Lung cancer: current therapies and new targeted treatments

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Lung cancer is the most frequent cause of cancer-related deaths worldwide. Every year, 1·8 million people are diagnosed with lung cancer, and 1·6 million people die as a result of the disease. 5-year survival rates vary from 4–17% depending on stage and regional differences. In this Seminar, we discuss existing treatment for patients with lung cancer and the promise of precision medicine, with special emphasis on new targeted therapies. Some subgroups, eg—patients with poor performance status and elderly patients—are not specifically addressed, because these groups require special treatment considerations and no frameworks have been established in terms of new targeted therapies. We discuss prevention and early detection of lung cancer with an emphasis on lung cancer screening. Although we acknowledge the importance of smoking prevention and cessation, this is a large topic beyond the scope of this Seminar.

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Introduction

Every year, 1·8 million people are diagnosed with lung cancer and 1·6 million die of the disease.[1] 5-year survival in populations with lung cancer varies from 4–17% depending on stage and regional differences.[2] Much progress has been made in research, lung cancer screening, and personalised therapy (precision medicine) in recent years.

Early lung cancer detection using spiral CT

The National Lung Screening Trial (NLST)[3] enrolled 53 000 individuals aged 55–74 years with a 30-pack-year smoking history. Participants were randomly assigned to radiography or low-dose CT and screened at baseline with two annual follow-up scans. Maximum follow-up lasted for 7 years. The low-dose CT group had a 20% reduction in lung cancer mortality and a 6·7% reduction in all-cause mortality.[3] The high rates of false-positive findings (27% at baseline, 28% at 1-year follow-up, 16·6% at 2-year follow-up) were concerning (table 1).[3]

The International Early Lung Cancer Action Program retrospectively analysed the outcomes of more than 21 000 prospectively enrolled patients who underwent lung cancer screening after the completion of the NLST.[6] Different size thresholds for nodule diameter resulted in different cancer diagnosis rates. Increasing the threshold from 5·0 mm to 6·0, 7·0, 8·0, or 9·0 mm also changed the frequencies of positive results. Depending on where the size threshold was reset from 5·0 mm, the diagnostic work-up frequency could be reduced by 36% for 6·0 mm, 56% for 7·0 mm, 68% for 8·0 mm, or 75% for 9·0 mm. With annual screening, the resultant delay in eventual diagnosis was not associated with a reduction in curative-intent surgery.[6]

In NELSON,[4] a Dutch and Belgian randomised screening trial, a two-part criterion for potential cancer was tested using analysis of the diameter change of a nodule. Of the 7155 prospective participants in the CT screening group, the sensitivity of CT screening was 92·4% and the specificity was 90·0%, which suggests that efficient case detection was feasible. In the UK Lung Cancer Screening Trial,[5] for the 2028 patients randomly assigned to CT screening, 536 patients had nodules greater than 5 mm in diameter, and 41 of the 536 patients had lung cancer. The false-positive rate was reported to be 3·6%.[5]

The American College of Radiology (ACR) proposed Lung-RADS, a classification system similar to the system that the ACR use for breast cancer screening, in order to standardise the routine clinical management of lung cancer detection.[7] When this approach was retrospectively applied to the NLST data, they revealed a proportion of false-positive results at baseline of 12·8%, in contrast to 26·6% reported by the NLST.[8] The corresponding false-positive proportion after baseline was 5·5% for Lung-RADS, versus 21·8% for NLST.[8] These efforts suggest lung cancer screening management can be delivered with greater efficiency than the approach used 10 years ago in the NLST.[3]

Other changing aspects of CT screening include the use of lower medical radiation doses for imaging.[9] Updates to the international lung cancer pathology classification have improved delineation of the types of lung processes associated with invasive versus benign clinical behaviour.[10] A review[11] of the outcomes of 57 496 international screening cases substantiated the indolent behaviour of non-solid pulmonary nodules, and suggests that, in this setting, a more conservative approach to surgical resection is appropriate. This finding complements a number of reports about better management of screen-detected lung cancer and reducing the potential for surgical overtreatment.[12,13]

The UK Lung Cancer Screening Trial[5] reported the cost-effectiveness of one-time screening was £8466 per quality-adjusted life-year. This is similar to the robust actuarial cost projection for lung cancer screening in the USA.[14] Inclusion of best-practice tobacco cessation

Search strategy and selection criteria

We did our primary search from Nov 1, 2015, to Jan 31, 2016, with continuous monitoring of the literature until June 30, 2016. Searches were done in PubMed in English using the phrase "lung cancer" in combination with "early stage", "advanced stage", "targeted therapy", and "immunotherapy". Relevant studies were chosen based on the expertise of the co-authors. Additional reports were taken from international conferences in the USA, Europe, and Asia.

	Stage I (%)*	Round 1			Round 2		
		Total patients screened (n)	Cancer diagnoses (n)	Proportion of patients diagnosed with cancer (%)	Total patients screened (n)	Cancer diagnoses (n)	Proportion of patients diagnosed with cancer (%)
National Lung Screening Trial[3]	66	24 715	168	0·67	24 102	211	0·87
NELSON[4]	73·7	7289	40	0·5	7289	57	0·8
UK Lung Cancer Screening Trial[5]	66·7	2028	34	1·7	2028	8	0·4

*Proportion of detected cancers that were stage I. Results are from the first year of screening, except for NELSON, in which round 2 and 3 screening data are presented together, reflecting the study design.

Table 1: **Cancer detection and frequency of stage I cancer detection in clinical trials**

services in the screening process reduces the overall health-care cost by about a third.[14] However, a 2015 survey[15] of US screening centres suggested that only 36·6% of these sites were prepared to provide optimal intensity tobacco cessation services.

