National Cancer Medicines Advisory Group (NCMAG) Programme

NCMAG120 Pomalidomide in combination with bortezomib plus dexamethasone| Advice Document v1.0 |February 2025

Pomalidomide in combination with bortezomib plus dexamethasone for the treatment of adult patients with multiple myeloma who have received at least one prior treatment regimen including lenalidomide.[A]

NCMAG Decision | this off-patent use is **supported**

This advice applies only in the context of National framework confidential pricing agreements in NHSScotland for generic pomalidomide, upon which the decision was based, or confidential pricing agreements or list prices that are equivalent or lower.

[A] NCMAG considers proposals submitted by clinicians for use of cancer medicines outwith Scottish Medicines Consortium remit. For more detail on NCMAG remit please see our website.

Decision rationale

After consideration of all the available evidence regarding the clinical benefits and harms, the Council were satisfied with the clinical effectiveness case for pomalidomide in combination with bortezomib plus dexamethasone in the proposed population. After consideration of all relevant information under the Decision-making framework for value judgements the Council made a decision to support this use.

Governance Arrangements

Each NHS board must ensure all internal governance arrangements are completed before medicines are prescribed. The benefits and risks of the use of a medicine should be clearly stated and discussed with the patient to allow informed consent.

Proposal Details	
Proposers	NHSScotland Haematologists
Medicine Name	Pomalidomide, bortezomib plus dexamethasone
Cancer type	Multiple myeloma
Proposed use[B]	Pomalidomide in combination with bortezomib plus dexamethasone for the treatment of adult patients with multiple myeloma who have received at least one prior treatment regimen including

	lenalidomide. This review covers on-label and off-label dosing for bortezomib and dexamethasone.
Medicine Details	**Cycle 1 to 8 (21-day cycle)** Pomalidomide 4mg orally once daily, Day 1 to 14 Bortezomib subcutaneous injection 1.3mg/m^2 (Day 1, 8, 15): off-label dosing Dexamethasone oral 20mg once daily on day of bortezomib and day after (that is day 1, 2, 8, 9, 15, 16): off-label dosing **OR** Pomalidomide 4mg orally once daily, Day 1 to 14 Bortezomib subcutaneous injection 1.3mg/m^2 (Day 1, 4, 8, 11): on-label dosing Dexamethasone oral 20mg once daily on day of bortezomib and day after (that is day 1, 2, 4,5 8, 9, 11,12): on-label dosing **Cycle 9 onwards (21-day cycle)** Pomalidomide 4mg orally once daily, Day 1 to 14 Bortezomib subcutaneous injection 1.3mg/m^2 (day 1 and 8 only) Dexamethasone oral 20mg once daily on day of bortezomib and day after (that is day 1, 2, 8, 9) Treatment with pomalidomide combined with bortezomib and dexamethasone should be given until disease progression or until unacceptable toxicity occurs.
Advice inclusion criteria	• Have had at least one prior treatment regimen, including lenalidomide • Have experienced disease progression on last therapy • An anti-CD38 monoclonal antibody is not appropriate • 18 years of age or older • Eastern Cooperative Oncology Group Performance Status 0 to 2

[B] Pomalidomide has a marketing authorisation for the following indications:

- Pomalidomide in combination with bortezomib and dexamethasone is indicated in the treatment of adult patients with multiple myeloma who have received at least one prior treatment regimen including lenalidomide[1]. The proposed use includes off-label bortezomib and dexamethasone dosing.
- Pomalidomide in combination with dexamethasone is indicated in the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least two prior treatment regimens, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy.

1. Current Management Context

Multiple myeloma symptoms, incidence and prognosis

Multiple myeloma (MM) is an incurable haematological cancer caused by the proliferation of malignant plasma cells. This leads to the destruction of bone and bone marrow, resulting in bone fractures, anaemia, low platelet counts, susceptibility to infections, high calcium levels, kidney dysfunction, and neurological complications[2].Approximately 500 new cases of myeloma are diagnosed each year in Scotland[3], of whom about 75% of patients diagnosed are 65 years or older[3].

Multiple myeloma is characterised by periods of remission and relapse due to drug resistance, with each additional line of treatment associated with shorter remission times and worse outcomes[2].Survival rates for MM have improved in recent years. The estimated five-year age-standardised net survival is 62%[4].

Multiple Myeloma Treatment Pathway in Scotland

There are an increasing number of treatments available for MM, with the choice of treatment decided on a patient-by-patient basis. Factors such as age, symptoms, disease burden, fitness, co-morbidities, and patient preference (e.g., preference for an all-oral treatment) are considered.

First line treatment is determined by eligibility for autologous stem cell transplant (ASCT). Patients eligible for ASCT usually receive induction therapy followed by high-dose chemotherapy, ASCT, consolidation treatment, and maintenance with lenalidomide. For patients who do not receive a stem cell transplant due to fitness or preference, first line treatment typically involves a lenalidomide-containing regimen.

