RECENT ADVANCES IN LUNG-CANCER TREATMENT

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Recent Advances in Lung-Cancer Treatment

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In the past decades, lung cancer is one of the most frequently diagnosed and fatal cancers in the world regardless of race, sex and country. Although the advocation of cigarette cessation slightly lower the incidence of lung cancer, the high mortality did not substantially drop for years. In the past two decades, the discovery of novel small-molecule targeting drugs and immune checkpoints inhibitors, the development of surgery tools and the improvement of radiotherapy protocols benefit the treatment of lung cancer. In this review, ameliorated techniques or new drugs that contributes to better efficacy of treatment will be introduced, in respect of surgery, chemotherapy, targeted therapy, immunotherapy and radiotherapy.

Introduction

Lung cancer is one of the most frequently diagnosed and lethal cancers revealed in demographics, with estimated 2.20 million new cases and 1.79 million deaths yearly[1]. In the US, lung cancer ranks second among all types of cancer in the number of estimated new cases in males and females respectively, and first in combination[2]. The causation can be binarily grouped into cigarette smoking and non-smoking (*e.g.*, second-hand smoke, biomass burning, air pollution, radiation exposure, genetic factors, infections, *etc.*), while the former contributes to 81% of lung cancer deaths via tobacco carcinogens[2,3]. With the positive correlation between cigarette uptake and lung cancer, the implementation of cigarette cessation and avoidance campaigns in developed countries has moderately alleviated the onset of lung cancer, which provides a paradigm of lung cancer prevention to the governments in less developing regions[3].

Lung cancer is universally classified into two main histologic types, small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), respectively, and NSCLC encompasses squamous cell lung cancer (SQCLC), adenocarcinoma (AdenoCA) and large cell anaplastic carcinoma (LCAC)[4]. In a historically welcome but currently less recommended staging method, both SCLC and NSCLC can be classified as either limited or extensive. Compared with the eighth edition of TNM staging and stage grouping for lung cancer, benign lung cancer in stage I, II and III is approximately scoped in limited stage characterized for its hemithorax localization, and the malignant form, or stage IV, is bracketed in the extensive stage that metastasizes beyond hemithorax[5,6]. In this review, both staging systems are assimilated in respect of that clinic data generated under limited/extensive staging remains valuable and it is not accurate to translate the older use to TNM staging.

Approximately 15% of patients with lung cancer are diagnosed as SCLC[7]. Developed from neuroendocrine cell precursors, cancerous cells of SCLC proliferate rapidly and are prone to early metastasis, leading to poor prognosis and consequently low overall survival (OS) rate (5-year OS: 10%)[7–9]. If cancerous cells have disseminated beyond hemithorax before diagnosis and systematic management, the estimated 2-year OS of patients is merely 8%[6]. Its proliferation nature and innate biology implicate corresponding clinical therapy, and the commonly suggested standard therapies in current SCLC clinical guidelines are platinum-based chemotherapy with cisplatin-etoposide (EP) doublet or concurrent chemoradiotherapy using cisplatin-EP and fractioned irradiation[10–12]. Optionally, surgical resection, prophylactic cranial irradiation (PCI) and adjuvant targeted/immune therapy can significantly enhance the OS of patients in specific stages[7]. Nevertheless, the lack of satisfying advances in the management of SCLC in the past three decades limits the OS of SCLC greatly[13]. Despite a lowering death rate in SCLC these years, Feuer and his colleagues[14] point out that the decline in incidences was almost the mere reason accounting for the reduced death rate in SCLC after evaluating the correlation of the advances in SCLC and death rate according to data from 2001 through 2016 in SEER-18 registry. Hence, a move in

therapy should be achieved to better manage SCLC clinically.

The majority of lung cancer is NSCLC, and its OS is comparatively higher than that of SCLC due to substantial improvement in management. Data in the US suggests that the 5-year relative survival (RS) rate of NSCLC is 26% in 2022, which is 19% higher than the RS of SCLC[15]. A gradual decline in the death rate to incidence rate ratio was also witnessed through data mining on the SEER-18 registry database, suggesting stepping progress in the management of NSCLC[14]. With platinum-based chemotherapy as the standard of care for NSCLC in the past decades, the progress is correlated with the advent of numerous novel immunotherapies or targeted therapies for patients with advanced NSCLC[16]. Surgery is also optional for either stage I, II or III NSCLC, while postoperative radiotherapy is recommended only for stage III patients[4,17]. If the tumor is unresectable, primary radiotherapy can be utilized for patients, for instance, stereotactic body radiotherapy (SBRT)[17].

In this paper, recent advances in management of lung cancer, either SCLC or NSCLC, will be described by reviewing the corresponding clinical trials and previously conducted meta-analyses. Progress in surgery, chemotherapy, targeted therapy, immunotherapy and radiotherapy will be mentioned, and attention will be stressed on recent benefits from small-molecule targeted drugs and monoclonal antibodies against immune checkpoints.

Surgery

Surgical Resection

The benefit of surgical resection on SCLC remains controversial. A meta-analysis found that the OS of patients in stage I, II and III SCLC was significantly increased in 13 respective studies (HR=0.56, 95% CI: 0.49–0.64, p<0.001), but just the contrast in two earlier-conducted randomized control trials (RCTs) (HR=0.77, 95% CI: 0.32–1.84, p=0.55)[18]. A similar systematic review of three selected RCTs indicated that surgical resection did not play a role in the management of LS-SCLC[19]. Interestingly, both reviews share two common reference RCTs in their study spectrum, which reflects the lack of currently available clinical data revealing the efficacy of surgical resection. Meanwhile, the low quality of evidence also limited the reliability of the results.

Despite the lack of a convincible deterministic conclusion, the clinical utilization of surgical resection has been performed on patients in LS-SCLC. The American College of Chest Physicians (ACCP) proposes a reference guideline for the care of SCLC, indicating that patients in clinical stage I SCLC are suggested, after adequate evaluation on metastasis, for surgical resection over non-surgical treatments, and adjuvant platinum-based chemotherapy is of recommendation[20]. This guideline is also endorsed by the American Society of Clinical Oncology (ASCO) after a thorough review[11]. Surgical resection is also recommended by the European Society for Medical Oncology (ESMO) and National Comprehensive Center Network (NCCN). ESMO suggests patients in clinical stage I-II (cT1-2N0) undergo surgery followed by adjuvant cisplatin-etoposide chemotherapy or concurrent chemoradiotherapy (CRT) in respect of postoperative pathological staging result[10]. NCCN similarly recommends patients in clinical stage I-IIA (T1-2, N0, M0) receive surgical resection as long as pathologic mediastinal staging is negative, and lobectomy is the preference[12].

