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Journal

Cancer, 127(6)

ISSN

0008-543X

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Publication Date

2021-03-15

DOI

10.1002/cncr.33321

Original Article

Efficacy of Inotuzumab Ozogamicin in Patients With Philadelphia Chromosome–Positive Relapsed/Refractory Acute Lymphoblastic Leukemia

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BACKGROUND: Patients with relapsed/refractory (R/R) Philadelphia chromosome–positive (Ph+) acute lymphoblastic leukemia (ALL) have a poor prognosis and limited treatment options. **METHODS:** The efficacy of inotuzumab ozogamicin (InO), a humanized anti-CD22 monoclonal antibody conjugated to the cytotoxic antibiotic calicheamicin, was evaluated in R/R ALL patients in the phase 1/2 study 1010 (NCT01363297) and open-label, randomized, phase 3 study 1022 (INO-VATE; NCT01564784). This analysis focused specifically on Ph+ R/R ALL patients. In study 1022, Ph+ patients were randomly assigned 1:1 to InO (n = 22) or standard intensive chemotherapy (SC) (n = 27) and 16 Ph+ patients in study 1010 received InO. **RESULTS:** In study 1022, rates of complete remission/complete remission with incomplete hematologic recovery (CR/CRi) and minimal residual disease (MRD) negativity (patients achieving CR/CRi) were higher with InO (CR/CRi = 73%; MRD = 81%) versus SC (CR/CRi = 56%; MRD = 33%). The corresponding rates in study 1010 were 56% (CR/CRi) and 100% (MRD). The hematopoietic stem cell transplantation (HSCT) rate in study 1022 was 41% versus 19% for InO versus SC; however, there was no benefit in overall survival (median OS: 8.7 vs 8.4 months; hazard ratio, 1.17 [95% CI, 0.64-2.14]). The probability of being event-free (progression-free survival) at 12 months was greater with InO versus SC (20.1% vs 4.8%). **CONCLUSION:** Given the substantial improvement in responses and rates of HSCT, InO is an important treatment option for patients with R/R Ph+ ALL. Future studies need to consider better characterization of disease characteristics, more sensitive MRD measurements, MRD-directed therapy before HSCT, and potentially combination therapies, including tyrosine kinase inhibitors. ***Cancer* 2021;127:905-913**.

KEYWORDS: acute lymphoblastic leukemia, efficacy, hematopoietic stem cell transplantation, inotuzumab ozogamicin, Philadelphia chromosome.

INTRODUCTION

The Philadelphia chromosome (Ph) is the most common cytogenetic abnormality (15%-30%) in adult patients with acute lymphoblastic leukemia (ALL).[1-3] The incidence of Ph-positive (Ph+) ALL increases with age and may be as high as 40% to 50% for patients aged ≥60 years.[4] Historically, patients with Ph+ ALL have had poorer prognoses, with higher rates of relapse and worse long-term survival, compared with patients who have Ph-negative (Ph−) ALL.[5] The introduction of tyrosine kinase inhibitors (TKIs) as a treatment for patients with Ph+ ALL substantially improved their outcomes.[5,6] Thus, TKIs in combination with corticosteroids and/or chemotherapy are currently the standard of care for patients with Ph+ ALL.

Despite the improved outcomes with the use of TKIs, patients with Ph+ ALL are still at high risk of relapse, especially those with suboptimal molecular responses and those who do not receive an allogeneic hematopoietic stem cell transplantation (HSCT) following first complete remission (CR).[7] Outcomes are also poor with single-agent

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We thank Chu Kong Liew for medical writing support.

Additional supporting information may be found in the online version of this article.

DOI: 10.1002/cncr.33321, **Received:** June 9, 2020; **Revised:** August 30, 2020; **Accepted:** September 25, 2020, **Published online** November 24, 2020 in Wiley Online Library (wileyonlinelibrary.com)

TKIs for the treatment of relapsed or refractory (R/R) ALL, and there are limited data available for combining TKIs with other agents in the relapsed setting. Relapse following treatment with first- or second-generation TKIs is often associated with mutations in the ABL-kinase domain, particularly at threonine 315, which is often mutated to an isoleucine (T315I).[8] Ponatinib, a third-generation TKI, is currently one of the few treatment options that has shown activity in Ph+ ALL with a *T315I* mutation.[9] Thus, effective treatments are needed for patients with R/R Ph+ ALL.

A number of studies have demonstrated the efficacy of inotuzumab ozogamicin (InO) in R/R ALL, with the achievement of high rates of minimal residual disease (MRD)–negative remissions and the ability to proceed to potentially curative allogeneic HSCT.[10-13] Given the observed efficacy of InO in patients with R/R ALL and its potential ability to target Ph+ ALL regardless of ABL-kinase mutational status, we analyzed the efficacy of InO in these patients. The presence of Ph+ patients in both study 1022 (INO-VATE)[13] and the phase 1/2 study 1010[12] allowed us to conduct a retrospective analysis to assess the efficacy of InO in patients with R/R Ph+ ALL. Our objective was to compare efficacy outcomes (CR/CR with incomplete hematologic recovery [CRi], MRD, overall survival [OS], and progression-free survival [PFS]) among Ph+ patients with R/R ALL treated with InO versus standard intensive chemotherapy (SC) and to describe the rate of access to HSCT following InO therapy as a potentially curative strategy for patients with advanced disease. We were particularly interested in the ability of InO to induce MRD negativity in patients with R/R Ph+ ALL compared with SC. Increasing the rate of MRD negativity, which would enable more patients to proceed to HSCT, would constitute a significant advance for this patient population, given their poor prognoses and limited treatment options.

