# Iberdomide plus dexamethasone in heavily pretreated late-line relapsed or refractory multiple myeloma (CC-220-MM-001): a multicentre, multicohort, open-label, phase 1/2 trial

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## Summary

**Background** Iberdomide is a novel cereblon E3 ligase modulator with enhanced tumouricidal and immune-stimulatory effects compared with immunomodulatory drugs. In preclinical myeloma models, iberdomide has shown synergy with dexamethasone, proteasome inhibitors, and CD38 monoclonal antibodies. We aimed to evaluate the safety and clinical activity of iberdomide plus dexamethasone in patients with heavily pretreated relapsed or refractory multiple myeloma.

**Methods** We conducted a multicohort, open-label, phase 1/2 trial (CC-220-MM-001) at 42 treatment centres in Europe, Canada, and the USA. Patients aged 18 years or older with multiple myeloma who had received at least two previous lines of therapy, including lenalidomide or pomalidomide and a proteasome inhibitor, were enrolled into the dose-escalation cohort. Patients received escalating doses of oral iberdomide (0·3–1·6 mg on days 1–21 of each 28-day cycle) plus oral dexamethasone (40 mg [20 mg if age >75 years] once per week). A dose-expansion cohort at the recommended phase 2 dose was planned for patients who had received at least three previous lines of therapy and had triple-class refractory disease (refractory to immunomodulatory drugs, proteasome inhibitors, and CD38 antibodies). Treatment continued until progressive disease or unacceptable toxicity. The primary outcomes were the recommended phase 2 dose (in the dose-escalation cohort, phase 1) and overall response rate (defined as complete response or partial response; in the dose-expansion cohort, phase 2) in the full analysis set. This trial is ongoing and is registered with ClinicalTrials.gov, NCT02773030.

**Findings** Between Dec 5, 2016, and Dec 16, 2020, 460 patients were assessed for eligibility across all cohorts and 197 were enrolled and treated with iberdomide plus dexamethasone (90 patients in the dose-escalation cohort and 107 in the dose-expansion cohort). In the dose-escalation cohort, 47 (52%) patients were female and 43 (48%) were male, 70 (78%) were White, and the median number of previous lines of therapy was 5 (IQR 4–8). In the dose-expansion cohort, 47 (44%) were female and 60 (56%) were male, 84 (79%) were White, and the median number of previous lines of therapy was 6 (IQR 5–8). At data cutoff (June 2, 2021), median follow-up was 5·8 months (IQR 3·0–13·7) in the dose-escalation cohort and 7·7 months (5·3–11·4) in the dose-expansion cohort. Two dose-limiting toxicities (both infections, at 1·2 mg and 1·3 mg) were observed in the dose-escalation cohort, and 1·6 mg was selected as the recommended phase 2 dose. In the dose-escalation cohort, the overall response rate was 32% (95% CI 23–43; 29 of 90 patients) across all doses, and the maximum tolerated dose was not reached. In the dose-expansion cohort, the overall response rate was 26% (95% CI 18–36; 28 of 107 patients). The most common grade 3 or worse adverse events were neutropenia (48 [45%] of 107 patients), anaemia (30 [28%]), infection (29 [27%]), and thrombocytopenia (23 [22%]). Serious adverse events occurred in 57 (53%) patients. There was one (1%) treatment-related death (sepsis) and five (5%) patients discontinued iberdomide due to adverse events.

**Interpretation** Iberdomide plus dexamethasone was generally safe and showed meaningful clinical activity in heavily pretreated patients with multiple myeloma, including in disease that was refractory to immunomodulatory drugs. These data suggest that further evaluation of iberdomide plus dexamethasone or other standard antimyeloma therapies is warranted.

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## Research in context

### Evidence before this study

To ascertain the treatment landscape in patients with relapsed or refractory multiple myeloma who have received multiple lines of anti-myeloma therapy, and whose disease was refractory to immunomodulatory drugs, proteasome inhibitors, and CD38 monoclonal antibodies (triple-class refractory), we searched PubMed on Aug 1, 2021, from Jan 1, 2010, to Aug 1, 2021, with no language restrictions, using the terms including "relapsed", "refractory", "late-line", and "multiple myeloma". Our search showed few early-phase single-arm trials in patients who had been triple-class exposed or refractory. Melphalan flufenamide plus dexamethasone, selinexor plus dexamethasone, and belantamab mafodotin were identified as three active treatments in this population, with overall response rates ranging from 24% to 31%, but all were associated with some noteworthy toxicities. Novel therapies in this setting that have shown promise include CAR T-cell therapies and bispecific antibodies, which have shown overall response rates of greater than 60%; however, these therapies might not be available or appropriate for all patients. Overall, an unmet medical need remains in late-line relapsed or refractory multiple myeloma, where none of the available therapies are curative and each has limitations. Iberdomide is a novel, potent cereblon E3 ligase modulator that shares structural similarities to the immunomodulatory drugs lenalidomide and pomalidomide, but binds cereblon with 20 times higher potency and induces degradation of substrate targets with significantly faster kinetics.

### Added value of this study

Cereblon modulation is a recognised therapeutic target in multiple myeloma, as immunomodulatory drugs have become foundational therapies in the treatment of the disease. To our knowledge, this is the first study to evaluate iberdomide up to doses of 1·6 mg in combination with dexamethasone in patients with heavily pretreated late-line relapsed or refractory multiple myeloma, including those with triple-class refractory disease. Iberdomide plus dexamethasone showed clinical activity with durable responses and was generally safe, and there were few treatment discontinuations due to adverse events. This study also assessed the immunomodulatory activity of iberdomide, including effects on T-cell and natural-killer-cell proliferation.

### Implications of all the available evidence

This study provides preliminary evidence that iberdomide in combination with dexamethasone has meaningful clinical activity in multiple myeloma that is resistant to multiple drugs, and an encouraging safety profile. The results of this study suggest that iberdomide could offer a novel treatment option, and support the evaluation of iberdomide-based combination regimens in multiple myeloma. On the basis of this evidence, a phase 3 trial of iberdomide in combination with daratumumab and dexamethasone in patients with relapsed or refractory multiple myeloma (NCT04975997) is ongoing.

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## Introduction

Multiple myeloma is characterised by the persistence of residual disease during combination therapy, leading to multiple successive cycles of remission and relapse.[1] Each subsequent line of therapy is generally associated with poorer outcomes and an increased risk of treatment-related and disease-related complications, and this is particularly relevant in older patients who tend to have substantial non-myeloma-related comorbidities.[2–4] Disease that is refractory to immunomodulatory drugs, proteasome inhibitors, and CD38 monoclonal antibodies (triple-class refractory) is particularly difficult to treat effectively, as fewer therapeutic options remain and deep, durable responses are rarely obtained.[2,5] While each new therapy continues to address the high unmet medical need in late-line relapsed or refractory multiple myeloma, each has limitations, and, ultimately, few treatment options remain.[6–8] Patients who have received multiple therapies are generally frail and are likely to struggle with tolerability, and many patients will not have access to newly available therapies. Therefore, there is a need for new antimyeloma therapies that are not only efficacious, but are also tolerable and convenient, with the versatility to be administered as a backbone agent in conjunction with both conventional and novel antimyeloma therapies.