For patients with NSCLC, surgical resection is the standard of care for those in stage I, II or some stage IIIA disease. Two systematic reviews investigated the efficacy of surgery on ES-NSCLC drawing a similar conclusion that it was difficult to determine the benefits of surgery on locoregional NSCLC, though several independently conducted trials put forward an overall positive perspective on surgery[21,22]. The result is also limited by the low quality of data outcome given sample insufficiency and methodological weakness. Nevertheless, both reviews accentuated: (1) The better efficacy of consecutive resection and mediastinal lymph node resection than that of resection with consequent lymph node sampling for patients with operable stage I-IIIA NSCLC; (2) Increased risk of tumor locoregional relapse after limited resection compared with total resection (*i.e.*, lobectomy) (HR=0.67, 95% CI: 0.44-1.02, p=0.062); (3) An elevated survival rate supporting surgery instead of radiotherapy follows chemotherapy as a regimen for stage IIIA NSCLC disease (HR=0.8, 95% CI: 0.45-1.42, p=0.456). With the

breakthroughs in methods and technology in diagnosis, staging and operation techniques, ESMO, NCCN, and ASCO now make consensus statements for operable patients with ES-NSCLC to undergo resection (lobectomy in preference) with adjuvant therapies[23–25].

Video-Assisted Thoracoscopic Surgery (VATS)

In recent years, the growing trend in the utilization of VATS on NSCLC patients releases the recovery pain and postoperative quality of life through its minimally invasive feature. Surgeons cut off small pieces of the chest wall instead of opening the thorax to remove cancer tissues with the assistance of a tiny camera and surgical tools. Compared with anterolateral thoracotomy, stage I NSCLC patients receiving VATS lobectomy were deemed to have a significantly lower clinically relevant pain in the first 24 hrs (VATS 38%, 95% CI 0.28-0.48 *vs* thoracotomy 63%, 95% CI 0.52-0.72, p=0.0012) and significantly less frequent episodes of moderate-to-severe pain ($p<0.0001$)[26]. Having superiority in the shorter hospitalization and less frequent postoperative complication, the efficacy of VATS lobectomy is not substantially impacted on the aspect of nodal upstaging, 30-day mortality and long-term survival compared to thoracotomy[27]. These results mark VATS as a promising next-level surgical technique for the current clinical management of ES-NSCLC.

Chemotherapy and Combination Targeted Therapy or Immunotherapy

Several types of chemotherapy drugs have been developed to kill cancer cells, most of which takes the advantage of cancer cells' rapid proliferation nature[28]. Lung cancers, especially SCLC, are typically feasible for chemotherapy with respect to the relatively short doubling time[8]. To date, there are six major groups of anticancer drugs, based on the mechanism of action, being under research or approved by FDA then available clinically, and briefly, they are: (1) alkylating agents that break DNA; (2) antibiotics that interrupt enzymes involved in DNA replication; (3) anti-metabolites that substitute natural building blocks of nucleic acid; (4) topoisomerase inhibitors that blocks the unwind of DNA hence repressing replication; (5) mitotic inhibitors that subdue cell division; (6) side-effect releasing drugs[28].

Drugs for SCLC

Among all drugs, platinum-based doublets, *e.g.*, cisplatin-etoposide, are the most widely utilized anticancer drugs for SCLC, taking the advantage of that SCLC consists of rapidly doubling cancer cells. Cisplatin is an alkylating agent that modifies DNA with alkyl group to induce cell cycle arrest and apoptosis, and etoposide is the inhibitor for topoisomerase II, which in combination significantly represses the normal cell function and proliferation. Clinically, regimen that four to six cycles of cisplatin/carboplatin in combination of etoposide/irinotecan chemotherapy is highly recommended for first-line therapy of SCLC with strong evidence according to ASCO, and four-cycles regimen is preferred for LS-SCLC[11].

Unfortunately, although SCLC usually response to cisplatin-etoposide chemotherapy during the first-line therapy, many patients relapse and develop refractory disease, who are deemed to move on for subsequent-line therapies. The drug resistance for cisplatin-etoposide is mostly because of drug detoxification, drug-accumulation inhibition, DNA repairment, competitive inhibition, *etc*[29]. Hence, several works were published in recent years focusing on enhancing the efficacy of platinum-based chemotherapy, most of which were combination targeted therapy or immunotherapy (suppl. table 1).

Veliparib

Poly (ADP-ribose) polymerase (PARP) is an enzyme family that catalyze the addition of ADP-ribosyl group to serval substrates including DNA, histones and nonhistone protein, which accounts for DNA damage repair via base excision mechanism primarily, and its inactivation induces synthetic lethality to genetic vulnerable cells[30,31]. Because SCLC overexpress PARP compared with adjacent normal lung epithelial cells, PARP is a potential target for the inhibition of cancerous proliferation[32].

In 2018, Eastern Cooperative Oncology Group (ECOG) published a phase II trial (ECOG-ACRIN 2511) investigating the efficacy of veliparib, a PARP inhibitor, in

combination with the first-line cisplatin-etoposide (CE) chemotherapy[32]. One hundred and twenty-eight participants were enrolled and randomly assigned to either CE+veliparib or CE+placebo arm, and the outcomes were satisfying. The median progression-free survival of CE+veliparib *v.s.* CE+placebo was 6.1 *v.s.* 5.5 months (HR=0.75, one-sided p=0.06), the median OS was 10.3 *v.s.* 8.9 months (HR=0.83, 80% CI: 0.64-1.07, one-sided p=0.17) and the overall response rate (ORR) was 71.9% *v.s.* 65.6% (p=0.57). The result showed that the addition of veliparib in first-line chemotherapy have efficacy in patients with ES-SCLC. Another phase II trial published two years later investigated the role of maintenance veliparib after CE+veliparib (CE+veliparib+maintenance veliparib), with the maintenance placebo as control (CE+veliparib+maintenance placebo)[33]. The result revealed an improved of median PFS in treated arm but no benefits on median OS.

Anlotinib

SCLC is featured by its high vascularization through high expression of vascular endothelial growth factor (VEGF) and its receptor (VEGFR), platelet-derived growth factor receptor-β (PDGFR-β), stem cell factor and c-kit on the surface of cells[34]. Anlotinib is a multitarget anti-angiogenesis drug inhibiting VEGFR-1/2/3, fibroblast growth factor receptor (FGFR)-1-4, PDGFR-α/β and c-kit[35]. Previously it has been approved by National Medical Products Administration (NMPA) as a third-line therapy for NSCLC[36].

Recently, a phase II study evaluated the efficacy of anlotinib as a third- or further- line therapy in SCLC[34]. A total of 82 and 38 participants were randomly assigned to anlotinib or placebo arm. During this fifteen-months trial, the median PFS had a significantly improvement in anlotinib arm (4.1 months, 95% CI: 2.8-4.2 months) in comparison to placebo arm (0.7 months, 95% CI: 0.7-0.8; HR=0.19, 95% CI: 0.12-0.32, p<0.0001). The prolonged OS was also witnessed in anlotinib *v.s.* placebo (7.3 months, 95% CI: 6.1-10.3 *v.s.* 4.9 months, 95% CI: 2.7-6.0; HR=0.53, 95% CI: 0.34-0.81, p=0.0029). Therefore, anlotinib is a promising third- or further- line therapy of SCLC for its improved PFS and OS over placebo.

