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A Phase 1 First-in-Human Study of the MCL-1 Inhibitor AZD5991 in Patients with Relapsed/Refractory Hematologic Malignancies

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ABSTRACT

Purpose: AZD5991, a human MCL-1 inhibitor, was assessed for safety, tolerability, pharmacokinetics, and antitumor activity as monotherapy and in combination with venetoclax in patients with relapsed or refractory hematologic malignancies.

Patients and Methods: In the monotherapy cohort ($n = 61$), patients with hematologic malignancies received AZD5991 intravenously in escalating doses either once or twice weekly, following intrapatient dose escalation, during a 3-week cycle. In the combination cohort ($n = 17$), patients with acute myeloid leukemia and myelodysplastic syndrome received escalating doses of AZD5991 and venetoclax during either a 3- or 4-week cycle. Primary objectives were safety and maximum tolerated dose; secondary objectives included plasma pharmacokinetics and antitumor activity.

Results: The most common ($\geq 30\%$) adverse events were diarrhea (59.0%), nausea (55.1%), and vomiting (47.4%). Four deaths occurred because of adverse events: cardiac arrest, sepsis, tumor lysis syndrome, and acute respiratory failure; only tumor lysis syndrome was related to AZD5991. Dose-limiting toxicities occurred in five patients. Three patients with myelodysplastic syndrome achieved an objective response: one marrow complete remission without hematologic improvement, one partial remission with AZD5991 monotherapy, and one marrow complete remission with AZD5991 + venetoclax. Asymptomatic elevations of troponin I or T were observed in eight (10.3%) patients. *Post hoc* retrospective analysis revealed elevated troponin T in 14/31 patients before any AZD5991 dose and in 54/65 patients after any AZD5991 dose at or after Cycle 1. No associations were found between elevated troponin and cardiovascular risk factors.

Conclusions: Treatment with AZD5991 was associated with high incidence of laboratory troponin elevation and a low overall response rate.

Introduction

Hematologic malignancies are a major global health concern, accounting for ~6% of all cancers globally (1, 2). An estimated 1.3 million new hematologic malignancies were reported worldwide in 2020 that led to 700,000 deaths (3). Recent progress in treatment modalities has improved the chance of 10-year survival for patients with many hematologic malignancies (4). Despite these improvements, treatment resistance after relapse remains highly prevalent, in >85% of cases, making it challenging to treat relapsed/refractory (R/R) hematologic neoplasms (5–7).

B-cell lymphoma-2 (BCL-2)–family proteins are the central regulators of apoptosis consisting of both pro-apoptotic (e.g., BAX, BAK, BAD, and BIM) and anti-apoptotic proteins [e.g., BCL-2, BCL-xL, and myeloid cell leukemia 1 (MCL-1)], and their dysregulation may result in tumor initiation and progression, as well as lack of response to chemotherapy (8, 9). BCL-2 and MCL-1, two members of the anti-apoptotic subfamily, are important survival factors for many hematologic cancers. Overexpression of these proteins is associated with treatment resistance and poor prognosis (10–13). Venetoclax is a potent and selective BCL-2 inhibitor approved by the FDA and the European Medicines Agency for the treatment of acute myeloid leukemia (AML) and chronic lymphocytic leukemia (CLL; refs. 8, 12). Venetoclax has also shown promising activity in patients with $t(11; 14)$ multiple myeloma (MM; ref. 14). However, decreased sensitivity to venetoclax has been observed in patients with AML who relapsed after chemotherapy and is associated with overexpression of MCL-1 (13). Similarly, upregulation of MCL-1 has also been observed in patients with myelodysplastic syndrome (MDS; refs. 15, 16). Additionally, loss of MCL-1 sensitizes non-Hodgkin lymphoma (NHL) cells to BCL-2 inhibition (17). Thus, combination of a BCL-2 inhibitor and an MCL-1 inhibitor may be a useful approach to overcome resistance observed with monotherapy treatment (8, 11, 18).

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Translational Relevance

The prognosis remains poor for patients with various relapsed and refractory hematologic malignancies, and novel targeted therapies with fewer side effects are needed to improve the survival of patients with these cancers. Anti-apoptotic protein B-cell lymphoma-2 (BCL-2) and myeloid cell leukemia (MCL-1) are two major survival factors for many hematologic cancers. AZD5991 is a potent and selective BCL-2 homology 3 mimetic with nanomolar potency against human MCL-1 and >5,000-fold selectivity over other prosurvival BCL-2 family member proteins. In this phase 1 study, systemic administration of AZD5991 alone or in combination with venetoclax was shown to have limited clinical activity across different hematologic malignancies except in myelodysplastic syndrome. Additionally, a high incidence of troponin elevation was observed in patients across all dose levels with unknown clinical significance. These issues precluded further clinical development of AZD5991.

BCL-2 homology 3 (BH3) mimetics are a class of molecules that disrupt protein–protein interactions between prosurvival BCL-2 and pro-apoptotic BCL-2 family members (9, 19, 20). Overexpression of anti-apoptotic proteins and their binding to the BH3 α-helical domain of pro-apoptotic proteins inhibit the function of pro-apoptotic proteins and prevent the initiation of apoptosis. BH3 mimetics competitively bind to the hydrophobic cleft of the anti-apoptotic BCL-2 proteins and displace the pro-apoptotic proteins from the groove, thereby allowing the initiation of an apoptotic cascade (21–23). Hence, the approach of targeting the BH3 domain-binding groove of anti-apoptotic proteins may be beneficial in preventing inhibition of apoptosis and halting tumorigenesis (19, 21).

AZD5991 is a potent and selective BH3 mimetic with nanomolar potency against human MCL-1 (IC_{50} < 0.0031 μmol/L) and >5,000- and >8,000-fold selectivity over other prosurvival BCL-2 family member proteins such as BCL-2 and BCL-xL, respectively (18). Preclinical studies demonstrated that AZD5991 induces rapid time- and concentration-dependent activation of a sequence of hallmark apoptotic events through an MCL-1-dependent mechanism in human MM cell lines, human AML cell lines, and AML mouse models (11, 18, 24). In combination with proteosome inhibitor bortezomib, AZD5991 demonstrated enhanced efficacy in the NCI-H929 human MM xenograft model compared with either bortezomib or AZD5991 alone (18). Additionally, the combination of AZD5991 with venetoclax in vitro exhibited enhanced antitumor activity compared with single agents in AML human cell lines and mouse models (10, 18, 24). Therefore, BH3 mimetics, specifically MCL-1 inhibitors in combination with venetoclax, may help overcome resistance by increasing the sensitivity of the MCL-1 protein machinery and enhancing the apoptogenic activity of venetoclax (11, 18, 24).

Current data strongly support the use of BH3 mimetics with and without venetoclax in many different hematologic malignancies. The MCL-1 inhibitor VU661013 in combination with venetoclax causes regressions of the AML xenograft tumor model (25), and the selective MCL-1 inhibitor, S63845, demonstrated antitumor activity in preclinical hematologic and solid tumor models (26–30).

This study was a first-in-human, phase 1, open-label, dose escalation and dose expansion study that evaluated the safety, preliminary efficacy, and pharmacokinetic (PK) profile of AZD5991 monotherapy and in combination with venetoclax in adult patients with R/R hematologic malignancies.

Patients and Methods

Patients

Patients were enrolled at 15 centers in the United States. Eligible patients were aged 18 to 85 years, with histologically confirmed active R/R hematologic malignancies [AML, CLL, cutaneous T-cell lymphoma (CTCL), diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), mantle cell lymphoma, MDS, MM, mycosis fungoides (MF), Richter syndrome (RS), Sezary syndrome (SS), and Waldenstrom macroglobulinemia (WM)] with the Eastern Cooperative Oncology Group performance status (ECOG PS) ≤2. Patients with MM had to have received at least two prior lines of therapy for MM, including an immunomodulatory agent (e.g., lenalidomide), a proteasome inhibitor, and daratumumab. Patients with AML or MDS had to have received at least one prior line of therapy. Patients in both treatment groups must have had no treatment options available. R/R disease was defined as recurrence of disease after response to prior line(s) of therapy or progressive disease after completion of the treatment regimen preceding entry into the study.