Iberdomide (CC-220) is a novel, potent cereblon E3 ligase modulator that has a 20 times higher binding affinity to cereblon than the immuno-modulatory drugs lenalidomide or pomalidomide, resulting in more efficient degradation of target proteins, including the transcription factors Ikaros and Aiolos.[9] Loss of Aiolos and Ikaros proteins has been shown to inhibit proliferation and induce apoptosis in multiple myeloma cells and other malignant cells of B-cell origin.[10,11] Aiolos and Ikaros also have key roles in regulating immune cell activity; downregulation of these proteins results in immunomodulatory effects, including B-cell depletion, co-stimulation of T-cell activity, enhancement of interleukin-2 and interferon-γ production, and increased natural killer (NK)-cell proliferation.[9,11–16] Consequently, iberdomide has tumouricidal and antiproliferative effects in myeloma cells and stimulates the anti-myeloma immune activity of T cells and NK cells.[17,18] In preclinical myeloma models, iberdomide has also shown synergy with dexamethasone as well as other anti-myeloma therapies, such as proteasome inhibitors and CD38 monoclonal antibodies.[17,19–22] We aimed to evaluate the safety and clinical activity of iberdomide in combination with dexamethasone in patients with heavily pretreated late-line relapsed or refractory multiple myeloma.

## Methods

### Study design and participants

See Online for appendix

We conducted a multicohort, open-label, phase 1/2 trial (CC-220-MM-001) at 42 treatment centres in Europe, Canada, and the USA (appendix pp 18–21). The trial consisted of two parts: phase 1, which evaluated escalating doses of iberdomide plus dexamethasone (dose-escalation cohort); and phase 2, where the recommended phase 2 dose of iberdomide was evaluated in combination with dexamethasone (dose-expansion cohort; appendix p 11). The study included additional cohorts evaluating iberdomide monotherapy or the addition of other standard treatments (bortezomib, carfilzomib, or daratumumab) to the iberdomide and dexamethasone regimen, which are not reported in this manuscript.

Eligible patients were adults aged 18 years or older with relapsed or refractory multiple myeloma who had measurable disease at screening and an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2. All patients were required to have progressive disease during or within 60 days after their last myeloma therapy. Patients in the dose-escalation cohort had received at least two previous lines of myeloma therapy including lenalidomide or pomalidomide and a proteasome inhibitor. Patients in the dose-expansion cohort had received at least three previous lines of therapy and had disease that was refractory to immunomodulatory drugs (lenalidomide or pomalidomide), proteasome inhibitors, CD38 monoclonal antibodies, and corticosteroids (triple-class refractory). Patients were excluded if they had a neutrophil count of less than $1·0\times10^9$ cells per L, platelet count of less than $75\times10^9$ cells per L, corrected calcium concentration of 13·5 mg/dL or greater, alanine aminotransferase or aspartate aminotransferase concentration of at least 2 times the upper limit of normal (ULN), alkaline phosphatase concentration and serum total bilirubin concentration of at least 1·5 times the ULN, creatinine clearance of less than 50 mL/min (later modified to <45 mL/min by protocol amendment on July 8, 2020), had tested positive for HIV or hepatitis B, or had active hepatitis A or C infection. Additionally, patients were excluded if they had non-secretory multiple myeloma, plasma cell leukaemia, amyloidosis, grade 2 or worse peripheral neuropathy, previous history of malignancies (unless free of the disease for ≥5 years, or non-invasive malignancies), clinically significant abnormal electrocardiogram (ECG), or clinically significant cardiovascular disease. Patients in the dose-expansion cohort were also excluded if they had previous treatment with any gene-based therapy, investigational cellular therapy, or BCMA-targeted therapy. Additional eligibility criteria are listed in the protocol (appendix pp 81–85).

The study was conducted in accordance with the International Council for Harmonisation guidelines on Good Clinical Practice and the general principles outlined in the Declaration of Helsinki. The protocol was approved by each participating centre's institutional review board or ethics committee before initiation, and all patients provided written informed consent. This study was ongoing during the COVID-19 pandemic, which had some effect on study sites during the recruitment stage. Measures and assessments were taken to characterise and minimise the effect on the study and the data analysis. The effect of the COVID-19 pandemic on data integrity and study conduct was minimal or was mitigated successfully. No protocol amendments were implemented as a result of the pandemic.

### Procedures

In the dose-escalation cohort, patients received oral iberdomide at doses ranging from 0·3 mg to 1·6 mg plus oral dexamethasone at a dose of 40 mg (20 mg if age >75 years; appendix p 11). Iberdomide was given on days 1–21 of each 28-day cycle. Dexamethasone was given on days 1, 8, 15, and 22 of each cycle. Treatment continued until progressive disease or unacceptable toxicity. In the dose-expansion cohort, patients received iberdomide at the recommended phase 2 dose plus dexamethasone, using the same schedule as in the dose-escalation cohort. A group sequential design[23] was used to assess the activity and safety of the regimen; results from an interim analysis that included the first 40 patients did not cross the futility boundary and, therefore, enrolment continued per protocol. Safety laboratory tests and vital signs assessments were performed more frequently in the initial four cycles, and on day 1 of every subsequent cycle; physical examinations were performed on day 1 of every cycle; and an ECG was done in cycle 1 and as clinically indicated thereafter. Evaluation of adverse events was continuous until 28 days after the end of treatment. Severity of adverse events was graded using the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. Response was assessed using International Myeloma Working Group uniform response criteria.[24] Response assessments, including serum and urinary protein electrophoresis and free light chain assays, were performed on day 1 of every cycle starting from cycle 2. For patients with plasmacytomas, radiological assess-ments were conducted in cycle 3 and every three cycles thereafter. All patients required thromboembolism prophylaxis, consisting of low-dose aspirin, low-molecular-weight heparin, or other equivalent antithrombotic or anticoagulant drug. Instructions for dose modifications were included in the protocol for both iberdomide and dexamethasone, including specific instructions for iberdomide in the event of neutropenia, thrombocytopenia, rash, thromboembolism, peripheral neuropathy, and other grade 3–4 adverse events. If iberdomide was withheld or discontinued, dexamethasone was also discontinued; if dexamethasone was withheld or discontinued, patients could continue to receive iberdomide. Neutropenia was managed with dose interruptions, dose reductions, and granulocyte-colony

stimulating factor (G-CSF). Prophylactic use of G-CSF was not permitted during the cycle 1 dose-limiting toxicity evaluation period in the dose-escalation cohort.

Pharmacokinetics samples were collected on days 8, 15, and 22 in cycles 1–4. We used a population pharmacokinetics approach to estimate exposure (area under the concentration curve over a 24-h dosing interval [$AUC_t$]). Peripheral blood samples were collected on cycle 1 day 1, and on day 15 of cycles 2 and 4, for immune analysis by multicolour flow cytometry. Changes in Ikaros and Aiolos protein concentrations were assessed in CD138-positive cells in bone marrow samples at screening and on cycle 2 day 15 by duplex immunohistochemistry staining.

## Outcomes

In the phase 1 dose-escalation cohort, the primary outcome was to determine the recommended phase 2 dose of iberdomide when combined with dexamethasone. Secondary outcomes were safety, pharmacokinetics and pharmacodynamics, and preliminary activity.

In the phase 2 dose-expansion cohort, the primary outcome was overall response rate, defined as complete response or partial response. Primary activity analysis was based on review by investigator and by an independent response adjudication committee (IRAC). Secondary outcomes were safety, time to response (time from enrolment to first documented response of partial response or better), duration of response (time from first documented response to disease progression), progression-free survival (time from first dose of study treatment to disease progression or death due to any cause), and overall survival (time from first dose of study treatment to death due to any cause).

Dose-limiting toxicity was defined as any of the following events occurring in the first treatment cycle: grade 4 neutropenia for more than 5 days or grade 3 neutropenia with fever; grade 4 thrombocytopenia or grade 3 thrombocytopenia with bleeding or requiring platelet transfusion; any grade 4 haematological adverse event (excluding anaemia) that did not resolve to pretreatment levels within 72 h; any grade 3 or worse non-haematological adverse event (excluding alopecia or nausea controlled by medical management); or any treatment interruption for longer than 2 weeks due to an adverse event. The recommended phase 2 dose was determined by the dose escalation committee on the basis of safety, pharmacokinetic, pharmacodynamic, and preliminary activity data.

