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## **Ponatinib in childhood Philadelphia chromosome–positive leukaemias: an international registry of childhood chronic myeloid leukaemia study**

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1 **Ponatinib in Childhood Philadelphia Positive Leukemias: an International Registry of**  
2 **Childhood Chronic Myeloid Leukemia (I-CML-Ped) Study.**

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32 **Key words:** children, ponatinib, chronic myeloid leukemia, Philadelphia chromosome-positive acute  
33 lymphoblastic leukemia

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1 **Summary**

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**Background.** Ponatinib is effective in adults with Philadelphia positive (Ph+) leukemias but scant data are available regarding the use of this tyrosine kinase inhibitor in children.

**Aims.** To describe the tolerance and efficacy of compassionate use of ponatinib in a pediatric cohort of Ph+ leukemias.

**Methods.** Data from 11 children with chronic myeloid leukemia (CML) registered to the I-CML-Ped-Study and from 3 children with Ph+ acute lymphoblastic leukemia (Ph+ ALL) treated with ponatinib were collected retrospectively.

**Results.** In 11 girls and 3 boys (median age 14 years) ponatinib was used as a second to eighth line treatment. Ponatinib was administered as single therapy (9 patients) or in combination with chemotherapy (8 patients). The status of the disease when ponatinib was started was: CML in advanced phases (n=8), CML in chronic phase without achievement of molecular response (n=2) or presence of T315I mutation (n=1) and Ph+ ALL in molecular (n=1) or marrow (n=2) relapses. The median dose administered was 21.4 mg/m<sup>2</sup> and median duration of ponatinib was 2.5 months. Ponatinib alone or in combination with chemotherapy administered on 16 occasions led to achievement of major molecular response (MMR) in 50% of cases. Ponatinib was used as a bridge to transplant in 4 cases. Among the 9 patients treated with ponatinib alone, toxicity grade 3-4 (2 patients) was exclusively hematologic. No vascular events related to ponatinib were observed.

**Conclusion.** Ponatinib may be a reasonable additional treatment option for children with Ph+ leukemias who have failed several lines of therapy.

1 **1. Introduction**

2

3 Tyrosine kinase inhibitors (TKIs) have revolutionized the treatment of patients with Philadelphia  
4 chromosome positive (Ph+) chronic myeloid leukemia (CML) and acute lymphoblastic leukemia (Ph+  
5 ALL) by targeting the BCR-ABL onco-protein underlying the malignant process. Imatinib was the first  
6 available TKI for the treatment of CML and Ph+ ALL and 2<sup>d</sup> generation TKIs, such as dasatinib and  
7 nilotinib, were successfully introduced in patients with failure or intolerance to imatinib. Recently,  
8 ponatinib, a 3<sup>d</sup> generation TKI, was developed to overcome resistance to first and second-generation  
9 TKIs in patients with CML and Ph+ ALL.

10 CML and Ph+ ALL are rare diseases in children and adolescents. Clinical studies have demonstrated  
11 the efficiency of 1<sup>st</sup> and 2<sup>d</sup> generation TKIs in children and adolescents with CML and Ph+ ALL.<sup>1,2,3,4</sup>  
12 However, scant data are available on the use of ponatinib in the pediatric population. The aim of this  
13 study was to describe the profile of tolerance and efficacy of compassionate use of ponatinib in  
14 children and adolescents with Ph+ leukemias.

15

16 **2. Methods**

17

18 Children less than 18 years with chronic myeloid leukemia (CML) diagnosed after 2000 enrolled in  
19 the international registry for childhood CML (I-CML-Ped Study at [www.clinicaltrials.gov](http://www.clinicaltrials.gov),  
20 #NCT01281735) treated with ponatinib and children with Ph+ acute lymphoblastic leukemia (Ph+  
21 ALL) treated with ponatinib in the I-BFM study group were the subjects of the study.

