Safety and Tolerability of AZD0466 as Monotherapy for Patients with Advanced Hematological Malignancies. Preliminary Results from an Ongoing Phase I/II Trial

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Introduction

- Anti-apoptotic proteins of the BcL-2 family (e.g. Bcl-2 and Bcl-xL) are critical to tumor survival and associated with resistance to anticancer therapy.[1]
- The Bcl-2 inhibitor venetoclax has benefit in patients with acute myeloid leukemia (AML), but resistance often develops due to upregulation of anti-apoptotic proteins such as Bcl-xL and Mcl-1.[2]
- Dual inhibition of Bcl-2 and Bcl-xL has potential for broader activity than is observed with venetoclax.[3]
- AZD0466 is a novel drug-dendrimer conjugate, where the Bcl-2/xL dual inhibitor AZD4320 is chemically conjugated to Starpharma's clinically validated DEP® dendrimer platform and gradually released by hydrolysis. Drug conjugation with the dendrimer results in lower peak plasma levels than direct infusion of AZD4320 at similar doses, reducing the potential for the on-target toxicity associated with Bcl-xL inhibition.[3,4]
- AZD0466 has shown preclinical efficacy in solid[5] and hematological malignancies.[3,4]
- Preliminary results from a first-in-human study (NCT04214093) in patients with advanced solid malignancies indicated that AZD0466 is well tolerated, with no dose-limiting toxicities (DLTs) reported.

Methods

Study design

- NIMBLE (drug deNdrIMer targeting BCL2/xL in acute Leukemias; NCT04865419) is a modular, non-randomized phase I/II trial
- Module 1, Part A is a dose-escalation study of AZD0466 monotherapy (**Figure 1**) in patients who meet the following eligibility criteria:
  - Age ≥18 years
  - Eastern Cooperative Oncology Group (ECOG) performance status ≤2
  - Relapsed/refractory AML, acute lymphocytic leukemia (ALL), or intermediate or higher risk myelodysplastic syndrome (MDS) as defined by >10% blasts, and/or risk score >3 per Revised International Prognostic Scoring System
  - Received ≥1 prior line of therapy
  - No standard-of-care treatment available
  - No active central nervous system involvement
  - No treatment with reversible CYP3A inhibitors and moderate or strong mechanism-based inhibitors or inducers of CYP3A4 which cannot be discontinued within 14 days prior to the first dose of study treatment and withheld throughout the study until 14 days after the last dose of AZD0466
  - Adequate organ function; adequate cardiac function measured by left ventricular ejection fraction >50%
  - Predicted life expectancy ≥8 weeks
- No minimum platelet count at study entry is specified but patients must have a white blood cell count <10 x 10^9/L, and transfusions are permitted as part of supportive care

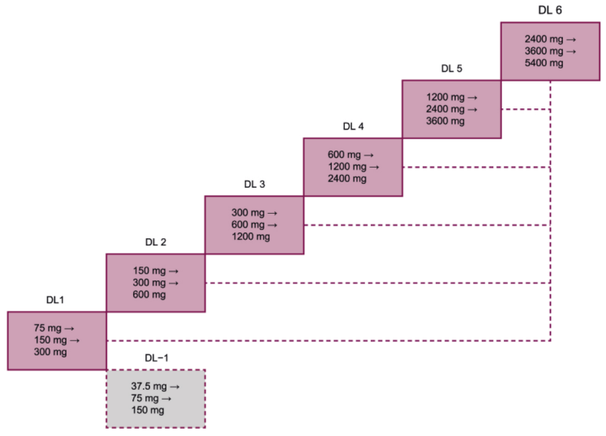
Dose escalation of AZD0466

- AZD0466 IV administration starts with a dose ramp-up on days 1 and 4 and continues with weekly administration of the target dose from day 8 of cycle 1 onwards (**Figure 1**)
- Cycle length: cycle 1 (DLT evaluation period) = 35 days; subsequent cycles = 28 days
- Decisions on escalation/de-escalation are based on an mTPI-2 design[6]
- Patients are treated until disease progression, unacceptable toxicity, or withdrawal of consent

Study objectives

- Primary objectives [endpoints]:
  - Safety and tolerability of AZD0466 in patients with advanced hematological malignancies [DLT according to predefined criteria and occurring during cycle 1, maximum tolerated dose (MTD), and recommended phase 2 dose (RP2D)]
- Secondary objectives:
  - Pharmacokinetic (PK) profile of AZD0466 following IV administration via the PK profile of the active moiety AZD4320 in plasma
  - Preliminary antitumor activity of AZD0466 by assessment of complete response, time to response, duration of response, and overall survival in patients with advanced hematologic malignancies
- Exploratory endpoints:
  - Risk of potential heart rate-corrected QT interval (QTc) prolongation of AZD0466 by concentration-QTc modeling
  - PK of AZD0466 in urine following IV administration
  - Presence, identity, and PK of plasma AZD4320 metabolites
  - Hematological improvement in patients with intermediate and higher risk MDS

