

8 August 2023

Dr Mark Chakravarty

Lead non-executive director for appeals

National Institute for Health and Care Excellence 2nd Floor

2 Redman Place London E20 1JQ

Dear Dr Chakravarty,

Re: Appeal against the Final Appraisal Determination for belantamab mafodotin for treating relapsed or refractory multiple myeloma after 4 or more therapies [ID2701]

### Introduction

Myeloma UK is appealing against the recent decision by NICE not to recommend Belantamab mafodotin ("belantamb") for treating relapsed or refractory multiple myeloma after 4 or more therapies, and the decision to refuse Managed Access, as set out in final draft guidance [ID2701].

Myeloma UK is appealing the decision because we believe that the decision is unfair and unreasonable. The Appraisal Committee has acknowledged that there is an unmet need for people triple-class refractory multiple myeloma after 4 or more treatments, and that there is no established standard care for people whose disease relapses after fifth-line treatment.

The Committee has said that its decision not to recommend this treatment is because it is not possible to reliably estimate the cost effectiveness of belantamab mafodotin. This conclusion derives from difficulties in comparing belantamab mafodotin with the other existing treatments (noting that this is a rapidly evolving area in which there is there is no established standard of care and little/limited evidence to support use). We consider that it was unreasonable not to give sufficient weight to certain evidence which would have allowed for an assessment of cost effectiveness. Additionally, the decision unfairly does not explain with adequate reasons why such evidence was not given weight.

The decision also unfairly fails to adequately to explain the basis for the Appraisal Committee rejecting the alternative option of Managed Access. The decision does not demonstrate that

the Committee gave the option of Managed Access full consideration in accordance with paragraph 5.5.23 of the NICE health technology evaluations: the manual.

Myeloma is a highly individual and complex cancer originating from abnormal plasma cells in the bone marrow. It is a relapsing and remitting cancer which evolves over time, becomes resistant to treatment, and brings severe complications such as kidney failure and bone destruction. Effective treatment can halt myeloma’s progress and improve quality of life. Multiply relapsed patients, particularly those with triple-class refractory disease who have had four or more therapies, are faced with a significant disease burden and limited treatment options. Indeed, patients at this advanced stage of the pathway have almost no choice left before facing an end-of-life treatment regime. Belantamab, as the first non-cellular technology to be appraisal by NICE that targets the B-Cell Maturation Antigen (BCMA) protein, represents an important step change in the treatment landscape for myeloma. Denying belantamab approval for use on the NHS in England and Wales will remove access to a potential life- extending treatment for a highly disadvantaged group of myeloma patients.

### Executive summary of appeal

Myeloma UK is appealing against this decision on the following grounds:

* Ground 1a – NICE has failed to act fairly.
* Ground 2 – The recommendation is unreasonable in light of the evidence submitted.

Under Ground 1a, we believe that NICE has not provided adequate reasons for rejecting plausible evidence that would have enabled it to make a decision as to the cost effectiveness of this treatment. The reasoning for rejecting the data from a comparison using Named Patient Program ("NPP") data which supported belantamab, because it lacked validity and added further uncertainty, and instead preferring randomised subgroup data from DREAMM-3, which clinical experts highlighted had weaknesses, is insufficient for stakeholders to understand the justification for the preference.

Also, under Ground 1a, we believe that NICE has not provided adequate reasons for refusing the option of allowing Managed Access. The Committee's only reason for concluding that Managed Access was not a feasible option appears to be that additional data collection would be unlikely to resolve the uncertainty around the efficacy of belantamab compared with the relevant comparators for this evaluation. The decision fails to fully address the reality that managed access can help to address evidence gaps or uncertainties and that it would generate RWE that could be of value. Fairness requires that a decision maker provides reasons,

particularly where Myeloma UK had provided comments about this particular aspect of the draft decision.