Under the provisions of the Affordable Care Act, public and private insurers in the USA are required to cover the cost of recommended cancer screening services without cost to the consumer.[12] As evidence for screening increases and favourable cost data emerge, international interest in this new service is spreading, as reflected by reports outlining national lung cancer screening guidelines for China and Canada.[16,17] Biomarker testing is also an area of intense ongoing interest. However, further research into improving screening efficiency is key to optimisation of its potentially great but fragile benefit.[18] To reduce financial stress on health-care systems, screening should be delivered with integrated tobacco cessation.

Treatment of early-stage lung cancer

Surgery is the recommended treatment for patients with stage I–II non-small-cell lung cancer (NSCLC).[19] 5-year survival is 77–92% for clinical stage IA, 68% for stage IB, 60% for stage IIA, and 53% for stage IIB. By pathological stage, 5-year survival is 80–90% for stage IA, 73% for stage IB, 65% for stage IIA, and 56% for stage IIB.[20] Results of large meta-analyses[21] have shown that video-assisted techniques give better quality of life and long-term outcomes compared with open lobectomy, and studies in stage I disease show equal or better survival after video-assisted techniques. The role of perioperative chemotherapy has been addressed in many randomised studies,[22] and a meta-analysis[23] found a survival benefit for patients with stage IB–IIIA disease, with a reduced hazard ratio (HR) of 0·83–0·92 and absolute survival benefits of 5·4–6·9% at 5 years. In a pooled analysis by the Lung Adjuvant Cisplatin Evaluation collaborative group,[22] the 5-year survival for the control group was 87·7% (including all-cause mortality). The role of targeted therapies in this setting is not defined.[24,25] Results of a large randomised trial (ECOG 1505) showed no benefit to using adjuvant bevacizumab in unselected early stage patients.[26] Results from the large prospective placebo-controlled RADIANT study[24] showed no benefit from the use of adjuvant epidermal growth factor receptor tyrosine kinase inhibitor (EGFR TKI) erlotinib; however, the study was not designed specifically for patients with tumours harbouring *EGFR* mutations.[24] Results of other studies have shown no effect of EGFR TKIs as adjuvant therapy in unselected patients.[25] Ongoing large prospective studies (eg, the ALCHEMIST screening trial, NCT02194738) and other studies are investigating the role of EGFR TKIs in the *EGFR*-mutant population, ALK inhibitors in the *ALK*-positive population, and immunotherapy in the non-biomarker-selected population.[27,28]

For patients with clinical stage I NSCLC who have medical contraindications to surgical resection or who refuse surgery, high-dose stereotactic body radiation therapy resulted in high local tumour control and low toxicity. Although there are no randomised data comparing stereotactic body radiation to other non-operative first-line approaches such as radiofrequency ablation, standard radiotherapy, and chemotherapy, several phase 2 trials cite local tumour-control rates of more than 85% at 5 years.[29,30] Stereotactic body radiation uses highly sophisticated planning and delivery technology, and the most common regimen delivers three fractions of 18·0 Gy, each to the target volume.

For patients with locally advanced NSCLC (stages IIIA–B) not amenable to surgical resection, and with good performance status, the current standard of care involves a 6-week course of thoracic radiotherapy with the concurrent delivery of doublet chemotherapy using either cisplatin or carboplatin and a second drug per week or every 3 weeks.[31,32] The recommended total radiotherapy dose is 60–66 Gy, and best practice includes CT-based planning and the use of either three-dimensional planning and delivery or intensity modulated radiation therapy.[33] No targeted agent has yet been established as effective in conjunction with this chemotherapy and radiotherapy regimen. Multicentre trials have reported median survival times in excess of 2 years, and 5-year survival of 15–20%.[33,34]

Treatment of advanced lung cancer

Therapeutic progress for subgroups of NSCLC can largely be attributed to the accumulation of molecular knowledge through emerging technology platforms (eg, next-generation sequencing and other omics platforms) and the development of new drugs that specifically target molecular abnormalities (appendix). Patients who have neoplasms with specific genomic aberrations have benefited from molecular targeted therapies (table 2). Up to 69% of patients with advanced NSCLC could have a potentially actionable molecular target (figure, table 3).[35]

