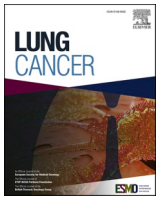
Lung Cancer 204 (2025) 108580

Contents lists available at ScienceDirect

Lung Cancer

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



A prospective study on clinicians' attitudes and survival outcomes for patients with advanced NSCLC and poor performance status in the immunotherapy era: PICASO (GOIRC-04-2020)

Francesco Facchinetti [a,b,*], Andrea Camerini [c], Chiara Bennati [d], Paola Bordi [e], Elisa De Carlo [f], Francesca Mazzoni [g], Giulio Metro [h], Federica Bertolini [i], Lucia Longo [j], Serena Ricciardi [k], Sara Pilotto [l], Donatella Giardina [m], Francesco Passiglia [n], Vieri Scotti [o], Paolo Piacentini [p], Stefano Frega [q], Luana Calabrò [r], Annalisa Guida [s], Maria Antonietta Grosso [c], Jenny Longobardi [d], Alessandra Merlini [n], Federica Cosso [g], Alessandro Leonetti [e], Eleonora Gariazzo [h], Giorgia Guaitoli [i], Lorenzo Belluomini [l], Alessandra Bearz [f], Michele Tognetto [b], Emilio Bria [t], Diego Luigi Cortinovis [u], Silvia Novello [n], Massimo Di Maio [v,1], Marcello Tiseo [b,e,w,1]

[a] *Lowe Center for Thoracic Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, USA*
[b] *Gruppo Oncologico di Ricerca Clinica (GOIRC), Parma, Italy*
[c] *Medical Oncology, Versilia Hospital, Azienda USL Toscana Nord Ovest, Lido di Camaiore, Italy*
[d] *Department of Onco-Hematology, AUSL della Romagna, Ravenna, Italy*
[e] *Medical Oncology Unit, University Hospital of Parma, Italy*
[f] *Department of Medical Oncology, Centro di Riferimento Oncologico di Aviano (CRO), Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS), Aviano, Italy*
[g] *Department of Oncology, Careggi University Hospital, Florence, Italy*
[h] *Medical Oncology, Santa Maria della Misericordia Hospital, University of Perugia, Italy*
[i] *Division of Medical Oncology, Azienda Ospedaliero-Universitaria Policlinico, Modena, Italy*
[j] *Medical Oncology Unit, Sassuolo Hospital, AUSL Modena, Italy*
[k] *Oncology Pneumology Unit, San Camillo Forlanini, Roma, Italy*
[l] *Section of Oncology, Department of Engineering for Innovation Medicine, University of Verona, Italy*
[m] *UOC Oncologia di Prossimità, Ospedale B. Ramazzini di Carpi, AUSL Modena, Italy*
[n] *Department of Oncology, University of Turin, San Luigi Hospital, Orbassano, Turin, Italy*
[o] *Radiation Oncology Unit, Oncology Department, AOU Careggi Firenze, Italy*
[p] *Department of Medical Oncology, AULSS 9 Scaligera, Verona, Italy*
[q] *Oncologia 2, Istituto Oncologico Veneto (IOV) IRCCS, Padua, Italy*
[r] *Oncology Unit, University Hospital of Ferrara, Italy*
[s] *Dipartimento di Oncologia, Azienda Ospedaliera Santa Maria of Terni, Italy*
[t] *UOSD Oncologia Toraco-Polmonare, Comprehensive Cancer Center, Fondazione Policlinico Universitario A. Gemelli IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy*
[u] *Department of Medicine and Surgery, Oncology, Fondazione IRCCS San Gerardo dei Tintori, Monza, Italy*
[v] *Department of Oncology, University of Turin, AOU Città della Salute e della Scienza di Torino, Turin, Italy*
[w] *Department of Medicine and Surgery, University Hospital of Parma, Italy*

ARTICLE INFO

Keywords:
Non-small cell lung cancer
Performance status 2
Unfit

ABSTRACT

Background: Therapeutic strategies for patients with advanced NSCLC and an ECOG performance status (PS) 2 at diagnosis are supported by limited evidence.
Patients and methods: We led a prospective, observational study in 20 Italian centers on patients with advanced NSCLC and ECOG PS 2. Patients with *EGFR* mutations, *ALK* fusions or receiving first-line targeted treatments

* Corresponding author at: Lowe Center for Thoracic Oncology, Dana-Farber Cancer Institute, Harvard Medical School, 360 Longwood Ave, 02215 Boston, MA, USA.
E-mail address: francesco_facchinetti@dfci.harvard.edu (F. Facchinetti).
[1] These Authors share co-last authorship.

https://doi.org/10.1016/j.lungcan.2025.108580
Received 14 February 2025; Received in revised form 5 May 2025; Accepted 7 May 2025
Available online 8 May 2025

Real-world
First-line

were excluded. We recorded physicians' attitudes in addressing first-line treatments and clinical outcomes. The primary endpoint was progression-free rate at six months.
Results: From March 2022 to October 2023, 198 consecutive patients were included. Median age was 73 years (range 43–91). Forty-four patients (22%) were candidate to best supportive care, 49 (25%) to single agent chemotherapy, 14 (7%) to platinum doublet, 40 (20%) to mono-immunotherapy, 52 (26%) to chemo-immunotherapy. At a median follow-up of 9.4 months (95 % CI 7.2 – 11.7), 6-month progression-free rate was 15.3%, with a median progression-free survival of 1.6 months (95 % CI 1.3 – 1.9). Six-months overall survival (OS) rate was 27.7%, with a median OS of 2.8 months (95 % CI 2.0 – 3.6). Patients receiving chemo-immunotherapy (PD-L1 $<$ 50%) had 6-month progression-free and OS rates of 22.9% and 29.1% respectively, with median PFS 1.9 months and median OS 3.7 months; mono-immunotherapy for patients with PD-L1 $\geq$ 50% led to slightly better outcomes. Among 155 patients receiving active treatment, no clinical-pathological characteristic harbored a prognostic role. One third of patients receiving immunotherapy-containing regimens encountered early clinical progression or death before the first radiological evaluation. No relevant safety signals emerged across treatments.
Conclusions: Less than half of patients with NSCLC and ECOG PS 2 were candidates to the regimens recommended for fit pts, *i.e.* mono-immunotherapy or chemo-immunotherapy according to PD-L1. Even with immunotherapy, most of these patients have dismal outcomes, suggesting that trials dedicating to PS 2 perform an intrinsic patient selection.

1. Introduction

The therapeutic landscape of advanced non-small cell lung cancer (NSCLC) has been reshaped during the past decade by immune checkpoint inhibitors (ICI), currently a cornerstone of first-line treatment for patients with no targetable molecular alterations [1,2]. The application in the clinical setting of regimens emerged from pivotal trials is sometimes challenging, mainly due to the patient selection taking care in practice-changing studies [3].

Patients with an Eastern Cooperative Oncology Group performance status 2 (ECOG PS 2) represent up to one third of the diagnosis of advanced NSCLC [4], and are usually excluded from clinical trials. Despite poor PS is a prominent negative prognostic factor [5,6], scant evidence supports treatment decisions in this setting. The challenging management of this patient population is moreover hampered by its clinical definition and intrinsic heterogeneity [7]. Platinum-pemetrexed was considered the treatment of choice, at least in non-squamous histology, given the superiority over single agent pemetrexed [8]. Moreover, poor PS itself accounts for more than half of the cases not deemed candidate to platinum-based regimens [9,10].

Despite clinical trials have been designed to evaluate ICI for patients with poor PS in the first-line setting (Table 1), no prospective evidence concerning chemo-immunotherapy is thus far available for this population. Inhibition of PD-1/PD-L1 alone with single agents has proven satisfactory in this setting, with one-year survival rates between 30% (when durvalumab was administered regardless of PD-L1 status) to 45% [11–14]. The phase 3 IPSOS trial was dedicated to the precise population of platinum-ineligible patients, and ECOG PS 2/3 accounted for more than 80% of the cases. Atezolizumab showed an overall survival (OS) benefit compared to vinorelbine or gemcitabine, yet more marked in PS 0–1 compared to PS 2 patients [10].

The combination of nivolumab and ipilimumab led to divergent results in two different studies, with regard to the population with ECOG PS 2. In CheckMate 817, the outcomes were in line with the ones observed with anti-PD-1/PD-L1 inhibition alone across the trials, with median OS of 9 months [15]. On the other hand, in the randomized phase 3 ENERGY study, median OS was 2.9 months, with six-month and one-year OS rates of around 30% and 20%, respectively [16]. These results were disappointing compared to the control arm of platinum doublet (median OS 6.1 months, six-month and one-year OS rates 50% and 30%, respectively), prompting a halt in randomization following a pre-planned interim analysis showing futility. Again, this suggests a certain degree of heterogeneity among patients with advanced NSCLC and PS 2 included in clinical trials.

