Lung Cancer in Israel

Roxana D. Grinberg, MD,[a] Yael Refaely, MD,[a] Liora Boehm Cohen, MD,[a] Dorith Shaham, MD,[b] Elizabeth Dudnik, MD,[c] Rephael Pfeffer, MD,[d] Aaron Allen, MD,[e] Nir Peled, MD, PhD[a,*]

Introduction

Israel is a small country with just over 8 million citizens. It has had universal health coverage since the introduction of a progressively financed statutory health insurance system in 1995.[1]

All its citizens can choose from among four competing, non–profit-making health plans, which provide a broad package of benefits stipulated by the government. In the health plans, the patients have a great deal of freedom in choosing their physicians in most specialties and in most areas of the country.[1]

The system is financed primarily through a combination of a health-specific payroll tax and general taxation.[1] Although public financing remains the primary source of health care, the citizens can opt for private insurance and private care provisions. Israel spent 7.4% of its gross domestic product on health in 2017.[2]

Historically, Israel has had a very high physician-to-population ratio, but this ratio has seen a marked decline.[1] In 2016, the ratio was 3.1 physicians per 1000 inhabitants and five nurses per 1000 inhabitants.[2] The number of beds per 1000 inhabitants in 2017 was reported as being three.

Epidemiology

According to the Israeli Ministry of Health, the number of cases of lung cancer increased by 33% (not per capita) within a decade, with 200 new cases diagnosed every month.[3]

In 2015, a total of 11,117 Israeli residents died of cancer; of these, 5719 were men (4835 Jewish, 625 Arabic, and 259 others) and 5398 were women (4691 Jewish, 452 Arabic, and 255 others).

In 2015, the lung cancer mortality rate reached 26% of the mortality rate from all cancers. In men, the percentage of lung cancer death was significantly higher among Arabs (33.6%) than among Jews (20.3%). In women, the percentage of deaths attributed to lung cancer was higher in Jews (12.9%) than in Arabs (9.5%).

The smoking rate in Israel among those aged 21 years and above, corrected for the year 2017, was 20.5%, according to the National Health Survey, "Health Knowledge, Attitudes, and Behavior in Israel 2013"—updated in 2017. In Israel, the smoking rate was 25.9% among men and 15.3% among women, and it was 22.9% in the Arab population and 20% in the Jewish population.[4,5]

The price of a cigarette pack rose by 72.4% in 7 years (2010–2017) as a result of not only tax increase but also an increase in wholesale tobacco price. As a result, the purchase of cigarette packs decreased by 24.8%.[4]

According to an Israeli government report, tobacco sales for water pipes rose 28% from 2016 to 2017. In the same period, sales of loose tobacco grew by 9.3%. In an effort to reduce smoking, the Israeli government is trying to implement a new taxation system that will increase the price of loose tobacco to that of a pack of cigarettes.

*Corresponding author.

[a]The Legacy Heritage Oncology Center & Dr. Larry Norton Institute, Soroka Medical Center & Ben-Gurion University, Beer-Sheva, Israel, [b]Hadassah Medical Center and Hebrew University Faculty of Medicine, Jerusalem, Israel, [c]Thoracic Cancer Service, Davidoff Cancer Center, Rabin Medical Center, Petah Tikva, Israel, [d]Oncology Institute, Assuta Medical Center, Tel Aviv, Israel, and [e]Sackler School of Medicine, American Program, Rabin Medical Center, Tel Aviv University, Petah Tikva, Israel.

Disclosure: Dr. Dudnik reports grants and personal fees from Roche Holding AG and Boehringer Ingelheim and personal fees from AstraZeneca, Pfizer, Merck Sharp & Dohme, Bristol-Myers Squibb, Novartis, and Takeda, outside of the submitted work. Dr. Peled reports grants and personal fees from AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, Merck Sharp & Dohme, Novartis, Pfizer, Roche Holding AG, NovellusDx, FMI, and Gaurdant360, outside of the submitted work. The remaining authors declare no conflict of interest.

