

Supplementary table 1: Clinical properties of agents targeting EGFR

Treatment regimen	Response rate	Median progression-free survival	Median overall survival	Trial & Reference
Metastatic lung cancer				
Erlotinib vs. Placebo Second-line treatment of patients w/ stage IIIB/IV lung cancer regardless of <i>EGFR</i> mutational status	9% 1%	2.2 m 1.8 m	6.7 m 4.7 m	BR.21 ¹
Erlotinib vs. Carboplatin + gemcitabine First-line treatment of Chinese patients with <i>EGFR</i> L858R or exon 19 deletions	83% 36%	13.1 m 4.6 m	Pending	OPTIMAL ²
Erlotinib vs. Cisplatin/carboplatin + docetaxel/gemcitabine First-line treatment of European patients with <i>EGFR</i> L858R or exon 19 deletions	64% 18%	9.7 m 5.2 m	19.3 m 19.5 m	EURTAC ³
Erlotinib vs. Placebo Maintenance treatment of patients without progressive disease after 4 cycles of platinum-based first-line chemotherapy. 70% of patients positive for <i>EGFR</i> on immunohistochemistry, and patients entered regardless of <i>EGFR</i> mutation status. Patients with activating <i>EGFR</i> mutations experienced greatest benefit in PFS with maintenance therapy ⁴ .	11.9% 5.4%	12.3 wks 11.1 wks	12 m 11 m	SATURN ⁵
Gefitinib vs. Carboplatin + paclitaxel Patients with <i>EGFR</i> mutant metastatic lung cancer who were part of a cohort of East-Asian non-smokers or light-smokers	71.2% 47.3%	9.5 m 6.3 m	21.6 m 21.9 m ($p = 0.99$)	IPASS ⁶
Gefitinib vs. Carboplatin + paclitaxel	74% 31%	10.8 m 5.4 m	27.7 26.6 ($p = 0.483$)	NEJ-02 ^{7,8}

First-line treatment of <i>EGFR</i> mutant predominantly Japanese patients				
Gefitinib vs. Cisplatin + docetaxel First-line treatment of exon 19 or L858R <i>EGFR</i> mutant predominantly Japanese patients w/ stage IIIB/IV disease.	62% 32%	9.2 m 6.3 m	Pending	WJTOG3405 ⁹
Gefitinib vs. Placebo Maintenance treatment of East Asian patients with stage IIIB/IV lung cancer after 4 cycles of platinum-based chemotherapy, ~25% of whom had activating <i>EGFR</i> mutations.	24% 1%	4.8 m 2.6 m	18.7 m 16.9 m ($p = 0.26$)	INFORM; C-TONG 0804 ¹⁰
Cetuximab + cisplatin + vinorelbine vs. Cisplatin + vinorelbine First-line treatment of <i>EGFR</i> positive patients.	36% 29%	4.8 m 4.8 m	11.3 m 10.1 m ($p = 0.044$)	FLEX ¹¹
Cetuximab + carboplatin + taxane vs. Carboplatin + taxane First-line treatment of patients unselected for <i>EGFR</i> expression.	25.7% 17.2 % ($p = 0.007$)	4.4 m 4.24 m ($p = 0.24$)	9.7 m 8.4 m ($p = 0.17$)	BMS-099 ¹²
Head and neck				
Cetuximab + platinum + 5-FU vs. Platinum + 5-FU Patients with untreated recurrent or metastatic squamous cell carcinoma.	36% 20%	5.6 m 3.3 m	10.1 m 7.4 m	EXTREME ¹³
Cetuximab + radiation vs. Radiation Patients with locoregionally-advanced (stage III or IV, nonmetastatic) squamous cell carcinoma.	74% 64%	17.1 m 12.4 m	49 m 29.3 m	¹⁴
Colorectal cancer				
Cetuximab + FOLFIRI vs. FOLFIRI First-line treatment of <i>EGFR</i> positive patients w/	57% 40%	9.9 m 8.4 m	23.5 m 20 m	CRYSTAL ¹⁵

