

A phase 2 study of ibrutinib in combination with bortezomib and dexamethasone in patients with relapsed/refractory multiple myeloma

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Abstract

Objective: We evaluated ibrutinib, a once-daily inhibitor of Bruton's tyrosine kinase, combined with bortezomib and dexamethasone in patients with relapsed or relapsed/refractory multiple myeloma who had received 1-3 prior therapies.

Methods: This was a phase 2, single-arm, open-label, multicentre study (NCT02902965). The primary endpoint was progression-free survival (PFS).

Results: Seventy-six patients were enrolled; 74 received ≥ 1 dose of study treatment. After median follow-up of 19.6 months, median PFS was 8.5 months (95% CI: 6.2-10.8); median overall survival was not reached. Overall response rate was 57% (95% CI: 45-68), and median duration of response was 9.5 months (95% CI: 6.9-10.6). Grade 3/4 AEs occurred in 73% of patients and fatal AEs occurred in 15% of patients. Incidence of major haemorrhage was 5%; one patient died from cerebral haemorrhage. After an observed increased incidence of serious (42%) and fatal (11%) infections, enrolment was suspended to implement risk-minimisation measures. The safety profile was otherwise consistent with known safety profiles of the individual drugs.

Conclusion: Ibrutinib combined with bortezomib and dexamethasone elicited clinical responses. However, efficacy assessments conducted at potential restart of enrolment indicated that the targeted PFS could not be reached with additional patient enrolment, and the study was terminated.

KEYWORDS

bortezomib, dexamethasone, ibrutinib, multiple myeloma

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1 | INTRODUCTION

Multiple myeloma (MM) is a malignancy of terminally differentiated plasma cells and is the second most common haematological malignancy after non-Hodgkin's lymphoma.^{1,2} Although novel drug combinations have improved outcomes for patients with MM, most patients will eventually relapse after initial treatment and the efficacy of salvage regimens declines with each subsequent relapse.¹ Treatment choices in the relapsed setting are influenced by various factors, such as age, performance status, comorbidities, and/or efficacy and toxicity of previous treatments; the optimal treatment remains uncertain and an area of unmet clinical need.³ Current treatment strategies involve the use of multiple agents that target specific signalling pathways involved in tumour cell growth and survival.

Bruton's tyrosine kinase (BTK) is overexpressed on MM tumour cells relative to normal plasma cells and has been implicated in the growth and survival of MM tumour cells.^{4,5} Overexpression of BTK in side population cells may contribute to the development of drug resistance in MM tumour cells.⁵ In particular, BTK-overexpressing cells demonstrated increased activity of the ATP-binding cassette (ABC) transporter efflux pump and increased expression of the ABCB1 transporter protein, thereby promoting resistance to bortezomib, doxorubicin, and etoposide.⁵ Inhibition of the drug efflux pump was able to restore sensitivity to bortezomib.⁵

Ibrutinib, a first-in-class, once-daily oral inhibitor of BTK, is approved in the United States and European Union for the treatment of various B-cell malignancies.^{6,7} Ibrutinib has been shown to suppress tumour growth and improve MM-induced bone lysis in a murine model⁴ and has demonstrated *in vitro* cytotoxicity and synergy with bortezomib and lenalidomide in malignant plasma cells from patients with MM.⁸ In patients with relapsed/refractory (R/R) MM, ibrutinib demonstrated encouraging activity in combination with dexamethasone⁹ and in combination with carfilzomib plus dexamethasone,¹⁰ warranting further investigation of ibrutinib with steroids and proteasome inhibitors. Bortezomib, in combination with dexamethasone, is currently approved for the treatment of R/RMM.^{11,12}

This study was designed to assess the efficacy, safety, and tolerability of the addition of ibrutinib to the established treatment regimen of bortezomib and dexamethasone in patients with relapsed or R/R MM.

