Lung cancer

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Lung cancer is one of the most frequently diagnosed cancers and the leading cause of cancer-related deaths worldwide with an estimated 2 million new cases and 1·76 million deaths per year. Substantial improvements in our understanding of disease biology, application of predictive biomarkers, and refinements in treatment have led to remarkable progress in the past two decades and transformed outcomes for many patients. This seminar provides an overview of advances in the screening, diagnosis, and treatment of non-small-cell lung cancer and small-cell lung cancer, with a particular focus on targeted therapies and immune checkpoint inhibitors.

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Introduction

With an estimated 2·20 million new cases and 1·79 million deaths per year, lung cancer is one of the most frequently diagnosed cancers and the leading cause of cancer-related deaths worldwide.[1] Substantial improvements in general understanding of disease biology, application of predictive biomarkers, and refinements in treatment have led to remarkable progress and transformed outcomes for many patients.[2] Furthermore, public health measures to reduce smoking rates have contributed to reduced incidence of lung cancer and improved survival in high-income countries.[3–5] Incidence of lung cancer is declining twice as fast in men than in women, reflecting the historical delay in tobacco uptake and cessation by women.[5,6] However, new lung cancer diagnoses continue to increase in low-income countries, where public health initiatives for smoking cessation have lagged behind and access to health-care is scarce.[3,4,7] In addition, lung cancer continues to be diagnosed in people who have never smoked. This Seminar provides an overview of advances in the screening, diagnosis, and treatment of non-small-cell lung cancer (NSCLC) and small-cell lung cancer (SCLC), with a particular focus on targeted therapies and immune checkpoint inhibitors (ICIs).

Screening

Implementing screening programmes to diagnose patients at an earlier stage is one of the major steps needed to decrease lung cancer-related deaths and improve survival. Historically, screening studies that used chest radiographs, with or without sputum cytology, did not show an improvement of patient outcomes.[8] However, in two randomised controlled trials (RCTs) screening at-risk individuals with low-dose CT significantly improved lung cancer mortality.[9,10] In the National Lung Screening Trial (NLST),[9] roughly 50 000 patients with a high-risk history of smoking were randomly assigned to screening with annual low-dose CT or chest radiographs over 3 years. The smaller NELSON study[10] randomly assigned men who were at high risk of lung cancer (and added a smaller population of women later in the study) to low-dose CT at baseline, followed by four scans during a 15 year period or no intervention. Both the NLST and NELSON studies showed a clear reduction in lung cancer mortality (NLST: hazard ratio [HR] 0·80, p=0·004; NELSON: 0·76, p=0·01) and NLST also showed a 6·7% improvement in overall mortality (p=0·02).

Although the NELSON and NLST studies mainly pertain to White men, minority ethnic groups are disproportionately burdened by lung cancer mortality rates and are under-represented in studies.[11] Similarly, women also comprised a minority of the studies' populations, despite evidence that they are more likely to benefit from screening than are men.[10,12] Furthermore, current US screening recommendations primarily use smoking history to identify patients who are at high risk. However, lung cancer is found across all smoking histories.[13] Other risk factors, such as exposure to air pollution, are not included in screening criteria in general.

Since 2013, lung cancer survival has improved primarily due to new treatments rather than screening; however, this is due to low uptake of screening despite clear evidence that it improves cancer mortality.[2] There is hope that, as screening is adopted, survival from lung cancer will improve as a result, particularly if ongoing trials help to personalise and optimise screening intervals on the basis of initial scan findings.[14] Barriers include the stigma associated with smoking and the cost of screening.[15,16] Coordinated efforts by health-care providers and governments are crucial to harness the full potential of screening. Other methods for screening are being investigated, including circulating tumour DNA (ctDNA), analysis of volatile organic compounds in breath, and artificial intelligence enhanced interpretation.

Histology

Lung cancer is a heterogenous disease with wide-ranging clinicopathological features.[17] Lung cancer is classified

Search strategy and selection criteria

We identified references for this Seminar with searches of MEDLINE, PubMed, and references from relevant articles with the term "lung cancer" in combination with search terms "epidemiology", "screening", "radiotherapy", "targeted therapies", "immunotherapy", and "immune checkpoint". Our search focused on publications in English from Jan 1, 2014, to Jan 7, 2020, although seminal papers outside this period were included. We have included articles published only in the form of abstracts or conference proceedings.

See Online for appendix

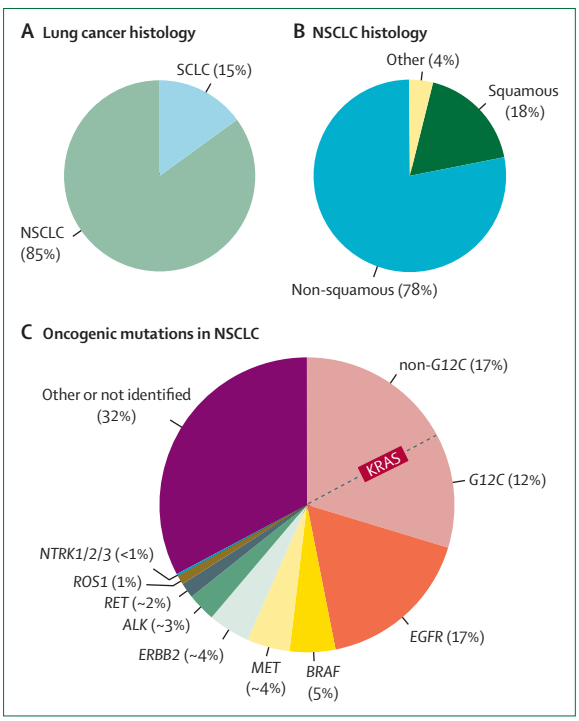

***Figure 1*: Lung cancer histology**
Lung cancers are classified into SCLC or NSCLC (A), which are subdivided into squamous and non-squamous histology (B). (C) The frequencies of common oncogenic driver mutations in NSCLC. Based on a cohort of 4064 patients with metastatic NSCLC by Singal and colleagues.[19] NSCLC=non-small-cell lung cancer. SCLC=small-cell lung cancer.

broadly as NSCLC (85% of total diagnoses) or SCLC (15% of total diagnoses). Within NSCLC classifications, adenocarcinomas are the most common subtype of lung cancer,[18] followed by squamous-cell carcinomas (figure 1).[17] The incidence of squamous-cell carcinomas, which was the most common histology, has substantially decreased, partly due to reductions in smoking rates in high-income countries and changes in cigarette composition.[20]

Biomarker testing

The management of advanced lung cancer was anchored in chemotherapy and based on histology. However, during the past decade, the discovery of predictive biomarkers has created new therapeutic opportunities with targeted therapy and immunotherapy (figure 2).

Tumour PD-L1 expression

The expression of PD-L1 on the surface of tumour cells, detected by immunohistochemistry, is a predictive biomarker used to guide treatment decisions with anti-PD-1 or anti-PD-L1 antibodies in patients with NSCLC. PD-L1 expression is associated with increased likelihood of response to PD-1 pathway blockade, but responses to ICIs can also be seen in patients with no tumour PD-L1 expression. This response is probably due to several host, tumour, and clinical factors (appendix p 1).[21,22] Furthermore, PD-L1 expression is heterogeneous, both intratumorally and intertumorally.[23,24]

Despite these issues, tumour PD-L1 expression should be assessed in all patients with newly diagnosed advanced NSCLC as it informs the use of ICIs and identifies patients in whom the chemoimmunotherapy approach is preferred.

Tumour mutational burden (TMB)

High TMB is predictive of response to ICIs, although there is no prospective validation.[25] TMB testing is currently not recommended for NSCLC and SCLC but warrants brief discussion in light of the US Food and Drug Administration (FDA) approval of the PD-1 inhibitor, pembrolizumab, for pretreated patients with high TMB (≥10 mutations per megabase) regardless of tumour type. Results from a preplanned analysis of ten cohorts of roughly 700 patients showed an improved overall response in the group that had high TMB (29%, 95% CI 21–39) compared with the group that did not have high TMB (6%, 5–8) for people given pembrolizumab.[26] A higher proportion of patients with high TMB were alive at 3 years after the first dose of pembrolizumab than those who did not have high TMB (32% *vs* 22%). TMB was an independent predictor of response to single-agent ICI. The results of this study do not influence first-line treatment of patients with lung cancer, in which ICI with or without chemotherapy is established as the standard of care. However, TMB might provide additional predictive information regarding response to ICI, although further research is required to standardise testing platforms and clarify thresholds for tumour types.

