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Inaticabtagene Autoleucel (CNCT19) in adult relapsed or refractory B-cell acute lymphoblastic leukemia

Tracking no: ADV-2024-014182R3

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Abstract:
Prior to November 2023, CD19 CAR-T therapies had not been approved in China for patients with relapsed or refractory B-cell acute lymphoblastic leukemia (r/r B-ALL), leaving a significant unmet need. In response, Inaticabtagene Autoleucel (Inati-cel), a novel CD19 CAR-T therapy with a distinct scFv (HI19α), was developed and showed promising efficacy in preliminary clinical research. We conducted a phase 2, single-arm, multicenter study of Inati-cel in adult CD19+ r/r B-ALL in China. The primary endpoint was the overall remission rate (ORR) at the end of Month 3. Forty-eight patients who underwent Inati-cel infusion were evaluated for both efficacy and safety. Among them, thirty-four patients achieved and maintained remission beyond 3 months, with 3-month ORR of 70.8% (95%CI, 55.9-83.1). The best ORR was 85.4% with all responders reaching minimal residual disease (MRD) negativity. With median follow-up of 23.7 months, the median DOR was 20.7 months (95%CI, 6.4-not reached), and the median OS was not reached (95%CI, 13.0 months-not reached). Additionally, grade 3 or higher cytokine release syndrome and neurologic events occurred in 12.5% and 6.2% of patients respectively. The 2-year follow-up data suggest that Inati-cel demonstrated an encouraging and durable responses with manageable safety profiles in r/r B-ALL. Based on the data from this pivotal trial, Inati-cel was approved as the first CAR-T therapy for adult r/r B-ALL in China and underscores its potential therapeutic benefits for this patient population. NCT04684147

Conflict of interest: COI declared - see note

COI notes: Disclosures: Jianxiang Wang, Advisor of Abbvie. Lulu Lv, Jienan Ren, Yi Feng, Yan Zhou and Yiping Deng own stock option of Juventas Cell Therapy Ltd.. All other authors declare no competing interests.

Preprint server: No;

Author contributions and disclosures: Ying Wang: designed research, performed research, data interpretation, writing-review editing, data supervision, and validation (directly accessed and verified the underlying data reported in the manuscript). Lulu Lv: designed research, performed research, writing-review editing (directly accessed and verified the underlying data reported in the manuscript). Yongping Song: designed research, data interpretation, writing-review editing. Xudong Wei: performed research, data interpretation, writing-review editing. Hongsheng Zhou: performed research, data interpretation, writing-review editing. Qifa Liu: performed research, data interpretation, writing-review editing. Kailin Xu: performed research, data interpretation, and writing-review editing. Dongmei Yan: performed research, data interpretation, writing-review editing. Cheng Zhang: performed research, data interpretation, and writing-review editing. Shuangyou Liu: performed research, data interpretation, writing-review editing. Jie Jin: performed research, data interpretation, and writing review-editing. Heng Mei: performed research, data interpretation, and writing-review editing. Ting Niu: performed research, data interpretation, and writing-review editing. Aibin Liang: designed research, data interpretation, writing-review editing. Runxia Gu: literature search, writing-review editing. Jienan Ren: designed research, performed research, data interpretation, and writing-review editing(directly accessed and verified the underlying data reported in the manuscript). Yi Feng: designed research, performed research, data interpretation, writing-review editing, literature search. Wei Jin: designed research, data analysis, figures (directly accessed and verified the underlying data reported in the manuscript). Yan Zhou: performed research, data collection, and project administration. Yiping Deng: data interpretation, writing-review editing. Jianxiang Wang: designed research, performed research, data interpretation, data-supervision, writing-original draft.

Non-author contributions and disclosures: Yes; Thank to Prof. Ying Yuan (The University of Texas MD Anderson Cancer Center) for advice and assistance in the statistical analysis and result discussion. The authors sincerely thank Zheng Ye, PhD (Shanghai Daotian Evidence-based Technology Co., China) for assisting with language and medical editing. The authors sincerely thank Inati-cel development team members, patients, and their families for their contributions to this clinical trial (HY001201).

Agreement to Share Publication-Related Data and Data Sharing Statement: For original data, please contact wangjx@ihcams.ac.cn.

Clinical trial registration information (if any): Registered with ClincialTrials.gov, NCT04684147.

Original Research Article

Title: Inaticabtagene Autoleucel (CNCT19) in adult relapsed or refractory B-cell acute lymphoblastic leukemia

Running Title: Inati-cel in adult r/r B-ALL

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Word count (Abstract: 229; Main article: 3237)

Figure/table count (Tables: 3; Figures: 2)

Reference count: 22

Data sharing：Please contact wangjx@ihcams.ac.cn.

Key words: Inaticabtagene Autoleucel; CNCT19; leukemia; Trial; CAR-T therapy

Key points:

1. Inati-cel can induce high and durable responses in r/r B-ALL patients with best ORR achieving 85.4% and median DOR being 20.7 months.

2. At the median follow-up of 23.7 months, Inati-cel showed a manageable long-term safety profile and no new safety signal finding.