See Online for appendix

	Mutations					Rearrangements				Copy number gain
	EGFR[35-40]	*KRAS*[41,42]	*BRAF*[43-46]	*HER2*[47,48]	*MET*[49,50]	*ALK*[51-59]	*ROS1*[60-65]	*RET*[66-68]	*NTRK*[69]	*MET*[49,70]
Molecular features	>90% exon 19 deletions and exon 21 activating mutations, exclusive of other driver aberrations; Thr790Met mutations are present in about half of the cases after tyrosine kinase inhibitor resistance	Codon 12 (>90%), codon 13 (<10%); exclusive of other driver aberrations	Activating mutations of the tyrosine kinase domain; about half are Val600Glu mutations	Activating exon 20 insertions; exclusive of other driver aberrations	Exon 14 skipping mutations; some overlap with MET amplification and other drivers	Fusions of partner gene with exon 20 of *ALK*; partners in the 27 known fusion variants are *EML4*, *KIF5B*, *TFG*, and *KLC1*; exclusive of other driver aberrations	Nine fusion proteins described with the *FIG*, *SCL34A2*, *TPM3*, *SDC4*, *EZR*, *LRIG3*, *KDELR2*, and *CCDC6* genes; exclusive of other driver aberrations	Fusions described with four partner genes: *KIF5B*, *CCDC6*, *NCOA4*, and *TRIM33*; exclusive of other driver aberrations	Fusions of *NTRK1* and *NTRK2* occur with a range of partners; *NTRK3* fusions are rare	Several definitions; preferable: MET:CEP7 ratio >5; might be associated with other driver anomalies if definition criteria not strict
Diagnostic tests	PCR, next-generation sequencing (mandatory in non-SCC or non-smokers with NSCLC)	PCR, Sanger, next-generation sequencing	PCR, next-generation sequencing	PCR, next-generation sequencing	PCR, next-generation sequencing	FISH, immunohistochemistry (mandatory in non-SCC or nonsmokers with NSCLC)	FISH, immunohistochemistry (recommended in EGFR and ALK with adenocarcinoma)	FISH	FISH	FISH
Frequency	40% Asians, 10–20% non-Asians	25% adenocarcinoma, 5% SCC	3–5%	<2% adenocarcinoma	4% adenocarcinoma	2–7% NSCLC	1–2% NSCLC	1–2% NSCLC	2–3% NSCLC	4–6% NSCLC with high copy number gain
Histology	Mostly adenocarcinoma, infrequent in SCC	Mostly adenocarcinoma, less frequent in SCC	Mainly adenocarcinoma, aggressive features in cases with Val600Glu mutation	Adenocarcinoma	Adenocarcinoma, some poorly differentiated	Mostly adenocarcinoma, frequently with acinar or solid pattern and signet-ring cells	Mostly adenocarcinoma, frequently high-grade	Mostly adenocarcinoma, frequently poorly differentiated	Any	Any
Clinical characteristics	Female sex, Asians, never or light smokers	Younger age, smokers, non-Asians	Val600Glu mutations occur in smokers and non-smokers; more frequent in females; non-Val600Glu mutations are typical of smokers	Female sex, never or light smokers		Younger age, Asians, never or light smokers	Younger age, female sex, Asians, never or light smokers	Younger age, female sex, never or light smokers	Unrelated to age, sex, or smoking history	None
Approved drugs	Gefitinib, erlotinib, afatinib, osimertinib (Thr790Met, resistant disease)	None	None	None	None	Crizotinib, ceritinib, alectinib (crizotinib-resistant)	None	None	None	None
Agents of potential interest	Rociletinib	Selumetinib, trametinib, abemaciclib	Dabrafenib, vemurafenib, trametinib	Dacomitinib, transtuzumab, T-DM1	Crizotinib, cabozantinib, capmatinib, other MET inhibitors	Brigatinib, PF06463922, other ALK inhibitors	Crizotinib, ceritinib, cabozantinib, other ROS inhibitors	Vandetanib, cabozantinib, other RET inhibitors	Entrectinib, LOXO-101	Crizotinib, other MET inhibitors

NSCLC=non-small-cell lung cancer. SCC=squamous cell lung cancer. FISH= fluorescence in-situ hybridisation

Table 2: **Molecular, histological, and clinical features of some NSCLC subsets with driver genomic aberrations potentially amenable to targeted treatment**

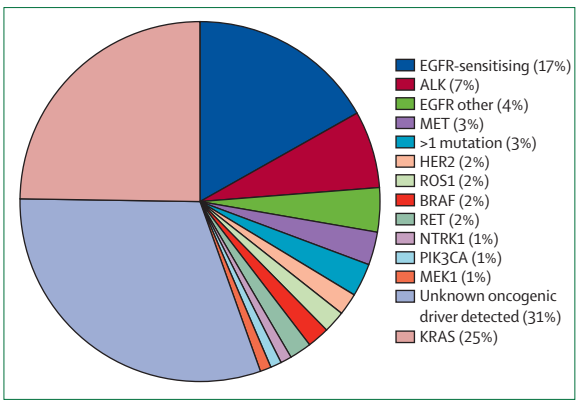

Figure: **Frequency of molecular aberrations in driver oncogenes in lung adenocarcinomas**

Molecular targeted therapies have advanced most for younger patients with adenocarcinoma, who are mostly never-smokers. For patients with advanced NSCLC who do not fit an approved molecular targeted therapy, the standard first-line treatment remains platinum-based doublet therapy with or without bevacizumab. Note that bevacizumab is not applicable to squamous cell histology.

An understanding of the immune landscape of tumours, including immune-evasion strategies, has led to breakthrough therapeutic advances and made a platform for future therapeutic developments.

EGFR-activating mutations

EGFR mutations occur in 10–20% of patients not of east Asian descent with NSCLC and in about 40% of Asian patients, mostly in adenocarcinoma, younger women and girls, and never-smokers.[35,71] EGFR TKI-sensitising mutations are most frequently seen in exon 19 (deletions) or in exon 21 (Leu858Arg). Nine large phase 3 randomised controlled trials (RCTs)[36,37,72–74] established the superiority of EGFR TKIs as the first-line treatment in *EGFR*-mutated NSCLC in terms of progression-free survival, objective response rate, and quality of life compared with chemotherapy. The impact of EGFR TKIs on survival has not been properly assessed in these trials of small sample size and high rate of cross-over, although a pooled analysis of the LUX-Lung 3 and LUX-Lung 6 trials did show an improvement in overall survival with EGFR TKIs compared with chemotherapy.[75] The LUX-Lung studies also provide prospective data on afatinib use in uncommon mutations and some differences in outcome between *EGFR* mutations.[75]

Although second-generation TKIs (eg, afatinib) show an encouraging improvement in overall survival, they also have more toxic effects than first-generation TKIs. Therefore, which one is preferable as front-line treatment remains a question. Results from the LUX-Lung 7 study,[38] a randomised phase 2b study of 319 patients comparing afatinib with gefitinib as first-line therapy, showed a statistically significant prolongation of progression-free survival (median 11·0 months [95% CI 10·6–12·9] *vs* 10·9 months [9·1–11·5]), with HR of 0·73 (p=0·0165) in favour of afatinib, and an objective response rate of 70% with afatinib versus 56% with gefitinib (p=0·008). The main adverse effects of afatinib were diarrhoea (12·5%) and rash or acne (9·4%). Drug-related interstitial lung disease was not seen in any patients treated with afatinib, but was reported in four patients treated with gefitinib.[38]

