Emerging therapeutic agents for lung cancer

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Abstract
Lung cancer continues to be the most common cause of cancer-related mortality worldwide. Recent advances in molecular diagnostics and immunotherapeutics have propelled the rapid development of novel treatment agents across all cancer subtypes, including lung cancer. Additionally, more pharmaceutical therapies for lung cancer have been approved by the US Food and Drug Administration in the last 5 years than in previous two decades. These drugs have ushered in a new era of lung cancer management that have promising efficacy and safety and also provide treatment opportunities to patients who otherwise would have no conventional chemotherapy available. In this review, we summarize recent advances in lung cancer therapeutics with a specific focus on first in-human or early-phase I/II clinical trials. These drugs either offer better alternatives to drugs in their class or are a completely new class of drugs with novel mechanisms of action. We have divided our discussion into targeted agents, immunotherapies, and antibody drug conjugates for small cell lung cancer (SCLC) and non-small-cell lung cancer (NSCLC). We briefly review the emerging agents and ongoing clinical studies. We have attempted to provide the most current review on emerging therapeutic agents on horizon for lung cancer.

Keywords: Lung cancer, Targeted agents, Immunotherapy, Phase I/II clinical trial

Background
Lung cancer is the second most commonly diagnosed cancer and is the leading cause of cancer-related death in both men and women. Implementation of tobacco control, low-dose spiral computed tomography screening programs, and advances in multidisciplinary treatments have resulted in the slow decline of both incidence and mortality. However, 52–58% of lung cancer patients present with advanced-stage disease, and a vast majority of these patients do not survive despite treatment. Similarly, the prognosis remains poor even in locally advanced disease because of the high relapse rate and early formation of micrometastases [1].

One of the most important therapeutic advances of lung cancer treatment in the last decade was identification of specific driver mutations and the development of small molecular tyrosine kinase inhibitors (TKIs) [2]. In 2009, erlotinib was the first selective epidermal growth factor receptor (EGFR) inhibitor approved by the US Food and Drug Administration (FDA) [3]. This was quickly followed by crizotinib, which was initially developed as a MET (mesenchymal-to-epithelial transition/hepatocyte growth factor receptor) inhibitor and was found to be highly active against small subset of non-small-cell lung cancer (NSCLC) cases harboring anaplastic lymphoma kinase (ALK) rearrangement [4]. These drugs promise around a 70% response rate; however, resistance development is almost universal, and second/third generation TKIs are being developed to overcome these issues. Novel targeted agents directed against EGFR, ALK, ROS1, MET, RET, BRAF, and many more are under investigation. Figure 1 provides summary of targets with specific focus on the drugs that currently in early-phase clinical trials in lung cancer. In addition to these drugs, next-generation sequencing and cell-free DNA (cfDNA) technologies have provided rapid and convenient tools for gene abnormality testing and the development of targeted therapies [5]. Additionally, personalized medicine has become part of daily practice, and tailoring treatment for individual patients is becoming a reality.

Immunotherapy in the form of checkpoint inhibitors represents a landmark success in NSCLC treatment, and
patients have experienced durable responses with good tolerability. Pembrolizumab and nivolumab exert antitumor activity by blocking programmed death receptor-1 (PD-1) on T lymphocytes. These drugs are currently approved as second-line therapies for advanced NSCLC based on pilot studies that show improved and durable responses compared to docetaxel [6–8]. Most recently, the FDA approved pembrolizumab for the treatment of patients with metastatic NSCLC whose tumors express strong PD-L1 in the first-line setting based on significant improvement in progression-free survival (PFS) and overall survival (OS) [9]. Trials are underway to test using these agents as first-line therapies for patients with NSCLC either alone or in combination with chemotherapy, TKIs, radiation, and other immunotherapies [9–12]. For example, combinations of CTLA-4 and PD-1 inhibitors have been investigated in patients with NSCLC and small cell lung cancer (SCLC). Preliminary results from a phase I study demonstrated that ipilimumab and nivolumab can be effectively and safely combined as first-line treatment of advanced NSCLC [10]. This combination is currently being tested in ongoing phase III study. Similarly, increased antitumor activity was also seen in SCLC with this combination [11]. Multiple studies are underway to investigate the clinical activities of combined chemotherapy and checkpoint inhibitors. Studies to investigate the roles of checkpoint inhibitors in adjuvant and neoadjuvant settings in early-stage lung cancers are ongoing as well. These exciting developments have fuelled rapid progress in the field, and multiple molecules targeting different aspects of host-tumor immune interactions are currently being investigated. Figure 2 provides the summary of ongoing strategies and efforts in immunotherapy of lung cancer.

In this review, we have discussed recently published data on the first-in-human clinical trials and some of the most promising drugs in pipeline. Literature was searched for phase 1/2, first in human clinical trials in lung cancer by using PubMed, Google scholar, and the American Society of Clinical Oncology (ASCO) meeting abstracts. Each study was individually reviewed and data points have been summarized.

