Clinical Study Report Synopsis	
Drug Substance	AZD2811
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A Phase I/II, Open-Label, Multicentre 2-Part Study to Assess the Safety, Tolerability, Pharmacokinetics, and Efficacy of AZD2811 as Monotherapy or in Combination in Treatment-Naïve or Relapsed/Refractory Acute Myeloid Leukaemia Patients Not Eligible for Intensive Induction Therapy

Study dates:	First subject enrolled: 31 July 2017 Last subject last visit: 25 March 2021 Date of early study termination: 03 February 2021 The analyses presented in this report are based on a clinical database lock date of 31 August 2021.
Phase of development:	Clinical pharmacology (I)/Therapeutic exploratory (II)
International Co-ordinating Investigator:	PPD PPD PPD PPD PPD, USA Tel: PPD
Sponsor's Responsible Medical Officer:	PPD PPD AstraZeneca, PPD PPD

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

Study centre(s)

The study was conducted at 11 sites overall: Australia (1 site), United States (10 sites)

Publications

At the time of writing this report, the following publication has been published: Donnellan WB, Atallah EL, Asch AS, Patel MR, Yang J, Eghtedar A, et al. A Phase I/II study of AZD2811 nanoparticles (NP) as monotherapy or in combination in treatment-naïve or relapsed/refractory AML/MDS patients not eligible for intensive induction therapy. Blood. 2019;134 (Suppl 1):3919.

Objectives and criteria for evaluation

Table S1 Objectives and Endpoints

Objectives	Endpoints
Primary	
• **Part A:** To determine the MTD [a] and assess the safety and tolerability of AZD2811 monotherapy or with combination agent(s) in patients with relapsed/ refractory AML [b] or treatment-naïve patients [c] not eligible for intensive induction therapy (unless representing the labelled indication of the combination partner).	• The MTD [a] was the highest dose level at which the predicted probability of a DLT was less than target probability default = 25% (see CSP Section 5.1.5) • Incidences of DLTs, AEs, and abnormal laboratory test results.
• **Part B [d]:** To assess the safety and tolerability of AZD2811 monotherapy or with combination agent(s) in patients with relapsed/refractory AML [b] or treatment-naïve patients [c] not eligible for intensive induction therapy (unless representing the labelled indication of the combination partner).	• Incidences of DLTs, AEs, and abnormal laboratory test results. [d]
Secondary	
• To characterise the PK of total AZD2811 monotherapy or with combination agent(s) in whole blood in AML patients [e]	• The following PK parameters were planned to be calculated in Part A for AZD2811, data permitting: Cycle 1 Days 1 and 4: C_{max}, t_{max}, AUC, $AUC_{(0-t)}$, $t_{1/2\lambda z}$, CL, and V_z. [e]
• To characterise the PK of venetoclax when administered in combination with AZD2811 (venetoclax combination arm [Part A only]) [e]	• The following PK parameters were planned to be calculated in Part A Group 3 (Arms A and B) for venetoclax, data permitting: Cycle 1 Day 4: C_{max}, t_{max}, and $AUC_{(0-t)}$. [e]
• To determine the biological effective dose of AZD2811 monotherapy or with combination agent(s) in AML patients in Part A [f]	• The biological effective dose was related to a clinical sign of AZD2811 activity, eg, blast cell reduction > 50% at any time after AZD2811 administration. [f]
• To evaluate the effect of AZD2811 monotherapy or with combination agent(s) on the levels of leukaemic blasts in the blood and marrow samples by standard of care analysis (morphology, flow cytometry, cytogenetics, molecular genetics) including biomarkers of activity [g]	• The number (%) of patients with bone marrow blasts categories [g]
• To assess the effect of AZD2811 monotherapy or with combination agent(s) on the rate of CR (total CR), CR + CRi, ORR (CR + CRi + PR), PR and overall survival at 6 months [h]	• Total CR, which is CR+ CRi (Dohner et al 2014) • ORR; PR; and overall survival at 6 months. [h]

[a] The MTD/RP2D dose and schedule were not determined due to early termination of the study.
[b] Prior to Amendment 4 (dated 31 Jan 2019) of the CSP, MDS patients were also enrolled in the AZD2811 monotherapy and AZD2811 + azacitidine group cohorts and are included in the safety analyses.
[c] Per protocol, treatment-naïve patients were not permitted to be enrolled in the AZD2811 + venetoclax arms.
[d] Part B dose expansion was not initiated due to early termination of the study.
[e] PK concentrations only (no PK parameters) are reported in this abbreviated clinical study report due to early termination of the study. Prior to Amendment 4 (dated 31 Jan 2019) of the CSP (see Appendix 16.1.1), MDS patients were also enrolled in the AZD2811 monotherapy and AZD2811 + azacitidine treatment groups and are included in the PK analyses.
[f] The biological effective dose was not determined.
[g] PD are not reported within this abbreviated CSR.
[h] Total CR for Part B (dose expansion), and PR and OS at 6 months were not analysed due to early termination of the study.

