)
Sex	
Female	19 (40%)
Male	29 (60%)
Smoking status	
Smoker	25 (52%)
Former smoker	16 (33%)
Never smoker	1 (2%)
Unknown	6 (13%)
Stage	
IV	41 (85%)
III	7 (15%)
PD-L1 ≥ 50% (local testing)	
Yes	38 (79%)
No	10 (21%)
NGS perfomred	
Yes	28 (58%)
No	20 (42%)
KRAS mutation	5 (10%)
Previous radiotherapy and/or surgery	17 (39%)
Subtype of NSCLC	
Adenocarcinoma	28 (59%)
Squamous cell carcinoma	17 (35%)
NSCLC not otherwise specified	3 (6%)
Extent of metastatic disease	
Lymph nodes	32 (67%)
Lung	25 (52%)
Bone	11 (23%)
Brain	7 (15%)
Liver	7 (15%)

CI:1–32), respectively. Treatment was permanently discontinued in 41 pts (85%). The most frequent reasons for treatment discontinuation were death, observed in 16 pts (39%), and disease progression in 12 pts (29%).

Efficacy assessment

The primary endpoint OS at 6 months was 60% (90% CI: 48–72%). OS at 6 months after amending the inclusion criteria to exclude pts with initially relevant respiratory symptoms was 67% (95% CI: 46–84%, n = 27) and 52% (95% CI: 30–74%, n = 21) in the pts who were recruited before the amendment without this exclusion criterium. Median OS was 8.5 months (95% CI: 4.4–16.7) (Figure 1A). ORR and median PFS were 17% (95% CI: 8–30%) and 2.5 months (95% CI: 1.8–7.1) (Figure 2A). Median duration of response was 22.8 months (95% CI: 3.8-not reached (NR)). ORR and median duration of response according to iRECIST were 19% (95% CI: 9–33%) and 34.5 months (95% CI: 3.8-NR). Median OS and median PFS for the subgroup of pts after the protocol amendment were 16.2 months (95% CI: 4.3-NR) and 5.2 months (95% CI: 1.8–8.6). Median OS and median PFS for the subgroup of pts before the protocol amendment were 6.3 months (95% CI: 0.8–9.1) and 1.8 months (95% CI: 0.8–5.5) (Figure 1B and Figure 2B). Due to the limitation of the PD-L1 level set at 25%, which was utilized in previous durvalumab studies, we have also investigated the effectiveness in the subgroups with PD-L1 levels ≥ 50% and ≥ 90%. No significant difference in OS could be detected compared to the subgroup of PD-L1 < 50% versus ≥ 50% or < 90% versus ≥ 90%, respectively (median OS for PD-L1 ≥ 50% was 8.8 months (95% CI: 4.3–16.7, n = 38) and 8.4 months (95% CI: 0.8-NR, n = 10, p = 0.548) for PD-L1 < 50%, median OS for PD-L1 ≥ 90% was 11.2 months (95% CI: 2.5-NR, n = 15) and 7.2 months (95% CI: 3.2–16.2, n = 33, p = 0.399) for PD-L1 < 90%).

Safety assessment and toxicities

Thirty-three pts have died at the timepoint of this analysis. One patient died due to colonic perforation that occurred nine months following treatment initiation and was considered treatment-related (1/48; 2%). The other deaths were attributed to progressive disease (23/33; 70%), infection (4/33; 12%), heart failure (3/33; 9%), respiratory insufficiency and stroke (1/33; 3% each). Four out of the first 7 early fatal events (4/7; 57%) were related to respiratory failure in pts with initially advanced symptomatic primary lung tumors which has been already described elsewhere [17]. Three more early fatal events occurred after the protocol amendment. Thirty-nine pts (81%) had an AE grade ≥ 3 (G3). The most frequent AEs ≥G3 were lung infection (19%), dyspnea (15%), hypertension (10%) and respiratory failure (10%). Treatment-related AEs ≥G3 were reported in 9 pts (19%) and included colonic perforation in one patient (grade 5), colitis in 4 pts (8%), increased lipase in 3 pts (6%), and hepatitis in 2 pts (4%) (Table 2). Treatment-related AEs of any grade at least possibly related to durvalumab can be found in the supplementary material (Table 1 suppl).

