Efficacy and toxicity outcomes of belantamab mafodotin in relapsed/refractory myeloma: UK-wide real-world study of the compassionate use programme

Project Protocol

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Contents

Acronyms

Acronym	Definition
AE	Adverse Events
ASCT	Autologous Stem-Cell Transplantation
BCMA	B-cell maturation antigen
CCI	Charlson Co-morbidity Index
CR	Complete response
Dex	Dexamethasone
DOR	Duration of Response
DPA	Data Protection Act (2018)
DPIA	Data Protection Impact Assessment
eCRF	Electronic Case Record Form
GDPR	General Data Protection Regulations
HR	High-Risk
HRA	Health Research Authority
IMiD	Immunomodulatory Agent
IMWG	The International Myeloma Working Group
IG	Information Governance
ISS	The International Staging System
LTS	Long term support
MR	Minor response
NICE	National Institute of Clinical Excellence
ORR	Overall Response Rate
OUHFT	Oxford University Hospitals NHS Foundation Trust
PFS	Progression Free Survival
PI	Proteasome Inhibitor
PFS	Progression Free Survival
PR	Partial response
REC	Research Ethics Committee
RRMM	Relapsed/Refractory Multiple Myeloma
s.CR	Stringent complete response
SSH	Secure Shell
SR	Standard-Risk
SD	Stable disease
VGPR	Very good partial response
VM	Virtual Machine

Document History

Doc #	Title	Version	Date	Description	Author
MMY-98	Project Manual	2.0	14/10/2021	Initial version	Dr. Faouzi Djebbari Dr Karthik Ramasamy Dr Grant D. Vallance
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Project Outline

Project Rationale

B-cell maturation antigen (BCMA) is a cell-surface receptor of the tumour necrosis superfamily required for plasma cell survival. BMCA is universally detected on patient-derived myeloma cells and has emerged as a selective antigen to be targeted by novel treatments in multiple myeloma.

Belantamab mafodotin is a humanised IgG1 monoclonal antibody–drug conjugate that binds specifically to BCMA. The parent antibody is conjugated to the tubulin polymerisation inhibitor monomethyl auristatin F (MMAF) by a protease-resistant maleimidocaproyl linker. Upon binding to the cell surface, belantamab is rapidly internalised and the active cytotoxic drug (cys-mcMMAF) is released inside the cell. Additionally, the antibody is afucosylated, which increases binding to FcγRIIIa (low-affinity Igγ Fc receptor III-A) receptors, enhances recruitment and activation of immune effector cells, and enhances the killing of tumour cells by antibody-dependent cellular cytotoxicity. This potential immunogenic cell death mechanism has been shown to further induce macrophage-mediated phagocytosis. These various mechanisms of action result in significant against myeloma cell lines.

DREAMM-2 is an open-label, two-arm, phase 2 study done at 58 multiple myeloma specialty centres in eight countries. Patients (aged ≥18 years) with relapsed or refractory multiple myeloma with disease progression after three or more lines of therapy and who were refractory to immunomodulatory drugs and proteasome inhibitors, and refractory or intolerant (or both) to an anti-CD38 monoclonal antibody with an ECOG of 0–2 were recruited, centrally randomly assigned (1:1) to receive 2·5 mg/kg or 3·4 mg/kg belantamab mafodotin iv every 3 weeks on day 1 of each cycle until disease progression or unacceptable toxicity. The intention-to-treat population comprised all randomised patients, regardless of treatment administration. The primary outcome was the proportion of randomly assigned patients in the intention-to-treat population who achieved an overall response, as assessed by an independent review committee.

