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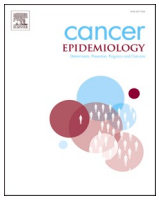

Characteristics of patients with lung cancer in clinical practice and their potential eligibility for clinical trials evaluating tyrosine kinase inhibitors or immune checkpoint inhibitors☆

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ABSTRACT

Introduction: In- and exclusion criteria of randomized clinical trials (RCTs) aim to include a homogeneous study-population. This study compared characteristics of lung cancer patients from phase III RCTs evaluating tyrosine kinase inhibitors (TKIs) or immune checkpoint inhibitors (ICIs) with characteristics of lung cancer patients in a real world setting in the United Kingdom.
Methods: A retrospective study was conducted using the Clinical Practice Research Datalink GOLD. Patients (N = 9239) with a first ever lung cancer registration between 2014 and 2018 were identified. Eligibility for inclusion was assessed for twelve RCTs (evaluating TKIs or ICIs). Reasons for potential exclusion and the number of unmet criteria were assessed for each RCT independently. OS was assessed using Kaplan-Meier and Cox proportional hazards analyses.
Results: The proportion of potentially eligible patients was 74.3% and 51.9% for TKI and ICI RCTs, respectively. History of another malignancy, renal insufficiency or concomitant drug-use were main reasons for exclusion. OS was considerably longer for potentially eligible patients. Hazards ratios varied from 1.17 (95% confidence interval, 1.11–1.24) to 1.35 (1.20–1.42) across the RCTs.
Conclusion: This study showed that a considerable proportion of lung cancer patients in a real-world setting would have been ineligible for participation in phase III RCTs and that potentially ineligible patients experienced a shorter OS.

1. Introduction

Lung cancer is the most common cause of cancer related deaths among men worldwide and among women in more developed countries [1]. Lung cancer can be subdivided into small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). In the United Kingdom (UK), approximately 87% of patients with lung cancer have NSCLC and their 5 year survival rate is 9.5% [2]. Survival is strongly influenced by the disease stage at diagnosis, i.e. early stage disease is associated with much better prognosis compared with diagnosis at an advanced-stage [3]. Around 75% of the patients with lung cancer in the UK are diagnosed with an advanced (stage III or IV) disease [4]. For those patients a curative approach is no longer available and systemic therapy is normally considered a cornerstone of treatment. Over the past 15 years, tyrosine kinase inhibitors (TKIs) and immune checkpoint inhibitors (ICIs) have become available. The efficacy of TKIs and ICIs have been

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evaluated in large phase III randomized clinical trials (RCTs), with strict in- and exclusion criteria [5–16].

It is unclear whether patients who participated in those RCTs [5–16] are good representatives for patients with lung cancer in clinical practice. RCTs often exclude patients with a wide range of comorbidities, abnormal laboratory measurements or concomitant drug use. In real life, a considerable number of patients with lung cancer have chronic comorbidities such as cardiovascular disease, chronic obstructive pulmonary disease, and type 2 diabetes mellitus [17,18], often related to tobacco smoking [19–22]. Previous studies have shown that NSCLC patients who received chemotherapy or first-generation TKIs in clinical practice did not possess the eligibility criteria of the underlying RCTs that provided evidence for the efficacy of these treatments [23–26]. Substantial differences between the studied clinical trial population and the population seen in daily clinical practice may lead to less favorable treatment outcomes, as has been shown for chemotherapy treatment in patients with lung cancer [27].

Whereas the efficacy of osimertinib, alectinib, nivolumab, pembrolizumab, atezolizumab, durvalumab in the treatment of selected NSCLC-patients is well-established [5–16], the representativeness of the patients included in the RCTs leading to market approval, has not been evaluated.

Therefore, the primary aim of this study was to compare the characteristics of patients included in phase III RCTs that evaluated TKIs or ICIs for treatment of lung cancer with the characteristics of patients with lung cancer in a real world setting in the UK from 2014 through 2018. The secondary aim was to compare overall survival (OS) among real world lung cancer patients in the UK who would have been eligible for inclusion in these phase III RCTs with that of patients who did not meet those eligibility criteria.

2. Methods

2.1. Data source

Data were obtained from the Clinical Practice Research Datalink GOLD, (CPRD (www.cprd.com)), hereafter referred to as CPRD. The CPRD contains computerized medical records from 674 primary care practices in the UK, representing 6.9% of the population in 2013 [28]. The CPRD features demographic information, prescription details, clinical events, preventive care provided, specialist referrals, hospital admissions and major outcomes since 1987, with on-going data collection. The clinical events in the CPRD are classified using Read-codes, which is an hierarchical system used to specify medical conditions and clinical events [29]. The validity of lung cancer recording in the CPRD has been reported by others, as the concordance of lung cancer registration between CPRD and the cancer registry was $\geq$ 90% [30,31].