## Statistical analysis

A 3+3 design was used to determine the maximum tolerated dose and recommended phase 2 dose in the dose-escalation cohort. Additional patients could be enrolled into a dose-level cohort beyond the approximations of the design, at the discretion of the dose escalation committee, to further explore the safety, activity, and pharmacokinetics and pharmacodynamics of iberdomide.

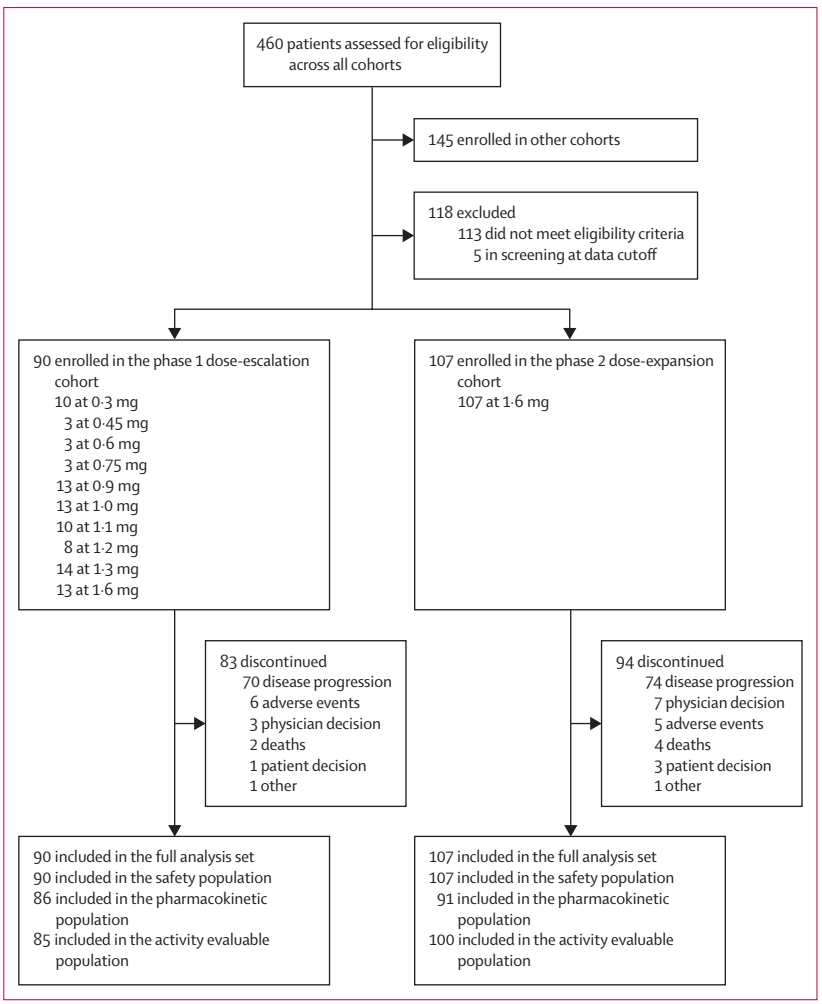


***Figure 1:*** **Trial profile**

For the dose-expansion cohort, sample size was calculated on the basis of a group sequential design[23] for a one-sample binomial test with normal approximation. One interim analysis for futility at 40% information and one final analysis were planned. The null hypothesis was accepted if overall response rate was 12% or less and the alternative hypothesis was accepted if overall response rate was greater than 12%. Assuming a treatment benefit of overall response rate of 24% or greater, a sample size of 101 patients would provide 90% power at a one-sided α level of 0·025 (sample size calculation used EAST version 6.4).

The dose-expansion cohort interim analysis was conducted using the June 30, 2020, data version, where 43% of data (43 patients) were included in the analysis.

For the dose-escalation cohort, safety endpoints such as dose-limiting toxicities, treatment-emergent adverse events, serious adverse events, and adverse events of special interest were summarised by cohort and dose level.

| | Dose-escalation cohort (n=90) | Dose-expansion cohort (n=107) |
|---|---|---|
| Age, years | | |
| Median (IQR) | 65 (58–71) | 64 (58–73) |
| ≥75 | 13 (14%) | 18 (17%) |
| Sex | | |
| Male | 43 (48%) | 60 (56%) |
| Female | 47 (52%) | 47 (44%) |
| Race | | |
| White | 70 (78%) | 84 (79%) |
| Black or African American | 12 (13%) | 15 (14%) |
| Other | 2 (2%) | 3 (3%) |
| Not reported | 6 (7%) | 5 (5%) |
| Ethnicity | | |
| Hispanic or Latino | 2 (2%) | 3 (3%) |
| Non-Hispanic or non-Latino | 80 (89%) | 97 (91%) |
| Not reported | 8 (9%) | 6 (6%) |
| Unknown | 0 | 1 (1%) |
| ECOG performance status | | |
| 0 | 31 (34%) | 42 (39%) |
| 1 | 50 (56%) | 55 (51%) |
| 2 | 9 (10%) | 10 (9%) |
| Cytogenetic risk category | | |
| High* | 14 (16%) | 32 (30%) |
| Standard† | 11 (12%) | 18 (17%) |
| Missing‡ | 65 (72%) | 57 (53%) |
| Time since diagnosis, years | 7·5 (5·8–10·0) | 6·9 (5·2–10·3) |
| ISS stage at study entry | | |
| I | 43 (48%) | 46 (43%) |
| II | 26 (29%) | 45 (42%) |
| III | 21 (23%) | 16 (15%) |
| Previous HSCT | 74 (82%)§ | 84 (79%)¶ |
| Number of previous lines of therapy | 5 (4–8) | 6 (5–8) |
| (Table 1 continues in next column) | | |

| | Dose-escalation cohort (n=90) | Dose-expansion cohort (n=107) |
|---|---|---|
| (Continued from previous column) | | |
| Type of previous therapy | | |
| Immunomodulatory drugs | 90 (100%) | 107 (100%) |
| Lenalidomide | 90 (100%) | 107 (100%) |
| Pomalidomide | 63 (70%) | 107 (100%) |
| Proteasome inhibitors | 90 (100%) | 107 (100%) |
| Bortezomib | 89 (99%) | 106 (99%) |
| Carfilzomib | 44 (49%) | 73 (68%) |
| CD38 monoclonal antibodies | 68 (76%) | 107 (100%) |
| Alkylating agents | 86 (96%) | 103 (96%) |
| Refractory to previous therapy | | |
| Immunomodulatory drugs | 86 (96%) | 107 (100%) |
| Lenalidomide | 76 (84%) | 91 (85%) |
| Pomalidomide | 57 (63%) | 102 (95%) |
| Proteasome inhibitors | 70 (78%) | 104 (97%) |
| CD38 monoclonal antibodies | 67 (74%) | 107 (100%) |
| Triple-class refractory‖ | 53 (59%) | 104 (97%) |
| Extramedullary plasmacytomas | | |
| Yes | 16 (18%) | 27 (25%) |
| No | 74 (82%) | 80 (75%) |

Data are n (%) or median (IQR). ECOG=Eastern Cooperative Oncology Group. ISS=International Staging System. HSCT=haematopoietic stem-cell transplantation. *Defined as presence of any abnormality for del(17p), t(4:14), t(14,16), or amplification 1q21. †Defined as absence of abnormality for all del(17p), t(4:14), t(14,16), and amplification 1q21. ‡Patients were not evaluable because of insufficient bone marrow aspirate material for complete cytogenetic analysis. §67 patients had previous autologous HSCT, one had allogeneic HSCT, and six had both. ¶76 patients had previous autologous HSCT and eight had both autologous and allogeneic HSCT. ‖Defined as refractory to at least one immunomodulatory drug, at least one proteasome inhibitor, and at least one CD38 monoclonal antibody.