unresectable metastases. Patients with wildtype <i>KRAS</i> had improved PFS (HR = 0.68) compared to patients with mutant <i>KRAS</i> .				
Cetuximab vs. Best supportive care <i>KRAS</i> wildtype patients with no remaining standard chemotherapy options.	12.8% 0%	3.7 m 1.9 m	9.5 m 4.8 m	CO.17 ¹⁶
Cetuximab + erlotinib <i>KRAS</i> wildtype patients with treatment failure of 5-FU, irinotecan, and oxaliplatin and no prior anti-EGFR therapy.	41%	5.6 m	12.9 m	DUX ¹⁷
Cetuximab vs. Cetuximab + irinotecan Patients with irinotecan-refractory disease, <i>KRAS</i> testing not performed .	10.8% 22.9%	1.5 m 4.1 m	6.9 m 8.6 m ($p = 0.48$)	BOND ¹⁸
Panitumumab + FOLFOX vs. FOLFOX First-line treatment of <i>KRAS</i> wildtype patients.	55% 48%	9.6 m 8.0 m	23.9 m 19.7 m ($p = 0.072$)	PRIME ¹⁹
Panitumumab + FOLFIRI vs. FOLFIRI Second-line treatment with panitumumab beneficial in patients with wild-type <i>KRAS</i> , while no benefit seen in patients with mutant <i>KRAS</i> .	35% 10%	5.9 m 3.9 m	14.5 m 12.5 m ($p = 0.12$)	²⁰
Panitumumab vs. Best supportive care	17% 0%	3.1 m 1.8 m	8.1 m 7.6 m (non-significant)	²¹
Pancreatic cancer				
Erlotinib + gemcitabine vs. Gemcitabine Patients with metastatic, unresectable, or locally advanced pancreatic cancer. Previous treatment with chemo-RT for local disease allowed.	8.6% 8.0%	3.75 m 3.55 m ($p = 0.004$)	6.24 m 5.91 m ($p = 0.38$)	NCIC CTG PA.3 ²²

Supplementary table 2: Clinically validated mechanisms of resistance to drugs that target EGFR

Lung cancer

Primary resistance – erlotinib and gefitinib

<i>EGFR</i> exon 20 insertion	~100-fold decreased sensitivity to TKIs ²³ . Occur in ~9% of patients with <i>EGFR</i> -mutant lung cancer ^{24,25} .	Dacomitinib may be more effective compared to erlotinib/gefitinib: In a phase I trial, of 5 patients with an exon 20 insertion, 1 had a partial response and 2 stable disease ²⁶ .
<i>BIM</i> mutation	Germline intronic deletion found in ~12% of East Asian individuals, but not in European or African populations, disrupts a splice site in <i>BIM</i> , leading to protein that lacks the BH3 domain necessary to effect apoptosis ²⁷ . This deletion is found in a cell line resistant to gefitinib (HCC2779). Patients with <i>EGFR</i> mutant lung cancer who also carry a <i>BIM</i> deletion have a shorter progression-free survival with gefitinib treatment, and <i>BIM</i> RNA levels predict clinical response to <i>EGFR</i> TKIs ²⁸ . <i>BIM</i> expression is required for apoptosis induced by erlotinib/gefitinib in <i>EGFR</i> mutant lung cancer cell lines ²⁹⁻³² .	<ul style="list-style-type: none"> • BH3 mimetic small molecules (i.e. ABT-737) reverse sensitivity to gefitinib in resistant cell lines that harbor <i>BIM</i> deletion. • The HDAC inhibitor vorinostat increases expression of wild-type <i>BIM</i> in cell lines with a deletion polymorphism, possibly via epigenetic mechanisms, and restores sensitivity to <i>EGFR</i> TKIs³³.
<i>EGFR</i> T790M	Identified in 0.5%-3% of patients and is associated with resistance to <i>EGFR</i> TKI treatment ^{34,35} .	Irreversible and mutant-selective inhibitors may be treatment options (discussed below)
Acquired resistance – erlotinib and gefitinib		
<i>EGFR</i> T790M ³⁶	Found in ~50% of patients with acquired resistance. May be present in a small number of cells in the primary tumor, prior to <i>EGFR</i> TKI treatment ^{34,37} . The T790M mutation increases <i>EGFR</i> affinity for ATP by ~5-fold, which abrogates sensitivity to ATP competitive inhibitors like erlotinib/gefitinib ³⁸ . Germline T790M mutation reported in family with multiple cases of lung cancer across generations ³⁹ . Other mutations such as D761Y, L747S, G796A, and T854A confer resistance to <i>EGFR</i> TKIs, and occur with much less frequency	<ul style="list-style-type: none"> • Irreversible inhibitors like afatinib, canertinib, dacomitinib, and T790M mutant-specific inhibitors like WZ-4002, CO-1686, and AZD9291 overcome resistance⁴². • Midostaurin and AP26113, two reversible kinase inhibitors developed for AML and <i>ALK</i>-fusion positive lung cancer, selectively and reversibly inhibit <i>EGFR</i> T790M in cell lines and mouse models^{43,44}. • Combination of afatinib + cetuximab induced

