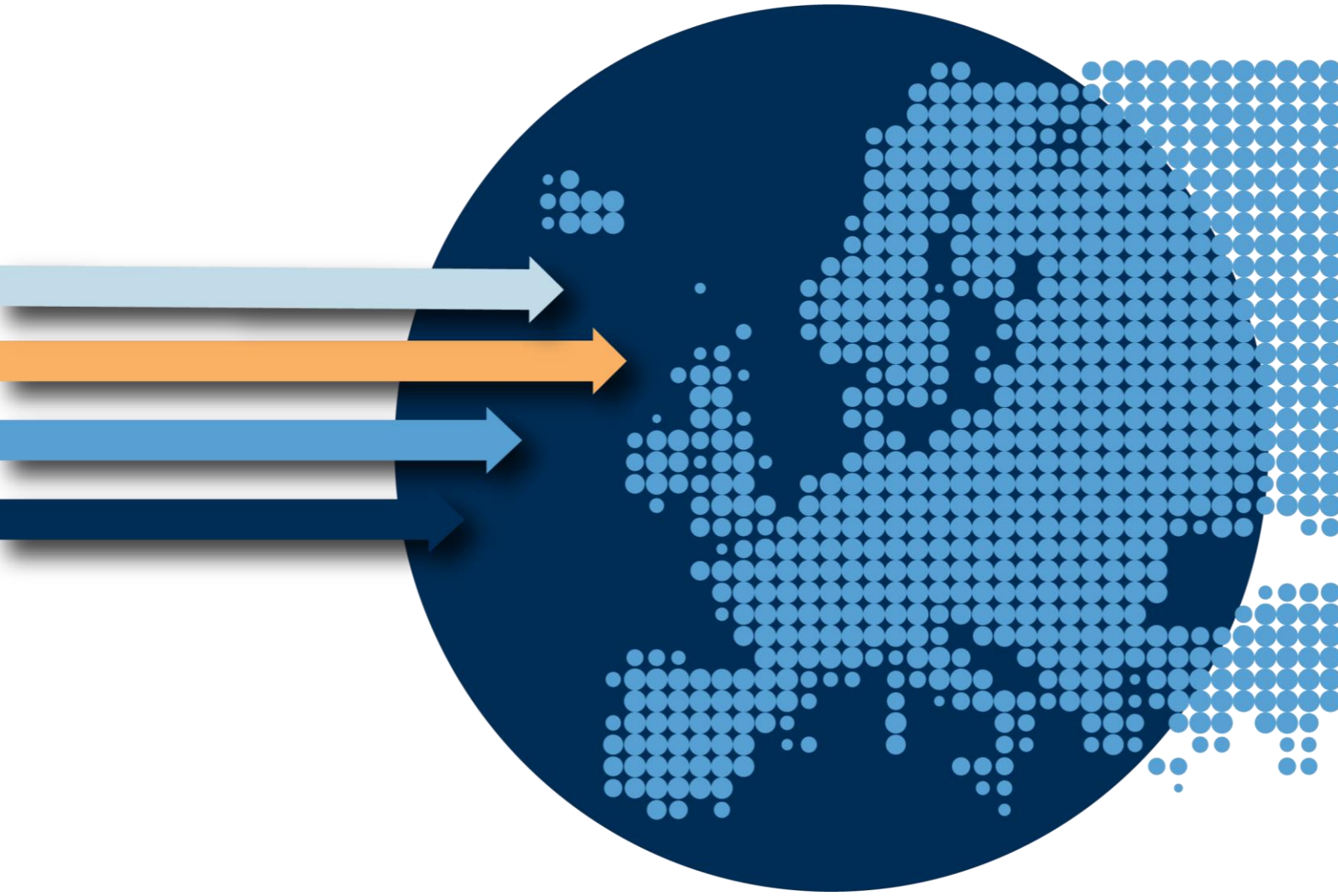
DIAGNOSED BUT NOT TREATED: HOW TO IMPROVE PATIENT ACCESS TO ADVANCED NSCLC TREATMENT IN EUROPE



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IHE REPORT
2022:2

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Please cite this report as:
Hofmarcher T, Lindgren P, Wilking N. Diagnosed but not treated: How to improve patient access to advanced NSCLC treatment in Europe. IHE Report 2022:2. IHE: Lund, Sweden.

This report was commissioned and funded by Merck Sharp & Dohme (MSD) and based on independent research delivered by IHE. MSD has had no influence or editorial control over the content of this report, and the views and opinions of the authors are not necessarily those of MSD.

IHE REPORT 2022:2
e-ISSN: 1651-8187
ISSN: 1651-7628

The report can be downloaded from IHE's website.

Foreword

Cancer is one of the most intensely discussed health policy issues in Europe. Reinforced by the Europe's Beating Cancer Plan published in February 2021, cancer is increasingly seen as a strategic health priority. Nonetheless, great disparities in access to treatment and outcomes of cancer patients remain across the continent. Access levels and outcomes correlate with countries economic strength, but there is also lots of variation across countries with similar economic strength. A better understanding of the drivers of this variation is needed.

The Swedish Institute for Health Economics (IHE) has been a pioneer in analyzing access to cancer drugs in Europe. The basic question that we have been trying to answer is: *Do patients have access to treatment?* In previous analyses, access was solely inferred from the magnitude of aggregated drug sales data. This provided some indication of the delay in access as well as the level of uptake of new cancer drugs. This report takes this type of analysis one step further and matches aggregated sales data to estimates of the patient need for drug treatment.

This report builds on an analysis of a multitude of countries in Europe. It focuses on non-small cell lung cancer, a common cancer type with a great unmet need. The first part of the report describes the general patient journey and the many drug treatment options that have been launched during the last couple of years for this cancer type. The second part is pioneering work on the calculation of drug treatment rates in a comparable manner across countries. The third part identifies barriers to achieving high drug treatment rates and using the state-of-the-art mix of drug treatment options. Initial results of the analysis have been validated and discussed through an online survey and several country-level workshops.

IHE wants to thank all survey respondents and participants in the workshops for contributing with their expertise to this report.

Lund, January 2022

Peter Lindgren
Managing Director, IHE

Acknowledgement

Abeer Ahmad, Gunnar Brådvik, Katarina Gralén, Andreas Nilsson, Filip Siegfrids (all IHE) provided research support for this report. Christer Svedman, MD (Karolinska Institutet) provided expertise in the description of the treatment options. Prof. Bengt Jönsson (Stockholm Schools of Economics in Sweden) provided expertise in the conceptualization of the treatment rate calculations.

Local teams at MSD in all countries covered in this report helped with sourcing local data, contacting clinical experts, answering a survey, organizing virtual workshops, as well as providing valuable feedback on earlier drafts of the report.

An important part of this report is based on survey answers from local clinical experts. We want to express our sincere gratitude to the following clinical experts for their time and valuable insights:

Belgium

Karin Pat, MD (Jessa ziekenhuis Hasselt) and Thierry Pieters, MD (Cliniques universitaires Saint-Luc)

Bulgaria

Dr. Krassimir Koynov (MHAT Serdika Sofia)

Finland

Jussi Koivunen, MD, PhD (Oulu University Hospital)

Greece

Zenia Saridaki, MD, PhD (Asklepeion Crete Hospital)

Hungary

Gyula Ostoros, MD, PhD (Korányi National Institute of Pulmonology)

Ireland

Dr. Greg Korpanty, MD, PhD (University Hospital Limerick)

Netherlands

Hans J.M. Smit, MD, PhD (Rijnstate Arnhem)

Norway

(undisclosed name)

Poland

Prof. Dariusz M. Kowalski (Marie Skłodowska-Curie National Research Institute of Oncology)

Portugal

António Araújo, MD, PhD (Centro Hospitalar Universitário do Porto)

Romania

Dr. Andrei Ungureanu (Amethyst Cancer Center Cluj-Napoca)

United Kingdom

Dr. Neal Navani (University College London Hospital)

IHE also held a series of virtual workshops (or similar format) with local lung cancer experts representing different specialties, such as oncologists, pulmonologists, nurses, and patient representatives, between May and October 2021 in most countries covered in this report. We want to express our sincere gratitude to all workshop participants for sharing their insights.

Disclaimer: This report does not necessarily reflect the views of local experts or their organizations.

List of abbreviations

ALK	Anaplastic lymphoma kinase
ATC	Anatomical therapeutic chemical
BRAF	B-Raf proto-oncogene serine/threonine kinase
CPI	Checkpoint inhibitor
CT	Computed tomography
DCO	Death certificate only
DRG	Diagnosis related groups
EBUS	Endobronchial ultrasound
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
EPAS	Electronic pre-approval system
ESMO	European Society for Medical Oncology
EUS	Endoscopic ultrasound
FDA	Food and Drug Administration
GLOBOCAN	Global Cancer Observatory
GP	General practitioner
MDT	Multidisciplinary team
MRI	Magnetic resonance imaging
NGS	Next-generation sequencing
NHIF	National Health Insurance Fund
NSCLC	Non-small cell lung cancer
NTRK	Neurotrophic tyrosine receptor kinase
PCR	Polymerase chain reaction
PD-L1	Programmed death ligand 1
PET	Positron emission tomography
PMDA	Pharmaceuticals and Medical Devices Agency
PS	Performance status
RATS	Robot-assisted thoracic surgery
SBRT	Stereotactic body radiotherapy
TKI	Tyrosine kinase inhibitors
VATS	Video-assisted thoracoscopic surgery
WHO	World Health Organization

Country abbreviations

BEL	Belgium
BUL	Bulgaria
FIN	Finland
GRE	Greece
HUN	Hungary
IRE	Ireland
NET	Netherlands
NOR	Norway
POL	Poland
POR	Portugal
ROM	Romania
UK	United Kingdom

Executive summary

Why lung cancer is a priority

Lung cancer is the leading cause of cancer death in Europe. There is a high unmet need in lung cancer patients, with 5-year survival rates ranging from around 10% to 20% across most countries in Europe. There is great potential for the reduction of the disease burden of lung cancer. On the one hand, prevention can have a major impact on reducing the number of newly diagnosed cases, as around 80% of all lung cancer cases are caused by cigarette smoking. On the other hand, the clinical work-up and treatment received by diagnosed patients affects their chances of survival. Access to the recent wave of innovations in medical technology (diagnostics and treatment) is imperative to realize the potential of personalized medicine and thereby improve survival. The latter is especially true for non-small cell lung cancer (NSCLC), which accounts for around 85% of all lung cancer cases

What we know and do not know about accessing care and treatment

Previous research has highlighted the difficulties faced by lung cancer patients in accessing care. The pathway from first symptoms until diagnosis may take a long time, because most of the common symptoms of lung cancer are more likely to be caused by something other than lung cancer. Symptoms of lung cancer are also usually mild in early stages and may remain unnoticed. Most lung cancer patients are therefore diagnosed at a locally advanced or metastatic stage. Many of the diagnoses are made at the emergency unit rather than in primary care.

Less research has been conducted about potential barriers that lung cancer patients with an initial diagnosis face until they can access treatment. Once diagnosed, the typical patient pathway involves many steps. Delays at all stages of the patient journey are a concern, starting with slow diagnostic procedures, multiple specialist consultations, slow assessments by multi-disciplinary teams, and slow scheduling of surgery, and radiotherapy, and/or systemic therapy. In addition, the kind of treatment that patients can access will determine treatment success.

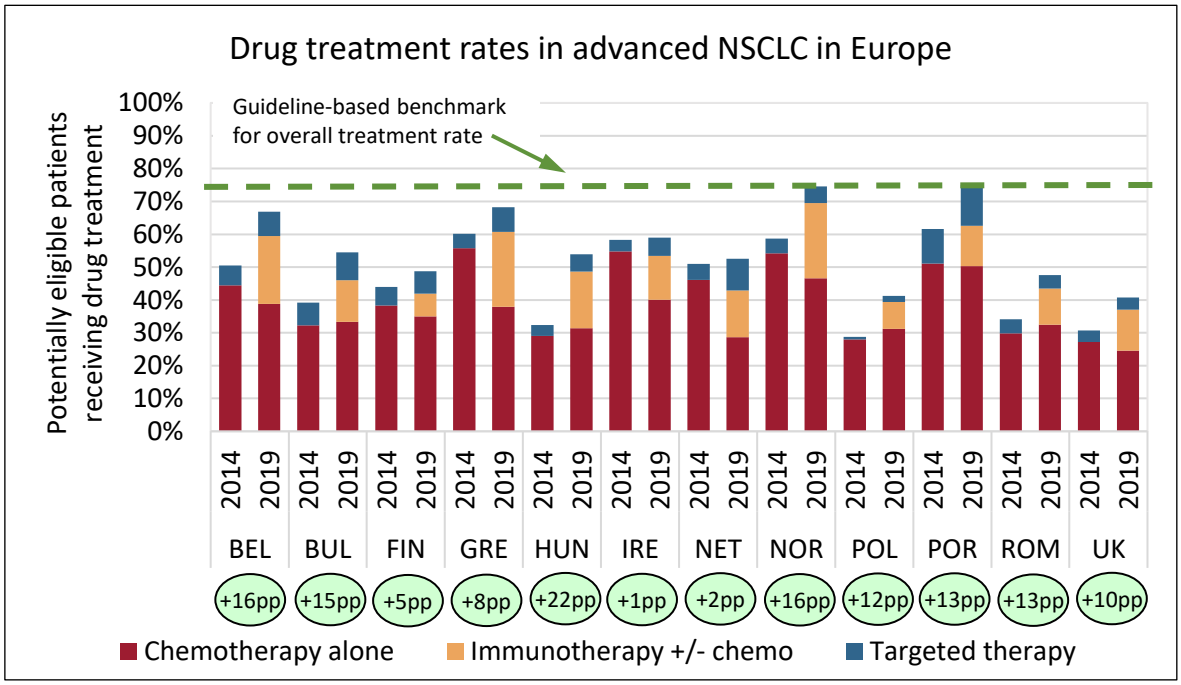
New drug treatment options in NSCLC and patient access

Systemic therapy of lung cancer has recently undergone major changes. Lung cancer was the solid tumor type with the highest number of new drugs (around 20) approved by the European Medicines Agency in the last decade. Almost all of these newly introduced drugs were approved for use in NSCLC, in particular advanced stage NSCLC. The drug therapy landscape in advanced NSCLC has changed especially radically between 2015 and 2019, with altered standard-of-care treatment in all lines of treatment and histological and molecular subtypes.

Limited patient access to newly approved cancer drugs is a constant challenge in European countries due to lengthy reimbursement processes. Patient access to newly reimbursed cancer drugs necessitates the modification of clinical routines and updating of treatment guidelines. It also necessitates the continuous training of medical staff to keep up to date with medical information. Increasing the number of patients receiving adequate state-of-the-art drug treatment is essential. This could generate significant health benefits for patients and also have a positive impact on family members and society at large.

Drug treatment rates in advanced NSCLC

The quantitative part of this report assesses quality in cancer care by measuring whether eligible patients have (i) access to any drug treatment and (ii) access to modern guideline-recommended drug treatment. Drug treatment rates in advanced NSCLC were defined as the ratio of "the number of patients treated with systemic therapy (i.e., chemotherapy, immunotherapy, targeted therapy)" and "the number of potentially eligible patients for systemic therapy". Treated patients were estimated by combining national sales volume data of cancer drugs used in NSCLC with estimations on average drug use per NSCLC patient. Potentially eligible patients were estimated from national epidemiological data and encompassed both first line (newly diagnosed cases at an advanced stage and recurrent cases from earlier stages), second line (progressing cases from first line), and third line (progressing cases from second line) patients.



The results of the analysis of drug treatment rates in 12 countries in Europe between 2014 and 2019 are shown in the figure above. Drug treatment rates were also calculated for 2020 but are less robust

due to the uncertain impact of COVID-19 on patient numbers (official cancer registry data are often published with a 2–3-year delay) and on drug sales volume (stockpiling). It is also important to emphasize that this analysis is an approximation based on best available aggregated national data. It should be viewed as a complement to registry-based studies with analysis of patient-level data.

Several observations can be made from the analysis of drug treatment rates:

(1) Overall treatment rates

a. The proportion of treated patients increased markedly over time in most countries, whereas in Finland, Ireland, and the Netherlands it remained stable. This increase coincided with the introduction of immunotherapy. The change in the standard-of-care might have sparked renewed interest in treating this patient group after almost two decades of only platinum-based chemotherapy, which was characterized by comparatively poor outcomes. Despite the improvements, most countries missed the approximate ESMO-guideline-based benchmark for the overall treatment rate of around 75% in all years between 2014 and 2019.

b. There were very large differences in treatment rates across countries. Belgium, Greece, Norway, and Portugal had the highest treatment rates in 2019. They also more or less met the approximate ESMO-guideline-based benchmark for the overall treatment rate that year. By contrast, Poland and the UK had the lowest treatment rates in both 2014 and 2019, and they only seemed to treat around half of the patients for which guidelines recommend drug treatment.

c. There seemed to be no correlation between the economic strength of a country and the magnitude of the overall treatment rates. For example, the country pairs of Portugal and Norway, Romania and Finland, and Poland and the UK all exhibit similar rates despite large differences in economic strength.

(2) Composition of the treatment rates

a. The entry of immunotherapy and new druggable targets for targeted therapy led to profound changes of the kind of drug treatment administered. The general pattern in nearly all countries between 2014 and 2020 was that the proportion of patients treated with targeted therapy increased slightly, the proportion of immunotherapy (monotherapy or combination with chemotherapy) increased considerably over time after initial reimbursement, while the proportion of chemotherapy (platinum-based combination or monotherapy) declined.

b. Patients did not seem to receive standard-of-care treatment compared the approximate ESMO-guideline-based benchmark. Underuse of both targeted therapy and immunotherapy was common. This was independent of whether a country had a high or low overall treatment rate. In fact, countries that met the ESMO-guideline-based benchmark for the overall treatment seemed to lag about 2–3 years behind the kind of treatment options that ESMO guidelines recommend.

Finding explanations for the observed drug treatment rates

The qualitative part of this report draws on survey answers and input collected during workshops with local experts. It identifies (i) barriers to achieving high drug treatment rates and (ii) barriers to using modern drug treatment options in each country.

Barriers to achieving high drug treatment rates

There is typically not just one single barrier preventing a country from achieving high drug treatment rates. Many identified barriers are shared by several countries, even though there are also country-specific barriers. In general, patients remain untreated because of the following reasons.

- **Poor functional status at the time of diagnosis**. Many patients are diagnosed very late. Late diagnosis increases the proportion of frail patients (ECOG PS 3–4). These patients are generally not recommended to receive systemic therapy in clinical guidelines which is why a treatment rate of around 75% (and not 100%) is a realistic benchmark. In addition, co-morbidities (such as cardiovascular diseases or kidney problems) and old age might make it unfeasible to administer systemic therapy, although these patients are mostly the same as those with poor ECOG PS.
- **Delays in time from diagnosis to treatment**. Long delays between diagnosis and start of treatment can make patients ineligible to systemic therapy because their functional status might deteriorate during this time. Delays in diagnostic testing (pathological analysis and genomic testing) are the main bottleneck. There can also be long delays in reaching a treatment decision and initiating treatment. These delays are caused by limited testing infrastructure, shortages in human resources (especially pathologists), and general capacity shortages of hospital beds and care places. Patients may also be lost when being referred from one hospital to another during the diagnostic process leading up to treatment start.
- **Narrow eligibility criteria for receiving drug treatment**. Some national clinical guidelines and/or reimbursement guidelines might not recommend/cover administering systemic therapy to patients with fair functional status (ECOG PS 2). In addition, national clinical practices for treating patients diagnosed with stage IIIB and IIIC differ (either (i) treatment

as metastasized disease with systemic therapy, (ii) surgery preceded by chemotherapy and/or radiotherapy, or (iii) chemoradiotherapy followed by maintenance immunotherapy) and might restrict receipt of systemic therapy.

- **Treatment refusal by patients**. Some patients might refuse to receive systemic therapy, e.g., because of stigma (among current/former smokers), fear of treatment side effects, or low trust in health care professionals and/or the health care system.

Barriers to administering modern drug treatment options

Several barriers prevent countries from administering modern drug treatment options to all patients. Such barriers exist in all countries – both in those with high and with low overall treatment rates. In general, patients receive outdated treatment options because of the following reasons.

- **Delays in reimbursement of modern drugs**. The local reimbursement of new drugs (or new indications of existing drugs) which are recommended as standard-of-care might take several years after EMA approval. During this time most patients can only access older treatment options.
- **Limited public drug budgets**. Slow reimbursement of new drugs is caused by constrained public health care budgets or constrained public (cancer) drug budgets. In addition, even reimbursed drugs might not be available for all patients if hospital budgets are restricted.
- **Limited resources for testing**. Genomic testing and immunohistochemistry are prerequisites for administering targeted therapies and immunotherapies. Extensive genomic testing for less common genomic alterations (e.g., ROS1, NTRK) might not be done because of practical reasons (lack of high-quality tumor tissue), limited testing capacity (both infrastructure and human resources such as pathologists), or financial reasons (lack of reimbursement of testing).
- **Limited continuing medical education**. The rapidly changing treatment landscape in advanced NSCLC posed a challenge for the fast diffusion of new treatment practices. In certain patient sub-groups, medical staff faced a new treatment paradigm on a yearly basis. Lack of continuous training of all involved medical staff at all treating hospitals across the whole country prevents the rapid adoption of new treatment options.

Recommendations for improving drug treatment in advanced NSCLC

The starting point to improve the status quo needs to be the measurement of patient access through a treatment rate-metric. Some countries, such as the Netherlands, Norway, and the UK, have already started to measure overall treatment rates based on patient-level data from national registries. The

Netherlands and Norway have in addition started to measure the kind of treatment options that were administered. Other countries should follow these examples and collect this kind of data from national cancer registries. In countries where national registries do not exist or are of lower quality, such as Bulgaria, Greece, Hungary, Poland, Romania, insurance claims data from national health insurance funds could be used instead.

When measuring patient access though a treatment-rate metric, it would be important for countries to not just analyze the subset of treated patients (as in the Netherlands), but rather to focus on all diagnosed patients irrespective of treatment administration. Only the latter will be able to put the spotlight on patients who for some reason do not receive treatment despite being diagnosed. Analyzing the kind of treatment received by those patients who get treated would need to be the second step.

The fact that there are multiple barriers to achieving high drug treatment rates and to administering modern drug treatment options in every country, mean that there is no single solution to improve the status quo. The following general recommendations apply to most countries.

Low treatment rates could mainly be improved by:

- **Earlier diagnosis**: Improve the awareness of lung cancer symptoms among patients and primary care physicians coupled with rapid referral to diagnostic services as well as the introduction of lung cancer screening
- **Faster time to treatment upon diagnosis**:
    - Introduce rapid care pathways with clearly defined steps and timelines to help avoid unnecessary delays in the diagnostic process
    - Improve the infrastructure to perform diagnostic testing
    - Recruit and train scarce staff categories (especially pathologists)
    - Reimburse immunohistochemistry and molecular testing for all patients
- **Broadening and harmonizing the eligibility criteria for drug treatment**: Review national clinical guidelines and clinical practices and/or reimbursement guidelines in view of European clinical guidelines and the situation in well-performing countries, in particular regarding patients with fair functional status (ECOG PS 2) and patients diagnosed with stage IIIB and IIIC
- **Obtaining evidence of drug effectiveness in less evident groups:** Conduct real-world studies to assess the benefit of modern drug treatment options in the elderly patient

population and in patients with ECOG PS 2 and ECOG PS 3–4, and then an international scientific organization (such as ESMO) should publish recommendations next to existing recommendations from randomized clinical trials

- **Convincing patients of the benefits of receiving modern drug treatment options:** Explain the clinical benefits of newer treatment options introduced since 2015 over previous standard of care, while respecting patient choice
- **Improving the general capacity of lung cancer care:** Recruit additional medical staff and improve the infrastructure of hospitals (hospital beds, outpatient care places, etc.)

The use of outdated treatment options could mainly be improved by:

- **Faster local reimbursement of new drugs which are recommended as standard-of-care**: Prioritize drugs with substantial clinical benefits in the reimbursement process
- **Higher public drug budgets**: Increase the budget to facilitate faster local reimbursement and to remove access restrictions to already reimbursed drugs
- **Greater resources to improve testing capacity**: Modernize testing infrastructure (e.g., switch to NGS testing) and recruit and train scarce clinical staff categories (e.g., pathologists)
- **Ensuring continuing medical education**: Regularly train all relevant medical staff at all treating hospitals across the country

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1. Background

Lung cancer is the leading cause of cancer death globally and also in Europe (1). In 2020, the estimated number of lung cancer deaths was 384,200 compared to 477,500 newly diagnosed cases in Europe[1] (2). Men represent about 68% of the mortality numbers (2). Around 32% of lung cancer deaths occur before the age of 65 in Europe (2), similar to patterns at the global level (3). The considerable share of premature deaths during working age results in a high number of years of potential working life lost and high indirect costs (4). This adds to the health care costs of treating lung cancer and costs of informal caregiving (5).

Lung cancer and smoking

The major cause of lung cancer is cigarette smoking (6). Trends in both incidence and mortality relate to gradual shifts in smoking habits. There has been a decline in male smokers but on the other hand an increase in female smokers in many European countries in recent decades (7). There has also been an increase of lung cancer in non-smokers, especially in women. Recent estimates for Europe and the US show that around 80% of all newly diagnosed lung cancer cases are related to modifiable risk factors – mainly to cigarette smoking (8-10). Other causes of lung cancer include occupational exposures and air pollution (11, 12). The potential of prevention is thus very large. Improved public awareness, increased taxation of cigarettes, age limits on access, and restriction of smoking in public places are warranted.

While lung cancer remains an enormous burden on European health services, in men mortality has actually declined, partly due to decreased smoking. In the EU-27 countries, there was a linear decrease in the age-standardized mortality rate in men from 77/100,000 inhabitants in 1994 to 57/100,000 inhabitants in 2012, although there was considerable variability between countries (13). On the other hand, age-standardized mortality among women rose from 15/100,000 inhabitants in 1994 to 21/100,000 inhabitants in 2012, partly due to increased smoking, with the male–female ratio gap narrowing from 5.1 to 2.8 during this period (13). Globally, female lung cancer mortality is also on the rise and may surpass breast cancer mortality by 2030 to become the leading cause of female cancer death (14).

[1] Europe refers here to 40 countries, the EU-27 countries, all remaining countries in Western Europe and on the Balkans, as well as Belarus, Moldova, Russia, and Ukraine.

Current epidemiological situation

There are major differences in lung cancer incidence and mortality between countries. Greece, Denmark, and Belgium have almost twice as high incidence rates and mortality rates as Sweden, Finland, Luxembourg, and Malta; see Figure 1. Mortality rates are generally only somewhat lower than incidence rates in all countries, which hints at low survival of lung cancer patients.

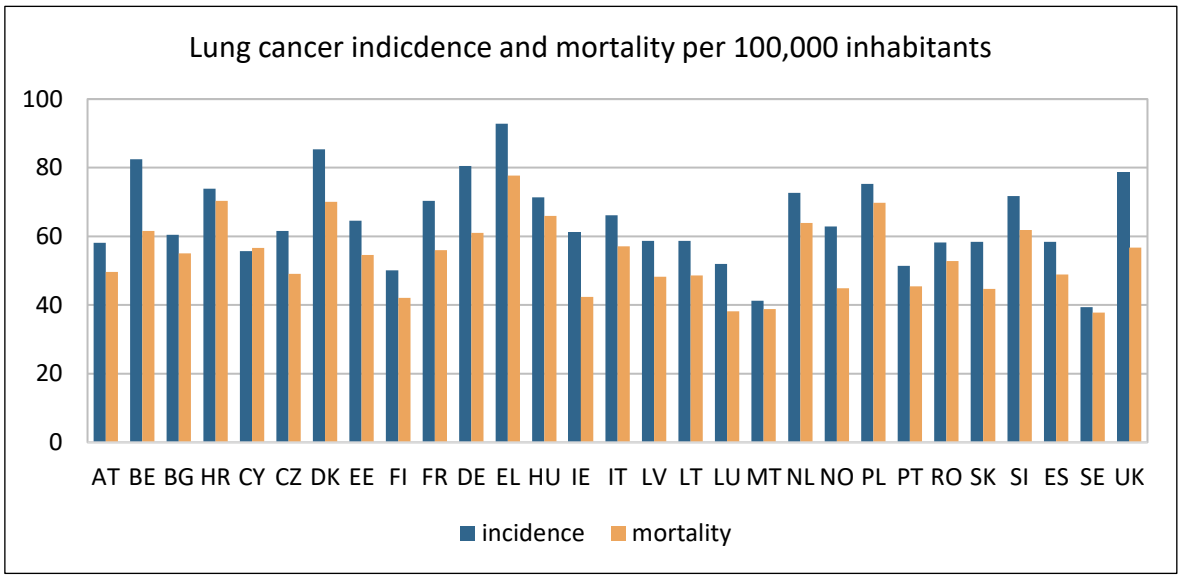


Figure 1: Lung cancer incidence and mortality cases per 100,000 inhabitants in European countries (crude rates for both sexes), 2018

Source: (15) and for HU in 2016 (16).

The survival rate of lung cancer in Europe is low. The average 5-year relative survival for both sexes was 13% in the EUROCARE-5 study, covering the years 2000–2007 (17). In the more recent CONCORD-3 study covering the years 2010–2014, 5-year relative survival was still in the range of 10–20% in most European countries (18); see Figure 2. By comparison, survival in breast cancer was at 80–90% in the CONCORD-3 study. Nonetheless, lung cancer survival rates are expected to have improved since then, as many new drug therapy options have been introduced in recent years. For instance, the latest data for the period 2014–2018 from the cancer registry in Belgium indicate that 5-year survival is now at 20% in men and 28% in women (19).

One reasons for low survival in lung cancer is late diagnosis. The diagnosis is usually made when the disease is already advanced and has started to spread to other organs. Resection of the primary tumor is then no longer performed and, at least until the mid-2000s, only chemotherapy or palliative care was given to relieve the symptoms. Survival in younger lung cancer patients is on average higher than in older patients. In the EUROCARE-5 study, the 5-year survival for men aged 15–44 was 22%, dropping to 7% for those aged ≥75 (17). This is partly explained by more radical treatment options

being used in younger patients than in older patients who often have co-morbidities and lower performance status.

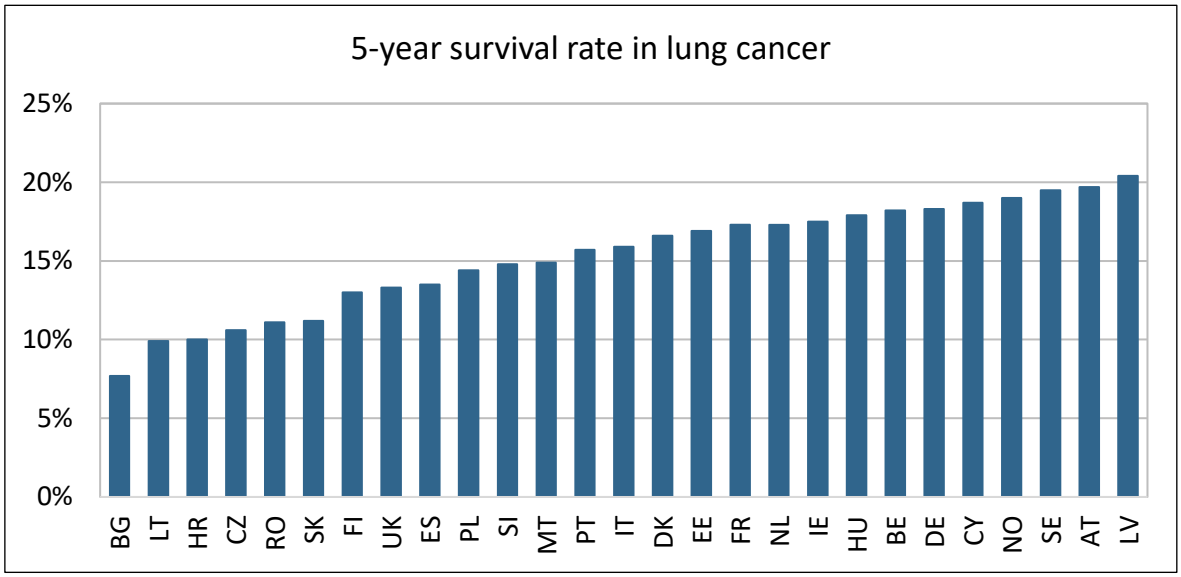


Figure 2: 5-year age-standardized net survival rates for lung cancer in adult patients (15–99 years) in European countries, 2010–2014

Notes: Numbers for DE, ES, FR, IT, and RO are based on regional data. No data available for Greece. Source: (18) and for HU (20).

A new era for drug treatment

Aside from leukemia, lung cancer was the cancer type that has seen the highest number of new drugs being introduced over the last decade. Between 2011 and 2020, the European Medicines Agency (EMA) approved 20 new drugs for use in lung cancer. Most of these drugs were targeted therapies that act on specific mutations that are involved in the growth and survival of lung cancer cells. Four immunotherapy drugs, all of them checkpoint inhibitor treatments that help the body's immune system to recognize and attack cancer cells, have also been approved for use in lung cancer (4).

Limited patient access to lung cancer drugs despite regulatory approval by the EMA is a major challenge in many countries in Europe (4). This might partly explain the large country differences in survival rates observed in Figure 2. However, to what extent eligible patients miss out on drug treatment is unclear. Exactly why eligible patients miss out on drug treatment in a particular country is also unclear. Potential determinants of the latter are late diagnosis, underuse or lack of a fast-track system, long waiting times, low awareness and use of genetic testing, compartmentalization in access to treatment (e.g., whether hospitals administer immunotherapy), lack of quality indicators, and overly strict guidelines on drug treatment based on patients' performance status.

Increasing the number of patients receiving timely and adequate state-of-the-art drug treatment could generate a significant and long-lasting impact on patients, family members, and society at large.

1.1 Objective

The objective of this report is to research disparities in drug treatment rates in non-small cell lung cancer (NSCLC), which accounts for around 85% of all lung cancer cases, across a sample of European countries. Both the "what" (*How high are treatment rates?*) and the "why" (*What explains country differences in treatment rates?*) are addressed.

Using quantitative and qualitative research methods, the report:

- Provides a narrative description of the patient journey from time of diagnosis to drug treatment initiation,
- Calculates country-specific drug treatment rates in NSCLC patients based on publicly available data, and
- Identifies determinants of disparities in drug treatment rates across countries based on targeted expert interviews.
- Provides policy recommendations to improve drug treatment in NSCLC patients.

The study population in the analysis of drug treatment rates and their determinants are patients with advanced NSCLC (i.e., stage IIIB/C and stage IV). This is a patient group with a high unmet need. Virtually all lung cancer drugs approved by the EMA over the last decade have been approved in this patient group. The initial reference period for the analysis were the years 2014 to 2019 in order to capture the dynamic development surrounding the introduction of major immunotherapies and targeted therapies in NSCLC. The year 2020 was added later on to study the effect of COVID-19 on treatment rates.

The geographic scope of the analysis encompasses the following countries:

- Belgium
- Bulgaria
- Finland
- Greece
- Hungary
- Ireland
- Netherlands
- Norway
- Poland
- Portugal
- Romania
- United Kingdom

These countries were selected as they were under the jurisdiction of the EMA between 2014 and 2020 and local teams at MSD could offer help in sourcing local data, providing contact details to clinical experts, and organizing workshops.

2. Patient journey and treatment options

This chapter provides a description of the lung cancer patient journey from diagnosis to treatment; see Figure 3 for a stylized overview. It covers the main stages of the patient journey, starting with symptoms and diagnosis and then – for NSCLC only – focusing on treatment decision and initial therapy as well as follow-up therapy. The chapter also describes the development of drug therapy options in advanced stages of NSCLC over the last decades.

The description of the patient journey in this chapter does not aim to portray the exact situation in a particular European country. Instead, it aims to describe the state-of-the-art care options that are relevant in a European context and that can serve as a benchmark for individual countries.

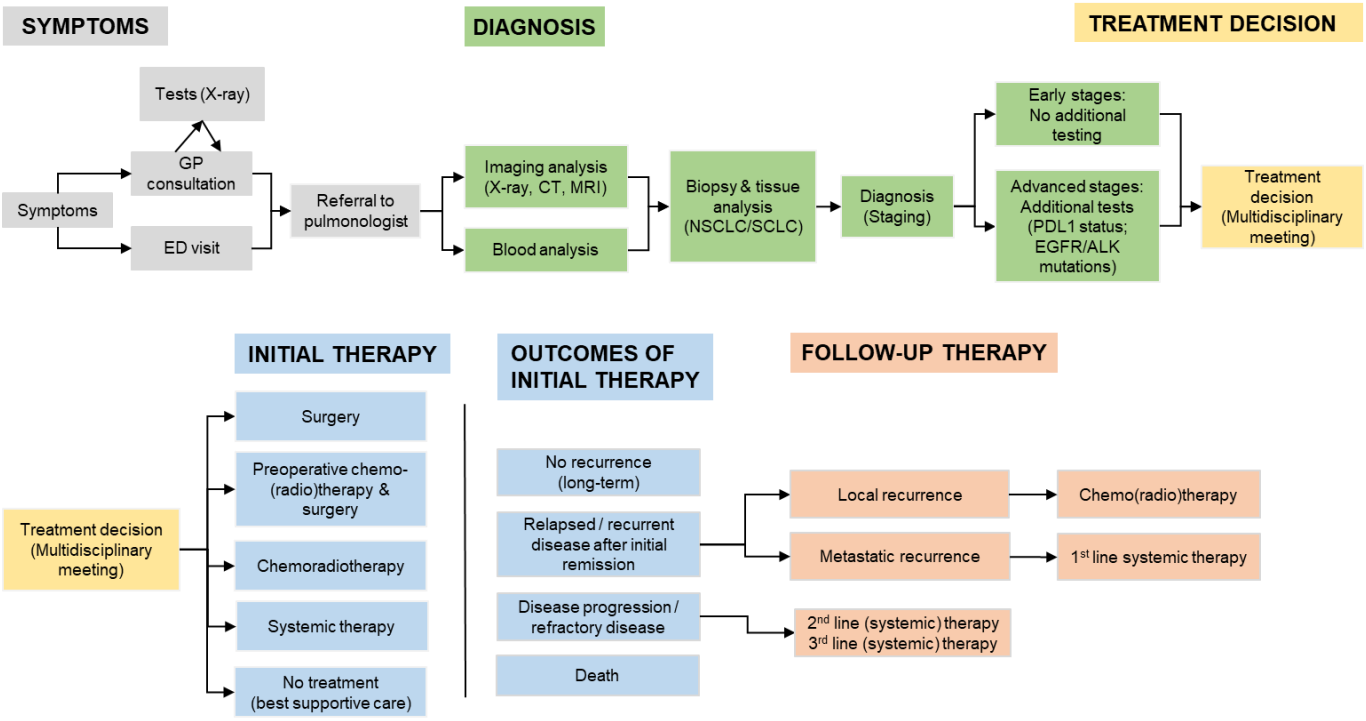


Figure 3: Patient journey in lung cancer

2.1 Symptoms

Symptoms of lung cancer are usually mild or absent in early stages. Common symptoms are persistent cough or changes of chronic smoker's cough, coughing up mucous and blood, breathlessness, wheezing, chest pain that gets worse with deep breathing, loss of appetite, unintentional weight loss, hoarseness, and persistent chest infections (21). A challenge is that most of these symptoms are more likely to be caused by something other than lung cancer, such as chronic obstructive pulmonary disease, asthma, bronchitis, chronic heart failure, and more recently also COVID-19.

