Oncogenic drivers and immunotherapy: staying one step ahead of lung cancer

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Lung cancer remains the single biggest cause of cancer-related mortality, responsible for nearly a quarter of all deaths.[1] Although major breakthroughs in the treatment of the most common form – non-small-cell lung cancer (NSCLC) – have been heralded in the past decade, many challenges remain. Here, we discuss how attempts to address these challenges are the driving force behind a continuing paradigm shift in lung cancer treatment.

EGFR and ALK: a model of targeted drug development

The majority of newly diagnosed lung cancers are NSCLC, and about half of those are adenocarcinomas (Figure 1).[2] Over the past decade there has been a significant evolution in the understanding and treatment of lung adenocarcinoma, mostly stemming from a greater appreciation of the distinct pathologies and unique molecular signatures of these tumors. Genomic characterization of the molecular signatures has led to the identification of numerous key genetic alterations that drive lung cancer. The dependency of lung tumors on these genetic drivers has enabled the pharmacological development of targeted therapies that exploit this vulnerability.

The best studied of these drivers are mutations in the epidermal growth factor receptor (*EGFR*) gene and rearrangements in the anaplastic lymphoma kinase (*ALK*) gene, both of which encode proteins that are members of the receptor tyrosine kinase family – the master regulators of cellular signaling that regulate an array of intracellular signaling cascades.[3] The 2 most common *EGFR* alterations

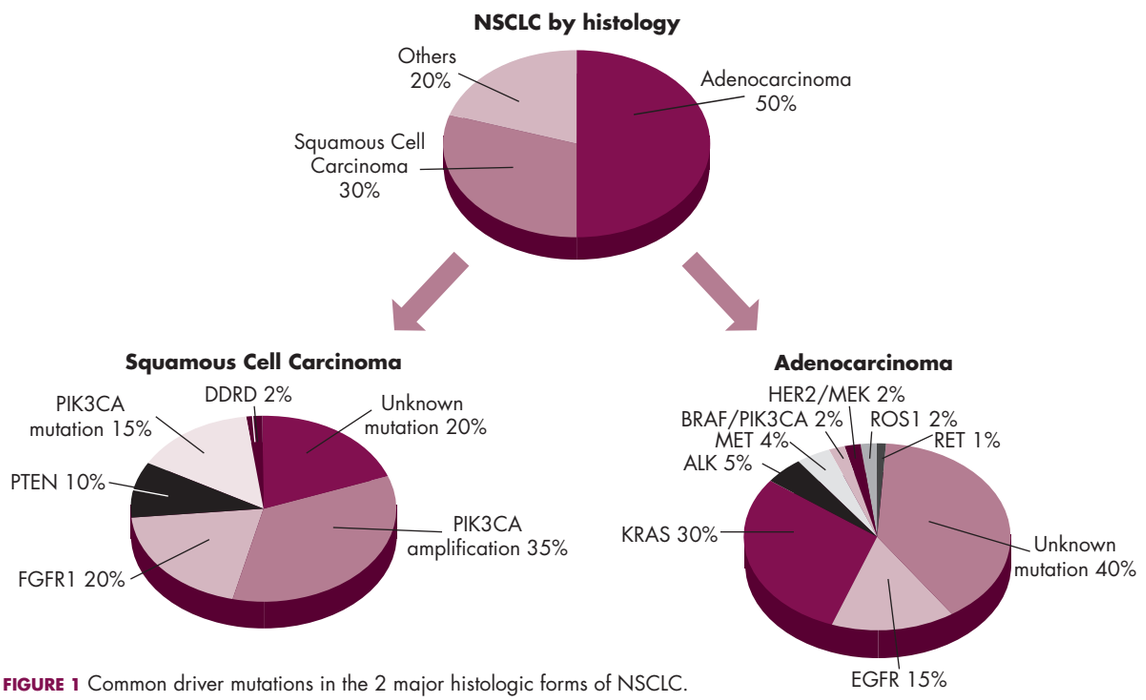

FIGURE 1 Common driver mutations in the 2 major histologic forms of NSCLC.

