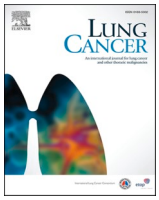
Lung Cancer 183 (2023) 107318

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan



Pembrolizumab as first-line treatment for advanced NSCLC in older adults: A phase II clinical trial evaluating geriatric and quality-of-life outcomes

Remei Blanco [a,*], Manuel Dómine [b], José Luis González [c], Sami Loutfi [d], Jordi Alfaro [a], Juana Saldaña [e], Jaime Rubio [b], Begoña Campos [f], Julia Hidalgo [g], Andrés Barba [h], Diego Márquez [i], Maria Martin [j], Amaya Olaverri [k], Ernest Nadal [e]

[a] Department of Medical Oncology, Consorci Sanitari de Terrassa, Terrassa, Spain
[b] Department of Medical Oncology, Hospital Universitario Fundación Jiménez Díaz. IIS-FJD, Madrid, Spain
[c] Department of Medical Oncology, Hospital Clínico San Carlos, Madrid, Spain
[d] Department of Geriatrics, Consorci Sanitari de Terrassa, Terrassa, Spain
[e] Department of Medical Oncology, Oncobell Program, Institut Català d'Oncologia (ICO), IDIBELL, L'Hospitalet de Llobregat, Spain
[f] Department of Medical Oncology, Hospital Universitario Lucus Augusti, Lugo, Spain
[g] Department of Medical Oncology, Hospital Lluis Alcanyís de Xàtiva, Valencia, Spain
[h] Department of Medical Oncology, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain
[i] Department of Medical Oncology, Hospital Universitario Miguel Servet, Zaragoza, Spain
[j] Department of Medical Oncology, Hospital Universitario Doctor Peset, Valencia, Spain
[k] Department of Medical Oncology, Hospital Virgen de la Luz, Cuenca, Spain

ARTICLE INFO

Keywords:
Non-small cell lung cancer
Older adults
Pembrolizumab
Overall survival
Quality of life
Geriatric outcomes

ABSTRACT

Objectives: Since specific data on immunotherapy in older adults with advanced non-small cell lung cancer (aNSCLC) are scarce, we designed this study to determine the overall survival (OS) at one year of first-line pembrolizumab in patients older than 70 years with aNSCLC expressing PD-L1. Secondary objectives included progression-free survival, disease-specific survival, response rate, tolerability, quality of life (QoL) changes, and geriatric assessments.

Materials and methods: A single-arm, open-label, phase II clinical trial was carried out by the Spanish Lung Cancer Group between February 2018 and November 2019 at ten active sites in Spain. We included patients 70 years old and older with histological or cytological documented stage IIIB or IV aNSCLC and PD-L1 expression $\geq$ 1%. Each subject received 200 mg of intravenous pembrolizumab every three weeks for a maximum of two years.

Results: 83 patients were recruited for the study and 74 were finally analysed. Most were male ($N = 64$, 86.5%) and former smokers ($N = 51$, 68.9%). 24 patients (32.4%) completed at least one year of treatment, 62 (83.7%) discontinued treatment, and 30 (40.5%) experienced disease progression. The median follow-up of our cohort was 18.0 months [range: 0.1–47.7] and 46 patients (62.2%) died during the period of study. The estimated OS at one year was 61.7% (95% CI: 49.6–71.8%) and the median OS of our cohort was 19.2 months (95% CI: 11.3–25.5). QoL tended to improve throughout the study, although the differences were not statistically significant. The main geriatric scores remained stable, except for a worsening in nutritional status ($P = 0.004$) and an improvement in frailty ($P = 0.028$).

Conclusion: Our results support treating older adults with aNSCLC expressing PD-L1 with pembrolizumab in monotherapy. The stability of most geriatric scores and the positive trend on the patients' QoL should be highlighted, although our results did not reach statistical significance.

1. Introduction

Non-small cell lung cancer accounts for 80% to 90% of lung cancers [1] and has a median onset at 70 years of age. Around 14% of these patients are over 80 years old [2]. Previous randomised clinical trials evaluating first-line platinum-based chemotherapy in patients with

* Corresponding author at: Department of Medical Oncology, Consorci Sanitari de terrassa, Ctra. De Torrebonica, s.n. 08227 Terrassa, Spain.
E-mail address: rblanco@cst.cat (R. Blanco).

https://doi.org/10.1016/j.lungcan.2023.107318
Received 23 May 2023; Received in revised form 28 July 2023; Accepted 29 July 2023
Available online 2 August 2023

advanced non-small cell lung cancer (aNSCLC) have shown median overall survival (OS) between seven and nine months in the subgroup of older adults [3].

Because of their favourable toxicity profile, immunomodulatory agents are particularly attractive to treat older adults [4,5]. However, the concept of "older adults" or "elderly" is far from being agreed upon, both in healthcare practice and in the scientific literature [6]. Until a few years ago, most studies continued to establish the age of 65 as the cut-off for the definition of older adult, but more recent publications have advocated delaying this threshold to 70, 75 [7], or even 80 years old. Probably, a definition based on the results of geriatric scales would be much more appropriate, but in the context of a clinical trial this approach could be very impractical.

Pembrolizumab is one of several immune checkpoint inhibitors that have proven superior in monotherapy to platinum doublets for patients with aNSCLC expressing PD-L1 over 50% [8–10]. The efficacy of these immune checkpoint inhibitors compared to chemotherapy, in patients with any expression of PD-L1, has also been reported [9,11]. However, older adults are underrepresented in most clinical trials evaluating immunotherapy treatments for aNSCLC [11–13]. The European Organization for research and treatment on Cancer (EORTC) stated, eleven years ago, that studies including this population should be a priority in this scenario [14]. Besides, the International Society of Geriatric Oncology (SIOG) recommends that trials conducted in older adults should consider the Quality of Life (QoL), functional status, and independence of the patient as relevant endpoints [15].

Therefore, the primary outcome of this study was to determine the efficacy, in terms of OS at one year, of first-line treatment with pembrolizumab in patients older than 70 years with aNSCLC expressing PD-L1. Secondary outcomes included evaluating additional efficacy measures (OS at two years, progression-free survival [PFS], disease-specific survival [DSS], and objective response rate [ORR]), the tolerability profile, QoL changes, and the impact of first-line pembrolizumab on geriatric outcomes in our patients.

2. Methods

2.1. Study design

This was a single-arm, open-label, prospective, and multicentre phase II clinical trial carried out by the Spanish Lung Cancer Group between February 2018 and November 2019 at ten sites in Spain. The trial was registered at the EU Clinical Trials Register EudraCT 2016–004353-32 and was approved by the Clinical Research Ethics Committee of Consorci Sanitari de Terrassa, Spain. We obtained written informed consent from all study participants.

2.2. Patients

We included patients 70 years old and older with histological or cytological documented stage IIIB, who were not candidates for thoracic radiotherapy, or IV (according to the 7th lung cancer TNM classification) aNSCLC and PD-L1 expression $\geq$ 1% confirmed by the IHC 22C3 pharmDx assay at one of the participating institutions. Included patients had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1, measurable disease by CT or MRI per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria, and an adequate organ function. Patients with CNS metastases could be included if asymptomatic or clinically controlled after holocraneal radiotherapy, which had to be finished at least one week before administering the first dose of pembrolizumab.

We excluded patients with prior systemic treatment for aNSCLC, EGFR mutated / ALK translocated tumours, and with previous malignancies (except non-melanoma skin cancer and in situ cancer of bladder, stomach, colon, cervix, melanoma, and breast), unless a complete remission was achieved at least two years before entering the study. We also excluded patients with autoimmune diseases or other disorders requiring systemic immunosuppressive drugs, including corticosteroids (>10 mg daily prednisone or equivalent), symptomatic interstitial lung disease, a positive test for hepatitis B virus surface antigen or hepatitis C virus ribonucleic acid, and those testing positive for HIV. Geriatric exclusion criteria comprised advanced dementia (Global Deterioration Scale > 6), moderate or severe functional dependence (Barthel Index < 35), and a life expectancy of less than one year due to comorbidities other than lung cancer.

2.3. Treatment

Each subject received 200 mg of intravenous pembrolizumab every three weeks, continued for a maximum of two years or until disease progression, unacceptable toxicity, or patient-consent withdrawal. Pembrolizumab treatment was allowed to continue beyond progression, and up to a maximum of 24 months, if the investigator considered that the clinical benefit to the patient persisted.

Subjects who stopped pembrolizumab before 24 months of study therapy with stable disease or better, for reasons other than disease progression or intolerability, were eligible for up to one year of additional pembrolizumab treatment, at the discretion of the investigator, if no other anti-cancer treatment had been administered since the last dose of pembrolizumab and disease progression was observed.

2.4. Outcomes and measures

During the screening phase, all patients underwent a thoracic and abdominal CT and a cerebral CT or MRI; bone scintigraphy or a PET-TC was performed if symptoms of bone metastasis were present. At baseline, we evaluated QoL with the EORTC Quality of Life Questionnaire (QLQ-C30). We measured 15 different scales and calculated them according to the official algorithm of the EORTC QLQ-C30 Scoring Manual [16]. We also evaluated the QLQ-C30 Summary Score [17]. We completed the QoL evaluation with the QLQ-ELD14, specific for older cancer patients [18], and the Lung Cancer Symptom Scale (LCSS) questionnaires, specific for lung cancer patients [19].

The comprehensive geriatric assessment, also conducted during the screening phase, evaluated frailty with the Edmonton frail scale (EFS), comorbidities, polypharmacy (intake of > 5 drugs), Charlson Index, functional status (by means of the Barthel index and the Short physical performance battery), cognitive status (according to the mini-mental state examination [MMSE]), emotional status (by means of the Geriatric depression scale 15 [GDS-15]), and nutritional status (according to the mini-nutritional assessment [MNA]). We also performed other geriatric assessments (the number of falls since the last visit, the number of episodes of confusion since the last visit, the Clock-drawing test, and the social support) described in Supplementary Table S4.

