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# POSTER ABSTRACTS

## 614.ACUTE LYMPHOBLASTIC LEUKEMIAS: THERAPIES, EXCLUDING TRANSPLANTATION AND CELLULAR IMMUNOTHERAPIES

### Efficacy and Safety of Recombinant *Erwinia* Asparaginase (JZP458) in Acute Lymphoblastic Leukemia (ALL) or Lymphoblastic Lymphoma (LBL): Complete Follow-up of the Children's Oncology Group (COG) AALL1931 Study

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Background:
L-asparaginase is an important component of multi-agent treatment regimens for pediatric and adult patients with ALL/LBL. However, hypersensitivity reactions to *E. coli*-derived asparaginases often lead to treatment delay or discontinuation. JZP458, a recombinant *Erwinia* asparaginase (ASP) derived from a *Pseudomonas fluorescens* expression platform, was evaluated in study AALL1931, a 2-part, open-label, phase 2/3 trial conducted with the Children's Oncology Group investigating efficacy, safety, and pharmacokinetics (PK) of JZP458 in patients with ALL/LBL (ClinicalTrials.gov ID: NCT04145531). Based on interim results from part A of AALL1931, intramuscular (IM) JZP458 (Rylaze®) was approved by the US Food and Drug Administration for treatment of ALL/LBL in June 2021. Here, we report the efficacy and safety of JZP458 at the completion of AALL1931.
Methods:
Eligible patients with ALL/LBL who daeveloped hypersensitivity (grade ≥3 allergic reaction or silent inactivation) to *E. coli*-derived pegaspargase received JZP458 as part of their multi-agent treatment plan. Each dose of pegaspargase was substituted with 6 doses of JZP458 administered either IM (part A) or intravenously (IV, part B) on Monday/Wednesday/Friday (MWF) over 2 weeks, defined as 1 course. The study enrolled 3 IM cohorts [1a (25 mg/m $^2$ MWF), 1b (37.5 mg/m $^2$ MWF), and 1c (25/25/50 mg/m $^2$ MWF)], and 1 IV cohort (25/25/50 mg/m $^2$ MWF). Efficacy was assessed by proportion of patients maintaining therapeutic nadir serum ASP activity (NSAA) ≥0.1 IU/mL at the last 72-hour (primary endpoint) or 48-hour (key secondary endpoint) timepoint during course 1. A population PK (PPK) model was developed based on serum ASP activity (SAA) data from AALL1931 to characterize the PK of JZP458 and simulations using the PPK model were performed to provide additional information on alternative dosing regimens.
Results:
At the final cutoff date of November 22, 2022, a total of 167 patients received IM JZP458 (1a, n=33; 1b, n=83; 1c, n=51) and 61 patients received IV JZP458. The median (range) of JZP458 courses received was 5 (0, 14), 4 (0, 15), 5 (1, 10), and 3 (0, 15) for IM cohorts 1a, 1b, 1c, and IV cohort, respectively. **Table 1** shows the proportion of patients who achieved therapeutic NSAA levels and the mean SAA levels per cohort in course 1. With IM cohort 1c (25/25/50 mg/m $^2$ MWF), the proportion (95% CI) of patients achieving NSAA levels ≥0.1 IU/mL at 72 and 48 hours were 90% (81, 98) and 96% (90, 100), respectively.
Treatment-related adverse events (TRAEs) ≥ grade 3 occurred in 126/228 (55%) patients; but no TRAE led to death. **Table 2** shows the most commonly reported (≥10% of patients) nonhematologic TRAEs. A total of 22 patients (13%) across all IM cohorts (2 patients in 1a, 14 in 1b, and 6 in 1c) and 20 patients (33%) in the IV cohort experienced a TRAE leading to treatment discontinuation.The most common TRAEs leading to treatment discontinuation were pancreatitis (6%) in the IM cohort, and drug hypersensitivity (15%) in the IV cohort.
PPK model-based simulations predicted that therapeutic NSAA levels are achieved in the vast majority of patients when JZP458 is administered IM at 25 mg/m $^2$ every 48 hours (7 doses) or 25/25/50 mg/m $^2$ MWF (6 doses), when JZP458 is admin-

istered IV at 25 mg/m $^2$ every 48 hours (7 doses), or when JZP458 is administered IV at 25 mg/m $^2$ M/W and IM at 50 mg/m $^2$ F (6 doses).
Conclusions:
Results at the completion of AALL1931 in patients with ALL/LBL and allergic reactions or silent inactivation to *E. coli*-derived asparaginase show the safety profile of JZP458 is consistent with other asparaginases, with no new adverse safety signals. Treatment-related discontinuation rates with IV JZP458 were greater than with IM, primarily due to increased incidence of hypersensitivity/infusion-related reactions along with nausea and vomiting; however, the study was not statistically powered to compare different dosing cohorts. Observed and PPK modeling data demonstrate JZP458 achieves therapeutic NSAA levels via multiple IM and IV dosing schedules, with IM dosing having more sustained SAA, and therefore providing flexibility to patients and physicians.

