Drug Sales Confirm Clinical Advantage of Multi-Target Inhibition of Drug Escapes by Anticancer Kinase Inhibitors

Short Title: Advantage of Inhibition of Drug Escapes

Shangying Chen¹, Sheng Yong Yang², Zhe Chen³, Ying Tan¹, Yu Yang Jiang^{1*} and Yu Zong Chen^{4*}

¹The State Key Laboratory of Chemical Oncogenomics, Key Laboratory of Chemical Biology, Tsinghua University Shenzhen Graduate School, Shenzhen Technology and Engineering Laboratory for Personalized Cancer Diagnostics and Therapeutics, Shenzhen Kivita Innovative Drug Discovery Institute, Guangdong, P. R. China

²Molecular Medicine Research Center, State Key Laboratory of Biotherapy, West China Hospital, West China School of Medicine, Sichuan University, Chengdu, China.

³Zhejiang Key Laboratory of Gastro-intestinal Pathophysiology, Zhejiang Hospital of Traditional Chinese Medicine, Zhejiang Chinese Medical University, No. 54 Youdian Road, Hangzhou 310006, China

⁴Bioinformatics and Drug Design Group, Department of Pharmacy, National University of Singapore, 18 Science Drive 4, 117543, Singapore

*Correspondence

Yu Zong Chen

Bioinformatics and Drug Design Group, Department of Pharmacy, National University of Singapore, 18 Science Drive 4, 117543, Singapore

Tel: (+65)65166877; Fax: (+65) 67791554; E-mail: phacyz@nus.edu.sg

Yu Yang Jiang:

The State Key Laboratory of Chemical Oncogenomics, Key Laboratory of Chemical Biology

E-mail: jiangyy@sz.tsinghua.edu.cn

Acknowledgments

We acknowledge the support from Shenzhen Municipal Government grants JCYJ20160324163734374, JCYJ20170413113448742 and 20151030A0610001; National NSF of China grant 81202459, NSF Project of CQ CSTC grant CSTC2012JJA10116.

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: [10.1002/ddr.21486](https://doi.org/10.1002/ddr.21486)

Abstract

The clinical advantage of co-targeting cancer drug escape has been indicated by the percentage of these co-targeting drugs among all multi-target drugs in clinics and clinical trials. This clinical advantage needs to be further interrogated from such perspectives as the clinical impact of multi-target inhibition of drug escape mediators. This impact may be reflected by drug sales data, i.e., multi-target inhibition of higher number of drug escape mediators favours the expanded coverage of drug resistant patients leading to higher sales. We investigated whether this expectation is followed by the 25 FDA-approved anticancer kinase inhibitors, which were divided into 11 groups of comparable therapeutic mechanisms and approval years. We found 19 (76%) drugs to follow and 3 (12%) drugs not to follow this expectation. The remaining 2 (8%) and 1 (4%) drugs cannot be assessed due to insufficient data and incomparability. Therefore, drug sales strongly indicate the clinical advantage of multi-target inhibition of cancer drug escapes.

KEYWORDS

Anticancer; co-target; drug escape pathways; multi-target

Abbreviations: DEM, drug-escape mediator; FDA, US Food and Drug Administration; DSC, drug sales comparison; TTD, Therapeutic target database; C_{free} , free drug concentration in plasma of clinical study; C_{max} , total drug concentration in plasma of clinical study; DEM-EI, DEM effective inhibition

1| INTRODUCTION

Drug escape signalling [in cancers](#) is a major type of resistance mechanism against targeted anticancer therapeutics [Kanda et al. 2013; Mitchell et al. 2017; Ng et al. 2012; Qi et al. 2011; Toyokawa and Seto 2015; Turner and Reis-Filho 2012; Wilson et al. 2012]. A target-associated drug-escape mediator (DEM) [promotes](#) drug resistance by activation of alternative signalling, down-stream cascade, and counteractive feedback loops that evade the drug modulation of a target [Avril et al. 2017; Boshuizen et al. 2018; Tao et al. 2015]. These drug escape actions can be overcome by co-inhibiting the target-associated DEMs [Dienstmann et al. 2012; Kanda et al. 2013; Karamouzis et al. 2009; Ng et al. 2012; Poulikakos and Solit 2011; Sawyers 2007] using multi-target drugs [Katakami et al. 2013; Schlumberger et al. 2015] and drug combinations [Qi et al. 2011]. The clinical advantage of co-inhibiting DEMs has been indicated by the count of the DEM co-targeted drugs among [all](#) the multi-target anticancer drugs in clinics and clinical trials, with the majority (73.9-75.0%) of the approved and phase III drugs and the minority (53.6%-62.8%) of phase I and II drugs co-inhibiting at least one target-associated DEM [Tao et al. 2015].

