ORIGINAL ARTICLE
LUNG CANCER

New drugs in thoracic oncology: needs and knowledge – an online ERS Lung Cancer Assembly survey

Thierry Berghmans[1], Matthew Evison[2], Torsten Gerriet Blum[3], Nir Peled[4] and Jacques Cadranel[5]

Affiliations: [1]Dept of Intensive Care, and Oncological Emergencies and Thoracic Oncology, Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium. [2]Manchester Thoracic Oncology Centre, Manchester University NHS Foundation Trust, Wythenshawe Hospital, Manchester, UK. [3]Lungenklinik Heckeshorn, Helios Klinikum Emil von Behring, Berlin, Germany. [4]Soroka Cancer Center, Ben-Gurion University, Beer Sheva, Israel. [5]Chest Dept and Thoracic Oncology Expert Center, AP-HP Hôpital Tenon and Medicine Sorbonne University, Paris, France.

Correspondence: Thierry Berghmans, Institut Jules Bordet, Rue Héger-Bordet, 1 B1000 Brussels, Belgium. E-mail: thierry.berghmans@bordet.be

ABSTRACT In the last decade, systemic therapy for advanced lung cancer has become diverse, complex and personalised. These new therapies (monoclonal antibodies, tyrosine kinase inhibitors (TKIs) and immunotherapy) have a far different toxicity profile compared to chemotherapy. Furthermore, clinical indications and reimbursement criteria can vary across Europe. The aim of the present online survey was to assess the knowledge, views and challenges facing the European respiratory community in this rapidly changing field.

A 15-question web survey was sent to all European Respiratory Society members through the Society's monthly electronic communication.

A total of 315 questionnaires were completed. Most of the respondents were male (59.1%), were above 40 years of age (52.9%) and were working in university/academic hospitals (74.8%), the majority as pulmonologists (90%). Only 55% of the participants were aware of the legal processes for drug recognition. Except for epidermal growth factor receptor TKI, up to 38% did not know about the specific toxicities of anaplastic lymphoma kinase/ROS proto-oncogene 1 TKIs, monoclonal antibodies and immune checkpoint inhibitors. Of the respondents, 92% showed an interest in an online platform reporting new drugs' toxicities.

Despite a large amount of publicity and integration of new drugs into therapeutic algorithms and clinical guidelines, physicians taking care of lung cancer patients have a need for up-to-date information on systemic therapy toxicity management and legal constraints.

@ERSpublications
Physicians have a need for up-to-date information on new drug toxicity management in thoracic oncology http://ow.ly/j3YA30kOtBz

Cite this article as: Berghmans T, Evison M, Blum TG, *et al.* New drugs in thoracic oncology: needs and knowledge – an online ERS Lung Cancer Assembly survey. *ERJ Open Res* 2018; 4: 00040-2018 [https://doi.org/10.1183/23120541.00040-2018].

Received: March 08 2018 | Accepted after revision: July 01 2018

Introduction

Until the turn of the 21st Century, tumour-specific treatment in lung cancer was based on the triplet surgery–radiotherapy–chemotherapy, either alone or in combination according to disease extent. A better knowledge of cancer biology including cell cycle control, metastatic process and immune cell–tumour interactions led to substantial modifications in the current therapeutic strategies, mainly for stage IV nonsmall cell lung cancer (NSCLC) [1]. Monoclonal antibodies targeting epidermal growth factor receptor (EGFR) [2] or vascular endothelial growth factor (VEGF) [3] demonstrated survival improvement when combined with first-line platinum-based chemotherapy, while a small oral drug with anti-angiogenic properties, nintedanib [4], had the same result in combination with docetaxel for salvage therapy in an adenocarcinoma sub-group. In addition to these encouraging data, more successes were noted in selected patients with oncogenic driver mutations, EGFR and proto-oncogene B-Raf (BRAF) mutations, or anaplastic lymphoma kinase (ALK) and ROS proto-oncogene 1 (ROS-1) translocations. Small oral tyrosine kinase inhibitors (TKIs) allowed significant improvement in progression-free survival duration with limited toxicity in comparison with conventional chemotherapy [5–16]. The last advances were recently noted with the introduction of immune checkpoint inhibitors targeting either the programmed cell death 1 (PD1)/programmed death ligand 1 (PDL1) or cytotoxic T-lymphocyte-associated protein 4 (CTLA4) axes [16–21]. The Food and Drug Administration (FDA) in North America and the European Medicines Agency (EMA) in Europe have currently approved three drugs (pembrolizumab, nivolumab and atezolizumab) and the diversification in the (pneumo)oncologist's armamentarium is set to continue as other targeted therapies, immunotherapies and combined regimens are under investigation.

