ALL-774

Safety and Efficacy of AZD0486 in Adolescent and Adult Patients With Relapsed or Refractory B-Cell Acute Lymphoblastic Leukemia: Early Results From the Phase 1/2 SYRUS Study

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Objective

- To report preliminary results of a dose-escalation study (Part A of a phase 1/2 study) of intravenous AZD0486 using triple step-up dosing (3SUD) in R/R B-cell acute lymphoblastic leukemia (B-ALL) (SYRUS; NCT06137118)

Conclusions

- Preliminary results from the SYRUS dose-escalation study suggest AZD0486 is active and well tolerated in patients with R/R B-ALL
  - Favorable efficacy in R/R B-ALL including those who previously received CD19-targeted therapy
  - 83% CR rate at the highest tested dose – 15 mg
  - Encouraging activity in patients with high disease burden and extramedullary disease
  - Clinical response durable up to 56 weeks
- 3SUD mitigated cytokine production for safe delivery of AZD0486 target doses up to 15 mg
- The study continues to enroll patients for dose optimization (Part B) and expansion (Part C)

Plain language summary

Why did we perform this research?

- B-cell acute lymphoblastic leukemia (B-ALL) is a type of cancer that affects the blood and bone marrow. AZD0486 is a new type of therapy that binds to both the cancer cell and a certain type of immune cell (called a T cell) to stimulate the immune system to kill the cancer cells. Early studies of AZD0486 suggest it may cause fewer toxicities than other similar medications. This study evaluated the safety and efficacy of AZD0486 in people with B-ALL who had received prior lines of therapy

How did we perform this research?

- The participants in the study were given increasing doses of AZD0486 over the first month of treatment, followed by one of three different target doses
- Blood tests and disease status evaluations were performed at pre-planned time points to assess how the participants' disease was responding to the treatment (efficacy) and how well they were tolerating the drug (safety)

What were the findings of this research?

- AZD0486 was well tolerated at increasing doses and showed good disease response rates, including in the participants who had previously received multiple prior therapies

What are the implications of this research?

- This research will help identify the best dose of AZD0486 that is both effective and well tolerated
- New treatments that are effective and safe are essential to improve outcomes and provide optimal treatment options for people with B-ALL

Where can I access more information?

- Information about the medicine being used in this study and the people who could participate can be found here: https://www.clinicaltrials.gov/study/NCT06137118

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Poster presented at the Society of Hematologic Oncology (SOHO) Annual Meeting; September 3–6, 2025; Houston, TX by Dr. Gautham Borthakur.

Poster

Supplementary material

Please scan this quick response (QR) code with your smartphone camera or app to obtain a copy of these materials.

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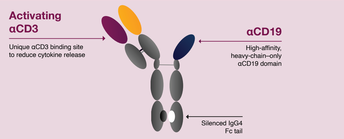
Presented at the Society of Hematologic Oncology (SOHO) Annual Meeting; September 3–6, 2025; Houston, TX

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Introduction

- AZD0486 is a novel IgG4 fully human CD19×CD3 bispecific T-cell engager[1] designed for low-affinity CD3 binding to reduce cytokine release from T-cell activation while preserving T-cell cytotoxicity against malignant B cells (**Figure 1**)
- A phase 1, FIH trial in patients with B-NHL (NCT04594642) demonstrated activity and tolerability of AZD0486 in R/R follicular lymphoma and diffuse large B-cell lymphoma[2,3]
- Here, we present the preliminary results from a dose-escalation study of AZD0486 in patients with R/R B-ALL (SYRUS; NCT06137118)

Figure 1. AZD0486 Structure



Methods (Part A Dose Escalation)

Key Eligibility Criteria

- Age 16y+
- CD19+ (any level of expression)
- R/R after ≥2 prior lines or after 1L if not eligible or has no other available SoC options
- Ph(-); Ph(+) with R/R disease despite treatment with ≥2 different TKIs, or with intolerance or contraindications to TKIs
- Prior exposure to CD19 treatment allowed independent of response

Assessments

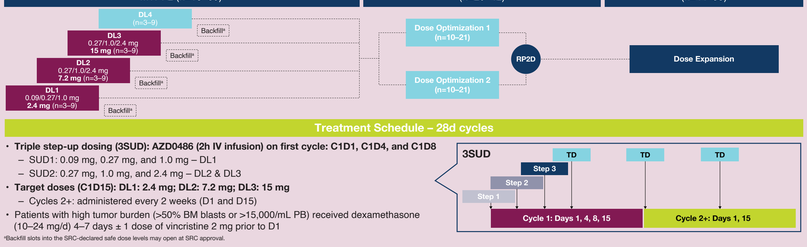
- Bone marrow and peripheral blood assessments including PET/CT if needed to confirm EMD involvement
- CRS and ICANS graded using ASTCT criteria[4]
- Disease assessment at end of each cycle following ELN 2022/NCCN criteria using MFC (local lab) and central NGS for MRD assessment

Objectives

- Primary: Safety/ tolerability of AZD0486
- Secondary: Efficacy, PK,[a] immunogenicity[a]

[a]Detailed data on PK and immunogenicity not yet available.

