The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 22, 2020 VOL. 383 NO. 17

Dasatinib–Blinatumomab for Ph-Positive Acute Lymphoblastic Leukemia in Adults

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ABSTRACT

BACKGROUND

Outcomes in patients with Philadelphia chromosome (Ph)–positive acute lymphoblastic leukemia (ALL) have improved with the use of tyrosine kinase inhibitors. Molecular remission is a primary goal of treatment.

METHODS

We conducted a phase 2 single-group trial of first-line therapy in adults with newly diagnosed Ph-positive ALL (with no upper age limit). Dasatinib plus glucocorticoids were administered, followed by two cycles of blinatumomab. The primary end point was a sustained molecular response in the bone marrow after this treatment.

RESULTS

Of the 63 patients (median age, 54 years; range, 24 to 82) who were enrolled, a complete remission was observed in 98%. At the end of dasatinib induction therapy (day 85), 29% of the patients had a molecular response, and this percentage increased to 60% after two cycles of blinatumomab; the percentage of patients with a molecular response increased further after additional blinatumomab cycles. At a median follow-up of 18 months, overall survival was 95% and disease-free survival was 88%; disease-free survival was lower among patients who had an *IKZF1* deletion plus additional genetic aberrations (*CDKN2A* or *CDKN2B*, *PAX5*, or both [i.e., *IKZF1*^{plus}]). *ABL1* mutations were detected in 6 patients who had increased minimal residual disease during induction therapy, and all these mutations were cleared by blinatumomab. Six relapses occurred. Overall, 21 adverse events of grade 3 or higher were recorded. A total of 24 patients received a stem-cell allograft, and 1 death was related to transplantation (4%).

CONCLUSIONS

A chemotherapy-free induction and consolidation first-line treatment with dasatinib and blinatumomab that was based on a targeted and immunotherapeutic strategy was associated with high incidences of molecular response and survival and few toxic effects of grade 3 or higher in adults with Ph-positive ALL. (Funded by Associazione Italiana per la Ricerca sul Cancro and others; GIMEMA LAL2116 D-ALBA EudraCT number, 2016-001083-11; ClinicalTrials.gov number, NCT02744768.)

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N Engl J Med 2020;383:1613-23.
DOI: 10.1056/NEJMoa2016272

A Quick Take is available at NEJM.org

The prognosis in adults with Philadelphia chromosome (Ph)–positive acute lymphoblastic leukemia (ALL) has markedly improved since the advent of ABL-specific tyrosine kinase inhibitors. The use of these agents, with or without systemic chemotherapy, allows most patients to have a complete hematologic response.[1-15] Over the past 15 years, the GIMEMA (Gruppo Italiano Malattie Ematologiche dell'Adulto) cooperative trial group has adopted a chemotherapy-free induction strategy involving prephase treatment with glucocorticoids for a 7-day period, during which all the patients who are enrolled in the ALL trials are centrally evaluated for the presence or absence of the *BCR-ABL1* gene fusion. Patients with Ph-positive ALL then undergo an induction phase involving the use of a tyrosine kinase inhibitor (plus glucocorticoids) and central nervous system (CNS) prophylaxis but no systemic chemotherapy.[16-19] This treatment has resulted in a complete hematologic response in 94 to 100% of patients, irrespective of age, and virtually no deaths during the induction phase.

In ALL, the achievement of a profound and sustained decrease in minimal residual disease is associated with an increased chance of cure. In clinical trials of first-line treatment for patients with ALL of all ages for whom the goal is a decreased likelihood of relapse, the primary end point is a reduction in the tumor burden to less than 1 tumor cell in 10,000 bone marrow mononuclear cells.

In the phase 2, single-group GIMEMA LAL2116 D-ALBA trial of first-line treatment in adults (with no upper age limit) who had newly diagnosed Ph-positive ALL, dasatinib induction was followed by consolidation with the bispecific anti-CD3 and anti-CD19 monoclonal antibody blinatumomab.[20] Dasatinib, a second-generation inhibitor of the ABL tyrosine kinase, is more potent than imatinib. The bifunctional antibody was designed to activate T cells with its anti-CD3 group and bind to tumor cells with its anti-CD19 group to promote cellular cytotoxicity.

Methods

Trial Design and End Points

The design of the trial is shown in Figure S1 and detailed in the Supplementary Methods section, both in the Supplementary Appendix (available with the full text of this article at NEJM.org). Before the patients received dasatinib, they received prephase treatment with a glucocorticoid for 7 days. Glucocorticoids were continued for 24 more days and discontinued on day 31. Dasatinib (at a dose of 140 mg once daily) was administered as induction therapy for 85 days. All the patients who completed the induction phase received postinduction consolidation treatment with blinatumomab at a dose of 28 μg per day; before each blinatumomab cycle, dexamethasone (at a dose of 20 mg) was administered. To prevent CNS adverse events, levetiracetam (at a dose of 500 mg twice daily) was administered. A minimum of two cycles was mandatory; up to three additional cycles were allowed. Dasatinib was continued during treatment with blinatumomab and after the administration of blinatumomab, except in a few patients in whom a T315I mutation was detected during the induction phase.

