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RESEARCH ARTICLE

Recommendations for diagnosis and management of non-small-cell lung carcinoma patients with ex20ins *EGFR* mutations: insights from a Delphi consensus

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Abstract

Purpose Patients with non-small-cell lung carcinoma (NSCLC) harboring exon 20 insertion (ex20ins) mutations in the epidermal growth factor receptor (*EGFR*) face a particularly poor prognosis. This consensus aimed to consolidate expert opinions on the diagnosis and management of these patients in view of recent advances in diagnostic and therapeutic approaches.

Methods A comprehensive literature review was conducted to summarize evidence on managing NSCLC patients with ex20ins mutations. Using the Delphi methodology, the perspectives of 30 healthcare professionals (HCPs) from the Spanish National Healthcare System were collected regarding the diagnosis, therapeutic strategies, and patient perspectives of the disease.

Results Experts emphasized the critical role of next-generation sequencing (NGS) in diagnosing NSCLC patients, highlighting the need for detailed molecular profiling to optimize therapeutic decisions. Amivantamab was identified as a potential preferred therapeutic option due to its demonstrated benefit in clinical trials, including patients with brain metastases. Additionally, the HCPs underscored the importance of incorporating patient-reported outcomes (PROs) into clinical evaluation and ensuring access to therapies with proven efficacy.

Conclusions This consensus provides a valuable guideline for diagnosing and managing NSCLC patients with ex20ins *EGFR* mutations, emphasizing the integration of advanced diagnostic tools, evidence-based therapies, and patient-centered care to enhance clinical outcomes and improve patient quality of life.

Keywords NSCLC · Ex20ins · NGS · EGFR-TKI · Amivantamab · EGFR

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Introduction

Lung cancer remains the leading cause of cancer-related mortality worldwide, and it is categorized into two primary subtypes: non-small cell lung carcinoma (NSCLC), accounting for approximately 85% of cases, and small-cell lung carcinoma (SCLC), which represents the remaining 15% [1]. Among European NSCLC patients, approximately 10–15% of the tumors harbor activating mutations in the epidermal growth factor receptor (*EGFR*). Within these patients, approximately 6% are insertions in exon 20 (ex20ins) of the *EGFR* gene [2]. Patients with ex20ins mutations present similar symptomatology to other cancer patients, however, the prognosis for ex20ins mutations is particularly poor, with a 5-year real-world survival rate of around 8% [3]. Moreover, the identification of over 104 distinct ex20ins variants has complicated the diagnosis and subsequent therapeutic management of these patients [4].

Aiming at improving patient prognosis, there has been a paradigm shift in recent years from traditional therapies towards targeted approaches that utilize molecules designed to specifically attack tumors and their microenvironment while minimizing harm to healthy tissues [5]. Among these, *EGFR* tyrosine kinase inhibitors (EGFR-TKIs) have shown significant efficacy in improving survival and clinical outcomes for patients with *EGFR* mutations. Nonetheless, ex20ins mutations present a unique challenge, as they alter the conformation of the kinase-active site, impairing the effectiveness of these inhibitors, thereby limiting the use of this approach in these patients [6]. The development of new EGFR-TKIs specifically targeting the ex20ins mutation phenotype has been challenged by limited efficacy and high toxicity [7, 8]. However, some emerging candidates are demonstrating promising efficacy in patients harboring these mutations [9–11]. On the other hand, low responses have been obtained to anti-PD-1/PD-L1 agents [12]. Consequently, platinum-based chemotherapy has remained the standard treatment for these patients for decades, an approach offering low to moderate efficacy and frequently associated with undesirable toxic side effects [13].

The importance of enhancing diagnostic precision is increasingly recognized, with recent consensus aligned with the recommendations of the European Society for Medical Oncology (ESMO), encouraging the use of high-sensitive techniques to improve detection [14] since traditional techniques, such as polymerase chain reaction (PCR) have shown suboptimal sensitivity, with false-negative rates of up to 50% for ex20ins mutations detection [15].