MATERIALS AND METHODS

Study Design

The study design, patient population, and treatment arms for the 1010 and 1022 studies were published previously.[12,13] Protocols were conducted in accordance with the Declaration of Helsinki and International Council for Harmonisation Guidelines for Good Clinical Practice and was approved by Institutional Review Boards at each participating institution. Participants provided written informed consent before initiation of study-related activities. Patients with R/R ALL received InO in both studies. Study 1010 (NCT01363297) was a phase 1 InO dose-finding/phase 2 study.[12] Study 1022 (NCT01564784) was an open-label, randomized, phase 3 trial (INO-VATE) comparing InO with SC.[13] It is important to note that neither study 1022 nor study 1010 were designed to assess the efficacy of InO specifically in patients with Ph+ ALL. In both studies, only a minority of patients had Ph+ ALL, and in study 1022, patients were not stratified by Ph+ status. Patients in both study arms were not permitted to receive TKIs concurrent with study treatment but could be given TKIs after study treatment. Assessment of Ph+ status is described in the Supporting Information.

This analysis is based on the final study database of INO-VATE (last-patient/last-visit date, January 4, 2017) and study 1010 (last-patient/last-visit date, January 15, 2016).

Study 1010[12]

Adults with R/R CD22+ ALL, including Ph+ patients for whom standard TKI treatment had failed, received InO. Phase 1 focused on dose escalation to determine the recommended phase 2 dose (RP2D), followed by a dose expansion phase at the RP2D. In phase 2, the InO starting dose was 0.8 mg/m^2 on day 1 followed by 0.5 mg/m^2 on days 8 and 15 of each 21-day cycle.

Study 1022[13]

Adults with R/R CD22+ ALL in first or second salvage treatment were randomly assigned 1:1 to receive InO or SC. InO was delivered intravenously at a starting dose of 1.8 mg/m^2. Patients received 0.8 mg/m^2 InO on day 1 and 0.5 mg/m^2 on days 8 and 15 of a 21- to 28-day cycle for up to 6 cycles. Patients achieving CR/CRi were dose-reduced to 1.5 mg/m^2/cycle. SC treatment was the investigator's choice of chemotherapy, consisting of either FLAG (fludarabine, cytarabine [Ara-C], and granulocyte colony–stimulating factor), Ara-C plus mitoxantrone, or high-dose Ara-C.

Outcomes

Details of the primary efficacy and safety endpoints have been described.[12,13] For the current analysis, efficacy outcomes CR/CRi, MRD negativity, OS, and PFS were analyzed in all Ph+ patients treated with InO or SC based on final data from each study. Outcomes based on whether patients had proceeded to HSCT were also examined.

RESULTS

Patients

In all, 5 and 6 patients (InO and SC, respectively) in study 1022 had Ph+ confirmed only by medical history; all other patients were confirmed by local laboratory results and/or fluorescence in situ hybridization analysis performed at a central laboratory. A total of 22 Ph+ patients in study 1022 were randomly assigned to InO and 27 to SC (22 received SC) (Fig. 1). In study 1010, 16 Ph+ patients received InO during phase 1 dose escalation (n = 4), phase 1 dose expansion (n = 3), and phase 2 dose expansion (n = 9) (Fig. 1).

In study 1022, the proportion of Ph+ patients with CD22 expression <90% of ALL blasts was similar to that observed for the entire study population (36% vs 26%, respectively). Moreover, in study 1022, wherein the CD22 density was measured, the median CD22 density on leukemic blasts of Ph+ patients (n = 20 vs 24, InO vs SC) was similar to that of patients with normal (diploid) karyotype (3262.0 vs 3586.5), where density is expressed as molecules of equivalent soluble fluorochrome.

Ph+ patients in both studies had similar median white blood cell (WBC) counts at baseline compared with the entire study population. In study 1022, the median WBC counts (range) were 5.2 (0.8-19.5), 4.1 (0.0-47.4), 4.6 (0.6-42.2), and 4.0 (0.1-68.8) $10^3/mm^3$ for Ph+ InO recipients, all InO recipients, Ph+ SC recipients, and all SC recipients, respectively. The median WBC counts (range) for study 1010 were 4.07 (0.7-67.2) $10^3/mm^3$ for Ph+ patients and 4.40 (0.5-67.2) $10^3/mm^3$ for the entire study population.

