A phase II study of ponatinib for prevention of relapse after allogeneic transplantation in *FLT3* internal tandem duplication mutation-positive (*FLT3*-ITD$^+$) acute myeloid leukemia: the PONALLO trial

Ponatinib is a third-generation tyrosine kinase inhibitor (TKI) that could prove useful as maintenance therapy after allogeneic hematopoietic stem cell transplantation (allo-HSCT) for patients with FMS-like tyrosine kinase 3 (*FLT3*)-mutated acute myeloid leukemia (AML). This hypothesis was tested here in 22 patients. Due to a very low rate of enrollment, the study had to be stopped prematurely. Half of the patients had to stop ponatinib for toxicity but most ponatinib-related adverse events were grade 1 and 2 (75%) with no cardiovascular events. However, a high rate of relapse post-transplant was observed.

For patients with AML, relapse remains a major issue after allo-HSCT.[1] For the approximately 25% of patients harboring an *FLT3*-internal tandem duplication mutation (*FLT3*-ITD),[1] survival has been shown to be significantly improved with the use of sorafenib as maintenance therapy after allo-HSCT.[2,3] This first-generation small molecule TKI, provided a reduced incidence of relapse in two phase III randomized studies comparing sorafenib *versus* placebo. The SORMAIN trial[2] showed a 2-year relapse-free survival (RFS) of 85% compared to 53% for the placebo group. Xuan *et al*.[3] reported 2-year RFS of 79% *versus* 57% and a relapse incidence of 15% *versus* 36% at 5 years post-transplant. As a consequence, sorafenib is now recommended as post-transplant maintenance and has become a standard of care in this population in most centers.[4] However, a recent real-world analysis revealed high rates of toxicity-related interruption of this treatment.[5] This study suggested the feasibility of re-challenging with sorafenib and/or of switching to other maintenance approaches for patients displaying toxicity. In fact we know that midostaurine is associated with no benefit post-transplant.[6] Among them, gilteritinib could be a valuable alternative, based on the results of the MORPHO study.[7] Of note, gilterinib may be of benefit only in patients with detectable measurable residual disease (MRD) before or after transplant, supporting the relevance of an MRD-based maintenance strategy.[7]

Ponatinib is a multikinase inhibitor that is approved for the treatment of Philadelphia chromosome-positive acute lymphoblastic and chronic myelogenous leukemias. It has also activity against *FLT3*-mutants including ITD and IT-D691L but not D835 within the Flt3 activation segment.[8] Ponatinib is active by itself against AML.[9] Ponatinib could thus represent an option for maintenance after allo-HSCT in *FLT3*-ITD-mutated AML patients, with potentially higher effectiveness for preventing relapse. Of note, there is no data currently regarding the use of ponatinib after transplantation in this context.

This prompted the design of a multicenter phase II non-randomized prospective study testing the efficacy and tolerability of ponatinib after allo-SCT in *FLT3*-ITD-mutated AML

Table 1. *FLT3*-internal tandem duplication mutation-positive acute myeloid leukemia patient characteristics (total number of patients =22).

Characteristics	Values
Sex: male/female, N	8/14
Median age at transplant, years (range)	50 (22-70)
Median WBC count at diagnosis, x10^9/L (range)	46.1 (0-168.8)
Median % of bone marrow blasts at diagnosis (range)	82 (24.5-95.5)
Median *FLT3*-ITD ratio at diagnosis (range)	0.51 (0.08-1.73)
ELN 2017 classification, N Favorable/Intermediate/adverse/unknown	 1/15/6/1
Cytogenetics, N Normal karyotype (*NPM1* mutation) Trisomy 8 (+trisomy 5) Trisomy 13 Monosomy 7/ del 7q t(11;22) (*KMT2A*+) Unknown	 14 (8) 3 1 1/1 1 1
Previous allograft, N	1
Pre-graft anti-FLT3 inhibitor administration, N Midostaurin Gilteritinib	 19 2
Status at transplant, N CR1 (*NPM1*$^+$ molecular relapse) CR2 Refractory	 18 (1) 2 2
Conditioning regimen: RIC/MAC/sequential, N	11/7/4
Donor type, N Geno-identical Pheno-identical Haplo-identical One mismatch unrelated	 4 9 8 1

WBC: white blood cells; CR: complete remission; RIC: reduced-intensity conditioning; MAC: myeloablative conditioning.

patients, the PONALLO trial registered at *clinicaltrials gov. Identifier: NCT03690115*.

