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ORIGINAL ARTICLE

INO-CD22: A multicenter, real-world study of inotuzumab ozogamicin safety and effectiveness in adult patients with relapsed/refractory acute lymphoblastic leukemia

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Abstract

Background: Inotuzumab ozogamicin (IO) has helped to change the treatment paradigm in B-cell acute lymphoblastic leukemia (B-ALL) but real-world data are limited.

Methods: The INO-CD22 study is a multicenter retrospective cohort study of adult patients with relapsed/refractory B-ALL treated with IO in 24 Italian centers from 2014 to 2019, with the aim of assessing the response, survival, and toxicity of IO.

Results: Data for 73 eligible patients were obtained: the median age at the start of IO treatment was 52.7 years (I–III quartiles, 51.9–53.5 years), the median number of previous lines was three (I–III quartiles, two to four), and prior exposure to induction standard chemotherapy and blinatumomab occurred in 85% and 57.5% of cases, respectively. IO was administered following the label schedule. A 74.0% overall response rate was achieved, with a 69.8% complete remission rate and a 4.1% complete remission with incomplete hematologic reconstitution rate. The median

This trial was registered at ClinicalTrials.gov (NCT03898128).

Giovanni Marconi and Giovanni Martinelli contributed equally to this article.

duration of response was 4.4 months (I–III quartiles, 2.3–11.2 months). With a median follow-up of 37.2 months, the median overall survival (OS) was 7.9 months (95% CI, 6.08–12.42 months) with a 3- and 5-year OS of 21.2% (95% CI, 11.9%–32.3%) and 5.3% (95% CI, 9.6%–29.8%), respectively. Overall, 37% of patients were able to proceed to allogeneic hematopoietic stem cell transplantation. Eight patients (11.0%) experienced veno-occlusive disease/sinusoidal obstruction syndrome; the most frequent grade ≥3 nonhematologic adverse events were liver toxicities and pneumonia (two grade 4 and one grade 5, respectively).

Conclusions: Despite the limitations of retrospective studies, the INO-CD22 study highlights the favorable safety profile and clinical activity of IO within a real-world context.

KEYWORDS
B-cell acute lymphoblastic leukemia (B-ALL), inotuzumab ozogamicin (IO), real-world data, relapsed/refractory B-ALL

INTRODUCTION

Acute lymphoblastic leukemia (ALL) is a critical hematologic malignancy where the treatment landscape has been profoundly reshaped by the advent of targeted therapies, particularly for patients with relapsed or refractory (R/R) disease.[1] Despite notable advancements in therapeutic strategies, the prognosis for adult patients with ALL remains unfavorably dismal, which has driven the ongoing pursuit of more effective and tolerable treatments.[2] Inotuzumab ozogamicin (IO), an anti-CD22 antibody conjugated with calicheamicin, stands at the forefront of this quest, and promises to redefine the standards of care for patients with ALL.[3,4]

CD22, a sialic acid–binding immunoglobulin-like lectin, is prevalently expressed on B-cell acute lymphoblastic leukemia (B-ALL) blasts, which makes it an ideal target for antibody-based therapies. IO, by conjugating a CD22 antibody with the cytotoxic agent calicheamicin, delivers a targeted attack on B cells by offering an action mechanism that uniquely suits the pathological profile of ALL.[5–7] Pivotal trials have not only confirmed the high efficacy of IO in inducing complete remission (CR) but also highlighted its potential as a bridge to curative stem cell transplantation, the only potentially curative option in the long term for patients with ALL.[8–13] Furthermore, the widespread adoption of IO in treatment protocols reflects its transformative impact on the therapeutic landscape of ALL by offering a targeted approach that has significantly improved patient outcomes and expanded the range of tools available to combat this challenging disease.[14–22]

However, since the introduction of IO, new challenges have arisen, particularly concerning toxicity management. The risk of veno-occlusive disease (VOD) associated with IO requires a careful and informed approach to treatment by balancing the expected activity with potential adverse events (AEs).[12,23–25] Confirming the effectiveness of IO in a real population and updating the information on toxicities outside the strict window of clinical trials make real-world data invaluable by encompassing a diverse patient population and a more varied clinical practice setting.[26] At present, only four sets of real-world studies have been reported. One of the studies only included US patients from academic institutions, whereas another focused on different novel therapies in Japan. Furthermore, one study only included patients who were bridged to allogeneic hematopoietic stem cell transplantation (HSCT), whereas a fourth was based on an early compassionate program for IO.[12,27–29] The INO-CD22 study embraces the real-world approach by analyzing the outcomes of patients treated with IO across many Italian centers.

