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**Pharmacogenomic Biomarkers as Inclusion Criteria in Clinical Trials of Oncology Targeted  
Drugs: A Mapping of ClinicalTrials.gov**

Short Running title: Pharmacogenomic Biomarkers in Oncology Targeted Drugs Trials

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## **ABSTRACT**

**Purpose:** To describe pharmacogenomics-based inclusion criteria (enrichment) and main characteristics of clinical trials involving oncology targeted therapies.

**Methods:** Clinical trials of oncology targeted therapies approved after 2005 with pharmacogenomic testing required or recommended in their label were retrieved from a mapping of clinicaltrials.gov database.

**Results:** We included 12 drugs and 858 trials. Overall, 434 trials (51%) were enriched on the biomarker first mentioned in the label and 145 (17%) on another biomarker whereas 270 (31%) trials included all patients. The median proportion of trials corresponding to both the drug's indication and drug's target was 35%. Among the 361 trials which tested drugs in another disease than the first one in the label, 219 (61%) were without enrichment and 87 (24%) were actually enriched but on another biomarker than the first one in the label.

**Conclusions:** Several drugs have been tested in trials enriched on many different biomarkers.

Nonetheless, most of targeted therapies have been developed only in biomarker-positive patients and, therefore, exclusion of biomarker-negative patients from treatment relies on only pre-clinical data and on biological understanding of the disease and target.

**Key Words:** Clinical Trials; Biomarkers; Pharmacogenomics; Food and Drug Administration; Personalized Medicine.

## INTRODUCTION

In recent years oncology care has been completely transformed by the development and growth of molecular targeted therapies,<sup>1</sup> which has led to the concept of precision (or personalized or genomic) oncology.<sup>2,3</sup> A landmark example is imatinib, which has revolutionized the treatment of chronic myeloid leukemia. Other examples are vemurafenib for melanoma, trastuzumab and ado-trastuzumab for breast cancer, and crizotinib for lung cancer. These drugs need a pharmacogenomic biomarker to guide treatment decision-making<sup>4</sup> because the indications for these drugs are biomarker-based (e.g., "*unresectable or metastatic melanoma with BRAF V600E mutation*" for vemurafenib). However, some targeted therapies, such as bevacizumab, do not require a biomarker assessment before prescription. This does not mean that no pharmacogenomic biomarker actually exists but that none has yet been validated or even found. Furthermore, some drugs, such as everolimus, may have one biomarker-based indication ("*advanced hormone receptor-positive, HER2-negative breast cancer*") and another non-biomarker-based indication ("*advanced renal cell carcinoma*"). Currently, the label of 140 US Food and Drug Administration (FDA)-approved drugs mentions a pharmacogenomic biomarker, one-third indicated in oncology<sup>5</sup>.

A drug that has been tested only in a biomarker-positive subpopulation would have an implicit requirement for genetic testing,<sup>5,6</sup> and one may consider that a high-quality trial with only biomarker-positive patients (i.e., an enriched trial) correspond to an acceptable level of evidence for targeted therapies.<sup>7,8</sup> Nonetheless, if no clinical data are available for biomarker-negative patients, the use of a biomarker to restrict treatment to a subgroup of patients may not be relevant, as noted by several regulatory agencies.<sup>6,9,10</sup> It may seem natural and logical to study a targeted drug in only patients with tumors harboring this target, and, therefore, the hallmark trial design for targeted therapy is an enriched design. This design increases the study power and therefore reduces the sample size and time to detect an effect<sup>11,12</sup> but does not provide information about the drug efficacy in biomarker-negative patients. Actually, considering the treatment effect to be null in biomarker-negative patients *a priori* means withdrawing treatment for some patients based on only preclinical data and the biological understanding of the drug mechanism of action and its target. Therefore, if the biomarker is not a

perfect predictor of response (because of the test intrinsic qualities or because the treatment is also effective in some true negative patients), one may deny patients a treatment they would have otherwise benefitted from.<sup>9,13,14</sup>

We have several examples of this risk of denying some potential patients treatment. For example, some patients with HER2-negative tumors have benefitted from trastuzumab.<sup>15</sup> Indeed, 16 of 22 HER2-negative patients with HER-2 extracellular domain level > 15 ng/ml showed a clinical benefit, which led to the concept of "hidden" HER-2-positive breast cancer.<sup>16</sup> Furthermore, contrary to expectations, the level of HER-2 did not predict clinical response and showed a U-shaped relationship, which suggested that trastuzumab could be effective in HER2-negative tumors.<sup>17</sup> Another example is cetuximab, the anti-EGFR drug, originally studied in only patients with EGFR-expressing tumors until it was found also beneficial for some patients with EGFR-negative tumors.<sup>18,19</sup> Later, retrospective analyses of randomized clinical trial data revealed that only patients with RAS wild-type tumors benefitted from the treatment.<sup>20,21</sup> The anti-EGFR therapies cetuximab and panitumumab are now restricted to patients with RAS wild-type tumors.

The emergence of targeted therapies has also transformed drug development.<sup>19,22–25</sup> The ideal goal in personalized medicine is the co-development of the drug and the biomarker (i.e., the biomarker is found in the early stages of drug development and both the drug and the biomarker test are developed concurrently). Nonetheless, for some drugs, the biomarker could have been discovered after the drug approval, and for other drugs, supplemental biomarkers could have been discovered after the discovery of the first one; hence, a targeted drug could have several pharmacogenomic biomarkers. Both drug–target development and characteristics of clinical trials evaluating targeted therapies—especially pharmacogenomic biomarkers used as inclusion criteria—are of crucial importance to understand how those drugs are studied.

We aimed to map the clinical trial development for oncology targeted therapies in order to assess the main characteristics of clinical trials involving oncology targeted therapies and their evolution after first FDA approval. We analyzed (i) the characteristics of oncology targeted therapies with pharmacogenomic testing required or recommended on their label; (ii) the characteristics of

corresponding registered clinical trials, especially the use of an enrichment design; and (iii) the evolution of these characteristics over the drug development period.

## **METHODS**

### **List of Drugs**

On November 10, 2014, we extracted the list of oncology targeted therapies from the US National Cancer Institute website.<sup>26</sup> We then selected drugs from the FDA Table of Pharmacogenomic Biomarkers in Drug Labeling<sup>27</sup> for which the label required or recommended genetic testing, based on a previous work.<sup>5</sup> We excluded drugs approved before 2005 because the International Committee of Medical Journal Editors required prospective registration of clinical trials as a precondition for publication in September 2004.<sup>28</sup> For each included drug, we searched ClinicalTrials.gov on November 10, 2014 using the name of drug as a keyword and extracted all retrieved studies without any additional limits.

### **Eligibility of Clinical Trials**

Clinical trials were included if they were interventional clinical trials evaluating one included targeted drug as an experimental treatment (alone or combined with another drug). Two authors (AV and JL) independently assessed eligibility; any disagreements were resolved by consensus.

