Patients with FLT3-mutant AML Needed to Enroll on FLT3-Targeted Therapeutic Clinical Trials

Taylor Bucy
Oregon Health & Science University

John M. Zosca
Oregon Health & Science University

Motomi Mori
Oregon Health & Science University

Uma Borate
OHSU-PSU School of Public Health

Follow this and additional works at: https://pdxscholar.library.pdx.edu/sph_facpub

Part of the Medicine and Health Sciences Commons

Let us know how access to this document benefits you.

Citation Details

This Article is brought to you for free and open access. It has been accepted for inclusion in OHSU-PSU School of Public Health Faculty Publications and Presentations by an authorized administrator of PDXScholar. For more information, please contact pdxscholar@pdx.edu.
Patients with FLT3-mutant AML needed to enroll on FLT3-targeted therapeutic clinical trials

Taylor Bucy,1,2 John M. Zosck III,1,2 Motomi Mori,1,2 and Uma Borate1
1Knight Cancer Institute, Oregon Health & Science University, Portland, OR; and 2Oregon Health & Science University–Portland State University School of Public Health, Portland, OR

We sought to identify the total number of therapeutic trials targeting FLT3-mutant acute myeloid leukemia (AML) to estimate the number of patients needed to satisfy recruitment when compared with the incidence of this mutation in the US AML population. A systematic review of all therapeutic clinical trials focusing on adult FLT3-mutated AML was conducted from 2000 to 2017. An updated search was performed using ClinicalTrials.gov for trials added between October 2017 and December 2018. Analysis was performed for ClinicalTrials.gov search results from 2000 to 2017 to provide descriptive estimates of discrepancies between anticipated clinical trial enrollment using consistently cited rates of adult participation of 1%, 3%, and 5%, as well as 10% participation identified by the American Society of Clinical Oncology in 2008. Twenty-five pharmaceutical or biological agents aimed at treating FLT3-mutant AML were identified. Pharmaceutical vs cooperative group/nonprofit support was 2.3:1, with 30 different pharmaceutical collaborators and 13 cooperative group/nonprofit collaborators. The number of patients needed to satisfy study enrollment begins to surpass the upper bound of estimated participation in 2010, noticeably surpassing projected participation rates between 2015 and 2016. The number of patients needed to satisfy study enrollment surpasses 3% and 5% rates of historical participation for US-only trials in 2017. We estimate that 15% of all US patients with FLT3-mutant AML would have to enroll in US and internationally accruing trials to satisfy requirements in 2017, or approximately 3 times the upper level of historical participation rates in the United States. The current clinical trial agenda in this space requires high percentage enrollment for sustainability.

Introduction

In the present era of precision oncology, there is growing recognition that the number of patients needed for enrollment in clinical trials investigating agents with similar mechanisms of action may be greater than the number of patients with specific targetable mutations.1 The therapeutic approaches of precision oncology and immuno-oncology have become more widely used, especially as advancements in sequencing allow relatively inexpensive and rapid characterization of tumor tissue relevance.2,3 In tumor types such as melanoma, the success of immunotherapy heralded by the approval of ipilimumab opened the door for anti-PD-1/ PD-L1 and anti-CTLA-4/CTLA-4 directed therapy in multiple tumor types, and the broad efficacy of this approach led to James P. Allison and Tasuku Honjo being awarded the 2018 Nobel Prize in Physiology and Medicine.4,5
Despite tremendous success in targeting the immune system across various cancers, a study by Tang et al noted 164 agents targeting PD-1/PD-L1, with 50 of the 164 agents in clinical stages (45 agents in phase I–III clinical trials, 5 approved). This highlights the large number of similar agents being investigated in the absence of head-to-head comparisons. The increasing number of clinical trials investigating agents that target similar pathways has created challenges for investigators, patients, and regulatory agents, and has prompted some to suggest adjustments to current clinical trial design and regulation. In addition, accrual requirements for investigational studies often exceed the number of patients in an eligible population harboring a particular tumor type or mutation. Several studies (Carlisle et al8 and Mattina et al9) have expressed concern regarding redundant and duplicative trial agendas in systematic reviews focusing on sunitinib and sorafenib, respectively. Despite an abundance of trials using agents that target the same or similar immune or molecular locations, only 5% of clinically tested agents move towards approval by the US Food and Drug Administration. This prompts a closer look into the repercussions this may have on clinical trial participants and the quality of this research.