The main objective was the incidence of relapse at 2 years post-transplant with the hypothesis of reducing it from 30% to 15%. Seventy-seven patients had to be included to reach this goal. All patients with an *FLT3*-ITD-mutated (at diagnosis or at relapse) AML could be included if aged between 18 and 70 years, in cytologic complete remission (CR, <5% of bone marrow blasts) and with documented engraftment at the time of ponatinib initiation after an allo-HSCT. Any type of conditioning regimen and donor were acceptable. At the time of inclusion, a controlled graft-*versus*-host disease (GVHD) was mandatory, as well as a platelet count ≥70x10^9/L, a neutrophil count ≥1x10^9/L, and no cardiovascular contra-indication. The study was supported by Incyte. All patients signed an informed consent and the study was approved by an ethical committee which is the Comité de Protection des Personnes NORD OUEST III, Caen University Hospital, France.

Initially, ponatinib administration was planned to start between day +60 and +90/100 at a dosage of 30 mg/day for 1 year. However, because of excessive hematopoietic toxicity, an amendment was proposed after the 14th patient, recommending to start ponatinib between day 100 and day 120 post-allo-HSCT. During the study, it was allowed to restart ponatinib at a 15 mg/day, after the resolution of toxicities which occurred at the 30 mg dosage. Yet, the duration of the maintenance was programmed for 1 year after which it was neither allowed to continue ponatinib nor to start a new FLT3 inhibitor.

Of the 23 patients included between December 2019 and April 2022, 22 were effectively treated. The last patient included did not receive ponatinib due to liver abnormalities incompatible with the start of the drug. Moreover, because of a very low rate of enrollment, the trial was closed prematurely in accordance with the sponsor in December 2022. Results for the 22 treated patients are reported here. Patient characteristics are given in Table 1. Of note, all patients but one had received FLT3 inhibitors before transplant as part of induction and/or consolidation chemotherapies (midostaurin N=19, gilteritinib N=2). With a median follow-up of 24.72 months (interquartile range [IQR], 20.66-29.93), 1- and 2-year overall survival (OS) were 81% (95% confidence interval [CI]: 66-100) and 65% (95% CI: 47-90) respectively. One- and 2-year leukemia-free survival (LFS) were 55% (95% CI: 37-80) and 50% (95% CI: 32-76), respectively. Ten relapses occurred at a median of 186 days (range, 69-481) after allo-HSCT with a cumulative incidence of relapse of 37% (95% CI: 17-57) at 1 year and 42% (95% CI: 21-62) at 2 years. Half of the patients (N=14) with normal karyotype relapsed while three of eight (37.5%) patients with abnormal or unknown karyotype (trisomy 8+5

