



Comparison between dasatinib-blinatumomab vs ponatinib-blinatumomab chemo-free strategy for newly diagnosed Ph+ acute lymphoblastic leukemia patients. Preliminary results of the GIMEMA ALL2820 trial

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INTRODUCTION

The outcome of Philadelphia positive acute lymphoblastic leukemia (Ph+ ALL) has markedly improved in the last decade, due with the introduction in the clinical practice of tyrosine kinase inhibitors (TKIs). A further improvement has been obtained with the addition of blinatumomab as a consolidation strategy in newly diagnosed patients of all ages. In the induction/consolidation chemotherapy-free frontline trial with dasatinib followed by blinatumomab (GIMEMA LAL2116, D-ALBA); the preliminary results showed that after 2 cycles of blinatumomab (primary endpoint) molecular responses were achieved in 60% of patients and the overall and disease-free survival (OS, DFS) were 95% and 88% at a median follow-up of 18 months (Foà et al, NEJM 2020). An updated follow-up at 53 months (Foà et al, JCO, in press) confirmed the favorable long-term outcomes with OS and DFS of 75.8% and 80.7%, respectively. A total of 9 relapses occurred. The median time to relapse was 4.4 months (1.9-25.8); 4 were at the central nervous system (CNS). To further improve the outcome of these patients, we designed a phase III trial (GIMEMA ALL2820) in which in the experimental arm dasatinib was substituted by ponatinib, followed - in the consolidation phase - by at least 2 cycles of blinatumomab. The trial is currently enrolling.

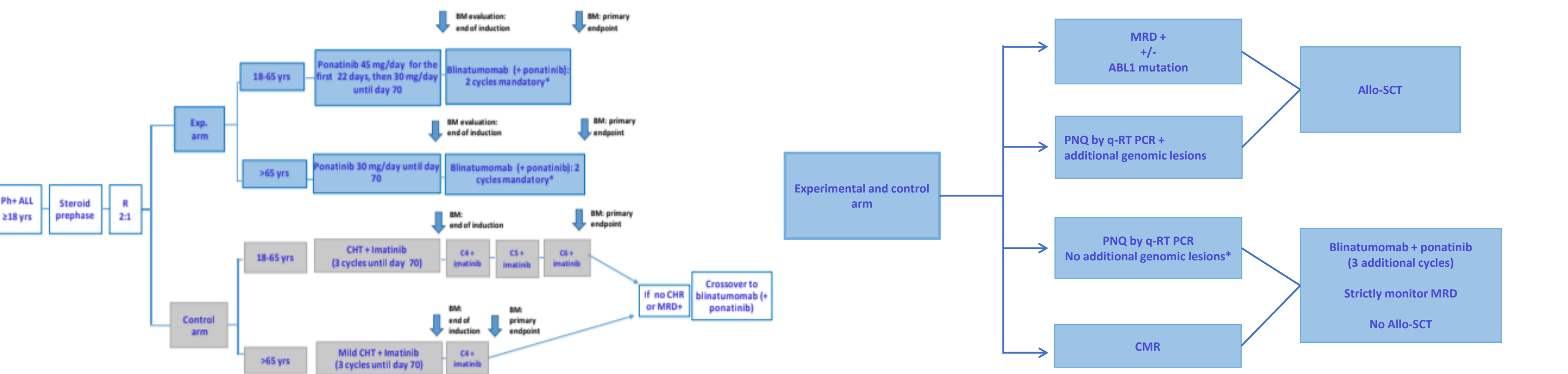
AIM

To compare the efficacy of the combination of ponatinib followed by blinatumomab (GIMEMA ALL2820, experimental arm) with that reported with dasatinib followed by blinatumomab for the management of newly diagnosed adult Ph+ ALL patients.

