Therapeutic Strategies Utilized in the Setting of Acquired Resistance to EGFR Tyrosine Kinase Inhibitors

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Abstract

Patients with EGFR mutant lung cancer derive significant therapeutic benefit from treatment with EGFR tyrosine kinase inhibitors (TKIs). Unfortunately, acquired resistance is an inevitable consequence of this treatment strategy, with a broad variety of resistance mechanisms including acquired EGFR mutations (e.g., T790M) and activation of bypass signaling pathways, such as MET and HER2. Several therapeutic strategies hypothesized to delay or overcome resistance have been tested in clinical trials, including ‘next-generation’ EGFR TKIs and rational combinations of targeted agents. However, to date, there are no FDA approved therapies for patients with acquired resistance to first-line EGFR TKI therapy. There remains a critical need for more effective and better tailored treatments in this setting in order to match treatments to the individual patient and specific resistance mechanism at hand. In this review, we will discuss known mechanisms of resistance to first-line EGFR TKI therapy and describe previous and ongoing strategies to overcome resistance.
Introduction

Acquired resistance to EGFR TKI therapy

For patients with advanced EGFR mutant lung cancer, treatment with an EGFR tyrosine kinase inhibitor (TKI), such as erlotinib, gefitinib or afatinib (Table 1), is associated with superior radiographic response and prolonged progression-free survival (PFS) compared to standard cytotoxic chemotherapy (1-3). EGFR TKIs are now standard first-line therapy for patients with advanced EGFR mutant lung cancer. Most patients will develop clinical evidence of acquired resistance (AR) after a median of 12 months (1,4). Study of tumor samples from patients at the time of resistance has identified several potential mechanisms whereby tumors evade EGFR inhibition (5, 6). These resistance mechanisms can be broadly classified into four categories: (1) second site mutations within the EGFR kinase domain (7,8); (2) acquired mutations in other oncogenes such BRAF and PIK3CA (6, 9); (3) up-regulation of parallel signaling pathways, including MET, HER2, FGFR and AXL (10-16) , to bypass the inhibited EGFR protein; and (4) histological transformation, specifically epithelial to mesenchymal transition and small cell transformation (6).

Overview of therapeutic strategies

Though acquired resistance appears to be an inevitable consequence of EGFR TKI treatment, successful treatment strategies to overcome acquired resistance have been elusive. More than 75 studies have looked at over 50 investigational drugs and drug combinations in the setting of AR to first generation EGFR TKI therapy, with the majority of studies reporting little to no efficacy in this population (Table 2). In this review, we will discuss completed and ongoing efforts to overcome resistance.

Therapeutic Strategies Targeting EGFR

Standard treatment with addition of continued EGFR inhibition beyond progression

Management of patients with progression on first-line EGFR TKI therapy is largely dependent on clinical factors such as symptoms and disease burden. Some patients may have RECIST
progression based on tumor measurements, but with continued clinical benefit from therapy. In this setting, many asymptomatic patients can delay a change in therapy for several months to over a year (17). This approach is being studied prospectively in the ASPIRATION trial (18). If there is limited progression, local therapy and continued EGFR inhibition can be considered (19,20). For patients with oligometastatic disease, a prolonged PFS after local therapy of 6-10 months was achieved in several small series (19,20).

There are limited prospective data to support continued EGFR TKI in addition to chemotherapy in the AR setting. Erlotinib has been combined with platinum doublet chemotherapy with toxicity that is similar to chemotherapy alone (4). In a retrospective series of 78 patients with EGFR mutant lung cancer and AR, the odds ratio for response rate was 0.20 favoring chemotherapy with concurrent erlotinib compared to chemotherapy alone (21). In a trial comparing afatinib and paclitaxel to chemotherapy alone in patients with disease progression on single agent EGFR TKI, there was an increase in PFS with continuation of EGFR TKI (5.6 vs 2.8 months, HR 0.60) (22). There are several ongoing prospective studies that may result in a definitive recommendation regarding the combination of chemotherapy and erlotinib (NCT01928160, NCT02064491, NCT02098954) or gefitinib (NCT01544179) in the AR setting.