Between June 2018, and Jan 2019, 293 patients were screened and 196 were included (97 in the 2·5 mg/kg cohort and 99 in the 3·4 mg/kg cohort). As of June 21, 2019 (the primary analysis data cutoff date), 30 (31%; 97·5% CI 20·8–42·6) of 97 patients in the 2·5 mg/kg cohort and 34 (34%; 23·9–46·0) of 99 patients in the 3·4 mg/kg cohort achieved an overall response. The most common grade 3–4 adverse events in the safety population were keratopathy (in 26 [27%] of 95 patients in the 2·5 mg/kg cohort and 21 [21%] of 99 patients in the 3·4 mg/kg cohort), thrombocytopenia (19 [20%] and 33

[33%]), and anaemia (19 [20%] and 25 [25%]); 38 (40%) of 95 patients in the 2·5 mg/kg cohort and 47 (47%) of 99 in the 3·4 mg/kg cohort reported serious adverse events. Two deaths were potentially treatment related (one case of sepsis in the 2·5 mg/kg cohort and one case of haemophagocytic lymphohistiocytosis in the 3·4 mg/kg cohort). Single-agent belantamab mafodotin showed anti-myeloma activity with a manageable safety profile in patients with relapsed or refractory multiple myeloma.

A compassionate use scheme was provided by GSK for novel agent belantamab mafodotin (using 2.5mg/kg/dose), and is aimed at patients who relapsed to all available lines of therapy and who would otherwise be palliated. Achieving an objective response can control myeloma and translate into extended overall survival.

The aim of project is to evaluate the efficacy and tolerability from the routine care usage of single agent belantamab mafodotin, and to optimise outcomes and its role in the treatment of relapsed refractory multiple myeloma. This project will also focus on ocular baseline assessments, ocular toxicities on therapy, in order to identify the best strategy for an optimal frequency of ophthalmology review, and the optimal dosing modality which can deliver good clinical outcomes whilst limiting the impact of ocular abnormalities on patients' quality of life. The rationale for this focus is further described in the following section below.

Exploratory outcomes of this project are to attempt to describe real world indicators of patients' quality of life (OoL) during and at the end of the follow up. We have an opportunity to provide patients with a non-dexamethasone containing anti myeloma therapy. Understanding the effects of this regimen in real world setting would be useful. But, standard PRO would cause recall bias in a retrospective data collection, we have devised surrogate predictors of patient QoL in this study. This includes any changes compared to baseline of: fatigue, performance status, pain; in addition to the evaluation of the impact of AEs (e.g. infections, sepsis etc) on patients' overall experience such as the incidence and duration of hospital admissions.

Focus on baseline/follow up ocular assessments, and eye toxicities

Cataract and glaucoma are common causes that lead to visual impairment as demonstrated by many general population studies (Reidy 1998, Flaxman 2017). The approximate incidence of cataract was >30% in people aged above 50 years old and >55% (Klein 1998) in those aged above 65 years old. These conditions could adversely affect quality of life, especially in relapsed/refractory myeloma (RMM), where patients present with advanced age and age-related ocular morbidities.

In addition to age, patients with RRMM are at risk of accumulated ocular toxicities from prior lines of treatments. Dry eyes and blepharitis have been commonly reported with bortezomib (Puri 2014). Long term or dominant use of steroids in myeloma treatment protocols, such as dexamethasone, is also associated with development of cataract and glaucoma.

In DREAMM-2 Phase I trial of belantamab mafodotin, keratopathy was the most commonly reported adverse event, and is characterised by microcyst-like epithelial changes (MECs) visible on slit lamp examination which can manifest with or without symptoms. At 13 months follow up of DREAMM-2 safety data, rate of keratopathy was 68%, rate of symptom and or ≥2-line best corrected visual acuity (BCVA) decline in better seeing eye was 56%, rate of BCVA change to 20/50 or worse was 18%, and rate of discontinuation due to corneal events was 3% (Lional 2020).

In a post-hoc analysis of DREAMM-2 trial (Popat 2020), all patients (n=221) underwent ophthalmic examination at baseline, which included corneal exam, measurement of BCVA, lids/lashes/lacrimal system exam, slit lamp exam and dilated fundoscopy. Patients also completed the eye-specific National Eye Institute Visual Function Questionnaire 25 (NEI-VFQ-25) prior to treatment (Popat 2020)

Median age was 66 (34-89) years, median number of prior therapies was 6 (3-21), prior bortezomib was received in 98%. Of 218 patients with ocular history, 60% had a prior cataract diagnosis, 35% had prior intraocular/later treatment, 20% had prior diagnosis of dry eye, 6% had prior glaucoma, and 12% had ocular disease requiring treatment (Popat 2020).

