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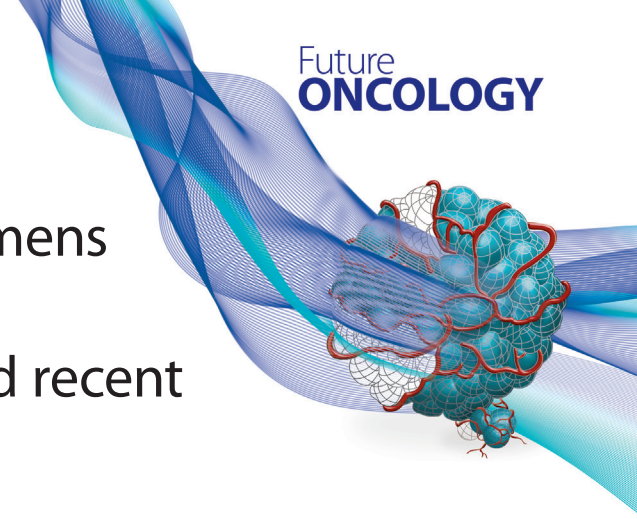

REVIEW

Afatinib-based combination regimens for the treatment of solid tumors: rationale, emerging strategies and recent progress

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In oncology, there is a clinical need for novel combination therapy regimens that maximize efficacy and delay resistance to individual treatment modalities. Given the role of aberrant ErbB receptor signaling in the pathogenesis of many human cancers, there is rationale for incorporating afatinib, an irreversible pan-ErbB tyrosine kinase inhibitor, into such combinations. This review focuses on: pharmacological properties of afatinib that facilitate its use in combination; preclinical rationale for the combination of afatinib with other agents; and recently completed, and ongoing, clinical trials of afatinib-based combinations across tumor types. Based on these data, we emphasize a number of areas of high unmet medical need that could benefit from afatinib-based combinations, including patients with relapsed/refractory non-small-cell lung cancer.

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KEYWORDS
• afatinib • combination • EGFR • non-small-cell lung cancer • squamous cell carcinoma

For many years it has been recognized that the ErbB family of receptors, comprising the EGFR (ErbB1), HER2 (ErbB2), HER3 (ErbB3) and HER4 (ErbB4) play a fundamental role in the pathogenesis of several human cancers [1]. Key examples include (but are not restricted to): the role of *EGFR* mutations in a subset of non-small-cell lung cancers (NSCLC) [2,3]; dysregulation of ErbB receptors in patients with squamous cell carcinoma (SCC) of the lung and head and neck [4]; amplification and/or mutation of *HER2* in breast and gastric cancer [5,6]; oncogenic *ErbB3* mutations in colon and breast cancer [7]; *HER4* mutations in melanoma [8]; and overexpression of EGFR and HER2 in urothelial and bladder cancer [9–12]. While the normal physiological role of the ErbB receptors is to regulate cellular proliferation, molecular aberrations lead to the aberrant activation of a myriad of intracellular signaling pathways including Ras/Raf/MEK/ERK and PI3K/Akt/TOR, leading to tumorigenesis [4]. Based on this accumulated knowledge, a number of therapeutic approaches have been developed to target ErbB receptors in patients with cancer, including small-molecule tyrosine kinase inhibitors (TKIs) and monoclonal antibodies. Such agents have demonstrated striking efficacy, with acceptable tolerability, in the clinic.

Although ErbB receptor-targeted therapies have undoubtedly revolutionized the treatment of several cancers over the past decade or more, there remains a considerable challenge in that almost all patients ultimately relapse on these treatments. The selective pressure of targeting specific pathways/molecules inevitably leads to the emergence and propagation of cancer cells that are resistant to treatment, ultimately leading to disease progression. The molecular basis for resistance is twofold: either the target itself accrues mutations that prevent interaction with the drug, or tumor

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cells bypass inhibition via crosstalk and feedback loops of intracellular pathways [13]. There is a rationale, therefore, for the development of novel treatment regimens that target multiple aberrant pathways, with a view to eliciting more durable clinical responses.

The irreversible ErbB family blocker, afatinib, was developed with the aim of delaying acquired resistance, thus improving clinical outcomes versus first-generation EGFR inhibitors. Indeed, across a range of therapy areas and indications, afatinib monotherapy has demonstrated durable clinical activity that appears to compare favorably with other targeted therapies. In two Phase III trials in patients with *EGFR* mutation-positive NSCLC, first-line afatinib significantly improved progression-free survival (PFS) versus platinum-based chemotherapy [14,15], including patients with uncommon *EGFR* mutations [16] and other difficult-to-treat patient subpopulations such as those with asymptomatic brain metastases [17]. In contrast to first-generation EGFR-TKIs, afatinib conferred overall survival (OS) advantage in patients with *Del19 EGFR* mutations in both trials, based on prespecified subanalyses [18,19]. Also, perhaps due to its broader inhibitory profile, afatinib has recently demonstrated superior PFS and OS versus erlotinib in patients with relapsed/refractory SCC of the lung, a disease characterized by overexpression of EGFR and a heterogeneous mix of molecular aberrations affecting other ErbB receptors and their downstream pathways [20]. Another recent Phase III study demonstrated that afatinib improved PFS versus methotrexate in patients with SCC of the head and neck (HNSCC) who had progressed on platinum-based chemotherapy, thus achieving its primary end point [21].

In all these trials, afatinib had a well-defined safety profile with predominantly gastrointestinal and cutaneous adverse events (AEs). The most frequent treatment-related grade ≥3 AEs with afatinib were diarrhea (5.4–14.4%), rash/acne (9.7–16.2%) and stomatitis/mucositis (5.4–8.7%). There is a paucity of direct head-to-head data to facilitate direct comparisons of the safety profile of afatinib and first-generation EGFR-TKIs. The only published head-to-head trial that has directly compared afatinib with a first-generation TKI (erlotinib in patients with SCC of the lung) showed that the overall grade ≥3 AE burden (afatinib: 57.1%; erlotinib: 57.5%) and serious AEs (44.1% in both arms) were similar [20]. The most frequent treatment-related grade ≥3 AEs were diarrhea (afatinib: 10.5%; erlotinib: 2.5%), rash/acne (afatinib: 5.9%; erlotinib: 10.4%) and stomatitis (afatinib: 4.1%; erlotinib: 0%). Moreover, in all clinical trials to date, a well-established dose reduction scheme, and supportive care measures, were generally sufficient to allow patients to remain on afatinib therapy for as long as they experienced clinical benefit without compromising efficacy [14,15,20–22]. Furthermore, all Phase III trials of afatinib integrated comprehensive patient-reported outcome (PRO) and health-related quality-of-life (HRQoL) end points in their study designs. Notably, afatinib has consistently been associated with improved PROs and overall HRQoL compared with comparator arms across trials [21,23,24].