	than T790M ^{40,41} .	<p>partial responses in 29% of patients with previous erlotinib/gefitinib treatment and a T790M mutation^{45,46}.</p> <ul style="list-style-type: none"> • Modulation of tyrosine kinase inhibitor dosing • Hsp90 inhibitors inhibit EGFR T790M signaling and block the growth of lung cancers with this mutation in mice^{47,48}.
<i>HER2</i> amplification	<i>HER2</i> amplification observed in 12% of tumor samples from patients with acquired resistance, in contrast to 1% of treatment-naïve patients, and occurs exclusive to <i>EGFR</i> T790M ⁴⁹ .	Afatinib plus cetuximab or panitumumab abrogates Her2 signaling.
<i>MET</i> amplification and activation	Amplification found in 5-20% of patients with acquired resistance ^{50,51} . Small populations of <i>MET</i> amplified cells may be present prior to treatment in patients who go on to develop resistance via <i>MET</i> amplification ⁵² . <i>MET</i> a receptor tyrosine kinase; activation leads to ERBB3/PI3K/AKT signaling, rendering cells resistant to EGFR TKIs. Hepatocyte growth factor (HGF) is an activating ligand for <i>MET</i> that triggers proliferation via GAB1 signaling ⁵² . Patients with resistance to EGFR TKIs who lack the T790M mutation or <i>MET</i> amplification displayed increased tumor levels of HGF ⁵³ . Patients with intrinsic resistance to EGFR TKIs also have elevated HGF expression, and tumor-associated fibroblasts have been shown to secrete HGF ^{54,55} . Acquired resistance to WZ-4002 is also triggered by HGF expression and ERK activation, but can be restored through co-treatment with the <i>MET</i> TKI E7050 ³³ , and the MEK inhibitor CI-1040 ⁵⁶ , respectively.	<ul style="list-style-type: none"> • Phase III clinical trials of erlotinib + a <i>MET</i> inhibitor (tivatinib (ARQ197), MARQUEE) and erlotinib + an anti-<i>MET</i> antibody (onartuzumab, MetLung) underway^{57,58}. • HGF (AMG102, TAK-701) and ERBB-3 (MM-121) specific antibodies are in clinical development. TAK-701 inhibits the proliferation of <i>EGFR</i> mutant cells transfected to overexpress HGF <i>in vitro</i> and in mouse models⁵⁹. • Hsp90 inhibitors trigger apoptosis in cells rendered resistant to EGFR TKIs by HGF addition⁶⁰. • The dual <i>MET</i>/VEGF kinase inhibitor E7050 restores sensitivity to EGFR TKIs in cell lines and in mouse tumor models, and prevents the emergence of EGFR TKI resistance^{61,62}. • The PI3K/mTOR inhibitor BEZ235 is active alone against <i>EGFR</i> mutant tumor cell lines in the presence or absence of HGF <i>in vitro</i> and <i>in vivo</i>⁶³. • Low <i>BRCA1</i> expression may abrogate the

		negative effect of pretreatment <i>EGFR</i> T790M mutations on PFS ⁶⁴ .
NF-κB	NF-κB, which contributes to tumor cell proliferation, was identified as a mediator of erlotinib resistance in an siRNA screen of erlotinib-resistant cells of unknown mechanism. Patients with <i>EGFR</i> mutant lung cancer without a T790M mutation who were treated with erlotinib and who had low levels of the NF-κB inhibitor, IκB, had a decreased progression-free survival ⁶⁵ .	The IκB kinase inhibitor BMS-345541 restores sensitivity to erlotinib in cells with NF-κB activation.
PIK3CA activation	Occur in ~2% of lung cancer patients, and has been reported to occur along with activating <i>EGFR</i> mutations ⁶⁶ . PIK3 activating mutations are sufficient to abrogate gefitinib-mediated apoptosis in lung cancer cell lines ⁶⁷ . <i>PTEN</i> loss is associated with activation of PI3K signaling and resistance ⁶⁸ .	
<i>BRAF</i> mutation	V600E and G469A <i>BRAF</i> mutations noted in 1% of lung cancers with acquired resistance ⁶⁹ .	<i>BRAF</i> V600E is sensitive to vemurafenib
Small cell transformation	Noted in patients with acquired resistance ^{70,71} .	Etoposide + cisplatin chemotherapy
Epithelial-mesenchymal transition (EMT)/AXL, Notch-1 or TGF-β activation	EMT observed in patients and cell lines as a resistance mechanism to EGFR TKIs ^{72,73} . AXL kinase is upregulated in erlotinib-resistant tumor xenografts generated in mice, and in tumor samples from patients with acquired resistance. AXL expression ⁷⁴ , Notch-1 activation ⁷⁵ , and TGF-β/IL-6 secretion ^{76,77} are associated with the epithelial-mesenchymal transition.	Inhibition of TGF-β signaling by LY2157299 and AXL kinase activity by MP-470, SGI-7079, and XL-880 restores sensitivity to EGFR TKIs.
Colorectal cancer		
Primary resistance – EGFR mAbs		
<i>KRAS</i> mutations	Occur in ~40% of patients with metastatic colorectal cancers and render tumors resistant to inhibition of EGFR signaling by cetuximab and panitumumab, likely	