In the PICASO study, we aimed to systematically approach the population of patients diagnosed with an advanced NSCLC and an poor PS, to understand their management now that ICI, alone or in combination with chemotherapy, are first-line treatment options irrespective of PS. PICASO is a prospective, observational study designed to assess the treatment distribution of unselected PS 2 patients in a clinical setting, and to report their outcomes in terms of activity, efficacy and safety according to the administered regimens.

2. Patients and methods

2.1. Study population

PICASO (GOIRC-04-2020) is an observational, prospective study led by the *Gruppo Oncologico Italiano di Ricerca Clinica* (GOIRC). For inclusion in the study, the following criteria had to be met: 1) Patients with diagnosis of advanced (stage IIIB/IV) NSCLC; 2) ECOG PS = 2; 3) Age $\geq$ 18 years; 4) Patients previously untreated for advanced disease; 5) Informed consent signature. Subjects were not eligible for the study if they fulfilled any of the following exclusion criteria: 1) ECOG PS = 1, 3 or 4; 2) Activating mutations of *EGFR* or rearrangements of *ALK*; activating molecular alterations in additional genes (e.g. *ROS1*, *RET*, *BRAF*, *MET*, *NTRK*) that led to first-line targeted treatment; 3) The presence of a disease (other than lung cancer) not under clinical control and hampering survival outcomes.

The study was designed to enroll a minimum of 150 to a maximum of 250 patients (Supplementary Table 1), in 20 Italian centers with expertise in thoracic oncology. The study was planned to have an accrual of one year, since the first enrolled patient in each center, although some centers had an enrollment period of less than one year, due to delays in local activation.

2.2. Data collection

This study includes five cohorts:

1. Patients receiving single agent chemotherapy (single agent CT) were expected to receive vinorelbine (intravenous, IV, or oral), gemcitabine, or paclitaxel.

2. Patients receiving platinum doublets (combination CT) were expected to receive carboplatin with either pemetrexed (non-squamous histology) or gemcitabine or (nab)paclitaxel (squamous histology).

3. Patients receiving anti-PD-1/PD-L1 monotherapy (single agent IO) had a PD-L1 $\geq$ 50% and received either pembrolizumab, atezolizumab or cemiplimab.

4. Patients receiving chemo-immunotherapy combinations (CT-IO) were expected to receive pembrolizumab or nivolumab/ipilimumab with either carboplatin/pemetrexed (non-squamous histology) or (nab) paclitaxel (squamous histology), according to Keynote-189, CheckMate

9LA, and Keynote-407 regimens [17–19].

5. Patients deemed candidate to best supportive care (BSC) did not receive active treatment.

Given the observational nature of this study, investigators were completely autonomous in their clinical decisions, and no guidance or clinical recommendations were provided beforehand.

According to Italian approval and reimbursement, chemo-immunotherapy combinations could only be administered in cases with PD-L1 expression < 50%. For patients whose tumors had PD-L1 expression ≥ 50%, "off-label" administration could be demanded on a case-by-case basis, but it is not routinely used.

Standard clinical and pathological parameters for patients with NSCLC were collected. Performance status was additionally assessed according to the Karnofsky score. The Charlson comorbidity index assessed the burden of comorbidities for each patient and was meant to be reported as descriptive information [20]. ECOG PS was assessed at inclusion (specifying if the disease burden was conditioning the poor PS or it was attributable to comorbidities) and at every treatment course.

Table 1
Prospective study evaluating fist-line immunotherapy in patients with advanced NSCLC and poor performance status.

Study	Phase Primary endpoints	Global population	Drugs	IO-treated PS 2 patients	Reponse rates PS 2 patients	Median PFS (95% CI) PS 2 patients	Landmark PFS PS 2 patients	Median OS (95% CI) PS 2 patients	Landmark OS PS 2 patients	PS 2 patients with treatment-related advesrse events
PePS2 Middleton Lancet Resp Med 2020 [12]	II DCB, safety	PS 2	Pembrolizumab	First line n = 24	ORR 21%	4.3 months (1.9–13.1)	6-month ≈ 45% 1-year ≈ 30%	7.9 months (2.6-NR)	6-month ≈ 55% 1-year ≈ 45%	Grade 3–5, at least possibly treatment-related: 15% of the 60 patients (regardless of treatment line)
Shaverdashvili eClinicalMedicine 2023 [13]	II OS, safety	PS 2	Durvalumab	n = 47	Among 38 patients evaluated: ORR 26% DCR 73% Among the total 47: ORR 21%	3 months (1–4)	NA	6 months (4–10)	6-month ≈ 50% 1-year 31%	Any grade: 51% Grade 3–4: 19%
SAKK 19/17 Mark EJC 2024 [14]	II 6-month OS	PS 2 PD-L1 TPS ≥ 25%	Durvalumab	n = 48	ORR 17%	2.5 months (1.8–7.1)	6-month ≈ 40% 1-year ≈ 20%	8.5 months (4.4–16.7)	6-month = 60% 1-year ≈ 45%	Grade ≥ 3: 19%
IFCT-1802 SAVIMMUNE Gounant ESMO 2024 [15]	II Safety	PS 2–3 PD-L1 TPS ≥ 25%	Durvalumab	PS 2 n = 40 PS 3 n = 10	PS 2–3 ORR 26% DCR 44% PD32 % Not evaluable 24%	3.5 months (1.8–9.4)	NA	9.7 months (4.4-NR)	1-year 47.7%	PS 2–3 Any grade: 50% Grade 3–4: 14%
IPSOS Lee Lancet 2023 [11]	III OS	Platinum doublet inelegible (PS 0–3)	Atezolizumab vs Gemcitabine or Vinorelbine	n = 228	NA	4.1 vs 4.2 HR global 0.87 (0.70–1.07) Unstratified HR PS 2 0.89 (0.70–1.14)	NA	9.7 vs 10.4 HR global 0.78 (0.63–0.97) Unstratified HR PS 2 0.86 (0.67–1.10)	NA	Any grade: 57% vs 80% Grade 3–4: 16% vs 33% Treatment-related deaths: 1% vs 3%
CheckMate 817 Ready JITC 2023 [16]	IIIB Safety in PS 0–1	No restrictions	Nivolumab Ipilimumab	n = 139	ORR 20.9%	3.6 months (2.8–5.4)	1-year 25.6% 2-year 13.7% 3-year 6.3%	9.0 months (5.5–12.9)	1-year 44% 2-year 26.5% 3-year 18.7%	Any grade: 64% Grade 3–4: 27.3%
GFPC 08–2015 ENERGY Léna Lancet Resp Med 2024 [17]	III OS	Elderly, PS 2 Almost all PD-L1 < 50%	Nivolumab Ipilimumab vs Carboplatin doublet	n = 39	NA	NA	NA	2.9 (1.4–4.8) vs 6.1 (3.5–10.4) HR 1.32 (0.82–2.11)	6-month ≈ 30% 1-year ≈ 20%	NA in the specific population of PS 2

DCB: Durable clinical benefit; OS: Overall survival; PS: Performance status; TPS: Tumor proportional score; ORR: Objective response rate; DCR: Disease-control rate; SD: Stable disease; PR: Partial response; NA: Not available; PFS: Progression-free survival; 95% CI: 95% Confidence interval; HR: Hazard ratio; NR: Not reached.

We recorded leucocyte composition at baseline, to derive the neutrophils-to-lymphocytes ratio (N/L ratio). We queried the concomitant steroid administration (≥ 10 mg prednisone daily, or equivalent) and if patients were treated with antibiotics in the 30 days before first-line treatment initiation.

We also queried physicians about the propensity (in a scale 0–100) to administer to each patient one of the five treatments listed above.

Doses of chemotherapy at treatment initiation were recorded.

Considering the observational nature of the study, radiological assessments were performed according to clinical practice (approximately every eight to twelve weeks). Adverse events were recorded according to the CTCAE v5.0 during the treatment phase and follow-up.

Follow-up assessments included additional therapy after the first-line one and respective outcomes, as well as OS data.

Data were recorded in participating centers by fulfilling electronic case report forms (eCRFs).