**Targeted agents**

**EGFR inhibitors**

EGFR is a member of the ErbB tyrosine kinase receptor (TKR) family and is referred to as ErbB1 or HER1. Gefitinib was first tested for EGFR-expressing NSCLC. It targets the ATP cleft within EGFR, which is
overexpressed in 40–80% of NSCLC cases. Later, Lynch et al. demonstrated that only the tumors with somatic mutations in tyrosine kinase domain of the \(EGFR\) gene responded to gefitinib [13]. Testing for driver mutations in newly diagnosed, advanced NSCLC cases has become the standard of care. In patients who carry the targetable driver mutation, a first-line treatment with targeted agents is recommended over conventional chemotherapy. These drugs are well tolerated and give predictable objective response. A phase 2 trial in neo-adjuvant settings has shown an improved response rate compared to chemotherapy in \(EGFR^+\) NSCLC [14]. Driver mutations in \(EGFR\) (exon 19 deletion or exon 21 L858R substitution) are found in 15–20% of all lung adenocarcinomas (ACs) that account for the largest group of lung cancer patients. Erlotinib, gefitinib, and afatinib are approved as first-line treatments for targetable \(EGFR\) alterations. The median progression-free survival (PFS) from these agents is 9.2–13.1 months [15–17]. Dacomitinib is a small molecule, irreversible inhibitor active against all HER family of tyrosine kinases. In randomized trials, it has comparable efficacy to erlotinib. The subgroup with \(EGFR\) exon 19 deletion has better PFS with dacomitinib compared to erlotinib (HR 0.585, \(P = 0.058\)) [18, 19]. A recent phase 3 trial (NCT01040780) comparing icotinib with gefitinib as the first-line EGFR TKI treatment showed similar results in Chinese patients [20].

**T790M mutant-selective EGFR TKIs**

After the initial response to EGFR TKI, resistance development through various mechanisms is inevitable. The \(EGFR\) T790M mutation causes acquired resistance to the first- and second-generation TKIs. T790M mutation-selective third-generation EGFR TKIs (osimertinib, rociletinib) have been developed with encouraging overall response rates up to 60% [21, 22]. Osimertinib was approved in 2015 by the FDA for confirmed \(EGFR\) T790M mutation-positive NSCLC. A first-line trial (NCT02296125) is underway to compare osimertinib vs erlotinib or gefitinib. This should give information on ideal sequencing on these agents. ASP8273 and olmutinib (B1482694) are other third-generation T790M-selective EGFR TKIs. Early-phase studies (NCT02113813, NCT01588145) in T790M-positive NSCLC showed an overall response rate (ORR) of 31% and disease control rate (DCR) of 57% for ASP8273, as well as a 61% ORR and 90% DCR for B1482694. The median PFS was 6.8 and 8.3 months, respectively [23, 24]. EGFR816 is another agent that showed an ORR of 44% and DCR of 91% in a phase 1 study (NCT02108964) [25]. Typical EGFR TKI-related adverse events were observed with all three drugs.

**CNS-penetrant EGFR TKIs**

Central nervous system (CNS) metastasis is a common site of disease progression in \(EGFR^+\) NSCLC, leading to failure of the first-line TKIs. AZD3759 is a potent CNS-penetrant EGFR TKI currently being evaluated along with osimertinib in a phase 1 (BLOOM) study (NCT02228369) in patients with progressive CNS metastasis who have already had first-line treatment with EGFR TKI. AZD3759 showed activity in 20 patients with measurable brain metastasis evaluable for RECIST assessment; 8 had tumor shrinkage in the brain, 3 had confirmed partial response (PR), and 3 had unconfirmed PR [26]. In 12 patients taking osimertinib, 7 had radiological PR, 2 had stable disease, and 3 were not evaluable after 12 weeks [27].
Epitinib is another small-molecule TKI being developed for its favorable CNS penetration. In a dose-expansion phase, 12 patients with \textit{EGFR}+ NSCLC and CNS metastasis received epitinib. Among those 12 evaluable patients, 5 reached PR (all treatment naive) and showed dramatic shrinkage of brain lesions. The five prior-TKI-treated patients had stable disease (SD) in the brain [28] (NCT02590952).

**ALK inhibitors**

\textit{ALK} fusion oncogene-associated NSCLC is a distinct subset of lung cancer amenable to targeted therapy. \textit{ALK} rearrangement is found in 3–13% of NSCLC cases, with a higher prevalence among younger patients, never or light smokers, and adenocarcinoma with signet ring or acinar histology [29]. Crizotinib is a multi-targeted TKI that is active against \textit{ALK}, \textit{ROS1}, and \textit{MET} [4]. It has been approved as a first-line treatment for \textit{ALK}+ or \textit{ROS1}+ NSCLC. Cerititinib and alectinib are second-generation \textit{ALK} TKIs approved for crizotinib-resistant or intolerant cases [30–32]. Resistance development and CNS progression are major issues, and the following \textit{ALK} TKIs are currently under investigation.

Brigatinib was given to 222 patients with crizotinib-refractory, \textit{ALK}+ NSCLC under a phase II study (ALTA, NCT02094573). A PFS of 8.8 and 11.1 months was noted among those receiving lower and higher doses of brigatinib, respectively. An encouraging intracranial ORR of 67% was seen in nine patients with measurable CNS metastasis. Early onset pulmonary toxicity was seen in 6% of the patients [33]. A phase III trial (NCT02737501) against crizotinib in a front-line setting for \textit{ALK}+ NSCLC has been initiated.

Lorlatinib (PF-06463922) was tested in phase I/II study (NCT01970865) of \textit{ALK}+/\textit{ROS}1+ NSCLC. A majority of the participants had a prior treatment with ≥2 \textit{ALK} TKIs. Among 41 evaluable patients, an ORR 46% and median PFS of 11.4 months were seen. The intracranial ORR was 44%, including a few complete responses (CRs) [34]. Interestingly, the drug was active against diseases caused by the \textit{ALK} G1202R mutation which confers resistance to ceritinib, alectinib, and brigatinib [35].

Ensartinib (X-396) is a novel \textit{ALK} inhibitor with additional activity against \textit{ROS1}, \textit{MET}, \textit{SLK}, \textit{Axl}, \textit{LTK}, \textit{ABL}, and \textit{EPHA2}. Partial responses were seen in 60% crizotinib-naive (30 patients) and 88% crizotinib-resistant patients (12 patients) (NCT01625234). CNS responses were also observed in both groups [36]. A phase 3 study (NCT02767804) comparing ensartinib and crizotinib in a front-line setting is currently recruiting patients.

