Electronic Supplementary Material (ESI) for Molecular BioSystems

Supplementary Material

Supplement to JX.Zhang. *et al.* Analysis of bypass signaling in EGFR pathway and profiling of bypass genes for predicting response to anticancer EGFR tyro-sine kinase inhibitors

Supplementary Table S1 The bypass genes, regulated bypass signaling or regulatory genes, and the relevant bypass mechanisms in the treatment of NSCLC

Bypass Gene	Regulated Bypass Signaling	Bypass Mechanism
HER2	Compensatory signaling via EGFR-HER2 transactivation, and subsequent activation of RAS and AKT pathways	EGFR inhibition upregulated HER2 and induced compensatory EGFR-HER2 heterodimerisation to promote alternative signaling (Citri and Yarden, 2006; Kong *et al*., 2008)
	Alternative signaling via HER2-HER3 and HER2-HER4 transactivation, and subsequent activation of RAS and AKT pathways	EGFR inhibition upregulated HER2 and induced HER2-HER3, HER2-HER4 heterodimerisation to promote alternative signaling(Citri and Yarden, 2006; Kong *et al*., 2008)
HER3	Compensatory signaling via EGFR-HER3 transactivation, and subsequent activation of ATK pathway	EGFR inhibition elevated HER3 and subsequently induced compensatory transactivation of HER3 signaling (Sergina *et al*., 2007)
	Alternative signaling via HER2-HER3 transactivation, and subsequent activation of RAS and ATK pathways	EGFR inhibition upregulated HER2 and induced HER2-HER3 heterodimerisation to promote alternative signaling(Engelman and Cantley, 2006; Kong *et al*., 2008)
	Alternative signaling via HER3 autophosphorylation, and subsequent activation of ATK pathway	HER3 may autophosphorylate to produce weak kinase activity that may contribute to the resistance of EGFR inhibitor(Shi *et al*., 2010)
	Alternative signaling via PDGFR-HER3 transactivation, and subsequent activation of RAS and ATK pathway	EGFR inhibition countered by PDGFR transactivation of HER3 signaling(Sawyers, 2007)

IGF1R	Compensatory signaling via EGFR-IGF1R transactivation, and subsequent activation of RAS and ATK pathway	EGFR inhibition upregulated IGF1R and induced EGFR-IGF1R heterodimerization and activation of IGFR signaling(Morgillo *et al*., 2007)
	Alternative signaling via IGF1R activation, and subsequent activation of RAS and ATK pathway	EGFR inhibition reduced IGF-binding protein IGFBP-3 and IGFBP-4 to derepresses IGFIR signaling(Guix *et al*., 2008)
c-MET	Compensatory signaling via EGFR-MET transactivation, and subsequent activation of RAS and ATK pathway	EGFR inhibition countered by focal amplification of MET that physically interacts with EGFR to promote transactivation(Agarwal *et al*., 2009; Sawyers, 2007), Met activation in NSCLC is associated with de novo resistance to EGFR inhibitors and the development of metastasis(Benedettini *et al*., 2010)
	Alternative signaling via MET-HER3 transactivation, and subsequent activation of RAS and AkT pathways	EGFR inhibition countered by focal amplification of MET that transactivates HER3 to drive HER3-dependent activation of PI3K(Engelman *et al*., 2007)
	Alternative signaling via MET-HER2 transactivation, and subsequent activation of RAS and AkT pathways	EGFR inhibition countered by focal amplification of MET that physically interacts with HER2 to promote alternative signaling(Agarwal *et al*., 2009; Sawyers, 2007)
	Alternative signaling via HGF-induced MET activation, which subsequently activate MAPK and AKT pathways independent of EGFR and HER3	HGF-induced MET activation re-stimulated the MAPK and AKT pathways independent of EGFR and HER3 and restored cell proliferation, which is a novel mechanism of cetuximab resistance in CRC. Inhibition of the HGF-MET pathway may improve response to EGFR inhibitors in CRC(Liska *et al*., 2011)
PDGFR	Alternative signaling via PDGFR-HER3 transactivation, and subsequent activation of RAS and AkT pathways	EGFR inhibition countered by PDGFR transactivation of HER3 signaling(Sawyers, 2007)
	Alternative signaling via PDGFR autophosphorylation, and subsequent activation of RAS and AkT pathways	PDGF, PDGFR are expressed in certain NSCLC cell-lines, EGFR inhibition induced PDGFR autophosphorylation(Thomson *et al*., 2008)
FGFR	Alternative signaling via FGF-FGFR autocrine pathway, and subsequent activation of RAS and AkT	FGFR contributed to EGFR inhibitor resistance via alternative signaling(Thomson *et al*., 2008), an FGF-FGFR autocrine pathway

	pathways	dominates in some NSCLC cell-lines to promote the switch to FGFR signaling(Kono *et al*., 2009)
VEGFR2	Alternative signaling via VEGFR2 pathway, and subsequent activation of RAS and AkT pathways	EGFR inhibition shifts tumor population towards a less EGFR-dependent and more VEGF-dependent phynotype, combined blockade of VEGFR and EGFR pathways can abrogate resistance to EGFR inhibitors(Naumov *et al*., 2009)
Integrin β1	Compensatory signaling via EGFR-Integrin beta1 transactivation, and subsequent activation of RAS and AkT pathways	Integrin beta1 over-expression associates with resistance to gefitinib in NSCLC (21053345), it associates with EGFR, c-SRC and P130 to activate EGFR(Cabodi *et al*., 2009; Zeller *et al*.)
	Alternative signaling via integrin beta1 recruitment of FAK and a PP2-sensitive kinase to activate AkT pathway	Integrin β1 over-expression associates with resistance to gefitinib in NSCLC(Ju et al.), it activates AkT pathway by recruiting either FAK or an upstream PP2-sensitive non SRC tyrosine kinase to activate PI3K(Velling *et al*., 2008)
MDGI	Compensatory signaling via enhanced accumulation of internalized EGFR, and enhanced activation of RAS and AkT pathways	MDGI regulated EGFR subcellular localization, MDGI over-expression increased intracellular accumulation of EGFR and may be a biomarker for responsiveness to anti-EGFR antibody therapy(Nevo *et al*., 2009)
IL-6	Alternative signaling via IL-6 activation of MEK and JAK/STAT	IL-6 is upregulated in Erlotinib-resistant cells and required for their survival, and the up-regulation is mediated by TGF-β signaling, IL-6 activated gp130/JAK/STAT pathway to decrease sensitivity to erlotinib(Yao *et al*., 2010), EGFR can activate JAK/STAT via Mek, elevated IL can activate JAK/STAT and Mek to substitute EGFR activation of Mek and STAT(Sriuranpong *et al*., 2003)
Cox2	Alternative signaling by PGE2 mediated activation of PKC-MEK-ERK pathway and Gβγ-PI3K pathway	Cox2 over-expression caused resistance to Gefitinib and Erlotinib inhibition of Erk(Kim et al., 2009), Cox2 activated Erk via PGE2–EP receptors-PKC-Ras-Mek, Cox2 activated PI3K via PGE2-EP receptors-Gβγ-PI3K, Cox2 also activated EGFR via PGE2-EP receptors – Src – TGFα –EGFR and PGE2-EP receptors – Amphelegulin-EGFR(Wu *et al*.)

Supplementary Table S2 The downstream genes, regulated bypass signaling or regulatory genes, and the relevant bypass mechanisms in the treatment of NSCLC

Drug Resistant Downstream Gene	Bypass Signaling	Resistance Mechanism
KRAS	Compensatory signaling via EGFR-independent activation of KRAS	KRAS activating mutation mediated EGFR-independent signaling and contributed to EGFR inhibitor resistance(Linardou *et al*., 2008; Raponi *et al*., 2008)
PTEN	Compensatory signaling via enhanced activation of AKT pathway to reduce the level of dependence on EGFR	PTEN loss or inactivating mutation contributed to EGFR inhibitor resistance by activation of Akt and EGFR(Mellinghoff *et al*., 2007; Sos *et al*., 2009), PTEN-associated resistance to EGFR inhibitors is phenocopied by expression of dominant negative Cbl and can be overcome by more complete EGFR inhibition(Vivanco *et al*., 2010)
PIK3CA	Compensatory signaling via EGFR-independent activation of AKT pathway	PIK3CA activating mutation mediated EGFR-independent AKT signaling and contributed to EGFR inhibitor resistance(Sartore-Bianchi *et al*., 2009)
AKT		AKT activating mutation mediated EGFR-independent AKT signaling and could lead to resistance against EGFR inhibitor(Laurent-Puig *et al*., 2009)

Supplementary Table S3 The genetic and expression profiles of the main target, downstream genes and regulator, and bypass genes of 53 NSCLC cell-lines, and the predicted and actual sensitivity of these cell-lines against 3 kinase inhibitors: gefitinib (D1), erlotinib (D2), and lapatinib (D3).