**Second-generation EGFR TKIs**

Second-generation EGFR TKIs bind to the EGFR tyrosine kinase domain irreversibly and have broader ERBB inhibition (Table 1). Afatinib is a dual EGFR/HER2 inhibitor that is now FDA-approved for the first-line treatment of lung cancers with EGFR L858R mutations or exon 19 deletions. This approval is based on a phase 3 trial that demonstrated a superior PFS for afatinib compared to cisplatin and pemetrexed (13.6 vs 6.9 months) in patients with EGFR mutant lung cancer (3).

While afatinib has proven useful in the first-line setting, its role in AR is less clear. The LUX-Lung 1 trial randomized molecularly unselected patients, who had previously been treated with erlotinib or gefitinib for at least three months, to receive afatinib or placebo (23). The
response rate (RR) (7% vs <1%) and PFS (3.3 vs 1.1 months) were superior with afatinib compared to placebo, but there was no improvement in overall survival (the primary endpoint) in all study participants or in the subset of patients with known EGFR mutant lung cancer.

Neratinib has activity against both EGFR and HER2 and was evaluated in a phase II study in patients with non-small cell lung cancer (NSCLC) (24). The RR was 2% among those patients with EGFR mutations, but there were no responses in patients with EGFR T790M. Dacomitinib, a pan-HER inhibitor, was administered to patients with NSCLC whose disease had progressed on chemotherapy and erlotinib (25). In the subset of patients with EGFR mutant lung cancer, the RR was 8%; no responses were seen in patients with EGFR T790M. The dual EGFR/VEGFR inhibitors, XL647 and Vandetanib, have also been tested in the acquired resistance setting with limited efficacy observed (26, 27).

**EGFR antibodies**

Cetuximab, an EGFR monoclonal antibody, binds to the extracellular domain of EGFR and prevents ligand-dependent receptor activation. Cetuximab has predominantly been used in combination therapy with EGFR TKIs in the resistance setting. In a phase 1/2 study of erlotinib plus cetuximab in patients with AR to erlotinib, no responses (0/19 evaluable patients) were seen (28). However, the combination of cetuximab and afatinib has shown more promise (29). In a clinical trial of afatinib and cetuximab in 100 patients with AR to erlotinib or gefitinib, treatment with the combination led to a 30% overall RR and a median PFS of 4.7 months (30). Responses were seen in patients with both EGFR T790M positive and T790M negative tumors. The most common toxicities were rash, diarrhea and fatigue. Randomized trials of afatinib plus cetuximab are planned in both the first-line and AR settings.

**Mutant specific EGFR inhibitors**

A relatively new class of drugs irreversibly inhibits mutant EGFR, in particular EGFR T790M, with much less activity against wild-type EGFR (Table 1). The first drug in this class, WZ4002, is 30-100 fold more potent against EGFR T790M and up to 100 fold less potent against wild type
EGFR in preclinical models (31). This discovery led to the subsequent development of other compounds in this same class. AP26113 is a reversible dual ALK and EGFR inhibitor that has selectivity for the mutant forms of EGFR, both activating and resistance mutations, in pre-clinical models (32). The phase 1/2 of AP26113 demonstrated no objective responses in 12 patients with EGFR T790M containing tumors (33).

CO-1686 targets mutant EGFR, including T790M, and is active in EGFR mutant xenografts and murine models of erlotinib resistance (34). The phase 1 study of single-agent CO-1686 is complete with a small range of doses being tested in the ongoing phase 2 study (35). CO-1686 has the notable adverse event of hyperglycemia as a frequent adverse event (38%, any grade). The reported overall RR is 58% in 40 patients with centrally confirmed EGFR T790M tumors. Median PFS has not been reached, but is estimated at >12 months (35).

AZD9291 is another mutant specific EGFR currently being tested clinically (36). A phase 1 study of AZD9291 in patients with advanced NSCLC who had progression on first- or second-generation EGFR TKI therapy is nearing completion (37). As of April 2014, 232 patients had received AZD9291 with no dose limiting toxicities identified. Diarrhea (14%, any grade) and rash (24%, any grade) were the most frequent toxicities. The RR in 107 patients with EGFR T790M tumors to date was 64%.

Several other EGFR-mutant specific TKIs are being tested in phase 1 studies currently, including HM61713 (NCT01588145), EGF816 (NCT02108964), and ASP8273 (NCT02113813). Preliminary results with HM61713 were recently presented (38). 118 patients have received the drug, and a RR of 22% was noted in the 83 evaluable patients. The RR was 29% in the 48 patients with EGFR T790M containing tumors. EGF816 similarly has selective activity against mutant EGFR in cellular assays and xenograft models (39).