Currently, ESMO, the National Comprehensive Cancer Network (NCCN), the National Consensus of the Spanish Society of Pathology (SEAP), and the Spanish Society of Medical Oncology (SEOM) strongly recommend the use of NGS for the diagnosis of NSCLC patients. These guidelines also advocate for the use of targeted therapies, such as amivantamab, as a potential therapeutic strategy [14, 16, 17]. Although the aforementioned Spanish consensus addresses some aspects related to the diagnosis and treatment of patients with *EGFR* mutations, this study aimed to gather the opinion of 30 experts in light of recent advances in diagnosis and therapeutic approaches. Through an extensive literature review and a Delphi consensus process, the expert panel identified key unmet needs and proposed strategies to optimize this patient population's diagnosis, treatment, and overall care, providing a valuable additional guideline for clinical routine practice and daily decision-making processes.

Methods

Study design

The Delphi methodology was employed to achieve a consensus on key topics concerning the management of NSCLC patients. This controlled, systematic, structured, and defined process is specifically oriented to gather expert opinions, ensuring credibility through the systematic collection of insights. The study comprised two stages: an extensive literature review, and a Delphi consultation to define the recommendations.

Literature review

An extensive search was conducted using Pubmed and Cochrane databases to compile the available evidence about NSCLC patients with ex20ins *EGFR* mutations. This review was performed employing search filters and the combination of MeSH and open terms using the boolean connectors"OR" and"AND"(Supplementary material). Additionally, manual searches of the gray literature were performed using the websites of the main national and international scientific societies involved in the management of NSCLC, such as the American Society of Clinical Oncology (ASCO) and ESMO. Publications in English and Spanish were included, encompassing observational studies, systematic literature reviews, meta-analyses, consensus statements, and clinical practice guidelines published from January 2018 to January 2023. The literature review concluded in September 2023.

Scientific committee

A total of nine experts (three medical oncologists, three hospital pharmacists, two pathologists, and one molecular

biologist) specialized in the management of NSCLC patients with ex20ins *EGFR* mutations and belonging to hospitals within the Spanish National Healthcare System formed the scientific committee. Utilizing the findings from the literature and guided by a moderator, the committee synthesized and grouped the available evidence by topic, extracting the key points. With the information retrieved, an electronic questionnaire was developed for the Delphi consultation.

Delphi consultation

A two-round Delphi consultation was conducted to collect experts'insights about the management of NSCLC patients with ex20ins *EGFR* mutations. An electronic version of the questionnaire was sent to all the participants to evaluate their level of agreement with the affirmations. After addressing their sociodemographic and professional characteristics, the panelists evaluated the recommendations in the first round using a Likert scale of 7 points, where 1 represented"total disagreement"and 7"total agreement". A consensus was reached when at least 75% of the experts agreed (Likert 6–7) or disagreed (Likert 1–2) about a given recommendation. Those affirmations that did not reach consensus were reformulated in a second round. The affirmations presented were categorized into three sections: diagnostic management of the patient (12 items), therapeutic management of the patient (12 items), and patient's perspective (4 items). Statements regarding diagnostic management of the patients and the patient's perspective (Sections 1 and 3) were formulated using two different perspectives: (1) the current use (if the affirmation adheres to the routine clinical practice) and (2) the adequacy (the necessity of reaching the proposed affirmations to improve patients' management). The percentages of consensus for each recommendation were calculated using a spreadsheet.

Panelists

Given the specific subpopulation of NSCLC patients presenting the ex20ins *EGFR* mutations, the focus group invited 30 healthcare professionals to participate based on their proven experience managing these patients. The survey was completed by the panelists between April and July 2024.

Results

Sociodemographic characteristics of the participants

A total of 30 participants completed the first round of the Delphi consultation, while 29 responses were compiled in the second round (96.67% compared to the first round). The sociodemographic and professional characteristics of the participants are detailed in Table 1. The panelists had a mean (SD) age of 18.30 (7.70) years of professional experience, evenly distributed across related fields: pathology/molecular biology (33.33%), hospital pharmacy (33.33%), and medical oncology (33.33%).

Consensus: patient's management and patient's perspective

Out of 26 affirmations related to the patient's management (covering both diagnostic and therapeutic aspects) and the patient's perspective, 22 reached consensus among the experts (84.62%), with 20 of these affirmations (90.91%) reaching consensus in the first round. However, only 4 recommendations were considered highly implemented in current clinical practice (> 75%).

