Lung Cancer 204 (2025) 108576

Contents lists available at ScienceDirect

Lung Cancer

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

Research Paper

Real-world outcomes of subsequent treatment strategies after durvalumab consolidation in stage III unresectable non-small cell lung cancer

Veronica Crespi [a,b], Marco Donatello Delcuratolo [a,c], Gabriele Minuti [d], Michele Montrone [e], Sara Pilotto [f], Elisa Roca [g], Giulio Metro [h], Alessandro Leonetti [i], Giacomo Pelizzari [j], Carlo Genova [k,l], Emanuela Olmetto [m], Diego Cortinovis [n], Alessandro Russo [o], Giulia Pasello [p,q], Alessandra Bulotta [r], Francesco Grossi [s], Roberta Buosi [t], Alessandro Del Conte [u], Claudio Sini [v], Carlo Greco [w,x], Alessandro Morabito [y], Daniele Pignataro [z], Maria Pagano [aa], Stefania Gori [ab], Diana Giannarelli [ac], Silvia Novello [a,*], Francesco Passiglia [a]

[a] Department of Oncology, University of Turin, S. Luigi Gonzaga Hospital, Orbassano, TO, Italy
[b] Medical Oncology Division, ASST dei Sette Laghi, Varese, Italy
[c] Medical Oncology Unit, Foundation IRCCS, Casa Sollievo della Sofferenza, San Giovanni Rotondo, FG, Italy
[d] Clinical Trial Unit: Phase 1 and Precision Medicine, National Cancer Institute, IRCCS, Regina Elena (IRE), Rome, Italy
[e] Medical Thoracic Oncologu Unit, IRCCS Isituto Tumori "Giovanni Paolo II", Bari, Italy
[f] Department of Engineering for Innovation Medicine University of Verona, Section of Oncology, Verona, Italy
[g] Thoracic Oncology, Lung Unit, P. Pederzoli Hospital, Peschiera Del Garda, Italy
[h] Medical Oncology Department, Ospedale S. Maria della Misericordia, Perugia, Italy
[i] Medical Oncology Unit, University Hospital of Parma, Parma, Italy
[j] Dipartimento di Oncologia di Udine, Azienda Sanitaria Universitaria Friuli Centrale, Udine, Italy
[k] UO Clinica di Oncologia Medica, IRCCS Ospedale Policlinico San Martino, Genoa, Italy
[l] Department of Internal Medicine and Medical Specialties, University of Genoa, Italy
[m] Radiation Oncology Unit, Azienda Ospedaliera Universitaria Careggi, Florence, Italy
[n] Fondazione IRCCS San Gerardo dei Tintori Monza, Monza, Department of Medicine, University of Milano-Bicocca, Milan, Italy
[o] Medical Oncology Department, Humanitas Istituto Clinico Catanese, Misterbianco, Catania, Italy
[p] Department of Surgery, Oncology and Gastroenterology, University of Padova, Italy
[q] Medical Oncology 2, Veneto Institute of Oncology IOV-IRCCS, Padova, Italy
[r] Department of Oncology, IRCCS Ospedale San Raffaele, Milan, Italy
[s] Department of Medicine and Technological Innovation, University of Insubria, Varese, Italy
[t] Oncology Unit, S. Spirito Hospital, Casale Monferrato, Italy
[u] Centro di Riferimento Oncologico di Aviano (CRO), National Cancer Institute, IRCCS, 33081 Aviano, Italy
[v] Medical Oncology, Ospedale Giovanni Paolo II - ATS Sardegna - ASSL Olbia, Olbia, Italy
[w] Department of Radiation Oncology, Fondazione Policlinico Universitario Campus Bio-Medico di Roma, Italy
[x] Università Campus Bio-Medico di Roma, Italy
[y] Thoracic Medical Oncology, National Cancer Institute "IRCCS Fondazione G Pascale," Naples, Italy
[z] Medical Oncology, Cardinal Massaia Hospital, Asti, Italy
[aa] Oncologia Medica, Azienda USL-IRCCS Reggio Emilia, Reggio Emilia, Italy
[ab] Department of Oncology, IRCCS Sacro Cuore Don Calabria Hospital, Negrar di Valpolicella, Verona, Italy
[ac] Fondazione Policlinico Universitario A. Gemelli, IRCCS - Facility of Epidemiology and Biostatistics, Rome, Italy

ARTICLE INFO

Keywords:
Stage III
Locally advanced
Unresectable
Immunotherapy
Rechallenge
Non-small cell lung cancer

ABSTRACT

Background: The PACIFIC trial established chemoradiation followed by 1-year durvalumab consolidation as standard of care for unresectable locally advanced non-small cell lung cancer (LA-NSCLC). This study aims to investigate therapeutic strategies and clinical outcomes after durvalumab failure in the real-world.
Materials and methods: Patients with stage III LA-NSCLC from 23 Italian centres were retrospectively enrolled at durvalumab progression. Subsequent treatments (Sub-Tx) were prospectively collected and classified as follows: chemo-immunotherapy (subgroup-1), platinum-based chemotherapy (subgroup-2), non-platinum-based chemotherapy (subgroup-3), and targeted therapy (subgroup-4). Durvalumab progression free survival (Dur-

* Corresponding author at: Department of Oncology, University of Turin, S. Luigi Hospital, Orbassano, TO, Italy.
E-mail address: silvia.novello@unito.it (S. Novello).

https://doi.org/10.1016/j.lungcan.2025.108576
Received 11 February 2025; Received in revised form 28 April 2025; Accepted 2 May 2025
Available online 3 May 2025

PFS) and overall survival (Dur-OS), as well as outcomes of Sub-Tx (Sub-PFS and Sub-OS) were estimated by using the Kaplan-Meier approach.
Results: A total of 122 patients were enrolled. Median Dur-PFS was 9.3 months (95 % CI: 7.1 – 11.4) and median Dur-OS 24.2 months (95 % CI: 18.7 – 29.7). Out of 93 patients receiving a Sub-Tx, 21.5 %, 43.0 %, 28.0 %, and 7.5 % were in the subgroup 1, 2, 3, and 4, respectively. Median Sub-PFS were 12.0, 4.1, 2.7, and 6.0 months, respectively. Patients who completed 12 months of durvalumab were 65.0 %, 27.5 %, 19.2 %, and 42.9 % across the four subgroups. In univariate analysis, the duration of durvalumab therapy was an independent factor for selecting Sub-Tx ($p < 0.007$). Median time to next treatment (TTNT) was 6.7 months with chemo-immunotherapy and 2.1 with chemotherapy ($p = 0.009$). Out of 15 patients with a TTNT > 1 year, 40 % were rechallenged with immunotherapy.
Conclusion: Platinum-based chemotherapy was the predominant treatment after durvalumab consolidation. Immunotherapy rechallenge was associated with the best survival outcome in selected cases, warranting further investigation.

1. Background

Lung cancer is the second most commonly diagnosed cancer in the United States, and with its estimated 124′730 deaths in 2025 it remains the leading cause of cancer mortality in both sexes [1]. More than 80 % of cases are non-small cell lung cancers (NSCLCs), and approximately one-third of them present with stage III at diagnosis [2,3].

Locally advanced NSCLC (LA-NSCLC) is a highly heterogeneous disease that often displays an intricate clinical profile and includes tumours with different prognosis and treatment options [4]. Multidisciplinary team discussion is mandatory to define the best personalised strategy considering the extent of the disease, the local expertise, and patient's comorbidities and preferences [5].

Most LA-NSCLC cases are classified as unresectable due to either high tumour burden or patient's characteristics [6]. Platinum-based chemotherapy administered concurrently or sequentially with radiotherapy has been the historical treatment for this setting, until the practice-changing PACIFIC trial established one-year consolidation immunotherapy with durvalumab as the current standard of care [6–8].