Even though lung cancer is a common disease, most general practitioners (GPs) only see one or two new cases a year. A study in the UK on more than 20,000 cases found that patients who have visits to GPs before diagnosis are more likely to die (22, 23). Based on a patient's symptoms, GPs may either order tests (such as a chest X-ray) for re-assessment by themselves or directly refer patients to a pulmonologist for diagnostic confirmation. A recent study by Lung Cancer Europe found that 44% of lung cancer patients who reported symptoms had three or more visits with a GP before being referred to a specialist (24).

Many patients with lung cancer are actually diagnosed in the emergency unit. Data from 11 hospitals in 8 countries in Europe showed that on average 23% of patients with lung cancer were diagnosed as part of an emergency, ranging from 13% to 48% (25). These patients have worse outcomes due to a higher proportion of late-stage disease (26, 27).

The patient journey from initial symptoms to diagnosis can thus be complex and take a lot of time and depend on awareness of both patients and health care professionals. Delays in diagnosis are common and affects stage of disease negatively (28). Delays in diagnosis have come even more in focus in relation to the outbreak of the COVID-19 pandemic. An initial modelling study estimated that around 1,300 additional patients with lung cancer would die in the UK due to delayed diagnosis between March 2020 and March 2021 over a five-year horizon (29).

Lung cancer screening

Aside from increasing awareness of early symptoms of disease, lung cancer screening among former and current smokers has in the last decade emerged as a possible means to help diagnose patients earlier. In Europe, lung cancer screening is not yet implemented on a national basis in any country, except in Croatia. Croatia was the first country to present plans in early 2020 (30), and a national screening program has started to be rolled out since October 2020 (31). There is a strong clinical recommendation at a European level to implement lung cancer screening in the coming years (32-34). Convincing evidence on the cost-effectiveness of a lung cancer screening program is still scarce however, with some results indicating cost-effectiveness (at a rather high cost-effectiveness ratio) in European countries with high smoking prevalence (35), similar to findings for the US (36), but unlike findings for Australia (37). Properly defining the patient population (current/former smokers), the age range (e.g., 50–70 years), the screening interval (e.g., every other year), and whether health care visits for lung cancer screening can be combined with other visits (such as mammography in women) is essential for cost-effectiveness (38).

2.2 Care pathway

Delays are a concern at all stages of the patient journey. As described above, there can be long delays between first symptoms and referral to secondary care (pulmonologist). After there is a clinical suspicion of lung cancer, the biggest delays in secondary care are caused by slow diagnostic procedures, multiple specialist consultations, slow multidisciplinary team (MDT) assessments, slow scheduling of surgery and radiotherapy (39). The European Cancer Organisation recommends that clear care pathways should be defined to help avoid unnecessary delays (39). Patient navigators or case managers can help to guide patients through the pathway. For instance, NICE in the UK recommend lung cancer patients to have access to a named clinical nurse specialist in their latest lung cancer quality standard guidelines (40). Apart from diagnosis and initial treatment, follow-up, support and care for long-term survivorship, and palliative care, should also be part of a care pathway.

The challenges with timely diagnosis and treatment and the lack of acknowledgement in clinical guidelines was recently highlighted in a report by the Economist Intelligence Unit (41). Fast-tracking within specific timeframes is essential to ensure that lung cancer is diagnosed as early as possible. Once the disease has been detected, rapid referral pathways need to be embedded to ensure that a patient receives secondary or tertiary care without delay. Reviewing clinical guidelines of European countries, the Economist Intelligence Unit found that:

- 41% of clinical guidelines do not include fast-tracking people suspected of having lung cancer for diagnostic testing
- 44% do not include a specific timeframe for obtaining diagnostic testing
- 52% do not include rapid referral for newly diagnosed patients to obtain treatment

2.3 Diagnosis

The diagnosis and staging of lung cancer is complex. There are challenges in both overstaging and understaging lung cancer, especially concerning infiltration of the mediastinum or suspected distant metastases. It is essential that experienced specialists – including radiologists, pulmonologists, pathologists, and nuclear medicine specialists – determine results from imaging and pathological samples. A successful management plan for better patient outcomes, especially in case of radical interventions, depends on their input to the MDT that makes the treatment decision.

2.3.1 Radiology

The initial investigation for suspected lung cancer is usually a chest X-ray followed by a computed tomography (CT) scan. Further investigations for staging assessment may include positron emission tomography (PET)/CT, brain magnetic resonance imaging (MRI) or CT, bone scintigraphy, and upper abdomen CT, adapted according to the treatment intent (curative or palliative) and the patient's condition.

^{18}F-FDG PET/CT allows more precise disease staging in lung cancer and is essential when curative treatment (i.e., surgery or chemoradiotherapy) is intended and should be available at all treatment centers or in close proximity to those centers.

2.3.2 Biopsy

If a suspected tumor was discovered in the imaging analysis, a biopsy on the tumor is performed. It can be challenging to obtain adequate biopsy samples of lung cancer both in quantity and quality. The site having the best chance for a valuable pathological sample should be chosen as early as possible. There are different biopsy techniques depending on location (central or peripheral). Biopsy is commonly carried out by fiberoptic bronchoscopy, extended with endobronchial ultrasound (EBUS) and/or endoscopic ultrasound (EUS) to evaluate lymph nodes. Other biopsy procedures include image-guided needle biopsy, thoracoscopy, and mediastinoscopy. Biopsies from any suspected metastatic organ should also be considered.

2.3.3 Histological classification and staging

There must be a pathological confirmation of the cancer to be able to determine the appropriate treatment plan for patients, especially with targeted therapies and immunotherapy (42). Results from the pathological examination of the tissue sample obtained from the biopsy enable a histological classification of the tumor. Lung cancers are classified according to the World Health Organization (WHO) histology classification (43). There are two main histological groups: small cell lung carcinoma (SCLC, around 15% of all lung cancers) and non-small cell lung carcinoma (NSCLC, around 85% of all lung cancers). NSCLC is further subcategorized into squamous cell carcinoma and non-squamous cell carcinoma (including adenocarcinoma and large cell carcinoma).

NSCLC is staged according to the TNM (tumor, node, metastasis) system. The TNM staging has undergone significant revisions over time with the latest, 8th edition, being effective from 2018 and introducing stage IIIC as a new sub-stage (44). NSCLC has four main stages (45, 46):

- Stage I: Cancer is found in the lung but has not spread outside the lung.
- Stage II: Cancer is found in the lung and nearby lymph nodes.
- Stage III: Cancer is found in the lung and lymph nodes in the middle of the chest.
    - Stage IIIA: Cancer is found in lymph nodes, but only on the same side of the chest where the tumor first started growing. The tumor is 5 cm or smaller.
    - Stage IIIB: Cancer has spread to lymph nodes on the opposite side of the chest or to lymph nodes above the collarbone. The tumor is 5 cm or smaller.
    - Stage IIIC: Cancer has spread to lymph nodes on the opposite side of the chest or to lymph nodes above the collarbone. The tumor may be of any size.
- Stage IV: Cancer has spread to both lungs, into the area around the lungs, or to distant organs.

Due to the symptoms of lung cancer usually being mild or absent in early stages, most patients are diagnosed at a locally advanced or metastatic stage (stage IIIB/C and IV), when the disease is no longer amenable to curative surgery or chemoradiotherapy (47). As an example, Figure 4 illustrates the stage distribution of NSCLC in Belgium. Around 60% of patients are diagnosed with stage IIIB/C and IV. Table A5 in the Appendix shows that the stage distribution in other European countries looks very similar with 60–70% of patients diagnosed at an advanced stage.

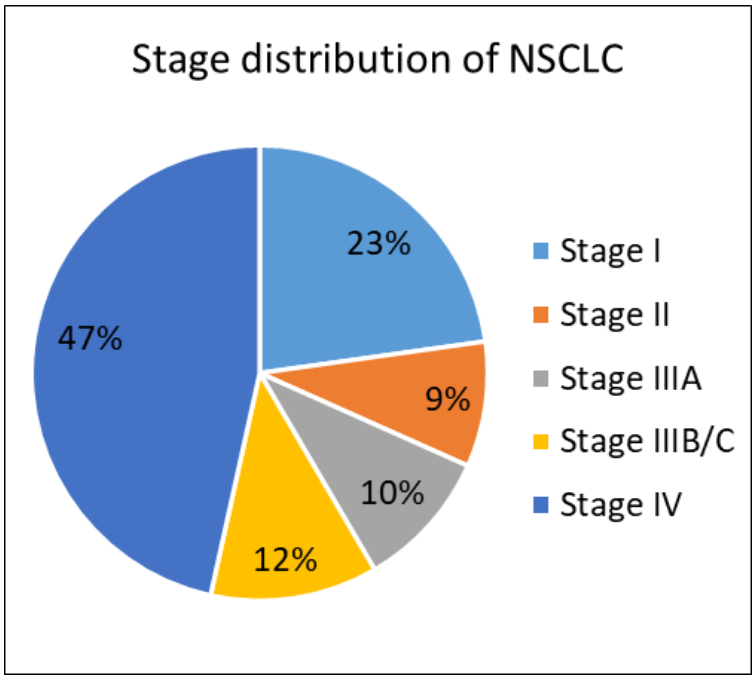


Figure 4: Stage distribution of NSCLC in Belgium
Source: Belgian Cancer Registry (19).

2.3.4 Tests of genomic alterations and immunohistochemistry

Molecular diagnostics is nowadays extremely important to be able to identify actionable targets for new drugs. This involves different tests using the tissue sample obtained from the biopsy before the treatment decision is made. These are tests of specific genomic alterations for which targeted drugs are available and of programmed death ligand 1 (PD-L1) expression for which immunotherapy drugs are available. In practice, molecular diagnostics for all new targeted drugs for lung cancer may not be available, and expertise in interpreting molecular findings and their clinical significance may also be lacking (48).

Assessing genomic alterations (such as EGFR, ALK, ROS1, BRAF, NTRK) in NSCLC is a prerequisite for administering targeted drugs. Extensive mutational profiling using next-generation sequencing (NGS) has emerged as the main alternative to meet the clinical need. NGS is however expensive, and the turnaround time is frequently more than a week leading to (some) patients being initiated on therapy already prior to available NGS results which limits the use of NGS. In countries that cannot afford NGS, sequential testing of specific alterations (typically starting with EGFR) is used instead. This is challenging due to the number of different tests that are warranted, resulting in depletion of tissue samples and incomplete assessments. A pan-cancer polymerase chain reaction (PCR) panel has recently been developed that covers actionable alterations across 11 genes of interest in NSCLC (CE mark) which may be an alternative, as sensitivity and specificity as well as turnaround time and price may be advantageous compared to NGS (49). There are several barriers to a more universal biomarker testing in NSCLC. It may be difficult to obtain an adequate amount of tumor tissue, turnaround time for the test, and costs of the test. An alternative may be the use of blood-based liquid biopsies, a technique presently being developed and potentially very valuable especially in NSCLC (50).

Immunohistochemistry for PD-L1 is the only available biomarker that can guide treatment with immune checkpoint inhibitors in NSCLC. A challenge in the initial years of their use was that manufactures of immune checkpoint inhibitors had each developed their own proprietary PD-L1 biomarker assays, and correlation between some of these assays (assay for atezolizumab vs. assays for nivolumab and pembrolizumab) was not perfect (51). Efforts were put in place to validate tests on different platforms (52), because it is impractical to perform several different assays because of costs and because of limited availability of tumor tissue that is also need for other tests of genomic alterations (53, 54). The issue started to be resolved after 2016. The National Comprehensive Cancer Network in the US nowadays recommends that all advanced NSCLC samples are tested with PD-L1 immunohistochemistry (51).

2.4 Treatment decision

The treatment of NSCLC can be highly complex. Current guidelines include many options and uncertainties, owing to various levels of evidence and rapidly evolving therapeutic possibilities, particularly in medical treatment. Patient performance status and detailed assessment of patient suitability, including co-morbidities, and informed decisions together with patients are fundamental parts of NSCLC treatment planning.

Multidisciplinary teams (MDTs) (also called tumor boards) are teams of health care professionals representing different specialties who review and discuss the medical condition and treatment options of a patient (55). MDTs are vital for the selection of the best strategies for both local and advanced disease, and the initial treatment plan may change in a significant number of cases due to the input of the MDT (56). The use of MDT meetings to discuss new cases has been reported to be low in some countries (57), and regional differences within countries have also been reported (58).

The European Cancer Organisation published its "Essential Requirements for Quality Cancer Care (ERQCC)" in lung cancer in 2020 (39), and the statements most relevant in relation to MDT are:

- Treatment strategies for all patients with lung cancer must be decided on, planned, and delivered as a result of consensus among an MDT.
- The heart of this decision-making process is normally a weekly or more frequent MDT meeting where all cases are discussed with the objective of balancing the recommendations of clinical guidelines with the needs of the individual lung cancer patient.
- To properly treat lung cancer, it is essential that the core MDT comprises health professionals from the following disciplines: pulmonology/respiratory medicine, pathology, radiology, nuclear medicine, thoracic surgery, radiation oncology, medical oncology, and nursing.

Lung cancer is one of the few cancers for which systematic reviews of multidisciplinary management have been published (59-61), but there is limited evidence on effect on outcomes. Benefits for patients of MDTs include concordance with guidelines, more accurate assessment and staging, and better patient satisfaction and quality of life, which is particularly important in patients with metastatic disease.

2.5 Initial treatment of NSCLC

2.5.1 Treatment by disease stage

Stage I and II

Patients with high performance status should be offered surgery to resect the tumor. Minimally invasive lobectomy using video-assisted thoracoscopic surgery (VATS) or robot-assisted thoracic surgery (RATS) are preferred to open thoracotomy because of better outcomes and reduced morbidity (62, 63). Pneumonectomy and sleeve lobectomy should be restricted to selected cases when lobectomy is not feasible. Segmentectomy for very small T1a tumors is under investigation.

Stereotactic body radiotherapy (SBRT) is the preferred option for patients unfit for or declining surgery for tumors less than 5 cm and not centrally located. If centrally located, SBRT should be discussed for feasibility and to determine the most appropriate technique, depending also on local conditions whether there is broad access to surgery or SBRT or vice versa. The same holds for local ablative therapies (i.e., “burning” the tumor through radiofrequency ablation or microwave ablation or “freezing” the tumor through cryoablation), which may have a role in non-surgical candidates with tumors up to 3 cm. Adjuvant chemotherapy is a standard for completely resected stage II disease where there is no contraindication.

Stage III

Patients with locally advanced disease may be offered perioperative therapy (chemotherapy or chemoradiotherapy) plus surgery in case of resectable tumors. However, most patients have unresectable tumors at this stage. The main choice in these patients is chemoradiotherapy, ideally delivered concomitantly (i.e., not sequentially - chemotherapy followed by radiotherapy) when feasible and tolerable (64). Radiotherapy is given every weekday for about 4 to 6 weeks. Maintenance immunotherapy in non-progressing patients with unresectable tumors following the completion of concomitant chemoradiotherapy has recently become standard of care (65). When a tumor is not suited for local therapy, patients should be offered induction chemotherapy before a new evaluation for local therapy or be treated as stage IV.

Stage IV

For patients with metastatic disease, surgery is generally not an option. These patients have a wide range of systemic therapy options consisting of chemotherapy, immunotherapy, combined chemo-immunotherapy, and targeted drugs in case of actionable molecular alterations (such as EGFR, ALK,

ROS1, BRAF, NTRK); see section 2.5.3. A significant share of patients might however be unsuitable for systemic therapy due to co-morbidities and poor performance status.

Outcomes of NSCLC treatment by stage

The high rate of diagnosis at an advanced stage is a major challenge in NSCLC, and the therapeutic approach must take into account patient choice, performance status, and co-morbidities such as cardiovascular disease, renal disease, and hepatic disease. Elderly patients must be informed of treatment options and should not remain untreated unless through choice, and patients in poor condition should not be denied treatment but evaluated based on the therapeutic opportunities.

There are wide variations in patient outcomes by stage of disease. As an example, Figure 5 illustrates 1-year and 5-year net survival rates of lung cancer in England. Only half of the patients with stage III are still alive one year after diagnosis and less than one fifth of patients with stage IV. Five years after diagnosis almost all patients with stage IV have died. Even among patients who were initially diagnosed with stage I, almost half of them had died within five years.

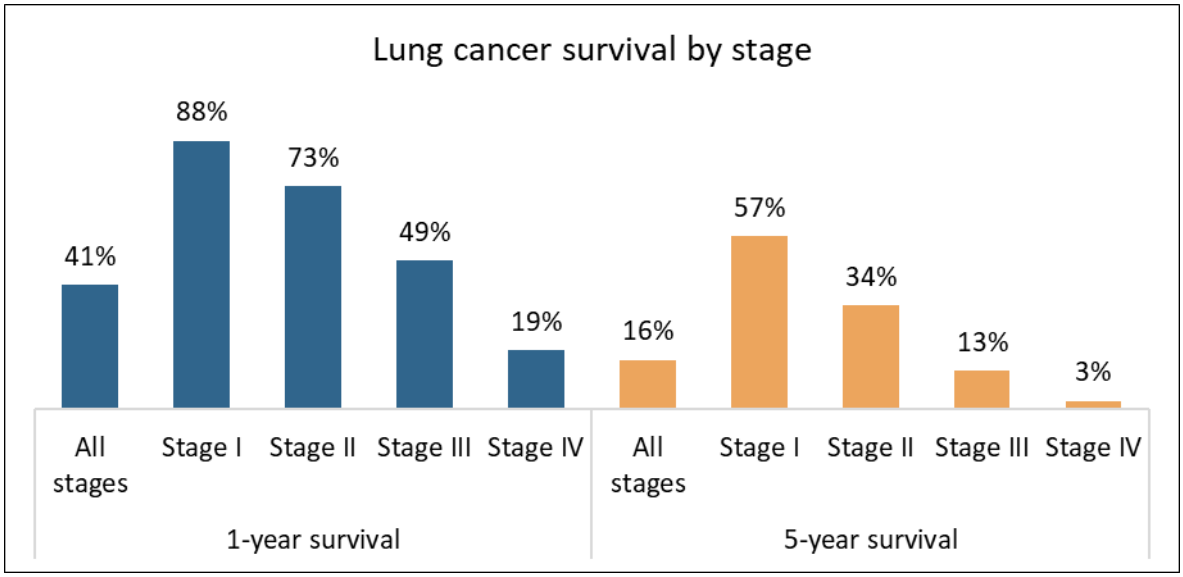


Figure 5: Lung cancer net survival by stage in England, 2013–2017
Notes: Adults (aged 15–99 years) diagnosed between 2013 and 2017 and followed up to 2018. Source: (66).

Other data from England also show that there can be great variation in survival even within a country. The proportion of patients with lung cancer alive after one year varied from 55% in the best-performing institution down to just 12% in the worst-performing institution in England in 2013. If outliers were removed, the variation still ranged from 48% down to 20% (67).

2.5.2 Surgery and radiotherapy

The majority of NSCLC patients are not eligible for surgery due to advanced stage disease, and it is essential that MDTs work with all stages of the disease. Tumor resection surgery can be complex, challenging and at high risk. Better outcomes may be achieved by surgeons specializing in thoracic surgery (68), although patients may be operated on by cardiothoracic surgeons or general surgeons.

At high volume centers, minimally invasive techniques such as VATS and RATS with lower morbidity are usually in use. It has been estimated that if all areas of the UK had similar access to surgery at centers with the highest resection rate, over 5,000 deaths from lung cancer would be prevented every 3 years (69). Lung cancer units with high patient volumes seem to achieve better outcomes even if the mix of patients is taken into account, including differences in co-morbidities and socioeconomic status (70-72).

Access to advanced radiotherapy technology and techniques such as intensity-modulated radiotherapy (IMRT) and SBRT is essential to provide optimal care (73). However, access to radiotherapy varies between European countries and availability of the necessary resources, both in terms of equipment and trained personnel, is a challenge in many countries (74, 75).

2.5.3 Systemic therapy

Systemic therapy for patients with advanced NSCLC (mostly stage IIIB/C with unresectable tumors and stage IV) has undergone major changes in recent decades. During the 1990s, systemic therapy underwent its first major change. Single-drug chemotherapy, or just upfront palliative care without any systemic therapy, was substituted with combinations of different chemotherapy drugs, mainly with a platinum salt as a backbone. This was called platinum-based doublet chemotherapy. Platinum (cisplatin or carboplatin) was combined with either a taxane (paclitaxel or docetaxel), gemcitabine, vinorelbine, irinotecan, or (after 2008) pemetrexed. Even though one-year survival almost doubled with combination treatment, long-term outcome was still poor. A landmark study published in 2002 compared four chemotherapy regimens (cisplatin and paclitaxel vs. cisplatin and gemcitabine vs. cisplatin and docetaxel vs. carboplatin and paclitaxel) and none of them offered a significant advantage over the others in the treatment of advanced NSCLC, resulting in a median survival of 7.9 months, a one-year survival of 33%, and a two-year survival of 11% (76). The combination of pemetrexed with cisplatin also did not improve survival in a first-line setting (compared to cisplatin and gemcitabine), yet there was a small gain of 1.4 months for non-squamous disease, leading to a histology-based approval in 2008 (77).

The angiogenesis inhibitor bevacizumab was approved in 2007 in non-squamous disease as first-line treatment in combination with carboplatin and paclitaxel. The survival gain over the platinum doublet was 2 months and there were initially also safety concerns in some patients (78). In addition, the high cost of bevacizumab at that time resulted in an inconclusive cost-effectiveness profile (79). This limited the use of bevacizumab in practice.

In 2004, the era of personalized medicine and targeted therapies in NSCLC began with the description of treatment benefit derived from inhibitors of EGFR mutations (80, 81). A deeper understanding of the biology of NSCLC and mapping genomic alterations subsequently enabled the development of many tyrosine kinase inhibitor (TKI) drugs targeting various genomic alterations; see Figure 6. Most of these mutations occur in non-squamous disease (predominantly adenocarcinoma) but can also be found in squamous disease. The proportion of NSCLC patients with actionable alterations continues to increase and is now about 30% in Caucasian patients and over 50% in East Asian patients. New agents are rapidly moving to first line in advanced NSCLC and even to the adjuvant setting of early-stage NSCLC where there is a potential for increased cure rates.

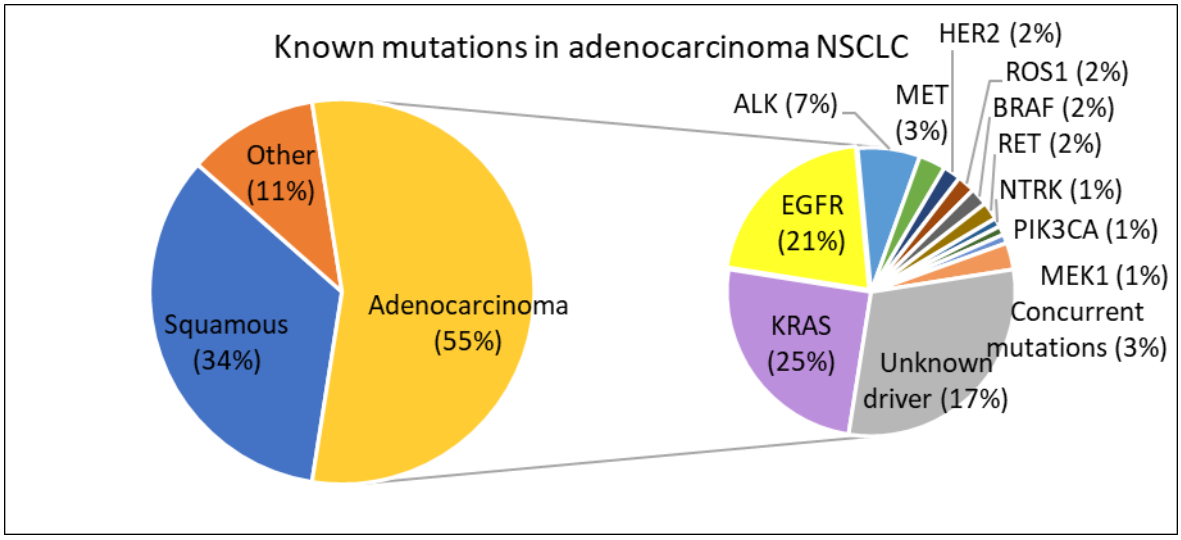


Figure 6: Genomic alterations in lung adenocarcinomas
Source: (82, 83).

The latest additions to the treatment arsenal are immune checkpoint inhibitors (CPIs), first introduced in 2015 in NSCLC in Europe; see further below for a more detailed description. They are mainly used in patients without targetable genomic alterations. Over 50% of locally advanced or metastatic NSCLC patients have a positive PD-L1 expression (84), in which CPIs offer benefit, although they have lately also demonstrated benefit irrespective of PD-L1 expression. CPIs have quickly moved to first line and are now standard of care. They are also being studied in the adjuvant setting of early-stage NSCLC (83).

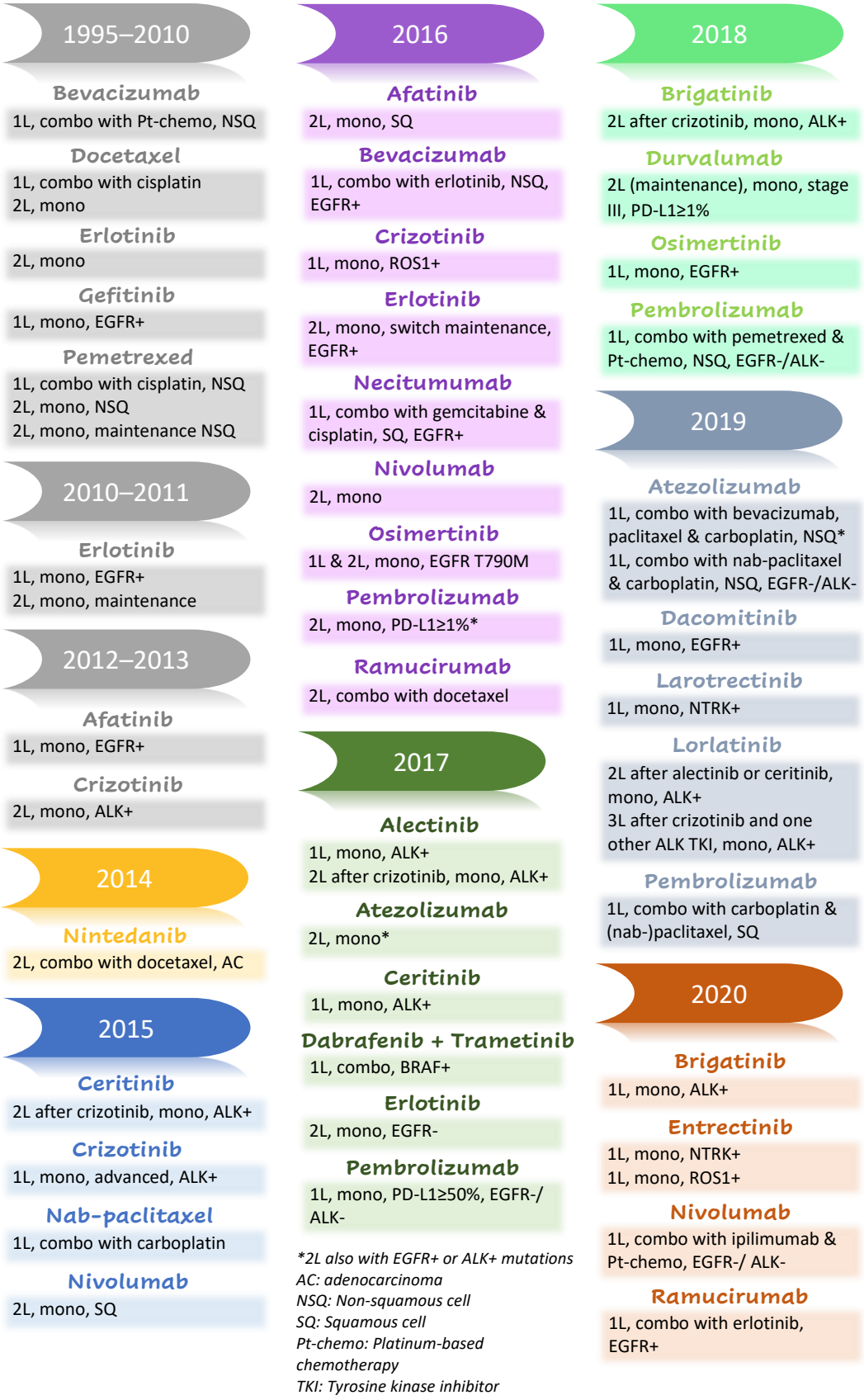


Figure 7: EMA-approved drug indications in NSCLC, 1995–2020

Notes: Indications in locally advanced and metastatic NSCLC. The drugs carboplatin, cisplatin, gemcitabine, paclitaxel, and vinorelbine are also used in practice but were launched before the establishment of the EMA in 1995.

Figure 7 shows a timeline of drug-indication approvals in NSCLC by the EMA between 1995 and 2020; see also Table A8 in the Appendix (85). Approvals have been accelerating considerably since 2015, with a least four new indications being approved every year. Even though this is a most welcome development in a patient group with a great unmet need, it is challenging to keep up with this pace in clinical practice as medical staff needs to be trained, routines have to be modified, and guidelines have to be updated.

Tyrosine kinase inhibitors

Drugs targeting EGFR

The relevance of certain activating mutations in EGFR in defining treatment benefit from EGFR inhibitors was first described in 2004 (80, 81). There are now multiple approved EGFR inhibitors, first-generation inhibitors (erlotinib, gefitinib), second-generation inhibitors (afatinib, dacomitinib, necitumumab), and third-generation inhibitors (osimertinib) (86-90).

The rate of EGFR mutations varies by ethnicity; in Caucasians approximately 15% of patients have EGFR mutations while in East Asian patients the rate is frequently 40–50% (91), but the type of alterations is similar. The more recently developed agents (e.g., osimertinib) have higher potency and activity in alterations, as EGFR T790M causes treatment resistance to first-generation EGFR inhibitors. Osimertinib was initially approved in second line in patients progressing on an EGFR targeted therapy and detected EGFR T790M resistance and in first line in patients with EGFR T790M. It was later approved for first-line treatment in EGFR with proven efficacy superior to first-generation inhibitors (88). In May 2021, osimertinib was approved by the EMA in adjuvant stage IB to IIIA disease, making it the first TKI in NSCLC to do so (92).

Drugs targeting ALK

At most 5% of patients with NSCLC have ALK fusions as a driver gene mutation (93-95) and there are multiple approved drugs targeting ALK fusions (crizotinib, ceritinib, alectinib, brigatinib, and lorlatinib) (96-100). The more recently developed agents, ceritinib, alectinib, and brigatinib, have higher potency and pass the blood-brain barrier compared to the first ALK inhibitor, crizotinib, approved by the EMA in 2012, which has led to these agents being moved from second line after crizotinib to preferred first-line options. For these newly approved drugs there is currently no data indicating the best first-line therapy. Lorlatinib has approvals in more heavily pre-treated patients, progressing on alectinib or ceritinib, or having received crizotinib and one more line of ALK-inhibitor treatment.

Drugs targeting ROS1

ROS1 fusions are detected in 1–2% of patients with NSCLC (101), and both crizotinib and entrectinib are approved as first-line agents (102, 103). Lorlatinib has also demonstrated activity in ROS1 fusion patients including those previously treated with crizotinib but is not yet approved (104, 105).

Drugs targeting BRAF

Mutations in BRAF were first described in malignant melanoma but are also detected in around 2–4% of patients with NSCLC (106-108). Based on a single arm phase II study, the BRAF V600E inhibitor dabrafenib in combination with the MEK inhibitor trametinib received approval in NSCLC patients (109). V600E mutations account for most (>90%) BRAF mutations in melanoma but only around half (50%) in NSCLC (108, 110).

Drugs targeting NTRK

NTRK fusions are rare events occurring in 0.3–0.5% of NSCLC patients. Despite the limited patient population available for treatment, two NTRK inhibitors, larotrectinib and entrectinib, have been approved in 2019 and 2020, respectively (111-113).

TKI drugs with EMA approval after 2020 and with imminent approval

Fusions in RET are present in 1–2% of patients with NSCLC. Two RET inhibitors were approved by the US FDA in 2020, selpercatinib and pralsetinib (114, 115). The former was approved by the EMA in February 2021 and the latter in November 2021.

MET exon 14 skipping mutation is present in approximately 3% of NSCLC tumors (116). Capmatinib and tepotinib were approved by the FDA in the US and the PMDA in Japan respectively in 2020 (117, 118). EMA approvals are still pending at the close of 2021.

Genomic alterations with candidate drugs in late-stage development

EGFR exon 20 insertions are seen in about 2% of NSCLC tumors and indicate resistance to available EGFR inhibitors. There are several drugs, such as mobocertinib (US FDA approval in September 2021) (119), amivantamab (US FDA approval in May 2021), a bispecific antibody directed against EGFR and MET (120), and poziotinib (121), that have demonstrated efficacy in small phase II trials.

HER2 exon 20 insertions are seen in about 2% of patients with NSCLC and multiple candidate drugs, such as pyrotinib and trastuzumab deruxtecan, are in clinical development (122-124).

KRAS mutations are common in many different tumors and are seen in about 25% of NSCLC patients and have been an evasive target for many years. Multiple KRAS inhibitors are in development. Sotorasib targeting KRAS G12C mutations was approved by the US FDA in May 2021 and adagrasib is also close to approval with fairly robust data demonstrating efficacy in KRAS G12C mutations (125, 126). These specific mutations appear in about half of the NSCLC patients with KRAS mutations.

Checkpoint inhibitors

The first two CPIs, nivolumab and pembrolizumab, were initially approved as second-line treatment options, after prior chemotherapy, in 2015 and 2016 respectively by the EMA. Pembrolizumab has since then moved up to first line. In 2017, it was approved as monotherapy in patients with a PD-L1 expression of 50% or higher, and afterwards also in combination with pemetrexed and platinum-based chemotherapy in non-squamous NSCLC and in combination with carboplatin and either paclitaxel or nab-paclitaxel in squamous NSCLC, both times irrespective of PD-L1 expression. Nivolumab received a first-line approval in combination with ipilimumab and two cycles of platinum-based chemotherapy by the EMA in late 2020. All first-line approvals of nivolumab and pembrolizumab (except in squamous NSCLC) exclude patients with EGFR and ALK mutations.

Atezolizumab is another CPI that was initially approved in second-line therapy after prior chemotherapy in 2017 by the EMA. In 2019, it moved to first line in combination with bevacizumab, paclitaxel, and carboplatin as well as in combination with nab-paclitaxel and carboplatin. Both first-line approvals are in non-squamous NSCLC and irrespective of PD-L1 expression and the latter excludes patients with EGFR and ALK mutations while the former permits a use as second-line therapy after failure of appropriate TKIs.

Durvalumab is the latest CPI to be approved by the EMA in NSCLC in 2018. It is different from the three others, as it is only indicated in stage III in unresectable cases with a PD-L1 expression of 1% or higher who have not progressed following platinum-based chemoradiotherapy.

In Europe, guidelines by the European Society for Medical Oncology (ESMO) (version from September 2020) recommend pembrolizumab as the preferred CPI for first-line treatment of patients with a PD-L1 of 50% or higher (127). In patients with a PD-L1 of less than 50%, the guidelines recommend the combination of pembrolizumab with carboplatin and (nab-)paclitaxel as standard choice in squamous disease, while the combination of pembrolizumab with pemetrexed and platinum-based chemotherapy is recommended as standard option in non-squamous disease. The combination of atezolizumab with carboplatin and nab-paclitaxel represents a new standard treatment opportunity in non-squamous disease, according to the guidelines. In the US, guidelines by the

National Comprehensive Cancer Network (NCCN) recommend the same treatment options, except for atezolizumab, where the combination with bevacizumab, paclitaxel, and carboplatin is recommended instead (51).

2.6 Follow-up treatment of NSCLC

Follow-up and rehabilitation are important components in patients undergoing initial treatment with a curative intent. Patients progressing on their initial treatment still have different medical treatment options that can be explored. In reality, best supportive care (e.g. narcotic and non-narcotic analgesics, corticosteroids, gastrointestinal medication) is provided to a majority of progressing lung cancer patients as they are typically close to end of life (128). Close communication with contact nurses is vital for patient quality of life. Informal caregivers also play a central role and need support from the health care system and the social security system.

2.6.1 Local recurrence in early-stage patients

In around 13–24% of early-stage lung cancer patients who had undergone curative surgery, the cancer recurs locally (129). The median time from surgical resection of the primary tumor to local recurrence is around 14 months (130). Chemoradiotherapy, ideally delivered concomitantly when feasible and tolerable, is the main choice in these patients.

2.6.2 Metastatic recurrence in early-stage patients

Metastatic recurrence (i.e., presence of distant metastases) in early-stage lung cancer patients who have undergone curative surgery is more common than local recurrence, and occurs in around 20–45% of cases (130, 131). The median time from surgical resection of the primary tumor to distant recurrence is around 12.5 months (130). The main treatment choice in these patients is systemic therapy, starting with the first-line treatment options described in section 2.5.3.