Study Design



Treatment Schedule – 28d cycles

- **Triple step-up dosing (3SUD): AZD0486 (2h IV infusion) on first cycle: C1D1, C1D4, and C1D8**
  - SUD1: 0.09 mg, 0.27 mg, and 1.0 mg – DL1
  - SUD2: 0.27 mg, 1.0 mg, and 2.4 mg – DL2 & DL3
- **Target doses (C1D15): DL1: 2.4 mg; DL2: 7.2 mg; DL3: 15 mg**
  - Cycles 2+: administered every 2 weeks (D1 and D15)
- Patients with high tumor burden (>50% BM blasts or >15,000/mL PB) received dexamethasone (10–24 mg/d) 4–7 days ± 1 dose of vincristine 2 mg prior to D1

[a]Backfill slots into the SRC-declared safe dose levels may open at SRC approval.

Results

Demographics and disposition

- As of March 31, 2025, a total of 31 patients were enrolled in the study with a median of 3 prior lines of therapy (**Table 1**)
- Majority of patients had prior exposure to blinatumomab and/or CAR-T therapy
- 26% of patients were previously exposed to both blinatumomab and CAR-T (double-exposed)
- Mean (range) of bone marrow blasts was 61% (5%–97%)

Safety

- Infections, febrile neutropenia, and cytopenias were the most common G3+ adverse events (**Table 2**)
- 2 patients experienced DLTs:
  - Both had prolonged cytopenia in the context of MLFS; 1 also had grade 3 AST increased with concomitant use of posaconazole
  - Both continue to receive the target dose without significant cytopenia
- AEs leading to treatment discontinuation were reported in 4 (13%) patients and were deemed unrelated to AZD0486
- One patient had a G3 CRS event during SUD2 (**Table 3**), and 1 patient had a G3 ICANS event after the 7.2-mg TD (**Table 4**)
  - No G4+ CRS or ICANS events were reported

Pharmacodynamics

- 3SUD effectively suppressed cytokine production, with substantial decreases observed within 48 hours of the first dose of AZD0486 for IFN-γ, TNF-α, IL-1β, IL-2, and IL-10 (**Figure 2**)

Efficacy

- Median follow-up was 3.2 months (range, 35–420 days)
- ORR at EoC1 was dose dependent, increasing from 46% in DL1 to 83% in DL3 (**Table 5**)
  - 18/31 (58%) patients achieved a response by EoC1, among whom 94% (17/18) achieved MRDneg status (local flow)
  - High ORR was seen in patients with prior CD19-targeted therapy
    - ORR of 50% with prior blinatumomab treatment, 64% with prior CAR-T, and 63% who were double-exposed
  - 80% (4/5) of patients with EMD responded to treatment
- 81% (13/16) of patients who were MRDneg by local flow (and had an identified clonotype) were also MRDneg 10^{-5} by central lab NGS (**Figure 3**)
- 10 patients remain on treatment
  - 6 patients discontinued treatment while in CR MRDneg (local flow and/or ClonoSEQ; ≤10^{-4}) and proceeded to allo-SCT (n=5) or DLI (n=1)
  - 2/18 patients relapsed after initial CR (on C2 and end of C3)
- 6-month DOR was 86.5% (DOR range, 1–392 days)

Figure 2. Cytokine Production Following AZD0486 Dosing Up to C2D1

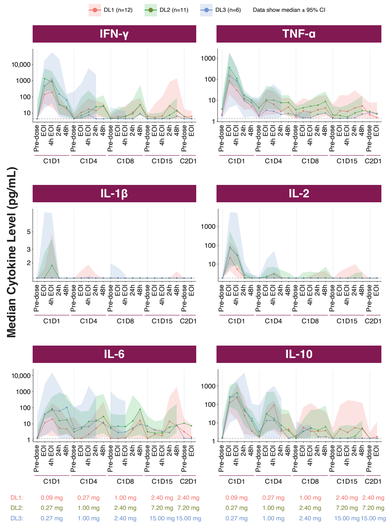
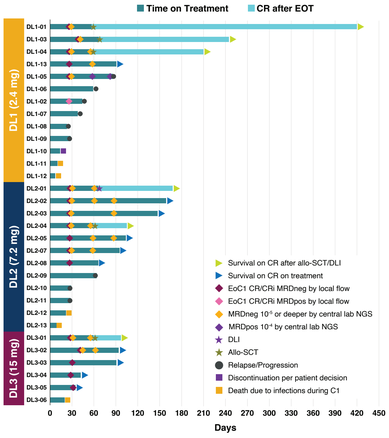


Figure 3. Response Assessment at End of C1



Data cut-off: 31 March 2025. Central lab: Clonoseq or Genetron (China).

Table 1. Demographic and Baseline Characteristics

Characteristic	Total (N=31) n (%)
Age, median (range), y	56 (17–75)
Female	13 (42)
Ph(+)	6 (19)
Median (range) prior therapies	3 (2–9)
Prior CD19-targeted therapy exposure	19 (61)
Blinatumomab-exposed	16 (52)
CAR-T-exposed	11 (35)
Double-exposed	8 (26)
Allo-SCT	10 (32)
Mean (range) bone marrow blasts	61% (5%–97%)
≥50% bone marrow blasts	21 (68)

Values are n (%) unless otherwise specified.