In PACIFIC, patients treated with durvalumab achieved a median progression-free survival (PFS) of 16.9 months (IC 95 % 13.0 – 23.9) and a median overall survival (OS) of 47.5 months (IC 95 %38.1 – 52.9) [9]. Durvalumab showed a manageable safety profile, and grade 3 or worse adverse events (AEs) occurred in 30 % of patient, with the most common severe AE being pneumonia (4 %) and 15 % of patients discontinuing study drug due to AEs [7]. Patients were included in PACIFIC irrespective of PD-L1 expression level, however optional pre-CRT archival tumour samples were tested retrospectively for 63 % of participants [7]. Antonia et al stratified those with available PD-L1 status at a tumour proportion score (TPS) 25 % cut-off, and pre-specified PD-L1 level did not affect durvalumab efficacy [7]. Later, the European Medicines Agency (EMA) mandated a post-hoc sub-group analysis according to PD-L1 TPS with a cut-off of 1 % and, based on the lack of meaningful benefit yielded by durvalumab in terms of OS in PD-L1 negative patients, restricted the use of durvalumab to PD-L1 positive LA-NSCLCs [10,11].

Despite the significant and meaningful survival benefit from durvalumab consolidation therapy, most patients eventually experience disease progression. In PACIFIC study, 50 % of patients progressed between the 12th and the 18th month from durvalumab initiation [6,7,9]. Durvalumab re-treatment was permitted for selected patients who completed 12 months of immunotherapy consolidation and progressed during the follow-up period without receiving another systemic anticancer therapy [9]. Overall, 34 of 476 (7.1 %) patients in the experimental arm were re-treated with immunotherapy, 4 of them (11.8 %) completed 12 months of treatment and 23 (67.6 %) early discontinued durvalumab [9]. A median time to second progression of 48 months was observed, with 34 % of patients being alive at 5 years [9]. Almost 50 % of patients in the durvalumab arm received at least 1 subsequent anticancer therapy: 33 % cytotoxic chemotherapy, 20 % radiotherapy, 13 % immunotherapy (primarily nivolumab or pembrolizumab), and 10 % other systemic therapies including tyrosine kinase inhibitors (TKIs) [9]. However, the efficacy of standard treatments in the recurrent disease is unknown.

This observational study was designed to describe the current real-world clinical practice in the post-durvalumab setting and to investigate the efficacy of different treatments and patients' outcomes following durvalumab consolidation failure.

2. Materials and methods

2.1. Study design and eligibility criteria

This is a multi-centre clinical study involving 23 Italian centres. We enrolled consecutive patients diagnosed with stage III LA-NSCLCs who progressed after standard of care chemoradiotherapy (CRT) and durvalumab consolidation.

Patients were included if they met to the following criteria: 1) adult patients aged ≥ 18 years with histological diagnosis of LA-NSCLC; 2) unresectable and candidates for definitive CRT according to a multidisciplinary team discussion as per local practice; 3) experiencing disease progression to durvalumab consolidation treatment at the time of enrolment or within the prior 6 months.

The primary objective of this observational study was to describe the treatment strategies and clinical outcomes after disease progression to durvalumab consolidation in the Italian real-world scenario. Secondary objectives were: 1) to evaluate efficacy outcomes of subsequent treatments after disease progression to durvalumab consolidation; 2) to describe clinical, pathological and molecular characteristics at initial diagnosis of LA-NSCLC patients who developed disease recurrence; 3) to describe the characteristics of the patients who early discontinued durvalumab consolidation therapy (i.e. within 12 months) due to disease progression or unacceptable toxicities; 4) to describe the clinical management and treatment strategies of LA-NSCLCs adopted in clinical practice from diagnosis to study enrolment, with the related efficacy and toxicity outcomes.

A retrospective-prospective cohort study design was chosen to address the primary and secondary objectives. Patients were recruited at disease progression to durvalumab consolidation therapy (also referred to as index date) or within 6 months after disease progression and followed up until data cut-off date (with the exception of patients that were prematurely discontinued or excluded from the study). For each patient, the retrospective follow-up window was comprised between the LA-NSCLCs cancer diagnosis and the enrolment date, while the prospective follow-up window was comprised between the index date and the end of the prospective observation period (Supplementary Fig. 1). Reasons for prematurely discontinuation of the prospective follow-up period were: a) informed consent withdrawal; b) death; c) loss to follow-up; d) pregnancy or breast-feeding; e) enrolment in studies imposing a specific patient's management strategy which does not correspond to the site's standard clinical practice. To reduce selection bias, also deceased patients and patients lost at follow up meeting the study eligibility criteria were included when the period between the

index date and the date of enrolment did not exceed 6 months.

In the retrospective phase (from initial stage III unresectable NSCLC diagnosis to durvalumab progression), participants were described with respect to clinical, pathological, and molecular characteristics, and information regarding CRT and durvalumab therapy were retrospectively collected.

In the prospective phase (after disease progression to consolidation durvalumab), real-world treatments were collected and classified based on specific drugs/strategies (i.e. chemo-immunotherapy, platinum-based chemotherapy, non-platinum-based chemotherapy, and targeted therapy). The first treatment used after progression was registered as first line treatment, and maintenance after doublet or triplet therapy was considered as part of the first line treatment. The initiation of a new systemic treatment for any reason was identified as second line. If participants experienced disease progression after second line therapy, the subsequent treatment strategy was considered as third line treatment. For each treatment line, the CRF included type of treatment, patient's ECOG performance status, start and end date, best response, and disease progression (when applicable). Last date of follow-up and, if applicable, date of death, was also collected for the study participants.

An electronic Case Report Form (CRF) was designed to record participants information and was completed by the study investigator for each patient enrolled in the study.

This observational study received approval by the ethics committee of the promoting center San Luigi Gonzaga Hospital under the protocol number of 97/2020. Approval was subsequently granted by the ethics committees of all the other participating Institutions.

2.2. Statistical analysis

A descriptive analysis was performed for the study participants.

Continuous variables were summarized using the median. Categorical variables were summarized using number of observations (n), absolute and relative frequency, and percentages of participants within the analysis set. All proportions were presented along with 95 % confidence intervals (CIs).

The statistical analysis included the set of the evaluable patients for the primary endpoint, defined as all subjects with confirmed progressive disease to durvalumab consolidation treatment at the time of enrolment or within the prior 6 months and with available information regarding the treatment strategies chosen after disease progression.

PFS after durvalumab consolidation therapy (also referred to as Dur-PFS) was measured from the initiation date of durvalumab until the occurrence of either disease progression (i.e. index date) or death from any cause, whichever occurred first. Radiological recurrence was evaluated by using the Response Evaluation Criteria in Solid Tumours version 1.1 (RECIST 1.1) [12]. Overall survival of consolidative durvalumab therapy (also referred to as Dur-OS) was calculated from the initiation of consolidative durvalumab therapy until patients' death from any cause.

PFS after subsequent treatment strategies in post-durvalumab setting (also referred to as Sub-PFS) was measured from the start date of systemic therapy post consolidative durvalumab treatment until the occurrence of either lung cancer progression or death from any cause, whichever came first. Treatment response to the subsequent strategies after progression to durvalumab consolidation was assessed as per investigator's review according to the RECIST 1.1 and reported as complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD) [12]. Overall survival of subsequent treatment strategies after durvalumab progression (also referred to as Sub-OS) was defined as the length of time between the index date and the time of death of any cause.

Survival analysis were performed for durvalumab consolidation therapy and first line treatment to estimate the median time to event occurrence by Kaplan-Meier method. Treatments were stratified according to either main drug or therapeutic class for each line. Median and two-sided 95 % CIs were calculated, and Kaplan-Meier plots for both PFS and OS (i.e. Dur-PFS, Dur-OS, Sub-PFS, and Sub-OS) were provided as appropriate. Patients not experiencing the event of interest or lost to follow-up were censored at the time of database lock (i.e. 20 August 2024), while patients experiencing the event of interest were considered as failures and excluded from the analysis.