These advances are leading to complexity in therapeutic decisions. Furthermore, all these new drugs are presenting with far different toxicity profiles compared to the well-known chemotherapeutic agents. (Pneumo)oncologists must now update their knowledge regarding the mechanisms of action and toxicities but should additionally be aware of the respective national legal prescription pathways and reimbursement criteria for these drugs. In order to obtain a picture of the current situation in Europe, the ERS Thoracic Oncology Assembly-driven Clinical Research Collaboration (CRC) RATIONALE designed an online survey focusing on any physicians involved in lung cancer diagnosis or treatment.

Methodology

An ERS grant was obtained in 2015 through a CRC application, with the main objective being the development of an online platform regarding toxicity of new drugs in thoracic oncology. Before developing this prospective registry, a survey was designed with the primary aim of providing a picture of physicians' current knowledge of the legal processes and toxicities of new systemic therapies available for lung cancer treatment.

After consensual agreement, 15 questions and one optional comment section constituted the survey (table 1). The survey was sent anonymously through the ERS monthly electronic communication to all ERS members, whatever their main specialty. A recall was done once and the data capture was finally closed on October 31, 2017.

Results

The survey ran from May 2017 to November 2017 and 315 questionnaires were obtained. The main characteristics of the respondents are presented in table 2. There were a slight majority of males, above 40 years of age, working essentially in university and academic hospitals. Respondents were representative of most European countries with the following distribution: Spain (n=40), United Kingdom (n=25), Germany and Greece (both n=22), Portugal (n=21), France (n=20), Italy (n=14), the Netherlands (n=12), Austria (n=11), Belgium (n=9), Poland (n=8), Serbia (n=7), Romania (n=6), Finland and Switzerland (both n=5), Hungary, Bulgaria and the Czech Republic (n=4 each), Norway and Macedonia (both n=3), Croatia and Luxembourg (n=2 each). In addition people from Turkey (n=10), the Philippines (n=8), Australia and Israel (n=2 each) also answered the questionnaire.

Six questions concerned legal constraints, indications and toxicities of new drugs in lung cancer, focusing on targeted therapies (EGFR, ALK and ROS-1 TKIs, monoclonal antibodies directed against EGFR or with anti-angiogenic activity and immunotherapy regarding either the PD1/PDL1 or CTLA4 axes). There is clearly a lack of knowledge of the legal processes for drug prescription in Europe (138 positive answers among 253 responses (54.5%)), while the EMA was recognised by 86.6% of the respondents (219 out of 253). Table 3 summarises this information in countries that have more than 10 respondents, while table 4 summarises the knowledge of the lung cancer community about indications and general toxicity of the new systemic therapies (showing the need for further information with the exception of EGFR TKI). In addition, a lot of physicians do not recognise potential toxicities related to these new drugs (table 5). Toxicity management is coordinated primarily by the chest physicians while medical oncologists were also