**Therapeutic Strategies Targeting Alternate Pathways**

**MET inhibition**
MET is a receptor tyrosine kinase which, when activated by its ligand, hepatocyte growth factor (HGF), can mediate cell proliferation, evasion of apoptosis, and metastasis (40). MET amplification is seen in untreated patients with NSCLC at a rate of approximately 4% (41, 42), and is detected in approximately 5% of tumors with acquired resistance to EGFR TKI (5, 6). De novo MET amplification has been associated with primary resistance to EGFR TKIs (43). Therapeutic targeting of MET may be an effective strategy in MET amplified tumors (44,45).

Results from a phase 2 study of cabozantinib (an oral MET/VEGFR2/RET inhibitor) in patients with EGFR mutant lung cancer and progression on EGFR TKI resulted in 3 partial responses out of 35 patients treated (46). There are several ongoing clinical trials of MET TKIs or MET MAbs in combination with EGFR TKIs with the majority of studies selecting for patients that are MET positive by various assays (Table 3). An ongoing phase 1 study of INC280 and gefitinib in EGFR mutant patients with AR who have either MET amplification or MET overexpression has modest activity, with a 15% unconfirmed RR (6/41 patients) (47). In addition to MET amplification, MET activation through increased production of HGF is a potential mechanism of resistance to EGFR TKIs (48). Lung cancer cell lines made resistant to EGFR TKIs by HGF overexpression were sensitive to dual EGFR and MET blockade (49). Prospective clinical validation of anti-HGF directed monoclonal antibodies is pending.

**HER2 and HER3 inhibition**

The ErbB family of receptor tyrosine kinases is composed of 4 members – EGFR (ErbB1), HER2 (ErbB2), HER3 (ErbB3), and HER4 (ErbB4). HER2 amplification has been detected in 12% of tumors with AR to EGFR TKI therapy (13), resulting in sustained downstream signaling, even in the continued presence of the EGFR TKI. Combination strategies involving dual EGFR/HER2 blockade are being explored. The combination of the dual HER2/EGFR TKI, afatinib plus cetuximab, has been studied in patients with AR to erlotinib (30), as described above. In a phase 1/2 clinical trial of erlotinib plus the HER3 monoclonal antibody, MM-121
(NCT00994123), one EGFR TKI naïve patient had a partial response and 5/8 patients with EGFR mutant/TKI resistant disease had stable disease (50).

**IGF-1R inhibition**

The insulin like growth factor-1 receptor (IGF-1R) is a receptor tyrosine kinase that is activated by the IGF-1 or IGF-2 ligands (51). Up-regulation of IGF-1R signaling has previously been described to mediate acquired resistance to first generation EGFR TKIs (52) as well as to the irreversible EGFR inhibitors PF299804 and WZ4002 (53). Though IGF-1R was implicated in the pathogenesis of EGFR mutant lung cancer, clinical testing of combined EGFR/IGF-1R blockade has not proven to be effective. A randomized phase 2 study of erlotinib alone or in combination with the IGF-1R/Insulin receptor TKI, OSI-906, in patients with advanced EGFR mutant NSCLC (NCT01221077) closed early after an interim analysis in March 2013 showed there would be no benefit to the combination.

**AXL inhibition**

Activation of the receptor tyrosine kinase AXL has been reported as a mechanism of resistance to erlotinib. Recent studies have demonstrated increased AXL activation, without EGFR T790M mutation, in both *in vitro* and *in vivo* models of EGFR mutant/TKI resistant lung cancer (10). Combined inhibition of AXL and EGFR in these models restored therapeutic efficacy. More recently, increased AXL expression was observed in 5/26 patients (19%) of patients with AR to gefitinib (54). AXL inhibitors are in early clinical development (NCT00697632, ISRCTN00759419 and (55)).

