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Safety and Efficacy of AZD0486, a CD19xCD3 T-cell Engager, in Relapsed or Refractory Diffuse Large B-cell Lymphoma

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Objective

- To present the results from an ongoing phase 1 trial of AZD0486 in patients with R/R DLBCL (NCT04594642)

Conclusions

- AZD0486 at target doses ≥7.2 mg showed promising efficacy with durable response and manageable safety in patients with R/R DLBCL, including patients who are CD19 CAR-T–exposed
- Target doses up to 25 mg have been tested without exceeding maximum tolerated dose
- Safety and efficacy evaluations are ongoing. In addition, later-phase studies and studies in combinations are ongoing or planned

Plain language summary

Why did we perform this research?

- Diffuse large B-cell lymphoma (DLBCL) is the most common form of aggressive B-cell non-Hodgkin lymphoma
- Treatment can be very challenging for patients with DLBCL who have received two or more prior therapies
- AZD0486 is an investigational medicine that stimulates certain cells in the immune system to kill tumor cells
- This study evaluates the activity and tolerability of increasing doses of AZD0486 in patients with DLBCL who have previously received treatment

How did we perform this research?

- Patients participating in this study had study visits with their medical team periodically after receiving AZD0486
- Blood tests and imaging studies were performed at pre-planned intervals to assess how their disease was responding to the treatment (efficacy) and how well they were tolerating the drugs (safety)

What were the findings of this research?

- In this study, AZD0486 showed anti-cancer activity in patients with DLBCL who had previously received treatment
- AZD0486 was well tolerated up to doses as high as 25 mg using a treatment schedule that includes two smaller doses prior to the full target dose

What are the implications of this research?

- Patients with DLBCL who have previously received two or more lines of treatment have poor survival outcomes
- New treatments that are effective and well tolerated are essential for these patients

Where can I access more information?

- Information about the medicine(s) being used in this study and the people who could participate can be found here: https://www.clinicaltrials.gov/study/NCT04594642

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

Poster

Supplementary material

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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

- Treating R/R DLBCL is challenging despite recent advances
- AZD0486 is an IgG4 fully human CD19xCD3 bispecific TCE with attenuated CD3 binding to minimize cytokine release (**Supplemental Figure 1**)[1]
- In patients with heavily pretreated follicular lymphoma, AZD0486 has shown promising safety and efficacy, with an ORR and CR rate of 96% and 85%, respectively, at TDs ≥2.4 mg[2]
- Here, we present safety and efficacy of an ongoing phase 1 study of AZD0486 in the cohort of patients with R/R DLBCL

Methods

Key Eligibility Criteria

- Adults with R/R B-NHL
- CD19+ by flow cytometry or IHC
- ≥2 prior lines of therapy
- Prior anti-CD19 therapies, CAR-T cells, and anti-CD20 TCE allowed
- ≥1 measurable lesion
- No active CNS disease
- No leukemic presentation
- ECOG PS ≤2

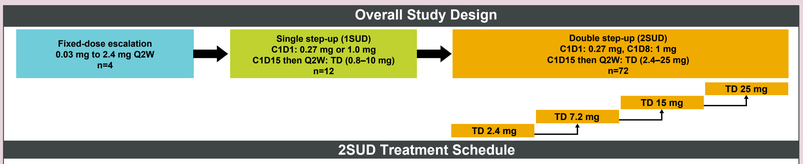
Assessments

- Disease response: PET-CT by RECIL by ICR[3]
- CRS and ICANS: ASTCT criteria[4]
- AEs: CTCAE v5.0
- MRD: PhasED-Seq CLARITY assay in plasma ctDNA (approximately <1 part/million detection limit)

Endpoints

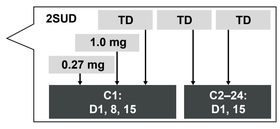
- **Primary:** safety/tolerability, PK, MTD, and RP2D
- **Secondary:** antitumor activity

Overall Study Design



2SUD Treatment Schedule

- AZD0486 is administered intravenously
- 2SUD on C1D1, C1D8 with TD on C1D15, then on D1, D15 each 28-day cycle up to 2 years
  - Cycle 1 doses were inpatient
- Patients with CR on 2 consecutive scans may receive AZD0486 every 4 weeks after C6



NCT04594642; data cutoff: 14 January 2025.

