Clinical and Translational Oncology (2024) 26:3218–3225
https://doi.org/10.1007/s12094-024-03511-7

RESEARCH ARTICLE

Advanced non-squamous NSCLC with no actionable oncogenic driver in Spain: a cross-sectional descriptive analysis of data from the Thoracic Tumor Registry

Enric Carcereny[1] · Delvys Rodriguez-Abreu[2] · Rafael Lopez[3] · Fabio Franco[4] · Maria Guirado[5] · Bartomeu Massutí[6] · Manuel Cobo[7] · Ana Blasco[8] · Guillermo Suay[9] · Edel del Barco[10] · Ana Laura Ortega[11] · Maria Angeles Sala[12] · Patricia Cordeiro[13] · Reyes Bernabé[14] · José Luís González Larriba[15] · Joaquim Bosch-Barrera[16] · Julia Calzas[17] · Joaquín Casal[18] · Airam Padilla[19] · Alfredo Sánchez-Hernandez[20] · Mariano Provencio[4]

Received: 6 March 2024 / Accepted: 26 April 2024 / Published online: 11 June 2024

Abstract

Background Non-small cell lung cancer (NSCLC) accounts for the vast majority of all diagnosed lung cancers. According to their histology, most NSCLCs are considered non-squamous cell carcinoma (NSCC), and up to 85% of the latter may lack either one of the two main actionable oncogenic drivers (i.e., *EGFR* mutations and *ALK* rearrangements).

Objective Our analysis aimed to describe the clinical and epidemiological characteristics of Spanish patients suffering from NSCC with no actionable oncogenic driver in daily clinical practice.

Design A retrospective, cross-sectional, descriptive analysis.

Methods We analyzed the records of all Spanish patients with advanced NSCC diagnosed between January 2011 and January 2020 and included in the Spanish Thoracic Tumor Registry database. We evaluated the presence of metastasis and molecular profiling at the time of diagnosis and treatments received. We also assessed overall survival (OS) and progression-free survival (PFS) according to first-line treatment.

Results One thousand seven hundred ninety-seven Spanish patients with NSCC were included. They were mainly men (73.2%), smokers (current [44.4%] and former [44.4%]) and presented adenocarcinoma histology (97.6%). Most patients had at least one comorbidity (80.4%) and one metastatic site (96.8%), and a non-negligible number of those tested were PD-L1 positive (35.2%). Notably, the presence of liver metastasis indicated a shorter median OS and PFS than metastasis in other locations ($p < 0.001$). Chemotherapy was more often prescribed than immunotherapy as first-, second-, and third-line treatment in that period. In first-line, the OS rates were similar in patients receiving either regimen, but PFS rates significantly better in patients treated with immunotherapy ($p = 0.026$). Also, a high number of patients did not reach second- and third-line treatment, suggesting the failure of current early diagnostic measures and therapies.

Conclusions This analysis of the most lethal tumor in Spain could highlight the strengths and the weaknesses of its clinical management and set the ground for further advances and research.

Keywords Non-small-cell lung cancer · Non-squamous cell carcinoma · Oncogenic driver · Metastasis · Spain

Introduction

Among cancers, worldwide estimates place lung cancer as the most commonly diagnosed and the most common cause of death [1]. Smoking habit is behind most cases; globally, cigarette smoking is responsible for 81% of lung cancers in men and 58% in women [2]. Non-small cell lung cancer (NSCLC) accounts for 85% of all diagnosed lung cancers, [3] and locally advanced NSCLC represent around one-third of all NSCLC at diagnosis [4, 5]. Most lung cancer patients present metastases at the time of diagnosis, which severely impacts their survival prognosis [6]. From a histological point of view, approximately 70% to 78% of NSCLCs are considered non-squamous cell carcinoma (NSCC) [7, 8]. The latter can be classified at the molecular level according to the presence of oncogenic drivers essential for tumor proliferation and survival. Among those, the druggable targets

Extended author information available on the last page of the article

account for a small portion, with *EGFR* mutations (10–15%) and *ALK* rearrangements (2–3%) representing the most prevalent actionable oncogenic drivers [9, 10]. Consequently, 77% to 85% of NSCC patients lack one of these druggable oncogenic drivers [8].

The Spanish Thoracic Tumor Registry (TTR) is a National Registry of lung cancer cases managed and sponsored by the Spanish Lung Cancer Group (SLCG) (*Grupo Español de Cáncer de Pulmón*). The TTR was opened to all Spanish hospitals and the first patient was enrolled in August 2016. The recruitment is still ongoing with more than 75 hospitals taking part. The methodology group of the SLCG designed specifically an electronic questionnaire to be used by the TTR. Based on the TTR, several epidemiological studies on small-cell lung cancer and NSCLC have been published and have proven to be a valuable asset for clinicians and researchers [11–13].

