Advancements in Non-Small Cell Lung Cancer

Challenges and controversies in resectable non-small cell lung cancer: a clinician's perspective

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The Lancet Regional Health - Europe 2024;38: 100841
Published Online 4 March 2024
https://doi.org/10.1016/j.lanepe.2024.100841

Summary

The treatment landscape of resectable early-stage non-small cell lung cancer (NSCLC) is transforming due to the approval of novel adjuvant and neoadjuvant systemic treatments. The European Medicines Agency (EMA) recently approved adjuvant osimertinib, adjuvant atezolizumab, adjuvant pembrolizumab, and neoadjuvant nivolumab combined with chemotherapy, and the approval of other agents or new indications may follow soon. Despite encouraging results, many unaddressed questions remain. Moreover, the transformed treatment paradigm in resectable NSCLC can pose major challenges to healthcare systems and magnify existing disparities in care as differences in reimbursement may vary across different European countries. This Viewpoint discusses the challenges and controversies in resectable early-stage NSCLC and how existing inequalities in access to these treatments could be addressed.

Keywords: Non-small-cell lung cancer; Lung neoplasms; Immune checkpoint inhibitors; Protein kinase inhibitors; Disease-free survival; Humans; Europe; United States; United States Food and Drug Administration; Access to primary care; Adjuvant chemotherapy; Biomarkers; Surgery

Introduction

In the accompanying Series paper on resectable non-small cell lung cancer (NSCLC), we reviewed the changing treatment landscape for resectable early-stage (stages I–IIIA) NSCLC, focusing on the promising results of new immuno-oncology (IO) and targeted therapy studies.[1] Despite their potential, there are still many questions and concerns. Here, we aim to identify these uncertainties and to discuss the challenges in healthcare access these new treatments may bring about, emphasizing the need to address inequalities.

DOIs of original articles: https://doi.org/10.1016/j.lanepe.2024.100873, https://doi.org/10.1016/j.lanepe.2024.100840, https://doi.org/10.1016/j.lanepe.2024.100838, https://doi.org/10.1016/j.lanepe.2024.100839
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Treatment considerations

Neoadjuvant and perioperative IO therapy

Methodological uncertainties in neoadjuvant, perioperative, and adjuvant IO studies arise from including varied patient groups, characterized by disease stages ranging from stages I to IIIC, and differences in inclusion of patients with *EGFR* and *ALK* alterations.[2–8] These variations can lead to divergent outcomes and complicate comparisons between trials due to patient selection heterogeneity, which directly influences treatment efficacy. Another major concern is the lack of a clear definition of resectability in all current studies, particularly with regard to stage III disease. Inconsistencies in patient inclusion complicate the comparison of results across different trials and hinder the identification of specific patient subgroups that would benefit most from specific neoadjuvant treatments. International efforts are underway to establish a consensus in the definition of resectable stage III NSCLC. One such effort is the initiative led by the European Organisation for Research and Treatment of Cancer (EORTC) in collaboration with other scientific societies, aiming to ensure more uniform patient inclusion criteria in future studies.[9]

Another key methodological issue in neoadjuvant and perioperative studies is the consistent use of chemotherapy as the control arm treatment across all stages of NSCLC from IB to IIIC, which may not reflect the actual standard of care.[2–6] In routine clinical practice, patients presenting with stages IB and II typically undergo initial surgery, followed by adjuvant chemotherapy, rather than the reverse. For stage IIIA, and especially for stages IIIB and IIIC, there is no clear standard treatment, as surgery has not been shown to be superior to chemoradiotherapy.[10,11] Different stage III subtypes might need other neoadjuvant approaches, with some requiring neoadjuvant chemoradiotherapy.[12] This inconsistency with clinical practice and issues with clustering disease stages pose challenges when interpreting study results. Furthermore, although neoadjuvant trials were conducted primarily in patients presenting with initially resectable NSCLC, many studies have lacked detailed information on stage III substages that are relevant for surgical decision-making. The latter includes the extent of tumor invasion into surrounding structures and the involvement of mediastinal lymph nodes, including their number, bulkiness, and invasiveness. Understanding these factors within each subgroup of NSCLC can guide the best treatment combinations for each patient, whether it involves surgery, radiotherapy, or a combination thereof.

