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RESEARCH ARTICLE

A phase 1b/2 study evaluating efficacy and safety of MP0250, a designed ankyrin repeat protein (DARPin) simultaneously targeting vascular endothelial growth factor (VEGF) and hepatocyte growth factor (HGF), in combination with bortezomib and dexamethasone, in patients with relapsed or refractory multiple myeloma

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Abstract

MP0250 is a designed ankyrin repeat protein that specifically inhibits both vascular endothelial growth factor A (VEGF-A) and hepatocyte growth factor (HGF), aiming at potentiating cancer therapy by disrupting the tumour microenvironment. Encouraging

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results from a phase 1 trial of MP0250 in patients with solid tumours prompted further investigation in multiple myeloma (MM) as both MP0250 targets are reported to be drivers of MM pathogenesis.

In this open-label, single-arm phase 1b/2 study (NCT03136653) in patients with proteasome inhibitor- and/or immunomodulatory drug-relapsed or refractory MM, MP0250 was administered every 3 weeks with standard bortezomib/dexamethasone regimen.

Thirty-three patients received at least one dose of MP0250. The most frequent treatment-related adverse events were arterial hypertension (58.1%), thrombocytopenia (32.3%), proteinuria (29.0%) and peripheral oedema (19.4%). Of the 28 patients evaluable for response (median age: 60 [range 44–75]), nine achieved at least partial response, corresponding to an overall response rate of 32.1% (95% confidence interval [CI]: 17.9%, 50.7%), with a median duration of response of 8 months (95% CI 5–NR). An additional three patients achieved minimal response and nine stable diseases as the best overall response. Overall median progression-free survival was 4.2 months (95% CI 1.9–7.1).

These findings are in line with the results of recent trials testing new agents on comparable patient cohorts and provide initial evidence of clinical benefit for patients with refractory/relapsed MM treated with MP0250 in combination with bortezomib/dexamethasone. Further clinical evaluation in the emerging MM treatment landscape would be required to confirm the clinical potential of MP0250.

KEYWORDS
anti-HGF, anti-VEGF, DARPin, MP0250, refractory/relapsed multiple myeloma

1 | INTRODUCTION

Research in multiple myeloma (MM) over the last few decades has provided an increasing number of useful treatment options. The original mainstays of MM treatment, that is, steroids and cytostatic agents, have been complemented, or in part replaced by immunomodulatory drugs (IMiDs) such as lenalidomide or pomalidomide (these also have anti-angiogenic activity), and proteasome inhibitors (PIs) such as bortezomib and carfilzomib [1]. Monoclonal antibodies targeting several antigens markedly present on myeloma cells are now established in clinical use, notably daratumumab (targeting CD38) [2] and elotuzumab (targeting signalling lymphocytic activation molecule family member 7 (SLAMF7)) [3]. More recently, chimaeric antigen receptor modulated T-cells (CAR T-cells) specific for myeloma cell antigens such as BCMA (B cell maturation antigen) [4], and bi-specific T-cell engager antibodies (BiTEs) [5] have come into clinical play. However, MM remains mostly incurable with transient treatment responses as myeloma cells often become therapy-refractory. Consequently, new strategies are still necessary for further therapeutic improvement.

Experimental studies implicate key roles for vascular endothelial growth factor A (VEGF-A) and hepatocyte growth factor (HGF) in the pathogenesis of MM [6, 7]; both factors are involved in neoangiogenesis and the formation of a vascular niche/permissive tumour microenvironment (TME) in the bone marrow of MM patients [6–17]

In the clinic, the antiangiogenic activities reported for key drugs used in relapsed or refractory MM (RRMM) treatment, including PIs and IMiDs [18] seem likely to contribute to their efficacy, but phase 2 combination studies with the anti-VEGF monoclonal antibody bevacizumab and bortezomib or lenalidomide failed to show increased activity in the desired magnitude [18–20]. The role of HGF inhibition is less clear as no specific inhibitor of HGF or cMET has been tested in MM patients. Negative results obtained with tivantinib, reported initially to be a MET inhibitor, in MM patients in a small phase 2 study are unreliable as several groups published data questioning the role of tivantinib as a specific MET inhibitor whilst indicating its principal activity to be microtubule disruption [21]. Therefore, the effect of inhibiting HGF alone, or together with VEGF, was yet to be tested in MM patients. The present study was an attempt to address this open question using the investigative drug candidate MP0250 in combination with bortezomib to disrupt the TME in MM.

MP0250 is a designed ankyrin repeat protein (DARPin) that inhibits VEGF-A and HGF and also binds to human serum albumin to prolong half-life in the circulation [22] (Figure 1). DARPins are a class of small, engineered proteins exhibiting high specificity and