Figure 1. Study design showing dose escalation of AZD0466



DL, dose level

Results

Table 1. Patient and disease characteristics at baseline*

AZD0466 dose	300 mg (n=4)	600 mg (n=4)	1200 mg (n=7)	2400 mg (n=3)	Total (n=18)
Median age, years (range)	67.5 (33–77)	71.0 (69–78)	66.0 (37–82)	50.0 (41–80)	69.0 (33–82)
Male, n (%)	3 (75.0)	2 (50.0)	4 (57.1)	1 (33.3)	10 (55.6)
Female, n (%)	1 (25.0)	2 (50.0)	3 (42.9)	2 (66.7)	8 (44.4)
Race, n (%)					
Asian	0	1 (25.0)	1 (14.3)	0	2 (11.1)
Black/African American	1 (25.0)	0	0	0	1 (5.6)
White	1 (25.0)	3 (75.0)	6 (85.7)	3 (100)	13 (72.2)
Other	1 (25.0)	0	0	0	1 (5.6)
Not reported	1 (25.0)	0	0	0	1 (5.6)
Ethnicity, n (%)					
Hispanic/Latino	2 (50.0)	0	1 (14.3)	0	3 (16.7)
Not Hispanic/Latino	2 (50.0)	4 (100)	6 (85.7)	3 (100)	15 (83.3)
ECOG performance status, n (%)					
0	0	0	3 (42.9)	1 (33.3)	4 (22.2)
1	1 (25.0)	4 (100)	4 (57.1)	2 (66.7)	11 (61.1)
2	3 (75.0)	0	0	0	3 (16.7)

*Information reflects data as of 24 September, 2022
AML, acute myeloid leukemia; ALL, acute lymphocytic leukemia; ECOG, Eastern Cooperative Oncology Group

Table 2. Disease and molecular characteristics at baseline*

AZD0466 dose	300 mg (n=4)	600 mg (n=4)	1200 mg (n=7)	2400 mg (n=3)	Total (n=18)
Disease, n (%)					
AML/secondary AML	2 (50.0)	3 (75.0)	6 (85.7)	3 (100)	14 (77.8)
ALL	2 (50.0)	1 (25.0)	1 (14.3)	0	4 (22.2)
AML or acute Leukemia of ambiguous lineage**					
AML subtype, n (%)					
M4 – Myelomonocytic leukemia	0	1 (25.0)	1 (14.3)	0	2 (11.1)
M5 – Monocytic leukemia	0	0	1 (14.3)	0	1 (5.6)
M6 – Erythroleukemia	1 (25.0)	0	0	0	1 (5.6)
Minimal maturation	0	0	2 (28.6)	1 (33.3)	3 (16.7)
Undifferentiated AML	1 (25.0)	1 (25.0)	0	0	2 (11.1)
Not applicable	0	1 (25.0)	1 (14.3)	2 (66.7)	4 (22.2)
AML type, n (%)					
De novo AML	0	1 (25.0)	2 (28.6)	3 (100)	6 (33.3)
Prior history of myeloproliferative neoplasm	0	0	2 (28.6)	0	2 (11.1)
Other	1 (25.0)	0	0	0	1 (5.6)
Secondary to chemotherapy	1 (25.0)	2 (50.0)	1 (14.3)	0	4 (22.2)
Changes in subtype/classification since initial diagnosis, n (%)					
No	2 (50.0)	3 (75.0)	5 (71.4)	2 (66.7)	12 (66.7)
Yes	0	0	0	1 (33.3)	1 (5.6)
Molecular characteristics, n (%)					
inv(3) (q21.3q26.2) or t(3;3) (q21.3;q26.2); *GATA2, MECOM*	0	0	0	1 (33.3)	1 (5.6)
BCR-ALB1	0	0	1 (14.3)	0	1 (5.6)
NPM1	0	0	1 (14.3)	0	1 (5.6)
RUNX1	0	1 (25.0)	0	0	1 (5.6)
TP53	0	1 (25.0)	0	0	1 (5.6)
Other	0	2 (50.0)	3 (42.9)	0	5 (27.8)
ALL					
B-cell ALL lineage (n=4), n (%)					
Common ALL	2 (50.0)	0	1 (14.3)	0	3 (16.7)
Not applicable	0	1 (25.0)	0	0	1 (5.6)
Changes in classification since initial diagnosis, n (%)					
No	2 (50.0)	1 (25.0)	1 (14.3)	0	4 (22.2)
Molecular characteristics, n (%)					
t (v;11q23.3); KMT2A rearranged	0	0	1 (14.3)	0	1 (5.6)
Other	0	0	1 (14.3)	0	1 (5.6)

*Information reflects data as of 24 September, 2022
**Patients with myelodysplastic syndrome were included with Protocol version 3
AML, acute myeloid leukemia; ALL, acute lymphocytic leukemia

Safety

- A summary of adverse events (AEs) is shown in **Table 3**
- No DLTs, treatment-related serious AEs, treatment-related deaths, or AEs leading to treatment discontinuation had been observed until September 24, 2022
- Eight patients experienced 17 AEs possibly related to treatment (**Table 4**)

