Update on recent key publications in lung oncology: picking up speed

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Shareable abstract (@ERSpublications)
In the past two decades, an increasing number of new drugs received EMA approval. The reason for this is an increasingly better understanding of lung cancer, and decreasing mandatory intervals before approval between early and late trials. https://bit.ly/3g1jfpq

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Abstract

Introduction As incidence rates for lung cancer are still very high and lung cancer remains the most deadly cancer since the turn of the millennium, efforts have been made to find new approaches in cancer research. This systematic review highlights how therapeutic options were extended and how the development of new drugs has picked up speed during the last 20 years.

Methods A systematic search was performed in PubMed, Cochrane Library and the European Union Trial Register and 443 records were identified. Our inclusion criteria constituted completed phase I, II and III studies investigating drugs approved by the European Medicines Agency (EMA). Overall, 127 articles were analysed.

Results During the 5 year interval from 2015 to 2020, significantly more drugs were approved after phase III, and occasionally after phase II, trials than between 2000 and 2005 (p=0.002). Furthermore, there was a significant time difference (p=0.00001) indicating an increasingly briefer time interval between the publication of phase I and phase III results in the last few years.

Discussion Due to novel therapeutic approaches, numerous new drugs in lung oncology were approved. This has improved symptoms and prognoses in patients with advanced lung cancer. However, faster approval could make it difficult to scrutinise new options regarding safety and efficacy with sufficient diligence.

Introduction

The incidence of all cancer types in Europe continues to increase from 2.1 million cases in 1995 to 3.1 million cases in 2018. This corresponds to an increment rate of around 50% in one generation. In the European Union (EU) more than 312 000 people were diagnosed with lung cancer in 2018. Lung cancer causes approximately 20% of all cancer deaths in the EU [1–3]. In 2018, lung cancer accounted for 15% of all newly diagnosed malignancies in men. Lung cancer remains the most fatal cancer among men [4, 5]. Following a rise in cigarette smoking among women, lung cancer incidence increased from 10% in the late 1990s to 14% in 2018. Thus, nowadays lung cancer is the second most common fatal cancer type among women after breast cancer [6, 7].

In the last two decades, there has been significant progress in the treatment of lung cancer due to substantial breakthroughs in the understanding of molecular pathology and cancer immunology [8, 9]. At the turn of the millennium, platinum-based chemotherapy was the gold standard in lung cancer treatment.

Starting with the IPASS trial, compounds targeting the endothelial growth factor receptor (EGFR) (gefitinib and erlotinib) and other molecules targeting driver mutations have been developed. Fluorescence *in situ* hybridisation or immune histochemistry and, recently, the possibility of RNA-next generation sequencing (NGS) have made it possible to detect larger gene rearrangements, as in the ALK and ROS1 genes [10]. If a targetable mutation can be detected in an individual lung cancer patient, therapy can be initiated with an oral tyrosine kinase inhibitor (TKI) that precisely addresses this mutation. Crizotinib was the first approved TKI to be used for first-line therapy for advanced ROS1 and ALK-positive nonsmall cell lung cancer (NSCLC) [11].

Checkpoint inhibition (CPI) has been successfully introduced into lung cancer treatment since 2015. CPI started with second-line therapy for metastatic NSCLC but rapidly broadened its scope to first-line therapy for NSCLC, combination strategies, extensive stage small cell lung cancer (SCLC) and the earlier stages of NSCLC.

All of these new therapeutic approaches resulted in significant improvements in survival [8]. This review addresses the essential key publications that have led to the approval of new drugs for the treatment of lung cancer. We address the time trends of new developments in lung cancer and the duration from first clinical evidence to approval.

Methods

Using the electronic databases the Cochrane Library, MEDLINE (*via* PubMed) and the European Union Clinical Trial Register, a systematic search was performed from inception to 1 June 2020. In addition, a desktop search was implemented, and the reference lists of published full-text articles and systematic reviews were manually scanned for pertinent studies. Based on our clinical trial publications, we also searched for additional literature on the approved drugs like updates, health-related quality of life (HRQoL) research in clinical trials and biomarker analyses.

The search terms were: “lung cancer” (OR “canceration” OR “cancerized” OR “cancerous” OR “neoplasms” OR “non-small cell lung” OR “non-small cell lung cancer” OR “non-small-cell carcinoma” OR “small cell lung cancer”) AND “metastatic” OR advanced” AND “clinical trial phase I” OR “phase II” OR “phase III” AND “approval” (OR “approved” OR “approving” AND “clinical trial” OR “clinical trials as topic”). These terms were combined to search through titles, abstracts and keywords. After selecting articles, we merged the results from the three databases and eliminated duplicates. The time range for our research was defined as 1 January 2000 to 1 May 2020. The database searches were limited to English language publications, independent of country of origin.

