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RESEARCH

# Real-world outcomes of inotuzumab ozogamicin treatment for adult relapsed or refractory acute lymphoblastic leukemia: a result from Korea post-marketing surveillance

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## Abstract

Inotuzumab ozogamicin (InO), a CD22-targeted antibody-drug conjugate, delivers the cytotoxic agent, calicheamicin, to B-cell precursor of relapsed or refractory B-cell precursor acute lymphoblastic leukemia (R/R B-ALL) cells. It has demonstrated efficacy in phase 3 trials, leading to approval in multiple countries, including the U.S., Japan, and South Korea. In our post-marketing surveillance (PMS) study, we evaluated the safety and effectiveness of InO in adults with R/R B-ALL based on approximately 5 years of PMS data. A prospective, observational, multicenter PMS study was conducted in Korea to evaluate the real-world safety and effectiveness of InO in adult patients with R/R B-ALL (NCT04307134). A total of 107 patients were included in the safety analysis, with a median treatment duration of 43.0 days and a median of 2.0 InO cycles. Common adverse events (AEs) were hematologic (58.9%), infectious (50.5%), and gastrointestinal (45.8%), with neutropenia (27.1%) and febrile neutropenia (26.2%) among the most frequent. Serious AEs occurred in 31.8% of patients, most commonly infections such as septic shock (6.5%) and pneumonia (4.7%). Veno-occlusive disease was observed in 2.8% of patients. In the effectiveness analysis set ($N=94$), median progression-free survival was 3.6 months (95% CI: 3.0–4.7 months), overall survival was 10.2 months (95% CI: 6.0–NA months), and duration of remission was 3.8 months. (95% CI: 3.0–5.4 months). These findings support the clinical utility and safety profile of InO in Korean patients with R/R B-ALL, reflecting real-world outcomes.

**Keywords** Acute lymphoblastic leukemia · Antibody-drug conjugate · Post-marketing surveillance · Veno-occlusive disease · Inotuzumab ozogamicin

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## Introduction

Acute lymphoblastic leukemia (ALL) is a malignancy of immature lymphoid cells affecting the bone marrow and extramedullary sites [1]. In 2025, an estimated 6,100 new cases and 1,400 deaths are expected in the United States [2], while 1,060 new cases were reported in Korea in 2022 (incidence rate 2.1 per 100,000) [3]. In adults, B-cell ALL accounts for 75% of cases; although most achieve complete remission (CR) after induction, many are refractory or relapse [4].

Before the advent of novel agents, outcomes for adults with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (R/R B-ALL) were poor due to the limited efficacy of salvage therapies [5–9]. Inotuzumab ozogamicin (InO), a CD22-targeted antibody–drug conjugate linked to calicheamicin, has since shown significant efficacy in phase 3 trials [10–13], leading to regulatory approvals worldwide, including in the EU (2017) and Korea (2019) [14–16].

The pivotal INO-VATE phase 3 study provided compelling evidence for InO's efficacy. InO monotherapy was associated with significantly higher complete remission/complete remission with incomplete (CR/CRi) and minimal residual disease (MRD)-negative rates translating into improvements in progression-free survival (PFS) and overall survival (OS) compared with standard-of-care (SOC) chemotherapy in adults with R/R B-ALL [17, 18]. In the primary results published in 2016 [17], patients receiving InO had higher CR/CRi rates (80.7% [95% confidence interval [CI]: 72.1% to 87.7%] vs. 29.4% [95% CI: 21.0% to 38.8%], $P < 0.001$), greater MRD negativity (78.4% [95% CI: 68.4 to 86.5] vs. 28.1% [95% CI: 13.7 to 46.7], $P < 0.001$), and longer median PFS (5.0 months [95% CI: 3.7 to 5.6 months] vs. 1.8 months [95% CI: 1.5 to 2.2 months], hazard ratio (HR): 0.45 [97.5% CI: 0.34 to 0.61], $P < 0.001$). Median OS also improved (7.7 months [95% CI: 6.0 to 9.2 months] vs. 6.7 months [95% CI: 4.9 to 8.3 months], HR: 0.77 [97.5% CI: 0.58 to 1.03], $P = 0.04$), with 2-year survival at 23% (95% CI: 16% to 30%) vs. 10% (95% CI: 5% to 16%). Another key finding was that significantly more patients proceeded directly to allogeneic hematopoietic stem cell transplantation (allo-HSCT) after treatment in the InO group compared with SOC (41% vs. 11%; $P < 0.001$) [17].

Despite these favorable outcomes, concerns remain regarding the safety profile of InO, particularly its hepatotoxicity [18–23]. InO has been associated with an increased risk of veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS), particularly in patients undergoing subsequent allo-HSCT [18–23]. The incidence and severity are higher in this group, with some cases leading to fatal multiorgan failure [23]. To mitigate this risk, ongoing assessment and early identification of risk factors for VOD/SOS are essential for the effective management and prevention of this potentially life-threatening complication [21–23].

Since the final INO-VATE publication in 2019 [24], its data — along with findings from post-marketing surveillance (PMS) and real-world studies — have been combined to inform benefit–risk profiles and guide risk management in clinical practice [25].

Yoon et al. evaluated 100 patients with R/R B-ALL, including 25 Philadelphia chromosome-positive (Ph+) and 75 Ph–, who received a median of two InO cycles (range 1–5). The weekly regimen consisted of 0.8 mg/m² in week 1 followed by 0.5 mg/m² in weeks 2 and 3; patients in CR after the first cycle continued at 0.5 mg/m² weekly in cycle 2. At baseline, 7.0% were primary refractory, 36.0% had relapsed during or after consolidation, and 57.0% relapsed following one ($n = 47$) or two ($n = 10$) prior allo-HSCTs. After one cycle, the overall response rate (ORR) was 60%; after two cycles, the best response rate reached 67.0%, with 63.1% achieving MRD negativity. The 2-year OS rate was 20.4%, and 58.2% proceeded to allo-HSCT. Relapse patterns included isolated bone marrow relapse (61%), isolated extramedullary relapse (11.0%), and combined relapse (28.0%) [26].

Similarly, Badar et al. reported an ORR of 63% after a median of two InO cycles (range 1–6), with 44% achieving CR with MRD negativity. Median OS was 11.6 months, and VOD occurred in 2% of patients, including one fatal case [11]. The study population (n not specified here) had a median age of 50 years (range 20–87), 51% male, and 82% with Karnofsky performance status 80–100. Cytogenetic abnormalities were present in 68%, including Ph+ (27.5%) and KMT2A/MLL rearrangements (7.5%). CNS disease was documented in 11% at diagnosis and 25% at progression. Prior blinatumomab exposure occurred in 48%, and 27% received InO after allo-HSCT relapse, with a cumulative dose of 3.3 mg/m². InO was combined with chemotherapy with or without a tyrosine kinase inhibitor (TKI) in 15.5% [27].