Acute myeloid leukemia (AML) is a hematologic malignancy with growing identification of prognostically significant mutations with the potential for therapeutic inhibition or alteration. AML comprises 1.3% of all new cancer diagnoses in the United States every year, with an estimated 21,380 new cases in 2017. Research and clinical advances have allowed for further disease classification and the generation of targeted therapies. One such mutation that has gained attention is the FMS-like tyrosine kinase 3 (FLT3) mutation. FLT3 mutations are deemed one of a few “actionable” mutations, and occur in 30% of de novo AML cases; 25% are internal tandem duplication (FLT3-ITD) mutations, and 5% are tyrosine kinase domain mutations. A normally functioning FLT3 protein, after binding to its ligand FL and undergoing phosphorylation, plays a role in the promotion of cellular proliferation and anti-apoptotic activity, and influences hematopoietic precursor cells. Both ITD and tyrosine kinase domain mutations result in constitutive pathway activation via a conformational change and interference with inhibitory effects of the activation loop, respectively.

With an estimated 21,380 new AML cases in 2017, approximately 5,345 individuals will harbor FLT3-ITD mutations, and 1,069 will possess a tyrosine kinase domain mutation. Multiple small-molecule, tyrosine/multikinase inhibitors have been developed for FLT3-mutated AML. In April 2017, the tyrosine/multikinase inhibitor midostaurin was the first such targeted agent approved by the US Food and Drug Administration for the treatment of FLT3-mutated AML, based on the findings of the phase 3 randomized CALGB 10603/RATIFY clinical trial. Most recently, gilteritinib was approved for relapsed/refractory FLT3-mutant AML in November 2018, based on the interim analysis results of the ADMIRAL trial (NCT02421939). With the advancement of genetic and molecular testing during the past decade, the focus on targeted therapies for the treatment of AML has expanded. In turn, this has led to more clinical trials focusing on specific molecular mutations.

The FLT3-mutated AML population was chosen to reflect on a larger discussion within clinical hematology/oncology, specifically the development and conduct of potentially duplicative clinical trials in the United States. We sought to examine how many investigational FLT3 agents developed and studied in therapeutic clinical trials targeted FLT3-mutated AML within a specified timeframe. We hypothesized that therapeutic trials examining FLT3 inhibitors require a sizable percentage of patients with FLT3-mutated AML, and that the number of patients needed for recruitment to these trials exceeds the number of eligible patients who are willing and able to participate in clinical trials.

Methods

We conducted a systematic review of all therapeutic clinical trials investigating FLT3 inhibitors targeting patients with FLT3-mutated AML registered in ClinicalTrials.gov from 2000 to 2017. We sought to estimate what percentage of patients with AML with FLT3 mutations would need to enroll in clinical trials to satisfy anticipated recruitment needs each year during this period.

Methodology was guided by the PRISMA 2009 guidelines (Figure 1; supplemental Appendices 1 and 2). We performed an advanced search, using ClinicalTrials.gov to identify clinical trials focusing on adult FLT3 AML from 1 January 2000 to 11 October 2017 (day of initial search). An additional search was then performed in PubMed for adult FLT3 AML clinical trials cataloged from 1 January 2000 to 31 December 2017. Duplicate removal and a search for associated publications was performed using the ClinicalTrials.gov identifier (NCT identifier) and official study title as the primary and secondary identifiers, respectively (Figure 1). Results produced from both the ClinicalTrials.gov and PubMed searches were assessed for eligibility, and relevant variables extracted. A complete methodology is described in supplemental Appendix 2, with exclusionary criteria detailed in both Figure 1 and supplemental Appendix 2D. After screening and eligibility assessment, there were 78 therapeutic studies focusing on FLT3 AML remaining, and an attempt was made to find abstract or full-article publications for these trials. The 78 clinical trials and publications were sorted into 4 groups: group A: newly diagnosed/treatment naive; group B: relapsed/refractory; group C: newly diagnosed and/or relapsed/refractory; and group D: other, nonspecific inclusion language. All unique pharmaceutical agents used for the study of possible FLT3-mutant inhibition were subsequently identified and confirmed through review of available literature.