NSCLC Cell lines	**Profile of Main Target (EGFR) Related to Drug Sensitivity**				**Profile of Main Target (EGFR) Related to Drug Resistance**	**Profile of Downstream Signaling Gene or Regulator Directly Contributing to Drug Resistance**				**Profile of Bypass Gene Directly Contributing to Drug Resistance**							**Predicted (Pre) and Actual (Act) Sensitivity to Gefitinib (D1) and Erlotinib (D2)**			**Predicted (Pre) and Actual (Act) Sensitivity to Lapatinib (D3)**	
	over exp	amp (copy no>4)	amp (copy no>3)	s-mut	r-mut	RAS a-mut	BRAF a-mut	PIK3CA a-mut	PTEN loss	HER2 over exp (Not applicable to D3)	HER3 over exp	FGFR1 over exp	IGF1R over exp	VEGFR2 over exp	c-MET over exp	PDGFR over exp	Pre by M1, M2, M3, A1, E1, E2, C1, C2, C3, C4, C5, C6, C7	Act (D1)	Act (D2)	Pre by M1, M2, M3, A1, E1, E2, C1, C2, C3, C4, C5, C6, C7	Act (D3)
Calu3	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0	R,S,R,R,R,R,R,R,R,R,R,R,R	S	NA	R,S,R,R,R,R,R,R,R,R,R,R,R	S
H3255	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	S,S,S,S,S,S,S,S,S,S,S,S,S	S	S	S,S,S,S,S,S,S,S,S,S,S,S,S	S
HCC2279	0	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	S,S,S,S,R,R,S,S,S,S,S,S,S	S	S	S,S,S,S,R,R,S,S,S,S,S,S,S	R
HCC2935	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	S,S,S,R,S,S,S,S,S,S,S,S,S	S	S	S,S,S,R,S,S,S,S,S,S,S,S,S	S
HCC4006	0	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	S,S,S,S,R,R,S,S,S,S,S,S,S	S	S	S,S,S,S,R,R,S,S,S,S,S,S,S	S
HCC827	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	S,S,S,S,S,S,S,S,S,S,S,S,S	S	S	S,S,S,S,S,S,S,S,S,S,S,S,S	S
A549	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	R,R,R,R,R,R,R,R,R,R,R,R,R	R	R	R,R,R,R,R,R,R,R,R,R,R,R,R	R
Calu1	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	R,R,R,R,R,R,R,R,R,R,R,R,R	R	R	R,R,R,R,R,R,R,R,R,R,R,R,R	R
Calu6	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	R,R,R,R,R,R,R,R,R,R,R,R,R	R	R	R,R,R,R,R,R,R,R,R,R,R,R,R	R
H1299	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	R,R,R,R,R,R,R,R,R,R,R,R,R	R	R	R,R,R,R,R,R,R,R,R,R,R,R,R	R
H1355	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	R,R,R,R,R,R,R,R,R,R,R,R,R	R	R	R,R,R,R,R,R,R,R,R,R,R,R,R	R
H1395	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	R,S,R,R,R,R,R,R,R,R,R,R,R	R	R	R,S,R,R,R,R,R,R,R,R,R,R,R	R
H1437	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	R,S,R,R,R,R,R,R,R,R,R,R,R	R	R	R,S,R,R,R,R,R,R,R,R,R,R,R	R
H157	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	R,R,R,R,R,R,R	R	R	R,R,R,R,R,R,R	R

																,R,R,R,R,R,R			,R,R,R,R,R,R	
H1648	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	R,S,R,R,R,R,R,R,R,R,R,R,R,R	R	R	R,S,R,R,R,R,R,R,R,R,R,R,R,R	S
H1650	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	S,S,S,R,R,R,S,S,R,R,R,S,S	R	R	S,S,S,R,R,R,S,S,R,R,R,S,S	R
H1666	0	0	0	0	0	0	1	0	0	0	1	0	0	0	0	0	R,S,R,R,R,R,R,R,R,R,R,R,R	R	R	R,S,R,R,R,R,R,R,R,R,R,R,R	S
H1770	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	R,S,R,R,R,R,R,R,R,R,R,R,R	R	R	R,S,R,R,R,R,R,R,R,R,R,R,R	
H1792	0	0	1	0	0	1	0	0	0	0	0	0	0	0	0	1	R,R,R,R,R,R,R,R,R,R,R,R,R	NA	R	R,R,R,R,R,R,R,R,R,R,R,R,R	R
H1819	0	0	1	0	0	0	0	0	0	1	1	0	0	0	0	0	R,S,R,R,R,R,R,R,R,R,R,R,R	R	R	R,S,R,R,R,R,R,R,R,R,R,R,R	S
H1975	0	0	1	1	1	0	0	0	0	0	0	0	0	0	0	0	S,S,R,R,R,R,R,R,R,R,R,R,R	R	R	S,S,R,R,R,R,R,R,R,R,R,R,R	R
H1993	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	R,S,R,R,R,R,R,R,R,R,R,R,R	R	R	R,S,R,R,R,R,R,R,R,R,R,R,R	R
H2009	0	0	0	0	0	1	0	0	0	0	0	0	0	0	1	0	R,R,R,R,R,R,R,R,R,R,R,R,R	R	R	R,R,R,R,R,R,R,R,R,R,R,R,R	R
H2052	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	R,S,R,R,R,R,R,R,R,R,R,R,R	NA	R	R,S,R,R,R,R,R,R,R,R,R,R,R	R
H2087	0	0	0	0	0	1	1	0	0	0	1	0	0	0	0	0	R,R,R,R,R,R,R,R,R,R,R,R,R	R	R	R,R,R,R,R,R,R,R,R,R,R,R,R	R
H2122	0	0	0	0	0	1	0	0	0	0	1	0	0	0	0	0	R,R,R,R,R,R,R,R,R,R,R,R,R	R	R	R,R,R,R,R,R,R,R,R,R,R,R,R	R
H2126	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	R,S,R,R,R,R,R,R,R,R,R,R,R	R	R	R,S,R,R,R,R,R,R,R,R,R,R,R	R
H23	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	R,R,R,R,R,R,R,R,R,R,R,R,R	NA	R	R,R,R,R,R,R,R,R,R,R,R,R,R	R
H2347	0	0	0	0	0	1	0	0	0	0	1	0	0	0	1	0	R,R,R,R,R,R,R,R,R,R,R,R,R	R	R	R,R,R,R,R,R,R,R,R,R,R,R,R	R
H28	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	R,S,R,R,R,R,R,R,R,R,R,R,R	NA	R	R,S,R,R,R,R,R,R,R,R,R,R,R	R
H2882	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	R,S,R,R,R,R,R,R,R,R,R,R,R	R	R	R,S,R,R,R,R,R,R,R,R,R,R,R	R
H2887	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	R,R,R,R,R,R,R,R,R,R,R,R,R	R	R	R,R,R,R,R,R,R,R,R,R,R,R,R	R
H3122	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	R,S,R,R,R,R,R,R,R,R,R,R,R	NA	R	R,S,R,R,R,R,R,R,R,R,R,R,R	R
H322	0	0	1	0	0	0	0	0	0	0	1	0	0	0	0	0	R,S,R,R,R,R,R,R,R,R,R,R,R	R	R	R,S,R,R,R,R,R,R,R,R,R,R,R	R
H358	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	R,R,R,R,R,R,R,R,R,R,R,R,R	R	R	R,R,R,R,R,R,R,R,R,R,R,R,R	R
H441	0	0	0	0	0	1	0	0	0	0	1	0	0	1	0	0	R,R,R,R,R,R,R,R,R,R,R,R,R	R	R	R,R,R,R,R,R,R,R,R,R,R,R,R	R
H460	0	0	0	0	0	1	0	1	0	0	0	0	0	0	0	0	R,R,R,R,R,R,R,R,R,R,R,R,R	R	R	R,R,R,R,R,R,R,R,R,R,R,R,R	R
H661	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	R,S,R,R,R,R,R	NA	R	R,S,R,R,R,R,R	R

																,R,R,R,R,R,R			,R,R,R,R,R,R	
H820	0	0	1	1	1	0	0	0	0	0	1	0	0	0	0	0	S,S,R,R,R,R,R ,R,R,R,R,R,R	R	R	S,S,R,R,R,R,R, R,R,R,R,R,R	R
HCC1171	0	0	0	0	0	1	0	0	0	0	1	0	0	0	0	0	R,R,R,R,R,R,R ,R,R,R,R,R,R	R	R	R,R,R,R,R,R,R ,R,R,R,R,R,R	R
HCC1195	0	0	1	0	0	1	0	0	0	0	1	0	0	0	0	0	R,R,R,R,R,R,R ,R,R,R,R,R,R	R	R	R,R,R,R,R,R,R ,R,R,R,R,R,R	R
HCC1359	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	R,S,R,R,R,R,R ,R,R,R,R,R,R	R	R	R,S,R,R,R,R,R ,R,R,R,R,R,R	R
HCC15	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	R,R,R,R,R,R,R ,R,R,R,R,R,R	R	R	R,R,R,R,R,R,R ,R,R,R,R,R,R	R
HCC1833	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	R,S,R,R,R,R,R ,R,R,R,R,R,R	NA	R	R,S,R,R,R,R,R ,R,R,R,R,R,R	R
HCC193	1	0	1	0	0	0	0	0	0	0	0	0	0	0	1	0	R,S,R,R,S,R,R ,S,R,S,R,S,R	R	R	R,S,R,R,S,R,R, S,R,S,R,S,R	R
HCC2429	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	R,S,R,R,R,R,R ,R,R,R,R,R,R	NA	R	R,S,R,R,R,R,R ,R,R,R,R,R,R	R
HCC2450	0	0	0	0	0	0	0	1	0	0	1	0	0	0	0	0	R,S,R,R,R,R,R ,R,R,R,R,R,R	NA	R	R,S,R,R,R,R,R ,R,R,R,R,R,R	R
HCC366	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	R,S,R,R,S,S,R, R,S,S,S,S,S	R	R	R,S,R,R,S,S,R, R,S,S,S,S,S	R
HCC44	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	R,R,R,R,R,R,R ,S,R,R,R,R,R	R	R	R,R,R,R,R,R,R ,S,R,R,R,R,R	R
HCC461	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	R,R,R,R,R,R,R ,R,R,R,R,R,R	R	R	R,R,R,R,R,R,R ,R,R,R,R,R,R	R
HCC515	0	0	0	0	0	1	0	0	0	0	1	0	0	0	0	0	R,R,R,R,R,R,R ,R,R,R,R,R,R	R	R	R,R,R,R,R,R,R ,R,R,R,R,R,R	R
HCC78	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	R,S,R,R,R,R,R ,R,R,R,R,R,R	R	R	R,S,R,R,R,R,R ,R,R,R,R,R,R	R
HCC95	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	R,S,R,R,R,R,R ,R,R,R,R,R,R	R	R	R,S,R,R,R,R,R ,R,R,R,R,R,R	R

Notes: “1” and “0” indicates the corresponding profile is positive (over-expressed, amplified or mutated) and negative (not over-expressed, amplified or mutated) respectively. “S”, “R”, “NA”, “s-mut”, “r-mut”, ‘a-mut’, “amp”, “over exp”, “pre”, and “act” stands for sensitive to drug, resistant to drug, no available drug sensitivity, drug sensitive mutation, drug resistance mutation, activating mutation, amplification, over expression, predicted drug sensitivity, and actual drug sensitivity respectively. The prediction methods M1, M2, M3, A1, E1, E2, C1, C2, C3, C4, C5, C6, and C7 are described in the text.

