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Real-life management of stage III non-small cell lung cancer patients in Italy: the BE-PACIFIC observational study

Paolo Bironzo [a,*], Alessandro Morabito [b], Sonia Silipigni [c], Vincenzo Adamo [d], Enrica Capelletto [a], Sabrina Rossi [e], Marcello Tiseo [f,g], Michele Montrone [h], Ivan Facilissimo [i], Gianpiero Romano [j], Luna Chiara Masini [k], Giovanni Luca Ceresoli [l], Cesare Gridelli [m], Antonio Lugini [n], Sara Pilotto [o], Pierosandro Tagliaferri [p], Emilio Bria [q,r], Diego Cortinovis [s], Erika Rijavec [t], Paolo Borghetti [u], Matteo Brighenti [v], Anna Maria Carta [w], Libero Ciuffreda [x], Raffaele Giusti [y], Marianna Macerelli [z], Francesco Verderame [aa], Francesca Zanelli [ab], Rossana Berardi [ac], Vanesa Gregorc [ad], Concetta Sergi [ae], Emanuela Vattemi [af], Roberto Ferrara [ag], Pier Luigi Piovano [ah], Lorenzo Livi [ai], Gloria Borra [aj], Stefania Gori [ak], Michele Aieta [al], Alessandro Bertolini [am], Fabiana Letizia Cecere [an], Giulia Pasello [ao,ap], Danilo Rocco [aq], Giuseppe Lo Certo [ar], Livia Marrone [ar], Lucia Simoni [as], Barbara Roncari [as], Silvia Novello [a], Sara Ramella [at,c], on behalf ofBE-PACIFIC Study Group [^]

[a] *Department of Oncology, University of Torino, AOU San Luigi Gonzaga, Orbassano, Turin, Italy*
[b] *Istituto Nazionale Tumori I.R.C.C.S. Fondazione G. Pascale, Naples, Italy*
[c] *Fondazione Policlinico Universitario Campus Bio-Medico, Rome, Italy*
[d] *Clinical Trial Center Oncology Department, A.O. Papardo, Messina, Italy*
[e] *Istituto Clinico Humanitas, Rozzano (MI), Italy*
[f] *Department of Medicine and Surgery, University of Parma, Parma, Italy*
[g] *Medical Oncology Unit, University Hospital of Parma, Parma, Italy*
[h] *Istituto Tumori Giovanni Paolo II, Bari, Italy*
[i] *Ospedale San Giovanni Bosco, Turin, Italy*
[j] *Ospedale Vito Fazzi, Lecce, Italy*
[k] *Divisione di Oncologia Medica, Spedali Riuniti di Livorno, Dipartimento Oncologico, Azienda USL Toscana Nord Ovest, Livorno, Italy*
[l] *Humanitas Gavazzeni, Bergamo, Italy*
[m] *AORN San Giuseppe Moscati, Avellino, Italy*
[n] *AO San Giovanni Addolorata, Rome, Italy*
[o] *Section of Innovation Biomedicine - Oncology Area, Department of Engineering for Innovation Medicine (DIMI), University of Verona and University and Hospital Trust (AOUI) of Verona, Italy*
[p] *AOU Renato Dulbecco e Dipartimento di Medicina Sperimentale e Clinica Università Magna Graecia, Catanzaro, Italy*
[q] *Università Cattolica del Sacro Cuore, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy*
[r] *Ospedale Isola Tiberina - Gemelli Isola, Rome, Italy*
[s] *Fondazione IRCCS San Gerardo dei Tintori Monza; Università degli Studi Milano-Bicocca, Milano, Italy*

* Corresponding author.
E-mail addresses: paolo.bironzo@unito.it (P. Bironzo), a.morabito@istitutotumori.na.it (A. Morabito), s.silipigni@policlinicocampus.it (S. Silipigni), vadamo@unime.it (V. Adamo), enrica.capelletto@gmail.com (E. Capelletto), sabrina.rossi@humanitas.it (S. Rossi), mtiseo@ao.pr.it (M. Tiseo), m.montrone@oncologico.bari.it (M. Montrone), ivan.facilissimo@aslcittaditorino.it (I. Facilissimo), giampieroromano@tiscali.it (G. Romano), lunachiara.masini@gmail.com (L.C. Masini), giovanniluca.ceresoli@gmail.com (G.L. Ceresoli), cgridelli@libero.it (C. Gridelli), alugini@hsangiovanni.roma.it (A. Lugini), sara.pilotto@univr.it (S. Pilotto), tagliaferri@unicz.it (P. Tagliaferri), emilio.bria@policlinicogemelli.it (E. Bria), diegoluigi.cortinovis@irccs-sangerardo.it (D. Cortinovis), erika.rijavec@policlinico.mi.it (E. Rijavec), paolobor82@yahoo.it (P. Borghetti), m.brighenti@asst-cremona.it (M. Brighenti), annamaria.carta@aob.it (A.M. Carta), lciuffreda@cittadellasalute.to.it (L. Ciuffreda), rgiusti@ospedalesantandrea.it (R. Giusti), marianna.macerelli@asuiud.sanita.fvg.it (M. Macerelli), francescoverderame1@gmail.com (F. Verderame), zanelli.francesca@ausl.re.it (F. Zanelli), rossana.berardi@ospedaliriuniti.marche.it (R. Berardi), vanesa.gregorc@ircc.it (V. Gregorc), consergi1974@gmail.com (C. Sergi), manuela.vattemi@sabes.it (E. Vattemi), ferrara.roberto@hsr.it (R. Ferrara), plpiovano@ospedale.al.it (P.L. Piovano), lorenzo.livi@unifi.it (L. Livi), gloria.borra@maggioreosp.novara.it (G. Borra), stefania.gori@sacrocuore.it (S. Gori), aietamichele83@gmail.com (M. Aieta), alessandro.bertolini@asst-val.it (A. Bertolini), fabiana.cecere@gmail.com (F.L. Cecere), giulia.pasello@iov.veneto.it (G. Pasello), danilorocc@yahoo.it (D. Rocco), giuseppe.locerto@astrazeneca.com (G.L. Certo), livia.marrone@astrazeneca.com (L. Marrone), lucia.simoni@iqvia.com (L. Simoni), barbara.roncari@iqvia.com (B. Roncari), silvia.novello@unito.it (S. Novello), s.ramella@policlinicocampus.it (S. Ramella).

