Review Article

# Targeted therapy for non-small cell lung cancer: current standards and the promise of the future

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**Abstract:** In recent years, there has been a major paradigm shift in the management of non-small cell lung cancer (NSCLC). NSCLC should now be further sub-classified by histology and driver mutation if one is known or present. Translational research advances now allow such mutations to be inhibited by either receptor monoclonal antibodies (mAb) or small molecule tyrosine kinase inhibitors (TKI). Whilst empirical chemotherapy with a platinum-doublet remains the gold standard for advanced NSCLC without a known driver mutation, targeted therapy is pushing the boundary to significantly improve patient outcomes and quality of life. In this review, we will examine the major subtypes of oncogenic drivers behind NSCLC as well as the development of targeted agents available to treat them both now and in the foreseeable future.

**Keywords:** Non-small cell lung carcinoma; targeted therapy; epidermal growth factor receptor (EGFR); anaplastic lymphoma kinase (ALK)

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## Introduction

Lung cancer remains by far the single most common cause of cancer-related mortality with nearly 1.6 million deaths worldwide in 2012 or nearly 20% of cancer mortality as a whole (1). Over the last decade, molecular translational research advances have heralded major breakthroughs in the understanding, diagnosis and management of lung cancer, particularly for the more common (~80%) non-small cell lung cancer (NSCLC). Conversely, treatment for small cell lung cancer remains chemotherapy-based and whilst there are promising results with novel cytotoxics, its platinum-etoposide backbone holds strong (2).

The term '*Theranostics*' whereby therapeutics and diagnostics have been meaningfully combined to achieve personalised pharmacotherapy has now become commonplace in oncology. Sequencing of the human genome has permitted more efficient identification of epigenetic mutations, tumour-suppressor-gene inactivation as well as oncogene driver mutations that are potential targets for therapy (3-8). Such examples include trastuzumab for HER-2 over-expressing breast cancer and vemurafenib for BRAF-mutant melanoma (9,10).

It is now accepted that NSCLC is not a singular entity but is in fact multiple pathologies with unique molecular signatures that we are only beginning to unravel and understand (11-13). Broadly speaking, the main subtypes are pulmonary adenocarcinoma, squamous cell carcinoma (SCC) and large cell carcinoma. This distinction alone allows for a more tailored selection of cytotoxic chemotherapy in advanced NSCLC without a driver mutation, as seen with enhanced efficacy with pemetrexed in adenocarcinoma (14,15) or the toxicity concerns of bevacizumab in patients with squamous histology (16).

Optimal management of NSCLC now requires that tumours be screened for a range of predictive and prognostic biomarkers that help to predict sensitivity to targeted therapy and estimate prognosis respectively (17). For NSCLC, much of the work in the last decade has been focussed on mutations of the epidermal growth factor receptor (EGFR) and on the abnormal fusion of the anaplastic lymphoma kinase

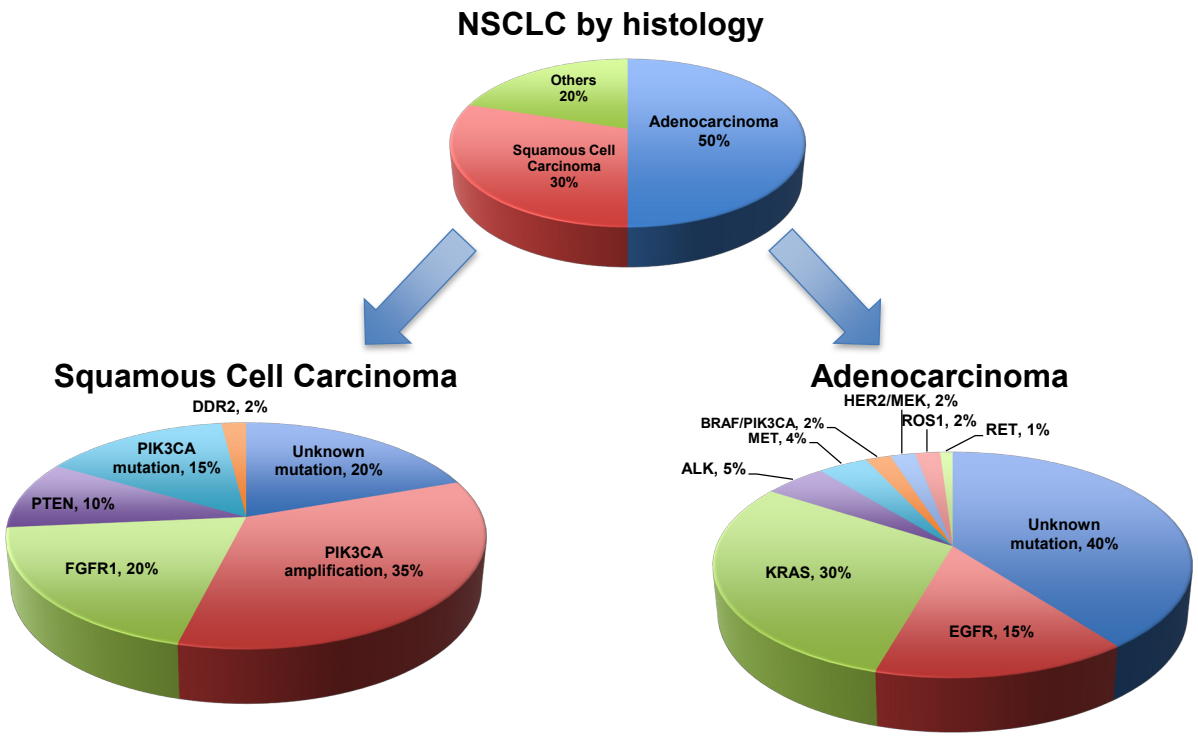


**Figure 1** NSCLC by histology and mutations. NSCLC, non-small cell lung cancer.

(ALK) being inhibited successfully with EGFR tyrosine kinase inhibitors (TKI) and crizotinib respectively. Targeted agents are now being rationally designed to inhibit particular mutations leading to a more streamlined clinical trial process. In this review, we will examine the major subtypes of driver mutations that have been identified in NSCLC and relevant targeted therapies available both now, and in the foreseeable future.