Previous studies describing the epidemiological status of NSCC have been performed in other European and Asian countries, especially focused on treatments and metastases occurrence [6, 14, 15]. However, none of those reports differentiated between patients with and without actionable oncogenic drivers. The distinction may be important to characterize the two populations correctly and could also be informative on the appropriate treatment management of each subgroup. Therefore, the aim of this analysis was to describe the clinical and epidemiological characteristics of Spanish patients suffering from NSCC with no actionable oncogenic driver.

Methods

Study design and participants

Ours was a retrospective, cross-sectional, and descriptive analysis carried out with data recorded in the TTR. We included data from all Spanish patients with advanced NSCC diagnosed between January 2011 and January 2020. We excluded all patients who presented major driver alterations (*EGFR* mutations and *ALK* rearrangements). The TTR has been approved by the Clinical Research Ethics Committee of Puerta de Hierro University Hospital.

Outcomes and measure

We analyzed the comorbidities of our patients and the presence of metastasis, especially in the liver, at the time of diagnosis. We also examined the molecular profile by oncogenic driver of our patients and the treatments they received in first-, second-, and third-line. Besides, we evaluated overall survival (OS) and progression-free survival (PFS) of our cohort according to the first-line treatment prescribed. We calculated OS from the date of diagnosis to the date of last follow-up or death. We determined PFS from the date of diagnosis until the date of clinical or radiographic progression or death.

Statistical analysis

We described categorical variables as absolute frequencies and percentages and continuous variables as mean and standard deviation (SD). We compared the frequency of categorical variables using the Pearson $\chi 2$ test (Fisher exact test for 2×2 contingency tables). We estimated OS and PFS curves from diagnosis with the Kaplan–Meier method, reporting median survival times with the 95% confidence interval (95% CI). We used the log-rank test to compare OS and PFS curves of different groups of patients, using the Benjamini & Hochberg method for correcting p values in multiple comparisons. We reported two-sided p values and set the statistical significance level at p value < 0.05. Data were analyzed using the statistical package R (version 4.2.0).

Results

Demographic and clinical characteristics

Out of the 5049 patients with advanced NSCLC included in the TTR at the time of analysis, 1797 (35.6%) presented non-squamous histology and no actionable *EGFR* and *ALK* alterations and were analyzed here. Our cohort showed a high proportion of men (73.2%) and current (44.4%) and former smokers (44.4%). The mean age was 62.8 years (SD 10.1 years) and adenocarcinoma was the predominant histology (97.6%). Most patients presented at least one comorbidity (80.4%) and the most common were hypertension (39.2%), dyslipidemia (27.8%), and diabetes mellitus (17.5%).

Metastasis and molecular profiling

The vast majority presented metastasis (96.8%), mainly localized in lungs (39.3%), bones (35.2%), and the central nervous system (21.2%). Patients presenting liver metastasis were more likely to have more than two metastatic sites than those with metastases in locations other than the liver (53.1% vs. 20.9%, $p < 0.001$) (Fig. 1). In addition, patients with liver metastasis had significantly shorter median OS ($p < 0.001$) and PFS rates ($p < 0.001$) than those with metastases in other parts of their bodies (Fig. 2).

Patients were mainly tested for the presence of *EGFR*, *ALK*, *ROS*, and *BRAF* mutations and PD-L1 expression. Remarkably, 258 (35.2%) patients showed a positive result on PD-L1 testing.