An updated search was performed in ClinicalTrials.gov, using the above-mentioned search criteria to account for studies posted between 11 October 2017 and 31 December 2018. This produced 18 additional trials; however, only 7 met criteria for inclusion.

Analysis of trends in trial recruitment

Analysis was performed on all studies registered to ClinicalTrials.gov from 2000 to 2017 that met criteria for inclusion, as detailed in the methods (n = 66). Accrual duration (D) was calculated using the study start date and estimated primary completion date, with variable D used to calculate the average number of patients needed to be enrolled per year (Q) to correspond to the estimated or completed enrollment number. If enrollment was ongoing, Q was found by dividing estimated enrollment by accrual duration, D; if enrollment was completed, the number of persons enrolled at completion was used in place of estimated enrollment. The average number of patients needed to be enrolled per year (Q) was used to...
estimate the average number of patients accrued in each year of study (P; Table 1).

Analysis to identify trends in trial recruitment was performed to provide estimates of discrepancies in anticipated clinical trial enrollment. This was done using consistently cited rates of adult clinical trial participation of 1%, 3%, and 5% vs the participant recruitment needed to fulfill specified accrual numbers for primary completion.\textsuperscript{26-28} The decision was made to exclude the 12 unique publications available through the PubMed search, as study duration was not consistently reported. The updated search performed from October 2017 to December 2018 produced 7 additional studies that had not yet reached completion and are also not included in statistical analysis.

Two assumptions were made for the analysis: accrual rate is constant during the duration of the trial, and the rate of FLT3 mutations has been constant, at 30%, since 2000. Data were obtained and analyzed using the Centers for Disease Control and Prevention and Prevention and Surveillance, Epidemiology, and End Results databases; literature review; and Microsoft Excel.

**Results**

**Descriptive findings**

Of the 85 included trials and publications, the majority were phase 2 trials (n = 27; 31.8%) and were actively recruiting (n = 32; 37.6%) or completed (n = 29, 34.1%; supplemental Appendix 3). Twenty-five unique pharmaceutical or biological agents, either known FLT3 inhibitors or investigational agents used with the intent of analyzing a FLT3 mutant populations’ response, were identified and corroborated by literature review (Figure 2).\textsuperscript{16,29-52} Thirty different pharmaceutical companies acted as collaborators or sole sponsors.
of these interventional studies (supplemental Appendix 3). Eighteen studies did not list sponsorship/collaboration as coming from a pharmaceutical company. Additional sponsors include the academic universities acting as primary sites, as well as cooperative groups, nonprofit and charitable foundations, and subdivisions of the National Institutes of Health. Of the 30 unique pharmaceutical companies offering sponsorship/collaboration, 25 were the pharmaceutical developers of the proposed FLT3 inhibitors (Figure 2). Pharmaceutical vs nonprofit/cooperative group involvement was 2.3:1. The most prominent pharmaceutical sponsorships were Novartis (midostaurin, PKC 412) and Arog (crenolanib), which sponsored/collaborated on 13 and 8 trials, respectively.

**Representation of subgroups**

These 85 studies were further divided into 4 groups on the basis of language used in inclusion criteria: group A: newly diagnosed or untreated (n = 19); group B: relapsed/refractory (n = 27); group C: both newly diagnosed or relapsed/refractory (n = 11); and group D: nonspecific language in their inclusion criteria (n = 28), such as: AML in complete remission, patients status after allogeneic stem cell transplant, relapsed/refractory or unfit for induction because of age/comorbidity/other factors per principal investigators discretion, refusal of induction therapy, or AML for which no standard treatment is available (supplemental Appendix 3). Interventional studies represented both international and US sites: 44.4% of the studies included in group A, 52% of the studies included in group B, 36.4% of the studies in group C, and 46.2% of the studies in group D took place in the United States only.

Midostaurin, crenolanib, sorafenib, quizartinib, pacritinib, gilteritinib, sunitinib, lestaurtinib, and SU5416 were used as an interventional agent by more than 1 subgroup (supplemental Appendix 3). Midostaurin was predominately used in trials aimed at targeting newly diagnosed/untreated individuals (group A; n = 9), and was used a total of 8 times across the other 3 groups. Only 1 study (NCT03258931) proposed a head-to-head comparison, exploring the efficacy of midostaurin vs crenolanib. This randomized trial is recruiting as of 15 August 2018, and plans to accrue 510 subjects; estimated primary completion is in November 2022.