Molecular testing

Current guidelines (eg, College of American Pathologists, International Association for the Study of Lung Cancer, and the Association of Molecular Pathology) recommend that all patients with newly diagnosed advanced lung adenocarcinoma are tested for *EGFR* mutations; *ALK* and *ROS-1* rearrangements; BRAF Val600Glu (*BRAF*^{V600E}); *RET* rearrangements; and *MET* exon 14 skipping mutations.[27,28] However, broader testing, inclusive of other targetable alterations, such as *NTRK* fusions, HER-2 overexpression, and *HER-2* mutations, is recommended in light of drug approvals (appendix p 2).[28] Historically, oncogenic driven NSCLCs were thought to occur in patients with adenocarcinoma histology and a never or light smoking history;[29,30] however, driver mutations can be found across all histologies, ages, and smoking histories. *BRAF*-positive,[31,32] *MET*-amplified,[33] and *KRAS*-positive NSCLCs are found in higher proportion in smokers than in non-smokers. Therefore, all patients with newly diagnosed metastatic lung adenocarcinoma should have broad molecular testing.

Multiplex testing with next-generation sequencing is recommended for molecular testing as this process

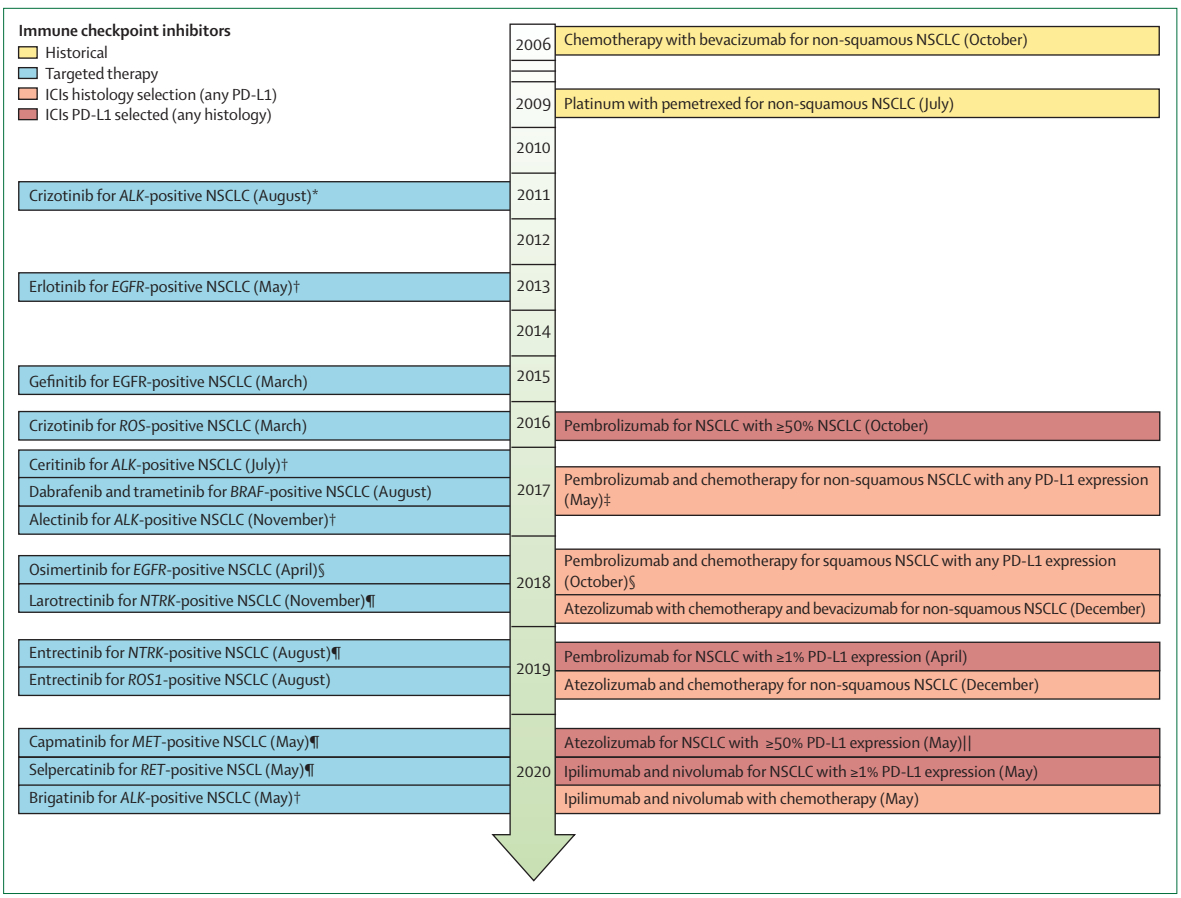

***Figure 2*: Timeline of selected US Food and Drug Administration drug approvals for patients with treatment-naive metastatic NSCLC**
Cytotoxic chemotherapy regimens were approved in the 2000s, followed by the rapid approvals of targeted therapies for oncogene driven NSCLC and immune checkpoint inhibitors, with or without chemotherapy, on the basis of histology and tumour PD-L1 expression (or both). Historical treatments are those that are still used, but are no longer the gold-standard treatment. ICI=immune checkpoint inhibitor. NSCLC=non-small-cell lung cancer. *Received full approval for *ALK*-positive NSCLC in 2013. †Received previous approval for second-line or later treatment. ‡Subsequent full approval in 2017. §Received earlier approval for *EGFR* Thr790Met-positive NSCLC. ¶Accelerated approval only. ||Also approved for PD-L1-positive tumour-infiltrating immune cells covering 10% or more tumour area.

abrogates the need for multiple testing when there might be little tissue availability.[28] Single gene assays for specific genetic alterations can be used, but these are often done sequentially, which delays time to treatment.

Biology of oncogenic drivers

The discovery of somatic activating mutations in *EGFR* was the first to show that some NSCLCs harbour oncogenic driver mutations that confer sensitivity to tyrosine-kinase inhibitors (TKIs).[34–36] Fundamentally, oncogene-driven lung cancers follow common biological frameworks. Oncogenic driver alterations: result in constitutive activation of kinase signalling pathways that normally require ligand-dependent activation (figure 3A);[37] appear to be early clonal events in the evolution of the tumour, and are maintained in all subclones that develop during tumour progression;[38] are typically mutually exclusive of other drivers;[39,40] and lead to so-called oncogene addiction with the cancer cells dependent on the activated signalling pathway for survival. These characteristics form the basis for directed use of TKIs against these oncogenic drivers.

Despite the success of targeted therapies, resistance inevitably occurs (figure 3B).[41] Acquired resistance can be classified into three categories (figure 3C). On-target resistance describes alterations in the target gene, which can include target gene amplification or second site mutations that interfere with drug binding.[42–44] Off-target resistance often occurs through reactivation of downstream oncogenic signalling pathways, despite ongoing inhibition of the target kinase.[42,43,45–47] The third category is phenotypic transformation, in which biopsies done in patients during disease progression on targeted therapies have shown a transformation from NSCLC to SCLC.[42,43,45,48–50]

Liquid biopsies

Tumour samples should be obtained at the time of diagnosis and during disease progression when the patient is receiving targeted therapies to guide therapeutic decisions.