This advantage needs to be further interrogated from such perspectives as the clinical impact of the multi-target inhibition of multiple DEMs by these drugs. This impact may be reflected by the drug sales [data](#), such that multi-target inhibition of higher number of [DEMs by a drug](#) favors [more](#) expanded coverage of [the](#) drug-resistant patients [than the drugs covering less DEMs](#), leading to higher sales [for the drugs targeting higher number of DEMs](#). We investigated whether this expectation is followed by the [25 anticancer multi-target kinase](#)

inhibitor drugs approved by US Food and Drug Administration (FDA). These drugs are from 7 target classes approved before 2016 for the treatment of 5 different cancers, and with available annual sales and kinase inhibitory data for our investigation.

2| METHODS

2.1 | Analysis procedure

Our analysis procedure is outlined in **Figure 1**. We first collected a total of 25 FDA-approved anticancer kinase inhibitor drugs together with their therapeutic kinase target, targeted cancer from the literatures and relevant databases. The 25 drugs were divided into drug sales comparison (DSC) groups of the same kinase target, same cancer, and comparable FDA approval years. Next, we collected from the literatures the DEMs associated to the 7 kinase targets of the 25 drugs, and the experimental potency of the 25 drugs against their kinase target and the target-associated DEMs from the ChEMBL database [Gaulton et al. 2017]. Then, the human plasma free drug concentration of the 25 drugs were deduced from the clinical data reported in the literatures and FDA website, which were subsequently used as cut-off for judging whether the DEMs are likely to be effectively inhibited by the drugs under clinical conditions. We further collected annual sales data of these drugs from the annual reports of the respective pharmaceutical companies. Based on these data, we analysed the sales-DEM co-inhibition relationship for each drug to determine whether it follows the expectation that inhibition of higher number of DEMs records higher sales within the DSC group.

2.2 | Collections of FDA approved drugs and their efficacy targets

The 25 multi-target kinase inhibitor drugs, the FDA approval year, and their efficacy target(s) were collected from the annual reports of FDA drug approval reports in Nature Reviews Drug Discovery February Issues [Mullard 2016] and the Therapeutic target database (TTD) [Li et al. 2018, Zhu et al. 2010] (**Supplementary Table S1**). The efficacy target(s) of each drug was evaluated or searched from the literatures [Li et al. 2018; Zhu et al. 2010] by finding the reported *in-vitro* and *in-vivo* evidence of the association between target modulation and therapeutic effects against the drug-targeted cancers [Overington et al. 2006].

2.3 | Rational division of drugs into sales comparison groups

Apart from the competitive properties of the drugs, drug sales can be influenced by such non-drug factors as the patient population size in the drug-targeted cancer or subtypes, and the market advantage of earlier drug launches. A recent study of drug entry time effects has shown the evidence that the first movers in the follow-on drug market typically capture and maintain greater market share for a long period of time [Andrade et al. 2016]. In order to optimally exclude these non-drug factors, we divided the 25 drugs into DSC groups (**Table 1**), where the drugs in each DSC group have been approved within 0-4 years apart for the treatment of the same cancer or subtype by inhibiting the same target. Specifically, the 25 drugs were firstly grouped into 8 DSC groups with the drugs in each group targeting the same kinase target for the treatment of the same cancer. Then, the four drugs in each of the three DSC groups, the Abl, EGFR and VEGFR2 renal cell carcinoma group, were further split into two DSC groups for each original DSC group, each split DSC group contains drugs of

comparable FDA approval year (within 0-4 years apart), resulting in six DSC groups each containing 2 drugs of comparable drug approval years. These six DSC groups are Abl-DSC1, Abl-DSC2, EGFR-DSC1, EGFR-DSC2, VEGFR2-DSC1, and VEGFR2-DSC2. Overall, there are 22 drugs grouped into 11 DSC groups of 7 targets against 5 cancers (**Table 1**). These 11 DSC groups, each composed of 2-3 drugs, are two Abl-DSC groups for chronic myelogenous leukemia, two EGFR-DSC groups and one Alk-DSC group for non-small cell lung cancer, two VEGFR2-DSC and one mTOR-DSC group for renal cell carcinoma, one VEGFR2-DSC group for thyroid cancer, and one BRaf-DSC and one Mek-DSC group for melanoma. The remaining one drug, the Abl inhibitor imatinib, cannot be grouped into any Abl-DSC group because Imatinib has been approved 5-11 years earlier than the other Abl inhibitors.