**Trends in trial recruitment**

The 66 ClinicalTrials.gov studies represent 33 US-only trials, 17 international-only trials, 13 studies active both at international and US sites, and 3 trials for which no site location was available at the time of data collection. Projected accrual is as follows: 3802 participants for the combined US and international studies (includes the 3 trials with unlisted location), 2109 participants for international-only trials, and 1704 participants for US-only trials.

Seventeen (25.8%) of the 66 registered trials were newly diagnosed FLT3-mutant AML, and 19 (28.8%) of the 66 registered trials were for relapsed/refractory FLT3-mutant AML. Total accrual for newly diagnosed trials (n = 17) was projected at 3432, with an average of 201.88 patients per trial. Of the 17 newly diagnosed trials, 8 were US only, 6 were international only, and 3 were both US and international. Of the 19 relapsed/refractory trials, 11 were US only, 5 were international only, and 3 were US + international. Projected accrual mean and standard deviation for newly diagnosed and relapsed/refractory trials are included in Table 2. Projected accrual by trial phase for newly diagnosed/untreated and relapsed/refractory or unfit for induction because of age/comorbidity/other factors per principal investigators discretion, refusal of induction therapy, or AML for which no standard treatment is available (supplemental Appendix 3).

We used the study start dates and primary completion dates of all 66 clinical trials from ClinicalTrials.gov remaining after duplicate

---

**Table 1. Methodology for analysis of the 66 studies registered to ClinicalTrials.gov from 2000 to 2017 that met criteria for inclusion**

<table>
<thead>
<tr>
<th>Process step</th>
<th>Variable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accrual duration (D) of each study from ClinicalTrials.gov</td>
<td>$D = (\text{estimated primary completion date} - \text{study start date})/365.25$</td>
</tr>
<tr>
<td>The average number of patients needed to be enrolled per year (Q) to correspond to the estimated (or completed) enrollment number</td>
<td>$Q = \frac{\text{Estimated Enrollment (or completed enrollment)/D}}{}$</td>
</tr>
<tr>
<td>Estimated average number of patients accrued in each year of study</td>
<td>$P_{ij} = \frac{Q}{12 \text{ mo}} \times \text{number of months study accrual was active that year (M)}$</td>
</tr>
<tr>
<td>Estimate for number of patients needed for enrollment in final study year</td>
<td>$P_{i} = \text{Estimated Enrollment} - \text{Sum of all previous } P_{j}$</td>
</tr>
</tbody>
</table>

---

**Figure 2. Unique pharmaceutical agents identified in search and used with the intent of treating FLT3 AML.**
removal and screening to identify the duration of each trial. These 66 trials were identified in the initial search. Primary completion date was chosen, as this was consistently reported across trials. Incidence data were collected from the Centers for Disease Control and Prevention and Surveillance, Epidemiology, and End Results databases or from publications.26,27 These data were analyzed within the context of the anticipated enrollment across all trials from 2000 to 2017, and contrasted with 1%, 3%, and 5%, clinical trial participation rates. Historical clinical trial participation at 1%, 3%, and 5% was chosen on the basis of evidence suggesting that 5% or less of all individuals with cancer in the United States enroll and partake in clinical studies.26-28 An additional bar depicting projections for 10% clinical trial participation was added to represent the potential for increased enrollment taking place outside the United States and at National Cancer Center-designated cancer centers, based on the American Society of Clinical Oncology statement on minimum standards and exemplary attributes of clinical trial sites.55

As seen in Figure 3A-B, the number of FLT3-positive patients needed to satisfy study enrollment for FLT3-targeted therapeutic trials begins to surpass the upper bound of estimated participation in 2010 and noticeably surpasses projected participation rates between 2015 and 2016. Beginning with 2015 in Figure 3B (US + international trials), approximately 6.82% of all patients newly diagnosed with FLT3-mutated AML would need to enroll in a clinical trial to satisfy accrual for that year. In 2016, this grows to 10.88% of all FLT3-mutated AML, and in 2017, this number grows to 14.76%, or approximately 3 times the percentage of individuals with any cancer type who will enroll in a clinical study. Enrollment needs to satisfy recruitment surpassed a 10% participation rate for US + international trials in 2016 (Figure 3B). The number of patients needed to satisfy study enrollment surpassed 5% estimated participation for US-only trials in 2017, and 3% estimated participation in 2016 (Figure 3C).

