Received: 10 January 2024 | Accepted: 7 March 2024

DOI: 10.1002/hem3.67

HemaSphere EHA EUROPEAN HEMATOLOGY ASSOCIATION

LETTER

Ponalfil trial for adults with Philadelphia chromosome-positive acute lymphoblastic leukemia: Long-term results

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The introduction of tyrosine kinase inhibitors (TKI) has significantly changed the outcome of children and adults with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL).[1] Several phase 2 trials have shown improved outcomes with the incorporation of ponatinib to first-line therapy, either in combination with chemotherapy or with blinatumomab,[2–4] and a matching adjusted indirect comparison of ponatinib versus imatinib as frontline treatment for Ph+ ALL showed a significant survival advantage for ponatinib over imatinib containing regimens.[5] A phase 3 trial comparing imatinib versus ponatinib in combination with attenuated chemotherapy has shown a significantly higher measurable residual disease (MRD)-negative rate at the end of induction in adults with newly diagnosed Ph+ ALL treated with ponatinib.[6] The phase 2 PONALFIL trial from the Spanish PETHEMA (Programa Español de Tratamientos en Hematología) group combined ponatinib with standard induction and consolidation chemotherapy followed by allogeneic hematopoietic stem cell transplantation (alloHSCT) in 30 adult patients (18–60 years, median age 49 years) with newly diagnosed Ph+ ALL.[7] End-induction and postconsolidation complete molecular response (CMR) rates were 47% and 71%, respectively. With a median follow-up of 2.1 years, the 2-year event-free survival (EFS, considering molecular relapse as an event) and overall survival (OS) rates were 70% and 96%, respectively. Only pre-emptive administration of TKI (30 mg/d for the first year and 15 mg/d during the second year) was prescribed by the trial, and 18 out of the 26 transplanted patients did not receive any TKI after the transplant. We hereby report the follow-up of the study, with a median of 4 years.

Figure 1 shows the updated flowchart of the study. All patients ($n = 30$) achieved complete cytologic response (CCR), although two abandoned the trial due to retina artery thrombosis and severe gastrointestinal infection requiring partial intestinal resection (one patient each). Both patients received dasatinib and remain alive and in CMR. End-induction CMR was attained in 14/30 patients (47%), 5/30 (17%) achieved MMR, and the remaining 11 patients did not achieve molecular response. Two patients discontinued the trial after consolidation. The first showed molecular relapse and due to specific circumstances had to be treated with vincristine, steroids, and dasatinib; this patient is currently alive and in CMR under maintenance with ponatinib. The second patient was removed from the trial by physician criteria because of the lack of molecular response, being treated with blinatumomab and alloHSCT, and is currently under maintenance with dasatinib. AlloHSCT was performed in 26 patients, two of whom died due to the procedure (severe graft versus host disease—GVHD, and severe cytomegalovirus infection, one patient each) at 3 and 24 months after transplant, respectively. One patient withdrew from the trial due to severe transplant-related liver toxicity.

Clinical or molecular relapse was observed in six of the remaining 23 transplanted patients. The isoforms of relapsed patients were p190 ($n = 3$), p210 ($n = 2$), and p230 ($n = 1$). One patient

