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Review

Co-targeting cancer drug escape pathways confers clinical advantage for multi-target anticancer drugs

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ABSTRACT

Recent investigations have suggested that anticancer therapeutics may be enhanced by co-targeting the primary anticancer target and the corresponding drug escape pathways. Whether this strategy confers statistically significant clinical advantage has not been systematically investigated. This question was probed by the evaluation of the clinical status and the multiple targets of 23 approved and 136 clinical trial multi-target anticancer drugs with particular focus on those co-targeting EGFR, HER2, Abl, VEGFR2, mTOR, PI3K, Alk, MEK, KIT, and DNA topoisomerase, and some of the 14, 7, 13, 20, 6, 5, 7, 2, 4 and 10 cancer drug escape pathways respectively. Most of the approved (73.9%) and phase III (75.0%), the majority of the Phase II (62.8%) and I (53.6%), and the minority of the discontinued (35.3%) multi-target drugs were found to co-target cancer drug escape pathways. This suggests that co-targeting anticancer targets and drug escape pathways confer significant clinical advantage and such strategy can be more extensively explored.

Abbreviations: Abl, Abelson murine leukemia viral oncogene homolog 1; AKT, protein kinase B; Alk, anaplastic lymphoma kinase; APAF-1, apoptotic protease activating factor 1; BIM, Bcl-2-like protein 11; c-KIT, mast/stem cell growth factor receptor; CML, chronic myeloid leukemia; Cox2, cyclooxygenase 2; EGFR, epidermal growth factor receptor; EphB4E, phrin type-B receptor 4; FAK, focal adhesion kinase; Flt3, FMS-like tyrosine kinase-3; GPCR, G protein-coupled receptor; HER2, human epidermal growth factor receptor 2; HER3, human epidermal growth factor receptor 3; HER4, human epidermal growth factor receptor 4; IGF1R, insulin-like growth factor 1 receptor; IL6, interleukin 6; IL6R, interleukin 6 receptor; GP130, glycoprotein 130; IRS1, insulin receptor substrate 1; IRS2, insulin receptor substrate 2; KIT, mast/stem cell growth factor receptor; MDGI, mammary-derived growth inhibitor; MET, hepatocyte growth factor receptor; mTOR, mammalian target of rapamycin; NSCLC, non-small cell lung cancer; PDGF-C, platelet-derived growth factor C; PDGFR, platelet-derived growth factor receptor; PI3K, phosphoinositide 3-kinase; PKC-ϵ, protein kinase C-ϵ; PLCγ, phospholipase Cγ; PTEN, phosphatase and tensin homolog; Shb, Src homology 2 domain containing adaptor protein B; VEGF, vascular endothelial growth factor; VEGFR2, vascular endothelial growth factor receptor 2; VEGFR3, vascular endothelial growth factor receptor 3.

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Contents

1. Introduction

Apart from the classical drug resistance mechanisms mediated by the efflux pumps, drug target alterations and pro-survival pathways [1,2], recent investigations have consistently suggested that clonal heterogeneities that promote drug escape signalling is a major resistance mechanism against targeted anticancer therapies [3–6], and the multi-targeting of the primary cancer target and the corresponding drug escape pathways may reduce drug resistance and thus enhance anticancer effects [4,7–10]. For instance, a deletion polymorphism in Bcl-2-like protein 11 (BIM) mediates resistance and inferior clinical response to Abl and EGFR inhibitors in chronic myeloid leukemia (CML) and non-small cell lung cancer (NSCLC) respectively, which may be overcome by co-targeting BIM substrates or down-stream pathway [4]. In another case, Hepatocyte growth factor receptor (MET) overexpression induces gefitinib resistance in NSCLC partly by down-regulating several miRNAs that subsequently reduces BIM, APAF-1 and PKC-ϵ, which could be overcome by simultaneously inhibiting MET and EGFR [11].

A number of multi-target drugs, such as the dual-target EGFR and HER2 inhibitor Afatinib [12] and VEGFR2 and VEGFR3 inhibitor Lenvatinib [13], have shown clinical efficacies and approved for the treatment of various cancers (e.g., Afatinib for metastatic non-small cell lung cancers, and Lenvatinib for thyroid cancer not responding to radioiodine). Additional number of multi-target drugs such as the EGFR, VEGFR2, HER2 and EphB4 inhibitor XL647 [14] have shown promising results in clinical trials. The question is whether the multi-target anticancer drugs co-targeting the primary cancer target and the corresponding drug escape pathways indeed confer clinical advantage over the multi-target anticancer drugs not co-targeting these pathways. It is possible to study this question because as many as 159 multi-target anticancer drugs have been clinically tested so far (Table 1, Supplementary Table S1) and a significant number of cancer drug escape pathways have been exposed for various targeted anticancer drug classes that include most of the 159 multi-target anticancer drugs (Table 2, Supplementary Tables S2–4), which enables the analysis of these multi-target drugs from the perspectives of their inhibition of the corresponding drug escape pathways.