At the time of entry into study 1022, nearly all patients with Ph+ ALL in the InO versus SC groups had received 1 (n = 12/22 [55%] vs 12/27 [44%]) or 2 (n = 9/22 [41%] vs 15/27 [56%]) prior lines of treatment (Supporting Table 1). At study entry, most patients (>85%) in each group had received treatment with at least 1 second-generation (most commonly dasatinib) or third-generation TKI. Four of 22 (18.2%) patients in the InO group and 8 of 27 (29.6%) patients in the SC group had received prior ponatinib; approximately one-third of patients in each group (n = 7/22 [32%] vs n = 9/27 [33%]) had previously undergone HSCT.

At the time of study entry, patients in study 1010 were generally more heavily pretreated than patients in study 1022. Almost all patients in study 1010 (n = 15/16 [94%]) had received ≥2 salvage treatments (Supporting Table 1). Per protocol, all patients with Ph+ ALL were previously treated with TKIs; however, 1 patient with a variant Ph+ translocation was not reported to have received TKIs previously. Half of the patients (n = 8/16) in study 1010 had previously undergone HSCT. Although the majority of patients (>70%) in both arms of study 1022 exhibited a complete response to the most recent prior induction therapy (Supporting Table 1), the proportion of patients exhibiting a previous complete response in study 1010 was lower (44%).

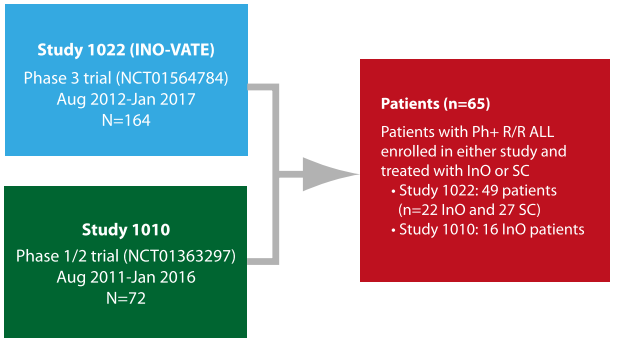

Figure 1. Patient population. Abbreviations: ALL, acute lymphoblastic leukemia; InO, inotuzumab ozogamicin; Ph+, Philadelphia chromosome–positive; R/R, relapsed/refractory; SC, standard chemotherapy.

Efficacy

In study 1022, the proportion of patients achieving CR/CRi was higher in the InO group (n = 16/22 [73%]) compared with the SC group (n = 15/27 [56%]) (rate difference 17.2 [95% CI, –13.0 to 47.4]; $P = .1075$) (Table 1). A similar trend was observed for patients achieving CR in the InO group (n = 10/22 [46%]) versus the SC group (n = 8/27 [30%]) (rate difference 15.8 [95% CI, −15.1 to 46.7]; $P = .1265$). In study 1010, CR/CRi and CR were achieved by 56% (n = 9/16) and 25% (4/16) of InO-treated patients, respectively. The rate of MRD negativity among patients who achieved CR/CRi in study 1022 was higher ($P = .009$) in the InO group (n = 13/16 [81%]) versus SC (n = 5/15 [33%]) (Table 1). All 9 responding patients who achieved CR/CRi in study 1010 also achieved MRD negativity (100%) (Table 1), which was similar to the MRD rate for the InO group in study 1022 (81%).

In study 1022, OS for Ph+ patients was similar between the InO and SC treatment arms, with a median OS of 8.7 and 8.4 months, respectively (hazard ratio [HR], 1.17 [95% CI, 0.64-2.14]; $P = .6912$) (Table 1, Fig. 2).

TABLE 1. Efficacy Endpoints

Efficacy Endpoints	Study 1022			Study 1010
	InO (n = 22)	SC (n = 27)	*P*	InO (n = 16)
CR/CRi, n (% [95% CI])	16 (72.7 [49.8-89.3])	15 (55.6 [35.3-74.5])	.1075	9 (56.3 [29.9-80.3])
CR, n (% [95% CI])	10 (45.5 [24.4-67.8])	8 (29.6 [13.8-50.2])	.1265	4 (25.0)
CRi, n (% [95% CI])	6 (27.3 [10.7-50.2])	7 (25.9 [11.1-46.3])	.4577	5 (31.3)
MRD negativity, n (% [95% CI])[a]	13 (81.3 [54.4-96.0])	5 (33.3 [11.8-61.6])	.009	9 (100.0 [66.4-100.0])
OS				
Median, mo (95% CI)	8.7 (3.6-14.1)	8.4 (5.0-14.3)		7.4 (4.3-11.3)
HR (95% CI)	1.17 (0.64-2.14)		.6912	—
PFS				
Median, mo (95% CI)	3.9 (2.1-9.2)	3.1 (1.1-6.2)		4.4 (1.8-5.9)
HR (95% CI)	0.65 (0.34-1.25)		.0963	—

Abbreviations: CR/CRi, complete remission/complete remission with incomplete hematologic recovery; HR, hazard ratio; InO, inotuzumab ozogamicin; MRD, minimal residual disease; OS, overall survival; PFS, progression-free survival; SC, standard chemotherapy.
[a]Percentage of patients who achieved CR/CRi (16 InO patients and 15 SC patients in study 1022 and 9 patients in study 1010).