Supplementary Table S4 The distribution and coexistence of amplification and expression profiles, and the drug resistance mutation and expression profiles in NSCLC cell-lines

Cancer: NSCLC
Main Target for the Treatment of Specific Cancer: EGFR
Drugs Evaluated: gefitinib (D1), erlotinib (D2), and lapatinib (D3)

Drug Sensitizing or Resistance Profile (*index*)	**Number of Cell-Lines with This Profile**	**Number of These Cell-Lines with Another Sensitizing Profile**		**Number of These Cell-Lines with Another Resistance Profile**												**Number of These Cell-Lines Sensitive/ Resistant to Drug**		
		Drug Sensitizing Profile		***Drug Resistance Profile***														
Drug Sensitizing profile		***S1***	***S2***	***R1***	***R2***	***R3***	***R4***	***R5***	***R6***	***R7***	***R8***	***R9***	***R10***	***R11***	***R12***	***D1***	***D2***	***D3***
EGFR amp(copy no≥3) (***S1)***	12		3	2	2				1	4	1	1				4/7	4/8	4/8
EGFR over exp (***S2***)	5	3									1					3/2	3/1	3/2
Drug Resistance profile																		
EGFR r-mut (***R1***)	2									1						0/2	0/2	0/2
RAS a-mut (***R2***)	22					1				7	2				1	0/20	0/22	0/21
BRAF a-mut (***R3***)	3				1					1						0/3	0/3	1/2
PIK3CA a-mut (***R4***)	2									2						0/1	0/2	0/2
PTEN loss (***R5***)	0																	
HER2 over exp (***R6***)	2									2						1/1	0/1	2/0
HER3 over exp (***R7***)	18			1	7	1	2		2		1				1	1/14	0/17	3/12
MET over exp (***R8***)	5				2					1						0/5	0/5	1/4
PDGFR over exp (***R9***)	4																	
IGF1R over exp (***R10***)	0																	
FGFR1 over exp (***R11***)	0																	
VEGFR2 over exp (***R12***)	1				1					1						0/1	0/1	0/1

Supplementary Table S5 List of the 148 gefitinib response biomarkers selected by our SVM-RFE method from the 38 and 6 gefitinib resistant and sensitive NSCLC cell-lines, the biomarkers selected by a previously published study or as the gefitinib target or bypass gene are marked in the Table

SVM-RFE selected biomarker			**Biomarker commonly selected by a previous published study**		**Biomarker as gefitinib target or bypass gene**
Probeset ID	Gene Symbol	Gene Description	Selected by the study of (Kakiuchi *et al.*, 2004)	Selected by the study of (Coldren *et al.*, 2006)	
212895_s_at	ABR	active BCR-related gene			
202982_s_at	ACOT1	acyl-CoA thioesterase 2			
218795_at	ACP6	acid phosphatase 6, lysophosphatidic			
202666_s_at	ACTL6A	actin-like 6A			
219199_at	AFF4	AF4/FMR2 family, member 4			
202054_s_at	ALDH3A2	aldehyde dehydrogenase 3 family, member A2			
221825_at	ANGEL2	angel homolog 2 (Drosophila)			
206200_s_at	ANXA11	annexin A11			
221653_x_at	APOL2	apolipoprotein L, 2			
203025_at	ARD1A	ARD1 homolog A, N-acetyltransferase (S. cerevisiae)			
219335_at	ARMCX5	armadillo repeat containing, X-linked 5			
207076_s_at	ASS1	argininosuccinate synthetase 1			
209492_x_at	ATP5I	ATP synthase, H+ transporting, mitochondrial F0 complex, subunit E			
218631_at	AVPI1	arginine vasopressin-induced 1			
203304_at	BAMBI	BMP and activin membrane-bound inhibitor homolog (Xenopus laevis)			
202331_at	BCKDHA	branched chain keto acid dehydrogenase E1, alpha polypeptide			
201101_s_at	BCLAF1	BCL2-associated transcription factor 1			
211715_s_at	BDH1	3-hydroxybutyrate dehydrogenase, type 1			
218792_s_at	BSPRY	B-box and SPRY domain containing		√	

218462_at	BXDC5	brix domain containing 5			
219240_s_at	C10orf88	chromosome 10 open reading frame 88			
217969_at	C11orf2	chromosome 11 open reading frame2			
219099_at	C12orf5	chromosome 12 open reading frame 5			
218940_at	C14orf138	chromosome 14 open reading frame 138			
218183_at	C16orf5	chromosome 16 open reading frame 5			
219260_s_at	C17orf81	chromosome 17 open reading frame 81			
212574_x_at	C19orf6	chromosome 19 open reading frame 6			
213528_at	C1orf156	chromosome 1 open reading frame 156			
220477_s_at	C20orf30	chromosome 20 open reading frame 30			
219329_s_at	C2orf28	chromosome 2 open reading frame 28			
219008_at	C2orf43	chromosome 2 open reading frame 43			
213148_at	C2orf72	chromosome 2 open reading frame 72			
218646_at	C4orf27	chromosome 4 open reading frame 27			
206016_at	CCDC22	coiled-coil domain containing 22			
218026_at	CCDC56	coiled-coil domain containing 56			
213743_at	CCNT2	cyclin T2			
204306_s_at	CD151	CD151 molecule (Raph blood group)			
204693_at	CDC42EP1	CDC42 effector protein (Rho GTPase binding) 1			
203493_s_at	CEP57	centrosomal protein 57kDa			
212228_s_at	COQ9	coenzyme Q9 homolog (S. cerevisiae)			
206918_s_at	CPNE1	copine I			
201983_s_at	EGFR	epidermal growth factor receptor (erythroblastic leukemia viral (v-erb-b) oncogene homolog, avian)			√
201313_at	ENO2	enolase 2 (gamma, neuronal)			
217941_s_at	ERBB2IP	erbb2 interacting protein			
202454_s_at	ERBB3	v-erb-b2 erythroblastic leukemia viral oncogene homolog 3 (avian)		√	√
218481_at	EXOSC5	exosome component 5			

207813_s_at	FDXR	ferredoxin reductase			
219901_at	FGD6	FYVE, RhoGEF and PH domain containing 6			
207822_at	FGFR1	fibroblast growth factor receptor 1			√
206095_s_at	FUSIP1	FUS interacting protein (serine/arginine-rich) 1			
203987_at	FZD6	frizzled homolog 6 (Drosophila)			
218313_s_at	GALNT7	UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase 7 (GalNAc-T7)			
206920_s_at	GLE1	GLE1 RNA export mediator homolog (yeast)			
201501_s_at	GRSF1	G-rich RNA sequence binding factor 1			
201470_at	GSTO1	glutathione S-transferase omega 1			
201007_at	HADHB	hydroxyacyl-Coenzyme A dehydrogenase/3-ketoacyl-Coenzyme A thiolase/enoyl-Coenzyme A hydratase (trifunctional protein), beta subunit			
218460_at	HEATR2	HEAT repeat containing 2			
210982_s_at	HLA-DRA	major histocompatibility complex, class II, DR alpha			
202854_at	HPRT1	hypoxanthine phosphoribosyltransferase 1			
212221_x_at	IDS	iduronate 2-sulfatase			
221548_s_at	ILKAP	integrin-linked kinase-associated serine/threonine phosphatase 2C			
213392_at	IQCK	IQ motif containing K			
217938_s_at	KCMF1	potassium channel modulatory factor 1			
212303_x_at	KHSRP	KH-type splicing regulatory protein			
201776_s_at	KIAA0494	KIAA0494			
217906_at	KLHDC2	kelch domain containing 2			
206316_s_at	KNTC1	kinetochore associated 1			
202594_at	LEPROTL1	leptin receptor overlapping transcript-like 1			
209205_s_at	LMO4	LIM domain only 4			
201569_s_at	LOC100131861	sorting and assembly machinery component 50 homolog (S. cerevisiae)			
220130_x_at	LTB4R2	leukotriene B4 receptor 2			
203497_at	MED1	mediator complex subunit 1			

211599_x_at	MET	met proto-oncogene (hepatocyte growth factor receptor)			√
209124_at	MYD88	myeloid differentiation primary response gene (88)			
219946_x_at	MYH14	myosin, heavy chain 14		√	
37005_at	NBL1	neuroblastoma, suppression of tumorigenicity 1			
200854_at	NCOR1	nuclear receptor co-repressor 1			
203245_s_at	NCRNA00094	non-protein coding RNA 94			
219726_at	NLGN3	neuroligin 3			
205895_s_at	NOLC1	nucleolar and coiled-body phosphoprotein 1			
214661_s_at	NOP14	NOP14 nucleolar protein homolog (yeast)			
209628_at	NXT2	nuclear transport factor 2-like export factor 2			
201282_at	OGDH	oxoglutarate (alpha-ketoglutarate) dehydrogenase (lipoamide)			
212858_at	PAQR4	progestin and adipoQ receptor family member IV			
211048_s_at	PDIA4	protein disulfide isomerase family A, member 4			
202464_s_at	PFKFB3	6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3			
219235_s_at	PHACTR4	phosphatase and actin regulator 4			
217954_s_at	PHF3	PHD finger protein 3			
211668_s_at	PLAU	plasminogen activator, urokinase			
206080_at	PLCH2	phospholipase C, eta 2			
203735_x_at	PPFIBP1	PTPRF interacting protein, binding protein 1 (liprin beta 1)			
201300_s_at	PRNP	prion protein			
201705_at	PSMD7	proteasome (prosome, macropain) 26S subunit, non-ATPase, 7			
219938_s_at	PSTPIP2	proline-serine-threonine phosphatase interacting protein 2			
221808_at	RAB9A	RAB9A, member RAS oncogene family			
205037_at	RABL4	RAB, member of RAS oncogene family-like 4			
201039_s_at	RAD23A	RAD23 homolog A (S. cerevisiae)			
210621_s_at	RASA1	RAS p21 protein activator (GTPase activating protein) 1			
212646_at	RFTN1	raftlin, lipid raft linker 1			
218564_at	RFWD3	ring finger and WD repeat domain			