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TABLE 1 Clinical evaluation of EGFR TKIs in NSCLC

Drug	Manufacturer	Status of ongoing clinical testing
Erlotinib (Tarceva)	OSI	FDA approved in locally advanced or metastatic disease after failure of prior chemotherapy (2004), for maintenance therapy in patients with locally advanced or metastatic disease after first-line chemotherapy (2010), for first-line treatment of metastatic disease in patients with *EGFR* mutations (2013) Ongoing clinical trials include: Phase 3 in patients with surgically resected disease (NCT02193282)
Gefitinib (Iressa)	AstraZeneca	FDA approved (2003) Approval withdrawn and indication limited to patients who previously benefited from gefitinib (2005) Use discontinued in the US (2011) Ongoing clinical trials include: Phase 3 vs vinorelbine/platinum therapy as adjuvant treatment in stage II-IIIA disease with *EGFR* mutations (ADJUVANT; NCT01405079) Phase 3 intercalated for induction therapy in combination with chemotherapy in patients with *EGFR* mutations (NeoIntercal; NCT02326285) Phase 3 as intercalating and maintenance therapy vs chemotherapy (NCT01404260)
Afatinib (Gilotrif)	Boehringer Ingelheim	FDA approved as first-line treatment for patients with metastatic disease with *EGFR* alterations (2013) Ongoing clinical trials include: Phase 3 +/- cetuximab in patients with EGFR-positive newly diagnosed stage IV or recurrent disease (NCT02438722) Phase 3 in advanced disease with *EGFR* mutations (NCT01953913)
Rociletinib (CO-1686)	Clovis	FDA breakthrough therapy designation for second-line treatment of T790M-mutant NSCLC patients (2014); to be submitted for NDA in July. Ongoing trials include: Phase 3 vs single-agent chemotherapy in patients with *EGFR*-mutant disease who failed prior therapy with at least one TKI and platinum doublet chemotherapy (TIGER-3; NCT02322281) Phase 2 as second-line therapy in patients with *EGFR*-mutant disease (TIGER-2; NCT02147990) Phase 2 vs erlotinib in patients with *EGFR*-mutant disease (TIGER-1; NCT02186301)
AZD9291	AstraZeneca	Ongoing trials include: Phase 3 vs gefitinib or erlotinib in locally advanced or metastatic disease (FLAURA; NCT02296125) Phase 3 vs platinum-based doublet chemotherapy in locally advanced or metastatic disease (AURA3; NCT02151981) Phase 3 + anti-PDL1 antibody MEDI4736 vs monotherapy in *EGFR T790M* mutation-positive disease after prior TKI therapy (CAURAL; NCT02454933)
HM61713	Hanmi	Ongoing trials include: Phase 2 in patients with *EGFR*-positive disease (NCT02444819)

FDA, US Food and Drug Administration; EGFR, epidermal growth factor receptor; NDA, new drug application; NSCLC, non-small-cell lung cancer TKI, tyrosine kinase inhibitor; PDL-1, programmed cell death ligand-1 NSCLC, non-small-cell lung cancer

found in lung cancer patients are exon 19 deletions and L858R missense substitutions.[4-6] Meanwhile, *ALK* alterations most commonly involve a chromosomal inversion, in which chromosome 2 (on which the *ALK* gene is located) is broken and part of the DNA reinserts into the chromosome in the reverse orientation, the result being a fusion between the *ALK* gene and the echinoderm microtubule associated protein like 4 (*EMLA*) gene.[7] Both *EGFR* mutations and *ALK* rearrangements ultimately lead to the inappropriate activation of the kinase activity of these receptors.

The development of small molecule inhibitors of EGFR and ALK designed to suppress their activation have subsequently revolutionized the treatment of patients with lung adenocarcinoma whose tumors harbor these genetic changes. For patients with *EGFR* mutations, erlotinib[8] and, more recently, afatinib[9] have been approved in the United States. Gefitinib was initially approved, but approval was withdrawn and use in the US

