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# Treatment patterns and survival outcomes for patients with non-small cell lung cancer in the United Kingdom in the pre-immunology era: a REAL-Oncology database analysis from the I-O Optimise initiative



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# Treatment patterns and survival outcomes for patients with non-small cell lung cancer in the United Kingdom in the pre-immunology era: a REAL-Oncology database analysis from the I-O Optimise initiative

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**ABSTRACT *[300/300 words]***

**Objectives**

To report characteristics, treatment and overall survival (OS) trends, by stage and pathology, of patients diagnosed with non-small cell lung cancer (NSCLC) at Leeds Teaching Hospital NHS Trust in 2007–2018.

**Design**

Retrospective cohort study based on electronic medical records.

**Setting**

Large NHS university hospital in Leeds.

**Participants**

3739 adult patients diagnosed with incident NSCLC from January 2007–August 2017, followed until March 2018.

**Main outcome measures**

Patient characteristics at diagnosis, treatment patterns, OS.

**Results**

34.3% of patients with NSCLC were clinically diagnosed (without pathological confirmation). Among patients with known pathology, 45.2% had non-squamous cell carcinoma (NSQ); 33.3% had squamous cell carcinoma (SQ). The proportion of patients diagnosed at stage I increased (16.4%–27.7% in 2010–2017); those diagnosed at stage IV decreased (57.0%–39.1%). Surgery was the most common initial treatment for patients with pathologically confirmed stage I NSCLC. Use of radiotherapy alone increased over time in patients with clinically diagnosed stage I NSCLC (39.1%–60.3%); chemoradiation increased in patients with stage IIIA NSQ (21.6%–33.3%) and SQ (24.2%–31.9%). Initial treatment with systemic

anticancer therapy (SACT) increased in patients with stage IIIB–IV NSQ (49.0%–67.5%); the proportion of untreated patients decreased (30.6%–15.0%). Median OS improved for patients diagnosed with stage I NSQ and SQ and stage IIIA NSQ over time. Median OS for patients with stage IIIB–IV NSQ and SQ remained stable; <10% were alive 3 years after diagnosis. Median OS for clinically diagnosed stage IIIB–IV patients was 1.2 months in both periods.

**Conclusions**

OS for stage I and IIIA patients improved over time, likely due to increased stereotactic ablative radiation, surgery (stage I) and chemoradiation (stage IIIA) use. Conversely, OS outcomes remained poor for stage IIIB–IV patients despite increasing use of SACT for NSQ. Many patients with advanced-stage disease remained untreated.

**Article summary**

Strengths and limitations of this study

- This retrospective analysis of the REAL-Oncology database analysed the characteristics, treatment and overall survival trends for patients diagnosed with non-small cell lung cancer (NSCLC) over a 10-year period in a large regional hospital in the United Kingdom
- Data on prescribed systemic anticancer therapy, and pathology and radiology records were extracted from electronic medical records for adult patients diagnosed with incident NSCLC between 2007 and 2017 based on confirmed pathology or clinical data
- These data reflect outcomes and trends for a single site in the United Kingdom; however, the REAL-Oncology study represents an unselected population, which is relevant to real-world practice and enables long-term (>10 years) analyses across numerous subgroups
- This analysis included patients with a clinical diagnosis of NSCLC who, despite representing a large proportion of patients with NSCLC, are often not captured in real-world studies

## INTRODUCTION

In the United Kingdom, lung cancer is the third most common type of cancer and the leading cause of cancer death.[1] Around 85% of patients with lung cancer have non-small cell lung cancer (NSCLC), which consists predominantly of non-squamous cell carcinoma (NSQ) and squamous cell carcinoma (SQ).[2] Early diagnosis of lung cancer can be challenging.[3] Consequently, approximately two-thirds of patients present with advanced or metastatic NSCLC (stage III–IV), for which treatment options are limited and prognosis is poor;[4,5] 5-year survival rates for patients with metastatic disease are less than 5%.[5,6]

Surgery and radiotherapy can be used successfully in patients diagnosed with early-stage NSCLC; adjuvant chemotherapy is also indicated for selected patients who have undergone resection for stage II–III disease and can improve outcomes.[7] For advanced-NSCLC (stage IIIB–IV), chemotherapy with platinum-based agents has long been the standard of care for patients with good performance status (PS), and vascular endothelial growth factor–targeting therapies have been used in the first-line setting in patients with NSQ.[8] However, increased understanding of NSCLC driver mutations, such as those in the epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) genes, has led to the development of targeted therapies, including tyrosine kinase inhibitors (TKIs). These allow for more personalized treatment approaches in selected patients with actionable driver mutations.[8]

The development of immunotherapeutic agents has transformed the NSCLC treatment landscape. Since 2015, immune checkpoint inhibitors (ICIs) targeting the programmed death-1/programmed death ligand 1 axis have been approved in Europe and are now recommended for first- or second-line treatment of patients with metastatic NSCLC.[9] In addition, ongoing clinical trials are investigating neoadjuvant and adjuvant use of ICIs for patients diagnosed at earlier stages of NSCLC.[10-12] As with any new treatment, there is a need to assess how ICIs impact patient survival in real-world clinical practice to help inform future treatment decisions, which requires an understanding of the NSCLC landscape prior to their

availability. Real-world databases include a wealth of information that can be used to complement data from clinical trials and are a valuable source of evidence in a rapidly changing treatment landscape.

We report the characteristics, treatment and overall survival (OS) trends for patients diagnosed with NSCLC at a large teaching hospital in England prior to routine availability of ICIs. This study, based on the REAL-Oncology database, is part of the I-O Optimise program, an ongoing initiative leveraging real-world data sources to provide insights into the evolving landscape of thoracic malignancies, including NSCLC.[13]

## METHODS

### *Study setting*

REAL-Oncology is a research partnership between Leeds Cancer Centre (LCC), the University of Leeds and IQVIA®, using NHS oncology patient data to answer various research questions. LCC is a major NHS cancer centre that serves a metropolitan catchment area of 750 000 people for secondary care and over 5 million for tertiary care.

### *Ethics approval and consent to participate*

This study was completed with UK Health Research Authority approval through the National Institute for Health Research Integrated Research Approvals System. The research was performed in accordance with the Leeds Teaching Hospitals NHS Trust research governance framework; as a noninterventional retrospective descriptive study using existing patient records, the need for ethics approval was waived. The study was performed in accordance with the Declaration of Helsinki.

## *Study design*

Data on prescribed chemotherapy and pathology and radiology records were extracted from electronic medical records (EMRs) at the Leeds Teaching Hospitals NHS Trust. The study included patients aged ≥18 years with an incident diagnosis of NSCLC (International Statistical Classification of Diseases and Related Health Problems, 10th Revision [ICD-10] code for malignant neoplasm of the trachea [C33] or malignant neoplasm of bronchus and lung [C34]) between January 2007 and August 2017 at Leeds Teaching Hospital. All patients diagnosed by the lung multidisciplinary team were included, including those clinically identified solely on the basis of history, clinical examination and computed tomography (CT), and those with confirmed pathology (ie, *International Classification of Diseases for Oncology*, 3rd Edition [ICD-O-3] code for NSCLC histology, online supplementary appendix table S1). Patients were excluded if their first diagnosis of NSCLC was confirmed in another NHS hospital trust, they had missing data on age or sex, their ICD-O-3 morphology codes indicated small cell lung cancer (80413–80459), or they had a concomitant (within 5 years prior to NSCLC diagnosis) primary tumour at time of diagnosis, except for non-metastatic non-melanoma skin cancers or *in situ* or benign tumours. Patients with missing data on tumour, node, metastasis (TNM) classification were also excluded from the present analyses.

The end of follow-up was the date of death or end of study (April 2018). The date of death was confirmed by reconciliation of EMRs with Office for National Statistics death certifications. Patient sociodemographic (age, sex, World Health Organisation PS) and clinical characteristics (TNM stage, tumour pathology) were extracted on/at the nearest date to NSCLC diagnosis (index date). TNM classification at diagnosis was recorded according to the 6th edition of the TNM classification up to 31 December 2009[14]; the 7th edition from 1 January 2010[6]; and the 8th edition from 1 January 2017.[15] Tumour pathology was defined as NSQ (including adenocarcinoma and large cell carcinoma), SQ, NSCLC

not otherwise specified (NOS), “Other” (neuroendocrine carcinoma and other miscellaneous carcinoma) or “Unconfirmed” (clinically diagnosed unknown pathology).

The date of initial treatment was defined as the first instance of lung surgery, radiotherapy or systemic anticancer therapy (SACT) occurring within 6 months of diagnosis, and initial treatment categories were defined using all treatment received within a specified time period following this date (online supplementary appendix table S2). A line of therapy (LoT) was defined as one or more cycles of chemotherapy or continuous oral treatment for targeted agents in patients with incident stage IIIB–IV NSCLC. REAL-Oncology developed an algorithm to determine first and subsequent LoTs, and LoT outputs were clinically validated in reference to each patient cohort (online supplementary appendix table S2).

### *Analyses*

Patient characteristics at diagnosis are described using summary statistics. The evolution of treatment patterns and OS over time were investigated in two sub-cohorts defined by date of diagnosis: January 2007 to December 2012, and January 2013 to August 2017. Therapy received and treatment duration are described by LoT for advanced-stage patients using the same time periods. Time periods for the receipt of initial SACT are based on the date of diagnosis (January 2007–December 2012, and January 2013–August 2017). Time periods for receipt of second LoT are based on the start date for the second LoT over both the study and follow-up period (January 2007–December 2012, and January 2013–April 2018). Survival outcomes were captured through April 2018. OS was estimated using Kaplan–Meier methods. The proportions of patients surviving to 1, 2 or 3 years after the date of diagnosis were estimated and are reported with corresponding two-sided 95% confidence intervals. Differences in OS between time periods were compared using log-rank hypothesis tests.

To comply with patient confidentiality requirements, data outputs relating to groups of fewer than five patients were masked. In some circumstances, data relating to larger patient subgroups were also masked to avoid extrapolation of counts of fewer than five patients.

## Results

### *Patients*

Overall, 4225 patients diagnosed with NSCLC met the REAL-Oncology study eligibility criteria between January 2007 and August 2017. Of these, 486 were excluded because of missing TNM staging information, resulting in an analysis cohort of 3739 patients. Patients had a median (interquartile range [IQR]) age of 73 (65–80) years and were evenly split by sex (table 1). Pathology findings were available for 2458 patients (65.7%), with the remaining 1281 (34.3%) being clinically diagnosed without pathological confirmation. Where pathology was available, NSQ was the most frequent subtype (45.2%), followed by SQ (33.3%), NOS (17.9%) and "Other" NSCLC (3.6%; table 1).

Over the study period, 717 patients (19.2%) were diagnosed with stage I disease, 434 (11.6%) with stage II, and 806 (21.6%) with stage III; almost half of patients (47.7%) were diagnosed with stage IV disease. The proportion of patients diagnosed with stage I disease increased from 16.4% in 2010 to 27.7% in 2017 (figure 1), while diagnoses of stage IIIA and IIIB NSCLC remained stable over time. There was an overall reduction in the proportion of patients diagnosed at stage IV, from 57.0% in 2010 to 39.1% in 2017.

### *Treatments*

Over the study period, 2337 patients (62.5%) received an initial treatment within 6 months after diagnosis. As expected, treatment rates declined with increasing disease stage, from 78.2% for patients

diagnosed with stage I disease to 49.8% for those diagnosed with stage IV. The proportion of patients with early-stage (stage I–IIIA) NSCLC who did not receive treatment decreased over time; 21.2% of patients with stage I–IIIA disease remained untreated 6 months after diagnosis in 2013–2017 compared with 32.3% in 2007–2012 (data not shown). The proportion of patients with stage IV disease remaining untreated decreased among those with NSQ, while no changes were observed among those with SQ (figure 2).

*Initial treatments over time (stages I–IV)*

Figure 2 shows the evolution of initial treatments by TNM stage between 2007–2012 and 2013–2017 in patients with NSQ and SQ and in those who were clinically diagnosed. Over the study period, patients diagnosed with pathologically confirmed stage I disease were most commonly treated with curative surgery alone or, to a lesser extent, curative radiotherapy alone. The proportion receiving surgery alone as initial treatment increased between 2007–2012 and 2013–2017; conversely, the proportion receiving radiotherapy alone decreased. Among patients with clinically diagnosed stage I disease, the proportion receiving radiotherapy increased between 2007–2012 and 2013–2017 (from 39.1% to 60.3%; figure 2).

For patients with pathologically confirmed stage II disease, there was no notable difference in the use of surgery (alone or with adjuvant therapy) between 2007–2012 and 2013–2017. In 2013–2017, among patients with NSQ and SQ, respectively, 37.3% and 29.7% received surgery alone and 21.6% and 17.6% received surgery associated with (neo)adjuvant therapy (mostly adjuvant SACT). Radiotherapy alone was the most common treatment for patients with clinically diagnosed stage II disease, with 30.9% treated in 2007–2012 compared with 45.5% in 2013–2017.

Among the patients diagnosed with pathologically confirmed stage IIIA disease, the proportion receiving SACT plus radiotherapy (chemoradiation) increased to around one-third in 2013–2017. Some differences in the use of surgery were observed according to histology. In 2013–2017, one-third of patients with

NSQ received surgery (surgery alone, 12.3%; surgery associated with adjuvant therapy, 17.5%), and only around 15% of patients with SQ disease received surgery (mostly surgery alone).

For patients diagnosed with stage IIIB or IV NSQ, initial treatment with SACT (with or without radiotherapy) increased between 2007–2012 and 2013–2017, largely as the proportion of untreated patients decreased; it is likely that some patients with stage IIIB disease received chemoradiation with curative intent. Treatment of patients with stage IIIB or IV SQ disease remained similar between the two time periods.

### *Patterns of SACT use in advanced NSCLC (stages IIIB–IV)*

Of the 2119 patients diagnosed with stage IIIB–IV NSCLC during the study period, 648 (30.6%) received a first LoT, 223 (10.5%) received a second LoT and 60 (2.8%) received a third LoT. Similar proportions of patients with stage IIIB–IV NSQ and SQ received a first LoT (45.0% and 45.5%, respectively). Higher proportions of patients with stage IIIB or IV NSQ received second and third LoTs (17.9% and 5.6%, respectively) compared with SQ NSCLC (13.6% and 2.8%, respectively).

The most common first LoT regimens for patients with stage IIIB–IV NSCLC were platinum-based chemotherapy doublets; in 2007–2012, carboplatin plus gemcitabine was the most common (39.9% of treated patients; data not shown); in 2013–2017, carboplatin plus pemetrexed was the most common (28.7% of treated patients; table 2). The proportions of patients with NSQ receiving cisplatin- and pemetrexed-based regimens increased between 2007–2012 and 2013–2017 (table 2).

Among 119 patients with NSQ receiving a second LoT, the most common treatment was a TKI (65.5%); however, use of TKIs in the second line decreased over time. Among 54 patients with SQ receiving a second LoT, the most common treatment was also a TKI (53.7%); use of TKIs in the second line also decreased over time in this sub-cohort, concomitant with an increase in use of platinum-based

chemotherapies. Given the late introduction of ICIs with respect to the study cohort (January 2017), a relatively small proportion of patients with stage IIIB–IV NSQ and SQ received second-line treatment with an ICI in 2013–2018.

*Duration of SACT treatment (stages IIIB–IV)*

For patients with stage IIIB–IV NSCLC who received first-line platinum-based chemotherapy, treatment duration was similar over the analysis period. In 2013–2017, the median (IQR) treatment duration was 2.8 (1.4–3.2) months for patients with NSQ and 2.2 (1.4–2.8) months for patients with SQ.

Among the small number of patients with stage IIIB–IV NSQ who received a TKI in the first line, median treatment durations were consistent over time at around 5 months. For patients with stage IIIB–IV NSCLC who received a second LoT, the median (IQR) treatment duration for those treated in 2013–2018 was 2.5 [1.4–5.4] months for those with NSQ and 2.1 [1.4–2.4] months for those with SQ.

## *Overall survival*

*Overall survival over time (stages I, II and IIIA)*

For patients with stage I NSQ, median (IQR) OS from diagnosis was 55.3 (24.8–98.5) months for those diagnosed in 2007–2012 and was not reached (NR; 34.2 months–NR) for those diagnosed in 2013–2017; median OS increased among patients with stage I SQ (from 37.3 [18.5–66.8] to 51.1 [32.6–NR] months) (figure 3A). Median (IQR) OS for patients with stage I NSCLC without pathological diagnosis increased slightly from 16.7 (5.8–33.1) to 20.9 (8.0–40.3) months between 2007–2012 and 2013–2017, respectively.

Median (IQR) OS for patients with stage II NSQ was 34.3 (10.6–80.0) months for those diagnosed in 2007–2012 and 26.4 (10.2–58.0) months for those diagnosed in 2013–2017; in patients with stage II SQ, the respective median OS was 17.2 (8.6–58.2) and 19.9 (7.2–53.9) months (figure 3B). For patients

without pathological diagnosis and stage II disease, median (IQR) OS increased slightly from 8.9 (2.9–16.8) to 11.3 (5.4–26.9) months, respectively, over the same periods.

Among patients with stage IIIA NSQ, median (IQR) OS increased from 9.9 (6.5–38.6) months for those diagnosed in 2007–2012 to 24.0 (10.6–NR) months for those diagnosed in 2013–2017; median (IQR) OS also increased among patients with stage IIIA SQ (from 10.7 [4.4–21.1] to 14.5 [8.4–36.0] months) (figure 3C). Significant improvement in 1-year OS was observed in patients with NSQ, which increased from 45% (33%–61%) to 74% (63%–87%). Median (IQR) OS among patients with stage IIIA NSCLC without confirmed pathology remained low over the study period at around 5 months.

*Overall survival over time (stage IIIB–IV)*

Median OS and landmark OS rates for patients with stage IIIB–IV NSQ or SQ were similar for those diagnosed in 2007–2012 and 2013–2017, with no notable changes over time (figure 3D). During both periods, less than 10% of patients with stage IIIB–IV NSQ or SQ were alive 3 years after diagnosis. Median OS for clinically diagnosed patients with stage IIIB–IV NSCLC was 1.2 months for both time periods (figure 3D).

## Discussion

These data from the REAL-Oncology database, part of I-O Optimise, provide insight into NSCLC management largely prior to the reimbursement of immunotherapies in the United Kingdom. Over the analysis period (2007–2017, with follow-up to 2018), most patients with NSCLC in this database were diagnosed with advanced disease. This is consistent with the overall proportion of patients with NSCLC and available TNM staging diagnosed in England in 2017, of whom around 50% had stage IV disease,[16] and with real-world evidence across Europe from the same period.[17,18]

Nevertheless, in our analysis, there was an 11.6% increase in the proportion of patients diagnosed with stage I NSCLC between 2010 and 2017. The Cancer Reform Strategy,[19] implemented in England in 2007, aimed to build upon advances made following the introduction of the NHS Cancer Plan in 2000,[19] which was designed to close the survival gap for patients with cancer in England compared with those in countries with similar heathcare systems. The strategy further aimed to improve cancer prevention, early diagnosis and patient management and led to the establishment of the National Cancer Equality initiative (2008)[20] and the National Awareness and Early Diagnosis Initiative (NAEDI)[21] in collaboration with Cancer Research UK (2008).[22] Consequently, the increased proportion of patients diagnosed with stage I NSCLC in the present analysis may partly reflect the impact of these reforms on cancer diagnosis in England during the study period. Notably, the proportion of patients diagnosed with early-stage NSCLC in the REAL-Oncology database was slightly higher than that reported for all lung cancers in the 2017 National Audit for England (20% diagnosed at stage I; 8% at stage II).[16]

At the time of our analysis, no national lung cancer screening programme existed in the United Kingdom. However, a pilot programme originally funded by NAEDI began in Leeds in 2011 with the aim of assessing lung cancer outcomes in response to a range of public health interventions[23]. Consequently, between 2008–2010 and 2013–2015, there was an 80.8% increase in community referrals for chest X-rays and a significant stage-shift in diagnosis, with an 8.8% increase in patients diagnosed at stage I–II and a 9.3% reduction in those diagnosed at stage III–IV[23]. While these results are promising, lack of a concurrent control population over the same period meant that the relative contribution of other factors impacting diagnosis could not be determined. Final results from the NELSON study reported a significant reduction in 10-year mortality from lung cancer among male smokers who received regular CT screening compared with those who did not[24]. Similarly, the large US National Lung Screening Trial reported a 20% decreased risk of death from lung cancer among high-risk individuals screened with CT compared with those screened with radiography[25]. Taken together, these findings support the feasibility

of a UK-wide lung cancer screening programme, which could decrease the number of patients diagnosed with advanced NSCLC. In addition to the impact of screening, transition from the 6th to the 7th Edition of TNM classification for NSCLC in 2010 is likely to have impacted tumour staging at diagnosis.[26] Specifically, in the 7th edition, tumour size cutoffs for the T descriptor were revised, and the importance of pleural effusions and mediastinal invasion for the M descriptor were acknowledged, resulting in the upstaging of some tumours and the downstaging of others[6].

Consistent with National Audit data from England and with real-world evidence from Europe, the largest proportion of patients with available pathological data in the REAL-Oncology database had NSQ, mostly adenocarcinoma.[16,17,27] Our database also allowed the identification of clinically diagnosed patients, who accounted for 34% of the analysis population and tended to be older and have higher PS compared with those with confirmed pathology.[28]

Around 60% of analysed patients received at least one treatment, consistent with the 2017 National Audit (59%) for all lung cancers in England.[29] The initial treatment rate declined sequentially with increasing disease stage, a pattern previously observed in Europe.[17] There was a notable increase in the proportion of patients with stage I NSCLC who received surgery alone, possibly due to the aforementioned pilot program in Leeds during that time. In England and Wales, the proportion of patients undergoing resection for histologically confirmed NSCLC increased from 14% in 2008 to 22% in 2012. This may reflect both improvements in earlier diagnosis and changes in surgical practice.[28,30-32]

The proportion of patients with clinically diagnosed NSCLC receiving radiotherapy alone increased markedly, concomitant with a decrease in the proportion of untreated patients. This may reflect the increased use of stereotactic body radiation therapy as an alternative to surgery for patients with early-stage disease and contraindications for surgery. There was also a notable increase in the use of chemoradiation for patients with stage IIIA NSCLC over the study period, similar to reports from other

European population-based studies.[17,33] This followed the publication of data from several clinical trials, as well as a meta-analysis, demonstrating a significant survival benefit with concomitant versus sequential chemoradiation for patients with locally advanced NSCLC.[34] Additionally, advances in staging procedures, such as the use of positron emission tomography (PET)-CT, have enabled the identification of stage III patients with low nodal involvement who may benefit from chemoradiation. [35]

The observed changes in treatment patterns among patients with stage I–IIIA NSCLC in the REAL-Oncology database were mirrored by changes in survival. Survival outcomes for patients diagnosed with stage I NSCLC tended to improve over time. Again, the pilot screening programme in Leeds and/or the increase in surgical interventions among patients with NSQ and SQ and in radiotherapy use in patients who were clinically diagnosed could have driven these improvements. These findings are consistent with marginal improvements in survival among patients diagnosed with early-stage NSCLC in England during the period of our study.[36] Additionally, this may reflect the effects of super staging, with the introduction of PET scanning and endoscopic sampling of lymph nodes.[37] Improved survival outcomes for patients diagnosed with stage IIIA NSCLC may be related to the increased use of surgery with SACT or radiotherapy, and chemoradiation during the latter diagnostic period. Furthermore, transition to the 7th Edition of TNM classification for NSCLC in 2010 may have influenced subsequent treatment allocations and survival outcomes for some patients.[26]

Changes in the recommended management of advanced NSCLC in Europe from 2005, including the use of pemetrexed as maintenance therapy in the first-line setting for platinum-treated NSQ patients and the advent of new TKIs for patients with EGFR and ALK mutations, likely influenced the observed treatment patterns.[38,39] Additionally, during the course of our study, some patients with advanced NSCLC in England were granted access to ICIs via the Early Access to Medicines Scheme,[40,41] which is reflected by the small proportions of patients who received these treatments. Nevertheless, despite changes in treatment patterns, there was little change in survival outcomes for patients with advanced

NSCLC during the analysis period; the prognosis for these patients, particularly those with SQ, remained poor. Indeed, less than 10% of patients diagnosed with advanced NSCLC remained alive 3 years after diagnosis. While previous real-world studies have demonstrated similarly poor survival outcomes for patients with stage IIIB and IV NSCLC,[17,42] survival rates for patients with advanced lung cancer in the United Kingdom have historically been low compared with other developed countries. This has led to the implementation of several healthcare reforms and initiatives since 2000, which have so far made only limited progress at closing this survival gap, as reflected here.[43,44]

The REAL-Oncology database represents an unselected population, which is relevant to real-world practice and enables robust analyses across numerous subgroups over a long timeframe (>10 years). Furthermore, this data source allowed the identification of clinically diagnosed patients, a population not often captured and representing here more than one-third of patients with NSCLC. However, the current study includes only data from Leeds trust and may not be representative of clinical practice elsewhere in England. Additionally, limited information was available regarding radiotherapy at the time of this analysis (date of administration) and it was not therefore possible to formally differentiate palliative radiotherapy from radiotherapy with curative intent. It is hoped that improvements to the algorithm used and the subsequent availability of more detailed data regarding radiotherapy will address this limitation. Finally, data on biomarkers and comorbidities were not available.

Our findings provide valuable insight into the real-world treatment and survival outcomes for patients in the pre-immunotherapy era in Leeds and demonstrate that, irrespective of changes in treatment patterns and against a background of policy reforms, long-term survival for patients diagnosed with metastatic NSCLC remains poor. Future analyses from the REAL-Oncology database will help evaluate the impact of new TKIs and ICIs on OS for patients with NSCLC.

**FUNDING**

REAL-Oncology is a collaboration between Leeds Teaching Hospital NHS Trust, the University of Leeds and IQVIA. Commercial clients of IQVIA include Bristol Myers Squibb, which funded the project this work is based on. REAL-Oncology retains all operational, scientific, and communications controls.

**COMPETING INTERESTS**

REAL-Oncology is a collaboration between Leeds Teaching Hospital NHS Trust and IQVIA. Commercial clients of IQVIA include Bristol Myers Squibb Company (BMS), which funded the project this work is based on. REAL-Oncology retains all operational, scientific and communications controls. GH is an employee of the University of Leeds and holds an honorary contract with Leeds Teaching Hospital NHS Trust. GH leads the Leeds Teaching Hospitals NHS Trust real-world evidence team collaboration with IQVIA and, as part of this collaboration, IQVIA funds the staff who support this work. GH also reports partial grant funding for a collaboration outside this study from IQVIA. MS was an employee at Leeds Teaching Hospital NHS Trust at the time of the study, and he holds an honorary contract with Leeds Teaching Hospital NHS Trust. MS, MT and MR are employees of IQVIA. WS and SC are subcontracted to IQVIA and hold honorary contracts with Leeds Teaching Hospital NHS Trust. MS receives consultancy fees from BMS. CC, MD and JP are employees of BMS. CC and JP report stock ownership in BMS. LL was contracted (paid) as a consultant by BMS to support the I-O Optimise initiative and is an employee of Epi-Fit. There are no further conflicts of interest.

**AUTHOR CONTRIBUTIONS**

LL, CC, MD and JP conceived and designed the study, with contributions from MS, MT and WS. GH is the lead for the Leeds Teaching Hospital NHS Trust Real world programme, clinical lead for the Patient Pathway Manager (the Electronic Health Record) and Professor of Cancer Medicine and Digital Health (University of Leeds). SC is the Senior Information Officer working with the REAL-Oncology team at Leeds Teaching Hospital NHS Trust. MS provided expertise to REAL-Oncology regarding the management of

lung cancer. MS, MT, WS and MR analysed the data. All authors contributed to the interpretation of the data, the drafting of the work and subsequent critical revision of the manuscript. MS accepts full responsibility for the work and the conduct of the study and had full access to the data.

**DATA SHARING**

The data analysed during the current study are available from the corresponding author on reasonable request. Study outputs will be made publicly available on Leeds Teaching Hospital NHS Trust website following publication.

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**TABLES**

**Table 1 Demographic and clinical characteristics of full patient population***

| | All NSCLC | NSQ | SQ | NSCLC NOS | Other NSCLC | Clinically diagnosed unknown pathology |
|---|---|---|---|---|---|---|
| **All stages** | **N=3739** | **n=1112** | **n=819** | **n=439** | **n=88** | **n=1281** |
| Age, years | | | | | | |
| Mean (SD) | 72.3 (10.9) | 68.6 (11.0) | 70.8 (9.4) | 68.9 (10.6) | 70.1 (10.7) | 78.0 (9.3) |
| Median (Q1–Q3) | 73 (65-80) | 69 (62-77) | 71 (64-77) | 69 (63-77) | 71 (63-78) | 79 (72-85) |
| Range | 18-101 | 31-101 | 33-96 | 18-92 | 42-91 | 43-99 |
| Male, n (%) | 1881 (50.3) | 519 (46.7) | 505 (61.7) | 220 (50.1) | 49 (55.7) | 588 (45.9) |
| TNM stage, n (%) | | | | | | |
| IA | 469 (12.5) | 152 (13.7) | 65 (7.9) | 15 (3.4) | 9 (10.2) | 228 (17.8) |
| IB | 248 (6.6) | 71 (6.4) | 62 (7.6) | 15 (3.4) | 10 (11.4) | 90 (7.0) |
| IIA | 244 (6.5) | 72 (6.5) | 69 (8.4) | 20 (4.6) | 8 (9.1) | 75 (5.9) |

| | | | | | | |
|---|---|---|---|---|---|---|
| IIB | 190 (5.1) | 41 (3.7) | 63 (7.7) | <20 (<5.0) | <5 (<6.0) | 62 (4.8) |
| IIIA | 469 (12.5) | 110 (9.9) | 164 (20.0) | 54 (12.3) | 8 (9.1) | 133 (10.4) |
| IIIB | 337 (9.0) | 89 (8.0) | 117 (14.3) | <55 (<12.3) | <5 (<6.0) | 77 (6.0) |
| IV | 1782 (47.7) | 577 (51.9) | 279 (34.1) | 263 (59.9) | 47 (53.4) | 616 (48.1) |
| Pathology, n (%) | | | | | | |
| Adenocarcinoma | 1019 (27.3) | 1019 (91.6) | 0 | 0 | 0 | 0 |
| SQ | 819 (21.9) | 0 | 819 (100.0) | 0 | 0 | 0 |
| NSCLC NOS | 439 (11.7) | 0 | 0 | 439 (100.0) | 0 | 0 |
| Large cell carcinoma | 93 (2.5) | 93 (8.4) | 0 | 0 | 0 | 0 |
| Other NSCLC | 88 (2.4) | 0 | 0 | 0 | 88 (100.0) | 0 |
| Clinically diagnosed, unknown pathology | 1281 (34.3) | 0 | 0 | 0 | 0 | 1281 (100.0) |
| WHO performance score, n (%) | | | | | | |
| 0 | 292 (7.8) | 149 (13.4) | 70 (8.6) | 38 (8.7) | 12 (13.6) | 23 (1.8) |
| 1 | 1031 (27.6) | 445 (40.0) | 319 (39.0) | 144 (32.8) | 37 (42.2) | 86 (6.7) |

| | | | | | | |
|---|---|---|---|---|---|---|
| 2 | 758 (20.3) | 230 (20.7) | 230 (28.1) | 80 (18.2) | 25 (28.4) | 193 (15.1) |
| 3 | 933 (25.0) | 154 (13.9) | 118 (14.4) | 97 (22.1) | <15 (<17.0) | 553 (43.2) |
| 4 | 372 (10.0) | 39 (3.5) | 16 (2.0) | 26 (5.9) | 0 | 291 (22.7) |
| Missing | 353 (9.4) | 95 (8.5) | 66 (8.1) | <55 (<12.5) | <5 (<5.7) | 135 (10.5) |

*For some categories including low numbers of patients, data have been masked to conceal patient identities. Includes 6 patients diagnosed in 2006.