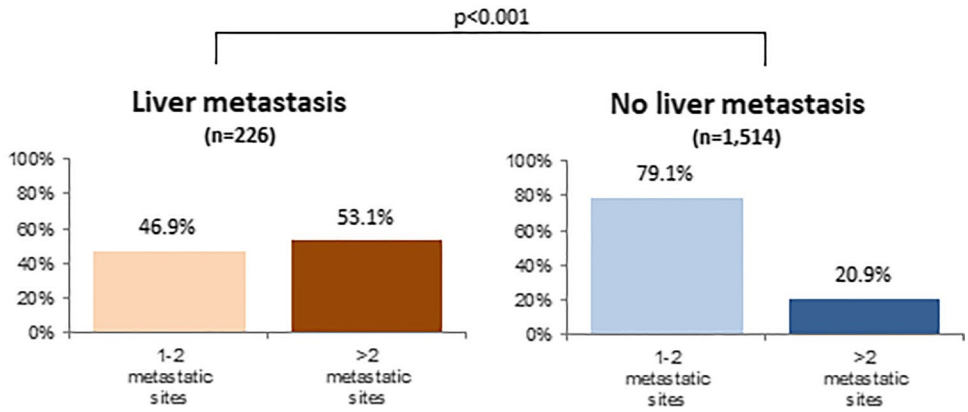

Fig. 1 Number of metastatic sites according to the presence of liver metastasis

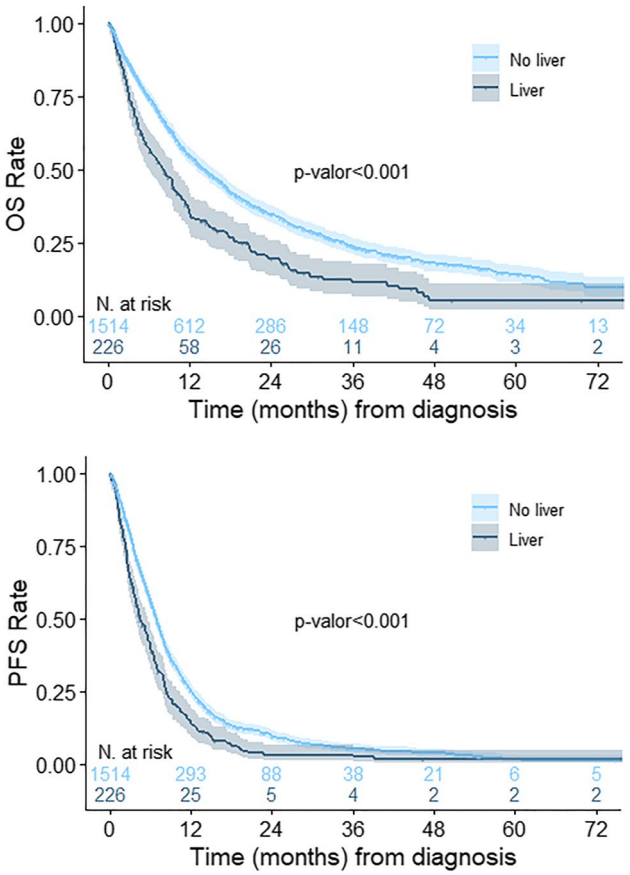

Fig. 2 Overall survival (OS) and progression-free survival (PFS) rates of patients with liver metastasis and with metastasis in other locations. Patients with liver metastasis: median OS 8.1 months (95% confidence interval [95% CI] 6.1–9.7 months). Patients with metastasis in other locations: median OS 14.4 months (95% CI 13.0–15.8 months; $p < 0.001$). Patients with liver metastasis: median PFS 4.5 months (95% CI 3.8–5.7 months). Patients with metastasis in other locations: median PFS 6.9 months (95% CI 6.6–7.3 months; $p < 0.001$)

Treatments

In first-line, 218 (12.1%) patients did not receive pharmacological treatment, 1403 (78.1%) were treated with chemotherapy and 176 (9.8%) with immunotherapy. The most often prescribed treatments were, among chemotherapies, a platinum-based combination with pemetrexed (72.6%), and among immunotherapies, pembrolizumab (85.8%). A total of 934 (52.0%) patients did not receive pharmacological treatment in second-line, whereas 544 (30.3%) were treated with chemotherapy and 319 (17.8%) with immunotherapy. The most used drugs were docetaxel (23.5%) as chemotherapy and nivolumab (62.1%) as immunotherapy. Finally, in third-line, 1384 (77.0%) patients did not receive pharmacological treatment; 247 (13.7%) were treated with chemotherapy,

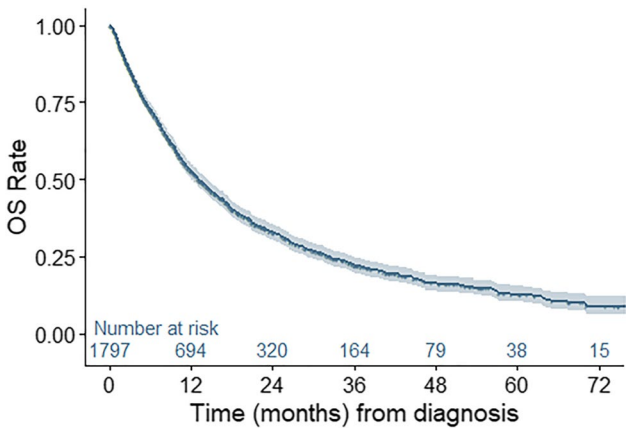

Fig. 3 OS rate from diagnosis of the cohort. Median OS 13.1 months (95% CI 12.0–14.5 months). Estimated OS at 6 months: 72.9% (95% CI 70.7–75.0%), at 12 months: 52.5% (95% CI: 49.9–55.0%), at 18 months: 40.4% (95% CI: 37.8–43.0%), and at 24 months after diagnosis: 33.0% (95% CI 30.4–35.6%). *95% CI* 95% confidence interval; *OS* Overall survival

139 (7.7%) with immunotherapy, and 27 (1.5%) with other therapies. Again, docetaxel (22.7%) among chemotherapies and nivolumab (74.1%) among immunotherapies were the most prescribed drugs.

The median OS of the cohort was 13.1 months (95% CI 12.0–14.5 months) (Fig. 3), and the median PFS was 6.7 months (95% CI 6.3–7.0 months) (Fig. 4). OS rates were not significantly different between patients receiving immunotherapy and those receiving chemotherapy as first-line treatment ($p = 0.524$), but PFS rates were significantly better in the group treated with immunotherapy ($p = 0.026$). On the contrary, patients receiving no pharmacological treatment showed, invariably, significantly lower OS and PFS rates than those treated with chemotherapy ($p < 0.001$ for OS and PFS) and immunotherapy ($p < 0.001$ for OS and PFS) (Figs. 5 and 6).

