blood advances

Midostaurin: its odyssey from discovery to approval for treating acute myeloid leukemia and advanced systemic mastocytosis

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Midostaurin was a prototype kinase inhibitor, originally developed as a protein kinase C inhibitor and subsequently as an angiogenesis inhibitor, based on its inhibition of vascular endothelial growth factor receptor. Despite promising preclinical data, early clinical trials in multiple diseases showed only modest efficacy. In 1996, the relatively frequent occurrence of fms-like tyrosine kinase 3 (*FLT3*) activating mutations in acute myeloid leukemia (AML) was first recognized. Several years later, midostaurin was discovered to be a potent inhibitor of the FLT3 tyrosine kinase and to have activity against mutant forms of KIT proto-oncogene receptor tyrosine kinase, which drive advanced systemic mastocytosis (SM). Through a series of collaborations between industry and academia, midostaurin in combination with standard chemotherapy was evaluated in the Cancer and Leukemia Group B 10603/RATIFY study, a large, phase 3, randomized, placebo-controlled trial in patients with newly diagnosed *FLT3*-mutated AML. This was the first study to show significant improvements in overall survival and event-free survival with the addition of a targeted therapy to standard chemotherapy in this population. Around the same time, durable responses were also observed in other trials of midostaurin in patients with advanced SM. Collectively, these clinical data led to the approval of midostaurin by the US Food and Drug Administration and the European Medicines Agency for both newly diagnosed *FLT3*-mutated AML and advanced SM.

Introduction

Midostaurin (CGP41251; PKC412) is a multikinase inhibitor recently approved for 2 indications in adult patients: (1) newly diagnosed acute myeloid leukemia (AML) with fms-like tyrosine kinase 3 (*FLT3*) mutations and (2) advanced systemic mastocytosis (SM).[1,2] Its clinical development proceeded in 3 stages. First, based upon activity against protein kinase C (PKC), it was evaluated in clinical trials as monotherapy in chronic lymphocytic leukemia (CLL) and melanoma, and as a single agent or in combination with chemotherapy against solid tumors without preselection according to tumor genotype.[3-7] These studies provided safety and pharmacokinetic data for the compound. Secondly, supported by its vascular endothelial growth factor receptor and angiogenesis inhibition, it was evaluated in patients with diabetes-related macular degeneration.[8,9] Stages 1 and 2 demonstrated inadequate efficacy to warrant further clinical development. Following the identification of additional targets, stage 3 focused on inhibition of FLT3 in AML and KIT proto-oncogene receptor tyrosine kinase (KIT) in advanced SM.[10,11] In these latter studies, patients were selected based on a genotype associated with a clearer oncogene addiction (to *FLT3* and *KIT*, respectively).[12,13]

Midostaurin and its active metabolites target mutant forms of FLT3 and KIT along with additional protein kinases implicated in leukemogenesis.[14] The pivotal AML trial focused on patients bearing *FLT3* mutations and trials in advanced SM on patients with activating *KIT* D816 mutations. For AML, a key

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Table 1. Stages of clinical development of midostaurin

	Stage 1 (1994-2000)	Stage 2 (1998-2002)	Stage 3 (2002-2017)
Target(s)	PKC	VEGF; angiogenesis	FLT3; KIT
Indication(s)	Solid tumors; B-cell malignancies	Diabetic retinopathy	*FLT3*$^+$ AML; advanced SM
Patient selection	No	No	Yes (AML: *FLT3* mutations; advanced SM: *KIT* D816V mutations in >80% of patients, but unselected)
Treatment	Single agent; chemotherapy combination	Single agent	*FLT3* mutant AML: combination with induction/consolidation chemotherapy + single-agent maintenance; advanced SM: single agent
Key findings	Favorable safety (mild/moderate GI toxicity and cytopenias); no MTD characterized; time-dependent PK; modest activity (in CLL)	Modest improvement in macular edema and visual acuity; limiting GI toxicity	*FLT3*-mutant AML (first line): improvement in OS and EFS, favorable safety profile; advanced SM (high overall response rate, durable responses, reduction in disease burden, improvement in quality of life; mild/moderate GI toxicity and cytopenias); PK: 3 active metabolites, DDI potential characterized

Development included 22 phase 1 studies, 9 phase 2 studies, 1 phase 3 study, and 42 phase 4 studies, with >2600 patients enrolled to date. Development in solid tumors and ophthalmology was discontinued due to lack of prominent signs of efficacy. Development is ongoing for AML and advanced SM, with submission to the US Food and Drug Administration and European Medicines Agency in 2016 and approvals in 2017.