2. Drug escape mechanisms and pathways in cancers

Cancers are frequently addicted to [15] or heavily rely on [16] certain oncogenes for growth and survival, which have been exploited for developing effective anticancer drugs inhibiting these oncogenes [15]. Nonetheless, cancers can escape the targeted therapies by multiple mechanisms and pathways [4,7–9]. The typical mechanisms of the activation of the drug escape signalling are illustrated in Figs. 1–4 by using EGFR pathway as an example. Fig. 1 shows the EGFR pathway together with its downstream effectors. It has 14 drug escape signalling routes regulated by 18 genes (Supplementary Table S3). These drug escape signalling routes can be divided into three classes. The first class (Fig. 2) includes down-stream EGFR-independent signalling via EGFR inhibitor resistant mutations (D1) [17–19], activating mutations in Raf (D2), Ras (D3), PI3K (D5), and AKT (D6) [18,20–22], PTEN loss of function (D4) [23], and the elevated EGFR internalization driven by MDGI (D7) [24].

The second class (Fig. 3) involves compensatory signalling from EGFR transactivation with HER2 (C1) [25,26], MET (C2) [8,27], IGF1R (C3) [28], Integrin β1 (C4) [29], and HER3 (C4) [30]. C3, C4 and C5 activate PI3K via IRS1/IRS2, FAK or a PP2-sensitive kinase, and direct interaction respectively. The ligands of EGFR or certain other receptor tyrosine kinases, e.g., ErbB family members, are capable of inducing not only its own receptor homodimers but also heterodimers with other selected receptor tyrosine kinases and GPCRs [31,32], which significantly expands the signalling potential of EGFR [31,32] and enables the escape of EGFR inhibition in cancers [8,25–28,30].

The third class (Fig. 4) covers alternative signalling of VEGFR2 activation (A1) [33], HER2–MET transactivation (A2) [8,27], PDGFR activation (A3) [34], IGF1R activation (A4) [35], HER2–HER3 transactivation (A5) [26,36], HER2–HER4 transactivation (A6) [26,36], MET–HER3 transactivation (A7) [37], PDGFR–HER3 transactivation (A8) [8], Integrin β1 activation (A9) [29], IL6 activation of IL6R–GP130 complex (A10) [38], and Cox2 mediated activation of EP receptors (A11) [39]. Specificaly, VEGFR activates Raf and Mek via the PLCγ–PKC route and activates PI3K via the Shb–FAK route, IGFR activates PI3K via IRS1/IRS2, and HER2–HER3, HER2–HER4, MET–HER3, and PDGFR–HER3 hetrodimers activate PI3K directly. The routes A9, A10, and A11 are via non-kinase receptors with a certain downstream protein activating MEK and/or AKT pathways.

3. Typical modes of actions of the multi-target anticancer drugs that co-target anticancer target and escape pathway

Figs. 5 and 6 illustrate the typical modes of actions of multi-target anticancer drugs in co-targeting anticancer targets and escape pathways. An example of such drug is Pazopanib approved for the treatment of metastatic soft-tissue sarcoma [40]. This drug is a multi-target VEGFR2, VEGFR3, PDGFR, c-KIT inhibitor developed primarily as a VEGFR targeted antitumor and antiangiogenic agent [41]. Angiogenesis activity of VEGFR is complemented by PDGFR [42], PDGF-C induces maturation of blood vessels and attenuates the response to anti-VEGF treatment [43], VEGF-null cells have been found to require PDGFR alpha signaling-mediated stromal fibroblast recruitment for tumorigenesis [44]. Kit inhibitor reportedly reduces angiogenesis by inhibiting Kit-mediated VEGF expression [45]. Therefore, the multi-target activity of Pazopanib against PDGFR and c-KIT is expected to complement its primary VEGFR inhibitory activities by hindering the PDGFR and c-KIT mediated alternative angiogenic signaling.

Another example is Afatinib approved for the treatment of advanced metastatic NSCLC after failure of erlotinib, gefitinib and chemotherapy [46] and in phase III trial for lung adenocarcinoma