CNS lumbar punctures were performed at diagnosis, at days 14, 22, 43, 57, and 85, and at the end of each blinatumomab cycle, for a total of 12 procedures. The choice of postconsolidation treatment, including allogeneic hematopoietic stem-cell transplantation and subsequent administration of a tyrosine kinase inhibitor, was made by the investigators. Data on follow-up and treatment after blinatumomab consolidation are being collected in an ancillary trial (GIMEMA LAL2217; ClinicalTrials.gov number, NCT03318770).

The primary end point of our trial was a molecular response (a complete molecular response and a positive nonquantifiable response [i.e., minimal residual disease–positive samples outside the quantitative range]) with induction therapy involving dasatinib plus glucocorticoids followed by two cycles of blinatumomab. The secondary end points were a decreased level of minimal residual disease associated with blinatumomab; disease-free survival, overall survival, and the cumulative incidence of relapse; the safety profile of dasatinib–blinatumomab; and the molecular response and overall and disease-free survival according to the molecular characteristics at baseline, including the type of fusion protein (190-kd fusion protein [p190] or 210-kd fusion protein [p210]) and the presence or absence of additional genomic lesions. Translational research end points included an analysis of copy-number aberrations, screening for *ABL1* mutations in patients who had an increase in

minimal residual disease, and monitoring of the host immunologic compartment.

ASSESSMENTS

Assessment of Hematologic Response

A complete hematologic response was defined as 5% bone marrow blasts or less, the absence of blasts in the peripheral blood, no extramedullary involvement, and a full recovery of the peripheral-blood count (i.e., a neutrophil count of >1500 cells per cubic millimeter and a platelet count of >100,000 per cubic millimeter). Hematologic relapse was defined as the presence of blasts in the peripheral blood or in any nonhematologic site, or at least 5% bone marrow blasts.

Molecular Analysis and Molecular Response

Molecular analyses of bone marrow samples were performed at a central laboratory. At diagnosis, a multiplex reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay[21] was used to detect the p190 or p210 forms of the *BCR-ABL1* fusion product during prephase treatment with glucocorticoids. Monitoring of minimal residual disease with quantitative RT-PCR was performed at days 22, 45, 57, and 85 of induction therapy and at the end of each blinatumomab cycle. The number of *BCR-ABL1* copies and the interpretation of results were determined according to the European Study Group on MRD [minimal residual disease] Detection in ALL (EuroMRD).[22,23]

A complete molecular response was defined as a ratio of *BCR-ABL1* to *ABL1* of 0. A positive nonquantifiable response was defined according to the new EuroMRD guidelines[23]; both a complete molecular response and a positive nonquantifiable response were considered to be evidence of a molecular response. A molecular relapse was defined as a 2-log or greater increase in minimal residual disease measured with the use of quantitative RT-PCR.

ABL1 *Mutational Screening and Copy-Number Aberration Analysis*

ABL1 mutations were evaluated by means of Sanger sequencing in patients who had an increase in minimal residual disease. We used the SALSA MLPA Probemix P335 ALL-*IKZF1* kit (MRC Holland) to evaluate recurrent deletions in diagnostic genomic DNA in 46 patients for whom genomic material was available. The assay is described by Fedullo et al.[24] The product of *IKZF1*, the Ikaros gene, is involved in chromatin remodeling and alteration of gene expression, and deletions of *IKZF1* are common in patients with ALL.[25]

Host Immunologic Compartment

Peripheral-blood mononuclear cells were obtained after centrifugation with Ficoll–Histopaque (Axis-Shield). The distribution of CD4+ T cells, CD8+ T cells, natural killer cells, natural killer T cells, and regulatory T cells (Tregs) was analyzed by means of direct immunofluorescence to assess immunologic changes after treatment with blinatumomab, as described by Duell and colleagues.[26]

TRIAL OVERSIGHT

The trial was designed by GIMEMA, in collaboration with the academic authors. The trial was approved by the ethics committee at each participating center and was conducted in accordance with the Good Clinical Practice guidelines of the International Council for Harmonisation and the provisions of the Declaration of Helsinki. All the patients provided written informed consent. Data were collected by the trial investigators and staff members and analyzed by GIMEMA. All the authors interpreted the data, collaborated in the preparation of the manuscript and in the decision to submit it for publication, and vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol (available at NEJM.org). All the authors, their institutions, and GIMEMA were required to maintain data confidentiality during the trial.