Patients (except for those with AML or MDS) had adequate hematologic function with absolute neutrophil count (ANC) ≥1.0 × 10^9/L and platelet count ≥(75 × 10^9/L) or ≥35 × 10^9/L with bone marrow involvement. Enrolled patients had adequate hepatic and renal functions, defined as serum AST and ALT ≤3.0 × upper limit of normal (ULN), bilirubin ≤1.5 × ULN (except for Gilbert syndrome or a disease of nonhepatic origin), serum creatinine ≤1.5 × ULN with a creatinine clearance rate of ≥50 mL/minutes. Patients could not have had any history of pancreatitis and had to have lipase ≤1.5 × ULN and serum amylase ≤1.5 × ULN at study entry. Patients with history of a prior nonhematologic malignancy were excluded, except for those with no signs of active disease for >2 years and those with adequately treated skin cancer and carcinoma in situ. Patients with history of uncontrolled systemic disease, such as severe lung, cardiac, renal, or hepatic disease, active bleeding disorders, HIV infection, active hepatitis B or C infection, cytomegalovirus infection, central nervous system lymphoma, leptomeningeal disease or spinal cord compression, or AML with known active central nervous system involvement, hyperuricemia, or patients who had a high risk of developing renal impairment, were also excluded. A washout period of 14 days was required for any investigational study, chemotherapy, immunotherapy, or anticancer agents except for patients who required treatment sooner. Patients who had any cardiac events or procedures (i.e., angina pectoris, supraventricular arrythmia, myocarditis, heart failure NYHA Class ≥2, myocardial infarction, coronary artery bypass graft, angioplasty, vascular stent, any ventricular arrhythmia requiring therapy, stroke) in the preceding 6 months were excluded. Patients with ECG abnormalities (e.g., QT prolongation, third-degree heart block, complete bundle branch block) or patients who had left ventricular ejection fraction <55% (AML/MDS) or <40% (all other malignancies), as observed with an echocardiogram, a multigated acquisition scan, or a cardiac MRI, were also excluded. A protocol amendment excluded patients with any troponin assay reading greater than the critical value during screening. Patients who showed elevated troponin ≥ULN at screening but less than the critical value per assay were eligible for enrollment if they met all other cardiac criteria,

including a cardiac MRI and clearance by cardiology consultation. All patients provided written informed consent. Supplementary Table S1 presents data on the representativeness of our study population.

Study design and treatment

This was a phase 1, three-part, open-label, multicenter, non-randomized, first-in-human study. Part 1 involved a dose escalation of AZD5991 monotherapy in various hematologic malignancies; Part 2 was planned as monotherapy expansion in patients with R/R AML or MDS and in patients with R/R MM; however, it was not initiated, and no patients were enrolled. Part 3 involved a dose escalation of AZD5991, which was combined with venetoclax in patients with AML or MDS. A detailed study design schema is illustrated in **Fig. 1**.

In the monotherapy cohort, AZD5991 was administered intravenously in escalating doses (dose escalation starting at 100 mg), either once or twice weekly (QW or BIW), following intrapatient dose escalation during a 3-week cycle. In the combination cohort, patients with R/R AML or MDS received escalating doses of AZD5991 (starting at 150 mg QW or BIW) and venetoclax (200 or 400 mg orally once daily) during either a 3- or 4-week cycle. The study was conducted in accordance with the ethical principles originating in the Declaration of Helsinki and were consistent with the International Conference on Harmonization/Good Clinical Practice guidelines and applicable regulatory requirements. The study protocol was approved by an institutional review board or independent ethics committee prior to initiation of the study.

Study endpoints

The primary endpoints for this study were to determine the safety and the MTD of AZD5991 alone and in combination with venetoclax. Secondary endpoints were to assess the plasma PK and preliminary antitumor response of AZD5991 monotherapy and in combination with venetoclax. Exploratory endpoints included urine PK parameters, pharmacodynamics, and biomarkers to detect response or resistance, and to assess measurable residual disease. The MTD was defined as the highest dose level for which <33% of the patients experience a dose-limiting toxicity (DLT) during the DLT review period.

Safety

Safety and tolerability were measured by adverse events (AEs), serious AEs (SAEs), and laboratory assessments (i.e., hematology, clinical chemistry, and urinalysis). The frequency, severity, and relationship of AEs to study drug or abnormalities of laboratory tests were monitored. Safety assessments also included reporting on DLTs, SAEs, and AEs that led to discontinuation of study treatment. Regular protocol-defined assessments included vital signs, standard 12-lead electrocardiogram (ECG), troponin levels, change to ECOG PS, and physical examination. AEs were summarized by the *Medical Dictionary for Regulatory Activities* (MedDRA) version 25.0 system organ class and preferred term, with further categorization by maximum Common Terminology Criteria for AEs (CTCAE) grade (version 5.0). AEs were defined as any AE with a start date on or after the study treatment first-dose date, or any AE that had started before treatment and worsened on or after the study treatment first-dose date, and up to 30 days post last dose of study treatment.

Dose-limiting toxicity

For the AZD5991 monotherapy group, DLT was defined as the occurrence of any grade 5 toxicity, any grade ≥3 nonhematologic toxicity except nausea controlled by medical management, any grade 4 neutropenia lasting >7 days while receiving growth factor support, grade 4 thrombocytopenia or grade 3 thrombocytopenia with bleeding, grade ≥3 febrile neutropenia of any duration, grade 4 unexplained anemia, dosing delay caused by drug-related toxicity for >21 consecutive days, any laboratory tumor lysis syndrome (TLS) that did not resolve within 72 hours despite medical management, or clinical TLS not resolving within 7 days or resulting in end-organ damage. For patients with AML, MDS, or acute lymphocytic leukemia (ALL), grade 4 neutropenia lasting ≥42 days from start of cycle in absence of evidence of active leukemia was considered as a DLT. Patients with AML, MDS, or ALL have many disease-related symptoms and therefore expected complications from treatment including grade 3 fatigue, asthenia, nausea, fever, anorexia, or constipation, nausea, vomiting, diarrhea, expected complication of active leukemia, cytokine release syndrome resolving within 72 hours, TLS resolving within 7 days, and grade 3 or 4 electrolyte imbalance were excluded from consideration as DLTs. For the AZD5991 and venetoclax combination group, in addition to the above criteria, DLTs included grade ≥2 cardiac events such as myocardial infarction, myocarditis, heart failure, any troponin elevations associated with clinical symptoms, ECG changes, or any other objective clinical findings (e.g., echocardiogram, cardiac MRI) not attributable to an extraneous cause and possibly related to AZD5991 administration.

Tumor response

Tumor response was assessed using standard response criteria for objective response rate (ORR), complete remission rate, duration of response, progression-free survival, and overall survival. ORR was defined as the proportion of patients who achieved either a partial remission (PR) or complete remission (CR), as assessed by investigators before receiving any other anticancer therapy. Patients were assessed for response approximately every 4 weeks (±7 days) from the first dose of study drug, prior to the start of the next cycle, based on response criteria for AML and International Working Group criteria in myelodysplasia for MDS (31, 32). Best objective response (BOR) was calculated based on the overall visit responses from each response assessment. BOR was defined as the best response a patient had following first dose, but before starting any subsequent cancer therapy and up to and including progression, or the last evaluable assessment in the absence of progression or death from any cause. Tumor response in patients with ALL, CLL, NHL, CTCL, or MM was evaluated through standard response assessment (33–37).