Another layer of complexity emerges due to the differences in duration of the neoadjuvant treatment phase of recent phase III neoadjuvant and perioperative IO trials. For instance, CheckMate 816 administered three neoadjuvant cycles of chemoimmunotherapy (chemo-IO) without adjuvant IO, while AEGEAN, KEYNOTE-671, and CheckMate 77T investigated four cycles of chemo-IO, followed by adjuvant IO.[2–5] Neotorch differed further by exploring three cycles of chemo-IO, followed by surgery, and then a fourth chemo-IO cycle postoperatively followed by adjuvant IO.[6] To address these variations, the recently launched phase III neoSCORE II trial is set to compare three *vs* four cycles of neoadjuvant chemo-IO in resectable squamous cell NSCLC, both followed by adjuvant IO, aiming to identify an ideal duration for the neoadjuvant phase.[13]

Neoadjuvant and perioperative IO studies are associated with a risk that patients may not undergo planned surgery due to treatment-related toxicities. In neoadjuvant chemo-IO studies, up to 20% of patients do not proceed to surgery due to disease progression, treatment-induced deterioration or due to having inoperable tumors. For instance, in CheckMate 816, 17% of patients from the nivolumab-chemotherapy group and 25% from the chemotherapy-alone group did not undergo surgery.[2] Other studies reported similar rates.[3–6] In many instances, disease progression was not the reason for avoiding surgery, but instead due to toxicity of the induction therapy. In addition, unrealistic expectations of tumor downstaging could be a contributory factor. This highlights concerns that unwarranted optimism about new induction therapies could lead to missed opportunities for initiating other effective treatments such as chemoradiotherapy followed by durvalumab.[14] It is essential to ensure that a timely Multidisciplinary Tumor Board (MDT) assessment of resectability is performed prior to initiating neoadjuvant therapy. In ambiguous cases, the PACIFIC regimen could be an option as initial definitive chemoradiotherapy does not preclude surgery. However, the benefits of integrating surgery following definitive chemoradiotherapy in such patients remain unclear and warrant further research.

A large and growing body of evidence demonstrates that the quality of surgery is important to ensure good clinical outcomes.[15,16] The rates of adherence to guideline-recommended surgical quality metrics have been reported to be suboptimal.[17,18] Although only limited details of specific surgical quality measures and outcome data from current neoadjuvant chemo-IO trials are available, the overall quality of surgery appears to be high, as evidenced by the low rates of complications and mortality reported and by the improvement in survival observed.[2–6] Nevertheless, surgical quality metrics should be prospectively collected in future trials, and ultimately lead to a better understanding of trials results and allow for trial cross-comparisons. It will be interesting to see whether the promising trial results to date will also be observed at institutions that did not participate in these trials, especially in patients with more advanced stage III NSCLC, for whom the surgical challenges are likely to be the highest.[19]

Despite the current neoadjuvant and perioperative IO (Table 1),[20,21] the superiority of surgery over non-surgical approaches like the PACIFIC regimen for