STATISTICAL ANALYSIS

The trial was designed to evaluate the activity of dasatinib plus blinatumomab in inducing a molecular response in adults with Ph-positive ALL. Consideration was given to reject the null hypothesis, which was based on data on the historical control group in the GIMEMA LAL1509 trial[19] — that 40% of the patients who received dasatinib plus blinatumomab would have a response — as compared with the alternative hypothesis, fixed at 60% of the patients, with 90% power and a 5% significance level with a single-stage phase 2 design.

Estimates of median disease-free and overall survival were calculated with the use of the reverse Kaplan–Meier method, and the distribution

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.

Characteristic	Enrolled Patients (N = 63)
Age — yr	
Median	54
Range	24–82
Sex — no. (%)	
Male	29 (46)
Female	34 (54)
White-cell count — per mm^3	
Median	13,000
Range	600–88,000
Fusion protein — no. (%)	
p190	41 (65)
p210	17 (27)
p190 and p210	5 (8)

of time-to-event end points was calculated with the Kaplan–Meier method. Overall survival was calculated from the date of the initiation of treatment to death from any cause, and disease-free survival and the cumulative incidence of relapse were calculated from the end of induction therapy (day 85) for patients having a complete hematologic response to hematologic relapse. The cumulative incidence of relapse was calculated with the cumulative incidence method, with death in patients who had a complete hematologic response as a competing risk.

Differences between the groups were analyzed with the use of two-sided log-rank tests. Kaplan–Meier estimates at 1 year with 95% confidence intervals are reported. Hazard ratios with 95% confidence intervals were estimated with the Cox proportional model. The 95% confidence intervals were not adjusted for multiple comparisons and should not be used to infer definitive treatment effects.[27,28]

RESULTS

CHARACTERISTICS OF THE PATIENTS

Between May 9, 2017, and January 9, 2019, a total of 63 adults with newly diagnosed Ph-positive ALL were enrolled (Table 1). The median age was 54 years (range, 24 to 82), 54% of the patients were women, and the median white-cell count was 13,000 per cubic millimeter (range, 600 to 88,000).

A total of 41 patients had the p190 fusion protein, 17 had the p210 fusion protein, and 5 had both; for all analyses, the latter two subgroups were considered together. Copy-number analysis showed that the *IKZF1* deletion was the most frequent aberration (in 25 of 46 patients [54%]); other aberrations involved *CDKN2A* or *CDKN2B* (in 13 patients [28%]), *PAX5* (in 10 patients [22%]), *RB1* (in 6 patients [13%]), and *EBF1* (in 5 patients [11%]). A total of 11 of 46 patients (24%) were classified as having *IKZF1*^{plus} (i.e., *IKZF1* associated with *PAX5* deletions, *CDKN2A* or *CDKN2B* deletions, or both) (Fig. S2).

RESPONSE TO TREATMENT

A total of 61 patients completed induction with dasatinib. A 73-year-old woman withdrew from the trial because of toxic effects after she received dasatinib for 10 days and she later died of pneumonia, and an 82-year-old woman withdrew from the trial because of pneumonia and pneumonitis that occurred while she had a complete hematologic response.

At the end of the induction phase (day 85), 98% of the patients (62 of 63 patients) had a complete hematologic response, including the patient in complete hematologic response who withdrew from the trial; 29% (17 of 59 patients) had a molecular response. Overall, no significant differences in molecular response were noted between patients with p190 rearrangement products and those with p210 rearrangement products (32% and 24%, respectively), even though a faster molecular clearance was observed in patients with p190 than in those with p210 (Fig. S3). The number of patients with a molecular response after induction therapy was lower among those with *IKZF1*^{plus} (1 of 11 patients) than among those with *IKZF1* alone and among those with no deletions (9 of 33 patients).

Of the 61 patients who completed the induction phase, 58 received one cycle of blinatumomab, 56 received two cycles, 45 received three cycles, 37 received four cycles, and 29 received five cycles (Fig. 1). The median time from the end of induction therapy to the start of blinatumomab was 10 days (range, 7 to 41). At the end of the second cycle of blinatumomab, 60% of the patients (33 of 55 patients) had a molecular response. In the intention-to-treat population

(all the patients who entered the trial), 52% of the patients had a molecular response. The percentages of patients with a molecular response further increased after subsequent cycles of blinatumomab — to 70% (28 of 40 patients) after the third cycle, 81% (29 of 36 patients) after the fourth cycle, and 72% (21 of 29 patients) after the fifth cycle (Table 2).

After two cycles of blinatumomab, no significant differences were noted between patients with p190 and those with p210 with respect to a molecular response; similarly, there were no significant differences between patients with *IKZF1*^{plus} and those with *IKZF1* alone or with no *IKZF1* deletions after the administration of blinatumomab.