Abstract:

Prior to November 2023, CD19 CAR-T therapies had not been approved in China for patients with relapsed or refractory B-cell acute lymphoblastic leukemia (r/r B-ALL), leaving a significant unmet need. In response, Inaticabtagene Autoleucel (Inati-cel), a novel CD19 CAR-T therapy with a distinct scFv (HI19α), was developed and showed promising efficacy in preliminary clinical research. We conducted a phase 2, single-arm, multicenter study of Inati-cel in adult CD19+ r/r B-ALL in China. The primary endpoint was the overall remission rate (ORR) at the end of Month 3. Forty-eight patients who underwent Inati-cel infusion were evaluated for both efficacy and safety. Among them, thirty-four patients achieved and maintained remission beyond 3 months, with 3-month ORR of 70.8% (95%CI, 55.9-83.1). The best ORR was 85.4% with all responders reaching minimal residual disease (MRD) negativity. With median follow-up of 23.7 months, the median DOR was 20.7 months (95%CI, 6.4-not reached), and the median OS was not reached (95%CI, 13.0 months-not reached). Additionally, grade 3 or higher cytokine release syndrome and neurologic events occurred in 12.5% and 6.2% of patients respectively. The 2-year follow-up data suggest that Inati-cel demonstrated an encouraging and durable responses with manageable safety profiles in r/r B-ALL. Based on the data from this pivotal trial, Inati-cel was approved as the first CAR-T therapy for adult r/r B-ALL in China and underscores its potential therapeutic benefits for this patient population. NCT04684147

Funding: Juventas Cell Therapy Ltd.

Introduction

Chimeric antigen receptor (CAR) T-cell therapy targeting CD19 has emerged as a promising therapy for relapsed or refractory B-cell acute lymphoid leukemia (r/r B-ALL).[1,2] Promising data from clinical trials, such as ZUMA-3, indicated that 71% of adult patients achieved remission following Brexu-cel infusion.[3] Furthermore, the overall remission rate (ORR) reached 81% among children and young adults who received Tisa-cel infusion in ELIANA trial, underscoring the potential of this therapy for r/r B-ALL.[4] However, as of November 2023, there remains a significant gap in the evaluative data available for the Chinese population, primarily due to the absence of approval for CAR-T cell therapy for r/r B-ALL in China.

Despite the success of CAR-T therapy, questions persist regarding the safety and efficacy of therapies derived from alternative single-chain variable fragments (scFv) in r/r B-ALL. Therefore, we have developed Inaticabtagene Autoleucel (Inati-cel; CNCT19), an autologous CD19-specific CAR T-cell product with scFv derived from HI19α clone. This scFv binds to a different but high-affinity epitope on the CD19 compared to FMC63, as demonstrated in preclinical data.[5] The HI19α scFv was used to construct the CAR T cells (CNCT19) with four other components: CD8 hinge, CD8-α transmembrane, 4-1BB costimulatory domain, and CD3 zeta. Preclinical data showed CNCT19 mediated cytotoxicity and our prior clinical pilot data demonstrated remarkable clinical efficacy,[6,7] prompting the initiation of this phase 2 pivotal study (NCT04684147) to evaluate its safety, effectiveness, and pharmacokinetics in adult patients with r/r B-ALL.

Based on the data from this pivotal trial, Inati-cel was approved as the first CAR-T therapy for adult r/r B-ALL in China.. Furthermore, this study serves as a crucial step towards

enhancing the therapeutic landscape for patients with r/r B-ALL, offering the potential for improved outcomes and extended survival.

Methods

Study design and patients.

This phase 2 of single-arm, multicenter, open-label clinical trial enrolled patients at 10 centers across China. Eligible participants were aged 18 to 65 years old, with Eastern Cooperative Oncology Group (ECOG) performance status of 0-1, diagnosed with relapsed or refractory B- ALL with ≥5% morphological bone marrow blasts at enrollment. Inclusion criteria included primary refractory, first relapse with the first remission lasting less than 12 months, relapsed or refractory after at least two previous lines of systemic therapy, or relapsed or refractory after hematopoietic stem cell transplantation (HSCT). Exclusion criteria included active infection, active central nervous system (CNS) leukemia, and prior receipt of CAR-T cell therapy.

This study adhered to the Declaration of Helsinki and International Conference of Harmonisation guidelines for Good Clinical Practice. Written informed consent was obtained from all patients, and the protocol was approved by the China Center for Drug Evaluation and the institutional review boards of the participating centers. Detailed clinical protocol is provided in the appendix.

Procedures

Eligible patients underwent leukapheresis to obtain T cells for Inati-cel manufacturing. Inati-cel was produced in a CGMP facility by Juventas Cell Therapy (Tianjin, China). T cells were isolated using an antibody-affinity method, transduced with the CD19 CAR lentiviral vector, and cultured in a serum-free medium (OpTmizer). Expansion was achieved using a WAVE bioreactor, and manually filled in sterile cryobags. The manufacturing process takes a median

of 7 days (range 6-10 days) . The median transduction efficiency was 52.2%, with a median proportion of CD3+CD4+ and CD3+CD8+ cell of 47.7% and 49.1%, respectively.