2.3. Objectives and endpoints

The primary objective was to collect clinical outcomes of unselected patients with advanced NSCLC lacking targetable molecular drivers and an ECOG PS 2 NSCLC, who were evaluated for first-line treatment.

Secondary objectives included the report of clinicians' attitudes in the choice of treatment, and patients' outcomes according to administered therapy, PD-L1 status, the reason conditioning the poor PS and other factors known to influence immunotherapy outcomes.

The primary end-point was the definition of the proportion of patients without disease progression six months after the start of treatment (6-month progression-free rate) in the whole study population, and according to each of the five treatment categories reported above in Section 2.2. Secondary end-points included: i) The propensity of treating physicians in allocating each patient to receive one of the five treatments reported above; ii) Objective response rates (ORR) and disease control rates (DCR), according to RECIST criteria 1.1. Atypical patterns of response (e.g. pseudo-progressions) were recorded; iii) Progression-free survival (PFS); iv) OS; v) Incidence and severity of drug-related adverse events; vi) Differential outcomes according to the clinical factors conditioning the poor ECOG PS (disease burden and/or comorbidities) and other factors known to influence immunotherapy outcomes (e.g. PD-L1 expression levels, steroids, antibiotics, N/L ratio).

We interrogated clinical outcomes and potential prognostic factors in the whole study population and among patients candidate to active treatment.

2.4. Statistical plan and considerations

This study was designed with a descriptive aim, without a hypothesis-driven fixed sample size.

The precision in the estimations of the outcome depended on the number of patients enrolled.

The primary outcome measure being the 6-month progression-free rate in the whole study population, we defined beforehand three different outcome scenarios (Supplementary Table 1), already used in our previous work [21]: 1) "Optimistic" scenario: 6-month progression-free rate 50 % (corresponding to the outcome observed in patients with ECOG performance status 0–1 and PD-L1 ≥ 50% in the KEYNOTE-042 trial) [22]; 2) "Intermediate" scenario: 6-month progression-free rate 40% (corresponding to the outcome observed in patients with ECOG performance status 0–1 treated with platinum plus pemetrexed in KEYNOTE-189 trial) [23]; 3) "Pessimistic" scenario: 6-month progression-free rate 30% (pooling patients with ECOG performance status 2 treated with either single-agent pemetrexed or carboplatin-pemetrexed in the trial by Zukin *et al*) [8]. This scenario was considered pessimistic because it implies that the use of ICI has not improved the outcome of patients in this setting compared to chemotherapy only.

Investigators' propensity for treatment choice was described, for each patient, in 2 ways: (1) number of treatment options with a propensity more than 20 in a scale from 0 to 100; (2) delta (from 0 to 100) between the first and the second choice.

PFS was calculated from the date of first treatment administration (or the date of the visit with decision of BSC alone) and the date of disease progression (clinical, or radiologically assessed according to RECIST criteria, by local investigators) or death (whichever occurred first). OS was calculated from the date of first treatment administration (or the date of the visit with decision of treating with best supportive care alone) and the date of death. Response rate was defined by the number of radiological responses out of the total of actively treated subjects. Radiological assessments were performed per clinical practice, with no centralized review.

A minimum follow-up of six months since the last patient enrolled was required for data analysis.

Kaplan-Meyer method was used to derive survival estimates, and median follow-up was calculated according to the so-termed 'reverse Kaplan-Meier' (Kaplan-Meier estimate of potential follow-up) technique. SPSS software was used for data analyses.

The comparison among treatment groups was designed to be only exploratory.

3. Results

3.1. Patients' characteristics

From March 2022 to October 2023, 198 consecutive patients were

Table 2
Baseline patients' characteristics.

Total patients	198
Age (median, range)	73 (43–91)
Sex	
Male	118 (60%)
Female	80 (40 %)
Smoking history	
Active	85 (43%)
Past	94(47%)
Never	14 (7%)
Unknown	5 (3%)
PS according to Karnofsky score	
60	116 (59%)
50	82 (41%)
Disease burden conditions the poor PS	
Yes	177 (89%)
No	21 (11%)
Comorbities present	
Yes	182 (92%)
No	16 (8%)
Charlson Comorbidity Index, median (range)	10 (6–21)
Histology	
Adenocarcinoma	131 (66%)
Squamous cell carcinoma	55 (28%)
Other	12 (6%)
PD-L1 expression	
< 50 %	117 (59%)
≥ 50 %	49 (25%)
Unknown	32 (16%)
N/L ratio (165 patients), median (range)	5.9 (0.7–44.7)
Patients receiving active treatment	155 (78%)
Ongoing steroids (prednisone ≥ 10 mg/die or equivalent)	
Yes	59 (38%)
No	96 (62%)
Antibiotic in the 30 days before treatment	
Yes	21 (14%)
No	134 (86%)
Hospital regimen	
Outpatients	133 (86%)
Inpatients	22 (14%)

PS: Performance status; N/L: Neutrophils/Lymphocytes.

found eligible and included in the analysis (Table 2). Median age of patients was 73 years, and 118 (60%) were males. The large majority were ever-smokers (n = 179, 90%). Disease burden conditioned the poor PS in approximately 90% of the patients (n = 177), and a similar proportion had at least one comorbidity (n = 182). Cardiac, vascular and pulmonary were the most frequent comorbidities, observed respectively in 90 (45%), 88 (44%) and 79 (40%) patients. The median Charlson Comorbidity Index, collected for all the patients, was 10 (range 6–21). During the three months before the diagnosis of NSCLC, 78 patients (39%) reported unintended weight loss (median 8 kg).

The pathological diagnoses accounted for 131 adenocarcinomas (66%) and PD-L1 expression was ≥ 50% in 49 (25%) (Table 2). *KRAS* mutations were detected in 50 cases (25%). Two patients harbored a *MET* exon 14 skipping alteration, while one case each had *HER2* mutation and *NTRK* fusion. Of note, MET inhibitors are only approved and reimbursed in Italy for the second or later lines of therapy.

Before starting (or being evaluated for) first-line therapy, 46 (23%) of the patients underwent radiotherapy, in five and 41 cases with curative and palliative intent, respectively.

N/L ratio was available for 165 patients, with a median of 5.9 (range 0.7–44.7); 33 patients (20%) had a N/L ratio less then 3 (Table 2). Similar corresponding values were found across the 134 patients candidate to systemic therapy, with an available N/L ratio (data not shown).