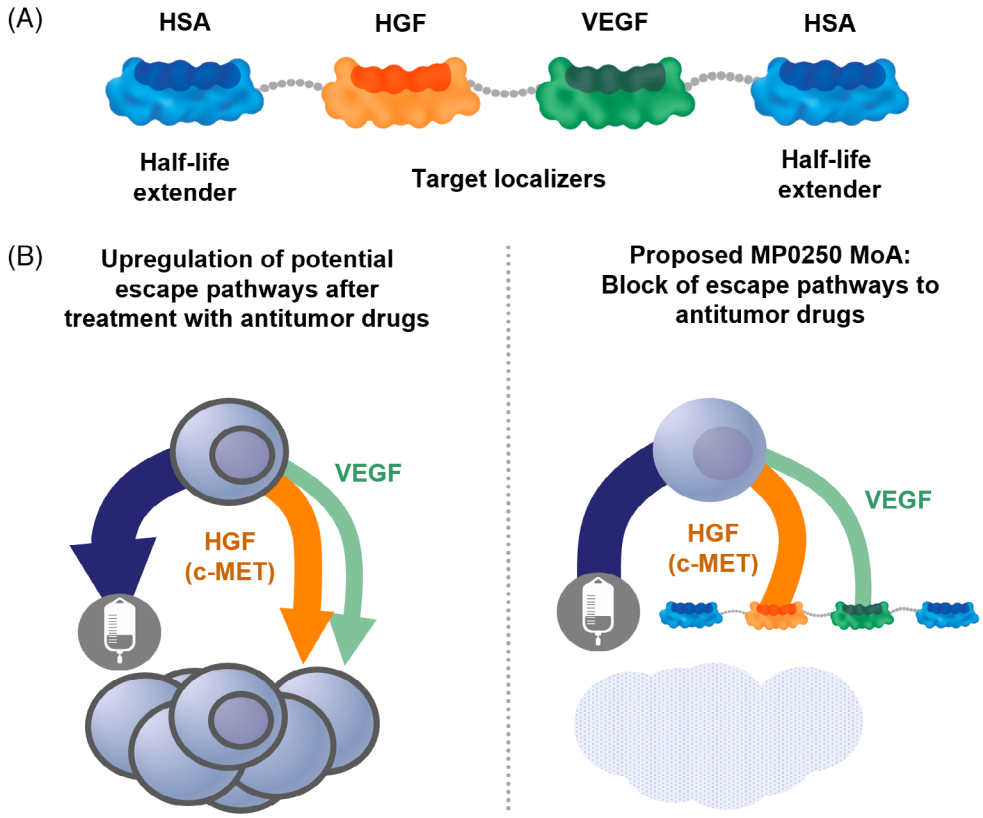

FIGURE 1 MP0250 DARPin structure and proposed mechanism of action. MP0250 is a 4-domain DARPin molecule containing VEGF-A (green) and HGF (orange) binding domains which bind the growth factors in a sub-picomolar range and human serum albumin (blue) binding domains to give the molecule an antibody-like half-life in the circulation (A). Some tumours develop adaptive off-target resistance to antitumour drugs by up-regulating escape pathways driven by VEGF and HGF. Blocking these adaptive escape pathways simultaneously with MP0250 is hypothesized to restore clinical sensitivity to the antitumour drugs (B). HGF, hepatocyte growth factor; HSA, human serum albumin; VEGF, vascular endothelial growth factor.

high-affinity binding that can be linked together in a single molecule to build multi-specific proteins [23]. Preclinical studies have shown that the dual growth factor inhibition by MP0250 results in greater effects on tumour growth and angiogenesis than is achieved by individual inhibition of the growth factors in a wide range of tumours. Also, potentiation of the activity of approved cytotoxic and immunomodulatory agents was demonstrated, including enhancing the activity of bortezomib in an orthotopic MM model [24]. The antiangiogenic activity of MP0250 in MM has been confirmed in the 5T33MM syngeneic mouse model, with higher efficiency measured for combination treatment with MP0250 and bortezomib [25].

A phase 1 trial in patients with a variety of advanced solid tumours showed MP0250 monotherapy to have a suitable safety and pharmacokinetics profile for clinical development, with initial signs of antitumor activity [26].

Based on these literature reports and our own preclinical and clinical phase 1 findings, we set out to further explore the utility of MP0250. MM was selected as an appropriate indication as both its VEGF and HGF targets are reported to support the TME and thus be drivers of tumour pathogenesis. Herein we present data from a phase 1b/2 study of MP0250 in combination with bortezomib in patients with RRMM.

2 | PATIENTS AND METHODS

2.1 | Study design and treatment regimes

This phase 1b/2 open-label, single-arm, multicenter study accrued patients from May 2017 to May 2020, in 24 hospitals in several European countries (NCT03136653).

Based on the phase 1 study on MP0250 monotherapy for patients with advanced solid tumours (NCT02194426) [26], patients received MP0250 intravenously (iv) over 1 h on day 1 added to a typical bortezomib/dexamethasone (VD) regime, with bortezomib given subcutaneously (sc) at 1.3 mg/m^2 on days 1, 4, 8 and 11, and oral dexamethasone at 20 mg if the patients were < 75 years old or 12 mg if ≥ 75 years old, on days 1, 2, 4, 5, 8, 9, 11, and 12 of each 21-day cycle. Study treatment was continued until disease progression, unacceptable toxicity, or withdrawal of consent, whichever occurred first.

Part 1 was a lead-in, dose-escalation phase 1b study starting at an MP0250 dose of 8 mg/kg iv on day 1 combined with VD. Part 2 was a phase 2 trial to assess the efficacy and safety of MP0250 at the identified recommended phase 2 dose (maximum tolerated dose [MTD]) iv added on day 1 of a 3-week VD regime in RRMM.

TABLE 1 Statistical analysis sets.

