Single Technology Appraisal

Daratumumab with lenalidomide and dexamethasone for untreated multiple myeloma when stem cell transplant is unsuitable [ID4014]
Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Daratumumab with lenalidomide and dexamethasone for untreated multiple myeloma when stem cell transplant is unsuitable [ID4014]

Contents:

The following documents are made available to stakeholders:

Access the **final scope** and **final stakeholder list** on the NICE website.

Pre-technical engagement documents

1. **Company submission from Janssen**

2. **Clarification questions and company responses**

3. **Patient group, professional group, and NHS organisation submissions** from:
   a. Myeloma UK
   b. UK Myeloma Forum

4. **External Assessment Report** prepared by Bristol Technology Assessment Group

5. **External Assessment Report – factual accuracy check**

Post-technical engagement documents

6. **Technical engagement response from Janssen**

7. **Technical engagement responses and statements from experts:**
   - Professor Gordon Cook, Professor of Haematology, clinical expert nominated by Janssen & Dr Neil Rabin, Consultant Haematologist & Chair of UKMS, clinical expert nominated by UK Myeloma Society

8. **Technical engagement response from Myeloma UK**

9. **External Assessment Group critique of company response to technical engagement** prepared by Bristol Technology Assessment Group

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

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Single technology appraisal

Daratumumab with lenalidomide and dexamethasone for untreated multiple myeloma when stem cell transplant is unsuitable [ID4014]

Document B

Company evidence submission

May 2022

File name	Version	Contains confidential information	Date
ID4014_Janssen_Daratumumab_Document B_ FINAL [ACIC]_Fully Redacted	FINAL	Yes	25th May 2022

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B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 *Decision problem*

This submission covers the technology's full marketing authorisation for this indication: daratumumab in combination with lenalidomide and dexamethasone (DLd), for the treatment of adult patients with newly diagnosed multiple myeloma (NDMM) who are ineligible for autologous stem cell transplant (ASCT).[1] The decision problem addressed in this submission, compared to that defined in the final scope issued by NICE, is summarised in Table 1.[2]

DLd is positioned in line with its marketing authorisation and the population of the MAIA trial, for the treatment of adult patients with NDMM who are ineligible for ASCT. Clinical expert feedback received by Janssen (gathered in an advisory board meeting with eight clinicians on 9th March 2022 [3]) indicate that the most relevant comparator for this indication is lenalidomide and dexamethasone (Ld). Results from the fully incremental cost effectiveness analysis (Section B.3.9.3) support this, as Ld dominates all other comparators. In addition, bortezomib with an alkylating agent and corticosteroid is used in a minority of patients. Thalidomide-based combinations are not considered relevant comparators given their negligible use in English clinical practice.

For the bortezomib with an alkylating agent and corticosteroid comparator, bortezomib, melphalan and prednisone (BMP) is used to represent this class of treatments, with bortezomib, cyclophosphamide and dexamethasone (BCd) considered in a scenario analysis (see Appendix N). Whilst treatment with both Ld and bortezomib are restricted to adult patients unsuitable for thalidomide, Ld represents National Health Service (NHS) standard of care (SoC) for the majority of NDMM ASCT-ineligible patients in England, regardless of their eligibility for thalidomide, with bortezomib-based therapy used by a minority of patients.

Guidance for thalidomide-based combinations such as cyclophosphamide, thalidomide and dexamethasone (CTd) or melphalan, thalidomide and dexamethasone (MPT) was published in 2011 and these regimens are now rarely used due to the toxicity profile associated with thalidomide, and following NICE's recommendation for Ld in 2019 (TA587).[4-7] For completeness, in line with the final scope, comparisons against CTd and MPT are provided in the appendices supporting this submission.

Table 1: The decision problem

	Final scope issued by NICE[2]	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with untreated multiple myeloma when stem cell transplant is unsuitable	Adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant	This wording is in line with the marketing authorisation for DLd and the population of the MAIA trial;[8, 9] otherwise, this is in line with the final NICE scope.
Comparator(s)	• Thalidomide with alkylating agent and corticosteroid For people who are unable to tolerate, or have contraindications to thalidomide: • Bortezomib with alkylating agent and corticosteroid • Lenalidomide with dexamethasone (Ld)	The main comparators considered within this submission are: • Lenalidomide and dexamethasone (Ld) • Bortezomib with alkylating agent and corticosteroid In addition, for completeness, comparisons are provided for : • Thalidomide with alkylating agent and corticosteroid	DLd is positioned as a treatment option for adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant, irrespective of eligibility for thalidomide-containing regimens. Clinical expert feedback received by Janssen indicates that Ld represents current NHS SoC with bortezomib with an alkylating agent and corticosteroid used to treat a minority of patients.[3] Given that Ld represents current NHS SoC, and dominates bortezomib- and thalidomide-based therapies in fully incremental cost-effectiveness analysis, results against Ld only are presented in in Section B.3. Full results versus bortezomib- and thalidomide-based therapies are presented in Appendix N.
Outcomes	The outcome measures to be considered include: • Overall survival (OS) • Progression-free survival (PFS) • Response rates • Minimal residual disease-negative status • Adverse effects (AEs) of treatment	Outcomes included in this submission are: • Overall survival (OS) • Progression-free survival (PFS) • Overall response rate (ORR) • Minimal residual disease (MRD) negativity • Adverse events (AEs) of treatment • Health-related quality-of-life	All outcomes requested in NICE's final scope are presented, with additional outcomes included to capture as fully as possible the important health benefits for DLd.

	• Health-related quality-of-life (HRQoL)	(HRQoL) • Time to disease progression (TTP) • Time to subsequent anticancer therapy • Progression-free survival on next line of therapy (PFS2) • Time to response • Duration of response (DOR)	
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention or comparator technologies will be taken into account. The availability and cost of biosimilar products should be taken into account.	The cost-effectiveness of the treatments evaluated in this appraisal is expressed in terms of incremental cost per QALY. A lifetime time horizon was adopted to capture all relevant costs and health-related utilities. Costs were considered from an NHS and PSS perspective. All costs and utilities were discounted at a rate of 3.5% per year in alignment with the NICE guide to the methods of technology appraisal.	N/A – in line with final scope.

Abbreviations: AE: adverse event; BCd; bortezomib, cyclophosphamide and dexamethasone; BMP: bortezomib, melphalan and prednisone; CTd: cyclophosphamide, thalidomide and dexamethasone; DLd: daratumumab, lenalidomide and dexamethasone; DOR: duration of response; HRQoL: health-related quality-of-life; IPD: individual patient data; Ld: lenalidomide and dexamethasone; MAIC: matching adjusted indirect comparison; MPT: melphalan, prednisone and thalidomide; MRD: minimal residual disease; N/A: not applicable; NCRAS: National Cancer Registration and Analysis Service; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; PFS2: progression-free survival on next line of therapy; PSS: Personal Social Services; QALY: quality-adjusted life year; SoC: standard of care; TTP: time to disease progression.

B.1.2 *Description of the technology being evaluated*

The summary of product characteristics (SmPC) and European public assessment report (EPAR) are provided in the reference pack accompanying this submission (see Appendix C). A description of the technology being appraised, DLd, is presented in Table 2.

Table 2: Technology being appraised

UK approved name and brand name	Daratumumab (Darzalex®)
Mechanism of action	Daratumumab is a first-in-class, fully human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody (mAb) that binds to the CD38 glycoprotein, expressed at a high level on the surface of MM tumour cells, in addition to other cell types and tissues at various levels.[1, 10, 11] CD38 plays a key role in the growth and survival of MM cells, and is involved in receptor mediated adhesion, signalling and enzymatic activity.[1] Based on *in vitro* studies, daratumumab binding to CD38 induces tumour cell death through multiple mechanisms, including direct on-tumour and indirect immunomodulatory actions. These processes include immune-mediated mechanisms of action (i.e. complement-dependent cytotoxicity [CDC], antibody-dependent cell-mediated cytotoxicity [ADCC] and antibody-dependent cellular phagocytosis [ADCP]) as well as induction of myeloma cell apoptosis and various immunomodulatory mechanisms.[12]
Marketing authorisation/CE mark status	Marketing authorisation was granted by the European Commission for DLd on 19th November 2019.[13]
Indications and any restriction(s) as described in the SmPC	The licenced indications for daratumumab are:[1] • "in combination with lenalidomide and dexamethasone (DLd) or with bortezomib, melphalan and prednisone (DBMP) for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant" • "in combination with bortezomib, thalidomide and dexamethasone (DBTd) for the treatment of adult patients with newly diagnosed multiple myeloma who are eligible for autologous stem cell transplant". • "in combination with lenalidomide and dexamethasone (DLd), or bortezomib and dexamethasone (DBd), for the treatment of adult patients with multiple myeloma who have received at least one prior therapy" • "in combination with pomalidomide and dexamethasone (DPd) for the treatment of adult patients with multiple myeloma who have received one prior therapy containing a proteasome inhibitor and lenalidomide and were lenalidomide-refractory, or who have received at least two prior therapies that included lenalidomide and a proteasome inhibitor and have demonstrated disease progression on or after the last therapy" [daratumumab subcutaneous (SC) formulation only] • "as monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma, whose prior therapy included a proteasome inhibitor and an immunomodulatory agent and who have demonstrated disease progression on the last therapy" • "in combination with bortezomib, cyclophosphamide and

	dexamethasone (DBCd) for the treatment of adult patients with newly diagnosed systemic light chain (AL) amyloidosis" [daratumumab SC formulation only]
Method of administration and dosage	Daratumumab is available as either a solution for intravenous (IV) infusion or as a fixed dose subcutaneous (SC) injection when used as part of the DLd combination.[14] Daratumumab administered subcutaneously is available as a 1,800 mg/15 mL solution for injection (120 mg daratumumab per mL). Daratumumab is administered once weekly during Weeks 1 to 8, followed by every two weeks during Weeks 9 to 24. From Week 25 onwards, daratumumab is administered every four weeks until disease progression. Drug administration should be done by a healthcare professional, and the first dose should be administered in an environment where resuscitation facilities are available. The SC formulation of daratumumab reduces treatment time to 3–5 minutes, with comparable efficacy to IV dosing and fewer injection site reactions and IRRs.[1, 15, 16] Daratumumab administered via IV infusion is available in two single dose vials 100 mg/5 mL (20 mg/mL) and 400 mg/20 mL (20 mg/mL). The recommended dose of daratumumab is 16 mg/kg body weight administered as an IV infusion according to the same dosing schedule described above (as solution for injection) and requires dilution and administration by a healthcare professional.[1]
Additional tests or investigations	Daratumumab has the requirement for a blood test to be carried out prior to initiation of therapy in order to type and screen patients for antibodies.[1]
List price and average cost of a course of treatment	• List Price 1,800 mg (fixed-dose vial; SC injection) = £4,320.00 (excl. VAT). This is equivalent to the cost of a 1,200 mg IV infusion (i.e. cost parity assuming an average daratumumab patient weight of 75 kg).[14] • List Price 100 mg (IV infusion) = £360.00 (excl. VAT).[14] • List Price 400 mg (IV infusion) = £1,440.00 (excl. VAT).[14]
Patient access scheme (if applicable)	A patient access scheme (PAS) for daratumumab of [redacted] is included for daratumumab in the cost-effectivness model (see Section B.3.5 for further information). [redacted]

Abbreviations: ADCC: antibody-dependent cell-mediated cytotoxicity; ADCP: antibody-dependent cellular phagocytosis; CAA: commercial access agreement; CD38: cluster of differentiation 38; CDC: complement-dependent cytotoxicity; DBd: daratumumab, bortezomib and dexamethasone; DBMP: daratumumab, bortezomib, melphalan and prednisone; DBTd: daratumumab, bortezomib, thalidomide and dexamethasone; DLd: daratumumab, lenalidomide and dexamethasone; IgG1κ: immunoglobulin G1 kappa; IRR: infusion-related reaction; mAb: monoclonal antibody; IWMG: International Myeloma Working Group; IV: intravenous; MM: multiple myeloma; NHSE: National Health Service England; SC: subcutaneous; SmPC: summary of product characteristics.

B.1.3 *Health condition and position of the technology in the treatment pathway*

B.1.3.1 Disease overview

MM is a rare and incurable haematological cancer characterised by the excessive proliferation of malignant plasma cells within the bone marrow and the overproduction of M-protein.[17-19] Over time, these components accumulate in the bones, blood and multiple organs throughout the body. This leads to progressive morbidity and eventual mortality by lowering resistance to infection and causing serious complications which require immediate medical treatment, including elevated calcium levels (hypercalcemia), renal impairment, anaemia and bone disease (CRAB).[17, 20] Additional presenting features include fatigue, bone pain, recurrent or persistent infection and hyperviscosity, all of which severely impact patients' quality of life (QoL) on a daily basis.[17, 20, 21]

MM is a highly heterogeneous disease with a variable clinical course, and as such, prognosis varies greatly from patient to patient depending on a number of factors. At a genetic level, heterogeneity exists in the form of mutations and genetic translocations. This, combined with further heterogeneity at the clonal and cell differentiation level, can increase the challenges in terms of treatment options that effectively target and eliminate all malignant plasma cells.[22] Clinical outcomes, including progression-free survival (PFS) and overall survival (OS), vary depending on a number of prognostic factors, such as age, International Staging System (ISS) stage and whether the patient is considered high-risk, amongst other determinants.[23, 24]

MM has a median age at presentation of ~70 years, with 75% of patients in the UK being diagnosed over the age of 65.[25, 26] For patients with NDMM, high-dose therapy (HDT) followed by an ASCT represents standard of care (SoC) for those patients who are fit enough to receive these interventions.[27] HDT-ASCT is an intensive treatment option and involves giving high doses of chemotherapy (typically melphalan) to kill myeloma cells and then infusing stem cells back into the patient, allowing the bone marrow to recover. The interplay between disease- and patient-specific factors such as age, fitness, performance status and comorbidities are ultimately used to determine a patient's eligibility for ASCT.[28-32] The ASCT-ineligible population are a heterogenous clinical group that includes fit elderly patients as well as patients considered as unfit or frail. ASCT-ineligible patients account for approximately two-thirds of all NDMM patients in England.

The international treatment landscape of MM has evolved considerably in recent years with the introduction of several novel agents. Since 2000, the expected survival of ASCT-ineligible newly diagnosed MM (NDMM) patients has improved from 2.6 years to 4.3 years. [33] Despite recent therapeutic advances in the treatment of MM, there remain limited treatment options available for ASCT-ineligible patients in England whose prognosis and long-term outcomes lag significantly behind younger or fitter patients eligible to receive a transplant.[27] Patients who are not eligible for ASCT are particularly at risk of developing adverse events (AEs), and are therefore more likely to discontinue treatment relative to transplant-eligible patients.[34] Overall, there is a high unmet need for novel combination therapies to bring about a shift in patient prognosis by tackling clonal heterogeneity and delivering higher rates of deep and sustained response.[35]

B.1.3.2 Epidemiology

In 2017, there were 5,034 new cases of MM in England, accounting for 2% of all new cancer cases.[25] Over the last decade, MM incidence rates have increased by approximately 15% in the

UK and are projected to rise a further 11% between 2014 and 2035; this increase is largely a reflection of the changing prevalence of risk factors and improvements in diagnosis.[25]

The annual age-standardised incidence rate for MM is slightly higher among men than women, at 2.2 per 100,000 compared with 1.5 per 100,000, respectively.[36] Additionally, the incidence of MM varies considerably by race. Estimates from England, supported by the European Society of Medical Oncology (ESMO), suggest that the incidence among black people is approximately twice that among white people.[37, 38]

MM remains an incurable disease and all surviving patients will eventually relapse and progress, due to the presence of residual disease.[25] In England, the 5- and 10-year survival rates for all adults with NDMM are approximately 52.3% and 29.1% respectively (2013–2017).[25] Multiple studies have shown that patients who are ineligible for ASCT demonstrate a poorer OS relative to patients who are eligible for ASCT, with median OS ranging from 25.0 months to 45.1 months.[39-42]

B.1.3.3 Effect of MM on patients and carers

Effect on patients

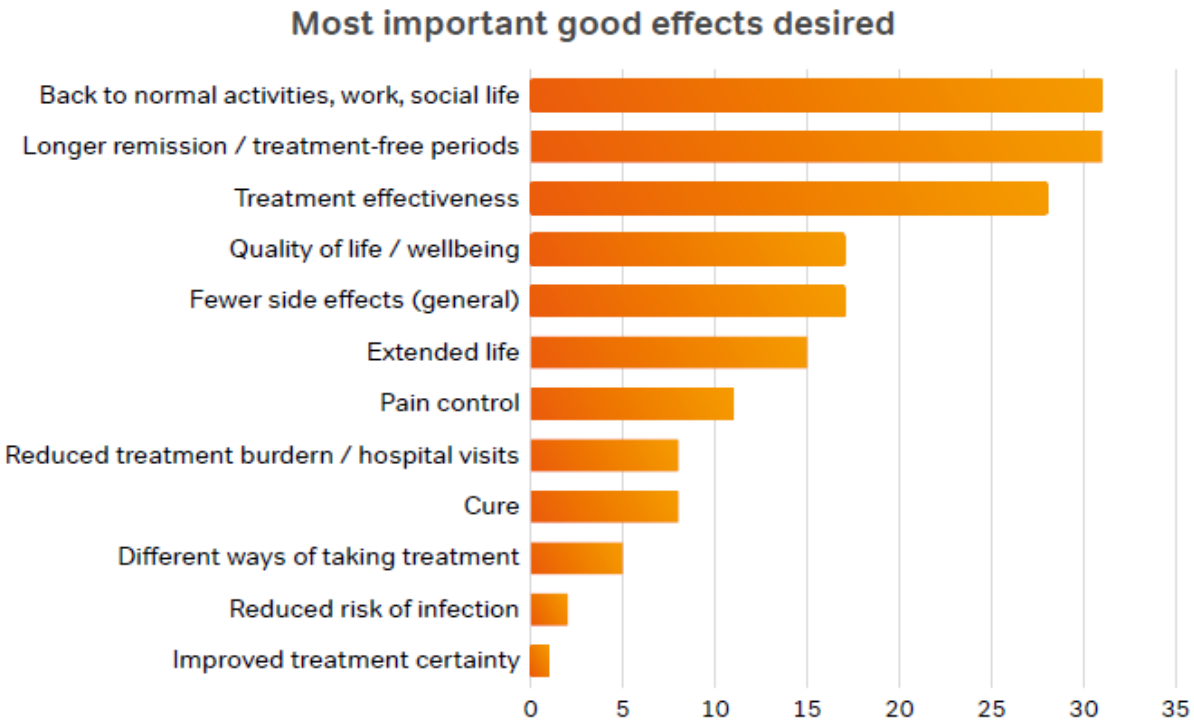
A diagnosis of MM has a profound impact on patients and their carers. Indeed, there is evidence that patients with MM report worse symptoms and HRQoL than those with other haematological cancers, including lymphoma or leukaemia.[43] The clinical burden of MM is influenced by both progressive disease symptoms and treatment-associated complications such as weakness, fatigue, bone pain, weight loss, confusion, excessive thirst and constipation.[44]

A diagnosis of MM also has a substantial psychological impact, with patients living in fear of relapse.[45] Uncertainty about the future causes ongoing anxiety and often affects patients' relationships with family and friends who may act as informal caregivers.[45, 46] This leads to decreased independence and increased social isolation.[45] Patients experience fear as a direct result of their diagnosis and its unpredictability, with some describing myeloma as a 'time bomb'.[47] This continued uncertainty is demonstrated in worsening HRQoL scores at one year follow up, with over a third of patients worrying about their future health and one in five patients worrying about dying.[48] Anxiety is common in myeloma patients, and depression can affect one in four patients.[49]

As such, treatments that achieve lasting remission, optimise life expectancy and deliver early and sustained improvement in HRQoL are highly valued by patients. A recent discrete choice experiment across France, Germany and the UK demonstrated that patients with MM (n=300; newly diagnosed, transplant eligible, n=108; newly diagnosed, transplant ineligible, n=105; relapsed-refractory, n=87) elicited preferences for eight attributes: increased life expectancy, increased time to relapse, pain, fatigue, risk of infection, administration [route and duration], frequency of administration, and monitoring. Preference data were then analysed to calculate life expectancy trade-offs. Such is the impact of symptoms, that patients with MM valued treatments that reduced pain and fatigue and were willing to trade lower life expectancy for improvements in these symptoms.[50] Patients would sacrifice 2.8-years of life expectancy (95% CI: 2.4, 3.1) to remove extreme pain and 2.0-years of life expectancy (95% CI: 1.6, 2.3) to remove constant fatigue. Patients from the UK, relative to the overall sample, placed more value on reducing the level of pain from extreme pain to no pain. The study also found that health state affects patient preferences; patients in a better health state were willing to sacrifice less life expectancy to avoid extreme pain.[50, 51]

In a recent European study of patient perceptions regarding MM treatment (n=30), patient preferences on key efficacy and safety outcomes were elicited.[52] The mean age of the patients in was 60.3 years, and the study included 10 ASCT-ineligible NDMM patients. Results from qualitative interviews revealed increased life expectancy (87%), remission/response (80%) and reduced fatigue (80%) as the most important treatment preferences. Amongst patients with NDMM, cognitive impairment was the most frequently mentioned side-effect (94% of respondents).[52] These findings are broadly consistent with results from a recent qualitative survey undertaken by NICE's Science Policy and Research programme in collaboration with Myeloma UK. In the survey of 97 UK MM patients, 72% of which were aged between 56 and 75 years old, respondents were asked what the most important positive effects (or characteristics) they would want from any treatment for myeloma. The highest ranked attribute was to return to normal activities, work and social life, closely followed by longer remission / treatment-free periods (Figure 1).[53]

Figure 1: Treatment effects most desired by MM patients



Source: Myeloma UK (2019).[53]

The symptom burden associated with MM was also highlighted in the responses from this survey, with fatigue and tiredness; other symptoms and side effects; mobility and daily activities; and pain and discomfort, being reported by patients as the aspects of MM that have the greatest impact on their lives.[53] The negative effects of treatment that patients would most want to avoid were also assessed as part of the survey, thus highlighting the need for treatments that themselves have minimal disruption on patient's health (i.e. avoidance of AEs) and normal activities.

Across all three studies, it is clear that longer remission, increased life expectancy and reduced symptom burden are goals of therapy that are highly valued by patients with MM. Moreover, the profound impact of COVID-19, and indeed long COVID, has increased understanding amongst the general population of how debilitating fatigue can be. The increased understanding, and

societal recognition of the debilitating impact of fatigue are arguably not recognised in the valuation of health state utility estimates, and so cannot be fully captured in the HRQoL data presented in this submission.

Effect on carers

Most of the clinical management of MM is provided in the outpatient setting; therefore the bulk of care is informal and provided by carers.[54] Carers may perform complicated technical procedures (e.g. dressing changes, intravenous line care and injections), assist the patient with daily living, attend appointments and take in complex information.[54] Therefore, the detrimental effects of MM on working life are not only experienced by patients, but also their carers.[49] Family members in particular may have psychological changes related to a diagnosis of MM. Almost half (49%) of the partners of patients with MM report symptoms of anxiety and 14% report symptoms of depression.[49]

Family members can neglect their own needs while providing practical and emotional support to patients. Thus, the emotional impact experienced by carers of patients with MM further hinders their ability to work, leading to loss of productivity and missed work days which contribute to the overall economic impact of MM. Caregivers can suffer financial difficulties as a result of a relative being diagnosed with MM; they may suffer from loss of wages, difficulty in paying bills, lack of sick leave and premature use of retirement funds.[54] In addition, MM causes productivity losses, on average carers lost 104.5 working hours per year due to providing informal care.[55]

In a study carried out amongst 118 caregivers of patients with MM, negative associations between QoL and burden ($r=-0.741$, $p<0.001$), information needs ($r=-0.277$, $p=0.002$), financial needs ($r=-0.194$, $p=0.035$), emotional needs ($r=-0.505$, $p< 0.001$) and psychological morbidity ($r=-0.529$, $p<0.001$) were found. These were maintained across cargiver sex, experience in care, choice to be a caregiver, marital status, work status and patient disease stage.[56]

The unmet need in supportive care is considerable and carers have specifically reported a need for help to manage the side effects and complications experienced by patients due to treatment for MM.[49]

B.1.3.4 The importance of front-line treatment in MM

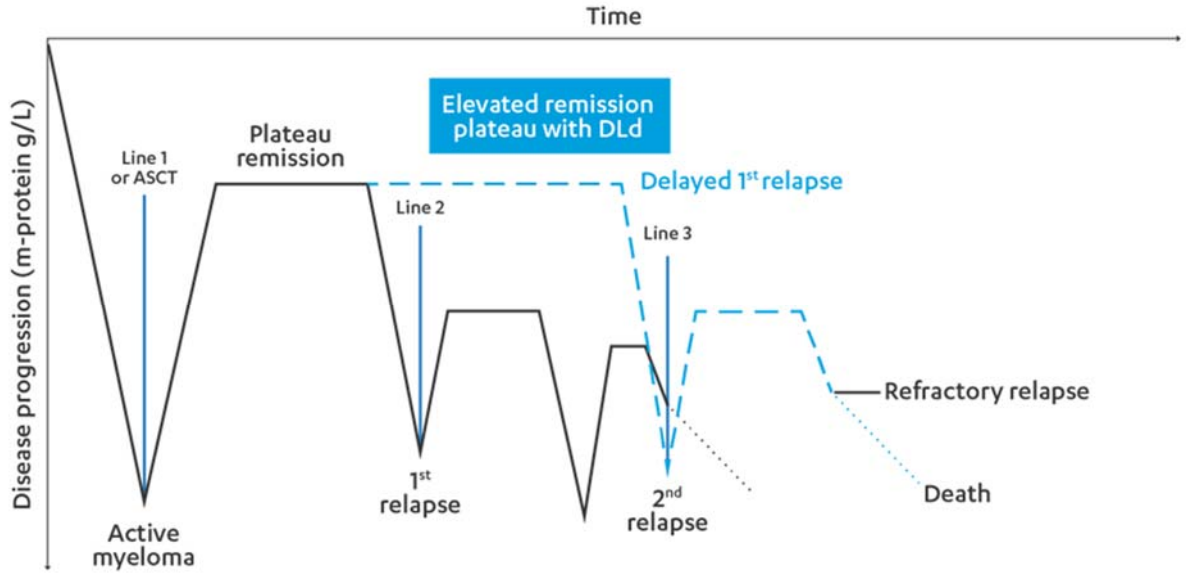
MM follows a relapsing-remitting course where all newly diagnosed patients eventually become refractory to therapy over time.[57-60] Many patients relapse because of the continued presence of resistant plasma cells in the bone marrow in the form of minimal residual disease (MRD) (see Section B.1.3.3), or they will discontinue therapy due to the cumulative burden of treatment toxicity. Moreover, each subsequent relapse holds a greater risk of additional clones arising due to genetic mutations within the myeloma cells. This confers resistance to therapy, which highlights the importance of using the most effective treatment in the front-line setting.[61] The pattern of remission and relapse in MM supports the use of continuous therapy to suppress residual disease, maximise depth of response and prolong the first remission, a key determinant of long-term outcomes.

Also, it is notable that MM becomes progressively more difficult to treat at each subsequent relapse, with each additional line of therapy associated with a shorter remission period, lower rates of deep response, and increased rates of toxicities and comorbidities (Figure 1).[26, 62, 63] This is partly due to the unfit and/or elderly nature of the transplant-ineligible population, and as such, prognosis and patients' health-related quality of life (HRQoL) for those with relapsed/refractory

disease is much poorer than those with NDMM.[34] Furthermore, patients ineligible for ASCT may not respond to salvage therapy at first relapse, or survive long enough to benefit from subsequent treatment lines.[30] This is supported by findings from a large real-world evidence (RWE) study, which included 753 patient records from the UK. This study investigated MM patient characteristics, treatment durations, outcomes and patient burden, and found that the proportion of patients ending treatment due to disease progression, toxicity or poor performance status increased with later lines of therapy.[63]

As such, the use of optimal front-line therapies is critical to maximise overall survival by inducing the deepest levels of response and stabilising the disease for as long as possible whilst maintaining HRQoL. As visualised in Figure 1, a more effective front-line treatment can extend the period of first remission, and therefore positively shift the subsequent outcomes of surviving patients. This was emphasised by clinical experts, who indicated that this may be the only treatment line that offers patients a durable response.[64]

Figure 2: Disease and treatment progression of multiple myeloma



Abbreviations: ASCT: autologous stem cell transplant; DLd: daratumumab, lenalidomide and dexamethasone.
Source: Adapted from Hajek *et al*. 2013.[65]

B.1.3.5 Depth of response and minimal residual disease (MRD)

Achieving deep and durable responses by eliminating as many clonal types as possible is one of the primary aims of treatment in the front-line setting and is associated with improved long-term outcomes for both survival and disease progression.[66]

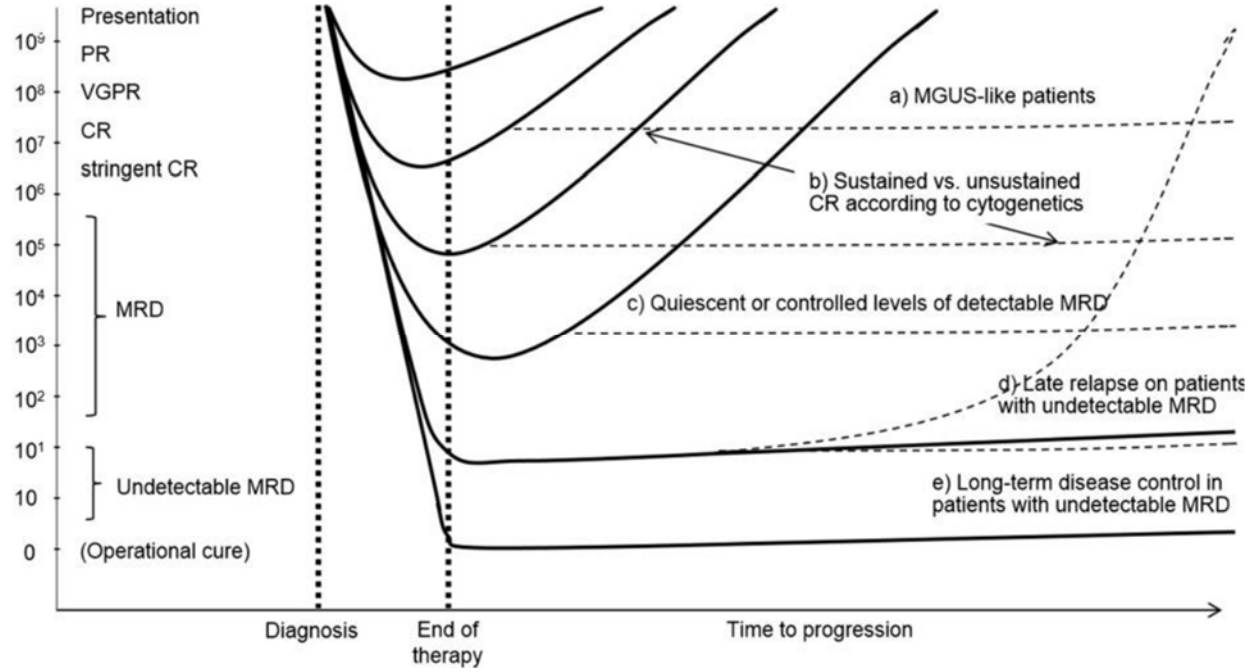
With the introduction of more effective multidrug combinations over the past 15 years, approximately 75% of patients are achieving a very good partial response (VGPR) or complete response (CR) in front-line treatment.[67] Current techniques that are used as part of the standard International Myeloma Working Group (IMWG) response criteria, are unable to identify a small but clinically relevant population of myeloma cells that persist in MM patients who appear to have achieved CR. As such, there is a need for a deeper measure of response.

MRD is the most sensitive measure of response currently available and has been recommended in the updated IMWG response assessment criteria.[68] MRD refers to a small number of cancer cells that remain in the bone marrow after achieving CR, and has been suggested to contribute to the relapse of patients with cancer.[69, 70] MRD negative status is associated with substantial improvements in PFS and OS and is therefore an important prognostic factor in patients with MM.[66, 71-73]

High sensitivity assays are needed for the detection of MRD in patients with MM. All MM patients will eventually experience relapse, therefore MRD diagnostics are essential to assessing treatment effectiveness. Because an optimal balance between treatment efficacy and toxicity is of utmost importance in unfit and/or elderly patients with MM, sensitive MRD monitoring may be particularly valuable in this patient population.[74]

Figure 3 provides a representative comparison of time to progression based on traditional measures of response and MRD.

Figure 3: Schematic representation to illustrate the depth of response in relation to PFS



Abbreviations: CR : complete response ; MGUS : monoclonal gammopathy of undetermined significance; MRD: minimal residual disease; PR: partial response; VGPR: very good partial response.
Source: Paiva *et al*. (2015).[66]

IMWG criteria for MRD

The definitions of treatment response and disease progression developed by the IMWG are widely used in clinical practice and clinical trials. A summary of the IMWG response criteria for MRD is provided in Table 3. These response criteria have been revised over the years as detection assays have become more sensitive and the understanding of the link between depth of response to therapy and long-term outcomes has evolved. The IMWG guidelines recommend that data on MRD should be obtained over the disease course, rather than at a single time point when CR is first documented, to provide a more robust evaluation of disease.[68]

Table 3: IMWG criteria for MRD

Response subcategory	Response criteria[a]

Sustained MRD negative	MRD negativity in the bone marrow confirmed ≥1 year apart by NGF, NGS, or both and by imaging (see flow MRD negative category).
Flow MRD negative	Absence of phenotypically aberrant clonal plasma cells by NGF on bone marrow aspirates using EuroFlow (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells or higher.
Sequencing MRD negative	Absence of clonal plasma cells by NGS on bone marrow aspirate Presence of a clone is defined as <2 identical sequencing reads from bone marrow aspirates using the LymphoSIGHT platform (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells or higher.
Imaging positive MRD negative	MRD negativity as defined by NGF or NGS, plus at least one of the following criteria: • Disappearance of every area of increased tracer uptake found at baseline or a preceding PET/CT. • Decrease to less mediastinal blood pool SUV. • Decrease to less than that of surrounding normal tissue.

[a]These criteria are based on those used by Zamagni and colleagues and expert panel (IMPetUs; Italian Myeloma criteria for PET Use). Baseline positive lesions were identified by presence of focal areas of increased uptake within bones, with or without any underlying lesion identified by CT and present on ≥2 consecutive slices. Alternatively, SUVmax=2.5 within osteolytic CT areas >1 cm in size, or SUVmax=1.5 within osteolytic CT areas ≤1 cm in size were considered positive. Imaging should be performed once MRD negativity is determined by multiparameter flow cytometry or NGS.
Abbreviations: CT: computed tomography; IMWG: International Myeloma Working Group; MRD: minimal residual disease; NGF: next generation flow; NGS: next generation sequencing; PET: positron emission tomography; SUV: standardised uptake value.
Source: Kumar *et al*. (2016).[68]

B.1.3.6 Treatment guidelines

Treatment guidelines for the management of MM are available from the British Society of Haematology (BSH), European Haematology Association and European Society for Medical Oncology (EHA-ESMO), European Myeloma Network (EMN), National Comprehensive Cancer Network (NCCN) and NICE (refer to NG35).[31, 75-77]

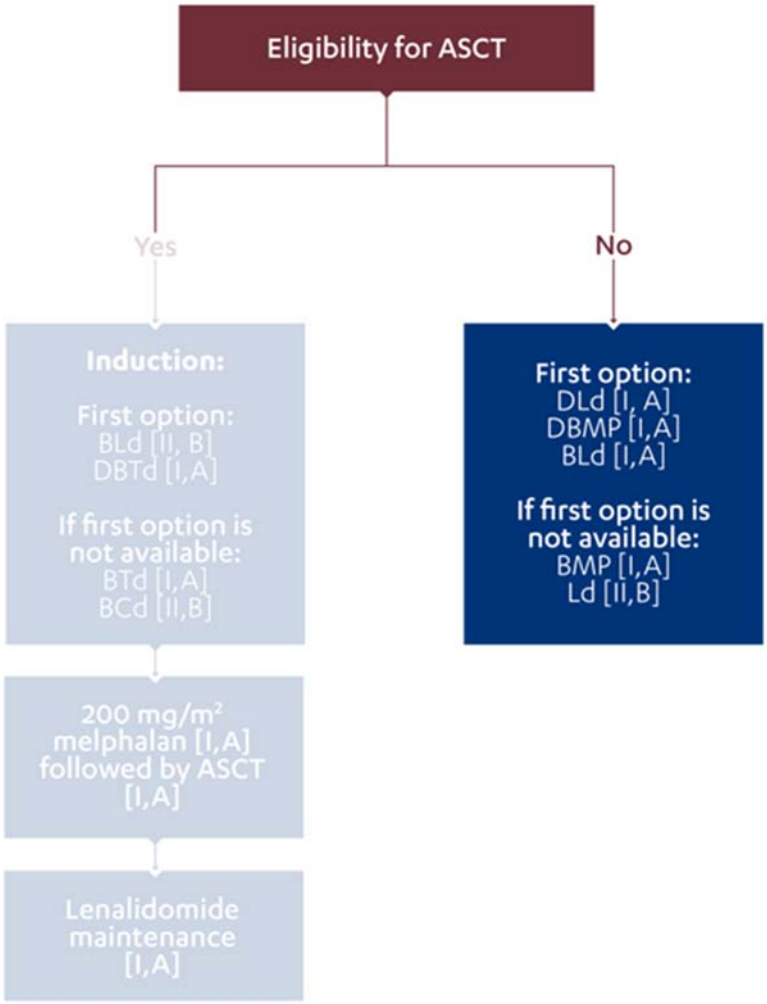
Recommended front-line treatment options are a doublet or preferably triplet regimen that includes daratumumab, a proteasome inhibitor (PI) such as bortezomib, or an immunomodulatory agent (IMiD) such as thalidomide or lenalidomide.[30, 76] Recent studies have indicated that multiple drug combinations are superior over single- or double-agent combinations in treating MM.[78, 79] Combination treatment strategies are now recommended for routine clinical practice by the IMWG.[68]

DLd is recognosed in both national and international treatment guidelines as a front-line treatment choice for newly diagnosed transplant-inelible patients. BSH guidelines published in 2021 recommend DLd, noting the improved response rates and PFS rates providing evidence of benefit.[80]

Furthermore, updated EHA-ESMO guidelines state that DLd is recommended as a first option for ASCT-ineligible patients, based on strong evidence for efficacy with a substantial clinical benefit

(Grade A).[81] Other first option treatments recommended by EHA-ESMO for transplant-ineligble NDMM include daratumumab, bortezomib, melphalan and prednisone (DBMP) and bortezomib, lenalidomide and dexamethasone (BLd; Figure 4).[27] None of the EHA-ESMO recommended first options for ASCT-ineligible patients are currently available in the UK.

Figure 4: EHA-ESMO guidelines for front-line treatment of symptomatic MM



Abbreviations: ASCT: autologous stem cell transplant; BCd: bortezomib, cyclophosphamide and dexamethasone; BLd: bortezomib, lenalidomide and dexamethasone; BMP: bortezomib, melphalan and predisone; BTd: bortezomib, thalidomide and dexamethasone; DBMP: daratumumab, bortezomib, melphalan and prednisone; DBTd: daratumumab, bortezomib, thalidomide and dexamethasone; DLd: daratumumab, lenalidomide and dexamethasone; EHA-ESMO: European Haematology Association and European Society for Medical Oncology; Ld: lenalidomide and dexamethasone.
Source: Dimopoulos *et al.* 2021.[27]

B.1.3.7 Description of the clinical care pathway

NDMM patients are typically categorised into two subpopulations usually defined by their fitness and suitability for the subsequent approach to treatment. 'Fitter' patients typically receive an induction/consolidation regimen followed by treatment with high-dose chemotherapy and ASCT. For those patients not considered suitable for transplant, longer-term treatment with multi-agent

combinations including alkylators, high-dose steroids, and novel agents are currently considered as standards of care.

Despite recent therapeutic advances in the treatment of MM and the availability of multiple treatment options for relapsed disease, there remain limited treatment options available in England for patients with NDMM who are ineligible for ASCT. Treatment can broadly be divided into three categories: lenalidomide-based (Ld) regimens, bortezomib-based regimens (e.g. BMP, BCd), and thalidomide-based (e.g. MPT, CTd) regimens.

NICE recommends the following options for the front-line treatment of ASCT-ineligible MM (Table 4):[31]

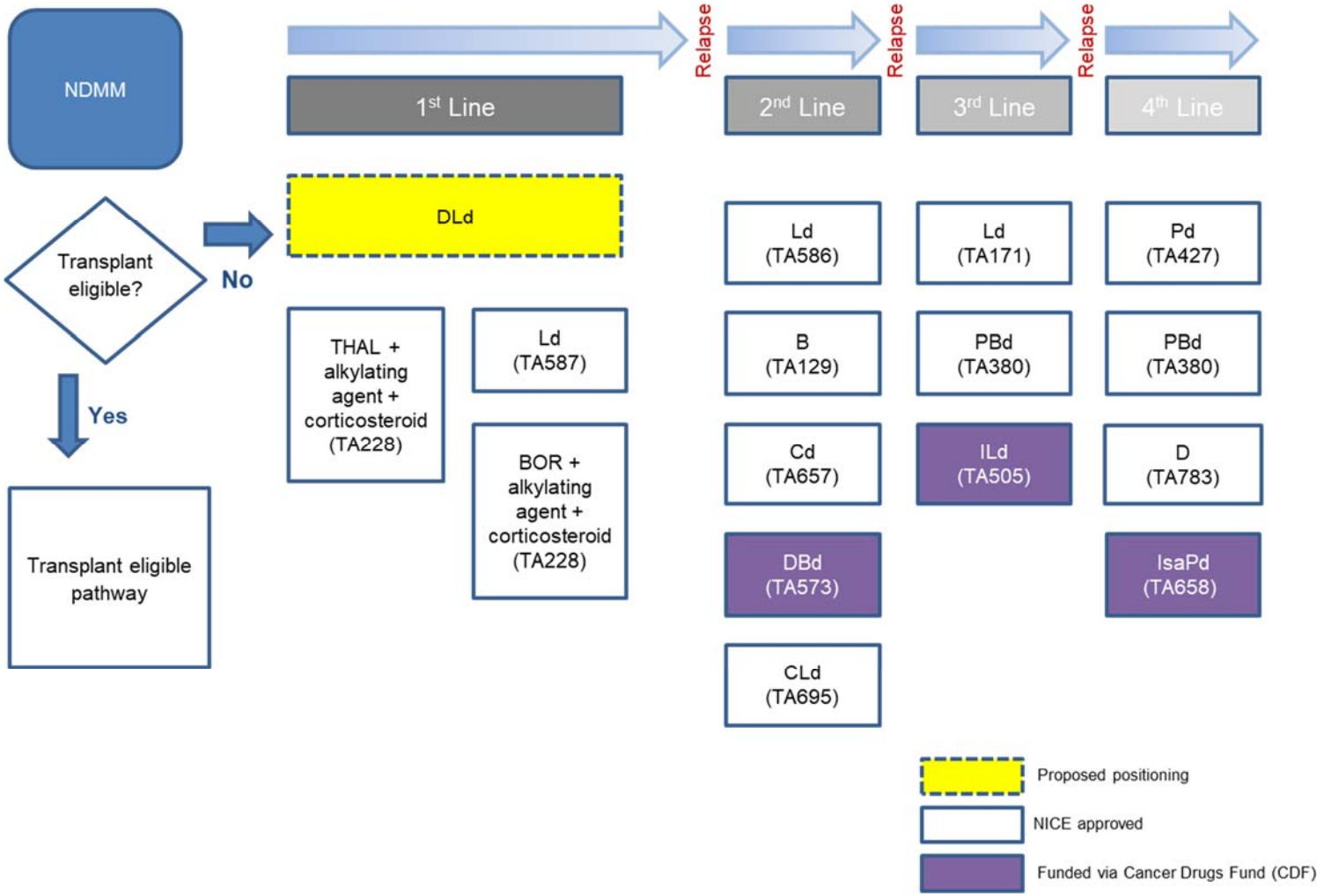
Table 4: NICE recommendations for front-line ASCT-ineligible MM

	Title	Date	Summary
NICE TA587[4]	Ld for previously untreated multiple myeloma	2019	Ld is recommended as an option for previously untreated MM in adults who are not eligible for a stem cell transplant, only if: • thalidomide is contraindicated (including for pre-existing conditions that it may aggravate) or; • the person cannot tolerate thalidomide, and; the company provides lenalidomide according to the commercial agreement.
NICE MTA No. 228[82]	Bortezomib and thalidomide for the front-line treatment of multiple myeloma	2011	Bortezomib in combination with an alkylating agent and a corticosteroid is recommended as an option for the front-line treatment of multiple myeloma if high-dose chemotherapy with ASCT is considered inappropriate and the person is unable to tolerate or has contraindications to thalidomide.
			Thalidomide in combination with an alkylating agent and a corticosteroid is recommended as an option for the front-line treatment of multiple myeloma in people for whom high-dose chemotherapy with ASCT is considered inappropriate.

Abbreviations: ASCT: autologous stem cell transplant; Ld: lenalidomide and dexamethasone; MM: multiple myeloma; MTA: multiple technology appraisal; NICE: National Institute for Health and Care Excellence.

The proposed positioning of DLd, as well as the current NHS MM treatment pathway, can be found below in Figure 5.

Figure 5: Current UK NHS MM treatment pathway



Abbreviations: ASCT; autologous stem cell transplant; B: bortezomib; Bd: bortezomib and dexamethasone; BCd: bortezomib, cyclophosphamide and dexamethasone; BTd: bortezomib, thalidomide and dexamethasone; Cd: carfilzomib and dexamethasone; CDF: Cancer Drugs Fund; D: daratumumab; DBd: daratumumab, bortezomib, and dexamethasone; DBTd: daratumumab, bortezomib, thalidomide and dexamethasone; HDT: high-dose therapy; ILd: ixazomib, lenalidomide and dexamethasone; ITT: intention-to-treat; Ld: lenalidomide and dexamethasone; NDMM: newly diagnosed multiple myeloma; NICE: National Institute for Health and Care Excellence; PBd: panobinostat, bortezomib and dexamethasone; Pd: pomalidomide and dexamethasone.

Ld represents current NHS SoC in the NDMM transplant-ineligible population. Feedback from a clinical advisory meeting held in March 2022 indicated that Ld is the current SoC in England, accounting for 60% of the proportion of patients in England currently receiving treatment, as supported by HARMONY IQVIA data, reporting 55% Ld usage.[3] Given the benefit of an oral administration, the usage of Ld for this population has increased during the COVID-19 pandemic and clinicians do not expect this to reverse.[64]

Bortezomib in combination with an alkylating agent and a corticosteroid is used in a minority of patients, with use decreasing following the availability of oral Ld in 2019, and throughout the COVID-19 pandemic.

Bortezomib is licensed in combination with melphalan and prednisone (BMP), based on the findings from the VISTA study. The VISTA study demonstrated significant improvements in both time to progression and overall survival for BMP, compared to MP alone.[83] In addition to BMP, BCd is an alternative bortezomib-based combination. Although BCd is not licensed, this bortezomib combination is sometimes used in UK clinical practice.[84] Bortezomib-based combinations (BMP and [as a scenario] BCd) are included as comparators based on expert opinion and clinical guidelines.[3, 80] Thalidomide-based regimens are not considered as relevant comparators due to very low usage nationally, but comparisons versus thalidomide based regimens are provided for completeness.[3]

Current treatments remain associated with known safety and tolerability issues which, along with patient factors such as comorbidities, may affect treatment choice for individual patients.[85] Given that the majority of ASCT-ineligible MM patients are unfit and/or elderly, often presenting with multiple comorbidities, there is an unmet need for an effective treatment option that does not confer additional toxicity.

B.1.3.7.1 Future clinical pathway

Access to DLd in the front-line transplant-ineligible setting is important to optimise clinical outcomes for newly diagnosed MM patients with the highest unmet need and imperative to build the foundation for the future myeloma pathway in the UK.

Early usage of daratumumab in the UK MM pathway is pivotal for future innovation in MM. In particular, it will mean UK myeloma patients in the relapsed setting will be eligible for participation in new clinical trials studying future innovations in anti-CD38 exposed patients.

Current clinical trials investigating novel immunological options such as bispecifics, are investigating relapsed disease where patients are triple class exposed, including CD38 monoclonal antibody (mAb). For example, multiple studies of early stage MM compounds (MajesTEC-1, KarMMa-2, KarMMa-3, NCT05137054 and studies of REGN5458 and TNB-383B) have trial inclusion criteria which stipulates prior therapy including an anti-CD38 mAb.[86-90]

Conversely, the absence of an anti-CD38 treatment in newly diagnosed, transplant ineligible MM patients will severely curtail future options for patients both in terms of enrolment into clinical trials and in terms of access to therapies whose marketing authorisations will specify anti-CD38 exposure. This benefit of having access to DLd is not captured in the QALY framework.

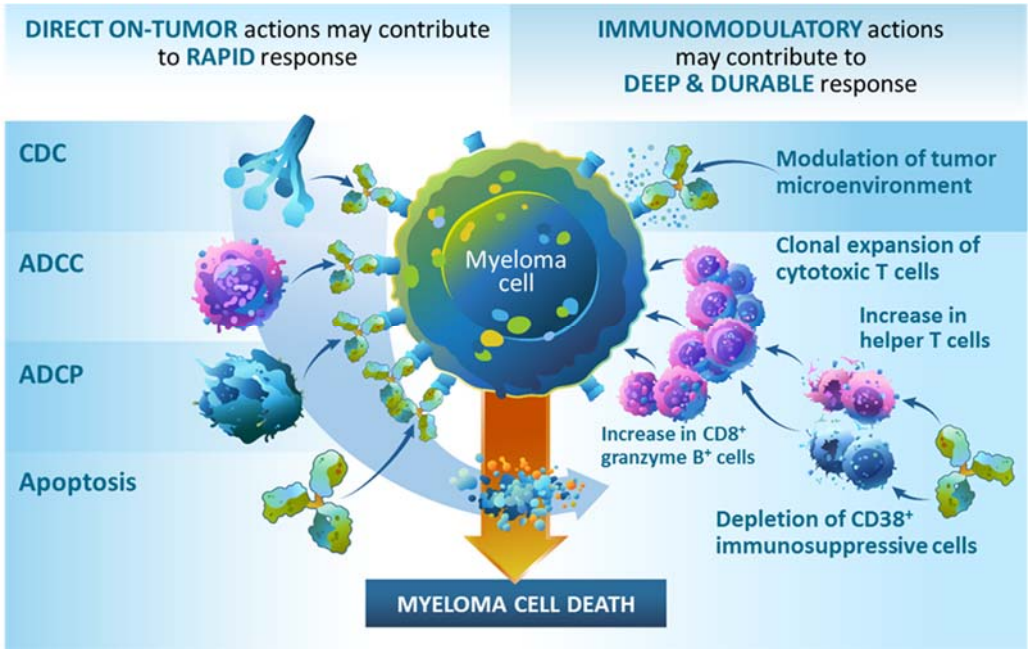
In addition, published analyses looking at treatment sequences have suggested that starting with DLd in patients with NDMM who are ASCT-ineligible may provide up to 3.5 years of additional OS gain with the currently available 2L treatments, compared to reserving for later usage.[91] The

additional mean OS benefit was consistently more than 2 years, when DLd was used first. This gain could increase with new agents currently in development, reinforcing the importance of using the best agents first, to increase the probability of patients benefitting from treatments currently in development.

B.1.3.8 Daratumumab in combination with lenalidomide

Daratumumab is a first-in-class, fully human IgG1κ mAb that binds to CD38, a protein that is overexpressed on the surface of MM cells. It works by targeting the tumour directly and indirectly, as well as uniquely modulating the immune system in a way that is not typically seen in monoclonal antibodies; put simply, it boosts patients' immune system.[10, 11] It is the combination of these direct and indirect immunomodulatory effects that explain the step-change in efficacy for this indication observed with daratumumab.

Figure 6: The multiple mechanisms of action of daratumumab



Abbreviations: ADCC: antibody-dependent cell-mediated cytotoxicity; ADCP: antibody-dependent cellular phagocytosis; CDC: complement-dependent cytotoxicity.

CD38 is a distinct and novel target from those of other approved agents for multiple myeloma (MM) due to its universal expression in plasma and myeloma cells. This universal expression not only allows daratumumab to induce myeloma cell death through multifactorial mechanisms (see above), but also means daratumumab is effective, irrespective of clonal heterogeneity. Given it's distinctness from other approved agents, together with its high efficacy and favourable safety profile, daratumumab is an ideal candidate for combination therapy.

Clonal heterogeneity is a consequence of the genetically complex nature of MM, which develops from the continued accumulation of genetic abnormalities over time. This results in sub clones of plasma cells with considerable genetic heterogeneity that contribute to the progression of MM and the development of drug resistance.[21, 92-94]

One of the challenges of treatment to date has been to find options that effectively target and eliminate all clonal and subclonal mutations – clones that remain following treatment will re-populate the disease via clonal expansion and evolution. The concept of clonal heterogeneity

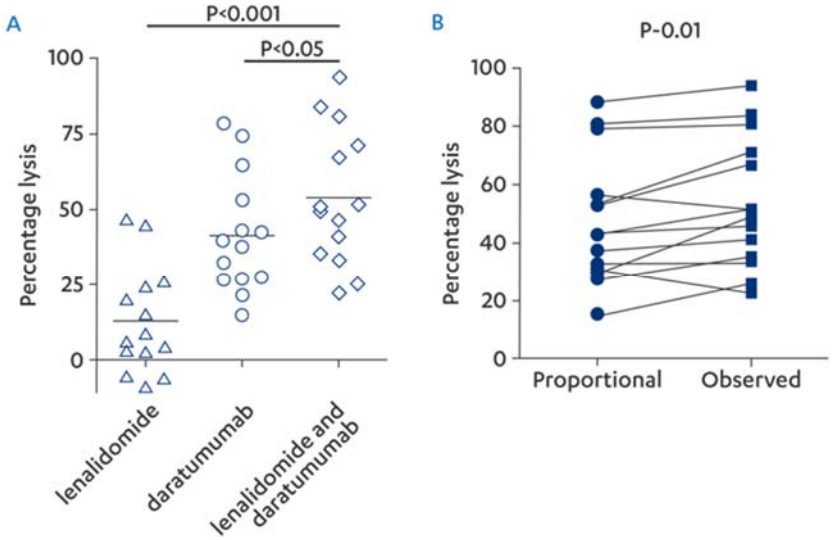
contributing to disease progression in MM led to the strategy of adopting combination therapies to eradicate both the dominant and minor clones.

Contingent on the premise that the combined agents have non-overlapping and synergistic mechanism of actions, the immediate and effective targeting of the tumours with multiple agents has been a successful strategy in improving the clinical outcome of MM therapy. Such a strategy is in agreement with the emerging concept that the genetic signature of MM, and consequently the patient's susceptibility to a specific agent, will be highly heterogeneous, which may lead to drug resistance. Nevertheless, the CR rate of the best chemotherapeutic combination is currently <50%, and all current combination therapies eventually induce drug resistance.[95]

Lenalidomide is an immunomodulatory (IMiD) agent that is thought to mediate antimyeloma activity by three main mechanisms: 1) direct antitumour effect; 2) inhibition of the microenvironment support for tumour cells; and 3) an immunomodulatory role.[96] Direct tumour effect is described both as growth inhibition of myeloma cell lines and induction of apoptosis. The microenvironment support is affected by downregulation of cell adhesion molecules (e.g. intercellular adhesion molecule), thus inhibiting stromal cell interaction with tumour cells, and inhibition of growth factors (e.g. insulin growth factor 1 and vascular endothelial growth factor) induced by myeloma cell adhesion. Finally, lenalidomide exhibits immunomodulatory activity including inhibition of proinflammatory signalling molecules (cytokines) such as tumour necrosis factor α, IL-1β, and IL-6, the latter of which is a known growth factor for myeloma cells.[97] Importantly, it has also been shown that lenalidomide causes upregulation of natural killer (NK) cells in myeloma,[96] and enhances the effector cells of ADCC.[98, 99]

When compared with lenalidomide alone, daratumumab and lenalidomide have demonstrated a powerful combined effect, which mediates the lysis of MM cells (Figure 7A). A mixed model analysis revealed that daratumumab and lenalidomide act in a synergistic fashion to induce lysis in 20% more MM cells than when compared with the expected additive effects of each agent alone (Figure 7B).[79, 100, 101]

Figure 7: Improvement of daratumumab-induced ADCC by lenalidomide in bone marrow mononuclear cells from patients with MM



(A) Bone marrow mononuclear cells of 14 patients with MM were incubated for 47 hours with the control antibody, with lenalidomide (3 μM) and/ or daratumumab (0.1 μg/mL). Surviving MM cells were enumerated by Fluorescence-activated Cell Sorting analysis of CD138+ cells. The percentages of lysis of MM cells treated with lenalidomide, daratumumab and Ld were calculated by the Tukey's post hoc analysis of repeated measures analysis of variance.
(B) The observed effect (% lysis) of the combination treatment was compared with the expected additive effect (proportional) of the combined treatments. Mixed model analysis supported the conclusion that the combination treatment was synergistic.
Abbreviations: ADCC: antibody dependent cell mediated cytotoxicity; Ld: lenalidomide and daratumumab; MM: multiple myeloma.
Source: Van der Veer *et al.* 2011.[100]

Additionally, the specific combination of DLd has also demonstrated strong efficacy in the relapsed/refractory MM setting. The POLLUX study demonstrated a statistically significant and clinically meaningful improvement in OS with DLd versus Ld, after more than 6 years of median follow up.[81]

B.1.4 *Equality considerations*

There is one equality issue related to the use of daratumumab combination therapy (i.e. DLd) for the treatment of patients with NDMM who are ineligible for ASCT.

In the younger, newly diagnosed, transplant-eligible patient population, patients have the opportunity to receive effective treatments, often resulting in prolonged remission, and the consequent potential for improved prognosis. Standard of care treatments in the transplant eligible population include induction, for example with daratumumab plus bortezomib, thalidomide and dexamethasone (DBTd) (TA763), followed by high dose chemotherapy, ASCT, consolidation, and maintenance therapy. This standard of care in the transplant eligible setting is highly effective and can significantly improve prognosis for these patients.

In contrast, newly diagnosed patients who are classified as ineligible for ASCT currently have an inequity in access to highly effective treatments. Currently, only lenalidomide and bortezomib based regimens are available to these patients, with thalidomide not considered suitable for the majority of patients. There is therefore an urgent need for access to novel effective treatments which can result in prolonged remission for patients with newly diagnosed MM who are ineligible for ASCT. Access to DLd for these patients can help to address an avoidable health inequity, where ASCT ineligible patients fail to receive novel highly effective treatments, compared to the transplant eligible population.

B.2 Clinical effectiveness

Summary of clinical effectiveness

- The efficacy and tolerability of DLd versus Ld in patients with NDMM who are ASCT-ineligible was assessed in a randomised, open-label, active controlled, parallel-group, multicentre, Phase III clinical trial, MAIA (MMY3008).[102]
- This submission primarily focuses on the most recent results for the MAIA trial with a clinical cut-off of 21st October 2021 (64.5 months [>5 years] median follow-up).
- Eligible patients were randomised to receive either DLd (n=368), or Ld (n=369), the latter of which represents the main comparator for this submission.[102]
- Baseline characteristics were balanced between arms, with a trial population generalisable to the UK population.[8]
- DLd provides groundbreaking efficacy in patients with NDMM who are ASCT-ineligible, compared with Ld:
  - Risk of disease progression or death was significantly lowered by 45% for patients treated with DLd compared with those receiving Ld (HR: 0.55; 95% CI: 0.45, 0.67; [redacted]).[102]
  - Risk of death was significantly decreased by 34% for patients treated with DLd compared with those receiving Ld (HR: 0.66; 95% CI: 0.53, 0.83; [redacted]).[102]
  - The median PFS was nearly two-fold greater among patients treated with DLd compared with those receiving Ld (61.9 months versus 34.4 months). The median PFS for patients treated with DLd is broadly similar to the median OS for patients treated with Ld (65.5 months), which demonstrates the outstanding added benefit of DLd compared to Ld.[102]
  - Deeper responses were achieved in patients treated with DLd versus Ld, with improved ≥CR rates in the DLd group compared to the Ld group ([redacted] versus [redacted]).[102]
  - The MRD negativity rate at 10^{-5} was significantly higher (p<0.0001) and approximately [redacted] for the DLd group ([redacted]) compared with the Ld group ([redacted]) (odds ratio [OR]: [redacted]), with patients achieving MRD negativity in the DLd group resembling general population mortality (GPM).[102]
  - Patients in the DLd group demonstrated significantly higher sustained MRD negativity as per the IMWG criteria, at the sensitivity threshold of 10^{-5}, compared with the Ld group ([redacted] versus [redacted], OR: [redacted]; 95% CI: [redacted]).[102]
- Greater improvement in HRQoL was observed in the DLd group with clinically meaningful improvement across key scales such as global health status, pain symptoms, and VAS.[102]
- DLd has a well characterised safety profile with proportionally fewer treatment discontinuations due to AEs compared with Ld ([redacted] versus [redacted], respectively). The observed safety profile of DLd in patients with front-line ASCT-ineligible NDMM is consistent with previous studies of daratumumab and combination therapy.[102]

B.2.1 *Identification and selection of relevant studies*

Three systematic literature reviews (SLRs), one each on randomised controlled trials (RCTs), single-arm trials, and observational RWE study, were conducted to identify the relevant clinical efficacy and safety data for DLd (and comparators) as a treatment for patients with NDMM who

are ineligible for ASCT (refer to Appendix D where the full SLR methodology and results are presented).

One RCT was identified, MMY3008 (MAIA), that included patients with NDMM who are ineligible for ASCT receiving DLd, with results from the second interim analysis (data cut-off 24th September 2018) reported in Facon *et al*. (2019).[103] This also served as the primary PFS analysis. Updated results from a subsequent interim analysis, which served as the primary OS analysis (data cut-off 19th February 2021) have been reported in Facon *et al*. (2021).[104] The key results presented in this submission are from the most recent efficacy and safety analysis (data cut-off 21st October 2021, which are shortly to be included in the SmPC). In addition to the published evidence sources, the following non-published evidence from MAIA have also been included within this submission:

- The IA2 trial Clinical Study Report (CSR) (2019)[8]
- The Health Economics, Market Access & Reimbursement (HEMAR) Report, October 2021 Data-Cut (2022)[9]
- The CSR reporting the October 2021 Data-Cut (2022)[102]

B.2.2 *List of relevant clinical effectiveness evidence*

MAIA (NCT02252172) is an ongoing, randomised, open-label, active controlled, parallel-group, multicentre, Phase III clinical trial that enrolled patients at 176 hospitals in 14 countries across North America, Europe, the Middle East, and the Asia-Pacific region (see B.2.3.1). Evidence from the MAIA trial was used as the primary source of data to support the use of DLd in this indication in the marketing authorisation application to the European Medicines Agency (EMA).

Clinical inputs used in the cost-effectiveness model were derived from the MAIA trial (refer to Section B.3.3).

Table 5: Clinical effectiveness evidence

Study	MAIA (NCT02252172)
Study design	• Randomised, open-label, active-controlled, parallel-group, multicentre, Phase III study. • Patients were randomised in a 1:1 ratio to treatment Arm A (Ld) or treatment Arm B (DLd).
Population	Adult patients with previously untreated MM who are ineligible for ASCT.
Intervention(s)	Patients in the DLd arm (n=368), received: • Daratumumab 16 mg/kg administered by IV infusion weekly for eight weeks (Cycles 1 to 2), then every other week for 16 weeks (Cycles 3 to 6), then every four weeks (Cycle 7 and beyond). • Lenalidomide 25 mg orally on Days 1 through 21 of each 28-day cycle (10 mg every 24 hours for patients with creatinine clearance 30 to 50 mL/min). • Dexamethasone 40 mg on Days 1, 8, 15 and 22 of each cycle (patients >75 years of age or with body mass index <18.5 kg/m^2 could receive 20 mg weekly). Patients continued treatment until disease progression or unacceptable toxicity.

Comparator(s)	Patients in the Ld arm (n=369), received: • Lenalidomide 25 mg orally on Days 1 through 21 of each 28-day cycle (10 mg every 24 hours for patients with creatinine clearance 30 to 50 mL/min). • Dexamethasone 40 mg on Days 1, 8, 15 and 22 of each cycle (patients >75 years of age or with body mass index <18.5 kg/m^2 could receive 20 mg weekly). Patients continued treatment until disease progression or unacceptable toxicity.		
Indicate if trial supports application for marketing authorisation	Yes	**Indicate if trial used in the economic model**	Yes
Rationale if study not used in model	MAIA represents the primary source of efficacy and safety data for DLd in this indication. Data reported from MAIA are relevant to the decision problem and have been used in the health economic model.		
Reported outcomes specified in the decision problem	**Primary outcome:** • **Progression-free survival (PFS)**, defined as the duration from the date of randomisation to either progressive disease, or death, whichever occurred first. Disease progression was determined according to the IMWG criteria. For patients who had not progressed and were alive, data were censored at the last disease evaluation before the start of any subsequent anti-myeloma therapy. Relapse from CR by positive immunofixation or trace amount of M-protein was not considered to be progressive disease and was not included in the PFS calculation. **Secondary outcomes:** • **Overall survival (OS)**, measured from the date of randomisation to the date of the patient's death. If the patient is alive or the vital status is unknown, then the patient's data is censored at the date the patient was last known to be alive. • Progression-free survival on next line of therapy (PFS2), defined as the time from randomisation to progression on the next line of treatment or death, whichever comes first. Disease progression is based on investigator judgment. For those patients who are still alive and not yet progressed on the next line of treatment, they are censored on the last date of follow-up. • Time to next treatment, defined as the time from randomisation to the start of the next-line treatment. • Time to response, defined as the time between the randomisation and the first efficacy evaluation that the patient has met all criteria for CR or PR. For patients without response (CR/PR), data is censored either at the date of progressive disease or, in the absence of progressive disease, at the last disease evaluation before the start of subsequent anti-myeloma therapy. • Duration of response (DOR), calculated from the date of initial documentation of a response (PR or better) to the date of first documented evidence of progressive disease,		

	as defined in the IMWG criteria. For patients who have not progressed, data is censored at the last disease evaluation before the start of any subsequent anti-myeloma therapy. • Time to disease progression (TTP), defined as the time from the date of randomisation to the date of first documented evidence of PD, as defined in the IMWG criteria. For patients who have not progressed, data is censored at the date of the disease evaluation before the start of any subsequent anti-myeloma therapy. • Overall response rate (ORR), defined as the proportion of patients who achieve PR or better, according to the IMWG criteria, during or after the study treatment. • Complete response (CR) rate, defined as the percentage of patients achieving CR, as defined: o Negative immunofixation of serum and urine. o Disappearance of any soft tissue plasmacytomas. o <5% PCs in bone marrow. o For those patients with negative SPEP and suspected daratumumab interference on immunofixation, a reflex assay using anti-idiotype antibody is utilised to confirm daratumumab interference and rule out false positive immunofixation. Patients who have confirmed daratumumab interference, but meet all other clinical criteria for CR or sCR, are considered CR/sCR. • Stringent complete response (sCR) rate, defined as the percentage of patients achieving CR in addition to having a normal FLC ratio and an absence of clonal cells in bone marrow by immunohistochemistry, immunofluorescence, 2–4 colour flow cytometry. • Better than very good partial response (≥VGPR), defined as the proportion of patients achieving VGPR and CR (including sCR) according to the IMWG criteria during or after the study treatment at the time of data cut-off. • Minimal residual disease (MRD) negativity rate, defined as the proportion of patients assessed as MRD negative, at any timepoint after the date of randomisation, as determined by NGS, at the sensitivity threshold of 10^{-5}, in patients achieving ≥CR. • **Health related quality of life (HRQoL),** to evaluate treatment effects on patient reported outcomes and health economic/resource utilisation. • **Adverse events (AEs),** to assess the safety and tolerability of daratumumab when administered in combination with lenalidomide.
All other reported outcomes	**Secondary outcomes:** • To evaluate clinical efficacy of DLd in high-risk molecular subgroups compared to Ld alone. • To evaluate the impact of DLd compared to Ld on patient-reported perception of global health.

	Exploratory outcomes: • To assess biomarkers predictive of response and resistance to therapy. • To assess the durability of MRD negativity.

Bold text indicates the outcome is used in the cost-effectiveness model.
Abbreviations: AE: adverse event; ASCT: autologous stem cell transplantation; CR: complete response; DOR: duration of response; DLd: daratumumab, lenalidomide and dexamethasone; HRQoL: health related quality of life; Ld: lenalidomide and dexamethasone; MRD: minimal residual disease; NGS: next generation sequencing; ORR: overall response rate; OS: overall survival; PD: progressive disease; PFS: progression-free survival; PFS2: time to progression on the next line of therapy; sCR: stringent complete response; TTP: time to progression; VGPR: very good partial response.
Source: MAIA Protocol. [Data on File]. 2016.[95]

B.2.3 *Summary of methodology of the relevant clinical effectiveness evidence*

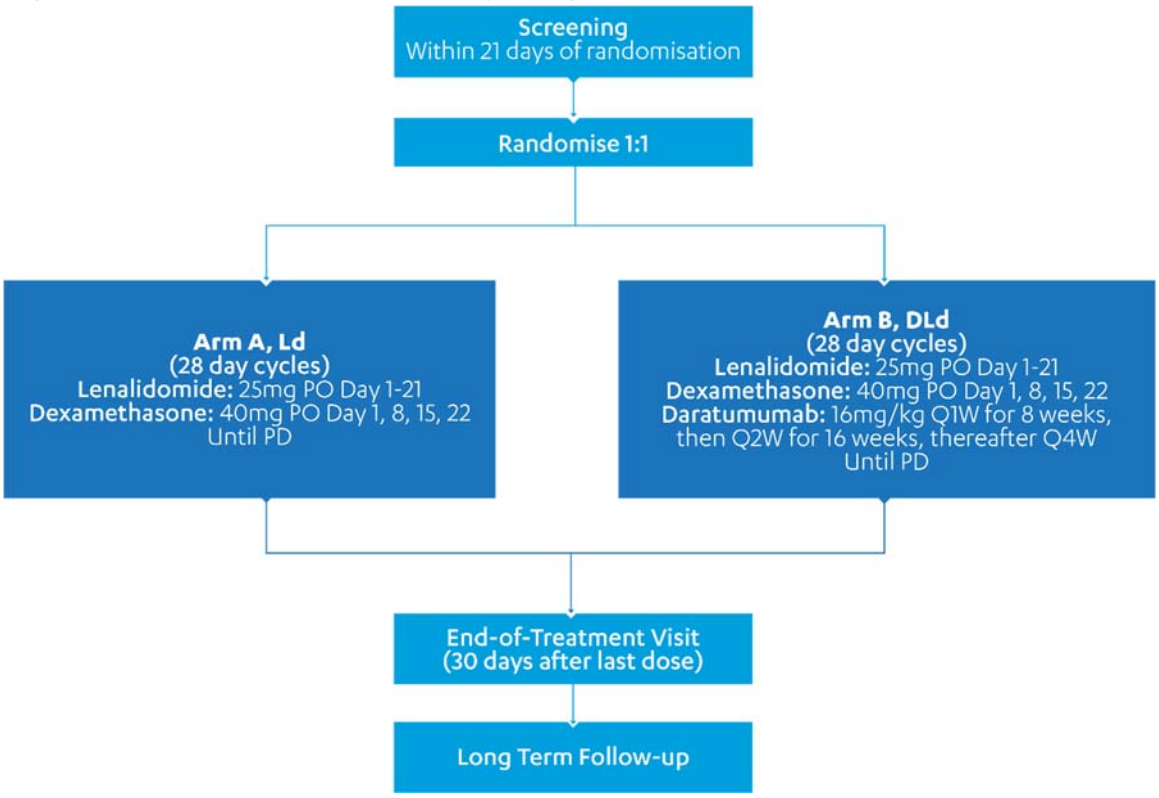
B.2.3.1 Study design

MAIA was designed to compare the efficacy of DLd with that of Ld in terms of PFS in patients with NDMM who are ineligible for ASCT. Patients eligible for inclusion in the study were aged 18 years or older, had NDMM, had an Eastern Cooperative Oncology Group (ECOG) performance status score of 0–2, and were ineligible for high-dose chemotherapy with ASCT. Patients were considered ASCT-ineligible if they were ≥65 years of age or if they were <65 years of age with comorbid conditions that would have a negative impact on tolerability to high-dose chemotherapy used in ASCT.[104] A retrospective subgroup analysis was also performed by frailty status.[105] Details of this subgroup analysis are presented in Section B.2.3.2 and Section B.2.7.1,respectively.

Eligible patients were stratified by International Staging System (ISS) (I, II or III), region (North America versus Other), and age (<75 versus ≥75 years). Patients were randomised in a 1:1 ratio to treatment Arm A (Ld) or treatment Arm B (DLd).

An overview of the MAIA study design is presented in Figure 8.

Figure 8: Overview of the MAIA study design



Abbreviations: DLd: daratumumab, lenalidomide and dexamethasone; Ld: lenalidomide and daratumumab; PD: progressive disease; PO: *per os* (oral); Q1W: every week; Q2W: every 2 weeks; Q4W: every 4 weeks.
Source: MAIA CSR (October 2021 data cut). [Data on file]. 2022.[102]

During the Treatment Phase, patients in both treatment arms received:

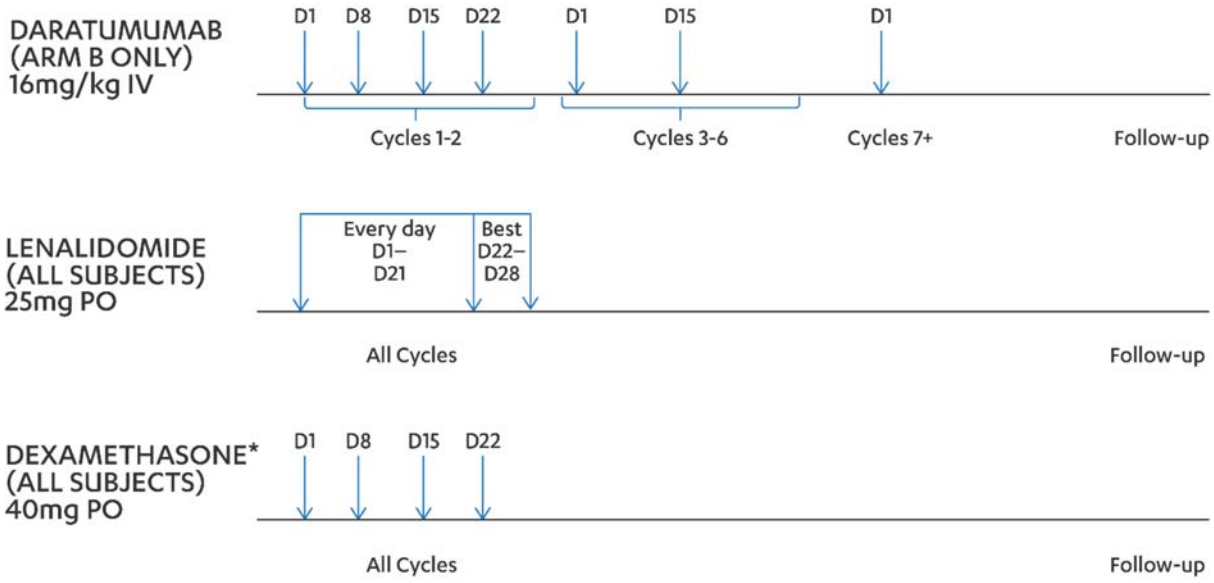
- Lenalidomide 25 mg orally on Days 1 through 21 of each 28-day cycle (10 mg every 24 hours for patients with creatinine clearance 30 to 50 mL/min)
- Dexamethasone 40 mg orally on Days 1, 8, 15 and 22 of each cycle (patients >75 years of age or with BMI <18.5 kg/m^2 could receive 20 mg weekly).

In addition, patients randomised to treatment with DLd received daratumumab 16 mg/kg weekly for eight weeks (Cycles 1 to 2), then every other week for 16 weeks (Cycles 3 to 6), then every four weeks (Cycle 7 and beyond).[8]

Patients in both treatment arms continued treatment until disease progression or unacceptable toxicity. The end of the study is planned for when 390 patients have died.

A schematic representation of the dosing schedule is provided in Figure 9.

Figure 9: Overview of MAIA dosing schedule



* On days when daratumumab was administered, dexamethasone was administered to patients in Arm B in the clinic and served as the treatment dose of steroid as well as the required pre-medication prior to daratumumab infusion.
Abbreviations: D: day; PO: *per os* (oral).
Source: MAIA Protocol. [Data on File]. 2016. Figure 4.[95]

The key study characteristics are presented in Table 6 below.

Table 6: Key study characteristics for MAIA

(Primary) Study objective	To compare the efficacy of DLd with that of Ld alone in NDMM patients ineligible for high-dose chemotherapy and ASCT in terms of prolonging PFS.
Study location	MAIA enrolled patients at 176 hospitals in 14 countries: Austria (4 sites), Australia (9 sites), Belgium (3 sites), Canada (8 sites), Denmark (3 sites), France (45 sites), Germany (14 sites), Ireland (2 sites), Israel (4 sites), Italy (4 sites), Netherlands (3 sites), Sweden (7 sites), United Kingdom (14 sites), United States (56 sites).
Study period	Study end date is planned for when 390 patients have died.
Trial design	Randomised, open-label, active controlled, parallel-group, multicentre, Phase III study.
Method of allocation	Patients were randomised in a 1:1 ratio using randomly permuted blocks (block size 4) by an interactive web response system to treatment Arm A (Ld) or treatment Arm B (DLd). The stratification factors for randomisation, comprised of ISS staging (I versus II versus III), region (North America or Other), and age (<75 versus ≥75 years).
Key inclusion criteria	• Patients ≥18 years of age. • Patients with documented MM satisfying the diagnostic criteria of CRAB, monoclonal plasma cells in the bone marrow ≥10% or presence of a biopsy proven plasmacytoma, and measurable disease. Measurable disease, as assessed by the central laboratory, is defined by any of the following: o IgG myeloma: Serum monoclonal paraprotein (M-protein) level ≥1.0 g/dL or urine M-protein level ≥200 mg/24 hours;

	○ IgA, IgM, IgD, or IgE MM: serum M-protein level ≥0.5 g/dL or urine M-protein level ≥200 mg/24 hours; ○ Light chain MM without measurable disease in serum or urine: Serum Ig FLC ≥10 mg/dL and abnormal serum immunoglobulin kappa lambda FLC ratio. • Newly diagnosed and not considered candidate for high-dose chemotherapy with ASCT due to: ○ Being ≥65 years of age. ○ In patients <65 years of age: presence of important comorbid condition(s) likely to have a negative impact on tolerability of high-dose chemotherapy with ASCT. Sponsor review of these comorbid conditions and approval required before randomisation. • Patient must have an ECOG performance status score of 0, 1 or 2. • Patient must have pre-treatment clinical laboratory values meeting the following criteria during Screening Phase: ○ Haemoglobin ≥7.5 g/dL (>5 mM/L; prior red blood cell transfusion or recombinant human erythropoietin use is permitted); ○ Absolute neutrophil count ≥1.0 x 10^9/L (granulocyte colony stimulating factor use is permitted; ○ Platelet count ≥70 x 10^9/L for patients in whom <50% of bone marrow nucleated cells are plasma cells; otherwise platelet count >50 × 10^9/L (transfusions are not permitted to achieve this minimum platelet count); ○ Aspartate aminotransferase ≥2.5 x upper limit of normal; ○ Alanine aminotransferase ≥2.5 x upper limit of normal; ○ Total bilirubin ≥2.0 x upper limit of normal, except in patients with congenital bilirubinemia, such as Gilbert syndrome (direct bilirubin ≥2.0 x upper limit of normal); ○ Creatinine clearance ≥30 mL/min (for lenalidomide dose adjustment for patients with creatinine clearance 30-50 mL/min. Creatinine clearance can be calculated using the Cockcroft-Gault formula; or for patients with over- or underweight, creatinine clearance may be measured from a 24-hours urine collection; ○ Corrected serum calcium ≤14 mg/dL (≤3.5 mM/L); or free ionised calcium ≤6.5 mg/dL (≤1.6 mM/L). A full list of inclusion criteria are presented in the MAIA Protocol.
Key exclusion criteria	• Patient has a diagnosis of primary amyloidosis, monoclonal gammopathy of undetermined significance, or smouldering MM. Monoclonal gammopathy of undetermined significance is defined by presence of serum M-protein <3

	g/dL; absence of lytic bone lesions, anaemia, hypercalcemia, and renal insufficiency related to the M-protein; and (if determined) proportion of plasma cells in the bone marrow of 10% or less. Smouldering MM is defined as asymptomatic MM with absence of related organ or tissue impairment end organ damage. • Patient has a diagnosis of Waldenström's disease, or other conditions in which IgM M-protein is present in the absence of a clonal plasma cell infiltration with lytic bone lesions. • Patient has prior or current systemic therapy or ASCT for MM, with the exception of an emergency use of a short course (equivalent of dexamethasone 40 mg/day for four days) of corticosteroids before treatment. • Patient has a history of malignancy (other than MM) within five years before the date of randomisation (exceptions are squamous and basal cell carcinomas of the skin and carcinoma in situ of the cervix, or malignancy that in the opinion of the investigator, with concurrence with the sponsor's medical monitor, is considered cured with minimal risk of recurrence within 5 years). • Patient has plasma cell leukaemia (according to WHO criterion: ≥20% of cells in the peripheral blood with an absolute plasma cell count of more than 2 × 109/L) or POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes). A full list of exclusion criteria are presented in the MAIA Protocol.
Study drugs	**In the DLd arm:** Daratumumab (16 mg/kg) was administered by IV infusion weekly on days 1, 8, 15 and 22 for two 28-day cycles, then every two weeks for the remaining induction and consolidation cycles based on treatment assignment. **In both the DLd and Ld arms:** • Lenalidomide 25 mg was administered orally on Days 1 through 21 of each 28-day cycle (10 mg every 24 hours for patients with creatinine clearance 30 to 50 mL/min) • Dexamethasone 40 mg was administered once weekly (patients >75 years of age or with body mass index <18.5 kg/m^2 could receive 20 mg weekly). Patients in both treatment arms continued treatment until disease progression or unacceptable toxicity.
Permitted and disallowed concomitant medications	Permitted concomitant medications: • Antivirals • Antihistamines • Corticosteroids • Immunostimulants • Analgesics • Antibacterials • Acid related disorders drugs • Antithrombotic agents • Bone disease drugs Prohibited concomitant medications:

	• Any other antineoplastic therapy for MM treatment • Medications that target CD38 • Clarithromycin • Systemic corticosteroids
Primary outcome	• **Progression-free survival (PFS)**
Secondary outcomes[a]	• Time to disease progression (TTP) • Complete response (CR) rate • Minimal residual disease (MRD) negativity rate • Progression-free survival on next line of therapy (PFS2) • **Overall survival (OS)** • Stringent complete response (sCR) rate • Time to next treatment • Overall response rate (ORR) • Better than very good partial response (≥VGPR) • Time to response • Duration of response (DOR) • **Health related quality of life (HRQoL)** • **Adverse events (AEs)**
Pre-specified subgroups	• Sex (male, female) • Race (white, other) • Age (<75 years, ≥75 years) • Region (North America, other) • Baseline renal function, CrCl (>60 mL/min, ≤60 mL/min) • Baseline hepatic function (normal, impaired) • ISS staging (I, II, III) • Type of MM (IgG, non-IgG) • Cytogenetic risk at study entry (high risk, standard risk) • ECOG performance score (0, 1, ≥2)
Efficacy and safety evaluations	• Efficacy outcomes for disease response and progression are based on assessments from IMWG Guidelines. • Daratumumab detection on serum immunofixation has been demonstrated in patients treated with 16 mg/kg, and may interfere with the traditional IMWG criteria of negative serum IFE for complete response or stringent complete response. To mitigate this interference, the sponsor developed a reflex assay that utilises anti-idiotype antibody to bind daratumumab and confirm its interference on IFE. • For all patients with VGPR, and a negative endogenous M-protein by serum M-protein quantitation by SPEP, reflex IFE testing is performed to confirm the presence of daratumumab on IFE. • Disease evaluations were required to be performed as outlined in the Time and Events Schedule on the scheduled assessment day (±3 days) as per the protocol. • Assessment of MRD was conducted on bone marrow samples using a validated NGS sequencing assay in accordance with the IMWG MRD guidelines. • Safety was evaluated by adverse events, laboratory test results, ECGs, vital sign measurements, physical examination findings, and assessment of ECOG performance status score. Any clinically relevant changes

	occurring during the study is recorded on the Adverse Event section of the eCRF. • Any clinically significant abnormalities persisting at the end of the study/early withdrawal was followed by the investigator until resolution or until a clinically stable endpoint is reached. • Based on the previous human experience with daratumumab, in vitro studies, and animal toxicological findings, infusion-related reactions/allergic reactions, haemolysis, and thrombocytopenia were closely monitored. As a biologic agent, immunogenicity also were monitored. • Any of the safety monitoring assessments may have been performed more frequently, and AEs were evaluated by the investigator according to the standard practice, if clinically indicated. • Blood samples were drawn for assessment of pharmacokinetic parameters, immunogenicity, and biomarker evaluations.

[a]Only the secondary outcomes presented in this submission have been included here.
Abbreviations: AE: adverse event; ASCT: autologous stem cell transplant; COPD: chronic obstructive pulmonary disease; CRAB: calcium elevation, renal insufficiency, anaemia and bone abnormalities; CR: complete response; DLd: daratumumab, lenalidomide and dexamethasone; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; FEV1: forced expiratory volume in 1 second; FLC: free light chain; IFE: immunogixation electrophoresis; Ig: immunoglobulin; HRQoL: health-related quality of life; IMWG: International Myeloma Working Group; ISS: International Staging System; IV: intravenous; Ld: lenalidomide and dexamethasone; MGUS: monoclonal gammopathy of undetermined significance; MM: multiple myeloma; MRD: minimal residual disease; NCI CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; ORR: overall response rate; OS: overall survival; PC: plasma cell; PFS: progression-free survival; POEMS: polyneuropathy, organomegaly, endocrinopathy, monoclonal protein and skin changes; PRO: patient reported outcome; sCR: stringent complete response; SPEP: serum protein electrophoresis; VGPR: very good partial response; WHO: World Health Organization.
Source: MAIA Abbreviated CSR. [Data on File] 2021;[106] MAIA Protocol. [Data on file]. 2016;[95] ClinicalTrials.gov, NCT02252172.[107]

B.2.3.2 Baseline characteristics of trial participants

Baseline patient demographics and disease characteristics are presented in Table 7. The median age in the MAIA study population was 73 years; [redacted] of patients were women. Most ([redacted]) patients were white and [redacted] of patients were black or African American.

Baseline ECOG scores of 0 or 1 were reported for 83.4% of patients. The majority of patients had serum measurable disease in IgG (61.9%) and IgA (17.8%). A total of 642 patients (87%) had a cytogenetic risk assessment, of which 92 (14.3%) patients had a high-risk cytogenetic abnormality. ISS staging was 27.3%, 43.3% and 29.4% for Stage I, II and III respectively, with a numerically higher proportion of patients classified as Stage II in the DLd (44.3%) arm compared with the Ld arm (42.3%). Clinical expert feedback suggests that the two treatment arms were generally well balanced, and that unlike any other key trials in this indication, the patients recruited to the MAIA trial included a sizeable proportion of patients over 75 years of age, reflective of the ASCT-ineligible population in clinical practice in England.[3]

Table 7: Baseline patient demographics and disease characteristics in the MAIA trial (ITT population)

Characteristic	DLd (n=368)	Ld (n=369)	Total (n=737)
Sex (female), n (%)	179 (48.6)	174 (47.2)	353 (47.9)
Age, years, n (%)			

<65	4 (1.1)	4 (1.1)	8 (1.1)
65–<70	74 (20.1)	73 (19.8)	147 (19.9)
70–<75	130 (35.3)	131 (35.5)	261 (35.4)
≥75	160 (43.5)	161 (43.6)	321 (43.6)
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	73.0	74.0	73.0
Range	(50, 90)	(45, 89)	(45, 90)
Race, n (%)			
White	[redacted]	[redacted]	[redacted]
Black or African American	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]
Native Hawaiian or other pacific islander	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]
Not reported	[redacted]	[redacted]	[redacted]
Weight (kg), n (%)			
<50	[redacted]	[redacted]	[redacted]
50–< 65	[redacted]	[redacted]	[redacted]
65–< 85	[redacted]	[redacted]	[redacted]
≥ 85	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]
Baseline ECOG score, n (%)			
0	127 (34.5)	123 (33.3)	250 (33.9)
1	178 (48.4)	187 (50.7)	365 (49.5)
2	63 (17.1)	59 (16.0)	122 (16.6)
Type of measurable disease,[a] n (%)			
IgG	225 (61.1)	231 (62.6)	456 (61.9)
IgA	65 (17.7)	66 (17.9)	131 (17.8)
Other[a,b]	9 (2.4)	10 (2.7)	19 (2.6)
Urine only	40 (10.9)	34 (9.2)	74 (10.0)
Serum FLC only	29 (7.9)	28 (7.6)	57 (7.7)
ISS staging,[c] n (%)			
I	98 (26.6)	103 (27.9)	201 (27.3)
II	163 (44.3)	156 (42.3)	319 (43.3)
III	107 (29.1)	110 (29.8)	217 (29.4)
Revised ISS staging,[d] n (%)			
I	[redacted]	[redacted]	[redacted]
II	[redacted]	[redacted]	[redacted]
III	[redacted]	[redacted]	[redacted]

Cytogenetic risk,[e] n (%)			
N	319	323	642
Standard risk	271 (85.0)	279 (86.4)	550 (85.7)
High risk[f,g]	48 (15.0)	44 (13.6)	92 (14.3)
Time since initial diagnosis to randomisation (months)			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	0.95	0.89	0.92
Range	(0.1, 13.3)	(0.0, 14.5)	(0.0, 14.5)

[a] Includes patients without measurable disease in serum and urine.
[b] Includes IgD, IgM, IgE and biclonal.
[c] ISS staging is derived based on the combination of serum β2-microglobulin and albumin.
[d] Determination is based on three factors: International Staging System (ISS); presence of chromosomal abnormalities of t(4; 14), t(14; 16), or del17p by FISH or Karyotype testing and serum lactate dehydrogenase (LDH) at baseline.
[e] Cytogenetic risk is based on FISH or karyotype testing.
[f] Patient may have had at least one high-risk abnormality [del17p, t(4;14) or t(14;16)].
[g] High risk is defined as positive for any of del17p, t(14;16) or t(4;14) by FISH/Karyotype.
Abbreviations: DLd: daratumumab-lenalidomide-dexamethasone; FLC; free light chain; ISS; International Staging System; ITT: intention to treat; MM; multiple myeloma.
Source: Facon *et al*. (2021). Table 1;[104] Facon *et al.* (2019). Table 1;[103] MAIA CSR (September 2018 data cut). [Data on File]. 2019. Table 3.[8]

B.2.4 *Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence*

B.2.4.1 Study population and patient disposition

For the MAIA study, a total of 737 patients (DLd: 368; Ld: 369) were randomised between 10th March 2015 and 24th September 2018 at 176 centres in 14 countries (Table 6).[104] 14 sites were located in the UK, across 12 locations: Aberdeen, Canterbury, Dundee, Leeds, London, Manchester, Nottingham, Oxford, Plymouth, Southampton, Truro and Wolverhampton.[106, 108] The patient flow is shown in Figure 10.

Eight patients (four patients in each treatment group) were randomised but did not receive treatment. Of these patients, two patients (both in the DLd group) died of an AE before receiving treatment and the remaining six patients were not treated as they withdrew from the study prior to Cycle 1 Day 1.[104]

As of the clinical cut-off date of 21st October 2021, [redacted] patients ([redacted]) in the DLd group and [redacted] patients ([redacted]) in the Ld group discontinued treatment. The most common reason for treatment discontinuation was progressive disease ([redacted] in the DLd group and [redacted] in the Ld group). [redacted] participants in the DLd group discontinued treatment due to COVID-19 ([redacted] due to an AE; [redacted] due to death; and [redacted] due to 'other'). No patients in the Ld group discontinued treatment due to COVID-19.[102]

Figure 10: Participant flow in the MAIA Study

Source: MAIA CSR (October 2021 data cut). [Data on file]. 2022.[102]

The study populations used for the analysis of outcomes from the MAIA trial are presented in Table 8. The efficacy outcomes presented in this submission are based on the intention-to-treat (ITT) analysis set, which includes all randomised participants. Safety outcomes are presented for the population of all treated patients. DOR outcomes are presented for the response-evaluable population, which includes all patients with MM and measurable disease at baseline, who received at least one component of the study and have adequate post-baseline disease assessments.[95]

Table 8: Summary of data sets analysed

Study population	Description	DLd (n)	Ld (n)
ITT analysis set	Included all randomised patients.	368	369
Safety analysis set	Included all randomised patients who received at least one dose of study drug and contributed any safety data after the start of study treatment.	364	365
Response-evaluable analysis set	Included all patients who have a confirmed diagnosis of MM and measurable disease at baseline or screening, have received at least one component of study treatment and have adequate post-baseline disease assessments.	■	■

Abbreviations: DLd: daratumumab, lenalidomide and dexamethasone; Ld: lenalidomide, and dexamethasone; ITT: intention-to-treat; MM: multiple myeloma.
Source: MAIA CSR (September 2018 data cut). [Data on File]. 2019. Tables 3, 5 and 10.[8]

B.2.4.2 Statistical analyses

Details of the statistical methods for the Primary Analysis for MAIA are presented Table 9.

Table 9: Statistical methods for the Primary Analysis for MAIA

Hypothesis objective	The primary efficacy analysis was performed by testing the null hypothesis that there was no difference in the PFS rate between DLd and Ld in patients with newly diagnosed MM who are eligible for ASCT.
Statistical analysis	**Primary endpoint: PFS** For the primary endpoint of PFS, the Primary Analysis consisted of a stratified log-rank test for the comparison of the PFS distribution between the two treatment arms. The Kaplan-Meier method was used to estimate the distribution of overall PFS for each treatment. The treatment effect hazard ratio (HR) and its two-sided 95% CIs were estimated using a stratified Cox regression model with treatment as the sole explanatory variable. **Secondary and exploratory endpoints** The distribution of OS for the two treatment groups were compared based on a log-rank test stratified with ISS staging (I, II, III), region (North America versus Other), and age (<75 years versus ≥75 years) as randomised. The HR and its 95% CI were estimated based on a Cox proportional hazards model with treatment as the sole explanatory variable and stratified with ISS staging (I, II, III), region (North America versus Other), and age (<75 years versus ≥75 years) as randomised. A HR<1 indicates an advantage for DLd. A modified linear alpha spending function was performed to strongly control the family-wise type I error rate at 0.05 (2-sided). The pre-specified stopping boundary was p=0.0244. Other time-to-event efficacy endpoints, including TTP, PFS2 and time to next treatment, were analysed similarly to PFS. Comparison between the two treatment arms of ORR, VGPR or better rate, CR or better rate, MRD negativity rate, and other binary endpoints were conducted using the stratified Cox regression model with treatment as the sole explanatory variable and stratified with ISS staging (I, II, III), region (North America vs. Other), and age (<75 years vs. ≥75 years) as randomised. Other time-to-event efficacy endpoints, including TTP, PFS2, OS, and time to subsequent anti myeloma treatment, were analysed similarly. DOR was analysed descriptively using the Kaplan-Meier method. Analysis of primary and secondary efficacy variables were based on the intention-to-treat (ITT) population. All safety analyses were based on the safety analysis set.
Sample size, power calculation	Approximately 730 patients (365 per group) were planned to be randomised in the MAIA study. The sample size calculation was based on the following assumption:

	• Based on the published data, the median PFS for the Ld group was assumed to be approximately 24 months. Assuming that DLd could reduce the risk of the disease progression or death by 25%, i.e., assuming an HR (DLd versus Ld) of 0.75, a total of 390 PFS events was needed to achieve a power of 80% to detect this HR with a log-rank test (two-sided alpha is 0.05). The sample size calculation took into consideration an annual dropout rate of 5%, and the planned interim efficacy analysis used the O'Brien-Fleming alpha spending function. PFS and responses were derived using the same validated computer algorithm as used in previous daratumumab studies. Long-term survival follow-up was initially planned to continue until 330 OS events or five years after the last patient was randomised, whichever occurred first. This was subsequently amended to continue until 390 deaths had been observed. The study was to achieve approximately 80% power to detect a 27% reduction in the risk of death (HR=0.73) with a log-rank test (two-sided alpha=0.05).
Data management, patient withdrawals	A patient was to be withdrawn from the study for any of the following reasons: • Lost to follow-up • Withdrawal of consent for study participation • Death • The study investigator or Sponsor, for any reason, stopped the study or stopped the patient's participation in the study • The procedures scheduled for End-of-Treatment Visit were to be performed at the time of early withdrawal as specified in the Time and Events Schedule in the protocol. For PFS, patients were censored at the date of last disease assessment before subsequent anti-myeloma therapy or withdrawal of consent to study participation, whichever occurred first. For PFS2, patients were censored at the start of the next line of therapy if the next line of therapy was started without disease progression on study treatment, or at the date of last follow-up if the patient was still alive and the next line of therapy was not started after progression on the study treatment or if the patient was still alive and had not yet progressed on the next line of therapy. For OS, patients were censored at the last date at which they were known to be alive.

Abbreviations: ASCT: autologous stem cell transplant; CI: confidence interval; DLd: daratumumab, lenalidomide, and dexamethasone; HR: hazard ratio; ISS: International Staging System; ITT: intention-to-treat; ISS: International Staging System; Ld: lenalidomide, and dexamethasone; MM: multiple myeloma; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; PFS2: progression-free survival on next line of therapy; TTP: time to progression; VGPR: very good partial response.
Source: MAIA CSR (September 2018 data cut). [Data on File]. 2019;[8] MAIA Protocol. [Data on File]. 2016;[95] Facon *et al*. 2021.[104]

B.2.4.3 Summary of MAIA data cut-offs

Table 10 presents a summary of the data cut-offs upon which the evidence for the clinical efficacy of DLd versus Ld is based. Overall, this submission includes results from the following data cuts:

- A top-line summary of results from the second interim analysis, which also served as the Primary PFS Analysis, with a clinical cut-off of 24th September 2018 (median follow-up of 28.0 months)
- Detailed results from the most recent IA with a clinical cut-off of 21st October 2021 (median follow-up of 64.5 months)

Table 10: Summary of MAIA data-cuts reported in the submission

Data cut-off	Median follow-up	Population included	Outcomes assessed	Rational for inclusion
24th September 2018	**28.0 months**	ITT population Safety population	**Primary endpoint:** • PFS **Secondary endpoints:** • ≥CR rate • ≥VGPR • MRD negativity • ORR • OS • TTP • Time to next treatment • Time to response • DOR • PFS2 • HRQoL • Safety and tolerability	This interim analysis was conducted to evaluate cumulative interim safety and efficacy data, and served as the primary PFS analysis
8th June 2020	47.9 months			[redacted]
19th February 2021	56.2 months			This prespecified interim analysis was conducted to provide updated efficacy and safety data, and served as the primary OS analysis
21st October 2021	64.5 months			This analysis provides the most recent efficacy and safety findings from the MAIA study

Abbreviations: CR: complete response; DOR: duration of response: HRQoL: health related quality of life; MRD: minimal residual disease; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; PFS2: time to progression on the next line of therapy; TTP: time to progression; VGPR: very good partial response.
Source: MAIA Protocol. [Data on File]. 2016;[95] MAIA CSR (September 2018 data cut). [Data on File]. 2019;[8] MAIA Abbreviated CSR. [Data on File] 2021;[106] MAIA HEMAR report. [Data on file] 2022;[9] Kumar et al. 2020.[109]

B.2.5 *Critical appraisal of the relevant clinical effectiveness evidence*

The MAIA trial and other relevant comparator trials were assessed for quality using the Cochrane Risk-of-Bias assessment tool.[110] The results of these quality assessments are presented in Appendix D. The overall risk of bias in the MAIA trial was considered to be low.

A summary of the quality of the MAIA trial is also presented in Table 11, using the criteria adapted from Systematic reviews: CRD's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination).

The limitations of the evidence base are discussed in Section B.2.12.

Table 11: Quality assessment of the MAIA trial

	Response	Risk of bias
Was randomisation carried out appropriately?	Yes, a centralised randomisation was implemented in this study; patients were randomised using a central IWRS.	Low, as patients were randomised using a central IWRS.
Was the concealment of treatment allocation adequate?	MAIA was an open-label trial. Following the review of data from the second interim analysis on 29 October 2018, the IDMC recommended that the sponsor unblind the study results, as the pre-specified statistical boundary for PFS was crossed.	Potential risk of bias as open label design could have influenced investigator's assessment of PFS events
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes. Baseline disease characteristics were well-balanced between the two treatment groups.	Low, as patients were randomised using a central IWRS.
Were the care providers, participants and outcome assessors blind to treatment allocation?	MAIA was an open label study. The study was unblinded following the review of data from the second interim analysis on 29th October 2018, the IDMC recommended that the sponsor unblind the study results, as the pre-specified statistical boundary for PFS was crossed.	Low, as an IDMC reviewed the data.
Were there any unexpected imbalances in drop-outs between groups?	No, of the 737 randomised patients, 729 patients were treated; 364 patients received DLd and 365 patients received Ld. Eight patients (4 patients in each treatment group) were randomised but did not receive treatment. Of these patients, 2 patients (both in the DLd group) died of an adverse event before receiving treatment and the remaining 6 patients were not treated as they withdrew from the study prior to Cycle 1 Day 1.	Low

	Fewer patients in the DLd group ([redacted]) discontinued study treatment than in the Ld group ([redacted]). The most common reasons for treatment discontinuation were progressive disease and adverse events.	
Is there any evidence to suggest that the authors measured more outcomes than they reported?	None	Low
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes, the ITT population was used for analysis of the primary endpoint and other time-to-event efficacy endpoints, which included all randomised patients	Low

Abbreviations: DLd: daratumumab, lenalidomide, and dexamethasone; IDMC: independent data monitoring committee; ITT: intention-to-treat; IWRS: interactive web response system; Ld: lenalidomide, and dexamethasone; PFS: progression-free survival.
Source: MAIA Protocol. [Data on File]. 2016;[95] MAIA Abbreviated CSR. [Data on File] 2021;[106] MAIA CSR (October 2021 data cut). [Data on file]. 2022;[102] Facon *et al*. (2021).[104]

B.2.6 *Clinical effectiveness results of the relevant studies*

B.2.6.1 Summary of key clinical efficacy results

A top-line summary of the results from the second interim analysis (24th September 2018) at a median follow-up of 28.0 months is presented below. Detailed results from the 21st October 2021 analysis are then provided, representing a median follow-up of 64.5 months, as these are the most recent data available and informsthe cost-effectiveness model for this submission. The final MAIA OS analysis is currently estimated in [redacted], which will occur after 390 deaths have been observed.[104, 108, 111]

MAIA Primary Analysis (Clinical cut off 24th September 2018)

At a median follow-up of 28.0 months, treatment with DLd resulted in a statistically significant and clinically meaningful improvement in PFS, with a 44% reduction in the risk of disease progression or death compared with Ld alone (HR: 0.56; 95% CI: 0.43, 0.73; p<0.0001). Disease progression or death had occurred in 240 patients (26.4% or 97 patients in the DLd group, and 38.8% or 143 patients in the Ld group). Prespecified subgroup analysis of PFS also demonstrated a consistent treatment effect across all subgroups, with the exception of patients with hepatic impairment at baseline. Importantly, the PFS benefit was maintained among patients 75 years of age or older demonstrating favourable efficacy of the DLd combination in this difficult-to-treat unfit and/or elderly population. Despite relatively short study follow-up, there was a clear trend toward OS improvement with a 22% reduction in the risk of death, although median OS had not been reached in either arm (HR: 0.78; 95% CI: 0.56, 1.10; p=0.1528).[8]

In terms of response, the overall response rate (ORR) was 92.9% for DLd compared with 81.3% for Ld while the percentage of patients with a ≥CR was 47.6% in the DLd group and 24.9% in the Ld group (p<0.0001). In addition, the percentage of patients negative for MRD was more than three times as high for DLd (24.2%), compared with Ld (7.3%) (p<0.0001.). The depth of

response observed for DLd in MAIA supports the synergistic effect of combining daratumumab with lenalidomide at eliminating residual myeloma cells.[103]

In this interim analysis, DLd demonstrated a significantly longer PFS, a higher response rate, an increased depth of response and a longer duration of response when compared with lenalidomide and dexamethasone alone.

PFS and OS benefit over time

Since the Primary Analysis has reported, results from the MAIA trial have demonstrated a statistically significant and clinically meaningful improvement on PFS and OS in patients who received DLd compared with Ld alone, which has been sustained over time with five years median follow-up. Moreover, there is a clear trend supporting an improved treatment effect in favour of DLd for OS with a lower HR and narrower confidence interval with longer study follow-up. A summary of PFS and OS HRs across subsequent data-cuts is presented in Table 12.

Table 12: Improvement in PFS and OS over time

MAIA data cut	Clinical cut-off	Median follow-up	PFS HR	OS HR
Primary PFS analysis (pre specified interim analysis)	Sept 2018	28.0 months	0.55 (0.43, 0.72)	[redacted]
9m snapshot (conference data cut)	June 2019	36.4 months	0.56 (0.43, 0.73)	[redacted]
ASH 2020 (conference data cut)	June 2020	47.9 months	0.54 (0.43, 0.67)	[redacted]
263 OS events (prespecified interim analysis)	Feb 2021	56.2 months	0.53 (0.43, 0.66)	0.68 (0.53, 0.86)
Updated analysis (regulatory data cut)	**Oct 2021**	**64.5 months**	**0.55 (0.45, 0.67)**	**0.66 (0.53, 0.83)**

Abbreviations: ASH: American Society of Haematology; HR: hazard ratio; OS: overall survival; PFS: progression-free survival.
Source: Facon *et al*. (2019);[103] Facon *et al*. (2021);[104] MAIA CSR (September 2018 data cut). [Data on File]. 2019;[8] MAIA Abbreviated CSR. [Data on File] 2021;[106] Kumar et al. 2020.[109] MAIA HEMAR report. [Data on file] 2022;[9] MAIA CSR (October 2021 data cut). [Data on file]. 2022. [102]

A summary of the key clinical efficacy results from the primary PFS analysis is presented alongside data from the most recent data cut (21st October 2021) in Table 13.

Table 13: Summary of key clinical efficacy results

	24th September 2018 data-cut (median follow-up = 28.0 months)		21st October 2021 data-cut (median follow-up = 64.5 months)	
	DLd	Ld	DLd	Ld
PFS, n (%)				
PFS HR (95% CI)	0.56 (0.43, 0.73)		0.55 (0.45, 0.67)	
p-value	p<0.0001		[redacted]	
OS, n (%)				
OS HR (95% CI)	[redacted]		0.66 (0.53, 0.83)	
p-value	[redacted]		[redacted]	
Overall response, n (%)				
Overall response	342 (92.9)	300 (81.3)	[redacted]	[redacted]
Odds ratio (95% CI)	[redacted]		[redacted]	
p-value	[redacted]		[redacted]	
sCR/CR, n (%)				
sCR	112 (30.4)	46 (12.5)	[redacted]	[redacted]
CR	63 (17.1)	46 (12.5)	[redacted]	[redacted]
≥CR	175 (47.6)	92 (24.9)	[redacted]	[redacted]
Odds ratio (95% CI)	[redacted]		[redacted]	
p-value	[redacted]		[redacted]	
VGPR, n (%)				
VGPR	117 (31.8)	104 (28.2)	[redacted]	[redacted]
≥VGPR	292 (79.3)	196 (53.1)	[redacted]	[redacted]
Odds ratio (95% CI)	[redacted]		[redacted]	
p-value	[redacted]		[redacted]	
MRD, n (%)				

MRD negativity rate (10^{-5} sensitivity threshold)	89 (24.2)	27 (7.3)	[redacted]	[redacted]
Odds ratio (95% CI)	[redacted]		[redacted]	
p-value	[redacted]		[redacted]	

Abbreviations: CI: confidence interval; CR: complete response; DLd: daratumumab, lenalidamide and dexamethasone; HR: hazard ratio; Ld: lenalidamide and dexamethasone; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; sCR: stringent complete response; VGPR: very good partial response.
Source: Facon *et al*. (2019);[103] Facon *et al*. (2021);[104] MAIA CSR (September 2018 data cut). [Data on File]. 2019;[8] MAIA Abbreviated CSR. [Data on File] 2021;[106] Kumar *et al.* (2020);[109] MAIA HEMAR report. [Data on file] 2022;[3]

B.2.6.2 MAIA: Updated analysis (data cut-off 21st October 2021)

As described above, the remainder of this submission will primarily focus on this latest data from the MAIA trial, which informs the cost-effectiveness model.

B.2.6.2.1 PFS (primary endpoint)

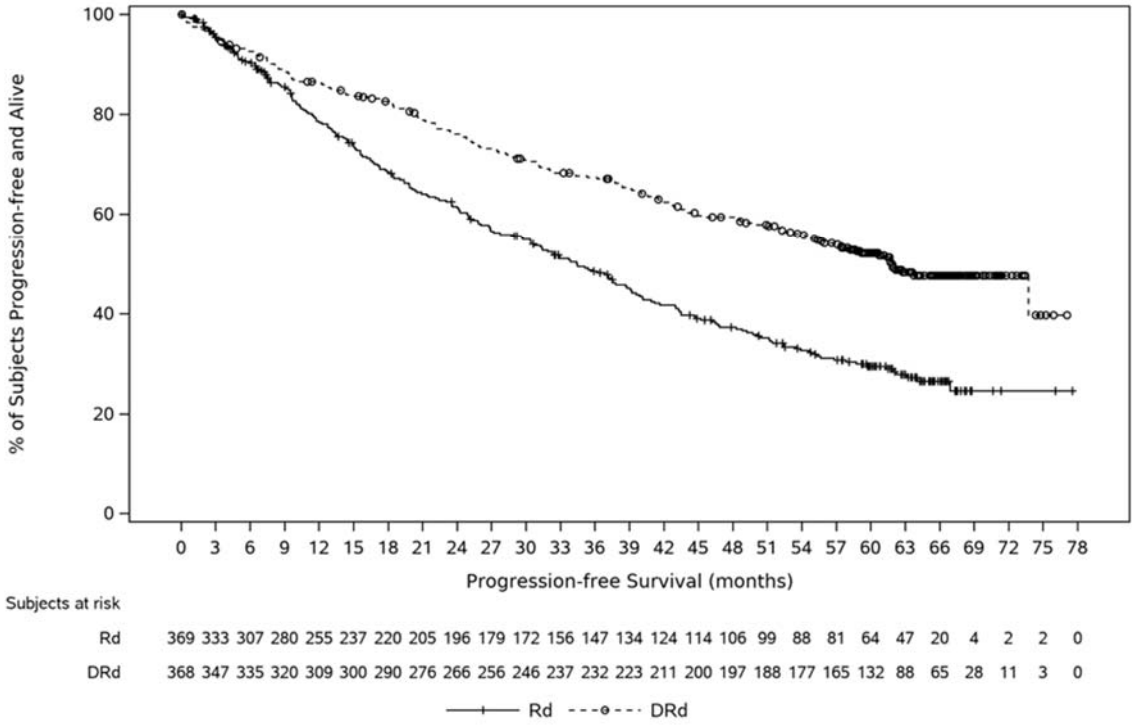
After a median follow-up of 64.5 months, [redacted] patients ([redacted]) in the DLd group and [redacted] participants ([redacted]) in the Ld group had progressive disease or had died. Consistent with the Primary Analysis, a significant improvement in PFS was observed for patients in the DLd group compared with Ld group (HR: 0.55; 95% CI: 0.45, 0.67; [redacted]). This represents a 45% reduction in the risk of disease progression or death for the DLd group compared with the Ld group. The median PFS was 61.9 months in the DLd group and was 34.4 months in the Ld group. A summary of PFS at a median follow-up 64.5 months is presented in Table 14 and Figure 11.[102] This improvement in PFS demonstrated by DLd was considered by clinicians to be highly compelling, given the significant follow-up period, and directly addresses MM patient preferences of longer remission and increased life expectancy.[50, 52, 64]

Table 14: Summary of PFS in the MAIA trial (ITT population) (data cut-off 21st October 2021)

	DLd (n=368)	Ld (n=369)
Number of events (%)	[redacted]	[redacted]
Median (95% CI)	61.86 [redacted]	34.4 [redacted]
HR (95% CI)	0.55 (0.45, 0.67)	
p–value	[redacted]	
12-month PFS rate, % (95% CI)	[redacted]	[redacted]
24-month PFS rate, % (95% CI)	[redacted]	[redacted]
36-month PFS rate, % (95% CI)	[redacted]	[redacted]
48-month PFS rate, % (95% CI)	[redacted]	[redacted]
60-month PFS rate , % (95% CI)	[redacted]	[redacted]

Abbreviations: CI: confidence interval ; Ld: lenalidomide and dexamethasone; DLd: daratumumab, lenalidomide and dexamethasone; PFS: progression-free survival
Source: MAIA CSR (October 2021 data cut). [Data on file]. 2022. Table 6.[102]

Figure 11: Kaplan–Meier estimate of PFS in the MAIA trial (ITT population) (data cut-off 21st October 2021)



Abbreviations: DRd: daratumumab, lenalidomide and dexamethasone (referred to as DLd throughout this submission); PFS: progression-free survival; Rd: lenalidomide and dexamethasone (referred to as Ld throughout this submission)..
Source: MAIA CSR (October 2021 data cut). [Data on file]. 2022. Figure 3.[102]

B.2.6.2.2 TTP (secondary endpoint)

At a median follow-up of 64.5 months, a total of [redacted] patients had progressive disease or died due to progressive disease, including [redacted] patients ([redacted]) in the DLd group, and [redacted] patients ([redacted]) in the Ld group.[9] TTP was significantly improved with DLd and was associated with a [redacted] reduction in the risk of disease progression compared with Ld ([redacted]).[9] The median time to disease progression or death was not reached for DLd and was [redacted] months for Ld. A summary of TTP at a median follow-up of 64.5 months is presented in Table 15 and Figure 12.

Table 15: Summary of TTP in the MAIA trial (ITT population) (data cut-off 21st October 2021)

	DLd (n=368)	Ld (n=369)
Number of events (days)	[redacted]	[redacted]
Median (95% CI)	[redacted]	[redacted]
p-value	[redacted]	
HR (95% CI)	[redacted]	

Abbreviations: CI: confidence interval ; DLd: daratumumab, lenalidomide and dexamethasone; HR: hazard ratio; Ld: lenalidomide and dexamethasone; NE: not estimable.
Source: MAIA HEMAR report. [Data on file]. TEFTTP01. 2022.[9]

Figure 12: Kaplan–Meier estimate of TTP in the MAIA trial (ITT population) (data cut-off 21st October 2021)

Abbreviations: DRd: daratumumab, lenalidomide and dexamethasone (referred to as DLd throughout this submission); Rd: lenalidomide and dexamethasone (referred to as Ld throughout this submission); TTP: time to progression.
Source: MAIA HEMAR report. [Data on file]. GEFTTP01. 2022.[9]

B.2.6.2.3 Time to subsequent anticancer therapy (secondary endpoint)

At a median follow-up of 64.5 months, the time to subsequent antimyeloma therapy was significantly prolonged for DLd versus Ld (median: [redacted] vs [redacted] months, respectively; [redacted]). A total of [redacted] patients in the DLd group and [redacted] patients in the Ld group did not receive subsequent anti-myeloma therapy at 60 months.[102] A summary of time to next treatment at a median follow-up of 64.5 months is presented in Table 16 and Figure 13.

Table 16: Summary of time to next treatment in the MAIA trial (ITT population) (data cut-off 21st October 2021)

	DLd (n=368)	Ld (n=369)
Number of events (months)	[redacted]	[redacted]
Median (95% CI)	[redacted]	[redacted]
p-value	[redacted]	
HR (95% CI)	[redacted]	

Abbreviations: CI: confidence interval ; DLd: daratumumab, lenalidomide and dexamethasone; HR: hazard ratio; Ld: lenalidomide and dexamethasone; NE: not estimable.
Source: MAIA CSR (October 2021 data cut). [Data on file]. 2022. Table 12.[102]

Figure 13: Kaplan–Meier estimate of time to subsequent antimyeloma therapy in the MAIA trial (ITT population) (data cut-off 21st October 2022)

Abbreviations: DRd: daratumumab, lenalidomide and dexamethasone (referred to as DLd throughout this submission); Rd: lenalidomide and dexamethasone (referred to as Ld throughout this submission).
Source: MAIA HEMAR report. [Data on file]. GEFTTSAT01. 2022.[9]

B.2.6.2.4 Progression-free survival on the subsequent line of therapy (secondary endpoint)

Progression-free survival on the subsequent line of therapy (PFS2) represents the time interval between the date of randomisation to the date of progressive disease on the next line of subsequent treatment or death from any cause. At a median follow-up of 64.5 months, a total of [redacted] patients in the DLd group and [redacted] patients in the Ld group had a PFS2 event. The median PFS2 was [redacted] months for DLd versus [redacted] months for Ld ([redacted]); 48-month PFS2 rates were [redacted] versus [redacted], and 60-month PFS2 rates were [redacted] versus [redacted] for DLd and Ld, respectively.[9] These results demonstrate that the PFS benefit of DLd is maintained beyond the next line of therapy received, providing patients with hope for the future and alleviating the constant fear of relapse often experienced by MM patients.[45] A summary of PFS2 at a median follow-up of 64.5 months is presented in Table 17 and Figure 14.