Pharmacokinetics

Venous blood samples were collected for the determination of concentrations of AZD5991 in plasma. Within the daily dose-escalation cohort, samples were collected at predose and at the end of infusion for intrapatient escalation Days 1 to 3 or Days 1 to 4; at predose; mid infusion; end of infusion; and 0.5, 1, 3, 5, 8, and 12 hours after end of infusion for Cycle 1 Day 1 (C1D1), and at 24 hours after the end of infusion on Day 8 for C1D2. For C1D4 and D1 of each cycle ≥2, samples were collected at predose and end of infusion. For the combination cohort, samples were collected at predose, mid infusion, and at various time points after end of infusion for AZD5991 and at predose and various time points

Figure 1.
Study design. Dosage shows target dose levels after the intrapatient dose escalation. AZD5991 was administered intravenously, and venetoclax was administered orally. BIW, twice weekly; D, Day; QD, once daily; QW, once weekly; V, venetoclax.
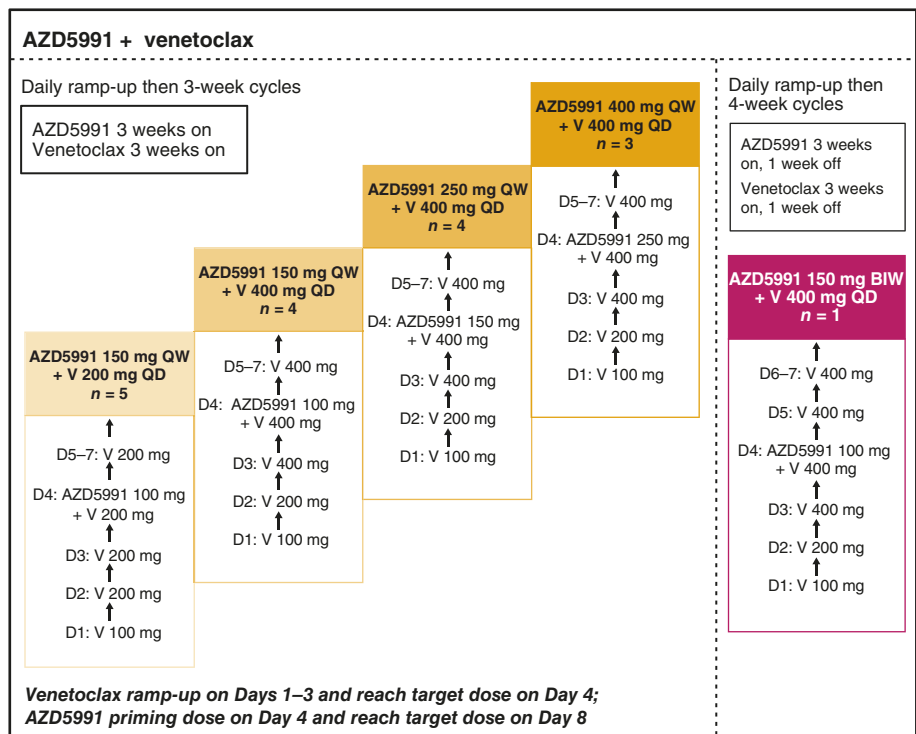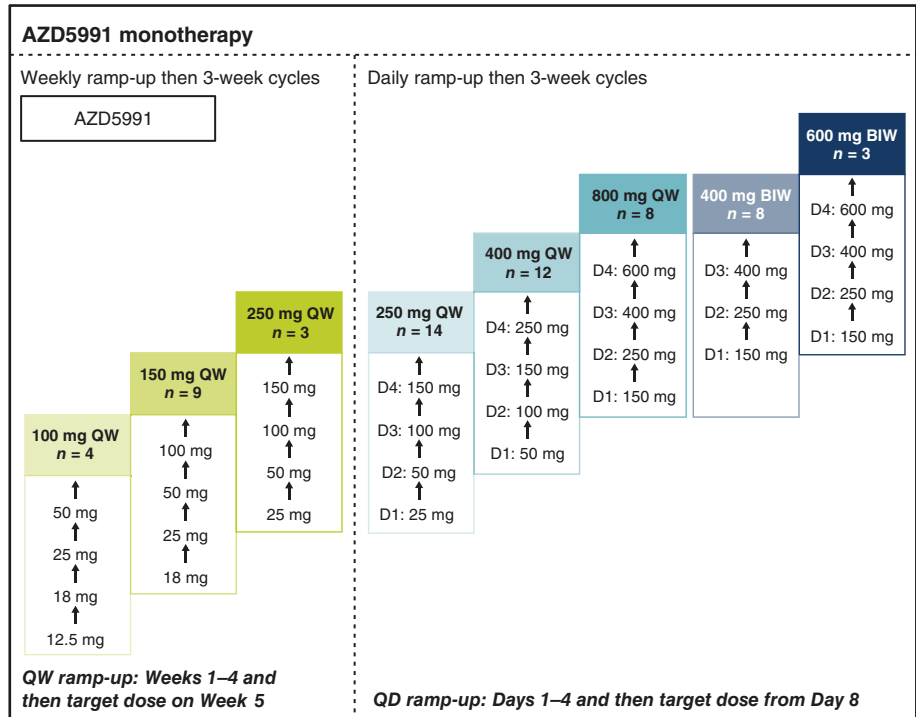
postdose for venetoclax. Blood samples for PK analysis were drawn from a site distant from where the study drug was infused to prevent erroneous drug concentrations. Samples for determination of AZD5991 and venetoclax concentrations in plasma were analyzed using an appropriate bioanalytical method (e.g., protein precipitation or HPLC-MS/MS).

Post hoc retrospective troponin analysis

A retrospective analysis of high-sensitivity troponin T (Roche cobas Elecsys Troponin T Gen 5 STAT) using stored plasma PK samples (374 samples collected at baseline and at multiple time points after AZD5991 treatment) was conducted after observing asymptomatic troponin elevation during study. Among the 66

patients, 36 had AML and 30 had non-AML disease. Samples were collected at various time points spanning from C1D1-pre, C1D1 8 hours, C1D1 12 hours, C1D1 24 hours, C2D1, and C3D1 to C4D1, with the largest number of samples at 24 hours after target dose. A validation curve to confirm assay sensitivity and specificity was performed before testing for troponin levels in the stored samples. Risk factors for the troponin elevation correlation analysis included sex, age groups, hypertension, cardiac ischemia, cardiac arrhythmia, previous anthracycline use, and other cardiovascular risk factors.

Statistical analyses

Descriptive statistics (including means, standard deviations and medians for continuous variables and proportions and confidence intervals for discrete variables) were used to summarize patient characteristics, efficacy, and PK parameters. All AEs were listed and summarized descriptively by count (n) and percentage (%). All patients who received at least one dose of AZD5991 were included in the safety analysis set, and a retrospective troponin analysis was performed. A logistic regression model was fit to determine the effects of risk factors on troponin elevation. The PK analysis set included dosed patients for whom an adequate plasma concentration was obtained and who had no important AE or protocol deviations observed that may have affected PK. The efficacy analysis set included all dosed patients with a baseline and posttreatment disease assessment. BOR, ORR, and complete remission rate were summarized by tumor types. The corresponding 95% two-sided Clopper–Pearson confidence interval was derived. All DLTs were listed along with the corresponding dose and investigator's assessment of severity and relationship to the study drug. Reasons for deaths and their relationship to AEs or study treatment were summarized. All statistical analyses were performed using SAS version 9.4 or later.

Data availability

Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure. Data for studies directly listed on Vivli can be requested through Vivli at www.vivli.org. Data for studies not listed on Vivli could be requested through Vivli at https://vivli.org/members/enquiries-about-studies-not-listed-on-the-vivli-platform/. AstraZeneca Vivli member page is also available, and it outlines further details: https://vivli.org/ourmember/astrazeneca/.

Results

Patients

As of July 26, 2022, 78 patients were treated (AZD5991 monotherapy, $n = 61$; AZD5991 + venetoclax, $n = 17$). Overall, 38 patients had AML, five had MDS, 12 had MM, six had DLBCL, five had CLL, four had RS, four had mantle cell lymphoma, two had CTCL, one had FL, and one had WM. Patient demographics and baseline disease characteristics are reported in **Table 1**. Overall, median (range) patient age was 65 (20–84) years. Most (70.5%) patients had received ≥3 prior systemic therapies; 19.2% patients had received prior radiotherapy. A total of 38 (48.7%) patients had received prior venetoclax, of whom 25 had AML (13 received AZD5991 monotherapy and 12 received AZD5991 + venetoclax). Disease progression and AEs were the primary reasons for AZD5991 discontinuation; 42/61(68.8%) patients in the monotherapy and 5/17 (29.41%) patients in the combination group discontinued the treatment because of disease progression. A total of eight patients (four in each group) discontinued AZD5991 because of AEs.