Analysis Set	Part 1		Part 2	Pooled Part 1 and Part 2	Total (% of total)
	8 mg/kg	12 mg/kg	8 mg/kg	8 mg/kg	
Patients screened	–	–	–	–	51
Screen failures	–	–	–	–	18[a]
SAS (*n* [%][b])	8 (24.2)	3 (9.1)	22 (66.7)	30 (90.9)	33 (100)
Completed DLT assessment period (*n* [%][c])	6 (75.0)	2 (66.7)	–	–	8 (24.2)
FAS (*n* [%][c])	8 (100)	–	20 (90.9)	28 (93.3)	28 (84.8)

Abbreviations: DLT, dose-limiting toxicity; FAS, full analysis set; *n*, number of patients; SAS, safety analysis set.

[a]Main reasons for screen failures included failure to meet required haemoglobin level ≥ 8.0 g/dL ($n = 4$ patients), platelet count ≥ 50,000/ m^3 ($n = 3$) and/or creatinine clearance ≥ 50 mL/min ($n = 6$) at screening.

[b]Percentage of all enrolled patients ($n = 33$).

[c]Percentage of total patients in the respective dosing cohort SAS.

An independent data monitoring committee (IDMC) reviewed all safety and pharmacokinetic data in Part 1. In Part 2, the IDMC reviewed safety data for unexpected safety signals (see also File S1).

The study was approved by the institutional review board/independent ethics committee of each participating institution and conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonization Guidelines for Good Clinical Practice.

2.2 | Patient eligibility

Eligible patients were ≥ 18 years old with RRMM, had no objective response to or progression during or within 60 days of the immediate prior line of therapy, and with ≥ 2 prior lines of therapy including a PI (bortezomib, carfilzomib or ixazomib) and/or an IMiD (thalidomide, lenalidomide and/or pomalidomide). Refractory disease was defined as no response or progression within 60 days of the immediate prior therapy in Part 1 and as a response no better than stable disease (SD) or progression on treatment, or within 60 days of stopping a bortezomib- or carfilzomib-based regimen as last prior line of therapy in Part 2. All patients signed an informed consent before enrolment in the study.

2.3 | Study endpoints and procedures

The primary endpoint was the overall response rate (ORR) in both study parts, defined as the proportion of patients achieving stringent complete response (sCR), CR, very good partial response (VGPR), or partial response (PR) as assessed by the investigator and based on response categories defined by the International Myeloma Working Group (IMWG) [27]. The safety profile of MP0250 was assessed as a secondary endpoint. Adverse events (AEs) were coded according to the Medical Dictionary for Regulatory Activities (MedDRA) V23.0 and assessed using the NCI CTCAE criteria V4.03. Treatment-emergent adverse events (TEAEs) were defined as an AE that first occurred or increased in severity/frequency after the first MP0250 dose and within 28 days after treatment discontinuation. The definitions of dose-limiting toxicities (DLTs) for part 1 are displayed in File S1. Additional secondary endpoints included pharmacokinetics, pharmacodynamics, immunogenicity, progression-free survival (PFS) and duration of response (DoR).

2.4 | Statistical analyses

All Part 1 and 2 analyses employed descriptive statistics unless otherwise specified (Table 1). The safety analysis set (SAS) consisted of all patients who were enrolled and received at least one dose of MP0250. The full analysis set (FAS) was defined as all patients who received at least one dose of MP0250 at the MTD, had measurable disease and completed at least one post-baseline response assessment. Estimated ORR was calculated with the 95% confidence interval (95% CI). PFS was defined as the time from the first dose of study medication to disease progression or death, whichever came first and was analyzed using the Kaplan-Meier method.

The overall sample size for the study was calculated using an optimal Simon's two-stage design and based on a one-sided test at significance level $\alpha = 0.05$ and $\beta = 80\%$ and with a null hypothesis of ORR ≤ 20% versus the alternate hypothesis assuming an ORR of ≥ 40%. Part 1 (lead-in phase 1b), aimed to identify the MTD of MP0250 when combined with bortezomib and dexamethasone, and included 11 patients. For Part 2, the optimal Simon's two-stage design required 43 patients. In the first stage, 13 patients were to be accrued and if four or more patients in this group responded, the study was to be continued with up to 43 patients. Therefore, the planned enrolment for this study was up to 54 patients. However, patient recruitment had to be stopped prematurely at 33 patients in May 2020 due to patient accrual being slowed to an unworkable level by the coronavirus disease 2019 (COVID-19) pandemic. The overall risk-benefit assessment of the study had not

changed at this time and no specific unexpected safety signals had been observed.

3 | RESULTS

3.1 | Patient demographics and baseline characteristics

The patients' baseline demographics and disease characteristics are summarised in Table 2. A total of 33 patients with a diagnosis of MM were accrued: 18 were female (54.5%) and 15 were male (45.5%). The patients' median age was 60 years (range 44–75 years). Their Eastern Cooperative Oncology Group performance status was 0 (15 patients) or 1 (18 patients). Most patients (18; 54.5%) had an immunoglobulin G MM subtype. Monoclonal light chains were predominantly of the κ type (25 patients; 75.8%). All patients had RRMM as defined by the IMWG. Patients had received a median of 3 lines of pre-treatment (range 2–9 lines) prior to entering the trial, with the last line including bortezomib-containing regimes in 11 patients, carfilzomib in six patients, and ixazomib in two. The remaining 14 patients had been treated with regimes containing IMiDs (9 patients) or daratumumab (5 patients). The median time between the discontinuation of the previous treatment line and the start of MP0250 therapy was 1.4 months (range 0.5–73.1 months).