Diagnostic management of the patient

The panelists recommended the detection of ex20ins mutations in metastatic or advanced NSCLC patients (Table 2), an approach highly implemented in current clinical practice

Table 1 Sociodemographic and professional characteristics of the panelists

Variable	Panelists ($n = 30$)
Age in years, mean (SD)	49 (7.80)
Sex, *n* (%)	
Men	13 (43.33)
Women	17 (56.67)
Years of experience, mean (SD)	18.30 (7.70)
Specialty, *n* (%)	
Pathology/molecular biology	10 (33.33)
Hospital pharmacy	10 (33.33)
Medical oncology	10 (33.33)
NSCLC patients per week, mean (SD)	99 (88.40)
Region, *n* (%)	
Andalucía	3 (10)
Aragón	1 (3.33)
Asturias	1 (3.33)
Canarias	1 (3.33)
Cantabria	1 (3.33)
Cataluña	10 (33.33)
Comunidad Valenciana	4 (13.33)
Galicia	2 (6.67)
Madrid	4 (13.33)
Navarra	2 (6.67)
País Vasco	1 (3.33)

NSCLC non-small cell lung carcinoma, *SD* standard deviation

Table 2 Results of Delphi consensus about the diagnostic management of the patient

Item	Agreement (%)	
	Current use	Adequacy
It is recommended the detection of ex20ins *EGFR* mutations in patients with:		
Metastatic non-squamous NSCLC	70	100
Metastatic squamous NSCLC	50*	48*
Resectable NSCLC	30	74
Advanced NSCLC	75	95
It is recommended to implement a sample collection protocol (tissue or cytological) that allows an anatomopathological and molecular diagnosis	75	100
In general, the detection of the ex20ins *EGFR* mutations from plasma (ctDNA/cfDNA) of NSCLC patients is appropriate when the amount of tissue is insufficient or if the diagnostic result is negative	50	75
If possible, it is recommended the analysis of both tissue and liquid biopsy samples	40*	63
If possible, molecular reflex analysis should be performed to accelerate the diagnosis	70	100
Provided the hospital has the necessary resources, NGS should be prioritized as the first-choice diagnostic method for detecting the ex20ins *EGFR* mutations in NSCLC patients	60	100
After the detection of the ex20ins *EGFR* mutations using NGS, it is essential to prepare a standardized molecular report following a reproducible and detailed nomenclature	75	100
A molecular diagnosis is recommended before initiating the first-line treatment of NSCLC patients with ex20ins *EGFR* mutations	75	100
The establishment of a molecular tumor board is recommended to evaluate the results and determine the optimal treatment of NSCLC patients following a multidisciplinary approach	50	95

cfDNA circulating free DNA, *ctDNA* circulating tumor DNA, *DNA* desoxyribonucleic acid, *EGFR* epidermal growth factor receptor, *NGS* next-generation sequencing, *NSCLC* non-small cell lung carcinoma

*Disagreement

for advanced cases. A consensus was reached on the adequacy of implementing a sample collection protocol for diagnosis, using plasma samples in cases of negative results or insufficient tissue samples. The panelist recommended a reflex analysis, using NGS as a first diagnosis strategy, followed by a standardized molecular report with a reproducible nomenclature. A consensus was also reached in the constitution of molecular tumor boards to provide a multidisciplinary approach. Despite this, the panelists identified limited resources as a significant barrier to implementing these diagnostic steps and establishing multidisciplinary committees to facilitate a comprehensive strategy for patient management.

Therapeutic management of the patient

The panelists' insights regarding different therapeutic approaches are detailed in Table 3. The use of immune checkpoint inhibitors was considered a less effective therapeutic strategy, and the panel did not recommend the use of EGFR-TKIs such as osimertinib as first-line strategies. New personalized therapeutical approaches to treat NSCLC patients with ex20ins mutations were recommended by the panelists. In this context, amivantamab was suggested as a potentially effective second-line treatment for these patients. The experts pointed to findings from the PAPILLON phase III clinical trial, which postulates this molecule as the first-line therapeutical strategy when combined with chemotherapy due to its longer duration of response and higher response rate, along with predictable and manageable adverse events. The panelists also recommended providing patients with detailed information and involving other medical specialists to ensure proper management of potential toxicities.

Patient's perspective

Finally, the panelists assessed the patients' perspective in the context of NSCLC. The participants emphasized the importance of measuring patient-reported outcomes (PROs) such as dyspnea, fatigue, cough, pain (specific to lung cancer), and adverse reaction-related symptoms such as diarrhea, dry skin, rash, and decreased appetite, using standardized patient-related outcomes measures (PROMs) instruments and promoting patients' access to new therapeutic approaches with proven efficacy and safety (Table 4). Nevertheless, the panelists outlined that these recommendations are not adequately implemented in current practice.