2.6.3 Progression on systemic therapy in advanced-stage patients

Second line and beyond in patients with driver alterations

Patients with EGFR and ALK driver mutations who have progressed on appropriate TKIs in first line are eligible for further targeted therapy or for immunotherapy. Patients with an EGFR mutation treated with first-generation inhibitors would receive osimertinib if they have an EGFR T790M driver. Other patients and those who received osimertinib in first line would receive platinum-based

chemotherapy or immunotherapy. Similarly, patients with an ALK mutation who received crizotinib in first line would receive newer inhibitors in second line followed by lorlatinib in third line, while patients who received the newer inhibitors in first line would receive lorlatinib in second line, or alternatively platinum-based chemotherapy or immunotherapy. The two viable CPI options are atezolizumab and pembrolizumab, both in combination with chemotherapy drugs.

Patients progressing on ROS1, BRAF, and NTRK inhibitors can be considered for the same chemotherapeutic regimens as patients without driver mutations.

Second line and beyond in patients without driver alterations

Patients who progress on platinum-based chemotherapy or on immunotherapy (atezolizumab or pembrolizumab, both in combination with chemotherapy) are eligible for docetaxel monotherapy, pemetrexed monotherapy (only in non-squamous disease and unless already used in first line with pembrolizumab), docetaxel in combination with nintedanib (only for adenocarcinoma disease), or docetaxel in combination with ramucirumab. The latter combination was approved in 2016, but only yields a small gain in survival over docetaxel monotherapy resulting in an unfavorable cost-effectiveness profile (132).

Patients who progress on first-line platinum-based chemotherapy can receive immunotherapy (atezolizumab, nivolumab, or pembrolizumab). Patients who progress on first-line monotherapy pembrolizumab are typically treated with platinum doublet as they are chemotherapy naive and expected to derive benefit from such therapy.

Patients progressing on second-line therapy have some options left. Typically older chemotherapies given as a single agent without platinum (e.g., docetaxel, gemcitabine, paclitaxel, pemetrexed, vinorelbine) or possibly erlotinib are used in third-line treatment (133). The average treatment duration is comparatively short (e.g., around 2 months with erlotinib).

2.7 Overview of first-line and later-line systemic therapy

The recent wave of new drugs has radically changed the drug therapy landscape. Figure 8 and Figure 9 illustrate the standard-of-care treatment options in mid-2014 and mid-2020, respectively. They show that much has changed in all lines of treatment and histological and molecular subtypes within the lapse of only a few years. One key question of the remainder of this report is to understand how well European countries have handled this development in terms of enabling patient access to state-of-the-art treatment.

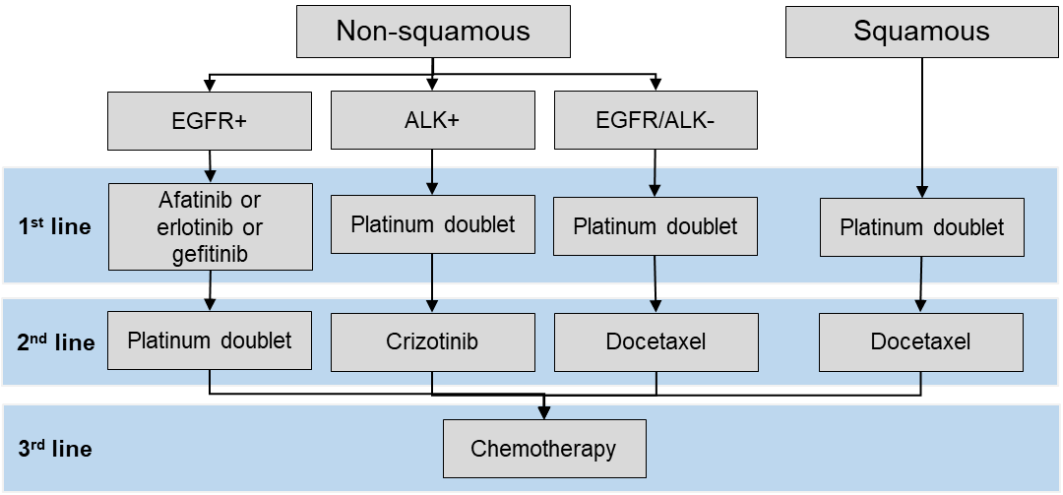


Figure 8: Treatment protocol of patients with advanced stage NSCLC in 2014
Source: Adapted from (134), and adjusted according to EMA-approved drugs on Jun 30, 2014.

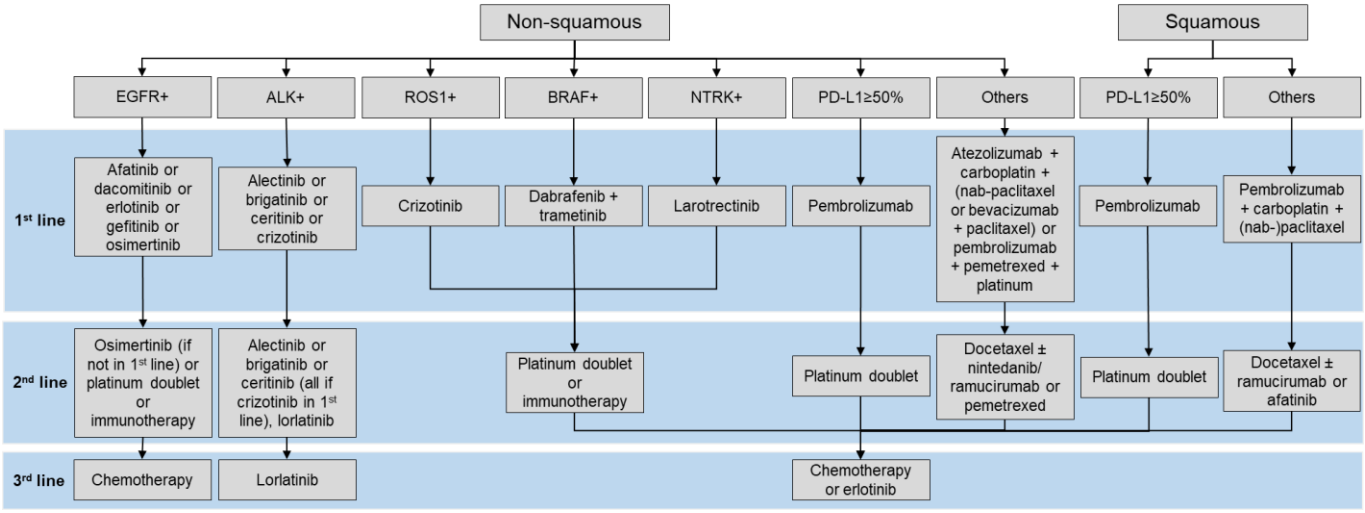


Figure 9: Treatment protocol of patients with advanced stage NSCLC in 2020
Source: Adapted from (16), and adjusted according to EMA-approved drugs on Jun 30, 2020.

2.8 Key points

- Most lung cancer patients are diagnosed at a locally advanced or metastatic stage when the disease is no longer amenable to curative surgery or chemoradiotherapy.
    - There is a need for increased awareness among patients, GPs, and other health care professionals in identifying early symptoms of disease.
    - Lung cancer screening among former and current smokers might help to diagnose patients earlier. Convincing evidence on the cost-effectiveness of a lung cancer screening program is still scarce.
- Delays at all stages of the patient journey are a concern.

  - Slow diagnostic procedures, multiple specialist consultations, slow MDT assessments, slow scheduling of surgery and radiotherapy are all delaying access to treatment. Care pathways with clearly defined timelines can help avoid unnecessary delays.
  - Clinical guidelines often fail to establish fast-track systems or specific timeframes for diagnostic testing. This also holds for rapid referral systems for newly diagnosed patients to obtain treatment.

- The diagnosis of lung cancer requires the joint work of several experienced specialists to determine results from imaging and pathological samples and provide accurate staging.
  - Work-up of patients with lung cancer must include radiological evaluation, tissue sampling, pathological examination (histological classification and staging), molecular diagnostics, and immunohistochemistry.
  - PET/CT allows more precise disease staging in lung cancer and is important when curative treatment (i.e., surgery or chemoradiotherapy) is intended.
  - Molecular diagnostics to assess genomic alterations in lung cancer is required to identify actionable targets for targeted drugs. Expertise in interpreting molecular findings and their clinical significance is essential.
  - NGS for genomic profiling is warranted but expensive, and the turnaround time is frequently more than a week which delays treatment start. Sequential testing is cheaper than NGS but challenging due to the number of different tests needed, resulting in depletion of tissue samples and incomplete assessments as well as possibly longer turnaround time due to several rounds of assessment.
  - Immunohistochemistry for PD-L1 is the only available biomarker that can guide treatment with checkpoint inhibitors.

- Treatment decisions should be based on assessments by multidisciplinary teams.
  - MDTs are essential in selecting patients for surgery with a curative intent, and patients eligible for preoperative chemo-/radiotherapy or palliative treatment. They need to define the optimal treatment algorithm for each patient, taking into account the findings from genomic profiling and immunohistochemistry especially in patients with advanced disease.
  - The therapeutic approach must also take into account patient choice, performance status, and co-morbidities. Patients in poor condition should not be denied treatment but evaluated based on the therapeutic opportunities by disease stage.

- Systemic therapy for patients with advanced NSCLC has undergone major changes in recent decades.
    - In the 1990s, single-drug chemotherapy was replaced by platinum-based doublet chemotherapy.
    - In the mid-2000s, the era of personalized medicine and targeted therapies began. The proportion of patients with actionable alterations continues to increase and is now about 30% in Caucasian patients.
    - In 2015, the era of immune checkpoint inhibitors began. They are mainly used in patients without targetable genomic alterations.
- Drug approvals have been accelerating considerably since 2015, with at least four new indications being approved every year until 2020 in Europe.
    - Standard-of-care treatment has been altered in all lines of treatment and histological and molecular subtypes within the lapse of only a few years.
    - The fast-changing drug options require continuous training of medical staff, modification of routines, and updating of treatment guidelines.
    - The task of ascertaining the optimal timing and sequencing of targeted therapy, immunotherapy, and chemotherapy is becoming increasingly challenging.

3. Calculating drug treatment rates

This chapter outlines the method and presents the results of the calculation of country-specific drug treatment rates. The aim is to (i) understand how high drug treatment rates are and (ii) uncover the kind of drug treatment received by patients with advanced NSCLC. The results are presented in a descriptive manner in this chapter, while possible drivers of the results are analyzed in chapter 4.

Several studies and reports have previously calculated drug treatment rates in advanced NSCLC in different European countries. Examples are:

- **England+Wales**: 66% of patients with stage IIIB–IV NSCLC and ECOG performance status 0–1 received systemic therapy with cancer drugs in 2018, according to the National Lung Cancer Audit (135)
- **Netherlands**: Almost 90% of stage IV NSCLC patients with active tumor treatment (i.e., excluding those receiving best supportive care) received systemic therapy (including chemoradiotherapy) with cancer drugs as first-line treatment in 2019, according to the Dutch Lung Cancer Audit study (136)
- **Norway**: Around 50% of stage III–IV NSCLC patients diagnosed in January–October 2019 received systemic therapy (including chemoradiotherapy) with cancer drugs as first-line treatment in 2019 in three (out of four) health care regions (137)
- **Portugal 1**: 76% of patients with stage IIIB–IV NSCLC diagnosed in 2015–2016 received at least one line of systemic therapy with cancer drugs in IPO-Porto, Portugal's largest oncology hospital (138)
- **Portugal 2**: 50% of patients with metastatic lung cancer diagnosed in 2014–2015 received at least one line of chemotherapy and 6% received at least one line of immunotherapy, according to data from the regional cancer registry of Southern Portugal (139)

These studies have in common that they are based on data obtained from cancer registries or hospital records. However, they use different definitions to define the number of patients treated (the numerator of the treatment rate) and the number of patients eligible for treatment (the denominator of the treatment rate). These treatment rates are thus not comparable across countries, and also not within countries in the case of Portugal. Therefore, this report aims to calculate drug treatment rates that are comparable across countries.

3.1 Method

3.1.1 Overview of method

The method to calculate comparable drug treatment rates across countries takes its starting point in drug sales data; see Figure 10. The basic idea is to use national sales data of cancer drugs ("Total drug sales in a country" in Figure 10) as a measure of the total amount of drugs administered to patients in a country. This information is then combined with the average use of a certain drug in the treatment of a patient ("Average drug use per patient"). This yields an estimate of the number of patients treated with a certain drug. Treated patient numbers across all drugs are then summed up ("Number of patients treated"). The total number of patients to be possibly eligible for drug treatment is calculated based on available national epidemiological data ("Number of potentially eligible patients"). The drug treatment rate is obtained by dividing the number of patients receiving drug treatment with the number of potentially eligible patients for drug treatment.

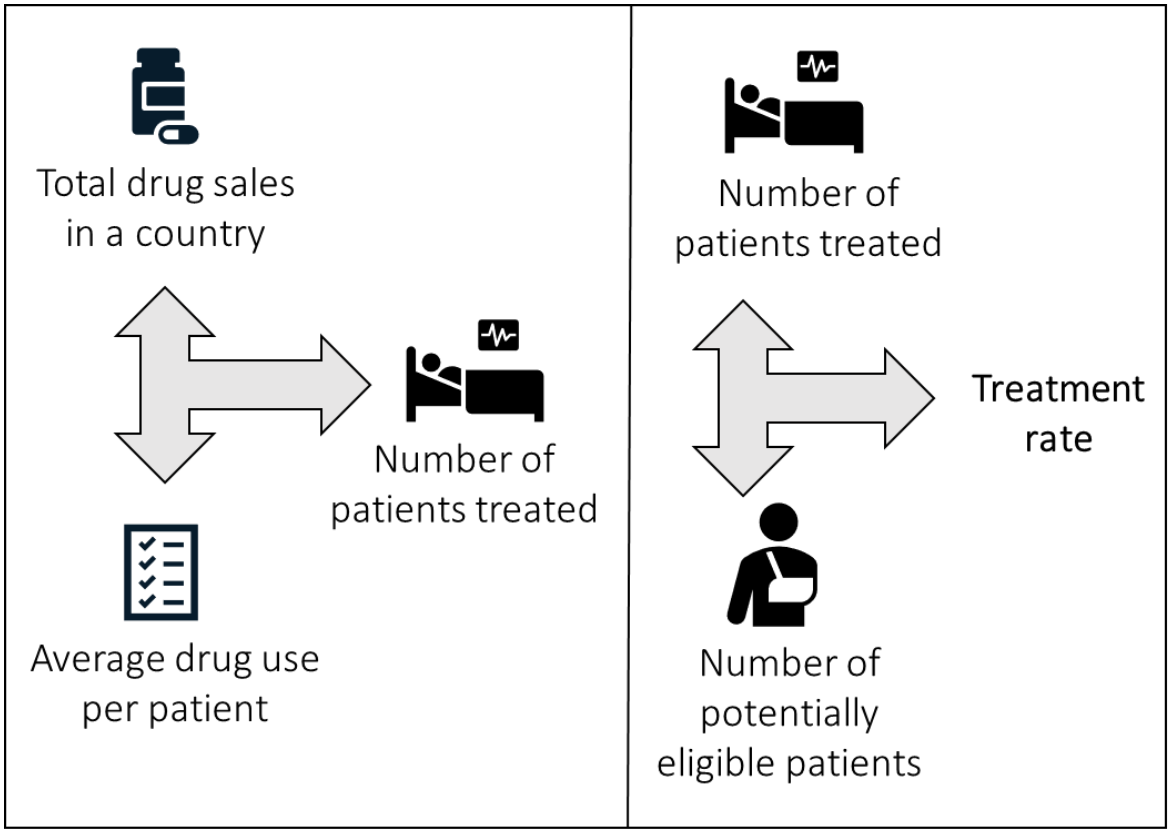


Figure 10: Elements used to calculate drug treatment rates

The study population in this report are patients with advanced NSCLC. This is defined as patients with stage IIIB/C and stage IV. Patients in the current year are the sum of (i) newly diagnosed patients with stage IIIB/C+IV in the current year, (ii) newly diagnosed patients with stage I–IIIA in the previous year whose disease is assumed to recur at an advanced stage in the current year, (iii) patients

with advanced disease who could have received first-line systemic therapy in the previous year and who progress to second-line systemic therapy in the current year, and (iv) patients progressing to third-line systemic therapy in the current year. Section 3.1.4 explains this in more detail.

The study period of the initial analysis was 2014 (pre-immunotherapy era) to 2019 (pre-COVID-19 era) and was later extended to 2020 (first year with COVID-19). All cancer drugs that have been potentially used in the treatment of advanced NSCLC during this period are considered. Section 3.1.2 explains the drug selection in more detail. The estimation of the number of patients treated with those drugs is explained in section 3.1.3. The geographic coverage encompasses the following countries: Belgium, Bulgaria, Finland, Greece, Hungary, Ireland, Netherlands, Norway, Poland, Portugal, Romania, United Kingdom.

The calculation of the drug treatment rates was carried out in a three-step process. First, calculations were made based on country-specific publicly available data sources and remaining assumptions were based on other published literature. Second, the preliminary results for the years 2014 to 2019 and assumptions made in the calculations were validated through an online survey in each country of scope by two experts – one representing the medical field (such as a pulmonologist, medical oncologist) and one the pharmaceutical industry.[2] The preliminary results were then revised based on the input received. Additional feedback obtained in local workshops with a broader audience (local lung cancer experts representing different specialties, such as oncologists, pulmonologists, nurses, and patient representatives) also led to a revision of certain assumptions. Third, results for 2020 were calculated according to the same methodology, taking into account the effect of the pandemic on patient numbers; see Appendix A1.

3.1.2 Drugs considered in the analysis

All drugs used in systemic anti-cancer therapy (chemotherapy, immunotherapy, targeted therapy) of advanced NSCLC were considered. This includes drugs with an approved indication in advanced NSCLC by the EMA between January 1, 1995 and December 31, 2020. It also includes older drugs that came into clinical use before the establishment of the EMA. Inclusion of these older drugs was based on whether treatment guidelines by ESMO (versions from 2014 to 2020) mentioned their use in metastatic NSCLC. Table 1 provides an overview of the drugs used in the treatment of advanced NSCLC, and Table A8 in the Appendix provides a more detailed overview of approved indications.

[2] In Belgium, two clinical experts (one from Flanders and one from Wallonia) answered the survey due to local differences in the health care system. Experts from the pharmaceutical industry were from MSD and often comprised a cross-functional team that submitted a joint answer.

These drugs generally have approved indications in first-line and/or second-line systemic therapy. The only drug with a third-line indication is lorlatinib in ALK-positive patients since May 2019.[3]

Table 1: Drugs used in the treatment of advanced NSCLC

Chemotherapy	Immunotherapy	Targeted therapy
Carboplatin*ǂ	Atezolizumab	*EGFR inhibitors*
Cisplatin*ǂ	Durvalumab	Afatinib
Docetaxel	Nivolumab°	Dacomitinib
Gemcitabine*	Pembrolizumab	Erlotinib
Paclitaxel*		Gefitinib
Paclitaxel-nab		Necitumumab
Pemetrexed		Osimertinib
Vinorelbine*		
		ALK/ROS1 inhibitors
Angiogenesis inhibitors		Alectinib
Bevacizumab ǂ		Brigatinib
Nintedanib ǂ		Ceritinib
Ramucirumab ǂ		Crizotinib
		Lorlatinib
		Other inhibitors
		Dabrafenib + trametinib ǂ
		Entrectinib
		Larotrectinib

Notes: * Not approved by the EMA. ° Nivolumab also received EMA approval in combination with ipilimumab in late 2020. ǂ These drugs are always given in combination with other drugs and were therefore not included in the calculations to avoid double counting (see section 3.1.3).

The drug vinorelbine was excluded in the preliminary calculations of the drug treatment rates in all countries, because ESMO guidelines recommend very limited use in metastatic NSCLC. The online survey asked whether vinorelbine or any other drug (except entrectinib which was first approved in 2020) not listed in Table 1 should be included in the final calculations because it was "*routinely used in systemic treatment of advanced NSCLC in 2014–2019*". Based on the survey responses from the clinical representatives, vinorelbine was included in Belgium, Bulgaria, Finland, Greece, Netherlands, Norway, Poland, Portugal, and Romania.

3.1.3 Patients treated with drugs

Two inputs are required to estimate the number of patients with advanced NSCLC treated with cancer drugs. The first one is the total volume of drugs administered in a country in a certain year in patients with advanced NSCLC. The second one is the average drug use per patient with advanced NSCLC.

[3] Other drugs, mostly older chemotherapies, are usually used off-label in third-line therapy. There are few patients fit enough to receive third-line or later-line systemic therapy in reality.

Volume of cancer drugs administered

As a measure of the volume of cancer drugs administered to patients, data on sales of all cancer drugs listed in Table 1 were obtained from IQVIA, a global provider of pharmaceutical sales data.[4,5] The data contain information on the milligrams sold per drug per year per country.[6] For Greece, sales data were obtained from the Ministry of Health, EOPYY (National Organisation for Healthcare Services Provision), and IDIKA (e-government center for social security platform).

A major drawback of using aggregated drug sales data is the lack of information on the use of a drug in a certain indication, such as in advanced NSCLC. For drugs that only have approved indications in advanced NSCLC, such as afatinib and most other targeted therapies, this is naturally not a concern. Off-label use of these kinds of drugs is likely very limited because of their targeted nature. By contrast, many chemotherapies have approved indications in the treatment of early-stage NSCLC and in many other cancer types. Similarly, immunotherapies have a broad range of approved indications in different cancer types.

To estimate the use of a certain drug in cancer types other than NSCLC, a scale factor, ranging from 0 to 1, was defined. This scale factor was calculated individually for every drug in every year and every country. The exact calculation of the scale factor was based on:

- The indications that a drug is reimbursed for in a certain year
- The potential patient numbers in the reimbursed indications
- The median treatment duration in the reimbursed indications

The general formula for the scale factor of drug A in year t in country c was:

$$\text{Scale factor}_{A,t,c} = \frac{\text{Incidence}_{NSCLC} * \text{TrDu}_{NSCLC}}{\sum_{Indication\ i=1}^{Indication\ N} \text{Incidence}_i * \text{TrDu}_i}$$

[4] IQVIA data are typically based on sales to drug wholesalers. There might be parallel trade of drugs in some countries that can run in both directions (import and export) and that is not fully captured by this data. Thus, there might be a discrepancy between the volume sold and the volume administered to patients in a country. The industry representative in Belgium indicated that IQVIA data might not be fully representative of real sales in that country.

[5] IQVIA data were adjusted in the following cases with inscrutable outliers. In Belgium, the 2015 value of paclitaxel was replaced by an average of the 2014 and 2016 values. In Bulgaria, the 2017 value of gefitinib was replaced by an average of the 2016 and 2018 values. In Ireland, the 2017–2020 values of gemcitabine were estimated based on year-on-year growth rates observed in the UK. In Portugal, the 2017 and 2018 values of pemetrexed were replaced by an average of the 2016 and 2019 values. In Romania, the 2016 value of paclitaxel was replaced by an average of the 2015 and 2017 values.

[6] Some drug molecules are used with a salt. To remove the weight of the salt in IQVIA data, a salt factor needs to be applied to sales data to obtain the sole weight of the drug molecule.

where Incidence is the potential number of patients in indication i, N is the number of reimbursed indications i, and TrDu is the treatment duration in indication i.

For all EMA-approved drugs included in the analysis, indications in cancer types other than NSCLC were based on approvals up until December 31, 2020. For older non-EMA-approved drugs, approved indications were based on a targeted literature search in ESMO treatment guidelines of all solid cancer types and information in the Swedish drug information system (FASS); see Table A9 in the Appendix. The reimbursement date of each EMA-approved indication in every country was sourced through local contacts by MSD, except for the UK where this information was directly sourced from the website of NICE. All older non-EMA-approved drugs were assumed to be reimbursed in all approved indications in all years from 2014 to 2020 in every country.

Potential patient numbers in the reimbursed indications were based on data from the Global Cancer Observatory (GLOBOCAN) (15).[7] Incidence numbers for the year 2018 were used as a proxy in all years of 2014 to 2020.[8] Incidence was supposed to serve as a proxy for actual patient numbers receiving a certain drug. The choice of incidence (rather than, e.g., mortality) was motivated by the fact that all newly diagnosed patients might at least at some point during their treatment receive systemic therapy. Incidence numbers were also adjusted according to line of therapy of the reimbursed indication. For drugs with a first-line indication in a specific cancer type, incidence numbers were used as is, while for drugs with only a second-line indication in a specific cancer type, half of the incidence numbers (50%) of that cancer type were used.[9] If a drug had multiple reimbursed first-line or second-line indications in a cancer type, incidence numbers were only applied once. If a drug had reimbursed indications in both first line and second line in a cancer type, only incidence numbers in first line were applied.

The median treatment duration in the reimbursed indications of a drug was based on data from pivotal clinical trials; see Table A10 in the Appendix.[10] Median progression-free survival (PFS) was

[7] GLOBOCAN provides estimates of incidence numbers by broad cancer type (e.g., breast cancer, bladder cancer, pancreatic cancer), which may be more or less precisely estimated from country to country. For the calculation of the scale factor, the accuracy of the absolute size of all incidence numbers of different cancer types is of less importance as only the relative size of the incidence numbers between different cancer types enters the calculations.

[8] As incidence numbers of cancer types change relatively little over the course of seven years and also in relation to each other, the use of data from a single year has arguably a limited influence on the results.

[9] This assumption is based on a 50% progression rate to second-line treatment across all cancer types to simplify the analysis. In reality, these progression rates are not uniform across cancer types and might also change over time if new first-line treatments are introduced.

[10] As pointed out by several clinical representatives in the survey and the workshops, there is always a gap between daily practice and a clinical trial setting. Most of the time, patients in daily practice are more co-morbid and therefore the treatment duration is shorter than in the clinical trial. A shorter treatment duration leads to an underestimation of the treatment rates in this study.

obtained for every indication (distinguishing between cancer type and first-line or second-line therapy) of drugs that are administered until disease progression or unacceptable toxicity. For drugs (mostly chemotherapy drugs) that are typically only administered for a limited number of treatment cycles, the median number of administered cycles in the pivotal clinical trials was used instead of PFS.

One additional adjustment was made to the scale factor of drugs that are used in early-stage NSCLC (stage I to IIIA). Among the EMA-approved drugs, this concerned only durvalumab, which is approved in stage III and PD-L1>1% only. Based on the fact that sub-stages IIIA and IIIB/C are mostly diagnosed in equal proportions in all countries (see Table A5 in the Appendix), half of the sales (50%) of durvalumab in NSCLC were removed. Among the non-EMA-approved drugs, this concerned only vinorelbine, which is a recommended treatment option in stage I and stage II, a potential treatment option in stage III, and a potential treatment option in stage IV in patients with performance status 2.[11] In absence of data to inform an evidence-based choice, three fourths of the sales (75%) of vinorelbine in NSCLC were removed.

For the two tumor-agnostic therapies, entrectinib and larotrectinib, a uniform scale factor across years and countries was used. NTRK mutations that are targeted by these drugs appear in up to 19 different cancer types (140-142). For larotrectinib, one third (33%) of sales were assumed to be used in NSCLC. For entrectinib, 75% of sales were assumed to be used in NSCLC, given a frequency of NTRK mutations of around 0.3% in NSCLC and a frequency of ROS1 mutations (for which entrectinib is also indicated) of around 1.5% in NSCLC.

An important consequence of calculating the scale factor as described above is its implicit assumption on drug sales outside of the reimbursed indications. This concerns private drug sales in EMA-approved but non-reimbursed indications as well as off-label use. In these cases, the drug volume sold is either not counted at all (i.e., the scale factor is zero if a drug has no reimbursed indication in advanced NSCLC) or fully ascribed to the reimbursed indications (i.e., the scale factor is too high if a drug has off-label use in other cancer types).

The volume of drug A, measured in milligrams, administered in advanced NSCLC in year t in country c was calculated as:

[11] We reviewed ESMO guidelines for early and locally advanced NSCLC in 2013 and 2017 and guidelines for metastatic NSCLC in 2014–2020. Aside from vinorelbine, any mentioning of the drugs gemcitabine and paclitaxel was reviewed. Gemcitabine might be used in stage I and II, but it is not the standard treatment option. Paclitaxel is not mentioned at all as a treatment option in stage I–IIIA. Carboplatin and cisplatin were not considered here, as they were excluded from the analysis to avoid double counting.

$$\text{Sales in advanced NSCLC}_{A,t,c} = \text{Total sales}_{A,t,c} * \text{Scale factor}_{A,t,c}$$

Average drug use per patient

The average use of drug A per patient with advanced NSCLC, measured in milligrams, in year t in country c was calculated as:

$$\text{Drug use per patient}_{A,t,c} = \text{Dosage}_{A,t,c} * \text{TrDu}_{A,t,c}$$

where Dosage is measured in milligrams per month and TrDu is the treatment duration in months.

The recommended dosage in milligrams per drug per treatment cycle was sourced for all drugs from Medscape (143), and then converted to a dosage per month. Table A7 in Appendix shows details on the exact dosage used per drug. The same dosage was used in all years and countries.

The treatment duration with each drug was based on data from pivotal clinical trials. Median PFS was obtained for every indication and used as a proxy for treatment duration for drugs that are used until disease progression or unacceptable toxicity. For drugs that are only administered for a limited number of treatment cycles, the median number of administered cycles observed in the pivotal clinical trials was used. Table A8 in Appendix shows the treatment duration used for each indication. The following heuristics were applied to calculate the treatment duration with drug A in advanced NSCLC in year t:

- If drug A is initially reimbursed in second line only in year t, the full treatment duration is used in the initial year of reimbursement, without any caps or consideration of reimbursement approval happening close to the end of this year.[12]
- If drug A has been reimbursed only in second line in previous years and then receives a first-line reimbursement in year t, a weighted mean of the treatment durations in first-line and second-line indication is calculated in year t based on the length of the concomitant reimbursement period in year t.[13]
- If drug A has a first-line and a second-line indication reimbursed during the entire year t, the treatment duration of the first-line indication is used.

[12] This adjustment is motivated by the fact that IQVIA data often show sales already some months before reimbursement.
[13] For the special case of two or more first-line indications receiving reimbursement during the same year, the mean duration of these indications is first calculated and the earliest reimbursement date among the first-line indications is used to determine the length of the concomitant reimbursement period with the second-line indication.

- If drug A has either several first-line indications (or only several second-line indications) reimbursed in year t, an unweighted mean of the treatment durations of these indications is used.
- If the calculated treatment duration for drug A in year t exceeds twelve months, the duration is capped at twelve months.

Number of patients treated with drugs

Using the results above, the number of patients with advanced NSCLC treated with drug A in year t in country c was calculated as:

$$\text{Treated patients}_{A,t,c} = \frac{\text{Sales in advanced NSCLC}_{A,t,c}}{\text{Drug use per patient}_{A,t,c}}$$

This was done for all drugs listed in Table 1 above. Before summing up all patients treated with these drugs, some adjustments had to be made to avoid double counting. This applies to all cases when a drug is given in combination with others; see Table A8 in the Appendix. For the following drugs, sales were not counted:

- Carboplatin and cisplatin as they are only used in combination with other drugs
- Bevacizumab as it is only used in combination with either platinum-based chemotherapy, immunotherapy, or targeted therapy
- Nintedanib and ramucirumab as they are only used in combination with docetaxel
- Trametinib as it is only used in combination with dabrafenib

For four drugs – gemcitabine, paclitaxel, paclitaxel-nab, pemetrexed – used as part of first-line platinum-based chemotherapy, sales volumes (and hence patient numbers) were capped[14] starting from the year when the first first-line immunotherapy indication – either atezolizumab, nivolumab, or pembrolizumab – got reimbursed in a country.[15,16] This was done because growth in sales volumes

[14] Using the sales volume in the year preceding the first reimbursement of any of the cited first-line indications.
[15] For pemetrexed, sales volumes were further adjusted downwards starting from the year when the first-line indication of the combination of pemetrexed plus pembrolizumab and platinum got reimbursed in a country, based on a constant factor related to the new longer treatment duration as observed in the pivotal clinical trial. For Hungary, this adjustment was already made from the year when the first-line indication of pembrolizumab monotherapy got reimbursed, because patients could access the combination with pemetrexed as part of the named patient system.
[16] The sales volume of gemcitabine would also have been capped if the first-line indication of necitumumab plus gemcitabine and cisplatin got reimbursed, but no country reimbursed this indication until the end of 2020.

of these chemotherapies might be more related to increased use in combination with immunotherapy in first line rather than increased use in second line or in third line.

The total number of patients with advanced NSCLC treated with any drug in year t in country c was calculated as:

$$\text{Treated patients}_{t,c} = \sum_{i=A}^{N} \text{Treated patients}_{i,t,c}$$

across all drugs (A to N) that are not excluded to avoid double counting as explained above. Patient numbers were also summed up by three types of systemic therapy: chemotherapy alone (possibly including angiogenesis inhibitors), immunotherapy (as monotherapy or in combination with chemotherapy), targeted therapy.

3.1.4 Patients eligible for drug treatment

The number of patients with advanced NSCLC who are potentially eligible for drug treatment was defined as the sum of:

1. Newly diagnosed patients at advanced stages
2. Recurrent patients from earlier stages
3. Progressing patients from first-line systemic therapy of advanced disease to second-line systemic therapy
4. Progressing patients from second-line systemic therapy of advanced disease to third-line systemic therapy

The number of newly diagnosed patients at advanced stages was calculated based on lung cancer patient numbers (ICD-10: C33–C34) [17] from national cancer registries (if available) and complementary studies on histology and stage distribution at diagnosis. Advanced stages refer to stage IIIB/C and stage IV. The general formula used for year t was:

$$\text{Newly diagnosed patients}_t = \text{Incidence}_{\text{Lung cancer, t}} * \%\ \text{NSCLC} * \%\ \text{stage IIIB/C+IV}$$

Table A1 in the Appendix provides an overview of the incidence of lung cancer in 2012 to 2019 used in the calculations, and Table A2 shows the sources used to estimate the incidence in 2020 as the

[17] C33 is cancer of the trachea and C34 is cancer of the bronchus and lung. The primary focus was on C34, but most cancer registries reported only joint numbers for C33–C34, yet C33 cases are typically 1000 times less common than C34 cases.

COVID-19 pandemic affected access to health care and diagnosis. Table A4 shows the histological distribution of newly diagnosed lung cancer cases used in the calculations. The proportion of NSCLC was around 85% in all countries and the same country-specific proportion was used in all years in the calculations. Table A5 shows the stage distribution of newly diagnosed NSCLC cases, and the same country-specific proportions were used in all years in the calculations.

Recurrent patients from earlier stages have been initially diagnosed with NSCLC in stage I–IIIA. Many of those patients experience a relapse after initial therapy for early-stage disease. If the cancer comes back at an advanced stage, patients become eligible for first-line systemic treatment.[18] The general formula used for year t was:

$$\text{Recurrent patients}_t = \text{Incidence}_{\text{Lung cancer, t–1}} * \%\ \text{NSCLC} * \%\ \text{stage I–IIIA} * \text{Recurrence rate}$$

Incidence numbers refer to year t–1, i.e., the year before year t. This is motivated by studies showing that the median time to recurrence from earlier stages is around 12 months (130), as explained in section 2.6. Information on country-specific histological distribution (Table A4) and stage distribution (Table A5) was used analogously to the calculation of newly diagnosed patients described above. Previous studies indicate a wide range of recurrence rates depending on the exact definition of the study population and the initial therapy for early-stage disease received (e.g., surgery, radiotherapy, or chemoradiotherapy) and the study follow-up period (129-131, 144, 145). A recurrence rate of 50% in stage I–IIIA patients was assumed in all years in the initial calculations.[19] The online survey asked whether a 50% recurrence rate reflects the clinical reality in a specific country. The clinical representatives confirmed the 50%-rate in every country except in Romania (70%), and these rates were then applied in the final analysis.[20]

Progressing patients from first-line systemic therapy can receive second-line systemic therapy if they are fit enough for further treatment. If they progress on second-line systemic therapy, they can receive third-line therapy if they are fit enough. The general formulas used for year t were:

$$\text{Progressing patients 1L to 2L}_t = (\text{Newly diagnosed}_{t-1} + \text{Recurrent patients}_{t-1}) * \text{Progression rate}$$

$$\text{Progressing patients 2L to 3L}_t = \text{Patients with 2L therapy}_t * \text{Progression rate}$$

[18] This was assumption was confirmed in the survey by the clinical representative in every country.
[19] The recurrence rate of 50% was supposed to encompass primarily patients with distant recurrence and partly also patients with local recurrence in whom the disease comes back again at an advanced stage after curative treatment.
[20] One clinical representative in Belgium indicated a rate of 40%, but this was later confirmed to be "between 40% and 50%, and probably closer to 50%".

The numbers of newly diagnosed patients and recurrent patients refer to the year t–1, i.e., the year before year t. This is motivated by the median time to progression for first-line systemic therapy being nowadays closer to 12 months for immunotherapy and targeted therapy, compared to less than 6 months for platinum-based chemotherapy (76). Previous studies indicate a wide range of progression rates depending on the exact definition of the study population (e.g., all patients diagnosed or only those who received first-line systemic therapy) with estimates of 8–53% in a review of 12 international studies (133), 44% and 47% in two other studies from the US (146, 147), and 57% in a study from Portugal (148). A progression rate of 40% to second-line treatment was assumed in all years in the initial calculations.[21] The online survey asked whether a 40% progression rate reflects the clinical reality in a specific country. The clinical representatives confirmed the 40%-rate in every country except in Belgium (60%), Finland (50%), Greece (67.5%)[22], the Netherlands (35%), and Romania (60%), and these rates were then applied in the final analysis.

Patients progressing from second-line to third-line systemic therapy were assumed to do so during the same year as they receive second-line therapy. This is motivated by the median time to progression in second-line therapy being around 3 to 5 months; see Table A8 in the Appendix. Few patients are fit enough for third-line therapy, with published estimates ranging from 21% to 55% of those who have received second-line therapy in a review of nine international studies (133). Similar magnitudes have also been reported for Austria (41%) and the US (48%) (149), and more recently for Portugal (30%) (148). A progression rate of 40% from second-line to third-line therapy was assumed in all years in all countries in the initial calculations.[23] This rate was later confirmed by the clinical representative for Greece, whereas deviating progression rates were used for Belgium (33%), Bulgaria (20%), Ireland (25%), the Netherlands (10%), Norway (30%), Poland (20%), Portugal (30%), the UK (10%) after consultations with clinical representatives as part of local workshops or e-mail contact. Based on the feedback from these clinical representatives, the default rate of 40% was lowered to 30% in the remaining countries.

Patients progressing from third-line systemic therapy to later lines were not included. Few patients survive that many lines of therapy and are still fit enough for any further systemic treatment.