## Signalling pathway targets in NSCLC

The traditional and now over-simplified histological distinctions within NSCLC include adenocarcinoma, SCC and large cell carcinoma (*Figure 1*). Up to 60% of lung adenocarcinoma and up to 50-80% of SCC have a known oncogenic driver mutation (*Figure 1*) (18,19). These mutations in receptors or protein kinases can stimulate a complex cascade of cross signalling pathways such as the RAS-RAF-MEK-ERK or MAPK, PI3K-AKT-mTOR or JAK-STAT pathways (*Figure 2*) (3,4,7,18,20). Ultimately these lead to uncontrolled growth, proliferation and survival. Successful targeted therapy involves the identification and inhibition of these up-regulated pathways by either small molecule inhibitors or receptor monoclonal antibodies (mAb). The best studied in NSCLC is the interaction between EGFR and its downstream pathways.

## Epidermal growth factor receptor (EGFR)

The epidermal growth factor receptor (EGFR or ErbB1 or HER1) belongs to a family of receptor tyrosine kinases that can trigger a vast array of signalling pathways leading to cell growth, proliferation and survival (20,21). Such flow-on pathways include the RAS-RAF-MEK-ERK or MAPK pathway and the PI3K-AKT-mTOR pathways.

There are three main mechanisms leading to EGFR activation: increased expression of EGFR on malignant cells; enhanced ligand production by malignant cells; and activating mutations of EGFR within malignant cells. EGFR is overexpressed in up to 40-80% of NSCLC and was a promising translational therapeutic target however it was subsequently discovered that activating mutations rather than overexpression of EGFR was the prime therapeutic target. The two most common mutations are exon 19 deletions (60%) and L858R missense substitutions at position 858 (35%) where leucine is replaced by arginine

 

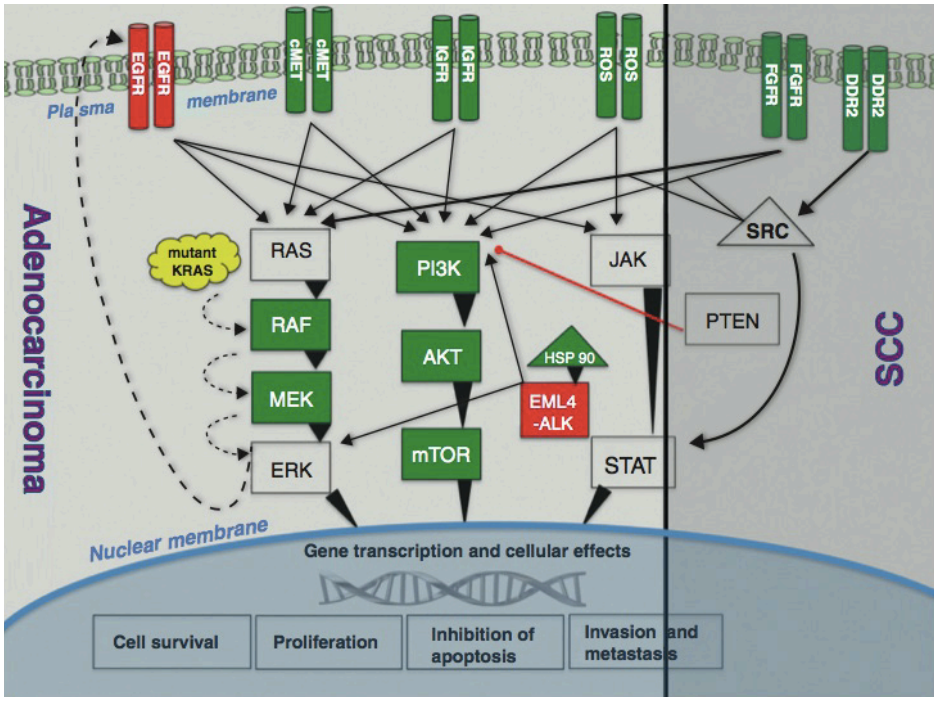


**Figure 2** Overview of molecular pathways and potential targets in non-small cell lung cancer (NSCLC) [(from Alamgeer *et al*. (18)].

resulting in constitutive activation of the receptor without ligand binding (21-23). Mutant EGFR can be inhibited either by small molecule TKI (such as gefitinib and erlotinib) or mAb (such as cetuximab).

Gefitinib and erlotinib were the first EGFR TKIs to be developed. Both are reversible competitive inhibitors of ATP for the tyrosine kinase domain of EGFR resulting in blockade of downstream pathways. Early trials used EGFR TKIs in an unselected population as these predated the now known clinical and molecular predictive biomarkers (24-28). As trials matured, subgroup analyses identified characteristics that correlated with response such as adenocarcinoma histology, Asian ethnicity and minimal smoking history (24-26,29-34). Molecular testing of tissue samples from those who had responded to TKIs revealed that somatic activating mutations in EGFR underpinned the responses seen (29,30,35-37). The incidence of EGFR mutation varies with ethnicity, with Asian populations having up to 50% of adenocarcinomas driven by activating EGFR mutations compared to only 10% to 15% in Caucasians (37). Unfortunately, there are no reliable clinical phenotypes or characteristics that allow for accurate prediction of an EGFR mutation, thus all tumours must undergo specific mutational testing (38).