Results of baseline ocular examination of 218 patients demonstrated: mean BCVA in worse eye 0.12, mean BCVA in better eye 0.025, BCVA score of 20/50 or worse in both eyes (2%), BCVA score of 20/50 or worse in one eye (9%), blepharitis in right eye (21%), blepharitis in left eye (20%), abnormal corneal epithelium in right eye (43%), abnormal corneal epithelium in left eye (43%), Melbomian gland dysfunction in right eye (33%), Melbomian gland dysfunction in left eye (33%), median Schirmer's test in worse eye 8.2mm (normal is >15mm). Slit lamp examination showed glaucoma in 50% of patients. Of 218 patients, 8% had evidence of prior cataract surgery with implanted lens. Dilated fundoscopy identified abnormal optic nerve in 10%, half of which had glaucomatous cupping. Median (range) overall composite vision score by NEI-VFQ-25 was 95.3 (28-100) (Popat 2020), which is comparable to what was reported in other patients aged >65 years (Nickels 2017).

As demonstrated from baseline assessments in this post-hoc analysis, glaucoma is more common than in the general population (likely due to age, prior bortezomib, and prior steroids), it is important to assess these baseline in belantamab patients receiving therapy in the real-world outside the clinical trial setting in order to further assess ocular abnormalities at baseline, and define an optimal frequency for further ophthalmology follow up. It is also crucial for this project to examine in detail ocular belantamab-related toxicities in those patients and the degree of spontaneous keratopathy resolution, in order to identify best strategies for optimal dosing which can achieve good myeloma outcomes whilst limiting the impact on patients' quality of life.

Project aims and Objectives

1. Baseline ocular assessment, and ophthalmology follow up data during treatment
2. Efficacy outcomes of belantamab: ORR, DOR, PFS, TTNT, and OS
3. Dosing of belantamab in the routine care
4. Efficacy outcomes based on previous therapies (IMiDs and PIs, refractoriness, and daratumumab exposure)
5. Efficacy outcomes based on cytogenetic features
6. Influence of co-morbidities and age on outcomes
7. Full evaluation of adverse events (AEs) / severity including COVID-19 and their resolution
8. Detailed analysis of ocular toxicities (incidence, grading of keratopathy, and rate of spontaneous recovery to baseline or better).
9. Patient QoL on Belantamab

Design and Methods

This is a non-interventional retrospective multi-centre evaluation of relapsed multiple myeloma patients who have received compassionate use single agent belantamab mafodotin in the UK

Outcome measures:

- ORR according to IMWG definition: complete response (CR), stringent CR (s.CR), very good partial response (VGPR), partial response (PR), minor response/stable disease (MR/SD), and progressive disease (PD)
- Duration of response (DOR)
- PFS defined as the time from the start of the first dose of belantamab to the date of first documentation of disease progression or death from any cause.
- TTNT defined as the time from the start of the first dose to the date of first dose of the next line of therapy or death from any cause.
- PFS2 defined as the time from the start of subsequent therapy (following belantamab) to the date of first documentation of disease progression or death from any cause.
- OS defined as the time from the start of the first dose to the date of death
- All toxicities as per CTCAE v4.03, including infections and infusion reactions
- Detailed analysis of timing and severity of ocular toxicities
- Number and proportion of patients who discontinued treatment, frequency of treatment/dose interruptions, reason for discontinuation.
- Inpatient admission duration and frequency due to AEs. Median duration of admissions.
- Characterise dosing intensity and safety outcomes in relation to pre-existing co-morbidities

- Quality of life indications at the end of follow up within the study: e.g. improvement/deterioration in fatigue, performance status, and pain, impact of AEs on patients' treatment experience (e.g. high grade AEs, incidence and duration of hospital admissions)

Data collection database and supportive information

The data collection will be on secure web-based pre-designed eCRFs (OpenClinica). Data will be entered anonymously with no patient identifiable information.