MATERIALS AND METHODS

Study design and data source

This is an observational cohort study aimed at investigating the effectiveness and safety of IO in adult patients with R/R ALL treated at 24 Italian sites from 2014 to 2019, before drug reimbursement in Italy. Patients participating in a clinical trial were excluded. Data were retrospectively retrieved from patients' medical records and reported in electronic case report forms (eCRFs). Central monitoring and queries were performed to guarantee as much data integrity and completeness as possible.

Outcomes

The main end points were CR (including complete remission with incomplete hematologic recovery [CRi]), event-free survival (EFS), overall survival (OS), and grade ≥3 AE incidence. CR was defined as bone marrow blasts of <5%, and CRi was defined as a complete remission with incomplete recovery of platelets (<100,000/mm^3) or neutrophils of <500/mm^3. For patients with CR/CRi, the duration of

response was defined as the time, in months, from remission to relapse or death from any cause. EFS was defined as the time, in months, between the start of IO and relapse, treatment failure, disease progression, or death from any cause, whichever occurred first, censored at the last valid disease assessment; OS was defined as the time, in months, between the start of IO and death from any cause, censored at the last known date alive. Regarding IO safety and tolerability, all AEs or severe adverse events (SAEs) were collected in the patient's medical record, whether reported by the patient or noted by study personnel, from the administration of the first dose of IO up to 28 calendar days after the last treatment with IO, and reported in the eCRFs. Any SAE that was suspected to be related to IO or any cause, such as any grade venoocclusive disease/sinusoidal obstruction syndrome (VOD-SOS), was reported even if it occurred after the reporting period.

Statistical analysis

Data were summarized by a median, first quartile (IQ), and third quartile (IIIQ) for continuous variables and by means of absolute frequencies and percentages for categorical ones.

Time-to-event outcomes were analyzed with the Kaplan–Meier method, the log-rank test for group comparisons, and the Cox proportional hazards model for effects estimates. The association between HSCT and survival was tested, including transplant as a time-dependent covariate in the Cox model. Results are reported as medians and in terms of hazard ratios (HRs) and corresponding 95% confidence intervals (CIs). The median follow-up time was computed with the reverse Kaplan–Meier method. Analyses were performed with STATA 15.0 software (College Station, Texas) and R, version 4.3.1. The cumulative incidence functions for VOD-SOS and death from any cause were computed with the mstate package.

Ethical considerations

The study was conducted in accordance with the Declaration of Helsinki by following the ethical standards of EU regulation 679 (General Data Protection Regulation) and applicable Italian laws; it was approved by the ethics committee of the coordinating institution (CEROM, protocol 9296/2018) and by the ethics committee of each participating institution. The study is registered under ClinicalTrials.gov ID NCT03898128. Informed consent was obtained from patients still contactable.

RESULTS

Patient population

Overall, 84 adult patients with R/R ALL were enrolled. However, because of missing data for most of the relevant information, only 73 patients were finally analyzed. Most of the patients were male (54.8%). The median age at ALL diagnosis was 50.7 years (minimum–maximum, 33.8–54.1 years), which increased to 52.7 years at IO initiation (Table 1). Sixty-nine patients received IO between January 2014 and March 2019; four patients received IO outside the protocol observation window but were included in the analysis. Cytogenetics at diagnosis was available for 49 of 73 patients, of whom 21 (28.8%) had Philadelphia chromosome (Ph)–positive ALL, and five patients had adverse cytogenetics, including two r-*MLL* and three hypodiploid. Ph-like alterations were not tested in this patient population. As per previous treatments, 52 Ph-negative patients received chemotherapy regimens as induction, nine with asparaginase-based regimens; within the Ph-positive subgroup, 12 patients received a tyrosine kinase inhibitor alone, nine in combination with chemotherapy.