DDI, drug–drug interaction; GI, gastrointestinal; MTD, maximum tolerated dose; PK, pharmacokinetics; VEGF, vascular endothelial growth factor.

decision was to focus early on first-line therapy (in combination with chemotherapy) instead of taking the traditional approach of focusing first in relapsed/refractory disease. Midostaurin demonstrated a favorable safety profile in both indications. In registrational trials, midostaurin improved overall survival (OS) in AML and showed compelling evidence of disease control as a single agent in advanced SM.[10,11,15] This review describes the developmental journey of midostaurin from its initial discovery as a PKC inhibitor to its current role as a multikinase inhibitor (Table 1).

Early development and characterization

Midostaurin emerged as a development candidate from a drug discovery program aimed to improve on the selectivity of staurosporine toward PKC,[16] which was considered to be an attractive therapeutic target in oncology and several other indications.[17-19] Staurosporine, an alkaloid first isolated from *Streptomyces* staurosporeus,[20-22] was one of the first compounds shown to inhibit cell proliferation through protein kinase inhibition.[23-26] In 1986, staurosporine was reported to potently inhibit the enzymatic activity of PKC at low nanomolar concentrations.[27] The availability of adequate amounts of staurosporine, via fermentation within Ciba-Geigy, enabled medicinal chemists to embark on a program to discover novel, potent, and selective inhibitors of PKC. However, at that time, the idea of moving any inhibitor of kinase signaling from bench to clinic was met with apprehension, given the difficulty in reaching an appropriate level of target selectivity.[28,29]

Early kinase inhibitors in the clinic

Despite this skepticism surrounding the feasibility of developing kinase inhibitors as tolerated drugs, the first kinase inhibitor to reach the market was fasudil (Japan, 1995), approved as a vasodilator[30,31] and subsequently found to act by RhoA/Rho kinase inhibition.[32,33] In 2000, the natural product sirolimus, a mammalian target of rapamycin inhibitor,[34] was approved in the United States for preventing kidney transplant rejection.[20] Imatinib, the first protein kinase inhibitor approved in oncology, was indicated for the treatment of chronic myeloid leukemia (CML) and later gastrointestinal stromal tumors.[35]

Development and characterization of midostaurin

Preclinical development

Midostaurin was first synthesized by Giorgio Caravatti in 1986.[36] Studies to investigate its potential as a PKC inhibitor revealed that it inhibited cell proliferation by interfering with cell-cycle activity.[37,38] It also inhibited solid tumor growth in murine xenograft models.[38] Furthermore, midostaurin demonstrated antiproliferative activity in a range of solid tumor lines, including lung, colon, breast, melanoma, and glioblastoma.[17] A key aspect in the clinical development of midostaurin, a highly insoluble drug, was the identification of a microemulsion formulation that allowed for rapid absorption and high bioavailability.[39] Following oral administration, midostaurin is metabolized primarily by the cytochrome P450 3A4 pathway to produce 3 major active metabolites.[9,40] Over time, it has become clear that, like midostaurin, these metabolites target not only PKC but also many other serine-threonine and tyrosine kinases (Figure 1).[14]

Stage 1: PKC and angiogenesis inhibitor in solid tumors

First-in-human studies commenced in 1994.[7] Low-grade gastrointestinal and hematologic toxicities were frequent but manageable. A maximum tolerated dose was not formally identified, because dose escalation was limited by the number of capsules to be ingested daily. A dosage of 150 mg/day was determined to be adequate for further phase 2 testing as a single agent. Subsequent studies of midostaurin in combination with 5-fluorouracil in patients with solid tumors,[5] in combination with gemcitabine and cisplatin in non–small cell lung cancer,[4] and as monotherapy in metastatic melanoma[3] and low-grade lymphoproliferative disorders[6] showed that the preclinical effects of midostaurin on these tumor types did not correlate with clinical outcomes (a modest decrease in lymphocyte counts was observed in CLL). However, the pharmacokinetic properties of midostaurin were characterized, showing that biologically relevant concentrations of the drug could be achieved at tolerated doses.