		3			
218323_at	RHOT1	ras homolog gene family, member T1			
214700_x_at	RIF1	RAP1 interacting factor homolog (yeast)			
201823_s_at	RNF14	ring finger protein 14			
208540_x_at	S100A11	S100 calcium binding protein A11 pseudogene			
201747_s_at	SAFB	scaffold attachment factor B			
203455_s_at	SAT1	spermidine/spermine N1-acetyltransferase 1			
201339_s_at	SCP2	sterol carrier protein 2			
202657_s_at	SERTAD2	SERTA domain containing 2			
216457_s_at	SF3A1	splicing factor 3a, subunit 1, 120kDa			
200753_x_at	SFRS2	splicing factor, arginine/serine-rich 2			
218878_s_at	SIRT1	sirtuin (silent mating type information regulation 2 homolog) 1 (S. cerevisiae)			
205896_at	SLC22A4	solute carrier family 22 (organic cation/ergothioneine transporter), member 4			
221020_s_at	SLC25A32	solute carrier family 25, member 32			
218041_x_at	SLC38A2	solute carrier family 38, member 2			
203579_s_at	SLC7A6	solute carrier family 7 (cationic amino acid transporter, y+ system), member 6			
202043_s_at	SMS	spermine synthase			
207390_s_at	SMTN	smoothelin			
205443_at	SNAPC1	small nuclear RNA activating complex, polypeptide 1, 43kDa			
201221_s_at	SNRNP70	small nuclear ribonucleoprotein 70kDa (U1)			
201522_x_at	SNRPN	small nuclear ribonucleoprotein polypeptide N			
203217_s_at	ST3GAL5	ST3 beta-galactoside alpha-2,3-sialyltransferase 5			
205339_at	STIL	SCL/TAL1 interrupting locus			
202786_at	STK39	serine threonine kinase 39 (STE20/SPS1 homolog, yeast)		√	
202260_s_at	STXBP1	syntaxin binding protein 1			
205759_s_at	SULT2B1	sulfotransferase family, cytosolic, 2B, member 1			

202384_s_at	TCOF1	Treacher Collins-Franceschetti syndrome 1			
220407_s_at	TGFB2	transforming growth factor, beta 2			
219580_s_at	TMC5	transmembrane channel-like 5		√	
219005_at	TMEM59L	transmembrane protein 59-like			
220431_at	TMPRSS11E	transmembrane protease, serine 11E			
206907_at	TNFSF9	tumor necrosis factor (ligand) superfamily, member 9			
207196_s_at	TNIP1	TNFAIP3 interacting protein 1			
202734_at	TRIP10	thyroid hormone receptor interactor 10			
209109_s_at	TSPAN6	tetraspanin 6			
213058_at	TTC28	tetratricopeptide repeat domain 28			
211285_s_at	UBE3A	ubiquitin protein ligase E3A			
219960_s_at	UCHL5	ubiquitin carboxyl-terminal hydrolase L5			
201903_at	UQCRC1	ubiquinol-cytochrome c reductase core protein I			
201831_s_at	USO1	USO1 homolog, vesicle docking protein (yeast)			
202664_at	WIPF1	WAS/WASL interacting protein family, member 1			
201760_s_at	WSB2	WD repeat and SOCS box-containing 2			
204022_at	WWP2	WW domain containing E3 ubiquitin protein ligase 2			
221423_s_at	YIPF5	Yip1 domain family, member 5			
212787_at	YLPM1	YLP motif containing 1			
201531_at	ZFP36	zinc finger protein 36, C3H type, homolog (mouse)			
203730_s_at	ZKSCAN5	zinc finger with KRAB and SCAN domains 5			
203247_s_at	ZNF24	zinc finger protein 24			
206829_x_at	ZNF430	zinc finger protein 430			

Supplementary Table S6 List of the 65 Erlotinib response biomarkers selected by our SVM-RFE method from the 46 and 7 Erlotinib resistant and sensitive NSCLC cell-lines, the biomarkers selected by a previously published study or as the Erlotinib target or bypass gene are marked in the Table

SVM-RFE selected biomarker			**Biomarker commonly selected by a previous published study**	**Biomarker as Erlotinib target or bypass gene**
Probeset ID	Gene Symbol	Gene Description	Selected by the study of (Balko *et al.*, 2006)	
219199_at	AFF4	AF4/FMR2 family, member 4		
202054_s_at	ALDH3A2	aldehyde dehydrogenase 3 family, member A2		
221825_at	ANGEL2	angel homolog 2 (Drosophila)		
204416_x_at	APOC1	apolipoprotein C-I		
203311_s_at	ARF6	ADP-ribosylation factor 6		
207076_s_at	ASS1	argininosuccinate synthetase 1		
214068_at	BEAN	brain expressed, associated with Nedd4		
217969_at	C11orf2	chromosome 11 open reading frame2		
221208_s_at	C11orf61	chromosome 11 open reading frame 61		
219260_s_at	C17orf81	chromosome 17 open reading frame 81		
220477_s_at	C20orf30	chromosome 20 open reading frame 30		
219329_s_at	C2orf28	chromosome 2 open reading frame 28		
213148_at	C2orf72	chromosome 2 open reading frame 72		
213322_at	C6orf130	chromosome 6 open reading frame 130		
206016_at	CCDC22	coiled-coil domain containing 22		
204306_s_at	CD151	CD151 molecule (Raph blood group)		
212648_at	DHX29	DEAH (Asp-Glu-Ala-His) box polypeptide 29		
200606_at	DSP	desmoplakin		
201983_s_at	EGFR	epidermal growth factor receptor (erythroblastic leukemia viral (v-	√	√

		erb-b) oncogene homolog, avian)		
217941_s_at	ERBB2IP	erbb2 interacting protein		
202454_s_at	ERBB3	v-erb-b2 erythroblastic leukemia viral oncogene homolog 3 (avian)		√
218481_at	EXOSC5	exosome component 5		
218898_at	FAM57A	family with sequence similarity 57, member A		
213646_x_at	FGFR3	fibroblast growth factor receptor 3		√
207966_s_at	GLG1	golgi apparatus protein 1		
203384_s_at	GOLGA1	golgi autoantigen, golgin subfamily a, 1		
206204_at	GRB14	growth factor receptor-bound protein 14	√	
201631_s_at	IER3	immediate early response 3		
221548_s_at	ILKAP	integrin-linked kinase-associated serine/threonine phosphatase 2C		
202419_at	KDSR	3-ketodihydrosphingosine reductase		
209205_s_at	LMO4	LIM domain only 4		
216908_x_at	LOC730092	RRN3 RNA polymerase I transcription factor homolog (S. cerevisiae) pseudogene		
217543_s_at	MBTPS1	membrane-bound transcription factor peptidase, site 1		
211599_x_at	MET	met proto-oncogene (hepatocyte growth factor receptor)		√
209124_at	MYD88	myeloid differentiation primary response gene (88)		
37005_at	NBL1	neuroblastoma, suppression of tumorigenicity 1		
203245_s_at	NCRNA00094	non-protein coding RNA 94		
218036_x_at	NMD3	NMD3 homolog (S. cerevisiae)		
209628_at	NXT2	nuclear transport factor 2-like export factor 2		
221538_s_at	PLXNA1	plexin A1		
37028_at	PPP1R15A	protein phosphatase 1, regulatory (inhibitor) subunit 15A		
221808_at	RAB9A	RAB9A, member RAS oncogene family		
205037_at	RABL4	RAB, member of RAS oncogene family-like 4		
210621_s_at	RASA1	RAS p21 protein activator (GTPase activating protein) 1	√	
218323_at	RHOT1	ras homolog gene family, member		

		T1		
208540_x_at	S100A11P	S100 calcium binding protein A11 pseudogene		
201339_s_at	SCP2	sterol carrier protein 2		
216457_s_at	SF3A1	splicing factor 3a, subunit 1, 120kDa		
200753_x_at	SFRS2	splicing factor, arginine/serine-rich 2		
205896_at	SLC22A4	solute carrier family 22 (organic cation/ergothioneine transporter), member 4		
221020_s_at	SLC25A32	solute carrier family 25, member 32		
203579_s_at	SLC7A6	solute carrier family 7 (cationic amino acid transporter, y+ system), member 6		
202043_s_at	SMS	spermine synthase		
218327_s_at	SNAP29	synaptosomal-associated protein, 29kDa		
200783_s_at	STMN1	stathmin 1/oncoprotein 18		
202260_s_at	STXBP1	syntaxin binding protein 1		
203449_s_at	TERF1	telomeric repeat binding factor (NIMA-interacting) 1		
219580_s_at	TMC5	transmembrane channel-like 5		
206907_at	TNFSF9	tumor necrosis factor (ligand) superfamily, member 9		
201546_at	TRIP12	thyroid hormone receptor interactor 12		
211758_x_at	TXNDC9	thioredoxin domain containing 9		
201649_at	UBE2L6	ubiquitin-conjugating enzyme E2L 6		
202664_at	WIPF1	WAS/WASL interacting protein family, member 1		
221423_s_at	YIPF5	Yip1 domain family, member 5		
212787_at	YLPM1	YLP motif containing 1		

Supplementary Table S7 List of the 98 Lapatinib response biomarkers selected by our SVM-RFE method from the 40 and 8 Lapatinib resistant and sensitive NSCLC cell-lines, the biomarkers as the Lapatinib target or bypass gene are marked in the Table