In the second line setting, for patients refractory to lenalidomide and unsuitable for anti-CD38, treatment options include carfilzomib and dexamethasone or bortezomib and dexamethasone[5-7]. Selinexor, bortezomib and dexamethasone has been recently accepted for use by the Scottish Medicines Consortium (SMC) in September 2024, however at the time of this review its use has not been established in Scotland and it has therefore not been considered as a comparator[8].

In the third line and beyond setting, pomalidomide in combination with dexamethasone or pomalidomide in combination with isatuximab and dexamethasone is available, along with a range of other treatment options including bi-specific T-cell engager medicines. Pomalidomide, bortezomib, and dexamethasone (PomBd) is expected to be predominately used in the second line and third line settings.

International Context for the proposed use

The European Society for Medical Oncology and National Comprehensive Cancer Network support the use of the combination of PomBd as a preferred option in lenalidomide-refractory patients fit for a triplet regimen and who have not demonstrated resistance to bortezomib.

Pharmacology of pomalidomide

Pomalidomide is an immunomodulatory drug that has a direct anti-myeloma effect by killing tumour cells, inhibiting angiogenesis, and stimulating the immune system to target myeloma cells[1]. Standard practice is for patients to receive concurrent thromboprophylaxis.

2. Evidence Review Approach

A literature search to identify clinical and economic evidence was conducted on key electronic databases including MEDLINE, Embase, the Cochrane Database of Systematic Reviews, major international health technology agencies, as well as a focused internet search. The search strategy comprised both Medical Subject Headings and keywords. The main search concepts were pomalidomide, bortezomib, dexamethasone, multiple myeloma and recurrent. Titles and abstracts were screened by one reviewer with a second opinion sought by another reviewer when required. The included key studies were critically appraised using the Cochrane risk of bias version 2.0 tool[9].

3. Clinical Evidence Review Summary

Clinical Efficacy Evidence

The key study supporting this proposal of using pomalidomide, bortezomib and dexamethasone is the OPTIMISMM study[10]. The OPTIMISMM study was a phase III randomised, open label, multicenter study which compared PomBd with bortezomib and dexamethasone (Bd) in patients with myeloma who had received at least one prior therapy including lenalidomide, which aligns with the submitted proposal[10]. Patients with an Eastern Cooperative Oncology Group (ECOG) Performance status (PS) of 0 to 2, and who had investigator assessed progressive disease on their previous antimyeloma treatment, were included in the study. Patients were randomised (1:1) to receive either PomBd (n=281) or Bd (n=278). Patients were stratified by age (≤75 versus >75 years), number of previous regimens (1 versus >1), and the concentration of β_2 microglobulin at screening (<3.5mg/L versus 3.5 to 5.5mg/L versus >5.5mg/L). Pomalidomide was given at a dose of 4mg orally on days 1 to 14 of each 21-day cycle. Bortezomib was administered either intravenously or subcutaneously at a dose of 1.3mg/m^2 body surface area (BSA) on days 1, 4, 8 and 11 of cycle 1 to 8 and on days 1 and 8 of cycle 9 and beyond and dexamethasone was given at a dose of 20mg orally on days 1, 2, 4, 5, 8, 9, 11 and 12 of cycles 1 to 8 and on days 1, 2, 8 and 9 of cycle 9 and beyond. The dosing of bortezomib and dexamethasone for cycles 1 to 8 is different to the proposed use. All patients in the PomBd arm received an anticoagulant for thromboprophylaxis. The primary outcome was progression-free survival (PFS) defined as time from randomisation to disease progression or death. Secondary outcomes include overall survival, overall response, health related quality of life (HRQoL) and safety. Response to treatment was defined according to the international myeloma working group (IMWG) criteria with masked assessment by an independent review adjudication committee.

Results from the OPTIMISMM study[10]

At the primary data cut off, October 2017, the median duration of follow up was 15.9 months (interquartile range [IQR] 9.9 to 22 months). The median age of patients was 67 years, 49% had an ECOG PS of 1 or 2, just over half had an international staging system (ISS) disease stage of 1 (51%), 70% were lenalidomide refractory and 40% had received one prior line of treatment with a median number of prior lines of 2 (IQR 1-2). The median number of treatment cycles and median treatment duration were 12 (IQR 6 to 21) and 8.8 months (IQR 4.4 to 15.4) in the PomBd arm, and 7 (IQR 3 to 12) and 4.9 months (IQR 2.1 to 9), in the Bd arm.

Results are presented for all patients in the OPTIMISMM study and show improvements across all outcomes except for overall survival, which, while numerically better the hazard ratio crossed 1.0, indicating no statistically significant difference.[10] In the subgroup of patients who had received only one prior line of therapy and who were lenalidomide refractory, the median PFS was 8 months longer in the PomBd arm compared to the Bd arm. In lenalidomide-refractory patients the differences between arms are similar to the full population with the same HR (Table 1).