During manufacturing, bridging therapies were permitted to stabilize the patient's condition. All patients underwent lymphodepletion with cyclophosphamide (500 mg/m^2 daily for two days [D-5 and D-4]) and fludarabine (30 mg/m^2 daily for four days [D-5 to D-2]). A single infusion of Inati-cel at a target dose range of 0.4×10^8 to 0.6×10^8 CAR-positive viable T cells was administered. Disease assessment was conducted via bone marrow aspirate.

Outcomes

The primary endpoint was the 3-month ORR, defined as the rate of complete remission (CR) or complete remission with incomplete hematological recovery (CRi) assessed by central bone marrow morphology at the end of Month 3. Secondary endpoints included best ORR (bORR), defined as the rate of CR/CRi achieved anytime, minimal residual disease (MRD) negativity (<0.01% by validated flow cytometry), duration of remission (DOR), relapse-free survival (RFS), overall survival (OS), safety, and pharmacokinetics.

DOR was defined as the time from the first CR/CRi to relapse or death from any cause (whichever occured first) after infusion. The subjects who underwent allo-HSCT while in remission were censored at the date of allo-HSCT. A supplementary analysis was conducted in which the DOR in subjects who received subsequent allo-HSCT were censored at the date of HSCT. RFS was the time from Inati-cel infusion to disease relapse or death from any cause, whichever occured first. The subjects who received new anticancer therapy excluding tyrosine kinase inhibitors (TKIs) while in remission were censored. OS was the time from Inati-cel infusion to death from any cause (more details in Supplementary protocol).

Adverse Events

Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0. Cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) were graded based on the criteria of the American Society for Transplantation and Cellular Therapy.[8]

Statistical Analysis

The study had approximately 90% power to distinguish the target 3-month ORR of 50% or higher from a prespecified historical control rate of 25%, with a one-sided significance level of 0.025.

An exact binomial test was used to compare the observed 3-month ORR with the historical control rate. Two-sided 95% confidence intervals (CIs) were calculated using the Clopper-Pearson method. DOR, RFS, and OS were each analyzed using the Kaplan-Meier method. Additional statistical analysis plan is provided in the appendix. The analyses were conducted using SAS software version 9.4, and figures were created with R version 4.3.2.

Role of the funding source

The sponsor collaborated with authors in study design, data collection, analysis, interpretation, and report writing.

Results

Between January 14, 2021, and April 02, 2024, a total of 92 patients with r/r B-ALL underwent screening, with 67 enrolled in the study representing the intention-to-treat (ITT) population. Inati-cel was successfully manufactured for 66 patients (one patient withdrew before manufacture). The median time from leukapheresis to Inati-cel manufacturing release was 20 days (range, 17 to 33 days), with a median CAR-T product viability of 87.5% (range, 76.8% to 93.7%). Notably, the majority of T cell subtypes in the final products were central memory T (Tcm) cells, while the Tcm population was lower in the corresponding leukapheresis products (eFigure 1). A total of 48 patients received a single dose of Inati-cel and 19 patients were not infused due to: active infection (n=8), disease progression (n=3), withdrawal (n=3), ineligibility (n=1) and physician decision (n=4) (Figure 1).

Patients

Among the 48 patients who were treated with Inati-cel, the median age was 32 years (range, 18 to 58). At enrollment, these patients had a median marrow blast percentage of 62.5% (range, 5% to 96.5%), with 60.4% having over 50% blasts in the bone marrow. Additionally, 35 patients (72.9%) underwent CAR-T cell therapy as a third or subsequent salvage treatment, with 8 patients (16.7%) having previously undergone HSCT. 60.4% of patients had at least one genetic alteration associated with a poor prognosis (Table 1). After lymphodepletion, these patients received a median total dose of 0.53×10^8 (range, 0.4×10^8 to 0.6×10^8 cells) transduced viable T cells, and the median time from completion of lymphodepletion to Inati-cel infusion was 1 day (range: 1-17 days).

Response rates

As of the cutoff date of April 02, 2024, all 48 patients had completed the 3-month efficacy assessment. The 3-month ORR was 70.8% (34 cases, 95% CI, 55.9-83.1, P<0.0001) compared to historical control rate of 25%, meeting the primary endpoint of the study (refer to Table 2). Best ORR reached 85.4% (35 achieved CR, 6 were in CRi), and all patients who responded to treatment were tested negative for MRD. Among the 41 responders, 12 (29.3%) underwent consolidative transplant while in remission. In an ITT population (n=67), the 3-month ORR was 50.7% (95%CI, 38.2-63.2) and the bORR was 61.2% (95% CI, 48.5-72.9).