2 | METHODS

2.1 | Study design and patients

PCYC-1139 (ClinicalTrials.gov identifier, NCT02902965) was a non-randomised, open-label, international, multicentre, sponsor-initiated, phase 2 study conducted at multiple sites in Europe. Eligible patients were aged ≥ 18 years with a diagnosis of active MM per International Myeloma Working Group (IMWG) criteria,¹³ had received one to three prior lines of therapy, and had demonstrated progressive disease (PD) since completion of their most

Novelty statements

- What is the new aspect of your work?
 - This study evaluated the novel combination of ibrutinib, a once-daily oral inhibitor of Bruton's tyrosine kinase, with bortezomib plus dexamethasone in patients with relapsed/refractory multiple myeloma. Bruton's tyrosine kinase is overexpressed on multiple myeloma cells and may contribute to development of drug resistance. Ibrutinib has demonstrated *in vitro* synergy with bortezomib and encouraging activity in combination with dexamethasone and carfilzomib plus dexamethasone in phase 1 and 2 studies in patients with relapsed/refractory multiple myeloma.
- What is the central finding of your work?
 - Ibrutinib in combination with bortezomib and dexamethasone elicited clinical responses. However, the study was closed early after efficacy assessments indicated that the targeted median progression-free survival of >12 months could not be reached with the enrolment of additional patients.
- What is (or could be) the specific clinical relevance of your work?
 - The optimal treatment for multiple myeloma in the relapsed/refractory setting remains uncertain and an area of unmet clinical need. Despite strong rationale based on preclinical and early clinical studies, the combination of ibrutinib with bortezomib and dexamethasone did not demonstrate sufficient activity to warrant further study in patients with relapsed/refractory multiple myeloma. Clinical studies evaluating the safety and efficacy of novel combinations are critical to identifying more effective salvage treatment options for patients with multiple myeloma. The information gained from these studies of novel combinations, regardless of the outcome, can help to inform future studies seeking to address this unmet clinical need.

recent treatment regimen. Patients could have received prior bortezomib treatment but must not have been refractory or non-responsive to bortezomib treatment. All patients were required to have measurable disease, defined as at least one of the following: serum monoclonal protein (SPEP) ≥ 1 g/dL (for patients with immunoglobulin [Ig] A, IgD, IgE, or IgM MM SPEP ≥ 0.5 g/dL) or urine monoclonal protein ≥ 200 mg by 24-hour urine electrophoresis. Additional inclusion criteria were Eastern Cooperative Oncology Group performance status ≤ 2 and adequate haematological (absolute neutrophil count $\geq 1.5 \times 10^9/L$; platelet count $\geq 75 \times 10^9/L$), hepatic, and renal function. Patients were excluded if they had primary refractory disease (defined as failure to achieve a minimal response or better with any therapy); had disease refractory



(defined as progression on treatment or within 60 days of completion) or non-responsive (defined as failure to achieve minimal response or better) to prior proteasome inhibitor therapy; had a history of plasma cell leukaemia, primary amyloidosis, or POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin abnormalities) syndrome within 12 months prior to first administration of study treatment; peripheral neuropathy grade ≥ 2 or grade 1 with pain at screening; had currently active or clinically significant cardiovascular disease (uncontrolled arrhythmia or class III or IV congestive heart failure as defined by the New York Heart Association Functional Classification), or a history of myocardial infarction, unstable angina, or acute coronary syndrome within 6 months prior to enrolment; had currently active, clinically significant hepatic impairment (mild impairment or worse by Child-Pugh classification); or required treatment with strong CYP3A inhibitors.

After 74 patients had initiated study treatment, study enrolment was suspended because of an initially observed increase of serious and fatal infections. During the enrolment halt, enrolled patients continued to receive treatment with the immediate implementation of risk-minimisation measures, which included modifications to the dexamethasone dosing regimen that effectively halved the dose of dexamethasone in the triple combination (described in "Treatments" section below), and strengthened guidance for infection prophylaxis. A Safety Review Committee was also established to evaluate the rate of new infections every 6 weeks following implementation of the risk-minimisation measures and enrolment was approved to restart approximately 6 months after the enrolment halt as a result of these risk-minimisation measures. However, an evaluation of the efficacy data performed at this time indicated that the primary endpoint was unlikely to be achieved. As a result, the study was terminated and enrolment was not restarted.

The study was conducted in accordance with International Conference on Harmonization guidelines for Good Clinical Practice and principles of the Declaration of Helsinki. The protocol and its amendments were approved by independent ethics committees of all participating institutions and all patients provided written informed consent.