### **Data Extraction**

Two authors (AV and JL) independently extracted data on biomarker-based criteria for including patients in clinical trials (i.e., enrichment) and, when appropriate, the names of the biomarkers. They compared all the data extracted and any disagreements were resolved by consensus. We considered studies in chronic myelogenous leukemia, a disease associated with Philadelphia chromosome, as being implicitly enriched on this biomarker because Philadelphia chromosome is part of this disease's definition.<sup>29</sup> Other trial characteristics were extracted from ClinicalTrials.gov. The primary outcome was coded as overall survival or event-free survival (progression-free, disease-free or any event-free survival as defined in the trial registration) or time to progression, following this hierarchical and exclusive classification. To classify the diseases studied in each trial, we mapped the MeSH terms from ClinicalTrials.gov records to the list of diseases from the global burden of disease 2013 study.<sup>30</sup>

From the Drugs@FDA database and as previously described,<sup>5</sup> we extracted the date of the drug approval, the date of the first label containing pharmacogenomic information, the first indication for the drug and, if different, the first indication for the drug with pharmacogenomic labeling, and the date the drug's sponsor submitted the application to the regulation agency. From the European Medicines Agency (EMA) website, we obtained the date of marketing authorization valid throughout the European Union and the date of submission of the application to the agency. We considered the first submission of an application to the FDA or EMA as a proxy for the end of drug development and the first approval of the drug by one agency as the start of drug marketing. Trials with a start date before the first submission of an application were classified as "before submission", trials with a start date after the drug approval by FDA or EMA application were classified as "after approval", and trials in between as "between submission and approval".

### **Statistical Analysis**

We used only descriptive statistics. Continuous variables are presented as median and interquartile range (IQR) because most variables are not normally distributed and qualitative variables as frequencies (percentage). Analyses were performed with R version 3.1.0 (R Core Team, Vienna, Austria).

## **RESULTS**

### **Included Drugs and Clinical Trials**

The NCI listed 69 oncology targeted therapies, 22 also included in the FDA Table of Pharmacogenomic Biomarkers in Drug Labeling and having a label requiring or recommending genetic testing. Nine drugs were approved before 2005 and were excluded. Everolimus was also excluded because this single drug represented more than half of trials and the majority corresponded to a new non-cancer indication (prevention of organ rejection). Thus, this single drug may need a separate evaluation. We included 12 drugs (detailed characteristics are displayed in Table S1). Overall, 935 studies corresponded to these drugs and were registered in ClinicalTrials.gov; we excluded 77 studies that did not fulfill inclusion criteria and therefore included 858 clinical trials (Figure S1).

## **Clinical Study Characteristics**

Characteristics of the 858 included studies are in Table 1. Half of the studies (n=434, 51%) were enriched on the first biomarker mentioned in the drug label and 145 (17%) on another biomarker and 270 (31%) included patients without restriction for a pharmacogenomic biomarker. Industry was the lead sponsor for 334 studies (39%). The median sample size was 65 patients (Q1-Q3 = 35-154). The most frequent primary outcomes were response rate (37%), event-free survival (19%) and toxicity/dose finding (15%). Most studies (72%) started after the first FDA approval, and only 4% ended before approval. Overall, 497 studies (58%) assessed drug effects for the same disease as for the first approval. More than half of the studies (60%) were single-group studies. For all drugs, the first biomarker was present at approval and corresponded to the drug's target. Figure 1 displays the number of trials and of patients enrolled in enriched trials and in single-arm trials by phase. Enriched trials as well as single-arm trials represented a large proportion of trials and of patients, especially phase 3 trials, which typically enrolled many patients.

## **Mapping of Clinical Trials Before and After FDA Approval**

Figure 2 displays for each drug, the number of trials by year and two characteristics of trials: (i) the use of a biomarker to restrict inclusion in the trial (treat-all patients, use of the same biomarker as the first one mentioned in the drug label, or use of another biomarker) and (ii) random assignment of treatment. Dates of first submission and first approval by the FDA or EMA (whichever came first) are shown by red and black vertical arrows, respectively. All drugs were tested in randomized trials restricted to the biomarker mentioned in the label (red areas). These trials could correspond to trials supporting drug approval and pharmacogenomic labeling. However, some drugs such as afatinib were also tested in non-enriched trials (green areas) and trials enriched on another biomarker (blue areas), whereas some drugs (e.g., dabrafenib) were tested almost exclusively in trials restricted to the biomarker mentioned in the label.<sup>21</sup> Of note, the first trials of afatinib and pertuzumab were not enriched on any biomarker. Vemurafenib was the only drug tested in biomarker-negative patients before FDA approval. After FDA approval, some drugs (e.g., vemurafenib, ado-trastuzumab) were tested in only one disease with trials enriched on the targeted biomarker. The most recent drugs (e.g., bosutinib, crizotinib) were obviously associated with a small number of trials after FDA approval.

Dasatinib and nilotinib were associated with more trials of other diseases than approval indication. Crizotinib was tested in biomarker-negative patients after FDA approval, after a post-marketing commitment of the FDA in its medical review.<sup>31</sup> Overall, among 237 trials started before FDA approval, 128 (54%) were enriched on the biomarker first mentioned in the label and 27 (11%) on another one, whereas among 614 trials started after FDA approval, 305 (50%) were enriched on the first biomarker and 117 (19%) on another biomarker.

### **Evolution of Biomarker and Disease Studied for Each Drug**

Table 1 also displays the main characteristics of clinical trials across three periods of drug development: (i) before the first submission to the FDA or EMA, (ii) after this submission and before first approval by the FDA or EMA, and (iii) after approval. The share of industry-sponsored trials dropped from 73% before submission to 28% after approval. The proportion of trials enriched on the label biomarker and for the corresponding indication ranged from 4% with panitumumab–EGFR+ patients to 88% with ado-trastuzumab–HER-2+ patients. This proportion was still high (sometimes higher) after drug approval.

Figures 3 and 4 show hive plots representing the mapping of the number of clinical trials for drugs, biomarkers and diseases. Multiple-disease trials are represented once for each studied disease, as are multiple-drugs trials. Two patterns of drugs seem to emerge: the first corresponds to drugs tested almost solely in biomarker-positive patients and with the same disease first described on the label (ado-trastuzumab, dabrafenib, vemurafenib) and the second includes drugs tested in trials enriched on other biomarkers, in treat-all trials or in other diseases (all other drugs). These patterns could be seen especially for recent drugs (e.g., ado-trastuzumab vs crizotinib). However, among the first group, dabrafenib and vemurafenib were tested with some other diseases but without expanding the biomarkers used to restrict trials. In the second group, dasatinib, lapatinib and nilotinib appear to be associated with the most diseases and biomarkers used in trials, resulting in very dense figures. Afatinib and bosutinib were tested with many diseases, but as compared to the drugs in the second group, with a relatively small number of biomarkers. Among the 361 trials testing a drug in a disease different than the first indication, there was no enrichment for 219 trials (61%), enrichment on the

biomarker described in the label for 48 trials (13%) , enrichment on a different biomarker for 87 trials (24%), and enrichment on multiple biomarkers for 7 trials (2%).

## DISCUSSION

This mapping of clinical trials of targeted drugs with biomarker labeling shows a great diversity in the drug development of targeted drugs. Indeed, some targeted therapies have been tested with only one biomarker (which is the drug target) and in only one disease whereas others drugs have been tested with several biomarkers (which are not the drug's target) and in several diseases. Another finding of this study is that, although the efficacy of some drugs was studied both in biomarker-positive and -negative patients, most trials were enriched single-arm trials and several drugs were developed with only biomarker-positive patients included in trials. For those drugs, we have therefore no formal clinical evidence for restricting treatment to biomarker-positive patients.