Additionally, bORR was summarized by baseline and clinical covariates, including gender, age, ECOG score, prior lines of therapy, type of relapse or refractory, blast percentage in bone marrow during the screening period, and high-risk cytogenetic alteration (eFigure 2). The results indicated that all patients with primary refractory disease, those who had received 4 lines of pre-CAR-T therapy, or those who relapsed after HSCT achieved CR/CRi following Inati-cel administration. Additionally, nine Ph-positive patients achieved CR/CRi after Inati-cel infusion, with only one patient categorized as a non-responder due to concomitant anti-cancer therapies with ponatinib, vindesine and dexamethasone. Over 80% of patients with a high disease burden and specific genetic abnormalities associated with poor prognoses, such as alteration of *IKZF1* and *MLL* rearrangements, experienced favorable outcomes.

DOR, RFS, OS

Following a median follow-up of 23.7 months (IQR, 6.2–23.7), the median DOR both with and without censoring patients at subsequent allo-HSCT was 20.7 months (95% CI, 6.4–not reached with censoring, 9.5–not reached without censoring; Figure 2A, B). The median RFS was 12.4 months (95% CI, 5.2-not reached), with an estimated RFS rate of 54.5% at 12 months and 35.8% at 24 months (Figure 2C). Of 11 patients with available data at relapse, 4

patients showed CD19+ recurrence and 7 patients showed CD19- recurrence (2 with concomitant CD19+ blasts). The median OS was not reached (95% CI, 13.0 months-not reached), with estimated OS rates of 72.1% at 12 months and 55.2% at 24 months (Figure 2D).

Safety Analysis

All patients experienced at least one treatment-emergent adverse event (TEAE), with 97.9% encountering ≥ grade 3 TEAEs, primarily within the initial three months post-infusion (eTable 1). Hematological adverse events were the most frequent ≥ grade 3 adverse events, with most patients able to recover well after remission from their primary disease. The most common non-hematologic adverse events of any grade suspected to be related to Inati-cel were CRS (87.5%), infection (68.8%), hypogammaglobulinemia (62.5%), alanine aminotransferase increased (45.8%) and globulins decreased (41.7%). The incidence of other Inati-cel-related adverse events of special interest, such as ICANS and hemophagocytic lymphohistiocytosis/ macrophage activation syndrome (HLH/MAS) were 8.3% and 6.2%, respectively (Table 3).

Overall, CRS was detected in 42 out of 48 patients (87.5%), with only 6 cases (12.5%) classified as severe (6 of grade 3, no grade 4 or 5). The median time for CRS onset was 4.5 days (range: 1-10 days) and the median duration was 9 days (range: 3-34 days). The most common CRS symptoms included fever (100%, 42/42), hypoxia (in 35.4%, 17/42), and hypotension (in 35.4%, 17/42). Among the 42 patients with CRS, 32 (76.2%) received tocilizumab, and 30 (71.4%) were treated with steroids. Four patients (8.3%) developed ICANS, occurring 5-7 days after the onset of CRS, with 3 patients (6.2%) experienced ≥ grade 3 ICANS characterized by epileptic seizures. HLH/MAS occurred in 3 patients

(6.2%) following grade 2 CRS, with two cases graded as grade 2 and one as grade 3. The median onset of HLH/MAS was on day 14 post-infusion (range: 10-33 days), with a duration of 10 days. All patients recovered without sequelae. Additionally, thirty patients (62.5%) developed hypogammaglobulinemia, with grades 1-2. The median onset time for hypogammaglobulinemia was on day 15 post-infusion (range: 4-90 days), with a median duration of 194.5 days (range: 7-272 days). Of note, 33 patients (68.8%) experienced infections, with 23 (47.9%) of them experiencing infections classified as ≥ grade 3.

Eighteen patients died, none within 30 days post Inati-cel infusion. Among the 7 non-responders, three died from disease progression and one died from adverse event (pseudomonal sepsis on day37). Of the 29 responders not receiving consolidated allo-HSCT, seven died from relapse, one from adverse event (soft tissue infection with thrombocytopenia on day49), and two from unknown causes. Of the 12 responders with subsequent consolidated allo-HSCT after Inati-cel infusion, two died from HSCT-mediated complications, and two from relapses after transplant (eTable 3).

Clinical pharmacology

The presence of CAR gene copies of Inati-cel in peripheral blood were assessed using qualitative polymerase chain reaction (qPCR). Following Inati-cel infusion, expansion of Inati-cel was observed, peaking around day 11 (range, 7-21) post-infusion, with a maximal concentration (C_{max}) of 1.75×10^5 copies/μg gDNA (eFigure 3, eTable 4). The median duration of Inati-cel persistence in blood was 92 days (range, 14.0-733.7 days), with detectability remaining at 24 months post-infusion in a patient maintaining CR status. Other pharmacokinetics parameters are detailed in eTable 4. The expansion, as measured by median C_{max} and the area under the concentration-time curve in blood ($AUC_{0\text{-}28d}$) of Inati-cel in

Responders was not significantly difference from Non-responders (n=7, eTable 5). The PK parameters (C_{max}, $AUC_{0\text{-}28d}$) values in patients with CRS or ICANS occurrence were numerically higher than in patients without CRS or ICANS occurrence, respectively, though this difference was not statistically significant. (eFigure 4).