Another phase II and single-arm trial was designed to research the efficacy of anlotinib as first-line therapy coapplied with cisplatin/carboplatin-etoposide chemotherapy[37]. From a total of 25 patients, the median PFS (10.3 months, 95% CI: 6.0-14.5), median OS (17.1 months, 95% CI: 11.1-19.3), ORR (90%) and disease control rate (DCR, 100%) were considerable and comparable. Thus, anlotinib is also promising for frontline therapy of SCLC and phase III RCT is warranted.

Bevacizumab

Bevacizumab is a humanized, monoclonal antibody against VEGF, whose efficacy in addition of standard chemotherapy to NSCLC has been proven via trial conducted by ECOG[38]. Because the feature of high angiogenesis in SCLC, the successful application on NSCLC predicts its utilization on SCLC. Consequently in 2009, ECOG established a phase II single-arm study (ECOG Study E3501, NCT00079040) to investigate the efficacy of frontline CE in combination of bevacizumab (CE+bevacizumab) to ES-SCLC[39]. The outcomes were satisfying that the median PFS was 4.7 months, the OS was 10.9 months and the ORR was 63.5%, suggesting larger RCT to evaluate it. In 2011, the result of SALUTE trial (NCT00403403) was published[40]. Among the 102 participants, 52 were assigned to bevacizumab in combination of platinum-etoposide chemotherapy and the rest were assigned to placebo arm with concurrent chemotherapy. The result showed improved median PFS (5.5 *v.s.* 4.4 months; HR=0.53, 95% CI: 0.32-0.86, in favor of bevacizumab), the ORR (58% *v.s.* 48%) and the median duration of response (DOR, 4.7 *v.s.* 3.2 months) but no significant benefit on median OS (9.4 *v.s.* 10.9 months). Hence, larger randomized phase III setting should be conducted to better assessing.

The GOIRC-AIFA FARM6PMFJM trial is a phase III, randomized study of cisplatin plus etoposide with or without bevacizumab as first-line treatment in extensive-disease SCLC[41]. Two hundred and four patients with untreated ES-SCLC were randomly assigned to either CE+bevacizumab arm (n=101) or CE arm (n=103). After a median follow-up of 34.9 months, median PFS of CE+bevacizumab *v.s.* CE was 6.7 *v.s.* 5.7 months (HR=0.72, 95% CI: 0.54-0.97, p=0.030), median OS was 9.8 *v.s.* 8.9 months, and 1-year survival rate was 37% *v.s.* 25% (HR, 0.78, 95% CI: 0.58 to 1.06, p=0.113). Therefore, although the significant increase was seen in median PFS, it did not translate to statistical significance in OS. However, maintenance treatment had a significant effect

on the OS (HR=0.6, 95% CI: 0.4-0.91, p=0.011), thus further evaluation of the maintenance treatment of bevacizumab in ES-SCLC was needed to better illustrate its efficacy.

Durvalumab and Tremelumumab

Programmed death-1 (PD-1) is an inhibitory receptor expressed by T lymphocyte that mediates the inhibition of immune response, avoiding overreaction of immune system to external or innate antigens[42]. In tumor microenvironment, the expression of PD-1 ligands (PD-L1/2) on tumor cells and antigen-presenting cells silences the infiltrating T cells, thus blocking the immune system[43]. Recently, the state-of-art antibodies against either PD-1 or PD-L1 greatly push the clinical immunotherapy to the front. Durvalumab, a selective, high-affinity human monoclonal antibody targeting PD-L1, has previously been indicated effective in management of stage III NSCLC after platinum-based chemotherapy[44,45].

Cytotoxic T-lymphocyte antigen-4 (CTLA-4) and CD28 are homologous but antagonistic in regulation of T cells, and the activation of CTLA-4 is associated with inhibition of immune response[46]. Both CTLA-4 and CD28 are able to specifically bind CD80 and CD86 but CTLA-4 shows relatively higher affinity to both CD80 and CD86, because of which, the relative up- or down- regulation of CTLA-4 and CD28 expression is analogous to volume control in immune checkpoint[46]. CTLA-4 blockade using monoclonal antibody is promising for cancer treatment, and tremelumumab is the very antibody[43].

In 2017, a phase 3 RCT, CASPIAN (NCT03043872), was launched to investigate the efficacy of platinum-based chemotherapy with or without durvalumab and tremelimumab to ES-SCLC[47]. An interim report was then published in 2019, regarding the comparing study of single factor, *i.e.,* the presence or absence of durvalumab, in first-line platinum-based chemotherapy. At that time, a total of 537 eligible patients was randomly assigned to either platinum-etoposide plus durvalumab group (n=268) or platinum-etoposide group (n=269). The OS of durvalumab group had a significant improvement (HR=0.73, 95% CI: 0.59-0.91, p=0.0047) with the median OS of durvalumab *v.s.* control group was 13.0 *v.s.* 10.3 months. The adverse events were comparably similar between both groups. Therefore, the interim findings endorsed the application of durvalumab plus platinum-based chemotherapy in first-line treatment of ES-SCLC.

However, the updated report from CASPIAN regarding the addition of tremelimumab to durvalumab plus platinum-based chemotherapy did not reveal improved efficacy[48]. At that time, the number of participants increase to 972. With the enlarged sampling, the efficacy of durvalumab plus chemotherapy remains consistent. But when evaluating platinum-based chemotherapy plus tremelimumab plus durvalumab group, no substantial improvement was witnessed in terms of OS, PFS, ORR and DOR compared with chemotherapy-only group. Overall, from the CASPIAN trial, durvalumab showed sustained OS benefits in addition to platinum-etoposide chemotherapy for the first-line treatment of ES-SCLC, but tremelimumab did not better improve the outcomes.

Pembrolizumab

Pembrolizumab is a high-affinity monoclonal antibody against PD-1, and the trials with unresectable stage III NSCLC patients revealed promising results[49]. In 2020, the result of a phase III RCT, regarding pembrolizumab or placebo plus platinum-based chemotherapy as first-line therapy for ES-SCLC, *i.e.*, KEYNOTE-604 (NCT03066778), was published[50]. In this trial, pembrolizumab group had a significantly improved PFS (HR=0.75, 95% CI: 0.61-0.91) and prolonged OS (HR=0.8, 95% CI: 0.64-0.98, p=0.0164), but the OS did not reach the significance threshold. No unexpected toxicity was witnessed in the treated group. Therefore, this result supports the benefit of pembrolizumab in ES-SCLC.