The rationale to test or not a targeted therapy in others patient than the ones who are positive for the target biomarker (i.e., biomarker-negative patients or patients positive for another biomarker) depends on the strength of preclinical data and the rationale for drug targeting,<sup>9,12</sup> the relevance of which we do not discuss here. However, this point deserves careful consideration because of the risk of restricting drug indications to the wrong subpopulation—as it has been initially the case for cetuximab and EGFR expression before predictive role of RAS mutations have been shown— which need to be balanced against the ethics dilemma to expose biomarker-negative patients to a drug from which one thinks they will not derived benefit and strategic consideration about drug development from the drug's sponsor. Moreover, enrichment-only drug development reduces the number of patients exposed to the drug and therefore may also hinder the validity of drug safety evaluation. However, as compared with the number of investigational drugs to be tested in clinical trials, in some therapeutic areas, only a few patients may be eligible; thus, restricting trials to biomarker-positive patients could allow for biomarker-negative patients to be included in another trial, which more likely to be beneficial for them. Of note, at least one health authority agency (the French *Haute Autorité de Santé*) considered a drug to be targeted only with a high level of evidence of qualitative treatment-by-marker

interaction (i.e., the treatment effective only in biomarker-positive patients) and recommended the randomize-all design with randomization stratified on biomarker results.<sup>9</sup>

Nearly one quarter (27%) of enriched trials used a biomarker other than the first one mentioned on the drug's label. For example, trametinib, a MEK kinase inhibitor, has also been studied in trials restricted to patients with KRAS mutations or HER-2 expression. Similarly, afatinib has been studied in several trials of HER-2-positive tumors although its first biomarker is EGFR. However, EGFR and HER-2 are both part of the ErbB family (ErbB-1 and ErbB-2, respectively) and afatinib has an affinity for HER-2. There are several reasons to test a drug with another biomarker than the first one. First, several post approval studies have attempted the discovery of response/resistance biomarkers and some of which are currently under clinical validation phase. Second, some included drugs are highly target selective drugs such as dabrafenib (which is a mutant BRAFV600 specific inhibitor) but others drugs do have affinity for other targets than the ones they were targeted for. This could explain the choice of biomarkers in some of those trials like crizotinib in ROS-1+ patients, dasatinib in PDGFR+ patients or nilotinib in KIT+ or PDGFRB+ patients.

Another likely explanation of the differences in development schemes could be the differences between drugs developed to target a specific mutation: (dasatinib, nilotinib, afatinib, bosutinib, crizotinib, dabrafenib, vemurafenib, and trametinib) and drugs developed to target a molecular pathway (lapatinib, panitumumab, pertuzumab, ado-trastuzumab). Development may be more targeted for the former group than for the latter. However, dabrafenib and vemurafenib both displayed a targeted development scheme (i.e., a small network) whereas trametinib displayed a much less targeted development scheme (i.e., a wider network) although these three drugs were developed to target the BRAF V600 mutations. Overall, the disease-biomarker pairs were similar across drugs, so the disease-biomarker association may be more specific than the drug-biomarker association.

Furthermore, several trials involved multiple biomarkers. These trials could test multiple biomarkers in one disease or with one drug, such as the AcSé (NCT02034981) or CREATE (Cross-tumoral Phase 2 with Crizotinib, NCT01524926) trials, and are called “basket” trials.<sup>32</sup> In contrast, “umbrella” trials such as NCI-MPACT<sup>33</sup> or SHIVA<sup>34</sup> tested multiple biomarkers across a broad range of tumor types.<sup>35</sup> In the open-label controlled, phase 2 SHIVA trial, patients with metastatic solid tumour refractory to

standard of care and with a molecular alteration in PI3K/AKT/mTOR, RAF/MEK or hormone receptor pathways were randomized between matched molecularly targeted agent in a histology-agnostic way and treatment at physician's choice. There were no differences in primary outcome (progression-free survival, PFS) between the two groups: median PFS was 2.3 months (95% CI 1.7–3.8) in the experimental group versus 2.0 months (1.8–2.1) in the control group (hazard ratio 0.88, 95% CI 0.65–1.19,  $p=0.41$ ).<sup>34</sup> These results suggest that relying solely on biomarker (i.e., without histology) to predict efficacy may not be yet possible in oncology.

Our results are consistent with a previous study of general oncology trials, finding that as compared with non-oncology trials, oncology trials were more often single-arm, open-label and non-randomized,<sup>36</sup> a pattern we also found for trials of targeted therapies. We did not specifically assess characteristics of pivotal trials in this study, but for the 55 oncology novel therapeutic agents approved by the FDA between 2005 and 2012, only half of the pivotal trials were randomized, 27% were double-blinded and only 16% had a clinical outcome as a primary end point, reflecting a lower level of evidence of studies for FDA approval in oncology as compared with non-oncology areas.<sup>37</sup> This finding could be explained in part by the high frequency of orphan drugs in oncology and the lower level of evidence for such drugs as compared with non-orphan oncology drugs.<sup>38</sup> This relatively low level of evidence of trials could also be explained by the high number of indication (either the first or subsequent ones) approved under the accelerated approval process as pivotal studies supporting accelerated approvals are often early phase, non-randomized trials using surrogate endpoints.<sup>36,37</sup> A study of pharmacogenomic information in drug labels approved by the EMA found that two thirds of pivotal trials for drugs with a biomarker-based indication have been conducted in only biomarker-positive patients,<sup>39</sup> a pattern we also found in our study of all (not only pivotal) trials.

One strength of this study is the use of data from ClinicalTrials.gov. Because clinical trials take a long time to complete, studies with registration on clinical trial registries can provide information before the end of trials and therefore provide a preview of which studies are currently ongoing. However, the drawback is no access to the results of those trials. This study has several limitations. We used only US data (labels from the FDA and trials registered at clinicaltrials.gov) because we made the assumption that a US-centric view represents biomarker usage in targeted

therapies trials. some trials may have been registered in another registry than clinicaltrials.gov but this would concern only trials conducted outside the United States because publication in ClinicalTrials.gov is mandatory for trials with at least one center in the United States). Some trials may have been conducted before trial registration was required and, thus, we excluded drugs approved before 2005. We analyzed data as provided by the trial's sponsor, which may suggest some errors in coding when the study was registered. Furthermore, we analyzed only targeted therapies with biomarker-based indications because we were interested in how targeted drugs that are restricted to biomarker-positive patients have been developed and especially if the development was targeted and how this might evolve after drug approval. Studying the use of biomarkers in clinical trials of targeted therapies without biomarker-based indication warrants further investigation

## **Conclusion**

Oncology targeted therapies have undoubtedly set the stage for precision medicine, but the drug–biomarker–diseases network is actually more complex than it would seem at first glance. The rationale to test or not a targeted therapy in others patient than the ones who are positive for the target biomarker (i.e., biomarker-negative patients or patients positive for another biomarker) deserves careful consideration because of the risk of over-restricting drug indications and that of exposing patients to a drug which they are not likely to derive benefit from.

## **SUPPLEMENTARY INFORMATION**

Supplementary information is available at the Genetics in Medicine website.