NOS, not otherwise specified; NSCLC, non-small cell lung cancer; NSQ, non-squamous cell carcinoma; Q, quartile; SD, standard deviation; SQ, squamous cell carcinoma; TNM, tumour, node and metastasis; WHO, World Health Organization.

**Table 2 First-line and second-line SACT in patients with stage IIIB–IV NSQ or SQ carcinoma***

| | NSQ | | SQ | |
|---|---|---|---|---|
| **First-line SACT†** | **2007–2012** | **2013–2017** | **2007–2012** | **2013–2017** |
| Patients receiving first-line SACT, N | **139** | **161** | **104** | **76** |
| Platinum-based chemotherapy, n (%)‡ | 109 (78.4) | 119 (73.9) | 97 (93.3) | 73 (96.1) |
| Carboplatin based | 93 (66.9) | 78 (48.4) | 88 (84.6) | 68 (65.4) |
| Cisplatin based | 11 (7.9) | 33 (20.5) | 9 (8.7) | <5 |
| Pemetrexed included | 58 (41.7) | 107 (77.0) | <5 | <5 |
| Non–platinum-based chemotherapy, n (%) | <5 | 0 | <5 | <5 |
| TKI, n (%) | 17 (12.2) | 34 (21.1) | 0 | <5 |
| Anti–PD-1/PD-L1 checkpoint inhibitors, n (%) | 0 | <5 | 0 | <5 |
| Clinical trial – unknown treatment, n (%) | 8 (5.8) | <5 | 5 (4.8) | 0 |

| **Second-line SACT[§]** | **2007–2012** | **2013–2018** | **2007–2012** | **2013–2018** |
|---|---|---|---|---|
| Patients receiving second-line SACT, N | **53** | **66** | **31** | **23** |
| Platinum-based therapy, n (%)[‡] | <5 | 13 (19.7) | 5 (16.1) | 8 (34.8) |
| Non–platinum-based chemotherapy, n (%) | <5 | 7 (10.6) | <5 | <5 |
| TKI, n (%) | 47 (88.7) | 31 (47.0) | 23 (74.2) | 6 (26.1) |
| Anti–PD-1/PD-L1 checkpoint inhibitors, n (%) | 0 | 10 (15.2) | 0 | 5 (21.7) |
| Clinical trial – unknown treatment, n (%) | 0 | <5 | 0 | 0 |

*For some categories including low numbers of patients, data have been masked to conceal patient identities. [†]Time periods for receipt of initial SACT are based on the date of diagnosis during two consecutive time periods (January 2007–December 2012 and January 2013–August 2017). [‡]Platinum based is defined as any regimen including a platinum agent (monotherapy or in combination) and is further defined as "carboplatin based," "cisplatin based" (including regimens in which carboplatin and cisplatin were both used) and "pemetrexed included" (any platinum-based regimen also including pemetrexed). [§]Time periods for receipt of second-line SACT are based on the start date for second-line treatment during three consecutive time periods (January 2007–December 2012, January 2013–December 2016, and January 2017–April 2018).

NSQ, non-squamous cell carcinoma; PD-1, programmed death 1; PD-L1, programmed death ligand 1; SACT, systemic anticancer therapy; SQ, squamous cell carcinoma; TKI, tyrosine kinase inhibitor.

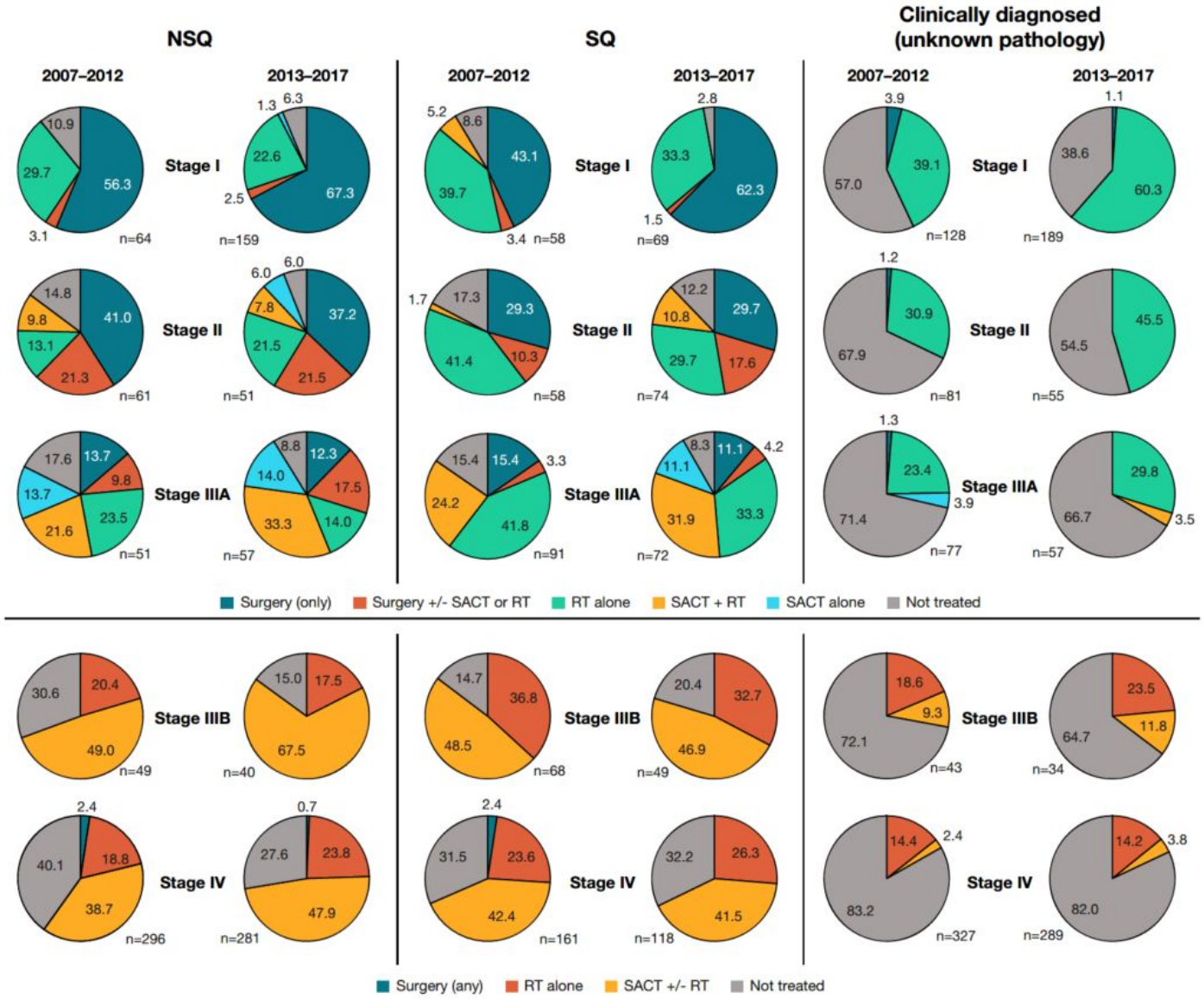
**FIGURES**

**Figure 1 TNM stage at NSCLC incident diagnosis, by year of diagnosis***


*Excludes six patients diagnosed in 2006. †Diagnosed up to 31 August 2017.

TNM, tumour, node and metastasis.

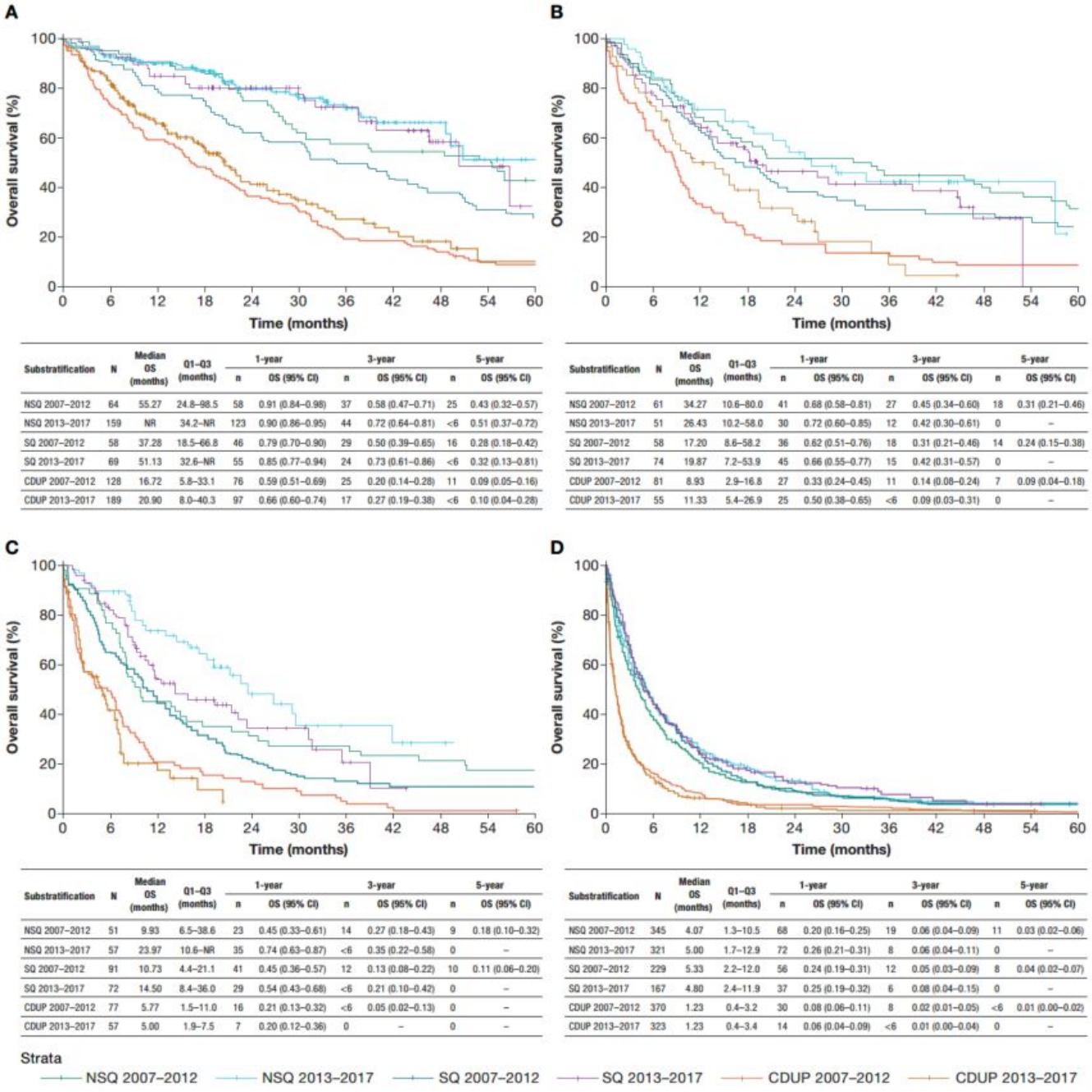
**Figure 2** Initial treatment by TNM stage and time period (2007–2012 vs 2013–2017) in patients with (A) NSQ, (B) SQ or (C) CDUP*,†



*Time periods for receipt of initial treatment are based on the date of diagnosis during two consecutive time periods (January 2007–December 2012 and January 2013–August 2017). †Where analytical groups included fewer than five patients, percentages are not shown as labels.

CDUP, clinically diagnosed with unknown pathology; NSQ, non-squamous cell carcinoma; RT, radiotherapy; SACT, systemic anticancer therapy; SQ, squamous cell carcinoma; TNM, tumour, node and metastasis; Tx, treatment.

**Figure 3 Evolution of OS in patients diagnosed with stage I (A), stage II (B), stage IIIA (C) or stage IIIB–IV (D) NSCLC with NSQ, SQ or CDUP**




| Substratification | N | Median OS (months) | Q1–Q3 (months) | 1-year n | 1-year OS (95% CI) | 3-year n | 3-year OS (95% CI) | 5-year n | 5-year OS (95% CI) |
|---|---|---|---|---|---|---|---|---|---|
| NSQ 2007–2012 | 64 | 55.27 | 24.8–98.5 | 58 | 0.91 (0.84–0.98) | 37 | 0.58 (0.47–0.71) | 25 | 0.43 (0.32–0.57) |
| NSQ 2013–2017 | 159 | NR | 34.2–NR | 123 | 0.90 (0.86–0.95) | 44 | 0.72 (0.64–0.81) | <6 | 0.51 (0.37–0.72) |
| SQ 2007–2012 | 58 | 37.28 | 18.5–66.8 | 46 | 0.79 (0.70–0.90) | 29 | 0.50 (0.39–0.65) | 16 | 0.28 (0.18–0.42) |
| SQ 2013–2017 | 69 | 51.13 | 32.6–NR | 55 | 0.85 (0.77–0.94) | 24 | 0.73 (0.61–0.86) | <6 | 0.32 (0.13–0.81) |
| CDUP 2007–2012 | 128 | 16.72 | 5.8–33.1 | 76 | 0.59 (0.51–0.69) | 25 | 0.20 (0.14–0.28) | 11 | 0.09 (0.05–0.16) |
| CDUP 2013–2017 | 189 | 20.90 | 8.0–40.3 | 97 | 0.66 (0.60–0.74) | 17 | 0.27 (0.19–0.38) | <6 | 0.10 (0.04–0.28) |

| Substratification | N | Median OS (months) | Q1–Q3 (months) | 1-year n | 1-year OS (95% CI) | 3-year n | 3-year OS (95% CI) | 5-year n | 5-year OS (95% CI) |
|---|---|---|---|---|---|---|---|---|---|
| NSQ 2007–2012 | 61 | 34.27 | 10.6–80.0 | 41 | 0.68 (0.58–0.81) | 27 | 0.45 (0.34–0.60) | 18 | 0.31 (0.21–0.46) |
| NSQ 2013–2017 | 51 | 26.43 | 10.2–58.0 | 30 | 0.72 (0.60–0.85) | 12 | 0.42 (0.30–0.61) | 0 | – |
| SQ 2007–2012 | 58 | 17.20 | 8.6–58.2 | 36 | 0.62 (0.51–0.76) | 18 | 0.31 (0.21–0.46) | 14 | 0.24 (0.15–0.38) |
| SQ 2013–2017 | 74 | 19.87 | 7.2–53.9 | 45 | 0.66 (0.55–0.77) | 15 | 0.42 (0.31–0.57) | 0 | – |
| CDUP 2007–2012 | 81 | 8.93 | 2.9–16.8 | 27 | 0.33 (0.24–0.45) | 11 | 0.14 (0.08–0.24) | 7 | 0.09 (0.04–0.18) |
| CDUP 2013–2017 | 55 | 11.33 | 5.4–26.9 | 25 | 0.50 (0.38–0.65) | <6 | 0.09 (0.03–0.31) | 0 | – |

| Substratification | N | Median OS (months) | Q1–Q3 (months) | 1-year n | 1-year OS (95% CI) | 3-year n | 3-year OS (95% CI) | 5-year n | 5-year OS (95% CI) |
|---|---|---|---|---|---|---|---|---|---|
| NSQ 2007–2012 | 51 | 9.93 | 6.5–38.6 | 23 | 0.45 (0.33–0.61) | 14 | 0.27 (0.18–0.43) | 9 | 0.18 (0.10–0.32) |
| NSQ 2013–2017 | 57 | 23.97 | 10.6–NR | 35 | 0.74 (0.63–0.87) | <6 | 0.35 (0.22–0.58) | 0 | – |
| SQ 2007–2012 | 91 | 10.73 | 4.4–21.1 | 41 | 0.45 (0.36–0.57) | 12 | 0.13 (0.08–0.22) | 10 | 0.11 (0.06–0.20) |
| SQ 2013–2017 | 72 | 14.50 | 8.4–36.0 | 29 | 0.54 (0.43–0.68) | <6 | 0.21 (0.10–0.42) | 0 | – |
| CDUP 2007–2012 | 77 | 5.77 | 1.5–11.0 | 16 | 0.21 (0.13–0.32) | <6 | 0.05 (0.02–0.13) | 0 | – |
| CDUP 2013–2017 | 57 | 5.00 | 1.9–7.5 | 7 | 0.20 (0.12–0.36) | 0 | – | 0 | – |

| Substratification | N | Median OS (months) | Q1–Q3 (months) | 1-year n | 1-year OS (95% CI) | 3-year n | 3-year OS (95% CI) | 5-year n | 5-year OS (95% CI) |
|---|---|---|---|---|---|---|---|---|---|
| NSQ 2007–2012 | 345 | 4.07 | 1.3–10.5 | 68 | 0.20 (0.16–0.25) | 19 | 0.06 (0.04–0.09) | 11 | 0.03 (0.02–0.06) |
| NSQ 2013–2017 | 321 | 5.00 | 1.7–12.9 | 72 | 0.26 (0.21–0.31) | 8 | 0.06 (0.04–0.11) | 0 | – |
| SQ 2007–2012 | 229 | 5.33 | 2.2–12.0 | 56 | 0.24 (0.19–0.31) | 12 | 0.05 (0.03–0.09) | 8 | 0.04 (0.02–0.07) |
| SQ 2013–2017 | 167 | 4.80 | 2.4–11.9 | 37 | 0.25 (0.19–0.32) | 6 | 0.08 (0.04–0.15) | 0 | – |
| CDUP 2007–2012 | 370 | 1.23 | 0.4–3.2 | 30 | 0.08 (0.06–0.11) | 8 | 0.02 (0.01–0.05) | <6 | 0.01 (0.00–0.02) |
| CDUP 2013–2017 | 323 | 1.23 | 0.4–3.4 | 14 | 0.06 (0.04–0.09) | <6 | 0.01 (0.00–0.04) | 0 | – |

CDUP, clinically diagnosed with unknown pathology; NSCLC, non-small cell lung cancer; NSQ, non-squamous cell carcinoma; OS, overall survival; SQ, squamous cell carcinoma.

**SUPPLEMENTARY APPENDIX**

## Appendix

**Table S1.** ICD-O-3 morphology codes for NSCLC.

| Morphology code | Type of NSCLC |
|---|---|
| | **Adenocarcinoma (non-squamous NSCLC)** |
| 81403 | Adenocarcinoma UNS |
| 81443 | Enteric adenocarcinoma |
| 82303 | Solid adenocarcinoma with mucin production |
| 82443 | MANEC mixed adenoneuroendocrine carcinoma |
| 82500 | Atypical adenomatous hyperplasia |
| 82502 | Adenocarcinoma in situ, non-mucinous |
| 82503 | Adenocarcinoma, bronchiolo-alveolar (BAC), bronchiolar carcinoma, (incl pathologic in situ-variant) |
| 82523 | Bronchiolo-alveolar carcinoma |
| 82532 | Adenocarcinoma in situ, mucinous |
| 82533 | Adenocarcinoma, mucinous bronchiolo-alveolar (BAC) |
| 82543 | Bronchiolo-alveolar carcinoma, mixed mucinous and non-mucinous |

| Morphology code | Type of NSCLC |
|---|---|
| 82553 | Adenocarcinoma, mixed with other types of carcinoma incl. squamous cell and small-cell carcinoma |
| 82563 | Minimally invasive adenocarcinoma, non-mucinous |
| 82573 | Minimally invasive adenocarcinoma, mucinous |
| 82603 | Papillary adenocarcinoma, NOS |
| 82653 | Micropapillary adenocarcinoma |
| 83103 | Clear cell adenocarcinoma |
| 83333 | Fetal adenocarcinoma |
| 84703 | Mucinous cystadenocarcinoma |
| 84803 | Mucinous adenocarcinoma |
| 84903 | Signet ring cell carcinoma |
| 85503 | Acinar cell carcinoma |
| 85513 | Acinar adenocarcinoma |
| | **Squamous cell carcinoma** |
| 80523 | Papillary squamous cell carcinoma |
| 80702 | Squamous cell carcinoma in situ |
| 80703 | Squamous cell carcinoma |

| Morphology code | Type of NSCLC |
|---|---|
| 80713 | Keratinizing squamous cell carcinoma |
| 80723 | Non-keratinizing squamous cell carcinoma |
| 80733 | Squamous cell carcinoma, small cell non-keratinizing |
| 80833 | Basaloid squamous cell carcinoma |
| 80843 | Squamous cell carcinoma, clear cell type |
| | **NSCLC NOS** |
| 80103 | Carcinoma, NOS |
| 80203 | Carcinoma, undifferentiated NOS |
| 80213 | Carcinoma, anaplastic NOS |
| 80463 | Carcinoma, non-small cell unspecified |
| | **Large cell carcinoma (non-squamous NSCLC)** |
| 80123 | Large-cell carcinoma, unspecified |
| | **Neuroendocrine NSCLC carcinoma (other specified NSCLC carcinoma)** |
| 80133 | Large cell neuroendocrine carcinoma |
| 82463 | Neuroendocrine carcinoma, NOS |
| | **Other miscellaneous NSCLC (other specified NSCLC carcinoma)** |

| Morphology code | Type of NSCLC |
|---|---|
| 80143 | Large cell carcinoma with rhabdoid phenotype |
| 80223 | Sarcomatoid carcinoma, pleomorphic |
| 80233 | NUT carcinoma |
| 80303 | Spindle cell and giant cell carcinoma |
| 80313 | Giant cell carcinoma |
| 80323 | Spindle cell carcinoma, NOS |
| 80333 | Pseudosarcomatous carcinoma |
| 81233 | Basaloid carcinoma |
| 82003 | Adenocystic carcinoma |
| 84303 | Mucoepidermoid carcinoma |
| 85603 | Adenosquamous carcinoma |
| 85623 | Epithelial-myoepithelial carcinoma |
| 89723 | Blastoma, pulmonary (pneumoblastoma) |
| 89803 | Carcinosarcoma, NOS |
| 89823 | Myoepithelial carcinoma |

ICD-O-3, *International Classification of Diseases for Oncology*, 3rd Edition; NOS, not otherwise specified; NSCLC, non-small cell lung cancer; UNS, unspecified.

**Table S2.** Initial treatment algorithm. Initial treatment was defined as the first treatment received within 6 months of diagnosis, associated with any other treatment received within a certain time period following first treatment as defined in the table below.

| **Initial treatment category** | **Definitions** |
|---|---|
| A. Surgery | Sum of all A sub-groups |
| A0. Surgery only | Surgery + no SACT or RT within 12 weeks after surgery |
| A1. Surgery + adjuvant SACT (only) – no RT within 6 months of SACT start | Surgery + identification of SACT only (start) within 84 days (12 weeks) after surgery |
| A2. Surgery + adjuvant RT (only) – no SACT within 6 months of RT start | Surgery + identification of RT only (start) within 84 days (12 weeks) after surgery |
| A3. Surgery + adjuvant RT and SACT | Surgery + identification of RT [or SACT] (start) within 84 days (12 weeks) after surgery + identification of SACT [or RT] (start) within 180 days (6 months) after RT [or SACT] |

| | |
|---|---|
| A4. Neoadjuvant SACT + surgery | SACT + identification of surgery within 120 days (4 months) after first SACT regimen start + no RT identification prior to surgery<br><br>AND: |
| A5. Neoadjuvant RT + surgery | RT + identification of surgery within 90 days (3 months) after first RT treatment start + no SACT identification prior to surgery AND: |
| A6. Neoadjuvant SACT and RT + surgery | RT and SACT + identification of surgery within 3 months after start + identification of SACT and RT prior to surgery<br><br>Note: Neoadjuvant SACT and RT corresponds to RT within 6 weeks of SACT start |
| B. Radiotherapy alone | RT + no SACT nor surgery within 90 days (3 months) after RT |
| C. SACT + Radiotherapy | Sum of C1, C2 and C3 |
| C1. RT followed by SACT | RT + identification of SACT within 90 days (3 months) after first SACT regimen start + no surgery within 6 months after first SACT start |

| | |
|---|---|
| C2. SACT followed by RT | SACT + identification of RT within 90 days (3 months) after first SACT regimen start + no surgery within 6 months after first SACT start |
| C3. Concurrent chemoradiation | SACT + [start RT within 6 weeks of SACT] + no surgery within 3 months after chemoradiation |
| D. SACT alone | SACT + no RT nor surgery within 90 days (3 months) after first SACT regimen start |
| E. Not treated | No SACT, surgery or RT identified over entire follow-up period |

RT, radiotherapy; SACT, systemic anticancer therapy

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Figure 1 TNM stage at NSCLC incident diagnosis, by year of diagnosis*

145x101mm (300 x 300 DPI)

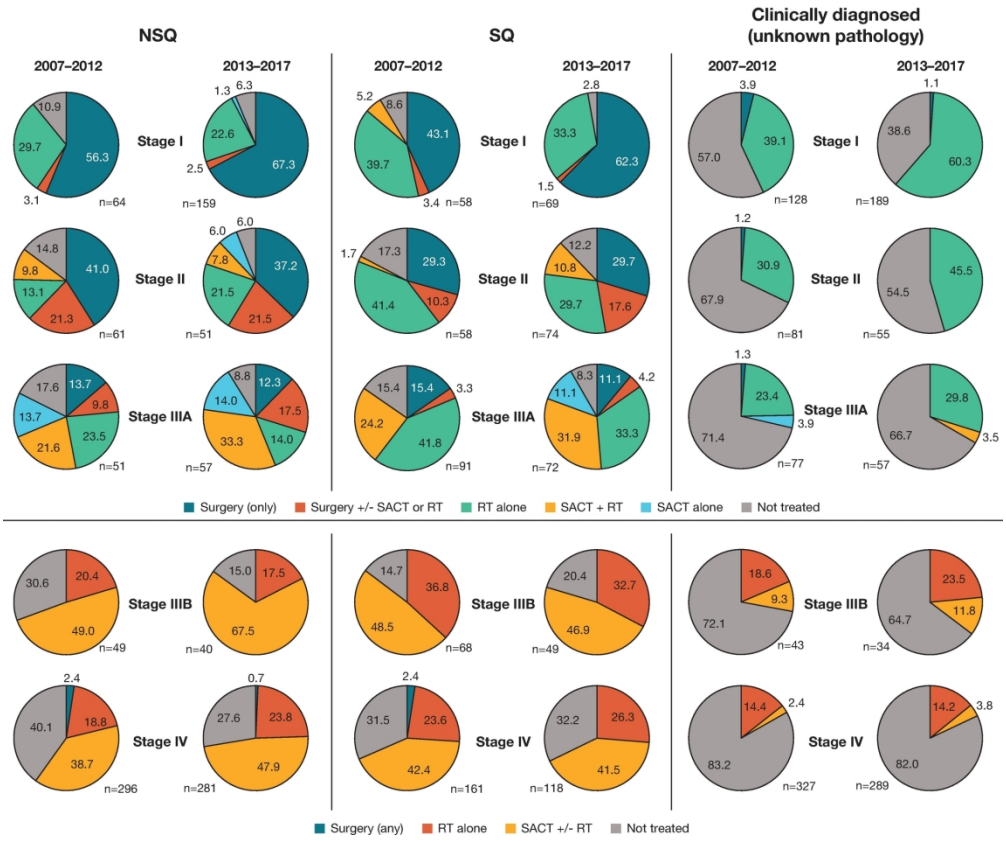
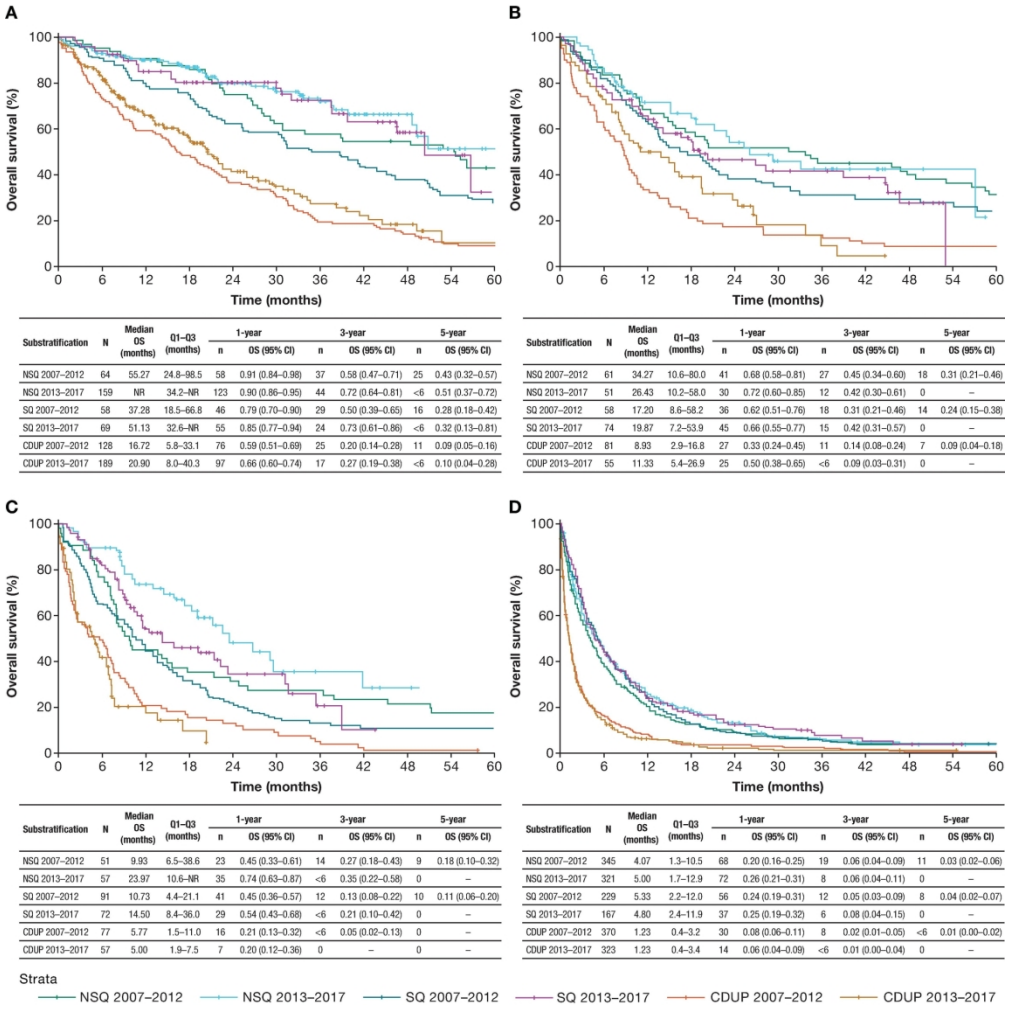



Figure 2 Initial treatment by TNM stage and time period (2007–2012 vs 2013–2017) in patients with (A) NSQ, (B) SQ or (C) CDUP*,†