Table 17: Summary of PFS2 in the MAIA trial (ITT population) (data cut-off 21st October 2021)

	DLd (n=368)	Ld (n=369)
Number of events (%)	[redacted]	[redacted]
Median (95% CI)	[redacted]	[redacted]
HR (95% CI)	[redacted]	
p–value	[redacted]	
12-month PFS2 rate, % (95% CI)	[redacted]	[redacted]
24-month PFS2 rate, % (95% CI)	[redacted]	[redacted]

36-month PFS2 rate, % (95% CI)	[redacted]	[redacted]
48-month PFS2 rate, % (95% CI)	[redacted]	[redacted]
60-month PFS2 rate, % (95% CI)	[redacted]	[redacted]

Abbreviations: CI: confidence interval ; Ld: lenalidomide and dexamethasone; DLd: daratumumab, lenalidomide and dexamethasone; NE: not estimable; PFS2: progression-free survival on next line of therapy.
Source: MAIA HEMAR report. [Data on file]. TEFPFS2. 2022.[9]

Figure 14: Kaplan–Meier estimate PFS2 in the MAIA trial (ITT population) (data cut-off 21st October 2021)

Abbreviations: DRd: daratumumab, lenalidomide and dexamethasone (referred to as DLd throughout this submission); PFS2: progression-free survival on next line of therapy; Rd: lenalidomide and dexamethasone (referred to as Ld throughout this submission).
Source: MAIA CSR (October 2021 data cut). [Data on file]. 2022. Figure 6.[102]

B.2.6.2.5 OS (secondary endpoint)

At the clinical cut-off of 21st October 2021, a total of [redacted] death events had occurred in the MAIA trial, including [redacted] patients ([redacted]) in the DLd group and [redacted] patients ([redacted]) in the Ld group (Table 18). OS was significantly improved with DLd and was associated with a 34% reduction in the risk of death compared with Ld (HR: 0.66; 95% CI: 0.53, 0.83; [redacted]). The median OS was not reached for the DLd group and was 65.5 months for the Ld group. The statistically significant reduction in risk of death demonstrated by DLd offers patients a clinically meaningful, increased life expectancy, aligned with key patient preferences.[52] A summary of OS at a median follow-up of 64.5 months is presented in Table 18 and the associated Kaplan Meier plot in Figure 15.

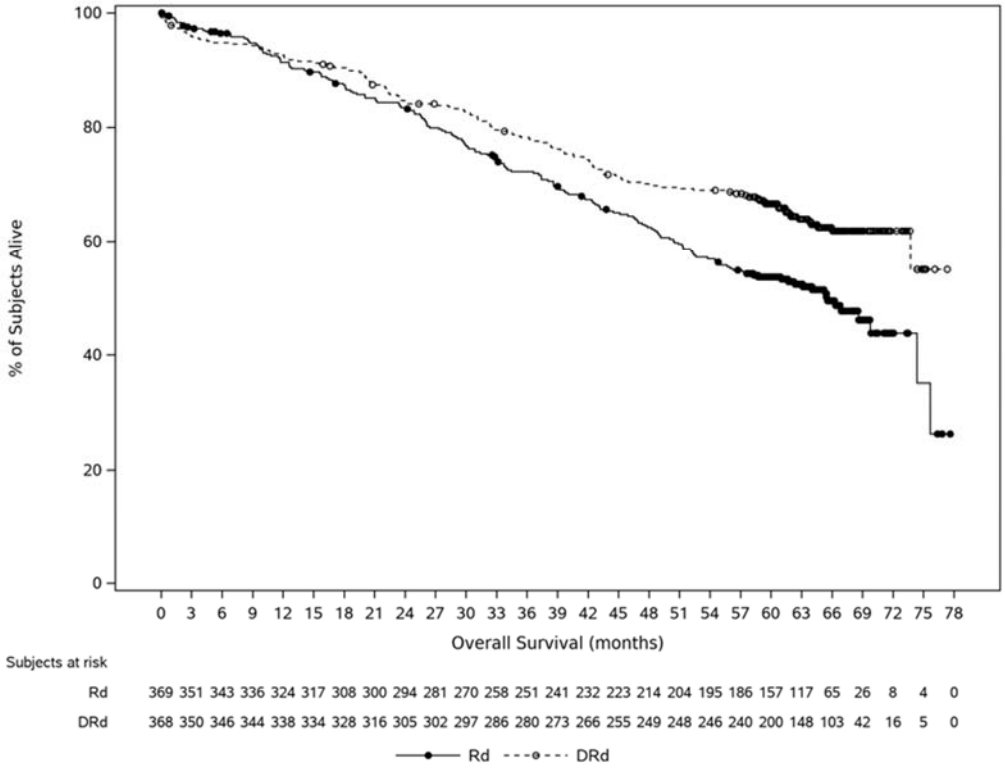
Table 18: Summary of OS in the MAIA trial (ITT population) (data cut-off 21st October 2021)

	DLd (n=368)	Ld (n=369)
Number of events (%)	[redacted]	[redacted]
Median (95% CI)	NE [redacted]	65.54 [redacted]
HR (95% CI)	0.66 (0.53, 0.83)	
p–value	[redacted]	

12-month PFS rate, % (95% CI)	[redacted]	[redacted]
24-month PFS rate, % (95% CI)	[redacted]	[redacted]
36-month PFS rate, % (95% CI)	[redacted]	[redacted]
48-month PFS rate, % (95% CI)	[redacted]	[redacted]
60-month PFS rate , % (95% CI)	[redacted]	[redacted]

Abbreviations: CI: confidence interval ; DLd: daratumumab, lenalidomide and dexamethasone; Ld: lenalidomide and dexamethasone; NE: not estimable; OS: overall survival.
Source: MAIA CSR (October 2021 data cut). [Data on file]. 2022. Table 10.[102]

Figure 15: Kaplan–Meier estimates of OS in the MAIA trial (ITT population) (data cut-off 21st October 2021)



Abbreviations: DRd: daratumumab, lenalidomide and dexamethasone (referred to as DLd throughout this submission); OS: overall survival; Rd: lenalidomide and dexamethasone (referred to as Ld throughout this submission).
Source: MAIA HEMAR report. [Data on file]. GEFOS01. 2022.[9]

B.2.6.2.6 OS-adjustment for CDF drugs and treatments not routinely commissioned in the UK

Due to the international study design, MAIA included a number of subsequent treatments not routinely available in NHS clinical practice. As such, adjustment was necessary to ensure generalisability of results to the UK setting, assess potential bias, and to comply with the NICE Position Statement on CDF drugs (see Appendix R).

NICE DSU Technical Support Document 16 recommends use of the following available complex methods to adjust for such biases introduced by treatment switching:[69]

- Rank Preserving Structure Failure Time Models (RPSFTM);
- Iterative Parameter Estimation (IPE);
- Two-stage method;

- Inverse Probability of Censoring Weights (IPCW).

Due to data limitations, and the nature of switching to a variety of subsequent therapies in MAIA, Janssen considered the first 3 methods not applicable (see Appendix R for further details). Additionally, the two-stage method was further judged to be unsuitable because it can only be applied if an appropriate secondary baseline can be defined, and availability of all relevant prognostic factors at this secondary baseline, to adjust for time-dependent confounding. These conditions were judged not to be true for MAIA with this scenario, as time between progression and/or discontinuation of randomised treatment to switch was highly variable, and availability of data on prognostic factors at time of this secondary baseline was limited.

As such, the IPCW method was selected as the only potentially viable method. IPCW has been accepted in previous NICE technology appraisals and is generally considered to be robust, providing that switching proportions are moderate, sample sizes are not too small, and sufficient data on prognostic factors have been captured over time to allow adjustment for time varying confounding.[36-38, 112]

To align with the modelled costs, the IPCW adjustment was performed for subsequent therapies received at 2L and 3L. Full details of this method are provided in Appendix R, with a summary of key methodology and results below.

Methods

The IPCW method involves censoring patients upon treatment switch, then controlling for this potentially informative censoring by weighting the follow-up information for patients who remain at risk for the event with a similar prognosis such that the original composition of the treatment groups is recovered.

Results

KM curves for DLd and Ld OS pre- and post-adjustment are presented in Figure 16 and HRs are presented in Table 19.

Figure 16: KM curves for DLd and Ld OS pre- and post-adjustment

Abbreviations: DRd: daratumumab, lenalidomide and dexamethasone (referred to as DLd throughout this submission); IPCW: Inverse Probability of Censoring Weighting; IPCW Inverse Probability of Censoring Weighting baseline adjusted; Rd: lenalidomide and dexamethasone (referred to as Ld throughout this submission); mFU: median follow-up.

Table 19: Hazard ratio for DLd versus Ld, pre- and post-adjustment

	DLd versus Ld OS HR (95%CI)
ITT analysis	0.66 (0.53, 0.83)
IPCW	[redacted]

Abbreviations: CI: confidence interval; DLd: daratumumab, lenalidomide and dexamethasone; HR: hazard ratio; IPCW: Inverse Probability of Censoring Weighting; ITT: intent-to-treat; Ld: lenalidomide and dexamethasone; OS: overall survival;

The results of the analysis demonstrate a higher OS benefit for DLd vs Ld following adjustment for bias introduced by subsequent treatments not available in the UK setting (indicated by a reduced HR).

To avoid introducing additional uncertainty into the economic model, the unadjusted DLd and Ld OS extrapolations are used in the base case (see Section B.3.3.1.1). Reassuringly, however, the IPCW-adjustment demonstrates that the relative treatment effect between DLd and Ld is greater following adjustment for treatments not available or only available via the CDF in UK clinical practice. As such, the use of unadjusted DLd and Ld data from MAIA can be considered conservative and may underestimate the relative difference in efficacy between the DLd and Ld arms expected in clinical practice.

B.2.6.2.7 ORR (secondary endpoint)

At the clinical data cut-off of 21st October 2021, a statistically significant improvement in response was observed for patients in the DLd group versus the Ld group. The ORR was significantly higher in the DLd group ([redacted]) than in the Ld group ([redacted]) ([redacted]). The rates of ≥VGPR were [redacted] in the DLd group, compared with [redacted] in the Ld group ([redacted]). The rates for ≥CR were also significantly higher in the DLd group ([redacted]) than in the Ld group ([redacted]) ([redacted]), with sCR more than doubled in the DLd group ([redacted]) compared with the Ld group ([redacted]) ([redacted]).[9]

The significant improvement in response rates can be attributed to daratumumab's unique mechanism of action and synergy with lenalidomide. Specifically, daratumumab's combination of direct and immunomodulatory effects harness the body's own immune system to target and eliminate malignant plasma cells. As such, the addition of daratumumab to Ld provides significantly deeper responses compared to SoC and addresses preferences of increased response and longer remission as a highly valued treatment preference amongst patients with MM.[102]

A summary of overall response from the MAIA trial is presented in Figure 17.

Figure 17: Summary of overall best confirmed response in the MAIA trial based on computerised algorithm (ITT population) (data cut-off 21st October 2021)

Abbreviations: CR: complete response; DLd: daratumumab, lenalidomide and dexamethasone; Ld: lenalidomide and dexamethasone; ORR: overall response; PR: partial response; sCR: stringent complete response; VGPR: very good partial response.
Source: MAIA HEMAR report. [Data on file]. TEFRESP01A. 2022.[9]

B.2.6.2.8 Time to response (secondary endpoint)

The median time to first response was rapid, occurring after 1 month of treatment. As of the clinical cut-off date 21st October 2021, the median time to best response in MAIA was [redacted] for the DLd group, compared with [redacted] months for Ld. Median time to VGPR or better ([redacted] versus [redacted] months) and median time to CR or better ([redacted] versus [redacted] months) was shorter for the DLd group versus the Ld group, respectively.[102]

Table 20: Summary of time to response in the MAIA trial based on computerised algorithm (response-evaluable analysis set) (data cut-off 21st October 2021)

	DLd (n=[redacted])	Ld (n=[redacted])
Responders (≥PR)	[redacted]	[redacted]
Time to first response[a] (months)		
N	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]
Time to best response[a] (months)		
N	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]
Time to ≥VGPR[a] (months)		
N	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]
Time to ≥CR[a] (months)		
N	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]

[a] Response PR or better.
Abbreviations: CR: complete response; DLd: daratumumab, lenalidomide and dexamethasone; Ld: lenalidomide-dexamethasone; PR: partial response; VGPR: very good partial response.
Source: MAIA CSR (October 2021 data cut). [Data on file]. 2022. TEFTTR02.[102]

B.2.6.2.9 DOR (secondary endpoint)

As of the clinical cut-off date 21st October 2021, the median DOR was not reached in the DLd group (95% CI: not reached, not reached) due to the majority of patient's data being censored. In the Ld group, the median DOR was [redacted] months ([redacted]) (Table 21, Figure 18).[9, 104, 106, 111] The increased DOR observed for DLd supports a durable delay in disease progression with long-term benefits for patients with MM.[102]

Table 21: Summary of DOR in the MAIA trial (Response-evaluable analysis set) (data cut-off 21st October 2021)

	DLd (n=[redacted])	Ld (n=[redacted])
Number of events (%)	[redacted]	[redacted]
Median (95% CI)	[redacted]	[redacted]
12-month event-free rate, % (95% CI)	[redacted]	[redacted]
24-month event-free rate, % (95% CI)	[redacted]	[redacted]
36-month event-free rate, % (95% CI)	[redacted]	[redacted]

48-month event-free rate, % (95% CI)	[redacted]	[redacted]
60-month event-free rate , % (95% CI)	[redacted]	[redacted]

Abbreviations: CI: confidence interval ; DLd: daratumumab, lenalidomide and dexamethasone; Ld: lenalidomide and dexamethasone; NE: not estimable.
Source: MAIA CSR (October 2021 data cut). [Data on file]. 2022. Table 11.[102]

Figure 18: Kaplan–Meier plot for duration of response based on computerised algorithm in the MAIA trial (Response–evaluable analysis set) (data cut-off 21st October 2021)

[redacted]

Abbreviations: DRd: daratumumab, lenalidomide and dexamethasone (referred to as DLd throughout this submission); Rd: lenalidomide and dexamethasone (referred to as Ld throughout this submission).
Source: MAIA HEMAR report. [Data on file]. GEFDOR01. 2022.[9]

B.2.6.2.10 MRD negativity rate (secondary endpoint)

Assessment of MRD was conducted on bone marrow samples using a US Food and Drug Administration (FDA) approved next generation sequencing (NGS) sequencing assay (ClonoSEQ V2.0) in accordance with the IMWG MRD guidelines. MRD assessments were carried out at baseline by a central laboratory (Adaptive Biotechnologies, Seattle, WA, USA); at the time of suspected CR or sCR; and at 12, 18, 24, 30, 36, 48, and 60 months after Cycle 1 Day 1 (±1 month) if the patient response was near a CR or sCR (if one of these timepoints occurred within 1 month of the suspected CR, a repeat assessment was not requested).

At the clinical cut-off date of 21st October 2021, the MRD negativity rate was approximately three times higher for the DLd group ([redacted]) compared with the Ld group ([redacted]).

Patients in the DLd group also demonstrated significantly higher durable MRD negativity at the sensitivity threshold of 10^{-5}, defined as having MRD negativity for at least one year without a positive result, compared with the Ld group (DLd: [redacted]). Both of these measures support deeper, and more sustained responses with DLd versus Ld.

As an exploratory evaluation, MRD analysis at the higher sensitivity threshold of 10^{-6} was conducted. The rates of MRD negativity at the 10^{-6} threshold was also significantly higher for the DLd group compared with the Ld group ([redacted])

(Table 22). There is an association between improved survival outcomes for MRD-negative patients and increasing MRD sensitivity thresholds up to 10^{-6}.[71]

A summary of MRD negativity results is presented in Table 22.

Table 22:Summary of MRD negativity results

	DLd (n=368)	Ld (n=369)
MRD (10^{-5}) n (%)		
MRD negativity rate	[redacted]	[redacted]
Odds ratio (95% CI)	[redacted]	
p-value	[redacted]	
MRD (10^{-6}) n (%)		
MRD negativity rate	[redacted]	[redacted]
Odds ratio (95% CI)	[redacted]	
p-value	[redacted]	
Durability of MRD negativity (MRD negativity for at least one year without a positive result), n (%)		
MRD negativity rate	[redacted]	[redacted]
Odds ratio (95% CI)	[redacted]	
p-value	[redacted]	

[a]Mantel-Haenszel estimate of the odds ratio for un-stratified tables is used. An odds ratio >1 indicates an advantage for DLd.
Abbreviations: CI: confidence interval; DLd: daratumumab, lenalidomide and dexamethasone; Ld: lenalidomide and dexamethasone; MRD: minimal residual disease.
Source: MAIA CSR (October 2021 data cut). [Data on file]. 2022. Table 8;[102] MAIA CSR appendices. TBMKMRD02. [Data on file]. 2022;[113] MAIA CSR appendices. TBMKMRD12. [Data on file]. 2022.[113]

Landmark analyses for survival by response

Achieving deep and durable responses by eliminating as many clonal types as possible is one of the primary aims of treatment in the front-line setting and is associated with improved long-term outcomes for both survival and disease progression.[66] MRD is the most sensitive measure of response currently available and has been recommended in IMWG response assessment criteria.[68]

To explore the impact of MRD negativity on survival outcomes in the MAIA trial, exploratory analyses were conducted to compare PFS and OS for patients who achieved MRD negativity versus those with an MRD-positive response. In order to mitigate the effect of immortal time bias (i.e. patients needed to live long enough to experience the event), a landmark analysis was performed using individual patient data (IPD) from the MAIA trial (data cut-off 21st October 2021) in which survival was assessed from the landmark timepoint, with patients who experienced the

event of interest (i.e. death or progression) before this timepoint being excluded from the analysis (represented by 'PD' and 'Death' groups in the figures below).

MRD was assessed at time points as outlined in the Time and Events Schedule prespecified in the protocol in MAIA.[95] The selection of the landmark time-point aimed to strike a balance between being too early and therefore miss the achievement of MRD negativity, and too late, resulting in less meaningful categorisation by excluding a significant number of events from the analysis. Due to the significant deepening in responses observed between 12- and 18-months (particularly for the DLd arm), the latter (18-month) time-point was chosen (refer to Table 23),

Table 23: Numbers of patients who achieve MRD negativity at potential landmark time points

	Potential landmark time point		
Numbers of patients categorised as MRD negative	12-month	18-month	24-month
DLd MRD negative patients (n, %)	[redacted]	[redacted]	[redacted]
Ld MRD negative patients (n, %)	[redacted]	[redacted]	[redacted]

Cox proportional hazard models were calculated using the R package 'survival' to determine the effect of treatment in each of the MRD groups for PFS and OS.

Kaplan-Meier plots for PFS from the 18-month landmark timepoint by MRD status are presented in **Error! Reference source not found.** for DLd and **Error! Reference source not found.** for Ld. Kaplan-Meier plots for OS from the landmark timepoint by MRD status are presented in Figure 22 and Figure 21, for DLd and Ld respectively.

As shown in the Kaplan-Meier plots below, patients achieving MRD negativity with DLd at the landmark time point of 18 months demonstrated significantly improved survival (PFS and OS) compared to those with an MRD-positive response. Whilst the same MRD effect was not observed for patients on the Ld arm, this is likely due to the lower sample size with only 17 patients assessed as MRD-negative at the landmark time point of 18-months.

Figure 20: Landmark analysis – DLd PFS from landmark timepoint of 18 months by MRD status

Abbreviations: DLd: daratumumab, lenalidomide and dexamethasone; CI: confidence interval; MRD: minimal residual disease; NE: not estimable; PFS: progression free survival.

Figure 19: Landmark analysis – Ld PFS from landmark timepoint of 18 months by MRD status

Abbreviations: Ld: lenalidomide and dexamethasone MRD: minimal residual disease; NE: not estimable; PFS: progression free survival.

Figure 21: Landmark analysis – DLd OS from landmark timepoint of 18 months by MRD status

Abbreviations: DLd: daratumumab, lenalidomide and dexamethasone; CI: confidence interval; MRD: minimal residual disease; NE: not estimable; OS; overall survival; PD: progressive disease.

Figure 22: Landmark analysis – Ld OS from landmark timepoint of 18 months by MRD status

Abbreviations: CI: confidence interval; Ld: lenalidomide and dexamethasone; MRD: minimal residual disease; NE: not estimable; OS; overall survival; PD: progressive disease.

An exploratory analysis to examine the benefit of durable MRD negativity on PFS was also conducted. A total of [redacted] patients in the MRD-negative group at the sensitivity threshold of 10^{-5} and who had MRD negativity for at least one year without a positive result (as per IMWG definition of sustained MRD negativity), experienced a PFS event compared with a total of [redacted] patients in the MRD-positive group.[102]

Indeed, for those patients who achieve MRD negativity following DLd treatment, the groundbreaking level of depth of response allows for long-term disease control and there is hope for a functional cure, with the mortality rate tracking outcomes resembling that seen in the UK general population after five years of follow-up (Figure 23).

Figure 23: Comparison of DLd patients who achieved MRD negative status to age matched GPM

Note: Outcomes of DLd MRD negative patients are higher than the general population, possibly due to the controlled nature, regular and active monitoring the clinical trial setting
Abbreviations: DRd: daratumumab, lenalidomide and dexamethasone; GPM: general population mortality; mFU: median follow-up; MRD: minimal residual disease.

Overall, these exploratory analyses support the notion that deeper responses translate to improved disease control and longer PFS/OS. Thus, the higher rate of MRD negativity achieved with DLd indicates that patients receiving this combination are more likely to achieve a deeper response and thus longer disease and progression-free intervals, aligned with established patient preferences in this setting.

B.2.6.2.11 Health-related quality of life assessment (secondary endpoint)

To measure functional status, wellbeing, and symptoms, the European Organisation for Research and Treatment of Cancer quality of life questionnaire (EORTC QLQ-C30) and the EuroQol 5-dimension, 5-level questionnaire (EQ-5D-5L) instruments were utilised.

Both questionnaires were completed at the timepoints outlined in the Time and Events Schedule prespecified in the protocol.[95] EORTC QLQ-C30 and EQ-5D-5L questionnaires were administered on Day 1 of Cycles 3, 6, 9 and 12 for Year 1, and then every 6th cycle thereafter until end of treatment. Questionnaires were administered prior to any other study procedures or assessments for that study visit. All PRO measures were collected via and electronic device (ePRO).

Compliance rates

Compliance with EORTC QLQ-C30 and EQ-5D-5L assessments was high and comparable between treatment groups across all timepoints. The compliance rates at baseline exceeded 90% in both groups for EQ-5D-5L and EORTC QLQ-C30. Compliance with the EORTC QLQ-C30 and EQ-5D-5L assessments was high and comparable between treatment groups for the first 12 Cycles and remained high with the prolonged exposure. Compliance rates were greater than 70% during the Treatment Phase through Cycle 60 (Appendix Q).

EORTC QLQ-C30

Baseline values for all subscales of the EORTC QLQ-C30 were comparable for patients treated with DLd and Ld (Appendix Q).

As of the clinical cut-off of 21st October 2021, the EORTC QLQ-C30 GHS subscale scores showed a continued numerical increase with longer follow-up, with slightly greater change from baseline observed in the DLd group.[9, 111] The numerical benefit for the DLd group compared with the Ld group was observed beginning at Cycle 3 (LS mean change; DLd: [redacted] through Cycle 48 (LS mean change; DLd: [redacted] (Figure 24). This increased change from baseline in EORTC QLQ-C30 GHS scores demonstrated by DLd indicate a sustained improvement in HRQoL, addressing MM patient preferences, as highlighted in Section B.1.3.3.

Figure 24: Change from baseline in EORTC QLQ-C30 GHS score in the MAIA trial (ITT analysis set) (data cut-off 21st October 2021)

Abbreviations: DLd: daratumumab, lenalidomide and dexamethasone; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer quality of life questionnaire; GHS: global health status; Ld: lenalidomide and dexamethasone.

Source: MAIA HEMAR report. [Data on file]. TPROQLQ05. 2022.[9]

Furthermore, the median time to improvement in GHS was shorter for the DLd group compared with the Ld group [redacted] and the median time to worsening of GHS was longer for DLd compared with the Ld group [redacted]. As such, patients treated with DLd experienced meaningful and continuous improvements in HRQoL, with a shorter time to improvement and longer delay in worsening of HRQoL compared with Ld.[102] A summary of time to worsening in EORTC QLQ-C30 GHS subscale scores is presented in Appendix Q.

In addition, results from the EORTC-QLQ-C30 pain subscale also indicated improvements in HRQoL in patients from both DLd and Ld groups. A summary of the mean change from baseline in pain scores is presented in Figure 25. The LS mean change from baseline to Cycle 66 was [redacted] for DLd and [redacted] for Ld. The LS mean difference in change from baseline between DLd and Ld was [redacted], indicating a statistically greater improvement in pain with DLd versus Ld (Figure 26). Further, within the DLd arm, mean changes (between [redacted] points) observed with treatment indicated a large meaningful reduction from baseline was maintained over the course of treatment.

Figure 25: Mean change from baseline in EORTC QLQ-C30 pain subscale scores in the MAIA trial (ITT analysis set) (data cut-off 21st October 2021)

Abbreviations: DLd: daratumumab, lenalidomide and dexamethasone; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer quality of life questionnaire; Ld: lenalidomide and dexamethasone.
Source: MAIA HEMAR report. [Data on file]. TPROQLQ02. 2022.[9]

Figure 26: LS-means of change from baseline in EORTC QLC C-30 pain subscale scores in the MAIA trial (ITT analysis set) (data cut-off 21st October 2021)

Abbreviations: DLd: daratumumab, lenalidomide and dexamethasone; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer quality of life questionnaire; ITT: intention-to-treat; Ld: lenalidomide and dexamethasone; LS: least squares.
Source: MAIA HEMAR report. [Data on file]. TPROQLQ05G. 2022.[9]

Patients treated with DLd also reported a numerically greater reduction in fatigue compared with patients treated with Ld at Cycle 9 through to Cycle 42 (Figure 27). As noted in B.1.3.3, symptoms such as pain and fatigue were characterised by patients with NDMM as aspects of the disease that have the greatest impact on their lives.[50, 53] Improvements in symptoms associated with MM for patients treated with DLd are therefore closely aligned to MM patient preferences.

Figure 27: LS-means of change from baseline in EORTC QLC C-30 fatigue subscale scores in the MAIA trial (ITT analysis set) (data cut-off 21st October 2021)

Abbreviations: DLd: daratumumab, lenalidomide and dexamethasone; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer quality of life questionnaire; ITT: intention-to-treat; Ld: lenalidomide and dexamethasone; LS: least squares.
Source: MAIA HEMAR report. [Data on file]. TPROQLQ05F. 2022.[9]

EQ-5D-5L

Baseline values for the EQ-5D-5L utility score and EQ-5D-5L visual analogue scale (VAS) were comparable between treatment groups (see Appendix Q).

As of the clinical cut-off of 21st October 2021, there were no differences were observed between the treatment groups in the median time to improvement in VAS (DLd: [redacted] months, Ld: [redacted] months). However, the median time to worsening of VAS was longer for the DLd group compared with the Ld group ([redacted] months versus [redacted] months, respectively). No differences were observed between the treatment groups in the median time to improvement in utility value (DLd: [redacted] months, Ld: [redacted] months). However, median time to worsening of utility score was longer for the DLd group compared with the Ld group ([redacted] months versus [redacted] months, respectively; [redacted]), indicating that HRQoL was sustained for a longer period for patients treated with DLd. Summaries of time to worsening in EQ-5D-5L VAS and utility scores are presented in Appendix Q.

Improvement in the VAS was maintained during treatment, with greater benefits reported in the DLd group compared with the Ld group early during treatment (LS mean change at Cycle 6: DLd: [redacted]). Similarly, both the DLd and Ld groups reported an improvement in health utility, with a numeric improvement for DLd at Cycle 42 (LS mean change: DLd: [redacted]) (Figure 28).

Figure 28: LS-means of change from baseline in EQ-5D-5L in the MAIA trial (ITT analysis set) (data cut-off 21st October 2021)

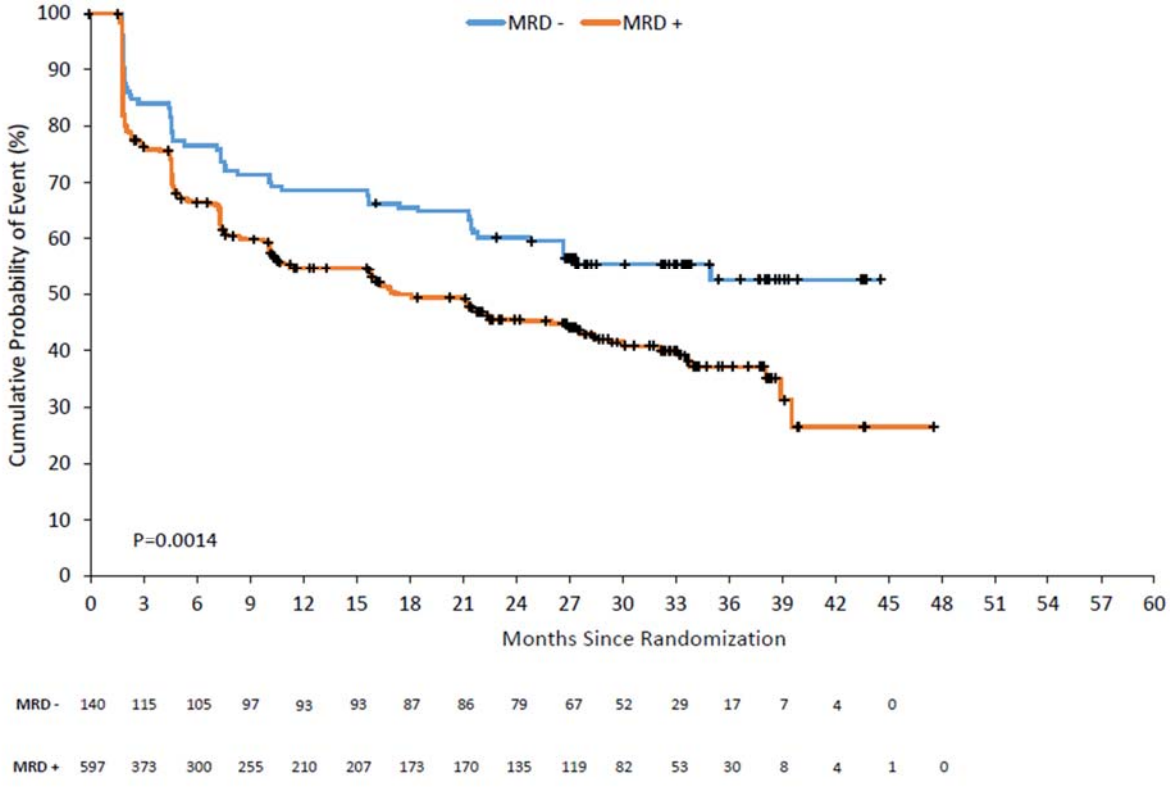
[redacted]

Abbreviations: DLd: daratumumab, lenalidomide and dexamethasone; EQ-5D-5L: EuroQol 5-dimension 5-level questionnaire; intention-to-treat; Ld: lenalidomide and dexamethasone; LS: least squares.
Source: MAIA CSR appendices. [Data on file]. TPROEQ05A. 2022.[113]

As of the clinical cut-off date 21st October 2021, the functional status and well-being results from the cancer-specific EORTC QLQ-C30 and the general health EQ-5D-5L, indicated improvements in HRQoL in patients who remained in the study in both the DLd and Ld groups. The results demonstrate a numerical benefit in the EORTC QLQ-C30 GHS subscale scores, a meaningful reduction in pain and an improvement in physical functioning with DLd, compared with Ld. A further increased and sustained improvement was also observed in VAS for patients in the DLd arm, compared with those in the Ld arm.

In addition, the impact of depth of response and MRD on HRQoL was assessed. A pooled analysis of MAIA and ALCYONE showed that the risk of worsening HRQoL was less in patients with greater depth of response. Median time to worsening of GHS was significantly longer in patients with deeper clinical response and in those who were MRD negative in MAIA (Figure 29). As such, the results showed that achieving MRD negativity and therefore obtaining the deepest clinical response provided the greatest benefit for HRQoL outcomes.[114]

Figure 29: Time to worsening of GHS by MRD status in the MAIA trial



Abbreviations: GHS: global health status; MRD: minimal residual disease
Source: Penaloza-Ramos *et al.* 2020.[114]

Overall, the HRQoL results show that patients treated with the DLd triplet therapy combination benefit from improved PFS and OS with no significant detriment to overall HRQoL, versus the existing SoC doublet therapy (Ld).The avoidance of symptoms such as pain and fatigue is a key issue for patients, as outlined in Section B.1.3.3. Generally, patients indicated that they would sacrifice 2.7 years of life expectancy to remove extreme pain, or 2.0 years to remove constant fatigue, respectively.[50]

B.2.7 *Subgroup analysis*

B.2.7.1 PFS

ITT population

At a median follow-up of 64.5 months, subgroup analyses of PFS (Figure 30) demonstrated that the treatment effect of DLd over Ld was consistent across the prespecified, clinically relevant subgroups, including patients 75 years of age or older, and patients with a poor prognosis such as those with advanced-stage disease (ISS Staging III) or renal impairment. As such, DLd offers a significant improvement in PFS across all age-groups and stages of disease.

Figure 30: Forest plots of subgroup analyses on PFS in the MAIA trial (ITT population) (data cut-off 21st October 2021)

Abbreviations: CI: confidence interval; CrCl: creatine clearance**;** DLd: daratumumab, lenalidomide and dexamethasone; ECOG: Eastern Cooperative Oncology Group; EVT: event; IgG: immunoglobin G; ISS: international staging system; Ld: lenalidomide and dexamethasone; N: number; NE: not estimable; PFS: progression-free survival.
Source: MAIA CSR (October 2021 data cut). [Data on file]. 2022. Figure 4.[102]

Frailty subgroup analysis

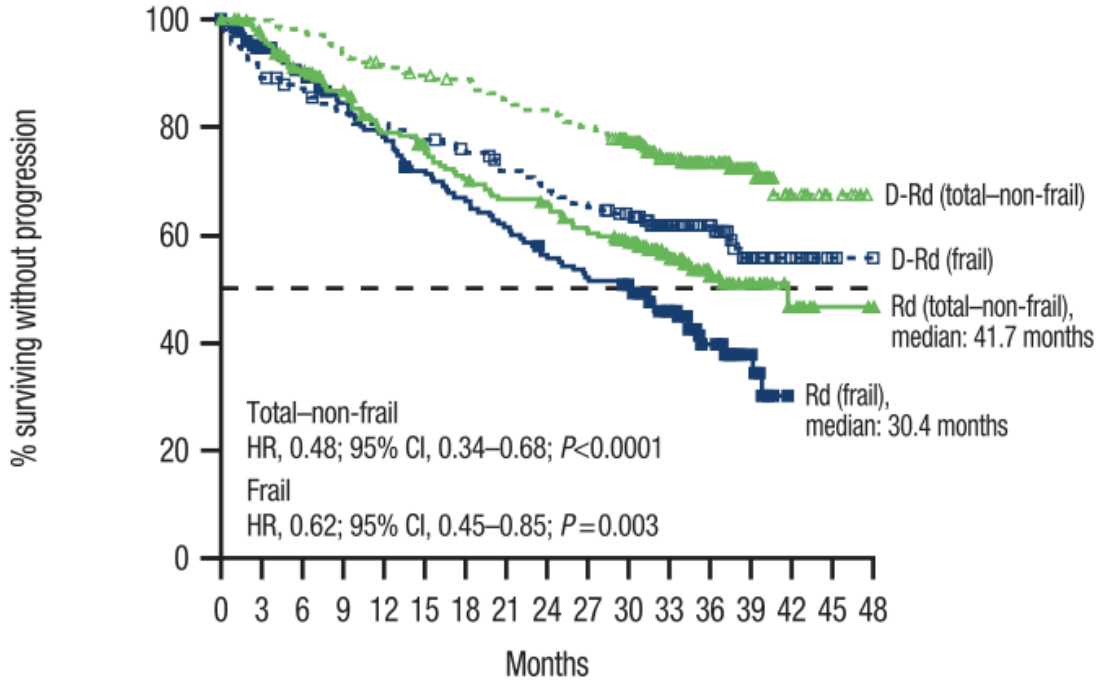
A subgroup analysis of MAIA by frailty status was performed reterospectively, using age, Charlson comorbidity index, and baseline ECOG performance status score. Patients were classified as fit, intermediate, non-frail (fit and intermediate), or frail. Frailty status was further

simplified into 2 categories: total–non-frail (a combination of the fit and intermediate subgroups) and frail.

Consistent with the overall study population, improved efficacy with DLd versus Ld was observed across frailty subgroups. PFS results demonstrated that DLd leads to outcomes in frail patients that are at least as good as those observed with Ld in fit patients.[105] Of the randomised patients 396 patients were non-frail (DLd, 196 [53.3%]; Ld, 200 [54.2%]) and 341 patients were frail (172 [46.7%]; 169 [45.8%]). At a median follow-up of 36.4 months, non-frail patients had longer PFS than frail patients, but the PFS benefit of DLd versus Ld was maintained across subgroups: non-frail (median: not reached versus 41.7 months; HR: 0.48; p<0.0001) and frail (median: NR versus 30.4 months; HR: 0.62; p=0.003).[105] These findings support the clinical benefit of DLd in NDMM patients who are ASCT-ineligible, regardless of frailty status.

A Kaplan-Meier curve demonstrating PFS in the total-non-frail and frail subgroups is presented in Figure 31.

Figure 31: Kaplan-Meier curve to show PFS in the total-non-frail and frail subgroups of the MAIA study



Patients at risk

Rd (total–non-frail)	200	188	173	159	142	134	124	117	115	104	96	64	40	21	10	2	1
D-Rd (total–non-frail)	196	195	190	183	176	171	168	161	157	151	136	106	78	43	12	5	0
Rd (frail)	169	145	134	121	112	102	95	87	79	73	65	49	24	12	0	0	0
D-Rd (frail)	172	152	145	137	133	129	122	115	109	105	97	68	53	27	12	2	1

Abbreviations: D-Rd: daratumumab, lenalidomide and dexamethasone (referred to as DLd throughout this submission); Rd: lenalidomide and dexamethasone (referred to as Ld throughout this submission).
Source: Facon *et al.* 2022.[105]

B.2.7.2 OS

OS subgroup analyses similarly demonstrated that the treatment effect of DLd over Ld was consistent across the pre-specified, clinically relevant subgroups including patients of 75 years of age or older, and patients with a poor prognosis such as those with advanced-stage disease (ISS

Staging III) or renal impairment, with the exception of the subgroup analysis of patients with impaired hepatic function at baseline (Figure 32).[115] Interpretation for this subgroup is limited by the small sample size ([redacted] and [redacted] patients in the DLd and Ld groups, respectively) and wide CI ([redacted]).

Figure 32: Forest plots of subgroup analyses on OS in the MAIA trial (ITT population) (data cut-off 21st October 2021)

Abbreviations: CI: confidence interval; CrCl: creatine clearance; DLd: daratumumab, lenalidomide and dexamethasone; ECOG: Eastern Cooperative Oncology Group; EVT: event; IGg: immunoglobin G; ISS: international staging system; Ld: lenalidomide and dexamethasone; N: number; NE: not estimable; OS: overall survival.
Source: MAIA HEMAR report. [Data on file]. GEFOSFP01. 2022.[9]

B.2.8 *Meta-analysis*

As only one relevant trial evaluating DLd was identified as part of the SLR, no meta-analysis is required.

B.2.9 *Indirect and mixed treatment comparisons*

Summary of indirect and mixed treatment comparisons

- As discussed in Section B.1.3.7, Ld represents the SoC for the majority of newly diagnosed ASCT-ineligible patients in England. The comparison between DLd and Ld is supported by the highest level of evidence (RCT evidence) as per the hierarchy outlined by NICE.
- However, for completeness, and to adhere to the final NICE scope, a comprehensive approach has been taken to generate indirect evidence versus bortezomib in combination with an alkylating agent and corticosteroid, and thalidomide with an alkylating agent and corticosteroid, although Janssen understand that the latter are now rarely used.
- In the clinical SLR, there was no clinical trial evidence or IPD available for bortezomib in combination with cyclophosphamide and dexamethasone (BCd) in this population. As such, given the availability of IPD, bortezomib with melphalan and prednisone (BMP) was used to represent bortezomib plus alkylating agent and corticosteroid. A scenario analysis comparing DLd versus BCd was conducted, with the assumption of clinical equivalence between BCd and BMP supported by a MAIC, a naïve RWE comparison, and clinical expert opinion.

Network meta-analysis

- In the absence of direct evidence (i.e., head-to-head trials) of DLd versus other comparators, it was necessary to conduct an NMA to investigate the relative efficacy of DLd versus other relevant treatment options for ASCT-ineligible newly diagnosed MM patients.
- Overall, DLd had the highest probability of being ranked first in all the endpoints (B.2.9.1), supporting the direct evidence available from MAIA.
- Within the network, a violation of the proportional hazard (PH) assumption was observed for PFS in the FIRST trial and OS in the MAIA trial. A limitation of the NMA, therefore is that the reported relative treatment effects may therefore be biased.
- In addition, given the relatively small number of trials included, there was uncertainty through the indirect comparison with the NMA. This was because of the long chain of evidence, involving intermediate treatments, especially for the comparison of DLd versus BMP.

Comparison versus bortezomib with an alkylating agent and corticosteroid: adjusted of data from ALCYONE

- Given the uncertainty with indirect comparison through the NMA, and in particular the violation of the proportional hazards assumption, a comparison of DLd versus BMP is presented using IPD from MAIA and ALCYONE (see Section B.2.9.2).
- The IPD from MAIA and ALCYONE have been used to adjust BMP data from ALCYONE to better match the DLd arm from MAIA in terms of patient characteristics. This approach is considered statistically robust, and more appropriate compared to utilising an NMA given the use of IPD for both treatments, allowing for adjustment to account for any differences in terms of patient population (where possible based on the available data).

This also has the higher potential for accuracy, given the use of IPD, compared to an NMA with a long chain of evidence.

- Inverse probability weighting (IPW), specifically the Average Treatment effect on the Treated (ATT) approach is considered a primary analysis. This methodology is described in the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 17 and endorsed in the Centre for Health Technology Evaluation (CHTE) 'Sources and synthesis of evidence' Task and Finish group report.[116, 117]
- The results of this analysis demonstrate that DLd is provides statistically significant benefits versus BMP for all outcomes with the ATT approach (PFS [HR: [redacted]], OS [HR: [redacted]] and TTD [HR: [redacted]]), and indeed across all other methodologies explored, with the ATT approach providing more conservative estimates of this benefit versus other approaches explored.
- Overall, the approach taken in this submission is considered comprehensive. Direct trial evidence versus Ld provides the best level of evidence against a directly relevant active comparator. An NMA was explored for other comparators (rarely used in clinical practice) included in the final scope, however is limited with a violation of the proportional hazards assumption and uncertainty with the long chain of evidence. An adjusted IPD analysis from MAIA and ALCYONE provides a robust indirect comparison of DLd versus BMP. The benefit of DLd was demonstrated with all methods and outcomes explored.

B.2.9.1 Network meta-analysis (CTd and MPT)

An NMA was conducted to determine the relative efficacy of relevant treatments, based on the output of the clinical SLR informing this submission. The NMA focused on Ld and BMP versus CTd and MPT and this was considered more appropriate given the number of connections in the network (as compared with comparisons against DLd); however, full results are presented below for completeness. Further information on the methodology and results from the SLR and NMA are provided in Appendix D.

Search strategy

An overview of the SLR methods undertaken for this submission is provided in Appendix D. In summary, systematic searches were carried out in MEDLINE-, Embase-, and CENTRAL-indexed databases for RCTs that were published up to 7th December 2021 and reported the clinical efficacy and safety of relevant therapies in newly diagnosed ASCT-ineligible MM. Additional manual grey literature searches were conducted in January 2022 to identify evidence published at key conference proceedings not (yet) indexed in Embase, or additional evidence included in prior technology appraisals. Comprehensive database search algorithms are provided in Appendix D.

Study selection for the network meta-analysis

The study selection criteria for the SLR of RCTs are described in

Table 24.

Table 24: Eligibility criteria used in the search strategy for the clinical effectiveness SLR (RCT data)

	Inclusion criteria	Exclusion criteria
Population	Newly diagnosed multiple myeloma (MM) patients ineligible for autologous cell transplant (ASCT)	Indications other than MM; transplant-eligible population; relapsed/refractory MM
Intervention/ Comparators	First-line systemic anticancer therapies[a]	Radiotherapy; second- or later-line treatment; non-anticancer treatment
Outcomes	Clinical efficacy outcomes, including OS, PFS, response (e.g., ORR, VGPR, ≥CR), TTP, MRD Clinical safety outcomes, including discontinuations due to AEs, Grade 3 or 4 AEs, serious AEs, specific AE (e.g., anaemia, neutropenia)	Any other outcomes
Study design and publication type	RCT	Observational studies, single-arm trials, pharmacokinetic or pharmacodynamic studies, editorials, economic studies, reviews, letters, opinion pieces, animal studies
Time restriction	No restriction on full-text publications Conference abstracts published since 2014	Conference abstracts published before 2014
Language restriction	English	Any other language

[a] Only BCd, BMP, CTd, DLd, Ld, and MPT are relevant based on the decision problem for this submission.
Abbreviations: AE: adverse event; ASCT: autologous cell transplant; BCd: bortezomib, cyclophosphamide and dexamethasone; BMP: bortezomib, melphalan and prednisone; ≥CR: complete response or better; CTd: thalidomide, cyclophosphamide and dexamethasone; DLd: daratumumab, lenalidomide and dexamethasone; Ld: lenalidomide with dexamethasone; MM: multiple myeloma; MPT: thalidomide, melphalan and prednisone; MRD: minimal residual disease; OS: overall survival; ORR: overall response rate; PFS: progression-free survival; RCT: randomised controlled trial; TTP: time to progression; VGPR: very good partial response.

Summary of trials included in the NMA

The SLR identified a total of 33 unique RCTs (reported by 108 publications) evaluating the efficacy and safety of at least one treatment regimen relevant to the decision problem for this submission. The relevant treatment regimens are listed below:

- Daratumumab, lenalidomide and dexamethasone (DLd)
- Lenalidomide with dexamethasone (Ld)
- Bortezomib, melphalan and prednisone (BMP)
- Bortezomib, cyclophosphamide and dexamethasone (BCd)
- Thalidomide, melphalan and prednisone (MPT)
- Thalidomide, cyclophosphamide and dexamethasone (CTd)

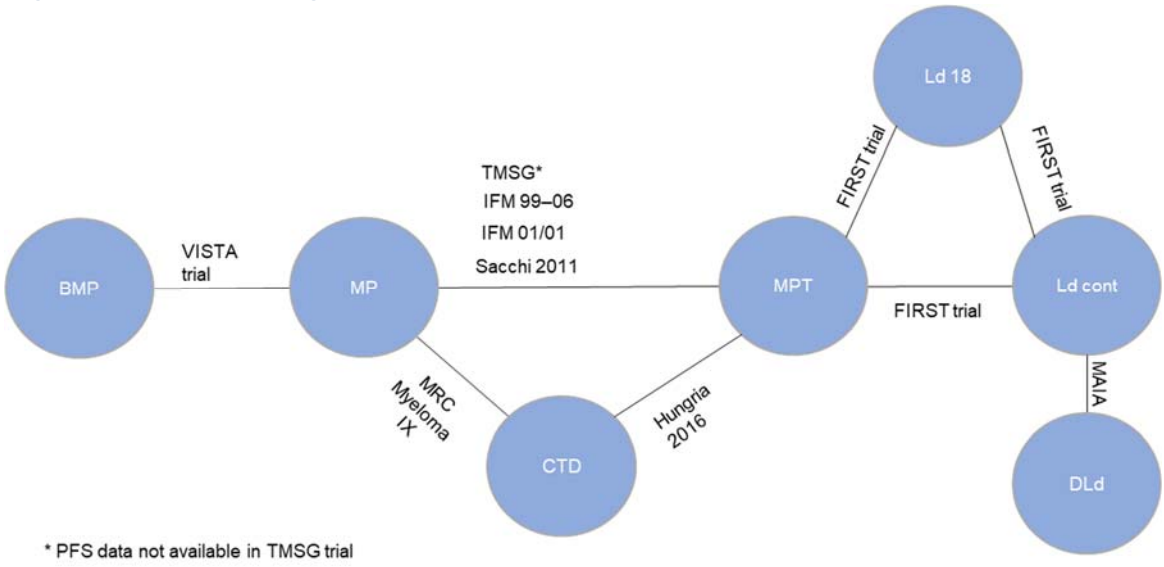
Nineteen of these trials were excluded because they evaluated only one relevant comparator and were not needed to form a connected network. A further three trials were excluded because they evaluated maintenance therapy. The rationale for excluding these trials was two-fold; first, it was considered inappropriate to pool trials with and without maintenance treatment as maintenance therapy was expected to impact relative efficacy results (e.g., overall and progression-free survival). Second, maintenance treatment strategies, such as MPT-T and MPL-L were not considered relevant based on the decision problem.

Another two trials were excluded because they were in a purely Asian patient population. Clinical practice in Asian countries differs considerably to NHS clinical practice, limiting the generalisability of evidence from these two studiers for the purposes of this submission.

Across the nine remaining trials, patient populations were largely similar, with the exception of the Hungria 2016 trial.[118] The Hungria 2016 trial included a higher proportion of female patients and patients with an ECOG PS of 2 and 3 compared to the other trials. The distribution of these patient characteristics, as well as the proportion of patients with an ISS score of II or III also differed considerably across treatment arms in the Hungria 2016 trial.[118] Given these differences, a sensitivity analysis excluding the Hungria 2016 trial was conducted.

The base-case network diagram with the nine trials included in the NMA is presented below in Figure 33. Full details of the included trials are provided in Appendix D.

Figure 33: Network diagram



Abbreviations: BMP: bortezomib, melphalan and prednisone; CTd: thalidomide, cyclophosphamide and dexamethasone; DLd: daratumumab, lenalidomide and dexamethasone; Ld: lenalidomide with dexamethasone; MP: melphalan and prednisone; MPT: thalidomide, melphalan, prednisone; PFS: progression-free survival.

Methods of NMA

An HR NMA was conducted for OS, PFS, ORR and ≥CR. Analyses of MRD negativity rate and TTD were not possible given the limited evidence available across the included trials. Furthermore, an analysis of safety data and health-related quality of life data were not considered feasible for inclusion in the NMA due to limited data availability, low event rates and high heterogeneity in the reported results (e.g., differences in categorisation and definitions for adverse events and quality of life tools used).

All NMAs were conducted in OpenBUGs (Version 1.4.3). The methodology for the analysis was as per the recommended methods published by the NICE Decision Support Unit.[119] The three NMA assumptions: similarity, heterogeneity and consistency, were tested. Both fixed and random effects models were considered for all the outcomes. When there were missing data for time-to-event outcomes (i.e., OS, PFS), the relative effectiveness with confidence interval (CI) was estimated following the validated methodology described by Guyot et al.[120]

A sensitivity analysis was conducted removing the Hungria 2016 trial from the network due to differences in patient baseline characteristics compared to the other trials and a high risk of bias.

Full details of the methodology of the NMA are provided in Appendix D, with plots enabling assessment of proportional hazards presented in Appendix O.

Results of the NMA

A fixed effects (FE) model was chosen for all endpoints due to a similar DIC score between FE and random effects (RE) models (OS and PFS networks) and the absence of considerable observed heterogeneity (OS, PFS, and response networks). Table 25 and Table 26 shows the relative treatment effects for OS and PFS, respectively.

The results showed an advantage of DLd over all relevant comparators for newly diagnosed MM ASCT-ineligible patients. In addition, the exclusion of the Hungria 2016 trial in the sensitivity analysis did not considerably impact the results or the probability of DLd ranking first. Full details of the NMA results are provided in Appendix D.

Table 25: NMA results for OS

HR (95% CI)	Ld cont	DLd	BMP	CTd	MPT
Ld cont	-	[redacted]	[redacted]	[redacted]	[redacted]
DLd	[redacted]	-	[redacted]	[redacted]	[redacted]
BMP	[redacted]	[redacted]	-	[redacted]	[redacted]
CTd	[redacted]	[redacted]	[redacted]	-	[redacted]
MPT	[redacted]	[redacted]	[redacted]	[redacted]	-

Those HRs in bold are used in the cost-effectiveness model; HRs for CTd and MPT versus Ld are used in the base case for these comparisons.
Abbreviations: BMP: bortezomib, melphalan and prednisone; CTd: cyclophosphamide and thalidomide, dexamethasone; DLd: daratumumab, lenalidomide and dexamethasone; Ld cont: lenalidomide and dexamethasone continuous; MPT: melphalan, prednisone and thalidomide; OS: overall survival.

Table 26: NMA results for PFS

HR (95% CI)	Ld cont	DLd	BMP	CTd	MPT
Ld cont	-	[redacted]	[redacted]	[redacted]	[redacted]
DLd	[redacted]	-	[redacted]	[redacted]	[redacted]
BMP	[redacted]	[redacted]	-	[redacted]	[redacted]
CTd	[redacted]	[redacted]	[redacted]	-	[redacted]
MPT	[redacted]	[redacted]	[redacted]	[redacted]	-

Those HRs in bold are used in the cost-effectiveness model; HRs for CTd and MPT versus Ld are used in the base case for these comparisons.
Abbreviations: BMP: bortezomib, melphalan and prednisone; CTd: cyclophosphamide, thalidomide and dexamethasone; DLd: daratumumab, lenalidomide and dexamethasone; Ld cont: lenalidomide, dexamethasone continuous; MPT: melphalan, prednisone and thalidomide; PFS: progression-free survival.

B.2.9.2 Adjustment of data from ALCYONE (BMP)

Whilst BMP is included in the network of evidence (see Section B.2.9.1), due to the number of studies required to connect DLd with BMP, Janssen consider it more statistically robust to use adjusted IPD based analyses leveraging ALCYONE to inform the indirect comparison in line with NICE DSU TSD 17 and as endorsed in the CHTE 'Sources and synthesis of evidence' Task and finish group report.[116, 117]

Similar to MAIA, ALCYONE is a recently conducted Phase III study in a newly diagnosed MM population who are ineligible for ASCT. Overall, MAIA and ALCYONE are comparable in study population and endpoints; in both studies, patients had newly diagnosed, symptomatic MM and were ineligible for ASCT. ASCT-ineligible was defined as aged ≥65 years, or <65 years of age with comorbid conditions that would have a negative impact on tolerability of high-dose chemotherapy used in ASCT. There were only minor differences in eligibility criteria (patients with Grade 2 or higher peripheral neuropathy were not eligible for ALCYONE, due to neuropathy associated to bortezomib and the requirement for renal function was different in ALCYONE [creatinine clearance of 40 ml/min] compared to MAIA [creatinine clearance of 30 ml/min] due to differences in backbone therapy). The primary endpoint was PFS for both trials and OS was assessed as a secondary endpoint. In terms of baseline characteristics, the populations were broadly similar. However, there were some differences:

- A greater proportion of patients were ≥75 years old in the MAIA study than in the ALCYONE study (43.6% versus 29.9%, respectively)
- Fewer participants in the DLd arm of the MAIA study had ISS Stage III disease than in the DBMP arm of the ALCYONE study (29.1% versus 40.6%, respectively)
- 16.6% of participants in the MAIA study had an ECOG performance score ≥2; while 24.6% of participants in the ALCYONE study had an ECOG performance score of 2

As IPD were available for both trials, adjustment of data from the BMP arm of ALCYONE towards the DLd arm of MAIA was conducted in order to account for differences in the patient populations across trials.

The methodology of this adjustment analysis is presented below, supplemented by Appendix R.

Analysis methods

Naïve comparisons between trials are typically biased due to confounding arising from imbalances between study populations in baseline characteristics prognostic for the outcomes of interest. In these situations, established methods such as propensity score (PS) based analyses are routinely used to estimate relative treatment effects while adjusting for observed differences between populations of interest.[117]

PS-based methods involve weighting, matching, regression adjustment or stratification based on an estimated PS. PSs represent the conditional probability that a patient is assigned to an intervention given their baseline observed covariates. These probabilities are derived using generalised linear models for binary outcomes (typically a logit or a probit model).

The overall aim of these analyses was to ensure that patients from ALCYONE who were dissimilar in terms of the selected baseline characteristics were balanced to patients in MAIA. A PS-based inverse probability weighting (IPW) approach was used as a base case analysis, and informs the cost-effectiveness model for this submission. IPW has advantages over PS matching, as it does not omit data and allows estimation of the treatment effect in the treatment cohort of interest (DLd), by reweighting the comparator cohort to reflect the population in which the treatment of interest was investigated. In this sense it is considered more efficient than PS matching methods (e.g. nearest neighbour matching) since it leverages information from all patients rather than a limited subset of patients with available data and similar PSs. A PS matching approach and covariate adjustment were conducted as sensitivity analyses.

Propensity score-based adjusted analysis

PS methods are used to mimic the effect of randomisation by creating a balance between two treatment groups in respect to clinically important, prognostic baseline covariates. The PS for an individual describes the probability of being assigned to a particular treatment, conditional on all relevant pre-treatment covariates, and is estimated using a multiple logistic regression model. These PS scores represent a summary of all characteristics included in the model for each patient.

Following calculation of the PS for each patient, IPW was used to adjust for baseline confounding variables. The IPW approach involves generating a pseudo-population in which each covariate combination is balanced between treatment groups, allowing for a population-based interpretation of results; this enables comparison to the trial population as if it had undergone a randomised control trial in which, counter to fact, both treatments were applied to each patient. Balance in covariates across both cohorts, before and after PS adjustment, was assessed by computing the standardised differences for each covariate. These standardised differences informed judgement of the most appropriate weighting approach for each data source.

The following weighting schemes were considered for the IPW approach:

- The Average Treatment effect on the Treated (ATT) approach attempts to generate a comparative arm reflecting the population enrolled in MAIA by reweighting the BMP ALCYONE cohort to match the DLd patients in MAIA. Treatment lines of treated patients receive a weight of 1, whilst control patients are reweighted by PS/(1-PS). ATT based estimates represent the relative treatment effect in the DLd population in MAIA, and for these analyses, a scaled ATT (sATT) approach was taken. In order to maintain the original sample size for the weighted populations and to properly reflect the associated uncertainty, the ATT weights were multiplied by the ratio of the original sample size versus the sum of the ATT weights making the sum of these recalculated weights equal to the original sample size. This approach is referred to as the ATT approach throughout the submission (although some figures may still be labelled as sATT).

- The Average Treatment Effect (ATE) approach estimates the ATE across both cohorts, as it weights up both propensity score distributions towards the middle. Weights are assigned to patients in the DLd cohort and the BMP cohort, creating a more similar distribution of the covariates between the two cohorts. Weights applied are Pr(treated)/PS for patients for the treated cohort and Pr(control)/(1-PS) for patients in the control cohort.

- The Average Treatment Effect for the Overlap Population (ATO) approach applies weights of 1-PS for patients in the DLd cohort and PS for patients in the BMP cohort. This approach downweights patients at both extremes of the distributions.

The ATT approach was considered for the base case of the cost-effectiveness model. The reason that the ATT approach was selected is that the DLd treatment arm of MAIA is the main intervention of relevance to this submission. With ATT weights, this population was left untouched (as all patients receive a weighting of 1) and the BMP arm from ALCYONE was reweighted such that the BMP population had a similar distribution in baseline characteristics as the DLd patients. In addition, as shown below, overlap between propensity score distributions using ATT is very high (as the observed populations were already very similar to start with) and the standardised mean differences (SMDs) after ATT weighting were small, representing good balance after ATT IPW. Other methodologies (such as covariate adjustment and matching) are more appropriate in case of poor overlap.

In the PS matching approach, the cohorts were matched with a ratio of 1:1 and using a caliper of 0.2 times the standard deviation of the PS distribution. An optimal matching approach was used, using SAS PSMATCH.[121]

Multivariable regression approach with direct adjustment for covariates (covariate adjustment)

Covariate adjustment based on a multivariable regression (Cox regression for time to event endpoints and logistic regression for binary endpoints) was considered as an alternative to PS based adjustment in adjusting for covariate imbalance and potential confounding for the Ld cohort.

The unbiased treatment effects were estimated using a multivariable model which included all relevant prognostic variables as covariates together with the treatment group indicator. The selected set of prognostic variables as covariates was specified in line with those described above. An advantage of covariate adjustment over the PS approach described in the previous section is that it provides a predictive model (including treatment) for the risk (hazard) of the outcome, which gives insight as to which covariates have the strongest influence on risk.

Identification of co-variates

To select covariates to balance, both clinical and statistical expertise was leveraged. Initially, a pool of potential prognostic variables was identified by reviewing published literature. Then, to be selected as a covariate, variables needed to be:

1. Prognostic variables of either OS or PFS (irrespective of standardised differences between comparators) in a pooled dataset of MAIA & ALCYONE (at 0.1 significance); OR
2. A variable recommended by clinical experts to be an important factor to adjust for

Potential covariates for consideration based on the above were:

- Age
- Gender
- ECOG performance status
- ISS stage at diagnosis
- Creatinine clearance

- Hepatic function
- MM type (IgG/not IgG)
- Cytogenetic risk factors
- Time since diagnosis
- Race
- Geography
- BM Plasma

Ultimately, the following covariates were included in the adjustment:

- Age
- Gender
- ECOG performance status
- ISS stage at diagnosis
- Creatinine clearance
- Cytogenetic risk factors
- Hepatic function
- MM type (IgG/not IgG)

These factors were validated by clinical expert opinion as the most important to consider when balancing characteristics from ALCYONE to those from MAIA.[64] Sensitivity analyses have been conducted assessing the impact of including additional factors in the adjustment (BM plasma cells, race and region). Results for these sensitivity analyses are presented in Appendix S.

Assessment of balance between treatment cohorts

The assessment of overlap between populations is described below.

The extent of overlap between populations with respect to the included variables was evaluated before and after adjustment. A histogram of the PSs from the two studies (Figure 34) and standardised differences for each of the variables included in the analysis suggest that, without adjustment, there was a very minor degree of heterogeneity between the populations but that in general, the populations were similar, even pre-adjustment (with none of the SMDs exceeding 0.20).

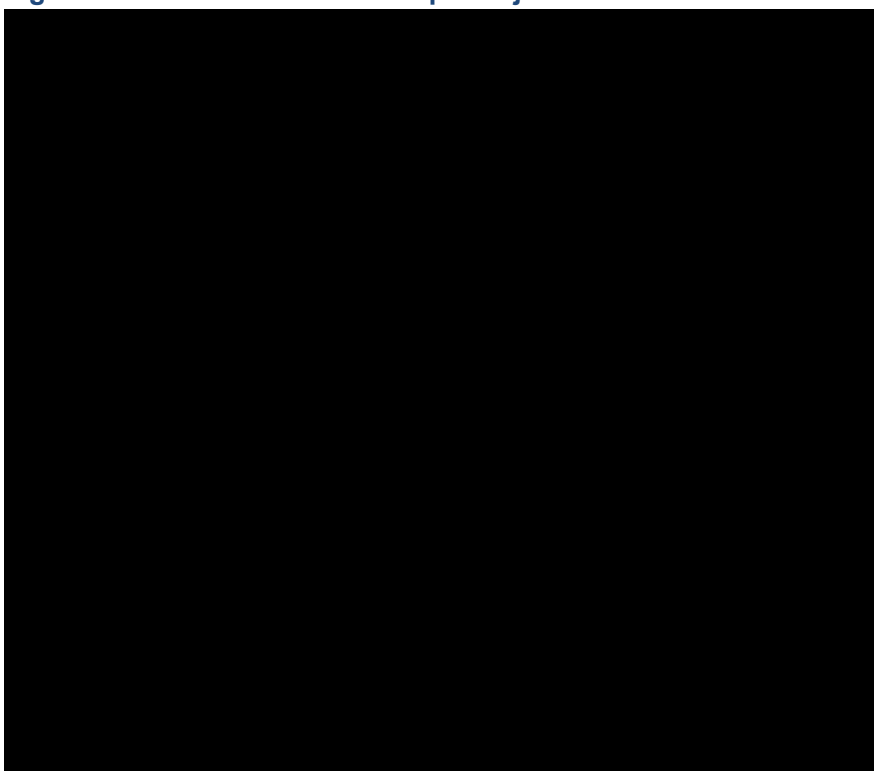
After adjusting using average treatment effect of the treated (ATT) weights, which allows to estimate the relative treatment effect in the DLd population, the balance between both treatments improved, as illustrated by the increased overlap between populations as depicted by the reweighted distribution of PSs (Figure 35) and the post-adjustment SMDs (Abbreviations: ATT: average treatment effect on the treated population; DRd: daratumumab, lenalidomide and dexamethasone (referred to as DLd throughout this submission); PS: propensity score; VMP: bortezomib, melphalan and prednisone (referred to as BMP throughout this submission).

Figure 36). In Abbreviations: ATT: average treatment effect on the treated population; DRd: daratumumab, lenalidomide and dexamethasone (referred to as DLd throughout this

submission); PS: propensity score; VMP: bortezomib, melphalan and prednisone (referred to as BMP throughout this submission).

Figure 36, if the standardised mean difference (SMD) lies within the dotted lines (i.e. ±0.20, a standard cut-off for assessing the degree of imbalance), then variables are deemed to be balanced between populations.

Figure 34: Distribution of PSs – pre-adjustment



Abbreviations: DRd: daratumumab, lenalidomide and dexamethasone (referred to as DLd throughout this submission); PS: propensity score; VMP: bortezomib, melphalan and prednisone (referred to as BMP throughout this submission).

Figure 35: Distribution of PSs – post-adjustment (ATT approach)

Abbreviations: ATT: average treatment effect on the treated population; DRd: daratumumab, lenalidomide and dexamethasone (referred to as DLd throughout this submission); PS: propensity score; VMP: bortezomib, melphalan and prednisone (referred to as BMP throughout this submission).

Figure 36: SMDs pre- and post-adjustment (ATT approach)

Abbreviations: ATT: average treatment effect on the treated population; SMD: standardised mean difference; VMP: bortezomib, melphalan and prednisone (referred to as BMP throughout this submission).

Results

The estimates of the effect of DLd relative to BMP before and after adjustment are presented in Table 27. The ATT approach is used in the base case for the health economic model for the reasons described above. Results for sensitivity analyses where additional variables are included in the adjustment are provided in Appendix R.

Table 27: Estimates of the effect of DLd relative to BMP pre- and post-adjustment

Comparison	OS HR (95% CI)	p-value	PFS HR (95% CI)	p-value	TTD HR (95% CI)	p-value
Naïve	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weighting						
ATT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ATE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ATO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Propensity score matching	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Covariate adjustment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ATC: average treatment effect for the control; ATE: average treatment effect; ATT: average treatment effect on the treated population; CI: confidence interval; HR: hazard ratio; OS: overall survival; PFS: progression-free survival; sIPW: stabilised inverse propensity weight; TTD: time to treatment discontinuation.

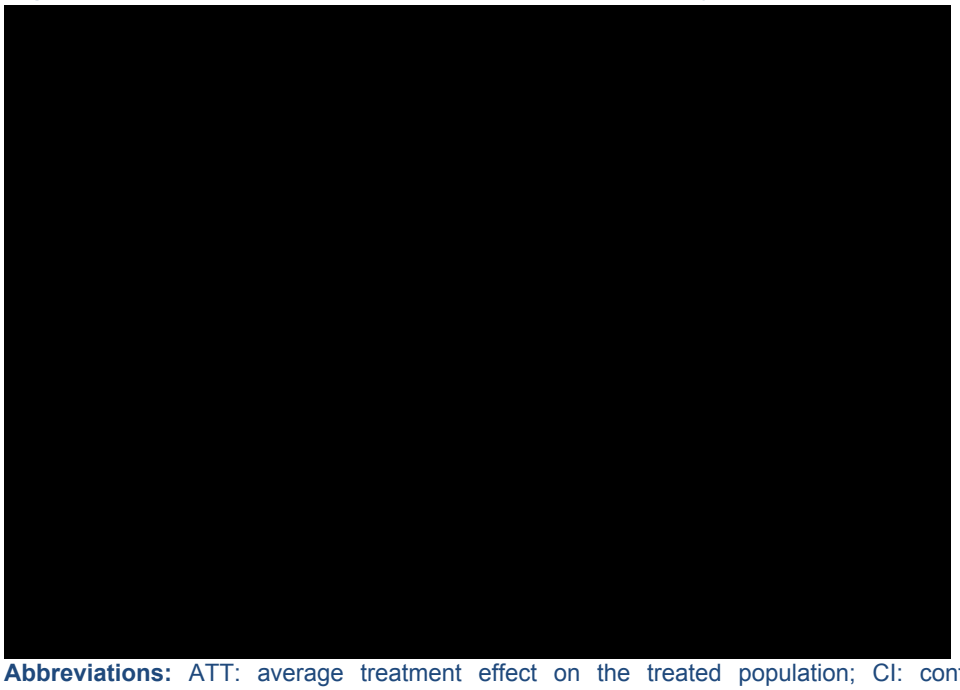
The results suggest that the approach taken in the base case cost-effectiveness model (the ATT approach) is conservative given other methodologies (specifically the propensity score matching and covariate adjustment approaches) generally lead to a lower HR across outcomes, indicating an even greater benefit for DLd versus BMP compared with the ATT approach. The provision of multiple approaches also provides an indication of upper and lower bounds for the HRs. In addition, the HRs are broadly similar across methodologies, indicating consistency in the results, supporting universally that DLd provides statistically significant benefit when compared to BMP.

The unweighted and ATT-reweighted KM curves for DLd alongside the curves for BMP are shown in Figure 37 to Figure 42 below for PFS, OS and TTD, respectively.

Figure 37: PFS KM curves for DLd and BMP (pre-adjustment)

Abbreviations: CI: confidence interval; DRd: daratumumab, lenalidomide and dexamethasone (referred to as DLd throughout this submission); KM: Kaplan-Meier; NE: not evaluable; PFS: progression-free survival; VMP: bortezomib, melphalan and prednisone (referred to as BMP throughout this submission).

Figure 38: PFS KM curves for DLd and BMP (post-adjustment; ATT approach)



Abbreviations: ATT: average treatment effect on the treated population; CI: confidence interval; DRd: daratumumab, lenalidomide and dexamethasone (referred to as DLd throughout this submission); KM: Kaplan-Meier; NE: not evaluable; PFS: progression-free survival; VMP: bortezomib, melphalan and prednisone (referred to as BMP throughout this submission).

Figure 39: OS KM curves for DLd and BMP (pre-adjustment)

Abbreviations: CI: confidence interval; DRd: daratumumab, lenalidomide and dexamethasone (referred to as DLd throughout this submission); KM: Kaplan-Meier; NE: not evaluable; OS: overall survival; VMP: bortezomib, melphalan and prednisone (referred to as BMP throughout this submission).

Figure 40: OS KM curves for DLd and BMP (post-adjustment; ATT approach)

Abbreviations: ATT: average treatment effect on the treated population; CI: confidence interval; DRd: daratumumab, lenalidomide and dexamethasone (referred to as DLd throughout this submission); KM: Kaplan-Meier; NE: not evaluable; OS: overall survival; VMP: bortezomib, melphalan and prednisone (referred to as BMP throughout this submission).

Figure 41: TTD KM curves for DLd and BMP (pre-adjustment)

Abbreviations: CI: confidence interval; DRd: daratumumab, lenalidomide and dexamethasone (referred to as DLd throughout this submission); KM: Kaplan-Meier; NE: not evaluable; TTD: time to discontinuation; VMP: bortezomib, melphalan and prednisone (referred to as BMP throughout this submission).

Figure 42: TTD KM curves for DLd and BMP (post-adjustment; ATT approach)

Abbreviations: ATT: average treatment effect on the treated population; CI: confidence interval; DRd: daratumumab, lenalidomide and dexamethasone (referred to as DLd throughout this submission); KM: Kaplan-Meier; NE: not evaluable; TTD: time to discontinuation; VMP: bortezomib, melphalan and prednisone (referred to as BMP throughout this submission).

B.2.9.3 Comparison against BCd

As a comparison between DLd and BCd in the NMA is not possible via studies identified in the SLR, an exploratory MAIC has been conducted to support the clinical equivalence of BCd and BMP. Given this MAIC is not used in the base case cost-effectiveness analysis, methodology and results are provided in the submission appendices (see Appendix N).

The assumption of equivalent efficacy was further supported by clinical expert feedback,[3, 122] and by three additional sources of evidence:

1. Sandecka et al. 2021 – An observational study conducted in 794 ASCT-ineligible NDMM patients between 2005 and 2017 in the Czech Republic. Of these, 377 (47.5%) and 172 (21.7%) received BCd and BMP, respectively. The data for PFS and OS after 23 months of follow-up are presented in Table 28 below.[123] The results show median PFS and OS was lower in patients treated with BCd compared to BMP (PFS: 22.3 versus 18.5; OS: 49.0 versus 41.7 for BCd and BMP, respectively). Probability of survival without progression and probability of survival was also lower in the BCd group compared to the BMP group, at 1, 2 and 5 years.

2. Jimenez-Zepeda et al. 2021 – An observational study conducted in 1,156 ASCT-ineligible NDMM patients between 2007 and 2018 in Canada. Of these, 377 (47.5%) and 172 (21.7%) received BCd/or prednisone and BMP, respectively. The KMs for PFS and OS are presented in Figure 43 and Figure 44, respectively. Median PFS was 21.0 and 21.1 months (p=0.0002) and median OS was 52.0 and 63.6 months (p=0.0001) in the BCd/p and BMP groups, respectively. There was no significant difference in PFS and OS between the two triplet bortezomib regimens (BMP and BCd/p).[124]

3. A real-world evidence data set from NHS Digital National Cancer Registration and Analysis Service (NCRAS) including patients diagnosed with MM in England between January 2015 and December 2019 inclusive. The data for OS and TTNT for patients who did not receive an ASCT are presented in Table 29. The results of this naïve comparison demonstrate the probability of survival and probability of not receiving a subsequent treatment similar or slightly lower in the BCd group compared to the BMP group, at 1, 2 and 5 years.

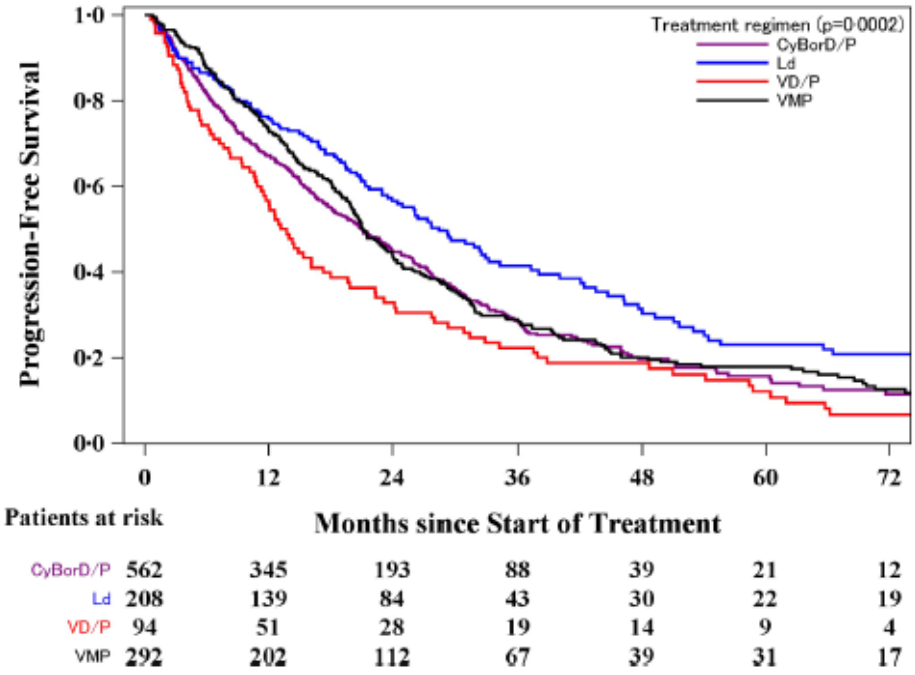
Table 28: PFS and OS data from Sandecka et al. 2021

	BMP (n=172)	BCd (n=377)
OS		
Median OS, months (95% CI)	49.0 (38.4, 59.6)	41.7 (33.9, 49.6)
Probability of survival, % (95% CI)		
1 year	92.2 (86.6, 95.5)	84.8 (80.8, 88.1)
2 years	81.1 (72.9, 87.1)	71.8 (66.6, 76.2)
5 years	43.2 (30.6, 55.1)	39.4 (30.4, 48.3)
PFS		
Median PFS, months (95% CI)	22.3 (19.6, 25.1)	18.5 (15.9, 21.2)
Probability of survival without progression or death related to MM, % (95% CI)		
1 year	73.9 (66.1, 80.2)	66.5 (61.2, 71.2)

2 years	42.8 (33.5, 51.9)	38.3 (32.8, 43.8)
5 years	15.7 (7.4, 26.8)	14.4 (8.6, 21.8)

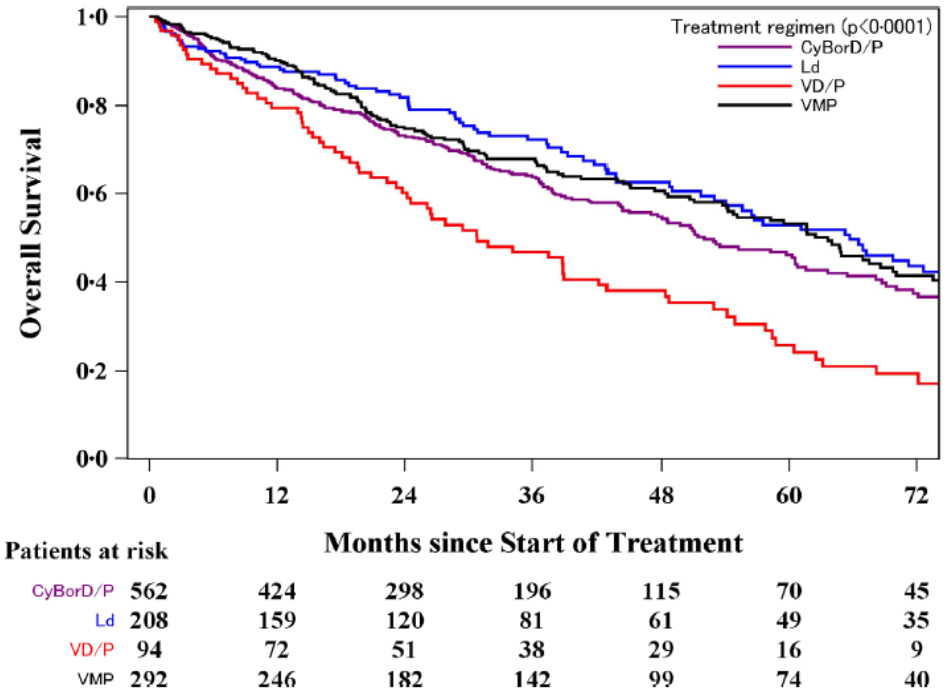
Abbreviations: BCd; bortezomib, cyclophosphamide and dexamethasone; BMP: bortezomib, melphalan and prednisone; CI: confident interval; OS: overall survival; PFS: progression-free survival; MM: multiple myeloma.
Source: Sandecka et al. 2021.[123]

Figure 43: Kaplan–Meier estimates of PFS in Jimenez-Zepeda et al. 2021



Abbreviations: CyBorD/P: bortezomib, cyclophosphamide and dexamethasone/or prednisone; Ld: lenalidomide and dexamethasone; Vd: bortezomib and dexamethasone; VMP: bortezomib, melphalan and prednisone.
Source: Jimenez-Zepeda et al. 2021.[124]

Figure 44: Kaplan–Meier estimates of OS in Jimenez-Zepeda et al. 2021



Abbreviations: CyBorD/P: bortezomib, cyclophosphamide and dexamethasone/or prednisone; Ld: lenalidomide and dexamethasone; Vd: bortezomib and dexamethasone; VMP: bortezomib, melphalan and prednisone.
Source: Jimenez-Zepeda et al. 2021.[124]

Table 29: OS and TTNT data from NHS Digital NCRAS for England between January 2015 and December 2019[a]

	BMP (n=[redacted])	BCd (n= [redacted])
Proportion of patients alive (%)		
1 year	[redacted]	[redacted]
2 years	[redacted]	[redacted]
5 years	[redacted]	[redacted]
Proportion of patients who have not received a subsequent treatment (%)		
1 year	[redacted]	[redacted]
2 years	[redacted]	[redacted]
5 years	[redacted]	[redacted]

[a] Comparisons presented are considered naïve with no attempt to adjust or match study populations.
Abbreviations: BCd; bortezomib, cyclophosphamide and dexamethasone; BMP: bortezomib, melphalan and prednisone; CTd: Cyclophosphamide, thalidomide and dexamethasone; NCRAS: National Cancer Registration and Analysis Service.

Overall, the above three sources and the MAIC (see Appendix D) support the similarity of OS and PFS estimates for patients treated with BCd compared to BMP, suggesting the assumption of equivalent efficacy in the model is appropriate with respect to the comparison of BCd versus DLd.

B.2.9.4 Uncertainties in the indirect and mixed treatment comparisons

As discussed throughout the submission, Ld represents the SoC for the majority of newly diagnosed ASCT-ineligible patients in England. The comparison between DLd and Ld is

supported by the highest level of evidence (RCT evidence) as per the hierarchy outlined by NICE. However, for completeness, as described above, to adhere to the final NICE scope and address additional comparators, a comprehensive approach has been taken to generate indirect evidence.

Violation of proportional hazards within the network of evidence

A violation of the PH assumption was observed for PFS in the FIRST trial and OS for the MAIA trial. The reported relative treatment effects from this NMA may therefore be biased. In addition, there were limitations in terms of the published IPD and KM data available to inform the NMA, and so a PH NMA was pursued.

Furthermore, the Sacchi 2011 and TMSG trials did not report HRs with corresponding CIs for OS and PFS, requiring an estimation of the relative effectiveness using the Guyot methodology.[120] Although this methodology is well established, a discrepancy in the results compared to the actual values is likely.

Further details of the NMA, and limitations associated with the NMA and MAIC are presented in Appendix D.

Adjusted ALCYONE analysis

The above analysis demonstrates that the MAIA and ALCYONE populations had minor differences with respect to the variables included in the analysis before adjustment. After adjustment, the two populations were better aligned and provided a more appropriate basis to compare the outcomes of interest between populations. Nevertheless, the analysis was limited by the presence of potentially important differences that could not be adjusted for. Whilst clinical expert opinion has confirmed that all key covariates were adjusted for in the analysis, there is a risk of unreported or unobserved confounding factors that could not be adjusted for.[64]

B.2.10 *Adverse reactions*

B.2.10.1 Data cut-off 24th September 2018

Safety was analysed as a secondary endpoint in the MAIA trial. In the MAIA Primary Analysis (data cut-off 24th September 2018), 100% of patients in the DLd group and 99.2% patients in the Ld group experienced at least one treatment emergent adverse event (TEAE). The incidence of serious TEAEs was similar in both treatment groups (62.9% in the DLd group and 62.7% in the Ld group). Although Grade 4 TEAEs were reported in a higher percentage of patients in the DLd group compared to the Ld group, fewer patients in the DLd group (7.1%) discontinued study treatment due to a TEAE compared to the Ld group (15.9%). TEAEs with an outcome of death (toxicity Grade 5; defined as a death that occurred on treatment or within 30 days of last study drug or is linked to an event that started within 30 days of last study drug and no subsequent therapy was started after treatment discontinuation) were balanced between treatment groups (6.9% in the DLd group and 6.3% in the Ld group).[8] The most common AEs of Grade 3 or 4 were neutropenia (50.0% in the DLd group versus 35.3% in the Ld group), anaemia (11.8% versus 19.7%), lymphopenia (15.1% versus 10.7%), and pneumonia (13.7% versus 7.9%).[103]

B.2.10.2 Data cut-off 21st October 2021

The safety data hereafter presented in this submission is based on the on the latest clinical cut-off from the MAIA trial (21st October 2021). The updated safety profile is broadly consistent with the findings from the September 2018 analysis. Summaries of AEs and other safety data are based on 729 patients (DLd: 364 patients, Ld: 365 patients) who were randomised, and received at least one dose of any study treatment.[104] A summary of treatment exposure, treatment-emergent adverse events (TEAEs) and SAEs in the MAIA trial are presented below. Results for the most common Grade 3 or 4 TEAEs, SAEs, TEAEs leading to discontinuation and causes of death are provided in Appendix F.

TEAE overall

At a median follow-up of 64.5 months, no new safety concerns were identified for DLd, despite the fact that the median treatment duration was more than twice as long in the DLd group than in the Ld group. An overview of TEAE as of the clinical cut-off 21st October 2021 is presented in Table 30.[102] These findings largely reflect the safety findings in the second interim analysis. Despite a slightly higher rate of Grade 3/4 serious TEAEs in the DLd group, the results demonstrate that DLd is generally well tolerated with a manageable safety profile, with lower treatment discontinuations due to AEs compared to Ld. As such, DLd offers an effective treatment option for patients with NDMM who are ineligible for ASCT, without conferring additional toxicity when compared to SoC.

Table 30: Overview of TEAEs in the MAIA trial (safety population) (data cut-off 21st October 2021)

	DLd (n=364)	Ld (n=365)
Any TEAE, n (%)	[redacted]	[redacted]
Any Grade 3 or 4 TEAE, n (%)	[redacted]	[redacted]
Serious TEAE, n (%)	[redacted]	[redacted]
TEAE leading to discontinuation of study treatment[a]	[redacted]	[redacted]
TEAEs leading to death, (%)	[redacted]	[redacted]

[a] Includes those patients indicated as having discontinued study treatment due to an adverse event on the end of treatment CRF page.
Abbreviations: DLd: daratumumab, lenalidomide and dexamethasone; Ld: lenalidomide and dexamethasone; TEAE: treatment-emergent adverse event.
Source: MAIA HEMAR report. [Data on file]. TSFAE01B. 2022.[9]

TEAE leading to dose modification

Per protocol, patients in both treatment arms received 25 mg of oral lenalidomide on Days 1 through 21 of each 28 day cycle until disease progression or unacceptable toxicity. Patients with a creatinine clearance of 30–50 mL/min were recommended a reduced lenalidomide dose of 10 mg. In addition, lenalidomide dose adjustments were recommended for patients who experienced TEAEs, such as neutropenia.[95] A higher rate of lenalidomide discontinuation due to TEAEs was reported for DLd versus Ld, ([redacted] versus [redacted], respectively).[9]

Lenalidomide dose modifications started early during treatment with [redacted] patients ([redacted]) in the DLd group and [redacted] patients ([redacted]) in the Ld group receiving a modified dose during Cycles 1–2. The highest percentage of patients received a modified dose of lenalidomide during Cycles 7+ in the DLd ([redacted] patients; [redacted]) and Ld ([redacted] patients; [redacted]) groups.[8]

The most common TEAEs (all grades) leading to dose modifications of lenalidomide were: neutropenia (DLd: [redacted]; Ld: [redacted]), diarrhoea (DLd: [redacted]; Ld: [redacted]), pneumonia (DLd: [redacted]; Ld: [redacted]) and thrombocytopenia (DLd: [redacted]; Ld: [redacted]) (at a median follow-up up of 28.0 months).[8] The rate of treatment discontinuation due to AEs for DLd was low and consistent with the safety profile of daratumumab-based regimens in the POLLUX and ALCYONE clinical trials.[125, 126]

A higher percentage of patients presented with creatinine clearances <60 mL/min in the DLd group ([redacted]) versus the Ld group ([redacted]) at baseline, which also could have, in part, accounted for lenalidomide dose modifications and lowered lenalidomide exposure in the DLd group.[8]

Treatment exposure

The median duration of study treatment was [redacted] months in the DLd group and [redacted] months in the Ld group. The median relative dose intensity of lenalidomide was [redacted] in the DLd group and [redacted] in the Ld group.[9] A summary of the duration of treatment and relative dose intensity in the MAIA trial is provided in Table 31.

Table 31: Summary of MAIA study duration of treatment (safety population) (data cut-off 21st October 2021)

	DLd (n=364)	Ld (n=365)
Median duration of treatment (months)	[redacted]	[redacted]
Daratumumab IV (mg/kg) relative dose intensity, %		
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Range	[redacted]	[redacted]
Lenalidomide (mg) relative dose intensity (%)		
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Range	[redacted]	[redacted]
Dexamethasone (mg) relative dose intensity (%)		
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Range	[redacted]	[redacted]

Abbreviations: DLd: daratumumab, lenalidomide and dexamethasone; Ld: lenalidomide and dexamethasone; MM: multiple myeloma; SD: standard deviation.
Source: MAIA HEMAR report. [Data on file]. TSIEXP02 and TSIEXP05. 2022.[9]

Given that the majority of patients with NDMM who are ineligible for ASCT are unfit and/or elderly and typically frail, a reduction in the Ld aspect of the DLd regimen may limit toxicity. This would offer a more manageable treatment option for these patients, where clinicians are able to modify dosage to improve tolerability, without compromising on efficacy.

Discontinuation in the DLd treatment arm

At a median follow-up of 64.5 months, [redacted] patients in the DLd group discontinued Ld but continued daratumumab, and an additional [redacted] patients discontinued lenalidomide but continued daratumumab and dexamethasone. Six patients in DLd discontinued daratumumab but continued Ld (Table 32).

Table 32: Selective discontinuation of components of the DLd regimen (safety population) (data cut-off 21st October 2021)

	DLd (n=364)
Patients that selectively discontinued lenalidomide[a]	[redacted]
Time to lenalidomide discontinuation (months)	
Mean (SD)	[redacted]
Duration of daratumumab treatment (months)	
Mean (SD)	[redacted]
Patients that discontinued lenalidomide alone, while continuing on daratumumab and dexamethasone	[redacted]
Patients that discontinued lenalidomide and dexamethasone, while continuing on daratumumab	[redacted]
Time to lenalidomide and dexamethasone discontinuation (months)[b]	
Mean (SD)	[redacted]
Duration of daratumumab treatment (months)	
Mean (SD)	[redacted]
Patients that discontinued daratumumab, while continuing on lenalidomide	[redacted]
Time to daratumumab discontinuation (days)	
Mean (SD)	[redacted]

[a] Includes patients that discontinued lenalidomide alone or lenalidomide + dexamethasone, while continuing on daratumumab
[b] In the case that lenalidomide and dexamethosone were stopped at different times, the later time is used for calculation
Abbreviations: DLd: daratumumab, lenalidomide and dexamethasone; SD: standard deviation.
Source: MAIA CSR (October 2021 data cut). [Data on File]. 2022. TSIEXP10.[113]

TEAE by preferred term

The verbatim terms used by investigators to identify AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class. The most common (at least 10%) TEAEs by MedDRA System Organ Class and preferred term are presented in Table 33. The most common (at least 5%) Grade 3 or higher TEAEs were neutropenia (54.1% of patients in the DLd group versus 37.0% of patients in the Ld group), pneumonia (19.5% versus 10.7%), anaemia (17.0% versus 21.6%), and lymphopenia (16.5% versus 11.2%). Grade 3 or higher infections were reported more frequently in the DLd group than in the Ld group.[102]

Table 33: Most common (at least 10%) TEAEs by MedDRA System Organ Class and preferred term in the MAIA trial (safety population) (data cut-off 21st October 2021)

	DLd (n = 364)	Ld (n = 365)
Infections and infestations	[redacted]	[redacted]
Bronchitis	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]
Influenza	[redacted]	[redacted]

Rhinitis	[redacted]	[redacted]
Gastroenteritis	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Oedema peripheral	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]
Chills	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Constipation	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]
Abdominal pain upper	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]
Back pain	[redacted]	[redacted]
Muscle spasms	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]
Pain in extremity	[redacted]	[redacted]
Musculoskeletal pain	[redacted]	[redacted]
Bone pain	[redacted]	[redacted]
Muscular weakness	[redacted]	[redacted]
Musculoskeletal chest pain	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]
Leukopenia	[redacted]	[redacted]
Lymphopenia	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]
Peripheral sensory neuropathy	[redacted]	[redacted]
Headache	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]
Paraesthesia	[redacted]	[redacted]
Tremor	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]
Cough	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]

Metabolism and nutrition disorders	[redacted]	[redacted]
Hypokalaemia	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]
Hypocalcaemia	[redacted]	[redacted]
Hyperglycaemia	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	[redacted]	[redacted]
Rash	[redacted]	[redacted]
Pruritus	[redacted]	[redacted]
Psychiatric disorders	[redacted]	[redacted]
Insomnia	[redacted]	[redacted]
Anxiety	[redacted]	[redacted]
Depression	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]
Hypotension	[redacted]	[redacted]
Deep vein thrombosis	[redacted]	[redacted]
Investigations	[redacted]	[redacted]
Weight decreased	[redacted]	[redacted]
Injury, poisoning and procedural complications	[redacted]	[redacted]
Fall	[redacted]	[redacted]
Renal and urinary disorders	[redacted]	[redacted]
Acute kidney injury	[redacted]	[redacted]
Chronic kidney disease	[redacted]	[redacted]
Eye disorders	[redacted]	[redacted]
Cataract	[redacted]	[redacted]
Cardiac disorders	[redacted]	[redacted]
Atrial fibrillation	[redacted]	[redacted]

Abbreviations: DLd: daratumumab, lenalidomide and dexamethasone; Ld: lenalidomide and dexamethasone; TEAE: treatment-emergent adverse event.
Source: MAIA HEMAR report. [Data on file]. TSFAE02AA. 2022.[9]

SAEs

Serious adverse events (SAEs) occurred in [redacted] of 364 patients in the daratumumab group and [redacted] of 365 patients in the Ld group, the most common of which was pneumonia, occurring in [redacted] of patients in the daratumumab group and [redacted] patients in the Ld group.[9] The higher rate of pneumonia may be due to a longer treatment duration for patients in the DLd arm (as of the latest data cut-off, the median duration of treatment was [redacted] months in the DLd group and [redacted] months in the Ld group). Whilst pneumonia was the most common SAE (and the most common infection at Grade 3+), the higher rate of pneumonia did not result in a high discontinuation rate due to infections or rate of fatal AEs due to infection for DLd or Ld, indicating that this AE is clinically manageable. Specifically, only [redacted] and [redacted] patients in the DLd and Ld arms, respectively discontinued due to pneumonia and death due to pneumonia only occurred in [redacted] and [redacted] of patients receiving DLd and Ld, respectively.

A summary of the most common SAEs is presented in Appendix F.

B.2.11 *Ongoing studies*

The MAIA trial is an ongoing study with an estimated end date of January 2026. A final OS analysis is expected to take place in [redacted] (which will occur after 390 deaths have been observed), providing longer follow-up for outcomes for Ld and DLd. In addition, the ALCYONE trial is ongoing, with an estimated study completion date of June 2023.[127] A final OS analysis for ALCYONE is expected to occur in [redacted] to provide longer-term follow-up for BMP outcomes.

There are no additional studies planned providing additional clinical evidence for the DLd combination in the front-line ASCT-ineligible NDMM setting.

A summary of the relevant clinical trials for the evaluation of daratumumab in the NDMM ASCT-ineligible population is provided in Table 34.

Table 34: Clinical trials for the evaluation of daratumumab in NDMM TIE MM patients

Study	Target indication/ population	Primary objective	Phase	N	Efficacy hypothesis	Trial start date	Estimated trial completion date	Interim data before completion?
MMY3008 (MAIA)	Daratumumab in combination with lenalidomide and dexamethasone for the treatment of patients with newly diagnosed multiple myeloma and who are not candidates for high dose chemotherapy and ASCT	To compare the efficacy of DLd to that of Ld, in terms of PFS in patients with newly diagnosed multiple myeloma who are not candidates for high-dose chemotherapy and ASCT.	III	737	The study is designed to achieve a power of 80% to detect a 25% reduction in the risk of disease progression or death (i.e. assuming the HR [DLd versus Ld] of 0.72 with a log rank test [two-sided alpha = 0.05])	February 2015	[redacted]	[redacted]
MMY3007 (ALCYONE)	Daratumumab in combination with bortezomib, melphalan and prednisone for the treatment of patients with previously untreated MM who are ineligible for high dose chemotherapy and ASCT	To determine if the addition of daratumumab to bortezomib, melphalan and prednisone will prolong PFS compared with BMP alone.	III	706	The study is designed to achieve a power of 85% to detect a 27.6% reduction in the risk of death (i.e. assuming the HR [DLd versus Ld] of 7.3 with a log-rank test [two-sided alpha = 0.05]).	December 2014	[redacted]	[redacted]
MMY3019 (CEPHEUS)	Daratumumab in combination with bortezomib, lenalidomide and dexamethasone for the treatment of adult patients with newly diagnosed MM for which an ASCT is not planned as initial therapy.	To determine if the addition of daratumumab to bortezomib, lenalidomide and dexamethasone will improve overall MRD negativity rate compared with BLd alone.	III		[redacted]	November 2018	[redacted]	[redacted]

Abbreviations: ASCT: autologous stem cell transplant; BMP: bortezomib, melphalan and prednisone; DLd: daratumumab, lenalidomide and dexamethasone; HR: hazard ratio; Ld: lenalidomide and dexamethasone; MM: multiple myeloma; MRD: minimal residual disease; PFS: progression free survival.

B.2.12 *Interpretation of clinical effectiveness and safety evidence*

Strengths and limitations of the clinical evidence base

MAIA was a registrational quality Phase III RCT that directly compared DLd against the most relevant active comparator in current NHS clinical practice, Ld, thus providing the highest level of evidence as per the NICE hierarchy. The trial was an active-controlled study conducted in line with ICH guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements. Steps taken to ensure the accuracy and reliability of the data included the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study-site personnel before the study, periodic monitoring visits by sponsor representatives, and direct transmission of clinical laboratory data from a central laboratory into the sponsor's data base. The study had an open-label design due to the difference in mode of administration for the trial drugs. However, the risk for bias was minimised since patients were randomised using a central interactive web response system (IWRS). In addition, outcomes were reviewed by an Independent Data Monitoring Committee (IDMC).[95]

In the MAIA trial, daratumumab was administered intravenously to the DLd group. More recently, daratumumab has become available as a SC formulation, which reduces the time associated with administration from several hours to approximately three to five minutes, and has fewer injection site reactions and IRRs[1, 15, 16] Based on clinical expert feedback, daratumumab would be administered almost exclusively as the SC formulation in clinical practice in England, with clinicians noting that the efficacy of the SC formulation is considered equivalent to that of the IV formulation, as supported by non-inferiority trial data.[15]

Generalisability of MAIA to clinical practice in England

MAIA was a multicentre, international trial that enrolled participants generally representative of patients with NDMM who are ineligible for ASCT in England. Fourteen sites were located in the UK, across 12 locations: Aberdeen, Canterbury, Dundee, Leeds, London, Manchester, Nottingham, Oxford, Plymouth, Southampton, Truro and Wolverhampton. A total of 67 patients were enrolled across these sites. Clinical experts considered that the patient characteristics of the MAIA trial are well balanced across treatment arms.[3] Moreover, clinicians confirmed that the most relevant comparator in this indication is Ld, indicating that the comparison made in the MAIA trial is the most relevant for English clinical practice.[3]

The generalisablity of the MAIA population to the UK MM ASCT-ineligible population was demonstrated in a recent RWE study commissioned by Janssen. This standing cohort study utilised routine population-level data available through the NHS Digital NCRAS to investigate PFS and OS for the NDMM ASCT-ineligible patient population. Out of [redacted] patients, the mean age of patients who did not receive an ASCT was [redacted] at diagnosis, compared with [redacted] years in the MAIA trial. The proportion of female patients who did not receive an ASCT was [redacted] and 47.9% in the NHS Digital NCRAS study and the MAIA trial, respectively. Of the patients who did not receive an ASCT with valid data for completeness for tumour stage in the NCRAS study, [redacted] had a non-zero performance status at diagnosis, compared with 66.1% of patients in the MAIA trial.[84]

Benefit for elderly ASCT-ineligible MM patients

As described in Section B.1.3.1, MM has a median age at presentation of ≥65 years in the UK, with elderly patients experiencing a reduced benefit from novel agents, due to a reduced ability to

tolerate these therapies often leading to treatment discontinuation. The selection of treatment in vulnerable elderly patients should also consider the risk of toxicity and the capability to tolerate treatment, since advanced age and the occurrence of severe adverse events may negatively affect survival.[128] MAIA shows that elderly patients generally experience clinical benefit from CD38 antibody-based regimens such as DLd.[129] This is confirmed by subgroup analyses, which also demonstrate that patients age 75 years or older benefit from DLd, with improved response rates and survival outcomes.[111] In addition, the improved efficacy of DLd versus Ld was observed across frailty subgroups.[105]

Principal findings of the clinical evidence base

In the MAIA trial, DLd resulted in a groundbreaking clinical benefit that was both statistically significant and clinically meaningful compared with Ld alone. After over five years of study follow-up, the addition of daratumumab to Ld resulted in a 34% reduction in the risk of death compared with Ld (HR: 0.66; 95% CI: 0.53, 0.83) with a trend towards relative OS improvement over time.[9] The significant PFS benefit from the primary PFS analysis was maintained in the DLd group over the Ld group, with a 45% reduction in the risk of disease progression or death (HR: 0.55; 95% CI: 0.45, 0.67). The median PFS in the DLd group was 61.86 months, compared with 34.43 months in the Ld group. Indeed, results at a median follow-up of 64.5 months suggested that the median PFS for patients treated with DLd is broadly similar to the median OS for patients treated with Ld. As such, DLd has the potential to delay disease progression for the same duration as patients are currently expected to survive for under SoC (Table 35).

Table 35: Median PFS and OS in the MAIA study (data cut-off 21st October 2021)

	DLd	Ld	HR (p-value)
PFS (months)	61.9	34.4	0.55 [redacted]
OS (months)	NE	65.5	0.66 [redacted]

Abbreviations: DLd: daratumumab, lenalidomide and dexamethasone; Ld: lenalidomide and dexamethasone; NE: not estimable; PFS: progression-free survival; OS: overall survival.
Source: MAIA HEMAR report. [Data on file]. 2022.[9]

This is in line with patient preferences, where patients highlight an increased life expectancy and longer remission/response as the most valued treatment attributes.[50, 52]

In MAIA, the MRD negativity rate was significantly higher in patients treated with DLd compared with those treated with Ld alone.[104] DLd achieved deep responses with a more than doubling of sCR and more than tripling of MRD negativity rates. MRD is a more sensitive measure of disease burden than the measures of clinical response defined by the IMWG revised uniform response criteria (including sCR, CR and VGPR), and has been linked to depth of response and long-term outcomes.[68]

Whilst the routine assessment of MRD negativity is not yet established in UK clinical practice, the positive link between MRD negativity and long-term survival outcomes means that MRD negativity is a highly relevant prognostic marker associated with substantial clinical benefit. Indeed, in the prior evaluation for daratumumab in combination for untreated MM when stem cell transplant is suitable (TA763), MRD negativity was considered to be likely to predict survival outcomes better than sCR.[130]

No new safety concerns were identified in the MAIA trial, and DLd has a well characterised safety profile. There were with fewer treatment discontinuations for DLd due to AEs compared with Ld and an observed safety profile in patients with front-line ASCT-ineligible MM that is consistent with

previous studies of daratumumab and combination therapy. Daratumumab is now available in an SC formulation and has a manageable safety profile in combination regimens, with little added toxicity aside from infusion related reactions, which is especially important in the ASCT-ineligible patient population, some of whom may elderly. No new safety concerns were identified in the MAIA trial, and treatment with DLd was well-tolerated, demonstrating a safety profile consistent with the known safety profiles for daratumumab, and Ld treatments. Grade 3 or higher infections were reported more frequently in the DLd group than in the Ld group, whereas the incidence of SAEs and the incidence of infections leading to treatment discontinuation were similar between the treatment groups. Pneumonia was the most common Grade 3 or higher infection and the most common SAE. However, these events were effectively managed in the clinical setting and did not result in an increase of treatment discontinuations and fatal TEAEs. In addition, DLd delivers early and sustained improvement in HRQoL and significantly greater reduction in pain symptoms when compared with SoC.[9]

Overall summary

As a highly innovative and effective therapy, the combination of DLd would represent a landmark advance in the management of newly diagnosed adult patients with MM who are ineligible for ASCT in the UK, with a significant positive impact to the MM pathway.

With over 5 years of median follow up available, MAIA showed a statistically significant and clinically meaningful PFS and OS benefit for DLd, versus the directly relevant active comparator (Ld) . DLd provides a PFS benefit for patients which is similar to the OS for Ld, , whilst significantly improving OS. In MAIA, compared to Ld, patients treated with DLd experienced a deeper response, with approximately [redacted] times higher rate of MRD negativity at the $x10^{-5}$ sensitivity ([redacted]%) , approximately [redacted] times higher rate of MRD at $x10^{-6}$ sensitivity ([redacted]) , and more than [redacted] times higher rates durable rates of MRD negativity rates [redacted]. The higher degree of MRD negativity achievement with DLd indicates that patients receiving this combination are more likely to achieve a deeper response and thus longer

DLd also offers a prolonged time to worsening of HRQoL than Ld, with a significantly greater reduction in pain symptoms, addressing the patient preferences outlined in section B.1.3.3. As such, the associated depth and durability of response addresses an unmet need, enabling patients and carers alike to have a prolonged period of quality time with loved ones.

B.3 Cost effectiveness

Summary of cost-effectiveness

- A cost-utility model was developed to estimate the cost-effectiveness of DLd versus relevant comparators for the treatment of NDMM patients who are ineligible for ASCT.
- As noted in Section B.1, Ld is the most relevant comparator for DLd. Bortezomib in combination with an alkylating agent and corticosteroid is considered as an additional comparator (represented by BMP [see Appendix N] and BCd [scenario analysis only; see Appendix N]), given usage in a minority of patients. Thalidomide-based combinations have negligible use in English clinical practice and are not considered relevant comparators; however, given such regimens are included in the final scope issued by NICE, comparisons against these treatments are provided in the submission appendices.
- The model was a partitioned survival model consisting of three mutually exclusive health states: (i) progression-free (PF), (ii) progressed disease (PD), and (iii) death.
- Baseline characteristics were informed by the MAIA trial. Clinical expert feedback confirmed that the two treatment arms were well balanced, and broadly reflective of clinical practice in England (noting the sizeable proportion of patients over 75 years of age included in MAIA).[64]
- Extrapolation of PFS and OS for DLd and Ld was performed using patient-level data from the MAIA trial and for bortezomib-based therapy (represented by BMP), extrapolation was performed using adjusted patient-level data from the ALCYONE trial (see Section B.2.9.2).
- CTd and MPT were modelled using HRs versus Ld, derived from an NMA.
- Health state utility values values were derived from the MAIA trial and AE disutilities was informed by the literature.
- The analysis was consistent with the NICE reference case and took a National Health Service (NHS) and Personal Social Services (PSS) perspective. Costs and benefits were discounted at a rate of 3.5% and a lifetime time horizon was adopted.
- The NICE Position Statement advises to exclude the consideration of products recommended for use in the CDF. Janssen note, however, that in the event of important changes in the treatment pathway, the Committee will want to understand the impact on cost-effectiveness of DLd (as per TA763).[130] Given the widespread usage of CDF treatments across the myeloma pathway, recommendation of these therapies for baseline commissioning over the course of this appraisal would constitute an important change to the treatment pathway. As such, analyses both including and excluding the costs of CDF treatments as subsequent therapies is presented to inform Committee decision making.
- In the deterministic base case economic analysis, both bortezomib-based (BMP) and thalidomide-based (CTd and MPT) comparators are dominated by Ld. Treatment with DLd at PAS price, compared with the main comparator Ld, was associated with increased life years (+2.64 per patient), increased QALYs ([redacted] per patient), at an incremental cost of £[redacted] per patient. As a result, DLd was associated with an ICER of £[redacted]/QALY gained.
- [redacted]
  - [redacted]

- [redacted]
- [redacted]
- The probabilistic cost-effectiveness analysis results were similar to the deterministic base case results, demonstrating that the results are robust to variation associated with model input parameters.

B.3.1 *Published cost-effectiveness studies*

SLRs were conducted in order to identify published economic evaluations of interventions for patients with NDMM who are ineligible for ASCT, evidence relating to the HRQoL and utility (humanistic burden) and cost/resource use (economic burden) that may be of relevance to this submission. Full details of all SLRs (including identified HRQoL and cost/resource studies) are presented in Appendix G, H and I, respectively.

The SLR of cost-effectiveness studies was originally conducted on 5th March 2021 and updated on 23rd February 2022. In total, the review identified 32 records, including 12 full-text articles, 16 conference posters/abstracts and four prior technology appraisals. As only three publications and three prior technology appraisals included a UK setting, the SLR was expanded to also present cost-effectiveness models from non-UK settings. No economic evaluations were identified for DLd in this indication.

B.3.2 *Economic analysis*

As no UK models which included DLd were identified in the SLR, a *de novo* cost-utility analysis (CUA) has been conducted for the purpose of this evaluation. This model is described in detail below.

The aim of the economic analysis was to determine the cost-effectiveness of DLd versus relevant comparators as a treatment for adult patients with ASCT-ineligible NDMM. The analysis has been conducted from the perspective of the NHS in England taking into account direct costs and benefits only.

The economic evaluation was approached as follows, in line with the NICE reference case:

- Health outcomes were measured both in terms of life years gained (LYG) and QALYs gained
- Primary outcome measure for the economic evaluation was the ICER (cost per QALY gained) for the comparison of DLd versus the relevant comparators
- Clinical effectiveness for DLd and the comparators was measured through OS and PFS outcomes (see Section B.3.3)
- All relevant costs are considered including:
  - Treatment acquisition costs (see Section B.3.5.1)
  - Administration costs (see Section B.3.5.1)
  - AE costs (see Section B.3.5.3)
  - Costs associated with subsequent treatments (see Section B.3.5.1)

- Concomitant medicines (see Appendix K)
- Resource use (see Section B.3.5.2)
- End-of-life costs (see Section B.3.5.2)

- The model used a lifetime time horizon (equivalent to 26 years; the maximum age that could be reached in the model is 100 years old)
- The discount rate is set to 3.5% for both costs and benefits, with scenario analysis provided with a discount rate of 1.5% for both costs and benefits (see Section B.3.10.2)

B.3.2.1 Patient population

The population of interest is patients with ASCT-ineligible NDMM. This is in line with the marketing authorisation for DLd in NDMM and the population of the MAIA trial.[8, 131]

The characteristics of patients entering the model were based on the baseline demographic and disease characteristics of the ITT population recruited in MAIA (Table 36). As discussed in Section B.2.3.2, these data are well balanced across treatment arms. Clinical expert feedback suggests that unlike any other key trials in this indication, the patients recruited in MAIA included a sizeable proportion of patients over 75 years of age, reflective of clinical practice in England. Furthermore, the baseline characteristics are also considered to be broadly generalisable to clinical practice in England based on a recent RWE study which used routine population-level data available through the NHS Digital NCRAS (see Section B.2.12 and Table 36).[84] Age and gender are included in the model to determine general population mortality inputs.

- Age is also used to inform general population utility values (refer to Section B.3.4.1)
- Body weight and body surface area (BSA) are included in the model in order to calculate the drug acquisition costs of treatments that are dosed based on weight (e.g. daratumumab IV formulation [scenario only] or BSA [e.g. bortezomib, melphalan, prednisone and carfilzomib; refer to Section B.3.5.1)

Table 36: Patient baseline characteristics in the cost-utility analysis and comparison to those from NHS Digital NCRAS RWE in England

Characteristic	MAIA ITT values (used in model)	NHS Digital RWE dataset
Mean age of patients (years)	[redacted]	[redacted]
Mean weight of patients (kg)	[redacted]	[redacted]
Mean BSA of patients (m^2)	[redacted]	[redacted]
Male (%)	[redacted]	[redacted]

Abbreviations: BSA: body surface area; ITT: intention-to-treat; NR: not reported; RWE: real-world evidence.
Source: MAIA CSR (October 2021 data cut). [Data on file]. 2022.[8]

B.3.2.2 Model structure

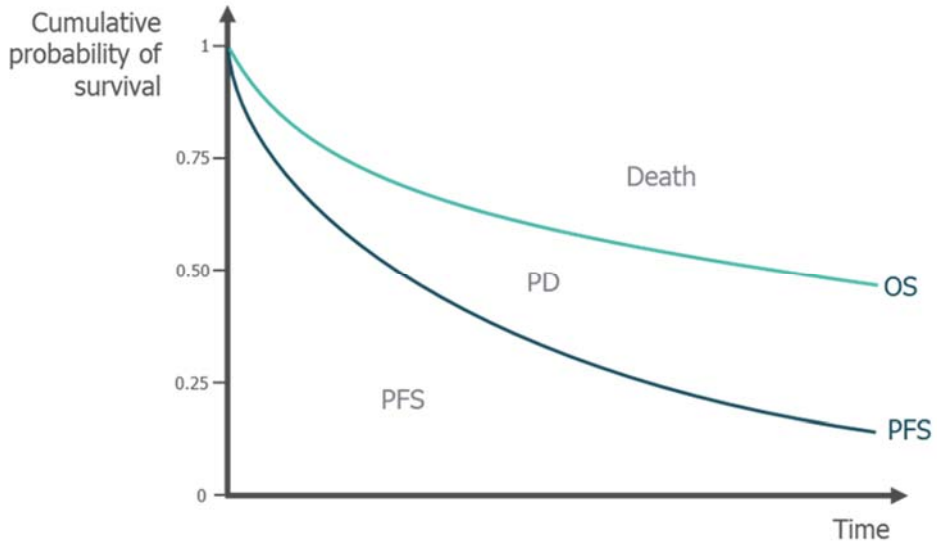
The developed model consists of three mutually exclusive health states: (i) progression-free (PF), (ii) progressed disease (PD), and (iii) death. In the base case analysis, the occupancy of health states over time was derived from the survival curves from the MAIA (DLd and Ld) and ALCYONE (BMP) trials, which represent the main sources of evidence for this submission. The proportion of patients occupying each health state was calculated using the PFS and OS survival curves, as described below and shown in Figure 45:

- The proportion of patients occupying the PF state was calculated as the proportion alive and progression-free (based on PFS curves)
- The proportion of patients occupying the PD state was calculated as the proportion alive (based on OS curve) minus the proportion of patients alive and progression-free (based on PFS curves)
- The proportion of patients occupying the death state was calculated as the proportion who had died (based on OS curve)

BMP has a fixed treatment duration, and DLd or Ld patients may discontinue treatment for reasons other than progression. As such, time to treatment discontinuation (TTD) was used to determine the time on treatment (ToT), to account for patients who may have discontinued treatment before progression. . This allows for the application of specific health-state costs, such as treatment acquisition, treatment administration and monitoring costs, to be applied only while patients are on or off treatment, while also allowing patients to occupy the PF and PD health-states regardless of whether they are on treatment.

The model uses a cycle duration of four weeks to align with the cycle lengths in the DLd and Ld regimens.

Figure 45: Partitioned survival model structure



Abbreviations: OS: overall survival; PD: progressed diseased; PFS: progression-free survival.

Justification for choice of model structure

A partitioned survival model (PSM) was deemed the most appropriate model structure to inform the cost-effectiveness of DLd for several reasons. The MAIA and ALCYONE trials are the key trials informing the efficacy for the model; the primary and key secondary endpoints in MAIA and ALCYONE were time-to-event outcomes (e.g. PFS and OS), which directly corresponds with survival functions used in the PSM. The PSM model structure therefore allows intuitive incorporation of the PFS and OS data collected from the key trials.

In addition, the MAIA trial has mature survival data; after a median follow-up of 64.5 months (over 5 years), disease progression or death had occurred in [redacted] participants ([redacted]) in the DLd group and [redacted] participants ([redacted]) in the Ld group. Median follow-up in ALCYONE was similarly mature with 40.1 months median follow-up.[3] Mature survival data reduces uncertainty in the

extrapolations, ensuring modelled events closely match observed data. Furthermore, the PSM structure allows uncertainty in long-term extrapolations to be explored through scenario analyses utilising alternative survival distributions (see Section B.3.10.2).[126, 132] Finally, as MM is a chronic, incurable disease, there is no requirement for functionality to move backwards between the health states.

There is also precedent from previous NICE evaluations for the use of PSMs in NDMM. A PSM was preferred by the ERG in TA228.[69] In TA587, a hybrid structure was used: a PSM using the Kaplan–Meier data for the first 92 weeks, and thereafter a multi-state Markov model with a constant transition probability between the three states: pre-progression, progressed disease and death. However, the Committee was unclear on the advantage given by this hybrid approach and highlighted that a partitioned survival analysis would have allowed more flexible modelling as it would have been possible to model OS and PFS independently.[4] In addition, PSMs have also been accepted for decision making in other previous daratumumab evaluations in MM (TA763 and TA311).[130, 133]

A limitation of the PSM is the lack of structural link between PFS and OS because each endpoint is modelled independently. This could lead to incongruent relationships of PFS and OS (e.g. the PFS and OS curves crossing). However, in this model, the PFS and OS curves produce plausible estimates across the modelled time horizon and therefore the PSM is considered appropriate to model the occupancy of the PF, PD and death health states.

The additional features of the economic analysis are outlined and justified in Table 37 below.

Table 37: Features of the economic analysis

Factor	Previous evaluations		Current evaluation	
	TA587	TA228 (SHTAC model)	Chosen values	Justification
Time horizon	Lifetime (25 years); 15 and 35 years are explored as scenario analyses	Lifetime (30 years)	Lifetime (26 years)	Sufficiently long to be considered a lifetime horizon based on patient starting age of [redacted] and sufficient to capture any differences in costs or outcomes between the technologies being compared
Treatment waning effect?	No treatment waning effect was applied	No treatment waning effect was applied	None	No treatment waning effect was applied in the base case analysis as there is no evidence to suggest if, or when, the treatment effect of daratumumab on survival would wane over time. Indeed, results from MAIA indicate a trend to a lower OS HR (increased treatment effect) with longer study follow-up. The sustained treatment effect of DLd with longer study follow-up is supported by the unique mechanism of action of daratumumab, which is to modulate the immune system to better fight the disease. Treatment waning was not considered in the previous NICE appraisals of daratumumab (TA763, TA573 and TA510),[4, 130, 134] and other previous appraisals in MM have not utilised a treatment waning effect (e.g. TA505).[135]

Source of utilities	Ld and MPT use EQ-5D data from the MM-020 trial. For BMP, QLQ-C30 data from VISTA (Delforge et al. 2012)[136] were mapped to EQ-5D using Proskorovsky et al. 2014.[137]	Gulbrandsen and colleagues from the mapping by McKenzie and van der Pol. (0.58 for treatment period, and 0.68 for post-treatment)[138, 139]	Utilities for pre- and post-progression were derived from MAIA. EQ-5D-5L scores from MAIA were cross walked to 3L using the mapping function developed by Hernández Alava et al. 2017.[140]	For consistency with the patient population and source of efficacy inputs for DLd and Ld (the main comparator) used in the model, pooled utility values were derived from MAIA. The mapping algorithm used was consistent with the NICE reference case.[141] Pooled utility data was used as there [redacted] using the generic EQ-5D-5L. However, given the benefits of increased depth of response that is achieved with DLd treatment (see Section B.2.12) and the statistically significant improvement in the EORTC-QLQ-C30 pain subscale (which does not translate to improved utility score on a generic instrument such as EQ-5D), this approach is considered conservative against DLd (see Section B.2.6).[9]
Source of costs	BNF; eMIT; NHS Reference Costs	BNF; eMIT; NHS Reference Costs	NHS reference costs, the British National Formulary and pharmaceutical electronic market information tool (eMIT). Costs included: • Drug acquisition and administration for front line and subsequent therapies • Concomitant medications (e.g. prophylaxis) • Monitoring costs	Cost inputs used in the model (administration costs, incidence of AEs, monitoring costs, end-of-life cost) have been aligned with previous evaluations in MM, including previous daratumumab evaluations (NICE TA573,[4] NICE TA510[134] and TA763[130]).