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[t] Fondazione Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy
[u] ASST Spedali Civili and University of Brescia, Brescia, Italy
[v] ASST Cremona, Cremona, Italy
[w] AO Brotzu-Ospedale Oncologico A. Businco, Cagliari, Italy
[x] AOU Città della Salute e della Scienza PO San Lazzaro, Turin, Italy
[y] AOU Sant'Andrea, Rome, Italy
[z] ASUFC–ASUI S. Maria della Misericordia, Udine, Italy
[aa] AO Riuniti Villa Sofia–Cervello, Palermo, Italy
[ab] AUSL IRCCS di Reggio Emilia, Reggio Emilia, Italy
[ac] AOU Ospedali Riuniti Umberto I, Ancona, Italy
[ad] Ospedale San Raffaele, Milan, Italy
[ae] ARNAS Garibaldi-Nesima, Catania, Italy
[af] Ospedale Centrale di Bolzano–AS Alto Adige, Bolzano, Italy
[ag] Istituto Nazionale dei Tumori, Milan, Italy
[ah] Ospedale Civile SS. Antonio e Biagio e Cesare Arrigo, Alessandria, Italy
[ai] AOU Careggi, Florence, Italy
[aj] AOU Maggiore della Carità, Novara, Italy
[ak] Medical Oncology, IRCCS Sacro Cuore Don Calabria Hospital, Negrar di Valpolicella (VR), Italy
[al] IRCCS CROB Ospedale Oncologico Regionale, Rionero in Vulture (PZ), Italy
[am] ASST Valtellina Ospedale di Sondrio, Sondrio, Italy
[an] Istituto Nazionale Tumori Regina Elena, Rome, Italy
[ao] Department of Surgery, Oncology and Gastroenterology, University of Padova, 35128 Padova, Italy
[ap] Oncologia Medica 2, Istituto Oncologico Veneto, IRCCS, 35128 Padova, Italy
[aq] AORN Ospedale dei Colli–Monaldi, Naples, Italy
[ar] AstraZeneca Italy, Milan, Italy
[as] IQVIA Solutions Italy SRL, Modena, Italy
[at] Università Campus Bio-Medico, Rome, Italy

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STRUCTURED ABSTRACT

Background: Stage III non-small cell lung cancer (NSCLC) includes a heterogeneous group of patients with diverse disease presentation, biological portrait, and prognosis. Optimal management requires tailored approaches and multimodal strategies through a multidisciplinary team (MDT) decision-making process. The BE-PACIFIC study primarily aimed at describing treatment strategies of stage III NSCLC according to the Italian standard clinical practice, diagnostic work-up and survival outcomes during observation.
Patients and Methods: The BE-PACIFIC is an observational multicentre retrospective and prospective cohort study, involving both primary data collection and secondary use of data. Adult patients with confirmed diagnosis of stage III NSCLC were included by 40 sites and followed up for 12 months after diagnosis.
Results: From 1st August 2019, to 31st July 2020, 311 subjects were enrolled: 296 (95.2%) were evaluable for the analyses. The median (25th-75th percentiles) duration of the diagnostic process was 30.4 (21.0-60.9) days. MDT was involved in treatment plan definition of 88.7% (n/N=260/293) of patients. Sixty (20.3%) patients had tumour resection, mostly associated with neoadjuvant (n=26, 43.3%) or adjuvant (n=22, 36.7%) treatment alone. Chemoradiation was used in 165 of 236 (69.9%) non-resected patients, followed by durvalumab in 80 cases (48.5%).
Conclusions: MDT was largely involved in stage III NSCLC management, with at least 75% of patients completing the diagnostic process within 2 months. Consolidation durvalumab was used in half of non-resected patients treated with chemoradiation, with favourable retention rates and response, consistently with the PACIFIC trial findings.

1. Introduction

In 2022, lung cancer was the most commonly diagnosed cancer worldwide and the leading cause of cancer-related mortality, accounting for approximately 2.48 million new cases and 1.8 million deaths. Incidence and mortality varied by sex and region and tended to increase with higher Human Development Index (HDI) levels. If these trends persist, the global burden is expected to reach 4.62 million new cases and 3.55 million deaths by 2050 [1]. The high mortality is also negatively influenced by the large proportion of patients who receive a diagnosis of advanced-stage disease [2]. More than 80% of lung cancer cases are non-small cell lung cancer (NSCLC) and about 30% of patients with NSCLC have stage III locally advanced disease at diagnosis [3]. In recent years, the definition of NSCLC histotype and biomarkers has become critical for the development of new personalised therapies [4]. Stage III NSCLC includes a heterogeneous group of patients with different disease presentation, biological characteristics, and prognosis. Therefore, there is no definitive or universal therapeutic approach, and the debate remains open regarding the definition of resectability[5] as well as the optimal timing, sequence and combination of surgery, chemotherapy (CT), and radiotherapy (RT) across the spectrum of locally advanced disease, which is highly case-specific. Given its complexity, optimal management of patients requires tailored approaches and multimodal strategies through a multidisciplinary team (MDT) decision-making process [6]. Treatment with radical intent is recommended in stage III NSCLC but only a small proportion of patients achieves a long-term benefit [7–9]. Before consolidation immunotherapy was included in guidelines for unresectable stage III after chemoradiation therapy (CRT), standard treatment for patients with unresectable stage III NSCLC has been represented by concurrent CRT or - if not possible - sequential CT followed by definitive RT [9]. However, an Italian web-based survey conducted in 2018 involving 421 thoracic oncologists found that only 54% of responders considered concurrent CRT the most appropriate treatment choice for unresectable locally advanced NSCLC patients, while 46% preferred concurrent CRT followed by chemotherapy or sequential CRT even in fit patients [10].

[^] The members of BE-PACIFIC Study Group will be listed in Acknowledgments.

Furthermore, the lack of a regularly planned multidisciplinary tumour board emerged in many situations [11].

Durvalumab, a selective, high-affinity, human IgG1 monoclonal antibody that blocks programmed death ligand 1 (PD-L1) binding to programmed death 1 (PD-1) and CD80, allowing T cells to recognise and kill tumour cells, was approved in 2018 by the European Medicine Agency (EMA) as monotherapy for the treatment of adults with locally advanced, unresectable NSCLC whose tumours express PD-L1 on $\geq$ 1% of tumour cells and whose disease has not progressed following platinum-based CRT, based on the results of the PACIFIC trial [12]. The results of the PACIFIC trial led to a change of the treatment paradigm in the setting of stage III unresectable disease, which had not undergone significant evolution for years and which now includes durvalumab as a beneficial consolidation immunotherapy following CRT [12,13]. In patients unfit for concurrent CRT, consolidation durvalumab showed after sequential CRT a similar safety profile to that observed after concurrent CRT in PACIFIC with encouraging though preliminary efficacy in this frail population[14,15] and was shown to be well tolerated and effective also in the real-world [16].