Table 3. Safety summary*

AZD0466 dose	300 mg (n=4)	600 mg (n=4)	1200 mg (n=7)	2400 mg (n=3)	Total (n=18)
Any AE, n (%)	4 (100)	4 (100)	6 (85.7)	0	14 (77.8)
Any treatment-related AE**, n (%)	3 (75.0)	2 (50.0)	3 (42.9)	0	8 (44.4)
Any SAE, n (%)	4 (100)	0	3 (42.9)	0	7 (38.9)
Any treatment-related SAE**, n (%)	0	0	0	0	0
DLTs, n (%)	0	0	0	0	0
Treatment-related deaths**, n (%)	0	0	0	0	0
AEs leading to treatment discontinuation, n (%)	0	0	0	0	0
Any grade ≥3, n (%)	4 (100)	2 (50.0)	5 (71.4)	0	11 (61.1)

*Patient treatment is ongoing and only safety data up to 24 September, 2022 are captured
**Reasonable possibility that the AE was caused by AZD0466, as assessed by the investigator
AE, adverse event; SAE, serious adverse event; DLT, dose limiting toxicity

Table 4. Summary of treatment-related AEs*

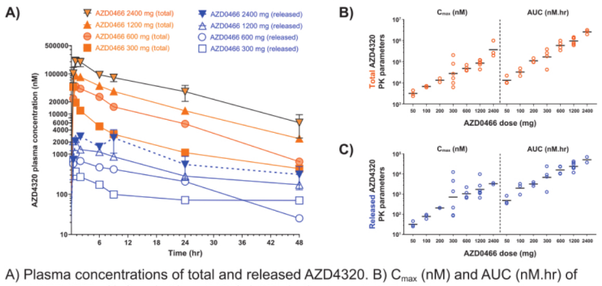
AZD0466 dose	300 mg (n=4)	600 mg (n=4)	1200 mg (n=7)	2400 mg (n=3)	Total (n=18)
Treatment-related AEs, n (%)	3 (75.0)	2 (50.0)	3 (42.9)	0	8 (44.4)
Dysgeusia	0	0	1 (14.3)	0	1 (5.6)
Diarrhea	0	0	1 (14.3)	0	1 (5.6)
Nausea	0	0	1 (14.3)	0	1 (5.6)
Febrile neutropenia	1 (25.0)**	0	2 (28.6)**	0	3 (16.7)
GGT increase	0	1 (25.0)**	0	0	1 (5.6)
Sinus tachycardia	0	1 (25.0)	0	0	1 (5.6)
Amylase increase	0	0	1 (14.3)	0	1 (5.6)
AST increase	2 (50.0)	1 (25.0)	0	0	3 (16.7)
ALT increase	1 (25.0)	1 (25.0)	0	0	2 (11.1)
Abnormal coagulation test	1 (25.0)	0	0	0	1 (5.6)
LDH increase	1 (25.0)	0	0	0	1 (5.6)
ALP increase	0	1 (25.0)	0	0	1 (5.6)

*Reasonable possibility that the AE was caused by AZD0466, as assessed by the investigator; patient treatment is ongoing and only safety data up to 24 September, 2022 are captured
**Grade 3 events; AE, adverse event; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; LDH, lactate dehydrogenase

Pharmacokinetics

- Following administration of AZD0466 2400 mg by IV infusion (**Figure 2**):
  - A dose-proportional increase in area under the concentration time curve (AUC) and maximum concentration (C_{max})
  - Released AZD4320 represents 1–5% of total AZD4320 (AUC and C_{max})
  - Released AZD4320 has a longer $T_{1/2}$ (~20 hours) relative to total AZD4320 (~10 hours)

Figure 2. Pharmacokinetics of AZD4320 following IV administration of AZD0466.



A) Plasma concentrations of total and released AZD4320. B) C_{max} (nM) and AUC (nM.hr) of total AZD4320. C) C_{max} (nM) and AUC (nM.hr) of released AZD4320.

Clinical activity

- As of September 24, 2022, no patient met the formal criteria of a response
- Of the 7 patients who had bone marrow blast counts available at screening and cycle 1 day 30, one patient showed a reduction in blast count between screening (51.0%) and the end of cycle 1 (24.4%)

Conclusions

- AZD0466 monotherapy is well tolerated, with no DLTs and no discontinuations due to treatment-related AEs observed in this trial as of September 24, 2022
- The trial continues to enroll and further dose escalation is planned

References

1. Warren C, et al. *Cell Death Disease*. 2019;21:177. 2. Lasica M & Anderson M. *J Pers Med*. 2021;11:463. 3. Patterson C, et al. *Commun Biol*. 2021;4:112. 4. Balachander S, et al. *Clin Cancer Res*. 2020;26:6535–49. 5. Arulananda S, et al. *Cell Death Discov*. 2021;7:122. 6. Guo W, et al. *Contemp Clin Trials*. 2017;58:23–33

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