Exploratory objectives planned in the protocol are not reported in the CSR.

AE, adverse event; AML, acute myeloid leukaemia; AUC, area under the concentration-time curve; $AUC_{(0-t)}$, area under the concentration-time curve from zero to the time of last measurable concentration; CL, clearance; C_{max}, maximum drug concentration after single dose; CR, complete remission; CRi, complete remission with incomplete recovery; CSP, clinical study protocol; CSR, clinical study report; DLT, dose-limiting toxicity; MDS, myelodysplastic syndrome; MTD, maximum tolerated dose; ORR, overall response rate; OS, overall survival; PD, pharmacodynamics; PK, pharmacokinetic(s); PR, partial remission; RP2D, recommended Phase 2 dose; $t_{1/2\lambda z}$, terminal elimination half-life; t_{max}, time to reach maximum concentration; V_z, volume of distribution.

Study design

This Phase I/II study was designed to determine the maximum tolerated dose (MTD) and schedule, safety, tolerability, pharmacokinetics (PK), and pharmacodynamics of AZD2811 as monotherapy or in combination therapy, in relapsed/refractory acute myeloid leukaemia (AML) patients (all 3 treatment groups: AZD2811 monotherapy, AZD2811 + azacitidine, and AZD2811 + venetoclax) or treatment-naïve AML patients (AZD2811 monotherapy and AZD2811 + azacitidine treatment groups only) who were not eligible for intensive induction therapy. The study was also planned to explore the potential clinical activity by assessing preliminary anti-tumour activity. Prior to Amendment 4 (dated 31 Jan 2019) of the clinical study protocol (CSP), patients with myelodysplastic syndrome (MDS) were enrolled in the AZD2811 monotherapy and AZD2811 + azacitidine group cohorts and are included in the safety analyses.

The study design consisted of 2 parts: Part A, dose escalation, and Part B, dose expansion. The study terminated prior to completion of Part A; Part B was not initiated. Individual patients were enrolled and allocated to the most appropriate treatment option according to the investigator's judgment (defined by the most positive risk/benefit analysis for the patient) and slot availability. An evaluable patient (from CSP Amendment 7 [dated 30 September 2019] onwards) was a patient that experienced a dose limiting toxicity (DLT) or received at least ≥ 50% of the planned Cycle 1 AZD2811 dose and ≥ 50% of the planned Cycle 1 combination agent dose. For reporting purposes, DLTs were as approved and documented by the Safety Review Committee (SRC).

Evaluation of additional dose and schedule cohorts in Groups 1, 2, and 3 was driven by establishing acceptable safety and tolerability at the prior dose level and schedule per the SRC evaluation. In addition, preliminary evidence of efficacy could be considered in the decision to continue escalation of the most appropriate group(s).

Table S2 Dose Escalation Dosing Schedules in Part A

Group/Arm	AZD2811 Dosing Schedule	Combination Dosing Schedule
Group 1 Arm A	AZD2811 Day 1 and 4	N/A
Group 1 Arm B	AZD2811 Day 1, 4, 15, and 18	N/A
Group 2 Arm A	AZD2811 Day 1 and 4	Azacitidine (SOC)
Group 2 Arm B	AZD2811 Day 1, 4, 15, and 18	Azacitidine (SOC)
Group 3 Arm A	AZD2811 Day 1 and 4	Venetoclax (SOC)
Group 3 Arm B	AZD2811 Day 1, 4, 15, and 18	Venetoclax (SOC)

Due to early termination of the study, no patients were assigned for treatment per the Group 3, Arm B schedule.
N/A, not applicable; SOC, standard of care.

Target population and sample size

The study included male and female patients aged ≥ 18 years with relapsed/refractory AML or treatment-naïve AML patients not eligible for intensive induction therapy for example, due to poor performance status, age or co-morbid conditions.

Approximately 100 evaluable patients were planned to be enrolled in Groups 1, 2, and 3 of Part A. Prior to CSP Amendment 4, MDS patients were also enrolled into AZD2811 monotherapy and AZD2811/azacitidine cohorts.

Investigational product(s): dosage, mode of administration and batch numbers

Details of the investigational products are presented in Table S3.