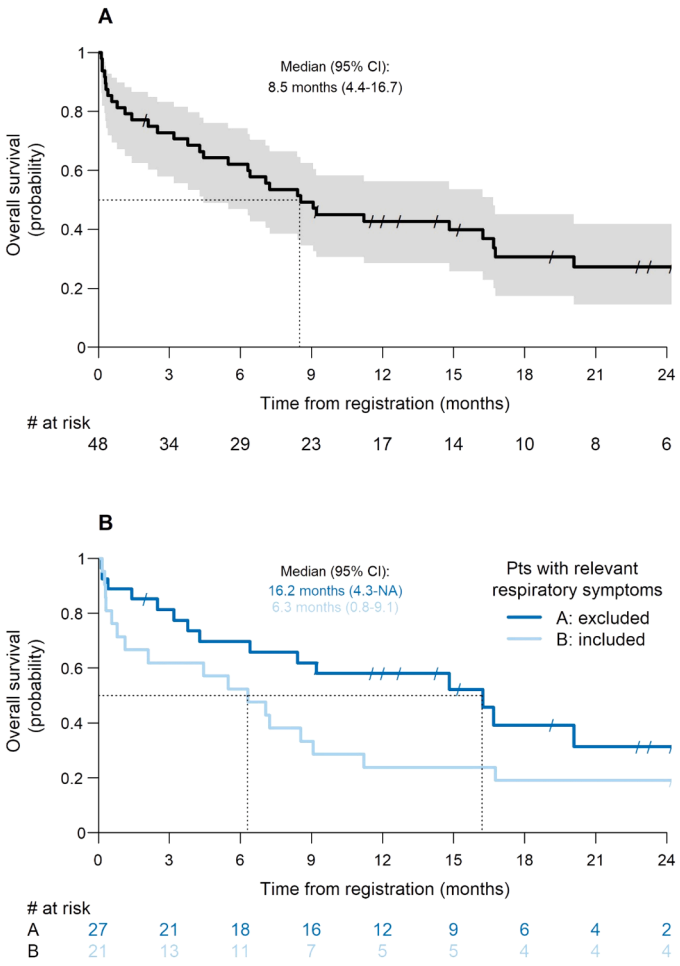

Fig. 1. Kaplan-Meier plot for OS of all population (Figure 1A) and of subgroups before and after the amendment (Figure 1B).

Quality of life and geriatric assessment

Ten out of 40 pts (25.0%) had improvement of their PS from 2 to 0–1 at 3 months, whereas 17 (43%) had PS stabilization (Table 3). QoL submission rate was high in pts who remained on treatment (>89% up to cycle 13). Median scores for global health status/ QoL (Figure 3), physical, role and emotional functioning remained stable or even improved for pts who remained on treatment, while social and cognitive functioning tended to worsen. Scores for symptom scales including fatigue, nausea/vomiting, general pain, insomnia, appetite loss, constipation, diarrhea, dyspnea, pain in chest, coughing, sore mouth,