Results

Demographics and disposition

- 86 patients with R/R DLBCL received at least 1 dose of AZD0486 at doses 0.09–25 mg
- DCO: 14 January 2025
  - Median age was 66 y with 55% male patients (**Table 1**)
- A total of 43 (49%) patients prematurely discontinued treatment (n=37 disease progression; n=2 physician decision; n=2 death due to unrelated AE; n=1 withdrawal by patient; n=1 achieved CR and proceeded to transplant)

Table 1. Demographic and Baseline Characteristics in Patients With DLBCL (Safety Population)

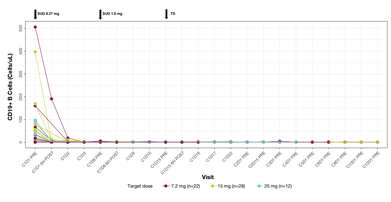
Characteristic	All Patients N=86	Patients Who Received TD ≥7.2 mg n=66
Age, median (range), y	66 (22–94)	66 (29–94)
Male	47 (55)	36 (55)
Race		
Asian	51 (59)	42 (64)
White	30 (35)	20 (30)
Black or African American	2 (2)	1 (2)
Not reported	3 (3)	3 (5)
ECOG PS at study entry		
0	37 (43)	31 (47)
1–2	49 (57)	35 (53)
Ann Arbor stage III–IV	65 (76)	52 (79)
CD20-negative disease at study entry	11 (13)[a]	8 (12)[b]
Bulky disease[c]	19 (22)	11 (17)
Elevated LDH[d]	60 (70)	44 (67)
Median prior lines of therapy (range)	3 (2–13)	3 (2–13)
3	25 (29)	16 (24)
4–5	23 (27)	18 (27)
>5	15 (17)	11 (17)
Primary refractory[e]	11 (13)	8 (12)
Refractory to last line of therapy[f]	65 (76)	49 (74)
Prior CD19-directed CAR-T	38 (44)	28 (42)
PD following prior CAR-T	9 (10)	5 (8)
3–6 mo since CAR-T	14 (16)	10 (15)
>6 mo since CAR-T	24 (28)	18 (27)
Prior types of treatment		
Polatuzumab vedotin	23 (27)	20 (30)
Lenalidomide	13 (15)	11 (17)
CD20 TCE	11 (13)	10 (15)
Autologous SCT	9 (10)	6 (9)
CD19 (non–CAR-T)	7 (8)	5 (8)
Allogeneic SCT	2 (2)	1 (2)

Values are n (%) unless otherwise noted.
[a]n=5 missing. [b]n=3 missing. [c]Defined as having the longest diameter ≥7 cm at baseline from baseline target lesion assessment. [d]Defined as LDH 1× or greater than upper limit of normal at baseline. [e]Defined as SD/PD as best response to frontline chemotherapy. [f]Defined as SD/PD as best response to last prior line of therapy or disease progression within 6 months of response to last LOT.

Mechanism of Action

- Depletion of peripheral CD19+ B cells was observed within 1 day of first priming dose of AZD0486 (**Figure 1**)

Figure 1. Peripheral B-cell Depletion Following AZD0486 Dosing (TD ≥7.2 mg)



Efficacy in Patients Receiving TDs ≥7.2 mg

- Median study follow-up was 6 mo at TDs ≥7.2 mg and responses were durable out to 35 months
- Increasing response rate was observed with increasing TD
  - A dose-dependent increase in ORR (CR/PR) was observed in patients who received TD ≥7.2 mg (**Table 2**)
  - CR was achieved in 33% (9/27) of patients who were previously CAR-T–exposed
- Of the 21 patients with CR and evaluable for MRD in the TD ≥7.2 mg cohorts, 20 (95%) achieved undetectable MRD in plasma (**Figure 2**)
- In patients who received ≥7.2 mg, median DOR was not reached; 12-mo DOR estimate was 77% (95% CI 53, 90) (**Figure 3**); 12-mo DOCR estimate was 87% (95% CI 58, 97)

Table 2. Response Rates by Target Dose (≥7.2 mg)