After EGFR TKI treatment, nearly all patients eventually had disease progression due to acquired resistance (although resistant clones might have been present before treatment commenced). Identified resistant mechanisms can be categorised as: secondary mutations in *EGFR*, bypass or alternative activations, or histological transformations.[36,76,77]

The gatekeeper Thr790Met mutation is the most frequent secondary *EGFR* mutation, occurring in 50–65% of resistant re-biopsies. A third-generation irreversible inhibitor (AZD9291, osimertinib) that targets both Thr790Met and EGFR TKI-sensitising mutations showed an objective response rate of 61% and a median progression-free survival of 9·6 months in patients with Thr790Met-positive NSCLC who progressed after previous TKI therapy.[39] The US Food and Drug Administration (FDA) and European Medicines Agency (EMA) approved osimertinib as a treatment for this population. Phase 1–2 studies of CO-1686 (rociletinib), HM61713, and others also reported impressive activity.[40,78] For patients whose tumours do not have Thr790Met at time of progression after first-line EGFR TKI, platinum-based chemotherapy seems to be a rational option for those not participating in clinical trials.

Treatments after progressive disease develops while taking a first-line EGFR TKI should be selected according to the patient's failure pattern.[79] For local progression, continuation of previous EGFR TKI therapy plus local intervention is recommended.[80] For slow progression, continuation of a first-line TKI with regular monitoring will hopefully result in the best outcome.[81] For rapid systemic progression, switching to a second-line treatment based on the genetic profile of acquired resistance is currently being explored, but switching to doublet chemotherapy is still the standard of care. In this setting, continued administration of gefitinib combined with doublet chemotherapy is not recommended, based on results from the IMPRESS trial.[82]

Studies with the Thr790Met EGFR inhibitors identified novel mechanisms of acquired resistance to these third-generation TKIs, including the gatekeeper *EGFR* Cys797Ser mutation, *HER2* and *MET* amplification, and *MAPK* activation.[83,84]

Because of the potential importance of genomic guided treatment at the time of progression and the frequent difficulty of obtaining sufficient tissue at the time of progression, much effort is going into the development of blood-based mutation assays. Encouraging results showed the detection of Thr790Met mutations in plasma with high specificity (90–100%) and sensitivity (85–90%).[85–87]

Combinations of EGFR TKIs with bevacizumab, chemotherapy, and checkpoint inhibition have been explored in clinical trials[88–90] and might pave a way forward in the Thr790Met-negative resistant subgroup.

Brain metastases are an emerging challenge associated with poor prognosis. New agents such as AZD3759 and epitinib (HMPL-813) that target *EGFR* mutations have been designed for excellent penetration of the central nervous system.[91]

The discovery in 2007 of oncogenic *ALK* gene rearrangements in NSCLC[92,93] led to the understanding of its implications in the biology and natural history of the disease, and subsequently, the development of targeted drugs that have dramatically impacted the outcome of patients.[51,94]

ALK rearrangements result from inversions or translocations on chromosome 2 that fuse variable regions of a partner gene with exon 20 of the *ALK* gene. The most common translocated partner gene in NSCLC *ALK* rearrangement is *EML4*. Altogether, 27 variants of *ALK* fusion have been described.[52]

ALK-driven tumours represent 2–7% of NSCLCs,[51,53] and the median age at diagnosis is around 50 years, mostly in never-smokers or light smokers with adenocarcinomas. Patients are more frequently Asian, and 50–60% are men.[51]

The reference diagnostic assay for detecting *ALK* fusions has been the Vysis LSI ALK Dual Color Break Apart FISH Probe (Abbott Molecular, IL, USA).[94] Immunohistochemistry is also approved as a diagnostic assay. Of note, *ALK* fusions are mutually exclusive with other oncogenic drivers, such as *EGFR, ROS1,* and *KRAS*, apart from in exceptional cases.[53]

Several ALK TKIs, including crizotinib, ceritinib, and alectinib, were developed and now constitute the backbone of treatment for patients with advanced *ALK*-positive NSCLC.[53] Crizotinib targets ALK, ROS1, and MET. Patients who received crizotinib had rapid and durable responses with a favourable toxic profile in an expanded phase 1 trial and a subsequent phase 2 trial of patients mostly previously exposed to chemotherapy.[94–96] Observed progression-free survival was 9·7 in the phase 1 trial and 8·1 months in the phase 2 trial. Based on these results, the FDA and countries including Japan granted approval to crizotinib in 2011. Two randomised trials have subsequently been completed that were the basis for regulatory approval by the EMA and other agencies. In the first trial (PROFILE 1007, n=347), crizotinib showed longer progression-free survival (7·7 *vs* 3·0 months) and higher objective response rate (65% *vs* 20%) than pemetrexed or docetaxel in patients with advanced *ALK*-positive NSCLC progressing after first-line platinum-based chemotherapy.[54] The second study (PROFILE 1014, n=343) showed the consistent superiority of crizotinib in terms of progression-free survival (10·9 *vs* 7·0 months) and objective response rate (74% *vs* 45%) over pemetrexed plus platinum chemotherapy in untreated patients.[55] Neither of these trials showed differences in overall survival among treatment groups, likely due to crossover of patients assigned to the chemotherapy regimen.