We evaluated subjects every nine weeks and until disease progression with thoracic and abdominal CT, the three QoL questionnaires, and the abovementioned geriatric scales. We only performed QoL and geriatric assessments on patients who remained on pembrolizumab treatment and for a maximum of one year.

OS was defined as the time from the start of pembrolizumab to death from any cause. Patients who were still alive at the time of data analysis were censored at the date of the last contact. On the basis of data from previous studies achieving a median OS of seven to nine months with platinum doublets chemotherapy [3], we considered that a 50% OS at one year would be a clinically appropriate endpoint. Additional efficacy measures included OS at two years, PFS (time from the start of pembrolizumab to the date of disease progression or death, whichever occurred first), DSS (time from diagnosis to cancer-related death), and ORR (percentage of patients with a confirmed complete or partial response or stable disease). We analysed patients according to their levels of PD-L1 expression and chose to divide them in three groups: low (<20%), intermediate (20%-49%), and high expression (≥50%). The

cut-off values were arbitrary and answered to an exploratory intention. Investigators made all treatment-based decisions using immune-related Response Criteria. However, we used the RECIST 1.1 criteria to determine ORR and PFS. We graded adverse events according to the NCI Common Terminology Criteria for Adverse Events version 4.0. Safety was assessed in the as-treated population, which included all patients who received at least one dose of pembrolizumab.

2.5. Statistical analysis and sample size

We determined that 74 patients recruited over 12 months, with 12 months of additional follow-up, would be enough to estimate a median OS of 12 months with an alpha error of 0.05 and a beta error of 0.10 (SWOG One Sample Survival). We assumed a 10% chance of loss to follow-up or inclusion failure, thus establishing the sample size at 82 patients. We performed the analyses on the intention-to-treat (ITT) population.

We used absolute frequencies and percentages to describe categorical variables and mean and standard deviation (SD) for quantitative variables (median and ranges when normality could not be assumed). We used the chi-squared test to compare the ORR for different groups of patients. To analyse the evolution of QoL and geriatric assessments at the different pembrolizumab cycles, we used the paired *t*-test (Wilcoxon signed rank test when normality could not be assumed). For dichotomous variables, we used the McNemar test with Edwards correction. We assessed OS, PFS, and DSS with the Kaplan-Meier product-limit method, using the log-rank test to compare curves for independent groups. We calculated two-sided *P*-values and set the statistical significance level at $P \leq 0.05$. We carried out all analyses using R 4.1.2 for Microsoft Windows.

3. Results

3.1. Baseline characteristics

A total of 83 patients were recruited between February 2018 and November 2019 (the last patient included finished treatment in November 2021), and 82 patients received treatment. Of these, 74 patients were finally analysed since eight were inclusion errors (Fig. 1). The main demographic and clinical characteristics of our patients are summarised in Table 1. The mean age of the analysed cohort was 78.1 years old (SD: 5.50) and 27 of them (36.5%) were 80 or older. Most of our patients were male ($N = 64$, 86.5%) and former smokers ($N = 51$, 68.9%). In our cohort, PD-L1 values were below 20% in 16 patients (21.6%), between 20% and 49% in 23 patients (31.1%), and equal to or above 50% in 35 patients (47.3%).

The baseline geriatric evaluation showed that most of our patients were not frail ($N = 44$, 61.1%) according to the EFS, although ten patients (13.9%) were considered severely frail (Supplementary Figure S1). A lower frailty index was observed in younger patients,

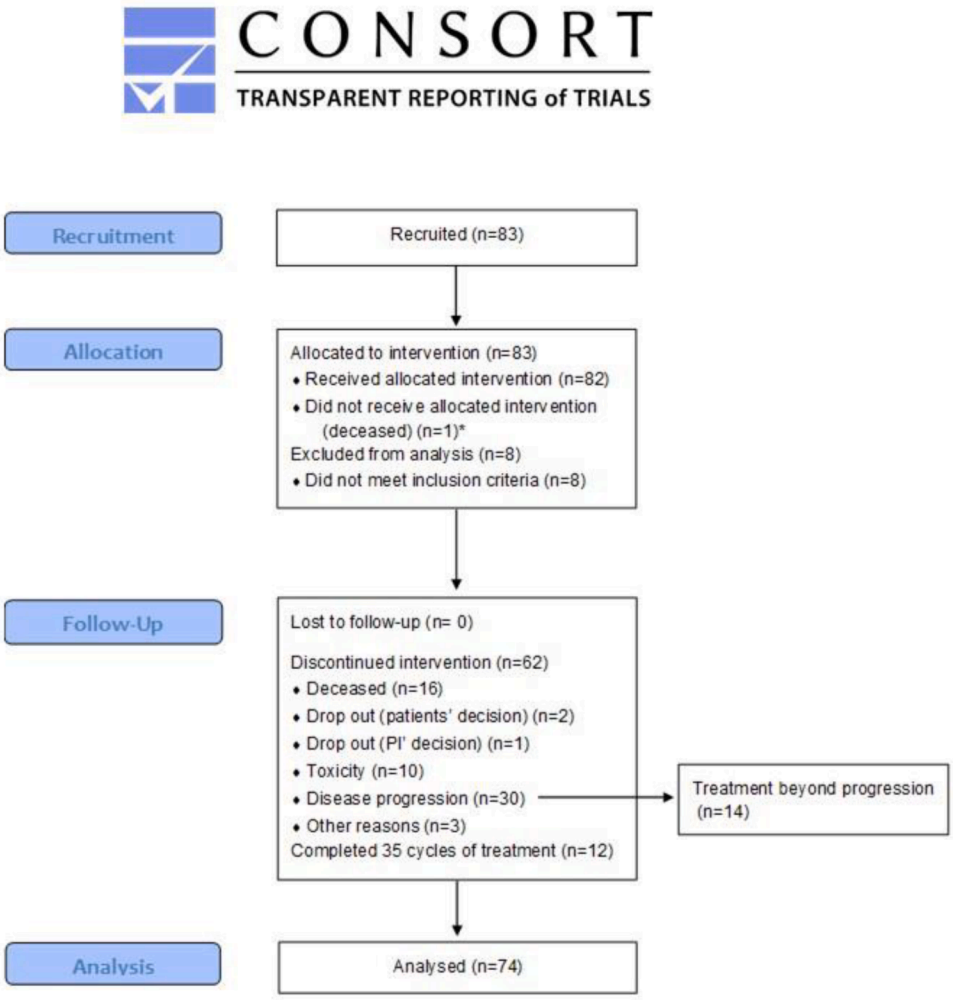


Fig. 1. Patient enrolment flow chart. * Died of cerebral haemorrhage before receiving treatment. ECOG PS: Eastern Cooperative Oncology Group Performance Status; PI: Principal investigator.

Table 1
Demographic and clinical characteristics of study participants. Figures are absolute numbers (and %) unless otherwise stated.

	Overall ($N = 74$)
Sex	
Female	10 (13.5)
Male	64 (86.5)
Age (years), *mean* (SD)	78.1 (5.50)
≥80	27 (36.5)
Race	
Caucasian	74 (100)
Smoking history	
Never (≤100 cigarettes/lifetime)	11 (14.9)
Former smoker (≥1 year)	51 (68.9)
Current smoker	12 (16.2)
ECOG performance Status at diagnosis	
0	18 (24.3)
1	56 (75.7)
Histology	
Adenocarcinoma	32 (43.2)
Squamous	33 (44.6)
Large cell carcinoma	2 (2.7)
Aden squamous	1 (1.4)
Not otherwise specified / Undifferentiated	6 (8.1)
Current cancer stage	
IIIB	6 (8.1)
IV	68 (91.9)
Brain metastasis	6 (8.1)
Previous antineoplastic treatments	**31 (41.9)**
Radiotherapy	24 (32.4)
Surgery	9 (12.2)
Adjuvant chemotherapy	6 (8.1)
Concurrent chemoradiotherapy	5 (6.8)
Neo-adjuvant chemotherapy	2 (2.7)
PD-L1	
1–19%	16 (21.6)
20–49%	23 (30.1)
≥50%	35 (47.3)

ECOG: Eastern Cooperative Oncology Group; SD: Standard deviation.

although these differences were not statistically significant ($P = 0.192$). The main comorbidities were hypertension ($N = 54$, 72.9%), dyslipidaemia ($N = 31$, 41.9%), heart disease ($N = 25$, 33.7%), diabetes mellitus ($N = 22$, 29.7%), and lung disease ($N = 17$, 22.9%). Polypharmacy was detected in 46 patients (62.2%). Most patients showed a Charlson index of 1 ($N = 14$, 18.9%), 2 ($N = 26$, 35.1%), or 3 ($N = 11$, 14.9%), and the mean Barthel score was 95.4, with 65 patients (87.8%) preserving the ability for instrumental activities. A total of 21 patients (28.4%) showed moderate or mild depression (score ≥ 4) according to the GDS-15 scale. Finally, the mean MMSE was 26, and, according to their MNA scores, 16 patients (21.9%) were considered malnourished, while 31 (42.5%) were at risk of malnutrition.

3.2. Treatment

Out of the 74 patients analysed, 24 (32.4%) completed at least one year of pembrolizumab treatment, 12 (16.2%) reached the maximum of two years, and 30 (40.5%) experienced disease progression (Fig. 1). Of these 30 patients, 14 (46.7%) continued treatment because of the sustained therapeutic benefit, and five of them (14.3%) completed the full 35-cycle treatment (Supplementary Figure S2). The 74 patients included in the analysis received 1 035 treatment cycles, and the median number of cycles was nine [range: 1–35].