2.4 | Search of DEMs associated with the efficacy targets of drugs

The DEMs associated with each of the 7 kinase targets (**Supplementary Table S2**) were from the literatures [Tao et al. 2015] by the criterion that, in *in-vitro* and *in-vivo* studies of the drug-targeted cancers, each DEM actively hinders target inhibition by the drug, or the resistance against the targeted-drugs can be significantly reduced by modulating the DEM, or the co-targeting of the target and each DEM by a drug combination synergistically inhibit the target and/or enhance the anticancer activity with respect to the individual targeted drug [Karamouzis et al. 2009; Ng et al. 2012; Poulikakos and Solit 2011; Sawyers 2007].

2.5 | Experimental potency of the drugs against their kinase target and target-associated DEMs

Author Manuscript

The experimental potency of each drug against its **kinase** target and **target-associated DEMs** (**Supplementary Table S4-S9**) were retrieved from the ChEMBL database (version 22) [Gaulton et al. 2017] and additional PubMed literature search using keyword combinations of drug name, “IC₅₀” and “Ki”. 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 DEM, the median potency [Chen et al. 2017] was used for representing the experimental potency of the drug against the target or DEM. For the majority (68%) of the 25 drugs, we were able to find the literature-reported experimental potency data of at least one kinase DEMs, but none of these drugs were found to show sufficient inhibitory potency to any non-kinase DEMs. Hence, there appears to be a need for additional experimental studies to probe the potential activities of these drugs against the non-kinase DEMs.

2.6 | **Human plasma free drug concentration and the criterion for the effective inhibition of drug target and associated DEMs under clinical conditions**

The DEMs that are likely to be effectively inhibited by a drug under clinical conditions were identified by the consideration that, at the FDA recommended dose, the drug concentrations in the patients be comparable to or exceed the level for potent inhibition of DEM. Specifically, we proposed a DEM effective inhibition (DEM-EI) criterion as follows: a drug is assumed to effectively inhibit a DEM under clinical conditions if its DEM inhibitory IC₅₀ or K_i value is comparable to or below the human plasma steady-state free drug concentration (C_{free}) at the FDA recommended dose. C_{free} was used because of its relevance to the *in-vivo*

drug activity [Smith et al. 2010]. It 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 et al. 2015]. The clinically-observed $C_{\max}$, unbound drug fraction, and the FDA recommended dose of drugs (**Supplementary Table S3**) were from the corresponding Medical and Clinical Pharmacology Reviews and Highlights of Prescribing Information pages of the FDA database (<https://www.fda.gov/Drugs>).

2.7 | Collections of annual sales data of the drugs

The annual sales of each of the 25 drugs during 2010-2016 (**Supplementary Table S10**) were searched from the drug manufacturer's annual reports and financial reports supplemented by the additional information from the EvaluateTM (<http://www.evaluategroup.com>) and the media reports. The sales of BRAf inhibitor dabrafenib and Mek inhibitor trametinib were reported together as a single figure in the GSK annual reports because these two drugs have been clinically used as a drug combination. Because 44% of the 25 drugs were approved since 2012, there is no or little sales data of these drugs in 2010-2013, hence we used the annual sales data within the period of 2014-2016 so that we can have reasonable amount of data for our analysis.

2.8 | Analysis of the sales-DEM co-inhibition relationship

The kinase target inhibitory IC_{50} or K_i values of 23 drugs are below the C_{free} , and that of 2 drugs are slightly above the C_{free} (sorafenib median $IC_{50} = 27$ nM and $C_{\text{free}} = 19$ nM, sunitinib median $IC_{50} = 18.9$ nM and $C_{\text{free}} = 17.26$ nM). As expected, all 25 drugs satisfy the DEM-EI

criterion for effective inhibition of their respective kinase target at FDA recommended dose. Using the DEM-EI criterion, we found 4, 7, 2, 2, 1 and 1 drugs may effectively inhibit 1, 2, 3, 4, 5 and 6 DEMs respectively. Hence, the currently available data cover sizeable number of drugs and DEMs for providing useful indication about the sales-DEM co-inhibition relationship. Nonetheless, for some drugs, their annual sales data are missing in some years in the period of 2014-2016. Therefore, the sales-DEM co-inhibition relationship in each DSC group was conducted by the comparative analysis of the number of effectively-inhibited DEMs and the total sales data of the drugs in the DSC group within a DSC-specific period of time. The DSC-specific period for time for each DSC group is the longest period of time with the annual sales data available for all drugs in the group.

3 | RESULTS

Table 1 provides the relevant information about the FDA approval year, the number and the list of the effectively inhibited DEMs, annual sales data and percentage of each drug sales in total sales for each DSC in the period of 2014-2016, and the sales-DEM co-inhibition relationship of the 25 drugs. Because of the lack of the annual sales data for some drugs in certain years in 2014-2016, the DSC-specific period of time varies among different DSC groups. There are 3, 3 and 5 DSC groups with the DSC-specific period of 1, 2, and 3 years respectively. The sales-DEM co-inhibition relationship of each drug was tentatively derived based on the annual sales data in the respective DSC-specific period of time despite the varying time frames.