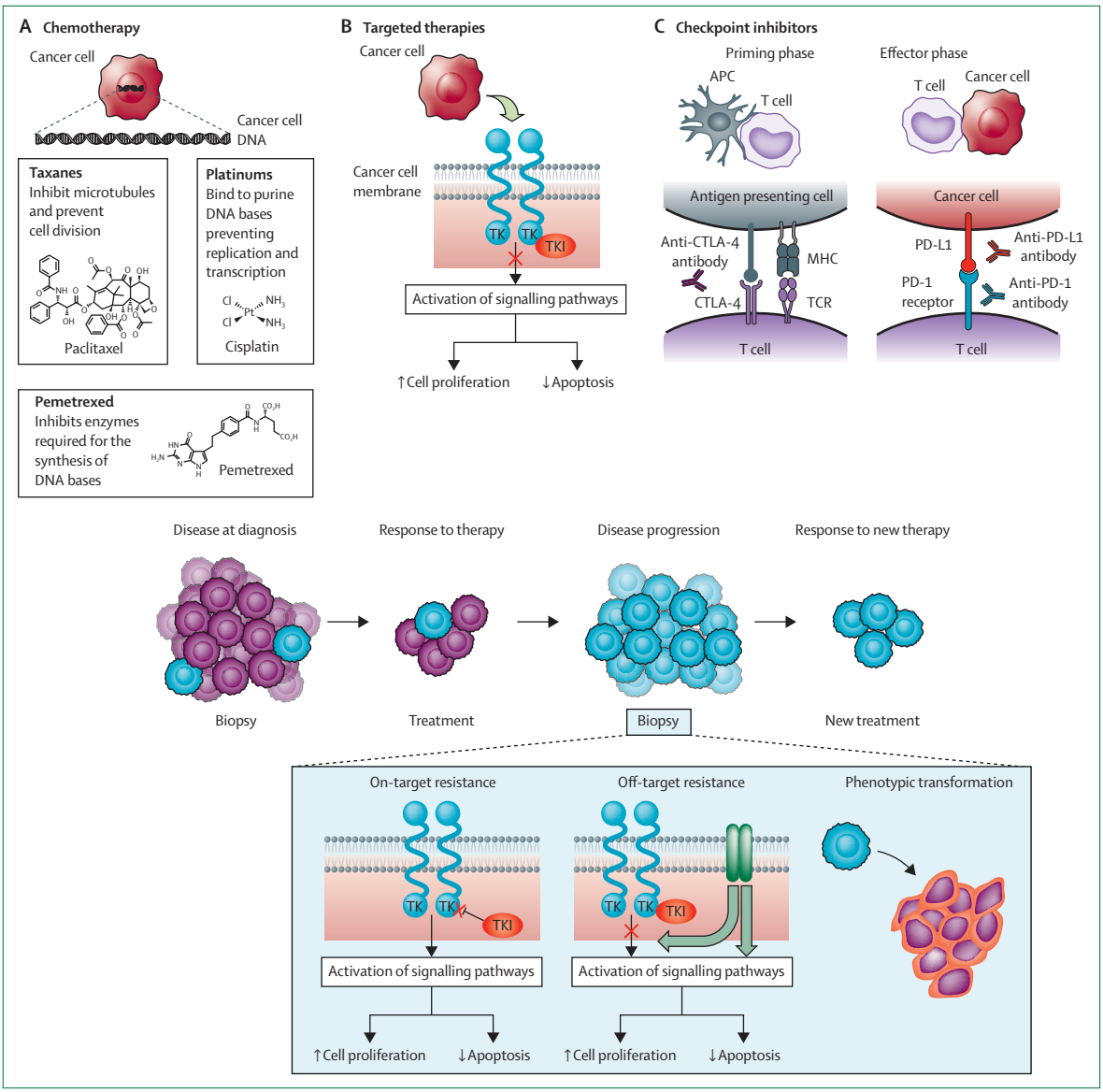

***Figure 3*: Mechanisms of anticancer therapies and evolution of resistance to targeted therapies**
(A) Generalised mechanisms of action of cytotoxic agents, TKIs, and immune checkpoint inhibitors are shown. TKIs inhibit the constitutive activation of kinase signalling pathways in cancer cells, thereby inducing apoptosis. Immune checkpoint inhibitors are monoclonal antibodies that target CTLA-4, and PD-1 and PD-L1. T-cell activation requires antigen presentation by MHC class II molecules on APCs. A second activation signal is required but can be blocked by CTLA-4 binding with CD80 or CD86. Anti-CTLA-4 antibodies, such as ipilimumab, inhibit the CTLA-4 binding negative regulatory signal. Another immune checkpoint occurs when PD-1 receptors, expressed on activated T cells, bind to its ligand, PD-L1, expressed on tumour cells, and promote T-cell apoptosis. Anti-PD-1 and anti-PD-L1 antibodies, such as pembrolizumab, inhibit this signal. (B) After response to TKIs, drug resistance inevitably develops. Biopsy at the time of progression can identify the dominant mechanism of resistance (C) and guide subsequent therapeutic decisions. Acquired resistance can be classified into three categories: on-target resistance, in which alterations in the target receptor tyrosine kinase prevent drug binding; off-target resistance, in which activation of alternative signalling pathways allow for ongoing cancer cell proliferation and survival despite ongoing target inhibition; and phenotypic transformation, in which there is acquisition of a new histology and dependence on oncogene signalling is generally lost. APC=antigen presenting cell. TK=tyrosine kinase. TKI=tyrosine-kinase inhibitor.

Patients might have only one site of progression and tissue biopsy might not be technically feasible or could carry unacceptable procedural risks; however, detection of ctDNA in plasma, otherwise known as liquid biopsies, can obtain molecular information if tissue is not available.[51]

Tumour DNA fragments are shed into the bloodstream and can be detected in plasma through identification of tumour-specific variant nucleotides.[52] The amount of detectable ctDNA varies and the sensitivity of detecting target mutations with ctDNA is 60–80%, depending on tumour location, size, vascularity, and the detection method used.[53,54] In current practice, detection of *EGFR* mutations with ctDNA, using PCR or next-generation sequencing, are the only FDA approved plasma tests.

Assessment of ctDNA is useful for patients whose disease has progressed on first-generation or second-generation TKIs to detect the *EGFR*Thr790Met (*EGFR*^{T790M}) mutation. ctDNA has also been used to show tumour heterogeneity and detect residual disease, but these uses are being investigated.[55]

Staging

Adequate staging is paramount in the investigation of patients with lung cancer to select the most appropriate therapy. Imaging methods, including fluorodeoxyglucose-PET (FDG-PET) scans and MRI, are often used to identify patients who are not candidates for curative treatment. Advances in bronchoscopic and radiological methods for tissue biopsy samples are beyond the scope of this Seminar but are reviewed in published guidelines.[56,57]

FDG-PET

FDG-PET is increasingly used with CT for staging lung cancer. FDG-PET alone does not provide detailed anatomical resolution, but it can depict metabolic activity in lesions that are 1 cm or larger. FDG-PET with CT is better than CT or FDG-PET alone for the detection of involved mediastinal lymph nodes, and has a reported sensitivity of 58–94% and specificity of 76–96%.[58] One of the benefits of FDG-PET is the identification of involved mediastinal lymph nodes and occult distant metastases in patients who might otherwise have resectable cancer. In RCTs, FDG-PET with CT has been shown to prevent up to a fifth of patients with lung cancer from having unnecessary thoracotomies.[59,60] It is important to note that the sensitivity of FDG-PET is low for lesions that are smaller than 1 cm; mediastinal lymph node sampling, by methods such as endobronchial ultrasound or mediastinoscopy, might be needed to ensure adequate staging.

Early-stage NSCLC

5 year survival for patients with stage I NSCLC is roughly 80%, and patients with stage II to stage III disease have a 5 year survival of 13–60%.[61] The standard of care for patients with stage I, stage II, and some stage IIIA disease is surgical resection. The addition of adjuvant chemotherapy in patients with stage II, stage IIIA, or selected stage IB disease can improve survival by 5–10%, but it is associated with substantial toxicities.[62] The opportunity for improving survival is pronounced in early-stage disease and is driving studies integrating targeted therapies and ICIs.

Resectable disease

Surgery

Video-assisted thoracoscopic surgery (VATS) is increasingly used as an alternative to open thoracotomy for patients having surgery for the management of early-stage NSCLC that is resectable. Compared with thoracotomy, VATS has shown reduced short-term morbidity over the first year in two RCTs,[63,64] with similar long-term oncological outcomes in a third RCT.[65]

There has been increasing use of uniportal VATS[66] and robotic VATS. Uniportal VATS uses a single incision, rather than the traditional two to three ports. Studies of uniportal VATS are small and from single institutions, but they report that uniportal VATS reduce postoperative pain, shorten duration of surgery, and shorten duration of chest tube drainage when compared with multiportal VATS.[67–69] Robotic VATS has similar outcomes to uniportal and multiportal VATS, but has resulted in more surgeons practising and, therefore, more patients benefiting from VATS.[70,71]

Anatomical resection (eg, lobectomy) is the gold standard in surgical approach for patients with stage I or stage II disease, driven by a single RCT,[72] which showed an increase in local recurrence in patients receiving sublobar resections. In the two decades since this RCT, preoperative imaging technology has improved, as have intraoperative techniques. Along with the increasing incidence of small and partial solid peripheral adenocarcinomas, this RCT[72] might no longer reflect modern practice.[73] Extrapolating from more contemporary retrospective analyses of patients with T1aN0M0 NSCLC is challenging as many patients have sublobar resection because they are physiologically unable to tolerate a lobectomy, thus have competing risks for increased mortality.[74–77] There are two ongoing RCTs assessing the efficacy of lobectomy versus sublobar resection in patients with T1a NSCLC (NCT00499330 and NCT03066297). Until the results are published, lobectomy is the gold standard in treatment for stage I and stage II NSCLC.