22 Written informed consent was obtained from the children and/or their guardians. The phase of the  
23 disease was classified according to the criteria of the European-leukemiaNet (ELN)  
24 recommendations.<sup>5</sup> The immunophenotype (myeloid or lymphoid) of blastic phases was determined  
25 by flow cytometry.<sup>6</sup> BCR-ABL1 transcript levels in the blood were performed using quantitative RT-  
26 PCR and were expressed according to the International Scale (IS).<sup>7</sup> Major molecular response (MMR),  
27 MR4 and MR4.5 were defined as a BCR-ABL/ABL ratio of <0.1%, <0.01% and <0.0032% respectively.<sup>7</sup>  
28 BCR-ABL1 kinase domain mutation analysis was performed as previously reported.<sup>8</sup> Overall survival  
29 was assessed from the diagnosis until the date of death or last follow-up and a survival curve was  
30 plotted using Kaplan Meier method.<sup>9</sup>

31

32 **3. Results**

33

34 **Patient characteristics:** Data were retrospectively collected from 14 children treated with ponatinib  
35 between April 2013 and March 2019. Characteristics of the patients and details of treatments are

1 reported in supplementary data. Eleven children were initially diagnosed with CML and 3 children  
2 with Ph+ ALL. The median age at diagnosis was 14 (range 4.5 to 17). There were 11 boys and 3 girls.  
3 Six children (4 with CML and 2 with Ph+ ALL) were previously transplanted before the introduction of  
4 ponatinib. Among them 1 patient was transplanted twice. Treatment with ponatinib was used as a  
5 second (n=2), third (n=6), fourth (n=1), fifth (n=3), sixth (n=1) or eighth (n=1) line of therapy.  
6 Ponatinib was administered as a single therapy in 9 children or in combination with chemotherapy in  
7 7 children (patients 3 and 14 received at 2 different times ponatinib alone and in combination with  
8 chemotherapy and patient 13 was treated twice with ponatinib in combination with chemotherapy).  
9 The type of chemotherapy administered in combination with ponatinib is reported in  
10 Supplementary data. This chemotherapy consisted of acute lymphoblastic leukemia-type or acute  
11 myeloblastic leukemia-type induction regimens. The median dose of ponatinib administered was  
12 21.4 mg/m<sup>2</sup> (range: 10.7-43.6 mg/m<sup>2</sup>). The median duration of ponatinib treatment was 2.5 months  
13 (range: 0.5 - 14 months). The status of the disease when ponatinib was started was advanced phase  
14 of CML (n=8; accelerated phase, n=2; blast phase, n=6), chronic phase CML without achievement of  
15 major molecular response (MMR, n=2) or in MR 4.5 with T315I mutation (n=1). Regarding the Ph+  
16 ALL patients, 1 patient was in molecular relapse and 2 patients were in marrow relapse when  
17 ponatinib was started. Three patients were treated a second time with ponatinib (alone or in  
18 combination with chemotherapy): at the onset of a second bone marrow relapse in a patient with  
19 Ph+ ALL (patient 13); in lymphoid blast phase in one patient (patient 3) with CML and as  
20 "consolidation" post allogeneic hematopoietic stem cell transplantation (HSCT) in 1 patient in MR5  
21 with Ph+ ALL (patient 14).

22 **Overall response:** Among the 8 patients with CML in advanced phases when ponatinib (alone in 4  
23 patients or in combination with chemotherapy in the 4 remaining patients) was started, no response  
24 was seen in 3 patients receiving ponatinib alone, MMR in 4 patients (including one receiving  
25 ponatinib alone) and MR4 in one patient receiving ponatinib in combination with chemotherapy.  
26 Among the 3 patients with CML in chronic phase at initiation of ponatinib alone, MMR was achieved  
27 in one patient, no response (non achievement of MMR) in one patient and loss of MR4.5 in the child  
28 harboring a T315I mutation. No response occurred in the children (patient 3) with CML who received  
29 a second course of ponatinib.

30 Among the 3 children with Ph+ ALL, the 2 patients with bone marrow relapse achieved response  
31 levels of MR4.5 and MR5, although one of these children did not respond to ponatinib and  
32 chemotherapy in a subsequent relapse; the third patient receiving ponatinib alone for molecular  
33 relapse did not respond.

34 **Ponatinib as a bridge to transplant:** Satisfactory response (MMR to MR5) to ponatinib alone or in  
35 combination with chemotherapy made HSCT possible in 4 children (CML n=3; Ph+ ALL n=1). Duration

1 of ponatinib administration pre HSCT in these patients was 15 days to 5 months. No response was  
2 observed in one patient in accelerated phase receiving ponatinib as exclusive therapy before  
3 transplantation. One of these transplanted children received ponatinib as maintenance after HSCT  
4 and remains in deep molecular response.

