Supplemental Methods
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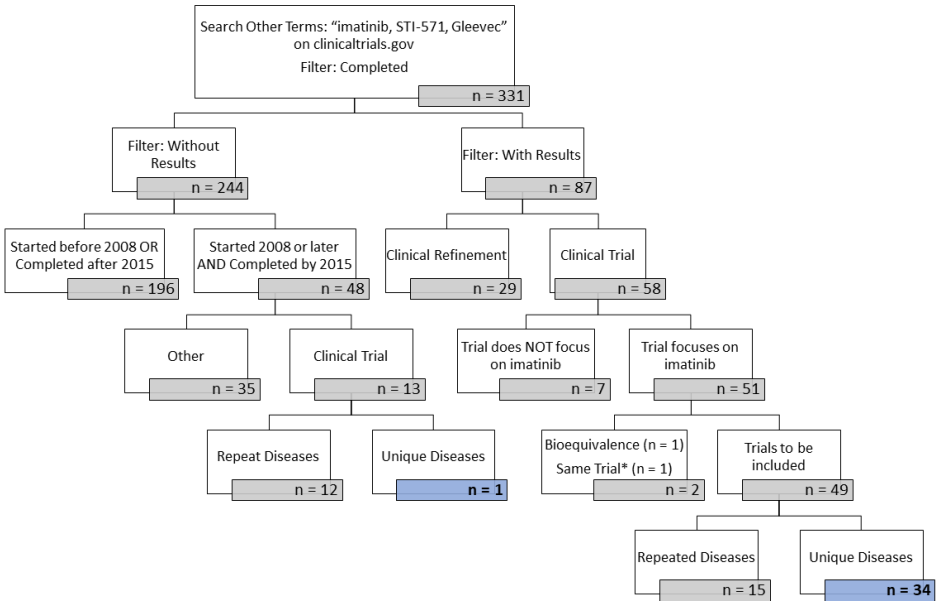
Methodology of Imatinib Clinical Trial Analysis

The meta-analysis began with the general search for "imatinib, STI-571, Gleevec" in the Other Terms search bar on the clinicaltrials.gov database. Next, the search was filtered for Completed, as only trials that were concluded could be analyzed. Then, the search was filtered for With Results, to specifically gather trials with known results so their outcomes could be analyzed. This yielded 87 trials (**Supplemental Figure 1**). For each trial, data was collected and recorded, including the trial's study ID (NCT number), study start date, dosage tested, disease tested, primary endpoint, rationale, and more. To see all data collected, reference the Imatinib Clinical Trial Analysis spreadsheet. Exclusion criteria was established, such that only trials in which imatinib was being tested in a disease were included in the analysis. First, clinical refinement trials were excluded. Clinical refinement trials were defined as trials that were run on previously approved indications for imatinib that were testing for something other than the approved treatment (i.e. either dose adjustments, treatment time periods, or the addition of other drugs) or were targeting a specific subset of patients, such as trials focused on children, the elderly, a certain demographic, or patients who have either received imatinib previously or are imatinib-resistant/intolerant. Another exclusion criteria involved excluding trials that did not focus on imatinib. For a trial to be considered focused on imatinib, the patients must have been receiving a new dose of imatinib either alone or in combination with another drug. These excluded trials in which patients were already receiving imatinib before the trial and trials that were comparison studies between imatinib and another drug. The final exclusion criteria was bioequivalence trials that tested imatinib against a similar drug from a different pharmaceutical company, as they would have the same effect in the same diseases.

*There was one trial that was registered twice, under two different NCT numbers, but was the same trial and was therefore only included once in the analysis. This left 49 trials to be included in the study, with 34 unique diseases.



Supplemental Methods Figure 1 - Flowchart of meta-analysis conducted on imatinib, showing which trials were included versus excluded and the unique diseases imatinib was tested in (blue boxes).