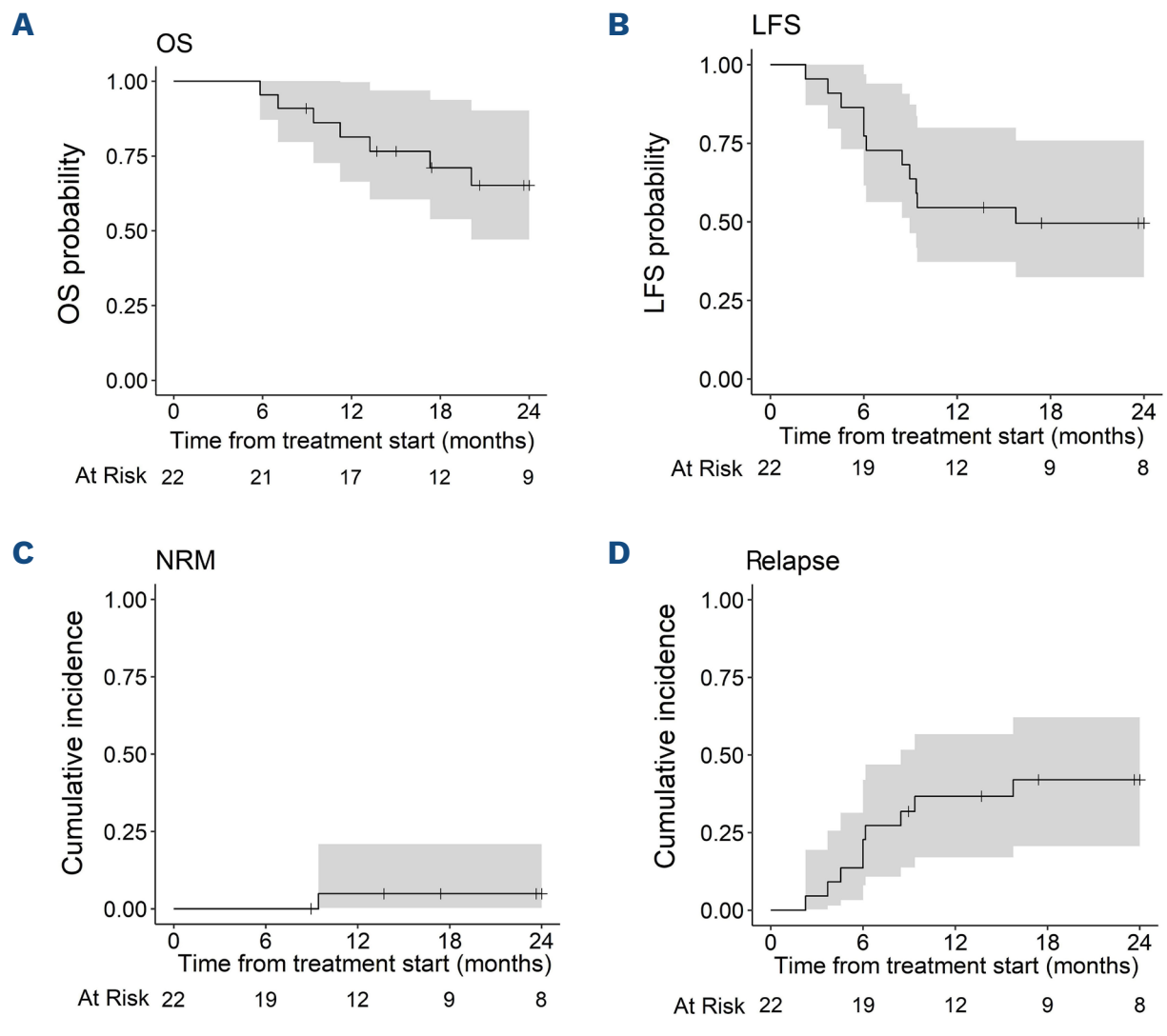

Figure 1. Various outcomes of the whole cohort (N=22). (A) Overall survival (OS). (B) Leukemia-free survival (LFS). (C) Non-relapse mortality (NRM). (D) Cumulative incidence of relapse.

N=1, trisomy 13 N=1, unknown N=1) relapsed. Among patients with normal karyotype (N=14), the proportion of relapse was the same between those who had *NPM1* mutation (N=4/8, 50%) and those who didn't have the *NPM1* mutation or an unknown molecular status (N=3/6, 50%, no other mutation N=3, *BCOR*$^{+}$ *RUNX1*$^{+}$ mutation N=1, unknown molecular status N=2). Non-relapse mortality was 4.9% (95% CI: 0.29-21) at both 1 and 2 years (Figure 1). Eight patients died, mainly of relapse (N=6). One patient died of sepsis and one of a methotrexate-induced leukoencephalopathy.