Table 1| OPTIMISMM primary and secondary outcomes in the intention-to-treat population[10]

	Pomalidomide, bortezomib and dexamethasone (n=281)	**Bortezomib and dexamethasone (n=278)**
Primary Outcome: PFS		
Median follow up, months (IQR)	15.9 (9.9 to 21.7)	
PFS events, %	154 (55%)	162 (58%)
Median PFS, months (95% CI)	11 (9.7 to 13.7)	7 (5.9 to 8.5)
Hazard ratio (95% CI)	0.6 (0.5 to 0.8)	
Subgroup analysis: PFS in patients with one prior line of therapy		
Events/patients in subgroup	**n=45/111**	**n=52/115**
Median PFS, months (95% CI)	21 (15 to 28)	12 (7.5 to 16)
Hazard ratio (95% CI)	0.5 (0.4 to 0.8)	
Subgroup analysis: PFS in patients with one prior line of therapy and lenalidomide-refractory[a]		
Median PFS, months (95% CI)	18 (12 to NE)	9.5 (6.3 to 16.2)
Hazard ratio (95% CI)	0.55 (0.33 to 0.94)	
Secondary Outcomes		
Overall response, n(%)	231 (82%)	139 (50%)
Odds ratio (95% CI)	5.0 (3.3 to 7.5)	
Median PFS2[b], months (95% CI)	22 (19 to NE)	17 (15 to 21)
Hazard ratio (95% CI)	0.76 (0.59 to 0.99)	
Overall survival (later data cut 13 May 2022)		
Overall event rate	70%	
Median follow up, months	64	
Median OS, months	36	32
Hazard ratio (95% CI)	0.94 (0.8 to 1.1)	

Key: PFS: progression-free survival; IQR: interquartile range; CI: confidence interval; OS: overall survival; NE: not estimable
[a]: No numbers for population included in the publication.
[b]: Median progression free survival after next line treatment.

Supportive Evidence

While there is direct evidence comparing PomBd with Bd, there is no direct evidence comparing PomBd with the other relevant comparators. A number of network-meta-analyses (NMA) were identified in the search, but were deemed to be unsuitable, due to reference treatment used and combination of different treatment regimens. Carfilzomib in combination with dexamethasome (Cd) is a relevant comparator in the NHSScotland context, and the ENDEAVOR study was identified in our systematic search[11]. In order to compare Cd with PomBd an in-house (NCMAG team) anchored indirect treatment comparison, via common comparator Bd, was performed in a population treated in second and later line based on data from the OPTIMISMM and ENDEAVOR studies[10, 11]. In the OPTIMISMM study the median follow-up for PFS was 15.9 months (IQR 9.9 to 21.7) with 55% of patients in the PomBd and 58% of patients in the Bd group having disease progression or death[10]. In the ENDEAVOR study median follow-up was reported as 11.9 months (IQR 9.3 to 16.1) in the Cd group and 11.1 months (8.2 to 14.3) in the Bd group[11]. In the Cd group 37% of patients had disease progression or death compared with 52% in the Bd group. The PFS HRs for each trial and populations can be found in Table 2. Comparisons were made using the ITT population as well as two subgroups of the ITT population. The first subgroup had received one prior line of therapy including lenalidomide. The second subgroup were refractory to lenalidomide. It was not possible to perform indirect comparisons for the OS and response outcomes due to inconsistent reporting across the trials. Analyses were performed in Excel following guidance set out in the British Medical Journal (BMJ)[12].

Table 2 | PFS hazard ratios for both trials in the indirect treatment comparison

Population	Original trial and treatments	HR (95% CI)
ITT population	OPTIMISMM PomBd (n=281) **versus** Bd (n=278)	0.65 (0.5 to 0.84)
	ENDEAVOR Cd (n=464) **versus** Bd (n=465)	0.53 (0.4 to 0.65)
One prior line of therapy	OPTIMISMM PomBd (n=111) **versus** Bd (n=115)	0.54 (0.36 to 0.82)
	ENDEAVOR Cd (n=231) **versus** Bd (n=229)	0.45 (0.33 to 0.61)
Refractory to lenalidomide	OPTIMISMM[a] PomBd (n=200) **versus** Bd (n=191)	0.65 (0.5 to 0.84)
	ENDEAVOR Cd (n=113) **versus** Bd (n=122)	0.80 (0.57 to 1.11)

Key: PFS: progression-free survival; ITT: intention to treat population; HR: hazard ratio; CI: confidence interval: PomBd; Pomalidomide, bortezomib and dexamethasone: Bd; bortezomib and dexamethasone: Cd; carfilzomib and dexamethasone:
[a]subgroup in the OPTIMISMM study were refractory to lenalidomide

Overall, the results of the analyses indicate similar efficacy in terms of PFS for PomBd and carfilzomib plus dexamethasone. None of the comparisons produced statistically significant differences with 95% confidence intervals including 1.0 (Table 3).