Table 2. Most Common G3+ Treatment-Emergent Adverse Events (>5%)

Adverse Events, N=31, n (%)	G3	G4	G5
Non-hematologic			
Infection	6 (19)[a]	1 (3)[b]	3 (10)[c]
Febrile neutropenia	6 (19)	–	–
ALT/AST increased	2 (6)	–	–
Hematologic			
Neutropenia	3 (10)	7 (23)	–
Lymphopenia	2 (6)	4 (13)	–
Thrombocytopenia	2 (6)	5 (16)	–
Anemia	2 (6)	–	–

Dash (-) indicates no patients with an event.
[a]Sepsis, COVID-19, corynebacterium infection, hepatitis candidiasis, herpes zoster disseminated, oral herpes, *Pneumocystis jirovecii* pneumonia, pneumonia, systemic candida (n=1 each). [b]Sepsis (n=1). [c]Sepsis, septic shock, and COVID-19 (n=1 each).

Table 3. CRS Events During SUD and After TD

IR-AEs, n (%)	During SUD: During SUD1 n=13	During SUD: During SUD2 n=18	After TD: After 2.4 mg n=10	After TD: After 7.2 mg n=12	After TD: After 15 mg n=6
CRS Any	4 (31)	13 (72)	3 (30)	3 (25)	–
CRS G2	2 (15)	5 (28)	1 (11)	1 (8)	–
CRS G3	–	1 (6)	–	–	–

Dash (-) indicates no patients with an event.

Table 4. ICANS Events During SUD and After TD

IR-AEs, n (%)	During SUD: During SUD1 n=13	During SUD: During SUD2 n=18	After TD: After 2.4 mg n=10	After TD: After 7.2 mg n=12	After TD: After 15 mg n=6
ICANS Any	–	4 (22)	–	1 (8)	–
ICANS G2	–	3 (17)	–	–	–
ICANS G3	–	–	–	1 (8)	–

Dash (-) indicates no patients with an event.

Table 5. Summary of ORR

Response, n/N (%)	DL1 (SUD: 0.09/ 0.27/1.0; TD: 2.4 mg) (n=13)	DL2 (SUD: 0.27/ 1.0/2.4; TD: 7.2 mg) (n=12)	DL3 (SUD: 0.27/ 1.0/2.4; TD: 15 mg) (n=6)
ORR EoC1 (CR/CRi) (ITT)	6/13 (46)	7/12 (58)	5/6 (83)
CR/CRi MRDneg (local flow [10⁻⁴])	5/6 (83)	7/7 (100)	5/5 (100)
Disease relapse	2/6 (33)	0/7	0/5
ORR (CR/CRi) by prior therapy subgroup[a,b]			
Blinatumomab-exposed	4/9 (44)	1/4 (25)	3/3 (100)
CAR-T-exposed	1/3 (33)	2/3 (67)	4/5 (80)
Double-exposed	1/3 (33)	1/2 (50)	3/3 (100)
Triple-exposed (+inotuzumab)	0/2 (0)	1/2 (50)	3/3 (100)
ORR (CR/CRi) (in patients with EMD)[a]	2/3 (67)	2/2 (100)	0/0

[a]Median follow-up: 97 days (range, 35–401 days). [b]Prior therapy subgroups are not mutually exclusive.

References

1. Malik-Chaudhry HK, et al. *MAbs*. 2021;313:1890411. **2.** Hou JZ, et al. *Blood*. 2024; 144(Suppl 1):341. **3.** Gabalia S, et al. *Blood*. 2024;144(Suppl 1):868. **4.** Lee DW, et al. *Biol Blood Marrow Transplant*. 2019;25:625-38.

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Abbreviations

ASTCT, American Society for Transplantation and Cellular Therapy; BM, bone marrow; C, cycle; CAR-T, chimeric antigen receptor T-cell; CR, complete response; CRi, complete response with incomplete hematologic recovery; CRS, cytokine release syndrome; DL, dosing level; DLI, donor lymphocyte infusion; DLT, dose-limiting toxicity; DOR, duration of response; ELN, European LeukemiaNet; EMD, extramedullary disease; EoC, end of cycle; EOI, end of infusion; EOT, end of treatment; FIH, first-in-human; ICANS, immune effector cell–associated neurotoxicity syndrome; IR-AE, immune-related adverse event; MFC, multiparametric flow cytometry; MLFS, morphologic leukemia-free state; MRD, minimal residual disease; mTPI-2, modified Toxicity Probability Interval; NGS, next-generation sequencing; PB, peripheral blood; PET/CT, positron-emission tomography/computerized tomography; Ph(-)/Ph(+), Philadelphia chromosome negative/positive; RP2D, recommended phase 2 dose; R/R, relapsed/refractory; SOC, standard of care; SRC, Safety Review Committee; TD, target dose; TKI, tyrosine kinase inhibitor