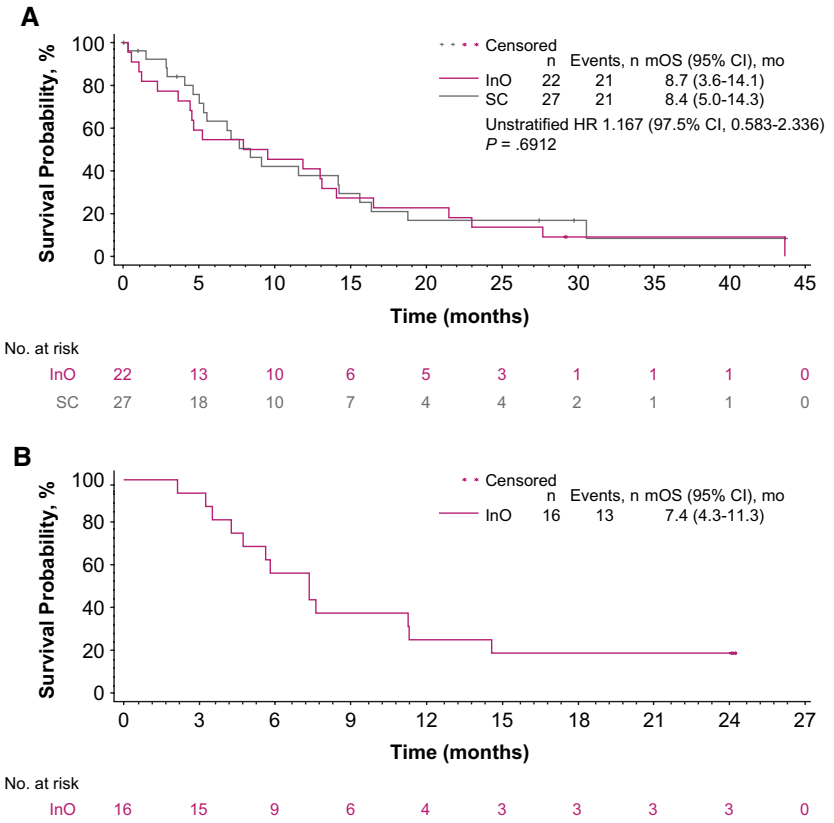

Figure 2. Kaplan–Meier plot of overall survival among Philadelphia chromosome–positive patients with acute lymphoblastic leukemia in (A) study 1022 and (B) study 1010. Abbreviations: HR, hazard ratio; InO, inotuzumab ozogamicin; mOS, median overall survival; SC, standard chemotherapy.

Similarly, in study 1010, the median OS was 7.4 months for Ph+ patients treated with InO. In study 1022, the median PFS was 3.9 months versus 3.1 months for InO versus SC (HR, 0.65 [95% CI, 0.34-1.25]; *P* = .0963) (Table 1, Fig. 3). For PFS, the probability of being alive and event-free at 12 months in study 1022 was higher for InO versus SC (20.1% vs 4.8%). In study 1010, the median PFS was 4.4 months.