Serplulimab

Serplulimab is another anti-PD-L1 antibody recently promising in treating SCLC[51]. The ASTRUM-005 trial (NCT04063163) interim report in 2022 revealed significant outcome of serplulimab plus platinum-based chemotherapy for ES-SCLC[52]. Among the 585 eligible patients, 246 (42.1%) completed the trial before the data cutoff (October 22, 2021). In the serplulimab group, the median OS (15.4 months, 95% CI: 13.3 months-not evaluable) was significantly prolonged compared with placebo group (10.9 months, 95% CI: 10.0-14.3 months; HR=0.63, 95% CI: 0.49-0.82; p<0.001). The median PFS is also longer in serplulimab group (5.7 months *v.s.* 4.3 months; HR=0.48, 95% CI: 0.38-0.59). For the adverse

events, 33.2% in serplulimab *v.s.* 27.6% in placebo was grade 3 or higher. The trial is still ongoing and current evidence support the use of serplimumab and platinum-based chemotherapy as the first-line treatment for ES-SCLC.

Drugs for NSCLC

Historically, cytotoxic combination chemotherapy was the standard of care for patients (PS 0-1 or appropriate 2) advanced NSCLC, but recent advances in understanding the biology of NSCLC and rapid development of targeted therapy and immunotherapy have changed the methodology regarding advanced NSCLC[16,53]. Combination of monoclonal antibody and standard chemotherapy has becoming widely accepted and applied. Compared with SCLC, more small-molecule cytotoxic medicine and monoclonal antibodies have been developed for NSCLC to target crucial proteins in proliferation/apoptosis pathway and immune checkpoints, repressing tumor cells' proliferation *in situ* and inducing apoptosis[16]. By November 2022, forty-two kinds of drugs/drug combinations treating NSCLC have been approved by FDA (duplicates removed), but the corresponding number for SCLC is merely nine, with only two (etoposide and lurbinectedin) are not found in the list of NSCLC[54]. Due to this advantage, patients with NSCLC are deemed to have more optimistic survival rate in comparison to SCLC[7].

In platinum-based chemotherapy, cisplatin or carboplatin is most usually adopted as platinum agent and the addition of paclitaxel, gemcitabine, docetaxel, vinorelbine or pemetrexed constitutes the frequently used chemotherapeutical regimens for patients with PS of 0 or 1[55]. Among the above combinations, no single regimen yielded significant best result from four large multicenter studies[53]. However, combination cytotoxic chemotherapy is not appropriate for some patients with PS over 2, thus shared decision making, single-agent therapy or palliative care therapy alone may be utilized for those fragile patients, and therapy should also be terminated when progression or stable disease is seen and/or adverse events are intolerable[55]. To increase the efficacy or lower the toxicity of standard chemotherapy, addition or single use of targeted medicine or monoclonal antibodies are adopted, and actually, targeted/immunotherapy has become the mainstay in management of advanced NSCLC (suppl. table 2).

Gefitinib

EGFR is often mutated in NSCLC, and EGFR tyrosine kinase inhibitors (EGFR-TKIs) are widely used to treat EGFR-mutation positive, advanced NSCLC patients[56]. Gefitinib is a kind of EGFR-TKI, thereby blocking the downstream intracellular signaling pathways that activate cell proliferation, cell migration, cell survival and angiogenesis[57]. And it has been approved by FDA on July 13, 2015, as a drug to metastatic NSCLC[58].

In phase III NEJ002 trial, the efficacy of gefitinib was assessed in comparison to carboplatin-paclitaxel doublet as the first-line therapy for EGFR-mutation positive, advanced NSCLC, and the result showed significantly improved PFS and comparable OS between two arms[56]. Considering the chance of combination use of gefitinib and chemotherapy and other benefits, the researchers strongly recommended gefitinib as the first-line therapy. And in the later NEJ009 trial, gefitinib plus chemotherapy improved PFS and median OS in patients with untreated stage IV NSCLC compared with gefitinib alone, and the toxicity profile was acceptable, but the OS benefits should be validated retrospectively[59]. However, if the progression was witnessed with previous gefitinib-treated NSCLC, IMPRESS (NCT01544179) trial showed no substantially prolonged PFS between gefitinib plus chemotherapy group and gefitinib group (HR=0.86, 95% CI: 0.65-1.13, p=0.27), suggesting withdrawal of gefitinib after progression and the chemotherapy remains the standard of care[60].

Several researches have been conducted to investigate the efficacy of postoperative adjuvant gefitinib for LS-NSCLC. In 2013, the NCIC CTG BR19 (NCT00049543) study investigated adjuvant gefitinib *v.s.* placebo in completely resected stage IB-IIIA NSCLC, but they didn't exclude EGFR-mutation negatives from the trials[61]. Unexpectedly, there were no differences in terms of the disease-free survival (DFS) and OS, and neither in subgroup analyses with cases having positive mutations of EGFR (HR=0.86, 95% CI: 0.65-1.13, p=0.27), probably because of the inadequate samples. In the later CTONG1104 (NCT01405079) trial reported in 2020, adjuvant gefitinib demonstrated improved DFS compared

with adjuvant chemotherapy, but the advantage did not translate to OS[62].

Erlotinib

Erlotinib is another EGFR-TKI that was approved by FDA in 2004 as monotherapy in management of locally advanced or metastatic NSCLC[63]. In recent years, several researches have completed the head-to-head data from large clinical trials, revising the efficacy of erlotinib in more contemporary frame. In 2012, phase III EURTAC (NCT00446225) trial compared erlotinib and chemotherapy in first-line treatment of advanced NSCLC with EGFR mutations among European patients[64]. Although the trial was halted because it met its primary endpoint, the median PFS of erlotinib at the data cutoff was significant improved compared with standard chemotherapy (HR=0.37, 95% CI: 0.25-0.54, p<0.0001). Similarly in later ENSURE (NCT01342965) trial that investigated same topic but was conducted in Asia, statistical significance of median PFS was found in erlotinib group versus chemotherapy (HR=0.34, 95% CI: 0.22-0.51, p<0.0001), but the difference in median OS was not significant (HR=0.91, 95% CI: 0.63-1.31, p=0.607)[65]. When it comes to second-line treatment, although TITAN (NCT00556322) trial also did not show OS advantage of erlotinib in comparison of docetaxel or pemetrexed (HR=0.96, 95% CI: 0.78-1.19, p=0.73), the difference on toxicity profile in treated group kept erlotinib as a choice for second-line therapy[66].