The list of publications was independently reviewed by two authors (A. Schiwitza, L. Sahovic) using the following inclusion criteria: a clinical trial in phase I, II or III; EMA approved drugs between 1 January 2000 and 1 May 2020; the inclusion of details on the study population characteristics, interventions and results. The Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) flowchart of the article selection process is depicted in figure 1. Any discrepancies were resolved by a third reviewer (A. Rittmeyer). Information on studies was assembled in a table and checked independently by A. Rittmeyer.

Pearson’s chi-square test was performed to detect whether there was a statistically significant difference regarding the number of approvals in different 5-year periods within the substance groups.

We defined as key publications those publications that led to drug approvals and distinguished speed and pace. We defined speed as the number of publications per time. Pace was defined as time from first clinical results, *i.e.* phase I results to publication of the key phase III publication leading to approval. We calculated pace, Δt, between the publication of phase I and phase III results for each compound approved. With the statsmodel library we performed a linear regression on the data.

To identify if the sample size of the studies follows a linear trend in time, we performed a linear regression to infer the parameters and the diagnostics. Figure 2 shows sample size plotted against time and the estimated regression line. We used Python 3.7.3, NumPy 1.17.3 and statsmodel 0.10.2 for our computations of the fits.

For conduct and reporting of this systematic review, we followed the PRISMA statement [12]. The completed PRISMA-p checklist is available in Supplementary tables S1a and S1b.

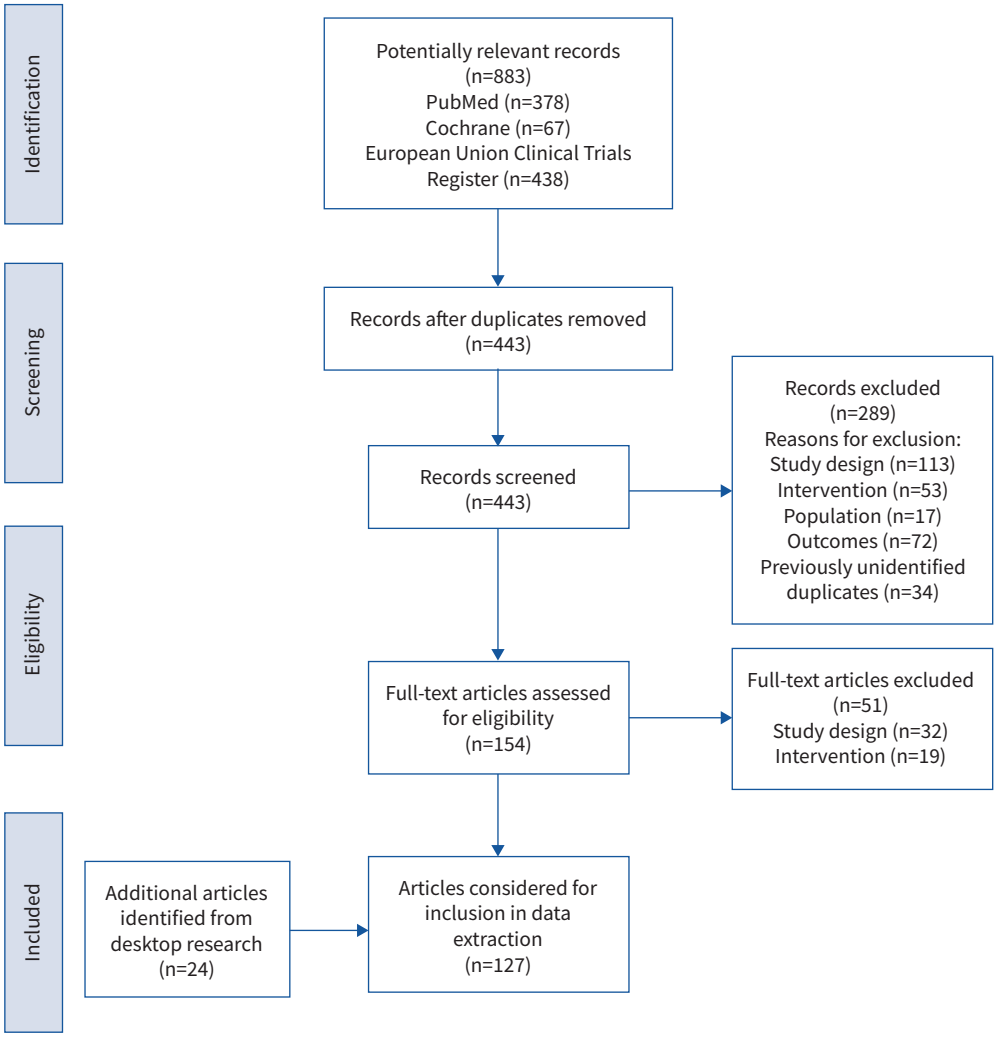

FIGURE 1 PRISMA flow diagram.