2.2. Literature search of clinical trials

We selected six newly approved drugs used to systemically treat patients with NSCLC: osimertinib and alectinib as TKIs, and pembrolizumab, nivolumab, atezolizumab and durvalumab as ICIs. A literature search was performed in PubMed to identify phase III RCTs published between 01 and 01–2014 and 31–12–2018 evaluating the efficacy of these drugs. The literature search was performed by using the different drug names in combination with 'randomized controlled trial', 'RCT', 'phase 3′ or 'NSCLC'. For nivolumab and pembrolizumab, only RCTs evaluating first-line use were included as studies of generalizability as RCTs evaluating second-line use of nivolumab and pembrolizumab had been published before [25]. In total, twelve RCTs were identified (Table A1.1, Appendix 1).

2.3. Study Cohort

A retrospective cohort study was conducted among patients aged $\geq$ 18 years with a first diagnosis of lung cancer between 01 January 2014 and 31 December 2018. Read codes used to identify lung cancer patients are shown in Appendix 2. The list was composed by one researcher (AV) and verified by a pulmonary oncologist (AD). The date of the first lung cancer diagnosis during valid data collection defined the index date (and thereby the start of follow-up).

2.4. Inclusion and exclusion criteria

The in- and exclusion criteria of the selected RCTs were evaluated, listed and grouped into comorbidities, medication use, and laboratory values (Appendix 3). Codelists for all comorbidities and drugs were independently reviewed by a pharmacist (AV) and a physician (SA). In case of disagreement, a third author (PS) did an additional review. For laboratory measurements, the registered unit of measurement was assessed for all laboratory values and all measurements with an appropriate unit were included. When a laboratory value was registered with an inappropriate or without an unit of measurement, the registered value was not included in the analysis. The in- and exclusion criteria were grouped according to eight sets of criteria (laboratory values, cancer, immune-related, cardiovascular, infections, psychiatric, drugs and other), as shown in Appendix 3. For the evaluation of laboratory measurements, reference values were used to identify deviant values (Appendix 4). In addition, if a laboratory value was not registered for a patient, it was assumed that the laboratory value was not deviant and potential exclusion would only be done when a deviant laboratory value was specifically registered. Some disease areas were only generally described in the protocols (e.g. immune-related diseases, serious infections, psychiatric diseases and organ transplant). To identify these broad terms, a set of relevant medical conditions was compiled for every broad term and those specific conditions were used as exclusion criteria. The selections were verified by a pulmonary oncologist (AD). A list of all used exclusion criteria is shown in Appendix 3.

Each comorbidity, laboratory measurement, or concomitant drug use had to be registered in a specific timeframe (time-window of exposure) before the diagnosis of lung cancer (index date) to be considered as active (Appendix 3). Study protocols of the included RCTs were reviewed to identify the time-window of exposure for the different exclusion criteria. When a time-window of exposure was not specified in the protocols, an appropriate time-window of exposure was selected by the researcher (AV). For each comorbidity the time-window of exposure was determined by the nature of the condition. For laboratory measurements and concomitant drug use a 3 month period was selected as time-window of exposure. The exclusion criteria per study and their corresponding time-window of exposure are shown in Appendix 5.

2.5. Data analysis

Descriptive analyses were used to summarize patient characteristics, both for full study period and by calendar year. To assess the eligibility of patients with lung cancer in CPRD for potential inclusion in each RCT, the numbers and proportions of patients who met all criteria for each individual RCT were determined. Furthermore, the reason for potential study exclusion (restricted to the eight sets of criteria previously specified [Appendix 3]) was assessed and the maximum number of unmet criteria were evaluated individually. For all lung cancer patients in CPRD, Kaplan-Meier analyses compared OS between those who met eligibility criteria for each individual RCT versus those did not meet eligibility criteria. Corresponding Kaplan-Meier curves compared OS in CPRD patients whose characteristics made them eligible or ineligible for inclusion in published RCTs (Table A1.1, Appendix 1). In addition, Cox proportional hazards analyses estimated crude and age-sex adjusted hazard ratios (HRs) for mortality of patients with lung cancer, comparing patients who would have been eligible for participation in RCTs (Table A1.1, Appendix 1) to those who would have been ineligible [5–16]. A sensitivity analysis was performed in which we evaluated

what the potential effect would be on potential study participation if the criteria for kidney function were less strict for the trials evaluating immunotherapy. All analyses were performed using the SAS software application (version 9.4: SAS Institute, Cary, NC, U.S.A.). This study was approved by the Independent Scientific Advisory Committee for MHRA database research.

3. Results

The baseline characteristics of the study population are shown in Table 1. A total number of 9239 adult patients with lung cancer were identified. The mean age of the included patients was 72.1 years, and more than half of the patients (51.0%) were male. Virtually all patients were previous or current smokers, as only 6.3% had never smoked before. Most patients had a body mass index (BMI) between 18.6 and 30.0 kg/m^2 (68.5% for the total population). A history of another malignancy within 5 years prior to the lung cancer diagnosis was the most frequent comorbidity responsible for potential study exclusion (10.2%). The most frequent types of other malignancies were breast, prostate or colorectal cancer. A low estimated glomerular filtration rate (eGFR $<$ 60 mL/min) recorded within the past 3 months was the most common deviant laboratory value (10.5%), and the most frequently concomitantly used drug was a systemic glucocorticoid (20.6%).