3.2 | Disposition of patients

Patient disposition is summarised in Figure 2. In part 1 in the MP0250 dose cohort of 8 mg/kg, one of six evaluable patients experienced dose-limiting toxicity (DLT; grade 3 hypertension). Of three additional patients subsequently enrolled on the 12 mg/kg dose cohort, two experienced a DLT (grade 3 epistaxis and grade 3 proteinuria). Hence, the part 2 dose (i.e., MTD) of MP0250 was set at 8 mg/kg and added on day 1 every 3 weeks (q3w) to a VD regime. At the cut-off date for final data analysis (13 January 2021), all patients had withdrawn from the study treatment; main reasons were disease progression and/or death (10 patients [30.3%]), study terminated by the sponsor (10 patients [30.3%]), patient refusal to continue study treatment (seven patients [21.2%]), other reasons (four patients [12.1%]) and lost to follow-up (two patients [6.1%]).

3.3 | Exposure to MP0250

The median number of MP0250 infusions administered to all 33 patients was 4 (range 1–43). The mean (standard deviation) overall exposure to MP0250 per 21-day cycle was 6.1 (2.1) mg/kg with an overall mean estimated MP0250 treatment compliance of 72.5% (20.3). The median duration of exposure to MP0250 was 64 days (Q1, Q3: 40.0, 183.0).

TABLE 2 Patient demographics and baseline characteristics.

Characteristics	Total ($n = 33$)
Sex, *n* (%)	
Female	18 (54.5)
Male	15 (45.5)
Age	
Mean (standard deviation), years	60.0 (8.4)
Median (Min, Max), years	60.0 (44, 75)
Patients ≥ 65 years of age, *n* (%)	11 (37%)
MM subtype, *n* (%)	
IgG	18 (54.5)
IgA	7 (21.2)
IgM	0
none	8 (24.2)
Kappa light chain only	25 (75.8)
Lambda light chain only	8 (24.2)
R-ISS stage, *n* (%) at initial diagnosis	
Stage I	9 (27.3)
Stage II	5 (15.2)
Stage III	5 (15.2)
Missing	14 (42.4)
ECOG performance status, *n* (%) at study entry	
0	15 (45.5)
1	18 (54.6)
Cytogenetic risk, *n* (%)	
High-risk	11 (33.3)
Standard-risk	11 (33.3)
Unknown or missing	11 (33.3)
Median (range) time from diagnosis to first dose, years	4.2 (2.6, 10.0)
Median (range) time from discontinuation of last MM cancer therapy to first MP0250 dose, months	1.4 (0.5, 73.1)
Number of prior lines of therapy, median (range)	3 (2–9)
Disease status before study entry, *n* (%)	33 (100)
Double refractory to IMiDs + PIs	10 (30.3)
Refractory to IMiD-containing regimen	9 (27.3)
Refractory to PI-containing regimen	9 (27.3)
Refractory to daratumumab monotherapy	5 (15.1)
Last prior MM treatment regimen received before study entry, *n* (patients)	33 (100)
Bortezomib + lenalidomide + dexamethasone	3
Bortezomib + pomalidomide + dexamethasone	1
Bortezomib + durvalumab + dexamethasone	1
Bortezomib + daratumumab + dexamethasone	2
Bortezomib + venetoclax	1
Bortezomib + lenalidomide + melphalan + doxorubicin + dexamethasone	1

(Continues)

TABLE 2 (Continued)

Characteristics	Total ($n = 33$)
Bortezomib + dexamethasone	1
Bortezomib + melphalan+ dexamethasone	1
Carfilzomib + pomalidomide + dexamethasone	1
Carfilzomib + lenalidomide + dexamethasne	2
Carfilzomib + cyclophosphamide + dexamethasone	1
Carfilzomib + dexamethasone	1
Carfilzomib + daratumumab + dexamethasone	1
Ixazomib + thalidomide + dexamethasone	2
Lenalidomide + dexamethasone	4
Lenalidomide + melphalan + dexamethasone	1
Pomalidomide + dexamethasone	2
Pomalidomide + durvalumab + dexamethasone	1
Pomalidomide + doxorubicin + cyclophosphamide + etoposide + dexamethasone	1
Daratumumab + dexamethasone	1
Daratumumab monotherapy	4
Prior HDC/ASCT and/or Allo-SCT, *n* (%)	30 (90.9%)

Abbreviations: ASCT, autologous stem cell transplantation; Allo-SCT, allogeneic stem cell transplant; CT, chemotherapy; HDC, high-dose chemotherapy; IgA, immunoglobulin A; IgD, immunoglobulin D; IgE, immunoglobulin E; IgG, immunoglobulin G; IgM, immunoglobulin; IMiDs, immunomodulatory agents; Mab, monoclonal antibodies; MM, multiple myeloma; n, number of patients; PIs, proteasome inhibitors; RISS, Revised International Staging System.
IMiDs include lenalidomide or thalidomide or pomalidomide.
PIs include bortezomib, carfilzomib or ixazomib.