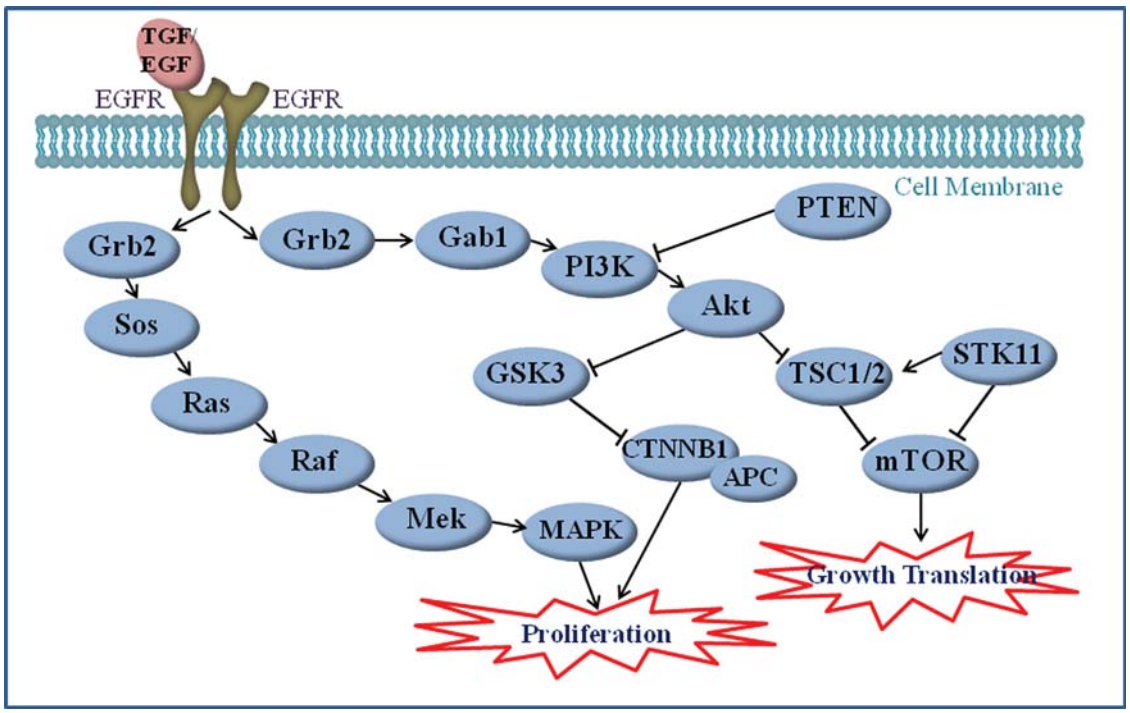

Fig. 1. Map of the major signaling pathways of the EGFR and downstream effectors relevant to cancers. Binding of specific ligands (e.g., EGF, heparin-binding EGF, TGF-a) may generate homodimeric complexes resulting in conformational changes in the intracellular EGFR kinase domain, which lead to autophosphorylation and activation. Consequently, signaling molecules, such as growth factor receptor-bound protein-2 (Grb-2), Shc and IRS-1 are recruited to the plasma membrane. Activation of several signaling cascades is triggered predominately by the RAS-to-MAPK and the PI3K/Akt pathways, resulting in enhanced tumour growth, survival, invasion and metastasis.