METHODS

From September 2021 to October 2023, 88 patients have been enrolled in the experimental arm based on ponatinib followed by at least 2 cycles of blinatumomab. The induction period was reduced from 85 to 70 days and the dose of ponatinib was either 45 mg or 30 mg, according to the patients' age. A dose reduction to 30 mg was foreseen by day 28 of induction, regardless of age, to avoid unacceptable toxicities. Furthermore, CNS prophylaxis was strengthened with a total of 15 medicated lumbar punctures and triple intrathecal therapy (methotrexate, aracytin and steroids). Finally, transplant allocation was established according to biological features (minimal residual disease and presence of the *IKZF1*^{plus} genotype, Fig. 1).

Figure 1. GIMEMA ALL2820 trial design



RESULTS

The median age of the 88 patients enrolled in the experimental arm, was 57 years (range 20-80), with 30% of patients being older than 65; 51% were males, the median WBC was 12 x10⁹/l (1-207). The p190 fusion protein was detected in 76% of cases, the p210 in 201% and p190/p210 in 3%. The *IKZF1*^{plus} genotype was present in 39% of cases (Table 1). The median follow-up is 4.4 months (0-23.4). Of the 88 patients enrolled, 60 have completed the induction phase, while 3 patients died in induction (a 77-year-old woman for unknown causes, a 68-year-old man due to an intestinal occlusion and a 52-year-old man due to pneumonia). The complete hematologic remission rate (CHR) is 95%, with no patient experiencing refractoriness. Fifty-two patients also completed the 2 mandatory blinatumomab cycles. Molecular responses are summarized in Table 2: overall, in the current trial a molecular response was achieved in 40% of cases at the end of induction, and in 69% after two cycles of blinatumomab. So far, a single patient has relapsed (WBC at onset: 121 x10⁹/l and a *IKZF1*^{plus} genotype) after 3 months from CHR: at relapse, this case harbored a T3151 mutation (wild type at diagnosis). Five patients were allografted in the current trial compared to 24 patients in the GIMEMA LAL2116 trial. As for toxicity, 72 grade ≥3 adverse events were recorded in 36 patients: 44 were deemed related to study drugs (prednisone in 2, ponatinib or ponatinib/blinatumomab in 38 and blinatumomab in 3 cases). The most frequent toxicities were hepatic (n=15), infectious (n=13), hematologic (n=11 neutropenias and n=7 thrombocytopenias), whereas pancreatic, cardiac and neurologic events were rare (n=6, 4 and 4, respectively).

Table 1. Clinico-biological features of patients enrolled in the GIMEMA ALL2820 trial (experimental arm)

ALL 2820 Patients' features (n=88)	
Age, median (range)	57 (20-80)
>65 years (%)	30
Gender	
Female	45
Male	43
WBC x 10 ⁹ /l, median (range)	12 (1-207)
BCR::ABL1 (%)	
p190	67 (76)
p210	18 (20)
p190/210	3 (3)
IKZF1 genotype, n (%)	
IKZF1 wt	31 (39)
IKZF1 alone	22 (28)
IKZF1 ^{plus}	26 (33)

* Not evaluable for 9 patients

Table 2. Molecular response at the end of induction and primary endpoint of patients enrolled in the GIMEMA ALL2820 (experimental arm) and in the the GIMEMA LAL2116 trial