- Individual secure log-in will be provided to collaborators
- Supportive documents are provided to aid data and standardise data collection.

  Appendix 1 OpenClinica User Guide Slides (separate document): illustrates navigation through the database eCRFs.

  Appendix 3 Belantamab Data_Collection_Supportive_Information (separate document): contains general IMWG definitions and CTCAE criteria to aid data collection.

  Appendix 6 Pseudonym Subject Log Example (separate document)

Data Analysis

Survival analysis for PFS, OS and TTNT will be presented in Kaplan Meier curves for time to event. Subgroup comparison analyses with log rank test and Cox model will be undertaken for PFS, TTNT and OS for the following subgroups:

- Outcomes according to the number of prior therapies
- Cytogenetics: HR vs SR
- ISS Staging: ISS I & II vs ISS III
- Prior ASCT vs No ASCT.
- Age: <75 vs. ≥75 years
- Co-morbidities: Charlson Co-morbidity Index (CCI): <5 vs. ≥5

Response rates, adverse events and toxicities, dose reductions and discontinuation rates, dose intensity, median duration of response; will presented using descriptive statistics in frequencies and mean/median.

Governance

We argue ethics approval from a Health Research Authority (HRA) is not required. This project of collecting routine care data of licensed therapy with aim of service evaluation is deemed to be a non-interventional service evaluation audit and does not fit the criteria used to define research Clarification and confirmation that this project does not require HRA REC. See: **Appendix 4 – Proposed Governance**.

Information Governance (IG)

The project collects data about patients undergoing chemotherapy regimen belantamab mafodotin. Given that individual patients are identified it is essential that the project complies with the requirements of the General Data Protection Regulations (GDPR) and the Data Protection Act 2018. To meet them we conducted a data protection impact assessment (DPIA), which was signed off by the Oxford University Hospitals Foundation NHS Trust (OUHFT) Information Governance Manager. See: **Appendix5 – Copy of DPIA**. Among other things this sets out the personal information used, legal basis for the processing the information, compliance with Caldicott Principles, data transfer, data storage, transparency, and a risk assessment. In summary, we use GDPR Principle 6 – 1e - Necessary for performance of a task carried out in public interest or in exercise of official authority, and GDPR Principle 9 - Necessary for provision of health and/or social care, including preventative or occupational medicine as our legal bases for processing data.

The OUHFT DPIA can be used as a model for local sites to obtain their own IG approvals.
The model this project adopts ***does not require the transfer of personal information*** – information that identifies an individual. The bare minimum of personal information is used to identify participants and their data at the sites. A pseudonym is created, logged, kept securely on site, and then the study data is then entered into the project database against this pseudonym. For example, John Smith is identified in Oxford as a participant. Oxford creates a suitable pseudonym OX-1; this is logged, and kept securely on site. See: **Appendix 6 – Pseudonym Subject Log Example (separate document)**. John Smith's data is entered into the project database against this pseudonym OX-1. Consequently, a data-sharing agreement is not required because personal information is not transferred.

The project data itself ***is not personal information***—it is extremely unlikely that it could be used to identify and individual. While gender *is* recorded in the database, along with date of death, these items *per se* are not personal information in this sense and the sense of the pertinent legislation.

Information Technology – Project Database

Hosting

The project is hosted DigitalOcean virtual machines (VM) hosted in their London infrastructure (see: https://www.digitalocean.com/).