Additionally, Jiang et al. analyzed 44 patients with B-ALL who received at least one dose of InO in frontline, MRD-positive, or R/R settings between June 2019 and April 2023. InO (1 mg or approximately 0.6 mg/m²) was given as monotherapy or in combination with chemotherapy and/or a TKI. Among Ph– patients, 9 received InO alone and 15 received InO plus chemotherapy; among Ph + patients, 15 received InO plus TKI and 5 received InO plus chemotherapy and TKI. In the frontline group, all patients achieved CR with a 1-year OS rate of 88.9%. In the MRD-positive group, 84.2% achieved MRD negativity with a 1-year OS rate of 91.7%. In the R/R group, 61.5% achieved CR/CRi, 38.5% achieved MRD negativity, and the 1-year OS rate was 36.9%. No VOD events were reported [28].

Beyond data from Korea, the United States, and China, retrospective studies from Italy, Spain, and Japan have further clarified the real-world use of InO in R/R B-ALL [29–31].

In Italy, the INO-CD22 multicenter study evaluated 73 adults, with a median of three prior lines of therapy and 57.5% previously treated with blinatumomab. After a median of two InO cycles, the CR/CRi rate was 74.0%. Median duration of response (DoR) was 4.4 months, and with a median follow-up of 37.2 months, median OS was 7.9 months (95% CI, 6.08–12.42). VOD/SOS occurred in 11.0% of patients ($n$ = 8); frequent grade ≥ 3 nonhematologic events were liver toxicity and pneumonia (two grade 4, one grade 5) [29].

In Spain, a compassionate-use program enrolled 34 patients and reported a 64% CR/CRi rate after a median of two cycles. Median DoR, PFS, and OS were 4.7 months (95% CI, 2.4–7.0), 3.5 months (95% CI, 1.0–5.0), and 4.0 months (95% CI, 1.9–6.1), respectively. Outcomes were significantly better in relapsed versus refractory patients (OS 10.4 vs. 2.5 months; $p$ = 0.01). No VOD occurred during InO treatment, although grade 3–4 SOS developed in 9% following subsequent allo-HSCT [30].

In Japan, a real-world treatment-pattern study included 194 patients, with 97 treated with InO and 97 with blinatumomab. Among InO-treated patients, 81.4% had received prior chemotherapy and 60.8% received subsequent treatment; sequential blinatumomab use was observed in 20.3%. That is, in real-world practice, InO treatment was relatively short (median 32.5 days, approximately 1to 2 cycles), with most patients not proceeding to HSCT [31].

These differences in findings highlight the inherent limitations of clinical trials—especially their restricted patient populations—and underscore the value of PMS and real-world evidence in identifying and managing safety concerns among patient groups often excluded from clinical trials [25]. Within prospective PMS, pharmacovigilance is critical for detecting adverse drug reactions (ADRs) not captured in controlled clinical settings [32, 33].

Here, we evaluate the safety and effectiveness profile of InO in adult patients with R/R B-ALL, drawing upon data accumulated approximately 5 years of PMS.

## Materials and methods

### Study design and participants

This was a prospective, observational, multicenter, cohort study aimed at investigating the safety and effectiveness of InO in adult patients with R/R B-ALL treated at 12 Korean hospitals. Patients received InO under real-world conditions according to the approved Korean prescribing information.

The study was approved by institutional review boards from each participating institution, and patients provided informed consent for the use of their medical records. It was conducted in accordance with International Society for Pharmacoepidemiology, Good Epidemiological Practice guidelines issued by the International Epidemiological Association, Pharmaceutical Research and Manufacturers Association guidelines, and Korea PMS regulations and/or guidelines. This study was registered in ClinicalTrials.gov under the identifier NCT04307134.

The primary objective was to identify and evaluate serious adverse events (SAEs), ADRs, known ADRs, non-serious ADRs, and additional safety and effectiveness data.

Patients who met all the following inclusion criteria and no exclusion criteria will be eligible for registration.

#### Inclusion criteria

Patients must meet all of the following inclusion criteria to be eligible for inclusion in the study:

1. Patients diagnosed as relapsed or refractory B-cell precursor lymphoblastic leukemia (ALL).
2. Evidence of a personally signed and dated informed consent document indicating that the patient (or a legally acceptable representative) has been informed of all pertinent aspects of the study.

#### Exclusion criteria

Patients meeting any of the following criteria will not be included in the study:

1. Any patients who does not agree that Pfizer and companies working with Pfizer use his/her information.
2. Patients to whom InO is contraindicated as per the local labeling.

### Data collection

The study investigators, who were treating physicians, conducted follow-up assessments and collected data at each site visit for administration of InO. The electronic health record served as the source document, and study data were recorded using an electronic case report form.

For each patient, the observation period extended from the date of informed consent to the last date of available follow-up. The end of the observation period was required to be at least 28 days after the last dose of InO.

The data collection period was from July 09, 2020 to December 24, 2024.

### Treatment schedule

For the first cycle, the recommended total dose of InO for all patients was 1.8 mg/m² per cycle, administered as three divided doses on Day 1 (0.8 mg/m²), Day 8 (0.5 mg/m²), and Day 15 (0.5 mg/m²). Cycle 1 was three weeks in duration but could have been extended to four weeks if the patient achieved a CR/CRi, and/or to allow recovery from toxicity.

For subsequent cycles, patients who achieved a CR/CRi, received a recommended total dose of 1.5 mg/m² per cycle, administered as three divided doses on Day 1 (0.5 mg/m²), Day 8 (0.5 mg/m²), and Day 15 (0.5 mg/m²). Subsequent cycles were four weeks in duration. In contrast, in patients who did not achieve a CR/CRi, the recommended total dose of InO was 1.8 mg/m² per cycle given as three divided doses on Day 1 (0.8 mg/m²), Day 8 (0.5 mg/m²), and Day 15 (0.5 mg/m²). Subsequent cycles were four weeks in duration. Patients who did not achieve a CR/CRi within three cycles were advised to discontinue treatment.

### Safety evaluation

Safety assessments were conducted in all patients who received at least one dose of InO and completed safety follow-up. AEs were categorized by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0 [34], and were analyzed by incidence, frequency, and relevant patient and treatment factors. Off-label use was excluded from the primary safety analysis set.

An AE was defined as any undesirable medical occurrence in a patient receiving InO, regardless of its causal relationship to the treatment. AEs included abnormal test findings, clinically significant symptoms, hypersensitivity, disease progression, lack of efficacy, drug abuse, or dependency. They could also have resulted from overdose, withdrawal, misuse, off-label use, drug interactions, extravasation, pregnancy or breastfeeding exposure, medication errors, or occupational exposure. An abnormal test finding qualifies as an AE if it was symptomatic, required further diagnostic testing or intervention, led to treatment modification, or was deemed an AE by the investigator. Routine test repetitions or errors did not constitute AEs.