	due to constitutive <i>KRAS</i> activation ⁷⁸ . Use of cetuximab and panitumumab are restricted to patients with <i>KRAS</i> wildtype tumors.	
<i>BRAF</i> mutation	In <i>KRAS</i> wildtype tumors, patients with <i>BRAF</i> mutations had an 8.3% response rate to cetuximab compared to a 38% response rate in <i>BRAF</i> wildtype tumors ⁷⁹ .	In tumors with <i>BRAF</i> V600E mutations, vemurafenib is synergistic with cetuximab and gefitinib/erlotinib ^{80,81}
<i>PIK3CA</i> exon 20 mutation	Patients with <i>PIK3CA</i> exon 20 mutations had a 0% response rate to cetuximab compared to 36.8% in wildtype patients ⁷⁹ .	
<i>PTEN</i> loss	<i>PTEN</i> wildtype associated with a ~23.9 odds ratio of response to cetuximab or panitumumab compared to <i>PTEN</i> loss ⁸² .	
Acquired resistance – cetuximab		
<i>EGFR</i> extracellular domain mutations	S492R mutation abrogates cetuximab binding to <i>EGFR</i> on tumor cells ⁸³ .	Panitumumab remains active
<i>KRAS</i> activation	<i>KRAS</i> amplification or secondary activating mutations mediate resistance to cetuximab and panitumumab ^{84,85} . The kinetics of the emergence of <i>KRAS</i> mutations in the serum of patients who develop resistance to panitumumab suggests populations of <i>KRAS</i> mutants may exist prior to treatment ⁸⁴ .	MEK inhibition reverses resistance ⁸⁵
<i>HER2</i> upregulation	Amplification observed in colon and lung cancer cell lines with resistance to cetuximab. <i>HER2</i> mediated resistance occurs via ERK1/2 signaling. Patients with <i>HER2</i> amplification treated with cetuximab have a significantly shorter overall survival (307 vs. 515 d) and patients treated with cetuximab with higher heregulin levels have a shorter OS (137 vs. 366 d) ⁸⁶	<ul style="list-style-type: none"> • Treatment with trastuzumab/lapatinib restores sensitivity to cetuximab. • ADAM17 is a metalloprotease that cleaves heregulin from the cell surface, promoting heterodimerization of Her2/Her3. INCB3619, an ADAM17 protease inhibitor enhances gefitinib sensitivity in cell lines that overexpress heregulin⁸⁷. • Pertuzumab restores sensitivity to cetuximab by disrupting Her2/Her3 heterodimers in preclinical models.

<i>MET</i> amplification	Identified in ctDNA prior to progression in patients treated with EGFR targeted mAbs; no mutations were observed in <i>KRAS</i> ⁸⁸ . <i>MET</i> amplification associated with cetuximab resistance in cell lines and patient-derived xenografts.	Treatment of patient-derived xenografts harboring <i>MET</i> amplification with crizotinib restores sensitivity to cetuximab.
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Supplementary table 3: Preclinical mechanisms of resistance to EGFR-targeted therapies