The study population was heavily pretreated, with 45 patients having already received more than two lines of therapy; the cohort had a median of three lines of therapy. Roughly half the patients (43.8%) underwent an allogeneic stem cell transplantation before IO, with a median time from this procedure to drug administration of 18 months (IQ–IIIQ, 8.0–29.6 months). Furthermore, 57.5% of the patients had previously been exposed to blinatumomab, which was given in an R/R setting in all cases but one, who was treated for a persistent measurable residual disease–positive (MRD+) status. The median duration of the last remission before IO was 5.1 months. Despite the advanced stage of their disease, most patients presented with a good performance status (Eastern Cooperative Oncology Group [ECOG], <1 in 83.6%) at the start of IO.

IO treatment

IO was administered as a single agent according to the standard schedule (0.8 mg/sqm on day 1, 0.5 mg/sqm on days 8 and 15 in 21-day course one; 0.5 mg/sqm on day 1, 8 and 15 from course two, in 28-day courses). A median of two courses was delivered, with 41.1% of patients receiving two cycles, 16.4% receiving three cycles, 5.5% receiving four cycles, 2.7% receiving five cycles, and 5.5% receiving six cycles. A total of 18 treatment variations were observed among 13 patients, mostly because of toxicity or physician decision (Table 2; Table S1).

Before IO administration, liver function was assessed by a serum test, which showed a normal total bilirubin value in 66 patients (for seven patients it was not available), with a median value of 0.45 mg/dL (IQ–IIIQ, 0.33–0.73 mg/dL).

The overall response rate (ORR) to IO treatment was 74.0%, including 51 patients with CR and three patients with CRi. The median time to CR/CRi achievement was 27 days (i.e., within the first course) and, notably, in 10 patients this was reached after the second course of treatment. The median duration of response was 4.4 months (IQ–IIIQ, 2.3–11.2 months) (Table 3). As far as MRD is concerned, this was assessed and reported in 45 of the 54 responding patients (not available in nine patients). Twenty-six patients achieved an MRD− status, and 19 patients achieved a CR/CRi with an MRD+ status.

TABLE 1 Patient characteristics (n = 73).

Characteristic	
Age at diagnosis, median (IQ–IIIQ), years	50.7 (48.9–52.1)
Gender, No. (%)	
Female	33 (45.2)
Male	40 (54.8)
Karyotype at diagnosis, No. (%)	
Hyperdiploidy	3 (4.5)
Hypodiploidy	3 (4.1)
Ph+ (*BCR-ABL*)	21 (28.8)
KMT2A (*MLL*) rearrangement	2 (2.7)
ETV6-RUNX1	1 (1.4)
Other	19 (26.0)
Not evaluable/not reported	24 (32.9)
First line therapy, No. (%)	
Tyrosine kinase inhibitors	12 (16.4)
Chemotherapy plus tyrosine kinase inhibitors	9 (12.3)
Chemotherapy	33 (45.2)
Chemotherapy regimens including asparaginase	19 (26.0)
Previous lines of therapy	
Median (IQ–IIIQ)	3 (2–4)
1, No. (%)	11 (15.1)
2, No. (%)	17 (23.3)
>2, No. (%)	45 (61.6)
Patients previously treated with blinatumomab, any line, No. (%)	42 (57.5)
Patients who received HSCT before IO, any line, No. (%)	32 (43.8)
Age at start of IO, median (IQ–IIIQ), years	52.7 (51.9–53.5)
Duration of last remission before IO, median (IQ–IIIQ), months	5.1 (2–11)
Pre-IO ECOG PS[a]	
Median (IQ–IIIQ)	1 (0–2)
0, No. (%)	31 (44.3)
1, No. (%)	30 (42.9)
2, No. (%)	9 (12.9)
Pre-IO CD22 expression, median (IQ–IIIQ),[b] %	63.0 (32.0–90.0)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; HSCT, allogeneic hematopoietic stem cell transplant; IIIQ, third quartile; IO, inotuzumab ozogamicin; IQ, first quartile; *MLL*, mixed-lineage leukemia; Ph, Philadelphia chromosome.

[a]Data are missing for three patients.

[b]Data are missing for 20 patients.

TABLE 2 Exposure at inotuzumab ozogamicin treatment.