<https://www.nature.com/articles/gim2015165>

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## REFERENCES

1. de Bono JS, Ashworth A. Translating cancer research into targeted therapeutics. *Nature*. 2010;467(7315):543-549. doi:10.1038/nature09339.
2. Schott AF, Perou CM, Hayes DF. Genome Medicine in Cancer: What's in a Name? *Cancer Res*. 2015;75(10):1930-1935. doi:10.1158/0008-5472.CAN-15-0174.
3. Gonzalez de Castro D, Clarke PA, Al-Lazikani B, Workman P. Personalized Cancer Medicine: Molecular Diagnostics, Predictive biomarkers, and Drug Resistance. *Clin Pharmacol Ther*. 2013;93(3):252-259. doi:10.1038/clpt.2012.237.
4. Stegmeier F, Warmuth M, Sellers WR, Dorsch M. Targeted cancer therapies in the twenty-first century: lessons from imatinib. *Clin Pharmacol Ther*. 2010;87(5):543-552. doi:10.1038/clpt.2009.297.
5. Vivot A, Boutron I, Ravaud P, Porcher R. Guidance for pharmacogenomic biomarker testing in labels of FDA-approved drugs. *Genet Med*. December 2014. doi:10.1038/gim.2014.181.
6. US Food and Drug Administration. Guidance for Industry. Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products. <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM332181.pdf>.
7. Wang B, Canestaro WJ, Choudhry NK. Clinical evidence supporting pharmacogenomic biomarker testing provided in US Food and Drug Administration drug labels. *JAMA Intern Med*. 2014;174(12):1938-1944. doi:10.1001/jamainternmed.2014.5266.
8. Simon R, Blumenthal G, Rothenberg M, et al. The role of nonrandomized trials in the evaluation of oncology drugs. *Clin Pharmacol Ther*. 2015;97(5):502-507. doi:10.1002/cpt.86.
9. Haute autorité de santé. Companion diagnostic test associated with a targeted therapy: scientific appendix. April 2014. [http://www.has-sante.fr/portail/jcms/c\\_1776662/en/companion-diagnostic-test-associated-with-a-targeted-therapy-scientific-appendix](http://www.has-sante.fr/portail/jcms/c_1776662/en/companion-diagnostic-test-associated-with-a-targeted-therapy-scientific-appendix).
10. European Medicines Agency. Reflection paper on methodological issues associated with pharmacogenomic biomarkers in relation to clinical development and patient selection. June 2011. [http://www.ema.europa.eu/ema/pages/includes/document/open\\_document.jsp?webContentId=W C500108672](http://www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=W C500108672).
11. Temple R. Enrichment of clinical study populations. *Clin Pharmacol Ther*. 2010;88(6):774-778. doi:10.1038/clpt.2010.233.
12. Sleijfer S, Bogaerts J, Siu LL. Designing Transformative Clinical Trials in the Cancer Genome Era. *J Clin Oncol*. 2013;31(15):1834-1841. doi:10.1200/JCO.2012.45.3639.
13. Messersmith WA, Ahnen DJ. Targeting EGFR in Colorectal Cancer. *N Engl J Med*. 2008;359(17):1834-1836. doi:10.1056/NEJMe0806778.

14. Graf AC, Posch M, Koenig F. Adaptive designs for subpopulation analysis optimizing utility functions. *Biom J*. 2015;57(1):76-89. doi:10.1002/bimj.201300257.
15. Paik S, Kim C, Wolmark N. HER2 Status and Benefit from Adjuvant Trastuzumab in Breast Cancer. *N Engl J Med*. 2008;358(13):1409-1411. doi:10.1056/NEJMc0801440.
16. Ardavanis A, Kountourakis P, Kyriakou F, et al. Trastuzumab plus Paclitaxel or Docetaxel in HER-2–Negative/HER-2 ECD–Positive Anthracycline- and Taxane-Refractory Advanced Breast Cancer. *The Oncologist*. 2008;13(4):361-369. doi:10.1634/theoncologist.2007-0207.
17. Tuma RS. Cancer Stem Cell Hypothesis and Trastuzumab in HER2-Negative Tumors. *J Natl Cancer Inst*. 2012;104(13):968-969. doi:10.1093/jnci/djs307.
18. Chung KY, Shia J, Kemeny NE, et al. Cetuximab Shows Activity in Colorectal Cancer Patients With Tumors That Do Not Express the Epidermal Growth Factor Receptor by Immunohistochemistry. *J Clin Oncol*. 2005;23(9):1803-1810. doi:10.1200/JCO.2005.08.037.
19. Phelps MA, Sparreboom A. A Snapshot of Challenges and Solutions in Cancer Drug Development and Therapy. *Clin Pharmacol Ther*. 2014;95(4):341-346. doi:10.1038/clpt.2014.15.
20. Atreya CE, Corcoran RB, Kopetz S. Expanded RAS: Refining the Patient Population. *J Clin Oncol*. 2015;33(7):682-685. doi:10.1200/JCO.2014.58.9325.
21. Amado RG, Wolf M, Peeters M, et al. Wild-Type KRAS Is Required for Panitumumab Efficacy in Patients With Metastatic Colorectal Cancer. *J Clin Oncol*. 2008;26(10):1626-1634. doi:10.1200/JCO.2007.14.7116.
22. Fridlyand J, Simon RM, Walrath JC, et al. Considerations for the successful co-development of targeted cancer therapies and companion diagnostics. *Nat Rev Drug Discov*. 2013;12(10):743-755. doi:10.1038/nrd4101.
23. Zineh I, Huang S-M. Biomarkers in drug development and regulation: a paradigm for clinical implementation of personalized medicine. *Biomark Med*. 2011;5(6):705-713. doi:10.2217/bmm.11.90.
24. Parkinson DR, Johnson BE, Sledge GW. Making Personalized Cancer Medicine a Reality: Challenges and Opportunities in the Development of Biomarkers and Companion Diagnostics. *Clin Cancer Res*. 2012;18(3):619-624. doi:10.1158/1078-0432.CCR-11-2017.
25. Woodcock J. The Prospects for “Personalized Medicine” in Drug Development and Drug Therapy. *Clin Pharmacol Ther*. 2007;81(2):164-169. doi:10.1038/sj.clpt.6100063.
26. Targeted Cancer Therapies. *Natl Cancer Inst*.  
<http://www.cancer.gov/cancertopics/factsheet/Therapy/targeted>. Accessed January 12, 2015.
27. US Food and Drug Administration. Genomics - Table of Pharmacogenomic Biomarkers in Drug Labeling.  
<http://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm>. Accessed June 20, 2014.
28. Dickersin K, Rennie D. The evolution of trial registries and their use to assess the clinical trial enterprise. *JAMA*. 2012;307(17):1861-1864. doi:10.1001/jama.2012.4230.

29. Kurzrock R, Kantarjian HM, Druker BJ, Talpaz M. Philadelphia Chromosome–Positive Leukemias: From Basic Mechanisms to Molecular Therapeutics. *Ann Intern Med*. 2003;138(10):819-830. doi:10.7326/0003-4819-138-10-200305200-00010.
30. GBD 2013 Mortality and Causes of Death Collaborators. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet*. December 2014. doi:10.1016/S0140-6736(14)61682-2.
31. US Food and Drug Administration. Center for drug evaluation and research. Application number:202570Orig1s000. Medical review(s). August 2011. [http://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2011/202570Orig1s000MedR.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/202570Orig1s000MedR.pdf).
32. Menis J, Hasan B, Besse B. New clinical research strategies in thoracic oncology: clinical trial design, adaptive, basket and umbrella trials, new end-points and new evaluations of response. *Eur Respir Rev*. 2014;23(133):367-378. doi:10.1183/09059180.00004214.
33. Kummar S, Williams M, Lih C-J, et al. NCI mpact: National Cancer Institute molecular profiling-based assignment of cancer therapy [abstract]. *J Clin Oncol*. 2014;32:5s.
34. Tourneau CL, Delord J-P, Gonçalves A, et al. Molecularly targeted therapy based on tumour molecular profiling versus conventional therapy for advanced cancer (SHIVA): a multicentre, open-label, proof-of-concept, randomised, controlled phase 2 trial. *Lancet Oncol*. September 2015. doi:10.1016/S1470-2045(15)00188-6.
35. Herbst RS, Gandara DR, Hirsch FR, et al. Lung Master Protocol (Lung-MAP)—A Biomarker-Driven Protocol for Accelerating Development of Therapies for Squamous Cell Lung Cancer: SWOG S1400. *Clin Cancer Res*. 2015;21(7):1514-1524. doi:10.1158/1078-0432.CCR-13-3473.
36. Hirsch BR, Califf RM, Cheng SK, et al. Characteristics of oncology clinical trials: Insights from a systematic analysis of clinicaltrials.gov. *JAMA Intern Med*. 2013;173(11):972-979. doi:10.1001/jamainternmed.2013.627.
37. Downing NS, Aminawung JA, Shah ND, Krumholz HM, Ross JS. Clinical trial evidence supporting FDA approval of novel therapeutic agents, 2005-2012. *JAMA*. 2014;311(4):368-377. doi:10.1001/jama.2013.282034.
38. Kesselheim AS, Myers JA, Avorn J. Characteristics of clinical trials to support approval of orphan vs nonorphan drugs for cancer. *JAMA*. 2011;305(22):2320-2326. doi:10.1001/jama.2011.769.
39. Ehmann F, Caneva L, Prasad K, et al. Pharmacogenomic information in drug labels: European Medicines Agency perspective. *Pharmacogenomics J*. 2015;15(3):201-210. doi:10.1038/tpj.2014.86.