Although it is possible that the inclusion of US-only as well as US + international trials may confound our results, it is unlikely to significantly alter our conclusions. Should trends in US-only clinical trial recruitment needs continue, enrollment needs beyond the available US patient population would need to come from international locations. Thus, Figure 3C would show a bigger discrepancy if the possibility of concurrent international and US accrual were not considered.

**Discussion**

Despite the investment in targeted therapies for FLT3-mutated AML, this distinct mutational subset only represents a quarter of all de novo AML cases.11,15,16,19,20 According to our analysis, approximately 15% of patients with FLT3-mutated AML in 2017 would have needed to participate in clinical trials to satisfy the eligibility requirements of all therapeutic FLT3 inhibitor studies. The current rate of clinical trial participation in the United States, at 3% to 5%, is not reflected in our data or in the results of our subsequent analysis.26 Given the heterogeneity of AML, it is not unlikely that the future of clinical trial development will include combinations of targeted agents. For example, IDH1 and IDH2 mutations co-occur with FLT3-ITD mutations in 15% to 27% and 8% to 30% of cases, respectively.56 With the approval of enasidenib (IDH2) and ivosidenib (IDH1) in 2018 and 2019, respectively, targeted combination trials may make more acute the difficulty in satisfying enrollment projections. There is also the potential for our results to underestimate the competition for patients with FLT3-mutant AML, given that some trials (eg, NCT03092674) allow for the treatment of both FLT3-mutant and FLT3-negative participants with a FLT3 inhibitor. Rates of participation may be slightly greater than 1% to 5% for AML if trials are recruiting mutant and wild-type participants as well. Competition for FLT3-mutant trial participants may also be enhanced by the promising clinical results of new therapies that are not FLT3-targeted agents, such as those described in the phase 1/2 results of the combination study of venetoclax with azacitidine or decitabine (NCT02203773).57 Treatment of FLT3-mutant patients under investigational protocols that do not include a FLT3 inhibitor puts further strain on the ability of inhibitor trials to fulfill accrual requirements.

Clinical trials in the era of precision medicine have led to the investigation of multiple therapeutic agents targeting similar and/or identical genomic variants or oncogenic pathways. One possible effect of this biomedical advance is a smaller pool of patients who harbor molecular or genetic abnormalities than may be eligible for trial participation.1 There is also a concern that an abundance of trials focusing on relatively narrow subsets of the population may

---

**Table 2. Projected accrual, mean, and standard deviation for newly diagnosed (n = 17, 25.8%) and relapsed/refractory (n = 19, 28.8%) trials**

<table>
<thead>
<tr>
<th>Type and location</th>
<th>n (%)</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Newly diagnosed</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>United States only</td>
<td>824 (24)</td>
<td>103</td>
<td>165.37</td>
</tr>
<tr>
<td>International only</td>
<td>1286 (38)</td>
<td>214.33</td>
<td>225.71</td>
</tr>
<tr>
<td>United States + international</td>
<td>1322 (39)</td>
<td>440.67</td>
<td>334.35</td>
</tr>
<tr>
<td>Total, N</td>
<td>3432</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Relapsed/refractory</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>United States only</td>
<td>1025 (34)</td>
<td>73.21</td>
<td>79.45</td>
</tr>
<tr>
<td>International only</td>
<td>1073 (36)</td>
<td>214.60</td>
<td>150.11</td>
</tr>
<tr>
<td>United States + international</td>
<td>924 (31)</td>
<td>308</td>
<td>74.71</td>
</tr>
<tr>
<td>Total, N</td>
<td>3022</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SD, standard deviation.