3.4 | Antitumour activity

Of the 33 patients who received at least one dose of MP0250, 28 met the FAS definition criteria and were evaluable for response. Five patients were excluded from the FAS due to receiving treatment dose above the MTD of 8 mg/kg ($n = 3$) and no measurable disease or post-baseline response assessment ($n = 2$). Overall, nine patients achieved PR or better: one sCR, three VGPRs and five PRs, yielding an estimated ORR of 32.1% (95% CI 17.9%–50.7%). (Table 3). In the responders, the median DoR was 8 months (95% CI 5–not reached [NR]). An additional three patients achieved minimal response (MR) and nine SD as best overall response. The Kaplan-Meier analysis of all patients resulted in an overall median PFS of 4.2 months (95% CI 1.9–7.1).

Seventeen of the patients evaluable for response were refractory or relapsed from a PI-containing regimen as the last prior treatment line before study entry. Of these, six patients achieved a response (PR or better). A total of 11 patients were refractory to bortezomib as a last line of therapy, of which four responded (one sCR, two VGPR and one PR) to the combination therapy. In addition, both of the patients with ixazomib as a last line of therapy achieved a response (two PR), while none of the four patients refractory to carfilzomib as a last line of therapy responded to the study treatment.

3.5 | Safety

Of 33 patients in the SAS, two patients treated with 8 mg/kg MP0250 were excluded due to a major protocol violation at the study site. The remaining 31 patients reported at least one TEAE (Table 4) and 27 patients (87.1%) had TEAEs that were related to MP0250. Overall, 71.0% had TEAEs that required MP0250 dose-adjustment and 32.3% had TEAEs that led to discontinuation of MP0250. The main reasons for discontinuation were proteinuria (n = 3), acute kidney injury (n = 2), nephrotic syndrome (n = 1), hypertensive crisis (n = 2), asthenia (n = 1) and abdominal abscess (n = 1). Among the patients with any kind of renal toxicity, none reached a degree of kidney damage to require dialysis. The most frequent (≥5%) TEAEs (Table 5) related to MP0250 were arterial hypertension/hypertensive crisis (51.7%), thrombocytopenia (42.0%), proteinuria (19.4%), asthenia (16.1%), anaemia (12.9%), lymphopenia (9.7%) and diverticulitis and leukopenia (6.5%, each). Two patients had TEAEs with fatal outcomes (grade 5): one patient treated at 8 mg/kg MP0250 developed an abdominal abscess complicated by sepsis, and another patient treated at 12 mg/kg MP0250 in part 1 had acute renal failure due to disease progression; both events were reported as not related to MP0250.

3.6 | Pharmacodynamics, pharmacokinetics and immunogenicity

The binding of MP0250 to both its targets, VEGF-A and HGF, in plasma was demonstrated. For VEGF-A, this was manifest as a reduction of plasma levels of free VEGF-A in all patients to undetectable for the duration of treatment and for HGF as an increase in plasma levels of HGF bound to MP0250 in all patients over time starting from treatment cycle 2.

Following the first infusion, MP0250 plasma concentrations decreased in a mono-exponential manner, with a geometric mean half-life (t1/2) of around 11 days (range 264–275 h). Steady-state was reached after infusion 3 when the t1/2 was around 15 days and $AUC_{(0\text{-}tau)}$ was 66.6 h*mg/mL. In general, the pharmacokinetic (PK) parameters of MP0250 appear consistent with linear PK and were similar to those reported in the phase 1 study [26].

Treatment-associated anti-drug antibody (ADA) titers (median: 50, maximum: 400) were detected in 4/31 (13%) of patients with no detectable effect on MP0250 exposure. Exposure was maintained even after extended periods of repeat dosing: eight patients were shown to have full exposure to MP0250 for at least 6 months with one patient treated for 20 months and one for 30 months.

4 | DISCUSSION

The results of this phase 1b/2 study show that treatment with the DARPin MP0250, a specific inhibitor of both VEGF-A and HGF, in combination with bortezomib is clinically feasible for patients with heavily pretreated RRMM and can lead to disease improvements.