## Figure Legends

**Figure 1.** Number of trials (left side) and of patients (right side) enrolled in trials registered on ClinicalTrials.gov by drug, 2005-2014. Top panel contrasts enriched trials (blue) vs non-enriched trials (violet). Bottom panel contrasts single-arm trials vs comparative trials.

**Figure 2.** Cumulative number of trials registered on ClinicalTrials.gov by calendar time, 2005-2014. Cumulative number of trials stratified by use of enrichment design and randomization regrouped into 6 categories: non-randomized and randomized trials enriched on the same pharmacogenomics as mentioned in the label (dark and light red, respectively), non-randomized and randomized trials enriched on another pharmacogenomics (dark and light blue, respectively), and non-randomized and randomized non-enriched trials (dark and light green, respectively). Red areas represent trials restricted to the biomarker mentioned in the label; blue, trials enriched on another biomarker; and green, non-enriched trials. Lighter areas represent randomized trials, darker areas represent non-randomized trials. The charts are sorted by number of trials. Vertical axes go up to 200 for the first row, 60 for the second, 40 for the third and 800 for the last row. Dates of first submission and first approval by the US Food and Drug Administration (FDA) or European Medicines Agency (EMA) are shown by red and black vertical arrows, respectively.

**Figures 3 and 4.** Graphical representation (hive plots) of the disease–biomarker network in trials registered on ClinicalTrials.gov.

Each hive plot represents a targeted therapy; within each plot, each trial is represented by a link between the biomarker used to restrict inclusion in the trial (vertical axis) and the disease studied (horizontal axis). The color of the link corresponds to the start year of the trial: green represents trials from 2002; yellow, studies from 2008; and red, trials from 2014; intermediate dates are represented by gradients between colors. Trials with treat-all design are linked to the group “None” in the vertical axis. Multiple-disease trials are represented once for each studied disease, and multiple-drug trials are represented once for each studied drug. Biomarker–indication pairs for which genetic testing is recommended or required are in bold and indicated below the drug name along with the proportion of corresponding trials.

**Table 1.** Main characteristics of included studies, overall and stratified by phase of drug development

		2. Between		
		1. Before	submission and	
	Overall	submission	approval	3. After approval
No.*	858	182 (21.2)	55 (6.4)	614 (71.6)
Phase				
1/2	116 (14)	15 ( 8)	4 ( 7)	97 (16)
2	581 (68)	127 (70)	39 (71)	409 (67)
3	161 (19)	40 (22)	12 (22)	108 (18)
PGx used for enrichment				
No PGx	270 (31)	65 (36)	15 (27)	185 (30)
Same as label PGx	434 (51)	93 (51)	35 (64)	305 (50)
Other than label PGx	145 (17)	23 (13)	4 ( 7)	117 (19)
Multiple PGx	9 ( 1)	1 ( 1)	1 ( 2)	7 ( 1)
Same disease as first label	497 (58)	105 (58)	33 (60)	357 (58.1)
Proportion of trials enriched on the label PGx and in the indication, No./total* (%)				
ado-trastuzumab	22/25 (88)	9/10 (90)	2/4 (50)	11/11 (100)
afatinib	13/59 (22)	6/39 (15)	2/9 (22)	5/11 (45)
bosutinib	5/11 (45)	3/9 (33)	0/0 (0)	2/2 (100)
crizotinib	9/20 (45)	3/5 (60)	0/0 (0)	6/15 (40)
dabrafenib	27/34 (79)	5/7 (71)	6/8 (75)	16/19 (84)
dasatinib	48/147 (33)	11/12 (92)	1/3 (33)	35/130 (27)
lapatinib	107/186 (58)	19/45 (42)	3/8 (38)	85/133 (64)
nilotinib	60/95 (63)	4/5 (80)	4/5 (80)	52/85 (61)
panitumumab	7/134 (5)	6/14 (43)	1/5 (20)	0/112 (0)
pertuzumab	35/55 (64)	12/23 (52)	2/3 (67)	21/27 (78)
trametinib	21/50 (42)	4/11(36)	4/8 (50)	13/31 (42)

vemurafenib	32/42 (76)	2/2 (100)	1/2 (50)	29/38 (76)
Sample size (median [IQR])	65 [35, 154]	110 [49, 328]	71 [40, 249]	60 [32, 129]
Trial duration, years (median [IQR])	4.0 [2.8, 5.9]	4.4 [2.8, 6.5]	3.8 [2.7, 4.8]	4.0[2.8, 5.8]
Sponsor				
Industry	334 (39)	133 (73)	27 (49)	171 (28)
NIH	63 ( 7)	18 (10)	2 ( 4)	43 ( 7)
Other	461 (54)	31 (17)	26 (47)	400 (65)
Allocation				
Missing	13 ( 2)	7 ( 4)	1 ( 2)	3 ( 0)
Non-randomized	551 (64)	108 (59)	29 (53)	410 (67)
Randomized	294 (34)	67 (37)	25 (45)	201 (33)
Design				
Controlled	334 (39)	79 (43)	30 (55)	223 (36)
Single-arm	513 (60)	98 (54)	25 (45)	386 (63)
Missing	11 ( 1)	5 ( 3)	0 ( 0)	5 ( 1)
Masking				
Missing	12 ( 1)	4 ( 2)	0 ( 0)	7 ( 1)
Double-blind	48 ( 6)	15 ( 8)	5 ( 9)	28 ( 5)
Open Label	796 (93)	162 (89)	50 (91)	578 (94)
Single Blind	2 ( 0)	1 ( 1)	0 ( 0)	1 ( 0)
Type of study				
Efficacy	216 (25)	32 (18)	10 (18)	174 (28)
Pharmacology	10 (1)	3 (2)	3 (6)	4 (1)
Safety	34 ( 4)	3 ( 2)	3 ( 5)	27 ( 4)
Safety/efficacy	502 (59)	120 (66)	34 (62)	346 (56)
Missing	96 (11)	24 (13)	5 (9)	63 (10)
Primary outcome				