The sum of newly diagnosed patients, recurrent patients, and progressing patients (first line to second line and second line to third line) is the total number of patients with advanced NSCLC potentially eligible for drug treatment. Table 2 summarizes the patient numbers used in the final analysis.

[21] After the introduction of immunotherapy in first-line therapy, the progression rate might have changed but no studies were identified to corroborate this.
[22] The clinical representative indicated a range of 65–70%.
[23] This assumption was not validated in the survey, because third-line patients were not included initially.

Table 2: Potentially eligible patients for drug treatment in advanced NSCLC

	2014	2015	2016	2017	2018	2019	2020
Belgium	10,041	10,161	10,061	10,081	10,387	10,652	10,644
Bulgaria	4,141	3,998	3,925	3,813	3,806	3,819	3,679
Finland	3,154	3,230	3,311	3,323	3,261	3,308	3,336
Greece	10,811	11,168	11,427	11,656	11,807	11,824	11,455
Hungary	9,217	9,282	9,322	9,291	9,253	9,244	8,583
Ireland	2,334	2,382	2,422	2,489	2,576	2,617	2,559
Netherlands	11,606	12,077	12,423	12,498	12,875	13,186	13,129
Norway	2,867	2,939	2,983	3,063	3,187	3,245	3,104
Poland	28,169	28,418	28,897	28,060	27,832	28,153	25,900
Portugal	4,890	5,090	5,290	5,490	5,690	5,823	5,642
Romania	15,643	15,637	15,740	15,482	15,142	14,789	14,112
UK	46,981	47,383	48,090	48,692	48,741	49,444	48,497

Notes: The number of potentially eligible patients for drug treatment in a given year is the sum of (i) newly diagnosed cases with stage IIIB/C+IV in that year, (ii) newly diagnosed cases with stage I-IIIA in the previous year whose disease recurs at an advanced stage, (iii) patients potentially eligible for first-line systemic therapy in the previous year and who progress to second-line systemic therapy, and (iv) patients who progress to third-line systemic therapy within the same year as they progressed to second-line systemic therapy.

3.1.5 Patient eligibility

Patient eligibility is defined in its broadest sense in this report. Factors such as ECOG performance status (PS), co-morbidities, or age affect clinical eligibility for systemic drug treatment in reality. The exact cut-off for eligibility may vary across countries. In order to calculate comparable treatment rates across countries, the same broad definition of eligibility was used.

ECOG performance status

ECOG PS measures the patient's level of functioning, ranging from 0 to 4 (5 is death), where 0 means fully active and 4 means completely disabled. Patients with ECOG PS 3 and 4 are generally too frail to tolerate systemic therapy. ESMO treatment guidelines for metastatic (stage IV) NSCLC recommend systemic therapy to be offered to all patients with ECOG PS 0–2 [I,A recommendation] (127). They also recommend targeted therapy to be offered to all patients with EGFR alterations with ECOG PS 3–4 [II,A recommendation] (127), and this was also mentioned in the 2016 version of the guidelines for ALK-positive patients [II,B recommendation] (150). The subjective nature of ECOG PS assessment can contribute to differences in assessment even between physicians working in the same institutions (151).

Reliable data on ECOG PS distribution among newly diagnosed NSCLC patients as well as recurrent patients could not be sourced consistently across countries for the purpose of this report. In general, around 70–75% of newly diagnosed patients with stage IV might have ECOG PS 0–2. For example, national data from the Netherlands for newly diagnosed patients with all stages of NSCLC in 2017–2019 show PS 0–1 = 68%, PS 2–4 = 22%, unknown PS =10% (136). Data from the Norwegian cancer

registry show the following distribution of ECOG PS in newly diagnosed lung cancer patients with stage IV in 2019: PS 0 = 17%, PS 1 = 35%, PS 2 = 20%, PS 3 = 17%, PS 4 = 8%, unknown PS = 3% (152). The Norwegian data also show that the ECOG PS distribution is more skewed towards lower PS scores in stage I (PS 3–4 = 4%), stage II (PS 3–4 = 9%), and stage III (PS 3–4 = 12%) of lung cancer (152). The frequency of PS 3–4 in lung cancer with stage IIIB/C+IV is thus likely somewhat lower than the 25% in stage IV in Norway.

Stage IIIB/C

Current ESMO treatment guidelines for metastatic NSCLC recommend systemic therapy only to patients with stage IV, instead of also to patients with stage IIIB/C (127). As described in section 2.5.1, stage III patients are either treated with (i) surgery preceded by chemotherapy and/or radiotherapy, or (ii) chemoradiotherapy (followed by maintenance immunotherapy), or (iii) systemic therapy. Until the 2016 version of the ESMO guidelines (150), the recommendation to offer systemic therapy included stage IIIB–IV at least for EGFR/ALK-positive patients, but this has been removed since the 2018 guidelines (127).

The exact wording of the approved indications of cancer drugs by the EMA also shows some variability regarding stage IIIB/C (85). For example, immunotherapies approved in first-line treatment (atezolizumab, nivolumab, pembrolizumab) are indicated in “metastatic” disease, whereas the same immunotherapies approved in second-line treatment are indicated in “locally advanced or metastatic” disease, and durvalumab is indicated in “locally advanced” disease only. The EMA-approved EGFR inhibitors are all indicated in “locally advanced or metastatic” disease, while the approved ALK/ROS1/BRAF inhibitors are indicated in “advanced” disease.

Patients diagnosed postmortem

All patients with a diagnosis of lung cancer in the local cancer registries were included in the sub-group of “newly diagnosed patients” in the calculations. This choice also spills over to the two other sub-groups of recurrent patients and progressing patients by way of calculation. In cancer registries, some of the newly diagnosed patients are not staged (i.e., stage is unknown). In the calculations these patients were allocated proportionally to patients with known stages (stage I–IV). An important reason for not being staged is that a cancer has been diagnosed postmortem. These cases are called death certificate only (DCO) cases. DCO cases are usually added to incidence numbers in cancer registries (153). Patients diagnosed postmortem are naturally not eligible to systemic treatment, because their cancer has remained undetected while the patient was still alive.

The size of the DCO cases varies considerably between countries with available data. In Bulgaria, 16% of all lung cancer incidence cases were DCO cases in 2015 (154). In Norway, 2% of all lung cancer incidence cases were DCO cases in 2015–2019 (152, 155). Hungary represents a special case in terms of how newly diagnosed patients were defined in this report. In absence of a nationwide population-based cancer registry, new lung cancer cases recorded in the National Health Insurance Fund (NHIF) database, which covers close to 100% of the population accessing health care services, were used (16). By definition, this excludes DCO cases as there can be no claims data for these cases. DCO cases in Hungary might be of considerable size owing partly to a comparatively high autopsy rate of hospital deaths (16). The size of the Hungarian DCO cases was estimated to be 24% based on a comparison of the size of mortality rates in the NHIF database and GLOBOCAN in 2012 (16).

3.2 Results

Drug treatment rates (in %) across countries and all years between 2014 and 2020 were defined as:

$$\text{Drug treatment rate} = \frac{\text{Number of treated patients}}{\text{Number of potentially eligible patients}}$$

To better understand both the size and the composition of the calculated drug treatment rates, this section first provides a benchmark for optimal treatment. Afterwards, the country-specific results are presented, and major time trends are described along with country differences.

3.2.1 Benchmark

The drug treatment rate in patients with advanced NSCLC can theoretically range from 0% (no patient gets treated) to 100% (all patients get treated). The upper limit of 100% is a hypothetical target. A certain proportion of patients will only receive “best supportive care” as first-line treatment, because factors such as poor ECOG PS, presence of certain co-morbidities (such as cardiovascular diseases or kidney problems), or old age limit the use of systemic therapy. It should also be noted that patients with a poor ECOG PS are mostly the same as those with severe co-morbidities and old age.

ESMO treatment guidelines for metastatic NSCLC only recommend systemic therapy for all patients with ECOG PS 0–2 and not with PS 3–4 (except for EGFR-positive patients) (127). As described in section 3.1.5, many countries lack exact public data on the distribution of ECOG PS in newly diagnosed NSCLC patients with stage IIIB/C+IV. Based on the limited information available, around 75% of newly diagnosed patients might have ECOG PS 0–2 in this patient group.

Figure 11 presents a benchmark for drug treatment rates, drawing on ESMO treatment guidelines for metastatic NSCLC in its versions from 2014, 2016, 2018, 2019, and 2020, as well as on year of approval of ESMO-recommended cancer drugs by the EMA. Overall drug treatment rates amount to 75% in all years from 2014–2020. The 75%-benchmark is based on the assumption that perhaps around 25% of newly diagnosed patients might not be recommended to receive any first-line systemic therapy due to poor ECOG PS and instead receive best supportive care (see the discussion in section 3.1.5). Among recurrent patients from earlier stages, the proportion of ineligible patients to first-line systemic therapy might actually be lower than 25%, although no studies could be identified to corroborate this. All patients progressing to second-line therapy and further on to third-line therapy are per default counted as to receive systemic therapy because of how progression rates were defined in this report (see section 3.1.4). This explains why Figure 11 does not contain any "2L/3L - Best supportive care" categories.

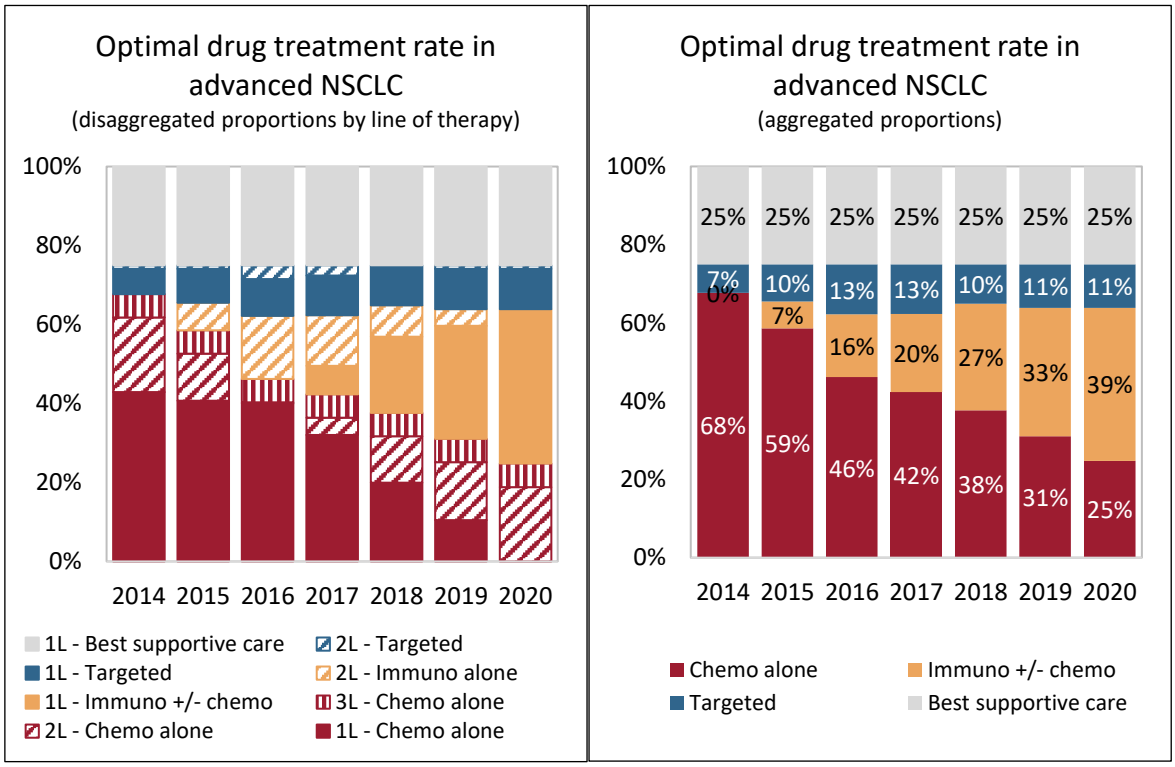


Figure 11: Optimal drug treatment rate in advanced NSCLC based on ESMO guidelines

Notes: 1L = first-line therapy, 2L = second-line therapy, 3L = third-line therapy. Chemo alone = chemotherapy as platinum-doublet or monotherapy, Immuno +/- chemo = immunotherapy as monotherapy or in combination with chemotherapy, Targeted = targeted therapy, Best supportive care = no cancer drug treatment. Advanced NSCLC refers to stage IIIB/C+IV, while ESMO guidelines (since 2018) solely refer to stage IV. 25% of both newly diagnosed patients and recurrent patients from earlier stages were assumed to receive only best supportive care as first-line therapy in all years. Of the newly diagnosed and recurrent patients 55% were assumed to have ECOG PS 0–1 and 20% ECOG PS 2, and all of these patients were assumed to receive systemic therapy. 40% of patients who receive first-line systemic therapy were assumed to receive second-line systemic therapy, and 30% of patients who receive second-line systemic therapy were assumed to receive third-line systemic therapy. Therefore no "2L or 3L - Best supportive care" is shown in the figure. Cancer histology was assumed to be 65% non-squamous disease (including all druggable mutations) and 35% squamous disease; the same histological proportions in first and second line were assumed. The proportion of druggable mutations was assumed to be EGFR 13%, ALK 4.5%, ROS1 1.5%, BRAF V600E 1.5%, NTRK 0.3% (see Table A6 in the Appendix; the same proportions in first and second line were assumed. The proportion of patients with PD-L1 ≥ 1% expression was assumed to be 54%, and 25% for PD-L1 ≥ 50% in both non-squamous disease (excluding all druggable mutations) and squamous disease, with same proportions also in first and second line (84).

Figure 11 also highlights the rapid change in recommended treatment options in different lines of therapy between 2014 and 2020. Key trends are the introduction of immunotherapy in second-line therapy for squamous disease in 2015 and an extension to non-squamous disease in 2016, thereby replacing chemotherapy. Immunotherapy in first-line therapy was introduced for high expressers of PD-L1 in 2017. Until 2020, immunotherapy had replaced chemotherapy as the sole first-line therapy in all patients[24] without treatable genomic alterations. The switch of immunotherapy from second-line to first-line therapy has also expanded the role of chemotherapy in second-line therapy again. Targeted therapy increased its share at the expense of chemotherapy in first-line therapy with the introduction of the first ALK inhibitor in 2015, ROS1 inhibitor in 2016, BRAF inhibitor in 2017, and NTRK inhibitor in 2019. Second-line targeted therapy in EGFR-positive patients replaced chemotherapy shortly between 2016 and 2018, before the switch of osimertinib to preferred first-line therapy. ESMO guidelines do not cover third-line therapy in detail except for ALK-positive patients. Following the treatment regimens in third line described in other sources and discussed in section 2.7, chemotherapy was assumed to be the standard treatment option in all years.

3.2.2 Country-specific results

The results of the calculation of the treatment rates with cancer drugs in patients with advanced NSCLC in the years from 2014 to 2020 are shown separately for each country in the figures below. Treatment rates for 2020 are less reliable than for other years due to the uncertain impact of the COVID-19 pandemic on official cancer patient numbers. Country differences are described in the next section. Several key observations can be made from the country-specific results.

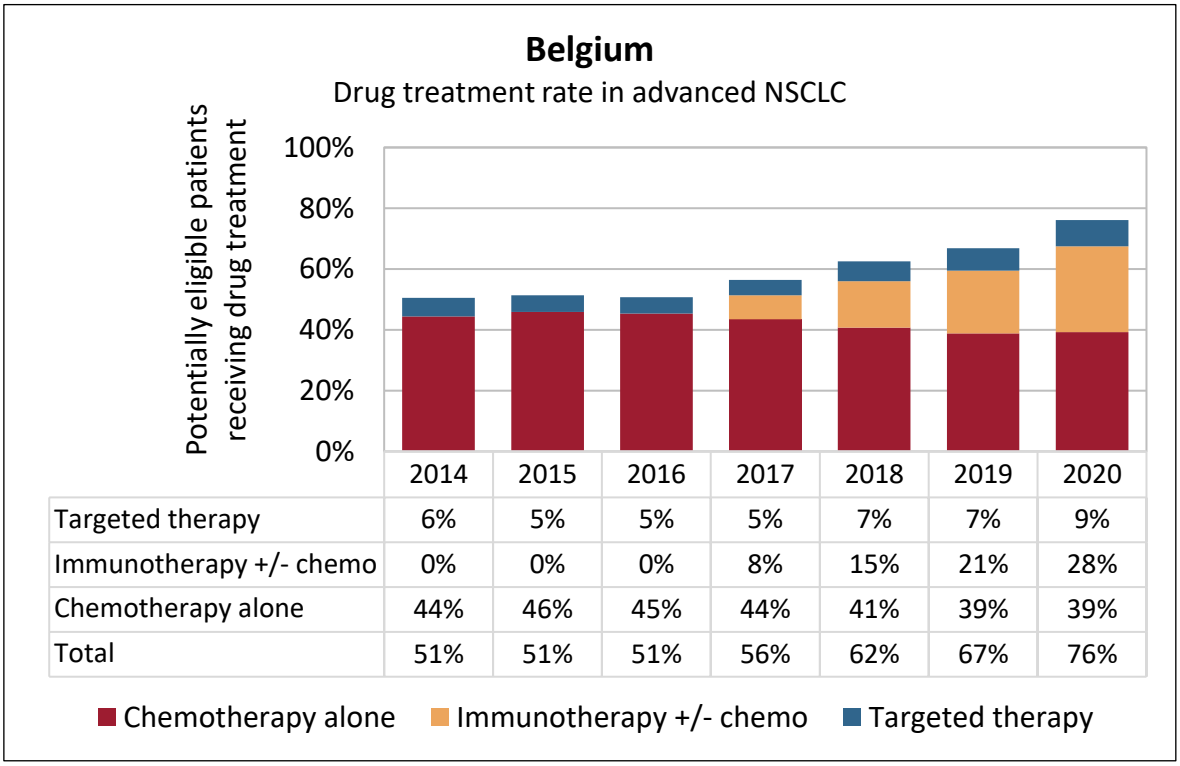
The overall drug treatment rates (i.e., describing whether diagnosed patients receive any cancer drug treatment) have generally increased over time. This means that the proportion of patients that only receive best supportive care (e.g., narcotic and non-narcotic analgesics, corticosteroids and gastrointestinal medication) to relieve symptoms and improve the quality of life decreased over time. Some patients may only receive radiotherapy or surgery, but usually they would also receive systemic therapy before or after these treatment modalities. This increase in overall drug treatments usually coincided with the introduction of immunotherapy. Yet in Finland, Ireland, and the Netherlands the

[24] ESMO guidelines did not recommend the combination of immunotherapy and chemotherapy in first-line therapy in patients with ECOG PS 2 (only in PS 0–1) until 2018, but they did recommend immunotherapy in second-line therapy in patients with ECOG PS 0–2 if first-line therapy was platinum-based chemotherapy. In the 2019-guidelines, the combination of immunotherapy and chemotherapy in first-line therapy was extended to PS 2, although platinum-based chemotherapy was still listed as an alternative. In the 2020 guidelines, platinum-based chemotherapy was removed and only immunotherapy with or without chemotherapy in first-line therapy was recommended in patients with PS 0–2.

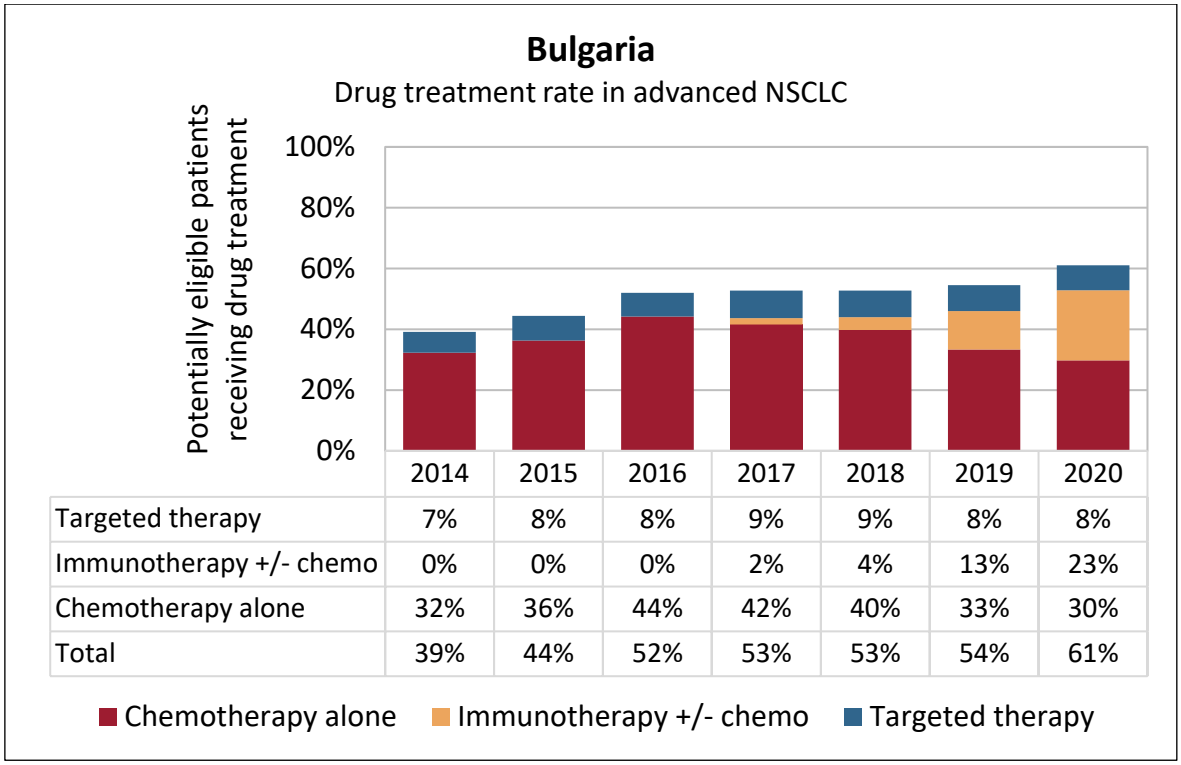
proportion of treated patients remained essentially unchanged even after the introduction of immunotherapy.

The composition of the drug treatment rates (i.e., describing the kind of cancer drug treatment administered to patients) has changed gradually over time, according to the following pattern:

- The proportion of patients treated with targeted therapy was rather small but increased slightly.
- The proportion of patients treated with immunotherapy (as monotherapy or in combination with chemotherapy) gradually expanded over time after initial reimbursement.
- The proportion of patients treated with chemotherapy (as monotherapy or as platinum-doublet or possibly including angiogenesis inhibitors) gradually decreased over time. The decreases were most often smaller than the simultaneous increases in targeted therapy and immunotherapy. Chemotherapy thus still seemed to be used in a considerable proportion of patients. This might be explained by its expanding role in second-line treatment, which compensated partly for the replacement in first-line treatment.

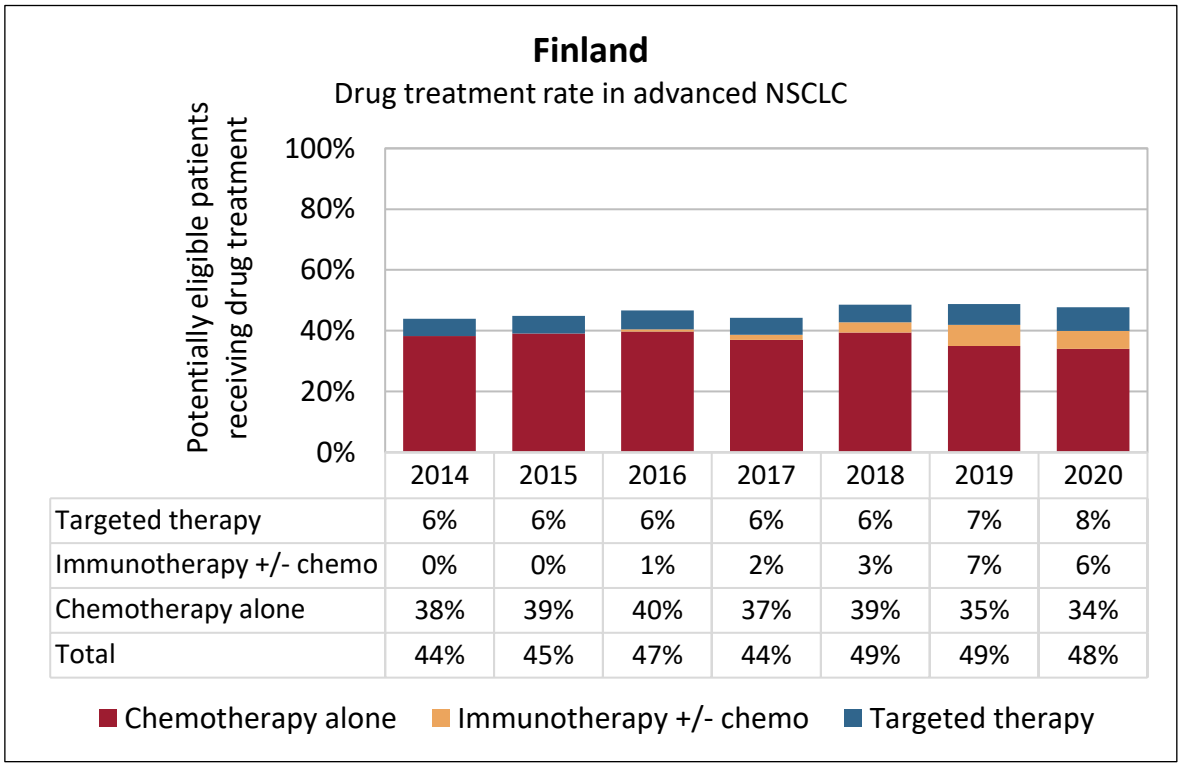


	2014	2015	2016	2017	2018	2019	2020
Targeted therapy	6%	5%	5%	5%	7%	7%	9%
Immunotherapy +/- chemo	0%	0%	0%	8%	15%	21%	28%
Chemotherapy alone	44%	46%	45%	44%	41%	39%	39%
Total	51%	51%	51%	56%	62%	67%	76%



	2014	2015	2016	2017	2018	2019	2020
Targeted therapy	7%	8%	8%	9%	9%	8%	8%
Immunotherapy +/- chemo	0%	0%	0%	2%	4%	13%	23%
Chemotherapy alone	32%	36%	44%	42%	40%	33%	30%
Total	39%	44%	52%	53%	53%	54%	61%

Notes: The increase in the proportion of chemotherapy from 2015 to 2016 is driven by a sudden increase in sales of pemetrexed in IQVIA data.

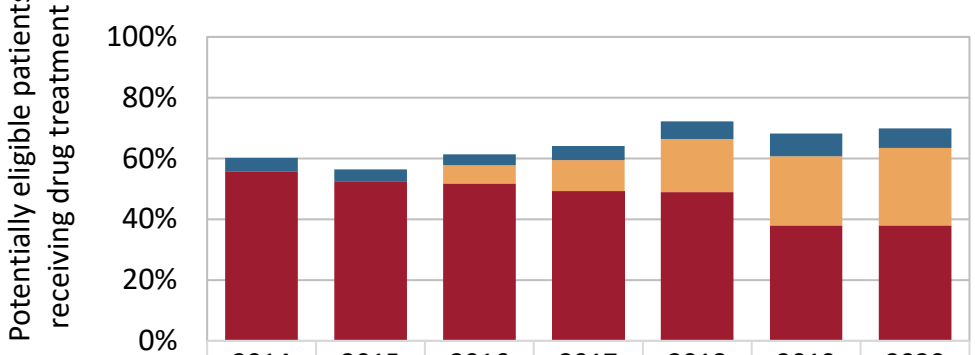


	2014	2015	2016	2017	2018	2019	2020
Targeted therapy	6%	6%	6%	6%	6%	7%	8%
Immunotherapy +/- chemo	0%	0%	1%	2%	3%	7%	6%
Chemotherapy alone	38%	39%	40%	37%	39%	35%	34%
Total	44%	45%	47%	44%	49%	49%	48%

Notes: As immunotherapy drugs are hospital drugs without precise reimbursement dates, the analysis is less robust as certain indications (both NSCLC and non-NSCLC) might be overestimated or underestimated. However, previous studies have also pointed to low use of immunotherapy drugs in Finland (based on IQVIA volume sales data) (4).

Greece

Drug treatment rate in advanced NSCLC

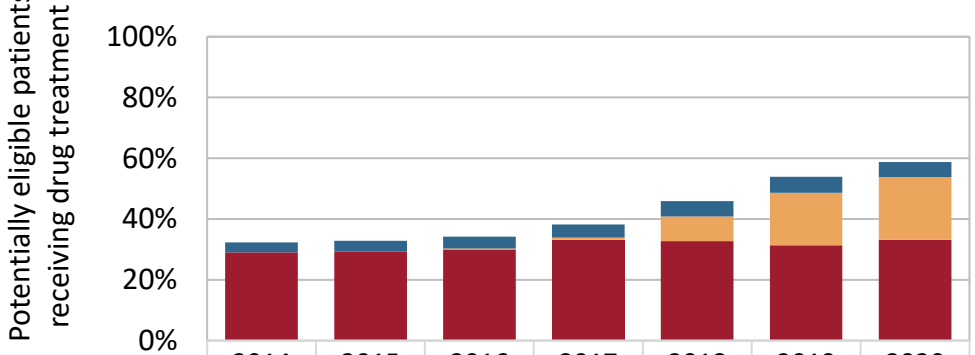


	2014	2015	2016	2017	2018	2019	2020
Targeted therapy	4%	4%	4%	5%	6%	7%	6%
Immunotherapy +/- chemo	0%	0%	6%	10%	17%	23%	25%
Chemotherapy alone	56%	53%	52%	49%	49%	38%	38%
Total	60%	56%	61%	64%	72%	68%	70%

Chemotherapy alone Immunotherapy +/- chemo Targeted therapy

Hungary

Drug treatment rate in advanced NSCLC

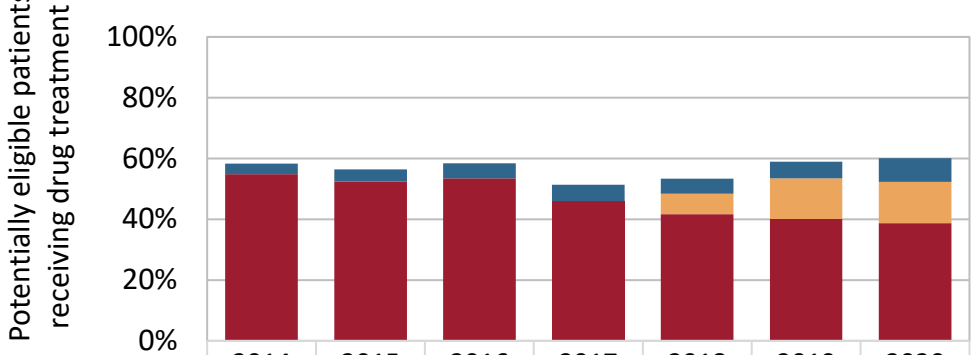


	2014	2015	2016	2017	2018	2019	2020
Targeted therapy	3%	4%	4%	4%	5%	5%	5%
Immunotherapy +/- chemo	0%	0%	0%	1%	8%	17%	21%
Chemotherapy alone	29%	29%	30%	33%	33%	31%	33%
Total	32%	33%	34%	38%	46%	54%	59%

Chemotherapy alone Immunotherapy +/- chemo Targeted therapy

Ireland

Drug treatment rate in advanced NSCLC

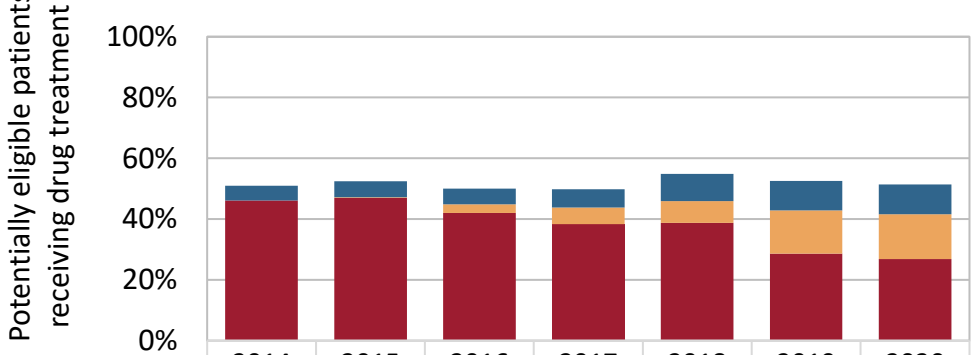


	2014	2015	2016	2017	2018	2019	2020
Targeted therapy	3%	4%	5%	5%	5%	6%	8%
Immunotherapy +/- chemo	0%	0%	0%	0%	7%	13%	14%
Chemotherapy alone	55%	52%	53%	46%	42%	40%	39%
Total	58%	56%	58%	51%	53%	59%	60%

Chemotherapy alone Immunotherapy +/- chemo Targeted therapy

Netherlands

Drug treatment rate in advanced NSCLC

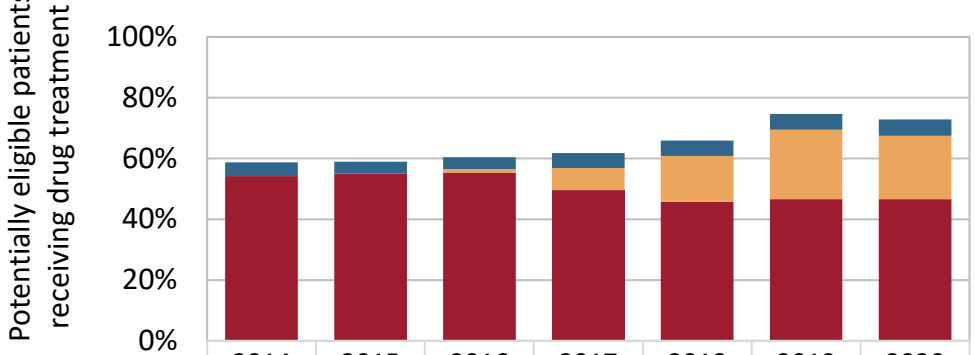


	2014	2015	2016	2017	2018	2019	2020
Targeted therapy	5%	5%	5%	6%	9%	10%	10%
Immunotherapy +/- chemo	0%	0%	3%	6%	7%	14%	15%
Chemotherapy alone	46%	47%	42%	38%	39%	29%	27%
Total	51%	52%	50%	50%	55%	53%	51%

Chemotherapy alone Immunotherapy +/- chemo Targeted therapy

Norway

Drug treatment rate in advanced NSCLC

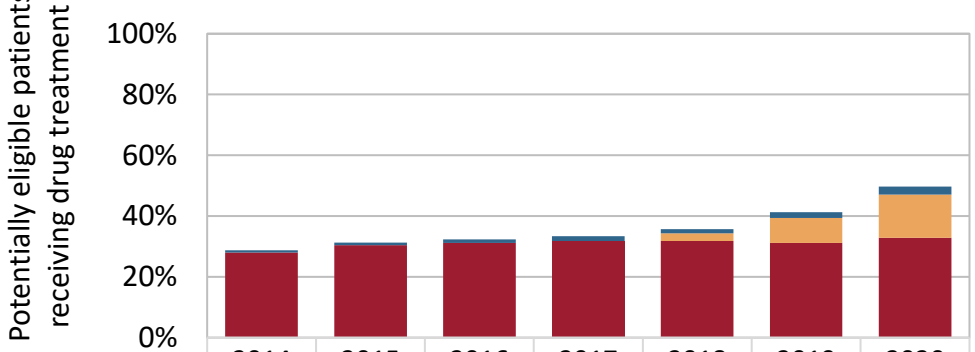


	2014	2015	2016	2017	2018	2019	2020
Targeted therapy	4%	4%	4%	5%	5%	5%	5%
Immunotherapy +/- chemo	0%	0%	1%	7%	15%	23%	21%
Chemotherapy alone	54%	55%	55%	50%	46%	47%	47%
Total	59%	59%	60%	62%	66%	75%	73%

Chemotherapy alone Immunotherapy +/- chemo Targeted therapy

Poland

Drug treatment rate in advanced NSCLC

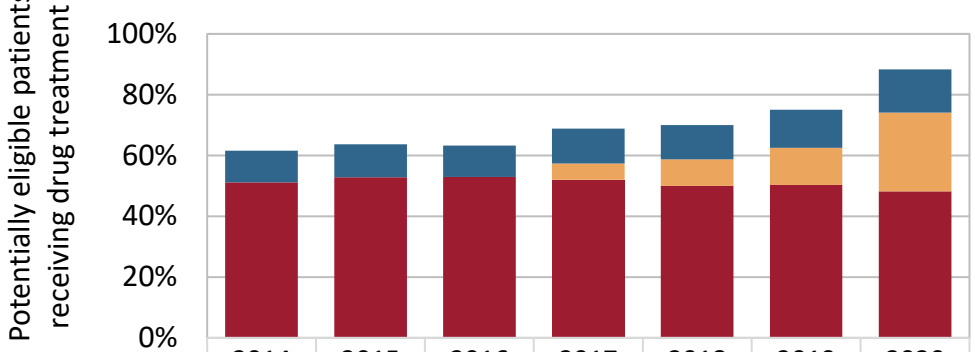


	2014	2015	2016	2017	2018	2019	2020
Targeted therapy	1%	1%	1%	2%	1%	2%	3%
Immunotherapy +/- chemo	0%	0%	0%	0%	3%	8%	14%
Chemotherapy alone	28%	30%	31%	32%	32%	31%	33%
Total	29%	31%	32%	33%	36%	41%	50%

Chemotherapy alone Immunotherapy +/- chemo Targeted therapy

Portugal

Drug treatment rate in advanced NSCLC



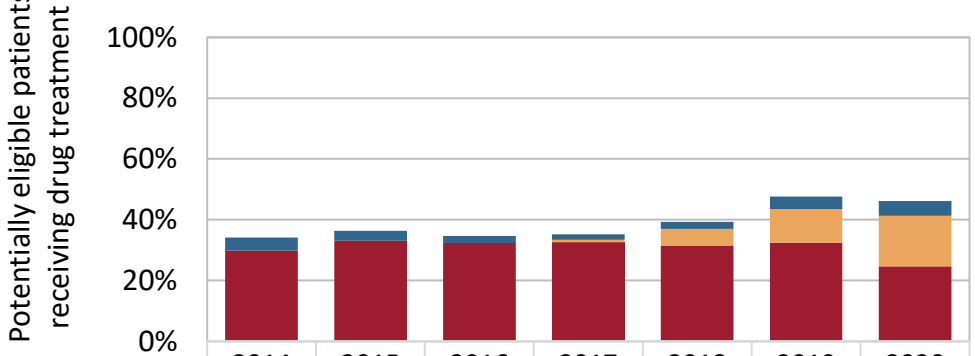
	2014	2015	2016	2017	2018	2019	2020
Targeted therapy	11%	11%	10%	11%	11%	12%	14%
Immunotherapy +/- chemo	0%	0%	0%	5%	9%	12%	26%
Chemotherapy alone	51%	53%	53%	52%	50%	50%	48%
Total	62%	64%	63%	69%	70%	75%	88%

Chemotherapy alone Immunotherapy +/- chemo Targeted therapy

Notes: The high proportion of targeted therapy compared to other countries might be the result of a higher incidence of EGFR and ALK mutations in Portuguese NSCLC patients; see Table A6.