Radiotherapy

Resection is the standard of care for patients with stage I NSCLC;[72,74] however, if patients are medically inoperable, fractionated radiotherapy for 4–6 weeks was viewed as an alternative. In the phase 3 CHISEL trial, stereotactic ablative body radiotherapy (SABR), in which high doses of radiotherapy are given during one to five fractions, has been shown to reduce local treatment failures for patients with medically inoperable stage I NSCLC compared with standard radiotherapy (9 of 66 [14%] patients had treatment failure *vs* 11 [31%] of 35, HR 0·32, 95% CI 0·13–0·77, p=0·01).[78] Improved survival was also observed in patients receiving SABR compared with standard radiotherapy (5 years *vs* 3 years, 0·53, 0·30–0·94). SABR is now the preferred treatment method for patients with medically inoperable stage I disease. Currently, there are two trials comparing surgery with SABR for patients with operable stage I disease (NCT02468024 and NCT02984761).

Historically, postoperative radiotherapy was considered for completely resected NSCLC with mediastinal nodal disease.[79–82] Published in 1998, a meta-analysis of nine RCTs showed that there is neither harm nor benefit of postoperative radiotherapy in patients with mediastinal

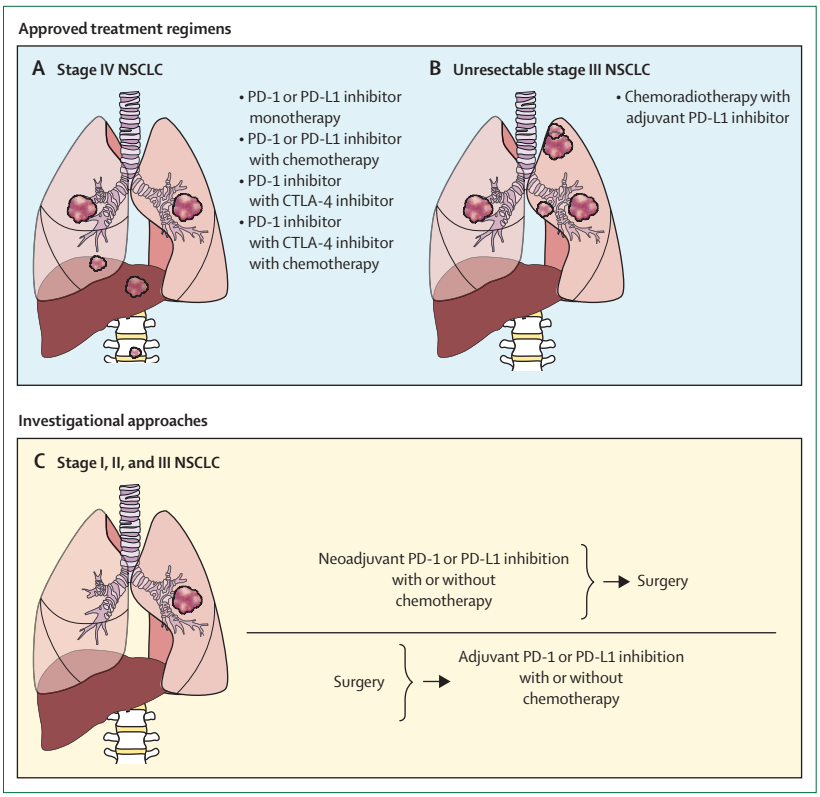

Figure 4: **Immunotherapy treatment approaches in NSCLC**
(A) Multiple regimens are approved for patients with stage IV NSCLC, on the basis of tumour histology and tumour PD-L1 expression. (B) For patients with unresectable stage III NSCLC, standard treatment consists of curative intent chemoradiotherapy and then 12 months of adjuvant PD-L1 inhibition. (C) It is hoped that benefit of immune checkpoint inhibitors in stage IV and stage III NSCLC can be shifted to earlier stage disease. Approaches being investigated include the use of neoadjuvant or adjuvant immune checkpoint inhibitors with or without chemotherapy. NSCLC=non-small-cell lung cancer.

nodal disease.[79] However, radiotherapy and surgical techniques have changed substantially since its publication. The Lung ART study[83] showed that postoperative radiotherapy does not provide a survival benefit for completely resected mediastinal nodal (N2)-positive NSCLC. Patients were randomly assigned to standard of care with or without postoperative radiotherapy. 3 year overall survival was 66·5% in the postoperative radiotherapy group and 68·5% in the observation group. Furthermore, more patients in the postoperative radiotherapy group died from cardiopulmonary causes than in the observation group (16 [16%] of 99 *vs* 2 (2%) of 102). The increased risk of cardiac toxicity from chest radiotherapy has been shown in the RTOG 0617 study,[84] which randomly assigned patients with unresectable stage III NSCLC to standard-dose (60 Gy) or high-dose (74 Gy) radiotherapy with concurrent chemotherapy. Patients receiving high-dose radiotherapy had poorer survival than those receiving standard-dose radiotherapy, and the higher heart dose was thought to cause this increased mortality. On the basis of these data, presented at conference proceedings, postoperative radiotherapy is not routinely recommended for completely resected mediastinal nodal disease; however, final publication of the study results are pending.

Neoadjuvant and adjuvant therapy

The use of neoadjuvant ICIs in patients with NSCLC is of particular interest as immune activation might be potentiated by the presence of neoantigens and intratumoural immune cells within the unresected cancer.[85–87] Neoadjuvant studies also present an opportunity for earlier assessment of efficacy compared with adjuvant studies (figure 4). Survival endpoints, such as overall survival, are considered the gold standard, but can take more than 10 years to mature.[88] Major pathological response, defined as less than or equal to 10% of viable residual tumour, is associated with a survival benefit in neoadjuvant chemotherapy trials and is an attractive surrogate endpoint, although, it is not currently recognised from a regulatory perspective and is yet to be validated in randomised trials.[88–92]

Studies have shown that 14–45% of patients had major pathological response when given neoadjuvant ICI therapy with agents such as atezolizumab, nivolumab, and durvalumab.[93–96] In a separate early-phase study, about 35 (80%) of 41 patients receiving neoadjuvant nivolumab and chemotherapy had a major pathological response.[97] There are numerous other studies also investigating the benefit of adjuvant ICIs.[98–106] Although survival outcomes are pending for these trials, interim results are promising.

Numerous studies are examining the role of adjuvant TKIs in early-stage oncogene-driven NSCLC (eg, *EGFR*-positive and *ALK*-positive NSCLCs).[107–109]

The ADAURA trial randomly assigned patients with resected stage IB–III *EGFR*-positive NSCLC to osimertinib or a placebo for up to 3 years after standard adjuvant chemotherapy.[110] The trial was unblinded early on the basis of the substantial improvements in disease-free survival with osimertinib.[111,112] Preliminary analyses showed a 2 year disease-free survival rate of 89% in the osimertinib group, compared with 53% in the placebo group (HR 0·21, 95% CI 0·16–0·28), but overall survival data are pending.[112]

Disease-free survival is often used as a surrogate endpoint in adjuvant trials, in which overall survival data require many years. However, a benefit in disease-free survival does not necessarily translate into an overall survival benefit. This was the case in an adjuvant *EGFR*-positive NSCLC study that randomly assigned patients to 24 months of gefitinib or four cycles of chemotherapy.[111] Therefore, it is not known whether adjuvant osimertinib is merely delaying residual disease progression. Regardless of this uncertainty, the compelling disease-free survival benefit seen with adjuvant osimertinib in *EGFR*-positive NSCLC after adjuvant chemotherapy is likely to change clinical practice. Currently, there is no evidence that adjuvant osimertinib can replace adjuvant chemotherapy in patients with resected *EGFR*-positive NSCLC.