			• Management of AEs (grade 3 and above, with incidence ≥5% in any treatment arm) • End-of-life costs	

Abbreviations: AE: adverse events; BMP: bortezomib, melphalan and prednisone; BNF: British National Formulary; CR: complete response; EQ-5D-5L: EuroQol-5D, 5 levels; eMIT: electronic market information tool; MRD; minimal residual disease; NHS: National Health Service; OS: overall survival; PD: progressed disease; PF: progression-free; PFS: progression-free survival; SHTAC; Southampton Health Technology Assessments Centre.

B.3.2.3 Intervention technology and comparators

Intervention

The intervention included in the cost-effectiveness model was DLd in patients with NDMM who are ineligible for ASCT. The treatment protocol included in the model in the DLd arm is consistent with that which was followed in the MAIA trial (apart from that an SC formulation of daratumumab was assumed to be utilised for all patients in the base case; refer to Section B.3.5.1 for full details), and the SmPC-recommended posology for daratumumab in this setting.[1, 8]

Comparators

As described in Section B.1.1, Ld is considered the main comparator of interest for this submission. At an advisory board held on the 9th March 2022, eight English clinicians specialising in MM agreed that Ld was the most common treatment for patients at front-line with NDMM who are ineligible for ASCT.

Bortezomib with an alkylating agent and corticosteroid (BMP) is also included as a comparator in the main submission following expert opinion and consultation of clinical guidelines.[80] BMP is considered the most appropriate regimen to represent bortezomib with an alkylating agent and corticosteroid given the availability of IPD from the ALCYONE trial. A comparison against BCd is provided as a scenario analysis, given there was a lack of direct evidence comparing DLd and BCd and that clinical experts, findings from a MAIC, and a naïve comparison of NHS Digital datasets indicate that BMP and BCd would provide similar efficacy in practice.

For completeness, and to adhere to the final NICE scope, a comparison against thalidomide-based regimens (CTd/MPT) is also provided; however feedback from clinical experts is that thalidomide is not used in clinical practice in England and data from HARMONY IQVIA suggests usage is very low (~5%).[3, 142] Inputs for the comparison against thalidomide-based regimens are provided in Appendix M.

B.3.3 *Clinical parameters and variables*

B.3.3.1 DLd, Ld and BMP

B.3.3.1.1 Extrapolations of PFS and OS and application of HRs

Extrapolation of PFS/OS for DLd and Ld was performed using patient-level data from the ITT population of MAIA. Similarly, for BMP, extrapolation was performed using patient-level data from the ITT population of ALCYONE, adjusted towards the DLd arm of MAIA as described in Section B.2.9. CTd and MPT were modelled via the application of HRs from the NMA detailed in Section B.2.9. Details of the modelling approach for CTd and MPT are presented in Appendix M.

Extrapolation of PFS and OS was performed in accordance with the guidance provided in the NICE DSU Technical Support Document (TSD) 14.[143] The full range of parametric distributions were explored (exponential, Weibull, loglogistic, lognormal, Gompertz, and generalised gamma), with each model assessed in terms of goodness-of-fit statistics (Akaike information criterion [AIC] and the Bayesian information criteria [BIC]), visual inspection of the hazard function and survival curves to the observed data from the MAIA and ALCYONE trials, and clinical plausibility of long-term survival predictions. Log-cumulative hazard plots from MAIA were assessed to determine

the type of hazards observed and whether proportional hazards could be assumed. The plots demonstrate crossing for both PFS and OS and therefore suggests that an assumption of proportional hazards may not be appropriate (refer to Appendix O). As such, independent models were fitted separately to the OS and PFS Kaplan-Meier data for DLd and Ld. The smoothed hazard plots can be found in Appendix P.

Curve selection

The choice of distribution for the base case for all OS and PFS curves was informed considering:

- **Graphical assessment of fit:** visual inspection regarding how well the predicted curve captured the shape of the observed Kaplan-Meier curve
- **Statistical fit:** AIC and BIC statistics were generated for each extrapolation, the best fit to the observed data is the curve with the lowest AIC and BIC
- **Clinical validation of long-term extrapolations for current treatments in clinical practice:** Given clinician experience with currently available treatments, an advisory board was conducted where clinicians were asked to provide lower plausible, most likely and upper plausible estimates of the proportion of patients in clinical practice expected to be progression-free and alive at 5-, 10- and 15-years following treatment with Ld and BMP. See Section B.3.13 for further details on the elicitation of clinical expert opinion.

Given mature survival data are available from MAIA (median PFS was met for both treatment arms and median OS was met for the Ld arm) and ALCYONE, the choice of curve was mainly informed by the best statistical fit using the AIC and BIC values. For Ld and BMP, the best statistically fitting curve was externally validated by comparing the survival estimates predicted by the model (see Table 40) with clinician estimates provided in the advisory board meeting (Table 39).

B.3.3.1.2 Progression-free survival

In the model, a cap was applied to the PFS curves to ensure PFS did not exceed OS. The extrapolated PFS curves included in the model (i.e. with the OS cap applied) are presented in Figure 46 for DLd, Figure 47 for Ld and Figure 48 for BMP, with AIC/BIC values and clinician estimates presented in Table 38 and Table 39, respectively. The modelled survival predictions at 5-, 10- and 15-years for each parametric curve is provided in Table 40.

Based on best statistical fit, the exponential, exponential and Weibull extrapolations were utilised in the base case for DLd, Ld and BMP, respectively. For DLd, alternative extrapolations have been provided using the next best statistical fit (Weibull; a more optimistic curve) and also using a more pessimistic curve (generalised gamma) to assess the impact on the results. For Ld and BMP, only alternative extrapolations based on the next best statistical fit are explored in scenario analyses as these curves also align with clinician estimates. Results using alternative extrapolations are provided in (Section B.3.10.2).

Table 38: Goodness-of-fit statistics for DLd, Ld and BMP PFS survival models

Survival model	DLd		Ld		BMP	
	AIC	BIC	AIC	BIC	AIC	BIC
Exponential	**1967.1**	**1971.0**	2274.1	**2278.0**	2334.9	2338.8
Weibull	1967.4	1975.2	2274.9	2282.8	**2304.2**	**2312.0**
Loglogistic	1971.6	1979.5	**2273.1**	2280.9	2326.6	2334.4
Lognormal	1984.1	1991.9	2277.8	2285.7	2360.6	2368.4
Generalised gamma	1968.6	1980.3	2273.5	2285.2	2304.3	2316.0
Gompertz	1968.8	1976.6	2276.1	2283.9	2307.2	2314.9

Footnote: Bold indicates lowest AIC/BIC value
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; BMP: bortezomib, melphalan and prednisone; DLd: daratumumab, lenalidomide and dexamethasone; Ld: lenalidomide and dexamethasone; PFS: progression-free survival.

Table 39: Clinician estimates of PFS (n=8*)

Treatment	Proportion of patients progression-free (%)								
	5 years			10 years			15 years		
	Lower plausible limit	Most likely value	Upper plausible limit	Lower plausible limit	Most likely value	Upper plausible limit	Lower plausible limit	Most likely value	Upper plausible limit
Ld	15.4	22.9	34.3	4.3	8.3	14.7	0.1	2.3	6.0
BMP	11.2	17.0	23.7	2.2	5.6	10.7	0.0	1.0	4.7

Note: one English clinician did not provide feedback.
Abbreviations: BMP: bortezomib, melphalan and prednisone; Ld: lenalidomide and dexamethasone; PFS: progression-free survival.

Table 40: Comparison of predicted survival rates for DLd, Ld and BMP PFS survival models (with OS cap)

Survival model	Proportion of patients progression-free (%)											
	DLd				Ld				BMP			
	Mean PFS (months)	5 years	10 years	15 years	Mean PFS (months)	5 years	10 years	15 years	Mean PFS (months)	5 years	10 years	15 years
Exponential	86.8	51.2	26.3	13.5	47.8	29.5	8.8	0.9	26.2	10.3	0.2	0.0
Weibull	91.2	51.6	28.9	16.6	46.9	28.7	7.4	0.9	24.1	4.5	0.0	0.0
Loglogistic	100.7	52.4	34.8	25.8	50.5	30.2	14.3	0.9	28.6	12.0	0.2	0.0
Lognormal	103.4	53.2	38.2	26.1	50.9	31.3	14.3	0.9	28.8	13.9	0.2	0.0
Generalised Gamma	82.9	51.5	25.4	11.3	48.9	29.5	10.8	0.9	26.9	6.6	0.1	0.0
Gompertz	92.6	51.4	29.0	17.7	47.6	29.4	8.4	0.9	23.3	1.8	0.0	0.0

Abbreviations: BMP: bortezomib, melphalan and prednisone; DLd: daratumumab, lenalidomide and dexamethasone; Ld: lenalidomide and dexamethasone; PFS: progression-free survival.

Figure 46: Extrapolation of PFS for DLd using IPD from MAIA (with OS cap)

Note: Extrapolations shown are with the OS cap applied
Abbreviations: DLd: daratumumab, lenalidomide and dexamethasone; IPD: individual patient data; KM: Kaplan-Meier: PFS: progression-free survival.

Figure 47: Extrapolation of PFS for Ld using IPD from MAIA (with OS cap)

Note: Extrapolations shown are with the OS cap applied
Abbreviations: Ld: lenalidomide and dexamethasone; IPD: individual patient data; KM: Kaplan-Meier: PFS: progression-free survival.

Figure 48: Extrapolation of PFS for BMP using adjusted IPD from ALCYONE (with OS cap)

Note: Extrapolations shown are with the OS cap applied
Abbreviations: BMP: bortezomib, melphalan and prednisone; IPD: individual patient data; KM: Kaplan-Meier: PFS: progression-free survival.

B.3.3.1.3 Overall survival

The risk of mortality for patients with MM is expected to be higher than those of the general population when matched for age and gender. To ensure that OS predicted by the model for each treatment did not exceed that of the general population, age- and gender-matched general population mortality (based on life tables for the UK from the Office for National Statistics 2020) was used in any cycle where the predicted rate of death was lower than general population mortality.

The extrapolated OS curves included in the model (i.e. with the GPM cap applied) are presented in Figure 49 for DLd, Figure 50 for Ld and Figure 51 for BMP. AIC/BIC values and clinician estimates are presented in Table 41 and Table 42, respectively, and a comparison of modelled survival predictions at 5, 10 and 15 years for each parametric curve with the GPM cap is provided in Table 43.

Given the maturity of the trial data with over five years median follow-up in MAIA, the extrapolations used in the base case were primarily selected based on statistical fit. As such, the exponential, Gompertz and Gompertz extrapolations were utilised in the base case for DLd, Ld and BMP, respectively. Reassuringly, for DLd (where there is greater inherent uncertainty), all models provide similar long-term estimates, with the exception of generalised gamma which appears a notable outlier.

Alternative, more flexible, survival models were also explored which indicate consistent results to the standard models (refer to discussion of splines in Section B.3.3.2).

For DLd, alternative extrapolations have been provided using the next best statistical fit (Weibull; a more optimistic curve) and also using a more pessimistic curve (Gompertz) to assess the impact on the results. For Ld and BMP, alternative extrapolations based on clinician estimates are explored in scenario analyses (see Section B.3.10.2). As none of the standard parametric extrapolations aligned to clinician estimates for BMP, an alternative extrapolation was generated using the average of the Gompertz and Weibull curves.

Table 41: Goodness-of-fit statistics for DLd, Ld, and BMP OS survival models

Survival model	DLd		Ld		BMP	
	AIC	BIC	AIC	BIC	AIC	BIC
Exponential	**1598.5**	**1602.4**	1993.3	1997.2	1374.4	1378.3
Weibull	1599.6	1607.4	1987.2	1995.0	1370.3	1378.1
Loglogistic	1603.2	1611.0	1992.5	2000.3	1376.0	1383.8
Lognormal	1618.4	1626.2	2011.7	2019.5	1396.7	1404.6
Generalised gamma	1599.3	1611.0	1987.5	1999.3	1367.6	1379.4
Gompertz	1600.4	1608.2	**1985.5**	**1993.3**	**1361.3**	**1369.0**

Footnote: Bold indicates lowest AIC/BIC value
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; BMP: bortezomib, melphalan and prednisone; DLd: daratumumab, lenalidomide and dexamethasone; Ld: lenalidomide and dexamethasone; OS: overall survival.

Table 42: Clinician estimates of OS (n=8*)

Treatment	Proportion of patients alive (%)								
	5 years			10 years			15 years		
	Lower plausible limit	Most likely value	Upper plausible limit	Lower plausible limit	Most likely value	Upper plausible limit	Lower plausible limit	Most likely value	Upper plausible limit
Ld	32.4	45.0	56.4	9.3	18.0	24.1	1.0	4.0	8.9
BMP	29.0	40.7	51.1	7.7	15.9	23.4	0.9	4.3	9.3

Note: one English clinician did not provide feedback.
Abbreviations: BMP: bortezomib, melphalan and prednisone; Ld: lenalidomide and dexamethasone; PFS: progression-free survival.

Table 43: Comparison of predicted survival rates for DLd, Ld and BMP OS survival models (with GPM cap)

Survival model	OS survival rates (%)											
	DLd				Ld				BMP			
	Mean OS (months)	5 years	10 years	15 years	Mean OS (months)	5 years	10 years	15 years	Mean OS (months)	5 years	10 years	15 years
Exponential	116.68	65.9	43.4	26.1	91.0	54.1	29.2	15.7	92.3	54.8	29.9	16.2
Weibull	118.74	66.0	45.4	27.4	81.6	53.5	23.0	8.9	76.1	50.7	19.9	6.8
Loglogistic	122.26	66.4	48.4	29.2	94.9	54.0	30.5	18.0	95.9	54.1	31.5	18.8
Lognormal	124.38	66.8	50.5	30.5	100.1	54.7	35.1	21.2	108.3	58.4	40.9	24.7
Generalised Gamma	106.13	66.0	39.9	18.7	70.6	53.7	15.5	1.5	55.6	48.9	1.5	0.0
Gompertz	115.12	66.0	42.3	25.0	69.5	53.8	14.3	0.9	53.1	41.1	0.2	0.0

Abbreviations: BMP: bortezomib, melphalan and prednisone; DLd: daratumumab, lenalidomide and dexamethasone; Ld: lenalidomide and dexamethasone; OS: overall survival.
.

Figure 49: Extrapolation of OS for DLd using IPD from MAIA (with GPM cap)

Note: Extrapolations shown are with the GPM cap applied
Abbreviations: DLd: daratumumab, lenalidomide and dexamethasone; GPM: general population mortality; IPD: individual patient data; KM: Kaplan-Meier; OS: overall survival.

Figure 50: Extrapolation of OS for Ld using IPD from MAIA (with GPM cap)

Note: Extrapolations shown are with the GPM cap applied
Abbreviations: Ld: lenalidomide and dexamethasone; GPM: general population mortality; IPD: individual patient data; KM: Kaplan-Meier; OS: overall survival.

Figure 51: Extrapolation of OS for BMP using adjusted IPD from ALCYONE (with GPM cap)

Note: Extrapolations shown are with the GPM cap applied
Abbreviations: BMP: bortezomib, melphalan and prednisone; GPM: general population mortality; IPD: individual patient data; KM: Kaplan-Meier; OS: overall survival.

Validation and clinical plausibility of survival outcomes

The final survival outcomes predicted by the model were compared against observed data from the MAIA and ALCYONE trials and to the VISTA (BMP versus MP) and FIRST (Ld versus MPT) trials. Overall, the model was seen to closely predict PFS and OS when compared to these trials, as shown in Figure 52 (DLd), Figure 53 (BMP) and Figure 54 (Ld). In addition, longer follow-up of the BMP arm from the VISTA trial supports the selection of Gompertz for BMP OS in the base case.

Figure 52: Patient survival over time from the cost-effectiveness model (DLd)

Abbreviations: DLd: daratumumab, lenalidomide and dexamethasone; GPM: general population mortality; OS: overall survival; PFS: progression-free survival.

Figure 53: Patient survival over time from the cost-effectiveness model (BMP)

Abbreviations: BMP: bortezomib, melphalan and prednisone; GPM: general population mortality; OS: overall survival; PFS: progression-free survival.

Figure 54: Patient survival over time from the cost-effectiveness model (Ld)

Abbreviations: GPM: general population mortality; Ld: lenalidomide and dexamethasone; OS: overall survival; PFS: progression-free survival.

B.3.3.1.4 Time to discontinuation

Extrapolation of TTD for DLd and Ld was performed using data from the MAIA trial. As BMP has a fixed treatment duration, there was no need to extrapolate data and so the KM TTD data from the ALCYONE trial was used directly and adjusted towards the MAIA trial as described in Section B.2.9.

Goodness-of-fit statistics for each parametric distribution explored are presented in Table 44 and the extrapolated curves are presented in Figure 55 for DLd, and Figure 56 for Ld. Curve selection was determined by best statistical fit and considering the relationship between PFS and TTD estimates. Based on these criteria, the Gompertz and Weibull extrapolations were selected in the base case for DLd and Ld, respectively. For DLd TTD, alternative extrapolations based on best statistical fit using the generalised gamma are explored in scenario analyses (see Section B.3.10.2). Despite having a better statistical fit, the generalised gamma was not considered in the base case for DLd due to the larger difference observed between PFS and TTD compared to the Gompertz curve. For Ld TTD, given the similarity between the clinician's preferred curve (generalised gamma) and the best statistical fitting curve (Weibull), no scenario analyses have been conducted.

Table 44: Goodness-of-fit statistics for DLd and Ld TTD survival models

Survival model	DLd		Ld	
	AIC	BIC	AIC	BIC
Exponential	2457.5	**2461.5**	2854.1	**2858.0**
Weibull	2459.5	2467.3	**2856.2**	2860.1
Loglogistic	2475.1	2482.9	2877.0	2884.8
Lognormal	2500.0	2507.9	2904.2	2912.1
Generalised Gamma	**2455.1**	2466.8	2853.1	2864.8
Gompertz	2457.9	2465.7	2855.1	2862.9

Footnote: Bold indicates lowest AIC/BIC value
Abbreviations: AIC: Akaike information criterion; DLd: daratumumab, lenalidomide and dexamethasone; Ld: lenalidomide and dexamethasone; TTD: time to discontinuation.

Figure 55: Extrapolation of TTD for DLd using IPD from MAIA

Footnote: In the model, TTD is capped by the PFS.
Abbreviations: DLd: daratumumab, lenalidomide and dexamethasone; IPD: individual patient data; KM: Kaplan-Meier; TTD: time to discontinuation.

Figure 56: Extrapolation of TTD for Ld using IPD from MAIA

Footnote: In the model, TTD is capped by the PFS.
Abbreviations: Ld: lenalidomide and dexamethasone; IPD: individual patient data; KM: Kaplan-Meier TTD: time to discontinuation.

B.3.3.2 Exploring spline modelling for DLd, Ld and BMP

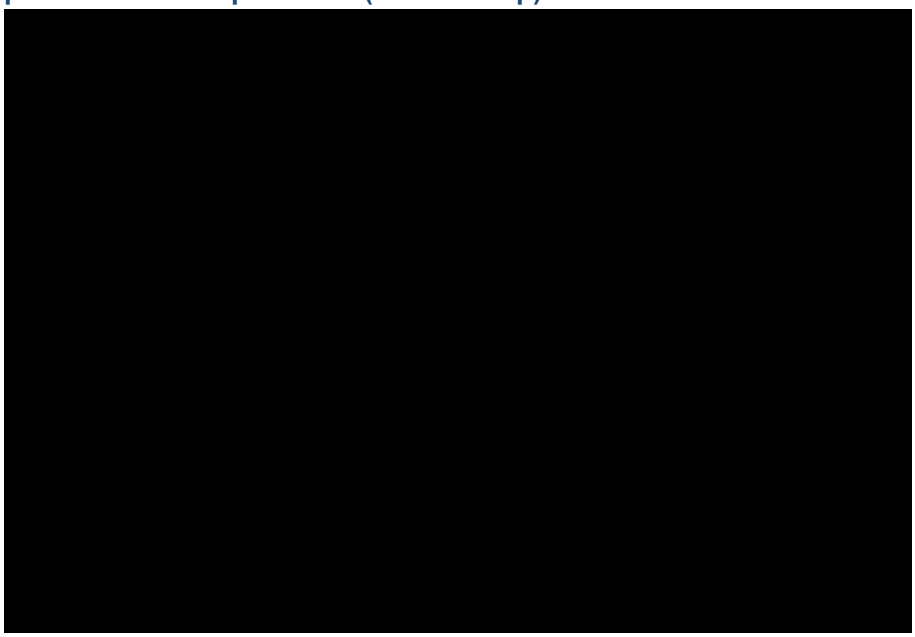
As shown in Figure 49 and Figure 50 for DLd and Ld OS, the standard parametric extrapolations fitted to the KM consistently underestimate survival compared to the observed data from MAIA and, based on clinical feedback for Ld (Table 42), may overestimate survival towards the end of the curves (i.e. beyond the trial follow-up). Therefore, in line with the methods detailed in NICE DSU TSD 21, a flexible parametric model incorporating splines was used to generate alternative extrapolations.[144]

In the spline-based survival model of Royston and Parmar (2002) the log cumulative hazard is modelled as a natural cubic spline function of log time.[145] This model can be fitted using the flexsurvspline function from the flexsurv R package.[146] The complexity of the function depends on the number of knots in the spline function. In the analysis presented below, the knots were chosen as equally-spaced quantiles of the log uncensored survival times (default software implementation). For example, at the median with one knot, or at the 33% and 67% quantiles of log time with two knots.

Results

The PFS and OS curves generated for DLd and Ld using one, two and three knots are presented in Figure 57 to Figure 60 below.

Figure 57: Extrapolation of PFS for DLd using spline methodology and standard paratmetric extrapolations (with OS cap)



Abbreviations: AIC: Akaike information criterion; DLd: daratumumab, lenalidomide and dexamethasone; OS: overall survival; PFS: progression-free survival.

Figure 58: Extrapolation of PFS for Ld using spline methodology and standard parametric extrapolations (with OS cap)

Abbreviations: AIC: Akaike information criterion; Ld: lenalidomide and dexamethasone; OS: overall survival; PFS: progression-free survival.

Figure 59: Extrapolation of OS for DLd using spline methodology and standard parametric extrapolations (with GPM cap)

Abbreviations: AIC: Akaike information criterion; GPM: general population mortality; OS: overall survival**;** Rd: lenalidomide and dexamethasone.

Figure 60: Extrapolation of OS for Ld using spline methodology and standard parametric extrapolations (with GPM cap)

Abbreviations: AIC: Akaike information criterion; GPM: general population mortality; OS: overall survival**;** Rd: lenalidomide and dexamethasone.

The extrapolations using the spline methodology with one, two and three knots, generated curves that were in line with the standard parametric extrapolations chosen in the base case based on best statistical fit. Only the spline model using one knot for DLd OS had a lower AIC than the standard parametric extrapolations. Spline models are also commonly associated with 'overfitting' (a phenonomenon where the fit of model corresponds too closely to the observed data) which can reduce the accuracy of the extrapolations, especially to the tails of curves where

there are the least events and highest levels of censoring. Given the consistency observed from the spline models, only standard parametric extrapolations were considered in the base case.

B.3.3.3 BCd

As described above, a comparison between DLd and BCd is provided as a scenario analysis only. BCd was modelled assuming equivalent efficacy to BMP in the base case (see Section B.2.9.2).

B.3.3.4 Adverse events

The AEs included in the model were treatment emergent Grade 3 and 4 events that were reported in at least 5% of patients in the any treatment arm. Grade 1 and 2 events were not included in the model as these are unlikely to be associated with considerable health-related costs or changes in patient HRQoL. The inclusion rule that events must have occurred in at least 5% of patients in any trial was selected in order to capture AEs that would impact patients consistently enough to have validity in a real-world setting where AEs are monitored in a less strict manner compared with a clinical trial setting. The MAIA trial was deemed to have captured the relevant AEs that would be expected to have a substantial impact on costs or quality of life, based on input from UK clinical experts.[3]

In the model, a proportion of patients were assumed to experience AEs during treatment, with rates informed by the MAIA trial (DLd and Ld) and the ALCYONE trial (BMP). For the scenario analysis versus BCd, AE rates were assumed equal to BMP, based on the assumption of clinical equivalence (see Section B.2.9.2). The AE rates are provided in Table 45.

The change in utility and costs associated with each AE are presented in Section B.3.4.4 and B.3.5.3, respectively. In line with approach taken in TA510, the cost and disutility of AEs were applied in the first cycle of the model (i.e. when all patients are still alive).[134]

Table 45: Incidence of AEs included in the model

AE	DLd	Ld	BMP	BCd	Source
Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]	DLd, BMP and Ld: Janssen data on file, ALCYONE CSR and MAIA HEMAR report Safety Population (Grade 3 or 4 Treatment-emergent AEs in at least 5% of patients in any treatment arm).[9, 147] For BCd: Assumed equal to BMP (see Section B.2.9.2).
Lymphopenia	[redacted]	[redacted]	[redacted]	[redacted]	
Thrombocytopenia	[redacted]	[redacted]	[redacted]	[redacted]	
Leukopenia	[redacted]	[redacted]	[redacted]	[redacted]	
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]	
Pneumonia	[redacted]	[redacted]	[redacted]	[redacted]	
Hypokalaemia	[redacted]	[redacted]	[redacted]	[redacted]	
Pulmonary embolism	[redacted]	[redacted]	[redacted]	[redacted]	
Hyperglycaemia	[redacted]	[redacted]	[redacted]	[redacted]	
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]	
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]	
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]	
Asthenia	[redacted]	[redacted]	[redacted]	[redacted]	

Acute kidney disease	[redacted]	[redacted]	[redacted]	[redacted]	
Chronic kidney disease	[redacted]	[redacted]	[redacted]	[redacted]	
Cataract	[redacted]	[redacted]	[redacted]	[redacted]	

Abbreviations: AE: adverse event; CSR: clinical study report; BCd: bortezomib, cyclophosphamide and dexamethasone; BMP: bortezomib, melphalan and prednisone; DLd: daratumumab, lenalidomide and dexamethasone; Ld: lenalidomide and dexamethasone.

B.3.4 *Measurement and valuation of health effects*

B.3.4.1 Health-related quality-of-life data from clinical trials

HRQoL was measured as a secondary outcome in the MAIA tria, using EORTC QLQ-C30 and EQ-5D-5L instruments. Both questionnaires were completed at the timepoints outlined in the Time and Events Schedule prespecified in the protocol.[95] EORTC QLQ-C30 and EQ-5D-5L questionnaires were administered on Day 1 of Cycles 3, 6, 9 and 12 for Year 1, and then every 6th cycle thereafter until end of treatment. Questionaires were also administered at Weeks 8 and 16 after disease progression occurred for patients. Questionnaires were administered prior to any other study procedures or assessments for that study visit. A summary of compliance rates and baseline values for each subscale of EORTC QLQ-C30 and EQ-5D-5L measures are presented in Appendix Q.

Overall, DLd demonstrated improvements in HRQoL compared with Ld, with greater benefits in GHS, pain, VAS, fatigue and health utility reported, as outlined in Section B.2.6.2.10.[102]

B.3.4.2 Mapping

HRQoL data were collected in the MAIA trial using the EQ-5D-5L.[8] In accordance with the NICE position statement in the use of EQ-5D-5L to derive utility values, the EQ-5D-5L descriptive scores from MAIA were mapped onto the 3L UK value set using the mapping function developed by Hernández Alava et al. (2017) through the NICE Decision Support Unit (DSU), using the EEPRU dataset (Hernández Alava et al. 2020).[140, 148, 149] The same approach was also taken for EQ-5D-5L dimension scores from the ALCYONE trial, used in scenario analysis (see Section B.3.10.2).

B.3.4.3 Health-related quality-of-life studies

A SLR of humanistic burden was conducted to identify evidence on HRQoL, patient-reported outcomes and utilities in patients with ASCT-ineligible NDMM (see Appendix H). In total, 11 publications were identified, including seven full-text articles and four conference abstracts and/or posters. From these 11 publications, EQ-5D utility values were reported based on data sources from four clinical trials (FIRST, VISTA, ALCYONE, and MAIA), while the remaining seven publications presented utilities that were derived from these original values.

HRQoL data for the FIRST and VISTA trials were reported using the EQ-5D instrument.[136, 150] Results were converted to utilities using the UK set based on the time trade-off valuation method. Notably, Blommestein et al. (2016) report utility values that had been generated with a Dutch EQ-5D-5L value set, while Usmani et al. (2016) reported health-state utility values based on a US

population.[151, 152] Mapping algorithms by Proskorovsky et al. were used to convert quality-of-life measured by QLQ-C30 to the value of EQ-5D.[137]

Scenario analyses have been provided using utility values from the ALCYONE trial. These values are unpublished are therefore were not identified in the SLR. All identified studies in the SLR reported utility values that either used a non-UK value set, were derived from a non-UK population or had not been cross-walked using Hernández Alava et al. (2017), in line with the NICE reference case, and therefore were not considered relevant to this submission.[141]

Further details of the health related quality of life SLR are presented in Appendix H.

B.3.4.4 Adverse reactions

One-off decrements in utility were applied in the model for the proportion of patients who experienced TEAEs. The utility decrements used in the model were primarily based on those used in previous UK HTA submissions for daratumumab (TA573 and TA510) and values from the literature, identified using targeted literature searches (Table 46).[4, 134] Asthenia was assumed equivalent to fatigue as patients experience similar symptoms.

As no disutility value could be found in the literature, the disutility for acute kidney injury (AKI) and chronic kidney disease (CKD) was calculated using utility values reported in Appendix K of the NICE Guidelines for AKI (NG148).[153] The utility values reported for AKI, stage 3/4 and stage 5 were converted to yearly values and a disutility was calculated for each stage by subtracting these utility values from the average general population utility value for this population. The average disutility value for Stage 3/4 and Stage 5 was used for CKD.

Taking into account the proportion of patients experiencing each AE in each treatment arm (Table 45), the total disutility across all events included in the model was -0.03 for DLd, -0.04 for Ld and -0.03 for BMP.

Table 46: Duration and utility decrements associated with AEs included in the model

AE	Disutility	Duration (days)	Source
Neutropenia	-0.15	7.00	Based on TA573/TA510 (Brown 2013/Partial Review TA171)[4, 134] Duration of AE assumption, aligning with TA510[134]
Lymphopenia	-0.07	15.50	
Thrombocytopenia	-0.31	7.00	
Leukopenia	-0.07	14.70	
Anaemia	-0.31	180.00	
Pneumonia	-0.19	7.00	
Hypokalaemia	-0.07	11.40	
Pulmonary embolism	-0.31	7.00	
Hyperglycaemia	-0.15	14.70	Assumed equivalent to hypertension
Diarrhoea	-0.10	12.00	Lloyd et al. 2006[154]
Fatigue	-0.12	14.60	
Hypertension	-0.15	11.40	Assumed equivalent to hypokalaemia
Asthenia	-0.12	14.60	Assumed equivalent to fatigue

Acute kidney disease	-0.18	7.00	Appendix K of the NICE Guidelines for AKI (NG148)[153]
Chronic kidney disease	-0.05	365.25	Appendix K of the NICE Guidelines for AKI (NG148)[153]
Cataract	-0.01	28.00	Goodsmith et al., 2019, supplementary data[155]

Abbreviations: AE: adverse event.

B.3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis

In the base case, utility values for the PF and PD health state were derived using EQ-5D-5L from the MAIA trial. Pooled utility values were used as there were [redacted].[8] Given the shorter median time to improvement and longer time to worsening in EORTC QLQ-C30 GHS score, and the statistically significant improvement in the EORTC-QLQ-C30 pain subscale for DLd (which does not translate to improved utility score on a generic instrument such as EQ-5D), Janssen consider this approach to be conservative (see Section B.2.6).

As detailed in B.3.4.2, utility values were derived using the cross-walk method reported by Hernández Alava et al. (2017) to map EQ-5D-5L dimension scores from the MAIA trial to utilities using the UK EQ-5D-3L value set.[141] In the model, health state utility values were also age-adjusted over the model time horizon UK population norm values for EQ-5D as reported in the HSE 2014 dataset by NICE DSU (see Appendix M).

The utility values for the PF and PD states used in the base case are presented in Table 47.

Table 47: Utility values derived from MAIA

	PF	PD
Mean (SD)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]

Abbreviations: PF: progression-free; PD: progressed disease; SD: standard deviation.

Utility values for the PF and PD health states were also available from the ALCYONE trial, however clinical experts indicated the small difference in utility values between the PF and PD health states lacked face validity (PF = [redacted], PD=[redacted]).[3] Furthermore, the ALCYONE trial included one arm with DBMP which is not relevant to this submission. To fully explore uncertainty, a scenario analysis was conducted using utility values from ALCYONE (see Section B.3.10.2).

B.3.5 *Cost and healthcare resource use identification, measurement and valuation*

An economic SLR was also conducted to identify cost/resource use studies associated with NDMM in the ASCT-ineligible setting, in the UK (see Appendix G). In total, the review identified seven publications, including six full-text articles and one conference poster, which reported cost/resource data relevant to this appraisal.

The health economic analysis was conducted from the perspective of the NHS in England and therefore included only costs that would be incurred by the health system. Appropriate sources of unit costs, such as NHS reference costs 2019–20, British National Formulary (BNF) and drugs and pharmaceutical electronic market information tool (eMIT) were used for cost inputs in the model.

B.3.5.1 Intervention and comparators' costs and resource use

B.3.5.1.1 Drug acquisition costs

Dosing Regimens

The dosing regimens for front-line treatments included in the model are presented in Table 49. These were based on the treatment protocols specified in the MAIA trial (DLd and Ld) and the ALCYONE trial (BMP), which used a reduced dosing regimen compared to the SmPC.[156, 157] This reduced dosing regimen was validated by clinicians as being reflective of the dosing used for BMP in clinical practice.[158] The dosing regimen included for the scenario considering BCd was based on the dosing regimen recommended by the Oxford Myeloma Group.[159]

Two treatment protocols exist for daratumumab: an SC formulation and an IV formulation, both of which are available in England. The SC formulation was used in the base case, as according to English clinicians, this is the formulation that would be expected to be almost exclusively used in English practice.[3] Furthermore, during the COVID-19 pandemic, physicians have tended to use fewer IV drugs and preferred SC dosages, where possible, to reduce the amount of time spent in the hospital. A scenario analysis has been conducted where [redacted] patients are assumed to receive IV daratumumab based on current Janssen UK sales data (see Section B.3.10.2).

Drug acquisition costs

In the MAIA trial, a proportion of patients discontinued lenalidomide or both lenalidomide and dexamethasone as part of the DLd regimen. Therefore, in order to ensure the modelled costs accurately reflect the modelled efficacy from the MAIA trial (as discontinuation may influence efficacy), patients were also modelled to discontinue lenalidomide or dexamethasone alone, based on data from the MAIA trial (Table 48).

Table 48: DLd discontinuation rates from MAIA

Treatment	% discontinuing	Discontinuation time point[a] (cycles)
Lenalidomide only	[redacted]	[redacted]
Lenalidomide + dexamethasone	[redacted]	[redacted]

Footnotes: [a]Mean time to lenalidomide discontinuation was used and converted to cycles
Source: MAIA CSR (September 2018 data cut). [Data on File]. 2019.[8]

The cost per administration for bortezomib (BSA-based dosing) was calculated using the mean BSA ([redacted] m^2) of patients included in the MAIA trial, with the mean weight ([redacted] kg) from MAIA also used for the IV formulation of daratumumab (weight-based dosing).[132] In the base case analysis, it was assumed that there would be no vial sharing (for any treatments for which this is relevant) and so the number of vials required per administration was rounded up to the nearest whole integer. A scenario analysis has been conducted where vial sharing is included (see

Section B.3.10.2). Drug costs were sourced from the BNF and eMIT. Details on how concomitant medications are included in the model are presented in Appendix K.

In the cost-effectiveness analysis presented in this submission, the cost per vial of bortezomib is based on the list price. However, the cost of bortezomib may vary in different regions because of negotiated procurement discounts and use of generic versions of the drug. Therefore, the lowest treatment regimen cost from eMIT was used as the list price.

Lenalidomide is available with a generic price following loss of exclusivity in January 2022, with further price erosion anticipated in the next 6-12 months as generic manufacturers continue to enter the market and supply is secured.[160] However, as the discounts remain confidential, only list prices have been included in the model. In addition, pomalidomide and panobinostat (considered as part of subsequent therapy regimens in the model; see Section B.3.5.1.2 below) are available with confidential commercial arrangements.

The total costs of therapy applied in the model are presented in Table 50. The total costs per model cycle at list price for DLd were £20,347.99 in cycles 1–2, £11,707.99 in cycles 3–6 and £7,387.99 in subsequent cycles. The total costs per model cycle for Ld, BMP and BCd were £3,067.99, £639.40 and £895.62 respectively. The unit costs and total costs per administration associated with the individual therapies are presented in Appendix K.

Table 49: Summary of dosing regimens for front-line treatment included in the model

Treatment	Treatment cycle duration	Dosing regimen	Administrations per model cycle[a]	Dose per model cycle	Source/Justification
DLd	4-week cycle, until disease progression	Daratumumab – 1,800 mg QW for 1 cycle	4.00	7,200 mg	Darzalex SmPC (in line with MAIA).[161] The dose per treatment cycle is 1,800 mg for SC and 16 mg/kg for IV.
		Daratumumab – 1,800 mg Q2W for 1 cycle	2.00	3,600 mg	
		Daratumumab – 1,800 mg Q4W for 1 cycle	1.00	1,800 mg	
		Lenalidomide 25 mg QD for 3 weeks	21.00	525 mg	
		Dexamethasone 40 mg QW	4.00	160 mg	
Ld	4-week treatment cycle, until disease progression	Lenalidomide 25 mg QD for 3 weeks	21.00	525 mg	Revlimid SmPC (in line with MAIA)[83]
		Dexamethasone 40 mg QW	4.00	160 mg	
BMP	9 treatment cycles of 6 weeks	Bortezomib – 1.3 mg/m^2 on days 1, 4, 8, 11, 22, 25, 29, and 32 of cycle 1 and on days 1, 8, 22, and 29 of cycles 2-9	4.44	6 mg/m²	ALCYONE[132]
		Melphalan – 9 mg/m^2 Day 1 to 4 of bortezomib cycle	2.67	24 mg/m²	
		Prednisone – 60 mg/m^2 Day 2 to 4 of bortezomib cycle	2.67	160 mg/m²	
BCd	8 cycles of 3 weeks	Cyclophosphamide – 500 mg QW on Days 1, 8 and 15	4.00	2,000 mg	Oxford Myeloma Group[159]
		Bortezomib – 1.3 mg/m^2 on Days 1, 8 and 15	4.00	5 mg/m^2	
		Dexamethasone – 20 mg on Days 1, 2, 8, 9, 15 and 16	8.00	160 mg	

[a] the cycle duration in the model was 4 weeks (28 days). [b] based on an average dose of 170 mg.
Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; BMP: bortezomib, melphalan and prednisone; BW: bi-weekly; DLd; daratumumab, lenalidomide and dexamethasone; Ld: lenalidomide and dexamethasone; IV: intravenous; QD: daily; QW: every week; Q2W: every 2 weeks; Q3W: every 3 weeks; SC: subcutaneous; SmPC: summary of product characteristics.

Table 50: Summary of drug acquisition costs for front-line treatment

Treatment	Drug costs per cycle[a]	Total regimen costs per cycle
DLd (1–2 cycles)		
Daratumumab	£17,280.00	£20,347.99 ([redacted] with PAS)
Lenalidomide	£3,057.60	
Dexamethasone	£10.39	
DLd (3–6 cycles)		
Daratumumab	£8,640.00	£11,707.99 ([redacted] with PAS)
Lenalidomide	£3,057.60	
Dexamethasone	£10.39	
DLd (subsequent cycles until disease progression)		
Daratumumab	£4,320.00	£7,387.99 ([redacted] with PAS)
Lenalidomide	£3,057.60	
Dexamethasone	£10.39	
Ld (until disease progression)		
Lenalidomide	£3,057.60	£3,067.99
Dexamethasone	£10.39	
BMP (9 cycles of 6 weeks)		
Bortezomib	£614.54	£639.40
Melphalan	£14.61	
Prednisone	£10.24	
BCd (8 cycles of 3 weeks)		
Bortezomib	£829.63	£895.62
Cyclophosphamide	£55.60	
Dexamethasone	£10.39	

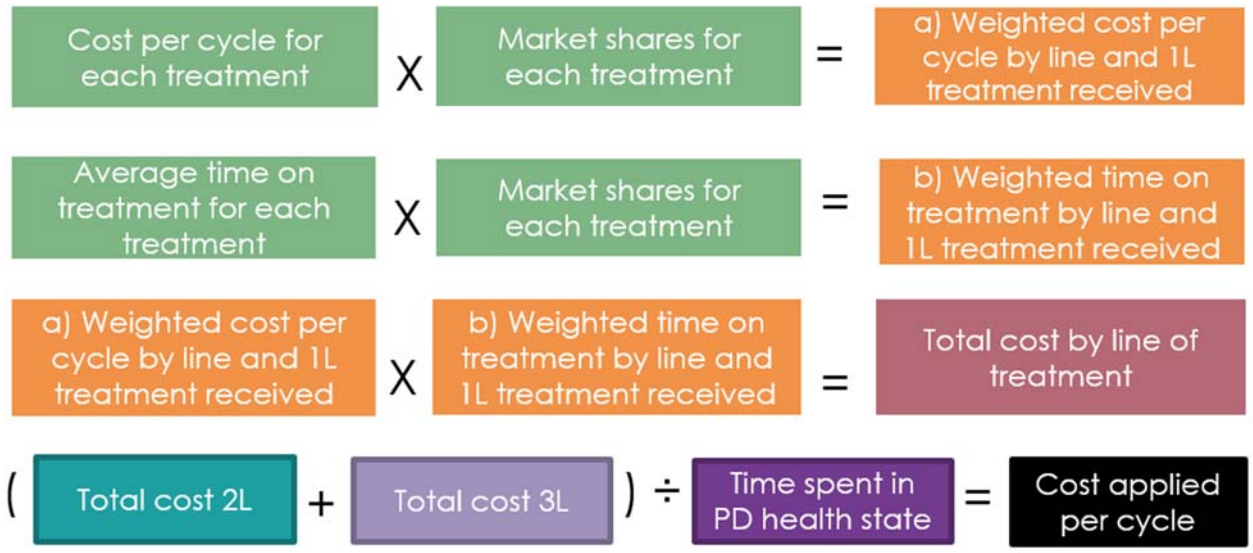
[a] the cycle duration in the model was 4 weeks (28 days).
Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; BMP: bortezomib, melphalan and prednisone; DLd: daratumumab, lenalidomide and dexamethasone; Ld: lenalidomide and dexamethasone; PAS: patient access scheme.

B.3.5.1.2 Subsequent therapies

In the model, which consists of only two alive health states (PF and PD), the cost of subsequent therapies across each subsequent line of therapy (second-line and third-line) has been included as a single, per-cycle cost, based on a weighted average, which is applied in all cycles for patients in the PD health state. An advantage of applying a per-cycle cost compared to applying the cost as a single, lump-sum cost is that the impact of annual discounting of costs in the model and the impact of deaths on the number of patients receiving subsequent treatment is captured. Fourth-line treatments were not included in the model, in line with the approach taken in TA587 and reflecting the fact that few transplant-ineligible patients are expected to progress beyond third-line.[4]

In order to calculate this total cost per cycle for all subsequent treatments, firstly the cost per cycle for each line of therapy was calculated. This was done by multiplying the cost per cycle for each line by the corresponding time on treatment, to calculate a weighted average cost per line of therapy based on market share estimates. ToT was based on median TTP or PFS reported from clinical trials for each regimen, presented in Table 53. The total costs for each line of therapy were summed to calculate the total subsequent therapies cost, which was divided by the total time spend in the progressed disease state in the model to give total subsequent therapies cost per model cycle. This cost was then applied throughout the time horizon. This approach is summarised in Figure 61.

Figure 61: Calculation of subsequent therapies cost



Abbreviations: 1L: front-line; 2L: second-line; 3L: third-line; PD: progressed disease.

The proportion of patients receiving treatment with each subsequent therapy excluding and including treatments available via the CDF (by line of therapy) is presented in Table 51 and Table 52, respectively.

The subsequent treatments included for each line of therapy were based on market shares estimates provided following an advisory board from seven clinical experts.[3] Clinicians noted the dominance of CDF drugs within the myeloma treatment pathway and commented on the hypothetical nature of the exercise when CDF drugs were excluded. Notably, daratumumab in combination with bortezomib and dexamethasone (DBd) represents current NHS standard of care at second-line and is scheduled for re-appraisal by NICE in February 2023.[162] Additionally, ixazomib in combination with lenalidomide and dexamethasone (ILd) represents standard of care at 3rd line, and has CDF re-appraisal ongoing.[163] Given the potentially important pathway changes during the appraisal process for DLd, Janssen consider it likely the Committee will want to understand its impact on the cost-effectiveness of DLd (as

per TA763).[130] As such, Janssen present base case results both including and excluding CDF treatments from cost inputs, consistent with the NICE Position Statement on the consideration of products recommended for use in the CDF.[3]

Subsequent therapies for BCd (scenario analysis only) and CTd/MPT were not gathered at the clinical advisory board. Therefore, subsequent treatments for BCd were assumed to be the same as for BMP, which has subsequently been validated by clinical experts who attended the advisory board.

To calculate the costs of treatment with bortezomib and dexamethasone (Bd) and panobinostat, bortezomib and dexamethasone (PBd), which both have a fixed duration of eight treatment cycles of 21 days (equivalent to six model cycles), the treatment cost per cycle was calculated as the total cost of therapy divided by the median PFS.

NICE recommendations for Ld, PBd, Pd and ILd[a] are subject to the manufacturers providing the relevant treatments (lenalidomide, panobinostat, pomalidomide and ixazomib) in accordance with the terms of a confidential commercial arrangement. In the base case of the cost-effectiveness model, these treatments have all been included at list price.

[a] ILd is currently recommended on the CDF.

Table 51: Distribution of patients to subsequent therapies excluding treatments available on the CDF (by line of therapy)

Line:	2nd line				
Subsequent therapy:	**Bd**	**Cd**	**Ld**	**CLd**	**BCd**
DLd	20%	20%	0%	0%	60%
Ld	20%	20%	0%	0%	60%
BMP	0%	10%	50%	40%	0%
BCd	0%	10%	50%	40%	0%
CTd/MPT	5%	10%	15%	60%	10%
Line:	3rd line				
Subsequent therapy:	**Ld**	**PBd**	**CTd**	**Bd**	**BCd**
DLd	5%	35%	60%	0%	0%
Ld	0%	35%	65%	0%	0%
BMP	25%	35%	40%	0%	0%
BCd	25%	35%	40%	0%	0%
CTd/MPT	35%	5%	0%	30%	30%

Abbreviations: Bd: bortezomib and dexamethasone; BCd: bortezomib, cyclophosphamide and dexamethasone; BMP: bortezomib, melphalan and prednisone; Cd; carfilzomib and dexamethasone; CLd: carfilzomib, lenalidomide and dexamethasone; DLd: daratumumab, lenalidomide and dexamethasone; Ld: lenalidomide and dexamethasone; PBd: panobinostat, bortezomib and dexamethasone; Pd: pomalidomide and dexamethasone.

Table 52: Distribution of patients to subsequent therapies including treatments available on the CDF (by line of therapy)

Line:	2nd line					
Subsequent therapy:	**Bd**	**Cd**	**DBd[a]**	**Ld**	**CLd**	**BCd**
DLd	20%	20%	0%	0%	0%	60%
Ld	0%	5%	90%	0%	0%	5%
BMP	0%	10%	30%	30%	30%	0%
BCd	0%	10%	30%	30%	30%	0%
CTd/MPT	0%	10%	90%	0%	0%	0%
Line:	3rd line					
Subsequent therapy:	**Ld**	**PBd**	**ILd[a]**	**CTd**	**Bd**	**BCd**
DLd	5%	30%	15%	50%	0%	0%
Ld	0%	30%	10%	60%	0%	0%
BMP	15%	15%	40%	30%	0%	0%
BCd	15%	15%	40%	30%	0%	0%
CTd/MPT	30%	5%	25%	0%	20%	20%

Footnote: [a] Currently available through the CDF.
Abbreviations: BMP: bortezomib, melphalan and prednisone; BCd: bortezomib, cyclophosphamide and dexamethasone, Bd: bortezomib and dexamethasone; Cd; carfilzomib and dexamethasone; CLd: carfilzomib, lenalidomide and dexamethasone; DBd: daratumumab, bortezomib and dexamethasone; DLd: daratumumab, lenalidomide and dexamethasone; ILd: ixazomib, lenalidomide and dexamethasone; Ld: lenalidomide and dexamethasone; PBd: panobinostat, bortezomib and dexamethasone; Pd: pomalidomide and dexamethasone.

Table 53: Median TTP/PFS for subsequent lines of treatment

Subsequent treatment	Time (model cycles)	Source
2nd to 3rd line (cycles)		
Cd	20.33	Median PFS (ITT) from ENDEAVOR (Dimopoulos 2016)[164]
Bd	8.72	CASTOR (NICE TA573 manufacturer submission) – median TTP[165]
DBd	30.04	Median TTP in 2L patients from CASTOR (NICE TA573 manufacturer submission)[165]
Ld	18.59	Median TTP from 1 prior therapy subgroup from Pooled MM-009 and MM-010 (Stadtmauer 2009)[166]
CLd	32.18	Median PFS (ITT) from ASPIRE, Dimopoulos et al., 2017[167]
BCd	11.09	Yong et al. 2016[63]
3rd to 4th line (cycles)		
Ld	15.33	Median TTP after 2/3 lines from TOURMALINE-MM1 (NICE TA505 manufacturer submission) [168]
Cd	20.33	Median PFS (ITT) from ENDEAVOR (Dimopoulos 2016)[164]
PBd	13.78	Median TTP after at least 2 therapies from PANORAMA-1 (Richardson 2016)[169]
Pd	5.11	Median TTP after at least 2 therapies from MM-003 (NICE TA427 manufacturer submission)[170]
lLd	31.31	Median TTP after 2/3 lines from TOURMALINE-MM1 (NICE TA505 manufacturer submission)[171]
CTd	15.87	Kim et al 2010 (B-CTd)[172]
Bd	7.07	Palumbo et al. 2016[173]
BCd	7.07	Assumed equivalent to Bd

Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; BMP: bortezomib, melphalan and prednisone; Bd: bortezomib and dexamethasone; Cd; carfilzomib and dexamethasone; CLd: carfilzomib, lenalidomide and dexamethasone; DBd: daratumumab, bortezomib and dexamethasone; DBMP: daratumumab, bortezomib, melphalan and prednisone; IPd: isatuxumab, pomalidomide and dexamethasone; ITT: intention-to-treat; Ld: lenalidomide and dexamethasone; PBd: panobinostat, bortezomib and dexamethasone; Pd: pomalidomide and dexamethasone; PFS: progression-free survival; TTP: time to progression.

The dosing regimens, unit costs and total costs per administration associated with the individual subsequent therapies included in the model are presented in Appendix K.The average cost per model cycle of Bd, Ld, PBd, Pd, Cd, CLd, IPd and BCd is presented in Table 54 and DBd in Table 55.

Table 54: Summary of drug acquisition costs for subsequent treatments

Treatment[a]	Drug costs per cycle[b]	Total regimen costs per cycle
Ld		
Lenalidomide	£3,057.60	£3,067.99
Dexamethasone	£10.39	
Bd		
Bortezomib	£1,474.90	£1,493.37
Dexamethasone	£18.47	
PBd (Cycles 1–8)		
Panobinostat	£6,208.00	£7,328.03
Bortezomib	£1,106.18	
Dexamethasone	£13.85	
PBd (Cycles 9–16)		
Panobinostat	£6,208.00	£6,768.01
Bortezomib	£553.09	
Dexamethasone	£6.93	
Pd		
Pomalidomide	£8,884.00	£8,894.39
Dexamethasone	£10.39	
Cd (Cycle 1)		
Carfilzomib	£9,856.00	£9,866.39
Dexamethasone	£10.39	
Cd (Cycles 2+)		
Carfilzomib	£12,672.00	£12,682.39
Dexamethasone	£10.39	
CLd (Cycle 1)		
Carfilzomib	£9,856.00	£12,923.99

Lenalidomide	£3,057.60	
Dexamethasone	£10.39	
CLd (Cycles 2+)		
Carfilzomib	£6,336.00	£9,403.99
Lenalidomide	£3,057.60	
Dexamethasone	£10.39	
BCd		
Bortezomib	£1,106.18	£1,175.63
Cyclophosphamide	£55.60	
Dexamthasone	£13.85	
ILd		
Ixazomib	£6,336.00	£9,398.79
Lenalidomide	£3,057.60	
Dexamethasone	£5.19	

[a] 'Cycle' in the first column of this table applies to a treatment cycle rather than a model cycle.[b] The cycle duration in the model was four weeks (28 days).
Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; Bd: bortezomib and dexamethasone; Cd; carfilzomib and dexamethasone; CLd: carfilzomib, lenalidomide and dexamethasone; DBd: daratumumab, bortezomib and dexamethasone; ILd: isatuximab, lenalidomide and dexamethasone; ILd: Ixazomib, lenalidomide and dexamethasone; PBd: panobinostat, bortezomib and dexamethasone; Pd: pomalidomide and dexamethasone.

For DBd, the number of daratumumab administrations per model cycle is not constant over time. Thus, an average cost per cycle until disease progression was calculated (hence these are presented separately in Table 55 for DBd). In the base case, [redacted]

Table 55: Summary of drug acquisition costs for subsequent treatments (DBd)

Treatment[a]	Drug costs per cycle	Total regimen costs per cycle	Median TTP (3-week cycles)	Total Cost	Average cost per cycle
DBd (Cycles 1–3)					
Daratumumab	[redacted]				
Bortezomib	£1,106.18	[redacted]	40.05	[redacted]	[redacted]
Dexamethasone	£13.85				
DBd (Cycles 4–8)					

Daratumumab	[redacted]	[redacted]			
Bortezomib	£1,106.18				
Dexamethasone	£13.85				
DBd (Cycles 9+; converted to 3-week treatment cycles)[b]					
Daratumumab	[redacted]	[redacted]			
Bortezomib	-				
Dexamethasone	-				

[a] 'Cycle' in the first column of this table applies to a treatment cycle rather than a model cycle. [b] From cycle 9 onwards, DBd regimen switches from 3-week cycles to 4-cycles.
Abbreviations: DBd: daratumumab, bortezomib and dexamethasone; TTP: time to treatment progression.

B.3.5.1.3 Administration costs

The cost of administration was included for both front-line treatment and subsequent therapies (Table 56). In line with the assumptions used in NICE TA573, for oral chemotherapy regimens, a one-off cost was applied on treatment initiation, whereas for therapies administered via SC injection (i.e. daratumumab), a cost was applied for each administration.[174] The cost of a blood test prior to the first administration of daratumumab was also included in the cost of administration for DLd, in line with the SmPC.[157]

In the base case, 100% patients are assumed to receive SC daratumumab in line with anticipated use in English clinical practice. However, a scenario has been conducted assuming 2% patients receive IV daratumumab to assess the impact of this on the cost-effectiveness results.[175]

Table 56: Administration costs

Drug	Parameter	Cost	Source
Subcutaneous drugs	First SC administration	£99.30	NHS Reference Costs 2019-20. N10AF Specialist nursing, cancer related, adult, face to face
	Subsequent SC administrations	£11.03	NHS Reference Costs 2019-20. N10AF: Specialist Nursing, Cancer Related, Adult, Face to face. Reduced visit time from 45 to 5 minutes, in line with Mateos et al. 2019[126]
	Blood test (prior to first administration)	£2.53	NHS Reference Costs 2019-20. DAPS05 Haematology
IV drugs	First IV administration	£1,431.72	NHS Reference Costs 2019-20. SB14Z Deliver complex chemotherapy, including prolonged infusion, at first attendance
	Subsequent IV administrations	£1,253.77	NHS Reference Costs 2019-20. SB15Z Deliver subsequent elements of a chemotherapy cycle
Oral chemotherapies	First administration only	£207.79	NHS Reference Costs 2019-20. SB11Z Outpatient: Deliver Exclusively Oral Chemotherapy

Abbreviations: IV: intravenous; NHS: National Health Service; SC: subcutaneous.

B.3.5.2 Health-state unit costs and resource use

Monitoring costs

Ongoing monitoring costs were included in the model, with the frequency of monitoring visits and tests dependent on whether patients were receiving active anti-cancer therapy (Table 57), based on ToT. It was assumed that patients would receive 'on-treatment' monitoring for as long as a patient is on some form of active treatment (front-line or subsequent), with the 'off-treatment' monitoring costs applied when not on active treatment (e.g. pre-progression, but after discontinuing treatment). This is of most relevance to patients treated with BMP, as it has a fixed

duration and therefore, patients spend longer periods in the 'off treatment' state before progressing.

The type and frequency of monitoring visits and tests were based on those used in NICE TA573, TA763 and SMC2302.[4, 130, 176]

Table 57: Monitoring costs

Item	Frequency per cycle		Unit cost	Source
	On-treatment	Off-treatment		
Haematologist visit	0.92	0.32	£171.18	NHS Reference Costs 2019–20. WF01A: Clinical Haematology (303). Non-Admitted Face-to-Face Attendance, Follow-up
Full blood count	0.84	2.56	£2.53	NHS Reference Costs 2019–20. DAPS05: Haematology
Biochemistry	0.76	1.32	£1.20	NHS Reference Costs 2019–20. DAPS04: Clinical Biochemistry
Protein electrophoresis	0.52	0.72	£1.20	
Immunoglobulin	0.48	0.76	£1.20	
Urinary light chain excretion	0.20	0.20	£1.20	
Total cost per 28 days	**£161.96**	**£64.86**	-	Calculated

Abbreviations: NHS: National Health Service.

End-of-life cost

A one-off cost representing the cost of terminal care was applied in the model for the proportion of patients that died in each cycle. The cost applied in the model (£8,534.05) was derived from the cost used in NICE TA573, inflated to 2020–2021 using the NHSCII Pay & Price Index to 2020–21.[4, 177]

B.3.5.3 Adverse reaction unit costs and resource use

The cost of managing AEs experienced by patients receiving treatment was included in the model. The costs per event were based on NHS reference costs 2019–20 and are presented in Table 58. These costs were applied to the proportion of patients experiencing each event in each of the treatment arms in the model (Table 45) and were applied in the first cycle of the model. The total cost across all events included in the model was £3,213.51 for DLd, £2,326.20 for Ld and £2,071.54 for BMP.

Table 58: AE costs

AE	Costs	Source
Neutropenia	£1,533.37	NHS Reference Costs 2019–20. Weighted average of SA08G–SA08J: Other haematological or splenic disorders, with CC score 0–6+, non-elective long stay and short stay
Lymphopenia	£1,533.37	NHS Reference Costs 2019–20. Weighted average of SA08G–SA08J: Other haematological

		or splenic disorders, with CC score 0–6+, non-elective long stay and short stay
Thrombocytopenia	£1,915.08	NHS Reference Costs 2019–20. Weighted average of SA12G–SA12K: Thrombocytopenia with CC score 0–8+, non-elective long stay and short stay
Leukopenia	£1,533.37	NHS Reference Costs 2019–20. Weighted average of SA08G–SA08J: Other Haematological or Splenic Disorders, with CC Score 0–6+, non-elective long stay and short stay
Anaemia	£1,212.47	NHS Reference Costs 2019–20. Weighted average of SA04G–SA04L: Iron Deficiency Anaemia with CC Score 0–14+, non-elective long stay and short stay
Pneumonia	£1,908.15	NHS Reference Costs 2019–20. Weighted average of DZ11K–DZ11V: Lobar, Atypical or Viral Pneumonia, with Multiple Interventions (CC Score 0–14+), with Single Intervention (CC Score 0–13+) and without Interventions (CC Score 0–14+), non-elective long stay and short stay
Hypokalaemia	£1,456.44	NHS Reference Costs 2019–20. Weighted average of KC05G–KC05N: Fluid or Electrolyte Disorders, with Interventions (CC Score 0–5+) and without Interventions (CC Score 0–5+), non-elective long stay and short stay
Pulmonary embolism	£1,525.01	NHS Reference Costs 2019–20. Weighted average of DZ09J–DZ09Q: Pulmonary Embolus with Interventions (CC Score 9+) and without interventions (CC Score 0–12+), non-elective long stay and short stay
Hyperglycaemia	£1,232.14	NHS Reference Costs 2019–20. Weighted average of KB01C–KB01F and KB02G–KB02K: Diabetes with Hypoglycaemic Disorders (CC Score 0–8+) and with Hyperglycaemic Disorders (CC Score 0–8+), non-elective long stay and short stay
Diarrhoea	£1,379.30	NHS Reference Costs 2019–20. Weighted average of FD01A– FD01J: Gastrointestinal Infections with Multiple Interventions (CC Score 0–5+), and without Interventions (CC Score 0–8+), non-elective long stay and short stay
Fatigue	£1,338.44	NHS Reference Costs 2019–20. Weighted average of WH17A – C: Admission Related to Social Factors with Interventions (CC Score 0–1+), non-elective long stay and short stay
Hypertension	£651.08	NHS Reference Costs 2019–20. EB04Z: Hypertension, non-elective long stay and short stay
Asthenia	£2,385.82	NHS Reference Costs 2019–20. Weighted average of SA03G– SA03H: Haemolytic Anaemia (CC Score 0–3+), non-elective long stay and short stay
Acute kidney disease	£1,997.64	NHS Reference Costs 2019–20. Weighted average of LA07H– LA07P: Acute Kidney Injury with Interventions (CC Score 0–11+) and without

		Interventions (CC Score 0–12+), non-elective long stay and short stay
Chronic kidney disease	£2,744.86	NHS Reference Costs 2019–20. Weighted average of LA08G– LA07P: Chronic Kidney Disease with Interventions (CC Score 0–6+) and without Interventions (CC Score 0–11+), non-elective long stay and short stay
Cataract	£1,138.75	NHS Reference Costs 2019–20. Weighted average of BZ24D–BZ24G: Non-Surgical Ophthalmology with Interventions and without Interventions (CC Score 0–5+)

Abbreviations: AE: adverse event; NHS: National Health Service.

B.3.5.4 Miscellaneous unit costs and resource use

No additional costs were included in the cost utility analysis.

B.3.6 *Severity*

The expected quality-adjusted life expectancy (QALE) for the general population was calculated in line with the methods provided by Schneider et al. (2022).[178] The total life expectancy for the modelled population (Table 59) was calculated using population mortality data from the ONS for 2018–2020.[179] The total life expectancy was quality-adjusted using UK population norm values for EQ-5D as reported by Hernández Alava et al. (2022) through the NICE DSU.[180]

The total QALYs for the current UK MM population on treatment was calculated using a real-world evidence data set from NHS Digital NCRAS including front-line patients who did not receive an ASCT diagnosed with MM in England between January 2015 and December 2019 inclusive. Mean OS and TTNT was used to determine the time spent in the PF, PD and death health states (Table 60). Utility values from MAIA (see Section B.3.4.5) were applied to calculate total QALYs for each treatment. Utilities were discounted at a rate of 3.5% per year in line with the NICE guide to the methods of technology appraisal.[149]

Table 59: Summary features of QALY shortfall analysis

Factor	Value	Reference to section in submission
Female (%)	[redacted]	B.3.2.1
Starting age	[redacted]	B.3.2.1

Abbreviations: QALY: quality adjusted life year.

Table 60: OS and TTNT data from NHS Digital NCRAS for England between January 2015 and December 2019[a]

Endpoint	Restricted mean		Extended mean	
	Months	Years	Months	Years
OS	[redacted]	[redacted]	[redacted]	[redacted]
TTNT	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BCd; bortezomib, cyclophosphamide and dexamethasone; BMP: bortezomib, melphalan and prednisone; CTd: Cyclophosphamide, thalidomide and dexamethasone; NCRAS: National Cancer Registration and Analysis Service.
Source: Janssen Data on File, NHS Digital NCRAS.[84]
Restricted mean: computes the mean survival time restricted to the longest follow-up time. **Extended mean:** computes the mean survival by exponentially extending the survival curve to zero

For all treatments, the absolute QALY shortfall and proportional QALY shortfall were below the threshold of 12 and 0.85, respectively, therefore a severity modifier of 1 is applied in the base case results (Table 61).

Table 61: Summary of QALY shortfall analysis

	Expected total QALEs for the general population	Total QALYs that people living with a condition would be expected to have with current treatment	Absolute QALY shortfall	Proportional shortfall
NCRAS data, restricted mean OS and TTNT	[redacted]	[redacted]	[redacted]	[redacted]
NCRAS data, extended mean OS and TTNT		[redacted]	[redacted]	[redacted]

Abbreviations: NCRAS: National Cancer Registration and Analysis Service; OS: overall survival; QALE: quality adjusted life expectancy; QALY: quality adjusted life year; TTNT: time to next treatment.

B.3.7 *Uncertainty*

PSMs rely on the extrapolation of survival data from clinical trials which can introduce uncertainty, especially if survival data are immature. However, mature survival data from MAIA are available (after a median follow-up of 64.5 months, disease progression or death had occurred in [redacted] participants [redacted] in the DLd group and [redacted] participants [redacted] in the Ld group) which reduces the uncertainty in the long-term extrapolations.[102] The PSM model structure allows intuitive incorporation of the mature PFS and OS data collected from the MAIA and ALCYONE trials. Extrapolations were informed by statistical fit and externally validated by comparing the survival estimates predicted by the model to survival estimates provided by UK clinical experts (for BMP and Ld).

Evaluating front-line MM treatments is also associated with uncertainty due to challenges associated with modelling subsequent therapies. This is largely because a substantial proportion of patients in clinical practice are expected to receive treatments available on the CDF, which are not considered in the base case for this submission in line with the NICE Position Statement. However, due to the widespread usage of CDF treatments across the myeloma pathway, and proximity of the CDF re-appraisals for DBd and ILd, an analysis including the costs of CDF treatments is also presented to inform Committee decision making. The challenge of the high level of CDF reimbursement for subsequent therapies in this setting is compounded by the fact that clinicians have indicated that a wide variety of treatments are used at each line of therapy, treatment regimens are not standardised across England and that different practices adapt different treatment regimens based on personal preference and the patient in question.[3] Furthermore, the MAIA trial started in 2014 and since then the treatment landscape for MM has changed.[102] Together, these challenges make defining the subsequent treatment pathway for each front-line treatment difficult. In order to model the treatment pathway as accurately as possible, subsequent treatment market shares for second and third-line were generated based on estimates from seven clinicians covering a wide range of geographical areas in England (see

Section B.3.5.1).[3] It is important to note, however, that clinicians found this exercise challenging, given the dominance of CDF treatments in the MM pathway.

The comparison of DLd versus BMP has been provided to fulfil the comparator specified in the final scope of bortezomib with an alkylating agent and corticosteroid. BCd is another bortezomib combination with an alkylating agent and corticosteroid, and the assumption of equivalent efficacy between BCd and BMP may also introduce uncertainty into the model. However, given data supporting clinical equivalence from two observation studies, a MAIC using data from one of these studies, validation with English clinical experts, and a real-world evidence data set of patients diagnosed with MM in England presented in Section B.2.9.2, this approach is considered justified.[122]

Finally, there is limited evidence on the efficacy of the thalidomide-based regimens. However, given the very limited use of thalidomide-based regimens in English practice (~5%), comparisons against CTd and MPT are not considered relevant for decision making. For completeness, scenarios using a HR versus both Ld and BMP have been provided (see Appendix N).

B.3.8 *Managed access proposal*

Janssen consider the evidence package for DLd sufficiently robust, and length of follow-up from MAIA sufficiently mature for a recommendation to be made for routine commissioning. With the latest available datacut, the MAIA trial has over five years of median follow-up and furthermore has demonstrated a statistically significant OS benefit in patients with NDMM who are ineligible for ASCT directly against current NHS best standard of care, Ld. Whilst a recommendation for the CDF remains an option for the Committee, it is expected that further follow-up of the MAIA trial will only confirm the current understanding of the significant clinical benefit of DLd in this setting, rather than resolving uncertainty underpinning the evaluation.

If the Committee deem that that a period of Managed Access would be necessary to resolve the uncertainty in the evaluation, potential sources of data would be:

- Additional follow-up from the MAIA trial (final OS analysis expected in [redacted]), to provide longer-term outcome data for DLd and Ld
- Additional follow-up from the final OS analysis of the ALCYONE trial (expected in [redacted]) to provide longer-term outcome data for BMP
- Real world effectiveness data for DLd from the Systemic Anti-Cancer Therapy (SACT) and linked NHS Digital datasets (data collection to commence following CDF approval date)
- Longer follow up from from NHS Digital datasets to provide real world effectiveness data for Ld

B.3.9 *Summary of base-case analysis inputs and assumptions*

B.3.9.1 Summary of base-case analysis inputs

A summary of inputs used in the base case analysis is presented in Table 62.

Table 62: Summary of variables applied in the economic model

Variable	Value	Reference to section

					in submission
Model settings					
Discount rate (costs and benefits)	3.5%				Section B.3.2
Time horizon	Lifetime (26 years)				
Patient baseline characteristics					
Mean age	[redacted]				Section B.3.2.1
Mean body weight	[redacted]				
Mean BSA	[redacted]				
% Male	[redacted]				
Survival inputs					
	PFS	**OS**	**ToT**		Section B.3.3
Extrapolation for DLd	Exponential	Exponential	Gompertz		
Extrapolation for Ld	Exponential	Gompertz	Weibull		
Extrapolation for BMP	Weibull	Gompertz	N/A (KM data)		
AEs					
	DLd	**BMP**	**Ld**	**BCd**	Section B.3.3.4
Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]	
Lymphopenia	[redacted]	[redacted]	[redacted]	[redacted]	
Thrombocytopenia	[redacted]	[redacted]	[redacted]	[redacted]	
Leukopenia	[redacted]	[redacted]	[redacted]	[redacted]	
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]	
Pneumonia	[redacted]	[redacted]	[redacted]	[redacted]	
Hypokalaemia	[redacted]	[redacted]	[redacted]	[redacted]	
Pulmonary embolism	[redacted]	[redacted]	[redacted]	[redacted]	
Hyperglycaemia	[redacted]	[redacted]	[redacted]	[redacted]	
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]	
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]	
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]	
Asthenia	[redacted]	[redacted]	[redacted]	[redacted]	
Acute kidney disease	[redacted]	[redacted]	[redacted]	[redacted]	
Chronic kidney disease	[redacted]	[redacted]	[redacted]	[redacted]	
Cataract	[redacted]	[redacted]	[redacted]	[redacted]	
Utility inputs					
PF (SD)	[redacted]				Section B.3.4.5
PD (SD)	[redacted]				
Adverse event disutility					
Neutropenia	-0.15				Section B.3.4.4
Lymphopenia	-0.07				

Thrombocytopenia	-0.31	
Leukopenia	-0.07	
Anaemia	-0.31	
Pneumonia	-0.19	
Hypokalaemia	-0.07	
Pulmonary embolism	-0.31	
Hyperglycaemia	-0.15	
Diarrhoea	-0.10	
Fatigue	-0.12	
Hypertension	-0.15	
Asthenia	-0.12	
Acute kidney disease	-0.18	
Chronic kidney disease	-0.05	
Cataract	-0.01	

Resource use			
	On treatment	**Off treatment**	
Haematologist visit	0.92	0.32	Section B.3.5.2
Full blood count	0.84	2.56	
Biochemistry	0.76	1.32	
Protein electrophoresis	0.52	0.72	
Immunoglobulin	0.48	0.76	
Urinary light chain excretion	0.20	0.20	

Cost inputs		
Daratumumab SC, cost per vial (1,800 mg)/ with PAS	£4,320.00 /[redacted]	Section B.3.5.1
Bortezomib, cost per vial (2.5 mg)	£207.41	
Melphalan, cost per pack	£16.48	
Prednisone, cost per pack	£29.12	
Carfilzomib, cost per vial (60 mg)	£1,056.00	
Ixazomib, cost per pack	£6,336.00	
Dexamethasone, cost per pack	£12.99	
Lenalidomide, cost per pack	£3,057.60	

Pomalidomide, cost per pack	£8,884.00				
Panobinostat, cost per pack	£4,656.00				
Subsequent therapies					
	DLd	**BMP**	**Ld**	**BCd**	Section B.3.5.1
Bd – 2nd line	20%	0%	20%	0%	
Cd – 2nd line	20%	10%	20%	10%	
BCd – 2nd line	60%	0%	60%	0%	
Ld – 2nd line	0%	50%	0%	50%	
CLd – 2nd line	0%	40%	0%	40%	
Ld – 3rd line	5%	25%	0%	25%	
PBd – 3rd line	35%	35%	35%	35%	
Bd – 3rd line	0%	0%	0%	0%	
CTd – 3rd line	60%	40%	65%	40%	
Bd – 3rd line	0%	0%	0%	0%	
BCd – 3rd line	0%	0%	0%	0%	
Subsequent therapies (including CDF)					
Bd – 2nd line	20%	0%	0%	0%	Section B.3.5.1
Cd – 2nd line	20%	10%	5%	10%	
DBd – 2nd line	0%	30%	90%	30%	
Ld – 2nd line	0%	30%	0%	30%	
CLd – 2nd line	0%	30%	0%	30%	
BCd – 2nd line	60%	0%	5%	0%	
Ld – 3rd line	5%	15%	0%	15%	
PBd – 3rd line	30%	15%	30%	15%	
ILd – 3rd line	15%	40%	10%	40%	
CTd – 3rd line	50%	30%	60%	30%	
Bd – 3rd line	0%	0%	0%	0%	
BCd – 3rd line	0%	0%	0%	0%	
Concomitant medication costs					
Antipyretic: oral paracetamol, cost per pack	£0.47				Appendix K
Antihistamine: oral/IV diphenhydramine, cost per pack	£3.16				
Corticosteroid: oral methylprednisolone, cost per pack	£17.17				
Antiviral: acyclovir, cost per pack	£1.78				
Administration costs					
First SC administration	£99.30				Section B.3.5.1

Subsequent SC administration	£11.03	
Blood test for daratumumab	£2.53	
Oral administration	£207.79	
Monitoring costs		
Haematologist visit	£171.18	Section B.3.5.2
Full blood count	£2.53	
Biochemistry	£1.20	
Protein electrophoresis	£1.20	
Immunoglobulin	£1.20	
Urinary light chain excretion	£1.20	
End of life costs	£8,534.05	
AE costs		
Neutropenia	£1,533.37	Section B.3.5.3
Lymphopenia	£1,533.37	
Thrombocytopenia	£1,915.08	
Leukopenia	£1,533.37	
Anaemia	£1,212.47	
Pneumonia	£1,908.15	
Hypokalaemia	£1,456.44	
Pulmonary embolism	£1,525.01	
Hyperglycaemia	£1,232.14	
Diarrhoea	£1,379.30	
Fatigue	£1,338.44	
Hypertension	£651.08	
Asthenia	£2,385.82	
Acute kidney disease	£1,997.64	
Chronic kidney disease	£2,744.86	
Cataract	£1,138.75	

Abbreviations: AE: adverse event; BMP: bortezomib, melphalan and prednisone; Bd: bortezomib and dexamethasone; BSA: body surface area; Cd: carfilzomib and dexamethasone; DBd: daratumumab, bortezomib and dexamethasone; DBMP: daratumumab, bortezomib, melphalan and prednisone; HR: hazard ratio; IPd: isatuxumab, pomalidomide and dexamethasone; IV: intravenous; Ld: lenalidomide and dexamethasone; MRD: minimal residual disease; OS: overall survival; PD: progressed disease; Pd: pomalidomide and dexamethasone; PFS: progression-free survival; PF: progression-free; SC: subcutaneous.

B.3.9.2 Assumptions

A list of the key assumptions used in the base case analysis is provided in Table 63 alongside a description of scenarios conducted to explore the impact of these assumptions on the cost-effectiveness results. The results of these scenario analyses are presented in Section B.3.10.2.

Table 63: Assumptions used in the cost effectiveness model

Parameter	Assumption (base case)	Justification	Addressed in scenario analysis; rationale for scenario analysis
Extrapolations for PFS and OS	DLd: Exponential distribution for the extrapolation of both PFS and OS BMP: Weibull distribution for the extrapolation of PFS and Gompertz distribution for the extrapolation of OS Ld: Exponential distribution for the extrapolation of PFS and Gompertz distribution for the extrapolation of OS	Given mature survival data for PFS is available from MAIA and ALCYONE (median PFS was met for all treatment arms and median OS was met for the Ld arm in MAIA), the choice of curve was mainly informed by the best statistic fit using the AIC and BIC values. For BMP and Ld, the curve with the lowest AIC/BIC was validated against clinician estimates. Survival outcomes predicted by the model were also validated against the observed data from the MAIA and FIRST trial for Ld and ALCYONE and VISTA for BMP (see Section B.3.3.1.3).[181, 182]	The following scenarios were conducted: DLd extrapolations • PFS – curve choice based on next best statistical fit (Weibull; a more optimistic curve) and also using a more pessimistic curve (generalised gamma). • OS – curve choice based on next best statistical fit (Weibull; a more optimistic curve) and also using a more pessimistic curve (Gompertz). BMP extrapolations • Curve choice based on clinical validation (PFS = generalised gamma, OS = weighted average of Gompertz and Weibull) Ld extrapolations • Curve choice based on clinical validation (PFS = Weibull)
Time on treatment	For BCd, CTd and MPT ToT was assumed equal to PFS until the end of the fixed treatment duration, at which point 100% of patients discontinue treatment.	This approach was taken due to the lack of TTD data for BCd, CTd and MPT. The assumption is considered clinically plausible, as any patient progressing would discontinue treatment.	Scenario analysis has been conducted whereby 100% of patients incur costs until the end of the fixed treatment duration to replicate the situation where no patients discontinue treatment.

Comparators	Ld is considered the main comparator for this submission.	A fully incremental analysis is presented in Section B.3.9.3. At both list and the daratumumab PAS price, all comparator treatments are [redacted] by Ld; therefore, given Ld is most commonly used in English practice, and that it is superior from a cost-effectiveness perspective to the other included comparators, Ld is considered the main comparator of interest for this evaluation. Janssen understand that CTd and MPT are now only very rarely used in clinical practice in England following the availability of Ld. For the comparison against bortezomib with an alkylating agent and corticosteroid, BMP is used, given the availability of adjusted IPD from the ALCYONE trial, and lack of evidence for BCd in this population.	For completeness, comparisons against BMP, MPT and CTd are provided in the document appendices, and versus BCd in a scenario analysis.
Daratumumab formulation	The cost of daratumumab was based on the fixed dose of 1,800 mg administered entirely via SC injection, with efficacy for DLd based on MAIA (weight-based dose and IV infusion). The efficacy has been shown to be equivalent in the Phase III COLUMBA study.[15]	Clinical expert opinion indicated that daratumumab would be administered almost entirely as SC injection in English practice.	A scenario analysis has been conducted whereby [redacted] patients are assumed to receive daratumumab as SC, based on current Janssen UK sales data for DLd, to replicate a situation where not all patients receive the SC formulation.
BMP dosing regimen	In the model, the dosing regimen for BMP is aligned to the regimen from ALCYONE, which is a slightly different dosing regimen to that indicated in the bortezomib SmPC but is the schedule	This approach was taken as clinical expert opinion indicated that the regimen from ALCYONE would be used in English clinical practice.	Given the base case assumption is aligned with the dosing regimen used in English clinical practice, no scenario analysis has been conducted varying this parameter.

	most adhered to in clinical practice.[132, 183]		
Subsequent treatments	Subsequent treatments (2nd and 3rd line) were included in the model based on clinical expert opinion as to the treatments used. Analyses are provided with and without treatments available via the CDF aligned with NICE Position statement and to take into account important treatment pathway changes should CDF treatments transition to routine commissioning over the course of an appraisal. 4th line treatments were not included in the model, in line with the approach taken in TA587.[4]	Only 2nd and 3rd line treatments are considered in the model as when 4th line treatments are considered, the estimated time patients would spend on treatment would exceed how long patients are in the PD health state, creating implausibly high subsequent treatment costs, especially in the Ld arm. Therefore, including 4th line therapy may lack face validity.	Analyses are presented with and without CDF treatments, aligned with the NICE Position Statement.
Vial sharing	No vial sharing was assumed	In the base case analysis, it was assumed that vials would not be shared or pooled across administrations. As such, drug wastage was assumed if the amount of drug required for a single dose was not an exact multiple of vial size.	With certain drugs administered in a hospital-based setting, there is the potential for vial sharing in clinical practice. A scenario was also conducted in which vial sharing was assumed to occur.
Utility values	Utility values for PF and PD were based on EQ-5D data from MAIA.	For consistency with the source of clinical inputs included in the model for DLd and Ld, and the relevance of data from the MAIA trial to the patient population of interest for this submission, the utility values used in the base case analysis were based on EQ-5D data from the MAIA trial.	To explore the impact of using alternative utility values, values from ALCYONE are used in a scenario analysis.

Abbreviations: BMP: bortezomib, melphalan and prednisone; CR: complete response; DBMP: daratumumab, bortezomib, melphalan and prednisone; EQ-5D: EuroQoL-5 Dimensions; HR: hazard ratio; IV: intravenous; Ld: lenalidomide and dexamethasone; MRD: minimal residual disease; NDMM: newly diagnosed multiple myeloma; OS: overall survival; PD: progressed disease; PF: progression-free; PFS: progression-free survival; SC: subcutaneous SmPC: summary of product characteristics.

B.3.9.3 Base-case incremental cost-effectiveness analysis results

A fully incremental analysis for all relevant comparators is presented in Table 64 and Table 65 below, for daratumumab at list price and PAS price, respectively, excluding CDF treatments at subsequent lines. In these analyses, [redacted].

Based on this, and that clinical expert feedback indicates that Ld represents the main current NHS SoC, with bortezomib-based combinations (e.g. BMP/BCd) used to treat a minority of patients, results in this section beyond the fully incremental analysis are versus Ld only.[3] For completeness, full results against BMP, CTd and MPT are presented in Appendix N.

Table 64: Fully incremental analysis – list price (base case excluding CDF treatments)

	Total costs	Total QALYs	Dominated?	Extendedly dominated?	Fully incremental ICER
Ld	[redacted]	[redacted]	-	-	-
BMP	[redacted]	[redacted]	Yes	-	Dominated by Ld
CTd	[redacted]	[redacted]	Yes	-	Dominated by Ld
MPT	[redacted]	[redacted]	Yes	-	Dominated by Ld
DLd	[redacted]	[redacted]	No	No	£189,319

Abbreviations: BMP: bortezomib, melphalan and prednisone; CTd: cyclophosphamide, thalidomide and dexamethasone; DLd: daratumumab, lenalidomide and dexamethasone; ICER: incremental cost-effectiveness ratio; Ld: lenalidomide and dexamethasone; MPT: melphalan, prednisone and thalidomide; QALY: quality-adjusted life-year.

Table 65: Fully incremental analysis – PAS price (base case excluding CDF treatments)

	Total costs	Total QALYs	Dominated?	Extendedly dominated?	Fully incremental ICER
Ld	[redacted]	[redacted]	-	-	-
BMP	[redacted]	[redacted]	[redacted]	-	[redacted]
CTd	[redacted]	[redacted]	[redacted]	-	[redacted]
MPT	[redacted]	[redacted]	[redacted]	-	[redacted]
DLd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BMP: bortezomib, melphalan and prednisone; CTd: cyclophosphamide, thalidomide and dexamethasone; DLd: daratumumab, lenalidomide and dexamethasone; ICER: incremental cost-effectiveness ratio; Ld: lenalidomide and dexamethasone; MPT: melphalan, prednisone and thalidomide; QALY: quality-adjusted life-year.

Fully incremental results including CDF treatments at subsequent lines are presented in Table 66 and Table 67 below.

Table 66: Fully incremental analysis – list price (base case including CDF treatments)

	Total costs	Total QALYs	Dominated?	Extendedly dominated?	Fully incremental ICER
CTd	[redacted]	[redacted]	-	-	-
MPT	[redacted]	[redacted]	No	No	£13,790

BMP	[redacted]	[redacted]	Yes	-	Dominated by MPT
Ld	[redacted]	[redacted]	No	No	£139,838
DLd	[redacted]	[redacted]	No	No	£141,102

Abbreviations: BMP: bortezomib, melphalan and prednisone; CTd: cyclophosphamide, thalidomide and dexamethasone; DLd: daratumumab, lenalidomide and dexamethasone; ICER: incremental cost-effectiveness ratio; Ld: lenalidomide and dexamethasone; MPT: melphalan, prednisone and thalidomide; QALY: quality-adjusted life-year.

Table 67: Fully incremental analysis – PAS price (base case including CDF treatments)

	Total costs	Total QALYs	Dominated?	Extendedly dominated?	Fully incremental ICER
CTd	[redacted]	[redacted]	[redacted]	[redacted]	-
MPT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ld	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BMP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DLd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BMP: bortezomib, melphalan and prednisone; CTd: cyclophosphamide, thalidomide and dexamethasone; DLd: daratumumab, lenalidomide and dexamethasone; ICER: incremental cost-effectiveness ratio; Ld: lenalidomide and dexamethasone; MPT: melphalan, prednisone and thalidomide; QALY: quality-adjusted life-year.

Given that the fully incremental analysis indicates Ld to be the main comparator, the deterministic base case results for DLd versus Ld is are presented in Table 68 and Table 69 for daratumumab at list and PAS price, respectively. Results including CDF treatments at subsequent lines are presented in Table 70 and Table 71 below. Net health benefit at the £20,000 and £30,000 thresholds are also presented.

Disaggregated results from the base case analysis are presented in Appendix J for:

- Costs by cost category (treatment acquisition, concomitant medications, AEs, resource use, end-of-life)
- Costs by health state (PF, PD and death)
- QALYs by health state (PF and PD)

The difference in costs between treatment arms was primarily due to differences in drug acquisition costs between DLd and Ld. The other sources of front line treatment costs applied in the model (e.g. administration, monitoring, concomitant medication, AEs) were broadly similar between the treatment arms. The difference in total costs between the intervention and Ld were largely attributable to the difference in drug acquisition costs in front line and the treatment mix received in subsequent lines of therapy. The difference in QALYs between treatment arms was primarily due to the difference in QALYs accrued in the PF health state. Consistent with the aims of front-line treatment, which are to delay progression and achieve sustained remission, the benefits of DLd treatment are realised in the model as an increase in time spent in the PF health state, as well as an increase in QALYs overall. Clinical outcomes (mean time spent in each health state, and PFS and OS outcomes predicted by the model) are presented in Appendix J.

Table 68: Base-case results for DLd with daratumumab at list price (deterministic; base case excluding CDF treatments)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. LYG (£)	Incr. costs	Incr. QALYs	ICER versus baseline (£/QALY)	NHB at £20,000	NHB at £30,000
DLd	[redacted]	7.81	[redacted]	-	-	-	-	-	-
Ld	[redacted]	5.17	[redacted]	2.64	[redacted]	[redacted]	£189,319	[redacted]	[redacted]

Abbreviations: DLd: Daratumumab, lenalidomide and dexamethasone; ICER, incremental cost-effectiveness ratio; Ld: Lenalidomide and dexamethasone; LYG, life years gained; NHB: net health benefit; QALY: quality adjusted life year.

Table 69: Base-case results for DLd with daratumumab at PAS price (deterministic; base case excluding CDF treatments)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. LYG (£)	Incr. costs	Incr. QALYs	ICER versus baseline (£/QALY)	NHB at £20,000	NHB at £30,000
DLd	[redacted]	7.81	[redacted]	-	-	-	-	-	-
Ld	[redacted]	5.17	[redacted]	2.64	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: DLd: Daratumumab, lenalidomide and dexamethasone; ICER, incremental cost-effectiveness ratio; Ld: Lenalidomide and dexamethasone; LYG, life years gained; NHB: net health benefit; QALY: quality adjusted life year.

Table 70: Base-case results for DLd with daratumumab at list price (deterministic; base case including CDF treatments)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. LYG (£)	Incr. costs	Incr. QALYs	ICER versus baseline (£/QALY)	NHB at £20,000	NHB at £30,000
DLd	[redacted]	7.81	[redacted]	-	-	-	-	-	-
Ld	[redacted]	5.17	[redacted]	2.64	[redacted]	[redacted]	£141,102	[redacted]	[redacted]

Abbreviations: DLd: Daratumumab, lenalidomide and dexamethasone; ICER, incremental cost-effectiveness ratio; Ld: Lenalidomide and dexamethasone; LYG, life years gained; NHB: net health benefit; QALY: quality adjusted life year.

Table 71: Base-case results for DLd with daratumumab at PAS price (deterministic; base case including CDF treatments)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. LYG (£)	Incr. costs	Incr. QALYs	ICER versus baseline (£/QALY)	NHB at £20,000	NHB at £30,000
DLd	[redacted]	7.81	[redacted]	-	-	-	-	-	-
Ld	[redacted]	5.17	[redacted]	2.64	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: DLd: Daratumumab, lenalidomide and dexamethasone; ICER, incremental cost-effectiveness ratio; Ld: Lenalidomide and dexamethasone; LYG, life years gained; NHB: net health benefit; QALY: quality adjusted life year.

B.3.10 *Exploring uncertainty*

B.3.10.1 Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was conducted in order to assess the impact of parameter uncertainty on the results of the CE model. The PSA was run for 5,000 iterations and in each iteration model inputs for all parameters were randomly drawn from specified distributions (e.g. gamma for costs; beta for proportions and lognormal for HRs). Where possible the standard error or standard deviation associated with the mean value was used to define the distribution, otherwise it was assumed that the standard error would be 10% of the mean value. The inputs and distributions used in the PSA are summarised in Appendix M.

The average incremental cost-effectiveness results from the PSA are presented in Table 72 and Table 73 for DLd at list and PAS price, respectively, excluding and including CDF treatments at subsequent lines. Taking into account the combined parameter uncertainty in the model, the ICERs for DLd versus Ld were seen to be similar (albeit marginally higher) to those reported in the deterministic base case.

Scatter plots showing the results of each iteration from the PSA on the cost-effectiveness plane are presented in Figure 62 to Figure 65 for DLd versus Ld, including and excluding the CDF treatments at subsequent lines.

Table 72: Average probabilistic cost-effectiveness results – list price

Comparison versus	Inc. costs	Inc. QALYs	ICER
Ld (excluding CDF)	[redacted]	[redacted]	£193,386
Ld (including CDF)	[redacted]	[redacted]	£145,100

Abbreviations: DLd: Daratumumab, lenalidomide and dexamethasone; ICER, incremental cost-effectiveness ratio; Ld: Lenalidomide and dexamethasone; QALY: quality adjusted life year.

Table 73: Average probabilistic cost-effectiveness results – PAS price

Comparison versus	Inc. costs	Inc. QALYs	ICER
Ld (excluding CDF)	[redacted]	[redacted]	[redacted]
Ld (including CDF)	[redacted]	[redacted]	[redacted]

Abbreviations: DLd: Daratumumab, lenalidomide and dexamethasone; ICER, incremental cost-effectiveness ratio; Ld: Lenalidomide and dexamethasone; QALY: quality adjusted life year.

Figure 62: Cost-effectiveness plane for DLd versus Ld – list price (base case excluding CDF treatments)

Abbreviations: DLd: daratumumab, lenalidomide and dexamethasone; Ld: lenalidomide and dexamethasone; PSA: probabilistic sensitivity analysis.

Figure 63: Cost-effectiveness plane for DLd versus Ld – PAS price (base case excluding CDF treatments)

Abbreviations: DLd: daratumumab, lenalidomide and dexamethasone; Ld: lenalidomide and dexamethasone; PAS: patient access scheme; PSA: probabilistic sensitivity analysis.

Figure 64: Cost-effectiveness plane for DLd versus Ld – list price (base case including CDF treatments)

Abbreviations: DLd: daratumumab, lenalidomide and dexamethasone; Ld: lenalidomide and dexamethasone; PSA: probabilistic sensitivity analysis.

Figure 65: Cost-effectiveness plane for DLd versus Ld – PAS price (base case including CDF treatments)

Abbreviations: DLd: daratumumab, lenalidomide and dexamethasone; Ld: lenalidomide and dexamethasone; PAS: patient access scheme; PSA: probabilistic sensitivity analysis.

B.3.10.2 Deterministic sensitivity analysis

Deterministic sensitivity analysis (DSA) was conducted by varying the input for each parameter in the model by ±10% of their mean value, whilst keeping all other inputs the same. For those parameters where 95% confidence intervals were available, the upper and lower limits of the

confidence intervals were used instead to vary the model input. The inputs used in the DSA are presented in Appendix M. Results from the PSA are presented in Figure 66 to Figure 69 below.

The parameters with the greatest impact on the ICER were the DLd OS exponential curve intercept and the DLd PFS exponential curve intercept. The decrease/increase in the ICER from the base case was less than £5,000 per QALY gained for all other parameters varied in the DSA.

Figure 66: ICER tornado plot from deterministic sensitivity analyses – top 10 parameters (DLd vs Ld) – list price (base case excluding CDF treatments)

Note: Only the expontential extrapolation was included in the DSA as it only includes one variable (the intercept)
Abbreviations: DLd: daratumumab, lenalidomide and dexamethasone; Ld: Lenalidomide and dexamethasone; HR: hazard ratio; ICER: incremental cost-effectiveness ratio; MRD: minimal residual disease; OS: overall survival; PFS: progression-free survival.

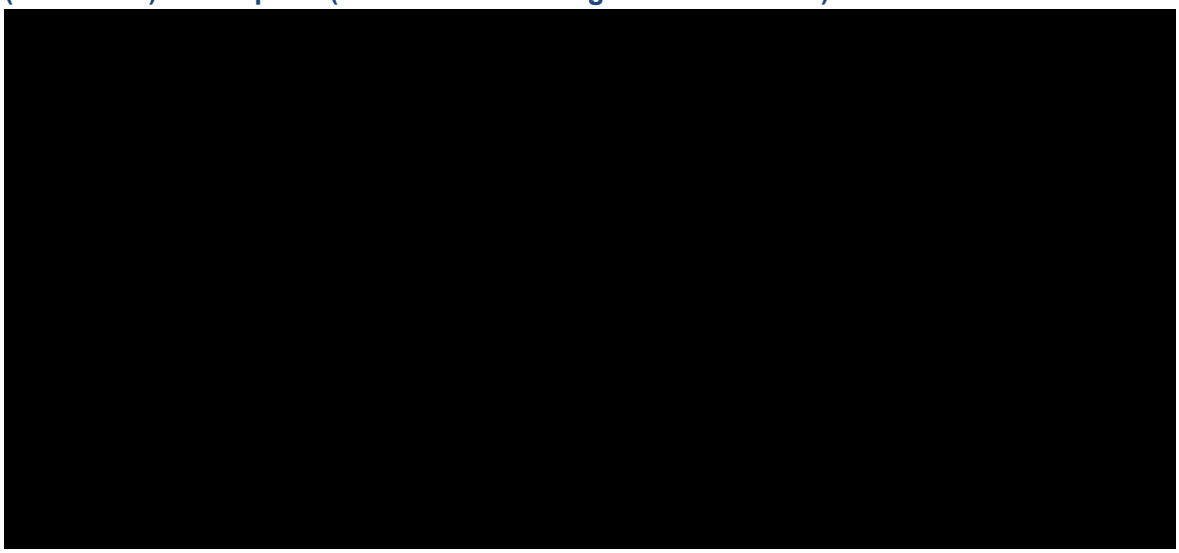
Figure 67: ICER tornado plot from deterministic sensitivity analyses – top 10 parameters (DLd vs Ld) – PAS price (base case excluding CDF treatments)

Note: Only the expontential extrapolation was included in the DSA as it only includes one variable (the intercept)
Abbreviations: DLd: daratumumab, lenalidomide and dexamethasone; Ld: Lenalidomide and dexamethasone; HR: hazard ratio; ICER: incremental cost-effectiveness ratio; Ld: lenalidomide and dexamethasone; MRD: minimal residual disease; OS: overall survival; PFS: progression-free survival.

Figure 68: ICER tornado plot from deterministic sensitivity analyses – top 10 parameters (DLd vs Ld) – list price (base case including CDF treatments)

Note: Only the expontential extrapolation was included in the DSA as it only includes one variable (the intercept)
Abbreviations: DLd: daratumumab, lenalidomide and dexamethasone; Ld: Lenalidomide and dexamethasone; HR: hazard ratio; ICER: incremental cost-effectiveness ratio; Ld: lenalidomide and dexamethasone; MRD: minimal residual disease; OS: overall survival; PFS: progression-free survival.

Figure 69: ICER tornado plot from deterministic sensitivity analyses – top 10 parameters (DLd vs Ld) – PAS price (base case including CDF treatments)



Note: Only the expontential extrapolation was included in the DSA as it only includes one variable (the intercept)
Abbreviations: DLd: daratumumab, lenalidomide and dexamethasone; Ld: Lenalidomide and dexamethasone; HR: hazard ratio; ICER: incremental cost-effectiveness ratio; Ld: lenalidomide and dexamethasone; MRD: minimal residual disease; OS: overall survival; PFS: progression-free survival.

B.3.10.3 Scenario analysis

For the main comparison versus Ld, a number of scenario analyses were explored in which model assumptions or parameters were altered. The rationale for each scenario is outlined in Table 74, and probabilistic results of the scenario analyses carried out are presented in Table 75 and Table 76, below.

Table 74: Summary of scenario analyses

#	Scenario analysis	Rationale
Base case		
1	DLd ToT Extrapolations: Generalised Gamma	In the base case, a Gompertz extrapolation is assumed for DLd ToT based on statistical fit and clinical plausibility between PFS and ToT. Generalised gamma has the best statistical fit but results in a larger difference between the PFS and ToT estimates. Therefore, a scenario has been conducted to demonstrate the effect of selecting this curve on the results.
2a	DLd OS extrapolation: Weibull	In the base case, an exponential extrapolation is assumed for DLd OS based on statistical fit. In this scenario, a Weibull curve is selected to offer a more optimistic view of DLd OS over time.
2b	DLd OS extrapolation: Gompertz	In the base case, an exponential extrapolation is assumed for DLd OS based on statistical fit. In this scenario, a Gompertz curve is selected to offer a more pessimistic view of DLd OS over time.
3a	DLd PFS extrapolation: Weibull	In the base case, an exponential extrapolation is assumed for DLd PFS based on statistical fit. In this scenario, a Weibull curve is selected to offer a more optimistic view of DLd PFS over time.
3b	DLd PFS extrapolation: Generalised Gamma	In the base case, an exponential extrapolation is assumed for DLd PFS based on statistical fit. In this scenario, a generalised gamma curve is selected to offer a more pessimistic view of DLd PFS over time.
4	Ld PFS extrapolation: Weibull	In the base case, an exponential extrapolation is assumed for Ld PFS based on statistical fit. In this scenario, a Weibull curve is selected as this selection has the second best statistical fit and is aligned with clinical validation.
5	Utility values: ALCYONE (PF = [redacted], PD=[redacted])	In the base case, utility values from MAIA for consistency with the source of clinical inputs included in the model for DLd and Ld, and the relevance of data from the MAIA trial to the patient population of interest for this submission. In addition, the values from MAIA show a logical decrease when comparing the PF and PD values, which is less pronounced in ALCYONE. However, given ALCYONE was also conducted in the ASCT-ineligible NDMM setting, a scenario has been conducted to demonstrate the effect of utilising these alternative values on the results.
6	Daratumumab medicinal forms: combination of SC and IV	In the base case, 100% patients are assumed to receive SC daratumumab in line with anticipated use in English clinical practice. However, a scenario has been conducted assuming 2% patients receive IV daratumumab to assess the impact of this on the cost-effectiveness results.
7	Vial sharing	In the base case, no vial sharing is assumed. However, as some treatments included in the model may allow for vial sharing to be implemented in practice, a scenario has been conducted to assess the impact of this on the cost-effectiveness results.

Abbreviations: ASCT: autologous stem cell transplant; BCd: bortezomib, cyclophosphamide and dexamethasone; BMP: bortezomib, melphalan and prednisone; CDF: Cancer Drugs Fund; DLd: daratumumab, lenalidomide and dexamethasone; ICER: incremental cost-effectiveness ratio; IV: intravenous; KM: Kaplan-Meier; Ld: lenalidomide and dexamethasone; MPT: melphalan, prednisone and thalidomide; NICE: National Institute of Health and Care Excellence; NMA: network meta analysis; OS: overall survival; PAS: patient access scheme; PD: progressive disease; PF: progression free; PFS: progression-free survival; SC: subcutaneous; NDMM: newly diagnosed multiple myeloma; ToT: time on treatment.

Table 75: Results of scenario analyses (PAS price)

Excluding CDF	Versus Ld		
	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Base case	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]
2a	[redacted]	[redacted]	[redacted]
2b	[redacted]	[redacted]	[redacted]
3a	[redacted]	[redacted]	[redacted]
3b	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]

Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; BMP: bortezomib, melphalan and prednisone; ICER: incremental cost-effectiveness ratio; Ld: lenalidomide and dexamethasone; PAS: patient access scheme; QALY: quality adjusted life year.

Table 76: Results of scenario analyses (list price)

Excluding CDF	Versus Ld		
	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Base case	[redacted]	[redacted]	£189,306
1	[redacted]	[redacted]	£208,203

2a	[redacted]	[redacted]	£187,595
2b	[redacted]	[redacted]	£211,152
3a	[redacted]	[redacted]	£193,177
3b	[redacted]	[redacted]	£191,577
4	[redacted]	[redacted]	£194,377
5	[redacted]	[redacted]	£204,550
6	[redacted]	[redacted]	£195,172
7	[redacted]	[redacted]	£193,514

Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone; BMP: bortezomib, melphalan and prednisone; ICER: incremental cost-effectiveness ratio; Ld: lenalidomide and dexamethasone; PAS: patient access scheme; QALY: quality adjusted life year.

B.3.11 *Subgroup analysis*

No cost-effectiveness analyses were conducted in subgroups.

B.3.12 *Benefits not captured in the QALY calculation*

There are a number of benefits of DLd which are not explicitly captured in the QALY calculation, which, if included, would improve the cost-effectiveness of DLd further.

Although pooled utility values were used in the cost-effectiveness model, this should be considered conservative against DLd. DLd was shown to improve QoL for patients as evidenced by the shorter median time to improvement and longer time to worsening in EORTC QLQ-C30 GHS score with DLd compared to Ld, and the statistically significant improvement in the EORTC-QLQ-C30 pain subscale in MAIA. These benefits do not translate to improved utility score on a generic instrument such as EQ-5D and were therefore not captured in the QALY calculation.

Providing benefits which are aligned to NDMM patient preferences are not considered in the QALY framework. The extended period of prolonged remission achieved with DLd will reduce the anxiety associated with relapse observed in both patients and carers. Prolonged remission leads to improvements in emotional functioning and the ability to return to social activities which are highly valued by NDMM patients, the value of which is not intrinsically captured in the QALY framework. Further, value of hope for the future associated with the prospect of achieving a state of no detectable disease (i.e. MRD negativity) and long-term disease control, is also not intrinsically captured.

In addition, the impact of the improved prognosis from DLd is also expected to reduce the burden on carers in patients with NDMM who are ASCT-ineligible, compared with Ld. This benefit is not explicitly captured in the analysis. As patients progress, they experience worse symptoms and require more intense care. As discussed in Section B.1.3.3, the bulk of clinical management of MM is provided in the outpatient setting; therefore the majority of care is informal and provided by carers.[54] Therefore, the detrimental effects of MM are not only experienced by patients, but also their carers.[49] The significantly lower risk of disease progression associated with DLd (see Section B.2.6) means a reduction in the rate of deterioration of the disease. Patients treated with DLd would therefore remain progression-free for longer and require a lower intensity of care for longer, thus reducing the burden on carers. In addition, carers have reported a need for treatments to reduce side effects and complications experienced by patients. In the MAIA trial, fewer patients in the DLd group ([redacted]%) discontinued study treatment due to a TEAE compared to the Ld group ([redacted]%), indicating DLd the side-effect profile of DLd is well-tolerated, reducing the need for carers to manage troublesome side effects. As such, there is potentially benefits from DLd on carer QALYs, which are not explicitly included in the model.

From a population health perspective, early usage of daratumumab in the UK pathway is pivotal for future innovation in multiple myeloma. In particular, it will mean UK myeloma patients in the relapsed setting will be eligible for participation in new clinical trials studying future innovations in anti-CD38 exposed patients. In addition, access to these new therapies once they are approved will be facilitated since UK patients will be anti-CD38 exposed. These benefits are not captured in the QALY calculation. Potential access to these therapies, would occur within the time horizon of this model and would add QALYs to patients in the DLd arm only.

Conversely, the absence of an anti-CD38 treatment in newly diagnosed transplant-ineligible multiple myeloma patients will severely curtail future options for patients both in terms of enrolment into clinical trials and in terms of access to therapies whose marketing authorisations will specify prior anti-CD38 exposure.

B.3.13 *Validation*

An advisory board meeting was held on the 9th March 2022 to to gather clinical expert feedback to inform this submission. In advance of the advisory board, experts received a pre-reading Microsoft PowerPoint slide-set presenting data relevant to the judgements they would be asked to provide during the advisory board. Participants were expected to respond based on their own experience and expertise only.

In order to validate clinical data and model assumptions, the following approaches were used to gather insights from clinical experts via facilitated discussions during the advisory board:

- **Quantitative expert elicitation** via feedback from a pre-reading document provided prior to the advisory board
- **Qualitative expert opinion** sought via discussions during the advisory board to validate clinical data and model assumptions

Microsoft PowerPoint slides were used to present relevant information, to which the experts were asked to respond and provide feedback.

The key discussion points were captured in the resulting advisory board report, which has been provided in the reference pack for this submission.[3] Additional detail on the validation approach is presented in section B.3.13.1.

The advisory board was conducted in line with the principles outlined by Bojke *et al.* (2021), ensuring transparency and recognising individual biases and variations across experts.[184] Internal validity, clinical plausibility versus previous trials in MM and external validity in terms of the clinical plausibility of long-term survival predictions were also carefully considered in the clinical validation of the cost-effectiveness analysis. The outcomes of this clinical advisory board represent clinical opinion and are not representative of RWE. Moreover, the advisory board panel was made up of teaching hospital clinicians, and as such, cannot be considered representative of clinical practice in district general hospitals.

B.3.13.1 Clinical validation of cost-effectiveness analysis

In order to clinically validate the survival extrapolations and treatment pathway for MM, an advisory board was conducted with eight English clinicians and two Scottish clinicians. Initially, a total of 11 clinicians were contacted to participate in the advisory board based on clinicians being a consultant haematologist who sees a large number of patients with MM in England. However, due to lack of availability, one clinician could not attend.

Given that the advisory board took place virtually in non-working hours (5–7:30pm), clinicians were compensated as per fair market value for a total of four hours of their time in attending the advisory board (2.5 hours) and reading pre-reading material (1.5 hours).Prior to the advisory board meeting, clinicians were sent a pre-read slide deck and asked to provide the following:

- Any AEs (beyond those presented) that would have a substantial impact on accrued costs and/or patient quality of life that they would expect to see following treatment with DLd or Ld
- Any AEs that require specific monitoring or follow-up appointments
- Estimates of the proportion of patients receiving each treatment at 1L, disregarding any interim COVID-19 guidelines
- Estimates of the proportion of patients receiving each subsequent treatment at first-, second-, third- and fourth-line following front-line treatment with DLd, Ld and BMP. Clinicians were asked to provide estimates including treatments available on the CDF and excluding treatments available on the CDF
- Estimates of the percentage of patients they would expect to be progression-free and alive at 5-, 10- and 15-years following treatment with BMP and Ld in UK clinical practice
- Estimated rankings of extrapolations for PFS, OS and TTD for BMP and Ld. Clinicians were also asked to list any extrapolations they believed to be clinically implausible

Due to time constraints, not all clinicians were able to provide the information above before the advisory board meeting. Feedback from two English clinicians was received and was presented for discussion in the main advisory board. Clinicians were given an opportunity to provide feedback verbally during the virtual meeting and discuss estimates with the other experts in attendance. Clinicians were also asked to raise their hand if they disagreed with any of the pre-read feedback provided at all. Following on from the advisory board meeting, the remaining clinicians provided their estimates from the pre-read feedback, except for one clinician who did not participate.

Opinions given in the meeting and those gathered after the meeting were recorded and written-up in the advisory board report. Based on this report, key feedback from clinical experts has been presented, where relevant, throughout this submission.

Validation and clinical plausibility of survival outcomes

Long-term PFS and OS extrapolations from the model were assessed using a combination of statistical goodness of fit criteria, visual inspection and aligning to clinician estimates of the percentage of patients they would expect to be progression-free and alive at 5-, 10- and 15-years with currently available treatments (see Section B.3.3.1).

The final survival outcomes predicted by the model were then compared against observed data from the MAIA and ALCYONE trials (see Section B.3.3.1) and careful consideration was then given to both internal validity (i.e. how well the predicted survival fit the observed data from the ALCYONE and MAIA trials), clinical plausibility versus previous trials in MM (including VISTA for BMP and FIRST for Ld),[181, 182] and external validity in terms of the clinical plausibility of long-term survival predictions.

Validity of the model compared to English clinical practice

For consistency with the evidence available for daratumumab and the relevant comparators in this indication, the inputs and assumptions used in the model were based on the trial design of MAIA and ALCYONE and the data that have been reported from these trials. As described in Section B.2.12, the populations of these trials were considered generalisable to the English

population with ASCT-ineligible NDMM.[3] Therefore, the outcomes of MAIA and ALCYONE are anticipated to be generalisable to England.

B.3.13.2 Technical validation of cost-effectiveness analysis

Internal validation

The model programming was checked by a health economist who was not involved in the original development of the model using a validation checklist reported by Büyükkaramikli et al. 2019.[185] This involved a quality control check of the formulae used in the model and stress testing of the model to ensure that it behaves as expected when extreme values are used. The stress test checklist used to validate the model and the results of this test are presented in Table 77.

The results indicate that the model behaved as expected and passed all of the stress tests implemented. All changes to the model were made by a health economist, and each change made after the performance of the stress test checklist was fully quality controlled by a second health economist.

Table 77: Stress test checklist used for cost-effectiveness model validation

#	Test	Expected effect	Observed effect equivalent to expected effect?
1	Set all efficacy data equal across treatments, and set disutility associated with adverse events to 0.	QALYs across all treatments should be equal.	As expected
2	Set mortality rate to 0% at all ages (and any other mortality in the model)	There are no deaths in the model.	As expected
3	Set mortality rate to 100% at all ages	All patients are dead in the first cycle.	As expected
4	Increase mortality rate	Costs are reduced.	As expected
5	Set the health state utilities the same for all states	Life years to QALY ratio should be the same across all treatments	Undiscounted results (after also removing age utility adjustment) are as expected
6	Set the utilities for all health states to 0 and adverse events to 0	All QALYS = 0.	As expected
7	Set the cost and utility consequences for adverse events and discontinuation to 0, then undo these changes and set all adverse event rates to 0	Results in both cases are the same	As expected
8	Set adverse event and discontinuation rates to 0, then undo these changes and set adverse and discontinuation rates to a high level	The first scenario should result in lower costs, higher life years and greater QALYs than the second	As expected
9	Decrease the utilities for all health states simultaneously whilst keeping event-based utility decrements constant	QALYs are reduced	As expected
10	Set equal the effectiveness, utility and safety-related model inputs for all treatment options	No difference between LYs and QALYs for each treatment arm, at any given time	As expected

11	Set the costs of treatments to 0	All treatments costs = 0	As expected
12	Double the costs of treatments	Treatment costs doubled	As expected
13	Increase body weight and/or body surface area (only relevant for weight/BSA dependent dosing)	Treatment costs (for weight/BSA dependent treatments) are increased	As expected
14	Set all administration costs to 0	All administration costs = 0	As expected
15	Double all administration costs	Administration costs doubled	As expected
16	Turn off/on vial sharing	Costs should increase without vial sharing	As expected (see Section B.3.10.2)
17	Set all monitoring/follow-up costs to 0	Monitoring/follow-up costs = 0	As expected
18	Double all monitoring/follow-up costs	Monitoring/follow-up costs doubled	As expected
19	Alter the time horizon	Total costs and QALYS increase/decrease in accordance with longer/shorter horizons	As expected
20	Set discount rates to 0%	Undiscounted results = discounted results	As expected
21	Set discount rates to 100%	Costs and QALYs reduce significantly.	As expected
22	Run the DSA/OWSA and check all input parameters affect results when values are changed	Any input parameters should affect the incremental QALYS, costs or both (unless it has an exactly equal effect on all arms in the model)	As expected, though some inputs do not affect the ICER because not relevant for all ICERs (e.g. costs for treatments that are not part of that comparator)

Abbreviations: BSA: body surface area; DSA: deterministic sensitivity analysis; OWSA: one-way sensitivity analysis; QALY: quality-adjusted life years.
Source: Büyükkaramikli et al (2019).[185]

B.3.14 *Interpretation and conclusions of economic evidence*

In summary, MM is an orphan disease for which there is currently no cure. MM becomes progressively harder to treat at each subsequent relapse, with each additional line of therapy associated with lower rates of response, and increased rates of toxicities and comorbidities. Achieving the longest initial PFS is critical to maximise overall survival and HRQoL.[26, 34, 61-63]

Despite significant advances in the treatment pathway of MM, current treatments for the transplant-ineligible population are limited, many of whom are unfit and/or elderly. There remains a high unmet need for new effective treatments which can increase overall survival, delay progression, drive deeper and more durable levels of response whilst maintaining tolerability and HRQoL.

The economic analysis presented in this submission is robust, makes best use of available data, and captures the treatment effect of DLd versus relevant comparators, particularly the key comparator in this setting, Ld. The cost-effectiveness of DLd as a treatment for adult patients with NDMM who are ineligible for ASCT was assessed via CUA from the perspective of the NHS

in England. The comparators included in the CUA were Ld (the key comparator), BMP, as well as CTd and MPT (as presented in the appendices). Ld is considered the key comparator that DLd would replace in practice, based on input from eight English clinical experts.

Extrapolation of PFS and OS for DLd and Ld was performed using patient-level data from the MAIA trial and for BMP, extrapolation was performed using adjusted patient-level data from the ALCYONE trial (see Section B.2.9.2). In a scenario, BCd was modelled to have equivalent efficacy to BMP, based on two observational studies, a MAIC detailed in Section B.2.9.2 using data from one of the observational studies, a real-world evidence data set of patients diagnosed with MM in England and feedback from UK clinical experts.[122]

Model extrapolations have been assessed based on consideration of statistical/visual fit, external validity against published data for relevant regimens, and clinical expert opinion. Reassuringly, for DLd, all models provide similar long-term estimates after the GPM cap is applied, with the exception of generalised gamma, which appears as a notable outlier, predicting substantially lower survival at 15- and 20-years. The generalised gamma for DLd OS was also a notable outlier in comparison to the splines curve presented in Section B.3.3.2. Janssen has also conducted multiple scenario analyses to explore the effect of selecting alternative curves for long-term extrapolations. In addition, whilst there are inherent challenges in the modelling of subsequent therapies in the NDMM setting (given the degree of CDF therapy use in the MM pathway), again, Janssen has explored this uncertainty and taken the most robust approach possible for the base case utilising the available information.

[redacted]

- [redacted]
- [redacted] B.3.10.2 [redacted]
- [redacted]

Importantly, there are extensive benefits not captured within the cost/QALY framework, which would further improve the cost-effectiveness of DLd. DLd was shown to improve QoL for patients by reducing pain, shown by the statistically significant improvement in the EORTC-QLQ-C30 pain subscale. These benefits do not translate to improved utility score on a generic instrument such as EQ-5D and were therefore not captured in the QALY calculation. The positive effect that treatment with DLd could have on informal carers in terms of reduced anxiety/depression and the ability to return to work is also not captured in the economic analysis. Similarly, the psychological impact of achieving sustained remission, in terms of the sense of hope that patients and carers may experience in place of the fear of relapse, is not intrinsically captured as part of the QALY framework.

Overall, DLd addresses the unmet need for a safe and effective therapy for NDMM patients who are ineligible for ASCT that can drive deep responses and prolong remission whilst maintaining HRQoL. As a highly innovative and effective therapy, the use of DLd earlier on in the MM treatment pathway would represent a landmark advance in the management of patients who are ineligible for ASCT.

Evidence from MAIA shows that patients treated with DLd experienced a significant extension to OS, and an outstanding PFS benefit, which is similar to the OS for the most relevant comparator in this indication, Ld. Additionally, patients with DLd experienced approximately [redacted] higher likelihood of achieving MRD negativity compared to Ld, which has been associated with improved long-term survival outcomes. As validated with clinical experts, these efficacy results are groundbreaking in this patient population.

Finally, given the rapidly evolving MM clinical trial research landscape, access to DLd in the front-line setting is not only urgently needed for newly diagnosed transplant-ineligible MM patients now, but also to ensure the UK remains at the forefront for the future of scientific innovation in the MM treatment landscape.

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Single Technology Appraisal

Daratumumab with lenalidomide and dexamethasone for untreated multiple myeloma when stem cell transplant is unsuitable [ID4014]

Clarification questions

June 2022

File name	Version	Contains confidential information	Date
ID4014_daratumumab_clarification_response_Janssen_FINAL_[ACIC].docx	1	Yes	4th July 2022

Notes for company

Highlighting in the template

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Section A: Clarification on effectiveness data

Risk of Bias Assessments

A1. MAIA study.

a) MAIA was an open-label study. However, it is not clear in the documentation whether outcome assessors were blinded to allocation across all outcomes. For PFS it is reported that the assessment was conducted via a 'computer algorithm', however no detail is given on the role of the site clinicians in outcome assessment (for each outcome). Additionally, it is not clear whether the outcome assessors for the primary outcomes were blinded to treatment allocation.

   Please could the company provide this information?