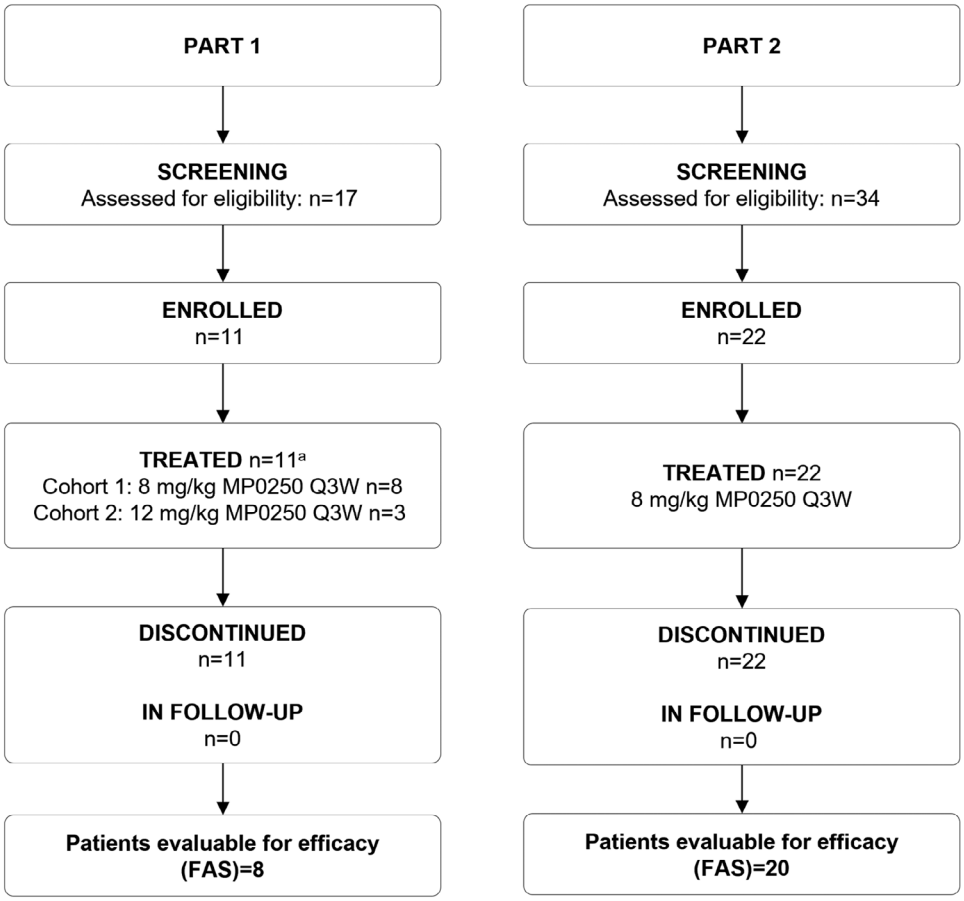

FIGURE 2 Patient Disposition (SAS). Display of the patient flow through Part 1 and Part 2. Part 1 was a lead-in, dose-escalation phase 1b trial. Cohort 1: 8 mg/kg of MP0250 iv on day 1 combined with VD. Cohort 2: 12 mg/kg of MP0250 iv on day 1 combined with VD. Part 2 was a phase 2 trial to assess the efficacy and safety of MP0250 at 8 mg/kg iv on day 1 in a 3-week schedule in combination with the VD regime in RRMM. [a]Two patients who received 8 mg/kg and one patient who received 12 mg/kg of MP0250 did not complete the full DLT period in Part 1. DLT, Dose-limiting toxicity; RRMM, refractory/relapsed myeloma; SAS, safety analysis set; VD, bortezomib/dexamethasone.

Phase 2 evidence on the use of this novel agent has so far been lacking.

A clinical benefit was documented in 21 of 28 patients evaluable for response (75%; 95% CI 56.6–87.3). Nine patients achieved PR or better including one sCR and three VGPR. The overall median PFS was 4.2 months (95% CI 1.9–7.1) and in responders, the median DoR was 8 months (95% CI 5–NR). PFS in these heavily pretreated RRMM patients was rather short. Nevertheless, a PFS in this order of magnitude was also reported in recent trials of other novel agents tested on comparable RRMM patient cohorts, such as BRAF/MEK [28], iberdomide plus dexamethasone [29], cemiplimab plus isatuximab [30] and mezigdomide plus dexamethasone [31]. For example, in this latter study in triple-class–refractory MM patients treated with the novel cereblon E3 ubiquitin ligase modulator mezigdomide the overall response was 41%, with a median DoR of 7.6 months and median PFS of 4.4 months. Adverse events of neutropenia and infection were reported in around 2/3 of the patients in the study.

Of note, no critical severe haematological drug toxicity was seen in any of our patients. MP0250 was stopped in two patients because of acute kidney toxicity and in one patient for nephrotic syndrome, but no patient experienced therapy-induced worsening of kidney function to the extent that would have required renal dialysis. In these three patients, the question of whether the deterioration of renal function was due to MP0250, or (at least in part) caused by the underlying disease remains open. Hypertension and proteinuria are typical side effects of antiangiogenic therapies, hence expected in the MP0250 protocol. Two patients died whilst in the study but both fatal events were considered unrelated to study treatment.

The negligible immunogenicity of MP0250 was confirmed in this study. The MP0250 PK profile was similar to that reported in the phase 1 study [26] with minimal ADA production and no detectable impact of ADAs on MP0250 exposure. The observed changes over time in the plasma levels of HGF and VEGF-A were also in line with those measured in the phase 1 study [26].

Although a significant proportion of the patients were responders, different responses depending on the prior PI treatment were seen. Six of 17 patients exposed to a prior PI regimen responded including four of 11 patients previously treated with bortezomib and two of two patients with prior ixazomib treatment, whilst none of the carfilzomib-pretreated patients achieved a response above MR or SD. This might

TABLE 3 Responses according to the International Myeloma Working Group (IMWG) in the full analysis set (FAS).

	8 mg/kg (*N* = 28)
Overall Response Rate (ORR)	
Responders, *n* (%)	9 (32.1)
Estimate ORR[a]	0.321
95% CI[b]	(0.179, 0.507)
Best response, all patients, *n* (%)	
sCR	1 (3.6)
PR	3 (10.7)
VGPR	5 (17.9)
MR	3 (10.7)
SD	9 (32.1)
PD	7 (25.0)

Abbreviations: CI, confidence interval; CR, complete response; FAS, full analysis set; IMWG, International Myeloma Working Group; MR, minimal response; n, number of patients; ORR, overall response rate; PD, progressive disease; PR, partial response; sCR, stringent complete response; SD, stable disease; VGPR, very good partial response.