Results

Initially, 883 potentially relevant records were identified. After the duplicates were deleted and the existing articles were checked for importance, 443 relevant publications remained. These were checked for eligibility, and 103 articles met our inclusion criteria. A desktop search, including the reviews of the bibliographic reference lists of related literature review articles, yielded 24 additional publications. Thus, we identified 127 unique records for our systematic review (figure 1).

If phase III trials were published after 1 January 2000 but their connected phase I trials had been published prior to this date, the phase I publications were still included in this review.

In the last 20 years, 27 individual active compounds and 10 combination therapies for advanced lung cancer have been approved by EMA (tables 1 and 2).

Between 2000 and 2005, three drugs had been approved, including two cytotoxic drugs, docetaxel and pemetrexed, and one of the first targeted drugs, namely erlotinib, a selective inhibitor of the epidermal growth factor (EGF) tyrosine kinase domain receptor. The latter was approved for NSCLC in Europe in 2005, but at that time without restrictions, for example, companion diagnostics to detect EGFR mutations (figure 2).

In the following 5 years, three targeted agents were approved. Between 2011 and 2015 the number of approved targeted drugs increased from three to five approvals. Furthermore, nivolumab was the first

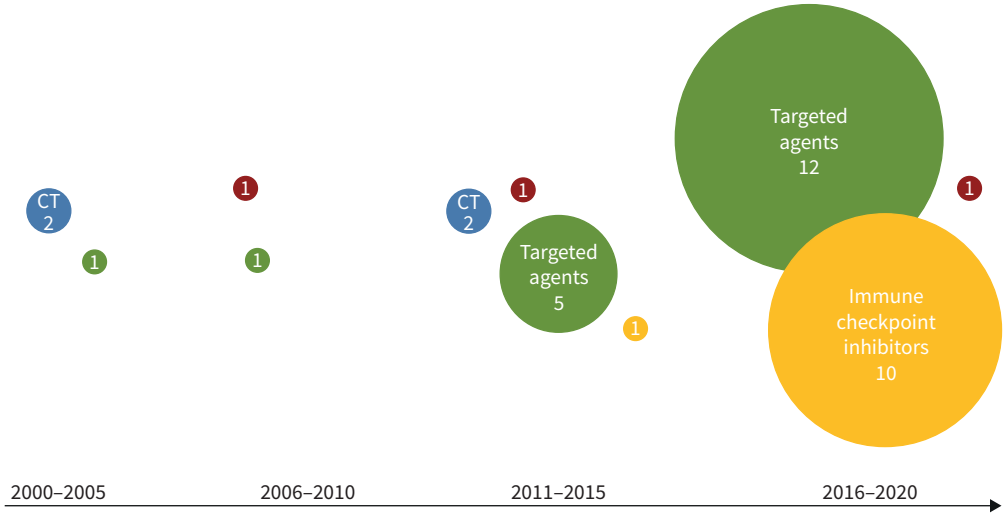

FIGURE 2 Numbers representing European Medicines Agency approved drugs within their substance class in lung oncology. Blue: chemotherapy (CT); green: targeted agents (tyrosine kinase inhibitors); red: VEGF-inhibitors; yellow: immune checkpoint inhibitors. VEGF: vascular endothelial growth factor.

checkpoint inhibitor to be approved. In the most recent 5 years, 23 new drugs for lung cancer were approved, including several drug combinations. Among them, primarily combinations of checkpoint inhibitors with standard chemotherapy according to lung cancer guidelines were approved. In addition, no new cytostatic therapy has received approval in the past 5 years. During the 5 year interval from 2015–2020, significantly more drugs were approved than in any other 5 year interval before (p=0.002) (Supplementary table S1c).

Figure 2 shows the development of approvals over the last two decades in 5 years intervals.

Most drugs were approved following large phase III trials. However, EMA has also approved several drugs following phase II trials (table 1), typically using median overall survival (MOS) and progression free survival (PFS) as primary end-points, with a few trials using objective response rate (ORR).

When looking at sample size and time of publication only for TKIs, decreasing sample sizes over time were detected (p=0.0116) (figure 3). If we excluded the two first publications on TKIs from the analysis, the sample sizes for TKI trials did not change over time. Neither combinations nor other single drugs showed a change in sample size throughout the last 20 years.