In MAIA, up until the Primary Analysis for PFS (median follow-up of 28-months, clinical cut off September 2018), the study team were blinded to study treatment arm, and hence the analysis of the primary endpoint by computer algorithm was blinded. Progression was determined by the use of a validated computer algorithm that combines laboratory results (eg, monoclonal [M]-protein level) and applicable imaging, and generates the outcome according to IMWG criteria [1],[2]. This algorithm previously showed very strong concordance with independent reviews in a Phase 2

[1] Durie BG, Harousseau JL, Miguel JS, et al. International uniform response criteria for multiple myeloma. Leukemia. 2006;20:1467–73. Corrigenda/Erratum in: Leukemia. 2007;21:1134-1135.
[2] Rajkumar SV, Harousseau J-L, Durie B, et al. Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1. Blood. 2011; 117:4691-4695.

study[3]. The algorithm remains blinded to the treatment group, as this is not taken into account by the algorithm. A central laboratory, which had no information on treatment allocation and so was blinded to treatment arm, was used for disease evaluations (quantitative immunoglobulin, M-protein, and serum free light chain measurements, and immunofixation determinations in serum and 24-hour urine).

However, there was an additional assessment of response by the investigators and as an open label study, the physicians were aware of the treatment for an individual patient and they performed the investigator assessment of response. However, this PFS assessment based on investigator assessment was presented separately in the CSR, and is not in the label. This is presented as a sensitivity analysis, and the results were consistent with the Primary Analysis assessed by computer algorithm. A similar sensitivity analysis based on investigator assessment for other key secondary endpoints, including Time to Disease Progression, Overall Response Rate, Rate of VGPR or Better, and Rate of CR or Better, was also conducted, which was consistent with the results using computerised algorithm.

b) The company notes that outcome assessments were reviewed by an Independent Data Monitoring Committee, however that does not by itself indicate that there were no concerns relating to the open-label design. Indeed, the risk of bias assessments provided in Appendix D (table 31) do not match those given in the main text of document B. Please can you update the main document to reflect the high rating for risk of bias for blinding?

Table 11 has been updated in the main document B (attached "ID4014_Janssen_Daratumumab_Document B_ FINAL [ACIC]_29thJune"), to reflect the potential risk of bias, as the open-label design may have influenced investigator's assessment of PFS events. As noted above, the results of the investigator assessment of PFS (sensitivity analysis) were consistent with the Primary Analysis assessed by computer algorithm.

Network Meta-Analysis

A2. Priority Question. Please provide the WinBUGS files used for the NMAs (Network Meta-Analyses) including the input data and initial values (only the code is provided in Appendix D).

Please find the input data, initial values, and codes in the attached Zip file "NICE Clarification A2".

A3. Priority Question. NCT01063179 (reported as Palumbo 2010) makes the same comparison as NCT00111319 (reported as VISTA) and so should be

[3] Lonial S, Weiss BM, Usmami SZ, et al. Daratumumab monotherapy in patients with treatment-refractory multiple myeloma (SIRUS): and open-label, randomised , phase 2 trial. Lancet. 2016;387(10027):1551-1560.

included in the NMA. Please provide additional NMA analyses which include NCT01063179.

We understand that the treatment comparison in the Palumbo 2010 trial (BMPT-BT vs. BMP) does not make the same comparison as in the VISTA trial (BMP vs. MP). Since BMPT is not a relevant comparator in the NICE final scope and is not needed to connect other relevant treatments to the network, we believe that the Palumbo 2010 trial should not be included in the NMA.

A4. Whilst we agree that clinical practice in Asian countries differs to NHS clinical practice and absolute outcomes are likely to differ, relative treatment effects may still be generalisable across populations. Please provide a scenario NMA analysis including the two Asian studies Song 2012 (CTd v MPT) and Suzuki 2019 (MPT vs MP)

As survival outcomes were not available for these two trials, a sensitivity analysis including the Song 2012[4] and Suzuki 2019[5] trials was only conducted for ORR and CR or better. The data inputs are presented in Table 1 below:

Table 1: Response data inputs for inclusion of Song, 2012 and Suzuki, 2019

Trial	Arm	N	ORR (%)	≥CR (%)
Song 2012	MPT	74	50 (67.6)	11 (14.9)
	CTD	83	68 (81.9)	17 (20.5)
Suzuki 2019	MPT	52	21 (40.4)	1 (1.9)
	MP	51	10 (19.6)	0 (0)*

Abbreviations: ≥CR = complete response or better; CTd: cyclophosphamide and thalidomide, MPT: melphalan, prednisone and thalidomide; ORR: overall response rate

* A zero-event rate would make the interpretation of the NMA results difficult. The solution proposed by the NICE DSU is applied in the analysis, adding 1 to the denominator and 0.5 to the numerator

The heterogeneity assumption was tested for both endpoints:

- ORR endpoint:

  MP versus MPT (Sacchi 2011, TMSG, IFM 01/01, Suzuki 2019 and IFM 99-06): the I2-test of MPT versus MP showed 13.9%, with a Q of 4.65 and a degree of freedom of 4, p-value = 0.33. There may exist heterogeneity in this network, but it is not statistically significant.

  CTD versus MPT (Song 2012 and Hungria 2016): the I2-test of CTD versus MPT showed 0%, with a Q of 0.75 and a degree of freedom of 1, p-value = 0.39. There is no indication for heterogeneity in this network.

[4] Song M-K, Chung J-S, Shin H-J, et al. Cyclophosphamide-containing regimen (TCD) is superior to melphalan-containing regimen (MPT) in elderly multiple myeloma patients with renal impairment. Annals of hematology 2012;91:889-896.
[5] Suzuki K, Doki N, Meguro K, et al. Report of phase I and II trials of melphalan, prednisolone, and thalidomide triplet combination therapy versus melphalan and prednisolone doublet combination therapy in Japanese patients with newly diagnosed multiple myeloma ineligible for autologous stem cell transplantation. International journal of hematology 2019;110:447-457.

- ≥CR endpoint:
  MP versus MPT (Sacchi 2011, TMSG, IFM 01/01, Suzuki 2019 and IFM 99-06): The I2-test showed 32.4%, with an Q of 5.91 and a degree of freedom of 4, p-value = 0.21. There may exist heterogeneity in this network, but it is not statistically significant.
  CTD versus MPT (Song 2012 and Hungria 2016): the I2-test of CT versus MPT showed 0%, with a Q of 0 and a degree of freedom of 1, p-value = 0.97. There is no indication for heterogeneity in this network.

Table 2 presents a comparison of the model fit across fixed effect (FE) and random effects (RE) models including the two Asian studies for ORR and ≥CR respectively. Given the small differences in the deviance information criterion (DIC) score and total residual deviance between the FE and RE models, plus the minor heterogeneity observed in each network, the FE model was chosen for the sensitivity analysis.

Table 2: Model fit data of sensitivity analysis with Asian studies

ORR

	Dbar	DIC	pD	Totresdev
FE	147	164	17.03	29.55
RE	140.3	161.2	20.94	22.9

≥CR

	Dbar	DIC	pD	Totresdev
FE	122.4	139.3	16.91	23.26
RE	121.4	140.2	18.78	22.27

Abbreviations: ≥CR = complete response or better; Dbar = the posterior mean of the deviance; DIC = deviance information criterion; FE = fixed effect model; ORR = overall response rate; pD = leverage; RE = random effects model; Totresdev = total residual deviance.

Some differences in other key baseline characteristics were noted between the two Asian studies and the other studies in the network. The proportion of patients with IgG-type MM in Song 2012 is lower than in the other trials. Besides, Song 2012 has the highest proportion of patients with International Staging System (ISS) III among the trials included in the analysis, more than a double of that in Suzuki 2019.

Despite those differences in baseline characteristics, the inclusion of the Song 2012 and Suzuki 2019 trials in the NMA did not materially change the results compared to the base-case analysis without these trials (Figure 1, Table 3, Table 4). The NMA results remained almost the same after adding the two trials with Asian populations. DLd retained the highest probability of being ranked first for both the ORR and CR or better endpoints.

Figure 1: Probability of being ranked first – Sensitivity analysis with Asian studies

Table 1: ORR odds ratio matrix – Sensitivity analysis with Asian studies

	Ld continuous	DLd	BMP	CTd	MPT
Ld continuous		[redacted]	[redacted]	[redacted]	[redacted]
DLd	[redacted]		[redacted]	[redacted]	[redacted]
BMP	[redacted]	[redacted]		[redacted]	[redacted]
CTd	[redacted]	[redacted]	[redacted]		[redacted]
MPT	[redacted]	[redacted]	[redacted]	[redacted]	

Abbreviations: BMP: bortezomib, melphalan, prednisone; CTd: cyclophosphamide, thalidomide, dexamethasone; prednisone; DLd: daratumumab, lenalidomide, dexamethasone; Ld continous: lenalidomide, dexamethasone continuous; MPT: melphalan, prednisone, thalidomide; ORR = overall response rate;

Table 2: ≥CR odds ratio matrix– Sensitivity analysis with Asian studies:

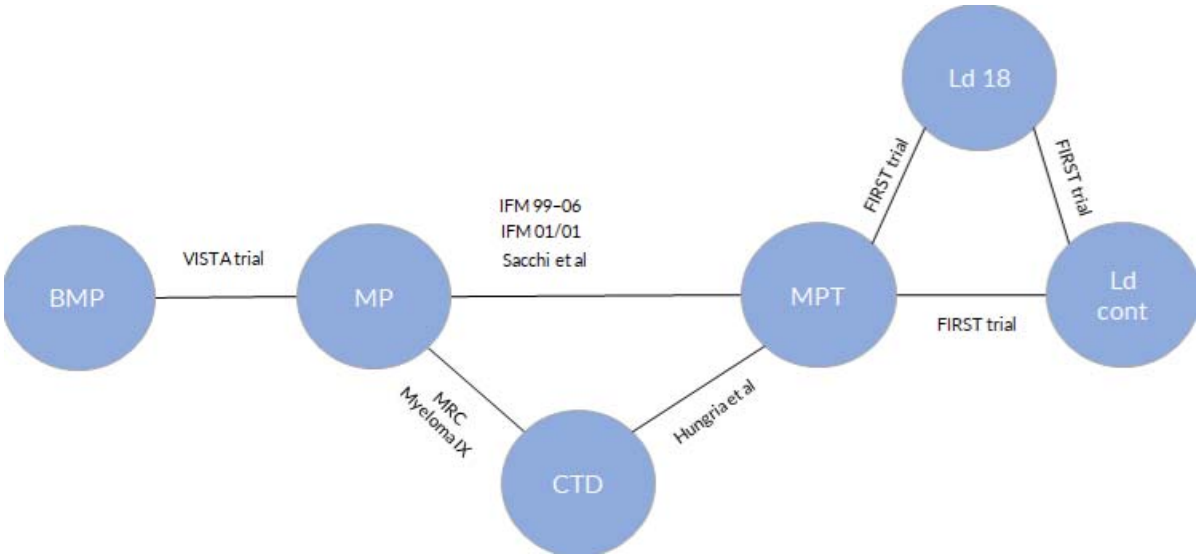
	Ld continuous	DLd	BMP	CTd	MPT
Ld continuous		[redacted]	[redacted]	[redacted]	[redacted]
DLd	[redacted]		[redacted]	[redacted]	[redacted]
BMP	[redacted]	[redacted]		[redacted]	[redacted]
CTd	[redacted]	[redacted]	[redacted]		[redacted]
MPT	[redacted]	[redacted]	[redacted]	[redacted]	

Abbreviations: BMP: bortezomib, melphalan, prednisone; ≥CR = complete response or better; CTd: cyclophosphamide, thalidomide, dexamethasone; prednisone; DLd: daratumumab, lenalidomide, dexamethasone; Ld continous: lenalidomide, dexamethasone continuous; MPT: melphalan, prednisone, thalidomide;

A5. Priority Question. It is stated (p.74 DocB) that proportional hazards does not hold in the FIRST and MAIA trials, and this is a reason to use the IPD adjusted comparison from MAIA and ALCYONE rather than the NMA. However, NMA models can be fitted that do not make the proportional hazards assumption (piecewise constant hazard ratios, fractional polynomials, accelerated failure time models, etc). Looking at the Kaplan-Meier plots from the studies suggests that a piecewise model may be appropriate with two different HRs estimated. This can be achieved by reconstructing Kaplan Meier data for each study and then estimating HRs on each time-period. Could you provide a NMA analysis that does not assume proportional hazards?

The proportional hazard assumption was assessed for all trials in the network of evidence for OS and PFS. Based on the inspection of the Kaplan Meier data, log cumulative hazard plots, Schoenfeld plots and Schoenfeld significance tests, a clear violation of proportional hazard assumption was observed for FIRST PFS (see Appendix A5) and for MAIA OS. An indication for a potential violation was found for all other trials included in the PFS network (i.e., time-varying hazard ratios (HRs) were found when inspecting the Schoenfeld plots; however, the p-values from the Schoenfeld test were non-significant).

Figure 2: Network of evidence OS & PFS



Abbreviations: BMP: bortezomib, melphalan and prednisone; CTd: thalidomide, cyclophosphamide and dexamethasone; Ld cont: lenalidomide with dexamethasone; MP: melphalan and prednisone; MPT: thalidomide, melphalan, prednisone

As a HR NMA assumes proportional hazards, this approach is not appropriate. To overcome this, several other NMA methods were considered:

1. **Parametric NMA: PFS and OS**

A parametric NMA, including MAIA, was explored and a brief overview of this approach and the results can be found below, with further explanation and results presented in Appendix A.5b.

Pseudo individual patient-level data (IPD) for each intervention were obtained for PFS and OS by reconstructing time-to-event data digitized from published Kaplan Meier curves using Engauge Digitizer software[6], and the algorithm published by Guyot et al.[7]

The methodology as described by Ouwens was used for the parametric NMA[8]. The Gompertz parametric NMA for OS was used, as that was the distribution reflecting the base case OS curves best (Gompertz for Ld and exponential for DLd). The exponential for PFS was explored as that was the base case distribution for PFS for both arms in the cost-effectiveness model. A scenario using the results of the parametric NMA is presented in the answer to question B.1 below.

2. **Piecewise Cox NMA PFS**

Given the violation of proportional hazards in MAIA, it is preferred to fit independent curves for Ld and DLd, due to the clear evidence of time varying HRs in the MAIA trial. As such, and given the interest in exploring the NMA to inform the comparison of Ld versus BMP in the network, MAIA has been excluded from the NMA.

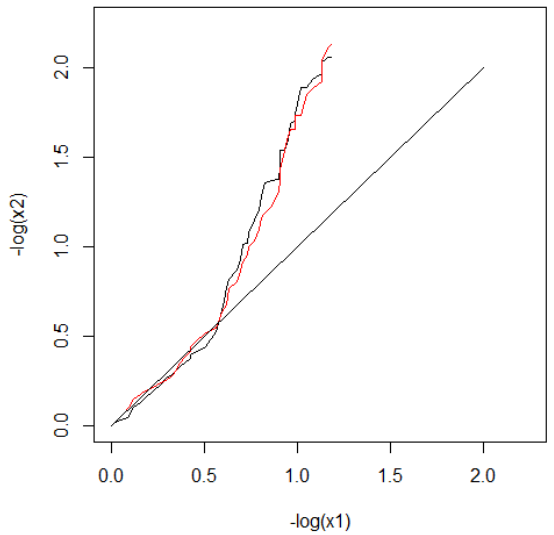
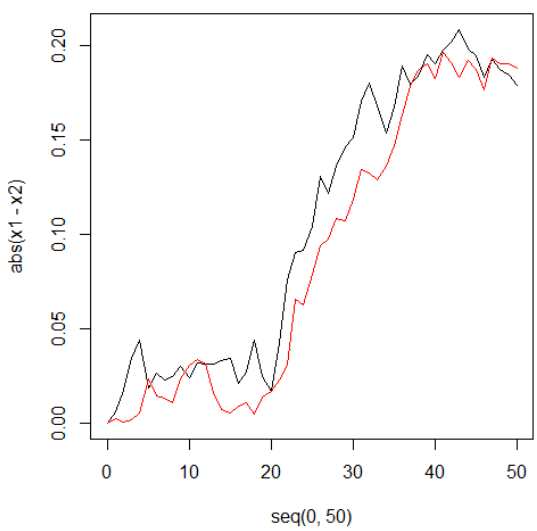
In addition to the parametric NMA, a piecewise Cox NMA was conducted on the network presented in Figure 2 above. This method allows to use a different HR for each time period observed in FIRST trial. As such, a separate NMA was conducted per time period. The timepoint at which the PFS FIRST data was split was determined by the demonstrated abrupt change of the log(HR) over time.

Table 5A present a plot in which the log(survival) of MPT and Ld18 is plotted against the log(survival) of Ld continuous. Table 5B presents a plot in which the vertical axis (abs(x1-x2)) represents absolute difference in survival of MPT and Ld18 versus Ld continuous and the

[6] Mitchell, M., B. Muftakhidinov, and T. Winchen, *Engauge digitizer software*. 2020.
[7] Guyot, P., et al., *Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves.* BMC medical research methodology, 2012. **12**(1): p. 9.
[8] Ouwens, M.J., Z. Philips, and J.P. Jansen, Network meta-analysis of parametric survival curves. Research synthesis methods, 2010. 1(3-4): p. 258-271.

horizontal axis represents time in months. Based on these plots, the timepoint on which the FIRST PFS data was split for the Cox piecewise NMA was set at month 20.

Table 5: Log survival plots FIRST PFS

A	B
	

A Cox piecewise NMA was conducted using the 0-20 months HR and the ≥20 HR for FIRST. A Cox model was fitted to both timeslots and provided two HR and 95% confidence intervals (95%CI). The overall PFS HR (95%CI) for Ld continuous versus MPT, the HR (95%CI) for timeslot 0-20 months, and the HR (95%CI) for timeslot ≥20 months is provided in Table 6. In line with what was presented in the original company submission, only a fixed effects model was considered.

For the remainder of the network of evidence, a constant HR was assumed.

Table 6: Overview HR (95%CI) FIRST PFS (Ld vs MPT)

Time period	HR (95%CI)
Overall	Ld vs MPT: 0.69 (0.59-0.79)
Month 0-20	Ld vs MPT: 0.97 (0.78-1.16)
Month 20+	Ld vs MPT: 0.42 (0.20-0.64)

Abbreviations: Ld: lenalidomide, dexamethasone continuous; MPT: melphalan, prednisone, thalidomide; PFS: progression free survival;

Results: Piecewise Cox PFS NMA

The results of the piecewise Cox PFS NMA are presented in Table 7 and

	Ld continuous	BMP	CTD	MPT
Ld continuous		[redacted]	[redacted]	[redacted]

BMP	[redacted]		[redacted]	[redacted]
CTD	[redacted]	[redacted]		[redacted]
MPT	[redacted]	[redacted]	[redacted]	

Abbreviations: BMP: bortezomib, melphalan, prednisone; CTd: cyclophosphamide, thalidomide, dexamethasone; prednisone; Ld continuous: lenalidomide, dexamethasone continuous; MPT: melphalan, prednisone, thalidomide PFS: progression free survival;

Table 8.

Table 7: Piecewise Cox PFS NMA results (timeslot 0-20 months)

	Ld continuous	BMP	CTD	MPT
Ld continuous		[redacted]	[redacted]	[redacted]
BMP	[redacted]		[redacted]	[redacted]
CTD	[redacted]	[redacted]		[redacted]
MPT	[redacted]	[redacted]	[redacted]	

Abbreviations: BMP: bortezomib, melphalan, prednisone; CTd: cyclophosphamide, thalidomide, dexamethasone; prednisone; Ld continuous: lenalidomide, dexamethasone continuous; MPT: melphalan, prednisone, thalidomide PFS: progression free survival;

Table 8: Piecewise Cox PFS NMA results (timeslot 20 months and beyond)

	Ld conti	BMP	CTD	MPT
Ld continous		[redacted]	[redacted]	[redacted]
BMP	[redacted]		[redacted]	[redacted]
CTD	[redacted]	[redacted]		[redacted]
MPT	[redacted]	[redacted]	[redacted]	

Abbreviations: BMP: bortezomib, melphalan, prednisone; CTd: cyclophosphamide, thalidomide, dexamethasone; prednisone; Ld continuous: lenalidomide, dexamethasone continuous; MPT: melphalan, prednisone, thalidomide PFS: progression free survival;

A scenario using the HR NMA for OS (BMP vs Ld) and Piecewise Cox NMA for PFS (BMP vs Ld) is presented in the answer to question B.1.

A.5 Summary

For this submission, the MAIA clinical trial provides direct evidence for DLd against the main comparator (Ld) in current NHS clinical practice, and hence should be considered the main source of evidence.

In the company submission, to supplement the indirect comparison through the NMA approach versus BMP, we have provided an IPD adjusted comparison using BMP data from ALCYONE. This is because Janssen have access to the individual patient data of the BMP arm from the ALCYONE study. The use of adjusted IPD analysis mitigates some of the known limitations of the NMA approach, in particular an NMA involving an extended network, with several trials/steps between treatment arms of interest. The adjusted IPD analysis remains company preferred approach to compare versus BMP. Given the extensive set of clinically relevant prognostic factors combined with the similarity of the observed MAIA and ALCYONE populations, the IPD based analyses is preferred, as it additionally may allow less chance of bias/potential for higher accuracy as well as greater precision.

The results of the cost-effectiveness analysis using the NMA models above continue to support the use of the IPD adjusted approach to the comparison against BMP in the base case (see B.1).

A6. Priority Question. Please provide reconstructed Kaplan-Meier data that you have extracted for studies in the NMA.

The published and reconstructed KM curves for Sacchi 2011 (OS and PFS) and TMSG (OS only) are presented in Appendix A6.

A7. Assessment of consistency between MP, MPT and CTD. Can you provide more details regarding inconsistency checks for the NMA (e.g. dev-dev plots showing the contribution to residual deviance for inconsistency vs consistency models)?

First, the Bucher method[9] was applied to assess the inconsistency for the MP-CTD-MPT loop of evidence. Second, both the consistency and the inconsistency model were applied to assess the level of inconsistency.[10]

The available direct evidence for OS of the MPT-MP-CTD loop in the network is presented in Table 9. Pooled estimate of Log HR (SE) was based on a weighted average by patient numbers.

Table 9: OS HR of the studies in MP-CTD-MPT loop

Comparison	Trial	HR (95% CI)	Log HR (SE)
MPT vs. MP	Sacchi et al.	[redacted]	[redacted]

[9] Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomised controlled trials. J Clin Epidemiol. 1997;50(6):683-691.
[10] Dias S, Welton NJ, Sutton AJ, Caldwell DM, Lu G, Ades AE. NICE DSU Technical Support Document 4: Inconsistency in Networks of Evidence Based on Randomised Controlled Trials [Internet]. London: National Institute for Health and Care Excellence (NICE); 2014 Apr. PMID: 27466656.

	IFM 01/01	[redacted]	
	IFM 99–06	[redacted]	
	TMSG study	[redacted]	
CTD vs. MP	MRC Myeloma IX	[redacted]	[redacted]
CTD vs. MPT	Hungria et al.	[redacted]	[redacted]

Abbreviations CTd: cyclophosphamide, thalidomide, dexamethasone; prednisone; MP: melphalan, prednisone; MPT: melphalan, prednisone, thalidomide; OS: overall survival; SE: standard error

The indirect effect of CTD vs. MPT was obtained from the paired comparisons of MPT vs. MP and of CTD vs. MP. The difference between log($indirect_{CTDMPT}$) and log($direct_{CTDMPT}$) is -0.25 (SE 0.41). The p-value is larger than 0.05 which indicates that there is no evidence of inconsistency in this loop, see Table 10.

Table 10: Inconsistency assessment for OS

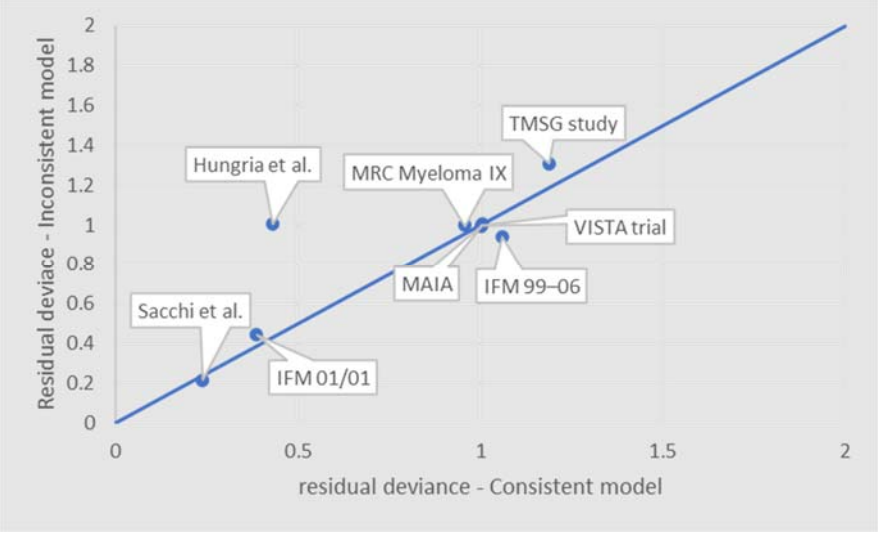
CTD vs. MPT	HR (SE)	Log HR (SE)
Indirect	[redacted]*	[redacted]
Direct	[redacted]	[redacted]
Difference	-	- 0.25 (0.41)
Z score = - 0.598, p-value = 0.56		

Abbreviations CTd: cyclophosphamide, thalidomide, dexamethasone; prednisone; MPT: melphalan, prednisone, thalidomide; OS: overall survival; SE: standard error

*calculated from Log HR (SE)

A plot of the individual data points' posterior mean deviance contribution in each of the two models is presented in Figure 3. The multi-arm trial FIRST is disregarded from the plot as this requires a different parametrization. These plots are based on 100,000 iterations on three chains after a burn-in period of 10,000 for the both the consistency and the inconsistency model.

Figure 3: Plot of the individual data points' posterior mean deviance contributions



Same method was applied to PFS, ORR, and CR/CR+ endpoints, the results are presented in Table 11.

Table 11 Inconsistency assessment results – PFS, ORR, and ≥ CR

CTD vs. MPT	Z score	p-value
PFS	-1.44	0.15
ORR	-2.27	0.02
≥ CR	0.11	0.92

Abbreviations ≥CR = complete response or better ; CTd: cyclophosphamide, thalidomide, dexamethasone; prednisone; MPT: melphalan, prednisone, thalidomide; PFS: progression free survival; OS: overall survival

The posterior mean deviance contributions of both the consistent and inconsistent models are presented in Figure 4, Figure 5, and Figure 6. A few data points show a much lower value of the posterior mean deviance in the inconsistency model, suggesting that a consistency model does not fit these points well. There is an indication for inconsistency in the ORR endpoint which might be caused by the difference in Hungria trial. A sensitivity analysis was conducted in the submission, removing Hungria from the NMA, and the results were comparable to the base case analysis.

Figure 4: Plot of the individual data points' posterior mean deviance contributions PFS

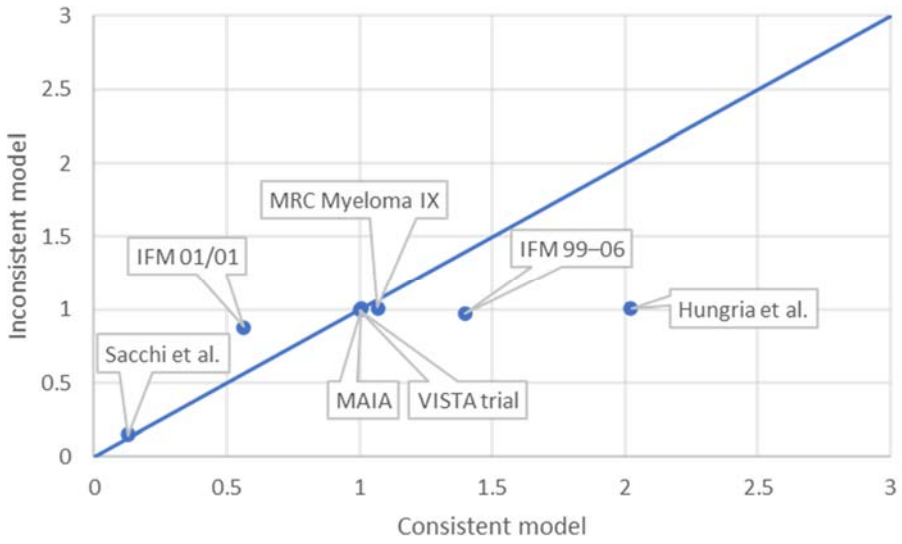


Figure 5:2 Plot of the individual data points' posterior mean deviance contributions ORR

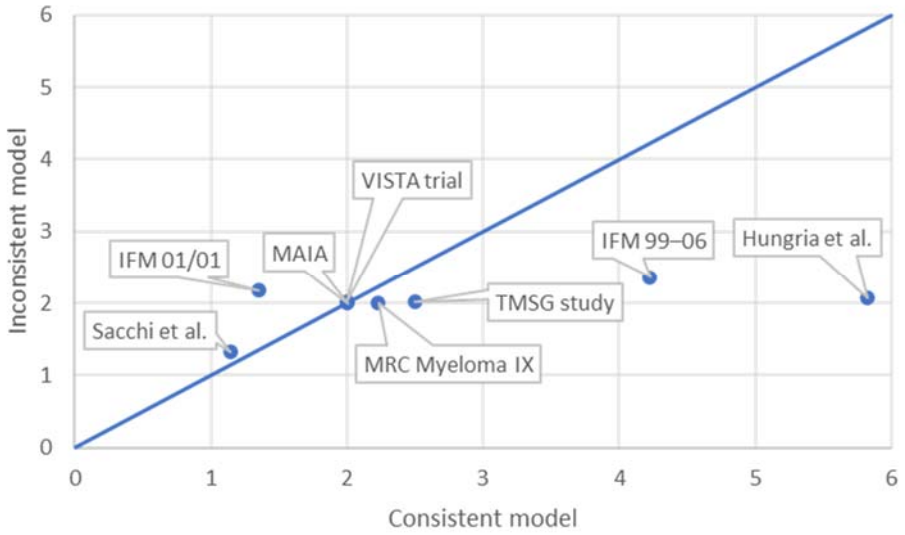
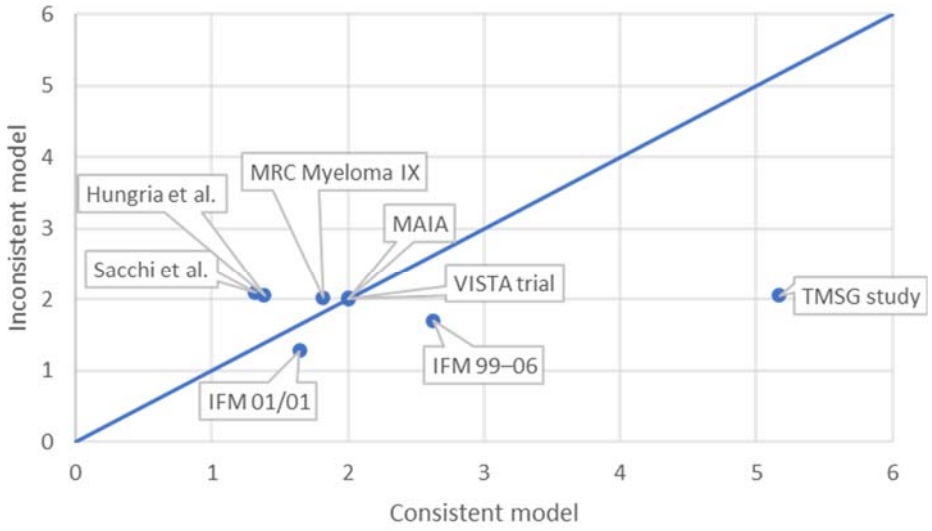


Figure 6: Plot of the individual data points' posterior mean deviance contributions ≥CR



A8. The information reported in Appendix D 1.10 (table 22) is insufficient to evaluate the model fit for the NMA. Following NICE DSU Technical Support Document 2, please could you also provide the residual deviance as an absolute measure of model fit, the number of effective parameters (pD), and the between-study standard deviation estimate (between-study heterogeneity from the RE models) and 95%

credible intervals. It would also be instructive to provide leverage plots or deviance contributions for the fixed and random effects analyses. See also clarification A2.

The model fit data for the base case analyses are presented in Table 12 below. There was a consistent trend of small differences in DIC scores and total residual deviance between the FE and RE models across all endpoints. Therefore, the FE model was chosen for all endpoints given the ease of interpretability and consistency in the analysis approach.

Table 12: Model fit data in base case analysis – OS, PFS, ORR, and ≥ CR

	FE model				RE model			
	Mean	**SD**	**Median**	**CrI**	**Mean**	**SD**	**Median**	**CrI**
OS								
resdev[1]	1.01	1.42	0.46	(0.00,5.06)	1.00	1.43	0.46	(0.00,5.07)
resdev[2]	0.96	1.35	0.43	(0.00,4.80)	0.96	1.37	0.43	(0.00,4.88)
resdev[3]	0.43	0.42	0.31	(0.00,1.52)	0.54	0.75	0.29	(0.00,2.57)
resdev[4]	1.00	1.41	0.45	(0.00,5.04)	1.00	1.41	0.46	(0.00,5.00)
resdev[5]	0.24	0.24	0.17	(0.00,0.88)	0.42	0.64	0.20	(0.00,2.18)
resdev[6]	0.39	0.55	0.18	(0.00,1.95)	0.64	0.95	0.28	(0.00,3.35)
resdev[7]	1.06	1.14	0.70	(0.00,4.10)	0.93	1.20	0.48	(0.00,4.27)
resdev[8]	1.19	0.80	1.04	(0.08,3.12)	0.98	1.05	0.67	(0.00,3.71)
resdev[9]	1.99	1.99	1.39	(0.05,7.32)	2.01	2.01	1.39	(0.05,7.39)
between-trial SD	NA	NA	NA	NA	0.18	0.21	0.13	(0.01,0.69)
Dbar	-12.09				-11.88			
DIC	-6.09				-4.40			
pD	6.00				7.48			
Totresdev	8.27				8.48			
PFS								
resdev[1]	1.00	1.42	0.45	(0.00,5.04)	0.99	1.41	0.45	(0.00,5.03)
resdev[2]	1.07	1.49	0.49	(0.00,5.31)	1.02	1.44	0.46	(0.00,5.12)
resdev[3]	1.00	1.41	0.45	(0.00,5.04)	1.00	1.41	0.46	(0.00,5.02)
resdev[4]	0.13	0.18	0.06	(0.00,0.65)	0.51	0.86	0.18	(0.00,2.96)
resdev[5]	0.56	0.75	0.28	(0.00,2.68)	0.75	1.09	0.34	(0.00,3.87)
resdev[6]	1.40	1.43	0.97	(0.00,5.18)	1.05	1.37	0.53	(0.00,4.89)
resdev[7]	2.02	1.01	1.89	(0.43,4.34)	1.29	1.31	0.92	(0.00,4.58)
resdev[8]	1.99	1.99	1.38	(0.05,7.3)	1.99	2.00	1.38	(0.05,7.39)
	NA	NA	NA	NA	0.29	0.39	0.19	(0.01,1.3)

	FE model				RE model			
	Mean	**SD**	**Median**	**CrI**	**Mean**	**SD**	**Median**	**CrI**
between-trial SD								
Dbar	-11.15				-11.72			
DIC	-5.15				-3.98			
pD	6.00				7.74			
Totresdev	9.17				8.60			
ORR								
resdev[1]	3.00	2.45	2.37	(0.21,9.36)	3.00	2.45	2.36	(0.21,9.32)
resdev[2]	2.00	1.99	1.39	(0.05,7.33)	2.00	2.00	1.38	(0.05,7.40)
resdev[3]	1.15	1.44	0.63	(0.02,5.24)	1.67	1.75	1.11	(0.04,6.43)
resdev[4]	1.35	1.50	0.87	(0.03,5.49)	1.78	1.83	1.22	(0.04,6.71)
resdev[5]	4.23	2.57	3.80	(0.60,10.4)	2.26	2.17	1.62	(0.06,7.99)
resdev[6]	2.01	2.02	1.39	(0.05,7.43)	1.99	1.99	1.38	(0.05,7.36)
resdev[7]	2.24	2.22	1.56	(0.06,8.19)	2.05	2.05	1.42	(0.05,7.58)
resdev[8]	5.82	1.99	5.54	(2.80,10.6)	2.79	2.37	2.19	(0.08,8.63)
resdev[9]	2.50	1.70	2.13	(0.39,6.87)	1.94	1.86	1.40	(0.05,6.88)
between-trial SD	NA	NA	NA	NA	0.67	0.53	0.54	(0.05,2.06)
Dbar	124.4				119.6			
DIC	139.4				137.8			
pD	15.04				18.19			
Totresdev	24.31				19.48			
≥ CR								
resdev[1]	3.01	2.45	2.37	(0.21,9.36)	3.00	2.45	2.37	(0.21,9.32)
resdev[2]	2.02	2.01	1.40	(0.05,7.4)	2.01	2.01	1.39	(0.05,7.44)
resdev[3]	1.32	1.49	0.83	(0.03,5.45)	1.58	1.67	1.04	(0.04,6.13)
resdev[4]	1.82	1.82	1.26	(0.05,6.73)	1.89	1.91	1.30	(0.05,7.03)
resdev[5]	1.64	1.51	1.20	(0.13,5.78)	1.77	1.70	1.28	(0.06,6.34)

	FE model				RE model			
	Mean	**SD**	**Median**	**CrI**	**Mean**	**SD**	**Median**	**CrI**
resdev[6]	1.38	1.52	0.89	(0.03,5.56)	1.66	1.73	1.12	(0.04,6.35)
resdev[7]	2.63	1.99	2.18	(0.18,7.65)	2.21	2.01	1.65	(0.07,7.43)
resdev[8]	2.01	2.01	1.40	(0.05,7.42)	2.00	1.99	1.39	(0.05,7.37)
resdev[9]	5.16	2.21	4.86	(1.8,10.41)	3.12	2.40	2.66	(0.11,8.89)
between-trial SD	NA	NA	NA	NA	0.72	0.64	0.56	(0.02,2.42)
Dbar	107				105.2			
DIC	122				122.2			
pD	14.98				17			
Totresdev	20.99				19.24			

Abbreviations: ≥CR = complete response or better; CrI = credible interval; Dbar = the posterior mean of the deviance; DIC = deviance information criterion; FE = fixed effect model; ORR = overall response rate; OS = overall survival; pD = leverage; PFS = progression-free survival; RE = random effects model; resdev[i] = deviance contribution of trial i; SD = standard deviation; Totresdev = total residual deviance.

A9. In Appendix D (p93) the company notes that baseline characteristics of patients were generally similar for trials included in the NMA except for the proportion of patients with IgG-type MM (within-trial differences in the Sacchi 201194 and TMSG101 trials), but that IgG-type was not considered a key prognostic factor based on clinical expert feedback. However, in Document B, p81, MM type (IgG/not IgG) is listed as a covariate for the MAIC based on clinical expert opinion. Furthermore, the subgroup analyses from MAIA (Document B, Figs 30 and 32) suggest MM-type may be a treatment effect modifier. Can you please comment on the differences between trials in the NMA by MM-type and the impact this may have on the NMA results? Is it possible to adjust for MM type?

The proportion of patients with IgG-type MM ranged from 58-64% across trials for all but the following:

- Hungria 2016: there were considerably fewer patients in this trial presented with IgG-type MM (52-55%) compared to patients in the other trials included in the network
- Sacchi 2011: there were imbalances in the proportions across the treatment arms (63% vs. 73%)
- TMSG: there were imbalances in the proportions across the treatment arms (71% vs. 83%)
- Information on the proportion of patients with IgG-type MM was not available for IFM 01/01 and IFM 99/06.

Evidence on the potential effect modification of IgG-type MM was inconclusive given the absence of subgroup analyses in the comparator trials and a considerable overlap in the confidence intervals in the subgroup analysis of the MAIA trial. An additional sensitivity analysis excluding the Sacchi 2011 and TMSG trials has been conducted to test the impact of IgG-type MM on the efficacy results. The results for OS, PFS and ORR remain extremely similar to the base-case results. However, for the endpoint CR or better, the removal of Sacchi 2011 and TMSG has generally resulted in DLd performing better against BMP, CTd and MPT.

An exclusion of the Hungria 2016 trial was not considered given that it is the only trial in the network comparing MPT with CTd. The exclusion of this trial would therefore only have a minor impact on the other comparisons in the network. In the sensitivity analysis presented in question C2, where Sacchi, TMSG and Hungria were excluded, there were no material differences for OS

and PFS, but we did see an impact on ORR and CR or better. The results and heterogeneity information are presented in C2.

Of note, the above discussion was based on the reported baseline characteristics. Information on other characteristics considered likely to be prognostic factors and/or effect modifiers, e.g., high-risk cytogenetic markers and kidney and liver function, was extremely limited. The impact of these characteristics on the NMA results could not be assessed. In contrast, all possible baseline and time-varying variables can be included in IPD analysis, reducing the potential bias in the analysis and potentially providing more robust as well as more precise results.

Figure 7: Probability of being ranked first – Sensitivity analysis without Sacchi and TMSG trial

Table 13: HR and OR of DLd against comparator regimens - Sensitivity analysis without Sacchi and TMSG trial

	OS HR	PFS HR	ORR OR	≥CR OR
Ld continuous	[redacted]	[redacted]	[redacted]	[redacted]
BMP	[redacted]	[redacted]	[redacted]	[redacted]
CTd	[redacted]	[redacted]	[redacted]	[redacted]
MPT	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ≥CR = complete response or better; BMP: bortezomib, melphalan and prednisone; CTd: thalidomide, cyclophosphamide and dexamethasone; Ld continuous: lenalidomide with dexamethasone; MPT: thalidomide, melphalan, prednisone; OS: overall survival; PFS: progression-free survival;

A10. Priority Question. In the network meta-analysis how did the studies differ in subsequent therapies (2nd or 3rd line) received? Was treatment switching adjusted for in any of the included studies?

There were differences in the published definitions as well as proportion of patients receiving second- or later-line therapy (including the type of therapy) across the trials. However, adjusted outcome data were not available. This accounts for a limitation in the NMA that cannot be adjusted for.

Table 3 Subsequent therapies in each trial

Trial	Treatment Arm	% of Patients in 2L	% of Patients in 3L+
FIRST[11]	Ld	56% (n=299/535)	34% (n=180/535)
	MPT	70% (n=381/547)	42% (n=231/547)
Hungria 2016	NR	NR	NR
IFM 01/01[12]*	MP	83% (n=70/84)	NR
	MPT	85% (n=61/72)	NR
IFM 99/06[13]**	MP	65% (n=126/193)	NR
	MPT	44% (n=55/124)	NR
MAIA[14]	Ld	[redacted]	[redacted]
	DLd	[redacted]	[redacted]
MRC Myeloma IX	NR	NR	NR
Sacchi 2011	NR	NR	NR
TMSG[15]	MP	14% (n=8/57) of patients crossed over from MP to MPT	NR
	MPT		NR
VISTA[16]	MP	73% (n=246/338)	NR
	BMP	63% (n=215/344)	NR

*IFM 01/01: percentages are based out of the numbers of patients who received treatment after disease progression
**IFM 99/06: percentages are based out of patients who are withdrawn from treatment (for death, progression, treatment toxicity, patient refusal, or other reason) and having received a second line-treatment
Abbreviations: BMP: bortezomib, melphalan and prednisone; CTd: thalidomide, cyclophosphamide and dexamethasone; DLd: daratumumab, lenalidomide with dexamethasone; Ld continuous: lenalidomide with dexamethasone; MPT: thalidomide, melphalan, prednisone; MP: melphalan, prednisone

[11] Facon, T., Dimopoulos, M., Dispenzieri, A., Catalano, J., Belch, A., & Cavo, M. et al. (2018). Final analysis of survival outcomes in the phase 3 FIRST trial of up-front treatment for multiple myeloma. Blood, 131(3), 301-310. doi: 10.1182/blood-2017-07-795047
[12] Hulin, C., Facon, T., Rodon, P., Pegourie, B., Benboubker, L., & Doyen, C. et al. (2009). Efficacy of Melphalan and Prednisone Plus Thalidomide in Patients Older Than 75 Years With Newly Diagnosed Multiple Myeloma: IFM 01/01 Trial. Journal Of Clinical Oncology, 27(22), 3664-3670. doi: 10.1200/jco.2008.21.0948
[13] Facon, T., Mary, J., Hulin, C., Benboubker, L., Attal, M., & Pegourie, B. et al. (2007). Melphalan and prednisone plus thalidomide versus melphalan and prednisone alone or reduced-intensity autologous stem cell transplantation in elderly patients with multiple myeloma (IFM 99–06): a randomised trial. The Lancet, 370(9594), 1209-1218. doi: 10.1016/s0140-6736(07)61537-2
[14] MAIA 64.5m. Data on file
[15] Beksac, M., Haznedar, R., Firatli-Tuglular, T., Ozdogu, H., Aydogdu, I., & Konuk, N. et al. (2010). Addition of thalidomide to oral melphalan/prednisone in patients with multiple myeloma not eligible for transplantation: results of a randomized trial from the Turkish Myeloma Study Group. European Journal Of Haematology, 86(1), 16-22. doi: 10.1111/j.1600-0609.2010.01524.x
[16] San Miguel, J., Schlag, R., Khuageva, N., Dimopoulos, M., Shpilberg, O., & Kropff, M. et al. (2013). Persistent Overall Survival Benefit and No Increased Risk of Second Malignancies With Bortezomib-Melphalan-Prednisone Versus Melphalan-Prednisone in Patients With Previously Untreated Multiple Myeloma. Journal Of Clinical Oncology, 31(4), 448-455. doi: 10.1200/jco.2012.41.6180

Population adjustment for BMP from ALCYONE

A11. Priority Question. In Document B (p.80) the Company states "*in order to maintain the original sample size for the weighted populations and to properly reflect the associated uncertainty, the ATT weights were multiplied by the ratio of the original sample size versus the sum of the ATT weights making the sum of these recalculated weights equal to the original sample size*." However, the IPW approach should reduce precision, giving a lower effective sample size reflecting the degree of covariate overlap. Please could the company either correct this by providing estimates without maintaining the original sample size or explain why their approach does not over-inflate the precision?

The correction factor to bring back the sample size of the weighted population to the original one is important in the situation where the number of patients significantly differs between both cohorts, and especially so when the external cohort is substantially smaller compared to the treatment cohort of interest. If this correction is not applied, the uncertainty expressed by the confidence interval is expected to be underestimated, as it would rather reflect the comparison between both cohorts, as if they would have similar sample sizes.
In cases where patient numbers are similar, or the external cohort is larger than the treatment cohort of interest, the impact of this correction is expected to be limited. In the case of the DLd vs BMP comparison, the sample sizes are very similar, which makes that the impact of this correction minimal, as expressed in Table 12 below. However, for the sake of consistency across studies, we still implemented this same approach.

Table 12: Estimates of ATT with and without rescaling to original sample size

Comparison	OS HR (95% CI)	p-value	PFS HR (95% CI)	p-value	TTD HR (95% CI)	p-value
Naïve	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weighting						
ATT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ATE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ATO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Propensity score matching	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Covariate adjustment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weighting - ATT without rescaling to original sample size						
ATT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ATE: average treatment effect; ATT: average treatment effect on the treated population; CI: confidence interval; HR: hazard ratio; OS: overall survival; PFS: progression-free survival; TTD: time to treatment discontinuation.

A12. Covariate adjustment was performed using a Cox regression (Document B, p.81), which assumes proportional hazards across covariate values. Can the company provide evidence that this assumption is reasonable?

The proportional hazards assumption can be checked using 1) statistical tests and 2) graphical diagnostics based on the scaled Schoenfeld residuals.

1) Statistical tests

The proportional hazards assumption for each covariate included in a Cox regression model fit is tested using the function *cox.zph()* [in the ***survival*** package]. For each covariate, the corresponding set of scaled Schoenfeld residuals is correlated with time to test for independence between residuals and time. Additionally, it performs a global test for the model as a whole. The proportional hazard assumption is supported by a non-significant relationship between residuals and time, and refuted by a significant relationship.

From the output below,

- OS : we can assume proportional hazards for all of the covariates (not statistically significant test results at 0.05 significance level). For this model, the global test is also statistically not significant indicating that proportional hazards can be assumed.
- PFS : PH assumption is met for most covariates except for treatment arm and ISS stage.

Table 13: OS: Test for PH assumption

	OS		PFS	
	Chi-sq	P value	Chi-sq	P value
Treatment arm	1.87	0.17	11.93	0.0006
ISS Stage	3.69	0.16	7.17	0.028
Cytogenetic Risk	0.19	0.91	2.22	0.330
Age	0.06	0.81	0.01	0.920
ECOG	4.96	0.08	3.86	0.145
Gender	1.39	0.24	3.21	0.073
MM type	1.3	0.25	0.02	0.897
Hepatic Function	0.39	0.82	2.71	0.258
Creatinine Clearance	3.69	0.05	0.21	0.649
Bone Marrow Plasma Cells	4.64	0.10	6.12	0.047

Race	0.4	0.53		0.12	0.728
Region	1.64	0.20		2.76	0.097
GLOBAL	25.64	0.08		39.95	0.001

2) Graphical diagnostics

In principle, the Schoenfeld residuals are independent of time. A plot that shows a non-random pattern against time is evidence of violation of the PH assumption.

Figure 8: OS: Graphical Diagnostics

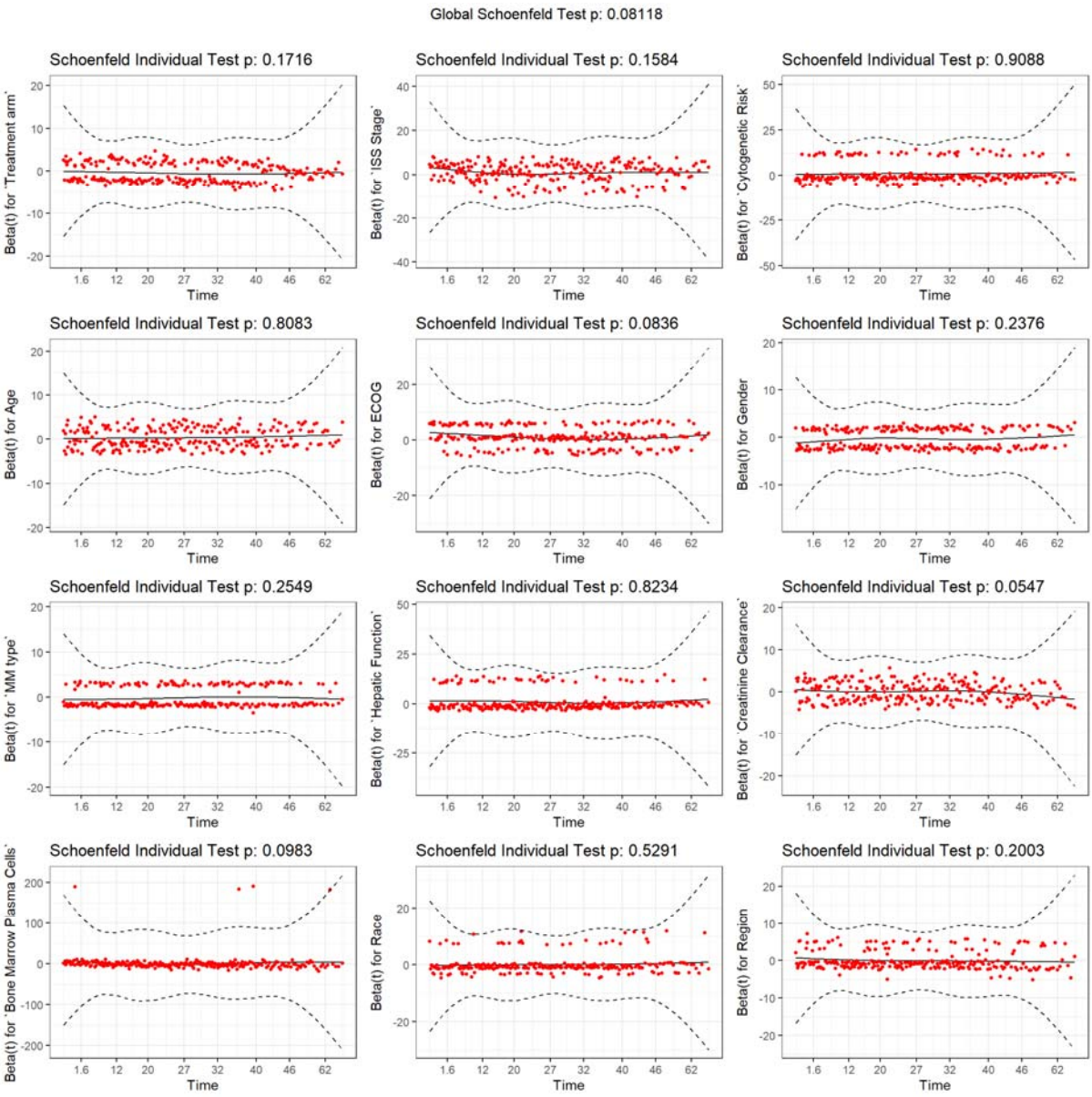
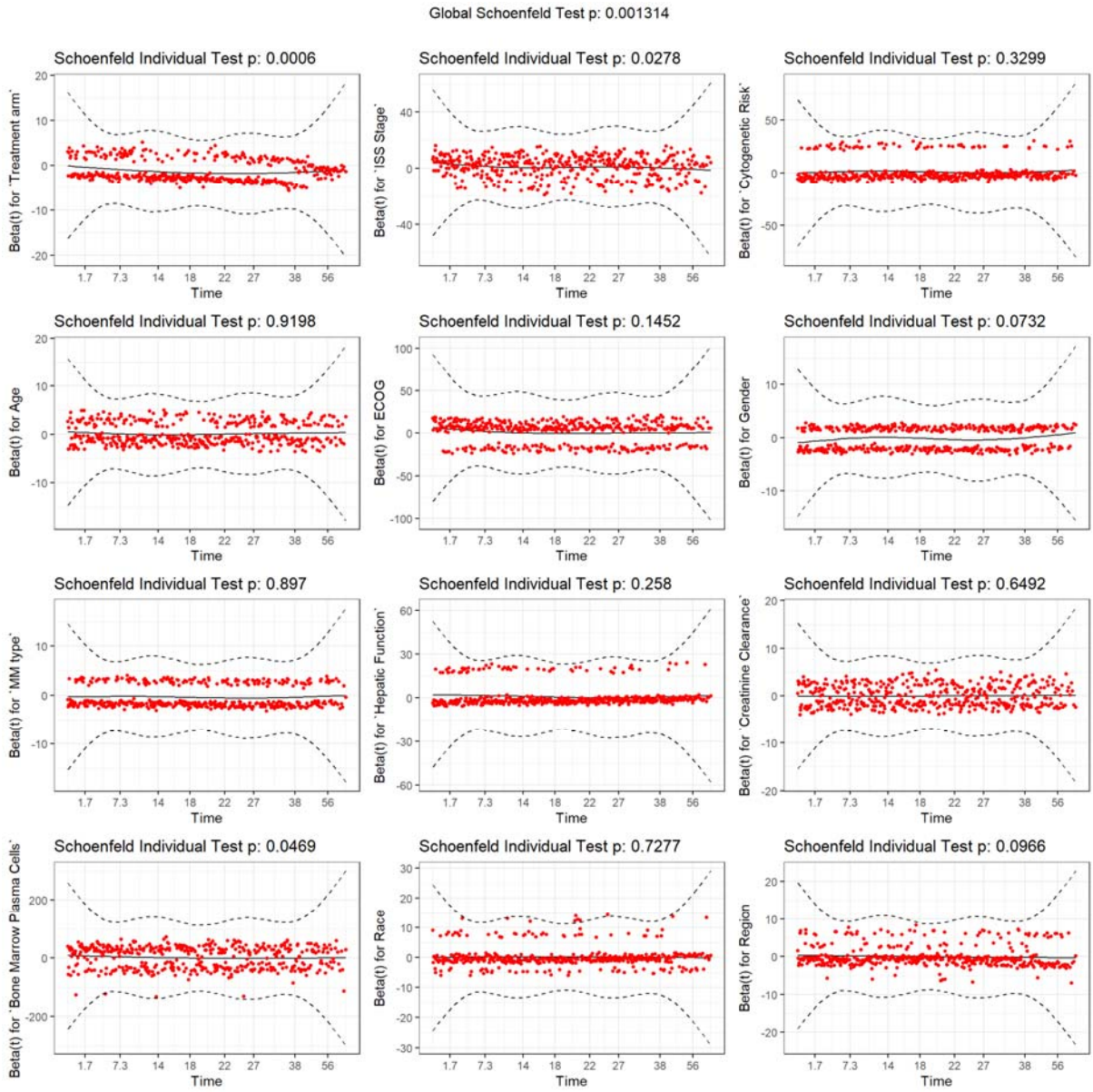


Figure 11: PFS: Graphical Diagnostics



Equivalence between BMP and BCd

A13. To establish the equivalence of BMP and BCd the company use a population adjusted analysis for BCd from Jimenez-Zepeda and BMP from ALCYONE. However, it is not necessary to make this comparison across data sources because there is data on BMP directly from the Jimenez-Zepeda study. Could the company provide results from an individual patient data adjusted comparison of BCd and BMP from the Jimenez-Zepeda data (which come from the same study design/source)?

As noted in the clarification call with the EAG, Janssen do not have access to the IPD from the Jimenez-Zepeda study. Therefore, unfortunately an individual patient data adjusted comparison of BCd and BMP from the same source (Jimenez-Zepeda) data is not available.

A14. Priority Question. The population adjusted estimates of BMP vs BCd from Jimenez-Zepeda and ALCYONE indicate that BCd could be more effective (PFS HR [redacted] and OS HR [redacted]. This suggests it is appropriate to model BCd separately. A population adjusted analysis could be conducted comparing BCd with Ld using the Jimenez-Zepeda and MAIA studies (matching the BCd data from Jimenez-Zepeda to the MAIA population). Could the company provide this analysis?

After receiving further clarification from the EAG, see answer for B.2 below to see an analysis of modelling BCd separately, using the HRs estimated for BMP vs BCd from the MAIC.

Section B: Clarification on cost-effectiveness data

Treatment efficacy

B1. Priority Question. Can you provide results from the economic model using the NMA results for all comparisons i.e. applying HRs for each treatment compared with Ld to the fitted curves for Ld.

Table 44 and Table 15 present results from the economic model with DLd PAS and list price respectively, employing the NMA results for all comparisons, as requested. Within each table,

- Scenario 1 shows model results generated using the parametric NMA described in question A5 for DLd and all comparators except BCd (BCd OS and PFS are assumed equivalent to BMP and TTD is assumed equivalent to PFS);
- Scenario 2 shows results using independent curve extrapolations from MAIA for DLd and Ld, while BMP is modelled via HRs vs Ld (standard NMA for OS, piecewise Cox NMA for PFS), as described in question A5.

Table 44: Scenario analyses applying HRs for each treatment compared with Ld to the fitted curves for Ld, PAS price

	DLd Vs BMP			DLd Vs Ld		
	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Updated base case*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 1: parametric NMA (see response A5)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 2: standard NMA for BMP OS, piecewise NMA for BMP PFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*The base case has been updated to incorporate dosage reductions, in response to question B12 in this document.

Notes: Scenario 2 comparison of BMP vs DLd uses OS HR of BMP vs Ld HR=[redacted] and Piecewise Cox PFS (HRs as reported in A.5)
Abbreviations: BMP: bortezomib, melphalan and prednisone; DLd: daratumumab, lenalidomide and dexamethasone; HR: hazard ratio; ICER: incremental cost-effectiveness ratio; Ld: lenalidomide and dexamethasone; NMA: network meta-analysis; OS: overall survival; PAS: patient access scheme; PFS: progression-free survival; QALY: quality adjusted life year.

Table 15: Scenario analyses applying HRs for each treatment compared with Ld to the fitted curves for Ld, list price

	DLd Vs BMP			DLd Vs Ld		
	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Updated base case*	[redacted]	[redacted]	£104,438	[redacted]	[redacted]	£173,843
Scenario 1: parametric NMA	[redacted]	[redacted]	£105,406	[redacted]	[redacted]	£164,992
Scenario 2: standard NMA for BMP OS, piecewise NMA for BMP PFS	[redacted]	[redacted]	£114,838	[redacted]	[redacted]	£173,843

*The base case has been updated to incorporate dosage reductions, in response to question B12 in this document.

Notes: Scenario 2 comparison of BMP vs DLd uses OS HR of BMP vs Ld HR=[redacted]) and Piecewise Cox PFS (HRs as reported in A.5)
Abbreviations: BMP: bortezomib, melphalan and prednisone; DLd: daratumumab, lenalidomide and dexamethasone; HR: hazard ratio; ICER: incremental cost-effectiveness ratio; Ld: lenalidomide and dexamethasone; NMA: network meta-analysis; OS: overall survival; PFS: progression-free survival; QALY: quality adjusted life year.

Overall, the use of the NMA methods result in similar ICERs to the use of the IPD adjusted analysis. All three methods for the indirect comparison versus BMP result in similar ICERs vs DLd. Given the support shown by the NMA methods and the advantages of the use of the IPD ALCYONE analysis (see answers to A.5 and C.6), Janssen believe the adjusted ALCYONE IPD analysis should be used as the base case for the indirect comparison versus BMP.

B2. Priority Question. Can you provide a scenario analysis where efficacy of BCd differs to that for BMP using the estimated HRs from the matched adjusted analysis from ALCYONE and Jimenez-Zepeda studies (BMP v BCd PFS HR [redacted] and OS HR [redacted].

As noted in the company submission, the comparison of BMP is provided to fulfil the comparator of bortezomib in combination with an alkylating agent and corticosteroid, as per the final scope. There are no RCT data for BCd in this population.

Results for the requested scenario are included in Table, where BCd efficacy has been derived by applying HRs from the MAIC to the BMP curve (extrapolated based on the ALCYONE trial). Please note that it has not been assessed whether the proportional hazard assumption holds, and therefore the appropriateness of applying the HRs from the MAIC is not clear.

The assumption of equivalency between BMP and BCd ('base case' in Table 16) is supported by the absence of a significant difference in the HR when adjusting for all prognostic factors for both PFS and OS, which indicates that there is no strong evidence that BCd differs to BMP (please see Section B.2.9.3 of the original Company Submission; Document B and Table 56 of the original Company Submission; Appendices).

In addition, visual inspection of the BCd and BMP curves in Jimenez-Zepeda showed similar efficacy between the two treatments. Despite the inherent limitations of a naïve comparison, results from the RWE study further support the assumption of equivalence.

Furthermore, it should be noted that both BMP and BCd are dominated by Ld in the fully incremental analysis, reducing the relevance of the ICERs generated when comparing DLd vs BMP and BCd. Furthermore, eight English clinicians specialising in MM agreed that Ld was the most common treatment for patients at front-line with NDMM who are ineligible for ASCT.[17]

Table 16: Scenario analysis with BCd efficacy derived via HRs vs BMP

DLd versus BCd	PAS Price			List Price		
	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Updated base case*: BCd equivalent to BMP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£105,733
Scenario 3: BCd derived via HR vs BMP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£113,793

*The base case has been updated to incorporate dosage reductions, in response to question B12 in this document.

Scenario 3 HRs: BCd vs BMP HRs: [redacted]

Abbreviations: BCd: bortezomib, cyclophosphamide and dexamethasone**;** BMP: bortezomib, melphalan and prednisone; DLd: daratumumab, lenalidomide and dexamethasone; HR: hazard ratio; ICER: incremental cost-effectiveness ratio; Ld: lenalidomide and dexamethasone; PAS: patient access scheme; QALY: quality adjusted life year.

B3. Priority Question. Can you provide a scenario analysis where efficacy of BCd differs to that for BMP using an adjusted analysis matching the BCd data from Jimenez-Zepeda to the MAIA population? (See clarification question A14).

Feedback from the EAG confirmed it was not necessary to provide answers to both questions B2 and B3; in light of this, please see answer to B2.

B4. Can you confirm whether treatment switching was accounted for in any of the efficacy estimates that went into the economic model? It is stated that the unadjusted

[17] Janssen. [Data on File]. Clinical Advisory Board Meeting Minutes. 2022.

estimates are used for DLd and Ld, but we were unclear whether the hazard ratios from the NMA and the BMP curve estimates accounted for treatment switching.

Treatment switching was not accounted for any of the efficacy estimates that went into the economic model, as adjusted outcome data to account for the impact of subsequent treatments were not available.

Subsequent (2nd and 3rd line) treatments

B5. Priority. Can you give the numbers of patients receiving each 2nd line treatment in MAIA by treatment arm. This information is given in Appendix R (Table 161) for treatments not available in England but is not given for treatments that are available in England. If you have information on 3rd line treatments, please can you provide this too? Similarly, if you have these figures for ALCYONE and Jimenez-Zepeda could you provide these?

The numbers of patients receiving each 2nd line and 3rd line treatment per treatment arm for MAIA and ALCYONE can be found below in Appendix B.5.

Janssen do not have access to the IPD for Jimenez-Zepeda, and so the numbers of patients receiving subsequent treatment by treatment arm is not available for Jimenez-Zepeda.

Utilities

B6. Do the utilities for PF and PD health states in Document B, Table 47 represent on-treatment or off-treatment periods? Over what follow-up time?

Utility values for the PF and PD health state were derived using EQ-5D-5L from the MAIA trial over 64.5 months follow-up, and represent the overall mean utility pooled across treatment arms (data were pooled as there was [redacted]).[18] These utility values are based on progression status (i.e. pre-progression and post-progression), in line with the modelled health states, and do not represent on- or off-treatment periods, but would implicitly capture patients who are both on- or off- treatment.

Costs

B7. Priority Question. Document B Table 31 provides median time on treatment. Please provide mean time on treatment if possible

The mean time on treatment is [redacted] months for Ld and [redacted] months for DLd, as per below.

[18] Janssen. [Data on File]. MMY3008. MAIA Clinical Study Report (October 2021 data cut). 2022.

	DLd (n=364)	Ld (n=365)
Median duration of treatment (months)	[redacted]	[redacted]
Mean duration of treatment (months)	[redacted]	[redacted]

Source: MAIA HEMAR Report, TSIEXP02

B8. Priority Question. Document B, p136. Total costs for Bd and PBd should be divided by mean PFS and not median PFS. Dividing by median will give larger costs. Can you correct this?

Please refer to the answer provided for B9 which concerns the same inputs and calculations.

B9. Priority Question. Document B, section B3.5.1.2: Subsequent therapies. When multiplying costs by time on treatment the mean time should be used if possible (rather than the median which will underestimate costs). Can you correct this?

To calculate the cost of subsequent treatments, a total cost is calculated by multiplying average time on treatment by the cost per cycle. For treatments with a fixed-duration (e.g. Bd and PBd) or a dosing regimen that changes over time (e.g. PBd), the cost per cycle is first calculated by multiplying the cost per each time-specific cycle by the time spent on that dosing regimen, and divided by the time on treatment. In an ideal world, the mean time to progression (TTP) or PFS would be used to inform all instances where time on treatment is required. However, in the sources that were identified and used in these calculations, all but one only reported median values.[19] Therefore, for consistency across all treatments, the median TTP/PFS was used in all instances, and not the mean.

Janssen appreciate that that the median and mean will differ, where typically, the median is less than the mean. For example, the mean PFS for DLd estimated in the cost-effectiveness model is 86.8 months, with a median PFS estimate of 61.6 months. In absence of mean data reported in the literature, Janssen has conducted a scenario which illustrates a hypothetical effect of changing all median TTP/PFS estimates to means, by changing all median values by a factor of 1.4. (using the relationship observed between mean and median PFS for DLd). Results for the main comparison versus Ld are presented in Table 17, illustrating the minimal impact this has on results.

Table 17: Scenario analysis for proxy mean TTP/PFS values for subsequent treatments

Excluding CDF, versus Ld	PAS Price			List Price		
	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Updated base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£173,843
Scenario 5: Increase all median PFS/TTP of subsequent treatments by x1.4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£173,252

[19] Richardson PG, Hungria VT, Yoon SS, et al. Panobinostat plus bortezomib and dexamethasone in previously treated multiple myeloma: outcomes by prior treatment. Blood 2016;127:713-21.

*The base case has been updated to incorporate dosage reductions, in response to question B12 in this document.

Abbreviations: CDF: Cancer Drug's Fund; ICER: incremental cost-effectiveness ratio; Ld: lenalidomide and dexamethasone; PAS: patient access scheme; PFS: progression-free survival; QALY: quality adjusted life year; TTP: time to progression.

B10. Priority Question. ToT (time on treatment) is assumed to equal PFS for BCd, CTD, and MPT (Appendix M.1.1), but for Ld, BMP, DLd it is taken from TTD curves which are different to PFS. Could you provide of estimates the HR for TTD vs PFS for each treatment arm from MAIA and ALCYONE? Based on this could you apply a HR to BCd, CTD, and MPT PFS curves to estimate TTD for those treatments and provide this as a scenario analysis?

Table18 shows a summary of the PFS vs TTD (and TTD vs PFS) HRs for DLd, BMP and Ld from MAIA and ALCYONE. In Scenario 6, the BMP HR has been applied to the PFS of CTd, MPT and BCd to derive the respective TTD curves. Results of this scenario (except BCd) are presented in Table19 and Table20, for PAS and list price respectively. The PFS vs TTD HR for BMP has been chosen given the closer alignment in dosing regimen (fixed duration) to the treatments of interest (BCd, CTd and MPT).

Table 21 shows results for Scenario 6 and Scenario 7 for BCd. In Scenario 7, BCd TTD is assumed equivalent to BMP TTD, in response to an additional request received from the EAG.

Table 18: PFS vs TTD HRs of DLd, Ld and BMP

Treatment	PFS vs TTD HR (95% CIs)	TTD vs PFS HR (95% CIs)
DLd	[redacted]	[redacted]
Ld	[redacted]	[redacted]
BMP	[redacted]	[redacted]

Abbreviations: BMP: bortezomib, melphalan and prednisone; CIs: confidence intervals; DLd: daratumumab, lenalidomide and dexamethasone; HR: hazard ratio:, Ld: lenalidomide and dexamethasone. PFS: progression free survival; TTD: time to treatment discontinuation.

Table 19: Deriving TTD via HR for CTd and MPT, PAS price

	DLd vs CTd			DLd vs MPT		
	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Updated base case*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 6: apply BMP TTD vs PFS HR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*The base case has been updated to incorporate dosage reductions, in response to question B12 in this document.

Abbreviations: BMP: bortezomib, melphalan and prednisone; CIs: confidence intervals; CTd: cyclophosphamide, thalidomide and dexamethasone; DLd: daratumumab, lenalidomide and dexamethasone; HR: hazard ratio:, ICER: incremental cost-effectiveness ratio; Ld: lenalidomide and dexamethasone; MPT: melphalan, prednisone and thalidomide; PAS: patient access scheme, PFS: progression free survival; TTD: time to treatment discontinuation.

Table 20: Deriving TTD via HR for CTd and MPT, list price

	DLd Vs CTd			DLd Vs MPT		
	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Updated base case*	[redacted]	[redacted]	£96,885	[redacted]	[redacted]	£114,502
Scenario 6: BMP TTD vs PFS HR	[redacted]	[redacted]	£97,123	[redacted]	[redacted]	£115,381

*The base case has been updated to incorporate dosage reductions, in response to question B12 in this document.

Abbreviations: BMP: bortezomib, melphalan and prednisone; CIs: confidence intervals; CTd: cyclophosphamide, thalidomide and dexamethasone; DLd: daratumumab, lenalidomide and dexamethasone; HR: hazard ratio:, ICER: incremental cost-effectiveness ratio; Ld: lenalidomide and dexamethasone; MPT: melphalan, prednisone and thalidomide; PFS: progression free survival; TTD: time to treatment discontinuation.

Table 21: Scenario analysis for BCd TTD

DLd vs BCd	PAS Price			List Price		
	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Updated base case*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£105,733
Scenario 6: BMP TTD vs PFS HR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£105,781
Scenario 7: assumed equivalent to BMP TTD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£105,875

*The base case has been updated to incorporate dosage reductions, in response to question B12 in this document.

Abbreviations: BMP: bortezomib, melphalan and prednisone; CIs: confidence intervals; DLd: daratumumab, lenalidomide and dexamethasone; HR: hazard ratio: ICER: incremental cost-effectiveness ratio; Ld: lenalidomide and dexamethasone; PAS: patient access scheme; PFS: progression free survival; TTD: time to treatment discontinuation.

B11. How is Time to Treatment Discontinuation (TTD) measured when patients dropped components of therapies in MAIA. Eg if a patient on DLd dropped dexamethasone would they be counted as having discontinued or not? What if they dropped lenalidomide and dexamethasone?

TTD is measured when patients discontinued all components of the regimen meaning patients who discontinued lenalidomide and dexamethasone as part of DLd were not included in the TTD measurement. This is illustrated by the mean TTD for the full regimen ([redacted] months), which is longer compared to the treatment duration for subjects that selectively discontinued lenalidomide ([redacted] months) or selectively discontinued lenalidomide and dexamethasone ([redacted] months).[20]

[20] Janssen. [Data on File]. MAIA MMY3008 Clinical Study Report. Appendices. 2022.

B12. Doc B, Section 3.5.1.1 Drug Acquisition Costs. Costs are adjusted to account for discontinuation of components of DLd in line with MAIA. There were also dose reductions of dexamethasone and lenalidomide ... were these accounted for in the costs? Also, did patients on Ld discontinue or reduce dose of dexamethasone (or lenalidomide)? If so, please give the proportions? Is this accounted for in the costs of Ld? If not, please include this.

Dose reductions of daratumumab, dexamethasone and lenalidomide for both treatment arms were recorded in the MAIA trial (see Table 31 of the original Company Submission; Document B); dose reductions of bortezomib, melphalan and prednisone were also recorded in the ALCYONE trial.[21] These reductions were not included in the original company base case. However, the option to incorporate relative dose intensity (RDI) when calculating the costs has now been included in the model, and now represents the updated company base case, as it is deemed including RDIs is a more accurate representation of what would happen in clinical practice. Results are presented in Table22 and Table23, for PAS and list price respectively. Data on the partial discontinuation of components for Ld (i.e. discontinuation of lenalidomide or dexamethasone) were not available, and therefore, have not been included in the calculations.

Please note that daratumumab dosage reductions are not included, as in the MAIA trial daratumumab was administered via the IV formulation (and therefore reductions refer to the IV administration), while in the model base case, all patients are assumed to receive treatment subcutaneously.

Table 22: Scenario analysis for lenalidomide and dexamethasone dosage reduction, PAS price

	DLd vs BMP			DLd vs Ld		
	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Previous base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Updated base case: RDIs implemented	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Notes: mean RDIs for DLd: lenalidomide [redacted] and dexamethasone [redacted]. Mean RDIs for Ld: lenalidomide [redacted] and dexamethasone [redacted]; mean RDIs for BMP: bortezomib [redacted] Melphalan [redacted] Prednisone [redacted].

Abbreviations: BMP: bortezomib, melphalan and prednisone; DLd: daratumumab, lenalidomide and dexamethasone; ICER: incremental cost-effectiveness ratio; Ld: lenalidomide and dexamethasone; PAS: patient access scheme; QALY: quality adjusted life year; RDI: relative dose intensity.

Table 23: Scenario analysis for lenalidomide and dexamethasone dosage reduction, list price

	DLd Vs BMP			DLd Vs Ld		
	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)

[21] Janssen [Data on file]. MMY007. ALCYONE CSR report. 2017.

Previous base case	[redacted]	[redacted]	£123,244	[redacted]	[redacted]	£189,319
Updated base case: RDIs implemented	[redacted]	[redacted]	£104,438	[redacted]	[redacted]	£173,843

Notes: RDIs used are reported in Table above.

Abbreviations: BMP: bortezomib, melphalan and prednisone; DLd: daratumumab, lenalidomide and dexamethasone; ICER: incremental cost-effectiveness ratio; Ld: lenalidomide and dexamethasone; QALY: quality adjusted life year; RDI: relative dose intensity.

B13. Document B, Section 3.5.2: End of life costs in the model use the same input as previous NICE TAs (TA573, TA457). Please could you confirm the original source for this input?

As per TA763, the cost applied in the model (£8,534.05) for end-of-life was derived from the cost used in NICE TA573, inflated to 2020–2021 using the NHSCII Pay & Price Index to 2020–21.[7] The original value was reported by Georghiou and Bardsley 2014.[22]

Model

B14. Has a half-cycle correction been applied in the model? If not, please correct this.

A half-cycle correction has been applied in the model (see, for example, the worksheet "DLd_Trace", columns AA:AD). This was included in the original submitted model supporting the Company Submission and therefore, no updates are required.

Section C: Textual clarification and additional points

C1. The answers given for the risk of bias assessment for the MAIA trial in Document B, table 11 (using the York CRD tool) differ to those given for the same domains in table 31 of the Appendix (using RoB). Table 11 essentially rates all domains as low, whereas table 31 says 'unclear' for allocation concealment, 'high' for blinding of participants and researchers and 'unclear' for blinding of outcome assessment. Please can you update the main document to reflect the high rating for the blinding domain risk of bias.

As per A1b, Table 11 has been updated in the main document B (attached "ID4014_Janssen_Daratumumab_Document B_ FINAL [ACIC]_29thJune"), to reflect the potential risk of bias, as the open label design may have influenced investigator's assessment of

[22] Georghiou T BM. Exploring the cost of care at the end of life. Available from: http://www.nuffieldtrust.org.uk/publications/exploring-cost-care-end-life [Last accessed: June 2022]. 2015.

PFS events. As noted, this was a sensitivity analysis, which was consistent with the primary analysis of PFS.

C2. In section D.1.11. of the Appendices assessing RoB, it states; "*The Hungria 2016 (trial51) was also associated with a high risk of bias due to selective outcome reporting. The impact of the high risk of bias on the overall NMA results were tested by excluding this trial from the network in a sensitivity analysis.*". However, in Table 31 there are other studies (e.g. VISTA, IFM 99/06) that are assessed as being 'high' or 'unclear' risk across multiple domains. Why were these not considered for inclusion in the sensitivity analysis?

The studies included in the network showed a high risk of bias in the blinding domain due to their open-label or single-blinded study design. A lack of blinding is unlikely to impact OS results but may impact response-based outcomes. Given that all studies were either of an open-label or single-blinded design, a sensitivity analysis to test the impact of this on response-based outcomes is not feasible. Some of the trials were associated with an unclear risk of bias in the randomisation and/or allocation concealment domains because they did not explicitly provide information on these in the publicly available materials. We assume that randomisation was conducted appropriately if the baseline characteristics are roughly equally balanced across the treatment arms. Given the imbalances in baseline characteristics between treatment arms, in Sacchi 2011 and TMSG, issues during the randomisation process may have been present.

In a newly conducted sensitivity analysis excluding the Sacchi 2011, TMSG and Hungria 2016 trials, OS and PFS results for DLd vs. comparator regimens remained largely unchanged. In the case of ORR and CR or better, the exclusion of these three trials resulted in an increased relative benefit of DLd compared to the other regimens. In the case of the comparison against BMP and CTD, sensitivity analysis results were also associated with a considerably higher uncertainty compared to the base-case results (See figure 12 and table 24 below).

The sensitivity analysis was also associated with a considerable change in heterogeneity regarding the response outcomes, albeit not statistically significant. For example, the comparison of MP vs MPT resulted in an I2 of 40.6% in the ORR network, with a Q of 1.68 and a degree of freedom of 1, p-value = 0.19; an I2 of 0% in the ≥CR network, with a Q of 0.01 and a degree of freedom of 1, p-value = 0.94. These are in contrast to an I2 of 0% and 47% for the ORR and ≥CR endpoints, respectively, in the base-case. No heterogeneity was observed for the OS and PFS endpoints, similar to the base-case analysis.

Figure 12 Probability of being ranked first – Sensitivity analysis without Sacchi, Hungria, and TMSG trial

Table 24: HR and OR for DLd versus the comparator regimens – Sensitivity analysis without Sacchi, Hungria, and TMSG trial:

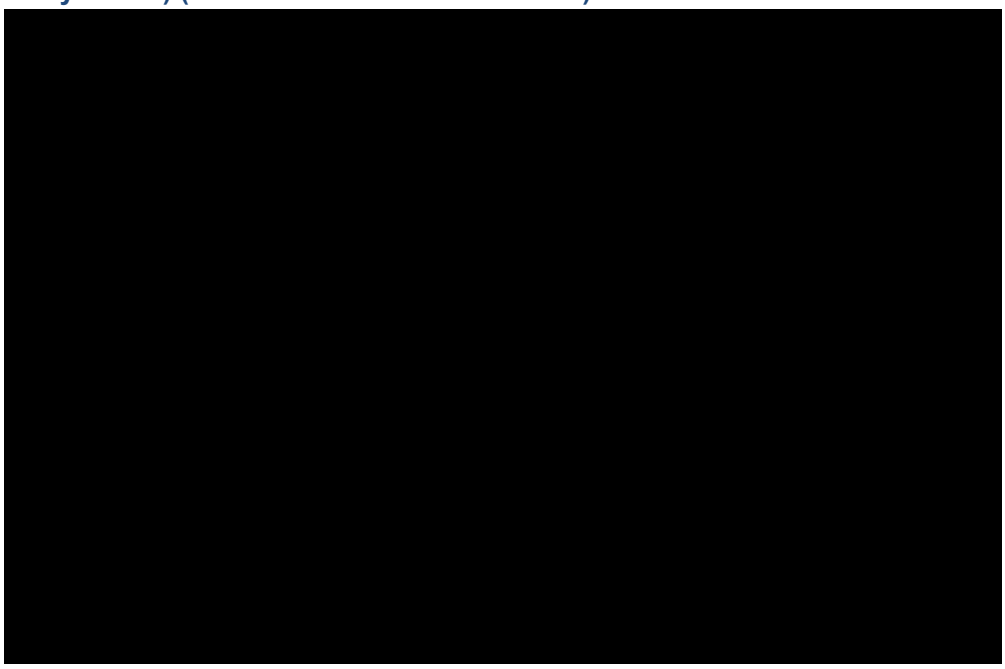
DLd versus	OS HR	PFS HR	ORR OR	≥CR OR
Ld conti	[redacted]	[redacted]	[redacted]	[redacted]
BMP	[redacted]	[redacted]	[redacted]	[redacted]
CTd	[redacted]	[redacted]	[redacted]	[redacted]
MPT	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ≥CR = complete response or better; BMP: bortezomib, melphalan and prednisone; CTd: thalidomide, cyclophosphamide and dexamethasone; Ld continuous: lenalidomide with dexamethasone; MPT: thalidomide, melphalan, prednisone; ORR: overall response rate; OS: overall survival; PFS: progression-free survival

C3. Document B, Figs 24 & 28. Please can you add error bars onto these plots?

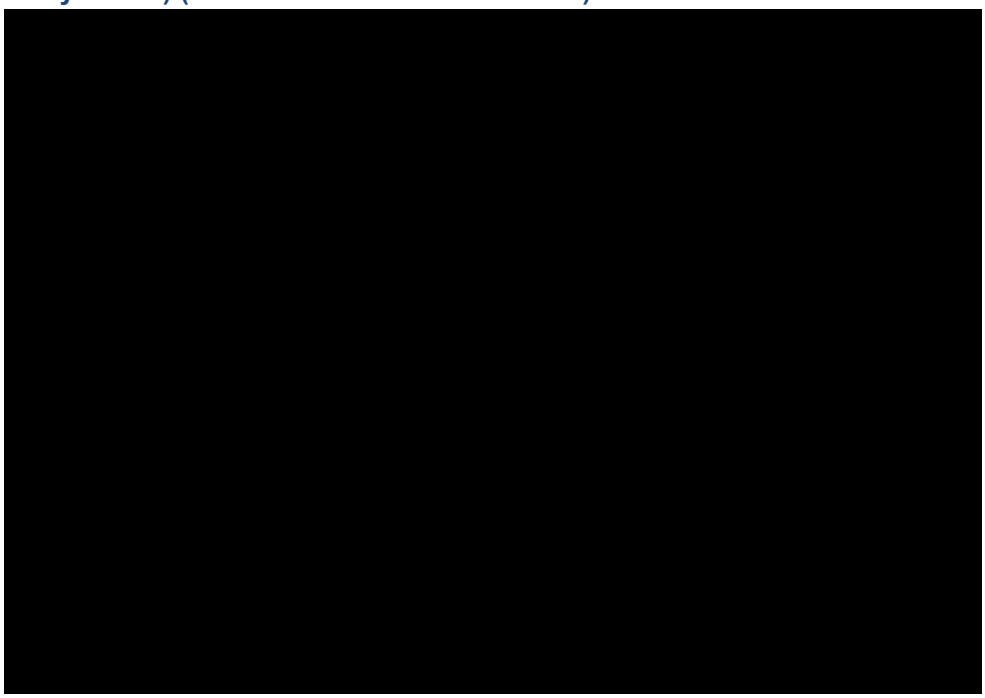
Updated figures including error bars for the 95% confidence interval are provided in Figure 13 to Figure 16 below. For clarity, these figures have been provided below with DLd and Ld plotted separately. The data presented for EORTC QLQ-C30 GHS and EQ-5D-5L is provided in Tables TPROQLQ05 and TPROEQ05A of the MAIA HEMAR Report 2022, which was included in the reference pack for the company submission.

Figure 13: Change from baseline in EORTC QLQ-C30 GHS score in the MAIA trial (ITT analysis set) (data cut-off 21st October 2021)



Abbreviations: DLd: daratumumab, lenalidomide and dexamethasone; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer quality of life questionnaire; GHS: global health status; ITT: intention-to-treat; Ld: lenalidomide and dexamethasone.
Source: MAIA HEMAR report. [Data on file]. TPROQLQ05. 2022.

Figure 14: Change from baseline in EORTC QLQ-C30 GHS score in the MAIA trial (ITT analysis set) (data cut-off 21st October 2021)



Abbreviations: EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer quality of life questionnaire; GHS: global health status; ITT: intention-to-treat; Ld: lenalidomide and dexamethasone.
Source: MAIA HEMAR report. [Data on file]. TPROQLQ05. 2022.

Figure 15: LS-means of change from baseline in EQ-5D-5L in the MAIA trial (ITT analysis set) (data cut-off 21st October 2021)

Abbreviations: DLd: daratumumab, lenalidomide and dexamethasone; EQ-5D-5L: EuroQol 5-dimension 5-level questionnaire; ITT: intention-to-treat; Ld: lenalidomide and dexamethasone; LS: least squares.
Source: MAIA CSR appendices. [Data on file]. TPROEQ05A. 2022.[5]

Figure 16: LS-means of change from baseline in EQ-5D-5L in the MAIA trial (ITT analysis set) (data cut-off 21st October 2021)

Abbreviations: DLd: daratumumab, lenalidomide and dexamethasone; EQ-5D-5L: EuroQol 5-dimension 5-level questionnaire; ITT: intention-to-treat; Ld: lenalidomide and dexamethasone; LS: least squares.
Source: MAIA CSR appendices. [Data on file]. TPROEQ05A. 2022.[5]

C4. Document B, Figs 30 & 32. Please can you provide subgroup analyses for UK vs non-UK centres?

The subgroup analyses for UK vs non-UK centres is provided below in Table 25. The results are similar to other subgroups analyses with small sample sizes, and it is important to note the limited numbers of patients within these subgroups (n=34) for the UK centres. Hence, we suggest no conclusions can be drawn from these results.

Table 25: UK vs non-UK subgroup analysis for PFS

	Ld		DLd		Hazard ratio (95% CI)
	EVT/N	Median, [95% LCL, UCL]	EVT/N	Median, [95% LCL, UCL]	
UK	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-UK	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI: confidence interval; DLd: daratumumab, lenalidomide and dexamethasone; EVT: event; Ld: lenalidomide and dexamethasone; N: number; NE: not estimable; PFS: progression-free survival.

The subgroup analyses for UK vs non-UK centres is provided below for OS (Table 26):

Table 26: UK vs non-UK subgroup analysis for OS

	Ld		DLd		Hazard ratio (95% CI)
	EVT/N	Median [95% LCL, UCL]	EVT/N	Median [95% LCL, UCL]	
UK	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-UK	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

C5. Document B, Table 20. Time to first response. Is there an error here, as N=1.05. Should this be the median?

Thank you for identifying this error, the corrected Table 20 is updated in the attached Document B ""ID4014_Janssen_Daratumumab_Document B_ FINAL [ACIC]_29thJune" , and copied below for reference

Table 5: Summary of time to response in the MAIA trial based on computerised algorithm (response-evaluable analysis set) (data cut-off 21st October 2021)

	DLd (n=[redacted])	Ld (n=[redacted])
Responders (≥PR)	[redacted]	[redacted]
Time to first response[a] (months)		
N	[redacted]	[redacted]

Median (range)	[redacted]	[redacted]
Time to best response[a] (months)		
N	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]
Time to ≥VGPR[a] (months)		
N	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]
Time to ≥CR[a] (months)		
N	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]

[a] Response PR or better.
Abbreviations: CR: complete response; DLd: daratumumab, lenalidomide and dexamethasone; Ld: lenalidomide-dexamethasone; PR: partial response; VGPR: very good partial response.

C6. Doc B, p75 top "*This also has the higher potential for accuracy, given the use of IPD, compared to an NMA with a long chain of evidence.*" This statement is incorrect. There is higher potential for precision, but much more chance of bias and hence lower potential for accuracy.

Indirect comparisons through NMA based on the comparison of relative treatment effects versus common comparator between trials, are expected to preserve randomisation and as such can provide unbiased estimates. However, it needs to be acknowledged that the validity of results is based on two assumptions:

1. The common comparator needs to be sufficiently common/ similar, and

2. Trial populations do not differ on patient/disease characteristics that impact the relative treatment effect.

The bias induced by imbalance on treatment effect modifiers can still be adjusted for using MAIC, however are only possible pairwise, and in case IPD are available for one of both trials. This is typically not feasible in NMA, with extended networks. Additionally, ITC/NMA based on comparison of relative treatment effects across trials induce additional uncertainty, induces by variances are simply being added up, as studies are independent. In case of an extended network, with several trials/steps between treatment arms of interest, this uncertainty increases by each additional step.
In the current network, the MAIA (providing data for the comparison for DLd) and VISTA trial (providing the comparison for BMP) are separated through a sparse network and linked through a single chain of evidence, and as such there is uncertainty in the indirect comparison estimates. In addition, due to the reliance of published baseline characteristics being available, it is unknown if there are missing covariates which could further bias the indirect comparison.

As noted in Document B (Section B.2.9.2), ALCYONE is a recently conducted Phase III study, also conducted by Janssen for daratumumab in a newly diagnosed MM population who are ineligible for ASCT.

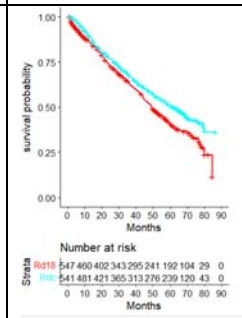
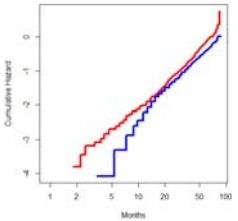
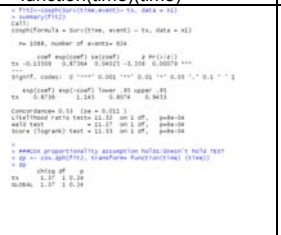
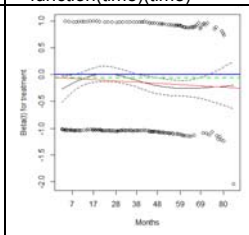
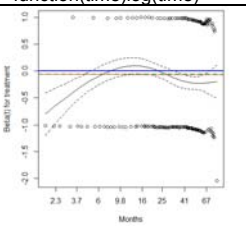
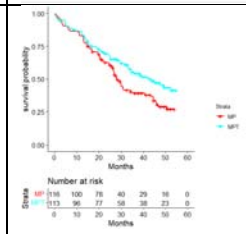
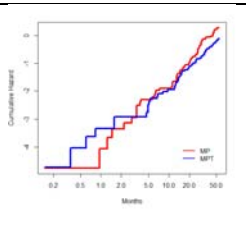
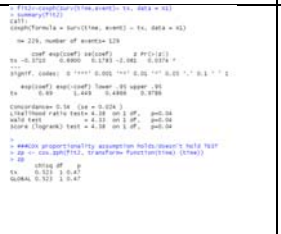
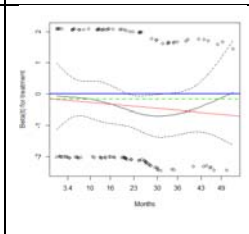
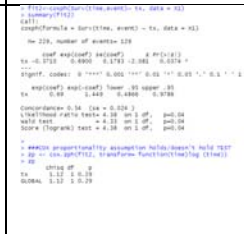
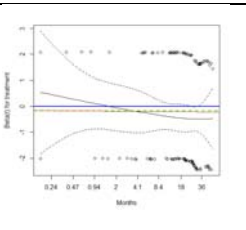
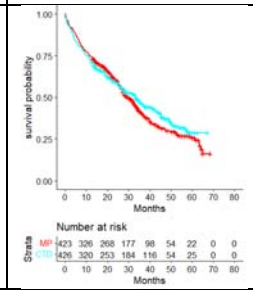
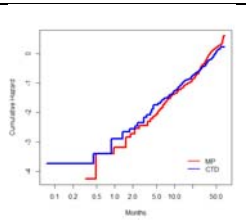
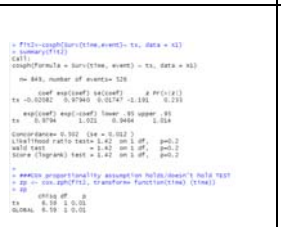
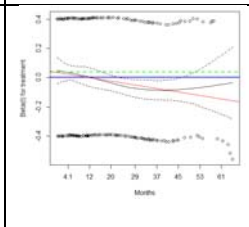
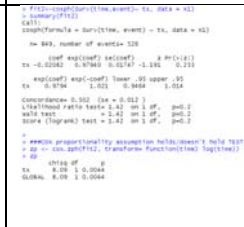
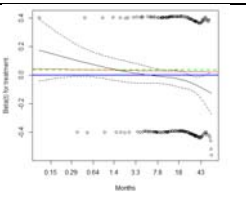
The indirect comparison approach through the NMA does not leverage the available evidence on outcomes in BMP patients from ALCYONE. The trial populations of MAIA and ALCYONE are very similar (as shown by the limited impact of ATT adjustment in the IPD based analyses). In comparison, patients in the VISTA trial are more different (which may be a minor limitation as long as there are no differences on treatment effect modifiers).

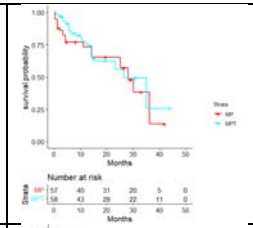
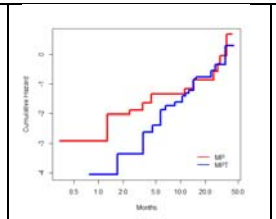
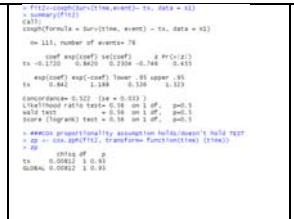
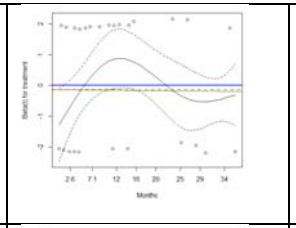
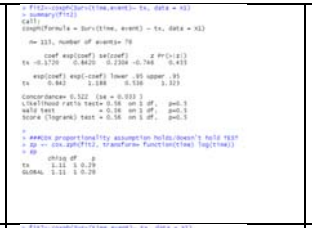
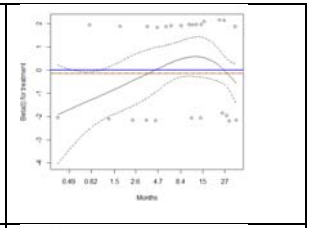
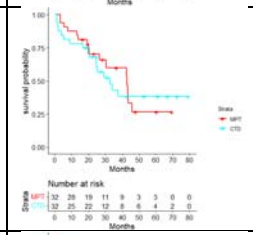
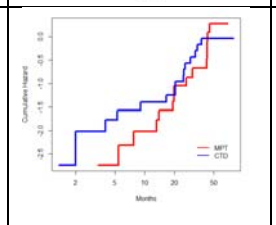
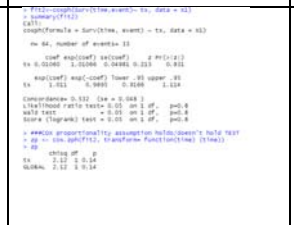
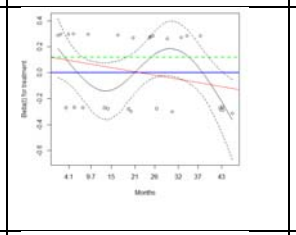
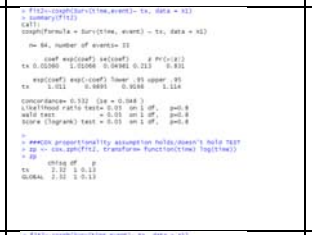
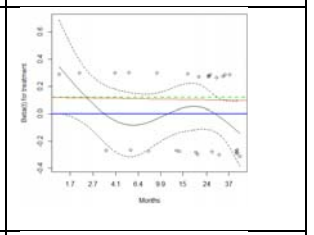
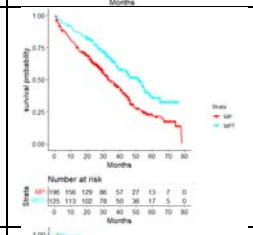
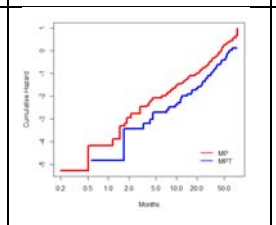
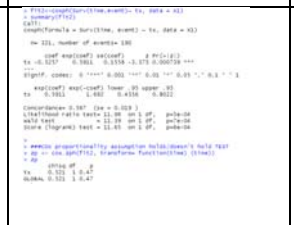
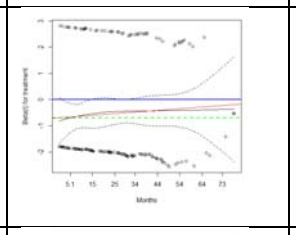
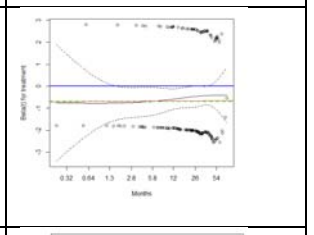
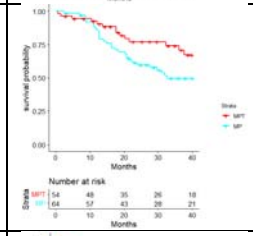
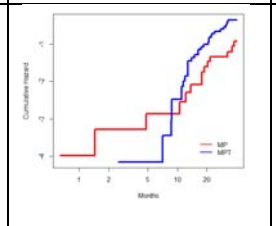
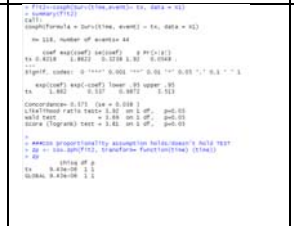
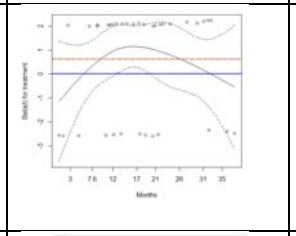
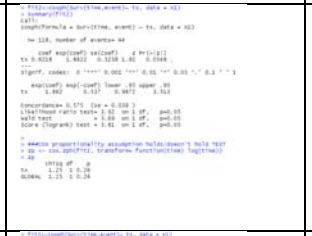
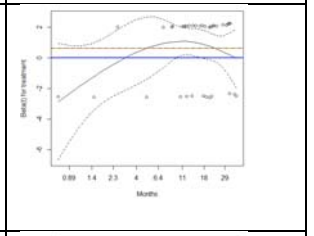
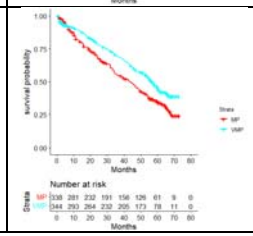
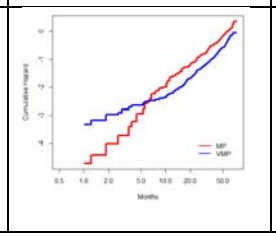
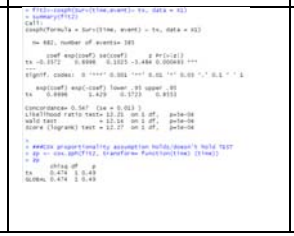
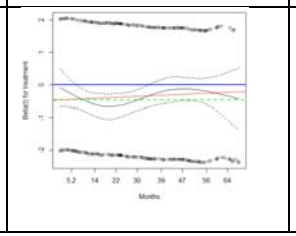
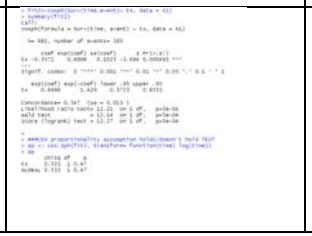
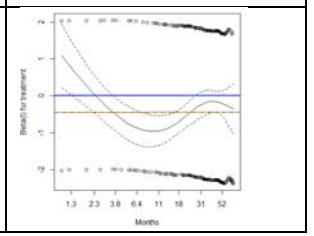
More importantly is that VISTA was a trial run between 2004 and 2007, when the available subsequent therapies differed to when the MAIA and ALCYONE trials were run.

IPD based analyses are generally considered to be more prone to generate biased results, as there is a need to adjust for any prognostic factor, instead of only treatment effect modifying variables. Obviously, as in any non-randomised study, residual confounding cannot be excluded. However, the risk for potential confounding bias needs to be assessed on a case by case basis, as it is related to the extent that prognostic factors are commonly available in both treatment cohorts to be compared, and by the differences in the observed patient populations, which is rather limited in the case of MAIA and ALCYONE. In addition, given the availability to Janssen of the comprehensive list of baseline and time varying covariates, the risk of missing any unknown confounders is minimised.

As such, the validity of both sets of assumptions behind NMA versus IPD ATT adjusted comparisons, needs to be evaluated. Janssen consider that, in this situation, where there exists uncertainty through the NMA, and the unusual advantageous situation where IPD is available both from MAIA and ALCYONE, that the IPD based analysis should be considered in the base case. In the current study, it can be argued, given the extensive set of clinically relevant prognostic factors combined with the similarity of the observed MAIA versus ALCYONE populations, that the IPD based analyses may be preferred, as additionally allows more robust as well as more precise estimates, with less uncertainty.

Appendix A5: Proportional Hazards assessment for trials in the network

OS			Transform =function(time)(time)	Transform =function(time)(time)	Transform =function(time)log(time)	Transform =function(time)log(time)
FIRST[2] (Rdc vs MPT)						
IFM0101[3] (OS)						
MRC[4] (OS)						

TMGS[5] (OS)						
Hungria[6] (OS)						
IFM 9906[7] (OS)						
Sacchi[8] (OS)						
VISTA[9] (OS)						

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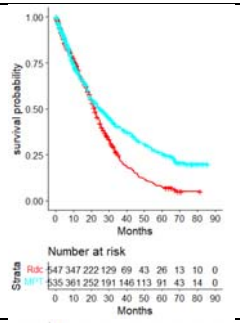
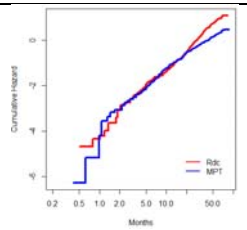
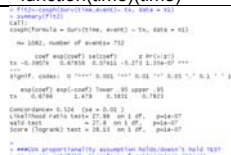
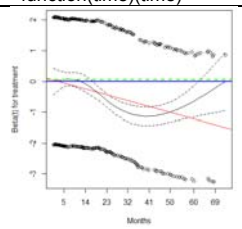
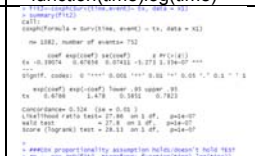
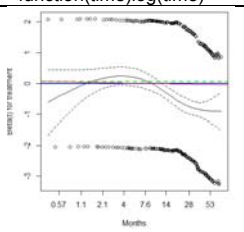
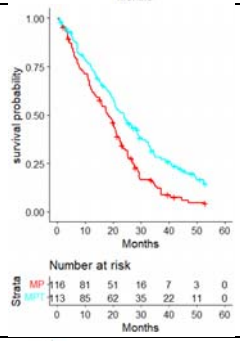
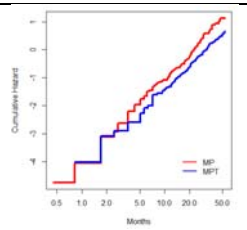
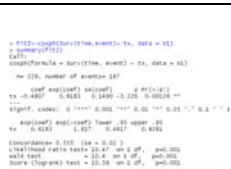
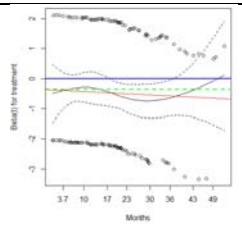
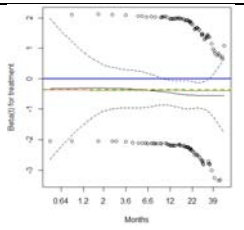
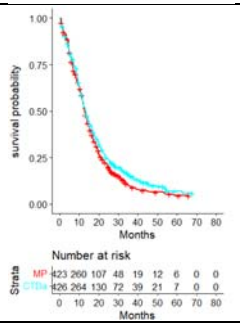
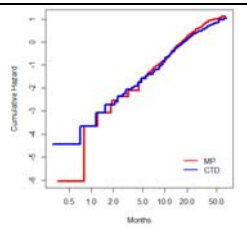
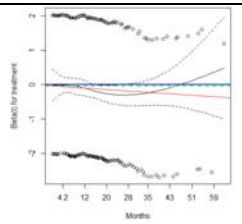
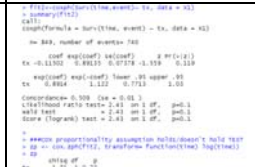
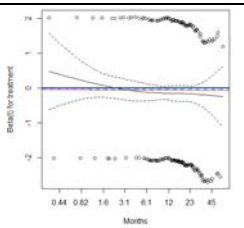
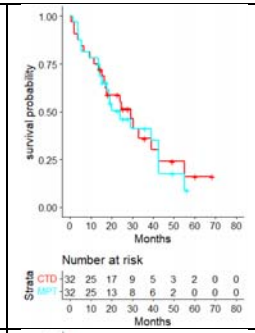
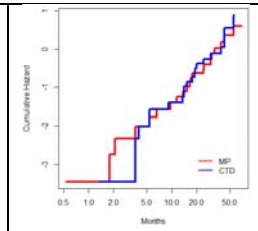
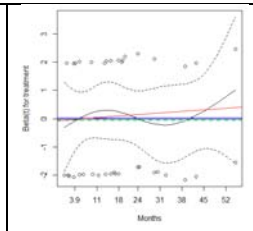
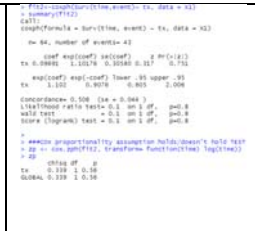
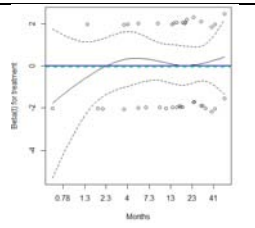
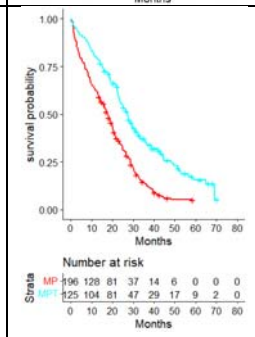
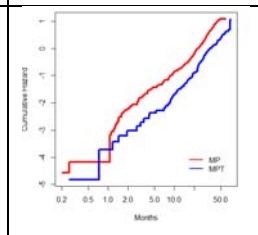
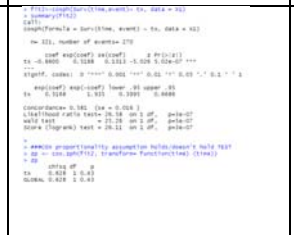
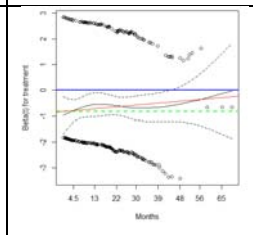
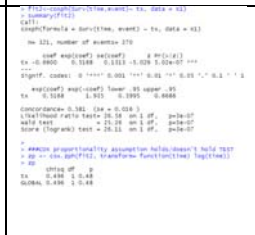
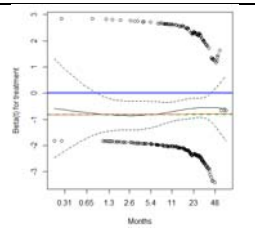
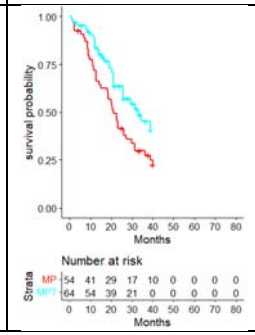
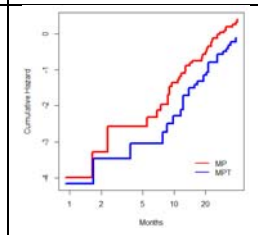
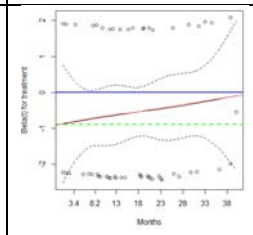
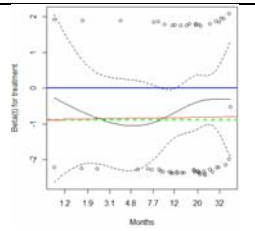
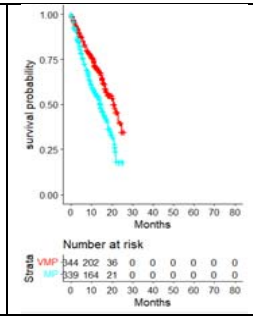
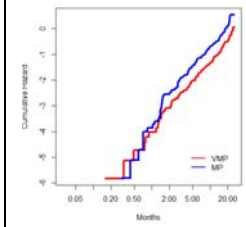
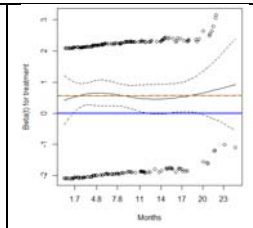
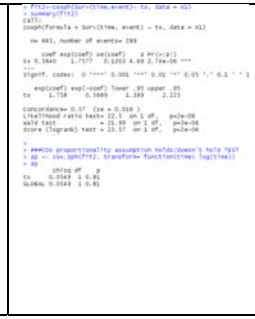
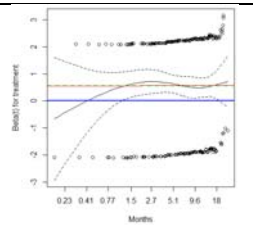
FIRST[2] (PFS)						
IFM0101[3] (PFS)						
MRC[4] (PFS)						

Hungria[6] (PFS)						
IFM 9906[7] (PFS)						
Sacchi[8] (PFS)						

VISTA[10]* (PFS)						

*In the absence of progression-free survival Kaplan Meier data, time to progression data was used.

Appendix A5b: Parametric NMA methodology and results

Progression free survival

Exponential

$S_{i,j}(t) = -\exp(-h_{i,j} * t)$

$h_{i,j} = \exp(\beta 0_i + \beta 1_j)$

t = time for each individual in months

i = study indicator MAIA= 1, FIRST=2, Hungria=3, MRC=4, IFM9906=5, IFm0101=6, Sacchi=7, VISTA=8

j = treatment indicator DRd =1 , Rdc=2, Rd18= 3, MPT= 4, CTD = 5, MP = 6, VMP =7

$\beta 1_1 = 0$ (for the reference treatment daratumumab)

Weak-informative a priori distributions are used:

β_{1_j}, $\beta_{0_i} \sim N(0,5)$

where N(0, 5) is the normal distribution with mean of zero and variance of 5.

Overall survival

Gompertz

$\beta_{ij} = \exp(\beta 0_i + \beta 1_j)$

$\alpha_{ij} = \alpha 0_i + \alpha 1_j$

$S_{i,j}(t) = \exp(-\beta_{ij} / \alpha_{ij} * (\exp(\alpha_{ij}) - 1))$

$h_{i,j,}(t) = \exp(\log(\beta_{ij}) + \alpha_{ij} * t)$

i = study indicator MAIA = 1, FIRST=2, Hungria=3, MRC=4, TMSG =5, IFM9906=6, IFm0101=7, Sacchi=8, VISTA=9

j = treatment indicator DRd =1 , Rdc=2, Rd18= 3, MPT= 4, CTD = 5, MP = 6, VMP =7

$\beta 1_1$= 0 (for the reference treatment daratumumab)

Weak-informative a priori distributions are used for beta:

β_{1_j}, β_{0_i}~ N(0,5)

For reasons of convergence for alpha the variance was reduced from 5 to 0.5.

α_{1_j}, α_{0_i}~ N(0,0.5)

Results

Progression free survival

Exponential

	mean	se_mean	sd	2.50%	50%	97.50%	n_eff	Rhat
beta_S[1]	-4.50356	0.001339	0.075692	-4.65632	-4.5021	-4.36093	3196.255	1.000287
beta_S[2]	-4.30955	0.002726	0.113896	-4.53129	-4.30724	-4.09263	1745.19	1.000388
beta_S[3]	-4.70964	0.003783	0.205628	-5.12045	-4.70712	-4.30967	2954.454	0.999833
beta_S[4]	-4.29218	0.003872	0.159288	-4.60589	-4.29058	-3.98826	1692.75	1.000214
beta_S[5]	-4.51156	0.003612	0.149239	-4.80736	-4.50848	-4.22109	1707.324	1.00052
beta_S[6]	-4.46012	0.003555	0.152581	-4.75977	-4.46047	-4.16057	1842.394	1.000416
beta_S[7]	-4.86586	0.003759	0.18118	-5.23015	-4.8613	-4.51929	2322.783	1.000063
beta_S[8]	-4.41352	0.003994	0.170324	-4.75446	-4.41138	-4.08644	1818.404	1.000291
beta_TT[1	0	NA	0	0	0	0	NA	NA
beta_TT[2	0.583442	0.002257	0.101084	0.390327	0.582617	0.781602	2005.442	1.000549
beta_TT[3	0.971503	0.002756	0.123614	0.730387	0.971538	1.210373	2011.778	1.000565
beta_TT[4	0.97483	0.003072	0.124603	0.734078	0.973439	1.219774	1645.227	1.000656
beta_TT[5	1.289592	0.003931	0.16491	0.972285	1.289672	1.61838	1760.187	1.000107
beta_TT[6	1.440231	0.003785	0.151565	1.14765	1.437501	1.743083	1603.405	1.000195
beta_TT[7	0.900496	0.004138	0.194206	0.52462	0.900076	1.289227	2202.163	1.000014

Overall survival

Gompertz

	mean	se_mean	sd	2.50%	50%	97.50%	n_eff	Rhat
beta_S[1]	-5.36868	0.009011	0.227791	-5.82121	-5.36392	-4.9469	639.0463	1.000838
beta_S[2]	-5.01869	0.023527	0.33274	-5.61578	-5.02321	-4.42449	200.0137	1.004622
beta_S[3]	-4.8108	0.027181	0.491967	-5.72194	-4.80628	-3.9599	327.599	1.002266
beta_S[4]	-4.59195	0.02626	0.354392	-5.19016	-4.59493	-4.0088	182.1329	1.006842
beta_S[5]	-4.66155	0.033598	0.457614	-5.49919	-4.65421	-3.90207	185.5101	1.010917
beta_S[6]	-5.11574	0.027696	0.395527	-5.79861	-5.12118	-4.44733	203.947	1.005986
beta_S[7]	-4.81247	0.02695	0.410387	-5.53521	-4.82122	-4.11406	231.8769	1.006319
beta_S[8]	-5.3004	0.035319	0.562919	-6.37218	-5.29731	-4.2965	254.0204	1.004508
beta_S[9]	-5.32986	0.028481	0.407646	-6.06856	-5.33364	-4.61628	204.8668	1.006471
beta_TT[1	0	NA	0	0	0	0	NA	NA
beta_TT[2	-0.10812	0.020659	0.309597	-0.67328	-0.10136	0.452149	224.5844	1.003757
beta_TT[3	0.012528	0.024085	0.368109	-0.66764	0.017663	0.668235	233.6027	1.003845
beta_TT[4	0.212782	0.026625	0.359277	-0.39436	0.21364	0.830467	182.0873	1.006152
beta_TT[5	0.901234	0.023317	0.325086	0.363104	0.905247	1.449683	194.3739	1.006209
beta_TT[6	0.637528	0.028008	0.367308	0.031376	0.641137	1.26613	171.9857	1.007447
beta_TT[7	-0.34927	0.025812	0.492973	-1.35817	-0.34107	0.593014	364.7543	1.002916
alpha_S[1	-0.00048	0.000208	0.008183	-0.01265	-0.00027	0.011462	1542.48	1.000999
alpha_S[2	-0.00809	0.000459	0.009285	-0.02283	-0.00783	0.006128	408.3336	1.003756
alpha_S[3	-0.01266	0.000292	0.014609	-0.04236	-0.01202	0.013625	2506.251	1.000423
alpha_S[4	-0.01935	0.000214	0.006028	-0.03074	-0.01913	-0.00847	794.756	1.001984
alpha_S[5	0.010292	0.000503	0.013891	-0.01645	0.010291	0.037293	761.7142	1.005889
alpha_S[6	-0.00547	0.000343	0.00843	-0.02155	-0.0053	0.01005	604.8154	1.002543
alpha_S[7	-0.01294	0.00034	0.010643	-0.0335	-0.01267	0.006764	981.7373	1.002157
alpha_S[8	-0.01231	0.000705	0.020565	-0.05356	-0.01193	0.026774	851.5961	1.002234
alpha_S[9	-0.01057	0.000312	0.008862	-0.02773	-0.01042	0.006167	807.3756	1.002698
alpha_TT[	0	NA	0	0	0	0	NA	NA
alpha_TT[	0.019967	0.000428	0.00907	0.006393	0.019719	0.03432	449.4208	1.003431
alpha_TT[	0.013865	0.000319	0.009143	-0.00176	0.013794	0.030399	823.2797	1.001426
alpha_TT[	0.019446	0.000302	0.011021	0.005417	0.019407	0.034501	1330.486	1.000695
alpha_TT[	0.019542	0.034384	0.515546	-0.96417	0.024874	1.03328	224.8131	1.001874
alpha_TT[	0.022936	0.000304	0.007131	0.009893	0.022768	0.036368	548.6796	1.00326
alpha_TT[	0.033978	0.001162	0.027593	0.012388	0.034989	0.057953	564.0811	1.003911

Predicted survival

Progression free survival
Exponential

Overall survival
Gompertz

Appendix A6: Published and reconstructed curves

The published and reconstructed KM curves for Sacchi 2011 (OS and PFS) and TMSG (OS only) are presented in Appendix A6.