Safety

Overall, the mean (standard deviation) total duration of exposure to AZD5991 and venetoclax was 5.3 (4.3) and 4.21 (5.9) weeks, respectively. The mean (standard deviation) relative dose intensity of AZD5991 and venetoclax were 86.7% ± 16.5% and 95.1% ± 8.4%, respectively.

All patients, except for one in the AZD5991 monotherapy group, reported ≥1 AE. The most frequently reported (≥25%) AEs in all patients were diarrhea (59.0%), nausea (55.1%), vomiting (47.4%), hypokalemia (29.5%), and fatigue (25.6%; **Table 2**). Grade ≥3 AEs occurred in 59 (75.6%) patients. Overall, febrile neutropenia (17.9%) and anemia (15.4%) were the most common hematologic grade ≥3 AEs. Sepsis (12.8%) and pneumonia (7.7%) were the most common nonhematologic grade ≥3 AEs. Treatment-related AEs occurred in 57 (73.1%) patients. AZD5991-related AEs occurred in 55 (70.5%) patients, 20 of whom had grade ≥3 AEs. The most frequently reported AEs possibly related to AZD5991 were nausea, diarrhea, and vomiting, which occurred in 33 (42.3%), 27 (34.6%), and 26 (33.3%) patients, respectively. AEs possibly related to venetoclax- and combination treatment occurred in four (5.1%) and six (7.7%) patients, respectively; four (5.1%) patients had ≥grade 3 in each treatment group. Seven (41.2%) patients who received venetoclax plus AZD5991 experienced AEs possibly related to venetoclax. The most frequently reported AEs possibly related to venetoclax were hyperphosphatemia (17.6%), anemia, decreased lymphocytes, and decreased white cells (11.8% each).

A total of 40 (51.3%) patients experienced an SAE. Thirteen patients had an SAE that was considered to be related to AZD5991; 1 SAE was fatal (grade 5 TLS). There was 1 SAE (anemia) possibly related to venetoclax. Overall, 8 out of 78 (10.3%) patients discontinued AZD5991 because of AEs; in the monotherapy group, 4/61 (6.6%) patients had AEs, which included leukocytosis ($n = 1$), myocarditis ($n = 1$), TLS ($n = 1$), and acute respiratory failure ($n = 1$). In the combination group, asymptomatic elevation of troponin I was detected in 3/17 (17.6%) patients and syncope without troponin I elevation occurred in 1/17 (5.9%) patients; none of them had any known history of cardiac disease or ECG abnormalities at baseline. A total of 22 (28.2%) patients had an infusion interruption of AZD5991, caused by an AE in 15 (19.2%) patients. AZD5991 dose reduction caused by an AE was reported for one (1.3%) patient, and AZD5991 dose withholding caused by an AE was reported in nine (11.5%) patients.

Fifteen (19.2%) patients died within 30 days of the last dose of study treatment, of whom 11 (14.1%) died because of disease progression and four died because of AEs (cardiac arrest, $n = 1$; sepsis, $n = 1$; TLS, $n = 1$; acute respiratory failure, $n = 1$). All grade 5 AEs were unrelated to AZD5991, except for TLS. The patient who died of cardiac arrest had history of multiple comorbidities, including atrial fibrillation, aortic aneurysm, and hypertension. No patients who received venetoclax experienced an AE resulting in death.

DLTs occurred in 5 out of 50 patients who were DLT evaluated. DLTs were grade 3 febrile neutropenia (250 mg QW), grade 3 sepsis (400 mg QW), grade 5 TLS (800 mg QW), grade 2 myocarditis (600 mg BIW), and grade 3 troponin I increase (400 mg QW + venetoclax). The DLT of grade 3 troponin I increase led to clinical hold of the study. Because of the early termination of the study, the MTD was not determined.

Table 1. Patient demographics and disease characteristics at baseline.

Characteristics	AZD5991 (n = 61)	AZD5991 + venetoclax (n = 17)	Total (N = 78)
Age at screening (years)			
Median (range)	67 (20–84)	63 (33–84)	65 (20–84)
≥65 years	32 (52.5)	8 (47.1)	40 (51.3)
Sex			
Male	38 (62.3)	9 (52.9)	47 (60.3)
Female	23 (37.7)	8 (47.1)	31 (39.7)
Race			
Asian	1 (1.6)	0	1 (1.3)
Black or African American	7 (11.5)	1 (5.9)	8 (10.3)
White	46 (75.4)	12 (70.6)	58 (74.4)
Not reported	7 (11.5)	4 (23.5)	11 (14.1)
Ethnicity			
Hispanic or Latino	4 (6.6)	2 (11.8)	6 (7.7)
Not Hispanic or Latino	50 (82.0)	14 (82.4)	64 (82.1)
Not reported	7 (11.5)	1 (5.9)	8 (10.3)
ECOG performance status			
0	9 (14.8)	3 (17.6)	12 (15.4)
1	33 (54.1)	12 (70.6)	45 (57.7)
2	18 (29.5)	2 (11.8)	20 (25.6)
3	1 (1.6)	0	1 (1.3)
Histology			
AML	22 (36.1)	16 (94.1)	38 (48.7)
MDS	4 (6.6)	1 (5.9)	5 (6.4)
NHL			
CLL	5 (8.2)	0	5 (6.4)
DLBCL	6 (9.8)	0	6 (7.7)
FL	1 (1.6)	0	1 (1.3)
Mantle cell lymphoma	4 (6.6)	0	4 (5.1)
RS	4 (6.6)	0	4 (5.1)
CTCL			
MF	1 (1.6)	0	1 (1.3)
SS	1 (1.6)	0	1 (1.3)
MM	12 (19.7)	0	12 (15.4)
WM	1 (1.6)	0	1 (1.3)
Time since initial diagnosis to first dose of study drug (years)			
Median (range)	3 (1–21)	2 (1–4)	2 (1–21)
Number of prior systemic therapies			
1	2 (3.3)	4 (23.5)	6 (7.7)
2	12 (19.7)	5 (29.4)	17 (21.8)
3+	47 (77)	8 (47.1)	55 (70.5)
Prior radiotherapy			
Yes	12 (19.7)	3 (17.6)	15 (19.2)
No	49 (80.3)	14 (82.4)	63 (80.8)
Prior venetoclax			
Yes	26 (42.6)	12 (70.6)	38 (48.7)[a]
No	35 (57.4)	5 (29.4)	40 (51.3)

NOTE: Data are presented as n (%), unless otherwise specified.
Abbreviations: AML, acute myeloid leukemia; CLL, chronic lymphocytic leukemia; CTCL, cutaneous T-cell lymphoma; DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; FL, follicular lymphoma; MDS, myelodysplastic syndrome; MF, mycosis fungoides; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; RS, Richter's syndrome; SS, Sezary syndrome; WM, Waldenstrom macroglobulinemia.
[a]Of the patients with prior venetoclax exposure, 25 patients had AML (13 received AZD5991 monotherapy and 12 received AZD5991 + venetoclax).

Efficacy

Three of the five patients with MDS achieved an objective response, of whom two were in the AZD5991 monotherapy group (1 mCR and 1 PR), and one patient (mCR without hematologic improvement) was in the combination group. None of the patients who showed ORR had prior venetoclax exposure. One patient with MDS achieved SD. Five of the 12 (41.7%) patients with MM achieved stable disease (SD). No objective responses were observed in patients with MM or other histologies (**Table 3**).

Pharmacokinetic and troponin safety

During the study, 8 out of 78 patients reported AEs of troponin I/troponin T elevation (troponin I in seven patients including two

Table 2. Adverse events (≥15% in total population, all grades) by preferred term and by all grades and grade ≥3 (safety analysis set).