Table 3 | Results from in-house indirect treatment comparison

Population	PomBd compared with	HR (95% CI)[a]
ITT population	carfilzomib plus dexamethasone	1.23 (0.89 to 1.7)
One prior therapy	carfilzomib plus dexamethasone	1.2 (0.72 to 2.01)
Refractory to lenalidomide	carfilzomib plus dexamethasone	0.81 (0.53 to 1.24)

Key: PomBd: pomalidomide, bortezomib and dexamethasone; HR: hazard ratio; CI: confidence interval; ITT: intention to treat

[a]A hazard ratio of less than 1 suggests better PFS with PomBd

Patient reported outcomes

Quality of life (QoL) was included as a secondary outcome in the OPTIMISMM study[10]. Data was collected using the global health status/QoL domain of the European Organisation for the Research and Treatment of Cancer (EORTC) questionnaire at baseline and then on day one of each 21-day cycle, prior to treatment administration. Data was assessable in 85% (240/281) and 75% (209/278) of the PomBd and Bd groups respectively. The study achieved 80% compliance up to cycle 20 across both treatment groups. Both groups were similar at baseline and maintained over time. There was no statistically or clinically meaningful differences found between the groups at any treatment cycle.

Safety evidence

Based on the data from the OPTIMISMM study, in the safety population for the PomBd (n=278) and Bd (n=270) groups respectively, the most frequently (>5%) reported grade 3 or higher adverse events (AE) were neutropenia (42% versus 9%); thrombocytopenia (27% versus 29%); infection (31% versus 18%) and peripheral sensory neuropathy (8% versus 4%)[10]. Serious adverse events (SAE) were reported in 57% and 42% of the PomBd and Bd groups respectively, with pneumonia being the most common (12% versus 6%)[10]. Serious AE thought to be drug related occurred in 30% of patients in the PomBd arm versus 15% in the Bd arm. Infections (14% versus 8%) and pneumonia (6% versus 4%) were the most common treatment related SAEs[10]. Eight deaths were reported to be treatment related, with 6 deaths in the PomBd arm and 2 in the Bd arm[10]. Dose reductions or treatment discontinuation due to AEs occurred in 72% or 24% respectively in the PomBd arm and in 51% or 17%, respectively, in the Bd arm[10].

Quality assessment of clinical evidence

The OPTIMISMM and the ENDEAVOR studies were phase III open label randomised multicentre studies [10, 11]. Overall, both studies were assessed to be at low risk of bias. Randomisation was completed using a validated interactive response technology system thus limiting the risk of selection bias. The studies used an open label design, but they masked assessment by an

independent review adjudication committee, which reduces the risk of outcome detection bias for subjective outcomes.

Clinical effectiveness considerations

PomBd improved PFS and ORR compared to Bd.

The OPTIMISMM study met its primary outcome, demonstrating that the PomBd regimen significantly improved independently-assessed PFS compared to Bd[10]. The median PFS was 11.2 months for PomBd, compared to 7.1 months for Bd, with an ORR of 82% compared to 50% for Bd.

The improvement in PFS was consistent across all subgroups, including patients who had only one prior line of therapy and those who are lenalidomide-refractory (70% of population), which reflects the proposed population.

There is uncertainty on the overall survival benefit of PomBd compared to Bd

At the time of the primary analysis for PFS there was no statistically significant difference between the treatment arms for overall survival. The data were immature at this point with only 31% and 32% of patients having died in the PomBd and Bd arms, respectively. An abstract from a later date, with a 70% event rate, is consistent with these results. Median OS was numerically longer with PomBd versus Bd but the confidence intervals crossed 1.0 (35.6 versus 31.6 months; HR [95% CI], 0.94 [0.77–1.15]) [13]. However, overall survival may be confounded by crossover to pomalidomide and other subsequent treatments, which was not statistically accounted for. Fifty-nine percent of patients allocated to Bd received subsequent pomalidomide compared to 39% in the PomBd group, which may confound the results.

There is some uncertainty on the comparative efficacy and safety of PomBd to other treatments available in NHSScotland.

The comparator arm in the OPTIMISMM study was Bd, a second line or later treatment option in Scotland[10]. However, carfilzomib and dexamethasone would likely be the preferred treatment for suitably fit patients. Due to the lack of comparative evidence an in-house indirect comparison was conducted to compare PomBd with carfilzomib and dexamethasone. Notwithstanding the other limitations typically associated with indirect treatment comparisons, including heterogeneity of study design and populations, the ITC offers some assurance that the treatments can be considered similar in efficacy.

In the third line setting and beyond, triplet regimens are available, and the relative efficacy of PomBd compared to these regimens is also uncertain. However, the wide range of treatment options for MM make the comparative efficacy and safety of most regimens uncertain. Treatment selection is tailored to the patient and based on a range of factors including prior treatments, with careful assessment of the benefit-harm balance for each individual patient.

The proposed bortezomib and dexamethasone dosing within PomBd is different to the dosing in the OPTIMISMM study.