179x148mm (300 x 300 DPI)




| Substratification | N | Median OS (months) | Q1–Q3 (months) | 1-year n | 1-year OS (95% CI) | 3-year n | 3-year OS (95% CI) | 5-year n | 5-year OS (95% CI) |
|---|---|---|---|---|---|---|---|---|---|
| NSQ 2007–2012 | 64 | 55.27 | 24.8–98.5 | 58 | 0.91 (0.84–0.98) | 37 | 0.58 (0.47–0.71) | 25 | 0.43 (0.32–0.57) |
| NSQ 2013–2017 | 159 | NR | 34.2–NR | 123 | 0.90 (0.86–0.95) | 44 | 0.72 (0.64–0.81) | <6 | 0.51 (0.37–0.72) |
| SQ 2007–2012 | 58 | 37.28 | 18.5–66.8 | 46 | 0.79 (0.70–0.90) | 29 | 0.50 (0.39–0.65) | 16 | 0.28 (0.18–0.42) |
| SQ 2013–2017 | 69 | 51.13 | 32.6–NR | 55 | 0.85 (0.77–0.94) | 24 | 0.73 (0.61–0.86) | <6 | 0.32 (0.13–0.81) |
| CDUP 2007–2012 | 128 | 16.72 | 5.8–33.1 | 76 | 0.59 (0.51–0.69) | 25 | 0.20 (0.14–0.28) | 11 | 0.09 (0.05–0.16) |
| CDUP 2013–2017 | 189 | 20.90 | 8.0–40.3 | 97 | 0.66 (0.60–0.74) | 17 | 0.27 (0.19–0.38) | <6 | 0.10 (0.04–0.28) |

| Substratification | N | Median OS (months) | Q1–Q3 (months) | 1-year n | 1-year OS (95% CI) | 3-year n | 3-year OS (95% CI) | 5-year n | 5-year OS (95% CI) |
|---|---|---|---|---|---|---|---|---|---|
| NSQ 2007–2012 | 61 | 34.27 | 10.6–80.0 | 41 | 0.68 (0.58–0.81) | 27 | 0.45 (0.34–0.60) | 18 | 0.31 (0.21–0.46) |
| NSQ 2013–2017 | 51 | 26.43 | 10.2–58.0 | 30 | 0.72 (0.60–0.85) | 12 | 0.42 (0.30–0.61) | 0 | – |
| SQ 2007–2012 | 58 | 17.20 | 8.6–58.2 | 36 | 0.62 (0.51–0.76) | 18 | 0.31 (0.21–0.46) | 14 | 0.24 (0.15–0.38) |
| SQ 2013–2017 | 74 | 19.87 | 7.2–53.9 | 45 | 0.66 (0.55–0.77) | 15 | 0.42 (0.31–0.57) | 0 | – |
| CDUP 2007–2012 | 81 | 8.93 | 2.9–16.8 | 27 | 0.33 (0.24–0.45) | 11 | 0.14 (0.08–0.24) | 7 | 0.09 (0.04–0.18) |
| CDUP 2013–2017 | 55 | 11.33 | 5.4–26.9 | 25 | 0.50 (0.38–0.65) | <6 | 0.09 (0.03–0.31) | 0 | – |

| Substratification | N | Median OS (months) | Q1–Q3 (months) | 1-year n | 1-year OS (95% CI) | 3-year n | 3-year OS (95% CI) | 5-year n | 5-year OS (95% CI) |
|---|---|---|---|---|---|---|---|---|---|
| NSQ 2007–2012 | 51 | 9.93 | 6.5–38.6 | 23 | 0.45 (0.33–0.61) | 14 | 0.27 (0.18–0.43) | 9 | 0.18 (0.10–0.32) |
| NSQ 2013–2017 | 57 | 23.97 | 10.6–NR | 35 | 0.74 (0.63–0.87) | <6 | 0.35 (0.22–0.58) | 0 | – |
| SQ 2007–2012 | 91 | 10.73 | 4.4–21.1 | 41 | 0.45 (0.36–0.57) | 12 | 0.13 (0.08–0.22) | 10 | 0.11 (0.06–0.20) |
| SQ 2013–2017 | 72 | 14.50 | 8.4–36.0 | 29 | 0.54 (0.43–0.68) | <6 | 0.21 (0.10–0.42) | 0 | – |
| CDUP 2007–2012 | 77 | 5.77 | 1.5–11.0 | 16 | 0.21 (0.13–0.32) | <6 | 0.05 (0.02–0.13) | 0 | – |
| CDUP 2013–2017 | 57 | 5.00 | 1.9–7.5 | 7 | 0.20 (0.12–0.36) | 0 | – | 0 | – |

| Substratification | N | Median OS (months) | Q1–Q3 (months) | 1-year n | 1-year OS (95% CI) | 3-year n | 3-year OS (95% CI) | 5-year n | 5-year OS (95% CI) |
|---|---|---|---|---|---|---|---|---|---|
| NSQ 2007–2012 | 345 | 4.07 | 1.3–10.5 | 68 | 0.20 (0.16–0.25) | 19 | 0.06 (0.04–0.09) | 11 | 0.03 (0.02–0.06) |
| NSQ 2013–2017 | 321 | 5.00 | 1.7–12.9 | 72 | 0.26 (0.21–0.31) | 8 | 0.06 (0.04–0.11) | 0 | – |
| SQ 2007–2012 | 229 | 5.33 | 2.2–12.0 | 56 | 0.24 (0.19–0.31) | 12 | 0.05 (0.03–0.09) | 8 | 0.04 (0.02–0.07) |
| SQ 2013–2017 | 167 | 4.80 | 2.4–11.9 | 37 | 0.25 (0.19–0.32) | 6 | 0.08 (0.04–0.15) | 0 | – |
| CDUP 2007–2012 | 370 | 1.23 | 0.4–3.2 | 30 | 0.08 (0.06–0.11) | 8 | 0.02 (0.01–0.05) | <6 | 0.01 (0.00–0.02) |
| CDUP 2013–2017 | 323 | 1.23 | 0.4–3.4 | 14 | 0.06 (0.04–0.09) | <6 | 0.01 (0.00–0.04) | 0 | – |



Figure 3 Evolution of OS in patients diagnosed with stage I (A), stage II (B), stage IIIA (C) or stage IIIB–IV (D) NSCLC with NSQ, SQ or CDUP

178x178mm (300 x 300 DPI)

## STROBE checklist

| Treatment patterns and survival outcomes for patients with non-small cell lung cancer in the United Kingdom in the pre-immunology era: a REAL-Oncology database analysis from the I-O Optimise initiative | | | **Snee, et al.** |
|---|---|---|---|
| **Checklist item -** | | | **Section** |
| **Title and abstract** | | | |
| | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract | *Title, abstract* |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | *Abstract* |
| **Introduction** | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | *Introduction, p5–6* |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | *Introduction, p5–6* |
| **Methods** | | | |
| Study design | 4 | Present key elements of study design early in the paper | *Methods, Study design, p6* |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | *Methods, Study setting, p6–7 Analyses, p7–8* |
| Participants | 6 | (*a*) *Cohort study*? Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up | *Methods, Study design, p6–7* |
| | | (*b*) *Cohort study*? For matched studies, give matching criteria and number of exposed and unexposed | *N/A* |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | *Methods, Analyses p7* |

| | | | |
|---|---|---|---|
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | *Methods, Analyses, p7* |
| Bias | 9 | Describe any efforts to address potential sources of bias | *N/A, retrospective study* |
| Study size | 10 | Explain how the study size was arrived at | *N/A, retrospective study* |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | *Methods, Analyses, p8* |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | *Methods, Analyses, p8* |
| | | (*b*) Describe any methods used to examine subgroups and interactions | *Methods, Analyses, p8* |
| | | (*c*) Explain how missing data were addressed | *Methods, Analyses, p8* |
| | | (*d*) *Cohort study*? If applicable, explain how loss to follow-up was addressed | *N/A, retrospective study* |
| | | (*e*) Describe any sensitivity analyses | *N/A* |
| **Results** | | | |
| Participants | 13* | (*a*) Report numbers of individuals at each stage of study? eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | *Results, Patients, p8* |
| | | (*b*) Give reasons for non-participation at each stage | *Results, Patients, p8* |
| | | (*c*) Consider use of a flow diagram | *Not included* |

| | | | |
|---|---|---|---|
| Descriptive data | 14* | (*a*)Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | *Results, Patients, p8–6* |
| | | (*b*) Indicate number of participants with missing data for each variable of interest | *N/A* |
| | | (*c*) *Cohort study*? Summarise follow-up time (eg average and total amount) | *N/A* |
| Outcome data | 15* | *Cohort study*? Report numbers of outcome events or summary measures over time | *Results, Overall survival, p12–13* |
| | | *Case-control study?* Report numbers in each exposure category, or summary measures of exposure | *N/A* |
| | | *Cross sectional study?* Report numbers of outcome events or summary measures | |
| Main results | 16 | (a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | *Results, Overall survival, p12–13* |
| | | (b) Report category boundaries when continuous variables were categorized | *N/A* |
| | | (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | *Not included* |
| Other analyses | 17 | Report other analyses done? eg analyses of subgroups and interactions, and sensitivity analyses | *N/A* |
| **Discussion** | | | |
| Key results | 18 | Summarise key results with reference to study objectives | *Discussion, p13* |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | *Discussion, p16* |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | *Discussion* |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | *Discussion, 16–17* |

| **Other information** | | | |
|---|---|---|---|
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | *Funding, p17* |
| | | | |

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

BMJ Open

# Treatment patterns and survival outcomes for patients with non-small cell lung cancer in the United Kingdom in the pre-immunology era: a REAL-Oncology database analysis from the I-O Optimise initiative



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# Treatment patterns and survival outcomes for patients with non-small cell lung cancer in the United Kingdom in the pre-immunology era: a REAL-Oncology database analysis from the I-O Optimise initiative

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**ABSTRACT *[300/300 words]***

**Objectives**

To report characteristics, treatment and overall survival (OS) trends, by stage and pathology, of patients diagnosed with non-small cell lung cancer (NSCLC) at Leeds Teaching Hospital NHS Trust in 2007–2018.

**Design**

Retrospective cohort study based on electronic medical records.

**Setting**

Large NHS university hospital in Leeds.

**Participants**

3739 adult patients diagnosed with incident NSCLC from January 2007–August 2017, followed until March 2018.

**Main outcome measures**

Patient characteristics at diagnosis, treatment patterns, OS.

**Results**

34.3% of patients with NSCLC were clinically diagnosed (without pathological confirmation). Among patients with known pathology, 45.2% had non-squamous cell carcinoma (NSQ); 33.3% had squamous cell carcinoma (SQ). The proportion of patients diagnosed at stage I increased (16.4%–27.7% in 2010–2017); those diagnosed at stage IV decreased (57.0%–39.1%). Surgery was the most common initial treatment for patients with pathologically confirmed stage I NSCLC. Use of radiotherapy alone increased over time in patients with clinically diagnosed stage I NSCLC (39.1%–60.3%); chemoradiation increased in patients with stage IIIA NSQ (21.6%–33.3%) and SQ (24.2%–31.9%). Initial treatment with systemic

anticancer therapy (SACT) increased in patients with stage IIIB–IV NSQ (49.0%–67.5%); the proportion of untreated patients decreased (30.6%–15.0%). Median OS improved for patients diagnosed with stage I NSQ and SQ and stage IIIA NSQ over time. Median OS for patients with stage IIIB–IV NSQ and SQ remained stable; <10% were alive 3 years after diagnosis. Median OS for clinically diagnosed stage IIIB–IV patients was 1.2 months in both periods.

**Conclusions**

OS for stage I and IIIA patients improved over time, likely due to increased stereotactic ablative radiation, surgery (stage I) and chemoradiation (stage IIIA) use. Conversely, OS outcomes remained poor for stage IIIB–IV patients despite increasing use of SACT for NSQ. Many patients with advanced-stage disease remained untreated.

**Article summary**

Strengths and limitations of this study

- This retrospective analysis of the REAL-Oncology database analysed the characteristics, treatment and overall survival trends for patients diagnosed with non-small cell lung cancer (NSCLC) over a 10-year period in a large regional hospital in the United Kingdom
- Data on prescribed systemic anticancer therapy, and pathology and radiology records were extracted from electronic medical records for adult patients diagnosed with incident NSCLC between 2007 and 2017 based on confirmed pathology or clinical data
- These data reflect outcomes and trends for a single site in the United Kingdom; however, the REAL-Oncology study represents an unselected population, which is relevant to real-world practice and enables long-term (>10 years) analyses across numerous subgroups
- This analysis included patients with a clinical diagnosis of NSCLC who, despite representing a large proportion of patients with NSCLC, are often not captured in real-world studies

## INTRODUCTION

In the United Kingdom, lung cancer is the third most common type of cancer and the leading cause of cancer death.[1] Around 85% of patients with lung cancer have non-small cell lung cancer (NSCLC), which consists predominantly of non-squamous cell carcinoma (NSQ) and squamous cell carcinoma (SQ).[2] Early diagnosis of lung cancer can be challenging.[3] Consequently, approximately two-thirds of patients present with advanced or metastatic NSCLC (stage III–IV), for which treatment options are limited and prognosis is poor;[4,5] 5-year survival rates for patients with metastatic disease are less than 5%.[5,6]

Surgery and radiotherapy can be used successfully in patients diagnosed with early-stage NSCLC; adjuvant chemotherapy is also indicated for selected patients who have undergone resection for stage II–III disease and can improve outcomes.[7] For advanced-NSCLC (stage IIIB–IV), chemotherapy with platinum-based agents has long been the standard of care for patients with good performance status (PS), and vascular endothelial growth factor–targeting therapies have been used in the first-line setting in patients with NSQ.[8] However, increased understanding of NSCLC driver mutations, such as those in the epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) genes, has led to the development of targeted therapies, including tyrosine kinase inhibitors (TKIs). These allow for more personalized treatment approaches in selected patients with actionable driver mutations.[8]

The development of immunotherapeutic agents has transformed the NSCLC treatment landscape. Since 2015, immune checkpoint inhibitors (ICIs) targeting the programmed death-1/programmed death ligand 1 axis have been approved in Europe and are now recommended for first- or second-line treatment of patients with metastatic NSCLC.[9] In addition, ongoing clinical trials are investigating neoadjuvant and adjuvant use of ICIs for patients diagnosed at earlier stages of NSCLC.[10-12] As with any new treatment, there is a need to assess how ICIs impact patient survival in real-world clinical practice to help inform future treatment decisions, which requires an understanding of the NSCLC landscape prior to their

availability. Real-world databases include a wealth of information that can be used to complement data from clinical trials and are a valuable source of evidence in a rapidly changing treatment landscape.

We report the characteristics, treatment and overall survival (OS) trends for patients diagnosed with NSCLC at a large teaching hospital in England prior to routine availability of ICIs. This study, based on the REAL-Oncology database, is part of the I-O Optimise program, an ongoing initiative leveraging real-world data sources to provide insights into the evolving landscape of thoracic malignancies, including NSCLC.[13]

## METHODS

### *Study setting*

REAL-Oncology is a research partnership between Leeds Cancer Centre (LCC), the University of Leeds and IQVIA®, using NHS oncology patient data to answer various research questions. LCC is a major NHS cancer centre that serves a metropolitan catchment area of 750 000 people for secondary care and over 5 million for tertiary care.

### *Ethics approval and consent to participate*

This study was completed with UK Health Research Authority approval through the National Institute for Health Research Integrated Research Approvals System. The research was performed in accordance with the Leeds Teaching Hospitals NHS Trust research governance framework; as a noninterventional retrospective descriptive study using existing patient records, the need for ethics approval was waived. The study was performed in accordance with the Declaration of Helsinki.

## *Study design*

Data on prescribed chemotherapy and pathology and radiology records were extracted from electronic medical records (EMRs) at the Leeds Teaching Hospitals NHS Trust. The study included patients aged ≥18 years with an incident diagnosis of NSCLC (International Statistical Classification of Diseases and Related Health Problems, 10th Revision [ICD-10] code for malignant neoplasm of the trachea [C33] or malignant neoplasm of bronchus and lung [C34]) between January 2007 and August 2017 at Leeds Teaching Hospital. All patients diagnosed by the lung multidisciplinary team were included, including those clinically identified solely on the basis of history, clinical examination and computed tomography (CT), and those with confirmed pathology (ie, *International Classification of Diseases for Oncology*, 3rd Edition [ICD-O-3] code for NSCLC histology, online supplementary appendix table S1). Patients were excluded if their first diagnosis of NSCLC was confirmed in another NHS hospital trust, they had missing data on age or sex, their ICD-O-3 morphology codes indicated small cell lung cancer (80413–80459), or they had a concomitant (within 5 years prior to NSCLC diagnosis) primary tumour at time of diagnosis, except for non-metastatic non-melanoma skin cancers or *in situ* or benign tumours. Patients with missing data on tumour, node, metastasis (TNM) classification were also excluded from the present analyses.

The end of follow-up was the date of death or end of study (April 2018). The date of death was confirmed by reconciliation of EMRs with Office for National Statistics death certifications. Patient sociodemographic (age, sex, World Health Organisation PS) and clinical characteristics (TNM stage, tumour pathology) were extracted on/at the nearest date to NSCLC diagnosis (index date). TNM classification at diagnosis was recorded according to the 6th edition of the TNM classification up to 31 December 2009[14]; the 7th edition from 1 January 2010[6]; and the 8th edition from 1 January 2017.[15] Tumour pathology was defined as NSQ (including adenocarcinoma and large cell carcinoma), SQ, NSCLC

not otherwise specified (NOS), “Other” (neuroendocrine carcinoma and other miscellaneous carcinoma) or “Unconfirmed” (clinically diagnosed unknown pathology).

The date of initial treatment was defined as the first instance of lung surgery, radiotherapy or systemic anticancer therapy (SACT) occurring within 6 months of diagnosis, and initial treatment categories were defined using all treatment received within a specified time period following this date (online supplementary appendix table S2). A line of therapy (LoT) was defined as one or more cycles of chemotherapy or continuous oral treatment for targeted agents in patients with incident stage IIIB–IV NSCLC. REAL-Oncology developed an algorithm to determine first and subsequent LoTs, and LoT outputs were clinically validated in reference to each patient cohort (online supplementary appendix table S2).

### *Analyses*

Patient characteristics at diagnosis are described using summary statistics. The evolution of treatment patterns and OS over time were investigated in two sub-cohorts defined by date of diagnosis: January 2007 to December 2012, and January 2013 to August 2017. Therapy received and treatment duration are described by LoT for advanced-stage patients using the same time periods. Time periods for the receipt of initial SACT are based on the date of diagnosis (January 2007–December 2012, and January 2013–August 2017). Time periods for receipt of second LoT are based on the start date for the second LoT over both the study and follow-up period (January 2007–December 2012, and January 2013–April 2018). Survival outcomes were captured through April 2018. OS was estimated using Kaplan–Meier methods. The proportions of patients surviving to 1, 2 or 3 years after the date of diagnosis were estimated and are reported with corresponding two-sided 95% confidence intervals. Differences in OS between time periods were compared using log-rank hypothesis tests.

To comply with patient confidentiality requirements, data outputs relating to groups of fewer than five patients were masked. In some circumstances, data relating to larger patient subgroups were also masked to avoid extrapolation of counts of fewer than five patients.

## Results

### *Patients*

Overall, 4225 patients diagnosed with NSCLC met the REAL-Oncology study eligibility criteria between January 2007 and August 2017. Of these, 486 were excluded because of missing TNM staging information, resulting in an analysis cohort of 3739 patients. Patients had a median (interquartile range [IQR]) age of 73 (65–80) years and were evenly split by sex (table 1). Pathology findings were available for 2458 patients (65.7%), with the remaining 1281 (34.3%) being clinically diagnosed without pathological confirmation. Where pathology was available, NSQ was the most frequent subtype (45.2%), followed by SQ (33.3%), NOS (17.9%) and "Other" NSCLC (3.6%; table 1).

Over the study period, 717 patients (19.2%) were diagnosed with stage I disease, 434 (11.6%) with stage II, and 806 (21.6%) with stage III; almost half of patients (47.7%) were diagnosed with stage IV disease. The proportion of patients diagnosed with stage I disease increased from 16.4% in 2010 to 27.7% in 2017 (figure 1), while diagnoses of stage IIIA and IIIB NSCLC remained stable over time. There was an overall reduction in the proportion of patients diagnosed at stage IV, from 57.0% in 2010 to 39.1% in 2017.

### *Treatments*

Over the study period, 2337 patients (62.5%) received an initial treatment within 6 months after diagnosis. As expected, treatment rates declined with increasing disease stage, from 78.2% for patients

diagnosed with stage I disease to 49.8% for those diagnosed with stage IV. The proportion of patients with early-stage (stage I–IIIA) NSCLC who did not receive treatment decreased over time; 21.2% of patients with stage I–IIIA disease remained untreated 6 months after diagnosis in 2013–2017 compared with 32.3% in 2007–2012 (data not shown). The proportion of patients with stage IV disease remaining untreated decreased among those with NSQ, while no changes were observed among those with SQ (figure 2).

*Initial treatments over time (stages I–IV)*

Figure 2 shows the evolution of initial treatments by TNM stage between 2007–2012 and 2013–2017 in patients with NSQ and SQ and in those who were clinically diagnosed. Over the study period, patients diagnosed with pathologically confirmed stage I disease were most commonly treated with curative surgery alone or, to a lesser extent, curative radiotherapy alone. The proportion receiving surgery alone as initial treatment increased between 2007–2012 and 2013–2017; conversely, the proportion receiving radiotherapy alone decreased. Among patients with clinically diagnosed stage I disease, the proportion receiving radiotherapy increased between 2007–2012 and 2013–2017 (from 39.1% to 60.3%; figure 2).

For patients with pathologically confirmed stage II disease, there was no notable difference in the use of surgery (alone or with adjuvant therapy) between 2007–2012 and 2013–2017. In 2013–2017, among patients with NSQ and SQ, respectively, 37.3% and 29.7% received surgery alone and 21.6% and 17.6% received surgery associated with (neo)adjuvant therapy (mostly adjuvant SACT). Radiotherapy alone was the most common treatment for patients with clinically diagnosed stage II disease, with 30.9% treated in 2007–2012 compared with 45.5% in 2013–2017.

Among the patients diagnosed with pathologically confirmed stage IIIA disease, the proportion receiving SACT plus radiotherapy (chemoradiation) increased to around one-third in 2013–2017. Some differences in the use of surgery were observed according to histology. In 2013–2017, one-third of patients with

NSQ received surgery (surgery alone, 12.3%; surgery associated with adjuvant therapy, 17.5%), and only around 15% of patients with SQ disease received surgery (mostly surgery alone).

For patients diagnosed with stage IIIB or IV NSQ, initial treatment with SACT (with or without radiotherapy) increased between 2007–2012 and 2013–2017, largely as the proportion of untreated patients decreased; it is likely that some patients with stage IIIB disease received chemoradiation with curative intent. Treatment of patients with stage IIIB or IV SQ disease remained similar between the two time periods.

### *Patterns of SACT use in advanced NSCLC (stages IIIB–IV)*

Of the 2119 patients diagnosed with stage IIIB–IV NSCLC during the study period, 648 (30.6%) received a first LoT, 223 (10.5%) received a second LoT and 60 (2.8%) received a third LoT. Similar proportions of patients with stage IIIB–IV NSQ and SQ received a first LoT (45.0% and 45.5%, respectively). Higher proportions of patients with stage IIIB or IV NSQ received second and third LoTs (17.9% and 5.6%, respectively) compared with SQ NSCLC (13.6% and 2.8%, respectively).

The most common first LoT regimens for patients with stage IIIB–IV NSCLC were platinum-based chemotherapy doublets; in 2007–2012, carboplatin plus gemcitabine was the most common (39.9% of treated patients; data not shown); in 2013–2017, carboplatin plus pemetrexed was the most common (28.7% of treated patients; table 2). The proportions of patients with NSQ receiving cisplatin- and pemetrexed-based regimens increased between 2007–2012 and 2013–2017 (table 2).

Among 119 patients with NSQ receiving a second LoT, the most common treatment was a TKI (65.5%); however, use of TKIs in the second line decreased over time. Among 54 patients with SQ receiving a second LoT, the most common treatment was also a TKI (53.7%); use of TKIs in the second line also decreased over time in this sub-cohort, concomitant with an increase in use of platinum-based

chemotherapies. Given the late introduction of ICIs with respect to the study cohort (January 2017), a relatively small proportion of patients with stage IIIB–IV NSQ and SQ received second-line treatment with an ICI in 2013–2018.

*Duration of SACT treatment (stages IIIB–IV)*

For patients with stage IIIB–IV NSCLC who received first-line platinum-based chemotherapy, treatment duration was similar over the analysis period. In 2013–2017, the median (IQR) treatment duration was 2.8 (1.4–3.2) months for patients with NSQ and 2.2 (1.4–2.8) months for patients with SQ.

Among the small number of patients with stage IIIB–IV NSQ who received a TKI in the first line, median treatment durations were consistent over time at around 5 months. For patients with stage IIIB–IV NSCLC who received a second LoT, the median (IQR) treatment duration for those treated in 2013–2018 was 2.5 [1.4–5.4] months for those with NSQ and 2.1 [1.4–2.4] months for those with SQ.

## *Overall survival*

*Overall survival over time (stages I, II and IIIA)*

For patients with stage I NSQ, median (IQR) OS from diagnosis was 55.3 (24.8–98.5) months for those diagnosed in 2007–2012 and was not reached (NR; 34.2 months–NR) for those diagnosed in 2013–2017; median OS increased among patients with stage I SQ (from 37.3 [18.5–66.8] to 51.1 [32.6–NR] months) (figure 3A). Median (IQR) OS for patients with stage I NSCLC without pathological diagnosis increased slightly from 16.7 (5.8–33.1) to 20.9 (8.0–40.3) months between 2007–2012 and 2013–2017, respectively.

Median (IQR) OS for patients with stage II NSQ was 34.3 (10.6–80.0) months for those diagnosed in 2007–2012 and 26.4 (10.2–58.0) months for those diagnosed in 2013–2017; in patients with stage II SQ, the respective median OS was 17.2 (8.6–58.2) and 19.9 (7.2–53.9) months (figure 3B). For patients

without pathological diagnosis and stage II disease, median (IQR) OS increased slightly from 8.9 (2.9–16.8) to 11.3 (5.4–26.9) months, respectively, over the same periods.

Among patients with stage IIIA NSQ, median (IQR) OS increased from 9.9 (6.5–38.6) months for those diagnosed in 2007–2012 to 24.0 (10.6–NR) months for those diagnosed in 2013–2017; median (IQR) OS also increased among patients with stage IIIA SQ (from 10.7 [4.4–21.1] to 14.5 [8.4–36.0] months) (figure 3C). Significant improvement in 1-year OS was observed in patients with NSQ, which increased from 45% (33%–61%) to 74% (63%–87%). Median (IQR) OS among patients with stage IIIA NSCLC without confirmed pathology remained low over the study period at around 5 months.

*Overall survival over time (stage IIIB–IV)*

Median OS and landmark OS rates for patients with stage IIIB–IV NSQ or SQ were similar for those diagnosed in 2007–2012 and 2013–2017, with no notable changes over time (figure 3D). During both periods, less than 10% of patients with stage IIIB–IV NSQ or SQ were alive 3 years after diagnosis. Median OS for clinically diagnosed patients with stage IIIB–IV NSCLC was 1.2 months for both time periods (figure 3D).

## Discussion

These data from the REAL-Oncology database, part of I-O Optimise, provide insight into NSCLC management largely prior to the reimbursement of immunotherapies in the United Kingdom. Over the analysis period (2007–2017, with follow-up to 2018), most patients with NSCLC in this database were diagnosed with advanced disease. This is consistent with the overall proportion of patients with NSCLC and available TNM staging diagnosed in England in 2017, of whom around 50% had stage IV disease,[16] and with real-world evidence across Europe from the same period.[17,18]

Nevertheless, in our analysis, there was an 11.6% increase in the proportion of patients diagnosed with stage I NSCLC between 2010 and 2017. The Cancer Reform Strategy,[19] implemented in England in 2007, aimed to build upon advances made following the introduction of the NHS Cancer Plan in 2000,[19] which was designed to close the survival gap for patients with cancer in England compared with those in countries with similar heathcare systems. The strategy further aimed to improve cancer prevention, early diagnosis and patient management and led to the establishment of the National Cancer Equality initiative (2008)[20] and the National Awareness and Early Diagnosis Initiative (NAEDI)[21] in collaboration with Cancer Research UK (2008).[22] Consequently, the increased proportion of patients diagnosed with stage I NSCLC in the present analysis may partly reflect the impact of these reforms on cancer diagnosis in England during the study period. Notably, the proportion of patients diagnosed with early-stage NSCLC in the REAL-Oncology database was slightly higher than that reported for all lung cancers in the 2017 National Audit for England (20% diagnosed at stage I; 8% at stage II).[16]

At the time of our analysis, no national lung cancer screening programme existed in the United Kingdom. However, a pilot programme originally funded by NAEDI began in Leeds in 2011 with the aim of assessing lung cancer outcomes in response to a range of public health interventions[23]. Consequently, between 2008–2010 and 2013–2015, there was an 80.8% increase in community referrals for chest X-rays and a significant stage-shift in diagnosis, with an 8.8% increase in patients diagnosed at stage I–II and a 9.3% reduction in those diagnosed at stage III–IV[23]. While these results are promising, lack of a concurrent control population over the same period meant that the relative contribution of other factors impacting diagnosis could not be determined. Final results from the NELSON study reported a significant reduction in 10-year mortality from lung cancer among male smokers who received regular CT screening compared with those who did not[24]. Similarly, the large US National Lung Screening Trial reported a 20% decreased risk of death from lung cancer among high-risk individuals screened with CT compared with those screened with radiography[25]. Taken together, these findings support the feasibility

of a UK-wide lung cancer screening programme, which could decrease the number of patients diagnosed with advanced NSCLC. In addition to the impact of screening, transition from the 6th to the 7th Edition of TNM classification for NSCLC in 2010 is likely to have impacted tumour staging at diagnosis.[26] Specifically, in the 7th edition, tumour size cutoffs for the T descriptor were revised, and the importance of pleural effusions and mediastinal invasion for the M descriptor were acknowledged, resulting in the upstaging of some tumours and the downstaging of others[6].