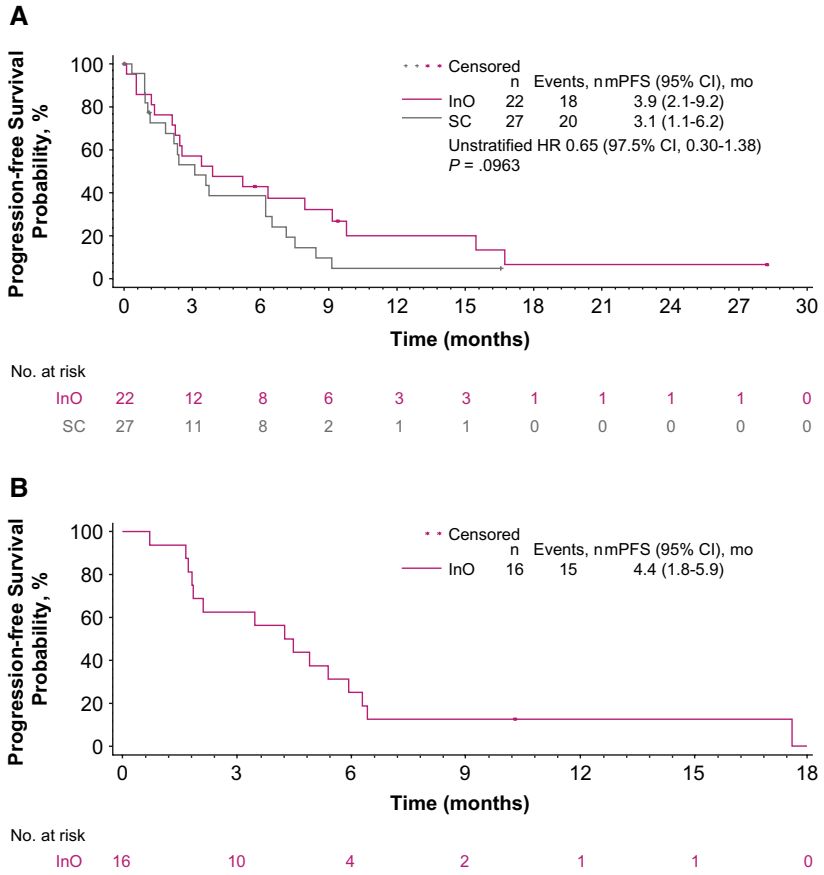

Figure 3. Kaplan–Meier plot of progression-free survival among Philadelphia chromosome–positive patients with acute lymphoblastic leukemia in (A) study 1022 and (B) study 1010. Abbreviations: HR, hazard ratio; InO, inotuzumab ozogamicin; mPFS, median progression-free survival; SC, standard chemotherapy.

TABLE 2. Efficacy Endpoints Stratified According to Whether Ph+ Patients Received Follow-up HSCT

	Study 1022				Study 1010	
	+ Follow-up HSCT		No Follow-up HSCT		+ Follow-up HSCT	No Follow-up HSCT
	InO (n = 9)	SC (n = 5)	InO (n = 13)	SC (n = 22)	InO (n = 3)	InO (n = 13)
PFS, mo, median (95% CI)	9.2 (1.3-NE)	6.5 (2.2-NE)	2.4 (0.6-6.3)	2.4 (1.0-6.2)	5.4 (4.3-NE)	3.5 (1.7-5.9)
OS, mo, median (95% CI)	16.5 (4.7-43.6)	16.4 (11.6-30.6)	4.4 (1.1-8.0)	6.9 (4.1-9.1)	11.3 (4.3-NE)	7.4 (3.5-11.3)

Abbreviations: HSCT, hematopoietic stem cell transplantation; InO, inotuzumab ozogamicin; NE, not evaluable; OS, overall survival; PFS, progression-free survival; Ph+, Philadelphia chromosome–positive; SC, standard chemotherapy.

Following treatment in study 1022, 41% (n = 9/22) of patients in the InO group and 19% (n = 5/27) in the SC group proceeded to HSCT. In study 1010, 19% (n = 3/16) of InO recipients proceeded to HSCT. The median time from CR/CRi to HSCT in study 1022 was 74 days versus 143 days for InO versus SC. In study 1010, the median time from CR/CRi to HSCT was 98 days.

The median PFS appeared to be longer for patients who proceeded to HSCT versus patients who did not, which was observed in both the InO (9.2 vs 2.4 months) and SC (6.5 vs 2.4 months) arms in study 1022 (Table 2). Of note, for InO-treated patients, PFS was similar for both Ph+ and Ph− patients who proceeded to HSCT (HR, 0.96 [95% CI, 0.41-2.24]; $P = .4577$). OS appeared to be longer for InO (median, 16.5 vs 4.4 months)

and SC (median, 16.4 vs 6.9 months) recipients who proceeded to HSCT compared with those who did not. The same trends were observed for InO recipients in study 1010 (Table 2).

InO and SC recipients had a similar duration of remission (DOR), with a median duration of 5.8 vs 4.0 months (HR, 0.56 [95% CI, 0.25-1.24]; $P = .073$) (Supporting Table 2). The majority of patients in each group had relapse as events for DOR following achievement of CR/CRi (InO, 76.9% [n = 10/13]; SC, 69.2% [n = 9/13]). A posttransplantation survival analysis was performed on the small number of Ph+ patients who proceeded to follow-up HSCT. InO recipients from both studies were pooled (n = 12) and compared with SC in study 1022 (n = 4). The median duration of posttransplantation survival was 12.1 months (95% CI, 2.9-40.7) for InO and 20.1 months (95% CI, 1.0-25.0) for SC (HR, 1.21 [97.5% CI, 0.27-5.43]; $P = .612$).

Safety

The most common nonhematologic grade 3-5 adverse events among Ph+ patients in the InO groups were multiorgan abnormalities (41%) in study 1022 and gastrointestinal disorders (31%) in study 1010 (Supporting Table 3). The incidence of increased grade ≥3 gammaglutamyltransferase among InO recipients in study 1022 (27.3%) was higher than for SC recipients (no incidents reported) and for study 1010 (6.3%). The incidence of grade ≥3 increased alanine aminotransferase and grade ≥3 aspartate aminotransferase, respectively, was low across the InO (4.5% and 0%) and SC (4.5% and 0%) groups in study 1022 and in study 1010 (0% and 6.3%). Two Ph+ patients in the InO group in each study (9% in study 1022 and 13% in study 1010) had veno-occlusive liver disease (VOD). Both cases of VOD in study 1022 were post HSCT, constituting 22.2% (n = 2/9) of all patients who proceeded to HSCT while in study 1010, 1 case of VOD (33.3%; 1/3 patients) occurred post HSCT; none of these patients had undergone HSCT before study treatment. One fatal event of post-HSCT VOD was recorded. Among patients in the SC group in study 1022, infection (59%) was the most common grade 3-5 nonhematologic event.