The VMs use the latest LTS version of Ubuntu 18.04 (see: https://wiki.ubuntu.com/BionicBeaver/ReleaseNotes). This operating system is regularly updated and patched. The machines are set up according to:
https://www.digitalocean.com/community/tutorials/initial-server-setup-with-ubuntu-18-04
and further locked down by only permitting remote access via SSH on a non-root account authenticated by public/private key. The only ports open on the machine are 80; 443; and 22. Furthermore, the only software installed directly on the machine is git, docker, and docker-compose reducing the attack footprint. (The other software elements are deployed via docker and docker-compose.

Physical access to the servers containing the VMs is only by DigitalOcean employees. A full overview of the security of DigitalOcean can be obtained here: https://www.digitalocean.com/legal/
Remote access to the servers is either via SSH as noted or via a local admin console within the DigitalOcean website for the user. SSH access requires a public key to be lodged on the server and the private key held by the user. Unless there is a weakness in the SSH service/protocol the only way access can be gained is if the private/private keys are compromised. The local admin console within the DigitalOcean website is protected by a password and 2-factor authentication (the same as for many banks). The password itself is lengthy and strong and is held in a password vault which is also protected by a lengthy and strong password. To complete the 2-factor authentication a personal mobile phone would need to be stolen and access would require a finger-print or knowledge of a long PIN.

These measures are compliant with the Cyber Security Essentials (although no certification has been obtained).

Database Software

At the application level we use OpenClinica (see: https://www.openclinica.com/), an open source electronic data capture application behind a web-proxy (nginx - see: https://www.nginx.com/) deployed on Docker containers (see: https://www.docker.com/). Ultimately, the containers will be orchestrated using Kubernetes (see: https://kubernetes.io/), but in the meantime we are simply using docker-compose (see: https://docs.docker.com/compose/).

OpenClinica itself is an application widely used to collect clinical trial data. The application itself is written in Java (see: https://www.java.com/en/) and deployed on Tomcat (see: http://tomcat.apache.org/) with Postgres (see: https://www.postgresql.org/) as the database.
Communication to the application will be restricted to port 443 (https://) and thus encrypted end-to-end. Remote communication to the hosting infrastructure will be restricted to port 22 (SSH) and thus encrypted end-to-end.

Project Timelines and Dissemination

Data collection deadline: ----------

References

https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(19)30788-0/fulltext

Appendix 1: OpenClinica User Guide Slides (separate document)

To be completed in due courrse

Appendix 2: Supportive information: refer to belantamab mafodotin treatment Protocol:

http://nssg.oxford-haematology.org.uk/myeloma/pdf-protocols/MM-55-belantamab-mafodotin.pdf

Appendix 3: Proposed Governance

Abstract

A critical issue to resolve is under which governance umbrella the Belantamab real-world data collection project should sit. Specifically, whether this project is audit/service improvement or research. We acknowledge that you *could* argue for either. However, our certification is that this is audit/service improvement. We base this on two factual data sources: (1) Precedent—similar projects have been assessed as audit/service improvement by an Ethics committee; (2) A detailed examination of the Health Research Agency (HRA) detailed criteria on what is 'research' and what is 'service evaluation' and 'clinical/non-financial audit'.

The Argument

We have run a number of real-world therapeutics projects and reported clinical outcomes to the myeloma community. We have examined IsaPomDex[1], VCD[2], DPACE[3], PanBorDex[4], Ixazomib/lenalidomide/Dex[5], Carfilzomib/Dex[6] and infections in newly diagnosed myeloma patients[7]. Each has been run as an audit/service improvement project and published in peer-reviewed journals or presented at international haematology conferences. The results have influenced conversations about clinical outcomes for real-world patients, as well as toxicities and their attendant management. The results have also influenced guidance to prescribers in TVCA myeloma network protocols. [8]

For IsaPomDex and PanBorDex, we received a declaration from a HRA Research Ethics Committee (REC) that the project did not require HRA ethical review. From this, we certified that these projects are considered audit/service improvement. Some partner organisation sponsor/governance departments did challenge our view. In our response, we outlined our position (providing the letter) and they evidentially agreed, and the project was delivered in these organisations.