5 ***Ponatinib in children with T315I mutation.*** The introduction of ponatinib was motivated by the  
6 identification of T315I mutation in 4 patients with CML in a context of lymphoid blast crisis and in  
7 one patient with Ph+ ALL in bone marrow relapse. The median time to emergence of T315I mutation  
8 was 29 months (range: 4 to 36 months) from the diagnosis of the disease. Treatment consisted of  
9 ponatinib (1.5 to 5 months) in combination with chemotherapy (4 patients) or ponatinib alone (47  
10 days) as a consolidation of response (MR4.5) to chemotherapy in the remaining children. A relapse  
11 of the lymphoid blast process occurred in this later patient under ponatinib alone, one patient did  
12 not respond and 3 patients achieved MMR to MR4.5 1, 2 and 4 months after introduction of  
13 ponatinib.

14

15 ***Toxicity:*** Side effects were recorded in 5 of 9 patients receiving ponatinib alone. The median dose  
16 administered was 25 mg/m<sup>2</sup> in these 5 patients (range: 12.5 – 30 mg/m<sup>2</sup>) with a median duration of  
17 treatment of 47 days (range: 15 days-14 months). Grade 1- 2 toxicities represented the majority of  
18 the events. Grade 3-4 toxicities were exclusively hematologic and were reported in 3 patients (Table  
19 1). Side effects were recorded in 5 of 8 patients treated with ponatinib in combination of  
20 chemotherapy but it was difficult to identify events related exclusively to ponatinib. No vascular  
21 events related to ponatinib were observed in these subgroups of patients.

22

23 ***Survival:*** With a median follow up of 41 months (range 10 – 152 months) from the diagnosis, 5  
24 deaths were recorded including 3 patients who were transplanted. These 5 deaths were related to  
25 the disease. Nine patients were alive at last follow up including 2 patients diagnosed with Ph+ ALL.  
26 Seven patients were at least in MMR and 2 patients did not achieve MMR. With a median follow-up  
27 of 41 months (range, 10 – 152 - months), the probability of 5-year overall survival of the cohort of  
28 children was 59% (CI 95%: 33-85%) (Figure 1).

29

#### 30 **4. Discussion**

31

32 In the present study, ponatinib alone or in combination with chemotherapy administered on 16  
33 occasions led to achievement of at least MMR in 50% of the cases indicating that ponatinib provided  
34 benefit for children with heavily pretreated CML or Ph+ ALL. Heiblig et al reported a cumulative

1 incidence of 81.8% of MMR at 18 months in a cohort of adult patients with CML in CP who had  
2 previously failed to at least 2 lines of TKI.<sup>10</sup>  
3 Ponatinib is active against the majority of BCR-ABL1 kinase mutants including ABL1 kinase domain  
4 mutant T315I which are known to be resistant to 1<sup>st</sup> and 2<sup>d</sup> generations TKI.<sup>11</sup> However, there are  
5 few data describing the responses in children. Nickel et al reported the control of the disease with  
6 ponatinib after occurrence of a T315I mutation and a cytogenetic relapse in a young boy treated with  
7 imatinib<sup>12</sup>. A recent multicenter retrospective analysis reported on 21 pediatric patients mostly with  
8 Ph+ ALL (n= 12, CML n= 9) treated with varying doses of ponatinib after failure of 1st and/or 2nd  
9 generation TKIs. Similar to our experience, 71% of the patients showed a decrease in disease burden  
10 after a median of three months with grade 3 toxicities being mostly hematologic and occurring in  
11 29% of the cohort.<sup>13</sup> In the present study, Ponatinib in combination of chemotherapy was effective in  
12 3 of 5 children with the T315I mutation. However the loss of molecular response under ponatinib in  
13 one of the 2 remaining children and the absence of response in the other one suggests that other  
14 mechanism than T351I kinase domain mutation contributed to resistance.

15

16 In the present work, we report the utility of ponatinib as salvage treatment allowing reduction of  
17 tumor burden and thus bridging to HSCT in 5 children with CML or Ph+ ALL as previously reported in  
18 the adult population.<sup>14</sup> Ponatinib was administered as maintenance after transplantation in only one  
19 of these children and was well tolerated in this setting as previously reported in adults.<sup>15</sup> However,  
20 the role of ponatinib post-HSCT remains to be confirmed.