Table 3 Results of Delphi consensus about the therapeutic management of the patient

Item	Agreement (%) Adequacy
The current first-line therapeutic approach for advanced NSCLC patients with ex20ins *EGFR* mutations involves platinum-based chemotherapy, either as a single regimen or in combination with immunotherapy, according to the expression levels of PD-L1	65
In general, immunotherapy based on immune checkpoint inhibitors is less effective, whether used as monotherapy or combined with platinum-based chemotherapy in NSCLC patients with ex20ins *EGFR* mutations	80
In general, depending on the specific mutations detected and according to the efficacy and safety results, EGFR tyrosine kinase inhibitors (EGFR-TKIs) such as osimertinib can be considered as the first-line treatment for advanced NSCLC patients with ex20ins *EGFR* mutations	90*[2]
In general, and depending on the efficacy and safety results, amivantamab can be considered as a second-line treatment for advanced NSCLC patients with ex20ins *EGFR* mutations once obtaining a favorable resolution for its reimbursement within the Spanish National Healthcare System	85
All patient subgroups, including those with previously treated asymptomatic brain metastases, are expected to benefit from amivantamab treatment	90[2]
Depending on the safety profile of amivantamab observed in the PAPILLON study, it can generally be concluded that the adverse effects of amivantamab are predictable and manageable events	75
It is essential to have alternative treatments with higher efficacy than chemotherapy for advanced NSCLC patients with ex20ins *EGFR* mutations	100
NSCLC patients with ex20ins *EGFR* mutations receiving targeted therapies distinct from conventional TKIs show improved survival. Thus, the development and access to personalized treatments are recommended	80
The combination of amivantamab with chemotherapy may offer a higher response rate and longer response duration compared to chemotherapy as a first-line treatment for NSCLC patients with ex20ins *EGFR* mutations, according to the results of the PAPILLON phase III trial	85
According to the results of the PAPILLON phase III trial, the combination of amivantamab with chemotherapy might represent the preferred therapeutic approach as a first-line treatment for the majority of advanced NSCLC patients with ex20ins *EGFR* mutations	80
In some instances, to ensure effective management of specific toxicities, it is necessary a multidisciplinary approach involving other specialties, such as dermatology and cardiology, among others	95
It is recommended that patients be provided with detailed information about the potential adverse effects of oncologic treatments and that specific action plans, both prophylactic and therapeutic, be established to address these toxicities	100

cfDNA circulating free DNA, *ctDNA* circulating tumor DNA, *EGFR* epidermal growth factor receptor, *EGFR-TKIs* EGFR tyrosine kinase inhibitors, *NSCLC* non-small cell lung carcinoma, *PD-L1* programmed death-ligand 1, *TKIs* tyrosine kinase inhibitors

*Disagreement

[2]Consensus achieved in the second round

Table 4 Results of Delphi consensus about the patient's perspective

Item	Agreement (%)	
	Current use	Adequacy
It is necessary to routinely measure PROs through appropriate PROMs instruments such as PRO-CTCAE, LCSS, VAS, EQ-5D, and QLQ-LC13	30*	85
It is essential to promote access within the national healthcare system to treatments and diagnostic methods that have demonstrated proven efficacy and safety	50	85

EQ-5D European quality of life-5 dimensions, *LCSS* lung cancer symptom scale, *PRO* patient-reported outcomes, *PRO-CTCAE* PROs version of the common terminology criteria for adverse events, *PROMs* patient-reported outcome measures, *QLQ-LC13* quality of life questionnaire-lung cancer 13

*Disagreement

Discussion

In the present study, the panelists have underscored the importance of NGS-based techniques for accurately diagnosing NSCLC patients with ex20ins *EGFR* mutations. A consensus has been reached on the need for personalized treatment strategies, advocating for the necessity of enhancing the availability and access in Spain to the approved molecules. Additionally, assessing PROs using standardized PROMs was highlighted as essential for enhancing patient management and overall quality of life.