Consistent with National Audit data from England and with real-world evidence from Europe, the largest proportion of patients with available pathological data in the REAL-Oncology database had NSQ, mostly adenocarcinoma.[16,17,27] Our database also allowed the identification of clinically diagnosed patients, who accounted for 34% of the analysis population and tended to be older and have higher PS compared with those with confirmed pathology.[28]

Around 60% of analysed patients received at least one treatment, consistent with the 2017 National Audit (59%) for all lung cancers in England.[29] The initial treatment rate declined sequentially with increasing disease stage, a pattern previously observed in Europe.[17] There was a notable increase in the proportion of patients with stage I NSCLC who received surgery alone, possibly due to the aforementioned pilot program in Leeds during that time. In England and Wales, the proportion of patients undergoing resection for histologically confirmed NSCLC increased from 14% in 2008 to 22% in 2012. This may reflect both improvements in earlier diagnosis and changes in surgical practice.[28,30-32]

The proportion of patients with clinically diagnosed NSCLC receiving radiotherapy alone increased markedly, concomitant with a decrease in the proportion of untreated patients. This may reflect the increased use of stereotactic body radiation therapy as an alternative to surgery for patients with early-stage disease and contraindications for surgery. There was also a notable increase in the use of chemoradiation for patients with stage IIIA NSCLC over the study period, similar to reports from other

European population-based studies.[17,33] This followed the publication of data from several clinical trials, as well as a meta-analysis, demonstrating a significant survival benefit with concomitant versus sequential chemoradiation for patients with locally advanced NSCLC.[34] Additionally, advances in staging procedures, such as the use of positron emission tomography (PET)-CT, have enabled the identification of stage III patients with low nodal involvement who may benefit from chemoradiation. [35]

The observed changes in treatment patterns among patients with stage I–IIIA NSCLC in the REAL-Oncology database were mirrored by changes in survival. Survival outcomes for patients diagnosed with stage I NSCLC tended to improve over time. Again, the pilot screening programme in Leeds and/or the increase in surgical interventions among patients with NSQ and SQ and in radiotherapy use in patients who were clinically diagnosed could have driven these improvements. These findings are consistent with marginal improvements in survival among patients diagnosed with early-stage NSCLC in England during the period of our study.[36] Additionally, this may reflect the effects of super staging, with the introduction of PET scanning and endoscopic sampling of lymph nodes.[37] Improved survival outcomes for patients diagnosed with stage IIIA NSCLC may be related to the increased use of surgery with SACT or radiotherapy, and chemoradiation during the latter diagnostic period. Furthermore, transition to the 7th Edition of TNM classification for NSCLC in 2010 may have influenced subsequent treatment allocations and survival outcomes for some patients.[26]

Changes in the recommended management of advanced NSCLC in Europe from 2005, including the use of pemetrexed as maintenance therapy in the first-line setting for platinum-treated NSQ patients and the advent of new TKIs for patients with EGFR and ALK mutations, likely influenced the observed treatment patterns.[38,39] Additionally, during the course of our study, some patients with advanced NSCLC in England were granted access to ICIs via the Early Access to Medicines Scheme,[40,41] which is reflected by the small proportions of patients who received these treatments. Nevertheless, despite changes in treatment patterns, there was little change in survival outcomes for patients with advanced

NSCLC during the analysis period; the prognosis for these patients, particularly those with SQ, remained poor. Indeed, less than 10% of patients diagnosed with advanced NSCLC remained alive 3 years after diagnosis. While previous real-world studies have demonstrated similarly poor survival outcomes for patients with stage IIIB and IV NSCLC,[17,42] survival rates for patients with advanced lung cancer in the United Kingdom have historically been low compared with other developed countries. This has led to the implementation of several healthcare reforms and initiatives since 2000, which have so far made only limited progress at closing this survival gap, as reflected here.[43,44]

The REAL-Oncology database represents an unselected population, which is relevant to real-world practice and enables robust analyses across numerous subgroups over a long timeframe (>10 years). Furthermore, this data source allowed the identification of clinically diagnosed patients, a population not often captured and representing here more than one-third of patients with NSCLC. However, the current study includes only data from Leeds trust and may not be representative of clinical practice elsewhere in England. Additionally, limited information was available regarding radiotherapy at the time of this analysis (date of administration) and it was not therefore possible to formally differentiate palliative radiotherapy from radiotherapy with curative intent. It is hoped that improvements to the algorithm used and the subsequent availability of more detailed data regarding radiotherapy will address this limitation. Finally, data on biomarkers and comorbidities were not available.

Our findings provide valuable insight into the real-world treatment and survival outcomes for patients in the pre-immunotherapy era in Leeds and demonstrate that, irrespective of changes in treatment patterns and against a background of policy reforms, long-term survival for patients diagnosed with metastatic NSCLC remains poor. Future analyses from the REAL-Oncology database will help evaluate the impact of new TKIs and ICIs on OS for patients with NSCLC.

**FUNDING**

REAL-Oncology is a collaboration between Leeds Teaching Hospital NHS Trust, the University of Leeds and IQVIA. Commercial clients of IQVIA include Bristol Myers Squibb, which funded the project this work is based on. REAL-Oncology retains all operational, scientific, and communications controls.

**COMPETING INTERESTS**

REAL-Oncology is a collaboration between Leeds Teaching Hospital NHS Trust and IQVIA. Commercial clients of IQVIA include Bristol Myers Squibb Company (BMS), which funded the project this work is based on. REAL-Oncology retains all operational, scientific and communications controls. GH is an employee of the University of Leeds and holds an honorary contract with Leeds Teaching Hospital NHS Trust. GH leads the Leeds Teaching Hospitals NHS Trust real-world evidence team collaboration with IQVIA and, as part of this collaboration, IQVIA funds the staff who support this work. GH also reports partial grant funding for a collaboration outside this study from IQVIA. MS was an employee at Leeds Teaching Hospital NHS Trust at the time of the study, and he holds an honorary contract with Leeds Teaching Hospital NHS Trust. MS, MT and MR are employees of IQVIA. WS and SC are subcontracted to IQVIA and hold honorary contracts with Leeds Teaching Hospital NHS Trust. MS receives consultancy fees from BMS. CC, MD and JP are employees of BMS. CC and JP report stock ownership in BMS. LL was contracted (paid) as a consultant by BMS to support the I-O Optimise initiative and is an employee of Epi-Fit. There are no further conflicts of interest.

**AUTHOR CONTRIBUTIONS**

LL, CC, MD and JP conceived and designed the study, with contributions from MS, MT and WS. GH is the lead for the Leeds Teaching Hospital NHS Trust Real world programme, clinical lead for the Patient Pathway Manager (the Electronic Health Record) and Professor of Cancer Medicine and Digital Health (University of Leeds). SC is the Senior Information Officer working with the REAL-Oncology team at Leeds Teaching Hospital NHS Trust. MS provided expertise to REAL-Oncology regarding the management of

lung cancer. MS, MT, WS and MR analysed the data. All authors contributed to the interpretation of the data, the drafting of the work and subsequent critical revision of the manuscript. MS accepts full responsibility for the work and the conduct of the study and had full access to the data.

**DATA SHARING**

The data analysed during the current study are available from the corresponding author on reasonable request. Study outputs will be made publicly available on Leeds Teaching Hospital NHS Trust website following publication.

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**TABLES**

**Table 1 Demographic and clinical characteristics of full patient population***

| | All NSCLC | NSQ | SQ | NSCLC NOS | Other NSCLC | Clinically diagnosed unknown pathology |
|---|---|---|---|---|---|---|
| **All stages** | **N=3739** | **n=1112** | **n=819** | **n=439** | **n=88** | **n=1281** |
| Age, years | | | | | | |
| Mean (SD) | 72.3 (10.9) | 68.6 (11.0) | 70.8 (9.4) | 68.9 (10.6) | 70.1 (10.7) | 78.0 (9.3) |
| Median (Q1–Q3) | 73 (65-80) | 69 (62-77) | 71 (64-77) | 69 (63-77) | 71 (63-78) | 79 (72-85) |
| Range | 18-101 | 31-101 | 33-96 | 18-92 | 42-91 | 43-99 |
| Male, n (%) | 1881 (50.3) | 519 (46.7) | 505 (61.7) | 220 (50.1) | 49 (55.7) | 588 (45.9) |
| TNM stage, n (%) | | | | | | |
| IA | 469 (12.5) | 152 (13.7) | 65 (7.9) | 15 (3.4) | 9 (10.2) | 228 (17.8) |
| IB | 248 (6.6) | 71 (6.4) | 62 (7.6) | 15 (3.4) | 10 (11.4) | 90 (7.0) |
| IIA | 244 (6.5) | 72 (6.5) | 69 (8.4) | 20 (4.6) | 8 (9.1) | 75 (5.9) |

| | | | | | | |
|---|---|---|---|---|---|---|
| IIB | 190 (5.1) | 41 (3.7) | 63 (7.7) | <20 (<5.0) | <5 (<6.0) | 62 (4.8) |
| IIIA | 469 (12.5) | 110 (9.9) | 164 (20.0) | 54 (12.3) | 8 (9.1) | 133 (10.4) |
| IIIB | 337 (9.0) | 89 (8.0) | 117 (14.3) | <55 (<12.3) | <5 (<6.0) | 77 (6.0) |
| IV | 1782 (47.7) | 577 (51.9) | 279 (34.1) | 263 (59.9) | 47 (53.4) | 616 (48.1) |
| Pathology, n (%) | | | | | | |
| Adenocarcinoma | 1019 (27.3) | 1019 (91.6) | 0 | 0 | 0 | 0 |
| SQ | 819 (21.9) | 0 | 819 (100.0) | 0 | 0 | 0 |
| NSCLC NOS | 439 (11.7) | 0 | 0 | 439 (100.0) | 0 | 0 |
| Large cell carcinoma | 93 (2.5) | 93 (8.4) | 0 | 0 | 0 | 0 |
| Other NSCLC | 88 (2.4) | 0 | 0 | 0 | 88 (100.0) | 0 |
| Clinically diagnosed, unknown pathology | 1281 (34.3) | 0 | 0 | 0 | 0 | 1281 (100.0) |
| WHO performance score, n (%) | | | | | | |
| 0 | 292 (7.8) | 149 (13.4) | 70 (8.6) | 38 (8.7) | 12 (13.6) | 23 (1.8) |
| 1 | 1031 (27.6) | 445 (40.0) | 319 (39.0) | 144 (32.8) | 37 (42.2) | 86 (6.7) |

| | | | | | | |
|---|---|---|---|---|---|---|
| 2 | 758 (20.3) | 230 (20.7) | 230 (28.1) | 80 (18.2) | 25 (28.4) | 193 (15.1) |
| 3 | 933 (25.0) | 154 (13.9) | 118 (14.4) | 97 (22.1) | <15 (<17.0) | 553 (43.2) |
| 4 | 372 (10.0) | 39 (3.5) | 16 (2.0) | 26 (5.9) | 0 | 291 (22.7) |
| Missing | 353 (9.4) | 95 (8.5) | 66 (8.1) | <55 (<12.5) | <5 (<5.7) | 135 (10.5) |

*For some categories including low numbers of patients, data have been masked to conceal patient identities. Includes 6 patients diagnosed in 2006.

NOS, not otherwise specified; NSCLC, non-small cell lung cancer; NSQ, non-squamous cell carcinoma; Q, quartile; SD, standard deviation; SQ, squamous cell carcinoma; TNM, tumour, node and metastasis; WHO, World Health Organization.

**Table 2 First-line and second-line SACT in patients with stage IIIB–IV NSQ or SQ carcinoma***

| | NSQ | | SQ | |
|---|---|---|---|---|
| **First-line SACT†** | **2007–2012** | **2013–2017** | **2007–2012** | **2013–2017** |
| Patients receiving first-line SACT, N | **139** | **161** | **104** | **76** |
| Platinum-based chemotherapy, n (%)‡ | 109 (78.4) | 119 (73.9) | 97 (93.3) | 73 (96.1) |
| Carboplatin based | 93 (66.9) | 78 (48.4) | 88 (84.6) | 68 (65.4) |
| Cisplatin based | 11 (7.9) | 33 (20.5) | 9 (8.7) | <5 |
| Pemetrexed included | 58 (41.7) | 107 (77.0) | <5 | <5 |
| Non–platinum-based chemotherapy, n (%) | <5 | 0 | <5 | <5 |
| TKI, n (%) | 17 (12.2) | 34 (21.1) | 0 | <5 |
| Anti–PD-1/PD-L1 checkpoint inhibitors, n (%) | 0 | <5 | 0 | <5 |
| Clinical trial – unknown treatment, n (%) | 8 (5.8) | <5 | 5 (4.8) | 0 |

| **Second-line SACT[§]** | **2007–2012** | **2013–2018** | **2007–2012** | **2013–2018** |
|---|---|---|---|---|
| Patients receiving second-line SACT, N | **53** | **66** | **31** | **23** |
| Platinum-based therapy, n (%)[‡] | <5 | 13 (19.7) | 5 (16.1) | 8 (34.8) |
| Non–platinum-based chemotherapy, n (%) | <5 | 7 (10.6) | <5 | <5 |
| TKI, n (%) | 47 (88.7) | 31 (47.0) | 23 (74.2) | 6 (26.1) |
| Anti–PD-1/PD-L1 checkpoint inhibitors, n (%) | 0 | 10 (15.2) | 0 | 5 (21.7) |
| Clinical trial – unknown treatment, n (%) | 0 | <5 | 0 | 0 |

*For some categories including low numbers of patients, data have been masked to conceal patient identities. [†]Time periods for receipt of initial SACT are based on the date of diagnosis during two consecutive time periods (January 2007–December 2012 and January 2013–August 2017). [‡]Platinum based is defined as any regimen including a platinum agent (monotherapy or in combination) and is further defined as "carboplatin based," "cisplatin based" (including regimens in which carboplatin and cisplatin were both used) and "pemetrexed included" (any platinum-based regimen also including pemetrexed). [§]Time periods for receipt of second-line SACT are based on the start date for second-line treatment during three consecutive time periods (January 2007–December 2012, January 2013–December 2016, and January 2017–April 2018).

NSQ, non-squamous cell carcinoma; PD-1, programmed death 1; PD-L1, programmed death ligand 1; SACT, systemic anticancer therapy; SQ, squamous cell carcinoma; TKI, tyrosine kinase inhibitor.

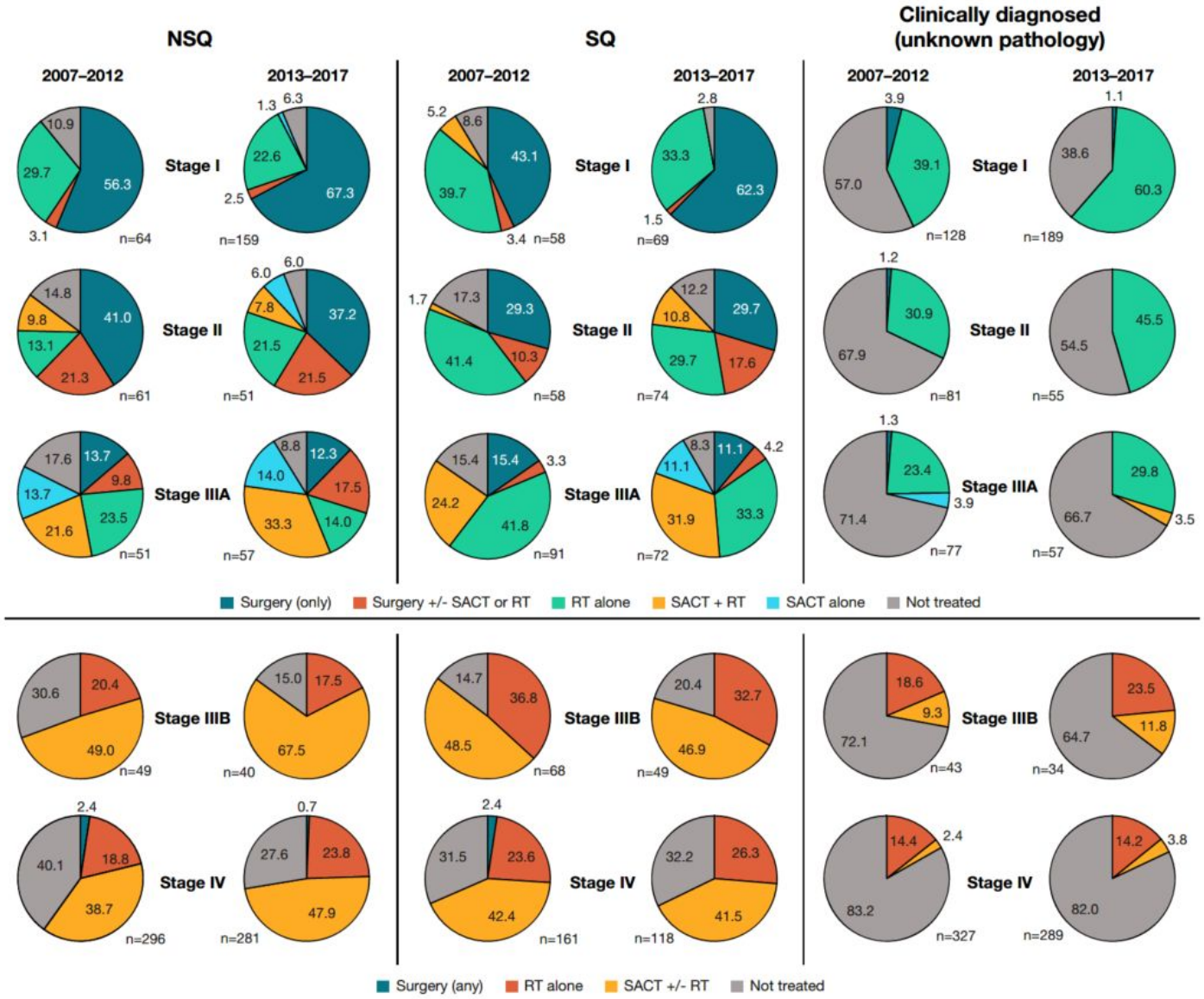
**FIGURES**

**Figure 1 TNM stage at NSCLC incident diagnosis, by year of diagnosis***


*Excludes six patients diagnosed in 2006. †Diagnosed up to 31 August 2017.

TNM, tumour, node and metastasis.

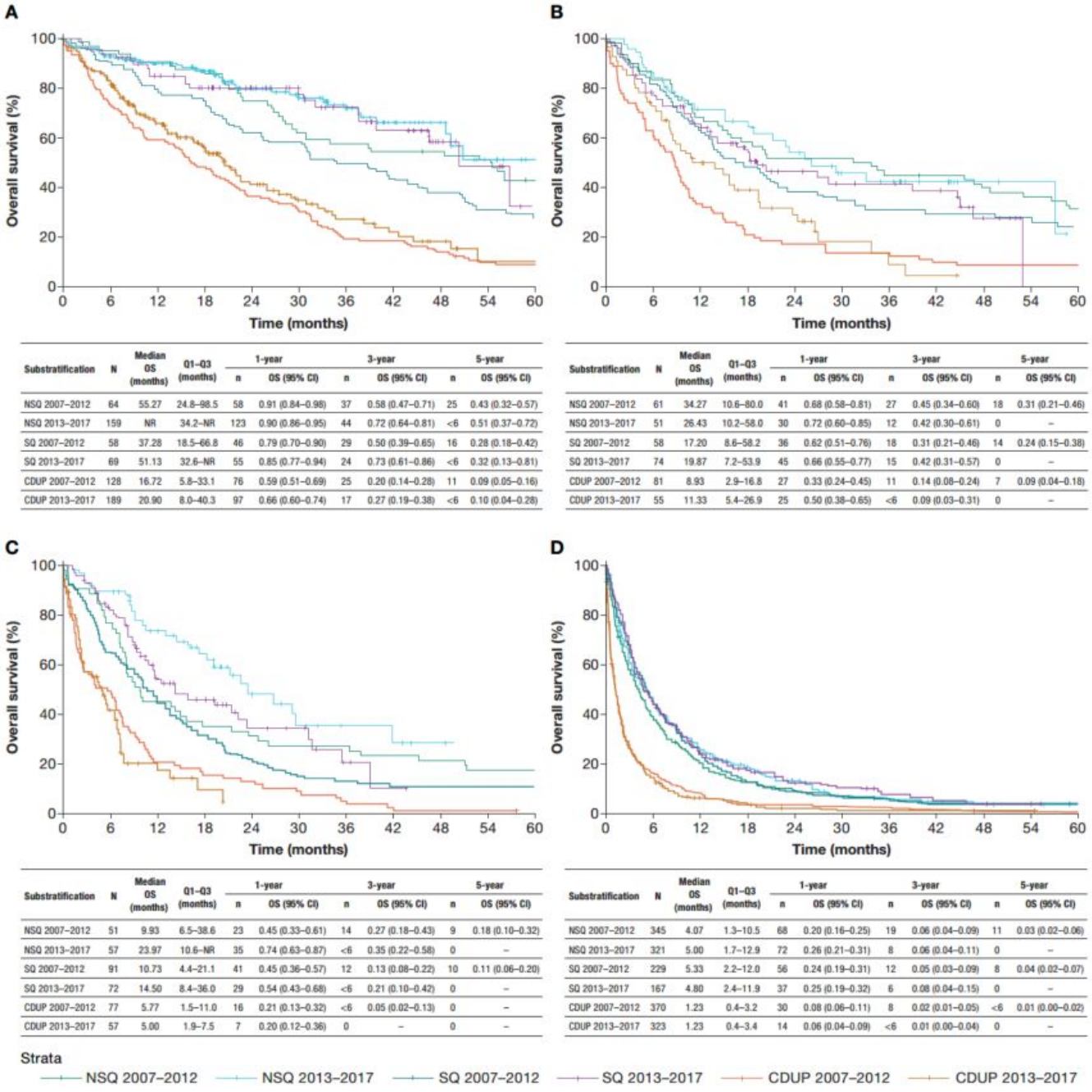
**Figure 2** Initial treatment by TNM stage and time period (2007–2012 vs 2013–2017) in patients with (A) NSQ, (B) SQ or (C) CDUP*,†



*Time periods for receipt of initial treatment are based on the date of diagnosis during two consecutive time periods (January 2007–December 2012 and January 2013–August 2017). †Where analytical groups included fewer than five patients, percentages are not shown as labels.

CDUP, clinically diagnosed with unknown pathology; NSQ, non-squamous cell carcinoma; RT, radiotherapy; SACT, systemic anticancer therapy; SQ, squamous cell carcinoma; TNM, tumour, node and metastasis; Tx, treatment.

**Figure 3 Evolution of OS in patients diagnosed with stage I (A), stage II (B), stage IIIA (C) or stage IIIB–IV (D) NSCLC with NSQ, SQ or CDUP**




| Substratification | N | Median OS (months) | Q1–Q3 (months) | 1-year n | 1-year OS (95% CI) | 3-year n | 3-year OS (95% CI) | 5-year n | 5-year OS (95% CI) |
|---|---|---|---|---|---|---|---|---|---|
| NSQ 2007–2012 | 64 | 55.27 | 24.8–98.5 | 58 | 0.91 (0.84–0.98) | 37 | 0.58 (0.47–0.71) | 25 | 0.43 (0.32–0.57) |
| NSQ 2013–2017 | 159 | NR | 34.2–NR | 123 | 0.90 (0.86–0.95) | 44 | 0.72 (0.64–0.81) | <6 | 0.51 (0.37–0.72) |
| SQ 2007–2012 | 58 | 37.28 | 18.5–66.8 | 46 | 0.79 (0.70–0.90) | 29 | 0.50 (0.39–0.65) | 16 | 0.28 (0.18–0.42) |
| SQ 2013–2017 | 69 | 51.13 | 32.6–NR | 55 | 0.85 (0.77–0.94) | 24 | 0.73 (0.61–0.86) | <6 | 0.32 (0.13–0.81) |
| CDUP 2007–2012 | 128 | 16.72 | 5.8–33.1 | 76 | 0.59 (0.51–0.69) | 25 | 0.20 (0.14–0.28) | 11 | 0.09 (0.05–0.16) |
| CDUP 2013–2017 | 189 | 20.90 | 8.0–40.3 | 97 | 0.66 (0.60–0.74) | 17 | 0.27 (0.19–0.38) | <6 | 0.10 (0.04–0.28) |

| Substratification | N | Median OS (months) | Q1–Q3 (months) | 1-year n | 1-year OS (95% CI) | 3-year n | 3-year OS (95% CI) | 5-year n | 5-year OS (95% CI) |
|---|---|---|---|---|---|---|---|---|---|
| NSQ 2007–2012 | 61 | 34.27 | 10.6–80.0 | 41 | 0.68 (0.58–0.81) | 27 | 0.45 (0.34–0.60) | 18 | 0.31 (0.21–0.46) |
| NSQ 2013–2017 | 51 | 26.43 | 10.2–58.0 | 30 | 0.72 (0.60–0.85) | 12 | 0.42 (0.30–0.61) | 0 | – |
| SQ 2007–2012 | 58 | 17.20 | 8.6–58.2 | 36 | 0.62 (0.51–0.76) | 18 | 0.31 (0.21–0.46) | 14 | 0.24 (0.15–0.38) |
| SQ 2013–2017 | 74 | 19.87 | 7.2–53.9 | 45 | 0.66 (0.55–0.77) | 15 | 0.42 (0.31–0.57) | 0 | – |
| CDUP 2007–2012 | 81 | 8.93 | 2.9–16.8 | 27 | 0.33 (0.24–0.45) | 11 | 0.14 (0.08–0.24) | 7 | 0.09 (0.04–0.18) |
| CDUP 2013–2017 | 55 | 11.33 | 5.4–26.9 | 25 | 0.50 (0.38–0.65) | <6 | 0.09 (0.03–0.31) | 0 | – |

| Substratification | N | Median OS (months) | Q1–Q3 (months) | 1-year n | 1-year OS (95% CI) | 3-year n | 3-year OS (95% CI) | 5-year n | 5-year OS (95% CI) |
|---|---|---|---|---|---|---|---|---|---|
| NSQ 2007–2012 | 51 | 9.93 | 6.5–38.6 | 23 | 0.45 (0.33–0.61) | 14 | 0.27 (0.18–0.43) | 9 | 0.18 (0.10–0.32) |
| NSQ 2013–2017 | 57 | 23.97 | 10.6–NR | 35 | 0.74 (0.63–0.87) | <6 | 0.35 (0.22–0.58) | 0 | – |
| SQ 2007–2012 | 91 | 10.73 | 4.4–21.1 | 41 | 0.45 (0.36–0.57) | 12 | 0.13 (0.08–0.22) | 10 | 0.11 (0.06–0.20) |
| SQ 2013–2017 | 72 | 14.50 | 8.4–36.0 | 29 | 0.54 (0.43–0.68) | <6 | 0.21 (0.10–0.42) | 0 | – |
| CDUP 2007–2012 | 77 | 5.77 | 1.5–11.0 | 16 | 0.21 (0.13–0.32) | <6 | 0.05 (0.02–0.13) | 0 | – |
| CDUP 2013–2017 | 57 | 5.00 | 1.9–7.5 | 7 | 0.20 (0.12–0.36) | 0 | – | 0 | – |

| Substratification | N | Median OS (months) | Q1–Q3 (months) | 1-year n | 1-year OS (95% CI) | 3-year n | 3-year OS (95% CI) | 5-year n | 5-year OS (95% CI) |
|---|---|---|---|---|---|---|---|---|---|
| NSQ 2007–2012 | 345 | 4.07 | 1.3–10.5 | 68 | 0.20 (0.16–0.25) | 19 | 0.06 (0.04–0.09) | 11 | 0.03 (0.02–0.06) |
| NSQ 2013–2017 | 321 | 5.00 | 1.7–12.9 | 72 | 0.26 (0.21–0.31) | 8 | 0.06 (0.04–0.11) | 0 | – |
| SQ 2007–2012 | 229 | 5.33 | 2.2–12.0 | 56 | 0.24 (0.19–0.31) | 12 | 0.05 (0.03–0.09) | 8 | 0.04 (0.02–0.07) |
| SQ 2013–2017 | 167 | 4.80 | 2.4–11.9 | 37 | 0.25 (0.19–0.32) | 6 | 0.08 (0.04–0.15) | 0 | – |
| CDUP 2007–2012 | 370 | 1.23 | 0.4–3.2 | 30 | 0.08 (0.06–0.11) | 8 | 0.02 (0.01–0.05) | <6 | 0.01 (0.00–0.02) |
| CDUP 2013–2017 | 323 | 1.23 | 0.4–3.4 | 14 | 0.06 (0.04–0.09) | <6 | 0.01 (0.00–0.04) | 0 | – |

CDUP, clinically diagnosed with unknown pathology; NSCLC, non-small cell lung cancer; NSQ, non-squamous cell carcinoma; OS, overall survival; SQ, squamous cell carcinoma.

**SUPPLEMENTARY APPENDIX**

## Appendix

**Table S1.** ICD-O-3 morphology codes for NSCLC.

| Morphology code | Type of NSCLC |
|---|---|
| | **Adenocarcinoma (non-squamous NSCLC)** |
| 81403 | Adenocarcinoma UNS |
| 81443 | Enteric adenocarcinoma |
| 82303 | Solid adenocarcinoma with mucin production |
| 82443 | MANEC mixed adenoneuroendocrine carcinoma |
| 82500 | Atypical adenomatous hyperplasia |
| 82502 | Adenocarcinoma in situ, non-mucinous |
| 82503 | Adenocarcinoma, bronchiolo-alveolar (BAC), bronchiolar carcinoma, (incl pathologic in situ-variant) |
| 82523 | Bronchiolo-alveolar carcinoma |
| 82532 | Adenocarcinoma in situ, mucinous |
| 82533 | Adenocarcinoma, mucinous bronchiolo-alveolar (BAC) |
| 82543 | Bronchiolo-alveolar carcinoma, mixed mucinous and non-mucinous |

| Morphology code | Type of NSCLC |
|---|---|
| 82553 | Adenocarcinoma, mixed with other types of carcinoma incl. squamous cell and small-cell carcinoma |
| 82563 | Minimally invasive adenocarcinoma, non-mucinous |
| 82573 | Minimally invasive adenocarcinoma, mucinous |
| 82603 | Papillary adenocarcinoma, NOS |
| 82653 | Micropapillary adenocarcinoma |
| 83103 | Clear cell adenocarcinoma |
| 83333 | Fetal adenocarcinoma |
| 84703 | Mucinous cystadenocarcinoma |
| 84803 | Mucinous adenocarcinoma |
| 84903 | Signet ring cell carcinoma |
| 85503 | Acinar cell carcinoma |
| 85513 | Acinar adenocarcinoma |
| | **Squamous cell carcinoma** |
| 80523 | Papillary squamous cell carcinoma |
| 80702 | Squamous cell carcinoma in situ |
| 80703 | Squamous cell carcinoma |

| Morphology code | Type of NSCLC |
|---|---|
| 80713 | Keratinizing squamous cell carcinoma |
| 80723 | Non-keratinizing squamous cell carcinoma |
| 80733 | Squamous cell carcinoma, small cell non-keratinizing |
| 80833 | Basaloid squamous cell carcinoma |
| 80843 | Squamous cell carcinoma, clear cell type |
| | **NSCLC NOS** |
| 80103 | Carcinoma, NOS |
| 80203 | Carcinoma, undifferentiated NOS |
| 80213 | Carcinoma, anaplastic NOS |
| 80463 | Carcinoma, non-small cell unspecified |
| | **Large cell carcinoma (non-squamous NSCLC)** |
| 80123 | Large-cell carcinoma, unspecified |
| | **Neuroendocrine NSCLC carcinoma (other specified NSCLC carcinoma)** |
| 80133 | Large cell neuroendocrine carcinoma |
| 82463 | Neuroendocrine carcinoma, NOS |
| | **Other miscellaneous NSCLC (other specified NSCLC carcinoma)** |

| Morphology code | Type of NSCLC |
|---|---|
| 80143 | Large cell carcinoma with rhabdoid phenotype |
| 80223 | Sarcomatoid carcinoma, pleomorphic |
| 80233 | NUT carcinoma |
| 80303 | Spindle cell and giant cell carcinoma |
| 80313 | Giant cell carcinoma |
| 80323 | Spindle cell carcinoma, NOS |
| 80333 | Pseudosarcomatous carcinoma |
| 81233 | Basaloid carcinoma |
| 82003 | Adenocystic carcinoma |
| 84303 | Mucoepidermoid carcinoma |
| 85603 | Adenosquamous carcinoma |
| 85623 | Epithelial-myoepithelial carcinoma |
| 89723 | Blastoma, pulmonary (pneumoblastoma) |
| 89803 | Carcinosarcoma, NOS |
| 89823 | Myoepithelial carcinoma |

ICD-O-3, *International Classification of Diseases for Oncology*, 3rd Edition; NOS, not otherwise specified; NSCLC, non-small cell lung cancer; UNS, unspecified.