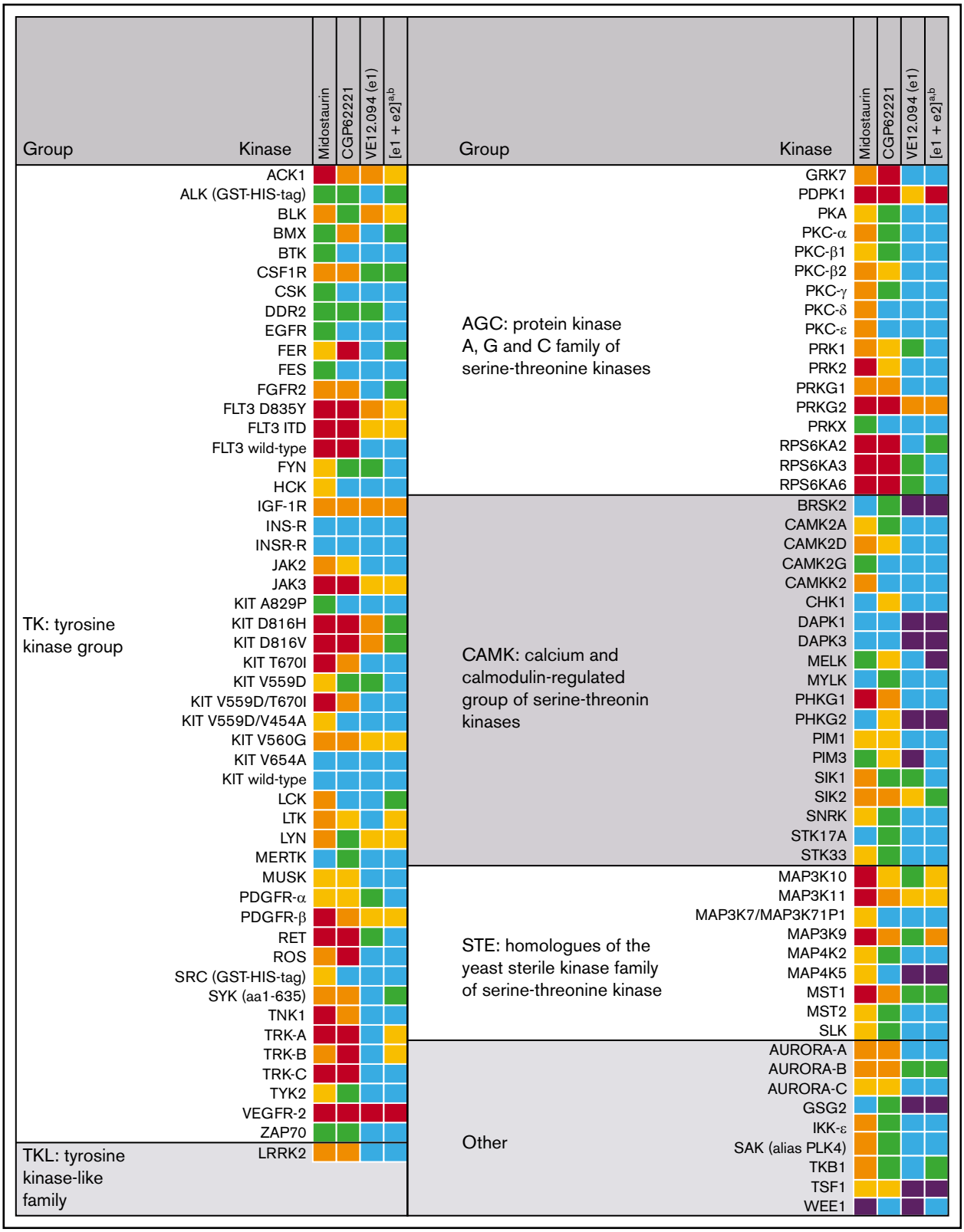

Figure 1. Midostaurin and its metabolites inhibit a variety of kinases. [a]e1 and e2 are 2 epimers of the previously reported metabolite CGP52421. [b]Apparent 50% inhibitory concentration for 1:1 mixture. Red denotes an 50% inhibitory concentration <0.1 μM; orange, 0.1 to <0.25 μM; yellow, 0.25 to <0.5 μM; green, 0.5 to <1 μM; blue, 1 to 10 μM; and purple, >10 μM.

Stage 2: angiogenesis inhibition in diabetes

Based on its activity against vascular endothelial growth factor receptor kinase and vascular endothelial growth factor–mediated effects in mouse models,[17] midostaurin was studied as an angiogenesis inhibitor for the treatment of diabetic retinopathy between 1999 and 2002.[8,9] Gastrointestinal toxicity was challenging for these patients, and the degree of efficacy, as assessed by macular edema and visual acuity, was insufficient at tolerated doses to support further development in diabetes.[8]

Stage 3: tyrosine kinase inhibition with patient selection in oncogene-addicted cancers

Clinical use of midostaurin for AML. In CML, the BCR-ABL1 tyrosine kinase inhibitor imatinib revolutionized the treatment of cancer by introducing the new paradigm of targeting the underlying genetic abnormality driving a malignancy.[41] In the mid-1990s, translational scientists reported that ~30% of patients with AML had an activating mutation in the transmembrane tyrosine kinase FLT3.[42,43] The more common internal tandem duplication (ITD) mutation was found to be particularly ominous, leading to rapid relapse and short survival with standard chemotherapy.[44]