Patients with unresectable stage III NSCLC have poor outcomes due to disease relapse.[61] Before now, the standard of care consisted of definitive chemoradiotherapy.[113,114] The most mature data of ICI therapy in stage III disease come from the PACIFIC study.[115–117] Progression-free survival (PFS) was significantly improved in patients receiving adjuvant durvalumab for 12 months after completion of chemoradiotherapy compared with patients receiving placebo (17·2 months *vs* 5·6 months, HR 0·51, 95% CI 0·41–0·63). Overall survival benefit was also significant; the 24 month overall survival rate was 66·3% in the durvalumab group and 55·6% in the placebo group.[115,116] A post-hoc analysis did not show a survival benefit in patients with PD-L1 expression of less than 1% on tumour cells, but this was an unplanned analysis of only a few patients and robust conclusions regarding this subgroup are difficult. Adjuvant durvalumab did not lead to an increase in side-effects.[115,116] The results from this trial represent the largest incremental improvement in survival for patients with stage III unresectable disease since chemoradiation and established the role of ICIs for patients with unresectable stage III NSCLC (figure 4). Studies examining the addition of other checkpoint inhibitors during or after chemoradiotherapy are ongoing.[118,119]

Metastatic NSCLC

EGFR mutations

EGFR mutations are the most common targetable driver mutations found in lung adenocarcinoma. There is marked geographical variation in prevalence, ranging from 15% in Europe to 62% in Asia.[120,121] *EGFR* exon 19 deletions and exon 21 Leu858Arg point mutations account for about 85% of somatic *EGFR* alterations and predict sensitivity to EGFR TKIs. By contrast, *EGFR* exon 20 insertions result in resistance to most EGFR TKIs.[122–125]

First-generation (eg, gefitinib and erlotinib) and second-generation (eg, afatinib and dacomitinib) EGFR TKIs have significantly improved PFS, and overall survival in the case of dacomitinib, compared with platinum-doublet chemotherapy in patients with sensitising *EGFR* mutations.[126–131] Overall survival benefit can be difficult to show in studies because nearly all studies will allow for crossover at disease progression.

Osimertinib is a third-generation EGFR TKI with activity against mutant EGFR and the most common *EGFR* TKI-resistance mutation, Thr790Met, found in approximately half of patients who have disease progression on earlier generation inhibitors.[132] Osimertinib has shown superior PFS compared with platinum and pemetrexed chemotherapy (10·1 months *vs* 4·4 months, HR 0·30, 95% CI 0·23–0·41) in patients who progressed on earlier generation TKIs and had the *EGFR*^{T790M} mutation and is well tolerated.[133–137]

Importantly, osimertinib had significant improvements in overall survival and had superior CNS activity, compared with erlotinib or gefitinib in patients with treatment-naive *EGFR*-positive NSCLC.[136–139] Median overall survival was 38·6 months (95% CI 34·5–41·8) for the group assigned to osimertinib versus 31·8 months (26·6–36·0) for the group assigned to erlotinib or gefitinib.[134,136,137] In subgroup analyses, no overall survival benefit was observed in patients with Asian ethnic origin or with exon 21 mutations; however, the study was not powered to analyse these subgroups. As such, these findings are hypothesis generating only, and osimertinib is the preferred first-line treatment for *EGFR*-positive NSCLC (figure 5).

To address the challenges of resistance and improve durability of response to EGFR TKIs, combination strategies with chemotherapy[166,167] and ICIs,[168,169] are being investigated. Improvement in survival was observed in patients in a phase 3 RCT in Japan; the median survival of treatment-naive patients receiving chemotherapy plus gefitinib was 50·9 months compared with 38·8 months for gefitinib alone (HR 0·72, p=0·02).[166] Unsurprisingly, severe adverse events were more common in the combination group (65% *vs* 31%), although the rate of treatment discontinuation was similar between groups. Similar interim results have also been shown in an RCT of gefitinib plus chemotherapy in India.[167] However, as the most up-to-date studies have resulted in osimertinib being the preferred first-line agent, we await the results from the combination of chemotherapy and osimertinib.[170] Some trials are addressing the challenge of optimal therapy in patients with osimertinib-resistant disease. Lazertinib, a third-generation EGFR TKI, and amivantamab, an EGFR-MET antibody, have also shown promising activity in early-phase trials when given alone, and in combination with each other, for patients who either have treatment-naive disease or are resistant to osimertinib.[171–173]

ALK gene rearrangements

ALK gene rearrangements lead to aberrant expression of constitutively active ALK fusion proteins and are found in 3–5% of patients with NSCLC (*ALK*-positive NSCLC; figure 1).[29,174,175] Crizotinib, a first-in-class ALK TKI,[176,177] was superior to cytotoxic chemotherapy in first-line and second-line settings in phase 3 trials, and produced unprecedented improvement in median overall survival in excess of 4 years as first-line therapy.[178]

CNS-penetrant second-generation ALK-TKIs that are more potent than crizotinib and have activity in crizotinib-resistant patients have been developed, including ceritinib,[179] alectinib,[143,180] brigatinib,[181] and ensartinib.[182,183] Three of these, alectinib,[143,180] brigatinib,[145] and ensartinib,[183] are superior to crizotinib as first-line therapy with improved median PFS (figure 5). Alectinib and brigatinib have received FDA approval for the upfront treatment of *ALK*-positive NSCLC. Investigator assessed median PFS is 34·8 months (95% CI 17·7 to not reached) for alectinib, and estimated to be 24 months (18·5 to not reached) for brigatinib.[143,145] An update from

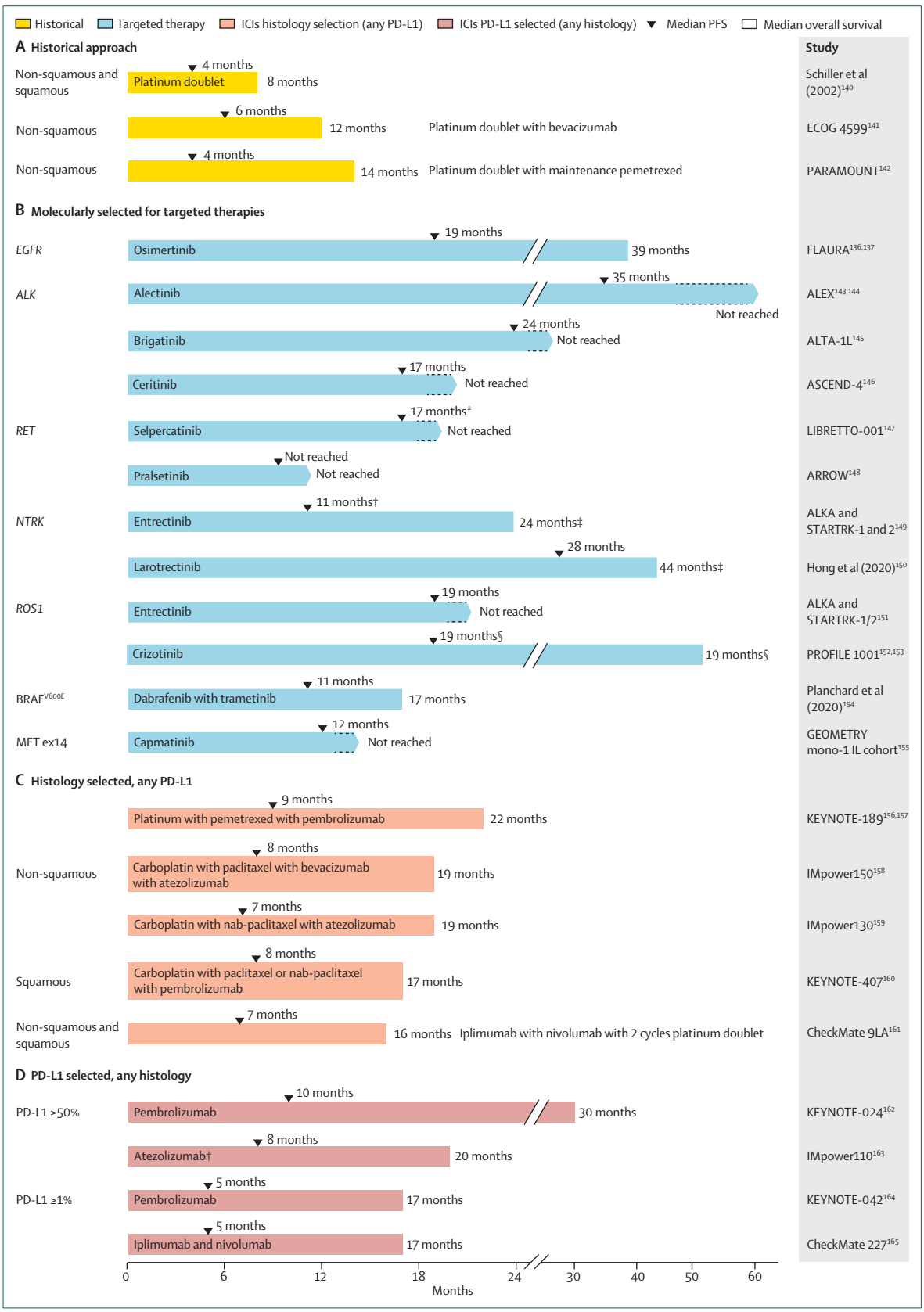

***Figure 5*: Selected US Food and Drug Administration approved therapies for upfront treatment of patients with metastatic NSCLC**