SURVIVAL

The median follow-up was 18 months (range, 1 to 25). Overall survival was 95% (95% confidence interval [CI], 90 to 100) (Fig. 2A), and disease-free survival was 88% (95% CI, 80 to 97) (Fig. 2B). The probability of disease-free survival among patients who had a molecular response at the end of induction therapy (day 85) was 100%, as compared with 85% among patients with a nonmolecular response (Fig. S4A). No significant differences with respect to disease-free survival were observed between patients with p190 (85%; 95% CI, 74 to 97) and those with p210 (95%; 95% CI, 86 to 100) (Fig. S4B). Inferior disease-free survival was observed among patients with *IKZF1*^{plus} deletions: disease-free survival among patients with no *IKZF1* deletions, *IKZF1* deletions alone, or *IKZF1*^{plus} deletions was 100% (95% CI, 100 to 100), 92% (95% CI, 79 to 100), and 64% (95% CI, 41 to 100), respectively (Fig. 3A). Similarly, overall survival was inferior among patients with *IKZF1*^{plus} deletions (100% among patients with no *IKZF1* deletions, 93% among those with *IKZF1* deletions alone, and 82% among those with *IKZF1*^{plus} deletions) (Fig. 3B).

ABL1 MUTATIONS AND GENOMIC ABERRATIONS

An *ABL1* mutational analysis was carried out in 15 patients who had evidence of an increase in minimal residual disease during the induction phase and in 1 patient who had an overt relapse. Of the 15 patients with minimal residual disease, 8 had wild-type disease, whereas mutations were detected in 7 patients (6 with T315I and 1 with E255K). All but one of the mutations occurred between day 57 and 85 (the end of induction therapy), before the initiation of blinatumomab, and all the mutations were cleared by blinatumomab. The only patient who was evaluated at relapse had a T315I mutation. A T315I mutation developed in 4 of the 11 patients with *IKZF1*^{plus} (36%).

RELAPSES AND DEATH

Overall, six relapses occurred. Three relapses were hematologic; one occurred in a patient with a major protocol violation (a delay in administration of blinatumomab of >2 months), one occurred after 12 months in the patient who discontinued the trial after receiving dasatinib for 12 days, and one occurred in a patient after the second cycle of blinatumomab. Two relapses were isolated in the CNS, and one relapse was nodal (Fig. 1). The cumulative incidence of relapse in the whole population was 8% (95% CI, 8 to 8) (Fig. 2C). At diagnosis, three of four patients with relapse had *IKZF1*^{plus} aberrations and one had an isolated *IKZF1* aberration; furthermore, five of six patients had a T315I mutation. As expected, the cumulative incidence of relapse was higher among patients with *IKZF1*^{plus} deletions (27%; 95% CI, 23 to 31) than among those with no *IKZF1* deletions (0%; 95% CI, 0 to 0) or among those with *IKZF1* deletions alone (8%; 95% CI, 6 to 9) (Fig. 3C). CD19+ expression was evaluated in five patients with relapse, and all were CD19+.

Four deaths occurred. A 73-year-old woman died from progression of pneumonia during the induction phase, two patients with a first complete hematologic response died (one patient with a mechanical aortic valve died from endocarditis, and one patient died from a veno-occlusive disorder after allogeneic stem-cell transplantation), and one patient with a second complete hematologic response died from disease progression after allogeneic stem-cell transplantation.

TOXIC EFFECTS

Overall, 60 adverse events occurred in 28 patients (Table S2). Adverse events of grade 3 or higher were cytomegalovirus (CMV) reactivation or infection (in 6 patients), neutropenia (in 4 patients), persistent fever (in 2 patients), pleural effusion (in 1 patient), pulmonary hypertension (in 1 patient), and a neurologic disorder (in 1 patient).