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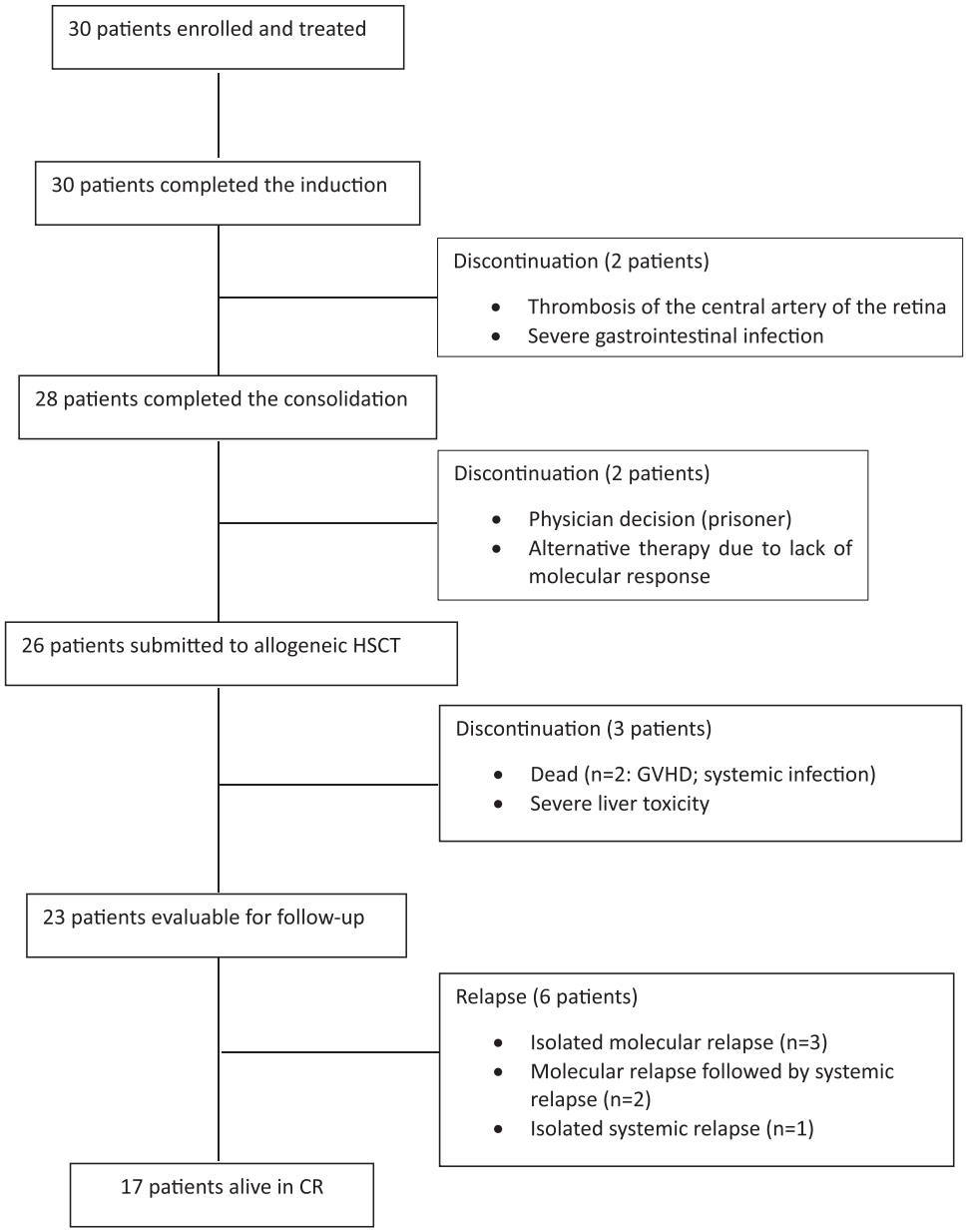

FIGURE 1 Patient disposition in the PONALFIL trial.

showed isolated pleural relapse 25 months after transplant and was re-treated with the same induction chemotherapy, followed by a second alloHSCT from a different donor. This patient is currently alive and in CMR 3 months after the second alloHSCT and receives ponatinib maintenance. Five patients experienced molecular relapse (median time from alloHSCT, 9 months, range 4–20), that was successfully treated with ponatinib (30 mg/d). This drug was removed due to grade 4 liver toxicity in one patient, who is currently in molecular remission. Two patients experienced bone marrow relapse. The first was treated with CD19 CAR T and is currently alive in CMR under ponatinib maintenance (30 mg/d) 3 months after the procedure. The second received rescue chemotherapy with FLAG Ida and ponatinib (30 mg/d) and remains in CMR 37 months after this therapy. The 17 remaining patients remain off-therapy at the last follow-up. The current median follow-up of living patients is 4.1 years (range 0.2–6.2 years), and the 4-year OS probability was 92% (95% confidence interval [CI], 72%–98%) (Figure 2A). Considering molecular relapse as an event, the 4-year EFS probability was 66% (95% CI, 45%–81%) (Figure 2B).

The follow-up of the PONALFIL trial confirms the preliminary results observed with a 2-year median follow-up and shows that long-term survival can be achieved after alloHSCT in a significant proportion of patients with a pre-emptive policy of ponatinib administration after HSCT. To date, pre-emptive versus prophylactic use of ponatinib after transplant has not been addressed in a controlled study. In our trial, only one patient showed isolated extramedullary relapse not anticipated with the regular bone marrow molecular follow-up after transplant. In addition, all patients with molecular relapses after HSCT were controlled with the reintroduction of ponatinib, although two experienced morphologic relapse successfully treated with CAR T and chemotherapy, respectively, both remaining alive under ponatinib maintenance.