Adverse events[a,b]	AZD5991 (n = 61)		AZD5991 + venetoclax (n = 17)		Total (N = 78)	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Patients with an AE, n (%)	60 (98.4)	45 (73.8)	17 (100)	14 (82.4)	77 (98.7)	59 (75.6)
Heme related AE, n (%)						
Anemia	10 (16.4)	9 (14.8)	3 (17.6)	3 (17.6)	13 (16.7)	12 (15.4)
Febrile neutropenia	9 (14.8)	8 (13.1)	6 (35.3)	6 (35.3)	15(19.2)	14 (17.9)
Nonheme related, n (%)						
Abdominal pain	7 (11.5)	0	3 (17.6)	0	10 (12.8)	0
AST increased	11 (18.0)	2 (3.3)	1 (5.9)	1 (5.9)	12 (15.4)	3 (3.8)
Decreased appetite	11 (18.0)	1 (1.6)	3 (17.6)	1 (5.9)	14 (17.9)	2 (2.6)
Diarrhea	35 (57.4)	1 (1.6)	11 (64.7)	1 (5.9)	46 (59.0)	2 (2.6)
Dyspnea	10 (16.4)	1 (1.6)	2 (11.8)	0	12 (15.4)	1 (1.3)
Fatigue	17 (27.9)	2 (3.3)	3 (17.6)	1 (5.9)	20 (25.6)	3 (3.8)
Headache	14 (23.0)	1 (1.6)	0	0	14 (17.9)	1 (1.3)
Hypocalcemia	9 (14.8)	4 (6.6)	6 (35.3)	1 (5.9)	15 (19.2)	5 (6.4)
Hypokalemia	17 (27.9)	1 (1.6)	6 (35.3)	3 (17.6)	23 (29.5)	4 (5.1)
Hypomagnesemia	12 (19.7)	0	4 (23.5)	0	16 (20.5)	0
Hypophosphatemia	9 (14.8)	1 (1.6)	5 (29.4)	0	14 (17.9)	1 (1.3)
Nausea	30 (49.2)	1 (1.6)	13 (76.5)	2 (11.8)	43 (55.1)	3 (3.8)
Edema peripheral	11 (18.0)	0	4 (23.5%)	0	15 (19.2)	0
Pyrexia	11 (18.0)	0	1 (5.9%)	0	12 (15.4)	0
Vomiting	28 (45.9)	0	9 (52.9)	0	37 (47.4)	0

Abbreviations: AE, adverse event; AST, aspartate aminotransferase; MedDRA, Medical Dictionary for Regulatory Activities.
[a]Preferred AE term from MedDRA version: 25.0.
[b]A patient with multiple severity grades for a given AE was counted only once under the maximum severity.

grades 3–4, troponin T in one patient). Of these eight patients, six had normal baseline troponin levels and two did not have baseline troponin data available. Of the elevated troponin AEs, five were considered to be related to AZD5991 and unrelated to venetoclax, and three were considered unrelated to AZD5991. No patients complained of any cardiovascular symptoms. One patient in the combination group (AZD5991 400 mg + venetoclax 400 mg) experienced grade 3 troponin I increase, the level of which was consistent with myocardial infarction. This AE was also reported as a DLT and led to clinical hold of the study.

To further understand the observed troponin elevations, we performed a *post hoc* retrospective analysis of troponin using a high-sensitivity troponin T assay on stored PK samples. This analysis revealed elevated troponin T in 14/31 (45.2%) patients before any AZD5991 dose and in 54/65 (83.1%) of patients after any AZD5991 dose at or after Cycle 1.

Among the 31 patients with baseline and postbaseline data from the *post hoc* troponin T analysis, 14 had preexisting elevated baseline levels, and 17 had normal baseline levels, 13 of whom developed troponin T elevation post-AZD5991 treatment. Among the 14 patients who had baseline-elevated troponin T, six were in the monotherapy group and eight were in the combination group (**Table 4**). Among the 54 patients who had elevated troponin T after any AZD5991 dose at Cycle 1 or later, 40 received AZD5991 monotherapy, and 14 received combination treatment (**Table 4**). The 19 patients who had cardiac AEs (tachycardia, cardiac arrest,

Table 3. Best overall response and objective response rate.

Best overall response	AML (n = 38)	MDS (n = 5)	Others[a] (n = 35)
ORR, n (%) 95% CI	0	3 (60) [14.7, 94.7]	0
Marrow CR[b]	0	2 (40)	0
PR	0	1 (20)	0
SD	0	1 (20)	5 (14)[c]
PD/TF/Relapse	25 (66)	1 (20)	21 (60)
Not evaluable	13 (34)	0	9 (25)

Abbreviations: AML, acute myeloid leukemia; CI, confidence interval; CLL, chronic lymphocytic leukemia; CR, complete remission; CTCL, cutaneous T-cell lymphoma; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MDS, myelodysplastic syndrome; MF, mycosis fungoides; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; ORR, objective response rate; PD, progressive disease; PR, partial remission; RS, Richter syndrome; SD, stable disease; SS, Sezary syndrome; TF, treatment failure; WM, Waldenstrom macroglobulinemia.
[a]Others include DLBCL, n = 6; MM, n = 12; CLL, n = 5; FL, n = 1; RS, n = 4; mantle cell lymphoma, n = 4; WM, n = 1; CTCL (SS and MF), n = 2.
[b]One patient achieved marrow CR without hematological improvement.
[c]All patients had MM.

Table 4. Summary statistics of troponin baseline and postbaseline values by treatment group.

Post hoc retrospective Troponin T analysis	AZD5991	AZD5991 + venetoclax	Total
Patients enrolled, *n*	61	17	78
Patients with data, *n* (%)	52 (85.2)	14 (82.4)	66 (84.6)
Patients with baseline data, *n* (%)	17 (32.7)	14 (100.0)	31 (47.0)
Patients with baseline level above reference range, *n* (%)	6 (35.3)	8 (57.1)	14 (45.2)
Patients with postbaseline data, *n*	51	14	65[a]
Patients with level above reference range ULN after ≥ 1 dose of AZD5991[b], *n* (%)			
>ULN	40 (78.4)	14 (100.0)	54 (83.1)
>3 × ULN	12 (23.5)	6 (42.9)	18 (27.7)
>5 × ULN	6 (11.8)	3 (21.4)	9 (13.8)
Patients with troponin data 24 hours after AZD5991 infusion, *n*	35	10	45
Patients with level above reference range ULN after 24 hours of AZD5991 infusion[c], *n* (%)			
>ULN	26 (74.3)	10 (100)	36 (80)
>3 × ULN	6 (17.1)	6 (60.0)	12 (26.7)
>5 × ULN	3 (8.6)	3 (30.0)	6 (13.3)

Abbreviations: h, hours; ULN, upper limit of normal.
[a]One patient had only baseline result and no posttreatment results; therefore, not included in the posttreatment calculation.
[b]Any time points after ramp-up or target dose.
[c]Twenty-four hours after target dose.

cardiomyopathy, supraventricular tachycardia) also had post-dose elevation during Cycle 1, with baseline troponin elevation in seven patients. Troponin elevations were present across all cohorts and different dose levels (**Fig. 2A**) and were independent of age, sex, histology, and other patient characteristics. Although a dose-proportional increase in AZD5991 was observed across the wide dose range used (**Fig. 2B**), frequent troponin elevation was observed in the different quartiles of AZD5991 exposure with no apparent exposure-driven relationship (**Fig. 2C**).

Discussion

This phase 1 study evaluated the safety, preliminary efficacy, and PK of AZD5991 monotherapy and in combination with venetoclax in patients with R/R hematologic malignancies. Limited clinical activity was observed with AZD5991 monotherapy and in combination with venetoclax across different hematologic malignancies. Three out of five patients with MDS achieved an objective response; none of the patients with other hematologic malignancies achieved any objective response. During the trial, asymptomatic troponin elevations without an impact on left ventricular ejection fraction or ECG changes were reported, including a grade 3 troponin elevation that resulted in a clinical hold of the study by the FDA. In the *post hoc* analysis using stored plasma samples, a high incidence of asymptomatic troponin elevation was detected in patients across all cohorts and different dose levels. Notably, elevated troponin levels were observed in many patients even before administration of AZD5991. However, elevated troponin levels were not associated with any significant ECG changes (RR, PR, or QT interval), and cardiovascular risk factors did not show a correlation with elevated troponin levels. AZD5991 did not show additional major safety concerns apart from elevated troponin levels. Eventually this study was stopped based on the results of the retrospective analysis of troponin elevations and cardiovascular risk factors,

evaluation of mitigation strategies, and the risk–benefit profile of AZD5991.

