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Targeting Src family kinases in anti-cancer therapies: turning promise into triumph

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Abstract

Src is a non-receptor tyrosine kinase that is deregulated in many types of cancer. Decades of research have revealed the crucial role of Src in many aspects of tumor development, including proliferation, survival, adhesion, migration, invasion and, most importantly, metastasis, in multiple tumor types. Despite extensive pre-clinical evidence which warrants targeting Src as a promising therapeutic approach for cancer, Src inhibitor(s) show only minimal therapeutic activity in various types of solid tumors as a single agent in recent early-phase clinical trials. In this review, we highlight the most recent advances from preclinical studies and clinical trials that shed light on potential clinical use of Src inhibitor-containing combinatorial regimens in overcoming resistance to current anti-cancer therapies and in preventing metastatic recurrence.

Src family kinases and cancer

The c-Src gene is a “proto-oncogene” in normal mammalian cells discovered in 1970s. The protein product of c-Src gene (Src) belongs to the Src family of kinases (SFKs), a group of non-receptor tyrosine kinases [1]. As SFKs are pleiotropic kinases involved in many cellular events, it is not surprising that aberrant activation of Src signaling contributes to diverse aspects of tumor development [1]. SFKs are important mediators of tumor cell proliferation and survival. The most prominent and well-studied function of Src is its extensive interaction with transmembrane receptor tyrosine kinases (RTKs) at the cell membrane via its SH2 and SH3 domains. Src has long been known to interact with epidermal growth factor receptor (EGFR), human epidermal growth factor receptor 2 (HER2 or ErbB2), platelet-derived growth factor receptor (PDGFR), insulin-like growth factor-1 receptor (IGF-1R) and c-Met/hepatocyte growth factor receptor (HGFR) (Figure 1). Through these interactions, Src integrates and regulates RTK signaling and directly transduces survival signals to downstream effectors e.g. phosphoinositide 3-kinases (PI3Ks), Akt and signal transducer and activator of transcription 3 (STAT3). Src can also be activated by other membrane receptors including integrins and erythropoietin receptor (EpoR) (Figure 1) [1, 2].

Src is also known to be crucial during tumor metastasis mainly due to its role in regulating the cytoskeleton, cell migration, adhesion and invasion [2]. Through interaction with p120 catenin, Src activation promotes dissociation of cell-cell adherens junctions and facilitates cell mobility (Figure 1). Through phosphorylation of focal adhesion kinase (FAK), Src activation also stabilizes focal adhesion complexes, which consists FAK, paxillin, RhoA and other components, and enhances cell adhesion to extracellular matrix (Figure 1) [2]. Additionally, Src also plays a role in regulating the tumor microenvironment. Under hypoxic

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conditions, Src activation promotes angiogenesis through stimulation of vascular endothelial growth factor (VEGF), matrix metalloproteinase (MMPs) and interleukin-8 (IL-8) expression. Src-mediated VEGF secretion elicits angiogenic signaling in endothelial cells and Src activation in osteoclasts facilitates osteolytic bone metastasis [1, 3].

Extensive pre-clinical evidence warrants targeting Src as a promising therapeutic approach for cancer. However, the therapeutic efficacies of Src inhibitors as a single agent in treating various types of solid tumors are not encouraging in phase II clinical trials. In this review, we revisited the extensive literature on Src by emphasizing the most recent advances from preclinical and clinical studies. We further discussed the potential clinical benefit of Src inhibitor-containing combinatorial regimens in cancer treatment and in overcoming resistance to current anti-cancer therapies.

Emerging new roles of SFKs in tumor progression and metastatic recurrence

The roles of Src in tumor progression and metastasis have been well-documented [1]. It is interesting that recent investigations have revealed some intriguing new roles of SFKs in tumor progression and metastasis.