Adverse events were recorded and graded according to The Common Terminology Criteria for Adverse Events (CTCAE) developed by the US National Cancer Institute (NCI) version 5.0 [13].

All statistical analyses were performed using the R (version 4.0.2, R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was defined as a 2-tailed p-value of < 0.05.

3. Results

3.1. Retrospective phase: From CRT initiation to durvalumab progression

From November 2021 to September 2024, a total of 122 patients with LA-NSCLCs who received CRT followed by durvalumab consolidation and experienced disease progression were included in the study. Participants' baseline characteristics are summarised in Table 1. The median age was 67 (range 62 – 73). Most of them presented with a stage IIIA (41.0 %) or stage IIIB (45.9 %) disease at the time of initial diagnosis, and histology was homogeneously represented, with 61 patients (50.0 %) affected by squamous and 59 patients (48.4 %) by non-squamous subtype. PD-L1 status was reported for 117 patients, 76 of

Table 1
Baseline patients characteristics.

Baseline characteristics	All Patients n = 122 (%)
Age	
(years, range)	67 (62 – 73)
Gender	
Female	28 (23.0)
Male	94 (77.0)
Smoking status	
Never	7 (5.7)
Current	71 (58.2)
Former	43 (35.2)
Unknown	1 (0.8)
ECOG PS	
0	51 (41.8)
1	58 (47.5)
2	10 (8.2)
Unknown	3 (2.5)
Histology	
Squamous	61 (50.0)
Non-squamous	59 (48.4)
Unknown	2 (1.6)
Stage	
IIIA	50 (41.0)
IIIB	56 (45.9)
IIIC	14 (11.5)
Unknown	2 (1.6)
PD-L1 level	
1–49 %	76 (62.3)
50–100 %	41 (33.6)
Unknown	5 (4.1)
PD-L1 assay	
SP263 assay (Ventana)	37 (30.3)
22C3 assay (pharmDx)	37 (30.3)
E1L3N assay (AmoyDx)	2 (1.6)
Unknown	46 (37.8)
Driver mutation	
KRAS	23 (18.8)
braf	5 (4.1)
EGFR	2 (1.6)
ALK	2 (1.6)
ROS1	1 (0.8)
METex14	1 (0.8)

Note: ECOG PS = performance status according to Eastern Cooperative Oncology Group; PD-L1 = programmed-death ligand 1.

them presenting a PD-L1 TPS between 1 and 49 %, and 34 patients (27.9 %) harboured a molecular alteration (see Supplementary Table 1).

A detailed description of retrospective phase treatments (i.e. CRT and durvalumab) and outcomes is reported in the Supplementary Tables 2-5. With respect to CRT, 59 patients had concomitant modality treatment (48.4 %), and 61 patients (50.0 %) received it sequentially. Median time from RT end to durvalumab initiation was 37 days. For most patients (62, 50.8 %), the RECIST-defined best response to durvalumab treatment was SD. As for the others, 23 patients (18.9 %) had a PR, 33 patients (27.0 %) a PD, and for 4 patients (3.3 %) the information was unknown. Median durvalumab treatment duration was 8.1 months (IQR: 6.6 – 9.5 months), with 41 participants (33.6 %) completing 12 months of consolidation. As for the remaining patients, 68 (55.7 %) discontinued durvalumab for disease progression after a median treatment duration of 5.6 months (IQR: 3.7 – 8.5); 12 patients (9.8 %) owing to AEs, and 1 patient (0.8 %) for a PD-related death. In our cohort median Dur-PFS was 9.3 months (95 % CI: 7.1 – 11.4) and median Dur-OS was 24.2 months (95 % CI: 18.7 – 29.7), respectively (Fig. 1).

Overall, 69 patients developed disease progression at a single site (38.5 % of those had a loco-regional relapse and 14.8 % a distant relapse), 20 patients (16.4 %) at multiple sites, and 33 patients (27.0 %) had this information missing. Only 6 patients continued durvalumab beyond progression whilst receiving locoregional treatments at the site of oligo-progression (lung, brain, and mediastinal lymph nodes) (see Supplementary Table 4).

In total, 21 patients (17.2 %) presented a grade 3 or 4 immune-mediated AE, with pneumonitis and gastrointestinal toxicity being the most common events (6 patients each, 4.9 % of the overall cohort). A detailed description of durvalumab adverse events is reported in the Supplementary Table 5.

In the univariate analysis, the median PFS was not influenced by standard baseline characteristics, e.g. histology, stage, or chemo-radiotherapy treatment strategies. Also, standard NSCLC prognostic factors (PD-L1 expression level, LDH or NLR) did not impact on patients' PFS. Since more than a half of our patients discontinued durvalumab for disease progression, durvalumab duration (less than or equal to 12 months) significantly correlated with PFS (HR 0.18, 95 % CI: 0.12–0.29, $p < 0.001$) (see Supplementary Table 6).

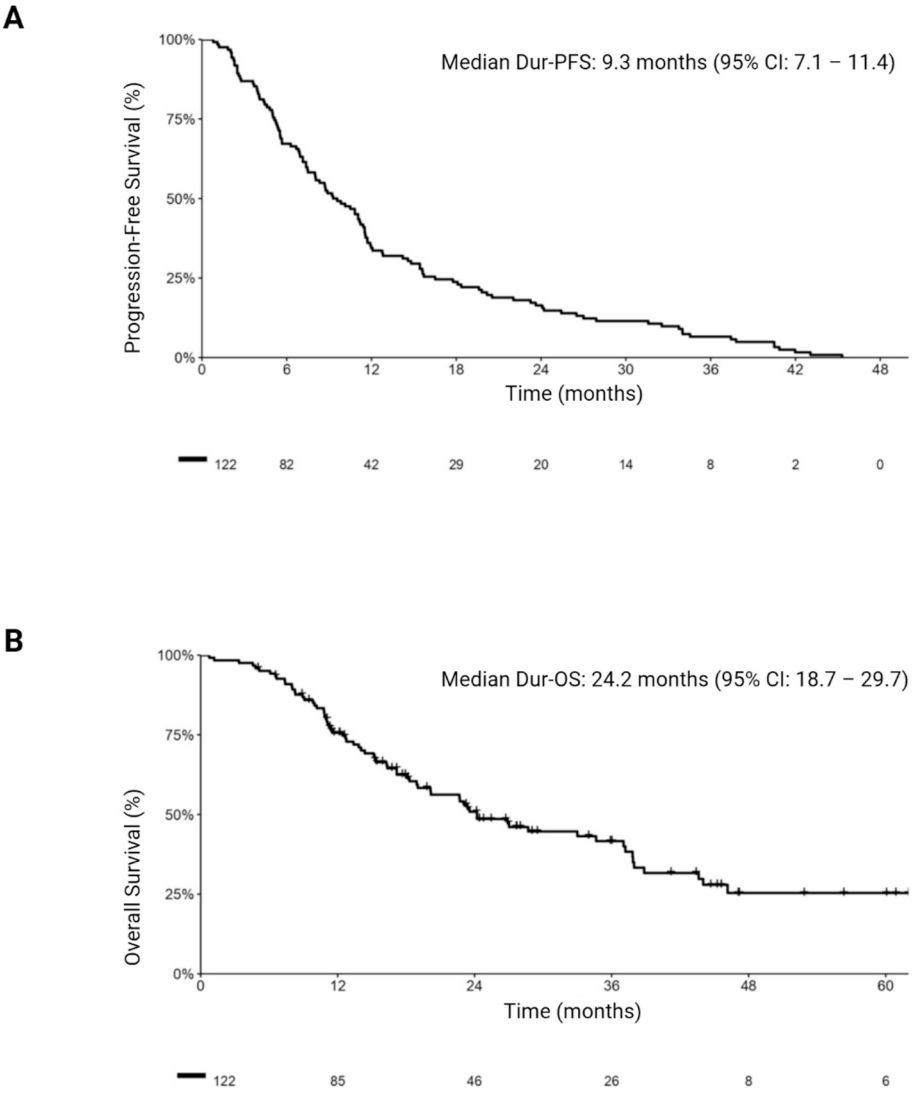

Fig. 1. Kaplan-Meier survival curves showing: A) progression free survival (Dur-PFS) and B) overall survival (Dur-OS) from durvalumab start date in all patients (N = 122). Note: Dur-OS = overall survival calculated from durvalumab start date; Dur-PFS = progression free survival calculated from durvalumab start date; 95 % CI = 95 % confidence interval.