Characteristic	
Treatment cycles, No. (%)	
1	21 (28.8)
2	30 (41.1)
3	12 (16.4)
4	4 (5.5)
5	2 (2.7)
6	4 (5.5)
Patients with treatment variations, No. (%)	13 (17.8)
Types of treatment variation (n = 18),[a] No. (%)	
Dose delayed	4 (22.2)
Dose withheld	7 (38.9)
Dose reduced	3 (16.7)
Permanent discontinuation	4 (22.2)

[a]The total number of treatment variations was 18 in 13 patients; three patients experienced two variations, and one patient had three variations. Reasons for treatment variation are reported in Table S1.

TABLE 3 Response to IO treatment.

Response	
CR/CRi, No. (%)	54 (74.0)
Treatment failure, No. (%)	13 (17.8)
Assessment not performed or not available, No. (%)	3 (4.1)
Early death,[a] No. (%)	3 (4.1)
Time to best response (CR/CRi), median (IQ–IIIQ), days	27 (21–53)
Duration of response (CR/CRi), median (IQ–IIIQ), months	4.4 (2.3–11.2)

Abbreviations: CR, complete remission; CRi, complete remission with incomplete hematologic reconstitution; IIIQ, third quartile; IO, inotuzumab ozogamicin; IQ, first quartile.

[a]Early deaths were reported 6 days after the first dose of IO, the day in which the patient received the third dose of IO, and 4 days after the third dose of IO, before any disease evaluation.

Receiving a previous HSCT or having past exposure to blinatumomab resulted in no impact on the achievement of response (Tables S2 and S3). As far as previous anti-CD19 treatment is concerned, it occurred in 42 patients, whereas 31 patients never underwent this therapy before IO. In terms of response, CR/CRi rates were similar in the two groups (79.5% and 82.1%, respectively), as were median time to best response (28 and 26 days, respectively) and median duration of response (4.5 and 3.9 months, respectively).

Survival after IO and bridge to HSCT

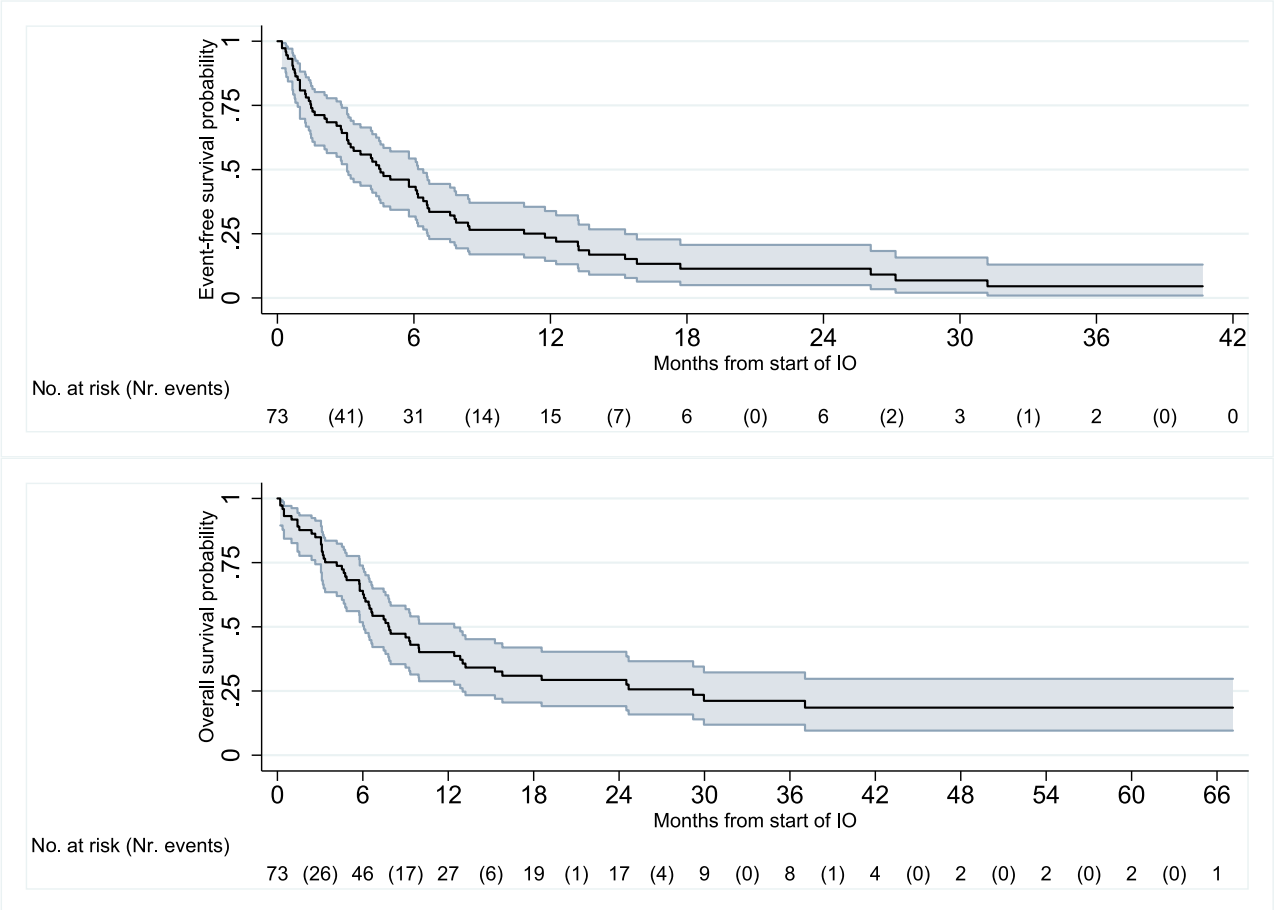
With a median follow-up of 37.2 months (95% CI, 25.4–45.5 months), the median OS was 7.9 months (95% CI, 6.08–12.42 months) and the