Afatinib has been proven to confer PFS benefit versus other treatment options in *EGFR* mutation-positive NSCLC, SCC NSCLC and HNSCC, probably reflecting the advantages of ErbB family inhibition; however, responses are transient. Therefore, there have been intensive efforts in identifying novel afatinib-based combination regimens that could conceivably improve duration of response and long-term outcomes. This review article summarizes progress to this end and discusses: the pharmacological characteristics of afatinib that facilitate combination with other agents; the biological rationale and preclinical data supporting its combination with other targeted agents and chemotherapeutics; and emerging progress in the clinic with afatinib-based combinations. In particular, we describe interesting evidence supporting the combination of afatinib with other ErbB-targeted agents ('vertical inhibition'). Also, given the recent emergence of effective immunotherapeutic agents in cancer, we discuss the prospects for combining afatinib with agents such as immune checkpoint inhibitors and tumor vaccines.

Pharmacological properties of afatinib that facilitate its use in combination regimens

• Pharmacokinetics

Compared with first-generation EGFR-TKIs, afatinib has a number of distinctive pharmacokinetic properties that potentially facilitate its use in combination with other agents. A key difference is the fact that afatinib undergoes minimal hepatic metabolism and is not a

substrate for CYP-dependent enzymes [25], thus reducing the possibility of drug–drug interactions. Also, cigarette smoking, which is well known to induce key CYP enzymes and can interfere with the metabolism of first-generation inhibitors [26,27], is unlikely to impact on afatinib. Furthermore, unlike erlotinib and gefitinib, afatinib is highly soluble throughout the physiological pH range 1–7.5 and consequently interactions with acid-reducing drugs, routinely used in cancer patients, are not expected [28]. As afatinib is a substrate of p-glycoprotein (p-gp) and breast cancer resistance protein, it is possible that drug–drug interactions may occur with agents that utilize these transporter proteins. Indeed, clinical studies have shown that ritonavir (a p-gp inhibitor) and rifampicin (a p-gp inducer) can potentially influence afatinib exposure [29]. However, these effects can be mitigated with staggered dosing regimens or 10-mg dose alterations as stipulated in the EU Summary of Product Characteristics and US Prescribing Information, respectively [28]. As with first-generation inhibitors, dose adjustments of afatinib are not routinely required in patients with hepatic or renal impairment [28]; moreover, patient body weight, age, gender or ethnicity do not have a clinically relevant effect on the clearance or exposure of afatinib [30].

• Pharmacodynamics & inhibitory profile

When considering the development of novel drug combination strategies based on EGFR-TKIs, it is important to note that afatinib has a different mechanism of action to erlotinib and gefitinib and blocks signaling from all homodimers and heterodimers formed by ErbB family members [31]. In contrast to gefitinib and erlotinib, afatinib inhibits EGFR, HER2 and ErbB4 at low nanomolar concentrations in cell-free *in vitro* kinase assays, by blocking transphosphorylation of tyrosine residues in the C-terminus (the first step in the activation of ErbB receptors) [31,32]. Afatinib also blocks the transphosphorylation of ErbB3 by its ErbB partner in the dimer [32].

Afatinib has consistently demonstrated superior affinity and potency than first-generation TKIs against both wild-type EGFR and EGFR harboring the common activating mutations *L858R* and *Del19* in cell-free *in vitro* assays and cell-based assays, with IC_{50} and EC_{50} values in the low nanomolar range [31,33,34]. Also, notably, afatinib inhibits EGFR harboring the resistance gatekeeper mutation, *T790M* [31,33,34]. As well as directly inhibiting ErbB receptors, afatinib has multiple inhibitory effects on downstream signaling pathways [32]. Afatinib inhibits cellular growth and induces apoptosis in cell-based and xenograft models of various tumors associated with ErbB receptor dysregulation, including lung, breast, colorectal and pancreatic cancer [32].

Overall, the pharmacological properties of afatinib indicate that it may represent an attractive backbone to novel combination regimens in situations where there is biological rationale for maintaining pan ErbB inhibition while simultaneously targeting other pathways.

Afatinib-based combination regimens in solid tumors

• Combination with inhibitors of intracellular signaling pathways

Once phosphorylated, the tyrosine residues in the intracellular C-terminal domains of ErbB receptors activate a myriad of signaling cascades including the PI3K/Akt/mTOR, Ras/Raf/MEK/ERK and JAK/STAT pathways [4,35]. These pathways demonstrate remarkable plasticity and cooperate to regulate proliferation, apoptosis and angiogenesis **(Figure 1)** [4]. There is a rationale, therefore, to combine afatinib with agents that target these intracellular pathways. Below, we summarize the biological rationale for combining afatinib with inhibitors of specific intracellular pathways and outline any completed, or ongoing, clinical trials that have assessed such combinations in cancer patients.

Afatinib plus PI3K/Akt/mTOR inhibitors

The PI3K/Akt/mTOR pathway is an important effector in cell signaling pathways, including ErbB signaling, and is deregulated in many cancers [36]. Furthermore, activation of PI3K/Akt/mTOR is implicated in the acquired resistance to EGFR inhibitors, including afatinib [37].

Several preclinical studies have highlighted that the combination of PI3K/Akt/mTOR inhibitors and afatinib is a promising approach in a range of human malignancies. For example, combination of PI-103, a dual PI3K and mTOR inhibitor, with afatinib has demonstrated synergistic inhibitory activity in NSCLC cell lines [38]. Afatinib plus rapamycin, an mTOR inhibitor, synergistically inhibited lung cancer growth in a transgenic *EGFR*-mutation positive NSCLC