4. Prospective phase: Treatment strategies following durvalumab progression

4.1. Patients' characteristics and treatments

After progression to durvalumab consolidation, 95 of 122 patients (77.8 %) received a subsequent systemic treatment. Of those, one patient treated with a single agent immunotherapy and one patient receiving a chemotherapy not otherwise specified were excluded from the subsequent analysis. Therefore, 93 patients (76.2 %) were available for the prospective phase analysis.

Patients were divided into 4 subgroups according to the specific type of treatment received: 1) chemo-immunotherapy (20, 21.5 %); 2) platinum-based chemotherapy (40, 43 %); 3) non-platinum-based chemotherapy (26, 28 %); 4) targeted therapy (7, 7.5 %) (see Supplementary Tables 7–10). The baseline patients' characteristics stratified by subsequent treatment strategies are reported in Table 2. In our cohort, gender, age, and durvalumab duration were independent factors for the selection of subsequent strategies after durvalumab progression. In particular, patients who received chemo-immunotherapy as subsequent therapy were more likely to have completed 12 months of durvalumab consolidation (65.0 % vs 35.0 %). Conversely, patients treated with platinum-based chemotherapy and non-platinum-based chemotherapy were more likely to have early discontinued durvalumab (72.5 % and 80.8 % of each subgroup, respectively). Patients included in the targeted therapy subgroup were homogeneously distributed for durvalumab duration (3 patients completed consolidation treatment, and 4 patients early interrupted durvalumab). Also, patients in the targeted therapy subgroup had a median age of 62 years (range 57 – 68), whereas patients in non-platinum-based subgroup had a median age of 73 years (range 65 – 77). Other baseline characteristics, (specifically ECOG, PD-L1 expression level, NLR, and onset of severe immune-mediated AEs) were similar between the four subgroups. Lastly, considering the subgroup of patients who did not receive any subsequent treatment (N = 27), 66.7 % of patients did not complete durvalumab consolidation therapy.

Table 2
Patients' characteristics stratified by subsequent treatment strategies.

Baseline char.	Chemo-ICI	PB chemo	Non-PB chemo	TT	P value
Age (years, range)	69 (66–71)	66 (63–72)	73 (65–77)	62 (57–68)	0.039
Gender					0.031
Female	5 (25.0)	11 (27.5)	4 (15.4)	5 (71.4)	
Male	15 (75.0)	29 (72.5)	22 (84.6)	2 (28.6)	
ECOG					0.44
0	11 (55.0)	16 (40.0)	9 (34.6)	5 (71.4)	
1	7 (35.0)	19 (47.5)	13 (50.0)	1 (14.3)	
2	1 (5.0)	2 (5.0)	3 (11.5)	1 (14.3)	
Unknown	1 (5.0)	3 (7.5)	1 (3.8)	0	
Durva duration					0.007
12 mo	13 (65.0)	11 (27.5)	5 (19.2)	3 (42.9)	
< 12 mo	7 (35.0)	29 (72.5)	21 (80.8)	4 (57.1)	
G3-4 IR AEs					0.96
Yes	3 (15.0)	5 (12.5)	4 (15.4)	1 (14.3)	
PD-L1					0.67
1–49 %	11 (64.7)	26 (65.0)	17 (68.0)	3 (42.9)	
50–100 %	6 (35.3)	14 (35.0)	8 (32.0)	4 (57.1)	
NLR					0.76
< 3	7 (36.8)	15 (42.9)	5 (21.7)	3 (42.9)	
≥ 3	12 (63.2)	20 (57.1)	18 (78.3)	4 (57.1)	

Note: char. = characteristics; durva = durvalumab; ECOG = Eastern Cooperative Oncology Group performance status; ICI = immune check point inhibitor; IR AEs = immune-related adverse events; mo = months; PB = platinum-based; PD-L1 = programmed-death ligand 1; TT = targeted therapy.

4.2. Median time to next treatment

The median time from durvalumab discontinuation to subsequent line treatment initiation (i.e. time to next treatment, TTNT) was 6.7 months for group 1, 2.1 months for group 2, 1.7 months for group 3 and 5.9 months for group 4, respectively.

A long-rank test using Cox proportional hazard model compared the subgroup of patients treated with chemo-immunotherapy (subgroup 1, N = 20) with the one treated with chemotherapy, irrespective of it being platinum-based or non platinum-based (subgroup 2 and 3, N = 66). Median TTNT was 6.7 months for patients treated with chemo-immunotherapy and 2.1 months for patients treated with chemotherapy and the difference was statistically significant (p = 0.009).

Overall, 15 of 93 patients (16.1 %) commenced the first line treatment more than 1 year after the end of durvalumab consolidation. They were not homogeneously distributed between the 4 subgroups: 8 of 20 patients (40 %) treated with chemoimmunotherapy; 4 of 40 patients (10.5 %) treated with platinum-based chemotherapy; 2 of 26 patients (7.7 %) treated with non-platinum-based chemotherapy; 1 of 7 (14.3 %) of patients treated with targeted therapy.

4.3. Survival outcomes according to subsequent treatments

The median Sub-PFS and Sub-OS for the 93 patients receiving any subsequent treatment were 4.1 months (95 % CI: 2.3–5.9) and 9.0 months (95 % CI: 6.7–11.3), respectively (Fig. 2).

After stratification according to subsequent treatment subgroup, the median Sub-PFS was 12.0 months (95 % CI: 1.6 – 22.4) in the immunotherapy-containing therapy group, 4.1 months (95 % CI: 2.7 – 5.5) in the platinum-based chemotherapy group, 2.7 months (95 % CI: 1.9 – 3.5) in the chemotherapy non-platinum-based group, and 6.0 months (95 % CI: 0 – 15.0) in the targeted therapy subgroup (Fig. 3).

The median Sub-OS was 12.1 months (95 % CI: 4.5 – 19.6) in the chemo-immunotherapy group, 9.8 months (95 % CI: 6.1 – 11.9) in the platinum-based chemotherapy group, 6.8 months (95 % CI: 0 – 13.8) in the chemotherapy non-platinum-based group, and 6.8 months (95 % CI: not evaluable) in the targeted therapy subgroup (Fig. 3).

4.4. Further treatment strategies

Out of the 93 patients treated with first line subsequent therapy, 28 (30.1 %) received a second line treatment after further disease progression (mostly single agent cytostatic treatment). Of those, 12 patients (12.9 % of the cohort treated after durvalumab) received a third line treatment (*See* Supplementary Tables 11 and 12). The Sankey diagram (Fig. 4) represents the distribution of second and third line treatments according to the specific therapy received upfront.

5. Discussion

This study investigated the selection of subsequent treatment strategies for stage III LA-NSCLC patients with disease progression after durvalumab consolidation therapy in the Italian real-world scenario. Currently, a standard subsequent treatment in patients recurring after durvalumab has not yet been established. In this clinical context, available treatment options are limited due to prior administration of platinum doublet chemotherapy and immunotherapy, and the efficacy of standard first line treatments for metastatic NSCLC remains uncertain.