We found 19 (76%) drugs in 9 DSC groups to follow and 3 (12%) drugs in 1-DSC group not to follow the expectation of higher sales associated with the inhibition of higher number of DEMs within each DSC group. For instance, in **Figure 2**, there are two drugs sunitinib and sorafenib in the VEGFR2-DSC1 group for the treatment of renal cell carcinoma. In 2014-2016, these two drugs recorded 3-year sales of \$3,389 millions and \$2,535 millions respectively, representing 57.2% and 42.8% of the total sales of the DSC group. They are likely to effectively inhibit 3 DEMs (c-Kit, CSF1R, and PDGFR β) and 2 DEMs (CRaf and VEGFR3) respectively. Therefore, the two drugs in this DSC group follow the expectation that higher sales are associated with the effective inhibition of higher number of DEMs. The three drugs (crizotinib, alectinib and ceritinib) not following the expectation are Alk inhibitors in the Alk-DSC group. Alk is a relatively new target with significantly less number of known target-associated DEMs than those of the other 5 targets of the other 8 DSC groups (8 kinase DEMs for Alk vs. 11-16 kinase DEMs for the other 5 assessed targets). Thus, more extensive knowledge of the DEMs may be needed to assess these three drugs.

The remaining 2 (8%) drugs in 1 DSC group and 1 (4%) drug not in any DSC group cannot be assessed due to insufficient DEM data and incomparability (inability to compare with another drug) respectively. Our study revealed that drug sales are strongly influenced by the number of DEMs inhibited by the kinase inhibitor drugs. The two drugs that cannot be assessed are everolimus and temsirolimus in the mTOR-DSC group, which have no published kinase potency data other than mTOR. These drugs are unlikely single kinase inhibitors, knowing that another mTOR inhibitor sirolimus of the same macrocyclic scaffold co-inhibits multiple kinases including two mTOR-associated DEMs [Bain et al. 2007]. A more

comprehensive experimental study of the kinase inhibitory profiles of these two drugs are needed for assessing the sales-DEM co-inhibition relationship for these drugs. Temsirolimus is a prodrug of sirolimus [Yuan et al. 2009]. Apart from the anticancer effect of temsirolimus, there have been studies for the anticancer effects of sirolimus [Hu et al. 2011]. However, sirolimus has thus far not been approved for anticancer treatment. Moreover, the manufacturer has not attributed the therapeutic mechanism of temsirolimus to its metabolite such as sirolimus. Therefore, we did not consider the potential contribution of the metabolites of temsirolimus in our analysis of the sales-DEM co-inhibition relationships.

4 | DISCUSSIONS

Taken together, drug sales strongly indicate the clinical advantage of multi-target inhibition of cancer drug escapes, such that the majority (at least 76%) of the 25 kinase inhibitor drugs follow the expectation of inhibition of higher number of DEMs records higher sales within the DSC group. The clinical advantages of the DEM-targeted drugs are also reflected by their impressive drug responses in clinical trials. Nonetheless, these advantages have only led to moderate improvement of survival rates in most cancers [Blumenthal et al. 2015; Molina et al. 2014]. Moreover, some of these drugs such as anti-angiogenesis VEGFR2 inhibitor pazopanib do not always achieve clinical efficacy in all the cancers they are expected to be effective [Jain et al. 2006; Weiss et al. 2014]. These moderate survival benefit and the limited clinical effectiveness are largely due to the ample abilities and multiple mechanisms possessed by the tumors in activating multiple drug escape and compensatory

pathways [Kamb et al. 2007; Sennino and McDonald 2012] for promoting robust drug resistance, survival and logistics (e.g. angiogenesis).

A considerable number of drug-escape pathways and DEMs have been and more will likely be discovered for every anticancer drug target class (**Supplementary Table S2**). Based on the currently available data, every approved and clinical trial multi-target drugs only co-inhibit a small fraction of the known DEMs of the respective target class (**Table 1**). Although these drugs may co-inhibit more DEMs than the numbers revealed by the current data, it is unlikely that these drugs individually are sufficient for coping with the activation of multiple drug escape and compensatory mechanisms. There is a need for the development of more diverse sets of multi-target drugs and drug combinations that collectively and dynamically co-target cancers and the active drug-escape and compensatory pathways in various patient subgroups for providing stratified and individualized anticancer therapeutics.