Tumor cell migration and local invasion, the first step in the metastatic cascade, requires the formation of actin-based membrane protrusions that promote directional migration and extracellular matrix (ECM) degradation. Twist1, a transcription factor, is well known to promote epithelial mesenchymal transition (EMT) and metastasis. Twist1 was recently shown to induce PDGFR α expression, protrusions formation on the cell membrane (e.g. invadopodia formation) and invadopodia-mediated matrix degradation through Src activation [4]. A Src inhibitor inhibited the invadopodia formation and prevented tumor cell migration [5]. In addition to actin-based invadopodia, tumor cells also form microtubule-based microtentacle (McTN) protrusions involved in capillary retention of circulating tumor cells to distant organ sites [6]. While constitutive activation of Src promotes invadopodia formation, invadopodia suppress McTN formation. Consistent with this, a Src inhibitor, SU6656, inhibited invadopodia formation while promoting McTN formation [6, 7]. These findings depict a dual role of Src in regulating cytoskeletal components. Src activation clearly promotes tumor cell invasion and migration at the primary tumor site when invadopodia formation is dominated, thus, inhibition of Src activity suppresses the tumor migration, invasion and dissemination from primary tumor sites to the circulation. However, once tumor cells are disseminated, inhibition of Src activity by Src inhibitor promotes higher level of McTN formation and may enhance McTN-mediated capillary retention of circulating tumor cells to distant organ sites [7]. The functional balance between invadopodia and McTN determines the final fate of disseminated tumor cells [6], which needs to be taken into careful consideration when designing Src-targeting therapies.

Src also plays a role in the survival of disseminated cells and metastatic recurrence after the cells arrive at distant organs. The gene signature of Src pathway activation was recently shown to be strongly associated with late recurrence of bone metastasis in breast cancer. Independent of breast cancer subtypes, SFK activation is crucial for disseminated tumor cells to maintain survival signaling in response to chemokine (C-X-C motif) ligand 12 (CXCL-12) and tumor necrosis factor (TNF)-related apoptosis-inducing ligands (TRAIL) in the bone microenvironment, which appears to be essential for metastatic recurrence in the bone [8]. Other recent findings also indicate that Src activation is an important contributor to metastatic recurrence. In a lung fibrosis model, the outgrowth of disseminated tumor cells (dormant metastatic cells) in the lung is dependent on β 1-integrin-Src signaling [9]. Src activation leads to extracellular signal-regulated kinase (ERK)-dependent formation of actin

stress fibers and subsequent activation of survival signals, which are critical for outgrowth of metastatic cells. This metastatic outgrowth can be completely suppressed by SFK inhibitors, e.g. saracatinib [9].

One of the prominent features of metastatic tumor cells is resistant to programmed cell death induced by dissociation from ECM (anoikis). Src activation also plays an important role in conferring anoikis resistance during tumor progression. In lung adenocarcinomas, tumor cells with hyper-activation of Src are resistant to anoikis, which can be reverted by treatment of ABT-263, a potent inhibitor for anti-apoptotic molecule Bcl-2 [10]. Src also serves as the cellular redox sensor. Increased angiopoietin-like 4 protein (ANGPTL4) in cancer cells hijacks integrin signaling to stimulate NADPH oxidase-dependent production of O_2^- . The resulting disrupted redox balance activates Src and its downstream PI3K-Akt pro-survival pathways, which makes tumor cells more resistant to anoikis [11].

Recently, interesting roles of Src signaling in regulating host immune response and tumor-initiating cells have been reported. Src activity is activated under hypoxic conditions through the hypoxia-inducible factor 1 α (HIF-1 α)-STAT3-Src axis [12], which activates hypoxia-induced autophagy enabling tumor cells to escape cytotoxic T cell-mediated killing [12]. The finding implies that targeting Src may potentially re-sensitize tumor cells to cytotoxic T cell-mediated host immune response, which may enhance the therapeutic efficacy of the current first-line anti-cancer therapies. Src signaling is also involved in B cell receptor signaling. Lyn, a member of the SFKs, negatively regulates B cell receptor signaling [13]. Overexpression of Lyn disrupts the balance of survival and apoptotic signaling resulting in B-cell chronic lymphocytic leukemia [13].