Trial/NCT identifier	Stage	No. of patients (%)	Event-free survival (median in months, 95% CI)		Hazard ratio (95% CI)	Co-primary endpoint
			Experimental arm	Control arm		
CheckMate 816[2,20] NCT02998528	All stages[a]	358 (100)	NR (31.6–NR)	21.1 (14.8–42.1)	0.68 (0.49–0.93)	pCR: CT + nivolumab 24.0% (43/179) *vs* CT 2.2% (4/179)
	IB-II	126 (35)	NR[b]	NR[b]	0.94[b,c]	
	IIIA	229 (64)	NR[b]	16.9[b]	0.57[b,c]	
CheckMate 77T[5] NCT04025879	All stages[d]	461 (100)	NR (28.9–NR)	18.4 (13.6–28.1)	0.58 (0.42–0.81)	None
	II	162 (35)	NR (22.6–NR)	NR (24.4–NR)	0.81[c] (0.46–1.43)	
	III	297 (64)	30.2 (26.9–NR)	13.4 (9.8–17.7)	0.51[c] (0.36–0.72)	
AEGEAN[4] NCT03800134	All stages[d]	740 (100)	NR (31.9–NR)	25.9 (18.9–NR)	0.68 (0.53–0.88)	pCR: CT + durvalumab 17.2% (63/366) *vs* CT + placebo 4.3% (16/374)
	II	214 (29)	NR (NR–NR)	31.1 (25.4–NR)	0.76[c] (0.43–1.34)	
	IIIA	338 (46)	NR (NR–NR)	19.5 (11.7–NR)	0.57[c] (0.39–0.83)	
	IIIB	186 (25)	31.9 (11.7–NR)	18.9 (11.8–NR)	0.83[c] (0.52–1.32)	
KEYNOTE-671[21] NCT03425643	All stages[d]	797 (100)	47.2 (32.9–NR)	18.3 (14.8–22.1)	0.59 (0.48–0.72)	OS[e] (stage II–IIIB): CT + pembrolizumab NR (NR–NR) *vs* CT + placebo 52.4 (45.7–NR) HR 0.72 (95% CI 0.56–0.93)
	II	239 (30)	Not reported	Not reported	0.59[c] (0.40–0.88)	
	IIIA	441 (55)	Not reported	Not reported	0.57[c] (0.44–0.74)	
	IIIB	117 (15)	Not reported	Not reported	0.57[c] (0.36–0.90)	
Neotorch[6] NCT04158440	All stages[d,f]	404 (100)	NR (24.4–NR)	15.1 (10.6–21.9)	0.40 (0.28–0.57)	MPR: CT + toripalimab 48.5% (98/202) *vs* CT + placebo 8.4% (17/202)
	IIIA	272 (67)	Not reported	Not reported	0.44[c] (0.29–0.66)	
	IIIB	129 (32)	Not reported	Not reported	0.30[c] (0.15–0.56)	

Abbreviations: NCT, national clinical trial; CI, confidence interval; NR, not reached; pCR, pathological complete response; CT, chemotherapy; OS, overall survival; HR, hazard ratio; MPR, major pathological response. Median follow-up (months): CheckMate 816, 41.4 m; CheckMate 77T, 25.4 m; AEGEAN, 11.7 m (among patients without an event); KEYNOTE-671, 36.6 m; Neotorch, 18.3 m. The number of patients in the substages may not add up to 100%. [a]American Joint Committee on Cancer (AJCC) seventh edition. [b]95% CI not reported. [c]Unstratified hazard ratio. [d]AJCC eighth edition. [e]Median in months with 95% CI. [f]Based on the first interim analysis of stage III patients.

***Table 1*: Summary of the primary endpoints in published phase III neoadjuvant and perioperative clinical trials in stages I–III non-small cell lung cancer.**

resectable stage IIIA and IIIB NSCLC remains unclear.[22] Earlier studies, such as INT0139 and ESPATUE, evaluated the benefits of surgery following chemoradiotherapy *vs* exclusive chemoradiotherapy with curative intent.[10,11] While the overall population of INT0139 did not show a survival benefit for surgery, patients undergoing a lobectomy had better outcomes than a nonsurgical approach. As we navigate the immunotherapy era, it is crucial to obtain randomized data to discern if neoadjuvant chemo-IO followed by surgery outperforms chemoradiotherapy followed by durvalumab, and, if it does, which specific substages and patients benefit most.