	Status
EGFR	
Gefitinib	Approved
Erlotinib	Approved
Afatinib	Approved
Osimertinib	Approved
Necitumumab	Approved
ALK	
Crizotinib	Approved
Alectinib	Approved
Ceritinib	Approved
Lorlatinib	Phase 2
Brigatinib	Phase 2
MET	
Crizotinib	Phase 2
Cabozantinib	Phase 2
HER2	
Trastuzumab emtansine	Phase 2
Afatinib	Phase 2
Dacomitinib	Phase 2
ROS1	
Crizotinib	Approved
Cabozantinib	Phase 2
Certinib	Phase 2
Lorlatinib	Phase 2
DS-6051b	Phase 1
BRAF	
Vemurafenib	Phase 2
Dabrafenib	Phase 2
RET	
Cabozantinib	Phase 2
Alectinib	Phase 2
Apatinib	Phase 2
Vandetanib	Phase 2
Ponatinib	Phase 2
Lenvatinib	Phase 2
NTRK1	
Entrectinib	Phase 2
LOXO-101	Phase 2
Cabozantinib	Phase 2
DS-6501b	Phase 1
MEK1	
Trametinib	Phase 2
Selumetinib	Phase 3
Cobimetinib	Phase 1
PIK3CA	
LY3023414	Phase 2
PQR 309	Phase 1

Table 3: **Developmental phases of available drugs against oncogenic proteins**

In patients treated with crizotinib, relapse occurs within 1–2 years. CNS is the most frequent, and often only, site of relapse or progression regardless of the presence of CNS involvement at baseline. This might be due to the poor penetrance of crizotinib to the CNS (pharmacokinetic resistance), which is the consequence of drug efflux mediated by the ABCB1 pump.[97] Various mechanisms of biological acquired resistance to crizotinib have been identified.[52,98]

Treatment strategies resemble those for *EGFR*-mutant tumours. Novel second-generation ALK TKIs, including ceritinib and alectinib, among others, with higher inhibitory potency to the wild-type fused ALK protein, better affinity for the secondarily mutated proteins, and improved penetrance to the CNS, represent valuable treatment alternatives to chemotherapy when crizotinib fails.[52,99] Approval was granted to ceritinib by FDA, EMA, and many other agencies for the treatment of *ALK*-positive NSCLC after failure on crizotinib (ie, disease progression), and alectinib was approved by FDA for patients who progress on crizotinib. Both drugs have shown durable response in a high proportion of patients, and ceritinib showed an objective response rate of 39–56% and a median progression-free survival of 5·7–6·9 months.[56,100] Phase 3 trials are comparing ceritinib with chemotherapy in platinum-exposed and chemotherapy-naive patients. Alectinib yielded responses in 45–56% of patients after failure of crizotinib treatment, with progression-free survival of 8·1–8·9 months in phase 1–2 trials.[57,101] Alectinib is now being compared against chemotherapy in patients with crizotinib failure. Importantly, ceritinib and alectinib have shown response in patients with identifiable crizotinib-resistant tumour mutations at baseline.

Both alectinib and ceritinib have shown impressive activity in crizotinib-naive patients in single-arm studies (objective response rate 93% for alectinib and 67% for ceritinib) with progression-free survival of 19 months for alectinib and 27 months for ceritinib.[102,103] Alectinib is being compared with crizotinib in treatment-naive patients in the ALEX phase 3 trial (NCT02075840), and one study (J-ALEX)[104] reported increased efficacy of alectinib compared with crizotinib. A number of resistance mechanisms for second-generation ALK inhibitors, including new secondary mutations and alternative signalling routes, result in differential sensitivity patterns to existing ALK TKIs. Continuous assessment of changes in the disease genotype (eg, re-biopsy) will be helpful for more precise treatment guidance.[52]

Other ALK inhibitors in development include brigatinib, X-396, and PF-06463922.[52,58,59]

Other actionable aberrations in NSCLC

Chromosomal rearrangement involving the *ROS1* gene on 6q22 is observed in 1–2% of NSCLC, mostly in adenocarcinomas.[60,93] Nine fusion protein variants have been identified in NSCLC.[60,93] A fluorescence in-situ hybridisation (FISH) assay is currently deemed the gold standard for *ROS1* fusion detection and is used in clinical studies.[61] Reports support the use of immunohistochemistry assays for screening.[62] Patients with *ROS1*-positive NSCLC are younger at diagnosis (median about 50 years of age), predominantly female, and never or light smokers.[60]

Crizotinib was assessed as an ROS1 inhibitor in a dedicated *ROS1*-positive NSCLC expansion cohort, and was approved by FDA for patients with *ROS1*-positive NSCLC.[61] Of 50 patients, mostly pretreated with chemotherapy, 72% responded to crizotinib, with a median progression-free survival of 19·2 months. A European retrospective study of 30 patients reported similar results.[63] Acquired resistance to crizotinib is mediated by secondary mutations of the kinase domain (*CD74-ROS1* G2032R)[64] or by bypass-tract activation, such as *c-KIT* or *KRAS*.[65] Several other ROS1 inhibitors are currently being assessed, including ceritinib, cabozantinib, entrectinib, and PF06463922.

RET fusion products are detected in 1–2% of NSCLC, with greater frequency in never or light smokers bearing adenocarcinomas or adenosquamous tumours.[105,106] Multi-targeted TKIs have shown activity against RET kinase in preclinical models, such as sunitinib, sorafenib, vandetanib, cabozantinib, alectinib, apatinib, lenvatinib, and ponatinib, and are now in phase 1 or 2 studies.[66]

Aberrant overexpression, amplification, and activating mutations of the MET receptor tyrosine kinase have been observed in specific subsets of lung tumours.[49] Two randomised trials[107,108] reported that outcomes for pretreated patients not selected for *MET* genomic abnormalities, who received a MET inhibitor (tivantinib or onartuzumab) in combination with erlotinib, were the same as those treated with the EGFR TKI alone. *MET* gene amplification occurs in about 4% of lung adenocarcinomas and 1% of squamous cell lung cancers (SCC).[49] Evidence suggests that patients with high amplification (ie, *MET*:*CEP7* ratio >5) might have a high response rate (>35%) to MET inhibitors such as crizotinib.[70]

Paik and colleagues[50] reported oncogenic mutations in *MET* exon 14 splice sites that cause exon 14 skipping and lead to increased kinase catalytic activity. This mutation is seen in 3–4% of lung adenocarcinomas, typically in the absence of other drivers. Paik and colleagues previously reported response to the MET inhibitors crizotinib and cabozantinib in five patients with lung adenocarcinomas bearing the *MET* exon mutation.