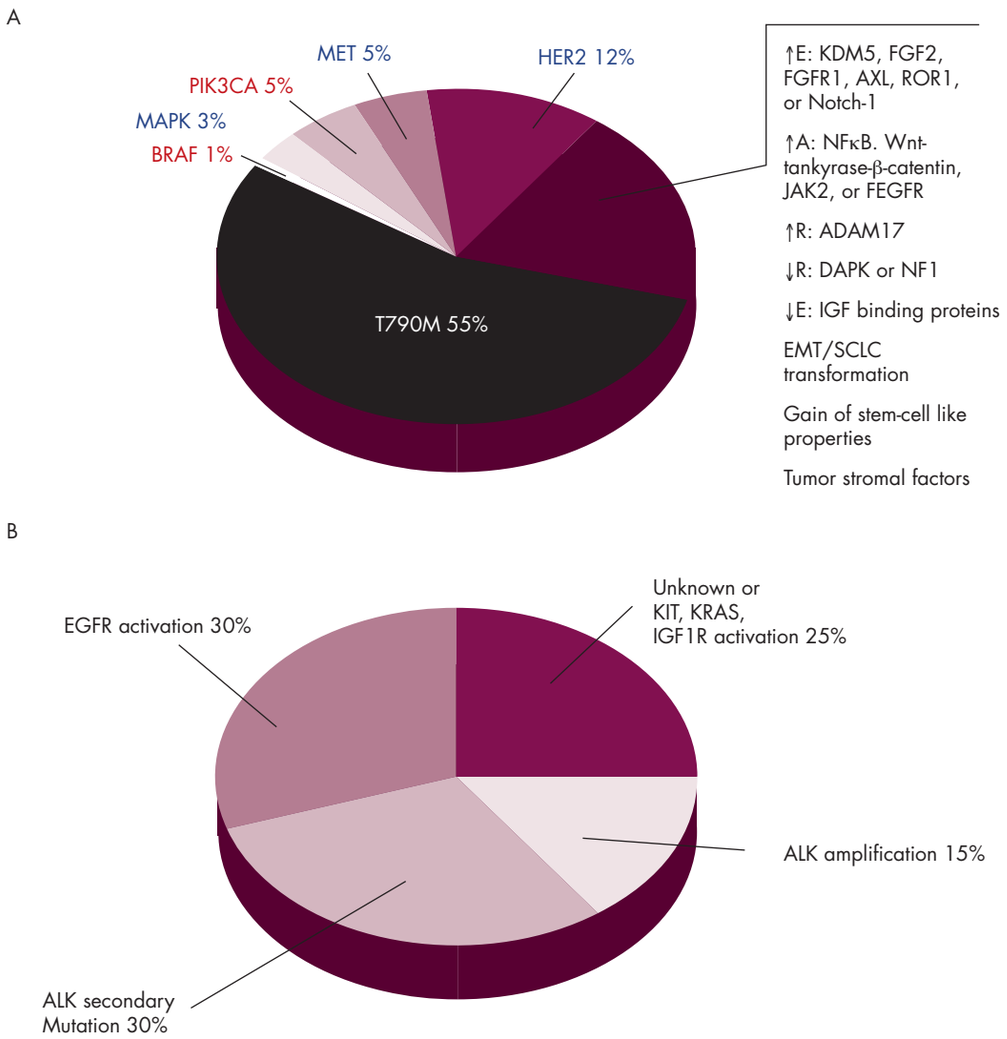

FIGURE 2 Mechanisms of resistance to EGFR and ALK inhibition in NSCLC
Summary of some of the reported mechanisms of resistance to first-generation (a) EGFR and (b) ALK tyrosine kinase inhibitors. Red text represents mutations, blue text represents amplifications. ↑E, increased expression; ↓E, loss of expression; ↑A, increased activation; ↑R, up-regulation; ↓R, down-regulation.

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discontinued after it failed to improve survival in subsequent clinical trials,[10] although numerous clinical trials are still ongoing in more select patient populations (Table 1). EGFR tyrosine kinase inhibitors (TKIs) have demonstrated superior response rates, progression-free survival (PFS), and quality of life compared with chemotherapy in patients with metastatic disease that is *EGFR* mutation positive.[11-16] None of the studies have demonstrated an overall survival (OS) benefit as yet, though this has been attributed to extensive cross-over after progression.[17]

For patients with *ALK* rearrangements, the small-molecule TKI crizotinib was awarded accelerated regulatory approval in 2011 for the treatment of patients with metastatic disease, a mere 4 years after the discovery of the *ALK-EML4* fusion in NSCLC patients. Full FDA approval followed in 2013, based on the demonstration of improved PFS compared with chemotherapy, coupled with a favorable toxicity profile, in the phase 3 PROFILE-1007 trial.[18,19] The rapid clinical development of crizotinib has been heralded as a model of successful and efficient drug development in a molecularly targeted patient population.