TABLE 1 Questionnaire summary

Questions and answer options
General characteristics of the respondents
Which is your gender?
Which is your age?
<30 years
30–39 years
40–49 years
50–59 years
⩾60 years
Which country do you currently work in?
In which setting do you currently work?
What is your specialty?
Indications, legal constraints and toxicity of new drugs in thoracic oncology
With regard to new systemic therapies in thoracic oncology, are you aware of the following?
The legal process for drug recognition in the European Community
The European Medicines Agency (EMA)
Are you aware of the clinical indications for the following systemic therapies in lung cancer?
EGFR TKIs
ALK inhibitors
ROS-1 inhibitors
Anti-EGFR antibodies
Anti-angiogenic antibodies (*e.g.* anti-VEGF)
Immunotherapy (PD1/PDL1 axis)
Immunotherapy (CTLA4 axis)
Monoclonal antibodies
Oral angiogenic inhibitors
Are currently you prescribing any of the following systemic therapies in lung cancer?
EGFR TKIs
ALK inhibitors
ROS-1 inhibitors
Anti-EGFR antibodies
Anti-angiogenic antibodies (*e.g.*anti-VEGF)
Immunotherapy (PD1/PDL1 axis)
Immunotherapy (CTLA4 axis)
Monoclonal antibodies
Oral angiogenic inhibitors
Do you feel you have a good understanding of the toxicity profile of the following systemic therapies in lung cancer?
EGFR TKIs
ALK inhibitors
ROS-1 inhibitors
Anti-EGFR antibodies
Anti-angiogenic antibodies (*e.g.*anti-VEGF)
Immunotherapy (PD1/PDL1 axis)
Immunotherapy (CTLA4 axis)
Monoclonal antibodies
Oral angiogenic inhibitors
Which of the following are potential pulmonary complications from the new systemic therapies in lung cancer listed above?
Haemoptysis
Bronchospasm
Pleural effusion
Interstitial lung disease
Pneumonia
At your current place of work, which is the primary specialty responsible for managing toxicity from new systemic therapies in lung cancer?
Pneumology
Medical oncology
Organ-specific specialist (depending on the site of toxicity)
General internal medicine physician
Oncology nurse
The To¨X¨csin Project: would you use an online platform such as this?
Yes
No
Not sure

Continued

TABLE 1 Continued

Questions and answer options
What do you think is the most important function of an online platform such as this?
What type of toxicity information should be reported on?
Only lung toxicity
All toxicity
At your institution, would you be willing to seek approval from a regulatory board and ethics committee to submit patient data to the To"X"csin system?
Yes
No
Maybe

EGFR: epidermal growth factor receptor; TKI: tyrosine kinase inhibitor; ALK: anaplastic lymphoma kinase; ROS-1: ROS proto-oncogene 1; VEGF: vascular endothelial growth factor; PD1: programmed cell death 1; PDL1: programmed death ligand 1; CTLA4: cytotoxic T-lymphocyte-associated protein 4.

frequently in charge. The role of the organ-specific specialist is infrequent, maybe reflecting the fact that toxicities were respiratory system centred (table 5).

The last four questions regarded the To"X"csin project, an online prospective registry coordinated through the ERS with the aim of reporting and describing toxicities related to new systemic therapies in lung cancer. Among 312 respondents, 235 would use the online platform while only 25 would abstain from it and 52 were unsure. Most of the participants (268 out of 309) estimated that the platform should focus on all types of toxicities while few (41 out of 309) considered only lung toxicities. In order to launch the online platform, the majority reported that needing regulatory board and ethics committee approval was either a certainty (147 out of 306) or a possibility (132 out of 306); however, for 27 respondents this seemed not to be mandatory in their national setting.

The proposals from the respondents for the platform's main functions can be summarised in five groups: 1) providing information and education, eventually on rare pathologies/events; 2) creating a network for information and data sharing/creation of a European database; 3) diffusion of information on unexpected/rare side effects; 4) allowing case discussions and contact with "specialists"; 5) connecting with competent authorities at the national and European levels.

TABLE 2 General characteristics of the respondents

Question	n
Which is your gender? (n= 308)#	
Male	182
Female	126
Which is your age? (n=310)#	
<30 years	12
30–39 years	79
40–49 years	85
50–59 years	100
⩾60 years	34
In which setting do you currently work? (n=310)#	
University/academic hospital	233
Community/private hospital	60
Cancer centre	9
Other	8
What is your Specialty? (n=311)#	
Pulmonology	284
Medical oncology	10
Thoracic surgery	4
Radiotherapy	1
Other	12

#: Value in parentheses is for the total number of respondents.