Discussion

This descriptive analysis showed that Spanish patients with NSCC were mainly men, smokers (current and former), and presented an adenocarcinoma histology. Most patients presented at least one comorbidity and one metastatic site, and a non-negligible number of those tested were PD-L1 positive. Chemotherapy was more often prescribed than immunotherapy as first-, second-, and third-line treatment. In first-line, the OS rates were similar in patients receiving either regimen, but PFS rates were significantly better in patients treated with immunotherapy.

In our analysis, NSCC patients with liver metastasis were more likely to have more than two metastatic sites and had shorter median OS and PFS than those with metastases in other locations. These results are in agreement with previous reports showing that liver metastatic diseases are usually multiple [16, 17] and that liver metastasis, solitary or in combination, is the worst prognostic factor among all

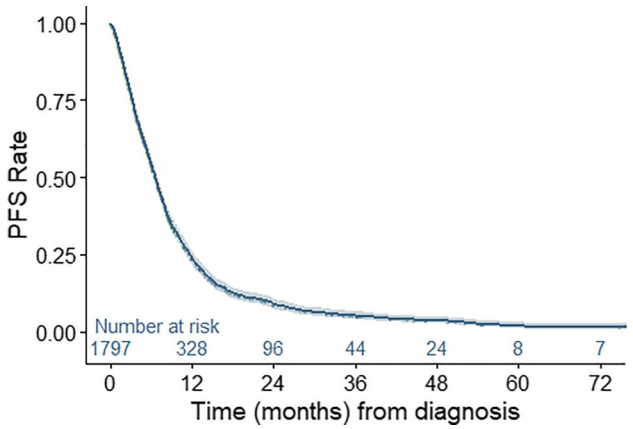

Fig. 4 PFS rate from diagnosis of the cohort. Median PFS 6.7 months (95% CI 6.3–7.0 months). Estimated PFS at 6 months: 54.5% (95% CI 52.1–56.9%), at 12 months: 23.8% (95% CI 21.7–26.0%), at 18 months: 12.4% (95% CI 10.7–14.2%), and at 24 months after diagnosis: 8.9% (95% CI 7.4–10.6%). *95% CI* 95% confidence interval; *PFS* Progression-free survival

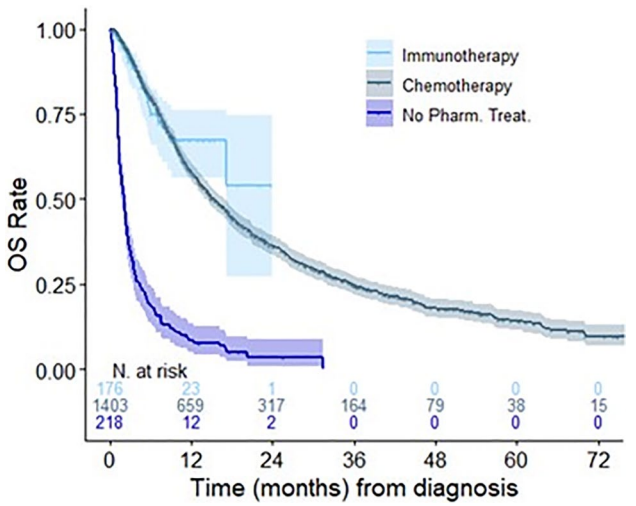

Fig. 5 OS rates according to first-line treatment. Patients receiving immunotherapy: estimated median OS > 24 months (not reached). Patients receiving chemotherapy: estimated median OS 15.4 months (95% CI 14.1–16.9 months). Patients with no pharmacological treatment: estimated median OS 2.1 months (95% CI 1.7–2.4 months). *95% CI* 95% confidence interval, *NR* Not reached, *OS* Overall survival

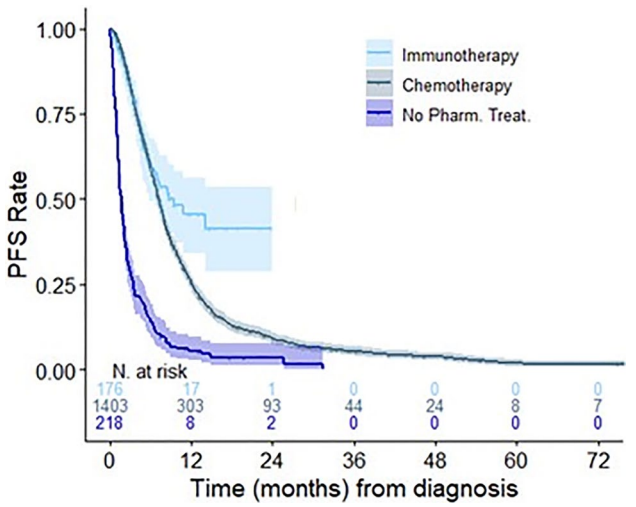

Fig. 6 PFS rates according to first-line treatment. Patients receiving immunotherapy: estimated median PFS 9.4 months (95% CI 5.9-NR months). Patients receiving chemotherapy: estimated median PFS 7.3 months (95% CI 6.9–7.9 months). Patients with no pharmacological treatment: estimated median PFS 1.7 months (95% CI 1.4–1.9 months). *95% CI* 95% confidence interval, *NR* Not reached, *PFS* Progression-free survival