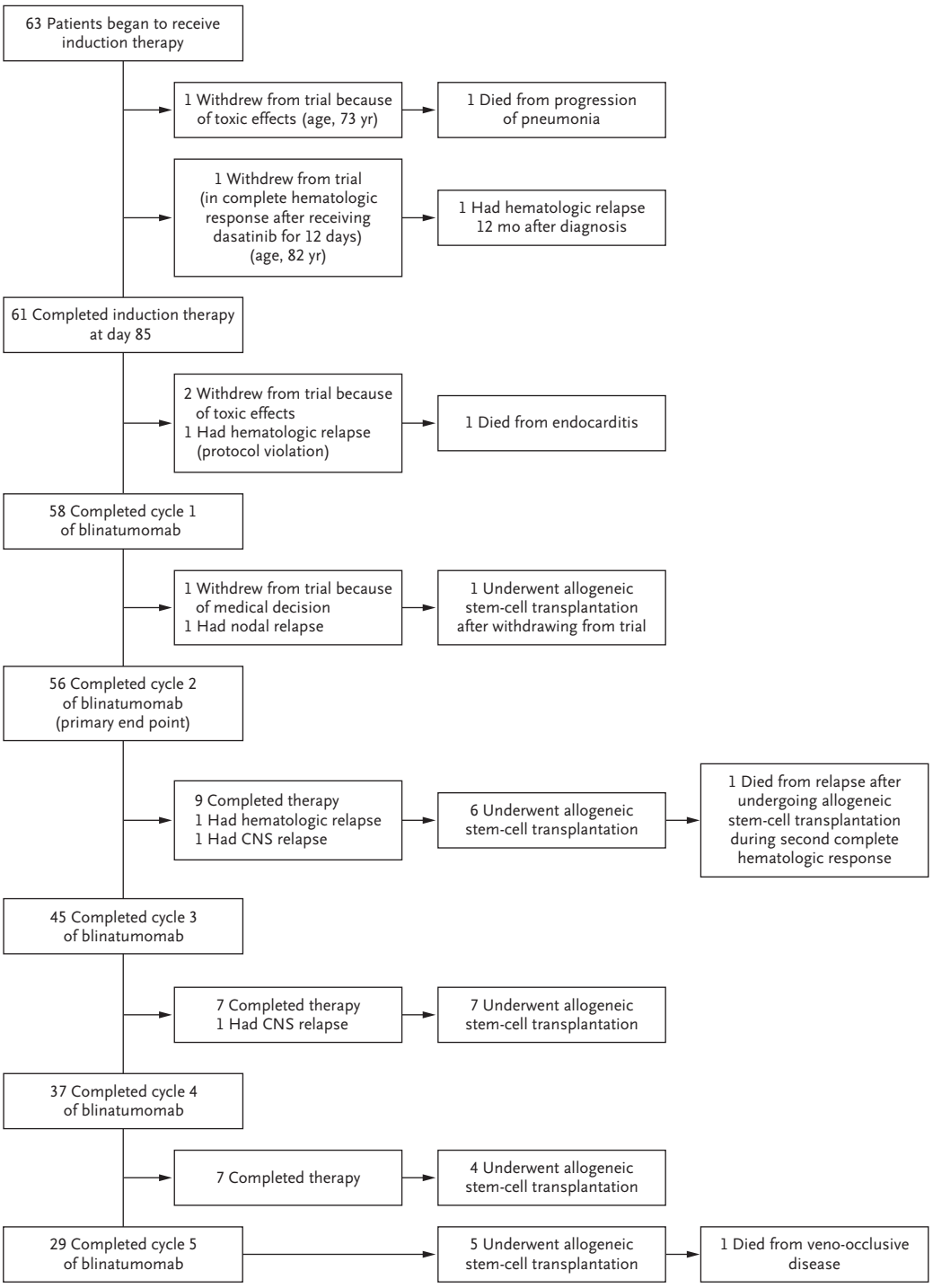


Figure 1. Enrollment and Outcomes.

Treatment was ongoing in one patient. CNS denotes central nervous system.

Table 2. Molecular Responses during Induction Therapy, at the End of Induction Therapy (Day 85), and after Each Blinatumomab Cycle.

Assessment	No Molecular Response	Complete Molecular Response	Positive Nonquantifiable Response	Overall Molecular Response
	number of patients/total number (percent)			
Induction period				
Day 22	48/58 (83)	3/58 (5)	7/58 (12)	10/58 (17)
Day 45	43/60 (72)	9/60 (15)	8/60 (13)	17/60 (28)
Day 57	38/56 (68)	11/56 (20)	7/56 (12)	18/56 (32)
Day 85	42/59 (71)	6/59 (10)	11/59 (19)	17/59 (29)
Blinatumomab cycle				
After cycle 1	20/55 (36)	19/55 (35)	16/55 (29)	35/55 (64)
After cycle 2	22/55 (40)	23/55 (42)	10/55 (18)	33/55 (60)
After cycle 3	12/40 (30)	20/40 (50)	8/40 (20)	28/40 (70)
After cycle 4	7/36 (19)	17/36 (47)	12/36 (33)	29/36 (81)
After cycle 5	8/29 (28)	16/29 (55)	5/29 (17)	21/29 (72)

TRANSPLANTATION

Of the 24 patients (median age, 52 years; range, 24 to 67) who received allografts, 23 received an allograft during the first complete hematologic response and 1 received an allograft during the second complete hematologic response (Fig. 1). Seven patients received an allograft from a sibling, 12 from an unrelated donor, and 5 from a haploidentical donor. Of the patients who underwent transplantation during the first complete hematologic response, 17 (74%) had minimal residual disease at the end of induction therapy and 6 had a molecular response; after two cycles of blinatumomab, 11 patients still had minimal residual disease. Fourteen patients had no graft-versus-host disease (GVHD), 9 had acute GVHD, and 1 had chronic GVHD. Of the 23 patients who underwent transplantation during the first complete hematologic response, 5 patients had received ponatinib and 1 had received a cycle of chemotherapy before transplantation, whereas the remaining 17 (74%) underwent the allogeneic hematopoietic stem-cell transplantation directly. Two deaths occurred (one from relapse and one from veno-occlusive disorder). The transplantation-related mortality was 4%.