Researchers at Novartis and Dana-Farber Cancer Institute had been closely interacting under an academic/industrial collaboration established in 1990. Within this established collaborative environment, Paul Manley selected a panel of receptor tyrosine kinase inhibitors as potential FLT3 inhibitors and sent these to James Griffin's group at Dana-Farber Cancer Institute in 2000 to evaluate their effects on FLT3-dependent cells. Ellen Weisberg tested these compounds in the Griffin laboratory using murine Ba/F3 cells rendered growth-factor independent via transfection with constructs that encoded either ITD or tyrosine kinase domain (TKD) point mutations in the FLT3 kinase. Midostaurin had potent antiproliferative activity by downregulating recombinant FLT3-catalyzed transphosphorylation in vitro and inhibiting the proliferation of the Ba/F3-FLT3-ITD cells at concentrations <10 nM, without affecting the viability of the parental cells at concentrations ≤ 100 nM.[45] Reduced cell growth was determined to be due to induction of apoptosis and cell-cycle arrest. Subsequently, the metabolites of midostaurin were also found to have activity against FLT3 at concentrations substantially below those attained at steady state following oral administration of therapeutic doses in patients.[45]

Around the same time, Gary Gilliland's laboratory developed a murine myeloproliferative neoplasm model by transfecting murine hematopoietic stem cells with mutant FLT3 constructs and then transplanting these cells into sublethally irradiated mice. When mice underwent transplant with bone marrow transduced with FLT3-ITD, all the animals dosed with an orally bioavailable formulation of midostaurin survived at 90 days compared with ~20% of control animals (Figure 2).[46] Of note, this model did not produce morphologic AML but rather a highly proliferative and aggressive neoplasm characterized by an overproduction of mature cells, thereby verifying the ability of mutated FLT3 to cause a proliferative thrust but also suggesting that it may not be central to the development of leukemia.

Preclinical studies such as these supported proceeding with a series of clinical trials of FLT3 inhibitors, although target selectivity and high protein binding were recognized as issues.[7,47] Midostaurin had an advantage over other investigational agents because a safe and tolerable dose had already been established in patients with solid tumors and diabetes.[7] Midostaurin and lestaurtinib were each tested in proof-of-concept trials that enrolled patients with advanced *FLT3* mutant AML.[48,49] Both trials demonstrated significant lowering of peripheral blood blast counts; however, complete remissions (defined as $<5\%$ blasts in the marrow together with adequate hematopoietic recovery) were rare, and this raised questions about the extent of single-agent efficacy. There were uncertainties surrounding whether adequate levels of sustained FLT3 inhibition were present and whether the relative resistance of marrow blasts resulted from their protection by the hematopoiesis-inducing microenvironment. Moreover, it seemed that FLT3 inhibition on its own would not be as effective in AML, as BCR-ABL1 inhibition was in chronic-phase CML, a less genetically diverse disease. Despite this, investigators proceeded with additional trials in AML. A dose-optimization study showed that twice-daily dosing of midostaurin was feasible and likely as effective as the 3-times-daily dosing used in its proof-of-concept trial.[45] Interestingly, a few patients with wild-type *FLT3 (FLT3*-WT) AML experienced blast reductions, although responses were more common in those with *FLT3*-mutated AML.

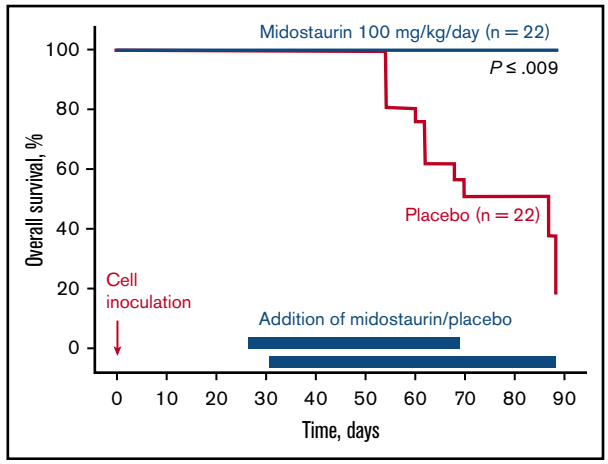

Figure 2. OS was assessed in BALB/c mice that underwent transplant with bone marrow transduced with *FLT3*-ITD and treated with midostaurin 100 mg/kg per day or placebo. Half of the mice were treated from days 30 to 88; the remaining mice were treated from days 25 to 68. Adapted from Weisberg et al[46] with permission.