metastatic locations in lung cancer [16, 18–22]. Importantly for clinical practice, patients with liver metastasis have been shown to not respond well to chemotherapy because of metabolism issues. [16, 17, 20]

According to current guidelines, the treatment of advanced NSCLC should take into account tumor histology and molecular pathology and patient's age, performance status, comorbidities, PD-L1 expression, and preferences [23]. In our cohort, the vast majority of patients presented a performance status of 0 or 1 and were PD-L1 negative. Therefore, the most commonly prescribed first-line treatment was platinum doublets with pemetrexed, in agreement with guidelines for patients with these characteristics [23, 24]. The European Medicines Agency approved bevacizumab in 2016 [25] and atezolizumab in 2019 [26] as first-line treatments for NSCC in combination with platinum doublets, which could help explain their underrepresentation in our results. In our analysis, pembrolizumab was the most used immunotherapy, certainly because it is the treatment of choice for patients overexpressing PD-L1 [23]. Similarly, nivolumab plus ipilimumab can be given in patients with a high tumor mutation burden [23], but this treatment was extremely rare in our cohort, most likely because this combination was not approved in Spain in that period.

The treatments of choice as second-line are PD-L1 and PD-1 inhibitors (nivolumab, pembrolizumab, and atezolizumab), but recommendations also include chemotherapy (pemetrexed, docetaxel) if the patient is not suitable to immunotherapy and was not previously exposed to these agents [23]. Accordingly, although chemotherapy was predominant as second-line treatment in our cohort, the proportion of patients treated with immunotherapy nearly doubled with respect to that in first-line, according to clinical practice in this period. Third-line therapies may include whatever agents have not been given in previous lines [24]. In our analysis, third-line treatments were mainly constituted of chemotherapy followed by immunotherapy. Of note, a small number of patients were treated with targeted therapies, implying a re-biopsy or liquid biopsy and biomarker testing in these cases to seek for druggable oncogenic drivers. This procedure would be in agreement with previous reports suggesting the feasibility and utility of re-biopsy in certain patients [27–29]. Notably, 52% of the analyzed patients were not treated in second-line and 77% in third-line, which could indicate either the patient's death after first- and second-line treatments or his/her ineligibility for following therapies. As previously mentioned, new treatments for NSCLC have continuously been approved in Europe in recent years (e.g., nivolumab in 2015 [30] and pembrolizumab in 2016 [31]). However, our analysis was performed on a wide time range covering nine years and could, thus, only partially reflect the current use of such novel therapies.

Although not directly comparable, our cohort's median OS (95% CI 12.0–14.3 months) was shorter than that reported in studies not differentiating between patients with and without actionable oncogenic drivers (median OS with pemetrexed plus bevacizumab: 95% CI 12.6–17.1 months) [32]. Interestingly, in the study based on the TTR population with small-cell lung cancer, median OS (95% CI 8.8–10.2 months) and PFS (95% CI 6.0–6.7 months) were shorter than those of our cohort, implying that small-cell lung cancer has one of the poorest prognoses among all lung cancers [33], even compared with NSCC without oncogenic drivers. As expected, patients not receiving any pharmacological treatment showed significantly lower OS and PFS rates than those treated, certainly due to their ineligibility for the available therapies or to the advanced stage of the disease.

Strengths and limitations

The main strength of our analysis was the uniformity of the studied histology, i.e., NSCC with no actionable oncogenic drivers, for which there were no available data until now. The large population studied here could also be considered a strong point of our analysis; however, this number was achieved at the expense of a broad enrollment time, which precluded homogeneity in therapies and survival. Notwithstanding the abovementioned, our analysis' main limitations were its retrospective and merely descriptive nature.

Conclusion

The results of our analysis described the largest and most comprehensive series of NSCC in the European population. Most patients included in the analysis were men, former or current smokers, and presented at least one comorbidity. Two or more metastatic sites were detected in around a third of patients and the most common location was the lungs. Besides, the presence of liver metastasis indicated a poorer prognosis than metastasis in other locations. Notably, a high number of patients did not reach second and third-line treatment, which may indicate that, although therapies have evolved greatly over the past decades, and there is still room for improvement. This analysis of the most lethal tumor in Spain could highlight the strengths and the weaknesses of its clinical management and set the ground for further advances and research.