Table S3 Details of study treatments

Investigational product	Dosage form and strength	Manufacturer	Batch number (Vendor or AZ lot ID)	P LOT ID (printed on label)
AZD2811	Frozen sterile nanoparticle suspension for constitution for infusion. Each vial contains 10 mg/mL	AstraZeneca [a]	CCI CCI CCI	CCI CCI and CCI CCI, CCI and CCI

Investigational product	Dosage form and strength	Manufacturer	Batch number (Vendor or AZ lot ID)	P LOT ID (printed on label)
Standard of care				
Azacitidine	Vials of 25 mg/mL powder for suspension for injection. After reconstitution, each vial contains a maximum of 100 mg.	Celgene Corporation [b]	NA	
Venetoclax	10 mg tablets 50 mg tablets 100 mg tablets	AbbVie Inc. [c]	CCI CCI CCI CCI	CCI CCI CCI CCI

[a] AZD2811 was supplied by AstraZeneca.

[b] Azacitidine was either sourced locally, as marketed commercially available material, or supplied by AstraZeneca in accordance with the requirements of a specific market.

[c] Venetoclax was supplied to the investigational sites by AstraZeneca.

NA=not applicable.

Duration of treatment

For the purposes of planning, 1 cycle consisted of a period of 28 days or 4 weeks.

AZD2811 was administered by intravenous (IV) infusion over 2 hours for doses up to and including a 600 mg infusion and over 4 hours for doses greater than 600 mg on Days 1 and 4 in Groups 1, 2, and 3 Arm A or on Days 1, 4, 15, and 18 in Groups 1 and 2 Arm B of each 28-day cycle. Patients continued to receive AZD2811 until disease progression, unacceptable tolerability, or discontinuation criteria were met.

Azacitidine 75 mg/m^2 of BSA by subcutaneous (SC) injection or IV infusion (per national prescribing information, if SC injection was not tolerated) was administered up to 60 minutes prior to the start of the AZD2811 infusion on Days 1 through 7 or for 5 consecutive weekdays (Days 1 through 5) with treatment holidays on the 2 weekend days (Days 6 and 7), and the remaining azacitidine dosing was administered on the first 2 weekdays of the 2nd week (Days 8 and 9) of each 28-day cycle. Patients continued to receive azacitidine until disease progression, unacceptable tolerability, or discontinuation criteria were met.

Venetoclax was administered orally, once daily, with an initial dose of 100 mg administered on Day 1, increased to 200 mg (from Day 2 onwards) daily in the first cohort and 400 mg (from Day 3 onwards) daily in the second cohort of the combination settings. The anti-fungal moderate CYP3A inhibitors fluconazole and isavuconazole were allowed in the venetoclax combination escalation but required dose adjustment of venetoclax according to the label (see

Table 2 of the CSP). Venetoclax was administered until disease progression, unacceptable tolerability, or discontinuation criteria were met.

Patients could continue AZD2811 if discontinued from the combination partner. Continuing the combination partner without AZD2811 was not permitted.

Statistical methods

No statistical testing was performed. All data were summarised descriptively including tables, listings and graphs, as appropriate.

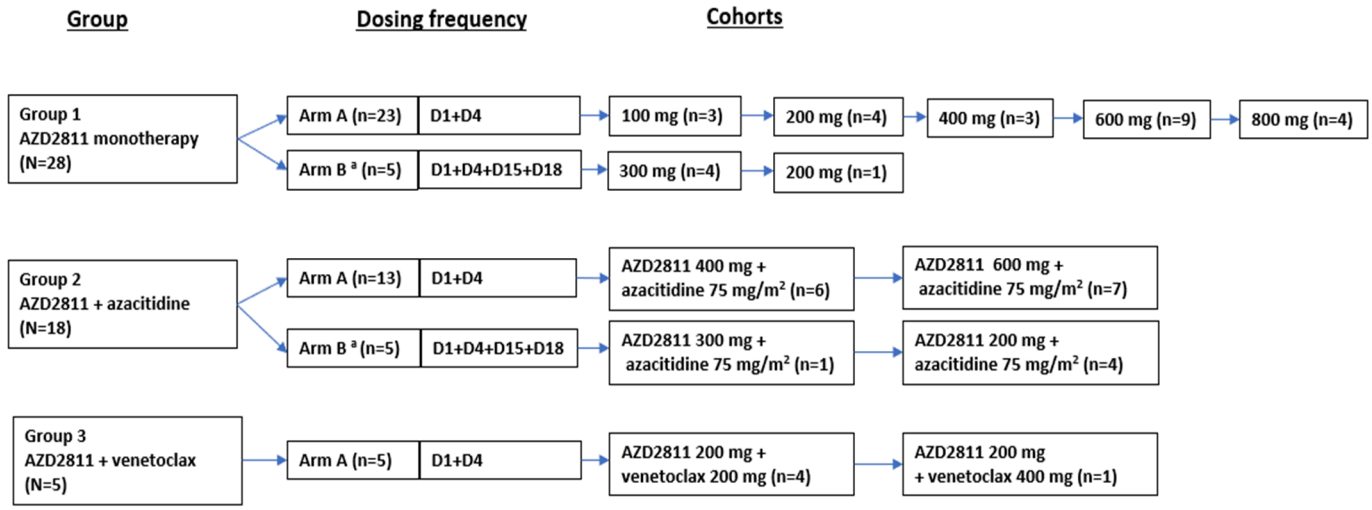
Study population

A total of 75 patients were enrolled (signed informed consent) in the study.