2.2 | Treatments

During cycles 1 to 8, patients received oral ibrutinib 840 mg once daily in combination with subcutaneous bortezomib 1.3 mg/m^2 on days 1, 4, 8, and 11 and oral dexamethasone 20 mg on days 1, 2, 4, 5, 8, 9, 11, and 12 of each 21-day cycle. With the implementation of risk-minimisation measures, dosing of dexamethasone was limited to days 1, 4, 8, and 11. During cycles 9 to 12, patients received ibrutinib 840 mg once daily in combination with bortezomib 1.3 mg/m^2 on days 1, 8, 22, and 29, and dexamethasone 20 mg on days 1, 2, 8, 9, 22, 23, 29, and 30 of each 42-day cycle. With the implementation of risk-minimisation measures, dosing of dexamethasone was limited to days 1, 8, 22, and 29. From cycle

13 onward, patients received ibrutinib 840 mg once daily in combination with dexamethasone 40 mg once weekly in each 28-day cycle. For patients aged >75 years, adjustment of the dexamethasone dose to 10 mg was recommended for cycles 1 to 12, and adjustment to 20 mg was recommended for cycle 13 onward, at the discretion of the investigator. Treatment with ibrutinib plus dexamethasone was continued until PD, unacceptable toxicity, or other protocol-specified reason for discontinuation.

2.3 | Outcomes and assessments

Efficacy endpoints were assessed by investigators according to IMWG criteria.¹³ The primary efficacy endpoint was progression-free survival (PFS), defined as the time from the first dose of study treatment to confirmed PD or death from any cause. Secondary endpoints were overall response rate (ORR), defined as partial response or better; PFS rate at landmark time points; duration of response, defined as the time from initial documentation of response to the first documented evidence of PD; overall survival (OS), defined as the time from the first dose of study treatment to death from any cause; time to progression, defined as the time from the first dose of study treatment until PD; and the safety and tolerability of ibrutinib in combination with bortezomib and dexamethasone. Pharmacokinetic characteristics of ibrutinib and bortezomib when given in combination with dexamethasone were assessed as an exploratory endpoint.

Response and progression were assessed per IMWG criteria¹³ every 3 weeks during cycles 2 to 12 and every 4 weeks thereafter. In case of suspected complete response, pertinent assessments were performed per the IMWG response assessment guidelines. Following confirmed PD, patients were contacted approximately every 12 weeks for long-term survival follow-up. Plasma samples for analysis of ibrutinib and bortezomib pharmacokinetics were collected predose and at 30 minutes; 1, 2, 4, and 6 hours postdose on day 1 of cycle 2; and predose on day 2 of cycle 2.

Safety assessments included adverse events (AEs), laboratory evaluations, physical examinations, and vital signs. Adverse events were monitored throughout treatment until 30 days after the last dose of study treatment. Adverse events were coded by preferred term using the Medical Dictionary for Regulatory Activities (MedDRA), version 21.1, and were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.

2.4 | Statistical analysis

Efficacy and safety were evaluated in all patients who received at least one dose of study treatment. Time-to-event endpoints were estimated using the Kaplan-Meier method. For PFS, two-sided 95% confidence intervals (CIs) were calculated using the Brookmeyer-Crowley method with the log-log transformed Greenwood variance estimate to test the null hypothesis. For ORR, two-sided 95% CIs were



calculated using the exact binomial method. Pharmacokinetics were analysed by non-compartmental methods using Phoenix WinNonlin (Certara USA Inc), and AEs were summarised descriptively.

A sample size of approximately 125 patients was required to achieve 80% power at a one-sided 0.025 significance level to test the null hypothesis of median PFS ≤ 8 months versus ≥ 12 months under the alternative hypothesis, with the assumption that the PFS follows an exponential distribution. However, a review of the available efficacy data at the time of potential restart of enrolment indicated that the primary endpoint was unlikely to be achieved; therefore, hypothesis testing for PFS was not performed.

2.5 | Data sharing statement

Requests for access to individual participant data from clinical studies conducted by Pharmacyclics LLC, an AbbVie Company, can be submitted through Yale Open Data Access (YODA) Project site at <http://yoda.yale.edu>.