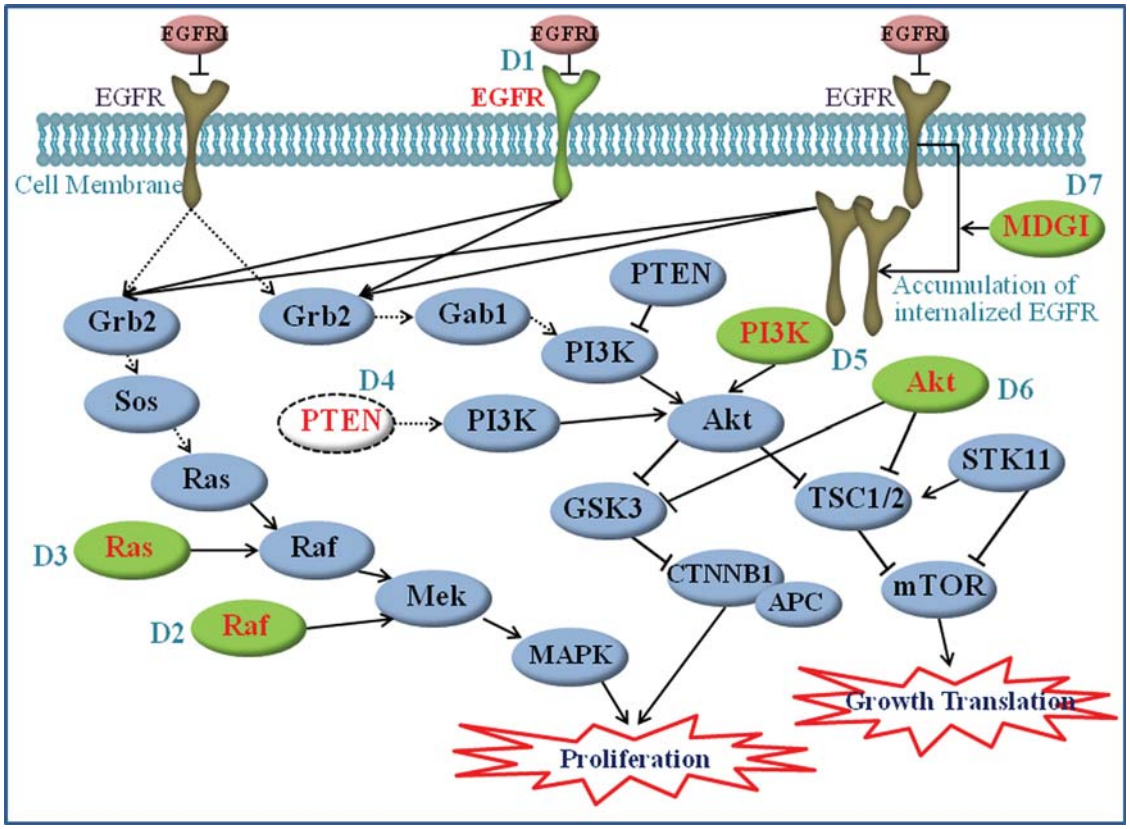

Fig. 2. Map of EGFR pathway showing EGFR tyrosine kinase inhibitor (EGFRI) bypass mechanisms due to downstream EGFR-independent signaling involving mutations resistant to EGFRI (D1), activating mutations in Raf (D2), Ras (D3), PI3K (D5), and AkT (D6), PTEN loss of function (D4), and enhanced accumulation of internalized EGFR by MDGI (D7). Proteins known to carry drug resistant mutations or activating mutations are in green color and red label. The loss of function of PTEN is represented by dashed elliptic plate.

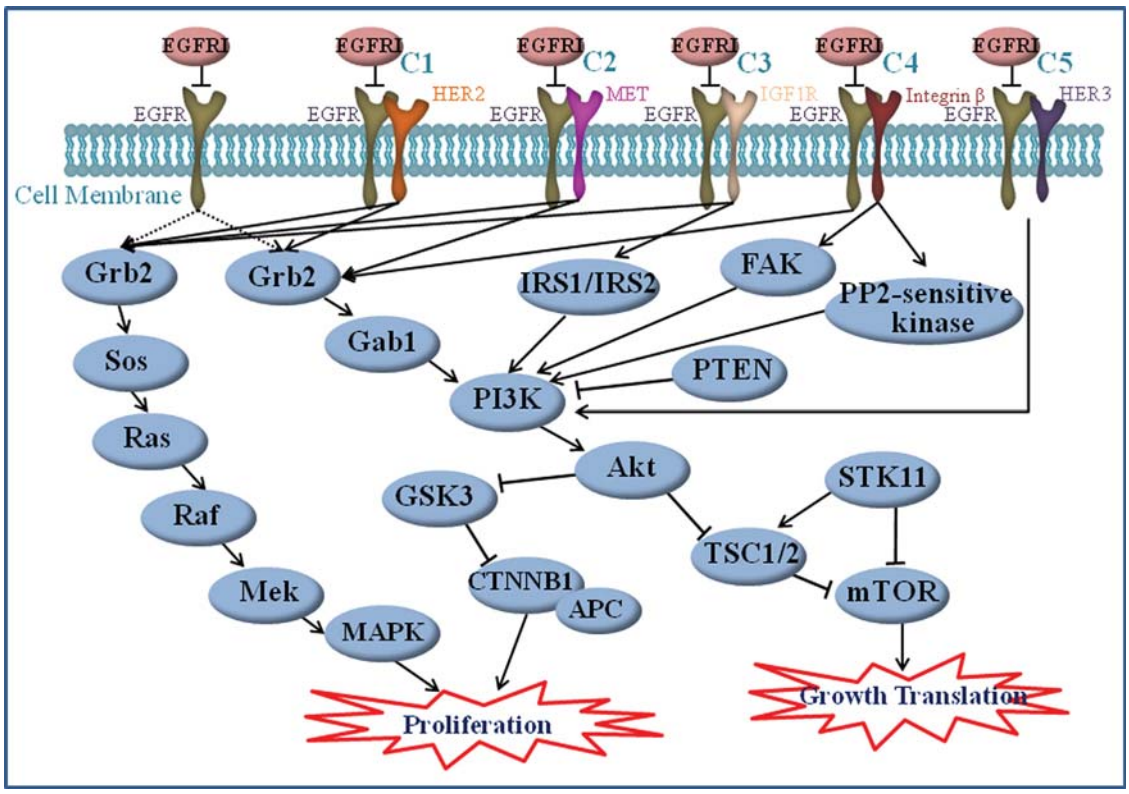

Fig. 3. Map of EGFR pathway showing EGFR tyrosine kinase inhibitor (EGFRI) bypass mechanisms due to compensatory signaling of EGFR transactivation with HER2 (C1), MET (C2), IGF1R (C3), Integrin β1 (C4), and HER3 (C5). In particular, C3, C4 and C5 activates PI3K via IRS1/IRS2, FAK or a PP2-sensitive kinase, and direct interaction respectively.