HER2 overexpression occurs in 35% of lung cancers, and amplification occurs in 10% of lung cancers. The data so far do not support routine clinical use of HER2-directed therapies in this population beyond clinical trials. *HER2* mutations are found in about 2% of NSCLC, mainly in women, never-smokers, and adenocarcinoma histology.[47] A phase 2 trial[48] of dacomitinib (objective response rate 12%) supports the

efficacy of anti-HER2 agents alone or in combination with chemotherapy.

BRAF mutations are detected in 3–5% of lung cancers, mainly in smokers bearing adenocarcinomas.[43,44] The Val600Glu mutation is reported in half of patients with *BRAF*-mutated lung adenocarcinomas. A study included 20 pre-treated patients with *BRAF*-mutated NSCLC, 18 of whom had the Val600Glu mutation.[45] The objective response rate was 42% and median progression-free survival was 7·2 months. A phase 2 study in the same patient population using dabrafenib gave consistent results.[46] A higher activity (objective response rate 63%) was documented with dabrafenib combined with the MEK1 inhibitor trametinib, as previously seen in melanoma.[109]

KRAS mutations are common aberrations in lung cancer and are frequently found in adenocarcinomas (25%), particularly in smokers of non-Asian ethnicity.[110] Development of therapeutics to target this phenotype has been remarkably frustrating. MEK inhibitors (trametinib and selumetinib) have shown signs of activity, more in combination with chemotherapy than as monotherapy.[41,42]

NTRK1 and *NTRK2* rearrangements are detected in 1–2% of NSCLC and several NTRK inhibitors are under investigation.[69]

The Cancer Genome Atlas reported that 96% of 178 lung SCCs harboured genomic abnormalities, including mutations or amplification of *FGFR*, the *PI3K* pathway, DDR2, *EGFR* and *HER2*, and the tumour suppressor genes *TP53* and *P16*.[111] *FGFR* amplification was seen in about 5–22% of SCC, and *DDR2* mutations were seen in about 4% of SCC.[112,113] None of these alterations defines a subset of SCC whose patients are known to benefit from specific therapies, although a number of agents targeting these dysregulated pathways are being assessed preclinically and in early clinical trials.

In SCLC, there is an almost universal inactivation of *TP53* and *RB1*, sometimes by complex genomic rearrangements.[114] About a quarter of cases show inactivating mutations in the *NOTCH* gene family.

Unlike other types of lung cancer, SCLC has had no breakthrough agents in the last 25 years, with only one agent approved, topotecan (for second-line treatment). SCLC is usually chemo-sensitive but in most cases resistance rapidly develops.[115] Thus, essentially all patients of any stage receive a doublet combination of etoposide (or irinotecan in Japan) with cisplatin or carboplatin.

Limited stage disease (ie, tumours that are located in the ipsilateral hemithorax and treatable with a single radiation field) occurs in only one-third of patients with SCLC and is potentially curable. Combined-modality therapy (chemotherapy and radiotherapy) has long been the mainstay of therapy for this condition, but more recent data suggest a role for surgery in early stage disease. Prophylactic cranial irradiation seems to improve outcomes in patients who have responded to initial therapy.[116]

Anti-VEGF inhibitors have been used in combination with chemotherapy for the treatment of lung cancer on the basis of modestly improved outcomes. For safety reasons, these agents have been restricted to patients with adenocarcinoma with a low risk of haemoptysis. A novel monoclonal antibody directed at the VEGF receptor, ramucirumab, has been approved by the FDA and EMA for use in combination with docetaxel in the second-line treatment of squamous and non-squamous NSCLC.[117] Another antiangiogenic agent,[118] the multikinase inhibitor nintedanib, resulted in similar survival benefits when combined with docetaxel, but only in patients with adenocarcinoma. Nintedanib is EMA approved but not FDA approved.

Necitumumab is another monoclonal antibody against EGFR, which was shown to improve survival in untreated patients with advanced SCC when combined with cisplatin and gemcitabine (HR 0·84, 95% CI 0·74–0·96; p=0·01).[118] The drug was approved by the FDA but restricted to those tumours with positive EGFR expression by the EMA.[119]

Immunotherapy

Lung cancer initiation and progression depends not only on the evolving genomics and molecular properties of cancer cells but also on their interaction with the tumour environment, specifically with the immune system.[120] Therapeutic approaches that modulate the immune system in patients with lung cancer have traditionally focused on vaccines, and have generally been ineffective, probably due to insufficient or inadequate immune activation (TG4010, which has shown some positive results, remains under investigation).[120–122] Immunotherapy approaches have focused on a series of ligands and receptors that inhibit or stimulate the immunological synapse.[123]

Inhibitory checkpoint molecules generated upon T-cell activation, such as those that regulate the immunological synapse between T cells and dendritic cells in lymph nodes (CTLA-4–B7.1), thereby suppressing T-cell activation, or between T cells and tumour cells in the tumour bed (programmed death-1 [PD-1]–programmed death-ligand [PD-L]1, PD-L2), hampering immune rejection or the effector phase, are currently the most relevant targets for immunotherapy. Antibody-directed therapies against these checkpoints have shown remarkable early success in many malignancies and already have a major role in the management of advanced lung cancer and other tumours (table 4).[124]

Several monoclonal antibodies directed to the PD-1 receptor (nivolumab, pembrolizumab) or its ligand PD-L1 (atezolizumab, durvalumab, avelumab) have reached the clinic, and others are in preclinical development. Early clinical trials with these agents have shown rapid and durable responses in about 14–20% of pre-treated patients with advanced NSCLC.[128–134] Importantly, even though progression-free survival figures are not impressive

