

## RESEARCH ARTICLE

# Combining kinase inhibitors for optimally co-targeting cancer and drug escape by exploitation of drug target promiscuities

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## Abstract

Cancers resist targeted therapeutics by drug-escape signaling. Multitarget drugs co-targeting cancer and drug-escape mediators (DEMs) are clinically advantageous. DEM coverage may be expanded by drug combinations. This work evaluated to what extent the kinase DEMs (KDEMs) can be optimally co-targeted by drug combinations based on target promiscuities of individual drugs. We focused on 41 approved and 28 clinical trial small molecule kinase inhibitor drugs with available experimental kinome and clinical pharmacokinetic data. From the kinome inhibitory profiles of these drugs, drug combinations were assembled for optimally co-targeting an established cancer target (EGFR, HER2, ABL1, or MEK1) and 9–16 target-associated KDEMs at comparable potency levels as that against the cancer target. Each set of two-, three-, and four-drug combinations co-target 36–71%, 44–89%, 50–88%, and 27–55% KDEMs of EGFR, HER2, ABL1, and MEK1, respectively, compared with the 36, 33, 38, and 18% KDEMs maximally co-targeted by an existing drug or drug combination approved or clinically tested for the respective cancer. Some co-targeted KDEMs are not covered by any existing drug or drug combination. Our work suggested that novel drug combinations may be constructed for optimally co-targeting cancer and drug escape by the exploitation of drug target promiscuities.

## KEYWORDS

anticancer, drug combinations, drug resistance

**Abbreviations:** ABL1, Abelson murine leukemia viral oncogene homolog 1;  $C_{free}$ , free drug concentration at human plasma; CML, chronic myeloid leukemia; DC-KDEM, drug combination-kinase drug-escape mediator; DEM, drug-escape mediator; EGFR, epidermal growth factor receptor; FDA, US Food and Drug Administration; HER2, human epidermal growth factor receptor 2; KDEM, kinase drug-escape mediator; MEK1, dual specificity mitogen-activated protein kinase kinase 1; NSCLC, non-small-cell lung cancer; TTD, therapeutic target database.

## 1 | INTRODUCTION

The development and clinical applications of the targeted anticancer drugs have significantly improved cancer treatment outcomes, but cancers frequently relapse with acquired drug resistance due to such drug resistance mechanisms as the activation of drug-escape signaling (Ng et al., 2012; Toyokawa & Seto, 2015; Turner & Reis-Filho, 2012; Wilson et al., 2012), drug efflux, and pro-survival activities (Holoan, Van Schaebybroeck, Longley, & Johnston, 2013; Szakacs, Paterson, Ludwig, Booth-Genthe, & Gottesman, 2006). Recent investigations have consistently shown that drug resistance in cancers can be reduced by co-targeting the cancer target(s) and the target-associated drug-escape mediators (DEMs) (Dienstmann, De Dosso, Felip, & Tabernero, 2012; Karamouzis, Konstantinopoulos, & Papavassiliou, 2009; Ng et al., 2012; Poulidakos & Solit, 2011; Sawyers, 2007). The multi-target drugs co-targeting the cancer target and the target-associated DEMs have shown clinical advantage over those not co-targeting DEMs (Tao et al., 2015). Drugs targeting higher number of the target-associated DEMs tend to record higher annual sales (Chen et al., 2019). The clinical-stage (approved or clinical trial) multitarget drugs and drug combinations (Liu et al., 2014; Tao et al., 2015) typically co-target 1–7 and 1–6 DEMs (Table S1) as opposed to the 14–33 known DEMs (Tao et al., 2015) prevalent in the drug-targeted cancers (Table S2). These together indicate a need for expanded coverage of the DEMs in the targeted cancer therapeutics.

Clinical-stage anticancer drug combinations have been constructed by several strategies. These include the collective inhibition of an individual target, parallel targets, redundant pathways or processes (Dancey & Chen, 2006), the co-targeting of the drug efflux responsible for drug resistance (Fletcher, Haber, Henderson, & Norris, 2010; Kervick, Flynn Jr., Alfonso, & Miller, 1990; Wang, Zhang, Kathawala, & Chen, 2014), and the minimization of the excessive side-effects by combining drugs of lower overlapping toxicities (Kummar et al., 2010). These strategies are highly useful for discovering synergistic drug combinations with anticounteractive, complementary, facilitating, or potentiating modes of actions (Jia et al., 2009). Significant progress has been made in the development of drug combination screening methods by *in silico* as well as other approaches (Flobak et al., 2015; Havaleshko et al., 2007; Huang et al., 2014; Huang, Jiang, & Chen, 2017; Jeon, Kim, Park, Lee, & Kang, 2018; Klinger et al., 2013; Li, Li, Quang, & Guan, 2018; Malyutina et al., 2019; Regan-Fendt et al., 2019; Stathias et al., 2018; Sun et al., 2015). In addition to these advanced methods for drug combinations of improved therapeutics, there is a need for further enhanced ability in finding drug combinations that co-target more DEMs.

In particular, kinase drug-escape mediators (KDEMs) constitute a large percentage (48–64%) of the DEMs associated with such well-established cancer targets as epidermal growth factor receptor (EGFR), human epidermal growth factor receptor 2 (HER2), Abelson murine leukemia viral oncogene homolog 1 (ABL1), and dual specificity mitogen-activated protein kinase kinase 1 (MEK1) (Table S2). Many clinical-stage anticancer drugs are kinase inhibitors with potent

activities against multiple kinases (Karaman et al., 2008), including some KDEMs (Table S4). These together raise a question about whether the kinome promiscuities of the clinical-stage kinase inhibitor drugs can be exploited for rational design of drug combinations. Specifically, based on their kinase inhibitory profiles at potency levels comparable to that of the target potency, whether these drugs can be combined to optimally co-target the cancer kinase target and the target-associated KDEMs prevalent in the targeted cancers.