An SAE was defined as any medical occurrence in a patient who received InO that resulted in death, was life-threatening, required or prolonged hospitalization, caused significant disability/incapacity, led to a congenital anomaly/birth defect, or was considered medically important.

The investigator assessed the causal relationship of each AE to InO using the World Health Organization–Uppsala Monitoring Centre (WHO-UMC) causality categories: Certain, Probable/Likely, Possible, Unlikely, Conditional/Unclassified, and Unassessable/Unclassifiable. Events not classified as "Unlikely" were considered ADRs.

### Effectiveness evaluation

Effectiveness was assessed according to the National Comprehensive Cancer Network (NCCN) Guideline Version 2.2016 for Acute Lymphoblastic Leukemia [35]. Hematologic response (CR, CRi, refractory, progressive, and relapsed disease) was evaluated after each cycle and at final assessment, and results were summarized descriptively.

### Statistical analysis

The sample size was calculated based on safety information from previous clinical trials and the prevalence of R/R B-ALL in Korea. At least 100 patients were planned for enrollment.

The safety analysis investigated AE occurrence in relation to baseline subject factors and treatment factors to identify potential safety influences. AEs were coded with the Medical Dictionary for Regulatory Activities Version 27.1. Subgroup analyses were conducted using chi-square ($X^2$) tests, Fisher's exact test, or a logistic regression model, if required.

Effectiveness parameters were summarized descriptively. Kaplan-Meier methods were used to calculate the median survival times (with corresponding 95% CIs) to plot curves for PFS, OS, and DoR. PFS was defined as the time from enrollment to the earliest occurrence of death, refractory disease, progressive disease, or relapsed disease. OS was defined as the time from the date of enrollment to death from any cause; patients last known to be alive were censored at the date of study completion or discontinuation. DoR was defined as the time from the date of first response (CR/CRi by investigator assessment) to the date of a PFS event. Responders without a PFS event were censored at the date of the last valid disease assessment, including any follow-up assessments.

## Results

### Baseline characteristics—patient disposition

A total of 108 patients were enrolled in the study. Of these, one patient was excluded from the safety analysis set ($N=107$) due to a violation of the inclusion or exclusion

criteria. Among the 107 patients in the safety analysis set, 13 patients were further excluded from the effectiveness analysis set ($N=94$) because they did not have any response evaluations (Figure S1).

## Patient demographics

The safety analysis population (Table 1) had a median age of 46.0 years (range: 19.0–83.0). Patients aged 55 years or older accounted for 29.9% ($n=32$) of the cohort, while those younger than 55 made up 70.1% ($n=75$). The study population was 60.8% male ($n=65$) and 39.3% female ($n=42$). Median height and weight were 166.4 cm (range: 143.0–185.0) and 61.0 kg (range: 41.0–135.1), respectively, with two patients missing both measurements. The median BSA was 1.7 m² (range: 1.3–2.6). No patients were pregnant or breastfeeding during the study. Pregnancy and breastfeeding data were not applicable for 60.8% ($n=65$) of patients, while 39.3% ($n=42$) were confirmed to be neither pregnant nor breastfeeding.

Regarding cytogenetic status, 32.7% ($n=35$) of patients had Ph+B-cell ALL, while 67.3% ($n=72$) had Ph−B-cell ALL. Disease duration varied widely, with a median of 416.0 days (range: 32.0–2816.0). The majority of patients experienced first relapsed disease (55.1%, $n=59$), while 28.0% ($n=30$) had a second relapse, and 8.4% ($n=9$) had a third or later relapse. Refractory disease was reported in 8.4% ($n=9$) of patients. All 107 patients (100%) had received prior systemic therapy. The number of previous systemic therapies ranged from 1.0 to 12.0, with a median of 4.0. No patients had prior exposure to chimeric antigen receptor T-cell (CAR-T) therapy. CR/CRi responses had been observed in 88 patients during prior induction therapy. The duration of first CR following previous induction therapy was assessable in 86 patients, with a median of 8.3 months (range, 0.0–62.1 months). Among these, 51 patients had a remission duration of less than 12 months, while 35 maintained remission for 12 months or longer.

Comorbid conditions were also evaluated. A total of 21.5% ($n=23$) of patients had a hepatic disorder and 6.5% ($n=7$) presented with a renal disorder. The remaining 78.5% ($n=84$) and 93.5% ($n=100$) of patients, respectively, had no documented hepatic or renal impairments. In addition, a total of 58 patients (54.2%) had previously undergone allo-HSCT, while 49 (45.8%) had not.

## Treatments (or exposure)

The total number of InO cycles was calculated based on patients who received at least one dose in their final treatment cycle. Among the 107 patients in the safety analysis population (Table 2), the median InO administration period was 43.0 days (range: 1.0–224.0 days). The median number of treatment cycles was 2.0 (range: 1.0–6.0 cycles). Most patients received two treatment cycles (58.9%, $n=63$), while 25.2% ($n=27$) received only one cycle. A smaller proportion of patients underwent three cycles (11.2%, $n=12$), four cycles (2.8%, $n=3$), five cycles (0.9%, $n=1$), or six cycles (0.9%, $n=1$). The median total dose of InO administered was 5.3 mg (range: 0.7–17.1 mg).

Among the 107 patients, 91 received InO monotherapy, while 16 patients received concomitant medications for the treatment of B-ALL. The most reported concomitant medications were methotrexate ($n=8$), cytarabine ($n=6$), and hydroxycarbamide ($n=5$). Notably, one patient with Ph+ALL received the TKI ponatinib for 19 days in combination therapy.

## Safety

### Adverse events

In a safety analysis of 107 subjects (Table 3), frequently reported AEs included hematologic (58.9%), infectious (50.5%), gastrointestinal (45.8%), and general disorders (38.3%). Frequent hematologic AEs included neutropenia (27.1%) and febrile neutropenia (26.2%). Common infections were bacteremia and COVID-19 (each 9.4%). Gastrointestinal issues mainly consisted of nausea (23.4%) and diarrhea (17.8%). Laboratory abnormalities, such as platelet count decrease (25.2%) and elevated liver function test (22.4%) were noted, with platelet decreases frequently considered drug-related (17.8%). Other categories (skin, musculoskeletal, metabolism, respiratory, nervous systems) showed moderate to low incidences. VOD-related adverse events were reported in four patients (3.7%), including three cases (2.8%) of VOD and one case (0.9%) of veno-occlusive liver disease.