Address for correspondence: Nir Peled, MD, PhD, Head of Oncology, The Legacy Heritage Oncology Center & Dr. Larry Norton Institute, Soroka Medical Center & Ben-Gurion University, Beer-Sheva, Israel. E-mail: peled.nir@gmail.com

ISSN: 1556-0864

https://doi.org/10.1016/j.jtho.2020.01.022

Screening

Lung cancer screening has been performed in Israel for over 20 years. Screening for lung cancer in Israel started in 1998 at the Hadassah Medical Center in Jerusalem, which is a member of the International Early Lung Cancer Action Program.[6] Lung cancer screening is currently being performed at additional institutions, including the Tel Aviv, Sheba, Rambam, Sha'aeri Zedek, Assuta, and Wolfson Medical Centers.

The Israeli Ministry of Health is interested in establishing a National Lung Cancer Program and appointed in January 2017 a multidisciplinary steering committee, which has been charged with the mission to prepare a plan for the implementation of such a program. The committee submitted its recommendations to the Ministry of Health in July 2017. Three applications for reimbursement, together with the Lung Cancer Advocacy group, have failed to succeed so far.

The target population for lung cancer screening was defined as comprising individuals aged 55 years to 74 years with a 30 pack-year smoking history who are current smokers or have quit within the past 15 years. Physician referral is required. The committee recommended following the American College of Radiology Technical Specifications for Lung Cancer Screening[7] and using a modified LungRads protocol[8] for the workup of pulmonary nodules. An additional recommendation was to perform lung cancer screening only at medical facilities with appropriate infrastructure to ensure continuity of care, including follow-up and workup of suspicious findings and treatment of diagnosed lung cancers, while taking a multidisciplinary approach. To allow for longitudinal follow-up as well as collection and analysis of data, the committee recommended setting up a National Registry.

The current main obstacle to start the National Israeli Lung Cancer Program is reimbursement. Every Israeli resident is entitled to health services under the National Health Insurance Law (1994), and these services are determined by the Healthcare Basket.[9] The Basket is annually updated by the Ministry of Health on the basis of the recommendations of a public committee. Unfortunately, the Healthcare Basket Committee has decided not to include lung cancer screening as an approved service, and the Ministry of Health is currently considering conducting a pilot for a portion of the eligible population in selected institutions.

Diagnosis

Pulmonary malignancy must be histologically defined before therapy. In Israel, the diagnosis of pulmonary lesions found during screening, incidentally or during hospitalization, is worked up, and their extent is determined by imaging techniques, including computed tomography (CT), magnetic resonance imaging, and positron emission tomography-CT. Fleschner's criteria are used to follow up the nodules.

Histologic examination is done by bronchoscopy, including if necessary, the endobronchial ultrasound bronchoscopy procedure using cryobiopsy, brush, transbronchial biopsy and the endobronchial ultrasound bronchoscopy procedure, or CT-guided biopsy. Imaging is performed in community-based or outpatient imaging units and CT-guided biopsies and bronchoscopies are performed in a hospital, either as an outpatient or an inpatient. All bronchoscopic procedures are performed by pulmonologists in the hospital in one of the 16 main public medical centers in the country (Table 1). Currently, there are approximately 200 practicing pulmonologists dispersed throughout the country.

Tissue genotyping is routinely performed in every patient with NSCLC at the time of advanced disease diagnosis. This includes testing for somatic alterations in the following genes: *EGFR* (Cobas or next-generation sequencing panel), *ALK* (anaplastic lymphoma kinase) (immunohistochemical staining optionally followed by fluorescence in situ hybridization), and *ROS1* (immunohistochemical staining followed by fluorescence in situ hybridization). Recently, molecular hotspot panels have been introduced at several tertiary cancer centers; these largely include testing for mutations in *BRAF*, *cMET*, *HER-2*, and *KRAS* genes. However, interinstitutional approach varies with regard to panel content and techniques used. Programmed death-ligand 1 (PD-L1) tumor testing is optional for patients with metastatic and locally advanced inoperable NSCLC. Mismatch repair genes testing for advanced SCLC and mesothelioma after progression on standard platinum-based chemotherapy has been implemented in Israel in 2018 and 2019.