SVM-RFE selected biomarker			**Biomarker as Lapatinib target or bypass gene**
Probeset ID	Gene Symbol	Gene Description	
212895_s_at	ABR	active BCR-related gene	
205512_s_at	AIFM1	apoptosis-inducing factor, mitochondrion-associated, 1	
204416_x_at	APOC1	apolipoprotein C-I	
221653_x_at	APOL2	apolipoprotein L, 2	
220658_s_at	ARNTL2	aryl hydrocarbon receptor nuclear translocator-like 2	
207076_s_at	ASS1	argininosuccinate synthetase 1	
209406_at	BAG2	BCL2-associated athanogene 2	
222000_at	C1orf174	chromosome 1 open reading frame 174	
218646_at	C4orf27	chromosome 4 open reading frame 27	
218026_at	CCDC56	coiled-coil domain containing 56	
219036_at	CEP70	centrosomal protein 70kDa	
213735_s_at	COX5B	cytochrome c oxidase subunit Vb	
203368_at	CRELD1	cysteine-rich with EGF-like domains 1	
201201_at	CSTB	cystatin B (stefin B)	
205399_at	DCLK1	doublecortin-like kinase 1	
209916_at	DHTKD1	dehydrogenase E1 and transketolase domain containing 1	
209190_s_at	DIAPH1	diaphanous homolog 1 (Drosophila)	
218976_at	DNAJC12	DnaJ (Hsp40) homolog, subfamily C, member 12	
222221_x_at	EHD1	EH-domain containing 1	
201313_at	ENO2	enolase 2 (gamma, neuronal)	
210930_s_at	ERBB2	v-erb-b2 erythroblastic leukemia viral oncogene homolog 2, neuro/glioblastoma derived oncogene homolog (avian)	√
217941_s_at	ERBB2IP	erbb2 interacting protein	
202454_s_at	ERBB3	v-erb-b2 erythroblastic leukemia viral oncogene homolog 3 (avian)	√
202766_s_at	FBN1	fibrillin 1	
213646_x_at	FGFR3	fibroblast growth factor receptor 3	√
214170_x_at	FH	fumarate hydratase	
215075_s_at	GRB2	growth factor receptor-bound protein 2	
201209_at	HDAC1	histone deacetylase 1	

208306_x_at	HLA-DRB4	major histocompatibility complex, class II, DR beta 4	
209417_s_at	IFI35	interferon-induced protein 35	
219209_at	IFIH1	interferon induced with helicase C domain 1	
202859_x_at	IL8	interleukin 8	
205051_s_at	KIT	v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog	
210111_s_at	KLHDC10	kelch domain containing 10	
209008_x_at	KRT8	keratin 8	
217892_s_at	LIMA1	LIM domain and actin binding 1	
209737_at	MAGI2	membrane associated guanylate kinase, WW and PDZ domain containing 2	
205192_at	MAP3K14	mitogen-activated protein kinase kinase kinase 14	
213927_at	MAP3K9	mitogen-activated protein kinase kinase kinase 9	
218440_at	MCCC1	methylcrotonoyl-Coenzyme A carboxylase 1 (alpha)	
200617_at	MLEC	malectin	
201710_at	MYBL2	v-myb myeloblastosis viral oncogene homolog (avian)-like 2	
209498_at	MYCN	v-myc myelocytomatosis viral related oncogene, neuroblastoma derived (avian)	
209124_at	MYD88	myeloid differentiation primary response gene (88)	
208754_s_at	NAP1L1	nucleosome assembly protein 1-like 1	
217286_s_at	NDRG3	NDRG family member 3	
202647_s_at	NRAS	neuroblastoma RAS viral (v-ras) oncogene homolog	
212316_at	NUP210	nucleoporin 210kDa	
215952_s_at	OAZ1	ornithine decarboxylase antizyme 1	
209043_at	PAPSS1	3'-phosphoadenosine 5'-phosphosulfate synthase 1	
203131_at	PDGFR	platelet-derived growth factor receptor, alpha polypeptide	√
219165_at	PDLIM2	PDZ and LIM domain 2 (mystique)	
221538_s_at	PLXNA1	plexin A1	
209317_at	POLR1C	polymerase (RNA) I polypeptide C, 30kDa	
209482_at	POP7	processing of precursor 7, ribonuclease P/MRP subunit (S. cerevisiae)	
204748_at	PTGS2	prostaglandin-endoperoxide synthase 2 (prostaglandin G/H synthase and cyclooxygenase)	√
212032_s_at	PTOV1	prostate tumor overexpressed 1	
203329_at	PTPRM	protein tyrosine phosphatase, receptor type, M	
206157_at	PTX3	pentraxin-related gene, rapidly induced by IL-1 beta	
211823_s_at	PXN	paxillin	
213878_at	PYROXD1	pyridine nucleotide-disulphide oxidoreductase domain 1	
219681_s_at	RAB11FIP1	RAB11 family interacting protein 1 (class I)	
208732_at	RAB2A	RAB2A, member RAS oncogene family	
210621_s_at	RASA1	RAS p21 protein activator (GTPase activating protein) 1	
208242_at	RAX	retina and anterior neural fold homeobox	

213718_at	RBM4	RNA binding motif protein 4	
205740_s_at	RBM42	RNA binding motif protein 42	
218323_at	RHOT1	ras homolog gene family, member T1	
216913_s_at	RRP12	ribosomal RNA processing 12 homolog (S. cerevisiae)	
218307_at	RSAD1	radical S-adenosyl methionine domain containing 1	
208540_x_at	S100A11P	S100 calcium binding protein A11 pseudogene	
203408_s_at	SATB1	SATB homeobox 1	
203889_at	SCG5	secretogranin V (7B2 protein)	
201339_s_at	SCP2	sterol carrier protein 2	
214016_s_at	SFPQ	splicing factor proline/glutamine-rich (polypyrimidine tract binding protein associated)	
202433_at	SLC35B1	solute carrier family 35, member B1	
204368_at	SLCO2A1	solute carrier organic anion transporter family, member 2A1	
218327_s_at	SNAP29	synaptosomal-associated protein, 29kDa	
205443_at	SNAPC1	small nuclear RNA activating complex, polypeptide 1, 43kDa	
204729_s_at	STX1A	syntaxin 1A (brain)	
210580_x_at	SULT1A3	sulfotransferase family, cytosolic, 1A, phenol-preferring, member 3	
203167_at	TIMP2	TIMP metallopeptidase inhibitor 2	
212165_at	TMEM183A	transmembrane protein 183A	
202688_at	TNFSF10	tumor necrosis factor (ligand) superfamily, member 10	
206907_at	TNFSF9	tumor necrosis factor (ligand) superfamily, member 9	
214550_s_at	TNPO3	transportin 3	
203050_at	TP53BP1	tumor protein p53 binding protein 1	
202734_at	TRIP10	thyroid hormone receptor interactor 10	
215111_s_at	TSC22D1	TSC22 domain family, member 1	
217979_at	TSPAN13	tetraspanin 13	
46167_at	TTC4	tetratricopeptide repeat domain 4	
211285_s_at	UBE3A	ubiquitin protein ligase E3A	
202316_x_at	UBE4B	ubiquitination factor E4B (UFD2 homolog, yeast)	
220419_s_at	USP25	ubiquitin specific peptidase 25	
205139_s_at	UST	uronyl-2-sulfotransferase	
201531_at	ZFP36	zinc finger protein 36, C3H type, homolog (mouse)	
218645_at	ZNF277	zinc finger protein 277	
218735_s_at	ZNF544	zinc finger protein 544	

Supplementary Table S8 Clinicopathological features of NSCLC cell-lines used in this study. The available gene expression data, EGFR amplification status, and drug sensitivity data for gefitinib, erlotinib, and lapatinib are included together with the relevant references.

Cell-line	Histological Type	Histological Subtype *	Source *	Gene Expression Sample ID at GEO Database((Zhou *et al.*, 2006)	EGFR Amplification (gene copy number >3)(Sos *et al.*, 2009)	EGFR Amplification (gene copy number >4) (Sos *et al.*, 2009)	Mutated Gene/Genes(Forbes *et al.*; Thomas *et al.*, 2007)	Sensitivity Data		
								Gefitinib(Amann *et al.*, 2005; Gandhi *et al.*, 2009)	Erlotinib(Gandhi *et al.*, 2009; Sos *et al.*, 2009)	Lapatinib(Sos *et al.*, 2009)
A427	NSCLC	NS	PT	NA			KRAS		R	R
A549	NSCLC	NS	PT	GSM108799			KRAS	R	R	R
Calu1	NSCLC	EC	PE	GSM108801			KRAS	R	R	R
Calu3	NSCLC	AD	PE	GSM108803				S		S
Calu6	NSCLC	APC	PT	GSM108805			KRAS	R	R	R
Colo699	NSCLC	AD	PF	NA	Y				R	R
DV90	NSCLC	AD	PE	NA			KRAS		R	R
EKVX	NSCLC	AD	PT	NA					R	R
H1155	NSCLC	LCC	PT	NA	NA	NA	KRAS,PTEN	R	R	
H1299	NSCLC	LCC	LN	GSM108807			NRAS	R	R	R
H1355	NSCLC	AD	PT	GSM108809			KRAS, BRAF	R	R	R
H1395	NSCLC	AD	PT	GSM108811			BRAF	R	R	R
H1437	NSCLC	AD	PT	GSM108813				R	R	R
H1563	NSCLC	AD	PT	NA			PIK3CA		R	R
H1568	NSCLC	AD	PT	NA	Y	Y			R	R
H157	NSCLC	SQ	PT	GSM108815			KRAS,PTEN	R	R	R
H1648	NSCLC	AD	LN	GSM108817				R	R	S
H1650	NSCLC	AD	PE	GSM108819	Y		EGFR	R	R	R
H1666	NSCLC	AD	PE	GSM108821			BRAF	R	R	S

H1734	NSCLC	AD	PT	NA	Y		KRAS		R	R
H1755	NSCLC	AD	Live	NA			BRAF		R	R
H1770	NSCLC	NE	LN	GSM108825				R	R	
H1781	NSCLC	AD	PE	NA			ERBB2	R	R	R
H1792	NSCLC	AD	PE	GSM171848	Y		KRAS		R	R
H1819	NSCLC	AD	LN	GSM108827	Y			R	R	S
H1838	NSCLC	AD	PT	NA	Y	Y			R	R
H1915	NSCLC	SCC	Brain	NA					R	R
H1944	NSCLC	AD	ST	NA			KRAS		R	R
H1975	NSCLC	AD	PT	GSM108829	Y		EGFR	R	R	R
H1993	NSCLC	AD	LN	GSM108831				R	R	R
H2009	NSCLC	AD	LN	GSM108833			KRAS	R	R	R
H2030	NSCLC	AD	LN	NA			KRAS		R	R
H2052	NSCLC	MT	PE	GSM171854					R	R
H2077	NSCLC	AD	PT	NA					R	R
H2087	NSCLC	AD	LN	GSM108835			BRAF, NRAS	R	R	R
H2110	NSCLC	NS	PE	NA					R	R
H2122	NSCLC	AD	PE	GSM108837			KRAS	R	R	R
H2126	NSCLC	LCC	PE	GSM108839				R	R	R
H2172	NSCLC	NS	PT	NA					R	R
H2228	NSCLC	AD	PT	NA					R	R
H23	NSCLC	AD	PT	GSM171868			KRAS, PTEN		R	R
H2347	NSCLC	AD	PT	GSM108841			NRAS	R	R	R
H2444	NSCLC	NS	PT	NA	Y		KRAS		R	R
H28	NSCLC	MT	PE	GSM171870					R	R
H2882	NSCLC	NS	PT	GSM108843				R	R	R
H2887	NSCLC	NS	PT	GSM108845			KRAS	R	R	R
H3122	NSCLC	AD	PT	GSM171874					R	R