A key strategic decision in the development of midostaurin in AML was to go straight from the first proof-of-concept single-agent trial in relapsed/refractory AML[48] to development as first-line treatment in combination with chemotherapy.[10,50] This approach skipped the traditional step of further trials in relapsed/refractory disease. In contrast to midostaurin, lestaurtinib was simultaneously moved into a phase 3 trial in relapsed/refractory *FLT3*-ITD–positive AML, in which salvage chemotherapy was given with or without lestaurtinib.[51] Response rates and OS were not improved with addition of lestaurtinib to chemotherapy. However, a novel, ex vivo plasma inhibitory assay was developed by Mark Levis, and it demonstrated that a large number of these patients had inadequate FLT3 inhibitory levels in plasma.[40] This result informed the hypothesis that the optimal setting to test a relatively nonspecific inhibitor would be in newly diagnosed patients AML to avoid the evolved resistance mechanisms which are the greatest challenge in relapsed disease.[52]

An opinion developed that the biological activity noted in the single-agent trials of midostaurin in AML could be improved by combining the drug with additional agents such as standard cytotoxic chemotherapy. Subsequently, a phase 1b trial in patients with newly diagnosed *FLT3*-unselected AML who received standard 7 + 3 (cytarabine plus daunorubicin) induction and high-dose cytarabine consolidation chemotherapy combined with various doses and schedules showed that continuous dosing with midostaurin at either 50 or 100 mg twice daily was not tolerated due to gastrointestinal toxicity.[53] Fortunately, schedules of midostaurin at 50 mg twice daily were feasible either on days 1 to 7 and 15 to 22 of the 28-day cycle or on days 8 to 22. Sequential dosing was chosen for further study, because, as noted by Donald Small, concomitant administration of midostaurin and chemotherapy might increase toxicity and perhaps be antagonistic from a cell-cycle standpoint.[54] A key finding from this trial was that patients with mutant *FLT3* experienced comparable outcomes to those in patients with *FLT3*-WT AML. Although encouraging, this result was based on only 13 patients with *FLT3*-mutated AML, 4 of whom harbored *FLT3*-TKD mutations, which have a somewhat better prognosis than *FLT3*-ITD–positive AML patients.

Investigators then proposed to compare standard chemotherapy to standard chemotherapy plus midostaurin in patients with newly diagnosed AML at the dose and schedule shown to be safe in the phase 1b trial. Debate ensued about whether this trial should stratify patients by *FLT3* mutation status or disregard the presence of a *FLT3* mutation. A trial that did not stratify would obviate the need for rapid genetic testing at diagnosis, but it would have to be powered to detect a benefit in only the 30% of patients with a *FLT3* mutation. The designers decided to develop rapid genetic testing at diagnosis and enroll only patients with a *FLT3* mutation. However, limiting enrollment onto the C10603/RATIFY trial to *FLT3* mutant AML would allow an assessment of the relative importance of FLT3 inhibition vs off-target effects by comparing the magnitude of benefit from midostaurin in ITD high vs low allelic ratio patients, with the latter being likely less dependent on FLT3 signaling. Also, potentially informative as to the importance of FLT3 inhibition for clinical efficacy, a limited number of correlative studies are currently being performed which assess the correlation of FLT3 autophosphorylation status at entry and outcome. To test the hypothesis that the multikinase inhibitor could potentially be active beyond FLT3 inhibition, a phase 3 trial in patients with AML without a *FLT3* mutation is currently being planned.

There were tremendous difficulties in performing a trial enrolling only the 30% of patients with AML harboring *FLT3* mutations. Fortunately, the global leukemia community united in this effort. This undertaking required access to patients from multiple cooperative groups worldwide (Figure 3),[55] the drug knowledge base, and substantial resources of a large pharmaceutical company, as well as a partnership with the Cancer Therapy and Evaluation Program of the National Cancer Institute. The Cancer and Leukemia Group B (CALGB), now the Alliance for Clinical Trials in Oncology, and Novartis reached an agreement whereby CALGB and Cancer Therapy and Evaluation Program sponsored the trial in the United States and Canada, and Novartis sponsored the trial in other countries. Moreover, to accomplish the necessary *FLT3* testing, investigators from 9 academic laboratories in 5 countries harmonized a polymerase chain reaction–based *FLT3* mutation testing method with rapid turnaround time (≤48 hours).[10] Overall, 3277 patients with AML were screened between May 2008 and October 2011 to identify the 717 eligible patients with *FLT3* mutations enrolled in the CALGB 10603/RATIFY trial, which involved 225 sites in 17 countries.[55] The crucial cooperation of expert leukemia investigators around the world cannot be overstated.