**MET inhibitors**

\textit{MET}, a receptor tyrosine kinase after binding with hepatocyte growth factor (HGF), activates the phosphatidylinositol-3-kinase (PI3K) and mitogen-activated protein kinases (MAPK) pathways. \textit{MET} gene amplification and exon-14-skipping mutations are characteristic abnormalities causing increased \textit{MET} signaling activation. Isolated \textit{MET} exon 14 mutation is found in 3% of NSCLC; however, it is an acquired \textit{EGFR} TKI resistance pathway in 15–20% of \textit{EGFR} mutation-positive NSCLC cases [37, 38]. Crizotinib has shown some activity in selected \textit{MET}-amplified and exon 14-skipping mutant NSCLC [39, 40] (NCT00585195). Cabozantinib, a multi-targeted \textit{MET} inhibitor, was given to five patients with exon 14 mutations and had a stable disease for 5 months [40]. Capmatinib (INC280) is a selective \textit{MET} inhibitor. In a phase 1 study (NCT01324479), relapsed NSCLC patients with high \textit{cMET} expression were given capmatinib. In subgroup of patients with \textit{MET}-amplified disease, the ORR was 63%, and the median PFS was 7.4 months [41]. Glesatinib (MGCD265) is another \textit{MET} blocker currently being studied in NSCLC (NCT00697632).

**Combined \textit{MET} + \textit{EGFR} inhibitors**

Acquired \textit{EGFR} TKI resistance is mediated by \textit{MET} up-regulation in a subset of NSCLC patients. One strategy to overcome this resistance is to combine a \textit{MET} inhibitor with an \textit{EGFR} TKI. A combination of capmatinib and gefitinib was tested in a phase 2 study (NCT01610336) in \textit{EGFR}+ NSCLC patients after their disease progressed while using gefitinib. \textit{EGFR} T790M NSCLCs were excluded and high \textit{cMET} expression was required. An ORR of 18%, an SD of 62%, and a DCR of 80% were observed in 65 evaluable patients. More responses were seen in tumors with \textit{MET} amplifications [42]. Tepotinib (MSC2156119I) with gefitinib was well tolerated in a phase 1 study (NCT01982955). Eighteen patients were treated, and five had a partial response [43]. A similar trial (NCT01900652) with emibetuzumab and an IgG4 anti-MET monoclonal antibody (mAb) with erlotinib in MET-expressing NSCLC with acquired erlotinib resistance showed some benefit in high cMET-expressing tumors [44].

**RET inhibitors**

The \textit{RET} proto-oncogene encodes a receptor tyrosine kinase for members of the glial cell line-derived neurotrophic factor (GDNF) family. \textit{RET} rearrangements are found in 1–2% lung adenocarcinoma and are mutually exclusive with mutations involving \textit{EGFR}, \textit{ALK}, or \textit{KRAS}. Vandetanib, sorafenib, sunitinib, lenvatinib, pona-tinib, and cabozantinib are multi-targeted TKIs with RET-blocking activity. They are currently approved for other malignancies. In a phase 2 study with cabozantinib, 38% PR was seen among 16 evaluable patients, and there was a median PFS of 7 months [45].
Vandetanib in advanced RET-rearranged NSCLC showed an ORR 53%, a DCR 88%, and a median PFS of 4.7 months in 17 eligible patients. The CCDC6-RET subtype had an ORR of 83% and a median PFS of 8.3 months [46] (UMIN000010095). In a phase 1 study (NCT01582191), vandetanib was combined with everolimus (mTOR (mammalian target of rapamycin) inhibitor) to prevent resistance development based on in vitro studies. Among 13 stage IV NSCLC patients, PR was achieved in five patients with RET fusion. Good CNS activity was seen in three patients with intracranial metastasis [47].

**BRAF/MEK inhibitors**

BRAF is a downstream signaling mediator of KRAS, which activates the MAP kinase pathway. BRAF mutations are found in 1–2% of NSCLC cases and are usually smoking related [48]. It is also described as one of the resistance mechanisms associated with EGFR TKIs. Vemurafenib and dabrafenib are currently approved for BRAF V600E-positive malignant melanomas, but single-agent activity in BRAF V600E-positive NSCLC is limited. Dabrafenib had an ORR of 33% in platinum refractory cases with a median duration of response of 9.6 months in single study [49] (NCT01336634).

**Combination BRAF + MEK inhibitors**

Sequential inhibition of BRAF and downstream MEK is an active area of lung cancer research after encouraging results were seen in melanoma patients. Dabrafenib with trametinib (MEK inhibitor) was associated with ORR of 63% in 57 evaluable patients and the DCR was 79% [50].

**Combination MEK inhibitor and immunotherapy**

MEK inhibition can result intratumoral T cell accumulation and MHC-1 upregulation and synergizes with anti-PD-L1 agent leading to tumor regression [51]. Cobimetinib is a selective MEK1 and MEK2 inhibitor. In a phase 1b study (NCT01988896), cobimetinib with atezolizumab (anti-PD-L1) was given to advanced solid cancer patients. In colorectal cancer cohort (MSI-low), ORR was 17% and responses were durable. Increased PD-L1 and CD8 T lymphocyte infiltration was demonstrated in serial biopsies [52]. Results on NSCLC cohort are pending.