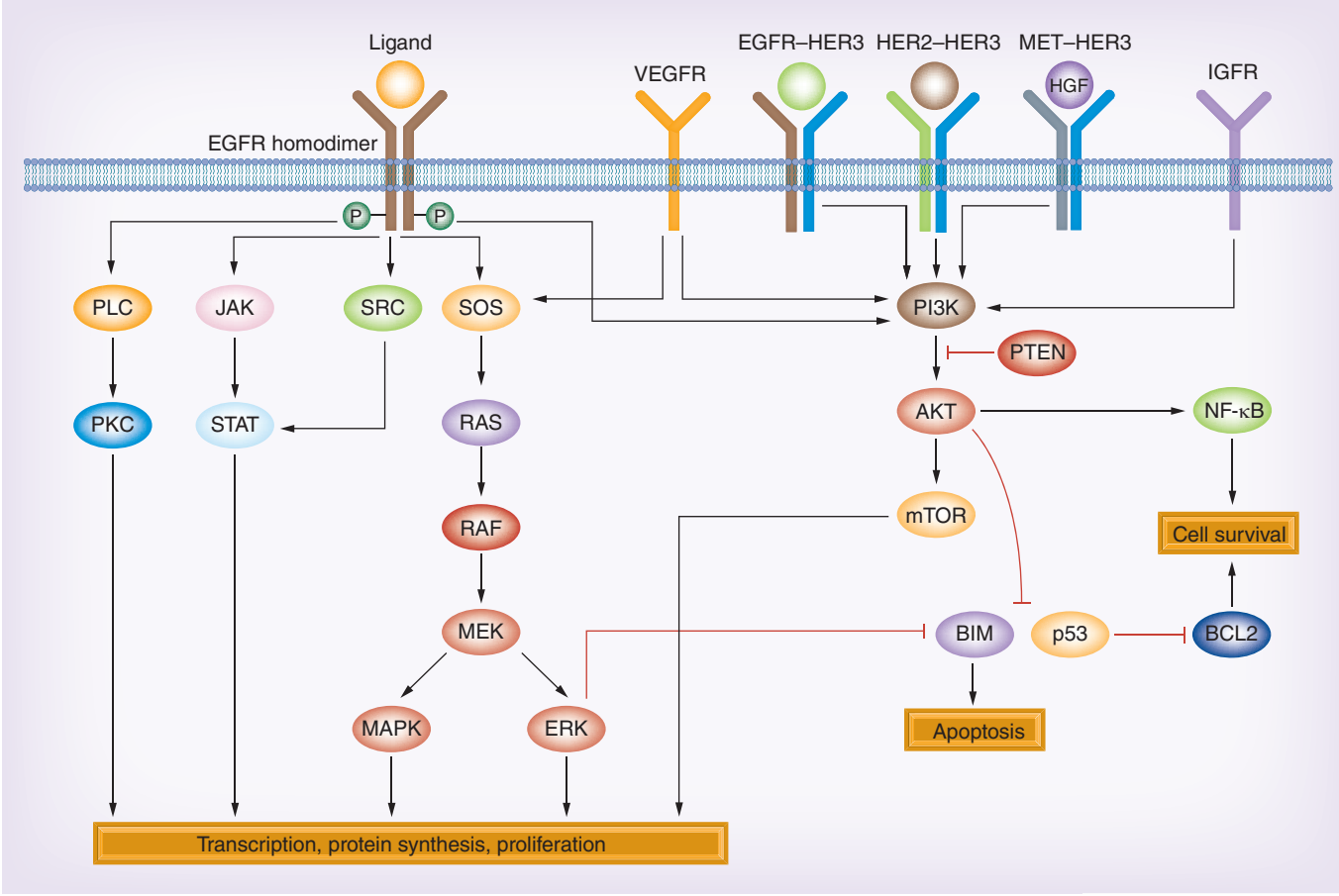

Figure 1. The plasticity of ErbB signaling pathways in the regulation of cell growth.
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model harboring *T790M* as well as transgenic and xenograft HER2 mutant models [33,39].

To date, few clinical studies have been undertaken to assess such combinations in patients. One Phase I trial, however, has assessed the combination of afatinib and sirolimus, an mTOR inhibitor, in patients with *EGFR* mutation-positive NSCLC with disease progression following erlotinib and gefitinib (Table 1). Out of 39 patients treated, four (10%) achieved a partial response (PR) and 23 (59%) had stable disease (SD) [40]. However, the combination had limited tolerability due to overlapping dose-limiting toxicities of diarrhea and mucositis. All responses were observed at doses exceeding the maximum tolerated dose (MTD) of afatinib 30 mg/day and sirolimus 1 mg/day.

Afatinib plus SRC kinase inhibitors

Preclinical experiments in PC9GR cells, an *EGFR* mutation-positive NSCLC cell line harboring *T790M*, have implicated SRC kinase in the resistance to afatinib. In proliferation and apoptosis assays, the SRC kinase inhibitor, dasatinib, sensitized cells to afatinib [57]. This translated into tumor regression in a PC9GR xenograft mouse model [57]. The combination of dasatinib and afatinib has also shown synergistic activity against triple-negative breast cancer cell lines [58]. The combination is currently being assessed in a Phase I trial in patients with NSCLC (NCT01999985, Table 1).

Afatinib plus Ras/Raf/MEK/ERK inhibitors

Oncogenic activation of the Ras/Raf/MEK/ERK pathway is implicated in the pathogenesis of about 20–30% human malignancies, largely due to mutations in *RAS* [59]. However, to date, small-molecule inhibitors that target this pathway have demonstrated only modest activity in preclinical and clinical studies [60,61]. A recent *in vitro* study indicated that upregulation of ErbB3 may be responsible for intrinsic resistance to MEK inhibitors. Moreover, experiments in

KRAS-mutant colorectal (CRC) and NSCLC cells demonstrated that afatinib acts synergistically with the MEK inhibitors, selumetinib and trametinib, to inhibit cell proliferation [59]. Interestingly, neither gefitinib nor CP724714 (an ErbB2 inhibitor) demonstrated synergy with selumetinib, indicating that inhibition of the whole ErbB family was required to potentiate MEK inhibition [59]. Based on these findings, afatinib plus selumetinib is currently being assessed in an ongoing Phase I/II trial in patients with advanced *KRAS*-mutant, CRC, NSCLC and pancreatic cancer (NCT02450656; **Table 1**).

Afatinib plus JAK/STAT inhibitors

STAT proteins are a family of transcription factors that play a key role in multiple cellular functions and are often constitutively activated in human cancers [62]. Interestingly, in recent preclinical studies, afatinib has been shown to activate the JAK/STAT pathway in NSCLC cell lines by upregulating the interleukin-6 receptor [62]. It is thought that this pathway may mediate *de novo* resistance to afatinib in NSCLC cells harboring *T790M*. This hypothesis is supported by experiments in a mouse xenograft model of H1975, a human *EGFR* mutation-positive NSCLC cell line harboring *T790M*. In these experiments, it was found that afatinib and pyridine-6, a pan-JAK inhibitor, had synergistic antitumor activity [62]. These findings provided rationale for a planned Phase I clinical study that will assess afatinib plus ruxolitinib, a pan-JAK inhibitor, in patients with pretreated advanced NSCLC (NCT02145637; **Table 1**).

• Combination with other growth factor receptor inhibitors

Afatinib plus VEGFR inhibitors

ErbB and vascular endothelial growth factor (VEGF) signaling pathways are known to communicate in the growth and survival of tumors **(Figure 1)**; it has been demonstrated that activation of EGFR in tumor cells stimulates the production of VEGF, which in turn stimulates proliferation and migration of endothelial cells [63]. There is a clear biological rationale, therefore, for the combination of EGFR inhibitors with antiangiogenic agents targeting VEGF or its receptors. However, to date, clinical evaluation of antibody-based combinations has generally been disappointing. For example, combination of VEGF- and EGFR-directed antibodies (bevacizumab and cetuximab) with standard chemotherapy in patients with CRC did not improve outcomes and reduced HRQoL [64], possibly reflecting the limited activity of antibodies on intracellular signaling events [65].

Several preclinical studies indicate that small-molecule combinations involving afatinib could have clinical application. For example, in a human CRC mouse xenograft model, the combination of afatinib with nintedanib, a multikinase VEGFR, PDGFR and FGFR inhibitor, showed strong tumor growth inhibition compared with either drug alone; in CRC cell lines, the combination had a synergistic inhibitory effect regardless of *KRAS* status [65]. Combination of afatinib with antiangiogenic antibodies also appears to be a promising approach. In mouse xenograft models of *EGFR-Del19/T790M* or *EGFR-L858R/T790M* NSCLC, the combination of the VEGF antibody, bevacizumab, and afatinib showed synergistic antitumor activity [66].

To date, few clinical studies have been undertaken to assess the combination of afatinib and antiangiogenic agents. Recently, an afatinib plus nintedanib regimen was assessed in a Phase I study in patients with advanced solid tumors. Unfortunately, the identified MTD (afatinib, 10 mg/day; nintedanib, 200 mg twice daily) was considered subtherapeutic for Phase II evaluation [41]. In another Phase I study, afatinib (20 mg/day) combined with bevacizumab (7.5 mg/kg every other week) and paclitaxel (80 mg/m^2 weekly) conferred acceptable tolerability with no relevant drug–drug interactions [42].