Figure 7. Sacchi 2011: published KM curve for OS

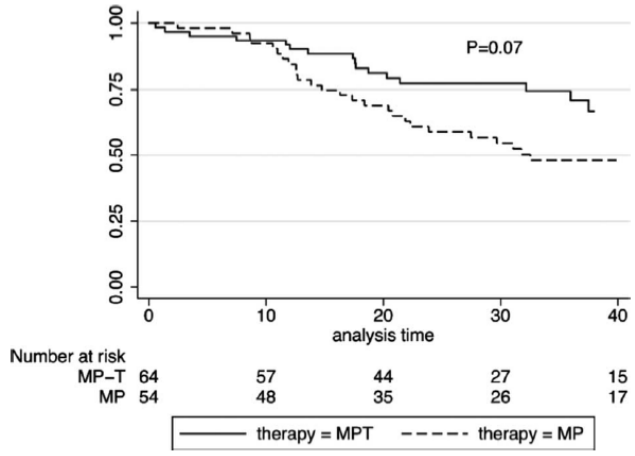


Figure 8. Sacchi 2011: reconstructed KM curve for OS

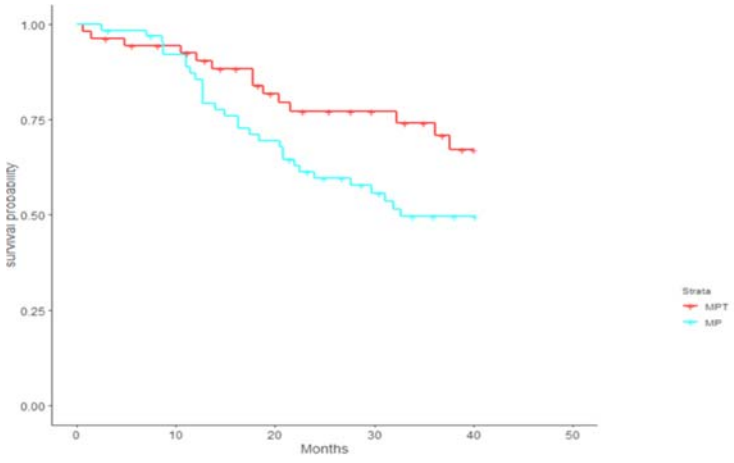


Figure 9. Sacchi 2011: published KM curve for PFS

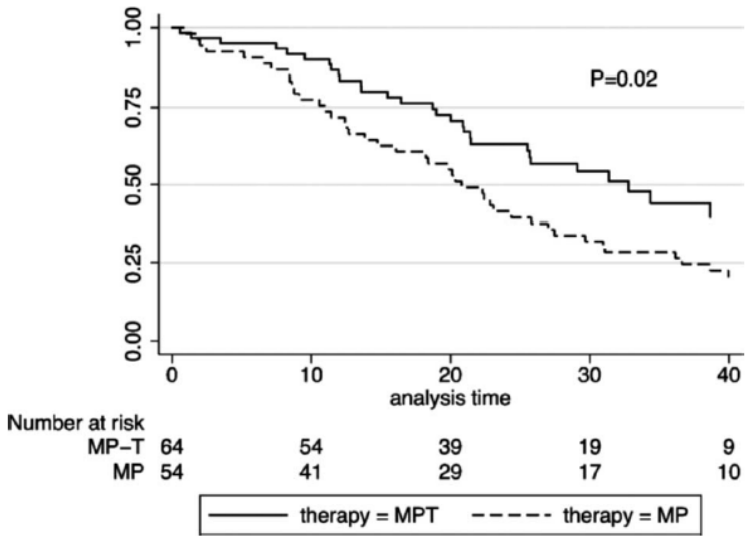


Figure 10. Sacchi 2011: reconstructed KM curve for PFS

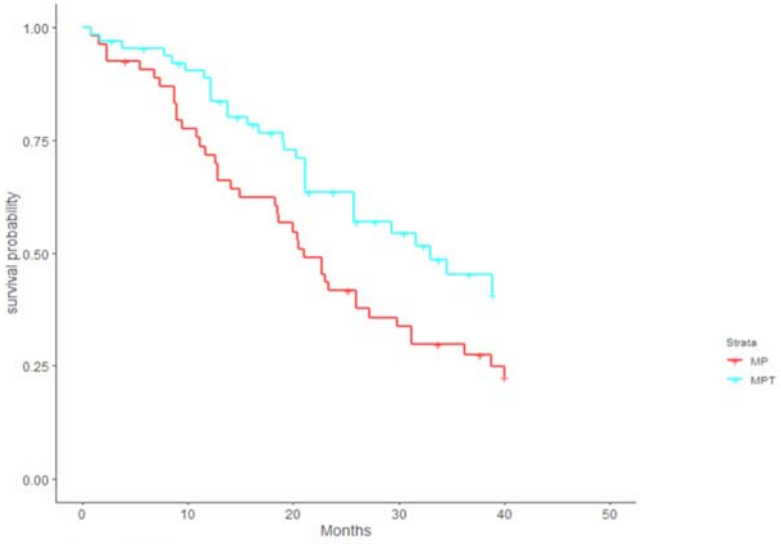


Figure 11. TMSG: published KM curve for OS

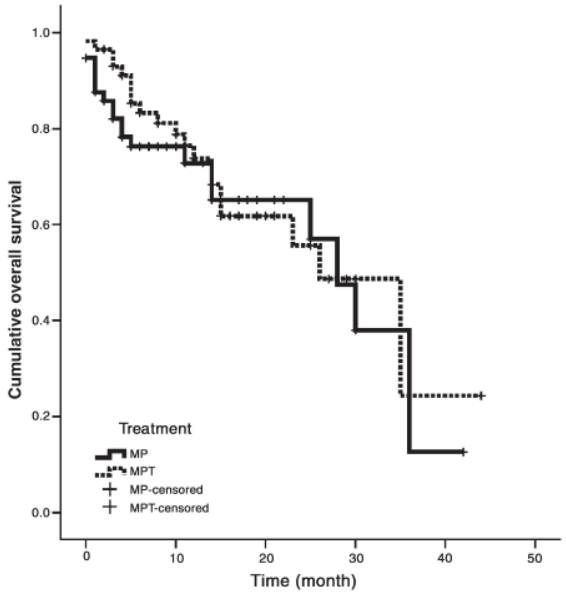
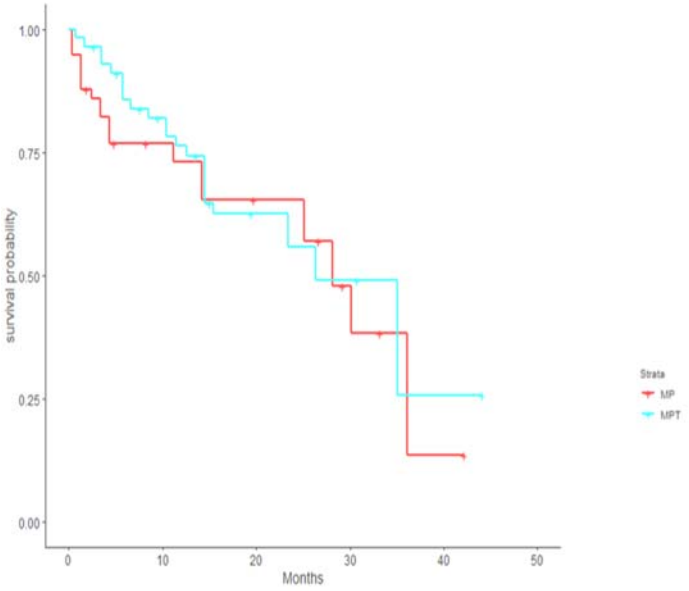


Figure 12. TMSG: reconstructed KM curve for OS



Appendix B5: Subsequent (2nd and 3rd line) treatments

MAIA

The numbers of patients receiving subsequent (2nd line and 3rd line) treatments can be found below for the MAIA trial.

	2L		3L	
	DLd	Ld	DLd	Ld
Subsequent treatment regimens	**N**	**N**	**N**	**N**
Apixaban+Bortezomib+Dexamethasone+Investigational Antineoplastic Drugs	[redacted]	[redacted]	[redacted]	[redacted]
Bendamustine+Bortezomib+Dexamethasone	[redacted]	[redacted]	[redacted]	[redacted]
Bendamustine+Dexamethasone	[redacted]	[redacted]	[redacted]	[redacted]
Bendamustine+Dexamethasone+Pomalidomide	[redacted]	[redacted]	[redacted]	[redacted]
Bendamustine+Rituximab	[redacted]	[redacted]	[redacted]	[redacted]
Bortezomib	[redacted]	[redacted]	[redacted]	[redacted]
Bortezomib+Carfilzomib+Cyclophosphamide+Dexamethasone	[redacted]	[redacted]	[redacted]	[redacted]
Bortezomib+Clarithromycin+Daratumumab+Melphalan+Pomalidomide	[redacted]	[redacted]	[redacted]	[redacted]
Bortezomib+Cyclophosphamide	[redacted]	[redacted]	[redacted]	[redacted]
Bortezomib+Cyclophosphamide+Daratumumab+Dexamethasone	[redacted]	[redacted]	[redacted]	[redacted]
Bortezomib+Cyclophosphamide+Dexamethasone	[redacted]	[redacted]	[redacted]	[redacted]
Bortezomib+Cyclophosphamide+Dexamethasone+Doxorubicin	[redacted]	[redacted]	[redacted]	[redacted]
Bortezomib+Cyclophosphamide+Dexamethasone+Lenalidomide	[redacted]	[redacted]	[redacted]	[redacted]
Bortezomib+Cyclophosphamide+Dexamethasone+Melphalan+Prednisone	[redacted]	[redacted]	[redacted]	[redacted]
Bortezomib+Cyclophosphamide+Dexamethasone+Prednisone	[redacted]	[redacted]	[redacted]	[redacted]
Bortezomib+Cyclophosphamide+Dexamethasone+Thalidomide	[redacted]	[redacted]	[redacted]	[redacted]
Bortezomib+Cyclophosphamide+Doxycycline+Methylprednisolone	[redacted]	[redacted]	[redacted]	[redacted]
Bortezomib+Cyclophosphamide+Lenalidomide+Prednisone	[redacted]	[redacted]	[redacted]	[redacted]
Bortezomib+Cyclophosphamide+Melphalan+Prednisone	[redacted]	[redacted]	[redacted]	[redacted]
Bortezomib+Cyclophosphamide+Prednisolone	[redacted]	[redacted]	[redacted]	[redacted]
Bortezomib+Daratumumab	[redacted]	[redacted]	[redacted]	[redacted]
Bortezomib+Daratumumab+Dexamethasone	[redacted]	[redacted]	[redacted]	[redacted]
Bortezomib+Daratumumab+Dexamethasone+Lenalidomide	[redacted]	[redacted]	[redacted]	[redacted]
Bortezomib+Daratumumab+Dexamethasone+Pomalidomide	[redacted]	[redacted]	[redacted]	[redacted]
Bortezomib+Daratumumab+Investigational Drug	[redacted]	[redacted]	[redacted]	[redacted]
Bortezomib+Daratumumab+Melphalan+Prednisone	[redacted]	[redacted]	[redacted]	[redacted]
Bortezomib+Daratumumab+Methylprednisolone Sodium Succinate	[redacted]	[redacted]	[redacted]	[redacted]
Bortezomib+Daratumumab+Prednisone	[redacted]	[redacted]	[redacted]	[redacted]
Bortezomib+Dexamethasone	[redacted]	[redacted]	[redacted]	[redacted]
Bortezomib+Dexamethasone+Doxorubicin	[redacted]	[redacted]	[redacted]	[redacted]
Bortezomib+Dexamethasone+Elotuzumab+Pomalidomide	[redacted]	[redacted]	[redacted]	[redacted]
Bortezomib+Dexamethasone+Lenalidomide	[redacted]	[redacted]	[redacted]	[redacted]

Bortezomib+Dexamethasone+Melphalan	[redacted]	[redacted]	[redacted]	[redacted]
Bortezomib+Dexamethasone+Melphalan+Prednisolone	[redacted]	[redacted]	[redacted]	[redacted]
Bortezomib+Dexamethasone+Panobinostat	[redacted]	[redacted]	[redacted]	[redacted]
Bortezomib+Dexamethasone+Pomalidomide	[redacted]	[redacted]	[redacted]	[redacted]
Bortezomib+Dexamethasone+Thalidomide	[redacted]	[redacted]	[redacted]	[redacted]
Bortezomib+Dexamethasone+Venetoclax	[redacted]	[redacted]	[redacted]	[redacted]
Bortezomib+Melphalan	[redacted]	[redacted]	[redacted]	[redacted]
Bortezomib+Melphalan+Methylprednisolone	[redacted]	[redacted]	[redacted]	[redacted]
Bortezomib+Melphalan+Prednisolone	[redacted]	[redacted]	[redacted]	[redacted]
Bortezomib+Melphalan+Prednisone	[redacted]	[redacted]	[redacted]	[redacted]
Bortezomib+Pomalidomide	[redacted]	[redacted]	[redacted]	[redacted]
Bortezomib+Prednisone	[redacted]	[redacted]	[redacted]	[redacted]
Carboplatin+Dexamethasone	[redacted]	[redacted]	[redacted]	[redacted]
Carfilzomib	[redacted]	[redacted]	[redacted]	[redacted]
Carfilzomib+Cyclophosphamide+Dexamethasone	[redacted]	[redacted]	[redacted]	[redacted]
Carfilzomib+Daratumumab	[redacted]	[redacted]	[redacted]	[redacted]
Carfilzomib+Daratumumab+Dexamethasone	[redacted]	[redacted]	[redacted]	[redacted]
Carfilzomib+Daratumumab+Dexamethasone+Pomalidomide	[redacted]	[redacted]	[redacted]	[redacted]
Carfilzomib+Dexamethasone	[redacted]	[redacted]	[redacted]	[redacted]
Carfilzomib+Dexamethasone+Isatuximab+Pomalidomide	[redacted]	[redacted]	[redacted]	[redacted]
Carfilzomib+Dexamethasone+Lenalidomide	[redacted]	[redacted]	[redacted]	[redacted]
Carfilzomib+Dexamethasone+Pomalidomide	[redacted]	[redacted]	[redacted]	[redacted]
Carfilzomib+Dexamethasone+Venetoclax	[redacted]	[redacted]	[redacted]	[redacted]
Cyclophosphamide	[redacted]	[redacted]	[redacted]	[redacted]
Cyclophosphamide+Daratumumab	[redacted]	[redacted]	[redacted]	[redacted]
Cyclophosphamide+Dexamethasone	[redacted]	[redacted]	[redacted]	[redacted]
Cyclophosphamide+Dexamethasone+Doxorubicin+Rituximab+Vincristine	[redacted]	[redacted]	[redacted]	[redacted]
Cyclophosphamide+Dexamethasone+Ixazomib	[redacted]	[redacted]	[redacted]	[redacted]
Cyclophosphamide+Dexamethasone+Ixazomib Citrate	[redacted]	[redacted]	[redacted]	[redacted]
Cyclophosphamide+Dexamethasone+Ixazomib+Lenalidomide	[redacted]	[redacted]	[redacted]	[redacted]
Cyclophosphamide+Dexamethasone+Lenalidomide	[redacted]	[redacted]	[redacted]	[redacted]
Cyclophosphamide+Dexamethasone+Pomalidomide	[redacted]	[redacted]	[redacted]	[redacted]
Cyclophosphamide+Dexamethasone+Thalidomide	[redacted]	[redacted]	[redacted]	[redacted]
Cyclophosphamide+Doxorubicin+Rituximab+Vincristine	[redacted]	[redacted]	[redacted]	[redacted]
Cyclophosphamide+Doxorubicin+Vincristine	[redacted]	[redacted]	[redacted]	[redacted]
Cyclophosphamide+Lenalidomide+Prednisone	[redacted]	[redacted]	[redacted]	[redacted]
Cyclophosphamide+Pomalidomide	[redacted]	[redacted]	[redacted]	[redacted]
Cyclophosphamide+Pomalidomide+Prednisone	[redacted]	[redacted]	[redacted]	[redacted]
Cyclophosphamide+Prednisolone	[redacted]	[redacted]	[redacted]	[redacted]
Cyclophosphamide+Prednisone	[redacted]	[redacted]	[redacted]	[redacted]
Daratumumab	[redacted]	[redacted]	[redacted]	[redacted]
Daratumumab+Dexamethasone	[redacted]	[redacted]	[redacted]	[redacted]

Daratumumab+Dexamethasone+Ixazomib	[redacted]	[redacted]	[redacted]	[redacted]
Daratumumab+Dexamethasone+Lenalidomide	[redacted]	[redacted]	[redacted]	[redacted]
Daratumumab+Dexamethasone+Pomalidomide	[redacted]	[redacted]	[redacted]	[redacted]
Daratumumab+Ixazomib	[redacted]	[redacted]	[redacted]	[redacted]
Daratumumab+Lenalidomide	[redacted]	[redacted]	[redacted]	[redacted]
Daratumumab+Methylprednisolone	[redacted]	[redacted]	[redacted]	[redacted]
Daratumumab+Pomalidomide	[redacted]	[redacted]	[redacted]	[redacted]
Daratumumab+Venetoclax	[redacted]	[redacted]	[redacted]	[redacted]
Dexamethasone	[redacted]	[redacted]	[redacted]	[redacted]
Dexamethasone Acetate+Lenalidomide	[redacted]	[redacted]	[redacted]	[redacted]
Dexamethasone+Elotuzumab	[redacted]	[redacted]	[redacted]	[redacted]
Dexamethasone+Elotuzumab+Lenalidomide	[redacted]	[redacted]	[redacted]	[redacted]
Dexamethasone+Elotuzumab+Pomalidomide	[redacted]	[redacted]	[redacted]	[redacted]
Dexamethasone+Ixazomib	[redacted]	[redacted]	[redacted]	[redacted]
Dexamethasone+Ixazomib Citrate	[redacted]	[redacted]	[redacted]	[redacted]
Dexamethasone+Ixazomib Citrate+Lenalidomide	[redacted]	[redacted]	[redacted]	[redacted]
Dexamethasone+Ixazomib Citrate+Pomalidomide	[redacted]	[redacted]	[redacted]	[redacted]
Dexamethasone+Ixazomib+Lenalidomide	[redacted]	[redacted]	[redacted]	[redacted]
Dexamethasone+Ixazomib+Pomalidomide	[redacted]	[redacted]	[redacted]	[redacted]
Dexamethasone+Lenalidomide	[redacted]	[redacted]	[redacted]	[redacted]
Dexamethasone+Melphalan Hydrochloride	[redacted]	[redacted]	[redacted]	[redacted]
Dexamethasone+Pomalidomide	[redacted]	[redacted]	[redacted]	[redacted]
Dexamethasone+Venetoclax	[redacted]	[redacted]	[redacted]	[redacted]
Fluorouracil+Folinic Acid+Oxaliplatin	[redacted]	[redacted]	[redacted]	[redacted]
Investigational Antineoplastic Drugs	[redacted]	[redacted]	[redacted]	[redacted]
Ixazomib Citrate	[redacted]	[redacted]	[redacted]	[redacted]
Ixazomib Citrate+Lenalidomide	[redacted]	[redacted]	[redacted]	[redacted]
Ixazomib Citrate+Pomalidomide	[redacted]	[redacted]	[redacted]	[redacted]
Lenalidomide	[redacted]	[redacted]	[redacted]	[redacted]
Lenalidomide+Melphalan	[redacted]	[redacted]	[redacted]	[redacted]
Melphalan	[redacted]	[redacted]	[redacted]	[redacted]
Melphalan+Prednisone	[redacted]	[redacted]	[redacted]	[redacted]
Monoclonal Antibodies	[redacted]	[redacted]	[redacted]	[redacted]
Other Antineoplastic Agents	[redacted]	[redacted]	[redacted]	[redacted]
Pomalidomide	[redacted]	[redacted]	[redacted]	[redacted]
Pomalidomide+Prednisone	[redacted]	[redacted]	[redacted]	[redacted]
Prednisolone+Thalidomide	[redacted]	[redacted]	[redacted]	[redacted]

ALCYONE

The numbers of patients receiving subsequent (2nd line and 3rd line) treatments can be found below for the ALCYONE trial.

	2L		3L	
	DBMP	BMP	DBMP	BMP
Subsequent treatment regimens	**N**	**N**	**N**	**N**
All Other Therapeutic Products	[redacted]	[redacted]	[redacted]	[redacted]
Bendamustine	[redacted]	[redacted]	[redacted]	[redacted]
Bendamustine Hydrochloride+Bortezomib+Cyclophosphamide+Dexamethasone+Prednisolone+Thalidomide	[redacted]	[redacted]	[redacted]	[redacted]
Bendamustine Hydrochloride+Prednisolone	[redacted]	[redacted]	[redacted]	[redacted]
Bendamustine+Bortezomib+Cyclophosphamide+Dexamethasone+Prednisolone+Thalidomide	[redacted]	[redacted]	[redacted]	[redacted]
Bendamustine+Dexamethasone+Lenalidomide	[redacted]	[redacted]	[redacted]	[redacted]
Bendamustine+Dexamethasone+Methylprednisolone	[redacted]	[redacted]	[redacted]	[redacted]
Bendamustine+Methylprednisolone Sodium Succinate+Thalidomide	[redacted]	[redacted]	[redacted]	[redacted]
Bendamustine+Methylprednisolone+Thalidomide	[redacted]	[redacted]	[redacted]	[redacted]
Bendamustine+Prednisolone+Thalidomide	[redacted]	[redacted]	[redacted]	[redacted]
Bortezomib	[redacted]	[redacted]	[redacted]	[redacted]
Bortezomib+Cyclophosphamide+Dexamethasone	[redacted]	[redacted]	[redacted]	[redacted]
Bortezomib+Cyclophosphamide+Dexamethasone+Lenalidomide	[redacted]	[redacted]	[redacted]	[redacted]
Bortezomib+Cyclophosphamide+Dexamethasone+Lenalidomide+Melphalan	[redacted]	[redacted]	[redacted]	[redacted]
Bortezomib+Cyclophosphamide+Dexamethasone+Prednisolone+Thalidomide	[redacted]	[redacted]	[redacted]	[redacted]
Bortezomib+Cyclophosphamide+Prednisolone	[redacted]	[redacted]	[redacted]	[redacted]
Bortezomib+Daratumumab+Dexamethasone	[redacted]	[redacted]	[redacted]	[redacted]
Bortezomib+Dexamethasone	[redacted]	[redacted]	[redacted]	[redacted]
Bortezomib+Dexamethasone+Doxorubicin	[redacted]	[redacted]	[redacted]	[redacted]
Bortezomib+Dexamethasone+Investigational Antineoplastic Drugs	[redacted]	[redacted]	[redacted]	[redacted]
Bortezomib+Dexamethasone+Lenalidomide	[redacted]	[redacted]	[redacted]	[redacted]
Bortezomib+Dexamethasone+Melphalan+Prednisolone+Thalidomide	[redacted]	[redacted]	[redacted]	[redacted]
Bortezomib+Dexamethasone+Panobinostat	[redacted]	[redacted]	[redacted]	[redacted]
Bortezomib+Dexamethasone+Selinexor	[redacted]	[redacted]	[redacted]	[redacted]
Bortezomib+Lenalidomide	[redacted]	[redacted]	[redacted]	[redacted]
Bortezomib+Melphalan+Methylprednisolone	[redacted]	[redacted]	[redacted]	[redacted]
Bortezomib+Melphalan+Prednisolone	[redacted]	[redacted]	[redacted]	[redacted]
Bortezomib+Melphalan+Prednisone	[redacted]	[redacted]	[redacted]	[redacted]
Bortezomib+Panobinostat	[redacted]	[redacted]	[redacted]	[redacted]
Carfilzomib	[redacted]	[redacted]	[redacted]	[redacted]
Carfilzomib+Cyclophosphamide+Dexamethasone+Lenalidomide	[redacted]	[redacted]	[redacted]	[redacted]
Carfilzomib+Daratumumab	[redacted]	[redacted]	[redacted]	[redacted]
Carfilzomib+Daratumumab+Dexamethasone	[redacted]	[redacted]	[redacted]	[redacted]

Carfilzomib+Dexamethasone	[redacted]	[redacted]	[redacted]	[redacted]
Carfilzomib+Dexamethasone Sodium Phosphate+Lenalidomide+Melphalan	[redacted]	[redacted]	[redacted]	[redacted]
Carfilzomib+Dexamethasone+Isatuximab	[redacted]	[redacted]	[redacted]	[redacted]
Carfilzomib+Dexamethasone+Lenalidomide	[redacted]	[redacted]	[redacted]	[redacted]
Carfilzomib+Dexamethasone+Lenalidomide+Prednisone	[redacted]	[redacted]	[redacted]	[redacted]
Carfilzomib+Lenalidomide	[redacted]	[redacted]	[redacted]	[redacted]
Cisplatin+Cyclophosphamide+Dexamethasone+Doxorubicin+Etoposide+Thalidomide	[redacted]	[redacted]	[redacted]	[redacted]
Clarithromycin+Dexamethasone+Lenalidomide	[redacted]	[redacted]	[redacted]	[redacted]
Cyclophosphamide	[redacted]	[redacted]	[redacted]	[redacted]
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Daratumumab+Dexamethasone+Lenalidomide	[redacted]	[redacted]	[redacted]	[redacted]

Daratumumab+Dexamethasone+Pomalidomide	[redacted]	[redacted]	[redacted]	[redacted]
Daratumumab+Lenalidomide	[redacted]	[redacted]	[redacted]	[redacted]
Dexamethasone	[redacted]	[redacted]	[redacted]	[redacted]
Dexamethasone Sodium Phosphate	[redacted]	[redacted]	[redacted]	[redacted]
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Dexamethasone+Dexamethasone Sodium Phosphate+Elotuzumab+Lenalidomide	[redacted]	[redacted]	[redacted]	[redacted]
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Investigational Antineoplastic Drugs	[redacted]	[redacted]	[redacted]	[redacted]
Isatuximab+Methylprednisolone Sodium Succinate	[redacted]	[redacted]	[redacted]	[redacted]
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Ixazomib+Lenalidomide+Prednisone	[redacted]	[redacted]	[redacted]	[redacted]
Ixazomib+Methylprednisolone	[redacted]	[redacted]	[redacted]	[redacted]
Lenalidomide	[redacted]	[redacted]	[redacted]	[redacted]
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Methylprednisolone+Thalidomide	[redacted]	[redacted]	[redacted]	[redacted]
Pomalidomide	[redacted]	[redacted]	[redacted]	[redacted]
Pomalidomide+Prednisone	[redacted]	[redacted]	[redacted]	[redacted]
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Thalidomide	[redacted]	[redacted]	[redacted]	[redacted]

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

[ID4014] - Daratumumab with lenalidomide and dexamethasone for untreated multiple myeloma when stem cell transplant is unsuitable

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

<table>
<tr><td>1.Your name</td><td>[redacted]</td></tr>
<tr><td>2. Name of organisation</td><td>Myeloma UK</td></tr>
<tr><td>3. Job title or position</td><td>[redacted]</td></tr>
<tr><td>4a. Brief description of the organisation (including who funds it). How many members does it have?</td><td>Myeloma UK is the only organisation in the UK dealing exclusively with myeloma and its associated conditions. Our broad and innovative range of services cover every aspect of myeloma from providing information and support, to improving standards of treatment and care through research and campaigning. We are not a membership organisation and rely almost entirely on the fundraising efforts of our supporters. We also receive some unrestricted educational grants and restricted project funding from a range of pharmaceutical companies.</td></tr>
<tr><td>4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.]
If so, please state the name of the company, amount, and purpose of funding.</td><td>
<table>
<tr><th>Name of Company</th><th>Grants and project specific funding</th><th>Gifts, Honoraria and Sponsorship</th><th>Total (£)</th></tr>
<tr><td>Celgene</td><td>-</td><td>5,000</td><td>5,000</td></tr>
<tr><td>BMS</td><td>40,000</td><td>-</td><td>40,000</td></tr>
<tr><td>Janssen-Cilag</td><td>25,000</td><td>950</td><td>25,950</td></tr>
</table>
The table above shows the audited 2021 income from the relevant manufacturers. Funding is received for a range of purposes and activities namely core grants, project specific work including clinical trials, and gifts, honoraria or sponsorship.
</td></tr>
<tr><td>4c. Do you have any direct or indirect links</td><td>No</td></tr>
</table>

with, or funding from, the tobacco industry?	
5. How did you gather information about the experiences of patients and carers to include in your submission?	The information included in this submission has been gathered from the myeloma patients and carers we engage with through our research and services programmes, including: - Structured telephone interviews with newly diagnosed myeloma patients who are ineligible for high-dose therapy and stem cell transplantation (HDT-SCT), and their family/carers, about living with myeloma, their experience and expectations of treatment, and their thoughts on the myeloma treatment pathway. ***Patient/family quotes from interviews are highlighted in italics.*** - A multi-criteria decision analysis study of 560 myeloma patients. The study, funded by Myeloma UK and run by the European Medicines Agency (EMA) and University of Groningen, explored patient preferences for different benefit and risk outcomes in myeloma treatment. It has also been informed by analysis of the experiences and views of patients, family members and carers gathered via our Myeloma Infoline, Patient and Family Myeloma Infodays and posts to our online Discussion Forum.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	***"Myeloma creeps up on you, engulfs you and, if you win the battle, leaves you wondering when it will come back."*** Myeloma is a highly individual and complex cancer originating from abnormal plasma cells in the bone marrow. There is currently no cure, but treatment can halt its progress and improve quality of life. The complications of myeloma can be significant, debilitating and painful and include severe bone pain, bone destruction, kidney damage, fatigue and a depleted immune system which can lead to increased infections. Myeloma is also a relapsing and remitting cancer which evolves over time and becomes resistant to treatment. Most patients can be successfully retreated at relapse; however, remission is usually associated with diminishing duration and depth of response over time. First remission is therefore widely held as the best opportunity to gain the deepest response with the longest period until disease progression.[i] It is also the point in their disease where many patients will be able to build on existing better quality of life since the burden of treatment and illness will be less than for patients who are multiply relapsed. ***"All the unknowns are hard. I would like to know everything because I want to be in control but with myeloma being so individual no one will give me a prognosis and I find this hard. My own guess is if I got one or two years of remission, I would be doing good. Now I am 18 months in remission, and I am finding it quite stressful going from my 3 monthly checkups in case things are beginning to change."*** Myeloma is also a disease which predominately affects older people. Over half of myeloma patients are over the age of 70, and many have other medical problems, mobility issues or need help from others with household tasks or personal care. Older, frailer patients can experience a higher rate of side effects whilst on treatment and may also experience more symptoms and complications. This can then affect how they tolerate and respond to treatment and therefore how quickly they might relapse. Treatment side effects and frequent hospital visits have a social and practical impact on patients' lives, including significant financial implications. Reduction in mobility over time and a perceived increase in reliance on carers and family members, also impacts on patients' sense of control.

	"It has been really hard. Especially through the pandemic, the risk of infection was too great. My wife and I are both retired but we weren't able do much. We were not seeing many people or going out for meals, stuff like that. We have now been out more but you have got to be really careful." The individual and heterogeneous nature of myeloma means that some patients may tolerate a treatment well and others may not. In addition, myeloma evolves and becomes resistant to treatment. It is therefore essential to have a range of treatment options with different mechanisms of action at all stages of the myeloma pathway. ***"To say, "Well you already have a treatment." That's not good enough. You always have to show myeloma something new."*** <u>Family & Carers</u> ***"I feel angry that I'm not going to get the future I wanted, but the hardest thing to feel is how my life at the moment is in limbo"*** A Myeloma UK study into the experiences of carers and family members found that looking after someone with myeloma has a significant emotional, social, and practical impact: - 94% of carers are emotionally impacted and found the uncertainty of myeloma a major factor - 25% of those in work had been unable to work or had to retire early to care for the person with myeloma - 84% always put the needs of their relative or friend with myeloma before their own - Only 42% of carers were not given enough information at diagnosis about how myeloma may affect them[ii] Living with myeloma is therefore often extremely challenging physically and emotionally for patients, carers, and family members. ***"I had to think of my husband. You are in this as a team, it is not an individual battle."***

	Family and carers have often spoken about the impact of a myeloma diagnosis on their own lives including a perceived lack of control, a change of roles/responsibilities within the household, daily lifestyle changes and missing out on important life events. ***"We had a role reversal. My husband used to do everything, but I now do it all. We actually moved house so it was something I could look after on my own when he relapses and goes back on treatment."*** ***"We have also altered what we eat. A lot more greens and a Mediterranean diet. When he was on treatment we slept in different rooms. I needed a full night's sleep to be able to take care of him throughout the day."*** ***"It has stopped us from travelling though it is hard to separate the myeloma from the restrictions due to COVID. You must be so careful…..My daughter and her family live in New Zealand and my younger son lives in southern France. We used to go twice a year to see them both but now with myeloma and covid it's not really possible."***

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Myeloma is an incredibly heterogenous condition with a large variability in age, comorbidities and fitness. Consequently, not all patients can receive the same treatment or intensity of dose. Therefore, treatment options must be based on the patient's fitness levels and ability to tolerate toxicities. The patient population covered in this appraisal make up more than half of all myeloma patients. They are generally older; they can be frailer/less fit and cannot tolerate intensive treatments such as high-dose therapy and stem cell transplantation (HDT-SCT). There are currently two main treatment options approved for use for newly diagnosed myeloma patients who are ineligible for HDT-SCT through the NHS. Bortezomib, in combination with an alkylating agent (usually melphalan or cyclophosphamide) and a corticosteroid (dexamethasone or prednisone) (NICE TA228) and lenalidomide & dexamethasone (NICE TA587). In NHS Clinical practice a patient is assessed by a myeloma frailty score or using clinical judgement to determine which treatment is most appropriate. Myeloma patients who are assessed as frailer/less fit require personalized, and dose modified treatments to improve tolerability and efficacy while maintaining quality of life.[iii] The all-oral treatment of lenalidomide plus dexamethasone is the current standard practice of treatment for newly diagnosed patients who are ineligible for HDT-SCT and generally frailer. This treatment has been used effectively during the pandemic as it is easy to administer and has kept patients out of hospital settings where they could be at risk of contracting COVID-19. ***"I found the whole experience very hard. I could handle COVID, and I think I would have handled the myeloma diagnosis but the two together was really hard."***

	For patients who are transplant ineligible but assessed as fitter than those above then they currently receive bortezomib based triplet regimens.[iv] In these patients, the treatment goal is obtaining disease remission and deep responses with minimal residual disease (MRD) negativity whilst maintaining/improving health related quality of life (HRQoL). The triplet combination of bortezomib, cyclophosphamide and dexamethasone (VCD) has become standard of practice for this patient population.[v] Treatment with bortezomib combinations comes with associated toxicities including neuropathy and cytopenias related to alkylating agents such cyclophosphamide. ***"The side effects were not good. I would have chemo on the Tuesday and by Wednesday teatime I was really ill and uncomfortable…… Over those days I would lie in bed or on the settee. I didn't eat much either. I sometimes had really bad constipation but then it could be really bad diarrhea. I was never sure which would come so I had to be careful which medicine I would take to help before I started my chemo."*** ***"I was completely ruined by the Velcade. All of the things I like doing were affected. I like to play the double bass but I had to stop due to the peripheral neuropathy in my fingers. I have since started playing again although I still struggle with the feeling in my fingers.*** ***"It can only be described as a feeling of walking on rocks. I had a constant burning sensation in my hands and feet, which got much worse at night and meant I struggled to sleep. This combined with having terrible fatigue related to my myeloma, meant that it impacted on my ability to do things."*** Crucially VCD is a fixed duration treatment meaning patients will not receive a maintenance therapy which can keep their myeloma under control for longer. Our patient engagement consistently shows that patients desire treatments which are effective and keep their myeloma under control. As myeloma is a highly individual, relapsing and remitting cancer which becomes resistant to treatment, patients need and want a range of effective treatment options including treatments with different mechanisms of action, administered in a range of ways, at every stage of the treatment pathway.

8. Is there an unmet need for patients with this condition?	As stated above the nature of myeloma mean it is essential to have a range of treatment options with different mechanisms of action at all stages of the myeloma pathway. Daratumumab is a CD38 monoclonal antibody and there is currently no treatment with this mechanism of action licensed at this point in the treatment pathway for transplant ineligible patients. Therefore, we would consider this an unmet need and if approved would be an innovative change to the treatment pathway. Further to this, daratumumab is available for newly diagnosed patients with multiple myeloma who are *eligible* for HDT-SCT (TA763) and we would like to see equity of access to this treatment for all newly diagnosed patients with multiple myeloma.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	We know from our engagement that patients value treatments which put their myeloma into remission for as long as possible, prolong their life and allow them to enjoy a normal day to day life. The MAIA Clinical trial compared daratumumab, lenalidomide and dexamethasone (DRd) to the standard treatment of lenalidomide and dexamethasone (Rd). The results[vi] from the trial show that after 5 years of follow up median progression-free survival had not been reached in the DRd arm with 52.5% of patients not experiencing a relapse of their myeloma. In the comparator arm the results show that after 5 years of follow up median progression-free survival had been reached at 34.4 months and 28.7% of patients not experiencing a relapse of their myeloma. Fewer deaths were observed in the DRd group (32%) compared with the Rd group (42%). Median overall survival was not reached in the DRd group vs 55.7 months in the Rd group, representing a statistically significant difference (hazard ratio (HR) = 0.68, 95% CI = 0.53–0.86, *P* = .0013).[vii] ***"A big positive is the median PFS not being met and the side effects look no worst than compared to the comparator. If I got 5 years, I would be delighted but I'm not expecting it. It brings me back to my own prognosis. But if I had the choice, I would go for it."*** This maintenance treatment would be highly desired by patients as it would keep their myeloma under control and in remission for longer. Considering that the first remission is likely to be the longest and deepest remission this is the best opportunity for patients to retain a relatively high quality of life (QOL). ***"The aim is to maintain the best possible quality of life for as long as possible."*** ***"For an extra drug with a deeper response and increased remission….. I would have bitten your hand off. Achieving a complete response would be a big win."*** The ability to now have daratumumab subcutaneously is also highly valued by patients.

	"I honestly can't pin any side effect to the daratumumab. I did react to the first infusion but I knew that was likely to happen….. Because the dara is now an injection as opposed to infusion, I take my pre- meds before I leave for the hospital, and I can be in and out in 15 minutes or so." It is now becoming standard clinical practice to treat myeloma with as many treatments with different mechanisms of action as possible up front. Daratumumab is a CD38 monoclonal antibody and there is currently no treatment with this mechanism of action licensed at this point in the treatment pathway. Therefore, this would be an innovative change to the treatment pathway. Myeloma patients who are ineligible to receive HDT-SCT, can often perceive that they are receiving a less effective treatment. It is very important therefore for patients and their families to know that the MAIA trial has shown that patients in the non-intensive pathway can have a near equivalent response to those patients undergoing HDT-SCT, providing much needed reassurance that they are receiving the best possible treatment regardless of their age or fitness. Finally, patients also desire treatments with minimal negative impact on quality of life, particularly those with as few side effects as possible and of low severity. In our engagement with patients across the myeloma pathway many have described daratumumab as a *"kinder"* treatment to take which does not increase toxicity in combination with other treatments. That said, data shows that patients will accept even severe side effects if the treatment has a superior efficacy, suggesting that efficacy is the strongest driver of treatment choice. ***"At the early stage of diagnosis and treatment, the most important thing for me was to get a degree of confidence that the treatment would be successful and give a good remission time. For me, I was happy to deal with the side effects (within reason)."***

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	***"The frustrating thing is I have never had any symptoms of the myeloma, it has all been treatment related side effects."*** Patients value treatments with fewer side effects with low severity ratings which stop when treatment ends. However, in practice patients will accept varying levels of toxicity in a treatment if it delivers good survival benefit and depending on the stage of their myeloma. The most common toxicities in the MAIA trial were grade 3/4 neutropenia (54% vs 37%), and grade 3/4 infections (41% vs 29%; pneumonia in 19% vs 11%); side effects causing the discontinuation of treatment 13% vs 23%; and, treatment-related deaths were comparable in the two groups (4% vs 3%).[viii] Overall adding daratumumab to lenalidomide and dexamethasone did not increase overall toxicity. The dosing schedule used is typical of real-world practice, and adverse events were clinically manageable and consistent with the known toxicities of daratumumab, lenalidomide and dexamethasone. Furthermore, some patients see symptoms and side effects as something to be expected as part of their disease and/or treatment, with many patients developing self-care strategies. ***"I am worried about relapsing. It then becomes another year of being unwell. When you are on chemo your life is severely restricted but if the doctor says you have got to do it then you have got to do it."*** When discussing side effects with patients some were concerned about the level of toxicity that a triplet combination might bring. However, one patient did say: **"*The number of drugs, 3 or 4 is irrelevant to me, it's the effectiveness of the treatment."*** The addition of daratumumab to Rd could mean extra hospital visits to receive the daratumumab by IV infusion. This does mean taking time out of the day to attend hospital. For some patients there are cost/capability issues associated with this and it can place an additional burden on carers who may have to accompany the patient to hospital.

	Our patient engagement has shown that there are also patients who welcome their treatment being delivered in the safety of a hospital environment and the opportunity to interact with clinical staff and other patients. However, mostly oral treatments are often valued by patients, particularly those who are working and have dependents. As said above the ability to have daratumumab subcutaneously would be highly appreciated by patients. Overwhelmingly though, clinical efficacy and the opportunity of a good remission outweighs any disadvantages in the method of administration.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	It is generally expected that the number of myeloma patients, especially of elderly patients, will increase worldwide in the future. This is in parallel with the increased life expectancy of the average population and the improved survival as the result of applying newer and better anti-myeloma agents. The individual and heterogeneous nature of myeloma means that some patients may tolerate a treatment well and others may not. In addition, myeloma evolves and becomes resistant to treatment. It is therefore essential to have a range of treatment options with different mechanisms of action at all stages of the myeloma pathway. As discussed above, for newly diagnosed myeloma patients it is clinical practice to assess their fitness level and tolerability for a stem cell transplant. There are a small number of patients who will exist at the border of being eligible/ineligible for a stem cell transplant. They may feel anxious about undergoing an intensive procedure such a stem cell transplant or the period of isolation. If this treatment were to be approved, then it would give this group of patients greater choice and re-assurance that they can receive an effective treatment. ***"I can still go back and do a stem cell transplant, but I am not too sure if I want to. I am not too keen on the isolation. No proper evaluation has been done to compare a stem cell transplant against the newer treatments which are available. They could be just as effective as a stem cell transplant."***

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	As stated above daratumumab is available for newly diagnosed patients with multiple myeloma who are *eligible* for HDT-SCT (TA763). We would like to see equity of access to this innovative treatment for all newly diagnosed patients with multiple myeloma.

Other issues

13. Are there any other issues that you would like the committee to consider?	No

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• The patient population covered in this appraisal make up more than half of all myeloma patients. They are generally older; they can be frailer/less fit and cannot tolerate intensive treatments such as a stem cell transplant. • However, they do need the best opportunity to achieve a deep remission and maintain a good standard of quality of life. For this, patients need treatments with as many different mechanisms of action as possible. • Data from the MAIA trial has shown that patients in the non-intensive pathway can have a near equivalent response to those patients undergoing HDT-SCT. Approving this treatment will provide much needed reassurance that this patient group are receiving the best possible treatment regardless of their age or fitness. • Adding daratumumab to lenalidomide and dexamethasone did not increase overall toxicity and has been described as a “kinder” treatment for myeloma. • Finally, daratumumab is an innovative therapy which has become a key treatment in the myeloma pathway. It is available for newly diagnosed patients who are eligible for HDT-SCT. We would like to see daratumumab with this mechanism of action available for all newly diagnosed myeloma patients.

Thank you for your time.

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Please select YES if you would like to receive information about other NICE topics - YES

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[i] Most patients can be successfully treated at relapse, however, each remission is usually associated with diminishing duration and depth of response over time. (Bird, S.A. and Boyd, K., (2019). Multiple myeloma: an overview of management. Palliative Care and Social Practice, 13, p.1178224219868235.)
[ii] *A Life in Limbo: A Myeloma UK research report on the experience of myeloma carers in the UK* 2016: https://www.myeloma.org.uk/documents/a-life-in-limbo/
[iii] Cook G et al. A clinical prediction model for outcome and therapy delivery in transplant-ineligible patients with myeloma (UK Myeloma Research Alliance Risk Profile): a development and validation study. Lancet Haematol. 2019 Mar;6(3):e154-e166. doi: 10.1016/S2352-3026(18)30220-5. Epub 2019 Feb 6. PMID: 30738834; PMCID: PMC6391517.
[iv] Rampotas A, Djebbari F, Panitsas F, et al. Efficacy and tolerability of VCD chemotherapy in a UK real- world dataset of elderly transplant-ineligible newly diagnosed myeloma patients. Eur J Haematol. 2021;106:563–573. https://doi.org/10.1111/ejh.13588
[v] Ibid
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[vii] Ibid
[viii] Ibid

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

[ID4014] - Daratumumab with lenalidomide and dexamethasone for untreated multiple myeloma when stem cell transplant is unsuitable

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you

1. Your name	[redacted]
2. Name of organisation	UK Myeloma Forum
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? **Yes** or No A specialist in the treatment of people with this condition? **Yes** or No A specialist in the clinical evidence base for this condition or technology? **Yes** or No Other (please specify):
5a. Brief description of the organisation (including who funds it).	UK Myeloma Forum is the only organisation that represents Physicians, Nursing staff, Pharmacists and Healthcare professional who are directly involved with providing clinical care or research for patients with myeloma. Membership is free by application and members of the executive are elected by the membership. It aims to improve the care of myeloma patients through the development and promotion of trials and provides education about myeloma to healthcare professionals.
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	UKMF has received an unrestricted educational grant from Janssen-Cilag (£12,000 per annum), and BMS-Celgene (BMS, £12,000 per annum). UKMF has also received unrestricted educational grants from other pharmaceutical companies.
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Myeloma is currently incurable. Most people diagnosed with myeloma will die as a result of complications of the disease. Symptoms and signs associated with active myeloma include bone pain, fractures secondary to bone deposits, fatigue, anaemia, recurrent infections, renal failure, high calcium levels and occasionally spinal cord compression. Treatment is primarily aimed at reducing these symptoms by controlling the disease. There is a direct association between how well the myeloma is controlled and the improvement in quality of life. Patients are clinically better if in complete response rather than partial response. Additional aims of treatment are to control the disease (and thereby symptoms) for as long as possible (i.e. lengthen the progression free survival / duration of response), lengthen life associated with the disease (i.e. increase overall survival) and prevent significant morbidity associated with progression of the disease.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	There are internationally agreed criteria for assessing response (International Myeloma Working Group Rajkumar et al. Blood 2011;117:4691-4695) These are based on the proportional reduction of serum paraprotein / serum free light chains (serological markers of myeloma), urine monoclonal protein and the bone marrow proportion of myeloma plasma cells. Generally, a Partial Response (PR) or better is considered clinically significant. Increasingly with more efficacious treatments the aim of the therapy is to achieve Complete Response (CR) or Very Good Partial Response (VGPR) for as many patients as possible. It is apparent in many studies that the greater the depth of response the longer the duration of the response (CR>VGPR>PR). Patients who achieve a CR have a longer survival than those who do not. Achieving minimal residual disease (MRD) is associated with an even longer duration of response and overall survival.

8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. Myeloma is incurable with current therapy for the majority of patients. First line therapy should be aimed at achieving the highest possible response rates and the deepest possible responses leading to the longest / most durable responses which thereby reduces the morbidity and mortality associated with the myeloma. Currently available first line therapies for transplant ineligible patients are Lenalidomide Dexamethasone (TA587) for those patients who are intolerant of Thalidomide, or a Bortezomib based regimen often given in combination with an alkylator such as Cyclophosphamide or Melphalan with Dexamethasone/Prednisolone, available via routine commissioning. A small number of patients may receive a Thalidomide based regimen (TA228). Although the majority of patients do respond to these therapies, there is a significant group that do not respond. Importantly the duration of response is often limited to 1-2 years, before a change in therapy is required. Gaining a good response with maximal disease control that is durable is imperative to limit complications related to myeloma and improve quality of life. It will also allow patients to be well enough to receive further treatment at relapse. This is often not possible with the current therapies for this elderly and often frail group of patients. There is therefore a clear unmet need to provide better treatments to induce a longer and more durable period of remission and limit, or prevent, myeloma associated complications.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	Currently available first line therapies for transplant ineligible patients are Lenalidomide Dexamethasone (TA587) for those patients who are intolerant of Thalidomide, or a Bortezomib based regimen often given in combination with an alkylator such as Cyclophosphamide or Melphalan with Dexamethasone/Prednisolone, available via routine commissioning. A small number of patients will receive a Thalidomide based regimen (TA228).
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	There are several options available to clinicians to treat patient with Myeloma who are not eligible for stem cell transplantation. Whilst there will be variation in practice, in my experience most patients in this category are treated with Lenalidomide and Dexamethasone, with a significant minority receiving a Bortezomib based regimen. It would unusual for patients to receive a Thalidomide based regimen as Lenalidomide is a better tolerated oral regimen.

9c. What impact would the technology have on the current pathway of care?	Daratumumab is a well-tolerated treatment that is widely used. It is given in combination with Bortezomib Thalidomide Dexamethasone in transplant eligible patients (TA763), in combination with Bortezomib and Dexamethasone (DVd) as 2nd line therapy (Cancer Drug Fund)), or as monotherapy as 4th line therapy (TA783). Clinicians have widespread experience of delivering this treatment and dealing with any associated toxicities. Daratumumab would be given in addition to Lenalidomide. It would easily fit into the current treatment algorithm and would be easily delivered.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Daratumumab would be given in addition to Lenalidomide. It would easily fit into the current treatment algorithm and would be easily delivered.
10a. How does healthcare resource use differ between the technology and current care?	Patients receiving Lenalidomide are receiving an oral based regimen. They would attend hospital for clinic visits, routine blood tests and for infusional treatments (such as bisphosphonates). There would be additional hospital attendance with the addition of Daratumumab to Lenalidomide where patients would need to attend chemotherapy day units on a regular basis. Giving Daratumumab subcutaneously (rather than intravenously) would reduce the amount of time patients spend in hospital. Those patients receiving a Bortezomib based regimen attend hospital on a weekly basis to receive a subcutaneous injection. The healthcare resource for these patients would be similar if they were to receive Daratumumab or Bortezomib. As mentioned, it is unlikely there are many patients receiving a Thalidomide based regimen. The same issues would apply as to those receiving Lenalidomide.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist clinics
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	None. Daratumumab is currently used in 1st, 2nd and 4th line as mentioned above. There is extensive UK experience of this drug.

11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes. The addition of Daratumumab to Lenalidomide and Dexamethasone improves both progression free and overall survival. These are both important outcomes. Importantly there are no safety concerns. See response below.
11a. Do you expect the technology to increase length of life more than current care?	Data from the phase III MAIA trial indicates that the addition of Daratumumab to Lenalidomide Dexamethasone induces deeper responses to treatment and increases both progression free survival and overall survival, compared to Lenalidomide Dexamethasone (considered a standard of care in UK clinical practice). The primary endpoint of the trial was progression-free survival, which was centrally assessed, and a secondary endpoint was overall survival (both assessed in the intention-to-treat population) At a median follow-up of 56·2 months (IQR 52·7–59·9) • Median progression-free survival was not reached (95% CI 54·8–not reached) in the daratumumab group versus 34·4 months (29·6–39·2) in the control group (hazard ratio [HR] 0·53 [95% CI 0·43–0·66]; p<0·0001). • Median overall survival was not reached in either group (daratumumab group, 95% CI not reached–not reached; control group, 95% CI 55·7–not reached; HR 0·68 [95% CI 0·53–0·86]; p=0·0013). • There was no concerning treatment-emergent adverse events • Treatment-related deaths were similar in the Daratumumab group (4% patients) and the control group (3% patients). Facon et al, Lancet Oncology Volume 12, Issue 11, P1582-1596, Nov 01, 2021
11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes. This is a well-tolerated regiment with limited and manageable side effect profile. There are no additional concerning adverse events with Daratumumab given in combination with Lenalidomide and Dexamethasone vs Lenalidomide Dexamethasone in the Phase III MAIA trial.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	Daratumumab is widely used. Healthcare professional will have experience of administration and dealing with potential complications. There will be additional health resources needed to deliver the addition of Daratumumab to the standard of care. Patients will need to spend more time on day units to receive Daratumumab. As Daratumumab will be delivered on the same day as Bortezomib the number of days at home or in hospital is unchanged. It is unlikely there will be added side effects with this new therapy.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Response is based on clinical response to treatment after between 2 and 4 cycles of induction treatment.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Yes. Quality of life is likely to be improved due to reduced myeloma associated complications.

16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes, this is the first in class monoclonal antibody to be licenced in multiple myeloma. Its use in first line treatment induces increased depth and durability of response reducing both morbidity and overall survival in what still remains a generally incurable but increasingly chronic disease.
16a. Is the technology a 'step-change' in the management of the condition?	Yes because it improves depth of response which correlates with improved survival. This will lead to reduced myeloma associated complications.
16b. Does the use of the technology address any particular unmet need of the patient population?	
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Daratumumab is well tolerated and unlikely to have any impact on quality of life. Significant infusion related events are unusual, manageable and are usually only associated with the first infusion. There are no other concerning side effects.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	MAIA study reflects how Lenalidomide Dexamethasone is given in current UK clinical practice. The addition of Daratumumab would reflect current experience of this drug. As mentioned there has been a move away from intravenous to subcutaneous Daratumumab as this is well tolerated and patients spend less time in hospital.

18a. If not, how could the results be extrapolated to the UK setting?	See comment above
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Depth of response. sCR, CR and MRD were measured in this trial. Survival has been assessed using PFS and OS. Toxicity was assessed and no concern has been highlighted.
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	sCR, CR and MRD were measured in this trial as surrogates for long term survival. There is a wealth of data to support depth of response correlating with long term survival. Importantly the MAIA study reports improvement in progression free and overall survival.
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA658]?	No

21. How do data on real-world experience compare with the trial data?	Reported outcome for the control arm (Lenalidomide Dexamethasone) reflects expected outcome in clinical practice in the group of patients reported in the phase III MAIA study.

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
22b. Consider whether these issues are different from issues with current care and why.	No

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.	• Comparator in the MAIA study is equivalent to UK practice • Daratumumab is well tolerated, there is widespread experience of using this drug • There are many unmet needs for myeloma patients • Improvement in progression free survival and overall survival with the addition of Daratumumab to Lenalidomide as reported in the MAIA study are undoubtably clinically meaningful outcomes • The reported outcomes for D-Rd in a phase 3 trial are internationally considered to set a new gold standard for 1st line treatment of newly diagnosed transplant ineligible myeloma

Thank you for your time.

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Daratumumab with lenalidomide and dexamethasone for untreated multiple myeloma when stem cell transplant is unsuitable [ID4014]
A Single Technology Appraisal

Produced by Bristol Technology Assessment Group, University of Bristol

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None of the Bristol TAG authors have any conflicts of interest to declare. Of our clinical advisors: Dr. Moore declares honoraria to contribute to an advisory board for Janssen and Dr. Hunter chairs the South West Myeloma group which receives funds from Janssen and others.

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Rider on responsibility for report
The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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Contributions of authors

JC and NJW critiqued the health economic analysis submitted by the company. DC, CC, RJ and ET summarised and critiqued the clinical effectiveness data reported within the company's submission. HP and NJW critiqued the statistical aspects of the submission. CC critiqued the company's search strategy. HH and SM provided advice on clinical aspects of the report. All authors were involved in drafting and commenting on the final report.

[redacted]

[redacted]

Abbreviations

Abbreviations	Definition
AEs	Adverse Events
AFT	Accelerated Failure Time
AIC	Akaike Information Criteria
ASCT	Autologous Stem Cell Transplant
ATT	Average Treatment effect on the Treated
BCd	Bortezomib with Cyclophosphamide and dexamethasone
Bd	Bortezomib and dexamethasone
BIC	Bayesian Information Criterion
BLd	Bortezomib with Lenalidomide and dexamethasone
BMP	Bortezomib with Melphalan and Prednisone
BNF	British National Formulary
BSA	Body Surface Area
CDF	Cancer Drugs Fund
CEA	Cost-Effectiveness Analysis
CKD	Chronic Kidney Disease
CMU	Commercial Medicines Unit
CR	Clinical Response
CRD	Centre for Reviews and Dissemination
CS	Company Submission
CTd	Cyclophosphamide, Thalidomide, and Dexamethasone
DBd	Daratumumab, Bortezomib, and Dexamethasone
DIC	Deviance Information Criteria
DFS	Disease-free Survival
DLd	Daratumumab with Lenalidomide and dexamethasone
DOR	Duration of Response
DSU	Decision Support Unit
eMIT	electronic Market Information Tool
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire Core 30
ECOG	Eastern Cooperative Oncology Group
EQ-5D-5L	EuroQol 5 dimensions 5 level
EAG	Evidence Assessment Group
EBMT	European Society for Blood and Marrow Transplantation
HR	Hazard Ratio
HRQoL	Health-Related Quality of Life
HSE	Health Survey England
ICER	Incremental Cost Effectiveness Ratio
IgG	Immunoglobulin G
IPCW	Inverse Probability of Censoring Weighting
IPD	Individual Participant Data
IPW	Inverse Probability Weighting

Abbreviations	Definition
ISS	International Staging System
IV	Intravenous
IMWG	International Myeloma Working Group
KM	Kaplan-Meier
Ld	Lenalidomide and dexamethasone
LDH	Serum Lactate Dehydrogenase
MAIC	Matching Adjusted Indirect Comparison
MPT	Melphalan, Prednisone and Thalidomide
MDRD	Modification of Diet in Renal Disease formula
MM	Multiple Myeloma
MRC	Medical Research Council
MRD	Minimal Residual Disease
MSM	Multi-State Model
NDMM	Newly Diagnosed Multiple Myeloma
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NMA	Network Meta-Analysis
NR	Not Reported
ORR	Overall Response Rate
OS	Overall Survival
PAS	Patient Access Scheme
PD	Progressed Disease
PF	Progression-Free
PFS	Progression-Free Survival
PFS2	Progression-Free Survival on next line of therapy
PH	Proportional Hazards
PS	Propensity Score
PSA	Probabilistic Sensitivity Analysis
PSM	Partitioned Survival Model
PSS	Personal Social Services
PY	Probably Yes
QALY	Quality-Adjusted Life Year
QoL	Quality of Life
RCT	Randomised Controlled Trial
RDI	Relative Dose Intensity
RoB	Risk of Bias
ROBIS	Risk Of Bias in Systematic Reviews tool
RR	Response Rate
RWE	Real World Evidence
SC	Subcutaneously
SD	Standard Deviation

Abbreviations	Definition
SLR	Systematic Literature Review
SoC	Standard of Care
STA	Single Technology Appraisal
TA	Technology Appraisal
TAG	Technology Assessment Group
TEAE	Treatment Emergent Adverse Event
TMSG	Turkish Society of Haematology Myeloma Study Group
TSD	Technical Support Document
TTD	Time To Treatment Discontinuation
TTP	Time To disease Progression
uITC	unanchored Indirect Treatment Comparison
UK	United Kingdom
VGPR	Very Good Partial Response
WHO	World Health Organisation

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1 EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the evidence assessment group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs). Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail. Section 1.7 provides a summary of the EAG's preferred assumptions and resulting ICER. Background information on the condition, technology and evidence and information on non-key issues are in the main EAG report (Section 2).

All issues identified represent the EAG's view, not the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Overview of the EAG's key issues

TABLE 1: KEY ISSUES

ID4014	Summary of issue	Report sections
Key Issue 1	Are thalidomide containing therapies a comparator at 1st line?	Section 2.2
Key Issue 2	Are results of MAIA generalisable to the NHS in England, considering currently available routine treatments?	Section 3.2.1
Key Issue 3	Is there sufficient follow-up for robust estimation of overall survival?	Section 3.2.2.2
Key Issue 4	Are the studies in the NMA similar enough for reliable inference?	Sections 3.3.1 and 3.4.2

Key Issue 5	What is the preferred source of evidence for the comparison of BMP vs DLd, the HR NMA, the Parametric NMA, the Piecewise NMA, or the unanchored indirect treatment comparison?	Sections 3.4.2, 3.4.4, and 4.2.6.2
Key Issue 6	Is it reasonable to assume equivalence between BMP and BCd?	Section 3.4.4.2 and 4.2.6.2
Key Issue 7	Should CDF drugs used at 2nd line and beyond be included in the company's model?	Sections 4.2.4.2 and 4.2.8
Key Issue 8	Which are the most appropriate parametric models for PFS, OS, and TTD for DLd, Ld, and BMP?	Section 4.2.8
Key Issue 9	Would the treatment effect for OS be maintained for a patient's lifetime or would there be waning of effect?	Section 4.2.6.2
Key Issue 10	Are the MAIA or ALCYONE health-state utilities more appropriate?	Section 4.2.7.2
Key Issue 11	Should costs for dose-reductions using RDIs be included in the model?	Section 4.2.8
Key Issue 12	What is the most appropriate market share of treatments used at 2nd and 3rd line in England?	Section 4.2.8

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are:

1. Applying a HR for BCd vs BMP for PFS and OS (as in Company Clarification Response Scenario3)
2. Using the piecewise NMA model to estimate HRs for BMP for PFS (excluding Hungria and Myeloma IX) and the parametric NMA for OS (EAG Scenario 2c)
3. Using the same parametric family (Gompertz) for OS extrapolations for Ld, DLd (EAG Scenario 4b)
4. Using the same parametric family (Weibull) for PFS extrapolations for Ld, DLd (EAG Scenario 5)
5. Using Exponential distribution for TTD for DLd (EAG Scenario 6b)
6. Treatment waning starts at 12 years for a duration of 7 years until HR=1 at 19 years (EAG Scenario 7c)

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the additional cost for every additional QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Increasing the time spent in the progression-free health state
- Assuming that the overall survival (OS) benefits are maintained for the whole duration of the time horizon (i.e. no waning of treatment benefits)

Overall, the technology is modelled to affect costs by:

- Increased treatment acquisition costs for 1st line treatment (DLd) compared with other treatment options
- Higher costs in the progression-free heath state due to higher resource use and adverse events
- Lower costs in the post-progression state due to lower acquisition costs for 2nd line treatment following 1st line DLd (slightly lower than Ld and substantially lower than for other 1st line treatments)

The modelling assumptions that have the greatest effect on the ICER are:

- Assumptions about treatment effect waning
- Incorporating dose reductions in the costs by using Relative Dose Intensities (RDIs)
- Parametric curve used to extrapolate Time to Treatment Discontinuation (TTD)
- Market share of subsequent treatments at 2nd and 3rd line

1.3 The decision problem: summary of the EAG's key issues

Issue 1: Are thalidomide containing therapies a comparator at 1st line?

Report section	Section 2.2
Description of issue and why the EAG has identified it as important	Thalidomide containing therapies are listed as a comparator in the NICE scope, but the company argues that these are rarely used in practice. The EAG agrees with the company, but notes this issue is important to determine which treatments DLd should be compared with.
What alternative approach has the EAG suggested?	None.
What is the expected effect on the cost-effectiveness estimates?	The incremental cost-effectiveness ratios (ICERs) for DLd compared with thalidomide containing therapies give different pairwise ICERs than those compared with Ld. However, Ld dominates thalidomide combinations in most scenarios explored.
What additional evidence or analyses might help to resolve this key issue?	Views of clinical experts on current practice.

1.4 The clinical effectiveness evidence: summary of the EAG's key issues

All ICERs reported in this section include the Patient Access Scheme (PAS) price for daratumumab.

Issue 2: Are results of MAIA generalisable to the NHS in England, considering currently available routine treatments?

Report section	Section 3.2.1
Description of issue and why the EAG has identified it as important	The external validity of MAIA is limited by the non-trivial proportion of participants who received 2nd and 3rd line therapies that are not routinely commissioned by NHS England.
What alternative approach has the EAG suggested?	The EAG requested a subgroup analysis by UK versus non-UK centres for PFS and OS. There was no robust evidence of a subgroup effect. However, the UK centre subgroup was very small (DLd: n=[redacted] and Ld: n=[redacted]) (data provided in response to clarification question C.4.) The EAG performed scenario analyses to the costs of subsequent treatments.
What is the expected effect on the cost-effectiveness estimates?	Unclear, but the ICERs are very sensitive to assumptions on the subsequent treatments used 2nd and 3rd line (see Issue 7 and Issue 12)
What additional evidence or analyses might help to resolve this key issue?	Some non-routine treatments used at 2nd and 3rd line in MAIA are currently accessible via the CDF. Information on timescales for the appraisals of treatments currently in the CDF in relation to the timescale for this appraisal.

Issue 3: Is there sufficient follow-up for robust estimation of Overall Survival?

Report section	Section 3.2.2.2
Description of issue and why the EAG has identified it as important	Results are provided from the 21st October 2021 data-cut and while there is a median follow-up of 64.5 months the overall survival data is still immature (median only just reached for Ld arm, and not yet reached for DLd arm). This means the extrapolations for overall survival and implied treatment differences in survival are uncertain.
What alternative approach has the EAG suggested?	The EAG has explored different extrapolations and treatment waning scenarios.
What is the expected effect on the cost-effectiveness estimates?	Overall survival for DLd has the largest impact on the ICER in the company's deterministic sensitivity analyses. See also Issue 8 and Issue 9

What additional evidence or analyses might help to resolve this key issue?	Longer follow-up would help to resolve this uncertainty. The company stated the final MAIA OS analysis is estimated to occur in [redacted].

Issue 4: Are the studies in the NMA similar enough for reliable inference?

Report section	Sections 3.3.1 and 3.4.2
Description of issue and why the EAG has identified it as important	The company considers the studies in the NMA to be heterogeneous and instead prefers to use single arms from the MAIA and ALCYONE studies to make an unanchored (observational) indirect comparison between BMP and Ld (See Issue 5). The company do, however, use the NMA for comparisons with MPT and CTd, creating an inconsistency in the evidence used for comparisons for different treatments. The EAG agrees that there are some differences between the study characteristics of the studies in the NMA, in particular the HUNGRIA and MYELOMA IX studies which connect CTd to the network. However, the CS notes that their sensitivity analysis excluding HUNGRIA from the network did not considerably impact the results.
What alternative approach has the EAG suggested?	The EAG has conducted further sensitivity analyses to inclusion of studies in the NMA to assess the robustness of results on clinical and cost-effectiveness.
What is the expected effect on the cost-effectiveness estimates?	For the comparison between BMP and Ld, the NMA results are robust to inclusion of different studies comparing MPT vs MP. NMA results and ICERs were not sensitive to excluding CTd studies from the network. However, as inclusion of CTd studies may introduce inconsistency and add little precision, the EAG prefer to exclude them from the network. These results run counter to the company's rationale for preferring the unanchored Indirect Treatment Comparison (uITC) on the basis that the studies in the NMA are too heterogeneous. See Issue 5.

What additional evidence or analyses might help to resolve this key issue?	Given the limitations in the available evidence the NMA scenario analyses conducted by the company and EAG are most appropriate to explore this issue.

Issue 5: What is the preferred source of evidence for the comparison BMP vs DLd, the HR NMA, the Parametric NMA, the Piecewise NMA, or the unanchored indirect treatment comparison?

Report section	Sections 3.4.2, 3.4.4, and 4.2.6.2
Description of issue and why the EAG has identified it as important	The relative efficacy of Ld vs BMP (and hence DLd vs BMP) depends on whether the unanchored indirect comparison or the NMA is used. The company prefers to use single arms from the MAIA and ALCYONE studies to make an unanchored (observational) indirect comparison between BMP and Ld, rather than use their NMA that assumes proportional hazards. This is because proportional hazards does not hold in the included studies and the NMA estimates are less precise due to the path of indirect comparisons. The EAG considers that the observational comparison may be subject to bias from unmeasured confounders and prefers an NMA analysis that does not assume proportional hazards because it relies on randomised evidence. See also Issue 4
What alternative approach has the EAG suggested?	The EAG suggested fitting NMA models that do not assume proportional hazards. The company provided two alternative approaches: (i) a parametric NMA model which estimates treatment effects for the parameters of a survival curve family, and (ii) a piecewise NMA model where the hazard ratio differs before and after 20 months for the FIRST study progression free survival outcome. The company did not provide data for the parametric NMA and so the EAG could not explore alternative parametric assumptions. The company only provided piecewise hazard ratios for the FIRST study and for the progression free survival outcome and so the EAG could not explore piecewise hazard ratios for the other studies nor for overall survival.
What is the expected effect on the cost-effectiveness estimates?	The ICER for DLd vs BMP varies from [redacted] in the company's updated base-case using the unanchored indirect comparison to [redacted] using the piecewise NMA. It is unclear what the impact would be of different

	parametric assumptions in the parametric NMA and incorporating piecewise hazard ratios for other studies and for overall survival in the piecewise NMA.
What additional evidence or analyses might help to resolve this key issue?	Further analyses exploring different parametric assumptions in the parametric NMA and incorporating piecewise hazard ratios for other studies and for overall survival in the piecewise NMA.

Issue 6: Is it reasonable to assume equivalence between BMP and BCd?

Report section	Section 3.4.4.2 and 4.2.6.2
Description of issue and why the EAG has identified it as important	There is no randomised evidence connecting BCd to any of the other treatments in the NMA. As such, the company assumed equal efficacy of BMP and BCd, supported by an (observational) Matched Adjusted Indirect Comparison (MAIC) using single arm evidence from ALCYONE (1) and Jimenez-Zepeda (2), as well as naïve comparisons from two observational sources of evidence and clinical opinion. However, the MAIC analysis resulted in a hazard ratio suggesting that BCd may be more effective than BMP for progression free survival, and the estimate for overall survival was in the same direction but very uncertain. This assumption has an impact on the benefits of DLd compared with BCd.
What alternative approach has the EAG suggested?	The EAG has suggested using the hazard ratios estimated by the company to obtain the efficacy for BCd rather than assume they have equivalent efficacy.
What is the expected effect on the cost-effectiveness estimates?	The ICER for DLd vs BCd increases from [redacted] in the company's updated base-case, to [redacted].
What additional evidence or analyses might help to resolve this key issue?	Ideally a randomised comparison of BCd compared to one of the treatments in the network would help resolve this issue, but this evidence is not available.

1.5 The cost-effectiveness evidence: summary of the EAG's key issues

All ICERs reported in this section include the Patient Access Scheme (PAS) price for daratumumab.

Issue 7: Should CDF drugs used at 2nd line and beyond be included in the company's model?

Report section	Sections 4.2.4.2 and 4.2.8
Description of issue and why the EAG has identified it as important	The company presents results including or excluding subsequent treatments at 2nd line and beyond that are currently available via the Cancer Drugs Fund (CDF). They argue that including CDF treatments is relevant as these may be available in routine commissioning soon. This issue is important because it has a big impact on the cost-effectiveness results for some comparisons.
What alternative approach has the EAG suggested?	The EAG prefers not to include subsequent CDF treatments because it is currently unknown if they will become available and if so at what price.
What is the expected effect on the cost-effectiveness estimates?	The ICERs for DLd vs Ld fall from [redacted] to [redacted] when CDF subsequent treatments are included. The ICERs compared with BMP and BCd also fall, whereas the ICERs compared with MPT and CTd increase.
What additional evidence or analyses might help to resolve this key issue?	Information on timescales for the appraisals of treatments currently in the CDF in relation to the timescale for this appraisal.

Issue 8: Which are the most appropriate parametric models for PFS, OS, and TTD for DLd, Ld, and BMP?

Report section	Section 4.2.8
Description of issue and why the EAG has identified it as important	Progression free survival (PFS) and overall survival (OS) are extrapolated beyond the trial data for DLd, Ld, and BMP, and time to treatment discontinuation (TTD) is extrapolated for DLd and Ld. Because the survival data are immature these extrapolations are uncertain. The company chose survival curves based on model fit validated against elicited clinical opinion. However, other parametric choices could have been chosen that give similar fit to the data and clinical opinion, but different long-term predictions.

What alternative approach has the EAG suggested?	The EAG has run scenario analyses to different choices of parametric survival curves.
What is the expected effect on the cost-effectiveness estimates?	The ICERs are sensitive to the choice of parametric model for Time to Treatment Discontinuation (TTD) for DLd with the ICER for DLd vs Ld ranging from [redacted] for Generalised Gamma, [redacted] for Gompertz, and [redacted] for Exponential. The ICER for the comparison DLd vs Ld was robust to choices of parametric curve for OS and PFS.
What additional evidence or analyses might help to resolve this key issue?	Longer follow-up could help to resolve this uncertainty if TTD will be collected. The company stated the final MAIA OS analysis is estimated to occur in [redacted].

Issue 9: Would the treatment effect for OS be maintained for a patient's lifetime or would there be waning of effect?

Report section	Section 4.2.6.2
Description of issue and why the EAG has identified it as important	As noted in key issue 2 the model extrapolates overall survival for a long time beyond the available evidence from the MAIA trial, and so there is uncertainty as to how long a treatment benefit would last and if there is a point at which the hazard ratio for DLd vs Ld starts to wane back towards 1 (no difference in hazard). This is important because overall survival for DLd has the largest impact on the ICER in the company's deterministic sensitivity analyses.
What alternative approach has the EAG suggested?	The EAG has explored scenarios where treatment effect waning is applied starting at different times with different durations until a hazard ratio of 1 is reached.
What is the expected effect on the cost-effectiveness estimates?	The ICER for DLd vs Ld ranges ranging from [redacted] if waning does not start until 15 years, [redacted] if waning starts at 12 years, [redacted] if waning starts at 10 years, and [redacted] if waning starts at 7 years.
What additional evidence or analyses might help to resolve this key issue?	Longer follow-up would help to resolve this uncertainty. The company stated the final MAIA OS analysis is estimated to occur in [redacted].

Issue 10: Are the MAIA or ALCYONE health-state utilities more appropriate?

Report section	Section 4.2.7.2
Description of issue and why the EAG has identified it as important	Health-related quality of life data showed higher utility in the progression free health state than the post-progression health state in the MAIA study, but little difference between health states in the ALCYONE study. Both studies measured utilities appropriately, and so it is not clear which is to be preferred. The company argue that the values from MAIA have better face-validity, which the EAG considers plausible as the ALCYONE values do not show a difference between pre- and pos-progression. Utilities contribute to the estimated Quality Adjusted Life Years (QALYs)
What alternative approach has the EAG suggested?	The EAG considers the MAIA study utilities that are used in the company's base-case have better face-validity.
What is the expected effect on the cost-effectiveness estimates?	Using the ALCYONE utilities increases the ICER for DLd vs Ld in the company's updated base-case from [redacted] to [redacted].
What additional evidence or analyses might help to resolve this key issue?	Clinical opinion on the face validity of the utilities from MAIA and ALCYONE.

Issue 11: Should costs for dose-reductions using RDIs be included in the model?

Report section	Section 4.2.8
Description of issue and why the EAG has identified it as important	The company's original model did not include the cost reductions associated with the dose-reductions of components of combination therapies that were observed in the MAIA and ALCYONE trials. In their updated base-case the company has included these by implementing relative dose intensities (RDIs) in their model. This impacts on the treatment costs.
What alternative approach has the EAG suggested?	The EAG suggested that the company capture dose-reductions in the treatment costs, which they have done in their updated base case (1st July 2022 version of the model).
What is the expected effect on the cost-effectiveness estimates?	Incorporating dose-reductions in the treatment costs has a big impact on the ICERs, reducing the ICER for DLd vs BMP

	from [redacted] to [redacted], and reducing the ICER for DLd vs Ld from [redacted] to [redacted].
What additional evidence or analyses might help to resolve this key issue?	Clinical opinion on the face-validity of assumed RDIs for each treatment.

Issue 12: What is the most appropriate market share of treatments used at 2nd and 3rd line in England

Report section	Section 4.2.8
Description of issue and why the EAG has identified it as important	There is a wide variation in clinical practice as to subsequent treatments after 1st line treatment. The company used an average of distribution of the market share of treatments at 2nd and 3rd line estimated by a panel of clinical experts. However, there was wide variation in estimates across the panel.
What alternative approach has the EAG suggested?	The EAG has run scenario analyses to see the sensitivity of results to using each of the individual clinical experts estimates of market share of 2nd and 3rd line treatments.
What is the expected effect on the cost-effectiveness estimates?	The ICERs are very sensitive to assumptions on the subsequent treatments used 2nd and 3rd line, ranging from [redacted] to [redacted] in the scenarios we explored.
What additional evidence or analyses might help to resolve this key issue?	It is challenging to see how additional evidence can help resolve this issue due to complexity of treatment pathway, variations in practice and changing treatment landscape.

1.6 Other key issues: summary of the EAG's view

There are no other key issues.

1.7 Summary of EAG's preferred assumptions and resulting ICER

Modelling errors identified and corrected by the EAG are described in Section 4.2.8.2, Section 6.1 and Appendix 5. For further details of the exploratory and sensitivity analyses done by the EAG, see Section 6. Table 2 shows the EAGs preferred assumptions and resulting ICER compared with Ld. Ld dominates all other treatments in each scenario and so comparisons with other treatments are omitted from Table 2. Full details of EAGs scenario analyses and preferred assumptions can be found in Section 6.

TABLE 2: SUMMARY OF EAG'S PREFERRED ASSUMPTIONS

Scenario	Incremental cost	Incremental QALYs	ICER DLd vs Ld (change from company base case)
Deterministic results, excluding CDF Treatments, PAS price for daratumumab			
1. Company updated base-case (including RDIs) with subsequent treatment costs corrected	[redacted]	[redacted]	[redacted]
2. Apply HRs for BCd vs BMP for PFS and OS	[redacted]	[redacted]	[redacted]
3. Piecewise HR NMA for BMP for PFS and HR NMA for OS, both excluding Hungria and Myeloma IX (EAG Scenario 2b)	[redacted]	[redacted]	[redacted]
4. Same parametric family (Gompertz) for OS extrapolations for Ld, DLd, and Gompertz/Weibull mix for BMP (EAG Scenario 4b)	[redacted]	[redacted]	[redacted]
5. Same parametric family (Weibull) for PFS extrapolations for Ld, DLd, and BMP (EAG Scenario 5)	[redacted]	[redacted]	[redacted]
6. TTD use Exponential for DLd (EAG Scenario 6b)	[redacted]	[redacted]	[redacted]
7. Treatment waning starts at 12 years for a duration of 7 years until HR=1 at 19 years (EAG Scenario 7c)	[redacted]	[redacted]	[redacted]
EAG's preferred base case 2+3+4+5+6+7	[redacted]	[redacted]	[redacted]
Probabilistic results, excluding CDF Treatments, PAS price for daratumumab			
Company updated base-case (including RDIs) with subsequent treatment costs corrected	[redacted]	[redacted]	[redacted]
EAG's preferred base case 2+3+4+5+6+7	[redacted]	[redacted]	[redacted]

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

This report provides a critique of the evidence submitted by the company (Janssen) in support of daratumumab with lenalidomide and dexamethasone (DLd) for untreated multiple myeloma (MM) when stem cell transplant is unsuitable. It considers the company

evidence submission (CS) (3) and the company's executable model (original version received on 26/05/2022 and updated model received on 04/07/2022). It also considers the company's response to clarification questions from the EAG received on 04/07/2022.

2.2 Background

Section B.1.3 of the CS provides an accurate overview of MM, its aetiology, epidemiology and prognosis.(3) The mechanisms of action for daratumumab in combination with lenalidomide are described in section B.1.3.8 of the CS.

The CS proposes DLd as a first-line treatment for newly diagnosed MM (NDMM) patients who are ineligible for autologous stem cell transplant (ASCT). The CS (Figure 5, P.23) reports the current and proposed National Health Service (NHS) treatment pathway for MM based on National Institute for Health and Care Excellence (NICE) recommendations in TA587 (4) and TA228 (5) and the company's own consultation regarding current clinical practice.(6) We have reproduced the CS pathway in Figure 1 of the EAG report. Following TA587 and TA228, current first-line therapies are thalidomide with alkylating agent and corticosteroid, bortezomib with alkylating agent and corticosteroid, or lenalidomide with dexamethasone (Ld). The CS states that thalidomide and bortezomib-based regimens are associated with known safety and tolerability issues and that Ld is the preferred standard of care for ASCT ineligible NDMM patients in England. The EAG's clinical advisors agreed that, due to the toxicity profile, thalidomide-containing regimens are rarely used in practice and that lenalidomide was the preferred standard of care. However, they also stated that the bortezomib-based regimens, bortezomib with melphalan and prednisone (BMP) and bortezomib with cyclophosphamide and dexamethasone (BCd), were commonly used as first-line therapies but BCd was better tolerated.

The EAG's clinical advisors also noted there is considerable variation in practice across centres/regions for treatments given at 2nd, 3rd, and 4th line and that this is changing rapidly as the treatment landscape evolves. This variation in clinical practice can also be seen in the estimates of market share elicited from the company's clinical experts.(6). The CS treatment pathway includes Cancer Drug Fund (CDF) treatments at 2nd line and beyond and the EAG note that these treatments may not be available for routine commissioning, after the CDF period ends.

The EAG agrees that the company's proposed positioning of DLd as a first-line therapy is appropriate**.** The EAG's clinical advisors agreed that DLd would be their first line therapy of choice for NDMM ineligible for ASCT if it were available. Both the CS and the patient organisation submissions highlight the current inequity in access to effective treatments for patients with NDMM who are ineligible for ASCT, given the limited treatment options available in comparison to transplant-eligible patients. This sentiment was echoed by the EAG's clinical advisors, who noted that transplant-eligible patients tend to be younger, have fewer co-morbidities and are less frail.

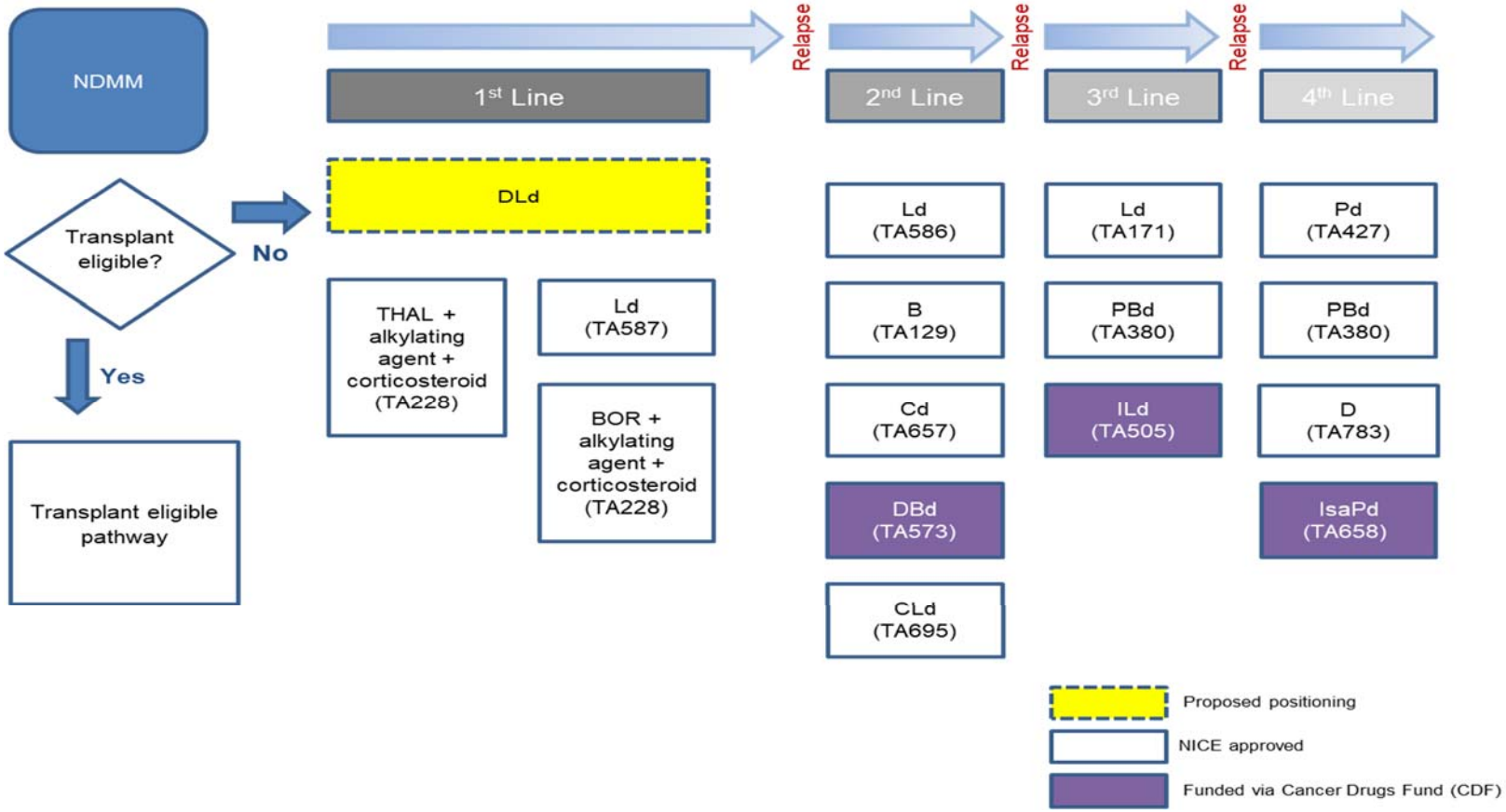
Key issue 1: Are thalidomide containing therapies a comparator at 1st line?

2.3 Critique of company's definition of decision problem

Table 3 summarises the decision problem as outlined in the NICE scope and provides a summary of how this was addressed in the CS.

The CS summary matches the final NICE scope, with the exception that thalidomide-containing combinations are not considered as main comparators. The EAG's clinical advisors agreed with the company that thalidomide is rarely used and that Ld was the most commonly used first-line therapy. In addition, the EAG notes that the CS provides an assessment of the relative effect of DLd versus melphalan with prednisone and thalidomide (MPT), BMP and BCd using indirect treatment comparisons and network meta-analytic methods (See section 3.4 of EAG report) and these are included as comparators in the economic model as a scenario analysis. The EAG accepts the company's definition of the decision problem as defined in the CS.

FIGURE 1: PROPOSED POSITION OF DARATUMUMAB IN THE CURRENT UK NHS MM TREATMENT PATHWAY (REPRODUCED FROM COMPANY SUBMISSION, FIGURE 5) **(3)**



Abbreviations: ASCT; autologous stem cell transplant; B: bortezomib; Bd: bortezomib and dexamethasone; BCd: bortezomib, cyclophosphamide and dexamethasone; BTd: bortezomib, thalidomide and dexamethasone; Cd: carfilzomib and dexamethasone; CDF: Cancer Drugs Fund; D: daratumumab; DBd: daratumumab, bortezomib, and dexamethasone; DBTd: daratumumab, bortezomib, thalidomide and dexamethasone; HDT: high-dose therapy; ILd: ixazomib, lenalidomide and dexamethasone; ITT: intention-to-treat; Ld: lenalidomide and dexamethasone; NDMM: newly diagnosed multiple myeloma; NICE: National Institute for Health and Care Excellence; PBd: panobinostat, bortezomib and dexamethasone; Pd: pomalidomide and dexamethasone

TABLE 3: SUMMARY OF DECISION PROBLEM

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Population	Adults with untreated multiple myeloma when stem cell transplant is unsuitable	Adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant	This wording is in line with the marketing authorisation for DLd and the population of the MAIA trial; (7, 8) otherwise, this is in line with the final NICE scope.	The population assessed in the CS matches the population stipulated in the NICE scope. The EAGs clinical advisors and the company's clinical experts both acknowledged that the age of patients included in the MAIA trial aligns with clinical practice in England.
Intervention	Daratumumab with lenalidomide and dexamethasone	As per scope	NA	The intervention assessed in the CS matches the NICE scope.
Comparator(s)	Thalidomide with alkylating agent and corticosteroid. For people who are unable to tolerate, or have contraindications to thalidomide: • Bortezomib with alkylating agent and corticosteroid • Lenalidomide with dexamethasone	The main comparators considered within this submission are: • Lenalidomide and dexamethasone (Ld) • Bortezomib with alkylating agent and corticosteroid	DLd is positioned as a treatment option for adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant, irrespective of eligibility for thalidomide-containing regimens.	The CS does not consider thalidomide containing regimens as a main comparator, but positions Ld as the standard of care (SoC). The EAG's clinical advisors agreed that thalidomide-based therapies are rarely used

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
		In addition, for completeness, comparisons are provided for: • Thalidomide with alkylating agent and corticosteroid	Clinical expert feedback received by Janssen indicates that Ld represents current NHS SoC with bortezomib with an alkylating agent and corticosteroid used to treat a minority of patients.(3) Given that Ld represents current NHS SoC, and dominates bortezomib- and thalidomide-based therapies in fully incremental cost-effectiveness analysis, results against Ld only are presented in Section B.3 of the CS.(3) Full results vs bortezomib- and thalidomide-based therapies are presented in CS Appendix N.(9)	in clinical practice, with Ld being the preferred SoC. However, they noted that BMP and BCd were commonly used in practice, with centre and regional preference shaping which combination was used.
Outcomes	• Overall survival (OS) • Progression-free survival (PFS) • Response rates	• Overall survival (OS) • Progression-free survival (PFS) • Overall response rate (ORR)	All outcomes requested in NICE's final scope are presented, with additional outcomes included to	The outcomes are consistent with those stated in the NICE scope.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	• Minimal residual disease-negative status • Adverse effects (AEs) of treatment • Health-related quality of life (HRQoL).	• Minimal residual disease (MRD) negativity • Adverse events (AEs) of treatment • Health-related quality-of-life (HRQoL) • Time to disease progression (TTP) • Time to subsequent anticancer therapy • Progression-free survival on next line of therapy (PFS2) • Time to response • Duration of response (DOR)	capture as fully as possible the important health benefits for DLd.	
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.	The cost-effectiveness of the treatments evaluated in this appraisal is expressed in terms of incremental cost per Quality Adjusted Life Year (QALY). A lifetime time horizon over 26 years was adopted to capture all relevant costs and health-related utilities.	N/A – in line with final scope.	EAG is satisfied the economic analysis is in line with NICE scope.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	Costs will be considered from an NHS and Personal Social Services (PSS) perspective. The availability of any commercial arrangements for the intervention or comparator technologies will be taken into account. The availability and cost of biosimilar products should be taken into account.	Costs were considered from an NHS and PSS perspective. All costs and utilities were discounted at a rate of 3.5% per year in alignment with the NICE guide to the methods of technology appraisal.		
Subgroups	No subgroups are identified in the NICE scope.	No subgroups are identified by the company in the decision problem.	NA	EAG considers this in line with scope.
Special considerations including issues related to equity or equality	None	The CS highlights inequity in access to effective treatments, stating that younger, newly diagnosed, transplant-eligible patients have the opportunity to receive effective treatments whereas newly diagnosed patients who are ineligible for transplant do not.	Inequity outlined in CS is not listed in NICE scope.	EAG and EAG clinical advisors agree that there is inequity caused by a lack of access to effective treatments in transplant ineligible patients compared to those eligible for transplant.

BMP = Bortezomib with melphalan and prednisone, BCd = Bortezomib with cyclophosphamide and dexamethasone, CS = Company submission, DLd = Daratumumab with lenalidomide and dexamethasone, EAG = External Assessment Group, Ld = Lenalidomide and dexamethasone, NA = not applicable, NHS = National Health Service, NICE = National Institute for Health and Care Excellence, PSS = Personal Social Services, SoC = Standard of Care

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review

The company conducted three, separate, *de novo* systematic literature reviews (SLR) to identify relevant clinical evidence on the efficacy and safety of DLd for patients with NDMM who are ineligible for ASCT (CS Appendix D).(9). The first SLR (SLR 1) focuses on randomised evidence in-line with the NICE scope. The second and third SLRs attempt to deal with a lack of directly randomised, comparative evidence for DLd and bortezomib based therapies. The CS reports a SLR for single-arm trials (SLR 2) and of observational studies (SLR 3) both focusing on BCd. We summarise the SLRs in
Table 4, focusing on SLR 1 as this identifies the studies used in the base-case for DLd, Ld, BMP, MPT and CTd. For SLR 2 and 3, we provide critique only where we identified concerns with conduct.

On balance, the EAG are content that SLR 1 was conducted adequately and that the randomised studies relevant to this appraisal have been identified. We used the ROBIS tool to support our assessment and the full details are reported in section 8.1 (Appendices). However, the EAG have some concerns regarding the company's decision to abandon SLR 2 without first providing an assessment of study quality for the three studies identified (CS Appendix D.3.7 (9)). The EAG are also concerned by the selection and of use of studies from SLR 3 in the unanchored Indirect Treatment Comparison (uITC) and unanchored Matching Adjusted Indirect Comparison (MAIC).

3.2 Critique of trials of the technology of interest, the company's analysis and interpretation

3.2.1 Study design and methods

The CS identifies a single RCT, referred to as MAIA(10), making the company's preferred comparison of DLd versus Ld. Section B.2.3.1 of the CS summarises the design and methodology of the MAIA trial. Study characteristics are presented in Table 6, page 34 of the CS.(3)

MAIA is a multicentre, open-label, randomised, phase III, parallel group trial that recruited patients across 14 countries. Study enrolment took place between March 2015 and January 2017. Follow up is ongoing and the CS reports at a median follow-up of 64.5 months (21st October 2021 data-cut). The population of interest in MAIA was adult patients with newly diagnosed multiple myeloma who are ineligible for ASCT. The EAG clinical advisors considered this matched the population as defined by the NICE scope. The primary outcome in MAIA was PFS, defined as the time from the date of randomisation to either progressive disease or death, defined according to the International Myeloma Working Group (IMWG) criteria. Secondary outcomes included: overall survival (OS); progression-free survival on next line of therapy (PFS2); time to next treatment; time to response; duration of response

(DOR); time to disease progression (TTP); overall response rate (ORR); complete response rate; stringent complete response rate; better than very good partial response; minimal residual disease (MRD) negativity rate; health-related quality of life (HRQoL); and adverse events (AEs).

Both treatment arms received oral Ld until disease progression or unacceptable toxic effects. Patients in the DLd arm also received intravenous daratumumab once weekly during cycles 1 and 2, every 2 weeks during cycles 3 through 6, and every 4 weeks thereafter. Due to the international design, the CS notes that a variety of 2nd and 3rd line treatments were used (Table 161, CS Appendix R (9)), some of which are not currently available via NHS England, and the exact regimens differed by treatment arm. Most patients progressing to 2nd or 3rd line therapies received a bortezomib-based regimen and the proportions were similar across the DLd and Ld arms. However, across both 2nd and 3rd line therapies combined, a greater proportion of participants in the Ld arm received a subsequent treatment not routinely commissioned in England [redacted] (Table 160, CS Appendix R (9)). In response to the EAG's clarification request, the company provided the numbers of patients receiving every 2nd and 3rd line treatment used in MAIA, by treatment arm. Based on data provided by the company in response to clarification question B.5, the EAG calculates that, of participants progressing to 2nd line therapy, [redacted] in the DLd arm and [redacted] in the Ld arm were given a treatment regimen containing at least one drug currently unavailable via the NHS in England (at 3rd line this was [redacted] and [redacted] respectively).

Key Issue 2: Are results of MAIA generalisable to the NHS in England, considering currently available routine treatments?

TABLE 4: SUMMARY OF THREE SYSTEMATIC LITERATURE REVIEWS (SLRS) CONDUCTED FOR CS

	SLR 1: randomised studies of all comparators	SLR 2: single arm studies of BCd	SLR 3: observational studies of BCd
Aim(s)	To identify and appraise studies reporting randomised trials for DLd vs the comparators listed in the NICE scope OR randomised trials of comparators listed in the NICE scope to support an NMA.	To identify and appraise single arm studies evaluating BCd.	To identify and appraise observational studies evaluating BCd.
Company's rationale for the SLR	A systematic review of direct and indirect randomised evidence was undertaken to align with the NICE scope.	This review supplemented a lack of randomised evidence identified in SLR 1 for BCd.	This review supplemented a lack of randomised evidence identified in SLR 1 and SLR 2 for BCd.
Searches	The searches focused on studies reporting randomised trials for patients at first line treatment receiving DLd OR comparators listed in the NICE scope. The searches were limited to English language, and they identified the randomised evidence relied upon by the company in their submission. A full appraisal of the CS search is reported in Appendix.	As it relates to this submission, the searches focused on BCd in first line treatment. Searches were limited to English language publication.	The searches focused on observational studies for patients at first line treatment receiving at least the interventions OR comparators listed in the NICE scope. The searches were limited to English language.
Inclusion criteria	Treatment regimens were eligible for inclusion: DLd or Ld or BMP or BCd or MPT or CTd. This aligns with NICE scope and the eligibility criteria for the NMA (CS Figure 33).	Single arm studies reporting evaluations BCd were eligible for inclusion.	Observational studies reporting evaluations of BCd were eligible for inclusion.
Study selection	Thirty-three studies were identified with nine studies eligible for inclusion. One study (MAIA) provided direct, head-to-head evidence of DLd to Ld (10). The EAG agrees that MAIA is the only directly relevant study for this appraisal. No head-to-head, randomised comparisons of DLd with either bortezomib or thalidomide-based regimens were identified. The company undertook an NMA which included nine studies (including MAIA). The EAG agree that the decision to undertake an NMA was justified. EAG critique of the methods and modelling assumptions for the NMA is reported in section 3.4.2 of the report.	Three studies evaluating BCd were identified by this SLR.(11-13) The CS subsequently excluded these studies due to the treatment regimen not aligning with review scope(11) and small sample size.(12, 13) SLR 2 is discontinued, with the CS favouring observational data from SLR 3. The EAG are concerned that the study selection process is not transparent for SLR 2.	Seven studies evaluating BCd were identified.(2, 14-19) Only two studies reported efficacy data for BCd: Sandecka (19) and Jimenez-Zepeda. Jimenez-Zepeda was selected as "*a more detailed reporting of baseline characteristics considered likely to be prognostic factors and/or effect modifiers was available*".(9) The EAG are concerned about the justification used to select Jimenez-Zepeda and discuss this further in section 3.3.2.

	SLR 1: randomised studies of all comparators	SLR 2: single arm studies of BCd	SLR 3: observational studies of BCd
Data extraction	Data were extracted on clinical efficacy outcomes (including OS and PFS) and clinical safety outcomes (including discontinuations due to AEs). The EAG are content data extraction aligned with scope and was accurate.	The three studies identified in SLR 2 were not extracted by the CS.	Outcomes were extracted as for SLR 1. However, they are only extracted for Jimenez-Zepeda and not Sandecka.
Quality assessment	The company used the Cochrane RoB tool (RoB V1) and the CRD assessment tool to assess the risk of bias in the MAIA trial and RoB version 1 to assess the studies contributing to the NMA. The use of the Cochrane tool was suitable and the EAG independently repeated the assessment, arriving at a broadly similar conclusion. The EAG note a more recent version of the Risk of Bias tool (20), is preferred as it provides a more robust and appropriate assessment for technology appraisal. The EAG assessed MAIA as low risk of bias (section 3.2.1) and report comparisons between the CS and EAG assessment in Table 5. The EAG report quality assessment of studies included in the NMA at Key Issue 4 and in Table 8. Broadly, the EAG agreed with the company's assessments for the studies included in the NMA. The EAG do not feel that these differences alter the overall understanding of Risk of Bias in the NMA according to RoB tool V1.	No quality assessment was undertaken for the 3 studies. However, the CS argues that not completing SLR 2 was justified as "*more robust data from an observational study was available*", identified from SLR 3. As this is a comparative judgement, requiring quality assessment of the 3 studies identified in SLR 2, the EAG have concerns about the transparency of the study selection process underpinning the uITC and MAIC (section 3.4).	The company undertook quality assessment of Jimenez-Zepeda using the ROBINS-I tool, and graded Risk of Bias at Low overall.(21) The EAG independently repeated ROBINS-I grading the study overall at Critical Risk of Bias. Critical risk of bias means that "*the study is too problematic to provide any useful evidence and should not be included in any synthesis*".(21) The EAG are concerned about the use of Jimenez-Zepeda as a basis for analysis (see 3.3.2).
Evidence synthesis	For the company's preferred comparison of DLd vs Ld, randomised data were available from one study, the MAIA study.(10) No synthesis of evidence was undertaken or required. For comparison of DLd with bortezomib and thalidomide-based regimens, a NMA of RCTs was conducted. See section 3.4 for the EAG's critique of methods and modelling assumptions for the NMA.	Studies identified from SLR 2 did not contribute to statistical analyses.	For DLd vs BMP the CS additionally reports an uITC using Inverse Probability Weightings to match data from MAIA (10), and ALCYONE (1). For DLd vs BCd the CS reports an unanchored MAIC to demonstrate equivalence between BMP and BCd, and therefore assumed the same relative effect for DLd versus BCd as for DLd versus BMP. The EAG had concerns with these approaches, as detailed in section 3.4.4.

AE = adverse event, BMP = Bortezomib with melphalan and prednisone, BCd = Bortezomib with cyclophosphamide and dexamethasone, CS = Company submission, CTd = cyclophosphamide, thalidomide and dexamethasone, DLd = Daratumumab with lenalidomide and dexamethasone, EAG = External Assessment Group, Ld = Lenalidomide and dexamethasone, MAIC = Matching Adjusted Indirect Comparison, MPT = thalidomide with melphalan and prednisone, NICE = National Institute for Health and Care Excellence, NMA=network meta-analysis, OS = overall survival, PFS= progression free survival, RCT = randomised controlled trial, RoB V1= Risk of Bias (version 1), SLR = systematic literature review, uITC = unanchored Indirect Treatment Comparison

Risk of Bias assessment for MAIA

The company assessed RoB using the Cochrane RoB tool version 1 (RoB V1) and rated the overall risk of bias in the MAIA study as low. It is not clear how the company arrived at a low risk of bias due to rating some domains as high risk and unclear risk. For direct comparison with the CS RoB assessment, the EAG undertook an independent review of MAIA using RoB V1 (see Table 5). The EAG rated allocation concealment and blinding of outcome assessment domains differently to the CS:

- The EAG judged 'allocation concealment' as 'low risk', as a web-based system was used for randomisation in MAIA; and
- The EAG judged 'blinding of outcome assessment' to be at 'low risk', as OS and time to treatment discontinuation (TTD) are objectively assessed outcomes. PFS was initially assessed by a computer algorithm (and investigator and a sensitivity analysis showed no difference).

However, the EAG favour an assessment of RoB using the recent Cochrane RoB version 2 (RoB 2) (20), because it assesses bias at the outcome level rather than of the trial overall, providing a more robust and appropriate assessment for technology appraisal. Using the RoB 2 tool, the EAG assessed risk of bias for the trial outcomes contributing to the economic model: PFS, OS, TTD (at 64.5 months follow up). Results are reported in Table 5. Risk of bias was considered low for all domains for OS and TTD. However, for PFS, the 'measurement of the outcome' domain was assessed by the EAG as having some concerns due to the possibility that unblinded investigator outcome assessment could have influenced the result. The EAG note that the CS provided a sensitivity analysis that showed no difference with a computer algorithm.

3.2.2 Results of the MAIA trial

3.2.2.1 Baseline characteristics

Baseline patient demographics and disease characteristics of the MAIA trial are reported in Table 7 in the CS (Document B). (3) Baseline characteristics were well balanced between the treatment arms and the EAG does not have any concerns regarding the comparability of the treatment groups. Clinical advice received by the EAG indicated that the baseline characteristics were broadly comparable to those observed in UK clinical practice. However, inclusion criteria for the pre-treatment clinical laboratory values were considered to be narrower than those used to determine treatment eligibility in current clinical practice, for example platelet count values, creatine clearance, total bilirubin. Clinical advice also indicated that, in practice, patients with an Eastern Cooperative Oncology Group (ECOG) performance status score of 3 would still be eligible for treatment. However, these issues were not considered to undermine the integrity of the MAIA trial results.

TABLE 5: RISK OF BIAS IN MAIA TRIAL ASSESSED BY COMPANY AND BY EAG AT TRIAL LEVEL AND BY EAG FOR EACH OUTCOME FEEDING INTO ECONOMIC MODEL

RoB version 1 (overall trial assessment)			RoB version 2 (outcome level assessment)			
Domain	CS	EAG	Domain	Outcomes		
				PFS	OS	TTD
Random sequence generation	Low	Low	Randomisation process	Low	Low	Low
Allocation concealment	Unclear	Low	Deviations from intended interventions	Low	Low	Low
Blinding of participants/ researchers	High	High	Missing Outcome Data	Low	Low	Low
Blinding of outcome assessment	Unclear	Low	Measurement of the outcome	Some concerns	Low	Low
Complete outcome assessment	Low	Low	Selection of the reported result	Low	Low	Low
Selective reporting	Low	Low	NA	NA	NA	NA
Overall	Low	Low	Overall	Some concerns	Low	Low

CS risk of bias assessments are reproduced from Table 31 of company submission.(3)

CS = company submission, EAG = External Assessment Group, NA = not applicable, OS = overall survival PFS = progression-free survival, RoB = Risk of Bias, TTD = time to treatment discontinuation

3.2.2.2 Efficacy results

A summary of the MAIA results from the second interim analysis (24th September 2018 data cut) and the results of the latest data cut analysis (dated 21st October 2021) are reproduced from CS Document B, in EAG report Table 6. The results of the latest data cut are reported at a median follow-up of 64.5 months and informed the cost-effectiveness model in the CS. (3)

The Hazard Ratio (HR) for PFS from the second interim analysis (at 28.0 months median follow-up) shows clear benefit of DLd compared with Ld and this effect persists to the later data-cut (64.5 months median follow-up). The data for PFS are mature and median PFS had been reached in both DLd and Ld arms at the most recent data-cut reported by the CS (64.5 months median follow-up). The EAG note, however, that the upper confidence interval could not yet be estimated for the DLd arm. Whilst the assumption of proportional hazards does not appear to hold, differences between DLd and Ld arms appear to increase with time, suggesting the PFS benefits of DLd persist in the latter part of the trial follow-up (see Figure 2; reproduced from Figure 11, CS Document B (9)). The HR for OS shows evidence of a benefit for DLd at the later data-cut. Figure 3 shows that differences between arms for OS become apparent after approx. 24 months (reproduced from Figure 15, CS Document B (9)) However, the EAG notes that OS data are relatively immature; the median OS for Ld has only just met by the latest data cut (21st October 2021) and median OS has not yet been reached for the DLd arm. The EAG consider the long-term benefit of DLd for OS to be uncertain and note it is a key outcome required for the cost-effectiveness model (See Section 4). The final OS analysis from MAIA is estimated to be available in [redacted].

Key Issue 3: Is there sufficient follow-up for robust estimation of Overall Survival (OS)?

Due to the international design of MAIA and the variation in subsequent treatments received by MAIA participants, the CS reports adjusted HRs for OS for switching to treatments not routinely available in England. The CS uses the Inverse Probability Censoring Weighting (IPCW) adjustment method. However, the IPCW approach assumes a constant HR over the study follow-up, and there is evidence that this may not be valid for OS (CS Appendix O.1.1. (9)). Furthermore, insufficient information was provided by the company for the EAG to validate and review this analysis in detail. Variability in subsequent treatments used in MAIA, and in clinical practice, adds uncertainty to the treatment effect estimates, and the EAG prefer the more conservative results that do not adjust for treatment switching or make an assumption regarding proportional hazards to be used in the economic model for OS.

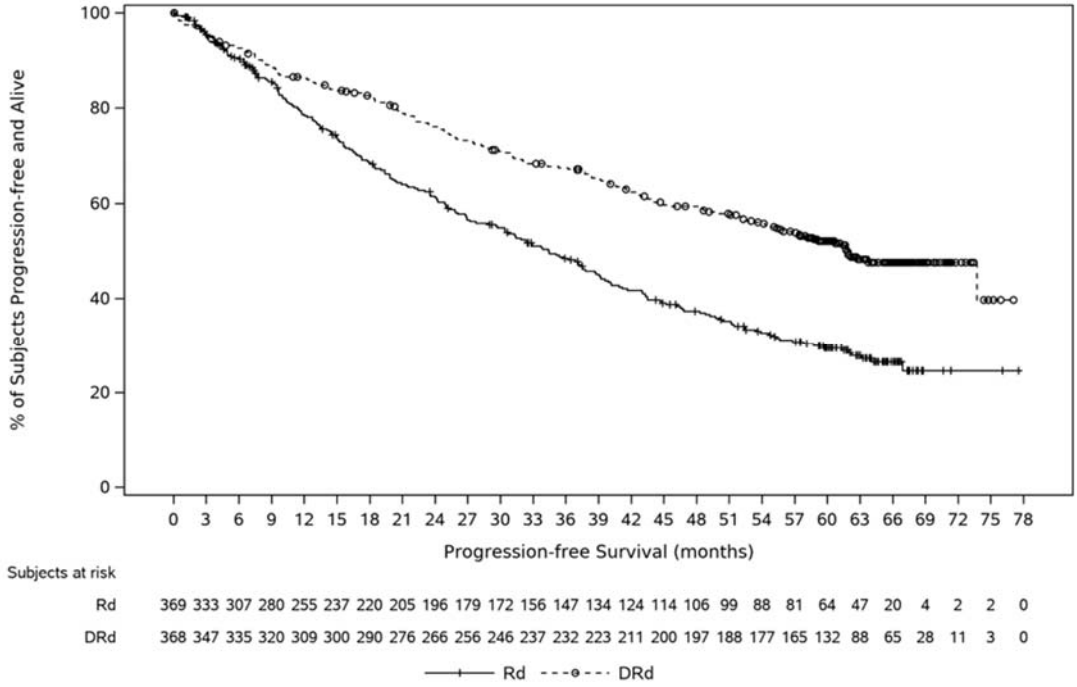
TABLE 6: SUMMARY OF KEY CLINICAL EFFICACY RESULTS (AMENDED FROM CS, TABLE 13)(3)

	24th September 2018 data-cut (median follow-up: 28.0 months)		21st October 2021 data-cut (median follow-up: 64.5 months)	
	DLd	Ld	DLd	Ld
PFS, n (%)				
Median PFS (95% CI)	Not reached	31.9 (NR)	61.86 [redacted]	34.4 [redacted]
PFS HR (95% CI)	0.56 (0.43, 0.73)		0.55 (0.45, 0.67)	
p-value	p<0.0001		[redacted]	
OS, n (%)				
Median OS (months)	Not reached	Not reached	NE [redacted]	65.54 [redacted]
OS HR (95% CI)	[redacted]		0.66 (0.53, 0.83)	
p-value	[redacted]		[redacted]	
Overall response, n (%)				
Overall response	342 (92.9)	300 (81.3)	342 (92.9)	301 (81.6)
Odds ratio (95% CI)	[redacted]		[redacted]	
p-value	[redacted]		p<0.0001	
sCR/CR, n (%)				
sCR	112 (30.4)	46 (12.5)	131 (35.6)	58 (15.7)
CR	63 (17.1)	46 (12.5)	57 (15.5)	53 (14.4)
≥CR	175 (47.6)	92 (24.9)	188 (51.1)	111 (30.1)
Odds ratio (95% CI)	[redacted]		[redacted]	
p-value	[redacted]		p<0.0001	
VGPR, n (%)				
VGPR	117 (31.8)	104 (28.2)	112 (30.4)	99 (26.8)
≥VGPR	292 (79.3)	196 (53.1)	300 (81.5)	210 (56.9)
Odds ratio (95% CI)	[redacted]		[redacted]	
p-value	[redacted]		p<0.0001	
MRD, n (%)				
MRD negativity rate (10^{-5} sensitivity threshold)	89 (24.2)	27 (7.3)	118 (32.1)	41 (11.1)
Odds ratio (95% CI)	[redacted]		[redacted]	
p-value	[redacted]		<0.0001	

Abbreviations: CI: confidence interval; CR: complete response; DLd: daratumumab, lenalidomide and dexamethasone; HR: hazard ratio; Ld: lenalidomide and dexamethasone; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; sCR: stringent complete response; VGPR: very good partial response.

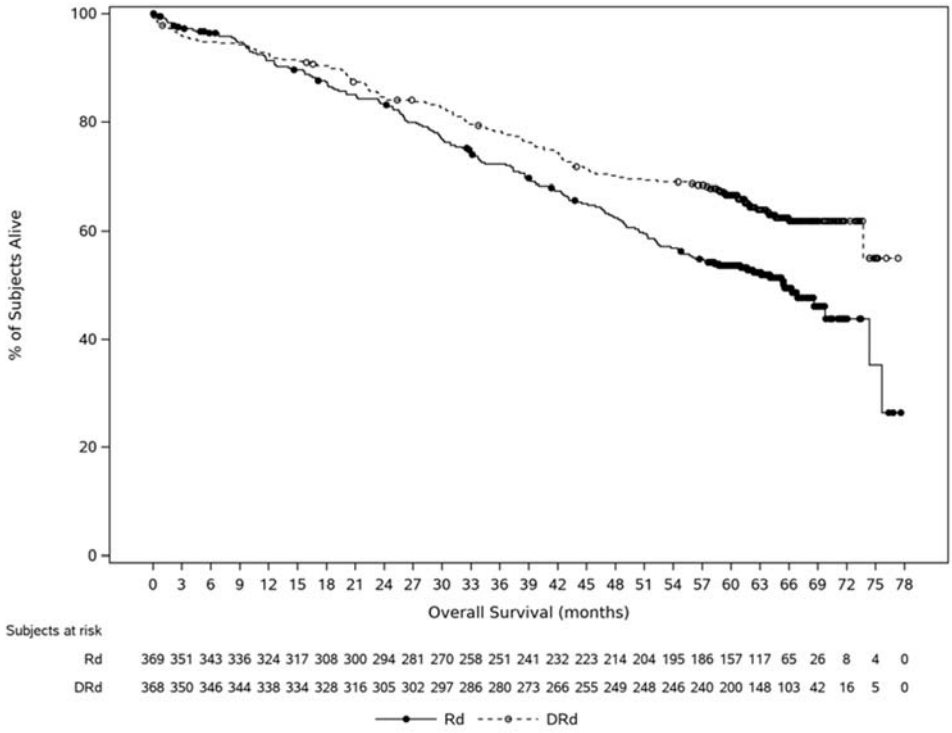
Source: Facon *et al*. (2019);(10) Facon *et al*. (2021);(22) MAIA CSR (September 2018 data cut). [Data on File]. 2019;(7) MAIA Abbreviated CSR. [Data on File] 2021;(8) Kumar *et al.* (2020);(23) MAIA HEMAR report. [Data on file] 2022;[3]

FIGURE 2: KAPLAN–MEIER ESTIMATE OF PFS IN THE MAIA TRIAL (ITT POPULATION) (DATA CUT-OFF 21ST OCTOBER 2021). REPRODUCED FROM FIGURE 11, CS DOCUMENT B.(3)



Abbreviations: DRd: daratumumab, lenalidomide and dexamethasone (referred to as DLd); PFS: progression-free survival; Rd: lenalidomide and dexamethasone (referred to as Ld).

FIGURE 3: KAPLAN–MEIER ESTIMATES OF OS IN THE MAIA TRIAL (ITT POPULATION) (DATA CUT-OFF 21ST OCTOBER 2021), REPRODUCED FROM FIGURE 15, CS DOCUMENT B.(3)



Abbreviations: DRd: daratumumab, lenalidomide and dexamethasone (referred to as DLd); PFS: progression-free survival; Rd: lenalidomide and dexamethasone (referred to as Ld).

3.2.2.3 Subgroup analyses

Section B.2.7 the CS reports subgroup analysis for the primary outcome of PFS (CS Figure 30) and secondary outcome OS (CS Figure 32) from the MAIA study.(3) Subgroup analyses for PFS and OS showed the treatment effect of DLd over Ld was broadly consistent across the following pre-specified subgroups: sex, age, race, region, baseline renal function, ISS staging, cytogenic risk at study entry, ECOG performance score. There was evidence showing impaired baseline hepatic function reduced the treatment effect of DLd for both PFS (normal: HR [redacted] vs impaired: HR [redacted]) and OS (normal: HR [redacted] vs impaired HR [redacted]).

A subgroup analysis of MAIA by frailty status for PFS was also reported in the CS (Section B. 2.7). Analysis was performed retrospectively using age, Charlson comorbidity index, and baseline ECOG performance status score, with patients classified into the following categories: fit, intermediate, non-frail (fit and intermediate), frail. Results of the subgroup analysis showed the PFS benefit of DLd versus Ld was maintained across subgroups: non-frail (median: not reached versus 41.7 months; HR: 0.48; p<0.0001) and frail (median: NR versus 30.4 months; HR: 0.62; p=0.003). The EAG note whilst the PFS benefit was maintained, the MAIA study population only included patients with an ECOG of 0-2, which may not reflect the frailty of patient populations treated in UK clinical practice. The EAG's clinicians stated that patients with an ECOG of 3 would still be treated and thus PFS benefit hasn't been explored in the MAIA trial in a frailer population.

In response to the EAG's request, a subgroup analysis by UK versus non-UK centres for PFS and OS is provided in Table 25 and Table 26 in the clarification response.(24) Treatment effect of DLd over Ld was shown to be consistent in this subgroup. However, the EAG notes the small sample size for the UK centre group ([redacted] in DLd and [redacted] in Ld).

3.2.2.4 HRQoL

The EORTC QLQ-C30 and the EQ-5D-5L instruments were used to measure functional status, well-being and symptoms. Data on HRQoL were collected on Day 1 of Cycles 3, 6, 9 and 12 for Year 1, and every 6th cycle thereafter until end of treatment. Results of the assessments are reported in section B.2.6.2.11 of the CS.(3) The EAG considers these measures appropriate to capture HRQoL. In response to a request for clarification from the EAG, the company provided the plots of mean change from baseline with error bars added for EORTC QLQ-C30 and EQ-5D-5L from which it can be seen that the error bars overlap at all follow-up times (confirmed by the company's response to clarification B6 that there were [redacted]).