The potential of erlotinib being used as adjuvant drug was assessed. The RADIANT (NCT00373425) trial investigated the efficacy of erlotinib versus placebo as postoperative adjuvant therapy[67]. All the patients (n=973) expressed EGFR in tumor tissues, but only 161 patients (16.5%) had EGFR mutations. Though the DFS outed by subgroup analyses in both EGFR-expressing and EGFR-mutation positive did not support erlotinib as adjuvant drug, the researchers considered further evaluation based on EGFR-mutation positive patients was warranted. In 2018, phase II SELECT trial reported that adjuvant erlotinib demonstrated prolonged 2-year DFS compared with historic genotype-matched controls, thus the efficacy of erlotinib as adjuvant therapy remains controversial but promising[68].

Afatinib

Afatinib is an orally available ErbB family inhibitor that irreversibly and selectively blocks homodimer or heterodimer forms of EGFR[69]. Two studies conducted in China, the Republic of Korea and Thailand, *i.e.*, LUX-Lung 3 (NCT01121393) and LUX-Lung 6 (NCT00949650), demonstrated significant improvement in terms of PFS (LUX-Lung 3: HR=0.54, p=0.1378; LUX-Lung 6: HR=0.47, p=0.1060) and ORR by afatinib in management of NSCLC with asymptomatic brain metastases and common EGFR mutations, compared with chemotherapy, as the first-line therapy[69]. In LUX-Lung 7 (NCT01466660) that compared afatinib with gefitinib, afatinib did not show a privilege outcome in OS versus gefitinib in management of stage IIIB/IV, EGFR-mutation positive NSCLC, but the PFS and ORR were increased in afatinib group with acceptable toxicity profile[70]. Another lateral trial, LUX-Lung 8 (NCT01523587), investigated afatinib and erlotinib comparatively as second-line treatment for stage IIIB/IV SQCLC, demonstrating prolonged OS (HR=0.81, 95% CI: 0.69-0.95, p=0.0077) and PFS (HR=0.81, 95% CI: 0.69-0.96, p=0.0103) in favoring of afatinib group[71]. In view of the promising results and the advantage of oral uptake, afatinib was approved by FDA as a drug treating metastatic NSCLC[72].

Pembrolizumab

Besides the benefits of ES-SCLC, pembrolizumab also performs well in the management of advanced NSCLC, and it has been proved by FDA to treat metastatic NSCLC[73]. The KEYNOTE-024 (NCT02142738) trial randomly assigned 305 patients into either pembrolizumab or chemotherapy group to compare the efficacy as first-line therapy managing advanced NSCLC[74,75]. All the participants had PD-L1 tumor proportion score >= 50%. The result showed improved median PFS (HR=0.50, 95% CI: 0.37-0.68, p<0.001), median OS (HR=0.62, 95% CI: 0.48-0.81) and ORR (44.8% *v.s.* 27.8%) over chemotherapy group. The later KEYNOTE-189 (NCT02578680) trial showed a significant longer estimated 12-month OS (HR=0.49, 95% CI: 0.38-0.64, p<0.001) and PFS (HR=0.52, 95% CI: 0.43-0.64, p<0.001) in pembrolizumab plus chemotherapy group compared with chemotherapy alone among patients with metastatic non-squamous NSCLC[76]. And a complimentary trial,

KEYNOTE-407 (NCT02775435), demonstrated the treatment advantage of combination pembrolizumab and chemotherapy in comparison of chemotherapy alone in first-line therapy for metastatic SQCLC[77]. The outcomes from trials above together illustrated the advantages of pembrolizumab in first-line therapy of PD-L1 highly-expressed advanced NSCLC.

Pembrolizumab is also effective for second-line therapy for previously treated, advanced PD-L1-positive NSCLC. The KEYNOTE-010 (NCT01905657) trial randomized eligible participants (n=1034) into either pembrolizumab or docetaxel group, the results showed prolonged stratified PFS and OS in pembrolizumab group either with a dose of 2 mg/kg or 10 mg/kg [78,79]. Moreover, the grade 3-5 adverse events were less common in pembrolizumab group. Thus, the result suggesting pembrolizumab was a new treatment option for the mentioned population.

Nivolumab

Nivolumab is a fully human IgG4 monoclonal antibody targeting PD-1 to restore antitumor immunity[80]. After initial approval for NSCLC, nivolumab is exclusively used for recurrent advanced disease and tumor with progression during the first-line chemotherapy[81]. CheckMate 017 (NCT01642004) and CheckMate 057 (NCT01673867) are the complementary researches that investigated the efficacy of nivolumab versus docetaxel as second-line therapy in SQCLC and non-squamous NSCLC, respectively[80,82,83]. In CheckMate 017, the result showed that the median OS for nivolumab and docetaxel were 9.2 months and 6.0 months (HR=0.59, 95% CI: 0.44-0.79, p<0.001); and the median OS from CheckMate 057 were 12.2 months and 9.4 months in favor of nivolumab (HR=0.73, 95% CI: 0.59-0.89, p=0.002). With substantially reduced grade 3-4 adverse events in nivolumab group of either trial, nivolumab demonstrated benefits in both efficacy and safety aspects with respect to second-line treatment of advanced NSCLC. Considering virtually all participants in both trials were Caucasians, a more recent phase III trial, CheckMate 078 (NCT02613507), was conducted to revise the same topic among patients that were predominantly Chinese[84]. Among 504 enrolled participants, the median OS in nivolumab and docetaxel were 12.0 months and 9.4 months, respectively (HR=0.68, 97.7% CI: 0.52-0.90, p=0.0006), indicating significant prolonged OS in nivolumab group. The frequency of grade 3 or greater adverse events was 10% with nivolumab and 48% with docetaxel, suggesting improved safety by nivolumab single-agent therapy.

In 2022, outcomes of CheckMate 816 (NCT02998528), a randomized phase 3 trial that evaluated neoadjuvant nivolumab and chemotherapy in resectable NSCLC, were published[85]. In this trial, eligible patients (n=505) with stage IB-IIIA NSCLC received either nivolumab plus chemotherapy or chemotherapy alone before undergoing surgical resection. After follow-up, the significantly prolonged median event-free survival (HR=0.63, 95% CI: 0.43-0.91, p=0.005) and pathological complete response (24.0% *v.s.* 2.2%, OR=13.94, 99% CI: 3.49-55.75, p<0.001) were witnessed, favoring combination neoadjuvant nivolumab and chemotherapy. Additionally, the addition of nivolumab did not increase the occurrence of adverse events or interfered surgical resection. Hence, nivolumab plus chemotherapy is promising as neoadjuvant therapy for resectable NSCLC.