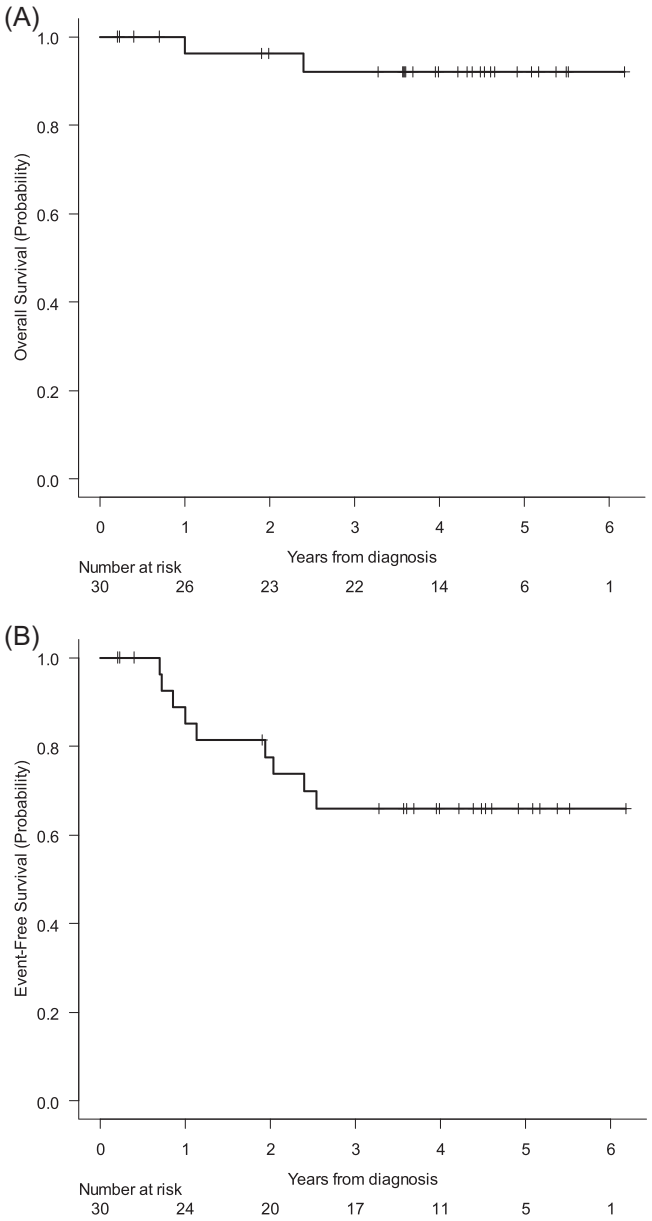

FIGURE 2 Overall survival (OS) and event-free survival (EFS). (A) OS for patients from diagnosis to death or last follow-up. (B) EFS for patients included in the PONALFIL trial from enrollment to failure of achieving CHR at Week 6, lack of molecular response before hematopoietic stem cell transplantation, molecular or hematologic relapse, or death by any cause.

The low treatment-related mortality rate (7.6%) observed in this study is also of note. This is in accordance with the D-ALBA trial which described a rate of 12.5% in 24 patients who received an alloHSCT in the first CCR by physician's choice in patients treated with dasatinib and blinatumomab.[8] The results from registry studies also confirm this low rate for transplanted patients with Ph+ ALL.[9] The frequency of patients not in CMR before HSCT was 28% in our trial and 45% in the D-ALBA trial. In the latter trial, the outcome of transplanted versus non-transplanted patients was similar, although the transplanted fraction of patients was enriched with those not in CMR.[8]

Although our results are comparable with those of phase 2 trials using second- or third-generation TKI and blinatumomab as first-line therapy,[4,8] our trial is only applicable to young adults fit for alloHSCT. The need for transplant in all patients with Ph+ ALL is being re-evaluated and could potentially be limited to patients not achieving CMR after consolidation or having poor molecular features (e.g., IKZF1^{plus} signature).[8,10–12] On the other hand, the pre-emptive strategy for ponatinib after transplantation was feasible and allowed a reduction of ponatinib exposure in 17 out of 26 transplanted patients. Re-treatment with ponatinib after molecular relapse is a possibility that can allow the control of the disease in most patients without additional cytotoxic chemotherapy. In our trial, the cases of systemic relapse were successfully managed with ponatinib, chemotherapy, and cell therapies, such as CAR T or a second alloHSCT.

AUTHOR CONTRIBUTIONS

Josep-Maria Ribera designed the study. Pau Montesinos, Isabel Cano-Ferri, Pilar Martínez, Jordi Esteve, Daniel Esteban, María García-Fortes, Natalia Alonso, José González-Campos, Arancha Bermúdez, Anna Torrent, Clara Maluquer, and Joaquín Martínez-López, collected the data. Jordi Ribera and Ramón García-Sanz performed the biologic studies. Josep-Maria Ribera and Mireia Morgades analyzed the data and drafted the manuscript. Eulàlia Genescà, Joaquín Martínez-López, and Ramón García-Sanz made critical revisions to the manuscript for important intellectual content. All authors approved the final manuscript and agreed to submit for publication.

CONFLICT OF INTEREST STATEMENT

Josep-Maria Ribera has received honoraria and travel grants from Incyte, Novartis, Takeda, AMGEN, and Pfizer. The rest of the authors have no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

FUNDING

This project was supported in part by the ISCIII (PI14/01971 and PI19/01828), co-funded by ERDF/ESF, "A way to make Europe"/"Investing in your future," CERCA/Generalitat de Catalunya SGR 2017 288 (GRC)/"La Caixa." This project has also been supported by Incyte Biosciences International S.a.r.l. with study medication and financial support. This project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 116026. This Joint Undertaking receives support from the "European Union's Horizon 2020 research and innovation and EFPIA."

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