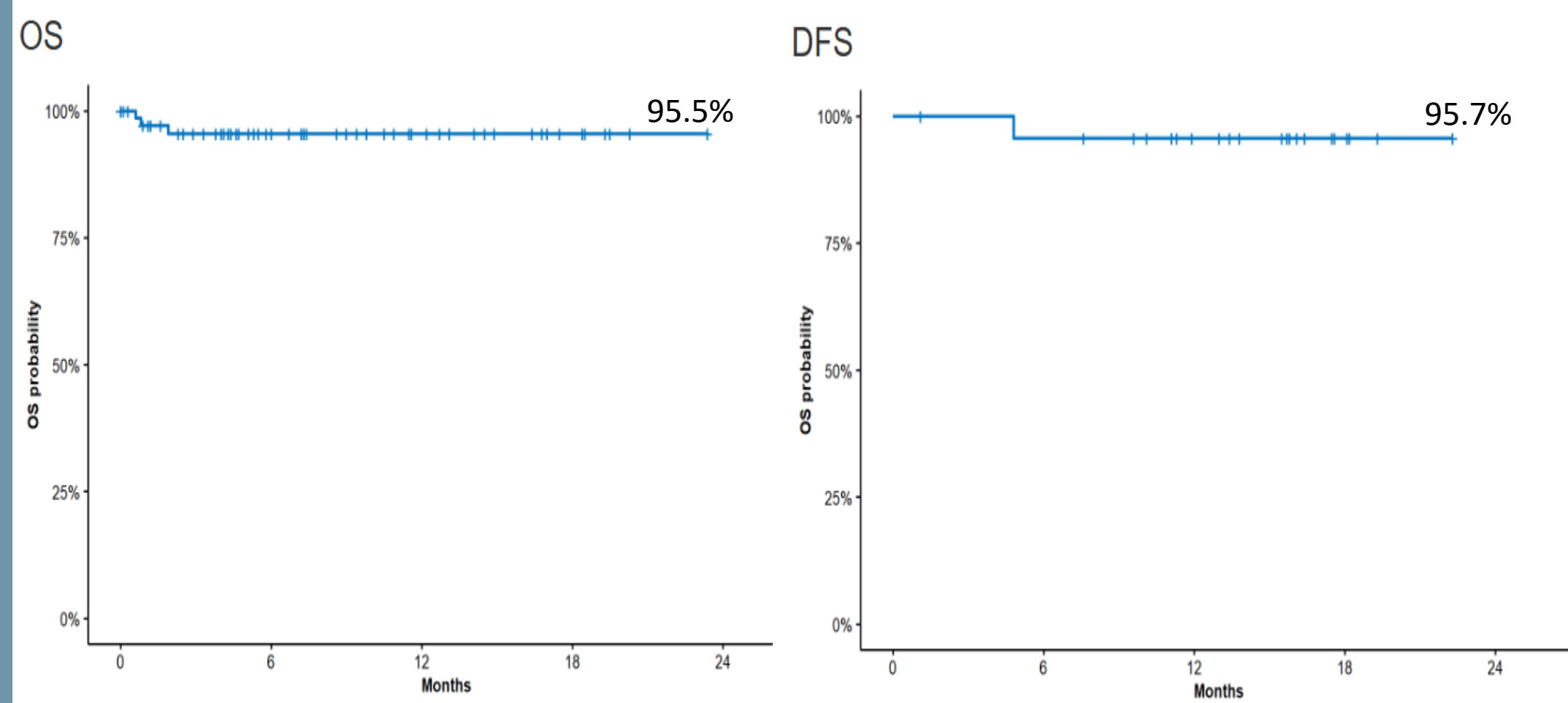
	ALL 2820 (day +70)	LAL2116 (day +85)
End of induction (evaluable patients)*	60	59
Non molecular response (%)	35 (58)	42 (71)
CMR (%)	16 (27)	6 (10)
PNQ (%)	8 (13)	11 (19)
Overall molecular response (%)	24 (40)	17 (29)
	ALL 2820 (after 2 cycles of blinatumomab)	LAL2116 (after 2 cycles of blinatumomab)
Primary endpoint (evaluable patients)*	52	55
Non molecular response (%)	15 (29)	22 (40)
CMR (%)	20 (38)	23 (42)
PNQ (%)	16 (31)	10 (18)
Overall molecular response (%)	36 (69)	33 (60)

* Molecular response evaluation ongoing for 1 patient

CONCLUSIONS

These findings prove the feasibility of the ponatinib-blinatumomab induction consolidation strategy for newly diagnosed Ph+ ALL of all ages, with a 95% CHR rate. Molecular responses at the end of induction and after 2 cycles of blinatumomab are superior in the current trial compared to the D-ALBA study: 40% vs 29% and 69% vs 60%, respectively. The benefit of the current trial appears to rely on a low relapse rate, with only 1 case being so far observed, while in the same time frame 3 relapses were documented in the D-ALBA study. Toxicity appears acceptable and, notably, the transplant rate is very low. With the caveat of a short follow-up, OS and DFS are excellent (Fig. 2).

Figure 2. OS and DFS



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