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 *EGFR* 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 *EGFR* 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 *EGFR* 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 EGFR on immunohistochemistry, and patients entered regardless of *EGFR* mutation status. Patients with activating *EGFR* 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 *EGFR* 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 *EGFR* mutant predominantly Japanese patients				
Gefitinib vs. Cisplatin + docetaxel First-line treatment of exon 19 or L858R *EGFR* 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 *EGFR* 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 EGFR 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 EGFR 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 EGFR positive patients w/	57% 40%	9.9 m 8.4 m	23.5 m 20 m	CRYSTAL [15]

unresectable metastases. Patients with wildtype *KRAS* had improved PFS (HR = 0.68) compared to patients with mutant *KRAS*.				
Cetuximab vs. Best supportive care *KRAS* 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 *KRAS* 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, *KRAS* 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 *KRAS* 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 *KRAS*, while no benefit seen in patients with mutant *KRAS*.	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

EGFR exon 20 insertion	~100-fold decreased sensitivity to TKIs [23]. Occur in ~9% of patients with EGFR-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].
BIM mutation	Germline intronic deletion found in ~12% of East Asian individuals, but not in European or African populations, disrupts a splice site in *BIM*, 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 *EGFR* mutant lung cancer who also carry a *BIM* deletion have a shorter progression-free survival with gefitinib treatment, and *BIM* RNA levels predict clinical response to EGFR TKIs [28]. *BIM* expression is required for apoptosis induced by erlotinib/gefitinib in *EGFR* mutant lung cancer cell lines [29-32].	• BH3 mimetic small molecules (i.e. ABT-737) reverse sensitivity to gefitinib in resistant cell lines that harbor *BIM* deletion. • The HDAC inhibitor vorinostat increases expression of wild-type *BIM* in cell lines with a deletion polymorphism, possibly via epigenetic mechanisms, and restores sensitivity to EGFR TKIs [33].
EGFR T790M	Identified in 0.5%-3% of patients and is associated with resistance to EGFR TKI treatment [34,35].	Irreversible and mutant-selective inhibitors may be treatment options (discussed below)

Acquired resistance – erlotinib and gefitinib

EGFR 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 EGFR TKI treatment [34,37]. The T790M mutation increases EGFR 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 EGFR TKIs, and occur with much less frequency	• Irreversible inhibitors like afatinib, canertinib, dacomitinib, and T790M mutant-specific inhibitors like WZ-4002, CO-1686, and AZD9291 overcome resistance [42]. • Midostaurin and AP26113, two reversible kinase inhibitors developed for AML and *ALK*-fusion positive lung cancer, selectively and reversibly inhibit *EGFR* T790M in cell lines and mouse models [43,44]. • Combination of afatinib + cetuximab induced

	than T790M [40,41].	partial responses in 29% of patients with previous erlotinib/gefitinib treatment and a T790M mutation [45,46]. • 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].
HER2 amplification	*HER2* amplification observed in 12% of tumor samples from patients with acquired resistance, in contrast to 1% of treatment-naïve patients, and occurs exclusive to *EGFR* T790M [49].	Afatinib plus cetuximab or panitumumab abrogates Her2 signaling.
MET amplification and activation	Amplification found in 5-20% of patients with acquired resistance [50,51]. Small populations of *MET* amplified cells may be present prior to treatment in patients who go on to develop resistance via *MET* amplification [52]. MET 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 MET that triggers proliferation via GAB1 signaling [52]. Patients with resistance to EGFR TKIs who lack the T790M mutation or *MET* 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 MET TKI E7050 [33], and the MEK inhibitor CI-1040 [56], respectively.	• Phase III clinical trials of erlotinib + a MET inhibitor (tivantinib (ARQ197), MARQUEE) and erlotinib + an anti-MET 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 *EGFR* mutant cells transfected to overexpress HGF *in vitro* and in mouse models [59]. • Hsp90 inhibitors trigger apoptosis in cells rendered resistant to EGFR TKIs by HGF addition [60]. • The dual MET/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 *EGFR* mutant tumor cell lines in the presence or absence of HGF *in vitro* and *in vivo* [63]. • Low *BRCA1* expression may abrogate the

		negative effect of pretreatment *EGFR* 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 *EGFR* 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 *EGFR* mutations [66]. PIK3 activating mutations are sufficient to abrogate gefitinib-mediated apoptosis in lung cancer cell lines [67]. *PTEN* loss is associated with activation of PI3K signaling and resistance [68].	
BRAF mutation	V600E and G469A *BRAF* mutations noted in 1% of lung cancers with acquired resistance [69].	*BRAF* 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		
KRAS 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 *KRAS* activation [78]. Use of cetuximab and panitumumab are restricted to patients with *KRAS* wildtype tumors.	
BRAF mutation	In *KRAS* wildtype tumors, patients with *BRAF* mutations had an 8.3% response rate to cetuximab compared to a 38% response rate in *BRAF* wildtype tumors [79].	In tumors with *BRAF* V600E mutations, vemurafenib is synergistic with cetuximab and gefitinib/erlotinib [80,81]
PIK3CA exon 20 mutation	Patients with *PIK3CA* exon 20 mutations had a 0% response rate to cetuximab compared to 36.8% in wildtype patients [79].	
PTEN loss	*PTEN* wildtype associated with a ~23.9 odds ratio of response to cetuximab or panitumumab compared to *PTEN* loss [82].	
Acquired resistance – cetuximab		
EGFR extracellular domain mutations	S492R mutation abrogates cetuximab binding to *EGFR* on tumor cells [83].	Panitumumab remains active
KRAS activation	*KRAS* amplification or secondary activating mutations mediate resistance to cetuximab and panitumumab [84,85]. The kinetics of the emergence of *KRAS* mutations in the serum of patients who develop resistance to panitumumab suggests populations of *KRAS* mutants may exist prior to treatment [84].	MEK inhibition reverses resistance [85]
HER2 upregulation	Amplification observed in colon and lung cancer cell lines with resistance to cetuximab. *HER2* mediated resistance occurs via ERK1/2 signaling. Patients with *HER2* 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]	• 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 heregulin [87]. • Pertuzumab restores sensitivity to cetuximab by disrupting Her2/Her3 heterodimers in preclinical models.