Even with these enormous logistical hurdles overcome, a trial with realistically achievable goals and end points still had to be designed. The investigative team understood that it was important to perform a prospective, randomized, placebo-controlled trial that included a maintenance phase to maximize the efficacy of midostaurin by keeping the mutant clone suppressed. Although event-free survival (EFS) was originally considered as a potential endpoint, investigators felt that OS would yield a real-world confirmation of the clinical benefit of midostaurin in this patient population, given the likelihood that allogeneic transplant would occur in a sizable minority of patients.

Concerns were expressed throughout the regulatory process that stem cell transplant might obscure any beneficial effect of midostaurin. However, the investigators insisted that the addition of midostaurin to initial chemotherapy could lower the residual disease burden prior to transplant and thus improve long-term outcomes. Moreover, there were concerns that if the primary end point required censoring at the time of transplant, too large a sample size would be required. Similarly, the question of maintenance therapy was also raised, pointing to the options of introducing a second randomization, a 2-by-2 design, or a separate trial. However, such designs would have made an already large study untenable. It was finally agreed to proceed with a primary end point based on OS uncensored for transplant, with final analysis when 75% of events (deaths) had occurred.

Study conduct went surprisingly well. The commitment displayed by European investigators manifested by key scientific contributions and prodigious accrual was essential. Because of the very rapid turnaround of the FLT3 genotyping, it was feasible to rapidly screen and enroll patients with *FLT3*-mutated AML within 2 to 3 days of presentation. The study was stratified based on the type of *FLT3* mutation: *FLT3*-TKD (relatively more favorable outcome), *FLT3*-ITD with a high allelic ratio (poor prognosis), and *FLT3*-ITD with low allelic ratio.[56] The allelic ratio was defined as the mutant to wild-type fraction and ranged from 0.05 to >1. A planned interim analysis was carried out when 50% of events occurred.[10] After ~500 patients had enrolled, it became clear that initial study assumptions underestimated the number of patients who would be transplanted in first remission and the number of patients with TKD mutation, both of which would yield less-frequent events. Therefore, an amendment expanded the trial from 500 to 714 patients.

Several years after the trial completed enrollment, it was evident that the expected number of events was not going to occur within a reasonable time frame. The number of deaths plateaued, forecasting the necessary 509 OS events to occur in 2025.[10] Therefore, the statistical plan was amended to allow the study to be analyzed when a sufficient number of EFS events (failure to achieve remission, relapse, or death from any cause) occurred.

Figure 3. The RATIFY phase 3 trial in patients with *FLT3*-mutated AML involved a global collaboration framework across academia, industry, and government.

When the study was unblinded, the midostaurin arm showed an improved OS in the analyses both censored and uncensored for transplant (Figure 4). Results were consistent across *FLT3* subgroups (Figure 5). The data from RATIFY led to approval for midostaurin in adults with newly diagnosed *FLT3*-mutated AML in the United States, European Union, and other countries (Table 2). In addition, for the purposes of US Food and Drug Administration approval of midostaurin, a companion *FLT3* diagnostic test was developed through a partnership between Novartis and Invivoscribe.

Clinical use of midostaurin for advanced SM. Following an initial case report in 1 patient with MCL,[57] studies in patients with advanced SM were performed. In this disease, midostaurin targets mutant forms of the KIT receptor tyrosine kinase, detected in >80% of patients.[11,56] Two single-arm, phase 2 studies, representing the largest prospective clinical trials program conducted in this rare disorder, demonstrated the efficacy of midostaurin 100 mg twice daily in advanced SM. Midostaurin elicited high rates of response in the A2213 study and the D2201 study (60% and 69%, respectively); responses were durable and associated with reduced disease burden and improved quality of life.[11,15] These studies led to the approval of midostaurin in advanced SM at the same time as the approval in AML.[1,2]

Lessons learned

The successful development of midostaurin provides several lessons for clinical trialists, in general and specifically in AML. Although they were not successful in terms of clinical outcomes in solid tumors, CLL, or diabetic retinopathy, the first 2 stages were crucial for having identified tolerable dosing, characterizing pharmacokinetics, and establishing the safety profile of midostaurin.