Atezolizumab

Atezolizumab is a monoclonal antibody that specifically binds to PD-L1, and its efficacy as first-line or second-line therapy for advanced NSCLC has been proved by several studies[86–91]. In IMpower110 (NCT02409342) trial, five hundred and fifty-two patients with PD-L1 TPS>=1% or tumor-infiltrating immune cells>=1% stage IV NSCLC were randomly assigned to either atezolizumab and chemotherapy group as first-line treatment[86]. In the subgroup analyses for high-expressing PD-L1 patients, the median OS was longer by 7.1 months (HR=0.59, p=0.01), and the adverse events did not differ substantially between the two arms for all patients. Parallelly, two complementary phase 3 trials, IMpower131 (NCT02367794) and IMpower132 (NCT02657434), investigated the combinational use of atezolizumab and chemotherapy in either SQSCLC or non-squamous NSCLC[87,88]. In the intent-to-treat population in IMpower131, both median PFS (HR=0.71, 95% CI: 0.60-0.85, p=0.0001) and median OS (HR=0.88, 95% CI: 0.73-1.05, p=0.16) improved in atezolizumab plus chemotherapy group compared with chemotherapy alone. And in IMpower132, a similar result was attained that the median PFS improvement was statistically significant (HR=0.60, 95% CI: 0.49-0.72, p<0.0001) and median OS

increase but was not significant (HR=0.86, 85% CI: 0.71-1.06, p=0.1546) in atezolizumab plus chemotherapy group for patients with non-squamous NSCLC. One step further, as the benefits of combination bevacizumab and chemotherapy in treatment of advanced NSCLC were formerly proved, the phase III IMpower150 (NCT02366143) trial studied the efficacy of atezolizumab (A) plus bevacizumab (B) plus chemotherapy (CP) as first-line therapy for stage IV non-squamous NSCLC[91]. The result showed insignificant improvement in terms of median OS and median PFS in A+B+CP group versus B+CP group, and no differences between A+CP and B+CP, suggesting slightly increased benefits of co-addition of atezolizumab and bevacizumab to first-line chemotherapy. The outcomes from the above four independent trials together supported atezolizumab to be added to frontline therapy for advanced NSCLC.

For second-line therapy to advanced NSCLC, atezolizumab also demonstrated benefits compared with docetaxel. Phase II POPLAR (NCT01903993) and phase III OAK (NCT02008227) trial investigated this topic recently[89,90]. Among all patients expressing PD-L1, atezolizumab benefited the OS in comparison of docetaxel, and the HR (95% CI) of deaths was 0.76 (0.58-1.00) and 0.78 (0.68-0.89) respectively in POPLAR and OAK. With consistent survival benefits and safety profile, atezolizumab was suggested being an option for previously treated advanced NSCLC[92].

Radiation

A high-energy beam is adopted to break the DNA in cancer cells, hence devastating tumors. Its features of high directivity and high energy enable technicians to eliminate cells in specific sites. Previously, we discuss the benefits of either invasive or minimally invasive surgery for patients with limited-stage lung cancer. In this part, radiotherapy is considered a surrogate for tumors that are thorax-localized and inoperable.

Chemoradiotherapy (CRT) in LS-SCLC

Concurrent CRT is the mainstay of treatment for LS-SCLC. Chemotherapy conducted with platinum-based doublet has long been the gold standard for patients with SCLC, and cisplatin-etoposide is the preferred regimen. Additionally, two meta-analyses published in 1992 validated the positive role of thoracic radiotherapy in the management of LS-SCLC[8]. Concurrent CRT is then introduced clinically, especially for patients having undergone surgical resection[10,12]. For inoperable SCLC, concurrent CRT is an alternative for patients with a performance status (PS) of 0-1, while sequential CRT is less toxic for more vulnerable patients (PS≥2)[10]. Detailed chemo-regimens will be discussed in the next section. Here, the dose, fractionation and timing of radiation will be reviewed.

To date, the standard of care for LS-SCLC is twice-daily concurrent CRT (BD-CRT)[93]. Two trials have investigated the superiority of either BD-CRT and once-daily concurrent CRT (OD-CRT) (INT0096[94] and CONVERT[95] [NCT00433563]).

The first trial indicated the superiority of BD-CRT[94]. It randomized the patients into two arms that were delivered with 4 cycles of cisplatin-etoposide chemotherapy and, concurrently, radiotherapy at a dose of either 1.8 Gy in 25 treatments within 5 weeks (once-daily group) or 1.5 Gy in 30 treatments within 3 weeks (twice-daily group). Radiotherapy commenced at the same time as the first 3-week cycle of chemotherapy and all the patients receive prophylactic cranial irradiation (PCI) after CRT. As a result, participants receiving twice-daily concurrent therapy had significantly improved survival compared with the one-daily arm (p=0.04), in terms of 2-year OS (twice-daily group 47±3% *vs* once daily group 41±3%) and 5-year OS (26±3% *vs* 16±3%), and the estimated HR of once-daily arm compared with twice-daily arm is 1.2 (95% CI: 1.0-1.6).

The other investigation, namely, CONVERT, was conducted to show the superiority of OD-CRT, but no significant improvement was witnessed[95]. In this phase III trial, patients were randomly assigned to receive radiotherapy at a dose of either 45 Gy within 30 twice-daily fractions of 1.5 Gy or 66 Gy within 33 once-daily fractions of 2 Gy commencing at the second 21-days cycle of cisplatin-etoposide chemotherapy (4-6 cycles in total). The absolute difference of 2-year OS (ΔOS2) between both arms was 5.3% (95% CI: -3.2%-13.7%) and ΔOS5 was 2.8% (95% CI: -6.4%-12.0%). Because the toxicity between both arms was similar, no superiority of OD-CRT

over BD-CRT was witnessed.

A phase II trial (NCT02041845) investigated the benefits of enhanced dosage of radiotherapy in BD-CRT[96]. The participants randomly assigned into two arms received either 45 Gy in 30 twice-daily fractions and 60 Gy in 40 twice-daily fractions, with intravenous cisplatin- or carboplatin-etoposide regimen. The 2-year OS of the 60 Gy group was higher than that of the 45 Gy group (74.2% [95% CI: 63.8%-82.9%] *vs* 48.1% [36.9%-59.5%]), and the odd ratio is 3.09 (95% CI: 1.62-5.89, p=0.0005), indicating significant survival improvement at higher radiotherapy dose of 60 Gy compared with conventional 45 Gy.

To summarize, the optimal management for LS-SCLC is concurrent CRT encompassing platinum-based chemotherapy and twice-daily high-dose radiotherapy. And the dosage of radiation has the potential to increase over currently prevailing protocols for better efficacy, but it still needs more validation.

Stereotactic Body Radiation Therapy in LS-NSCLC

SBRT, also termed stereotactic ablative radiotherapy (SABR), has become an outstanding alternative to surgery for medically inoperable patients with LS-NSCLC in recent years. The technicians deliver extremely precise and intense doses of radiation to eliminate cancer cells with minimal invasion of adjacent tissues[97]. There were 4 phase III trials investigating the efficacy advantage between SBRT and surgery (STARS[98] [NCT00840749], ROSEL[98] [NCT00687986], ACOSOG Z4099[99] [NCT01336894] and SABRTooth[100] [NCT02629458]). But unfortunately, all were terminated without achieving predefined targets because of poor accrual, since it is difficult to consent patients to be randomized into two different treatments. However, according to indirect comparisons, the survival rate of LS-NSCLC patients receiving SBRT is worse than those receiving surgical resection, which is probably because the patients with worse PS tend to take SBRT[101]. Therefore, SBRT is not the priority but is still considerable in the management of LS-NSCLC.