**PI3K inhibitors**

Phosphatidylinositol 3-kinase (PI3K) pathway is a central mediator of cell survival signals. PI3CA mutations are found in 4.4% of lung adenocarcinoma and 16% of squamous cell cancer. PI3CA amplifications are found in up to 40% of squamous cell lung cancer [53, 54]. PI3CA mutations also promote resistance to EGFR TKIs. PQR309 is a pan-PI3K, mTOR inhibitor. Its safety and maximum tolerated dose have been recently established in a phase 1 study (NCT02483858) with advance solid cancers. No response data are available for NSCLC cohort [55].

**HER3 inhibitors**

Patritumab is a fully human anti-HER3 mAb. HER3 is a member of the ErbB tyrosine kinase receptor family and is activated by heregulin. Preclinical studies with EGFR+ NSCLC cell lines have shown that increased heregulin level confers resistance to EGFR TKI. An initial phase 2 study (NCT01211483) failed to show the PFS benefit of adding patritumab to erlotinib compared to a placebo. However, the subgroup with increased soluble heregulin showed increased PFS (HR 0.41 [95% CI 0.18–0.90], P = 0.02) with patritumab [56]. A phase 3 placebo-controlled study (HER3-Lung, NCT02134015) in EGFR+ NSCLC is ongoing.

**Aurora A kinase inhibitors**

Aurora A is a member of a family of mitotic serine/threonine kinases which assist with cell proliferation. Alisertib (MLN-8237) is an aurora kinase A inhibitor. Based on in vitro synergism with EGFR TKIs, it was tested in 18 patients with EGFR+ NSCLC. The combination was well tolerated; one patient had a PR, while five other patients achieved SD [57]. Phase 2 recruitment is ongoing (NCT01471964).

**FGFR inhibitors**

The fibroblast growth factor receptor (FGFR) binds to members of the fibroblast growth factor family of proteins and promotes cell proliferation. BGI398 is a potent, selective pan-FGFR (fibroblast growth factor receptor). *FGFR1* amplification is found in around 21% of squamous NSCLC cases [58]. In a single phase 2 trial, 26 evaluable patients showed a PR of 15% and an SD if 35% in dose >100 mg [59]. Dovitinib is another FGFR inhibitor tested in squamous NSCLC. Among 26 patients, the ORR was 11.5%, the DCR was 50%, and the median PFS was 2.9 months [60].

**PARP inhibitors**

PARP (poly ADP ribose polymerase) plays an important role in DNA repair. PARP inhibitors have synergistic activity with platinum based chemotherapy (i.e., cisplatin) [61]. In a phase 2 study, veliparib in combination with carboplatin and paclitaxel was tested in first-line setting for advanced NSCLC. The combination was well tolerated, and there was a trend toward favorable PFS (HR 0.72 [95% CI 0.45–1.15, P = 0.17]) and OS (HR 0.80 [95% CI 0.54–1.18, P = 0.27]) in combination arm [62]. A phase 2 combining veliparib with chemoradiation in stage 3 NSCLC is recruiting (NCT02412371).
**Immunotherapies**

Immunotherapy has long been considered the holy grail of Oncology. Different attempts have been made to harness body's immune system to eradicate malignancy. Lung cancer has the second highest mutation burden after melanoma, which increases its susceptibility to immunotherapy [63]. One of the key advantages of immunotherapy is the durability of responses. Where resistance development is universal with chemotherapy and targeted agents, memory function of the immune system can lead to lasting remission. Check point inhibitors target the PD1/PD-L1 axis to remove the inhibitory signals on T lymphocytes to eradicate malignancy. Pembrolizumab and nivolumab are currently approved as second-line therapies for both adenocarcinoma and squamous cell carcinoma of lung. Atezolizumab is the first anti-PD-L1 agent approved by the FDA for NSCLC in second-line setting after encouraging results from phase 3 OAK trial showing superior OS (HR 0.73; P = 0.0003) [64]. A recent phase 3 study tested pembrolizumab vs platinum doublet chemotherapy in first-line NSCLC with at least 50% PD-L1 expression in tumor cells. Pembrolizumab was associated with better PFS (10.3 vs 6 months) and response rate (44.8 vs 27.8%) compared to chemotherapy. Estimated survival at 6 months was also better in patients treated with pembrolizumab (HR = 0.60, P = 0.005) [9]. This had led to approval of pembrolizumab as first-line therapy in NSCLC with >50% PD-L1 expression in tumor cells. A combination of ipilimumab and nivolumab as first-line treatment in advanced NSCLC is feasible, safe, and has shown good ORR [10]. Durvalumab (anti-PD-L1) and tremelimumab (anti-CTLA4) have been tested in phase 1b study and found to be safe with early evidence of clinical activity in relapsed NSCLC [65]. As these agents move quickly to treat early-stage lung cancers through clinical studies, other agents that target different aspects of the tumor-immune system milieu are being developed. Figure 2 demonstrates different strategies being utilized to enhance tumor recognition and elimination by the immune system [66].

**OX40**

OX40 (CD134) is a secondary costimulatory immune checkpoint receptor expressed on activated T cells that lead to expansion of effector and memory T cells after binding with OX40L (CD252) on antigen presenting cells. It is a part of tumor necrosis factor receptor (TNFR) superfamily and works in conjunction with B7 family members, such as PD1 and CTLA-4. GSK3174998 is a humanized IgG1 agonistic anti-OX40 monoclonal antibody (mAb) that promotes naïve CD4+ T- cells and suppresses their differentiation into immunosuppressive regulatory T cells (T_{reg}) [67, 68]. ENGAGE-1 (NCT02528357) is a first-in-human study of GSK3174998 alone and in combination of pembrolizumab. Murine studies have shown synergistic activity between PD-1 blockade and OX40 agonist mAb [69]. No dose-limiting toxicity was found in the initial dose escalation cohort alone and in combination with a 200-mg fixed dose of pembrolizumab every 3 weeks. This study is still recruiting patients.