(A) Historically, platinum-doublet chemotherapy was given irrespective of NSCLC histology. Subsequent cytotoxic regimens were identified that benefited the treatment of non-squamous NSCLC. (B) The discovery of somatic oncogenic driver mutations in some NSCLC tumours and the development of targeted therapies led to substantial gains in PFS and overall survival for these patients. The number of approved agents for specific targets is growing rapidly. (C) Chemoimmunotherapy regimens have been approved for squamous and non-squamous NSCLC, irrespective of PD-L1 expression. (D) Single-agent immune checkpoint inhibitors and dual blockade with ipilimumab and nivolumab are approved on the basis of tumour PD-L1 expression. Additional details about the studies can be found in the appendix (pp 3–4). This is a select list of US Food and Drug Administration approved agents only. There are other agents and combinations with documented activity. *BRAF*^{V600E}=*BRAF* Val600Glu mutation. ICI=immune checkpoint inhibitor. NSCLC=non-small-cell lung cancer. PFS=progression-free survival. *Median PFS in previously treated patients is 17 months (95 CI 14 to not recorded); median PFS in patients who had been previously treated was not reached. †Also approved for PD-L1-positive tumour-infiltrating immune cells 10% or more of tumour area. ‡PFS and overall survival data of patients with *NTRK*-positive tumours, including NSCLC, inclusive of patients who had been previously treated. §PFS and overall survival data of patients with treatment-naive and previously treated disease with *ROS1*-positive NSCLC.

Peters and colleagues[144] reported the 5 year overall survival rate was 62·5% in patients receiving alectinib.

Recently, a novel third-generation ALK TKI that can pass the blood–brain barrier, lorlatinib, has entered the clinic and shown broader activity against *ALK*-resistance mutations than second-generation ALK TKIs, including *ALK* Gly1202Arg, which confers resistance to crizotinib and second-generation inhibitors.[184–186] Lorlatinib has also been shown to improve PFS compared with crizotinib (not reached *vs* 9·3 months, HR 0·28, 95% CI 0·19–0·41) in the phase 3 CROWN study.[187] Lorlatinib is well tolerated; cognitive effects and peripheral neuropathy are common but are generally mild and are effectively managed with dose modification and supportive treatment.

Other oncogene driver alterations

ROS1

ROS1 rearrangements are found in roughly 1–2% of NSCLCs (figure 1).[19] Crizotinib was the first drug with clinical activity in *ROS1*-positive NSCLC. Median PFS (in patients with treatment-naive disease or who have had chemotherapy) was between 15·9 months and 19·3 months (figure 5).[152,153,188] Additional ROS1 inhibitors, such as entrectinib, lorlatinib, and repotrectinib, have increased CNS activity and have been evaluated in clinical trials.[189–194]

Entrectinib, an inhibitor of the neurotrophic tropomyosin receptor tyrosine kinases (NTRKs), ROS1, and ALK, has shown systemic and intracranial activity in patients with *ROS1*-positive NSCLC, with an overall response rate of nearly 80% and median PFS of 19 months (figure 5).[151] Crizotinib and entrectinib are FDA approved for the treatment of *ROS1*-positive NSCLC. More potent inhibitors than crizotinib and entrectinib, such as lorlatinib and repotrectinib, have also shown activity and have overcome various resistance mechanisms that develop in patients who have crizotinib-resistant *ROS1*-positive NSCLC.[195–198]

BRAF

Activating mutations in *BRAF* are found in roughly 4% of NSCLC (figure 1), but only half of these cases involve alterations in the Val600Glu residue.[31,32,199] Although initial trials have shown that there was activity of single-agent BRAF inhibitor in patients with $BRAF^{V600E}$-positive NSCLCs, combination therapy with BRAF and MEK inhibition resulted in higher response rates (overall response rate [ORR] roughly 60%) and longer median PFS (about 10 months; figure 5).[154,200–203] Side-effects observed were consistent with previous melanoma studies.[202–204]

NTRK

NTRK gene fusions can lead to oncogenic fusion proteins and are found in about 1% of patients with NSCLC (figure 1).[205] Two TRK inhibitors, larotrectinib and entrectinib, have received accelerated approval by the FDA for *NTRK*-positive solid cancers (figure 5). In phase 1 and 2 trials with larotrectinib, an ORR of 79% (95% CI 72–85) with median duration of response of 35·2 months (22·8 to not reached)[206,207] was observed in patients whose tumours harboured *NTRK* fusions.[150,208,209] Entrectinib showed an ORR of 57% (43·2–70·8) and median duration of response of 10 months (7·1 to not reached).[149] The efficacy of these drugs in *NTRK*-positive NSCLC appears similar to the overall efficacy across tumour types and was independent of fusion partner.[210,211] The most common serious side-effects observed were elevation in hepatic aminotransferases concentrations, fatigue, and cognitive impairment, which were seen in less than 5% of patients in either agent.[149,212]

MET

Oncogenic *MET* activation in lung cancer can occur with *MET* exon 14 skipping mutations, which reduces the degradation of the MET protein (figure 1), or with *MET* gene amplification.[33,213,214]

Capmatinib and tepotinib, both of which are MET inhibitors with intracranial activity, have been granted accelerated FDA approval for the treatment of NSCLC with *MET* exon 14 skipping mutations.[155,215] Capmatinib has shown an ORR of 68% (95% CI 48–84) and median duration of response of 12·6 months (29–53) in patients with treatment-naive disease; responses, albeit lower than in patients with treatment-naive disease, have also been seen in patients with pretreated disease (figure 5). An ORR of 44% (29–60) in patients with treatment-naive disease was reported for tepotinib and the median duration of response, reported for all patients regardless of previous therapy, was 11·1 months (7·2 to not reached).[216]

RET

RET rearrangements are found in 1–2% of lung adenocarcinomas (figure 1). New RET TKIs have been developed with more activity and less toxicity than multitargeted kinase inhibitors, such as cabozantinib. A phase 1/2 trial of selpercatinib (LOXO-292), a RET-specific TKI, showed an ORR of 64% for patients previously given chemotherapy and 85% for patients who had not been previously treated. Median PFS was 16·5 months in the pretreated group and was not reached in the treatment-naive group (figure 5).[147] The most common severe side-effects were hypertension and elevated concentrations of liver aminotransferases. Selpercatinib has received accelerated approval by the FDA. Pralsetinib (BLU-667) is another potent and selective RET TKI that has been approved by the FDA for patients with metastatic *RET*-positive NSCLC. Pralsetinib has shown an ORR of 73% in patients with treatment-naive disease and 61% in patients who have been previously treated.[148,217]

Emerging targets

The success of the targeted therapies described in this Seminar has led to ongoing efforts to identify and therapeutically target other driver mutations. We discuss

two emerging targets, HER2 (also known as ERBB2) and KRAS, but others, such as *NRG* rearrangements, are being examined.[218]

HER2

Two antibody drug conjugates, trastuzumab deruxtecan and trastuzumab emtansine, have shown activity in patients with NSCLC with *HER2* mutations. Trastuzumab deruxtecan has been granted breakthrough therapy designation by the FDA.[219–221] Responses were observed in 61·9% of patients receiving trastuzumab deruxtecan (95% CI 45·6–76·4) with an estimated PFS of 14 months.[219,222] In a trial of trastuzumab emtansine in patients that had previously been heavily treated, responses were observed in 31% of patients (18–47) with a median PFS of 5 months.[223] The role of these agents in NSCLC with HER2 protein overexpression is being investigated.[223,224]

KRAS

KRAS mutations are found in about 25% of patients with lung adenocarcinomas.[225] Targeting *KRAS* mutations is challenging,[225,226] but unique properties of the *KRAS* Gly12Cys mutation led to the development of novel compounds AMG510, MRTX849, and other *KRAS* Gly12Cys inhibitors. These agents bind to a groove on KRAS Gly12Cys and lock the protein in its inactive GDP-bound state, thereby inhibiting dependent signalling.[227–229] AMG510 and MRTX849 have entered early-phase clinical trials, with initial reports indicating activity in approximately 30–50% of patients.[228–230] Novel combinations with SHP2 inhibitors, EGFR TKIs, and ICIs are also being evaluated.