In this work, we investigated this question by determining to what extent a cancer kinase target and its associated patient-prevalent KDEMs can be optimally co-targeted by the combinations of two-, three-, and four- clinical-stage small molecule drugs, under the condition that the co-targeting is at potency level comparable to the human plasma free drug concentrations of the drug or potency of the primary drug against its target. We conducted a comparative analysis of the kinome inhibitory profiles of 41 approved and 28 clinical trial small molecule drugs against the 14, 9, 16, and 11 KDEMs associated with each of the four established cancer targets EGFR, HER2, ABL1, and MEK1. These four targets were selected for the following three reasons. The target is the primary target of sufficient number of approved small molecule drugs. There are additional clinical-stage small molecule drugs that co-target one or more KDEMs associated with each target. Each target is a well-established cancer target for the treatment of non-small cell lung cancer (NSCLC), HER2+ breast cancer, chronic myeloid leukemia (CML), or melanoma. Based on the kinase inhibitory profiles of these clinical-stage drugs, we screened the two-, three-, and four- drug combinations that co-target each target and the optimal number of target-associated KDEMs prevalent in the targeted cancers.

## 2 | METHODS

### 2.1 | Search of KDEMs associated with the efficacy targets EGFR, HER2, ABL1, and MEK1

The KDEMs associated with each target (Table S2) were searched (Tao et al., 2015) from the literatures by the following criterion: A kinase is regarded as a KDEM of a target if *in-vitro* and/or *in-vivo* studies have indicated that, in the targeted cancers, it actively reduces the effects of the drugs directed at the target, or the co-targeting of the target and the kinase by a drug combination synergistically enhances the effects of the drug directed at the target (Karamouzis et al., 2009; Ng et al., 2012; Poulidakos & Solit, 2011; Sawyers, 2007).

### 2.2 | Collections of FDA approved and clinically tested kinase inhibitor drugs and their efficacy targets

These drugs were collected from the Thomson Reuters Pharma database, the Therapeutic target database (TTD) (Yang et al., 2016), and PhRMA 2014–2016 report of medicines in development for cancer.

The previously-determined experimental potency ( $IC_{50}$  and  $K_i$ ) values of these drugs against single or multiple kinases were from the ChEMBL database (Gaulton et al., 2017) and additional search of the literature-reported kinome or individual kinase activity studies (Karaman et al., 2008). The combinations of drugs approved or in clinical trials were from the DCDB database (Liu et al., 2014), ClinicalTrials.gov database (Zarin, Tse, Williams, & Carr, 2016), and additional literature search using keyword combinations of “drug,” “combination,” “combo,” “clinical trial,” and “phase.” The efficacy target(s) of each drug was searched and/or evaluated by the following procedures used in the development of the TTD (Yang et al., 2016). For each drug with a single reported target in the searched sources, that target was tentatively recorded as its efficacy target. For each clinically tested kinase inhibitor without target information or with  $\geq 2$  targets (including different targets reported in different sources), its efficacy target(s) was (were) searched from the literatures on the basis that it (they) is (are) linked to the clinically intended therapeutics based on the established criterion of efficacy targets (Overington, Al-Lazikani, & Hopkins, 2006).

### 2.3 | Human plasma free drug concentration and the criterion for the effective inhibition of the target and associated KDEMs under clinical conditions

The KDEMs that are likely to be effectively inhibited by a drug under clinical conditions were identified by the consideration that, at the FDA recommended dose or clinical trial dose, the drug concentrations in the patients be comparable to or exceed the level for potent inhibition of the KDEM. In this study, we adopted our previously-used criterion (Chen et al., 2019) that a drug is assumed to effectively inhibit a KDEM under clinical conditions if its KDEM inhibitory  $IC_{50}$  or  $K_i$  value is comparable to or below the human plasma steady-state free drug concentration ( $C_{free}$ ) at the FDA recommended dose or at the maximum dose in clinical trial tests.  $C_{free}$  was deduced from the maximum human plasma steady state total drug concentration ( $C_{max}$ ) multiplied by unbound fraction of the drug in plasma from the plasma protein binding assay (Hamilton, Rath, & Burghuber, 2015). For the FDA approved drugs, the clinically observed  $C_{max}$ , unbound drug fraction, and the FDA recommended dose of drugs (Table S5) were from the corresponding “Medical and Clinical Pharmacology Reviews” and “Highlights of Prescribing Information” documents of the FDA database (<https://www.fda.gov/Drugs>), while for drugs in clinical trial Phase 2 or Phase 3, the  $C_{max}$ , unbound drug fraction and drug dose were searched from the literatures.

### 2.4 | Experimental potency of the drugs against their kinase target and target-associated KDEMs

The experimental potency of each drug against kinase targets (Table S6) were retrieved from the ChEMBL database (version 23) (Gaulton et al., 2017) and additional PubMed literature search

using keyword combinations of drug name, “ $IC_{50}$ ” and “ $K_i$ .” Each experimental potency collected from ChEMBL was checked by manual inspection of the assay descriptions. For each drug with multiple experimental potency values against a target or KDEM, the median potency (Chen et al., 2017) was used for representing the experimental potency of the drug against the target or KDEM (Table S7).