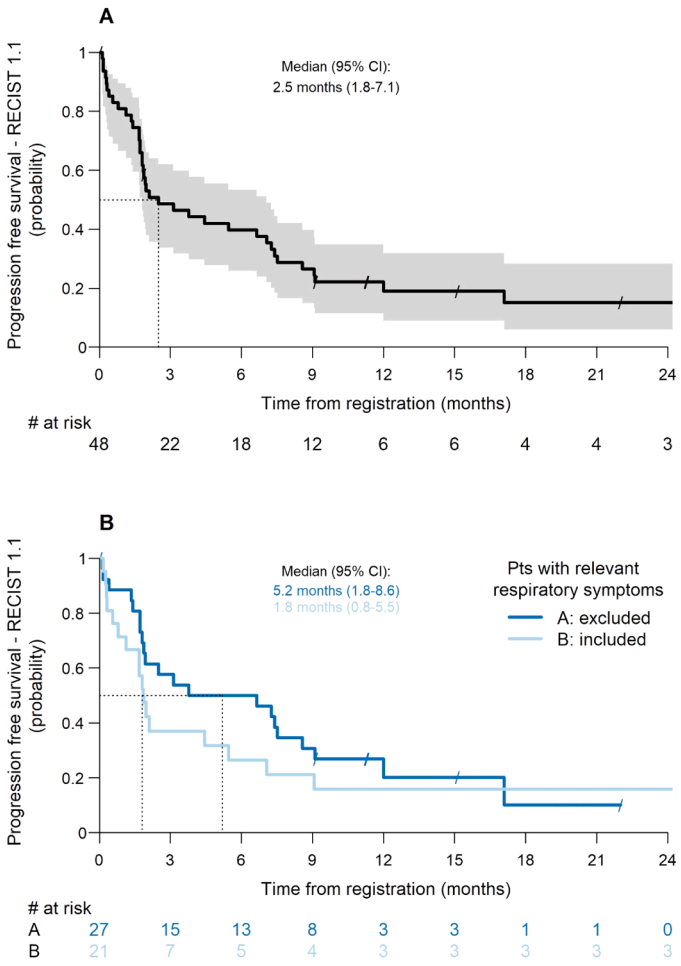

Fig. 2. Kaplan-Meier plot for PFS of all population (Figure 2A) and of subgroups before and after the amendment (Figure 2B).

Table 2
Adverse events (AEs) ≥G3.

	N = 48 (100%)
Patients with AE ≥G3	39 (81%)
Most frequent AEs ≥G3	
Lung infection	9 (19%)
Dyspnea	7 (15%)
Hypertension	5 (10%)
Respiratory failure	5 (10%)
Treatment-related AEs ≥G3 included	
Colonic perforation	1 (2%)
Colitis	4 (8%)
Hepatitis	2 (6%)
Increased lipase	3 (4%)

Table 3
ECOG/WHO Performance Status.

	N = 48 (100%)
Performance status at 3 months	
0	2 (4%)
1	8 (17%)
2	17 (35%)
Missing	8 (17%)
Patients who died within 3 months	13 (27%)

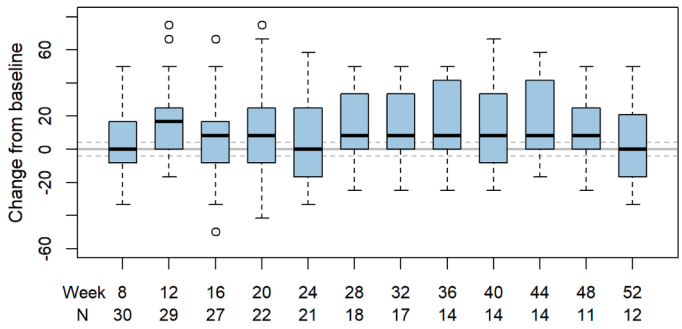

Fig. 3. Changes from baseline in global health status/QoL. Note: Horizontal lines: median values; solid boxes: 25th–75th percentile; whisker bars: lowest and highest value (without outliers); circles: outliers; horizontal dashed lines: minimally important change ≥ 4 points (2) positive changes represent improvement.

dysphagia, peripheral neuropathy, alopecia, and hemoptysis also remained stable or improved except for pain (supplementary material, Figure 1 suppl). The GA screening using the G8 cutoff score identified 45 of 48 pts (94%) as frail. Higher G8 median scores (better condition) were significantly (p-value 0.028) associated with being alive at 6 months after treatment initiation. IADL and CCI scores were not significantly associated with OS.