21

22 The heterogeneity of the dose of ponatinib administered in the present study reflects the absence of  
23 recommended doses in the pediatric population. Teenagers represented the majority of our patients  
24 and the doses administered were based on the adult data including reports indicating that reduction  
25 of the dose was associated with a reduction of thrombotic events.<sup>16, 17</sup>

26

27 Ponatinib used without additional chemotherapy was well tolerated in the 5/9 patients assessable  
28 for toxicity. Grade 3 toxicity was observed in only 3 patients and was exclusively related to  
29 hematologic adverse events (neutropenia, thrombocytopenia). Because of the small number of  
30 patients it is not possible to correlate the occurrence of these side effects with the doses  
31 administered. Mild toxicities were reported in the 7 children receiving a combination of ponatinib  
32 and polychemotherapy. Grade 3 pancreatitis was reported in one of our patients but it is difficult to  
33 incriminate ponatinib because of the concomitant administration of polychemotherapy. Grade 3 and  
34 4 increase in lipase level was observed in 14% of adults in a phase 3 trial using ponatinib.<sup>18</sup> As  
35 reported with imatinib in children and adolescent, an impact of ponatinib as a TKI class effect on

1 growth in children is suggested by the growth deceleration in a young boy receiving ponatinib for 2.8  
2 years.<sup>12, 19</sup> However, the treatment duration of ponatinib in the cohort described here was too short  
3 to assess the impact on growth.

4  
5 Frequently occurring cardiovascular toxicity was reported in adults patients with CML treated with  
6 Ponatinib.<sup>10, 18</sup> Interestingly, no vascular event related to ponatinib was observed in the present  
7 study. However, the duration of treatment with ponatinib (median time: 2.5 months) was shorter  
8 than the median times (11.5, 20.1 and 19.9 months) of onset of cardiovascular, cerebrovascular and  
9 peripheral arterial occlusive events, respectively, reported in the adult population treated with  
10 ponatinib.<sup>16</sup> In a case report, Nickel et al reported administration of Ponatinib for 2.8 years without  
11 cardiovascular toxicity in a 12-year-old boy with CML.<sup>12</sup>

12  
13 The sparse data on ponatinib use in children with Ph+ leukemia do not allow to draw definite  
14 conclusions. Ponatinib could be proposed in children with CML after failure of first and second  
15 generation TKIs. Children harboring T351I kinase domain mutation require treatment with this  
16 drug. Because the longterm outcome is poor in patients WITH cml who progressed to blast  
17 phase children should proceed to HSCT within 3 to 6 months and ponatinib can be used as a  
18 treatment for bridging this time window. A pediatric investigation plan comprising ongoing  
19 international prospective studies was set up in order to determine the appropriate dose and  
20 formulation, the tolerance and efficacy of ponatinib in children and adolescents with Ph+ leukemias.

## 21 22 **5. Conclusion**

23  
24 The present data provide insights into the efficiency and toxicity of ponatinib in heavily pretreated  
25 children. With the limitation of the retrospective nature of this study, ponatinib may be a reasonable  
26 additional treatment option for children with Ph+ leukemias who failed to several lines of therapy.  
27 Prospective studies are definitely needed in a larger cohort of children, a goal that can only be  
28 achieved by international cooperation due to the rarity of CML in pediatric patients.

29  
30 **Conflict of interest statement:** The authors declare no competing financial interest