Prophylactic Cranial Irradiation

PCI is feasible for both NSCLC and SCLC to prevent potential brain metastasis (BM) after surgery and CRT[102]. The brain is one of the most frequent metastatic sites of lung cancers, but the intact blood-brain barrier blocks the application of most cytotoxic drugs and even the immune system to kill disseminated cells, hence making the brain a sanctuary site or greenhouse for cancer[102]. PCI adopts the advantage of high penetration of radiation to deliver intense beams across the blood-brain barrier as prophylaxis. A meta-analysis in 2019 revised the efficacy of PCI in SCLC, via pooled analysis of seven selected studies (n=2114), and the outcome showed a decrease of BM (HR=0.45, 95% CI: 0.38-0.55, p<0.001) and improvement of OS (HR=0.81, 95% CI: 0.67-0.99, p<0.001) in PCI group[103]. But heterogeneity was found in terms of OS (I^2=74.1%, p=0.001), largely because of post-initial-CRT brain imaging. Another meta-analysis in 2018 selected seven RCTs to analyze the advantage of PCI to prevent BM in NSCLC[104]. Although the OS conclusion was not reported, BM decreased significantly by 13% (relative risk=0.33, 95% CI: 0.22-0.45). Li *et al*[105] analyzed 15 trials involving 2418 NSCLC participants in stage II-III, resulting that BM was significantly reduced in squamous cell carcinoma (p=0.02), but not in adenocarcinoma (p=0.07) and other pathological types(p=0.29), which reflected the different efficacy of PCI on BM in different subtypes of NSCLC.

The brain serves as a nerve center in the body, thus sophisticated research should be conducted to evaluate the neurological impairment induced by PCI, which is correlated with the patient's cognitive function and, consequently, quality of life (QoL). Results from NVALT-11/DLCRG-02 phase III study suggested that, with a median follow-up of 48.5 (95% CI: 39-54) months, PCI (36 Gy in 18 fractions, 30 Gy in 12 fractions, or 30 Gy in 10 fractions) had no significant clinically related impact on health-related quality of life (HRQoL) of patients with stage III NSCLC, but grade 1/2 memory impairment and cognitive disturbance were observed in PCI arm[106]. Stuschke *et al*[107] found that stage IIIA/IIIB NSCLC patients either receiving or not receiving PCI (30 Gy in 15 fractions) suffered impairments in attention and visual memory, and T2-weighted magnetic resonance imaging

revealed higher grade of white matter abnormalities in the PCI arm. For extensive-disease SCLC, a 3-year phase III trial found that mean scores for hair loss and fatigue were statistically significant between PCI (short and relatively low-dose scheme, not specified) and control arms, indicating expected treatment-related impact by PCI, and the initially significant time was 6 weeks post-PCI for both arms[108]. As a precaution to the negative effect of PCI, PREMER (NCT02397733) trial investigated whether hippocampal avoidance during PCI (25 Gy in 10 fractions) preserves the cognitive function of patients with SCLC, and the results revealed better conservation of cognitive function in scores of both delayed free recall (DFR) and Free and Cued Selective Reminding Test (FCSRT)[109]. However, the incidence of BM, OS and QoL were not significantly different between both groups.

By and large, PCI is effective for prophylaxis of BM for patients with lung cancer, but the possible treatment-related impairments should be informed to the patients. Hippocampal avoidance is a potential strategy to lower the decline in cognitive functions caused by PCI, but further investigations should be established to test its influence on PCI efficacy. Moreover, because of the neurological impairment, PCI should be applied after deliberation to avoid overtreatment.

Conclusion

Despite progress is achieved regarding conventional chemotherapy, radiotherapy and surgery in management of lung cancer, recent advances in understanding the biology of lung cancer and immune checkpoints tremendously benefit the methodology evolution in cancer therapy. Compared with NSCLC, fewer novel drugs are approved for clinical use to treat SCLC, which results in poor prognosis and relatively higher death rate. Recent progress of serplulimab in treating SCLC ignites the future of immunotherapy. Nevertheless, more clinical trials are warranted to further validate its benefits in treatment of different lines and stages SCLC with or without additional drugs. Future works should focus on developing optional drugs and treatment protocols for definitive therapy or precision medicine following staging and histology analysis of patients' cancer phenotype and even pedigree.

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Supplementary Table 1. Drugs tested for SCLC treatment in recent years.

Drugs	Role	Phase	Line	Cancer	Pub.	N	Arms	Reg. Nbr.
				Targeted therapy				
saracatinib	Src-kinase inhibitor	2	2	ES-SCLC	2014	23	Saracatinib	/
Sunitinib	VEGFR inhibitor	2	M	ES-SCLC	2015	138	CE+maintenance sunitinib v.s. CE+maintenance P	NCT00453154
Vismodegib	IGF-1R inhibitor	2	1	ES-SCLC	2016	152	CE+vismodegib *v.s.* CE	NCT00887159
vandetanib	Angiogenesis inhibitor	2	1	ES-SCLC	2016	74	PE+Vandetanib *v.s.* PE+P	NCT00613626
Pravastatin	Ras inhibitor	3	1	SCLC	2017	846	Std. ChT+pravastatin *v.s.* Std. ChT+P	NCT00433498
Veliparib	PARP inhibitor	2	1	ES-SCLC	2018	128	CE+veliparib *v.s.* CE+P	NCT01642251
		2	1	ES-SCLC	2021	181	CE+veliparib+maintenance veliparib v.s. CE+P	NCT02289690
Roniciclib	CDK inhibitor	2	1	ES-SCLC	2019	140	CE+roniciclib *v.s.* CE+placebo	NCT02161419
Anlotinib	Angiogenesis inhibitor	2	3	SCLC	2021	120	Anlotinib *v.s.* P	NCT03059797
		2	1	SCLC	2022	25	Anlotinib	/
				Immunotherapy				
Ipilimumab	Anti-CTLA-4 antibody	3	1	ES-SCLC	2016	1132	PE+Ipilimumab *v.s.* PE+P	NCT01450761
Bevacizumab	Anti-VEGF antibody	2	1	ES-SCLC	2009	63	CE+bevacizumab+maintenance bevacizumab	NCT00079040
		2	1	ES-SCLC	2011	102	PE+bevacizumab v.s. PE+P	NCT00403403
		3	1	ES-SCLC	2016	204	CE+bevacizumab+maintenance bevacizumab v.s. CE+P	/
Rilotumumab	Anti-HGF antybody	2	1	ES-SCLC	2017	185	PE+Rilotumumab *v.s.* PE+P	NCT00791154
Ganitumab	Anti-HGF antybody	2	1	ES-SCLC	2017	185	PE+Ganitumab *v.s.* PE+P	NCT00791154
Durvalumab	Anti-PD-L1 antibody	3	1	ES-SCLC	2019	537	PE+Durvalumab *v.s.* PE	NCT03043872
Durvalumab-Tremelimumab	Durvalumab: anti-PD-L1 antibody; Tremelimumab: anti-CTLA-4 antibody	3	1	ES-SCLC	2021	805	PE+Durvalumab+Tremelimumab *v.s.* PE+Durvalumab *v.s.* PE	NCT03043872
pembrolizumab	Anti-PD-1 antibody	1/2	1	LS-SCLC	2020	45	concurrent CRT+Pembrolizumab	/
		3	1	ES-SCLC	2020	453	PE+pembrolizumab *v.s.* PE+P	NCT03066778
serplulimab	Anti-PD-1 antibody	3	1	ES-SCLC	2022	585	Std. ChT+Serplulimab *v.s.* Std. ChT+P	NCT04063163
				Antibody-Drug Conjugate				
Rovalpituzumab Tesirine	Anti-DDL3 antibody	3	2	DLL3-High SCLC	2021	444	Rovalpituzumab-Tesirine *v.s.* Topotecan	NCT03061812
		3	M	DLL3-High SCLC	2021	748	PE+maintenance Rovalpitumab v.s. PE+maintenance P	NCT03033511