Follow-up Therapy After Study 1022

The proportion of patients who received induction therapy after treatment with InO or SC (follow-up induction therapy) due to R/R disease was similar for both the InO (40.9%) and SC (48.1%) groups in study 1022 (Supporting Table 4). However, compared with the SC group, a smaller proportion of patients in the InO group received TKI as part of their follow-up induction therapy (33.3% vs 13.6%), with more patients in the InO arm receiving chemotherapy (40.9% vs 29.6%). Similarly, the proportion of patients who received TKI as follow-up maintenance therapy after remission was smaller in the InO group (9.1%) compared with the SC group (22.2%).

DISCUSSION

CR/CRi was achieved by a substantial proportion of Ph+ patients with R/R Ph+ ALL treated with InO. The remission rate of patients achieving CR/CRi varied by study (73% of Ph+ InO recipients in study 1022 and 56% of Ph+ patients in study 1010), which likely reflects the different study populations (eg, patients in study 1010 were more heavily pretreated than those in study 1022). The proportion of InO-treated Ph+ patients who achieved MRD negativity in study 1022 was 81% (n = 13/16), compared with 33% (n = 5/15) of SC-treated patients. These results compare favorably with rates achieved with other therapies used to treat R/R Ph+ ALL, such as blinatumomab (a bispecific T cell engager). Martinelli et al[14] reported the results of an open-label phase 2 study that examined the efficacy of blinatumomab in patients with R/R Ph+ ALL wherein 36% (n = 16/45) of patients who received blinatumomab achieved CR/CR with partial hematologic recovery (CR/CRh), with a rate of MRD negativity of 88% (n = 14/16) in patients achieving CR/CRh. In study 1022, around twice as many patients in the InO group (n = 9 [41%]) proceeded to HSCT after treatment compared with the SC group (n = 5 [19%]). In the Martinelli et al study, the proportion of blinatumomab-treated patients who proceeded to HSCT was lower than that observed with InO in the current study.[14] Of the 45 patients in the intent-to-treat population, 7 patients (16%) could proceed to HSCT after blinatumomab treatment; however, these results should be interpreted in the context of the small size of the study.[14]

Despite the higher rates of CR/CRi, MRD negativity, and subsequent HSCT observed for InO compared with SC in study 1022, median OS was similar between groups (8.7 vs 8.4 months). The lack of a meaningful difference in patient survival between InO- and SC-treated patients may be due to several factors, including the use of follow-up therapies after study treatment, which can confound OS results. Compared

with the InO group, a larger proportion of the SC group received TKIs as induction (13.6% vs 33.3%) or maintenance (9.1% vs 22.2%) therapy after study treatment. Of these, the majority of patients in the InO group received second-generation TKIs (dasatinib and nilotinib), whereas more than half of the patients in the SC group received the third-generation TKI ponatinib. The greater use of follow-up TKIs—particularly ponatinib—in the SC group may have led to better outcomes for patients in this group, contributing to the lack of difference seen in PFS and OS between the InO and SC arms of study 1022. The limited sample size may also have prevented smaller differences between the 2 arms from being observed.

Although a large proportion of InO-treated patients achieved CR/CRi and MRD negativity, DOR remained relatively short and relapse from CR/CRi was the most common reason for the short DOR (Supporting Table 2). This result indicates that Ph+ ALL is generally resistant to monotherapy and points to the existence of continued leukemia below the threshold of sensitivity for MRD negativity by flow cytometry. The presence of residual disease may also have contributed to the similar survival rates between InO and SC recipients, while other factors, such as the higher rate of TKI use following SC (compared with InO), may also have contributed to the similar durability of response.

Differences in the prevalence of certain disease characteristics between the InO and SC groups may also have had an impact on survival rates. An increased prevalence of central nervous system disease, a specific transcript type (p190 vs p210), or *IKAROS* mutations in 1 treatment group may confer worse treatment outcomes and affect survival rates. However, neither transcript type nor mutational status were analyzed in these studies. The demographic and baseline characteristics of patients in study 1022 also suggest that Ph+ patients in the InO group were at higher risk (independent of Ph+ status) compared with the overall study population. Among InO-treated patients, those who were Ph+ (versus the overall population) were older (mean age, 54.4 vs 45.9 years), more likely to be in salvage 2 (proportion in salvage 2, 40.9% vs 31.1%), and had a shorter duration of CR to first induction therapy (median, 9.4 vs 11.4 months).