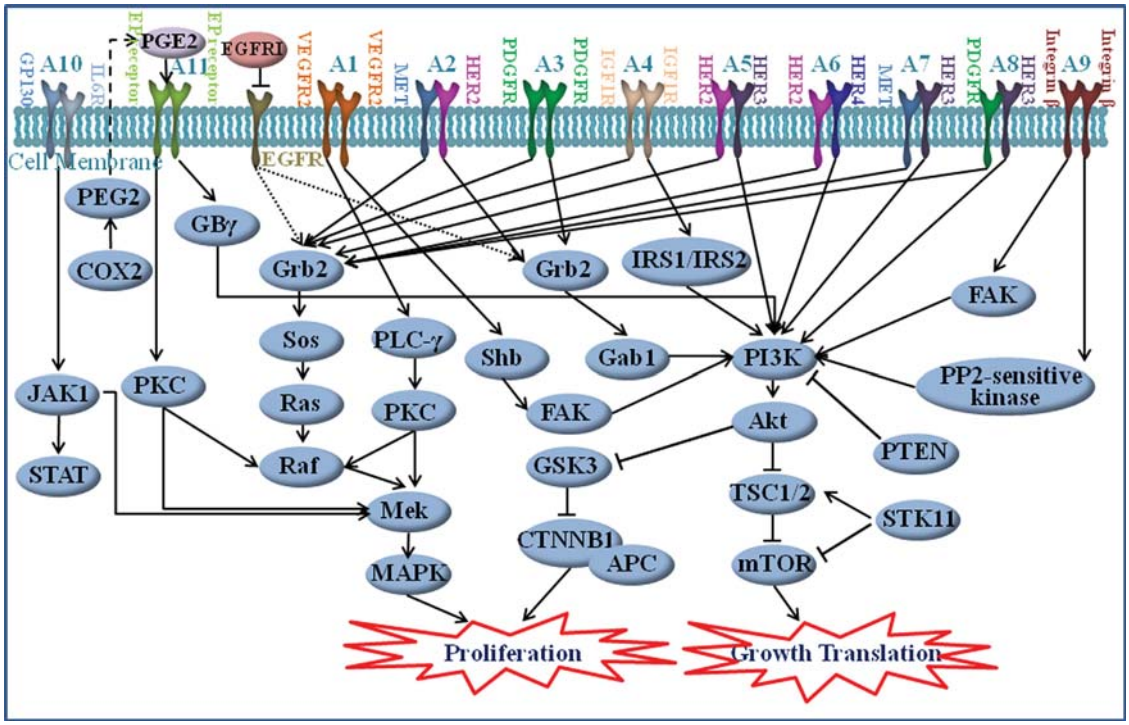

Fig. 4. Map of EGFR pathway showing EGFR tyrosine kinase inhibitor (EGFR-I) bypass mechanisms due to alternative signaling of VEGFR2 activation (A1), HER2–MET transactivation (A2), PDGFR activation (A3), IGF1R activation (A4), HER2–HER3 transactivation (A5), HER2–HER4 transactivation (A6), MET–HER3 transactivation (A7), PDGFR–HER3 transactivation (A8), Integrin β1 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 PLCγ–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.