For diagnostic management, a consensus was reached regarding the detection of ex20ins mutations in non-squamous NSCLC patients, which aligns with the guidance of the SEAP and the SEOM [14]. These recommendations are based on the ESMO endorsement, which suggests the use of tumor multigene NGS panel for profiling metastatic

cancers in accordance with the ESMO Scale for Clinical Actionability of molecular Targets (ESCAT) classification [18]. Routine clinical practice guidelines advocate using NGS technology to detect level 1 ESCAT alterations in the profile characterization of samples from non-squamous NSCLC patients [14]. The panelists also recommended the application of NGS for all advanced NSCLC cases. As emphasized by other authors, adopting advanced diagnostic technologies is crucial for improving patient outcomes and avoiding ineffective treatments [15]. Given the genetic heterogeneity within this cohort, transitioning from single-gene testing to NGS is pivotal in providing targeted therapies to NSCLC patients and, in particular, to patients with ex20ins-positive tumors [19]. Overall, the panelists recommended NGS as the primary diagnostic method, though hospital-associated limitations might hinder its implementation in clinical practice. This suggestion aligns with recent studies emphasizing that NGS is cost-effective within the context of lung cancer in the Spanish healthcare system [20]. The agreement in creating a standardized molecular report with a reproducible nomenclature overlaps with the national and international guidelines, suggesting that molecular reports should include patient data, detected mutations, and the sensitivity index for each technique data [14, 21].

The establishment of a protocol for the collection of patient samples to facilitate both histologic and molecular diagnosis was recommended by the participants. This approach has been previously suggested by guidelines recommending preserving samples in neutral buffers with concentrations and preservation times adjusted based on sample sizes [14]. These recommendations advise the availability of two molecular testing methods in cases requiring redundant testing. Additional considerations include using the most recent sample and evaluating the number of cells to be collected, which vary among techniques [22].

The panelists agreed on using plasma samples to detect ex20ins *EGFR* mutations in circulating-tumor/free DNA (ctDNA/cfDNA) when tissue samples are insufficient or when the results are negative, which aligns with the recommendations of the Spanish Societies of Pathology and Medical Oncology [14]. As detailed by other authors, the broad spectrum of ex20ins mutations requires comprehensive genomic profiling to detect all alterations, employing various diagnostic techniques [23]. These approaches have demonstrated an 86% detection rate for somatic alterations, comparable to tissue biopsy, and can identify genomic targets in patients inadequately tested during diagnosis or in subsequent testing to guide targeted therapies [24]. Moreover, the Spanish guidelines pointed out that PCR employing liquid biopsy of cell-free plasma DNA has high specificity (96%) but shows a 66% sensitivity, highlighting the need for ruling out false negative results in suspected patients [14]. The authors concur with the recent publication by Garzón-Ibañez et al., which underscores the necessity of employing liquid biopsy samples when tissue sampling is not feasible, although this technique presents a lower sensibility [25]. Additionally, they advocate for the implementation of a standardized protocol to minimize the risk of false-negative results. A precise molecular characterization of EGFR ex20ins mutations is critical for guiding subsequent therapeutic decisions. Since the work by Ou et al., which identified over 100 distinct ex20ins variants [4, 15], it has been characterized that approximately 90% of these mutations occur between amino acids 766 and 775, predominantly affecting the near and far loops [26]. Characterization of the mutation type is crucial, as treatment response varies according to the specific mutation, with insertions in the near loop demonstrating greater sensitivity to second-generation tyrosine kinase inhibitors (TKIs) compared to those in the far loop, as these last lead to significant structural changes that impede the TKIs union [27].

Regarding the implementation of biomarker reflex testing, which involves initiating molecular diagnosis without waiting for additional medical requests, a consensus was reached among the panelists. A retrospective study involving non-squamous NSCLC patients demonstrated a 55.1% reduction in turnaround time and a 48.9% increase in the detection of targetable mutations [28]. This strategy has been recommended in previous consensus studies since it contributes to adhering to NCCN guidelines regarding timing diagnosis and treatment initiation [29]. All the previously discussed evidence supports the expert recommendation of performing an accurate molecular diagnosis before initiating the treatment.

Finally, the establishment of a molecular tumor board, which would facilitate optimal therapy through a multidisciplinary approach, was strongly recommended by the panelists. As outlined previously, creating these boards fosters effective collaboration among professionals, improving the interpretation of complex molecular data [14]. However, implementing this methodology requires significant resources and time, involving extensive funding and the participation of numerous healthcare professionals [30].