median EFS was 4.5 months (95% CI, 3.06–6.41 months). Kaplan–Meier curves are reported in Figure 1, and Table S4 shows the results from univariate analysis. Twenty-seven patients (37.0%) received an HSCT after IO therapy, of whom nine had already undergone this procedure before in their past medical history. Six patients (22.0%) received one cycle of IO before transplant, 16 patients (59.3%) received two cycles, and six patients (22.0%) received more than two cycles. Twenty-three of 27 patients receiving HSCT (85.2%) were in CR/CRi; only two patients (7.4%) received further therapies before HSCT: one received blinatumomab, and one received chemotherapy; for one patient, the response status was not available. The median time from the last IO administration to HSCT was 0.9 months (IQ–IIIQ, 0.7–1.4 months).

At univariate analysis (Table S4) and after adjusting for age at IO start, ECOG status, and Ph status, HSCT was not associated with either OS or EFS (adjusted HR_{OS}, 1.33; 95% CI, 0.73–2.43; $p = .353$; adjusted HR_{EFS}, 1.08; 95% CI, 0.57–2.051; $p = .820$). Among the transplanted patients, the median OS from the date of transplant was 6.2 months (95% CI, 2.6–10.1 months), which reached 6.9 months (95% CI, 2.6–10.1 months) among responding patients (CR/CRi). The EFS among transplanted and responding patients from the date of transplant was 3.8 months (95% CI, 2.6–6.9 months).

Previous treatment with blinatumomab or pre-IO HSCT did not influence patient long-term outcomes (Figures S1 and S2), with a median EFS of 4.11 and 4.96 months in those who did not receive the drug and in those who underwent treatment, respectively. Superimposable results have been achieved in terms of median OS (9.33 and 6.41 months, respectively).

Because of the small number of treated patients, the real-life setting, and the limited physician expertise in the use of IO at that time, a nonstatistically significant difference in terms of outcome was achieved by patients who received the drug as a first salvage option,



	Median (95% CI)	1-year (95% CI)	2-year (95% CI)	3-year (95% CI)
EFS	4.5 (3.06–6.41)	23.5% (14.43%–33.84%)	11.39% (5.00% – 20.68%)	4.55% (0.93% – 12.99%)
OS	7.9 (6.08–12.42)	40.2% (28.80%–51.21%)	29.3% (19.10% – 40.29%)	21.2% (11.88% – 32.25%)

FIGURE 1 Kaplan–Meier curves of event-free survival and overall survival in the study population. CI indicates confidence interval; EFS, event-free survival; IO, inotuzumab ozogamicin; OS, overall survival.

compared to those dosed in more advanced disease phases, in contrast with what is known from the literature[7] (Figure S3). Therefore, combined strategies integrating both immunotherapy and chemotherapy have recently been developed, which have shown more durable responses over time.