Under Ground 2, we believe that Appraisal Committee's conclusions that (a) the GSK naive comparison using Named Patient Program (NPP) *data "lacked validity and added further uncertainty"*; that (b) the randomised subgroup data from DREAMM-3 was preferable to the non-randomised evidence presented by the company; and that (c) it had not been presented with sufficient evidence to confirm that belantamab is more clinically effective than pomalidomide plus dexamethasone at a population level, are individually and collectively unreasonable. The conclusion that the Committee did not believe it had been presented with sufficient evidence of clinical effectiveness is unreasonable because it derives from having rejected a valid source of data, namely the NPP comparison.

# Ground 1a: NICE has failed to act fairly

## 1(a).1 NICE has not provided adequate reasons for rejecting plausible evidence that would have enabled it to make a decision as to the cost effectiveness of this treatment

*Summary*

The reasoning for rejecting the data from a comparison using Named Patient Program ("NPP") data which supported belantamab, because it lacked validity and added further uncertainty, and instead preferring randomised subgroup data from DREAMM-3, which clinical experts highlighted had weaknesses, is insufficient for stakeholders to understand the justification for the preference. The inadequately explained rejection of the NPP data also leaves the overall decision, that the Committee had not been presented with sufficient evidence to confirm that belantamab is more clinically effective than pomalidomide plus dexamethasone at a population level, lacking in reasons.

*Grounds*

Myeloma UK's primary argument is set out below, that the decision that there was insufficient evidence in this matter to enable a decision is unreasonable. As set out below, we consider that there was adequate evidence of clinical effectiveness, particularly had the NPP data been given appropriate weight. However, our secondary argument is that it is not possible to discern with any clarity why the NPP data was rejected and the DREAMM-3 data considered preferrable, and hence how the Committee reached the point where it concluded there was insufficient data.

As is set out below, GSK undertook a naïve comparison using NPP data explaining that the NPP and NCRAS datasets were more comparable that the datasets used in the DREAMM-2 study. The clinical experts pointed out that any differences between the population having belantamab in the NPP and the population having pomalidomide plus dexamethasone in the NCRAS study were likely to be minor (see paragraph 3.8). Switching the efficacy source for belantamab from DREAMM-2 to NPP therefore provides the basis for a more logical comparison. It is not clear in paragraph 3.8 why the Committee concluded that the company’s updated naive comparison using NPP data, a real-world study which reflects the use of belantamab by clinicians, lacked validity.

## 1(a).2 NICE has not provided adequate reasons for refusing the option of allowing Managed Access

*Summary*

The Committee's only reason for concluding that Managed Access was not a feasible option appears to be that additional data collection would be unlikely to resolve the uncertainty around the efficacy of belantamab compared with the relevant comparators for this evaluation. The decision fails to fully address the reality that managed access can help to address evidence gaps or uncertainties and that it would generate RWE that could be of value. Fairness requires that a decision maker provides reasons, particularly where Myeloma UK had provided comments about this particular aspect of the draft decision.

*Grounds*

At paragraph 3.19 the draft Final Guidance states "*Having concluded that belantamab could not be recommended for routine use, the committee considered if it could be recommended with managed access. The committee recalled that the limitations in the clinical evidence meant that it had not been presented with a plausible, reliable cost effectiveness estimate (see section 3.18). It also discussed that additional data collection would be unlikely to resolve the uncertainty around the efficacy of belantamab compared with the relevant comparators for this evaluation (see sections 3.2 and 3.3). So, the committee concluded that managed access was not a feasible option*".

There is nothing to suggest that the Committee has engaged in the assessment, anticipated in the Process and Methods Manual, as to whether:

* it is feasible to collect and analyse the proposed outcome data within a reasonable timeframe
* the additional burden of data collection on patients, clinicians, and the NHS is proportionate.
* there is a reasonable likelihood that the proposed outcome data will be sufficient to support the case for adoption at the guidance update.
* the data collection can be started when patients get access to the technology.
* there are any ethical, equality, or patient safety concerns with the proposed data collection and analysis.
* there are other substantive barriers to implementing managed access

Specifically, the decision demonstrates no consideration of the comments made by Myeloma UK in which we explained that Managed Access would support the collection of more evidence on the clinical effectiveness of the treatment, which in turn would generate a more reliable cost- effectiveness estimate.