Adjuvant IO therapy

The benefits of adjuvant IO following neoadjuvant chemo-IO and surgery remain unclear, mainly because current trials have not directly compared an exclusively neoadjuvant approach with the perioperative approach. While an indirect comparison between the neoadjuvant-only CheckMate 816 and the perioperative CheckMate 77T could offer insights into the benefits and side effects of adding adjuvant nivolumab post-neoadjuvant chemo-IO, a randomized trial to address this question is crucial, especially as significantly higher costs are associated with the perioperative approach. Considering the focus of trials from the pharmaceutical industry that involve longer perioperative approaches, such a trial may best be initiated by independent cooperative oncology groups.

The optimal duration of adjuvant IO therapy is presently unclear. Phase III trials typically administer adjuvant IO for one year, but treatment adherence is low.[3–8] For example, only 73% of patients in KEYNOTE-671 received adjuvant pembrolizumab, and just 40% of enrolled patients completed the full year of treatment, suggesting a role for factors like treatment fatigue or late toxicities.[3] A shorter duration of adjuvant therapy such as the 6-month adjuvant phase investigated in the NADIM II trial, could possibly offer comparable efficacy, but fewer side effects.[23]

Adjuvant targeted therapy

The ADAURA trial demonstrated the overall survival (OS) benefits of adjuvant osimertinib in *EGFR* mutation-positive tumors, irrespective of whether patients had received chemotherapy or not.[24] The observed 10% 5-year OS increase from osimertinib could exceed the 5-year benefit of 5% using chemotherapy-alone that was reported by the LACE meta-analysis and NATCH trial.[25,26] Yet, focusing on stage II and III, the actual benefit of adjuvant chemotherapy likely falls between 10% and 15%.[27] Particularly for the patients with higher disease stages, the ADAURA findings should not deter from administering chemotherapy. In contrast, the ALINA trial, which reported DFS benefits for adjuvant alectinib in *ALK*-positive patients, did not include chemotherapy in its intervention arm, potentially affecting survival gains.[28] The full extent of the OS benefits in the ALINA trial remains to be seen with longer follow-up.

Despite the success of adjuvant osimertinib for *EGFR* mutation-positive tumors in ADAURA, data on adjuvant targeted therapies for other actionable

oncogenic drivers like *ROS-1* and *RET* are limited. The rarity of these mutations and the need for molecular diagnostics make large-scale phase III trials challenging. Addressing this issue requires international collaboration, and possibly use of non-traditional clinical trial formats.

Pathological and molecular biomarkers

In the current treatment landscape, testing for *EGFR* and *ALK* alterations is essential before initiating any treatment to determine eligibility for adjuvant targeted therapies, and potentially avoid chemoimmunotherapy in selected patients. In addition, tumor PD-L1 testing plays a significant role in choosing between upfront surgery and neoadjuvant therapy. However, as research evolves, comprehensive genomic profiling, including other actionable genomic alterations, will become increasingly important for fine-tuning the choice between neoadjuvant and adjuvant treatments.

The role of a pathological complete response (pCR) as an efficacy endpoint in trials for resectable NSCLC is a subject of ongoing debate, particularly regarding its association with OS. Earlier studies indicated that pCR after neoadjuvant treatments correlated with better OS.[29,30] Similar findings were suggested by the CheckMate 816 trial, although long-term data are pending.[31] Currently, the International Association for the Study of Lung Cancer (IASLC) is exploring the validity of pCR as a neoadjuvant trial endpoint.[32] A recent IASLC reproducibility study revealed excellent reliability in cases with no residual viable tumor (pCR) and good reliability for major pathological response (MPR), using the less than or equal to 10% cutoff for viable tumor after neoadjuvant treatment as recommended by the IASLC.[33] Further efforts are ongoing to establish pCR and MPR as predictors of long-term clinical benefit.

In addition, post-treatment pCR is being considered as a biomarker to guide the selection, duration, and timing of adjuvant therapy. While it indicates tumor response to neoadjuvant therapy, its role in guiding subsequent adjuvant treatments remains uncertain. For instance, if a patient achieves pCR, the need for further adjuvant therapy using the same immunotherapy agent might be questionable. Conversely, if there is a suboptimal pathological response, the appropriateness of continuing with the same agent during the adjuvant phase may also be questioned.