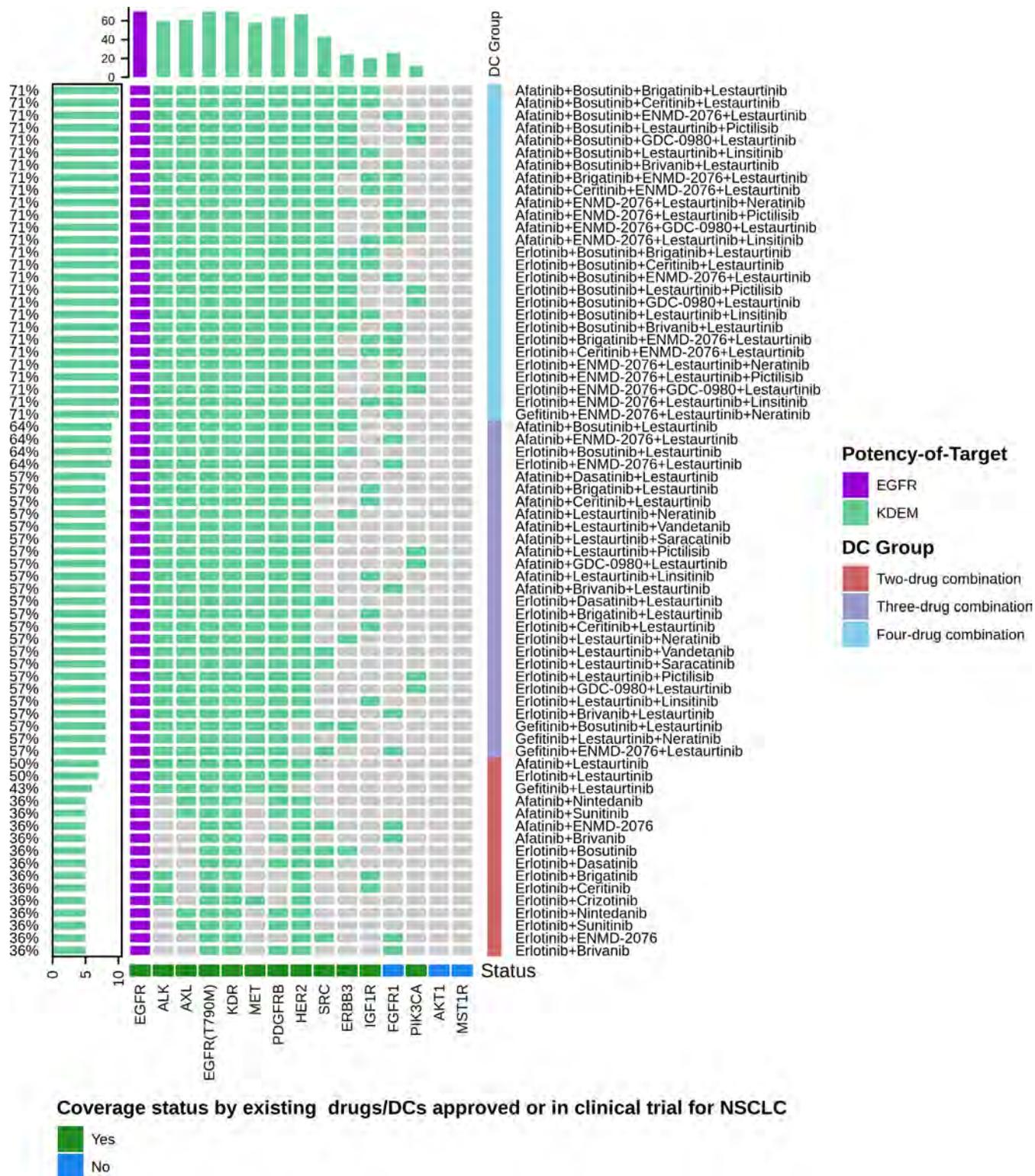
### 2.5 | Search of two-, three-, and four-drug combinations

The search of drug combinations for the four cancer targets EGFR, HER2, ABL1, and MEK1 was based on the KDEM profile of our collected kinase inhibitor drugs approved by FDA or in clinical trial. For instance, to search for the two-, three-, and fourth- drug combinations co-targeting EGFR and its KDEMs, we first selected one of the approved drugs whose efficacy target is EGFR, we then added the second, third, and fourth drug into the combination if the drug satisfies the following criteria: (a) its efficacy target is not EGFR; (b) it covers at least one KDEM of EGFR that is not covered by the first EGFR-targeted drug or drug(s) previously added into the combination. Then all the possible two-, three-, and fourth-drug combinations were ranked based on the number of co-targeted KDEMs of EGFR, respectively. The top-ranked drug combinations co-targeting higher number of KDEMs were selected and their drug combination-KDEM co-targeting (DC-KDEM) profile were analyzed. The figures demonstrating the DC-KDEM profiles of the selected drug combinations (Figures 1–4) were generated using ComplexHeatmap package (version 2.0.0) in R system (version 3.6).