### *EGFR-mutant NSCLC*

The most significant paradigm change in the last 10 years for NSCLC management was heralded by the use of EGFR TKIs as first-line therapy for patients with a targetable EGFR driver mutation. The landmark Iressa Pan-Asia Study (IPASS) randomised 1,217 patients from several East Asian countries with untreated stage IIIB or IV adenocarcinoma to gefitinib or carboplatin and paclitaxel chemotherapy (*Table 1*) (39). Subjects were clinically selected with no or minimal smoking history and EGFR was explored as a potential biomarker. IPASS met its primary endpoint with a 12-month progression-free survival (PFS) of 24.9% with gefitinib versus 6.7% with chemotherapy (39). EGFR status was known in approximately a third of patients, and of these, 60% harboured an activating mutation. For these patients, PFS was significantly prolonged with gefitinib compared to chemotherapy [HR 0.48 (95% CI, 0.36-0.64); P<0.001]. Conversely, patients with wild-type EGFR did better with chemotherapy [HR 2.85; (95% CI, 2.05-3.98); P<0.001]. The First-SIGNAL study (41) verified these findings by clinically selecting never smokers with adenocarcinoma then comparing chemotherapy to gefitinib first-line (*Table 1*). Overall PFS was not significantly different but

 

**Table 1** Phase III Trials comparing EGFR-inhibitors to chemotherapy in advanced stage IIIB/IV NSCLC

| Trial [year] (Ref) | Patient selection | Targeted therapy (TT) | Comparator (C) | Median PFS TT *vs*. C (mo.) | HR | P value |
|---|---|---|---|---|---|---|
| First-line EGFR TKI versus chemotherapy | | | | | | |
| IPASS [2009] (39,40) | n=1,217, clinical, non/light smokers, Adc, 60% EGFR mutant (Asia) | Gefitinib | Carboplatin; Paclitaxel | 9.8 *vs*. 6.4 | 0.48 | ≤0.001 |
| First-SIGNAL [2012] (41) | n=309, clinical, never smokers, Adc, 44% EGFR mutant | Gefitinib | Cisplatin; Gemcitabine | 5.8 *vs*. 6.4 | 1.198 | 0.138 |
| WJTOG3405 [2010] (42) | n=172, molecular EGFR mutant | Gefitinib | Cisplatin; Docetaxel | 9.2 *vs*. 6.3 | 0.489 | <0.0001 |
| NEJSG [2010] (43) | n=230, molecular EGFR mutant | Gefitinib | Carboplatin; Paclitaxel | 10.8 *vs*. 5.4 | 0.30 | <0.001 |
| OPTIMAL [2011] (44) | n=154, molecular EGFR mutant, 88% Adc | Erlotinib | Carboplatin; Gemcitabine | 13.1 *vs*. 4.6 | 0.16 | <0.0001 |
| EURTAC [2012] (45) | n=174, molecular EGFR mutant | Erlotinib | Platinum doublet | 9.7 *vs*. 5.2 | 0.37 | <0.0001 |
| LUX-Lung3 [2013] (46) | n=345, molecular EGFR mutant Adc | Afatinib | Cisplatin; Pemetrexed | 11.1 *vs*. 6.9 | 0.58 | 0.001 |
| LUX-Lung6 [2014] (47) | n=364, molecular EGFR mutant Adc | Afatinib | Cisplatin; Gemcitabine | 11.0 *vs*. 5.6 | 0.28 | <0.0001 |
| First-line EGFR therapy plus chemotherapy | | | | | | |
| INTACT-1 [2004] (48) | n=1,093, unselected, Adc + SCC | Gefitinib 500 mg/250 mg or placebo + chemotherapy | Cisplatin + Gemcitabine (chemotherapy alone) | 5.5 (500 mg), 5.8 (250 mg) *vs*. 6.0 | NR | 0.7633 |
| INTACT-2 [2004] (49) | n=1,037, unselected, Adc + SCC | Gefitinib 500 mg/250 mg or placebo + chemotherapy | Carboplatin + Paclitaxel (chemotherapy alone) | 4.6 (500 mg), 5.3 (250 mg) *vs*. 5.0 | NR | 0.0562 |
| TRIBUTE [2005] (50) | n=1,059, unselected, Adc + SCC | Erlotinib + chemotherapy then maintenance Erlotinib | Carboplatin; Paclitaxel | 5.1 *vs*. 4.9 | 0.937 | 0.36 |
| TALENT [2007] (51) | n=1,172, unselected, Adc + SCC | Erlotinib + chemotherapy | Cisplatin; Gemcitabine | 5.5 *vs*. 5.7 (23.7 *vs*. 24.6 wks.) | 0.98 | 0.74 |
| FLEX [2009] (52) | n=1,125, Adc + SCC, EGFR expression | Cetuximab + chemotherapy | Cisplatin; Vinorelbine | 4.8 *vs*. 4.8 | 0.943 | 0.39 |
| BMS099 [2010] (53) | n=676, unselected, Adc + SCC | Cetuximab + chemotherapy | Carboplatin; Paclitaxel or Docetaxel | 4.40 *vs*. 4.24 | 0.902 | 0.2358 |
| TORCH [2012] (54, 55) | n=760, unselected, Adc + SCC | Erlotinib (followed by Cisplatin Gemcitabine) | Cisplatin Gemcitabine (followed by Erlotinib) | 6.4 *vs*. 8.9 | 1.21 | NR |