The significant unmet need among the patient population relevant to this appraisal and the innovative nature of belantamab should be grounds for a more flexible approach to considering this treatment a candidate for managed access.

Myeloma UK is concerned that the Committee has not placed sufficient emphasis on the progression-free survival (PFS) data for patients who achieved a very good partial response (VGPR) or better in the DREAMM-2 clinical trial, which amounted to 19% of trial participants. The median PFS for these patients was 14 months, which is a substantial period of remission for multiply relapsed myeloma patients. This shows that belantamab mafodotin can deliver significant clinical benefit for the patients whose disease responds to this treatment. This should have provided a compelling reason to consider belantamab for managed access as the data collection under such an arrangement can serve to clarify the drug’s potential in this patient population.

# Ground 2: The recommendation is unreasonable in the light of the evidence submitted to NICE

## The Appraisal Committee's conclusions:

* + 1. **that the GSK naive comparison using Named Patient Program (NPP) data (which favoured belantamab compared with pomalidomide plus dexamethasone for all outcomes) "***lacked validity and added further uncertainty*"**;**

## that the randomised subgroup data from DREAMM-3 was preferable to the non- randomised evidence presented by the company; and

* + 1. **that it had not been presented with sufficient evidence to confirm that belantamab is more clinically effective than pomalidomide plus dexamethasone at a population level, are individually and collectively unreasonable.**

*Summary*

The conclusion, that the Committee did not believe it had been presented with sufficient evidence of clinical effectiveness is unreasonable because it derives from having rejected a valid source of data, namely the NPP comparison, which is the only and therefore the best data source given the paucity of efficacy data sources available for individual comparators.

*Grounds*

The final scope for the appraisal included "established clinical management without belantamab" as a comparator. It was acknowledged however, that there is no standard treatment for multiple myeloma after 4 or more treatments, when those treatments included at least 1 proteasome inhibitor, 1 immunomodulatory drug and 1 anti-CD38 monoclonal antibody. The Committee opted to focus on comparisons with **pomalidomide plus dexamethasone** or **panobinostat plus bortezomib and dexamethasone**. It concluded that in neither case was there clear evidence to be able to compare these treatments with belantamab.

### Pomalidomide plus dexamethasone

One existing treatment against which belantamab could be compared is **pomalidomide plus dexamethasone.** Myeloma UK considers this to be the most relevant comparator.

In the final draft Guidance, the Committee acknowledged that, after four or more treatments, "most people have pomalidomide plus dexamethasone" (page 1) and concluded that it was the most appropriate comparator as a fifth line treatment (para 3.2). However (see below) it then concluded that the evidence to make the comparison was insufficient.

### The Clinical Evidence

DREAMM-2 trial was a study absent of a comparator arm (the objective was to further explore the safety, activity, and clinical benefit profile of two doses of Belamaf). It was never intended to directly compare belantamab against another treatment and so evidence of the relative efficacy vs a relevant comparator had to be derived from indirect treatment comparisons. The

company used data from an ITT population (n=97) to inform the appraisal and economic model. The response rate was reported as 32% with median overall survival of 15.3 months and median progression-free survival of 2.8 months. The committee concluded that the DREAMM-2 results were relevant to its decision making, but it considered that the trial did not provide evidence of the relative efficacy of belantamab compared with the relevant comparators for this evaluation.

GSK then used an NCRAS study (in the absence of any alternative sources) to inform efficacy data for a comparison with **pomalidomide plus dexamethasone.** Outcomes for this population included a median overall survival of 10.2 months, a median TTNT (time to next treatment) (used as a proxy for progression-free survival) of 6.0 months and median TTD (time to treatment discontinuation) of 4.1 months. The Committee noted that the selected population was small and this introduced uncertainty around estimates of efficacy for pomalidomide plus dexamethasone. The Committee considered that the results from the naïve comparison using DREAMM-2 and NCRAS datasets were counterintuitive because they suggested a longer overall survival for belantamab but a shorter proxy progression-free survival and TTD when compared with pomalidomide plus dexamethasone. Further indirect treatment comparisons remained, in the Committee’s view, highly uncertain (para 3.7).