HOST IMMUNOLOGIC COMPARTMENT

Longitudinal time points could be evaluated after the initiation of blinatumomab in 17 patients. A decrease in the percentage of Tregs was observed in patients who had received the third cycle of blinatumomab, and this decrease was maintained after the fourth cycle and after the fifth cycle (Fig. S5). Similarly, the ratio of CD4+ to CD8+ T cells decreased over time, sustained by an increase in the median percentage of CD8+ T cells after the fourth cycle of blinatumomab and a small decrease in CD4+ T cells.

DISCUSSION

In our phase 2 trial, adults with newly diagnosed Ph-positive ALL received first-line treatment involving induction with dasatinib followed by consolidation with blinatumomab. The first analysis of the trial showed that this chemotherapy-free induction and consolidation strategy was feasible and safe, with only one death in the induction–consolidation period. In addition, there was a high incidence of molecular response (the primary end point), and the percentages of patients with a molecular response increased further with more cycles of blinatumomab. The data on overall and disease-free survival are promising, and no relapses were observed during induction and consolidation therapy. The responses were less favorable in patients with *IKZF1*^{plus} than in those with *IKZF1* alone or in those with no deletions. Blinatumomab was active on minimal residual

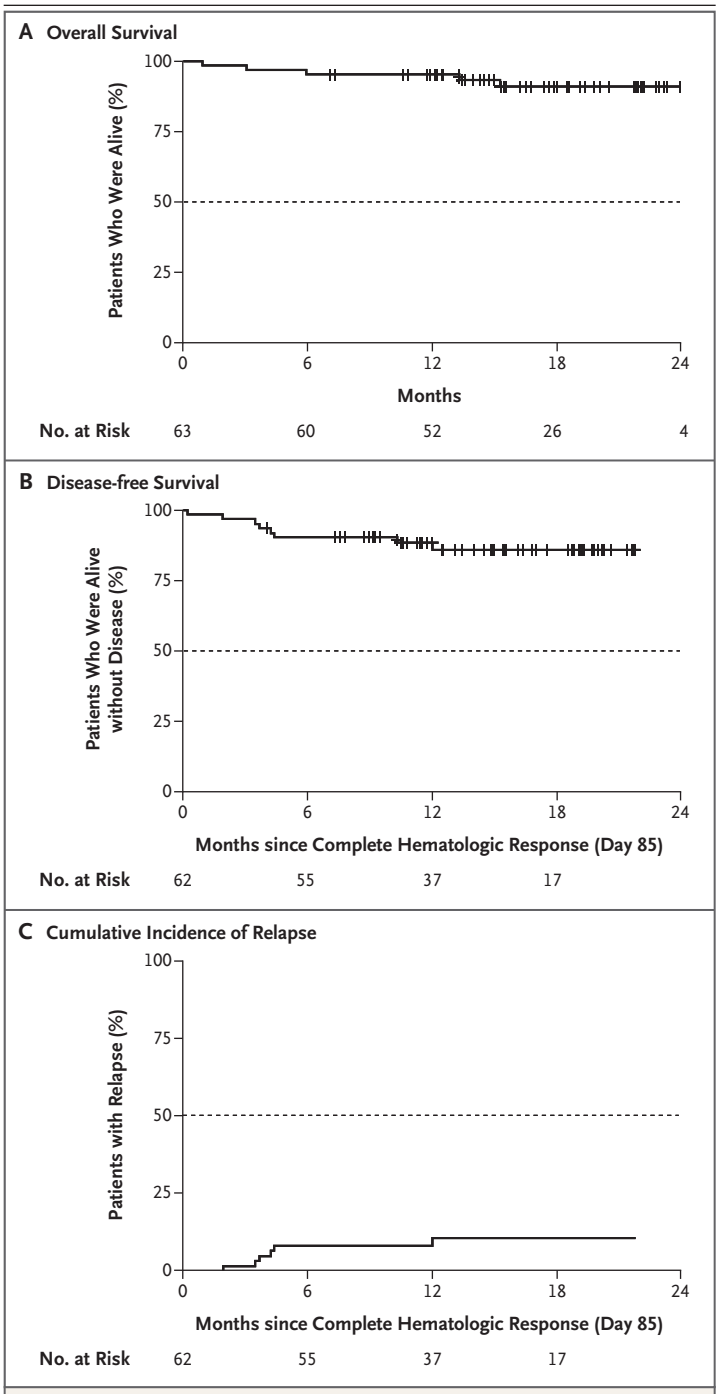


Figure 2. Overall Survival, Disease-free Survival, and Cumulative Incidence of Relapse.