The intervals between publications of phase I data and phase III trials has declined over time (p=0.00001) (figure 2). For the three drugs, pemetrexed, docetaxel and erlotinib, that were approved between 2000 and 2006, the average time between phase I and phase III amounted to 69.3 months. In summary, for the first five drugs approved for lung cancer after the millennium, the average time between phase I and phase III amounted to 73.6 months. In comparison, the release of phase III after phase I of the latest three drugs took 23.7 months, and for the last five approved drugs, 18.8 months (figure 4).

This change can also be observed with drug combinations. Phase III pemetrexed/cisplatin results were published 105 months after phase I. For atezolizumab/nabpaclitaxel/carboplatin, results were published 10 months after phase I (table 1).

Another approach to shorten the period of time from phase I trials to phase III trials is to include phase I as a run-in phase into a phase III trial, as was done for the drug combination atezolizumab/carboplatin/etoposide in SCLC.

On occasions, phase I results were published after phase III trials, as for the drug combinations pembrolizumab/pemetrexed/platinum, atezolizumab/paclitaxel/carboplatin/bevacizumab, atezolizumab/carboplatin/etoposide and pembrolizumab/(nab)paclitaxel/carboplatin.

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TABLE 1 Approved drugs in lung oncology, 2000–2020

Chemical name	Line of therapy	Phase I trial (first author [ref.])	Trial leading to approval (first author [ref.])	Sample size	EMA approval date	Approval trial phase	Histology	Class	Monoclonal antibody	Route of administration	Primary end-point trial leading to approval
Docetaxel	Second	Extra [13]	Shepherd [14]	n=103	6 February 2000	III	NSCLC	Chemotherapy	No	*i.v.*	MOS
Pemetrexed	Second	McDonald [15]	Hanna [16]	n=571	22 September 2004	III	nsNSCLC[#]	Chemotherapy	No	*i.v.*	MOS
Erlotinib	Second	Hidalgo [17]	Shepherd [18]	n=731	27 June 2005	III	NSCLC	Targeted agent[¶]	No	Oral	MOS
Gefitinib	Any	Baselga [19]	Mok [20]	n=1217	1 July 2009	III	nsNSCLC	Targeted agent	No	Oral	PFS
Erlotinib	First	Hidalgo [17]	Rosell [21]	n=174	1 November 2011	III	nsNSCLC	Targeted agent	No	Oral	PFS
Crizotinib	Second	Kwak [22]	Shaw [11]	n=347	24 October 2012	III	ROS1/ALK +NSCLC[+]	Targeted agent	No	Oral	PFS
Afatinib	First	Yap [23]	Sequist [24]	n=345	25 September 2013	III	EGFR +nsNSCLC	Targeted agent	No	Oral	PFS
Ceritinib	Second	Shaw [25]	Shaw [26]	n=231	8 May 2015	III	ALK+NSCLC	Targeted agent	No	Oral	PFS
Nivolumab	Second	Brahmer [27]	Brahmer [28]	n=272	20 July 2015	III	SqNSCLC	Immune checkpoint	Yes	*i.v.*	MOS
Crizotinib	First	Kwak [22]	Solomon [29]	n=343	24 November 2015	III	ROS1/ALK +NSCLC[+]	Targeted agent	No	Oral	PFS
Osimertinib	Second	Cross [30]	Mok [31]	n=419	3 February 2016	III	EGFR M +NSCLC	Targeted agent	No	Oral	PFS
Nivolumab	Second	Brahmer [27]	Borghaei [32]	n=582	6 April 2016	III	nsNSCLC	Immune checkpoint	Yes	*i.v.*	MOS
Afatinib	Second	Yap [23]	Thongprasert [33]	n=60	7 April 2016	III	EGFR +NSCLC	Targeted agent	No	Oral	ORR
Pembrolizumab	Second	Garon [34]	Herbst [35]	n=1034	2 August 2016	III	PD-L1 >1% +NSCLC	Immune checkpoint	Yes	*i.v.*	MOS PFS[§]
Pembrolizumab	First	Garon [34]	Reck [36]	n=305	31 January 2017	III	PD-L1 >50% NSCLC	Immune checkpoint	Yes	*i.v.*	PFS
Alectinib	Second	Seto [37]	Shaw [38]	n=87	21 February 2017	II	ALK+NSCLC	Targeted agent	No	Oral	ORR
Dabrafenib/ trametinib	Any	Falchook [39]	Planchard [40]	n=36	3 April 2017	II	BRAf V600E +NSCLC	Targeted agent	No	Oral	ORR
Atezolizumab	Second	Herbst [41]	Rittmeyer [42]	n=1125	22 September 2017	III	NSCLC	Immune checkpoint	Yes	*i.v.*	MOS[f]
Alectinib	First	Seto [37]	Peters [43]	n=303	21 December 2017	III	ALK+NSCLC	Targeted agent	No	Oral	PFS
Osimertinib	First	Cross [30]	Soria [44]	n=556	8 June 2018	III	EGFR M +NSCLC	Targeted agent	No	Oral	PFS
Durvalumab	Consolidation	Antonia [45]	Antonia [46]	n=709	27 July 2018	III	NSCLC	Immune checkpoint	Yes	*i.v.*	MOS PFS[§]