Pharmacodynamics biomarkers, including IL-6, IL-8, IL-10, IFN-γ, ferritin, and CRP, peaked within the first 10 days post Inati-cel infusion and returned to baseline levels within 28 days (eTable 6). Elevated serum levels of IL-6, IL-8, IL-10 and IFN-γ were associated with any grade CRS or ICANS ($p<0.05$) (eFigures 5 and 6). Elevated CRP and ferritin levels were only associated with any grade CRS ($p<0.05$).

Discussion

In this prospective, single-arm, multi-center, phase 2 clinical trial, we investigated the efficacy and safety of Inati-cel, a CD19-specific CAR-T therapy, in adult patients with r/r B-ALL. Our data revealed that 85.4% of patients achieved CR/CRi following Inati-cel administration, with all responders testing negative for MRD. Furthermore, 70.8% of infused patients remained in remission after 3 months without any anti-cancer therapy including HSCT and the median OS was not reached with a median follow-up of 23.7 months, indicating a profound and durable response to treatment. These efficacy results are comparable to those observed in the pivotal ZUMA-3 trials, which reported a 71% ORR rate within 3 months in adults. They also align with the 81% ORR noted in children and young adult patients in the ELIANA study, although direct comparisons are limited by differing patient characteristics such as disease stage and prior lines of therapy.[3,4] Particularly noteworthy was the efficacy seen in patients with high disease burden, heavily pretreated patients, and those harboring specific genetic abnormalities associated with poor prognoses, such as alterations of *IKZF1* and *MLL* rearrangements.[9-11] Furthermore, the safety profile of Inati-cel appears to be more tolerant than those observed in the referenced trials, which is an encouraging finding despite the limitations in direct comparisons. These findings underscore the potential of Inati-cel as a promising therapeutic option for patients with r/r B-ALL, particularly in achieving deep and sustained remissions.

Regarding the long-term response, the median DOR and RFS were 20.7 months and 12.4 months, respectively. The median OS was not reached, the estimated rates of OS showed favorable outcomes up to 24 months post-infusion, indicating long-term outcomes. These findings reinforce the potential of Inati-cel to maintain deep and durable remissions in patients with r/r B-ALL.

Despite the favorable efficacy profile of Inati-cel, the safety analysis revealed notable treatment-related adverse events (AEs), with the most frequent AEs being CRS and ICANS. However, severe CRS and ICANS (Grade 3 or higher) were infrequent, and most patients experiencing resolution without long-term sequelae with suitable management.[12-15] In this study, severe CRS affected only 12.5% of patients, a significantly lower rate compared to the 45% reported in the ELIANA study and 24% in the ZUMA-3 trials. Consistent results were observed in severe neurologic events; 6.2% of patients receiving Inati-cel experienced severe ICANS, while previous data in adult patients reported rates ranging from 25% to 50%.[3,4,16] Importantly, the study's safety profile remained acceptable even in patients with a high disease burden and extensive prior treatment, further indicating the reliable safety of Inati-cel.

Pharmacological characterization of Inati-cel cells revealed notable dynamics in their expansion, persistence, and immunological effects post-infusion. Comparing these findings with previous studies, such as ELIANA study and ZUMA-3 trials, reveals similarities in the kinetics of CAR-T cell expansion and immunological responses, highlighting the consistent trends across different CAR-T therapies. Previous research has demonstrated that individuals who do not respond typically exhibit limited CAR-T cell expansion.[17]

Nonetheless, there was no discernible variance in Inati-cel cells between the two patient cohorts, possibly due to differences in antigen affinity stemming from diverse scFVs. The high affinity of HI19α-derived scFv to the CD19 antigen, may mitigate suboptimal binding by rapid tumor cell proliferation or sparse CD19 antigen expression, thereby promoting robust CAR-T cell expansion in most patients. Additionally, the significant proportion of Tcm cells in final products enriched during the manufacturing processing may contribute to

the durable remission and low toxicity profile of Inati-cel,[18] which is in agreement with previous reports. [19-22] However, such enrichment of Tcm cell subsets was not seen in Tecartus[3], which could attribute to the differences in CAR structure and manufacturing process between these two products. Further study is warranted. A notable case involved a patient whose leukemia cell count exceeded 100×10^9/L cells shortly after the initial CAR-T infusion, requiring the addition of low-dose chemotherapy for control. During this period, CAR-T cells underwent rapid proliferation and promptly eradicated the tumor, further emphasizing the robust expansion and killing capabilities of Inati-cel cells. Additionally, these findings suggest that additional crucial factors beyond CAR-T cell expansion continue to play a role in the effectiveness of CAR-T therapy.