Real-world toxicity profiles

Within 28 days from the last IO administration, one case of VOD-SOS, two events leading to death (pneumonia and cerebral hemorrhage), 74 grade 3 or 4 AEs, and 52 grade 1 or 2 AEs were observed. The most common hematologic AEs were thrombocytopenia (20) and neutropenia (24), whereas the most common nonhematologic AEs were infections (17) and liver toxicities (9), as reported in Table 4; 19 SAEs occurred in 15 patients. Overall, eight cases of VOD-SOS were reported, which affected 10.9% of patients, seven of which occurred after HSCT, with a median onset time from stem cell infusion of 18 days (IQ–IIIQ, 11.5–25.0 days). The median time from the last IO administration to the onset of VOD-SOS was 46 days (IQ–IIIQ, 38–52.5 days). Notably, five of the seven transplanted patients who developed VOD-SOS received a double-alkylating conditioning regimen, which was fatal in three of these patients despite a normal liver function at the end of IO, which was evaluated by serum total bilirubin level (Table S5). All the patients in whom VOD occurred received no more than two courses of IO before HSCT, except for the only one who was not transplanted, who was treated with five cycles of therapy. The cumulative incidence of VOD-SOS over time is reported in Figure S4.

TABLE 4 Adverse events by grade from IO start to 28 days after the last IO dose administration.

AE	G1	G2	G3	G4	G5
Hematologic toxicity			4	1	
Anemia		3	3	1	
Leukopenia			4	1	
Febrile neutropenia			2		
Neutropenia			14	10	
Thrombocytopenia		3	9	8	
Asthenia	3	1			
Bronchospasm		1			
Constipation	1	1			
Edema	1				
Cerebral hemorrhage					1
Fever	5	3			
Headache	1				
Infection		8	1		
Nausea	2	1			
Liver toxicity	2	3	5	2	
Neurologic toxicity			1		
Pain	1	2			
Pneumonitis			4		1
Skin rash		1			
Tumor lysis syndrome		1	1		
VOD-SOS		1			
Vomiting		1			
Other	4	3	3		

Abbreviations: AE, adverse event; G, grade; VOD-SOS, venoocclusive disease/sinusoidal obstruction syndrome.

DISCUSSION

For many years, R/R ALL has been synonymous with a death sentence because neither chemotherapy nor HSCT was able to significantly modify outcomes in most patients. The introduction of immunotherapy, based on monoclonal antibodies, T-cell engagers, immunoconjugates, and chimeric antigen receptor t-cell (CAR-T), is revolutionizing the clinical and prognostic scenarios of these patients by offering them the chance to achieve a second or further remission and to proceed to a consolidation approach with HSCT. Among these options, IO, an anti-CD22 antibody conjugated with calicheamicin, has been approved as a single agent for treating patients with R/R CD22 Ph-negative ALL and for patients with Ph-positive ALL who have failed at least one tyrosine kinase inhibitor. The INO-VATE trial, which brought the drug on the market, showed impressive results in terms of CR rate, and a further post hoc analysis of these patients highlighted potential side effects, such as VOD, and how to prevent and manage them. As is well known, data from clinical trials are not always reproducible in real-life settings because the latter can be influenced by variables and factors, which are usually excluded in controlled studies. However, real-life studies are increasingly becoming more important by offering new insights into translating innovative approaches into everyday clinical practice settings.

The INO-CD22 study reported a cohort of adult patients with R/R ALL, heavily pretreated, with a median of three prior therapy lines, who, by definition, had dismal prognoses. The very narrow age range of this population (33.8–54.1 years) is explained by physician choice and expertise at that time in use of the drug. Consequently, mostly young patients, with a low comorbidity burden and potentially fit for a transplant option, were candidates for this treatment in this real-life setting.

Looking at the molecular alterations of these patients, a significant proportion had Ph-positive leukemia (21.9%), which still represents an unmet clinical need after tyrosine kinase inhibitors fail and requires innovative approaches. Notably, patient clinical features highlight more than 50% of the entire population with an ECOG score of ≥1, mostly due to the advanced disease status and the several comorbidities detected in their past medical histories, which

thus sets a difficult-to-treat stage compared with registrational trials. Accordingly, the preliminary reports by US colleagues on the compassionate use of the Spanish program and the treatment patterns observed in Japan[27–29] suggest IO's broader applicability and rationale even beyond the limited criteria of clinical trials, which have shown results comparable to our study. Such insights are crucial to understanding how therapies perform in real-life settings, where patient heterogeneity and treatment variations are more pronounced.