**Table S2.** Initial treatment algorithm. Initial treatment was defined as the first treatment received within 6 months of diagnosis, associated with any other treatment received within a certain time period following first treatment as defined in the table below.

| **Initial treatment category** | **Definitions** |
|---|---|
| A. Surgery | Sum of all A sub-groups |
| A0. Surgery only | Surgery + no SACT or RT within 12 weeks after surgery |
| A1. Surgery + adjuvant SACT (only) – no RT within 6 months of SACT start | Surgery + identification of SACT only (start) within 84 days (12 weeks) after surgery |
| A2. Surgery + adjuvant RT (only) – no SACT within 6 months of RT start | Surgery + identification of RT only (start) within 84 days (12 weeks) after surgery |
| A3. Surgery + adjuvant RT and SACT | Surgery + identification of RT [or SACT] (start) within 84 days (12 weeks) after surgery + identification of SACT [or RT] (start) within 180 days (6 months) after RT [or SACT] |

| | |
|---|---|
| A4. Neoadjuvant SACT + surgery | SACT + identification of surgery within 120 days (4 months) after first SACT regimen start + no RT identification prior to surgery<br><br>AND: |
| A5. Neoadjuvant RT + surgery | RT + identification of surgery within 90 days (3 months) after first RT treatment start + no SACT identification prior to surgery AND: |
| A6. Neoadjuvant SACT and RT + surgery | RT and SACT + identification of surgery within 3 months after start + identification of SACT and RT prior to surgery<br><br>Note: Neoadjuvant SACT and RT corresponds to RT within 6 weeks of SACT start |
| B. Radiotherapy alone | RT + no SACT nor surgery within 90 days (3 months) after RT |
| C. SACT + Radiotherapy | Sum of C1, C2 and C3 |
| C1. RT followed by SACT | RT + identification of SACT within 90 days (3 months) after first SACT regimen start + no surgery within 6 months after first SACT start |

| | |
|---|---|
| C2. SACT followed by RT | SACT + identification of RT within 90 days (3 months) after first SACT regimen start + no surgery within 6 months after first SACT start |
| C3. Concurrent chemoradiation | SACT + [start RT within 6 weeks of SACT] + no surgery within 3 months after chemoradiation |
| D. SACT alone | SACT + no RT nor surgery within 90 days (3 months) after first SACT regimen start |
| E. Not treated | No SACT, surgery or RT identified over entire follow-up period |

RT, radiotherapy; SACT, systemic anticancer therapy

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Figure 1 TNM stage at NSCLC incident diagnosis, by year of diagnosis*

145x101mm (300 x 300 DPI)

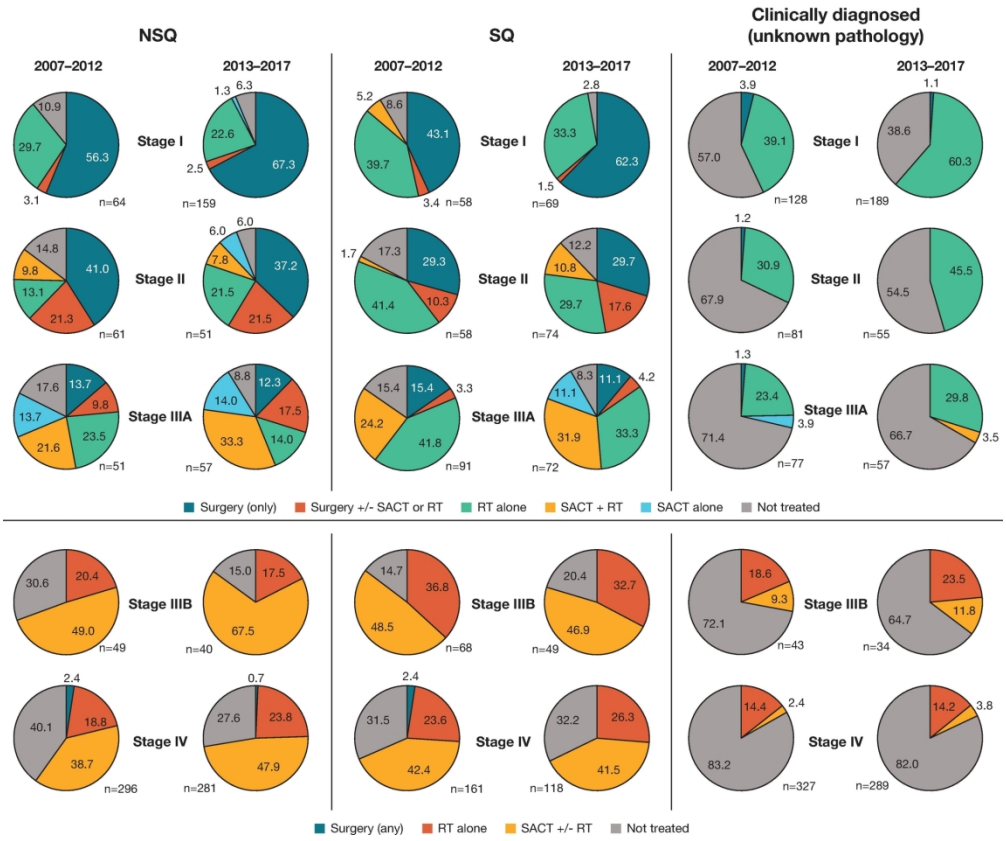
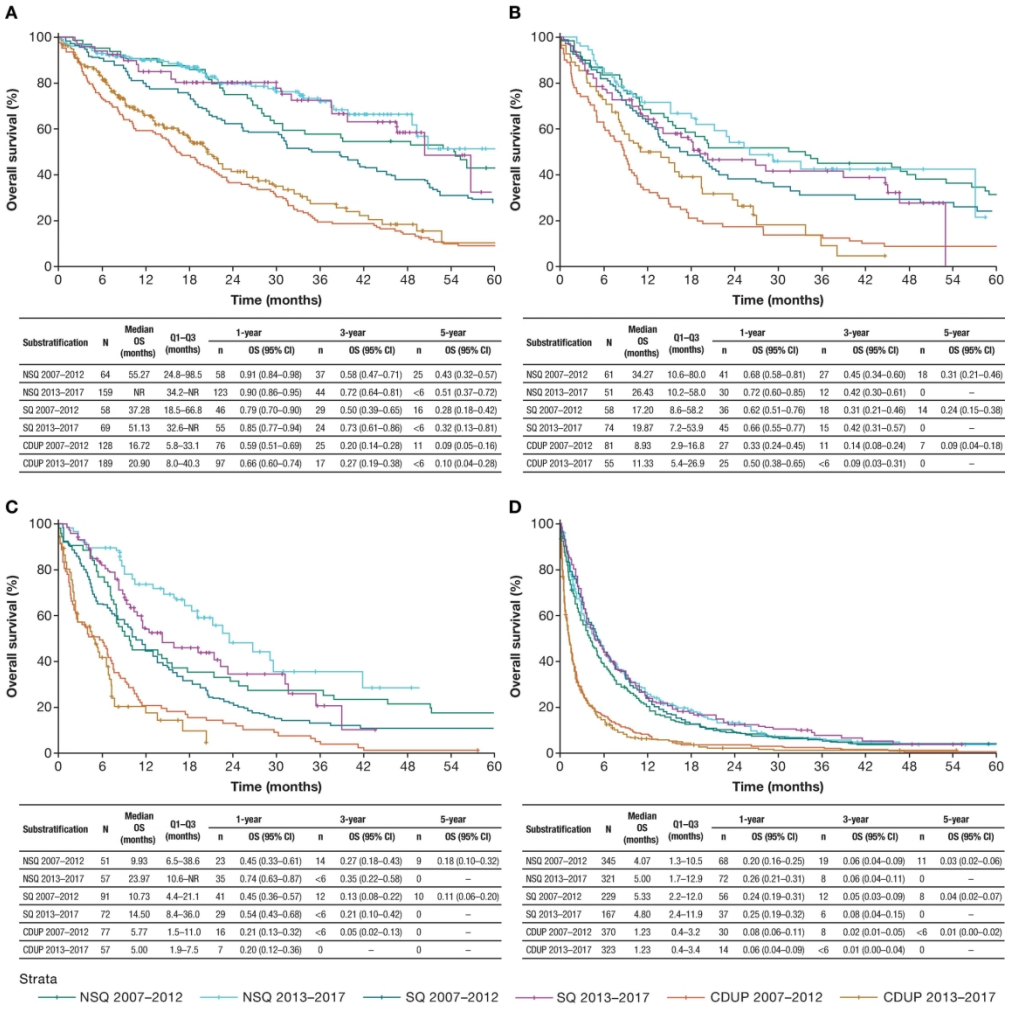



Figure 2 Initial treatment by TNM stage and time period (2007–2012 vs 2013–2017) in patients with (A) NSQ, (B) SQ or (C) CDUP*,†

179x148mm (300 x 300 DPI)




| Substratification | N | Median OS (months) | Q1–Q3 (months) | 1-year n | 1-year OS (95% CI) | 3-year n | 3-year OS (95% CI) | 5-year n | 5-year OS (95% CI) |
|---|---|---|---|---|---|---|---|---|---|
| NSQ 2007–2012 | 64 | 55.27 | 24.8–98.5 | 58 | 0.91 (0.84–0.98) | 37 | 0.58 (0.47–0.71) | 25 | 0.43 (0.32–0.57) |
| NSQ 2013–2017 | 159 | NR | 34.2–NR | 123 | 0.90 (0.86–0.95) | 44 | 0.72 (0.64–0.81) | <6 | 0.51 (0.37–0.72) |
| SQ 2007–2012 | 58 | 37.28 | 18.5–66.8 | 46 | 0.79 (0.70–0.90) | 29 | 0.50 (0.39–0.65) | 16 | 0.28 (0.18–0.42) |
| SQ 2013–2017 | 69 | 51.13 | 32.6–NR | 55 | 0.85 (0.77–0.94) | 24 | 0.73 (0.61–0.86) | <6 | 0.32 (0.13–0.81) |
| CDUP 2007–2012 | 128 | 16.72 | 5.8–33.1 | 76 | 0.59 (0.51–0.69) | 25 | 0.20 (0.14–0.28) | 11 | 0.09 (0.05–0.16) |
| CDUP 2013–2017 | 189 | 20.90 | 8.0–40.3 | 97 | 0.66 (0.60–0.74) | 17 | 0.27 (0.19–0.38) | <6 | 0.10 (0.04–0.28) |

| Substratification | N | Median OS (months) | Q1–Q3 (months) | 1-year n | 1-year OS (95% CI) | 3-year n | 3-year OS (95% CI) | 5-year n | 5-year OS (95% CI) |
|---|---|---|---|---|---|---|---|---|---|
| NSQ 2007–2012 | 61 | 34.27 | 10.6–80.0 | 41 | 0.68 (0.58–0.81) | 27 | 0.45 (0.34–0.60) | 18 | 0.31 (0.21–0.46) |
| NSQ 2013–2017 | 51 | 26.43 | 10.2–58.0 | 30 | 0.72 (0.60–0.85) | 12 | 0.42 (0.30–0.61) | 0 | – |
| SQ 2007–2012 | 58 | 17.20 | 8.6–58.2 | 36 | 0.62 (0.51–0.76) | 18 | 0.31 (0.21–0.46) | 14 | 0.24 (0.15–0.38) |
| SQ 2013–2017 | 74 | 19.87 | 7.2–53.9 | 45 | 0.66 (0.55–0.77) | 15 | 0.42 (0.31–0.57) | 0 | – |
| CDUP 2007–2012 | 81 | 8.93 | 2.9–16.8 | 27 | 0.33 (0.24–0.45) | 11 | 0.14 (0.08–0.24) | 7 | 0.09 (0.04–0.18) |
| CDUP 2013–2017 | 55 | 11.33 | 5.4–26.9 | 25 | 0.50 (0.38–0.65) | <6 | 0.09 (0.03–0.31) | 0 | – |

| Substratification | N | Median OS (months) | Q1–Q3 (months) | 1-year n | 1-year OS (95% CI) | 3-year n | 3-year OS (95% CI) | 5-year n | 5-year OS (95% CI) |
|---|---|---|---|---|---|---|---|---|---|
| NSQ 2007–2012 | 51 | 9.93 | 6.5–38.6 | 23 | 0.45 (0.33–0.61) | 14 | 0.27 (0.18–0.43) | 9 | 0.18 (0.10–0.32) |
| NSQ 2013–2017 | 57 | 23.97 | 10.6–NR | 35 | 0.74 (0.63–0.87) | <6 | 0.35 (0.22–0.58) | 0 | – |
| SQ 2007–2012 | 91 | 10.73 | 4.4–21.1 | 41 | 0.45 (0.36–0.57) | 12 | 0.13 (0.08–0.22) | 10 | 0.11 (0.06–0.20) |
| SQ 2013–2017 | 72 | 14.50 | 8.4–36.0 | 29 | 0.54 (0.43–0.68) | <6 | 0.21 (0.10–0.42) | 0 | – |
| CDUP 2007–2012 | 77 | 5.77 | 1.5–11.0 | 16 | 0.21 (0.13–0.32) | <6 | 0.05 (0.02–0.13) | 0 | – |
| CDUP 2013–2017 | 57 | 5.00 | 1.9–7.5 | 7 | 0.20 (0.12–0.36) | 0 | – | 0 | – |

| Substratification | N | Median OS (months) | Q1–Q3 (months) | 1-year n | 1-year OS (95% CI) | 3-year n | 3-year OS (95% CI) | 5-year n | 5-year OS (95% CI) |
|---|---|---|---|---|---|---|---|---|---|
| NSQ 2007–2012 | 345 | 4.07 | 1.3–10.5 | 68 | 0.20 (0.16–0.25) | 19 | 0.06 (0.04–0.09) | 11 | 0.03 (0.02–0.06) |
| NSQ 2013–2017 | 321 | 5.00 | 1.7–12.9 | 72 | 0.26 (0.21–0.31) | 8 | 0.06 (0.04–0.11) | 0 | – |
| SQ 2007–2012 | 229 | 5.33 | 2.2–12.0 | 56 | 0.24 (0.19–0.31) | 12 | 0.05 (0.03–0.09) | 8 | 0.04 (0.02–0.07) |
| SQ 2013–2017 | 167 | 4.80 | 2.4–11.9 | 37 | 0.25 (0.19–0.32) | 6 | 0.08 (0.04–0.15) | 0 | – |
| CDUP 2007–2012 | 370 | 1.23 | 0.4–3.2 | 30 | 0.08 (0.06–0.11) | 8 | 0.02 (0.01–0.05) | <6 | 0.01 (0.00–0.02) |
| CDUP 2013–2017 | 323 | 1.23 | 0.4–3.4 | 14 | 0.06 (0.04–0.09) | <6 | 0.01 (0.00–0.04) | 0 | – |



Figure 3 Evolution of OS in patients diagnosed with stage I (A), stage II (B), stage IIIA (C) or stage IIIB–IV (D) NSCLC with NSQ, SQ or CDUP

178x178mm (300 x 300 DPI)

## STROBE checklist

| Treatment patterns and survival outcomes for patients with non-small cell lung cancer in the United Kingdom in the pre-immunology era: a REAL-Oncology database analysis from the I-O Optimise initiative | | | **Snee, et al.** |
|---|---|---|---|
| **Checklist item -** | | | **Section** |
| **Title and abstract** | | | |
| | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract | *Title, abstract* |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | *Abstract* |
| **Introduction** | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | *Introduction, p5–6* |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | *Introduction, p5–6* |
| **Methods** | | | |
| Study design | 4 | Present key elements of study design early in the paper | *Methods, Study design, p6* |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | *Methods, Study setting, p6–7 Analyses, p7–8* |
| Participants | 6 | (*a*) *Cohort study*? Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up | *Methods, Study design, p6–7* |
| | | (*b*) *Cohort study*? For matched studies, give matching criteria and number of exposed and unexposed | *N/A* |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | *Methods, Analyses p7* |

| | | | |
|---|---|---|---|
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | *Methods, Analyses, p7* |
| Bias | 9 | Describe any efforts to address potential sources of bias | *N/A, retrospective study* |
| Study size | 10 | Explain how the study size was arrived at | *N/A, retrospective study* |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | *Methods, Analyses, p8* |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | *Methods, Analyses, p8* |
| | | (*b*) Describe any methods used to examine subgroups and interactions | *Methods, Analyses, p8* |
| | | (*c*) Explain how missing data were addressed | *Methods, Analyses, p8* |
| | | (*d*) *Cohort study*? If applicable, explain how loss to follow-up was addressed | *N/A, retrospective study* |
| | | (*e*) Describe any sensitivity analyses | *N/A* |
| **Results** | | | |
| Participants | 13* | (*a*) Report numbers of individuals at each stage of study? eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | *Results, Patients, p8* |
| | | (*b*) Give reasons for non-participation at each stage | *Results, Patients, p8* |
| | | (*c*) Consider use of a flow diagram | *Not included* |

| | | | |
|---|---|---|---|
| Descriptive data | 14* | (*a*)Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | *Results, Patients, p8–6* |
| | | (*b*) Indicate number of participants with missing data for each variable of interest | *N/A* |
| | | (*c*) *Cohort study*? Summarise follow-up time (eg average and total amount) | *N/A* |
| Outcome data | 15* | *Cohort study*? Report numbers of outcome events or summary measures over time | *Results, Overall survival, p12–13* |
| | | *Case-control study?* Report numbers in each exposure category, or summary measures of exposure | *N/A* |
| | | *Cross sectional study?* Report numbers of outcome events or summary measures | |
| Main results | 16 | (a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | *Results, Overall survival, p12–13* |
| | | (b) Report category boundaries when continuous variables were categorized | *N/A* |
| | | (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | *Not included* |
| Other analyses | 17 | Report other analyses done? eg analyses of subgroups and interactions, and sensitivity analyses | *N/A* |
| **Discussion** | | | |
| Key results | 18 | Summarise key results with reference to study objectives | *Discussion, p13* |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | *Discussion, p16* |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | *Discussion* |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | *Discussion, 16–17* |

| **Other information** | | | |
|---|---|---|---|
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | *Funding, p17* |
| | | | |

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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# Treatment patterns and survival outcomes for patients with non-small cell lung cancer in the United Kingdom in the pre-immunology era: a REAL-Oncology database analysis from the I-O Optimise initiative



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# Treatment patterns and survival outcomes for patients with non-small cell lung cancer in the United Kingdom in the pre-immunology era: a REAL-Oncology database analysis from the I-O Optimise initiative

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**ABSTRACT *[300/300 words]***

**Objectives**

To report characteristics, treatment and overall survival (OS) trends, by stage and pathology, of patients diagnosed with non-small cell lung cancer (NSCLC) at Leeds Teaching Hospital NHS Trust in 2007–2018.

**Design**

Retrospective cohort study based on electronic medical records.

**Setting**

Large NHS university hospital in Leeds.

**Participants**

3739 adult patients diagnosed with incident NSCLC from January 2007–August 2017, followed until March 2018.

**Main outcome measures**

Patient characteristics at diagnosis, treatment patterns, OS.

**Results**

34.3% of patients with NSCLC were clinically diagnosed (without pathological confirmation). Among patients with known pathology, 45.2% had non-squamous cell carcinoma (NSQ); 33.3% had squamous cell carcinoma (SQ). The proportion of patients diagnosed at stage I increased (16.4%–27.7% in 2010–2017); those diagnosed at stage IV decreased (57.0%–39.1%). Surgery was the most common initial treatment for patients with pathologically confirmed stage I NSCLC. Use of radiotherapy alone increased over time in patients with clinically diagnosed stage I NSCLC (39.1%–60.3%); chemoradiation increased in patients with stage IIIA NSQ (21.6%–33.3%) and SQ (24.2%–31.9%). Initial treatment with systemic

anticancer therapy (SACT) increased in patients with stage IIIB–IV NSQ (49.0%–67.5%); the proportion of untreated patients decreased (30.6%–15.0%). Median OS improved for patients diagnosed with stage I NSQ and SQ and stage IIIA NSQ over time. Median OS for patients with stage IIIB–IV NSQ and SQ remained stable; <10% were alive 3 years after diagnosis. Median OS for clinically diagnosed stage IIIB–IV patients was 1.2 months in both periods.

**Conclusions**

OS for stage I and IIIA patients improved over time, likely due to increased stereotactic ablative radiation, surgery (stage I) and chemoradiation (stage IIIA) use. Conversely, OS outcomes remained poor for stage IIIB–IV patients despite increasing use of SACT for NSQ. Many patients with advanced-stage disease remained untreated.

**Article summary**

Strengths and limitations of this study

- This retrospective analysis of the REAL-Oncology database analysed the characteristics, treatment and overall survival trends for patients diagnosed with non-small cell lung cancer (NSCLC) over a 10-year period in a large regional hospital in the United Kingdom
- Data on prescribed systemic anticancer therapy, and pathology and radiology records were extracted from electronic medical records for adult patients diagnosed with incident NSCLC between 2007 and 2017 based on confirmed pathology or clinical data
- These data reflect outcomes and trends for a single site in the United Kingdom; however, the REAL-Oncology study represents an unselected population, which is relevant to real-world practice and enables long-term (>10 years) analyses across numerous subgroups
- This analysis included patients with a clinical diagnosis of NSCLC who, despite representing a large proportion of patients with NSCLC, are often not captured in real-world studies

## INTRODUCTION

In the United Kingdom, lung cancer is the third most common type of cancer and the leading cause of cancer death.[1] Around 85% of patients with lung cancer have non-small cell lung cancer (NSCLC), which consists predominantly of non-squamous cell carcinoma (NSQ) and squamous cell carcinoma (SQ).[2] Early diagnosis of lung cancer can be challenging.[3] Consequently, approximately two-thirds of patients present with advanced or metastatic NSCLC (stage III–IV), for which treatment options are limited and prognosis is poor;[4,5] 5-year survival rates for patients with metastatic disease are less than 5%.[5,6]

Surgery and radiotherapy can be used successfully in patients diagnosed with early-stage NSCLC; adjuvant chemotherapy is also indicated for selected patients who have undergone resection for stage II–III disease and can improve outcomes.[7] For advanced-NSCLC (stage IIIB–IV), chemotherapy with platinum-based agents has long been the standard of care for patients with good performance status (PS), and vascular endothelial growth factor–targeting therapies have been used in the first-line setting in patients with NSQ.[8] However, increased understanding of NSCLC driver mutations, such as those in the epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) genes, has led to the development of targeted therapies, including tyrosine kinase inhibitors (TKIs). These allow for more personalized treatment approaches in selected patients with actionable driver mutations.[8]

The development of immunotherapeutic agents has transformed the NSCLC treatment landscape. Since 2015, immune checkpoint inhibitors (ICIs) targeting the programmed death-1/programmed death ligand 1 axis have been approved in Europe and are now recommended for first- or second-line treatment of patients with metastatic NSCLC.[9] In addition, ongoing clinical trials are investigating neoadjuvant and adjuvant use of ICIs for patients diagnosed at earlier stages of NSCLC.[10-12] As with any new treatment, there is a need to assess how ICIs impact patient survival in real-world clinical practice to help inform future treatment decisions, which requires an understanding of the NSCLC landscape prior to their

availability. Real-world databases include a wealth of information that can be used to complement data from clinical trials and are a valuable source of evidence in a rapidly changing treatment landscape.

We report the characteristics, treatment and overall survival (OS) trends for patients diagnosed with NSCLC at a large teaching hospital in England prior to routine availability of ICIs. This study, based on the REAL-Oncology database, is part of the I-O Optimise program, an ongoing initiative leveraging real-world data sources to provide insights into the evolving landscape of thoracic malignancies, including NSCLC.[13]

## METHODS

### *Study setting*

REAL-Oncology is a research partnership between Leeds Cancer Centre (LCC), the University of Leeds and IQVIA®, using NHS oncology patient data to answer various research questions. LCC is a major NHS cancer centre that serves a metropolitan catchment area of 750 000 people for secondary care and over 5 million for tertiary care.

### *Ethics approval and consent to participate*

This study was completed with UK Health Research Authority approval through the National Institute for Health Research Integrated Research Approvals System. The research was performed in accordance with the Leeds Teaching Hospitals NHS Trust research governance framework; as a noninterventional retrospective descriptive study using existing patient records, the need for ethics approval was waived. The study was performed in accordance with the Declaration of Helsinki.

## *Study design*

This retrospective analysis extracted data on prescribed chemotherapy, and pathology and radiology records that were entered into electronic medical records (EMRs) at the Leeds Teaching Hospitals NHS Trust as part of routine clinical practice. The study included patients aged ≥18 years with an incident diagnosis of NSCLC (International Statistical Classification of Diseases and Related Health Problems, 10th Revision [ICD-10] code for malignant neoplasm of the trachea [C33] or malignant neoplasm of bronchus and lung [C34]) between January 2007 and August 2017 at Leeds Teaching Hospital. All patients diagnosed by the lung multidisciplinary team were included, including those clinically identified solely on the basis of history, clinical examination and computed tomography (CT), and those with confirmed pathology (ie, *International Classification of Diseases for Oncology*, 3rd Edition [ICD-O-3] code for NSCLC pathology, online supplementary appendix table S1). Patients were excluded if their first diagnosis of NSCLC was confirmed in another NHS hospital trust, they had missing data on age or sex, their ICD-O-3 morphology codes indicated small cell lung cancer (80413–80459), or they had a concomitant (within 5 years prior to NSCLC diagnosis) primary tumour at time of diagnosis, except for non-metastatic non-melanoma skin cancers or *in situ* or benign tumours. Patients with missing data on tumour, node, metastasis (TNM) classification were also excluded from the present analyses.

The end of follow-up was the date of death or end of study (April 2018). The date of death was confirmed by reconciliation of EMRs with Office for National Statistics death certifications. Patient sociodemographic (age, sex, World Health Organisation PS) and clinical characteristics (TNM stage, tumour pathology) were extracted on/at the nearest date to NSCLC diagnosis (index date). TNM classification at diagnosis was recorded according to the 6th edition of the TNM classification up to 31 December 2009[14]; the 7th edition from 1 January 2010[6]; and the 8th edition from 1 January 2017.[15] Tumour pathology was defined as NSQ (including adenocarcinoma and large cell carcinoma), SQ, NSCLC

not otherwise specified (NOS), “Other” (neuroendocrine carcinoma and other miscellaneous carcinoma) or “Unconfirmed” (clinically diagnosed unknown pathology).

The date of initial treatment was defined as the first instance of lung surgery, radiotherapy or systemic anticancer therapy (SACT) occurring within 6 months of diagnosis, and initial treatment categories were defined using all treatment received within a specified time period following this date (online supplementary appendix table S2). A line of therapy (LoT) was defined as one or more cycles of chemotherapy or continuous oral treatment for targeted agents in patients with incident stage IIIB–IV NSCLC. An algorithm based on the sequencing of SACT treatments received was developed to determine first and subsequent LoTs. LoT outputs were validated by clinicians.

### *Analyses*

Patient characteristics at diagnosis are described using summary statistics. The evolution of treatment patterns and OS over time were investigated in two sub-cohorts defined by date of diagnosis: January 2007 to December 2012, and January 2013 to August 2017. Therapy received and treatment duration are described by LoT for advanced-stage patients using the same time periods. OS was estimated using Kaplan–Meier methods. The proportions of patients surviving to 1, 2 or 3 years after the date of diagnosis are reported with corresponding two-sided 95% confidence intervals. Differences in OS between time periods were compared using log-rank hypothesis tests.

To comply with patient confidentiality requirements, data outputs relating to groups of fewer than five patients were masked. In some circumstances, data relating to larger patient subgroups were also masked to avoid extrapolation of counts of fewer than five patients.

### ***Patient and public involvement***

Patients or the public were not involved in the design, conduct, reporting or dissemination plans of our research.

## Results

### *Patients*

Overall, 4225 patients diagnosed with NSCLC between January 2007 and August 2017were included in the study. Of these, 486 were excluded because of missing TNM staging information, resulting in an analysis cohort of 3739 patients. Patients had a median (interquartile range [IQR]) age of 73 (65–80) years and were evenly split by sex (table 1). Pathology findings were available for 2458 patients (65.7%), with the remaining 1281 (34.3%) being clinically diagnosed without pathological confirmation. Where pathology was available, NSQ was the most frequent subtype (45.2%), followed by SQ (33.3%), NOS (17.9%) and "Other" NSCLC (3.6%; table 1).

Over the study period, 717 patients (19.2%) were diagnosed with stage I disease, 434 (11.6%) with stage II, and 806 (21.6%) with stage III; almost half of patients (47.7%) were diagnosed with stage IV disease. TNM classification evolved during the study period, which might have contributed to some of the changes observed over time in the stage distribution at diagnosis. However, over the period when the 7$^{th}$ TNM classification was used (2010–2016), the proportion of patients diagnosed with stage I disease increased from 16.4% in 2010 to 24.8% in 2016 (Figure 1), while diagnoses of stage IIIA and IIIB NSCLC remained stable over time. There was an overall reduction in the proportion of patients diagnosed at stage IV, from 57.0% in 2010 to 45.0% in 2016.

### *Treatments*

Over the study period, 2337 patients (62.5%) received an initial treatment within 6 months after diagnosis. As expected, treatment rates declined with increasing disease stage, from 78.2% for patients diagnosed with stage I disease to 49.8% for those diagnosed with stage IV. The proportion of patients with early-stage (stage I–IIIA) NSCLC who did not receive treatment decreased over time; 21.2% of patients with stage I–IIIA disease remained untreated 6 months after diagnosis in 2013–2017 compared with 32.3% in 2007–2012 (data not shown). The proportion of patients with stage IV disease remaining untreated decreased among those with NSQ, while no changes were observed among those with SQ (figure 2).

*Initial treatments over time (stages I–IV)*

Figure 2 shows the evolution of initial treatments by TNM stage between 2007–2012 and 2013–2017 in patients with NSQ and SQ and in those who were clinically diagnosed. Over the study period, patients diagnosed with pathologically confirmed stage I disease were most commonly treated with curative surgery alone or, to a lesser extent, curative radiotherapy alone. The proportion receiving surgery alone as initial treatment increased between 2007–2012 and 2013–2017; conversely, the proportion receiving radiotherapy alone decreased. Among patients with clinically diagnosed stage I disease, the proportion receiving radiotherapy increased between 2007–2012 and 2013–2017 (from 39.1% to 60.3%; figure 2).

For patients with pathologically confirmed stage II disease, there was no notable difference in the use of surgery (alone or with adjuvant therapy) between 2007–2012 and 2013–2017. In 2013–2017, among patients with NSQ and SQ, respectively, 37.3% and 29.7% received surgery alone and 21.6% and 17.6% received surgery associated with (neo)adjuvant therapy (mostly adjuvant SACT). Radiotherapy alone was the most common treatment for patients with clinically diagnosed stage II disease, with 30.9% treated in 2007–2012 compared with 45.5% in 2013–2017.

Among the patients diagnosed with pathologically confirmed stage IIIA disease, the proportion receiving SACT plus concurrent radiotherapy (chemoradiation) increased to around one-third in 2013–2017. Some differences in the use of surgery were observed according to histology. In 2013–2017, one-third of patients with NSQ received surgery (surgery alone, 12.3%; surgery associated with adjuvant therapy, 17.5%), and only around 15% of patients with SQ disease received surgery (mostly surgery alone).

For patients diagnosed with stage IIIB or IV NSQ, initial treatment with SACT (with or without radiotherapy) increased between 2007–2012 and 2013–2017, largely as the proportion of untreated patients decreased; it is likely that some patients with stage IIIB disease received chemoradiation with curative intent. Treatment of patients with stage IIIB or IV SQ disease remained similar between the two time periods.

### *Patterns of SACT use in advanced NSCLC (stages IIIB–IV)*

Of the 2119 patients diagnosed with stage IIIB–IV NSCLC during the study period, 648 (30.6%) received a first LoT, 223 (10.5%) received a second LoT and 60 (2.8%) received a third LoT. Similar proportions of patients with stage IIIB–IV NSQ and SQ received a first LoT (45.0% and 45.5%, respectively). Higher proportions of patients with stage IIIB or IV NSQ received second and third LoTs (17.9% and 5.6%, respectively) compared with SQ NSCLC (13.6% and 2.8%, respectively).

The most common first LoT regimens for patients with stage IIIB–IV NSCLC were platinum-based chemotherapy doublets; in 2007–2012, carboplatin plus gemcitabine was the most common (39.9% of treated patients; data not shown); in 2013–2017, carboplatin plus pemetrexed was the most common (28.7% of treated patients; table 2). The proportions of patients with NSQ receiving cisplatin- and pemetrexed-based regimens increased between 2007–2012 and 2013–2017 (table 2).