Continued

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TABLE 1 Continued

Chemical name	Line of therapy	Phase I trial (first author [ref.])	Trial leading to approval (first author [ref.])	Sample size	EMA approval date	Approval trial phase	Histology	Class	Monoclonal antibody	Route of administration	Primary end-point trial leading to approval
Brigatinib	Second	Gettinger [47]	Camidge [48]	n=275	27 November 2018	III	ALK+ NSCLC	Targeted agent	No	Oral	PFS
Dacomitinib	First	Takahashi [49]	Wu [50]	n=452	3 April 2019	III	EGFR M +NSCLC	Targeted agent	No	Oral	PFS
Lorlatinib	Second	Shaw [51]	Solomon [52]	n=276	7 May 2019	II	ALK+NSCLC	Targeted agent	No	Oral	ORR[f]
Larotrectinib	Any	Drilon [53]	Drilon [53]	n=55	23 September 2019	II	NTRK +NSCLC	Targeted agent	No	Oral	ORR
Brigatinib	First	Gettinger [47]	Hubert [54]	n=222	6 April 2020	III	ALK+ NSCLC	Targeted agent	No	Oral	ORR

[#]: first approval was granted for any NSCLC but after subgroup analyses of three trials employing pemetrexed the approval was restricted to nsNSCLC for lack of efficiency in squamous NSCLC [62]. [¶]: although later approved as a targeted agent, the drug was first approved for any NSCLC without any mandatory companion diagnostic to detect a targetable mutation.[+]: Pfizer [55]. [§]: for details please refer to full publication as alpha was split applying different statistical plans. [f]: and intracranial tumour response. EMA: European Medicines Agency; NSCLC: nonsmall cell lung cancer; MOS: median overall survival; nsNSCLC: nonsquamous nonsmall cell lung cancer; PFS: progression free survival; ALK: anaplastic lymphoma kinase; EGFR: epidermal growth factor receptor; SqNSCLC: squamous nonsmall cell lung cancer; EGFR M+NSCLC: EGFR mutation positive NSCLC; ORR: objective response rate according to RECIST 1.1

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TABLE 2 Approved drug combinations in lung oncology, 2000–2020

Chemical name	Line of therapy	Phase I	Trial leading to approval	Sample size	EMA approval date	Approval trial phase	Histology	Class	Monoclonal antibody	Route of administration	Primary end-point trial leading to approval
Bevacizumab/paclitaxel/carboplatin	First	Willett (Phase I) [56]; Johnson (Phase II) [57]	Sandler [58]	n=878	23 August 2007	III	nsNSCLC	Targeted agent	Yes	*i.v.*	MOS
Pemetrexed/cisplatin	First	Thödtmann [59]	Scagliotti [60]	n=1725	28 October 2011	III	nsNSCLC	CT/CT	No	*i.v.*	MOS
Nintedanib/docetaxel	Second	Mross [61]	Reck [62]	n=1324	27 November 2014	III	nsNSCLC	Targeted agent	No	Oral	PFS
nabPaclitaxel/carboplatin	First	Rizvi [63]	Socinski [64]	n=1052	2 March 2015	III	SqNSCLC	Chemotherapy	No	*i.v.*	ORR
Docetaxel/ramucirumab	Second	Spratlin [65]	Garon [66]	n=1825	28 January 2016	III	nsNSCLC	Targeted agent	Yes	*i.v.*	MOS
Gemcitabine/cisplatin/necitumumab	First	Kuenen [67]	Thatcher [68]	n=1093	24 February 2016	III	SqNSCLC	Targeted agent	Yes	*i.v.*	MOS
Pembrolizumab/(nab) Paclitaxel/carboplatin	First	Gadgeel [69]	Paz-Ares [70]	n=559	14 March 2019	III	SqNSCLC	ICP/CT/CT	Yes	*i.v.*	MOS PFS
Pembrolizumab/pemetrexed/platin	First	Gadgeel [69]	Gandhi [71]	n=616	15 March 2019	III	nsNSCLC	ICP/CT/CT	Yes	*i.v.*	MOS PFS
Atezolizumab/carboplatin/etoposide	First	Horn [72]	Horn [72]	n=403	6 September 2019	III	SCLC	ICP/CT/CT	Yes	*i.v.*	MOS PFS
Atezolizumab/nab-Paclitaxel/carboplatin	First	Liu [73]	West [74]	n=723	6 September 2019	III	nsNSCLC	ICP/CT/CT	Yes	*i.v.*	MOS PFS
Atezolizumab/paclitaxel/carboplatin/bevacizumab	First	Liu [73]	Socinski [75]	n=692	6 September 2019	III	nsNSCLC	ICP/CT/CT/TA	Yes	*i.v.*	MOS PFS