MEDI6383 (NCT02221960) is another OX40 agonist mAb currently being studied with durvalumab, an anti-PD-1 antibody. Lirilumab/BMS-986015 (NCT01714739) is anti-KIR mAb, which is a natural killer (NK)-cell checkpoint inhibitor that is being evaluated with nivolumab.

**Lymphocyte activation gene 3**

Lymphocyte activation gene 3 (LAG-3, CD223) is another checkpoint inhibitor on activated T lymphocytes that inhibits immune function after binding with major histocompatibility complex (MHC) II [70]. Urelumab is an anti-LAG3 mAb currently being studied for NSCLC in combination with anti-PD1 agents (NCT01968109, NCT02460224).

**T cell immunoglobulin and mucin-domain containing-3**

T cell immunoglobulin and mucin-domain containing-3 (TIM-3) is Th1 (T helper-1)-specific regulator of macrophage responses. Recently, murine studies showed TIM-3 upregulation in the tumor microenvironment in an anti-PD1 resistant NSCLC model [71]. MBG453 and TSR-022 are anti-TIM3 mAbs currently being studied in two phase 1 trials (NCT02817633, NCT02608268).

**B7-H3**

B7-H3 is widely expressed among tumors and is associated with immune escape and metastasis. MGD009 is a humanized B7-H3 and CD3 dual-affinity re-targeting (DART) protein designed to engage T cells to B7-H3 expressing cells. Antitumor activity in multiple in vivo models has been demonstrated. A phase 1 trial (NCT02628535) in advanced B7-H3 expressing tumors, including NSCLC, is recruiting patients [72]. Prior anti-PD1 therapy is allowed.

**MUC1**

MUC1 is widely expressed in many malignancies, including NSCLC. TG4010 is a modified vaccinia Ankara expressing MUC1 and interleukin 2 (IL2). In a recent phase 2b study, TG4010 or placebo were given with chemotherapy as a first-line therapy for metastatic NSCLC (mNSCLC) without EGFR mutations and MUC1 expression in minimum 50% of tumor cells. Significant improvement in PFS (hazard ratio 0.74, 95% CI 0.55–0.98, P = 0.019) was noted. The phase 3 component is ongoing [73].
A combination study with anti-PD1 is underway [74]. In a phase 1/2 study (NCT01433172), GM.CD40L + CCL21 did not improve PFS, and the median OS was comparable to single-agent chemotherapy in advanced adenoNSCLC. A combination study with anti-PD1 is underway [74].

**Antibody drug conjugates**

Antibody drug conjugates (ADCs) are an important class of biologics currently being investigated for range of malignancies. The chemotherapy molecule is attached to a target-specific antibody for tumor-directed cytotoxicity but sparing of normal tissue. Brentuximab vedotin (CD30 directed) and trastuzumab emtansine (HER2 directed) are ADCs currently available for relapsed Hodgkin lymphoma and metastatic HER2-positive breast cancer, respectively. The following ADCs are currently being studied in phase 1 trial for lung cancer.

**Sacituzumab govitecan (IMMU-132)**

Trop-2 is widely expressed among solid tumors. Sacituzumab govitecan is made from a humanized anti-Trop-2 monoclonal antibody (hRS7) that is conjugated with the active metabolite of irinotecan, SN-38. In a phase 1/2 study (NCT01631552), the single-agent sacituzumab govitecan was given to patients with advanced epithelial malignancies. In the NSCLC cohort, an objective response of 31% and median PFS of 3.9 months was observed. The SCLC cohort showed a similar response rate, a median PFS of 4.6 months, and a median OS of 8.3 months [75, 76]. Diarrhea and neutropenia were common adverse events. These are encouraging results in platinum refractory patients. It has received the FDA breakthrough therapy designation for triple-negative breast cancer.

**Rovalpituzumab tesirine (SC16LD6.5)**

Rovalpituzumab tesirine also known as Rova-T is an antibody (SC16) targeting delta-like protein 3 (DLL3) and is linked to pyrrolobenzodiazepine (PBD). DLL3, an inhibitory Notch ligand, is expressed in >80% of SCLCs. The first biomarker directed trial for advanced SCLC showed an objective response rate of 18% and a clinical benefit rate of 68% as a second or third line of therapy in evaluable patients. Interestingly, 27 patients with high DLL3-tumor expression had a response rate of 44 and 45% in the second- and third-line settings, respectively [77]. Thrombocytopenia, a skin rash, and serosal effusions were dose-limiting toxicities. A phase 2 study (TRINITY; NCT02674568) is recruiting patients with DLL3-expressing SCLC.

**Cancer stemness inhibitors**

Cancer stem cells are highly resistant to traditional therapies and cause disease relapse after initial response. Napabucasin (BBI608) is a first-in-class cancer stemness inhibitor that works through STAT3 pathway inhibition. It has shown activity in combination with paclitaxel. In a phase 2 study (NCT01325441), 27 heavily pretreated NSCLC patients were given a combination of napabucasin and weekly paclitaxel. Among 19 evaluable patients, there was a PR of 16%, a DCR of 79%, and a median PFS of 4 months [78]. Demcizumab (VS-6063) is a humanized IgG2 anti-DLL4 (delta-like ligand 4) antibody that inhibits tumor growth by suppressing the Notch pathway. A phase 1b study (NCT01189968) tested demcizumab with carboplatin and pemetrexate as first-line therapies for lung adenocarcinoma. Results showed complete responses in one (3%) of 40 patients and partial responses in 19 (47%) patients [79]. A randomized, placebo-controlled phase 2 trial (DENALI) (NCT02259582) has opened for first-line non-squamous NSCLC. Another study (NCT01859741) of first-line chemotherapy for SCLC is still recruiting patients.