In addition to efficacy and safety, the cost-effectiveness of InO is another important consideration for clinicians. Pfizer recently submitted clinical- and cost-effectiveness evidence for InO to the National Institute of Health and Care Excellence (NICE) in the United Kingdom.[15] Following a review by an independent evidence review group and consideration by the NICE Appraisal Committee, the final incremental cost-effectiveness ratio was between £33,749 and £37,497 per quality-adjusted life-years gained compared with SC.[15] Based on this result, the appraisal committee recommended InO as a treatment option for R/R CD22-positive B cell precursor ALL in adults and also recommended that patients with Ph+ ALL should have received at least 1 TKI. Notably, the NICE appraisal did not include blinatumomab as a comparator. In a recent US study supported by Amgen, the authors concluded that the cost-effectiveness for blinatumomab compared with InO in R/R B cell precursor ALL patients with 1 or no prior salvage therapy ranged from $4006 to $20,737 per quality-adjusted life-years gained.[16]

A strength of our study is that the analyses were performed in a difficult-to-treat population with few treatment options, for whom more research and clinical advances are clearly needed. The current analysis also incorporated long-term follow-up data from study 1022. The limitations of this study included the small number of patients analyzed, the lack of detailed biological data (transcript and mutation type, as well as cytogenetic and expression data) for patients at progression, and the post hoc analysis. Furthermore, the heterogeneity of prior therapy received by patients is a consideration: although most patients received TKIs and chemotherapy, a smaller proportion received TKIs and steroids. Lastly, randomization between InO and SC in study 1022 was not stratified according to Ph status.

These results highlight the need for further studies to better understand the disease characteristics that influence treatment outcome in Ph+ ALL patients and to prospectively evaluate additional therapeutic strategies for patients achieving remission after InO treatment, particularly those who do not proceed to subsequent HSCT. Prior to treatment, factors such as the presence of central nervous system disease, TKI use, *BCR-ABL1* isoform, transcript levels, and ABL-kinase mutation status and other cooccurring mutations should be carefully characterized. Ph+ ALL patients may also benefit from more sensitive measures of MRD negativity to confirm depth of response before transplantation. Given that outcomes for patients with R/R Ph+ ALL are very poor, and there are few treatment options available, it is critical to tailor treatments for maximum efficacy. We suggest that TKIs may be used as maintenance therapy after InO treatment and after HSCT. The choice of TKI employed should be determined by pretransplantation resistance mutations.

TKIs used in combination with InO may also be worth studying in future trials as a means of enhancing response rates and durability. A recent study in patients with R/R ALL or chronic myelogenous leukemia in lymphoid blast phase reported that the combination of InO and bosutinib was well tolerated, with demonstrable clinical activity.[17] In a recently published case report, a patient with Ph+ ALL who had relapsed after a second HSCT was able to achieve long-term molecular remission after treatment with InO and ponatinib.[18] Blinatumomab may also be a useful treatment option following InO, given the efficacy of blinatumomab in eradicating MRD. Further optimization of InO treatment to improve posttransplantation outcomes (including OS and PFS) is clearly needed in this patient population.

Given that HSCT remains the best curative treatment for patients with R/R ALL, the value of InO in increasing the rate of MRD negativity and the proportion of Ph+ patients who can proceed to HSCT to >40% should not be underestimated. Patients in the current study who were able to proceed to HSCT appeared to have improved outcomes compared with those who did not undergo transplantation (Table 2).

As previously reported for the full study populations,[12,13] treatment with InO was associated with manageable toxicities, with cytopenias and liver-related toxicities among the most common adverse events. In this high-risk population, the proportion of Ph+ InO recipients (9%) who developed grade ≥3 VOD in study 1022 was similar to that of the entire cohort of InO recipients (9%); however, this observation should be treated with caution given the small number of Ph+ patients in this study.[13]

In conclusion, an unmet clinical need currently exists for patients with R/R Ph+ ALL, who have poor prognoses. The population in these studies primarily represented patients already exposed to second- or third-generation TKIs and therefore had few treatment options available. The results confirm that InO is an important treatment option for achieving subsequent remission in patients with R/R Ph+ ALL, with potentially beneficial clinical effects in patients with resistant and difficult-to-treat disease in whom prior TKIs have failed. InO recipients in study 1022 had higher rates of CR/CRi, MRD negativity, and subsequent HSCT than SC recipients; consistent results were also observed in the more heavily pretreated population of study 1010. Yet, this did not translate to prolonged PFS or OS; these findings may have been impacted by lower utilization of maintenance TKI therapy among InO recipients compared with SC recipients. Future studies should evaluate the impact of more sensitive MRD measurements, MRD-directed therapy prior to HSCT, and the potential combined or sequential use of targeted therapies with both novel and existing targeted TKIs or other therapeutic approaches[19,20] under development for patients with ALL.

DATA SHARING STATEMENT

Upon request, and subject to certain criteria, conditions, and exceptions (see https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information), Pfizer will provide access to individual deidentified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines, and medical devices 1) for indications that have been approved in the United States and/or the European Union or 2) in programs that have been terminated (ie, development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary, and statistical analysis plan. Data may be requested from Pfizer trials 24 months after study completion. The deidentified participant data will be made available to researchers whose proposals meet the research criteria and other conditions, and for which an exception does not apply, via a secure portal. To gain access, data requestors must enter into a data access agreement with Pfizer.