Drug sales are influenced not only by factors related to the co-inhibition of DEMs, but also by other factors such as drug dosage forms. Taking the two drugs in the Abl-DSC1 group as an example, nilotinib has been marketed as Tasigna in a 14 days package of 28 capsules (150mg pills) with a recommended dose of 2 capsules per day while dasatinib has been marketed as Sprycel in a 30 days package of 30 capsules (100mg pills) with a recommended dose of 1 capsule per day. A question is whether the lower dose and dose intensity of dasatinib may contribute to its higher sales. It has been reports about physicians' varied preferences for prescribing the doses of anticancer chemotherapy drugs [Sakai et al. 2015]. Moreover, cancer patients' attitude and adherence to drug prescriptions can be affected by drug doses [Timmers et al. 2014; Barthelemy et al. 2015] and dose intensities

[Iwamoto et al. 2018; Shirotake et al. 2016]. However, the contribution of these clinical factors is complicated. For instance, physicians are not necessarily in favor of lower doses of chemotherapy drugs when faced with potential side effects in cancer patients [Sakai et al. 2015]. Metastatic renal cell carcinoma patients receiving higher relative dose intensity first-line sunitinib treatment have a longer progression-free survival and overall survival than the lower relative dose intensity group [Iwamoto et al. 2018]. A more comprehensive study is needed for accurately probing the contribution of these and other factors to drug sales.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

- Andrade LF, Sermet C, Pichetti S. 2016. Entry time effects and follow-on drug competition. *The European Journal of Health Economics* 17(1):45-60.
- Avril S, Dincer Y, Malinowsky K, Wolff C, Gundisch S, Hapfelmeier A, Boxberg M, Bronger H, Becker KF, Schmalfeldt B. 2017. Increased PDGFR-beta and VEGFR-2 protein levels are associated with resistance to platinum-based chemotherapy and adverse outcome of ovarian cancer patients. *Oncotarget* 8(58):97851-97861.
- Bain J, Plater L, Elliott M, Shpiro N, Hastie CJ, McLauchlan H, Klevernic I, Arthur JS, Alessi DR, Cohen P. 2007. The selectivity of protein kinase inhibitors: a further update. *Biochemical Journal* 408(3):297-315.

- Barthelemy P, Asmane-De la Porte I, Meyer N, Duclos B, Serra S, Dourthe LM, Ame S, Litique V, Giron C, Goldbarg V and others. 2015. Adherence and patients' attitudes to oral anticancer drugs: a prospective series of 201 patients focusing on targeted therapies. *Oncology* 88(1):1-8.
- Blumenthal GM, Karuri SW, Zhang H, Zhang L, Khozin S, Kazandjian D, Tang S, Sridhara R, Keegan P, Pazdur R. 2015. Overall response rate, progression-free survival, and overall survival with targeted and standard therapies in advanced non-small-cell lung cancer: US Food and Drug Administration trial-level and patient-level analyses. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 33(9):1008-14.
- Boshuizen J, Koopman LA, Krijgsman O, Shahrabi A, van den Heuvel EG, Ligtenberg MA, Vredevoogd DW, Kemper K, Kuilman T, Song JY and others. 2018. Cooperative targeting of melanoma heterogeneity with an AXL antibody-drug conjugate and BRAF/MEK inhibitors. *Nature medicine* 24(2):203-212.
- Chen B, Ma L, Paik H, Sirota M, Wei W, Chua MS, So S, Butte AJ. 2017. Reversal of cancer gene expression correlates with drug efficacy and reveals therapeutic targets. *Nature communication* 8:16022.
- Dienstmann R, De Dosso S, Felip E, Tabernero J. 2012. Drug development to overcome resistance to EGFR inhibitors in lung and colorectal cancer. *Molecular oncology* 6(1):15-26.

- Gaulton A, Hersey A, Nowotka M, Bento AP, Chambers J, Mendez D, Mutowo P, Atkinson F, Bellis LJ, Cibrian-Uhalte E and others. 2017. The ChEMBL database in 2017. *Nucleic acids research* 45(D1):D945-D954.
- Hamilton G, Rath B, Burghuber O. 2015. Pharmacokinetics of crizotinib in NSCLC patients. *Expert opinion on drug metabolism & toxicology* 11(5):835-42.
- Hu M, Ekshyyan O, Herman Fernandez L, Rong X, Caldito G, Nathan CO. 2011. Efficacy and comparative effectiveness of sirolimus as an anticancer drug. *Laryngoscope* 121(5):978-82.
- Iwamoto K, Ishihara H, Takagi T, Kondo T, Yoshida K, Iizuka J, Tanabe K. 2018. Evaluation of relative dose intensity during the early phase of first-line sunitinib treatment using a 2-week-on/1-week-off regimen for metastatic renal cell carcinoma. *Medical Oncology* 35(6):78.
- Jain RK, Duda DG, Clark JW, Loeffler JS. 2006. Lessons from phase III clinical trials on anti-VEGF therapy for cancer. *Nature clinical practice. Oncology* 3(1):24-40.
- Kamb A, Wee S, Lengauer C. 2007. Why is cancer drug discovery so difficult? *Nature reviews. Drug discovery* 6(2):115-20.
- Kanda R, Kawahara A, Watari K, Murakami Y, Sonoda K, Maeda M, Fujita H, Kage M, Uramoto H, Costa C and others. 2013. Erlotinib resistance in lung cancer cells mediated by integrin beta1/Src/Akt-driven bypass signaling. *Cancer research* 73(20):6243-53.