	CheckMate 017 phase 3[125]		CheckMate 057 phase 3[126]		KEYNOTE-010 phase 3[127]			POPLAR phase 2[128]		Durvalumab phase 1b[129]	Avelumab phase 1b[130]
	Nivolumab	Docetaxel	Nivolumab	Docetaxel	Pembrolizumab 2 mg/kg	Pembrolizumab 10 mg/kg	Docetaxel	Atezolizumab	Docetaxel	Durvalumab	Avelumab
Patients (n)	135	137	292	290	345	346	343	144	143	198	184
Response rate (%)											
All patients	20	9	19	12	18	19	9	15	15	16	14
PD-L1 positive	21	8	36	13	30	29	8	38	13	27	16
PD-L1 negative	15	12	10	14	NA	NA	NA	8	10	5	10
Median progression-free survival (months)											
All patients	3·5	2·8	2·3	4·2	3·9	4·0	4·0	2·7	3·0	NA	2·9
PD-L1 positive	4·8	3·1	5·0	3·8	5·0	5·2	4·1	2·8	3·0	NA	3·0
PD-L1 negative	4·2	2·9	2·1	4·2	NA	NA	NA	1·7	4·1	NA	1·4
Median overall survival (months)											
All patients	9·2	6·0	12·2	9·4	10·4	12·7	8·5	12·6	9·7	NA	8·9
PD-L1 positive	10	6·4	19·4	8·1	14·9	17·3	8·2	15·5	9·2	NA	8·4
PD-L1 negative	8·5	6·1	9·8	10·1	NA	NA	NA	9·7	9·7	NA	4·6
Histology	SCC	SCC	Non-SCC	Non-SCC	All comers	All comers	All comers	All comers	All comers	All comers	All comers
Setting	Second line	Second line	Second line	Second line	Second line	Second line	Second line	Second line	Second line	Pre-treated	Pre-treated
PD-L1 expression											
Positive	≥5%	≥5%	≥5%	≥5%	Highly positive ≥50%; positive ≥1%	Highly positive ≥50%; positive ≥1%	Highly positive ≥50%; positive ≥1%	Tumour cell 1–3 or tumour-infiltrating immune cells 1–3		≥25%	≥1%
Negative	<5%	<5%	<5%	<5%	<1% (not included)	<1% (not included)	<1% (not included)	Tumour cell 0 and tumour-infiltrating immune cells 0		<25%	<1%

Percentages rounded. PD-1=programmed death-1. PD-L1=programmed death ligand-1. SCC=squamous cell cancer. NA=not available.

Table 4: **Trials of anti-PD-1/PD-L1 inhibitors in patients with advanced NSCLC who were pre-treated with chemotherapy**

(median 2–4 months; progression-free survival at 1 year 20%), survival outcomes are remarkable. In the 27-month follow-up of a cohort of 129 patients with NSCLC treated with nivolumab,[131] 2-year survival was 24% in the overall population and 42% in the subset of patients treated at the dose selected for further development (3 mg/kg every 2 weeks); 3-year survival was 18% in the overall population and 27% in the development dose subset of patients. Clinical efficacy appeared independent of histology, but in most of the trials greater benefit was observed in smokers and in patients with PD-L1-positive expression. The toxic profile of these agents is quite favourable, with about 10% of patients developing severe (grades III–IV) adverse events.[125–130,132–134] The most frequent adverse effects observed were asthenia, fatigue, loss of appetite, nausea, and diarrhoea. Less than 10% of patients developed immune-related side-effects including rash, colitis, transaminitis, pneumonitis, and endocrinopathies.

Clinical efficacy and safety of the anti-PD-1 or anti-PD-L1 agents is supported by four randomised studies.[125–128] Two trials compared nivolumab to docetaxel in patients who progressed to platinum-based chemotherapy, in SCC (CheckMate 017 trial)[125] and non-SCC NSCLC (CheckMate 057 trial).[126] In patients with SCC, nivolumab resulted in improved survival (median 9·2 *vs* 6·0 months, HR 0·59; p<0·001), progression-free survival (3·5 *vs* 2·8, 0·62; p<0·001), and response rate (20% *vs* 9%, p<0·008) over docetaxel.[130] Nivolumab benefits were largely independent of clinical and tumour characteristics, including PD-L1 expression. In the non-SCC trial, nivolumab improved survival (median 12·2 *vs* 9·4 months, HR 0·73) and response rate (p<0·02) but not progression-free survival in the overall population.[126] Treatment effect was seen in all patient subgroups except for never-smokers and those with wild-type *EGFR* tumours. In non-SCC, PD-L1 expression emerged as a substantial determinant of nivolumab benefit. Nivolumab has obtained regulatory approval in the USA (SCC and non-SCC) and the EU (SCC) for the treatment of advanced disease in patients who have progressed on first-line chemotherapy.

Irrespective of the use of a different clone and assay for PD-L1 determination, along with different criteria for positivity (ie, staining of immune cells within the tumour was taken into account), the benefit from the checkpoint inhibitor was mostly restricted to the PD-L1-positive tumour population. A randomised phase 3 trial of pembrolizumab versus docetaxel in patients harbouring PD-L1-positive tumours (>1% of cells) favoured the anti-PD-1 treatment, and the magnitude of the survival benefit was related to PD-L1 expression (HR of 0·53 if

PD-L1 >50%; HR of 0·76 if PD-L1 expression 1–49%).[127] Pembrolizumab has been FDA approved for second or further lines of treatment if tumour expression of PD-L1 is encountered in ≥50% of cells, independent of histology. Although results from comparative studies of immune therapy and chemotherapy as first-line treatment for advanced NSCLC are still pending, Merck announced that a large study[135] met its endpoints of progression-free survival and overall survival benefit for pembrolizumab versus chemotherapy in patients with PD-L1-expressing tumours (≥50%).