To account for all completed clinical trials for imatinib, next, the search was filtered for Without Results. Only trials that started after 2008 and were completed by 2015 were considered for the analysis. This timeframe was selected because the clinicaltrials.gov results database was not established until 2008, therefore, we assumed that trials started before then may not have been able/required to report results; additionally, if the trial was completed by 2015, we assumed that the results should have been reported by the the time of our analysis, as it has been 5 years since the study was completed. Of the 48 trials fitting the 2008-2015 timeline, only 13 trials did not fall under our exclusion criteria (Supp. Fig. 1). The term "Other" on the flowchart (Supp. Fig. 1) encompasses the categorization of these studies (Other: clinical refinement trials, observational studies, bioequivalence studies, pharmacokinetic studies, drug interaction studies, trials not focused on imatinib, trials on healthy patients). For a full, detailed summary of why each trial was excluded or included, the Imatinib Clinical Trial Analysis spreadsheet can be referenced. Of the 13 trials that could have been included in our analysis, only 1 involved a unique disease, and was therefore included. The other 12 trials were trials of diseases that were already captured in the previous search of trials that were filtered being Completed and With Results. This resulted in a total of 35 unique diseases to be included in the analysis, of which, 6 were approved indications for imatinib and the other 29 were new, unique diseases being tested. Once again, see the Imatinib Clinical Trial Analysis and Summary Table spreadsheets for more details on specific trials.

To determine a trial's ultimate success or failure, the primary end point of each trial was assessed. Three main criteria were considered, including whether the trial had been published as

a paper, whether a follow-up trial was conducted, and whether the response seen was better than the current standard of care. If a trial met all or most of this criteria, then the primary end point was marked as met. If none of these criteria were met, the primary end point for a trial was marked as not met. Meeting the criteria did not always indicate that the primary endpoint was met, as occasionally, a paper may have been published, but it stated the trial failed. As such, the status of the primary endpoint was always first considered based on a paper's indication of success or failure, followed by the evaluation of the criteria. Some trials linked to the publication of results directly on clinicaltrials.gov, whereas others needed to be searched on PubMed using keywords, such as imatinib, the disease, and the name of the primary investigator if available. After establishing whether every trial's primary endpoint was met, all trials for a unique disease were analyzed. If all trials did not meet their primary endpoint, the treatment of that disease with imatinib was marked an obvious failure. If all trials succeeded, this was an obvious success. Ultimately, all approved indications were given a label of being successful, as they are currently approved indications for imatinib. In the instances of a unique disease having multiple different trials with different outcomes, an individual decision was made, whether to label them as ongoing, successful or failed. See the Summary Table Spreadsheet for the full explanations of each of these instances.

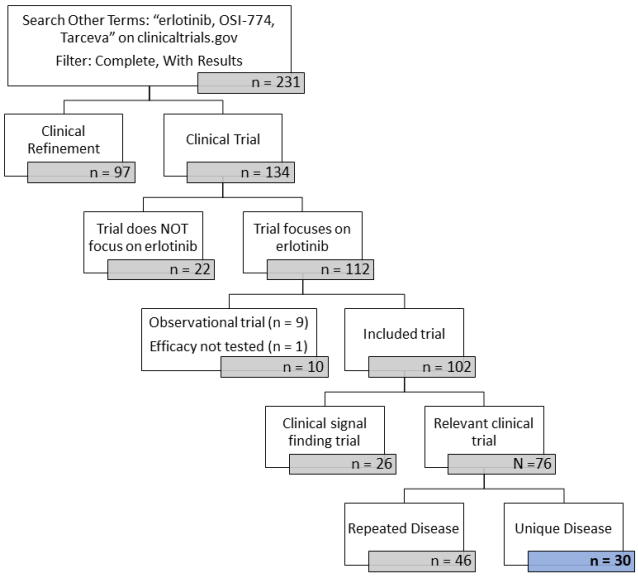
The other main piece of data collected in a detailed fashion was each trial's *in vitro* rationale. Ultimately, three labels were developed for this: clear *in vitro* rationale in disease model, clear *in vitro* rationale in a non-disease model, and no *in vitro* rationale but some available. In determining the label a trial received, the following steps were developed. First, if a trial had a published paper, this was examined to see if any *in vitro* rationale was present and cited either in the abstract, introduction, or discussion. If present, the citation was followed to gather whether it was for a disease or non-disease model. If in a disease model, the trial was labelled as clear *in vitro* rationale in a disease model. If in a non-disease model, then additional searches needed to be done. If there was no *in vitro* rationale present, but rather, other clinical trials being used as references for their rationale, those referenced trials were then opened to see if any of them cited any *in vitro* rationale. If so, the trial was again given the label clear *in vitro* rationale in a disease model. If not, additional searches needed to be done. If no *in vitro* rationale was present in the paper, a trial the paper referenced, or the rationale was in a non-disease model, then a PubMed search was conducted, in an effort to find any *in vitro* evidence showing that imatinib had an *in vitro* effect (specifically on proliferation or cell viability) in a disease model. The PubMed search typically included keywords such as imatinib, the disease of interest, and *in vitro*. If a paper with *in vitro* evidence in a disease model was found, the trial was given the label no *in vitro* rationale, but some available (if originally a clear in vitro rationale in a non-disease model, note was made on Summary Table Spreadsheet). In two instances, no *in vitro* evidence was available in a disease model, and as such, these diseases remained labelled as clear *in vitro* rationale in a non-disease model. These trials were ultimately excluded from the analysis, as their *in vitro* data was inaccurate in predicting the success or failure of a trial. Next, if no paper was published for a