**Table 1** (*continued*)

**Table 1** (*continued*)

| Trial [year] (Ref) | Patient selection | Targeted therapy (TT) | Comparator (C) | Median PFS TT *vs*. C (mo.) | HR | P value |
|---|---|---|---|---|---|---|
| Second- or third-line EGFR TKI versus placebo | | | | | | |
| BR.21 [2005] (56) | n=731, unselected, Adc + SCC | Erlotinib | Placebo | 2.2 *vs*. 1.8 (OS 6.7 *vs*. 4.7, P<0.001) | 0.61 | <0.001 |
| ISEL [2005] (57) | n=1,692, unselected, Adc + SCC | Gefitinib | Placebo | 3.0 *vs*. 2.6 | 0.82 | 0.0006 |
| Second or third-line EGFR TKI versus chemotherapy | | | | | | |
| INTEREST [2008] (31) | n=1,433, unselected, Adc + SCC, EGFR mutant subgroup | Gefitinib | Docetaxel | 2.2 *vs*. 2.7 | 1.04 | 0.47 |
| V-15-32 [2008] (32) | n=489, unselected, Adc + SCC | Gefitinib | Docetaxel | 2.0 *vs*. 2.0 | 0.9 | 0.335 |
| ISTANA [2010] (33) | n=161, unselected, Adc + SCC | Gefitinib | Docetaxel | 3.3 *vs*. 3.4 (6 months PFS 32% *vs*. 13%) | 0.729 | 0.04 |
| TITAN [2012] (34) | n=424, unselected, Adc + SCC | Erlotinib | Docetaxel or Pemetrexed (physician's choice) | 1.4 *vs*. 1.9 (6.3 *vs*. 8.6 wks.) | 1.19 | 0.089 |
| TAILOR [2013] (58) | n=222, molecular EGFR wild type, KRAS testing, Adc + SCC | Erlotinib | Docetaxel | 2.9 (Docetaxel) *vs*. 2.4 (Erlotinib) in EGFR wild type | 0.71 | 0.02 |

Adc, adenocarcinoma; SCC, squamous cell carcinoma; PFS, progression-free survival; HR, hazard ratio; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; mo, months; wks, weeks.

upon review of patients treated with gefitinib, an activating EGFR mutation did predict for superior overall response rate (ORR) (84.6% *vs*. 25.9%, P<0.001) and significantly longer PFS (HR 0.377; 95% CI, 0.21-0.67; P<0.001) (41).

Further confirmatory trials (*Table 1*) compared gefitinib (42,43), erlotinib (44,45) or afatinib (46,47) to chemotherapy specifically in EGFR-mutated NSCLC rather than simply by the clinical enrichment criteria of earlier studies. All found that first-line EGFR TKIs afforded superior ORR, PFS and quality of life compared to chemotherapy. Thus upfront tumour interrogation for predictive biomarkers has now become standard and if EGFR demonstrates an activating mutation, then EGFR TKIs should be given as first-line therapy. However, despite mature follow up data for IPASS (40) and other studies, no EGFR TKI in first-line has demonstrated an overall survival benefit most likely due to extensive crossover after progression (59).

Currently, there are no published head to head trials directly comparing the efficacy of first-line EGFR TKIs. In general, these agents all demonstrate similar efficacy so the choice of agent depends on toxicity or clinician preference at the present time (60). Results of the phase IIb LUX-Lung 7 study directly comparing afatinib to gefitinib as first-line treatment for EGFR-mutant adenocarcinoma are eagerly anticipated and may address this (ClinicalTrials.gov Identifier: NCT01466660).

The role of adjuvant EGFR TKIs for resected stage I to III NSCLC remains uncertain (*Table 2*). Adjuvant erlotinib after surgery, specifically in EGFR-mutants, is currently being investigated in the RADIANT trial, with or without chemotherapy and is expected to complete in 2016 (ClinicalTrials.gov identifier: NCT00373425). Data from this study will be particularly interesting as a previous trial, NCIC BR19 (66), in an unselected patient population using adjuvant gefitinib, proved negative.

### *EGFR wild type and EGFR-unknown advanced NSCLC*

Most tumours do not harbour an activating EGFR mutation (known as EGFR wild-type) and the role of TKIs in this specific population is contentious. With regards to first-line therapy, guidelines discourage the use of first-line TKIs based on the IPASS (39,40) and TORCH (54,55) trials which both demonstrated inferior survival compared to up-front chemotherapy (67,68). For second-line therapy (*Table 1*), the TAILOR trial (58) compared erlotinib to docetaxel specifically in EGFR wild-type tumours. All endpoints of ORR, PFS and overall survival (OS), were significantly better with docetaxel compared to erlotinib (58). This supports the continuing role for cytotoxic chemotherapy as the preferred therapeutic option in NSCLC without targetable driver mutations (69).

Four trials investigated whether adding EGFR TKIs to standard platinum doublet chemotherapy could improve outcomes (*Table 1*). The INTACT 1 (48) and INTACT 2 (49) looked at gefitinib whereas the TRIBUTE (50) and TALENT (51) trials used erlotinib. All proved to be negative trials with no improvement in efficacy or survival compared to standard chemotherapy alone.

The prognosis for patients remains poor for those who progress after initial platinum doublet chemotherapy. Both docetaxel (70) and pemetrexed (71) are approved active agents in the second-line setting, but more therapeutic options were needed, especially for those unable to have further chemotherapy. The INTEREST study was a multinational phase III randomised trial that compared gefitinib to docetaxel in unselected second-line patients (*Table 1*) (31). Gefitinib was non-inferior with respect to median OS of 7.6 months with gefitinib and 8.0 months with docetaxel, HR 1.02 (95% CI , 0.905-1.150). Further trials with second-line gefitinib (32,33) and erlotinib (34) showed superior response rates, PFS and quality of life without significant differences in OS compared to chemotherapy.