Molecular profiling is controlled by the health maintenance organizations, and therefore, it has not been done yet as a reflex test in most centers. Although molecular profiling is covered only for *EGFR* (beyond *PD-L1*, *ALK*, *ROS1*), multiplex panels (mainly Oncomine) have been performed in most centers. Hybrid capture–based next-generation sequencing is available through private coverage, for example, Foundation Medicine, TEMPUS, Gaurdant360, and Liquid Foundation. For patients who are progressing under EGFR tyrosine kinase inhibitors (TKIs), polymerase chain reaction–based circulating free DNA is covered, but only once.

The time-to-report for histologic examination is 2 weeks on average, whereas full molecular profiling takes 3 weeks to 4 weeks on average. Unfortunately, the health maintenance organization requires that an oncologist order the molecular test; therefore, there is a further delay of 2 weeks to 3 weeks for having the full molecular profiling.

Table 1. Availability and Expenses of Imaging and Invasive Procedures in Israel

Test/ Procedure	CT	MRI	PET-CT	Bronchoscopy	EBUS	VATS	Robotics	VMAT Accelerators	SBRT/SRS Accelerators	SRS
Number of devices	80 10/10^6 [a]	40 5.2/10^6 [a]	8	15 units	10 units	10	12[b]	30	28	28
Number of procedures/y	N/A	N/A	N/A	~7000	~800	740	40 (thoracic)	N/A	N/A	N/A
Price in USD	200	570	1385	450	1240	13,200	17,400	140-160[c]	140-160[c]	140-160[c]
Reimbursement	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Waiting time	1-4 wks	2-8 wks	1-4 wks	1-3 wks	1-3 wks	1-2 wks	1-3 wks	4-5 wks	4-5 wks	2-3 wks

[a]number of machines per 1,000,000 inhabitants.
[b]number of total machines in the country.
[c]Per field treated.
EBUS, endobronchial ultrasound bronchoscopy procedure; CT, computed tomography; PET-CT, positron emission tomography-CT; MRI, magnetic resonance imaging; VATS, video-assisted thoracoscopic surgery; VMAT, volumetric modulated arc therapy; SBRT, stereotactic radiation therapy; SRS, stereotactic radiosurgery.

Surgical Approaches

A total of 740 lung resections for NSCLC are performed each year in 16 different medical centers in Israel. Lung resection for NSCLC includes wedge resection, segmentectomy, lobectomy, sleeve lobectomy, and, rarely, pneumonectomy. The accepted standard of lung cancer resection is lobectomy with lymph node dissection.

Most of the lung resections in Israel are done thoracoscopically using either the three-hole approach or the uniportal approach. As many as 40 lobectomies for NSCLCs were performed using the da Vinci robotic system in 2018 (Table 1).

Lung resection through thoracotomies is reserved for complicated resections such as postneoadjuvant treatment, centrally located tumors, and large tumors. Less than lobar resection (wedge and segmentectomy with lymph node dissection) is usually performed in cases of early-stage lung cancer, usually with ground glass opacification nodules less than 1 cm to 2 cm, or in cases of patients with low respiratory reserves or significant comorbidities.

Patients with stage I NSCLC would be advised to undergo resection only. Those with stage II would undergo resection and adjuvant treatment, and those with stage IIIA would receive neoadjuvant treatment followed by restaging and resection. Neoadjuvant treatments involving immunotherapy or biological treatment might be performed under a clinical trial.

Only in rare cases, patients with stage IIIB or stage IV NSCLC would undergo lung resection after radiotherapy or systemic treatment. The encouraging results with the new treatment modalities such as biological and immunologic therapy, provoke multidisciplinary discussions about expanding the indications for surgical involvement in those with advanced stages. For example, significant downstaging of a locally advanced disease would be brought up for discussion to decide whether to offer the patient lobectomy for the minimal residual disease or continue with systemic therapy, etc.

Palliative care for stage IV patients who suffer from symptomatic malignant pleural or pericardial effusion includes invasive procedures done either by a radiologist or a thoracic surgeon. These procedures include talc pleurodesis (thoracoscopic or bedside), indwelling pleural catheter insertion, or pericardial drainage.