There has been a significant interest in developing selective MCL-1 inhibitors; however, to date, few have entered clinical trials (Supplementary Table S2). Because of their complex protein structure, the design of specific MCL-1 inhibitors without off-target activity is difficult (18, 38). AZD5991 is a potent and direct inhibitor of MCL-1, with high selectivity and subnanomolar-binding affinity versus other BCL-2 family proteins. AZD5991 was designed to disrupt MCL-1 protein complexes, while sparing BCL-2 and BCL-xL protein complexes and thus displays the hallmarks of a specific MCL-1 inhibitor (18). Furthermore, significant cytotoxic activity of AZD5991 observed in preclinical models supported the selection of AZD5991 as a clinical candidate for the treatment of patients with hematologic malignancies (18).

Despite showing promising preclinical results, MCL-1 inhibitors in clinical trials demonstrated reduced efficacy along with unwanted cardiac side effects. S63845/S64315, which is similar to AZD5991, showed good preclinical efficacy in mantle cell lymphoma, AML, and ALL, alone or in combination with venetoclax (26–30); however, it exhibited limited clinical activity in the phase 1 study for the treatment of R/R lymphoma and MM, and the trial was stopped (NCT02992483). A phase I dose-escalation study of S64315 in patients with AML or MDS (NCT02979366) showed several DLTs related to cardiovascular function, and the study was eventually discontinued because of lack of efficacy (39). Clinical studies with S64315 in combination with other drugs such as azacitidine (NCT04629443) and VOB560 (NCT04702425) are ongoing; however, these studies are listed as active, not recruiting. A phase I study to evaluate safety, tolerability, PK, and efficacy of MCL-1 inhibitor AMG 397 in patients with selected R/R hematologic malignancies (NCT03465540) was put on hold after observing a cardiac toxicity signal (40) and was subsequently terminated. Another phase 1 study with AMG 176 showed acceptable tolerability in a preliminary analysis and is currently enrolling patients with R/R MM and AML (NCT02675452) after a brief clinical hold (40). In the AMG 176
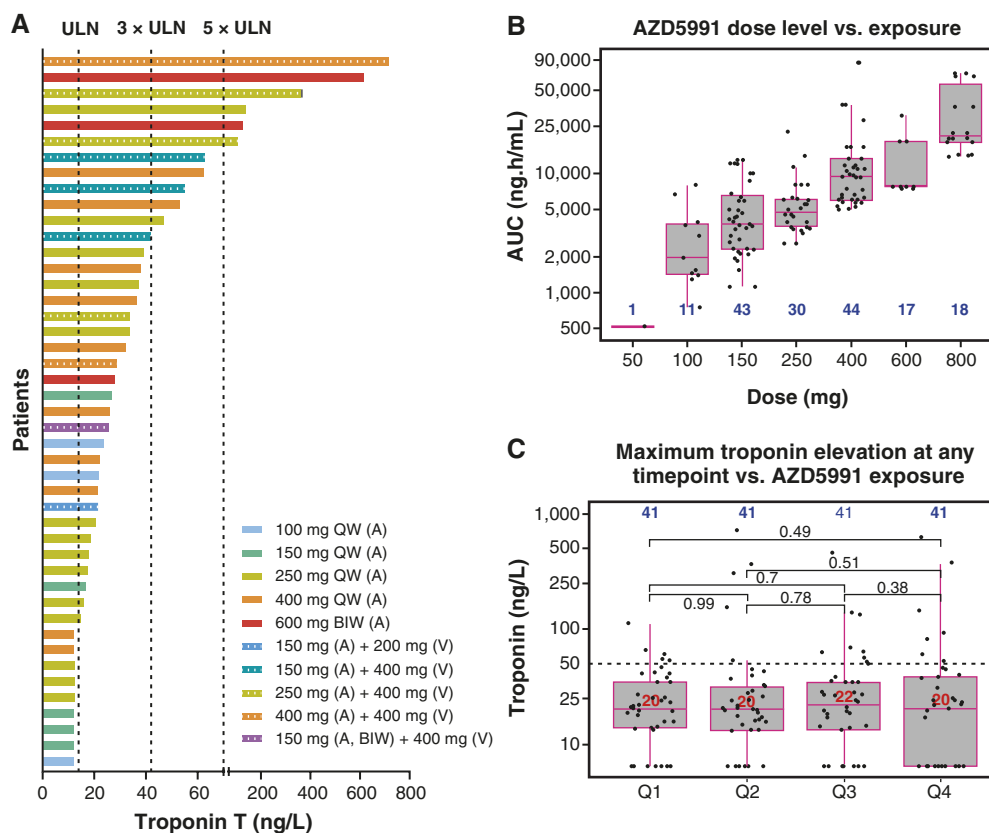
Figure 2.
Pharmacokinetics and retrospective troponin analysis. Individual patient level data on troponin elevation observed with various doses (**A**). AZD5991 dose level versus exposure (**B**). Relationship of troponin elevation with AZD5991 exposure (**C**). A, AZD5991; AUC, area under curve; BIW, twice weekly; Q, quartile; QW, once weekly; ULN, upper limit of normal; V, venetoclax.

study, grade ≥3 AEs occurred in 62% of patients, the most common of which were neutropenia, anemia, and hypertension. Although no cardiac toxicity was disclosed, there were two fatal AEs, one of which (TLS) was because of treatment. Eleven patients had SD as best response (41). A phase 1 clinical study with AMG 176 in combination with venetoclax (NCT03797261) was terminated because of safety concerns despite this combination showing robust response in AML tumor models and primary patient samples (42). Similar to the current study, the phase 1 first-in-human study with ABBV-467 in patients with R/R MM observed troponin elevation in four/eight patients, one of which was a DLT leading to study discontinuation (43). However, another MCL-1 inhibitor, PRT1419, demonstrated an acceptable safety and tolerability in a phase 1 study in patients with advanced/metastatic solid tumors. The most common AEs observed were neutropenia, nausea, diarrhea, and vomiting, and no cardiac toxicity was reported. Stable disease was recorded as the BOR (44). Clinical trials of PRT1419 alone or in combination with azacitidine or venetoclax are ongoing (45).

In summary, findings from other phase 1 trials with MCL-1 inhibitors were consistent with those observed in our study of AZD5991. We observed asymptomatic transient elevation of troponin levels in approximately half of the patients. Common grade ≥3 AEs were anemia, febrile neutropenia, AST elevation, diarrhea, and nausea, similar to the AEs observed in the phase 1

studies with AMG 176 and PRT1419. Like the dose-escalation study of S64315, several DLTs (with or without relation to cardiac events) were observed. A grade 5 TLS was also observed in our study, similar to the study with AMG 176. Of note, the combination of BCL-2 and MCL-1 inhibitors has been shown to induce severe and fatal TLS in patient-derived xenograft models, especially in models with high tumor burden (46). The risk of TLS persists with most of the novel and targeted therapy for hematologic malignancies (47). MCL-1 inhibitors may contribute to TLS, especially in patients with bulky or proliferative forms of myeloma, lymphoma, or acute leukemia (48). A few patients with MDS achieved objective response in our study, whereas a total of six patients (MDS and MM) had SD. Based on the available evidence, cardiotoxicity observed because of the systemic administration of AZD5991 may be assumed as a class effect of MCL-1 inhibitors (10, 49). MCL-1 regulates the mitochondrial network homeostasis, and inhibition of MCL may lead to the disruption of mitochondrial dynamics within cardiomyocytes, resulting in abnormal cardiac function (50). There is *in vitro* evidence that AZD5991 results in mitochondrial depolarization, mitophagy, reduced mitochondrial mass, and increased oxidative phosphorylation in NHL cells. Additionally, a decrease in mitochondrial respiratory capacity was observed in DLBCL and mantle cell lymphoma cells in response to AZD5991 (51).