3.2.2.5 Adverse events

AEs were reported in Section B.2.10 in the CS.(3) The company present data from the second interim analysis (24th September 2018) and the latest clinical data cut-off (21st

October 2021). Although the treatment emergent adverse events (TEAEs) were similar across arms, there were more Grade 3 or 4 and Serious TEAEs in the DLd arm compared with Ld, whereas discontinuation of treatment due to AEs was more common for Ld. TEAEs leading to dose-modification was common in both arms of MAIA, and a higher rate of reduced dose of lenalidomide was seen in the DLd arm.

3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

3.3.1 Studies included in the network meta-analysis (RCTs)

No head-to-head, randomised comparisons of DLd with either bortezomib or thalidomide-based comparator regimens were identified by the CS in SLR 1. Therefore, for comparison of DLd with bortezomib and thalidomide-based regimens, as per the NICE scope, the CS includes a NMA of RCTs for outcomes PFS, OS, ORR and ≥CR. Analyses of MRD negativity and TTD were not conducted.(3) See section 3.4 of the EAG report for critique of the methods used for network meta-analysis in the CS.

RCT studies included in the CS NMA were identified and appraised as part of SLR 1, where the company searched more broadly than DLd as the intervention of interest.(3) The EAG consider that the search for RCT studies was appropriate and that the conduct of the review was adequate. Of the 33 RCTs identified in SLR 1, nine were included in the NMA: FIRST(25), Hungria(26), IFM 01/01(27), IFM 99-06(28), MAIA(10), MRC Myeloma IX(29), Sacchi(30),Turkish Society of Haematology Myeloma Study Group (TMSG)(31), and VISTA(32). The selection of studies for the NMA was appropriate. Included RCTs compared at least two interventions of interest to the scope and formed a connected network following the appropriate guidance from NICE Decision Support Unit Technical Support Document TSD 1 (33). The network of randomised comparisons included BMP, MP, MPT, CTd, Ld, and DLd (See Figure 4 reproduced from Figure 2, CS Appendix D (9)). However, the EAG notes two further studies met the inclusion criteria but were excluded from the NMA by the company as they were conducted in Asian populations. Song (2012) compared CTd vs MPT(34), and Suzuki (2019) compared MPT vs MP(35). Further details on these two additional studies are provided at the end of Section 3.3.1. No randomised comparison of BCd with sufficient data was found by SLR 1.

Table 7 compares the study design, interventions, inclusion criteria, outcomes and definition of PFS for the studies included in the NMA. Baseline characteristics for each study can be found in Table 16 of CS Appendix D(9), and discrepancies identified by the EAG are reported in Appendix 3 in section 8.3 of the EAG report. The EAG considers there is some evidence of clinical heterogeneity across the studies in the network. The following observations in relation to inclusion criteria and baseline characteristics of NMA studies are of note:

- Inclusion criteria for ASCT and age thresholds differed, with studies using varying age thresholds as a proxy for ASCT ineligibility. However, baseline characteristics

show that median age was broadly comparable across studies (~70-73 years old, where reported). The EAG note that patients in IFM 01/01(27) and Sacchi(30) were noticeably older, on average (~78 years old). Both studies compared MPT and MP. ASCT ineligibility was not reported to be an inclusion criterion for MRC Myeloma IX (MP vs CTd) and age criteria were adults ≥18 years old. However, the median age of participants at baseline was 73 years old.(29),

- For MM type, the proportion of immunoglobulin G (IgG) patients by arm ranged from 52% to 83% in studies included in the NMA. The TMSG study(31) had a higher proportion (MPT: 83%; MP: 71%) and Hungria(26) had a lower proportion (MPT: 51.7%; CTd: 55.2%) of IgG patients compared to the other studies in the NMA. Sacchi(30) and TMSG were noted to be imbalanced in IgG type between study arms (Sacchi MP: 63%; MPT: 73%). However, clinical advice received by the EAG indicated that treatment pathways did not differ by MM type, and it was not likely to be a treatment effect modifier. This was supported by the MM type subgroup analysis for PFS and OS in MAIA (Section B.2.7 of CS).(3)
- For disease stage measured via the International Staging System (ISS) inclusion criteria were broadly comparable across the network. Hungria(26), FIRST(25) and TMSG(31) had a higher percentage of patients with an ISS stage of III (Hungria: MPT 46.7%, CTd 41.9%; FIRST: Ld continuous 40%, Ld18 40%, MPT 41%; TMSG: MPT 43.1%, MP 40.4%). Sacchi(30) was noted to be imbalanced between treatment arms for ISS stage I (MP 22%; MPT 34%) and ISS stage III (MP 30%; MPT 22%).
- For performance status, inclusion criteria varied across studies both in terms of scale used and degree of impairment. Inclusion criteria for the two Ld controlled studies (MAIA(10) and FIRST(25)) was ECOG 0-2 and for the MPT vs MD studies was ECOG: ≤3(30), ECOG: ≤2 and WHO <3(27),(28). Across the network, Hungria(26) and Sacchi(30) had a high proportion of patients with ECOG score of 3-4 (Hungria: MPT 16.7%, CTd 12.5%; Sacchi: MP 9%, MPT 12%), compared to the other studies. TMSG showed imbalances between treatment arms for ECOG (MPT: 0 = 3.5%, 1= 49.1%, 2= 43.9%, 3= 3.5%, MP: 0 = 10.5%, 1= 36.8%, 2= 49.1%, 3= 3.5%).
- Across the network of studies, Hungria and TMSG had the highest proportions of patients with baseline performance scores of 2 or higher (Hungria(26) [ECOG: MPT 53.4%, CTd 50.4%] and TMSG [WHO: MPT 47.4%, MP 52.6%]). For comparison, the proportion of MAIA participants with ECOG ≥2 was DLd 17.1%, Ld 16% (all at level 2).(10)

In particular, the population in the Hungria study(26) was noted in the CS as being substantially different to other included studies, as it included a higher proportion of patients with an ECOG score of 2 and 3, and an ISS score of III. These characteristics were also imbalanced across treatment arms within the study. Due to this, the CS includes a sensitivity analysis removing Hungria from the network (see section 3.5 of EAG report). Hungria is the only study in the CS NMA comparing CTd and MPT. The EAG notes that ASCT eligibility was not listed as an inclusion criterion for the MRC Myeloma IX study (CTd vs MP) and performance status at baseline was not reported, making it difficult to assess comparability. Excluding both Hungria and Myeloma IX from the network would also remove the CTd comparator (Figure 4, reproduced from CS Appendix D (9)). However, the

EAG considers the comparison with CTd potentially prone to bias and notes that there was statistical inconsistency observed in the CS NMA when both studies were included (see section 3.5). There are also concerns with the studies comparing MPT vs MP where baseline imbalance across arms brings into question the internal validity of the TMSG and Sacchi trials.

Additionally, the EAG note that the following trial design and methods also differ and may introduce heterogeneity and inconsistency in the NMA:

- The studies varied in sample size: FIRST (n=1623), MRC Myeloma IX (n=849), MAIA (n=737) and VISTA (n=682), IFM 99/06 (n=321), IFM 01/01 (n=229), Sacchi (n=118), TMSG (n=122), Hungria (n=82).
- The outcomes measured and the definitions of PFS are comparable across all nine studies. However, PFS data were not available for the TMSG trial (MPT vs MP). (31)
- Follow-up durations differed considerably across trials included in the NMA and ranged from a median of 23 months (TMSG(31)) to a median of 67 months (FIRST(25)) (Table 20, CS Appendix D.1.7. (9)).
- Pre-specified within-study subgroup analyses were performed in the MAIA study (PFS and OS) and the FIRST study(25) (PFS) by age, ECOG performance status and ISS. The VISTA study(32) also included subgroup analyses for age and ISS for the time to progression outcome. There was no evidence of subgroup effects observed in the three trials.

TABLE 7: STUDY DETAILS FOR STUDIES INCLUDED IN THE NETWORK META-ANALYSIS

Trial	VISTA	IFM 01/01	IFM 99/06	Sacchi 2011	TMSG	MRC Myeloma IX	Hungria 2016	FIRST	MAIA
Design	Phase III, multicentre, open-label RCT	Phase III, multicentre, double-blind RCT	Phase III, multicentre, open-label RCT	Phase III, multicentre, open-label RCT	Phase III, multicentre, open-label RCT	Phase III, multicentre, open-label RCT	Phase II, multicentre, open-label RCT	Phase III, multicentre, open-label RCT	Phase III, multicentre, open-label RCT
Intervention	BMP (n=344) MP (n=338)	MPT (n=113) MP (n=116)	MPT (n=125) MP (n=196)	MPT (n=64) MP (n=54)	MPT (n=60) MP (n=62)	CTd (n=426) MP (n=423)	CTd (n=32) Td (n=18) MPT (n=32)	Ld (n=535) Ld-18 (n=541) MPT (n=547)	DLd (n=368) Ld (n=369)
Inclusion criteria	Ineligible for ASCT because of age ≥65 or coexisting conditions	≥75	65-75; <65 if ineligible for ASCT	>65, ≤65 if ineligible for ASCT	>55 & ineligible for ASCT	≥18	>65 & ineligible for ASCT	≥65, <65 if ineligible for ASCT	Ineligible for ASCT due to being ≥65 or coexisting conditions
	Untreated, symptomatic, measurable NDMM	NDMM (Stage ii or iii)	MM (Stage ii or iii)	NDMM (Stage ii or iii)	Symptomatic MM	NDMM, symptomatic	NDMM (Stage ii or iii)	Previously untreated MM	NDMM
	Karnofsky performance status ≤70%	WHO performance index: <3	WHO performance index: <3	ECOG: ≤3	ECOG: ≤2	NR	NR	ECOG: 0-2	ECOG: 0-2
	Europe, North & South America, Asia	Europe	Europe	Europe	Middle East	United Kingdom	South America	Asia-Pacific, Europe, North America	North America, Europe, Middle East, Asia–Pacific.
Outcomes	TTP	OS	OS	OR*	Treatment Response Toxicity	OR*	ORR	PFS	PFS

	Rate of complete response, DOR, Time to 2nd line therapy, OS, PFS, Complete + partial RR, Complete RR, Time to first response, Global health status	Safety Response rates PFS	RR PFS Survival after progression Toxicity	PFS RR Toxicity	DFS OS	PFS QoL Toxicity	OS PFS Toxicity	OS ORR DOR Time to response Time to treatment failure Time to 2nd line therapy QoL Safety	TTP RR OS TTR DOR Efficacy in subgroup of patients with high risk cytogenic profile Safety
PFS definition	EBMT criteria	Time from random assignment to progression or death	Time from random assignment to progression	Time from random assignment to disease progression, date of last observation or death (any cause)	PFS data not available	Time from randomization to documented progression or death	Time between randomization and relapse, progression, or death (any cause)	IMWG criteria	IMWG criteria

*Not specified as primary outcome but listed first

AE = adverse event, ASCT = autologous stem cell transplantation, BMP = bortezomib, melphalan and prednisone, BMPT-BT = bortezomib, melphalan, prednisone and thalidomide followed by maintenance with bortezomib and thalidomide, CTd = cyclophosphamide, thalidomide and dexamethasone, DFS = disease-free survival, DLd = daratumumab, lenalidomide and dexamethasone, DOR = duration of response, EBMT = European Society for Blood and Marrow Transplantation, ECOG = Eastern Cooperative Oncology Group performance status scale, IMWG = International Myeloma Working Group, Ld = lenalidomide and dexamethasone, Ld-18 = lenalidomide and dexamethasone in 18 cycles, MM = multiple myeloma, MP = melphalan and prednisone, MPT = melphalan, prednisone and thalidomide, NDMM = newly diagnosed multiple myeloma, NR= not reported, OR = overall response, ORR = overall response rate, OS = overall survival, PFS = progression-free survival, QoL = quality of life, RCT = randomised controlled trial, RR = response rate, Td = thalidomide and dexamethasone, TTP = time to progression, TTR = time to response, WHO = world health organisation

3.3.1.1.1 Studies excluded from the NMA of RCTs

The EAG assessed the 19 studies excluded from the CS NMA and considered two(34) (35) met the inclusion criteria, addressed a relevant treatment comparison, and were connected to the network. The CS states they were excluded from the NMA as they were conducted in entirely Asian populations. Song (2012)(34) compared CTd vs MPT in South Korean elderly patients with NDMM, ECOG ≥2 and renal impairment (<90 ml/min/1.73 m2) in chronic kidney disease (CKD) classification calculated by the Modification of Diet in Renal Disease (MDRD) formula. The median age of patients was 69, with 28 patients above 75. Approximately half of the sample were ISS stage III. The study explored response, event-free survival, OS and AEs. It had a sample size of 157 patients (74 MPT vs 83 CTd) and the median follow-up time was 36 months. Suzuki (2019)(35) compared MPT and MP, and was a phase II double-blind RCT in Japan. Suzuki included patients ≥20 years old with untreated symptomatic MM who were ineligible for ASCT. The median age of patients was 77 years, with those ≥75 accounting for 67%. The primary outcome was ORR according to European Society for Blood and Marrow Transplantation (EBMT) criteria. Other outcomes were: response rate at each time point, time to response and duration of response. It had a sample size of 103 patients (52 MPT and 51 MP). Patients were not selected due to frailty but due to median age of 77 years, the authors say a substantial number of frail patients were likely in the study population.

The EAG's clinical experts did not expect relative treatment effects to differ for Asian patients but agreed with the CS that clinical practice in Asian health care systems may not be generalisable to a United Kingdom (UK) setting. In response to the EAG's clarification request for a NMA sensitivity analysis including Song and Suzuki the company noted that survival outcomes (PFS and OS) were not available. Instead, they provide sensitivity analyses for the ORR and ≥CR outcomes, which do not feed into the economic model. Statistical results for the NMA are described in section 3.4 of the EAG report.

Key issue 4: Are the studies in the NMA similar enough for reliable inference?

Risk of Bias assessment for RCTs in NMA

The company assessed risk of bias of the RCTs included in the NMA using the Cochrane RoB tool version 1 (36). The results of these assessments are presented in the CS (Table 31, CS Appendix D.1.11.(9)). For comparison with the CS judgments, the EAG reviewed the CS risk of bias assessments using the same Cochrane RoB tool (version 1). The company's and EAG's judgements are shown in Table 8 and differences noted here:

- Allocation concealment: the CS rated this domain as 'low' for IFM 01/01(27) and Sacchi(30). The EAG rated this domain as unclear, due to a lack of information in the study reports.
- Blinding of outcome assessment: the CS rated this domain as being at 'high' risk of bias for IFM 99/06(28) and MRC Myeloma IX(29). However, the EAG rated it as 'unclear' due to a lack of information of outcome assessment and whether outcome assessors were blinded. The EAG notes that all trials were 'open-label'. TMSG(31) was rated as low for this domain by the CS and unclear by the EAG. The

study report for TMSG states *"Data were monitored by an independent contract research organization (CRO; OMEGA, Ankara, Turkey), who also performed statistical analyses*" (Page 17). However, no information was provided regarding outcome assessors.

- Complete outcome assessment: the CS rated this domain as being at 'low' risk of bias for the FIRST study(25). The EAG rated it as 'unclear', as the reasons for discontinuation were not reported in the CONSORT diagram.
- Selective reporting: the CS rated this domain as unclear in the FIRST study compared to a low rating by the EAG. The EAG considered all outcomes for FIRST were appropriately reported in the study report (25) and its supplementary appendix.

The EAG do not consider these differences alter the overall assessment of risk of bias of the studies contributing to the NMA, as based on RoB version 1. Risk of Bias assessments for the MAIA study are discussed in section 3.2.1 of this report.

3.3.2 Studies included in the unanchored Indirect Treatment Comparison and Matched Adjusted Indirect Comparison

Two further "supplementary" SLRs were reported by the CS: SLR 2 focused on single arm studies and SLR 3 focused on observational studies to identify clinical data on BCd. These additional SLRs assessed studies for an unanchored Indirect Treatment Comparison (uITC) of DLd vs BMP and a Matched Adjusted Indirect Comparison (MAIC) to estimate the relative effect of DLd versus BCd, based on an assumption of BMP and BCd clinical equivalence. The CS justifies the additional observational analyses and SLRs due to the uncertainty in the BMP vs DLd effect estimate from the NMA, the questionable assumption of proportional hazards used in the CS NMA and the absence of a randomised comparison including BCd. However, as evidence is available for BMP vs DLd from a NMA that respects randomisation and that relaxes the proportional hazards assumption (see section 3.4.2), the EAG do not consider the justification for these supplementary SLRs, or the uITC and MAIC analyses they contribute to, to be compelling.

TABLE 8: COMPANY AND ERG ASSESSMENTS OF RISK OF BIAS OF STUDIES IN THE NMA USING ROB TOOL (VERSION 1) (36)

Trial	FIRST		Hungria 2016		IFM 01/01		IFM 99/06		MAIA		MRC Myeloma IX		Sacchi 2011		TMSG		VISTA	
	CS	EAG	CS	EAG	CS	EAG	CS	EAG	CS	EAG	CS	EAG	CS	EAG	CS	EAG	CS	EAG
Random sequence generation	Low	Low	Low	Low	Unc	Unc	Unc	Unc	Low	Low	Low	Low	Unc	Unc	Unc	Unc	Unc	Unc
Allocation concealment	Low	Low	Unc	Unc	**Low**	**Unc**	Unc	Unc	**Unc**	**Low**	Low	Low	**Low**	**Unc**	Unc	Unc	Unc	Unc
Blinding of participants /researchers	High	High	High	High	High	High	High	High	High	High	High	High	High	High	High	High	High	High
Blinding of outcome assessment	Unc	Unc	Unc	Unc	Unc	Unc	**High**	**Unc**	**Unc**	**Low**	**High**	**Unc**	**High**	**Unc**	**Low**	**Unc**	High	High
Complete outcome assessment	**Low**	**Unc**	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Selective reporting	**Unc**	**Low**	High	High	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low

CS = company submission, EAG = evidence assessment group, RoB = Risk of Bias, unc = unclear risk of bias

The EAG consider that the search for single arm and observational studies was appropriate and that the conduct of the review was adequate. Across both reviews 10 studies were potentially eligible, however only two identified from SLR 3 (2), (19) were considered useable by the CS and, as outlined in
Table 4 the EAG have concerns about the transparency of the study selection process underpinning the uITC and MAIC. The CS reports that Jimenez-Zepeda (2021) was more suitable than Sandecka (2021) for the MAIC as it reports more baseline characteristics considered likely to be prognostic factors and/or effect modifiers. The EAG agrees that it is important to adjust for potential effect modifiers and prognostic factors to improve the validity of the MAIC. However, the EAG do not think the decision to use the Jimenez-Zepeda study instead of Sandecka is clear cut (Table 51, Appendix D of CS) and the EAG would have liked to see the MAIC based on Sandecka to compare with and validate the results from Jimenez-Zepeda.

Three studies (MAIA(10), ALCYONE (1) and Jimenez-Zepeda (2)) underpinned the uITC of DLd vs BMP and MAIC of BMP vs BCd in the CS. The ALCYONE study was identified in SLR 1 but was not eligible for inclusion in the NMA as it only evaluated one relevant comparator for the analysis (DBMP vs BMP). It is sponsored by Janssen and the Individual Participant Data (IPD) are therefore accessible for the present CS. The DLd arm was based on the MAIA study, the BMP arm from ALCYONE and the BCd arm was based on Jimenez-Zepeda, identified from SLR 3. The inclusion criteria and baseline characteristics are reproduced from the CS (Table 51, CS Appendix D.4.7 (9)) for all three studies in EAG Table 9 and Table 10. The EAG noted the following differences in study design and between arms in MAIA, ALCYONE, and Jimenez-Zepeda:

- The proportions of MM type (IgG vs non-IgG) differed across MAIA and ALCYONE but was not reported in Jimenez Zepeda. The DLd arm in MAIA had 61.1% IgG MM type, whereas ALCYONE BMP had 39.3% IgG MM type. The EAG are unable to comment on the comparability of MM type for the MAIC, but we note that whilst our clinical advisors did not consider MM type to be an effect modifier it is a prognostic factor for outcomes. Unanchored indirect comparisons such as uITC and MAIC need to adjust for both effect modifiers and prognostic factors, and since it is not reported in Jimenez-Zepeda it is not possible to adjust for MM type in the comparison between BMP and BCd. (37)
- The proportion of male participants was considerably higher in Jimenez (59.3%) than in either MAIA (DLd arm) (51.4%) or ALCYONE (46.9%). The proportion of Asian participants was 0.8% in the MAIA DLd arm and 12.6% in ALCYONE. Race was not reported in Jimenez-Zepeda (2021).
- Jimenez-Zepeda (2021) had larger number of patients with ISS stage III (45.13%) compared to ALCYONE (36.2%) and MAIA (29.1%).
- Jimenez-Zepeda (2021) had 37.7% of patients with an unknown cytogenic risk profile making it hard to compare to other studies. ALCYONE had 85.1% of patients with standard risk, MAIA 85%, Jimenez-Zepeda (2021) 44.5%.

Risk of Bias assessment for studies included in uITC and MAIC

The company assessed risk of bias of the studies included in the uITC and MAIC using the following tools: MAIA – RoB version 1 (V1) (36) and CRD assessment tool (38); ALCYONE – CRD assessment tool and Jimenez-Zepeda – ROBINS -I (Risk of Bias in Non-Randomised Studies – of Interventions) (21).

The company's quality assessment for the ALCYONE study is reported in the CS (Table 53, Appendix D.5). Seven questions are included in the CRD assessment tool addressing randomization, concealment, similarity in prognostic factors, blinding, imbalances in drop-outs, outcome reporting and ITT analysis. The company rated the risk of bias as low across all seven domains. The EAG undertook an assessment of RoB of the ALCYONE study using the Cochrane RoB tool (V1)(36), reported in Table 11. Whilst the EAG agreed with most of the company's judgements, the EAG deemed the study at high risk of bias in the following domains: blinding of participants and personnel; blinding of outcome assessment and selective reporting. As stated in the ALCYONE protocol the study was open-label and blinding procedures were not applicable, therefore the EAG judged the two blinding domains to be at high risk. The EAG also judged the selective reporting domain to be high risk. The study protocol listed Time to disease progression; Progression-free survival on Next line of Therapy; Time to next treatment and impact of D-VMP compared to VMP on patient-reported perception of global health as secondary outcomes. However, these outcomes were not reported in the study report.

The company provided a risk of bias assessment for the Jimenez-Zepeda (2021) using the ROBINS-I tool (21) (Table 52, CS Appendix D.4.8 (9)). The company judged the study to be low risk across the seven domains resulting in low overall risk of bias. The EAG independently assessed Jimenez-Zepeda (2021) for risk of bias using the ROBINS-I tool, focusing on the primary outcomes OS and PFS. In contrast to the company's assessment, the EAG deemed the study to be at critical risk of bias. This is due to the study not accounting for all potential confounders which have been identified in the randomized studies included in the CS. Further details of the EAG's ROBINS-I assessment are given in Appendix 4, Section 8.4.1.

The company's assessment and the EAG's independent review of the MAIA RoB are discussed in section 3.2.1 of this report.

TABLE 9: STUDY DETAILS FOR STUDIES INCLUDED IN THE UNANCHORED INDIRECT TREATMENT COMPARISONS

	MAIA	ALCYONE	Jimenez-Zepeda (2021)
Study design	Open-label randomised controlled trial	Open-label randomised controlled trial	Observational study
Intervention	DLd (n=368) Ld (n=369)	BMP (n=356) DBMP (n=350)	BCd/P (n=562), BMP (n=292) BD/P (n=94), Ld (n=208)
Inclusion criteria	≥65 Ineligible for ASCT	≥65 Ineligible for ASCT	Ineligible for ASCT
	NDMM	NDMM	NDMM
	ECOG: 0-2	ECOG: 0-2	NR
	North America, Europe, the Middle East, and the Asia–Pacific region.	North America, South America, Europe, and the Asia-Pacific region.	Canada
Outcomes	PFS	PFS	Depth of response
	TTP, Response rates, OS, TTR, DOR, Efficacy in subgroup of patients with high risk cytogenic profile Safety	ORR Rate of partial response or better, Complete response or better, Negative status for MRD OS, Safety, Side effect profile, TTR, DOR	PFS, OS
PFS definition	IMWG criteria	Time from randomisation to progression or death, whichever occurs first	Time from treatment initiation to progression, death or last follow-up

ASCT = autologous stem cell transplantation, BCd/P = bortezomib, cyclophosphamide and dexamethasone or prednisone, BMP = bortezomib, melphalan and prednisone, BD/P = bortezomib and dexamethasone or prednisone, DBMP = daratumumab, bortezomib, melphalan and prednisone, DLd = daratumumab, lenalidomide and dexamethasone, DOR = duration of response, ECOG = Eastern Cooperative Oncology Group performance status scale, IMWG = International Myeloma Working Group, Ld = lenalidomide and dexamethasone, MRD = minimal residual disease, NDMM = newly diagnosed multiple myeloma, ORR = overall response rate, OS = overall survival, PFS = progression-free survival, TTP = time to progression, TTR = time to response

TABLE 10: BASELINE CHARACTERISTICS OF STUDY ARMS INCLUDED IN THE UNANCHORED INDIRECT COMPARISONS

Trial (Arm)	Age (median)	Sex	ECOG performance status	ISS stage* at diagnosis	Creatinine clearance	Cytogenetic risk factors/high risk cytogenetic abnormality*	Hepatic function	MM type (IgG/not IgG)	Race
MAIA (DLd)	73 years	Female: 48.6%	0 34.5% 1 48.4% 2 17.1%	I 26.6% II 44.3% III 29.1%	>60 ml/min 56% ≤60 ml/min 44%	Standard: 85% High:15%	Normal: 91% Impaired: 9%	IgG 61.1%	White: [redacted] Black: Asian:
ALCYONE (BMP)	71 years	Male: 46.9%	0 27.8% 1 48.6% 2 23.6%	I 18.8% II 44.9% III 36.2%	NR	Standard: 85.1% High: 14.9%	NR	IgG 39.3%	White: 85.4% Black: 0.8% Asian: 12.6%
Jimenez-Zepeda (BMP)	74.7 years	Female: 45.55%	NR	I 19.68% II 35.64% III 44.68%	Median creatinine, umol/l (range) 99 (38–1590)	Standard 22.9% High 9.3%	NR	NR	NR
Jimenez-Zepeda (BCd/P)	69.7 years	Female: 40.75%	NR	I 20.35% II 34.51% III 45.13%	Median creatinine, umol/l (range) 107 (29–1085)	Standard 44.5% High 17.8%	NR	NR	NR

*Where total does not equal 100%: characteristic not reported or unknown
BCd/P = bortezomib, cyclophosphamide and dexamethasone or prednisone, BMP = bortezomib, melphalan and prednisone, DLd = daratumumab, lenalidomide and dexamethasone, ECOG = Eastern Cooperative Oncology Group performance status scale, IgG = immunoglobulin G, ISS= International Staging System MM = multiple myeloma, NR= not reported

TABLE 11: EAG'S ROB VERSION 1 ASSESSMENT OF ALCYONE(1) STUDY

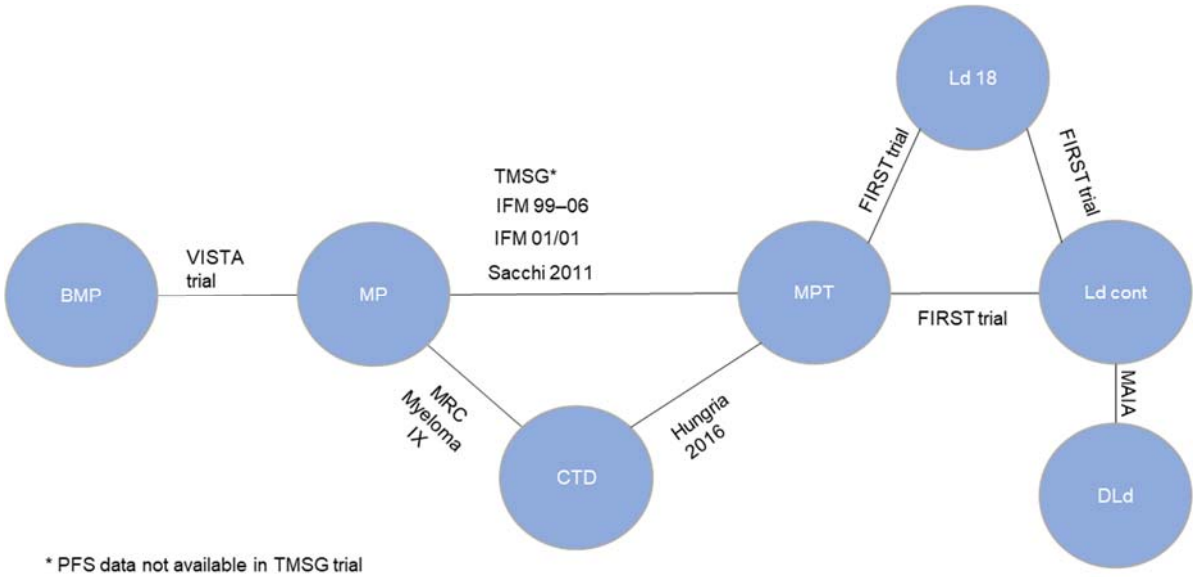
Source of bias	EAG judgement
Random sequence generation	Low
Allocation concealment	Low
Blinding of participants and personnel	High
Blinding of outcome assessment	High
Incomplete outcome data	Low
Selective reporting	High

3.4 Critique of the indirect comparison and/or multiple treatment comparison

3.4.1 Evidence networks and data extraction check

The company performed NMAs of HRs based on studies identified in SLR 1 and critiqued in Section 3.3.1 for OS, PFS, ORR and ≥CR. Nine RCTs were included, comparing six different treatments (Ld restricted to 18 cycles of use was included in the analysis but did not contribute to comparisons of interest) (Figure 4). The CS notes that although MP was not considered as a relevant comparator in the NICE decision scope, it was included in the NMA for the network to connect (Table 14, CS Appendix D.1.7 (9)). MP was compared in six of the nine trials included in the NMA (IFM 01/01 (27), IFM 99-06 (28), MRC Myeloma IX (29), Sacchi 2011 (30), Turkish Society of Haematology Myeloma Study Group (TMSG) (31) and VISTA (32)). Except for MPT vs MP (4 studies), all remaining comparisons are informed by single studies. Of the two potentially eligible studies excluded from the network (34), (35) only Song (CTd vs MPT) reported PFS and OS. The EAG agree with the company that data for these outcomes were not in an extractable form. The EAG also note that Suzuki was a small trial and would be unlikely to alter the MPT vs MP relative effect estimate. Following the EAG's clarification request, the company re-ran the NMA including Song(34) for ORR and ≥CR and results were very similar to the company's base case.

FIGURE 4: NETWORK PLOT OF STUDIES INCLUDED IN THE CS NMA. REPRODUCED FROM FIGURE 2, CS APPENDIX D(9).



Abbreviations: BMP: bortezomib, melphalan and prednisone; CTd: cyclophosphamide, thalidomide, and dexamethasone; DLd: daratumumab, lenalidomide and dexamethasone; Ld: lenalidomide with dexamethasone; MP: melphalan and prednisone; MPT: melphalan, prednisone and thalidomide; PFS: progression-free survival.

The EAG checked the company's data extraction for the NMA and found no errors. For data extracted from Kaplan Meier curves the company used the methodology of Guyot et al. (39) which performs reasonably providing the publication quality of the curves is good. The EAG were not provided with the reconstructed data, but in the company's response to clarification questions they provide plots of the reconstructed data alongside the published curves for Sacchi (30), which shows a good fit.

3.4.2 Methods used for network meta-analysis

The company used a Bayesian framework following methods described in NICE TSD 2.(40) Fixed and random effects models were compared to explore heterogeneity, and for all outcomes a fixed effects model was selected based on DIC and low heterogeneity. Consistency was assessed using the Bucher method in the loop of comparison between MP, MPT and CTd.(41) The EAG found the company's approach for assessing homogeneity and consistency reasonable.

The CS noted that their NMA model assumed proportional hazards, but that there is evidence that this assumption did not hold for OS and PFS for DLd versus Ld in MAIA (Figures 34-37, CS Appendix O (9)). The company used this to justify instead using results from an unanchored Indirect Treatment Comparison (uITC) rather than their NMA for DLd versus BMP in their economic model because it does not assume proportional hazards. The EAG agrees with the company that the proportional hazards assumption is violated in many of the studies in the NMA based on survival curves from KM plots. However, it is possible to perform NMA of survival outcomes without assuming proportional hazards.(42) The log-cumulative hazard plots indicate that there are potentially two pieces of time with very different hazard ratios (with more benefit seen later on). This suggests a piecewise model may be appropriate.

In response to clarification questions from the EAG, the company provided two approaches to allow for time-varying HRs in the NMA for the comparisons between BMP, Ld, and DLd that relaxed the proportional hazards assumption. In the first they fitted a parametric NMA following the approach of Ouwens et al (43) where an NMA model is applied to parameters of the survival distribution, using a Gompertz distribution OS, and an Exponential distribution for PFS. The company's justification for this choice of parametric distributions was based on the distributions chosen in their base case for Ld and DLd for PFS and Ld for OS. The data were not provided so the EAG could not confirm whether these were the best fitting functions across all studies in the NMA, and it was not possible to validate the results or explore alternative modelling assumptions or distributional assumptions in sensitivity analyses.

For the second approach, the company fitted a piecewise Cox NMA that allowed for estimation of a different HR for 0-20 and ≥20 months. The company only found statistically significant evidence of violation of the proportional hazards assumption for PFS in the FIRST study (Clarification response Appendix A.5), and therefore only estimated a piecewise Cox model for PFS and for the comparison Ld vs MPT, with other comparisons estimated

assuming proportional hazards. Despite evidence of time-varying HRs in MAIA for OS, the company did not estimate a piecewise Cox NMA model for OS. The company still preferred the observational uITC for their base-case (section 3.4.4) and chose not to use the NMA results for BMP in their base-case.

The EAG prefers to use results from a NMA because it is based on randomised comparisons. Given that there was a suggestion of time-varying HRs in other studies and outcomes (albeit not statistically significant), the EAG would prefer a model that relaxes the proportional hazards assumption for both PFS and OS and for all comparisons. The parametric NMA is the only approach that achieves this and fits curves to all treatments simultaneously assuming the same parametric distributional form for each treatment, which is in line with recommendations from TSD14 (44) and would be the EAGs preference. However, since the company only provided the code and not the input data to the NMA, these results could not be validated and their sensitivity to the choice of distribution could not be assessed. Therefore, the EAG's preferred results for PFS are from the fixed effect piecewise Cox NMA model. However, the piecewise NMA was only provided for PFS and not for OS, and so the EAG prefers the parametric NMA for OS.

As discussed in section 3.3.1, the EAG noted that the TMSG and Sacchi trials were imbalanced across arms which may affect their internal validity, and the Hungria and MRC Myeloma IX studies were different in inclusion criteria and baseline characteristics to the other studies. The EAG therefore ran additional analyses exploring the impact of excluding these studies and found that studies investigating CTd (Hungria and MRC Myeloma IX) contributed very little additional information, likely due to the small sample size of Hungria (see section 3.5). Given that there are no gains in precision from including these studies and that the inclusion of CTd in the network may introduce inconsistency due to different study characteristics, the EAG prefers to exclude Hungria and MRC Myeloma IX from their base-case analysis.

For ORR and ≥CR the results from the fixed effects NMAs are given in Tables 25 and 26 of CS Appendix D.1.10.(9)

3.4.3 Assessment of heterogeneity and inconsistency in the network meta-analysis

Whilst there were some differences in inclusion criteria and baseline population characteristics between trials in the NMA and some evidence of baseline imbalance indicating lack of internal validity of the TMSG and Sacchi studies (Section 3.3.1) low heterogeneity was estimated for all the NMAs, though given the small number of studies investigating the same treatment comparison there was limited power to assess this.

The company identified inconsistency in the network for ORR (p=0.034) and argued that the likely cause of this was the Hungria 2016 trial (26), perhaps due to differences in baseline characteristics. The EAG agree with this in their critique of included studies (Section 3.3.1). The company ran a sensitivity analysis (CS Appendix D.1.8 (9)) that excluded this study and

found that results for DLd versus BMP were insensitive to this, most likely because the sample size of Hungria was small and thus relatively limited indirect information is gained from inclusion of the MPT -> CTd -> MP loop in the network.

Given that the NMA in which there was some evidence for heterogeneity was ORR, the EAG also ran a random effects NMA excluding Hungria to assess the impact (see section 3.5).

3.4.4 Methods used for unanchored indirect treatment comparisons (uITC)

3.4.4.1 DLd vs BMP

The company performed an uITC to compare DLd vs BMP for OS, PFS and TTD using IPD from MAIA and ALCYONE. The uITC method is an observational comparison using the BMP arm from ALCYONE and weighting it to match the MAIA trial population characteristics. They considered this to be a more robust estimate than that derived from the NMA due to the violation of proportional hazards and indicated that this was as suggested by NICE Technical Support Document TSD 18 (37). However, TSD 18 states that "*unanchored methods for population adjustment are problematic and should not be used when anchored methods can be applied*" (page 7). Based on this the EAG believes that anchored results from the NMA should be preferred, as this preserves randomisation and makes fewer assumptions, and the updated NMA models the company provided in response to clarification questions relaxes the proportional hazards assumption.

The company used a propensity score Inverse Probability Weighting (IPW) approach to adjust for prognostic variables in both trials, creating a pseudo-population in which combinations of covariates are balanced on both treatments. The objective of this is to estimate a population-level comparison that would be equivalent to that obtained from a randomised trial. However, this makes the assumption that all important prognostic factors and effect modifiers have been correctly adjusted for which is a strong assumption, particularly given that not all prognostic factors may have been reported in both trials. There is also no approach to test the validity of this assumption.

Although propensity score IPW was used as the base-case, covariate adjustment and propensity score matching were also explored as sensitivity analyses. The EAG did not find the company's justification for preferring IPW over covariate adjustment compelling given that they state there are some advantages of covariate adjustment (CS Section B.2.9.2). However, results of the sensitivity analyses showed similarity between the different approaches, and IPW gave the most conservative results, which the EAG found acceptable.

The company reweighted the BMP ALCYONE (45) cohort to match the population in the MAIA trial which they named the Average Treatment effect on the Treated (ATT). They included a weighting correction to rescale the sample size of the weighted population, which had only very minimal impact on precision, as shown in the clarification response. They also reported results weighted for the average treatment effect and the average

treatment effect for the overlap population. The EAG found this acceptable, as the MAIA population was considered sufficiently generalisable to the UK population.

The company used the following eight covariates to calculate the propensity scores and for the covariate adjustment approach:

- Age
- Gender
- ECOG performance status
- ISS stage at diagnosis
- Creatinine clearance
- Cytogenetic risk factors
- Hepatic function
- MM type (IgG/not IgG)

The EAG were unclear from the CS whether non-linear effects of these covariates, or their interactions, were considered. Time since diagnosis was also mentioned as a potentially important covariate, though this was not included in any of the adjustment analyses.

A further three covariates (bone marrow plasma cells, race and region) were considered to be important prognostic factors, though the company excluded them because their inclusion reduced covariate balance (CS Appendix S.2 (9)).

These additional covariates were identified as potentially important prognostic factors by both the company and the EAG's clinical experts and failing to include them in the adjustment may have introduced bias. Given that both good covariate balance and adjustment for all important prognostic factors and effect modifiers are important to minimise bias, this suggests that both the analysis including eight covariates and the sensitivity analysis with the additional three covariates reported by the company may provide biased estimates of the relative efficacy between DLd and BMP.

However, a sensitivity analysis including the three additional covariates was explored by the company (CS Appendix S.2 (9)) and the EAG believe that, although their inclusion may reduce covariate balance, the HR may be sensitive to them (particularly the inclusion of region for OS) and is more conservative than the company's estimates (Table 14). The EAG would have preferred to use results from this analysis, though weighted Kaplan-Meier data were not available for it. This is therefore an area of additional uncertainty in the uITC analysis.

Finally, after reweighting the population the company estimated a single HR from this analysis. Given that the company argues the advantage of the uITC approach is to avoid assuming proportional hazards, the EAG finds it inappropriate to summarise the results with a hazard ratio. Following clarification questions, the company provided evidence of tests for proportional hazards. There was evidence (globally and for several covariates, including treatment) that assuming proportional hazards was not appropriate for PFS, and no results of these tests were provided for TTD.

For TTD, given the absence of a randomised network of comparisons, the uITC analysis is the only approach for comparing DLd and BMP. Although the EAG's preference would be to use the analysis that adjusted for all 11 covariates, weighted Kaplan-Meier data were only provided for the model adjusting for 8 covariates. Given that using the HR from the 11 covariate-adjusted model would require assuming proportional hazards, and the impact on the HR is quite small, the EAG have used the weighted Kaplan-Meier data from the 8 covariate-adjusted model for TTD. However, the EAG's view remains that the uITC analysis is not a robust approach for comparing DLd and BMP. The pros and cons of different approaches to different approaches for estimating relative effects are summarised in Table 12).

Key Issue 5: What is the preferred source of evidence for the comparison BMP vs DLd, the HR NMA, the Parametric NMA, the Piecewise NMA, or the unanchored indirect treatment comparison?

3.4.4.2 Equivalence between BMP vs BCd

Estimates for DLd versus BCd could not be obtained from the NMA because BCd was not anchored to the network. To address this the company assumed equivalence between BCd and BMP and therefore assumed the relative efficacy for DLd versus BCd would be the same as for DLd versus BMP. To demonstrate equivalence, they performed a Matched Adjusted Indirect Comparison (MAIC) to compare BMP versus BCd. The company also provided naïve comparisons from two observational sources of evidence (Sandecka et al. 2021 (19) and National Cancer Registration and Analysis Service data) as well as clinical opinion. The EAG disagreed with the assumption of equivalence for reasons described below.

MAIC is a method used to adjust IPD from one study to match the covariate distribution of another study for which only aggregate data are reported. In this instance, the company reweighted BMP IPD from ALCYONE to match aggregate data on BCd from an observational study conducted in ASCT-ineligible patients, Jimenez-Zepeda et al. 2021 (2).

The following variables were used for reweighting:

- Median age
- Gender
- ISS I, ISS II and ISS III
- Bone disease
- Median albumin
- Median creatinine, µmol/l
- Median calcium, mmol/l
- Median Hb, g/l
- Median β2M, mg/l
- Median BMPC
- Median LDH, U/l
- High-risk cytogenetic risk

TABLE 12: ANALYTIC APPROACHES FOR ESTIMATING RELATIVE EFFECTS

Analytic approach	Pros	Cons	Company base-case	EAG base-case
Parametric NMA model	Analyses all the data simultaneously Relaxes proportional hazards assumption Same parametric form assumed across treatments Preserves randomised comparisons	Data not available to validate model Data not available to explore sensitivity of different parametric curves Assumes no imbalance in effect modifiers		
NMA model incorporating piecewise Cox model for Ld vs MPT	Relaxes proportional hazards assumption for Ld vs MPT (in which this is most severely violated) Preserves randomised comparisons	DLd vs Ld obtained from separate analysis of MAIA Assumes constant HR for other treatment comparisons Assumes no imbalance in effect modifiers		✓
NMA model assuming proportional hazards for all comparisons	Preserves randomised comparisons	Assumes proportional hazards for all comparisons (clearly violated for DLd vs Ld and Ld vs MPT) Assumes no imbalance in effect modifiers		
uITC	Uses IPD Adjusts for several prognostic factors	Risk of confounding by unadjusted prognostic factors and effect modifiers Non-randomised comparison Proportional hazards assumption not met for PFS Separate assumptions and analyses for different treatments	✓	

NMA=Network Meta-Analysis, DLd=daratumumab, lenalidomide and dexamethasone; Ld=lenalidomide with dexamethasone; MPT=melphalan, prednisone and thalidomide, uITC = unanchored Indirect Treatment Comparison, PFS=Progression Free Survival

The EAG's clinical experts agreed that these would be important prognostic factors or effect modifiers. However, they also stated that plasma cell leukaemia was an important factor, and whilst most RCTs excluded these patients (meaning that adjusting for them when matching MAIA and ALCYONE was not necessary), the data in Jimenez-Zepeda might still be expected to include them. Matching will therefore fail to account for this, which may bias results in favour of BMP as this population does not include patients with plasma cell leukaemia.

MM-type is another key prognostic factor that was not reported in Jimenez-Zepeda and so could not be used for reweighting. The EAG's clinical experts also highlighted this as important, and the company included it as a covariate in their adjusted uITC analysis (Section 3.4.4.1). The region in which patients lived was also not accounted for, which may be a confounder as the care pathway is known to vary in different parts of the world and Jimenez-Zepeda was a Canadian study. Furthermore, the different design of studies included in the MAIC (RCT and observational) would be likely to result in differences in other important prognostic factors. Overall, there were several important prognostic factors and effect modifiers the EAG identified that were unlikely to be balanced in the populations.

NICE TSD 18 (37) states that an unanchored MAIC should only be used when anchored methods cannot be applied. The EAG accepts that an unanchored comparison is necessary here, though they do not believe that this analysis has fully accounted for all important prognostic factors and effect modifiers, and thus estimated HRs are likely to be biased in an unknown direction. Several of the standardised weights (Figure 10, CS Appendix D.7 (9)) were also high, suggesting that the samples were not well matched.

Although the company reported that the MAIC-adjusted HRs for OS and PFS to show equivalence between BMP and BCd on the basis of statistical significance at the 5% level, the EAG do not believe that this constitutes sufficient evidence of equivalence. A non-inferiority approach should have been used to assess equivalence. There is also some evidence that the hazards differ. For PFS the MAIC-adjusted HR is [redacted], implying that BCd may be better than BMP.

The company also provided naïve comparisons from two observational sources of evidence that made no adjustments for potential confounders (Sandecka et al. 2021 (19) and National Cancer Registration and Analysis Service data). Whilst the survival estimates in these studies were not substantially different for BMP and BCd they did not provide meaningful evidence of equivalence and were considered to be of less value than the results from the MAIC in informing BMP vs BCd. The company stated that their clinical experts were of the opinion that BMP and BCd were equivalent, though there was no formal elicitation process to determine this.

The EAG would have preferred to be provided with an unanchored MAIC that directly compared BCd from Jimenez-Zepeda to DLd using data from MAIA, as this would have avoided making multiple uncertain comparisons (an unanchored MAIC followed by an uITC

analysis). In the absence of this the EAG prefer to use the HRs estimated from the MAIC of BMP vs BCd, rather than assuming equivalence.

As in the uITC for DLd versus BMP (Section 3.4.4.1), the MAIC assumes proportional hazards in order to estimate the HR to demonstrate equivalence between BMP and BCd. Given that this does not hold for other comparisons in the NMA (CS Appendix O (9)) it may also be violated here.

Following reweighting, the HR for OS for BMP vs BCd changes direction ([redacted]), giving a result with greater face validity than the unweighted estimate when compared to the HR for PFS. However, the EAG still acknowledges that this is likely to be a biased estimate due to incomplete adjustment of prognostic factors/effect modifiers and potential violation of the proportional hazards assumption.

Key Issue 6: Is it reasonable to assume equivalence between BMP and BCd?

3.4.5 Results from the unanchored indirect treatment comparisons

3.4.5.1 DLd vs BMP

The company use the uITC to create a BMP "arm" matched to the MAIA study population that is then analysed as if it were an additional arm of the MAIA study. This is what the company use for their base-case model for comparisons with BMP. For the uITC, the EAG prefer to use weighted Kaplan-Meier data from the IPW PS model to avoid the need to assume constant HRs (Table 13, and CS Document B Figures 38, 40 & 42 (3)). The EAG also notes that the median OS is not reached for either DLd or BMP in the uITC making the long term differences in survival curves uncertain (see Section 4.2.6). The EAG argue that a randomised comparison from a NMA is more reliable for the comparison of DLd vs BMP for OS and PFS.

As noted in Section 3.4.4.1, the EAG would have preferred to use results from the IPW PS model that adjusted for 11 covariates, but Kaplan-Meier data were not available. Adjusted-HRs for both models for PFS, OS and TTD are shown in Table 14. Whilst differences between the model results are mostly minor, the HR for OS and TTD are less favourable in the model adjusting for all 11 covariates.

TABLE 13: ATT WEIGHTED ESTIMATES FROM UITC FOR DLD AND BMP FROM THE PS IPW MODEL ADJUSTED FOR 8 COVARIATES

	DLd (n=368)	BMP (n=356)
Number of PFS events (%)	[redacted]	[redacted]
Median PFS (95% CI)	[redacted]	[redacted]
Number of OS events (%)	[redacted]	[redacted]
Median OS (95% CI)	[redacted]	[redacted]
Number of TTD events (%)	[redacted]	[redacted]

Median TTD (95% CI)	[redacted]	[redacted]

Abbreviations: DLd: daratumumab, lenalidomide, dexamethasone; BMP: bortezomib, melphalan, prednisone; ATT: Average Treatment Effect on the Treated; PFS: Progression-free survival; OS: Overall survival; TTD: Time to treatment discontinuation; NE: Not estimable

TABLE 14: ATT WEIGHTED HRS FROM UITC FOR DLD AND BMP FROM THE PS IPW MODEL ADJUSTED FOR 8 COVARIATES AND 11 COVARIATES

	8 covariates used for adjustment	11 covariates used for adjustment
PFS HR (95% CI)	[redacted]	[redacted]
OS HR (95% CI)	[redacted]	[redacted]
TTD HR (95% CI)	[redacted]	[redacted]

Abbreviations: DLd: daratumumab, lenalidomide, dexamethasone; BMP: bortezomib, melphalan, prednisone; ATT: Average Treatment Effect on the Treated; PFS: Progression-free survival; OS: Overall survival; TTD: Time to treatment discontinuation; NE: Not estimable; HR: Hazard ratio

3.4.5.2 BMP vs BCd

The company use the results from their MAIC (Table 15) to justify the assumption that PFS and OS for BCd were equal to that for BMP in their model. Reweighted results from the MAIC showed greater face validity than naïve (unweighted) results, with HRs for both PFS and OS in the same direction suggesting that BMP may have poorer PFS than BCd (Table 15). This may be a result of better tolerability of BCd meaning that patients remain on treatment for longer and so benefit more. Given the magnitude and certainty of HRs the EAG were unconvinced by the company's justification for equivalence between BMP and BCd and prefer to apply the estimated hazard ratios from the MAIC to the BMP OS and PFS curves to obtain OS and PFS curves for BCd. The EAG acknowledges the limitations of the MAIC approach applied to observational and single arm studies (See Section 3.4.4.2), however it is the best source of evidence available.

TABLE 15: MAIC RESULTS FOR BMP VS BCD (REPRODUCED FROM TABLE 56, CS APPENDIX D (9))

Endpoint	BMP vs BCd	
	Naïve comparison (all patients)	MAIC adjusting for prognostic variables
OS (BMP vs BCd), HR (95% CI)	[redacted]	[redacted]
PFS (BMP vs BCd), HR (95% CI)	[redacted]	[redacted]

Abbreviations: BCd: cyclophosphamide, bortezomib and dexamethasone; BMP: bortezomib, melphalan and prednisone; CI: confidence interval; HR: hazard ratio; MAIC: matching adjusted indirect comparison.

3.5 Additional work on clinical effectiveness undertaken by the EAG

Given the heterogeneity observed in the NMA for ORR, the EAG also ran a random effects NMA excluding Hungria to assess the impact. The between-study SD reduced slightly from [redacted] in the base-case to [redacted] in the analysis excluding Hungria.

Further sensitivity analyses investigated by the EAG are given below (Sections 3.5.1 and 3.5.2). We would have liked to explore sensitivity of different parametric models from the parametric NMA but did not have the data with which to do this.

3.5.1 Sensitivity analyses for OS and PFS NMAs excluding Hungria(26) and MRC Myeloma IX(29)

Given the differences in study inclusion criteria and baseline characteristics between studies investigating CTd (Hungria (26) and MRC Myeloma IX (29)) and other studies in the network, the EAG performed sensitivity analyses excluding these studies for OS and PFS. NMAs assuming constant HRs and fitting a piecewise Cox model for PFS were investigated. Results for both the sensitivity analyses and corresponding HRs from the company's NMAs including all the studies are given in Table 16, Table 17, Table 18 and Table 19.

Results were slightly more favourable for Ld compared with BMP in the analyses excluding CTd, and therefore this would be expected to favour DLd compared with BMP. The impacts were very minor for OS, and only makes a small difference for PFS, where the HRs at ≥20 months follow-up for BMP vs Ld changes from [redacted] when CTd studies are excluded. No additional precision is gained from the inclusion of CTd, likely due to the small sample size of Hungria making this connection very weak.

Given that there are no gains in precision and that the inclusion of CTd may introduce inconsistency due to baseline imbalances in Hungria (Section 3.4.2), the EAG prefers to exclude studies comparing CTd from the analysis as their base-case.

TABLE 16: RESULTS FOR PFS FROM FIXED EFFECTS HR NMA INCLUDING (UPPER TRIANGLE) AND EXCLUDING (LOWER TRIANGLE) CTD STUDIES (HUNGRIA(26) AND MRC MYELOMA IX(29))

HR (95% CI)	Ld cont	DLd	BMP	MPT
Ld cont	-	[redacted]	[redacted]	[redacted]
DLd	[redacted]	-	[redacted]	[redacted]
BMP	[redacted]	[redacted]	-	[redacted]
MPT	[redacted]	[redacted]	[redacted]	-

Results for the NMA excluding CTd studies are shown in the lower left part of the table, in which a HR<1 favours the row-defined treatment.

Results for the NMA from the overall dataset (including CTd) are shown in the top right part of the table, in which a HR<1 favours the column-defined treatment. This allows easier numerical comparison between results from both analyses.
Abbreviations: DLd: daratumumab, lenalidomide, dexamethasone; BMP: bortezomib, melphalan, prednisone; prednisone; Ld cont: lenalidomide, dexamethasone continuous; MPT: melphalan, prednisone and thalidomide PFS: progression free survival;

TABLE 17: RESULTS FOR PFS (<20 MONTHS) FROM FIXED EFFECTS PIECEWISE COX NMA INCLUDING (UPPER TRIANGLE) AND EXCLUDING (LOWER TRIANGLE) CTD STUDIES (HUNGRIA(26) AND MRC MYELOMA IX(29))

HR (95% CI)	Ld cont	BMP	MPT
Ld cont	-	[redacted]	[redacted]
BMP	[redacted]	-	[redacted]
MPT	[redacted]	[redacted]	-

Results for the NMA excluding CTd studies are shown in the lower left part of the table, in which a HR<1 favours the row-defined treatment.
Results for the NMA from the overall dataset (including CTd) are shown in the top right part of the table, in which a HR<1 favours the column-defined treatment. This allows easier numerical comparison between results from both analyses.
Abbreviations: BMP: bortezomib, melphalan, prednisone; Ld cont: lenalidomide, dexamethasone continuous; MPT: melphalan, prednisone and thalidomide PFS: progression free survival;

TABLE 18: RESULTS FOR PFS (≥20 MONTHS) FROM FIXED EFFECTS PIECEWISE COX NMA INCLUDING (UPPER TRIANGLE) AND EXCLUDING (LOWER TRIANGLE) CTD STUDIES (HUNGRIA(26) AND MRC MYELOMA IX(29))

HR (95% CI)	Ld cont	BMP	MPT
Ld cont	-	[redacted]	[redacted]
BMP	[redacted]	-	[redacted]
MPT	[redacted]	[redacted]	-

Results for the NMA excluding CTd studies are shown in the lower left part of the table, in which a HR<1 favours the row-defined treatment.
Results for the NMA from the overall dataset (including CTd) are shown in the top right part of the table, in which a HR<1 favours the column-defined treatment. This allows easier numerical comparison between results from both analyses.
Abbreviations: BMP: bortezomib, melphalan, prednisone; Ld cont: lenalidomide, dexamethasone continuous; MPT: melphalan, prednisone and thalidomide PFS: progression free survival;

TABLE 19: RESULTS FOR OS FROM FIXED EFFECTS NMA INCLUDING (UPPER TRIANGLE) AND EXCLUDING (LOWER TRIANGLE) CTD STUDIES (HUNGRIA(26) AND MRC MYELOMA IX(29))

HR (95% CI)	Ld cont	DLd	BMP	MPT
Ld cont	-	[redacted]	[redacted]	[redacted]
DLd	[redacted]	-	[redacted]	[redacted]
BMP	[redacted]	[redacted]	-	[redacted]

MPT	[redacted]	[redacted]	[redacted]	-

Results for the NMA excluding CTd studies are shown in the lower left part of the table, in which a HR<1 favours the row-defined treatment.
Results for the NMA from the overall dataset (including CTd) are shown in the top right part of the table, in which a HR<1 favours the column-defined treatment. This allows easier numerical comparison between results from both analyses.
Abbreviations: DLd: daratumumab, lenalidomide, dexamethasone; BMP: bortezomib, melphalan, prednisone; Ld cont: lenalidomide, dexamethasone continuous; MPT: melphalan, prednisone and thalidomide OS: overall survival;

3.5.2 Sensitivity analyses for OS and PFS NMAs using only IFM 99/06(28) for MPT vs MP

The EAG highlighted potential differences in baseline characteristics in studies comparing MPT vs MP and identified that IFM 99/06(28) was likely to have the most similar baseline characteristics to MAIA (Section 3.3.1). Sensitivity analyses were therefore conducted using only this study for the comparison of MPT vs MP (excluding Sacchi, IFM 01/01 and TMSG) for both OS and PFS (both assuming constant HRs and fitting a piecewise Cox model). Results for both the sensitivity analyses and corresponding HRs from the company's NMAs including all the studies are given in Table 20, Table 21, Table 22 and Table 23.

HRs are slightly more favourable to Ld (and DLd for OS) when using only IFM 99/06 but the differences are minimal and precision is lower. Given that results from the overall analysis are broadly consistent with those from the sensitivity analyses and that there is greater precision, the EAG choose to include all studies for MPT vs MP in the network.

TABLE 20: RESULTS FOR PFS FROM FIXED EFFECTS NMA USING ONLY IFM 99/06(28) FOR MPT VS MP

HR (95 % CI)	Ld cont	DLd	BMP	CTd	MPT
Ld cont	-	[redacted]	[redacted]	[redacted]	[redacted]
DLd	[redacted]	-	[redacted]	[redacted]	[redacted]
BMP	[redacted]	[redacted]	-	[redacted]	[redacted]
CTd	[redacted]	[redacted]	[redacted]	-	[redacted]
MPT	[redacted]	[redacted]	[redacted]	[redacted]	-

Results for the NMA using only IFM 99/06(28) for MPT vs MP are shown in the lower left part of the table, in which a HR<1 favours the row-defined treatment.

Results for the NMA from the overall dataset are shown in the top right part of the table, in which a HR<1 favours the column-defined treatment. This allows easier numerical comparison between results from both analyses.
Abbreviations: DLd: daratumumab, lenalidomide, dexamethasone; BMP: bortezomib, melphalan, prednisone; CTd: cyclophosphamide, thalidomide, and dexamethasone; prednisone; Ld cont: lenalidomide, dexamethasone continuous; MPT: melphalan, prednisone and thalidomide PFS: progression free survival;

TABLE 21: RESULTS FOR PFS (<20 MONTHS) FROM FIXED EFFECTS PIECEWISE COX NMA USING ONLY IFM 99/06(28) FOR MPT VS MP

HR (95% CI)	Ld cont	BMP	CTd	MPT
Ld cont	-	[redacted]	[redacted]	[redacted]
BMP	[redacted]	-	[redacted]	[redacted]
CTd	[redacted]	[redacted]	-	[redacted]
MPT	[redacted]	[redacted]	[redacted]	-

Results for the NMA using only IFM 99/06 for MPT vs MP are shown in the lower left part of the table, in which a HR<1 favours the row-defined treatment.
Results for the NMA from the overall dataset are shown in the top right part of the table, in which a HR<1 favours the column-defined treatment. This allows easier numerical comparison between results from both analyses.
Abbreviations: BMP: bortezomib, melphalan, prednisone; CTd: cyclophosphamide, thalidomide, and dexamethasone; prednisone; Ld cont: lenalidomide, dexamethasone continuous; MPT: melphalan, prednisone and thalidomide PFS: progression free survival;

TABLE 22: RESULTS FOR PFS (≥20 MONTHS) FROM FIXED EFFECTS PIECEWISE COX NMA USING ONLY IFM 99/06(28) FOR MPT VS MP

HR (95% CI)	Ld cont	BMP	CTd	MPT
Ld cont	-	[redacted]	[redacted]	[redacted]
BMP	[redacted]	-	[redacted]	[redacted]
CTD	[redacted]	[redacted]	-	[redacted]
MPT	[redacted]	[redacted]	[redacted]	-

Results for the NMA using only IFM 99/06 for MPT vs MP are shown in the lower left part of the table, in which a HR<1 favours the row-defined treatment.
Results for the NMA from the overall dataset are shown in the top right part of the table, in which a HR<1 favours the column-defined treatment. This allows easier numerical comparison between results from both analyses.
Abbreviations: BMP: bortezomib, melphalan, prednisone; CTd: cyclophosphamide, thalidomide, and dexamethasone; prednisone; Ld cont: lenalidomide, dexamethasone continuous; MPT: melphalan, prednisone and thalidomide PFS: progression free survival;

TABLE 23: RESULTS FOR OS FROM FIXED EFFECTS NMA USING ONLY IFM 99/06(28) FOR MPT VS MP

HR (95 % CI)	Ld cont	DLd	BMP	CTd	MPT

Ld cont	-	[redacted]	[redacted]	[redacted]	[redacted]
DLd	[redacted]	-	[redacted]	[redacted]	[redacted]
BMP	[redacted]	[redacted]	-	[redacted]	[redacted]
CTd	[redacted]	[redacted]	[redacted]	-	[redacted]
MPT	[redacted]	[redacted]	[redacted]	[redacted]	-

Results for the NMA using only IFM 99/06 for MPT vs MP are shown in the lower left part of the table, in which a HR<1 favours the row-defined treatment.
Results for the NMA from the overall dataset are shown in the top right part of the table, in which a HR<1 favours the column-defined treatment. This allows easier numerical comparison between results from both analyses.
Abbreviations: DLd: daratumumab, lenalidomide, dexamethasone; BMP: bortezomib, melphalan, prednisone; CTd: cyclophosphamide, thalidomide, and dexamethasone; prednisone; Ld cont: lenalidomide, dexamethasone continuous; MPT: melphalan, prednisone and thalidomide OS: overall survival;

3.6 Conclusions of the clinical effectiveness section

The company's submitted evidence is in line with the scope. The company argues that the main comparator is Ld, but also provide randomised comparisons with BMP, BCd, CTd, and MPT. The EAG agree with the company that thalidomide containing combinations are rarely used at 1st line for NDMM patients, ineligible for ASCT.

The estimates of clinical effectiveness and safety for DLd vs Ld come from the MAIA trial which the EAG considers to be at low risk of bias and broadly generalisable to UK practice (Section 3.2). However, the EAG are concerned that generalisability of survival outcomes is limited by the non-trivial proportion of participants who received 2nd and 3rd line therapies that are not routinely commissioned by NHS England. Based on the latest data-cut from MAIA (at median follow up 64.5 months), there is evidence that DLd is effective compared with Ld for most trial outcomes measured, except for HRQoL for which there was no evidence of a difference. The EAG note that the data for OS are relatively immature given the good prognosis of NDMM patients ineligible for ASCT, with median OS not achieved for patients on the DLd arm and only just met for Ld. DLd is associated with more grade 3 and 4, and more serious TEAEs than Ld.

For comparisons between DLd and other treatments, the company uses a variety of different evidence sources and analyses and these differ by comparator. The company prefer to use the uITC to compare DLd with BMP, even though this is an observational comparison based on single arms from different studies. The EAG prefer using a NMA which is based on randomised comparisons, but relaxes the proportional hazard assumption. The EAG prefers the piecewise Cox model for PFS, but because this is not provided the parametric NMA is preferred for OS. However, there are some concerns about the piecewise Cox model because the piecewise analysis is only applied to the comparison with MPT vs Ld, and proportional hazards is assumed for other comparisons in the NMA which is questionable here. There are also concerns about differences in inclusion criteria and

populations of the trials included in the NMA (Section 3.3.1), but assessment of statistical heterogeneity, inconsistency, and sensitivity analyses suggest that the results are reasonably robust for PFS and OS (Section 3.5). For TTD there is a paucity of randomised evidence for BMP, CTd, BCd, and MPT, and so the EAG acknowledge that data from the uITC analysis is the best option for the comparison with BMP for the TTD outcome only. For ORR and ≥CR the company's NMA estimates are credible.

In contrast to the company's assessment of low risk of bias for all three studies contributing to the MAIC, the EAG rated these as being at low risk(10), unclear risk(1), and at critical risk of bias (2) (section 3.2.1 and section 3.3.2). The company's MAIC comparing BCd and BMP may suffer from bias. However, this is the only evidence available to estimate the BCd vs BMP effect and has better face validity than a naïve indirect comparison. The EAG do not consider the company's assumption of equivalence of OS and PFS between BMP and BCd to be justifiable and prefer to use the hazard ratios estimated from the companys MAIC in the model.

4 COST EFFECTIVENESS

4.1 EAG comment on company's review of cost-effectiveness evidence

The company report a systematic literature review (CS Appendix G) (9) aiming to review the evidence for 'the cost-effectiveness of DLd and relative comparators for newly diagnosed MM ASCT-ineligible patients. Comparators were defined by the company as: BCd, BMP, CTd, Ld, and MPT (see CS Appendix G.4). (9)

4.1.1 Search strategy

The company report searches of MEDLINE, Embase, EconLit and the Cost-Effectiveness Analysis (CEA) Registry to identify economic and cost-effectiveness analyses. The searches were last updated in February 2022 and broadly align with the aim of the systematic review. The EAG notes that the searches were restricted to English language publications, but the EAG do not consider this a limitation of the review on this occasion. (46)

4.1.2 Inclusion/exclusion criteria

Searches were independently screened by two reviewers (with a third reviewer available to resolve any disagreements). This approach to selecting evidence aligns with best practice guidance. (46)

The population for the review aligns with the NICE scope and the outcomes align with the aim of the systematic review set out above. (47) Only evaluations of BCd, BMP, CTd, DLd, Ld, and MPT were eligible for inclusion in this review, which the EAG considers appropriate and in line with the scope.

4.1.3 Identified studies

Previous cost-effectiveness analyses (UK and non-UK) and previous technology appraisals are summarised in Tables 77-79 respectively, of CS Appendix G.(9) Of these only 2 studies specifically consider DLd for the NDMM ASCT ineligible population: Narispur 2021 (48) which compared DLd, BLd and Ld using a Markov model (partitioned survival model) in a US setting, and the CADTH technology appraisal CADTH PC0189-000 (49) which compared DLd, BMP, BCd, and Ld using a partitioned survival time model. Both models used data from the MAIA study (7), and both concluded that DLd was not cost-effective without a price reduction.

Other relevant previous studies on the NDMM ASCT ineligible population are: NICE TA228 (5) comparing MPT, MP, BMP, CTd and BMP using a Markov model, SMC 1096/15 (50) comparing Ld and BMP, using a partitioned survival model, and NICE TA587 (28) comparing Ld with BMP using a hybrid Kaplan-Meier and Markov model.

The EAG agrees that there is no previous cost-effectiveness model comparing DLd with BCd, BMP, CTd, DLd, Ld, and MPT in the UK setting, but that the models listed above are relevant sources for model structure, assumptions, inputs, and validation.

4.2 Summary and critique of the company's submitted economic evaluation by the EAG

The company developed a *de novo* economic model to estimate incremental cost effectiveness ratios (ICERs) in terms of additional cost per additional quality-adjusted life year (QALY) gained for DLd compared with Ld, BMP, and BCd, and also included comparisons with CTd and MPT. The model was submitted in Microsoft Excel®, and an updated version of the model was submitted in response to clarification questions. The updated model incorporates relative dose intensities (RDI) to capture cost implications of dose-reductions of components of combination therapies, provides scenarios for different estimates for PFS and OS using different sources/NMA models, and scenarios for assumptions about time on treatment. We focus on the company's updated base-case in the critique and results presented below. The company presents results including and excluding treatments currently available via the Cancer Drugs Fund (CDF). We only explore model assumptions and scenarios excluding treatments currently on the CDF, in line with section 2.2.15 of the NICE Manual. (46) We present results including a Patient Access Scheme (PAS) for Daratumumab only in this document, but provide results with PAS prices for Carfilzomib, Pomalidomide, Panobinostat, and Ixazomib, together with Commercial Medicines Unit (CMU) price for Melphalan (CS uses British National Formulary (BNF) price), and electronic Market Information Tool (eMIT) price for Cyclophosphamide (CS uses BNF price) in a confidential appendix.

4.2.1 NICE reference case checklist

TABLE 24: NICE REFERENCE CASE CHECKLIST

Element of health technology assessment	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Consistent with the NICE reference case
Perspective on costs	NHS and PSS	Consistent with the NICE reference case
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Consistent with the NICE reference case
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	The CS used a time-horizon of 26 years (similar to TA587, but less than TA228). By 26 years only 1% of patients were still alive in the model, and so the EAG considers the time horizon appropriate for this model.
Synthesis of evidence on health effects	Based on systematic review	Systematic review appropriate, but CS used a network meta-analysis for some treatment effects and unanchored indirect treatment comparisons for other treatment effects. **Key issues 4-6**
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	The company used EQ-5D-5L data mapped onto the 3L UK value set in accordance with NICE guidance.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	The CS used patient-reported HRQoL outcomes taken from patients enrolled in the MAIA clinical trial (51) to assign utilities to health states. Utilities were age-adjusted using population HRQoL analysis from HSE
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	HRQoL analysis of patients enrolled in the MAIA trial comprised an international sample of patients, with a small

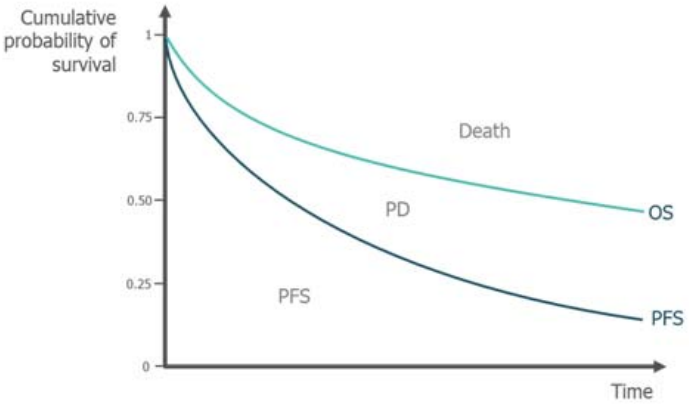
Element of health technology assessment	Reference case	EAG comment on company's submission
		subset from the UK which may not be fully representative of the UK NDMM population.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	CS is consistent with the NICE reference case
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	The CS is consistent with the NICE reference case
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	The CS is consistent with the NICE reference case
PSS, personal social services; QALYs, quality-adjusted life years; EQ-5D, standardised instrument for use as a measure of health outcome.		

4.2.2 Model structure

4.2.2.1 Summary of model structure in CS

The company produced cost-utility analyses using a health economic model programmed in Microsoft Excel®. The company used a partitioned survival model approach, including three health states in their model structure: progression-free, progressed disease, and death. Health state transition was determined by extrapolated survival curves developed using survival data from two RCTs (MAIA (7) (8) and ALCYONE (45)). The probability of a patient in the cohort (treated with DLd, Ld, or BMP) being in any given health state at a given time was determined by Overall Survival (OS) and Progression Free Survival (PFS) in the extrapolated survival curves constrained so that OS did not exceed that in the general population. To model survival outcomes in patients treated with other comparators (CTd, MPT) treatment effects were applied to the model's survival curves using hazard ratios which were estimated in a network meta-analysis.

FIGURE 5: THE PARTITIONED SURVIVAL MODEL STRUCTURE (REPRODUCED FROM FIGURE 45, CS DOCUMENT B).(3)



PFS=Progression Free Survival, PD= Progressed Disease, OS = Overall Survival

Patients who transition to the progressed disease health state move to subsequent lines of therapy, where outcomes for 2nd, 3rd and later lines of treatments are assumed to be captured in the OS curves assumed in the CS. Costs of 2nd and 3rd line treatments were included in the model, but not costs of 4th line, in alignment with TA587. The company estimated the proportion of patients assigned to each subsequent treatment through discussions with clinicians.

Time on treatment for DLd and Ld was modelled using survival curves extrapolated from the trial data. The company included options for the user to select a choice of parametric survival models to extrapolate beyond the length of the trial period. In the CS base case, Gompertz and Weibull extrapolations were used to model DLd and Ld, respectively. TTD for BMP was modelled using TTD Kaplan-Meier plots from the ALYCONE trial. TTD was not available for MPT, CPD, and BCd, and so it was assumed TTD was equivalent to PFS for these treatments.

4.2.2.2 EAG critique of model structure

The EAG acknowledges the precedent for using partitioned survival model in previous TAs in this therapy area. An alternative would be to use a Multi-State Model (MSM) which can capture the dependencies between PFS and Post Progression Survival (PPS), the costs and benefits of the treatment pathway 2nd line and beyond, and may give different results. (52) MSMs require individual patient data (IPD) to estimate which would be possibly for the DLd and Ld arms, but not for some of the other comparators. The EAG deems the company's use of a PFS model type as appropriate in the context of the available evidence on patient outcomes and comparability with previous TAs. Some previous models have incorporated response to treatment in the model (minimal/partial/complete response), which may be more sensitive to capture the impact of different treatment options and could potentially have been used here. The use of a single post-progression state does not directly capture the treatment pathway 2nd line and beyond, however given the complexity and variation in clinical practice in subsequent therapies the EAG considers the single post-progression health state a pragmatic choice and notes the structural similarities with health economic models used in the therapy area (NICE TA228 (5), SMC 1096/15 (50), NICE TA587 (4)).

4.2.3 Population

4.2.3.1 Summary of modelled population in CS

The CS models a population of ASCT-ineligible NDMM with demographic and disease characteristics assumed to match the ITT population recruited in the MAIA trial. Key patient characteristics used in the model are age, sex, body weight and body surface area (Table 36 B3.2.1 of CS). (3) Age and sex are used to determine general population mortality rates and age is also used for general population utilities. Weight and body surface area (BSA) are used to determine drug acquisition costs of treatments where dose is based on weight (DLd IV formulation) or BSA (bortezomib, melphalan, prednisone and carfilzomib).

4.2.3.2 EAG critique of modelled population

The EAGs clinical advisers felt that the MAIA population was narrower than that seen in clinical practice but that, unusually for trials in this area, the average age was similar to ASCT-ineligible NDMM patients. This is also seen in the close agreement in mean age between MAIA and NHS Digital RWE on a cohort of NDMM patients in England (53) (Table 36 B3.2.1) (3), although MAIA appears to under-represent male ASCT-ineligible NDMM patients (52.1% in MAIA compared with [redacted] in the NHS Digital RWE in England cohort). The impact on the model of increasing the proportion of male patients is to increase general population mortality slightly and to increase the cost of treatments with weight or BSA based dosing. This has a negligible impact on the ICER, and the EAG therefore considers the company's assumptions reasonable.

4.2.4 Interventions and comparators

4.2.4.1 Summary of interventions and comparators in CS

Although DLd was administered intravenously (IV) in the MAIA trial (10), in the model it is assumed that DLd will be administered subcutaneously (SC). The company provides a scenario analysis where [redacted] of patients receive IV DLd.

The company considered Ld and a bortezomib containing regimen (BMP or BCd) to be the main comparators used in clinical practice and argued that thalidomide containing regimens (CTd and MPT) are rarely used despite being included in the NICE scope. (47) CTd and MPT are however included in the model and results are provided on their cost-effectiveness. BMP is used as the bortezomib containing regimen in the company's base-case but results are provided for BCd under an assumption of equal efficacy of BMP and BCd.

The company model includes costs of subsequent treatments at 2nd and 3rd line and assumes that these will depend on the treatment received at 1st line. The assumed treatment pathway including treatment options at 2nd line and beyond in the CS are shown in Figure 1 and CS Document B Fig 5. (3) This includes treatments that are currently available only on the Cancer Drugs Fund (CDF). The company provides results in its base-case including and excluding CDF treatments on the basis that CDF treatments may become available in routine commissioning in the near future. The proportion of patients assumed

to receive 2nd and 3rd line treatments depending on their 1st line treatment was based upon an advisory board with 7 clinicians (6) (Tables 51 and 52 of CS Document B). (3)

4.2.4.2 EAG critique of interventions and comparators

The EAG's clinical advice suggested that DLd would be administered SC for the majority of patients and IV administration would only be used for a very small number of patients with very little subcutaneous fat. The EAG therefore considers it appropriate to assume SC administration when deriving costs for DLd for the majority of patients. However, the efficacy outcomes PFS, OS and TTD in the model are all based upon the MAIA trial (10, 54) which used an IV administration. Our clinical advice was that efficacy of SC and IV administration were likely to be similar, and safety might be better for SC administration. This view is in line with findings from the COLUMBA study which found a relative risk of response for SC compared with IV administration of daratumumab of 1.11 (95%CI 0.98, 1.37) in relapsed or refractory MM. (55) The EAG consider that although no comparative evidence is available for IV vs SC DLd in NDMM unsuitable for ASCT patients it is reasonable to assume equal efficacy and safety in the model.

The NICE recommendations for Ld (TA587 (4)) and bortezomib in combination with an alkylating agent and a corticosteroid (TA228 (5)) are for patients contraindicated or unable to tolerate thalidomide, however none of the company's clinical experts said they would use thalidomide at 1st line. (6) The EAGs clinical advisors confirmed that thalidomide is rarely used in practice at 1st line for NDMM patients unsuitable for ASCT due to its toxicity. The EAG agrees with the company that thalidomide is rarely used in clinical practice and can be excluded as a comparator. There is variation in treatments used at 1st line across centres, but Ld is the most common treatment used (in approximately 50% - 75% (6)) with bortezomib containing regimens (BMP, BCd) also used. (6) The choice between BMP and BCd varies across centres, although whether a patient can tolerate MP is an important factor. The EAG does not agree with the company that efficacy of bortezomib containing regimens are necessarily equal as the company's MAIC does not support this (see section 3.4.4.2), suggesting BCd may be more effective for PFS. The EAG agrees with the company that the main comparators are Ld, BMP, and BCd, however BCd may be more effective than BMP and should be included in the company's base-case.

The EAG's clinical advisors described a high level of variation in practice across centres/regions for treatments given at 2nd, 3rd, and 4th line and that this is changing rapidly as the treatment landscape evolves. The variation in clinical practice can also be seen in the estimates of market share across the company's clinical experts. (6) Currently CDF treatments are used at 2nd line and beyond, however these treatments may not be made available for routine commissioning after the CDF period ends, and even if they do move to routine commissioning their cost is unknown. In line with NICE's methods guide 2022 section 2.2.15 (46) the EAGs view is that CDF treatments should not be included in the model. The EAG is aware however that the availability of CDF treatments may change during the course of this appraisal, adding uncertainty to the subsequent treatment options

available. While the company provided a scenario analysis which included CDF treatments in subsequent lines of therapy, no sensitivity analyses were performed to explore the uncertainty in the estimated distribution of the proportion of patients undergoing each 2nd and 3rd line treatment. The EAG explores this uncertainty in scenario analyses (see sections 4.2.8.2 and 6.1.4).

Key Issue 7: Should CDF drugs used at 2nd line and beyond be included in the company's model?

4.2.5 Perspective, time horizon and discounting

The analysis includes costs and benefits from an NHS England and PSS perspective. The company uses a 26 year time horizon in order to capture lifetime costs and benefits associated with the intervention and its comparators. As all patients in the CS model are predicted to have died by the 27th year in all treatment arms, this was considered by the EAG to be an appropriate assumption in the CS model. All costs and benefits were discounted at 3.5% per annum in alignment with the NICE reference case.

4.2.6 Treatment effectiveness and extrapolation

4.2.6.1 Summary of treatment effectiveness and extrapolation in CS

Different methods and evidence sources were used to obtain estimates of progression free survival (PFS), overall survival (OS), and time to treatment discontinuation (TTD) for the different treatment options in the model in the CS. PFS, OS, and TTD estimates for DLd and Ld were obtained by fitting and extrapolating parametric survival curves separately to the DLd and Ld arms of the MAIA trial data (data cut-off 21st October 2021). (51) Curves were fitted separately to the different treatment arms because it was not considered reasonable to assume proportional hazards (CS Appendix O). (9) PFS, and OS estimates for BMP were obtained by fitting and extrapolating parametric survival curves to the BMP arm of the ALCYONE trial (45) after using propensity score weightings to adjust the ALCYONE data to match the characteristics of the MAIA trial in an unanchored indirect treatment comparison (uITC) (described in section B.2.9.2 of CS). (3) TTD for BMP was obtained directly from the Kaplan-Meier data obtained from the uITC applied to the BMP arm of the ALCYONE trial to match to the MAIA population. Extrapolation of TTD was unnecessary for BMP because it has a fixed dose period. Survival outcomes of patients undergoing BCd were assumed to be equivalent to those treated with BMP due to the lack of head-to-head clinical studies and based on a MAIC using observational data from the Jimenez-Zepeda study (2) and the BMP arm of the ALCYONE trial (45) (described in section B.2.9.3 of CS) (3), as well as naïve comparisons from two observational sources of evidence and clinical opinion. However, as discussed in sections 3.4.4.2 and 3.4.5.2, the company's MAIC comparing BMP and BCd estimated hazard ratios for BMP vs BCd [redacted] for OS and [redacted] PFS (Table 56, CS Appendix D.6.3) which indicate there may be a benefit of BCd over BMP possibly due to improved tolerability. (9). The company provided a sensitivity analysis to this in their response to clarification question B2.

The PFS and OS estimates for CTd and MPT were derived by applying hazard ratios estimated from a NMA (CS Appendix D.1.10 (9)) to the survival curves for Ld. In a sensitivity analysis hazard ratios for CTd and MPT relative to BMP are applied to the estimated PFS and OS curves for BMP (CS Appendix M).(9) TTD for CTd, MPT, and BCd are all assumed equal to PFS due to lack of data on TTD. In response to clarification question B10 the company provided a scenario where a hazard ratio for TTD vs PFS is taken from the BMP analysis and applied to obtain TTD curves for CTd and MPT.

Choice of parametric curves for extrapolation of PFS, OS, and TTD curves for DLd, Ld, and BMP were based on visual inspection of fit, AIC and BIC goodness-of-fit criteria, and clinical plausibility of model predictions compared with PFS and OS proportions at 5, 10, and 15 years elicited from a survey of 9 clinicians (of whom 8 responded) (6) (section B.3.3.1 of CS).(3) PFS curves were capped by the OS curves, and the OS curves were capped at the rate of general population mortality based on average age and sex.

Table 25 summarises the parametric curves chosen in the company's base-case for DLd, Ld, BMP, and BCd, the data used to estimate them, the rationale for selection of the parametric curves, and comments from the EAG.

Following the clarification process the company presented scenarios where parametric NMAs were fitted to make comparisons between Dld, Ld, and BMP using a Gompertz distribution for OS and an Exponential distribution for PFS (see section 3.4.2). They also presented a scenario where a piecewise Cox model was used for the FIRST study (Ld vs MPT), but constant HRs used for other comparisons in the network (see sections 3.4.2 and 3.5).

TABLE 25: PARAMETRIC DISTRIBUTIONS CHOSEN FOR PFS AND OS FOR DLD, LD, BMP, AND BCD IN THE COMPANY'S BASE-CASE AND RATIONALE

Outcome	Treatment	Data used to estimate survival	Parametric Distribution	Rationale	EAG Comments
PFS	DLd	MAIA DLd arm	Exponential	Lowest AIC and BIC validated against visual fit to MAIA	Exponential, Weibull, Generalised Gamma, and Gompertz all give similarly low AIC. Exponential gives lowest BIC, followed by Weibull and Gompertz
PFS	Ld	MAIA Ld arm	Exponential	Best statistical fit based on BIC validated against clinical expert opinion, and visual fit to MAIA	Exponential, Weibull, Log-logistic, and Generalised Gamma all give similarly low AIC. Exponential, Weibull, Log-logistic all give similarly low BIC. Of these the Exponential, Weibull, and Generalised Gamma are in line with elicited estimates from clinical experts.
PFS	BMP	ALCYONE BMP arm adjusted to match the MAIA population	Weibull	Best statistical fit based on AIC and BIC validated against clinical expert opinion, and visual fit to adjusted ALCYONE data	Weibull and Generalised Gamma give similarly low AIC. Weibull and Gompertz give similarly low BIC. None of these curves give predictions that are in line with the elicited estimates from clinical experts. The fitted curves predict less time in PFS than clinical opinion.

PFS	BCd	BMP curve	Weibull	Assumed equivalent to BMP	The CS estimates a hazard ratio for BMP vs BCd of [redacted] for PFS, suggesting they are not equivalent.
OS	DLd	MAIA DLd arm	Exponential	Best statistical fit based on AIC and BIC	Exponential, Weibull, Generalised Gamma and Gompertz all gave similarly low AIC. Exponential gave lowest BIC, followed by Weibull and Gompertz.
OS	Ld	MAIA Ld arm	Gompertz	Best statistical fit based on AIC and BIC, validated against clinical expert opinion and visual fit to MAIA and FIRST	Gompertz, Weibull, and Generalised Gamma all gave similarly low AIC. Gompertz and Weibull gave similarly low BIC. Of these, Gompertz and Generalised Gamma were in line with estimates elicited from clinical experts. The shape of the fitted Gompertz curve is in line with FIRST
OS	BMP	ALCYONE BMP arm adjusted to match the MAIA population	Gompertz	Best statistical fit based on AIC and BIC, validated against clinical expert opinion and visual fit to adjusted ALCYONE data and VISTA	Gompertz gives the best fit using AIC and BIC criteria. The Gompertz gives predictions that are in line with clinical opinion at 5 years, but with lower survival at 10-15 years than the estimates elicited from clinical experts. The shape of the fitted Gompertz curve differs from the curve from VISTA.

OS	BCd	BMP curve	Gompertz	Assumed equivalent to BMP	The CS estimates a hazard ratio for BMP vs BCd of [redacted] for OS, and so it is unclear whether they are equivalent.
TTD	DLd	MAIA DLd arm	Gompertz	Statistical fit and validity compared with PFS	Generalised Gamma, Exponential, and Gompertz have similarly low AIC. Exponential has lowest BIC followed by Gompertz and Generalised Gamma.
TTD	Ld	MAIA Ld arm	Weibull	Statistical fit and validity compared with PFS	The Weibull does not have the best statistical fit on either AIC or BIC. Generalised Gamma, Exponential, and Gompertz have similarly low AIC, followed by the Weibull. Exponential, Weibull, and Gompertz have similarly low BIC, followed by Generalised Gamma. Predictions very similar for all these curves, so Weibull appropriate.
TTD	BMP	ALCYONE BMP arm adjusted to match the MAIA population	KM curve	A fixed treatment duration means no need for extrapolation	A fitted curve over the fixed treatment duration will give smoother predictions, but unlikely to have a big impact on results.
TTD	BCd	BMP PFS curve	Weibull	No data on TTD, so assumed equivalent to PFS	Unclear why PFS and OS is assumed equivalent for BMP and BCd, but not TTD

Abbreviations: DLd: daratumumab, lenalidomide, dexamethasone; BMP: bortezomib, melphalan, prednisone; Ld lenalidomide, dexamethasone; BCd: bortezomib, cyclophosphamide and dexamethasone; OS: overall survival; PFS: progression free survival

4.2.6.2 EAG critique of treatment effectiveness and extrapolation

4.2.6.2.1 Evidence sources and assumptions

There is a lack of consistency in approach because the company uses different evidence sources and analysis methods for different treatments in the model. The PFS, OS, and TTD outcomes for DLd and Ld come directly from the MAIA trial which is the only RCT that compares DLd and Ld in the NDMM ASCT ineligible population. The EAG agrees this is the most appropriate evidence source for this comparison. For BMP the company uses an unanchored indirect treatment comparison (uITC) matched to the MAIA population, and whilst they have adjusted for many potential effect modifiers and prognostic factors there were important factors that were not adjusted for (see section 3.4.5.1) and this is an observational comparison across single arms taken from different studies and susceptible to bias. There could be differences between studies in confounding factors, such as unmeasured patient characteristics and other contextual factors that might influence outcomes. BMP is connected to Ld in a network of randomised evidence making it possible to make the comparison using the company's NMA (Figure 2, CS Appendix D). (9) The company prefer their uITC because it does not rely on the proportional hazards assumption, and they have individual patient data from both MAIA and ALCYONE enabling more precise estimation. The EAG agrees that proportional hazards does not hold and that an uITC with IPD for both study arms is better than an unanchored MAIC with IPD on one arm and aggregate data on another. However, the EAG considers that the benefits of a randomised comparison from a NMA assuming proportional hazards may outweigh the disadvantages of bias due to an observational comparison and note that the company are using the NMA for comparisons with CTd and MPT, but not for other treatment comparisons. Alternative approaches for the NMA that do not assume proportional hazards suggested by the EAG include: fitting an accelerated failure time (AFT) model; fitting piecewise models with different hazard ratios on each piece; fitting parametric NMA models (43); or fitting flexible models such as fractional polynomials or spline models. (42) The EAG prefers to use an NMA rather than the company's uITC because it is based on randomised data. In response to clarification questions the company provided a scenario where parametric NMAs were fitted for all treatments using a Gompertz distribution for OS and an Exponential distribution for PFS, and a scenario where a piecewise Cox model was used for the FIRST study, but constant HRs used for other comparisons in the network. The piecewise NMA model is an attractive choice because inspection of the survival plots show two clear pieces of the curves where treatment effects differ, and the log-log plots (see company response to clarification question A5) indicate that the proportional hazards assumption appears valid within each piece of the curve. However, the company only adjusts for non-proportional hazards for the FIRST study and the PFS outcome and does not adjust for non-proportional hazards for any of the other studies/outcomes. The company's parametric NMA model has the advantage that it is fitted to all treatments simultaneously assuming the same parametric distributional form across treatments, which is in line with recommendations from TSD14. (44) However, the EAG could not validate the model nor obtain results for different parametric distributions to assess robustness of the economic model to these assumptions. Furthermore, the parametric choice made by the company for PFS differed from the EAGs preferred parametric choice (Weibull as described below), although agreed

with the EAGs parametric choice for OS. Given this the EAG prefers the results from the piecewise NMA as inputs to the economic model for PFS and the parametric NMA for OS, where the hazard ratios are applied to a parametric curve fitted to the MAIA trial data. (See **Key Issue 5**)

The company assume that BCd has the same efficacy as BMP based on their matched adjusted indirect comparison (MAIC) comparing BCd and BMP giving confidence intervals for hazard ratios that contain 1 (no effect), as well as based on weaker evidence from naïve comparisons from two observational sources of evidence and clinical opinion. However, the estimated hazard ratio for BMP vs BCd is [redacted] for PFS which is very nearly statistically significant at the 5% level and the effect for OS is in the same direction albeit with a wider confidence interval [redacted]. To demonstrate equivalence an approach based on non-inferiority bounds would be required rather than a test for statistical significance. The EAG does not agree that equivalence of BMP and BCd has been demonstrated, based on this comparison, although acknowledges limitations in the MAIC analysis that has been conducted (see section 3.4.4.2). Following clarification questions the company have provided a scenario where the hazard ratios for BCd vs BMP from their MAIC are applied to the BMP curves to estimate PFS and OS for BCd. The EAG recognises that the estimated treatment effect from the MAIC is an observational comparison and vulnerable to bias (section 3.2.1 and section 3.3.2), however this is the only estimate of BCd vs BMP available and is preferable to making the assumption that they are equivalent. (See **Key Issue 6**)

Due to lack of TTD data for CTd, MPT, and BCd, it is assumed that TTD is equal to PFS for these treatments. Whilst the EAG understands that assumptions must be made when data is not available, some patients do discontinue treatment prior to disease progression, for example due to adverse events, and this may differ across treatments. Regimens containing Thalidomide are known to have high toxicity and so it is expected that there may be a difference between TTD and PFS. For BCd given that other efficacy parameters are assumed equivalent to that for BMP it would be consistent to also assume TTD was the same for BCd and BMP, although the EAG heard from their clinical advisors that BCd may be better tolerated than BMP and so patients may stay on treatment for longer. The EAG considers the TTD estimates used for BCd, CTd, and MPT to be uncertain and likely overestimates. In response to clarification question B10 the company provided a scenario where TTD for BCd is equal to that for BMP, and also a scenario analysis where the HR for TTD vs PFS from BMP was applied to treatments where TTD was not available. These had minimal impact on the ICERs and so the EAG does not consider the company's assumptions for TTD for CTd, MPT, and BCd to be a key issue.

4.2.6.2.2 Choice of parametric curves for extrapolation

Because there is evidence that the proportional hazards assumption does not hold for OS, PFS, and TTD the EAG agrees that it is appropriate to fit separate survival curves to each treatment arm based largely on statistical fit and validation with clinical experts. However different parametric curves are selected for different treatments in the company's model (Table 25, and CS Document B section B.3.3.1 (3)). The Decision Support Unit Technical

Support Document TSD14 recommends that where parametric models are fitted separately to individual treatment arms it is sensible to use the same 'type' of model (ie the same parametric family) unless justified using clinical expert judgement, biological plausibility, and robust statistical analysis. (44) When comparing AIC and BIC values to assess statistical fit, the EAG considers that differences below 2 or 3 are not meaningful (56) and so models that give an AIC or BIC within 2 or 3 units are similarly good candidates on the basis of statistical fit.

For PFS the Weibull and Generalised Gamma curves give similar statistical fit with the lowest AIC for all of the 3 treatments (DLd, Ld, and BMP), and this is also true of the BIC for the Weibull (Table 25 and CS Document B Tables 38-40 (3)). There is therefore no robust statistical reason not to use the same parametric family (the Weibull) for all treatments. The predictions from the Weibull are in line with the estimates elicited from the clinical experts for Ld. None of the predictions from any of the parametric distributions is in line with the estimates elicited from the clinical experts for BMP, but the Weibull does give the best statistical fit to the BMP data based on AIC and BIC. The EAG considers that the extrapolations are uncertain, especially the extrapolation for BMP, but prefers to use the same parametric family (the Weibull) for all treatments in the absence of a rationale not to do so. The EAG prefers to use the HRs from the piecewise NMA for BMP applied to the Weibull curve fitted to Ld from MAIA in its base-case.

For OS the CS uses the Gompertz distribution for both Ld and BMP, and the Exponential for DLd on the basis of lowest AIC and BIC (CS Document B Table 41 (3)). For Ld the Weibull and Generalised Gamma give similar fit to the Gompertz, but for BMP none of the other distributions fit as well as the Gompertz. For DLd the Gompertz gives a similar fit to the Exponential for DLd based on AIC (1600.4 compared with 1598.5), suggesting that the Gompertz is appropriate for all treatments based on statistical fit. The EAG therefore prefers the Gompertz for all treatments, but notes that the estimated curves for DLd from the Exponential and Gompertz models are very similar (CS Document B Figure 49 (3)), and so results are unlikely to be sensitive to this choice. The Gompertz model predictions were in line with estimates elicited from clinical experts for Ld and the shape of the fitted curve is in line with the Ld arm of the FIRST study (CS Document B Figure 54 (3)). However, none of the parametric distributions fitted gave predictions in line with the estimates elicited from clinical experts for BMP, and the shape of the Kaplan-Meier curve from the VISTA study (57) differs from that from ALCYONE (1) and the fitted curve (CS Document B Figure 53 (3)). To address this the company provide a scenario analysis using an average of the Gompertz and Weibull models (CS Document B Figure 51 (3)). The EAG considers the survival curve fit for BMP to be very uncertain with potentially implausible long-term predictions. The EAG prefers to use the parametric NMA for BMP applied to the Gompertz curve fitted for Ld in its base-case, and presents a scenario analysis using an average of the Gompertz and Weibull for BMP OS from the uICT from ALCYONE adjusted to MAIA.

For DLd TTD the Generalised Gamma, Exponential, and Gompertz have similarly low AIC, although the Exponential gives the lowest BIC. The 3 curves do give difference extrapolations and so results may be sensitive to the choice. The company chose the

Gompertz on the basis that it was closer to the PFS curve than the Generalised Gamma. It is not clear to the EAG that a curve closer to PFS would necessarily be preferred because patients could discontinue treatment prior to disease progression, and so the EAG conducts scenario analyses using the Generalised Gamma or Exponential in place of the Gompertz, and prefers the Exponential in the EAG base-case because it gives the lowest BIC. For Ld the company chose the Weibull model on the basis of statistical fit, but the EAG note that the Weibull wasn't the model with either lowest AIC or BIC. However, predictions from all the parametric models giving adequate fit were very similar (CS Document B Figure 53 (3)) and so the EAG does not expect results to be sensitive to choice of model for TTD on Ld and considered the Weibull model to be appropriate. For BMP the company use the adjusted Kaplan-Meier curve from ALCYONE matched to MAIA, and do not fit a curve to extrapolate this because there is a fixed treatment duration for BMP when all patients will stop treatment. The EAG prefers to fit a model to the Kaplan-Meier data to use for predictions for the treatment duration period because this smooths the curve so that predictions are more generalisable beyond the ALCYONE cohort, however does not expect this to have a big impact on model results.

Key Issue 8: Which are the most appropriate parametric models for PFS, OS, and TTD for DLd, Ld, and BMP?

4.2.6.2.3 Waning of treatment effect for overall survival

All the company's models for OS assume that the treatment benefits persist throughout a patients life-time. Whilst the EAG agrees that the OS curves remain separated at the latest data-cut, the OS data is relatively immature with the median OS only just met for Ld and not yet met for DLd. It is therefore unclear how long the OS HR for DLd vs Ld will continue at the same level or whether it will eventually start to wane (HR increase towards 1). Note that a HR of 1 would still give survival curves that are separated, but they would move closer together. Due to the uncertainty in the long-term treatment effect on OS the EAG conducted scenario analyses (section 6.1) to different waning assumptions.

Key Issue 9: Would the treatment effect for OS be maintained for a patient's lifetime or would there be waning of effect?

4.2.7 Health related quality of life

4.2.7.1 Summary of health related quality of life (HRQoL) in CS

The company used a systematic literature review to identify relevant studies reporting HRQoL, resulting in 11 publications summarised in Table 91 in Appendix H of CS. (9) The company argues that these studies either used a non-UK value set, were derived from a non-UK population or had not been cross-walked using Hernández Alava et al. (2017) (58) and therefore were not relevant. Instead they use data from MAIA in their base-case and provide a scenario using data from ALCYONE.

Utilities were assigned to patients based on their health state and an age-based utility modifier was applied. In the CS base-case the company used data from the MAIA study's EQ-5D-5L responses mapped to the EQ-5D-3L using the algorithm developed by Hernandez Alava et al. (2017). (59) Data were pooled across treatments because there were [redacted]. (51) The utilities derived from MAIA and ALCYONE are summarised in Table 26. The company prefer the estimates from MAIA because the ALCYONE estimates give similar values for both health-states which the company argue lacks face-validity.

TABLE 26: UTILITIES VALUES ASSIGNED TO EACH HEALTH STATE REPRODUCED FROM CS DOCUMENT B (TABLE 47)

Mean (95% CI)	Progression Free	Progressive Disease
MAIA	[redacted]	[redacted]
ALCYONE	[redacted]	[redacted]

Abbreviations: PF: progression-free; PD: progressed disease; CI: confidence interval

Age-related utility adjustments were applied based on population EQ-5D scores recorded in the 2014 HSE (60), weighted according to the proportion of males in the MAIA ITT population.

HRQoL decrements were applied to patients experiencing treatment-emergent adverse events (Grade 3 or 4 with at least 5% of patients in any trial treatment arm). The proportion of patients experiencing each adverse event were based on data from MAIA and ALCYONE for DLd, Ld, and BMP (Table 45, CS Document B (3)) and MYELOMA XI for MPT and CTd (Table 132, CS Appendix M)(9). It was assumed the proportions for BCd were the same as for BMP.

The company sourced AE-related utility decrements from previously published literature, including sources used in previous NICE TAs (Table 46 of Document B CS (3)). The company used utility decrements from the NICE guidelines on Acute Kidney Injury (61) for the acute kidney injury and chronic kidney disease adverse events, due to a paucity of available evidence.

4.2.7.2 EAG critique of health related quality of life

The EAG agrees that the MAIA and ALCYONE trials provide the most relevant source for utilities for NDMM health states, although studies shouldn't be discounted if they use the Van Hout value set (62) instead of Hernández Alava. (58) Pooling utilities across treatments seems appropriate, although note that treatment arms do differ in adverse event profile and the effect of this will be averaged over in the state utilities. Given that disutilities due to adverse events are captured separately the EAG is content with the approach taken to estimate health state utilities in the model. The EAG agrees that the health state utility values in Table 26 from ALCYONE lack face-validity and that the values from MAIA are preferred. Note however that both the MAIA and ALCYONE trials are a international sample

of patients with only a small subset of patients recruited in the UK. The results therefore may not be fully representative of the UK NDMM transplant ineligible population.

Key Issue 10: Are the MAIA or ALCYONE health-state utilities more appropriate?

The EAGs clinical advisors agreed that the adverse event profiles assumed by the company were reasonable. The SC administration of DLd may have lower adverse events than the IV formulation, so using the adverse event profile from MAIA may overestimate adverse events for DLd administered subcutaneously. The EAG heard that BCd may be better tolerated than BMP so the assumption that the adverse event profile for BCd is the same as BMP may overestimate the adverse events associated with BCd. However, the EAG considers the approach to modelling the disutilities due to adverse events to be reasonable.

4.2.8 Resources and costs

4.2.8.1 Summary of assumptions on resources and costs in CS

The company included costs from an NHS England and PSS perspective. In the CS model, costs are assigned to first-line treatments, concomitant medications, subsequent second- and third-line treatments, drug administrations, monitoring and follow-up, and treatment-emergent adverse events.

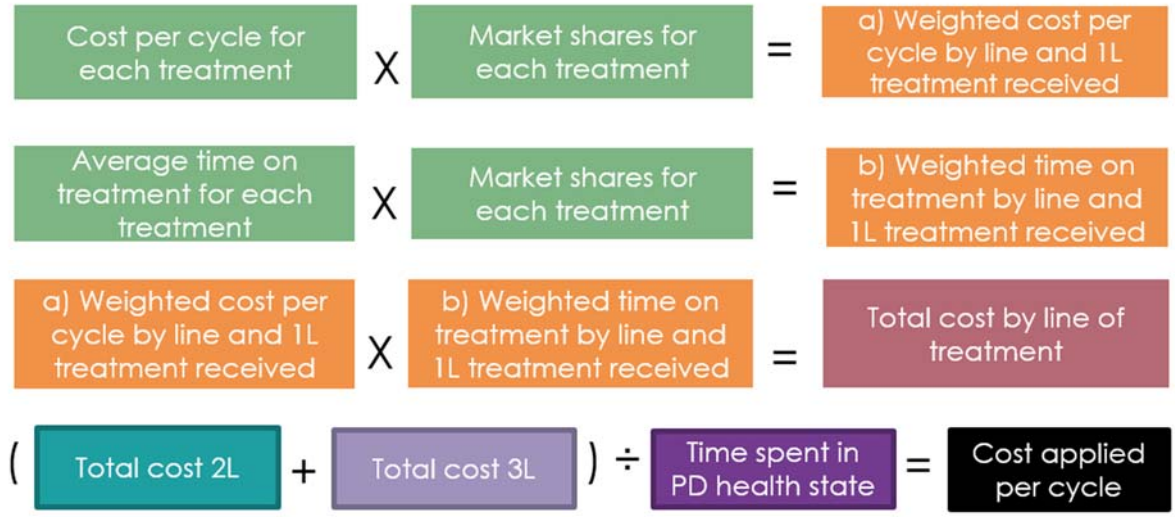
All drug costs were sourced from the 2022 BNF, with the exception of bortezomib and dexamethasone which were sourced from the electronic market information tool (eMIT). Drug costs were calculated by applying unit costs to the dosing schedules used in the clinical trials (Table 49 Document B CS (3). DLd was assumed to be administered subcutaneously (SC) with a scenario where [redacted] of patients receive IV administration. The dosing regimen for BMP was assumed to match the regimen used in the ALCYONE study. The company assumed that some patients would drop components of combination therapies (eg dropping dexamethasone in DLd) in the proportions that were observed in MAIA for DLd and Ld, and ALCYONE for BMP. Following the clarification process the company updated its base case model to also include the cost reductions associated with those dose reductions by assuming relative dose intensities (RDI) in line with those observed in MAIA and ALCYONE (Response to Clarification question B12). The company assumes no vial sharing for treatments where this is relevant.

Drug administration costs were applied for the intervention, comparators and subsequent treatments. Administration costs were applied based on administration type, an additional cost was applied to the first subcutaneous and intravenous administration. A fixed administration cost was applied to all oral chemotherapies. The CS assumed that all administrations of Daratumumab were taken subcutaneously - the EAG's clinical advisors described this assumption as reasonable.

The cost of subsequent treatments was obtained by multiplying weighted average times on treatment and costs (Table 54 Document B CS (3)) weighted by the market share of each subsequent treatment (Fig 61 Document B CS(3) and Figure 6 below). In the clarification

process the company confirmed that median times (given in Table 53 Document B CS (3)) were used in the calculations.

FIGURE 6: CALCULATION OF SUBSEQUENT THERAPIES COST (REPRODUCED FROM FIGURE 61, CS DOCUMENT B)(3)



The market share for each subsequent treatment depends on line of therapy and the treatment received at 1st line and was based on an average of elicited values from a panel of 7 clinicians (6), given in Tables 51 and 52 in Document B CS (3) excluding and including CDF treatments respectively. The company reported two sets of base case results: one where costs of subsequent drugs in the cancer drugs fund (CDF) were excluded from the analysis, and one where subsequent treatments in the CDF were included. (See **Key Issue 7**)

Monitoring costs (Table 57 Document B, CS (3)) were assumed to depend on whether a patient is on or off treatment, and otherwise did not depend on the treatment received. End-of-Life costs were taken from a previous NICE TA573 which was taken from previous NICE TA457. Costs of adverse events were taken from NHS reference costs (Table 58 Document B, CS).(3)

4.2.8.2 EAG critique of assumptions on resources and costs

As discussed in section 4.2.4.2 the EAG considers it appropriate to assume SC administration when deriving costs for DLd for the majority of patients, although acknowledge that a very small proportion may receive the IV formulation.

The EAGs clinical advisors confirmed that dose-adjustment and dropping components of combination therapies reflects clinical practice due to toxicity and side effects and felt the proportions dropping dexamethasone and lenalidomide seen in MAIA are likely to be an underestimate compared with clinical practice. The EAG considers it appropriate to include RDIs to reflect dose-reductions as implemented in the company's updated base-case.

The dose of melphalan assumed in the companys base-case is 9mg/m^2, but our clinical advisers said that 7mg/m^2 is more commonly used in practise, which would reduce the cost of BMP slightly and so increase the ICER for DLd compared with BMP. However, the companys revised base-case model incorporated dose-reductions which may capture the lower dose typically used in practice. The EAGs clinical advice was that bortezemib is typically administered weekly in practice with 3 weeks on and 1 week off per cycle. The company assumes this regimen for bortezomib when given in BCd, but for BMP the company does not include a 1 week break per cycle. Allowing for a 1 week break for borzezomib when used in BMP would reduce the costs and increase the ICER for DLd vs BMP.

The EAGs clinical experts said that vial sharing is unlikely to happen in practice and so it is appropriate to assume no vial sharing.

Key Issue 11: Should costs for dose-reductions using RDIs be included in the model?

The company applied drug administration costs of the intervention and comparators based on the dosing schedules of the clinical trials and in the case of BCd, from recommendations by the Oxford Myeloma group. This resulted in differing dosing schedules and administration costs being applied to bortezomib when used in BCd than when used in BMP. Our clinical advisors said that both regimens would likely be very similar and in line with that assumed for BCd in the model. The EAG believes that applying equivalent administration costs for Bortezomib for BCd and BMP would be a more accurate reflection of UK clinical practice and explores this in a scenario.

Costs of subsequent (2nd and 3rd line) treatments are modelled assuming an estimated distribution of market share from 7 clinical advisors. The EAG notes that this approach differs to the approach taken to capture efficacy of subsequent treatments, which are assumed to be already captured in the extrapolations based on MAIA, and ALCYONE. This means that the treatment benefits at 2nd and 3rd line are based on the distributions of treatments received in the randomised controlled trials whereas the treatment costs are based on elicited clinical opinion. It would be preferable if the costs and efficacy of subsequent treatments were based on the same assumptions and that these are representative of practice in England. 4th line treatments were not included in the company's model, but the EAG agrees that the small proportion of patients receiving 4th line treatment means this is unlikely to have a big impact on the model results. Furthermore, this is in line with TA587. (4) The market share estimates differed between the company's clinical advisors (Tables 12 – 23 in the minutes of the Clinical Advisory Board meeting (6)) and an average of these distributions was used in the CS. The EAG recognises that there is high variation in subsequent treatments used and so performs scenario analyses using each of the different clinician distributions (see section 6.1).

Key Issue 12: What is the most appropriate market share of treatments used at 2nd and 3rd line in England

The company multiplies a weighted average cost by a weighted average time on treatment for each 1st line treatment to obtain total costs (Figure 6). However, the EAG does not think this calculation is correct, and instead a weighted average of the cost x time should be calculated to obtain the total costs. In algebra the EAG thinks it should be

$$\sum_i weight_i cost_i time_i \qquad \text{(Eq. 1)}$$

rather than

$$\sum_i weight_i cost_i \sum_i weight_i time_i$$

Furthermore, the formula for 2nd line treatments was coded incorrectly in the company's Excel model. The EAG corrected the formulae to match Equation 1, and also corrected the coding for 2nd line treatments. The company provided an updated model on 22nd July 2022 to respond to the EAGs comments on the subsequent treatment costs which they clarified during the factual accuracy check also included corrections to the administration costs as well as the acquisition costs. The company also identified coding errors in the EAGs implementation. The EAG subsequently corrected the coding errors in the acquisition costs and adopted the companys updated formula for the administration costs. However, there is still a difference in the formula used by the company in the model they submitted on 22nd July 2022 and the corrected EAG formula for acquisition costs.

The median is used to estimate time on treatment, but the mean time on treatment is the preferred measure and can be quite different (typically longer than the median). In response to the EAG clarification question B8-B9, the company confirmed that the median was used due to lack of data on mean time on treatment for most of the studies. They also provided a scenario analysis where the ratio of the mean to the median was assumed equal to 1.4 for subsequent treatments based on the modelled PFS curve for DLd. The EAG prefers this scenario although the ratio of mean to median is likely to vary across treatments and so results may differ. The ICERs were not sensitive to this scenario and so the EAG is content that the summary used for time on treatment is unlikely to change results substantially.

The EAG considered the assumed monitoring costs to be in line with clinical practice. The end-of-life costs were based on old data, but were considered reasonable. The evidence available for the costs assumed for adverse events were limited, but the best available.

5 COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

The cost-effectiveness results presented in this section are from the company's updated base case model submitted on 1st July 2022 following clarification questions from the EAG. All results include the PAS price for Daratumumab unless stated otherwise. For the analysis

excluding CDF treatments a fully incremental analysis is given in Table 27 showing that in the company's updated base-case when excluding CDF treatments, all comparators are strictly dominated by Ld, with the exception of DLd with an incremental cost effectiveness ratio (ICER) of [redacted] per QALY gained. The incremental costs, QALYS, and pairwise ICERs are shown in Table 28 (excluding CDF treatments) and Table 29 (including CDF treatments). Including CDF treatments reduces the ICERs for DLd compared with Ld, BMP, and BCd, but increases the ICERs for DLd compared with MPT and CTd. This difference is due to the different subsequent treatment options depending on which combination is received at 1st line.

TABLE 27: FULLY INCREMENTAL COST-EFFECTIVENESS RESULTS FOR CS UPDATED BASE CASE AT THE PAS PRICE FOR DARATUMUMAB (EXCLUDING CDF TREATMENTS)

	Total costs	Total QALYs	Dominated?	Extendedly Dominated?	Fully Incremental ICER
Ld	[redacted]	[redacted]	-	-	-
BCd	[redacted]	[redacted]	[redacted]	-	-
BMP	[redacted]	[redacted]	[redacted]	-	-
CTd	[redacted]	[redacted]	[redacted]	-	-
MPT	[redacted]	[redacted]	[redacted]	-	-
DLd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

TABLE 28: RESULTS OF THE CS UPDATED BASE CASE AT THE PAS PRICE FOR DARATUMUMAB (EXCLUDING CDF TREATMENTS)

	Total costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER (DLd vs comparator)
DLd	[redacted]	[redacted]	-	-	-
BMP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ld	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CTd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MPT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BCd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

TABLE 29: RESULTS OF THE CS UPDATED BASE CASE AT THE PAS PRICE FOR DARATUMUMAB (INCLUDING CDF TREATMENTS)

	Total costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER (DLd vs comparator)
BMP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ld	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CTd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MPT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BCd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BMP: bortezomib, melphalan and prednisone; CTd: cyclophosphamide, thalidomide, and dexamethasone; DLd: daratumumab, lenalidomide and dexamethasone; ICER: incremental cost-effectiveness ratio; Ld: lenalidomide and dexamethasone; MPT: melphalan, prednisone and thalidomide; QALY: quality-adjusted life-year.

5.2 Company's sensitivity analyses

5.2.1 Deterministic sensitivity analyses

The company conducted one-way deterministic sensitivity analyses (Figure 7) which found DLd overall survival (OS) to be the most impactful factor effecting the ICER for DLd vs Ld, followed by DLd progression free survival (PFS).

FIGURE 7: DETERMINISTIC SENSITIVITY ANALYSIS COMPANY'S UPDATED BASE-CASE AT THE PAS PRICE FOR DARATUMUMAB (EXCLUDING CDF TREATMENTS)

[redacted]

Abbreviations: DLd, daratumumab, lenalidamide, and dexamethasone; ICER, incremental cost-effectiveness ratio

5.2.2 Probabilistic sensitivity analysis

The results from the probabilistic sensitivity analysis (PSA) based on 5000 iterations are given in Table 30 for the company's updated base-case (excluding CDF treatments). Ld dominates all other treatments except for DLd. The probabilistic ICER for DLd vs Ld is

[redacted]. The cost-effectiveness plane (Figure 8) shows the PSA samples are nearly all above the £30,000 threshold line.

TABLE 30: RESULTS OF THE PROBABILISTIC SENSITIVITY ANALYSIS FOR THE CS UPDATED BASE CASE AT THE PAS PRICE FOR DARATUMUMAB (EXCLUDING CDF TREATMENTS)

	Total costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER (DLd vs comparator)
DLd	[redacted]	[redacted]			
BMP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ld	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CTd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MPT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BCd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

FIGURE 8: PROBABILISTIC SENSITIVITY ANALYSIS RESULTS DLD VS LD – PAS PRICE FOR DARATUMUMAB (EXCLUDING CDF TREATMENTS)

[redacted]

5.2.3 Scenario analyses

The company included 16 scenario analyses in the model, the results of which are presented in Table 31 below for the CS updated base case in response to the clarification process. The

scenarios which had the largest impact on the ICER for DLd vs Ld were the inclusion of CDF treatments in subsequent lines of therapy, choice of parametric curve to extrapolate TTD for DLd, and use of a 1.5% discount rate.

TABLE 31: COST-EFFECTIVENESS RESULTS FROM SCENARIO ANALYSES FOR THE CS UPDATED BASE CASE (EXCLUDING CDF TREATMENTS EXCEPT IN SCENARIO 1), PAS PRICE FOR DARATUMUMAB

	Scenario	ICER Vs. Ld.	ICER vs BMP	ICER vs CTd	ICER vs MPT	ICER vs BCd
1	Subsequent treatments: Include CDF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	ToT for BMP: 100% discontinuation after fixed-duration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	TTD Extrapolations: 2nd choice curves (DLd: Gen Gamma)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	MPT Efficacy: HR vs BMP from NMA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	CTd Efficacy: HR vs BMP from NMA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	OS Extrapolations: Pessimistic curve choice (DLd: Gompertz)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7	OS Extrapolations: Optimistic curve choice (DLd: Weibull)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8	OS Extrapolations: 2nd choice curves (BMP: Weighted average of Gompertz and Weibull)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	PFS Extrapolations: Pessimistic curve choice (DLd: Generalised Gamma)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

10	PFS Extrapolations: Optimistic curve choice (DLd: Weibull)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
11	PFS Extrapolations: 2nd choice curves (BMP: Generalised Gamma)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	PFS Extrapolations: 2nd choice curves (Ld: Weibull)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
13	Utility values: ALCYONE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
14	Medicinal form					
15	Vial sharing					
16	Discount rate: 1.5%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BMP, Bortezomib ; CDF, Cancer Drugs Fund; ICER, Incremental Cost-effectiveness Ratio; Ld

In response to the EAG's points for clarification, the company submitted a range of additional scenario analyses (Table 32, Table 33). Most of these scenarios have a minimal impact on the ICERs, however the ICERs are sensitive to inclusion of relative dose intensity (RDIs) to capture the costs associated with dose-reductions, which reduces the ICER for DLd relative to the comparators. The company adopt this scenario as their updated base-case. The ICER for DLd vs BMP is sensitive to using a piecewise NMA rather than the uITC for the BMP efficacy (ICER [redacted] compared with [redacted]), but use of the parametric NMA does not have a big influence on the ICERs.

TABLE 32: ADDITIONAL SCENARIO ANALYSIS RESULTS FOLLOWING EAG CLARIFICATION QUESTIONS – PAS PRICE FOR DARATUMUMAB (CDF TREATMENTS EXCLUDED)

	DLd Vs BMP			DLd Vs Ld		
	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Original base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Updated base case (RDIs implemented)*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 1: parametric NMA (see response A5)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 2: standard NMA for BMP OS,	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

piecewise NMA for BMP PFS						
Scenario 5: Increase all median PFS/TTP of subsequent treatments by x1.4				[redacted]	[redacted]	[redacted]

TABLE 33: ADDITIONAL SCENARIO ANALYSIS RESULTS FOLLOWING EAG CLARIFICATION QUESTIONS – PAS PRICE FOR DARATUMUMAB (CDF TREATMENTS EXCLUDED)

	DLd Vs BCd		
	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Updated base case*: BCd equivalent to BMP	[redacted]	[redacted]	[redacted]
Scenario 3: BCd derived via HR vs BMP	[redacted]	[redacted]	[redacted]
Scenario 6: BMP TTD vs PFS HR	[redacted]	[redacted]	[redacted]
Scenario 7: assumed equivalent to BMP TTD	[redacted]	[redacted]	[redacted]

*THE BASE CASE HAS BEEN UPDATED TO INCORPORATE DOSAGE REDUCTIONS, IN RESPONSE TO QUESTION B12 IN THIS DOCUMENT.
SCENARIO 3 HRS: BCD VS BMP HRS: [redacted]
ABBREVIATIONS: BCD: BORTEZOMIB, CYCLOPHOSPHAMIDE AND DEXAMETHASONE; BMP: BORTEZOMIB, MELPHALAN AND PREDNISONE; DLD: DARATUMUMAB, LENALIDOMIDE AND DEXAMETHASONE; HR: HAZARD RATIO; ICER: INCREMENTAL COST-EFFECTIVENESS RATIO; LD: LENALIDOMIDE AND DEXAMETHASONE; PAS: PATIENT ACCESS SCHEME; QALY: QUALITY ADJUSTED LIFE YEAR.