**Future directions**

We discussed results of first-in-human phase I/II clinical trials with novel agents in lung cancer in this article. There are many new molecules which are currently being studied for a variety of targets. Histone deacetylase (HDAC) inhibitors and DNA hypomethylating agents target epigenetics for tumor growth suppression. In immunotherapy, new peptide vaccines targeting novel tumor antigens, alternative checkpoint inhibitors, and chimeric antigen receptor T cells (CAR-T) are being developed for the patients who have failed or intolerant to anti-PD1/anti-PD-L1 therapy. Novel small molecular inhibitors directed to inhibit variety of signaling pathways are being developed to overcome resistance to currently available targeted therapies. Table 1 summarizes currently open phase I/II clinical trials for lung cancer patients with pending results. The information in this table was collected from Clinicaltrls.gov (accessed on September, 2016). It can serve as a guide for clinicians who treat relapsed refractory lung cancer.
## Table 1  Currently open phase I/II clinical trials for lung cancer

| Drug class               | Drug                | Mechanism of action                                      | Clinical trials (phase) | Study design | Disease |
|--------------------------|---------------------|----------------------------------------------------------|-------------------------|--------------|---------|
| **Tumor epigenetics**    | Entinostat          | Histone deacetylase (HDAC) inhibitor                     | NCT02437136 (1/2)       | Combination  | NSCLC   |
|                          | HBI-8000            |                                                          | NCT02718066 (1/2)       | Combination  | NSCLC   |
|                          | ACY 241             |                                                          | NCT02635061 (1)         | Combination  | NSCLC   |
|                          | Epacadostat         |                                                          | NCT02298153 (1)         | Combination  | NSCLC   |
|                          | Mocentinostat       |                                                          | NCT02805660 (1/2)       | Combination  | NSCLC   |
|                          | CC-486              | DNA hypomethylation                                      | NCT02250326 (2)         | Combination  | NSCLC   |
|                          | Azacitidine         | DNA methylation, histone deacetylation, and lysine       | NCT02009436 (1)         | Monotherapy  | NSCLC   |
|                          | RRX-001             | drug methylation                                         | NCT02489903 (2)         | Monotherapy  | NSCLC   |
| **Tumor metabolism**     | Ethaselen           | Thioredoxin reductase                                     | NCT02166242 (1)         | Monotherapy  | NSCLC   |
|                          | TAE-114             | dUTPase                                                  | NCT02855125 (2)         | Combination  | NSCLC   |
|                          | ADI-PEG 20          | Pegylated arginine deiminase                             | NCT02029690 (1)         | Combination  | NSCLC   |
|                          | CCT245737           | Checkpoint kinase 1                                       | NCT02797977 (1)         | Combination  | NSCLC   |
|                          | LY2606368           |                                                          | NCT02860780 (1)         | Combination  | NSCLC   |
|                          | CB-839              | Glutaminase                                              | NCT02771626 (1/2)       | Combination  | NSCLC   |
| **Immunotherapy**        | CV301               | Tumor peptide vaccine                                    | NCT02840994 (1/2)       | Combination  | NSCLC   |
|                          | TG4010              |                                                          | NCT02823990 (2)         | Combination  | NSCLC   |
|                          | Gemogenovatucel-T   |                                                          | NCT02639234 (2)         | Combination  | NSCLC   |
|                          | CMB305              |                                                          | NCT02387125 (1)         | Monotherapy  | NSCLC   |
|                          | DC-CIK              | Dendritic cell vaccine                                   | NCT02688686 (1/2)       | Monotherapy  | NSCLC   |
|                          | DCVAC/LUCA          |                                                          | NCT02470468 (1/2)       | Monotherapy  | NSCLC   |
|                          | AGS-003-LNG         |                                                          | NCT02662634 (2)         | Monotherapy  | NSCLC   |
|                          | JNJ-64041757        | Listeria vaccine                                         | NCT02592967 (1)         | Monotherapy  | NSCLC   |
|                          | ADXS11-001          |                                                          | NCT02531854 (2)         | Combination  | NSCLC   |
|                          | DSP-7888            | WT1 vaccine                                              | NCT02498665 (1)         | Monotherapy  | NSCLC   |
|                          | S-588410            | (HLA)-a*2402-restricted epitope peptides                 | NCT02410369 (2)         | Monotherapy  | NSCLC   |
|                          | AD-MAGEA3 and MG1-MAGEA3 | MAGE-A3-expressing maraba virus            | NCT02879760 (1/2)       | Monotherapy  | NSCLC   |
|                          | L-DOS47             | Immunoconjugate                                          | NCT02340208 (1/2)       | Monotherapy  | NSCLC   |
|                          | DrRibbles           |                                                          | NCT01909752 (2)         | Monotherapy  | NSCLC   |
| **Checkpoint inhibitors**| Enoblituzumab (MGA271) | B7-H3 antibody                                          | NCT02475213 (1)         | Combination  | NSCLC   |
|                          | MGD009              |                                                          | NCT01391143 (1)         | Monotherapy  | NSCLC   |
|                          | CM-24               | CEACAM1 antibody                                         | NCT02628535 (1)         | Monotherapy  | NSCLC   |
|                          | Indoximod           | Indoleamine 2,3-dioxygenase (IDO) inhibitor              | NCT02346955 (1)         | Combination  | NSCLC   |
|                          | AMG 820             | Colony-stimulating factor 1 receptor (CSF1R)            | NCT02460367 (1/2)       | Combination  | NSCLC   |
|                          | PF-05082566         | 4-1BB agonist                                            | NCT02315066 (1)         | Combination  | NSCLC   |
|                          | PBF-509             | Adenosine A2a                                            | NCT02403193 (1/2)       | Combination  | NSCLC   |
|                          | CPI-444             |                                                          | NCT02655822 (1)         | Combination  | NSCLC   |
|                          | PF-04518600         | Anti-OX40 mAb                                            | NCT02315066 (1)         | Combination  | NSCLC   |
|                          | JNJ-61610588        | Anti-VISTA                                              | NCT02671955 (1)         | Monotherapy  | NSCLC   |
Table 1: Currently open phase I/II clinical trials for lung cancer (Continued)