ICIs

Targeting negative regulators of the immune response, known as immune checkpoints, has transformed the treatment for many cancers.[231–235] Two immune checkpoints with known activity in NSCLC are CTLA-4 and the PD-1 axis. CTLA-4, typically expressed on CD4-positive and CD8-positive T lymphocytes, provides an early inhibitory signal preventing T-cell activation. PD-1, expressed on T cells, B cells, and natural killer cells, has a role in modulating central and peripheral immune tolerance. PD-L1 can be upregulated on tumour cells as a means of immune escape by providing a negative immune regulatory signal (figure 3A).[236]

NSCLC was thought to be poorly immunogenic; however, anti-PD-1 and anti-PD-L1 antibodies consistently showed superior patient survival compared with second-line chemotherapy,[237–240] and have emerged as important therapies in patients with treatment-naive NSCLC (figure 4).[237–240]

Single-agent checkpoint inhibitor trials

Study populations of anti-PD-1 and anti-PD-L1 monotherapy trials were defined with PD-L1 tumour expression as a predictive biomarker (figure 5). Two agents, pembrolizumab and atezolizumab, are approved for upfront treatment of patients with NSCLC and PD-L1 expression in greater than or equal to 50% of tumour cells, and tumour-infiltrating immune cells of 10% or more for atezolizumab.[162–164,227,241] Median overall survival of patients assigned to pembrolizumab was superior to those assigned to platinum-doublet chemotherapy in a phase 3 RCT that only enrolled patients with PD-L1 expression in 50% or more tumour cells (26·3 months *vs* 14·2 months, HR 0·62, 95% CI 0·48–0·81).[162,241]

Two trials compared atezolizumab (IMpower110) or pembrolizumab (KEYNOTE-042) to chemotherapy in patients with 1% or more tumour PD-L1 expression. The survival benefit observed in the ICI groups was most pronounced in the greater or equal to 50% subgroup.[163,164] In these trials, severe treatment-related adverse effects were less frequent with immunotherapy (13–27% in the immunotherapy group *vs* 41–53% in the chemotherapy group).

Cemiplimab, an anti-PD-1 antibody, has also shown superior overall survival and PFS in patients with metastatic NSCLC with 50% or more PD-L1 tumour expression compared with chemotherapy and is in priority review by the FDA.[242] Two other studies investigating first-line nivolumab and durvalumab did not show a survival benefit compared with chemotherapy for various postulated reasons, including the use of different PD-L1 cutoffs and differences in patient characteristics between treatment groups.[243,244]

Chemotherapy and PD-1 or PD-L1 pathway blockade

In contrast to studies of single-agent ICIs, trials of chemotherapy with PD-1 and PD-L1 antibodies enrolled patients regardless of PD-L1 tumour expression (figure 5). In studies of non-squamous NSCLC, the combination of PD-1 or PD-L1 antibodies and platinum chemotherapy is superior to chemotherapy alone.

Median overall survival was longer in the pembrolizumab plus chemotherapy group than in the chemotherapy group; in the phase 3 KEYNOTE-189 trial, median survival was 22·0 months in the pembrolizumab plus chemotherapy group versus 10·7 months in the chemotherapy group (HR 0·56, 95% CI 0·45–0·70).[156,157,245] Improvements in overall survival were seen across all PD-L1 expression subgroups, including the subgroup with PD-L1 expression less than 1%. Combination treatment also resulted in a significantly higher response rate of 47·6% (42·6–52·5) compared with 18·9% (13·8–25·0) in the chemotherapy group. Severe treatment-related adverse effects, an initial concern with chemoimmunotherapy, were similar in both groups. Both sintilimab, an anti-PD-1 antibody, and sugemalimab, an anti-PD-L1 antibody, combined with chemotherapy have shown superior PFS compared with chemotherapy alone in randomised phase 3 trials in China.[246,247]

The addition of atezolizumab to chemotherapy also shows activity in untreated non-squamous NSCLC.[159,166,248] Patients receiving combination therapy of atezolizumab, carboplatin, paclitaxel, and bevacizumab (ABCP) had better survival than those receiving combination therapy of bevacizumab, carboplatin, and paclitaxel (BCP; 19·2 months *vs* 14·7 months, HR 0·78, 95% CI 0·64–0·96).[248] Of patients receiving ABCP, 56% had severe treatment-related adverse effects, compared with 48% in the BCP group.[248] In another study, IMpower130, the addition of atezolizumab to carboplatin and nab-paclitaxel also improved overall survival compared with chemotherapy alone (18·6 months *vs* 13·9 months, HR 0·79);[159] however, atezolizumab with carboplatin (or cisplatin) and pemetrexed for patients with non-squamous NSCLC improved PFS but did not show an overall survival benefit.[249] Nivolumab plus chemotherapy was not better than chemotherapy alone in patients with NSCLC regardless of PD-L1 expression.[250]

Chemotherapy plus pembrolizumab, ABCP, and carboplatin with nab-paclitaxel and atezolizumab have received FDA approval for the first-line treatment of patients with non-squamous NSCLC with no *EGFR* or *ALK* alterations (figure 5).

For patients with squamous histology, KEYNOTE-407 has shown improved response and survival in patients receiving treatment with chemotherapy (carboplatin with either paclitaxel or nab-paclitaxel) and pembrolizumab compared with chemotherapy alone.[160] In the chemoimmunotherapy group, the response rate was 57·9% (95% CI 51·9–63·8) and the median overall survival was 15·9 months (13·2 to not reached) compared with 38·4% (32·7–44·4) and 11·3 months (9·5–14·8) in the chemotherapy only group (figure 5). In the IMpower131 study, the addition of atezolizumab with chemotherapy did not improve overall survival compared with chemotherapy only in patients with squamous NSCLC.[160]

It is unclear whether patients with oncogene-driven lung cancer respond to immunotherapy. In IMpower150, a potential survival benefit was seen in patients with sensitising *EGFR* mutations receiving ABCP when compared with BCP,[158] but this subgroup was small and a separate trial of atezolizumab with carboplatin and nab-paclitaxel did not show a survival benefit for patients with *EGFR*-positive NSCLC.[159] Furthermore, retrospective analyses have shown that single-agent anti-PD-1 and anti-PDL1 antibodies are largely ineffective for patients with oncogene driven NSCLC.[251,252]

ICI combinations

In metastatic melanoma, combinations of anti-CTLA4 and anti-PD1 or anti-PD-L1 antibodies improve overall response and survival compared with monotherapy.[253–255] The trial compared nivolumab plus ipilimumab to chemotherapy in patients with untreated NSCLC.[165,256] Combination therapy improved the survival of patients regardless of tumour PD-L1 expression (PD-L1 <1%: overall survival 17·2 months *vs* 12·2 months, HR 0·62, 95% CI 0·48–0·79; PD-L1 ≥1%: 17·1 months *vs* 14·9 months, 0·79, 0·65–0·96).[165] Ipilimumab with nivolumab has been FDA approved for upfront treatment of patients with metastatic NSCLC with 1% tumour PD-L1 expression or more (figure 5). Approval did not extend to the less than 1% PD-L1 expression subgroup as it was an exploratory endpoint. Severe treatment-related adverse events were similar between the two groups but toxicities leading to discontinuation were higher in the ICI group (18·1% *vs* 9·1%).