Shown are the percentages of all patients with overall survival (Panel A), disease-free survival (Panel B), and relapse (Panel C). Tick marks indicate censored data.

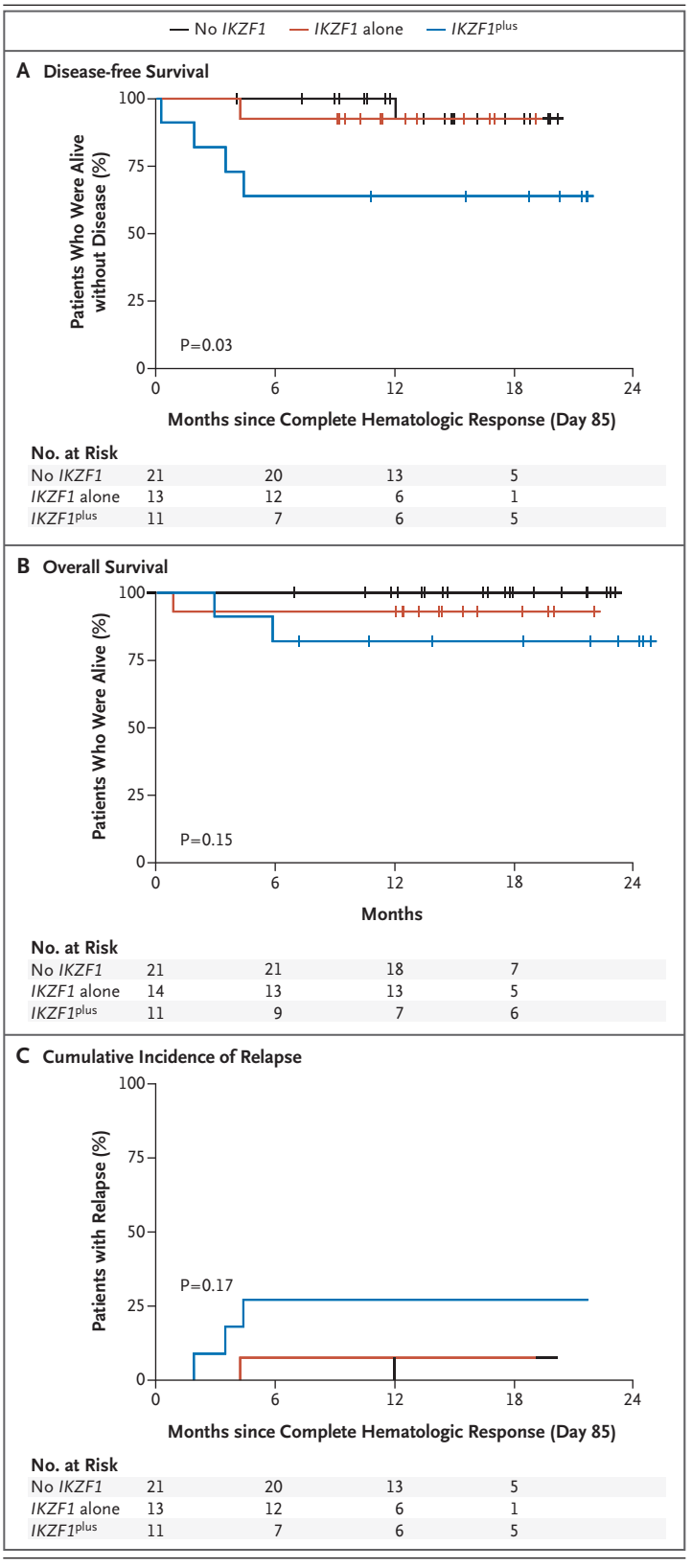
disease–positive cells carrying the *ABL1* mutation. Allotransplants in patients who had not received systemic chemotherapy were associated with a very low transplantation-related mortality.