Karamouzis MV, Konstantinopoulos PA, Papavassiliou AG. 2009. Targeting MET as a strategy to overcome crosstalk-related resistance to EGFR inhibitors. *The Lancet. Oncology* 10(7):709-17.

Katakami N, Atagi S, Goto K, Hida T, Horai T, Inoue A, Ichinose Y, Koboyashi K, Takeda K, Kiura K and others. 2013. LUX-Lung 4: a phase II trial of afatinib in patients with advanced non-small-cell lung cancer who progressed during prior treatment with erlotinib, gefitinib, or both. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 31(27):3335-41.

Li YH, Yu CY, Li XX, Zhang P, Tang J, Yang Q, Fu T, Zhang X, Cui X, Tu G and others. 2018. Therapeutic target database update 2018: enriched resource for facilitating bench-to-clinic research of targeted therapeutics. *Nucleic Acids Res* 46(D1):D1121-D1127.

Mitchell R, Hopcroft LEM, Baquero P, Allan EK, Hewit K, James D, Hamilton G, Mukhopadhyay A, O'Prey J, Hair A and others. 2017. Targeting BCR-ABL-Independent TKI Resistance in Chronic Myeloid Leukemia by mTOR and Autophagy Inhibition. *Journal of the National Cancer Institute* 110(5):467-478

Molina AM, Lin X, Korytowsky B, Matczak E, Lechuga MJ, Wiltshire R, Motzer RJ. 2014. Sunitinib objective response in metastatic renal cell carcinoma: analysis of 1059 patients treated on clinical trials. *European journal of cancer* 50(2):351-8.

Mullard A. 2016. 2015 FDA drug approvals. *Nature reviews. Drug discovery* 15(2):73-6.

- Ng KP, Hillmer AM, Chuah CT, Juan WC, Ko TK, Teo AS, Ariyaratne PN, Takahashi N, Sawada K, Fei Y and others. 2012. A common BIM deletion polymorphism mediates intrinsic resistance and inferior responses to tyrosine kinase inhibitors in cancer. *Nature medicine* 18(4):521-8.
- Overington JP, Al-Lazikani B, Hopkins AL. 2006. How many drug targets are there? *Nature reviews. Drug discovery* 5(12):993-6.
- Poulikakos PI, Solit DB. 2011. Resistance to MEK inhibitors: should we co-target upstream? *Sci Signal* 4(166):pe16.
- Qi J, McTigue MA, Rogers A, Lifshits E, Christensen JG, Janne PA, Engelman JA. 2011. Multiple mutations and bypass mechanisms can contribute to development of acquired resistance to MET inhibitors. *Cancer research* 71(3):1081-91.
- Sakai H, Katsumata N, Kadokura G. 2015. Attitudes and practice patterns for maintaining relative dose intensity of chemotherapy in outpatient clinics: results of a Japanese web-based survey. *BMC Cancer* 15:651.
- Sawyers CL. 2007. Cancer: mixing cocktails. *Nature* 449(7165):993-6.
- Schlumberger M, Jarzab B, Cabanillas ME, Robinson BG, Pacini F, Ball DW, McCaffrey JC, Newbold KL, Allison R, Martins RG and others. 2015. A Phase 2 Trial of the Multi-targeted Tyrosine Kinase Inhibitor Lenvatinib (E7080) in Advanced Medullary Thyroid Cancer (MTC). *Clinical cancer research : an official journal of the American Association for Cancer Research*.