For patients with unknown EGFR status who are unfit for chemotherapy, the phase III TOPICAL study (72) found a significant survival benefit with first-line erlotinib over placebo but only in those who developed a rash within 28 days. It should be noted that those who failed to develop a rash with erlotinib had inferior survival compared to placebo. Two early phase III trials investigated EGFR TKIs versus placebo in second- or third-line in unselected patients, prior to knowledge of predictive biomarkers (*Table 1*) (56,57). The BR.21 trial (56) was the first, and still the only phase III trial to show an overall survival benefit from an EGFR TKI (59). Survival with erlotinib was 6.7 months compared to 4.7 months with placebo (HR 0.70; 95% CI, 0.58-0.85; P<0.001) (56). In contrast, gefitinib failed to show a significant survival benefit in the ISEL trial (57). Icotinib, a novel EGFR TKI has also demonstrated non-inferiority in a head to head trial compared to gefitinib in previously treated, unselected advanced NSCLC (73). Therefore in patients with unknown or wild-type EGFR status, who have no further chemotherapy options, erlotinib may be beneficial as second- or third-line therapy after platinum-based chemotherapy.

Switch maintenance therapy to EGFR TKIs after initial induction chemotherapy has shown a modest but statistically

 

significant benefit (*Table 2*). The WJTOG0203 (61) and INFORM (63) trials used gefitinib whereas SATURN (62) and IFCT-GFPC 0502 (64) showed similar benefits for erlotinib. However the SWOG S0023 study (65) demonstrated no benefit with gefitinib compared to placebo following definitive chemoradiation. In fact, there appeared to potentially be harm from gefitinib in this setting as placebo paradoxically demonstrated a superior PFS and OS.

### *Anti-EGFR monoclonal antibodies*

Monoclonal antibodies represent an alternative way to inhibit EGFR activation and signalling. Apart from competitive inhibition of ligands binding to the extracellular domain, they can also form antibody-receptor complexes that are endocytosed and degraded. Available anti-EGFR mAbs now include cetuximab, necitumumab, panitumumab and matuzumab.Two phase III studies, FLEX (52) and BMS099 (53) have examined the combination of cetuximab with platinum doublet chemotherapy in advanced NSCLC (*Table 1*). Whilst the FLEX trial demonstrated a marginal improvement in median overall survival (11.3 months with cetuximab versus 10.1 months with chemotherapy alone), the smaller BMS099 trial was negative (52,53). Necitumumab is currently being investigated in two phase III studies. The ongoing INSPIRE study in non-squamous NSCLC (ClinicalTrials.gov identifier: NCT00982111) and the recently completed SQUIRE study for squamous NSCLC investigating cisplatin-gemcitabine with necitumumab. The SQUIRE study reportedly demonstrated an improved OS and formal publication of these results are eagerly anticipated (ClinicalTrials.gov identifier: NCT00981058). Other mAbs currently in phase II trials include panitumumab (ClinicalTrials.gov identifiers: NCT01038037 and NCT01088620) and matuzumab (ClinicalTrials.gov identifier: NCT00111839).

### *Resistance to EGFR targeted therapy*

Although EGFR TKIs have revolutionised treatment of EGFR-mutant NSCLC, most responses have not proved to be durable with many patients progressing after 7-12 months. Resistance can occur primarily (that is, *de novo*) or develop after exposure to targeted agents, and can exist as resistant clones within a tumour or in different tumours within the same patient. Most will develop 'acquired resistance', either through secondary EGFR mutations or activation of EGFR-independent pathways. Clinicians should therefore consider re-biopsy at progression to assess contemporaneous tumour biology (74-77). The most frequent mechanism (~50%) is via concurrent acquisition of a mutation in exon 20 of EGFR, encoding for T790M (74-80). Threonine is replaced by methionine, altering the configuration of the kinase domain and enhancing its affinity (over wild-type) for ATP, with corresponding decreased affinity for first-generation reversible TKIs (81). The second most common mechanism (in 5-20%) involves amplification of MET to circumvent EGFR inhibition via PI3K-AKT-mTOR signalling (74-76). Other resistance mechanisms include mutations in PIK3CA (75), HER2 (79,82), BRAF (83), STAT3 (84), AXL kinase (85), CRKL amplification (86) and in 5%,the unexpected transformation into small cell lung cancer (75,76). Despite significant advances in our understanding of the mechanisms of acquired resistance, up to 30% of resistance is mediated via an unknown mechanism and hence empirical cytotoxic chemotherapy remains the treatment of choice (75).

In contrast to chemotherapy, resistance to targeted therapy can be approached rationally once aberrant pathways are identified. Second-generation irreversible ErbB-family TKIs such as afatinib, which covalently binds to EGFR/HER1 and HER2, can overcome the T790M mutation as seen in LUX-Lung1 with 7% ORR and PFS improved from 1.1 months with placebo to 3.3 months (HR 0.38; 95% CI, 0.31-0.48, P<0.0001) (87,88). Dual EGFR blockade with EGFR TKIs and cetuximab are now being tested after success in murine models (89-91). Combined inhibition of MET and T790M has also shown promise in murine models (92) and is now undergoing clinical trials in humans with a MET/ALK inhibitor (crizotinib) plus a pan-HER inhibitor (dacomitinib) (ClinicalTrials.gov identifier: NCT01121575). Third generation EGFR TKIs such as CO-1868 and AP26113 that specifically target T790M have preliminary evidence of efficacy in acquired resistance with reasonable toxicity (93,94). Although addressing resistance to targeted therapy appears possible, the challenge for the future will be rationally choosing combinations and whether upfront combination therapy will be more effective than first-line single-agents whilst balancing toxicity and costs.