The patient outcomes were excellent, regardless of age, as indicated by the very low mortality. Unexpectedly, one of the most common adverse events was CMV reactivation. This phenomenon has been previously reported in patients who have received dasatinib.[29-31] After the second cycle of blinatumomab, 60% of the patients with data that could be evaluated had a molecular response; this percentage increased further (up to 81%) with additional cycles of blinatumomab; this finding suggests that as first-line treatment and in patients who had not received chemotherapy, blinatumomab was more active than previously reported. As a result of the high molecular response, overall survival was 95% and disease-free survival was 88% at a median follow-up of 18 months. These results compare favorably with those in other clinical trials, including those involving the use of ponatinib (a third-generation ABL inhibitor with activity against the main ABL resistance alteration, T315I, but with greater toxicity than dasatinib) with or without chemotherapy. In the first report of a trial conducted by Jabbour and colleagues,[32] among patients who received a combination of ponatinib and hyper-CVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone), the progression-free survival at 1 year was 96% and overall survival at 1 year was 86%. In a follow-up analysis, event-free and overall survival at 2 years were 81% and 80%, respectively; the combination was associated with notable (mainly cardiovascular) toxic effects, which led to substantial modifications to the regimen.[33] Similarly, in the GIMEMA LAL1811 trial[34] involving younger patients with coexisting conditions and elderly patients, the overall survival at 1 year among patients who received ponatinib alone was 87.5%.

In the current trial, among patients who had a molecular response at the end of induction and consolidation therapy, the probability of disease-free survival was 100%, as compared with 85% among those with minimal residual disease. No significant difference in survival was seen be-

Figure 3. Disease-free Survival, Overall Survival, and Cumulative Incidence of Relapse, According to the Presence or Absence of *IKZF1* or *IKZF1*^{plus} Deletions.

Shown are the percentages of patients with disease-free survival (Panel A), overall survival (Panel B), and relapse (Panel C), according to the absence of *IKZF1* deletions, the presence of *IKZF1* deletions alone, or the presence of *IKZF1*^{plus} deletions.



tween patients with p190 and those with p210. The presence of additional genomic lesions (i.e., in patients with *IKZF1*^{plus}) had an effect on disease-free survival (100% among patients with no lesions, 92% among those with *IKZF1* deletions alone, and 64% among those with *IKZF1*^{plus}). These findings underscore those from previous trials.[24,25,35] The effect of additional genomic lesions was less evident with respect to overall survival (100% among patients with no *IKZF1* deletions, 93% among those with *IKZF1* deletions alone, and 82% among those with *IKZF1*^{plus} deletions), which indicates that treatment intensification with blinatumomab might reduce the negative prognostic effect of this genotype. In the previous GIMEMA LAL1509 trial,[19] all patients with *IKZF1*^{plus} had disease relapse within 24 months; although a formal comparison cannot be carried out, we found a marked improvement in disease-free survival with the dasatinib–blinatumomab combination.

One major problem is presented by the development of *ABL1* mutations — particularly the gatekeeper T315I — on minimal residual disease–positive cells. All the mutations that occurred during induction (between days 57 and 85 of the induction phase) were cleared by blinatumomab. In 2 patients, a rapid therapeutic intervention (i.e., a switch to ponatinib and transplantation) prevented an overt relapse. A total of 11 patients were considered to have *IKZF1*^{plus}, and a T315I mutation developed in 4 of them. This observation strongly suggests that the *IKZF1*^{plus} phenotype is associated with a status of genomic instability that facilitates the acquisition of deleterious mutations.

Of the 24 patients who underwent transplantation, 2 died. Despite a median age of 52 years (range, 24 to 67), only 1 patient had a transplantation-related death, so the transplantation-related mortality was 4%, which is markedly lower than

that reported in previous studies. It is possible that patients who have not received systemic chemotherapy are less prone to serious transplantation-related complications than those who have received systemic chemotherapy. The other patient who died had undergone transplantation with a second complete hematologic response and died from disease recurrence.

In our trial, we investigated the host immunologic compartment in 17 patients, and we found a decrease in Tregs starting from the third cycle of blinatumomab onward and an increase in CD8+ cells beginning after the fourth cycle of blinatumomab. Duell and colleagues[26] have reported that the percentage of Tregs was inversely correlated with response. Overall, these findings suggest that in patients with newly diagnosed, Ph-positive ALL who have not received chemotherapy, an immunotherapeutic effect on the host immune system is widely observed.

In this trial, adult patients with Ph-positive ALL had a benefit from a chemotherapy-free induction and consolidation strategy with dasatinib followed by blinatumomab. This combination was associated with high incidences of complete hematologic response and molecular response and with impressive survival at 18 months.

Supported by grants from Associazione Italiana per la Ricerca sul Cancro (5x1000, Special Program Metastases, No. 21198, Milan, to Dr. Foà); and Finanziamento Medi Progetti Universitari 2015, Sapienza University of Rome and PRIN 2017 (No. 2017PPS2X4_002, to Dr. Chiaretti).

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank Elisabetta Lisi, Emilia Ippolito, Francesco Acquaviva, and Simona Sannicolò for collection and monitoring of case-report forms.

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