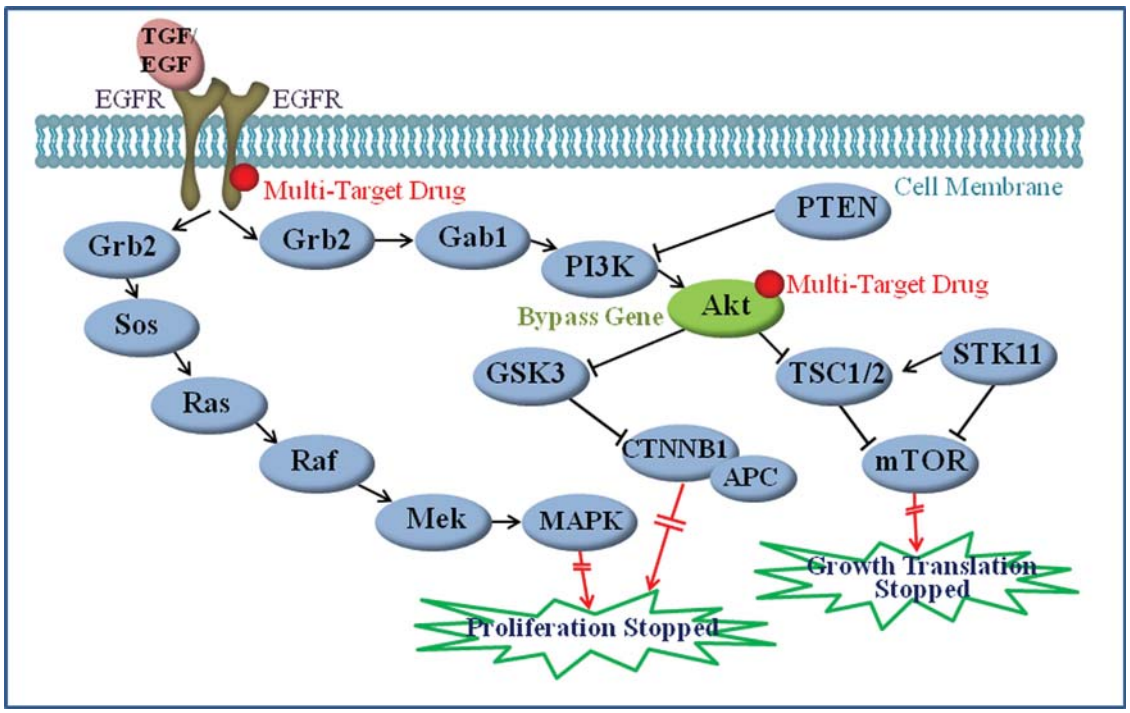

Fig. 5. Co-targeting of the EGFR and bypass signaling gene Akt in the EGFR and downstream pathways. Binding of specific ligands (e.g., EGF, heparin-binding EGF, TGF-a) may generate homodimeric complexes resulting in conformational changes in the intracellular EGFR kinase domain, which lead to autophosphorylation and activation. Consequently, signaling molecules, such as growth factor receptor-bound protein-2 (Grb-2), Shc and IRS-1 are recruited to the plasma membrane. Activation of several signaling cascades is triggered predominately by the RAS-to-MAPK and the PI3K/Akt pathways, resulting in enhanced tumour growth, survival, invasion and metastasis. Akt activating mutation mediated EGFR-independent Akt signaling and could lead to resistance against EGFR inhibitor. Co-inhibition of EGFR and Akt effectively inhibit both the EGF mediated and Akt activating mutation mediated growth signals.

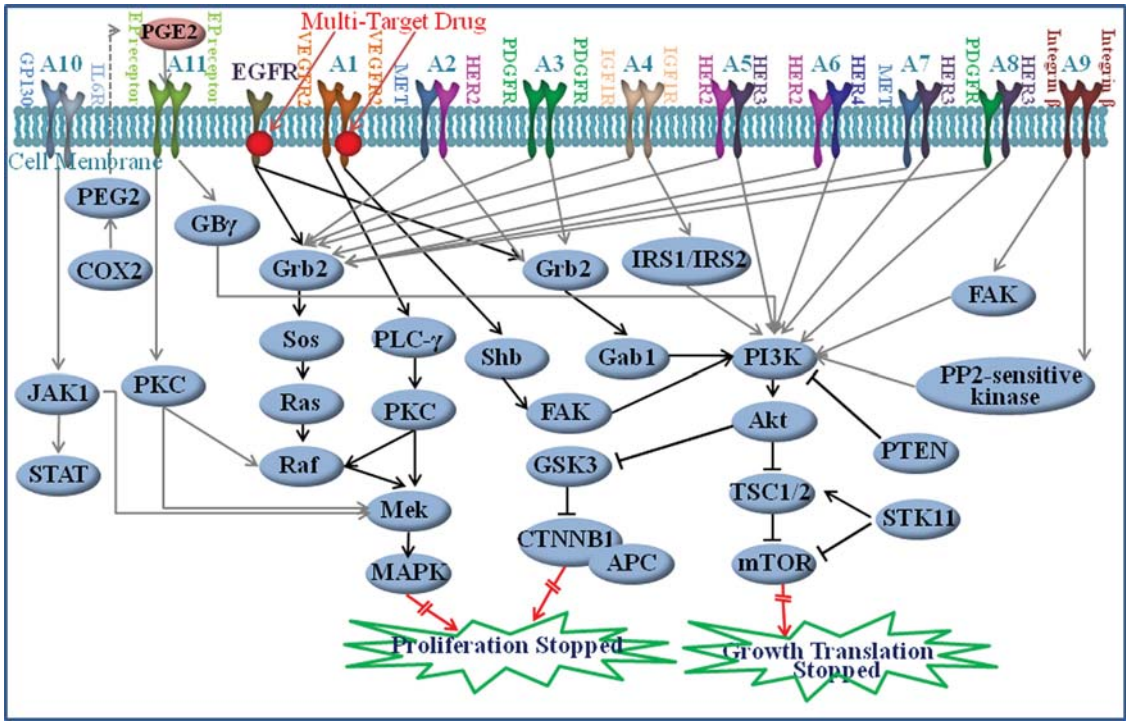

Fig. 6. Map of EGFR pathway showing EGFR tyrosine kinase inhibitor bypass mechanisms due to alternative signaling of VEGFR2 activation (A1), HER2–MET transactivation (A2), PDGFR activation (A3), IGF1R activation (A4), HER2–HER3 transactivation (A5), HER2–HER4 transactivation (A6), MET–HER3 transactivation (A7), PDGFR–HER3 transactivation (A8), Integrin a/ß 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 PLCγ–PKC path and activates PI3K via Shb–FAK path. The multi-target drug co-targeting EGFR and Ai ($i = 1, \ldots, 11$) effectively inhibit the EGFR signaling and Ai mediated bypass signaling.