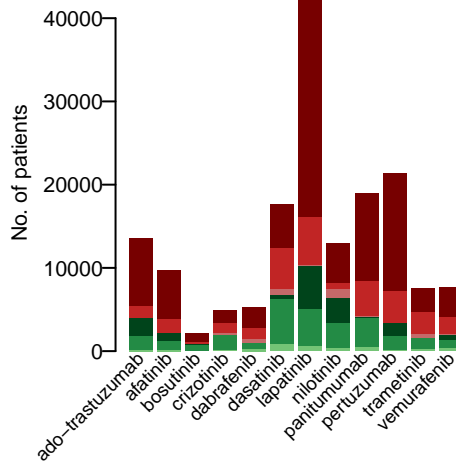
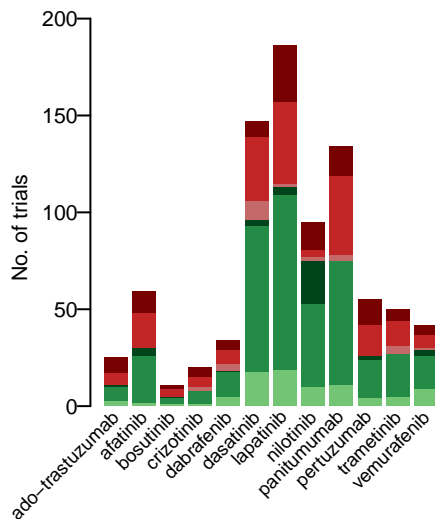
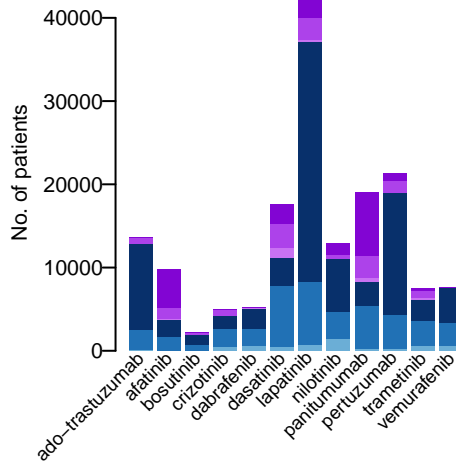
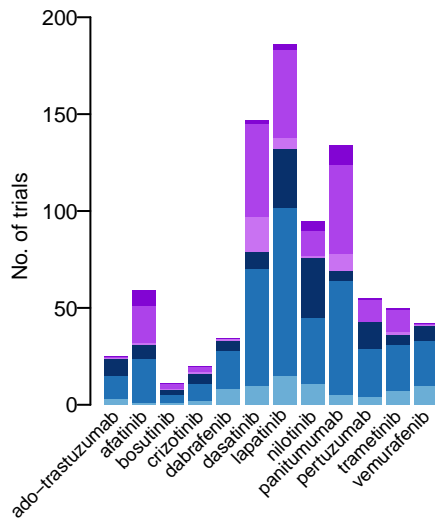
Event-free survival	162 (19)	40 (22)	10 (18)	111 (18)
Other/unclassified	172 (20)	24 (13)	14 (25)	130 (21)
Overall survival	73 (9)	14 (8)	3 (5)	56 (9)
Response rate	319 (37)	84 (46)	19 (35)	215 (35)
Time to progression	4 (0)	1 (1)	0 (0)	3 (0)
Toxicity / Dose finding	128 (15)	19 (10)	9 (16)	99 (16)

\* Data for start date of the trial were missing for 7 studies

Data are No. (%) unless otherwise specified.

IQR, interquartile range; NIH, PGx, Pharmacogenomic biomarker: US National Institutes of Health; wt, wild type