[a]ORR was defined as the proportion of patients achieving a confirmed sCR, CR, VGPR, or PR during treatment with MP0250 in combination with bortezomib plus dexamethasone as determined by the Investigator.

[b]Estimated using the Wilson confidence intervals.

be due to bortezomib- and ixazomib-resistance being transient whilst carfilzomib-refractoriness is usually irreversible.

Concerning the mechanism of action of MP0250, although pharmacodynamics (target binding) and safety (hypertension, generally manageable) results confirmed that MP0250 bound both its targets, it is not possible to determine whether the observed clinical benefit could be attributed to combined or single target inhibition. Given the limited effect of adding the VEGF inhibitor bevacizumab to bortezomib treatment seen in a phase 2 MM trial [20], attributing all the therapeutic benefits to VEGF inhibition in the current study could be questioned. With respect to HGF inhibition, no agent with the absolute HGF specificity of MP0250 has been evaluated in RRMM, so the clinical effect of sole HGF inhibition could not be judged. As outlined in the Introduction, HGF inhibition would be expected to have effects due to TME disruption but this was not investigated in the study. Given the above and the numerous reports of interacting/compensatory/synergistic roles for VEGF and HGF in RRMM [6–17], it appears most likely that dual inhibition of VEGF and HGF would have been responsible for the positive effects observed in our study. However, the possibility of HGF inhibition reversing treatment resistance of tumour cells should also be considered in further studies as resistance in a variety of cancers has been shown to be due to upregulation of the HGF-dependent MET-amplification escape pathway [32–35] – although, to our knowledge, this has not yet been reported in RRMM.

Limitations of the trial include the following. First, it was a single-arm study with no comparator. Second, patient recruitment suffered from the COVID-19 pandemic and was stopped early before the planned sample size was achieved. Third, the absence of an MP0250-only group left open the possibility that the beneficial effects seen could have been independent of VD and due to MP0250 alone: MP0250 has been shown to have single-agent antitumor activity in a range of solid tumours as well as MM in preclinical studies [24] and showed signs of activity in the phase 1 study in diverse solid tumours [26].

In conclusion, our phase 1b/2 trial showed that administration of the DARPin MP0250 was feasible in a heavily pretreated population of RRMM patients and the clinical benefit identified provided some proof-of-principle evidence in support of the potential value of the

TABLE 4 Overview of all treatment-emergent adverse events (TEAEs) observed (SAS).

Adverse event category, *n* (%) m	8 mg/kg (*N* = 28)	12 mg/kg (*N* = 3)	Total (*N* = 31)[a]
Any TEAE	28 (100) 525	3 (100) 78	31 (100) 603
Any TEAEs related to MP0250	24 (85.7) 237	3 (100) 41	27 (87.1) 278
Any TEAEs of NCI CTCAE Grade ≥3	26 (92.9) 140	3 (100) 29	29 (93.5) 169
Any TEAEs with an outcome of death	1 (3.6) 1	1 (33.3) 1	2 (6.5) 2
Any Serious TEAEs	14 (50.0) 19	2 (66.7) 3	16 (51.6) 22
Any Serious TEAEs related to MP0250	4 (14.3) 7	0	4 (12.9) 7
Any TEAEs requiring MP0250 dose adjustment	20 (71.4) 50	2 (66.7) 11	22 (71.0) 61
Any TEAEs leading to discontinuation of MP0250	9 (32.1) 12	1 (33.3) 1	10 (32.3) 13
Any TEAEs of special interest	7 (25.0) 12	0	7 (22.6) 12

Abbreviations: AE, adverse event; eCRF, electronic case report form; m, number of events; N/n, number of patients; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; SAS, Safety Analysis Set; TEAE, treatment-emergent adverse event.

Note: For each category, patients were included only once, even if they experienced multiple events in that category.

TEAEs were defined as those that first occurred or increased in severity or frequency after the first dose of the study drug and within 28 days after stopping the study medication. TEAEs of special interest included allergic or anaphylactic reactions, progressive renal impairment, severe hemorrhagic events, uncontrolled hypertension, thromboembolic events, and others as documented by the Investigator.

[a]Percentage calculations are based on 31 patients of the SAS (data of two patients in the SAS were excluded from the safety table due to a major protocol deviation in one site).

TABLE 5 Most frequently reported (≥5%) treatment-emergent adverse events (TEAEs)[a] of NCI CTCAE Grade ≥3.

System organ class (SOC) Preferred Term (PT), number of patients (%)	Grade ≥3 (*N* = 31)[b]
Any TEAEs	29 (93.5)
Vascular disorders	16 (51.6)
Hypertension	16 (51.6)
Hypertensive crisis	2 (6.5)
Blood and lymphatic system disorders	16 (51.6)
Thrombocytopenia	13 (41.9)
Anaemia	5 (16.1)
Lymphopenia	3 (9.7)
Neutropenia	2 (6.5)
Renal and urinary disorders	8 (25.8)
Proteinuria	6 (19.4)
Acute kidney injury	2 (6.5)
General disorders and administration site conditions	4 (12.9)
Oedema peripheral	0 (0.0)
Fatigue	0 (0.0)
Asthenia	4 (12.9)
Investigations	5 (16.1)
White blood cell count decreased	2 (6.5)
Metabolism and nutrition disorders	4 (12.9)
Hyperuricaemia	2 (6.5)
Infections and infestations	4 (12.9)
Diverticulitis	2 (6.5)

Abbreviations: AE, adverse event; m, number of events; MedDRA, Medical Dictionary for Regulatory Activities; n, number of patients; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; PT, preferred term; SAS, safety analysis set; SOC, system organ class; TEAE, treatment-emergent adverse event.