Table 2 shows that the proportion of patients with lung cancer from CPRD who would have been eligible for inclusion in RCTs ranged from 49.1% to 78.1%. The mean proportion of patients that would have been eligible for RCTs evaluating TKIs was 74.3% (range: 72.4–78.1%) and 51.9% for ICIs (range: 49.1–54.3%). For some of the drugs (osimertinib, alectinib, nivolumab and pembrolizumab) more than one RCT was included (Table A1.1, Appendix 1). Potential eligibility for RCTs evaluating the same drug was similar except for AURA3 (78.1%) and FLAURA (72.4%). A considerable number of patients with lung cancer in CPRD would have been excluded due to a single unmet criterion. RCTs evaluating TKIs had up to 4 unmet eligibility criteria. For RCTs evaluating ICIs the maximum number of unmet criteria was 6, with the exception of the nivolumab trials, for which the maximum number of unmet criteria was 5.

Table 3 shows the proportion of lung cancer patients who would be excluded for each individual RCTs set of in- and exclusion criteria. A history of malignancies or concomitant drug use were the most frequent criteria for potential exclusion. A history of a malignancy was applied as an exclusion criterion in all RCTs but one (AURA3) and led to exclusion of 7.2–10.2% of all patients in CPRD. In all RCTs, concomitant drug-use led to exclusion of $>$ 10% of patients and was highest in the CheckMate 017 and 057 trials (26.7%). In addition, laboratory values, serious infections and other criteria were applied in all RCTs, which would also lead to considerable exclusion. The specific criteria per RCT are shown in Appendix 5.

Table 4 and Appendix 6 show that mortality of lung cancer patients from CPRD was consistently lower for patients who would have been eligible for inclusion of the original RCTs versus patients who would have been ineligible. The age-sex adjusted HR varied between 0.74 (95% CI: 0.71 – 0.78; CheckMate 057 [6] to 0.85 (95% CI: 0.81 – 0.90; FLAURA [16])).

If the exclusion criterion for estimated creatinine clearance was relaxed to 10 mL per minute, for the studies in which immunotherapy were evaluated, the proportion of patients that would have been eligible increased. The increase was larger for the clinical trials which initially applied a more strict threshold value for the kidney function. The largest absolute increase was observed for the KEYNOTE-407 study as potential inclusion increased with 4.9% (from 50.0% to 54.9%), and varied from 0.4% to 4.9% for all immunotherapy trials.

4. Discussion

We found that a considerable proportion of patients with lung cancer in a real-world setting would have been ineligible to participate in one of the phase III RCTs evaluating TKIs or ICIs from 2014 through 2018. Lung cancer patients would often be excluded based on 1 or 2 unmet eligibility criteria. Previous or concurrent malignancies, a decreased eGFR or concomitant systemic glucocorticoid use were the most frequent reasons for hypothetical exclusion. OS of real-world patients was considerably shorter among those who would have been ineligible for potential inclusion compared with those who would have been eligible.

The hypothetical study eligibility of patients with lung cancer in clinical practice has been evaluated previously for other treatments, such as chemotherapy, earlier generation TKIs or ICIs applied as second-line treatment [23–26]. Some studies used specific in- and exclusion criteria applied in a particular RCT [23,24], while others used a more general, self-selected set of criteria, composed from more general criteria which are often used in RCTs [25,26], such as the performance status (PS), the number of previous treatments and possible registered comorbidities. Hypothetical study inclusion for multiple chemotherapy RCTs and for RCTs evaluating TKIs or ICIs was generally below 50%, apart from the FLEX and NEXUS-studies [23,24]. When the most stringent set of criteria were used in studies using self-selected criteria, only 30% of patients would have been eligible for potential participation [25,26]. Although the exact proportion of patients that would have been eligible for RCT participation was higher in our study, a considerable proportion of patients would have been ineligible for hypothetical trial participation. Other studies concluded that PS was one of the most important reasons for patient exclusion [23–26]. PS is not registered in the CPRD and could therefore not be incorporated in our study. This could have led to a potential underestimation of the proportion of CPRD patients who would have been ineligible for RCT inclusion. A lower hypothetical study inclusion of patients in real-life has also been seen for other types of cancer [32–36]. In most of these studies a shorter progression-free survival and OS was reported for the patients who would have been ineligible [32–34,36], which is in line with our findings.