The BE-PACIFIC (Italian oBsErvational study on Patient mAnagement strategies in real-world Clinical practice For patIents with loCally advanced (stage III) NSCLC) study was primarily designed to describe the real-life treatment strategies for stage III NSCLC adopted in the Italian clinical practice during the first 12 months after diagnosis. Secondary objectives were to describe the patients' clinical characteristics at diagnosis, the diagnostic process followed in Italian clinical practice for stage III NSCLC, and the tests performed to assess the presence of mutations and biomarker levels at diagnosis. Exploratory objectives were to evaluate the proportion of deceased patients and progressed patients during the observation period, and the presence of an MDT, its composition and involvement in the diagnostic work-up. Since the BE-PACIFIC was conducted during the COVID-19 outbreak, the pandemic impact on NSCLC diagnosis and treatment practice in Italy was also explored as additional study objective.

2. Materials and Methods

2.1. Study design and population

The BE-PACIFIC Study was an Italian observational multicentre retrospective and prospective cohort study, involving both a primary data collection (at enrolment and follow-up visit, for living patients) and the secondary use of data (during the retrospective observation period). Consecutive adult patients with confirmed stage III NSCLC diagnosis at enrolment or within the prior 6 months were included in the study, provided that they or their legally acceptable representatives had signed the Informed Consent & Privacy Form prior to data collection. To address and manage the risk of selection bias and immortal-time bias, also subjects deceased or declared to be untraceable were included. Patients with no available medical charts or information related to treatments received from diagnosis (if any), and pregnant or breast-feeding women were excluded. Patients were enrolled in 40 oncology centres throughout Italy, during an enrolment period of about 12 months. Each patient was followed up from the date of stage III NSCLC diagnostic process completion (index date) for a 12-month individual observation period, unless withdrawn from the study for any of the following reasons: death; loss to follow-up; informed consent withdrawal; disease progression leading to metastatic (stage IV) NSCLC; pregnancy or breast-feeding; enrolment in interventional clinical studies. Notably, patients were included regardless of their resectability status. Study scheme is shown in Figure 1.

All living participants signed an informed consent form before data collection, following the Declaration of Helsinki. Ethics approval was granted by all local ethics committees, with the first approval from the coordinating ethics committee – Comitato Etico Interaziendale A.O.U. San Luigi Gonzaga di Orbassano, AA.SS.LL. TO3-TO4-TO5 – on May 28, 2019 (protocol n. 60/2019/U).

2.2. Data source and statistical methods

All patients' data prospectively collected after enrolment and secondary data retrospectively collected from medical records were entered into an electronic Case Report Form (eCRF) at each participating site. Data were retrieved by either electronic or paper medical records, depending on the participating centre. Collected variables had been defined based on the study objectives and, according to the observational nature of the study, included data collected in clinical practice during routine clinical visits, without additional diagnostic or monitoring procedures.

Besides subject-level data collection, site-specific data on MDT management, availability of radiotherapy unit and other key sites' facilities were collected by means a survey to doctors to better address the study objectives.

Sample size was defined according to feasibility considerations. Further information can be found in the **Supplementary materials, including Table S1**.

No formal hypotheses were pre-specified for this observational study which had a descriptive aim. The statistical analyses were performed considering the set of evaluable patients, defined as eligible subjects (i.e., those meeting all inclusion criteria and not meeting any of the exclusion criteria) with available information related to the treatment strategy chosen after completion of stage III NSCLC diagnosis. Patients

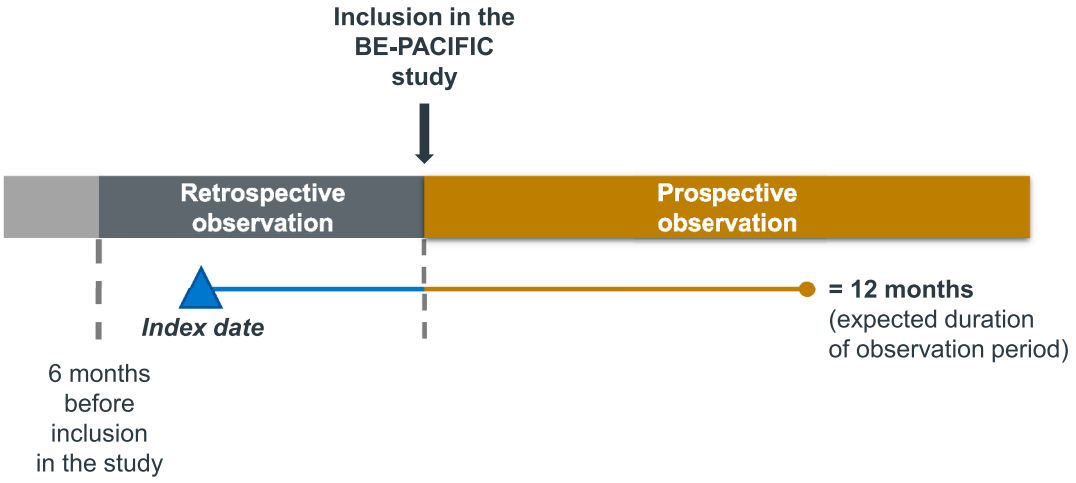

Figure 1. BE-PACIFIC Study scheme.

with missing data for one or more variables were not excluded from the study, their data were not imputed, and they were not considered for the descriptive analyses involving those variables. Descriptive analyses included mean and standard deviation (SD), median and quartiles, absolute and relative frequencies, according to the considered variables.

Response assessment over the course of treatments, including disease progression, was based on clinician-documented evaluations performed according to standard clinical practice. Compared to interventional studies which use specific assessment criteria, details on use of Response Evaluation Criteria in Solid Tumours (RECIST) or other standardised criteria for response definition were not collected in the study. Survival analyses were implemented to estimate the median time to event occurrence, by means of Kaplan-Meier curves. In these analyses, patients were considered as censored observations in case the event of interest (i.e., death for Overall Survival [OS]; disease progression or death for real-world Progression-Free Survival [PFS]) did not occur as long as the patient was under observation, while patients did count as failures in case the event of interest occurred.

The analyses were performed using SAS Enterprise Guide v. 7.12 and SAS 9.4 (SAS Institute, Cary, NC, USA). Study conduct, data monitoring, eCRF set-up and statistical analyses were performed by IQVIA Solutions Italy SRL (Modena, Italy), on behalf of AstraZeneca.

3. Results

3.1. Study patients

From 1st August 2019, to 31st July 2020, 311 subjects were enrolled (with a mean [SD] number of subjects per site of 8 [5]); 15 were excluded because they did not meet the main diagnostic inclusion criteria, and 296 (95.2%) were considered eligible and evaluable for the analyses (**Supplementary materials, Figure S1**). At the end of study, fixed on 14th July 2021, 154 (52.0%) subjects had prematurely discontinued the study, for the following main reasons: 95 (61.7%) for progressive disease to stage IV, 27 (17.5%) died, and 18 (11.7%) were lost to follow-up. The median (25th-75th percentiles [25th-75th P]) duration of the observation period among evaluable patients was 11.0 (6.3-12.2) months. Two hundred ninety (98.0%) patients were Hispanic/Caucasian and 219 (74.0%) were males. The median (25th-75thP) age at diagnosis of stage III NSCLC was 68.0 (62.5-72.0) years. A total of 257 out of 283 (90.8%) patients with available data were previous or current smokers at diagnosis, with a median (25th-75thP) duration of 41.0 (35.0-50.0) years of smoking.