In December 2014, AstraZeneca announced that the ongoing phase 3 PROFILE-1014 trial, in which criztonib is being evaluated as first-line therapy compared with platinum-pemetrexed chemotherapy in treatment-naïve patients, had met its primary endpoint of improved PFS (10.9 vs 7 months, respectively), with no unexpected safety issues, suggesting that crizotinib may become gold standard treatment for all lines of therapy in *ALK*-positive NSCLC.[20]

Gatekeepers of resistance

Depsite the success of EGFR- and ALK-targeted therapies in lung cancer, the significant responses observed with first and even second-generation (in the case of EGFR)

TABLE 2 Clinical evaluation of ALK inhibitors in NSCLC

Drug	Manufacturer	Status of ongoing clinical testing
Crizotinib (Xalkori)	Pfizer	FDA approved in ALK-positive metastatic disease (2013) Ongoing clinical trials include: Phase 3 in patients with ALK-positive stage Ib-IIIa disease that has been surgically resected (NCT02201992) Phase 3 vs alectinib in treatment-naïve ALK-positive advanced disease (ALEX; NCT02075840) Phase 3 vs chemotherapy in previously untreated ALK-positive East Asian patients (NCT01639001)
Ceritinib (Zykadia)	Novartis	FDA approved in ALK-positive metastatic disease after treatment with crizotinib (2014) Ongoing clinical trials include: Phase 3 vs chemotherapy in ALK-positive patients previously treated with platinum doublet chemotherapy and crizotinib (NCT01828112) Phase 3 vs chemotherapy in previously untreated patients with ALK-positive disease (NCT01828099)
Alectinib	Roche	Ongoing clinical trials include: Phase 3 expanded access study for patients with ALK-rearranged disease after progression on or intolerance to prior ALK inhibitor therapy Phase 3 vs crizotinib in treatment-naïve ALK-positive disease (ALEX; NCT02075840)
Brigatinib (AP26113)	Ariad	Ongoing clinical trials include: Phase 2 in ALK-positive locally advanced or metastatic disease that progressed on crizotinib therapy (ALTA; NCT02094573) Phase 1/2 in patients with advanced malignancies including ALK-positive NSCLC (NCT01449461)
X-396	Xcovery	Phase 1/2 first-in-human study in advanced solid tumors, including NSCLC (NCT01625234)

FDA, US Food and Drug Administration; ALK, anaplastic lymphoma kinase

agents is, all too often, not durable. The development of acquired resistance to these agents is all but inevitable, and patients typically progress within 1-2 years of initiating TKI therapy.

Analysis of tumors that progress have revealed a large number of molecular mechanisms underlying resistance (Figure 2), including secondary mutations in the therapeutic target and activation of alternate signaling pathways that can bypass the target. By far the most common mechanism of resistance to EGFR TKIs in lung cancer, found in more than half of all cases, is the secondary *EGFR* mutation, T790M. T790M is dubbed a "gatekeeper" mutation because it affects a threonine residue in the EGFR protein that controls access to the hydrophobic pocket within the active site of the kinase. The point mutation changes the threonine to a bulkier amino acid that disrupts the TKI's ability to bind to its target and/or alters the affinity of the kinase for adenosine triphosphate (ATP).[2,22,23]

Another common mechanism of resistance to EGFR TKIs is amplification of *MET*, which activates the downstream phosphatidylinositol-3-kinase (PI3K)-Akt-mammalian target of rapamycin (mTOR) pathway independently of EGFR activation.[22] Resistance to ALK TKIs is likewise complex, including an analogous gatekeeper mutation (L1196M), though this is far less common than T790M in EGFR TKI-treated patients. Indeed, although secondary ALK mutations and activation of EGFR are common, there is no single predominant mechanism of resistance to ALK TKIs.[2,24-26]

Efforts to overcome resistance have driven the development of second- and third-generation TKIs, which are designed to be more potent, irreversible inhibitors of the kinase or to specifically inhibit a particular mutant form, such as T790M. Most advanced in development are the EGFR TKIs rociletinib (CO-1686) and AZD9291, and the ALK TKIs alectinib, brigatinib (AP26113), and ceritinib (Table 2).

Rociletinib and AZD9291 are designed to inhibit the T790M and L858R *EGFR* mutant forms as well as EGFR TKI-sensitizing mutants, while sparing wild-type *EGFR*.[27,28] Enrollment is currently underway for a phase 3 trial of rociletinib in patients who failed prior TKI and chemotherapy, the TIGER-3 trial (NCT02322281), in addition to various other earlier stage trials.