The licensed dosing for bortezomib when used with pomalidomide is twice weekly, with dexamethasone given on the day of and the day after bortezomib, for cycles 1 to 8. However, in

clinical practice, and in other regimens, bortezomib is routinely dosed once weekly either in combination with dexamethasone or as triplet regimen. The supporting evidence for the weekly regimen, including randomised control trials, indicates it may be as efficacious with less toxicity, particularly for peripheral neuropathy[14-19].In the OPTIMISMM study patients received a median of 10 cycles of pomalidomide compared to 8 for bortezomib, which may suggest that the twice weekly bortezomib is not as well tolerated. The proposal is to use the once weekly dosing for bortezomib and dexamethasone rather than the licensed dosing used in the OPTIMISMM study, with one less dose of bortezomib and dexamethasone per cycle compared to the OPTIMISMM trial. This may reduce the generalisability of the results.

Eligibility criteria for the OPTIMISMM study were broad however there are some generalisability uncertainties for the proposed population

The OPTIMISMM study had broad eligibility criteria, enrolling patients with a performance status of 0 to 2 and co-morbidities, including those with non-severe renal, cardiac, and hepatic impairment[10]. The median age and performance status in the OPTIMISMM study suggest patients may be younger and fitter than those that will be treated in NHSScotland.

The study did not include details on prior exposure to anti-CD38 medicines (daratumumab and isatuximab), creating uncertainty about the efficacy of PomBd in patients previously treated with these medicines. Furthermore, details on subsequent treatments were not provided, which may affect the generalisability to patients treated in NHS Scotland.

There were higher rates of adverse events associated with PomBd compared to Bd.

There were higher rates of Grade 3 or worse adverse events in the PomBd group for peripheral neuropathy, neutropenia, infection, fatigue, constipation, and diarrhoea. Six treatment-related deaths (2%) were reported for PomBd compared to two for Bd. The increased rates of adverse events and deaths may be partially explained by the longer treatment duration in the PomBd arm.

Other treatments routinely available in the proposed patient population include carfilzomib and dexamethasone. In a phase III study comparing carfilzomib and dexamethasone to bortezomib and dexamethasone, Grade 3 or worse adverse events occurred at higher rates in the carfilzomib arm including anaemia, hypertension, pneumonia and cardiac failure. Deaths due to adverse events in the carfilzomib and dexamethasone arm occurred in 18 (4%) of patients[11].

4. Patient group summary

We received a statement from Myeloma U.K. who are a registered charity. Myeloma U.K. reported that pharmaceutical industry funding accounted for 5.6% of total funding received in 2023. A representative from Myeloma U.K. attended the NCMAG council meeting. The key points from the submission are documented below:

- Multiple myeloma is an incurable and complex cancer. It causes significant, debilitating and painful complications such as bone pain and destruction, kidney damage and fatigue, which

impacts the day-to-day life of patients, families and carers. Treatment requires hospital visits and therapies have side effects, and the condition has a social, practical and financial impact on lives.

- Myeloma patients are often older (50% are more than 70 years), frailer and with comorbidities. Due to the variation in patient clinical pictures, treatment pathways are complex and there is not always a suitable second line treatment available. Currently, there is an unmet need for an effective second line all-oral treatment regimen.

- Patients value treatments that induce remission, prolong life and allow for a normal independent day-to-day living. Pomalidomide in combination with bortezomib and dexamethasone offers a triplet therapy for patients that have received lenalidomide and it can, in some cases, be taken in the home or in the community setting, which will interfere less with normal life, holidays, and seeing friends.

5. Benefit-risk balance

The combination of PomBd is on-label and the UK medicines regulator has judged the regimen to have a favourable benefit-harm balance[20]. PomBd improves PFS compared to Bd, including in patients with lenalidomide-refractory disease. There is robust evidence for the off-label bortezomib and dexamethasone dosing schedule, suggested as an option in this proposal.

When compared to other treatments available in NHSScotland, the efficacy of PomBd appears comparable.

6. Council Review |Clinical benefit-risk balance evaluation

After consideration of all the available evidence regarding the clinical benefits and risks, the Council were satisfied that the case had been made for the clinical effectiveness of pomalidomide, bortezomib plus dexamethasone in the proposed population. Under the decision-making framework for value judgements, the Council considered the clinical case to be compelling.

7. Economic Evidence Review Summary

Economic Overview

PomBd for the treatment of adult patients with multiple myeloma who have received at least one prior treatment regimen was not recommended by SMC in 2019 due to a non-submission (SMC2219)[21]. Pomalidomide became off patent in 2024, and generic alternatives are available under NHSScotland national framework contract pricing.

The literature search for economic evidence on this topic returned no published cost-effectiveness studies. Two Health Technology Assessments were identified, one conducted by Canada's Drug Agency (CDA) and another by National Centre for Pharmacoeconomics (NCPE) in Ireland[22, 23]. The NCPE performed a rapid review, details of which were not available in the public domain. The economic evaluation by CDA and its generalisability to NHSScotland have been summarised below.

A published economic analysis from a Canadian payer perspective lacks generalisability to NHSScotland

The economic evaluation compared PomBd to Bd using clinical evidence from the OPTIMISMM trial (ITT population). A 15-year time horizon was used. The patient population in the model included adult patients with relapsed and refractory multiple myeloma who received at least one prior treatment regimen, including lenalidomide, which partially aligns with the proposed use in NHSScotland. All medicine prices were based on the list price of medicines in Canada.