SFKs in therapeutic resistance

Activation of Src signaling has been implicated in conferring therapeutic resistance to leukemia treatment, targeted anti-endocrine/RTK therapies, as well as traditional chemo and radiation therapies [14].

Resistance to current anti-leukemia treatment

SFKs are known to be functionally important in chronic myelogenous leukemia (CML) cells due to the interaction between SFKs and the oncogenic BCR-ABL fusion protein. Via kinase-dependent and -independent mechanisms, the SFK members Hck and Lyn readily interact with BCR-ABL, which cannot be inhibited by the BCR-ABL inhibitor imatinib [15]. Furthermore, this interaction between SFKs and BCR-ABL appears to be crucial for the transformation activity of BCR-ABL, which is particularly essential for BCR-ABL-driven B cell leukemia [16]. Clinically, abnormal activation of SFKs strongly correlates with imatinib and dasatinib resistance in a longitudinal study of patients with imatinib-resistant CML [17]. Recent evidence also suggested that SFK activation is common in CD9+ leukemia cells, the putative cancer stem cells (CSCs) of human B-cell acute lymphoblastic leukemia [18], which may lead to resistance to imatinib.

Endocrine resistance

Src signaling is involved in steroid receptor signaling and endocrine resistance. Several studies have demonstrated interactions and cross-talks among Src signaling, estrogen receptor (ER) and androgen receptor (AR) pathways. Src activation is observed in up to 40% of ER-positive breast cancers. Synergistic interaction between EGFR, ER and Src facilitates hormone receptor signaling and confers resistance to endocrine therapies [19]. Src activation is shown to contribute to tamoxifen resistance in pre-clinical models and is associated with a poor patient response to tamoxifen clinically [20]. Targeting Src together with anti-estrogen treatment can greatly suppress the proliferation of tamoxifen-resistant breast cancer cells

[21] (Figure 2, No. 5). In prostate cancer, Src is involved in the initial transition of prostate cancer from a castration-sensitive to a castration-resistant state. Inhibiting Src activity suppresses androgen-independent tumor cell proliferation [22]. Recent genomic profiling studies of prostate cancer cell lines also demonstrated an inverse correlation between Src activity and androgen signaling, implying that Src activity plays a role in endocrine resistant prostate tumors [23].

Resistance to RTK-targeting therapies

Trastuzumab is an iconic example of RTK-targeting therapy widely used for the treatment of patients with metastatic breast tumors overexpressing human epidermal growth factor receptor 2 (HER2). However, resistance to anti-HER2 therapy is a clinical challenge. Src activation plays a crucial role in conferring resistance to anti-HER2 therapy (trastuzumab and lapatinib) in HER2-overexpressing breast cancers [24]. HER2 directly associates with Src, activates Src signaling, and promotes Src protein synthesis and stability [25]. One of the important anti-tumor mechanisms of trastuzumab is inhibition of HER2-mediated Src activation and subsequent reactivation of the tumor suppressor PTEN (phosphatase and tensin homolog) [26]. However, Src signaling is significantly up-regulated in both *de novo* and acquired trastuzumab resistant tumors, antagonizing the efficacy of trastuzumab. Multiple up-stream alterations (e.g. RTK re-programming and PTEN deficiency) can lead to Src hyper-activation [24]. Similarly, the HER2 oncogenic variant HER2Delta16 also induces Src function and activates Src downstream survival signaling pathway to confer trastuzumab resistance [27]. Additionally, EpoR is co-expressed with HER2 in breast cancer cells and when recombinant human erythropoietin (rHuEPO) binds to EpoR, it leads to Jak2-mediated activation of Src and confers trastuzumab resistance [28]. Furthermore, transforming growth factor beta (TGF β) integrates HER2 receptor and integrin signaling, leading to Src-FAK pathway activation that confers trastuzumab resistance [29]. Recently, growth differentiation factor 15 (GDF15), which has a similar structure to TGF β , was shown to confer trastuzumab resistance via TGF β and Src-dependent hyper-phosphorylation of HER2. Inhibition of GDF15-mediated phosphorylation of Src restored trastuzumab response [30]. Screening of a large cohort of human breast cancers revealed that Eph receptor A2 (EphA2) is an important contributor to trastuzumab resistance, which results from engaging the PI3K/Akt pathway via activation of Src [31]. Beyond trastuzumab, phosphoproteomic profiling of the tyrosine phosphorylation changes between lapatinib-resistant breast cancer cell lines and their lapatinib-sensitive parental lines revealed a consistent increase of phosphorylation on SFKs and putative Src substrates in multiple lapatinib-resistant cells. Both *in vitro* and *in vivo* evidence demonstrated that the SFK inhibitor saracatinib in combination with lapatinib effectively overcomes lapatinib resistance [32]. Collectively, these data indicate that Src is a key signaling node of multiple resistance mechanisms to anti-RTK therapies (Figure 2).