The results of one such trial were presented at the 2015 annual meeting of the American Society of Clinical

Oncology in Chicago. TIGER-X is a phase 1/2 study of rociletinib in heavily pretreated patients with T790M-mutant *EGFR*-positive NSCLC. A 60% overall response rate (ORR) and 90% disease control rate (DCR) were observed in patients with centrally confirmed tissue T790M positivity who were treated at a recommended dose of 500 mg (n = 48). Across all dose groups (n = 243), ORR was 53% and DCR was 85%. Median PFS in patients without a history of central nervous system (CNS) metastases (n = 163) was 10.3 months. Responses were durable and the toxicity profile of rociletinib was tolerable. Of note is that about one-third of T790M-negative patients also responded, which could not be explained by retreatment effect.[29]

Rociletinib received breakthrough therapy designation from the FDA in May 2014 for second-line treatment of T790M-mutant NSCLC patients and data from the TIGER-X trial will be combined with data from the TIGER-2 study for the new drug application (NDA) package that is expected to be submitted in July.

AZD9291 is currently being evaluated in three phase 3 trials (FLAURA, AURA3, and CAURAL), as well as a number of phase 1 and 2 studies. Investigators recently published the results from the first-in-human AURA study of AZD9291 in which 253 patients with radiologically documented disease progression after prior EGFR TKI therapy received AZD9291 at doses of 20-240 mg once daily. ORR was 51% overall, but 61% in 127 patients with confirmed T790M mutation, compared with 21% for those without, and median PFS was 9.6 months in T790M-positive patients. The most common adverse events were diarrhea, rash, nausea and decreased appetite. The results of an expansion cohort from this study were also presented at ASCO. An ORR of 81% was reported in treatment-naïve patients with T790M-mutant NSCLC.[30]

In addition to being evaluated as monotherapy, the safety profile of AZD9291 suggested that it may be amenable to combination therapy and several combination trials are ongoing. Preliminary data from the multi-arm phase 1b TATTON study of AZD9291 in combination with the programmed cell death-ligand 1 (PD-L1) inhibitor MEDI4736, the MET inhibitor AZD6094 or the MEK inhibitor selumetinib in patients with advanced EGFR-mutant NSCLC were also presented at ASCO. All 3 combinations were escalated to their phase 2 monotherapy doses and, in the 42 patients enrolled to date, there have been 3 partial responses (PRs) in the MEDI4736 arm, 2 PRs in the AZD6094 arm and 2 PRs in the selumetinib arm, with favorable toxicity profiles.[31]

Similar to these novel EGFR TKIs, the second-generation ALK TKIs ceritinib, brigatinib, and alectinib have all demonstrated inhibitory activity against resistant mutant forms of ALK, including L1196M, G1269Y, and S1206Y.[32] In April 2014, ceritinib became the first drug to gain accelerated regulatory approval for the treatment of patients with metastatic NSCLC following crizotinib treatment, based on the demonstration of response rates of over 50% and a 7.4-month median duration of response.[33,34] Alectinib and brigatinib are hot on its heels and both have been given breakthrough therapy designation. Numerous studies for both agents were presented at ASCO, including preliminary data from a phase 1/2 study of brigatinib that showed promising antitumor activity in ALK-positive NSCLC patients, with and without prior crizotinib.[35]