- Sennino B, McDonald DM. 2012. Controlling escape from angiogenesis inhibitors. *Nature reviews. Cancer* 12(10):699-709.
- Shirotake S, Yasumizu Y, Ito K, Masunaga A, Ito Y, Miyazaki Y, Hagiwara M, Kanao K, Mikami S, Nakagawa K and others. 2016. Impact of Second-Line Targeted Therapy Dose Intensity on Patients With Metastatic Renal Cell Carcinoma. *Clinical Genitourinary Cancer* 14(6):e575-e583.
- Smith DA, Di L, Kerns EH. 2010. The effect of plasma protein binding on in vivo efficacy: misconceptions in drug discovery. *Nature reviews. Drug discovery* 9(12):929-39.
- Tao L, Zhu F, Xu F, Chen Z, Jiang YY, Chen YZ. 2015. Co-targeting cancer drug escape pathways confers clinical advantage for multi-target anticancer drugs. *Pharmacological research* 102:123-31.
- Timmers L, Boons CC, Kropff F, van de Ven PM, Swart EL, Smit EF, Zweegman S, Kroep JR, Timmer-Bonte JN, Boven E and others. 2014. Adherence and patients' experiences with the use of oral anticancer agents. *Acta Oncologica* 53(2):259-67.
- Toyokawa G, Seto T. 2015. Updated Evidence on the Mechanisms of Resistance to ALK Inhibitors and Strategies to Overcome Such Resistance: Clinical and Preclinical Data. *Oncology research and treatment* 38(6):291-8.
- Turner NC, Reis-Filho JS. 2012. Genetic heterogeneity and cancer drug resistance. *The Lancet. Oncology* 13(4):e178-85.
- Weiss JM, Villaruz LC, Socinski MA, Ivanova A, Grilley-Olson J, Dhruva N, Stinchcombe TE. 2014. A single-arm phase II trial of pazopanib in patients with advanced non-

small cell lung cancer with non-squamous histology with disease progression on bevacizumab containing therapy. *Lung cancer* 86(2):288-90.

Wilson TR, Fridlyand J, Yan Y, Penuel E, Burton L, Chan E, Peng J, Lin E, Wang Y, Sosman J and others. 2012. Widespread potential for growth-factor-driven resistance to anticancer kinase inhibitors. *Nature* 487(7408):505-9.

Yang H, Qin C, Li YH, Tao L, Zhou J, Yu CY, Xu F, Chen Z, Zhu F, Chen YZ. 2016. Therapeutic target database update 2016: enriched resource for bench to clinical drug target and targeted pathway information. *Nucleic acids research* 44(D1):D1069-74.

Yuan R, Kay A, Berg WJ, Lebowitz D. 2009. Targeting tumorigenesis: development and use of mTOR inhibitors in cancer therapy. *Journal of Hematology & Oncology* 2:45.

Zhu F, Han B, Kumar P, Liu X, Ma X, Wei X, Huang L, Guo Y, Han L, Zheng C. 2010. Update of TTD: Therapeutic Target Database. *Nucleic Acids Research* 38(Database issue):D787-91.

TABLE 1 The drug escape mediator inhibitory and sales profiles of the FDA approved multi-target kinase inhibitor drugs grouped into drug sales comparison (DSC) groups. Drugs in each DSC group target the same cancer (approved by FDA) and efficacy target, and are of comparable FDA approval year (within 0-4 years apart). The sales-DEM co-inhibition relationship is categorized as following (F), not following (N), or unclear (U) relationship to the expectation of higher sales associated with drug co-inhibition of higher number of DEMs within each DSC group. NA indicates the drug is not applicable because it is not in any DSC group.

Drug Targeted Cancer	Drug Efficacy Target	DSC Group	Drug	FDA Approval Year	No and List of DEMs Sufficiently Inhibited by Drug	Annual Drug Sales in USD \$Million (Year)	Drug Sales in the Longest Period with Available Data for All Drugs in the DSC group (Year-Year)	Percent of the Total Drug Sales of the DSC Group in the Period Specified in Previous Column	Sales-DEM Co-Inhibition Relationship [†]
Chronic myelogenous leukemia	Abl	None	Imatinib	2001	2 (c-Kit, Lyn)	4776 (14), 4658 (15), 3323 (16)	12756 (14-16)	NA	NA
		Abl-DSC1	Nilotinib	2007	0	1529 (14), 1632 (15), 1739 (16)	4900 (14-16)	49.9%	F
			Dasatinib	2006	6 (c-Kit, EphB4, FGR, Fyn, Hck, Lyn)	1493 (14), 1620 (15), 1800 (16)	4913 (14-16)	50.1%	F
		Abl-DSC2	Ponatinib	2012	5 (EphB4, FGR, Fyn, Hck, Lyn)	112.5 (15), 205 (16)	317.5 (15-16)	54.4%	F
			Bosutinib	2012	4 (EphB4, FGR, Hck, Lyn)	109 (15), 157 (16),	266 (15-16)	45.6%	F
Non-small cell lung cancer	EGFR	EGFR-DSC1	Erlotinib	2004	3 (HER2, PDGFR β , VEGFR2)	1292 (14), 1181 (15), 1024 (16)	3497 (14-16)	67.6%	F
			Gefitinib	2003	0	623 (14), 543 (15), 513 (16)	1679 (14-16)	32.4%	F
		EGFR-DSC2	Afatinib	2013	1 (HER2)	73.6 (14), 114.3 (15)	114.3 (15)	85.7%	F
			Osimertinib	2015	0	19 (15), 423 (16)	19 (15)	14.3%	F