GSK then did a naïve comparison using Named Patient Program (NPP) data, described at paragraph 3.8. The naïve unadjusted comparison favoured belantamab compared with **pomalidomide plus dexamethasone** for all outcomes.

The EAG considered that the company had not provided a valid reason for changing the efficacy source for belantamab from DREAMM-2 to NPP. The company explained that the NPP and NCRAS datasets were more comparable because they both included populations from the UK relevant to the decision problem. The DREAMM-2 study included only a very small number of people from the UK, as outlined in paragraph 3.4. Moreover, the clinical experts pointed out that any differences between the population having belantamab in the NPP and the population having pomalidomide plus dexamethasone in the NCRAS study were likely to be minor (see paragraph 3.8). Switching the efficacy source for belantamab from DREAMM-2 to NPP therefore provides the basis for a more logical comparison.

The NICE health technology evaluations Manual is clear that all types of evidence can be considered in its evaluations including includes “*evidence from published and unpublished data, data from non-UK sources, databases of ongoing clinical trials, end-to-end studies,*

*conference proceedings, and data from registries, real-world evidence and other observational sources*”1.

The Committee concluded that the company’s updated naïve comparison lacked validity and added further uncertainty around the efficacy of belantamab compared with pomalidomide plus dexamethasone.

In our submission the Committee decision to reject the NPP data was unreasonable because this is a UK real-world study that reflects the use of belantamab by clinicians in line with its licenced indication.

The DREAMM-3 trial also compared belantamab mafodotin and **pomalidomide plus dexamethasone** in patients but at 2nd line plus, therefore a broader population was included than was directly relevant for this (fifth line) treatment appraisal. Clinical experts and the company both highlighted that high uncertainties in relation to this trial data and the technically weak comparison.

However, the Committee decided that the results still provided evidence of comparative efficacy for belantamab in people with relapsed refractory multiple myeloma and concluded that the DREAMM-3 ITT population results were relevant to its decision making.

The Committee did note that, once further subgroup analysis was undertaken, there were limitations with the evidence, with the uncertainty around the results evidenced by wide confidence intervals. The Committee however stated that it considered that the uncertainty associated with the outcomes from the DREAMM-3 subgroup did not seem to be greater than that associated with the naïve unadjusted comparisons presented by the company and it decided that the randomised subgroup data from DREAMM-3 was preferable to the non- randomised evidence presented by the company. We feel that this is an unreasonable interpretation of the evidence available because during the first committee meeting the clinical experts explicitly highlighted the weakness of the subgroup analysis. Namely, the overestimation of PFS for pomalidomide plus dexamethasone in people who had had 4 or more previous treatments and the fact that broken randomisation resulted in a selected population that may not represent patients taking pomalidomide plus dexamethasone as a fifth-line treatment (see paragraph 3.7 of draft guidance).

1 Para 3.3 Page 50 Manual

In our submission the Committee decision to prefer the DREAMM-3 outcomes over the NPP comparisons is unreasonable given the clinical experts concerns about the weaknesses in its analysis.

In circumstances where the Committee accepted that there is an unmet need for people triple- class refractory multiple myeloma after 4 or more treatments, and that there is no established standard care for people whose disease relapses after fifth-line treatment, it is unreasonable that the Committee has adopted an unjustifiably rigid approach and has rejected numerous valid sources of evidence which could have led it to conclude that there was in fact sufficient evidence to confirm that belantamab is more clinically effective than pomalidomide plus dexamethasone and could therefore be recommended.

### Conclusion

For the reasons listed above, we believe that the appraisal of belantamab mafodotin was unfair and unreasonable. It is on this basis that we wish to appeal the FAD, via an oral appeal.

Your sincerely,

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XXXXXXXXXXXXXXXXXX, Myeloma UK