***Table 1:*** **Baseline characteristics**

Preliminary activity analyses were also performed in the safety population, which included all enrolled patients who received at least one dose of iberdomide. For the dose-expansion cohort, activity analyses were based on the full analysis set. A post-hoc analysis for overall response rate was performed in patients in the dose-escalation cohort who met key inclusion criteria for the dose-expansion cohort (ie, patients who had received at least three previous lines of therapy, with triple-class refractory disease). All patients enrolled in both cohorts were deemed eligible for the planned analyses.

Summary statistics for continuous variables included number, mean, SD, median, and IQR. For categorical variables, frequencies and percentages are presented. For time-to-event variables, the Kaplan-Meier method was used for descriptive summaries. 95% CIs for response rates (binary endpoints) were calculated using the exact Clopper-Pearson method. Two-sided 95% CIs for time-to-event endpoints were calculated using the Brookmeyer and Crowley method, by log-log transformation.

Data were analysed using SAS (version 9.1 or higher). This trial is ongoing and is registered with ClinicalTrials.gov, NCT02773030.

### Role of the funding source

The funder of the study had a role in the study design, data collection, data analysis, and data interpretation, and the preparation of the manuscript.

## Results

Between Dec 5, 2016, and March 9, 2020, 90 patients were enrolled in the phase 1 dose-escalation cohort and received iberdomide plus dexamethasone (figure 1). In addition to the patients enrolled for dose-limiting toxicity evaluations, additional patients were enrolled in the 0·3 mg, 0·9 mg, 1·0 mg, 1·1 mg, 1·3 mg, and 1·6 mg dose levels to collect additional pharmacodynamic, safety, and activity data at these dose levels. The number of patients enrolled per dose level was ten at 0·3 mg, three at 0·45 mg, three at 0·6 mg, three at 0·75 mg, 13 at 0·9 mg, 13 at 1·0 mg, ten at 1·1 mg, eight at 1·2 mg, 14 at 1·3 mg, and 13 at 1·6 mg. The median age was 65 years

| | Dose-escalation cohort (n=90) | | | | Dose-expansion cohort (n=107) | | | |
|---|---|---|---|---|---|---|---|---|
| | Grade 1–2 | Grade 3 | Grade 4 | Grade 5 | Grade 1–2 | Grade 3 | Grade 4 | Grade 5 |
| All infections | 33 (37%) | 21 (23%) | 2 (2%) | 0 | 33 (31%) | 26 (24%) | 3 (3%) | 0 |
| Fatigue | 31 (34%) | 1 (1%) | 1 (1%) | 0 | 22 (21%) | 2 (2%) | 1 (1%) | 0 |
| Insomnia | 28 (31%) | 1 (1%) | 0 | 0 | 14 (13%) | 1 (1%) | 0 | 0 |
| Diarrhoea | 20 (22%) | 1 (1%) | 0 | 0 | 24 (22%) | 1 (1%) | 0 | 0 |
| Muscle spasms | 20 (22%) | 0 | 0 | 0 | 8 (7%) | 0 | 0 | 0 |
| Cough | 19 (21%) | 0 | 0 | 0 | 11 (10%) | 0 | 0 | 0 |
| Arthralgia | 18 (20%) | 1 (1%) | 0 | 0 | 9 (8%) | 1 (1%) | 0 | 0 |
| Pyrexia | 18 (20%) | 2 (2%) | 0 | 0 | 12 (11%) | 1 (1%) | 0 | 0 |
| Rash | 17 (19%)* | 0* | 0 | 0 | 18 (17%)† | 3 (3%)† | 0 | 0 |
| Dyspnoea | 16 (18%) | 2 (2%) | 1 (1%) | 0 | 17 (16%) | 3 (3%) | 1 (1%) | 0 |
| Pain in extremity | 14 (16%) | 2 (2%) | 0 | 0 | 6 (6%) | 0 | 0 | 0 |
| Musculoskeletal chest pain | 14 (16%) | 1 (1%) | 0 | 0 | 7 (7%) | 2 (2%) | 0 | 0 |
| Nausea | 14 (16%) | 0 | 0 | 0 | 15 (14%) | 1 (1%) | 0 | 0 |
| Upper respiratory tract infection | 13 (14%) | 1 (1%) | 0 | 0 | 10 (9%) | 1 (1%) | 0 | 0 |
| Peripheral oedema | 13 (14%) | 0 | 0 | 0 | 14 (13%) | 2 (2%) | 0 | 0 |
| Back pain | 12 (13%) | 8 (9%) | 0 | 0 | 16 (15%) | 2 (2%) | 0 | 0 |
| Constipation | 12 (13%) | 1 (1%) | 0 | 0 | 23 (22%) | 0 | 0 | 0 |
| Anaemia | 11 (12%) | 23 (26%) | 1 (1%) | 0 | 14 (13%) | 30 (28%) | 0 | 0 |
| Vomiting | 10 (11%) | 0 | 0 | 0 | 6 (6%) | 2 (2%) | 0 | 0 |
| Myalgia | 10 (11%) | 0 | 0 | 0 | 3 (3%) | 0 | 0 | 0 |
| Bone pain | 9 (10%) | 2 (2%) | 0 | 0 | 7 (7%) | 7 (7%) | 0 | 0 |
| Headache | 9 (10%) | 2 (2%) | 0 | 0 | 10 (9%) | 1 (1%) | 0 | 0 |
| Nasopharyngitis | 8 (9%) | 0 | 0 | 0 | 3 (3%) | 0 | 0 | 0 |
| Urinary tract infection | 8 (9%) | 0 | 0 | 0 | 4 (3%) | 2 (2%) | 0 | 0 |
| Hypokalaemia | 7 (8%) | 1 (1%) | 1 (1%) | 0 | 10 (9%) | 1 (1%) | 0 | 0 |
| Asthenia | 7 (8%) | 1 (1%) | 0 | 0 | 14 (13%) | 3 (3%) | 0 | 0 |
| Decreased appetite | 7 (8%) | 1 (1%) | 0 | 0 | 13 (12%) | 1 (1%) | 0 | 0 |
| Neutropenia | 5 (6%) | 19 (21%) | 19 (21%) | 0 | 16 (15%) | 27 (25%) | 21 (20%) | 0 |
| Thrombocytopenia | 5 (6%) | 6 (7%) | 7 (8%) | 0 | 15 (14%) | 7 (7%) | 16 (15%) | 0 |
| Hyperglycaemia | 5 (6%) | 3 (3%) | 0 | 0 | 4 (4%) | 5 (5%) | 0 | 0 |
| Pneumonia | 4 (4%)‡ | 10 (11%)‡ | 0 | 0 | 6 (6%)§ | 7 (7%)§ | 2 (2%) | 0 |
| Bronchitis | 3 (3%) | 1 (1%) | 0 | 0 | 8 (8%) | 0 | 0 | 0 |
| Leukopenia | 2 (2%) | 9 (10%) | 3 (3%) | 0 | 8 (8%) | 11 (10%) | 11 (10%) | 0 |
| Lymphopenia | 0 | 8 (9%) | 1 (1%) | 0 | 2 (2%) | 11 (10%) | 6 (6%) | 0 |
| Febrile neutropenia | 0 | 3 (3%) | 0 | 0 | 0 | 4 (4%) | 1 (1%) | 0 |
| Acute kidney injury | 0 | 3 (3%) | 0 | 1 (1%) | 7 (7%) | 3 (3%) | 0 | 0 |
| General physical health deterioration | 0 | 1 (1%) | 0 | 1 (1%) | 4 (4%) | 0 | 0 | 7 (7%) |
| Sepsis | 0 | 1 (1%) | 0 | 0 | 0 | 1 (1%) | 0 | 1 (1%) |
| Death | 0 | 0 | 0 | 1 (1%) | 0 | 0 | 0 | 1 (1%) |
| Blood viscosity increased | 0 | 0 | 0 | 1 (1%) | 0 | 0 | 0 | 0 |
| Performance status decreased | 0 | 0 | 0 | 1 (1%) | 0 | 0 | 0 | 0 |
| COVID-19 | 0 | 0 | 0 | 0 | 1 (1%)¶ | 5 (6%)¶ | 2 (2%) | 3 (3%) |
| Abdominal sepsis | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1%) |
| Euthanasia | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1%) |