Acknowledgements The authors thank Matías Rey-Carrizo, PhD, of BCN Medical Writing, for providing editorial support.

Author contributions Enric Carcereny: Conceptualization, Writing—original draft of the manuscript. Delvys Rodriguez-Abreu, Rafael

Lopez, Fabio Franco, Maria Guirado, Bartomeu Massutí, Manuel Cobo, Ana Blasco, Guillermo Suay, Edel del Barco, Ana Laura Ortega, M. Angeles Sala, Patricia Cordeiro, Reyes Bernabé, Jose Luís Gonzalez Larriba, Joaquim Bosch-Barrera, Julia Calzas, Joaquín Casal, Airam Padilla, Alfredo Sánchez-Hernandez. Mariano Provencio: Conceptualization, Writing—review & editing. All authors take the responsibility for the decision to submit for publication. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Funding This report is independent research funded by the Spanish Lung Cancer Group (*Grupo Español de Cáncer de Pulmón*). The Spanish Lung Cancer Group funded the medical writing support.

Availability of data and materials Relevant anonymised patient level data are available from the corresponding author on reasonable request.

Declarations

Conflict of interest All authors have completed the ICMJE uniform disclosure form at www.icmje.org/disclosure-of-interest/and declare: EC has served as an advisor or consultant for AstraZeneca, Boehringer Ingelheim, BMS, MSD, Novartis, Roche, and Takeda; he has served as a speaker for AstraZeneca, Boehringer Ingelheim, BMS, MSD, Novartis, Pfizer, Roche, and Takeda; he has received grant support from MSD and has received honoraria from BMS, Pfizer, Roche, and Takeda. DR-A has served as an advisor for MSD, Regeneron, BMS, GSK & Lilly has received honoraria for lectures from MSD, Roche, BMS, Novartis, Takeda, Lilly, and AstraZeneca; he has received support for attending meetings and/or travel from Roche, MSD, Novartis and Sanofi. RL has received consulting fees from Roche, AstraZeneca, Boehringer Ingelheim, Novartis, and BMS; He has received payment or honoraria for lectures from Kyowa Kirin, Pierre-Fabre, Takeda, AstraZeneca, BMS, Novartis, Roche, and Pfizer; he has received support for attending meetings and/or travel from MSD. BM has served as an advisor for Roche, BMS, MSD, Boehringer Ingelheim, Takeda, and Abbvie; he has received support for attending meetings and/or travel from Roche, Pfizer, Merck Serono, Boehringer-Ingelheim, and AstraZeneca. GS has received honoraria from Sanofi and has received support for attending meetings and/or travel from Gilead and MSD. MAS has received honoraria from Takeda and Roche and has received support for attending meetings and/or travel from Roche and PharmaMar. PC has received honoraria from Roche, Janssen, Pfizer, Takeda, and BMS and has received support for attending meetings and/or travel from Roche, Janssen, Pfizer, Takeda, and BMS. RB has served as an advisor for AstraZeneca, Roche, Amgen, and MSD; he has received honoraria from BMS, Roche, AstraZeneca, Lilly, MSD, and Pfizer; he has received support for attending meetings and/or travel from AstraZeneca and Roche. JLGL has served as an advisor for MSD, Janssen-Cilag, BMS, Boehringer Ingelheim, and Amgen; he has received payment as an expert testimony from MSD, Janssen-Cilag, BMS, Boehringer Ingelheim, and Amgen; he has received honoraria from MSD, AstraZeneca, Roche, Pfizer, Janssen-Cilag, Novartis, Astellas, and BMS; he has received support for attending meetings and/or travel from MSD, Takeda, BMS, Roche, Pfizer, and Janssen-Cilag. JBB has received grants from Pfizer and Roche; he has received honoraria from AstraZeneca, Pfizer, MSD, BMS, Roche, and Sanofi; he has received support for attending meetings and/or travel from MSD, Takeda, and Roche. AP has served as an advisor for AstraZeneca; he has received payment as an expert testimony from AstraZeneca, Takeda, Roche, BMS, MSD, and Merck; he has received honoraria from AstraZeneca, Takeda, Roche, BMS, MSD, and Merck; he has received support for attending meetings and/or travel from Takeda, AstraZeneca & Merck. MP has been awarded research grants from AstraZeneca, Roche, BMS, Boehringer-Ingelheim, and Takeda; he has served as a consultant for AstraZeneca, BMS, Boehringer-Ingelheim, Celgene, MSD, Roche, Takeda, and Thermo-Fisher. All other authors declare no conflicts of interest.

Ethical approval and consent to participate Not required as this study only used anonymised and aggregated data.

Consent for publication Not applicable.

Informed consent The study was approved by Clinical Research Ethical Comitte from Puerta de Hierro Hospital, and patients alive in the moment their inclusion signed a informed consent.