FUNDING SUPPORT

This study was funded by Pfizer.

CONFLICTS OF INTEREST

Wendy Stock has received research support and/or honoraria from AbbVie, Agios, the American Society of Hematology, Amgen, Astellas, Jazz, Kite, Pfizer, UpToDate, and Xencor and has served on advisory boards and/or as a consultant for Adaptive Biotechnologies, Agios, Astellas, Amgen, Daiichi-Sankyo, Jazz, Kite, MorphoSys, Pfizer, and Servier. Giovanni Martinelli has served on speakers bureaus and/or as a consultant for ARIAD, Celgene, Pfizer, Roche, Bristol-Myers Squibb, and Novartis. Matthias Stelljes has received research support from Pfizer, consulting honoraria from Pfizer, and personal fees from Amgen and Jazz. Daniel J. DeAngelo has received research support from AbbVie, Blueprint Pharmaceuticals, GlycoMimmetics, and Novartis and has received personal fees from Agios, Amgen, Autolos, Blueprint Pharmaceuticals, Forty-Seven, Incyte, Jazz, Novartis, Pfizer, Servier, and Takeda. Nicola Gökbuget has received research support and/or honoraria from Amgen, Novartis, and Pfizer. Anjali S. Advani has received research support from AbbVie, Amgen, GlycoMimetics, and Macrogenics and honoraria from GlycoMimetics, KiTE Pharmaceuticals, Novartis, and Pfizer. Susan O'Brien has received research support from Acerta, Gilead, KiTE Pharmaceuticals, Pfizer, Pharmacyclics, Regeneron, Sunesis, and TG Therapeutics and honoraria from Alexion, Eisai, Gilead, Juno Therapeutics, Pfizer, Pharmacyclics, Sunesis, TG Therapeutics, and Verastem. Michaela Liedtke has received research support from Pfizer and personal fees from Amgen, Celgene, GlaxoSmithKline, Janssen, Oncopeptides, and Pfizer. Akil A. Merchant has received institutional support for clinical trials from

Pfizer, has received research support from the National Institutes of Health and Pfizer, has received personal fees from Pfizer, and has served on the advisory board for Pfizer. Ryan D. Cassaday has received research funding from Amgen, Kite/Gilead, Merck, Pfizer, Vanda Pharmaceuticals, and Seattle Genetics, and has received personal fees from Amgen and Pfizer. Tao Wang is an employee of and owns stock in Pfizer. Hui Zhang is an employee of and owns stock in Pfizer. Erik Vandendries is an employee of and owns stock in Pfizer. Elias Jabbour has received research funding from AbbVie, Amgen, Bristol-Myers Squibb, Pfizer, and Takeda; has received nonfinancial support from Adaptive Biotechnologies; has received personal fees from AbbVie, Adaptive Biotechnologies, Amgen, Astellas, Bristol-Myers Squibb, Genentech, Pfizer, and Takeda. David I. Marks has served on the advisory board and as a consultant for Pfizer. Hagop M. Kantarjian has received research grants from AbbVie, Amgen, Ascentage, Bristol-Myers Squibb, Daiichi-Sankyo, Immunogen, Jazz, Novartis, Pfizer, and Sanofi; has received honoraria from AbbVie, Adaptive Biotechnologies, Amgen, Aptitude Health, BioAscend, Daiichi-Sankyo, Delta Fly, Janssen Global, Novartis, Oxford Biomedical, Pfizer, and Takeda; and has served on the advisory board for Actinium.

AUTHOR CONTRIBUTIONS

Wendy Stock: Conceptualization, investigation, resources, writing–original draft, writing–review and editing. **Giovanni Martinelli:** Conceptualization, investigation, resources, writing–original draft, writing–review and editing. **Matthias Stelljes:** Conceptualization, investigation, resources, writing–original draft, writing–review and editing. **Daniel J. DeAngelo:** Conceptualization, investigation, resources, writing–original draft, writing–review and editing. **Nicola Gökbuget:** Conceptualization, investigation, resources, writing–original draft, writing–review and editing. **Anjali S. Advani:** Conceptualization, investigation, resources, writing–original draft, writing–review and editing. **Susan O'Brien:** Conceptualization, investigation, resources, writing–original draft, writing–review and editing. **Michaela Liedtke:** Conceptualization, investigation, resources, writing–original draft, writing–review and editing. **Akil A. Merchant:** Conceptualization, investigation, resources, writing–original draft, writing–review and editing. **Ryan D. Cassaday:** Conceptualization, investigation, resources, writing–original draft, writing–review and editing. **Tao Wang:** Formal analysis. **Hui Zhang:** Formal analysis. **Erik Vandendries:** Conceptualization, investigation. **Elias Jabbour:** Conceptualization, investigation, resources, writing–original draft, writing–review and editing. **David I. Marks:** Conceptualization, investigation, resources, writing–original draft, writing–review and editing. **Hagop M. Kantarjian:** Conceptualization, investigation, resources writing–original draft, writing–review and editing.

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