

Recombinant Erwinia Asparaginase (JZP458) in Acute Lymphoblastic Leukemia/Lymphoblastic Lymphoma (ALL/LBL): Post Hoc Analysis of Adverse Events of Interest From AALL1931

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Background

- L-asparaginase (ASP) is an important component of multi-agent treatment regimens for pediatric and adult patients with ALL/LBL... However, antibody-mediated hypersensitivity reactions occur in up to 30% of patients receiving Escherichia coli (E. coli)-derived ASP... The pivotal Children's Oncology Group Study AALL1931 (NCT04145531) evaluated JZP458, a recombinant Erwinia ASP, in patients with ALL/LBL who developed hypersensitivity/silent inactivation to E. coli-derived ASPs...

Objective

- To report on adverse events (AEs) of interest (AEIs; comprising allergic reactions, [including infusion reactions], pancreatitis, thrombosis, hepatotoxicity) and nausea/vomiting, and to summarize post hoc descriptive analyses of AEIs by timing and known risk factors (e.g., age and ethnicity)

Methods

Figure 1. Study Design

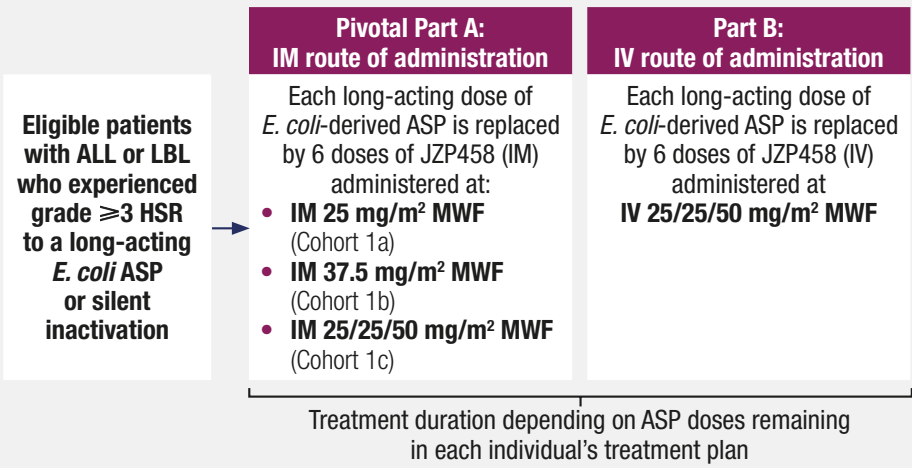


Table of Primary and Exploratory objectives. Primary objectives: Safety and efficacy of IM JZP458. Exploratory objectives: Efficacy and safety of IV JZP458.

- This two-part, open-label, phase 2/3 study evaluated IM and IV administration of JZP458... Each dose of long-acting E. coli-derived ASP was replaced by 1 course (6 doses) of JZP458 administered over 2 weeks... This post hoc descriptive analysis assessed rates of AEIs, and results were stratified by known risk factors (age and ethnicity); timing of AEIs and grade ≥2 nausea/vomiting... The timing of AEIs and nausea/vomiting were described by the median (range) number of doses on or before the first event and the number (frequency) of events after the 25 mg/m² doses and after the 50 mg/m² doses (before the next dose)

Results

Table 1. Demographic and Baseline Characteristics

Table with columns for Characteristics, IM JZP458 (25, 37.5, 25/25/50 mg/m² MWF), IM Total (N=167), and IV JZP458 (25/25/50 mg/m² MWF) (N=61). Rows include Age, Sex, BMI, Race, and Ethnicity.

\*Only patients with data available. <sup>a</sup>Based on 82 patients. <sup>b</sup>Based on 166 patients. <sup>c</sup>Self-reported. ALL, acute lymphoblastic leukemia; B-ALL, B-cell acute lymphoblastic leukemia; B-LBL, B-cell lymphoblastic lymphoma; BMI, body mass index; BSA, body surface area; IM, intramuscular; IV, intravenous; LBL, lymphoblastic lymphoma; MWF, Monday/Wednesday/Friday; NSAA, nadir serum ASP activity; TEAE, treatment-emergent adverse event.