Discussion

Monotherapy with an ICI has now become the standard of care in pts with metastatic NSCLC with PD-L1 expression in ≥ 50% of tumor cells and with an ECOG PS of 0–1. An essential question in everyday clinical practice is whether these data can be extrapolated to pts with PS2. PS assessment by ECOG is a rather raw tool, which does not take into account the reasons for impaired function, such as age, tumor burden, comorbidities, or polypharmacy. Moreover, PS relevantly differs among assessing physicians, and between physicians and pts [26,27]. Among the published trials evaluating ICIs in the NSCLC setting and involving PS2 pts, the safety profile for PS2 pts did generally not differ from that of the overall study population, although survival tended to be worse [5,9,10,28–31]. Only one of these studies [10] specifically addressed the activity of ICI monotherapy with pembrolizumab in a PS2 population, including both, treatment-naïve and pre-treated pts. Overall, of the 60 pts enrolled, nine were treatment-naive and 15 had a high PD-L1 expression (≥50%). Grade 3–4 toxicity occurred in 12% of pts. Pts with high PD-L1 expression were benefitting the most (median OS of 14.6 months in the PD-L1 ≥50% group versus 9.8 months overall).

To the best of our knowledge, our efficacy and safety analysis is the first investigating durvalumab in PS2 pts with untreated advanced NSCLC and high PD-L1 expression (≥25%). We could demonstrate a promising OS rate at 6 months of 60%. Furthermore, of the 48 pts included, there was only one fatal treatment-related event. All other treatment-related AEs were consistent with data reported in previous trials. Moreover, patient-reported outcomes demonstrated that functional and symptom-specific QoL remained stable or even improved for patients remaining on treatment. Furthermore, a substantial proportion of pts had improvement or at least stabilization of their PS during treatment. Frailty at baseline based on the G8 was significantly associated with OS, while performing daily activities, and comorbidities were not. An explanation may be that the G8, although only a screening tool, covers different GA domains, while the CCI and IADL focus each on a single domain. However, the evidence on the association between GA domains on OS is ambigious. Decoster et al found no association with any GA domain in older pts with lung cancer and explained it with limited impact of GA variables in cancers with low survival rate [32]. Other studies found that G8, IADL and CCI were associated with OS [33–36]. The small sample size and the fact that almost all pts were

considered as frail at baseline limits the interpretation of our results.

Importantly however, we observed a high number of early fatal events with seven deaths in the first 21 pts (33%) occurring after only one dose of durvalumab within the first five weeks. With respect to these early death cases, it is noteworthy that four (57%) of them were related to respiratory failure in symptomatic pts with advanced primary lung tumors. Consequently, a better pre-selection of pts for treatment with durvalumab or other ICIs, apart from PD-L1 expression $\geq$ 25% in the heterogenous population of PS2 pts, seemed warranted. According to our observation, it appears reasonable to exclude pts with symptomatic large lung tumors or severe dyspnea. After this adjustment we were able to show promising survival data (median OS of 16.2 months compared to 5.2 months after the amendment). In the aforementioned trials [9,10,28–31] no restrictions with respect to disease-related symptoms caused by the primary lung tumor were noted in the eligibility criteria for PS2 pts. Considering our results, additional selection criteria for PS2 pts could help to better define a subpopulation who draws benefit from front-line ICIs and in whom effects may be detrimental.

While the study excluded patients with EGFR, ALK, and ROS1 mutations, the pool of actionable mutations has expanded since the commencement of the study. Consequently, some patients may now qualify for targeted therapies through extended testing. However, in 58.3% of the included patients, an NGS analysis was conducted, revealing no activating mutation for a first-line treatment. It is possible that among the remaining 20 patients (41.7%) without NGS analysis, a targetable mutation may have been present, which could have potentially influenced the study resultsMore recent studies investigated the role of ICIs in pts with PS2. One of these was a retrospective, single-center analysis involving 237 pts with advanced NSCLC in whom ICI treatment was initiated [37]. Cox regression analysis was applied to compare the OS of NSCLC pts with PS$\geq$ 2 at ICI initiation with PS0–1 pts. Data analysis revealed that median OS was significantly shorter in PS$\geq$ 2 vs. PS0–1 (4.5 months vs. 14.3 months, P = 0.002). Moreover, among the pts who died, 28.8% of those with PS$\geq$ 2 had received ICI in their last 30 days of life compared to 10.8% of those with PS$\leq$ 2 (odds ratio, 0.29; P = 0.008). In their conclusion, the authors underscored the need for high-quality communication about potential tradeoffs of ICI, particularly in the second-line or later setting. Energy-GFPC 06–2015 is comparing nivolumab in combination with ipilimumab versus first-line carboplatin-based chemotherapy in elderly or PS2 pts [38]. A pre-planned interim analysis showed a risk of futility especially for PS2 pts leading to a halt in randomization. Another single-arm study involving durvalumab in PD-L1 unselected pts with treatment-naive NSCLC (NCT02879617) is presently recruiting pts. Lee et al presented for the first time a small OS benefit for first-line atezolizumab over single agent chemotherapy in frail pts with NSCLC deemed ineligible to receive platinum-doublet chemotherapy [12]. In our opinion, our study complements the efficacy and QoL results of this phase 3 trial as most of the pts also had a PS of 2. As the overall outcome of this population is still poor, a more specific patient selection could have potentially further improved the outcome of a subgroup of PS2 pts treated with ICI.