A recent study evaluated the effect of broadening eligibility criteria for trial inclusion in NSCLC patients, which showed that considerably more patients could be safely included [37]. In the different clinical trials evaluating the efficacy of immunotherapy, varying threshold values were applied for estimated creatinine clearance, from 30 mL per minute till 60 mL per minute). As monoclonal antibodies (large protein structures) are not renally eliminated, it could be rationalized that immunotherapy can be given to patients with an impaired kidney function [38]. When we lowered the threshold value for the kidney function to 10 mL per minute the inclusion would increase up to 4.9% (KEYNOTE-407, from 50.0% to 54.9%). In the future, a more tailored set of criteria based on the (pharmacokinetic) characteristics of the new drug could increase the number of potential patients eligible for study participation.

A strength of our study was the large number of included patients with a recording of lung cancer (N = 9239). This number was considerably larger compared with other studies [23–26]. In addition, for each patient, an extensive medical history could be retrieved. Given the population-based nature of CPRD we believe that this is a reliable reflection of the patients who are diagnosed with lung cancer in the UK's clinical practice.

Several studies have previously evaluated the validity of the registration of cancer cases in CPRD. CPRD's lung cancer codes have a high degree of concordance with the cancer registry, as the agreement in lung cancer registration between CPRD and the national cancer registry of England is higher than 90% [30,31]. However, all studies evaluating the concordance between CPRD and the national cancer registry of England stated that a minority of patients will be missed when using solely CPRD data [30,31,39,40]. In addition, a differential survival has been reported between patients registered in CPRD and patients registered in the cancer registry [39]. Patients who die shortly after their diagnosis are potentially less likely to be captured in CPRD. Given their medical

Table 1
Baseline characteristics of lung cancer patients in CPRD GOLD between 2014 and 2018, overall and stratified by calendar year.