Mechanism of resistance	Strategy to overcome resistance
Aurora: Increased Aurora kinase A and EGFR expression is associated with a poor prognosis in patients with squamous cell cancer of the head and neck ⁸⁹ .	Combination of an Aurora kinase inhibitor and EGFR mAb produced more potent inhibition than either alone ⁸⁹ .
CRKL: Amplification of the adapter protein <i>CRKL</i> activates RAS-RAF-ERK and AKT signaling and causes resistance to gefitinib ⁹⁰ .	
DAPK: DAPK is a kinase involved in apoptosis. Silencing of DAPK expression via promoter methylation is observed in cell lines resistant to erlotinib and cetuximab ⁹¹ . Knock-down of DAPK by siRNA is sufficient to induce resistance.	
EGFR: EGFR ubiquitination and activation of Src signaling leads to cetuximab resistance in cell lines ⁹² . Src-mediated EGFR ligand overexpression leads to EGFR internalization ⁹³ .	Dasatinib, a Src inhibitor resensitizes resistant cells to cetuximab ⁹⁷ , but failed to show activity in a clinical trial of patients with acquired resistance ⁹⁸ .
<i>EGFRvIII</i> overexpression (exon 2-7 deletion that lacks extracellular ligand-binding domain) induces resistance to cetuximab in head and neck cancer cell lines ⁹⁴ , and is sufficient to induce lung cancer in mice ⁹⁵ .	Development of EGFRvIII-specific antibodies or antibody-cytotoxins. EGFRvIII is sensitive to irreversible inhibitors like neratinib and dacomitinib.
Increased EGFR receptor internalization in response to ligand stimulation may alter binding of reversible inhibitors and lead to resistance ⁹⁶ . Nuclear localization of EGFR mediated by Src kinases associated with resistance to cetuximab in lung cancer cell lines ⁹³ .	Irreversible inhibitors overcome resistance in cells displaying altered EGFR trafficking. Dasatinib treatment decreased nuclear EGFR localization ⁹³ .
FGF: Increased expression of FGF is associated with acquired resistance in lung cancer ⁹⁹⁻¹⁰¹ .	Treatment with the FGF-specific inhibitor AZD4547 or PD173074 restores sensitivity to EGFR TKIs ^{99,100} .
HER2: <i>HER2</i> activating mutations lead to EGFR heterodimer formation and signaling that is independent of the EGFR kinase domain and resistant to EGFR TKIs ¹⁰² . <i>HER2</i> is reported to be upregulated in head and neck squamous cell	Treatment with Her2 inhibitors restores sensitivity ¹⁰² .

<p>carcinoma cell lines resistant to cetuximab¹⁰³.</p> <p>HER3: Activation of Her-3 by ligands such as heregulin mediates resistance to EGFR TKIs⁸⁷. <i>HER3</i> reported to be upregulated in head and neck squamous cell carcinoma cell lines resistant to cetuximab¹⁰³.</p>	<p>The ADAM protease cleaves heregulin from the cell membrane and inhibition of this protease by INCB3619 increases sensitivity to EGFR TKIs⁸⁷. MEHD7945A, a monoclonal antibody against EGFR and Her-3, is active in lung cancer and HNSCC cell lines resistant to cetuximab¹⁰⁴.</p>
<p>IGF: IGF1R signaling involved in resistance to gefitinib, dacomitinib, and the <i>EGFR</i> T790M mutant-specific inhibitor WZ-4002^{105,106}. Increased IGF expression correlates with resistance to EGFR mAb in <i>KRAS</i> wildtype colorectal cancer¹⁰⁷.</p>	<p>Dual inhibition of IGF1R and EGFR in mice restored sensitivity to gefitinib, and cells retained sensitivity to PI3K inhibitors¹⁰⁶. Cotreatment of colorectal cancer cell lines with erlotinib and the IGF inhibitor PQIP resulted in synergistic inhibition¹⁰⁸.</p>
<p>JAK2: <i>EGFR</i> mutant lung cancer cells selected for resistance to erlotinib demonstrate increased levels of phosphorylated JAK¹⁰⁹.</p>	<p>Treatment with erlotinib and a JAK inhibitor (JSI-124) results in inhibition of cell growth <i>in vitro</i> and in mouse models¹⁰⁹.</p>
<p>MED12: MED12 is a component of the MEDIATOR transcriptional adaptor complex. Loss of <i>MED12</i> was discovered in an RNAi screen to lead to crizotinib resistance in <i>ALK</i> fusion positive cell lines⁷⁷. <i>MED12</i> knockdown also resulted in resistance to EGFR TKIs in EGFR mutant cell lines, was associated with MEK/ERK and TGF-β pathway activation, and an EMT-like phenotype. MED12 is thought to negatively regulate TGF-β receptor surface expression by interfering with glycosylation.</p>	<p>The TGF-β receptor inhibitor LY2157299 restores sensitivity to gefitinib in lung cancer cells rendered resistant through <i>MED12</i> knockdown⁷⁷.</p>
<p>PTEN: <i>PTEN</i> loss and AKT activation identified in lung cancer cell lines resistant to erlotinib and irreversible EGFR inhibitors^{68,110}, and may occur by suppression of nuclear translocation of the EGR1 transcription factor, which regulates <i>PTEN</i> expression¹¹¹.</p>	<p>AKT/PI3K inhibition may restore sensitivity to EGFR TKIs in cells with loss of <i>PTEN</i> expression¹¹². Inhibition of survivin expression by YM155 restores EGFR TKI sensitivity in cells with <i>PTEN</i> loss¹¹³. Vandetanib (ZD6474) is effective in <i>EGFR</i> mutant lung cancer cells deficient in <i>PTEN</i>¹¹⁴.</p>
<p>PUMA: PUMA is a BH3 BCL-2 protein that mediates apoptosis upon inhibition of EGFR signaling in lung cancer¹¹⁵.</p>	<p>PUMA may be activated by nuclear translocation of the FOXO1 transcription factor in response to inhibition of PI3K-AKT signaling¹¹⁵. The FDA-approved antipsychotic trifluoperazine restores sensitivity to EGFR TKIs by blocking FOXO1 nuclear export¹¹⁶.</p>