Post-surgery circulating tumor DNA (ctDNA) shows promise as a marker for minimal residual disease, despite limitations.[34] Not all tumors release ctDNA, and current techniques lack the sensitivity to detect all tumors. Nevertheless, ctDNA clearance is gaining recognition as a measure of efficacy, as exemplified in CheckMate 816, where ctDNA clearance correlated with higher pCR rates and improved event-free survival.[2] However, the potential of ctDNA to guide adjuvant therapy decisions needs further exploration in clinical trials.

Variations in access to new treatments

While the accompanying Series paper on resectable NSCLC extensively discussed the reasons behind the existing regional access inequalities in Europe, here, we will explore potential strategies to address these disparities.[1]

Preferences and practices

Variations in care are not only influenced by unequal access to medications, but can also result from other factors including the absence of uniform definitions of resectability and the lack of stage-specific treatment guidelines based on reliable survival data.

In addressing these variations, it is essential to consider the influence of historical practices, healthcare infrastructures, institutional experiences, composition of MDTs, and patient choice, especially in stage III NSCLC. While treatments for stage I or II show considerable consistency worldwide, stage III treatments vary notably, even within countries.[35] For example, in the Netherlands, Switzerland, and the United States, chemoradiotherapy followed by surgery is a common approach.[36–38] However, Spain and other European countries favor use of a chemo-surgery approach.[38,39] Centers in Japan often opt for direct surgery without prior induction therapy, with as many as 75% of cN2 cases reflecting use of this approach.[40] These diverse approaches underline the absence of uniform resectability definitions and stage-specific treatment recommendations based on mature survival data, leading to divergent treatment preferences.

Discrepancies in surgical adherence among countries also highlight the need for detailed national datasets to understand stage III NSCLC treatment patterns. The experience in the United Kingdom is illustrative, as after identifying surgical disparities, improvements were seen in both resection rates and survival.[41,42] This observation highlights the potential of data-driven improvements pushing change. Unfortunately, comprehensive lung cancer data in Europe are often fragmented or missing.[43]

To effectively track epidemiological trends and understand care variations, establishing or improving (inter)national registries with standardized data items and definitions is critical. These registries are vital for robust data collection. Initiatives like the WHO's International Agency for Research on Cancer (IARC) and the European Health Data & Evidence Network (EHDEN) under the Innovative Medicines Initiative (IMI) are key steps toward harmonizing institutional data, thereby reducing heterogeneity in real-world data collection and enhancing the quality and utility of real-world evidence in NSCLC research and care.[44,45] These efforts are

particularly important as we anticipate shifts in treatment modalities with the rise of chemo-IO treatments.

Varying approaches to lung cancer screening across Europe might result in unequal opportunities for early detection and treatment. As more data is being generated on this subject, numerous countries are initiating their own studies and programs.[46] Despite this, there is still a lack of a robust global recommendation, which further contributes to these inconsistencies.

Inequality in access

Following marketing authorization by the European Medicines Agency (EMA), regional inequality in access to novel therapies can cause major variations in treatment patterns. These inequalities include budget constraints, long delays reaching reimbursement settlements, challenges in integrating novel therapies into clinical practice guidelines, limited access to high-quality diagnostics, healthcare infrastructure limitations, and suboptimal treatment pathways.[47] The Series paper on resectable NSCLC provides a more detailed list of causes that need attention.[1]

One notable obstacle is partial reimbursement, where coverage is restricted to specific patient subpopulations, limiting access compared to the broader population defined by the EMA label. Additionally, in certain countries, expensive therapies require individual approval from health insurance companies for each patient, creating a significant barrier for treating oncologists.[48] To overcome such barriers, a collaborative approach involving multiple stakeholders is needed, particularly in the post-approval reimbursement and post-reimbursement access stages.