Targeting SFKs dramatically enhances the therapeutic efficacy of anti-RTK drugs. Src inhibitor treatment universally sensitized trastuzumab-resistant breast cancer cells of various resistance mechanisms to trastuzumab [24]. Notably, this is not limited to HER2-overexpressing breast cancers. Src activation has also been shown to be crucial in resistance to anti-EGFR therapies. EGFR and Src activities are elevated in the majority of the lung, colorectal and pancreatic tumors [33]. EGFR interacts with Src, and the transformation capability of two EGFR catalytic domain mutants, originally identified in human lung cancers, is dependent on Src [34]. Src activation enhances EGFR activation and downstream PI3K-Akt signaling. Src is highly activated in non-small cell lung cancer cells (NSCLC) with acquired resistance to the anti-EGFR antibody cetuximab [35] (Figure 2, No. 1). Mechanistically, Src facilitates EGFR nuclear translocation, which confers resistance to cetuximab therapy [36]. In colorectal cancers, the EGFR-Src signaling axis is also important

for tumor proliferation. Targeting SFKs by dasatinib sensitized cetuximab-resistant colorectal tumors expressing mutant K-RAS to cetuximab [37]. A combination of dasatinib and the EGFR inhibitor erlotinib enhanced the therapeutic efficacy of erlotinib in inhibiting pancreatic tumor growth [33]. In addition, the combination of the SFK inhibitor saracatinib and RTK inhibitor sunitinib synergistically inhibited proliferation and migration of renal cell carcinomas [38] (Figure 2).

Targeting Src in cancer therapy

Major Src inhibitors in clinical development

Given the crucial role of Src in tumor development and extensive pre-clinical evidence of metastasis suppression by Src inhibition, several clinically applicable small molecule Src inhibitors have been developed and are undergoing clinical testing, particularly for metastatic diseases [3, 14]. Dasatinib (Sprycel, BMS354825, Bristol-Myers Squibb Oncology) is the first FDA-approved SFK/ABL dual inhibitor for the treatment of chronic myeloid leukemia and Philadelphia chromosome-positive acute lymphoblastic leukemia. Other SFK inhibitors under current or previous clinical testing include saracatinib (AZD0530, AstraZeneca) and bosutinib (SKI-606, Wyeth). Although Src inhibitors are generally well-tolerated with limited toxicity, the results from phase II clinical trials of Src inhibitor monotherapy on different types of solid tumors are not encouraging [14]. As a monotherapy, dasatinib showed modest clinical activity with < 25% clinical benefit rate in multiple phase II clinical trials of breast cancer, prostate cancer and melanoma [14] (Table 1). Dasatinib monotherapy showed no clinical benefit for small cell lung cancer [39] and for metastatic colorectal cancer [40]. Phase II trials of saracatinib monotherapy for advanced stage prostate cancer [41], pancreatic tumors [42], metastatic head and neck squamous cell cancer [43], gastric adenocarcinoma [44] and ER-/PR-negative metastatic breast cancer [45] also showed no significant clinical benefit, which led to the hold up of clinical development of saracatinib by AstraZeneca. Bosutinib, with a safety profile distinct from that of dasatinib, showed promising efficacy in prolonging time to progression in locally advanced or metastatic breast cancer patients [46]. Currently, none of the Src inhibitors have been FDA-approved for treatment of solid tumors. The future of targeting Src as a cancer therapy appears gloomy (Table 1).