3 | RESULTS

3.1 | Patients

A total of 76 patients were enrolled, and 74 patients received at least one dose of study treatment (Table 1). Median age was 67.5 years and 61% were aged ≥ 65 years (Table 2). All patients had received prior systemic therapy for MM; 61% of patients had received one line of therapy and 39% had received two or three lines of therapy. The most common prior systemic therapies (reported in $\geq 30\%$ of patients) were dexamethasone (88%), bortezomib (81%), cyclophosphamide (65%), lenalidomide (39%), and melphalan (31%). Overall, 39% of all patients were refractory to the last line of therapy. At the time of final analysis, all patients had discontinued study treatment; the most common reasons for discontinuation were PD (50%), AEs (18%), and patient withdrawal (14%) (Table 1). The median follow-up duration was 19.6 months (range, 0.2-24.6).

TABLE 1 Patient disposition

	Patients
Enrolled, n	76
Did not receive treatment, n	2
Started treatment, n	74
Discontinued treatment, n (%)	74 (100)
Progressive disease	37 (50)
Adverse event	13 (18)
Withdrawal by patient	10 (14)
Death	7 (9)
Physician decision	4 (5)
Study termination by sponsor	3 (4)

3.2 | Safety

The median duration of treatment was 5.7 months (range, 0.1-23.7) for ibrutinib, 4.5 months (range, 0.0-12.6) for bortezomib,

TABLE 2 Baseline demographic and disease characteristics

Characteristics	Patients N = 74
Age	
Median, years (range)	67.5 (37-86)
≥ 65 y, n (%)	45 (61)
Male sex, n (%)	35 (47)
White race, n (%)	71 (96)
ECOG PS, n (%)	
0	43 (58)
1	27 (36)
2	4 (5)
Median time since diagnosis, years (range)	4.2 (0.4-13.7)
ISS stage at baseline, n (%)	
I	25 (34)
II	29 (39)
III	20 (27)
Measurable disease, n (%)	
UPEP only	6 (8)
SFLC only	0
SPEP only	42 (57)
SPEP and UPEP	26 (35)
Immunoglobulin (Ig) heavy chain class, n (%)	
IgA	21 (28)
IgE	0
IgG	49 (66)
IgM	1 (1)
None	5 (7)
Median bone marrow plasma cell percentage (range)	23 (2-99)
Number of prior lines of therapy, n (%)	
1	45 (61)
2-3	29 (39)
Previous transplantation, n (%)	43 (58)
Prior systemic therapies, n (%)	
Dexamethasone	65 (88)
Bortezomib	60 (81)
Cyclophosphamide	48 (65)
Lenalidomide	29 (39)
Melphalan	23 (31)
Refractory to last line of therapy, n (%)	29 (39)

Note: Abbreviations: ANC, absolute neutrophil count; ECOG PS, Eastern Cooperative Oncology Group performance status; ISS, International Staging System; SFLC, serum-free light-chain assay; SPEP, serum monoclonal protein; UPEP, urine monoclonal protein.



and 5.6 months (range, 0.1-20.1) for dexamethasone. The most common AEs of any grade were thrombocytopenia (61% of patients), diarrhoea (55%), anaemia (38%), asthenia (30%), fatigue (28%), peripheral oedema (28%), upper respiratory tract infection (26%), nausea (24%), peripheral sensory neuropathy (24%), cough (20%), and back pain (20%) (Table 3). Grade 3/4 AEs were reported in 73% of patients, and fatal AEs were reported in 15% of patients. The most common grade 3 or higher AEs (occurring in $\geq 10\%$ of patients) were thrombocytopenia (34%), pneumonia (16%), anaemia (15%), and asthenia (14%). Serious AEs of any grade occurred in 47 patients (64%). The only serious AE occurring in $\geq 5\%$ of patients was pneumonia, which occurred in 11 patients (15%); serious AEs of pneumonia were grade 3/4 in nine patients (12%), and grade 5 in two patients (3%).