Financial considerations play a significant role in healthcare access. Middle-income countries may struggle with affording new NSCLC diagnostics and treatments. Negotiating drug prices at the state level can potentially improve affordability. In lower and lower-middle-income countries, focusing reimbursement on subgroups with proven survival and quality of life benefits could be a strategic approach. The Access to Oncology Medicines (ATOM) Coalition aims to improve access to oncology medicines and indicates the need for a collective effort to enhance accessibility to cancer treatments.[49]

Guidelines, such as those from NCCN or NICE, provide a basis of evidence, typically graded using methodologies like Grading of Recommendations Assessment, Development, and Evaluation (GRADE). It is essential for individual countries, especially those with limited resources, to be more stringent regarding the level of evidence required for implementing recommendations. However, a potential drawback of this approach is that many practice-changing results from large studies are based on single trials and might not reach a high level of GRADE evidence. This scenario leaves room for assessors to reject recommendations, which could be crucial for current neoadjuvant and adjuvant therapies in NSCLC. Therefore, a balance must be struck between being evidence-stringent and pragmatically adopting new, but promising, treatments.

High-quality staging is essential, this should include FDG-PET/CT chest-abdomen scan, (invasive) mediastinal (re)staging, and brain imaging in accordance with international guidelines.[12] NSCLC treatment guidelines recommend pre-induction FDG-PET scans before curative therapy for proper staging. However, the limited availability of PET scanners in certain regions can lead to variations in staging quality.[50] Additionally, the role of PET particularly in post-induction re-staging is not clearly defined, and therefore not widely implemented, but re-staging PET may help identifying post-neoadjuvant progressive disease, thus preventing patients from unnecessary surgeries. It is also worth noting that a nodal flare observed in post-induction PET-CT scans after immunotherapy or chemoimmunotherapy often indicates an immune response rather than metastasis, underscoring the continued need for surgery in these cases.[51]

Improvements in diagnosis is also universally important. The effectiveness of neoadjuvant and adjuvant therapies largely depends on biomarker testing. However, regional inequalities, particularly in Central and Eastern Europe, limit access due to restricted reimbursements.[52] The current focus on single-gene *EGFR* testing combined with PD-L1 and *ALK* testing should evolve to encompass broader molecular testing to maximize therapeutic outcomes (refer to the Viewpoint on advanced stage NSCLC).[53] Unfortunately, despite guidelines recommending their use, advanced technologies like next-generation sequencing remain largely inaccessible.[52,54] Advancements in molecular testing techniques and the centralization of these facilities, particularly in middle-income countries, could optimize the use of resources. With ongoing technological progress, we can anticipate a reduction in the costs of molecular testing, making comprehensive and upfront testing more affordable and widespread. Such developments will enable more precise and personalized treatments.

The role of MDTs is increasingly critical in lung cancer care, with many countries like the Netherlands, Germany, and England mandating near-universal MDT involvement. However, disparities exist in MDT participation, with significant regional differences within countries. In Italy, a 2019 survey exposed stark disparities with roughly 50% of radiologists reporting no MDTs at their hospitals, with regional variations from 27% in Northern, 39% Central, and 68% Southern Italy.[55] Comparable challenges persist in Central and Eastern European nations, and data from an Asian study showed just 32% of stage III NSCLC cases underwent MDT

Recommendation box

Research design

- Universal consensus on resectability criteria in stage III NSCLC is lacking and should therefore be consensually defined, at least for research purposes.
- Studies should be tailored to reflect the actual standard of care for each substage of NSCLC, especially for stage III substages involving radiotherapy.
- Study designs should consider incorporating ctDNA clearance and pCR for stratification of adjuvant therapy, as the role of these biomarkers for guiding adjuvant therapy still needs more clarification.
- Surgical study designs should encompass surgical quality metrics, enhancing the evaluation of surgical methods employed and optimizing resection quality and survival rates.