TABLE 3 Breakdown of the legal constraints knowledge in countries that have more than 10 respondents

Country	Number of respondents	No knowledge of legal constraints	Knowledge of EMA only
Austria	11	0	4
France	20	2	11
Germany	22	1	7
Greece	22	7	4
Italy	14	1	9
Portugal	21	1	1
Spain	39	8	20
The Netherlands	12	0	11
Turkey	10	4	3
United Kingdom	25	2	14
Country not given	25	4	9

EMA: European Medicines Agency.

Discussion

Lung cancer management has evolved from a simple "all-fit-in" strategy based on surgery, radiotherapy and conventional chemotherapy to a complex algorithm concerning specific biological entities (oncogenic driver mutations/inflammatory tumours) and new systemic therapies having specific mechanisms of action and toxicity profiles. This survey, the first milestone of the CRC RATIONALE masterplan, as an essential part of the ERS Thoracic Oncology Assembly, emphasised the need for providing information to lung cancer specialists about national and European legal processes of drug prescription and indications, as well as toxicity descriptions and management in three therapeutic fields: 1) targeted therapies; 2) monoclonal antibodies; and 3) immunotherapies.

Twenty years ago, lung cancer was separated into two distinct entities, small cell lung cancer (SCLC) and NSCLC, with dedicated therapeutic strategies. With the reporting of the first actionable oncogenic driver mutation in 2004 [22], a new era of targeted therapies was opened and other targets were rapidly discovered [23]. While advances were made they only concerned small groups of patients, moving from a common cancer to rare entities so that physicians have limited experience either for diagnosis, treatment or toxicity management. More recently, immunotherapy developments led to the introduction of anti-PD1/PDL1 antibodies into routine care for a very large group of NSCLC patients. However, physicians are now confronted by toxic autoimmune manifestations, an uncommon situation in lung cancer which justifies the assistance of organ-specialists who are in turn not aware of lung cancer

TABLE 4 Indication and toxicity knowledge of new systemic therapies

Drugs	Are you aware of the clinical indications for the following systemic therapies in lung cancer? (n=288)	Are you currently prescribing any of the following systemic therapies in lung cancer? (n=174)	Do you feel you have a good understanding of the toxicity profile of the following systemic therapies in lung cancer? (n=244)
Targeted therapies			
EGFR TKI	280 (97.2)	170 (97.7)	228 (93.4)
ALK inhibitors	257 (89.2)	148 (85.1)	173 (70.9)
ROS-1 inhibitors	183 (63.5)	91 (44.5)	102 (41.8)
Monoclonal antibodies			
Anti-EGFR	196 (68.1)	68 (45.9)	94 (38.5)
Anti-angiogenic	211 (73.3)	111 (63.8)	143 (58.6)
Immunotherapy			
PD1/PD-L1 axis	237 (82.3)	146 (83.9)	177 (72.5)
CTLA4 axis	150 (52.1)	49 (28.2)	92 (37.7)

Data is presented as n (%) based on the total number of respondents shown in the column headers and corresponds to the number of YES responses to the questions; EGFR: epidermal growth factor receptor; TKI: tyrosine kinase inhibitor; ALK: anaplastic lymphoma kinase; ROS-1: ROS proto-oncogene 1; PD1: programmed cell death 1; PDL1: programmed death ligand 1; CTLA4: cytotoxic T-lymphocyte-associated protein 4.

TABLE 5 Pulmonary complications and toxicity management

Question	n (%)
Which of the following are potential pulmonary complications from the new systemic therapies in lung cancer? (n=292)	
Haemoptysis	168 (57.5)
Bronchospasm	83 (28.4)
Pleural effusion	102 (34.9)
Interstitial lung disease	267 (91.4)
Pneumonia	153 (52.4)
At your current place of work, which is the primary specialty responsible for managing toxicity from new systemic therapies in lung cancer? (n=307)	
Pulmonologist	170 (55.4)
Medical oncologist	114 (37.1)
Organ-specific specialist	17 (5.5)
General internist	5 (1.6)
Oncology nurse	1 (0.3)