	ALK	ALK-DSC	Crizotinib	2011	2 (EML-ALK, ROS1)	488 (15), 561 (16)	1049 (15-16)	71.4%	N
			Alectinib	2015	0	67 (15), 182 (16)	249 (15-16)	17.0%	N
			Ceritinib	2014	2 (EML-ALK, IGF1R)	79 (15), 91 (16)	170 (15-16)	11.6%	N
Renal cell carcinoma	VEGFR2	VEGFR2-DSC1	Sunitinib	2006	3 (c-Kit, CSF1R, PDGFR β)	1174 (14), 1120 (15), 1095 (16)	3389 (14-16)	57.2%	F
			Sorafenib	2005	2 (CRaf, VEGFR3)	773 (14), 892 (15), 870 (16)	2535 (14-16)	42.8%	F
		VEGFR2-DSC2	Pazopanib	2009	4 (c-Kit, CSF1R, PDGFR β , VEGFR3)	410 (14), 565 (15), 729 (16)	1704 (14-16)	57.9%	F
			Axitinib	2012	0	410 (14), 430 (15), 401 (16)	1241 (14-16)	42.1%	F
	mTOR	mTOR-DSC	Everolimus	2009	0	1607 (15), 1516 (16)	3123 (15-16)	95.1%	U
			Temsirolimus (prodrug of sirolimus)	2007	0	90 (15), 70 (16)	160 (15-16)	4.9%	U
Thyroid cancer	VEGFR2	VEGFR2-DSC3	Vandetanib	2011	1 (EGFR)	112 (16)	112 (16)	32.7%	F
			Lenvatinib	2015	2 (FGFR2, VEGFR3)	189 (16)	189 (16)	55.2%	F
			Cabozantinib	2012	1 (c-MET)	41.9 (16)	41.9 (16)	12.1%	F
Melanoma	Braf	BRaf-DSC	Vemurafenib	2011	1 (CRaf)	301 (14), 214 (15), 213 (16)	728 (14-16)	35.2%	F
			Dabrafenib+ Trametinib	2013	2 (CRaf, MEK2)	135 (14), 534 (15), 672 (16)	1341 (14-16)	64.8%	F
	Mek1	Mek-DSC	Trametinib+ Dabrafenib	2013	2 (BRaf(V600E), MEK2)	672 (16)	672 (16)	93.7%	F
			Cobimetinib	2015	0	45 (16)	45 (16)	6.3%	F

[†]The sales - DEM co-inhibition relationship for each drug is F: follows the expectation of the inhibition of higher number of DEMs records higher sales within the DSC group, N: not follows the expectation, U: uncertain, NA: not applicable. The detail and references of the DEM inhibitory and sales profiles are provided in Supplementary Table **S3-S10**.

FIGURE 1 An outline of the analysis procedure of the study. The 25 FDA approved drugs were collected and divided into 11 DSC groups of 7 targets. The DEM information related to the 7 targets, experimental potency, *in vivo* free drug concentration and drug sales data of the 25 drugs were then collected respectively. The *in vivo* free drug concentration was used as cut-off to determine whether the DEMs were sufficiently inhibited by the drugs *in vivo*. Finally, the sales-DEM co-inhibition relationship for each drug was evaluated.

FIGURE 2 Illustration of an example of the two drugs (sunitinib and sorafenib) in VEGFR2-DSC1 group follow the expectation of the inhibition of higher number of DEMs records higher sales.

Minerva Access is the Institutional Repository of The University of Melbourne

Author/s:

Chen, S;Yang, SY;Chen, Z;Tan, Y;Jiang, YY;Chen, YZ

Title:

Drug sales confirm clinical advantage of multi-target inhibition of drug escapes by anticancer kinase inhibitors

Date:

2019-03-01

Citation:

Chen, S., Yang, S. Y., Chen, Z., Tan, Y., Jiang, Y. Y. & Chen, Y. Z. (2019). Drug sales confirm clinical advantage of multi-target inhibition of drug escapes by anticancer kinase inhibitors. DRUG DEVELOPMENT RESEARCH, 80 (2), pp.246-252. <https://doi.org/10.1002/ddr.21486>.

Persistent Link:

<http://hdl.handle.net/11343/285180>