With respect to future perspective, NSCLC treatment has obviously moved in the direction of combining immunotherapy with chemotherapy regimens. PS2 pts are often unable to tolerate standard therapies, particularly combination chemotherapy regimens, and given that there is a lack of prospective trial data, it is unclear whether treating PS2 pts with combination chemoimmunotherapy is appropriate. In a retrospective single-center analysis it was shown that pts with PS2 treated with combined chemo-immunotherapy had significantly shorter PFS and OS compared to pts with PS 0–1 [39]. In another retrospective analysis, the addition of chemotherapy to ICI did not improve survival compared to ICI alone but increased the incidence of higher-grade pneumonitis in elderly pts [40]. The fact that most of the pts were PS0–1 in this real-world study should cautious us to treat PS2 pts with such combination treatment. While awaiting more data from these trials with respect to ICIs' safety and efficacy in managing advanced NSCLC, a more accurate selection of PS2 pts appears warranted. We would propose to exclude pts with grade $\geq$ 3 dyspnea according to the mMRC dyspnea scale. In addition, we now recommend that PS2 be confirmed by a second physician, to account for the high interpersonal variance.

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Declaration of Competing Interest

Michael Mark: consulting fees: Amgen, Astra Zeneca, BMS, MSD, Pfizer, Takeda, Roche, Travel support: Astra Zeneca, Roche, Takeda.

Patrizia Froesch: consulting fees: Janssen, Sanofi, Takeda, Roche, Travel support: Merck.

Katrin Gysel: no conflict of interest.

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Alfredo Addeo: consulting fees: Amgen, Astra Zeneca, Astellas, BMS, MSD, Pfizer, Novartis, Takeda, Roche, Honoraria: Amgen, Novartis.

Christoph J. Ackermann:: no conflict of interest.

Sabrina Chiquet: no conflict of interest.

Martina Schneider: no conflict of interest.

Karin Ribi: no conflict of interest.

Angela Fischer Maranta: consulting fees: Merck, Travel support: Amgen, Janssen.

Sara Bastian: consulting fees: Astra Zeneca, BMS MSD, Travel support: Servier, Astra Zeneca, Roche.

Roger von Moos: consulting fees: Amgen, Roche, Gilead, Pierre Fabre Pharma Mar, Sanofi, MSD, Eli Lilly, Merck, Vifor, GSK, Travel support: Pierre Fabre, Takeda, research grants: Bayer.

Markus Joerger: consulting fees: Astra Zeneca, Novartis, BMS, MSD, Sanofi, Merck, Roche, Basilea Pharmaceutical, Innomedica, research grants: Astra Zeneca, Roche, Takeda, Daiichi Sancho, Basilea Pharmaceutical, Pfizer, Pharma Mar, Sanofi, BMS, Jannsen, Innomedica, Merck, Eli Lilly, Immunophotonics.

Martin Früh: consulting fees: Astra Zeneca, BMS, MSD, Roche, Böhringer Ingelheim, Pfizer, Takeda, research grants: Astra Zeneca, MSD.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2024.113600.

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