EMA: European Medicines Agency; nsNSCLC: nonsquamous nonsmall cell lung cancer; MOS: median overall survival; CT: chemotherapy; PFS: progression free survival; SqNSCLC: squamous nonsmall cell lung cancer; ORR: objective response rate; ICP: immune checkpoint; SCLC: small cell lung cancer; TA: targeted agent

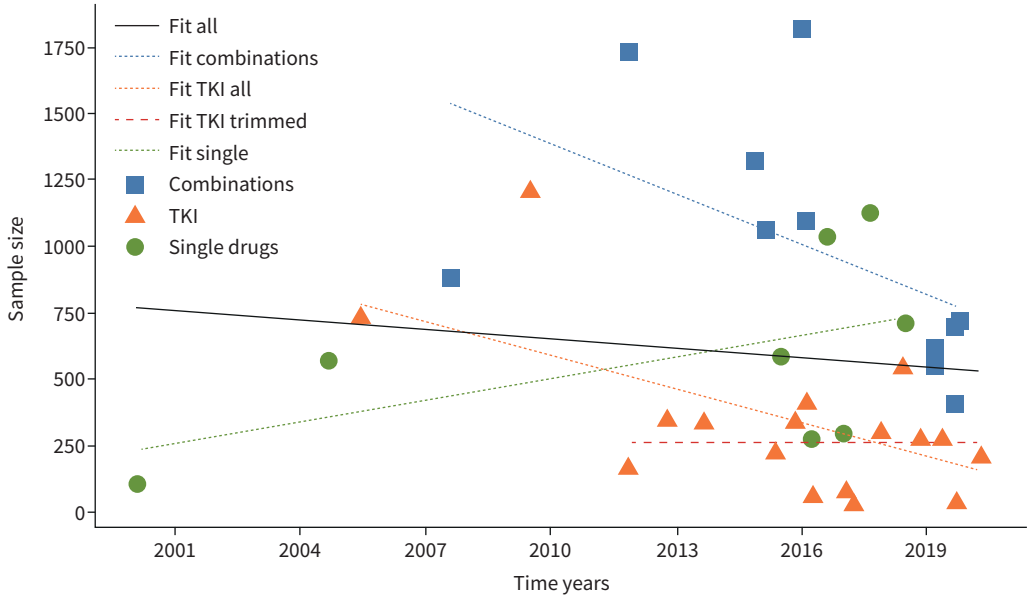

FIGURE 3 Correlation of sample size and date of publication regarding approved combinations (blue line and squares), TKIs (orange line and triangles) and single drugs except TKIs (green line and dots). The black line shows the correlation of sample size and date for all approved drugs and combinations. TKI trimmed (red line): shows data without the two first trials for erlotinib and gefitinib [18, 20]. TKI: tyrosine kinase inhibitor.

Discussion

This review demonstrates that key publications in lung cancer have gained speed and pace throughout the last 20 years.

With the advancement of cancer medicine, drug focus has changed, from classical chemotherapy "poisoning" cancer cells but also noncancer cells, to a more targeted approach.

As a first step in this direction, drugs targeting the vascular endothelial growth factor (VEGF)-pathway were developed leading to the approval of three drugs over more than 10 years [32, 53, 66]. However, the