specificities. Furthermore, at the difference of conventional chemotherapy and first/second generation EGFR TKI, there are not only very specific toxicities associated with new drugs (*e.g.* visual disturbances associated with ALK inhibitors) but also differences in the incidences of similar toxic events inside the same class of drugs (less skin reaction and diarrhoea for osimertinib compared to first/second generation EGFR TKIs (gefitinib, erlotinib and afatinib)) or therapeutic approaches (more immune adverse events with ipilimumab compared to anti-PD1). The present survey, mainly representing medical (pneumo) oncologists, underlines some deficits in knowledge amongst lung cancer clinicians in these different domains. The exception is EGFR mutation and TKI, probably because of less complexity than currently noted in the ALK translocated tumours and more than a decade of use in routine practice.

Respondents to this survey clearly supported the development of a user-friendly system providing updated information on toxicity prevalence and description of new systemic drugs in lung oncology. The CRC RATIONALE is building an industry-independent web platform (To"X"csin) where toxic events may be prospectively recorded. Their expectation is also to have the possibility of sharing experience with other specialists not only about lung toxicity but about any organ toxicity. We can question the current way of obtaining such information. There are numerous sources of data coming from the pharmaceutical industry but, without any value judgement in the present situation, these can be biased as was previously reported for psychiatric medications [24]. Furthermore, reporting adverse events to national and European medical agencies is a legal constraint; however, the response *via* information for the physicians sometimes seems limited or delayed, since regular updates on types and frequencies of adverse events are difficult to obtain and official modification of medical notices (often after substantial documentation of relevant adverse events) may take time due to bureaucratic processes. This emphasises the need for a new up-to-date and rapid communication platform, directed by and designed for the physicians, which will be ensured by the aspired to To"X"csin platform.

Two main questions arise for the survey. The first is regarding the number of participants, as the first call allowed us to obtain around 100 responses and with the second call we increased this number to more than 300. This appears to be a relatively low value according to the number of ERS members; however, it is evident that answers to surveys are generally low, especially amongst physicians of which only a minority are involved in lung cancer treatment and who receive many solicitations. The second question of importance is whether the respondents are representative of the European lung cancer community. Participants covered all the different parts of Europe and the slight male majority is also reflective of the current tendency in gender repartition. Age distribution shows that most respondents are active experienced physicians, although we observed some discrepancy regarding the site of activity with an excess of academics and universitarians. Despite this, the need for information remains important. Most of the respondents were pneumologists and very few were from other specialties. However, in most European countries, pneumologists are in charge of first-line lung cancer diagnosis and treatment.

Facing the evolving complexity in NSCLC management and the rapid introduction of new systemic therapies, the lung cancer community is requesting new information and communication modes for sharing experience with toxicities that are underlined by this online survey. Thus, the CRC RATIONALE within the ERS Thoracic Oncology Assembly has elaborated a website dedicated to this topic. We expect that To"X"csin will be available in 2018, provided that all legal constraints are reached.

Conflict of interest: J. Cadranel reports receiving grants and personal fees from Astra Zeneca, Novartis and Pfizer, personal fees from Boehringer Ingelheim, Roche, BMS and MSD, outside the submitted work.

Support statement: This survey is part of a European Respiratory Society Clinical Research Collaboration. Funding information for this article has been deposited with the Crossref Funder Registry.