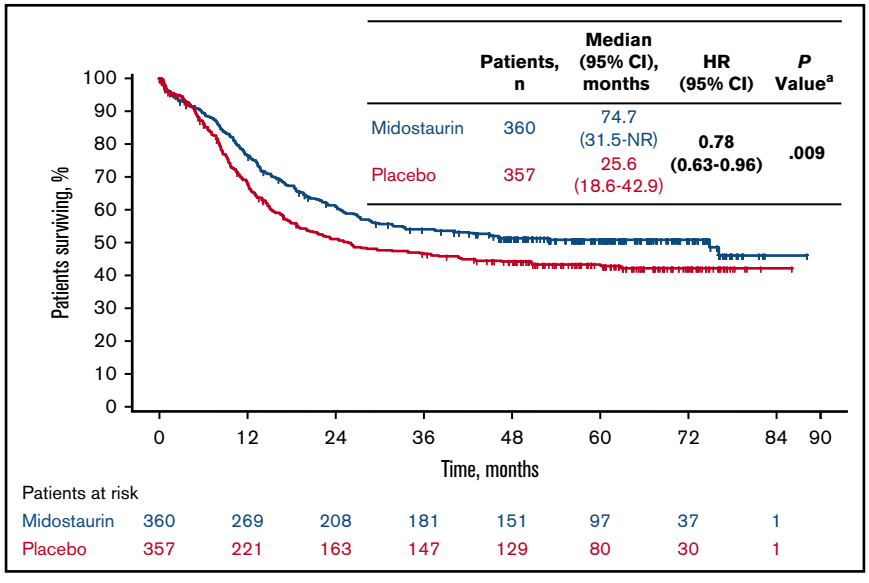

Figure 4. Kaplan-Meier analysis of OS not censored for transplant in RATIFY showed a 22% reduction in risk of death with midostaurin plus chemotherapy vs placebo + chemotherapy. [a]Cox model stratified on *FLT3* subtype; 1-sided, log-rank *P* value. Adapted from Stone et al[10] with permission. CI, confidence interval; NR, not reached.

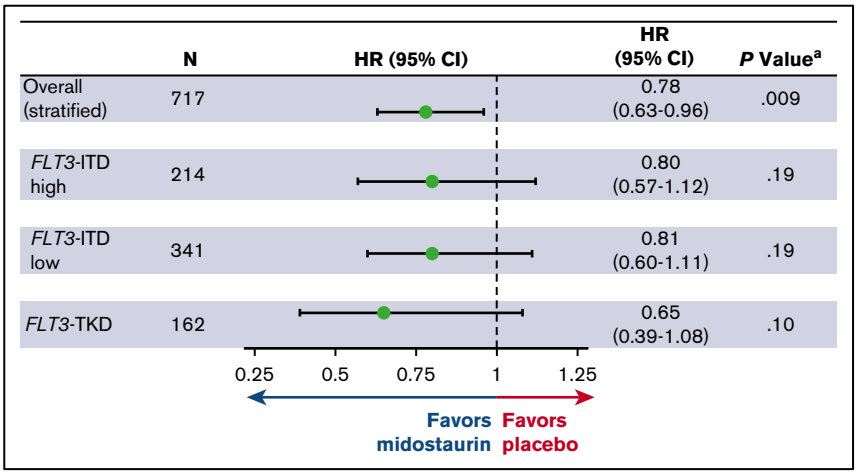

Figure 5. In RATIFY, OS not censored for transplant showed improvement across all *FLT3* subgroups. [a]*P* value is 1 sided for the overall (stratified) analysis; *P* values are 2 sided for the analyses by *FLT3* subgroup. *FLT3*-ITD-low, *FLT3*-ITD/-wild-type (WT) allelic ratio <0.7; *FLT3*-ITD-high, *FLT3*-ITD/-WT allelic ratio ≥0.7. Adapted from Stone et al[10] with permission.

This "early" work enabled investigators to efficiently design trials once AML was selected as a potential indication.

This journey shows the feasibility of conducting a large, international phase 3 trial in a subset of patients molecularly defined using a well-validated test before chemotherapy is initiated. Extensive coordination between clinical trial cooperative groups, the pharmaceutical industry, and governmental agencies (the Cancer Therapy Evaluation Program of the National Cancer Institute in particular) united in a common goal enabled the successful completion of the RATIFY study. Patience was required for industry and cooperative groups to understand each other well and align expectations to foster an open and transparent collaboration. For example, both entities had to be open to using different processes than normal to (1) preserve the independence of academic oversight while being cognizant of industrial requirements, and (2) involve a wide range of regulatory, technical, and scientific disciplines. The logistical support required was considerable but manageable. Additionally, the journey underscores the importance of quickly moving investigation of new therapies to the first-line setting whenever appropriate, considering the safety and efficacy profile of the drug, along with knowledge concerning the molecular target addressed by the new therapy.