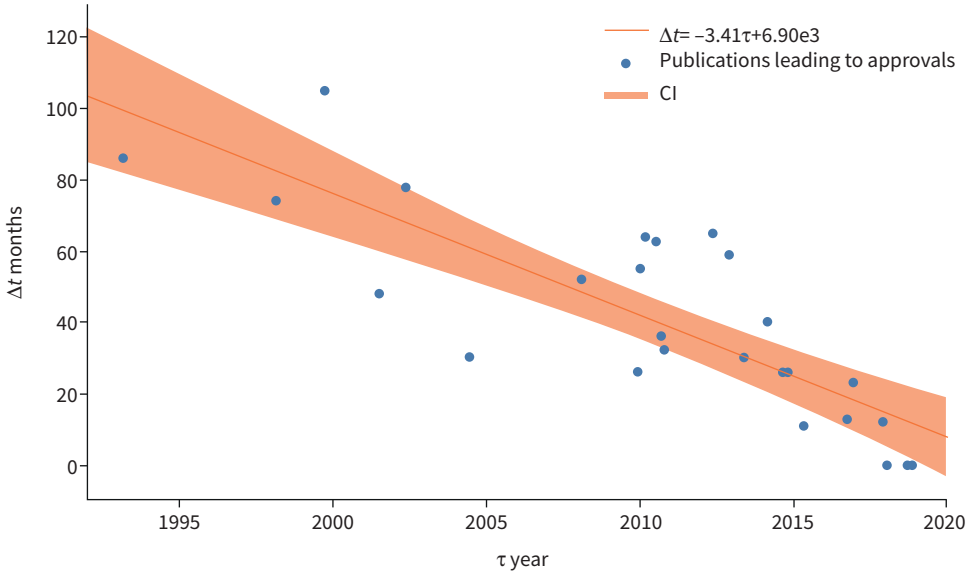

FIGURE 4 Time intervals between the publications of linked phase I and phase III trials. Correlation coefficient r= –0.82303; p=0.00001. Estimated rate over time shown along with a 95% credible region.

clinical effect of VEGF-compounds remained rather small and many drugs failed to show any significant improvement [76–78]. Another problem of targeting the VEGF-pathway is that the search for biomarkers helping to tailor VEGF-directed therapy has still not led to any predictive tool.

The importance of predictive tools can be highlighted by the "EGFR story". To target the EGFR seemed reasonable in the beginning of the century, leading to compounds such as erlotinib and gefitinib as TKIs targeting the intracellular EGFR tyrosine kinase. To target the extracellular part of the EGFR, antibodies, such as cetuximab, were developed. However, apart from the use of erlotinib in second-line therapy, none of those drugs showed any significant improvements [79–82]. This only changed when the importance of activating EGFR mutations was detected [83], leading to the pivotal IPASS trial [20, 84]. After having learned the EGFR lesson, the speed of approvals for targeted drugs increased. In this respect, the detection of anaplastic lymphoma kinase (ALK) rearrangements as a driver mutation inducing lung cancer is also interesting. Crizotinib had originally been developed to target the MET-receptor and the efficacy in patients with ALK-rearrangements was detected rather incidentally [11]. Nevertheless, after all these lessons had been learned, researchers had been able to address every single driver mutation more specifically by designing compounds that match a specific target [85].

However, performing clinical trials in this setting is often challenging as the low frequency of single mutations makes it difficult to recruit sufficient numbers of patients. It is, however, questionable if a classical randomised phase III design is appropriate to prove efficacy. In particular, it seems ambiguous from an ethical point of view to create a randomised clinical trial protocol for the very first compound for a given newly detected mutation without a mandatory crossover for those patients randomised to what is considered standard of care (most often standard chemotherapy). These factors have led to rather small trials and to approvals on the basis of phase I/II trials, as was the case for larotrectinib which was designed for NTRK fusion mutations that occur in no more than 0.1% of patients with NSCLC [53, 86].

Although the number of driver mutations is increasing every year, the number of patients who benefit from these innovations stays rather low at about 10% of patients with nonsquamous NSCLC. Thus the impact of the introduction of checkpoint inhibitors was much more profound as, in rapid succession, all patients with NSCLC (including squamous cell lung cancer) could be treated with cancer immunotherapy. Today, any patient with stage IV lung cancer, regardless of histology and PD-L1 expression (even including patients with SCLC), can be treated with a checkpoint inhibitor as a first-line therapy. The number of publications in the field of lung cancer immunotherapy and checkpoint inhibitions has skyrocketed in the last few years, leading in 2015 to the first approval for nivolumab as a monotherapy in second-line lung cancer treatment and expanding ever since. In this setting, the classical randomised phase III design leading to approval seems appropriate as the number of patients that could be enrolled into a trial is rather high.

Looking for alternative explanations to the increasing speed of lung cancer key publications we could show that the time from phase I to phase III trials has been reduced significantly ("pace"). In this context it seems striking that some phase I trials have been published after the phase III results [44, 70–72, 75]. This highlights what the market, represented by the high impact scientific journals, considers worth publishing and when the first phase I trial of nivolumab was published in the *Journal of Clinical Oncology* in 2010 [27], none of the following phase I experiences could ever get close.

Another explanation that we found not to be relevant for picking up speed was the suggestion that the sample size of trials leading to approval has been reduced over time. We could show a trend of decreasing sample size for TKI trials. However, this was mainly because the oldest two trials, investigating erlotinib without biomarkers and gefitinib in the IPASS trial, proved the importance of predictive tests in the newly discovered world of lung cancer driver mutations for the first time ever. For the more recent TKI trials, and for all other drugs or combinations, no correlations regarding sample size and date of publication could be detected.