The analysis assumed a distribution of PomBd treated patients of 10% in the second line setting, and 45% in the third and fourth line settings in accordance with Canadian practice. This may not be reflective of clinical practice in Scotland where PomBd is expected to be predominately used in the second- and third-line setting.

The results of the analysis showed a quality-adjusted life-year (QALY) gain of 0.37, which approximates to an extra four months of perfect health, for PomBd compared to Bd expected over the 15-year time horizon. However, due to the limitations of long-term survival extrapolations, the results were viewed to be uncertain.

Given concerns regarding the comparators and costs, the direct results from the CDA evaluation could not be generalised for use in decision making. Furthermore, the model was not accessible and could therefore not be adapted to the Scottish healthcare setting.

Type of Economic Evaluation

In the absence of an appropriate cost-effectiveness analysis for NCMAG decision making a cost comparison analysis was performed to understand the costs of the proposed treatment regimen relative to the regimens routinely used in the NHSScotland population.

Population, intervention, comparator and outcomes

The population used was adult patients with multiple myeloma who have received at least one prior treatment regimen including lenalidomide and where an anti-CD38 monoclonal antibody is not appropriate. The intervention was PomBd. Based on feedback from the clinical experts, a combination of two comparators, Bd and Cd, were considered as NHSScotland standard of care (SOC). Table 4 summarises the details of all treatment regimens. As a cost-comparison analysis was performed, quality-adjusted life-years (QALYs) were not included in the analysis.

Table 4 | Summary of treatment regimens and median duration

#	Regimen	Regimen component	Cycle length (days)	Dosing schedule description[a, b]	Median cycles
1	Pomalidomide, bortezomib plus dexamethasone	Pomalidomide	21	4 mg orally daily on Days 1 to 14.	13
		Bortezomib (Cycle 1 to 8)		1.3 mg/m² BSA SC on Days 1, 8, and 15.	

#	Regimen	Regimen component	Cycle length (days)	Dosing schedule description[a, b]	Median cycles
	(PomBd) - proposed off-label dosing	Bortezomib (Cycle 9 onwards)		1.3 mg/m² BSA SC on Days 1 and 8 only.	
		Dexamethasone	-	20 mg orally on the days of and the day after bortezomib administration.	
2	Bortezomib plus dexamethasone (Bd) - standard or once weekly regimen	Bortezomib (standard)	21	1.3 mg/m² BSA SC on Days 1, 4, 8, and 11.	8
		Bortezomib (once weekly)	35	1.3 mg/m² BSA SC on Days 1, 8, and 15, 22.	
		Dexamethasone	-	20 mg orally on the days of and the day after bortezomib administration.	
3	Carfilzomib plus dexamethasone (Cd)- standard or alternate regimen	Carfilzomib (Days 1 to 2)	-	First cycle: 20 mg/m² BSA IV on Day 1; or Days 1 and 2.	12
		Carfilzomib (Days 8 to 16)	-	First cycle: 56 mg/m² BSA IV on Days 8, 9, 15, and 16; or 70 mg/m² IV on Days 8 and 15.	
		Carfilzomib (cycle 2 onwards)	28	Subsequent cycles: 56 mg/m² BSA IV on Days 1, 2, 8, 9, 15, and 16; or 70 mg/m² BSA IV on Days 1,8, 15.	
		Dexamethasone	-	20 mg orally weekly (Days 1, 2, 8, 9, 15, 16, 22, 23); or 40 mg orally weekly (Days 1, 8, 15 for all cycles and day 22 for cycles 1-9 only).	

Key: BSA: body surface area; IV: intravenous; SC: subcutaneously.
[a] For non-oral medicines, average bodyweight of 70 kg and BSA of 1.8 m^2 was used for dose calculation.
[b] Dosing may differ in clinical practice due to differences in patient tolerability and co-morbidities.

Costs

The cost comparison included acquisition costs, administration costs and thromboprophylaxis costs. Confidential NHSScotland national framework prices (excluding VAT) were used to calculate the medicine acquisition cost.

Following patent expiry, NHSScotland National Procurement team undertook a tendering process for generic pomalidomide, however this was not finalised before the NCMAG Council consideration of this proposal in December 2024. The results corresponding to an upper estimate of the NHSScotland national framework contract price were used in confidence for decision-

making. In January 2025, NHSScotland national framework contract prices for all included generic pomalidomide products were confirmed to be lower than the estimate used for decision-making.

The duration of therapy was based on median cycles from published studies (ENDEAVOR and OPTIMISMM)[10, 24]. Table 4 summarises the details of all treatment regimens. It was noted that in Scottish clinical practice some of these medicines are administered using off-label dosing regimens. An assumption was made to include equal proportion of standard and alternative off-label dosing for costing such regimens. Dosing may differ in clinical practice due to differences in patient tolerability and co-morbidities.