Afatinib plus IGF-IR inhibitors

The IGF-IR signaling axis regulates cell growth differentiation and survival and its aberrant activation is implicated in the pathogenesis of several cancers, as well as resistance to chemotherapy, radiotherapy and anti-ErbB agents [67,68]. Several recent preclinical studies have provided a rationale for the combination of afatinib with IGF-IR inhibitors. For example, afatinib plus NVP-AEW541, an IGF-IR TKI inhibitor, induced synergistic growth inhibition in a range of pancreatic cancer cell lines [67]. In another study, Lee *et al.* found that the IGF-IR signaling pathway contributes to afatinib resistance in *EGFR* mutation-positive NSCLC cells harboring *T790M* [69]. Knockdown of IGF-IR increased the sensitivity of these cells to afatinib. Moreover, afatinib plus linsitinib, a potent small-molecule inhibitor of both IGF-1R and

Table 1. Clinical trials that have assessed afatinib-based combination regimens in oncology.

Regimen	Trial ID	Phase	Setting	n	MTD	Response (%)	AEs, all/grade ≥3 (%)	Ref.
Inhibitors of other intracellular signaling pathways								
Afatinib plus sirolimus (mTOR inhibitor)	NCT00993499	I	EGFR mutation-positive NSCLC and/or disease progression following prior clinical benefit on gefitinib/erlotinib	39	Afatinib: 30 mg/day Sirolimus: 1 mg/day 28-day cycles	PR: 10 SD: 59	Diarrhea: 95/28 Mucosal inflammation: 62/15 Rash: 54/3 Asthenia:44/5	[40]
Afatinib plus dasatinib (SRC inhibitor)	NCT01999985	I	EGFR mutation-positive NSCLC and disease progression following prior clinical benefit on gefitinib/erlotinib/ afatinib or known T790M mutation		Ongoing	Ongoing	Ongoing	
Afatinib plus selumetinib (MEK inhibitor)	NCT02450656	I/II	Advanced KRAS mutation-positive CRC, NSCLC and pancreatic cancer		Ongoing	Ongoing	Ongoing	
Afatinib plus ruxolitinib (JAK inhibitor)	NCT02145637	I	Treatment-refractory NSCLC		Planned	Planned	Planned	
Inhibitors of other growth factor receptors								
Afatinib plus nintedanib (VEGFR, PDGFR and FGFR inhibitor)	NCT00998296	I	Advanced solid tumors	28	Afatinib: 10 mg/day Nintedanib: 200 mg twice daily 28-day cycle	PR: 4 SD: 32	Diarrhea: 79/NA Nausea : 71/NA Anorexia: 50/NA Vomiting: 43/NA Fatigue: 43/NA	[41]
Afatinib plus bevacizumab (VEGF antibody) plus paclitaxel	NCT00809133	Ib	Advanced solid tumors	29	Not reported yet	Not reported yet	Not reported yet	[42]
Afatinib plus BI836845 (IGF antibody)	NCT02191891	I	EGFR mutation-positive NSCLC without T790M		Ongoing	Ongoing	Ongoing	
Other ErbB inhibitors								
Afatinib plus cetuximab (EGFR antibody)	NCT01090011	Ib	EGFR mutation-positive NSCLC and/or disease progression following clinical benefit on prior gefitinib/erlotinib	126	Afatinib: 40 mg/day Cetuximab: 500 mg/m^2 every 2 weeks	PR: 29 SD: 41	Rash: 90/20 Diarrhea: 71/6 Nail effects: 57/0 Stomatitis: 56/1	[43]
Afatinib plus nimotuzumab (EGFR antibody)	NCT01861223	Ib/II	EGFR mutation-positive NSCLC and/or disease progression following clinical benefit on prior gefitinib/erlotinib	37	Afatinib: 40 mg/day Nimotuzumab: 100 mg/week	OR: 38 SD: 43	Grade 3 AEs: 27	[44]
Afatinib plus cetuximab	NCT02438722	II/III	Treatment-naive EGFR mutation-positive NSCLC		Ongoing	Ongoing	Ongoing	
Afatinib plus cetuximab	NCT01919879	II	Refractory KRAS wild-type metastatic CRC		Ongoing	Ongoing	Ongoing	

AE: Adverse event; CR: Complete response; CRC: Colorectal cancer; HNSSC: Squamous cell carcinoma of the head and neck; HPV: Human papillomavirus; MTD: Maximum tolerated dose; NA: Not applicable; NR: Not reported; NSCLC: Non-small-cell lung cancer; OPSCC: Oropharyngeal squamous cell carcinoma; OR: Overall response; PR:Partial response; SD: Stable disease.

Table 1. Clinical trials that have assessed afatinib-based combination regimens in oncology (cont.).

Regimen	Trial ID	Phase	Setting	n	MTD	Response (%)	AEs, all/grade ≥3 (%)	Ref.
Inhibitors of other growth factor receptors (cont.)								
Afatinib plus trastuzumab (HER2 antibody)	NCT00950742	I	HER2-positive advanced breast cancer	18	Afatinib: 20 mg/day Trastuzumab: 4 mg/kg week 1; 2 mg/kg week thereafter	PR: 11 SD: 28	Diarrhea: 94/50 Rash: 56/0 Fatigue: 56/0 Nausea: 50/0	[45]
Afatinib plus trastuzumab (3 weekly)	NCT01649271	I	HER2-positive metastatic breast cancer		Ongoing	Ongoing	Ongoing	
Neoadjuvant afatinib plus trastuzumab	NCT01594177	II	Untreated HER2-positive breast cancer	65	Afatinib: 20 mg/day Trastuzumab: 6 mg/kg/3 weeks for 6 weeks, followed by afatinib, trastuzumab and paclitaxel (80 mg/m^2/week) for 12 weeks followed by epirubicin, cyclophosphamide and trastuzumab	pCR: 70	Diarrhea: 71/5 Rash: 52/0 Mucositis: 31/0 Fatigue: 26/0	[46]
Afatinib plus trastuzumab	NCT01522768	II	Advanced HER2-positive trastuzumab-refractory advanced esophagogastric cancer		Ongoing	Ongoing	Ongoing	
Immunotherapy								
Afatinib plus pembrolizumab (PD1 inhibitor)	NCT02364609		EGFR mutation-positive NSCLC and disease progression following prior clinical benefit on erlotinib		Planned	Planned	Planned	
Chemotherapy								
Afatinib plus docetaxel	NCT02171741	I	Advanced solid tumors	31	Afatinib: 20 mg/day (days 2–21) Docetaxel: 75 mg/m^2 (day 1) 21-day cycle	OR: 0 SD: 45	Diarrhea: 74/NR Neutropenia: 65/NR Rash: 39/NR	
Pulsatile afatinib plus docetaxel	NCT02171676	I	Advanced solid tumors	40	Afatinib: 90 mg/day (days 2–4) Docetaxel: 75 mg/m^2 (day 1) 21-day cycle	OR: 13 SD: 23	Alopecia: 50/0 Diarrhea: 50/5 Stomatitis: 50/0 Rash: 40/0	[47]
Afatinib plus paclitaxel	NCT00809133	I	Advanced solid tumors	16	Afatinib: 40 mg/day Paclitaxel: 80 mg/m^2 (days 1, 8, 15) 28-day cycle	PR: 31 SD: 13	Diarrhea: 94/0 Fatigue: 81/13 Rash/acne: 81/6 Mucosal inflammation:69/6 Decreased appetite: 69/0	[48]

AE: Adverse event; CR: Complete response; CRC: Colorectal cancer; HNSSC: Squamous cell carcinoma of the head and neck; HPV: Human papillomavirus; MTD: Maximum tolerated dose; NA: Not applicable; NR: Not reported; NSCLC: Non-small-cell lung cancer; OPSCC: Oropharyngeal squamous cell carcinoma; OR: Overall response; PR:Partial response; SD: Stable disease.