A supplementary analysis was conducted to evaluate the onset timing of AEs, focusing on those that occurred within 28 days from the first to the last administration of InO. Of the 845 AEs collected, 602 were included in this analysis. The incidence of AEs following each treatment cycle was 83.2% (89/107 patients) following Cycle 1 and 48.6% (52/107 patients) following Cycle 2 (Table S2). Most hematologic toxicity-related AEs were observed after Cycle 1. Treatment interruption due to AEs, either temporary or permanent, occurred in 20.6% of patients ($n=22$), while dose reduction was reported in 0.9% of patients ($n=1$).

### Serious adverse events

SAEs occurred in 31.8% patients ($n=34$), with the most frequently reported SAEs being infections and infestations

**Table 1** Baseline demographics

| | Safety Set ($N=107$) *n* (%) |
|---|---|
| Age (years) | |
| N | 107 |
| Median (Range) | 46.0 (19.0–83.0) |
| Elderly (≥55 years) | |
| <55 years | 75 (70.1) |
| ≥55 years | 32 (29.9) |
| Gender | |
| Male | 65 (60.8) |
| Female | 42 (39.3) |
| Height (cm) | |
| N | 105 |
| Median (Range) | 166.4 (143.0–185.0) |
| Missing | 2 |
| Weight (kg) | |
| N | 105 |
| Median (Range) | 61.0 (41.0–135.1) |
| Missing | 2 |
| Body Surface Area ($m^2$) | |
| N | 105 |
| Median (Range) | 1.7 (1.3–2.6) |
| Missing | 2 |
| Pregnancy | |
| Yes | 0 (0.00) |
| No | 42 (39.3) |
| NA | 65 (60.8) |
| Breastfeeding | |
| Yes | 0 (0.00) |
| No | 42 (39.3) |
| NA | 65 (60.8) |
| Cytogenetics | |
| Philadelphia (+) B-cell ALL | 35 (32.7) |
| Philadelphia (-) B-cell ALL | 72 (67.3) |
| Unknown | 0 (0.00) |
| Duration of disease (day) | |
| N | 105 |
| Median (Range) | 416.0 (32.0–2816.0) |
| Missing | 2 |
| Current disease status | |
| Refractory | 9 (8.4) |
| First relapsed | 59 (55.1) |
| Second relapsed | 30 (28.0) |
| Third or more relapsed | 9 (8.4) |
| Number of previous systemic therapies | |
| N | 107 |
| Median (Range) | 4.0 (1.0–12.0) |
| Time since last systemic therapy (months) | |
| N | 105 |
| Median (Range) | 1.4 (0.0–40.3.0.3) |
| Missing | 2 |
| Duration of first CR (months) | |
| N | 86 |
| Median (Range) | 8.3 (0.0–62.1.0.1) |
| <12 months | 51 (58.0) |
| ≥12 months | 35 (39.8) |

**Table 1** (continued)

| | Safety Set ($N=107$) *n* (%) |
|---|---|
| Hepatic disorder | |
| Yes | 23 (21.5) |
| No | 84 (78.5) |
| Renal disorder | |
| Yes | 7 (6.5) |
| No | 100 (93.5) |
| Previous allo-HSCT | |
| Yes | 58 (54.2) |
| No | 49 (45.8) |

**Table 2** Exposure data

| | Safety Set ($N=107$) *n* (%) |
|---|---|
| Inotuzumab ozogamicin total administration period (day) | |
| n | 107 |
| Median (Range) | 43.0 (1.0–224.0) |
| Number of Inotuzumab ozogamicin cycle | |
| n | 107 |
| Median (Range) | 2.0 (1.0–6.0) |
| Total Inotuzumab ozogamicin administration cycle | |
| Cycle 1 | 27 (25.2) |
| Cycle 2 | 63 (58.9) |
| Cycle 3 | 12 (11.2) |
| Cycle 4 | 3 (2.8) |
| Cycle 5 | 1 (0.9) |
| Cycle 6 | 1 (0.9) |
| Total Inotuzumab ozogamicin administration dose (mg) | |
| n | 107 |
| Median (Range) | 5.3 (0.7–17.1) |

(Table 3 & Table S1), reported in 19.6% of subjects, predominantly septic shock (6.5%) and pneumonia (4.7%). Other significant SAEs included neoplasm progression (6.5%), immune system disorders related to graft-versus-host disease (4.7%), and gastrointestinal disorders (2.8%). Two cases (1.9%) of VOD were classified as SAEs.

When adverse events were graded by CTCAE, infections and infestations were high in frequency; there were ten events in grade 3, five in grade 4, and thirteen as grade 5 (Table 3). Among these, pneumonia accounted for five fatal events, while septic shock accounted for three fatal events. Gastrointestinal disorders accounted for two grade 3 events and two grade 4 events, including necrotizing colitis and vomiting. Immune system disorders recorded six grade 3 events and one grade 5 due to acute and chronic graft-versus-host disease affecting the liver, lung, or gastrointestinal tract. Neoplasm progression (ALL disease progression) recorded seven grade 5 events. Importantly, VOD recorded one grade 2, one grade 3, and one grade 5 event.

### Adverse drug reactions

The most frequent ADRs were hematologic AEs (25.2%), specifically cytopenia, neutropenia and thrombocytopenia, as well as laboratory abnormalities (26.2%), which included liver enzyme elevations (Table 4). Gastrointestinal ADRs, primarily nausea, occurred in 13.1% of patients, while metabolic disturbances, such as decreased appetite and hypokalemia, were also relatively common. However, other organ-specific ADRs, including nervous system, musculoskeletal, and skin disorders were rare.

### Serious adverse drug reactions

Serious ADRs were relatively rare (Table 4), occurring in only 3.7% (4 patients) of the safety population with individual incidences occurring in ≤ 1% of patients. No ADRs were reported at grade 1 or grade 2 severity (Table 4). The most notable serious ADRs involved hepatic failure, consistent with known InO-associated hepatotoxicity, and cytopenia, consistent with known hematologic toxicity, with isolated cases of renal and gastrointestinal system disorders.

## Effectiveness

### Best overall response (BOR)

In the effectiveness analysis set ($N=94$), the BOR—defined as a CR or a CRi at any point during treatment—showed that 74 patients (78.7%, 95% CI: 69.1–86.5%) achieved CR/CRi.

When stratified by cytogenetic status at diagnosis, the CR/CRi rate was 73.3% (22/30) in patients with Ph + B-cell ALL and 81.3% (52/64) in those with Ph– B-cell ALL. The difference in BOR between the diagnostic groups was not statistically significant ($p=0.3820$).