MET amplification	Identified in ctDNA prior to progression in patients treated with EGFR targeted mAbs; no mutations were observed in *KRAS* [88]. *MET* amplification associated with cetuximab resistance in cell lines and patient-derived xenografts.	Treatment of patient-derived xenografts harboring *MET* amplification with crizotinib restores sensitivity to cetuximab.

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 *CRKL* 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].
EGFRvIII 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*:** *HER2* activating mutations lead to EGFR heterodimer formation and signaling that is independent of the EGFR kinase domain and resistant to EGFR TKIs [102]. *HER2* is reported to be upregulated in head and neck squamous cell	Treatment with Her2 inhibitors restores sensitivity [102].

carcinoma cell lines resistant to cetuximab [103].	
HER3: Activation of Her-3 by ligands such as heregulin mediates resistance to EGFR TKIs [87]. *HER3* reported to be upregulated in head and neck squamous cell carcinoma cell lines resistant to cetuximab [103].	The ADAM protease cleaves heregulin from the cell membrane and inhibition of this protease by INCB3619 increases sensitivity to EGFR TKIs [87]. MEHD7945A, a monoclonal antibody against EGFR and Her-3, is active in lung cancer and HNSCC cell lines resistant to cetuximab [104].
IGF: IGF1R signaling involved in resistance to gefitinib, dacomitinib, and the *EGFR* T790M mutant-specific inhibitor WZ-4002 [105,106]. Increased IGF expression correlates with resistance to EGFR mAb in *KRAS* wildtype colorectal cancer [107].	Dual inhibition of IGFR and EGFR in mice restored sensitivity to gefitinib, and cells retained sensitivity to PI3K inhibitors [106]. Cotreatment of colorectal cancer cell lines with erlotinib and the IGF inhibitor PQIP resulted in synergistic inhibition [108].
JAK2**:** *EGFR* mutant lung cancer cells selected for resistance to erlotinib demonstrate increased levels of phosphorylated JAK [109].	Treatment with erlotinib and a JAK inhibitor (JSI-124) results in inhibition of cell growth *in vitro* and in mouse models [109].
MED12: MED12 is a component of the MEDIATOR transcriptional adaptor complex. Loss of *MED12* was discovered in an RNAi screen to lead to crizotinib resistance in *ALK* fusion positive cell lines [77]. *MED12* 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.	The TGF-β receptor inhibitor LY2157299 restores sensitivity to gefitinib in lung cancer cells rendered resistant through *MED12* knockdown [77].
PTEN**:** *PTEN* 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 *PTEN* expression [111].	AKT/PI3K inhibition may restore sensitivity to EGFR TKIs in cells with loss of *PTEN* expression [112]. Inhibition of survivin expression by YM155 restores EGFR TKI sensitivity in cells with *PTEN* loss [113]. Vandetanib (ZD6474) is effective in *EGFR* mutant lung cancer cells deficient in *PTEN* [114].
PUMA: PUMA is a BH3 BCL-2 protein that mediates apoptosis upon inhibition of EGFR signaling in lung cancer [115].	PUMA may be activated by nuclear translocation of the FOXO1 transcription factor in response to inhibition of PI3K-AKT signaling [115]. The FDA-approved antipsychotic trifluoperazine restores sensitivity to EGFR TKIs by blocking FOXO1 nuclear export [116].

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].	Knockdown of ROR1 by siRNA inhibits the proliferation of lung cancer with acquired resistance to EGFR TKIs such as T790M.
Acquisition of stem cell properties: *EGFR* 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].	Gefitinib resistant cells were sensitive to the proteasome inhibitor bortezomib and the HDAC inhibitor vorinostat [118].
***VEGF*:** Increased VEGF production leads to cetuximab and EGFR TKI resistance [119].	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].

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 *EGFR* mutant positive patients	56% 23%	11.1 m 6.9 m	Pending	LUX-Lung 3 [123]
Afatinib *EGFR* mutant positive patients with ≤ 1 prior lines of treatment	62%	10.1 m	24.8 m	LUX-Lung 2 [124]
Afatinib Mostly (85%) *EGFR* 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 *EGFR* mutant positive patients with progression on erlotinib/gefitinib and an *EGFR* T790M mutation.	38%	4.7 m	Pending	[126]
Dacomitinib (Irreversible EGFR, Her2, Her4 inhibitor) First-line treatment of never/light smokers or known *EGFR* mutations	74% (*EGFR* 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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