**Table 3. Enrollment targets (United States only, international only, international + United States)**

<table>
<thead>
<tr>
<th></th>
<th>Total projected enrollment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newly diagnosed</td>
<td></td>
</tr>
<tr>
<td>Phase 1</td>
<td>88</td>
</tr>
<tr>
<td>Phase 1/2</td>
<td>93</td>
</tr>
<tr>
<td>Phase 2</td>
<td>948</td>
</tr>
<tr>
<td>Phase 2/3</td>
<td>540</td>
</tr>
<tr>
<td>Phase 3</td>
<td>1783</td>
</tr>
<tr>
<td>Relapsed/refractory</td>
<td></td>
</tr>
<tr>
<td>Phase 1</td>
<td>197</td>
</tr>
<tr>
<td>Phase 1/2</td>
<td>333</td>
</tr>
<tr>
<td>Phase 2</td>
<td>780</td>
</tr>
<tr>
<td>Phase 3</td>
<td>1652</td>
</tr>
</tbody>
</table>

Downloaded from https://ashpublications.org/bloodadvances/article-pdf/3/23/4055/1546929/advancesadv2019000532.pdf by guest on 19 December 2019
lead to duplicative analyses, a concern that has been addressed by prior research.6-9,58,59 With the approval of FLT3 inhibitors midostaurin and gilteritinib for newly diagnosed and relapsed/refractory AML, it is likely that more FLT3-mutant patients will receive FLT3 inhibitors that are not part of an investigational trial. Loosening inclusion and exclusion criteria that limit prior exposure to a FLT3 inhibitor could be a way to enhance enrollment numbers. An alternative approach would be to deploy alternative measures to determine effectiveness. The US Food and Drug Administration has provided some guidance by encouraging clinical investigators to develop minimum residual disease assays to be used as surrogates in measuring clinical benefit.60 However, larger phase 3 studies are still needed to evaluate meaningful clinical benefit through survival measures, such as event-free survival or overall survival.

There might also be benefit from broader efforts in both adult and pediatric oncology to enhance the supply of patients for clinical trial participation. In 2018, the National Cancer Institute loosened eligibility requirements for patients with brain metastases, HIV/AIDS, organ dysfunction, prior or current malignancies, and those younger than 18 years.61 This move was supported by additional professional organizations, such as the American Society of Clinical Oncology and Friends of Cancer Research. Promotion of the Children’s Oncology Group has resulted in 90% to 95% of pediatric patients 15 years old or younger receiving care from Children’s Oncology Group-affiliated institutions, with 50% to 60% of trial-eligible children treated on a study protocol if one is available.62,63 Pediatric patients diagnosed with acute lymphoblastic leukemia have seen great benefit from these collaborative initiatives, with cure rates rising from 10% to 90% since the 1960s, evidence that collective efforts to include and treat individuals on such protocols is promising.64-66 Improved clinical trial enrollment with the intent of improving cancer outcomes has been adopted in adult clinical trials in the United Kingdom as well. In 1999, survival rates were poor when compared with other European Union members, and clinical trial accrual was less than 3.5% of incident cases.61 There have been higher adult participation rates in clinical trials since implementation of the National Health Service Cancer Plan

Figure 3. Recruitment needs vs clinical trial participation rates at 1%, 3%, 5%, and 10% reflected by the green, yellow, gray, and red bars, respectively. This graph represents trials that accrued in the United States, internationally, and in the United States + internationally (A); in the United States and/or the United States + internationally (B); or in the United States only (C). The period reflects trials that were completed and/or enrolling between 2000 and 2017.
and Cancer Networks in the United Kingdom, where participation is as high as 12% of annual incident cases.65

The inability to successfully accrue subjects to clinical trials may lead to unpublished scientific findings and research data.8,9,26 Noncompletion of a clinical study can result in exposure of patients to investigational agents without thorough investigation into the benefits or adverse events this may elicit.26 Our findings have prompted supply-side suggestions for increasing clinical trial participation. However, it is worth considering the structure of demand as well. Statistical rigor of phase 2 and 3 clinical trials could be altered to increase acceptable false-positive rates or choose 1-sided instead of 2-sided tests. Phase 1 and 2 trials could concurrently examine efficacy and toxicity. This might represent too large a risk. Alternatively, more rigorous phase 1 and 2 trials could result in only the most beneficial results moving toward larger phase 3 trials. However, one could argue that the production of multiple drugs targeting similar pathways or mutations at any stage of development is good, in that it promotes competition among drug companies, ultimately leading to cheaper drugs for the patient.