To the best of our knowledge, reports of real-world data of subsequent treatments after durvalumab consolidation therapy are scarce. In the PACIFIC trial, durvalumab re-treatment was permitted for patients who achieved a disease control at completion of the 12-month consolidation period [7]. Also, in the 5-year follow-up analysis, authors reported that nearly 50 % of patients received a subsequent anticancer therapy after discontinuation of durvalumab, however details of the treatment regimens were not specified [9]. Previous retrospective

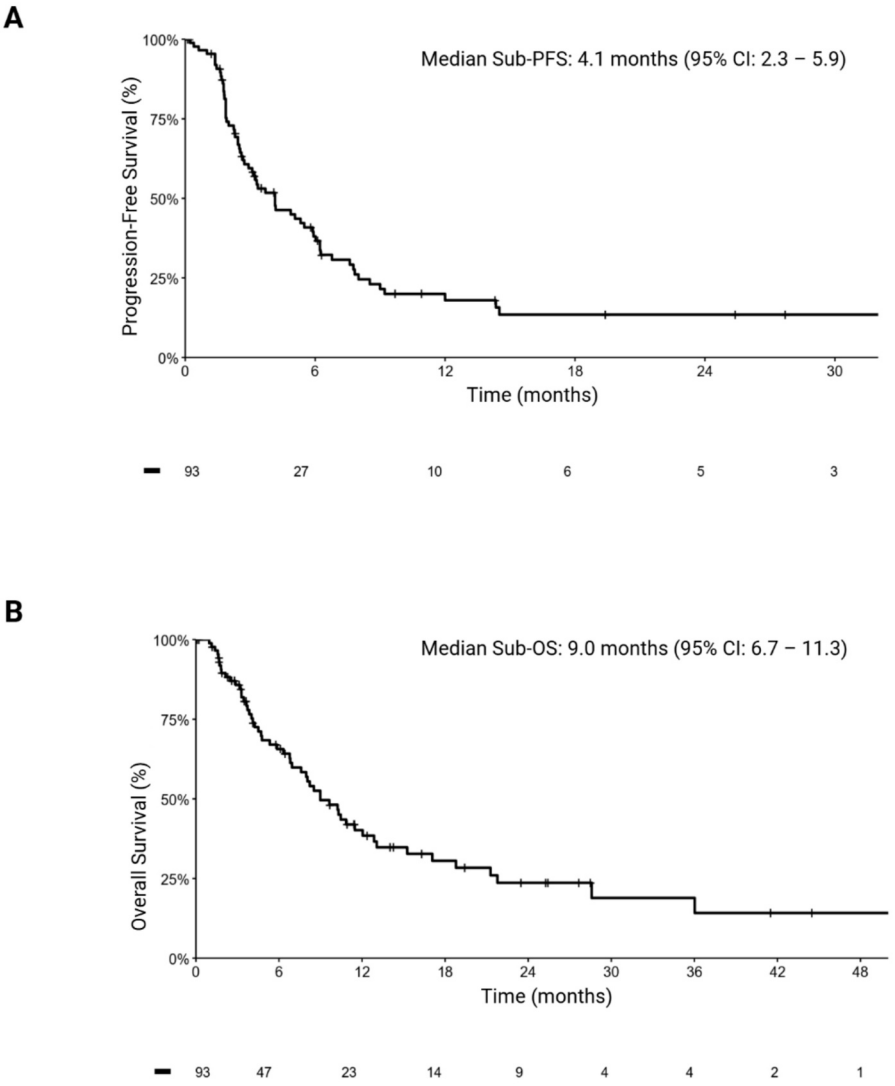

Fig. 2. Kaplan-Meier survival curves showing: A) progression free survival (Sub-PFS) and B) overall survival (Sub-OS) from any subsequent treatment start date in all patients (N = 93). Note: Sub-OS = overall survival calculated from subsequent treatment start date; Sub-PFS = progression free survival calculated from subsequent treatment start date; 95 % CI = 95 % confidence interval.

studies population showed that platinum-based chemotherapy was the most frequently administered subsequent treatment [14,15]. Another retrospective study in the Japanese population showed that patients with a durvalumab PFS longer than 1 year had a significantly longer median second PFS from first line treatment than those with a shorter PFS (13.2 vs 4.7 months, HR 0.45) [16]. More recently, Cortiula et al conducted a retrospective multicenter study on a cohort of 197 patients treated after durvalumab consolidation progression [17]. Authors observed that those receiving an ICI-containing treatment had statistically significant longer median PFS and OS as compared to those treated with chemotherapy alone [17]. Also, patients with a durvalumab PFS longer than 1 year experienced a significantly longer median OS when treated with immunotherapy rather than chemotherapy alone (14.6 vs 8.9, HR 0.61) [17].

In our study, we recruited 122 patients progressing to durvalumab consolidation, 93 of which received a subsequent anticancer treatment. The median Sub-PFS and Sub-OS of the overall cohort were 4.1 and 9.0 months, respectively, thus very similar to the previously reported studies [17]. Aligning with the previous findings, we observed that platinum-based chemotherapy was the predominant subsequent therapy after failure of durvalumab maintenance (adopted in nearly 45 % of patients), followed by non-platinum-based chemotherapy (administered to approximately 30 % of patients), with docetaxel, vinorelbine and pemetrexed being the favoured single agents [14,15]. Overall, up to 21 % of patients received chemo-immunotherapy, and only 7 patients were treated with a targeted agent.

Some reports have evaluated the significance of re-treatment with ICI in metastatic NSCLC population [18,19]. Schoenfeld et al. recommend that patients who discontinued immunotherapy for reasons other than disease progression should be retreated with PD-1/PD-L1 blockade, if the free-interval from the prior administration is longer than 6 months [19]. The aforementioned study in the post-durvalumab setting observed that the proportion of patients receiving rechallenge with immunotherapy was higher among the group with longer PFS after durvalumab consolidation [14]. Cortiula et al observed that durvalumab consolidation was discontinued more often due to progressive disease in patients treated with chemotherapy alone as compared to the immunotherapy-containing group [17]. In our study, we observed that durvalumab duration was an independent factor for selection of subsequent strategies at durvalumab progression. Patients re-challenged with immunotherapy were more likely to have completed the 12 months of consolidation with durvalumab. Conversely, the sub-groups of patients

