Abbreviated Clinical Study Report Synopsis	
Drug Substance	AZD5991
Study Code	D6910C00001
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A Phase 1/1b/2a, 3-Part, Open-Label, Multicentre Study to Assess the Safety, Tolerability, Pharmacokinetics and Preliminary Anti-tumour Activity of Ascending Doses of AZD5991 Monotherapy and in Combination with Venetoclax in Patients with Relapsed or Refractory Haematologic Malignancies

Study dates:	First patient enrolled: 02 August 2017 Last patient last visit: 08 October 2021 The analyses presented in this report are based on a clinical data lock date of 26 July 2022
Phase of development:	Clinical pharmacology (I) Therapeutic exploratory (II)
Sponsor's Responsible Medical Officer:	Marcio Andrade Campos, MD PhD Academy House, 136 Hills Road, Cambridge CB2 8PA, United Kingdom

This study was performed in compliance with International Council for Harmonisation (ICH) Good Clinical Practice, including the archiving of essential documents.

This document contains trade secrets and confidential commercial information, disclosure of which is prohibited without providing advance notice to AstraZeneca and opportunity to object.

Study centre(s)

Patients were enrolled in 15 centres in the United States of America.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Objectives and Endpoints

Objectives	Endpoints
Part 1 and Part 2*	
Primary	
Assess the safety and the MTD of AZD5991 in patients with relapsed or refractory haematologic malignancies	• AEs • Laboratory data • Vital signs • ECG changes • ECOG status
Secondary	
• Assess the plasma PK parameters of AZD5991 • Assess preliminary tumour response	• AZD5991 concentration in plasma • Responses assessed according to protocol-specified criteria by each histology for: Best objective response, objective response rate, complete remission rate, duration of response, progression-free survival, and overall survival
Part 3	
Primary	
Assess the safety and the MTD of AZD5991 in combination with venetoclax in patients with relapsed or refractory AML/MDS	• AEs • Laboratory data • Vital signs • ECG changes • ECOG status

Objectives	Endpoints
Secondary	
• Assess the plasma PK parameters of AZD5991 and venetoclax • Assess preliminary tumour response	• AZD5991 and venetoclax concentrations in plasma • Responses assessed according to protocol-specified criteria by each histology for: best objective response, objective response rate, complete remission rate, duration of response, progression-free survival, and overall survival

Abbreviations: AE = adverse event; AML = acute myeloid leukaemia; ECG = electrocardiogram; ECOG = Eastern Co-operative Oncology Group; MDS = myelodysplastic syndromes; MTD = maximum tolerated dose; PK = pharmacokinetic(s).
* No patients were enrolled under Part 2.

Results for the secondary and exploratory objectives are not included in the abbreviated clinical study report.

Study design

This study was a 3-part, open-label, nonrandomised, multicentre, first-in-human study. Part 1 was a dose escalation of AZD5991 monotherapy; Part 2 was planned as 2 monotherapy expansions to assess efficacy in patients with acute myeloid leukaemia/myelodysplastic syndromes (AML/MDS) and in multiple myeloma (MM). Part 3 was added to explore ascending doses of AZD5991 combined with venetoclax in patients with AML/MDS.

Target population and sample size

Patients were adults with acute lymphocytic (lymphoblastic) leukaemia (ALL), AML, chronic lymphocytic leukaemia (CLL), MM, MDS, or non-Hodgkin lymphoma (NHL).

Initially, a total of about 121 patients were planned to be enrolled in this study. The number of evaluable patients in each cohort is provided in Table S2.