## 3 | RESULTS AND DISCUSSIONS

By comprehensive search of the literatures (Tao et al., 2015), we found 14, 9, 16, and 11 KDEMs associated with EGFR, HER2, ABL1, and MEK1, respectively (Table 1 and Table S2). These KDEMs are prevalent in the respective targeted patients of NSCLC, breast cancer, leukemia, and melanoma, respectively (Table S2). Specifically, 13 of the 14 EGFR-associated KDEMs, namely EGFR(T790M), HER2, ERBB3, IGF1R, MET, PDGFRB, FGFR1, KDR, SRC, AXL, PIK3CA, AKT1, and ALK are expressed in 79, 25, 23.6, 53.8, 48.1, 37.7, 25.2, 54.2, 23, 55, 37, 73, and 6.7% NSCLC patients. And 8 of the 9 HER2-associated KDEMs: EGFR, ERBB3, IGF1R, MET, KDR, AXL, SRC, and PI3KCA are expressed in 26.6, 27.3, 25, 22.9, 83.7, 75, 46, and 40% breast cancer patients. While 5 of the 16 ABL1-associated KDEMs LYN, KIT, FLT3 AKT1, and MTOR are expressed in 33, 7.7, 22.9, 41.2, and 70.4% CML patients. The 9 of 11 MEK1-associated KDEMs: ERK2, ERK1, AKT1, BRAF, ERBB3, MET, PIK3CA, MTOR, and STK11 are expressed in 100, 100, 77, 71, 40, 38.6, 11, 10.4, and 10% melanoma patients.

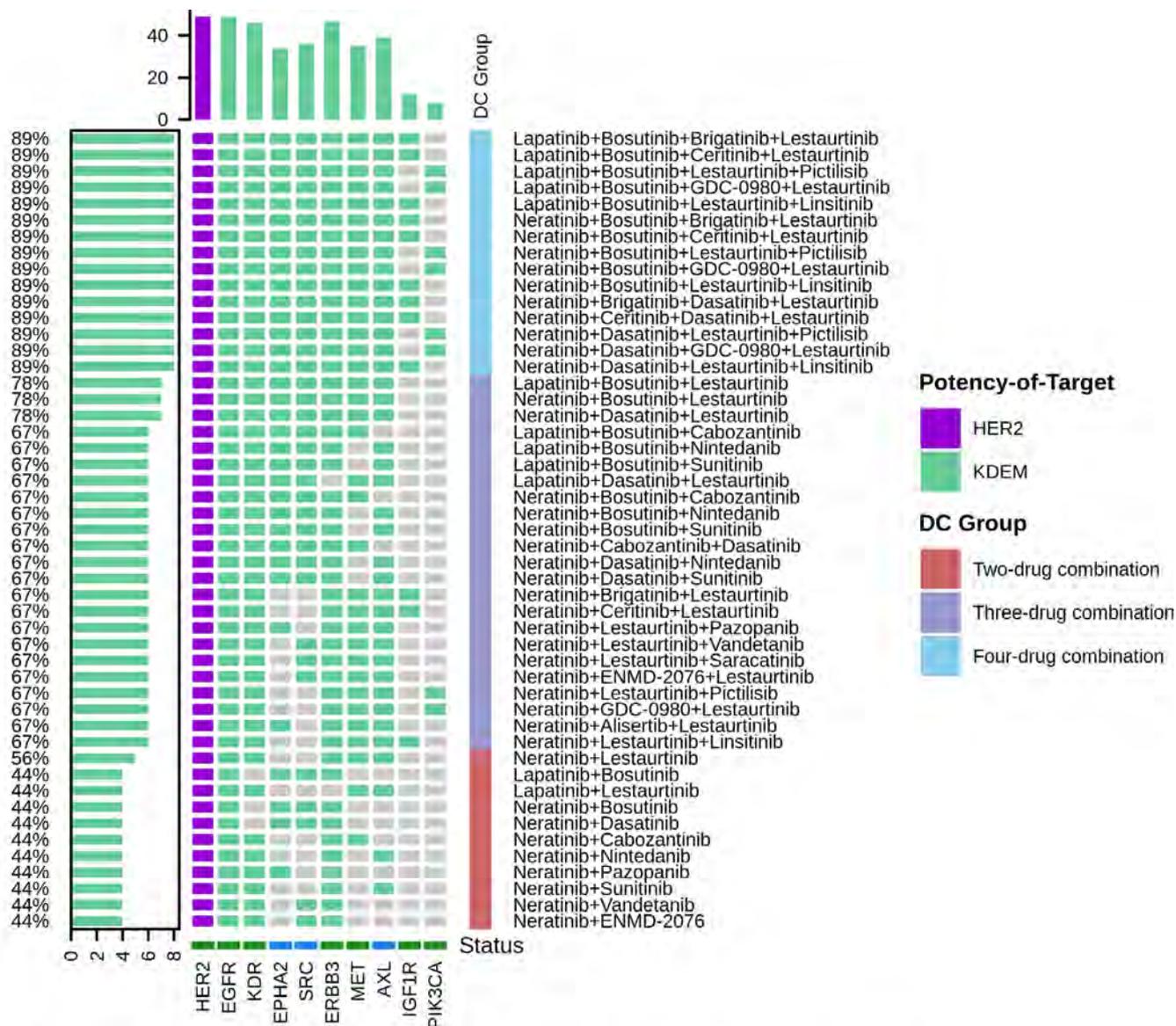
We initially collected 41 approved and 115 clinical trial small molecule kinase inhibitor drugs (Table S3) from the literatures and