**Disclosures Maese:** *Jazz Pharmaceuticals:* Consultancy, Speakers Bureau. **Choi:** *Jazz Pharmaceuticals:* Current holder of *stock options* in a privately-held company, Ended employment in the past 24 months. **Lin:** *Jazz Pharmaceuticals:* Current holder of *stock options* in a privately-held company, Ended employment in the past 24 months. **Aoki:** *Jazz Pharmaceuticals:* Current Employment, Current holder of *stock options* in a privately-held company. **Agarwal:** *Jazz Pharmaceuticals:* Current Employment, Current holder of *stock options* in a privately-held company. **Chandrasekaran:** *Jazz Pharmaceuticals:* Current Employment, Current holder of *stock options* in a privately-held company. **Liang:** *Jazz Pharmaceuticals:* Current Employment, Current holder of *stock options* in a privately-held company. **Girgis:** *Jazz Pharmaceuticals:* Current Employment, Current holder of *stock options* in a privately-held company. **Chen:** *Jazz Pharmaceuticals:* Current Employment, Current holder of *stock options* in a privately-held company. **Iannone:** *Jazz Pharmaceuticals:* Current Employment, Current holder of *stock options* in a privately-held company. **Silverman:** *Servier Pharmaceuticals:* Membership on an entity's Board of Directors or advisory committees; *Jazz Pharmaceuticals:* Membership on an entity's Board of Directors or advisory committees. **Raetz:** *Pfizer:* Research Funding; *Bristol Myers Squibb:* Membership on an entity's Board of Directors or advisory committees. **Rau:** *Servier Pharmaceuticals:* Membership on an entity's Board of Directors or advisory committees; *Jazz Pharmaceuticals:* Membership on an entity's Board of Directors or advisory committees.

**OffLabel Disclosure:** JZP458 (asparaginase erwinia chrysanthemi [recombinant]-rywn) is a recombinant Erwinia asparaginase derived from a novel expression platform. It is used in treatment of patients with acute lymphoblastic leukemia/lymphoblastic lymphoma who developed hypersensitivity/silent inactivation to Escherichia coli-derived asparaginases.

**Table 1.** Proportion of Patients Achieving NSAA Levels ≥0.1 IU/mL and Mean SAA Levels

| | IM Cohort 1a: 25 mg/m² MWF | | IM Cohort 1b: 37.5 mg/m² MWF | | IM Cohort 1c: 25/25/50 mg/m² MWF | | IV 25/25/50 mg/m² MWF | |
|---|---|---|---|---|---|---|---|---|
| | 48 hours (n=32) | 72 hours (n=28) | 48 hours (n=83) | 72 hours (n=77) | 48 hours (n=49) | 72 hours (n=49) | 48 hours (n=59) | 72 hours (n=50) |
| Proportion of patients (95% CI) | 97% (91, 100) | 64% (47, 82) | 99% (96, 100) | 91% (85, 97) | 96% (90, 100) | 90% (81, 98) | 90% (82, 98) | 40% (26, 54) |
| Mean (95% CI) NSAA levels (IU/mL) | 0.45 (0.37, 0.53) | 0.16 (0.12, 0.19) | 0.88 (0.76, 1.01) | 0.33 (0.28, 0.39) | 0.66 (0.54, 0.77) | 0.47 (0.35, 0.59) | 0.25 (0.20, 0.29) | 0.10 (0.07, 0.13) |

**Table 2.** Most Commonly Reported (≥10% of Patients) Nonhematologic TRAEs (Safety Analysis Set)

| Patients, n (%) | IM Cohort 1a: 25 mg/m² MWF (n=33) | | IM Cohort 1b: 37.5 mg/m² MWF (n=83) | | IM Cohort 1c: 25/25/50 mg/m² MWF (n=51) | | IM Total (n=167) | | IV 25/25/50 mg/m² MWF (n=61) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | All grades | Grade 3/4 | All grades | Grade 3/4 | All grades | Grade 3/4 | All grades | Grade 3/4 | All grades | Grade 3/4 |
| Nausea | 7 (21) | 1 (3) | 20 (24) | 6 (7) | 13 (26) | 2 (4) | 40 (24) | 9 (5) | 27 (44) | 7 (12) |
| Vomiting | 7 (21) | 0 | 22 (27) | 3 (4) | 10 (20) | 1 (2) | 39 (23) | 4 (2) | 36 (59) | 8 (13) |
| Abdominal pain | 2 (6) | 0 | 9 (11) | 2 (2) | 6 (12) | 0 | 17 (10) | 2 (1) | 3 (5) | 1 (2) |
| Febrile neutropenia | 2 (6) | 2 (6) | 11 (13) | 11 (13) | 4 (8) | 4 (8) | 17 (10) | 17 (10) | 3 (5) | 3 (5) |
| Fatigue | 3 (9) | 1 (3) | 17 (21) | 0 | 3 (6) | 0 | 23 (14) | 1 (1) | 8 (13) | 0 |
| Drug hypersensitivity | 2 (6) | 2 (6) | 6 (7) | 3 (4) | 2 (4) | 2 (4) | 10 (6) | 7 (4) | 10 (16) | 7 (12) |
| Decreased appetite | 3 (9) | 1 (3) | 12 (15) | 3 (4) | 9 (18) | 1 (2) | 24 (14) | 5 (3) | 5 (8) | 0 |
| Hyperglycaemia | 3 (9) | 1 (3) | 5 (6) | 2 (2) | 7 (14) | 3 (6) | 15 (9) | 6 (4) | 7 (12) | 6 (10) |
| ALT increased | 2 (6) | 2 (6) | 14 (17) | 8 (10) | 8 (16) | 3 (6) | 24 (14) | 13 (8) | 11 (18) | 7 (12) |
| AST increased | 2 (6) | 0 | 12 (15) | 4 (5) | 4 (8) | 0 | 18 (11) | 4 (2) | 6 (10) | 3 (5) |

*TRAEs were reported as MedDRA (version 22.1) preferred terms.

ALT, alanine transaminase; AST, aspartate transaminase; IM, intramuscular; IV, intravenous; MedDRA, Medical Dictionary for Regulatory Activities; MWF, Monday/Wednesday/Friday; NSAA, nadir serum asparaginase activity; TRAE, treatment-related adverse event.

**Figure 1**

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