trial, and no *in vitro* rationale was present on the registered trial on clinicaltrials.gov (or is present but not referenced), a PubMed search was again conducted to find whether *in vitro evidence* was available for the disease model. If found, the trial was labelled no *in vitro* rationale, but some available (if present but not referenced, and evidence found matches rationale present, then labelled clear in vitro rationale in disease model). After finding the in vitro rationale for a trial, whether it was through a paper or PubMed search, the IC-50 or effective concentration that imatinib caused an effect was recorded.

*For trials that were combination drug treatments, in vitro rationale that matched the combination was attempted to be found, but if only imatinib was able to be found, that was also recorded.

Methodology of Erlotinib Clinical Trial Analysis

Retrospectively after the analysis of imatinib trials, it was understood that the clinicaltrials.gov database automatically searches for trials linked to a drug's synonymous names during drug-based searches. This sometimes means that a search with more name terms can result in an insignificant, but a slightly lesser number of trials compared to a search with just the generic name. And so, to make sure the greatest number of erlotinib trials was brought up, the erlotinib analysis initiated on August 19th, 2020 began with a search with only "erlotinib" in the Other Terms search bar. After the search was filtered for Completed and With Results trials, it yielded 231 trials. Trials were sorted in a manner similar to imatinib (**Supplemental Methods Figure 2**).



Supplemental Methods Figure 2 - Flowchart of meta-analysis conducted on erlotinib, showing which trials were included versus excluded and the unique diseases erlotinib was tested in (blue boxes).

Additionally, for erlotinib trials testing in non-small cell lung cancer (NSCLC), information about molecular hypotheses was collected. Given that the most recent approvals for erlotinib is in NSCLC with specific EGFR mutations and only about 30% of all NSCLC cases fall into this category, it was necessary to indicate if trials tested an unstratified or stratified molecular hypothesis at enrollment. An unstratified molecular hypothesis means that patients did not receive treatment based on their mutational status and/or patients' molecular statuses were examined retrospectively; a stratified molecular hypothesis means that patients received treatment based on their mutational status. This was not necessary for imatinib trials because BCR-ABL is associated with almost all cases of chronic myeloid leukemia (CML) and imatinib has only been approved in Ph+ acute lymphoblastic leukemia (ALL).