Ponatinib was initiated at a median of 69 days post-allo-HSCT (range, 60-130). The median duration of treatment was 75.5 days (range, 4-369). Only three patients received 1 year of treatment at 30 mg/day as per protocol. The reasons for stopping ponatinib were toxicity in 11 patients (50%), relapse in six, toxicity then relapse in one, GVHD then relapse in one. Among the 13 patients who stopped ponatinib for toxicity or GVHD, ponatinib was re-initiated for six, at 15 mg for five and at 30 mg for one, then withdrawn again for toxicity (N=4) or progression (N=2). A total of 39 adverse events related to ponatinib were documented in 17 patients. The majority was grade 1 or 2 (N=27, 69%) while ten grade 3 (26%) and two grade 4 (5%) occurred (Table 2). No cardiovascular events occurred. Unfortunately, no MRD data were available before the graft or at the initiation of ponatinib, either by flow cytometry nor by *FLT3*-ITD variant allele frequency analysis.

First, this study illustrates the challenges of properly conducting a prospective study, since the trial had to be terminated prematurely owing to an inadequately slow recruitment. As for the SORMAIN study,[2] this occurred in the context of concurrent trials and off-trial access to other FLT3 inhibitors, which may be more manageable than as part of a clinical trial.

Second, it remains unlikely that ponatinib would have shown a benefit in this cohort, with a 50% rate of relapse. However, a real comparative prospective phase III study with a control group without ponatinib is required to confirm this statement. Indeed, these poor results are difficult to explain since most patients were in CR1 and classified as intermediate-risk according to the ELN2017 classification. Moreover, inclusion criteria, namely by except detectable pre- or post-transplant MRD, were the same as in the three prospective phase III studies that had shown a major benefit of FLT3 TKI.[2,3,7] The median FLT3 ratio was relatively high (>0.5) but this has been shown not to impact outcome after allo-HSCT in *FLT3*-ITD AML patients.[10] Only the high median white blood cell count (46x10^{9}/L) at diagnosis may have contributed to the poor response to ponatinib, since this has been reported as a high risk factor,[11] although this was not the case in the Chinese study.[3] Also, all patients but one had received an FLT3 inhibitor before transplant. This was the case for only nine patients in the SORMAIN study (including patients in both the placebo and experimental groups) and for 59% of the patients in the study by Xuan *et al.*[3] In fact, the impact of receiving FLT3 inhibitors prior to allo-HCT remains unclear, even though this has become a standard of care not only in first-line therapy (with midostaurin[12] or quizartinib[13]) but also in relapse (with gilteritinib[14]). Could this early therapy impact the effectiveness of FLT3 inhibitors in maintenance therapy post-transplant? This could be the case, owing to the high relapse rate observed in this trial, suggesting the development of resistance to FLT3 inhibitors. Indeed, the acquisition of on-target or secondary *FLT3* mutations is a well-known mechanism, among others, of resistance to treatment with FLT3 inhibitors.[15] Finally, we have to mention that the lack of efficacy of ponatinib maintenance may have been related to the short duration of treatment received (less than 3 months) because of toxicity. Another potential difference between ponatinib and sorafenib in terms of efficacy is the immunomodulatory effect of sorafenib stimulating graft-*versus*-leukemia effect,

Table 2. Ponatinib-related adverse events according to investigators (total adverse events N=39 in 17 patients).