Screening of AZD5991 in a diverse set of *in vitro* radioligand binding, enzyme, and functional and electrophysiological assays (including hERG and other cardiac ion channels) did not identify any off-target activities within 100-fold of the MCL-1 FRET IC_{50} (<0.0031 μmol/L; ref. 18). Nonetheless, elevations in troponin levels following combination treatment with AZD5991 and venetoclax were observed. The reason for the observed elevations in troponin levels is not entirely clear, as the results of a *post hoc* analysis of cardiovascular events factors were inconclusive. A limitation of this study was conducting a *post hoc* analysis using stored samples rather than a direct investigation of potential reasons for troponin elevation while the study was ongoing. Moreover, approximately half of the patients had an elevated troponin level at baseline. Future studies are planned to explore the mechanism behind cardiac biomarker abnormalities and possible cardiac dysfunction with AZD5991. In summary, MCL-1 inhibitors alone or in combination with current available therapies could be a promising therapeutic approach in patients with R/R malignancies if the toxicity profile of the monotherapy or combination is carefully monitored and addressed (52, 53). Given the findings of the study with regard to current toxicities, selective MCL1 inhibitors geared toward hematopoietic stem and progenitor cells may be of interest for future development.

Conclusion

Except in MDS, limited clinical activity was observed with AZD5991 monotherapy and in combination with venetoclax across different hematologic malignancies. Furthermore, a high incidence of troponin elevation was observed in patients across all dose levels. The study was discontinued to evaluate the presence of asymptomatic troponin elevations and assess the therapeutic index of AZD5991. Based on the retrospective analysis of troponin elevations and cardiovascular risk factors, as well as the risk–benefit profile of AZD5991, the study was ultimately terminated early.

Authors' Disclosures

Authors' Contributions

P. Desai: Investigation, writing–original draft, writing–review and editing. **S. Lonial:** Investigation, writing–original draft, writing–review and editing. **A. Cashen:** Data curation, writing–original draft, writing–review and editing. **M. Kamdar:** Investigation, writing–original draft, writing–review and editing. **I. Flinn:** Investigation, writing–original draft, writing–review and editing. **S. O'Brien:** Investigation, writing–original draft, writing–review and editing. **J.S. Garcia:** Investigation, writing–original draft, writing–review and editing. **N. Korde:** Investigation, writing–original draft, writing–review and editing. **J. Moslehi:** Investigation, writing–original draft, writing–review and editing. **M. Wey:** Conceptualization, writing–original draft, writing–review and editing. **P. Cheung:** Formal analysis, writing–original draft, writing–review and editing. **S. Sharma:** Writing–original draft, writing–review and editing. **D. Olabode:** Writing–original draft, writing–review and editing. **H. Chen:** Writing–original draft, writing–review and editing. **F. Ali Syed:** Writing–original draft, writing–review and editing. **M. Liu:** Validation, writing–original draft, writing–review and editing. **J. Saeh:** Supervision, writing–original draft, writing–review and editing. **M. Andrade-Campos:** Conceptualization, supervision, writing–original draft, writing–review and editing. **T.M. Kadia:** Investigation, writing–original draft, writing–review and editing. **J.S. Blachly:** Investigation, writing–original draft, writing–review and editing.

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References

1. Shapira S, Kazanov D, Mdah F, Yaakobi H, Herishanu Y, Perry C, et al. Feasibly of CD24/CD11b as a screening test for hematological malignancies. J Pers Med 2021;11:724.

2. Zhang N, Wu J, Wang Q, Liang Y, Li X, Chen G, et al. Global burden of hematologic malignancies and evolution patterns over the past 30 years. Blood Cancer J 2023;13:82.

3. Chen L, Zheng Y, Yu K, Chen S, Wang W, Gale RP, et al. Changing causes of death in persons with haematological cancers 1975–2016. Leukemia 2022;36: 1850–60.

4. Pulte D, Jansen L, Brenner H. Changes in long term survival after diagnosis with common hematologic malignancies in the early 21st century. Blood Cancer J 2020;10:56.

5. Hofmann W-K, Trumpp A, Müller-Tidow C. Therapy resistance mechanisms in hematological malignancies. Int J Cancer 2023;152:340–7.

6. Ahmed A, Killeen RB. Relapsed and refractory multiple myeloma [updated 2023 May 30]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023.

7. Zhang J, Gu Y, Chen B. Mechanisms of drug resistance in acute myeloid leukemia. Onco Targets Ther 2019;12:1937–45.

8. Perini GF, Ribeiro GN, Pinto Neto JV, Campos LT, Hamerschlak N. BCL-2 as therapeutic target for hematological malignancies. J Hematol Oncol 2018;11: 65.

9. Delbridge ARD, Strasser A. The BCL-2 protein family, BH3-mimetics and cancer therapy. Cell Death Differ 2015;22:1071–80.

10. Bolomsky A, Vogler M, Köse MC, Heckman CA, Ehx G, Ludwig H, et al. MCL-1 inhibitors, fast-lane development of a new class of anti-cancer agents. J Hematol Oncol 2020;13:173.

11. Carter BZ, Mak PY, Tao W, Warmoes M, Lorenzi PL, Mak D, et al. Mcl-1/ CDK9 targeting by AZD5991/AZD4573 overcomes intrinsic and acquired venetoclax resistance in vitro and in vivo in PDX model of AML through modulation of cell death and metabolic functions. Blood 2018;132:768.

12. Roberts AW. Therapeutic development and current uses of BCL-2 inhibition. Hematology Am Soc Hematol Educ Program 2020;2020:1–9.

13. Wei AH, Roberts AW, Spencer A, Rosenberg AS, Siegel D, Walter RB, et al. Targeting MCL-1 in hematologic malignancies: rationale and progress. Blood Rev 2020;44:100672.

14. Kumar SK, Harrison SJ, Cavo M, de la Rubia J, Popat R, Gasparetto C, et al. Venetoclax or placebo in combination with bortezomib and dexamethasone in patients with relapsed or refractory multiple myeloma (BELLINI): a randomised, double-blind, multicentre, phase 3 trial. Lancet Oncol 2020;21:1630–42.

15. Jilg S, Reidel V, Müller-Thomas C, König J, Schauwecker J, Höckendorf U, et al. Blockade of BCL-2 proteins efficiently induces apoptosis in progenitor cells of high-risk myelodysplastic syndromes patients. Leukemia 2016;30: 112–23.

16. Reidel V, Kauschinger J, Hauch RT, Müller-Thomas C, Nadarajah N, Burgkart R, et al. Selective inhibition of BCL-2 is a promising target in patients with high-risk myelodysplastic syndromes and adverse mutational profile. Oncotarget 2018;9:17270–81.

17. Phillips DC, Xiao Y, Lam LT, Litvinovich E, Roberts-Rapp L, Souers AJ, et al. Loss in MCL-1 function sensitizes non-Hodgkin's lymphoma cell lines to the BCL-2-selective inhibitor venetoclax (ABT-199). Blood Cancer J 2015; 5:e368.

18. Tron AE, Belmonte MA, Adam A, Aquila BM, Boise LH, Chiarparin E, et al. Discovery of Mcl-1-specific inhibitor AZD5991 and preclinical activity in multiple myeloma and acute myeloid leukemia. Nat Commun 2018;9:5341.

19. Townsend PA, Kozhevnikova MV, Cexus ONF, Zamyatnin AA Jr, Soond SM. BH3-mimetics: recent developments in cancer therapy. J Exp Clin Cancer Res 2021;40:355.

20. Bhatt S, Pioso MS, Olesinski EA, Yilma B, Ryan JA, Mashaka T, et al. Reduced mitochondrial apoptotic priming drives resistance to BH3 mimetics in acute myeloid leukemia. Cancer Cell 2020;38:872–90.e6.