Radiotherapy Approaches

Radiotherapy is integrated with systemic therapy after multidisciplinary discussion. There are seven large radiotherapy departments in Israel, all attached to university-affiliated oncology centers. These centers have between three and five linear accelerators each, and there are two smaller centers with two linear accelerators each that opened recently and are satellites of the larger existing centers. All of the radiotherapy departments have linear accelerators capable of performing CT-based image-guided radiotherapy. Positron emission tomography-CT staging is routine for all patients with lung cancer. All centers have dedicated CT simulators capable of 4-dimensional planning.

Stereotactic body radiotherapy is offered to patients with early-stage NSCLC who are medically inoperable. It is performed using standard protocols of 54 Gy in three fractions for peripheral lesions or 50 Gy in five fractions for centrally located tumors and lesions close to the ribs. In Israel, patients with early stage III disease are often treated surgically, sometimes after preoperative chemoradiation, given usually at a dose of 60 Gy in 2-Gy daily fractions. More advanced stage III disease is treated with chemoradiation at a dose of 60 Gy to 74 Gy, depending on each center's protocol. Postchemoradiation durvalumab is approved and is already included in the Ministry

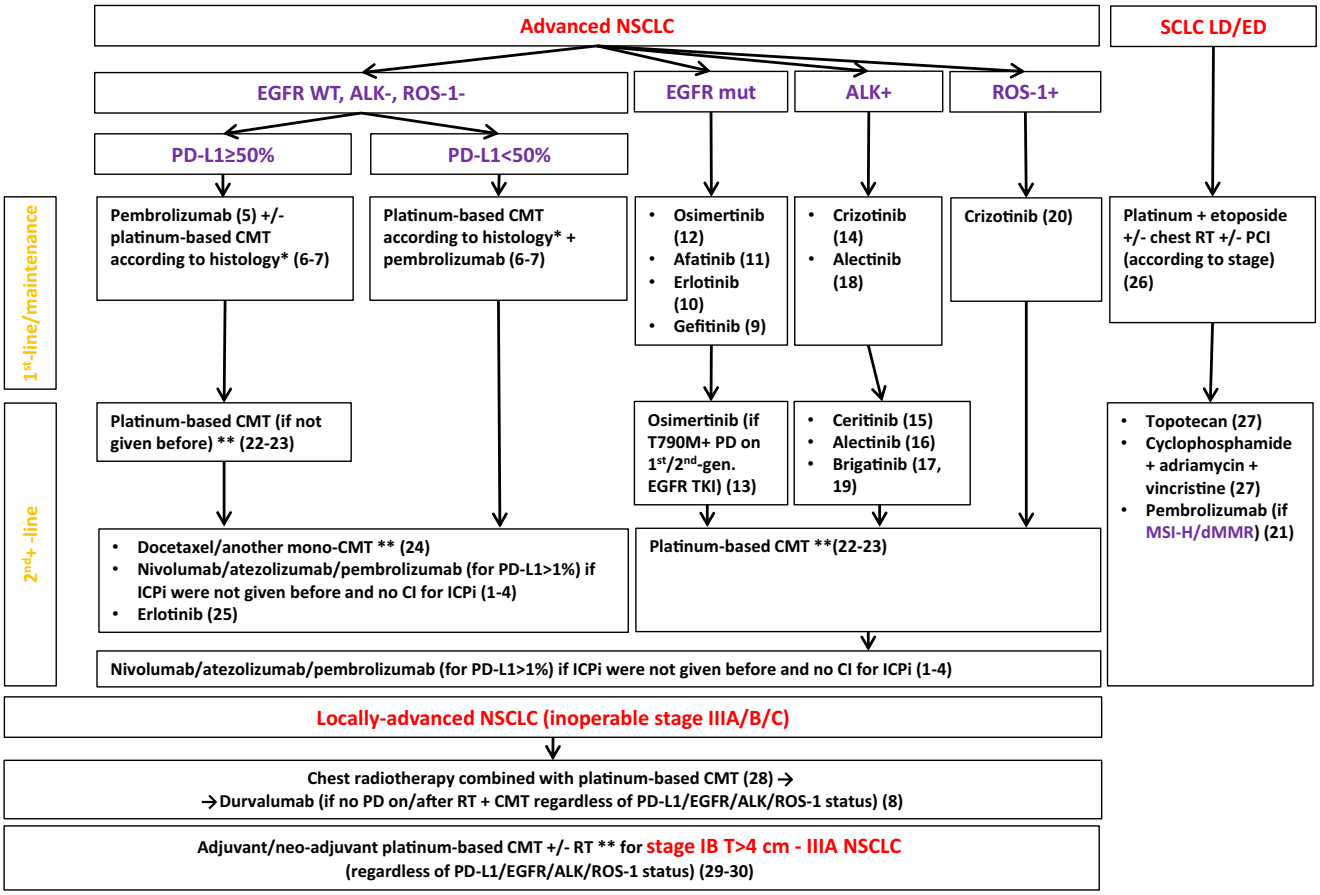

Figure 1. Systemic therapy. * Non-sq. histology: cisplatin/carboplatin + pemetrexed → pemetrexed maintenance (if CI for ICPi - cisplatin/carboplatin + pemetrexed/paclitaxel with or without bevacizumab → pemetrexed with or without bevacizumab maintenance); sq. histology: carboplatin + paclitaxel (if CI for ICPi - another platinum-based regimen can be used); ** Physician choice. ALK, anaplastic lymphoma kinase; CI, contraindication; CMT, chemotherapy; dMMR, mismatch repair deficient; ED, extensive disease; gen., generation; ICPi, immune check-point inhibitors; LD, limited disease; MSI-H, microsatellite instability high; mut, mutant; non-sq., non-squamous-cell; PCI, prophylactic cranial irradiation; PD, progressive disease; PD-L1, programmed death-ligand 1; RT, radiotherapy; sq., squamous-cell; TKI, tyrosine kinase inhibitors; WT, wild type.

of Health coverage for patients with inoperable stage III disease (Fig. 1).