AE	Grade 1	Grade 2	Grade 3	Grade 4
N of AE (N of patients)	10 (6/17)	17 (12/17)	10 (7/17)	2 (2/17)
Hematogical, N				
Neutropenia	-	-	-	1
Thrombocytopenia	-	2	2	-
Pancytopenia	-	1	-	1 (+sepsis)*
Gastro-intestinal, N				
Abdominal pain	-	1	-	-
Diarrhea	1	-	-	-
Anorexia	1	-	1	-
Nausea	1	1	-	-
Vomiting	1	-	-	-
Hepatic, N				
Cytolysis	1	1	1	-
Cholestasis	1	1	1	-
GVHD, N		2		
Cutaneous, N				
Erythema	2	3+1*	1	-
Oedema	-	1	-	-
Neurological, N				
Headache	-	1	-	-
Myoclonia	-	-	1	-
Psychiatric, N				
Depression	-	-	1*	-
Rheumatic, N				
Arthralgia	2	-	-	-
Myalgia	-	-	1*	-
Low back pain	-	1	-	-
Reproductive system, N				
Loss of libido	-	1	-	-
Viral infection, N				
Chickenpox	-	-	1*	-
Cardio-vascular, N	0	0	0	0

*Serious adverse event (AE). GVHD: graft-*versus*-host disease.

which may not be the case for ponatinib.[16]
Third, it is however worth noting that safety was not an issue in this study as respectively only 17% and 8% of grade 3 and 4 ponatinib-related adverse events were documented and no cardiovascular events occured. This result seems comparable with what has been reported with sorafenib.[2,3]
As for sorafenib also, some patients could restart ponatinib after discontinuing treatment due to toxicity.[2,3]
In conclusion, ponatinib administration after allo-HSCT, although associated with a good toxicity profile, did neither reduce relapse nor improve survival in this small cohort of *FLT3*-ITD mutated AML patients. Other FLT3 inhibitors, such as sorafenib and gilteritinib, must be considered for maintenance after allo-HSCT in this context.

Authors

Patrice Chevallier,[1,2] Anne Thiebaut,[3] Sylvie François,[4] Sylvain Chantepie,[5] Marie-Thérèse Rubio,[6] Hélène Labussiere-Wallet,[7] Eolia Brissot,[8] Natacha Maillard,[9] Anne Huynh,[10] Valérie Coiteux,[11] Maxime Jullien,[1] Alice Garnier,[1] Amandine Le Bourgeois,[1] Pierre Peterlin[1] and Thierry Guillaume.[1,2]

[1]Hematology Department, Nantes University Hospital, Nantes; [2]INSERM UMR1232, CRCINA IRS-UN, University of Nantes, Nantes; [3]Hematology Department, Grenoble University Hospital, Grenoble; [4]Hematology Department, Angers University Hospital, Angers; [5]Hematology Department, Caen University Hospital, Caen; [6]Hematology Department, Nancy University Hospital, Nancy; [7]Hematology Department, Hôpital Lyon Sud, Hospices Civils de Lyon, Pierre Bénite; [8]Hematology Department, Hôpital St-Antoine, AP-HP, Paris; [9]Hematology Department, Poitiers University Hospital, Poitiers; [10]Hematology Department, IUCT Oncopole, Toulouse and [11]Hematology Department, Lille University Hospital, Lille, France

Correspondence:
P. CHEVALLIER - patrice.chevallier@chu-nantes.fr

https://doi.org/10.3324/haematol.2025.287681

Received: February 27, 2025.
Accepted: April 9, 2025.
Early view: April 17, 2025.

Disclosures

PC discloses advisory board participation at Takeda, Servier, Abbvie and Priothera; as well as international congress particpiations for Abbvie. All other authors have no conflicts of interest to disclose.

Contributions

PC designed, conducted and coordinated the research, included patients, analyzed and interpreted the data, and wrote the manuscript. MJ performed statistical analyses and generated the figures. He also included patients, contributed data and commented on the manuscript. AT, SF, SC, MTR, HLW, EB, NM, AH, VC, AG, ALB, PP, and TG included patients, contributed data and commented on the manuscript. All authors had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis and approved the final version to be published.

Acknowledgments

We thank Versailles University Hospital, France, for promoting the study, and especially Mrs Laure Morisset and Mrs Virginie Chatagnier. Medical writing assistance was provided by MPIYP (MC Béné), Paris, France.

Funding

The study was funded by Incyte and ponatinib was provided free of charge by Incyte. The funder had no role in the study design, data collection, data analysis, data interpretation or writing the report.