**FIGURE 1** EGFR-targeted two-, three-, and four-drugs combinations and their KDEM co-targeting profiles. The number of drug combinations against the target and KDEM is shown by the vertical bar-chart in the top. The number of co-targeted KDEMs is shown as the horizontal bar-chart on the left side. The target EGFR, co-targeted KDEMs covered and not covered by the clinically used or tested drugs and drug combinations are in purple, green, and light-blue color, respectively

relevant databases. Among these 156 drugs, we found 5, 2, 5, and 2 approved, and 12, 8, 5, and 6 clinical trial drugs whose anticancer efficacy target is EGFR, HER2, ABL1, and MEK1, respectively

(Table 1; Table S3). The human plasma free drug concentration of the 41 approved drugs were deduced from the clinical data reported in the literatures and FDA database. However, we were only able to find



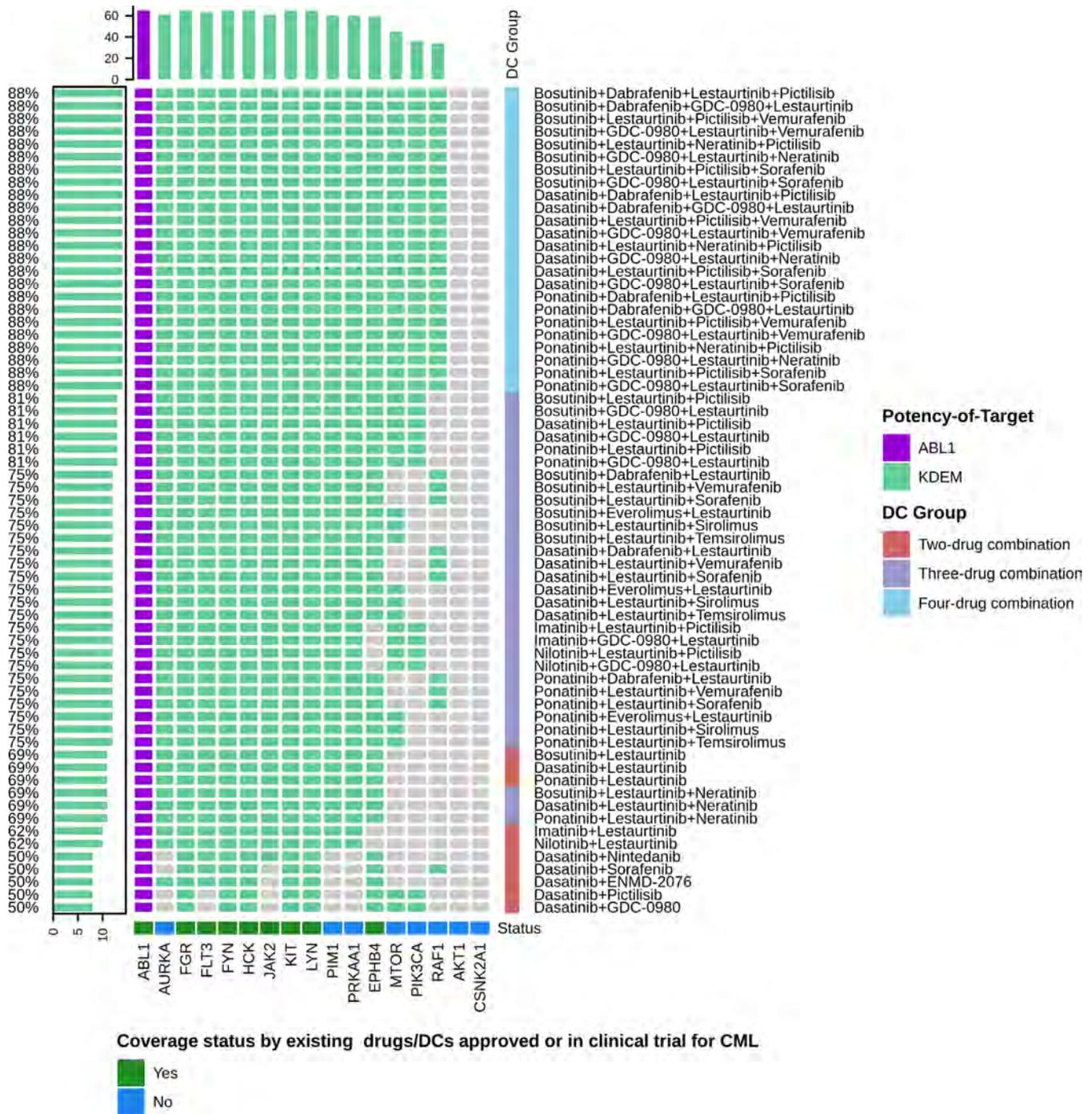
**Coverage status by existing drugs/DCs approved or in clinical trial for breast cancer**



**FIGURE 2** HER2-targeted two-, three-, and four-drug combinations and their KDEM co-targeting profiles. Figure layout and coloring schemes are the same as Figure 1

pharmacokinetic data of 28 out of 115 clinical trial drugs for deducing human plasma free drug concentration. Thus 41 approved and 28 clinical trial drugs were further analyzed. Among these 69 drugs, we found the first set of 5, 2, 5, and 2 approved drugs whose anticancer efficacy target is EGFR, HER2, ABL1, and MEK1, respectively (Table 1), and the second set of 22 approved and 13 clinical trial drugs with available experimental potency values for inhibiting multiple kinases and covering  $\geq 1$  KDEM (Table S4), while the remaining set of 4 approved and 11 clinical trial drugs not covering any KDEM of EGFR, HER2, ABL1, and MEK1.