Data are n (%). Adverse events of grade 1–2 occurring in at least 10% of patients, grade 3–4 occurring in at least 5% of patients, and grade 5 occurring in any patients, and adverse events of special interest, are shown. The full list of grade 1–5 adverse events is shown in the appendix (p 2). Grade 3–4 adverse events by dose levels in the dose-escalation cohort are shown in the appendix (p 9). *Includes erythematous rash, maculopapular rash, popular rash, and pruritic rash. †Includes maculopapular rash, erythematous rash, and pruritic rash. ‡Includes *Pneumocystis jirovecii* pneumonia, influenza pneumonia, and streptococcal pneumonia. §Includes viral pneumonia, cryptococcal pneumonia, and pneumococcal pneumonia. ¶Includes COVID-19 pneumonia.

***Table 2:*** **Adverse events**

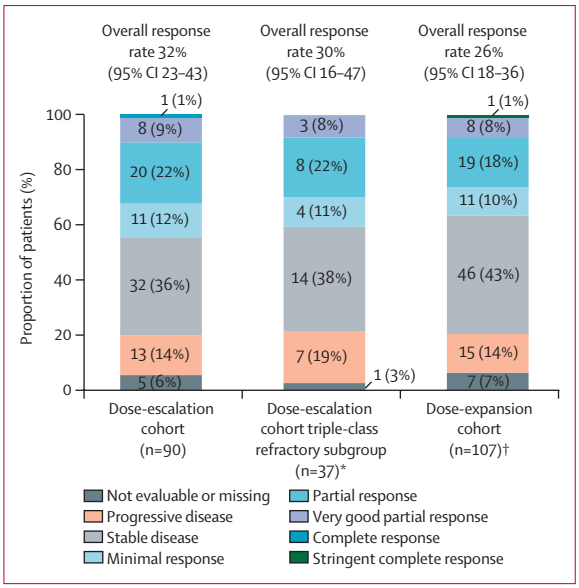


***Figure 2:*** **Overall response rate by cohort**
Percentages might not sum to 100% due to rounding. *Dose-escalation cohort triple-class refractory subgroup had received at least three previous lines of therapy and had triple-class refractory disease. †Two patients who had stable disease and minimal response discontinued treatment because of death due to COVID-19.

(IQR 58–71), and 13 (14%) of 90 patients were aged 75 years or older (table 1). All patients were included in the safety and activity analyses. Two dose-limiting toxicities were reported: one patient had grade 4 sepsis at the 1·2 mg dose level and one patient had grade 3 pneumonia at the 1·3 mg dose level. After reviewing the safety, preliminary activity, pharmacokinetics, and pharmacodynamics (ie, changes in the immune compartment), 1·6 mg was selected as the recommended phase 2 dose for the dose-expansion cohort. The maximum tolerated dose was not reached.

At data cutoff (June 2, 2021), seven (8%) of 90 patients remained on therapy and 83 (92%) had discontinued treatment due to progressive disease (70 [78%] patients), adverse events (six [7%]), physician decision (three [3%]), death (two [2%]), patient withdrawal (one [1%]), or other reasons (one [1%]). The median follow-up was 5·8 months (IQR 3·0–13·7), median treatment duration was 16 weeks (9·6–42·1), and the median relative dose intensity was 94% (83–99), which suggests that treatment was generally well tolerated. 54 (60%) of 90 patients required one or more dose interruptions and 22 (24%) required one or more dose reductions due to treatment-emergent adverse events. 89 (99%) patients had at least one treatment-emergent adverse event, and 75 (83%) had at least one grade 3–4 treatment-emergent adverse event. The most common grade 3 or worse treatment-emergent adverse events were neutropenia (38 [42%] patients), anaemia (24 [27%]), and infection (23 [26%]; table 2; appendix p 2). The frequency of other grade 3 or worse non-haematological treatment-emergent adverse events was generally low, including gastrointestinal disorders (three [3%] patients) and fatigue (two [2%]). Serious treatment-emergent adverse events were reported in 48 (53%) patients, and six (7%) patients had treatment-emergent adverse events that led to discontinuation of iberdomide. Five (6%) patients died during the treatment period, including three deaths due to myeloma progression, one death due to acute kidney injury (within the context of myeloma progression), and one death of unknown cause; none of these deaths were considered related to study treatment.

The $AUC_{\tau}$ of iberdomide increased in a dose-related manner between 0·3 mg and 1·6 mg, with moderate exposure variability (coefficient of variation approximately 18–73%; appendix p 13). Median time to maximum plasma concentration of iberdomide was 2·5–4·0 h after dosing, with an elimination half-life of about 9–13 h. Reductions in Ikaros and Aiolos protein concentrations in CD138-positive tumour cells in bone marrow were observed at all dose levels (appendix p 14). A dose of 1·1 mg induced a greater than 90% decrease in Aiolos concentrations. Pharmacodynamic changes in the immune compartment showed a dose-dependent or exposure-dependent reduction in mature B cells, decreasing by a median of 22% (IQR –77 to 13) at the 0·3 mg dose and 96% (–91 to –99) at the 1·6 mg dose by cycle 2 day 15 (appendix pp 15–16). Similar to changes in B cells, dose-related and exposure-related increases in T-cell and NK-cell proliferation were also observed. Notably, pharmacodynamic activity in the immune compartment appeared to saturate at higher doses or exposure.

29 of 90 patients in the dose-escalation cohort had complete response or partial response (overall response rate 32%, 95% CI 23–43), including one (1%) patient with a complete response, eight (9%) with a very good partial response, and 20 (22%) with a partial response (figure 2). An additional 32 (36%) patients had stable disease; the median duration of stable disease was 2·8 months (95% CI 2·0–2·8) and 25 (23%) patients remained in stable disease for at least two cycles. Clinical activity was observed across all dose levels, however deeper responses of very good partial response or complete response were only observed at higher doses (0·9 mg or higher; appendix p 10). In the post-hoc subgroup analysis of 37 patients in the dose-escalation cohort who had received at least three previous lines of therapy and were triple-class refractory, 11 had a complete response or partial response (overall response rate 30%, 95% CI 16–47; figure 2). The median time to response was 8·1 weeks (IQR 5·0–12·1) and the median duration of response was 10·4 months (95% CI 4·6–15·7).

Between Oct 28, 2019, and Dec 16, 2020, 107 patients were enrolled in the phase 2 dose-expansion cohort and received iberdomide at the 1·6 mg dose level in combination with dexamethasone (figure 1). The median age was 64 years (IQR 58–73), and 18 (17%) of 107 patients

were aged 75 years or older (table 1). Extramedullary plasmacytomas were present in 27 (25%) patients and 32 (30%) had high-risk cytogenetics (57 [53%] patients were not tested or not evaluable).

The interim analysis result of overall response rate did not cross the futility boundary, and so the dose-expansion cohort continued to the final analysis. All 107 patients were included in the safety and activity analyses. 28 of 107 patients in the dose-expansion cohort had a complete response or partial response (overall response rate 26%, 95% CI 18–36), including eight (8%) patients who had a very good partial response and one (1%) who had a stringent complete response (figure 2); 46 (43%) patients had stable disease. Response rates by investigator assessment were consistent with the IRAC assessment (data not shown). Overall response rates were generally consistent across subgroups, with the exception of patients with extramedullary disease (overall response rate 11%, 95% CI 2–29; three of 27 patients; appendix p 17). Because of the small sample size in some subgroups, the subgroup analysis results should be interpreted with caution. Median time to response was 4·2 weeks (IQR 4·1–10·9) and the median duration of response was 7·0 months (95% CI 4·5–11·3; figure 3A. 85 (79%) of 107 patients had progression-free survival events of disease progression or death, and the estimated median progression-free survival was 3·0 months (95% CI 2·8–3·7; figure 3B). 51 (48%) of 107 patients died; the estimated median overall survival was 10·7 months (95% CI 8·8–not evaluable; figure 3C).