The median (25th-75thP) duration of stage III NSCLC between diagnosis and study inclusion was 2.5 (1.3-4.2) months. At diagnosis most subjects with available data had ECOG-PS of 0 (n/N=174/288, 60.4%) or 1 (n/N=105/288, 36.5%). In relation to comorbidities, 243 (82.1%) evaluable patients had previous or concomitant medical conditions at diagnosis, the most common being hypertension in 134 (45.3%). History of other cancers was reported in 42 (14.2%) subjects, most commonly bladder (in 9 subjects, 3.0%) and breast cancer (in 6 subjects, 2.0%). Overall patients' clinical characteristics at diagnosis are detailed in Table 1.

3.2. NSCLC features at diagnosis

Among the 296 evaluable subjects, 115 patients (38.9%) had squamous-cell carcinoma at diagnosis, 170 patients (57.4%) a non-squamous cell carcinoma, 164 of whom had adenocarcinoma (55.4%). The remaining 11 cases (3.7%) were diagnosed as not otherwise specified (NOS). Stage IIIB NSCLC (according to the 8th lung cancer TNM classification and clinical staging system[19]) was diagnosed in 51.2% of patients with available substage. The majority of cases were T3-T4 tumours (30.8% and 39.7%, respectively), with a higher occurrence of mediastinal lymph node involvement (N2 in 63.6% of cases). NSCLC features at diagnosis are summarised in Table 1.

Table 1
Clinical characteristics and NSCLC features at diagnosis of stage III disease among patients included in the BE-PACIFIC Study.

	Evaluable patients N = 296
Patients with NSCLC-related signs and symptoms at diagnosis, n (%)	149 (50.3)
Type of signs and symptoms[a], n (%)	
Cough	100 (33.8)
Dyspnoea	44 (14.9)
Chest pain	27 (9.1)
Fatigue/Asthenia	23 (7.8)
Haemoptysis	22 (7.4)
Loss of weight	18 (6.1)
Pain in other sites	17 (5.7)
Fever	11 (3.7)
Decreased appetite	7 (2.4)
Dysphonia	6 (2.0)
Nausea/Vomit	1 (0.3)
Other	15 (5.1)
ECOG-PS, n (%)	
0	174 (60.4)
1	105 (36.5)
2	9 (3.1)
Unknown	8
Patients with comorbidities or history of relevant medical conditions at diagnosis, n (%)	**243 (82.1)**
Type of comorbidities[b]	
Hypertension	134 (45.3)
Hypercholesterolemia/Dyslipidaemia	59 (19.9)
Chronic obstructive pulmonary disease	56 (18.9)
Diabetes	49 (16.6)
Other cancer	42 (14.2)
Cardiomyopathy	23 (7.8)
History of stroke	15 (5.1)
Tumour histology, n (%)	
Squamous cell carcinoma	115 (38.9)
Non-squamous cell carcinoma	170 (57.4)
Adenocarcinoma	164 (55.4)
Large-cell carcinoma	2 (0.7)
Mixed	2 (0.7)
Other	2 (0.7)
NSCLC not otherwise specified	11 (3.7)
Tumour (T) and Node (N) description at index date, n (%)	
T1	32 (11.0)
T2	54 (18.5)
T3	90 (30.8)
T4	116 (39.7)
N0	19 (6.5)
N1	37 (12.6)
N2	187 (63.6)
N3	51 (17.3)
Tumour stage[c], n (%)	
IIIA	117 (40.2)
IIIB	149 (51.2)
IIIC	25 (8.6)
Not further specified stage III	5
% of tumour cells expressing PD-L1 (Tumour Proportion Score)[d], n (%)	
<1	60 (30.8)
≥1	133 (68.2)
Indeterminate result	2 (1.0)
Missing	1
PD-L1 level (%)[e]	
Median (25th–75thP)	50.0 (10.0-60.0)

NSCLC, Non-Small Cell Lung Cancer; ECOG-PS, Eastern Cooperative Oncology Group - Performance Status; PD-L1: programmed cell death ligand 1; 25th–75thP, 25th–75th percentiles.

[a] Note. A patient could have had more than one sign/symptom at diagnosis.

[b] Note. Comorbidities present in ≥5% of patients are listed. A patient could have had more than one relevant medical condition/disease.

[c] Tumour stage assessment according to the 8th lung cancer TNM classification and clinical staging system[20]

[d] Considering only patients with PD-L1 level tested before index date (N=196)

[e] PD-L1 level (%) specified only for patients with available Tumour Proportion Score ≥1%.

3.3. NSCLC diagnostic process and PD-L1 test

The median (25^{th}-75^{th}P) duration of the diagnostic process was 30.4 (21.0-60.9) days, with 144 (48.6%) patients completing the work-up in a single oncology centre. In the diagnostic process, an MDT, defined as a formal tumour board composed of different specialised professionals who meet regularly to work together on patient management, was involved in 88.7% (n/N=260/293) of cases, including medical oncologists, radiation oncologists, radiologists, pneumologists, surgeons and pathologists in more than half of cases.

Among diagnostic procedures, radiological/imaging examinations for clinical staging and cyto/histopathologic analyses for pathological confirmation were performed in all patients. A positron emission tomography (PET) scan was carried out in 238 (80.4%) patients. A bronchoscopy was performed in 134 (45.3%) patients. Details on the diagnostic work-up are reported in Table 2.

A total of 222 (75.0%) patients were diagnosed before the first COVID-19 lockdown imposed in Italy on 10^{th} March 2020; 74 (25.0%) patients completed the diagnostic process during the pandemic outbreak. During the pandemic, 26 of the 40 (65.0%) participating centres declared impact on the diagnostic process, mainly delays in radiological/imaging examinations (**Supplementary materials, Figure S2**). The critical impact on patient management was highlighted through important changes in the composition and frequency of MDT periodical meetings. During the most acute phase of the pandemic, 5 of the 39 (12.8%) centres with available data reported absence of MDT meetings, and 22 (56.4%) reported reduced MDT activity with respect to pre-COVID-19 outbreak. Treatment practices were less impacted and underwent changes, but to a lesser extent than diagnostic and monitoring processes. Delayed surgical procedures were reported by 13 of the 40 (32.5%) participating centres; 5 (12.5%) centres reported delayed treatment initiation, 5 (12.5%) reported changes in ongoing treatment type, and 7 (17.5%) reported changes in treatment administration schedule (**Supplementary materials, Figure S3**).