Table 1
Statistics of the approved, clinical trials, and discontinued multi-target anticancer drugs targeting and not targeting a known cancer drug escape pathway.

Drug category	Total no. of multi-target drugs	No. (%) of multi-target drugs targeting a known cancer drug escape pathway	No. (%) of multi-target drugs not targeting any known cancer drug escape pathway
Approved	23	17 (73.9%)	6 (26.1%)
Phase III	20	15 (75.0%)	5 (25.0%)
Phase II	43	27 (62.8%)	16 (37.2%)
Phase I	56	30 (53.6%)	26 (46.4%)
Discontinued	17	6 (35.3%)	11 (64.7%)
Total	159	94 (59.1%)	65 (40.9%)

with EGFR mutations [47]. This drug is a dual-target EGFR and HER2 inhibitor, which has been developed primarily as a new generation EGFR inhibitor against lung cancers such as NSCLC [48] and lung adenocarcinoma tumors harboring EGFR mutations [49]. It has been found that, EGFR inhibition leads to HER2 upregulation and subsequent induction of compensatory EGFR–HER2, HER2–HER3, HER2–HER4 heterodimerisation, which promotes alternative signaling that escapes EGFR inhibition [25,26,36,50]. This alternative signalling is blocked by the HER2 inhibitory activity of Afatinib to complement its EGFR inhibitory activity for enhanced anticancer efficacies.

4. Analysis of the multi-target anticancer drugs in clinical use and trials

We evaluated the clinical trial status and the multiple targets of the 23 approved and 136 clinical trial multi-target anticancer drugs. There are 14, 7, 13, 20, 6, 5, 7, 2, 4 and 10 literature-reported cancer drug escape pathways for EGFR, HER2, Abl, VEGFR2, mTOR, PI3K, Alk, MEK, KIT, and DNA topoisomerase inhibitors (Table 2, Supplementary Tables S2–4), and 95 and 64 clinically tested multi-target anticancer drugs co-targeting and not co-targeting these pathways (Table 1, Supplementary Table S1) respectively. The approved, clinical trial, and discontinued clinical trial multi-target anticancer drugs were from Thomson Reuters Pharma™ database 2010 version, the TTD Therapeutic target database 2014 version [51], and 2014 report of medicines in development for cancer released by the PhRMA with the multiple targets of every drug evaluated based on their reported relevance to anticancer efficacies in in-vitro and in-vivo tests [52]. The cancer drug escape pathways and their regulatory proteins were from literature search based on the reports that each protein induces drug resistance which be significantly reduced by modulating the protein in in-vitro or in-vivo tests [4,7–9].

5. Clinical advantage of the multi-target anticancer drugs that co-target anticancer target and escape pathway

Most of the approved (73.9%) and phase III (75.0%), the majority of the Phase II (62.8%) and I (53.6%), and the minority of the discontinued (35.3%) multi-target drugs were found to co-target a cancer drug escape pathway (Table 1). This indicates that multi-target drugs that co-target known cancer drug escape pathways have significantly higher probability of entering advanced clinical trial phases and thus appear to be clinically more advantageous than multi-target drugs not co-targeting such a pathway. This is also consistent with and provides partial explanation for a recent finding that clinically tested anticancer kinase inhibitors have lower attrition rates than other anticancer drugs [53]. It is noted that a significantly higher percentage of clinically tested kinase inhibitors are multi-target drugs co-targeting a cancer escape pathway. Specifically, 27.3% and 2.9% of the clinically tested anticancer kinase inhibitors and non-kinase-inhibitor drugs are multi-target drugs co-targeting cancer drug escape pathways respectively. Therefore, in addition to the critical roles of the targeted kinases in cancers, the lower clinical attrition rates of kinase inhibitors may be partly attributed to the co-targeting of cancer drug escape pathways.

6. Perspectives

Our analysis indicates the significant clinical advantage of multi-target drugs co-targeting cancer drug escape pathways. In spite of these statistically indicated advantages, clinical trial studies nonetheless have shown that some multi-target drugs effective in certain cancers are not as effective in other cancers [54,55], even though some of these cancers are supposedly treatable by the respective drug [55]. For instance, the multi-target VEGFR, PDGFR, FGFR and c-KIT angiogenesis inhibitor Pazopanib, approved for the advanced/metastatic renal cell carcinoma and advanced soft tissue sarcomas, has been reported to produce limited activity in NSCLC-NS patients who have experienced disease progression upon bevacizumab treatment [55]. The low drug efficacy in these patients may be partly due to the tumor activation of multi-pathway signaling and the compensatory actions [56,57] that promote more robust growth, survival or logistics (e.g., angiogenesis) in adaptation to the previous treatment (e.g., bevacizumab therapy), some of which is beyond the reach of a new treatment (e.g., Pazopanib therapy). Because of the considerable number of drug-escape pathways against each anticancer drug (Supplementary Table S2), an individual multi-target drug with limited target coverage is insufficient in coping with the multiple escape mechanisms. There is a need for the development of a set of multi-target drugs or drug combinations that individually cover subset and collective cover all of the drug-escape pathways and compensatory actions.