Clinical trial conduct and enrollment in the United States is a complex issue without a clear fix. Investment in past and present trends is a promising start. “Venture philanthropy” has incentivized industry and federal partnerships by sharing financial risk, contributing to shortened translational processes and a focus on “human return.”66 Partnerships between foundations and academic institutions have also improved early development by enhancing access both to patients for clinical trial participation and disease specialists for study design consultation.66 For example, growth of the Multiple Myeloma Research Consortium has led to standardized language for clinical trial agreements to allow for multisite integration and further investment and input from industry-led trials.66 The Multiple Myeloma Research Consortium represents partnerships among industry, the US Food and Drug Administration, and the Multiple Myeloma Research Foundation.66 Another method is to work within existing precompetitive public-private partnerships or to advocate for the formation of new partnerships.67 Public-private partnerships offer a groundwork for governmental, university, patient organizations/foundations, and industry collaboration.67 Last, umbrella or basket/master trials allow the opportunity for treatment assignment on the basis of genetic, molecular, cellular, or immune markers, creating a “funneled” screening approach that can increase patient participation and “fit.”68 This again requires flexible partnerships among regulatory agencies, pharmaceutical industries, genomic testing, and academic and clinical sites.68 Examples of umbrella and basket/master trials are the National Cancer Institute Match trial, the TAPUR trial, the Lung-MAP trial, and the Beat AML master trial.68 Encouraging and facilitating ongoing collaboration and partnerships across disciplines is a promising effort to enhance clinical trial participation for patients with FLT3-mutant AML and other malignancies.

Limitations of our study
Systematic review and data extraction were performed by a single person, and are therefore subject to human error. The graphical representations for subgroup analysis are based on US incidence counts only and do not consider the incidence of AML in each international location. In addition, US incidence counts do not include the relapsed/refractory AML population.

Accrual duration was calculated using study start date and primary completion date, where the primary completion date represents the date of data collection for primary endpoint measures. Although it is the most consistently reported measure on ClinicalTrials.gov, study accrual can end before primary completion date, and therefore the duration of accrual could potentially be shorter for many of the included studies. All calculations were made with the assumption that accrual rate has been constant over the course of the trial; this does not account for instances in which accrual varies drastically between years. Our data collection methodology does not account for patients who may have enrolled on multiple therapeutic studies for the treatment of AML, particularly early-phase studies, with targeted or nonspecific agents. This may occur in both FLT3 inhibitor trials and trials of other targeted agents. We anticipate this to be a relatively small patient population, as early-phase studies are available at a limited number of cancer centers. More specific to FLT3 inhibitor trials, we note that before the approval of midostaurin in 2017, some FLT3 inhibitor studies would not allow patients with prior FLT3 inhibitor exposure or prior treatment to enroll on new FLT3-targeted trials (eg, NCT01657682), thus making it difficult for a patient to be on multiple FLT3 inhibitor studies. However, inclusion and exclusion criteria were amended in several such studies after FLT3 inhibitors were added as standard of care (eg, NCT02421939).

There is also the possibility of discrepancies in the incidence data from literature publications vs the Centers for Disease Control and Prevention, as mathematical projections could have differed. The use of incidence data alone does not account for relapsed and refractory patients and underestimates a potential pool of patients with FLT3 AML eligible for clinical trials. However, the prevalence data on patients with relapsed or refractory AML are not easily available, and the preliminary analysis indicates that the number of patients with relapsed and refractory FLT3 AML may be quite small after accounting for remission rate, relapse rate, and overall survival.

In addition, 1%, 3%, and 5% accrual is mostly based on solid tumor data. Patients with AML and hematologic malignancy may be seen more often at academic centers, and may have a higher proportion of accrual. Rates of 1%, 3%, and 5% represent accrual to clinical trials with primary locations in the United States. It could be argued that subject recruitment needed beyond the available patient population in the United States would require international participation to reach projected accrual numbers.

Authorship
Contribution: T.B. and U.B. designed the research and wrote the paper; J.M.Z. and M.M. analyzed results; and J.M.Z. made the figures.

Conflict-of-interest disclosure: U.B. is a consultant for Gentech, Novartis, and Jazz pharmaceuticals. The remaining authors declare no competing financial interests.

ORCID profile: M.M., 0000-0003-1390-4917.

Correspondence: Uma Borate, Department of Hematology and Medical Oncology, Oregon Health & Science University Knight Cancer Institute, 3181 SW Sam Jackson Park Rd, Portland, OR 97239; e-mail: borate@ohsu.edu.
References