## EML4-ALK positive NSCLC

The *ALK* gene was first discovered in 1994 in the context of a subtype of Non-Hodgkin lymphoma where ALK was fused to nucleophosmin (NPM) as a result of a chromosomal translocation (95). In 2007, Soda *et al.* screened NSCLC tumours and found the same ALK

 

**Table 2** Phase III Trials comparing EGFR-inhibitors to chemotherapy in maintenance and adjuvant settings

| Trial [year] (Ref) | Patient selection | Targeted therapy (TT) | Comparator (C) | Median PFS TT *vs*. C (mo.) | HR | P value |
|---|---|---|---|---|---|---|
| Maintenance | | | | | | |
| WJTOG0203 [2010] (61) | n=604, unselected, Adc + SCC (EGFR predictive biomarker not known) | Gefitinib (in those without PD after 3× cycles platinum doublet) | Platinum doublet (up to 6 cycles) | 4.6 (Gefitinib) *vs*. 4.3 (chemo) | 0.68 | <0.001 |
| SATURN [2010] (62) | n=884, unselected for entry, Adc + SCC, 7% EGFR mutant | Erlotinib (in those without PD after 4× cycles platinum doublet) | Placebo | 2.8 *vs*. 2.6 (12.3 *vs*. 11.1 wks.) | 0.71 | <0.0001 |
| INFORM [2012] (63) | n=296, unselected, Adc + SCC (known EGFR status excluded) | Gefitinib (in those without PD after 4× cycles platinum doublet) | Placebo | 4.8 *vs*. 2.6 | 0.42 | <0.0001 |
| IFCT-GFPC 0502 [2012] (64) | n=464, unselected, Adc + SCC | Erlotinib or Gemcitabine maintenance (in those without PD after 4× cycles cisplatin gemcitabine) | Observation | 2.9 *vs*. 1.9 (Erlotinib)<br>3.8 *vs*. 1.9 (Gemcitabine) | 0.69<br>0.56 | 0.003<br><0.001 |
| SWOG S0023 [2008] (65) | n=243, unselected, Adc + SCC, closed after unplanned interim analysis after ISEL trial | Gefitinib (after chemoradiation and docetaxel in inoperable stage III) | Placebo | 8.3 *vs*. 11.7 | 0.80 | 0.17 |
| Adjuvant | | | | | | |
| BR.19 [2013] (66) | n=503, unselected, Adc + SCC, closed after unplanned interim analysis after ISEL trial | Gefitinib (after completely resected stage IB, II or IIIA NSCLC) | Placebo | 50.4 *vs*. not yet reached (4.2 years *vs*. not yet reached) | 1.22 | 0.15 |

Adc, adenocarcinoma; SCC, squamous cell carcinoma; PFS, progression-free survival; HR, hazard ratio; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; mo, months; wks, weeks.

gene but this time fused to Echinoderm Microtubule-associated protein-like protein 4 (EML4) as a result of a small inversion within chromosome 2p (96). The EML4-ALK fused oncogene is present in up to 3-7% of NSCLC and promotes malignant growth and proliferation (96). As with EGFR, ALK rearrangements are more likely to be seen in specific populations; younger patients who are light or never-smokers with adenocarcinoma and frequent signet ring cells seen on histology (97-101). Tumours carrying ALK rearrangements are mutually exclusive from those harbouring EGFR or KRAS mutations and represent the prototype for 'oncogene addiction' where a single gene product can result in malignancy (97,102,103).

Unlike the history of EGFR, lessons learnt since have allowed a more logical approach for ALK as a therapeutic target; from discovery, prospective tumour genotyping and specifically designed trials to test inhibitors and achieve positive patient outcomes. Crizotinib is an oral small molecule inhibitor of the ALK, MET and ROS tyrosine kinases (104). It was granted FDA approval in 2011 after only phase I/II studies showed impressive response rates (ORR 57%, including one complete response) in pre-treated patients (98). Final results revealed a PFS of 9.7 months (95% CI, 7.7-12.8 months) (105). Median OS data are awaited but a retrospective analysis of ALK-positive NSCLC suggests that crizotinib is associated with a survival advantage compared to those who did not have crizotinib available (106). Importantly, ALK-positivity itself is not a favourable prognostic factor as those without treatment have similar poor outcomes to the general population of NSCLC (106).

Crizotinib has also proved its superiority over second-line chemotherapy in those who had previously received a platinum doublet (101). Median PFS was 7.7 months with crizotinib versus 3.0 months with pemetrexed or docetaxel chemotherapy (HR 0.49; 95% CI, 0.37-0.64, P<0.001) (101). Overall survival was no different, likely due to extensive crossover and immature follow up for survival. This was all achieved with relatively few adverse effects, mainly mild visual disturbances (photopsia, blurred vision) and gastrointestinal side effects. Elevations in liver aminotransferases were severe in 16%, and one progressed to fatal hepatic failure. Interstitial lung disease was seen in 2% with two fatalities. Overall patients still reported superior reduction of symptoms and improvements in overall quality of life with crizotinib (101).

The phase III PROFILE 1014 study is currently investigating crizotinib as first-line therapy compared to platinum-pemetrexed chemotherapy in untreated patients and has now completed recruitment (ClinicalTrials.gov Identifier: NCT01154140). Results are expected shortly and if positive, will cement crizotinib as the gold standard treatment for all lines of therapy for ALK-positive NSCLC.

As with EGFR TKIs, resistance can also develop to crizotinib for ALK rearranged NSCLC. Unfortunately a wide variety of mechanisms are being discovered including; ALK amplification, EGFR/HER1, HER2 and HER3 up-regulation, cKIT amplification and various ALK mutations including L1196M (analogous to T790M for EGFR) (107-110). In those with acquired resistance to crizotinib, a phase I trial has just shown that a second-generation ALK inhibitor, ceritinib (LDK378), had an ORR of 56% (95% CI, 45-67%) (111). It is up to 20 times a more potent ALK inhibitor than crizotinib, explaining its potential to overcome the L1196M mutation (111-113). Particularly encouraging is that response rates were similar for patients with various known resistance mechanisms as well as those without an identifiable mutation (114). Other similar second generation ALK inhibitors such as alectinib are under investigation but, as is the case with EGFR, a rational approach to overcoming ALK-resistance holds promise for the future (115-117).