Based on the first and second sets of drugs, we searched for the two-, three-, and four-drug combinations that co-target each of the four cancer targets and the optimal number of the target-associated KDEMs, under the requirement that the potency against every KDEM be at a level comparable to or better than that of the KDEM-targeting drug against its own efficacy target (i.e., the  $IC_{50}$  or  $K_i$  value of a drug against a KDEM is of the same order of magnitude or lower with respect to its free drug concentration at human plasma). Our search resulted in a substantial number of two-, three-, and four-drug combinations that co-target each of the four targets and a significantly

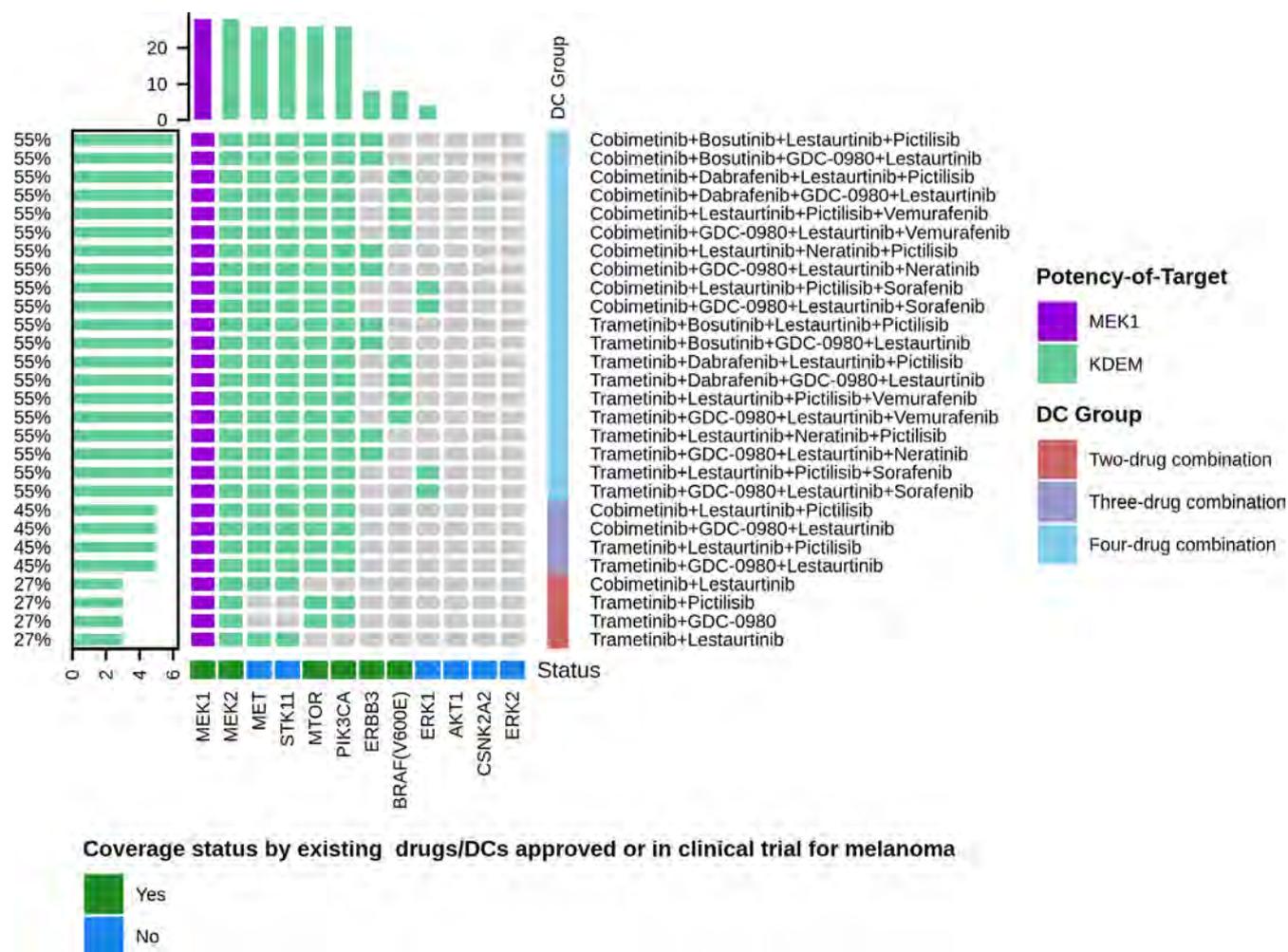


**FIGURE 3** ABL1-targeted two-, three-, and four-drugs combinations and their KDEM co-targeting profiles. Figure layout and coloring schemes are the same as Figure 1

higher number of KDEMs than those of the multitarget drugs and drug combinations in clinical use or trial (Table S8; Table 2).