	Overall (N=58)			CAR-T Naive (n=31)			CAR-T Exposed (n=27)		
	n	ORR	CR rate	n	ORR	CR rate	n	ORR	CR rate
7.2 mg	24	46%	33%	9	67%	44%	15	33%	27%
15 mg	26	62%	39%	16	75%	38%	10	40%	40%
25 mg	8	75%	63%	6	83%	67%	2	50%	50%

Figure 2. MRD in Plasma by TD (≥7.2 mg)

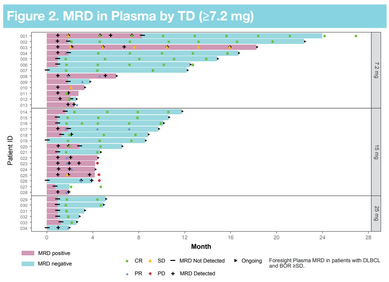
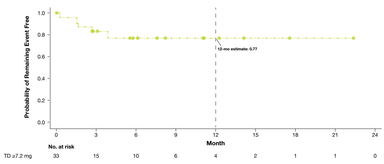


Figure 3. Duration of Response in Efficacy-evaluable Population (TD ≥7.2 mg)



Safety

- Any-grade TEAEs affecting ≥15% of patients are shown in **Table 3**
  - Grade 3/4 TEAEs observed in ≥5% of patients were neutropenia (24%), anemia (7%), and ICANS (6%)
- Higher doses were not associated with greater rates of toxicity including high-grade AEs, infections, CRS, ICANS, or serious AEs
- Among patients receiving 2SUD (n=70):
  - CRS events occurred in 34 (49%) patients; all were grade ≤2 (**Table 4**)
    - Median (IQR) time to first CRS: 1 day (1.0, 1.0)
    - 19 (27%) patients received tocilizumab
  - Grade 1–2 ICANS occurred in 10 (14%) patients; grade 3 ICANS occurred in 4 (6%) patients
    - Median (IQR) time to first ICANS: 1 day (1.0, 1.0)
    - No seizures occurred

Table 3. Summary of TEAEs

Safety population (N=86)	n (%)		
Any TEAE	86 (100)		
Serious TEAEs	34 (40)		
TEAE grade ≥3	51 (59)		
TEAE leading to discontinuation	1 (1)		
TEAE leading to dose reduction	6 (7)[a]		
Most common AEs (≥15%)	**Any grade**	**Grade 3**	**Grade 4**
CRS	42 (49)	0	0
Infections and infestations[b]	39 (45)	10 (12)	1 (1)
Neutropenia	29 (34)	9 (10)	15 (17)
Constipation	21 (24)	0	0
Anemia	20 (23)	14 (16)	0
Fatigue	20 (23)	3 (3)	0
ICANS	17 (20)	5 (6)	0
Hypogammaglobulinemia	16 (19)	0	0
Nausea	16 (19)	1 (1)	0
Diarrhea	14 (16)	0	0
Pyrexia	13 (15)	0	0

Values are n (%).
[a]All patients eventually received TD.
[b]Grouped by system organ class. One grade 5 event reported (pneumonia). COVID-19 infections reported in 9 (10%) patients (n=3 grade 1; n=6 grade 2).

Table 4. CRS and ICANS Events

AZD0486 2SUD cohort (n=70), n (%)	Grade 1	Grade 2	Grade 3	Grade ≥4	Total
CRS	30 (43)	4 (6)	0	0	34 (49)
ICANS	4 (6)	6 (9)	4 (6)	0	14 (20)

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Abbreviations

AE, adverse event; B-NHL, B-cell non-Hodgkin lymphoma; BOR, best overall response; C, cycle; CNS, central nervous system; CR, complete response; CRS, cytokine release syndrome; ctDNA, circulating tumor DNA; DCO, data cutoff; DLBCL, diffuse large B-cell lymphoma; DOCR, duration of complete response; DOR, duration of response; Fc, fragment crystallizable; ICANS, immune effector cell–associated neurotoxicity syndrome; ICR, independent central review; IHC, immunohistochemistry; mo, month; MRD, measurable residual disease; MTD, maximum tolerated dose; ORR, overall response rate; PD, progressive disease; PK, pharmacokinetics; PR, partial response; RP2D, recommended phase 2 dose; R/R, relapsed/refractory; SCT, stem cell transplantation; SD, stable disease; SUD, step-up dosing; TCE, T-cell engager; TD, target dose; TEAE, treatment-emergent adverse event