Why is Src inhibitor monotherapy ineffective?

Despite almost 30 years of study of Src signaling pathways in cancer and extensive pre-clinical evidence that targeting Src is a promising anti-cancer strategy, it seems we are still missing the complete picture of the tumor biology of Src signaling. Some recent studies provide valuable clues which shed new light on the direction of further pre-clinical studies, which might ultimately lead to clinical success.

One challenging issue in the clinical development of Src inhibitors is that we are short of effective response biomarkers to guide our design of clinical trials, partly due to the enormous complexity of Src signaling. All the completed clinical trials of Src inhibitors were performed in unselected patients. To address this issue, a recent preclinical study was carried out to screen for the biomarkers that may indicate response to the Src inhibitor saracatinib. In the 23 colorectal cancer cell lines tested, Src pathway activation positively correlated with sensitivity of cancer cells to saracatinib treatment [47]. This highlights the importance of identifying patients who have tumors with activated Src signaling and who are likely to benefit from saracatinib treatment. Similarly, pancreatic cancer patients had a poorer survival if their tumors contained more membrane-associated Src (activated Src) compared with those having tumors of high cytoplasmic Src expression. Pancreatic cancer cells with aberrant Src activation are sensitive to dasatinib treatment [48]. Conversely,

diminished Src signaling resulting from alternative oncogenic pathways may contribute to *de novo* resistance to Src inhibitors. For example, phosphoproteomic profiling of 346 metastatic renal cell carcinoma (RCC) specimens revealed that Src signaling is hyper-activated in RCC cells with wild-type von Hippel-Lindau (VHL) gene expression [49]. Interestingly, VHL wild-type RCC cells with hyper Src activation, but not VHL-deficient RCC cells, are sensitive to dasatinib treatment. Mechanistically, sensitivity to the Src inhibitor appeared to be dependent on HIF-regulated Src signaling output through tyrosine phosphatase 1B (PTP1B). Exogenous overexpression of HIF, which phenocopies VHL deficiency, suppresses Src signaling *via* down-regulation of PTP1B. As a result, the VHL-deficient RCC cells with diminished Src signaling are resistant to dasatinib [49]. These limited studies demonstrate that activated Src signaling (target availability/activation) may potentially serve as a biomarker for successful targeting of Src and clinical efficacy. Further clinical studies are needed to develop more reliable biomarkers that can guide clinical trials.

In addition, other molecular alterations in cancers may impact on the response of cancer cells to Src inhibitors. Gastric cancer cell lines with c-Met RTK amplification were shown to be resistant to dasatinib [50]. Recently, it was also suggested that the autophagy pathway plays an important role in conferring resistance to Src inhibitors. Suppression of the autophagy pathway sensitizes tumor cells to Src inhibitor treatment [51]. In addition, ER+ breast cancers rapidly developed acquired resistance to the SFK inhibitor saracatinib through reactivation of the mTOR pathway [52, 53]. Taken together, these findings show that resistance to SFK inhibitors can result from multiple genetic and epigenetic alterations in cancer cells.