It is our conviction that the increasing speed of key lung cancer publications leading to approvals reflects the pace of science that has improved the landscape of lung cancer, especially in terms of patient survival [8]. In 2000, before the approval of docetaxel, the MOS of lung cancer (NSCLC) patients that were deemed fit to be treated with cisplatin was about 8 months [87]. Today, this MOS has doubled in patients without driver mutations and without high PD-L1 expression. In subgroups that can include up to one-third of all patients, such as a tumour proportion score (TPS) >50%, MOS has increased to more than 2 years. What seems even more important for individual patients is the fact that about 15% of unselected patients

survive more than 5 years, which would have been close to impossible in 2000 [86], and in the PD-L1-high subgroup this is possibly even higher. Survival improval is even more pronounced in patients with driver mutations showing a MOS ranging from 27 [88] to 51 months [89].

The achievements in lung cancer therapy throughout the last 20 years have been extraordinary and we fully appreciate the arrival of so many new treatment options. However, in line with others we think that there are some caveats that have to be considered [90].

For example, the approval of larotrectinib was based on just 55 patients, including only four patients with lung cancer. It is certainly helpful to have another option for those very few patients harbouring this rearrangement; however, do we really know that larotrectinib is the best choice in first-line treatment? How low can the number of patients included be to convince us that a drug is the best choice in other driver mutations? Is the combination of dabrafenib/trametinib, approved based on two single-arm phase II trials including 57 and 36 patients [40, 90], favourable compared with a combination of a CPI and chemotherapy or CPI alone in patients with a high TPS? Only recently, some researchers have started publishing results of patients harbouring driver mutations treated with checkpoint inhibitors revealing that in some patients with KRAS, MET and BRAF mutations, CPIs tend to have an effect close to the effects seen in patients without any mutation whereas in patients with classical nonsmoker mutations CPIs tend to have little effect [91, 92]. What can be accepted as a proof of superior efficacy regarding newly tested drugs, such as, for example, the compound targeting G12C-KRAS-mutations?

Is full-dose chemotherapy combined with CPI really the best choice in first-line treatment of metastatic NSCLC given the fact that phase I experiences with pembrolizumab include 74 patients and with atezolizumab 76 patients? In both phase I trials, patients were treated in three arms with different chemotherapies at full dose, leaving only 25 patients for each arm and lower doses of chemotherapy which have never been tested.

We should be careful to jump to conclusions too early as we have seen very convincing phase II results in the past, for example for Onartuzumab, with very disappointing phase III results [91, 93–95].

End-points for clinical trials intended to file for approval should be very carefully selected and preferably discussed with the authorities in advance. These primary end-points should reflect the supposed benefit of the new drug as well as possible. When choices were few MOS has always been the end-point of choice. However, particularly in driver mutated lung cancer, in which several lines of extremely efficacious drugs can be applied sequentially, PFS may often be an adequate choice. ORR, even by blinded independent central review, seems challenging in our opinion and should rather not be used for approval.

We listed the primary end-points of the trials leading to approval in table 1. However, we did not go into detail about the secondary end-points of these trials as a wide variety of secondary end-points had been employed. Additionally, secondary end-points can only lead to new hypotheses as the alpha power of each trial is restricted to the primary end-points.

One limitation of our study is that we have arbitrarily chosen four 5-year periods for the analyses of time trends. Furthermore, the included publications were not scored according to the risk of bias within the study as suggested by PRISMA (Supplementary table 1). However, we feel that reporting bias would have no impact on our findings as we do not address effectiveness of therapy. Another limitation is that we focused on positive results leading to approval only. Negative results could also be considered as key publications. However, as many negative results have not been published in peer reviewed journals at all, it seemed favourable to us to concentrate on positive trials as they have truly changed clinical practice.

Finally, it seems important to mention that progress for the treatment of lung cancer has not been restricted to drugs, and advances have also been made in diagnostics and multimodal therapeutic approaches, which we consider to be very important and evolving topics; although ones that would have gone beyond the scope of this review and which should be addressed separately.

In conclusion, we have witnessed two decades of remarkable advances regarding therapy of metastatic (and locally advanced) lung cancer with increasing speed and pace. However we should be aware that new questions arise that should be carefully considered when new drugs are approved. Many details need to be considered in the process of any new pharmacological trial. Foremost, it is essential to continuously ensure the best possible safety in clinical trials, even in an expeditious growing market.

Provenance: Commissioned article, peer reviewed.

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