As of June 2, 2021, 13 (12%) of 107 patients remained on therapy and 94 (88%) had discontinued treatment due to progressive disease (74 [69%] patients), physician decision (seven [7%]), adverse events (five [5%]), death (four [4%]), patient withdrawal (three [3%]), or other reasons (one [1%]). Two (2%) patients discontinued treatment due to COVID-19-related death. The median follow-up was 7·7 months (IQR 5·3–11·4).

The median treatment duration in the dose-expansion cohort was 16·0 weeks (IQR 9·1–28·0). Overall, 60 (56%) patients required one or more dose interruptions and 20 (19%) required at one or more dose reductions. All patients had at least one treatment-emergent adverse event, and 88 (82%) had at least one grade 3 or worse treatment-emergent adverse event. The most common grade 3 or worse treatment-emergent adverse events were neutropenia (48 [45%] patients), infection (29 [27%], including COVID-19 [seven (7%)] and pneumonia [nine (8%)]), anaemia (30 [28%]), leukopenia (22 [21%]), and thrombocytopenia (23 [22%]; table 2; appendix p 2). There were few grade 3 or worse non-haematological treatment-emergent adverse events, including gastrointestinal disorders (six [6%]), fatigue (three [3%]), and rash (three [3%]). There were no cases of venous thromboembolism. Serious treatment-emergent adverse events were reported in 57 (53%) of 107 patients; five (5%) discontinued iberdomide due to adverse events. At the data cutoff, 51 (48%) patients had died, of whom 37 (35%) died after the treatment period and 14 (13%) died during the treatment period; of these, seven deaths were disease-progression related, five were due to

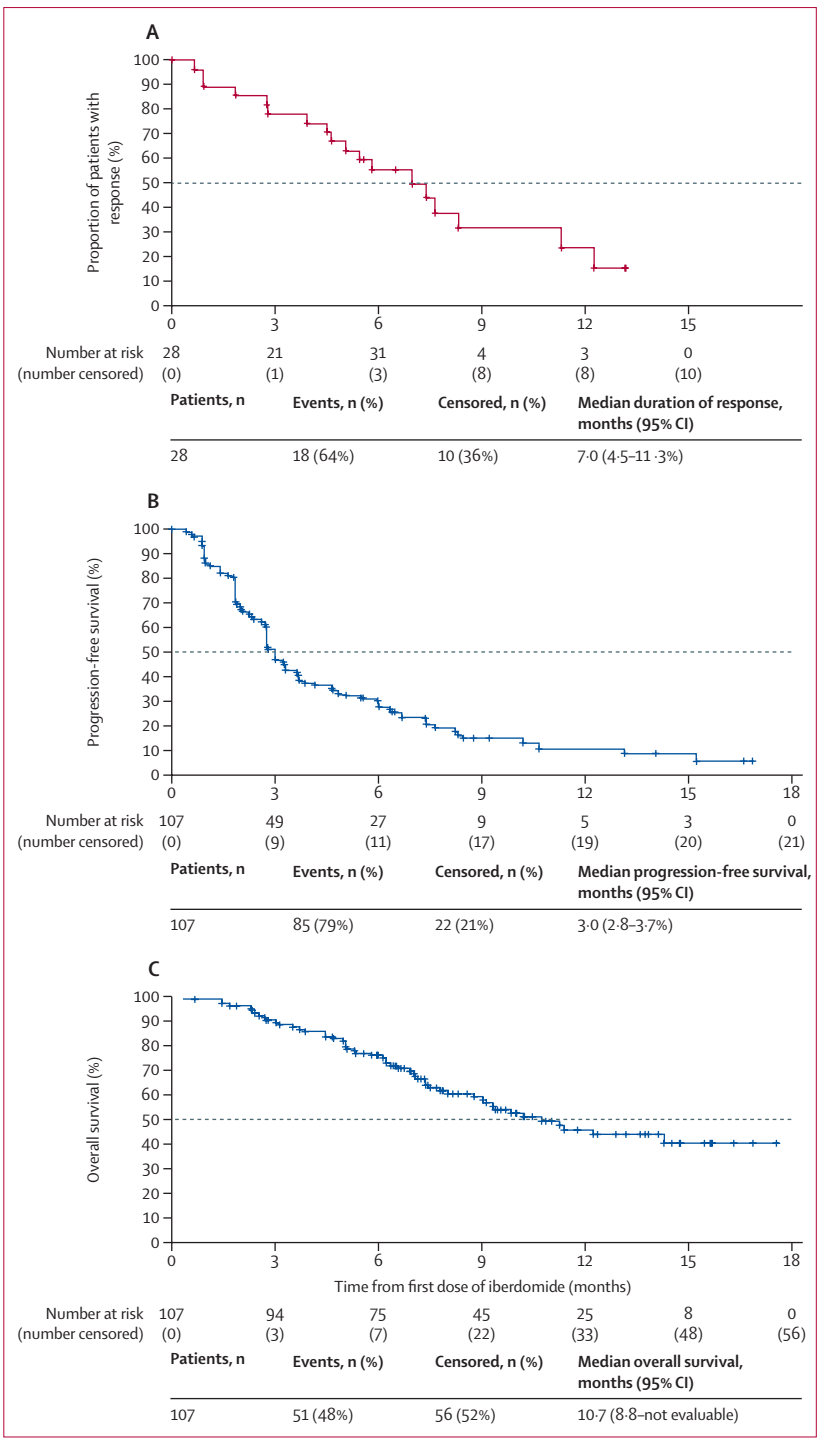


***Figure 3:*** **Duration of response, progression-free survival, and overall survival in the dose-expansion cohort**
(A) Duration of response. (B) Progression-free survival. (C) Overall survival. Ticks indicate censored patients. Horizontal lines at 50% show medians.

infection (three related to COVID-19, one abdominal sepsis, and one sepsis), one was due to euthanasia (in a patient with progressive concurrent bladder cancer), and one had an unknown cause (patient died at home without further evaluation). One death (1%) that occurred during the treatment period was considered treatment-related (abdominal sepsis).