**FGFR inhibition**

More recently, *in vitro* studies have demonstrated increased expression of fibroblast growth factor receptor 2 (FGFR2) and its ligand, fibroblast growth factor 1 (FGF1), in EGFR mutant cell lines derived to be resistant to gefitinib or afatinib (14,15). Combined inhibition of EGFR and FGFR in these models improved therapeutic responses in the EGFR TKI resistant cell lines. Validation of these findings in clinical models has yet to be demonstrated.
**MAPK pathway inhibition**

Activation of the MAPK signaling pathway (Fig. 1) can drive EGFR TKI resistance in both preclinical models as well as in patient tumor samples. In a large series of tumor biopsy samples from patients with EGFR mutant/TKI resistant lung cancer, 2/195 (1%) were found to have mutations in BRAF (9). Concomitant inhibition of EGFR and MEK was an effective therapeutic strategy in models of EGFR TKI resistance driven by MAPK pathway activation (9). Erlotinib resistance has also been associated with reduced expression of neurofibromin, a RAS GTPase-activating protein (GAP) encoded by the *NF1* gene which functions as a negative regulator of RAS (56). In preclinical models of EGFR TKI resistance, erlotinib failed to fully inhibit MAPK signaling in the context of low neurofibromin levels, however, these tumors responded to the combination of an EGFR TKI with a MEK inhibitor. Downregulation of *NF1* expression was also seen in clinical samples from patients with EGFR TKI resistance. There are several ongoing clinical trials of MEK inhibitors plus EGFR TKIs in EGFR mutant lung cancer (Table 3). In addition, one of the few described mechanisms of resistance to the mutant-specific EGFR TKIs is aberrant activation of ERK signaling (57). The MAPK pathway may become increasingly relevant as we develop combination strategies to prevent or overcome resistance to EGFR mutant-specific TKIs.

**PI3K-AKT-mTOR pathway inhibition**

Analogous to the MAPK pathway, activation of the PI3K-AKT-mTOR pathway (Fig. 1) also drives EGFR TKI resistance. PIK3CA mutations can co-occur with *EGFR* mutations and may portend a poorer response to EGFR TKIs (58-60). In addition, acquired *PIK3CA* mutations have been detected in a small percentage (~5%) of EGFR mutant lung cancers with AR to EGFR TKIs (6). Preclinical data have shown that introduction of activating *PIK3CA* mutations into EGFR mutant cell lines confers resistance to EGFR TKIs (61). A phase 2 clinical trial combining erlotinib with the PI3K inhibitor, BKM120, is ongoing in patients with advanced NSCLC previously sensitive to erlotinib or whose tumors harbor an EGFR mutation (NCT01487265),
although no PIK3CA mutation or aberration is required. A phase 2 study combining erlotinib with the AKT inhibitor, MK-2206, in patients with EGFR mutant lung cancers and progression on erlotinib demonstrated a 9% RR (4/46 patients) (62). Pre-clinical data also supports the use of mTOR inhibitors in the context of EGFR TKI resistance (63), although a small study of EGFR TKI and everolimus in patients who previously responded to EGFR TKI demonstrated no responses (64). Concomitant inhibition of EGFR and mTOR in patients with AR is currently being evaluated further in a phase 1 trial of afatinib plus sirolimus (NCT00993499).

**HSP90 inhibitors**

Heat shock protein 90 (HSP90), a molecular chaperone for several oncogenic kinases, is required for protein folding and stabilization of mutant EGFR. Single agent activity of the HSP90 inhibitor, AUY922, has been documented in patients with EGFR mutant lung cancer, with a RR of 20% (7/35 patients) (65). In a phase 2 study combining AUY922 with erlotinib, in patients with EGFR mutant/TKI resistant lung cancer, the overall RR was 2/16 (13%) (66). Several HSP90 inhibitors are in clinical development for use in both EGFR TKI sensitive and EGFR TKI resistant patient populations (Table 3).

**Immune Therapy**

Another potential strategy which has garnered much attention recently is the use of immune checkpoint inhibitors, either as single agents or in combination with EGFR TKIs. An intriguing hypothesis is that tumor cell death triggered by targeted therapies results in antigen release and immunomodulation that can prime tumors and potentiate anti-tumor immune responses (67). Pre-clinical data in EGFR mutant lung cancer cell lines and mouse models has demonstrated that mutant EGFR signaling drives expression of programmed death-ligand 1 (PD-L1), and that blockade of the PD-1 receptor improved survival of mice with EGFR mutant tumors (68). A phase 1 clinical trial of erlotinib plus the anti-PD-L1 antibody, MPDL3280A, in the first line setting (NCT02013219), a phase 1/2 study of pembrolizumab in combination with erlotinib or gefitinib (NCT02039674), and a study of erlotinib and nivolumab (NCT01454102) are all
currently ongoing. Preliminary results indicate activity of the nivolumab and erlotinib combination; an overall RR of 19% (4/21 patients) was reported, with 3 of 4 responders having previously progressed on erlotinib monotherapy (69).