Based on clinical opinion, for non-oral medicines, the prices of subcutaneous formulations, where available, were preferred in the calculation. For intravenous (IV) medicines, dosing was based on average body surface area (1.8 m^2) or bodyweight (70 kg). The calculation included wastage for non-oral medicines. The cost associated with unused medicine resulting from dose reductions or treatment interruptions were not considered.

The administration cost for IV medicines was calculated using the hourly infusion administration cost of £333 (according to NHS Reference Cost 2022/23, inflation-adjusted). In the absence of a specific tariff for subcutaneous drug administration, the specialist nursing tariff of £111 for adult cancer services was used (according to National Cost Collection 22-23).

The costs associated with implementing thromboprophylaxis to reduce the incidence of thromboembolic events in patients treated with pomalidomide were included. Based on clinical expert opinion, it was assumed that 90% of patients would be prescribed apixaban 2.5mg twice daily and rest would receive enoxaparin 40mg SC once daily, for the duration of pomalidomide treatment.

Results

All figures in cost-comparison exclude VAT.

The Council considered results using confidential NHSScotland medicine pricing agreements in decision making. NCMAG is unable to publish the results using confidential pricing due to commercial in confidence pricing contracts. Base case cost-comparison results suggested that treatment with PomBd would result in cost-saving compared to NHSScotland SOC. The main source of these cost savings was the lower treatment administration cost.

Cost-effectiveness considerations

Generalisability of the cost comparison

NHSScotland PAS price and national framework contract pricing for the medicines were considered in confidence to increase the generalisability of the net costs.

Limitations of the cost comparison

A published cost-effectiveness analysis was not generalisable to NHSScotland

The results from the economic evaluation published by CDA lacks generalisability to NHSScotland. Due to an absence of cost-utility analysis relevant for NHSScotland decision-making, an analysis

which only compared costs was considered. An estimate of cost-effectiveness can be made by modelling the benefits over a longer period and comparing with costs. In the absence of direct comparative evidence, the actual cost-effectiveness remains unknown.

There are uncertainties in the comparator and treatment pathways in NHSScotland.

The treatment landscape for myeloma refractory to lenalidomide is dynamic, with many emerging therapies in clinical trials. It was challenging to identify relevant comparators for a rapidly evolving treatment pathway and with multiple factors involved in selecting the appropriate therapy. The two currently used regimens in NHSScotland were identified in consultation with the clinical expert and an equal proportion of patients who receive them was assumed in calculating the combined cost of NHSScotland SOC arm (50% Cd and 50% Bd). However, the choice of treatment is decided on a patient-by-patient basis and the proportion could vary. As carfilzomib is administered intravenously and is currently on patent, an increase in proportion of Cd use would increase the overall cost of the comparator arm.

There is uncertainty around sequencing of PomBd. For simplicity, the cost-comparison assumes that PomBd would be predominately used in the second line setting. However, the proposed use applies to adult patients with at least one prior treatment which means that some patients may get PomBd in later lines of therapy. The comparators could differ by line of therapy and may be influenced by multiple factors. Any estimates of these would add to the uncertainty and were not considered in the analysis. If PomBd displaces a higher proportion of later-line therapies, the cost-saving may be more given that high-cost on-patent medicines are used in these later lines.

There is uncertainty around subsequent treatments, which will depend on the patient's exposure history and refractory status. At a median follow up of 15.9 months in the OPTIMISMM study, patients who had been treated with PomBd as a second line therapy had longer PFS2 compared to patients who had received Bd in second line[10]. These results suggest a sustained benefit of PomBd compared to Bd beyond progression. However, due to generalisability concerns it is uncertain whether the sustained benefit would translate to clinical practice. Moreover, the availability of PomBd in second line could move Cd as a treatment option for some patients to later lines of therapy, and other high-cost on-patent medicines are also now approved for use in later lines. Therefore, the cost-comparison analysis did not include potential costs, or cost avoidance, of subsequent treatments.

The cost-comparison excluded dosing adjustments and adverse event monitoring costs.

The dosing was not adjusted to account for dose reductions or treatment interruptions. The duration and dosing may vary in real-world setting due to multiple factors like comorbidities, tolerability etc. Due to issues of data paucity, adjusting for these factors would likely increase the uncertainty of estimated medicine acquisition costs and were therefore not considered in the calculation. In addition, the calculation included wastage of non-oral medicines. However, in clinical practice this cost could potentially be lower when pragmatic approaches to avoid wastage are practiced.

The costs of implementing thromboprophylaxis was included for PomBd regimen only. The cost of other supportive medicines prescribed alongside PomBd and SOC were not included; however, these are expected to have a minimal impact on overall costs. Due to the lack of comparative safety data for PomBd against NHSScotland SOC, cost associated with adverse event management were considered equal across the two arms and not included in the cost-comparison.