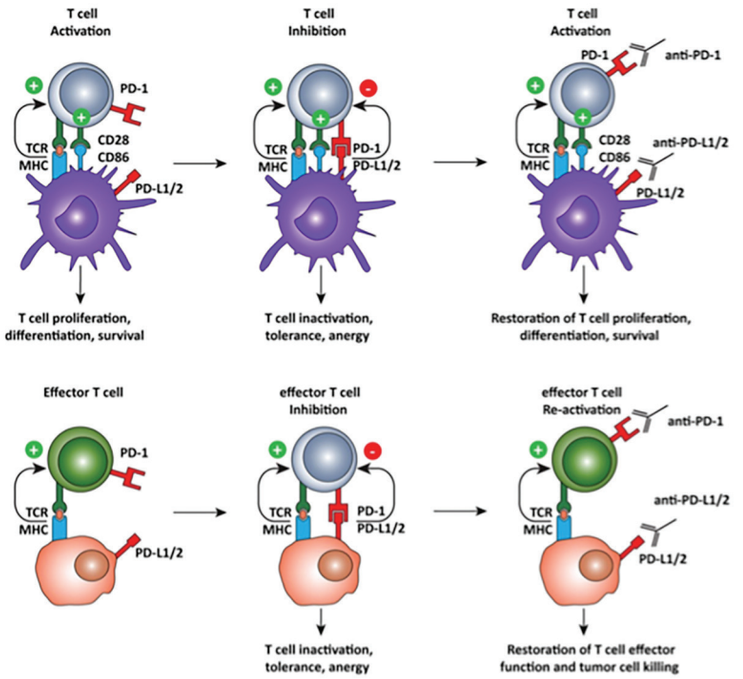

FIGURE 3 PD-1 pathway blockade. PD-1 is an inhibitory receptor expressed on the surface of T cells that, under normal conditions, switches off the cytotoxic T cells of the immune system at the appropriate time to avoid damaging normal tissues. Tumor cells often exploit this by expressing PD-1 or promoting the expression of PD-L1/L2 in the tumor microenvironment to inhibit T-cell activity and downregulate the anti-tumor immune response. Inhibiting PD-1 and its ligands helps to reinstate the anti-tumor immune response and overcome this mechanism of immune evasion.

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TABLE 3 Clinical evaluation of targeted therapies in SCLC

Drug	Manufacturer	Mechanism of action	Status of ongoing clinical testing in SCLC
Nintedanib (BIBF1120)	Boehringer Ingelheim	Multikinase inhibitor	Phase 2 in platinum-sensitive disease (NCT02152059)
Pazopanib (Votrient)	GlaxoSmithKline	Multikinase inhibitor	Phase 2 as maintenance therapy (NCT01797874) Phase 2 in relapsed/refractory disease (NCT01713296)
Ganetespib (STA-9090)	Synta	Hsp90 inhibitor	Phase 1/2 + doxorubicin (NCT02261805)
Navitoclax (ABT-263)	AbbVie	Bcl-2 inhibitor	Phase 1/2 + trametinib (NCT02079740)
OMP-59R5	OncoMed	Notch 2/3 inhibitor	Phase 1/2 + etoposide and platinum therapy in extensive stage disease (PINNACLE; NCT01859741)
Roniciclib (BAY1000394)	Bayer	Cyclin dependent kinase inhibitor	Phase 2 + chemotherapy (CONCEPT-SCLC; NCT02161419)
Veliparib (ABT-888)	AbbVie	PARP inhibitor	Phase 1 + carboplatin/etoposide in treatment-naïve extensive stage disease (NCT02289690)
Ipilimumab (Yervoy)	Bristol-Myers Squibb	CTLA-4 inhibitor	Phase 3 + etoposide vs platinum therapy + etoposide vs platinum therapy alone (NCT01450761) Phase 2 in limited disease (STIMULI; NCT02046733) Phase 2 + carboplatin + etoposide in extensive stage disease (ICE; NCT01331525)
Nivolumab (Opdivo)	Bristol-Myers Squibb	PD-1 inhibitor	Phase 1/2 as monotherapy or + ipilimumab (NCT01928394)

Hsp90, heat shock protein 90; Bcl-2, B-cell lymphoma 2; PARP, poly(ADP) ribose polymerase; CTLA-4, cytotoxic T-lymphocyte antigen-4; PD-1, programmed cell death-1

A common site of metastasis in patients with advanced NSCLC is the central nervous system (CNS), which can be particularly challenging to treat because many drugs have limited penetration of the CNS. The results of 2 trials presented at ASCO demonstrate the significant activity of alectinib in patients with CNS progression. In 69 patients who progressed on crizotinib, ORR was 47.8% and DCR was 79.7%, and in patients with measurable CNS disease, ORR and DCR were 68.8% and 100%, respectively. In a second trial of 122 patients who failed prior crizotinib therapy, ORR was 49.2% and DCR was 79.5%, with an ORR of 55.9% in patients with baseline CNS progression, including 5 complete responses (CRs), and median PFS was 8.9 months.[36,37] These data are to be submitted to the FDA as part of an NDA for alectinib.

Immunotherapy: hope for more challenging forms of lung cancer

Although rationally designed targeted therapies continue to improve outcomes for patients with lung adenocarcinoma, other forms of lung cancer have proven significantly more challenging. Both the squamous form of NSCLC and other histological subtypes of lung cancer, such as small-cell lung cancer (SCLC) – the most aggressive subtype – have not benefited from targeted therapies, despite initial promise and extensive investigation (Table 3).