Note: Adverse events were coded using MedDRA version 23.0. For each SOC and PT, patients are included only once, even if they experienced multiple events in that SOC or PT. TEAEs are defined as those which first occur or increase in severity or frequency after the first dose of the study drug.

[a]Table reports all TEAEs, independent of the relationship to MP0250. Overall, a total of 31 patients experienced any TEAE, including 27 patients reporting TEAEs related to MP0250.

[b]Percentage calculations are based on 31 patients of the SAS (data of two patients in the SAS were excluded from the safety table due to a major protocol deviation in one site).

novel mode of action of MP0250. However, with the emergence of new treatments like CD38- and BCMA-targeting regimens, the observed antitumor activity of MP0250 was not deemed sufficient to continue clinical evaluation of the MP0250 plus VD regimen in RRMM at this stage. Nevertheless, the hypothesised potential of MP0250 to disrupt the TME and/or inhibit the HGF/MET drug resistance escape pathway could be worth considering as an orthogonal component of new combination regimens.

AUTHOR CONTRIBUTIONS

Conception and design: Stefan Knop; Michael T. Stumpp; Keith M. Dawson; Nicolas Leupin; Philippe Legenne and Hartmut Goldschmidt. *Collection and assembly of data*: All authors. *Data analysis and interpretation*: All authors. *Manuscript writing*: All authors. Final approval of manuscript and accountability for all aspects of the work: All authors.

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CONFLICT OF INTEREST STATEMENT

Stefan Knop: Honoraria from AMGEN, Bristol-Myers Squibb, Janssen-Cilag, Oncopeptides, Novartis, Sanofi, Pfizer, Takeda, Stemline, and Molecular Partners; and on Advisory Boards from Bristol-Myers Squibb, Janssen-Cilag, ONYX, Oncopeptides Sanofi, AMGEN, Pfizer GmbH and Takeda. Monika Szarejko: declares no conflict of interest. Norbert Grząśko: Honoraria from Abbvie and Novartis. Sara Bringhen: Participation in speakers' bureaus: Amgen, Bristol Myers Squibb, GlaxoSmithKline, Janssen, Sanofi and AbbVie; Participation in advisory boards: Bristol Myers Squibb, Janssen, Takeda, Pfizer, Stemline Therapeutics and Oncopeptides; Consultancy fees: Sanofi. Karolin Trautmann-Grill: Participation in speakers' bureaus: Amgen, GlaxoSmithKline, Novartis and Roche; Participation in advisory boards: Amgen, GSK, Sanofi, Takeda, Pfizer and Novartis; Travel support: Janssen. Artur Jurczyszyn: declares no conflict of interest. Angelo Vacca: declares no conflict of interest. Cyrus Khandanpour: Participation in speakers' bureaus: Amgen, Bristol Myers Squibb, GlaxoSmithKline, Janssen, Sanofi, AbbVie, Takeda, Pfizer, Stemline Therapeutics and Oncopeptides. Barbara Gamberi: Advisory Board: Takeda, Sanofi, Amgen, Janssen; Honoraria: Janssen, BMS, GSK and Sanofi. Ludek Pour: declares no conflict of interest. Katrine F. Iversen: declares no conflict of interest. Hartmut Goldschmidt: Grants and/or provision of Investigational Medicinal Product: Amgen, Array Biopharma/Pfizer, BMS/Celgene, Chugai, Dietmar-Hopp-Foundation, Janssen, Johns Hopkins University, Mundipharma GmbH and Sanofi. Research Support/ Forschung und Studien: Amgen, BMS, Celgene, GlycoMimetics Inc., GSK, Heidelberg Pharma, Hoffmann-La Roche, Karyopharm, Janssen, Incyte Corporation and Millenium Pharmaceuticals Inc., Molecular Partners, Merck Sharp and Dohme (MSD), MorphoSys AG, Pfizer, Sanofi, Takeda and Novartis; Advisory Boards: Amgen, BMS, Janssen, Sanofi and Adaptive Biotechnology; Honoraria: Amgen, BMS, Chugai, GlaxoSmithKline (GSK), Janssen, Novartis, Sanofi and Pfizer; Support for attending meetings and/or travel: Amgen, BMS, GlaxoSmithKline (GSK), Janssen, Novartis, Sanofi and Pfizer. Michael T. Stumpp, Philippe Legenne, Vaia Stavropoulou, Keith M. Dawson are employee of Molecular Partners AG and hold a financial interest. Cosima Suter, Christof Zitt, Martin F. Fey and Nicolas Leupin were employees of Molecular Partners AG.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The study was approved by the institutional review board/independent ethics committee of each participating institution and conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonization Guidelines for Good Clinical Practice.

PATIENT CONSENT STATEMENT

All patients signed an informed consent before enrolment onto the study.

CLINICAL TRIAL REGISTRATION

The study was registered at ClinicalTrials.gov (NCT03136653).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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