As a result of AstraZeneca's strategic review across the AZD2811 programme, AstraZeneca decided not to initiate Part B, and to close enrolment.

An overview of the dosing cohorts in all treatment groups is presented in Figure S1.

Figure S1 Overview of dosing cohorts



The cohorts displayed above include patients with AML and MDS assigned to and eligible for treatment. One patient in the Group 1, Arm A 600 mg cohort was not treated due to a deterioration in ECOG PS.

[a] In Arm B (D1+D4+D15+D18) of the AZD2811 monotherapy treatment group, DLTs at the initially explored dose of 300 mg resulted in a dose reduction to 200 mg; this dose reduction was also implemented in Arm B of the AZD2811 + azacitidine combination treatment group. Although doses are presented in the figure above in order of occurrence (300 mg followed by 200 mg), doses are presented in the statistical outputs in ascending order (200 mg followed by 300 mg).

Abbreviations: n, number of patients in cohort assigned to treatment; N, number of patients in group assigned to treatment.

A total of 57 patients enrolled in the study were diagnosed with AML; 41 were assigned to treatment and 40 were treated. A total of 18 patients enrolled in the study were diagnosed with MDS; 10 were assigned to treatment and 10 were treated.

Group 1 AZD2811 monotherapy patients with AML (Arm A: D1+D4): A total of 16 patients were assigned to study treatment per the Arm A schedule. Of these, 15 (93.8%) patients were treated: 3 in the AZD2811 100 mg cohort, 1 in the AZD2811 200 mg cohort, 1 in the AZD2811 400 mg cohort, 6 in the AZD2811 600 mg cohort, and 4 in the AZD2811 800 mg cohort. One patient assigned to the AZD2811 600 mg cohort was not treated due to a deterioration in Eastern Cooperative Oncology Group Performance status (ECOG PS). All 15 patients treated permanently discontinued from AZD2811; the main reason was progressive disease (13 [86.7%] patients). One patient (6.7%) in the 800 mg cohort permanently discontinued study treatment due to an adverse event (AE). At data cut-off, the majority of patients (11 [73.3%]) had completed follow up. One (6.7%) patient terminated the study due to death.

Group 1 AZD2811 monotherapy patients with AML (Arm B: D1+D4+D15+D18): A total of 5 patients were assigned to study treatment and treated in Arm B: 1 in the AZD2811 200 mg cohort, and 4 in the AZD2811 300 mg cohort. All 5 patients treated permanently discontinued from AZD2811; the main reason was progressive disease (2 [40.0%] patients). One (20.0%) patient in the 300 mg cohort discontinued study treatment due to an AE. At data cut-off, 2 [40.0%]) had completed follow up. Two (40.0%) patients terminated the study due to death.

Group 1 AZD2811 monotherapy patients with MDS (Arm A: D1+D4): A total of 7 patients were assigned to study treatment and treated per the Arm A schedule: 3 in the AZD2811 200 mg cohort, 2 in the AZD2811 400 mg cohort, and 2 in the AZD2811 600 mg cohort. All 7 patients treated permanently discontinued from AZD2811; the main reason was progressive disease (5 [71.4%] patients). The remaining 2 (28.6%) patients, both discontinued study treatment due to AEs. At data cut-off, the majority of patients (6 [85.7%]) had completed follow up. One (14.3%) patient terminated the study due to death.

Group 2 AZD2811 + azacitidine patients with AML (Arm A: D1+D4): A total of 10 patients were assigned to study treatment and treated per the Arm A schedule: 3 in the AZD2811 400 mg + azacitidine cohort and 7 in the AZD2811 600 mg + azacitidine cohort. All 10 patients treated permanently discontinued from AZD2811; the main reason for discontinuation of AZD2811 and azacitidine was progressive disease (6 [60.0%] patients). One (10.0%) patient in the 400 mg + azacitidine cohort discontinued both study treatments

due to an AE. At data cut-off, half of patients (5 [50.0%]) had completed follow up. Two (20.0%) patients terminated the study due to death.