The strengths of this study encompass its prospective design, multi-center collaboration, and comprehensive evaluation of efficacy and safety outcomes. Additionally, it stands as the inaugural prospective, single-arm, multi-center, phase 2 clinical trial of a CD19-specific CAR-T conducted to endorse a New Drug Application (NDA) submission in China for adult patients with r/r B-ALL. However, several limitations should be acknowledged. As a single-arm trial with a relatively small sample size, the potential for selection bias and confounding factors cannot be entirely ruled out. Additionally, the lack of a control arm limits the ability to directly compare the outcomes with alternative treatment modalities. However, ongoing follow-up and future large-scale studies will provide further insights into the long-term efficacy and safety of Inati-cel in this patient population. Furthermore, considering that the scFV of Inati-cel cells targets a distinct CD19 binding site comparing to approved CD19 CAR-T therapies,[6] it would be valuable to assess if it could provide an alternative option for patients who have relapsed after treatment with CD19 CAR-T therapies based on the FMC63 clone. Additionally, exploring the integration of Inati-cel into the early phases of B-ALL

treatment through combination with other agents (i.e., blinatumomab/inotuzumab) or immunomodulatory strategies should be explored to enhance its efficacy and broaden its applicability across different patient populations.

The findings of this study have significant implications for clinical practice, offering a promising therapeutic option for adult patients with r/r B-ALL who have exhausted standard treatments. Inati-cel's high remission rates and manageable safety profile suggest its potential to become a cornerstone in B-ALL management, particularly where conventional therapies have failed.

In conclusion, the findings from this phase 2 study support the potential of Inati-cel as a promising therapeutic option for adult patients with r/r B-ALL, demonstrating high rates of 85.4% MRD negativity ORR and durable responses with manageable safety profiles. The success of Inati-cel highlights the potential of CAR-T cell therapy in addressing unmet medical needs in leukemia management and underscores the importance of continued research and development in this field to advance patient care and treatment strategies. Further research and ongoing clinical trials will continue to refine our understanding of the optimal use of CAR-T therapies in the management of hematological malignancies, paving the way for improved outcomes and personalized treatment approaches in the future.

Acknowledgements

Thank to Prof. Ying Yuan (The University of Texas MD Anderson Cancer Center) for advice and assistance in the statistical analysis and result discussion.

The authors sincerely thank Zheng Ye, PhD (Shanghai Daotian Evidence-based Technology Co., China) for assisting with language and medical editing.

The authors sincerely thank Inati-cel development team members, patients, and their families for their contributions to this clinical trial (HY001201).

Authorship Contribution

Ying Wang: designed research, performed research, data interpretation, writing-review editing, data supervision, and validation (directly accessed and verified the underlying data reported in the manuscript). Lulu Lv: designed research, performed research, writing-review editing (directly accessed and verified the underlying data reported in the manuscript). Yongping Song: designed research, data interpretation, writing-review editing. Xudong Wei: performed research, data interpretation, writing-review editing. Hongsheng Zhou: performed research, data interpretation, writing-review editing. Qifa Liu: performed research, data interpretation, writing-review editing. Kailin Xu: performed research, data interpretation, and writing-review editing. Dongmei Yan: performed research, data interpretation, writing-review editing. Cheng Zhang: performed research, data interpretation, and writing-review editing. Shuangyou Liu: performed research, data interpretation, writing-review editing. Jie Jin: performed research, data interpretation, and writing review-editing. Heng Mei: performed research, data interpretation, and writing-review editing. Ting Niu: performed research, data interpretation, and writing-review editing. Aibin Liang: designed research, data interpretation, writing-review editing. Runxia Gu: literature search, writing-review editing. Jienan Ren: designed research, performed research, data interpretation, and writing-review editing (directly accessed and verified the underlying data reported in the manuscript). Yi Feng: designed research, performed research, data interpretation, writing-review editing, literature search. Wei Jin: designed research, data analysis, figures (directly accessed and verified the underlying data reported in the manuscript). Yan Zhou: performed research, data collection, and project administration. Yiping Deng: data interpretation, writing-review

409 editing. Jianxiang Wang: designed research, performed research, data interpretation, data-
410 supervision, writing-original draft.
411
412 **Declaration of interests**
413 Disclosures: Jianxiang Wang, Advisor of Abbvie. Lulu Lv, Jienan Ren, Yi Feng, Yan Zhou
414 and Yiping Deng own stock option of Juventas Cell Therapy Ltd.
415 All other authors declare no competing interests.

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Figure 1. Flow diagram

The reasons for patients not enrolling in the study after screening included 2 patients withdrawing voluntarily, 4 patients did not meet inclusion criteria（<5% blasts in the bone marrow at the screening) and 19 patients met the exclusion criteria(including: *Hepatitis B* infection, *Hepatitis C* infection, EBV infection, CMV infection or uncontrolled infection in 11 patients; physician decision in 4 patients due to rapid disease progression; ineligible for apheresis procedure in 3 patients and central nervous system leukemia in 1 patient). All patients who completed screening and whose apheresis product was received by the manufacturing facility were enrolled in the study. Reasons for treatment discontinuation before lymphodepletion included: uncontrolled infection (n=6), voluntary withdrawal (n=3), physician decision (n=2, one patient remitted after bridging chemotherapy and the other one was diagnosed as mixed-phenotype acute leukemia), ineligibility (n=1). After lymphodepletion, seven patients did not proceed to Inati-cel infusion due to physician decision (n=2, one patient accompanied with teratoma and one patient remitted), uncontrolled infection (n=2), and rapid disease progression (n=3)

Figure 2. Duration of remission, relapse-free survival, and overall survival

(A, B) Kaplan-Meier estimates the duration of remission, with (A) censoring patients at subsequent allogeneic stem-cell transplant and (B) without censoring. (C) Kaplan-Meier estimate of relapse-free survival by investigator assessment, with patients censored at subsequent allogeneic stem-cell transplant. (D) Kaplan-Meier estimate of overall survival. CR=complete remission. CRi=complete remission with incomplete hematological recovery. NE=not estimable.