Frail elderly patients with stage III disease may receive exclusive radiotherapy or sequential radiotherapy and systemic treatment. Patients with limited disease SCLC are treated with concomitant chemoradiation at a dose of 60 Gy in 30 daily fractions and are offered prophylactic whole-brain irradiation. Accelerated radiotherapy (45 Gy in twice-daily fractions) is offered to fit, younger patients. Patients with extensive disease who respond to chemotherapy are offered consolidative lung radiotherapy (Fig. 1).

Symptomatic bone metastases are usually treated with single-fraction palliative radiotherapy. Patients with good performance status and with up to 15 brain metastases are preferentially treated with stereotactic radiosurgery. Stereotactic body radiotherapy is offered to patients with oligometastases and for recurrent bone metastases including spine.

Systemic Therapy

In Israel, tissue genotyping is routinely performed for every patient with NSCLC at the time of advanced disease diagnosis. Immune checkpoint inhibitors as second- and third-line treatment of advanced NSCLC after progression on platinum-based chemotherapy are reimbursed in Israel since 2016 (nivolumab, since 2016; pembrolizumab, since 2017; atezolizumab, since 2018).[10-13] However, their use has diminished substantially with the implementation of pembrolizumab as a first-line monotherapy for PD-L1 greater than 50% in advanced NSCLC (reimbursed since 2017)[14] and, most recently, in combination with platinum-based chemotherapy first-line treatment regardless of PD-L1 expression (reimbursed since 2019).[15,16] Durvalumab for consolidation treatment of locally advanced inoperable NSCLC after the completion of combined chemoradiotherapy has been implemented since 2019 and is reimbursed regardless of PD-L1 tumor status.[17]

Table 2. Drug Availability per Tissue Type or Mutation Identified

Line	EGFR	ALK	ROS	BRAF	c-MET	Adenocarcinoma	Squamous
First	Osimertinib Afatinib Erlotinib Gefitinib	Crizotinib Alectinib	Crizotinib	Dabrafenib/ Trametinib[a]	Crizotinib[a]	Carboplatin or Cisplatin/ Pemetrexed/ Pembrolizumab	Carboplatin or Cisplatin/Paclitaxel/ Pembrolizumab
Second	Osimertinib (T790M)	Ceritinib Alectinib Brigatinib		Dabrafenib/ Trametinib[a]			
Third							

[a]Available with private insurance.
ALK, anaplastic lymphoma kinase; c-MET, mesenchymal-epithelial transition factor.