Table 1. Clinical trials that have assessed afatinib-based combination regimens in oncology (cont.).

Regimen	Trial ID	Phase	Setting	n	MTD	Response (%)	AEs, all/grade ≥3 (%)	Ref.
Chemotherapy (cont.)								
Afatinib plus paclitaxel	NCT01085136	III	NSCLC following chemotherapy, erlotinib/gefitinib and afatinib (≥12 weeks clinical benefit on each line of TKI therapy)	132	Afatinib: 40 mg/day Weekly paclitaxel 80 mg/m^2/week 28-day cycle	CR: 1 PR: 31 SD: 43	Diarrhea: 54/12 Alopecia: 33/1 Asthenia: 27/8 Decreased appetite: 22/2	[49]
Afatinib plus paclitaxel, cisplatin	NCT00716417	I	Advanced solid tumors	26	Afatinib 20 mg/day Paclitaxel 175 mg/m^2 day 1 Cisplatin 75 mg/m^2 day 1 21-day cycle	CR: 7 PR: 12 SD:35	Diarrhea: 89/23 Nausea: 85/19 Fatigue: 62/31 Anemia: 62/8	[50]
Afatinib plus paclitaxel plus carboplatin	NCT01732640	I/II	Induction therapy in patients with HPV-negative HNSSC		Ongoing	Ongoing	Ongoing	
Afatinib plus paclitaxel, carboplatin, ribovarin	NCT01721525	I	Induction therapy in patients with HPV-associated OPSCC		Ongoing	Ongoing	Ongoing	
Afatinib plus vinorelbine	NCT00906698	I	Advanced solid tumors known to overexpress EGFR and/or HER2	55	Afatinib: 40 mg/day Vinorelbine: 25 mg/m^2/week iv or 60–80 mg/m^2/week po	PR: 5 SD:45	Diarrhea: 52/NA Asthenia: 50/NA Nausea: 35/NA Decreased appetite: 33/NA	[51]
Afatinib plus vinorelbine	NCT01214616	I	Japanese patients with advanced solid tumors	17	Afatinib: 40 mg/day Vinorelbine: 25 mg/m^2/week	PR: 11 SD: 17	Leukopenia: 100/59 Neutropenia: 100/71 Diarrhea: 94/0 Anemia: 71/12	[52]
Afatinib plus vinorelbine	NCT01125566	III	HER2-positive metastatic breast cancer patients after one prior trastuzumab treatment	339	Afatinib: 40 mg/day Vinorelbine: 25 mg/m^2/week	Not reported	Diarrhea: 80/NA Neutropenia: 75/NA Rash: 45/NA	[53]
Afatinib plus vinorelbine	NCT01441596	II	HER2-positive metastatic breast cancer patients with brain metastases	38	Afatinib: 40 mg/day Vinorelbine: 25 mg/m^2/week	OR: 8 SD: 63	Diarrhea: 84/24 Rash: 54/5 Neutropenia:51/38 Mucosal inflammation: 32/8	[54]
Afatinib plus cisplatin, 5-fluorouracil	NCT00716417	I	Advanced solid tumors	21	Afatinib 30 mg/day 5-fluorouracil: 750 mg/m^2 over days 1–4 Cisplatin 75 or 100 mg/m^2 day 1 21-day cycle	CR: 5% SD: 24%	Nausea: 91/24 Diarrhea: 86/19 Fatigue: 76/29 Decreased appetite: 76/43	[50]
Afatinib plus cisplatin, 5-fluorouracil	NCT01743365	II	Patients with inoperable gastric cancer		Ongoing	Ongoing	Ongoing	

AE: Adverse event; CR: Complete response; CRC: Colorectal cancer; HNSSC: Squamous cell carcinoma of the head and neck; HPV: Human papillomavirus; MTD: Maximum tolerated dose; NA: Not applicable; NR: Not reported; NSCLC: Non-small-cell lung cancer; OPSCC: Oropharyngeal squamous cell carcinoma; OR: Overall response; PR:Partial response; SD: Stable disease.

Table 1. Clinical trials that have assessed afatinib-based combination regimens in oncology (cont.).

Regimen	Trial ID	Phase	Setting	n	MTD	Response (%)	AEs, all/grade ≥3 (%)	Ref.
Chemotherapy (cont.)								
Afatinib plus pemetrexed	NCT01169675	I	Advanced solid tumors	23	Afatinib: 30 mg/day Pemetrexed: 500 mg/m^2 day 1 21-day cycle	CR: 4% SD: 26%	Diarrhea: 90/NA Stomatitis: 60/NA Rash: 55/NA Fatigue: 55/NA	[55]
Afatinib plus gemcitabine	NCT01251653	I	Relapsed or refractory solid tumors	19	Afatinib: 40 mg/day Gemcitabine: 1000 mg/m^2 days 1, 8 21-day cycle	Not reported	Diarrhea: 90/NA Rash: 63/NA	[56]

AE: Adverse event; CR: Complete response; CRC: Colorectal cancer; HNSSC: Squamous cell carcinoma of the head and neck; HPV: Human papillomavirus; MTD: Maximum tolerated dose; NA: Not applicable; NR: Not reported; NSCLC: Non-small-cell lung cancer; OPSCC: Oropharyngeal squamous cell carcinoma; OR: Overall response; PR:Partial response; SD: Stable disease.

the insulin receptor, synergistically inhibited tumor growth in a mouse xenograft model [69]. An ongoing Phase Ib trial is assessing the combination of afatinib and BI836845, an IGF-1 neutralizing antibody, in patients with *EGFR* mutation-positive NSCLC with progression following a prior EGFR-TKI (NCT02191891; **Table 1**).

• Combination with other ErbB inhibitors

Afatinib plus EGFR antibodies

Several preclinical studies have assessed the concept of combining different ErbB-targeted agents, with the aim of maximizing ErbB pathway silencing and thus delaying the development of resistance to a single agent. Interestingly, afatinib has demonstrated synergistic activity with both cetuximab and panitumumab in mouse xenograft models of human NSCLC harboring *L858R/T790M*-positive tumors [70,71]. Such combinations have shown preclinical activity in other tumor types. For example, the combination of afatinib plus ICR62, an EGFR antibody, potently inhibited proliferation of CRC cells [72]. Although the mechanism by which the combination of afatinib and EGFR antibodies confers potent antitumor activity *in vivo* has not been fully elucidated, the combination appears to have synergistic effects on the inhibition of EGFR, HER2, ErbB3 and Erk and Akt phosphorylation [71]. The broad inhibitory profile offered with afatinib appears to cooperate with anti-EGFR antibodies to overcome recognized mechanisms of resistance to single-agent EGFR inhibitors, including the accrual of *T790M* and HER2 amplification [70,71].