	Total		2014		2015		2016		2017		2018	
	N = 9239		N = 2426		N = 2114		N = 1795		N = 1510		N = 1394	
	N	%	N	%	N	%	N	%	N	%	N	%
Sex												
No. of Males	4710	51.0	1290	53.2	1080	51.1	901	50.2	745	49.3	694	49.8
Age (years)												
Mean (SD)	72.1 (10.5)		71.8 (10.8)		72.0 (10.3)		72.3 (10.5)		72.1 (10.3)		72.4 (10.2)	
< 50.0 years	258	2.8	84	3.5	46	2.2	53	3.0	39	2.6	36	2.6
50.0 – 64.9 years	2055	22.2	551	22.7	493	23.3	386	21.5	335	22.2	290	20.8
65.0 – 79.9 years	4880	52.8	1249	53.3	1126	53.3	960	53.5	792	52.5	753	54.0
≥ 80.0 years	2046	22.1	542	22.3	449	21.2	396	22.1	344	22.8	315	22.6
BMI (kg/m^2)												
≤ 18.5	611	6.6	155	6.4	150	7.1	98	5.5	111	7.4	97	7.0
18.6 – 25.0	3490	37.8	947	39.0	834	39.4	665	37.0	532	35.2	512	36.7
25.1 – 30.0	2836	30.7	728	30.0	633	29.9	540	30.1	481	31.9	454	32.6
30.1 – 35.0	1260	13.6	326	13.4	266	12.6	255	14.2	228	15.1	185	13.3
> 35.0	514	5.6	117	4.8	122	5.8	124	6.9	76	5.0	75	5.4
Missing	528	5.7	153	6.3	109	5.2	113	6.3	82	5.4	71	5.1
Smoking status												
Current	3462	37.5	942	38.8	805	38.1	639	35.6	550	36.4	526	37.7
Former	5106	55.3	1317	54.3	1155	54.6	1028	57.3	846	56.0	760	54.5
Never	582	6.3	145	6.0	132	6.2	109	6.1	103	6.8	93	6.7
Missing	89	1.0	22	0.9	22	1.0	19	1.1	11	0.7	15	1.1
Cancer-related												
Previous malignancies[a]	939	10.2	243	10.0	219	10.4	185	10.3	147	9.7	145	10.4
Immune-related diseases												
Vasculitis[b]	57	0.6	15	0.6	17	0.8	11	0.6	10	0.7	< 6	< 0.5
Coeliac disease[b]	48	0.5	14	0.6	10	0.5	11	0.6	10	0.7	< 6	< 0.5
Crohn's disease[b]	58	0.6	19	0.8	10	0.5	12	0.7	11	0.7	6	0.4
Ulcerative colitis[b]	114	1.2	33	1.4	22	1.0	21	1.2	24	1.6	14	1.0
Grave's disease[b]	21	0.2	6	0.2	6	0.3	5	0.3	< 6	< 0.4	< 6	< 0.5
Multiple sclerosis[b]	26	0.3	9	0.4	< 6	< 0.3	< 6	< 0.4	9	0.6	< 6	< 0.5
Myasthenia gravis[b]	7	0.1	< 6	< 0.3	< 6	< 0.3	< 6	< 0.4	< 6	< 0.4	< 6	< 0.5
Ankylosing spondylitis[b]	21	0.2	< 6	< 0.3	8	0.4	< 6	< 0.4	< 6	< 0.4	< 6	< 0.5
Dermatomyositis[b]	< 6	< 0.1	< 6	< 0.3	< 6	< 0.3	< 6	< 0.4	0	0.0	< 6	< 0.5
Polymyalgia rheumatic[b]	189	2.0	44	1.8	39	1.8	39	2.2	36	2.4	31	2.2
Psoriatic arthritis[b]	36	0.4	8	0.4	7	0.3	7	0.4	6	0.4	8	0.6
Rheumatoid arthritis[b]	283	3.1	69	2.8	68	3.2	51	2.8	56	3.7	39	2.8
Psoriasis[b]	558	6.0	142	5.9	111	5.3	115	6.4	98	6.5	92	6.6
Sarcoidosis[b]	12	0.1	< 6	0.3	< 6	< 0.3	< 6	< 0.4	< 6	< 0.4	0	0.0
Systemic lupus erythematous[b]	19	0.2	< 6	0.3	< 6	< 0.3	10	0.6	< 6	< 0.4	< 6	< 0.5
Cardiovascular disease												
Heart failure[b]	460	5.0	111	4.6	95	4.5	101	5.6	71	4.7	82	5.9
Heart rhythm disturbances[bc]	77	0.8	16	0.7	16	0.8	16	0.9	15	1.0	14	1.0
Myocardial infarction[bd]	51	0.6	11	0.5	6	0.3	13	0.7	12	0.8	9	0.6
Poor controlled hypertension[d]	< 6	< 0.1	< 6	< 0.3	0	0.0	0	0.0	0	0.0	0	0.0
Unstable angina pectoris[d]	< 6	< 0.1	0	0.0	< 6	< 0.3	0	0.0	0	0.0	< 6	< 0.5
Serious infections												
Meningitis[e]	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Pneumonia[e]	118	1.3	23	0.9	23	1.1	30	1.7	22	1.5	20	1.4
Sepsis[e]	18	0.2	< 6	< 0.3	< 6	< 0.3	< 6	< 0.4	< 6	< 0.4	< 6	< 0.5
Hepatitis[f]	< 6	< 0.1	< 6	< 0.3	< 6	< 0.3	< 6	< 0.4	0	0.0	0	0.0
Psychiatric diseases												
Bipolar disorder[b]	33	0.4	7	0.3	11	0.5	7	0.4	< 6	< 0.4	6	0.4
Dementia[b]	275	3.0	59	2.4	74	3.5	46	2.6	43	2.8	53	3.8
Schizophrenia[b]	64	0.7	21	0.9	16	0.8	7	0.4	12	0.8	8	0.6
Other												
HIV/aids[b]	13	0.1	< 6	< 0.3	< 6	< 0.3	< 6	< 0.4	< 6	< 0.4	< 6	< 0.5
Organ transplant[b]	14	0.2	< 6	< 0.3	< 6	< 0.3	< 6	< 0.4	< 6	< 0.4	< 6	< 0.5
Substance abuse[g]	17	0.2	< 6	< 0.3	< 6	< 0.3	< 6	< 0.4	< 6	< 0.4	< 6	< 0.5
Pregnancy[f]	< 6	< 0.1	0	0.0	0	0.0	< 6	< 0.4	0	0.0	0	0.0
Deviant laboratory values[h]												
eGFR[d]	969	10.5	267	11.0	201	9.5	196	10.9	153	10.1	152	10.9
Alkaline phosphatase[d]	106	1.1	25	1.0	28	1.3	25	1.4	15	1.0	13	0.9
ALAT[d]	123	1.3	27	1.1	28	1.3	27	1.5	28	1.9	13	0.9
ASAT[d]	34	0.4	11	0.5	< 6	< 0.3	< 6	< 0.4	7	0.5	8	0.6
Total bilirubin[d]	116	1.3	29	1.2	21	1.0	22	1.2	25	1.7	19	1.4
Lymphocyte[d]	35	0.4	8	0.3	< 6	< 0.3	12	0.7	8	0.5	< 6	< 0.5
Neutrophils[d]	14	0.2	6	0.2	0	0.0	< 6	< 0.4	< 6	< 0.4	< 6	< 0.5
WBC[d]	< 6	< 0.1	< 6	< 0.3	< 6	< 0.3	< 6	< 0.4	< 6	< 0.4	< 6	< 0.5
Platelets[d]	26	0.3	12	0.5	6	0.3	< 6	< 0.4	< 6	< 0.4	< 6	< 0.5
Hemoglobin[d]	106	1.1	26	1.1	22	1.0	26	1.4	16	1.1	16	1.1
INR[d]	293	3.2	81	3.3	57	2.7	60	3.3	54	3.6	41	2.9
TSH[d]	341	3.7	84	3.5	75	3.5	72	4.0	54	3.6	56	4.0

(*continued on next page*)

Table 1 (*continued*)