Regarding the therapeutic management, although platinum-based chemotherapy remains the standard therapy, its beneficial effect is unsatisfactory in ex20ins *EGFR* patients. A retrospective real-world study highlighted that the effectivity of this approach on patients with this particular subtype of molecular disease is similar to that in other *EGFR* mutant NSCLC [31]. Thus, novel alternative strategies are necessary to improve the outcomes of this subgroup.

The panelists expressed concerns regarding an alternative therapeutic approach efficacy of immunotherapy based on immune checkpoint inhibitors for patients with ex20ins *EGFR* mutations. A phase II clinical trial demonstrated that using these molecules is ineffective, with 11 out of 25 advanced NSCLC patients with *EGFR* mutations showing no response [32]. Moreover, additional research employing these compounds on patients with ex20ins insertions demonstrated suboptimal results [12, 33], with an overall response rate of 6.7% and a trend towards a shorter overall survival from the time of diagnosis (12.9 months vs. 25.2 months, of patients who did not receive immunotherapy), with a significant association of immunotherapy with a shorter overall survival in the multivariate analysis ($p = 0.04$) [12, 34].

The use of EGFR-TKIs in patients with ex20ins *EGFR* mutations is not recommended except for those that display sensitivity [35]. Insertions in the *EGFR* gene cause conformational changes that constitutively activate the protein, impairing the effectiveness of EGFR-TKIs [6]. For example, osimertinib has demonstrated limited efficacy, showing a 24% response rate when the dose is doubled from 80 to 160 mg [36]. Ex20ins EGFR-specific candidates have yielded heterogeneous results. While mobocertinib and poziotinib have shown modest efficacy [7, 8], the last with a notable high toxicity profile in phase II clinical trials [37], emerging agents such as sunvozertinib and furmonertinib have demonstrated more favorable efficacy and tolerability profiles [9–11]. Nonetheless, further clinical studies are neccesary before considering these compounds as effective therapeutic alternatives for patients with ex20ins mutations. Consequently, the experts recommend developing alternative therapeutic strategies that provide greater benefits than chemotherapy alone.

A recommended treatment for NSCLC patients with ex20ins *EGFR* mutations is amivantamab. This drug received approval from the EMA and FDA in 2021 following the results of the CHRYSALIS clinical trial, which demonstrated an overall response rate of 40% (95% CI 29–51) and a median progression-free survival of 8.3 months [38]. These results were maintained during long-term follow-up, even in elderly patients, patients with previous treatment lines, or patients who are refractory or sensitive to platinum-based chemotherapy [39].

These findings were further corroborated in the phase III PAPILLON study, which demonstrated progression-free survival was significantly longer in amivantamab-treated patients than in the chemotherapy group (median, 11.4 months vs 6.7 months, hazard ratio (HR), 0.40; 95% CI 0.30–0.53; $p < 0.001$). At 18 months, the survival rate was 31% for patients treated with amivantamab, compared to just 3% for those receiving chemotherapy alone. Furthermore, both groups exhibited a comparable incidence of serious adverse events. Among patients treated with avimantamab, most grade or 3 or higher adverse events were related to EGFR-mediated skin toxicities, including rash, paronychia, and acneiform dermatitis [40]. Based on the results obtained in the aforementioned study, which included 23% of brain metastatic patients, the authors suggest that patients with asymptomatic brain metastasis might benefit from amivantamab treatment. Lastly, results in real-world settings have confirmed the effectivity of this molecule [41], postulating amivantamab as an effective therapeutic option.

Finally, the involvement of other specialists in managing NSCLC patients with ex20ins *EGFR* mutations was suggested as a multidisciplinary approach. Previous studies have suggested that prevention plans assessing patients'risk of developing these adverse events and prophylactic treatments, such as tetracycline or corticosteroids, at least 14 days before initiating therapy can reduce these side effects [42].

To include the patient perspective, the panelists recommend using standardized patient-reported outcome measures (PROMs) to assess patient-reported outcomes (PROs) in patients with ex20ins *EGFR* mutations. PROs evaluation, particularly the symptoms, is linked to an improvement in patients'quality of life and survival [43]. The use of tools such as the patient-reported outcomes version of the common terminology criteria for adverse events PRO-CTCAE, visual analog scale (VAS), EuroQol-5D (EQ-5D), and quality of life questionnaire—lung cancer module (QLQ-LC13) can significantly improve patient management by incorporating the patient's perspective to accurately define the frequency and severity of symptoms [44]. However, the panelists noted that the routine application of these methodologies remains limited in clinical practice.