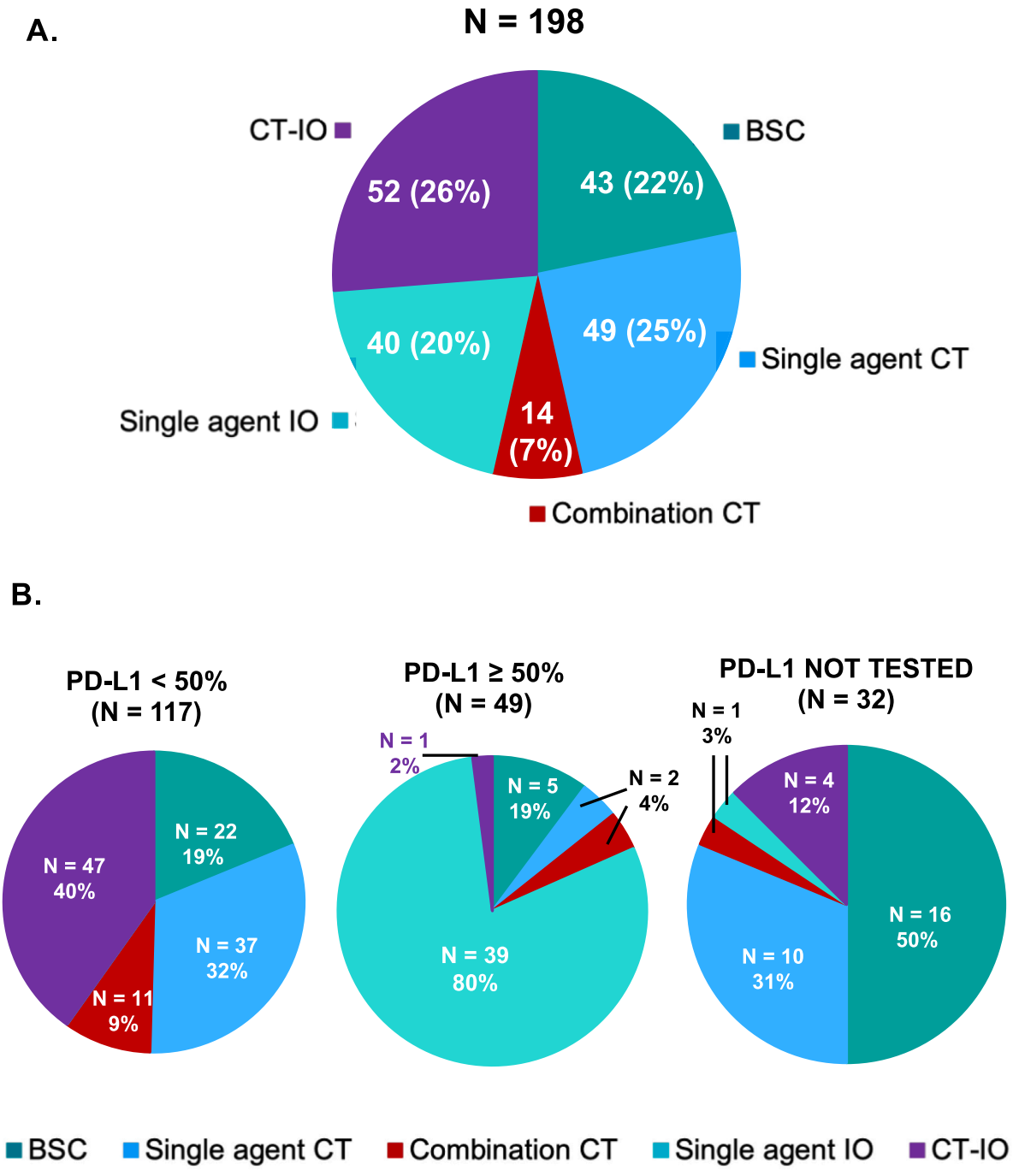


Fig. 1. Treatment distribution in the whole population (A), and according to PD-L1 status (B). BSC: Best supportive care; Single agent CT: Single agent chemotherapy; Combination CT: Platinum doublets; Single agent IO: Anti-PD-1/PD-L1 monotherapy; CT-IO: Chemo-immunotherapy combinations.

3.2. Treatment distribution in the whole population

Across the global population, 52 patients (26%) were candidate to CT-IO. Single agent CT was administered in 49 (25%) of the cases, and single agent IO in 40 (20%). Combination CT were the less frequently adopted first-line regimens (n = 14, 7%), and 43 patients (22%) were candidate to BSC only (Fig. 1A). Precise treatments (type of chemotherapy and immunotherapy) are reported in Supplementary Table 2. Metronomic vinorelbine was the regimen most frequently used as single agent chemo, whereas carboplatin-pemetrexed, with or without IO, was the most commonly used chemotherapy combination. Among single agent IO, pembrolizumab was administered in 22/40 cases (55%). Chemotherapy was prescribed at a reduced dose in approximately one half of the patients (e.g. carboplatin AUC4, pemetrexed < 500 mg/m2, data not shown). Among the 155 patients who received active therapy, 59 (38%) were receiving steroids (equivalent to prednisone ≥ 10 mg daily) at the moment of treatment initiation, and 21 (14%) had received antibiotic in the 30 days before. In the majority of the cases (n = 133, 86%), active treatment was initiated in an outpatient setting (Table 2).

3.3. Estimation of clinicians' propensity to allocate patients in each treatment group

For each patient included in this study, we asked the treating physician to provide the propensity (0–100) to allocate them in each of the five treatment groups, with no "threshold" effect (*i.e.* the sum of the propensity for each patient could be > 100). Among the 192 patients with treatment propensity available, the majority (n = 117, 61%) had at least two treatment options with a propensity higher than 20 in a scale from 0 to 100, indicating some uncertainty in the treatment choices (Supplementary Fig. 1A). In more than half of the cases, the delta in the treatment propensity between the first and second treatment options was < 50 (Supplementary Fig. 1B).

3.4. Clinical and pathological factors influencing treatment distribution

We assessed treatment distribution according to PD-L1 levels (Fig. 1B). Among the 117 patients with PD-L1 < 50%, 47 (40%) received chemo-IO and 37 (32%) single agent chemotherapy. Single agent IO was the most commonly administered agent among cases with PD-L1 ≥ 50% (39/49, 80%). Of note, in this group of patients, chemo-IO was administered in one case only. Among the patients eventually treated with single agent IO, physicians would have opted for those chemo-IO regimens, if approved for PD-L1 ≥ 50%, in 27% of the cases. Among the 32 patients with an unknown PD-L1 status, 10 (31%) and 4 (12%) received single agent chemotherapy and chemo-IO, respectively. The proportion of patients candidate to BSC only was higher in this latest subgroup (16/32, 50%), suggesting that PD-L1 testing was omitted because systemic options besides targeted agents were not feasible. Patients candidate to BSC only represented the 19% (n = 22) of the subgroup with PD-L1 < 50%, and 10% (n = 5) of the ones with PD-L1 ≥ 50%.

We then evaluated additional clinical and pathological factors that could have influenced treatment allocation. There was a significant correlation between age and administered treatment, as patients candidate to chemotherapy doublets and chemo-IO were younger (median age 68 years) compared to the ones candidate to single agent chemo or BSC (median age 78 and 76 years, respectively) (Supplementary Table 3). Median age of patients receiving single agent IO was 72 years. No difference in treatment distribution was observed regarding other clinico-pathological factors. With the limitation of the low number of patients without comorbidities (n = 16), they were frequently candidate to chemo-IO, and less to single-agent CT or BSC, compared to the ones with comorbidities (p = 0.062) (Supplementary Table 3). This trend suggests that in cases when disease burden alone conditioned poor PS, clinicians were prone to candidate patients to relatively more intense treatment regimens.

3.5. Clinical outcomes

At data cut-off (June 30th 2024), the median follow-up was 9.4 months (95 % CI 7.2 – 11.7). Median PFS in the global population of 198 ECOG PS 2 patients was 1.6 months (95 % confidence interval, 95% CI, 1.3–1.9), with a 6-month progression-free rate of 15.3% (Fig. 2A). These results were worse than the "pessimistic" scenario delineated for evaluating the primary endpoint (Supplementary Table 1). When assessing only the 155 patients who received active treatment, median PFS was 1.9 months (95% CI 1.6–2-2), with a 6-month progression-free rate of 17.5% (Supplementary Fig. 2A). We observed a significant difference in PFS between the five treatment groups (p < 0.001), as single agent IO and chemo-IO led to the best outcomes, with 6-months progression-free rate of 29.6% and 22.9%, respectively (Fig. 2B). The difference in PFS was statistically significant also if considering the four groups of active treatments (p = 0.013).

The median OS among the 198 patients was 2.8 months (95% CI 2.0–3.6), with a 6-month OS rate of 27.7% (Fig. 2C). Among the 155 patients receiving active treatment, median OS and 6-month OS rate were 3.5 months (95% CI 2.5–4.5) and 31.6%, respectively (Supplementary Fig. 2B). We observed a significant impact of the administered treatment on OS (p < 0.001), with 6-month OS rate of 39.4% and 30.9% in the single agent IO and chemo-IO groups, respectively (Fig. 2D). Of note, single-agent IO was the only treatment group to reach a 1-year OS rate of 20%. When considering the four groups of active treatments only, no difference in OS was found (p = 0.443).

The median number of first-line treatment courses was two (range 1–17 + ongoing). Out of 135 patients progressing on the first-line treatment, 19 (14%) received a second-line therapy, seven and 12 with a baseline ECOG PS at the time of second line of 1 and 2, respectively. The most frequently administered regimen was single agent CT, and radiological response were six partial responses (PR, 3/3 in patients receiving targeted agents), three stable diseases (SD), and five disease progressions, while additional five patients progressed clinically or died before the first radiological evaluation. Two patients received third-line therapy.

3.6. Evaluation of potential prognostic factors

We interrogated the potential impact of clinical and pathological characteristics on PFS and OS in the global population (Supplementary Table 4) and among patients receiving active treatment (Supplementary Table 5).

We did not observe differences in PFS and OS between patients whose poor PS contributed to disease burden (n = 177) or not (only comorbidities, n = 21) (Supplementary Fig. 3A-B, respectively p = 0.75 and p = 0.76), also when excluding patients candidate to BSC alone (Supplementary Fig. 3C-D).

A general trend towards better outcomes was observed in patients with PD-L1 ≥ 50 % (Supplementary Fig. 4), with statistical significance when assessing the PFS of all the patients included in the study (Supplementary Tables 4–5). Among the respective subgroups of patients with PD-L1 < 50 % and ≥ 50 %, the administered treatments retained a prognostic impact (Supplementary Fig. 5).