5.3 Model validation and face validity check

The company conducted an internal clinical validation and technical validation of the cost-effectiveness analysis and conducted and hosted an advisory board meeting with clinical experts based in England and Scotland. The clinical advisory board was used to assess the clinical validity of the model assumptions through discussions and expert feedback on pre-read documents prior to the meeting.

The company performed an internal technical validation check of the cost-effectiveness analysis by a health economist employed by the company who was not involved in the model's development, and checked for quality control by a second health economist. The company applied the validation checklist by Buyukkaramikli et al. (63) and reported the results of several stress tests whereby the expected effects were stated and adherence of the observed effects to the expected effects was described. A summary of the stress tests performed can be found in table 77 of the CS Document B. The company concluded that all

results in the model behaved as expected and the model passed all the stress tests that were implemented.

The EAG considers that the company's model validation was appropriate. The EAG reviewed the model in detail and identified an error with the way that the costs of subsequent costs were calculated both in terms of the method used and the way it was implemented (see Section 4.2.8.2).

6 EVIDENCE ASSESSMENT GROUP'S ADDITIONAL ANALYSES

6.1 Exploratory and sensitivity analyses undertaken by the EAG

The EAG corrected the calculation of subsequent treatment costs (see Section 4.2.8.2) by adapting the companys updated base-case model submitted on 1st July 2022. During the factual accuracy check the company clarified that their updated model submitted on 22nd July 2022 had both acquisition costs and administration costs updated, and also noted some coding errors in the EAG adapted model. In response to this, the EAG corrected the coding errors of the acquisition costs in their adapted version of the companys 1st July model, and also incorporated the companys updated administration costs from their 22nd July 2022 model into their 1st July 2022 model. The 1st July model was adapted rather than use the 22nd July model due to differences in the formulae used for the acquisition costs in the EAGs adapted model and the companys 22nd July model. The changes to the company's updated model are detailed in the Sub Tx Costs tab in the file "EAG IBC1.xlms". All of the EAGs scenario and base-case analyses are for the company's updated base-case 1st July 2022 model with the EAGs corrections to acquisition costs and the company correction to administration costs applied. All results include the PAS price for Daratumumab unless stated otherwise.

6.1.1 Scenarios for relative effects for OS and PFS

The EAG performs scenarios analyses to explore the impact of using various different analyses to inform the relative treatment effects for OS and PFS (see section 3.4):

- Scenario 1: The company's parametric NMA is used for all OS and PFS extrapolations (Sections 4.2.6.2 and 3.4.2), with HRs for BCd vs BMP taken from the MAIC (Section 3.4.4.2). Implemented by:
    - selecting the relevant option in cells I 42, I43, I46, and I47 in the Settings tab

- Scenario 2a: The company's piecewise HR NMA for BMP for PFS (Sections 4.2.6.2, 3.4.2 and 3.5.1), the company's HR NMA for OS (Sections 4.2.6.2, 3.4.2 and 3.5.1), with HRs for BCd vs BMP taken from the MAIC (Section 3.4.4.2). Implemented by:
    - selecting the relevant options in cells I42, I43, I46, and I47 in the Settings tab

- Scenario 2b: As for Scenario 2a but excluding the Hungria and Myeloma IX studies from the NMAs (Section 3.5.1). Implemented by:
    - As for 2a, but changing the values in cells I37 – N37 in the Efficacy tab of the company updated model to match the HR estimates in the lower triangle of Table 17 and Table 18 for piecewise PFS model excluding Hungria and MyelomaIX

- Scenario 2c: The company's piecewise HR NMA for BMP PFS (Sections 4.2.6.2, 3.4.2 and 3.5.1), the company's parametric NMA for BMP OS (Sections 4.2.6.2, 3.4.2), with HRs for BCd vs BMP taken from the MAIC (Section 3.4.4.2). Implemented by:
    - selecting the relevant options in cells I42, I43, I46, and I47 in the Settings tab

- Scenario 3a: The company's HR NMA for BMP for PFS and OS (Sections 3.4.2), with HRs for BCd vs BMP taken from the MAIC (Section 3.4.4.2). Implemented by:
    - as for 2a, but changing the values in cells I37 – N37 in the Efficacy tab to the values in the upper triangle BMP vs Ld cell of Table 16, using the same values for <20m and >20m to obtain the HR NMA model (since this isn't an option in the model).

- Scenario 3b: As for Scenario 3a but excluding the Hungria and Myeloma IX studies from the NMAs (Section 3.5.1).
    - as for 3a, but using the values in the lower triangle BMP vs Ld cell of Table 16

6.1.2 Scenarios for parametric extrapolations for OS, PFS, and TTD

The EAG explored alternative parametric curves for extrapolations of OS, PFS and TTD (Section 4.2.6.2.2)

- Scenario 4a: Same parametric family (Gompertz) for OS extrapolations for Ld, DLd, and BMP. Implemented by:
    - Selecting the Gompertz for OS in cells I45, J45, K45 of the Efficacy tab

- Scenario 4b: Same parametric family (Gompertz) for OS extrapolations for Ld, DLd, and Gompertz/Weibull mix for BMP. Implemented by:
    - Selecting the Gompertz for OS in cells I45, K45 and "Average of Gompertz and Weibull" in cell J45 of the Efficacy tab

- Scenario 5: Same parametric family (Weibull) for PFS extrapolations for Ld, DLd, and BMP. Implemented by:
    - Selecting Weibull in cells I42, J42, K42 in the Efficacy tab

- Scenario 6a: Use Generalised Gamma for extrapolations of TTD for DLd. Implemented by:
    - Selecting Generalised Gamma in cell I48 in the Efficacy tab

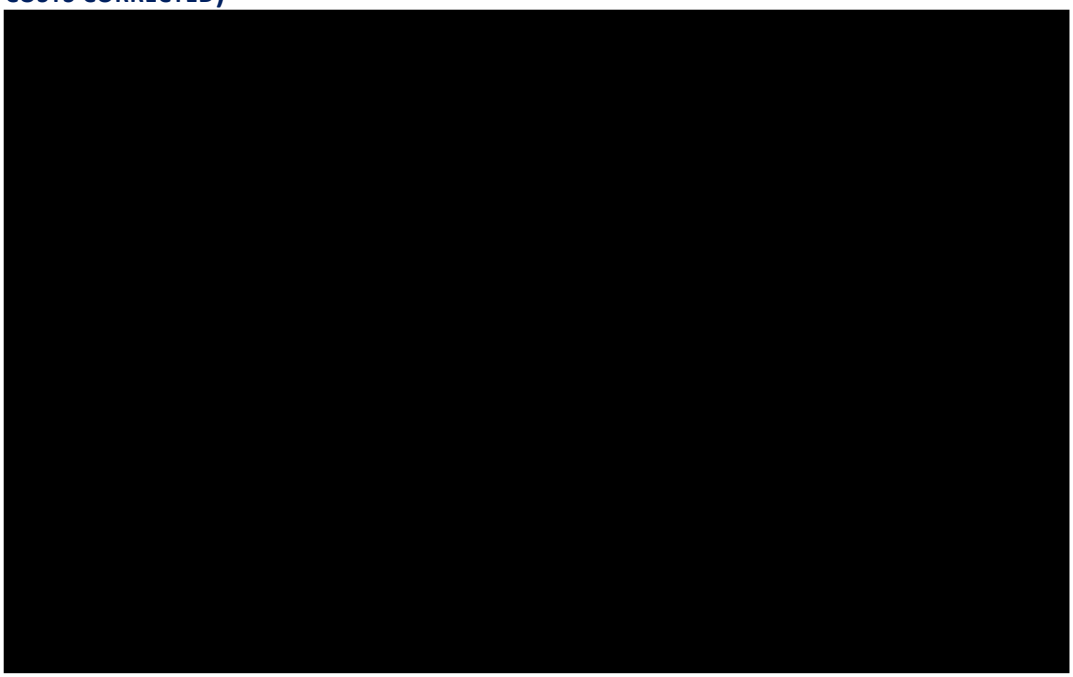
- Scenario 6b: Use Exponential for extrapolations of TTD for DLd. Implemented by:
    - Selecting Exponential in cell I48 in the Efficacy tab

6.1.3 Scenarios for duration of treatment effect for OS

Alternative assumptions about the duration of treatment effect for OS were explored by introducing a linear waning of the HR for DLd vs Ld from a specified starting point to a HR of 1 after waning period (Section 4.2.6.2.3). Note that the survival curves will converge much later than the point the HR equals 1. The changes to the model to implement these scenarios are given in Appendix 5 (Section 8.5.1) and the survival curves are displayed in Figure 9.

- Scenario 7a: Treatment waning starts at 7 years for a duration of 5 years until HR=1 at 12 years
- Scenario 7b: Treatment waning starts at 10 years for a duration of 5 years until HR=1 at 15 years
- Scenario 7c: Treatment waning starts at 12 years for a duration of 7 years until HR=1 at 19 years
- Scenario 7d: Treatment waning starts at 15 years for a duration of 10 years until HR=1 at 25 years

FIGURE 9: OVERALL SURVIVAL FOR DLD UNDER DIFFERENT WANING SCENARIOS (7A – 7D) PLOTTED WITH DLD AND LD FROM THE COMPANIES UPDATED BASE-CASE (ALL WITH SUBSEQUENT TREATMENT COSTS CORRECTED)



6.1.4 Scenarios for distribution of market share of subsequent treatments

There was variability in the elicited distribution of subsequent treatments across clinicians (Section 4.2.8.2). We explored the sensitivity of the results to this by running scenario analyses for each of the clinicians distributions where there was sufficient information to do so.

- Scenarios 8a-8g: Subsequent treatment distributions for each of the clinical experts. Implemented by:
    - changing the values of the market shares in cells I16: N20 and cells I25:P29 to the distribution elicited from a clinician (Tables 12 – 23 in the minutes of the Clinical Advisory Board meeting (6))
    - Note insufficient data was available to run these for clinicians 2, 5, and 7, so results are presented for 8a, 8c, 8d, 8f

Deterministic results are presented for all scenarios, however we would expect the ICERs to increase for probabilistic results as they did in the company updated base-case (Sections 5.1 and 5.2.2). We provide probabilistic results for the EAGs preferred base-case in Section 6.3.

6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the EAG

The results of the EAGs additional analyses are presented in Table 34. Correcting for subsequent treatment costs mainly affects the ICERs for DLd vs BCd. This is because BCd is modelled to have more expensive subsequent therapy at 2nd line.

In all scenarios Ld dominates BMP and BCd, except for scenarios 8c and 8d (subsequent treatment distributions from clinicians 3 and 4). However, the ICERs for DLd vs BMP and BCd are very high for those scenarios. Focussing on the ICER for DLd vs Ld, the scenarios that have the largest impact on the cost-effectiveness results are:

- Incorporating dose reductions using RDIs (reduces the ICERs for DLd vs all comparators)
- Treatment waning scenarios with the ICERs for DLd vs Ld ranging from £89,674 if waning doesn't start until 15 years, £102,718 if waning starts at 12 years, £121,849 if waning starts at 10 years, and £165,778 if waning starts at 7 years.
- Assumed distribution for TTD for DLd, with the ICER ranging from £74,478 for the Generalised Gamma and £91,445 for the Exponential.
- Distribution of market share of subsequent treatments, where the ICER for DLd vs Ld varied from £46,787 to £117,311 in the scenarios that we explored.

TABLE 34: EAGS ADDITIONAL SCENARIO ANALYSES. ALL SCENARIOS FOR THE COMPANY'S UPDATED BASE-CASE, WITH PAS FOR DARATUMUMAB (CDF TREATMENTS EXCLUDED). DETERMINISTIC RESULTS.

	DLd vs BCd			DLd vs BMP			DLd vs Ld		
EAG Scenario	**Incr. Costs**	**Incr. QALYs**	**ICER**	**Incr. Costs**	**Incr. QALYs**	**ICER**	**Incr. Costs**	**Incr. QALYs**	**ICER**
Company Original base case	[redacted]								
Company Updated base case (RDIs implemented)									
Company Updated base case with subsequent treatment costs updated (CS)									
Company Updated base case with subsequent treatment costs corrected (EAG)									
Scenario 1: Parametric NMA for all OS and PFS extrapolations, HRs for BCd vs BMP									
Scenario 2a: Piecewise HR NMA for BMP for PFS, HR NMA for OS, HRs for BCd vs BMP									
Scenario 2b: Piecewise HR NMA for BMP for PFS [excluding Hungria and Myeloma IX]. HR NMA for OS [excluding Hungria and Myeloma IX], HRs for BCd vs BMP.									
Scenario 2c: Piecewise HR NMA for BMP for PFS [excluding									

Hungria and Myeloma IX]. Parametric NMA for BMP.									
Scenario 3a: HR NMA for BMP for PFS and OS, HRs for BCd vs BMP. MAIA extrapolations for DLd and Ld	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 3b: HR NMA for BMP for PFS and OS [excluding Hungria and Myeloma IX], HRs for BCd vs BMP. MAIA extrapolations for DLd and Ld	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 4a: Same parametric family (Gompertz) for OS extrpolations for Ld, DLd, and BMP.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 4b: Same parametric family (Gompertz) for OS extrpolations for Ld, DLd, and Gompertz/Weibull mix for BMP.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 5: Same parametric family (Weibull) for PFS extrapolations for Ld, DLd, and BMP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 6a: TTD use Generalised Gamma for DLd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 6b: TTD use Exponential for DLd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 7a: Treatment waning starts at 7 years for a duration of 5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Scenario 7b: Treatment waning starts at 10 years for a duration of 5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 7c: Treatment waning starts at 12 years for a duration of 7 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 7d: Treatment waning starts at 15 years for a duration of 10 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 8a: Subsequent treatment distributions Clinician 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 8c: Subsequent treatment distributions Clinician 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 8d: Subsequent treatment distributions Clinician 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 8f: Subsequent treatment distributions Clinician 6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

6.3 EAG's preferred assumptions

The EAGs preferred assumptions are:

1. Incorporating dose reductions in the costs using RDIs, as in the company's updated base-case with the subsequent treatment costs coding corrected.
2. Applying a HR for BCd vs BMP for PFS and OS (as in Company Clarification Response Scenario3)
3. Using the piecewise NMA model to estimate HRs for BMP for PFS (excluding Hungria and Myeloma IX) and the parametric NMA for OS (EAG Scenario 2c)
4. Using the same parametric family (Gompertz) for OS extrapolations for Ld, DLd (EAG Scenario 4b)
5. Using the same parametric family (Weibull) for PFS extrapolations for Ld, DLd (EAG Scenario 5)
6. Use Exponential distribution for TTD for DLd (EAG Scenario 6b)
7. Treatment waning starts at 12 years for a duration of 7 years until HR=1 at 19 years (EAG Scenario 7c)

The deterministic results for the EAGs preferred assumptions are shown in Table 35 for DLd compared with each treatment, adding each assumption incrementally to culminate with the EAG base-case (EAG IBC7_start12_for7_corrected (ran).xlsm). The probabilistic results for the company updated base case with the subsequent treatment costs corrected (assumption 1) and for the EAG preferred base case (assumptions 1+2+3+4+5+6+7) are given in Table 36 and Table 37 respectively. The fully incremental probabilistic results for the EAG preferred base case (assumptions 1+2+3+4+5+6+7) are shown in Table 38.

TABLE 35: EAG PREFERRED ASSUMPTIONS AND BASE-CASE (PAS PRICE FOR DARATUMUMAB, EXCLUDING CDF TREATMENTS). DETERMINISTIC RESULTS.

EAG Assumption Number	Treatment	Total Costs	Total QALYs	Incremental Costs	Incremental QALYS	ICER (£/QALY)
1	Company updated base-case (including RDIs) with subsequent treatment costs corrected					
	DLd	[redacted]	[redacted]	-	-	-
	BMP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Ld	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	CTd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	MPT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	BCd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1+2	+ Apply HRs for BCd vs BMP for PFS and OS					
	DLd	[redacted]	[redacted]	-	-	-
	BMP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Ld	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	CTd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	MPT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	BCd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1+2+3	+ Using the piecewise NMA model to estimate HRs for BMP for PFS (excluding Hungria and Myeloma IX) and the parametric NMA for OS (EAG Scenario 2c)					
	DLd	[redacted]	[redacted]	-	-	-
	BMP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Ld	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	CTd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	MPT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	BCd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1+2+3+4	+ Using the same parametric family (Gompertz) for OS extrapolations for Ld, DLd (EAG Scenario 4b))					
	DLd	[redacted]	[redacted]	-	-	-

	BMP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Ld	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	CTd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	MPT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	BCd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1+2+3+4+5	+ Same parametric family (Weibull) for PFS extrapolations for Ld, DLd (EAG Scenario 5)					
	DLd	[redacted]	[redacted]	-	-	-
	BMP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Ld	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	CTd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	MPT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	BCd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1+2+3+4+5+6	+ TTD use Exponential for DLd (EAG Scenario 6b)					
	DLd	[redacted]	[redacted]	-	-	-
	BMP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Ld	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	CTd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	MPT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	BCd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1+2+3+4+5+6+7 = EAG BASE CASE	+ Treatment waning starts at 12 years for a duration of 7 years until HR=1 at 19 years (EAG Scenario 7c)					
	DLd	[redacted]	[redacted]	-	-	-
	BMP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Ld	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	CTd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	MPT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	BCd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

TABLE 36: RESULTS OF THE COMPANY UPDATED BASE-CASE (INCLUDING RDIS) WITH SUBSEQUENT TREATMENT COSTS CORRECTED (EAG ASSUMPTION NUMBER 1) AT THE PAS PRICE FOR DARATUMUMAB (EXCLUDING CDF TREATMENTS) PROBABILISTIC RESULTS

	Total costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER (DLd vs comparator)
DLd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BMP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ld	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BCd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CTd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MPT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

TABLE 37: RESULTS OF THE EAG BASE CASE (EAG ASSUMPTIONS 1+2+3+4+5+6+7) AT THE PAS PRICE FOR DARATUMUMAB (EXCLUDING CDF TREATMENTS) PROBABILISTIC RESULTS

	Total costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER (DLd vs comparator)
DLd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BMP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ld	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BCd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CTd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MPT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

TABLE 38: FULLY INCREMENTAL PROBABILISTIC RESULTS FOR EAG BASE CASE (EAG ASSUMPTIONS 1+2+3+4+5+6+7) AT THE PAS PRICE FOR DARATUMUMAB (EXCLUDING CDF TREATMENTS)

	Total costs	Total QALYs	Dominated?	Extendedly Dominated?	Fully Incremental ICER
Ld	[redacted]	[redacted]	-	-	-
BMP	[redacted]	[redacted]	[redacted]	[redacted]	-
BCd	[redacted]	[redacted]	[redacted]	[redacted]	-
CTd	[redacted]	[redacted]	[redacted]	[redacted]	-
MPT	[redacted]	[redacted]	[redacted]	[redacted]	-
DLd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

6.4 Conclusions of the cost effectiveness section

The company have submitted a de novo cost-effectiveness model that addresses the decision problem defined in the final scope. Thalidomide containing regimens are in the scope but are rarely used, however the company has included them in their model for completeness. The model structure is appropriate, has face validity and is largely aligned with prior NICE submissions in newly diagnosed multiple myeloma. The company argue that subsequent treatments only available on the CDF should be included in their model, however the EAG considers that these should be excluded in line with the NICE Manual (46). The EAG is aware however that the availability of CDF treatments may change during the course of this appraisal, adding uncertainty to the subsequent treatment options available.

The company updated their base-case model in response to the EAGs clarification questions to incorporate the costs of dose-reductions that were observed in the trial and would be expected to occur in clinical practice, which the EAG considers appropriate. The company also conducted a wide range of scenarios in their submission and in response to the EAGs clarification questions which resolved several of the EAGs concerns with the model and inputs to the model. The company provided network meta-analyses of OS and PFS that relaxed the proportional hazards assumption, and the EAG prefers these analyses although it could not explore different distributions for the parametric NMA approach. For this reason the EAG preferred the piecewise NMA approach to obtain the comparisons with BMP, MPT, and CTd. Because Ld dominates MPT, BMP, BCd, and CTd in all of the scenarios the fully incremental ICER of interest is for DLd vs Ld, which is robust to different approaches to modelling relative efficacy in the short-term. The company used median time on treatment to estimate subsequent treatment costs, instead of the mean time on treatment which would be preferred by the EAG. However, the EAG understands that mean times were not always available, and the company's scenario analysis indicates that the impact on the ICER would negligible.

Some key uncertainties remain however which have a substantial impact on the ICERs. The OS data is relatively immature (median not yet reached in the DLd arm of MAIA). The latest datacut results show evidence of a sustained treatment benefit at median follow up 64.5 months, but there is considerable uncertainty as to the long-term duration of treatment benefits of DLd vs Ld far beyond the follow-up of MAIA. The company's model assumes that the relative treatment effect is extrapolated into the long-term without any waning of effect. The EAG considered it plausible that there may be some waning of effect in the longer term and preferred a scenario where the full treatment benefit continues until 12 years but then the HR wanes over 7 years towards a HR of 1 at 19 years, although scenarios where waning starts sooner were also plausible and substantially increase the ICERs. The QALYS gained and hence the ICER are very sensitive to assumptions about waning of treatment effect. Uncertainty about treatment waning would require longer follow-up data (the final data-cut for MAIA is expected [redacted] which would be informative, although uncertainties about longer term benefits would still remain).

Choice of parametric curve for the extrapolation of Time to Treatment Discontinuation (TTD) for DLd is another key uncertainty that has an impact on the ICER for DLd compared with other treatments. The Gompertz (company base-case), Generalised Gamma, and Exponential (EAG base-case) give similarly good fit based on AIC, but differ in their long-term extrapolations. The EAG preferred the Exponential because it gave the best fit on the BIC, but the extrapolation is uncertain. Longer follow-up from the MAIA study could potentially provide further information on TTD to help reduce this uncertainty.

The market share of subsequent treatments at 2nd and 3rd line is a key uncertainty that has a varying impact on the ICER. The EAGs scenario analyses to using the market share elicited from each clinician separately shows the wide variation in practice and the large impact it can have on the ICER. Given this wide variation in practice, the EAG considers that the company's approach to use an average across the clinician's elicited distributions is as good an approach as any, but this is a key unresolved uncertainty.

7 SEVERITY, UNCERTAINTY, and MANAGED ACCESS

7.1 Severity

For all treatments, the absolute QALY shortfall and proportional QALY shortfall were below the threshold of 12 and 0.85 (Table 61, Document B CS (3)), respectively, therefore a severity modifier of 1 is applied in the base case results. The EAG agrees that the absolute and proportional QALY shortfall are well below the thresholds for a severity modifier to be applied, so a value of 1 is appropriate.

7.2 Uncertainty

The company highlight the uncertainty associated with subsequent treatments in NDMM ASCT ineligible patients due to many receiving CDF treatments and the changing treatment landscape with forthcoming CDF re-appraisals for DBd and ILd. The EAG agree that the modelling of subsequent treatments is challenging and this is a key uncertainty that has an impact on the ICER based on EAGs Scenario analyses 8a-8f.

7.3 Managed Access

The company note that whilst DLd could be a candidate for the CDF they expect that further follow-up of the MAIA trial will only confirm the clinical benefit of DLd in this setting, rather than resolving uncertainty underpinning the evaluation. The EAG however feels that the long-term extrapolation of TTD for DLd and potential waning of future treatment effects are important uncertainties that future follow-up for MAIA could helpfully shed light on.

8 APPENDICES

8.1 Appendix 1: ROBIS assessment

8.1.1 Concerns with the review process

The purpose of the ROBIS assessment was to determine whether the evidence identified and synthesized by the company's systematic review of randomised evidence (SLR 1) can reliably be used to inform the economic model. This critique is based on the information provided in the CS.(3). The overall assessment reached applies to SLR 1 only.

The EAG's overall assessment of SLR 1 is that the review of RCTs was appropriate.
The key for ROBIS judgements: Y=YES, PY=PROBABLY YES, PN=PROBABLY NO, N=NO, NI=NO INFORMATION

DOMAIN 1: STUDY ELIGIBILITY CRITERIA	
Objectives: "*A systematic literature review (SLR) of randomised controlled trials (RCTs) was initially conducted to assess the efficacy/effectiveness and safety of DLd and relevant comparators as treatment for newly diagnosed MM patients who are ineligible for autologous stem cell transplantation (ASCT-ineligible).*" (CS, Appendix D. Page 13) Full inclusion criteria for SLR 1 were as follows: • RCTs • Adults with newly diagnosed MM ASCT-ineligible • Any RCT including at least one of the following relevant comparators: ➢ Daratumumab, lenalidomide and dexamethasone (DLd) ➢ Lenalidomide with dexamethasone (Ld) ➢ Bortezomib, melphalan and prednisone (BMP) ➢ Bortezomib, cyclophosphamide and dexamethasone (BCd) ➢ Melphalan, prednisone and thalidomide (MPT) ➢ Cyclophosphamide, thalidomide, and dexamethasone (CTd) • No time restrictions on full-text publications; • Conference abstracts published since 2018, English language publication.	
1. Did the review adhere to pre-defined objectives and eligibility criteria?	Y
2. Were the eligibility criteria appropriate for the scope?	Y
3. Were eligibility criteria unambiguous?	N
4. Were any restrictions in eligibility criteria based on study characteristics appropriate (e.g. date, sample size, study quality, outcomes measured)?	Y
5. Were any restrictions in eligibility criteria based on sources of information appropriate (e.g. publication status or format, language, availability of data)?	PY
Concerns that application of the eligibility criteria could have resulted in studies relevant to the scope being excluded from the review	**LOW**

Rationale for concern: The question addressed by the review was in line with the NICE Scope for the appraisal. Eligibility criteria matched population, intervention, comparator and outcomes of interest. Studies were restricted to English Language.

DOMAIN 2: IDENTIFICATION AND SELECTION OF STUDIES

Searches for relevant RCTs were conducted in a wide range of sources including the following databases:

- Medline (via PubMed)
- Embase (via Embase.com)
- Cochrane Database of Systematic Reviews (CDSR; via Cochrane Library)
- Cochrane CENTRAL (via Cochrane Library)

The latest search update from 7th December 2021 was conducted via Ovid for all databases. Syntaxes were adjusted to Ovid's search interface. Searches were also carried out in various grey literature sources to locate unpublished data including conference proceedings; health technology assessments and clinical trial registries and bibliography checks.

Search strategies were designed to include the disease area and population of interest; study design terms; interventions of interest combined with terms for first-line therapy; exclusion terms for studies indexed as case reports, case studies, letters, and editorials; limits to articles in English.

"In accordance to CRD's guidance for undertaking reviews in health care, screening was conducted in two stages—title/abstract and full-text screening—following the Population, Intervention, Comparator, Outcomes, and Study design (PICOS) criteria outlined above. Screening was conducted by two independent investigators at both screening levels to determine the record's suitability for inclusion in the SLR. Discrepancies between these investigators were addressed via discussion, with any remaining disagreements resolved by a third investigator." (CS, Appendix D.1.4. Page 36).(9)

1. Did the search include an appropriate range of databases/electronic sources for published and unpublished reports?	Y
2. Were methods additional to database searching used to identify relevant reports?	Y
3. Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	Y
4. Were restrictions based on date, publication format, or language appropriate?	Y
5. Were efforts made to minimise error in selection of studies?	Y
Concerns that the searches and selection methods could missed studies relevant to the scope	**LOW**

Rationale for concern: The searches were conducted in an appropriate range of databases, including the grey literature. The search terms and search structure were appropriate to retrieve as many eligible studies as possible. The process of study selection was well described and conducted in a way to minimize bias in the selection of studies.

DOMAIN 3: DATA COLLECTION AND STUDY APPRAISAL

"Data from included studies were extracted using pre-approved, standardised data extraction tables. Extractions were conducted by one investigator, with a second investigator independently validating all extractions." (CS, Appendix D.1.4. Page 36). (9) *"The risk of bias of the RCTs included in the NMA was assessed using the Cochrane Risk of Bias tool. This tool evaluates the methodological quality across six elements: random sequence generation, allocation concealment, blinding of participants and researchers, blinding of outcome assessment, complete outcome assessment, and selective reporting. For each element, a rating of 'high risk', 'low risk' or 'unclear risk for bias' was given, as shown in Table 31."* (CS, Appendix D.1.11. Page 2). (9) *"A summary of the quality of the MAIA trial is also presented in Table 11, using the criteria adapted from Systematic reviews: CRD's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination)."* (CS Document B, page 44) (3)	
1. Were efforts made to minimise error in data collection? 2. Were sufficient study characteristics available for both review authors and readers to be able to interpret the results? 3. Were all relevant study results collected for use in the synthesis? 4. Was risk of bias (or methodological quality) formally assessed using appropriate criteria? 5. Were efforts made to minimise error in risk of bias assessment?	Y N Y PY NI
Concern that the methods used to collect data and appraise studies may have impacted the results	**LOW**
Rationale for concern: Data extraction was completed using a pre-defined, standardized table and independently checked by a second reviewer, minimizing bias in the data collection process. However, information was not available/reported on the data items collected. The risk of bias tool used follows NICE guidance, however it is not the latest most robust tool for assessing risk of bias in RCTs, therefore risk of bias was not assessed by individual outcome but by individual trials. No information was provided in who conducted the risk of bias assessments.	

DOMAIN 4: SYNTHESIS AND FINDINGS	
For one study(10) identified in SLR 1, no synthesis was conducted. However, a network meta-analysis was also conducted based on studies identified in the same SLR.	
1. Did the synthesis include all studies that it should? 2. Were all pre-defined analyses reported or departures explained? 3. Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies? 4. Was between-study variation minimal or addressed in the synthesis? 5. Were findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses? 6. Were biases in primary studies minimal or addressed in the synthesis?	PY NI PN PY Y Y
Concerns that the synthesis for SLR 1 (randomised evidence only) may have produced biased estimates for input into the economic model	**LOW**

Rationale for concern: The NMA excluded two studies(34), (35) which could have been included, however they were excluded due to being in Asian populations and because outcomes were not reported in a way that the information could be extracted. The study authors could have been contacted for the information in a usable form. The NMA model assumed proportional hazards - which the company noted was not reasonable. Further models relaxing the assumption were fitted. However, since data were not provided by the company for the EAG's preferred parametric NMA model it could not be validated by the EAG and the sensitivity to the choice of distribution could not be assessed. There was clinical heterogeneity across the nine studies in terms of inclusion criteria and baseline characteristics. Despite this, the company reported outcomes from fixed effects NMA analyses. The company identified inconsistency in the network for ORR (p=0.034) and argued that the likely cause of this was the Hungria 2016 trial (26), perhaps due to differences in baseline characteristics. However, a sensitivity analysis excluding Hungria suggests NMA results were insensitive. The EAG note that the CS prefers the uITC for the base-case and not the NMA.

8.1.2 Judging risk of bias: summary of concerns identified in 8.1.1

Domain	Concern	Rationale for concern
1. Concerns that application of the eligibility criteria could have resulted in studies relevant to the scope being excluded from the review	Low	The eligibility criteria were considered to be appropriate and to have resulted in all the relevant studies being included in the review.
2. Concerns that the searches and selection methods could missed studies relevant to the scope	Low	Searches for relevant studies were deemed appropriate and selection methods were conducted in a way to minimize bias.
3. *Concerns regarding methods used to collect data and appraise studies*	Low	Although an up-to-date risk of bias tool was not used, data collection and risk of bias assessments were carried out appropriately.
4. *Concerns that the synthesis may have produced biased estimates for input into the model*	Low	Assessment of statistical heterogeneity, inconsistency, and sensitivity analyses suggest that the results are reasonably robust for PFS and OS in the NMA. However, the CS prefers the uITC for the base-case and not the NMA.

8.2 Appendix 2 Full details of Risk of Bias 2.0 assessment for MAIA

8.2.1 Risk of bias in the effect of assignment to intervention

For effectiveness outcomes the key effect of interest is assignment to the intervention – the intention to treat effect.

Domain	Signalling question	PFS	OS	TTD	Comments

Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	Y	Y	The allocation sequence was random. Allocation concealment is not explicitly outlined but seems likely this was concealed in a large trial using a web-based system.
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	PY	PY	PY	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	N	N	There were no baseline differences between groups that would suggest issues with randomisation
	Risk of bias judgement	**Low**	**Low**	**Low**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	Y	Y	Y	This is an open-label trial. The study team were blinded up until the primary analysis. At later timepoints participants and study team could have knowledge of their allocation.
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y	Y	Y	
	2.3. Were there deviations from the intended intervention that arose because of the experimental context?	PN	PN	PN	Deviations from the intervention due to trial context are not mentioned and no reason to suspect they occurred.
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	Y	Y	Intention-to-treat analysis used
	Risk of bias judgement	**Low**	**Low**	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	Y	Y	Four patients in each group did not receive treatment due to withdrawing from the study (6 pts) or death (2 pts in DLd group). Treatment discontinuation was mostly due to disease progression and adverse events. Patients who discontinued treatments for reasons other than disease progression and remained in trial were followed-up for the primary endpoint.
	Risk of bias judgement	**Low**	**Low**	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	N	N	Methods of measuring were reported and considered appropriate for all outcomes.
	4.2 Could measurement or ascertainment of the outcome have differed	PN	N	N	For PFS it seems unlikely that measurement or ascertainment of the outcome, PFS, would have differed

	between intervention groups?				between groups. Possible due to investigator's assessment but a computer algorithm used to measure PFS.
	4.3 Were outcome assessors aware of the intervention received by study participants?	PY	Y	Y	A computer algorithm determined PFS. It was also assessed by investigators who were aware of the intervention received by this point.
	4.4 Could assessment of the outcome have been influenced by knowledge of intervention received?	Y	N	N	For PFS outcome assessment could have been influenced but a sensitivity analysis shows the blinded computer algorithm results aligned with the unblinded investigator results. For OS assessment of outcome could not have been influenced.
	4.5 Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	PN	NA	NA	
	Risk of bias judgement	**Some concerns**	**Low**	**Low**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y	Y	Y	Data were analysed in line with a pre-specified statistical analysis plan, finalised in 14 Jul 2014.
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	N	N	Outcomes and timepoints prespecified in protocol.
	5.3 ... multiple eligible analyses of the data?	N	N	N	Analysis pre-planned in protocol.
	Risk of bias judgement	**Low**	**Low**	**Low**	
Overall bias	**Risk of bias judgement**	**Some concerns**	**Low**	**Low**	

8.3 Appendix 3: Baseline Characteristics of Studies in CS NMA

The EAG compared the CS extraction of baseline characteristics with our extractions and noted the following discrepancies:

- FIRST study – CS reports 48% of females for the MPT group vs 52% in the EAG table. The EAG notes this may be a reporting error in the CS table as 48% were reported as male in the study report.
- FIRST study – CS only reported group 1 ECOG performance scores (Ld cont: 48%; Ld18: 49%; MPT: 50%). The EAG notes this may be a reporting error in the CS

- table as the heading for this measure was “ECOG performance status 0- I, 2, 3-4 (%)” so a combined percentage for scores 0 and 1 should have been reported.
- MAIA study– MM type-IgG reported in the trial and document B was 61.1% (DLd) and 62.6% (Ld Cont.). MM type-IgG reported in Table 16 was 65.5% (DLd) and 66.7% (Ld Cont.)

8.4 Appendix 4 ROBINS-I assessment for Jimenez-Zepeda(2)

8.4.1 ROBINS-I Assessment for Progression Free Survival and Overall Survival

Domain	Signalling question	PFS	OS	Comments
Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	Y	Y	Study did not account for all confounders. Study did not measure MM type, ECOG and hepatic function.
	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	N	N	Participants selected retrospectively from the Canadian Myeloma Research Group database (CMRG-DB).
	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	N	N	Authors only adjusted for the following: "data were adjusted for known differences between the groups for creatinine, age, B2M, albumin and FISH".
	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	NI	NI	Authors stated they used retrospective data from the Canadian Myeloma Research Group database (CMRG-DB). No information was provided for post-intervention variables.
	Risk of bias judgement	**Critical**	**Critical**	
Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?	PN	PN	Although the study used retrospective data, it was only stated that patients were enrolled based on their first line treatment:
	2.4. Do start of follow-up and start of intervention coincide for most participants?	PN	PN	Patients who received first line treatment between January 2007 until May 2018 were evaluated. It is unclear that treatment was continuous during this time period for all patients. Reverse censoring was conducted.
	2.5. Were adjustment techniques used that are likely to correct for the presence of selection biases?	NI	NI	No adjustment techniques discussed
	Risk of bias judgement	**Serious**	**Serious**	

Bias in classification of interventions	3.1 Were intervention groups clearly defined?	Y	Y	"The BCR regimens included CyBorD/P, VMP and VD/P." "Ld was given to patients according to standard guidelines and dose modifications were allowed at physician's discretion."
	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Y	Y	Patients were evaluated from the Canadian Myeloma Research Group database
	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	N	N	
	Risk of bias judgement	**Low**	**Low**	
Bias due to deviations from intended interventions	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	PN	PN	Authors stated "The selection of a particular bortezomib regimen and subsequent dose reductions were made at the discretion of the individual treating physician. Ld was given to patients according to standard guidelines and dose modifications were allowed at physician's discretion". No further information was provided regarding deviations.
	Risk of bias judgement	**Low**	**Low**	
Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	Y	Y	Yes data available for all participants "A total of 1156 patients met eligibility and received a BCR or Ld as their front-line treatment between January 2007 to May 2018".
	5.2 Were participants excluded due to missing data on intervention status?	NI	NI	No information provided for eligibility criteria of the study or whether exclusion was made based on missing data.
	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	NI	NI	No information available.
	Risk of bias judgement	**Moderate**	**Moderate**	

Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	PY	PN	No access to protocol. It is possible that the measurement of the outcome and the subsequent analysis was influenced by knowledge of the intervention received.
	6.2 Were outcome assessors aware of the intervention received by study participants?	NI	NI	No information regarding outcome assessors and no protocol.
	6.3 Were the methods of outcome assessment comparable across intervention groups?	NI	NI	No information.
	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	NI	NI	No access to protocol.
	Risk of bias judgement	**Serious**	**Low**	
Bias in selection of the reported result	7.1. ... multiple outcome *measurements* within the outcome domain?	PN	PN	No access to protocol. "OS was measured from the time of treatment initiation to death or last follow-up". KM curve presented in Figure 2. of the study report, which also documented the number of patients at risk at varying time points.
	7.2 ... multiple *analyses* of the intervention-outcome relationship?	NI	NI	No access to protocol.
	7.3 ... different *subgroups*?	PN	PN	No access to protocol. However, results presented for OS based on the whole cohort.
	Risk of bias judgement	**Low**	**Low**	
Overall bias	**Risk of bias judgement**	**Critical**	**Critical**	

8.5 Appendix 5: Changes to the Economic Model in Excel

8.5.1 Incorporating treatment waning

In the DLd_trace sheet we have inserted a new column Q, so all columns from Q onwards in the company model are now in columns R onwards. Column Q contains the mortality rates updated to incorporate waning as described below. The OS Extrapolation Column (S previously R) is adjusted to use the mortality rates from Column Q with waning (eg row 32):

=S32*(1-MAX(Q32:R32))
where R contains the general population mortality rate (GPM Mortality)

Column Q is calculated using the following nested IF statement to use the mortality rates in column P prior to waning starting, then the HR for DLd vd Ld changes linearly from the HR at the start of waning to 1 by the end of waning, then the Ld mortality rates are used after the end of waning (eg row 32(:

=IF(ROW(Q32)<(L11+1), P32, IF(ROW(Q32)<(L13+1),(N11+((ROW(Q32)-L11)/(L13-L11))*(1-N11)*Ld_Trace!P32),Ld_Trace!P32))

where

L11 constains the row number when waning begins
L13 = L11+13*L12 is the row number where waning ends
L12 is the duration of the waning period in years (13 rows per year)

N11 = N9/N10 is the HR for DLd vs Ld at start of waning
N9 =INDIRECT("P"&L11) is the mortality rate for DLd at start of waning
N10 =INDIRECT("Ld_Trace!P"&L11) is the mortality rate for Ld at start of waning

- Scenario 7a: Treatment waning starts at 7 years for a duration of 5 years until HR=1 at 12 years. L11 = 108, L12 = 5
- Scenario 7b: Treatment waning starts at 10 years for a duration of 5 years until HR=1 at 15 years. L11 = 147, L12 = 5
- Scenario 7c: Treatment waning starts at 12 years for a duration of 7 years until HR=1 at 19 years. L11 = 173, L12 = 7
- Scenario 7d: Treatment waning starts at 15 years for a duration of 10 years until HR=1 at 25 years. L11 = 212, L12 = 10

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Response to factual accuracy check and confidential information check

Daratumumab with lenalidomide and dexamethasone for untreated multiple myeloma when stem cell transplant is unsuitable [ID4014]

Major Issues

Issue 1 Error in EAG's implementation of change to subsequent treatment cost coding, and resulting errors in EAG's presented ICERs throughout EAG report

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Error in the EAG's economic model in implementing EAG's change as detailed on P89 (Key Issue 12, EAG's change to formulae for subsequent treatment costs). On 15th July 2022, Janssen received two additional clarification questions from the EAG, one of which related to the formula used for subsequent treatment costs. In response, Janssen provided an amended economic model on 22nd July via NICE Docs, which included the EAG's suggested change to the formula for subsequent treatments. It appears from the EAG report that this model has not been used by the EAG in their report. Instead, the EAG implemented changes to the costs of subsequent treatments directly	Janssen have reviewed the EAG's model, and suggest that: • Firstly, only the calculations for acquisition costs have been updated to use the EAG's preferred method, the administration costs are still calculated using the company's original method. • Secondly, the formula in cell P17 on the 'Sub Tx Costs' tab currently uses the market shares for Ld, when it should use the market shares for BCd. The formula therefore should be "=IF(Cd_2L_Cycles>1,BCd_2L_Cd*Cd_1_Acq+(Cd_2L_Cycles-1)*BCd_2L_Cd*Cd_2_Acq, BCd_2L_Cd*Cd_1_Acq)" • In addition, cells Q15:19 currently use the cycle length for BCd and the acquisition costs for	Due to these errors in the EAG's model, which have been used to generate the EAG's ICERs throughout the document, Janssen have provided updated results for use in the EAG report (see Appendix 1). These results have been generated using an updated company's cost-effectiveness model, which includes the correct subsequent treatment calculations (from 22nd July, using the EAG's preferred method). Whilst we anticipate that the model results included in the EAG report will subsequently be updated with this error corrected, we were not able to replicate all of the current EAG's scenarios with the model provided.	The EAG had only queried the acquisition costs and it was not made clear to the EAG that the model the company submitted on 22nd July had also made changes to the administration costs, and so we were unaware of these changes. We used our own coding of the acquisition costs, partly due to time constraints, and also because we did not think that the companys coding of this was correct in the model submitted on 22nd July. We have now reviewed the companys formula for the administration costs in the model submitted on 22nd July and agree that these are appropriate. We also acknowledge the errors identified by the company for the subsequent treatment acquisition costs in the EAG's adapted model.

to the original CS model, and this model has subsequently been used to generate ICERs in the EAG report. A number of errors have been identified in the EAG's implementation of the change to the subsequent treatment cost coding, with resulting errors in the ICERs presented throughout the EAG report.	BMP, not DBd. These formulae should be instead be in line with Cell Q14 as follows: "=X_2L_DBd*DBd_Acq*'Sensitivity Analysis Filter!O68" where X is the 1L treatment • Finally, the EAG's implementation of treatment waning currently causes treatment waning to start (and finish) one cycle later than specified by the user's settings. This is because the formula in Column Q of the 'DLd_Trace' includes a +1 when referring to the row number – this +1 should therefore be removed		We have updated the subsequent treatment acquisition costs in the EAG adapted version of the 1st July CS model including: • Treatment administration costs for subsequent treatments adopted from the company's 22nd July model • Fixed the formula in cell p17 in the 'Sub Tx Costs' tab • Fixed the formulae in cells Q15:Q19 in the 'Sub Tx Costs' tab For treatment waning we have removed +1 from Column Q of 'DLd_Trace', although this did not change the results for the deterministic analysis and only very minor changes for the probabilistic analyses. We have re-run all analyses with these corrections. Note that the results do not agree with those in CS FAC Appendix 1 due to the different way that the acquisition costs have been coded in the

			companys 22nd July model which we believe to be incorrect. We have added the companys results from the 22nd July model into Table 34 so these results are available in the report. We retain the updated base-case from the 1st July model as the companys base-case with which to compare results with. In the report we have edited section 4.2.8.2 to clarify the additional changes to the acquisition costs, and have also made it clear in the Results section 6.1 which models the results are from.

Minor issues

Issue 2 Error in EAG's stated preferred treatment waning assumption included in Executive Summary

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
There is a slight error in the treatment waning assumption (EAG Scenario 7b) included in the Executive Summary (Section 1.1, p12), which is	On p12, it is currently stated that the EAG prefer to include: *6. Treatment waning starting at 10 years with HR coming to 1 over a 5 year period (EAG Scenario 7b)*	Whilst this may be a minor copying error, Janssen believe it is important to be corrected, given that it appears in the Executive Summary.	Thanks for picking this up. We have corrected as suggested.

inconsistent with preferred assumption as documented in the remainder of the EAG report (EAG Scenario 7c). Janssen suggest the assumption in the Executive Summary is changed to align with the rest of the document.	Given this is inconsistent with the rest of the document, as well as modelled scenarios used in the EAG's preferred assumptions, we suggest this should be amended to: *Treatment waning starts at **12 years for a duration of 7 years until HR=1 at 19 years (EAG Scenario 7c)***	The treatment waning assumption (EAG Scenario 7b) in the Executive Summary (Section 1.1) is inconsistent with the EAG's preferred assumption in the remainder of the document (EAG Scenario 7c), as per the following sections: Table 2, p22 Section 6.3, p104 Table 35, p106 Section 6.4, p108	

Issue 3 Conclusion on rationale for selecting the Inverse Probability Weighting (IPW) as base case method

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
P58. Whilst describing the methods used for the unanchored indirect treatment comparison (Section 3.4.4.1), the EAG report states:	Removal of this sentence, given the explanation provided in the CS.	The following was stated in B.2.9.2 (P79 of Document B), which makes it clear why the IPW approach was considered the most appropriate: *The reason that the ATT approach was selected is that the DLd treatment arm of MAIA is the main intervention of relevance to this submission. With ATT weights, this*	We have reworded this sentence to read: *"The EAG did not find the company's justification for preferring IPW over covariate adjustment compelling given that they state there are some advantages of covariate adjustment (CS Section B.2.9.2)."*

The EAG were unclear on why IPW was preferred by the company over covariate adjustment, particularly given that they state there are some advantages of covariate adjustment (CS Section B.2.9.2).		*population was left untouched (as all patients receive a weighting of 1) and the BMP arm from ALCYONE was reweighted such that the BMP population had a similar distribution in baseline characteristics as the DLd patients. In addition, as shown below, overlap between propensity score distributions using ATT is very high (as the observed populations were already very similar to start with) and the standardised mean differences (SMDs) after ATT weighting were small, representing good balance after ATT IPW. Other methodologies (such as covariate adjustment and matching) are more appropriate in case of poor overlap.*	However, this is not a key issue as the company has performed sensitivity analyses that show that the two approaches give very similar results.

Issue 4 Ambiguous conclusion regarding HRQoL data in MAIA

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
P69.	Janssen suggest the sentence is amended as per below:	We suggest this amended for clarity, as the current wording may be interpreted that DLd may	We agree that the wording was ambiguous, however the EAG believes it is more

In the conclusions of the clinical effectiveness section (section 3.6), the EAG report states: *Based on the latest data-cut from MAIA (at median follow up 64.5 months), there is evidence that DLd is effective compared with Ld for most trial outcomes measured, except for HRQoL.*	*Based on the latest data-cut from MAIA (at median follow up 64.5 months), there is evidence that DLd is effective compared with Ld for most trial outcomes measured, except for HRQoL,* ***where there was no significant detriment to overall HRQoL when daratumumab was added to Ld.***	have a negative impact on HRQoL, which is incorrect.	appropriate to conclude that there is "no evidence" of an effect (positive or negative) rather than to frame it directionally. We have amended the sentence to reflect this: "Based on the latest data-cut from MAIA (at median follow up 64.5 months), there is evidence that DLd is effective compared with Ld for most trial outcomes measured, except for HRQoL for which there was no evidence of a difference."

Issue 5 Error in description of capping of OS curves

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
P78 In Section 4.2.6.1 (Summary of treatment effectiveness and extrapolation in CS), the EAG report states: *PFS curves were capped by the OS curves, and the OS curves were capped at the*	We suggest this statement is slightly amended for clarity: *PFS curves were capped by the OS curves, and the OS curves were capped at the* ***rate of general population mortality*** *based on average age and sex.*	This is currently factually incorrect. As per the CS (Document B, Section B.3.3.1.3, p116), to ensure that OS predicted by the model for each treatment did not exceed that of the general population, age- and gender-matched general population mortality (based on life tables for the UK from the Office for National Statistics 2020) was used in any cycle	Amended as suggested.

general population survival based on average age and sex.		where the predicted rate of death was lower than general population mortality.	

Issue 6 Additional wording for clarity required in EAG's summary of Issue 4 (p15)

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
P15, Issue 4 The EAG report states: The NMA results and ICERs are not sensitive to the inclusion of HUNGRIA and MYELOMA IX.	This should be clarified. Two rows above (p15, Issue 4), the EAG state: *'For the comparison between BMP and Ld the NMA results are robust to inclusion of different studies making the MPT vs MP comparison,* ***but sensitive to inclusion of HUNGRIA and MYELOMA IX****.'*	Inconsistent conclusion of sensitivity of NMA results of inclusion of HUNGRIA and MYELOMA IX trials within Issue 4 summary.	The EAG have amended and added clarifying text to the summary of Issue 4. We have now made it clear that results are not sensitive to the inclusion of HUNGRIA and MYELOMA IX.

Issue 7 Misrepresentation of company rationale for equal efficacy between BMP and BCd

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
At multiple times throughout the document, the EAG suggests that the MAIC was the only source of evidence used for the company assumption of equivalent efficacy between BMP and BCd: P16, Issue 6 P60, Key Issue 5 P77 P83	We suggest this is amended to reflect the rationale presented in Document B Section B.2.9.3. P16: *As such, the company assumed equal efficacy of BMP and BCd, supported by **3 sources of evidence, clinical opinion,** and an (observational) Matched Adjusted Indirect Comparison using single arm evidence from ALCYONE (1) and Jimenez-Zepeda (2).* P60: *To demonstrate equivalence, they **sought advice from clinical experts, presented 3 additional sources of evidence and** performed a Matched Adjusted Indirect Comparison (MAIC) to compare BMP versus BCd,* P:77 *Survival outcomes of patients undergoing BCd were assumed to be equivalent to those treated with BMP due to the lack of head-to-head clinical studies, **expert clinical opinion, 3 additional data sources,** and based on a MAIC using*	As per Section B.2.9.3 of Document B of the CS, this is not the only evidence that was presented in support of the equal efficacy of BCd and BMP assumption.	The EAG has amended the report to reflect the company's rationale, but to highlight their preferred hierarchy of evidence: P16: *"As such, the company assumed equal efficacy of BMP and BCd, supported by an (observational) Matched Adjusted Indirect Comparison using single arm evidence from ALCYONE (1) and Jimenez-Zepeda (2), as well as naïve comparisons from two observational sources of evidence and clinical opinion."* p60: *"To demonstrate equivalence, the company performed a Matched Adjusted Indirect Comparison (MAIC) to compare BMP versus BCd. They also provided naïve comparisons from two observational sources of evidence (Sandecka et al. 2021 and*

	observational data from the Jimenez-Zepeda study (2) P83: *The company assume that BCd has the same efficacy as BMP based* ***clinical expert opinion, 3 additional data sources, and*** *on their matched adjusted indirect comparison (MAIC) comparing BCd and BMP giving confidence intervals for hazard ratios that contain 1 (no effect).*		*NCRAS) as well as clinical opinion."* p62: "*The company also provided naïve comparisons from two observational sources of evidence that made no adjustments for potential confounders (Sandecka et al. 2021 and NCRAS). Whilst the survival estimates in these studies were not substantially different for BMP and BCd they did not provide meaningful evidence of equivalence and were considered to be of less value than the results from the MAIC in informing BMP vs BCd. The company stated that their clinical experts were of the opinion that BMP and BCd were equivalent, though there was no formal elicitation process to determine this."* p77: *"Survival outcomes of patients undergoing BCd were assumed to be equivalent to those treated with BMP due to the lack of head-to-head clinical studies and based on a MAIC using observational data from the Jimenez-Zepeda study (2) and the*

			BMP arm of the ALCYONE trial (45) (described in section B.2.9.3 of CS) (3), as well as naïve comparisons from two observational sources of evidence and clinical opinion." p83: *"The company assume that BCd has the same efficacy as BMP based on their matched adjusted indirect comparison (MAIC) comparing BCd and BMP giving confidence intervals for hazard ratios that contain 1 (no effect), as well as based on weaker evidence from naïve comparisons from two observational sources of evidence and clinical opinion."*

Misreporting from the CS and typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
p1-	Daratumumab with lenalidomide and dexamethasone for untreated multiple myeloma when stem cell transplant is unsuitable [ID4014] A ~~s~~Single Technology Appraisal	Minor typo	This has been corrected.
P11, Table 1	What is the preferred source of evidence for the comparison **of** BMP vs DLd, the HR NMA,	Missing word in sentence	This has been corrected.
P12	5. ~~Use~~ Using the Exponential distribution for TTD for DLd (EAG Scenario 6b)	Minor typo	This has been corrected.
P14	However, the UK centre subgroup was very small (DLd: n=[redacted] and Ld: n=[redacted]) (data provided in response to clarification question ~~B.5~~ C.4.)	The subgroup analyses were provided in response to question C.4 rather than B.5.	This has been corrected.
P16	The ICER for DLd vs BMP **(with PAS)** varies from [redacted] in the company's updated base-case using the unanchored indirect comparison to [redacted] using the piecewise NMA.	The EAG should clarify that these results are with PAS. Additionally, this should be clarified for when ICERs with PAS are presented throughout the EAG report.	We have stated *"All ICERs reported in this section include the Patient Access Scheme (PAS) price for daratumumab."* at the beginning of sections 1.4, and 1.5 so it is clear that all the ICERs

			in these sections are with the PAS included. We have made it clear throughout whether ICERs are with or without the PAS price.
P18	The ICERs are sensitive to the choice of parametric model for Time to Treatment Discontinuation **(**~~TTS~~ **TTD)**	Minor typo	This has been corrected.
P20	Using the ALCYONE utilities increases the ICER for DLd vs Ld in the company's updated base-case from [redacted] to £[redacted]. ~~by approx.~~	Minor typo	This has been corrected.
P31	~~H~~However, across both 2nd and 3rd line therapies combined, a greater proportion of participants in the Ld arm received a subsequent treatment not routinely commissioned in England ([redacted] vs [redacted] (Table ~~161~~ **160**, CS Appendix R (9)).	Minor typo	This has been corrected.
P 37	There is a formatting error after reference to Table 6. Suggest to remove the 'page break' from this location.	Minor formatting error	This has been corrected.
P42	The network of randomised comparisons included BMP, MP**,** MPT**,** CTd, Ld, and DLd	Typo- additional commas added	This has been corrected.

P43	Across the network of studies, Hungria and TMSG had the highest proportions of patients with baseline performance scores of 2 or higher (Hungria(26) [ECOG: MPT 53.4%, CTd ~~51.4~~ **50.4%**] Across the network, Hungria(26) and Sacchi(30) had a high proportion of patients with ECOG score of 3-4 (Hungria: MPT 16.7%, CTd 12.5%; Sacchi: MP 9%, MPT 12%),	Error: this should be 50.4% as per the information in Table 16 of the appendices. Error: The 9–12% for the Sacchi study in Table 16 in the appendices refers to ECOG 0–2, rather than ECOG 3-4 as per the EAG report.	We have corrected 51.4 to 50.4% as highlighted. We have checked Table 16 in the CS appendices and 9-12% is reported for ECOG 3-4. Table 16 shows 85% (MP) and 83% (MPT) of patients had an ECOG of 0-2. Perhaps this is a reporting error in CS Table 16? No change made.
P44	The studies varied in sample size: FIRST (n=1623), MRC Myeloma ~~XI~~ **IX** (n=~~842~~ **849**)	This should be Myeloma IX rather than XI, and n should be 849 based on the values in Table 16 of the appendices.	This has been corrected.
P50	Three studies (MAIA(10), ALCYONE (1) and Jimenez-Zepeda (2)) underpinned the uITC of DLd vs BMP and MAIC of ~~DLd~~ **BMP** vs BCd in the CS.	Typo, as the MAIC presented is for BMP vs DLd	We think you mean BMP vs BCd. This has been corrected as suggested.
P50	The proportion of male participants was considerably higher in Jimenez (59.3%) than in either MAIA **(DLd arm)** (51.4%) or ALCYONE (46.9%). The proportion of Asian	Stated values in the text correspond to DLd arm of MAIA only, and the text should reflect this	This has been corrected.

	participants was 0.8% in **the MAIA DLd arm** and 12.6% in ALCYONE.		
P52	BCd/P (n=562), BMP (n=292) B~~M~~**D**/P (n=94), Ld (n=208)	Minor typo. In addition, the key below the table should be updated.	This has been corrected.
P55	Following the EAG's clarification request, the company re-ran the NMA including Song(34) for ORR and ~~CTR~~ ≥**CR** and results were very similar to the company's base case.	Minor typo	This has been corrected.
P64, Table 14	PFS HR for 8 covariates used for adjustment: [redacted] TTD HR for 11 covariates used for adjustment: [redacted]	Error	Corrected.
P65, Formatting	Cross reference to relevant Section in EAG report should be amended, as currently it is stated: Given that there are no gains in precision and that the inclusion of CTd may introduce inconsistency due to baseline imbalances in Hungria (Section **Error! Reference source not found.**),	Minor formatting error	This has been corrected
P73	The probability of a patient in the cohort (treated with ~~LDd~~ **DLd**, Ld, or BMP) being in any given health state at a given time	Minor typo	This has been corrected.
P74	The company included options for the user to select a choice of parametric survival models	Minor typo	This has been corrected.

	to extrapolate beyond the length of the trial period.		
P74	The EAG deems the company's use of a ~~PFS~~ **PSM** model type as appropriate in the context of the available evidence on patient outcomes and comparability with previous TAs	Minor typo	This has been corrected.
P78	Following the clarification process the company presented scenarios where parametric NMAs were fitted to make comparisons between Dld, Ld, and BMP using a Gompertz distribution for OS and an Exponential distribution for PFS (see sections 3.4.2 and).	Missing reference at end of sentence	Corrected (only 1 section to cross-reference here).
P85	… and so the EAG conducts scenario analyses ~~to~~ using the Generalised Gamma or Exponential in place of the Gompertz,	Minor typo	This has been corrected.
P89	The EAGs clinical ~~avice~~ **advice** was that **bortezomib** is typically administered weekly in practice with 3 weeks on and 1 week off per cycle	Minor typo	This has been corrected.
P91	ICERs included in Table 29 are incorrect, and should be corrected as per Appendix 2	Errors in ICERs	We have corrected the figures for Total Costs and Total QALYs in Table 29. Note however that the figures in the company FAC Appendix 2 for Ld do not match those

			obtained from the companys model submitted on 1st July 2022. We have used the figures from the Excel model for Ld.
P93	Table 31, ICER vs Ld in Scenario should be [redacted] rather than [redacted]	Error	We have checked this and the [redacted] is correct and comes directly from the Excel model submitted by the company on 1st July 2022 (see response to the point above also). No change made.
P107, Title of Table 36	The title of the table should be amended to: Results of the ~~CS~~ **EAG** updated base case at the PAS price (excluding CDF treatments) Probabilistic Results	Minor typo	This has been corrected.

Confidentiality highlighting amendment

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
P14, P41, of EAG report	Numbers of patients to inform UK subgroup analysis of MAIA should be marked as AIC	However, the UK centre subgroup was very small (DLd: n=[redacted] and Ld: n=[redacted])	All changes to highlighting have been made as requested
P75, P87	% of patients in scenario where 2% of patients receive IV should be marked as CIC, as this is based on Janssen sales data.	P75: The company provides a scenario analysis where [redacted] of patients receive IV DLd. P87: DLd was assumed to be administered subcutaneously (SC) with a scenario where [redacted] of patients receive IV administration.	
P41	These data are published and therefore the AiC markings can be removed.	Results of the subgroup analysis showed the PFS benefit of DLd versus Ld was maintained across subgroups: non-frail (median: not reached versus 41.7 months; HR: 0.48; p<0.0001) and frail (median: NR versus 30.4 months; HR: 0.62; p=0.003).	
P53, Table 10	These data are not published and so should be AiC	MAIA, Race: White: [redacted] Black: [redacted]	

		Asian: [redacted] ALCYONE,MM type (IgG/not IgG): IgG [redacted]	
P65	These data are not published and so should be AiC	The impacts were very minor for OS, but for PFS the difference was more meaningful, particularly for HRs at ≥20 months follow-up in which the HR for BMP vs Ld changes from [redacted]	
P75	These data are not published and so should be AiC	This is also seen in the close agreement in mean age between MAIA and NHS Digital RWE on a cohort of NDMM patients in England (53) (Table 36 B3.2.1) (3), although MAIA appears to under-represent male ASCT-ineligible NDMM patients (52.1% in MAIA compared with [redacted] in the NHS Digital RWE in England cohort).	

Company FAC Appendix 1 removed from EAG response.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Daratumumab with lenalidomide and dexamethasone for untreated multiple myeloma when stem cell transplant is unsuitable [ID4014]

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

The deadline for comments is the end of **21 October 2022**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we

received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	**Timothy Ming**
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	**Janssen-Cilag Ltd**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**N/A**

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Key Issue 1 Are thalidomide containing therapies a comparator at 1st line?	No	As per Section B.1.1 of our company submission (CS), **Janssen consider Ld (lenalidomide and dexamethasone) the most relevant comparator for this appraisal, and that thalidomide-based combinations are not clinically relevant given their negligible use in English clinical practice**. This was based on consensus feedback from a clinical expert advisory board meeting held on the 9 h of March 2022 involving 8 English-based clinicians, the minutes of which were submitted as part of the appendices in the CS (Data on file, Janssen Clinical Advisory Board Meeting minutes). Janssen's position is consistent with the EAG's clinical expert feedback, and statement from the UK Myeloma Forum (UKMF) which commented only 'a small number of patients will receive a thalidomide based regimen' (p271/297 of TE papers). Moreover, there are known tolerability issues with thalidomide-based treatment with the UKMF noting, 'It would [be] unusual for patients to receive a Thalidomide based regimen as Lenalidomide is a better tolerated oral regimen'. In summary, Janssen consider the main comparator of relevance for this submission to be Ld, for which MAIA provides direct, randomised evidence with over 5 years median follow-up. As per

		Key Issue 5 below, we note that Ld dominates all other comparators in most scenarios explored, and therefore, the ICER versus Ld is the most relevant ICER for Committee decision making.
Key Issue 7 Should CDF drugs used at 2nd line and beyond be included in the company's model?	Yes	**It will be important for scenarios including DBd at 2L to be available to committee, to support process efficiency and speed of patient access.** Janssen note there are two treatments for multiple myeloma (MM) currently on the CDF with imminent routine commissioning decisions, which impact the modelling of subsequent treatments: **1) CDF exit of DBd at 2L (in process)** Janssen note that the appraisal committee meeting for daratumumab with bortezomib and dexamethasone (DBd) for previously treated multiple myeloma (Review of TA573) [ID4057] is scheduled for 8th February 2023 (a few weeks after DLd on 12th January 2023). DBd represents standard of care in England at second-line, and its inclusion as a subsequent treatment has a material impact on the cost-effectiveness of DLd. Janssen acknowledge and agree with the NICE position statement regarding the inclusion of CDF drugs as either comparators or subsequent treatments. Given the unique circumstance, however, of the proximity of the two appraisals for the same molecule by the same manufacturer and the material impact of including subsequent DBd on the cost-effectiveness results, Janssen request a degree of pragmatism and flexibility by NICE for the EAG and Committee to consider scenarios **conditional** on a DBd recommendation for routine commissioning. [redacted]

		2) CDF exit of IxaLd at 3L (in process) The latest stakeholder communication from NICE regarding the decision for ixazomib with lenalidomide and dexamethasone [NICE ID1635] [redacted] Unlike the DBd appraisal, Janssen do not have visibility on the expected outcome of the IxaLd decision. As per the EAG's request during the Technical Engagement call, Janssen have updated the cost-effectiveness model with functionality to only consider a CDF scenario including DBd at second-line. Scenarios including the impact of IxaLd at 3L in the treatment pathway are provided below, to facilitate the Committee having the most up to date information at the time of decision making.
Key Issue 2 Are results of MAIA generalisable to the NHS in England, considering currently available routine treatments?	Yes	**Janssen consider the results of MAIA to be generalisable to the NHS in England and results using the IPCW analysis suggest the cost effectiveness results (using the unadjusted MAIA data) may be conservative**. MAIA was a registrational quality Phase III RCT which included patients from the UK, that directly compared DLd against the most relevant active comparator in current NHS clinical practice, Ld. In MAIA, a total of [redacted] of patients across fourteen sites were included from the UK, across 12 locations: Aberdeen, Canterbury, Dundee, Leeds, London, Manchester, Nottingham, Oxford, Plymouth, Southampton, Truro and Wolverhampton. The majority of subsequent treatments that patients received in MAIA are routinely available in the UK. However, due to the international study design, MAIA included a number of subsequent treatments which are not routinely available in NHS clinical practice. The proportion of patients receiving such treatments was balanced across treatment arms ([redacted]%) in the DLd and Ld arms respectively at second-line), which helps to minimise any potential bias. As detailed in Section B.2.6.2.6 of the CS, the impact of non-routinely commissioned subsequent treatments on the observed efficacy has been extensively explored with a number of statistical

		methods considered. An IPCW OS analysis was conducted as the only potentially viable method to explore the impact of potential bias as a result of including non-routinely commissioned treatments. Reassuringly, the results of the IPCW analysis demonstrate an even greater OS benefit for DLd vs Ld (indicated by a reduced HR), following adjustment to exclude subsequent treatments not available in the UK setting (Observed OS HR: 0.66: 95% CI: 0.53, 0.83; IPCW Adjusted OS HR: [redacted]). As such, Janssen consider the unadjusted DLd versus Ld hazard ratio from MAIA to be conservative and likely to underestimate the relative survival benefit of DLd expected in clinical practice in England. In summary, Janssen consider the results of MAIA generalisable to the NHS in England with likely conservative estimates of the relative treatment effect; some bias against DLd. The generalisability of MAIA is further supported by the statement from UKMF that the reported outcomes for the control arm reflects the expected outcomes of Ld in UK clinical practice (Q 21, p277 of TE papers).
Key Issue 3 Is there sufficient follow-up for robust estimation of overall survival?	No	**Janssen consider the available evidence package for DLd to be robust, and length of follow-up from MAIA sufficiently mature for robust estimation of overall survival and a recommendation to be made for routine commissioning.** Janssen consider the duration of follow up from MAIA (over 5 years) sufficient for robust estimation of overall survival and Committee decision making. Whilst a recommendation for the CDF remains an option for the Committee, it is expected that additional follow-up from MAIA will only confirm the current understanding of the significant clinical benefit of DLd in this setting, rather than help to resolve inherent uncertainty of long-term survival estimates for this chronic life-long condition. **Significance of MAIA results and follow-up in the context of other Haemato-Oncology NICE appraisals**

		Regulatory approval for DLd was granted based on the results of the MAIA primary PFS analysis, with a median follow-up of 28 months. Since then, subsequent MAIA datacuts have consistently demonstrated a statistically significant and clinically meaningful improvement in survival outcomes (PFS and OS) for DLd patients compared with Ld alone. Based on the outstanding efficacy results from MAIA, DLd is internationally regarded as the frontline treatment choice for newly diagnosed transplant-ineligible patients in both national and international treatment guidelines (Dimopoulos MA, 2021) (Sive J, 2021). The clinical significance of the MAIA results was acknowledged by the UKMF, who describe the improvement in PFS and OS from MAIA as 'undoubtedly clinically meaningful outcomes', and 'the reported outcomes for D-Rd in a phase 3 trial are internationally considered to set a new gold standard for 1st line treatment of newly diagnosed transplant ineligible myeloma'. Furthermore, the follow-up from MAIA is now similar to the follow-up from the FIRST trial (median follow up of 67 months), which provided the clinical evidence for the NICE approval of Ld (TA587) in 2019. As noted by the ERG at the time (p15 of ERG report, TA587): 'the [FIRST] trial results can be considered mature with a median follow up of 67 months at the most recent data cut-off'. Therefore, with a median follow up of similar magnitude, MAIA should be considered similarly appropriate for decision making. **Robustness of OS extrapolations** The EAG state that extrapolations for OS, in particular for the DLd arm, are uncertain. **Whilst Janssen acknowledge inherent uncertainty with long-term estimates of OS, the similarity of the DLd OS predictions from multiple models, including more flexible methods, indicate that the follow-up from MAIA is sufficiently mature for robust estimation of OS.** Based on the follow-up available from MAIA, all DLd extrapolations (with the exception of the generalised gamma, which represents a notable outlier) provide strikingly similar long-term OS estimates. In addition, exploration of more flexible methods, including spline models with one, two

		and three knots, generated curves that were in line with the standard parametric extrapolations (Section B.3.3.2, Document B). Long-term outcomes between the EAG's preferred OS extrapolation for DLd (Gompertz) and the company base case (Exponential) are similar (mean 115.1 months versus 116.7 months respectively), indicating that there is sufficient follow-up for robust estimation of OS. **Follow-up from final MAIA OS analysis** The EAG state that longer follow-up from MAIA would help to resolve the uncertainty in the OS extrapolations. It is unclear, however, the extent to which the additional follow-up from the final MAIA OS analysis will help resolve the inherent uncertainty associated with modelling a lifetime time-horizon for a chronic condition such as untreated ASCT-ineligible MM. The final MAIA OS analysis is currently expected to occur in [redacted] and will add approximately [redacted] months additional follow-up. Janssen consider that while this additional follow-up would reduce uncertainty in estimates of overall survival (which as noted above are already strikingly similar in the company and EAG base cases) it could not resolve or materially reduce uncertainty pertaining to for example survival at 20 years or the long-term duration of benefit. As such, we believe the evidence base is sufficient for a routine commissioning recommendation.
Key Issue 4 Are the studies in the NMA similar enough for reliable inference?	No	**Janssen consider the approach taken for the indirect comparison against bortezomib-based treatments in this submission as suitably robust and comprehensive. The comparison of DLd vs Ld, using the direct evidence from MAIA, is most relevant for Committee decision making.** Our base case comparison of DLd against BMP leveraged individual patient-level data (IPD) from another phase 3 Janssen study in this same population, ALCYONE, to perform an IPD unanchored indirect comparison using propensity score weights. A scenario analysis was also performed using a standard NMA approach and, at the request of the EAG, Janssen has explored more flexible methods to counter observed violation of the proportional hazards assumption of some studies included in the network for PFS/OS.

		Whilst we agree that the studies within the evidence network are sufficiently similar for reliable inference through the NMA, there are important advantages and disadvantages to the different methods. We note, however, that regardless of the indirect comparison method selected, Ld dominates all other treatments in each scenario. **As such Janssen consider the ICER of DLd versus Ld, using direct evidence from MAIA, as most relevant for Committee decision making.**
Key Issue 5 What is the preferred source of evidence for the comparison of BMP vs DLd, the HR NMA, the Parametric NMA, the Piecewise NMA, or the unanchored indirect treatment comparison?	Yes	**Regardless of the indirect comparison methodology explored, the ICER of DLd versus Ld remains the most relevant for committee decision making and is supported by high-quality randomised phase 3 evidence.** As noted above, Janssen consider the unanchored indirect comparison leveraging individual patient data from MAIA and ALCYONE most robust to inform the indirect comparison of BMP versus DLd. By contrast, the EAG prefer an NMA approach, utilising randomised evidence despite the long chain linking the two studies. Due to the observed violation of proportional hazards for some studies in the network, the EAG suggest an NMA model that relaxes the proportional hazards assumption for both PFS and OS and for all comparisons. The parametric NMA is the only approach that achieves this and fits curves to all treatments simultaneously assuming the same parametric distributional form for each treatment, which is in line with recommendations from TSD14. Therefore, we have provided supplementary analyses focusing on the parametric NMA (both including and excluding CTD), which are detailed in Appendix A and B. Other advanced NMA methods considered included the piecewise HR or piecewise parametric NMA. However, the disadvantage of these piecewise methods is that they require splitting the data into two timeslots. The timepoint where the data is split may be arbitrary and should be consistent for all trials, even if the optimal timepoint to split the data varies across the trials in the

network. Given that the standard parametric NMA fits the data well overall, Janssen consider that other advanced NMA methods are likely to only introduce further complexity to the analysis and require unnecessarily strong assumptions for the indirect comparison.

Full exploration of the parametric NMA (including CTD in the network, Table 1) approaches show that selections of Gompertz for OS and Weibull for PFS are the best fitting curves, based on the lowest LOOIC.

Table 1: Parametric NMA (including CTD) LOOIC, OS & PFS

Distribution	LOOIC (OS)
Exponential	27079.1
Weibull	27030.2
Gompertz	27024.6
Loglogistic	27147.6
Lognormal	27316.6

Distribution	LOOIC (PFS)
Exponential	27763.2
Weibull	27656.5
Gompertz	27711.6
Loglogistic	27717.2
Lognormal	No convergence

Full exploration of the parametric NMA (excluding CTD in the network, Table 2) approaches show that selections of Gompertz for OS and Gamma for PFS are the best fitting curves, based on the lowest LOOIC.

Table 2: Parametric NMA (excluding CTD) LOOIC, OS & PFS

Distribution	LOOIC (OS)
Exponential	21710.94
Weibull	21679.72
Gompertz	21661.93
Loglogistic	21771.26

Distribution	LOOIC (PFS)
Exponential	21553.5
Weibull	21460.8
Gompertz	21495.8
Loglogistic	21541.4

Lognormal	21900.14
Gamma	21684.03

Lognormal	21698.5
Gamma	21458.6

Table 3 presents the summary results from multiple approaches that have been explored for the indirect comparison vs BMP.

Table 3: Summary results when using parametric NMA to compare vs BMP (excluding CDF treatments)

Comparison vs BMP	ICER vs BMP	BMP dominated by Ld?
Parametric NMA (excluding CTD), OS: Gompertz, PFS: Gamma	[redacted]	Dominated by Ld
Parametric NMA (including CTD), OS: Gompertz, PFS: Weibull	[redacted]	Dominated by Ld
Unanchored indirect comparison (ALCYONE IPW, OS: Gompertz, PFS: Weibull)	[redacted]	Dominated by Ld
Parametric NMA (excluding CTD), OS: Gompertz Piecewise NMA, PFS: Weibull	[redacted]	Dominated by Ld

It can be seen from multiple approaches for the indirect comparison:

1) When using the MAIA data to inform the comparison of DLd vs Ld, Ld dominates BMP, thus supporting the conclusion that the DLd vs Ld is the most relevant ICER for decision making

2) ICERs vs BMP are largely consistent with the base case analysis

Key Issue 6 Is it reasonable to assume equivalence between BMP and BCd?	No	**As noted above, the comparison of DLd vs Ld, using the direct MAIA evidence, remains the focus for Committee Decision making.** A comprehensive approach has been taken for the indirect comparison of DLd versus bortezomib in combination with an alkylating agent and corticosteroid. In addition to providing a comparison vs BMP (Key Issue 4 and 5), BCd is an alternative bortezomib-based triplet treatment which is used in UK clinical practice. However, BCd is not licensed for use in this population and the clinical SLR identified no randomised evidence investigating BCd. As such, there is an absence of robust high-quality evidence to inform the indirect comparison of BCd with either BMP or DLd. Based on the clinical SLR results, the Jimenez-Zepeda study (Jimenez-Zepeda VH, 2021) represents the most informative observational evidence for BCd. This study demonstrated no statistically significant differences in PFS and OS versus BMP. To further explore the relative efficacy of BCd versus BMP, Janssen conducted a MAIC utilising patient level data from the phase 3 ALCYONE trial. Consistent with the observational evidence, the MAIC results were inconclusive with PFS and OS HRs close to 1 and wide 95% confidence intervals crossing 1 (PFS HR [redacted]) and OS HR [redacted]), Appendix D.6.3). Janssen does not consider the MAIC evidence sufficiently robust to incorporate in the economic model. The EAG noted similar concerns regarding the use of Jimenez-Zepeda as a basis for analysis (EAG report, p33) and noted the study was at 'Critical Risk of Bias', concluding 'the study is too problematic to provide any useful evidence and should not be included in any synthesis'. As such, we consider the use of the observational data inappropriate to inform the efficacy for the ICER of DLd vs BCd. We therefore considered results from the MAIC, naïve comparisons from two different observational sources of evidence (Jimenez-Zepeda VH, 2021; Sandecká V, 2021), as well as clinical opinion from 8 English-based clinicians (Janssen), to support the assumption that BMP and BCd are clinically equivalent, as two bortezomib based triplet therapies (Section B.2.9.3 of

		company submission). In addition to the published RWE studies (Sandecká V, 2021; Jimenez-Zepeda VH, 2021), Janssen note that the results from the NHS Digital National Cancer Registration and Analysis Service (NCRAS) (Section B.2.9.3 of Company Submission) support the conclusion of clinical equivalence between BMP and BCd. Whilst there is no one source of evidence which unequivocally demonstrates clinical equivalence, taken together, there is consistency in the totality of evidence which supports clinical equivalence of the bortezomib based treatments. With the current evidence base, we suggest that a robust comparison vs BCd is an unresolvable uncertainty. The clinical comparison of BMP vs DLd represents a reasonable proxy for the clinical effectiveness of bortezomib based triplet treatments, as per the NICE scope. Regardless, given that Ld dominates all other treatments in all scenarios explored, the comparison of DLd vs Ld, using the direct MAIA evidence, remains the focus for Committee Decision making.
Key Issue 8 Which are the most appropriate parametric models for PFS, OS, and TTD for DLd, Ld, and BMP?	YES	**For DLd OS, given the similarity in survival outcomes, Janssen acknowledge that both Exponential and Gompertz are plausible outcomes.** **For DLd TTD, the Generalised Gamma and Gompertz have similarly good statistical fit for AIC and BIC to the Exponential. The observed MAIA data supports an increasing divergence between PFS and TTD over time, which would be inconsistent with the EAG's selection of the Exponential TTD, which represents an extreme scenario.** The EAG prefer to model BMP using results from the NMA therefore our response to Key Issue 8 is focussed on consideration of appropriate parametric survival models for DLd and Ld. **PFS & OS** As noted by the EAG, 'The ICER for the comparison DLd vs Ld was robust to choices of parametric curve for OS and PFS' (EAG report, page 18). Indeed, for OS, the EAG's preferred selection of Gompertz results in very similar long-term survival estimates for DLd as the Exponential used in the Company base case, with less than a 2-month difference in the mean

predicted OS over the time horizon of the model (Gompertz mean=115.1 months, Exponential mean=116.7 months).

Given the similarity in long-term outcomes, and comparability of statistical fit, Janssen consider that both Exponential and Gompertz are clinically plausible selections. Table 4 provides a comparison of the ICER assuming an Exponential and Gompertz distribution for DLd OS:

Table 4: Base case ICERs with DLd OS Gompertz and Exponential

Scenario	ICER vs Ld, excluding CDF treatments (with PAS)
Revised company base case (DLd OS Gompertz)	[redacted]
Revised company base case (DLd OS Exponential)	[redacted]

The comparability of long-term outcomes and stability of the ICER across different OS curve selections reflects maturity of the trial data with over 5-years median follow-up from MAIA and provides reassurance regarding the limited extent of residual uncertainty.

TTD

For DLd TTD, the EAG explore scenarios based on statistical fit using:

- Generalised Gamma
- Gompertz
- Exponential

The EAG prefer exponential based on the lowest BIC value however Janssen consider the statistical fit for each to be broadly comparable, with exponential and generalised gamma providing an upper- and lower-bound respectively (Latimer, 2011). Arguably, the generalised

		gamma curve has best statistical (lowest AIC) and visual fit to the observed Kaplan Meier data. On balance, however, Janssen considers Gompertz the most appropriate curve choice for decision making, sitting comfortably within the clinically plausible range. We do not believe that there is sufficient evidence to consider the exponential curve as the base case; as it sits at an extreme end of the plausible scenarios. **Figure 1: DLd PFS and TTD** 

To further inform the selection of TTD curve, Janssen explored the relationship between TTD and PFS observed in MAIA (Figure 1). Specifically, Janssen conducted a piecewise Cox analysis splitting the data into equal intervals of 12-months. Results from this analysis (Table 5) demonstrate a consistent trend, with the HR point estimate decreasing over the trial follow-up period.

Table 5: Piecewise Cox model analysing relationship between DLd PFS and TTD

Period (MAIA)	HR [95%CI]	P-value
<=12 months follow up	[redacted]	[redacted]
>12 months - <=24 months		
>24 months - <=36 months		
>36 months- <=48 months		
>48 months - <=60 months		
>60 months- <=72 months		

HR= hazard ratio

Whilst the confidence intervals overlap, the point estimates demonstrate a consistent decreasing trend. This observation is also clinically plausible as, for many patients, the option to stop treatment prior to progression is likely to be after a period of sustained deep response (e.g. sustained CR, or MRD negativity) or treatment fatigue and build-up of unacceptable toxicity. Moreover, the expectation that some patients may stop treatment prior to progression is aligned with MM patient preferences, where patients highlight longer treatment-free periods as the most valued treatment attribute (Myeloma UK, 2019).

		Given the observed trend in MAIA, it is reasonable to expect that the difference between PFS and TTD would continue to widen over time. Janssen note that this does not support selection of Exponential for DLd TTD which tracks broadly parallel to PFS. Adherence is also likely to be lower in the real-world setting, where patients are not actively monitored as part of a clinical trial. In this respect, the difference between TTD and PFS may be expected to be even larger. As such, for Committee decision making, Janssen consider the Gompertz to represent a reasonable estimate for DLd TTD, given this is within the upper plausible range (Exponential) and lower plausible range (Generalized Gamma), and is supported by the observed MAIA relationship between PFS and TTD.
Key Issue 9 Would the treatment effect for OS be maintained for a patient's lifetime or would there be waning of effect?	YES	Janssen acknowledges the inherent uncertainty with long-term survival estimates in the context of modelling a lifetime time horizon. Our understanding from the Technical Engagement call is that the EAG have included assumptions for OS treatment waning in their base case as a way of exploring the uncertainty. However, the inclusion of an OS treatment waning effect solely for DLd is not evidence-based, inconsistent with prior NICE appraisals for this indication (TA587 and TA228), and not supported by clinical understanding of disease biology. Our position is supported by: 1) Understanding the importance of depth of response in MM and the biological plausibility of waning in this disease setting 2) Observed MAIA data, indicating an OS benefit increasing over time 3) Lack of face validity for applying an OS waning assumption solely to the DLd arm Further details for each of these points are provided below. **1) <u>Depth of response and biological plausibility of a waning of OS benefit over time</u>** In MM, achieving deep and sustained responses is recognised as one of the primary goals of front-line treatment, resulting in a fundamental shift in the trajectory of the disease course and

		long-term outcomes for patients. This was recognised by UKMF in their response to this appraisal and is supported by extensive evidence that deeper responses translate to improved long-term PFS and OS (Lahuerta JJ, 2008; Chanan-Khan AA, 2010; Kapoor P, 2013; Harousseau JL, 2009; Munshi NC A.-L. H., 2017; Munshi, 2019). Results from MAIA demonstrate that patients receiving DLd achieve deeper and longer sustained responses compared with existing standard of care, Ld (Section B.2.6.2 of company submission). A waning of the relative treatment effect is inconsistent with broad clinical consensus regarding the long-term survival benefit conferred by deeper responses. Indeed, the UK Myeloma Forum comment that DLd represents a step change in the management of the condition (Q16a), specifically because DLd 'improves depth of response which correlates with improved survival' (p275 of the Technical Engagement papers). The Minimal Residual Disease (MRD) results from MAIA indicate that the depth of response following DLd treatment allows for long-term disease control. MRD is the most sensitive measure of response currently available. The evidence for the survival benefit of MRD is significant, with a recently published meta-analysis of results from 45 studies (93 publications) finding that outcomes for both PFS (N=8,098) and OS (N=4,297) were significantly improved for MRD-negative patients compared with MRD-positive patients (PFS HR: 0.33; 95% CI: 0.29, 0.37; OS HR: 0.45; 95% CI: 0.39, 0.51; p<0.001 for both) (Munshi NC A.-L. H., 2020). Specifically in the newly diagnosed ASCT-ineligible subgroup, PFS (HR 0.32; 95% CI, 0.27-0.39; P<0.01) and OS (HR 0.50; 95% CI, 0.42-0.59; P<0.01) was significantly improved with MRD negativity. In addition, Munshi et al. (2020) report improvements in OS (and PFS) outcomes associated with increasingly stringent MRD sensitivity thresholds with OS most improved with MRD negativity at the sensitivity threshold of 10^{-6} (HR: 0.26; 95% CI: 0.13, 0.51; p<0.001). As noted in Section B.2.6.2.10 (Document B), for the DLd group, the MRD negativity rate was approximately three times higher at the 10^{-5} threshold, and approximately four times higher at the higher sensitivity threshold of 10^{-6} . Patients in the DLd group demonstrated significantly higher 'durable MRD negativity' at the sensitivity threshold of 10^{-5}, defined as having MRD negativity for

		at least one year without a positive result, compared with the Ld group (DLd: [redacted] ts who achieve MRD negativity is tracking outcomes resembling that seen in the UK general population after five years of follow-up (Figure 23, Document B). As such, an OS waning of treatment effect for DLd is be inconsistent with substantial clinical evidence that deeper responses change the trajectory of the disease course, translate into improved long term outcomes. Studies investigating daratumumab in the relapse setting (POLLUX and CASTOR) provide further evidence of a substantial survival benefit driven by deeper responses after more than 6-years of follow-up, with no indication of an OS waning effect. Indeed, the POLLUX study (Figure 2) provides consistent evidence that the statistically significant and clinically meaningful OS benefit for DLd is driven by deeper responses that can be attributed to daratumumab's unique mechanism of action and synergy with lenalidomide. Specifically, daratumumab's combination of direct and immunomodulatory effects harness the body's own immune system to target and eliminate malignant plasma cells.

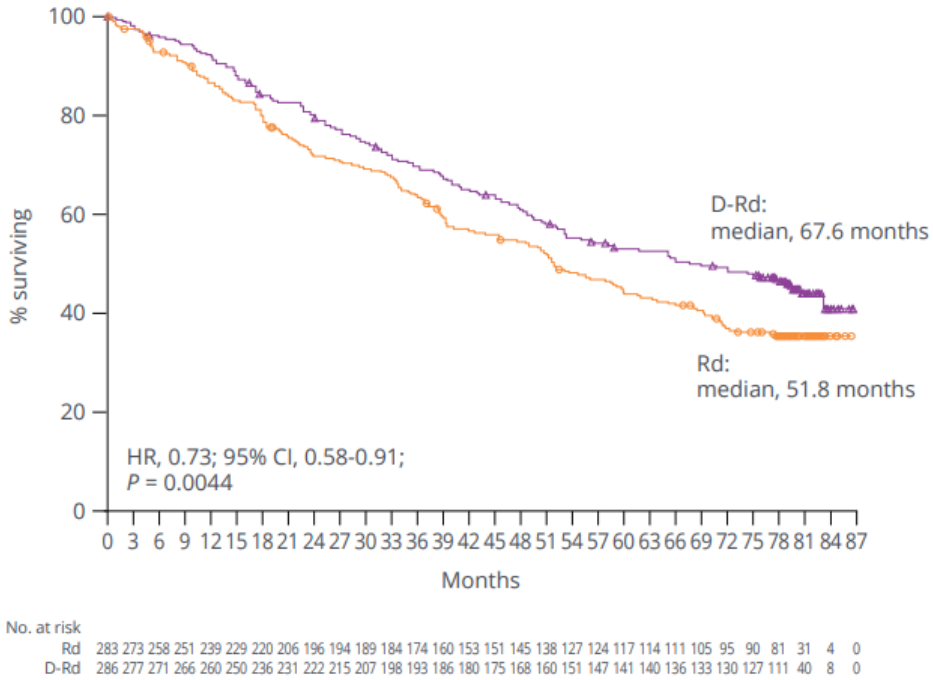
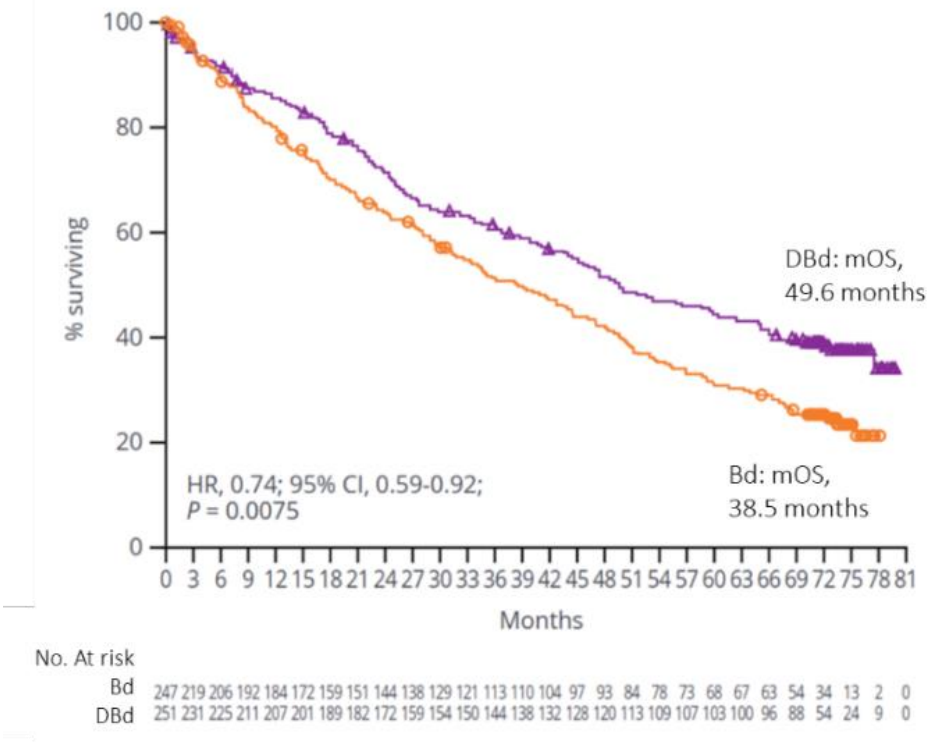
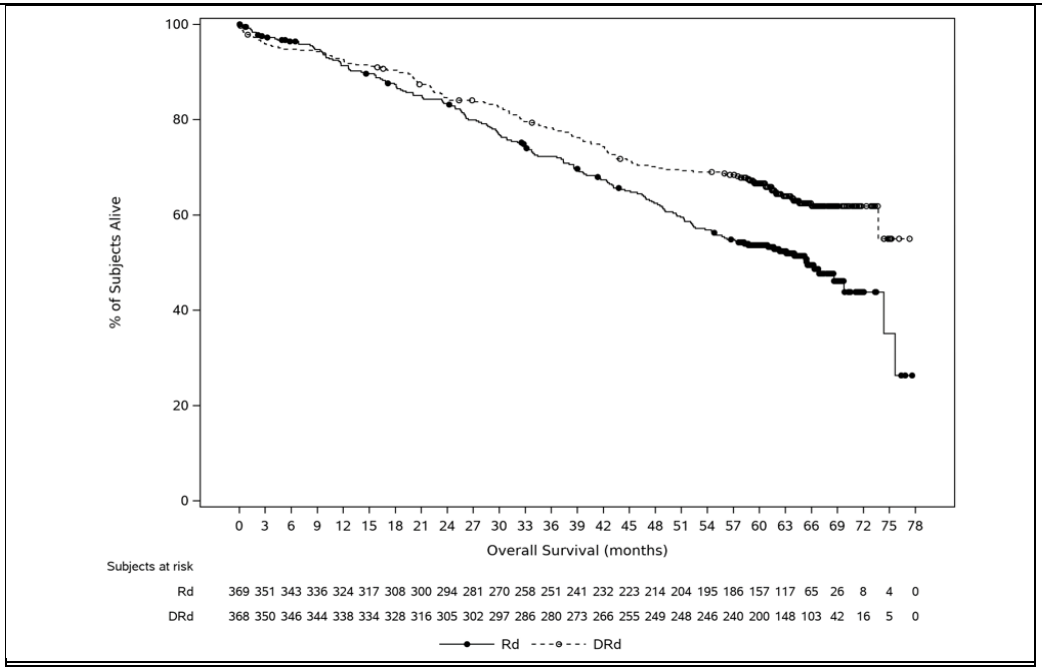
		Figure 2: Kaplan–Meier estimates of OS in the POLLUX trial (ITT population); median follow up 79.7 months (Dimopolous, 2022) **FIGURE 3. OS in the ITT population.**  OS, overall survival; ITT, intent-to-treat; D-Rd, daratumumab plus lenalidomide/dexamethasone; Rd, lenalidomide/dexamethasone; HR, hazard ratio; CI, confidence interval. This is also observed in longer follow up from the CASTOR trial, which demonstrated the efficacy of DBd versus bortezomib with dexamethasone (Bd) in patients with relapsed or refractory multiple myeloma (Figure 3).

Figure 3: Kaplan-Meier plot for overall survival among patients treated with DBd or Bd in the CASTOR trial (ITT population); median follow-up: 72.6 months (Sonneveld P, 2022)



Overall, there is significant evidence to support deeper, and more sustained responses with DLd versus Ld. Furthermore, additional follow up from CASTOR and POLLUX (DBd and DLd in the relapsed setting) does not support any OS waning. The inclusion of an OS waning assumption

		for the DLd arm can therefore be considered a non-evidence based approach, and is in fact inconsistent with the evidence that deeper responses translate into improved long term outcomes. **2) <u>Analyses on the observed MAIA OS data indicates the OS benefit of DLd is improving over time</u>** With over 5 years of follow up available, visual inspection of the observed MAIA KM OS data (Figure 4) shows no evidence of any waning of the DLd OS treatment effect. In contrast to the inclusion of a OS waning assumption, the observed data suggest an improving OS benefit over time; at the end of follow up KM curves are continuing to separate. **<u>Figure 4: Kaplan–Meier estimates of OS in the MAIA trial (ITT population) (data cut-off 21st October 2021) (as per Section B.2.6.25 of Document B)</u>**



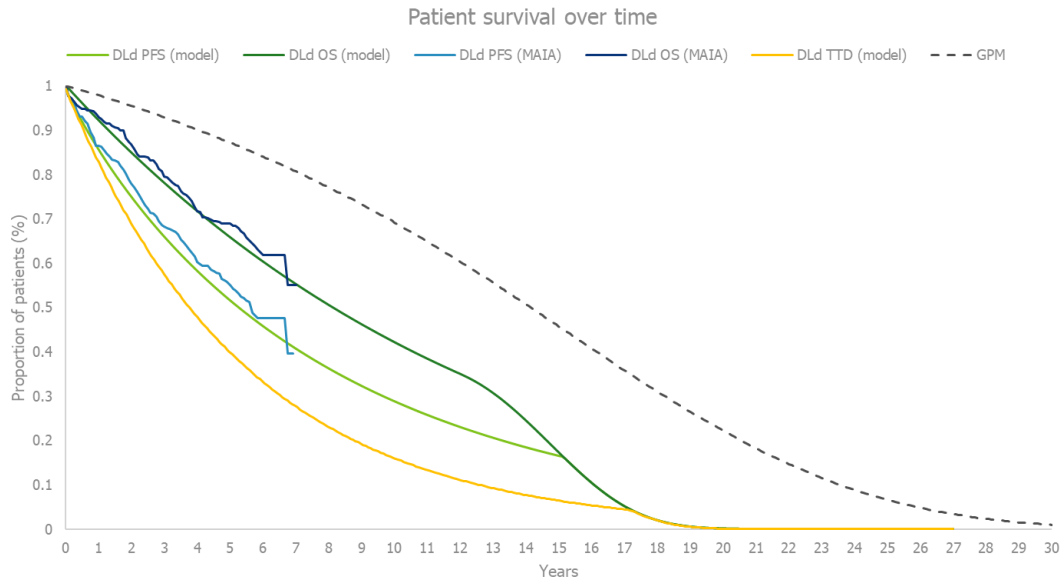
This is supported by an exploratory analysis examining the MAIA OS HR over time, using additional MAIA follow up as it became available. The analysis below considers the estimated OS HR after partitioning the follow up from MAIA into increasing 6 month periods. The analysis shows that, with the inclusion of each additional 6 month follow up from MAIA, the overall OS HR is decreasing, indicating an improving OS benefit for DLd over time (Table 6).

Table 6: Analysis of MAIA OS data: Piecewise Cox of MAIA OS over time

MAIA Follow up duration (months)	*OS HR*	*95% CI*	*P value*
≤6	[redacted]	[redacted]	[redacted]
≤12			
≤18			
≤24			
≤30			
≤36			
≤42			
≤48			
≤54			
≤60			
≤66			
≤72			
≤78			

3) Applying the OS waning assumption solely to the DLd arm lacks face validity

The EAG include an OS waning effect only for the DLd OS curve in their preferred assumptions. From a face validity perspective, given that both DLd and Ld are treat-to-progression treatments, any 'waning' of treatment effect would be expected to be similar across arms with the relative treatment effect maintained. In addition, we note that no waning of OS benefit was included in the Committee's decision making assumptions in the appraisal of Ld (TA587), which was conducted in the same patient population. As such, including an OS waning effect solely for DLd is inconsistent with this approach in previous NICE decision making. Given that the EAG has not applied any waning to the Ld OS benefit, it would be inappropriate to decrease the OS benefit for DLd in isolation.

		Reviewing the overall coherency of solely including an OS waning assumption for DLd, we also note the relatively sharp decrease to the DLd OS curve at the time that waning is included. There is also a significant impact on DLd PFS and TTD outcomes, as a result of increasing the HR to 1 over a relatively short duration of 7 years (Figure 5). Intuitively, a longer TTD would correlative to a longer OS. Relative to the company base case, however, the EAG prefer a longer TTD for DLd (exponential), in addition to a shorter OS curve, by including an OS waning assumption. The overall consistency of this logic does not make sense. **Figure 5: EAG base case (OS waning between 12-19 years): DLd patient survival over time (OS: Gompertz, PFS: Weibull, TTD: exponential)** 

Key Issue 10 Are the MAIA or ALCYONE health-state utilities more appropriate?	No	The EAG consider the MAIA utilities, as used in the company base case, to have better face validity. Similarly, Janssen also consider the MAIA utilities to be most appropriate and to have better face validity. This is because the MAIA utilities reflect the primary treatments of interest for this appraisal (DLd and Ld), and are also aligned with the efficacy data used for the decision problem. In contrast, utilities from the ALCYONE study were derived from BMP and DBMP treatment arms. The inclusion of DBMP reduces the relevance of the utilities from the ALCYONE trial for the current appraisal, as utility estimates derived from DBMP (as a quadruplet treatment) would may not be as representative of treatments used in UK clinical practice.
Key Issue 11 Should costs for dose-reductions using RDIs be included in the model?	No	Janssen consider that RDIs to reflect dose-reductions should be included in the model for decision making. This is aligned with the EAG's perspective, as well as the perspective of the EAG's clinical advisor. In addition, Janssen note that, based on the feedback received from clinical advisors in the EAG report, the current ICER can be considered a conservative upper estimate. This because the EAG's clinical advisors 'felt the proportions dropping dexamethasone and lenalidomide seen in MAIA are likely to be an underestimate compared with clinical practice' (p87 of EAG report). Relative to Ld, if more patients in clinical practice discontinue dexamethasone and lenalidomide, then the total costs for DLd would be expected to decrease, resulting in a decrease to the DLd ICER.
Key Issue 12 What is the most appropriate market share of treatments used at 2nd and 3rd line in England?	Yes	Related to Key Issue 7, Janssen consider it is most appropriate to include modelled treatments at 2nd and 3rd line which reflect MM treatments used in the UK treatment pathway conditional to these treatments being routinely commissioned.

		The EAG agree that the current methodology (using an average across the clinicians elicited distributions) to estimate the % market share for subsequent treatments is as good approach as any. Whilst the EAG state there may be high variation in subsequent treatments used, it is clear from the clinical feedback received (Table 17 of clinical advisory board minutes, Data on File) that almost all patients will receive DBd at 2L following receipt of Ld at frontline. Over half (n=4/7) of the responses indicated that 100% of patients would receive DBd at 2L (average market share of 88%), and thus DBd should be included in the pathway for efficient decision making once routinely commissioned. Given the significance of DBd on the cost effectiveness of DLd, we have therefore provided sensitivity analyses for: 1) Excluding treatments currently on CDF 2) Including DBd (2L), and excluding IxaLd (3L) 3) Including DBd (2L), and including IxaLd (3L) The market shares of 2L and 3L treatments in each of these scenarios are included in the economic model (subsequent treatments tab).

Additional issues

All: Please use the table below to respond to additional issues in the EAR that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage).

Table 3 Additional issues from the EAR

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Pricing of lenalidomide generics	N/A	No	[redacted]

Additional issue 2: EAG's methodology for costing of subsequent treatments	Section 6.1, EAG report (post FAC: P96	No	In the original model submitted by Janssen (May 2022), the costs for subsequent treatments were derived by calculating the weighted costs and weighted time on treatment per line and 1L treatment received separately, and then multiplying these figures together to give the total costs by line of treatment. Time on treatment (ToT) was based on median TTP or PFS reported from clinical trials for each regimen. This can be summarised using the formula: $\sum weights * cost + \sum weights * time$. During the clarification questions process, the EAG requested this formula was updated to calculate the weighted costs and time on treatment line per line simultaneously, using the formula $\sum weights * costs * time$. Janssen agree with the EAGs preferred approach and updated the CEM accordingly in the 22nd July version shared with the EAG. In these calculations, the company first calculates a cost per model cycle for subsequent treatments with a fixed regimen by dividing the total cost for the whole treatment regimen by the median TTP/PFS. This approach spreads the costs of the subsequent treatments with fixed regimens over the TTP/PFS, thus accounting for the fact some subsequent treatment regimens are shorter than the corresponding PFS. The cost per model cycle is then used to inform the costs in the EAGs preferred formula by multiplying the market share, calculated cost per model cycle and ToT for each regimen.

			However, in their own model version (post FAC), the EAG have implemented a different approach which multiplies the market share, acquisition costs per cycle and ToT for each regimen. Janssen disagrees with this approach because it overestimates the cost per cycle for subsequent treatment regimens with a fixed duration that is shorter than the corresponding median PFS/PD, given this approach applies the cost per cycle for each regimen for the full time spent on treatment. As such, Janssen maintain the updated methodology, as per the model submitted on 22nd July.

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)

Key Issue 8	• DLd PFS: exponential • DLd OS: exponential	As per EAG's preferred assumptions: • DLd PFS: Weibull • DLd OS: Gompertz	ICER vs Ld: • Base case before TE: [redacted] • Base case after TE: [redacted] = [redacted]
Key Issue 5	Comparison vs BMP using unanchored indirect comparison	Comparison vs BMP using parametric NMA, excluding CTD (OS: Gompertz, PFS: Gamma)	N/A- no impact on ICER vs Ld
Company's base case following technical engagement (or revised base case) (excluding CDF treatments)	Incremental QALYs vs Ld: [redacted]	Incremental costs vs Ld: [redacted]	Revised base-case ICER (excluding CDF treatments) with PAS = [redacted]

Sensitivity analyses around revised base case

As noted above in Key Issue 7, Janssen have provided the below sensitivity analyses around the revised base case:

Company's base case following technical engagement (or revised base case)	Incremental QALYs vs Ld: [redacted]	Incremental costs vs Ld: [redacted]	ICER vs Ld: Revised base-case ICER with PAS = [redacted]
Scenario including CDF treatments: DBd (2L)	Incremental QALYs vs Ld: [redacted]	Incremental costs vs Ld: [redacted]	ICER vs Ld (with PAS): [redacted]
Scenario including CDF treatments: DBD (2L) and IxaLd (3L)	Incremental QALYs vs Ld: [redacted]	Incremental costs vs Ld: [redacted]	ICER vs Ld (with PAS): [redacted]

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Single Technology Appraisal: Daratumumab with lenalidomide and dexamethasone for untreated multiple myeloma when stem cell transplant is unsuitable [ID4014]

Technical Engagement Appendix: Parametric Network Meta-Analysis

This document is provided as part of the Janssen NICE Technical Engagement response for the STA of daratumumab with lenalidomide and dexamethasone for untreated multiple myeloma when stem cell transplant is unsuitable [ID4014].

It is intended to provide further information provides further detailed information regarding the exploration of the parametric NMA, for Technical Engagement Key Issue 5 (What is the preferred source of evidence for the comparison of BMP vs DLd, the HR NMA, the Parametric NMA, the Piecewise NMA, or the unanchored indirect treatment comparison?).

There were two versions of the parametric NMA explored as part of the Technical Engagement response:

1) Parametric NMA including CTD (Appendix A)
2) Parametric NMA excluding CTD (Appendix B)

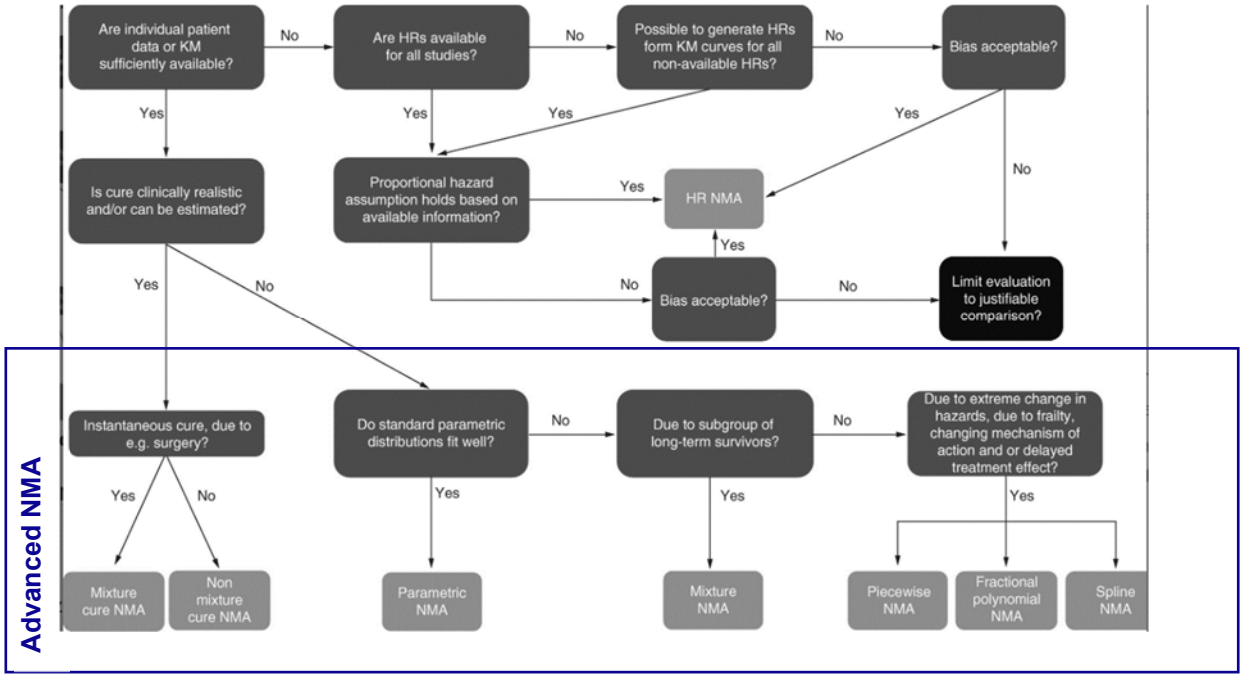
The comparison using both of these parametric NMAs is available in the economic model which is included as part of the Technical Engagement response ('Settings', 'I43, I44').

Choice of Advanced NMA method

There is an indication of proportional hazards violation in the evidence network for both OS and PFS. Therefore, the standard HR NMA should be interpretated with caution with respect to the comparative efficacy of daratumumab versus its treatment comparators.

The flow diagram in Figure 1 from Heeg et al. (2022) for time-to-event NMAs was used to guide the selection of the most appropriate NMA method, based on the observed data and clinical plausibility. Based on the framework below, advanced NMA methods such as (non-)mixture cure NMA, parametric NMA, mixture NMA, piecewise NMA, fractional polynomial NMA, and spline NMA should be considered when the PHA does not hold.

Figure 1 Considerations of advanced time-to-event NMA methods



[1] Heeg, B., Garcia, A., Beekhuizen, S. V., Verhoek, A., Oostrum, I. V., Roychoudhury, S., Cappelleri, J. C., Postma, M. J., & Nicolaas Martinus Ouwens, M. J. (2022). Novel and existing flexible survival methods for network meta-analyses. Journal of comparative effectiveness research, 10.2217/cer-2022-0044. Advance online publication. https://doi.org/10.2217/cer-2022-0044

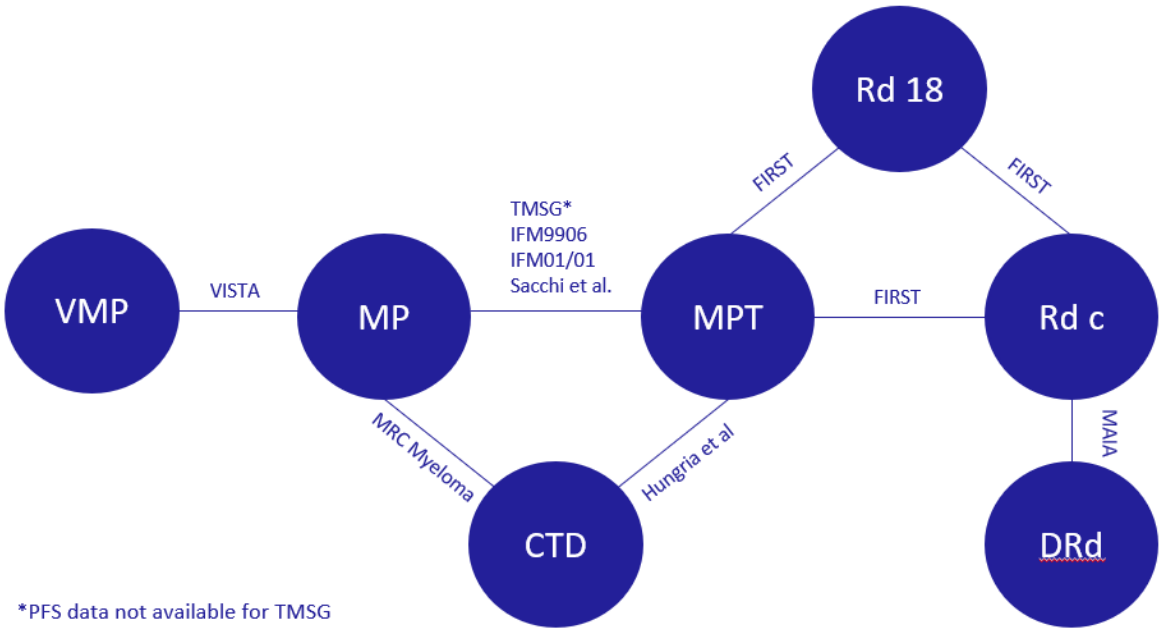
The PNMA allows for time-varying HRs in the network. As the PNMA fitted the data well there is no need to consider other advanced NMA methods. Given that the standard parametric NMA fits the data well overall, other advanced NMA methods might introduce further complexity in the analysis and require unnecessarily strong assumptions for the indirect comparison.

Appendix A: Parametric Network Meta-Analysis (including CTD)

Methods

For the parametric NMA, only trials that included treatments relevant to the decision problem were considered. Therefore, the following trials were included in the parametric NMA: VISTA trial[3, 4], MRC Myeloma[5], TMSG trial[6], IFM99-06[7], IFM01/01[8], Sacchi et al[9]., Hungria et al.[10], FIRST trial[11], and MAIA trial[12]. The network of evidence is presented in Figure 2. Pseudo-individual patient-level data (IPD) for each intervention were obtained by reconstructing time-to-event data digitized from published Kaplan Meier (KM) curves using Engauge Digitizer software[13] and the algorithm published by Guyot et al[14]. The corresponding reconstructed KM data for OS, and PFS accompanied by results of the proportional hazards tests are presented in the Appendix A1. Trial data were available for the MAIA trial.

Figure 2 Network of treatments (including CTD)



CTD=cyclophosphamide-thalidome-dexamethasone; DRd=daratumumab-lenalidomide-dexamethasone; MP= melphalan-prednisone; MPT= melphalan-prednisone-thalidomide; Rd 18= lenalidomide-dexamethasone 18 cycles; Rd c= lenalidomide-dexamethasone continued; VMP= bortezomib-melphalan-prednisone

Statistical Methodology

The planned analyses include the parametric NMA for time-to-event endpoints OS and PFS will be conducted. The five commonly known parametric distributions were used; Weibull, Gompertz, Exponential, Lognormal and Loglogistic.
For all models, the corresponding equations are presented in Table 1. A fixed-effects model was preferred to a random-effects model due to a limited network of evidence with only two trials with the same comparison.

Table 1 Model equations

Distribution	Equation
Parametric NMA	$S_{i,j}(t) = S_{i,j}^{ds}(t)$
Exponential	$\mathrm{S}_{\mathrm{i,j}}^{\mathrm{ds}}(\mathrm{t}) = \exp\left(-\exp\left(\alpha 0_i + \alpha 1_j\right)t\right)$
Weibull	$\mathrm{S}_{\mathrm{i,j}}^{\mathrm{ds}}(\mathrm{t}) = \exp\left(-\left(\frac{\mathrm{t}}{\exp\left(\alpha 0_{\mathrm{i}} + \alpha 1_{\mathrm{j}}\right)}\right)^{\left(\exp\left(\beta 0_{\mathrm{i}} + \beta 1_{\mathrm{j}}\right)\right)}\right)$
Gompertz	$\mathrm{S}_{\mathrm{i,j}}^{\mathrm{ds}}(\mathrm{t}) = \exp\left(-\frac{\exp\left(\alpha 0_{\mathrm{i}} + \alpha 1_{\mathrm{j}}\right)}{\exp\left(\beta 0_{\mathrm{i}} + \beta 1_{\mathrm{j}}\right)}\left(\exp\left(\exp\left(\beta 0_{\mathrm{i}} + \beta 1_{\mathrm{j}}\right)t\right) - 1\right)\right)$
Lognormal	$\mathrm{S}_{\mathrm{i,j}}^{\mathrm{ds}}(\mathrm{t}) = 1 - \Phi\left(\frac{\log(t) - \left(\alpha 0_{\mathrm{i}} + \alpha 1_{\mathrm{j}}\right)}{\exp\left(\beta 0_{\mathrm{i}} + \beta 1_{\mathrm{j}}\right)}\right)$
Loglogistic	$\mathrm{S}_{\mathrm{i,j}}^{\mathrm{ds}}(\mathrm{t}) = \frac{1}{1 + \left(\frac{t}{\exp\left(\alpha 0_{\mathrm{i}} + \alpha 1_{\mathrm{j}}\right)}\right)^{\exp\left(\beta 0_{\mathrm{i}} + \beta 1_{\mathrm{j}}\right)}}$
Where,	

S = survival all-cause mortality
i = trial coefficient
j = treatment coefficient
t = time
Sds = disease-specific survival
-Reference therapy in the network is docetaxel
exp(α0i + α1j)= scale for study i and treatment j, where α0i is the log scale of the reference therapy for study i, and α1j codes for the treatment effect of treatment j vs. reference therapy, α1 = 0 for the reference therapy
exp(β0i + β1j)= shape for study i and treatment j, where β0i is the log shape of the reference therapy for study i, and β1j codes for the treatment effect of treatment j vs. reference therapy, β1 = 0 for the reference therapy

Parametric Network Meta-Analysis

The parametric NMA model assumes that the long-term survival of each treatment population in an evidence network follows one of the commonly used parametric distributions. The parametric distribution functions were applied in the NMA setting as described by the equations in Table 1, for which the parameters are written as the sum of study effect and treatment effect, thereby not breaking randomization.

General Statistical Approach

Both OS and PFS parametric NMAs were performed using the RStan package in R Statistical Software (version 1.2-0)[15]. These analyses were fitted with weakly informative priors [15]. For all modelled parameters, we applied normal priors with a mean of 0 and a standard deviation (SD) of 5.

The models were run with two chains of 2,000 iterations, and 1,000 were burn-in iterations to generate the posteriors for the defined parameters. Convergence of the two chains was tested using the Rhat test[16].
The parametric NMA models were compared based on leave-one-out information criterion (LOOIC), mean and incremental mean survival. The LOOIC is an indication of statistical fit in which a lower LOOIC indicates a better fit. The base case model was selected based on the lowest LOOIC. General population mortality was not considered in the analyses as the outcomes of survival were already corrected for general population mortality in the health economic model. All analyses presented used the MAIA trial as the reference study.

Results

Overall survival

The proportional hazard assumption in OS was violated for MRC Myeloma trial and indicated a potential violation based on visual inspection for MAIA and IFM01/01. The proportional hazard assumption was not violated for the other trials (see Appendix A1). Table 2 presents the LOOIC per model and shows that the Gompertz has the best statistical fit with a LOOIC of 27025.6. The estimated mean OS per treatment per model is demonstrated in Table 3, and the incremental OS with DLd as reference treatment is presented in Table 4.

The OS predictions per model are depicted in Figure 3 (short term and long term). Note that, due to the impact of general population mortality capping in the economic used for this appraisal, there are difference between the statistical output and the modelled survival outcomes. All models fit the KM data of MAIA relatively well, except for the Lognormal model, as the extrapolated survival curves do not fit the MAIA data well. The study- and treatment-specific parameters are presented in the Appendix A1 for the base case model (Gompertz for OS).