31  
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Pt #	Sex	Age (years)	Diag	Disease phase	Treatments (month of start)	Reason for treatment changes (month of change)	Duration of Ponatinib treatment	Response to Ponatinib +/- CT *	Mutation/time point of assessment	Outcome (months from diagnosis)
1	M	13.6	CML	CP	HU / IM / Das (M4) / <b>Ponatinib (M6)</b> / HSCT(M9)	Hematologic toxicity M4 / <b>AP(M5)</b>	15 days	None	none M3 and M10	Alive not in MMR M13
2	M	11.7	CML	CP	HU / IM / Das (M22) / CT <sup>1</sup> + Nil (M24) / HSCT (M28)+Nil (stop M89) / Nil (M91) / <b>Ponatinib + CT<sup>2</sup></b> (M118)	transcript level increase (M22) /BPM (M24)/ Loss MMR (M91) <b>AP (M118)</b>	6 months	MMR after 4 months	none M12, M15,M22; F317L M24; none M91, M94, M115	Alive M125 MR5
3	M	14.4	CML	CP	IM / Das (M8) / HSCT (M9) + Das (stop M20) / Nil (M30) / <b>Ponatinib (M36)</b> / CT <sup>1</sup> (M37)+ <b>Ponatinib (M42)</b> / CT <sup>2</sup> (M44)	BPL (M8) / BPL (M30) / <b>BPL (M36)/ No response(M37-42)</b>	15 days 2 months	None None	T315I & E255K M36	† M56 (disease)
4	M	9.3	CML	CP	IM / Das (M5) / HSCT 1 (M10) / Nil (M30) / <b>Ponatinib + CT (M30)</b> / HSCT 2 (M34) / HSCT 3 (M36)	BPL (M5) / <b>BPL (M30)</b>	1.5 months	MR4 after 2 months	T315I M30	MMR M62 - Alive M67
5	M	10.8	CML	CP	IM / <b>Ponatinib + CT (M4)</b> / HSCT (M10)	<b>BPL (M4)</b>	5 months	MMR after 4 months	T315I M4	MMR M10 - Alive M22
6	M	15.0	CML	AP	HU+Das / CT+Das (M1) / <b>Ponatinib (M5)</b> / HSCT (M6)	BPL (M1) / <b>BPL (M4)</b>	15 days	MMR after 13 days	ND	Alive MMR M10
7	F	15.2	CML	CP	IM / Das (M32) / <b>Ponatinib + CT<sup>1</sup></b> (M105) / CT <sup>2</sup> (M110)	Digestive toxicity M32/ AP M103 / <b>BPM (M105)/</b> BPM (M110)	5 months	MMR after 1 month	none M21, M93, M105	† M114 (disease)
8	M	12.8	CML	CP	Nil / IM (M5) / <b>Ponatinib (M22)</b>	Hepatic Toxicity (M5) / <b>No MMR (M22)</b>	14 months	MMR after 7 months	none M4, M16, M20	Alive MMR M36
9	F	17.2	CML	AP	IM / Das (M8) / <b>Ponatinib (M13)</b>	BPL M8 / <b>BPM (M13)</b>	24 days	None	ND	† M14 (disease)
10	M	8.6	CML	BPL	CT <sup>1</sup> +Ima / HSCT(M5) / CT <sup>2</sup> +Das (M26) / CT <sup>3</sup> +Das (M29) / <b>Ponatinib (M30)/CT<sup>4</sup></b> (M32)	BPL (M26) / BM (M29) / <b>BM relapse (M32)</b>	47 days	None	T315I M29	† M34 (disease)
11	F	14.0	CML	CP	HU+CT**+IM / Das(M8) / <b>Ponatinib (M39)</b>	No CCR (M8= / No MMR (M39)	5 months	None	none M3, M29	Alive M45 no MMR

Pt #	Sex	Age (years)	Disease phase	Treatments (month of start)	Reason for treatment changes (month of change)	Duration of Ponatinib treatment	Response to Ponatinib +/- CT *	Mutation/time point of assessment	Outcome (months from diagnosis)
12	M	4.5	ALL Ph+	CT <sup>1</sup> +IM / HSCT (M6) / Das (M17) / HSCT (M19) / Das (M46) / Nil (M92) / CT <sup>2</sup> (M95) / <b>Ponatinib</b> (M96) / CT <sup>3</sup> (M102) - IFN peg / CT <sup>4</sup> (M147)	BM Relapse (M17) / Molecular Relapse (M46) / MMR loss( M92) / <b>MMR loss (M95)</b> / BM relapse (M102) / CNS Relapse(M147)	5 months	None	E225K M95	MMR M150 - Alive M152
13	M	14.5	ALL Ph+	CT <sup>1</sup> +IM / HSCT (M6) / Das (M8) / <b>Ponatinib+CT<sup>2</sup></b> (M8) / <b>Ponatinib+CT<sup>3</sup></b> (M12) / CT <sup>4</sup> (M14)	BM Relapse (M8) / <b>BM Relapse (M12)</b> / Disease progression (M14)	2.5 months 2 months	Pona+CT <sup>2</sup> : MR4.5 after 1 month Pona+CT <sup>3</sup> : none	T315I M8 T315I & E255K M12	† M17 (disease)
14	M	14.0	ALL Ph+	CT <sup>1</sup> +IM / <b>Ponatinib+CT<sup>2</sup></b> (M32) / HSCT (M36) / <b>Ponatinib</b> post HSCT	<b>BM Relapse (M32)</b> <b>Consolidation post HSCT (MR5)</b>	4 months 5 months	Pona+CT <sup>2</sup> : MR5 after 3 months	None M32	MR5 M47 Alive