## Discussion

The recommended phase 2 dose of iberdomide for the dose-expansion cohort was 1·6 mg. Iberdomide showed pharmacodynamic activity at all doses tested. While iberdomide exposure increased in a dose-proportional manner between 0·3 mg and 1·6 mg, it's pharmacodynamic activity appeared to saturate between 1·0 mg and 1·6 mg. The regimen was generally well tolerated: two dose-limiting toxicities (both infections) were observed in the dose-escalation cohort, at the 1·2 mg and 1·3 mg dose levels. The maximum tolerated dose was not reached, and no dose-limiting toxicities were observed at the recommended phase 2 dose. The most common adverse event was neutropenia, which is expected in this heavily pretreated patient population, and there were few cases of febrile neutropenia (three [3%] of 90 patients in the dose-escalation cohort, five [5%] of 107 in the dose-expansion cohort; all were grade 3–4); notably, occurrence of grade 3–4 neutropenia in the dose-expansion cohort was similar (45% *vs* 42%) to that in the dose-escalation cohort, which also included lower doses of iberdomide. Other adverse events were largely related to myelosuppression, including anaemia and thrombocytopenia. Most of these events were manageable, and there were few treatment discontinuations due to adverse events (six [7%] patients in the dose-escalation cohort, five [5%] in the dose-expansion cohort). Grade 3–4 infections were observed in 23 (26%) of 90 patients in the dose-escalation cohort and 29 (27%) of 107 in the dose-expansion cohort, and were mainly upper respiratory tract infections and lower respiratory tract infections. Frequency of other grade 3–4 non-haematological treatment-emergent adverse events was generally low; grade 3–4 rash, a frequent side-effect of immunomodulatory drugs, was observed in only three (3%) patients in the dose-expansion cohort (none in the dose-escalation cohort). Occurrence of grade 3–4 peripheral neuropathy was also low, being observed in one [1%] patient in the dose-escalation cohort and none in the dose-expansion cohort. The safety and tolerability of iberdomide are particularly encouraging, compared with alternative approved treatments in this setting, which are associated with non-haematological adverse events that could lead to treatment discontinuation;[6–8,25] for example, selinexor is associated with gastrointestinal disorders, such as grade 3–4 nausea (in 9% of patients) and diarrhoea (in 6%), which have been rarely observed following treatment with iberdomide plus dexamethasone (grade 3–4 nausea in none in the dose-escalation cohort and one [1%] in the dose-expansion cohort; grade 3–4 diarrhoea in one [1%] and one [1%]).

Like lenalidomide and pomalidomide, iberdomide acts by co-opting cereblon to achieve degradation of specific target proteins, including Ikaros and Aiolos, via the ubiquitin-proteasome system.[9,11,17,26,27] Iberdomide has 20 times higher affinity for cereblon compared with lenalidomide and pomalidomide, and preclinical data suggest this higher affinity enables more rapid and sustained degradation of target proteins and increased myeloma cell death—including in lenalidomide-resistant and pomalidomide-resistant myeloma cell lines.[9,17] Unlike lenalidomide and pomalidomide, iberdomide is administered as a single enantiomer (the S isomer) rather than as a racemic mixture of R and S isomers. In vivo, iberdomide is relatively resistant to racemisation compared with S-isomer of lenalidomide and pomalidomide, thus maintaining its S-isomeric structure. This structural difference between iberdomide and other thalidomide analogues might help to avoid some of the dose-limiting side-effects, such as sedation and fatigue, which have been attributed to the R isomer, while also increasing systemic exposure to the S isomer, which has increased cereblon binding affinity.[9,28,29] In preclinical models, iberdomide has shown synergistic anti-myeloma activity when combined with other standard anti-myeloma drugs, inducing greater tumouricidal effects than similar combinations based on a lenalidomide or pomalidomide backbone,[17,19–22] suggesting iberdomide might be effectively combined with other anti-myeloma drugs in vivo.

The combination of iberdomide and dexamethasone had notable clinical activity in this heavily pretreated population. The overall response rate was 32% in the dose-escalation cohort (median duration of response 10·4 months, 95% CI 4·6–15·7) and 26% in the dose-expansion cohort (7·0 months, 4·5–11·3). Similar overall response rates were observed across most patient subgroups (including by sex, region, and age), which shows the consistent activity of iberdomide; although decreased overall response rates in patients with more aggressive disease characteristics is expected, further exploration is warranted in this population with high-risk late-line disease.

The response rates of iberdomide align with results observed with selinexor (approved in penta-refractory patients) and belantamab mafodotin, but has a potentially more manageable safety profile and fewer treatment interruptions; selinexor plus dexamethasone showed an overall response rate of 25% (21 of 83 patients),[6] and belantamab mafodotin monotherapy showed an overall response rate of 31% (30 of 97).[7] Other novel therapies have shown high activity, including chimeric antigen receptor (CAR) T-cell therapy: the overall response rate of idecabtagene vicleucel was 72% (72 of 100 patients), including a 28% stringent complete response rate,[8] and the response rate of ciltacabtagene autoleucel was 98% (95 of 97), including a 78% (76 of 97) stringent complete response

rate.[25] Similarly, bispecific antibodies have also shown promise, with overall response rates ranging from 61% to 83% across studies of various antibodies.[30] However, it is important to consider the management of patients beyond the clinical trial setting, and these therapies might not be available or appropriate for all patients. Because iberdomide is an oral drug with favourable tolerability, it can be administered in combination with drugs from different classes, forming a complementary backbone in the multiple myeloma treatment paradigm. Additionally, given the immune-stimulatory properties observed, which are more potent than those of currently available immunomodulatory drugs, iberdomide could work in synergy with immune therapies, such as monoclonal antibodies, bispecific antibodies, and CAR T-cell therapies.

Limitations of this study were the non-randomised, single-arm design, and short follow-up period to assess overall survival and secondary cancers. Although further investigation is warranted, the results from this study are encouraging. The results observed with the oral combination of iberdomide and dexamethasone support further investigation of treatment regimens and the initiation of phase 3 combination studies. This ongoing study continues to evaluate iberdomide in combination with other active agents (bortezomib, carfilzomib, and daratumumab) to further explore the potential role of iberdomide as a foundation of combination therapy for relapsed or refractory multiple myeloma.

#### Contributors

SL, MC, TVN, TP, and MA participated in the concept and design of the study. MC performed the data analysis. YC performed the pharmacokinetic data analysis. All authors contributed to data acquisition and data interpretation. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

#### Declaration of interests

SL reports consulting fees from AbbVie, Bristol Myers Squibb, GlaxoSmithKline, Janssen Pharmaceuticals, and Takeda; institution grants or contracts from Bristol Myers Squibb, Janssen, and Takeda; membership on an entity's Board of Directors or advisory committees for TG Therapeutics; and stock ownership in TG Therapeutics. RP reports honoraria and travel grants from Bristol Myers Squibb. CH reports honoraria from AbbVie, Amgen, Bristol Myers Squibb, Cilag, Janssen Pharmaceuticals, Sanofi, and Takeda. SJ reports consulting fees from Bristol Myers Squibb, Elsevier, Janssen Pharmaceuticals, Karyopharm Therapeutics, Legend Biotech, Sanofi, and Takeda. AO reports honoraria and consulting fees from Amgen, Bristol Myers Squibb, GlaxoSmithKline, Janssen Pharmaceuticals, and Sanofi. PGR reports institution grants or contracts from Bristol Myers Squibb, Karyopharm Therapeutics, Oncopeptides, and Takeda; consulting fees from AstraZeneca, Bristol Myers Squibb, GlaxoSmithKline, Karyopharm Therapeutics, Oncopeptides, Protocol Intelligence, Regeneron, Secura Bio, Sanofi, and Takeda. KW reports institution grants or contracts from Amgen, Bristol Myers Squibb, Celgene, Janssen Pharmaceuticals, GlaxoSmithKline, and Sanofi; honoraria and consulting fees from AbbVie, Adaptive Biotechnologies, Amgen, Bristol Myers Squibb, GlaxoSmithKline, Karyopharm Therapeutics, Novartis, Oncopeptides, Pfizer, Roche, Sanofi, and Takeda; and membership of an advisory board for German Society for Hematology and Medical Oncology and Stiftung Immunonkologie. MCM reports honoraria from Alnylam Pharmaceuticals, Bristol Myers Squibb, Cilag, Gilead Sciences, Janssen Pharmaceuticals, and Medscape; travel grants from Celgene, a Bristol Myers Squibb Company; and membership on an entity's Board of Directors or advisory committees for Bristol Myers Squibb. AZB reports research support from GlaxoSmithKline. SK reports honoraria, research support, and consulting fees from Bristol Myers Squibb. EAS reports institution grants or contracts from AbbVie and Bristol Myers Squibb; consulting fees from AbbVie, Amgen, Bristol Myers Squibb, and GlaxoSmithKline; and membership on an entity's Board of Directors or advisory committees for Amgen. YC, TVN, AA, and TP are employees of Bristol Myers Squibb and have stock ownership in Bristol Myers Squibb. MA is an employee of Bristol Myers Squibb, has stock ownership in Bristol Myers Squibb, and has received travel grants from Bristol Myers Squibb. MC is an employee of Bristol Myers Squibb. NWCJvdD reports institution grants or contracts from Amgen, Cellectis, and Janssen Pharmaceuticals; and membership on an entity's Board of Directors or advisory committees for Adaptive Biotechnologies, Amgen, GlaxoSmithKline, Janssen Pharmaceuticals, Novartis, Roche Sanofi, and Takeda. All other authors declare no competing interests.