Group 2 AZD2811 + azacitidine patients with AML (Arm B: D1+D4+D15+D18): A total of 5 patients were assigned to study treatment and treated in Arm B: 4 in the AZD2811 200 mg + azacitidine cohort, and 1 in the AZD2811 300 mg + azacitidine cohort. All 5 patients treated permanently discontinued from AZD2811 and azacitidine; the main reason for discontinuation of AZD2811 and azacitidine was physician decision (2 [40.0%] patients). In the 200 mg + azacitidine cohort, 1 (20.0%) patient discontinued both study treatments due to an AE, 1 (20.0%) due to death, and 1 (20.0%) due to progressive disease. At data cut-off, 3 (60.0%) patients had completed follow up. Two (40.0%) patients terminated the study due to death.

Group 2 AZD2811 + azacitidine patients with MDS (Arm A: D1+D4): A total of 3 patients were assigned to study treatment and treated per the Arm A schedule in the AZD2811 400 mg + azacitidine cohort. All 3 patients treated permanently discontinued from AZD2811 and azacitidine; the main reason for discontinuation of AZD2811 and azacitidine was physician decision (2 [66.7%] patients). The remaining patient (33.3%) discontinued AZD2811 and azacitidine due to an AE. At data cut-off, 2 (66.6%) patients had completed follow up.

Group 3 AZD2811 + venetoclax patients with AML (Arm A: D1+D4): A total of 5 patients were assigned to study treatment and treated per the Arm A schedule: 4 in the AZD2811 200 mg + venetoclax 200 mg cohort and 1 in the AZD2811 200 mg + venetoclax 400 mg cohort. All 5 patients treated permanently discontinued from AZD2811 and venetoclax; the main reason for discontinuation of AZD2811 and venetoclax was progressive disease (2 [40.0%] patients). One (20.0%) patient in the AZD2811 + venetoclax 200 mg cohort discontinued both study treatments and terminated the study due to death. At data cut-off, 3 (60.0%) patients had completed follow up.

The demographics and baseline characteristics of the patients who received study treatment appropriately represented the intended study population:

Group 1 AZD2811 monotherapy patients with AML (Arm A: D1+D4 and Arm B: D1+D4+D15+D18): The median age was PPD (range: PPD) in Arm A with 53.3% aged ≥ 75 years. In Arm B the median age was PPD (range: PPD) with 80.0% aged ≥ 75 years. Half of the patients were male (46.7% in Arm A and 60.0% in Arm B) and the majority were white (93.3% in Arm A and all patients [100%] in Arm B). At baseline, the majority of patients had an ECOG PS of 1 (73.3% in Arm A and 80.0% in Arm B).

Group 1 AZD2811 monotherapy patients with MDS (Arm A: D1+D4): The median age was PPD (range: PPD) with 42.9% aged ≥ 75 years. The majority of patients (85.7%)

were male and all were white. At baseline, the majority of patients in had an ECOG PS of 1 (85.7%).

Group 2 AZD2811 + azacitidine patients with AML (Arm A: D1+D4 and Arm B: D1+D4+D15+D18): The median age was PPD (range: PPD) in Arm A with 20.0% aged ≥ 75 years. In Arm B the median age was PPD (range: PPD) with 100% of patients aged < 75 years. Approximately half of the patients were male (50.0% in Arm A and 60.0% in Arm B), and the majority were white (90.0% in Arm A and 100% in Arm B). At baseline, the majority of patients had an ECOG PS of 1 (70.0% in Arm A and 60.0% in Arm B).

Group 2 AZD2811 + azacitidine patients with MDS (Arm A: D1+D4): The median age was PPD (range: PPD) with 33.3% aged ≥ 75 years. The majority of patients (66.7%) were male, and all were white. At baseline, the majority of patients had an ECOG PS of 1 (66.7%).

Group 3 AZD2811 + venetoclax patients with AML (Arm A: D1+D4): The median age was PPD (range: PPD) with 60.0% aged ≥ 75 years. The majority of patients (60.0%) were male, and all were white. At baseline, the majority of patients had an ECOG PS of 1 (80.0%).

Summary of efficacy results

The secondary endpoint of the effect of AZD2811 as monotherapy or with combination agent(s) on the rate of complete remission (CR: total CR), CR + complete remission with incomplete recovery (CRi), overall response rate (ORR: CR + CRi + partial response [PR]), and PR was assessed.

Responses for evaluable patients with AML are described below. Per statistical analysis plan (SAP), a blast count of > 20% was required at baseline to be included in the evaluable for response analysis set (Version 3.0, Appendix 16.1.9). No patients with MDS were evaluable for response or included in the evaluable for response analysis set as they did not have a baseline bone marrow blast count of > 20% rendering them not interpretable for ORR. All patients with AML who were excluded from the efficacy analysis were not evaluable for response as they did not have a baseline bone marrow blast count of > 20%, except for 1 who did not receive any study treatment. A response was considered a CR, CRi, or PR.