Paradigm shifting in current clinical trials: turning promises into triumph

To turn hopeful promises of targeting Src into clinical triumphs, we need a paradigm shift in our current design of clinical trials. First, we need to develop effective biomarkers to monitor Src activity and other associated genetic changes in patients' tumors that are critical for tailoring personalized treatment. Pre-clinical studies have clearly demonstrated the importance of hyper-activated Src signaling for therapeutic efficacy of Src inhibitors [47]. Although the overall clinical benefit rate is low among unselected patients in phase II clinical trials of Src inhibitors, apparent activity has been observed in certain patients [54, 55], which again re-emphasizes the importance of pre-selection of patients based on predictive biomarkers for response to Src inhibitors in the clinic. Second, we need to rationally design combinatorial regimens for future clinical development of Src inhibitors. Src is a key downstream transducer of many RTKs, including EGFR, HER2, and c-Met. The cross-talks between Src signaling and RTKs facilitates RTK-addicted tumor growth. For HER2 overexpressing breast cancer, we and others recently demonstrated that Src inhibitor alone is not effective in treatment of trastuzumab or lapatinib-resistant tumors. However, targeting Src signaling by Src inhibitor significantly sensitized resistant tumors to anti-HER2 therapies [24, 32]. For tumors with c-Met amplification, targeting Src inhibits Met signaling, and suppresses Met-addicted gastric carcinoma and colorectal cancer cell growth [56]. In head and neck cancer, although sustained c-Met activation mediates resistance to Src inhibitor monotherapy, concurrent inhibition of Src and c-Met exhibits a synergistic cytotoxic effect [57]. The phenomenon also holds true in gefitinib-resistant NSCLC with c-Met amplification [58] and breast cancer cell lines intrinsically resistant to anti-EGFR tyrosine kinase inhibitor (TKI) [59]. In addition, although ER+ breast tumors rapidly developed resistance to saracatinib through reactivation of the mTOR pathway, combinatorial treatment of saracatinib and anti-estrogen therapy effectively induced cell cycle arrest *via* p27 and delayed the development of resistance [52]. All these data strongly argues for rationally designed combinatorial therapies that might induce synthetic lethality in cancer cells in future clinical trials (Figure 2). Third, we need to develop clinical

strategies to test Src inhibitors in early adjuvant trials. The role of Src during tumor development predicts a limited benefit from targeting Src in late stage metastatic tumors, which have multiple genetic alterations driving tumor progression. Src activation appears to be a facilitator but may not necessarily a driving force for tumor progression as shown in some pre-clinical models [1, 3, 24]. Therefore, it is not surprising that Src inhibitor monotherapy is largely ineffective in the treatment of late stage solid tumors. Important pre-clinical findings may guide the choice of optimal clinical setting of targeting Src. Src inhibitors may have a role in advanced disease, particularly, in combination with agents targeting major tumor drivers, e.g. HER2. In addition, the Src's role in the migration and invasion steps of the metastatic cascade might imply the potential for Src inhibitors in the early adjuvant setting to reduce the risk of metastatic recurrence during or after definitive therapies, but may not in disseminated cancers cells.

Concluding remarks

Src undoubtedly is one of the most important (proto)-oncogenes discovered. However, given the intrinsic complexity of Src signaling and redundant pathways involved in tumor development, the translation into the clinic from numerous preclinical studies on Src and its role in cancer is challenging. As the lack of therapeutic efficacy of Src inhibitors when used as a single agent limits the clinical usage of Src inhibitors, more basic research is clearly warranted to further define the signaling networks that might be crucial for effective targeting of Src in the clinic. Importantly, pre-selection of potential responders to anti-Src therapies or combination of Src-targeting agents with first-line or other types of cancer therapies may potentially enhance the clinical benefit. Innovative design of clinical studies that rationally and seamlessly integrate pre-clinical knowledge is critical for the development of Src-targeting therapies and it represents another frontier for successful translational cancer research.