**Future Directions**

Despite the tremendous success of first generation EGFR TKIs in patients with EGFR mutant lung cancer, the emergence of resistance remains a significant barrier for the successful management of patients with this disease. Several strategies are beginning to show promise. In particular, continued clinical development of the new mutant specific EGFR TKIs has the potential to dramatically change our treatment paradigm for patients with EGFR mutant lung cancers. However, acquired resistance that does not involve EGFR T790M is a heterogeneous clinical problem with more limited success.

Moving forward, there are several critical issues that remain to be addressed: (1) How clinically relevant is heterogeneity in resistance mechanisms to first generation EGFR TKIS? Published reports have already documented co-occurrence of more than one resistance mechanism (e.g., EGFR T790M and MET amplification) within a given tumor sample, and among different sites of disease. (2) As patients are treated with multiple lines of EGFR-targeted therapies, what are the mechanisms to mutant specific EGFR inhibitors as sequential treatment? How does sequential treatment with multiple EGFR inhibitors affect tumor evolution and resistance? Will mutant specific EGFR inhibitors make EGFR T790M rare? (3) What are the optimal sequences of anti-EGFR directed therapies and combination therapies? Will combination therapies and mutant-specific EGFR TKI be successful in the first line setting? Will combination strategies - including combinations of small molecules inhibiting various targets or combinations of EGFR inhibitors with chemotherapy or immune therapy – overcome resistance? (4) What are the best treatments for patient with lung cancers harboring non-canonical EGFR mutations, such as exon 20 insertions? (5) Are immune therapies useful in molecularly defined cohorts? As repeat biopsies increasingly become the standard of care, matching treatments
targeting a specific resistance mechanism to patients whose tumors harbor that mechanism will allow us to more accurately assess therapeutic efficacy. Additional study of EGFR TKI resistance may provide clinicians with a greater understanding of therapeutic resistance across the numerous other cancers in which targeted therapies are being employed.

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References


Table 1. Lineage of EGFR tyrosine kinase inhibitors in clinical development. This table provides an overview of the various EGFR inhibitors in clinical development. Erlotinib is FDA approved for (a) first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations; (b) maintenance treatment of patients with locally advanced or metastatic NSCLC whose disease has not progressed after four cycles of first line platinum-based chemotherapy; (c) treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of at least one prior chemotherapy regimen. Erlotinib is EMA approved for (a) first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have activating EGFR mutations; (b) maintenance treatment of patients with locally advanced or metastatic NSCLC whose disease has not progressed after four cycles of first line platinum-based chemotherapy; (c) treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of at least one prior chemotherapy regimen. Gefitinib is EMA approved for the treatment of patients with metastatic lung cancer whose tumors have activating EGFR mutations. Afatinib is FDA approved for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations. Afatinib is EMA approved for the treatment of patients with metastatic lung cancer whose tumors have activating EGFR mutations. FDA: Food and Drug Administration. EMA: European Medicines Agency. CFDA: China Food and Drug Administration.
<table>
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Table 2. Published or presented studies with results in patients with EGFR mutant lung cancer and acquired resistance to EGFR TKI. A = Afatinib; G = gefitinib; E= erlotinib; P = placebo; NR = Not Reported; EGFRm = EGFR mutant; PR = partial response; SD = stable disease; PD = progressive disease. *Response rate and PFS with MM-121 + E is in unselected patients.