Among 119 patients with NSQ receiving a second LoT, the most common treatment was a TKI (65.5%); however, use of TKIs in second line decreased over time. Among 54 patients with SQ receiving a second LoT, the most common treatment was also a TKI (53.7%); use of TKIs in second line also decreased over time in this sub-cohort, concomitant with an increase in use of platinum-based chemotherapies. Given the late introduction of ICIs with respect to the study cohort (January 2017), a relatively small proportion of patients with stage IIIB–IV NSQ and SQ received second-line treatment with an ICI in 2013–2018.

*Duration of SACT treatment (stages IIIB–IV)*

For patients with stage IIIB–IV NSCLC who received first-line platinum-based chemotherapy, treatment duration was similar over the analysis period. In 2013–2017, the median (IQR) treatment duration was 2.8 (1.4–3.2) months for patients with NSQ and 2.2 (1.4–2.8) months for patients with SQ.

Among the small number of patients with stage IIIB–IV NSQ who received a TKI in the first line, median treatment durations were consistent over time at around 5 months. For patients with stage IIIB–IV NSCLC who received a second LoT, the median (IQR) treatment duration for those treated in 2013–2018 was 2.5 [1.4–5.4] months for those with NSQ and 2.1 [1.4–2.4] months for those with SQ.

## *Overall survival*

*Overall survival over time (stages I, II and IIIA)*

For patients with stage I NSQ, median (IQR) OS from diagnosis was 55.3 (24.8–98.5) months for those diagnosed in 2007–2012 and was not reached (NR; 34.2 months–NR) for those diagnosed in 2013–2017; median OS increased among patients with stage I SQ (from 37.3 [18.5–66.8] to 51.1 [32.6–NR] months) (figure 3A, online supplementary appendix table S3). Median (IQR) OS for patients with stage I NSCLC

without pathological diagnosis increased slightly from 16.7 (5.8–33.1) to 20.9 (8.0–40.3) months between 2007–2012 and 2013–2017, respectively.

Median (IQR) OS for patients with stage II NSQ was 34.3 (10.6–80.0) months for those diagnosed in 2007–2012 and 26.4 (10.2–58.0) months for those diagnosed in 2013–2017; in patients with stage II SQ, the respective median OS was 17.2 (8.6–58.2) and 19.9 (7.2–53.9) months (figure 3B, online supplementary appendix table S3). For patients without pathological diagnosis and stage II disease, median (IQR) OS increased slightly from 8.9 (2.9–16.8) to 11.3 (5.4–26.9) months, respectively, over the same periods.

Among patients with stage IIIA NSQ, median (IQR) OS increased from 9.9 (6.5–38.6) months for those diagnosed in 2007–2012 to 24.0 (10.6–NR) months for those diagnosed in 2013–2017; median (IQR) OS also increased among patients with stage IIIA SQ (from 10.7 [4.4–21.1] to 14.5 [8.4–36.0] months) (figure 3C, online supplementary appendix table S3). Significant improvement in 1-year OS was observed in patients with NSQ, which increased from 45% (33%–61%) to 74% (63%–87%). Median (IQR) OS among patients with stage IIIA NSCLC without confirmed pathology remained low over the study period at around 5 months.

*Overall survival over time (stage IIIB–IV)*

Median OS and landmark OS rates for patients with stage IIIB–IV NSQ or SQ were similar for those diagnosed in 2007–2012 and 2013–2017, with no notable changes over time (figure 3D, online supplementary appendix table S3). During both periods, less than 10% of patients with stage IIIB–IV NSQ or SQ were alive 3 years after diagnosis. Median OS for clinically diagnosed patients with stage IIIB–IV NSCLC was 1.2 months for both time periods (figure 3D, online supplementary appendix table S3).

## Discussion

These data from the REAL-Oncology database, part of I-O Optimise, provide insight into NSCLC management prior to the reimbursement of immunotherapies in the United Kingdom. Over the analysis period (2007–2017, with follow-up to 2018), most patients with NSCLC in this database were diagnosed with advanced disease. This is consistent with the overall proportion of patients with NSCLC and available TNM staging diagnosed in England in 2017, of whom around 50% had stage IV disease,[16] and with real-world evidence across Europe from the same period.[17,18]

Nevertheless, in our analysis, there was an 11.6% increase in the proportion of patients diagnosed with stage I NSCLC over 2010–2017. The Cancer Reform Strategy,[19] implemented in England in 2007, aimed to build upon advances made following the introduction of the NHS Cancer Plan in 2000,[19] which was designed to close the survival gap for patients with cancer in England compared with those in countries with similar heathcare systems. The strategy further aimed to improve cancer prevention, early diagnosis and patient management, and led to the establishment of the National Cancer Equality initiative (2008)[20] and the National Awareness and Early Diagnosis Initiative (NAEDI)[21] in collaboration with Cancer Research UK (2008).[22] Consequently, the increased proportion of patients diagnosed with stage I NSCLC in the present analysis may partly reflect the impact of these reforms on cancer diagnosis in England during the study period. Notably, the proportion of patients diagnosed with early-stage NSCLC in the REAL-Oncology database was slightly higher than that reported for all lung cancers in the 2017 National Audit for England (20% diagnosed at stage I; 8% at stage II).[16]

At the time of our analysis, no national lung cancer screening programme existed in the United Kingdom. However, a pilot programme originally funded by NAEDI began in Leeds in 2011 aiming to assess lung cancer outcomes in response to a range of public health interventions[23]. Consequently, between 2008–2010 and 2013–2015, there was an 80.8% increase in community referrals for chest X-

rays and a significant stage-shift in diagnosis, with an 8.8% increase in patients diagnosed at stage I–II and a 9.3% reduction in those diagnosed at stage III–IV[23]. While these results are promising, lack of a concurrent control population over the same period meant that the relative contribution of other factors impacting diagnosis could not be determined. Final results from the NELSON study reported a significant reduction in 10-year mortality from lung cancer among male smokers who received regular CT screening compared with those who did not[24]. Similarly, the large US National Lung Screening Trial reported a 20% decreased risk of death from lung cancer among high-risk individuals screened with CT compared with those screened with radiography[25]. These findings support the introduction of a UK-wide lung cancer screening programme, which could decrease the number of patients diagnosed with advanced NSCLC. In addition to the impact of screening, transition from the 6th to the 7th Edition of TNM classification for NSCLC in 2010 is likely to have impacted tumour staging at diagnosis,[26] as reported in Sweden and Denmark over the same period based on national registries data [Ekman et al. *in press*]. Specifically, in the 7th edition, tumour size cutoffs for the T descriptor were revised, and the importance of pleural effusions and mediastinal invasion for the M descriptor were acknowledged, resulting in the upstaging of some tumours and the downstaging of others[6].

Consistent with National Audit data from England and with real-world evidence from Europe, the largest proportion of patients with available pathological data in the REAL-Oncology database had NSQ, mostly adenocarcinoma.[16,17,27] Our database also allowed the identification of clinically diagnosed patients, who accounted for 34% of the analysis population and tended to be older and have higher PS compared with those with confirmed pathology.[28] These patients were either not deemed suitable for treatment or had an early stage peripheral tumour invisible on bronchoscopy and compromised respiratory function; therefore, biopsy confirmation was not justified. Our findings are consistent with an International Cancer Benchmarking Partnership study showing that the rate of clinical diagnosis (i.e., no pathological confirmation) for lung cancer over 2004–2007 was higher in the United Kingdom (26.0%) compared with

Australia (14.4%), Canada (18.2%), Denmark (13.5%), Norway (10.1%) and Sweden (5.2%)[29]. Although the National Lung Cancer Audit in England set a target of 75% for pathological confirmation, there remains wide variation. For example, Khakwani et al. (2013) found that the rates of pathologically confirmed lung cancer in England varied widely according to age, sex, PS, comorbidity, and the method of referral to a specialist. The two most important patient features were age and PS, with less than 50% of patients aged ≥75 with PS >2 having a pathological confirmation [30].

Around 60% of analysed patients received at least one treatment, consistent with the 2017 National Audit (59%) for all lung cancers in England.[31] The initial treatment rate declined sequentially with increasing disease stage, a pattern previously observed in Europe.[17] There was a notable increase in the proportion of patients with stage I NSCLC who received surgery alone, possibly due to the aforementioned pilot program in Leeds during that time. In England and Wales, the proportion of patients undergoing resection for histologically confirmed NSCLC increased from 14% in 2008 to 22% in 2012. This may reflect both improvements in earlier diagnosis and changes in surgical practice.[28,32-34]

The proportion of patients with clinically diagnosed NSCLC receiving radiotherapy alone increased markedly, concomitant with a decrease in the proportion of untreated patients. This may reflect the increased use of stereotactic body radiation therapy as an alternative to surgery for patients with early-stage disease and contraindications for surgery. There was also a notable increase in the use of chemoradiation for patients with stage IIIA NSCLC over the study period, similar to reports from other European population-based studies.[17,35] This followed the publication of data from several clinical trials, as well as a meta-analysis, demonstrating a significant survival benefit with concomitant versus sequential chemoradiation for patients with locally advanced NSCLC.[36] Additionally, advances in staging procedures, such as the use of positron emission tomography (PET)-CT, have enabled the identification of stage III patients with low nodal involvement who may benefit from chemoradiation. [37]

The observed changes in treatment patterns among patients with stage I–IIIA NSCLC in the REAL-Oncology database were mirrored by changes in survival. Survival outcomes for patients diagnosed with stage I NSCLC tended to improve over time. Again, the pilot screening programme in Leeds and/or the increase in surgical interventions among patients with NSQ and SQ and in radiotherapy use in patients who were clinically diagnosed could have driven these improvements. These findings are consistent with marginal improvements in survival among patients diagnosed with early-stage NSCLC in England during the period of our study.[30] Additionally, this may reflect the effects of super staging, with the introduction of PET scanning and endoscopic sampling of lymph nodes.[38] Improved survival outcomes for patients diagnosed with stage IIIA NSCLC may be related to the increased use of surgery with SACT or radiotherapy, and chemoradiation during the latter diagnostic period. Furthermore, transition to the 7th Edition of TNM classification for NSCLC in 2010 may have influenced subsequent treatment allocations and survival outcomes for some patients.[26]

Changes in the recommended management of advanced NSCLC in Europe from 2005, including the use of pemetrexed as maintenance therapy in the first-line setting for platinum-treated NSQ patients and the advent of new TKIs for patients with EGFR and ALK mutations, likely influenced the observed treatment patterns.[39,40] Additionally, during the course of our study, some patients with advanced NSCLC in England were granted access to ICIs via the Early Access to Medicines Scheme,[41,42] which is reflected by the small proportions of patients who received these treatments. Nevertheless, despite changes in treatment patterns, there was little change in survival outcomes for patients with advanced NSCLC during the analysis period; the prognosis for these patients, particularly those with SQ, remained poor. Indeed, less than 10% of patients diagnosed with advanced NSCLC remained alive 3 years after diagnosis. This is in contrast to reports of temporal improvements in OS among patients with stage IIIB/IV NSCLC based on registry data from Sweden and Denmark over 2005–2015 [Ekman et al. in press], and a recent study showing a decline in mortality due to NSCLC in the US over 2016–2016[43]. While

previous real-world studies have demonstrated similarly poor survival outcomes for patients with stage IIIB and IV NSCLC,[17,44] survival rates for patients with advanced lung cancer in the United Kingdom have historically been low compared with other developed countries. This has led to the implementation of several healthcare reforms and initiatives since 2000, which have so far made only limited progress at closing this survival gap, as reflected here.[29,45]

Despite some improvements in patient outcomes over time, real-world estimates of OS among patients with stage IIIB/IV NSCLC are often below those reported in randomized controlled trials (RCTs). In a systematic review of 23 RCTs published over 2001–2010 comparing first-line chemotherapy for patients with stage IIIB/IV NSCLC, median OS was 6.2–11.8 months for those with SQ, 7.5–11.8 months for NSQ, and 21.6–30.9 for EGFR+ NSCLC[46]. These values are substantially higher than the median OS reported here for patients with advanced disease. Notably, median patient age was lower in the RCTs at 56–67 years (versus 73 years in our analysis), and the majority of patients had a PS of 1 (versus 35.4% of patients with a PS 0–1 in our analysis). Thus, real-world data from patients treated in routine clinical practice are important to supplement clinical trial data, which may over-estimate real-world outcomes[47].

The REAL-Oncology database represents an unselected population, which is relevant to real-world practice and enables robust analyses across numerous subgroups over a long timeframe (>10 years). Furthermore, this data source allowed the identification of clinically diagnosed patients, a population not often captured and representing here more than one-third of patients with NSCLC. However, the current study includes only data from Leeds trust and may not be representative of clinical practice elsewhere in England. Additionally, limited information was available regarding radiotherapy at the time of this analysis (date of administration, dose, and type of radiotherapy) and it was not therefore possible to formally differentiate palliative radiotherapy from radiotherapy with curative intent, nor to identify the use of stereotactic ablative radiotherapy in early stage patients. However, the increased use of RT

over time in early stage patients with clinically diagnosed NSCLC was almost certainly due to SABR. It is hoped that improvements to the algorithm used and the subsequent availability of more detailed data regarding radiotherapy will address this limitation. It is also acknowledged that the follow-up duration was relatively short, at 7 months, for patients diagnosed at the end of the study period. Finally, data on biomarkers and comorbidities were not available.

Our findings provide valuable insight into the real-world treatment and survival outcomes for patients in the pre-immunotherapy era in Leeds and demonstrate that, irrespective of changes in treatment patterns and against a background of policy reforms, long-term survival for patients diagnosed with metastatic NSCLC remains poor. Future analyses from the REAL-Oncology database will help evaluate the impact of new TKIs and ICIs on OS for patients with NSCLC.

**FUNDING**

REAL-Oncology is a collaboration between Leeds Teaching Hospital NHS Trust, the University of Leeds and IQVIA. Commercial clients of IQVIA include Bristol Myers Squibb, which funded the project this work is based on. REAL-Oncology retains all operational, scientific, and communications controls.

**COMPETING INTERESTS**

REAL-Oncology is a collaboration between Leeds Teaching Hospital NHS Trust and IQVIA. Commercial clients of IQVIA include Bristol Myers Squibb Company (BMS), which funded the project this work is based on. REAL-Oncology retains all operational, scientific and communications controls. GH is an employee of the University of Leeds and holds an honorary contract with Leeds Teaching Hospital NHS Trust. GH leads the Leeds Teaching Hospitals NHS Trust real-world evidence team collaboration with IQVIA and, as part of this collaboration, IQVIA funds the staff who support this work. GH also reports partial grant funding for a collaboration outside this study from IQVIA. MS was an employee at Leeds Teaching Hospital NHS Trust at the time of the study, and he holds an honorary contract with Leeds

Teaching Hospital NHS Trust. MS, MT and MR are employees of IQVIA. WS and SC are subcontracted to IQVIA and hold honorary contracts with Leeds Teaching Hospital NHS Trust. MS receives consultancy fees from BMS. CC, MD and JP are employees of BMS. CC and JP report stock ownership in BMS. LL was contracted (paid) as a consultant by BMS to support the I-O Optimise initiative and is an employee of Epi-Fit. There are no further conflicts of interest.

**AUTHOR CONTRIBUTIONS**

LL, CC, MD and JP conceived and designed the study, with contributions from MS, MT and WS. GH is the lead for the Leeds Teaching Hospital NHS Trust Real world programme, clinical lead for the Patient Pathway Manager (the Electronic Health Record) and Professor of Cancer Medicine and Digital Health (University of Leeds). SC is the Senior Information Officer working with the REAL-Oncology team at Leeds Teaching Hospital NHS Trust. MS provided expertise to REAL-Oncology regarding the management of lung cancer. MS, MT, WS and MR analysed the data. All authors contributed to the interpretation of the data, the drafting of the work and subsequent critical revision of the manuscript. MS accepts full responsibility for the work and the conduct of the study and had full access to the data.

**DATA SHARING**

The data analysed during the current study are available from the corresponding author on reasonable request. Study outputs will be made publicly available on Leeds Teaching Hospital NHS Trust website following publication.

**ACKNOWLEDGEMENTS**

Professional writing and editorial assistance was provided by Lisa Jolly, PhD, of Parexel, funded by Bristol Myers Squibb.

**TABLES**

**Table 1 Demographic and clinical characteristics of full patient population***

| | All NSCLC | NSQ | SQ | NSCLC NOS | Other NSCLC | Clinically diagnosed unknown pathology |
|---|---|---|---|---|---|---|
| **All stages** | **N=3739** | **n=1112** | **n=819** | **n=439** | **n=88** | **n=1281** |
| Age, years | | | | | | |
| Mean (SD) | 72.3 (10.9) | 68.6 (11.0) | 70.8 (9.4) | 68.9 (10.6) | 70.1 (10.7) | 78.0 (9.3) |
| Median (Q1–Q3) | 73 (65-80) | 69 (62-77) | 71 (64-77) | 69 (63-77) | 71 (63-78) | 79 (72-85) |
| Range | 18-101 | 31-101 | 33-96 | 18-92 | 42-91 | 43-99 |
| Male, n (%) | 1881 (50.3) | 519 (46.7) | 505 (61.7) | 220 (50.1) | 49 (55.7) | 588 (45.9) |
| TNM stage, n (%) | | | | | | |
| I | 717 (19.2) | 223 (20.1) | 127 (15.5) | 30 (6.8) | 19 (21.6) | 318 (24.8) |
| II | 434 (11.6) | 113 (10.2) | 132 (16.1) | <40 (<9.1) | <13 (<14.8) | 137 (10.7) |
| IIIA | 469 (12.5) | 110 (9.9) | 164 (20.0) | 54 (12.3) | 8 (9.1) | 133 (10.4) |

| | | | | | | |
|---|---|---|---|---|---|---|
| IIIB | 337 (9.0) | 89 (8.0) | 117 (14.3) | <55 (<12.3) | <5 (<6.0) | 77 (6.0) |
| IV | 1782 (47.7) | 577 (51.9) | 279 (34.1) | 263 (59.9) | 47 (53.4) | 616 (48.1) |
| Pathology, n (%) | | | | | | |
| Adenocarcinoma | 1019 (27.3) | 1019 (91.6) | 0 | 0 | 0 | 0 |
| SQ | 819 (21.9) | 0 | 819 (100.0) | 0 | 0 | 0 |
| NSCLC NOS | 439 (11.7) | 0 | 0 | 439 (100.0) | 0 | 0 |
| Large cell carcinoma | 93 (2.5) | 93 (8.4) | 0 | 0 | 0 | 0 |
| Other NSCLC | 88 (2.4) | 0 | 0 | 0 | 88 (100.0) | 0 |
| Clinically diagnosed, unknown pathology | 1281 (34.3) | 0 | 0 | 0 | 0 | 1281 (100.0) |
| WHO performance score, n (%) | | | | | | |
| 0 | 292 (7.8) | 149 (13.4) | 70 (8.6) | 38 (8.7) | 12 (13.6) | 23 (1.8) |
| 1 | 1031 (27.6) | 445 (40.0) | 319 (39.0) | 144 (32.8) | 37 (42.2) | 86 (6.7) |
| 2 | 758 (20.3) | 230 (20.7) | 230 (28.1) | 80 (18.2) | 25 (28.4) | 193 (15.1) |
| 3 | 933 (25.0) | 154 (13.9) | 118 (14.4) | 97 (22.1) | <15 (<17.0) | 553 (43.2) |

| | | | | | | |
|---|---|---|---|---|---|---|
| 4 | 372 (10.0) | 39 (3.5) | 16 (2.0) | 26 (5.9) | 0 | 291 (22.7) |
| Missing | 353 (9.4) | 95 (8.5) | 66 (8.1) | <55 (<12.5) | <5 (<5.7) | 135 (10.5) |

*For some categories including low numbers of patients, data have been masked to conceal patient identities. Includes 6 patients diagnosed in 2006.

NOS, not otherwise specified; NSCLC, non-small cell lung cancer; NSQ, non-squamous cell carcinoma; Q, quartile; SD, standard deviation; SQ, squamous cell carcinoma; TNM, tumour, node and metastasis; WHO, World Health Organization.

**Table 2 First-line and second-line SACT in patients with stage IIIB–IV NSQ or SQ carcinoma***

| | NSQ | | SQ | |
|---|---|---|---|---|
| **First-line SACT†** | **2007–2012** | **2013–2017** | **2007–2012** | **2013–2017** |
| Patients receiving first-line SACT, N | **139** | **161** | **104** | **76** |
| Platinum-based chemotherapy, n (%)‡ | 109 (78.4) | 119 (73.9) | 97 (93.3) | 73 (96.1) |
| Carboplatin based | 93 (66.9) | 78 (48.4) | 88 (84.6) | 68 (65.4) |
| Cisplatin based | 11 (7.9) | 33 (20.5) | 9 (8.7) | <5 |
| Pemetrexed included | 58 (41.7) | 107 (77.0) | <5 | <5 |
| Non–platinum-based chemotherapy, n (%) | <5 | 0 | <5 | <5 |
| TKI, n (%) | 17 (12.2) | 34 (21.1) | 0 | <5 |
| Anti–PD-1/PD-L1 checkpoint inhibitors, n (%) | 0 | <5 | 0 | <5 |
| Clinical trial – unknown treatment, n (%) | 8 (5.8) | <5 | 5 (4.8) | 0 |

| **Second-line SACT[§]** | **2007–2012** | **2013–2018** | **2007–2012** | **2013–2018** |
|---|---|---|---|---|
| Patients receiving second-line SACT, N | **53** | **66** | **31** | **23** |
| Platinum-based therapy, n (%)[‡] | <5 | 13 (19.7) | 5 (16.1) | 8 (34.8) |
| Non–platinum-based chemotherapy, n (%) | <5 | 7 (10.6) | <5 | <5 |
| TKI, n (%) | 47 (88.7) | 31 (47.0) | 23 (74.2) | 6 (26.1) |
| Anti–PD-1/PD-L1 checkpoint inhibitors, n (%) | 0 | 10 (15.2) | 0 | 5 (21.7) |
| Clinical trial – unknown treatment, n (%) | 0 | <5 | 0 | 0 |

*For some categories including low numbers of patients, data have been masked to conceal patient identities. [†]Time periods for receipt of initial SACT are based on the date of diagnosis: January 2007–December 2012 and January 2013–August 2017. [‡]Platinum based is defined as any regimen including a platinum agent (monotherapy or in combination) and is further defined as "carboplatin based," "cisplatin based" (including regimens in which carboplatin and cisplatin were both used) and "pemetrexed included" (any platinum-based regimen also including pemetrexed). [§]Time periods for receipt of second-line SACT are based on the start date for second-line treatment: January 2007–December 2012, January 2013–April 2018.

NSQ, non-squamous cell carcinoma; PD-1, programmed death 1; PD-L1, programmed death ligand 1; SACT, systemic anticancer therapy; SQ, squamous cell carcinoma; TKI, tyrosine kinase inhibitor.

**FIGURES**

**Figure 1 TNM stage at NSCLC incident diagnosis, by year of diagnosis**

†Diagnosed up to 31 August 2017.

TNM, tumour, node and metastasis.

**Figure 2 Initial treatment by TNM stage and time period (2007–2012 vs 2013–2017) in patients with (A) NSQ, (B) SQ or (C) CDUP*,†**

*Time periods for receipt of initial treatment are based on the date of diagnosis during two consecutive time periods (January 2007–December 2012 and January 2013–August 2017). †Where analytical groups included fewer than five patients, percentages are not shown as labels.

CDUP, clinically diagnosed with unknown pathology; NSQ, non-squamous cell carcinoma; RT, radiotherapy; SACT, systemic anticancer therapy; SQ, squamous cell carcinoma; TNM, tumour, node and metastasis; Tx, treatment.

**Figure 3 Evolution of OS in patients diagnosed with stage I (A), stage II (B), stage IIIA (C) or stage IIIB–IV (D) NSCLC with NSQ, SQ or CDUP**

CDUP, clinically diagnosed with unknown pathology; NSCLC, non-small cell lung cancer; NSQ, non-squamous cell carcinoma; OS, overall survival; SQ, squamous cell carcinoma.

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Figure 1 TNM stage at NSCLC incident diagnosis, by year of diagnosis

145x100mm (300 x 300 DPI)

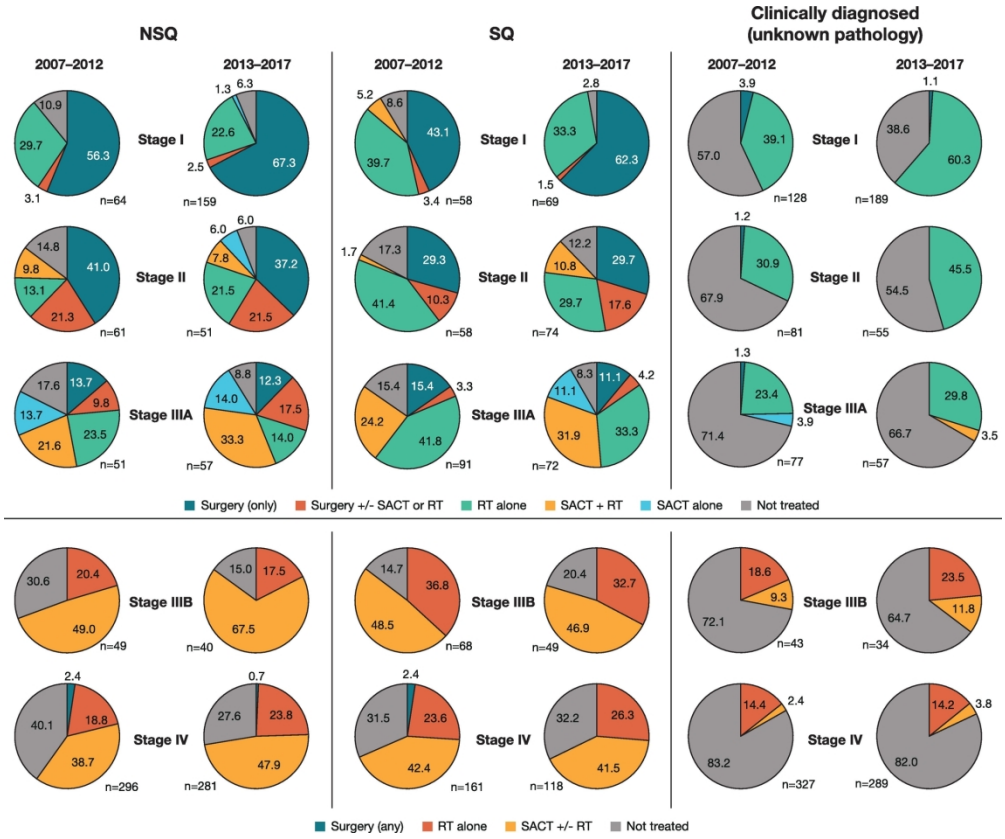


Figure 2 Initial treatment by TNM stage and time period (2007–2012 vs 2013–2017) in patients with (A) NSQ, (B) SQ or (C) CDUP*,†

179x148mm (300 x 300 DPI)

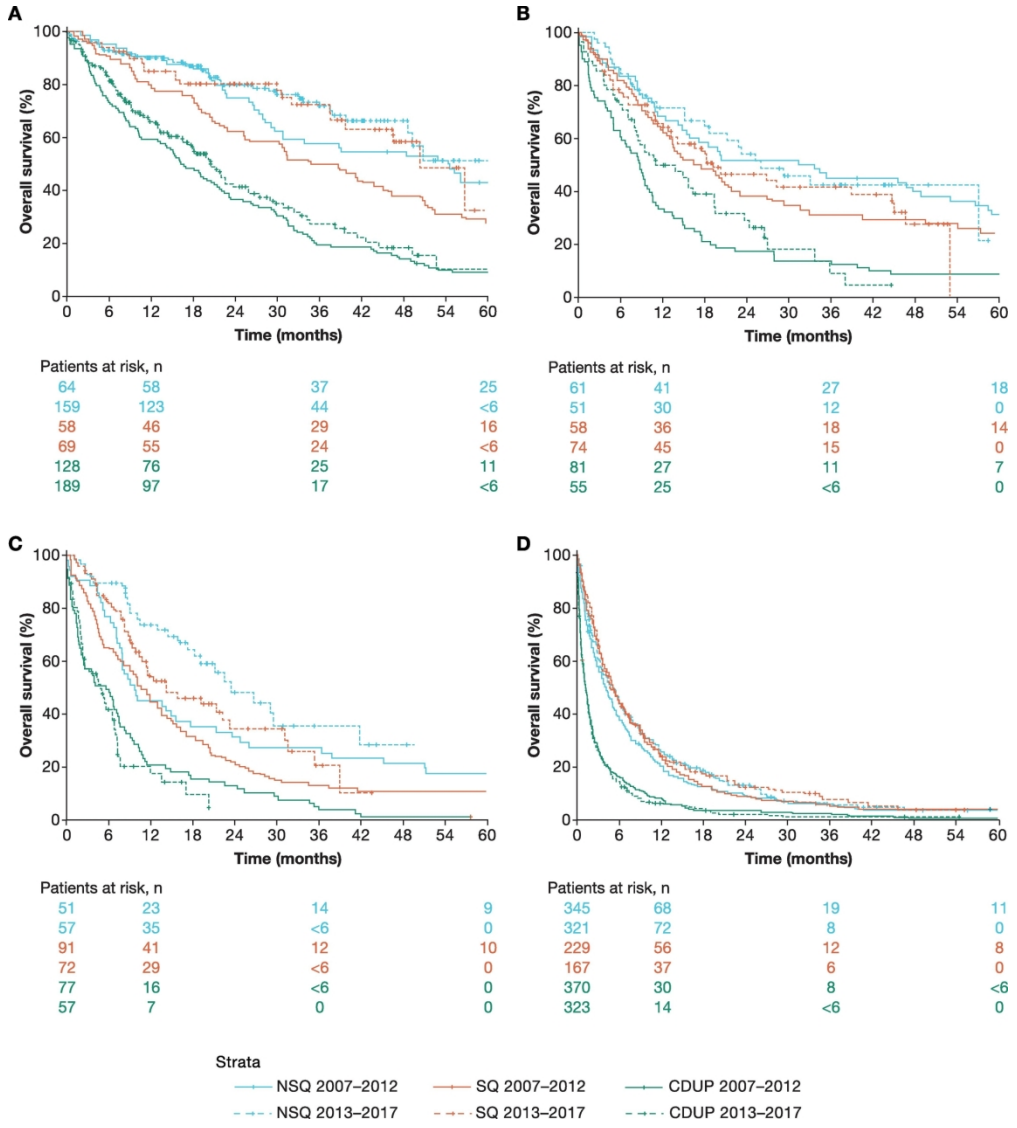


Figure 3 Evolution of OS in patients diagnosed with stage I (A), stage II (B), stage IIIA (C) or stage IIIB–IV (D) NSCLC with NSQ, SQ or CDUP

178x198mm (300 x 300 DPI)

## STROBE checklist

| Treatment patterns and survival outcomes for patients with non-small cell lung cancer in the United Kingdom in the pre-immunology era: a REAL-Oncology database analysis from the I-O Optimise initiative | | | **Snee, et al.** |
|---|---|---|---|
| **Checklist item -** | | | **Section** |
| **Title and abstract** | | | |
| | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract | *Title, abstract* |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | *Abstract* |
| **Introduction** | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | *Introduction, p5–6* |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | *Introduction, p5–6* |
| **Methods** | | | |
| Study design | 4 | Present key elements of study design early in the paper | *Methods, Study design, p6* |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | *Methods, Study setting, p6–7 Analyses, p7–8* |
| Participants | 6 | (*a*) *Cohort study*? Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up | *Methods, Study design, p6–7* |
| | | (*b*) *Cohort study*? For matched studies, give matching criteria and number of exposed and unexposed | *N/A* |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | *Methods, Analyses p7* |

| | | | |
|---|---|---|---|
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | *Methods, Analyses, p7* |
| Bias | 9 | Describe any efforts to address potential sources of bias | *N/A, retrospective study* |
| Study size | 10 | Explain how the study size was arrived at | *N/A, retrospective study* |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | *Methods, Analyses, p8* |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | *Methods, Analyses, p8* |
| | | (*b*) Describe any methods used to examine subgroups and interactions | *Methods, Analyses, p8* |
| | | (*c*) Explain how missing data were addressed | *Methods, Analyses, p8* |
| | | (*d*) *Cohort study*? If applicable, explain how loss to follow-up was addressed | *N/A, retrospective study* |
| | | (*e*) Describe any sensitivity analyses | *N/A* |
| **Results** | | | |
| Participants | 13* | (*a*) Report numbers of individuals at each stage of study? eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | *Results, Patients, p8* |
| | | (*b*) Give reasons for non-participation at each stage | *Results, Patients, p8* |
| | | (*c*) Consider use of a flow diagram | *Not included* |

| | | | |
|---|---|---|---|
| Descriptive data | 14* | (*a*)Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | *Results, Patients, p8–6* |
| | | (*b*) Indicate number of participants with missing data for each variable of interest | *N/A* |
| | | (*c*) *Cohort study*? Summarise follow-up time (eg average and total amount) | *N/A* |
| Outcome data | 15* | *Cohort study*? Report numbers of outcome events or summary measures over time | *Results, Overall survival, p12–13* |
| | | *Case-control study?* Report numbers in each exposure category, or summary measures of exposure | *N/A* |
| | | *Cross sectional study?* Report numbers of outcome events or summary measures | |
| Main results | 16 | (a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | *Results, Overall survival, p12–13* |
| | | (b) Report category boundaries when continuous variables were categorized | *N/A* |
| | | (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | *Not included* |
| Other analyses | 17 | Report other analyses done? eg analyses of subgroups and interactions, and sensitivity analyses | *N/A* |
| **Discussion** | | | |
| Key results | 18 | Summarise key results with reference to study objectives | *Discussion, p13* |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | *Discussion, p16* |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | *Discussion* |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | *Discussion, 16–17* |

| **Other information** | | | |
|---|---|---|---|
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | *Funding, p17* |
| | | | |

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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# Treatment patterns and survival outcomes for patients with non-small cell lung cancer in the United Kingdom in the pre-immunology era: a REAL-Oncology database analysis from the I-O Optimise initiative

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# Treatment patterns and survival outcomes for patients with non-small cell lung cancer in the United Kingdom in the pre-immunology era: a REAL-Oncology database analysis from the I-O Optimise initiative

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**ABSTRACT *[300/300 words]***

**Objectives**

To report characteristics, treatment and overall survival (OS) trends, by stage and pathology, of patients diagnosed with non-small cell lung cancer (NSCLC) at Leeds Teaching Hospital NHS Trust in 2007–2018.