Classification of Clinical Resistance Status for Drug:Variant Pairs

To develop our truth table classifying drug:variant pairs on clinical resistance status, we considered clinical trial results and NCCN guidelines. With regards to imatinib, we aggregated data across multiple trials; Branford et al Blood 2003; Cortes et al Blood 2007; Kim et al Hematol Oncol 2009; Bengio et al Leuk Lymphoma 2011, Hochaus Blood 2013. This data was previously aggregated and published in Leighow et. al. Cell Reports 2020. We observed 263 mutations across these imatinib resistance studies. Counts of individual mutations ranged from N=1 for mutations like K247L to N=38 for the T315I mutation. The definition of recurrence was set to an N of 3 or more mutations, i.e. a mutation had to be seen at least 3 times in aggregate across all studies to be called resistant to imatinib and to be included in our truth table. This left us with the 19 most abundant ABL mutations. While this criterion did exclude known resistance mutations like H396P (which had an N of 2 and has been experimentally validated), we decided to err on the conservative side since 3 occurrences captured >90% of clinical resistance cases. All of these mutations in ABL were marked as FALSE in the truth table to represent the fact that these mutations are resistant to imatinib treatment. In the case of nilotinib, 2 separate studies have published clinical data on nilotinib resistance, and a meta-analysis; Kantarjian et al NEJM 2006; Kantarjian et al Blood 2007; Rivera et al. Blood 2015. In these studies, if at least 4 people with a mutation were treated, and 2 or more responded, and the response rate was ~ 30 percent or more they were marked as sensitive to Nilotinib (the examples of borderline mutations were F317L where 2/8 (25%) patients had CCYR and M351T where 4/15 (27%) patients had CCYR, but both are considered sensitive by the NCCN guidelines, have additional support from patient case studies and thus they were included as "TRUE"). Moreover, Hochaus et al. Blood 2013 examined resistance mutations to frontline nilotinib treatment in the ENESTND trial (again N=3 was considered resistant (Y253H, E255K and T315I are all resistant by this criteria and are consistent with the response data in the second line Kantarjian studies). However, combining this data with the NCCN guidelines brought up our first instance where our truth table was more conservative than the clinically accepted NCCN guidelines. V299L was not observed in either

Kantarjian study, or the Hochaus study. This makes sense because V299L is a resistance mutation to dasatinib and bosutinib (not nilotinib) because it only inhibits binding of "DFG-in" chemical matter (Jabbour et al. Blood 2012). There are case studies of V299L mutations responding to nilotinib and the NCCN guidelines allow the use of nilotinib for patients with V299L with high confidence, but because it was not found at all in the larger studies that we analyzed, we chose to be conservative and to simply label V299L as NA (in spite of the fact that we agree with the NCCNs definition) in order to maintain a rigorous, consistent standard across drug:variant pairs. We followed similar logic for dasatinib, bosutinib, and ponatinib and have referenced the studies used in Supplemental Table 4.

Derivation of Drug Kill Rate (α)

The method of calculating drug kill rate from a dose response assay was discussed in Zhao et al. In brief, the approach assumes that cells in a drug dose assay (x) grow according to the differential equation:

$$\frac{dx}{dt} = bx - dx - \alpha x$$

where b is the natural birth rate, d is the natural death rate, and α is the effect of the drug. The solution of the differential equation is a straightforward exponential:

$$x(t) = e^{(b-d-\alpha)t}$$

Relative viability (commonly the y-axis of a dose-response curve) is the viability of cells exposed to drug relative to the untreated control (when $\alpha = 0$). Thus, relative viability y can be written:

$$y = \frac{x_{treated}}{x_{untreated}} = \frac{e^{(b-d-\alpha)t}}{e^{(b-d)t}}$$

Solving for α, we find that the drug kill rate for a drug dose assay can be calculated as

$$\alpha = -\frac{\ln(y)}{t}$$

where t is the duration of the assay.

Analysis of Multi-variate Models

Additionally, some of these models drew counterintuitive conclusions about the relationship between predictors and resistance based upon a single positive re-classification. For example, the lowest LOOCV error was observed in the model that considers effective C_{ave} alpha and volume of distribution. However, the model assigns a negative relationship between volume of distribution and clinical efficacy, contrary to what would be expected for a drug targeting leukemic cells. This is likely a result of the challenge of fitting coefficients given variables that display multicollinearity and it leads us to favor a simpler univariate model using only the effective C_{ave}.