References

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015;136:E359–86.
2. Whiteman DC, Wilson LF. The fractions of cancer attributable to modifiable factors: a global review. Cancer Epidemiol. 2016;44:203–21.
3. Langer CJ, Besse B, Gualberto A, Brambilla E, et al. The evolving role of histology in the management of advanced non–small-cell lung cancer. J Clin Oncol. 2010;28:5311–20.
4. Park K, Vansteenkiste J, Lee KH, Pentheroudakis G, et al. Pan-Asian adapted ESMO Clinical Practice Guidelines for the management of patients with locally-advanced unresectable non-small-cell lung cancer: a KSMO-ESMO initiative endorsed by CSCO, ISMPO, JSMO, MOS. SSO and TOS Ann Oncol. 2020;31:191–201.
5. Goldstraw P, Chansky K, Crowley J, Rami-Porta R, et al. The IASLC lung cancer staging project: Proposals for revision of the TNM stage groupings in the forthcoming (eighth) edition of the TNM Classification for lung cancer. J Thorac Oncol. 2016;11:39–51.
6. Girard N, Cozzone D, De Leotoing L, Tournier C, et al. Extra cost of brain metastases (BM) in patients with non-squamous non-small cell lung cancer (NSCLC): A French national hospital database analysis. ESMO Open. 2018;3: e000414.
7. Melosky B, Chu Q, Juergens RA, Leighl N, et al. Breaking the biomarker code: PD-L1 expression and checkpoint inhibition in advanced NSCLC. Cancer Treat Rev. 2018;65:65–77.
8. Griesinger F, Eberhardt W, Nusch A, Reiser M, et al. Biomarker testing in non-small cell lung cancer in routine care: analysis of the first 3,717 patients in the German prospective, observational, nation-wide CRISP Registry (AIO-TRK-0315). Lung Cancer. 2021;152:174–84.
9. Cardarella S, Johnson BE. The impact of genomic changes on treatment of lung cancer. Am J Respir Crit Care Med. 2013;188:770–5.
10. Mayekar MK, Bivona TG. Current landscape of targeted therapy in lung cancer. Clin Pharmacol Ther. 2017;102:757–64.
11. Provencio M, Carcereny E, Rodríguez-Abreu D, López-Castro R, et al. Lung cancer in Spain: Information from the Thoracic Tumors Registry (TTR study). Transl Lung Cancer Res. 2019;8:461–75.
12. Ruano-Raviña A, Provencio M, Calvo De Juan V, Carcereny E, et al. Lung cancer symptoms at diagnosis: Results of a nationwide registry study. ESMO Open. 2020;5:e001021.
13. Franco F, Carcereny E, Guirado M, Ortega AL, et al. Epidemiology, treatment, and survival in small cell lung cancer in Spain: data from the thoracic tumor registry. PLoS ONE. 2021;16: e0251761.