To further explore differences across patient subgroups, we conducted a comparative analysis between our real-world study and the INO-VATE trial, extending the evaluation of

**Table 3** Incidence of treatment-emergent adverse events

| Adverse Events | | |
|---|---|---|
| System Organ Class | Patients with AEs, *n* (%) | Most Common AEs with frequency > 20% (%) |
| Blood and lymphatic system disorders | 63 (58.9%) | Neutropenia (27.1%), Febrile neutropenia (26.2%) |
| Gastrointestinal disorders | 49 (45.8%) | Nausea (23.4%) |
| Investigations (Lab test abnormalities) | 48 (44.9%) | Platelet count decreased (25.2%), Liver function test increased (22.4%) |
| General disorders and administration site conditions | 41 (38.3%) | Pyrexia (27.1%) |
| Serious Adverse Events | | |
| System Organ Class | Patients with SAEs, *n* (%) | Most Common SAEs with frequency > 2% (%) |
| Infections and infestations | 21 (19.6%) | Septic shock (6.5%), Pneumonia (4.7%), Pyelonephritis acute (2.8%) |
| Neoplasms (benign, malignant, unspecified) | 7 (6.5%) | Neoplasm progression (6.5%) |
| Grade 5 (Fatal) Adverse Events | | |
| System Organ Class | Patients with Grade 5 (Fatal) events, *n* (%) | Events (%) |
| Infections and infestations | 11 (10.3%) | Pneumonia (4.7%), Septic shock (2.8%), Pyelonephritis acute (0.9%), Sepsis (0.9%), Bacteremia (0.9%), Bacterial infection (0.9%), Device-related infection (0.9%) |
| Metabolism and nutrition disorders | 1 (0.9%) | Tumor lysis syndrome (0.9%) |
| Respiratory, thoracic, and mediastinal disorders | 1 (0.9%) | Acute respiratory distress syndrome (0.9%) |
| Nervous system disorders | 2 (1.9%) | Cerebral infarction (0.9%), Hemorrhage intracranial (0.9%) |
| Immune system disorders | 1 (0.9%) | Acute graft-versus-host disease in intestine (0.9%) |
| Neoplasms benign, malignant, and unspecified | 7 (6.5%) | Neoplasm progression (6.5%) |
| Vascular disorders | 1 (0.9%) | Veno-occlusive disease (0.9%) |
| Hepatobiliary disorders | 1 (0.9%) | Hepatic failure (0.9%) |

**Table 4** Incidence of treatment-emergent adverse drug reactions

| Adverse Drug Reactions | | |
|---|---|---|
| System Organ Class | Patients with ADRs, *n* (%) | Most Common ADRs with > 1% Incidence (%) |
| Investigations (Laboratory abnormalities) | 28 (26.2%) | Platelet count decreased (17.8%), Liver function test increased (12.2%), Neutrophil count decreased (7.5%), Weight decreased (1.9%) |
| Blood and lymphatic system disorders | 27 (25.2%) | Neutropenia (9.4%), Febrile neutropenia (5.6%), Anemia (6.5%), Thrombocytopenia (3.7%), Cytopenia (2.8%) |
| Gastrointestinal disorders | 14 (13.1%) | Nausea (9.4%), Dyspepsia (3.7%), Stomatitis (2.8%), Vomiting (1.9%), Diarrhea (1.9%) |
| Metabolism and nutrition disorders | 8 (7.5%) | Decreased appetite (4.7%), Hypokalemia (2.8%) |
| General disorders and administration site conditions | 6 (5.6%) | Pyrexia (2.8%) |
| Nervous system disorders | 3 (2.8%) | Dizziness (1.9%) |
| Serious Adverse Drug Reactions | | |
| System Organ Class | Serious ADRs n (%) | Serious ADRs (%) |
| Infections and infestations | 1 (0.9%) | Septic shock (0.9%) |
| Hepatobiliary disorders | 1 (0.9%) | Hepatic failure (0.9%) |
| Blood and lymphatic system disorders | 1 (0.9%) | Cytopenia (0.9%) |
| Renal and urinary disorders | 1 (0.9%) | Hematuria (0.9%) |
| Gastrointestinal disorders | 1 (0.9%) | Stomatitis (0.9%) |
| Adverse Drug Reactions (Grade 3 to 5) | | |
| System Organ Class | Patients who had Grade 3–5 adverse events n (%) | Grade 3–5 adverse events (grade) |
| Gastrointestinal disorders | 1 (0.9%) | *Stomatitis (G3)* |
| Blood and lymphatic system disorders | 1 (0.9%) | *Cytopenia (G4)* |
| Infections and infestations | 1 (0.9%) | *Septic shock (G3)* |
| Renal and urinary disorders | 1 (0.9%) | *Hematuria (G3)* |
| Hepatobiliary disorders | 1 (0.9%) | *Hepatic failure (G5)* |

BOR by categorical factors (Figure S2). BOR rates among all patients were similar between studies, with a non-significant difference of −2.0% (95% CI: −13.1 to 9.1; $P=0.7220$). Among patients aged ≥ 55 years, our study showed a higher BOR rate of 92.3% compared to 81.4% in INO-VATE, producing a rate difference of + 10.9% (95% CI: −4.6 to 26.4; $P=0.2121$) but it was not statistically significant. In contrast, among patients < 55 years, our study showed a lower BOR rate of 73.5% compared to 80.3% in INO-VATE, with a non-significant difference of −6.8% (95% CI: −21.0 to 7.4; $P=0.3526$). Patients without a prior transplant showed similar BOR rate (84.4% vs. 81.5% in INO-VATE) with a + 2.9% difference (95% CI: −10.3 to 16.2; $P=0.6725$).

Likewise, patients with a prior transplant had similar BOR rates between the two studies; PMS 73.5% vs. 76.5% with a difference of −3.0% (95% CI: −26.7 to 20.7; $P=0.8074$).

### Progression-free survival

In the effectiveness analysis set ($N=94$), a total of 39 events occurred, defined as death, refractory disease, progressive disease, or relapse (Fig. 1). Patients who had not experienced an event at the time of analysis were censored. The median PFS was 3.6 months (95% CI: 3.0–4.7 months). When stratified by cytogenetic status at diagnosis, the median PFS was 3.6 months (95% CI: 1.5–3.7 months) among patients with Ph + B-cell ALL ($n=30$), while in patients with Ph − B-cell ALL ($n=64$), the median PFS was 4.7 months (95% CI: 3.0–5.4 months). The difference in PFS between the two groups was statistically significant ($p=0.0266$) (Fig. 2).

The median follow-up duration, based on the 94 patients included in the effectiveness analysis, was 88.0 days (range: 33.0–311.0).