PD-L1 expression was assessed before completion of the diagnostic process (index date) in 196 (66.2%) patients (Table 1), mainly on histological specimens (80.9% of cases; n/N=157/194 tested patients with available sample data) and on cytological samples in 19.1%. In 68.2% of cases, ≥1% of tumour cells expressed PD-L1, with a median (25^{th}-75^{th}P) level of PD-L1 expression of 50.0% (10.0-60.0%). In other 59 patients, PD-L1 level was assessed later during the observation period on already available specimens or on additional samples collected after the diagnosis.

Table 2
NSCLC diagnostic procedures among patients included in the BE-PACIFIC Study.

Healthcare providers/specialists involved in the MDT during diagnostic process[a], n (%)	Evaluable patients N = 296
Medical oncologist	281 (95.3)
Radiologist	256 (86.8)
Pneumologist/Bronchoscopist	212 (71.9)
Surgeon	195 (66.1)
Pathologist	189 (64.1)
Radiation oncologist	173 (58.6)
Nuclear medicine physician	104 (35.3)
Molecular biologist	95 (32.2)
Other specialist	14 (4.7)
Type of diagnostic evaluation[b], n (%)	
Cyto-histopathologic sample collection	
Fine-needle aspiration biopsy (FNAB)	69 (23.3)
Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA)	40 (13.5)
Core-needle biopsy (CNB)	39 (13.2)
Trans-bronchial needle aspiration (TBNA)	36 (12.2)
Percutaneous needle biopsy	33 (11.1)
Endobronchial ultrasound needle aspiration (EBUS-NA)	30 (10.1)
Bronchial aspiration/brushing	22 (7.4)
Thoracotomy	12 (4.1)
Lymph node excision biopsy	10 (3.4)
Thoracoscopy	6 (2.0)
Bronchoalveolar lavage (BAL)	5 (1.7)
Bronchial washing	5 (1.7)
Oesophageal ultrasound needle aspiration (EUS-NA)	4 (1.4)
Mediastinoscopy	3 (1.0)
Other examination	15 (5.1)
Unknown	27 (9.1)
Radiological/imaging examination	
Computed tomography (CT) scan	273 (92.2)
Positron emission tomography (PET) scan	238 (80.4)
X-ray	49 (16.6)
Magnetic resonance imaging (MRI)	20 (6.8)
Bone scintigraphy	7 (2.4)
Other examination	2 (0.7
Bronchoscopy	134 (45.3)

NSCLC, Non-Small Cell Lung Cancer; MDT, Multidisciplinary Team.

[a] More healthcare providers/specialists were involved in the same diagnostic process.

[b] A patient could have had more than one type of examination during the diagnostic process.

3.4. Treatment strategies

The initial treatment approach was tumour resection in 29 (9.8%) patients including 19 (6.4%) patients with tumour resection performed during the diagnostic process. In the 267 not initially resected patients, CRT was the most frequent first treatment approach (163 patients, 61.0%), followed by CT alone in 83 (31.1%), RT alone in 5 (1.9%), and targeted therapies alone or combined with CT in 11 (4.1%) (Table 3).

Considering the whole observation period, tumour resection was performed overall in 60 (20.3%) patients, 34 (56.7%) of them diagnosed with stage IIIA NSCLC, and 26 (43.3%) with stage IIIB or IIIC NSCLC. Among patients operated after index date, the median (25^{th}-75^{th}P) time

Table 3
Chemotherapy and radiotherapy strategies in the first 12 months after stage III NSCLC diagnosis among patients included in the BE-PACIFIC Study.

Patients with no tumour resection (N=236)[a], n (%)	Evaluable patients N=296
Concurrent CRT	80 (33.9)
Sequential CRT	62 (26.3)
CT	52 (22.0)
CT followed by Concurrent CRT	12 (5.1)
Concurrent CRT followed by CT or RT	7 (3.0)
RT	5 (2.1)
CT alone followed by RT alone (without other treatments) as distinct strategies	5 (2.1)
Sequential CRT followed by CT or RT	4 (1.7)
Treatment other than CT, RT or CRT	3 (1.3)
RT alone followed by CT alone	1 (0.4)
Patients with tumour resection (N=60)[b], n (%)	
Neoadjuvant setting (n=31, 51.7%)	
CT	20 (33.3)
Concurrent CRT	10 (16.7)
CT alone followed by Concurrent CRT	1 (1.7)
Adjuvant setting (n=27, 45.0%)	
CT	17 (28.3)
Concurrent CRT	3 (5.0)
Sequential CRT	3 (5.0)
CT alone followed by RT alone	1 (1.7)
RT	1 (1.7)
Systemic treatment other than CT, RT or CRT	2 (3.3)

NSCLC, Non-Small Cell Lung Cancer; CT: chemotherapy; RT: radiotherapy; CRT: chemoradiotherapy.

[a] Five patients without any NSCLC surgical resection reported no treatment (e.g. due to premature study withdrawal: disease progression leading to stage IV NSCLC, or death).

[b] Five patients undergoing NSCLC surgical resection received both neoadjuvant and adjuvant treatments. Seven patients reported no neoadjuvant and/or adjuvant treatment (e.g. due to premature study withdrawal).

interval from diagnosis to tumour resection was 120.5 (102.0–170.0) days, and the most frequent type of surgical resection was lobectomy, adopted in 33 patients. Tumour resection was mostly associated with neoadjuvant treatment alone (n/N=26/60, 43.3%) or adjuvant treatment alone (n/N=22/60, 36.7%). A neoadjuvant and adjuvant sequential treatment approach was adopted in 5 out of 60 (8.3%) patients.

CRT without other concomitant anticancer treatments was used in 165 (69.9%) of 236 non-resected patients, followed by durvalumab consolidation in n/N=80/165 (48.5%) cases after a median (25^{th}-75^{th}P) time interval of 5.4 (4.0-7.7) weeks from the CRT completion. Among patients treated with durvalumab, concurrent CRT was used in 65.0% (n/N=52/80) of cases. The most frequent CT regimen used, as CRT component and overall, was carboplatin plus paclitaxel (**Supplementary materials, Table S2**). Overall, 82 (27.7%) received durvalumab, including 2 patients for which previous treatment setting or CRT regimen could not be confirmed, with a median (25^{th}-75^{th}P) number of 10 (6-16) administrations during the defined 12-month study observation period starting from the date of completion of the diagnostic process for NSCLC. At the end of observation, durvalumab was still ongoing in 58 (70.7%) treated patients.

The CT and RT approaches adopted during the study observation in both non-resected and resected patients are summarised in Table 3. Detailed information, including CT drugs used, can be found in the **Supplementary materials, Tables S2-S3**.

Other therapies were given to 28 (9.5%) of the overall patients, mainly pembrolizumab (n=16), and in a few cases, nivolumab, atezolizumab, osimertinib, alectinib, gefitinib, and nintedanib (**Supplementary materials, Table S4**).