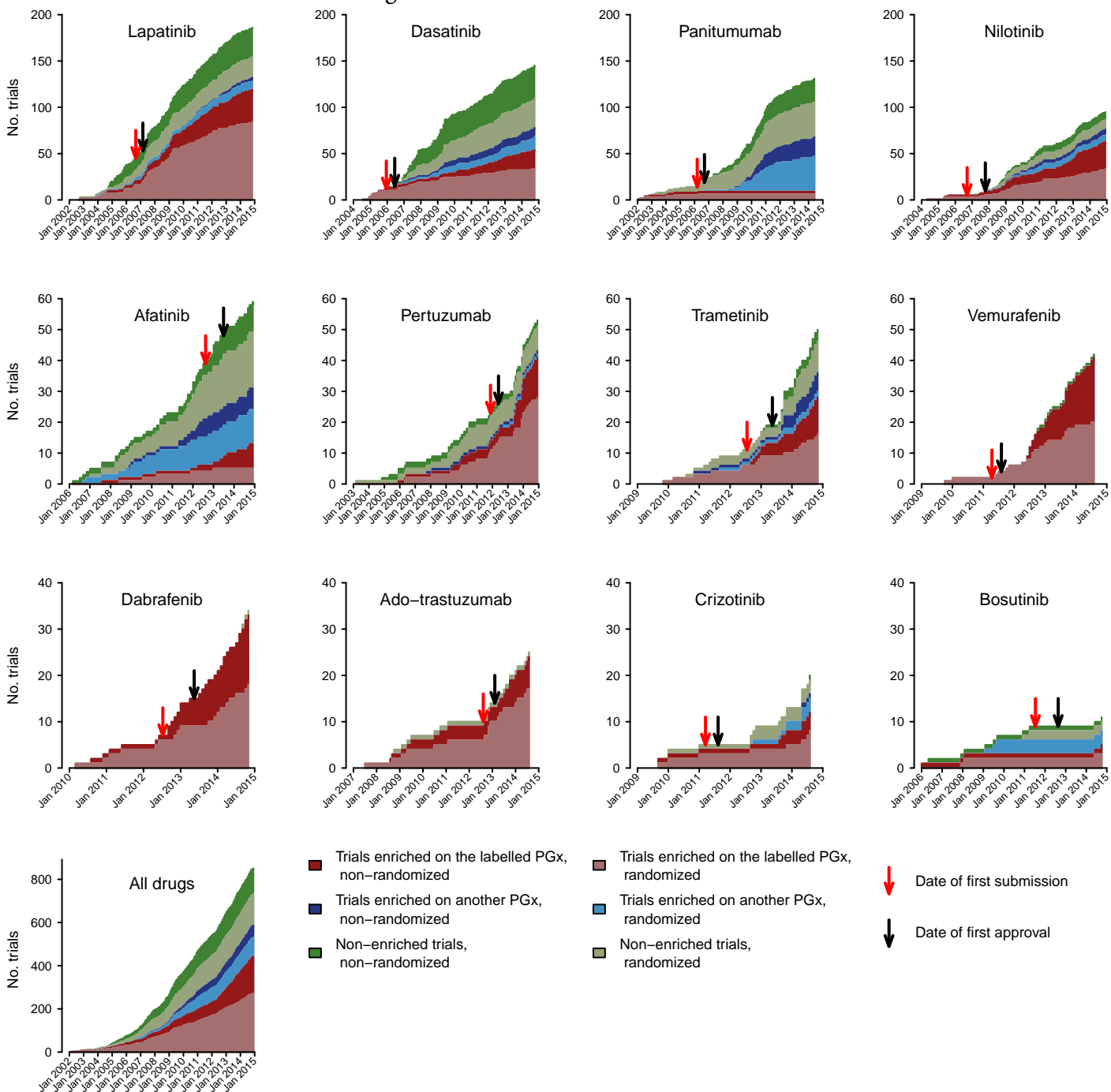
Figure 1

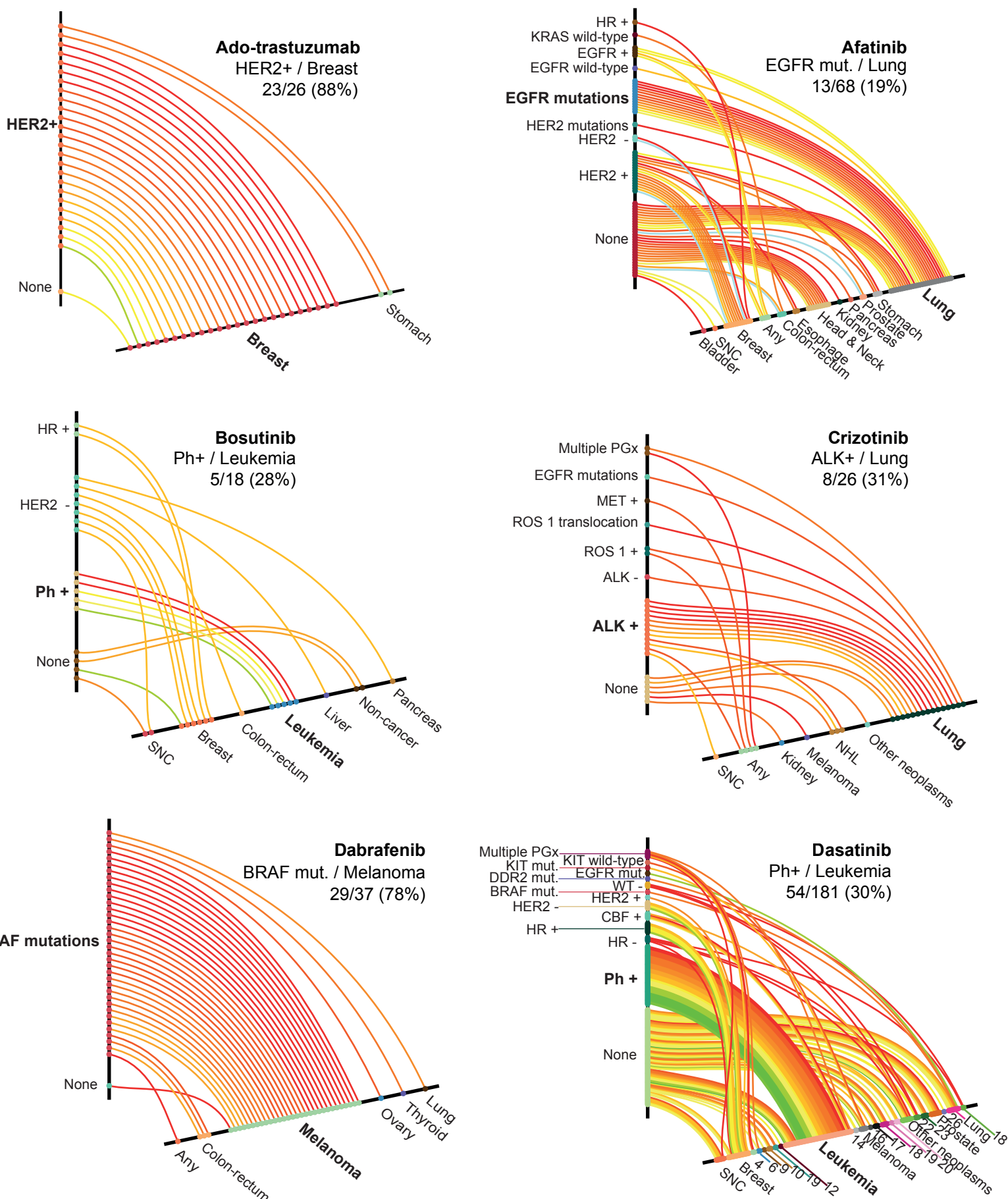


Enriched trials, phase 1/2  
Enriched trials, phase 2  
Enriched trials, phase 3  
Non-enriched trials, phase 1/2  
Non-enriched trials, phase 2  
Non-enriched trials, phase 3

Single-arm trials, phase 1/2  
Single-arm trials, phase 2  
Single-arm trials, phase 3  
Comparative trials, phase 1/2  
Comparative trials, phase 2  
Comparative trials, phase 3

Figure 2





2002 → 2008 → 2014

- |   |  |   |
|---|--|---|
| 1: Bladder cancer ( Bladder )               | 11 : Hodgkin's disease (Hodgkin)                   | 21 : Other neoplasms (Other neoplasms)        |
| 2 :Brain and nervous system cancers (SNC )  | 12 : Kidney and other uriry organ cancers (Kidney) | 22 :Ovarian cancer (Ovary )                   |
| 3: Breast cancer (Breast)                   | 13 : Leukemia ( Leukemia )                         | 23:Pancreatic cancer (Pancreas )              |
| 4 : Cancer, any (Any )                      | 14 : Liver cancer (Liver)                          | 24:Prostate cancer (Prostate )                |
| 5 : Cervical cancer (Cervix)                | 15 : Malignt melanoma of skin (Melanoma)           | 25:Stomach cancer ( Stomach )                 |
| 6 : Colon and rectum cancers (Colon-rectum) | 16 : Mouth cancer (Mouth)                          | 26:Testicular cancer (Testicular)             |
| 7 : Esophageal cancer (Esophage)            | 17 : Multiple myeloma (Myeloma)                    | 27:Thyroid cancer (Thyroid)                   |
| 8 : Gallbladder and biliary tract cancer    | 18 : non cancer (Non -cancer)                      | 28:Trachea, bronchus, and lung cancers (Lung) |
| 9 : GIST                                    | 19 : Non -Hodgkin lymphoma (NHL)                   | 29:Uterine cancer (Uterus)                    |
| 10 : Head and Neck cancer (Head & Neck )    | 20 : Non-melanoma skin cancer (Skin )              |   |

**Figure 1**

The figure consists of six chord diagrams arranged in a 3x2 grid, each representing a different drug and its associated genomic features across various cancer types. The diagrams are as follows:

- Lapatinib**: HER2+ / Breast (102/220 (46%)). Genomic features include PI3K/AKT act., KRAS mut., HR -, PI3K wild-type, Multiple PGx, ERB4 mut., HR +, EGFR +, HER2 -, and HER2 mutations. Cancer types include SNC, Bladder, Breast, Any, 5, 6, 7, 8, Head & Neck, 14, 15, 16, 20, 21, 18, Stomach, 29, 28, 22, 23, 24.
- Nilotinib**: Ph+ / Leukemia (61/102 (60%)). Genomic features include Multiple PGx, PDGFRA +, PDGFR mut., KIT mut., and KIT +. Cancer types include Ph +, None, Any, SNC, GIST, Leukemia, Melanoma, Non-cancer, and Other neoplasms.
- Panitumumab**: EGFR+ / Colon-rectum (6/157 (4%)) and KRAS wt / Colon-rectum (40/157 (25%)). Genomic features include Multiple PGx, HER2 -, HR +, BRAF mut., PI3K wild-type, BRAF wild-type, NRAS wild-type, KRAS mut., KRAS wild-type, EGFR -, and EGFR +. Cancer types include 1, 2, 3, 4, 5, Breast, Colon-rectum, Esophagus, 9, 8, 12, 14, 16, 20, 18, 21, 22, 23, 24, Lung, 25.
- Pertuzumab**: HER2+ / Breast (35/61 (57%)). Genomic features include Multiple PGx, HR -, KRAS wild-type, EGFR +, BRAF mut., and HER3 -. Cancer types include None, SNC, Breast, Any, Esophagus, Colon-rectum, Ovary, Pancreas, Prostate, Stomach, Lung, and Thyroid.
- Trametinib**: BRAF mut. / Melanoma (22/63 (35%)). Genomic features include Multiple PGx, HR +, HER2 -, GQ mut., G11 mut., NRAS mut., KRAS mut., and BRAF wild-type. Cancer types include None, Any, Breast, Colon-rectum, Cervix, Liver, & Leukemia, Melanoma, Mouth, Myeloma, Ovary, Other neoplasms, Pancreas, Prostate, Thyroid, Uterus, and Vagina.
- Vemurafenib**: BRAF mut. / Melanoma (32/44 (72%)). Genomic features include Multiple PGx, NRAS mut., and KRAS mut. Cancer types include None, Any, Colon-rectum, Leukemia, Melanoma, and Myeloma.