Patients

- As of the final database lock, 167 patients received IM JZP458 (1a, n=33; 1b, n=83; 1c, n=51) and 61 patients received IV JZP458 (Table 1)

Table 2. Summary of Overall AEs and Any-Grade Treatment-Related AEIs by Age Group

Table comparing Overall AEs and Any-Grade Treatment-Related AEIs by Age Group for IM JZP458 and IV JZP458 across various age brackets (<6, 6 to <12, 12 to <18, ≥18 years) and total cohorts.

Note: ALT/AST increased includes the terms ALT increased, AST increased, and transaminase increased. Bilirubin increased includes the terms blood bilirubin increased and conjugated bilirubin increased. AE, adverse events; AEIs, adverse events of interest; ALT, alanine aminotransferase; AST, aspartate aminotransferase; IM, intramuscular; IV, intravenous; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

AEIs by age group

- There were no apparent increases in rates of TEAEs or TRAEs by age group across dosing cohorts (Table 2)... Rates of any-grade treatment-related allergic reactions, pancreatitis, thrombosis, increased alanine aminotransferase (ALT)/aspartate aminotransferase (AST), and increased bilirubin in the IM cohort were 11%, 7%, 1%, 16%, and 7%, respectively, and 26%, 5%, 2%, 18%, and 5% in the IV cohort... Subgroup analyses showed no consistent trends in rates of any-grade treatment-related AEIs by age group (Table 2)

Table 3. Summary of Any-Grade Treatment-Related AEIs by Ethnicity

Table comparing Any-Grade Treatment-Related AEIs by Ethnicity for Hispanic/Latino (n=74) and Non-Hispanic/Latino (n=140) patients.

Note: ALT/AST increased includes the terms ALT increased, AST increased, and transaminase increased. Bilirubin increased includes the terms blood bilirubin increased and conjugated bilirubin increased. \*Numbers and frequencies of AEIs from the IM and IV cohorts were pooled by ethnicity. AEI, adverse events of interest; ALT, alanine aminotransferase; AST, aspartate aminotransferase; IM, intramuscular; IV, intravenous.

AEIs by ethnicity

- Rates of any-grade treatment-related allergic reactions, pancreatitis, thrombosis, increased ALT/AST, and increased bilirubin were similar between Hispanic patients (n=74) and non-Hispanic patients (n=140) (Table 3)

Table 4. Timing and Dose Information of Treatment-Related Any-Grade AEIs and Grade ≥2 Nausea/Vomiting

Table detailing Timing and Dose Information of Treatment-Related Any-Grade AEIs and Grade ≥2 Nausea/Vomiting, including median (range) number of doses on/before the onset of AEs for various conditions like Allergic reactions, Pancreatitis, Thrombosis, etc.

Percentages may not add up to 100 due to rounding. \*Includes anaphylactic reaction, (drug) hypersensitivity, infusion-related reaction, rash, rash erythematous, rash maculopapular, and urticaria. <sup>a</sup>Frequencies were derived based on the number of events.

Timing of AEIs and nausea/vomiting

- Timing of any-grade AEIs and grade ≥2 nausea/vomiting by route of administration is shown in Table 4, including the median number of doses on/before the onset of AEs... Consistent with literature reports on native Erwinia ASP, treatment-related allergic reactions (including infusion reactions) were observed more frequently in patients receiving IV JZP458 compared with patients receiving IM JZP458... Treatment-related allergic reactions occurred after both the 25 mg/m² dose and 50 mg/m² dose, regardless of administration route... Among patients who developed treatment-related allergic reactions, the events occurred during course 1 in 39% of patients (7/18) receiving IM JZP458, and 62% of patients (10/16) receiving IV JZP458... Treatment-related grade ≥2 nausea/vomiting occurred in 21% of patients across IM cohorts and 61% of patients in the IV cohort

Conclusions

- The safety profile of JZP458 is consistent with other ASPs in patients with ALL/LBL being treated with multi-agent chemotherapy; rates of treatment-related pancreatitis, thrombosis, and hepatotoxicity were similar for the IM and IV cohorts and in line with the safety profile expected with ASPs in general... The rates of AEIs were generally similar across age subgroups and between Hispanic and non-Hispanic patients... Consistent with literature reports on native Erwinia ASP, treatment-related allergic reactions were more frequent in the IV cohort than in the IM cohort. Rates of nausea and vomiting were also more frequent in the IV cohort... Frequencies of allergic reactions and grade ≥2 nausea/vomiting following the 25 mg/m² and 50 mg/m² doses were broadly similar... These post hoc analyses were limited by the relatively small number of patients in each subgroup at a certain dose level

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