3.5. Treatment response and survival outcomes

Clinician-documented best response (i.e., maximum therapeutic response) among patients treated with CT alone, RT alone and CRT are listed in Table 4, including time to achievement of best response.

An overall response during durvalumab treatment was registered in 17 out of 71 (23.9%) patients with available best response data: 1 patient achieved a complete response, 16 patients (22.5%) a partial response. Forty patients (56.3%) had stable disease, and 14 (19.7%) disease progression (Table 4).

Disease progression or death occurred in 153 (51.7%) patients during observation, regardless of treatment. Median real-world PFS, from the date of completion of stage III NSCLC diagnostic work-up to first progressive disease as per investigator's judgment or death due to any cause, was 11.1 (95%CI: 9.8-12.7) months. In the overall evaluable population, 135 (45.6%) patients experienced disease progression during the observation period, mainly with the occurrence of metastases (n=94) in the bones and in the central nervous system, followed by an increase in primary tumour size (n=48), and clinical/symptomatic progression (n=23). Death occurred in 27 (9.1%) patients during observation. Median OS had not been reached at the time the database was locked.

Table 4
Best response achieved with chemotherapy, radiotherapy, chemoradiotherapy and durvalumab treatment among patients included in the BE-PACIFIC Study[a].

	Patients treated with CT (N=104)[b]	Patients treated with RT (N=16)[b]	Patients treated with CRT (N=163)[b]	Patients treated with CRT followed by durvalumab (N=71)[b,c]
Complete Response, n (%)	3 (2.9)	1 (6.3)	6 (3.7)	1 (1.4)
Partial Response, n (%)	38 (36.5)	5 (31.3)	76 (46.6)	16 (22.5)
Stable Disease, n (%)	28 (26.9)	5 (31.3)	52 (31.9)	40 (56.3)
Disease Progression, n (%)	35 (33.7)	5 (31.3)	29 (17.8)	14 (19.7)
Time to best response achievement (months), median (25^{th}-75^{th}P)	2.2 (1.8-3.2)	2.7 (2.3-3.6)	3.3 (2.1-6.0)	-

CT: chemotherapy; RT: radiotherapy; CRT: chemoradiotherapy; 25^{th}-75^{th}P: 25^{th}-75^{th} percentiles.

[a] Response rates refer to the overall BE-PACIFIC study cohort, without distinction between patients with tumour resection and patients with no tumour resection.

[b] Percentages were calculated over the number of: evaluable patients treated with CT alone and with best response data available (N=104), evaluable patients treated with RT and with best response data available (N=16), evaluable patients treated with CRT and with best response data available (N=163), evaluable patients treated with durvalumab and with available best response data (N=71). The following two by two categories are mutually not exclusive: "Patients treated with CT" and "Patients treated with RT"; "Patients treated with CRT" and "Patients treated with CRT followed by durvalumab".

[c] Durvalumab best response was unknown for 3 patients. For 8 patients, the best response was available, but out of the observation period.

4. Discussion

Locally advanced NSCLC is a highly heterogeneous disease and patient management in this setting requires targeted and personalised strategies, and multidisciplinary management. The BE-PACIFIC study shows how the treatment of these patients is approached under real-life conditions in Italy and which healthcare professionals are involved, highlighting the importance of a correct classification of the stage and resectability of the disease, especially in light of the recent evidence emerging on chemoimmunotherapy in early stage resectable disease [6].

In total, 296 eligible patients were evaluable out of 311 enrolled patients. Patients had a median age of 68.0 years and were mostly men (74.0%), current or former smokers (90.8%), with comorbidities (82.1%), characteristics which are comparable with those of stage III patients from different studies, including the Phase 3 PACIFIC trial[12] as well as other real-world cohorts[16]. In relation to diagnostic work up, bronchoscopy was the main diagnostic test performed to obtain cyto-histological samples. Bronchoscopy, with all its recent technical improvements, remains crucial for the staging of NSCLC, enhancing medical practice and patient prognosis [18,19]. Most tumours were adenocarcinomas (55.4%), which are increasingly becoming the predominant histologic type of stage III NSCLC [3]. According to the AJCC staging system 8^{th} edition, NSCLC patients included in the study had mainly stage IIIB disease (51.2%), with a high frequency of mediastinal nodal involvement (stage III-N2; 63.6%). It is worth noting that over 60% of evaluable patients were N2 (similarly to other published real-world studies[17]), a condition associated with a poor prognosis, [20] and over 80% of patients had previous or concomitant conditions, mainly cardiometabolic and respiratory diseases, which have been reported to be associated with worse survival outcomes in stages I-III NSCLC [21].

Patients with positive PD-L1 expression were the majority (68.2%) of the 195 tested patients with available data, irrespective of surgical resection, consistently with previous reports [22].

In relation to treatment approaches, there is a lack of clear evidence demonstrating a significant survival benefit for either surgery [with neoadjuvant or adjuvant CT/neoadjuvant CRT] or CRT, potentially followed by immunotherapy consolidation depending on the PD-L1 status [23]. A lack of a consensus definition of resectability of N2 disease makes the decision-making process even more complex and variable [24]. However, notably, the EORTC-Lung Cancer group initiative was presented at World Conference on Lung Cancer 2023 with the aim to

establish a consensus on this question, in order to reduce variability in the inclusion criteria related to resectability in clinical trials [5].

Among patients enrolled in BE-PACIFIC, tumour resection, mainly lobectomy, was performed overall in a minority of patients (60; 20.3%), in half of them as initial treatment approach and in the other half later during the study observation period and was mostly associated with neoadjuvant or adjuvant treatment alone. CRT was performed in 70% of non-resected patients, including mainly carboplatin and paclitaxel. Durvalumab consolidation therapy was administered in nearly half of these cases, mainly associated with concurrent CRT. Since the study was not focused on any specific drug, information about the reason for not initiating durvalumab or other therapies was not collected, but the interpretation of this data should take into account that durvalumab treatment in the EU is indicated in adults whose tumours express PD-L1 on $\geq$1% of tumour cells, and only in patients whose disease has not progressed following CRT [25].

It is worth noting that the treatment with durvalumab was ongoing at the end of observation period for 70.7% of treated patients, showing a good retention rate. It must also be noted that the median number of durvalumab treatment administrations (10) described in the BE-PACIFIC study does not include additional durvalumab administrations performed after the end of observation, planned 12 months ($\pm$30 days) of index date at the latest.