Study limitations and conclusions

The limitations of this study are similar to those found in other consensus studies based on the participants'opinions and experiences, with a potential risk of selection biases. On the other hand, the participants belong to the Spanish National Healthcare System; thus, the described results must be extrapolated considering this framework. However, the extensive experience of the participants in managing this type of patient and the diversity in their professional competencies allow us to determine that valuable recommendations have been detailed. The present study aims to serve as a guideline to assist in routine clinical practice, contributes to the knowledge of the current reality in clinical practice regarding the diagnosis and therapeutic management of patients with NSCLC and ex20ins *EGFR* mutations, serving as a helpful tool to improve patients' quality of life.

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Declarations

Conflict of interest Dra. Isla reports consulting honoraria from AbbVie, Amgen, AstraZeneca, Bayer, BMS, Beigene, Boehringer Ingelheim, F. Hoffmann-La Roche, Johnson & Johnson, Lilly, Merck, MSD, Pfizer, Pharmamar, Sanofi, Takeda and speaker honoraria from Amgen, AstraZeneca, Bayer, BMS, Boehringer Ingelheim, F. Hoffmann-La Roche, Johnson & Johnson, Lilly, MSD, Pfizer, Pharmamar, and Takeda. Also institutional financial interests in clinical trials from AbbVie, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, BMS, Daiichi Sankyo, F. Hoffmann-La Roche, GSK, Johnson & Johnson, Lilly, Merck, Mirati, MSD, Novartis, Pfizer, Pharmamar, Sanofi and research grants from AstraZeneca, BMS, F. Hoffmann-La Roche, and GSK. Dra. Conde reports serving in a consulting or advisory role for Johnson & Johnson, AstraZeneca, and Roche; receiving honoraria from Johnson & Johnson, AstraZeneca, Thermo Fisher, Roche, Lilly, and Pfizer; receiving research funding from Roche and Thermo Fisher. Dra. Romero has received the GECP grant sponsored by Janssen outside of the submitted work. Dra Garrido Siles reports serving in a consulting or advisory role for AstraZeneca, Takeda, and Roche: receiving support for attending meetings and/or travel from Roche, Merck Sharp & Dohme, and Novartis. Dr. Marin reports serving in a consulting or advisory role for Johnson & Johnson; receiving honoraria from Takeda, Daiichi Sankyo, Roche, AstraZeneca, and receiving support for attending meetings and/or Travel from Takeda, Merck Sharp & Dohme, Roche, Daiichi Sankyo and Boehringer Ingelheim. Dr. Massutí reports serving in a consulting or advisory role for Roche, BMS, Boehringer Ingelheim, Takeda, Beigene, Pharmamar and receiving support for attending meetings and/or travel from Roche, Pfizer, MSD, Astra-Zeneca. Dr. Abdulkader received honoraria for speaker, consultancy, or advisory role from Astra-Zeneca, Janssen, Merck-Serono, Roche, Pfizer, BMS, Lilly, Amgen, Astellas, MSD, and grant or travel support from Janssen, and Pfizer. Dra. Carreras reports serving in a consulting or advisory role, receiving honoraria from Johnson & Johnson; Novartis, Menarini Stemline España SLU, Jazz Pharmaceuticals, Takeda Pharmaceuticals international and Regeneron; and receiving support for attending meetings and/or Travel from Roche. Dra. Marina and Dr. Calderón are current employees of Johnson & Johnson. Dr. Gil-Bazo reports serving in a consulting or advisory role for Johnson & Johnson, Lilly, and Boehringer Ingelheim; receiving payment or honoraria from Johnson & Johnson, Amgen, AstraZeneca, Merck Sharp & Dohme, and Takeda; receiving support for attending meetings and/or travel from Johnson & Johnson, Merck Sharp & Dohme, Daiichi Sankyo, and Sanofi. The other authors declare that they have no conflict of interest.

Ethical approval This study did not involve patients or access to patient data and was conducted solely with healthcare professionals. Accordingly, it was exempt from formal ethics committee review in accordance with national regulations.

Consent to participate All participants received detailed information about the study's objectives and procedures. Informed consent wasobtained by their voluntary completion of the first-round questionnaire.

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