H322	NSCLC	AD	PT	GSM171876	Y			R	R	R
H322M	NSCLC	AD	PT	NA					R	S
H3255	NSCLC	AD	PT	GSM108847	Y	Y	EGFR	S	S	S
H358	NSCLC	AD	PT	GSM108849			KRAS	R	R	R
H441	NSCLC	AD	PT	GSM108851			KRAS	R	R	R
H460	NSCLC	LCC	PE	GSM108853			KRAS, PIK3CA	R	R	R
H520	NSCLC	SQ	PT	NA				R	R	R
H522	NSCLC	AD	PT	NA	Y				R	R
H596	NSCLC	AD	PT	NA	Y		PIK3CA		R	R
H647	NSCLC	ADSQ	PE	NA			KRAS		R	R
H661	NSCLC	LC	LN	GSM171884					R	R
H820	NSCLC	AD	LN	GSM108855	Y		EGFR	R	R	R
HCC1171	NSCLC	NS	PT	GSM108857			KRAS	R	R	R
HCC1195	NSCLC	ADSQ	PT	GSM108859	Y		NRAS	R	R	R
HCC1359	NSCLC	SGC	PT	GSM108861				R	R	R
HCC15	NSCLC	SQ	PT	GSM108863			NRAS	R	R	R
HCC1833	NSCLC	AD	PT	GSM171898					R	R
HCC193	NSCLC	AD	PT	GSM108865	Y			R	R	R
HCC2279	NSCLC	AD	PT	GSM108867	Y	Y	EGFR	S	S	R
HCC2429	NSCLC	NS	PT	GSM171900					R	R
HCC2450	NSCLC	SQ	PT	GSM171902			PIK3CA		R	R
HCC2935	NSCLC	AD	PE	GSM108869			EGFR	S	S	S
HCC364	NSCLC	AD	PT	NA			BRAF		R	R
HCC366	NSCLC	ADSQ	PT	GSM108871				R	R	R
HCC4006	NSCLC	AD	PE	GSM108873	Y	Y	EGFR	S	S	S
HCC44	NSCLC	AD	PT	GSM108875			KRAS	R	R	R
HCC461	NSCLC	AD	PT	GSM108877			KRAS	R	R	R
HCC515	NSCLC	AD	PT	GSM108879			KRAS	R	R	R

HCC78	NSCLC	AD	PE	GSM108881				R	R	R
HCC827	NSCLC	AD	PT	GSM108883	Y	Y	EGFR	S	S	S
HCC95	NSCLC	SQ	PE	GSM108885				R	R	R
HOP62	NSCLC	AD	PT	NA			KRAS		R	R
HOP92	NSCLC	AD	PT	NA	Y				R	R
LCLC103H	NSCLC	LCC	PE	NA					R	R
LCLC97TM	NSCLC	LCC	PT	NA			KRAS		R	R
LouNH91	NSCLC	SQ	PT	NA	Y		EGFR		R	R
PC9	NSCLC	AD	PT	NA	Y		EGFR	S	S	R
SKLU1	NSCLC	AD	PT	NA			KRAS		R	R

* Determined from the ATCC (http://www.atcc.org) and DSMZ (http://www.dsmz.de) websites, and references therein.

Abbreviations: AD, lung adenocarcinoma; APC, anaplastic carcinoma; EC, epidermoid carcinoma; LCC, large cell lung cancer; LN, lymph node; MT, mesothelioma; NA: not available; NE, neuroendocrine neoplasm; NS, not specified; NSCLC: non-small cell lung cancer; PE, pleural effusion; PF, pleural fluid; PT, primary tumor; R, resistant; S, sensitive ; SCC, small-cell carcinoma; SGC: spindle and giant cell carcinoma; ST, soft tissue; Y, gene amplified

Supplementary Table S9 Sensitivity data of NSCLC cell-lines treated with gefitinib, erlotinib, and lapatinib

NSCLC Cell-line	Sensitivity of Cell-line to Gefitinib Inhibition [#]	Reported Potency (IC50) of Gefitinib Inhibition (µM)		Sensitivity of Cell-line to Erlotinib Inhibition [#]	Reported Potency (IC50/ED50) of Erlotinib Inhibition (µM)		Sensitivity of Cell-line to Lapatinib Inhibition [#]	Reported Potency (ED50) of Lapatinib Inhibition (µM)
		Ref (Gandhi *et al.*, 2009)	Ref (Amann *et al.*, 2005)		Ref (Gandhi *et al.*, 2009)	Ref (Sos *et al.*, 2009)		Ref (Sos *et al.*, 2009)
A427				R		1.24	R	9.4406
A549	R	25		R	60	10	R	10
Calu1	R		41	R		10	R	10
Calu3	S	0.78		-	1.29	0.7	S	0.1679
Calu6	R		34	R		9.65	R	2.7542
Colo699				R		4.26	R	5.8884
DV90				R		3.95	R	1.4125
EKVX				R		10	R	10
H1155	R	183		R	8.63			
H1299	R	26.4		R	41.9	10	R	10
H1355	R	325		R	27	3.31	R	5.6885
H1395	R	71		R	10.5	5.05	R	6.6834
H1437	R	62		R	12.5	10	R	10
H1563				R		10	R	10
H1568				R		1.08	R	2.541
H157	R	115		R	128	10	R	10
H1648	R	36.7		R	34	7.77	S	0.9441
H1650	R	11.7		R	15	2.13	R	3.8905
H1666	R	180		R	13	3.31	S	0.5957

H1734				R		3.79	R	4.3652
H1755				R		7.5	R	10
H1770	R	160		R	111	10		
H1781	R	19		R	44	2.54	R	2.9174
H1792				R		10	R	10
H1819	R	19		R	6.3	3.92	S	0.7328
H1838				R		3.47	R	10
H1915				R		10	R	10
H1944				R		1.83	R	10
H1975	R	25		R	33	10	R	10
H1993	R	17.9		R	5.2	8.06	R	4.3152
H2009	R	33.2		R	25.8	10	R	10
H2030				R		4.95	R	5.0119
H2052				R		8.98	R	10
H2077				R		10	R	10
H2087	R	18.4		R	9.9	10	R	10
H2110				R		4.5	R	2.7861
H2122	R	35		R	76.8	10	R	10
H2126	R	21.4		R	13	10	R	10
H2172				R		10	R	8.9125
H2228				R		10	R	10
H23				R		10	R	5.6234
H2347	R	60		R	5.2	10	R	5.9566
H2444				R		4.22	R	7.6736
H28				R		10	R	1.6032
H2882	R	19.2		R	66	10	R	5.1286

H2887	R	110		R	101	10	R	10
H3122				R		10	R	10
H322	R	120		R	56	2.21	R	2.4831
H322M				R		1.29	S	0.4416
H3255	S	0.089		S	0.129	0.02	S	0.309
H358	R	12.5		R	6.2	1.11	R	1.6032
H441	R	15.7		R	7.1	3.61	R	10
H460	R	16.9		R	72	10	R	3.3113
H520	R	13.6		R		10	R	6.8391
H522				R		5.83	R	8.7096
H596				R		1.2	R	10
H647				R		10	R	10
H661				R		10	R	10
H820	R	3		R	7.1	10	R	10
HCC1171	R	127		R	160	10	R	10
HCC1195	R	27.6		R	175	10	NA	
HCC1359	R	65		R	88	10	R	10
HCC15	R	52		R	100	10	R	10
HCC1833				R		10	R	2.6915
HCC193	R	21.1		R	20.5	10	R	1.7378
HCC2279	S	0.0479		S	0.093	0.01	R	10
HCC2429				R		10	R	5.9566
HCC2450				R		10	R	10
HCC2935	S	0.11		S	0.163	0.07	S	0.2344
HCC364				R		4.19	R	10
HCC366	R	30		R	11	0.99	R	10

HCC4006	S	0.23		S	0.124	0.04	S	0.537
HCC44	R	57.8		R	28	10	R	10
HCC461	R	13.9		R	16	9.04	R	10
HCC515	R	120		R	154	1.85	R	9.5499
HCC78	R	81		R	21.2	10	R	4.1687
HCC827	S	0.04		S	0.0388	0.02	S	0.7943
HCC95	R	24		R	18.4	10	R	3.2359
HOP62				R		10	R	5.4325
HOP92				R		10	R	10
LCLC103H				R		10	R	10
LCLC97TM				R		5.26	R	7.3282
LouNH91				R		3.05	R	5.1286
PC9	S	0.0309		S		0.02	R	1.4962
SKLU1				R		10	R	10

* A cell-line with IC50≤ 1 μmol/L for gefitinib, erlotinib, and lapatinib was considered to be sensitive (S) to a given drug[(Oprea *et al.*, 2009)], otherwise it was considered as resistant (R) to the drug. - : cell-line with inconsistent sensitivity data, which is not included in this study.

Supplementary Table S10 6 normal Cell-lines from the lung bronchial epithelial tissues obtained from GEO database

Gene Expression Sample ID of Normal Cell-line at GEO Database	Cell-lines	Source of Cell-lines	Reference
GSM427196	NHBE	Normal human bronchial epithelial cells	Ref (Kadara *et al.*, 2009)
GSM427197	NHBE	Normal human bronchial epithelial cells	
GSM427198	BEAS-2B	Immortalized bronchial epithelial cells	
GSM427199	BEAS-2B	Immortalized bronchial epithelial cells	
GSM427200	1799	Immortalized lung epithelial cells	
GSM427201	1799	Immortalized lung epithelial cells	

Supplementary Table S11 Drug related sensitizing/resistant mutations of EGFR and cancer related activating mutations of EGFR, PIK3CA, RAS, and BRAF, and inactivation mutations of PTEN.