Treatment protocols

- Patients with resectable stage III disease without driver mutations could benefit from neoadjuvant immunotherapy combined with chemotherapy, while the added value of adjuvant immunotherapy to neoadjuvant chemoimmunotherapy still needs to be evaluated.
- For those with resectable stage IB to II disease, adjuvant chemotherapy continues to be a primary recommendation. In those exhibiting positive tumor PD-L1 expression, the possibility of neoadjuvant chemoimmunotherapy or adjuvant immunotherapy after adjuvant chemotherapy could be considered.
- Patients with resectable *EGFR* mutation-positive NSCLC, especially in stages II and III, should receive adjuvant chemotherapy followed by adjuvant osimertinib and should not receive neoadjuvant chemoimmunotherapy.

Molecular testing

- Molecular testing for *EGFR*, *ALK*, and PD-L1 should be performed before initiating treatment.
- Broad, comprehensive molecular testing, emphasizing sequencing of DNA and RNA, is to be preferred over single-gene testing.
- Prioritizing reimbursement for diagnostic tests that align with already reimbursed medicines is essential.

Data collection and health infrastructure

- National and international registries with standardized data items and definitions should be established or improved to effectively map epidemiological patterns in resectable NSCLC to show care disparities and impact of new treatments.
- The critical role of multidisciplinary teams (MDTs) in the evolving therapeutic strategies for early-stage lung cancer should be acknowledged and underscored.
- Discrepancies in MDT advice should be minimized, and efforts should be oriented toward bolstering access to approved novel treatments and strengthening the MDT infrastructure.

Policy harmonization and access

- Partnerships aiming for parallel submission and review processes with international regulatory bodies should be pursued to speed up patient access.
- Health policies across European countries should seek regional harmonization, with an aim to streamline administrative procedures for swifter approvals from health insurance companies.

discussions.[56,57] Barriers like infrastructure, logistics, financial limitations, and expert shortages hinder MDT adoption.[58]

Conclusion

While the advent of novel adjuvant and neoadjuvant systemic treatments marks a fundamental shift in the management of patients with a resectable NSCLC tumor, it also brings about a set of challenges and questions that have yet to be addressed. The inequalities in access due to regional differences in healthcare systems and reimbursements across European countries bring significant concerns. As we move forward, it is imperative to address these disparities, ensuring that advancements in treatments translate into improved care and equal access for all NSCLC patients.

Contributors

I.H. contributed with conceptualization, data curation, formal analysis, methodology, project administration, resources, visualization, writing—original draft, writing—review & editing. R.A.M.D., N.R., M.P., A.L., R.D., C.P., M.D.M., M.T., A.B., and S.P. contributed with data curation, investigation, resources, validation, writing—review & editing. C.D. contributed with conceptualization, data curation, formal analysis, methodology, project administration, resources, supervision, validation, visualization, writing—original draft, writing—review & editing. C.A.G. contributed with data curation, formal analysis, resources, supervision, validation, visualization, writing—review & editing. S.S. contributed with conceptualization, investigation, methodology, project administration, resources, supervision, validation, writing—original draft, writing—review & editing. I.B. contributed with conceptualization, formal analysis, investigation, methodology, project administration, resources, supervision, validation, visualization, writing—original draft, writing—review & editing.

Declaration of interests

I.H., C.D., R.A.M.D., N.R., and I.B. declare no competing interests. C.A.G. has received grants or contracts from Boehringer Ingelheim, Astellas, Celgene, Sanofi, Janssen-Cilag, Bayer, Amgen, Genzyme, Merck, Gilead, Novartis, AstraZeneca, Roche, NIH, and ASCERTAIN, all payments were made to the institute, outside the submitted work. M.P. has received research funding from MSD, AstraZeneca, Roche, Boehringer Ingelheim, and Takeda, outside the submitted work; consulting fees from Bristol-Meyers, Roche, MSD, AstraZeneca, Takeda, Eli Lilly, F Hoffman-La Roche, Janssen, Pfizer, and Takeda, outside the submitted work; honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Bristol-Meyers, Roche, MSD, AstraZeneca, Takeda, Eli Lilly, F Hoffman-La Roche, Janssen, and Pfizer, outside the submitted work; and support for attending meetings and/or travel from AstraZeneca, Boehringer Ingelheim, Bristol-Meyers Eli Lilly, F Hoffman-La Roche, Phierre Fabre Pharmaceuticals, and Takeda, outside the submitted work. A.L. has received grants for academic research from PharMamar, Beigene, Roche, AstraZeneca, and Amgen, outside the submitted work. R.D. has received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Roche, AstraZeneca, Takeda, Novartis, BMS, MSD, Pfizer, and Amgen, outside the submitted work; support for attending meetings and/or travel from Pfizer, outside the submitted work; drug samples from Novartis, outside the submitted work; and participated on a Data Safety Monitoring Board or Advisory Board of GlaxoSmithKline, outside the submitted work. C.P. has received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from AstraZeneca, outside the submitted work. M.D.M. has received institutional research