For example, with today's knowledge that the clonal heterogeneity of AML is much higher at diagnosis than at relapse,[58] the RATIFY data support the hypothesis that a compound targeting multiple kinases relevant to AML would be more appropriate for newly diagnosed disease to capture this clonal heterogeneity. The improved survival observed in RATIFY is in line with that hypothesis as well as with prior in vitro work suggesting that less specific FLT3 inhibitors (eg, midostaurin) have better antiproliferative effect than more specific inhibitors in patient samples taken at diagnosis vs samples taken at relapse.[57,59]

In retrospect, several aspects of this development could have been improved. Since the initial study design a decade ago, much has been learned about AML disease biology, and many important technological innovations have been introduced. For example, although samples have been collected by some participating groups and will be analyzed in the future, measurable residual disease (MRD) and comprehensive genetic profiling were not formal end points. This information could be very useful in better understanding the striking effect of midostaurin in patients who received a transplant in first complete remission immediately after induction and consolidation chemotherapy, which could be due to a lower disease burden prior to transplant. This technology could also be useful to characterize the effect of maintenance therapy. The collection of MRD data are now strongly recommended for clinical trials.[60] In addition, samples collected during the trial will be used to construct a comprehensive genetic profile for each patient at diagnosis to determine which genetic subpopulations of patients are more likely to benefit from the addition of midostaurin to chemotherapy. For example, data investigating the impact of *NPM1* comutations on the outcomes of these patients will be reported shortly. However, including biomarkers and complex genetics in the initial study design for all patients would have added even more complexity to a trial that was already large and complex. The RATIFY trial also illustrates the challenges of selecting appropriate end points. OS clearly remains the gold standard, but it is increasingly difficult to interpret in AML owing to the increase in the use of transplant in first complete remission and the availability of more effective salvage therapies. In addition, OS requires extensive follow-up; in RATIFY, the time from the start of enrollment to the primary analysis took 7 years. Although harboring their own methodological challenges, alternative end points less influenced by

Table 2. Midostaurin FDA and EMA approved indications

	Indications
FDA[1]	Midostaurin is a kinase inhibitor indicated for the treatment of adult patients with newly diagnosed AML that is *FLT3*-mutation positive as detected by an FDA-approved test, in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation. Limitations of use: midostaurin is not indicated as a single-agent induction therapy for the treatment of patients with AML, ASM, SM-AHN, or MCL.
EMA[2]	Midostaurin is indicated (1) in combination with standard daunorubicin and cytarabine induction and high-dose cytarabine consolidation chemotherapy and for patients in complete response followed by midostaurin single-agent maintenance therapy, for adult patients with newly diagnosed AML who are *FLT3*-mutation positive; and (2) as monotherapy for the treatment of adult patients with ASM, SM-AHN, MCL.

ASM, aggressive systemic mastocytosis; EMA, European Medicines Agency; FDA, US Food and Drug Administration; MCL, mast cell leukemia; SM-AHN, systemic mastocytosis with associated hematological neoplasm.

postrelapse therapy (eg, EFS) are increasingly used in contemporary phase 3 trials.

Future directions

Despite limitations, the RATIFY trial represents a shining example of a successful worldwide collaboration among industry, government, and academia. This model may be a paradigm for making progress in orphan diseases, which are increasingly defined by oncogenic drivers that occur even less frequently than *FLT3* or *KIT*. The RATIFY study led to the first targeted therapy for AML with midostaurin benefitting a sizable subset of AML patients with a historically poor prognosis. On the other hand, the 16-year period between the discovery that midostaurin had preclinical efficacy as an FLT3 inhibitor to the approval of the drug was unacceptably long. While carefully conducted sequential clinical trials undoubtedly contributed to this success, a more rapid readout end point than OS would have been ideal. Alternative innovative trial designs are imperative to cope with a rapidly increasing number of potential new therapies available for clinical trial investigation. Smaller randomized controlled trials using a surrogate end point (eg, EFS) or the achievement of an MRD-negative state may be a quicker way to determine the efficacy of multiple novel targeted agents.

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Authorship

Contribution: R.M.S., R.A.L., and R.C. designed and performed research; collected, analyzed, and interpreted data; and drafted and approved the manuscript; and P.W.M. designed research, analyzed and interpreted data, and drafted and approved the manuscript.

Conflict-of-interest disclosure: R.M.S. is a consultant for Novartis, Amgen, Celator, Bristol-Myers Squibb, Karyopharm, Janssen, Jazz Pharmaceuticals, Orsenix, Fujifilm, Ono, Pfizer, Celgene, Astellas, Juno, Abbvie, Cornerstone, Seattle Genetics, Arog, Merck, and Sumitomo; has received clinical research support to his institution from Novartis, Celator, Karyopharm, Arog, and Daichi-Sankyo; served on the Data Safety Monitoring Board for Sunesis, Celgene, and Argenix; and received clinical research support to the cooperative group for investigator meetings and data support. R.A.L. is a consultant for Novartis and Astellas. R.C. and P.W.M. are employees of Novartis AG. R.C. has equity ownership of Novartis Pharma AG.

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