Atezolizumab showed benefit over docetaxel in a randomised phase 2 trial including all NSCLC histologies.[128]

Overall data suggest PD-1 inhibitors are a preferred second-line treatment over standard chemotherapy in SCC and at least in PD-L1-positive, non-SCC of the lung. However, a remaining question is the optimal definition of PD-L1 expression in terms of prediction of benefit. Not all patients with PD-L1-positive NSCLC benefit from these agents, and some PD-L1-low-expressing or PD-L1-negative tumours do. All the PD-L1 assays differ in terms of antibodies used, assessment methods, targeting cells, and cutoffs for positive and negative results.[136] To elucidate similarities and differences between the different PD-L1 assays, comparative studies are ongoing on a standardised set of NSCLC tumours.[136]

In previously untreated patients, results of early trials have reported encouraging results with anti-PD-1 or anti-PD-L1 inhibitors, including 1-year survival exceeding 70% in PD-L1-positive tumours.[117,137] Several trials are currently comparing these agents with platinum combination regimens as front-line therapy. Trials are also ongoing in earlier disease settings (stage III, post-surgery), and early data are encouraging in other thoracic malignancies, such as small-cell lung cancer (SCLC) and mesothelioma.[138,139]

Maintenance therapy for patients with advanced NSCLC

The optimal duration of treatment for patients with advanced NSCLC has been investigated in several studies. The administration of 4–6 cycles of combination chemotherapy followed by observation has become the standard of care for the first-line treatment of advanced NSCLC.[140,141]

To date, both switch therapy strategies (in which a different therapy than the first-line therapy is used) with pemetrexed[142] and erlotinib,[143] or continuation maintenance with pemetrexed[144] improved outcomes, including overall survival and progression-free survival (table 5). Several meta-analyses have supported the impact of maintenance treatment approaches on efficacy outcomes and toxicity.[150,151] Overall, these studies substantiated a highly significant impact from maintenance therapy on progression-free survival (HR 0·53–0·67) and, to a lesser extent, on overall survival (0·85–0·88), with some increases in clinically relevant toxicities but maintaining the quality of life of treated patients. Switch maintenance strategies are not used frequently in practice compared with continuation maintenance, as physicians and patients most often prefer to extract the maximum benefit from a given therapy before switching to an alternative treatment.

	n	Maintenance drug	Progression-free survival HR (95% CI)	Overall survival HR (95% CI)
Switch maintenance trials				
Westeel et al[145]	181	Vinorelbine	0·77 (0·56–1·07)	1·08 (0·79–1·47)
Fidias et al[146]	309	Docetaxel	0·71 (0·55–0·92)	0·84 (0·65–1·08)
Cappuzzo et al[143]	889	Erlotinib	0·71 (0·62–0·82)	0·81 (0·70–0·95)
Ciuleanu et al[142]	663	Pemetrexed	0·60 (0·49–0·73)	0·79 (0·65–0·95)
Continuation maintenance trials				
Paz-Ares et al[144]	539	Pemetrexed	0·62 (0·49–0·79)	0·78 (0·64–0·96)
Brodowicz et al[147]	206	Gemcitabine	0·69 (0·56–0·86)	0·84 (0·52–1·30)
Belani et al[148]	255	Gemcitabine	1·09 (0·81–1·45)	0·97 (0·72–1·30)
Perol et al[149]	309	Gemcitabine	0·56 (0·44–0·72)	0·89 (0·67–1·15)

HR=hazard ratio.

Table 5: **Efficacy of maintenance chemotherapy in clinical trials in advanced non-small-cell lung cancer**

Maintenance therapy with an EGFR inhibitor is indicated for patients with activating EGFR TKI-sensitising tumour mutations who for any reason (eg, delayed information on *EGFR* mutation profiling) are given first-line chemotherapy.[152]

Several factors influence the decision to implement maintenance therapy. These included tumour histology (pemetrexed being indicated only in patients with non-squamous NSCLC), genomics, response to induction, patient health status (performance status ≥2 precludes benefit from this approach) and, most importantly, patient choice.[141] From the patient's perspective, an overall survival benefit of at least several months (eg, 3 months in the Paramount trial)[144] or better symptom control is expected, to balance mild-to-moderate side-effects.

Conclusion

Although lung cancer has long been a disease characterised by late-stage diagnosis and no progress in treatment options, the last decade has yielded encouraging results with lung cancer screening in high-risk populations and substantial progress with systemic therapies for molecular subgroups of patients with advanced disease. Further progress is expected for these patient subgroups through the development of next-generation drugs that have more-specific target effects, and target of specific resistant mutations, creating a chronic therapeutic pathway.

Furthermore, new molecular targets are continuously detected, prompting the development of new therapies. For many subgroups of patients with NSCLC, future combination therapy (using targeted therapies or immunotherapies) could be the ultimate curative option.

Contributors

Each author wrote a section of the manuscript. FRH coordinated the integration and editing of the manuscript and provided the figure. JLM, GVS, and LP-A provided the tables. All authors revised and edited the manuscript.

Declaration of interests

FRH has received compensation for participating in scientific advisory boards for Bristol-Myers Squibb, Genentech-Roche, AstraZeneca, Merck, Lilly Oncology, Celgene, Clovis, Boehringer Ingelheim, and Pfizer, outside the submitted work. GVS reports personal fees from Eli Lilly, Roche, Pfizer, AstraZeneca, and Clovis Oncology, outside the submitted work. Y-LW reports personal fees from Roche, AstraZeneca, Eli Lilly, Pfizer, and Sanofi, outside the submitted work. LP-A reports personal fees from BMS, MSD, Roche, Lilly, AstraZeneca, Clovis, Novartis, and Boehringer Ingelheim, outside the submitted work. JLM, RK, and WJC declare no competing interests.

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