3.3. Efficacy measures

The median global follow-up of our cohort was 18.0 months [range: 0.1–47.7] and 46 patients (62.2%) died during the period of study. The estimated OS at one year was 61.7% (95% confidence interval [CI]: 49.6–71.8%). The median OS of our cohort was 19.2 months (95% CI: 11.3–25.5), and the estimated OS at 24 months was 40.2% (95% CI: 28.6–51.5%) (Fig. 2A). In a non-pre-planned analysis, we studied the OS as a function of PD-L1 expression in our group of patients. The median OS from the start of treatment for patients with a PD-L1 under 50% was 16.5 months (95% CI: 6.8–24.6), whereas that of patients with a PD-L1 greater than or equal to 50% was 23.3 months (95% CI: 14.8-Not reached [NR]). The difference did not reach statistical significance (Fig. 2B).

Of the 74 patients analysed in our study, 53 (71.6%) progressed during follow-up. The estimated median PFS of our cohort was 6.1 months (95% CI 4.6–8.4 months) (Fig. 2C). Out of the 46 patients who died during follow-up, 36 deaths (78.3%) were related to lung cancer and ten (21.7%) to other causes. The estimated median DSS of our cohort was 22.5 months (95% CI: 16.5-NR) (Fig. 2D).

Nine patients, from the 74 analysed, experienced an early symptomatic deterioration (four died in the first cycle, four in the second, and one in the third) and their response to pembrolizumab could not be assessed. However, they were included in the ITT analysis for response rates. No complete response was observed, but 29 patients (39.2%) achieved a partial response and 20 (27.0%) had stable disease. Therefore, a global 66.2% disease control rate was reached.

In another non–pre-planned analysis, we studied the ORR as a function of PD-L1 expression in the 74 analysed patients. We observed a response rate of 12.5% for patients with low PD-L1 expression (<20%), 34.8% for patients with intermediate PD-L1 expression (between 20% and 49%), and 54.3% for patients with high PD-L1 expression (≥50%). The only statistically significant difference was found between the low PD-L1 group and the other two groups ($P = 0.034$).

3.4. Safety profile

Table 2 summarises the recorded adverse events related to treatment present in>5% of the population or grade 3. No grade 4 or 5 adverse events were reported. A total of 59 patients (79.7%) presented a treatment-related adverse effect, and, of those, seven (9.5%) were of grade 3 (two diarrhoea, two pneumonitis, one hyperuricemia, one acute renal failure, and one thrombocytopenia plus infection). The most common adverse events were fatigue (23, 31.1%) and anorexia (12, 16.2%). Notable adverse effects by their frequency included diarrhoea grade 1 (11, 14.9%) and grade 2 (1, 1.4%), hyper or hypothyroidism grade 1 (13, 17.6%) and grade 2 (3, 4.1%), and pruritus or rash grade 1 (25, 33.8%) and grade 2 (2, 2.7%).

3.5. Quality of life

The mean QLQ-C30 Summary Score of the patients on treatment improved between the first and the last pembrolizumab cycle, although the differences were not statistically significant for those who had completed all cycles (Fig. 3A). Detailed results of the QLQ-C30 questionnaire can be found in Supplementary Table S1. Most items on the QLQ-ELD14 questionnaire improved (mobility, worries about others, future worries, and burden of illness) throughout the study, but the joint stiffness, family support, and maintaining purpose items remained constant (Supplementary Table S2). However, only the improvement in future worries was significant ($P = 0.048$). The mean burden of illness perceived by those patients on treatment decreased from 36.1 (SD: 26.6) to 20.2 (SD: 21.2). However, considering only the patients that remained on treatment for one year, the difference was not statistically significant (Fig. 3B). Regarding the LCSS, the aggregate score of all nine patient-reported items decreased from 27.5 (SD: 17.0) at the first pembrolizumab cycle to 16.0 (SD: 13.8) at the last cycle, although the difference did not reach statistical significance (Fig. 3C). Of note, only the question related to cough showed a significant decrease ($P = 0.025$). All observer items decreased in severity, but only the differences in the aggregate score of observer items ($P = 0.038$) and cough were significant ($P = 0.046$) (Supplementary Table S3).

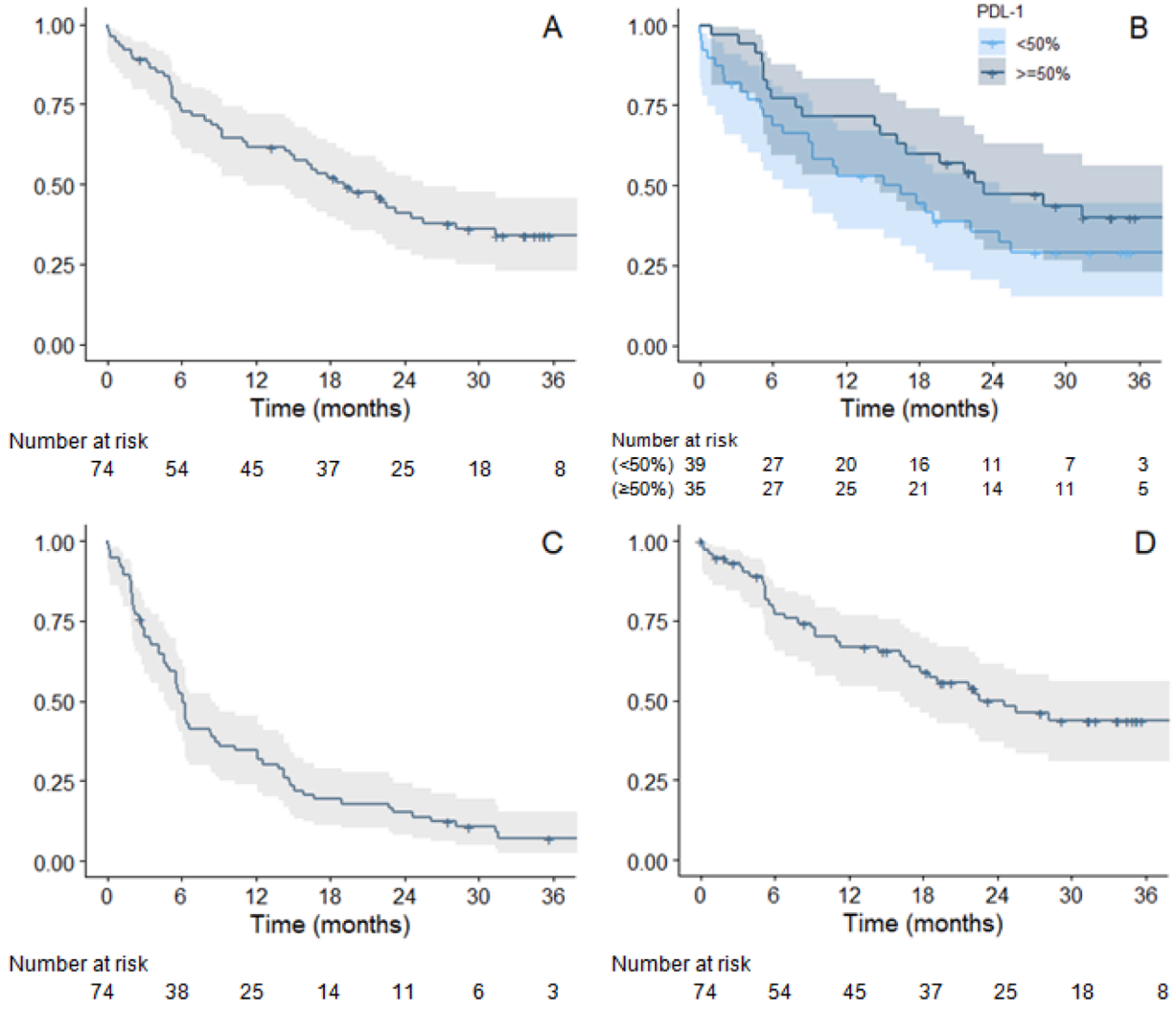


Fig. 2. A) Overall survival (OS), median OS: 19.2 months (95% confidence interval [CI]: 11.3–25.5); B) OS for patients with PD-L1 expression < 50% (median OS: 16.5 months [95 %CI: 6.8–24.6]) and ≥ 50% (median OS: 23.3 months [95 %CI: 14.8-NR]); C) Progression-free survival (PFS), median PFS: 6.1 months (95 %CI: 4.6–8.4); and D) Disease-specific survival (DSS), median DSS: 24.6 months (95% CI: 16.5-NR). NR: Not reached.

3.6. Geriatric outcomes

A total of 273 geriatric assessments were carried out, representing 93% of those planned. The mean scores of our cohort in most geriatric scores evaluating functional (Barthel Index), cognitive status (MMSE), and the ability to carry out instrumental activities remained stable throughout the study (Fig. 4 and Supplementary Table S4), but the nutritional status (MNA) worsened significatively ($P = 0.004$). Conversely, a significant improvement was observed in frailty measurements ($P = 0.028$).

4. Discussion

In our study, pembrolizumab was shown to be an effective and safe treatment for aNSCLC patients expressing PD-L1 and older than 70 years. In addition, clinical, patient-reported, and geriatric parameters tended to improve or remained stable over the study period, except for a worsening of nutritional status.

The introduction of immunotherapy was a landmark in the management of aNSCLC [20]. However, specific data concerning older adults are scarce [21], and in most cases, they come from subgroup analyses. In a pooled analysis from the KEYNOTE-010, KEYNOTE-024, and KEYNOTE-042 studies, pembrolizumab was shown to be superior to platinum-based chemotherapy in older adults in terms of efficacy and tolerability [22]. Nevertheless, prospective phase II and III trials specifically designed and focused on older adults are necessary. Our patient sample was representative of the geriatric population of Western countries with aNSCLC: mainly male patients, ex-smokers, with cardiovascular and pulmonary diseases secondary to tobacco abuse, and a high rate of polypharmacy. In our cohort, the ratio of patients with high PD-L1 expression (≥50%) was higher than that of previous studies [23–25]. perhaps because of an involuntary bias in the selection process. However, ageing has been associated with increased tumour mutational burden and increased expression and decreased promoter methylation of *PDL1* and other immune checkpoint genes (*CD80*, *HAVCR2*, *LAG3*, *PDL2*, and *CXCL9*) in older patients with different cancer types [26,27].