Table S2 Number of evaluable patients by cohort

Part	Cohort	Number of patients
1	1* 100 mg QW NHL/CLL/MM	4
	2* 150 mg QW NHL/CLL/MM	9
	Cohort 3a* 50 mg QW NHL/CLL/MM	3
	Cohort 3 250 mg QW NHL/CLL/MM	6
	Cohort 4 400 mg QW NHL/CLL/MM	7
	Cohort 5a 400 mg BIW NHL/CLL/MM	3
	Cohort 5b 800 mg QW NHL/CLL/MM	3
	Cohort 3 250 mg QW AML/MDS	8
	Cohort 4 400 mg QW AML/MDS	5
	Cohort 5a 400 mg BIW AML/MDS	5
	Cohort 5b 800 mg QW AML/MDS	5
	Cohort 6a 800 mg BIW AML/MDS	3
3a	Cohort 11 150 mg QW + venetoclax 200 mg QD AML/MDS	[redacted]
	Cohort 12 150 mg QW + venetoclax 400 mg QD AML/MDS	[redacted]
	Cohort 13 250 mg QW + venetoclax 400 mg QD AML/MDS	[redacted]
	Cohort 14 400 mg QW + venetoclax 400 mg QD AML/MDS	[redacted]
3c	Cohort 51 150 mg BIW + venetoclax 400 mg QD AML/MDS	[redacted]
	TOTAL	78

* Once weekly ramp up for Cohort 1, Cohort 2 and Cohort 3a. All the other cohorts are daily accelerated ramp up.

Abbreviations: AML = acute myeloid leukaemia; BIW = twice a week; CLL = chronic lymphocytic leukaemia; MDS = myelodysplastic syndromes; MM = multiple myeloma; NHL = non-Hodgkin lymphoma; QD = once daily; QW = once weekly.

Investigational product and comparator(s): dosage and mode of administration

AZD5991 50, 100, 150, 250, 400, or 800 mg once weekly or twice weekly intravenously, except for daily dosing as outlined for the accelerated intrapatient dose-escalation cohorts.

Venetoclax 200 or 400 mg orally once daily.

Duration of treatment

AZD5991 was administered for up to 9 cycles (1 cycle = 21 days) provided it was well tolerated and providing clinical benefit.

Venetoclax was administered until disease progression or unacceptable toxicity was observed.

Statistical methods

Descriptive statistics (including means, standard deviations, and medians for continuous variables and proportions and confidence intervals for discrete variables) were used to summarise data as appropriate.

Study population

A total of 78 patients were enrolled and received study treatment. Death and confirmed disease progression were the primary reasons for discontinuation from the study for 36 (46.2%) patients and 24 (30.8%) patients, respectively.

Sixty-one patients were enrolled into Part 1, of which there were 35 patients with NHL/CLL/MM and 26 patients with AML/MDS. There was a [redacted] in Part 3a ([redacted] with MDS and [redacted] with AML) and [redacted] AML [redacted] enrolled into Part 3c.

Summary of safety results

- The overall mean total treatment duration of exposure to AZD5991 was 5 weeks, and 4 weeks to venetoclax.
- The most frequently reported AEs overall were diarrhoea and nausea. These AEs were also the most frequently reported AEs possibly related to AZD5991. The most frequently reported AEs possibly related to venetoclax were in the blood and lymphatic disorders, investigations, and metabolism and nutrition disorders system organ classes.
- Overall, 55 (70.5%) patients experienced treatment-emergent adverse events (TEAEs) of Common Terminology Criteria for Adverse Events Grades 3-4 and 4 (5.1%) patients experienced TEAEs of Grade 5.
- Overall, 13 patients experienced a serious adverse event that the investigator considered related to AZD5991, one of which was fatal (an event of tumour lysis syndrome reported by a patient in Cohort 5b). There was only one serious AE related to venetoclax.
- During the study, 8 patients reported TEAEs of Grade 1 or 3 asymptomatic troponin I increased/ troponin T increased. Of these events, 5 were considered by the investigator to be related to AZD5991; none were related to venetoclax. No patient showed any cardiovascular symptoms. [redacted] patient in Cohort 14 (400 mg AZD5991 + 400 mg venetoclax) experienced Grade 3 troponin I increased, which was also reported as a DLT that led to clinical hold of the study. Further investigation was initiated and the results were reported internally.
- There were no clinically significant safety concerns raised by the laboratory data, vital signs, or electrocardiograms.
- Due to early termination of the study, the MTD was not determined.

Conclusion(s)

- AZD5991 may exhibit on-target class effect of cardiotoxicity. This has been observed in a few study patients with troponin elevation. But no additional cardiotoxicity was reported. Otherwise, AZD5991 does not show additional safety concerns; TEAEs were generally of low grade and manageable.

- Early efficacy analysis showed limited signal, therefore the benefit risk profile did not support continuation of the trial.