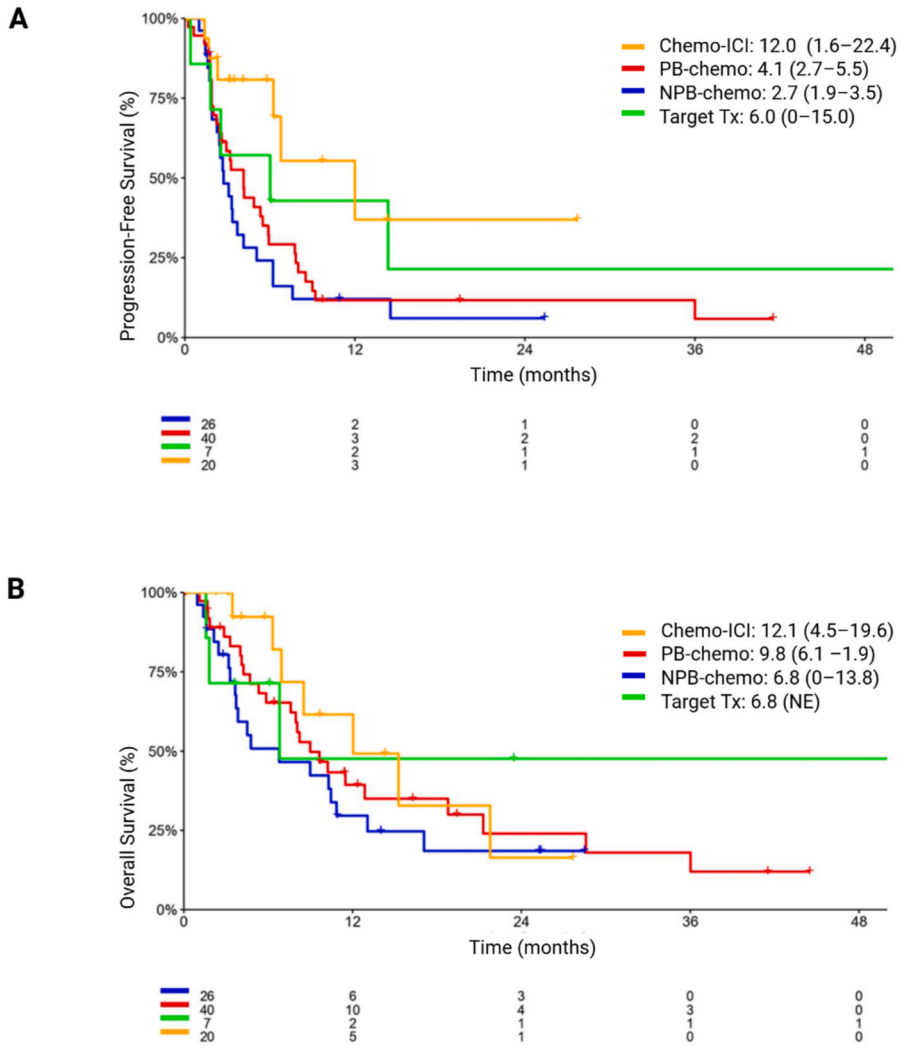

Fig. 3. Kaplan-Meier survival curves showing A) progression free survival from start date of subsequent treatments (Sub-PFS) and B) overall survival from start date of subsequent treatments (Sub-OS) stratified by treatment subgroup. Note: Chemo-ICI (yellow line) = chemo-immunotherapy; NE = not evaluable; NPB-chemo (blue line) = non-platinum-based chemotherapy; PB-chemo (red line) = platinum-based chemotherapy; Target Tx (green line) = target therapy. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

treated with chemotherapy alone (either platinum-based or non-platinum-based) and the proportion of those who did not receive any subsequent treatment mostly comprised participants who early discontinued durvalumab for disease progression or unacceptable immune-mediated toxicities. Thus, median TTNT was shorter in patients treated with chemotherapy (irrespective of containing a platinum agent or not) as compared to those who received chemo-immunotherapy. Also, among the 15 patients who recurred more than one year after the end of durvalumab consolidation, re-administration of immunotherapy combined with platinum-based chemotherapy was the most common treatment strategy. Therefore, the choice of immunotherapy rechallenge may depend on the duration on durvalumab consolidation and on the free interval from progression. Interestingly, in our cohort, only 1 patient was rechallenged with a single agent immunotherapy, even though approximately 30 % had a PD-L1 equal to or greater than 50 at diagnosis and none of them underwent tissue re-biopsy for molecular testing and PD-L1 assessment at durvalumab failure.

Our study found an association between the type of first line treatment strategy and survival outcomes. Patients treated with ICI-combined regimens had a longer median Sub-PFS (12 months) as compared to the second PFS observed in the other subgroups. Also, Sub-OS of this subgroup, measured from the start of first line treatment, was longer. As expected, non-platinum-based chemotherapy group had the shortest Sub-PFS (only 2.7 months) and Sub-OS (6.8 months). Therefore, despite the failure of immunotherapy as post-CRT maintenance, ICI re-treatment might be an option, though clinical biomarkers to predict the outcomes of immunotherapy is yet to be identified. Also, similarly to the results of Stalker et al, we observed that an intensified first line treatment with a triplet, quadruplet or doublet therapy confers the best outcomes [15].

We acknowledge that this study has several limitations. As expected, the median Dur-PFS of 9.3 months and Durv-OS of 24.2 months of our cohort were shorter than the outcomes reported in PACIFIC [7,9]. Indeed, our cohort was entirely constituted of a real-world population that eventually progressed during or after completion of durvalumab consolidation and the main aim of our study was focusing on subsequent lines of treatment. Therefore, it does not allow to depict the Italian real-world outcomes of durvalumab consolidation therapy. For its retrospective nature, the possibility of biases in patients' and treatments' selection could not be ruled out. In addition, differences in patient characteristics might have influenced the treatment outcomes of subsequent therapy in each treatment regimen. Also, the number of participants in each subsequent treatment subgroup, especially in patients who received a targeted therapy, was not sufficient to adequately

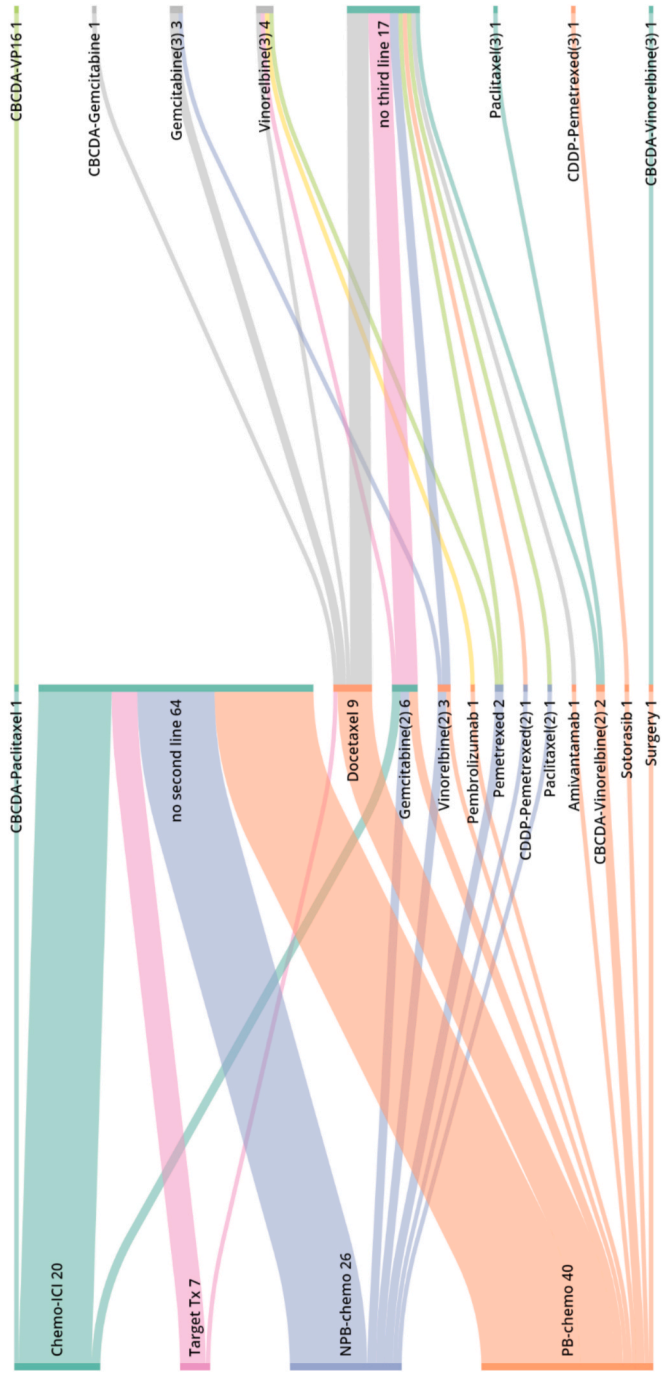

Fig. 4. Sankey diagram of treatment strategies in patients who underwent first, second and third-line treatment. Note: (2) second line therapy; (3) third line therapy; Chemo-ICI = chemo-immunotherapy; NPB-chemo = non-platinum-based chemotherapy; PB-chemo = platinum-based chemotherapy; TargetTx = targeted therapy.

compare in terms of statistical significance the differences in PFS and OS. Lastly, our targeted treatment group was not homogeneous, including only 7 patients treated with 5 different TKIs, whose efficacy cannot be accurately measured.

Despite its limitations, this is one of the few studies that tries to depict the patterns of treatments and outcomes in the real-world post-durvalumab setting, that still represents and unanswered question of the post-PACIFIC era. Further prospective studies (as the CONDOR trial, NCT05568212) with an adequate number of cases to identify predictive factors for a more tailored treatment approach are warranted.