## K-RAS mutation in NSCLC

K-RAS (Kirsten rat sarcoma 2 viral oncogene homolog) belongs to a family of GTPases that transduce growth signals from multiple tyrosine kinases including EGFR and MET (*Figure 2*) (18). Activating mutations in KRAS leading to constitutive signalling are present in about 30% of adenocarcinoma and 4% of SCC (118,119). KRAS mutations are more likely to be found in Caucasians, former or current smokers and are mutually exclusive from EGFR or ALK mutations (103,119-121). They have also been associated with a poorer prognosis as well as resistance to chemotherapy and EGFR TKIs (122-125). Despite KRAS being one of the earliest known oncogenic drivers in NSCLC (126), effective targeting remains a therapeutic challenge. Direct RAS inhibition with salirasib was unsuccessful (127), so novel approaches are currently attempting to inhibit downstream molecules in the RAS/RAF/MEK/ERK and PI3K/AKT/mTOR pathways (119). Other approaches include targeting the heat shock protein (HSP90) which KRAS mutant cells have increased dependence upon (92,119). Selumetinib (AZD6244; ARRY-142866) a MEK1/MEK2 inhibitor showed a PFS advantage when combined with docetaxel in a recent phase II trial in advanced KRAS-mutant NSCLC (128). It

 

is now being investigated in a confirmatory phase III study, SELECT-1 (ClinicalTrials.gov Identifier: NCT01933932), in addition to preclinical combinations with AKT inhibitors (129).

## MET amplification in NSCLC

Amplification of mesenchymal-epithelial transition (MET) factor is found in about 5% of lung adenocarcinoma and results in overexpression of its gene product—hepatocyte growth factor receptor (HGFR)—which is involved in cell proliferation, migration, invasion and metastasis (130). Various strategies to inhibit MET/HGFR mediated growth are in development including: HGF antagonists, anti-HGFR mAb, anti-MET mAb and MET TKIs such as tivantinib (ARQ197), cabozantinib (XL184) and of course crizotinib (131).

MET and EGFR appear to be synergistic for growth and MET amplification is also the second most common cause of acquired EGFR TKI resistance. Dual EGFR and MET inhibition, with erlotinib and tivantinib respectively, was tested in non-squamous NSCLC in the much anticipated global phase III trial MARQUEE (132), after phase II data (133) suggested improved PFS for KRAS-mutants. Onartuzumab, a monoclonal antibody against MET also showed promise in a phase II trial (134) so was brought to phase III in the MetLung study where it was combined with erlotinib for MET-positive NSCLC (ClinicalTrials.gov Identifier: NCT01456325) (135).

Despite these early promising results, confirmatory studies using MET TKIs and MET mAb have yielded disappointing results and early trial closures for both phase III trials. MARQUEE (132) was closed in late 2012 due to an interim analysis declaring futility in its primary outcome of overall survival (136). MetLung was also terminated early due to lack of efficacy (137). Interestingly, subset analyses from MARQUEE were presented at the European Cancer Conference 2013, which suggested that in tumours with strong MET immunostaining, there was a PFS and OS benefit (138). Only 40% of tumours in MARQUEE had tissue for MET expression analysis and it appears that the future progress with MET inhibition is likely to require a clear predictive biomarker to enhance appropriate patient selection moving into the future.

## ROS1 rearrangements in NSCLC

ROS1 rearrangements were first seen in 2007 with around 1-2% of NSCLC harbouring different ROS1 fusion variants (139,140). Whilst its function in humans is yet unknown, its highest expression is seen in normal lung tissue (141). Like many other receptor tyrosine kinases, ROS1 feeds into multiple downstream pathways such as the RAS/RAF/MEK or MAPK, JAK/STAT3 and PI3K/AKT/mTOR pathways (*Figure 2*) (141,142). Both rearrangements share similar clinical phenotypes: younger, non-smokers with adenocarcinomas (141,143). There also appears to be ~50% sequence homology between ROS1 and ALK, and fortunately ALK inhibitors such as crizotinib can and do inhibit both kinases (139,141). Indeed crizotinib has shown some early activity in the phase I setting (144), but again, acquired resistance appears to limit the long-term efficacy of kinase inhibition (ClinicalTrials.gov Identifiers: NCT01449461, NCT01284192) and specific ROS1 inhibitors, such as foretinib are currently under investigation (145).

## RET fusions in NSCLC

The RET (rearranged during transfection) is a novel fusion gene with various partners including KIF5B (kinesin family member 5B) and others such as CCDC6, NCOA4, and TRIM33 (146). It is found in around 1-2% of lung adenocarcinomas and predominantly in non-smokers (143,147). No specific RET inhibitors are currently available but multi-kinase inhibitors such as vandetanib (phase II) and cabozantinib (phase III) are being trialled in RET fusion-positive NSCLC (ClinicalTrials.gov Identifiers: NCT01823068 and NCT01639508).

## HER2 overexpression and mutations in NSCLC

Human epidermal growth factor 2 (HER2/ErbB2/neu), like EGFR/HER1, is a member of the ErbB family of tyrosine kinase receptors that are activated by homo- or hetero-dimerisation with other ErbB receptors (21). HER2 overexpression is seen in up to 20% of NSCLC (148,149) but HER2 mutation rates occur less frequently in up to 3-4% (149,150). Rationale for blockade in NSCLC was borrowed from successes seen in HER2-positive breast cancer (9), however phase II trials combining trastuzumab with chemotherapy in NSCLC have so far been negative to date (148,149).