	Total		2014		2015		2016		2017		2018	
	N = 9239		N = 2426		N = 2114		N = 1795		N = 1510		N = 1394	
	N	%	N	%	N	%	N	%	N	%	N	%
Drug use												
Systemic glucocorticoids[i]	1903	20.6	490	20.2	420	19.9	383	21.3	336	22.3	274	19.7
Other immunosuppressants												
Ciclosporin[d]	< 6	< 0.1	0	0.0	< 6	< 0.3	< 6	< 0.4	< 6	< 0.4	0	0.0
Everolimus[d]	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Sirolimus[d]	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Tacrolimus[d]	< 6	< 0.1	< 6	< 0.3	0	0.0	< 6	< 0.4	< 6	< 0.4	< 6	< 0.5
Strong CYP3A4-inhibitors												
Erythromycin[d]	131	1.4	46	1.9	43	2.0	18	1.0	13	0.9	11	0.8
Clarithromycin[d]	860	9.3	267	11.0	209	9.9	156	8.7	130	8.6	98	7.0
Itraconazole[d]	7	0.1	< 6	< 0.3	< 6	< 0.3	< 6	< 0.4	< 6	< 0.4	< 6	< 0.5
Ketoconazole[d]	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Ritonavir[d]	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Voriconazole[d]	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0

Abbreviations: N = number; % = percentage; HIV = human immunodeficiency virus; aids = acquired immune deficiency syndrome; eGFR = estimated glomerular filtration rate; ALAT = alanine transaminase; ASAT = aspartate transaminase; WBC = white blood cell count; INR = international normalized ratio; TSH = thyroid-stimulating hormone;

[a] time-window of exposure for previous or concurrent malignancies and laboratory values differed between the twelve clinical trials, as can be seen in Appendix 3 in which all specific exclusion criteria are shown per trial. The results shown in this table are corresponding with the most strict threshold, which would exclude the most patients.

[b] time-window of exposure was ever before index date.

[c] For heart rhythm disturbances three specific conditions were used: complete left bundle branch block, second degree heart block and third degree heart block.

[d] time-window of exposure was 3 months before index date.

[e] time-window of exposure was 1 month before index date.

[f] time-window of exposure was 1 year before index date.

[g] time-window of exposure was 5 years before index date.

[h] For some laboratory values specific threshold values were reported in the study protocols, and those were used to identify lung cancer patients in CPRD with deviant laboratory values. For other laboratory values reference values were used as threshold. The used threshold values were not exactly similar for all twelve studies. In this table the results are shown for the most strict threshold value, which would exclude the highest number of patients. Specific threshold values for all laboratory variables can be seen in Appendix 4.

[i] For systemic glucocorticoids included the following substances: dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone and triamcinolone.

Table 2
Proportion of lung cancer patients in CPRD GOLD eligible for enrollment in twelve randomized clinical trials of new treatments for non-small cell lung cancer and the number of unmet criteria when ineligible.

Name of trial	Eligible (%)	Number of unmet eligibility criteria (N and %)						
		Range	1	2	3	4	5	6
Osimertinib – AURA3 [10]	78.1%	1 – 4	1758 (19.0)	233 (2.5)	29 (0.3)	3 (0.0)	–	–
Osimertinib – FLAURA [16]	72.4% (61.1)	1 – 4	2166 (23.4)	340 (3.7)	42 (0.5)	5 (0.1)	–	–
Alectinib – ALEX [13]	73.7% (61.3)	1 – 4	2129 (23.0)	277 (3.0)	20 (0.2)	1 (0.0)	–	–
Alectinib – J-ALEX [9]	73.7% (61.3)	1 – 4	2129 (23.0)	277 (3.0)	20 (0.2)	1 (0.0)	–	–
Alectinib – ALUR [11]	73.6% (61.2)	1 – 4	2132 (23.1)	280 (3.0)	22 (0.2)	1 (0.0)	–	–
Nivolumab – CheckMate 017 [7]	53.9% (45.6)	1 – 5	2916 (31.6)	1059 (11.5)	229 (2.5)	44 (0.5)	10 (0.1)	–
Nivolumab – CheckMate 057 [6]	54.3% (45.9)	1 – 5	2906 (31.5)	1045 (11.3)	224 (2.4)	39 (0.4)	9 (0.1)	–
Pembrolizumab – KEYNOTE-024 [14]	49.1% (40.0)	1 – 6	3206 (34.7)	1120 (12.1)	285 (3.1)	67 (0.7)	19 (0.2)	4 (0.0)
Pembrolizumab – KEYNOTE-189 [8]	52.2% (42.5)	1 – 6	3176 (34.4)	995 (10.8)	199 (2.2)	41 (0.4)	6 (0.1)	1 (0.0)
Pembrolizumab – KEYNOTE-407 [12]	50.0% (40.7)	1 – 6	3229 (34.9)	1084 (11.7)	248 (2.7)	49 (0.5)	11 (0.1)	1 (0.0)
Durvalumab – PACIFIC [5]	53.0% (43.1)	1 – 5	3137 (34.0)	942 (10.2)	218 (2.4)	45 (0.5)	3 (0.0)	–
Atezolizumab – OAK [15]	50.7% (41.4)	1 – 6	3004 (32.5)	1142 (12.4)	327 (3.5)	63 (0.7)	16 (0.2)	2 (0.0)