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<td>Everolimus + Gefitinib or Erlotinib</td>
<td>Ref. 64</td>
<td>2</td>
<td>PR on TKI or 6 months SD + EGFRm</td>
<td>13 (62)</td>
<td>0</td>
<td>3</td>
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<tr>
<td>Everolimus</td>
<td>Ref. 74</td>
<td>2</td>
<td>Prior TKI x 1 month</td>
<td>43 (0)</td>
<td>2</td>
<td>2.7</td>
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<tr>
<td>IPI-504</td>
<td>Ref. 75</td>
<td>2</td>
<td>PD on TKI</td>
<td>28 (100)</td>
<td>4</td>
<td>2.8</td>
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<tr>
<td>AUY-922 + Erlotinib</td>
<td>Ref. 66</td>
<td>1/2</td>
<td>Jackman Criteria</td>
<td>22 (100)</td>
<td>16</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>AUY-922</td>
<td>Ref. 65</td>
<td>2</td>
<td>EGFRm and prior EGFR TKI</td>
<td>35 (100)</td>
<td>18</td>
<td>NR</td>
<td></td>
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<tr>
<td>Erlotinib + Vorinostat</td>
<td>Ref. 76</td>
<td>1/2</td>
<td>EGFRm after PD on at least 3 month TKI</td>
<td>33 (100)</td>
<td>0</td>
<td>2</td>
<td></td>
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<tr>
<td>INC280 + Gefitinib</td>
<td>Ref. 47</td>
<td>1</td>
<td>EGFRm, MET positive and PD on TKI</td>
<td>46 (100)</td>
<td>17</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>Ref.</td>
<td>PR or SD x 3 months on TKI</td>
<td>PR or SD x 6 months on TKI or EGFRm</td>
<td>11 (100)</td>
<td>0 (D+E)</td>
<td>0.9</td>
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<tr>
<td>-------------------------------</td>
<td>------</td>
<td>---------------------------</td>
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<td>---------</td>
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<tr>
<td>Cabozantinib</td>
<td>46</td>
<td>EGFRm and PD on TKI</td>
<td>5 (HCQ+E)</td>
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<td>Dasatinib + Erlotinib</td>
<td>77</td>
<td></td>
<td>0 (HCQ)</td>
<td></td>
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<td>Hydroxychloroquine +/- Erlotinib</td>
<td>78</td>
<td></td>
<td>2 (74)</td>
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</tbody>
</table>
Table 3. Ongoing studies without results in patients with EGFR mutant lung cancers. A=afatinib, E=erlotinib, G=gefitinib