Regarding the basal geriatric evaluation, our patients had low or moderate rates of frailty, and their functional status was good. However, a striking finding was the high prevalence of malnutrition, which has been shown to affect a high percentage of aNSCLC patients, especially older adults, and has a clear impact on their QoL [28,29]. In addition, malnutrition is a predisposing factor for the development and worsening of lung cancer [30–32]. Different nutritional interventions have been tested in patients with aNSCLC and have been shown to improve both nutritional parameters and QoL [33,34].

Notably, a long treatment time was observed in our study, with ten

Table 2
Adverse events in the As-treated population.[a,b] Figures are absolute numbers (and %).

	Total ($N = 74$)			
	Any Grade[c]	Grade 1	Grade 2	Grade 3
Treatment-related[d]	59 (79.7)	23 (31.1)	29 (39.2)	7 (9.5)
Non-immune-mediated[e]				
Fatigue	23 (31.1)	11 (14.9)	12 (16.2)	0 (0.0)
Anorexia	12 (16.2)	10 (13.5)	2 (2.7)	0 (0.0)
Increased creatinine level	5 (6.8)	4 (5.4)	0 (0.0)	1 (1.4)[f]
Anaemia	4 (5.4)	2 (2.7)	2 (2.7)	0 (0.0)
Constipation	4 (5.4)	4 (5.4)	0 (0.0)	0 (0.0)
Immune-mediated[e]				
Pruritus	19 (25.7)	18 (24.3)	1 (1.4)	0 (0.0)
Diarrhoea	14 (18.9)	11 (14.9)	1 (1.4)	2 (2.7)
Dry skin	12 (16.2)	9 (12.2)	3 (4.1)	0 (0.0)
Hyperthyroidism	9 (12.2)	6 (8.1)	3 (4.1)	0 (0.0)
Rash acneiform	8 (10.8)	7 (9.5)	1 (1.4)	0 (0.0)
Hypothyroidism	7 (9.5)	7 (9.5)	0 (0.0)	0 (0.0)
Pneumonitis	7 (9.5)	1 (1.4)	3 (4.1)	3 (4.1)
Decreased in platelet count	6 (8.1)	3 (4.1)	2 (2.7)	1 (1.4)
Other	9 (12.2)	5 (6.8)	4 (5.4)	0 (0.0)

[a] The as-treated population included all patients who received at least one dose of a trial treatment.
[b] No grade 4 and 5 adverse events were reported.
[c] Here are summarised the adverse events that occurred with a frequency ≥ 5% or those grade 3.
[d] Events were attributed to treatment by the investigator and are listed as indicated by the investigator on the case-report form.
[e] Events are listed in descending order of frequency in the total population.
[f] This patient presented an acute renal failure attributed to concomitant NSAIDs use.

patients completing two years of treatment. This could be due, in part, to the possibility of keeping patients on treatment beyond progression according to the investigator's decision. This is a widely established practice in the immunotherapy setting that has clearly demonstrated a positive impact on OS in patients with aNSCLC [35] and other tumours [36–38].

The primary endpoint of our study, OS at one year, fulfilled our expectation to be at least 50%. Studies undertaken before the introduction of immunotherapy established 12 months as a difficult-to-improve median survival in the general adult population [39,40]. However, in older adults (defined with different chronological age thresholds depending on the studies), the median survival never exceeded seven to nine months [3]. In our study, we aimed to achieve a median survival of at least 12 months and our results exceeded that objective (median OS: 19.2 months). The OS at two years and DSS were also encouraging. The EORTC and the SIOG established that DSS should be recorded in trials where older patients with cancer are included because deaths resulting from other causes occur much more frequently in older adults [41].

The analysis of the median OS according to PD-L1 expression (<50% or ≥ 50%) was undertaken to evaluate the possible bias produced by our high number of high PD-L1 expressors. We observed a higher, although not statistically significant, OS in patients with high PD-L1 expression (23.3 months), similar to that observed in the KEYNOTE 024 and the Impower 110 trials in the same population (26.3 and 20.2 months, respectively). Nevertheless, even patients expressing PD-L1 < 50% achieved a median OS longer than one year (16.5 months). Our results should be viewed with great caution since they correspond to a phase II trial. However, in the IMpower-110 phase 3 trial, patients with a tumour proportion score of 1% to 49% achieved the same median OS as that of our study (16.5 months) with atezolizumab [9], and in the KEYNOTE-042 study, a median OS of 13.4 months with pembrolizumab was observed in this same population [11]. In both cases, these results were not significantly different to those obtained in both control arms with chemotherapy. Conversely, these and other studies have shown important differences regarding toxicity between immunotherapy and chemotherapy [9,11,22], which prompted the FDA approval of pembrolizumab as a single agent for the first-line treatment of aNSCLC patients with PD-L1 expression ≥ 1% and with no EGFR or ALK genomic aberrations [42]. Along this line, the results of the phase III IPSOS study are also interesting [43], although the population analysed was not exactly the same as that of our study. We included patients with an ECOG PS of 0 or 1 and ≥ 70 years, whereas the IPSOS study evaluated patients of any age with an ECOG PS of 2 or 3 or otherwise ineligible for platinum treatment because of comorbidities. The differences in terms of efficacy in the IPSOS study slightly favoured the experimental arm with atezolizumab, but, more importantly in our opinion, the experimental arm showed fewer grade 3/4 (16% vs 33%) and grade 5 (1% vs 3%) treatment-related adverse events than the chemotherapy control. Other prospective studies are currently ongoing that compare the outcomes of some immunomodulators with those of chemotherapy and are focused on older adults [44–47].

As expected from other studies with checkpoint inhibitors [9,48], the ORR in our trial was better in patients with high PD-L1 expression. We were also interested in comparing the ORR of patients with intermediate and low PD-L1 expression. However, our results did not allow us to draw any significant conclusion, perhaps because of the small number of patients in each group.

The toxicity profile observed in our study was moderate and predictable, with mostly grade 1 or 2 adverse events. However, some of these patients dropped out of the study, reflecting the impact of sustained mild toxicities on older adults' QoL. The current knowledge on checkpoint inhibitors' safety and efficacy has been recently summarised in an International Experts Panel Meeting in Italy [49], concluding that they are safe in older adults, at least when used in monotherapy. However, checkpoint inhibitors may present a different toxicity profile in older and in younger patients, with a somewhat higher incidence of pneumonitis and skin immune-related adverse events in older adults. At the same time, younger patients are more subject to experiencing endocrine toxicities [50–54].

To our knowledge, this is the first prospective study with immunotherapy in older adults with aNSCLC addressing not only QoL but also geriatric issues. Importantly, to avoid consequential biases, we tested the statistical significance on the differences between the baseline measurements and those in cycle 18 only in those patients who completed at least one year of treatment. Since the sample size was drastically reduced, statistically significant improvements became hard to reach, although QoL and geriatric assessments tended to remain stable or improve, except for nutritional status. Considering the large number of patients who were still alive a year after starting the study, even if they had discontinued treatment, we believe that further geriatric and QoL assessments every nine weeks in all living patients would certainly have promoted identifying these improvements. In any case, the trends observed were in agreement with previous reports [55,56]. Of note, a recent metanalysis of 8 341 patients from 17 randomised trials disclosed that patients treated with immune checkpoint inhibitors delay their clinical deterioration, their QoL decline and have a more favourable difference in mean change in QoL parameters from baseline to follow-up than those treated with standard chemotherapy [57].

The scores related to our patients' functional and cognitive status remained stable throughout the study. Notably, the ability of our patients to carry out instrumental activities was maintained, in contrast with previous studies involving chemotherapy [58,59] and immunotherapy [60]. Importantly, occupational therapy has shown to be beneficial in maintaining the functionality of older adults with cancer and their interaction with the environment [61].

Despite the stability or improvement of other geriatric parameters, our cohort's nutritional status worsened throughout treatment. This fact highlights the importance of encouraging nutritional interventions in older adults with cancer. Finally, the frailty of our patients improved significantly at the end of the study, which could be attributed to the