Abbreviations: N = number, % = percentage.
Eligibility was based on the characteristics of lung cancer patients registered in the CPRD and compared with eligibility criteria used in clinical trials evaluating drugs used in the treatment of non-small cell lung cancer patients.

condition, these patients would probably have been ineligible for study inclusion. This could have caused an overestimation of the OS of the group of patients that would have been ineligible for RCT participation in our study. In addition, the classification of lung cancer patients in CPRD is lacking specific details. The RCTs included in our analyses solely evaluated drugs for the treatment of patients with NSCLC, whereas the Read codes used in CPRD do not differentiate between NSCLC and SCLC (Appendix 2). Furthermore, information on disease stage is not available in CPRD. A proportion of patients in our cohort, therefore, do not match with the target patient population of the RCTs, as these focus on patients with locally advanced or metastatic NSCLC. However, in the UK the majority of patients with lung cancer (85%) are diagnosed with a non-small cell subtype [41] and approximately 75% are diagnosed with stage III or IV [4]. Therefore, the majority of patients registered in CPRD match with the target population of the pivotal RCTs. We believe that more detailed information on disease type and stage would have led to a decrease in the total number of included patients in our study as we were unable to differentiate between patients diagnosed with early-stage NSCLC and advanced NSCLC. Information about type and stage would have led to the exclusion of patients with an early-stage

Table 3
Hypothetical reason for exclusion of lung cancer patients in CPRD GOLD from the twelve clinical trials evaluating new drugs to treat non-small cell lung cancer patients.

	Hypothetical reason for exclusion							
Name of trial	A	B	C	D	E	F	G	H
Osimertinib – AURA [10]	7.5%	[a]	[a]	5.6%	0.0%	[a]	10.6%	0.2%
Osimertinib – FLAURA [16]	7.5%	7.2%	[a]	5.6%	0.0%	[a]	10.6%	0.2%
Alectinib – ALEX [13]	5.7%	8.4%	[a]	[a]	0.0%	4.0%	10.6%	0.3%
Alectinib – J-ALEX [9]	5.7%	8.4%	[a]	[a]	0.0%	4.0%	10.6%	0.3%
Alectinib – ALUR [11]	5.8%	8.4%	[a]	[a]	0.0%	4.0%	10.6%	0.3%
Nivolumab – CheckMate 017 [7]	6.2%	7.2%	11.4%	[a]	1.5%	4.0%	26.7%	0.2%
Nivolumab – CheckMate 057 [6]	5.6%	7.2%	11.4%	[a]	1.5%	4.0%	26.7%	0.2%
Pembrolizumab – KEYNOTE024 [14]	18.7%	10.2%	11.4%	[a]	1.5%	4.0%	20.6%	0.5%
Pembrolizumab – KEYNOTE189 [8]	13.1%	10.2%	11.4%	[a]	1.5%	4.0%	20.6%	0.5%
Pembrolizumab – KEYNOTE407 [12]	17.2%	10.2%	11.4%	[a]	1.5%	4.0%	20.6%	0.3%
Durvalumab – PACIFIC [5]	7.5%	10.2%	11.4%	5.7%	1.5%	4.0%	20.6%	0.3%
Atezolizumab – OAK [15]	7.4%	10.2%	11.4%	6.1%	1.5%	[a]	26.7%	0.3%

Reason for exclusion summarized per set of criteria, in detail specified in Appendix B, with corresponding time-window of exposure for each criterion individually.
A = Laboratory values
B = Cancer-related
C = Immune related diseases
D = Cardiovascular diseases
E= Serious infections
F = Psychiatric diseases
G = Concomitant drug-use
H = Other
[a] The corresponding set of criteria was not part of the exclusion criteria used for this specific study. Therefore, no lung cancer patients in CPRD would hypothetically be excluded because of this set of criteria.

Table 4
Hazard ratios for mortality of lung cancer patients in CPRD GOLD hypothetically eligible for study inclusion in twelve randomized clinical trials of new treatments for non-small cell lung cancer compared to hypothetically ineligible lung cancer patients in CPRD GOLD.

Trial	HR, unadjusted	95% CI	HR, age-sex adjusted	95% CI
Osimertinib – AURA3 [10]	0.75	0.71 – 0.80	0.79	0.74 – 0.84
Osimertinib – FLAURA [16]	0.83	0.78 – 0.87	0.85	0.81 – 0.90
Alectinib – ALEX [13]	0.83	0.79 – 0.88	0.84	0.80 – 0.89
Alectinib – J-ALEX [9]	0.83	0.79 – 0.88	0.84	0.80 – 0.89
Alectinib – ALUR [11]	0.83	0.79 – 0.88	0.84	0.79 – 0.89
Nivolumab – CheckMate 017 [7]	0.75	0.71 – 0.79	0.74	0.71 – 0.78
Nivolumab – CheckMate 057 [6]	0.75	0.71 – 0.78	0.74	0.71 – 0.78
Pembrolizumab – KEYNOTE-024 [14]	0.76	0.72 – 0.80	0.79	0.75 – 0.83
Pembrolizumab – KEYNOTE-189 [8]	0.76	0.72 – 0.80	0.78	0.74 – 0.82
Pembrolizumab – KEYNOTE-407 [12]	0.76	0.73 – 0.81	0.79	0.75 – 0.84
Durvalumab – PACIFIC [5]	0.77	0.73 – 0.81	0.79	0.75 – 0.84
Atezolizumab – OAK [15]	0.80	0.76 – 0.84	0.80	0.76 – 0.85