#### Data sharing

Bristol Myers Squibb's policy on data sharing can be found at https://www.bms.com/researchers-and-partners/clinical-trials-and-research/disclosure-commitment.html.

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#### References

1 van de Donk NWCJ, Pawlyn C, Yong KL. Multiple myeloma. *Lancet* 2021; **397:** 410–27.

2 Gandhi UH, Cornell RF, Lakshman A, et al. Outcomes of patients with multiple myeloma refractory to CD38-targeted monoclonal antibody therapy. *Leukemia* 2019; **33:** 2266–75.

3 Jagannath S, Roy A, Kish J, et al. Real-world treatment patterns and associated progression-free survival in relapsed/refractory multiple myeloma among US community oncology practices. *Expert Rev Hematol* 2016; **9:** 707–17.

4 Hari P, Romanus D, Luptakova K, et al. The impact of age and comorbidities on practice patterns and outcomes in patients with relapsed/refractory multiple myeloma in the era of novel therapies. *J Geriatr Oncol* 2018; **9:** 138–44.

5 Pick M, Vainstein V, Goldschmidt N, et al. Daratumumab resistance is frequent in advanced-stage multiple myeloma patients irrespective of CD38 expression and is related to dismal prognosis. *Eur J Haematol* 2018; **100:** 494–501.

6 Karyopharm Theraperutics. Xpovio (selinexor) prescribing information. Newton, MA: Karyopharm Theraperutics, 2019. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/212306s000lbl.pdf (accessed April 6, 2022).

7 GlaxoSmithKline. Blenrep (belantamab mafodotin) prescribing information. Brentford: GlaxoSmithKline, 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/761158s000lbl.pdf (accessed April 6, 2022).

8 Celgene. Abecma (idecabtagene vicleucel) prescribing information. Princeton, NJ: Celgene, 2021. https://packageinserts.bms.com/pi/pi_abecma.pdf (accessed April 6, 2022).

9 Matyskiela ME, Zhang W, Man H-W, et al. A cereblon modulator (CC-220) with improved degradation of Ikaros and Aiolos. *J Med Chem* 2018; **61:** 535–42.

10 Bjorklund CC, Lu L, Kang J, et al. Rate of CRL4(CRBN) substrate Ikaros and Aiolos degradation underlies differential activity of lenalidomide and pomalidomide in multiple myeloma cells by regulation of c-Myc and IRF4. *Blood Cancer J* 2015; **5:** e354.

11 Gandhi AK, Kang J, Havens CG, et al. Immunomodulatory agents lenalidomide and pomalidomide co-stimulate T cells by inducing degradation of T cell repressors Ikaros and Aiolos via modulation of the E3 ubiquitin ligase complex CRL4(CRBN.). *Br J Haematol* 2014; **164:** 811–21.

12 Holmes ML, Huntington ND, Thong RPL, et al. Peripheral natural killer cell maturation depends on the transcription factor Aiolos. *EMBO J* 2014; **33:** 2721–34.

13 Nakayama Y, Kosek J, Capone L, Hur EM, Schafer PH, Ringheim GE. Aiolos overexpression in systemic lupus erythematosus B cell subtypes and BAFF-induced memory B cell differentiation are reduced by CC-220 modulation of cereblon activity. *J Immunol* 2017; **199:** 2388–407.

14 O'Brien S, Thomas RM, Wertheim GB, Zhang F, Shen H, Wells AD. Ikaros imposes a barrier to CD8+ T cell differentiation by restricting autocrine IL-2 production. *J Immunol* 2014; **192:** 5118–29.

15 Georgopoulos K, Winandy S, Avitahl N. The role of the Ikaros gene in lymphocyte development and homeostasis. *Annu Rev Immunol* 1997; **15:** 155–76.

16 Schmitt C, Tonnelle C, Dalloul A, Chabannon C, Debré P, Rebollo A. Aiolos and Ikaros: regulators of lymphocyte development, homeostasis and lymphoproliferation. *Apoptosis* 2002; **7:** 277–84.

17 Bjorklund CC, Kang J, Amatangelo M, et al. Iberdomide (CC-220) is a potent cereblon E3 ligase modulator with antitumor and immunostimulatory activities in lenalidomide- and pomalidomide-resistant multiple myeloma cells with dysregulated *CRBN*. *Leukemia* 2020; **34:** 1197–201.

18 Amatangelo M, Van Oekelen O, Rahman AH, et al. Multidimensional single cell analysis shows increased T/NK cell subsets in both blood and bone marrow of iberdomide (CC-220) treated relapsed/refractory multiple myeloma patients. *Blood* 2019; **134** (suppl 1)**:** 1775 (abstr).

19 Amatangelo M, Bjorklund C, Kang J, Polonskaia A, Viswanatha S, Thakurta A. Iberdomide (CC-220) has synergistic anti-tumor and immunostimulatory activity against multiple myeloma in combination with both bortezomib and dexamethasone or in combination with daratumumab in vitro. *Blood* 2018; **132** (suppl 1)**:** 1935 (abstr).

20 Amatangelo M, Bjorklund C, Kang J, et al. Preclinical and translational support for clinical development of iberdomide in combination with proteasome inhibitors: mechanism of synergy in clinical trial CC-220-MM-001. *Blood* 2020; **136** (suppl 1)**:** 1358 (abstr).

21 Amatangelo M, Bjorklund C, Ma P, et al. Preclinical and translational data support development of iberdomide in combination with CD38- and SLAMF7-directed monoclonal antibodies: evidence for rational combinations. *Blood* 2020; **136** (suppl 1)**:** 1359 (abstr).

22 Lonial S, Amatangelo M, Rakesh P, et al. Translational, and clinical evidence of a differentiated profile for the novel CELMoD, iberdomide (CC-220). *Blood* 2019; **134** (suppl 1)**:** 3119 (abstr).

23 Jennison C, Turnbull BW. Group sequential methods with applications to clinical trials. Boca Raton, FL: CRC Chapman & Hall, 1999.

24 Kumar S, Paiva B, Anderson KC, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. *Lancet Oncol* 2016; **17:** e328–46.

25 Janssen Biotech. Carvykti (ciltacabtagene autoleucel) prescribing information. Horsham, PA: Janssen Biotech, 2022. https://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/CARVYKTI-pi.pdf (accessed April 29, 2022).

26 Krönke J, Udeshi ND, Narla A, et al. Lenalidomide causes selective degradation of IKZF1 and IKZF3 in multiple myeloma cells. *Science* 2014; **343:** 301–05.

27 Lu G, Middleton RE, Sun H, et al. The myeloma drug lenalidomide promotes the cereblon-dependent destruction of Ikaros proteins. *Science* 2014; **343:** 305–09.

28 Höglund P, Eriksson T, Björkman S. A double-blind study of the sedative effects of the thalidomide enantiomers in humans. *J Pharmacokinet Biopharm* 1998; **26:** 363–83.

29 Mori T, Ito T, Liu S, et al. Structural basis of thalidomide enantiomer binding to cereblon. *Sci Rep* 2018; **8:** 1294.

30 Lancman G, Sastow DL, Cho HJ, et al. Bispecific antibodies in multiple myeloma: present and future *Blood Cancer Discov* 2021; **2:** 423–33.