Clinico-pathological characteristics such as PS according to Karnofsky, histology (other vs adenocarcinoma), and N/L ratio impacted on PFS and/or OS in the global population (Supplementary Table 4). Yet, when extensively assessing those parameters in the 155 patients receiving active treatment, none influenced PFS outcomes, while a N/L ratio ≥ 3 (p = 0.045) and steroids at therapy start (p = 0.021) correlated with shorter OS (Supplementary Table 5, Supplementary Fig. 6). Nevertheless, these two factors were not independently affecting OS in the multivariable analysis (Supplementary Table 6).

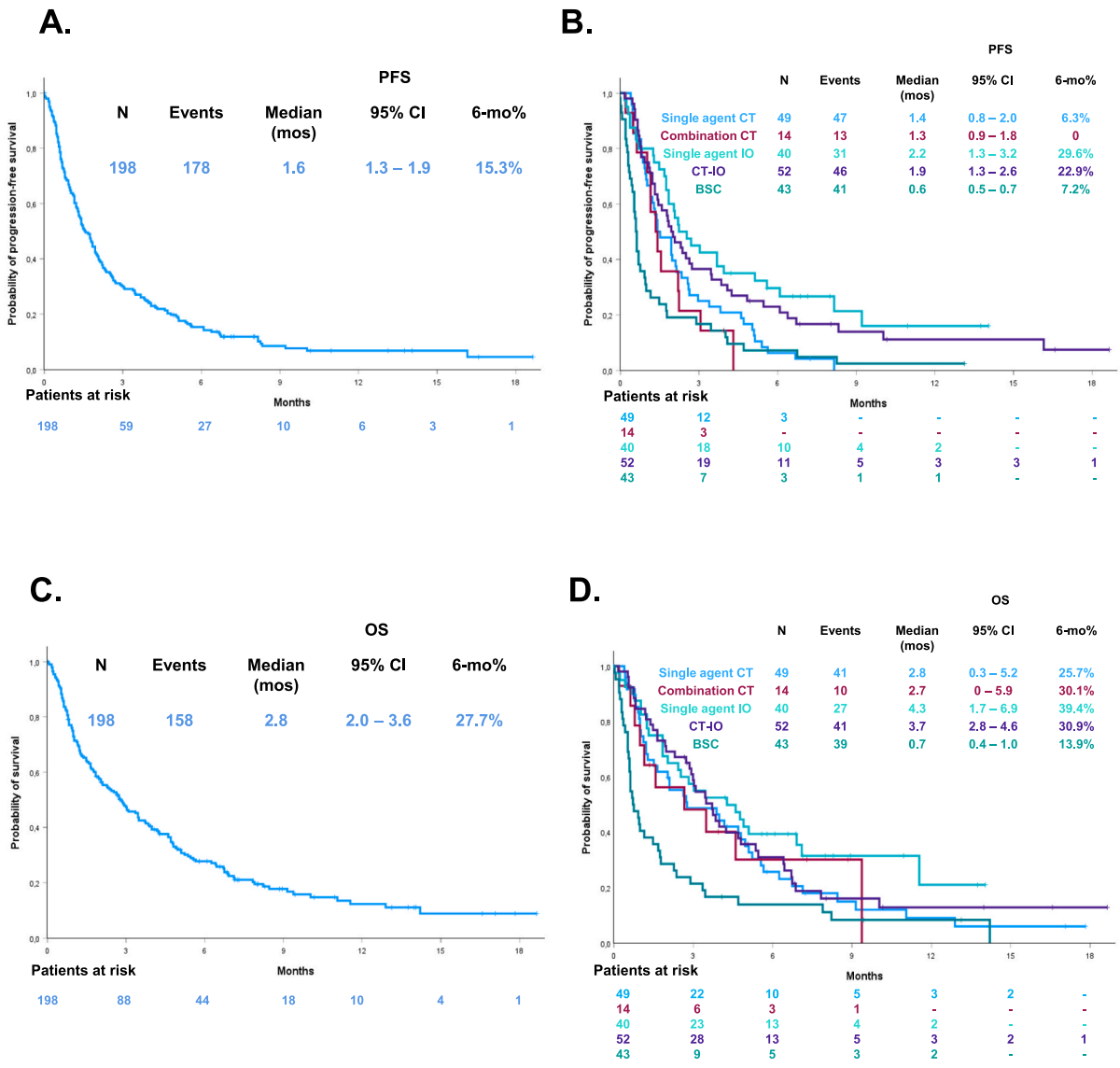


Fig. 2. PFS and OS in the whole population (A, C) and according to the treatment groups (B, D). PFS; Progression-free survival; mo: Month; 95% CI: 95% confidence interval; 6-mo%: 6-month rate; OS: Overall survival; BSC: Best supportive care; Single agent CT: Single agent chemotherapy; Combination CT: Platinum doublets; Single agent IO: Anti-PD-1/PD-L1 monotherapy; CT-IO: Chemo-immunotherapy combinations.

3.7. Disease responses across treatment groups

Radiological responses in 154 patients receiving active treatment were recorded (Table 3). Partial responses and stable diseases were observed in 16% and 12% of this population. Approximately half of the patients treated with either single agent CT or a combination CT experienced early clinical progression or death before the first radiological evaluation. The proportion of patients that did not undergo radiological evaluation was approximately a third when pooling single agent IO and CT-IO. IO-containing regimens were the only achieving a disease-control rate (SD + PR) > 25% ($p = 0.275$), and led to the highest radiological responses ($p = 0.022$). ECOG PS improvement was obtained in 10%, 0%, 26% and 12% of the patients receiving single agent CT, combination CT, single agent IO and CT-IO, respectively.

3.8. Safety

No safety issues emerged among the 155 patients receiving active treatments (Table 4). Among immune-related adverse events (irAEs), only diarrhea was observed in ≥ 10% of patients receiving IO-based regimens. Grade 3–4 irAEs were rare: one case each of pulmonary and hepatic toxicity in the chemo-IO group, and two cases of hypothyroidism in the single agent IO group.

4. Discussion

The introduction of regimens containing ICI in the first-line setting of non-oncogene addicted NSCLC has dramatically improved patients' outcomes. In patients with a poor PS, the evidence generated on ICI in dedicated prospective trials (resumed in Table 1) is thus far encouraging. The efficacy/toxicity ratio could indeed favor PD-1/PD-L1 inhibitors (with or without anti-CTLA-4 agents) over standard chemotherapy regimens in patients with ECOG PS 2. Our study on the other hand, prospectively evaluating an unselected population of patients with poor PS, revealed a category of patients heterogeneous in terms of treatment indications and clinical outcomes, that remained overall dismal.

Globally, less than half of the patients in our cohort received the recommended regimens for fit patients, *i.e.* single agent IO and CT-IO, for PD-L1 ≥ 50% and regardless of PD-L1 expression, respectively.

Table 3
Radiological responses and PS improvement.

	Clinical PD/death	PD	SD	PR	PS improvement
Total (n = 154)	62 (40%)	50 (32%)	18 (12%)	24 (16%)	21 (13%)
Single agent CT (n = 49)	24 (49%)	14 (28%)	9 (18%)	2 (4%)	5 (10%)
Combination CT (n = 14)	8 (57%)	4 (29%)	1 (7%)	1 (7%)	0 (0%)
Single agent IO (n = 40)	12 (30%)	13 (32%)	6 (15%)	9 (23%)	10 (26%)
CT-IO (n = 51)	18 (35%)	19 (37%)	2 (4%)	12 (24%)	6 (12%)

PD: Progressive disease; SD: Stable disease; PR: Partial response; PS: Performance status.
Single agent CT: Single agent chemotherapy; Combination CT: Platinum doublets; Single agent IO: Anti-PD-1/PD-L1 monotherapy; CT-IO: Chemo-immunotherapy combinations.

Table 4
Treatment-related adverse events.