Table 1. Demographic and Baseline Clinical Characteristics of the patients

Variables	Enrolled patients N=67	Treated patients N=48
Age, Median (range), years	33 (18–59)	32 (18–58)
Sex		
Female	33 (49.3%)	22 (45.8%)
Male	34 (50.7%)	26 (54.2%)
ECOG Grade, n (%)		
0	29 (43.3%)	20 (41.7%)
1	38 (56.7%)	28 (58.3%)
Disease status at screening, n (%)		
Relapse (first relapse with the first remission lasting less than 12 months)	12 (17.9%)	9 (18.8%)
Refractory	55 (82.1%)	39 (81.2%)
Refractory Subcategories		
a) Primary refractory	13 (19.4%)	12 (25.0%)
b) Relapse after 2 or more CRs	11 (16.4%)	8 (16.7%)
c) First relapse, no remission after at least one salvage therapy	20 (29.9%)	11 (22.9%)
d) Relapsed or refractory after HSCT	11 (16.40%)	8 (16.7%)
Type of HSCT		
Autologous	4 (6.0%)	3 (6.2%)
Allogeneic	7 (10.4%)	5 (10.4%)
Maximum Prior Lines of Therapy, n (%)		
Median (range)	2.0 (1-7)	2 (1–4)
1 line	15 (22.4%)	13 (27.1%)
2 lines	35 (52.2%)	25 (52.1%)
3 lines	10 (14.9%)	7 (14.6%)
4 lines	5 (7.5%)	3 (6.2%)
5 lines	1 (1.5%)	0
7 lines	1 (1.5%)	0
CD19 Positive, n (%)		

Variables	Enrolled patients N=67	Treated patients N=48
Yes	67 (100%)	48 (100%)
No	0	0
Blast in bone marrow at screening, %		
Mean (SD)	57.1 (29.3)	53.8 (29.5)
Median	65.0	62.5
Min, Max	5.0, 97.0	5.0, 96.5
Blast in bone marrow at screening, n (%)		
≥5% and ≤25%	13 (19.4%)	11 (22.9%)
>25% and ≤50%	11 (16.4%)	8 (16.7%)
>50% and ≤75%	18 (26.9%)	13 (27.1%)
>75% and ≤100%	25 (37.3%)	16 (33.3%)
Extramedullary disease at screening, n (%)		
Yes	2 (3.0%)	2 (4.2%)
No	65 (97.0%)	46 (95.8%)
Cytogenetic alterations, n (%)		
Alterations of *IKZF1*	15 (22.4%)	11 (22.9%)
Ph-positive	14 (20.9%)	10 (20.8%)
MLL rearrangements	10 (14.9%)	7 (14.6%)
TP53 gene deletion/mutation	10 (14.9%)	7 (14.6%)
E2A-PBX1 fusion gene	2 (3.0%)	2 (4.2%)
Ph-like	4 (6.0%)	2 (4.2%)

ECOG: Eastern Cooperative Oncology Group; CR: complete remission; HSCT: hematopoietic stem cell transplantation; SD: standard deviation

Table 2. Overall remission rate and MRD negativity rate

Variables	**Best ORR N=48**	**3-Month ORR N=48**
ORR, n (%)	41 (85.4%)	34 (70.8%)
95% CI	72.2, 93.9	55.9, 83.1
CR	35 (72.9%)	29 (60.4%)
CRi	6 (12.5%)	5 (10.4%)
MRD negativity rate in responders, n (%)	41 (100%)	32 (94.1%)
95% CI	91.4, 100.0	80.3, 99.3

CI: confident interval; CR: complete remission; CRi: complete remission with incomplete hematological recovery; MRD: minimal residual disease; ORR: overall remission rate.

Table 3. Treatment-emergent adverse events (TEAEs) suspected to be related to Inati-cel that occurring in at least 20% of patients and adverse event of special interest.