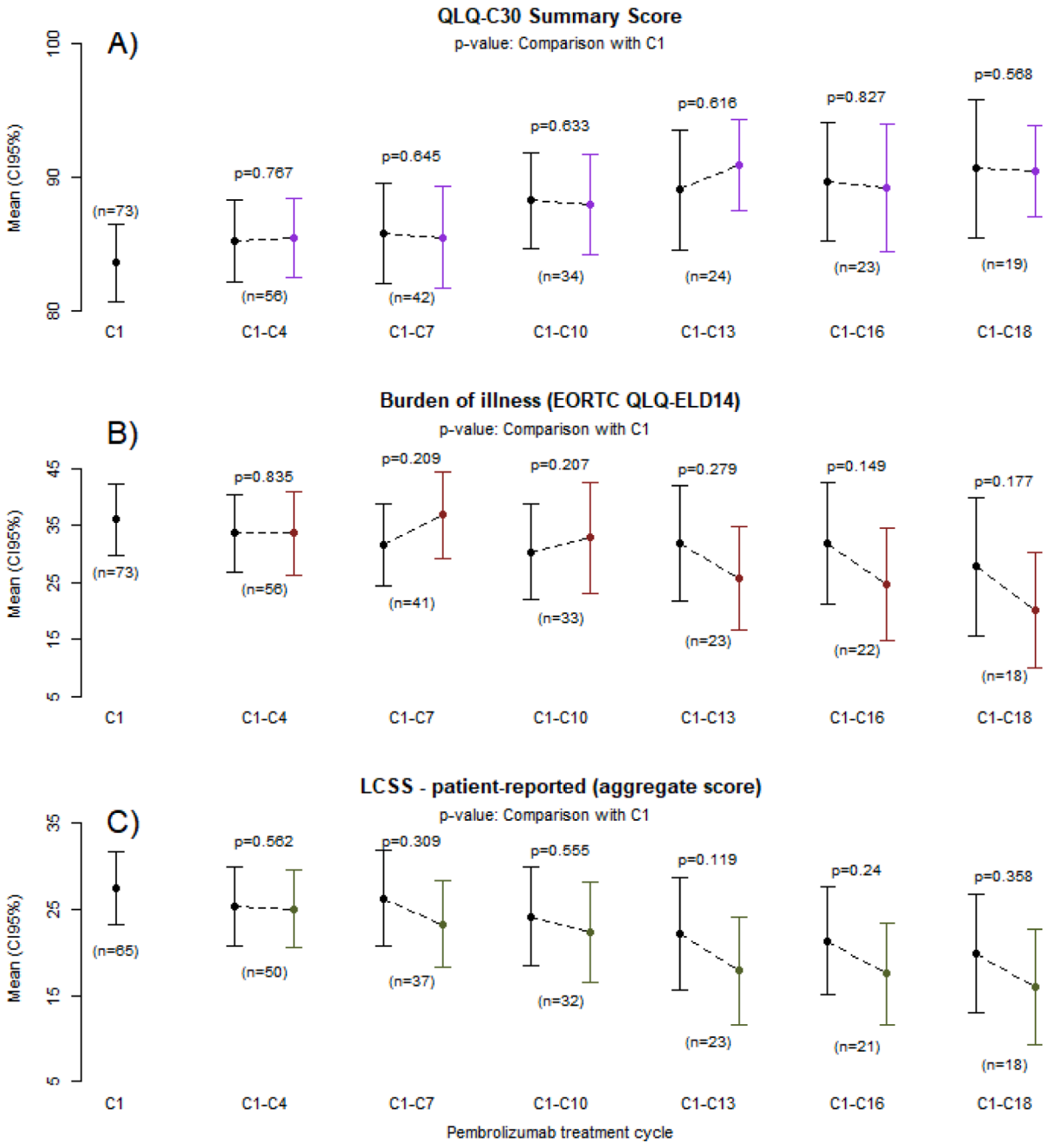


Fig. 3. Evolution of the mean scores of quality-of-life questionnaires at the different pembrolizumab cycles (C1 to C18). A) QLQ-C30 Summary score, B) QLQ-ELD14 Burden of illness, and C) Lung Cancer Symptom Scale summarising patient-reported items Vertical lines represent 95% confidence intervals. *N* and *P*-values correspond to those patients with measures at C1 and at each reference cycle. *P*-values were calculated using paired sample *t*-test (Wilcoxon signed rank test when normality could not be assumed).

improvement in some items with greater potential for reversibility collected in the EFS, such as the global perception of health and mood.

The findings of this study must be interpreted in light of its limitations beyond those intrinsic to a phase II trial. The sample size was calculated based on the main objective (i.e., OS), but the study was probably not powered to detect significant changes in geriatric parameters or QoL, as discussed above. In addition, the proportion of cases with high expression of PD-L1 was higher than usual, and the efficacy outcomes were not centrally evaluated.

5. Conclusion

The encouraging survival data and the toxicity profile found in our study support the feasibility and convenience of treating older adults with aNSCLC expressing PD-L1 with pembrolizumab in monotherapy. In addition, and despite the limitations of a phase II trial, a positive trend was observed in the QoL (measured with three validated questionnaires) and geriatric outcomes of our patients throughout the treatment. There is a need to monitor the nutritional status of these patients. We consider that our results should prompt future studies specifically designed for older adults.

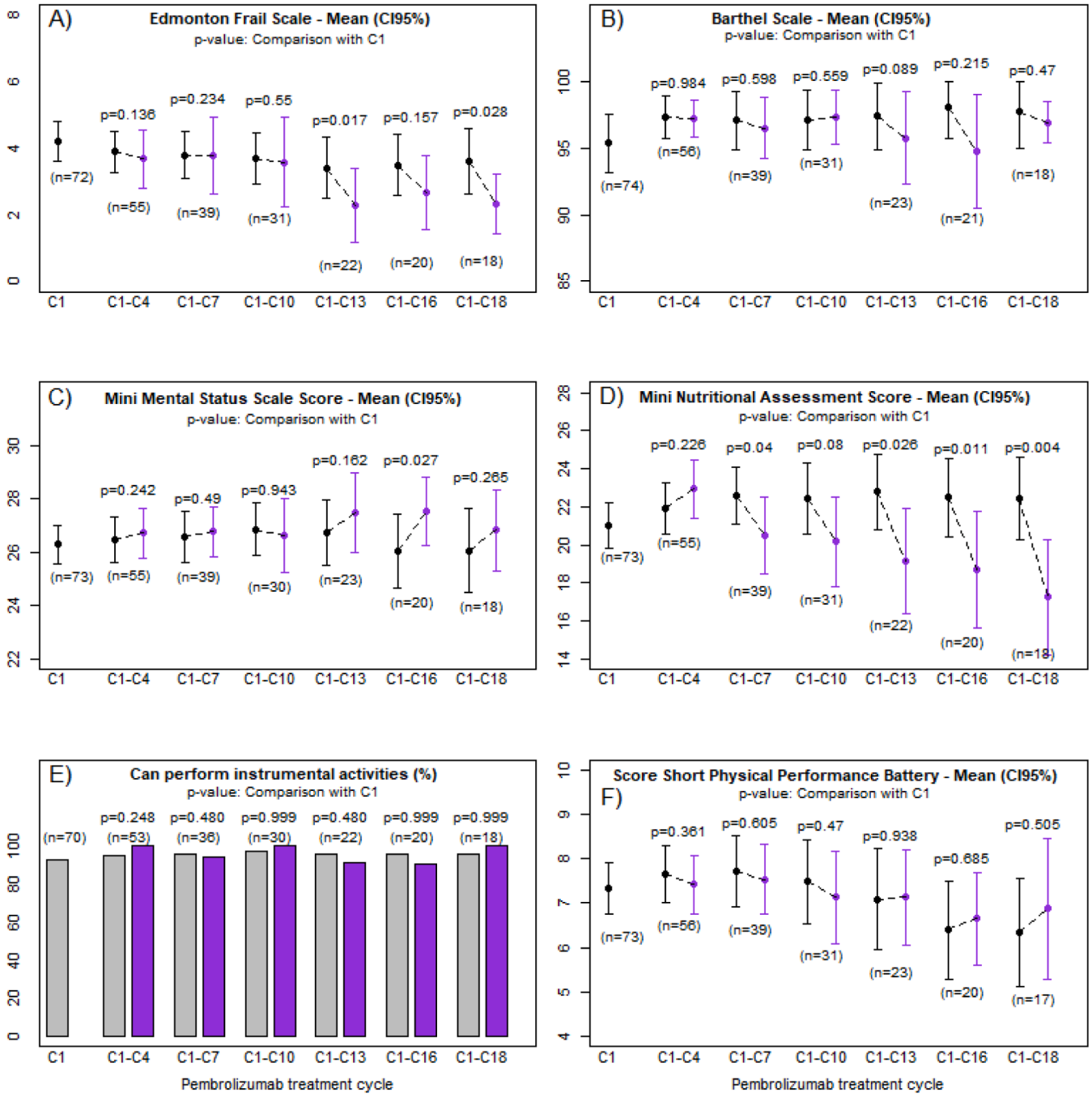


Fig. 4. Evolution of the mean scores of geriatric assessments at the different pembrolizumab cycles (C1 to C18). A) Edmonton frail score (scale 0–17, higher scores correspond to more frailty), B) Barthel index (scale 0–100, lower scores indicate increased disability) C) Mini mental status (scale 0–30, lower scores imply worse cognition), D), Mini nutritional assessment (scale 0–30, lower scores indicate malnutrition), E) Instrumental activities (percentage of patients able to perform these activities), and F) Short physical performance battery (scale 0–12, lower scores correspond to worse physical condition). Vertical lines represent 95% confidence intervals. *N* and *P*-values correspond to those patients with measures at C1 and at each reference cycle. *P*-values were calculated using paired sample *t*-test for each reference with respect to C1 (Wilcoxon signed rank test when normality could not be assumed). For dichotomous variables, *P*-value calculated with McNemar test with Edwards correction.

CRediT authorship contribution statement

Remei Blanco: Conceptualization, Methodology, Investigation, Supervision, Writing – original draft. **Manuel Dómine:** Resources, Writing – review & editing. **José Luis González Larriba:** Resources, Writing – review & editing. **Sami Loutfi:** Resources, Writing – review & editing. **Jordi Alfaro:** Resources, Writing – review & editing. **Juana Saldaña:** Resources, Writing – review & editing. **Jaime Rubio-Perez:** Resources, Writing – review & editing. **Begoña Campos:** Resources, Writing – review & editing. **Julia Hidalgo-Coloma:** Resources, Writing – review & editing. **Andrés Barba:** Resources, Writing – review & editing. **Diego Márquez-Medina:** Resources, Writing – review & editing. **Maria Martin:** Resources, Writing – review & editing. **Amaya Olaverri:** Resources, Writing – review & editing. **Ernest Nadal:** Resources, Writing – review