Romania

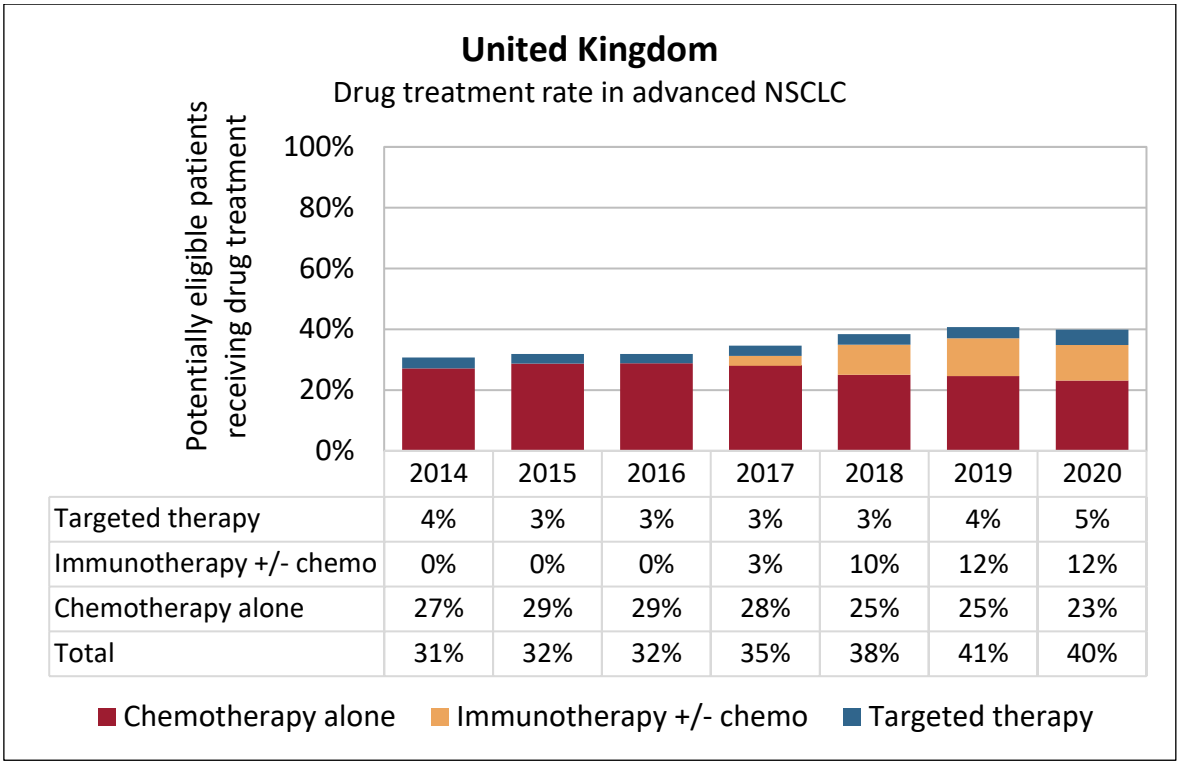
Drug treatment rate in advanced NSCLC



	2014	2015	2016	2017	2018	2019	2020
Targeted therapy	4%	3%	2%	2%	2%	4%	5%
Immunotherapy +/- chemo	0%	0%	0%	1%	6%	11%	17%
Chemotherapy alone	30%	33%	32%	33%	31%	32%	25%
Total	34%	36%	35%	35%	39%	48%	46%

Chemotherapy alone Immunotherapy +/- chemo Targeted therapy

Notes: The decrease in the proportion of targeted therapy from 2014 to 2017 is driven by a continuous sales decrease of erlotinib without an offsetting development in other EGFR inhibitors.



	2014	2015	2016	2017	2018	2019	2020
Targeted therapy	4%	3%	3%	3%	3%	4%	5%
Immunotherapy +/- chemo	0%	0%	0%	3%	10%	12%	12%
Chemotherapy alone	27%	29%	29%	28%	25%	25%	23%
Total	31%	32%	32%	35%	38%	41%	40%

Notes: The national (England + Wales) drug treatment rate for NSCLC patients with stage IIIB/C+IV with any ECOG PS was 35% in 2018, according to the National Lung Cancer Audit (data presented by Prof. Michael D. Peake during the local workshop). This is very close to the 38% for 2018 in the UK calculated in this report.

3.2.3 Country comparison

The comparison of the estimated drug treatment rates between all countries yields several noteworthy results. Firstly, drug treatment rates varied widely between countries in all years; see Figure 12. In 2014, they ranged from around 30% in Hungary, Poland, and the UK to almost 60% in Greece, Ireland, Norway, and Portugal. The gap between countries with the lowest and the highest treatment rates did not become much smaller over time. In 2019, treatment rates ranged from around 40% in Poland and the UK to 75% in Norway and Portugal, while most other countries had treatment rates of around 50–60%.

Secondly, most countries missed the ESMO-guideline-based benchmark of around 75% for the overall drug treatment rates in all years, despite improvements over time in all countries between 2014 and 2019; see Figure 12. Norway and Portugal were they only countries to clearly meet the benchmark in 2019, while Belgium and Greece were fairly close to meeting it. It is also interesting to point out how treatment rates in Finland, Ireland, and the Netherlands remained virtually constant over time while other countries seemed to start to treat many additional patients.

Thirdly, there is no clear correlation between the economic strength of countries and their overall drug treatment rates. The correlation coefficient of the strength of the relationship between the overall

drug treatment rates and gross domestic product (GDP) per capita (measured in purchasing power parities; sourced from Eurostat) was +0.23 in 2014 and +0.04 in 2019.

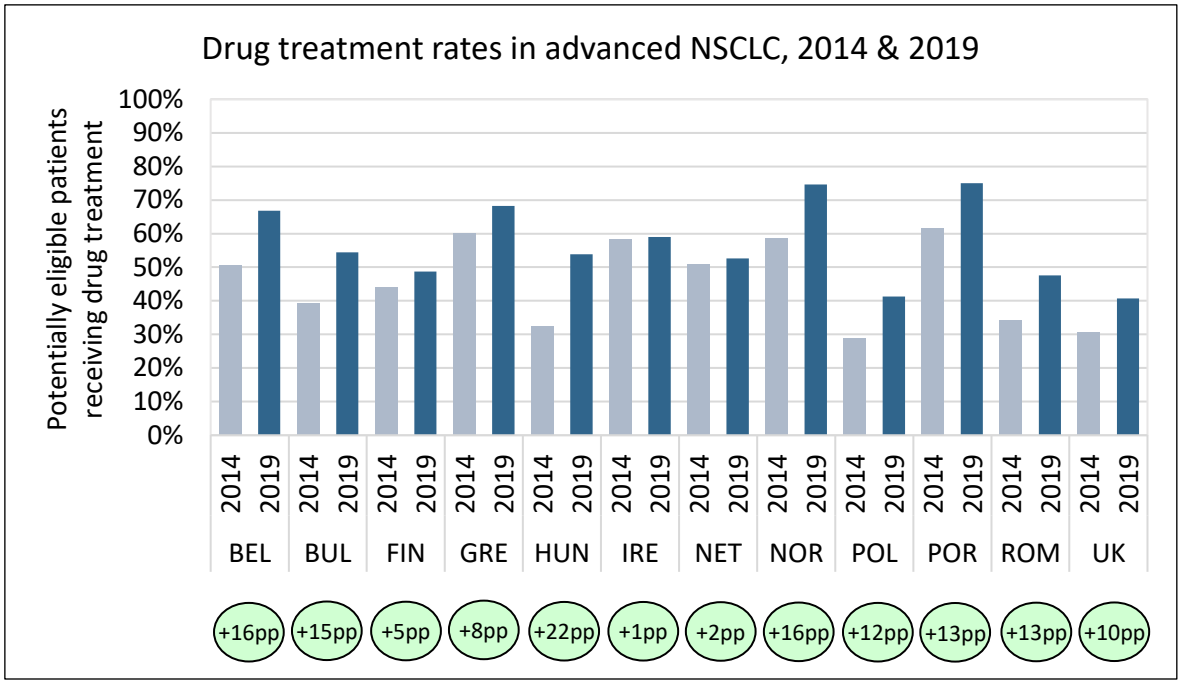


Figure 12: Drug treatment rates (overall) in advanced NSCLC in 2014 & 2019

Notes: pp = percentage points. The comparatively high number of death certificate only cases among the incidence numbers in Hungary introduces a downward bias to the treatment rates.

Fourthly, the composition of the drug treatment rates changed profoundly between 2014 and 2019; see Figure 13. The typical pattern was that the proportion of patients receiving targeted therapy increased slightly, immunotherapy (as monotherapy or in combination with chemotherapy) entered during this period and was administered to an increasing number of patients while chemotherapy (as monotherapy or as platinum-doublet) was administered to a decreasing number of patients.

Fifthly, the composition of the drug treatment rates in 2019 deviated considerably from the ESMO-guideline-based benchmark in that year; see Figure 13 and the benchmark in Figure 11. This suggests that many patients did not receive optimal drug treatment. Underuse of both targeted therapy (except in Portugal) and immunotherapy was evident, and instead patients seemed to receive – most of the times clinically inferior – chemotherapy. In fact, the composition of the treatment rates in 2019 resembled the benchmark from the years 2016–2017 in many countries. The discrepancy between guideline-recommended treatment and actual treatment administered was noticeable in all years and especially evident after 2015 when immunotherapy was initially approved by the EMA. The discrepancy was also noticeable irrespective of the overall drug treatment in a country.

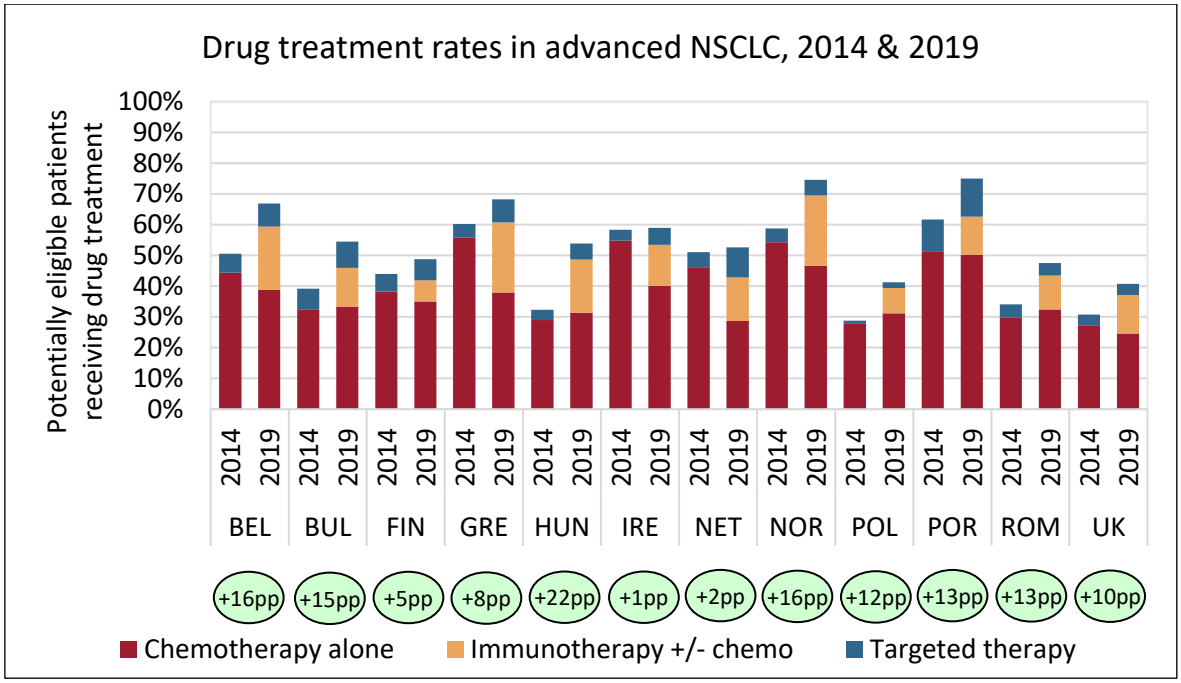


Figure 13: Drug treatment rates (by type of therapy) in advanced NSCLC in 2014 & 2019

Notes: pp = percentage points. The comparatively high number of death certificate only cases among the incidence numbers in Hungary introduces a downward bias to the treatment rates.

The five key results described above apply also if the time range is extended to year 2020. However, the estimations of the drug treatment rates in 2020 are more uncertain due to the uncertain influence of the COVID-19 pandemic on potentially eligible patient numbers; see the discussion in Appendix A1. Figure 14 compares drug treatment rates in 2019 and 2020. In about half of the countries, the overall drug treatment rate remained essentially unchanged. In absolute terms, these countries treated fewer patients in 2020 than in 2019, as the number of potentially eligible patients also had decreased from 2019 to 2020; see Table 2. In the remaining countries, the overall drug treatment rate increased quite considerably (while the number of potentially eligible patients decreased). Such large increases might seem implausible and rather reflect an overestimation of the negative effect of the pandemic on newly diagnosed lung cancer patient numbers (especially those with advanced stage) and/or a stockpiling effect of cancer drugs.

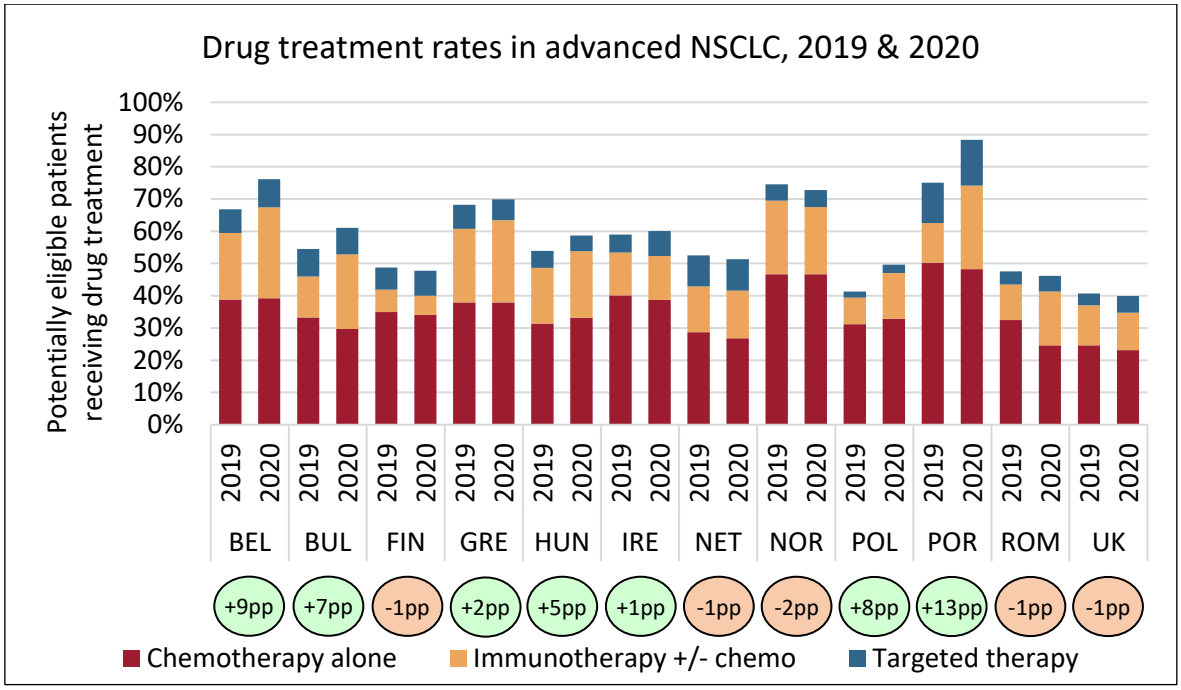


Figure 14: Drug treatment rates (by type of therapy) in advanced NSCLC in 2019 & 2020

Notes: pp = percentage points. The comparatively high number of death certificate only cases among the incidence numbers in Hungary introduces a downward bias to the treatment rates.

The results in this chapter showcase that most countries achieved far from optimal overall drug treatment rates in 2014–2020, despite improvements over time. In addition, the composition of the drug treatment rates points to an underuse of modern treatment options (immunotherapy and targeted therapy) at the expense of an overuse of chemotherapy. This calls for a better understanding of the drivers of these patterns.

3.2.3.1 Limitations

It is important to emphasize that the calculation of the drug treatment rates is an approximation based on best available aggregated national data. It should be viewed as a complement to registry-based studies with analysis of patient-level data. Some limitations are noteworthy when interpreting the overall size as well as the composition of the drug treatment rates.

- IQVIA sales data: The quality and completeness of the volume sales data might not be perfectly accurate in some countries. Newer patent-protected drugs with only a single provider are easier to capture than older drugs with generic availability (chemotherapy drugs) where multiple providers exist. Data smoothing was applied to remove extreme outliers in the sales data in several countries.

- Patients in clinical trials: Sales data from IQVIA do not capture the use of drugs in patients enrolled in clinical trials (at least not in the treatment arm). This results in an underestimation of the treated patients with advanced NSCLC.
- Early/expanded/managed access program: Patients receiving new non-reimbursed drugs as part of an early/expanded/managed access program are not counted. This results in an underestimation of the treated patients with advanced NSCLC in countries where this exists.
- Off-label use: Use of drugs in different patient groups was inferred from their reimbursed indications. Off-label use outside of the reimbursed indications can either lead to an overestimation of the treated patients with advanced NSCLC (if a drug is reimbursed in NSCLC but used in other non-reimbursed indications) or to an underestimation (if a drug is not reimbursed in NSCLC but still used in NSCLC).
- Dosing of drugs: The average dosage per patient was based on the approved dosage. If the dosage is decreased in some patients, e.g., due to side effects, then this could result in an underestimation of the treated patients with advanced NSCLC. This is however only true if opened vials that are not fully used cannot be given to other patients – usually leftover drugs are not given to other patients and have to be discarded, in which case there is no underestimation.
- Treatment length: The treatment length per patient was based on the median length observed in clinical trials. Shorter treatment length in clinical practice compared to clinical trials (e.g., caused by different patient characteristics or even by limited numbers of reimbursed treatment cycles) would lead to an underestimation of the treated patients with advanced NSCLC.
- Recurrence and progression rates: The recurrence rate from earlier stages and the progression rates to second-line and third-line therapy were informed by previously published studies to obtain default values. These default values were validated by national experts both in the survey and workshops, but there is no guarantee that these rates are perfectly accurate without a detailed analysis of national patient-level data. The rates might also have changed over time along with the changing treatment landscape in different lines of therapy in advanced NSCLC.
- Later-line therapy: Patients treated until third-line therapy were included. Some patients might still be fit enough to receive further systemic therapy. Their exclusion leads to a slight underestimation of the patients potentially eligible for drug treatment. The drug use of patients beyond third line is ascribed to patients in earlier lines, which leads to a slight overestimation of the treated patients with advanced NSCLC.

- Estimates for 2020: The calculated potentially eligible number of patients is uncertain. In all countries with available evidence, there was a decrease in newly diagnosed lung cancer patients. The decrease in lung cancer patients might have been larger among earlier stages and smaller among later stages. In this case, patient numbers would be underestimated, as the same stage distribution was applied in all years. In addition, the calculated treated number of patients might be overestimated if there was stockpiling of certain drugs, as any drug sales in a certain year were assumed to be administered to patients in that year. Taken together, there might be an overestimation of the treatment rates in 2020.

3.3 Key points

- Comparable data on drug treatment rates in advanced NSCLC based on patient-level data from national cancer registries or hospital records are not available.
    - Published studies differ in how the number of patients treated (the numerator of the treatment rate) and the total number of patients eligible for treatment (the denominator of the treatment rate) are defined. This limits a comparison of drug treatments across countries.
    - The use of aggregated national data – both on volume sales of cancer drugs as well as on patient numbers – can serve as an approximation of drug treatment rates. Such an estimation has to be based on several assumptions and naturally yields crude results. It should be viewed as a complement to registry-based studies with analysis of patient-level data.
- The analysis in this report shows that a considerable proportion of potentially eligible patients with advanced NSCLC across Europe remains untreated with cancer drugs despite a clinical recommendation to receive cancer drug treatment.
    - There were very large differences in treatment rates across countries. Norway and Portugal had the highest treatment rates in 2019 and were the only countries that seemed to clearly meet the approximate ESMO-guideline-based benchmark of around 75% for the overall treatment rate that year. By contrast, Poland and the UK had the lowest treatment rates both in 2014 (around 30%) and in 2019 (around 40%), and thus only seemed to treat around half of the patients for which guidelines recommend drug treatment.
    - The proportion of treated patients increased markedly over time in most countries, whereas in Finland, Ireland, and the Netherlands it remained stable. This increase coincided with the introduction of immunotherapy. The change in the standard-of-

care might have sparked renewed interest in treating this patient group after almost two decades of only platinum-based chemotherapy, which was characterized by comparatively poor outcomes.

  - There seemed to be no correlation between the economic strength of a country and the magnitude of the overall treatment rates. For example, the country pairs of Portugal and Norway, Romania and Finland, and Poland and the UK all exhibit similar rates despite large differences in economic strength.

- The analysis in this report shows that many patients with advanced NSCLC who receive cancer drug treatment are treated with outdated treatment options.
  - The general pattern in most countries between 2014 and 2020 shows a slight increase in the proportion of patients treated with targeted therapy, a considerable increase in the proportion of patients treated with immunotherapy (monotherapy or combination with chemotherapy) after initial reimbursement, and a decline in the proportion of patients treated with chemotherapy (platinum-based combination or monotherapy).
  - The launch of immunotherapy and new druggable targets for targeted therapy has led to profound changes of the recommended drug treatment options. Patients did not seem to receive standard-of-care treatment compared the approximate ESMO-guideline-based benchmark. Underuse of both targeted therapy and immunotherapy was common. This was independent of whether a country had a high or low overall treatment rate. In fact, countries that met the ESMO-guideline-based benchmark for the overall treatment seemed to lag about 2–3 years behind the kind of treatment options that ESMO guidelines recommend.

4. Explaining drug treatment rates

The previous chapter has shown that drug treatment rates in patients with advanced NSCLC are surprisingly low. They are not just less than 100% in all countries, but most often less than 75%, which as a more realistic benchmark given the size of the patient population in which drug treatment is not recommended. In addition, many patients who do receive drug treatment do not seem to receive treatment with modern recommended drug treatment options. This chapter seeks explanations for the magnitude and composition of the drug treatment rates calculated in chapter 3 on a country-by-country basis.

4.1 Method

Possible explanations for the calculated suboptimal drug treatment rates in every country were sourced through external expert input. A two-step approach was applied. In the first step, an online survey was created and sent to external experts to obtain explanations. In every country, two experts (the same as the ones used to validate assumptions made in the calculation of the treatment rates in chapter 3) – one representing the medical field (such as a pulmonologist, medical oncologist) and one the pharmaceutical industry – answered the survey. The survey was completed by most respondents in April–May 2021 and by remaining respondents in June–September 2021. The survey was used to obtain a crude picture of possible explanations.

In the second step, the results from the survey were presented and discussed at local workshops (conducted from May–October 2021) with a broader audience (local lung cancer experts representing different specialties, such as oncologists, pulmonologists, nurses, and patient representatives). The input of the workshop participants was added to get a more robust idea of possible explanations.

The aim of the online survey was to find explanations for (i) why drug treatment rates are less than 100% and (ii) why treatment with modern drugs is comparatively low compared to the ESMO-guideline-based benchmark described in section 3.2.1. A set of pre-defined explanations causing *suboptimal* drug treatment rates (i.e., low overall treatment rates and/or small proportion of immunotherapy and targeted therapy) was assembled; see Figure 15. Survey respondents also had the opportunity to add additional explanations. The pre-defined explanations were primarily derived from the description of the patient journey in chapter 2. This included a review of ESMO treatment guidelines (127), and the European Cancer Organisation's Essential Requirements for Quality Cancer for lung cancer (39). Additional reviewed sources were recent lung cancer studies in the Netherlands and the UK (135, 136), and an older source describing the situation prior to 2010 (156).

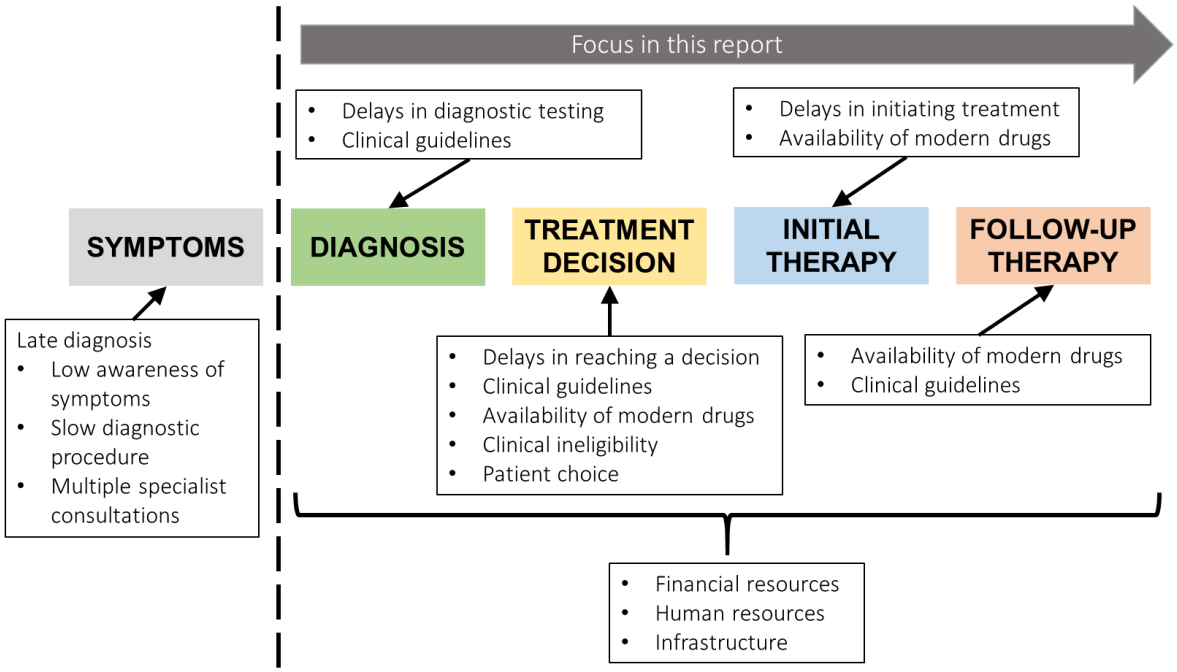


Figure 15: Patient journey in NSCLC and potential barriers to drug treatment

The pre-defined explanations for suboptimal drug treatment rates in the survey related to five broader areas:

- Clinical ineligibility and patient choice
- Delays in time from diagnosis to treatment start
- Availability of modern drugs
- Clinical guidelines
- Financial resources, human resources, and infrastructure

Before providing answers to possible explanations in one of the five broad areas, survey respondents were always reminded that the target population is stage IIIB/C+IV NSCLC. The exact explanations are listed in more detail below. Some of the explanations are naturally intertwined and some can be a reason for both low overall treatment rates and use of outdated treatment options.

Area 1: Clinical ineligibility and patient choice

General motivation: Patients might be deemed ineligible to receive systemic therapy because of non-metastatic disease stage or poor performance status (as defined in clinical guidelines). Patients with good performance status might be deemed ineligible because of co-morbidities (such as diabetes, chronic heart failure) and side effects of systemic therapy. Patients might also refuse systemic therapy, e.g., because of stigma (in the case of current/former smokers) leading to feelings of

unworthiness about receiving (state-of-the-art) treatment, because of lack of or inaccurate knowledge/awareness of modern treatment options and/or side effects, or because of low trust in health care professionals and/or the health care system.

- **Disease stage IIIB/C**: Is systemic therapy the most common first-line therapy option for newly diagnosed patients with stage IIIB/C?
- **ECOG PS 2 (functional status)**: Do all patients with ECOG PS 0–2 typically receive systemic therapy (both in first and second line)?
- **Functional status (%)**: How many patients do not receive systemic therapy (first-line therapy) because of poor[25] ECOG PS?
- **Co-morbidities and side effects (%)**: How many patients do not receive systemic therapy (first-line therapy) because of co-morbidities and side effects, despite good ECOG PS?
- **Treatment refusal by patient (%)**: How many patients do not receive systemic therapy (first-line therapy) because they do not want to receive drug treatment, despite good ECOG PS?

Area 2: Delays in time from diagnosis to treatment start

General motivation: Long delays between diagnosis and start of treatment can make patients ineligible to systemic therapy, because their performance status might deteriorate during this time.

- **Delays in diagnostic testing**
    - **Turnaround time pathology**: Long turnaround time for pathological confirmation after biopsy
    - **Turnaround time genomic testing**: Long turnaround time for tests of genomic alterations (EGFR, ALK, ROS1, etc.)
    - **Turnaround time immunohistochemistry**: Long turnaround time for immuno-histochemistry
    - **Technical equipment**: Lack of technical equipment to perform tests
    - **Staff**: Lack of staff to perform and analyze tests

[25] The survey did not further specify "poor" and "good" ECOG PS. Some respondents may have interpreted this question and the following two questions differently, with some assuming that "patients with either poor or good ECOG PS are 100%" and not – as was the intention here – to have 100% refer to all patients irrespective of ECOG PS.

    - **Tumor tissue**: Lack of tumor tissue to perform testing

- **Delays in reaching a treatment decision**
    - **Intra-hospital coordination**: Difficult coordination between relevant clinical departments (pulmonology, radiology, medical oncology, etc.) within the same hospital
    - **Multidisciplinary teams**: Multidisciplinary teams do not meet as often as needed (e.g., only every two weeks)
    - **Staff**: Lack of staff to go through all patient cases
- **Delays in initiating treatment**
    - **Inter-hospital referral**: Patients need to be referred from general hospitals to specialized hospitals to administer treatment (e.g., immunotherapy)
    - **Capacity of general hospitals**: Insufficient care places in the ambulatory or hospital setting
    - **Capacity of specialized hospitals**: Insufficient capacity of specialized hospitals to receive referred patients
    - **Staff**: Lack of staff to treat patients

Area 3: Availability of modern cancer drugs

General motivation: Many drugs have been approved in advanced NSCLC by the EMA since 2014. A positive reimbursement decision by national/regional authorities or sickness funds is essential for patients to receive access to approved drugs. Older drugs might be used if reimbursement of modern drugs is lacking or restricted.

- **General availability**: Do all patients who would medically benefit from modern cancer drugs receive them?
- **Lack of reimbursement**: An EMA-approved but non-reimbursed drug cannot be administered even though it would benefit a specific patient more than the administration of a reimbursed but less beneficial drug.
- **Hospital budget**: A drug is reimbursed, but it cannot be administered due to a limited hospital budget.
- **Restricted reimbursement**: The number of treatment cycles (e.g., only 6 treatment cycles) is limited because of restrictions in reimbursement criteria and/or a limited hospital budget.

Area 4: Clinical guidelines

General motivation: Inadequate clinical guidelines can prevent eligible patients from receiving any systemic therapy or lead to the administration of outdated systemic therapy.

- **Up-to-dateness**: National/regional/local clinical guidelines are outdated (e.g., immunotherapies not included)
- **Eligibility criteria**: Criteria to define eligibility for drug treatment are too restrictive (e.g., only patients with PS 0–1)
- **Adherence**: Adherence to current guidelines is low (e.g., because of lack of continuing medical education of medical staff; because current guidelines are not reasonable to follow)

Area 5: Financial resources, human resources, and infrastructure

General motivation: A lack of financial resources, human resources, and infrastructure can prevent eligible patients from receiving any systemic therapy or lead to the administration of outdated systemic therapy.

- **Hospital budget**: Limited hospital budgets and high costs of drugs
- **Budget for cancer drugs**: Limited budget for cancer drugs to provide patients with the best possible care
- **Medical staff**: Lack of medical staff overall or of certain staff categories (e.g., nurses, pathologists, pulmonologists, medical oncologists, radiologists)
- **Technical equipment**: Lack of technical equipment (used for diagnostics, imaging analysis, etc.)
- **Hospital beds and care places**: Lack of hospital beds and outpatient care places

4.2 Results

The country-specific tables below highlight barriers to achieving high drug treatment rates and barriers to administering modern drug treatment options. The results in the tables are based on answers to the online survey sent to one clinical representative (column “Clinician”) and one pharmaceutical industry representative (column “Industry”) in every country. Based on their experience, they were asked whether pre-defined explanations in five broad areas constitute a barrier, and they could also elaborate on their answers (column “Comment”). They could also add additional barriers (rows below “Additional barriers”) not covered by the pre-defined explanations.

Color scheme used in the country-specific tables:

	No barrier
	Potential barrier
	Barrier
	No answer provided or not applicable

For many countries, local workshops were held to discuss the barriers in the country-specific tables with a broader audience. The general feedback was that the survey answers – both the ones from the clinical representatives and the industry representatives – provide a fair picture of the local situation. A summary of points made by the local experts in these workshops on barriers is provided below the country-specific tables.

4.2.1 Belgium

BELGIUM – Barriers				
	C1	C2	Industry	Comment
Area 1: Clinical ineligibility and patient choice				
Disease stage IIIB/C				C1: IIIB and IIIC receive chemoradiotherapy because it is more effective; IIIC is relatively new and was not considered throughout the first years of 2014–2019 C2: IIIB receives surgery preceded by chemotherapy and/or radiotherapy or chemoradiotherapy because it is more effective; IIIC receives chemoradiotherapy because it is more effective
ECOG PS 2				C2: Patients receive best supportive care with a small role also of radiotherapy
Poor functional status (%)	5%	5%	21%	C1: Very low rate of patients coming with very poor ECOG
Co-morbidities and side effects (%)	5%	2%	21%	C1: Those patients are mostly the same as those with poor ECOG
Treatment refusal by patients (%)	1%	2%	20%	C1: This is the exception, at least in my practice
Area 2: Delays in time from diagnosis to treatment start				
(1) Delays in diagnostic testing	FD	FD	PD	
Turnaround time pathology				
Turnaround time genomic testing				I: NGS turnaround time can be 1 week
Turnaround time immunohistochemistry				
Technical equipment				

Staff				
Tumor tissue				C1: The most important explanation for long delays is the difficulty to obtain for a minority of patients (perhaps 15%) cytologic or histologic valuable samples to perform the complete sequence of diagnostic testing C2: Negative sample after first attempt to take a tissue sample (bronchoscopy, EBUS, TTP, etc.)
(2) Delays in reaching a treatment decision	FD	FD	PD	C1: Such delays are rare in academic centers or equivalent. I recently have seen a patient for a second opinion because the primary caregiver was on holidays.
Intra-hospital coordination				
Multidisciplinary teams				
Staff				
(3) Delays in initiating treatment	FD	FD	FD	C2: The COVID pandemic led to delays
Inter-hospital referral				
Capacity of general hospitals				
Capacity of specialized hospitals				
Staff				
Area 3: Availability of modern cancer drugs				
General availability	AA	>50%	>50%	
Lack of reimbursement	<50%	AN	<50%	
Hospital budget	AN	AN	AN	
Restricted reimbursement	AN	AN	AN	
Area 4: Clinical guidelines				
Up-to-dateness	FD	FD	PA	
Eligibility criteria	PD	FD	FD	
Adherence	PA	PD	FD	
Area 5: Financial resources, human resources, and infrastructure				
Hospital budget	AN	AN	<50%	
Budget for cancer drugs	PA	PA	PA	
Medical staff	AN	AN	AN	
Technical equipment	AN	AN	AN	
Hospital beds and care places	AN	AN	AN	
Additional barriers				
C1: I think there is a heterogeneity in the therapeutic approach according to who is treating the NSCLC patient. Most onco-pulmonologists are aware of the modern treatments and more active in the initiation of novel therapies while medical oncologists are lagging behind a little bit.				

Notes: C = clinician, I = industry, AN = almost never, AA = almost always, 50% = about half the time, <50% = less than half the time, >50% = more than half the time, FA = fully agree, PA = partly agree, PD = partly disagree, FD = fully disagree.

In Belgium, the results on the treatment rates, the identified barriers, and the recommendations were discussed in an Advisory Board with key scientific leaders. The discussions of this meeting were not disclosed.

4.2.2 Bulgaria

BULGARIA – Barriers			
	Clinician	Industry	Comment
Area 1: Clinical ineligibility and patient choice			
Disease stage IIIB/C			C: IIIB and IIIC receive chemoradiotherapy because local guidelines do not recommend systemic therapy I: IIIB receive chemoradiotherapy; only IIIC receive systemic therapy
ECOG PS 2			C & I: Part of these patients receive only best supportive care
Poor functional status (%)	(70%)	(80%)	C & I: % of patients with poor functional status left untreated
Co-morbidities and side effects (%)	25%	15%	C: Heart failure, not controlled DM, renal failure, cirrhosis I: Poorly controlled advanced chronic diseases (liver, renal, metabolic, cardiac)
Treatment refusal by patients (%)	5%	5%	I: Poor health literacy of lay public
Area 2: Delays in time from diagnosis to treatment start			
(1) Delays in diagnostic testing	FA	PA	
Turnaround time pathology			
Turnaround time genomic testing			
Turnaround time immunohistochemistry			
Technical equipment			
Staff			
Tumor tissue			
(2) Delays in reaching a treatment decision	PD	PD	
Intra-hospital coordination			
Multidisciplinary teams			C: MDT take place once per week and delays in reaching treatment decision are very rare
Staff			
(3) Delays in initiating treatment	FD	FD	C & I: No delay in start of treatment
Inter-hospital referral			
Capacity of general hospitals			
Capacity of specialized hospitals			
Staff			

Area 3: Availability of modern cancer drugs			
General availability	>50%	>50%	
Lack of reimbursement	<50%	<50%	
Hospital budget	50%	50%	
Restricted reimbursement	AN	AN	
Area 4: Clinical guidelines			
Up-to-dateness	FD	PD	
Eligibility criteria	FD	FD	
Adherence	PA	FD	
Area 5: Financial resources, human resources, and infrastructure			
Hospital budget	<50%	50%	
Budget for cancer drugs	PD	PD	
Medical staff	AN	AN	
Technical equipment	AN	AN	
Hospital beds and care places	AN	AN	
Additional barriers			
C: Patients arrive too late at diagnosis with ECOG PS>2, i.e., problems with early diagnosis I: Late diagnosis leading to patients with higher ECOG PS>2			
C: Problems with health literacy I: Low health literacy			
C: Lack of a National Cancer Plan			
I: Biomarker and genomic testing is not reimbursed by payers and not mandatory			
I: Time to treatment is delayed because diagnostic facilities and oncology centers are centralized in bigger cities; rural area patients have to travel. Not all oncology centers have all necessary diagnostic facilities.			