### Overall survival

In the effectiveness analysis set ($N=94$), a total of 17 patients (18.1%) died during the study period, while 77 patients (81.9%) remained alive (censored) at the time of analysis (Fig. 1). The median OS was 10.2 months (95% CI: 6.0–NA months). When stratified by cytogenetic status at diagnosis, the median was not reached (NA) in the Ph + B-cell ALL group (95% CI: 4.0–NA months), whereas it was 10.2 months (95% CI: 6.0–NA) in the Ph − B-cell ALL group. The difference in OS between the groups was not statistically significant ($p=0.4746$) (Fig. 2).

The median duration of the post-treatment period following the completion of InO therapy was 29.0 days (range: 0.0–259.0). The post-treatment period was defined as the period from the last InO administration date to the last follow-up date for each patient. A total of 24 patients (25.5%) were confirmed to have undergone allo-HSCT after InO treatment. Subsequent therapies were reported in 41 patients, with the most administered agents including cytarabine ($n=10$), hydroxycarbamide ($n=6$), mercaptopurine ($n=6$), blinatumomab ($n=5$), and ponatinib ($n=3$) (Table 5).

### Duration of remission

The median DoR was 3.8 months (95% CI: 3.0–5.4 months). Of the 94 patients in the effectiveness set, 74 achieved CR/CRi. Among these, 18 (24.3%) experienced a PFS event after achieving CR/CRi, while the remaining 56 patients (75.7%) were censored. When stratified by cytogenetic status at diagnosis, the median DoR was 3.0 months (95% CI: 1.3–NA months) in the Ph + B-ALL group ($n=22$), and 4.2 months (95% CI: 3.3–6.0 months) in the Ph − B-ALL group ($n=52$). The difference in DoR between the two groups was statistically significant ($p=0.0296$) (Fig. 2).

## Discussion

Our analysis of approximately 5 years of PMS data on the safety and effectiveness of InO offers valuable clinical insights into the real-world management of R/R B-cell precursor ALL. Variations in outcomes compared to similar studies are likely driven by differences in baseline characteristics, disease burden, and overall health status at the time of treatment initiation. A key distinction from the INO-VATE trial lies in the prior systemic therapies: whereas INO-VATE trial included R/R B-cell precursor ALL patients who received the first or second salvage treatment, our study did not limit the number of previous treatments. This explains why our median number of previous therapies is four, which would have affected both safety and effectiveness outcomes in this PMS. Additionally, the prevalence of Ph + B-cell ALL was higher in our cohort (32.7% vs. 13.0%), further reflecting a higher-risk group. Hepatic (21.5%) and renal (6.5%) comorbidities were also observed in our population, which may have influenced both safety and response outcomes. Despite these differences, patient demographics were generally comparable between studies, with similar median ages (46 vs. 47 years) and gender distribution, though our study included a slightly higher proportion of male patients (60.8% vs. 56.0%) [17].

In terms of PFS, we observed a median PFS of 3.6 months compared to 5.0 months in the INO-VATE trial, and we also confirmed a comparable median DoR (3.8 months vs. 4.6 months) [7]. Among the 94 subjects in this PMS effectiveness set, the median DoR for the 74 who achieved CR/CRi was 3.8 months (95% CI: 3.0–5.4). This is comparable to the INO-VATE trial, where the median DoR was 4.6 months (95% CI: 3.9–5.4) in 85 of 164 subjects treated with InO who achieved CR/CRi.

However, the median OS achieved in our PMS study is longer than that reported in INO-VATE; 10.2 months vs. 7.7 months with an upper CI that was not estimable (Fig. 1). Further, this 2.5-month increase represents a 32% relative improvement. In aggressive hematologic malignancies like R/R ALL, even modest gains in survival can have a substantial impact.

In addition, the findings from our PMS study are consistent with previously reported real-world data. In terms of BOR, the CR/CRi rate of 78.7% observed in our cohort exceeds that reported in the Italian INO-CD22 study (74.0%), the Spanish compassionate program (64%), and the US RWE study (63%) [29–31]. Furthermore, the median OS of 10.2 months in our