With regard to EGFR TKIs, gefitinib, erlotinib, afatinib, and, most recently, osimertinib are approved in Israel as a first-line treatment of advanced EGFR mutant NSCLC.[18-21] For patients who progress on first- or second-generation EGFR TKIs, osimertinib is approved after diagnosis of T790M mutation by droplet digital polymerase chain reaction in the blood, and is covered as well.[22] Sequential use of two different ALK TKIs is reimbursed for *ALK*-positive advanced NSCLC; the physician is free to decide among crizotinib, ceritinib, alectinib, and brigatinib.[23-26] It is important to emphasize that alectinib is approved as a first-line treatment as well,[27] whereas brigatinib can be used after progression on either crizotinib or alectinib.[28] Patients with *ROS1Mod*-rearranged advanced NSCLC are eligible for crizotinib, which is reimbursed for this indication since 2018.[29]

Pembrolizumab is approved for patients with mismatch repair–deficient advanced SCLC (reimbursed since 2018) and mesothelioma (reimbursed since 2019) after progression on standard platinum-based chemotherapy (reimbursed since 2018).[30]

The sequential use of all the available systemic treatment options is depicted in Figure 1.

Challenges

As mentioned previously, lung cancer screening is not included as an approved service in the Israeli Healthcare Basket. Although two excellence programs conducted in the private healthcare service are available to citizens who pay private insurance, the lack of screening covered by the health care system is a challenge and an issue that needs to be resolved. Low-dose CT scans are also available in most centers but not as a defined screening program.

Availability of imaging facilities is not optimal because queues are longer than required clinically. Invasive procedures are usually available within 2 weeks; however, the time to obtain pathologic reports is long. Molecular testing is available, but not in a reflex manner.

In terms of treatment, all Food and Drug Administration–approved therapies are approved in Israel also, and most of them are also reimbursed (Table 2). Drug approval for expensive therapies (e.g., immunotherapy) has a multiple requirement process, and its renewal every 3 months leads to delays in treatment and overwhelms the system with unnecessary tests. Treatment beyond progression is a difficult matter. There is a huge shortage of radiation oncologists, and the availability of accelerators is suboptimal, particularly in the periphery, where there is one accelerator per 600,000 citizens.

In summary, the Israeli health services provide updated services for lung cancer; however, they suffer from lack of screening and lack of imaging and radiation infrastructure and require administrative optimization for drug approval and reflex molecular profiling. With the already seen increased overall survival in this disease, we explore the urgent need for more experts in this field of practice.

References

1. Rosen B, Waitzbeg R, Merkur S. Israel: health system review. *Health Syst Transit*. 2015;17:1-212.
2. OECD (2020). Health spending (indicator) http://doi.org/10.1787/8643de7e-en. Accessed February 23, 2019.
3. Cancer data in Israel. Israeli Ministry of Health. https://www.health.gov.il/PublicationsFiles/cancer_israel.pdf. Accessed January X, 2019.
4. M. Amir and Co. Taxation of tobacco in Israel, 2018. http://meiramir.co.il/?dl_id=96. Accessed January X, 2019.
5. Data on smoking in Israel. Ministry of Health. https://www.health.gov.il/UnitsOffice/ICDC/HealthAndLifestyle/smoking/Pages/MOH_report.aspx. Accessed January X, 2019.
6. Shaham D, Breuer R, Copel L, et al. for the HM-ELCAP Cooperative Group. Computed tomography screening for lung cancer: applicability of an international protocol in a single-institution environment. *Clin Lung Cancer*. 2006;7:262-267.
7. Lung CT. Screening reporting & data system. https://www.acraccreditation.org/~/media/ACRAccreditation/Documents/LCS/Lung-Cancer-Screening-Technical-Specifications.pdf?la=en. Accessed January X, 2019.
8. Adult lung cancer screening technical specifications. https://www.acr.org/Clinical-Resources/Reporting-and-Data-Systems/Lung-Rads. Accessed January X, 2019.