Rational multi-target drug discovery methods that explore network approaches [58,59], structure-activity relationships [60], quantitative-structure activity relationships [61–63], pharmacophore [64], modeling [65] machine learning [66,67] techniques have been developed and applied to the discovery of multi-target drugs [68–71]. Multi-target drug discovery efforts have also been directed at more extensive exploration of new molecular types [72] and natural products [73]. These and other efforts will enable more extensive and personalized targeting of cancer drug escape pathways for enhanced anticancer therapeutics.

Conflicts of interest

The authors declare no competing financial interests.

Author contributions

Y.Z. C. and Y.Y. J. conceived and designed the research. L. T., F. Z., F. X., and Z. C. collected and analyzed the data. Y.Z. C., L. T., and F. Z. contributed to the preparation of the manuscript and wrote the paper.

Table 2
Cancer escape pathways targeted by the approved, clinical trial, and discontinued multi-target anticancer drugs.

Drug class	Targeted cancers	No. of known cancer drug-escape pathways	No. of drug escape regulatory proteins	Drug escape regulatory protein (escape pathway) targeted by multi-target anticancer drugs	No. of multi-target anticancer drugs targeting the bypass protein					Total no. of multi-target drugs targeting/not targeting a known drug escape pathway
					Approved	Phase III	Phase II	Phase I	Discontinued	
EGFR inhibitor	Lung, pancreatic, colon, head and neck, liver, brain	14	18	HER2 (ErbB)	2	3	3	5	0	19/0
				HER3 (ErbB)	0	0	5	0	0	
				VEGFR2 (VEGF)	1	0	0	0	0	
				IGF1R (IGFR)	0	0	1	0	0	
				ALK (ALK)	0	0	1	0	0	
HER2 inhibitor	Breast	7	11	EGFR (ErbB)	2	3	3	5	0	14/1
				HER3 (ErbB)	0	0	3	0	0	
BCR-Abl inhibitor	Leukemia	13	20	Src (SFK-dependent)	2	0	1	0	2	11/2
				Aurora (Aurora)	0	0	2	0	1	
				PDGFR(PDGFR & SFK-dependent)	2	0	0	0	0	
				Kit (Kit)	2	0	0	0	0	
				Fyn (SFK-dependent)	1	0	1	0	0	
				Lyn (SFK-dependent)	0	0	1	0	0	
				JAK2 (Jak2/Stat5, apoptosis)	0	0	1	0	0	
				Flt3 (Flt3)	0	0	0	0	1	
VEGFR2 inhibitor	GIST, kidney, liver, renal, lung, colon, breast, AML leukemia, solid tumor	20	28	PDGFR (PDGFR)	6	4	3	2	1	37/6
				VEGFR3 (VEGF)	3	4	2	5	0	
				c-Met (HGFR)	1	0	3	1	0	
				FGFR (FGFR)	2	4	3	2	0	
				Kit (Kit)	3	2	2	2	1	
				EGFR (ErbB)	1	1	0	0	0	
				CSF-1R (CSF1R mediated pathways)	1	1	0	0	0	
				Heparanase (SFK-RTK)	0	0	1	0	0	
				Raf (MAPK)	1	0	0	1	0	
mTOR inhibitor	Breast, brain, lung, renal, solid tumor	6	7	PI3K (Akt-mTOR)	0	0	4	5	0	9/1
PI3K inhibitor	Breast, brain, NSCLC, solid tumor	5	5	mTOR (Akt-mTOR)	0	0	4	5	0	12/0
				Akt (Akt-mTOR)	0	0	0	1	0	
				Plk1 (Plk-PTEN-Akt)	0	1	0	0	0	
				HDAC (HDAC-histone H3 acetylation –Akt)	0	0	0	1	0	
Alk inhibitor	Non-small cell lung cancer	7	6	ROS1 (FIG-ROS1)	2	0	0	1	0	6/1
				c-MET (HGFR)	1	0	0	0	0	
				IGF1R (IGFR)	1	0	0	0	0	
				EGFR (ErbB)	0	0	1	0	0	
				TRK (TRK)	0	0	0	2	0	
				RET (RET)	1	0	0	0	0	
Mek inhibitor	Solid tumor	2	3	Raf (MAPK)	0	0	0	4	0	5/0
				MEKK (MAPK)	0	0	0	1	0	
Kit inhibitor	Solid tumor, melanoma, pancreas	4	5	PDGFR (PDGFR)	4	5	2	1	1	13/1
DNA Topoisomerase inhibitor	Breast, head and neck, leukemia, ovary, prostate	10	20	XIAP (Apoptosis)	0	1	0	0	0	1/11

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.phrs.2015.09.019.

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