The role of IO therapy as a "bridge to HSCT" has been widely assessed on the basis of results coming from clinical trials but the feasibility and effectiveness of such an integrated approach also require testing in the clinical daily setting. To this aim, our study does not gainsay this strategy, by confirming a high response rate to IO, which allowed a significant proportion of patients to proceed to an HSCT, which still represents the only potentially curative tool for this population. The lack of HSCT benefit observed in our study may depend on the fact that safety mitigation strategies were not fully implemented in the early stages of IO treatment in our country, as demonstrated by the incidence of VOD related to the extensive use of double-alkylating conditioning (Table S5), other than the low number of patients and the data details. However, we confirmed that response to IO could be achieved after a few weeks, regardless of the number of previous therapies, exposure to other immunotherapies, or HSCT, which thus recommends the use of IO as a salvage therapy option for these patients to be consolidated with further strategies to achieve prolonged survival.[10–12,21,30–37]

Notably, our enrolled population is enriched with patients already exposed to blinatumomab (42 of 73 patients), which was already available at that time and frequently chosen as the first salvage approach in R/R ALL in clinical daily practice. The feasibility of a sequential approach, based on anti-CD19 as the first salvage antibody, followed by IO at the following relapse is also confirmed in our series, as is the effectiveness of IO despite a previous immunotherapy strategy, which addresses a different target. Nevertheless, as also already reported by the literature,[39] the long-term outcome of these patients remains poor, which thus confirms the need for more intensive salvage strategies based on combined instead of single agent–based approaches.

By focusing on practical guidelines to be followed in our clinical daily practice, before starting patients on IO therapy, a balanced evaluation should consider its potential benefits and define how to prevent and manage potential AEs. Expert recommendations strongly indicate that patients with HSCT should receive no more than two courses of IO and avoid the double-alkylating regimen within the conditioning schedule to reduce the occurrence of VOD-SOS. In our report, which collected patients treated before the drug approval, when the ability to use the drug was still suboptimal compared to our current expertise, these strategies have not been widely and carefully adopted, which thus justifies, at least in part, the occurrence of VOD in eight patients. Even if the incidence of this complication was lower than predicted, a more careful management of transplantation, especially in the choice of conditioning regimen, could have reasonably contributed to reducing its occurrence and severity.

In addition to the clinical efficacy and safety profile, IO's adaptability to more than one clinical setting could make it a determinant treatment option because there is no direct comparison with blinatumomab or CAR-T, and indirect comparisons never demonstrate a marked superiority of one or another approach.[38–42] The economic implications, good patient-reported outcomes, and IO's low hospitalization burden are important considerations, particularly in health care systems where resource allocation and cost-effectiveness are paramount, and warrant further real-world assessment.[43–47]

Despite its strengths, the study acknowledges the inherent limitations of retrospective observational research. Potential biases, variability in data quality, and the absence of a randomized control group are some factors that might affect the interpretation of the results. Our monitoring strategy was conceived to minimize these biases, which, however, cannot be abrogated.

The collective experiences from various real-world settings, as documented in this and other global studies, contribute to a growing body of evidence supporting IO's role in ALL treatment strategies.[48] Nevertheless, despite the potential benefit of this approach as a single agent, data from the literature and real-life experiences show that the duration of response is still short and unable to significantly change the natural history of the disease in most cases. Therefore, combining IO with a multidrug-based schedule has been explored in this setting, and data published so far have shown impressive results in terms of deeper and more prolonged responses. Jabbour et al. reported on 96 patients with R/R Ph-negative ALL who received a mini-hyper-CVD schedule with IO, with or without blinatumomab, and achieved an ORR of 80% and a 3-year OS rate of 33%.[20] Based on these positive results, the following step, still ongoing within many clinical trials, is to integrate the use of antibodies, including IO, into the frontline treatment of ALL, both in elderly and young populations.[14,15,17–19,22] In this setting, in the INITIAL-1 phase 2 trial, 43 newly diagnosed elderly patients received IO, followed by age-adapted German Multicenter Study Group for Adult ALL–based consolidation and maintenance chemotherapy. All the patients achieved a CR/CRi and, after a median follow-up of 2.7 years, OS at 1 and 3 years was 91% (95% CI, 82%–99%) and 73% (95% CI, 59%–87%), respectively.[15]

In such an evolving field, insights from real-world studies such as INO-CD22 will be invaluable in shaping future research, treatment guidelines, and patient care strategies and properly allocating the drug in the therapeutic journey of patients with B-ALL.