We also sought a similar letter declaring the Belantamab project did not require HRA ethical review.[9] However, HRA RECs no longer offer this service. Rather, they require a self-certification whether a project is research and requires HRA REC approval. This self-certification is based on an algorithm[10] delineating (simply) the boundary between research and not-research and set of criteria[11]

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[1] Faouzi Djebbari et al., 'Efficacy Outcomes of Isatuximab with Pomalidomide and Dexamethasone Are Comparable to (ICARIA-MM) Trial Data: Initial Results of a UK-Wide Real-World Study of Relapsed Myeloma Patients', *Blood* 138, no. Supplement 1 (5 November 2021): 1963, https://doi.org/10.1182/blood-2021-145408.

[2] Alexandros Rampotas et al., 'Efficacy and Tolerability of VCD Chemotherapy in a UK Real-World Dataset of Elderly Transplant-Ineligible Newly Diagnosed Myeloma Patients', *European Journal of Haematology* 106, no. 4 (2021): 563–73, https://doi.org/10.1111/ejh.13588.

[3] Faouzi Djebbari et al., 'DPACE-Based Chemotherapy in the Era of Myeloma Novel Agents: A UK Multicentre Study', *European Journal of Haematology* 105, no. 2 (2020): 231–33, https://doi.org/10.1111/ejh.13422.

[4] Nadjoua Maouche, 'Panobinostat in Combination with Bortezomib and Dexamethasone for Heavily Pre-Treated Myeloma: A UK Real-World Multi-Centre Cohort' (62nd ASH Annual Meeting and Exposition, ASH, 2020), https://ash.confex.com/ash/2020/webprogram/Paper141630.html.

[5] Nadjoua Maouche et al., 'Ixazomib, Lenalidomide, and Dexamethasone Is Effective and Well Tolerated in Multiply Relapsed (≥2nd Relapse) Refractory Myeloma: A Multicenter Real World UK Experience', *Leukemia & Lymphoma* 62, no. 6 (12 May 2021): 1396–1404, https://doi.org/10.1080/10428194.2020.1864355.

[6] Faouzi Djebbari et al., 'Carfilzomib Therapy for Relapsed Myeloma: Results of a UK Multicentre Experience', *British Journal of Haematology* 188, no. 4 (2020): e57–60, https://doi.org/10.1111/bjh.16324.

[7] Faouzi Djebbari et al., 'Infection-Related Morbidity Reduced Overall Survival in a Large Real-World Cohort of Transplant Ineligible Newly Diagnosed Myeloma Patients Treated with UK Standard of Care', *Blood* 134, no. Supplement_1 (13 November 2019): 4768, https://doi.org/10.1182/blood-2019-128139.

[8] 'Myeloma NSSG Webpage', accessed 8 December 2021, http://nssg.oxford-haematology.org.uk/myeloma/myeloma.html.

[9] For most of the projects listed above, each had the same structure and aims, the only difference being the drug(s) of interest.

[10] See: http://www.hra-decisiontools.org.uk/research/index.html

[11] See: http://www.hra-decisiontools.org.uk/research/docs/DefiningResearchTable_Oct2017-1.pdf

delineating the boundaries between research, service evaluation, clinical/non-financial audit and usual practice.

The algorithm is based on three questions.

One, “Are the participants in you study randomised to different groups?” No.

Two, “Does your study protocol demand changing treatment/care/services from accepted standards for any of the patients/service users involved?” No.

Three, “Is your study designed to produce generalisable or transferable findings?” We would argue, no. Treatment received by patients is biased by both patients consenting to it (a cohort) and physicians offering therapy in their centre (select centres). Therefore, this cannot be generalised to every myeloma patient as the rational process leading to therapy application is influenced by both patient, physician choice as well as drug availability.