	Single agent CT (n = 49)	Combination CT (n = 14)	Single agent IO (n = 39)	CT-IO (n = 52)
Patients experincing toxicities - any grade	26% (6%)	57% (29%)	26% (10%)	44% (13%)
Anemia	12% (0%)	29% (14%)	8% (0%)	25% (10%)
Neutropenia	4% (4%) *	14% (7%)	0% (0%)	11% (4%)
Thrombocytopenia	4% (2%)	14% (14%)	3% (3%)	10% (4%)
Nausea	14% (0%)	21% (7%)	0% (0%)	8% (0%)
Vomiting	4% (0%)	14% (7%)	3% (0%)	6% (0%)
Diarrhea	2% (0%)	0% (0%)	10% (3%)	12% (2%)
Anorexia	8% (0%)	21% (7%)	8% (0%)	17% (2%)
Asthenia	18% (0%)	29% (14%)	15% (0%)	25% (10%)
Fever	2% (0%)	21% (7%)	0% (0%)	6% (0%)

Events registered in ≥ 10 % of patients in at least one treatment group are reported. The incidence of grade 3–4 events is reported between brackets.
BSC: Best supportive care; single agent CT: Single agent chemotherapy; Combination CT: Platinum doublets; Single agent IO: Anti-PD-1/PD-L1 monotherapy; CT-IO: Chemo-immunotherapy combinations.
* One febrile neutropenia.

More than 20% of patients (43/198) were not considered fit for any kind of active treatment, and this could be an underestimation. Indeed, patient's consent was required to enter the study, and investigators could have encountered practical difficulties in obtaining a signed consent from patients candidate to BSC only (especially if evaluated in other services at the moment of diagnosis).

The presence of a PD-L1 expression ≥ 50% represented a strong incentive to administer single agent IO, and only 1/49 patients with PD-L1 ≥ 50% received CT-IO. Italian approval and reimbursement, restricting the use of CT-IO in cases with PD-L1 expression < 50%, could have discouraged physicians towards this choice, despite the possible "off-label" administration on a case-by-case basis for cases with PD-L1 expression ≥ 50%. Nevertheless, specifically questioned on the subject, investigators would have opted for CT-IO only in a minority of the cases with PD-L1 ≥ 50 % (27%), witnessing the preference towards single agent-IO in patients with poor PS. Despite CT-IO were the regimens more frequently adopted, a comparable number of patients received single agent CT, especially for PD-L1 < 50% and in cases with PD-L1 not performed, in this latter case likely because it would have not influenced treatment decisions.

The outcomes observed in the study population are objectively dismal, with median PFS and OS of 1.6 and 2.6 months, and corresponding 6-month rates of 15.3% and 27.7%, respectively. Despite the patients candidate to BSC only were conditioning these poor outcomes, the survival estimations did not dramatically change when evaluating only the 155 patients receiving active treatment (Supplementary Fig. 2). For reference, the outcomes observed in the pemetrexed monotherapy control arm in the trial by Zukin *et al* were as follows: median PFS 2.8 months, 6-months progression-free rate 18.4%, median OS 5.3 months and 6-month overall survival rate 44.9% [8].

In oncogene-addicted NSCLC, a poor PS at diagnosis can be substantially reverted by targeted agents, and even patients presenting with poor PS at diagnosis of extensive-stage SCLC have outcomes comparable to patients with good PS, likely due to the high chemosensitivity of the disease [24–27]. In stark contrast with these examples, the clinical evolution of the patients in our study was strongly impacted by their performance status. Given that ICI-containing regimens have not transformed the prognosis of these patients, conservative approaches with BSC only or single-agent chemotherapy are still valid options. These considerations should reassure clinicians that in front of a patient with advanced NSCLC and poor PS, the clinical judgment is likely the most important factor for addressing treatment choices.

Still, the best outcomes were observed in patients receiving IO-containing regimens, with a numerical superiority for single agent IO in patients with PD-L1 ≥ 50% (Fig. 2). The outcomes we observed for single agent IO are in line with the one we reported in our previous retrospective study dedicated to patients with ECOG PS and PD-L1 ≥ 50% receiving pembrolizumab [21]. In prospective trials including patients with lower PD-L1 expression, and having single agent IO as the most used regimens, the outcomes were more favorable (see Table 1), suggesting a global selection of patients even among the ones with poor PS.

We report here the first prospective data on CT-IO in patients with ECOG PS 2, in a population highly enriched for PD-L1 expression < 50%. The numerical better outcomes observed in patients receiving single agent IO, compared to the ones who received CT-IO, could lie on the prognostic/predictive role of high PD-L1 expression (*i.e.* ≥ 50%), required to receive single agent IO. Nevertheless, as our group and others have previously shown [13,21,28], patients who are highly symptomatic due to tumor burden have low probability of benefit from single agent IO. Therefore, dose-personalized CT-IO regimens could be considered when clinically possible and feasible according to approval and registration, even for patients with PD-L1 ≥ 50% in this category.

When exploring clinical and pathological elements potentially impacting on the outcomes of these patients, we were not able to detect any relevant element with an independent prognostic role. In our previous work on pembrolizumab in ECOG PS 2 patients with PD-L1 ≥ 50%, we documented that the presence of a cancer disease burden conditioning the poor PS is an independent prognostic factor [22]. In the present study, the lack of confirmation of this previous finding, can be explained by several reasons. Our previous retrospective work was dedicated to the precise population receiving pembrolizumab for PD-L1 ≥ 50%, and the proportion of patients with a disease burden conditioning the poor PS was lower compared to the current study (73% vs 89%). Thus, the low number of patients with a PS conditioned by comorbidities only in the present study (n = 21, 11%), as well as the variety of treatment administered, likely concur to the lack of confirmation of our previous finding.

The observation that half of the patients receiving mono CT or CT

combo, and a third of the ones receiving IO-based regimens, could not undergo a first radiological evaluation, is a further confirmation of the bad prognosis observed across this population. No relevant toxicity signals emerged from the analysis of the adverse events, suggesting that efficacy of the treatment regimens is the parameter of major interest for further studies in this patient population.

Real-world studies evaluating the effectiveness of ICI-containing regimens in first-line advanced NSCLC have shown outcomes comparable with clinical trials for patients with ECOG PS 0-1 [29,30]. Our prospective, observational study provide evidence on a population of patients with whose clinical management is more challenging. The main take-out from our data is that patients with advanced NSCLC and ECOG PS 2 represent a heterogeneous population in terms of treatment administered, and their outcomes remain poor. Conducting dedicated interventional clinical studies in this patient population is the only way to provide new treatment recommendation. Yet, the differential outcomes observed between our study and the majority of prospective trials evaluating ICI-bases regimens in patients with poor PS (Table 1) suggest that these latter are not always representative of the patient population itself. The only notable exception is represented by the poor outcomes reported with nivolumab and ipilimumab in the phase 3 Energy trial, enrolling patients candidate to a platinum doublet [16]. Moving from these premises, our data recommend caution in incorporating into the clinical practice the recent evidence generated by the randomized phase 3 trial IPSOS [10]. An intrinsic selection of patients enrolled in this registrational study could explain the median OS of around 10 months for patients with PS 2 in both the atezolizumab and mono-chemotherapy arms. We hope that a better and objective refinement of "performance status" (e.g. through the assessment of physical activity with wearable devices) [31,32], could help to stratify patients and help treatment decisions.

Our study has limitations. Defining a patient as having an ECOG PS 2 is *per se* subjective [33,34]. A multicenter study like the current one could therefore have included patients within a spectrum of poor PS, according to the subjective evaluation of treating physicians, and an independent confirmation by a second clinician was not requested. The time intervals for radiographic evaluations were not fixed, and their centralized, independent review was not performed, concurring to a variability in the estimations of PFS and disease responses. The number of patients included in the analyses, especially if considering the five treatment groups separately, was limited. Our estimation could therefore have been more precise if we had a larger population, and we could not perform an evaluation of prognostic factors within the treatment groups. The observational nature of this study precludes recommendations to be driven from our data. The approval of CT-IO combinations only for patients with PD-L1 expression $< 50\%$ in Italy could moreover have had an impact on treatment recommendations for patients with PD-L1 expression $\geq 50\%$. The limited number of registered adverse events could suggest some degree of under-reporting, as a strict data monitoring was not present in this observational, academic study.

Taken together, by assessing an unselected population of patients with NSCLC and PS 2 in the era of immunotherapy, we were led to the acknowledgment of its high clinical heterogeneity, in terms of treatment recommendations and clinical outcomes, that remain overall dismal. The clinical judgment should guide treatment choices, also aiming to avoid overtreatment of patients with an intrinsic poor prognosis.