| Trial Identifier | Treatment Type | Target | Clinical Trials |
|------------------|----------------|--------|-----------------|
| NCT02460224      | Combination    | NSCLC/SCLC |
| NCT02812875      | Monotherapy    | NSCLC/SCLC |
| NCT02584634 (2)  | Combination    | NSCLC |
| NCT02335918 (1)  | Combination    | NSCLC |
| NCT02829099 (1)  | Monotherapy    | NSCLC/SCLC |
| NCT02133196 (2)  | Monotherapy    | NSCLC |
| NCT02766348 (2)  | Monotherapy    | NSCLC |
| NCT02886897 (1/2) | Combination    | NSCLC |
| NCT02459067 (2/3) | Monotherapy    | NSCLC |
| NCT02592577 (1/2) | Monotherapy    | NSCLC |
| NCT02118415 (2)  | Monotherapy    | NSCLC |
| NCT02408016 (1/2) | Monotherapy    | NSCLC |
| NCT02387307 (1)  | Monotherapy    | NSCLC |
| NCT02523469 (1/2) | Combination    | NSCLC |
| NCT02009449 (1)  | Monotherapy    | NSCLC |
| NCT02538432 (2)  | Monotherapy    | NSCLC |
| NCT02661100 (1/2) | Combination    | NSCLC/SCLC |
| NCT02650635 (1)  | Monotherapy    | NSCLC |
| NCT02735850 (2)  | Combination    | NSCLC |
| NCT02661100 (1/2) | Combination    | NSCLC/SCLC |
| NCT02365662 (1)  | Monotherapy    | NSCLC |
| NCT02448251 (1/2) | Monotherapy    | NSCLC |
| NCT02616393 (2)  | Monotherapy    | NSCLC |
| NCT02609776 (1)  | Monotherapy    | NSCLC |
| NCT02716116 (1/2) | Monotherapy    | NSCLC |
| NCT02538627 (1)  | Monotherapy    | NSCLC |
| NCT02369198 (1)  | Monotherapy    | NSCLC |
| NCT02520778 (1)  | Combination    | NSCLC |
| NCT02695550 (1)  | Monotherapy    | NSCLC |
| NCT02356991 (2)  | Monotherapy    | NSCLC |
| NCT02364362 (1)  | Combination    | NSCLC/SCLC |
| NCT02219711 (1)  | Monotherapy    | NSCLC |
| NCT02452424 (1/2) | Combination    | NSCLC |
| NCT02388919 (2/3) | Monotherapy    | NSCLC |
| NCT02568267 (2)  | Monotherapy    | NSCLC |
| NCT02495233 (1/2) | Combination    | NSCLC/SCLC |
|                | Target Pathway | Clinical Trials | Phase | Disease |
|----------------|----------------|-----------------|-------|---------|
| **PI3K/mTOR pathway inhibitors** |                |                 |       |         |
| MLN1117        | PI3K           | NCT02393209     | 1/2   | Combination NSCLC |
| AZD8186        |                | NCT01884285     | 1     | Monotherapy NSCLC |
| LY3023414      | PI3K, mTOR     | NCT02443337     | 2     | Combination NSCLC |
| **Other miscellaneous target inhibitors** |                |                 |       |         |
| LEE011         | CDK 4/6        | NCT02292550     | 1/2   | Combination NSCLC |
| Abemaciclib    |                | NCT02308020     | 2     | Monotherapy NSCLC |
|                |                | NCT02779751     | 2     | Monotherapy NSCLC |
|                |                | NCT02079636     | 1     | Combination NSCLC |
| INK128         | TORC1/2        | NCT02503722     | 1     | Monotherapy NSCLC |
| Alisertib      | Aurora kinase inhibitor | NCT01471964 | 1/2 | Combination NSCLC |
| Ibrutinib      | BTK            | NCT02321540     | 1/2   | Monotherapy NSCLC |
| TAK-659        | Syk            | NCT02834247     | 1     | Combination NSCLC |
| Pyrotinib      | HER2           | NCT02535507     | 2     | Monotherapy NSCLC |
| EphB4-HSA      | sEphB4         | NCT02495896     | 2     | Combination NSCLC |
| Fidlatuzumab   | Hepatocyte growth factor (HGF) | NCT02318368 | 2 | Combination NSCLC |
| AMG 479        | IGFR-1         | NCT01061788     | 1     | Combination NSCLC/SCLC |
| MM-121         | HER3           | NCT02387216     | 2     | Combination NSCLC |
| Defactinib     | Focal adhesion kinase (FAK) | NCT02758587 | 1/2 | Combination NSCLC |
| JNJ-42756493   | FGFR           | NCT02699606     | 2     | Monotherapy NSCLC |
| INC0054828     | NTRK1/2/3      | NCT02393248     | 1/2   | Monotherapy NSCLC/SCLC |
| LOXO-101       |                 | NCT02576431     | 2     | Monotherapy NSCLC/SCLC |
| RXDX-101       |                 | NCT02097810     | 1     | Monotherapy NSCLC/SCLC |
| Rh-endostatin  |                 | NCT02375022     | 2     | Combination NSCLC |
| Cediranib      |                 | NCT02498613     | 2     | Combination NSCLC/SCLC |
| GSK3052230     | FGF ligand trap | NCT01868022     | 1     | Combination NSCLC/SCLC |
| TRC105         | Endoglin (CD105) | NCT02492843 | 1 | Combination NSCLC |
| MEK162         | MEK            | NCT01859026     | 1     | Combination NSCLC |
| PD-0325901     |                 | NCT02022982     | 1/2   | Combination NSCLC |
| Selumetinib    | RAS/RAF/MEK/ERK | NCT01586624     | 1     | Combination NSCLC |
| Pacritnib      | JAK2           | NCT02342353     | 1/2   | Monotherapy NSCLC |
| AT13387        | Heat shock protein 90 | NCT02535338 | 1/2 | Combination NSCLC |
| AUY922         |                 | NCT01922583     | 2     | Monotherapy NSCLC |
| Galunisertib   | TGFβ signaling  | NCT02423343     | 1/2   | Combination NSCLC/SCLC |
| MSC2156119J    | MET            | NCT01982955     | 1/2   | Combination NSCLC |
| Ralimetinib    | MAPK           | NCT02860780     | 1     | Combination NSCLC/SCLC |
| LTT462         |                 | NCT02711345     | 1     | Monotherapy NSCLC |
| PF-06671008    | P-cadherin     | NCT02659631     | 1     | Monotherapy NSCLC/SCLC |
| BGB324         | Axl            | NCT02424617     | 1/2   | Combination NSCLC |
| DNA repair     | VX790          |                 |       |         |
| Veliparib      | PARP           | NCT01386385     | 1/2   | Combination NSCLC |
| Olaparib       |                 | NCT02498613     | 2     | Combination NSCLC/SCLC |
**Table 1** Currently open phase I/II clinical trials for lung cancer (Continued)