The combination of afatinib and cetuximab has shown promising activity in the clinic. In a recent Phase Ib study in patients with advanced *EGFR* mutation-positive NSCLC with acquired resistance to erlotinib/gefitinib (n = 126), afatinib plus cetuximab conferred an overall response rate (ORR) of 29%, with similar response rates in patients harboring *T790M*-positive and -negative tumors (32 vs 25%; p = 0.341) [43]. The median duration of response was 5.6 (range: 1.8–24.4) and 9.5 (range: 2.9–14.8) months, respectively, in patients with *T790M*-positive and -negative tumors. Median PFS was 4.6 and 4.8 months, respectively. The combination had a manageable safety profile. Grade 3 AEs occurred in nearly half of the patient population; however, the discontinuation rate due to treatment-related AEs was only 13% due to the implementation of

an effective dose reduction/interruption scheme. Recent data indicate that other EGFR-directed antibodies, when combined with afatinib, are active in patients with NSCLC who have failed on erlotinib/gefitinib. In a Phase I /II study of patients with advanced *EGFR* mutation-positive NSCLC (n = 37), afatinib plus nimotuzumab conferred an ORR of 38%, disease control rate (DCR) of 81% and median PFS of 4.2 months (95% CI: 2.4–6.0 months) [44].

These data are interesting because they demonstrate that tumors with acquired resistance to first-generation EGFR-TKIs remain dependent upon EGFR signaling for survival. However, it seems likely that broad ErbB inhibition, as offered by afatinib, is required when combining a TKI with an antibody; notably, no overall responses (ORs) have been observed in trials of cetuximab in combination with erlotinib or gefitinib [73,74]. This observation probably reflects the heterogeneity of resistance mechanisms. In addition to accrual of *T790M* (49–68% of patients) [75,76], there is evidence that activation of other tyrosine kinase receptors, either due to overexpression or mutations, leads to compensatory signaling via proliferative pathways known to be inhibited by afatinib, such as PI3K/Akt/mTOR and JAK2/STAT3 [77]. Receptors implicated in the resistance to first-generation EGFR inhibitors include HER2 [71], ErbB3 [78] and the MET receptor [79,80].

Despite the ongoing development of third-generation EGFR-TKIs that are targeted against *T790M*, such as AZD-9291 [81], rociletinib (CO-1686) [82] and BI1482694 (HM-61713) [83,84] there is a major unmet need for treatment options in patients with acquired resistance to reversible EGFR-TKIs, particularly those with *T790M*-negative tumors. In recent Phase I/II studies, AZD9291, rociletinib and BI1482694 have shown remarkable activity in patients with *T790M*-positive tumors (ORRs of 55–61%) with favorable AE profiles [81,82,84]. However, response rates were much lower in patients with *T790M*-negative tumors [81–83]. Also, resistance mechanisms to third-generation inhibitors are currently poorly understood. It is possible, therefore, that the combination of afatinib and EGFR-directed antibodies may be a useful therapeutic option in two areas of unmet medical need: in patients with *T790M*-negative tumors and in patients with *T790M*-positive tumors who progress on third-generation EGFR-TKIs. With this in mind, it is interesting to note that preclinical studies have identified increased mTORC1 signaling as a putative resistance mechanism to treatment with afatinib plus cetuximab, thus revealing a potential therapeutic strategy once patients become resistant to the combination [85]. As well as studies in patients with acquired resistance to erlotinib/gefitinib, an ongoing Phase II/III study is assessing the combination of afatinib and cetuximab, versus afatinib alone, in a frontline setting in patients with *EGFR* mutation-positive NSCLC (NCT02438722; **Table 1**). The combination is also being assessed in other tumor types. A Phase II trial is assessing afatinib plus cetuximab versus cetuximab alone in patients with chemotherapy-refractory wild-type KRAS metastatic CRC (NCT01919879).

Afatinib plus HER2 antibodies

Preclinical evidence suggests that, as with EGFR antibodies, synergism may exist between afatinib and HER2 monoclonal antibodies. For example, the combination of afatinib and trastuzumab was more effective than either agent alone in inhibiting cell proliferation of eight breast cancer cell lines with or without resistance to lapatinib [86]. Indeed, there is a biological rationale for assessing this combination in patients with trastuzumab-resistant breast cancer. Preclinical evidence suggests that EGFR and HER3 expression is increased after long-term exposure of cell lines to trastuzumab, leading to primary resistance [87]. Furthermore, HER2/HER3 heterodimerization is believed to have a key role in driving tumorigenesis in HER2-overexpressing breast cancer [88].

Several early-phase clinical studies have assessed the combination of afatinib and trastuzumab. In a Phase I study of patients with advanced or metastatic HER2-positive breast cancer, the MTD for afatinib was 20 mg daily plus the recommended weekly dose of trastuzumab; however additional dose-limiting toxicities were observed in the expansion cohort, meaning that this combination could not be recommended for Phase II development without strict diarrhea management [45]. In a Phase I/II study, patients with locally advanced or operable breast cancer receiving taxane/anthracycline-containing chemotherapy were treated with neoadjuvant afatinib plus trastuzumab. The combination was well tolerated with a pathologic complete response rate comparable with other

anti-HER2 doublets; however, the trial did not reach its primary efficacy goal [46].

As well as in breast cancer, the combination of afatinib and trastuzumab is currently being assessed in other tumor types. For example, an ongoing Phase II trial is assessing the combination in patients with advanced HER2-positive trastuzumab-refractory esophagogastric cancer (NCT01522768; **Table 1**); preliminary data from this trial indicated that afatinib monotherapy was well tolerated and showed clinical activity in this setting [89]; the addition of trastuzumab to afatinib was mandated in a protocol amendment.

• Combination with immune checkpoint inhibitors

In recent years, there has been a great deal of interest in the development of therapeutic agents that target immune checkpoint controls. These constitute receptor–ligand interactions that tightly regulate the activation of T cells and thus modulate the intensity and duration of physiological immune responses [90]. Accumulating evidence has shown that many tumors hijack these control mechanisms in order to evade detection by the immune system [91]. Key checkpoint receptors include CTLA4, PD-1 and its ligand PDL-1; antibodies have been developed against these targets and have shown remarkable efficacy in clinical trials in various tumor types [92]. For example, in recent Phase III trials, the PD-1 inhibitor, nivolumab, increased OS versus docetaxel (9.2 vs 6.0 months; $p < 0.001$) in patients with relapsed/refractory SCC of the lung, an area of particular unmet medical need [93]. Nivolumab also increased OS versus docetaxel in patients with relapsed/refractory nonsquamous NSCLC (12.2 vs 9.4 months; $p = 0.002$) [94].