In Checkmate 227, a subset of patients had rapid progression. To mitigate these events, Checkmate 9LA explored combining nivolumab and ipilimumab with two cycles of platinum-doublet chemotherapy. This combination was better than chemotherapy, regardless of tumour PD-L1 expression (PD-L1 <1%: HR 0·62, 95% CI 0·45–0·85; PD-L1 ≥1%: 0·64, 0·50–0·82). As expected, severe treatment-related adverse events were higher in the combination group compared with the chemotherapy only group (47 *vs* 38%).[161] The FDA has approved the combination of ipilimumab and nivolumab with two cycles of chemotherapy for patients with NSCLC (figure 5). By contrast, durvalumab with tremelimumab did not improve PFS or overall survival compared with chemotherapy alone in the MYSTIC trial.[244] No survival benefit was shown in a separate study of durvalumab and tremelimumab plus chemotherapy versus durvalumab and tremelimumab.[257]

In aggregate, these data show that ICIs are important in the initial management of metastatic NSCLC. Currently, in patients with tumours expressing 50% PD-L1 or more, pembrolizumab or atezolizumab monotherapy, chemo-immunotherapy, or dual immune checkpoint blockade with or without chemotherapy can be used. Based on available data, one common approach is to use single-agent PD-1 or PD-L1 pathway blockade in patients without rapidly progressive or symptomatic disease.

For patients with tumours expressing less than 50% PD-L1, chemotherapy plus PD-1 or PD-L1 blockade is the standard approach. Despite approval for pembrolizumab monotherapy, it is seldom used as the benefit is mostly observed in patients with 50% tumour or more PD-L1 expression. Nivolumab and ipilimumab with chemotherapy is also approved for patients regardless of PD-L1 expression, and nivolumab plus ipilimumab is also available for patients with tumour PD-L1 of 1% or more.

Immune-mediated toxicities

Unique toxicities associated with ICI therapy arise from immunological enhancement and can occur at any point during or after treatment, which is an important consideration as ICIs can be given for up to 2 years. The incidence of serious immune-related adverse events is 3–6% in patients with NSCLC receiving PD-1 and PD-L1

inhibition[258] and it increases with ICI combination approaches.[259] If managed appropriately, immune-related adverse events are usually transient but, in rare cases, they can be life threatening.

Immunosuppression, typically with local or systemic corticosteroids, and ICI cessation, is the mainstay treatment of moderate to severe immune-related adverse events.[260,261] Guidelines for the diagnosis and management of immune-related adverse events have been developed by the American Society of Clinical Oncology, the European Society for Medical Oncology, and the Society for Immunotherapy of Cancer.[260–262]

Duration of therapy

The optimal duration of anti-PD-1 and PD-L1 antibody therapy is yet to be defined. Results from an exploratory endpoint in the Checkmate 153 trial show that overall survival is longer in patients with stable or responding disease who continue nivolumab compared with patients who stopped at 12 months (not reached *vs* 32·5 months, HR 0·61, 95% CI 0·37–0·99).[263] The results of the study are informative, but the analysis was an exploratory endpoint only. Outcomes from two earlier trials showed excellent survival in patients who completed 24 months of nivolumab and pembrolizumab.[264,265] Only some patients progressed on cessation and most responded to treatment upon rechallenge. Therefore, current data supports ICI treatment for at least 2 years for patients who maintain disease stability or response on therapy.

SCLC

SCLC is characterised by its rapid growth, tendency to metastasize, and poor survival rates. SCLC is staged as limited-stage SCLC, in which disease is contained within the hemithorax and considered curable, and extensive-stage SCLC, in which disease extends beyond the hemithorax and is usually managed with chemoimmunotherapy with or without consolidative radiation.[266,267] Limited-stage SCLC is managed with chemoradiotherapy and then prophylactic cranial irradiation. In a study by Peters and colleagues,[268] the addition of nivolumab with ipilimumab as consolidation therapy did not improve PFS compared with observation in patients with limited-stage SCLC who completed chemoradiotherapy and prophylactic cranial irradiation. There are several other studies assessing the efficacy of chemoradiotherapy with or without consolidative ICI.[269,270]

The first-line management of extensive-stage SCLC has been platinum with etoposide; however, ICIs have altered the treatment for this disease.[271–273] Three studies have examined the benefit of the addition of an anti-PD-1 or anti-PD-L1 antibody to platinum and etoposide treatment for extensive-stage SCLC.[274–278] Of these treatments, the addition of atezolizumab or durvalumab to chemotherapy resulted in superior overall survival compared with platinum and etoposide treatment. Overall survival of pembrolizumab plus platinum and etoposide did not reach the prespecified significance threshold compared with chemotherapy alone.[278]

IMpower133 randomly assigned patients with untreated extensive-stage SCLC to four cycles of platinum and etoposide with or without atezolizumab, and the CASPIAN study randomly assigned patients to platinum and etoposide with or without durvalumab. Patients continued on maintenance ICI or placebo until progressive disease. In the IMpower133 study, the median overall survival was 12·3 months in the atezolizumab group and 10·3 months in the placebo group (HR 0·76, 95% CI 0·60–0·95; p=0·0154).[279] Similar improvements in overall survival were seen in the CASPIAN study. Rates of grade 3 or worse toxicities were equivalent in both groups. The addition of atezolizumab or durvalumab to platinum and etoposide has been approved by the FDA.[276,277] PD-L1 is not a predictive biomarker of response to ICIs in SCLC.[275,280]

In the second-line setting, topotecan has been the only FDA approved agent.[281–283] In a phase 3 RCT, nivolumab was not shown to be better than topotecan.[285] Lurbinectedin has shown activity in the second-line setting in a phase 2 study, and has received accelerated approval by the FDA; however, lurbinectedin with doxorubicin did not show a survival benefit compared with standard second-line chemotherapy in a phase 3 study.[285,286] Poly (ADP-ribose) polymerase inhibitors with chemotherapy have also shown promising activity in early-phase studies of relapsed SCLC.[287–289] Although there is clearly a need to improve the outcomes of patients with SCLC, the study results, particularly with ICIs, have made great steps in the right direction.

Conclusions

The past decade in lung cancer research has been characterised by a greater understanding of cancer biology, acceleration in drug development, and application of therapies to early-stage disease. The substantial improvements in survival in the studies discussed in this Seminar, importantly, translate into improved survival in the clinical setting. However, there are ongoing challenges. Smoking rates are high and the introduction of electronic cigarettes is problematic; the relationship of electronic cigarettes with lung cancer is unclear but there is concern over their popularity and the renormalisation of smoking behaviour. Furthermore, many agents described in this Seminar are not affordable in most parts of the world. The cost of drugs poses substantial challenges for individuals and health-care systems and, as a result, equitable access to drugs vary among countries. Despite these challenges, the outlook for patients is improving.

Contributors

All authors drafted the article outline, prepared the manuscript, and contributed to the literature research and assessment. AAT, BJS, JFG, and RSH prepared the figures. All authors contributed to the revision and final approval of the manuscript.

Declaration of interests

BJS reports personal fees from Pfizer, Novartis, Roche/Genentech, AstraZeneca, Merck, Bristol Myers Squibb, Amgen, and Loxo Oncology outside the submitted work. JFG has served as a consultant or received honoraria from Bristol-Myers Squibb, Genentech, Ariad/Takeda, Loxo/Lilly, Blueprint, Oncorus, Regeneron, Gilead, Helsinn, EMD Serono, AstraZeneca, Pfizer, Incyte, Novartis, Merck, Agios, Amgen, and Array; has had research support from Novartis, Genentech/Roche, Ariad/Takeda, Bristol-Myers Squibb, Tesaro, Moderna, Blueprint, Jounce, Array Biopharma, Merck, Adaptimmune, and Alexo; and has an immediate family member who is an employee of Ironwood Pharmaceuticals. LVS reports grants and personal fees from AstraZeneca; grants from Novartis and Boehringer Ingelheim; grants and consulting fees from Genentech Blueprint and Merrimack Pharmaceuticals; and consulting fees from Janssen and grants from LOXO, all outside the submitted work. LVS has a patent about treatment of *EGFR*-mutant cancer pending. RSH reports honoraria from Novartis, Merck KGaA, Daichii Sankyo, Pfizer, Roche, Apollomics, Tarveda, and Boehringer Ingelheim; and grants from Novartis, Genentech Roche, Corvus, Incyte, Exelixis, Abbvie, Daichii Sankyo, Agios, Mirati, Turning Point, and Lilly when writing this Seminar. AAT declares no competing interests.

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