The question goes on to clarify, “Generalisable in this context means the findings can be reliably extrapolated from the study to a broader population of patients/service users and/or applied to settings or contexts other than those in which they were tested.” We contend that the findings of the study could *not* reliably be extrapolated to a broader population of patients/service users and/or applied to settings or contexts other than those in which they were tested. We are not seeking to extrapolate—merely report and aggregate ours and others experiences of using this drug in a real-world setting. We are seeking to observe the effects of Belantamab in routine care population who fit the definitive clinical trial criteria of belantamab[12] and the hypothesis is that Belantamab would be efficacious in a real-world (non-trial) population as it did in the trial population.[13] We are not seeking to go beyond what the published trials assert, nor is the project designed to provide evidence that we could extrapolate to a broader population.

On the ‘transferable’ point, the question goes on clarify, “Transferable in this context means the findings of a qualitative study can be assumed to be applicable to a similar context or setting. Most qualitative studies are not usually generalisable but can often be transferable.” Consequently, the concept is only applicable if our project is a *qualitative* study. We would argue that our project is a *quantitative* study and consequently ‘transferable’ in this sense does not apply. This said, we would assume what we find *would be* applicable in a similar context or setting, specifically other UK sites who use belantamab. However, the evidence provided for this assumption by this project is relatively weak because it is retrospective.

If one answers, “No” to all the questions then the project is *not* deemed to be ‘research’. If any of the questions are answered, “Yes” then it is deemed to be ‘research’ and possibly (but not necessarily) requiring HRA REC approval. On the basis of the above we would answer “No” to all of the questions.

[12] ‘Belantamab Mafodotin for Relapsed or Refractory Multiple Myeloma (DREAMM-2): A Two-Arm, Randomised, Open-Label, Phase 2 Study’, *The Lancet Oncology* 21, no. 2 (1 February 2020): 207–21, https://doi.org/10.1016/S1470-2045(19)30788-0.

[13] We know that often definitive clinical trials do not represent the real-world populations in which the drug (or protocol) is used. This is because of inclusion and exclusion criteria provide a trial population which is not equivalent to real world. Typically, this is because the inclusion and exclusion criteria select a fitter population than real-world.

There is another algorithm for determining whether the 'research' requires HRA REC approval.[14] The opening page notes, "Post Market Surveillance is NOT usually considered research. However, there are some circumstances where an NHS REC review may be required. Select YES below to determine if your post market surveillance requires NHS REC review."

In every sense, what we are performing *is* Post Market Surveillance" as Belantamab is EMA licensed and marketed in Europe. However, the sense meant is ostensibly applicable to Post Market Surveillance studies of CE marked devices meeting various criteria.[15] Interestingly, if you take away the criterion of it being CE marked devices and change references to product to drug then our project meets the criteria for it being Post Market Surveillance.

Nevertheless, if you follow the algorithm you get to a set of questions, one of which is, "Will your study involve potential research participants identified in the context of, or in connection with, their past or present use of services (NHS and adult social care), including participants recruited through these services as healthy controls?" The answer is clearly yes and thus according to that algorithm, the project requires HRA REC approval *if* it is 'research' according to the previous algorithm.

The algorithms are potentially useful tools. However, they do depend on how you interpret the questions and different interpretations give different answers. Now there are other criteria concerning whether a project is 'research', 'service evaluation', 'clinical/non-financial audit', or 'usual practice'.[16] Unfortunately these do not give a clear-cut answer to this project suggesting, as we acknowledge, that you could argue our project is either research OR/ service evaluation, clinical/non-financial audit.[17] Worse, for our project the criteria does not distinguish whether it is service evaluation OR/ clinical/non-financial audit but some hybrid of both.

So, let's first look at the criteria for 'research' and whether they are applicable. The first question in these criteria determines whether the project is 'research' or not and the remaining criteria delineate some of the characteristics. The yes answers to remaining questions only apply if the first question is answered yes, otherwise they would not apply.