Summary

The NHSScotland national framework contract price was not finalised ahead of the NCMAG Council consideration of this proposal in December 2024. Provisional decision-making was based on an upper estimate for generic pomalidomide products. Based on this estimate, PomBd was cost-saving compared to NHSScotland SOC. In January 2025, NHSScotland national framework contract prices for all included generic pomalidomide products were lower than the estimate used for provisional decision-making. With the lower price, the analysis indicates that the overall conclusion remains unchanged, however the cost-savings are to a greater degree.

8. Council review | Cost-effectiveness evaluation

After consideration of the available evidence, the Council accepted that in the absence of a cost-effectiveness analysis, the cost-effectiveness remained unknown. In this situation Council was able to consider other relevant information including service impact and estimated net medicines budget impact under the Decision-making framework for value judgements.

9. Service Impact

PomBd is not expected to have a significant service impact. It may spare day bed unit capacity if it displaces intravenous carfilzomib and dexamethasone.

10. Budget Impact

In the absence of a generalisable cost-effectiveness analysis, a detailed budget impact analysis was conducted.

Patient uptake

Approximately 500 new cases of myeloma are diagnosed each year in Scotland[3]. Based on clinical expert opinion and local prescribing data, between 40 to 80 patients per year are estimated to be eligible for treatment with PomBd in the proposed setting. Discontinuation and mortality rates were not included. Therefore, the budget impact base case assumed that 80 patients per year would receive PomBd.

Per patient medicine cost and treatment duration

Confidential NHSScotland national framework prices (including VAT) were used to calculate the net medicines budget impact.

Based on feedback from the clinical experts, a combination of two comparators, Bd and Cd in equal proportion, were considered as NHSScotland SOC in the base case. An additional scenario using alternate proportion of patients for each regimen (83% Cd and 17% Bd) was considered.

The duration of therapy was based on median cycles from published studies (ENDEAVOR and OPTIMISMM)[10, 24]. Since PomBd has a median duration longer than a year, the medicine acquisition costs in the first year was capped at 12 cycles and a higher medicine acquisition cost corresponding to the 13 cycles in the steady state (second year onwards) was considered. This approach accounts for patients who begin their treatment in the first year and continue into the second year, assuming they do not discontinue therapy during this time.

Comparator displacement

Based on clinical expert opinion, the introduction of PomBd was assumed to displace 100% of current SOC in NHSScotland (that is, Bd and Cd) in the proposed patient population.

Results

All figures in the budget impact include VAT and are based on NHSScotland confidential price of medicines.

The Council considered results using confidential NHSScotland medicine pricing agreements in decision making. NCMAG is unable to publish the results using confidential pricing due to commercial in confidence pricing contracts. Based on the confidential upper estimate of the national framework price of pomalidomide generic product (including VAT) used for provisional decision making, the use of PomBd would decrease the net medicines budget for this patient group when compared to NHSScotland SOC.

Scenario considerations

Additional scenarios exploring the impact of alternative assumptions were conducted to aid decision-making. Exploratory scenarios with annual uptake (40 patients), treatment duration of PomBd (8 cycles), and alternate assumption for proportion of comparators (83% Cd and 17% Bd) were considered. NCMAG is unable to publish the results using confidential pricing due to commercial in confidence pricing contracts. Based on the confidential upper estimate of the national framework price of pomalidomide generic product (including VAT) used for provisional decision making, in all exploratory scenarios the results indicated the use of PomBd would decrease the net medicines budget for this patient group when compared to NHSScotland SOC.

Limitations

There is uncertainty around sequencing of PomBd. For simplicity, the budget impact assumes that PomBd would be predominately used in the second line setting. However, the proposed use applies to adult patients with at least one prior treatment which means that some patients may receive PomBd in later lines of therapy. The comparators could differ by line of therapy and may be influenced by multiple factors. Any estimates of these would add to the uncertainty and were not considered in the analysis. If PomBd displaces a higher proportion of later-line therapies, the cost-saving may be more given that high-cost on-patent medicines are used in these later lines.

The consultation with clinical experts suggests that there is uncertainty in the number of eligible patients and could range between 40 to 80 patients per year. Additional scenarios were presented, in confidence, to explore alternate assumptions.

Summary

The Council considered the net medicines budget impact using confidential NHSScotland medicine pricing agreements in decision making. NCMAG is unable to publish the budget impact using confidential pricing due to commercial in confidence issues.

Based on confidential upper estimate of national framework price of pomalidomide generic product (including VAT) used for provisional decision making, the use of PomBd will decrease the net medicines budget for this patient group when compared to NHSScotland SOC. In January 2025, NHSScotland national framework contract prices for all generic pomalidomide products were confirmed to be lower than the estimate used for decision-making. With the lower price, the analysis indicates that the overall net medicines budget is decreased to a greater degree.

Separate information will be supplied by the boards to facilitate budget impact assessment.

11. Council review | Overall proposal evaluation

After consideration of all relevant information under the Decision-making framework for value judgements the Council made a decision to support this use.

12. Acknowledgements

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This advice represents the view of the NCMAG Council and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

Minor document amendments

Date	Previous version	Amendment	Updated version	Approved by