Notes: C = clinician, I = industry, AN = almost never, AA = almost always, 50% = about half the time, <50% = less than half the time, >50% = more than half the time, FA = fully agree, PA = partly agree, PD = partly disagree, FD = fully disagree.

The local workshop in Bulgaria involved the presentation of preliminary findings of this report and discussions among several lung cancer experts.

- Participating experts: Prof. Assen Dudov, Dr. Krasimir Koynov, Prof. Galina Kurteva, Dr. Antoaneta Tomova, Prof Dimitar Kostadinov, Prof. Svetla Hristova, Prof. Danail Petrov

The following main points were made by the experts:

- Late presentation of lung cancer patients is a major challenge. There are long delays in making a diagnosis. GPs do not recognize lung cancer symptoms, which leads to untimely

diagnosis. The process from first symptoms to diagnosis is slowed down and leads to the progression of the disease. Many patients are eventually diagnosed very late and arrive in a condition not suitable for systemic therapy.

- Bronchoscopies for diagnosis are not performed in most regions of the country. Hospital managers do not invest in equipment for bronchoscopies due to the low return caused by the low funding of clinical pathways for pulmonary diagnostics. As a result, the equipment is very old in most places. General anesthesia for bronchoscopies is not reimbursed and therefore much of the diagnosis is performed with local anesthesia. There is also a lack of trained and working specialists to perform bronchoscopies. The process of bronchoscopic diagnosis should be centralized and consolidated throughout the country. There must be an established and binding protocol that is binding and to be followed.
- The financing of tests of genomic alterations and immunohistochemistry is not working well. Biomarker testing is not reimbursed. Pharmaceutical companies are covering expenses for biomarker testing, whereas immunohistochemistry not reimbursed by anyone. Patients have to pay for immunohistochemistry themselves, which leads to a delay in diagnosis. In pulmonary hospitals all patients receive immunohistochemistry to clarify the histology of the tumor but pay for it out-of-pocket. In addition, manual measurement of immunohistochemistry (without a machine) is still widespread, which slows down the process significantly. Mass machine measurement should be introduced, which would speed up the process. However, buying a machine requires a large number of examinations per year to pay off the machine financially. Centralizing the pathological assessment to laboratories with a large volume of activity and which have the necessary equipment and regular quality control could help.
- A shortage of pathologists limits the testing capacity and leads to delays. Pathologists work in several places in different hospitals, which in leads to congestion and has a negative effect on the quality of their work. The best thing that could be done after bronchoscopy is to do biomarker testing in parallel with immunohistochemistry to save time, but the platforms are different for different drugs, which complicates and slows down the process.
- Patient interaction and knowledge of surgeons and pulmonologists about non-surgical treatment options is a challenge. Results of the biopsy are often only communicated in written form to the patient, without any face-to-face talk. Patients do not receive enough guidance on what to do and why to do it. This leads to delays in the patient's care process. Non-surgical treatment options are not communicated adequately.

- Lack of clinical pathways are a serious problem for hospital funding. Currently, not all activities along the patient pathway are financed. Diagnosis related groups (DRG) have helped many European countries to get good management of hospital health care funds and services, but in Bulgaria they remain only as a plan and is not clear when DRG will be implemented. Switching to DRG would allow hospital managers to plan, monitor, and manage costs and know how efficiently they spend resources.
- Limited regulation and financial resources affect the administration of modern drugs. There are no established medical standards that – on a legally regulated basis – determine which drugs can and which should not be used for a certain disease. Currently, there are no sanctions if physicians do not live up to medical standards. There is also an insufficient number of specialists who can administer modern treatment options.
- Many pulmonary hospitals have been transformed into "COVID-only" hospitals. This has led to a significant reduction in the number of diagnosed patients. Due to COVID restructuring, a large number of highly qualified specialists (surgeons, anesthesiologists, bronchoscopists) are leaving the hospital.

On a separate occasion, the preliminary findings of this report were also discussed with members of the Bulgarian Cancer Patients Association "One of Eight". The following main points were made by the experts:

- Lung cancer patients lack a clear understanding of the patient journey. Physicians do not have time to explain it in detail to patients. Patients do not know what their options are, what to do, where to go, they feel lost. There is no place where they could find this information. If the patient does not accept what is recommended by the physician, he or she is simply sent home without any options being explained. This is happening in many oncology clinics. There is also no dedicated lung cancer patient association in Bulgaria which could support lung cancer patients in their patient journey.
- Out-of-pocket payments for diagnostics and treatment are a challenge. Overall drug therapy is reimbursed for lung cancer, but immunohistochemistry is paid out of pocket by patients and not all patients are ready to pay for it. Full reimbursement of diagnostics and treatment could shorten the patient journey and ultimately increase the treatment rate.
- There is a lack of communication between oncology specialists and GPs as well as a lack of psychological support. After being referred by a GP to a hospital for diagnosis, a lung cancer patient is under the care of a specialist, but the patient's GP does not have clarity on diagnosis and treatment decisions and choices. In case of any support would be needed, the GP is neither involved nor engaged. In addition, upon leaving the hospital, the patient has to pay

out of pocket for psychological support or consultations. Ensuring free of charge psychological support for cancer patients even after leaving the hospital could increase the adherence to treatment thereby their survival.

4.2.3 Finland

FINLAND – Barriers			
	Clinician	Industry	Comment
Area 1: Clinical ineligibility and patient choice			
Disease stage IIIB/C			C: IIIB receive chemoradiotherapy because it is more effective; only IIIC receive systemic therapy I: IIIB receive chemoradiotherapy because local guidelines do not recommend systemic therapy
ECOG PS 2			I: Palliative approach with single chemotherapy, radiotherapy
Poor functional status (%)	30%	50% (all three)	
Co-morbidities and side effects (%)	15%		
Treatment refusal by patients (%)	2%		
Area 2: Delays in time from diagnosis to treatment start			
(1) Delays in diagnostic testing	FD	FD	
Turnaround time pathology			
Turnaround time genomic testing			
Turnaround time immunohistochemistry			
Technical equipment			
Staff			
Tumor tissue			
(2) Delays in reaching a treatment decision	FD	PA	
Intra-hospital coordination			
Multidisciplinary teams			
Staff			
(3) Delays in initiating treatment	FD	FD	
Inter-hospital referral			
Capacity of general hospitals			
Capacity of specialized hospitals			
Staff			
Area 3: Availability of modern cancer drugs			
General availability	50%	50%	
Lack of reimbursement	AN	AA	
Hospital budget	AN	AN	
Restricted reimbursement	<50%	AA	
Area 4: Clinical guidelines			
Up-to-dateness	FD	FD	
Eligibility criteria	FD	FD	

Adherence	FD	PA	I: Guidelines have been updated, but they are not publicly available. Guidelines are only recommendations and thus do not have to be followed.
Area 5: Financial resources, human resources, and infrastructure			
Hospital budget	<50%	AN	
Budget for cancer drugs	PA	FD	
Medical staff	AN	AN	
Technical equipment	AN	AN	
Hospital beds and care places	AN	AN	
Additional barriers			
C: Many lung cancer patients are in borderline condition and physicians are often reluctant to initiate expensive medications on these patients			
I: Patients do not recognize symptoms and seek help from primary care early enough. Primary care physicians do not suspect lung cancer. This causes delays until diagnosis.			
I: The system of two public funding streams for drugs leads to suboptimization, as no one has the overall responsibility for the patient's care path.			
I: No transparency in use of drugs in hospitals. Only overall statistics for the total (non-indication-specific) use of drugs are available.			
I: Specialized care system is decentralized, with single hospitals having limited drug budgets funded by (groups of) municipalities.			

Notes: C = clinician, I = industry, AN = almost never, AA = almost always, 50% = about half the time, <50% = less than half the time, >50% = more than half the time, FA = fully agree, PA = partly agree, PD = partly disagree, FD = fully disagree.

The local workshop in Finland involved the presentation of preliminary findings of this report and discussions among several oncology and lung cancer experts.

- Participating experts: Satu Tiainen, Riitta Kaarteenaho, Petri Bono, Maria Silvoniemi, Tuula Vasankari, and three anonymous experts

The following main points were made by the experts:

- The main issue is that patients get their treatment too late because of delay in diagnosis, and thus their ECOG PS is poor.

- The availability of molecular testing is good, but no large panels are used. The main obstacle is the availability of targeted drugs. Patients are thus not tested for all molecular alterations, because it does not make sense to test for alterations linked existing drugs if they these drugs not reimbursed. These patients will be administered a platinum doublet with or without immunotherapy instead.
- Patient eligibility criteria are not entirely aligned with ESMO guidelines. Patients with ECOG PS 0–1 receive an immunotherapy-chemotherapy combination whereas patients with ECOG PS 2 receive immunotherapy as a monotherapy. In addition, stage IIIB patients receive chemoradiotherapy, but chemoradiotherapy used to be underused. Chemoradiotherapy also used to be given sequentially (instead of concomitantly) and with a too low dose of radiation.
- The current lung cancer care guidelines are from 2017 and oncologists around the country have access to them, but they are not published publicly. A couple of years ago "statements" were issued to provide updates to the guidelines. Leading lung cancer clinicians are aware that there has been a rapid development in the availability of new drugs. There is therefore a Lung Cancer Association (consisting of lung cancer clinicians) which has been working on and using a set of more rapidly updated guidelines at the hospitals. The plan is to update these guidelines twice or three times per year in the future. The guidelines are currently released to all hospitals and clinicians but not more widely.
- The special way drugs are reimbursed in Finland is reflected in the results of the composition of treatment rates:
    - There is one system for oral drugs (covering targeted therapies used in NSCLC), and these drugs are reimbursed on the national level. Lung cancer specialists try to use targeted therapy as much as possible. The comparatively good use of targeted therapies is thus not surprising.
    - There is another system for hospital drugs (i.e., intravenously administered drugs) (covering chemotherapies and immunotherapies used in NSCLC), and the reimbursement system for these drugs is more complicated and organized on the local level. It is not well-defined who decides, and there are local guidelines that differ from hospital to hospital. This has inhibited the use of immunotherapy in NSCLC as compared to melanoma where it was used much more. But things changed in 2020 and immunotherapy should now be used more also in NSCLC. Before 2020, lots of patients wanted to have a second opinion regarding the use of immunotherapy.

- The issue with the two funding streams for oral drugs and hospital drugs is increasingly pushed to its limits. In renal cancer, where IV-administered immunotherapy is supposed to be combined with oral targeted therapies, the dual system becomes dysfunctional as there are two payers per patient involved.

- The budget for hospital drugs is small and can vary depending on the municipality, because the financial situation of the municipalities differs.

4.2.4 Greece

GREECE – Barriers			
	Clinician	Industry	Comment
Area 1: Clinical ineligibility and patient choice			
Disease stage IIIB/C			C & I: IIIB receive chemoradiotherapy because it is more effective; only IIIC receive systemic therapy
ECOG PS 2			
Poor functional status (%)	15%	10%	I: Based on local market research data, 10% (out of the total 25% of patients not receiving systemic therapy as 1L therapy) is due to poor ECOG PS
Co-morbidities and side effects (%)	10%	5%	I: 5% (out of the total 25% of patients not receiving systemic therapy as 1L therapy) is due to co-morbidities and side-effects, despite good ECOG PS
Treatment refusal by patients (%)	5%	10%	I: 10% (out of the total 25% of patients not receiving systemic therapy as 1L therapy) is due to patients not wanting to receive drug treatment, despite good ECOG PS
Area 2: Delays in time from diagnosis to treatment start			
(1) Delays in diagnostic testing	FA	FA	C: Unavailability of biopsy performance in parts of the country
Turnaround time pathology			
Turnaround time genomic testing			
Turnaround time immunohistochemistry			
Technical equipment			
Staff			
Tumor tissue			
(2) Delays in reaching a treatment decision	FD	PD	
Intra-hospital coordination			
Multidisciplinary teams			
Staff			
(3) Delays in initiating treatment	PA	FD	

Inter-hospital referral			I: Mainly a challenge in rural areas
Capacity of general hospitals			
Capacity of specialized hospitals			
Staff			
Area 3: Availability of modern cancer drugs			
General availability	>50%	AA	
Lack of reimbursement	AN	AN	
Hospital budget	AN	AN	
Restricted reimbursement	AN	AN	
Area 4: Clinical guidelines			
Up-to-dateness	FD	FD	
Eligibility criteria	FD	FD	
Adherence	FD	FD	
Area 5: Financial resources, human resources, and infrastructure			
Hospital budget	50%	AN	
Budget for cancer drugs	PA	FD	I: see second comment under “Additional barriers”
Medical staff	50%	AN	
Technical equipment	<50%	AN	
Hospital beds and care places	<50%	AN	
Additional barriers			
C: The pre-authorization process (electronic pre-approval system - EPAS) for novel high-cost drugs in the public and private sector causes delays and discourages sometimes medical doctors (in understaffed public hospitals) to file the application and ask for these drugs due to lack of time, personnel, etc.			
I: The currently set public pharma budget does not include/ incorporate a dedicated fund for cancer drugs. Patients have 0% co-payment and have access to modern cancer therapies through a case-by-case electronic pre-approval system (EPAS). The Greek healthcare system is highly impacted by austerity mechanisms such as “rebates and clawback”, with the latter one being imposed once the public pharma budget is exceeded and with the excess being covered by the industry. This has resulted in a situation where spending continues to grow annually, while budget remains constant. This situation is creating sustainability issues for the future of the health care system and the pharmaceutical sector, as well as risks for the continuity of cancer patients' care.			

I: Geographical constraints, dispersion of a segment of population in many province areas (incl. islands)			
I: Aging population in terms of accessibility / supporting framework by caregivers			
I: Comprehensive cancer care places only available in major urban areas (fragmented care delivery model)			

Notes: C = clinician, I = industry, AN = almost never, AA = almost always, 50% = about half the time, <50% = less than half the time, >50% = more than half the time, FA = fully agree, PA = partly agree, PD = partly disagree, FD = fully disagree.

In Greece, a local patient organization was invited to provide feedback on treatment barriers through an online survey. A representative of FairLife L.C.C. (Lung Cancer Care) made the following points:

- Poor performance status (ECOG PS 2–4) does only deter physician from administering cancer drugs in less than half the times.
- Patients almost never refuse to receive cancer drug treatment if they have good performance status.
- The main reasons for low treatment rates are delays in the diagnostic pathway, limited number of specialized centers to perform EBUS, and not enough biological material obtained. Apart from delays in diagnostic testing, the average time from having a complete diagnosis until reaching a treatment decision is also too long.
- There are only three biomarkers reimbursed by the national health system (KRAS, EGFR, ALK). Comprehensive genomic profiling and PD-L1 testing are not reimbursed.
- The possibilities to receive modern cancer drugs are good and more than 50% of patients who would medically benefit from modern cancer drugs receive them. All immunotherapies and targeted therapies are locally approved following EMA approval and are available, but they require an application procedure per patient which might take up to three weeks to be approved.
- Limited hospital budgets and high costs of drugs as well as lack of certain medical staff constitute barriers to administering modern cancer drugs.
- Regarding clinical guidelines, the criteria to define who is eligible for drug treatment are too restrictive in current guidelines. In addition, the adherence to current guidelines is low.

4.2.5 Hungary

HUNGARY – Barriers			
	Clinician	Industry	Comment
Area 1: Clinical ineligibility and patient choice			
Disease stage IIIB/C			C: IIIB/C receive chemoradiotherapy because local guidelines do not recommend systemic therapy & because of reimbursement I: IIIB/C receive chemoradiotherapy, because of financial protocol restrictions
ECOG PS 2			C & I: Best supportive care
Poor functional status (%)	25%	28%	
Co-morbidities and side effects (%)	5%	11%	
Treatment refusal by patients (%)	2%	3%	
Area 2: Delays in time from diagnosis to treatment start			
(1) Delays in diagnostic testing	PA	PD	
Turnaround time pathology			
Turnaround time genomic testing			
Turnaround time immunohistochemistry			
Technical equipment			
Staff			
Tumor tissue			
(2) Delays in reaching a treatment decision	PA	PD	C: The treatment possibilities are well organized; treatment decision is not delaying.
Intra-hospital coordination			
Multidisciplinary teams			
Staff			
(3) Delays in initiating treatment	PD	PA	C: Administrative delays in reimbursement procedure (not all cases) I: Administrative delays of 1 to 8 weeks in several cases caused by special (“named patient”) reimbursement system
Inter-hospital referral			
Capacity of general hospitals			
Capacity of specialized hospitals			
Staff			
Area 3: Availability of modern cancer drugs			
General availability	>50%	>50%	
Lack of reimbursement	<50%	<50%	
Hospital budget	AN	AN	
Restricted reimbursement	AN	AN	
Area 4: Clinical guidelines			
Up-to-dateness	PD	PA	

Eligibility criteria	PD	PA	
Adherence	PD	PD	
Area 5: Financial resources, human resources, and infrastructure			
Hospital budget	AN	<50%	
Budget for cancer drugs	FD	PD	
Medical staff	AN	AN	
Technical equipment	AN	AN	
Hospital beds and care places	AN	AN	
Additional barriers			
I: A special, two-stage ("named patient") reimbursement system that means years of delay until full access to modern drugs			

Notes: C = clinician, I = industry, AN = almost never, AA = almost always, 50% = about half the time, <50% = less than half the time, >50% = more than half the time, FA = fully agree, PA = partly agree, PD = partly disagree, FD = fully disagree.

In Hungary, no local workshop was conducted to collect additional feedback on barriers.

4.2.6 Ireland

IRELAND – Barriers			
	Clinician	Industry	Comment
Area 1: Clinical ineligibility and patient choice			
Disease stage IIIB/C			I: IIIB/C commonly receive surgery preceded by chemotherapy and/or radiotherapy, but some might also receive systemic therapy only
ECOG PS 2			I: Best supportive care
Poor functional status (%)	(90%)	20%	C: % of patients with poor functional status left untreated. Majority of patients present with advanced disease.
Co-morbidities and side effects (%)	5%	10%	C: Very small number of patients
Treatment refusal by patients (%)	5%	4%	C: Very small number of patients
Area 2: Delays in time from diagnosis to treatment start			
(1) Delays in diagnostic testing	FA	PA	
Turnaround time pathology			
Turnaround time genomic testing			C: Outsourcing the tests to multiple vendors
Turnaround time immunohistochemistry			
Technical equipment			
Staff			
Tumor tissue			
(2) Delays in reaching a treatment decision	FA	PD	C: Lack of availability of staging radiology tests and results of

			molecular panel and PD-L1 delay treatment decisions
Intra-hospital coordination			I: Poor IT systems is a big issue (even before the recent cyber-attack). A lot of patient records are still on paper and there is no national system for electronic health records
Multidisciplinary teams			
Staff			
(3) Delays in initiating treatment	FA	PD	C: Lack of availability of staging radiology tests and results of molecular panel and PD-L1 delay treatment start
Inter-hospital referral			
Capacity of general hospitals			
Capacity of specialized hospitals			
Staff			
Area 3: Availability of modern cancer drugs			
General availability	>50%	<50%	I: Until February 2021, very few patients who would medically benefit from modern cancer drugs received them. In February 2021, due to a significant investment in the budget 2021, a large number of new drugs became available. So currently more than 50% of patients who would medically benefit from modern cancer drugs receive them.
Lack of reimbursement	<50%	<50%	
Hospital budget	AN	AN	
Restricted reimbursement	AN	AN	
Area 4: Clinical guidelines			
Up-to-dateness	FD	FD	
Eligibility criteria	PD	FD	
Adherence	FD	FD	
Area 5: Financial resources, human resources, and infrastructure			
Hospital budget	AN	AN	
Budget for cancer drugs	FD	FD	
Medical staff	AN	>50%	
Technical equipment	AN	<50%	
Hospital beds and care places	<50%	<50%	
Additional barriers			
I: Ireland's reimbursement system for new drugs is very slow. Delays can be up to 2.5 years post EMA approval.			
I: There are significant issues with human resources to help support with managing toxicities, i.e., not enough specialist nurse roles.			

Notes: C = clinician, I = industry, AN = almost never, AA = almost always, 50% = about half the time, <50% = less than half the time, >50% = more than half the time, FA = fully agree, PA = partly agree, PD = partly disagree, FD = fully disagree.

The local workshop in Ireland involved the presentation of preliminary findings of this report and discussions among several lung cancer experts.

- Participating experts active in diagnostics/treatment/care: Greg Korpanty, Martin Barr, Aileen O'Meara
- Participating experts active as patient representatives: Anne-Marie Baird, Helen Forristal

The following main points were made by the experts active in diagnostics/treatment/care:

- Early diagnosis is a challenge. The recent development of Rapid Access Lung Clinics will hopefully help to diagnose patients earlier and then patients should also be more fit for treatment. Right now, the problem is that many patients are diagnosed stage IV and may not be fit for treatment.
- There are delays in the diagnostic process.
    - Pathology and cytology analysis are not always taking place on the same site. Different diagnostic tasks are being outsourced to different centers. But even though the collaboration between centers might work well, in terms of getting the results quickly, this is not ideal. Turnaround time for genomic testing is sometimes two weeks and is definitely a barrier, whereas immunohistochemistry is quicker. Pathology might take three weeks.
    - Where patients are diagnosed matters. Unless they are diagnosed in one of the Designated Cancer Centers with a rapid access lung clinic, the question is whether they are referred to those. There might also be delays in that. In addition, COVID-19 has led to delays in radiology at the rapid access lung clinics. Already before COVID-19, a challenge was that many patients with an abnormal chest x-ray but who were very unlikely to have lung cancer were referred to these clinics by their GP. Streamlining/triaging those patients is something that should be done.
    - The complexity of the diagnostic pathway in lung cancer patients is increasing. There is an increasing amount of information that you would need to have available upfront (staging and imaging, PD-L1, molecular testing). This takes more and more time.
    - Staff shortages for pathology and testing are an important barrier, as genomic testing requires expertise.

- There is no agreed on national molecular testing approach. This may thus be done differently in, e.g., Dublin or Cork. Very often samples are just tested for EGFR and ALK but not for newer druggable targets, although some patients will be tested more extensively. Testing is not done with NGS.
- The scarcity of tumor tissue is an issue. Current methods rely on small biopsies to make a diagnosis. There may not be enough material to do both molecular testing and PD-L1 testing.
- Staff shortages and capacity shortages of general hospitals are major issues that are getting increasingly worse. Since patients can get more treatments and living longer, day centers are bulging. This also leads to waiting lists to start patients on treatment, which is something that was not common just a few years ago. Recruiting trained staff, including nurses that specialize in oncology, is a huge issue and will be one also going forward. Without sufficient staff, it is difficult to give patients new treatments.
- Co-morbidities can prevent patients from receiving treatment. Ireland has a quite high incidence of auto-immune diseases, such as active rheumatoid arthritis, and immunotherapy is not given to those patients. ECOG PS and age also play an important role in determining who gets treated. The ESMO-benchmark is therefore difficult to reach.
- Patients with ECOG PS 2 generally receive systemic therapy. In general, there is a tendency to treat lung cancer patients who are even a bit frailer compared to what the drug was approved for.
- Stage IIIB/C is unresectable disease, and these patients are generally treated as metastatic disease.
- Patient refusal of treatment happens, but this differs partly based on socio-economic background. Not everyone is willing to accept the anticipated toxicities. The frequency of patient refusal will also differ depending on your institution’s catchment area. Tertiary centers tend to have a younger patient population who is more motivated to get treatment. In other places, there are more patients who are more difficult to convince to undergo treatment.
- There are significant delays in the reimbursement of new drugs. The combination immunotherapy and chemotherapy only became reimbursed in 2021. This should change the composition of the treatment rates in the future.

The following main points were made by the patient representatives:

- Health promotion regarding smoking is particularly important in underserved communities.

- In recent years, a lot of effort has been made on awareness of early signs of lung cancer and de-stigmatizing lung cancer to help people present themselves early with lung cancer. Seeking care earlier and not feeling blamed because you were/are a smoker is important.
- During the COVID-pandemic, symptoms that seemed to be caused by COVID-19 were actually caused by lung cancer. Patients got a negative COVID-19 test result and were then relieved that it was not COVID-19. But their symptoms persisted, and the symptoms became normalized instead of being checked up properly. Increasing awareness on this is important.
- Staff shortages are a challenge. Recruiting additional advanced nurse practitioners will be something that could be important to reduce barriers to treatment to some degree.
- The lack of scientists to help with NGS testing or lack of radiologists are an issue all over Europe, and Ireland is no exception. This development might get worse over the next couple of years.
- The reimbursement of drugs takes around two years after EMA-approval, and this is a clear barrier to receiving newer treatment options.

4.2.7 Netherlands

NETHERLANDS – Barriers			
	Clinician	Industry	Comment
Area 1: Clinical ineligibility and patient choice			
Disease stage IIIB/C			C: IIIB/C receive chemoradiotherapy, because it is more effective & local guidelines do not recommend systemic therapy & patient group was not considered in clinical trials I: IIIB receive chemoradiotherapy because it is more effective; only IIIC receive systemic therapy
ECOG PS 2			I: Best supportive care
Poor functional status (%)	(70%)	(60%)	C & I: % of patients with poor functional status left untreated I: Based on input from a panel of health care professionals in 2019
Co-morbidities and side effects (%)	10%	15%	C: E.g., psychiatric or severe kidney problems
Treatment refusal by patients (%)	20%	5%	C: Depends clearly on the doctor's view
Area 2: Delays in time from diagnosis to treatment start			
(1) Delays in diagnostic testing	PA	FD	
Turnaround time pathology			
Turnaround time genomic testing			

Turnaround time immunohistochemistry			
Technical equipment			
Staff			
Tumor tissue			
(2) Delays in reaching a treatment decision	FD	FD	C: It hardly happens
Intra-hospital coordination			
Multidisciplinary teams			I: No full alignment in MDT concerning treatment decision(s)
Staff			
(3) Delays in initiating treatment	FD	PD	
Inter-hospital referral			
Capacity of general hospitals			
Capacity of specialized hospitals			
Staff			
Area 3: Availability of modern cancer drugs			
General availability	>50%	>50%	
Lack of reimbursement	<50%	<50%	
Hospital budget	AN	AN	
Restricted reimbursement	>50%	AN	
Area 4: Clinical guidelines			
Up-to-dateness	PD	PD	
Eligibility criteria	PD	PA	
Adherence	FD	FA	
Area 5: Financial resources, human resources, and infrastructure			
Hospital budget	<50%	AN	
Budget for cancer drugs	FA	PA	
Medical staff	AN	AN	
Technical equipment	AN	AN	
Hospital beds and care places	AN	AN	
Additional barriers			
C: When patients need to be referred to other hospitals, the treatment rates will drop significantly due to patients' and doctors' attitude			
I: Patients' choice not to be treated			
I: Conservative health care professionals in treating lung cancer			

Notes: C = clinician, I = industry, AN = almost never, AA = almost always, 50% = about half the time, <50% = less than half the time, >50% = more than half the time, FA = fully agree, PA = partly agree, PD = partly disagree, FD = fully disagree.

The local workshop in the Netherlands involved the presentation of preliminary findings of this report and discussions among several lung cancer experts.

- Participating experts active in diagnostics/treatment: Hans J.M. Smit, Noël Schlösser, Bonne Biesma, Fabian Laugs, Harry Groen
- Participating experts active as patient representatives: Lidia Barberio

The following main points were made by the experts active in diagnostics/treatment:

- The actual drug treatment rate is probably somewhat higher than the one calculated by IHE, because a small proportion of patients who fall into the non-treated group received off-label treatment in the Netherlands. This does not happen as often in other countries, because drugs are often reimbursed more quickly there. In the Netherlands, targeted therapy was given off-label. Moreover, the treatment culture between countries is very different, e.g., Belgium treats faster, more aggressively, and more often than the Netherlands.
- Not all patients need to be treated, e.g., patients who are admitted and die soon after, and a higher treatment rate does not always mean an improvement. Not administering any active therapy (best supportive care) is a form of therapy, provided this has been decided based on shared decision-making. If the choice is made in consultation with the patient, this is considered optimal. Patients on active treatment should also have the possibility to gradually stop the treatment, e.g., by making some adjustments such as extending the treatment interval or lowering the dosage.
- Cultural background of patients plays a role. Oncologists are not yet sufficiently specialized to enter into discussions with patients from a different (non-European) culture, as completely different factors can play a role in the treatment consideration by patients. In some hospitals, an imam is hired to support patients.
- Poor physical condition (ECOG PS) is the single most important factor for not administering active treatment, but there is little you can do about this. There is however a grey area in terms of assessment. Pulmonologists might often assess a patient to be better than they actually are. With a targeted therapy you can also treat patients with somewhat poorer condition.
- The presence of co-morbidities is an important barrier for administering active treatment. Co-morbidities are even more difficult to resolve than the ECOG PS status.
- Not all pulmonologists have an oncology-focus and will provide optimal information to lung cancer patients. In principle, all lung cancer patients should see a lung oncologist, but often patients come to the consultation without a suspicion of cancer, meaning they may visit any kind of pulmonologist first. A non-oncology-focused pulmonologist looks at the patient very differently and may misinform the patient on treatment options. If such a pulmonologist already paints a negative picture for the patient and suggests no active treatment, it is difficult for the lung oncologist to persuade the patient to receive active treatment.
- There are differences in terms of diagnosis, especially if the patient ends up with non-oncology-focused pulmonologist. They might not always do biomarkers testing for EGFR

and ALK in all patients. Moreover, it can be difficult for many pulmonologists to read a pathology report, as it contains many abbreviations that are unclear to them.

- The time until the full diagnosis report is ready, especially biomarker testing for specific mutations, is quite long. During this time a patient can progress too far to receive treatment.
- Some patients, e.g., those with a BRAF mutation, who are eligible to receive treatment will have to travel to a university hospital to receive treatment. The patient thus has to be willing and able to travel/drive to a university hospital, which takes up a lot of energy. Many patients say “never mind”, even if they can be treated.
- Some hospitals do not administer immunotherapy and they have to refer patients to other hospitals. Some patients will be lost there and may end up not receiving any treatment. At the same time, there are the “we-can-do-it-all” hospitals. They do not refer patients and want to provide all the care themselves, but they cannot provide optimal treatment.
- Collaboration with and referral to a center of expertise can be improved by keeping the referral centers more involved. It is important to maintain good relationships between the centers within the region. Concentration of care is not necessarily better for the treatment rate.
- Some pulmonologists might want to take “social responsibility” and not simply prescribe anything that is available, also with a view to the costs of (newer) drugs to society.
- Reimbursement is crucial before a drug can be readily prescribed. This would also limit off-label use of drugs.

The following main points were made by the patient representative:

- Shared decision-making by the clinician and the patient should be improved.
- There are oncologists who treat patients with ECOG PS 2 and others who do not. The assessment of ECOG PS might not always be correct either, and something that would make the assessment more objective would be needed. The patient’s assessment of whether he/she will be able to handle treatment also needs to be considered.
- More comprehensive diagnostics to detect patients with rare mutations that are treatable needs to be done.
- Time to reimbursement of new cancer drugs is long.

4.2.8 Norway

NORWAY – Barriers	Clinician	Industry	Comment
Area 1: Clinical ineligibility and patient choice			
Disease stage IIIB/C			C: IIIB/C receive chemoradiotherapy because it is more effective I: IIIB receive adjuvant immunotherapy; only IIIC receive systemic therapy
ECOG PS 2			
Poor functional status (%)	10%	23%	C: Best guess I: According to recent data (INSPIRE)
Co-morbidities and side effects (%)	0%	5%	C: With the new combinations available, patients in good ECOG will always be able to receive at least 1 type of systemic therapy
Treatment refusal by patients (%)	0%	2%	C: Many years since my last patient refused any treatment
Area 2: Delays in time from diagnosis to treatment start			
(1) Delays in diagnostic testing	PD	FD	
Turnaround time pathology			
Turnaround time genomic testing			
Turnaround time immunohistochemistry			
Technical equipment			
Staff			
Tumor tissue			
(2) Delays in reaching a treatment decision	FD	PD	C: Some cases are too complex to reach a quick decision I: Not perceived as a significant barrier
Intra-hospital coordination			
Multidisciplinary teams			
Staff			
(3) Delays in initiating treatment	FD	FD	C: Not a barrier I: No systemic factor that causes delay - if any, then primarily due to the status of the patient
Inter-hospital referral			
Capacity of general hospitals			
Capacity of specialized hospitals			
Staff			
Area 3: Availability of modern cancer drugs			
General availability	AA	see comment	I: Access for NSCLC patients is good, but the major hurdle is the HTA process and time delays created by it
Lack of reimbursement	AN	AA	
Hospital budget	AN	-	
Restricted reimbursement	AN	AN	

Area 4: Clinical guidelines			
Up-to-dateness	FD	FD	
Eligibility criteria	FD	FD	
Adherence	FD	FD	
Area 5: Financial resources, human resources, and infrastructure			
Hospital budget	AN	AN	
Budget for cancer drugs	FA	PD	
Medical staff	AN	AN	
Technical equipment	AN	AN	
Hospital beds and care places	AN	AN	
Additional barriers			
I: Uptake of drugs is good after reimbursement, but the time delays until reimbursement are significant			

Notes: C = clinician, I = industry, AN = almost never, AA = almost always, 50% = about half the time, <50% = less than half the time, >50% = more than half the time, FA = fully agree, PA = partly agree, PD = partly disagree, FD = fully disagree.

In Norway, no local workshop was conducted to collect additional feedback on barriers.

4.2.9 Poland

POLAND – Barriers			
	Clinician	Industry	Comment
Area 1: Clinical ineligibility and patient choice			
Disease stage IIIB/C			C & I: IIIB receive chemoradiotherapy because local guidelines do not recommend systemic therapy; only IIIC receive systemic therapy
ECOG PS 2			C: Best supportive care
Poor functional status (%)	(81%)	(no data available)	C: % of patients with PS 3 and 4 left untreated
Co-morbidities and side effects (%)	10%		
Treatment refusal by patients (%)	10%		
Area 2: Delays in time from diagnosis to treatment start			
(1) Delays in diagnostic testing	PA	FA	
Turnaround time pathology			
Turnaround time genomic testing			
Turnaround time immunohistochemistry			
Technical equipment			
Staff			
Tumor tissue			
(2) Delays in reaching a treatment decision	PD	PA	
Intra-hospital coordination			
Multidisciplinary teams			

Staff			
(3) Delays in initiating treatment	FD	FA	I: Diagnostics (performed in toracosurgical and pulmonary centers) and systemic treatment (administered in oncology centers) happen in different health care facilities in many cases. Some tests need to be repeated for referred patients as well as additional procedures performed to meet the treatment qualification criteria for drugs reimbursed under the drug program.
Inter-hospital referral			
Capacity of general hospitals			
Capacity of specialized hospitals			
Staff			
Area 3: Availability of modern cancer drugs			
General availability	AA	AN	
Lack of reimbursement	50%	>50%	
Hospital budget	50%	<50%	
Restricted reimbursement	AA	<50%	
Area 4: Clinical guidelines			
Up-to-dateness	FA	FD	I: Most oncologists follow ESMO guidelines, as Polish guidelines currently do not include immuno-chemotherapy as standard options, but this should not prevent patients from receiving treatment
Eligibility criteria	FA	PD	
Adherence	FA	PA	
Area 5: Financial resources, human resources, and infrastructure			
Hospital budget	>50%	>50%	
Budget for cancer drugs	FD	FD	
Medical staff	AN	<50%	
Technical equipment	AN	<50%	
Hospital beds and care places	AN	AN	
Additional barriers			
I: Underestimating symptoms, lack of screening, low oncological vigilance in primary care			

Notes: C = clinician, I = industry, AN = almost never, AA = almost always, 50% = about half the time, <50% = less than half the time, >50% = more than half the time, FA = fully agree, PA = partly agree, PD = partly disagree, FD = fully disagree.

The local workshop in Poland involved the presentation of preliminary findings of this report and discussions among several lung cancer experts.

- Participating experts: Prof. Joanna Chorostowska-Wynimko, Prof. Beata Jagielska, Prof. Rafal Krenke, Prof. Maciej Krzakowski, Prof. Renata Langfort, Prof. Adam Maciejczyk, Prof. Pawel Sliwinski

The following main points were made by the experts:

- Regarding the barriers in area 1 relating to clinical eligibility, the ECOG PS classification depends on the underlying reason. Co-morbidities and old age are the main reason for having a poor ECOG PS.
- Regarding the barriers in area 2 relating to delays in time to treatment, there are large differences in the answers between the clinician and the industry. The experts agree that the answers by the industry are much closer to the reality of the whole country.
- Early diagnosis is important. There are significant delays in the time from the GP to referral to the hospital with a median time of 130 days. It takes another median time of 52 days from first diagnostic visit to treatment start.
- Immunohistochemistry, including predictive immunohistochemical tests evaluating the expression of ALK and PD-L1 proteins, are not reimbursed.
- A major challenge and inefficiency is the financing system for diagnostics in the ambulatory setting. Currently, molecular diagnostics in ambulatory care is reimbursed exclusively for the biopsies/samples collected in the past but not for material collected in the outpatient setting. Patients are instead hospitalized to perform molecular diagnostics, because then the molecular tests are reimbursed.
- On top of molecular diagnostics, there are also challenges with pathomorphological diagnostics. There are long waiting times for the results, a lack of pathologists, high costs of the tests, no financial outlays (e.g., for expensive immunohistochemical antibodies), and low quality of the tissue material (e.g. due to the fact that the material from the collection site is sent to pathomorphology departments only after a few days).
- The barrier relating to “tumor tissue” is somewhat special. The challenge is not necessarily the volume/size of the tissue obtained, but rather the handling of the tissue obtained (substandard preservation and shipment conditions). This is a big challenge in the coming years for the administration of modern drugs. NGS testing will not solve problems in this area. NGS requires good quality samples, but currently the quality of the tissue samples is the main problem.