Research Criteria	Applies to project
The attempt to derive generalisable or transferable new knowledge to answer questions with scientifically sound methods* including studies that aim to generate hypotheses as well as studies that aim to test them, in addition to simply descriptive studies.	**N**
Quantitative research – can be designed to test a hypothesis as in a randomised controlled trial or can simply be descriptive as in a postal survey.	**N**
Qualitative research – can be used to generate a hypothesis, usually identifies/explores themes.	**N/A**
Quantitative research - addresses clearly defined questions, aims and objectives.	**Y**
Qualitative research – usually has clear aims and objectives but may not establish the exact questions to be asked until research is underway.	**N/A**

[14] See: http://www.hra-decisiontools.org.uk/ethics/
[15] See: http://www.hra-decisiontools.org.uk/ethics/glossary.html#P
[16] See: http://www.hra-decisiontools.org.uk/research/docs/DefiningResearchTable_Oct2017-1.pdf
[17] Keen readers would have noticed 'usual practice' is not mentioned in this list. The concept of 'usual practice' is aligned to population and public health and therefore not applicable. We won't look into it further.

Quantitative research – may involve evaluating or comparing interventions, particularly new ones. However, some quantitative research such as descriptive surveys, do not involve interventions.	**N**
Qualitative research – seeks to understand better the perceptions and reasoning of people.	**N/A**
Usually involves collecting data that are additional to those for routine care but may include data collected routinely. May involve treatments, samples or investigations additional to routine care. May involve data collected from interviews, focus groups and/or observation.	**N** (some aspects are **Y**)
Quantitative research – study design may involve allocating patients/service users/healthy volunteers to an intervention. Qualitative research – does not usually involve allocating participants to an intervention.	**N/A**
May involve randomisation.	**N**

Now let us look at the criteria for 'service evaluation' and whether they are applicable. Again, the first question in the criteria determines whether the project is 'service evaluation' or not and the remaining criteria delineate some of the characteristics.

Service Evaluation Criteria	Applies to project
Designed and conducted solely to define or judge current care.	**Y**
Designed to answer: "What standard does this service achieve?"	**Y**
Measures current service without reference to a standard	**Y**
Involves an intervention in use only. The choice of treatment, care or services is that of the care professional and patient/service user according to guidance, professional standards and/or patient/ service user preference.	**Y**
Usually involves analysis of existing data but may also include administration of interview(s) or questionnaire(s).	**Y**
No allocation to intervention: the care professional and patient/ service user have chosen intervention before service evaluation.	**Y**
No randomisation.	**Y**

As we can see the project aligns very strongly as being a 'service evaluation'. Now let us look at the criteria for 'clinical/non-financial audit' and whether they are applicable.

Clinical/Non-financial Audit Criteria	Applies to project
Designed and conducted to produce information to inform delivery of best care.	**Y**
Designed to answer: "Does this service reach a predetermined standard?"	**Y**
Measures against a standard.[18]	**Y**
Involves an intervention in use only. The choice of treatment, care or services is that of the care professional and patient/service user according to guidance, professional standards and/or patient/ service user preference.	**Y**
Usually involves analysis of existing data but may also include administration of interview(s) or questionnaire(s).	**Y**
No allocation to intervention: the care professional and patient/ service user have chosen intervention before audit.	**Y**
No randomisation.	**Y**

[18] The definitive clinical trial.

Note that the project entirely aligns with being a clinical/non-financial audit. The problem is that depending on how you answer the first question it could also be 'research' and it also fully meets the criteria for being a 'service evaluation' too.

The crux of the matter is that 'research' normally requires HRA REC review, whereas 'service evaluation' and 'clinical/non-financial audit' do not. It is our view that the project does not require HRA REC review and be part of the research governance framework because there is a case that it is not 'research' in the sense described by the regulators, and it either entirely or almost entirely aligns with 'service evaluation' and 'clinical/non-financial audit'.

It is our view given how closely the project aligns with 'service evaluation' and 'clinical/non-financial audit', and there is a case that this is not 'research' in the normal sense that this project be consider a hybrid service evaluation clinical/non-financial audit and not requiring HRA REC review (and be part of the research governance framework).

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Appendix 4: Pseudonym Subject Log Example (separate document)

Available as a separate excel spreadsheet