**Design**

Retrospective cohort study based on electronic medical records.

**Setting**

Large NHS university hospital in Leeds.

**Participants**

3739 adult patients diagnosed with incident NSCLC from January 2007–August 2017, followed until March 2018.

**Main outcome measures**

Patient characteristics at diagnosis, treatment patterns, OS.

**Results**

34.3% of patients with NSCLC were clinically diagnosed (without pathological confirmation). Among patients with known pathology, 45.2% had non-squamous cell carcinoma (NSQ); 33.3% had squamous cell carcinoma (SQ). The proportion of patients diagnosed at stage I increased (16.4%–27.7% in 2010–2017); those diagnosed at stage IV decreased (57.0%–39.1%). Surgery was the most common initial treatment for patients with pathologically confirmed stage I NSCLC. Use of radiotherapy alone increased over time in patients with clinically diagnosed stage I NSCLC (39.1%–60.3%); chemoradiation increased in patients with stage IIIA NSQ (21.6%–33.3%) and SQ (24.2%–31.9%). Initial treatment with systemic

anticancer therapy (SACT) increased in patients with stage IIIB–IV NSQ (49.0%–67.5%); the proportion of untreated patients decreased (30.6%–15.0%). Median OS improved for patients diagnosed with stage I NSQ and SQ and stage IIIA NSQ over time. Median OS for patients with stage IIIB–IV NSQ and SQ remained stable; <10% were alive 3 years after diagnosis. Median OS for clinically diagnosed stage IIIB–IV patients was 1.2 months in both periods.

**Conclusions**

OS for stage I and IIIA patients improved over time, likely due to increased stereotactic ablative radiation, surgery (stage I) and chemoradiation (stage IIIA) use. Conversely, OS outcomes remained poor for stage IIIB–IV patients despite increasing use of SACT for NSQ. Many patients with advanced-stage disease remained untreated.

**Article summary**

Strengths and limitations of this study

- These data reflect outcomes and trends for a single site in the United Kingdom; however, the REAL-Oncology study represents an unselected population, which is relevant to real-world practice and enables long-term (>10 years) analyses across numerous subgroups
- This analysis included patients with a clinical diagnosis of NSCLC who, despite representing a large proportion of patients with NSCLC, are often not captured in real-world studies
- Limited information on radiotherapy was available at the time of the analysis; thus, it was not possible to formally differentiate radiotherapy with palliative intent from that with curative intent
- The follow-up duration was relatively short for patients diagnosed at the end of the study period, at 7 months
- Data on co-morbidities that might have explained why a significant proportion of patients with advanced disease did not receive any systemic anticancer therapy, were not available

## INTRODUCTION

In the United Kingdom, lung cancer is the third most common type of cancer and the leading cause of cancer death.[1] Around 85% of patients with lung cancer have non-small cell lung cancer (NSCLC), which consists predominantly of non-squamous cell carcinoma (NSQ) and squamous cell carcinoma (SQ).[2] Early diagnosis of lung cancer can be challenging.[3] Consequently, approximately two-thirds of patients present with advanced or metastatic NSCLC (stage III–IV), for which treatment options are limited and prognosis is poor;[4,5] 5-year survival rates for patients with metastatic disease are less than 5%.[5,6]

Surgery and radiotherapy can be used successfully in patients diagnosed with early-stage NSCLC; adjuvant chemotherapy is also indicated for selected patients who have undergone resection for stage II–III disease and can improve outcomes.[7] For advanced-NSCLC (stage IIIB–IV), chemotherapy with platinum-based agents has long been the standard of care for patients with good performance status (PS), and vascular endothelial growth factor–targeting therapies have been used in the first-line setting in patients with NSQ.[8] However, increased understanding of NSCLC driver mutations, such as those in the epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) genes, has led to the development of targeted therapies, including tyrosine kinase inhibitors (TKIs). These allow for more personalized treatment approaches in selected patients with actionable driver mutations.[8]

The development of immunotherapeutic agents has transformed the NSCLC treatment landscape. Since 2015, immune checkpoint inhibitors (ICIs) targeting the programmed death-1/programmed death ligand 1 axis have been approved in Europe and are now recommended for first- or second-line treatment of patients with metastatic NSCLC.[9] In addition, ongoing clinical trials are investigating neoadjuvant and adjuvant use of ICIs for patients diagnosed at earlier stages of NSCLC.[10-12] As with any new treatment, there is a need to assess how ICIs impact patient survival in real-world clinical practice to help inform future treatment decisions, which requires an understanding of the NSCLC landscape prior to their

availability. Real-world databases include a wealth of information that can be used to complement data from clinical trials and are a valuable source of evidence in a rapidly changing treatment landscape.

We report the characteristics, treatment and overall survival (OS) trends for patients diagnosed with NSCLC at a large teaching hospital in England prior to routine availability of ICIs. This study, based on the REAL-Oncology database, is part of the I-O Optimise program, an ongoing initiative leveraging real-world data sources to provide insights into the evolving landscape of thoracic malignancies, including NSCLC.[13]

## METHODS

### *Study setting*

REAL-Oncology is a research partnership between Leeds Cancer Centre (LCC), the University of Leeds and IQVIA®, using NHS oncology patient data to answer various research questions. LCC is a major NHS cancer centre that serves a metropolitan catchment area of 750 000 people for secondary care and over 5 million for tertiary care.

### *Ethics approval and consent to participate*

This study was completed with UK Health Research Authority approval through the National Institute for Health Research Integrated Research Approvals System. The research was performed in accordance with the Leeds Teaching Hospitals NHS Trust research governance framework; as a noninterventional retrospective descriptive study using existing patient records, the need for ethics approval was waived. The study was performed in accordance with the Declaration of Helsinki.

## *Study design*

This retrospective analysis extracted data on prescribed chemotherapy, and pathology and radiology records that were entered into electronic medical records (EMRs) at the Leeds Teaching Hospitals NHS Trust as part of routine clinical practice. The study included patients aged ≥18 years with an incident diagnosis of NSCLC (International Statistical Classification of Diseases and Related Health Problems, 10th Revision [ICD-10] code for malignant neoplasm of the trachea [C33] or malignant neoplasm of bronchus and lung [C34]) between January 2007 and August 2017 at Leeds Teaching Hospital. All patients diagnosed by the lung multidisciplinary team were included, including those clinically identified solely on the basis of history, clinical examination and computed tomography (CT), and those with confirmed morphology (ie, *International Classification of Diseases for Oncology*, 3rd Edition [ICD-O-3] code for NSCLC pathology, online supplementary appendix table S1). Patients were excluded if their first diagnosis of NSCLC was confirmed in another NHS hospital trust, they had missing data on age or sex, their ICD-O-3 morphology codes indicated small cell lung cancer (80413–80459), or they had a concomitant (within 5 years prior to NSCLC diagnosis) primary tumour at time of diagnosis, except for non-metastatic non-melanoma skin cancers or *in situ* or benign tumours. Patients with missing data on tumour, node, metastasis (TNM) classification were also excluded from the present analyses.

The end of follow-up was the date of death or end of study (April 2018). The date of death was confirmed by reconciliation of EMRs with Office for National Statistics death certifications. Patient sociodemographic (age, sex, World Health Organisation PS) and clinical characteristics (TNM stage, tumour pathology) were extracted on/at the nearest date to NSCLC diagnosis (index date). TNM classification at diagnosis was recorded according to the 6th edition of the TNM classification up to 31 December 2009[14]; the 7th edition from 1 January 2010[6]; and the 8th edition from 1 January 2017.[15] Tumour pathology was defined as NSQ (including adenocarcinoma and large cell carcinoma), SQ, NSCLC

not otherwise specified (NOS), “Other” (neuroendocrine carcinoma and other miscellaneous carcinoma) or “Unconfirmed” (clinically diagnosed unknown pathology).

The date of initial treatment was defined as the first instance of lung surgery, radiotherapy or systemic anticancer therapy (SACT) occurring within 6 months of diagnosis, and initial treatment categories were defined using all treatment received within a specified time period following this date (online supplementary appendix table S2). A line of therapy (LoT) was defined as one or more cycles of chemotherapy or continuous oral treatment for targeted agents in patients with incident stage IIIB–IV NSCLC. An algorithm based on the sequencing of SACT treatments received was developed to determine first and subsequent LoTs. LoT outputs were validated by clinicians.

### *Analyses*

Patient characteristics at diagnosis are described using summary statistics. The evolution of treatment patterns and OS over time were investigated in two sub-cohorts defined by date of diagnosis: January 2007 to December 2012, and January 2013 to August 2017. Therapy received and treatment duration are described by LoT for advanced-stage patients using the same time periods. OS was estimated using Kaplan–Meier methods. The proportions of patients surviving to 1, 2 or 3 years after the date of diagnosis are reported with corresponding two-sided 95% confidence intervals. Differences in OS between time periods were compared using log-rank hypothesis tests.

To comply with patient confidentiality requirements, data outputs relating to groups of fewer than five patients were masked. In some circumstances, data relating to larger patient subgroups were also masked to avoid extrapolation of counts of fewer than five patients.

### *Patient and public involvement*

Patients or the public were not involved in the design, conduct, reporting or dissemination plans of our research.

## Results

### *Patients*

Overall, 4225 patients diagnosed with NSCLC between January 2007 and August 2017were included in the study. Of these, 486 were excluded because of missing TNM staging information, resulting in an analysis cohort of 3739 patients. Patients had a median (interquartile range [IQR]) age of 73 (65–80) years and were evenly split by sex (table 1). Pathology findings were available for 2458 patients (65.7%), with the remaining 1281 (34.3%) being clinically diagnosed without pathological confirmation. Where pathology was available, NSQ was the most frequent subtype (45.2%), followed by SQ (33.3%), NOS (17.9%) and "Other" NSCLC (3.6%; table 1).

Over the study period, 717 patients (19.2%) were diagnosed with stage I disease, 434 (11.6%) with stage II, and 806 (21.6%) with stage III; almost half of patients (47.7%) were diagnosed with stage IV disease. TNM classification evolved during the study period, which might have contributed to some of the changes observed over time in the stage distribution at diagnosis. However, over the period when the 7$^{th}$ TNM classification was used (2010–2016), the proportion of patients diagnosed with stage I disease increased from 16.4% in 2010 to 24.8% in 2016 (Figure 1), while diagnoses of stage IIIA and IIIB NSCLC remained stable over time. There was an overall reduction in the proportion of patients diagnosed at stage IV, from 57.0% in 2010 to 45.0% in 2016.

## *Treatments*

Over the study period, 2337 patients (62.5%) received an initial treatment within 6 months after diagnosis. As expected, treatment rates declined with increasing disease stage, from 78.2% for patients diagnosed with stage I disease to 49.8% for those diagnosed with stage IV. The proportion of patients with early-stage (stage I–IIIA) NSCLC who did not receive treatment decreased over time; 21.2% of patients with stage I–IIIA disease remained untreated 6 months after diagnosis in 2013–2017 compared with 32.3% in 2007–2012 (data not shown). The proportion of patients with stage IV disease remaining untreated decreased among those with NSQ, while no changes were observed among those with SQ (figure 2).

*Initial treatments over time (stages I–IV)*

Figure 2 shows the evolution of initial treatments by TNM stage between 2007–2012 and 2013–2017 in patients with NSQ and SQ and in those who were clinically diagnosed. Over the study period, patients diagnosed with pathologically confirmed stage I disease were most commonly treated with curative surgery alone or, to a lesser extent, curative radiotherapy alone. The proportion receiving surgery alone as initial treatment increased between 2007–2012 and 2013–2017; conversely, the proportion receiving radiotherapy alone decreased. Among patients with clinically diagnosed stage I disease, the proportion receiving radiotherapy increased between 2007–2012 and 2013–2017 (from 39.1% to 60.3%; figure 2).

For patients with pathologically confirmed stage II disease, there was no notable difference in the use of surgery (alone or with adjuvant therapy) between 2007–2012 and 2013–2017. In 2013–2017, among patients with NSQ and SQ, respectively, 37.3% and 29.7% received surgery alone and 21.6% and 17.6% received surgery associated with (neo)adjuvant therapy (mostly adjuvant SACT). Radiotherapy alone was the most common treatment for patients with clinically diagnosed stage II disease, with 30.9% treated in 2007–2012 compared with 45.5% in 2013–2017.

Among the patients diagnosed with pathologically confirmed stage IIIA disease, the proportion receiving SACT plus concurrent radiotherapy (chemoradiation) increased to around one-third in 2013–2017. Some differences in the use of surgery were observed according to histology. In 2013–2017, one-third of patients with NSQ received surgery (surgery alone, 12.3%; surgery associated with adjuvant therapy, 17.5%), and only around 15% of patients with SQ disease received surgery (mostly surgery alone).

For patients diagnosed with stage IIIB or IV NSQ, initial treatment with SACT (with or without radiotherapy) increased between 2007–2012 and 2013–2017, largely as the proportion of untreated patients decreased; it is likely that some patients with stage IIIB disease received chemoradiation with curative intent. Treatment of patients with stage IIIB or IV SQ disease remained similar between the two time periods.

### *Patterns of SACT use in advanced NSCLC (stages IIIB–IV)*

Of the 2119 patients diagnosed with stage IIIB–IV NSCLC during the study period, 648 (30.6%) received a first LoT, 223 (10.5%) received a second LoT and 60 (2.8%) received a third LoT. Similar proportions of patients with stage IIIB–IV NSQ and SQ received a first LoT (45.0% and 45.5%, respectively). Higher proportions of patients with stage IIIB or IV NSQ received second and third LoTs (17.9% and 5.6%, respectively) compared with SQ NSCLC (13.6% and 2.8%, respectively).

The most common first LoT regimens for patients with stage IIIB–IV NSCLC were platinum-based chemotherapy doublets; in 2007–2012, carboplatin plus gemcitabine was the most common (39.9% of treated patients; data not shown); in 2013–2017, carboplatin plus pemetrexed was the most common (28.7% of treated patients; table 2). The proportions of patients with NSQ receiving cisplatin- and pemetrexed-based regimens increased between 2007–2012 and 2013–2017 (table 2).

Among 119 patients with NSQ receiving a second LoT, the most common treatment was a TKI (65.5%); however, use of TKIs in second line decreased over time. Among 54 patients with SQ receiving a second LoT, the most common treatment was also a TKI (53.7%); use of TKIs in second line also decreased over time in this sub-cohort, concomitant with an increase in use of platinum-based chemotherapies. Given the late introduction of ICIs with respect to the study cohort (January 2017), a relatively small proportion of patients with stage IIIB–IV NSQ and SQ received second-line treatment with an ICI in 2013–2018.

*Duration of SACT treatment (stages IIIB–IV)*

For patients with stage IIIB–IV NSCLC who received first-line platinum-based chemotherapy, treatment duration was similar over the analysis period. In 2013–2017, the median (IQR) treatment duration was 2.8 (1.4–3.2) months for patients with NSQ and 2.2 (1.4–2.8) months for patients with SQ.

Among the small number of patients with stage IIIB–IV NSQ who received a TKI in the first line, median treatment durations were consistent over time at around 5 months. For patients with stage IIIB–IV NSCLC who received a second LoT, the median (IQR) treatment duration for those treated in 2013–2018 was 2.5 [1.4–5.4] months for those with NSQ and 2.1 [1.4–2.4] months for those with SQ.

## *Overall survival*

*Overall survival over time (stages I, II and IIIA)*

For patients with stage I NSQ, median (IQR) OS from diagnosis was 55.3 (24.8–98.5) months for those diagnosed in 2007–2012 and was not reached (NR; 34.2 months–NR) for those diagnosed in 2013–2017; median OS increased among patients with stage I SQ (from 37.3 [18.5–66.8] to 51.1 [32.6–NR] months) (figure 3A, online supplementary appendix table S3). Median (IQR) OS for patients with stage I NSCLC

without pathological diagnosis increased slightly from 16.7 (5.8–33.1) to 20.9 (8.0–40.3) months between 2007–2012 and 2013–2017, respectively.

Median (IQR) OS for patients with stage II NSQ was 34.3 (10.6–80.0) months for those diagnosed in 2007–2012 and 26.4 (10.2–58.0) months for those diagnosed in 2013–2017; in patients with stage II SQ, the respective median OS was 17.2 (8.6–58.2) and 19.9 (7.2–53.9) months (figure 3B, online supplementary appendix table S3). For patients without pathological diagnosis and stage II disease, median (IQR) OS increased slightly from 8.9 (2.9–16.8) to 11.3 (5.4–26.9) months, respectively, over the same periods.

Among patients with stage IIIA NSQ, median (IQR) OS increased from 9.9 (6.5–38.6) months for those diagnosed in 2007–2012 to 24.0 (10.6–NR) months for those diagnosed in 2013–2017; median (IQR) OS also increased among patients with stage IIIA SQ (from 10.7 [4.4–21.1] to 14.5 [8.4–36.0] months) (figure 3C, online supplementary appendix table S3). Significant improvement in 1-year OS was observed in patients with NSQ, which increased from 45% (33%–61%) to 74% (63%–87%). Median (IQR) OS among patients with stage IIIA NSCLC without confirmed pathology remained low over the study period at around 5 months.

*Overall survival over time (stage IIIB–IV)*

Median OS and landmark OS rates for patients with stage IIIB–IV NSQ or SQ were similar for those diagnosed in 2007–2012 and 2013–2017, with no notable changes over time (figure 3D, online supplementary appendix table S3). During both periods, less than 10% of patients with stage IIIB–IV NSQ or SQ were alive 3 years after diagnosis. Median OS for clinically diagnosed patients with stage IIIB–IV NSCLC was 1.2 months for both time periods (figure 3D, online supplementary appendix table S3).

## Discussion

These data from the REAL-Oncology database, part of I-O Optimise, provide insight into NSCLC management prior to the reimbursement of immunotherapies in the United Kingdom. Over the analysis period (2007–2017, with follow-up to 2018), most patients with NSCLC in this database were diagnosed with advanced disease. This is consistent with the overall proportion of patients with NSCLC and available TNM staging diagnosed in England in 2017, of whom around 50% had stage IV disease,[16] and with real-world evidence across Europe from the same period.[17,18]

Nevertheless, in our analysis, there was an 11.6% increase in the proportion of patients diagnosed with stage I NSCLC over 2010–2017. The Cancer Reform Strategy,[19] implemented in England in 2007, aimed to build upon advances made following the introduction of the NHS Cancer Plan in 2000,[19] which was designed to close the survival gap for patients with cancer in England compared with those in countries with similar heathcare systems. The strategy further aimed to improve cancer prevention, early diagnosis and patient management, and led to the establishment of the National Cancer Equality initiative (2008)[20] and the National Awareness and Early Diagnosis Initiative (NAEDI)[21] in collaboration with Cancer Research UK (2008).[22] Consequently, the increased proportion of patients diagnosed with stage I NSCLC in the present analysis may partly reflect the impact of these reforms on cancer diagnosis in England during the study period. Notably, the proportion of patients diagnosed with early-stage NSCLC in the REAL-Oncology database was slightly higher than that reported for all lung cancers in the 2017 National Audit for England (20% diagnosed at stage I; 8% at stage II).[16]

At the time of our analysis, no national lung cancer screening programme existed in the United Kingdom. However, a pilot programme originally funded by NAEDI began in Leeds in 2011 aiming to assess lung cancer outcomes in response to a range of public health interventions[23]. Consequently, between 2008–2010 and 2013–2015, there was an 80.8% increase in community referrals for chest X-

rays and a significant stage-shift in diagnosis, with an 8.8% increase in patients diagnosed at stage I–II and a 9.3% reduction in those diagnosed at stage III–IV[23]. While these results are promising, lack of a concurrent control population over the same period meant that the relative contribution of other factors impacting diagnosis could not be determined. Final results from the NELSON study reported a significant reduction in 10-year mortality from lung cancer among male smokers who received regular CT screening compared with those who did not[24]. Similarly, the large US National Lung Screening Trial reported a 20% decreased risk of death from lung cancer among high-risk individuals screened with CT compared with those screened with radiography[25]. These findings support the introduction of a UK-wide lung cancer screening programme, which could decrease the number of patients diagnosed with advanced NSCLC. In addition to the impact of screening, transition from the 6th to the 7th Edition of TNM classification for NSCLC in 2010 is likely to have impacted tumour staging at diagnosis,[26] as reported in Sweden and Denmark over the same period based on national registries data [Ekman et al. *in press*]. Specifically, in the 7th edition, tumour size cutoffs for the T descriptor were revised, and the importance of pleural effusions and mediastinal invasion for the M descriptor were acknowledged, resulting in the upstaging of some tumours and the downstaging of others[6].

Consistent with National Audit data from England and with real-world evidence from Europe, the largest proportion of patients with available pathological data in the REAL-Oncology database had NSQ, mostly adenocarcinoma.[16,17,27] Our database also allowed the identification of clinically diagnosed patients, who accounted for 34% of the analysis population and tended to be older and have higher PS compared with those with confirmed pathology.[28] These patients were either not deemed suitable for treatment or had an early stage peripheral tumour invisible on bronchoscopy and compromised respiratory function; therefore, biopsy confirmation was not justified in either case. Our findings are consistent with an International Cancer Benchmarking Partnership study showing that the rate of clinical diagnosis (i.e., no pathological confirmation) for lung cancer over 2004–2007 was higher in the United Kingdom (26.0%)

compared with Australia (14.4%), Canada (18.2%), Denmark (13.5%), Norway (10.1%) and Sweden (5.2%)[29]. Although the National Lung Cancer Audit in England set a target of 75% for pathological confirmation, there remains wide variation. For example, Khakwani et al. (2013) found that the rates of pathologically confirmed lung cancer in England varied widely according to age, sex, PS, comorbidity, and the method of referral to a specialist. The two most important patient features were age and PS, with less than 50% of patients aged ≥75 with PS >2 having a pathological confirmation [30].

Around 60% of analysed patients received at least one treatment, consistent with the 2017 National Audit (59%) for all lung cancers in England.[31] The initial treatment rate declined sequentially with increasing disease stage, a pattern previously observed in Europe.[17] There was a notable increase in the proportion of patients with stage I NSCLC who received surgery alone, possibly due to the aforementioned pilot program in Leeds during that time. In England and Wales, the proportion of patients undergoing resection for histologically confirmed NSCLC increased from 14% in 2008 to 22% in 2012. This may reflect both improvements in earlier diagnosis and changes in surgical practice.[28,32-34]

The proportion of patients with clinically diagnosed NSCLC receiving radiotherapy alone increased markedly, concomitant with a decrease in the proportion of untreated patients. This may reflect the increased use of stereotactic body radiation therapy as an alternative to surgery for patients with early-stage disease and contraindications for surgery. There was also a notable increase in the use of chemoradiation for patients with stage IIIA NSCLC over the study period, similar to reports from other European population-based studies.[17,35] This followed the publication of data from several clinical trials, as well as a meta-analysis, demonstrating a significant survival benefit with concomitant versus sequential chemoradiation for patients with locally advanced NSCLC.[36] Additionally, advances in staging procedures, such as the use of positron emission tomography (PET)-CT, have enabled the identification of stage III patients with low nodal involvement who may benefit from chemoradiation. [37]

The observed changes in treatment patterns among patients with stage I–IIIA NSCLC in the REAL-Oncology database were mirrored by changes in survival. Survival outcomes for patients diagnosed with stage I NSCLC tended to improve over time. Again, the pilot screening programme in Leeds and/or the increase in surgical interventions among patients with NSQ and SQ and in radiotherapy use in patients who were clinically diagnosed could have driven these improvements. These findings are consistent with marginal improvements in survival among patients diagnosed with early-stage NSCLC in England during the period of our study.[30] Additionally, this may reflect the effects of super staging, with the introduction of PET scanning and endoscopic sampling of lymph nodes.[38] Improved survival outcomes for patients diagnosed with stage IIIA NSCLC may be related to the increased use of surgery with SACT or radiotherapy, and chemoradiation during the latter diagnostic period. Furthermore, transition to the 7th Edition of TNM classification for NSCLC in 2010 may have influenced subsequent treatment allocations and survival outcomes for some patients.[26]

Changes in the recommended management of advanced NSCLC in Europe from 2005, including the use of pemetrexed as maintenance therapy in the first-line setting for platinum-treated NSQ patients and the advent of new TKIs for patients with EGFR and ALK mutations, likely influenced the observed treatment patterns.[39,40] Additionally, during the course of our study, some patients with advanced NSCLC in England were granted access to ICIs via the Early Access to Medicines Scheme,[41,42] which is reflected by the small proportions of patients who received these treatments. Nevertheless, despite changes in treatment patterns, there was little change in survival outcomes for patients with advanced NSCLC during the analysis period; the prognosis for these patients, particularly those with SQ, remained poor. Indeed, less than 10% of patients diagnosed with advanced NSCLC remained alive 3 years after diagnosis. This is in contrast to reports of temporal improvements in OS among patients with stage IIIB/IV NSCLC based on registry data from Sweden and Denmark over 2005–2015 [Ekman et al. in press], and a recent study showing a decline in mortality due to NSCLC in the US over 2016–2016[43]. While

previous real-world studies have demonstrated similarly poor survival outcomes for patients with stage IIIB and IV NSCLC,[17,44] survival rates for patients with advanced lung cancer in the United Kingdom have historically been low compared with other developed countries. This has led to the implementation of several healthcare reforms and initiatives since 2000, which have so far made only limited progress at closing this survival gap, as reflected here.[29,45]

Despite some improvements in patient outcomes over time, real-world estimates of OS among patients with stage IIIB/IV NSCLC are often below those reported in randomized controlled trials (RCTs). In a systematic review of 23 RCTs published over 2001–2010 comparing first-line chemotherapy for patients with stage IIIB/IV NSCLC, median OS was 6.2–11.8 months for those with SQ, 7.5–11.8 months for NSQ, and 21.6–30.9 for EGFR+ NSCLC[46]. These values are substantially higher than the median OS reported here for patients with advanced disease. Notably, median patient age was lower in the RCTs at 56–67 years (versus 73 years in our analysis), and the majority of patients had a PS of 1 (versus 35.4% of patients with a PS 0–1 in our analysis). Thus, real-world data from patients treated in routine clinical practice are important to supplement clinical trial data, which may over-estimate real-world outcomes[47].

The REAL-Oncology database represents an unselected population, which is relevant to real-world practice and enables robust analyses across numerous subgroups over a long timeframe (>10 years). Furthermore, this data source allowed the identification of clinically diagnosed patients, a population not often captured and representing here more than one-third of patients with NSCLC. However, the current study includes only data from Leeds trust and may not be representative of clinical practice elsewhere in England. Additionally, limited information was available regarding radiotherapy at the time of this analysis (date of administration, dose, and type of radiotherapy) and it was not therefore possible to formally differentiate palliative radiotherapy from radiotherapy with curative intent, nor to identify the use of stereotactic ablative radiotherapy (SABR) in early stage patients. However, the increased use

of RT over time in early stage patients with clinically diagnosed NSCLC was almost certainly due to SABR, which was available in our centre from May 2009. It is hoped that improvements to the algorithm used and the subsequent availability of more detailed data regarding radiotherapy will address this limitation. It is also acknowledged that the follow-up duration was relatively short, at 7 months, for patients diagnosed at the end of the study period. Finally, data on biomarkers and comorbidities were not available.

Our findings provide valuable insight into the real-world treatment and survival outcomes for patients in the pre-immunotherapy era in Leeds and demonstrate that, irrespective of changes in treatment patterns and against a background of policy reforms, long-term survival for patients diagnosed with metastatic NSCLC remains poor. Future analyses from the REAL-Oncology database will help evaluate the impact of new TKIs and ICIs on OS for patients with NSCLC.

**FUNDING**

REAL-Oncology is a collaboration between Leeds Teaching Hospital NHS Trust, the University of Leeds and IQVIA. Commercial clients of IQVIA include Bristol Myers Squibb, which funded the project this work is based on. REAL-Oncology retains all operational, scientific, and communications controls.

**COMPETING INTERESTS**

REAL-Oncology is a collaboration between Leeds Teaching Hospital NHS Trust and IQVIA. Commercial clients of IQVIA include Bristol Myers Squibb Company (BMS), which funded the project this work is based on. REAL-Oncology retains all operational, scientific and communications controls. GH is an employee of the University of Leeds and holds an honorary contract with Leeds Teaching Hospital NHS Trust. GH leads the Leeds Teaching Hospitals NHS Trust real-world evidence team collaboration with IQVIA and, as part of this collaboration, IQVIA funds the staff who support this work. GH also reports partial grant funding for a collaboration outside this study from IQVIA. MS was an employee at Leeds

Teaching Hospital NHS Trust at the time of the study, and he holds an honorary contract with Leeds Teaching Hospital NHS Trust. MS, MT and MR are employees of IQVIA. WS and SC are subcontracted to IQVIA and hold honorary contracts with Leeds Teaching Hospital NHS Trust. MS receives consultancy fees from BMS. CC, MD and JP are employees of BMS. CC and JP report stock ownership in BMS. LL was contracted (paid) as a consultant by BMS to support the I-O Optimise initiative and is an employee of Epi-Fit. There are no further conflicts of interest.