- Regarding the barriers in areas 3 and 5 relating to availability of modern cancer drugs, the structure of the drug budget program is okay. The main challenge relates to the way the money is spent, because it limits the access. The key issue are liquidity problems of hospitals. The National Health Fund reimburses drugs with a delay, so hospitals have to pay upfront. Smaller hospitals do not participate in the reimbursed drug program because of this.
- Innovative drugs are included in a separate fund. The combination of immunotherapy and chemotherapy was reimbursed only in 2021 and explains the composition of the drug treatment rates.
- Regarding the barriers in area 4 relating to clinical guidelines, the guidelines are no longer a barrier. In 2021, the guidelines were updated. The only challenge is that they are not mandatory to follow for clinicians, and they sometimes do not follow them if there is a problem with drug availability in some centers (due to financial liquidity issues in the hospital for example).
- Regarding the barriers in area 5, there is a lack of health care staff in the years to come. Already now, there are only around 150 thoracic surgeons and 1000 medical oncologists, whereas there should be around 400 pathologists and 1500 medical oncologists to achieve a good physician per capita ratio.
- A general problem is that cancer care is disorganized. There is no comprehensive care system of lung cancer units. There is no network of diagnostic centers (including both clinicians and laboratories) and treatment centers.

4.2.10 Portugal

PORTUGAL – Barriers			
	Clinician	Industry	Comment
Area 1: Clinical ineligibility and patient choice			
Disease stage IIIB/C			C: IIIB receive chemoradiotherapy
ECOG PS 2			I: Best supportive care
Poor functional status (%)	12%	(80%)	I: % of patients with poor functional status left untreated
Co-morbidities and side effects (%)	5%	20%	I: Minor proportion due co-morbidities
Treatment refusal by patients (%)	1%	-	
Area 2: Delays in time from diagnosis to treatment start			
(1) Delays in diagnostic testing	PA	PA	I: Internal processes in each hospital differ (e.g., the need to send the

			tumor sample to an external lab, or patient consent forms to be signed)
Turnaround time pathology			
Turnaround time genomic testing			
Turnaround time immunohistochemistry			
Technical equipment			
Staff			
Tumor tissue			
(2) Delays in reaching a treatment decision	PA	PA	C: There is no delay in reaching a treatment decision
Intra-hospital coordination			
Multidisciplinary teams			
Staff			
(3) Delays in initiating treatment	FD	FA	
Inter-hospital referral			
Capacity of general hospitals			
Capacity of specialized hospitals			
Staff			
Area 3: Availability of modern cancer drugs			
General availability	>50%	>50%	
Lack of reimbursement	<50%	AA	
Hospital budget	AN	<50%	
Restricted reimbursement	AN	50%	
Area 4: Clinical guidelines			
Up-to-dateness	PD	FD	
Eligibility criteria	PA	PD	
Adherence	PD	FA	
Area 5: Financial resources, human resources, and infrastructure			
Hospital budget	AN	<50%	
Budget for cancer drugs	FD	FD	
Medical staff	AN	<50%	
Technical equipment	AN	<50%	
Hospital beds and care places	AN	<50%	
Additional barriers			
C: Financing model of hospitals – Hospitals are financed by the state budget, which is not adapted or correlated to the cost of drugs			
I: Lack of GP awareness on lung cancer symptoms, causing delayed referral; lack of awareness in the general population of symptoms			

Notes: C = clinician, I = industry, AN = almost never, AA = almost always, 50% = about half the time, <50% = less than half the time, >50% = more than half the time, FA = fully agree, PA = partly agree, PD = partly disagree, FD = fully disagree.

In Portugal, no local workshop was conducted to collect additional feedback on barriers.

4.2.11 Romania

ROMANIA – Barriers			
	Clinician	Industry	Comment
Area 1: Clinical ineligibility and patient choice			
Disease stage IIIB/C			C: Concomitant chemoradiotherapy followed by durvalumab as maintenance I: Chemoradiotherapy is more effective, but entry of new drugs might change this soon
ECOG PS 2			
Poor functional status (%)	15%	-	C: Usually patients with extensive brain metastases with ECOG PS 3-4 I: No public data available
Co-morbidities and side effects (%)	5%	-	C: Very old patients with other diseases I: No public data available
Treatment refusal by patients (%)	5%	-	C: Fear of treatment effects I: No public data available
Area 2: Delays in time from diagnosis to treatment start			
(1) Delays in diagnostic testing	PA	PA	C: In the COVID-era pneumology clinics were turned into COVID clinics. In 2020, patients were not diagnosed due to that situation.
Turnaround time pathology			
Turnaround time genomic testing			I: Lack of prescription protocol for testing & reimbursement
Turnaround time immunohistochemistry			
Technical equipment			
Staff			
Tumor tissue			
(2) Delays in reaching a treatment decision	PA	FA	I: Patients looking for second opinion
Intra-hospital coordination			
Multidisciplinary teams			
Staff			
(3) Delays in initiating treatment	FD	PA	
Inter-hospital referral			C: Patients not referred to medical oncology departments I: Limited mobility of cancer patients
Capacity of general hospitals			
Capacity of specialized hospitals			
Staff			
Area 3: Availability of modern cancer drugs			
General availability	>50%	See comment	I: Differences between targeted therapy distributed in retail (90%) and hospital products e.g. immunotherapy (50%)
Lack of reimbursement	AN	AA	

Hospital budget	AN	50%	
Restricted reimbursement	AN	AN	
Area 4: Clinical guidelines			
Up-to-dateness	FD	FD	I: There are no therapeutic guidelines for lung cancer to position each medicine/class in the treatment pathway.
Eligibility criteria	PD	FD	
Adherence	PD	FD	
Area 5: Financial resources, human resources, and infrastructure			
Hospital budget	AN	<50%	
Budget for cancer drugs	PA	PA	
Medical staff	AN	>50%	
Technical equipment	AN	>50%	
Hospital beds and care places	AN	>50%	
Additional barriers			
C: Strict audits from the National Health Insurance House (CNAS) with financial penalties for doctors. There are doctors that are afraid to prescribe drugs for borderline patients due to financial implications.			
C: Tumor board decisions do not have a legal value. It is the prescriber's decision and her/his own responsibility.			
I: Delays in time to treatment are caused by lack of digitalization (online-appointments, telemedicine), uneven geographical distribution of oncology centers / hospitals, high bureaucracy, high patients-to-physician ratio			
I: Lack of knowledge regarding immunotherapy at the level of physicians			

Notes: C = clinician, I = industry, AN = almost never, AA = almost always, 50% = about half the time, <50% = less than half the time, >50% = more than half the time, FA = fully agree, PA = partly agree, PD = partly disagree, FD = fully disagree.

The local workshop in Romania involved the presentation of preliminary findings of this report and discussions among decision-makers, specialists and researchers from the medical sector, health care experts, and representatives of non-governmental organizations and patient associations.

- Participating experts active as decision-makers, specialists and researchers from the medical sector, and health care experts: Prof. Dr. Tudor Ciuleanu, Dr. Dana Stănculeanu, Dr. Michael Schenker, Dr. Șerban Negru, Dr. Andrei Ungureanu, Dr. Daniela Zob, Dr. Marius Geantă, Oana Mocanu, Felicia Ciulu-Costinescu, Adrian Pană

- Participating experts from non-governmental organizations and patient associations: Alina Comănescu, Mihaela Geoana, Victoria Asanache, Dr. Silvia Coman

The following main points were made by decision-makers, specialists and researchers from the medical sector, and health care experts:

- Late diagnosis is the main challenge. There is a significant delay in time from symptom onset to diagnosis. Even after diagnosis it takes time until treatment start. More than six months my pass from the first symptoms until treatment is initiated.
    - The COVID-19 pandemic has amplified the problem of delays. All pneumology centers have been managing COVID-19 cases and the access to resources and specialists to diagnose lung cancer was limited.
    - Delays between first symptoms and treatment have also increased in recent years because of increased molecular testing, which takes additional time.
- Coordination of multidisciplinary care is a challenge, including the coordination of care in the same hospital and between hospitals and regions. A clear pathway of the patient's journey is lacking. This leads to variability between regions in terms of diagnosis and treatment and this has an impact on survival and the quality of life.
- The number and capacity of highly-quality clinical centers that can perform modern examinations beyond bronchoscopy are limited. At the regional level there are deficits regarding access to standard procedures such as bronchoscopy.
- Fragmentation of cancer care leads to important differences between the tests performed before diagnosis and the ones before treatment start.
- Molecular diagnostics is not reimbursed, and instead the costs of the tests are covered by the pharmaceutical companies. There are no official testing guidelines promoted by the public payer.
- There is limited access to comprehensive biomarker panels. Comprehensive testing is needed upfront, which can shorten the time spent until a correct diagnosis is established and the right treatment initiated. Comprehensive biomarker testing is recommended by current guidelines, but the most frequent strategy is to test one biomarker at a time. This limits the administration of effective therapies.
- There are only prescription protocols issued for each new drug upon reimbursement approval, but there are no disease-based national clinical guidelines in line with ESMO

recommendations to help guide the administration of proper treatment options. This leads to differences in treatment across the country.

- Most of the new cancer drugs approved by the EMA for NSCLC are available in Romania, but patients do not have timely access to those drugs. Access to new cancer drugs has generally improved but it is essential that other innovations are implemented in the health system to ensure that these drugs reach the patients who most need them.
- Access to clinical trials has become a valuable resource for patients since 2014. Although there are few institutions where clinical trials are conducted, Romanian patients rely on clinical trials to have access to the newest drugs. A lack of coordination of cancer care is however impairing patient recruitment to clinical trials.

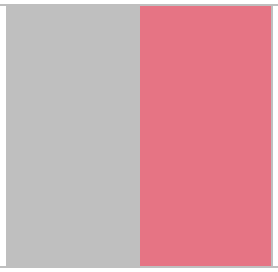
The following main points were made by experts from non-governmental organizations and patient associations:

- Major delays in the time until a diagnosis is the main challenge and should be the first step to shorten the patient journey. There are also significant regional discrepancies in these delays.
- There are inequalities in terms of access to immunotherapy between the main university centers and small regional hospitals. During the COVID-19 pandemic, regional hospitals could not ensure timely access to immunotherapy for patients because they did not have approved procedures for requesting the immunotherapies and it would have taken at least three months to get the request approved.
- There are no good procedures to enroll patients in clinical trials. Oncologists may ask patient organizations to find patients willing to enroll but it this difficult to do in practice.

4.2.12 United Kingdom

UNITED KINGDOM – Barriers			
	Clinician	Industry	Comment
Area 1: Clinical ineligibility and patient choice			
Disease stage IIIB/C			
ECOG PS 2			C: Radiotherapy is given I: Best supportive care is given
Poor functional status (%)	20%	(76%)	I: 10-year data from Leeds hospital trust show 1052 out of 1383 patients not treated with SACT/RT had ECOG PS ≥2

Co-morbidities and side effects (%)	20%	10%	C: Often co-morbid COPD and cardiovascular disease
Treatment refusal by patients (%)	5%	10%	
Area 2: Delays in time from diagnosis to treatment start			
(1) Delays in diagnostic testing	FA	FA	I: There are significant delays in diagnostics, including scanning, biopsy, biomarker testing
Turnaround time pathology			
Turnaround time genomic testing			
Turnaround time immunohistochemistry			
Technical equipment			
Staff			
Tumor tissue			
(2) Delays in reaching a treatment decision	FA	FA	I: Workforce problems / vacancies cause some delays here
Intra-hospital coordination			
Multidisciplinary teams			
Staff			
(3) Delays in initiating treatment	FA	PA	
Inter-hospital referral			
Capacity of general hospitals			
Capacity of specialized hospitals			
Staff			
Area 3: Availability of modern cancer drugs			
General availability	>50%	AA	I: No barrier due to access of modern drugs. National access granted quite early on.
Lack of reimbursement	AN	AN	
Hospital budget	AN	AN	
Restricted reimbursement	AN	AN	
Area 4: Clinical guidelines			
Up-to-dateness	PD	FD	I: No barrier with guidelines other than some clinicians not perhaps being fully aware
Eligibility criteria	PA	FD	
Adherence	PD	FD	
Area 5: Financial resources, human resources, and infrastructure			
Hospital budget	AN	AN	
Budget for cancer drugs	PD	PD	
Medical staff	<50%	AN	
Technical equipment	AN	AN	
Hospital beds and care places	>50%	AN	
Additional barriers			
I: Hesitancy amongst Black, Asian, and Minority Ethnic (BAME) communities resulting in late presentation to primary care			

I: Due to the NHS public funded structure and the barriers to access care that comes from this (vs. other private health care systems), treatment rates are lower than in systems where patients can access specialist care as soon as they have a symptom that they are not sure about	

Notes: C = clinician, I = industry, AN = almost never, AA = almost always, 50% = about half the time, <50% = less than half the time, >50% = more than half the time, FA = fully agree, PA = partly agree, PD = partly disagree, FD = fully disagree.

The local workshop in the UK involved the presentation of preliminary findings of this report and additional presentations by UK-based speakers on the topic of overall drug treatment rates. More than 50 health care professionals attended the workshop. The composition of the drug treatment rates was not discussed.

- Participants (speakers): Dr. Alastair Greystoke (Royal Victoria Infirmary), Dr. Saleheen Kadri (Queen Elizabeth The Queen Mother Hospital), Prof. Michael D. Peake OBE (University of Leicester)

The following main points on the overall drug treatment rate were made by the speakers:

- The national (England + Wales) drug treatment rate for NSCLC patients with stage IIIB/C+IV with any ECOG PS was 35% in 2018, according to the National Lung Cancer Audit. This is very close to the rates estimated by IHE.
- Late presentation of lung cancer patients is a major challenge. Many patients have multiple consultations prior to referral for specialist care where the diagnosis can be made. Co-morbidities and patient fitness (ECOG PS) limit access to drug treatment. The presentation of patients with lung cancer has been impacted negatively by the COVID-19 pandemic.
- Patients with ECOG PS 2 (and PS 3–4) generally do not receive drug treatment. The reimbursement of drugs is limited to ECOG PS 0–1.
- Drug treatment varies greatly across NHS trusts. The range of the systemic anti-cancer treatment rate by trust (i.e., trust first seen) was 32–98% for those with ECOG PS 0–1 and NSCLC stage IIIB/C+IV diagnosed in 2018, against a national average (England and Wales) of 66%, according to numbers from the National Lung Cancer Audit. Even after adjusting for age, sex, stage, ECOG PS, and socioeconomic status, there are great differences between the trusts. Bringing up all trusts below the national average up to the average would already greatly improve treatment rates.
- There are delays in the treatment pathway. Targets on the time from referral to treatment have been established, but it is challenging to meet the targets. There are delays in first CT

scan and subsequent image-guided biopsy, manpower issues with biopsy (EBUS), limited access and delays in molecular testing, staff and resource shortage, data entry issues, old buildings. In rural areas, the geography is an additional barrier when patients have to be referred between different care facilities.

After the presentations, the workshop attendees could vote – based on their experience – which one of a given set of factors has the biggest impact on low systemic treatment rates in advanced NSCLC. The top three factors (almost 90% of the votes) were "Performance status", "Prolonged intervals between referral and treatment", "Shortages of workforce". Remaining voted on factors were "Lack of clinical nurse specialist (CNS) support" and "Concern that treatment won't make a significant, positive difference in long-term outcomes". Factors that did not receive any votes were "Lack of availability of drugs in the NHS", "Patient choice", "Access for all patients to the most highly specialized MDTs", "Poor access to molecular diagnosis".

4.3 Key points

Barriers to achieving high drug treatment rates and to using modern drug treatment options are manyfold in every country. Many identified barriers are also shared by several countries.

In general, patients remain untreated because of the following reasons.

- **Poor functional status at the time of diagnosis**. Many patients are diagnosed very late. Late diagnosis increases the proportion of frail patients (ECOG PS 3–4). These patients are generally not recommended to receive systemic therapy. In addition, co-morbidities (such as cardiovascular diseases or kidney problems) and old age might make it unfeasible to administer systemic therapy, although these patients are mostly the same as those with poor ECOG PS.
- **Delays in time from diagnosis to treatment**. Long delays between diagnosis and start of treatment can make patients ineligible to systemic therapy because their functional status might deteriorate during this time. Delays in diagnostic testing (pathological analysis and genomic testing) are the main bottleneck. There can also be long delays in reaching a treatment decision and initiating treatment. These delays are caused by limited testing infrastructure, shortages in human resources (especially pathologists), and general capacity shortages of hospital beds and care places. Patients may also be lost when being referred from one hospital to another during the diagnostic process leading up to treatment start.
- **Narrow eligibility criteria for receiving drug treatment**. Some national clinical guidelines and/or reimbursement guidelines might not recommend/cover administering systemic

therapy to patients with fair functional status (ECOG PS 2). In addition, national clinical practices for treating patients diagnosed with stage IIIB and IIIC differ (either (i) treatment as metastasized disease with systemic therapy, (ii) surgery preceded by chemotherapy and/or radiotherapy, or (iii) chemoradiotherapy followed by maintenance immunotherapy) and might restrict receipt of systemic therapy.

- **Treatment refusal by patients**. Some patients might refuse to receive systemic therapy, e.g., because of stigma (among current/former smokers), fear of treatment side effects, or low trust in health care professionals and/or the health care system.

In general, patients receive outdated treatment options because of the following reasons – both in countries with high and with low overall treatment rates.

- **Delays in reimbursement of modern drugs**. The local reimbursement of new drugs (or new indications of existing drugs) which are recommended as standard-of-care might take several years after EMA approval. During this time most patients can only access older treatment options.
- **Limited public drug budgets**. Slow reimbursement of new drugs is caused by constrained public health care budgets or constrained public (cancer) drug budgets. In addition, even reimbursed drugs might not be available for all patients if hospital budgets are restricted.
- **Limited resources for testing**. Genomic testing and immunohistochemistry are prerequisites for administering targeted therapies and immunotherapies. Extensive genomic testing for less common genomic alterations (e.g., ROS1, NTRK) might not be done because of practical reasons (lack of high-quality tumor tissue), limited testing capacity (both infrastructure and human resources such as pathologists), or financial reasons (lack of reimbursement of testing).
- **Limited continuing medical education**. The rapidly changing treatment landscape in advanced NSCLC posed a challenge for the fast diffusion of new treatment practices. In certain patient sub-groups, medical staff faced a new treatment paradigm on a yearly basis. Lack of continuous training of all involved medical staff at all treating hospitals across the whole country prevents the rapid adoption of new treatment options.

5. Improving drug treatment rates

The comparatively low overall drug treatment rates identified in many countries in chapter 3 and the comparatively low use of modern cancer drugs even in countries with high drug treatment rates is worrying. They represent considerable deviations from what European clinical guidelines by ESMO recommend. This suggests that there is significant room to improve patient access to drug treatment in advanced NSCLC across Europe. Increasing the number of patients receiving timely and recommended state-of-the-art drug treatment could help address the high unmet clinical need in this patient group. At the same time, it is also important to respect patient choice. Yet it is the responsibility of the treating medical staff to inform patients about new treatment options that are different and clinically superior (as deemed by ESMO) to options that were recommended only 5–10 years ago.

How can drug treatment rates become a priority in cancer control? Building on the principle of *"what gets measured gets done"*, the first step is to explore the extent of the issue. Chapter 3 fills this knowledge gap. Few countries in Europe, e.g. England/Wales (135) and the Netherlands (136), have started to assess treatment rates on a regular basis and also to incorporated drug treatment rates as a key performance indicator in their audit studies of NSCLC. This report allows these leading countries to compare themselves also to their European peers for the very first time. Unfortunatley, Europe's Beating Cancer Plan, released by the European Commission in February 2021 and supposed to shape cancer policy in EU members states in the years to come, has not included the idea of measuring drug treatment rates (in any cancer type) (157). However, the envisioned "Cancer Inequalities Registry" mentioned in Europe's Beating Cancer Plan might be an opportunity to include such a metric.

The second step is to understand the drivers behind the issue. Chapter 4 explores barriers in different areas that could be of importance. Based on these findings, measures for future improvement can be identified. This is the purpose of this chapter. Many of the identified measures are naturally intertwined. For example, reimbursement of the more recent targeted therapy drugs (e.g., targeting ROS1, BRAF, NTRK) might be delayed because there is no capacity for NGS testing that would allow to identify suitable patients. At the same time, the expansion of NGS testing might not be prioritized because delayed reimbursement is anticipated in the first place. This simplified example emphasizes the fact that a comprehensive view on any measures to improve drug treatment rates is essential.

5.1 Method

The same two-step approach as described in section 4.1 was applied to derive recommendations on how to improve drug treatments. In the first step, recommendations were elicited from an online survey that was answered by one local representative of the medical field (such as a pulmonologist, medical oncologist) and one local representative of the pharmaceutical industry in every country. Respondents were asked to indicate "*the most important ways to improve drug treatment rates (both overall to get closer to 100% and increased use of modern drugs)*". Table 3 lists the pre-defined recommendations. Respondents could indicate one or several recommendations. Respondents could also add additional recommendations. Unless directly added by the respondents as an own recommendation, we also formulated recommendations based on the indicated barriers highlighted in other parts of the survey.

Table 3: Pre-defined recommendations to improve drug treatment rates in the survey

Broaden the eligibility criteria for drug treatment	Faster drug access in terms of faster local reimbursement
Obtain evidence of drug effectiveness in less evident groups (elderly population, ECOG PS>2)	More up-to-date clinical guidelines
Reduce time to treatment through faster patient pathways	Better continuing medical education to keep up to date with medical information
Better infrastructure to perform diagnostic testing	More financial resources
Better availability of modern cancer drugs	More human resources
Faster drug access in terms of faster EMA approval*	Better infrastructure at hospitals (hospital beds, outpatient care places, etc.)

Notes: * The recommendation is not country-specific but rather refers to EMA approval timelines of new drugs compared to the US FDA.

In the second step, the initial set of recommendations based on the survey were presented and discussed at local workshops in most countries. The workshops comprised a broader audience consisting of local lung cancer experts from the medical field and patient representatives. The recommendations formulated during the workshops broadly confirmed the ones obtained from the survey. Despite this overlap, recommendations derived during the workshops are presented separately from the recommendations derived from the survey. This makes it easier to compare the results across countries.

5.2 Country recommendations

The country-specific tables below summarize the key recommendations to improve drug treatment rates. Recommendations derived from the online survey and from the workshops are shown separately, even though there was generally a considerable overlap. The survey-derived recommendations were classified under the headings "Agreeing views" if both the clinical

representative and the industry representative provided the same recommendation, and under the headings “Additional views - Clinical perspective” and “Additional views - Industry perspective” otherwise. The workshop-derived recommendations were classified under the headings “Clinical perspective” and “Patient perspective”, although there was generally broad agreement between medical experts and patient representatives.

As section 4.2 already highlighted, there are many barriers to achieving optimal drug treatment. Therefore, there is not just one recommendation to improve drug treatment but many in every country.

5.2.1 Belgium

BELGIUM – Recommendations (based on survey answers)
Agreeing views
• Accelerate local reimbursement to improve the availability of modern cancer drugs • Accelerate access to new cancer drugs through faster EMA approval process
Additional views - Clinical perspective
• Support continuing medical education of onco-pulmonologist and medical oncologists to keep them up to date with medical information • Obtain evidence of drug effectiveness in less evident groups (elderly population, ECOG PS>2) Example of best practice: For BRAF V600E-mutated NSCLC, Belgium got approval of reimbursement only in April 2021 while EMA approval was obtained years ago [March 2017]. During this time period, we received the medication directly from the pharmaceutical company, but this was restrained to particular treatment centers (i.e., those centers where caregivers knew the possibility how to obtain the treatment).
Additional views - Industry perspective
• Improve the diagnostic infrastructure to speed up diagnostic testing, in particular NGS testing • Improve intra-hospital coordination to reach treatment decisions faster • Broaden the eligibility criteria for drug treatment

5.2.2 Bulgaria

BULGARIA – Recommendations (based on survey answers)
Agreeing views

• Shorten time to treatment through:
  ○ faster patient pathways
  ○ better diagnostic infrastructure to perform and speed up diagnostic testing
• Accelerate local reimbursement to improve the availability of modern cancer drugs
• Increase financial resources, including a greater budget for cancer drugs
• Improve early diagnosis by raising awareness of lung cancer symptoms of GPs as well as raising patients’ health literacy on lung cancer symptoms
• Improve patient attitudes towards receiving treatment

Additional views - Clinical perspective
• Obtain evidence of drug effectiveness in less evident groups (elderly population, ECOG PS>2)
Additional views - Industry perspective

- Support continuing medical education of lung cancer specialists to keep them up to date with medical information
- Make biomarker and genomic testing mandatory and have it reimbursed by payers
- Improve the geographic accessibility of diagnostics and treatments

Example of best practice: The pharma industry is covering expenses for biomarker and genetic testing which together with reimbursement of targeted and IO therapy leads to an increase of the treatment rate, valid for the whole country.

BULGARIA – Recommendations (based on local workshop)

Clinical perspective

- Treatment rates could be measured with data from the National Health Insurance Fund. Data from the national cancer registry are old and not so reliable and any conclusions drawn from it need to be made with caution.
- Early diagnosis needs to be improved. Raising awareness of lung cancer symptoms of GPs is important.
- Rapid and well-financed clinical pathways to allow fast diagnosis and treatment need to be established. In addition, switching to DRG would allow hospital managers to plan, monitor, and manage costs and know how efficiently they spend resources.
- The entire diagnostic process needs to be improved.
    - The process of bronchoscopic diagnosis should be centralized and consolidated throughout the country. There should be an established and binding protocol that is to be followed and reimbursed. Old equipment for bronchoscopies needs to be replaced.
    - The pathological assessment should be centralized and performed in university laboratories with a large volume of activity, necessary equipment, and regular quality control.
    - Immunohistochemistry and test of genomic alterations should be reimbursed by the health insurance fund.
    - The shortage of pathologists needs to be addressed.
- Surgeons and pulmonologists need to know about non-surgical treatment options in order to give better advice on available treatment options to patients. Patients need to receive more guidance on what to do and why to do it.
- Medical treatment standards need to be established should be legally binding to determine which drugs should be administered. If medical standards are not met, appropriate disciplinary action should be taken.
- Sufficient financial resources for drug treatment of NSCLC need to be provided.
- A National Cancer Plan should be established in accordance with Europe's Beating Cancer Plan. Lung cancer should be a priority in the cancer plan. If the plan is written in an adequate way and backed up by appropriate funding, it could help to improve diagnosis and treatment.

Patient perspective

- Lung cancer patients need to receive clear information on the patient journey. Having available somewhere on the web or on hard copy a lung cancer patient journey map with all needed actions and possible options would be very helpful.
- A dedicated lung cancer patient association needs to be established. Having a dedicated lung cancer patient association could support lung cancer patients in their patient journey.
- Out-of-pocket payments for diagnostics and treatment need to be reduced. This concerns primarily reimbursement of immunohistochemistry.
- Communication between oncology specialists and GPs needs to be improved. GPs can only get involved in supporting treatment if they receive information on the patient's diagnosis, treatment decisions and choices.
- Formal psychological support provided in an outpatient setting needs to be reimbursed. Support provided upon hospital discharge could increase adherence to treatment.

5.2.3 Finland

FINLAND – Recommendations (based on survey answers)
Agreeing views
• Increase the budget for cancer drugs to improve the general availability of modern cancer drugs (as only around 50% of patients who would medically benefit receive them) • Additional financial resources are needed to improve treatment rates and administer more modern drugs • Obtain evidence of drug effectiveness in less evident groups (elderly population, ECOG PS>2)
Additional views - Clinical perspective
• (-)
Additional views - Industry perspective
• Improve early diagnosis by raising awareness of lung cancer symptoms of GPs as well as raising patients' health literacy on lung cancer symptoms • Improve the transparency of treatment guidelines (currently not publicly available) and of the actual use of drugs in hospitals • Treatment guidelines should be followed more stringently rather than act as mere recommendations • Accelerate local reimbursement to improve the availability of modern cancer drugs • Improve the general infrastructure at hospitals (hospital beds, outpatient care places, etc.) • Reform the system of two public funding streams for oral drugs and hospital drugs to ensure overall responsibility for the patient's care path • Reform the specialized care system to ensure all hospitals having adequate drug budgets

FINLAND – Recommendations (based on local workshop)
Clinical perspective
• Early diagnosis needs to be improved. Raising awareness of lung cancer symptoms of GPs is important. • Molecular testing needs to switch to larger panels along with the increasing reimbursement of therapies targeting new genomic alterations. • Patient eligibility criteria could be reviewed, in particular regarding the treatment of patients with ECOG PS 2 and those with stage IIIB. • The current lung cancer care guidelines need to be updated more frequently. The guidelines should also be made publicly available. • The system with separate funding streams for oral drugs and hospital drugs needs to be reformed. It creates unequal access to hospital drugs (covering chemotherapies and immunotherapies used in NSCLC) across hospitals. • The budget for hospital drugs needs to be made more predictable and independent from the financial situation of the municipalities.

5.2.4 Greece

GREECE – Recommendations (based on survey answers)
Agreeing views*

• Shorten time to treatment through:*
  ○ faster patient pathways and rapid referral patterns from primary to secondary and tertiary oncology care
  ○ better diagnostic infrastructure to perform and speed up diagnostic testing
• Improve the general infrastructure at hospitals (hospital beds, care places, etc.)*
• Increase financial resources*
• Recruit additional human resources*

• Establish a proper and accurate cancer registry and put in place fully operational guidelines
Additional views - Clinical perspective
• Accelerate local reimbursement to improve the availability of modern cancer drugs° • Support access to locally available modern cancer drugs through simplifying the electronic pre-approval system (EPAS) • Accelerate access to new cancer drugs through faster EMA approval process • Support continuing medical education of lung cancer specialists to keep them up to date with medical information
Additional views - Industry perspective
• Improve the sustainability of access to modern cancer drugs through a supplementary public fund for cancer drugs, that will adequately cover patient's needs, based on the local epidemiological landscape • Ensure better geographical access to comprehensive lung cancer care in all areas (incl. islands) of the country • Support of CoE (Centers of excellence) in line with European Comprehensive Cancer Centers and development of Cancer Networks in lung cancer treatment • Promote smoking prevention with public health interventions

Notes: * These recommendations were also indicated by the representative from local patient organization. ° Following a major reform in 2018, access has since then been facilitated through the new the electronic pre-approval system (EPAS), that allows access to new drugs on a named-patient basis.

5.2.5 Hungary

HUNGARY – Recommendations (based on survey answers)
Agreeing views
• Accelerate and broaden access to modern cancer drugs through a reform of the “named patient reimbursement system” to avoid years of delay until full access for all patients, also supported by a greater budget for cancer drugs to meet patient needs • Reduce administrative delays in the current reimbursement procedure (“named patient system”) to shorten the time to treatment for the individual patient • Obtain evidence of drug effectiveness in less evident groups (elderly population, ECOG PS>2) to inform local treatment guidelines • Support continuing medical education of lung cancer specialists to keep them up to date with medical information
Additional views - Clinical perspective
• Shorten time to treatment through faster patient pathways • Improve the infrastructure to perform diagnostic testing • Improve the general infrastructure at hospitals (hospital beds, care places, etc.) • Increase financial resources • Recruit additional human resources
Additional views - Industry perspective
• Broaden the eligibility criteria for drug treatment • Ensure more up-to-date clinical guidelines

5.2.6 Ireland

IRELAND – Recommendations (based on survey answers)
Agreeing views
• Accelerate local reimbursement to improve the availability of modern cancer drugs, which necessitates a permanent (as opposed to the temporary government subsidy in the 2021 budget) increase of the public budget for drugs • Recruit additional human resources, in particular specialist nurses • Support continuing medical education of lung cancer specialists to keep them up to date with medical information
Additional views - Clinical perspective
• Shorten time to treatment through faster patient pathways, in particular speeding up the analysis of imaging tests, molecular panel testing and PD-L1 testing • Improve the infrastructure to perform diagnostic testing, in particular stop outsourcing the tests to multiple vendors • Broaden the eligibility criteria for drug treatment • Obtain evidence of drug effectiveness in less evident groups (elderly population, ECOG PS>2) • Improve the general infrastructure at hospitals (hospital beds, care places, etc.) • Accelerate access to new cancer drugs through faster EMA approval process
Additional views - Industry perspective
• Modernize the IT systems, including introducing a national system for electronic health records, to improve intra-hospital coordination of clinical departments

IRELAND – Recommendations (based on local workshop)
Clinical perspective
• The general financial resources of health care system need to increase to address shortages in staff and capacity of health services as well as access to newer drugs. • The recent development of rapid access lung clinics will help to diagnose patients earlier and then patients should also be more fit for treatment. But too many patients with an abnormal chest x-ray and who are very unlikely to have lung cancer are referred to these clinics by their GP. Streamlining/triaging those patients is something that should be done. • Streamlining the diagnostic process is the key to shorten time to treatment. There needs to be work towards an urgency of getting a proper diagnosis for lung cancer as fast and comprehensive as possible. Staff shortages for pathology and cytologists need to be addressed to improve turnaround time for tests. • Diagnostic testing for lung cancer needs to be standardized nationally. The same tests, on the same platforms, using the same antibodies need to be analyzed by well-trained pathologists. • The intra-hospital organization (the work across different MDTs that are involved in the treatment pathway from molecular, radiology, clinical specialty) could be improved to shorten time to treatment. • Recruiting and training additional staff, such as nurses and pathologists and other scientific staff, can help in the short-term. In the long-term, there needs to be better planning of future staff resources. The number of university study places for, e.g., pathologists, nurses, and medical scientists training in the molecular side of diagnostics needs to increase and they need to receive more incentives to choose oncology as a specialty. • Reimbursement of newer drugs should be accelerated and brought in line with other countries.
Patient perspective
• The general population needs to be better educated on early signs of lung cancer. They need to be encouraged to seek care and visit a rapid access lung clinic if necessary. • The introduction of lung cancer screening would be an important step towards earlier diagnosis. • Intra-hospital organization is something that hospitals have control over and that could be improved most easily, without necessarily requiring additional financial resources.

- Reimbursement of newer drugs should be accelerated and brought in line with other countries.
- The number of pulmonologists and especially those interested in lung cancer is too low and needs to be increased. Recruiting more nurses and other trained staff is important as well.

5.2.7 Netherlands

NETHERLANDS – Recommendations (based on survey answers)
Agreeing views
• Improve patient attitudes towards receiving treatment, also by shaping physicians' attitudes towards it • Improve turnaround time for tests of genomic alterations • Accelerate local reimbursement to improve the availability of modern cancer drugs
Additional views - Clinical perspective
• Broaden the eligibility criteria for drug treatment • Improve the inter-hospital referral system to avoid disruptions in the care process Example of best practice: NGS testing was already recommended in the guidelines before the clinical need for reimbursed drugs became clear. The system of NGS testing grew as a result and more cases of rare mutations were found. Because there were clinical trials (to get the drugs), this preliminary demand in the guidelines could be accounted for.
Additional views - Industry perspective
• Obtain evidence of drug effectiveness in less evident groups (elderly population, ECOG PS>2)

NETHERLANDS – Recommendations (based on local workshop)
Clinical perspective
• Drug treatment rates should be measured with local data. More precis numbers can be obtained from local registries. • Pulmonologists, especially those with a non-oncology focus, need to receive additional training. Clinical centers should teach each other what the newest treatment options are. Meetings / refresher courses for all pulmonologists should be arranged. • Physicians should be trained to better understand the needs and treatment considerations of patients with a different cultural background. • Differences in the comprehensiveness of diagnostic testing done by different pulmonologists need to be addressed. • Help with the interpretation of pathology reports should be provided to pulmonologists. • Additional pathologists should be trained and recruited as a means to shorten pathology lead time. • Referral of patients between hospitals needs to be improved and support provided to patients to able to travel to the specialized hospital. • Reimbursement of modern cancer drugs should be sped up.
Patient perspective
• Shared decision-making on the optimal treatment (active treatment or best supportive care) by the clinician and the patient should be improved. • The assessment of ECOG PS should be more objective and the treatment decision based on it (in particular for ECOG PS 2) should be more coherent and take into account patients' own assessment to handle treatment. • More comprehensive diagnostics to detect patients with rare mutations that are treatable needs to be done. • The time to reimbursement of new cancer drugs should be shortened.

5.2.8 Norway

NORWAY – Recommendations (based on survey answers)
Agreeing views
• Accelerate local reimbursement to improve the availability of modern cancer drugs through speeding up the HTA process • Obtain evidence of drug effectiveness in less evident groups (elderly population, ECOG PS>2)
Additional views - Clinical perspective
• Broaden the eligibility criteria for drug treatment
Additional views - Industry perspective
• Recruit additional human resources

5.2.9 Poland

POLAND – Recommendations (based on survey answers)
Agreeing views
• Improve the diagnostic infrastructure and recruit more staff to perform and speed up genomic testing and its analysis • Increase the financial resources to increase hospital budgets, in particular the budget for cancer drugs, to avoid restrictions in the administration of already reimbursed drugs • Accelerate local reimbursement to improve the availability of modern cancer drugs • Improve adherence to clinical guidelines and increase their up-to-dateness [note: guidelines were updated in 2021]
Additional views - Clinical perspective
• Recruit additional human resources • Improve the general infrastructure at hospitals (hospital beds, care places, etc.) • Improve patient attitudes towards receiving treatment • Accelerate access to new cancer drugs through faster EMA approval process
Additional views - Industry perspective
• Improve early diagnosis by raising awareness of lung cancer symptoms of GPs • Shorten time to treatment through faster patient pathways • Improve patient referral to oncology centers (inter-hospital) and avoid duplication of testing for referred patients • Broaden the eligibility criteria for drug treatment • Obtain evidence of drug effectiveness in less evident groups (elderly population, ECOG PS>2)

POLAND – Recommendations (based on local workshop)
Clinical perspective
• Treatment rates could be measured with data from the National Health Fund. It should be possible to get exact data on patient numbers from the National Health Fund for each line of therapy and also for different medical centers. • Early diagnosis needs to be improved. This includes both better awareness of lung cancer symptoms of GPs to reduce the time until referral to the hospital and the time from the first diagnostic visit to treatment start. • The organization of lung cancer care needs to be improved. There needs to be a comprehensive care system of lung cancer units. This includes establishing a network of diagnostic centers and treatment centers that ensures a smooth flow of information in both ways. • The diagnostic process needs to be sped up to decrease delays until treatment start and the quality needs to be improved. This includes both pathomorphological diagnostics and molecular diagnostics.