CRediT authorship contribution statement

Francesco Facchinetti: Writing – original draft, Visualization, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Andrea Camerini:** Writing – review & editing, Validation, Resources, Investigation, Conceptualization. **Chiara Bennati:** Writing – review & editing, Validation, Resources, Investigation. **Paola Bordi:** Resources, Investigation. **Elisa De Carlo:** Resources, Investigation. **Francesca Mazzoni:** Validation, Resources, Investigation. **Giulio Metro:** Resources, Investigation. **Federica Bertolini:** Writing – review & editing, Validation, Resources, Investigation. **Lucia Longo:** Writing – review & editing, Visualization, Resources, Investigation. **Serena Ricciardi:** Resources, Investigation. **Sara Pilotto:** Resources, Investigation. **Donatella Giardina:** Validation, Resources, Investigation. **Francesco Passiglia:** Writing – review & editing, Visualization, Validation, Resources, Investigation. **Vieri Scotti:** Resources, Investigation. **Paolo Piacentini:** Resources, Investigation. **Stefano Frega:** Resources, Investigation. **Luana Calabrò:** Validation, Resources, Investigation. **Annalisa Guida:** Validation, Resources, Investigation. **Maria Antonietta Grosso:** Resources, Investigation. **Jenny Longobardi:** Resources, Investigation. **Alessandra Merlini:** Visualization, Validation. **Federica Cosso:** Resources, Investigation. **Alessandro Leonetti:** Writing – review & editing, Visualization, Validation, Resources, Investigation. **Eleonora Gariazzo:** Resources, Investigation. **Giorgia Guaitoli:** Resources, Investigation. **Lorenzo Belluomini:** Validation, Resources, Investigation. **Alessandra Bearz:** Resources, Investigation. **Michele Tognetto:** Software, Project administration, Funding acquisition, Formal analysis, Data curation. **Emilio Bria:** Writing – review & editing, Visualization, Validation, Supervision, Resources, Investigation, Conceptualization. **Diego Luigi Cortinovis:** Writing – review & editing, Visualization, Validation, Supervision, Resources, Investigation, Conceptualization. **Silvia Novello:** Writing – review & editing, Visualization, Validation, Supervision, Resources, Investigation, Conceptualization. **Massimo Di Maio:** Writing – review & editing, Visualization, Validation, Supervision, Software, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Marcello Tiseo:** Writing – review & editing, Visualization, Validation, Supervision, Resources, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization.

Funding

This study was sponsored by Gruppo Oncologico Italiano di Ricerca Clinica (GOIRC).

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Francesco Facchinetti declares speaker fee from Roche. Francesca Mazzoni declares advisory role for Merck Sharp & Dohme, Roche, Regeneron, AstraZeneca; travel grant from Roche. Giulio Metro declares speaker fees from Daichii-Sankyio, AstraZeneca, Takeda, Amgen. Federica Bertolini declares advisory role and speaker fees from Merck Sharp & Dohme, Regeneron, Amgen, Novartis, Astra Zeneca, Bristol Myers Squibb. Sara Pilotto declares honoraria/speaker fees from AstraZeneca, Eli Lilly, Bristol-Myers Squibb, Merck Sharp & Dohme, Takeda, Amgen, Regeneron, Pfizer, Pierre-Fabre, Boehringer Ingelheim, Novartis, and Roche. Francesco Passiglia declares consultant/advisory roles from AstraZeneca, Amgen, Johnson & Johnson, BeiGene, Pfizer, Novartis, Pharmamar, Merck Sharp & Dohme, Bristol Myers Squibb, ThermoFisher Scientific; institutional research grant from Roche. Alessandro Leonetti declares speaker fees from AstraZeneca, Bristol Myers Squibb, Merck Sharp & Dohme, Sanofi and Takeda; advisory role for AstraZeneca, BeiGene, Novartis and Sanofi; editorial activities sponsored by Eli Lilly, Novartis and Roche; travel support from MSD, Novartis, Roche and Takeda; research funding from AstraZeneca. Giorgia Guaitoli declares advisory/editorial roles for Roche, Amgen, Novartis; speaker fee from Roche. Emilio Bria declares speaker and/or travel fees from AstraZeneca, Bristol Myers Squibb, Eli Lilly, Novartis, Pfizer and Roche; financial support as a speaker from Takeda Oncology; institutional research grants from AstraZeneca and Roche; he serves on the Data Safety and Monitoring Board of Merck Sharp & Dohme for activities outside of the submitted work. Diego Luigi Cortinovis declares advisory board compensations from Roche, Bristol Myers Squibb, AstraZeneca, Merck Sharp

& Dohme, Beigene, Pfizer, Takeda, Boehringer Ingelheim, Amgen; speaker fees from Bristol Meyer Squibb, AstraZeneca, Merck Sharp & Dohme, Janssen/Johnson & Johnson. Silvia Novello declares speaker or advisory board fees from Eli Lilly, Merck Sharp & Dohme, Roche, Takeda, Pfizer, AstraZeneca, Amgen, ThermoFisher Scientific, Novartis, Sanofi, Janssen. Massimo Di Maio declares advisory board or consultancy honoraria from Amgen, AstraZeneca, GlaxoSmithKline, Janssen, Merck Serono, Merck Sharp & Dohme, Novartis, Pfizer, Roche, Takeda, Daiichi Sankyo, Ipsen and Viatris; direct research funding from Tesaro/GlaxoSmithKline; institutional funding for work in clinical trials/contracted research from BeiGene, Exelixis, Merck Sharp & Dohme, Pfizer and Roche. Marcello Tiseo declares speaker and consultant fees from AstraZeneca, Pfizer, Eli Lilly, Bristol Meyer Squibb, Novartis, Roche, Merck Sharp & Dohme, Boehringer Ingelheim, Otsuka, Takeda, Pierre Fabre, Amgen, Sanofi; institutional research grants from AstraZeneca and Boehringer Ingelheim. Other authors have no conflicts of interest to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.lungcan.2025.108580.

References

[1] M. Reck, J. Remon, M.D. Hellmann, First-line immunotherapy for non-small-cell lung cancer, *J Clin Oncol*. 40 (6) (2022) 586–597, https://doi.org/10.1200/JCO.21.01497.

[2] L.E. Hendriks, K.M. Kerr, J. Menis, et al., Non-oncogene-addicted metastatic non-small-cell lung cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up, *Ann Oncol*. 34 (4) (2023) 358–376, https://doi.org/10.1016/j.annonc.2022.12.013.

[3] I.F. Tannock, E. Amir, C.M. Booth, et al., Relevance of randomised controlled trials in oncology, *Lancet Oncol*. 17 (12) (2016) e560–e567, https://doi.org/10.1016/S1470-2045(16)30572-1.

[4] REF294_NLCA-Annual-Report-v20220113_FINAL.pdf. Accessed January 10, 2025. https://www.hqip.org.uk/wp-content/uploads/2022/01/REF294_NLCA-Annual-Report-v20220113_FINAL.pdf.

[5] T. Kawaguchi, M. Takada, A. Kubo, et al., Performance status and smoking status are independent favorable prognostic factors for survival in non-small cell lung cancer: a comprehensive analysis of 26,957 patients with NSCLC, *J Thorac Oncol*. 5 (5) (2010) 620–630, https://doi.org/10.1097/JTO.0b013e3181d2dcd9.

[6] C.J. Sweeney, J. Zhu, A.B. Sandler, et al., Outcome of patients with a performance status of 2 in Eastern Cooperative Oncology Group Study E1594: a Phase II trial in patients with metastatic nonsmall cell lung carcinoma, *Cancer*. 92 (10) (2001) 2639–2647, https://doi.org/10.1002/1097-0142(20011115)92:10<2639::aid-cncr1617>3.0.co;2-8.

[7] A. Friedlaender, G.L. Banna, L. Buffoni, A. Addeo, Poor-Performance Status Assessment of Patients with Non-small Cell Lung Cancer Remains Vague and Blurred in the Immunotherapy Era, *Curr Oncol Rep*. 21 (12) (2019) 107, https://doi.org/10.1007/s11912-019-0852-9.

[8] M. Zukin, C.H. Barrios, J.R. Pereira, et al., Randomized phase III trial of single-agent pemetrexed versus carboplatin and pemetrexed in patients with advanced non-small-cell lung cancer and Eastern Cooperative Oncology Group performance status of 2, *J Clin Oncol*. 31 (23) (2013) 2849–2853, https://doi.org/10.1200/JCO.2012.48.1911.

[9] A. Camerini, A. Del Conte, A. Pezzuto, et al., Selection Criteria and Treatment Outcome for Advanced Non-Small Cell Lung Cancer (NSCLC) Patients Unfit for Platinum-Based First-Line Therapy: Results of the MOON-OSS Observational Trial, *Cancers (Basel)*. 14 (24) (2022) 6074, https://doi.org/10.3390/cancers14246074.