Among study secondary objectives, diagnostic procedures characteristics and duration were described. At least 75% of patients completed the diagnostic process within 2 months, and 48.6% of the entire patient population performed the work-up in a single cancer centre, avoiding time-consuming fragmentation of the diagnostic process. It is recognised that diagnosis and management of NSCLC needs the expertise of different specialists building an MDT, which has a paramount role in improving patients' outcomes [26]. Various experiences showed that MDT-led management improves the quality of care, survival and quality of life of patients with stage III NSCLC [27,28]. Nevertheless, lack of MDT in defining the treatment approach has been reported in real-world studies [29]. Major criticisms and barriers to the application of international guidelines for the management of locally advanced NSCLC in Italian clinical practice have been identified in the lack of a regular and complete MDT, paucity of well-trained staff and expertise, logistic issues, limited time for discussion of clinical cases, and long waiting lists for staging and therapeutic interventions [30]. It is noteworthy that in the BE-PACIFIC real-world study, an MDT in line with guideline recommendations was involved in 88.7% of cases, with participation of medical oncologists, radiation oncologists, radiologists, pneumologists, surgeons and pathologists in more than half of cases. The COVID-19 pandemic affected the planning of MDT meetings of participating centres; however, based on the study protocol no patient-level data are available on reasons for not discussing cases in these meetings.

Although not the primary objective of the study, treatment response data and survival outcomes were collected at study end. The median time to best response achievement was between 2.2 and 3.3 months with all treatment strategies, i.e., CT, RT, and CRT. The highest percentage of overall responses was obtained with CRT, whereas the highest rate of disease progression was observed in patients treated with CT alone. Overall, patients receiving durvalumab who had available best response data (n=71) showed an overall response rate in this real-world study (23.9%) consistent with the PACIFIC trial findings (Objective Response Rate - ORR of 28.4%) [31]. Disease progression or death occurred in 153 (51.7%) patients during observation, regardless of treatment.

A limitation of BE-PACIFIC is the fact that participating sites were not randomly sampled from the whole pool of oncological centres, although they were geographically distributed throughout Italy, to potentially reflect the real-world management of stage III NSCLC patients in the country. As many of the participating sites were academic hospitals and/or comprehensive cancer centres, we cannot rule out potential discrepancies in adherence to current guideline recommendations among all oncological centres. However, given the wide geographical distribution of the participating sites, our study provides valuable insights into the Italian diagnostic and treatment approaches for stage III NSCLC, which were found to be largely in agreement with current evidence. It is worth underlining that in Italy access to both PD-L1 testing and durvalumab consolidation after CRT is guaranteed by the National Health Service (Servizio Sanitario Nazionale, SSN), thereby reducing inequities across different sites. Other limitations include the lack of a centralised radiology review in the response assessment, the non-homogenous methods, the timing and criteria of the clinical evaluations in a real-world setting, and the limited observation period duration. However, the primary objective of the BE-PACIFIC study was to identify treatment modalities of stage III NSCLC in the Italian standard clinical practice, and survival outcomes were considered as an explorative aim. Retrospective data collection related to tumour characterisation, patient clinical characteristics at diagnosis, treatments and outcomes is another limitation of the study; nevertheless, data should be marginally affected by recall bias since they were already available in the patient's medical records according to the study eligibility criteria. To limit the risk of selection bias, all patients meeting the eligibility criteria at a participating site had to be enrolled in the study consecutively, including deceased and untraceable subjects. Treatment-naïve patients could also be enrolled. The retrospective observation window was limited to the years 2018-2020, and this is the reason why molecular characterisation, currently considered mandatory to provide a therapeutic direction in patients with resectable or unresectable stage III, has not been considered. Therefore, we cannot exclude that diagnostic patterns have changed since that period. Indeed, the introduction of neoadjuvant/perioperative chemo-immunotherapy approaches in resectable patients has changed treatment patterns in this subgroup. Worth mentioning is that the study was conducted during the COVID-19 pandemic, with most investigators complaining about its impact mainly on the diagnostic process, due to delays in imaging evaluations, rather than on treatment approaches. In the future, a prompt response to novel pandemic outbreaks would hopefully reduce such impact.

On the other hand, following the PACIFIC study, which has rekindled the spotlight on locally advanced disease, a heterogeneous and complex disease to treat, the BE-PACIFIC has the merit of providing a picture of the diagnostic process and the initial therapeutic approach to this disease in Italy, focusing also on the real-world involvement of an MDT. Furthermore, the study is very topical in light of new studies evaluating immunotherapy in resectable NSCLC in real-world practice[32,33], which will inevitably have an impact on the management and classification of stage III in the years to come.

5. Conclusions

The observational real-world BE-PACIFIC study allowed to describe the clinical characteristics of Italian stage III NSCLC patients and their diagnostic and therapeutic path. Notably, the MDT was largely involved in stage III NSCLC management, with at least 75% of patients completing the diagnostic process within 2 months. Tumour resection was performed overall in 20% of patients, mostly associated with neoadjuvant or adjuvant treatment alone. Consolidation durvalumab was used in 49% of non-resected patients treated with CRT, with favourable retention in treatment and response assessed by a real-world approach, consistent with the PACIFIC trial findings.

Authorship

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Compliance with ethics guidelines

All living participating patients received verbal and written information about the study and were given the opportunity to ask any questions to help them understand the study. They provided voluntary informed consent before data collection. The BE-PACIFIC Study was approved by the Ethics Committees of all participating institutions before the start of data collection and conducted in accordance with the Helsinki Declaration of 1964, its later amendments, and other applicable regulatory requirements.

Data sharing and data accessibility

The datasets generated and/or analysed during the current study are not publicly available due to the sensitive nature of the data collected in this study.

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Collaborators, including the BE-PACIFIC Study Group