Infections were reported in 59 patients (80%) and were grade 3 or higher in 32 patients (43%); the most common infections of any grade (occurring in $\geq 10\%$ of patients) were upper respiratory tract infection (26%), pneumonia (18%), bronchitis (15%), conjunctivitis (14%), nasopharyngitis (14%), and urinary tract infection (11%). Serious infections were reported in 31 patients (42%), with pneumonia being the most common serious infection (15%). Fatal infections were reported as AEs in eight patients (11%), coded as MedDRA-preferred terms of sepsis ($n = 3$) and pseudomonal sepsis ($n = 1$) for a total of four fatal infections due to sepsis; and pneumonia ($n = 2$), pneumonia *Escherichia* ($n = 1$), and pneumonia bacterial ($n = 1$) for a total of four fatal infections due to pneumonia. Additional fatal AEs were cerebral haemorrhage, death (unknown cause), and sudden death ($n = 1$ each).

Bleeding events of any grade were reported in 23 patients (31%). Major haemorrhage was reported in four patients (5%); one event (cerebral haemorrhage) resulted in treatment discontinuation and was subsequently fatal. Atrial fibrillation occurred in seven patients (9%) and was grade 3/4 in three patients (4%). Adverse events leading to dose reduction of ibrutinib, bortezomib, and dexamethasone occurred in 38 (51%), 30 (41%), and 19 (26%) patients, respectively, and AEs leading to discontinuation of ibrutinib, bortezomib, and dexamethasone occurred in 18 (24%), 22 (30%), and 20 (27%) patients, respectively. The most common AEs leading to ibrutinib discontinuation were pneumonia ($n = 3$; 4%), atrial fibrillation, diarrhoea, and sepsis ($n = 2$ each; 3%). The most common AEs leading to bortezomib discontinuation were polyneuropathy ($n = 3$; 4%), atrial fibrillation, diarrhoea, peripheral sensorimotor neuropathy, pneumonia, and sepsis ($n = 2$ each; 3%). The most common AEs leading to discontinuation of dexamethasone were atrial fibrillation, diarrhoea, pneumonia, and sepsis ($n = 2$ each; 3%).

3.3 | Efficacy

After a median follow-up of 19.6 months, PFS events had occurred in 55 patients (74%). The median PFS was 8.5 months (95% CI: 6.2-10.8) and estimated PFS at 20 months was 7% (Figure 1A).

The ORR was 57% (95% CI: 45-68), including complete response in one patient, very good partial response in 13 patients, and partial response in 28 patients (Table 4). Among 42 patients who achieved

partial response or better, the median duration of response was 9.5 months (95% CI: 6.9-10.6) and the median time to progression was 10.6 months (95% CI: 7.8-12.0). At the time of analysis, 27 patients (36%) had died and median OS was not reached (Figure 1B). Estimated OS at 24 months was 54%.

3.4 | Pharmacokinetics

Steady-state plasma exposures of ibrutinib at the 840 mg dose level in this study were similar to those observed in patients with R/R MM receiving ibrutinib in combination with carfilzomib in the PCYC-1119-CA study.¹⁰ Steady-state plasma exposures of bortezomib were consistent with those reported in the US prescribing information for bortezomib.¹⁴

4 | DISCUSSION

This phase 2 study evaluated the efficacy and safety of ibrutinib in combination with bortezomib plus dexamethasone in patients with R/R MM who had received one to three previous lines of therapy. After 74 patients had received at least one dose of study treatment, study enrolment was suspended as a risk-minimisation measure to address concerns over an increased incidence of serious and fatal infections compared with other studies of ibrutinib in R/R MM.^{9,10} While the incidence of infection of any grade in this study (80%) was similar

TABLE 3 Adverse events of any grade occurring in $\geq 15\%$ of patients

Adverse event, n (%)	Patients (N = 74)		
	Any Grade	Grade 3/4	Grade 5
Any adverse event	74 (100)	54 (73)	11 (15)
Thrombocytopenia	45 (61)	25 (34)	0
Diarrhoea	41 (55)	7 (9)	0
Anaemia	28 (38)	11 (15)	0
Asthenia	22 (30)	10 (14)	0
Fatigue	21 (28)	6 (8)	0
Oedema peripheral	21 (28)	0	0
Upper respiratory tract infection	19 (26)	2 (3)	0
Nausea	18 (24)	1 (1)	0
Peripheral sensory neuropathy	18 (24)	1 (1)	0
Back pain	15 (20)	2 (3)	0
Cough	15 (20)	0	0
Hypokalaemia	13 (18)	3 (4)	0
Pneumonia	13 (18)	10 (14)	2 (3) ^a
Pyrexia	13 (18)	0	0

^aDoes not include two additional grade 5 AEs of pneumonia reported as pneumonia *escherichia* and pneumonia bacterial ($n = 1$ each).