Disease	Type of Mutation	Percentage of 85 NSCLC Cell-lines or 40 Breast Cancer Cell-lines with This Type of Mutation	Specific Mutations (Number of NSCLC or Breast Cancer Cell-lines with This Mutation)
NSCLC	Gefitinib , erlotinib , and lapatinib sensitizing mutation of EGFR(Sharma *et al.*, 2007)	11.7%	E746_A750del (4) / E746_A750del, T751A(1) / E746_T751del, I ins(1) / L747_E749del, A750P(1) / L747_S752del, P753S(1) / L858R(2)
	Gefitinib , erlotinib , and lapatinib resistant mutation of EGFR(Sharma *et al.*, 2007)	2.4%	T790M (2)
	Gefitinib and erlotinib resistant mutation of HER2(Hynes and Schlange, 2006)	1.2%	G776VC (1)
	Activating mutation of KRAS(Bos, 1988)	32.9%	G12A (1) / G12C (9) / G12D (3) / G12R (1) / G12S (1) / G12V (4) / G13C (2) / G13D (4) / Q61H (2) / Q61K (1)
	Activating mutation of NRAS(Bos, 1988)	5.9%	Q61K (3) / Q61L (1) / Q61R (1)
	Activating mutation of BRAF (McDermott *et al.*, 2007)	7.1%	G466V(1) / G469A(3) / L597V(1) / V600E(1)
	Activating mutation PIK3CA (Bader *et al.*, 2006; Gymnopoulos *et al.*, 2007)	4.7%	E542K (1) / E545K (2) / H1047R(1)
	Inactivating mutation PTEN(Forgacs *et al.*, 1998)	4.7%	H61R(1) / G251C(1) / R233*(2)

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Supplementary Table S12 Cancer related and drug related specific mutations in 85 NSCLC cell-lines.

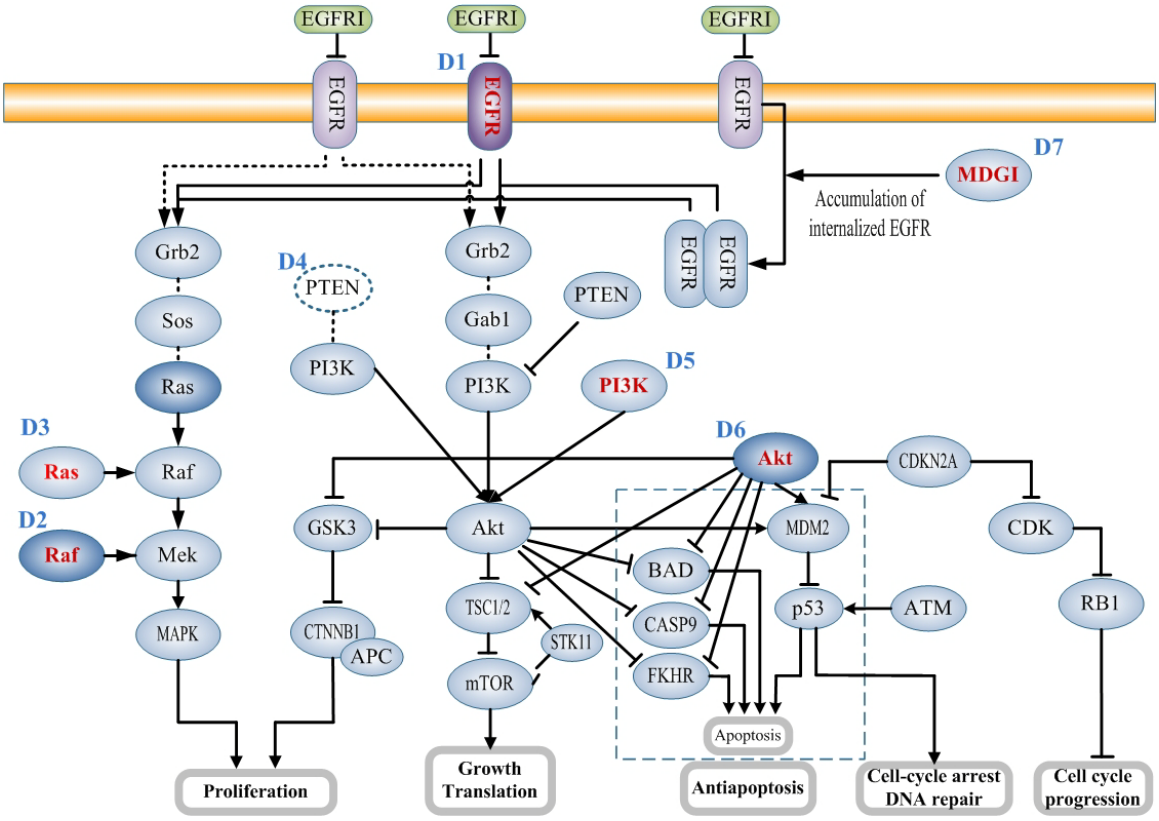
Cell-lines	Disease	Mutated Gene(Forbes *et al.*; Thomas *et al.*, 2007)	Type of Mutation	Mutation Details	
				Amino Acid	Nucleotide
A427	NSCLC	KRAS	Activating mutation	G12D	35G>A
A549	NSCLC	KRAS	Activating mutation	G12S	34G>A
Calu1	NSCLC	KRAS	Activating mutation	G12C	34G>T
Calu3	NSCLC	ND			
Calu6	NSCLC	KRAS	Activating mutation	Q61K	181C>A
Colo699	NSCLC	ND *			
DV90	NSCLC	KRAS	Activating mutation	G13D	38G>A
EKVX	NSCLC	ND			
H1155	NSCLC	KRAS	Activating mutation	Q61H	183A>T
H1155	NSCLC	PTEN	Inactivating mutation	R233*	697C>T
H1299	NSCLC	NRAS	Activating mutation	Q61K	181C>A
H1355	NSCLC	KRAS	Activating mutation	G13C	37G>T
H1355	NSCLC	BRAF	Activating mutation	G469A	1406G>C
H1395	NSCLC	BRAF	Activating mutation	G469A	1406G>C
H1437	NSCLC	ND			
H1563	NSCLC	PIK3CA*	Activating mutation	E542K	1624G>A
H1568	NSCLC	ND			
H157	NSCLC	KRAS	Activating mutation	G12R	34G>C
H157	NSCLC	PTEN	Inactivating mutation	G251C	751G>T
H157	NSCLC	PTEN	Inactivating mutation	H61R	182A>G
H1648	NSCLC	ND			
H1650	NSCLC	EGFR	EGFR sensitizing mutation	E746_A750del	2235_2249del15
H1666	NSCLC	BRAF	Activating mutation	G466V	1397G>T
H1734	NSCLC	KRAS	Activating mutation	G13C	37G>T
H1755	NSCLC	BRAF	Activating mutation	G469A	1406G>C
H1770	NSCLC	ND			

H1781	NSCLC	ERBB2*	gefitinib and erlotinib resistant mutation	G776VC	
H1792	NSCLC	KRAS	Activating mutation	G12C	34G>T
H1819	NSCLC	ND			
H1838	NSCLC	ND			
H1915	NSCLC	ND*			
H1944	NSCLC	KRAS*	Activating mutation	G13D	38G>A
H1975	NSCLC	EGFR	EGFR-I sensitizing mutation	L858R	2573T>G
H1975	NSCLC	EGFR	EGFR-I resistant mutation	T790M	2369C>T
H1993	NSCLC	ND			
H2009	NSCLC	KRAS	Activating mutation	G12A	35G>C
H2030	NSCLC	KRAS	Activating mutation	G12C	34G>T
H2052	NSCLC	ND			
H2077	NSCLC	ND*			
H2087	NSCLC	BRAF	Activating mutation	L597V	1789C>G
H2087	NSCLC	NRAS	Activating mutation	Q61K	181C>A
H2110	NSCLC	ND			
H2122	NSCLC	KRAS	Activating mutation	G12C	34G>T
H2126	NSCLC	ND			
H2172	NSCLC	ND*			
H2228	NSCLC	ND			
H23	NSCLC	KRAS	Activating mutation	G12C	34G>T
H23	NSCLC	PTEN	Inactivating mutation	R233*	697C>T
H2347	NSCLC	NRAS	Activating mutation	Q61R	182A>G
H2444	NSCLC	KRAS*	Activating mutation	G12V	
H28	NSCLC	ND			
H2882	NSCLC	ND			
H2887	NSCLC	KRAS*	Activating mutation	G12V	
H3122	NSCLC	ND			
H322	NSCLC	ND			