References

1 Novello S, Barlesi F, Califano R, *et al.* Metastatic non-small-cell lung cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2016; 27: Suppl. 5, v1–27.
2 Pujol JL, Pirker R, Lynch TJ, *et al.* Meta-analysis of individual patient data from randomized trials of chemotherapy plus cetuximab as first-line treatment for advanced non-small cell lung cancer. *Lung Cancer* 2014; 83: 211–218.
3 Soria JC, Mauguen A, Reck M, *et al.* Systematic review and meta-analysis of randomised, phase II/III trials adding bevacizumab to platinum-based chemotherapy as first-line treatment in patients with advanced non-small-cell lung cancer. *Ann Oncol* 2013; 24: 20–30.
4 Reck M, Kaiser R, Mellemgaard A, *et al.* Docetaxel plus nintedanib versus docetaxel plus placebo in patients with previously treated non-small-cell lung cancer (LUME-Lung 1): a phase 3, double-blind, randomised controlled trial. *Lancet Oncol* 2014; 15: 143–155.
5 Inoue A, Kobayashi K, Maemondo M, *et al.* Updated overall survival results from a randomized phase III trial comparing gefitinib with carboplatin-paclitaxel for chemo-naive non-small cell lung cancer with sensitive EGFR gene mutations (NEJ002). *Ann Oncol* 2013; 24: 54–59.
6 Mitsudomi T, Morita S, Yatabe Y, *et al.* Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. *Lancet Oncol* 2010; 11: 121–128.
7 Rosell R, Carcereny E, Gervais R, *et al.* Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol* 2012; 13: 239–246.
8 Wu Y-L, Zhou C, Liam C-K, *et al.* First-line erlotinib versus gemcitabine/cisplatin in patients with advanced EGFR mutation-positive non-small-cell lung cancer: analyses from the phase III, randomized, open-label, ENSURE study. *Ann Oncol* 2015; 26: 1883–1889.
9 Zhou C, Wu YL, Chen G, *et al.* Final overall survival results from a randomised, phase III study of erlotinib versus chemotherapy as first-line treatment of EGFR mutation-positive advanced non-small-cell lung cancer (OPTIMAL, CTONG-0802). *Ann Oncol* 2015; 26: 1877–1883.
10 Sequist LV, Yang JC, Yamamoto N, *et al.* Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. *J Clin Oncol* 2013; 31: 3327–3334.
11 Wu YL, Zhou C, Hu CP, *et al.* Afatinib versus cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-small-cell lung cancer harbouring EGFR mutations (LUX-Lung 6): an open-label, randomised phase 3 trial. *Lancet Oncol* 2014; 15: 213–222.
12 Shaw AT, Kim DW, Nakagawa K, *et al.* Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. *N Engl J Med* 2013; 368: 2385–2394.
13 Shaw AT, Kim TM, Crinò L, *et al.* Ceritinib versus chemotherapy in patients with ALK-rearranged non-small-cell lung cancer previously given chemotherapy and crizotinib (ASCEND-5): a randomised, controlled, open-label, phase 3 trial. *Lancet Oncol* 2017; 18: 874–886.
14 Solomon BJ, Mok T, Kim D-W, *et al.* First-line crizotinib versus chemotherapy in ALK-positive lung cancer. *N Engl J Med* 2014; 371: 2167–2177.
15 Soria J-C, Tan DSW, Chiari R, *et al.* First-line ceritinib versus platinum-based chemotherapy in advanced ALK-rearranged non-small-cell lung cancer (ASCEND-4): a randomised, open-label, phase 3 study. *Lancet* 2017; 389: 917–929.
16 Reck M, Rodríguez-Abreu D, Robinson AG, *et al.* Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. *N Engl J Med* 2016; 375: 1823–1833.
17 Brahmer J, Reckamp KL, Baas P, *et al.* Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. *N Engl J Med* 2015; 373: 123–135.
18 Borghaei H, Paz-Ares L, Horn L, *et al.* Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. *N Engl J Med* 2015; 373: 1627–1639.
19 Herbst RS, Baas P, Kim D-W, *et al.* Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *Lancet* 2016; 387: 1540–1550.
20 Rittmeyer A, Barlesi F, Waterkamp D, *et al.* Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. *Lancet* 2017; 389: 255–265.
21 Reck M, Luft A, Szczesna A, *et al.* Phase III randomized trial of ipilimumab plus etoposide and platinum versus placebo plus etoposide and platinum in extensive-stage small-cell lung cancer. *J Clin Oncol* 2016; 34: 3740–3748.
22 Lynch TJ, Bell DW, Sordella R, *et al.* Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *N Engl J Med* 2004; 350: 2129–2139.
23 Hirsch FR, Scagliotti GV, Mulshine JL, *et al.* Lung cancer: current therapies and new targeted treatments. *Lancet* 2017; 389: 299–311.
24 Turner EH, Matthews AM, Linardatos E, *et al.* Selective publication of antidepressant trials and its influence on apparent efficacy. *N Engl J Med* 2008; 358: 252–260.