& editing.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Remei Blanco has been awarded grants from AstraZeneca, MSD, and Roche, and Sanofi, has received payment or honoraria from Amgen, AstraZeneca, Boehringer, Bristol-Myers Squibb (BMS), MSD, and Sanofi, has received financial support for attending meetings from Lilly, MSD, and Roche, and has served as a consultant in advisory boards organized by Amgen and Boehringer. Manuel Dómine has received consulting fees for advisory boards from AstraZeneca, BMS, MSD oncology, Pfizer, Roche, and Takeda, has received payment or honoraria from AstraZeneca, BMS, MSD oncology, Pfizer, Roche, and Takeda, and has received financial support for attending meetings from AstraZeneca, MSD oncology, and Takeda. José Luis González Larriba has received payment or honoraria from AstraZeneca, MSD, Novartis, Roche, and Sanofi, has received payment as an expert testimony from AstraZeneca, MSD, and Sanofi, has received financial support for attending meetings from MSD, Pfizer, and Sanofi, and has served as consultant in advisory boards of AstraZeneca, MSD, Sanofi, and Takeda. Juana Saldaña has received payment or honoraria from Roche. Begoña Campos has received payment or honoraria from AstraZeneca, Bayer, BMS, Leo Pharma, Novartis, Pierre Fabre, Roche, and Rovi, has received financial support for attending meetings from BMS, Leo Pharma, Lilly, Novartis, and Roche, and has received consulting fees for advisory boards of AstraZeneca, BMS, and Roche. Andrés Barba has received payment for speaker bureaus from AstraZeneca, BMS, MSD, Novartis, Pfizer, Roche, and Sanofi, has received financial support for attending meetings from AstraZeneca, BMS, MSD, Roche, and Novartis, and has served as consultant in advisory boards of BMS and Sanofi. Diego Márquez-Medina has received consulting fees, payment or honoraria, payment for expert testimony, and financial support for attending meetings from AstraZeneca, BMS, MSD, Pfizer, Roche, and Takeda. Ernest Nadal has been awarded grants from BMS, Merck-Serono, Nanostring, and Roche, has received consulting fees and payment or honoraria from Amgen, AstraZeneca, Bayer, BMS, Boehringer, Janssen, Lilly, Merck-Serono, MSD, Pfizer, Roche, Sanofi, and Takeda, and has served as consultant in advisory boards organized by Apollomics and Roche. All other authors have declared no conflicts of interest related to the present study.

Acknowledgements

We thank the patients and their families for making this trial possible and the participating clinical study teams participating. We also thank Matías Rey-Carrizo at BCN Medical Writing for his editorial and medical writing support, which was funded by the Spanish Group of Lung Cancer in accordance with Good Publication Practice (GPP 2022) guidelines. Finally, we thank Dr Nuria Baixeras from the Department of Pathology of the Hospital Universitari de Bellvitge for evaluating the PD-L1 expression of all patients included in the study.

Funding

The Spanish Lung Cancer Foundation (Fundación GECP) sponsored the trial with financial support from the MSD Investigator-Initiated Studies Program (MISP) with number 55358.

Data sharing statement

The data used for this study is available from the corresponding author upon reasonable request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.lungcan.2023.107318.

References

[1] D. Planchard, S. Popat, K. Kerr, S. Novello, E.F. Smit, C. Faivre-Finn, T.S. Mok, M. Reck, P.E. Van Schil, M.D. Hellmann, S. Peters, Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up, Ann. Oncol. 29 (2018) iv192–iv237. doi: 10.1093/annonc/mdy275.

[2] F. Casaluce, A. Sgambato, P. Maione, A. Spagnuolo, C. Gridelli, Lung cancer, elderly and immune checkpoint inhibitors, J. Thorac. Dis. 10 (2018) S1474–S1481. doi: 10.21037/jtd.2018.05.90.

[3] R. Blanco, I. Maestu, M.G. de la Torre, A. Cassinello, I. Nuñez, A review of the management of elderly patients with non-small-cell lung cancer, Ann. Oncol. 26 (2015) 451–463, https://doi.org/10.1093/annonc/mdu268.

[4] R.A.N. Johnpulle, R.M. Conry, J.A. Sosman, I. Puzanov, D.B. Johnson, Responses to immune checkpoint inhibitors in nonagenarians, Oncoimmunology. 5 (2016) e1234572. doi: 10.1080/2162402X.2016.1234572.

[5] J.M. Mazarico Gallego, M. Herrera Juárez, L. Paz-Ares, The safety and efficacy of pembrolizumab for the treatment of non-small cell lung cancer, Expert Opin. Drug Saf. 19 (2020) 233–242, https://doi.org/10.1080/14740338.2020.1736554.

[6] S. Singh, B. Bajorek, Defining 'elderly' in clinical practice guidelines for pharmacotherapy, Pharm. Pract. (Granada). 12 (2014) 489, https://doi.org/10.4321/s1886-36552014000400007.

[7] Y. Ouchi, H. Rakugi, H. Arai, M. Akishita, H. Ito, K. Toba, I. Kai, Redefining the elderly as aged 75 years and older: Proposal from the Joint Committee of Japan Gerontological Society and the Japan Geriatrics Society, Geriatr. Gerontol. Int. 17 (2017) 1045–1047, https://doi.org/10.1111/ggi.13118.

[8] M. Reck, D. Rodríguez-Abreu, A.G. Robinson, R. Hui, T. Csőszi, A. Fülöp, M. Gottfried, N. Peled, A. Tafreshi, S. Cuffe, M. O'Brien, S. Rao, K. Hotta, M. A. Leiby, G.M. Lubiniecki, Y. Shentu, R. Rangwala, J.R. Brahmer, Pembrolizumab versus Chemotherapy for PD-L1–Positive Non–Small-Cell Lung Cancer, N. Engl. J. Med. 375 (2016) 1823–1833, https://doi.org/10.1056/nejmoa1606774.

[9] R.S. Herbst, G. Giaccone, F. de Marinis, N. Reinmuth, A. Vergnenegre, C.H. Barrios, M. Morise, E. Felip, Z. Andric, S. Geater, M. Özgüroğlu, W. Zou, A. Sandler, I. Enquist, K. Komatsubara, Y. Deng, H. Kuriki, X. Wen, M. McCleland, S. Mocci, J. Jassem, D.R. Spigel, Atezolizumab for First-Line Treatment of PD-L1–Selected Patients with NSCLC, N. Engl. J. Med. 383 (2020) 1328–1339, https://doi.org/10.1056/nejmoa1917346.

[10] A. Sezer, S. Kilickap, M. Gümüş, I. Bondarenko, M. Özgüroğlu, M. Gogishvili, H. M. Turk, I. Cicin, D. Bentsion, O. Gladkov, P. Clingan, V. Sriuranpong, N. Rizvi, B. Gao, S. Li, S. Lee, K. McGuire, C.I. Chen, T. Makharadze, S. Paydas, M. Nechaeva, F. Seebach, D.M. Weinreich, G.D. Yancopoulos, G. Gullo, I. Lowy, P. Rietschel, Cemiplimab monotherapy for first-line treatment of advanced non-small-cell lung cancer with PD-L1 of at least 50%: a multicentre, open-label, global, phase 3, randomised, controlled trial, Lancet 397 (2021) 592–604, https://doi.org/10.1016/S0140-6736(21)00228-2.

[11] T.S.K. Mok, Y. Wu, I. Kudaba, D.M. Kowalski, B.C. Cho, H.Z. Turna, G.C. Jr, V. Srimuninnimit, Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised , open-label, controlled, phase 3 trial, Lancet. 393 (2019) 1819–1830. doi: 10.1016/S0140-6736(18)32409-7.

[12] R.S. Herbst, P. Baas, D.-W. Kim, E. Felip, J.L. Pérez-Gracia, J.-Y. Han, J. Molina, J.-H. Kim, C.D. Arvis, M.-J. Ahn, M. Majem, M.J. Fidler, G. de Castro, M. Garrido, G. M. Lubiniecki, Y. Shentu, E. Im, M. Dolled-Filhart, E.B. Garon, Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): A randomised controlled trial, Lancet 387 (10027) (2016) 1540–1550.

[13] M.A. Socinski, R.M. Jotte, F. Cappuzzo, F. Orlandi, D. Stroyakovskiy, N. Nogami, D. Rodríguez-Abreu, D. Moro-Sibilot, C.A. Thomas, F. Barlesi, G. Finley, C. Kelsch, A. Lee, S. Coleman, Y. Deng, Y. Shen, M. Kowanetz, A. Lopez-Chavez, A. Sandler, M. Reck, Atezolizumab for First-Line Treatment of Metastatic Nonsquamous NSCLC, N. Engl. J. Med. 378 (2018) 2288–2301, https://doi.org/10.1056/nejmoa1716948.

[14] A.G. Pallis, A. Ring, C. Fortpied, B. Penninckx, M.C. van Nes, U. Wedding, G. VonMinckwitz, C.D. Johnson, L. Wyld, A. Timmer-Bonte, F. Bonnetain, L. Repetto, M. Aapro, A. Luciani, H. Wildiers, EORTC workshop on clinical trial methodology in older individuals with a diagnosis of solid tumors, Ann. Oncol. 22 (2011) 1922–1926, https://doi.org/10.1093/annonc/mdq687.

[15] A. Hurria, H.J. Cohen, M. Extermann, Geriatric oncology research in the cooperative groups: A report of a SIOG special meeting, J. Geriatr. Oncol. 1 (2010) 40–44, https://doi.org/10.1016/j.jgo.2010.03.005.

[16] P.M. Fayers, Interpreting quality of life data: Population-based reference data for the EORTC QLQ-C30, Eur. J. Cancer 37 (2001) 1331–1334, https://doi.org/10.1016/S0959-8049(01)00127-7.

[17] J.M. Giesinger, J.M. Kieffer, P.M. Fayers, M. Groenvold, M.A. Petersen, N.W. Scott, M.A.G. Sprangers, G. Velikova, N.K. Aaronson, Replication and validation of higher order models demonstrated that a summary score for the EORTC QLQ-C30 is robust, J. Clin. Epidemiol. 69 (2016) 79–88, https://doi.org/10.1016/j.jclinepi.2015.08.007.

[18] S. Wheelwright, A.-S. Darlington, D. Fitzsimmons, P. Fayers, J.I. Arraras, F. Bonnetain, E. Brain, A. Bredart, W.-C. Chie, J. Giesinger, E. Hammerlid, S.