Among the identified drug combinations that co-target EGFR and EGFR-associated KDEMs prevalent in NSCLC patients (Table S8; Figure 1), there are 3, 1, and 13 two-drug combinations co-targeting 7 (50%), 6 (43%) and 5 (36%) KDEMs, 4 and 23 three-drug combinations co-targeting 9 (64%) and 8 (57%) KDEMs, and 27 four-drug combinations co-targeting 10 (71%) KDEMs, respectively. In contrast, the top-ranked EGFR-targeted multitarget drug and drug combination

in clinical stages co-target 4 (29%) and 5 (36%) KDEMs, respectively (Table S1). The KDEMs co-targeted by our identified two-drug combinations are EGFR(T790M), and KDR by all 17 combinations, HER2 by 16 combinations, and PDGFR by 10 combinations. The KDEMs co-targeted by our identified three-drug combinations are ALK, AXL, EGFR(T790M), KDR, MET, and PDGFRB by all 27 combinations, HER2 by 12 combinations, and SRC by 6 combinations. The KDEMs co-targeted by our identified four-drug combinations are ALK, AXL, EGFR(T790M), HER2, KDR, MET, PDGFRB, and SRC by all



**FIGURE 4** MEK1-targeted two-, three-, and four-drugs combinations and their KDEM co-targeting profiles. Figure layout and coloring schemes are the same as Figure 1

**TABLE 1** Statistics of the clinically validated (approved or clinical trial) drugs with EGFR, HER2, ABL1, and MEK1 as efficacy target, and the number of the known drug escape mediators associated with each target

Target	Targeted cancers	No. of known DEMs	No. of known KDEMs	No. of targeted drugs				
				Approved	Phase III	Phase II	Phase I	Total
EGFR	Nonsmall cell lung cancer, pancreatic, colon, head and neck, liver, and brain cancers	27	14	5	1	6	5	17
HER2	Breast cancer	14	9	2	1	1	3	10
ABL1	Leukemia	33	16	5	0	4	1	10
MEK1	Melanoma and solid tumor	18	12	2	0	4	2	8

27 combinations, ERBB3, IGF1R, and FGFR1 by more than 10 combinations, and PIK3CA by 8 combinations.

In the identified HER2-targeted drug combinations (Table S8 and Figure 2), there are 1 and 10 two-drug combinations co-targeting 5 (56%) and 4 (44%) KDEMs, 3 and 20 three-drug combinations co-targeting 7 (78%) and 6 (67%) KDEMs, and additional set of 15 four-drug combinations co-targeting 8 (89%) KDEMs

associated with HER2 and prevalent in HER2+ breast cancer patients. For comparison, the top-ranked HER2-targeted multitarget drug and drug combination in clinical use or trial each co-target 3 (33%) KDEMs, respectively (Table S1). The KDEMs co-targeted by our identified two-drug combinations are EGFR by all 11 combinations, ERBB3 by 10 combinations, and KDR by 8 combinations. The KDEMs co-targeted by our identified three-drug combinations are

**TABLE 2** Statistics of the two-, three-, and four- drug combinations that co-target an anticancer target (EGFR, HER2, ABL1, or MEK1) and optimal number of KDEMs associated with each target (all drug combinations are composed of CKIs that have been approved or in clinical trials)

Target	No. of drugs in drug combination	Max. no. (%) of KDEMs covered by combination	No. of possible drug combinations	Example of the drug combination and the covered KDEM
EGFR	Two-drug	7 (50%)	2	Afatinib + Lestaurtinib [ALK, AXL, EGFR(T790M), HER2, KDR, MET, PDGFRB]
	Three-drug	9 (64%)	4	Erlotinib + Bostinib + Lestaurtinib [ALK, AXL, EGFR(T790M), HER2, ERBB3, KDR, MET, PDGFRB, SRC]
	Four-drug	10 (71%)	27	Erlotinib + Bosutinib + Ceritinib + Lestaurtinib [ALK, AXL, EGFR(T790M), HER2, ERBB3, IGF1R, KDR, MET, PDGFRB, SRC]
HER2	Two-drug	5 (56%)	1	Neratinib + Lestaurtinib [AXL, EGFR, ERBB3, KDR, MET]
	Three-drug	7 (78%)	3	Lapatinib + Bosutinib + Lestaurtinib (AXL, EGFR, EPHA2, ERBB3, KDR, MET, SRC)
	Four-drug	8 (89%)	15	Neratinib + Brigatinib + Dasatinib + Lestaurtinib (AXL, EGFR, EPHA2, ERBB3, IGF1R, KDR, MET, SRC)
ABL1	Two-drug	11 (69%)	3	Dasatinib + Lestaurtinib (AURKA, EPHB4, FGR, FLT3, FYN, HCK, JAK2, KIT, LYN, PIM1, PRKAA1)
	Three-drug	13 (81%)	6	Bosutinib + Lestaurtinib + Pictilisib (AURKA, EPHB4, FGR, FLT3, FYN, HCK, JAK2, KIT, LYN, MTOR, PIK3CA, PIM1, PRKAA1)
	Four-drug	14 (88%)	24	Ponatinib + GDC-0980 + Lestaurtinib + Sorafenib (PIK3CA, KIT, FYN, MTOR, FLT3, JAK2, PIM1, FGR, PRKAA1, RAF1, LYN, AURKA, EPHB4, HCK)
MEK1	Two-drug	3 (27%)	4	Trametinib + Pictilisib (MEK2, MTOR, PIK3CA)
	Three-drug	5 (46%)	4	Cobimetinib + Lestaurtinib + Pictilisib (MEK2, MET, MTOR, PIK3CA, STK11)
	Four-drug	6 (54%)	20	Cobimetinib + Bosutinib + Lestaurtinib + Pictilisib (MET, MTOR, STK11, ERBB3, MEK2, PIK3CA)

EGFR, ERBB3 and AXL by 20 combinations, EPHA2, SRC, and MET by 10 combinations, IGF1R by 3 combinations, and PIK3CA by 2 combinations. The KDEMs co-targeted by our identified four-drug combinations are EGFR, HER2, KDR, MET, AXL, EPHA2, and SRC by all 15 combinations, IGF1R by 9 combinations, and PIK3CA by 6 combinations.