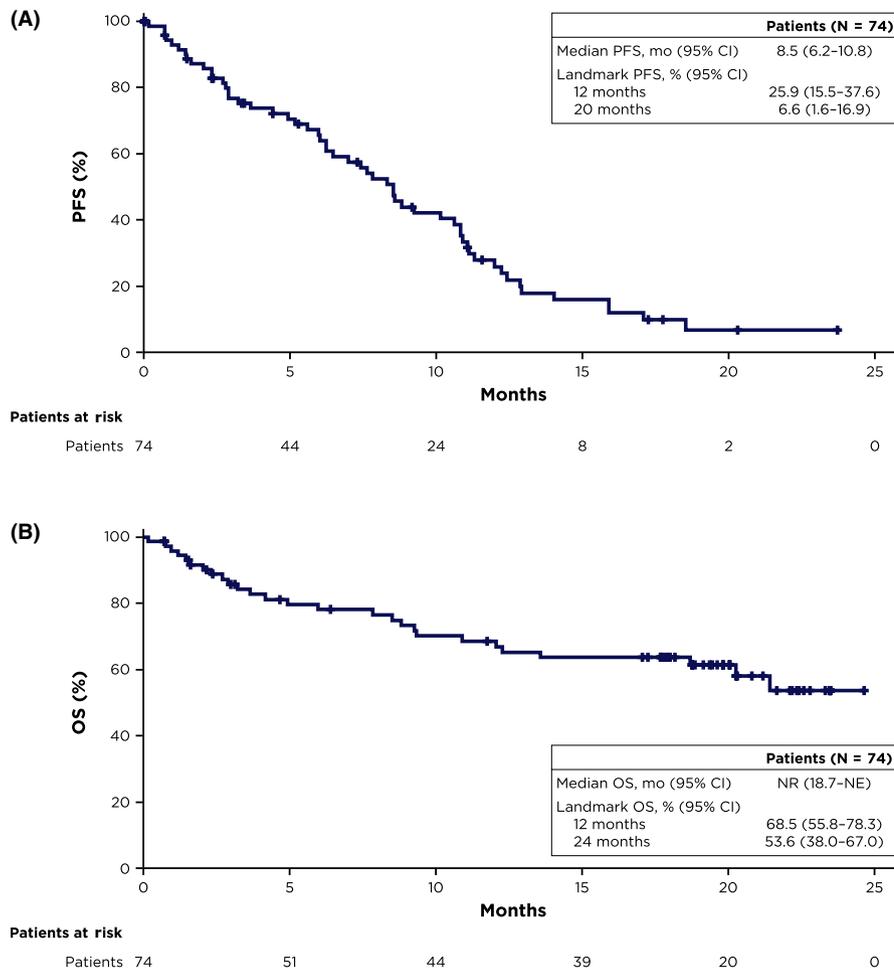


FIGURE 1 Kaplan-Meier estimates of (A) PFS per investigator assessment and (B) OS. NE, not estimable; NR, not reached; OS, overall survival; PFS, progression-free survival

to rates reported with ibrutinib in other haematological malignancies (68%–78%) over median follow-up durations of 9.4 to 33.4 months, the incidence of grade ≥ 3 infections (43%) was higher than rates previously reported with ibrutinib (7%–29%).^{15–20} However, it should be noted that a higher dose of ibrutinib (840 mg once daily) was used in the current study compared with other haematological malignancies (420 mg or 560 mg once daily). The ibrutinib dose used in the current study was chosen based on clinical activity and a favourable safety profile observed at the 840 mg dose level of ibrutinib in combination with carfilzomib with or without dexamethasone and in combination with dexamethasone in two early phase studies in MM.^{9,10} Plasma exposures to ibrutinib and bortezomib were consistent with those previously reported,^{10,14} suggesting that drug-drug interactions may not be contributing factors to the safety observations. Relative to other studies conducted in patients with MM, the incidence of grade ≥ 3 AEs observed with ibrutinib plus bortezomib and dexamethasone in the current study (88%) was similar to the incidence observed with ibrutinib plus carfilzomib with or without dexamethasone (86%),¹⁰ but higher than that observed with ibrutinib alone or in combination with dexamethasone without a proteasome inhibitor (57%).⁹