  - There is a need for more pathologists.
  - Costs for immunohistochemistry and costs for genomic testing for additional druggable targets need to be reimbursed.
  - The handling of the tumor tissue obtained from the biopsy needs to be improved through better preservation and shipment conditions to guarantee better quality and to avoid duplication.
- The reimbursement of (molecular) diagnostics needs to be reimbursed in ambulatory care instead of only in inpatient care.
- Access to outpatient diagnostics and treatment instead of inpatient care provision needs to be prioritized.
- Recruiting and training of additional staff, including nurses, clinicians, and pathologists, needs to be done.
- The reimbursement system of cancer drugs needs some revision. This includes foremost addressing the liquidity problems of (smaller) hospitals stemming from upfront payments for drugs and delayed reimbursement of these drug expenditure from the National Health Fund.

5.2.10 Portugal

PORTUGAL – Recommendations (based on survey answers)

Agreeing views

- Improve the diagnostic infrastructure to perform and speed up genomic testing and its analysis
- Improve the general infrastructure at hospitals (hospital beds, care places, etc.) to expand the capacity to treat patients
- Increase the financial resources and recruit additional human resources
- Accelerate local reimbursement to improve the availability of modern cancer drugs, also supported by a greater budget for cancer drugs to meet patient needs
- Obtain evidence of drug effectiveness in less evident groups (elderly population, ECOG PS>2)

Additional views - Clinical perspective

- Accelerate access to new cancer drugs through faster EMA approval process
- Improve the up-to-dateness of clinical guidelines
- Change the current financing model of hospitals via the state budget, which is not adapted or correlated to the cost of drugs

Example of best practice: Creation of dedicated pathways (for diagnosis and staging) for lung cancer.

Additional views - Industry perspective

- Shorten time to treatment through faster patient pathways
- Improve early diagnosis by raising awareness of lung cancer symptoms of GPs as well as raising patients' health literacy on lung cancer symptoms

Example of best practice: There is a pilot project in 2 hospitals called "Green/fast route for lung cancer" aiming to reduce delay between diagnosis and treatment. The project defines the recommended time period for each step of the patient journey (from GP referral to specialist to start of treatment).

5.2.11 Romania

ROMANIA – Recommendations (based on survey answers)

Agreeing views

- Shorten time to treatment through:
  - faster patient pathways
  - better diagnostic infrastructure to perform and speed up diagnostic testing
- Improve patient referral to medical oncology departments (inter-hospital), while addressing capacity shortages in these institutions to manage additional patients
- Accelerate local reimbursement to improve the availability of modern cancer drugs, requiring also a greater budget for cancer drugs
- Establish clearer rules on reimbursement of testing and prescription of drugs by the National Health Insurance House (CNAS)

Additional views - Clinical perspective

- Broaden the eligibility criteria for drug treatment
- Improve patient attitudes towards receiving treatment
- Accelerate access to new cancer drugs through faster EMA approval process
- Obtain evidence of drug effectiveness in less evident groups (elderly population, ECOG PS>2)

Additional views - Industry perspective

- Support continuing medical education of lung cancer specialists to keep them up to date with medical information
- Increase financial resources
- Recruit additional human resources
- Improve the general infrastructure at hospitals (hospital beds, outpatient care places, etc.)

Example of best practice: In the past, several (both public and private) clinics were able to improve drug treatment rates above the country average through a better collaboration between specialties (oncologists, pneumologists, pathologist) and fast access to medical investigations.

ROMANIA – Recommendations (based on local workshop)

Clinical perspective

- Early diagnosis needs to be improved. Raising awareness of lung cancer symptoms of GPs is important to decrease the time between symptom onset and diagnosis.
- Clear regulations defining each step of the patient's journey and the services to be received should be established.
  - Procedures for fast-tracking patients to secondary or tertiary centers for diagnostic testing should be put place.
  - Coordination between specialists in the same hospital and between hospitals needs to be improved.
- The number and capacity of highly-quality clinical centers that can perform modern examinations beyond bronchoscopy needs to be increased.
- Official testing guidelines should be issued by CNAS, and molecular diagnostics procedures should be reimbursed.
- Comprehensive biomarker testing carried out upfront instead of testing for one biomarker at a time should become the norm in clinical practice.
- National clinical guidelines for the treatment of advanced NSCLC in line with ESMO recommendations should be drawn up to help guide the administration of proper drug treatment options and their uniform use across the country.
- Patient access to clinical trials should be facilitated by better coordination of cancer care.

Patient perspective

- Measures to shorten the time from first symptoms until diagnosis should be a priority. Regional differences also need to be addressed.

- Access to immunotherapy should be guaranteed at all hospitals and not just the main university centers.
- Procedures to enroll patients in clinical trials where they can receive new drug treatment options need to be improved.

5.2.12 United Kingdom

UNITED KINGDOM – Recommendations (based on survey answers)

Agreeing views

- Shorten time to treatment through faster patient pathways, in particular through:
  - reducing turnaround times for pathology and genomic testing through better infrastructure
  - improving intra-hospital coordination
  - recruiting additional human resources
- Improve the general infrastructure at hospitals (hospital beds, outpatient care places, etc.) to address capacity shortages
- Support continuing medical education of lung cancer specialists to keep them up to date with medical information

Additional views - Clinical perspective

- Broaden the eligibility criteria for drug treatment
- Ensure more up-to-date clinical guidelines
- Improve patient attitudes towards receiving treatment
- Accelerate local reimbursement to improve the availability of modern cancer drugs
- Increase the financial resources

Additional views - Industry perspective

- Address hesitancy amongst Black, Asian, and Minority Ethnic (BAME) communities in seeking care resulting in late presentation to primary care
- Accelerate referral to specialist care upon first symptoms
- Obtain evidence of drug effectiveness in less evident groups (elderly population, ECOG PS>2)
- Improve efficiency of patient pathways in terms of reducing inputs required

UNITED KINGDOM – Recommendations (based on local workshop)

Clinical perspective

- Early diagnosis needs to be improved. Raising awareness of lung cancer symptoms among GPs is important.
- Efforts to help meet already established targets on the time from GP referral to initial treatment need to be taken. Improving access to and accelerating molecular testing as well as addressing shortages in the diagnostics-related health care workforce are of particular importance.
- General shortages in the health care workforce need to be addressed.
- Treatment recommendations for patients with ECOG PS 2 need to be reviewed. The national lung cancer audit has only established a 70%-target of patients with ECOG PS 0–1 receiving systemic therapy.
- MDTs should review their approach to offering systemic therapy to groups such as older patients and patients with comorbidities. This also requires improved continuing medical education.
- MDTs should review how they explain the risks and benefits of treatment to patients and their relatives. Improved patient information could help to reduce the number of patients refusing recommended treatment.
- The large regional variations in treatment rates across NHS trusts need to be evaluated. Actions to reduce variations need to be taken.

5.3 Key points

As there are many barriers to achieving high drug treatment rates and to using modern drug treatment options in every country, there are many ways to improve the situation. Many recommendations for improvement are also intertwined, requiring concerted action. The following general recommendations apply to most countries.

Low treatment rates could mainly be improved by:

- **Earlier diagnosis**: Improve the awareness of lung cancer symptoms among patients and primary care physicians coupled with rapid referral to diagnostic services as well as the introduction of lung cancer screening
- **Faster time to treatment upon diagnosis**:
    - Introduce rapid care pathways with clearly defined steps and timelines to help avoid unnecessary delays in the diagnostic process
    - Improve the infrastructure to perform diagnostic testing
    - Recruit and train scarce staff categories (especially pathologists)
    - Reimburse immunohistochemistry and molecular testing for all patients
- **Broadening and harmonizing the eligibility criteria for drug treatment**: Review national clinical guidelines and clinical practices and/or reimbursement guidelines in view of European clinical guidelines and the situation in well-performing countries, in particular regarding patients with fair functional status (ECOG PS 2) and patients diagnosed with stage IIIB and IIIC
- **Obtaining evidence of drug effectiveness in less evident groups:** Conduct real-world studies to assess the benefit of modern drug treatment options in the elderly patient population and in patients with ECOG PS 2 and ECOG PS 3–4, and then an international scientific organization (such as ESMO) should publish recommendations next to existing recommendations from randomized clinical trials
- **Convincing patients of the benefits of receiving modern drug treatment options:** Explain the clinical benefits of newer treatment options introduced since 2015 over previous standard of care, while respecting patient choice
- **Improving the general capacity of lung cancer care:** Recruit additional medical staff and improve the infrastructure of hospitals (hospital beds, outpatient care places, etc.)

The use of outdated treatment options could mainly be improved by:

- **Faster local reimbursement of new drugs which are recommended as standard-of-care**: Prioritize drugs with substantial clinical benefits in the reimbursement process
- **Higher public drug budgets**: Increase the budget to facilitate faster local reimbursement and to remove access restrictions to already reimbursed drugs
- **Greater resources to improve testing capacity**: Modernize testing infrastructure (e.g., switch to NGS testing) and recruit and train scarce clinical staff categories (e.g., pathologists)
- **Ensuring continuing medical education**: Regularly train all relevant medical staff at all treating hospitals across the country

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Appendix

A1. Patient numbers, staging, histology

Table A1: Lung cancer incidence (in absolute numbers)

	2012	2013	2014	2015	2016	2017	2018	2019
Belgium (19)	8,142	8,196	8,451	8,386	8,189	8,472	8,815	8,874
Bulgaria (154)	4,064	4,160	3,811	3,801	3,722	3,581	3,683*	3,649*
Finland (158)	2,505	2,693	2,740	2,797	2,883	2,810	2,749	2,908*
Greece‡ (15, 159-161)	7,217	7,625	7,869	8,104	8,216	8,424	8,415	8,411
Hungary§ (16)	9,111	9,021	9,143	9,186	9,205	9,117*	9,113*	9,116*
Ireland (162, 163)	2,376	2,454	2,453	2,542	2,550	2,671	2,750	2,750
Netherlands (164)	12,115	12,424	12,421	13,322	13,353	13,359	14,102	14,176
Norway (155)	2,902	2,856	3,019	3,035	3,080	3,214	3,351	3,320
Poland^ (161, 165)	25,574	25,975	25,344	26,110	26,417	24,843	25,480*	25,697*
Portugal° (15, 159, 160)	4,190	4,372	4,555	4,737	4,919	5,102	5,284	5,350
Romania^ (161, 166)	11,204	11,443	11,140	11,400	11,359	10,925	10,834	10,446
United Kingdom† (167)	44,443	44,783	45,304	45,593	46,588	46,888	46,609	48,060*

Notes: * Extrapolated number based on trend in national crude rates and on population statistics from Eurostat since 2010 (168). ǂ Incidence numbers were estimated based national mortality numbers sourced from Eurostat and applying the I/M ratio from Globocan estimates for 2012, 2018, 2020 (and interpolations for the remaining years), as raw Globocan estimates seemed imprecise (notably for 2018). § Incidence numbers were estimated based on incidence numbers from the NHIF database and adjusted upwards by a constant factor based on the difference in mortality rates in the NHIF database and Globocan. ^ Incidence numbers were estimated based on national mortality numbers by applying the I/M ratio from Bulgaria, as national incidence numbers from public sources were reported to be lower than mortality numbers. ° Interpolated numbers based on Globocan estimates for 2012, 2018, and 2020. † UK numbers are based on crude rates for England and population numbers for the UK from Eurostat (168).

The COVID-19 pandemic affected lung cancer patients in different ways (169). One effect was that patients could have remained undiagnosed, because people with symptoms did not dare to seek care, or because symptoms were not recognized early enough in primary care because they resembled COVID-19 symptoms, or because of delays in referrals from primary care to specialized care caused by shortages in the capacity of health care services. Another effect was that patients who had already been diagnosed with lung cancer before the pandemic did not attend follow-up visits for treatment due to fears of contracting COVID-19, or they did not receive treatment because of shortages in the capacity of health care services.

The COVID-19 pandemic affected countries in Europe differently in terms of patient numbers and ensuring capacity shortages of health care services as well as lockdowns. Table A2 shows estimates of how the pandemic affected lung cancer patients in 2020 compared to 2019. These estimates refer to newly diagnosed patients only. Note that the % reductions might be slightly overestimated[26], because of shifts in the stage distribution of newly diagnosed cases from early stages towards more

[26] This overestimation might be somewhat balanced by the fact that the % reductions were only applied to newly diagnosed cases and not also to recurrent patients and progressing patients in the final calculations, which would partly capture the effect of treatment delays of existing patients.

advanced stages of lung cancer, which might have been caused by delays in the diagnosis because of the COVID-19 pandemic. Figure A1 shows indeed that the decrease in newly diagnosed patient numbers with stage IV (-3.7% in 2020 compared to 2019) was lower than the overall decrease in newly diagnosed patient numbers with any stage (-5.8%) in England.

Table A2: Estimates of the effect of the COVID-19 pandemic on lung cancer patients

	Change in lung cancer patient numbers between 2019 and 2020	Estimated lung cancer incidence in 2020	Source
Belgium	2% fewer lung cancer diagnoses (based on a comparison January-December 2020 relative to January-December 2019)	8,697	Belgian Cancer Registry (170)
Bulgaria	(same as Romania)	3,411	No local data identified
Finland	3.0% fewer lung cancer diagnoses (based on diagnoses of all cancers in March-June 2020 compared to expected diagnoses) ^	2,821	Finnish Cancer Registry (171)
Greece	(same as Portugal)	7,797	No local data identified
Hungary	15% fewer lung cancer diagnoses in 2020 compared to 2019	7,749	Expert opinion
Ireland	approximately 5% fewer lung cancer diagnoses in 2020 compared to 2019	2,613	Royal College of Physicians of Ireland (172)
Netherlands	1.9% fewer lung cancer diagnoses (based on 14,176 estimated diagnoses in 2019 and 13,910 in 2020)	13,910	Netherlands Comprehensive Cancer Organisation (164)
Norway	9.6% fewer lung cancer diagnoses (based on 16% fewer lung cancer diagnoses in March-September 2020 compared to March-September 2019) *	3,001	Cancer Registry of Norway (173)
Poland	14.5% fewer lung cancer diagnoses (DILO cards issued) in 2020 compared to 2019	21,971	Maria Skłodowska-Curie Institute of Oncology (174)
Portugal	7.3% fewer lung cancer diagnoses (based on 19.6% fewer lung cancer diagnoses in March-June 2020 compared to March-June 2019) *	4,959	Portuguese Oncology Institute of Porto (175)
Romania	6.5% fewer lung cancer diagnoses (based on 13.0% fewer diagnoses of all cancers in 2020 than in 2019 - 51,831 vs. 59,606 new cases) °	9,767	National Center for Statistics and Informatics in Public Health (176)
United Kingdom	5.8% fewer lung cancer diagnoses (from 34,066 in 2019 to 32,105 in 2020) in England	45,272	Public Health England (177)

Notes: * Norway + Portugal: A 0% change in January and February and an average -1.0% decrease in October to December (-1.6% in July to December) was assumed based on monthly data from England. ^ Finland: Data for all cancers for March to June were compared to corresponding data from England, and a relative difference in the size of the decrease of approximately 0.5 in favor of Finland was observed. This relative difference was applied to the changes in diagnoses in England in the remaining months of 2020, while a 0% change was assumed for January and February. This yielded an estimated decrease in diagnoses of 5.9% in Finland in 2020. Based on data from England, the annual decrease in diagnoses for lung cancer (5.8%) was half as large as the decrease in diagnoses of all cancers (11.5%). Applying this ratio to Finland yields an estimated decrease in lung cancer diagnoses of 3.0%. Note that the Finnish number might also be slightly overestimated because the decrease in diagnoses was compared to the expected diagnoses and not the diagnoses from 2019 in the original source. ° Romania: Lung cancer diagnoses were estimated from national data for all cancers combined with the relative difference in lung cancer diagnoses vs. all cancer diagnoses in England.

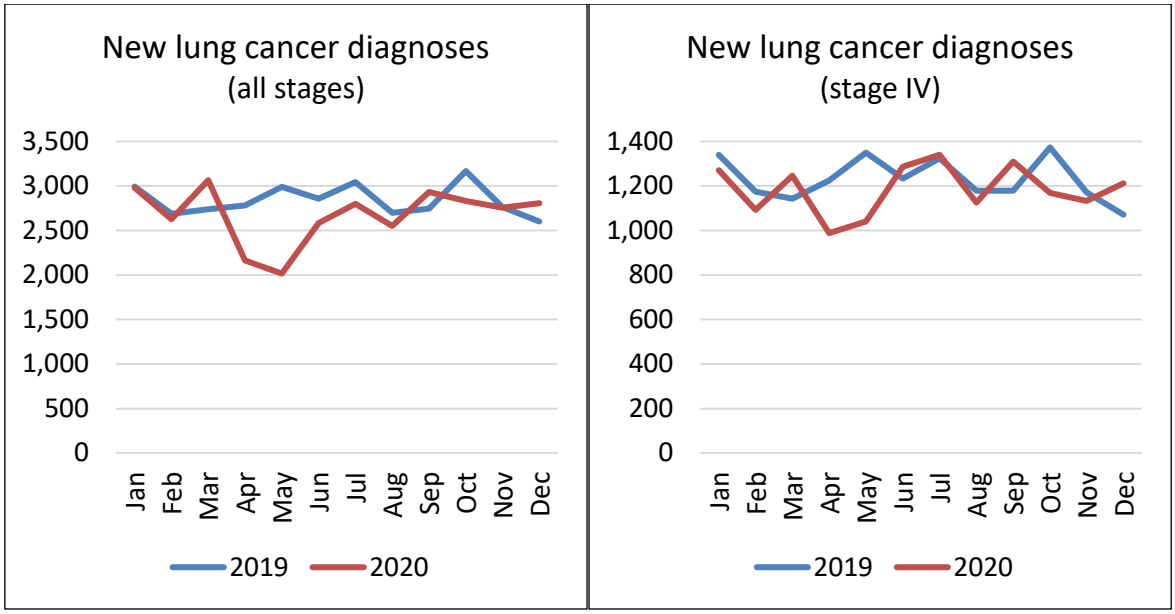

Figure A1: Number of newly diagnosed lung cancer cases by stage in England
Source: Public Health England (177).

Table A3: Lung cancer mortality (in absolute numbers)

	2012	2013	2014	2015	2016	2017	2018	2019
Belgium (178)	6,303	6,479	6,527	6,272	6,298	5,805	5,859	5,780*
Bulgaria (154)	3,594	3,624	3,485	3,452	3,355	3,362	3,425*	3,419*
Finland (158)	2,165	2,224	2,154	2,235	2,276	2,283	2,286	2,288*
Greece (161)	6,745	6,991	7,080	7,158	7,127	7,178	7,046	7,117
Hungary (16)	6,208	6,154	6,283	6,273	6,465	6,483*	6,562*	6,646*
Ireland (179)	1,801	1,830	1,932	1,827	1,911	1,911	1,819	1,942*
Netherlands (164)	10,322	10,289	10,357	10,432	10,688	10,396	10,374	10,233*
Norway (155)	2,185	2,162	2,158	2,175	2,234	2,138	2,201	2,126
Poland (165)	22,616	22,628	23,176	23,713	23,812	23,324	23,695	24,083*
Portugal (180)	3,675	4,010	3,937	4,023	4,085	4,240	4,317	4,405
Romania (161, 166)	9,908	9,969	10,187	10,353	10,239	10,257	10,075	9,790
United Kingdom† (167)	33,712	33,966	34,302	33,960	33,916	33,454	32,833	33,407*

Notes: * Extrapolated number based on trend in national crude rates and on population statistics from Eurostat (168). † UK numbers are based on crude rates for England and population numbers for the UK from Eurostat (168).

Table A4: Lung cancer - histological groups

	NSCLC	SCLC
Belgium (19)	85%	15%
Bulgaria (154)	85%	15%
Finland (181)	87.5%	12.5%
Greece	85%*	15%*
Hungary (20)	85%	15%
Ireland (182)	80%	20%
Netherlands (164)	85%	15%
Norway (183)	84%	16%
Poland	85%*	15%*
Portugal (184)	87%	13%
Romania	85%*	15%*
United Kingdom (135)	90%	10%

Notes: Cases with unknown histology were proportionally allocated to the two types. * For countries without country-specific information 85% for NSCLC and 15% for SCLC was assumed based on the most cited distribution for Western countries (185).

Table A5: NSCLC - stage distribution

	Stage I	Stage II	Stage IIIA	Stage IIIB/C	Stage IV
Belgium (19)	23%	9%	10%	12%	47%
Bulgaria (154)	9%	10%	16%*	17%*	49%
Finland (186)	16%	12%	10%*	12%*	50%
Greece (185)	30%			70%	
Hungary (187)	18%	11%	13%	13%	44%
Ireland (163)	20%	10%	11%*	13%*	46%
Netherlands (136)	22%	9%	10%*	11%*	48%
Norway (183)	28%	8%	10%	10%	43%
Poland (188)	13%		12%	15%	60%
Portugal (138)	34%			10%	56%
Romania (189)	5%	6%	17%*	19%*	53%
United Kingdom (135)	21%	8%	10%	12%	49%

Notes: Numbers do not sum to 100% due to rounding. Cases with unknown stage were proportionally allocated to all stages. Numbers refer in some cases to lung cancer rather than NSCLC in absence of more detailed data. * Share was only available for stage III and was split into sub-stages A and B/C based on the average relative share observed in Belgium, Hungary, Norway, Poland, UK. For Greece, a widely cited distribution for Western countries was assumed to be representative (185).

Table A6: NSCLC - share of mutations and PD-L1 expression

	EGFR+	ALK+	ROS1+	BRAF+	NTRK+	PD-L1+
Belgium	13%*	4.5%*	1.5%*	3.0%*	0.3%*	66% (19)
Bulgaria	13%*	4.5%*	1.5%*	3.0%*	0.3%*	52%*
Finland	13%*	2.3% (190)	1.5%*	3.0%*	0.3%*	65% (186)
Greece	10.6% (191)	3.7% (191)	1.5%*	2.5% (191)	0.3%*	60% (192)
Hungary	13%*	4.5%*	1.5%*	3.0%*	0.3%*	52%*
Ireland	13%*	4.5%*	1.5%*	3.0%*	0.3%*	51.5% (193)
Netherlands	13%*	4.5%*	1.5%*	3.0%*	0.3%*	56% (194)
Norway	11.6% (195)	4.5%*	1.5%*	1.7% (196)	0.3%*	52%*
Poland	11.8% (188)	4.5%*	1.5%*	3.0%*	0.3%*	52%*
Portugal	18.2% (148)	4.5% (148)	1.5%*	3.0%*	0.3%*	52%*
Romania	13%*	4.5%*	1.5%*	3.0%*	0.3%*	52%*
United Kingdom	14.2% (135)	4.5%*	1.5%*	3.0%*	0.3%*	52%*

Notes: * Share based on overview studies: Studies for EGFR+ suggest 9-17% (197-200); studies for ALK+ suggest 2-7% (94, 95), studies for ROS1+ suggest 1-2% (101), studies for BRAF+ suggests 1.5-3.5% (106), 1-4% (108), and 3.5-4% (201); studies for NTRK+ suggest 0.3% in European patients (202), real-world studies for PD-L1 TPS≥1% suggest 52% in Europe (84) compared to 67% in three Keynote trials (203).

A2. Dosage of drugs

Table A7: Dosage of drugs used in NSCLC

Active substance	ATC code	Trade name of original product	Dosage	Dosage per month (in mg)
Afatinib	L01XE13	Gilotrif	40 mg qDay	1,200
Alectinib	L01XE36	Alecensa	600 mg BID	36,000
Atezolizumab	L01XC32	Tecentriq	840 mg q2Weeks or 1200 mg q3Weeks	1,800
Bevacizumab	L01XC07	Avastin	15 mg/kg q3Weeks	1,607
Brigatinib	L01XE43	Alunbrig	180 mg qDay*	5,400
Carboplatin	L01XA02	Paraplatin	360 mg/m² q4Weeks	684
Ceritinib	L01XE28	Zykadia	450 mg qDay	13,500
Cisplatin	L01XA01	Platinol	100 mg/m² q4Weeks	190
Crizotinib	L01XE16	Xalkori	250 mg BID	15,000
Dabrafenib	L01XE23	Tafinlar	150 mg BID	9,000
Dacomitinib	L01XE47	Vizimpro	45 mg qDay	1,350
Docetaxel	L01CD02	Taxotere	75 mg/m2 q3Weeks	204
Durvalumab	L01XC28	Imfinzi	10 mg/kg IV q2Weeks	1,607
Entrectinib	L01XE56	Rozlytrek	600 mg qDay	18,000
Erlotinib	L01XE03	Tarceva	150 mg qDay	4,500
Gefitinib	L01XE02	Iressa	250 mg qDay	7,500
Gemcitabine	L01BC05	Gemzar	1000 mg/m² on days 1, 8, and 15 of each 28-day cycle	6,107
Larotrectinib	L01XE53	Vitrakvi	100 mg BID	6,000
Lorlatinib	L01XE44	Lorviqua	100 mg qDay	3,000
Necitumumab	L01XC22	Portrazza	800 mg on days 1 and 8 of each 3-week cycle	2,286
Nintedanib	L01EX09	Vargatef	200 mg BID on days 2-21 of each 21-day cycle	11,429
Nivolumab	L01XC17	Opdivo	240 mg q2Weeks or 480 mg q4Weeks	514
Osimertinib	L01XE35	Tagrisso	80 mg qDay	2,400
Paclitaxel	L01CD01	Taxol	135 mg/m² q3Weeks	366
Paclitaxel-nab	L01CD01	Abraxane	100 mg/m² on days 1, 8, and 15 of each 21-day cycle	814
Pembrolizumab	L01XC18	Keytruda	200 mg q3Weeks or 400 mg q6Weeks	286
Pemetrexed	L01BA04	Alimta	500 mg/m² on day 1 of each 21-day cycle	1,357
Ramucirumab	L01XC21	Cyramza	10 mg/kg on day 1 of each 21-day cycle	1,071
Trametinib	L01XE25	Mekinist	2 mg qDay	60
Vinorelbine	L01CA04	Navelbine	30 mg/m² qWeek (mono) or 25 mg/m² on days 1, 8, 15, and 22 of a 28-day cycle (combo)	224 °

Notes: A body surface of 1.9 m² and a body weight of 75 kg were used. 4.3 weeks per month and 30 days per month were assumed. mg=milligram. q=every. BID=twice per day. * Actual dosage is 90 mg qDay for the first 7 days and then 180 mg qDay if the initial 90 mg/day were tolerated. ° Average of monotherapy and combination therapy. Source for dosage: Medscape (143).

A3. Treatment length by drug indication

Table A8: Treatment length by NSCLC drug indication

Active substance	Indication (short name)	EMA approval date	Treatment duration (in months)
Afatinib	1L, mono, locally advanced/metastatic, EGFR+	25-Sep-2013	11.1
Afatinib	2L, mono, locally advanced/metastatic SQ	31-Mar-2016	2.4
Alectinib	2L after crizotinib, mono, advanced, ALK+	16-Feb-2017	9.6
Alectinib	1L, mono, advanced, ALK+	18-Dec-2017	30.0
Atezolizumab	2L, mono, locally advanced/metastatic**	21-Sep-2017	2.8
Atezolizumab	1L, combo with bevacizumab, paclitaxel & carboplatin, metastatic NSQ**	5-Mar-2019	8.3
Atezolizumab	1L, combo with nab-paclitaxel & carboplatin, metastatic NSQ, EGFR- & ALK-	25-Jul-2019	7.0
Bevacizumab	1L, combo with Pt-chemo, advanced/ metastatic/recurrent NSQ	21-Aug-2007	6.2
Bevacizumab	1L, combo with erlotinib, advanced/ metastatic/recurrent NSQ, EGFR+	2-Jun-2016	16.0
Brigatinib	2L after crizotinib, mono, advanced, ALK+	22-Nov-2018	12.9
Brigatinib	1L, mono, advanced, ALK+	1-Apr-2020	26.7
Carboplatin	1L, combo with other chemotherapies, locally advanced/metastatic/recurrent	*	2.8 °
Ceritinib	2L after crizotinib, mono, advanced, ALK+	6-May-2015	5.4
Ceritinib	1L, mono, advanced, ALK+	23-Jun-2017	16.6
Cisplatin	1L, combo with other chemotherapies, locally advanced/metastatic/recurrent	*	2.8 °
Crizotinib	2L, mono, advanced, ALK+	23-Oct-2012	7.7
Crizotinib	1L, mono, advanced, ALK+	23-Nov-2015	10.9
Crizotinib	1L, mono, advanced, ROS1+	25-Aug-2016	19.3
Dabrafenib	1L, combo with trametinib, advanced, BRAF V600+	29-Mar-2017	16.6
Dacomitinib	1L, mono, locally advanced/metastatic, EGFR+	2-Apr-2019	14.7
Docetaxel	2L, mono, locally advanced/metastatic	20-Jan-2000	2.8 °
Docetaxel	1L, combo with cisplatin, locally advanced/metastatic	9-Jan-2003	2.8 °
Durvalumab	2L (maintenance after chemoradiotherapy), mono, unresectable locally advanced, PD-L1≥1%	21-Sep-2018	9.3
Entrectinib	1L, mono, locally advanced/metastatic, NTRK+	31-Jul-2020	11.2
Entrectinib	1L, mono, advanced, ROS1+	31-Jul-2020	16.8
Erlotinib	2L, mono, locally advanced/metastatic	19-Sep-2005	2.2
Erlotinib	2L, mono, maintenance, locally advanced/metastatic	27-Apr-2010	2.8
Erlotinib	1L, mono, locally advanced/metastatic, EGFR+	24-Aug-2011	9.7
Erlotinib	2L, mono, switch maintenance, locally advanced/metastatic, EGFR+	25-Jan-2016	10.3

Erlotinib	2L, mono, locally advanced/metastatic, EGFR- if no other option	11-Dec-2017	2.2
Gefitinib	1L, mono, locally advanced/metastatic, EGFR+	24-Jun-2009	9.6
Gemcitabine	1L, combo with carboplatin or cisplatin, locally advanced/metastatic/recurrent	*	3.7 °
Larotrectinib	1L, mono, locally advanced/metastatic, NTRK+	19-Sep-2019	11.2
Lorlatinib	2L after alectinib or ceritinib, mono, advanced, ALK+	6-May-2019	6.9
Lorlatinib	3L after crizotinib and one other ALK TKI, mono, advanced, ALK+	6-May-2019	5.5
Necitumumab	1L, combo with gemcitabine & cisplatin, locally advanced/metastatic SQ, EGFR+	15-Feb-2016	5.7
Nintedanib	2L, combo with docetaxel, locally advanced/metastatic AC	21-Nov-2014	3.4
Nivolumab	2L, mono, locally advanced/metastatic SQ	28-Oct-2015	3.5
Nivolumab	2L, mono, locally advanced/metastatic	4-Apr-2016	2.9
Nivolumab	1L, combo with ipilimumab & Pt-chemo, metastatic, EGFR- & ALK-	5-Nov-2020	6.7
Osimertinib	1L & 2L, mono, locally advanced/metastatic, EGFR T790M+	2-Feb-2016	10.1
Osimertinib	1L, mono, locally advanced/metastatic, EGFR+	7-Jun-2018	18.9
Paclitaxel	1L, combo with carboplatin or cisplatin, unresectable and/or no radiotherapy possible	*	2.8 °
Paclitaxel-nab	1L, combo with carboplatin, unresectable and/or no radiotherapy possible	26-Feb-2015	5.2 ^
Pembrolizumab	2L, mono, locally advanced/metastatic, PD-L1≥1%**	29-Jul-2016	4.0
Pembrolizumab	1L, mono, metastatic, PD-L1≥50%, EGFR- & ALK-	27-Jan-2017	10.3
Pembrolizumab	1L, combo with pemetrexed & Pt-chemo, metastatic NSQ, EGFR- & ALK-	4-Sep-2018	9.0
Pembrolizumab	1L, combo with carboplatin & either paclitaxel or nab-paclitaxel, metastatic SQ	11-Mar-2019	6.4
Pemetrexed	2L, mono, locally advanced/metastatic	20-Sep-2004	2.9
Pemetrexed	1L, combo with cisplatin, locally advanced/metastatic NSQ	8-Apr-2008	4.4 ^^
Pemetrexed	2L, mono, locally advanced/metastatic NSQ	8-Apr-2008	2.7
Pemetrexed	2L after Pt-based chemo, mono, maintenance, locally advanced/metastatic NSQ	2-Jul-2009	4.3
Pemetrexed	2L, mono, maintenance, locally advanced/metastatic NSQ	24-Oct-2011	4.1
Ramucirumab	2L, combo with docetaxel, locally advanced/metastatic	25-Jan-2016	4.5
Ramucirumab	1L, combo with erlotinib, metastatic, EGFR+	23-Jan-2020	19.4
Trametinib	1L, combo with dabrafenib, advanced, BRAF V600+	27-Mar-2017	16.6
Vinorelbine	1L, combo with cisplatin, locally advanced/metastatic/recurrent	*	3.7 °

Notes: 1L=first line; 2L=second line; mono=monotherapy, combo=combination therapy, AC=adenocarcinoma, NSQ=non-squamous cell, SQ=squamous cell. Treatment duration is based on the median progression-free survival (PFS) for drugs administered until disease progression or unacceptable toxicity and based on the median number of administered cycles for drugs administered for a limited number of treatment cycles. *Older non-EMA-approved drugs. ° Assuming four cycles of 3-week or 4-week long cycles of chemotherapy. ^ Average of median PFS observed in control arms in IMpower130 and Keynote-407 trials. ^^ Based on the control arm in the Keynote-189 trial that also included maintenance therapy. **Also includes 2L in EGFR+ and ALK+ after failure of appropriate TKIs.
Source: EMA dates (85), information on treatment duration comes from key clinical trials used for EMA approval and summarized in the European public assessment reports (EPARs).

A4. Older cancer drugs

Table A9: Older cancer drugs with use in NSCLC and other cancer types

Gemcitabine	Paclitaxel	Vinorelbine
NSCLC, 1L	NSCLC, 1L	NSCLC, 1L
Bladder, 1L	Breast, 1L	Breast, 2L
Breast, 2L	Cervix, 1L	Cervix, 2L
Cervix, 2L	Corpus uteri, 1L	Nasopharynx, 2L
Nasopharynx, 1L*	Esophagus, 1L	
Ovary, 2L	Kaposi sarcoma, 2L	
Pancreas, 1L	Nasopharynx, 2L	
	Ovary, 1L	
	Stomach, 2L	
	Testis, 2L	

Notes: 1L= first-line treatment, 2L=second-line treatment. Carboplatin and cisplatin were not considered, as they were excluded in the final analysis to avoid double counting of treated patients. * Gemcitabine in first line nasopharynx was only assumed to be used since 2018 in all countries.

A5. Scale factor

Table A10: Treatment duration used for weighting of the scale factor for drugs used in other indications than NSCLC

Indication	Drugs	Treatment duration (in months)
	Chemotherapy drugs	
NSCLC, 2L	Docetaxel*	2.8
Breast, 1L	Docetaxel	5.6
Breast, 2L	Docetaxel	4.2
Head & neck, 1L	Docetaxel	2.1
Prostate, 1L	Docetaxel	4.2
Stomach, 1L	Docetaxel	4.2
NSCLC, 1L	Gemcitabine	3.7
Bladder, 1L	Gemcitabine	5.6
Breast, 2L	Gemcitabine	4.2
Cervix, 2L	Gemcitabine	2.1
Nasopharynx, 1L	Gemcitabine	4.2
Ovary, 2L	Gemcitabine	4.2
Pancreas, 1L	Gemcitabine	3.6
NSCLC, 1L	Paclitaxel	2.8
Breast, 1L	Paclitaxel	5.1
Cervix, 1L	Paclitaxel	4.2
Corpus uteri, 1L	Paclitaxel	4.2
Esophagus, 1L	Paclitaxel	1.2

Kaposi, 2L	Paclitaxel	5.1
Nasopharynx, 2L	Paclitaxel	2.8
Ovary, 1L	Paclitaxel	4.2
Stomach, 2L	Paclitaxel	2.8
Testis, 2L	Paclitaxel	2.8
NSCLC, 1L	Paclitaxel-nab	5.2
Breast, 2L	Paclitaxel-nab	5.3
Pancreas, 1L	Paclitaxel-nab	5.5
NSCLC, 1L	Pemetrexed	4.4
Mesothelioma, 1L	Pemetrexed	5.7
NSCLC, 1L	Vinorelbine	3.7
Breast, 2L	Vinorelbine	2.8
Cervix, 2L	Vinorelbine	2.1
Nasopharynx, 2L	Vinorelbine	2.8
	Immunotherapy drugs	
NSCLC, 1L	Atezolizumab	7.7
NSCLC, 2L	Atezolizumab	2.8
Bladder, 2L	Atezolizumab	2.1
Breast, 1L	Atezolizumab	7.5
Liver, 1L	Atezolizumab	6.8
Small-cell lung, 1L	Atezolizumab	5.2
NSCLC, 2L	Durvalumab	9.3
Small-cell lung, 1L	Durvalumab	5.1
NSCLC, 1L	Nivolumab	6.7
NSCLC, 2L	Nivolumab	2.9
Bladder, 2L	Nivolumab	1.9
Esophagus, 2L	Nivolumab	1.7
Head & neck, 2L	Nivolumab	2.1
Hodgkin, 2L	Nivolumab	14.7
Kidney, 1L	Nivolumab	12.2
Kidney, 2L	Nivolumab	4.6
Melanoma, 1L	Nivolumab	11.8
NSCLC, 1L	Pembrolizumab	9.2
NSCLC, 2L	Pembrolizumab	4.0
Bladder, 1L	Pembrolizumab	2.2
Bladder, 2L	Pembrolizumab	2.1
Head & neck, 1L	Pembrolizumab	6.7
Head & neck, 2L	Pembrolizumab	4.0
Hodgkin, 2L	Pembrolizumab	13.7
Kidney, 1L	Pembrolizumab	15.1
Melanoma, 1L	Pembrolizumab	14.5
	Targeted therapy drugs	
NSCLC, 1L	Dabrafenib/trametinib	16.6
Melanoma, 1L	Dabrafenib/trametinib	11.7
NSCLC, 1L	Erlotinib	9.7
Pancreas, 1L	Erlotinib	3.8

Notes: 1L = first-line therapy, 2L = second-line therapy. The treatment duration is either based on the median PFS or on the median number of administered cycles for drugs not given until disease progression or unacceptable toxicity. * For docetaxel only use in 2L NSCLC is assumed.

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