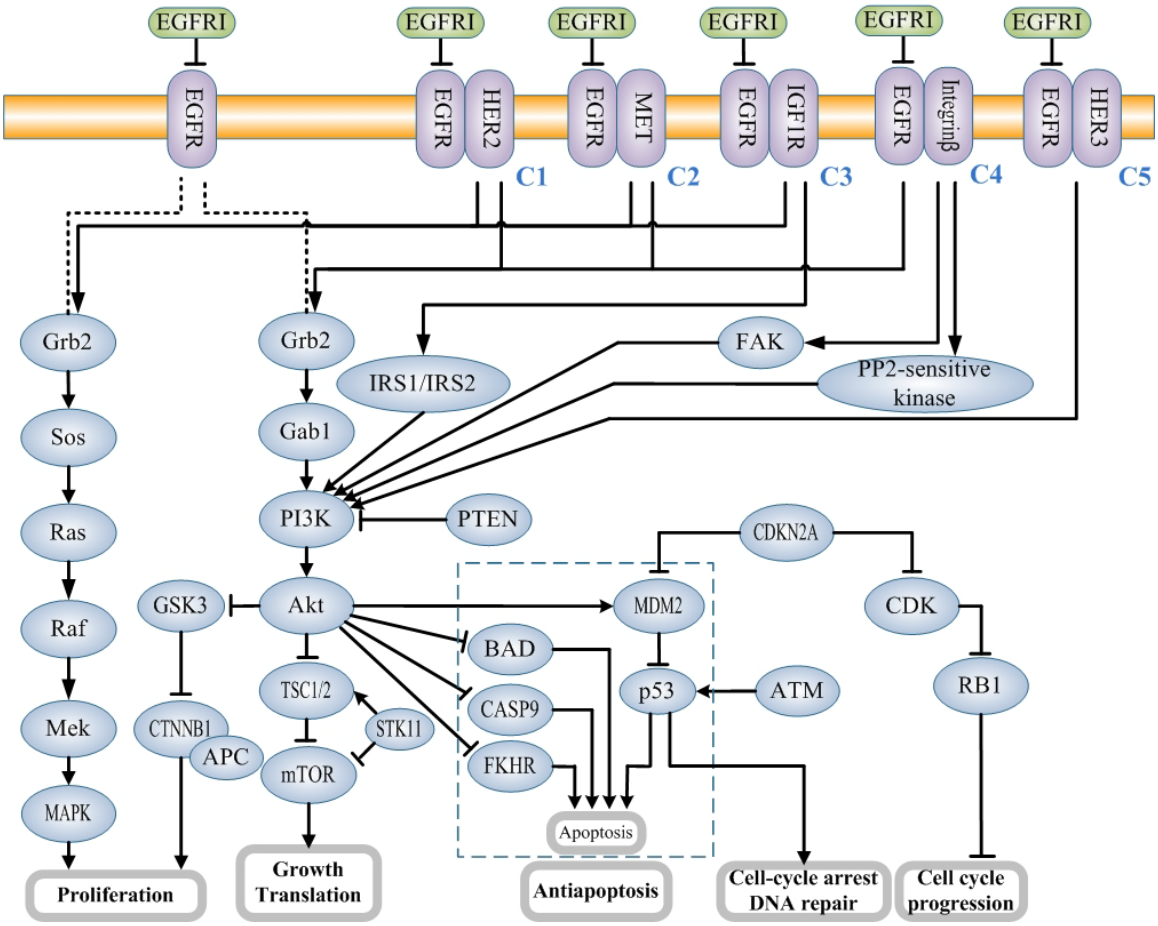
H3255	NSCLC	EGFR	EGFR-I sensitizing mutation	L858R	34G>T
H358	NSCLC	KRAS	Activating mutation	G12C	34G>T
H441	NSCLC	KRAS	Activating mutation	G12V	35G>T
H460	NSCLC	PIK3CA	Activating mutation	E545K	1633G>A
H460	NSCLC	KRAS	Activating mutation	Q61H	183A>T
H520	NSCLC	ND			
H522	NSCLC	ND			
H596	NSCLC	PIK3CA	Activating mutation	E545K	1633G>A
H647	NSCLC	KRAS	Activating mutation	G13D	38G>A
H661	NSCLC	ND			
H820	NSCLC	EGFR*	EGFR-I sensitizing mutation	E746_T751del, I ins	
H820	NSCLC	EGFR*	EGFR-I resistant mutation	T790M	2369C>T
HCC1171	NSCLC	KRAS*	Activating mutation	G12C	
HCC1195	NSCLC	NRAS*	Activating mutation	Q61L	
HCC1359	NSCLC	ND*			
HCC15	NSCLC	NRAS*	Activating mutation	Q61K	
HCC1833	NSCLC	ND*			
HCC193	NSCLC	ND*			
HCC2279	NSCLC	EGFR*	EGFR-I sensitizing mutation	E746_A750del	2235_2249del15
HCC2429	NSCLC	ND*			
HCC2450	NSCLC	PIK3CK*	Activating mutation	H1047R	3140A>G
HCC2935	NSCLC	EGFR*	EGFR-I sensitizing mutation	E746_A750del, T751A	
HCC364	NSCLC	BRAF	Activating mutation	V600E	1799T>A
HCC366	NSCLC	ND*			
HCC4006	NSCLC	EGFR*	EGFR-I sensitizing mutation	L747_E749del, A750P	
HCC44	NSCLC	KRAS*	Activating mutation	G12C	
HCC461	NSCLC	KRAS*	Activating mutation	G12D	
HCC515	NSCLC	KRAS*	Activating mutation	G13D	
HCC78	NSCLC	ND*			

HCC827	NSCLC	EGFR*	EGFR-I sensitizing mutation	E746_A750del	2235_2249del15
HCC95	NSCLC	ND*			
HOP62	NSCLC	KRAS	Activating mutation	G12C	34G>T
HOP92	NSCLC	ND			
LCLC103H	NSCLC	ND			
LCLC97TM	NSCLC	KRAS	Activating mutation	G12V	35G>T
LouNH91	NSCLC	EGFR*	EGFR-I sensitizing mutation	L747_S752del, P753S	
PC9	NSCLC	EGFR*	EGFR-I sensitizing mutation	E746_A750del	2235_2249del15
SKLU1	NSCLC	KRAS*	Activating mutation	G12D	35G>A

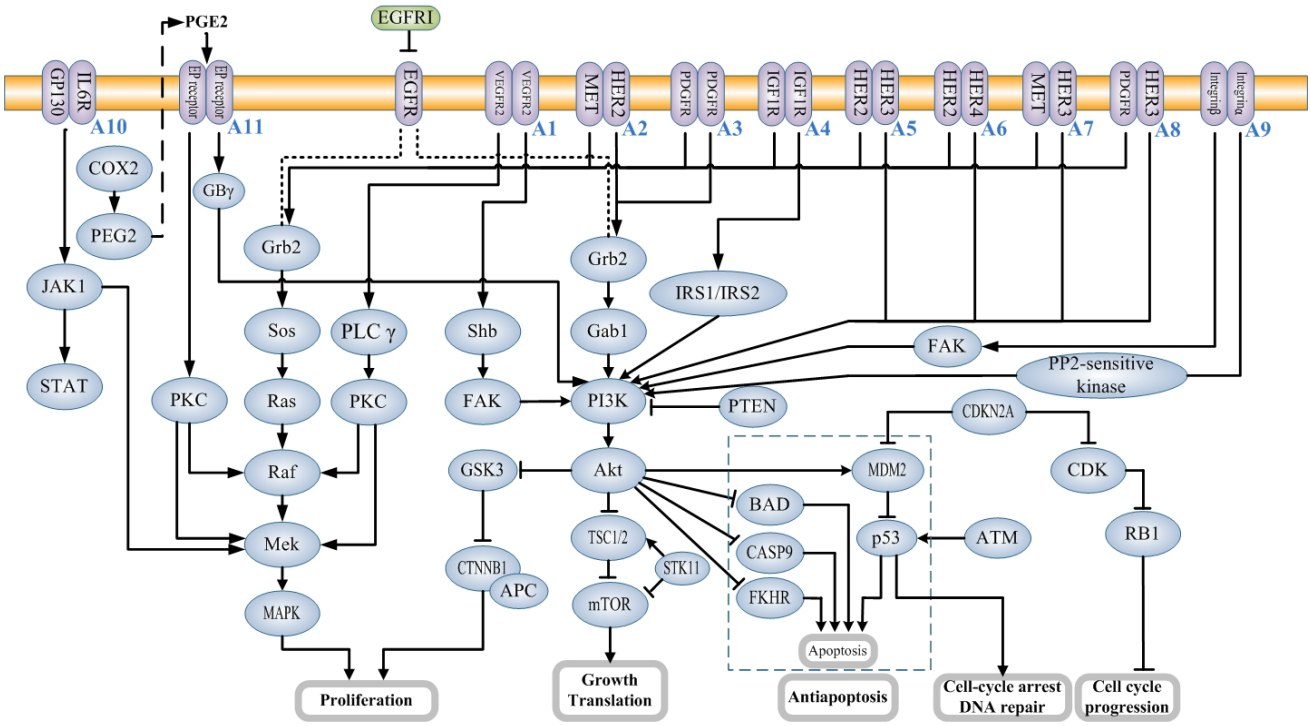
* Mutation was only reported in Ref (Thomas *et al.*, 2007); # PIK3CA mutation of JIMT-1 was reported by Ref (Jonsson *et al.*, 2007)
Abbreviations: ND, no sensitizing/resistant/activating mutation was detected according to COSMIC database and Ref 4.



Suplementary Figure S1 Map of EGFR pathway showing EGFR tyrosine kinase inhibitor (EGFRI) bypass mechanisms duo to downstream EGFR-independent signaling involving mutations resistant to EGFRI (D1), activating mutations in Raf (D2), Ras (D3), PI3K (D5), and AkT (D6), PTEN loss of function (D4), and enhanced accumulation of internalized EGFR by MDGI (D7). Proteins known to carry drug resistant mutations or activating mutations are in darker color and red label. The loss of function of PTEN is represented by dashed elliptic plate.



Supplementary Figure S2 Map of EGFR pathway showing EGFR tyrosine kinase inhibitor (EGFRI) bypass mechanisms duo to compensatory signaling of EGFR transactivation with HER2 (C1), MET (C2), IGF1R (C3), Integrin□1 (C4), and HER3 (C5). In particular, C3, C4 and C5 activates PI3K via IRS1/IRS2, FAK or a PP2-sensitive kinase, and direct interaction respectively



Supplementary Figure S3 Map of EGFR pathway showing EGFR tyrosine kinase inhibitor (EGFR-I) bypass mechanisms duo to alternative signaling of VEGFR2 activation (A1), HER2-MET transactivation (A2), PDGFR activation (A3), IGF1R activation (A4), HER2-HER3 transactivation (A5), HER2-HER4 transactivation (A6), MET-HER3 transactivation (A7), PDGFR-HER3 transactivation (A8), Integrin1 activation (A9), IL6 activation of IL6R-GP130 complex (A10), and Cox2 mediated activation of EP receptors (A11). In particular, VEGFR activates Raf and Mek via PLC□-PKC path and activates PI3K via Shb-FAK path, IGFR activates PI3K via IRS1/IRS2, and HER2-HER3, HER2-HER4, MET-HER3, and PDGFR-HER3 hetrodimers activate PI3K directly. The paths A9, A10, and A11 are via non-kinase receptors.

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