Group 1 AZD2811 monotherapy patients with AML (Arm A: D1+D4 and Arm B: D1+D4+D15+D18): The ORR was 7.7% (80% CI: 0.8%, 26.8%). In Arm B, of 4 evaluable patients, 1 (25.0%) patient in the AZD2811 300 mg cohort had a PR after 1 cycle of treatment that lasted 2.1 weeks. None of the 9 evaluable patients in Arm A had a response.

Group 2 AZD2811 + azacitidine patients with AML (Arm A: D1+D4 and Arm B: D1+D4+D15+D18): None of the 11 evaluable patients with AML had a response.

Group 3 AZD2811 + venetoclax patients with AML (Arm A: D1+D4): The ORR was 66.7% (80% CI: 19.6%, 96.5%). Of 3 evaluable patients, 2 patients in the AZD2811 200 mg + venetoclax 200 mg cohort had a response. One patient had a CRi after 2 cycles of treatment that lasted 7.3 weeks, and 1 patient had a CRi after 4 cycles of treatment that lasted 13.1 weeks.

Summary of pharmacokinetic results

The PK data indicated that the whole blood concentration of total AZD2811, when administered as monotherapy, increased in a manner approximately proportional to dose. Due to insufficient data (limited number of patients who received the same dose of venetoclax at Cycle 1 Day 4), venetoclax plasma concentrations over time for Group 3 were not summarised. Generally, the total AZD2811 geomean concentration-time profiles were similar at comparable doses as monotherapy or in combination with azacitidine (Arm A schedule; limited data for Arm B schedules for Group 1 and Group 2). The comparison of AZD2811 PK profiles between AZD2811 monotherapy and AZD2811 in combination with venetoclax was limited by sparse data in Group 3 Arm A.

Summary of safety results

Extent of Exposure

Group 1 AZD2811 monotherapy patients with AML (Arm A: D1+D4 and Arm B: D1+D4+D15+D18): The median duration of exposure to AZD2811 was 4.0 days (range: 4 to 32) in Arm A and 19.0 days (range: 17 to 43) in Arm B, with a median number of cycles of 1.0 (range: 1.0 to 2.0) in Arm A and 1.0 (range: 1.0 to 1.0) in Arm B.

Group 1 AZD2811 monotherapy patients with MDS (Arm A: D1+D4): The median duration of exposure to AZD2811 was 4.0 days (range: 1 to 32), with a median number of cycles of 1.0 (range: 1.0 to 1.0).

Group 2 AZD2811 + azacitidine patients with AML (Arm A: D1+D4 and Arm B: D1+D4+D15+D18): The median duration of exposure to AZD2811 was 4.0 days (range: 1 to 102) in Arm A and 56.0 days (range: 18 to 180) in Arm B, with a median number of cycles of 1.0 (range: 1.0 to 3.0) in Arm A and 2.0 (range: 2.0 to 3.0) in Arm B. The median duration of exposure to azacitidine was 9.0 days (range: 3 to 107) in Arm A and 45.0 days (range: 7 to 171) in Arm B, with a median number of cycles of 1.0 (range: 1.0 to 3.0) in Arm A and 2.0 (range: 2.0 to 2.0) in Arm B.

Group 2 AZD2811 + azacitidine patients with MDS (Arm A: D1+D4): The median duration of exposure to AZD2811 was 109.0 days (range: 32 to 137), with a median number of cycles of 4.0 (range: 2.0 to 5.0). The median duration of exposure to azacitidine was 114.0 days (range: 37 to 142), with a median number of cycles of 5.0 (range: 2.0 to 6.0).

Group 3 AZD2811 + venetoclax patients with AML (Arm A: D1+D4): The median duration of exposure to AZD2811 was 49.0 days (range: 4 to 103), with a median number of cycles of 2.0 (range: 1.0 to 3.0). The median duration of exposure to venetoclax was 57.0 days (range: 21 to 119), with a median number of cycles of 3.0 (range: 1.0 to 3.0).

Adverse events, DLTs, deaths, serious adverse events, and discontinuations of investigational product

Group 1 AZD2811 monotherapy patients with AML (Arm A: D1+D4):

AEs (any grade, regardless of causality) were reported in 14/15 (93.3%) patients; the most commonly reported (≥ 40% of patients) events by preferred term (PT) were anaemia and febrile neutropenia (6/15 [40.0%] patients each).

Grade 3 to 5 AEs were reported in 13/15 (86.7%) patients; the most commonly reported (≥ 30% of patients) events by PT were anaemia, febrile neutropenia (6/15 [40.0%] patients each), and platelet count decreased (5/15 [33.3%] patients).