J. O'Connor, S. Oerlemans, A. Pallis, M. Reed, N. Singhal, V. Vassiliou, T. Young, C. Johnson, International validation of the EORTC QLQ-ELD14 questionnaire for assessment of health-related quality of life elderly patients with cancer, Br. J. Cancer 109 (4) (2013) 852–858.
[19] P.J. Hollen, R.J. Gralla, M.G. Kris, L.M. Potanovich, Quality of life assessment in individuals with lung cancer: Testing the Lung Cancer Symptom Scale (LCSS), Eur. J. Cancer. 29 (1993) S51–S58. doi: 10.1016/S0959-8049(05)80262-X.
[20] Y. Zhang, Z. Zhang, The history and advances in cancer immunotherapy: understanding the characteristics of tumor-infiltrating immune cells and their therapeutic implications, Cell. Mol. Immunol. 17 (2020) 807–821, https://doi.org/10.1038/s41423-020-0488-6.
[21] C. Granier, A. Gey, S. Roncelin, L. Weiss, E. Paillaud, E. Tartour, Immunotherapy in older patients with cancer, Biomed. J. 44 (2021) 260–271, https://doi.org/10.1016/j.bj.2020.07.009.
[22] K. Nosaki, H. Saka, Y. Hosomi, P. Baas, G. de Castro, M. Reck, Y.L. Wu, J. R. Brahmer, E. Felip, T. Sawada, K. Noguchi, S.R. Han, B. Piperdi, D.A. Kush, G. Lopes, Safety and efficacy of pembrolizumab monotherapy in elderly patients with PD-L1–positive advanced non–small-cell lung cancer: Pooled analysis from the KEYNOTE-010, KEYNOTE-024, and KEYNOTE-042 studies, Lung Cancer 135 (2019) 188–195, https://doi.org/10.1016/j.lungcan.2019.07.004.
[23] C. Teixidó, N. Vilariño, R. Reyes, N. Reguart, PD-L1 expression testing in non-small cell lung cancer, Ther. Adv. Med. Oncol. 10 (2018) 1–17, https://doi.org/10.1177/1758835918763493.
[24] T. Hakozaki, Y. Hosomi, A. Shimizu, R. Kitadai, K. Mirokuji, Y. Okuma, Polypharmacy as a prognostic factor in older patients with advanced non-small-cell lung cancer treated with anti-PD-1/PD-L1 antibody-based immunotherapy, J. Cancer Res. Clin. Oncol. 146 (2020) 2659–2668, https://doi.org/10.1007/s00432-020-03252-4.
[25] R.S. Herbst, E.B. Garon, D.W. Kim, B.C. Cho, R. Gervais, J.L. Perez-Gracia, J. Y. Han, M. Majem, M.D. Forster, I. Monnet, S. Novello, M.A. Gubens, M. Boyer, W. C. Su, A. Samkari, E.H. Jensen, J. Kobie, B. Piperdi, P. Baas, Five Year Survival Update From KEYNOTE-010: Pembrolizumab Versus Docetaxel for Previously Treated, Programmed Death-Ligand 1–Positive Advanced NSCLC, J. Thorac. Oncol. 16 (2021) 1718–1732, https://doi.org/10.1016/j.jtho.2021.05.001.
[26] R. Erbe, Z. Wang, S. Wu, J. Xiu, N. Zaidi, J. La, D. Tuck, N. Fillmore, N.A. Giraldo, M. Topper, S. Baylin, M. Lippman, C. Isaacs, R. Basho, I. Serebriiskii, H.-J. Lenz, I. Astsaturov, J. Marshall, J. Taverna, J. Lee, E.M. Jaffee, E.T. Roussos Torres, A. Weeraratna, H. Easwaran, E.J. Fertig, Evaluating the impact of age on immune checkpoint therapy biomarkers, Cell Rep. 36 (8) (2021) 109599.
[27] L. Dang, K.W. Gallo, S. Garaud, H. Duvillier, J.N. Lodewyckx, C. Solinas, P. Da Silvia, C. Gu, C. Sibille, D. Bron, Aging and PD-1 & PD-L1 Gene Expression: Markers of Immunosenescence? PB1774, in: Eur. Hematol. Assoc., 2016. https://library.ehaweb.org/eha/2016/21st/134674/dominique.bron.aging.and.pd-1.26.pd-l1.gene.expression.markers.of.html.
[28] A. Bye, B. Sjøblom, T. Wentzel-larsen, B.H. Grønberg, V.E. Baracos, J. Marianne, N. Aass, R.M. Bremnes, Ø. Fløtten, M. Jordhøy, Muscle mass and association to quality of life in non- small cell lung cancer patients, J. Cachexia. Sarcopenia Muscle 8 (2017) 759–767, https://doi.org/10.1002/jcsm.12206.
[29] T. Naito, T. Okayama, T. Aoyama, T. Ohashi, Y. Masuda, M. Kimura, H. Shiozaki, H. Murakami, H. Kenmotsu, T. Taira, A. Ono, K. Wakuda, H. Imai, T. Oyakawa, T. Ishii, S. Omori, K. Nakashima, M. Endo, K. Omae, K. Mori, N. Yamamoto, A. Tanuma, T. Takahashi, Unfavorable impact of cancer cachexia on activity of daily living and need for inpatient care in elderly patients with advanced non-small-cell lung cancer in Japan : a prospective longitudinal observational study, BMC Cancer 17 (2017) 800, https://doi.org/10.1186/s12885-017-3795-2.
[30] A. Cortellini, P. Palumbo, G. Porzio, L. Verna, A.V. Giordano, C. Masciocchi, A. Parisi, K. Cannita, C. Ficorella, F. Bozzetti, Single-institution study of correlations between skeletal muscle mass, its density, and clinical outcomes in non-small cell lung cancer patients treated with fi rst-line chemotherapy, Thorac, Cancer 9 (2018) 1623–1630, https://doi.org/10.1111/1759-7714.12870.
[31] I. Trestini, A. Gkountakos, L. Carbognin, A. Avancini, M. Lanza, A. Mol, S. Friso, V. Corbo, G. Tortora, A. Scarpa, M. Milella, E. Bria, S. Pilotto, Muscle derangement and alteration of the nutritional machinery in NSCLC, Crit. Rev. Oncol. / Hematol. 141 (2019) 43–53, https://doi.org/10.1016/j.critrevonc.2019.06.007.
[32] Y. Wang, L. Luo, J. Li, Y. Wang, G. Che, X. Xie, Prognostic Value of Pretreatment Geriatric Nutrition Risk Index in Lung Cancer Patients: A Meta-Analysis, Nutr. Cancer 74 (2022) 3164–3171, https://doi.org/10.1080/01635581.2022.2059093.
[33] I. Trestini, I. Sperduti, M. Sposito, D. Kadrija, A. Drudi, A. Avancini, D. Tregnago, L. Carbognin, C. Bovo, A. Santo, M. Lanza, M. D'Onofrio, G. Tortora, E. Bria, M. Milella, S. Pilotto, Evaluation of nutritional status in non-small cell lung cancer: screening, assessment and correlation with treatment outcome, ESMO Open. 5 (3) (2020) e000689.
[34] M. Ester, S.N. Culos-Reed, A. Abdul-Razzak, J.T. Daun, D. Duchek, G. Francis, G. Bebb, J. Black, A. Arlain, C. Gillis, L. Galloway, L.C. Capozzi, Feasibility of a multimodal exercise, nutrition, and palliative care intervention in advanced lung cancer, BMC Cancer 21 (2021) 159, https://doi.org/10.1186/s12885-021-07872-y.
[35] X. Ge, Z. Zhang, S. Zhang, F. Yuan, F. Zhang, X. Yan, X. Han, J. Ma, L. Wang, H. Tao, X. Li, X. Zhi, Z. Huang, P. Hofman, A. Prelaj, G.L. Banna, L. Mutti, Y. Hu, J. Wang, Immunotherapy beyond progression in patients with advanced non-small cell lung cancer, Transl. Lung, Cancer Res. 9 (2020) 2391–2400, https://doi.org/10.21037/tlcr-20-1252.
[36] B. Escudier, R.J. Motzer, P. Sharma, J. Wagstaff, E.R. Plimack, H.J. Hammers, T. D. If, F. Donskov, H. Gurney, J.A. Sosman, T.D. If, P.G. Zalewski, U. Harmenberg, D.F. Mcdermott, T.K. Choueiri, M. Richardet, Y. Tomita, A. Ravaud, J. Doan, H. Zhao, H. Hardy, S. George, Treatment Beyond Progression in Patients with Advanced Renal Cell Carcinoma Treated with Nivolumab in CheckMate 025, Eur. Urol. 72 (2017) 368–376, https://doi.org/10.1016/j.eururo.2017.03.037.
[37] G.V. Long, J.S. Weber, J. Larkin, V. Atkinson, J.-J. Grob, D. Schadendorf, R. Dummer, C. Robert, I. Márquez-rodas, C. McNeil, H. Schmidt, K. Briscoe, J.-F. Baurain, F.S. Hodi, J.D. Wolchok, Nivolumab for Patients With Advanced Melanoma Treated Beyond Progression Analysis of 2 Phase 3 Clinical Trials, JAMA Oncol. 3 (2017) 1511–1519, https://doi.org/10.1001/jamaoncol.2017.1588.
[38] S.E. Rebuzzi, G. Bregni, M. Grassi, A. Damiani, M. Buscaglia, S. Buti, G. Fornarini, Immunotherapy beyond progression in advanced renal cell carcinoma: a case report and review of the literature, Immunotherapy 10 (13) (2018) 1123–1132.
[39] A. Sandler, R. Gray, M.C. Perry, J. Brahmer, J.H. Schiller, A. Dowlati, R. Lilenbaum, D.H. Johnson, Paclitaxel-Carboplatin Alone or with Bevacizumab for Non–Small-Cell Lung Cancer, N. Engl. J. Med. 355 (2006) 2542–2550, https://doi.org/10.1056/nejmoa061884.
[40] G.V. Scagliotti, P. Parikh, J. Von Pawel, B. Biesma, J. Vansteenkiste, C. Manegold, P. Serwatowski, U. Gatzemeier, R. Digumarti, M. Zukin, J.S. Lee, A. Mellemgaard, K. Park, S. Patil, J. Rolski, T. Goksel, F. De Marinis, L. Simms, K.P. Sugarman, D. Gandara, Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer, J. Clin. Oncol. 26 (2008) 3543–3551, https://doi.org/10.1200/JCO.2007.15.0375.
[41] H. Wildiers, M. Mauer, A. Pallis, A. Hurria, S.G. Mohile, A. Luciani, G. Curigliano, M. Extermann, S.M. Lichtman, K. Ballman, H.J. Cohen, H. Muss, U. Wedding, End Points and Trial Design in Geriatric Oncology Research: A Joint European Organisation for Research and Treatment of Cancer – Alliance for Clinical Trials in Oncology – International Society of Geriatric Oncology Position Article, J. Clin. Oncol. 31 (2013) 3711–3718, https://doi.org/10.1200/JCO.2013.49.6125.
[42] L. Pai-Scherf, G.M. Blumenthal, H. Li, S. Subramaniam, P.S. Mishra-Kalyani, K. He, H. Zhao, J. Yu, M. Paciga, K.B. Goldberg, A.E. Mckee, P. Keegan, R. Pazdur, FDA Approval Summary: Pembrolizumab for Treatment of Metastatic Non-Small Cell Lung Cancer: First-Line Therapy and Beyond, Oncologist 22 (2017) 1392–1399, https://doi.org/10.1634/theoncologist.2017-0078.
[43] S.-M. Lee, C. Schulz, K. Prabhash, D. Kowalski, A. Szczesna, B. Han, S. Peters, IPSOS: A Phase III, Global, Multicentre, Open-Label, Randomised, Controlled Study of First-Line Atezolizumab Versus Single-Agent Chemotherapy in Patients with Non-Small Cell Lung Cancer Ineligible for Treatment with a Platinum-Containing Regimen, SSRN. (2022). doi: 10.2139/ssrn.4307691.
[44] E. Quoix, C. Mascaux, Atezolizumab in Elderly Patients With Advanced Non-Small-Cell Lung Cancer and Receiving Carboplatin Paclitaxel Chemotherapy (ELDERLY). NCT03977194, ClinicalTrials.Gov. (2022). https://clinicaltrials.gov/ct2/show/NCT03977194 (accessed November 16, 2022).
[45] A. Jatoi, Testing the Effects of MK-3475 (Pembrolizumab) With or Without the Usual Chemotherapy Treatment for Patients 70 Years of Age and Older With Advanced Non-small Cell Lung Cancer. NCT04533451, ClinicalTrials.Gov. (2022). https://clinicaltrials.gov/ct2/show/NCT04533451 (accessed November 16, 2022).
[46] M.C. Piccirillo, F. Perrone, A Study Comparing Immunotherapy With Chemotherapy in the Treatment of Elderly Patients With Advanced NSCLC (MILES-5). NCT03975114, ClinicalTrials.Gov. (2022). https://clinicaltrials.gov/ct2/show/NCT03975114 (accessed November 16, 2022).
[47] J. Kuon, Durvalumab (MEDI4736) in Frail and Elder Patients With Metastatic NSCLC (DURATION). NCT03345810, ClinicalTrials.Gov. (2022). https://clinicaltrials.gov/ct2/show/NCT03345810 (accessed November 16, 2022).
[48] M. Reck, J. Remon, M.D. Hellmann, First-Line Immunotherapy for Non–Small-Cell Lung Cancer, J. Clin. Oncol. 40 (2022) 586–597, https://doi.org/10.1200/JCO.21.01497.
[49] C. Gridelli, S. Peters, V. Velcheti, I. Attili, F. de Marinis, 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), ESMO Open. 8 (2) (2023) 101192.
[50] D.Y. Wang, J. Salem, J.V. Cohen, S. Chandra, C. Menzer, F. Ye, S. Zhao, S. Das, K. E. Beckermann, L. Ha, W.K. Rathmell, K.K. Ancell, J.M. Balko, C. Bowman, E. J. Davis, D.D. Chism, L. Horn, G.V. Long, M.S. Carlino, B. Lebrun-vignes, Z. Eroglu, J.C. Hassel, A.M. Menzies, J.A. Sosman, R.J. Sullivan, J.J. Moslehi, D.B. Johnson, Fatal Toxic Effects Associated With Immune Checkpoint Inhibitors A Systematic Review and Meta-analysis, JAMA Oncol. 4 (2018) 1721–1728, https://doi.org/10.1001/jamaoncol.2018.3923.
[51] A. Paderi, S. Fancelli, E. Caliman, S. Pillozzi, E. Gambale, M.M. Mela, L. Doni, F. Mazzoni, L. Antonuzzo, Safety of Immune Checkpoint Inhibitors in Elderly Patients : An Observational Study, Curr. Oncol. 28 (2021) 3259–3267, https://doi.org/10.3390/curroncol28050283.
[52] C. Chen, B. Wu, C. Zhang, T. Xu, Immune-related adverse events associated with immune checkpoint inhibitors: An updated comprehensive disproportionality analysis of the FDA adverse event reporting system, Int. Immunopharmacol. 95 (2021), 107498, https://doi.org/10.1016/j.intimp.2021.107498.
[53] F. Gomes, P. Lorigan, S. Woolley, P. Foden, K. Burns, J. Yorke, F. Blackhall, A prospective cohort study on the safety of checkpoint inhibitors in older cancer patients e the ELDERS study, ESMO Open. 6 (2021), 100042, https://doi.org/10.1016/j.esmoop.2020.100042.
[54] C. Baldini, P. Romano Martin, A. Voisin, F.-X. Danlos, S. Champiat, S. Laghouati, M. Kfoury, H. Vincent, S. Postel-vinay, A. Varga, M. Kfoury, P. Vuagnat, V. Ribrag, L. Mezquita, B. Besse, A. Hollebecque, O. Lambotte, J. Michot, J. Soria, C. Massard, A. Marabell, Impact of aging on immune-related adverse events generated by anti e programmed death (ligand) PD-(L)1 therapies, Eur. J. Cancer 129 (2020) 71–79, https://doi.org/10.1016/j.ejca.2020.01.013.
[55] J.R. Brahmer, D. Rodríguez-Abreu, A.G. Robinson, R. Hui, T. Csőszi, A. Fülöp, M. Gottfried, N. Peled, A. Tafreshi, S. Cuffe, M. O'Brien, S. Rao, K. Hotta, J. Zhang,