CRediT authorship contribution statement

Veronica Crespi: Writing – review & editing, Writing – original draft, Investigation, Data curation. **Marco Donatello Delcuratolo:** Writing – review & editing, Investigation, Data curation, Conceptualization. **Gabriele Minuti:** Writing – review & editing. **Michele Montrone:** Writing – review & editing, Investigation. **Sara Pilotto:** Writing – review & editing, Investigation. **Elisa Roca:** Writing – review & editing, Investigation. **Giulio Metro:** Writing – review & editing, Investigation. **Alessandro Leonetti:** Writing – review & editing, Investigation. **Giacomo Pelizzari:** Writing – review & editing, Investigation. **Carlo Genova:** Writing – review & editing, Investigation. **Emanuela Olmetto:** Writing – review & editing, Investigation. **Diego Cortinovis:** Writing – review & editing, Investigation. **Alessandro Russo:** Writing – review & editing, Investigation. **Giulia Pasello:** Writing – review & editing, Investigation. **Alessandra Bulotta:** Writing – review & editing, Investigation. **Francesco Grossi:** Writing – review & editing, Investigation. **Roberta Buosi:** Writing – review & editing, Investigation. **Alessandro Del Conte:** Writing – review & editing, Investigation. **Claudio Sini:** Writing – review & editing, Investigation. **Carlo Greco:** Writing – review & editing, Investigation. **Alessandro Morabito:** Writing – review & editing, Investigation. **Daniele Pignataro:** Writing – review & editing, Investigation. **Maria Pagano:** Writing – review & editing, Investigation. **Stefania Gori:** Writing – review & editing, Investigation. **Diana Giannarelli:** Methodology, Formal analysis, Data curation. **Silvia Novello:** Writing – review & editing, Supervision, Conceptualization. **Francesco Passiglia:** Writing – review & editing, Validation, Supervision, Project administration, Methodology, Investigation, Data curation, Conceptualization.

Funding

None.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

None.

Disclosures.

Gabriele Minuti has received fees for membership of an advisory board or lectures or medical writer from AstraZeneca, Roche, BMS, Gilead, Novartis, Sanofi, Amgen, MSD, Johnson&Johnson, Daiichi Sankyo. Michele Montrone declares the following COI for honoraria/advisory boards: Amgen, Astra Zeneca, Bristol-Myers-Squibb, Merck-Sharp-Dohme, Novartis, Roche, Regeneron. Giulio Metro has received speakers' fee for Daicnhi-Sankyio, AstraZeneca, Amgen, Takeda. Alessandro Leonetti has received speakers' fee for AstraZeneca, BMS, MSD, Sanofi and Takeda, has been on advisory board for AstraZeneca, BeiGene, Novartis and Sanofi, has attended editorial activities sponsored by Eli Lilly, Novartis and Roche, received travel support from MSD, Novartis, Roche and Takeda, and received research grant from AstraZeneca. Giacomo Pelizzari declares the following COI: consulting or advisory role for Amgen, Johnson&Johnson, Roche, Novartis, Eli Lilly, AstraZeneca, MSD; speaker's bureau for Amgen, AstraZeneca; travel support from Sanofi, Roche, Novartis, Pfizer. Carlo Genova declares the following COI for honoraria/advisory boards: Amgen, Astra Zeneca, Bristol-Myers-Squibb, Daiichi-Sankyo, Eli Lilly, Merck-Sharp-Dohme, Novartis, Pierre Fabre, Roche, Regeneron. Alessandro Russo has received advisory board or speaker bureau honoraria from AstraZeneca, MSD, Novartis, Pfizer, BMS, Takeda, Amgen, Regeneron, Daiichi Sankyo, Merck, and Johnson & Johnson; compensated activity for editorial

projects from AstraZeneca, MSD, BMS, Novartis, Roche, and Regeneron. Alessandra Bulotta has received speakers' fee for AstraZeneca, BMS, MSD, Regeneron, has been on advisory board for AstraZeneca, Novartis, MSD, Regeneron, and has received travel support from MSD, Roche and Takeda, Johnson&Johnson. Francesco Grossi declares the following COI: advisory role for AstraZeneca, Bayer, Beigene, BMS, Boehringer Ingelheim, Daiichi Sankyo, Eli Lilly, Gilead, Italfarmaco, Merck, MSD, Novartis, Pierre Fabre, Regeneron, Roche, Takeda; speaker's bureau for Amgen, AstraZeneca, BMS, Bayer, Boehringer Ingelheim, Celgene, Eli Lilly, Johnson&Johnson, MSD, Merck, Novartis, Pfizer, Pierre Fabre, Roche, Sanofi, Takeda. Claudio Sini has received advisory board or speaker bureau honoraria from AstraZeneca, MSD, Novartis, BMS, Amgen, Merck Serono and compensated activity for editorial projects from MSD, BMS, Merck Serono. Alessandro Morabito has received payment or honoraria for lectures, presentations, speakers' bureaus, or educational events from Roche, AstraZeneca, BMS, MSD, Pfizer, Takeda, Sanofi, Lilly, Novartis, and Italfarmaco and participated on Advisory Board for Roche, AstraZeneca, Pfizer, MSD, BMS, Pierre-Fabre and Takeda. Diana Giannarelli has attended educational courses for Amgen and Astrazeneca and has has been on advisory board for Sanofi. Silvia Novello reports personal fees (as speaker bureau or advisor) from Eli Lilly, MSD, Roche, Takeda, Pfizer, Astra Zeneca, Amgen, Thermo Fisher, Novartis, Sanofi, Janssen, unrelated to the current work. Francesco Passiglia declared consultant/advisory fee from Astrazaneca, Janssen, Amgen, Brystol Myer Squibb, Merck Sharp and Dohne, Roche, Beigene, Novartis, Pfizer, Pharmamar, Thermofisher Scientific.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.lungcan.2025.108576.

References

[1] R.L. Siegel Mph, | Tyler, B. Kratzer, A.N. Giaquinto, | Hyuna, S. Phd, | Ahmedin, J. Dvm, Cancer statistics, 2025, CA Cancer J. Clin. 75 (2025) 10–45. Doi: 10.3322/CAAC.21871.

[2] N. Kristina Gregory, M. Lisa Hang, D.L. Aisner, W. Akerley, J.R. Bauman, D.S. Bruno, J.Y. Chang, L.R. Chirieac, M. DeCamp, A.P. Desai, T.J. Dilling, J. Dowell, G. A. Durm, S. Gettinger, T.E. Grotz, M.A. Gubens, A. Juloori, R.P. Lackner, P. Buffett Cancer Center Michael Lanuti, J. Lin, B.W. Loo, C.M. Lovly, F. Maldonado, E. Massarelli, D. Morgensztern, T.C. Mullikin, T. Ng, D. Owen, D.H. Owen, S.P. Patel, P.M. Polanco, J. Riess, T.A. Shapiro, A.P. Singh, J. Stevenson, A. Tam, T. Tanvetyanon, J. Yanagawa, S.C. Yang, E. Yau, NCCN Guidelines Version 7.2024 Non-Small Cell Lung Cancer Continue NCCN Guidelines Panel Disclosures, 2024. https://www.nccn.org/home/member-.

[3] D. Morgensztern, S.H. Ng, F. Gao, R. Govindan, Trends in stage distribution for patients with non-small cell lung cancer: a national cancer database survey, J. Thora. Oncol. 5 (2010), https://doi.org/10.1097/JTO.0b013e3181c5920c.

[4] F. Cortiula, B. Reymen, S. Peters, P. Van Mol, E. Wauters, J. Vansteenkiste, D. De Ruysscher, L.E.L. Hendriks, Immunotherapy in unresectable stage III non-small-cell lung cancer: state of the art and novel therapeutic approaches, Ann. Oncol. 33 (2022), https://doi.org/10.1016/j.annonc.2022.06.013.