Data-sharing statement

Data can be provided upon reasonable request to the corresponding author.

References

1. Döhner H, Wei AH, Appelbaum FR, et al. Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. Blood. 2022;140(12):1345-1377.
2. Burchert A, Bug G, Fritz LV, et al. Sorafenib maintenance after allogeneic hematopoietic stem cell transplantation for acute myeloid leukemia with FLT3-internal tandem duplication mutation (SORMAIN). J Clin Oncol. 2020;38(26):2993-3002.
3. Xuan L, Wang Y, Yang K, et al. Sorafenib maintenance after allogeneic haemopoietic stem-cell transplantation in patients with FLT3-ITD acute myeloid leukaemia: long-term follow-up of an open-label, multicentre, randomised, phase 3 trial. Lancet Haematol. 2023;10(8):e600-e611.
4. Bazarbachi A, Bug G, Baron F, et al. Clinical practice recommendation on hematopoietic stem cell transplantation for acute myeloid leukemia patients with FLT3-internal tandem duplication: a position statement from the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation. Haematologica. 2020;105(6):1507-1516.
5. Morin S, Giannotti F, Mamez AC, et al. Real-world experience of sorafenib maintenance after allogeneic hematopoietic stem cell transplantation for FLT3-ITD AML reveals high rates of toxicity-related treatment interruption. Front Oncol. 2023;13:1095870.
6. Maziarz RT, Levis M, Patnaik MM, et al. Midostaurin after allogeneic stem cell transplant in patients with FLT3-internal tandem duplication-positive acute myeloid leukemia. Bone Marrow Transpl. 2021;56(5):1180-1189.
7. Levis MJ, Hamadani M, Logan B, et al. BMT-CTN 1506/MORPHO

Study Investigators. Gilteritinib as post-transplant maintenance for AML with internal tandem duplication mutation of FLT3. J Clin Oncol. 2024;42(15):1766-1775.
8. Gao Y, Ding Y, Tai XR, Zhang C, Wang D. Ponatinib: an update on its drug targets, therapeutic potential and safety. Biochim Biophys Acta Rev Cancer. 2023;1878(5):188949.
9. Shah NP, Talpaz M, Deininger MW, et al. Ponatinib in patients with refractory acute myeloid leukaemia: findings from a phase 1 study. Br J Haematol. 2013;162(4):548-552.
10. Jentzsch M, Bischof L, Brauer D, et al. Clinical implications of the FLT3-ITD allelic ratio in acute myeloid leukemia in the context of an allogeneic stem cell transplantation. Cancers (Basel). 2023;15(4):1312.
11. How J, Sykes J, Gupta V, et al. Influence of FLT3-internal tandem duplication allele burden and white blood cell count on the outcome in patients with intermediate-risk karyotype acute myeloid leukemia. Cancer. 2012;118(24):6110-6117.
12. Stone RM, Mandrekar SJ, Sanford BL, et al. Midostaurin plus chemotherapy for acute myeloid leukemia with a FLT3 Mutation. N Engl J Med. 2017;377(5):454-464.
13. Erba HP, Montesinos P, Kim HJ, et al. Quizartinib plus chemotherapy in newly diagnosed patients with FLT3-internal-tandem-duplication-positive acute myeloid leukaemia (QuANTUM-First): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2023;401(10388):1571-1583.
14. Perl AE, Martinelli G, Cortes JE, et al. Gilteritinib or chemotherapy for relapsed or refractory FLT3-mutated AML. N Engl J Med. 2019;381(18):1728-1740.
15. Lang TJL, Damm F, Bullinger L, Frick M. Mechanisms of resistance to small molecules in acute myeloid leukemia. Cancers (Basel). 2023;15(18):4573.
16. Mathew NR, Baumgartner F, Braun L, et al. Sorafenib promotes graft-versus-leukemia activity in mice and humans through IL-15 production in FLT3-ITD-mutant leukemia cells. Nat Med. 2018;24(3):282-291.