21. Ni Chonghaile T, Letai A. Mimicking the BH3 domain to kill cancer cells. Oncogene 2008;27(Suppl 1):S149–57.

22. Villalobos-Ortiz M, Ryan J, Mashaka TN, Opferman JT, Letai A. BH3 profiling discriminates on-target small molecule BH3 mimetics from putative mimetics. Cell Death Differ 2020;27:999–1007.

23. Kale J, Osterlund EJ, Andrews DW. BCL-2 family proteins: changing partners in the dance towards death. Cell Death Differ 2018;25:65–80.

24. Zhang H, Nakauchi Y, Köhnke T, Stafford M, Bottomly D, Thomas R, et al. Integrated analysis of patient samples identifies biomarkers for venetoclax efficacy and combination strategies in acute myeloid leukemia. Nat Cancer 2020;1:826–39.

25. Ramsey HE, Fischer MA, Lee T, Gorska AE, Arrate MP, Fuller L, et al. A novel MCL1 inhibitor combined with venetoclax rescues venetoclax-resistant acute myelogenous leukemia. Cancer Discov 2018;8:1566–81.

26. Kotschy A, Szlavik Z, Murray J, Davidson J, Maragno AL, Le Toumelin-Braizat G, et al. The MCL1 inhibitor S63845 is tolerable and effective in diverse cancer models. Nature 2016;538:477–82.

27. Brennan MS, Chang C, Tai L, Lessene G, Strasser A, Dewson G, et al. Humanized Mcl-1 mice enable accurate preclinical evaluation of MCL-1 inhibitors destined for clinical use. Blood 2018;132:1573–83.

28. Opydo M, Mlyczyńska A, Mlyczyńska E, Rak A, Kolaczkowska E. Synergistic action of MCL-1 inhibitor with BCL-2/BCL-XL or MAPK pathway inhibitors enhances acute myeloid leukemia cell apoptosis and differentiation. Int J Mol Sci 2023;24:7180.

29. Dengler MA, Teh CE, Thijssen R, Gangoda L, Lan P, Herold MJ, et al. Potent efficacy of MCL-1 inhibitor-based therapies in preclinical models of mantle cell lymphoma. Oncogene 2020;39:2009–23.

30. Li Z, He S, Look AT. The MCL1-specific inhibitor S63845 acts synergistically with venetoclax/ABT-199 to induce apoptosis in T-cell acute lymphoblastic leukemia cells. Leukemia 2019;33:262–6.

31. Bloomfield CD, Estey E, Pleyer L, Schuh AC, Stein EM, Tallman MS, et al. Time to repeal and replace response criteria for acute myeloid leukemia? Blood Rev 2018;32:416–25.

32. Döhner H, Estey EH, Amadori S, Appelbaum FR, Büchner T, Burnett AK, et al. Diagnosis and management of acute myeloid leukemia in adults: recommendations from an international expert panel, on behalf of the European LeukemiaNet. Blood 2010;115:453–74.

33. Carbone PP, Kaplan HS, Musshoff K, Smithers DW, Tubiana M. Report of the Committee on Hodgkin's Disease Staging Classification. Cancer Res 1971;31: 1860–1.

34. Hallek M, Cheson BD, Catovsky D, Caligaris-Cappio F, Dighiero G, Döhner H, et al. iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. Blood 2018; 131:2745–60.

35. Olsen EA, Whittaker S, Kim YH, Duvic M, Prince HM, Lessin SR, et al. Clinical end points and response criteria in mycosis fungoides and Sézary syndrome: a consensus statement of the International Society for Cutaneous Lymphomas, the United States Cutaneous Lymphoma Consortium, and the Cutaneous Lymphoma Task Force of the European Organisation for Research and Treatment of Cancer. J Clin Oncol 2011;29:2598–607.

36. Palumbo A, Rajkumar SV, San Miguel JF, Larocca A, Niesvizky R, Morgan G, et al. International Myeloma Working Group consensus statement for the management, treatment, and supportive care of patients with myeloma not eligible for standard autologous stem-cell transplantation. J Clin Oncol 2014; 32:587–600.

37. SWOG; SWOG Data Operations Center. Oncology Research Professional (ORP) Manual 2016;1. [Online]. Available from: https://crawb.crab.org/txwb/ CRA_MANUAL/Vol1/ORP_INTRO.pdf.

38. Soderquist RS, Eastman A. BCL2 inhibitors as anticancer drugs: a plethora of misleading BH3 mimetics. Mol Cancer Ther 2016;15:2011–7.

39. ClinicalTrials.gov. NCT03672695. https://clinicaltrials.gov/study/NCT03672695. Accessed July 1, 2024.

40. Amgen. Amgen highlights new data from KYPROLIS® (carfilzomib) and oncology pipeline at IMW 2019. Thousand Oaks (CA): PRNewswire; 2019.

41. Spencer A, Rosenberg AS, Jakubowiak A, Raje N, Chatterjee M, Trudel S, et al. A phase 1, first-in-human study of AMG 176, a selective MCL-1 inhibitor, in patients with relapsed or refractory multiple myeloma. Clin Lymphoma Myeloma Leuk 2019;19:E53–54.

42. Caenepeel S, Brown SP, Belmontes B, Moody G, Keegan KS, Chui D, et al. AMG 176, a selective MCL1 inhibitor, is effective in hematologic cancer models alone and in combination with established therapies. Cancer Discov 2018;8:1582–97.

43. Yuda J, Will C, Phillips DC, Abraham L, Alvey C, Avigdor A, et al. Selective MCL-1 inhibitor ABBV-467 is efficacious in tumor models but is associated with cardiac troponin increases in patients. Commun Med 2023;3:154.

44. Falchook G, Patel M, McKean M, Philipovskiy A, Chiaverelli R, Sun W, et al. Abstract CT172: a phase 1, open-label, dose-escalation study of PRT1419, a selective induced myeloid leukemia cell differentiation protein (MCL-1) inhibitor, in patients (pts) with advanced/metastatic solid tumors. Cancer Res 2023;83:CT172.

45. Zuniga RR, Nair S, Keiffer G, Ravandi-Kashani F, Goldberg AD, Traer E, et al. Phase 1 study of PRT1419 (MCL1 inhibitor) as monotherapy or in combination with azacitidine or venetoclax in patients with relapsed/refractory myeloid or B-cell malignancies. Hematological Oncol 2023;41: 834–5.

46. Moujalled DM, Hanna DT, Hediyeh-Zadeh S, Pomilio G, Brown L, Litalien V, et al. Cotargeting BCL-2 and MCL-1 in high-risk B-ALL. Blood Adv 2020;4: 2762–7.

47. Howard SC, Trifilio S, Gregory TK, Baxter N, McBride A. Tumor lysis syndrome in the era of novel and targeted agents in patients with hematologic malignancies: a systematic review. Ann Hematol 2016;95:563–73.

48. Roberts AW, Wei AH, Huang DCS. BCL2 and MCL1 inhibitors for hematologic malignancies. Blood 2021;138:1120–36.

49. Prew MS, Adhikary U, Choi DW, Portero EP, Paulo JA, Gowda P, et al. MCL-1 is a master regulator of cancer dependency on fatty acid oxidation. Cell Rep 2022;41:111445.

50. Rasmussen ML, Taneja N, Neininger AC, Wang L, Robertson GL, Riffle SN, et al. MCL-1 inhibition by selective BH3 mimetics disrupts mitochondrial dynamics causing loss of viability and functionality of human cardiomyocytes. iScience 2020;23:101015.

51. Liu T, Lam V, Thieme E, Sun D, Wang X, Xu F, et al. Pharmacologic targeting of Mcl-1 induces mitochondrial dysfunction and apoptosis in B-cell lymphoma cells in a TP53- and BAX-dependent manner. Clin Cancer Res 2021;27:4910–22.

52. Wang H, Guo M, Wei H, Chen Y. Targeting MCL-1 in cancer: current status and perspectives. J Hematol Oncol 2021;14:67.

53. Xiang W, Yang C-Y, Bai L. MCL-1 inhibition in cancer treatment. Onco Targets Ther 2018;11:7301–14.