Abbreviations: HR = hazard ratio, CI = confidence interval.
HRs are calculated by comparing the mortality of eligible patients to the mortality of ineligible patients.

NSCLC. The inclusion of all patients with lung cancer could therefore have led to an overestimation of the proportion of patients that would have been eligible.

Another limitation of this study was possible misclassification of several in- and exclusion criteria. This could occur when a comorbidity or a laboratory value is not correctly registered or has changed over time without being properly updated. Only patients with a known registration of a comorbidity, deviant laboratory value or concomitant drug-use could be excluded. If no registration was available in CPRD it was assumed that the patient met the specific criteria. The effect of missing, or not-registered, data is unknown. However, this could only have led to a higher proportion of patients being excluded, as all patients without information about a specific criterion were assumed to meet that specific criterion. Furthermore, clinical lab test values are not routinely collected in CPRD, whereas in RCTs, these are measured at baseline or during a screening period. In CPRD we selected a 3-month time-window of exposure to capture non-routinely collected lab-test values. If clinical lab test results that were not requested by the general practitioner but by consultants are being captured in CPRD is uncertain. Our choice for a 3-month time-window was a trade-off between dealing with missing data and the assumption that the most recently recorded lab test value in the past 3 months would reflect baseline.

In all RCTs evaluating ICIs, patients were excluded when treated with $\geq$ 10 mg prednisone or an equivalent dose of another systemic glucocorticoid. We were not able to specify the prescribed daily dose of systemic glucocorticoids because this was only registered in 45% of all cases. Therefore, it was decided to exclude all patients with a glucocorticoid prescription within 3 months prior to the lung cancer diagnosis. As some patients will not have exceeded the threshold value of the equivalent glucocorticoid dosage, this approach may have led to erroneous exclusion of some patients. In addition, the prevalence of a COPD registration before the index date (lung cancer diagnosis) is almost 30% in this cohort, compared to 2% in the whole UK population. During a COPD exacerbation high dose glucocorticoids can be prescribed for a short period of time. The high number of COPD-patients in our cohort might explain the observed relatively high proportion of patients with a prescription for systemic glucocorticoid treatment. Furthermore, the situation in clinical practice is often more flexible than the data in a large database reflect. For instance, if a patient receives a systemic glucocorticoid or an antibiotic, which would be the only reason for exclusion, a physician could try to taper or stop the treatment with glucocorticoids, or select another antibiotic, which would make the patient eligible for clinical trial inclusion. This could have led to an underestimation of the eligibility rate of patients with lung cancer in the general population.

Although the limitations of various assumptions in our CPRD study may have led to uncertainties in the exact proportion of patients that would have been eligible, we believe that the analyses still give an insightful view on potential trial eligibility of patients with lung cancer in the general population. This study shows that a considerable proportion of patients in a real-world setting would have been ineligible for inclusion in RCTs evaluating TKIs or ICIs, and that OS was shorter for patients that would potentially have been ineligible for RCT participation compared with those that would have been eligible. Additional information about other criteria, such as PS, would lead to a higher degree of exclusion, while more specific information on drug-use, especially systemic glucocorticoids, would lead to the exclusion of a lower proportion of patients. Given the previously described efficacy-effectiveness gap for chemotherapy used in patients with stage IV NSCLC, further research is needed to determine the actual effectiveness of the evaluated TKIs and ICIs [27], as a large part of the patients in clinical practice is not well represented by the patients in pivotal phase III RCTs.

5. Conclusion

This study showed that a considerable proportion of patients, diagnosed with lung cancer between 2014 and 2018 in a real-world setting, would have been ineligible for inclusion in phase III RCTs evaluating TKIs or ICIs for the treatment of stage III/IV NSCLC patients. OS of patients who would have been ineligible for inclusion in these RCTs was considerably shorter compared with patients that would have been eligible.

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Contributors

AV and FV initiated the study and were responsible for the study concept and design. AV did the literature review and wrote the first draft of the paper. AV and PS analysed the data and was in a later stage QA-ed by JD. AV, PS and FV had full access to all of the data in the study. All authors participated in the interpretation of the data and critically revised the paper for intellectual content. All authors approved the final version to be published. AV and PS take responsibility for the integrity of the data and accuracy of the data analyses. FV is accountable for all aspects of the work.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.canep.2022.102149.

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