<p>ROR1: ROR1 is a pseudokinase that is regulated by the NKX2-1 transcription factor and mediates the balance between PI3-AKT survival signaling and apoptosis in lung cancer ¹¹⁷.</p>	<p>Knockdown of ROR1 by siRNA inhibits the proliferation of lung cancer with acquired resistance to EGFR TKIs such as T790M.</p>
<p>Acquisition of stem cell properties: <i>EGFR</i> mutant lung cancer cells cultured in the presence of gefitinib acquired stem cell like properties such as aldehyde dehydrogenase 1 overexpression and sphere formation in culture ¹¹⁸.</p>	<p>Gefitinib resistant cells were sensitive to the proteasome inhibitor bortezomib and the HDAC inhibitor vorinostat ¹¹⁸.</p>
<p>VEGF: Increased VEGF production leads to cetuximab and EGFR TKI resistance ¹¹⁹.</p>	<p>Vandetanib, a dual EGFR/VEGFR inhibitor overcomes resistance to cetuximab ¹²⁰. Vandetanib failed to demonstrate an overall survival benefit versus placebo in lung cancer patients previously treated with second or third line EGFR TKI ¹²¹. Treatment of mice with EGFR TKIs and VEGF inhibitors (bevacizumab, vandetanib) overcame resistance ¹²².</p>

Supplementary table 4: Clinical properties of “second-generation” EGFR inhibitors

Treatment regimen	Response rate	Median progression-free survival	Median overall survival	Trial & reference
Metastatic lung cancer - EGFR mutant positive				
Afatinib (Irreversible EGFR, Her2, Her4 inhibitor) vs. Cisplatin + pemetrexed First-line treatment of <i>EGFR</i> mutant positive patients	56% 23%	11.1 m 6.9 m	Pending	LUX-Lung 3 ¹²³
Afatinib <i>EGFR</i> mutant positive patients with ≤ 1 prior lines of treatment	62%	10.1 m	24.8 m	LUX-Lung 2 ¹²⁴
Afatinib Mostly (85%) <i>EGFR</i> mutation positive patients previously treated with second or third line erlotinib/ gefitinib for ≥ 3 months.	8.2%	4.4 m	19 m	LUX-Lung 4 ¹²⁵
Afatinib + cetuximab <i>EGFR</i> mutant positive patients with progression on erlotinib/ gefitinib and an <i>EGFR</i> T790M mutation.	38%	4.7 m	Pending	¹²⁶
Dacomitinib (Irreversible EGFR, Her2, Her4 inhibitor) First-line treatment of never/light smokers or known <i>EGFR</i> mutations	74% (<i>EGFR</i> exon 19 or 21 mutants)	17 m	Pending	¹²⁷
Metastatic or recurrent squamous cell carcinoma of the head and neck				
Afatinib vs. Cetuximab	16.1% 6.5% ($p = 0.09$)	15.9 wks 15.1 wks ($p = 0.93$)	NR	¹²⁸
Dacomitinib	12.7%	12.1 wks	34.6 wks	¹²⁹

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