G.M. Lubiniecki, A.C. Deitz, R. Rangwala, M. Reck, Health-related quality-of-life results for pembrolizumab versus chemotherapy in advanced, PD-L1-positive NSCLC (KEYNOTE-024): a multicentre, international, randomised, open-label phase 3 trial, Lancet Oncol. 18 (2017) 1600–1609, https://doi.org/10.1016/S1470-2045(17)30690-3.

[56] D.R. Spigel, M. McCleod, R.M. Jotte, L. Einhorn, L. Horn, D.M. Waterhouse, B. Creelan, S. Babu, N.B. Leighl, J.C. Chandler, F. Couture, G. Keogh, G. Goss, D. B. Daniel, E.B. Garon, L.S. Schwartzberg, R. Sen, B. Korytowsky, A. Li, N. Aanur, M. A. Hussein, Safety, Efficacy, and Patient-Reported Health-Related Quality of Life and Symptom Burden with Nivolumab in Patients with Advanced Non-Small Cell Lung Cancer, Including Patients Aged 70 Years or Older or with Poor Performance Status (CheckMate 153), J. Thorac. Oncol. 14 (2019) 1628–1639, https://doi.org/10.1016/j.jtho.2019.05.010.

[57] A. Boutros, M. Bruzzone, E.T. Tanda, E. Croce, L. Arecco, F. Cecchi, P. Pronzato, M. Ceppi, M. Lambertini, F. Spagnolo, Health-related quality of life in cancer patients treated with immune checkpoint inhibitors in randomised controlled trials: A systematic review and meta-analysis, Eur. J. Cancer 159 (2021) 154–166, https://doi.org/10.1016/j.ejca.2021.10.005.

[58] P. Maione, F. Perrone, C. Gallo, L. Manzione, F.V. Piantedosi, S. Barbera, S. Cigolari, F. Rosetti, E. Piazza, S.F. Robbiati, O. Bertetto, S. Novella, M. R. Migliorino, A. Favaretto, M. Spatafora, F. Ferraù, L. Frontini, A. Bearz, L. Repetto, C. Gridelli, Pretreatment quality of life and functional status assessment significantly predict survival of elderly patients with advanced non-small-cell lung cancer receiving chemotherapy: A Prognostic analysis of the multicenter italian lung cancer in the elderly s, J. Clin. Oncol. 23 (2005) 6865–6872, https://doi.org/10.1200/JCO.2005.02.527.

[59] T.M. Wildes, A.P. Ruwe, C. Fournier, F. Gao, K.R. Carson, J.F. Piccirillo, B. Tan, G. A. Colditz, Geriatric assessment is associated with completion of chemotherapy, toxicity, and survival in older adults with cancer, J. Geriatr. Oncol. 4 (2013) 227–234, https://doi.org/10.1016/j.jgo.2013.02.002.

[60] K. Welaya, K.P. Loh, S. Messing, E. Szuba, A. Magnuson, S.G. Mohile, R. J. Maggiore, Geriatric assessment and treatment outcomes in older adults with cancer receiving immune checkpoint inhibitors, J. Geriatr. Oncol. 11 (2020) 523–528, https://doi.org/10.1016/j.jgo.2019.05.021.

[61] C. Engels, R. Bairet, F. Canoui-Poitrine, M. Laurent, E. McKay, Leisure and Productivity in Older Adults with Cancer: A Systematic Review, Occup. Ther. Int. 2021 (2021) 1–11.