**Supplementary data.** Characteristics of the children and treatments.

CP: chronic phase; AP: accelerated phase; BPM : blastic phase (myeloid), BPL: blastic phase (lymphoid); CNS: central nervous system; CT<sup>1,2,3,4</sup>: 1<sup>st</sup> 2<sup>d</sup> 3<sup>d</sup> or 4<sup>th</sup> line of chemotherapy; CCR: complete cytogenetic response;HU : Hydroxyurea ; HSCT : allogeneic hematopoietic stem cell transplantation ; IFN: interferon; IM: imatinib; Das : Dasatinib; Nil : Nilotinib; M: month; MMR : major molecular response

\* months after the start of ponatinib \*\*Patient 11 received CT (while in PC) in addition of imatinib because of leucostasis

Details of chemotherapy administered in combination with ponatinib: Patient 2 CT<sup>2</sup> : Dexamethasone, Vincristine, Methotrexate, Cytosine Arabinoside; Patient 3 CT<sup>1</sup> : Prednisone and Vincristine; Patient 4 CT : Prednisolone, Vincristine, Daunorubicin, L-Asparaginase; Patient 5 CT : Prednisone, Vincristine, Daunorubicin, L-Asparaginase, intrathecal Methotrexate; Patient 7 CT<sup>1</sup> : hydroxycarbamide followed by Daunorubicin, Cytosine Arabinoside ; Patient 13 CT<sup>2</sup> : Dexamethasone, Vincristine and Doxorubicin; CT<sup>3</sup> : Methylprednisolone, Daunorubicin, Aracytine, Cytosine Arabinoside, Etoposide; Patient 14 CT<sup>2</sup> : Course A = Dexamethasone, Cyclophosphamide, Vincristine, Doxorubicin, intrathecal Methotrexate + Cytosine Arabinoside ; course B = Methotrexate, intrathecal Methotrexate + Cytosine Arabinoside

	<b>Ponatinib alone n= 5/9</b>	<b>Ponatinib with Chemotherapy n= 5/7</b>
<b>Hematologic toxicities</b>	Platelet grade 3 (n=2)	Platelet grade 3-4 (n=4)
	Platelet grade 4 (n=1)	Leucopenia grade 3-4 (n=4)
	Leucopenia grade 1 (n=1)	neutropenia grade 3 (n=1)
	Neutropenia grade 3 (n=1)	Lymphopenia grade 3 (n=2)
	Anemia grade 2 (n=1)	Anemia grade 2 (n=3) grade 3 (n=1)
<b>Non hematologic toxicities</b>	Nausea grade 1 (n=1)	Liver enzymes increased grade3-4 (n=2)
	Abdominal pain grade 2 (n=1)	Lipase increased grade 4 (n=1)
	Abdominal pain grade1 (n=2)	Hypertriglyceridemia grade 2 (n=1)
	Cutaneous grade1-2 (n=2)	Cutaneous grade 3 (n=3)
	Headache grade 1-2 (n=2)	Headache grade ND (n=1)
	Fatigue grade 1-2 (n=2)	Thromboembolic event * grade 1 (n=1)
	Infection grade 2 (n=1)	Infection grade ND (n=2)
		Oral mucositis grade 3 (n=1)
		Vomiting grade 3 (n=1)
		Diarrhea grade ND (n=1)
		Erectile dysfunction grade 1 (n=1)
		Angioedema grade 3 (n=1)
		Thoracic pain grade 1 (n=1)
		Osseous pain grade 3 (n=1)
	Neuropathy grade ND (n=1)	
	Toxic encephalopathy grade ND (n=1)	

**Table 1.** Side effects in children and adolescents treated with ponatinib (patients with 1 or more toxicities)

\* venous thrombosis treated with anticoagulant and diagnosed few days before the start of ponatinib

**Figure 1** : Kaplan–Meier Plot of the overall survival