Abbreviations: CE: cisplatin-etoposide; M: maintenance; N: number of patients; P: placebo; PE: platinum-etoposide; Pub.: published time; Reg. Nbr.: registration number; Std. ChT: standard chemotherapy.

Supplementary Table 2. Drugs tested for NSCLC treatment in recent years.

Drugs	Trial Name	Line	Cancer	Arms	Reg. Nbr.
			Targeted therapy		
Gefitinib	NEJ002	1	Advanced NSCLC	Gefitinib *v.s.* ChT	/
	NEJ009	1	Stage IV NSCLC	Gefitinib *v.s.* gefitinib +ChT	/
	NCIC CTG BR19	Adj.	Stage IB-IIIA NSCLC	Gefitinib *v.s.* P	NCT00049543
	IMPRESS	2	Advanced NSCLC	Gefitinib+ChT *v.s.* P+ChT	NCT01544179
	ADJUVANT-CTONG1104	Adj.	Stage II-IIIA NSCLC	Gefitinib *v.s.* ChT	NCT01405079
Erlotinib	EURTAC	1	Advanced NSCLC	Erlotinib *v.s.* ChT	NCT00446225
	TITAN	2	Advanced NSCLC	Erlotinib *v.s.* ChT	NCT00556322
	ENSURE	1	Stage IIIB/IV NSCLC	Erlotinib *v.s.* ChT	NCT01342965
	RADIANT	Adj.	Stage IB-IIIA NSCLC	Erlotinib *v.s.* P	NCT00373425
	OPTIMAL, CTONG-0802	1	Advanced NSCLC	Erlotinib *v.s.* ChT	NCT00874419
	SELECT	Adj.	Stage IA-IIIA NSCLC	Erlotinib	/
Afatinib	LUX-Lung 3	1	NSCLC with brain metastasis	Afatinib *v.s.* ChT	NCT01121393
	LUX-Lung 4	1	Stage IIIB-IV AdenoCA	Afatinib	NCT00711594
	LUX-Lung 6	1	NSCLC with brain metastasis	Afatinib *v.s.* ChT	NCT00949650
	LUX-Lung 7	1	Stage IIIB/IV NSCLC	Afatinib *v.s.* gefitinib	NCT01466660
	LUX-Lung 8	2	Stage IIIB/IV SQCLC	Afatinib *v.s.* erlotinib	NCT01523587
			Immunotherapy		
Pembrolizumab	KEYNOTE-010	2	Advanced NSCLC	Pembrolizumab *v.s.* docetaxel	NCT01905657
	KEYNOTE-024	1	Advanced NSCLC	Pembrolizumab *v.s.* ChT	NCT02142738
	KEYNOTE-189	1	Metastatic non-squamous NSCLC	Pembrolizumab+ChT *v.s.* P+ChT	NCT02578680
	KEYNOTE-407	1	Metastatic SQCLC	Pembrolizumab+ChT *v.s.* P+ChT	NCT02775435
Necitumumab	INSPIRE	1	Stage IV non-squamous NSCLC	Necitumab+ChT *v.s.*ChT	NCT00982111
	SQUIRE	1	Stage IV non-squamous NSCLC	Necitumab+ChT *v.s.* ChT	NCT00981058
Nivolumab	CheckMate 017	2	Recurrent stage IIIB/IV squamous-cell NSCLC	Nivolumab *v.s.* docetaxel	NCT01642004
	CheckMate 057	2	Stage IIIB/IV/recurrent non-squamous NSCLC	Nivolumab *v.s.* docetaxel	NCT01673867
	CheckMate 078	2	Stage IIIB/IV/recurrent NSCLC	Nivolumab *v.s.* docetaxel	NCT02613507
	CheckMate 227	2	Stage IV/recurrent NSCLC	Nivolumab+ipilimumab *v.s.* nivolumab *v.s.* ChT	NCT02477826
	CheckMate 816	Neoadj.	Stage IB to IIIA resectable NSCLC	Nivolumab+ipilimumab *v.s.* nivolumab+ChT *v.s.* ChT	NCT02998528
Atezolizumab	IMpower010	Adj.	Resected stage II–IIIA NSCLC	Atezolizumab after adjuvant ChT *v.s.* best supportive care after adjuvant ChT	NCT02486718
	IMpower110	1	Stage IV NSCLC	Atezolizumab *v.s.* ChT	NCT02409342

	IMpower131	1	Stage IV squamous NSCLC	Atezolizumab+carboplatin+paclitaxel *v.s.* atezolizumab+carboplatin+nab-paclitaxel *v.s.* carboplatin+nab-paclitaxel	NCT02367794
	IMpower132	1	Stage IV non-squamous NSCLC	Atezolizumab+ChT *v.s.* ChT	NCT02657434
	IMpower150	1	Stage IV non-squamous NSCLC	Atezolizumab+bevacizumab+ChT *v.s.* bevacizumab+ChT	NCT02366143
	POPLAR	2	Stage IIIB or IV NSCLC	Atezolizumab *v.s.* docetaxel	NCT01903993
	OAK	2	Stage IIIB or IV NSCLC	Atezolizumab *v.s.* docetaxel	NCT02008227

Abbreviations: Adj.: adjuvant; ChT: chemotherapy; Neoadj.: neoadjuvant; p: placebo; Reg. Nbr.: registration number.