Recently, findings from molecular profiling studies have begun to more clearly elucidate the molecular mechanisms underlying these tumor types and have highlighted their distinct and significantly more complex genetic signatures compared to non-squamous NSCLC, which may partly explain the limited success of targeted therapies tested to date.[38-40]

Immunotherapy has emerged as a novel treatment paradigm for the treatment of lung cancer and has enjoyed particular success in the treatment of squamous cell NSCLC. Early immunotherapeutic approaches had limited efficacy in the treatment of solid tumors such as lung cancer, but an increasing appreciation of the ability of tumors to suppress the immune response has led to the development of targeted immunotherapies that have catalogued a slew of remarkable results in solid tumors in the past few years.

Checkpoint proteins, which include the programmed cell death receptor 1 (PD-1) and its ligands (PD-L1 and PD-L2), act as the immune system's fail-safe mechanism, preventing damage to normal tissue by ensuring the cytotoxic T cells are switched on at the appropriate time and are switched off when no longer needed. Cancer cells manipulate the expression of checkpoint proteins to suppress T-cell activity and down-regulate the antitumor immune response, thus checkpoint inhibitors were developed that

TABLE 4 Clinical evaluation of immune checkpoint inhibitors in NSCLC

Drug	Manufacturer	Status of ongoing clinical testing
Tremelimumab	AstraZeneca	Ongoing clinical trials include: Phase 1 + gefitinib (GEFTREM; NCT02040064)
Ipilimumab (Yervoy)	Bristol-Myers Squibb	Ongoing clinical trials include: Phase 3 + paclitaxel and carboplatin (NCT02279732) Phase 2 + ionizing radiation (NCT02221739) Phase 1 + erlotinib or crizotinib in *EGFR* or *ALK*-positive disease (NCT01998126)
MEDI-4736	AstraZeneca	Ongoing clinical trials include: Phase 3 +/- tremelimumab vs standard of care (MYSTIC; NCT02453282) Phase 3 + tremelimumab and as monotherapy (ARCTIC; NCT02352948)
Pembrolizumab (Keytruda)	Merck	Ongoing clinical trials include: Phase 3 vs platinum-based chemotherapy (KEYNOTE-024; NCT02142738) Phase 3 vs platinum-based chemotherapy (KEYNOTE-042; NCT02220894)
Atezolizumab (MPDL3280A)	Roche	Ongoing clinical trials include: Phase 3 + cisplatin or carboplatin + pemetrexed (IMpower110; NCT02409342) Phase 3 vs gemcitabine + cisplatin or carboplatin (IMpower111; NCT02409355) Phase 3 + carboplatin + pemetrexed +/- bevacizumab (IMpower150) Phase 3 + carboplatin + nab-paclitaxel (IMpower130; NCT02367781) Phase 3 + carboplatin + paclitaxel or nab-paclitaxel (IMpower131; NCT02367794)
Nivolumab (Opdivo)	Bristol-Myers Squibb	FDA-approved for patients with advanced squamous NSCLC who progressed on or after platinum-based chemotherapy (2015) Ongoing clinical trials include: Phase 3 in previously treated patients (CheckMate153; NCT02066636) Phase 3 vs investigator's choice of chemotherapy as first-line therapy (CheckMate026; NCT02041533)

FDA, US Food and Drug Administration; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase

could help overcome tumor-induced immunosuppression by augmenting the tumor-specific T-cell response.[41]

A number of checkpoint inhibitors have been developed and are being evaluated in lung cancer (Table 4), but furthest along in clinical development is nivolumab. Nivolumab was granted accelerated approval for the treatment of patients with squamous NSCLC that has progressed on or after platinum-based chemotherapy in March 2015, following demonstration of a 3.2-month improvement in OS, marking a second approved indication for this drug.[42]

The FDA has also recently granted priority review to pembrolizumab for patients with advanced NSCLC across all histologies whose disease progressed after platinum-based chemotherapy, suggesting it may be joining nivolumab as an approved agent shortly (a final decision is expected in October 2015). Promising results from the phase 2 POPLAR study of another checkpoint inhibitor, atezolizumab (MPDL3280A), were presented at ASCO; it was shown to double OS compared with docetaxel chemotherapy.[43]

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