Two of 4 evaluable patients in the AZD2811 800 mg cohort had a DLT; 1 had Grade 2 febrile neutropenia and Grade 3 stomatitis and 1 had Grade 3 mucosal inflammation. All events were considered causally related to AZD2811 by the investigator.

One (6.7%) patient died, and the cause was due to underlying disease.

Serious adverse events (SAEs) were reported in 9/15 (60.0%) patients; the only event by PT reported in ≥ 2 patients was febrile neutropenia (6/15 [40.0%] patients).

One (6.7%) patient had an AE that led to permanent discontinuation of AZD2811 that was an event of Grade 3 mucosal inflammation.

Group 1 AZD2811 monotherapy patients with AML (Arm B: D1+D4+D15+D18):

AEs (any grade, regardless of causality) and those considered causally related to AZD2811 were reported in 5/5 (100%) patients; the most commonly reported (≥ 40% of patients) events were anaemia, hyperglycaemia, headache, diarrhoea (3/5 [60.0%] patients each), thrombocytopenia, leukopenia, fatigue, mucosal inflammation, decreased appetite, sepsis, hypotension, and tachycardia (2/5 [40.0] patients each).

Grade 3 to 5 AEs were reported in 4/5 (80.0%) patients; the most commonly reported (≥ 30% of patients) events were anaemia (3/5 [60.0%] patients), thrombocytopenia, leukopenia, and sepsis (2/5 [40.0%] patients each). Two of 3 evaluable patients in the AZD2811 300 mg cohort had a DLT; 1 had Grade 4 alanine aminotransferase (ALT) and aspartate aminotransferase (AST) increased and Grade 3 hypertension, and 1 had a fatal event of sepsis. All events were considered causally related to AZD2811 by the investigator.

Two (40.0%) patients died, both due to AEs. SAEs were reported in 3/5 (60.0%) patients; the only event by PT reported in ≥ 2 patients was sepsis (2/5 [40.0%] patients).

One (20.0%) patient permanently discontinued AZD2811 due to a fatal event of sepsis.

Group 1 AZD2811 monotherapy patients with MDS (Arm A: D1+D4):

AEs (any grade, regardless of causality) were reported in 7/7 (100%) patients; the most commonly reported (≥ 40% of patients overall) events by PT were anaemia, neutropenia, and thrombocytopenia (3/7 [42.9%] patients each).

Grade 3 to 5 AEs were reported in 7/7 (100%) patients; the most commonly reported (≥ 30% of patients) events by PT were anaemia, neutropenia, and thrombocytopenia (3/7 [42.9%] patients each). One of 2 evaluable patients in the AZD2811 600 mg cohort had a DLT of Grade 3 oesophageal infection considered causally related to AZD2811 by the investigator.

One (14.3%) patient died due to an AE. SAEs were reported in 5/7 (71.4%) patients; the only event by PT reported in ≥ 2 patients was febrile neutropenia (2 [28.6%] patients).

Two (28.6%) patients had AEs that led to permanent discontinuation of AZD2811; 1 had a Grade 2 event of intestinal mass and a Grade 2 event of oesophageal mass, and 1 had a Grade 3 event of oesophageal infection.

Group 2 AZD2811 + azacitidine patients with AML (Arm A: D1+D4):

AEs (any grade, regardless of causality) were reported in 10/10 (100%) patients; the most commonly reported (≥ 40% of patients) events by PT were anaemia, febrile neutropenia (5/10 [50.0%] patients each), diarrhoea, fatigue, and thrombocytopenia (4/10 [40.0%] patients each).

Grade 3 to 5 AEs were reported in 10/10 (100%) patients; the most commonly reported (≥ 30% of patients) events by PT were febrile neutropenia, anaemia (5/10 [50.0%] patients each), thrombocytopenia (4/10 [40.0%] patients), and pneumonia (3/10 [30.0%] patients). One

of 3 evaluable patients in the AZD2811 400 mg + azacitidine cohort had a DLT of Grade 4 neutropenia considered causally related to AZD2811 and azacitidine by the investigator.

Two (20.0%) patients died, both due to underlying disease. SAEs were reported in 7/10 (70.0%) patients; events by PT reported in ≥ 2 patients were febrile neutropenia (5 [50.0%] patients), pneumonia (3 [30.0%] patients), and bacteraemia (2 [20.0%] patients).

One (10.0%) patient had an AE that led to permanent discontinuation of AZD2811 and azacitidine that was an event of Grade 4 neutropenia.