Rossana Critelli, Elisa Cibrario Rocchietti, Simona Carnio, Francesco Passiglia, Valentina Bertaglia, Emanuela Olmetto (Orbassano, Turin); Carlo Greco, Edy Ippolito, Barbara Papi, Pierluigi Falco (Rome); Alessandra Ferro, Alessandro Dal Maso, Giulia Doria, Stefano Frega (Padua); Annalisa Nardone, Patrizia Petrillo (Bari); Gianluca Cuomo (Turin); Maria Bonomi, Valeria Nava, Marta Magni (Bergamo); Serena Verna (Rome); Claudia Proto, Rosa Maria Di Mauro, Giulia Galli, Giuseppe Lo Russo (Milan); Clara Fugazza, Maria Grazia Viganò, Chiara Lazzari (Milan); Paolo Maione, Maria Luisa Barzelloni, Angelo Cirocco (Avellino); Fiorella Lombardo, Lorenzo Belluomini, Jessica Insolda (Verona); Alessandra Marabese (Bolzano); Roberta Camisa, Alessandro Leonetti, Sebastiano Buti (Parma); Simona Damiano, Giuliano Palumbo (Naples); Alfredo Tartarone, Vittoria Lapadula, Emanuela Zifarone (Rionero in Vulture, Potenza); Stefania Crivellari, Silvia Zai, Fabio Giacchero (Alessandria); Chiara Bonfadini, Agostino Ponzetti, Enrica Milanesi, Tiziana Scirelli (Turin); Silvana Leo, Valeria Saracino, Amelia Vantaggiato, Loretta Paolelli (Lecce); Emma Maria Saba, Daniela Guerzoni (Cagliari); Jessica Imbrescia, Nuzhat Noreen (Brescia); Giacomo Allegrini, Irene Stasi, Chiara Finale, Luigi Coltelli, Gianna Musettini, Samanta Cupini, Azzurra Farnesi (Livorno); Veronica Franchina, Alessandro Russo, Graziella Rizzo, Antonino Scimone, Tindara Franchina (Messina); Marco Filetti (Rome); Maria Bonomi, Nicoletta Nanni (Cremona); Sabrina Vari, Consuelo D'Ambrosio, Elisabetta Bozzoli (Rome); Elisa Sala (Monza); Giovanna Finocchiaro, Luca Toschi, Lucia Damicis, Arianna Marinello, Lucia Ferraro (Milan); Elisabetta Menatti, Panagiotis Deligiannis (Sondrio); Oriana Commendatore, Francesco Avola (Catania); Maria Celeste Pirozzoli, Maria Anna Teberino, Emanuele Vita, Alessio Stefani (Rome); Michela Burattini, Zelmira Ballatore, Alessandra Lucarelli, Francesca Morgese, Filippo Merloni (Ancona); Candida Bonelli (Reggio Emilia); Claudia Bareggi, Francesca Barbìn (Milan); Alessandro Follador, Simona Rizzato, Ciro Rossetto, Barbara Bonifacio, Carla Corvaja, Giada Targato (Udine); Alessandro Inno, Fabiana Marchetti, Vincenzo Picece, Matilde Fiorini (Verona); Mariangela Lopreiato (Catanzaro); Francesca Spinnato, Anna Mangiaracina, Erika Lo Iacono, Enrico Bronte (Palermo); Vieri Scotti, Matteo Mariotti, Lucia Pia Ciccone, Damiano Dei, Marco Banini, Benedetta Agresti, Victoria Lorenzetti, Virginia Votino (Florence); Federica Biello, Paola Maggiora, Silvia Genestroni, Carmen Branni (Novara).

CRediT authorship contribution statement

Paolo Bironzo: Writing – review & editing, Writing – original draft, Investigation. **Alessandro Morabito:** Writing – review & editing, Investigation. **Sonia Silipigni:** Writing – review & editing, Investigation. **Vincenzo Adamo:** Writing – review & editing, Investigation. **Enrica Capelletto:** Writing – review & editing, Investigation. **Sabrina Rossi:** Writing – review & editing, Investigation. **Marcello Tiseo:** Writing – review & editing, Investigation. **Michele Montrone:** Writing – review & editing, Investigation. **Ivan Facilissimo:** Writing – review & editing, Investigation. **Gianpiero Romano:** Writing – review & editing, Investigation. **Luna Chiara Masini:** Writing – review & editing, Investigation. **Giovanni Luca Ceresoli:** Writing – review & editing, Investigation. **Cesare Gridelli:** Writing – review & editing, Investigation. **Antonio Lugini:** Writing – review & editing, Investigation. **Sara Pilotto:** Writing – review & editing, Investigation. **Pierosandro Tagliaferri:** Writing – review & editing, Investigation. **Emilio Bria:** Writing – review & editing, Investigation. **Diego Cortinovis:** Writing – review & editing, Investigation. **Erika Rijavec:** Writing – review & editing, Investigation. **Paolo Borghetti:** Writing – review & editing, Investigation. **Matteo Brighenti:** Writing – review & editing, Investigation. **Anna Maria Carta:** Writing – review & editing, Investigation. **Libero Ciuffreda:** Writing – review & editing, Investigation. **Raffaele Giusti:** Writing – review & editing, Investigation. **Marianna Macerelli:** Writing – review & editing, Investigation. **Francesco Verderame:** Writing – review & editing, Investigation. **Francesca Zanelli:** Writing – review & editing, Investigation. **Rossana Berardi:** Writing – review & editing, Investigation. **Vanesa Gregorc:** Writing – review & editing, Investigation. **Concetta Sergi:** Writing – review & editing, Investigation. **Emanuela Vattemi:** Writing – review & editing, Investigation. **Roberto Ferrara:** Writing – review & editing, Investigation. **Pier Luigi Piovano:** Writing – review & editing, Investigation. **Lorenzo Livi:** Writing – review & editing, Investigation. **Gloria Borra:** Writing – review & editing, Investigation. **Stefania Gori:** Writing – review & editing, Investigation. **Michele Aieta:** Writing – review & editing, Investigation. **Alessandro Bertolini:** Writing – review & editing, Investigation. **Fabiana Letizia Cecere:** Writing – review & editing, Investigation. **Giulia Pasello:** Writing – review & editing, Investigation. **Danilo Rocco:** Writing – review & editing, Investigation. **Giuseppe Lo Certo:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Funding acquisition, Conceptualization. **Livia Marrone:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Funding acquisition, Conceptualization. **Lucia Simoni:** Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Methodology, Formal analysis, Data curation, Conceptualization. **Barbara Roncari:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Methodology, Conceptualization. **Silvia Novello:** Writing – review & editing, Writing – original draft, Investigation, Conceptualization. **Sara Ramella:** Writing – review & editing, Writing – original draft, Investigation, Conceptualization.

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P. Bironzo has received payment or honoraria from AstraZeneca, Bristol Myers Squibb, MSD Oncology, Roche, Takeda, Novartis, Sanofi, Amgen, Daiichi Sankyo/Arqule, has received institutional research grants from Roche and Pfizer, and has had Consulting or Advisory Role for Roche, Janssen Oncology, Pierre Fabre, Amgen, Seagen, Regeneron

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S. Silipigni declares no conflict of interest.

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C. Gridelli received honoraria as speaker bureau and advisory board member from AstraZeneca, BMS, MSD and Roche.

A. Lugini declares no conflict of interest.

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A.M. Carta declares no conflict of interest.

L. Ciuffreda declares no conflict of interest.

R. Giusti declares no conflict of interest.

M. Macerelli declares no conflict of interest.

F. Verderame declares no conflict of interest.

F. Zanelli declares no conflict of interest.

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V. Gregorc declares no conflict of interest.

C. Sergi declares no conflict of interest.

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L. Livi declares no conflict of interest.

G. Borra declares no conflict of interest.

S. Gori declares no conflict of interest.

M. Aieta declares no conflict of interest.

A. Bertolini declares no conflict of interest.

F.L. Cecere declares no conflict of interest.

G. Pasello declares no conflict of interest.

D. Rocco declares no conflict of interest.

G. Lo Certo is an employee of AstraZeneca, Italy.

L. Marrone is an employee of AstraZeneca, Italy.

L. Simoni is an employee of IQVIA Solutions Italy SRL.

B. Roncari is an employee of IQVIA Solutions Italy SRL.

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Supplementary materials

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