As targeted therapies in oncology are associated with high response rates but modest PFS, and immunotherapies are associated with durable tumor control but lower response rates, combination regimens combining targeted agents and immunotherapies have been proposed and are undergoing clinical evaluation [95]. There is a preclinical rationale for combining ErbB inhibitors and immune therapy. It is known, for example, that *EGFR* mutation status is associated with PDL-1 expression, both in preclinical models and patients with NSCLC [96–98]. Furthermore, activation of EGFR, either by stimulation with EGF, or due to activating mutations, leads to upregulation of PD-L1; this effect is mediated via the Ras/Raf/MEK/ERK pathway [99]. Therefore, it is possible that an immune escape mechanism may contribute to treatment failure in patients treated with EGFR-targeted therapies. Furthermore, direct cytotoxicity of EGFR inhibitors on tumor cells may release tumor antigens that could help initiate and potentiate immune responses facilitated by immunotherapeutic agents [100]. However, there are no preclinical data to support such an approach with afatinib and, in a recent study, Chen *et al.* did not identify synergistic activity between EGFR-TKIs and an anti PD-1 antibody in a coculture system [99]. Data from ongoing preclinical studies may inform in the near future.

Ongoing or planned clinical trials are assessing the combination of afatinib with immunotherapies. Afatinib plus pembrolizumab, a PD-1 inhibitor, is being assessed in an ongoing Phase I study in patients with NSCLC (NCT02364609; **Table 1**). Indeed, combination of immune therapy and afatinib in SCC could be interesting given the recently observed efficacy of the two treatment modalities in this indication [20,93]. As another approach, a clinical development program is planned that will assess the combination of afatinib with a self-adjuvanted mRNA vaccine (CV9202) in patients with NSCLC. CV9202 targets six antigens commonly expressed in NSCLC [101].

• Combination with chemotherapeutic agents

Afatinib plus docetaxel

Preclinical data suggest that afatinib and docetaxel may have a synergistic effect on tumor cells; the combination improved inhibitory activity against SKOV-3 ovarian carcinoma cells, and had a greater impact on tumor shrinkage in a SKOV-3 xenograft mouse model, compared with single agents [102]. Based on these findings, the combination has been assessed in early-phase clinical trials.

A Phase I dose-escalation study assessed afatinib plus docetaxel in patients with heavily pretreated advanced cancer **(Table 1)**. The MTD was afatinib 20 mg/day (days 2–21) and docetaxel 75 mg/m^2 on day 1 of a 3-week cycle. Although this regimen had a manageable safety profile, it was deemed to be suboptimal with no ORs observed in 31 treated patients [103]. Accordingly, no Phase II recommendations

were made based on this study. As a different approach, Awada *et al.* assessed pulsatile 3-day administration of afatinib in combination with docetaxel in patients with advanced solid tumors [47]. In this Phase I study, the MTD was afatinib 90 mg/day (days 2–4) and docetaxel 75 mg/m^2 on day 1 of a 28-day cycle. Of 40 treated patients, 5 (12.5%) had an OR and 9 (22.5%) had durable (≥6 treatment cycles) SD. Treatment was particularly effective in patients with breast cancer and upper gastrointestinal cancers; one patient with HER2-positive breast cancer achieved a complete response (CR). The most frequent drug-related AEs were alopecia, diarrhea, stomatitis (all 50%) and rash (40%, all grade ≤2). As expected, no drug–drug interactions were observed between afatinib and docetaxel.

Afatinib plus paclitaxel

Paclitaxel has shown preclinical evidence for synergism with afatinib [102], possibly reflecting its ability to inactivate p70 S6 kinase leading to inhibition of the PI3K/Akt/mTOR pathway [104]. A Phase I study assessed afatinib plus paclitaxel in patients with advanced solid tumors **(Table 1)**. This study demonstrated that the combination was feasible, with an MTD of afatinib 40 mg/day and paclitaxel 80 mg/m^2 weekly [48].

Based on these data, a randomized Phase III study (LUX-Lung 5) was undertaken in heavily pretreated patients with NSCLC who had progressed following at least one line of chemotherapy and whose tumors had progressed following initial disease control (≥12 weeks) on erlotinib or gefitinib and thereafter afatinib monotherapy **(Table 1)** [49]. Patients who fulfilled these criteria were randomized 2:1 to receive afatinib plus paclitaxel (40 mg/day; 80 mg/m^2/weekly, n = 134) or investigators' choice of single-agent chemotherapy (n = 68). PFS (median 5.6 vs 2.8 months; p = 0.003) and ORR (32.1 vs 13.2%; p = 0.005) were significantly improved with afatinib plus paclitaxel, although there was no difference in OS. Global health status/quality-of-life was maintained with the combination over single-agent chemotherapy, despite prolonged exposure to treatment in the former group (133 vs 51 days) [105]. Treatment-related AEs were consistent with those previously reported for each agent. These data indicate that afatinib plus paclitaxel may have clinical utility in a late-line treatment setting and challenge the clinical orthodoxy of discontinuing one therapy on progression to be replaced by another and demonstrate the benefit of continued ErbB targeting post progression. Interestingly, in contrast to LUX-Lung 5, recent randomized trials have demonstrated that continued exposure to gefitinib or erlotinib, combined with chemotherapy, did not confer clinical benefit and increased toxicity versus chemotherapy alone in patients with activating *EGFR* mutations progressing after first-line therapy with a TKI [106,107].

Addition of afatinib to paclitaxel-based induction regimens has also been assessed in other clinical trials. A Phase I study assessed the combination of afatinib plus paclitaxel and cisplatin in patients with advanced solid tumors **(Table 1)** [50]. The MTD was determined as continuous afatinib 20 mg/day, paclitaxel 175 mg/m^2 on day 1 and 75 mg/m^2 cisplatin on day 1 of 21-day cycles. Antitumor activity with this combination was promising. Of 26 treated patients, five (19%) responded, including two CRs (both with HNSCC) and disease control was observed in 54% of patients. The most common AEs were diarrhea (89%), nausea (85%), anemia (62%) and fatigue (62%). Other, ongoing, early-phase studies are assessing afatinib/paclitaxel/carboplatin-based regimens as induction therapy in patients with HNSCC (NCT01732640) and oropharyngeal SCC (NCT01721525).

Afatinib plus vinorelbine

Overexpression of EGFR and HER3, and the formation of HER2/HER3 heterodimers, have been identified as mechanisms of resistance to trastuzumab in patients with HER2-positive breast cancer [87,88,108]. There is a biological rationale, therefore, for assessing afatinib in such patients. Furthermore, preclinical data indicate that the activity of afatinib in this setting could be enhanced by combining it with vinorelbine, a semisynthetic vinca alkaloid that interferes with tubulin polymerization and spindle formation during metaphase [109].

Phase I clinical studies have demonstrated that the combination of afatinib and vinorelbine is feasible with an MTD of continuous afatinib 40 mg/day and vinorelbine 25 mg/m^2 on days 1, 8, 15 and 22 of 28-day cycles **(Table 1)** [51,52]. The combination was associated with clinical activity. In one study, tumor shrinkage was observed in two-thirds of evaluable breast cancer patients [52].