| Chemotherapy | Tubulin-depolymerization | NCT02846792 (1/2) | Combination NSCLC |
|--------------|---------------------------|-------------------|------------------|
| Plinabulin   |                           | NCT02812667 (1)   | Combination NSCLC |
| PT-112       | Platinum based            | NCT02884479 (1/2)| Combination NSCLC/SCLC |
| NC-6004      | Micellar nanoparticle-encapsulated cisplatin | NCT02240238 (1/2) | Combination NSCLC |
| EC1456       | Folic acid-tubulin conjugate | NCT01999738 (1)  | Monotherapy NSCLC/SCLC |
| Oncolytic virus | CVA21 Coxsackievirus A21 | NCT02043665 (1)  | Monotherapy NSCLC |
|              |                           | NCT02824965 (1)   | Combination NSCLC |

ALK anaplastic lymphoma kinase, ATR ataxia telangiectasia and Rad3-related protein, AXL AXL receptor tyrosine kinase, BTK Bruton’s tyrosine kinase, CDK 4/6 cyclin-dependent kinase 4/6, CEACAM1 carcinoembryonic antigen-related cell adhesion molecule 1, dUTPase deoxyuridine triphosphatase, FAK focal adhesion kinase, FGF fibroblast growth factor, FLT1/3 fms-like tyrosine kinase 1/3, c-Kit proto-oncogene c-Kit, Her2 human epidermal growth factor receptor 2, HLA human leukocyte antigen, IGFR insulin-like growth factor receptor, JAK2 Janus kinase 2, MAGE3 melanoma-associated antigen 3, MAPK mitogen-activated protein kinase, MEK mitogen-activated protein kinase kinase, mTOR mammalian target of rapamycin, NTRK3 neurotrophin receptor tyrosine kinase 3, PARP poly ADP ribose polymerase, PEGFR platelet-derived growth factor receptor, PI3K phosphatidylinositol-3-kinase, s EphB4 soluble extracellular domain of EphB4, 5yK spleen tyrosine kinase, VEGFR vascular endothelial growth factor receptor, VISTA V-domain Ig suppressor of T cell activation, WT1 Wilms tumor protein

**Conclusions**

Oncology is changing at a fast pace, and improved outcomes are being observed in most human malignancies. Until now, lung cancer has lagged behind, but novel targeted agents and immunotherapies have shown promising results for this common and aggressive cancer. The rapid development of novel agents targeting those molecular driver alterations in lung cancer will likely further improve the clinical outcomes. The combination of agents that target non-overlap pathways will likely provide additive or synergistic activities. Many studies are ongoing to test new targets for immunotherapy such as inhibitory molecules TIM-3, LAG-3, IDO (Indoleamine-pyrrole 2,3-dioxygenase), BTLA (B- and T-lymphocyte attenuator), adenosine, VISTA (V-domain immunoglobulin containing suppressor of T cell activation), and stimulatory molecules such as 4-1BB, OX40, CD40, and CD27. A great number of clinical studies are underway to test the clinical activities of various immunotherapy combination strategies in different settings. However, there are challenges to conquer. Treatment with target agents inevitably leads to drug resistance. Understanding the resistance mechanisms and developing novel agents or strategies targeting the resistant tumors are largely needed. Although immunotherapy has shown durable response in some patients, the majority of patients do not benefit. Immunohistochemistry staining of PD-L1 on tumor cells is extensively studied but still remains as an imperfect biomarker. Discovery of new biomarkers or combination of biomarkers is required to guide the selection of patients who most likely benefit from treatment to avoid unnecessary costs and toxicities. Many pre-clinical and clinical studies are ongoing to address these needs.

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YL designed the study. BD and YL drafted the manuscript. WH and AS contributed.

**Competing interests**

The authors declare that they have no competing interests.

**Consent for publication**

This is not applicable for this review.

**Ethics approval and consent to participate**

This is not applicable for this review.

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