funding from Tesaro/GlaxoSmithKline and institutional funding for work in clinical trials/contracted research from Beigene, Exelixis, MSD, Pfizer and Roche, outside the submitted work; and personal fees for consultancy or participation to advisory boards from AstraZeneca, Boehringer Ingelheim, Janssen, Merck Sharp & Dohme (MSD), Novartis, Pfizer, Roche, GlaxoSmithKline, Amgen, Merck, and Takeda, outside the submitted work. M.T. has received institutional research funding from AstraZeneca, BMS, MSD, Roche, and Takeda, outside the submitted work; payment or honoraria (personal) for speakers bureaus from Amgen, AstraZeneca, Beigene, BMS, Boehringer Ingelheim, Celgene, Chugai, Daiichi Sankyo, GlaxoSmithKline, Janssen Oncology, Lilly, MSD, Novartis, Pfizer, Roche, Sanofi, and Takeda, outside the submitted work; and support for attending meetings and/or travel from AstraZeneca, BMS, Boehringer Ingelheim, Daiichi Sankyo, Janssen Oncology, Lilly, Merck, MSD, Novartis, Pfizer, Roche, Sanofi, and Takeda, outside the submitted work. A.B. has received consulting fees (personal) from AstraZeneca, BMS, MSD, and Roche, outside the submitted work; and payment or honoraria (personal) for lectures, presentations, speakers bureaus, manuscript writing or educational events from AstraZeneca, BMS, MSD, and Roche, outside the submitted work. S.P. has received consulting fees (personal) from Amgen, AstraZeneca, Bayer, Blueprint, BMS, Boehringer Ingelheim, Daiichi Sankyo, GSK, Guardant Health, Incyte, Janssen, Lilly, Merck Serono, MSD, Novartis, Roche, Takeda, Pfizer, Seattle Genetics, Turning Point Therapeutics, and EQRx, outside the submitted work; payment or honoraria (personal) for lectures, presentations, speakers bureaus, manuscript writing or educational events from AstraZeneca, Bayer, Guardant Health, Janssen, Merck Serono, Roche and Takeda, outside the submitted work; payment for expert testimony from Roche and Merck Serono, outside the submitted work; support for travel from Janssen and Roche, outside the submitted work; consulting fees for participation on an Advisory Board, outside the submitted work; unpaid leadership role in the British Thoracic Oncology Group, ALK Positive UK, Lung Cancer Europe, Ruth Strauss Foundation, Mesothelioma Applied Research Foundation, and ETOP-IBCSG Partners Foundation Board, outside the submitted work. S.S. has received research grants (institution) from AstraZeneca and personal honoraria for participating in the trial steering committee for immunotherapy in small cell lung cancer from AstraZeneca, outside the submitted work; consulting fees from AstraZeneca and BMS, outside the submitted work; speaker honoraria (self) from AstraZeneca, outside the submitted work; participates on a Data Safety Monitoring Board as a review panel member for lung toxicity adjudication with immunotherapy (MSD), outside the submitted work; and has a leadership role as an ETOP member of the scientific committee for lung cancer, outside the submitted work.

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