[10] S.M. Lee, C. Schulz, K. Prabhash, et al., First-line atezolizumab monotherapy versus single-agent chemotherapy in patients with non-small-cell lung cancer ineligible for treatment with a platinum-containing regimen (IPSOS): a phase 3, global, multicentre, open-label, randomised controlled study, *Lancet*. 402 (10400) (2023) 451–463, https://doi.org/10.1016/S0140-6736(23)00774-2.

[11] G. Middleton, K. Brock, J. Savage, et al., Pembrolizumab in patients with non-small-cell lung cancer of performance status 2 (PePS2): a single arm, phase 2 trial, *Lancet Respir Med*. 8 (9) (2020) 895–904, https://doi.org/10.1016/S2213-2600(20)30033-3.

[12] K. Shaverdashvili, V. Reyes, H. Wang, et al., A phase II clinical trial evaluating the safety and efficacy of durvalumab as first line therapy in advanced and metastatic non-small cell lung cancer patients with Eastern Cooperative Oncology Group performance status of 2, *EClinicalMedicine*. 66 (2023) 102317, https://doi.org/10.1016/j.eclinm.2023.102317.

[13] M. Mark, P. Froesch, K. Gysel, et al., 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, *Eur J Cancer*. 200 (2024) 113600, https://doi.org/10.1016/j.ejca.2024.113600.

[14] V. Gounant, L. Greillier, C. Mascaux, et al., 1324P Durvalumab in treatment-naive, stage IV non-small cell lung cancer (NSCLC) patients (pts), with ECOG performance status (PS) 2-3 and high PD-L1 tumour expression: Results of IFCT-1802 SAVIMMUNE phase II trial, *Ann. Oncol.*. 35 (2024) S842, https://doi.org/10.1016/j.annonc.2024.08.1379.

[15] N.E. Ready, C. Audigier-Valette, J.W. Goldman, et al., First-line nivolumab plus ipilimumab for metastatic non-small cell lung cancer, including patients with ECOG performance status 2 and other special populations: CheckMate 817, *J Immunother Cancer*. 11 (2) (2023) e006127, https://doi.org/10.1136/jitc-2022-006127.

[16] H. Léna, L. Greillier, C. Cropet, et al., Nivolumab plus ipilimumab versus carboplatin-based doublet as first-line treatment for patients with advanced non-small-cell lung cancer aged ≥70 years or with an ECOG performance status of 2 (GFPC 08-2015 ENERGY): a randomised, open-label, phase 3 study, *Lancet Respir Med*. S2213–2600 (24) (2024) 00264–00269, https://doi.org/10.1016/S2213-2600(24)00264-9. Published Online October 29.

[17] L. Gandhi, D. Rodríguez-Abreu, S. Gadgeel, et al., Pembrolizumab plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer, *N Engl J Med*. 378 (22) (2018) 2078–2092, https://doi.org/10.1056/NEJMoa1801005.

[18] L. Paz-Ares, T.E. Ciuleanu, M. Cobo, et al., First-line nivolumab plus ipilimumab combined with two cycles of chemotherapy in patients with non-small-cell lung cancer (CheckMate 9LA): an international, randomised, open-label, phase 3 trial, *Lancet Oncol*. 22 (2) (2021) 198–211, https://doi.org/10.1016/S1470-2045(20)30641-0.

[19] L. Paz-Ares, A. Luft, D. Vicente, et al., Pembrolizumab plus Chemotherapy for Squamous Non-Small-Cell Lung Cancer, *N Engl J Med*. 379 (21) (2018) 2040–2051, https://doi.org/10.1056/NEJMoa1810865.

[20] M.E. Charlson, P. Pompei, K.L. Ales, C.R. MacKenzie, A new method of classifying prognostic comorbidity in longitudinal studies: development and validation, *J Chronic Dis*. 40 (5) (1987) 373–383, https://doi.org/10.1016/0021-9681(87)90171-8.

[21] F. Facchinetti, G. Mazzaschi, F. Barbieri, et al., First-line pembrolizumab in advanced non-small cell lung cancer patients with poor performance status, *Eur J Cancer*. 130 (2020) 155–167, https://doi.org/10.1016/j.ejca.2020.02.023.

[22] T.S.K. Mok, Y.L. Wu, I. Kudaba, et al., 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 (10183) (2019) 1819–1830, https://doi.org/10.1016/S0140-6736(18)32409-7.

[23] S. Gadgeel, D. Rodríguez-Abreu, G. Speranza, et al., Updated Analysis From KEYNOTE-189: Pembrolizumab or Placebo Plus Pemetrexed and Platinum for Previously Untreated Metastatic Nonsquamous Non-Small-Cell Lung Cancer, *J Clin Oncol*. 38 (14) (2020) 1505–1517, https://doi.org/10.1200/JCO.19.03136.

[24] E. Iwama, Y. Goto, H. Murakami, et al., Alectinib for Patients with ALK Rearrangement-Positive Non-Small Cell Lung Cancer and a Poor Performance Status (Lung Oncology Group in Kyushu 1401), *J Thorac Oncol*. 12 (7) (2017) 1161–1166, https://doi.org/10.1016/j.jtho.2017.02.012.

[25] T. Fukui, N. Mamesaya, T. Takahashi, et al., A Prospective Phase II Trial of First-line Osimertinib for Patients with EGFR Mutation-positive Non-small Cell Lung Cancer and Poor Performance Status (OPEN/TORG2040), *J Thorac Oncol*. S1556–0864 (24) (2025) 02548-6, https://doi.org/10.1016/j.jtho.2024.12.027. Published online January 2.

[26] M. Agarwal, A. Liu, D. Almquist, et al., Chemoimmunotherapy in patients with extensive-stage small cell lung cancer and a poor performance status, *Cancer*. 129 (22) (2023) 3546–3553, https://doi.org/10.1002/cncr.34966.

[27] M. Agarwal, A. Liu, B.T. Langlais, et al., Chemoimmunotherapy as the First-Line Treatment for Patients With Extensive-Stage Small-Cell Lung Cancer and an ECOG Performance Status 2 or 3, *Clin Lung Cancer*. 24 (7) (2023) 591–597, https://doi.org/10.1016/j.cllc.2023.05.005.

[28] M. Mark, P. Froesch, E.I. Eboulet, et al., SAKK 19/17: safety analysis of first-line durvalumab in patients with PD-L1 positive, advanced nonsmall cell lung cancer and a performance status of 2, *Cancer Immunol Immunother*. 70 (5) (2021) 1255–1262, https://doi.org/10.1007/s00262-020-02757-8.

[29] A. Cortellini, M. Tiseo, G.L. Banna, et al., Clinicopathologic correlates of first-line pembrolizumab effectiveness in patients with advanced NSCLC and a PD-L1 expression of ≥ 50, *Cancer Immunol Immunother*. 69 (11) (2020) 2209–2221, https://doi.org/10.1007/s00262-020-02613-9.

[30] A. Leonetti, F. Perrone, M. Puntoni, et al., Real-world outcomes of Italian patients with advanced non-squamous lung cancer treated with first-line pembrolizumab plus platinum-pemetrexed, *Eur J Cancer*. 202 (2024) 114006, https://doi.org/10.1016/j.ejca.2024.114006.

[31] K. Ito, Y. Suzuki, T. Sakaguchi, et al., Physical Activity Using a Wearable Device as an Alternative to Performance Status in Patients With Advanced Lung Cancer, *JAMA Oncol*. 10 (5) (2024) 648–651, https://doi.org/10.1001/jamaoncol.2024.0023.

[32] Y. Jo, S. Puri, B. Haaland, et al., Augmenting Prognostication: Utilizing Activity Trackers to Enhance Survival Prediction in Metastatic Non-Small Cell Lung Cancer,

Clin Lung Cancer. 26 (1) (2025) 29–38, https://doi.org/10.1016/j.cllc.2024.10.001.

[33] A. Malalasekera, C.S.Y. Tan, V. Phan, et al., Eastern Cooperative Oncology Group score: Agreement between non-small-cell lung cancer patients and their oncologists and clinical implications, *Cancer Treatment Communications*. 5 (2016) 17–21, https://doi.org/10.1016/j.ctrc.2015.11.009.

[34] R. Chow, C. Zimmermann, E. Bruera, J. Temel, J. Im, M. Lock, Inter-rater reliability in performance status assessment between clinicians and patients: a systematic review and meta-analysis, *BMJ Support Palliat Care*. 10 (2) (2020) 129–135, https://doi.org/10.1136/bmjspcare-2019-002080.