In conclusion, the INO-CD22 study represents a significant step forward in our understanding of IO's role in treating R/R ALL. It provides a comprehensive overview of IO's real-world application, efficacy, and safety. As we move toward more personalized and effective treatment paradigms, studies such as this are instrumental in bridging the gap between clinical research and everyday clinical practice, and ultimately pave the way to more and more innovative approaches.

AUTHOR CONTRIBUTIONS

Cristina Papayannidis: Conceptualization, data curation, investigation, supervision, validation, writing–original draft, and writing–review and editing. **Elisabetta Petracci**: Data curation, formal analysis, supervision, validation, writing–original draft, and writing–review and editing. **Patrizia Zappasodi**: Investigation and writing–review and editing. **Nicola Fracchiolla**: Investigation and writing–review and editing. **Fabio Ciceri**: Investigation and writing–review and editing. **Chiara Sartor**: Investigation and writing–review and editing. **Elisa Roncoroni**: Investigation and writing–review and editing. **Francesco Di Raimondo**: Investigation and writing–review and editing. **Daniele Mattei**: Investigation and writing–review and editing. **Maria Benedetta Giannini**: Investigation and writing–review and editing. **Francesco Lanza**: Investigation and writing–review and editing. **Michele Gottardi**: Investigation and writing–review and editing. **Maria Ilaria Del Principe**: Investigation and writing–review and editing. **Erika Borlenghi**: Investigation and writing–review and editing. **Monica Fumagalli**: Investigation and writing–review and editing. **Daniele Vallisa**: Investigation and writing–review and editing. **Simona Sica**: Investigation and writing–review and editing. **Nicola Di Renzo**: Investigation and writing–review and editing. **Francesco Fabbiano**: Investigation and writing–review and editing. **Elisabetta Todisco**: Investigation and writing–review and editing. **Paolo de Fabritiis**: Investigation and writing–review and editing. **Mario Luppi**: Investigation and writing–review and editing. **Francesco Passamonti**: Investigation and writing–review and editing. **Paolo Corradini**: Investigation and writing–review and editing. **Fara Petruzziello**: Investigation and writing–review and editing. **Fabrizio Pane**: Investigation and writing–review and editing. **Felicetto Ferrara**: Investigation and writing–review and editing. **Greta Mambelli**: Data curation, validation, and writing–review and editing. **Roberta Volpi**: Data curation, validation, and writing–review and editing. **Federica Frabetti**: Data curation, validation, and writing–review and editing. **Chiara Zingaretti**: Data curation, validation, and writing–review and editing. **Giovanni Marconi**: Conceptualization, data curation, investigation, supervision, validation, writing–original draft, and writing–review and editing. **Giovanni Martinelli**: Conceptualization, data curation, funding acquisition, investigation, supervision, validation, writing–original draft, and writing–review and editing.

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CONFLICT OF INTEREST STATEMENT

Cristina Papayannidis reports professional activities for Otsuka Pharmaceutical, Servier Pharmaceuticals, Blueprint Medicines, Astellas Pharma, Bristol-Myers Squibb, Pfizer, AbbVie, and Amgen. Nicola Fracchiolla reports professional activities for AbbVie, Amgen, and Pfizer, and travel support from Pfizer. Erika Borlenghi reports professional activities and consulting for AbbVie. Francesco Passamonti reports consulting for AbbVie, Novartis, GlaxoSmithKline, Sumitomo Pharma, Karyopharm Therapeutics, AOP Health, Keros Therapeutics, Bristol-Myers Squibb, Celgene, Fondazione Internazionale Menarini, and Jazz Pharmaceuticals. Giovanni Marconi reports consulting for AstraZeneca, ImmunoGen, AbbVie, Astellas Pharma, Janssen Pharmaceuticals, Ryvu Therapeutics, Pfizer, Servier

Pharmaceuticals, Menarini International, and Syros Pharmaceuticals. The other authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data sets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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