2002 → 2008 → 2014

- |  |  |   |
|--|--|---|
| 1: Bladder cancer (Bladder)                | 11 : Hodgkin's disease (Hodgkin)                   | 21 : Other neoplasms (Other neoplasms)        |
| 2 :Brain and nervous system cancers(SNC )  | 12 : Kidney and other uriry organ cancers (Kidney) | 22 :Ovarian cancer(Ovary )                    |
| 3: Breast cancer (Breast)                  | 13 : Leukemia ( Leukemia )                         | 23:Pancreatic cancer (Pancreas )              |
| 4 : Cancer, any (Any)                      | 14 : Liver cancer (Liver)                          | 24:Prostate cancer (Prostate )                |
| 5 :Cervical cancer (Cervix)                | 15 :Malignt melanoma of skin(Melanoma)             | 25:Stomach cancer ( Stomach)                  |
| 6 :Colon and rectum cancers (Colon-rectum) | 16 :Mouth cancer(Mouth)                            | 26:Testicular cancer (Testicular)             |
| 7 :Esophageal cancer (Esophage)            | 17 : Multiple myeloma (Myeloma)                    | 27:Thyroid cancer (Thyroid)                   |
| 8 : Gallbladder and biliary tract cancer   | 18 :non cancer (Non -cancer)                       | 28:Trachea, bronchus, and lung cancers (Lung) |
| 9 : GIST                                   | 19 :Non-Hodgkin lymphoma (NHL)                     | 29:Uterine cancer (Uterus)                    |
| 10 : Head and Neck cancer (Head & Neck )   | 20 :Non-melanoma skin cancer (Skin )               |   |

## SUPPLEMENTARY TABLE

**Table S1.** List and main characteristics of included drugs (N = 12)

Drug	biomarker	Date of biomarker Labeling	Indication of the first approval
ado-trastuzumab	HER2+	22/02/2013	Breast cancer
afatinib	EGFR mutations	12/07/2013	Trachea, bronchus, and lung cancers
bosutinib	Ph+	04/09/2012	Leukemia
crizotinib	ALK+	26/08/2011	Trachea, bronchus, and lung cancers
dabrafenib	BRAF mutations	29/05/2013	Malignant melanoma of skin
dasatinib	Ph+	28/06/2006	Leukemia
lapatinib	HER2+	13/03/2007	Breast cancer
nilotinib	Ph+	29/10/2007	Leukemia
panitumumab	EGFR+	27/09/2006	Colon and rectum cancers
pertuzumab	HER2+	08/06/2012	Breast cancer
trametinib	BRAF mutations	29/05/2013	Malignant melanoma of skin
vemurafenib	BRAF mutations	17/08/2011	Malignant melanoma of skin

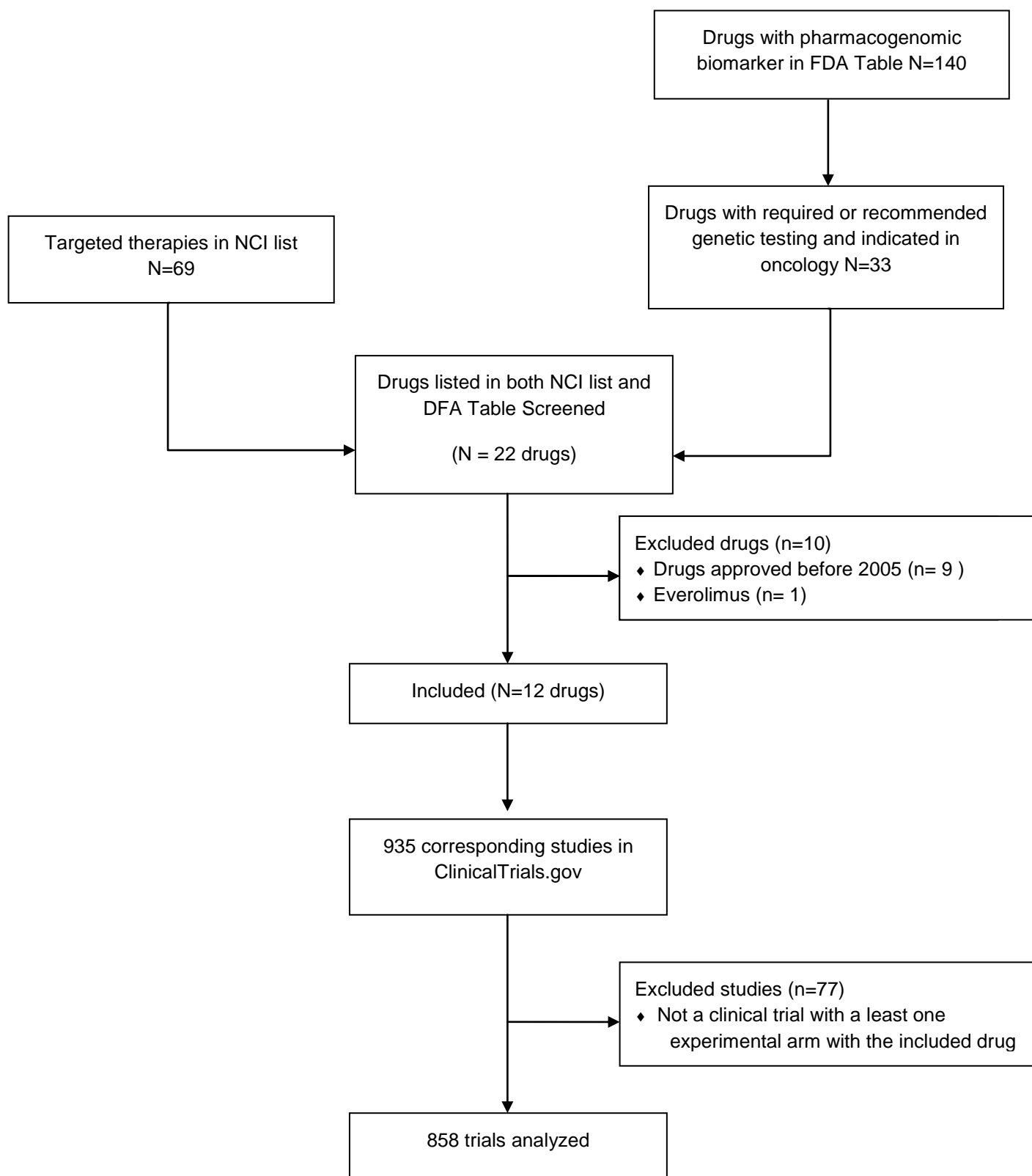


Figure S1. Flow diagram of the selection of drugs and corresponding trials.