9. The Medical Services Basket. https://www.health.gov.il/English/Topics/RightsInsured/RightsUnderLaw/Pages/SalServices.aspx. Accessed January X, 2019.
10. Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. *N Engl J Med*. 2015;373:123–135.
11. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. *N Engl J Med*. 2015;373:1627–1639.
12. Herbst RS, Baas P, Kim DW, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *Lancet*. 2016;387:1540–1550.
13. Rittmeyer A, Barlesi F, Waterkamp D, et al. Atezolizumab versus docetaxel in patients with previously treated non-small cell lung cancer (OAK): a phase 3, open-label, multicentre randomized controlled trial. *Lancet*. 2017;389:255–265.
14. Reck M, Rodríguez-Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small cell lung cancer. *N Engl J Med*. 2016;375:1823–1833.
15. Paz-Ares L, Luft A, Vicente D, et al. Pembrolizumab plus chemotherapy for squamous non-small-cell lung cancer. *N Engl J Med*. 2018;379:2040–2051.
16. Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. *N Engl J Med*. 2018;378:2078–2092.
17. Antonia SJ, Villegas A, Daniel D, et al. Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. *N Engl J Med*. 2017;377:1919–1929.
18. Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med*. 2009;361:947–957.
19. Rosell R, Carcereny E, Gervais R, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomized phase 3 trial. *Lancet Oncol*. 2012;13:239–246.
20. Yang J, Wu Y, Schuler M, et al. Afatinib versus cisplatin-based chemotherapy for EGFR mutation-positive lung adenocarcinoma (LUX-Lung 3 and LUX-Lung 6): analysis of overall survival data from two randomised, phase 3 trials. *Lancet Oncol*. 2015;16:141–151.
21. Soria JC, Ohe Y, Vansteenkiste J, et al. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. *N Engl J Med*. 2018;378:113–125.
22. Jänne PA, Yang J, Kim D, et al. AZD9291 in EGFR inhibitor-resistant non-small-cell lung cancer. *N Engl J Med*. 2015;372:1689–1699.
23. Solomon BJ, Mok T, Kim DW, et al. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. *N Engl J Med*. 2014;371:2167–2167.
24. Shaw AT, Kim TM, Crinò L, et al. Ceritinib versus chemotherapy in patients with ALK-rearranged non-small-cell lung cancer previously given chemotherapy and crizotinib (ASCEND-5): a randomised, controlled, open-label, phase 3 trial. *Lancet Oncol*. 2017;18:874–886.
25. Shaw AT, Gandhi L, Gadgeel S, et al. Alectinib in ALK-positive, crizotinib-resistant, non-small-cell lung cancer: a single-group, multicentre, phase 2 trial. *Lancet Oncol*. 2016;17:234–242.
26. Kim DW, Tiseo M, Ahn MJ, et al. Brigatinib in patients with crizotinib-refractory anaplastic lymphoma kinase-positive non-small-cell lung cancer: a randomized, multicenter phase II trial. *J Clin Oncol*. 2017;35:2490–2498.
27. Peters S, Camidge DR, Shaw AT, et al. Alectinib versus crizotinib in untreated ALK-positive non-small-cell lung cancer. *N Engl J Med*. 2017;377:829–838.
28. Hochmair M, Naber J, Schwab S, et al. Real-life experience with brigatinib in pretreated EML4-ALK translocated NSCLC patients. *J Thorac Oncol*. 2018;13:S799.
29. Shaw AT, Ou SH, Bang Y, et al. Crizotinib in ROS1-rearranged non-small-cell lung cancer. *N Engl J Med*. 2014;371:1963–1971.
30. Diaz L, Marabelle A, Kim T, et al. Efficacy of pemrolizumab in phase 2 KEYNOTE 164 and KEYNOTE 158 studies of microsatellite instability high cancers. *Ann Oncol*. 2017;28(suppl 5):v122–v141.