14. Moro-Sibilot D, Smit E, de Castro CJ, Lesniewski-Kmak K, et al. Outcomes and resource use of non-small cell lung cancer (NSCLC) patients treated with first-line platinum-based chemotherapy across Europe: FRAME prospective observational study. Lung Cancer. 2015;88:215–22.
15. Zhou Q, Song Y, Zhang X, Chen GY, et al. A multicenter survey of first-line treatment patterns and gene aberration test status of patients with unresectable Stage IIIB/IV nonsquamous non-small cell lung cancer in China (CTONG 1506). BMC Cancer. 2017;17:462.
16. Li J, Zhu H, Sun L, Xu W, et al. Prognostic value of site-specific metastases in lung cancer: a population based study. J Cancer. 2019;10:3079–86.
17. Kagohashi K, Satoh H, Ishikawa H, Ohtsuka M, et al. Liver metastasis at the time of initial diagnosis of lung cancer. Med Oncol. 2003;20:25–8.
18. Riihimäki M, Hemminki A, Fallah M, Thomsen H, et al. Metastatic sites and survival in lung cancer. Lung Cancer. 2014;86:78–84.
19. Huang Y, Zhu L, Guo T, Chen W, et al. Metastatic sites as predictors in advanced NSCLC treated with PD-1 inhibitors: a systematic review and meta-analysis. Hum Vaccines Immunother. 2021;17:1278–87.
20. Tamura T, Kurishima K, Nakazawa K, Kagohashi K, et al. Specific organ metastases and survival in metastatic non-small-cell lung cancer. Mol Clin Oncol. 2015;3:217–21.
21. Xu Q, Wang Y, Liu H, Meng S, et al. Treatment outcome for patients with primary NSCLC and synchronous solitary metastasis. Clin Transl Oncol. 2013;15:802–9.
22. Ren Y, Dai C, Zheng H, Zhou F, et al. Prognostic effect of liver metastasis in lung cancer patients with distant metastasis. Oncotarget. 2016;7:53245–53.
23. Planchard D, Popat S, Kerr K, Novello S, et al. Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2018;29:iv192-237.
24. Melosky B. Treatment algorithms for patients with metastatic non-small cell, non squamous lung cancer. Front Oncol. 2014;4:256.
25. European Medicines Agency. Avastin-H-C-582-II-0086 : EPAR - Assessment Report - Variation. 2016. https://www.ema.europa.eu/en/documents/variation-report/avastin-h-c-582-ii-0086-epar-assessment-report-variation_en.pdf (accessed 15 Oct 2021).
26. European Medicines Agency. Tecentriq-H-C-004143-II-0007-G : EPAR - Assessment report - Variation. 2019. https://www.ema.europa.eu/en/documents/variation-report/tecentriq-h-c-004143-ii-0007-g-epar-assessment-report-variation_en.pdf (accessed 15 Oct 2021).
27. Chouaid C, Dujon C, Do P, Monnet I, et al. Feasibility and clinical impact of re-biopsy in advanced non small-cell lung cancer: a prospective multicenter study in a real-world setting (GFPC study 12–01). Lung Cancer. 2014;86:170–3.
28. Kirita K, Izumo T, Matsumoto Y, Hiraishi Y, et al. Bronchoscopic re-biopsy for mutational analysis of non-small cell lung cancer. Lung. 2016;194:371–8.
29. Hotta K, Ninomiya K, Ichihara E, Kiura K. Significance of re-biopsy of histological tumor samples in advanced non-small-cell lung cancer in clinical practice. Int J Clin Oncol. 2019;24:41–5.
30. European Medicines Agency. Opdivo-H-C-3985-II-0001 : EPAR - Assessment Report - Variation. 2015. https://www.ema.europa.eu/en/documents/variation-report/opdivo-h-c-3985-ii-0001-epar-assessment-report-variation_en.pdf (accessed 15 Oct 2021).
31. European Medicines Agency. Keytruda-H-C-3820-II-0007 : EPAR - Assessment Report - Extension. 2016. https://www.ema.europa.eu/en/medicines/human/EPAR/keytruda#assessment-history-section (accessed 15 Oct 2021).
32. Patel JD, Paz-Ares L, Zinner RG, Barlesi F, et al. Pemetrexed continuation maintenance phase 3 trials in nonsquamous, non–small-cell lung cancer: focus on 2-year overall survival and continuum of care. Clin Lung Cancer. 2018;19:e823–30.
33. Karachaliou N, Pilotto S, Lazzari C, Bria E, et al. Cellular and molecular biology of small cell lung cancer: an overview. Transl Lung Cancer Res. 2016;5:2–15.

Authors and Affiliations

Enric Carcereny[1] · Delvys Rodriguez-Abreu[2] · Rafael Lopez[3] · Fabio Franco[4] · Maria Guirado[5] · Bartomeu Massutí[6] · Manuel Cobo[7] · Ana Blasco[8] · Guillermo Suay[9] · Edel del Barco[10] · Ana Laura Ortega[11] · Maria Angeles Sala[12] · Patricia Cordeiro[13] · Reyes Bernabé[14] · José Luís González Larriba[15] · Joaquim Bosch-Barrera[16] · Julia Calzas[17] · Joaquín Casal[18] · Airam Padilla[19] · Alfredo Sánchez-Hernandez[20] · Mariano Provencio[4]

✉ Enric Carcereny
ecarcereny@iconcologia.net

1 Institut Català D'oncologia Badalona- Hospital Germans Trias I Pujol, B-Argo Group, Badalona, Spain

2 Hospital Universitario Insular de Gran Canaria, Las Palmas de Gran Canaria, Spain

3 Hospital Clínico Universitario de Valladolid, Valladolid, Spain

4 Hospital Universitario Puerta de Hierro-Majadahonda, Madrid, Spain

5 Hospital General Universitario de Elche, Elche, Spain

6 Hospital General Universitario Dr. Balmis de Alicante, Alicante, Spain

7 Hospital Regional Universitario de Málaga, Málaga, Spain

8 Hospital General Universitario de Valencia, Valencia, Spain

9 Hospital Universitari I Politècnic La Fe, Valencia, Spain

10 Hospital Universitario de Salamanca, Salamanca, Spain

11 Hospital Universitario de Jaén, Jaen, Spain

12 OSI Bilbao Basurto, Bilbao, Spain

13 Complejo Hospitalario Universitario A Coruña, A Coruña, Spain

14 Hospital Universitario Virgen del Rocío, Seville, Spain

[15] Hospital Universitario Clínico San Carlos, Madrid, Spain

[16] Josep Trueta and Precision Oncology Group (OncoGIR-Pro), Institut d'Investigacions Biomèdiques de Girona (IDIBGI), Catalan Institute of Oncology, Hospital Universitari Dr, Girona, Spain

[17] Hospital Universitario de Fuenlabrada, Fuenlabrada, Madrid, Spain

[18] Complejo Hospitalario Universitario de Vigo, Vigo, Spain

[19] Hospital Universitario, Nuestra Señora De La Candelaria, Santa Cruz de Tenerife, Spain

[20] Hospital Provincial de Castellón, Castellón, Spain