**AUTHOR CONTRIBUTIONS**

LL, CC, MD and JP conceived and designed the study, with contributions from MS, MT and WS. GH is the lead for the Leeds Teaching Hospital NHS Trust Real world programme, clinical lead for the Patient Pathway Manager (the Electronic Health Record) and Professor of Cancer Medicine and Digital Health (University of Leeds). SC is the Senior Information Officer working with the REAL-Oncology team at Leeds Teaching Hospital NHS Trust. MS provided expertise to REAL-Oncology regarding the management of lung cancer. MS, MT, WS and MR analysed the data. All authors contributed to the interpretation of the data, the drafting of the work and subsequent critical revision of the manuscript. MS accepts full responsibility for the work and the conduct of the study and had full access to the data.

**DATA SHARING**

The data analysed during the current study are available from the corresponding author on reasonable request. Study outputs will be made publicly available on Leeds Teaching Hospital NHS Trust website following publication.

**ACKNOWLEDGEMENTS**

Professional writing and editorial assistance were provided by Lisa Jolly, PhD, of Parexel, funded by Bristol Myers Squibb.

**TABLES**

**Table 1 Demographic and clinical characteristics of full patient population***

| | All NSCLC | NSQ | SQ | NSCLC NOS | Other NSCLC | Clinically diagnosed unknown pathology |
|---|---|---|---|---|---|---|
| **All stages** | **N=3739** | **n=1112** | **n=819** | **n=439** | **n=88** | **n=1281** |
| Age, years | | | | | | |
| Mean (SD) | 72.3 (10.9) | 68.6 (11.0) | 70.8 (9.4) | 68.9 (10.6) | 70.1 (10.7) | 78.0 (9.3) |
| Median (Q1–Q3) | 73 (65-80) | 69 (62-77) | 71 (64-77) | 69 (63-77) | 71 (63-78) | 79 (72-85) |
| Range | 18-101 | 31-101 | 33-96 | 18-92 | 42-91 | 43-99 |
| Male, n (%) | 1881 (50.3) | 519 (46.7) | 505 (61.7) | 220 (50.1) | 49 (55.7) | 588 (45.9) |
| TNM stage, n (%) | | | | | | |
| I | 717 (19.2) | 223 (20.1) | 127 (15.5) | 30 (6.8) | 19 (21.6) | 318 (24.8) |
| II | 434 (11.6) | 113 (10.2) | 132 (16.1) | <40 (<9.1) | <13 (<14.8) | 137 (10.7) |
| IIIA | 469 (12.5) | 110 (9.9) | 164 (20.0) | 54 (12.3) | 8 (9.1) | 133 (10.4) |

| | | | | | | |
|---|---|---|---|---|---|---|
| IIIB | 337 (9.0) | 89 (8.0) | 117 (14.3) | <55 (<12.3) | <5 (<6.0) | 77 (6.0) |
| IV | 1782 (47.7) | 577 (51.9) | 279 (34.1) | 263 (59.9) | 47 (53.4) | 616 (48.1) |
| Pathology, n (%) | | | | | | |
| Adenocarcinoma | 1019 (27.3) | 1019 (91.6) | 0 | 0 | 0 | 0 |
| SQ | 819 (21.9) | 0 | 819 (100.0) | 0 | 0 | 0 |
| NSCLC NOS | 439 (11.7) | 0 | 0 | 439 (100.0) | 0 | 0 |
| Large cell carcinoma | 93 (2.5) | 93 (8.4) | 0 | 0 | 0 | 0 |
| Other NSCLC | 88 (2.4) | 0 | 0 | 0 | 88 (100.0) | 0 |
| Clinically diagnosed, unknown pathology | 1281 (34.3) | 0 | 0 | 0 | 0 | 1281 (100.0) |
| WHO performance score, n (%) | | | | | | |
| 0 | 292 (7.8) | 149 (13.4) | 70 (8.6) | 38 (8.7) | 12 (13.6) | 23 (1.8) |
| 1 | 1031 (27.6) | 445 (40.0) | 319 (39.0) | 144 (32.8) | 37 (42.2) | 86 (6.7) |
| 2 | 758 (20.3) | 230 (20.7) | 230 (28.1) | 80 (18.2) | 25 (28.4) | 193 (15.1) |
| 3 | 933 (25.0) | 154 (13.9) | 118 (14.4) | 97 (22.1) | <15 (<17.0) | 553 (43.2) |

| | | | | | | |
|---|---|---|---|---|---|---|
| 4 | 372 (10.0) | 39 (3.5) | 16 (2.0) | 26 (5.9) | 0 | 291 (22.7) |
| Missing | 353 (9.4) | 95 (8.5) | 66 (8.1) | <55 (<12.5) | <5 (<5.7) | 135 (10.5) |

*For some categories including low numbers of patients, data have been masked to conceal patient identities. Includes 6 patients diagnosed in 2006.

NOS, not otherwise specified; NSCLC, non-small cell lung cancer; NSQ, non-squamous cell carcinoma; Q, quartile; SD, standard deviation; SQ, squamous cell carcinoma; TNM, tumour, node and metastasis; WHO, World Health Organization.

**Table 2 First-line and second-line SACT in patients with stage IIIB–IV NSQ or SQ carcinoma***

| | NSQ | | SQ | |
|---|---|---|---|---|
| **First-line SACT†** | **2007–2012** | **2013–2017** | **2007–2012** | **2013–2017** |
| Patients receiving first-line SACT, N | **139** | **161** | **104** | **76** |
| Platinum-based chemotherapy, n (%)‡ | 109 (78.4) | 119 (73.9) | 97 (93.3) | 73 (96.1) |
| Carboplatin based | 93 (66.9) | 78 (48.4) | 88 (84.6) | 68 (65.4) |
| Cisplatin based | 11 (7.9) | 33 (20.5) | 9 (8.7) | <5 |
| Pemetrexed included | 58 (41.7) | 107 (77.0) | <5 | <5 |
| Non–platinum-based chemotherapy, n (%) | <5 | 0 | <5 | <5 |
| TKI, n (%) | 17 (12.2) | 34 (21.1) | 0 | <5 |
| Anti–PD-1/PD-L1 checkpoint inhibitors, n (%) | 0 | <5 | 0 | <5 |
| Clinical trial – unknown treatment, n (%) | 8 (5.8) | <5 | 5 (4.8) | 0 |

| **Second-line SACT[§]** | **2007–2012** | **2013–2018** | **2007–2012** | **2013–2018** |
|---|---|---|---|---|
| Patients receiving second-line SACT, N | **53** | **66** | **31** | **23** |
| Platinum-based therapy, n (%)[‡] | <5 | 13 (19.7) | 5 (16.1) | 8 (34.8) |
| Non–platinum-based chemotherapy, n (%) | <5 | 7 (10.6) | <5 | <5 |
| TKI, n (%) | 47 (88.7) | 31 (47.0) | 23 (74.2) | 6 (26.1) |
| Anti–PD-1/PD-L1 checkpoint inhibitors, n (%) | 0 | 10 (15.2) | 0 | 5 (21.7) |
| Clinical trial – unknown treatment, n (%) | 0 | <5 | 0 | 0 |

*For some categories including low numbers of patients, data have been masked to conceal patient identities. [†]Time periods for receipt of initial SACT are based on the date of diagnosis: January 2007–December 2012 and January 2013–August 2017. [‡]Platinum based is defined as any regimen including a platinum agent (monotherapy or in combination) and is further defined as "carboplatin based," "cisplatin based" (including regimens in which carboplatin and cisplatin were both used) and "pemetrexed included" (any platinum-based regimen also including pemetrexed). [§]Time periods for receipt of second-line SACT are based on the start date for second-line treatment: January 2007–December 2012, January 2013–April 2018.

NSQ, non-squamous cell carcinoma; PD-1, programmed death 1; PD-L1, programmed death ligand 1; SACT, systemic anticancer therapy; SQ, squamous cell carcinoma; TKI, tyrosine kinase inhibitor.

**FIGURES**

**Figure 1 TNM stage at NSCLC incident diagnosis, by year of diagnosis**

†Diagnosed up to 31 August 2017.

TNM, tumour, node and metastasis.

**Figure 2 Initial treatment by TNM stage and time period (2007–2012 vs 2013–2017) in patients with (A) NSQ, (B) SQ or (C) CDUP*,†**

*Time periods for receipt of initial treatment are based on the date of diagnosis during two consecutive time periods (January 2007–December 2012 and January 2013–August 2017). †Where analytical groups included fewer than five patients, percentages are not shown as labels.

CDUP, clinically diagnosed with unknown pathology; NSQ, non-squamous cell carcinoma; RT, radiotherapy; SACT, systemic anticancer therapy; SQ, squamous cell carcinoma; TNM, tumour, node and metastasis; Tx, treatment.

**Figure 3 Evolution of OS in patients diagnosed with stage I (A), stage II (B), stage IIIA (C) or stage IIIB–IV (D) NSCLC with NSQ, SQ or CDUP**

CDUP, clinically diagnosed with unknown pathology; NSCLC, non-small cell lung cancer; NSQ, non-squamous cell carcinoma; OS, overall survival; SQ, squamous cell carcinoma.

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Figure 1 TNM stage at NSCLC incident diagnosis, by year of diagnosis

145x100mm (600 x 600 DPI)

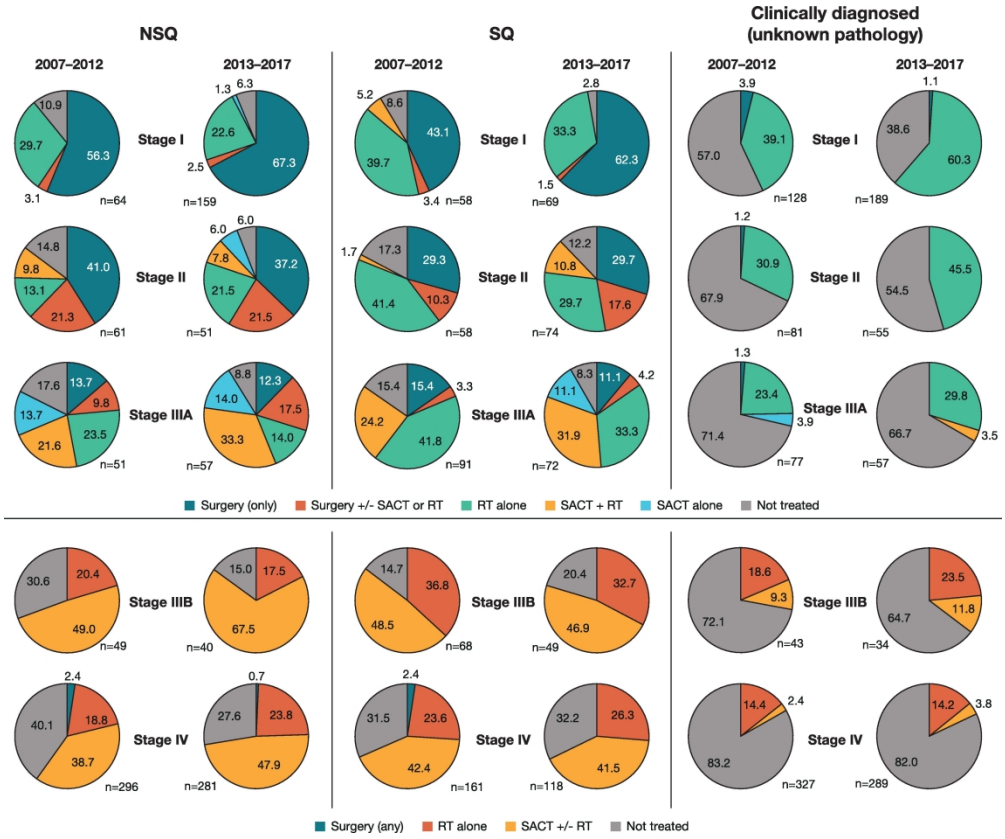


Figure 2 Initial treatment by TNM stage and time period (2007–2012 vs 2013–2017) in patients with (A) NSQ, (B) SQ or (C) CDUP*,†

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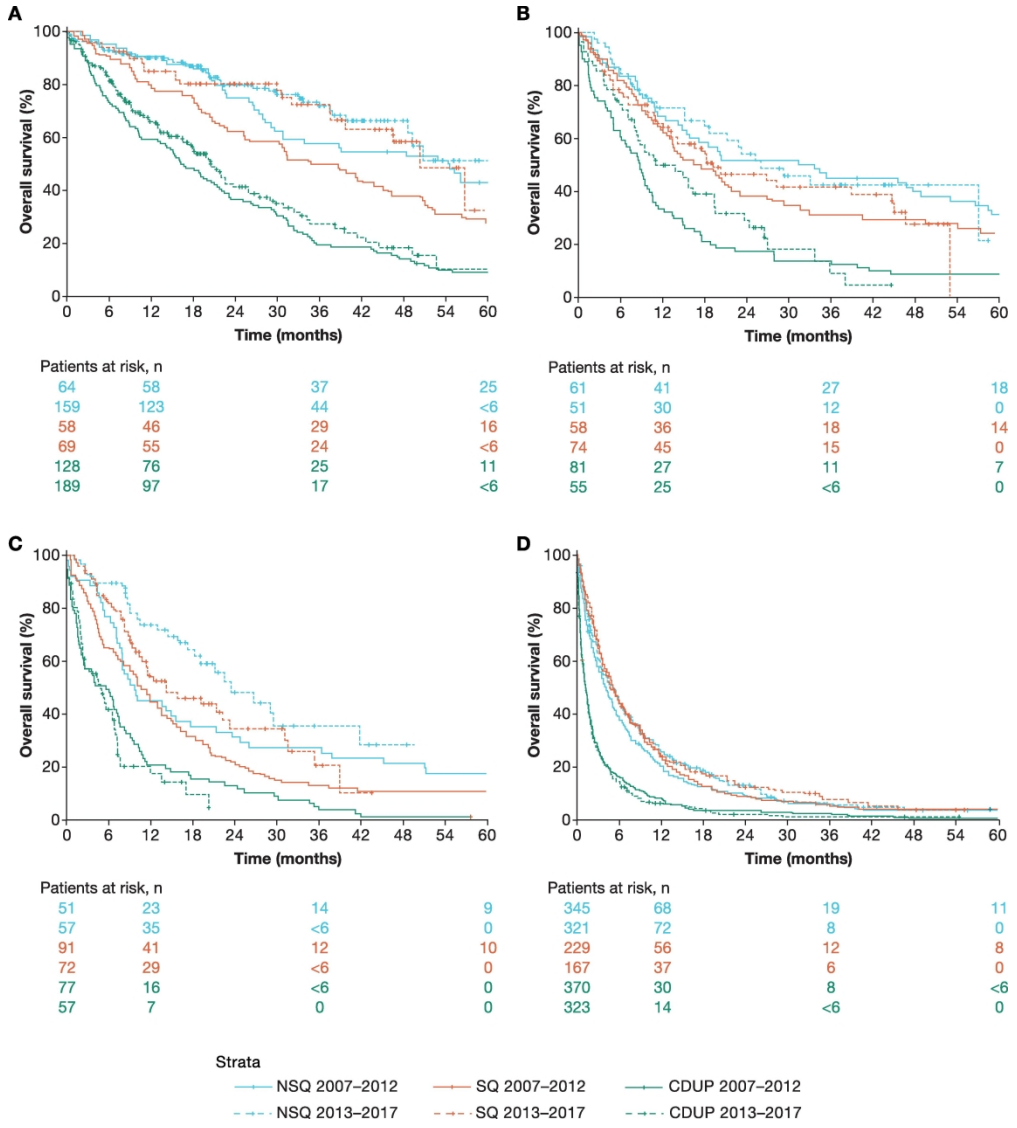


Figure 3 Evolution of OS in patients diagnosed with stage I (A), stage II (B), stage IIIA (C) or stage IIIB–IV (D) NSCLC with NSQ, SQ or CDUP

178x198mm (600 x 600 DPI)

**SUPPLEMENTARY FILE**

# Treatment patterns and survival outcomes for patients with non-small cell lung cancer in the United Kingdom in the pre-immunology era: a REAL-Oncology database analysis from the I-O Optimise initiative

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**SUPPLEMENTARY APPENDIX**

## Appendix

**Table S1.** ICD-O-3 morphology codes for NSCLC.

| Morphology code | Type of NSCLC |
|---|---|
| | **Adenocarcinoma (non-squamous NSCLC)** |
| 81403 | Adenocarcinoma UNS |
| 81443 | Enteric adenocarcinoma |
| 82303 | Solid adenocarcinoma with mucin production |
| 82443 | MANEC mixed adenoneuroendocrine carcinoma |
| 82500 | Atypical adenomatous hyperplasia |
| 82502 | Adenocarcinoma in situ, non-mucinous |
| 82503 | Adenocarcinoma, bronchiolo-alveolar (BAC), bronchiolar carcinoma, (incl pathologic in situ-variant) |
| 82523 | Bronchiolo-alveolar carcinoma |
| 82532 | Adenocarcinoma in situ, mucinous |
| 82533 | Adenocarcinoma, mucinous bronchiolo-alveolar (BAC) |
| 82543 | Bronchiolo-alveolar carcinoma, mixed mucinous and non-mucinous |

| Morphology code | Type of NSCLC |
|---|---|
| 82553 | Adenocarcinoma, mixed with other types of carcinoma incl. squamous cell and small-cell carcinoma |
| 82563 | Minimally invasive adenocarcinoma, non-mucinous |
| 82573 | Minimally invasive adenocarcinoma, mucinous |
| 82603 | Papillary adenocarcinoma, NOS |
| 82653 | Micropapillary adenocarcinoma |
| 83103 | Clear cell adenocarcinoma |
| 83333 | Fetal adenocarcinoma |
| 84703 | Mucinous cystadenocarcinoma |
| 84803 | Mucinous adenocarcinoma |
| 84903 | Signet ring cell carcinoma |
| 85503 | Acinar cell carcinoma |
| 85513 | Acinar adenocarcinoma |
| | **Squamous cell carcinoma** |
| 80523 | Papillary squamous cell carcinoma |
| 80702 | Squamous cell carcinoma in situ |
| 80703 | Squamous cell carcinoma |

| Morphology code | Type of NSCLC |
|---|---|
| 80713 | Keratinizing squamous cell carcinoma |
| 80723 | Non-keratinizing squamous cell carcinoma |
| 80733 | Squamous cell carcinoma, small cell non-keratinizing |
| 80833 | Basaloid squamous cell carcinoma |
| 80843 | Squamous cell carcinoma, clear cell type |
| | **NSCLC NOS** |
| 80103 | Carcinoma, NOS |
| 80203 | Carcinoma, undifferentiated NOS |
| 80213 | Carcinoma, anaplastic NOS |
| 80463 | Carcinoma, non-small cell unspecified |
| | **Large cell carcinoma (non-squamous NSCLC)** |
| 80123 | Large-cell carcinoma, unspecified |
| | **Neuroendocrine NSCLC carcinoma (other specified NSCLC carcinoma)** |
| 80133 | Large cell neuroendocrine carcinoma |
| 82463 | Neuroendocrine carcinoma, NOS |
| | **Other miscellaneous NSCLC (other specified NSCLC carcinoma)** |

| Morphology code | Type of NSCLC |
|---|---|
| 80143 | Large cell carcinoma with rhabdoid phenotype |
| 80223 | Sarcomatoid carcinoma, pleomorphic |
| 80233 | NUT carcinoma |
| 80303 | Spindle cell and giant cell carcinoma |
| 80313 | Giant cell carcinoma |
| 80323 | Spindle cell carcinoma, NOS |
| 80333 | Pseudosarcomatous carcinoma |
| 81233 | Basaloid carcinoma |
| 82003 | Adenocystic carcinoma |
| 84303 | Mucoepidermoid carcinoma |
| 85603 | Adenosquamous carcinoma |
| 85623 | Epithelial-myoepithelial carcinoma |
| 89723 | Blastoma, pulmonary (pneumoblastoma) |
| 89803 | Carcinosarcoma, NOS |
| 89823 | Myoepithelial carcinoma |

ICD-O-3, *International Classification of Diseases for Oncology*, 3rd Edition; NOS, not otherwise specified; NSCLC, non-small cell lung cancer; UNS, unspecified.

**Table S2.** Initial treatment algorithm. Initial treatment was defined as the first treatment received within 6 months of diagnosis, associated with any other treatment received within a certain time period following first treatment as defined in the table below.

| **Initial treatment category** | **Definitions** |
|---|---|
| A. Surgery | Sum of all A sub-groups |
| A0. Surgery only | Surgery + no SACT or RT within 12 weeks after surgery |
| A1. Surgery + adjuvant SACT (only) – no RT within 6 months of SACT start | Surgery + identification of SACT only (start) within 84 days (12 weeks) after surgery |
| A2. Surgery + adjuvant RT (only) – no SACT within 6 months of RT start | Surgery + identification of RT only (start) within 84 days (12 weeks) after surgery |
| A3. Surgery + adjuvant RT and SACT | Surgery + identification of RT [or SACT] (start) within 84 days (12 weeks) after surgery + identification of SACT [or RT] (start) within 180 days (6 months) after RT [or SACT] |

| | |
|---|---|
| A4. Neoadjuvant SACT + surgery | SACT + identification of surgery within 120 days (4 months) after first SACT regimen start + no RT identification prior to surgery AND: |
| A5. Neoadjuvant RT + surgery | RT + identification of surgery within 90 days (3 months) after first RT treatment start + no SACT identification prior to surgery AND: |
| A6. Neoadjuvant SACT and RT + surgery | RT and SACT + identification of surgery within 3 months after start + identification of SACT and RT prior to surgery Note: Neoadjuvant SACT and RT corresponds to RT within 6 weeks of SACT start |
| B. Radiotherapy alone | RT + no SACT nor surgery within 90 days (3 months) after RT |
| C. SACT + Radiotherapy | Sum of C1, C2 and C3 |
| C1. RT followed by SACT | RT + identification of SACT within 90 days (3 months) after first SACT regimen start + no surgery within 6 months after first SACT start |

| | |
|---|---|
| C2. SACT followed by RT | SACT + identification of RT within 90 days (3 months) after first SACT regimen start + no surgery within 6 months after first SACT start |
| C3. Concurrent chemoradiation | SACT + [start RT within 6 weeks of SACT] + no surgery within 3 months after chemoradiation |
| D. SACT alone | SACT + no RT nor surgery within 90 days (3 months) after first SACT regimen start |
| E. Not treated | No SACT, surgery or RT identified over entire follow-up period |

RT, radiotherapy; SACT, systemic anticancer therapy

**Table S3:** OS in patients diagnosed with NSCLC in 2007–2012 and 2013–2017 by stage and pathological subtype

| Substratification | N | Median OS (months) | Q1–Q3 (months) | 1-year | | 3-year | | 5-year | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | n | OS (95% CI) | n | OS (95% CI) | n | OS (95% CI) |
| **Stage I** | | | | | | | | | |
| NSQ 2007–2012 | 64 | 55.27 | 24.8–98.5 | 58 | 0.91 (0.84–0.98) | 37 | 0.58 (0.47– 0.71) | 25 | 0.43 (0.32–0.57) |
| NSQ 2013–2017 | 159 | NA | 34.2–NA | 123 | 0.90 (0.86–0.95) | 44 | 0.72 (0.64–0.81) | <6 | 0.51 (0.37–0.72) |
| SQ 2007–2012 | 58 | 37.28 | 18.5–66.8 | 46 | 0.79 (0.70–0.90) | 29 | 0.50 (0.39–0.65) | 16 | 0.28 (0.18–0.42) |
| SQ 2013–2017 | 69 | 51.13 | 32.6–NA | 55 | 0.85 (0.77–0.94) | 24 | 0.73 (0.61–0.86) | <6 | 0.32 (0.13–0.81) |
| CDUP 2007–2012 | 128 | 16.72 | 5.8–33.1 | 76 | 0.59 (0.51–0.69) | 25 | 0.20 (0.14 –0.28) | 11 | 0.09 (0.05–0.16) |
| CDUP 2013–2017 | 189 | 20.90 | 8.0–40.3 | 97 | 0.66 (0.60–0.74) | 17 | 0.27 (0.19–0.38) | <6 | 0.10 (0.04–0.28) |
| **Stage II** | | | | | | | | | |
| NSQ 2007–2012 | 61 | 34.27 | 10.6–80.0 | 41 | 0.68 (0.58–0.81) | 27 | 0.45 (0.34–0.60) | 18 | 0.31 (0.21–0.46) |
| NSQ 2013–2017 | 51 | 26.43 | 10.2–58.0 | 30 | 0.72 (0.60–0.85) | 12 | 0.42 (0.30–0.61) | 0 | – |
| SQ 2007–2012 | 58 | 17.20 | 8.6–58.2 | 36 | 0.62 (0.51–0.76) | 18 | 0.31 (0.21–0.46) | 14 | 0.24 (0.15–0.38) |
| SQ 2013–2017 | 74 | 19.87 | 7.2–53.9 | 45 | 0.66 (0.55–0.77) | 15 | 0.42 (0.31–0.57) | 0 | – |
| CDUP 2007–2012 | 81 | 8.93 | 2.9–16.8 | 27 | 0.33 (0.24–0.45) | 11 | 0.14 (0.08–0.24) | 7 | 0.09 (0.04–0.18) |
| CDUP 2013–2017 | 55 | 11.33 | 5.4–26.9 | 25 | 0.50 (0.38–0.65) | <6 | 0.09 (0.03–0.31) | 0 | – |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Stage IIIA** | | | | | | | | | |
| NSQ 2007–2012 | 51 | 9.93 | 6.5–38.6 | 23 | 0.45 (0.33–0.61) | 14 | 0.27 (0.18–0.43) | 9 | 0.18 (0.10–0.32) |
| NSQ 2013–2017 | 57 | 23.97 | 10.6–NA | 35 | 0.74 (0.63–0.87) | <6 | 0.35 (0.22–0.58) | 0 | – |
| SQ 2007–2012 | 91 | 10.73 | 4.4–21.1 | 41 | 0.45 (0.36–0.57) | 12 | 0.13 (0.08–0.22) | 10 | 0.11 (0.06–0.20) |
| SQ 2013–2017 | 72 | 14.50 | 8.4–36.0 | 29 | 0.54 (0.43–0.68) | <6 | 0.21 (0.10–0.42) | 0 | – |
| CDUP 2007–2012 | 77 | 5.77 | 1.5–11.0 | 16 | 0.21 (0.13–0.32) | <6 | 0.05 (0.02–0.13) | 0 | – |
| CDUP 2013–2017 | 57 | 5.00 | 1.9– 7.5 | 7 | 0.20 (0.12–0.36) | 0 | – | 0 | – |
| **Stage IIIB–IV** | | | | | | | | | |
| NSQ 2007–2012 | 345 | 4.07 | 1.3–10.5 | 68 | 0.20 (0.16–0.25) | 19 | 0.06 (0.04–0.09) | 11 | 0.03 (0.02–0.06) |
| NSQ 2013–2017 | 321 | 5.00 | 1.7–12.9 | 72 | 0.26 (0.21–0.31) | 8 | 0.06 (0.04–0.11) | 0 | – |
| SQ 2007–2012 | 229 | 5.33 | 2.2–12.0 | 56 | 0.24 (0.19–0.31) | 12 | 0.05 (0.03–0.09) | 8 | 0.04 (0.02–0.07) |
| SQ 2013–2017 | 167 | 4.80 | 2.4–11.9 | 37 | 0.25 (0.19–0.32) | 6 | 0.08 (0.04–0.15) | 0 | – |
| CDUP 2007–2012 | 370 | 1.23 | 0.4–3.2 | 30 | 0.08 (0.06–0.11) | 8 | 0.02 (0.01–0.05) | <6 | 0.01 (0.00–0.02) |
| CDUP 2013–2017 | 323 | 1.23 | 0.4–3.4 | 14 | 0.06 (0.04–0.09) | <6 | 0.01 (0.00–0.04) | 0 | – |

CDUP, clinically diagnosed with unknown pathology; NSCLC, non-small cell lung cancer; NSQ, non-squamous cell carcinoma; OS, overall survival; SQ, squamous cell carcinoma

## STROBE checklist

| Treatment patterns and survival outcomes for patients with non-small cell lung cancer in the United Kingdom in the pre-immunology era: a REAL-Oncology database analysis from the I-O Optimise initiative | | | **Snee, et al.** |
|---|---|---|---|
| **Checklist item -** | | | **Section** |
| **Title and abstract** | | | |
| | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract | *Title, abstract* |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | *Abstract* |
| **Introduction** | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | *Introduction, p5–6* |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | *Introduction, p5–6* |
| **Methods** | | | |
| Study design | 4 | Present key elements of study design early in the paper | *Methods, Study design, p6* |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | *Methods, Study setting, p6–7 Analyses, p7–8* |
| Participants | 6 | (*a*) *Cohort study*? Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up | *Methods, Study design, p6–7* |
| | | (*b*) *Cohort study*? For matched studies, give matching criteria and number of exposed and unexposed | *N/A* |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | *Methods, Analyses p7* |

| | | | |
|---|---|---|---|
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | *Methods, Analyses, p7* |
| Bias | 9 | Describe any efforts to address potential sources of bias | *N/A, retrospective study* |
| Study size | 10 | Explain how the study size was arrived at | *N/A, retrospective study* |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | *Methods, Analyses, p8* |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | *Methods, Analyses, p8* |
| | | (*b*) Describe any methods used to examine subgroups and interactions | *Methods, Analyses, p8* |
| | | (*c*) Explain how missing data were addressed | *Methods, Analyses, p8* |
| | | (*d*) *Cohort study*? If applicable, explain how loss to follow-up was addressed | *N/A, retrospective study* |
| | | (*e*) Describe any sensitivity analyses | *N/A* |
| **Results** | | | |
| Participants | 13* | (*a*) Report numbers of individuals at each stage of study? eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | *Results, Patients, p8* |
| | | (*b*) Give reasons for non-participation at each stage | *Results, Patients, p8* |
| | | (*c*) Consider use of a flow diagram | *Not included* |

| | | | |
|---|---|---|---|
| Descriptive data | 14* | (*a*)Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | *Results, Patients, p8–6* |
| | | (*b*) Indicate number of participants with missing data for each variable of interest | *N/A* |
| | | (*c*) *Cohort study*? Summarise follow-up time (eg average and total amount) | *N/A* |
| Outcome data | 15* | *Cohort study*? Report numbers of outcome events or summary measures over time | *Results, Overall survival, p12–13* |
| | | *Case-control study?* Report numbers in each exposure category, or summary measures of exposure | *N/A* |
| | | *Cross sectional study?* Report numbers of outcome events or summary measures | |
| Main results | 16 | (a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | *Results, Overall survival, p12–13* |
| | | (b) Report category boundaries when continuous variables were categorized | *N/A* |
| | | (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | *Not included* |
| Other analyses | 17 | Report other analyses done? eg analyses of subgroups and interactions, and sensitivity analyses | *N/A* |
| **Discussion** | | | |
| Key results | 18 | Summarise key results with reference to study objectives | *Discussion, p13* |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | *Discussion, p16* |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | *Discussion* |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | *Discussion, 16–17* |

| **Other information** | | | |
|---|---|---|---|
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | *Funding, p17* |
| | | | |

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.