## BRAF mutations in NSCLC

BRAF mutations in NSCLC are uncommon and seen in less than 5% of cases (151). As an important part of the RAS/RAF/MEK/ERK or MAPK pathway, BRAF inhibition

seemed logical, especially since TKIs were already available for melanoma (10). However, only around half of those identified harbour the specific V600E mutation for which effective therapies exist (151). Currently a phase II trial is looking at the combination of a BRAF and MEK inhibitor, dabrafenib and trametinib respectively, in stage IV NSCLC (ClinicalTrials.gov Identifier: NCT01336634).

## Squamous cell carcinomas (SCC)

Although many of the pathways and targeted agents described thus far apply primarily to adenocarcinoma, targeted therapy for SCC is now a focus of current research. Recent discoveries from the cancer genome atlas about the molecular pathology of SCC have identified several important signalling pathways (152). Although these pathways can be inhibited, clinically meaningful benefits are currently lacking but ongoing work should hopefully see the realisation of targeted agents for SCC in the near future.

The phosphatidylinositol 3-kinase (PIK3CA) pathway is one of the most commonly altered in SCC with PIK3CA mutation and amplification as well as loss of the PTEN tumour suppressor gene (4,153). Ongoing phase II trials of the PI3K inhibitor, buparlisib (BKM120) are underway in squamous NSCLC in combination with chemotherapy (ClinicalTrials.gov Identifiers: NCT01911325, NCT01820325).

The fibroblast growth factor receptor 1 (FGFR1) is another exploitable pathway with overexpression in up to 20% of SCC compared to only 3% of adenocarcinoma (154). FGFR inhibitors, such as brivanib (BMS-582664) and other multi-kinase inhibitors showed positive signals *in vitro* (154) and are now in early phase trials (ClinicalTrials.gov Identifier: NCT00633789) (155).

DDR2 (discoidin domain receptor 2) is a tyrosine kinase receptor seen in up to 4% of SCC (156). Again DDR2, with collagen as its ligand, is involved in cell migration, proliferation and survival (156). Early promise was seen *in vitro* and in murine models of DDR2 inhibition with dasatinib, a multi-TKI targeting BCR-Abl and the Src family of tyrosine kinases (156). The phase II trial was negative (157) but further research on DDR2 inhibition is ongoing.

## Angiogenesis inhibition in NSCLC

Disrupting tumour blood supply and angiogenesis has been a enticing target for many years now (158) with some successes in other malignancies such as colorectal cancer (159), ovarian (160) and now cervical cancer (161). Complex signalling pathways with multiple growth factors and cytokines are thought to regulate angiogenesis (162,163). Two key growth factors include vascular endothelial growth factor (VEGF) and platelet derived growth factor (PDGF) (162,163).

Two pivotal phase III trials provide evidence for targeting angiogenesis in NSCLC with both utilising the anti-VEGF monoclonal antibody, bevacizumab in combination with standard platinum chemotherapy doublets (164-166). The Eastern Cooperative Oncology Group ECOG 4599 study (164) reported a median OS advantage from 10.3 months with chemotherapy alone to 12.3 months with the addition of bevacizumab to chemotherapy and as maintenance (HR 0.79; 95% CI, 0.67-0.91; P=0.003). The AVAiL study (165) demonstrated an improved ORR and longer PFS although failed to demonstrate an improvement in overall survival. Toxicities with bevacizumab include bleeding, thromoboembolism, and hypertension (164,165). Major bleeding and haemoptysis was associated with squamous histology and cavitation, thus limiting its clinical use to non-squamous NSCLC after fatal pulmonary haemorrhagic events were noted in earlier phase II studies (164,167,168). A further phase III study (AVAPERL) in non-squamous NSCLC suggests that perhaps maintenance therapy with pemetrexed is improved by the addition of bevacizumab (169,170).

Small molecule TKI can also be utilised to inhibit the VEGF pathway. To date, several multi-TKIs have failed to demonstrate a clinically significant survival benefit in phase III trials (171-175). Nintedanib combined with second-line chemotherapy (LUME-Lung1) resulted in a very modest benefit in PFS without a benefit in OS, however, planned subgroup analyses suggest that patients with adenocarcinoma histology may benefit most (12.6 months with nintedanib plus docetaxel versus 10.3 months with docetaxel alone (HR 0.83; 95% CI, 0.70-0.99; P=0.0359) (176).

A novel class of anti-angiogenesis drugs known as tumour vascular disrupting agents did show some promise in pre-clinical trials. However vadimezan (ASA404) failed to show a benefit in phase III trials (177) and so further development has been abandoned. Further research is needed to elucidate appropriate predictive biomarkers for anti-angiogenic therapies in the future.

## Conclusions

Within the last decade, significant advances in molecular pathology have afforded an improved understanding of the underlying pathology and significant heterogeneity

of NSCLC. Multiple signalling pathways have now been identified as well as specific oncogenic driver mutations that lead to malignant transformations. Indeed in clinical practice, reflex molecular interrogation of tumour tissue for such driver mutations has now become commonplace. For the vast majority at present, no known drivers are detected and such patients are still empirically treated with standard cytotoxic chemotherapy. Whilst impressive clinical benefits have been observed for NSCLC with a known driver mutation, acquired resistance is frequently seen and presents us with the next challenge in the goal to deliver unique personalised medicine.

Building on past experience is helping to improve the approach to targeted therapy. For example, it took just over six years to progress from initiation of phase I to positive phase III trials of crizotinib in ALK-positive patients and just four years to achieve FDA approval with only phase II data—a truly remarkable achievement. The key to the future success of theranostics and truly personalised oncological management will be to ensure appropriate patient selection using predictive biomarkers to optimise limited resources and minimise harm. Addressing resistance, utilising the correct inhibitor, or combination of inhibitors, whilst minimising adverse effects will hopefully lead to the realisation of ongoing improvements in survival for patients in the future. Further to this, the real challenge will be bringing these agents into the management of patients with earlier stage disease with the hope of truly improving rates of cure for the devastating illness that is lung cancer.

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