<table>
<thead>
<tr>
<th>Target</th>
<th>Agents</th>
<th>Clinical trials</th>
<th>Phase</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt;/2&lt;sup&gt;nd&lt;/sup&gt; gen EGFR TKI</td>
<td>Erlotinib/Gefitinib</td>
<td>Pulsatile Erlotinib or Gefitinib (NCT01965275)</td>
<td>2</td>
<td>Ongoing</td>
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<tr>
<td></td>
<td>Erlotinib</td>
<td>High/low dose Erlotinib (first line) (NCT01967095)</td>
<td>1</td>
<td>Ongoing</td>
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<tr>
<td></td>
<td>Afatinib</td>
<td>Pulsatile Afatinib (NCT01647711)</td>
<td>1</td>
<td>Ongoing</td>
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<td>Afatinib + Nimotuzumab</td>
<td>(NCT01861223)</td>
<td>1B</td>
<td>Ongoing</td>
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<tr>
<td>Mutant-specific TKI</td>
<td>ASP8273</td>
<td>(NCT02113813)</td>
<td>1</td>
<td>Ongoing</td>
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<tr>
<td></td>
<td>EGF816</td>
<td>(NCT02108964)</td>
<td>1</td>
<td>Ongoing</td>
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<tr>
<td>Chemotherapy</td>
<td>Bevacizumab</td>
<td>Erlotinib +/- Bev (first-line) (NCT01532089)</td>
<td>2</td>
<td>Ongoing</td>
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<tr>
<td></td>
<td>Platinum/Gem</td>
<td>Erlotinib +/- chemo (first-line) (NCT02001896)</td>
<td>3</td>
<td>Not yet open</td>
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<tr>
<td></td>
<td></td>
<td>Erlotinib + chemo (NCT02098954)</td>
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<td>Not yet open</td>
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<tr>
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<td>Platinum/Pemetrexed</td>
<td>Chemo +/- Erlotinib (NCT01928160)</td>
<td>2</td>
<td>Not yet open</td>
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<tr>
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<td>Platinum doublet</td>
<td>Chemo +/- Erlotinib (NCT02064491)</td>
<td>2</td>
<td>Ongoing</td>
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<tr>
<td>MET</td>
<td>Crizotinib</td>
<td>Crizotinib + Dacomitinib (NCT01121575)</td>
<td>1</td>
<td>Completed</td>
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<tr>
<td></td>
<td>Tivantinib (ARQ197)</td>
<td>Erlotinib +/- ARQ197 (NCT00777309)</td>
<td>2</td>
<td>Completed</td>
</tr>
<tr>
<td></td>
<td>Cabozantinib (XL184)</td>
<td>XL184 +/- Erlotinib (NCT00596648)</td>
<td>1/2</td>
<td>Completed</td>
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<td></td>
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<td>XL184 + Erlotinib (NCT01866410)</td>
<td>2</td>
<td>Ongoing</td>
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<tr>
<td></td>
<td>INC280</td>
<td>INC280 + Gefitinib (NCT01610336)</td>
<td>2</td>
<td>Ongoing</td>
</tr>
</tbody>
</table>
| Target | Drug Combination | Study ID | Status
|--------|------------------|----------|--------
| Onartuzumab (METMab) | INC280 + Erlotinib (NCT01911507) | 1 | Ongoing
| | Erlotinib +/- METMab (first line) (NCT01887886) | 3 | Ongoing
| | LY2875358 +/- Erlotinib (NCT01900652) | 2 | Ongoing
| | MSC2156119J + Gefitinib in p1 (NCT01982955) | 1B/2 | Ongoing
| HGF | Rilotumumab (AMG102) + Erlotinib (NCT01233687) | 1/2 | Ongoing
| HER2 | Trastuzumab (NCT00004883) | 2 | Completed
| IGF-1R | OSI-906 +/- Erlotinib (NCT01221077) | 2 | On hold
| AXL | Foretinib + Erlotinib (NCT02034097) | 2 | Not yet open
| MEK | MEK162 + Erlotinib (NCT01859026) | 1 | Ongoing
| | AZD6244 +/- Erlotinib (NCT01229150) | 2 | Ongoing
| | Selumetinib + Gefitinib (NCT02025114) | 1B/2 | Not yet open
| AKT | MK-2206 + Gefitinib (NCT01147211) | 1 | Completed
| PI3K | BKM120 + Erlotinib (NCT01487265) | 2 | Ongoing
| | XL147 + Erlotinib (NCT00692640) | 1 | Completed
| mTOR | XL765 (also PI3K-I) + Erlotinib (NCT00777699) | 1 | Completed
<table>
<thead>
<tr>
<th>Treatment Category</th>
<th>Treatment</th>
<th>Combination</th>
<th>ID Number</th>
<th>Status</th>
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</thead>
<tbody>
<tr>
<td>Sirolimus</td>
<td>Sirolimus + Afatinib (NCT00993499)</td>
<td>1</td>
<td>Ongoing</td>
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<td>Everolimus</td>
<td>(NCT00124280)</td>
<td>2</td>
<td>Completed</td>
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<tr>
<td>HSP90</td>
<td>SNX-5422</td>
<td>SNX-5422 + Erlotinib (NCT01851096)</td>
<td>1</td>
<td>Completed</td>
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<tr>
<td></td>
<td>DS-2248</td>
<td>DS-2248 (NCT01288430)</td>
<td>1</td>
<td>Ongoing</td>
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<tr>
<td>Immunotherapy</td>
<td>MPDL3280A (PD-L1)</td>
<td>MPDL3280A + Erlotinib (first-line) (NCT02013219)</td>
<td>1B</td>
<td>Ongoing</td>
</tr>
<tr>
<td></td>
<td>MK-3475 (PD-1)</td>
<td>MK-3475 + Erlotinib, MK-3475 + Gefitinib (NCT02039674)</td>
<td>1/2</td>
<td>Ongoing</td>
</tr>
<tr>
<td>Other</td>
<td>Metformin</td>
<td>Gefitinib +/- Metformin (first-line) (NCT01864681)</td>
<td>2</td>
<td>Ongoing</td>
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<tr>
<td></td>
<td>Hydroxychloroquine</td>
<td>Hydroxychloroquine + Gefitinib (NCT00809237)</td>
<td>1/2</td>
<td>Ongoing</td>
</tr>
</tbody>
</table>
Figure 1. EGFR signaling pathways and receptor cross-talk. Activation of EGFR propagates downstream pro-growth signals through the MAPK pathway (RAS-RAF-MEK-ERK) and PI3K-AKT-mTOR pathway. Targets for potential combinatorial therapeutic strategies to overcome resistance are noted.
Figure 1:
Clinical Cancer Research

Therapeutic Strategies Utilized in the Setting of Acquired Resistance to EGFR Tyrosine Kinase Inhibitors

Helena A Yu, Gregory J. Riely and Christine M. Lovly

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