Among the identified ABL1-targeted drug combinations (Table S8; Figure 3), there are 3, 2, and 5 two-drug combinations co-targeting 11 (69%), 10 (62%), and 8 (50%) KDEMs, 6 and 25 three-drug combinations co-targeting 13 (81%) and 12 (75%) KDEMs, and 18 four-drug combinations co-targeting 14 (88%) KDEMs prevalent in chronic myeloid leukemia, respectively, while the top-ranked Abl-targeted multi-target drug and two-CKI combination used or tested in clinical trial each co-target 6 (38%) KDEMs, respectively, (Table S1). The KDEMs co-targeted by our identified two-drug combinations are FGR, FYN, HCK, KIT, and LYN by all 10 combinations, FLT3 and EPHB4 by 8 combinations, and JAK2 and AURKA by 6 combinations. The KDEMs co-targeted by our identified three-drug combinations are AURKA, FGR, FLT3, FYN, HCK, JAK2, KIT, LYN, PIM1, and PRKAA1 by all 31 combinations, EPHB4 by 27 combinations, and MTOR by 19 combinations. The KDEMs co-targeted by our identified four-drug combinations are and AURKA, EPHB4, FGR, FLT3, FYN, HCK, JAK2, KIT, LYN, MTOR, PIK3CA, PIM1, PRKAA1, and RAF1 by all

18 combinations, while the remaining two KDEMs AKT1 and CSNK2A1 are not co-targeted by any drug combination.

In the identified MEK1-targeted drug combinations (Table S8; Figure 4), there are 3, 4, and 20 two-, three-, and four-drug combinations co-targeting 3 (27%), 5 (46%), and 6 (54%) KDEMs prevalent in melanoma. On the other hand, the top-ranked MEK1-targeted multi-target drug and two-drug combination in clinical use or trial co-target 1 (9%) and 2 (18%) KDEMs, respectively (Table S1). The KDEMs co-targeted by our identified two-drug combinations are MEK2 by all 3 combinations, and MET, STK11, MTOR, and PI3KCA by 2 combinations. The KDEMs co-targeted by our identified three-drug combinations are MEK2, MET, STK11, MTOR, and PI3KCA by all 8 combinations. The KDEMs co-targeted by our identified four-drug combinations are MEK2, MET, STK11, MTOR, and PI3KCA by all 20 combinations, HER2 and BRAF(V600E) by 8 combinations, and ERK1 by 4 combinations.

In addition to the sets of drug combinations of significantly higher KDEM coverage, our method can identify drug combinations for co-targeting KDEMs beyond those co-targeted by an existing clinical-stage drug or drug combination against the four cancers (Table S8). Specifically, our identified EGFR-targeting, HER2-targeting, ABL1-targeting, and MEK1-targeting drug combinations co-target 1 KDEM (FGFR1), 3 KDEMs (EPHA2, SRC, and AXL), 4 KDEMs (AURKA, PIM1, PRKAA1,

and RAF1), and 3 KDEMs (MET, STK11, and ERK1), respectively, while these KDEMs are not co-targeted by an existing drug or drug combination approved or in clinical trial for NSCLC, breast cancer, CML, and melanoma, respectively (Figures 1–4). These additionally co-targeted KDEMs are expressed in substantial percentages of the targeted cancer patients (Table S2). FGFR1 is overexpressed in 25.5% NSCLC patients (Volm, Koomagi, Mattern, & Stammer, 1997), AXL and SRC are overexpressed in 75 and 46% breast cancer patients (Ahmed et al., 2015; Elsberger et al., 2009), MTOR is overexpressed in 70.4% CML patients (Li et al., 2012), and MET, ERK1, and STK11 are overexpressed in 38.6, 100, and 10% melanoma patients (Liu et al., 2012; Natali et al., 1993; Zhuang et al., 2005), respectively. Therefore, these identified drug combinations may be potentially useful for the treatment of more cancer patients, particularly those with KDEM-prompted drug resistances.

## 4 | CONCLUDING REMARKS

Our analysis indicates extensive opportunities in exploiting the target promiscuity of the available multitarget anticancer kinase inhibitor drugs for expanded co-targeting of the known KDEMs. In particular, two-, three-, and four-drug combinations may be designed for co-targeting up to 36–89% known KDEMs of the selected kinase targets of cancers. Nonetheless, a substantial number of the known KDEMs and most of the nonkinase DEMs are not co-targeted by the currently available drugs, particularly multitarget kinase inhibitor drugs. Some of these nontargeted DEMs are substantially prevalent in the targeted cancer patients. Extensive studies of cancers and drug resistances are promoting the discovery of more DEMs that may significantly affect the clinical efficacies of anticancer therapeutics (Granados et al., 2020; Han et al., 2020; Waldeck et al., 2020). There is a need for new drugs co-targeting these nontargeted and newly discovered DEMs. Advanced genomics-based (Jeon et al., 2018; Sun et al., 2015), biological network (Huang et al., 2014; Huang et al., 2017; Klinger et al., 2013; Li et al., 2018; Sun et al., 2015), cell-based (Flobak et al., 2015; Havaleshko et al., 2007; Malyutina et al., 2019), and combination (Regan-Fendt et al., 2019; Stathias et al., 2018) methods have been developed for facilitating the discovery and assessment of drug combinations. Our target promiscuity exploitation method may be combined with these advanced methods for finding clinically effective drug combinations.

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## CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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