A review of the data after the implementation of risk-minimisation measures showed a lower rate of serious infections and no fatal infections among patients already enrolled in the study. However, validation of the effectiveness of the risk-minimisation measures was

not possible as no new patients were enrolled. Apart from infections, the safety profile was consistent with the known safety profiles of the individual study drugs.^{6,7,11,12} While safety profiles in general may vary depending on dosage, combination with other drugs, and by disease histology, incidences of AEs of interest with ibrutinib were largely consistent with previous reports across a range of haematological malignancies, including chronic lymphocytic leukaemia, Waldenström's macroglobulinemia, and mantle cell lymphoma.^{15–20} The median PFS of 8.5 months with ibrutinib plus bortezomib and dexamethasone was slightly longer than that observed in patients with R/R MM treated with placebo plus bortezomib and dexamethasone in the PANORAMA-1 study (median 8.1 months).²¹ Such indirect comparisons should, however, be interpreted with caution given differences in study design. Clinical response was observed in 57% of patients and was generally durable, with a median response duration of 9.5 months. Overall survival data were not yet mature, with 64% of patients remaining alive after a median follow-up duration of 19.6 months. Assessment of efficacy at the time of potential restart of enrolment indicated that the target median PFS for the alternative hypothesis (≥ 12 months) could not be reached by enrolling additional patients, and therefore, enrolment was not restarted. Because enrolment was suspended due to safety concerns before the target sample size had been reached, the hypothesis testing for the median PFS was not performed.

**TABLE 4** Best response per investigator assessment

	Patients N = 74
ORR, % (95% CI) ^a	57 (45-68)
Best response, n (%)	
sCR	0
CR	1 (1)
VGPR	13 (18)
PR	28 (38)
MR	11 (15)
SD	13 (18)
PD	2 (3)
Unconfirmed PD	0
Not evaluable	1 (1)
Not done	5 (7)

Note: Abbreviations: CI, confidence interval; CR, complete response; MR, minimal response; ORR, overall response rate; PD, progressive disease; PR, partial response; sCR, stringent CR; SD, stable disease; VGPR, very good partial response.

^aConfirmed sCR + CR + VGPR + PR.

In summary, an initially increased incidence of serious infections was observed with ibrutinib in combination with bortezomib and dexamethasone, and in response, risk-minimisation measures were introduced. Following the implementation of risk-minimisation measures, very few serious and no fatal infections occurred, and regulatory authorities and ethics committees approved the restart of enrolment. Ibrutinib in combination with bortezomib and dexamethasone elicited clinical responses in patients with R/R MM. However, an efficacy assessment at the time of the potential restart of enrolment indicated that even with the pending enrolment of additional patients, the targeted endpoint of median PFS could not be reached and the study was terminated.

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CONFLICT OF INTEREST

RH reports honoraria and consultancy/advisory role from Amgen, Celgene, Takeda, Bristol-Myers Squibb, and Janssen, and research funding from Takeda, Novartis, Amgen, Janssen, Bristol-Myers Squibb, and Celgene. LP reports nothing to disclose. MO reports honoraria from Takeda and Amgen; research funding from Janssen, Celgene, Takeda, Archigen Biotech, Roche, Merck Sharp & Dohme, Bayer, AbbVie, and Novartis; and travel, accommodations, or other expenses from Bristol-Myers Squibb, Jazz, Roche, Sanofi, and Abdi

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AUTHOR CONTRIBUTIONS

RH designed the study in collaboration with the study sponsor. RH, LP, MO, JMS, RGS, AA, AO, NC, and IS collected data. YL, EMB, and ED confirmed the accuracy of the data, interpreted the data, and compiled it for analysis. YL performed statistical analyses. All authors had full access to the data, contributed to data interpretation, and vouch for accuracy of the data. All authors contributed to the manuscript preparation and approved the final version of the manuscript for submission.

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