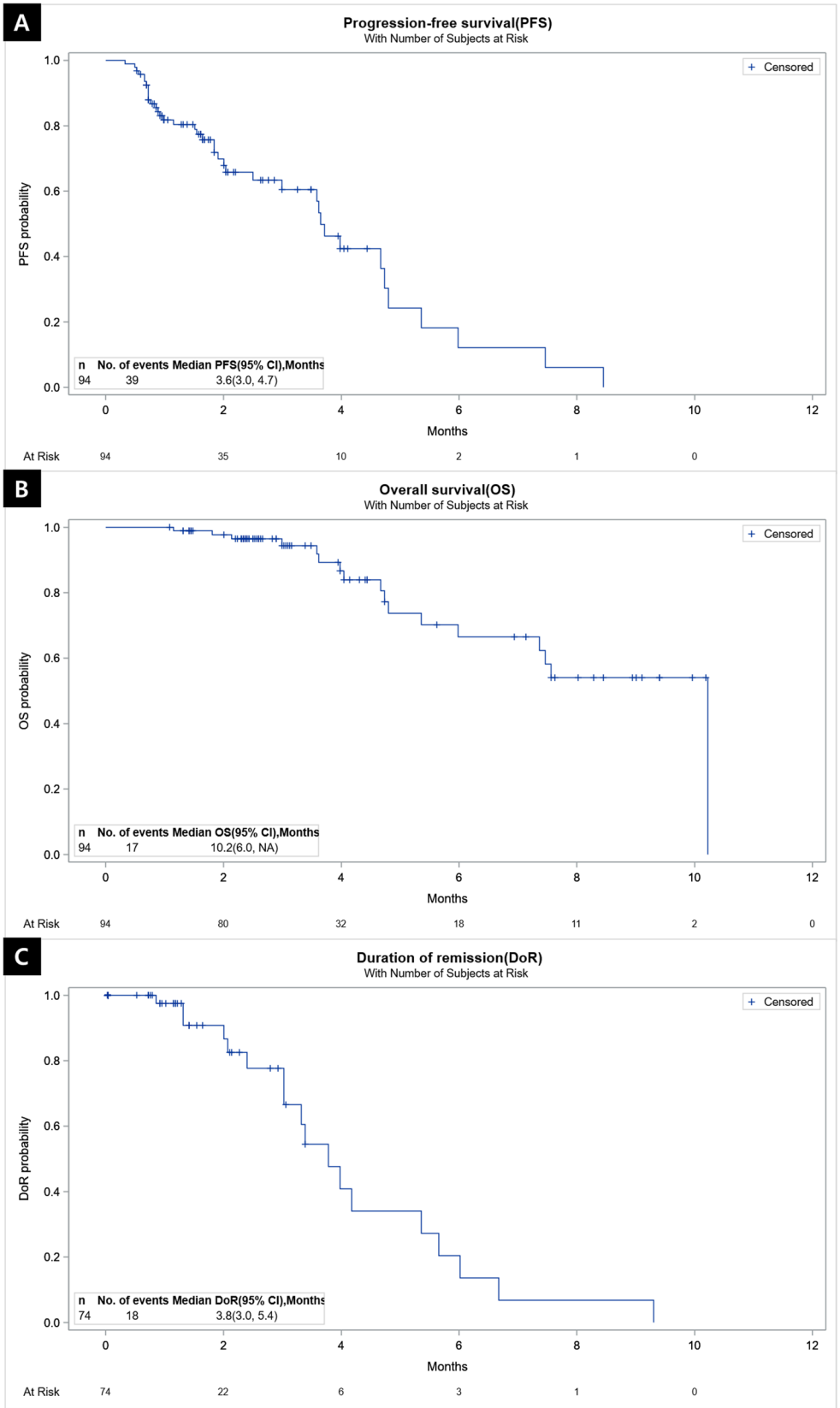


**Fig. 1** Kaplan–Meier survival curves in the effectiveness analysis set: (**A**) PFS, (**B**) OS and (**C**)

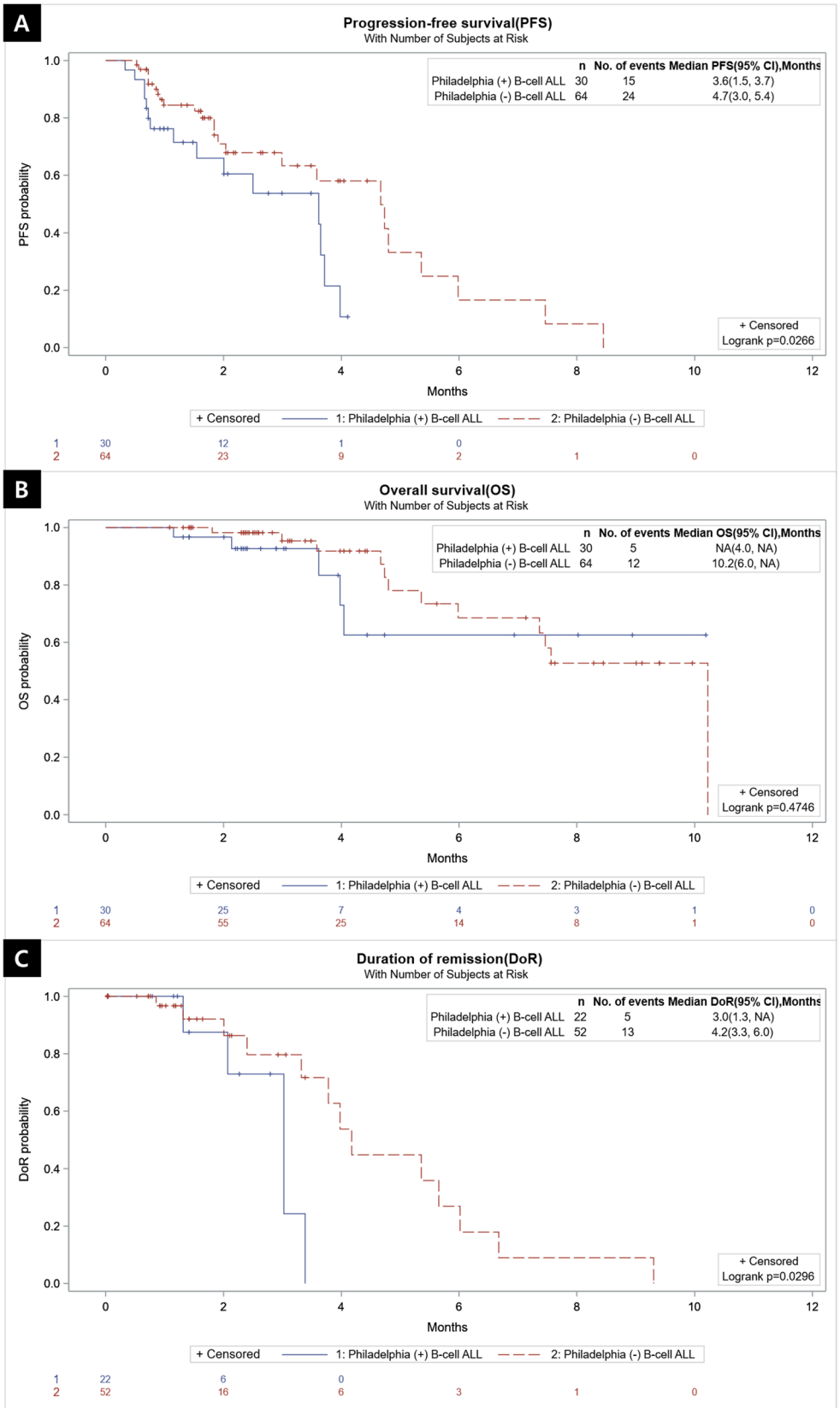


**Fig. 2** Kaplan–Meier survival curves stratified by cytogenetic status at diagnosis: (**A**) PFS, (**B**) OS, and (**C**) DoR in Ph + vs. Ph − B-cell ALL patients

**Table 5** Subsequent therapy

| Treatment | Safety set ($N=107$) *n* (%) |
|---|---|
| Allo-HSCT | 24 (25.5) |
| Cytarabine | 10 (9.3) |
| Fludarabine | 10 (9.3) |
| Methotrexate | 9 (8.4) |
| Hydroxycarbamide | 6 (5.6) |
| Mercaptopurine | 6 (5.6) |
| Blinatumomab | 5 (4.7) |
| Busulfan | 4 (3.7) |
| Etoposide | 3 (2.8) |
| Idarubicin | 3 (2.8) |
| Mitoxantrone | 3 (2.8) |
| Ponatinib | 3 (2.8) |
| Asparaginase | 1 (0.9) |
| Cyclophosphamide | 1 (0.9) |
| Melphalan | 1 (0.9) |
| Vincristine | 1 (0.9) |
| Total | **41 (38.3)** |

PMS population represents a favorable outcome compared to the Italian INO-CD22 study (7.9 months) and the Spanish compassionate program outcome (4.0 months) and is comparable to the US RWE data (11.6 months) [29–31]. These comparisons underscore the clinical relevance of our findings and support the effectiveness of InO in real-world settings.

Although the differences in PFS and DoR between the Ph+and Ph−B-cell ALL subgroups are statistically significant ($p=0.0266$ and $p=0.0296$, respectively), the absolute differences in median values are relatively small (1.1 months for PFS and 1.2 months for DoR). Given the overall short survival durations in both groups and the limited clinical impact of such marginal differences on treatment decision-making or patient outcomes, these findings are not considered clinically meaningful. Furthermore, the overlapping confidence intervals and the wide range observed in the Ph+group, particularly for DoR, with an upper bound not estimable, suggest variability that may limit the robustness of the observed statistical significance.