Group 2 AZD2811 + azacitidine patients with AML (Arm B: D1+D4+D15+D18):

AEs (any grade, regardless of causality) were reported in 5/5 (100%) patients. The most commonly reported (≥ 40% of patients) events by PT were oedema peripheral, hypophosphataemia (4/5 [80.0%] patients each), febrile neutropenia, hypoalbuminaemia, hypokalaemia, hyponatraemia (3/5 [60.0%] patients each), abdominal distension, constipation, vomiting, cough, dyspnoea, nausea, pleural effusion, oropharyngeal pain, blood creatinine increased, neutrophil count decreased, sinus bradycardia, and sinus tachycardia (2/5 [40.0%] patients each).

Grade 3 to 5 AEs were reported in 5/5 (100%) patients; the most commonly reported (≥ 30% of patients) events by PT were febrile neutropenia (3/5 [60.0%] patients) and neutrophil count decreased (2/5 [40.0%] patients). No patients had a DLT.

Two (40.0%) patients died; 1 due to an AE and 1 due to underlying disease.

SAEs were reported in 5/5 (100%) patients; all events by PT were reported in 1 patient each.

One (20.0%) patient had an AE that led to permanent discontinuation of AZD2811 and azacitidine that was an event of Grade 3 fungal infection.

Group 2 AZD2811 + azacitidine patients with MDS (Arm B: D1+D4):

AEs (any grade, regardless of causality) were reported in 3/3 (100%) patients; the most commonly reported (≥ 40% of patients) events by PT were febrile neutropenia, nausea (3/3 [100%] patients each), anaemia, thrombocytopenia, neutropenia, vomiting, constipation, mucosal inflammation, and oropharyngeal pain (2/3 [66.7%] patients each).

Grade 3 to 5 AEs were reported in 3/3 (100%) patients; the most commonly reported (≥ 30% of patients) events by PT were febrile neutropenia (3/3 [100%] patients), neutropenia, and thrombocytopenia (2/3 [66.7%] patients each). No patients had a DLT.

No patients died. SAEs were reported in 3/3 (100%) patients; The SAE reported in ≥ 2 patients was febrile neutropenia.

One (33.3%) patient had an AE that led to permanent discontinuation of AZD2811 and azacitidine that was an event of Grade 3 asthenia.

Group 3 AZD2811 + venetoclax patients with AML (Arm A: D1+D4):

AEs (any grade, regardless of causality) were reported in 5/5 (100%) patients; the most commonly reported (≥ 40% of patients) events by PT were neutropenia (3/5 [60.0%] patients), blood creatinine increased, diarrhoea, stomatitis, anaemia, thrombocytopenia, fatigue, oedema peripheral, headache, and hypomagnesaemia (2/5 [40.0%] patients each).

Grade 3 to 5 AEs were reported in 3/5 (60.0%) patients; the most commonly reported (≥ 30% of patients) events were neutropenia (3/5 [60.0%] patients), and thrombocytopenia (2/5 [40.0%] patients). No patients had a DLT.

One (20.0%) patient died, and the cause was due to an AE. SAEs were reported in 2/5 (40.0%) patients; All SAEs were reported in 1 patient each.

No patients had AEs that led to permanent discontinuation of AZD2811 and venetoclax.

Conclusion(s)

- The study was initially designed to explore AZD2811 in patients with AML and MDS; from CSP Amendment 4 onwards, only patients with AML were enrolled.
- As a result of AstraZeneca's strategic review across the AZD2811 programme, the study was terminated early. Part A data were collected for initial cohorts (no patients were assigned for treatment per the Group 3, Arm B schedule). Part B of the study was not initiated.
- The demographic and baseline characteristics of the patients who received study treatment appropriately represented the intended AML/MDS population.
- Due to early termination of the study, based on AstraZeneca's strategic review across the AZD2811 programme, the efficacy profile of AZD2811 in this patient population could not be determined with any certainty.
- There are limitations regarding the interpretation of the safety data in this patient population given the high incidence of haematological events and their downstream consequences in untreated AML/MDS patients. The safety of AZD2811 monotherapy, AZD2811 + azacitidine, and AZD2811 + venetoclax was assessed, and no new safety signal was identified in the patient populations taking part in this study.
- The MTD/RP2D dose and schedule were not determined due to early termination of the study, based on AstraZeneca's strategic review across the AZD2811 programme.

- AZD2811 monotherapy, AZD2811 + azacitidine, and AZD2811 + venetoclax had manageable safety profiles in the majority of patients across the studied doses, in these patient populations. In those patients with AML and MDS who experienced SAEs, the most common event across the treatment groups was febrile neutropenia. The majority of AEs were considered to be manageable through supportive care and/or dose modification.
- DLTs were observed within both the AZD2811 monotherapy-treated patients and AZD2811 plus azacitidine-treated patients. Almost all DLTs were observed in patients treated with higher total cycle doses of AZD2811 monotherapy.