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Abbreviation

SFK	Src family kinase
RTKs	receptor tyrosine kinases
EGFR	epidermal growth factor receptor
HER2	human epidermal growth factor receptor 2
PDGFR	platelet-derived growth factor receptor
IGF-1R	insulin-like growth factor-1 receptor
HGFR	hepatocyte growth factor receptor
PI3K	phospho-inositide 3-kinase
STAT3	signal transducer and activator of transcription 3
EpoR	erythropoietin receptor

FAK	focal adhesion kinase
VEGF	vascular endothelial growth factor
MMPs	matrix metalloproteinases
IL-8	interleukin-8
ECM	extracellular matrix
EMT	epithelial mesenchymal transition
McTN	microtentacle
CXCL12	chemokine (C-X-C motif) ligand 12
TRAIL	tumor necrosis factor (TNF)-related apoptosis-inducing ligands
HIF-1α	hypoxia-inducible factor 1 alpha
PTEN	phosphatase and tensin homolog
rHuEPO	recombinant human erythropoietin
SH2	Src homology 2 domain
SH3	Src homology 3 domain
TGF-β	transforming growth factor beta
GDF15	growth differentiation factor 15
EphA2	Eph receptor A2
VHL	Von Hippel–Lindau tumor suppressor
PTP1B	tyrosine phosphatase 1B
NSCLC	non-small cell lung carcinoma
TKI	tyrosine kinase inhibitor

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Figure 1.

Canonical Src signaling. Src involves in a number of cell signaling pathways. Src interacts with multiple RTKs and facilitates their downstream signaling, e.g. Akt, to promote cell survival. Src is also activated by RTKs and other membrane receptors including integrins and erythropoietin receptor (EpoR). Deficiency of PTEN leads to further enhancement of Src activity. The major downstream stream signalings upon Src activation include: 1) activation of Akt and enhancement of cell proliferation; 2) stat3 activation and transcriptional up-regulation of secretory factors involved in metastasis and angiogenesis, e.g. MMPs, VEGF and IL-8; 3) disruption of cell-cell adherens junctions through phosphorylation of p120-catenin; 4) stabilization of focal adhesion complex through phosphorylation of FAK.

Figure 2.

Src-targeting combinatorial strategies. Hyper-activation of Src has been known to confer therapeutic resistance to a number of current anti-cancer therapies (see main text). Based on this observation and pre-clinical evidence, combining Src inhibitor with current therapies will enhance the therapeutic efficacy and prevent or overcome therapeutic resistance. Src inhibition can be combined with targeted therapies including 1) anti-EGFR antibody Centuximab; 2) EGFR TKIs e.g. gefitinib; 3) anti-HER2 antibody trastuzumab; 4) EGFR/HER2 dual inhibitor lapatinib; 5) hormonal therapy, e.g. Tamoxifen. Additionally, Src inhibitor may also be combined with chemotherapies (6) and radiation therapies (7) to enhance the overall efficacy [14].

Table 1

Completed phase II Src inhibitor clinical trials for solid tumors

Drug name	Drug targets	Trial Type	Disease	Case (n)	Phase	CBR (%)	Ref
Dasatinib (BMS354825)	Src Bcr-Abl PDGFR	Monotheapy	HR+ or HER2+ breast cancer	70	II	13	[60]
	c-Kit	Monotheapy	TNBC	44	II	9	[14]
	EphA2	Monotheapy	CRPC	40	II	19	[14]
		Monotheapy	NSCLC	34	II	43	[55]
		Monotheapy	CRPC	48	II	17	[14]
		Combination with erlotinib	NSCLC	34	II	63	[54]
		Combination with FOLFOX and cetuximab	Colon cancer	30	II	56	[14]
Saracatinib (AZD0530)	Src Bcr-Abl	Monotheapy	CRPC	28	II	0	[41]
		Monotheapy	HNSCC	9	II	0	[43]
Bosutinib (SKI-606)	Src Bcr-Abl	Monotheapy	metastatic breast cancer	73	II	27	[46]

CBR: clinical benefit rate (stable disease >16 weeks); TNBC: triple negative breast cancer; NSCLC: non-small-cell lung cancer; CRPC: metastatic castration-resistance prostate cancer; HNSCC: metastatic head and neck squamous cell cancer