While effectiveness outcomes from this PMS are presented alongside those reported in randomized clinical trials (RCT) of InO, it is important to acknowledge that the inclusion and exclusion criteria between the two study designs are not identical. As such, direct comparisons should be interpreted with caution, and equivalence between the findings cannot be assumed. Furthermore, it should be noted that the real-world data and the RCT data were not collected contemporaneously. Temporal differences between the studies may reflect changes in clinical practice, diagnostic modalities, and supportive care strategies, which could have influenced treatment outcomes. Nevertheless, the real-world data may serve as indirect evidence supporting the clinical effectiveness of InO in a patient population reflective of routine clinical practice.

When comparing SAEs, differences emerge between studies. INO-VATE reports a higher overall SAE rate at 48.0% compared to 31.8% in our study. Infection-related SAEs are prominent in both; our study shows a rate of 19.6%, primarily driven by septic shock (6.5%) and pneumonia (4.7%), while INO-VATE reports significant infection-related SAEs, including pneumonia (4.0%), sepsis (2.0%), and septic shock (1.0%). Neoplasm progression rates are also comparable, with INO-VATE reporting 4.0% versus 6.5%. However, graft-versus-host disease and gastrointestinal disorders are explicitly reported only in our study, with frequencies of 4.7% and 2.8%, respectively, suggesting a potential difference in the proportion of patients undergoing stem cell transplantation or differing clinical management approaches between the two populations [17].

When we analyze continuous predictors of AEs using logistic regression, none of the variables—age, BSA, duration of disease, total administration period, or total dose—show statistically significant associations with AE occurrence. Age (odds ratio [OR] 0.98, $P=0.3509$) and total administration period (OR 0.99, $P=0.3418$) both trends slightly below 1.0, suggesting a potential but non-significant inverse relationship with AE risk. This indicates that neither older age nor longer treatment duration increased risk. Meanwhile, disease duration (OR 1.00, $P=0.8643$) shows no measurable effect, suggesting that baseline illness does not impact susceptibility to AEs.

The occurrence of VOD/SOS is significantly higher in INO-VATE compared with our study; VOD/SOS occurs in 13% of patients treated with InO, compared to less than 1% with SOC. In INO-VATE, liver-related toxicities are the most common non-hematologic AEs of grade 3 or higher following InO treatment [17]. Among those who underwent allo-HCT, the incidence is 22% with InO versus 3% with SOC, and a total of 29% of VOD/SOS cases following InO and allo-HCT result in death [11]. In contrast, our study shows an occurrence of 2.8% (3/107, 3 cases) for VOD, and 0.9% (1/107, 1 case) for veno-occlusive liver disease in all patients. One VOD case (grade 5) is classified as “Fatal” and “Not recovered”; one VOD case (grade 3) is classified as “Not recovered”; one VOD case (grade 2) and one veno-occlusive liver disease (grade 3) are classified as “recovered”. However, not only are the four cases not ADRs, but the investigators assessed that there is no causal relationship with InO. They conclude that factors, such as ALL or allo-HCT, are more likely associated with VOD. Similarly, Senapati, et al. report that allo-HSCT is significantly associated with higher odds of VOD in univariate analysis (OR 3.5, 95% CI: 1.5–8.2), but this association is not significant in multivariate analysis. They suggest that strategies, such as dose fractionation of InO, avoiding simultaneous use of azole antifungals, and using ursodiol prophylaxis during InO treatment and around the allo-HSCT period may help reduce the risk [36].

In addition, compared to other real-world studies, our Korea PMS study shows a relatively lower incidence of VOD/SOS (3.7%), with only one fatal case. Liver function test abnormalities are observed in 22.4% of patients, including elevated AST (4.7%), ALT (2.8%), and hyperbilirubinemia (0.9%), which does not represent a notably high rate of hepatotoxicity. In contrast, the Italian INO-CD22 study reports a VOD/SOS incidence of 10.9%, mostly post-HSCT; the Spanish compassionate program observes 9% grade 3–4 SOS post-HSCT; and the US RWE study reports hepatotoxicity in 46% of patients, including 4% VOD and 25% transaminase elevation [29–31]. Taken together, our PMS findings support current guidelines recommending close monitoring for hepatotoxicity, including VOD/SOS, following InO administration.

In terms of ADRs, both the INO-VATE trial and our study show that hematologic and liver-related toxicities are the most frequent, although INO-VATE reports higher rates. Febrile neutropenia, thrombocytopenia, and elevated liver enzymes (AST, ALT, and bilirubin) are more common in INO-VATE, with febrile neutropenia occurring in 12% and thrombocytopenia in 37% of patients, exceeding our rates of 5.6% and 3.7%, respectively. Pyrexia and nausea are reported at much lower rates in INO-VATE (3% and 1%, respectively) compared to 2.8% and 9.4% in our data [7]. Additionally, our data capture milder or less frequently reported ADRs, such as dizziness, decreased appetite, dyspepsia, and musculoskeletal pain, which are not listed in INO-VATE. This suggests real-world monitoring may elucidate and focus on a broader spectrum of ADRs arising from general safety monitoring, whereas the INO-VATE data highlights those more likely to be reported as part of clinical trial protocols [9].

Our study has several limitations. As a non-interventional, observational study conducted in routine clinical practice, it is susceptible to selection bias, confounding factors, and missing data. The absence of a comparator group limits the ability to fully interpret the effectiveness outcomes. Additionally, the lack of restrictions on concomitant treatments for the indication may introduce variability in patient management and outcomes.

## Conclusion

This PMS study supports the clinical utility and safety profile of InO for Korean patients with R/R B-cell precursor ALL in routine practice. While outcomes are generally consistent with previous reports, interpretation should consider differences in patient characteristics and study design. As a PMS study, limitations such as lack of a comparator group, potential selection bias, and variability in concomitant treatments may affect the generalizability of findings.

**Supplementary Information** The online version contains supplementary material available at https://doi.org/10.1007/s00277-026-06838-z.

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**Author contributions** SL, JY, JL, DY, JC, JB, KY, and JW reviewed the study design and data collection instruments. SL, JY, JL, DY, JC, JB, and KY conducted the study and investigation process, and data/evidence collection. JW managed and coordinated the study activity planning and execution. YK coordinated the research activity planning and data collection. All authors reviewed the analysis result and the original manuscript draft. All authors have read and approved the final version of the manuscript.

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**Data availability** The data supporting the findings of this study are available from the corresponding author upon reasonable request.

## Declarations

**Ethical approval** This study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Boards at all participating centers.

**Informed consent** Written informed consent was obtained from all patients prior to participation.

**Competing interests** The authors declare no competing interests.



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