Based on these studies, a Phase III randomized trial assessed afatinib plus vinorelbine versus trastuzumab plus vinorelbine in patients with HER2-overexpressing metastatic breast cancer who had progressed on trastuzumab monotherapy [53]. Recruitment to the study was stopped prematurely after a benefit/risk assessment by an independent Data Monitoring Committee was unfavorable for afatinib plus vinorelbine. PFS (median 5.49 vs 5.55 months) and ORR (46.1 vs 47.0%) were similar between treatment arms. However, OS was significantly longer with trastuzumab plus vinorelbine than with afatinib plus vinorelbine (median 28.6 vs 20.5 months; p = 0.0048). The most common treatment-related grade ≥3 AEs with afatinib plus vinorelbine were neutropenia (56.4%), leukopenia (19.0%) and diarrhea (17.8%). The AEs were as expected based on the individual drug profiles, but tolerability was poorer versus trastuzumab plus vinorelbine. It was concluded, therefore, that trastuzumab-based therapy remains treatment of choice in patients with HER2-positive metastatic breast cancer failing trastuzumab.

A three-arm, randomized, Phase II trial assessed afatinib monotherapy, afatinib plus vinorelbine and investigators' choice of therapy in patients with HER2-positive breast cancer progressing with brain metastases after prior trastuzumab and/or lapatinib-based therapy. In this study, the combination did not improve patient benefit at 12 weeks (primary end point), PFS or OS versus investigators' choice of therapy [54].

Afatinib plus agents that target thymidylate synthase

In NSCLC and CRC cell lines, afatinib has shown synergistic anticancer activity with chemotherapeutic drugs that target thymidylate synthase, such as 5-fluorouracil and pemetrexed [72,110]. Such synergism may be attributable to the observation that afatinib reduces expression of thymidylate synthase, thus making cells more susceptible to chemotoxic agents.

Given the apparent synergy, it is possible that afatinib could be combined with 5-fluorouracil-based regimens in the clinic. A recent Phase Ib trial assessed the combination of afatinib plus 5-fluorouracil and cisplatin in patients with advanced solid tumors [50]. The MTD was afatinib 30 mg/day on days 5–21 of a 21-day cycle, cisplatin 75 or 100 mg/m^2 on day 1 and 5-fluorouracil 750 mg/m^2 infused continuously over days 1–4. In 21 patients treated, the DCR was 29% of patients, including one CR and four unconfirmed PRs. The most common grade ≥3 AEs were decreased appetite (43%), vomiting (33%) and fatigue (29%). This combination regimen is currently being assessed in an ongoing Phase II trial in patients with inoperable gastric cancer (NCT01743365; **Table 1**).

A Phase I dose escalation trial has assessed the combination of afatinib (both pulsed-dose and continuous) in combination with pemetrexed in patients with advanced solid tumors [55]. The MTD was identified as continuous afatinib 30 mg/day and pemetrexed 500 mg/m^2 on day 1 of a 21-day cycle. Of 23 patients treated, seven (30%) had disease control, including one confirmed PR. The most frequent drug-related AEs were diarrhea (91%), stomatitis (60%), rash (55%) and fatigue (55%). No relevant pharmacokinetic interactions were observed.

Afatinib plus gemcitabine

In a Phase I study of 19 patients with relapsed or refractory solid tumors, the combination of afatinib and gemcitabine was found to be feasible with a MTD of continuous afatinib 40 mg/day and gemcitabine 1000 mg/m^2 on days 1 and 8 of a 21 day cycle [56]. The most frequent AEs were diarrhea (90%) and rash (63%). The efficacy of the combination was promising, with three (10%) confirmed PRs and 11 (42%) cases of SD.

Conclusion & future perspective

In conclusion, afatinib is a promising 'backbone' combination partner for a variety of novel regimens across a number of indications. Its pharmacological properties largely preclude drug–drug interactions [28]. Moreover, it offers highly potent, and irreversible, inhibition of signaling via all ErbB homodimers and heterodimers. Thus, afatinib can be used to target multiple 'crosstalk' and feedback loops of intracellular signaling pathways that are implicated in loss of response/resistance to single drugs caused by HER re-programming. Furthermore, increased understanding of the molecular basis of how intracellular oncogenic pathways interact have resulted in the undertaking of clinical trials of afatinib and other targeted agents including, MEK, SRC, JAK and mTOR inhibitors. The results of these trials are awaited with interest. There is also a biological rationale for combining afatinib with immunotherapies whose recent emergence look

to revolutionize treatment algorithms for several malignancies. One other particular area of interest is the apparent effectiveness of 'vertical' inhibition regimens that combine afatinib with other ErbB receptor inhibitors, especially in tumors with *EGFR* mutation-positive NSCLC that are resistant to EGFR-TKIs but do not have the gatekeeping *T790M* mutation. In addition to combination with targeted agents, there is also a direct biological rationale for combining afatinib with existing chemotherapeutic agents. Emerging clinical evidence indicates that such combinations could be of clinical utility, especially in patients with limited treatment options, including those for whom chemotherapy and prior EGFR inhibition have failed.

Overall, the development of novel afatinib-based combinations described herein demonstrate how increased knowledge of the molecular pathogenesis of tumors, especially with regards to the role of ErbB signaling cascades, have helped to drive new therapeutic strategies that could, in the foreseeable future, improve treatment outcomes in the clinic for a range of difficult-to-treat cancers.

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EXECUTIVE SUMMARY

- The ErbB family of receptors, EGFR, HER2, HER3 and HER4 play a fundamental role in the pathogenesis of several human cancers.
- Accordingly, the development of ErbB receptor-targeted therapies have revolutionized the treatment of several malignancies, including non-small-cell lung cancer.
- However, almost all patients ultimately relapse on these treatments due to the emergence and propagation of cancer cells that are resistant to treatment.
- There is a rationale for developing novel ErbB-based combination regimens to maximize efficacy and delay resistance to individual treatment modalities.
- Afatinib, an irreversible ErbB family blocker, has a broad ErbB inhibitory profile and is thus expected to block signaling from all relevant ErbB homo and heterodimers.
- Afatinib has low potential for drug–drug interaction making it a suitable combination partner for a variety of other anti-cancer agents.
- There is preclinical rationale for the combination of afatinib with: inhibitors of other intracellular signaling pathways, including PI3K/Akt/mTOR, SRC kinase, Ras/Raf/MEK/ERK and JAK/STAT; inhibitors of other growth factor receptors including VEGFR and IGF-1R; other ErbB inhibitors; and immune checkpoint inhibitors. A number of early-phase clinical trials have been completed, are ongoing, or are planned.
- A number of clinical trials have assessed the combination of afatinib with chemotherapeutic agents including docetaxel, paclitaxel, vinorelbine, 5-fluorouracil and pemetrexed.
- A recent Phase III study, LUX-Lung 5, demonstrated that the combination of afatinib plus paclitaxel improved PFS versus chemotherapy alone in heavily pretreated patients with non-small-cell lung cancer who had progressed following ≥1 line of chemotherapy, erlotinib/gefitinib and afatinib monotherapy (after initially benefiting from these agents). This data demonstrate the benefit of continued ErbB targeting postprogression.
- It is hoped that emerging clinical data from trials of novel afatinib-based combinations will drive the development of treatment options for a range of difficult-to-treat tumors in various clinical settings.

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