[5] C. Catania, G. Piperno, A. Russo, C. Greco, F. Agustoni, V. Scotti, C. Proto, C. Sangalli, F. Patani, A. Santacaterina, M. Di Pietro Paolo, B. Agresti, A.R. Filippi, S. Ramella, Open issues in the therapeutic management of unresectable stage III NSCLC in the immunotherapy era, Crit. Rev. Oncol. Hematol. 174 (2022), https://doi.org/10.1016/j.critrevonc.2022.103684.

[6] M.E. Daly, N. Singh, N. Ismaila, M.B. Antonoff, D.A. Arenberg, J. Bradley, E. David, F. Detterbeck, M. Früh, M.A. Gubens, A.C. Moore, S.K. Padda, J.D. Patel, T. Phillips, A. Qin, C. Robinson, C.B. Simone, Management of stage III non-small-cell lung cancer: ASCO guideline, J. Clin. Oncol. 40 (2022), https://doi.org/10.1200/JCO.21.02528.

[7] S.J. Antonia, A. Villegas, D. Daniel, D. Vicente, S. Murakami, R. Hui, T. Yokoi, A. Chiappori, K.H. Lee, M. de Wit, B.C. Cho, M. Bourhaba, X. Quantin, T. Tokito, T. Mekhail, D. Planchard, Y.-C. Kim, C.S. Karapetis, S. Hiret, G. Ostoros, K. Kubota, J.E. Gray, L. Paz-Ares, J. de Castro Carpeño, C. Wadsworth, G. Melillo, H. Jiang, Y. Huang, P.A. Dennis, M. Özgüroğlu, Durvalumab after chemoradiotherapy in stage III non–small-cell lung cancer, New England J. Med. 377 (2017), https://doi.org/10.1056/nejmoa1709937.

[8] J. Remon, J.C. Soria, S. Peters, Early and locally advanced non-small-cell lung cancer: an update of the ESMO Clinical Practice Guidelines focusing on diagnosis, staging, systemic and local therapy, Ann. Oncol. 32 (2021), https://doi.org/10.1016/j.annonc.2021.08.1994.

[9] D.R. Spigel, C. Faivre-Finn, J.E. Gray, D. Vicente, D. Planchard, L. Paz-Ares, J. F. Vansteenkiste, M.C. Garassino, R. Hui, X. Quantin, A. Rimner, Y.L. Wu, M. Özgüroğlu, K.H. Lee, T. Kato, M. De Wit, T. Kurata, M. Reck, B.C. Cho, S. Senan, J. Naidoo, H. Mann, M. Newton, P. Thiyagarajah, S.J. Antonia, Five-year survival outcomes from the PACIFIC Trial: Durvalumab after chemoradiotherapy in stage iii non-small-cell lung cancer, J. Clin. Oncol. 40 (2022), https://doi.org/10.1200/JCO.21.01308.

[10] L. Paz-Ares, A. Spira, D. Raben, D. Planchard, B.C. Cho, M. Özgüroğlu, D. Daniel, A. Villegas, D. Vicente, R. Hui, S. Murakami, D. Spigel, S. Senan, C.J. Langer, B. A. Perez, A.M. Boothman, H. Broadhurst, C. Wadsworth, P.A. Dennis, S.J. Antonia, C. Faivre-Finn, Outcomes with durvalumab by tumour PD-L1 expression in unresectable, stage III non-small-cell lung cancer in the PACIFIC trial, Ann. Oncol. 31 (2020) 798–806, https://doi.org/10.1016/J.ANNONC.2020.03.287.

[11] P.E. Postmus, K.M. Kerr, M. Oudkerk, S. Senan, D.A. Waller, J. Vansteenkiste, C. Escriu, S. Peters, Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO clinical practice guidelines for diagnosis, treatment and follow-up, Ann. Oncol. 28 (2017) iv1–iv21, https://doi.org/10.1093/annonc/mdx222.

[12] E.A. Eisenhauer, P. Therasse, J. Bogaerts, L.H. Schwartz, D. Sargent, R. Ford, J. Dancey, S. Arbuck, S. Gwyther, M. Mooney, L. Rubinstein, L. Shankar, L. Dodd, R. Kaplan, D. Lacombe, J. Verweij, New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1), Eur. J. Cancer 45 (2009), https://doi.org/10.1016/j.ejca.2008.10.026.

[13] A. Freites-Martinez, N. Santana, S. Arias-Santiago, A. Viera, Using the Common Terminology Criteria for Adverse Events (CTCAE – Version 5.0) to Evaluate the Severity of Adverse Events of Anticancer Therapies, Actas Dermosifiliogr. 112 (2021), https://doi.org/10.1016/j.ad.2019.05.009.

[14] T. Hasegawa, R. Ariyasu, H. Tanaka, R. Saito, Y. Kawashima, A. Horiike, T. Sakatani, T. Tozuka, J. Shiihara, M. Saiki, Y. Tambo, T. Sonoda, A. Miyazaki, S. Uematsu, Y. Tsuchiya-Kawano, N. Yanagitani, M. Nishino, Subsequent treatment for locally advanced non-small-cell lung cancer that progressed after definitive chemoradiotherapy and consolidation therapy with durvalumab: a multicenter retrospective analysis (TOPGAN 2021-02), Cancer Chemother. Pharmacol. 92 (2023), https://doi.org/10.1007/s00280-023-04547-2.

[15] M. Stalker, M. Marmarelis, C. Langer, R.B. Cohen, A. Singh, C. Aggarwal, L. Sun, Outcomes following treatment for progression in patients treated with durvalumab consolidation in LA-NSCLC, Clin. Lung Cancer (2024), https://doi.org/10.1016/j.cllc.2024.11.002.

[16] H. Kawachi, M. Tamiya, Y. Oya, G. Saito, Y. Taniguchi, H. Matsumoto, Y. Sato, T. Otsuki, H. Suzuki, Y. Fukuda, S. Tanaka, Y. Tsukita, J. Uchida, Y. Sakata, Y. Nakatani, R. Shibaki, D. Arai, A. Okada, S. Hara, K. Takayama, K. Nishino, Real-world outcomes of subsequent chemotherapy after progression following chemoradiation and consolidative durvalumab therapy in locally advanced non-small cell lung cancer: an exploratory analysis from the CRIMSON study (HOPE-005), Clin Lung Cancer (2024), https://doi.org/10.1016/j.cllc.2024.07.014.

[17] F. Cortiula, T.S. Kutiel, M.L. Hsu, L.E.L. Hendriks, A.H. Nassar, M. Moskovitz, S. Y. Kim, M.M. Mirsky, R. Jayakrishnan, M. Bortolot, J. Saddi, P. Borghetti, M. J. Chung, A.R. Filippi, D. De Ruysscher, J. Bar, Comparative efficacy of immunotherapy-based treatment versus chemotherapy-only in patients with unresectable NSCLC with disease progression post chemoradiation and durvalumab, Eur. J. Cancer 219 (2025), https://doi.org/10.1016/j.ejca.2025.115302.

[18] M. Giaj Levra, F.E. Cotté, R. Corre, C. Calvet, A.F. Gaudin, J.R. Penrod, V. Grumberg, B. Jouaneton, R. Jolivel, J.B. Assié, C. Chouaïd, Immunotherapy rechallenge after nivolumab treatment in advanced non-small cell lung cancer in the real-world setting: a national data base analysis, Lung Cancer 140 (2020), https://doi.org/10.1016/j.lungcan.2019.12.017.

[19] A.J. Schoenfeld, S.J. Antonia, M.M. Awad, E. Felip, J. Gainor, S.N. Gettinger, F. S. Hodi, M.L. Johnson, N.B. Leighl, C.M. Lovly, T. Mok, M. Perol, M. Reck, B. Solomon, J.C. Soria, D.S.W. Tan, S. Peters, M.D. Hellmann, Clinical definition of acquired resistance to immunotherapy in patients with metastatic non-small-cell lung cancer, Ann. Oncol. 32 (2021), https://doi.org/10.1016/j.annonc.2021.08.2151.