Inati-cel Adverse Reactions	N=48		
	All Grades n (%)	Grade 3/4 n (%)	Grade 5 n (%)
Adverse event of special interest			
CRS	42(87.5%)	6(12.5%)	0
ICANS	4(8.3%)	3(6.2%)	0
Hypogammaglobulinemia	30(62.5%)	0	0
Infection	33(68.8%)	21(43.8%)	2(4.2%)
HLH/ MAS	3(6.2%)	1(2.1%)	0
Hematologic			
Neutropenia	46(95.8%)	46(95.8%)	0
Leukopenia	46(95.8%)	46(95.8%)	0
Anemia	44(91.7%)	38(79.2%)	0
Thrombocytopenia	43(89.6%)	37(77.1%)	1(2.1%)
Lymphopenia	42(87.5%)	42(87.5%)	0
Hyperfibrinolysis	15(31.2%)	1(2.1%)	
Coagulopathy	10(20.8%)	3(6.2%)	0
Investigations			
Alanine aminotransferase increased	22(45.8%)	0	0
Globulins decreased	20(41.7%)	0	0
Blood fibrinogen decreased	19(39.6%)	10(20.8%)	0
Aspartate aminotransferase increased	16(33.3%)	2(4.2%)	0
γ -glutamyltransferase increased	15(31.2%)	4(8.3%)	0
Blood bilirubin increased	10(20.8%)	2(4.2%)	0
Metabolism and nutrition disorders			
Hypokalemia	24(50.0%)	4(8.3%)	0
Hypocalcaemia	13(27.1%)	1(2.1%)	0
Hypertriglyceridaemia	12(25.0%)	1(2.1%)	0
Hypoalbuminaemia	11(22.9%)	1(2.1%)	0

CRS: cytokine release syndrome; ICANS: immune effector cell-associated neurotoxicity syndrome; HLH/MAS: hemophagocytic lymphohistiocytosis/ macrophage activation syndrome.

Figure 1

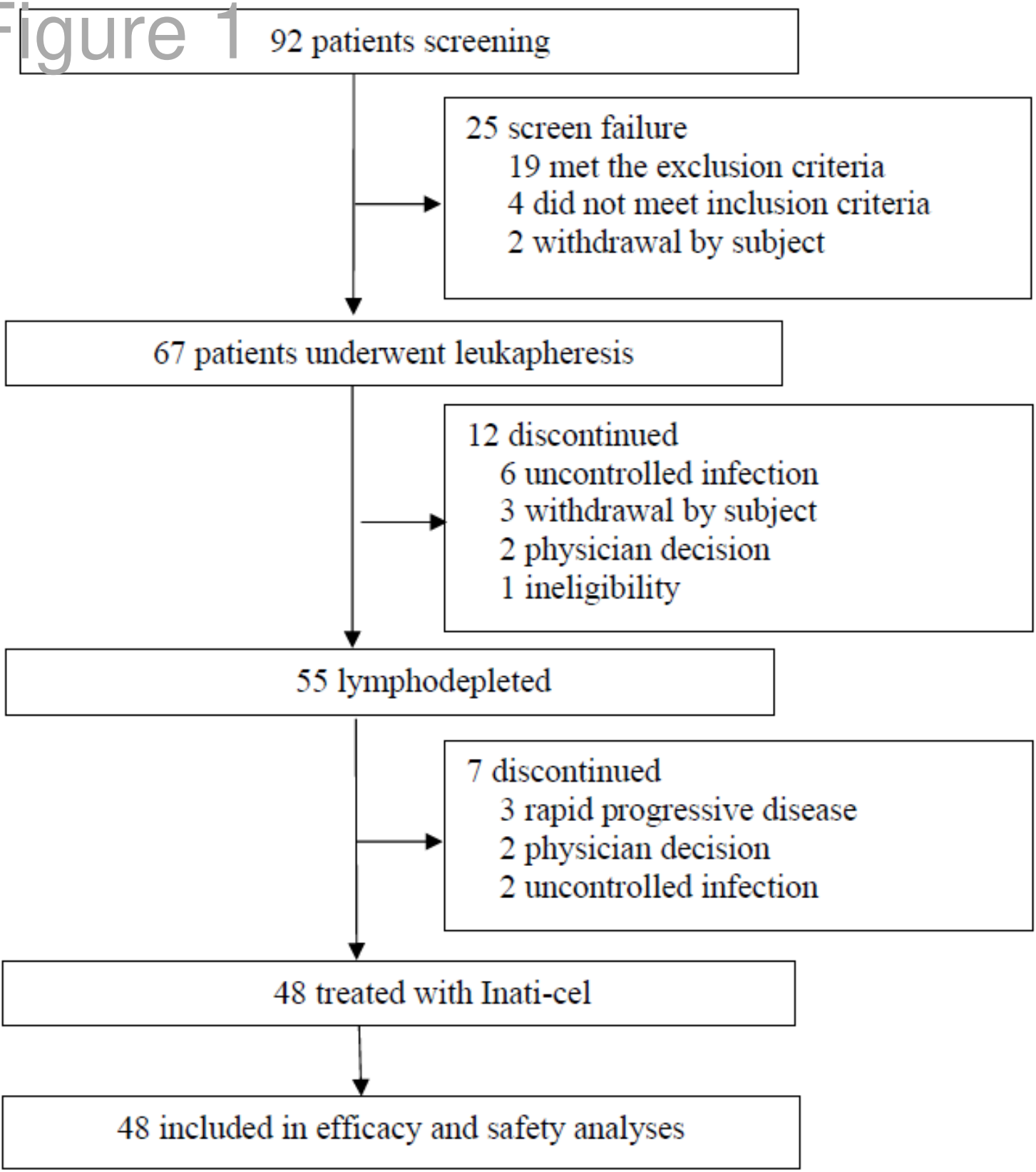

Figure 2