Table 2 LOOIC, OS

Distribution	LOOIC
Exponential	27079.1
Weibull	27030.2
Gompertz	27024.6
Loglogistic	27147.6
Lognormal	27316.6

Table 3 Mean OS, years (95% credible interval)

	Exponential	Weibull	Gompertz	Loglogistic	Lognormal
DLd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ld	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ld18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MPT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CTD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BMP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CTD=cyclophosphamide-thalidome-dexamethasone; DLd=daratumumab-lenalidomide-dexamethasone; MP= melphalan-prednisone; MPT= melphalan-prednisone-thalidomide; Ld 18= lenalidomide-dexamethasone 18 cycles; Ld= lenalidomide-dexamethasone continued; BMP= bortezomib-melphalan-prednisone

Table 4 Incremental mean OS, years (95% credible interval)

	Exponential	Weibull	Gompertz	Loglogistic	Lognormal
DLd	-	-	-	-	-
Ld	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ld18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MPT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CTD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BMP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CTD=cyclophosphamide-thalidome-dexamethasone; DLd=daratumumab-lenalidomide-dexamethasone; MP= melphalan-prednisone; MPT= melphalan-prednisone-thalidomide; Ld 18= lenalidomide-dexamethasone 18 cycles; Ld= lenalidomide-dexamethasone continued; BMP= bortezomib-melphalan-prednisone

*Figure 3 OS predictions by model**

CTD=cyclophosphamide-thalidome-dexamethasone; DLd=daratumumab-lenalidomide-dexamethasone; MP= melphalan-prednisone; MPT= melphalan-prednisone-thalidomide; Ld 18= lenalidomide-dexamethasone 18 cycles; Ld= lenalidomide-dexamethasone continued; BMP= bortezomib-melphalan-prednisone

* Note that, due to the impact of general population mortality capping in the economic used for this appraisal, there are difference between the statistical output and the long term modelled survival outcomes.

Progression-free survival

The proportional hazard assumption in PFS was violated for the FIRST trial. The proportional hazard assumption was not violated for the other trials (see Appendix). Table 5Table 2 presents the LOOIC per model and shows that the Weibull has the best statistical fit with a LOOIC of 27656.5. The lognormal parametric NMA did not converge, and results are therefore not presented. The estimated mean PFS per treatment per model is demonstrated in Table 6, and the incremental PFS with DLd as reference treatment is presented in Table 7. The PFS predictions per model are depicted in Figure 3 (short term and long term). All models fit the PFS KM data of MAIA relatively well, except for the Lognormal model. As this model did not converge, the results are not reliable.

Table 5 LOOIC, PFS

Distribution	LOOIC
Exponential	27763.2
Weibull	27656.5
Gompertz	27711.6
Loglogistic	27717.2
Lognormal	No convergence

Table 6 Mean PFS, years (95% credible interval)

	Exponential	Weibull	Gompertz	Loglogistic	Lognormal
DLd	[redacted]	[redacted]	[redacted]	[redacted]	Model not converged
Ld	[redacted]	[redacted]	[redacted]	[redacted]	
Ld18	[redacted]	[redacted]	[redacted]	[redacted]	
MPT	[redacted]	[redacted]	[redacted]	[redacted]	
CTD	[redacted]	[redacted]	[redacted]	[redacted]	
MP	[redacted]	[redacted]	[redacted]	[redacted]	
BMP	[redacted]	[redacted]	[redacted]	[redacted]	

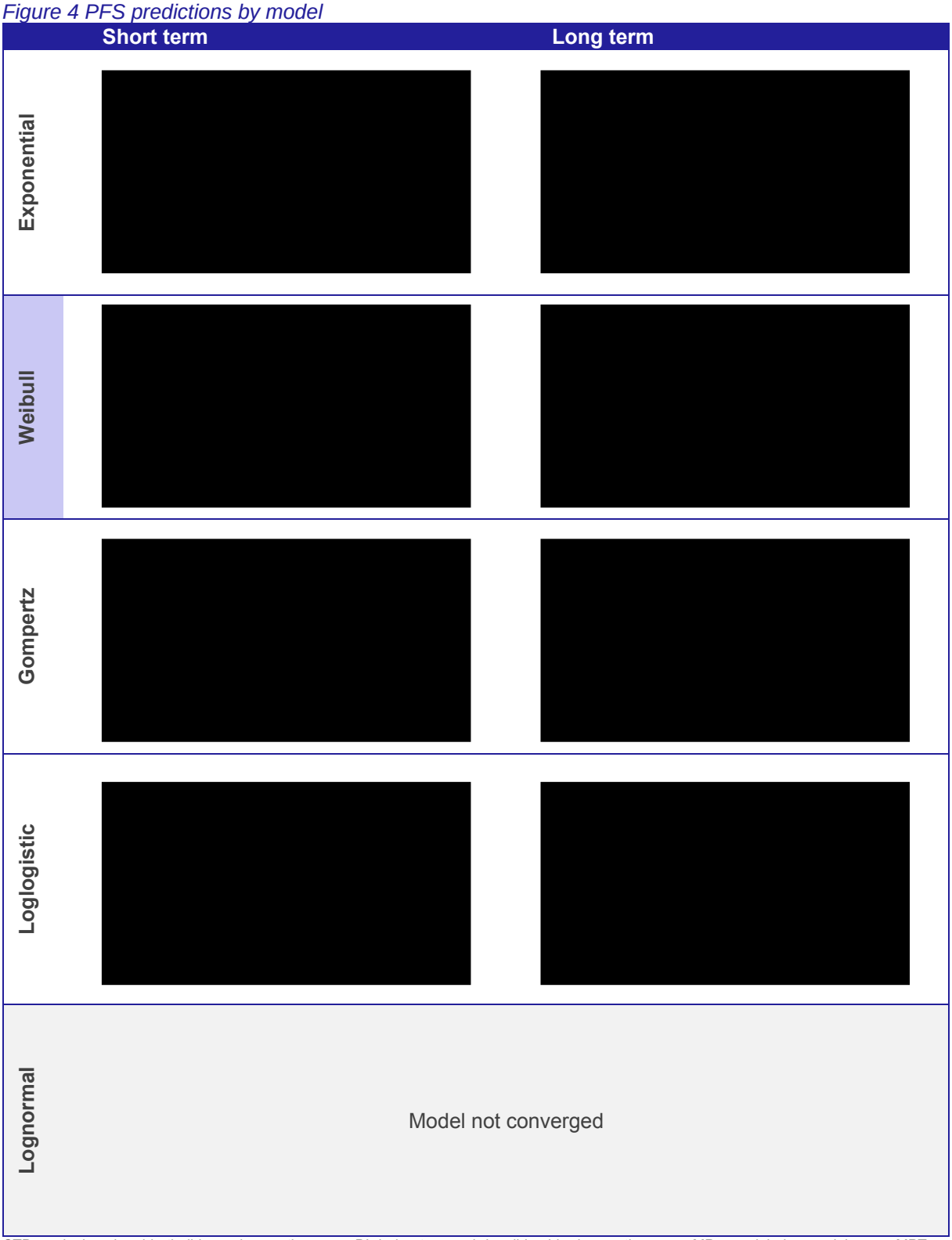
CTD=cyclophosphamide-thalidome-dexamethasone; DLd=daratumumab-lenalidomide-dexamethasone; MP= melphalan-prednisone; MPT= melphalan-prednisone-thalidomide; Ld 18= lenalidomide-dexamethasone 18 cycles; Ld= lenalidomide-dexamethasone continued; BMP= bortezomib-melphalan-prednisone

Table 7 Incremental mean PFS, years (95% credible interval)

	Exponential	Weibull	Gompertz	Loglogistic	Lognormal
DLd	[redacted]	[redacted]	[redacted]	[redacted]	Model not converged
Ld	[redacted]	[redacted]	[redacted]	[redacted]	
Ld18	[redacted]	[redacted]	[redacted]	[redacted]	
MPT	[redacted]	[redacted]	[redacted]	[redacted]	
CTD	[redacted]	[redacted]	[redacted]	[redacted]	
MP	[redacted]	[redacted]	[redacted]	[redacted]	
BMP	[redacted]	[redacted]	[redacted]	[redacted]	

CTD=cyclophosphamide-thalidome-dexamethasone; DLd=daratumumab-lenalidomide-dexamethasone; MP= melphalan-prednisone; MPT= melphalan-prednisone-thalidomide; Ld 18= lenalidomide-dexamethasone 18 cycles; Ld= lenalidomide-dexamethasone continued; BMP= bortezomib-melphalan-prednisone

Figure 4 PFS predictions by model



CTD=cyclophosphamide-thalidome-dexamethasone; DLd=daratumumab-lenalidomide-dexamethasone; MP= melphalan-prednisone; MPT= melphalan-prednisone-thalidomide; Ld 18= lenalidomide-dexamethasone 18 cycles; Ld= lenalidomide-dexamethasone continued; BMP= bortezomib-melphalan-prednisone

Discussion

For OS, the Gompertz model demonstrated the best statistical fit based on the lowest LOOIC, followed by the Weibull and exponential model. Of all treatments included in the NMA, DLd showed the longest OS irrespective of model choice. The Weibull model demonstrated the best statistical fit for PFS based on the lowest LOOIC. It should be noted the lognormal model did not converge for PFS. The results for the lognormal model should therefore also be disregarded. Also for PFS, DLd demonstrated the longest mean PFS. Although it is challenging to compare, these results are fairly in line with the traditional HR NMA.

This report presents the results of the parametric NMA. Other advanced NMA methods could be considered that allow for a violation of the proportional hazard assumption, e.g., piecewise HR or piecewise parametric NMA. However, the disadvantage of these piecewise methods is that they require splitting the data into two timeslots. The timepoint where the data is split may be arbitrary and should be consistent for all trials, even if the optimal timepoint to split the data varies across the trials in the network. Given that the standard parametric NMA fits the data well overall, other advanced NMA methods might introduce further complexity in the analysis and require unnecessarily strong assumptions for the indirect comparison.

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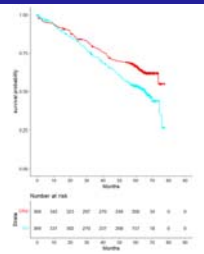
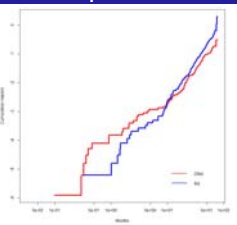
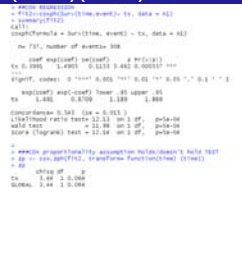
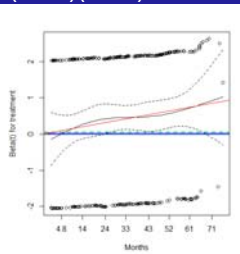
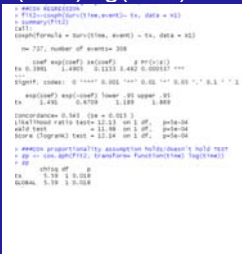
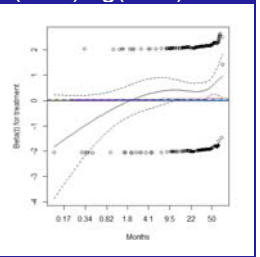
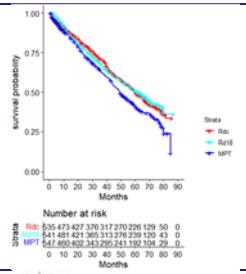
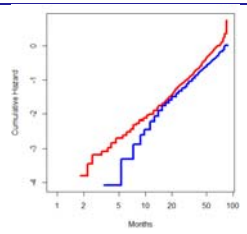
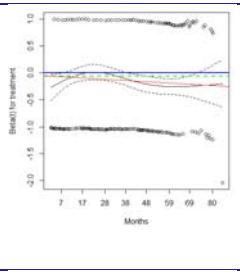
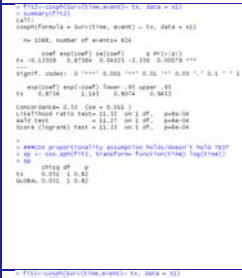
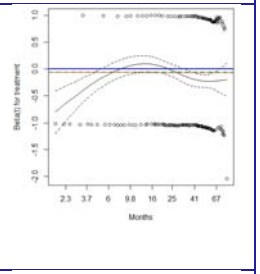
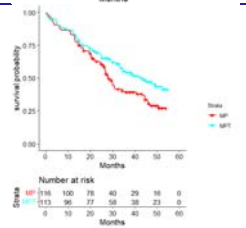
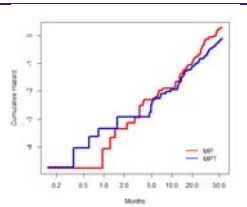
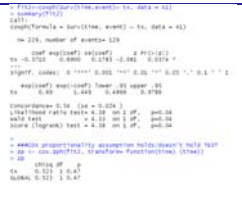
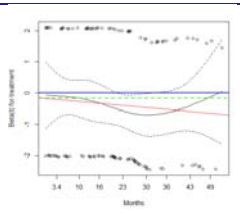
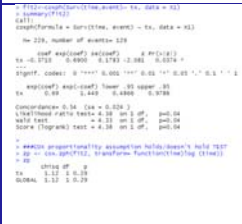
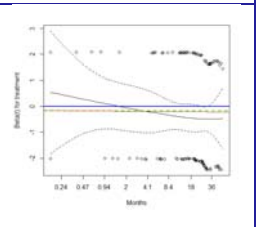
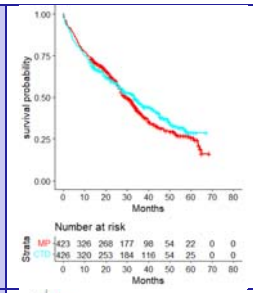
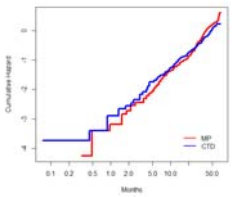
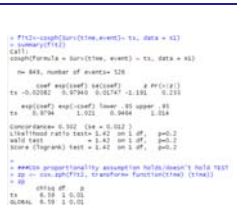
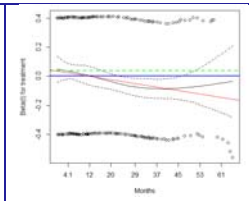
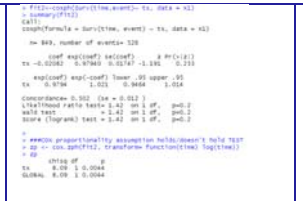
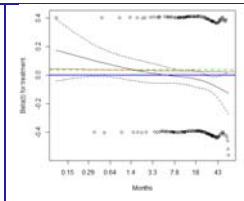
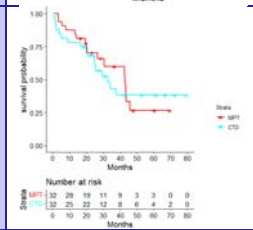
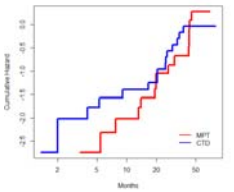
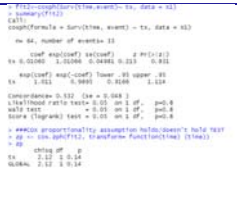
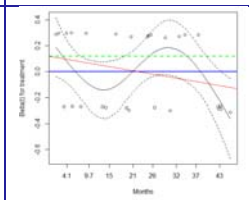
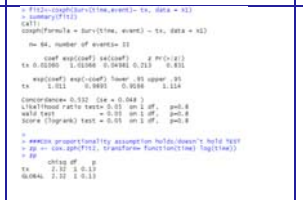
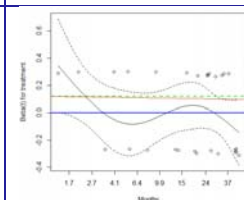
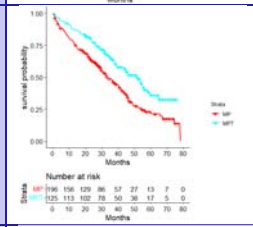
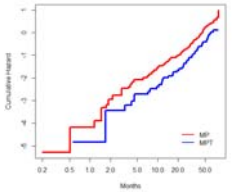
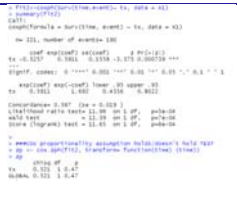
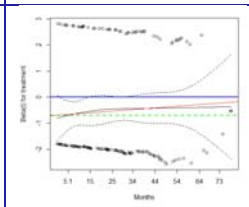
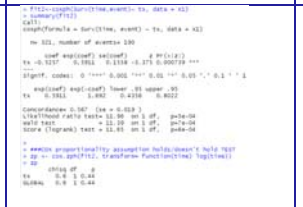
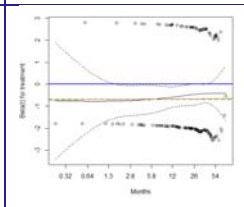
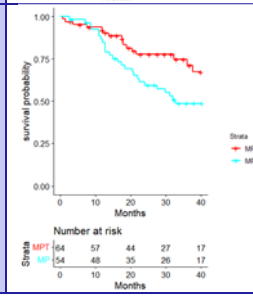
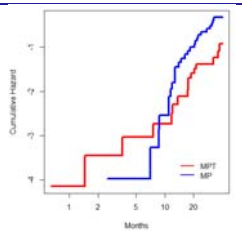
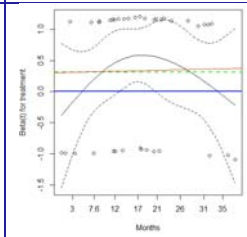
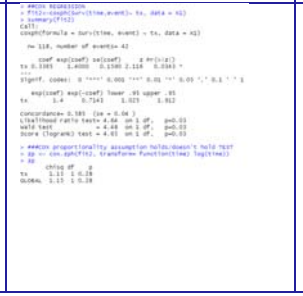
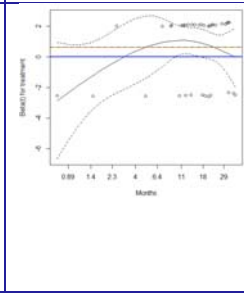
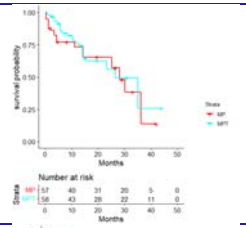
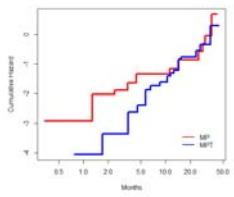
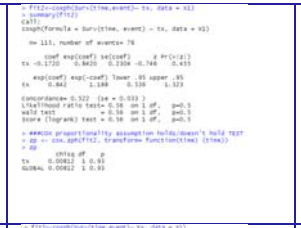
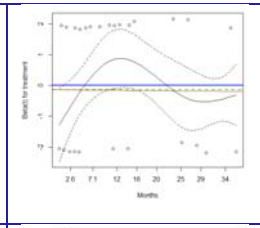
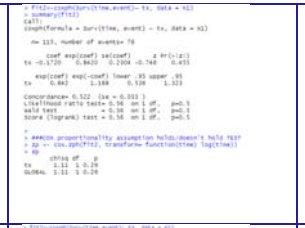
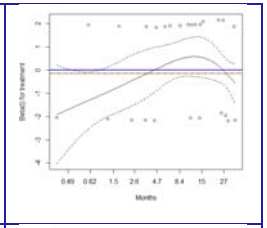
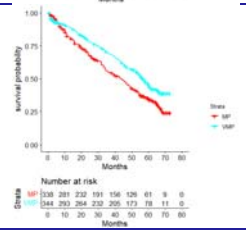
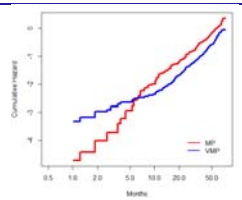
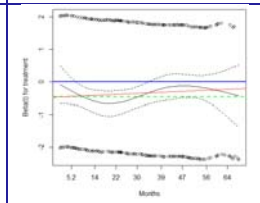
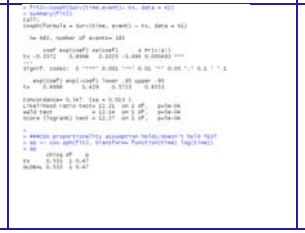
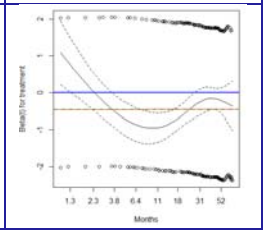
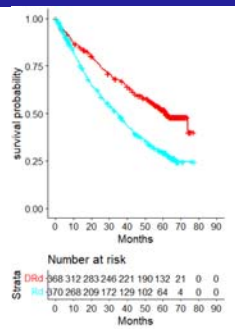
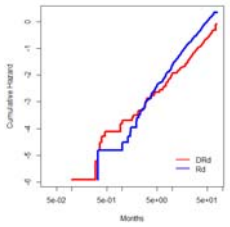
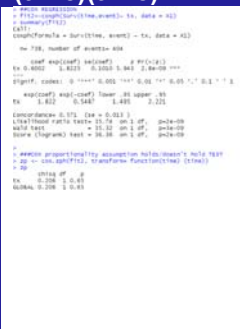
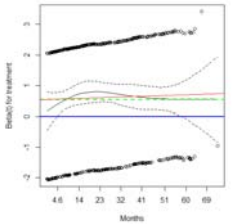
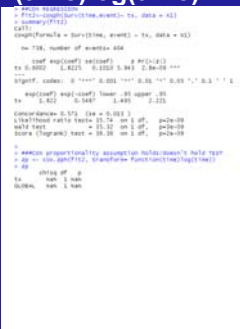
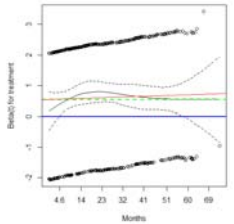
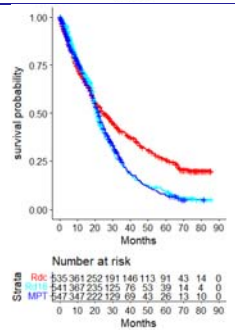
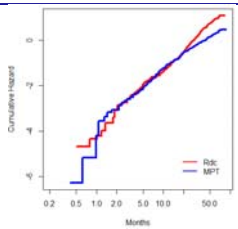
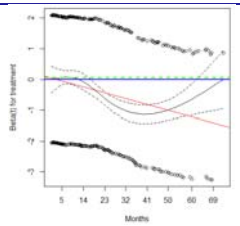
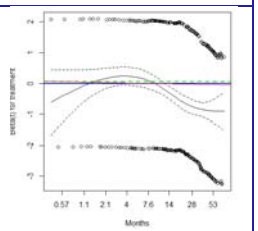
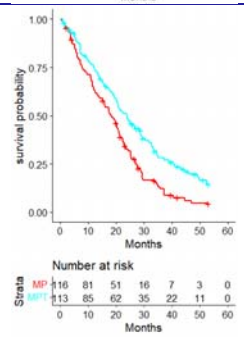
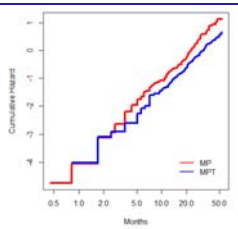
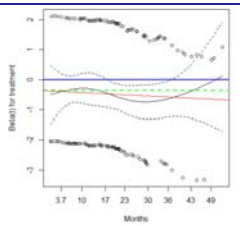
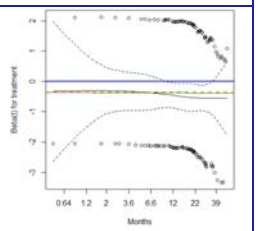
Appendix A1 (parametric NMA including CTD)
Proportional hazard testing, OS

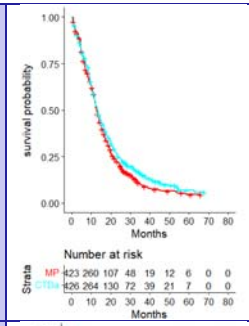
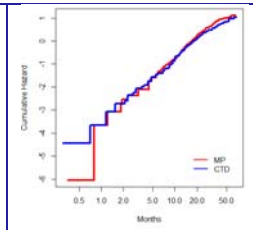
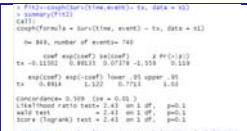
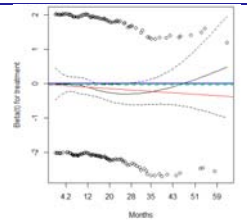
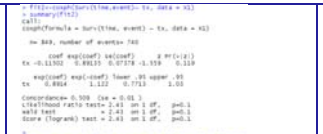
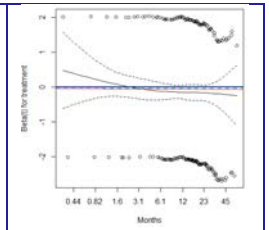
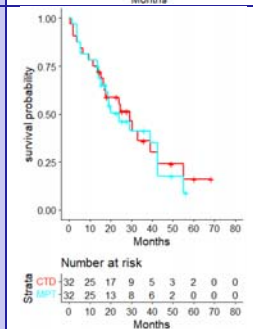
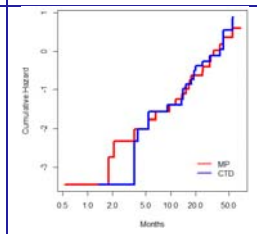
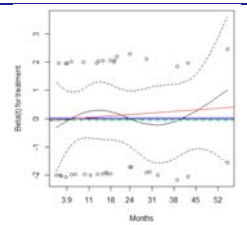
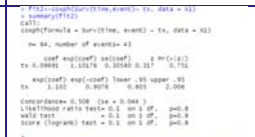
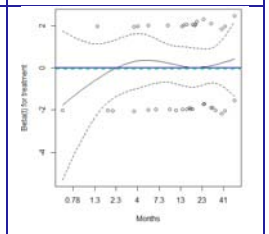
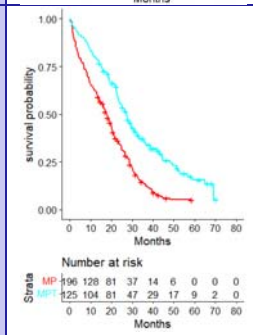
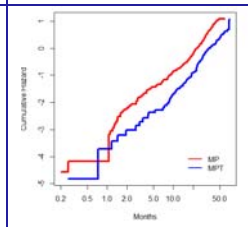
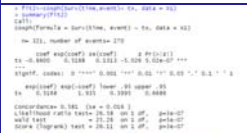
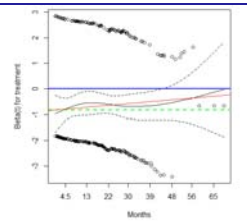
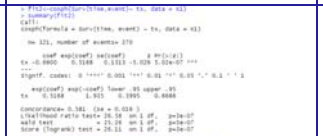
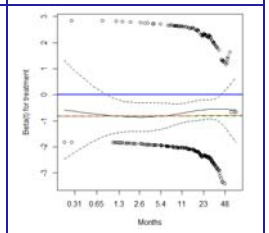
OS	KM	Log cumulative hazard plots	Schoenfeld test (time)(time)	Schoenfeld plot (time)(time)	Schoenfeld test (time)log(time)	Schoenfeld plot (time)log(time)
MAIA						
FIRST (Rdc vs MPT)						
IFM0101						

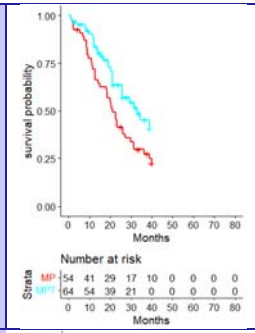
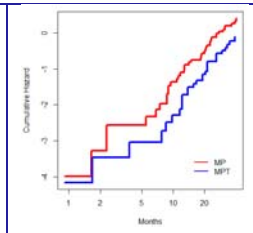
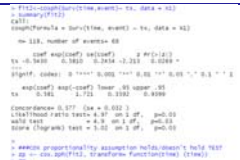
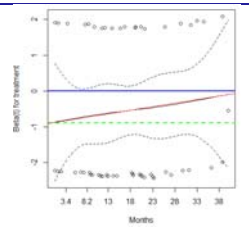
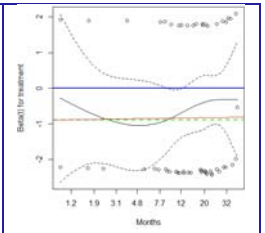
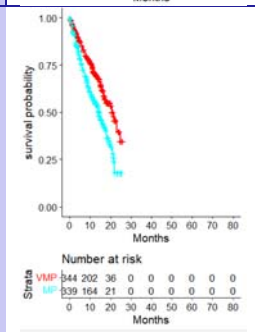
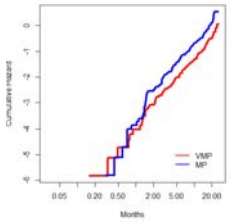
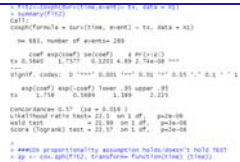
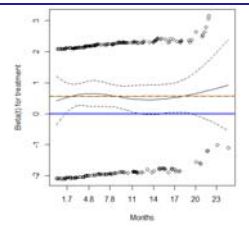
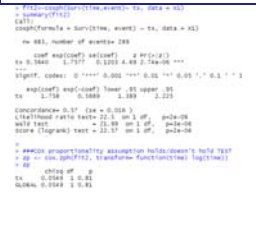
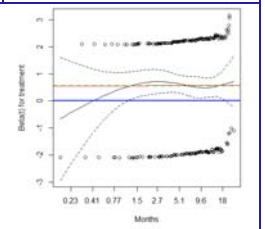
MRC Myeloma						
Hungria						
IFM 9906						
Sacchi						

TMSG						
VISTA						

Proportional hazard testing, PFS

PFS	KM	Log cumulative hazard plots	Schoenfeld test (time)(time)	Schoenfeld plot (time)(time)	Schoenfeld test (time)log(time)	Schoenfeld plot (time)log(time)
MAIA						
FIRST (MPT vs Rd c)						
IFM0101						

MRC Myeloma						
Hungria						
IFM 9906						

Sacchi						
VISTA						

Model parameters OS base case (Gompertz)

Study label (S)		Treatment label (TT)	
1	MAIA	1	DRd
2	FIRST	2	Rdc
3	Hungria	3	Rd18
4	MRC Myeloma	4	MPT
5	TMSG	5	CTD
6	IFM9906	6	MP
7	IFM0101	7	VMP
8	Sacchi		
9	VISTA		

	mean	se_mean	sd	2.50%	50%	97.50%	n_eff	Rhat
beta_S[1]	-4.9528	0.00509	0.163969	-5.2968	-4.94503	-4.63608	1037.841	1.00188
beta_S[2]	-4.72646	0.008712	0.25054	-5.24025	-4.7224	-4.23551	826.9755	1.004399
beta_S[3]	-4.49883	0.012314	0.412867	-5.34936	-4.48572	-3.71997	1124.089	1.002689
beta_S[4]	-4.34358	0.010965	0.32523	-5.00135	-4.33532	-3.72247	879.7539	1.001246
beta_S[5]	-4.35361	0.010997	0.362991	-5.06886	-4.34439	-3.64795	1089.623	1.001386
beta_S[6]	-4.71504	0.010601	0.31675	-5.35803	-4.70271	-4.11003	892.8019	1.000879
beta_S[7]	-4.45517	0.009681	0.318484	-5.08475	-4.45238	-3.84157	1082.284	1.001056
beta_S[8]	-4.85276	0.011908	0.399118	-5.63162	-4.85681	-4.09292	1123.412	0.999353
beta_S[9]	-4.86892	0.011036	0.337196	-5.53857	-4.85729	-4.2284	933.614	1.000514
beta_TT[1]	0	NA	0	0	0	0	NA	NA
beta_TT[2]	-0.04766	0.007817	0.226166	-0.48854	-0.05343	0.407504	836.9895	1.002306
beta_TT[3]	0.092246	0.009278	0.269118	-0.45048	0.093317	0.640594	841.3735	1.003275
beta_TT[4]	0.186438	0.009233	0.270246	-0.34437	0.181373	0.727628	856.7038	1.002362
beta_TT[5]	0.768314	0.011121	0.338105	0.143955	0.760683	1.450453	924.3423	1.001476
beta_TT[6]	0.551239	0.010605	0.312674	-0.04549	0.55144	1.181039	869.3152	1.001377

beta_TT[7]	0.061917	0.011556	0.372059	-0.65217	0.056032	0.766734	1036.652	1.00025
alpha_S[1]	-6.37E-05	0.00013	0.004627	-0.00938	-0.00023	0.00909	1257.899	1.002885
alpha_S[2]	-0.00389	0.000229	0.006681	-0.01657	-0.00401	0.00963	850.7321	1.006448
alpha_S[3]	-0.00797	0.000378	0.014184	-0.03535	-0.00782	0.020348	1408.735	1.003915
alpha_S[4]	-0.01268	0.000317	0.01007	-0.03239	-0.01304	0.007396	1011.898	1.001806
alpha_S[5]	0.011887	0.000342	0.012573	-0.01327	0.012046	0.035722	1351.074	1.001724
alpha_S[6]	-0.00196	0.000293	0.009002	-0.01891	-0.00196	0.016296	941.3366	1.000717
alpha_S[7]	-0.00813	0.000281	0.009705	-0.02728	-0.00809	0.0108	1191.054	1.001796
alpha_S[8]	-0.00538	0.000412	0.016046	-0.03689	-0.00577	0.025437	1517.717	0.999218
alpha_S[9]	-0.00648	0.00032	0.010085	-0.0259	-0.00645	0.012953	994.1006	1.001069
alpha_TT[1]	0	NA	0	0	0	0	NA	NA
alpha_TT[2]	0.01341	0.000205	0.006118	0.001197	0.013624	0.02509	888.4281	1.003363
alpha_TT[3]	0.008394	0.000238	0.007143	-0.00593	0.008458	0.022334	899.7199	1.00543
alpha_TT[4]	0.01362	0.000241	0.007161	-0.00087	0.013778	0.027057	882.6308	1.004188
alpha_TT[5]	-0.00176	0.000334	0.010889	-0.02306	-0.0017	0.01975	1063.779	1.002113
alpha_TT[6]	0.015915	0.000306	0.009304	-0.00198	0.016024	0.034008	925.9695	1.002476
alpha_TT[7]	0.020391	0.000341	0.011065	-0.00065	0.020245	0.041891	1054.326	1.000726

Model parameters PFS base case (Weibull)

Study label (S)		Treatment label (TT)	
1	MAIA	1	DRd
2	FIRST	2	Rdc
3	Hungria	3	Rd18
4	MRC Myeloma	4	MPT
5	IFM9906	5	CTD
6	IFM0101	6	MP
7	Sacchi	7	VMP
8	VISTA		

	mean	se_mean	sd	2.50%	50%	97.50%	n_eff	Rhat
beta_S[1]	4.553753	0.003813	0.093581	4.387041	4.547412	4.751449	602.3774	1.001996
beta_S[2]	4.385231	0.006038	0.127208	4.14253	4.382104	4.639174	443.8523	1.001029
beta_S[3]	4.724964	0.008503	0.205736	4.35559	4.716422	5.150932	585.4189	1.001464
beta_S[4]	4.340868	0.007285	0.155382	4.048576	4.340743	4.652717	454.9695	1.000818
beta_S[5]	4.557845	0.007077	0.149842	4.278846	4.555012	4.856282	448.3502	1.001132
beta_S[6]	4.512878	0.006892	0.147987	4.237086	4.508777	4.808805	461.0426	1.000487
beta_S[7]	4.816305	0.007268	0.168117	4.502639	4.816371	5.160563	535.0393	0.999735
beta_S[8]	4.358767	0.007526	0.165736	4.037699	4.358073	4.6921	485	1.000227
beta_TT[1]	0	NA	0	0	0	0	NA	NA
beta_TT[2]	-0.65556	0.005121	0.115182	-0.89012	-0.65139	-0.44031	505.9233	1.000876
beta_TT[3]	-1.01755	0.006023	0.131692	-1.28612	-1.01481	-0.76322	478.0468	1.000777
beta_TT[4]	-1.03277	0.006319	0.133606	-1.2992	-1.02908	-0.77318	447.0693	1.000695
beta_TT[5]	-1.32125	0.007347	0.16177	-1.64435	-1.31911	-1.01735	484.7708	1.000783
beta_TT[6]	-1.45541	0.007254	0.150056	-1.74433	-1.45415	-1.17971	427.903	1.001076
beta_TT[7]	-0.97615	0.007794	0.191607	-1.34222	-0.97824	-0.58743	604.4019	1.00072

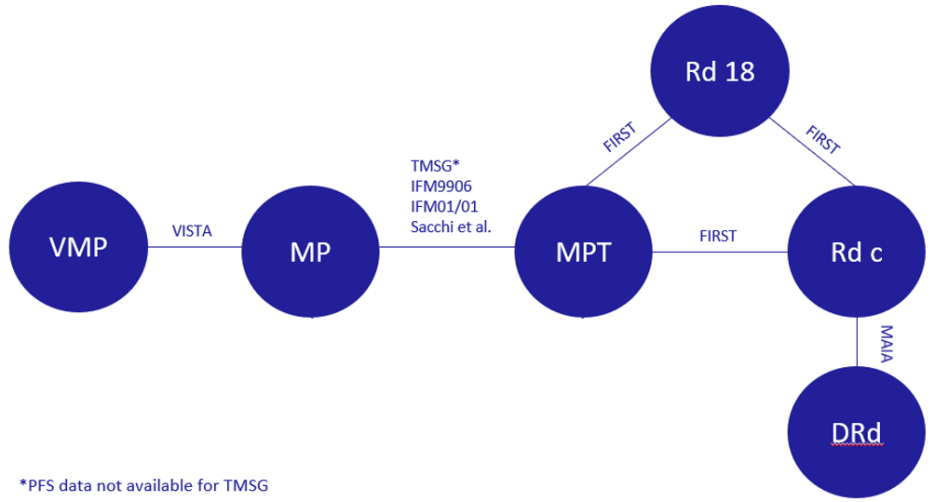
alpha_S[1]	-0.09258	0.002631	0.072036	-0.23815	-0.09078	0.045851	749.5204	0.999421
alpha_S[2]	-0.18634	0.004449	0.102151	-0.39256	-0.1853	0.01561	527.1929	0.99933
alpha_S[3]	-0.24352	0.006633	0.182276	-0.62003	-0.23825	0.109562	755.1574	0.999176
alpha_S[4]	-0.16605	0.006044	0.137767	-0.4331	-0.167	0.111977	519.6261	0.999404
alpha_S[5]	-0.20144	0.005587	0.131961	-0.45998	-0.20231	0.065836	557.8687	0.999354
alpha_S[6]	-0.09814	0.005754	0.132432	-0.36904	-0.10024	0.160248	529.7933	0.999465
alpha_S[7]	-0.06572	0.006149	0.156379	-0.36469	-0.0672	0.2493	646.7951	0.99942
alpha_S[8]	-0.15856	0.006315	0.148268	-0.44925	-0.16011	0.138526	551.2849	0.999725
alpha_TT[1]	0	NA	0	0	0	0	NA	NA
alpha_TT[2]	0.109897	0.003774	0.091775	-0.06967	0.111439	0.293672	591.5041	0.99909
alpha_TT[3]	0.441362	0.00451	0.108906	0.237748	0.439151	0.657478	583.166	0.999237
alpha_TT[4]	0.380257	0.004839	0.109552	0.163252	0.380379	0.595545	512.5	0.999608
alpha_TT[5]	0.248097	0.006086	0.143501	-0.03863	0.245602	0.522602	556.0043	0.999235
alpha_TT[6]	0.337327	0.005923	0.132362	0.068023	0.339233	0.594199	499.3359	0.999687
alpha_TT[7]	0.323442	0.006527	0.169787	-0.02775	0.326686	0.657835	676.6136	0.999388

Technical Engagement Appendix B: Parametric Network Meta-Analysis (excluding CTD)

For this separate version of the parametric NMA, CTD was excluded from the network of evidence, as per the EAG's preference (EAG report, Key Issue 4).

Therefore, the following trials were included in the parametric NMA: VISTA trial[3, 4], TMSG trial[6], IFM99-06[7], IFM01/01[8], Sacchi et al[9]., FIRST trial[11], and MAIA trial[12]. The network of evidence is presented in Figure 2. Pseudo-individual patient-level data (IPD) for each intervention were obtained by reconstructing time-to-event data digitized from published Kaplan Meier (KM) curves using Engauge Digitizer software[13] and the algorithm published by Guyot et al.[14] The corresponding reconstructed KM data for OS and PFS accompanied by results of the proportional hazards tests are presented in the Appendix B1. Trial data were available for the MAIA trial.

Figure 5. Network of treatments (excluding CTD)



DRd=daratumumab-lenalidomide-dexamethasone; MP= melphalan-prednisone; MPT= melphalan-prednisone-thalidomide; Rd 18= lenalidomide-dexamethasone 18 cycles; Rd c= lenalidomide-dexamethasone continued; VMP= bortezomib-melphalan-prednisone

Statistical Methodology

The planned analyses include the parametric NMA for the time-to-event endpoints OS and PFS. The six commonly known parametric distributions will be used; Weibull, Gompertz, Exponential, Lognormal, Loglogistic, and Gamma.

A fixed-effects model was preferred to a random-effects model due to a limited evidence network with only one comparison being informed by more than one trial.

Parametric Network Meta-Analysis

The parametric NMA model assumes that the long-term survival of each treatment population in an evidence network follows one of the commonly used parametric distributions. The parametric distribution functions were applied in the NMA setting for which the parameters are written as the sum of study effect and treatment effect, thereby not breaking randomization.

General Statistical Approach

Both OS and PFS parametric NMAs were performed using the RStan package in R Statistical Software (version 1.2-0).[15] These analyses were fitted with weakly informative priors.[15]

The models were run with two chains of 2,000 iterations, and 1,000 were burn-in iterations to generate the posteriors for the defined parameters. Convergence of the two chains was tested using the Rhat test[16].

The parametric NMA models were compared based on leave-one-out information criteria (LOOIC), mean and incremental mean survival. The LOOIC is an indication of statistical fit in which a lower LOOIC indicates a better fit. The base case model was selected based on the lowest LOOIC. General population mortality was not considered in the analyses as the outcomes of survival were already corrected for general population mortality in the health economic model. All analyses presented used the MAIA trial as the reference study.

Results

Overall Survival

The proportional hazard assumption in OS was potentially violated based on visual inspection for MAIA and IFM01/01, but not for the other trials (see Appendix B1). Table 2 presents the LOOIC per model and shows that the Gompertz distribution has the best statistical fit with a LOOIC of 21661.9. The estimated mean OS per treatment per model is demonstrated in Table 3, and the incremental OS with DRd as reference treatment is presented in Table 4. The OS predictions per model are depicted in Figure 3 (short term and long term).). Note that, due to the impact of general population mortality capping in the economic used for this appraisal, there are difference between the statistical output and the modelled survival outcomes.

All models fit the KM data of MAIA relatively well, except for the Lognormal model, as the extrapolated survival curves do not fit the MAIA data well. The study- and treatment-specific parameters are presented in the Appendix for the base case model (Gompertz for OS).

Table 8. LOOIC, OS

Distribution	LOOIC
Exponential	21710.94
Weibull	21679.72
Gompertz	**21661.93**
Loglogistic	21771.26
Lognormal	21900.14
Gamma	21684.03

Table 9. Mean OS, years (95% credible interval)

	Exponential	Weibull	Gompertz	Loglogistic	Lognormal	Gamma
DLd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ld	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ld18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MPT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BMP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

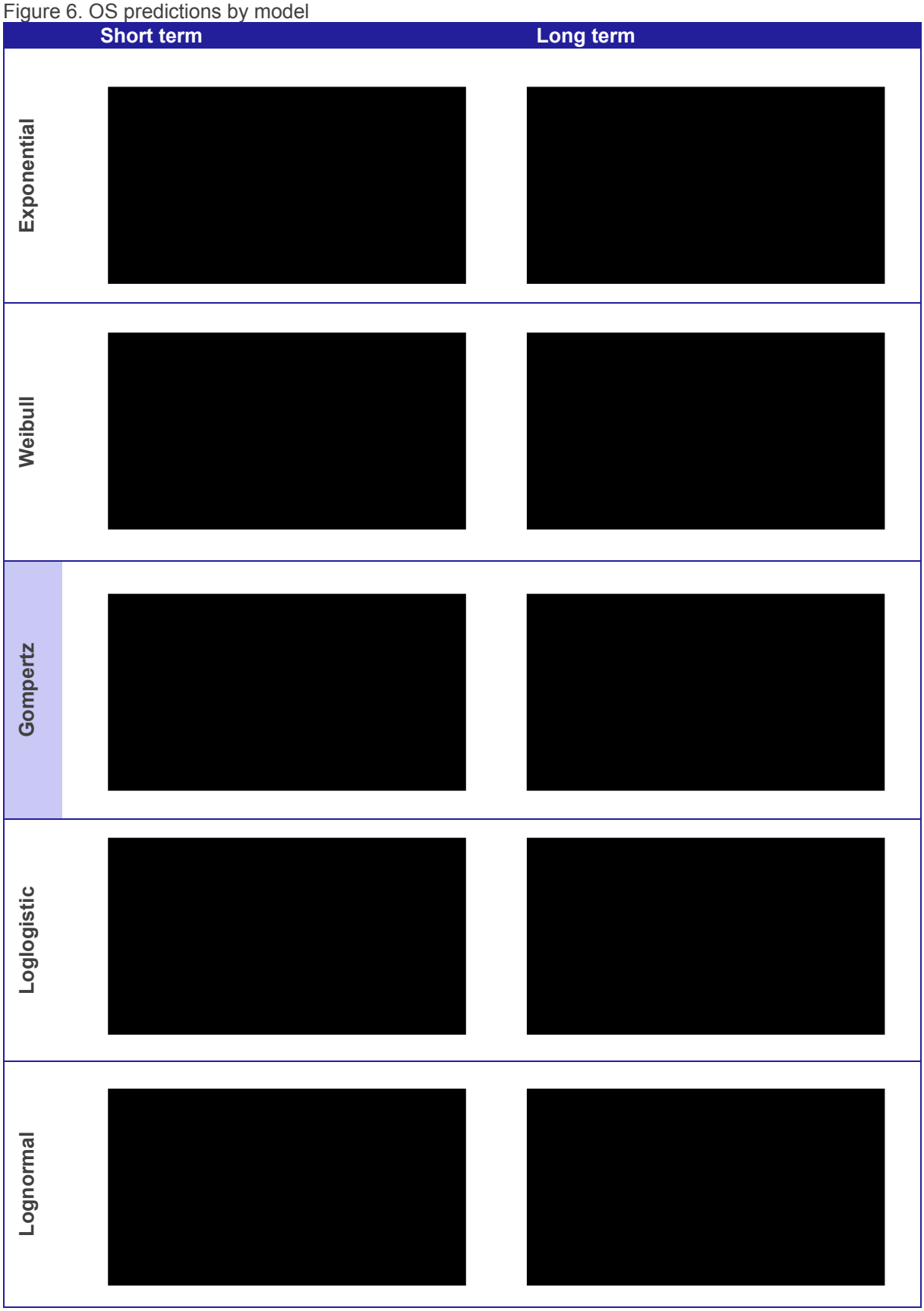
DLd=daratumumab-lenalidomide-dexamethasone; MP= melphalan-prednisone; MPT= melphalan-prednisone-thalidomide; Ld 18= lenalidomide-dexamethasone 18 cycles; Ld= lenalidomide-dexamethasone continued; BMP= bortezomib-melphalan-prednisone

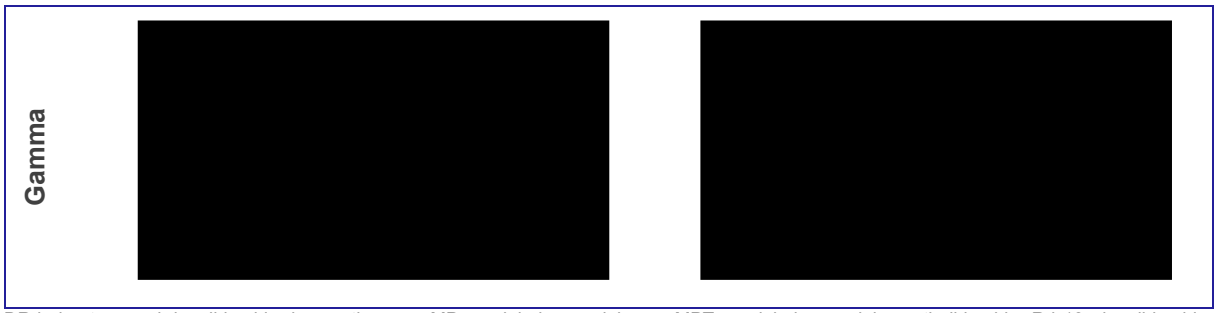
Table 10. Incremental mean OS, years (95% credible interval)

	Exponential	Weibull	Gompertz	Loglogistic	Lognormal	Gamma
DLd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ld	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ld18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MPT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BMP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

DLd=daratumumab-lenalidomide-dexamethasone; MP= melphalan-prednisone; MPT= melphalan-prednisone-thalidomide; Ld 18= lenalidomide-dexamethasone 18 cycles; Ld= lenalidomide-dexamethasone continued; BMP= bortezomib-melphalan-prednisone

Figure 6. OS predictions by model





DRd=daratumumab-lenalidomide-dexamethasone; MP= melphalan-prednisone; MPT= melphalan-prednisone-thalidomide; Rd 18= lenalidomide-dexamethasone 18 cycles; Rd c= lenalidomide-dexamethasone continued; PNMA=parametric network meta-analysis; VMP= bortezomib-melphalan-prednisone

Progression-free Survival

The proportional hazard assumption in PFS was violated for the FIRST trial, but not for the other trials (see Appendix). Table 5 presents the LOOIC per model and shows that the Gamma distribution has the best statistical fit with a LOOIC of 21458.6. The estimated mean PFS per treatment per model is demonstrated in Table 6, and the incremental PFS with DRd as reference treatment is presented in Table 7. The PFS predictions per model are depicted in Figure 3 (short term and long term). All models fit the PFS KM data of MAIA relatively well, except for the Lognormal model.

Table 11. LOOIC, PFS

Distribution	LOOIC
Exponential	21553.5
Weibull	21460.8
Gompertz	21495.8
Loglogistic	21541.4
Lognormal	21698.5
Gamma	**21458.6**

Table 12. Mean PFS, years (95% credible interval)

	Exponential	Weibull	Gompertz	Loglogistic	Lognormal	Gamma
DLd						
Ld						
Ld18						
MPT						
MP						
BMP						

DLd=daratumumab-lenalidomide-dexamethasone; MP= melphalan-prednisone; MPT= melphalan-prednisone-thalidomide; Ld 18= lenalidomide-dexamethasone 18 cycles; Ld= lenalidomide-dexamethasone continued; BMP= bortezomib-melphalan-prednisone

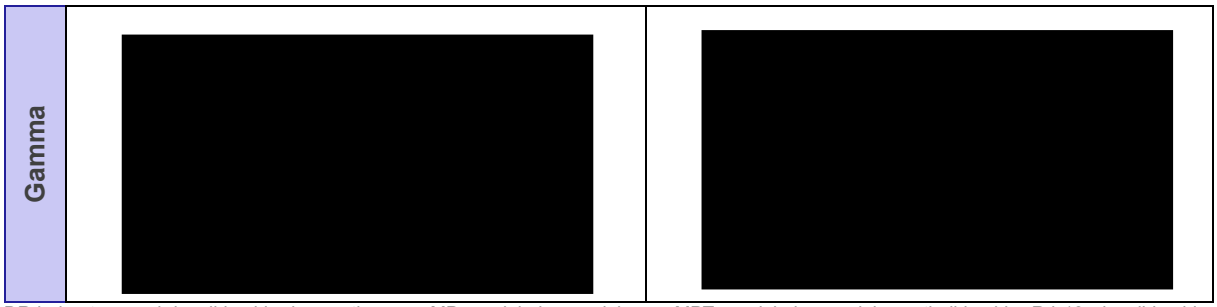
Table 13. Incremental mean PFS, years (95% credible interval)

	Exponential	Weibull	Gompertz	Loglogistic	Lognormal	Gamma
DLd						
Ld						
Ld18						
MPT						
MP						
BMP						

DLd=daratumumab-lenalidomide-dexamethasone; MP= melphalan-prednisone; MPT= melphalan-prednisone-thalidomide; Ld 18= lenalidomide-dexamethasone 18 cycles; Ld= lenalidomide-dexamethasone continued; BMP= bortezomib-melphalan-prednisone

Figure 7. PFS predictions by model

	Short term	Long term
Exponential		
Weibull		
Gompertz		
Loglogistic		
Lognormal		



DRd=daratumumab-lenalidomide-dexamethasone; MP= melphalan-prednisone; MPT= melphalan-prednisone-thalidomide; Rd 18= lenalidomide-dexamethasone 18 cycles; Rd c= lenalidomide-dexamethasone continued; PNMA=parametric network meta-analysis; VMP= bortezomib-melphalan-prednisone

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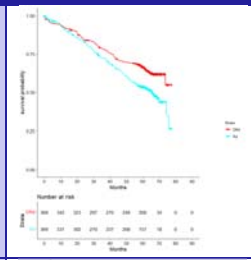
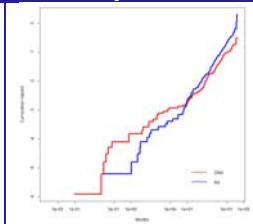
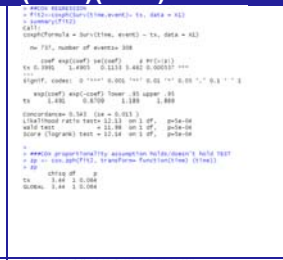
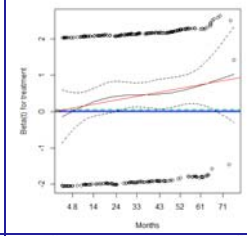
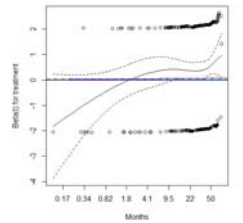
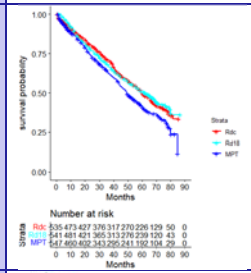
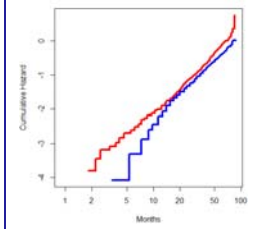
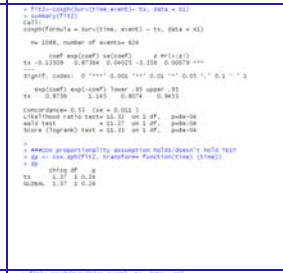
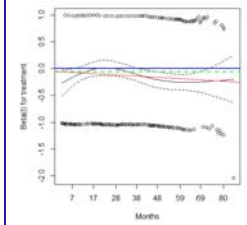
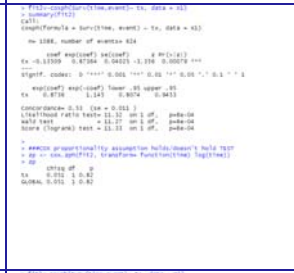
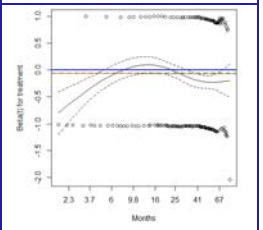
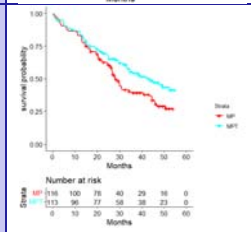
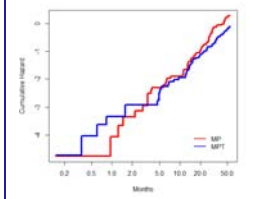
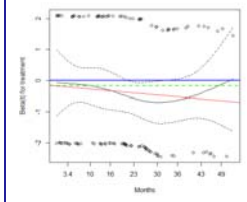
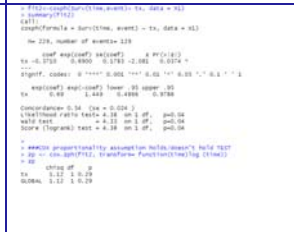
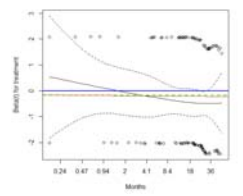
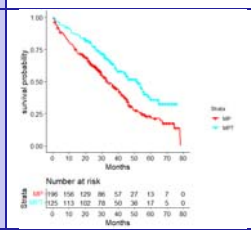
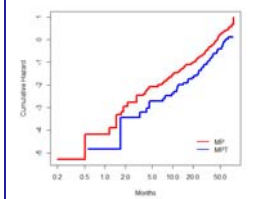
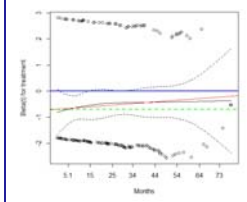
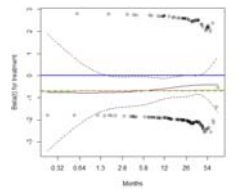
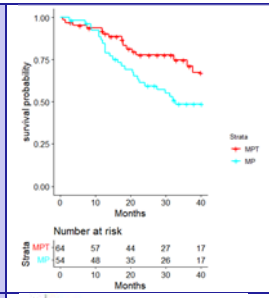
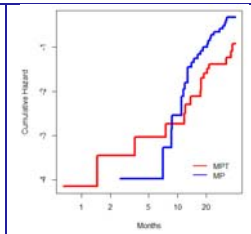
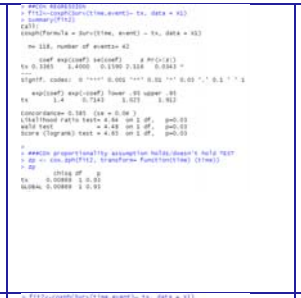
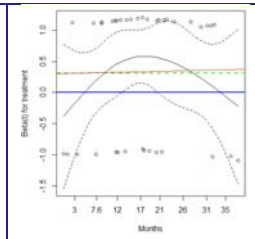
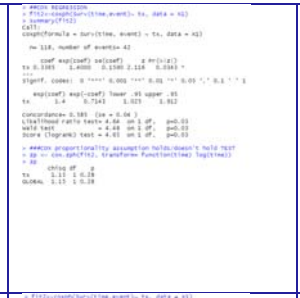
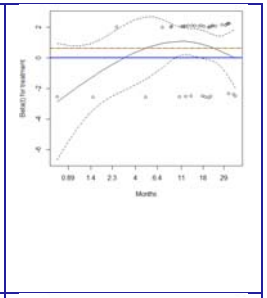
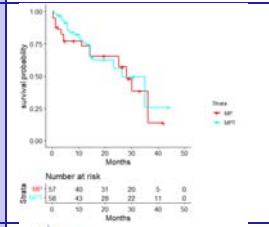
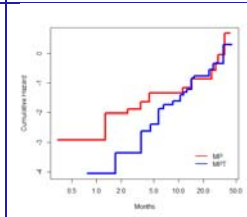
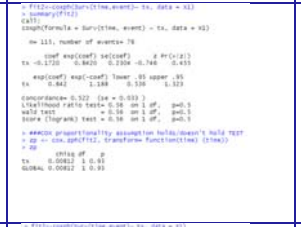
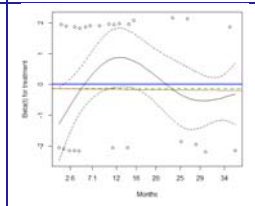
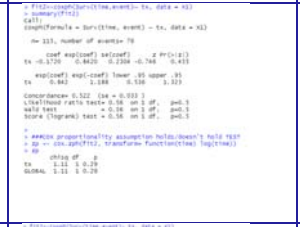
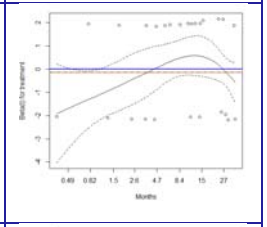
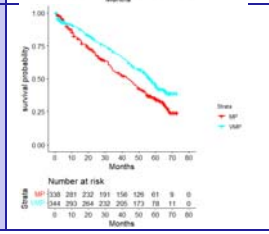
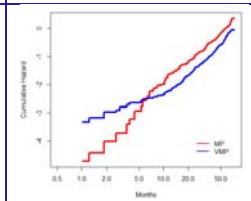
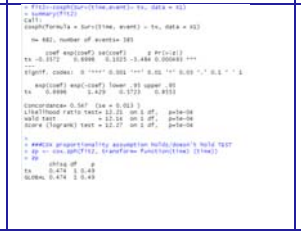
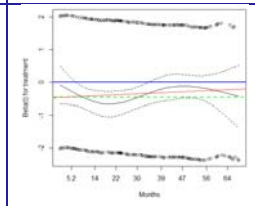
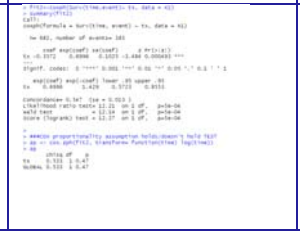
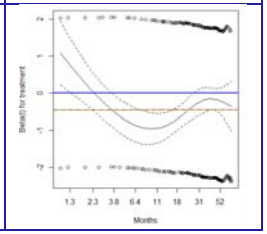
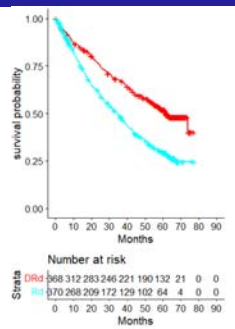
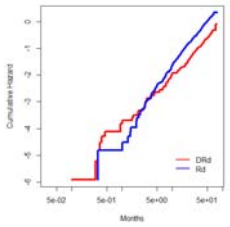
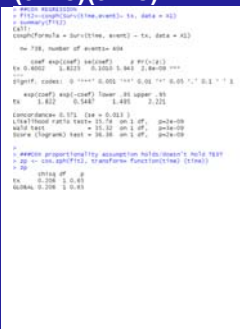
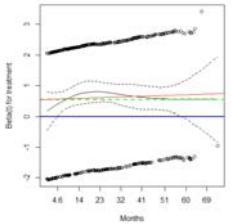
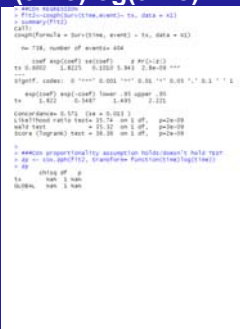
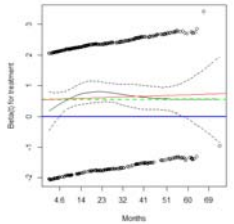
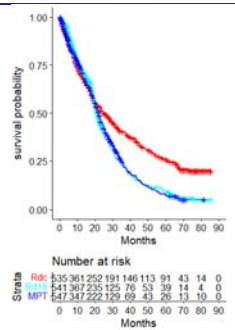
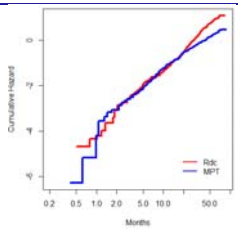
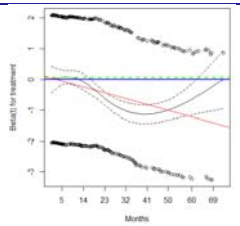
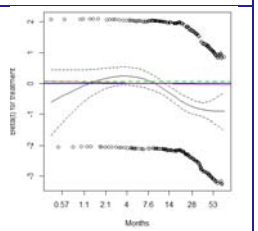
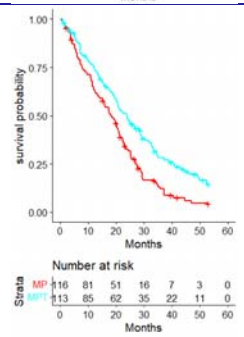
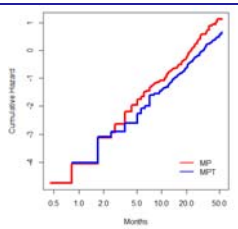
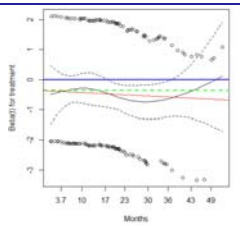
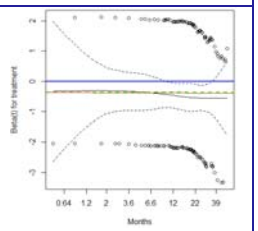
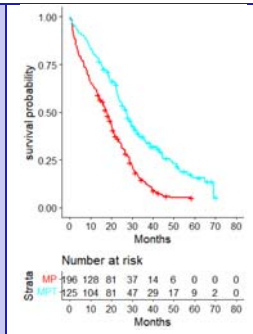
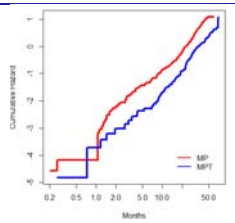
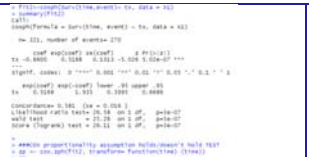
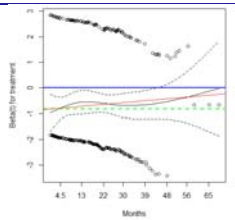
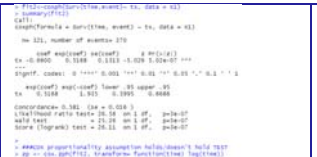
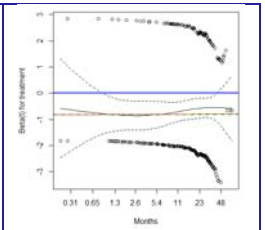
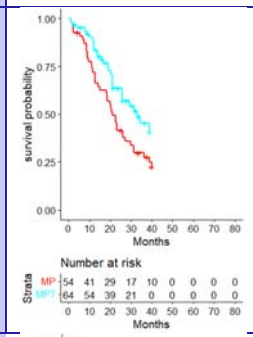
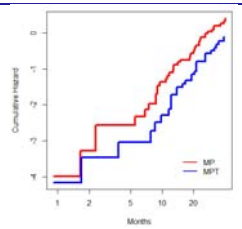
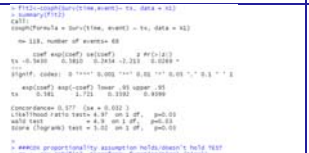
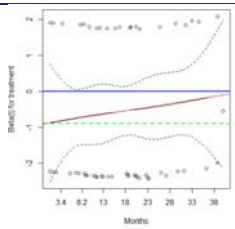
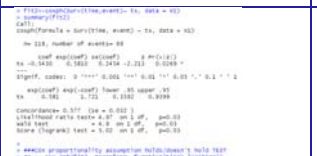
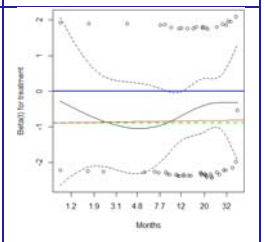
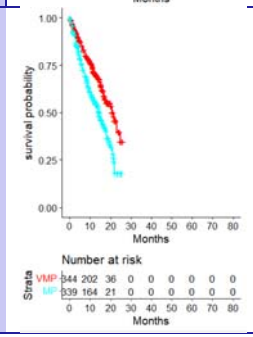
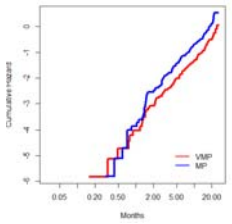
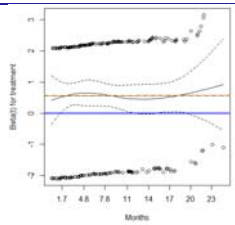
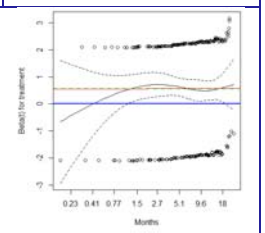
Appendix B1 (parametric NMA excluding CTD)
Proportional hazard testing, OS

OS	KM	Log cumulative hazard plots	Schoenfeld test (time)(time)	Schoenfeld plot (time)(time)	Schoenfeld test (time)log(time)	Schoenfeld plot (time)log(time)
MAIA						
FIRST (Rdc vs MPT)						
IFM0101						
IFM 9906						

Sacchi						
TMSG						
VISTA						

Proportional hazard testing, PFS

PFS	KM	Log cumulative hazard plots	Schoenfeld test (time)(time)	Schoenfeld plot (time)(time)	Schoenfeld test (time)log(time)	Schoenfeld plot (time)log(time)
MAIA						
FIRST (MPT vs Rd c)						
IFM0101						

IFM 9906						
Sacchi						
VISTA						

Model parameters OS base case (Gompertz)

Study label (S)		Treatment label (TT)	
1	MAIA	1	DRd
2	FIRST	2	Rdc
3	TMSG	3	Rd18
4	IFM9906	4	MPT
5	**IFM0101**	5	MP
6	Sacchi	6	VMP
7	VISTA		

	mean	se_mean	sd	2.50%	50%	97.50%	n_eff	Rhat
beta_S[1]	-4.9683	0.004366	0.165809	-5.29763	-4.96454	-4.65066	1442.075	1.002377
beta_S[2]	-4.75719	0.007615	0.251756	-5.26153	-4.7558	-4.28407	1092.974	1.001028
beta_S[3]	-4.38939	0.010641	0.360588	-5.11838	-4.38568	-3.717	1148.238	1.00123
beta_S[4]	-4.74564	0.010049	0.320528	-5.37343	-4.74218	-4.12583	1017.456	0.999863
beta_S[5]	-4.49406	0.009781	0.322428	-5.13385	-4.49808	-3.84866	1086.672	1.000344
beta_S[6]	-4.876	0.011051	0.39306	-5.65478	-4.86435	-4.11389	1265.113	0.999893
beta_S[7]	-4.89258	0.010485	0.338894	-5.55081	-4.89058	-4.22016	1044.699	1.000557
beta_TT[1]	0	NA	0	0	0	0	NA	NA
beta_TT[2]	-0.02303	0.006675	0.226021	-0.46772	-0.02766	0.431294	1146.443	1.00135
beta_TT[3]	0.115952	0.008154	0.27722	-0.4328	0.124554	0.664686	1155.891	1.001331
beta_TT[4]	0.224124	0.008262	0.266364	-0.27456	0.220956	0.738212	1039.344	1.001048
beta_TT[5]	0.580442	0.010145	0.317438	-0.0519	0.57918	1.205052	979.1223	1.000249
beta_TT[6]	0.083523	0.01115	0.37233	-0.64237	0.085234	0.810615	1115.089	1.001163
alpha_S[1]	0.000153	0.000124	0.004724	-0.00898	0.000162	0.009296	1441.84	1.001
alpha_S[2]	-0.00337	0.000201	0.006702	-0.01592	-0.00339	0.010392	1112.933	1.000611

alpha_S[3]	0.011923	0.000349	0.013005	-0.01382	0.011995	0.037183	1390.042	1.001596
alpha_S[4]	-0.00208	0.000286	0.009168	-0.02016	-0.00211	0.0159	1024.93	0.99988
alpha_S[5]	-0.0079	0.000298	0.010143	-0.02739	-0.00778	0.011609	1158.242	1.00014
alpha_S[6]	-0.00605	0.000393	0.015654	-0.03678	-0.00584	0.023949	1583.05	0.9995
alpha_S[7]	-0.00706	0.000315	0.010226	-0.02764	-0.0068	0.012011	1056.02	1.000294
alpha_TT[1]	0	NA	0	0	0	0	NA	NA
alpha_TT[2]	0.012983	0.000181	0.006224	0.000253	0.013153	0.025111	1181.145	1.000622
alpha_TT[3]	0.007949	0.000213	0.007291	-0.00669	0.007883	0.021726	1166.864	1.001185
alpha_TT[4]	0.012915	0.000217	0.007018	-0.00127	0.013089	0.026082	1045.342	1.000806
alpha_TT[5]	0.016455	0.000303	0.009556	-0.00237	0.016388	0.035978	994.1666	0.999803
alpha_TT[6]	0.020995	0.000333	0.011068	0.000118	0.020501	0.043154	1107.496	1.000873

Model parameters PFS base case (Gamma)

Study label (S)		Treatment label (TT)	
1	MAIA	1	DRd
2	FIRST	2	Rdc
3	IFM9906	3	Rd18
4	IFM0101	4	MPT
5	Sacchi	5	MP
6	VISTA	6	VMP

	mean	se_mean	sd	2.50%	50%	97.50%	n_eff	Rhat
beta_S[1]	-2.21278	0.007026	0.15468	-2.53335	-2.20651	-1.9195	484.7408	1.009319
beta_S[2]	-2.15669	0.013384	0.216762	-2.58095	-2.15755	-1.73457	262.2834	1.016698
beta_S[3]	-2.43608	0.017254	0.267276	-2.9478	-2.43631	-1.93137	239.9723	1.013456
beta_S[4]	-2.17262	0.017867	0.273798	-2.69316	-2.1776	-1.63902	234.8364	1.016299
beta_S[5]	-2.47438	0.018876	0.326167	-3.0865	-2.46808	-1.86661	298.5779	1.013829
beta_S[6]	-2.17363	0.019492	0.303575	-2.75494	-2.17221	-1.58404	242.5661	1.01548
beta_TT[1]	0	NA	0	0	0	0	NA	NA
beta_TT[2]	0.826969	0.011139	0.193102	0.463886	0.825145	1.200244	300.5316	1.013757
beta_TT[3]	1.788988	0.012738	0.227938	1.343612	1.787931	2.220096	320.1896	1.01449
beta_TT[4]	1.643216	0.014878	0.2301	1.215527	1.643118	2.080307	239.2071	1.017404
beta_TT[5]	2.034093	0.018172	0.273307	1.509155	2.027465	2.561012	226.1931	1.016463
beta_TT[6]	1.482394	0.019951	0.358474	0.782741	1.492042	2.164883	322.8277	1.010627
alpha_S[1]	-0.12311	0.003589	0.084306	-0.29274	-0.1209	0.03596	551.7737	1.008747
alpha_S[2]	-0.21325	0.007583	0.129	-0.46861	-0.21284	0.033045	289.3985	1.01559
alpha_S[3]	-0.27609	0.010717	0.17709	-0.62378	-0.2778	0.064604	273.052	1.011803
alpha_S[4]	-0.09226	0.011132	0.179364	-0.44348	-0.09143	0.260718	259.632	1.013801

alpha_S[5]	-0.06547	0.011701	0.217108	-0.47963	-0.06732	0.363739	344.281	1.01093
alpha_S[6]	-0.20006	0.011684	0.199035	-0.58528	-0.20255	0.186927	290.2049	1.013104
alpha_TT[1]	0	NA	0	0	0	0	NA	NA
alpha_TT[2]	0.145861	0.005951	0.113367	-0.06867	0.144172	0.367819	362.9392	1.012065
alpha_TT[3]	0.651968	0.007168	0.141294	0.381475	0.651219	0.931073	388.5538	1.011884
alpha_TT[4]	0.507993	0.008824	0.142064	0.24714	0.507063	0.78477	259.178	1.016032
alpha_TT[5]	0.447807	0.011185	0.180037	0.101025	0.448687	0.799934	259.0827	1.013771
alpha_TT[6]	0.400637	0.011709	0.224646	-0.04763	0.405826	0.836709	368.1225	1.010056

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Daratumumab with lenalidomide and dexamethasone for untreated multiple myeloma when stem cell transplant is unsuitable [ID4014]

Clinical expert statement and technical engagement response form

Thank you for agreeing to comment on the external assessment report (EAR) for this evaluation, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The EAR and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR. You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

The deadline for your response is **5pm** on **11 November 2022.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

Clinical expert statement

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Part 1: Treating multiple myeloma and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	[redacted]
2. Name of organisation	United Kingdom Myeloma Society (UKMS)
3. Job title or position	[redacted]
4. Are you (please tick all that apply)	☒ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with multiple myeloma? ☐ A specialist in the clinical evidence base for multiple myeloma or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☒ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A
8. What is the main aim of treatment for multiple myeloma?	Prolonged survivorship with improved quality of life through minimal treatment-related toxicity and maximal impact associated with limited disease-related morbidity.

(For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Achievement of at least a Partial Remission (>50% reduction in blood-borne markers), optimally better than a Very Good Partial Remission (>90% reduction in blood-borne markers) that is sustained and associated with improved quality of life.
10. In your view, is there an unmet need for patients and healthcare professionals in multiple myeloma?	There are many unmet needs in caring for patients with myeloma, relevant to this HTA is the needs of the transplant non-eligible (TNE) population, whose ability to get deep and meaningful responses associated with durability of responses are often limited by intolerance of treatment and multi-factorial disability and frailty. The advances in therapy-related survivorship seen in younger, fitter patients is yet to be realised in the TNE population.
11. How is multiple myeloma currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	The treatment "pathway" is delineated by multiple, non-linked NICE HTA decisions, including drug combination availability through the CDF. This has led to a some-what rigid artificial pathway that limits individualised patient treatment decision and clinical judgment in many cases. Consequentially there are differences of opinion from what we (the professionals) wish to do versus what we are allowed to do (dictated by NICE HTAs). Add to this the dogma of "one size does not fit all" and myeloma therapy is a complicated landscape that is well placed to become the beacon of personalised anti-cancer medicine. That said, the current technology under consideration is a "game-changer" across all variabilities, including molecular high risk disease and patient-specific stratification including frailty.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care?	The proposed regimen is a triplet, which will replace an all oral doublet. The third drug (Daratumumab) is a parentally administered drug, albeit as a relatively quick subcutaneous injection that is currently only delivered in a hospital basis. As such, there will be pharmacy preparation impact as well as impact on oncology day units, this impact is lessened by the use of subcutaneous drug delivery. There is unlikely to be any investment, though capacity in day units will need supporting.

• In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	We fully expect the technology to improve significant disease control, limiting disease-related morbidity and improving survivorship in TNE myeloma patients. This will translate into meaningful gains in quality of life for our patients.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	In accordance with the trial reports, all patient unmet need groups would benefit from this technology (older age, frail (in the *Leukemia* paper), molecular high risk disease, impaired end organ function, advanced disease stage). There is no information on the relative effectiveness on patients with extramedullary disease, which has a poorer prognosis on the standard of care.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	There is no issue about regimen delivery, as most units are familiar with daratumumab delivery now for over 2 years as a subcutaneous drug delivery system.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Only standard of care stop/start rules with no extra investment needed.

17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	We think the health-related benefits are mostly captured.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	This technology is a "game changer" in terms of advancing the disease control for patients with myeloma, limiting disease-related morbidity and improving survivorship.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Delivering daratumumab subcutaneously significantly reduces drug delivery-related toxicity. The longer term issue is the potentiation of disease-related immunepareisis with associated risk of infections. Such patients who experience this may need prophylactic antibiotics or intravenous immunoglobulin administration. There is no additive effect of daratumumab on lenalidomide/dexamethasone related side effects seen in standard of care.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials?	The proposed regimen is a triplet, which will replace doublet treatment with Lenalidomide Dexamethasone. A minority of patients currently receive a Bortezomib based regimen upfront. Daratumumab is widely used in the UK for the treatment of myeloma patients at different stages of the pathway. Depth of response, toxicity, PFS, OS and quality of life are important outcome measures and have been captured in the MAIA trial.

• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No, this has been correctly captured.
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance in this area.	No
23. How do data on real-world experience compare with the trial data?	There is limited published data on real world experience. We would expect real world experience to reflect the published trial data.
24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation	No equality issues.

• lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the EAR, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

Key Issue 1 **Are thalidomide containing therapies a comparator at 1st line?**	Thalidomide -containing regimens now are used in the smallest minority as first line therapy because of the universal use of its derivative Lenalidomide in patients not deemed eligible for up-front high dose procedure and stem cell transplant (TNE patients). As such, it is a considerably less relevant as a front line comparator.
Key Issue 2 Are results of MAIA generalisable to the NHS in England, considering currently available routine treatments?	As with all clinical trials, the trial population (as a consequence of trial inclusion/exclusion criteria) only partially reflects the real-world population. That said, the median age in the trial was 73, very close to real world median age at diagnosis, and over 40% of patients were older than 75. 19.9% were older than 80 years, and by a modified IMWG frailty score, over 40% were frail. So the population is very close to real world and therefore the trial results are relevant and generalisable to UK patients. There is one key difference, which is post-trial relapse therapy, which was not protocol specified, dependent on availability in the patients jurisdiction and the variance of NICE HTAs with real-world practice internationally.
Key Issue 3 **Is there sufficient follow-up for robust**	In the original Lancet Oncology publication, the median follow-up was 56.2 months. However, the median overall survival was not reached in either group but by a pre-specified end point there was a statistically significant

estimation of overall survival?	difference in OS between the arms with a HR of 0.68, and therefore further maturity of the data would secure the OS benefit of the triplet regimen.
Key Issue 4 **Are the studies in the NMA similar enough for reliable inference?**	The NMA included MRC Myeloma IX, which is outdated, and though included a thalidomide-based regimen, it was in comparison with standard chemotherapy. CRUK Myeloma XI is a far more suitable comparator trial where a Thalidomide-based regimen was compared to a Lenalidomide-based comparator, in the world's largest front line trial. Why Myeloma XI was not included is not clear. The other trials primarily contain thalidomide-based regimens, with little bortezomib-containing regimens, which is more relevant in current practice.
Key Issue 5 **What is the preferred source of evidence for the comparison of BMP vs DLd, the HR NMA, the Parametric NMA, the Piecewise NMA, or the unanchored indirect treatment comparison?**	
Key Issue 6 **Is it reasonable to assume equivalence between BMP and BCd?**	In essence, yes though BCd is generally more tolerable and in theory, patients in this population may end up receiving more of the RDI of BCd compared to BMP.
Key Issue 7 **Should CDF drugs used at 2nd line and beyond be included in the company's model?**	Yes as this reflects real world practice, especially as relapsed therapy in the MAIA trial was per protocol specified and left to local jurisdictions.

Key Issue 8 **Which are the most appropriate parametric models for PFS, OS, and TTD for DLd, Ld, and BMP?**	The technical documents is difficult to interpret in this regard. The company preferred uITC has issues about meeting proportional hazards for PFS, whereas the chosen EAG has too many assumptions in our opinion.
Key Issue 9 **Would the treatment effect for OS be maintained for a patient's lifetime or would there be waning of effect?**	The issue of "treatment waning" is not appropriate in the myeloma space, as discussed at several NICE HTA meetings. In the setting of the current appraisal, the question is *why would you include treatment waning*? What is the evidence to support its inclusion? There is no clinical evidence or even rational to include a segregated treatment waning effect on the experimental arm only, when if it exists (and that is a big "if"), then it would impact both arms. Should not be included in this appraisal.
Key Issue 10 **Are the MAIA or ALCYONE health-state utilities more appropriate?**	We believe that multi-state modelling to capture the impact of subsequent therapy is most appropriate incorporation of health state utilities.
Key Issue 11 **Should costs for dose-reductions using RDIs be included in the model?**	We believe that incorporating costs for RDIs would be a new addition to the health economic assessment, and one that would need to be validated not based on assumptions. How would one predict the rate of RDIs in the real world?
Key Issue 12 **What is the most appropriate market share of treatments used at 2nd and 3rd line in England?**	At 2nd Line, the estimated proportional split of choices through NICE/CDF would be : with 50% DaraBortDex, 25% CarfilLenaDex, 15% LenaDex and 10% for a thalidomide-based regimen. At 3rd Line, there is a bottle-neck as the standard triplet regiment used (IxaLenaDex) should not be used if first line LenaDex is used and patients show progression on the agents. Therefore the split of choices could be estimated as split in 20% IxaLenaDex, 10% LenaDex, 20% Bort-Dex-Ppano, 25% thalidomide-based regimen and 25% regimens not including a novel agent.

Are there any important issues that have been missed in EAR?	

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

The combination of Daratumumab, lenalidomide and dexamethasone is deliverable and tolerated in the transplant non-eligible patient population with myeloma
The combination of Daratumumab, lenalidomide and dexamethasone is highly effective at controlling disease in the transplant non-eligible patient population with myeloma
The combination of Daratumumab, lenalidomide and dexamethasone is game-changing therapy in prolonging disease control and promoting survivorship in the transplant non-eligible patient population with myeloma
Click or tap here to enter text.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Daratumumab with lenalidomide and dexamethasone for untreated multiple myeloma when stem cell transplant is unsuitable [ID4014]

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

The deadline for comments is the end of **11 November 2022**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we

received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Myeloma UK
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	NA

Table 1 About you

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Key Issue 1 Are thalidomide containing therapies a comparator at 1st line?	Yes/No	We would expect most patients to be receiving lenalidomide and dexamethasone rather than a thalidomide based treatment. Primarily a question for clinical experts.
Key Issue 2 Are results of MAIA generalisable to the NHS in England, considering currently available routine treatments?		Yes. The key comparator of lenalidomide and dexamethasone is relevant to NHSE practice. Note that UK practice would see clinically appropriate patients >65 years as being eligible for ASCT.
Key Issue 3 Is there sufficient follow-up for robust estimation of overall survival?		We consider 64.6 months follow up at October 2021 to be a significant period for follow up in myeloma clinical trials practice and in the context of data routinely considered by NICE.
Key Issue 4 Are the studies in the NMA similar enough for reliable inference?		Primarily a question for clinical experts.
Key Issue 5		Primarily a question for clinical experts.

What is the preferred source of evidence for the comparison of BMP vs DLd, the HR NMA, the Parametric NMA, the Piecewise NMA, or the unanchored indirect treatment comparison?		
Key Issue 6 Is it reasonable to assume equivalence between BMP and BCd?		Primarily a question for clinical experts.
Key Issue 7 Should CDF drugs used at 2nd line and beyond be included in the company's model?		Note that CDF drugs are often the standard of care in myeloma.
Key Issue 8 Which are the most appropriate parametric models for PFS, OS, and TTD for DLd, Ld, and BMP?		No comment
Key Issue 9 Would the treatment effect for OS be maintained for a patient's lifetime or would there be waning of effect?		Primarily a question for clinical experts.
Key Issue 10 Are the MAIA or ALCYONE health-state utilities more appropriate?		Quality of life is clearly a key issue for patients. Regretfully the information provided and question posed here are presented in such a way that it makes it very difficult for patients and patient representatives to meaningfully answer this question. We suggest that in future key factors in decision making of these kind are presented in a way that enables patients to contribute to this discussion.
Key Issue 11		No comment.

Should costs for dose-reductions using RDIs be included in the model?		
Key Issue 12 What is the most appropriate market share of treatments used at 2nd and 3rd line in England?		We suggest that this is a question that NHSE data from Blueteq forms should able to answer definitively.

Additional issues

All: Please use the table below to respond to additional issues in the EAR that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage).

Table 3 Additional issues from the EAR

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Insert additional issue	Please indicate the section(s) of the EAR that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue 2: Insert additional issue	Please indicate the section(s) of the EAR that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue N: Insert additional issue			[INSERT / DELETE ROWS AS REQUIRED]

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Insert key issue number and title as described in the EAR	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the EAR	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER.
Insert key issue number and title as described in the EAR	…	…	[INSERT / DELETE ROWS AS REQUIRED]
Company's base case following technical engagement (or revised base case)	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide company revised base-case ICER

Sensitivity analyses around revised base case
PLEASE DESCRIBE HERE

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Daratumumab with lenalidomide and dexamethasone for untreated multiple myeloma when stem cell transplant is unsuitable [ID4014]

EAG Response to Technical engagement response form

Confidential information is highlighted as [redacted], [redacted], and all information submitted under [redacted] in pink.

Key issues for engagement

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response	EAG Response
Key Issue 1 Are thalidomide containing therapies a compar	No	As per Section B.1.1 of our company submission (CS), **Janssen consider Ld (lenalidomide and dexamethasone) the most relevant comparator for this appraisal, and that thalidomide-based combinations are not clinically relevant given their negligible use in English clinical practice**. This was based on consensus feedback from a clinical expert advisory board meeting held on the 9th of March 2022 involving 8 English-based clinicians, the minutes of which were submitted as part of the appendices in the CS (Data on file, Janssen Clinical Advisory Board Meeting minutes). Janssen's position is consistent with the EAG's clinical expert feedback, and statement from the UK Myeloma Forum (UKMF) which commented	The EAG agrees with Janssen that thalidomide-based combinations are not commonly used in current NHS clinical practise. However, thalidomide-based combinations are listed in the scope and there is NICE guidance recommending them, so we feel this is a key issue that the committee needs to discuss, as it determines which cost-effectiveness results to focus on.

ator at 1st line?		only 'a small number of patients will receive a thalidomide based regimen' (p271/297 of TE papers). Moreover, there are known tolerability issues with thalidomide-based treatment with the UKMF noting, 'It would [be] unusual for patients to receive a Thalidomide based regimen as Lenalidomide is a better tolerated oral regimen'. In summary, Janssen consider the main comparator of relevance for this submission to be Ld, for which MAIA provides direct, randomised evidence with over 5 years median follow-up. As per Key Issue 5 below, we note that Ld dominates all other comparators in most scenarios explored, and therefore, the ICER versus Ld is the most relevant ICER for Committee decision making.	BMP and BCd are used in NHS clinical practise and so the EAG considers these to be relevant comparators alongside Ld.
Key Issue 7 Should CDF drugs used at 2nd line and beyond be included in the company's model?	Yes	**It will be important for scenarios including DBd at 2L to be available to committee, to support process efficiency and speed of patient access.** Janssen note there are two treatments for multiple myeloma (MM) currently on the CDF with imminent routine commissioning decisions, which impact the modelling of subsequent treatments: **1) CDF exit of DBd at 2L (in process)** Janssen note that the appraisal committee meeting for daratumumab with bortezomib and dexamethasone (DBd) for previously treated multiple myeloma (Review of TA573) [ID4057] is scheduled for 8th February 2023 (a few weeks after DLd on 12th January 2023). DBd represents standard of care in England at second-line, and its inclusion as a subsequent treatment has a material impact on the cost-effectiveness of DLd.	We thank the company for providing functionality in their model to explore the impact of including DBd at 2L without IxaLd at 3L. However, note that at this point in time we do not know the outcome of the CDF reviews for DBd at 2L or IxaLd at 3L, neither in terms of recommendation nor price.

		Janssen acknowledge and agree with the NICE position statement regarding the inclusion of CDF drugs as either comparators or subsequent treatments. Given the unique circumstance, however, of the proximity of the two appraisals for the same molecule by the same manufacturer and the material impact of including subsequent DBd on the cost-effectiveness results, Janssen request a degree of pragmatism and flexibility by NICE for the EAG and Committee to consider scenarios **conditional** on a DBd recommendation for routine commissioning. [redacted] **2) CDF exit of IxaLd at 3L (in process)** The latest stakeholder communication from NICE regarding the decision for ixazomib with lenalidomide and dexamethasone [NICE ID1635[redacted] Unlike the DBd appraisal, Janssen do not have visibility on the expected outcome of the IxaLd decision. As per the EAG's request during the Technical Engagement call, Janssen have updated the cost-effectiveness model with functionality to only consider a CDF scenario including DBd at second-line. Scenarios including the impact of IxaLd at 3L in the treatment pathway are provided below, to facilitate the Committee having the most up to date information at the time of decision making.	

Key Issue 2 Are results of MAIA generalisable to the NHS in England, considering currently available routine treatments?	Yes	**Janssen consider the results of MAIA to be generalisable to the NHS in England and results using the IPCW analysis suggest the cost effectiveness results (using the unadjusted MAIA data) may be conservative**. MAIA was a registrational quality Phase III RCT which included patients from the UK, that directly compared DLd against the most relevant active comparator in current NHS clinical practice, Ld. In MAIA, a total of [redacted]) of patients across fourteen sites were included from the UK, across 12 locations: Aberdeen, Canterbury, Dundee, Leeds, London, Manchester, Nottingham, Oxford, Plymouth, Southampton, Truro and Wolverhampton. The majority of subsequent treatments that patients received in MAIA are routinely available in the UK. However, due to the international study design, MAIA included a number of subsequent treatments which are not routinely available in NHS clinical practice. The proportion of patients receiving such treatments was balanced across treatment arms ([redacted]%) in the DLd and Ld arms respectively at second-line), which helps to minimise any potential bias. As detailed in Section B.2.6.2.6 of the CS, the impact of non-routinely commissioned subsequent treatments on the observed efficacy has been extensively explored with a number of statistical methods considered. An IPCW OS analysis was conducted as the only potentially viable method to explore the impact of potential bias as a result of including non-routinely commissioned treatments. Reassuringly, the results of the IPCW analysis demonstrate an even greater OS benefit for DLd vs Ld (indicated by a reduced HR), following adjustment to exclude subsequent treatments not available in the UK setting (Observed OS HR: 0.66: 95% CI: 0.53, 0.83; IPCW Adjusted OS HR: [redacted]). As such, Janssen consider the unadjusted DLd versus Ld hazard ratio from MAIA to be conservative	Note that although the proportions receiving treatments not available in the NHS was similar across arms at 2nd line, the proportions at 3rd line did differ ([redacted] and [redacted] in DLd and Ld respectively) (EAG report section 3.2.1), although this might be expected to favour Ld. The EAG therefore agree with the company that the results from MAIA may be conservative. However as noted in the EAG report section 3.2.2.2, the IPCW adjusted approach makes some strong assumptions, that could not be validated, and so we prefer the unadjusted results.

		and likely to underestimate the relative survival benefit of DLd expected in clinical practice in England. In summary, Janssen consider the results of MAIA generalisable to the NHS in England with likely conservative estimates of the relative treatment effect; some bias against DLd. The generalisability of MAIA is further supported by the statement from UKMF that the reported outcomes for the control arm reflects the expected outcomes of Ld in UK clinical practice (Q 21, p277 of TE papers).	
Key Issue 3 Is there sufficient follow-up for robust estimation of overall survival?	No	**Janssen consider the available evidence package for DLd to be robust, and length of follow-up from MAIA sufficiently mature for robust estimation of overall survival and a recommendation to be made for routine commissioning.** Janssen consider the duration of follow up from MAIA (over 5 years) sufficient for robust estimation of overall survival and Committee decision making. Whilst a recommendation for the CDF remains an option for the Committee, it is expected that additional follow-up from MAIA will only confirm the current understanding of the significant clinical benefit of DLd in this setting, rather than help to resolve inherent uncertainty of long-term survival estimates for this chronic life-long condition. **<u>Significance of MAIA results and follow-up in the context of other Haemato-Oncology NICE appraisals</u>** Regulatory approval for DLd was granted based on the results of the MAIA primary PFS analysis, with a median follow-up of 28 months. Since then, subsequent MAIA datacuts have consistently demonstrated a statistically significant and clinically meaningful improvement in survival outcomes	The EAG agrees that MAIA has demonstrated a survival benefit of DLd vs Ld in the mid-term, and longer term follow-up is very likely to show an overall survival benefit. What is uncertain is how the hazard ratio for DLd vs Ld changes over time beyond the follow-up period from MAIA, which affects over 50% of patients. The cost-effectiveness results are very sensitive to assumptions about treatment effect waning. Although the FIRST trial was considered sufficient for the appraisal of Ld (TA587), DLd has longer survival than Ld and therefore longer follow-up is needed. Based on the piecewise HRs for MAIA OS presented in Table 5 (this document), any changes in HRs beyond 24 months are minimal and differences too uncertain,

		(PFS and OS) for DLd patients compared with Ld alone. Based on the outstanding efficacy results from MAIA, DLd is internationally regarded as the frontline treatment choice for newly diagnosed transplant-ineligible patients in both national and international treatment guidelines (Dimopoulos MA, 2021) (Sive J, 2021). The clinical significance of the MAIA results was acknowledged by the UKMF, who describe the improvement in PFS and OS from MAIA as 'undoubtedly clinically meaningful outcomes', and 'the reported outcomes for D-Rd in a phase 3 trial are internationally considered to set a new gold standard for 1st line treatment of newly diagnosed transplant ineligible myeloma'. Furthermore, the follow-up from MAIA is now similar to the follow-up from the FIRST trial (median follow up of 67 months), which provided the clinical evidence for the NICE approval of Ld (TA587) in 2019. As noted by the ERG at the time (p15 of ERG report, TA587): 'the [FIRST] trial results can be considered mature with a median follow up of 67 months at the most recent data cut-off'. Therefore, with a median follow up of similar magnitude, MAIA should be considered similarly appropriate for decision making. **<u>Robustness of OS extrapolations</u>** The EAG state that extrapolations for OS, in particular for the DLd arm, are uncertain. **Whilst Janssen acknowledge inherent uncertainty with long-term estimates of OS, the similarity of the DLd OS predictions from multiple models, including more flexible methods, indicate that**	estimated from a small number of patients, to conclude a trend. A further [redacted] months additional follow-up from MAIA would provide information on whether these curves continue to remain apart or whether they begin to come together. However, we acknowledge that uncertainties beyond that time would still remain. Note that whilst the predicted mean overall survival for DLd may be similar for the different curves fitted to the MAIA data, all these curves may change with further follow-up data. Furthermore, what is important for the cost-effectiveness results is the difference between the DLd and Ld curves.

		the follow-up from MAIA is sufficiently mature for robust estimation of OS. Based on the follow-up available from MAIA, all DLd extrapolations (with the exception of the generalised gamma, which represents a notable outlier) provide strikingly similar long-term OS estimates. In addition, exploration of more flexible methods, including spline models with one, two and three knots, generated curves that were in line with the standard parametric extrapolations (Section B.3.3.2, Document B). Long-term outcomes between the EAG's preferred OS extrapolation for DLd (Gompertz) and the company base case (Exponential) are similar (mean 115.1 months versus 116.7 months respectively), indicating that there is sufficient follow-up for robust estimation of OS. **<u>Follow-up from final MAIA OS analysis</u>** The EAG state that longer follow-up from MAIA would help to resolve the uncertainty in the OS extrapolations. It is unclear, however, the extent to which the additional follow-up from the final MAIA OS analysis will help resolve the inherent uncertainty associated with modelling a lifetime time-horizon for a chronic condition such as untreated ASCT-ineligible MM. The final MAIA OS analysis is currently expected to occur in [redacted] and will add approximately [redacted] months additional follow-up. Janssen consider that while this additional follow-up would reduce uncertainty in estimates of overall survival (which as noted above are already strikingly similar in the company and EAG base cases) it could not resolve or materially reduce uncertainty pertaining to for example survival at 20 years or the long-term duration of benefit. As such, we believe the evidence base is sufficient for a routine commissioning recommendation.	

Key Issue 4 Are the studies in the NMA similar enough for reliable inferen ce?	No	**Janssen consider the approach taken for the indirect comparison against bortezomib-based treatments in this submission as suitably robust and comprehensive. The comparison of DLd vs Ld, using the direct evidence from MAIA, is most relevant for Committee decision making.** Our base case comparison of DLd against BMP leveraged individual patient-level data (IPD) from another phase 3 Janssen study in this same population, ALCYONE, to perform an IPD unanchored indirect comparison using propensity score weights. A scenario analysis was also performed using a standard NMA approach and, at the request of the EAG, Janssen has explored more flexible methods to counter observed violation of the proportional hazards assumption of some studies included in the network for PFS/OS. Whilst we agree that the studies within the evidence network are sufficiently similar for reliable inference through the NMA, there are important advantages and disadvantages to the different methods. We note, however, that regardless of the indirect comparison method selected, Ld dominates all other treatments in each scenario. **As such Janssen consider the ICER of DLd versus Ld, using direct evidence from MAIA, as most relevant for Committee decision making.**	We agree that MAIA is the best source of evidence for the DLd vs Ld comparison. See section 3.4 of the EAG report for our critique of the indirect comparison against bortezomib-based treatments. The relevant comparisons for decision-making is a matter for the committee to determine.
Key Issue 5 What is the preferre	Yes	**Regardless of the indirect comparison methodology explored, the ICER of DLd versus Ld remains the most relevant for committee decision making and is supported by high-quality randomised phase 3 evidence.**	See section 3.4 of the EAG report for our critique of the different approaches to the indirect comparison of DLd vs bortezomib containing treatments.

d source of evidence for the comparison of BMP vs DLd, the HR NMA, the Parametric NMA, the Piecewise NMA, or the unanchored indirect treatment comparison?		As noted above, Janssen consider the unanchored indirect comparison leveraging individual patient data from MAIA and ALCYONE most robust to inform the indirect comparison of BMP versus DLd. By contrast, the EAG prefer an NMA approach, utilising randomised evidence despite the long chain linking the two studies. Due to the observed violation of proportional hazards for some studies in the network, the EAG suggest an NMA model that relaxes the proportional hazards assumption for both PFS and OS and for all comparisons. The parametric NMA is the only approach that achieves this and fits curves to all treatments simultaneously assuming the same parametric distributional form for each treatment, which is in line with recommendations from TSD14. Therefore, we have provided supplementary analyses focusing on the parametric NMA (both including and excluding CTD), which are detailed in Appendix A and B. Other advanced NMA methods considered included the piecewise HR or piecewise parametric NMA. However, the disadvantage of these piecewise methods is that they require splitting the data into two timeslots. The timepoint where the data is split may be arbitrary and should be consistent for all trials, even if the optimal timepoint to split the data varies across the trials in the network. Given that the standard parametric NMA fits the data well overall, Janssen consider that other advanced NMA methods are likely to only introduce further complexity to the analysis and require unnecessarily strong assumptions for the indirect comparison. Full exploration of the parametric NMA (including CTD in the network, Table 1) approaches show that selections of Gompertz for OS and Weibull for PFS are the best fitting curves, based on the lowest LOOIC.	We thank the company for providing the new parametric NMAs for OS and PFS. The company have still not provided the full details (model code and data for analysis) for the EAG to validate their analyses. The company's assessment of model fit is based on Heeg et al. 2022, and they have stated that "standard parametric NMA fits the data well overall". However, no absolute measure of model fit (e.g. residual deviance) has been reported, and only **relative** measures of model parsimony are given (LOOIC). The EAG therefore cannot confirm that these models fit the data well, but given the visual fit of the selected parametric distributions to the MAIA Kaplan-Meier data given in the TE appendices we believe that this is likely to be valid. This suggests that the selected models are appropriate, our preference being for the analyses excluding CTD (results in TE Appendix B). We also agree with their justification for the choice of distribution (Gompertz for OS and Gamma for PFS). We note that for PFS, LOOIC for both Gamma and Weibull are very similar, suggesting either would be suitable. The company stated they selected the Gamma distribution for PFS, but their economic model actually uses the Weibull, which is line with the EAG preference for

Table 1: Parametric NMA (including CTD) LOOIC, OS & PFS

Distribution	LOOIC (OS)
Exponential	27079.1
Weibull	27030.2
Gompertz	27024.6
Loglogistic	27147.6
Lognormal	27316.6

Distribution	LOOIC (PFS)
Exponential	27763.2
Weibull	27656.5
Gompertz	27711.6
Loglogistic	27717.2
Lognormal	No convergence

Full exploration of the parametric NMA (excluding CTD in the network, Table 2) approaches show that selections of Gompertz for OS and Gamma for PFS are the best fitting curves, based on the lowest LOOIC.

Table 2: Parametric NMA (excluding CTD) LOOIC, OS & PFS

Distribution	LOOIC (OS)
Exponential	21710.94
Weibull	21679.72
Gompertz	21661.93
Loglogistic	21771.26
Lognormal	21900.14
Gamma	21684.03

Distribution	LOOIC (PFS)
Exponential	21553.5
Weibull	21460.8
Gompertz	21495.8
Loglogistic	21541.4
Lognormal	21698.5
Gamma	21458.6

Table 3 presents the summary results from multiple approaches that have been explored for the indirect comparison vs BMP.

Table 3: Summary results when using parametric NMA to compare vs BMP (excluding CDF treatments)

extrapolation. We note that the ICER for DLd vs BMP from the parametric NMA is slightly higher than for the piecewise NMA used the EAGs basecase [redacted] compared with [redacted] (companys analyses in Table 3, this document). The EAGs preferred base-case may therefore slightly favour DLd for the comparison with BMP and BCd. The comparison with Ld is unaffected.

The relevant comparisons for decision-making is a matter for the committee to determine.

<table>
<tr>
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<td>
<table>
<tr><th>Comparison vs BMP</th><th>ICER vs BMP</th><th>BMP dominated by Ld?</th></tr>
<tr><td>Parametric NMA (excluding CTD), OS: Gompertz, PFS: Gamma</td><td>[redacted]</td><td>Dominated by Ld</td></tr>
<tr><td>Parametric NMA (including CTD), OS: Gompertz, PFS: Weibull</td><td>[redacted]</td><td>Dominated by Ld</td></tr>
<tr><td>Unanchored indirect comparison (ALCYONE IPW, OS: Gompertz, PFS: Weibull)</td><td>[redacted]</td><td>Dominated by Ld</td></tr>
<tr><td>Parametric NMA (excluding CTD), OS: Gompertz
Piecewise NMA, PFS: Weibull</td><td>[redacted]</td><td>Dominated by Ld</td></tr>
</table>
It can be seen from multiple approaches for the indirect comparison:

1) When using the MAIA data to inform the comparison of DLd vs Ld, Ld dominates BMP, thus supporting the conclusion that the DLd vs Ld is the most relevant ICER for decision making
2) ICERs vs BMP are largely consistent with the base case analysis
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<tr>
<td>Key Issue 6 Is it reasonable to assume equivalence between BMP</td>
<td>No</td>
<td>As noted above, the comparison of DLd vs Ld, using the direct MAIA evidence, remains the focus for Committee Decision making.

A comprehensive approach has been taken for the indirect comparison of DLd versus bortezomib in combination with an alkylating agent and corticosteroid. In addition to providing a comparison vs BMP (Key Issue 4 and 5), BCd is an alternative bortezomib-based triplet treatment which is used in UK clinical practice. However, BCd is not licensed for use in this population and the clinical SLR identified no randomised evidence</td>
<td>The EAG considers none of the approaches comparing BMP and BCd to be robust and agree with the company that this is an unresolvable uncertainty. However, whilst confidence intervals crossing 1 do not rule out equal efficacy, they do not demonstrate equal efficacy. The confidence interval for PFS from the MAIC only just contains 1, suggestive of a potential PFS advantage for BCd. For this reason, the EAG felt it relevant to present a</td>
</tr>
</table>

and BCd?		investigating BCd. As such, there is an absence of robust high-quality evidence to inform the indirect comparison of BCd with either BMP or DLd. Based on the clinical SLR results, the Jimenez-Zepeda study (Jimenez-Zepeda VH, 2021) represents the most informative observational evidence for BCd. This study demonstrated no statistically significant differences in PFS and OS versus BMP. To further explore the relative efficacy of BCd versus BMP, Janssen conducted a MAIC utilising patient level data from the phase 3 ALCYONE trial. Consistent with the observational evidence, the MAIC results were inconclusive with PFS and OS HRs close to 1 and wide 95% confidence intervals crossing 1 (PFS HR [redacted] and OS HR [redacted]), Appendix D.6.3). Janssen does not consider the MAIC evidence sufficiently robust to incorporate in the economic model. The EAG noted similar concerns regarding the use of Jimenez-Zepeda as a basis for analysis (EAG report, p33) and noted the study was at 'Critical Risk of Bias', concluding 'the study is too problematic to provide any useful evidence and should not be included in any synthesis'. As such, we consider the use of the observational data inappropriate to inform the efficacy for the ICER of DLd vs BCd. We therefore considered results from the MAIC, naïve comparisons from two different observational sources of evidence (Jimenez-Zepeda VH, 2021; Sandecká V, 2021), as well as clinical opinion from 8 English-based clinicians (Janssen), to support the assumption that BMP and BCd are clinically equivalent, as two bortezomib based triplet therapies (Section B.2.9.3 of company submission). In addition to the published RWE studies (Sandecká V, 2021; Jimenez-Zepeda VH, 2021), Janssen note that the results from the NHS Digital National Cancer Registration and Analysis	scenario based on the HRs obtained from the MAIC. We acknowledge these results may be biased, but so too may the results from assuming BCd has equally efficacy to BMP. Hence, we prefer the MAIC estimate, which also better reflects our uncertainty in estimating the comparison (rather than assuming the HR is exactly 1 – i.e. equivalence). The relevant comparisons for decision-making is a matter for the committee to determine.

		Service (NCRAS) (Section B.2.9.3 of Company Submission) support the conclusion of clinical equivalence between BMP and BCd. Whilst there is no one source of evidence which unequivocally demonstrates clinical equivalence, taken together, there is consistency in the totality of evidence which supports clinical equivalence of the bortezomib based treatments. With the current evidence base, we suggest that a robust comparison vs BCd is an unresolvable uncertainty. The clinical comparison of BMP vs DLd represents a reasonable proxy for the clinical effectiveness of bortezomib based triplet treatments, as per the NICE scope. Regardless, given that Ld dominates all other treatments in all scenarios explored, the comparison of DLd vs Ld, using the direct MAIA evidence, remains the focus for Committee Decision making.	
Key Issue 8 Which are the most appropriate parametric models for PFS, OS, and TTD for	YES	**For DLd OS, given the similarity in survival outcomes, Janssen acknowledge that both Exponential and Gompertz are plausible outcomes.** **For DLd TTD, the Generalised Gamma and Gompertz have similarly good statistical fit for AIC and BIC to the Exponential. The observed MAIA data supports an increasing divergence between PFS and TTD over time, which would be inconsistent with the EAG's selection of the Exponential TTD, which represents an extreme scenario.** The EAG prefer to model BMP using results from the NMA therefore our response to Key Issue 8 is focussed on consideration of appropriate parametric survival models for DLd and Ld. **<u>PFS & OS</u>**	For TTD there is very little difference in model fit between the Exponential, Gompertz, and Generalised Gamma curves, however the ICER is sensitive to the choice of curve due to differences in extrapolations. All fitted curves demonstrate a reducing HR over time for TTD vs PFS and are consistent with the HRs reported in Table 5. Whilst there is a trend for the HR reducing over time in Table 5, there is a high level of overlap of the confidence intervals, and the confidence interval in the final year is very wide. How the HR for TTD vs PFS changes

<table>
<tr>
<td>DLd, Ld, and BMP?</td>
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<td>As noted by the EAG, ‘The ICER for the comparison DLd vs Ld was robust to choices of parametric curve for OS and PFS’ (EAG report, page 18). Indeed, for OS, the EAG’s preferred selection of Gompertz results in very similar long-term survival estimates for DLd as the Exponential used in the Company base case, with less than a 2-month difference in the mean predicted OS over the time horizon of the model (Gompertz mean=115.1 months, Exponential mean=116.7 months).

Given the similarity in long-term outcomes, and comparability of statistical fit, Janssen consider that both Exponential and Gompertz are clinically plausible selections. Table 4 provides a comparison of the ICER assuming an Exponential and Gompertz distribution for DLd OS:

<u>Table 4: Base case ICERs with DLd OS Gompertz and Exponential</u>
<table>
<tr><th>Scenario</th><th>ICER vs Ld, excluding CDF treatments (with PAS)</th></tr>
<tr><td>Revised company base case (DLd OS Gompertz)</td><td>[redacted]</td></tr>
<tr><td>Revised company base case (DLd OS Exponential)</td><td>[redacted]</td></tr>
</table>

The comparability of long-term outcomes and stability of the ICER across different OS curve selections reflects maturity of the trial data with over 5-years median follow-up from MAIA and provides reassurance regarding the limited extent of residual uncertainty.

<u>TTD</u></td>
<td>beyond 6 years is therefore unclear. Further follow-up from MAIA may help to resolve this uncertainty.</td>
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		For DLd TTD, the EAG explore scenarios based on statistical fit using: • Generalised Gamma • Gompertz • Exponential The EAG prefer exponential based on the lowest BIC value however Janssen consider the statistical fit for each to be broadly comparable, with exponential and generalised gamma providing an upper- and lower-bound respectively (Latimer, 2011). Arguably, the generalised gamma curve has best statistical (lowest AIC) and visual fit to the observed Kaplan Meier data. On balance, however, Janssen considers Gompertz the most appropriate curve choice for decision making, sitting comfortably within the clinically plausible range. We do not believe that there is sufficient evidence to consider the exponential curve as the base case; as it sits at an extreme end of the plausible scenarios.	

		Figure 1: DLd PFS and TTD  To further inform the selection of TTD curve, Janssen explored the relationship between TTD and PFS observed in MAIA (Figure 1). Specifically, Janssen conducted a piecewise Cox analysis splitting the data into equal intervals of 12-months. Results from this analysis (Table 5) demonstrate a consistent trend, with the HR point estimate decreasing over the trial follow-up period. **Table 5: Piecewise Cox model analysing relationship between DLd PFS and TTD**	

Period (MAIA)	HR [95%CI]	P-value
<=12 months follow up	[redacted]	[redacted]
>12 months - <=24 months	[redacted]	[redacted]
>24 months - <=36 months	[redacted]	[redacted]
>36 months- <=48 months	[redacted]	[redacted]
>48 months - <=60 months	[redacted]	[redacted]
>60 months- <=72 months	[redacted]	[redacted]

HR= hazard ratio

Whilst the confidence intervals overlap, the point estimates demonstrate a consistent decreasing trend. This observation is also clinically plausible as, for many patients, the option to stop treatment prior to progression is likely to be after a period of sustained deep response (e.g. sustained CR, or MRD negativity) or treatment fatigue and build-up of unacceptable toxicity. Moreover, the expectation that some patients may stop treatment prior to progression is aligned with MM patient preferences, where patients highlight longer treatment-free periods as the most valued treatment attribute (Myeloma UK, 2019).

Given the observed trend in MAIA, it is reasonable to expect that the difference between PFS and TTD would continue to widen over time. Janssen note that this does not support selection of Exponential for DLd TTD which tracks broadly parallel to PFS. Adherence is also likely to be lower in the real-world setting, where patients are not actively monitored as

		part of a clinical trial. In this respect, the difference between TTD and PFS may be expected to be even larger. As such, for Committee decision making, Janssen consider the Gompertz to represent a reasonable estimate for DLd TTD, given this is within the upper plausible range (Exponential) and lower plausible range (Generalized Gamma), and is supported by the observed MAIA relationship between PFS and TTD.	
Key Issue 9 Would the treatment effect for OS be maintained for a patient's lifetime or would there be waning	YES	Janssen acknowledges the inherent uncertainty with long-term survival estimates in the context of modelling a lifetime time horizon. Our understanding from the Technical Engagement call is that the EAG have included assumptions for OS treatment waning in their base case as a way of exploring the uncertainty. However, the inclusion of an OS treatment waning effect solely for DLd is not evidence-based, inconsistent with prior NICE appraisals for this indication (TA587 and TA228), and not supported by clinical understanding of disease biology. Our position is supported by: 1) Understanding the importance of depth of response in MM and the biological plausibility of waning in this disease setting 2) Observed MAIA data, indicating an OS benefit increasing over time 3) Lack of face validity for applying an OS waning assumption solely to the DLd arm Further details for each of these points are provided below. **1) <u>Depth of response and biological plausibility of a waning of OS benefit over time</u>**	1. Depth of Response. We agree with the company that MAIA has demonstrated a survival advantage for DLd which has persisted and widened with increasing follow-up, and that depth of response is a plausible mechanism driving this survival benefit. There are however few individuals towards the end of the survival curve meaning that we are uncertain whether this trend will continue into the longer term. The results from POLLUX (Fig 2) also show a widening of the curves until around 6.5years followed by a small attenuation of effect (although again small numbers at the end of the curves). The CASTOR study (Fig 3) also shows curves widening up to 6.5 years. The EAG does not disagree with the assumption that the distance between the curves widen up to around 7 years. However, it is unclear from the data whether this would continue beyond the

of effect?		In MM, achieving deep and sustained responses is recognised as one of the primary goals of front-line treatment, resulting in a fundamental shift in the trajectory of the disease course and long-term outcomes for patients. This was recognised by UKMF in their response to this appraisal and is supported by extensive evidence that deeper responses translate to improved long-term PFS and OS (Lahuerta JJ, 2008; Chanan-Khan AA, 2010; Kapoor P, 2013; Harousseau JL, 2009; Munshi NC A.-L. H., 2017; Munshi, 2019). Results from MAIA demonstrate that patients receiving DLd achieve deeper and longer sustained responses compared with existing standard of care, Ld (Section B.2.6.2 of company submission). A waning of the relative treatment effect is inconsistent with broad clinical consensus regarding the long-term survival benefit conferred by deeper responses. Indeed, the UK Myeloma Forum comment that DLd represents a step change in the management of the condition (Q16a), specifically because DLd 'improves depth of response which correlates with improved survival' (p275 of the Technical Engagement papers). The Minimal Residual Disease (MRD) results from MAIA indicate that the depth of response following DLd treatment allows for long-term disease control. MRD is the most sensitive measure of response currently available. The evidence for the survival benefit of MRD is significant, with a recently published meta-analysis of results from 45 studies (93 publications) finding that outcomes for both PFS (N=8,098) and OS (N=4,297) were significantly improved for MRD-negative patients compared with MRD-positive patients (PFS HR: 0.33; 95% CI: 0.29, 0.37; OS HR: 0.45; 95% CI: 0.39, 0.51; p<0.001 for both) (Munshi NC A.-L. H., 2020). Specifically in the newly diagnosed ASCT-ineligible subgroup, PFS (HR 0.32; 95% CI, 0.27-0.39; P<0.01) and OS (HR 0.50; 95% CI, 0.42-	observed data or start to attenuate as is perhaps seen in POLLUX (Fig 2). The EAG's base-case assumed that the curves would be extrapolated based on the MAIA data until 12 years (ie a further 5 years beyond the observed data and when most patients have stopped treatment). Waning only starts from this point onwards, and occurs at a slow rate over a period of 7 years. 2. MAIA data. Table 6 shows clearly that there is no survival benefit for the first 2 years, a HR of approx. 0.76 over the period 2- 4 years, then a HR of approx. 0.66 over the period 4-6 years. It is not clear however that the HR would continue to decrease beyond 6 years, as the HR is stable over the 4-6 year period, and the estimates towards the end of the curve are very uncertain. 3. The waning of treatment effect is modelled as a change in the **Hazard Ratio** for DLd relative to Ld. We applied this for the DLd curve **relative to** the Ld curve. So it is not a case of assuming waning for DLd and not Ld. It is a case of assuming waning of the hazard of DLd **relative to** the hazard for Ld. We could have applied the reciprocal of the HR to the DLd curve to bring the Ld curve up towards the DLd curve, but it would have given the same

		0.59; P<0.01) was significantly improved with MRD negativity. In addition, Munshi et al. (2020) report improvements in OS (and PFS) outcomes associated with increasingly stringent MRD sensitivity thresholds with OS most improved with MRD negativity at the sensitivity threshold of 10^{-6} (HR: 0.26; 95% CI: 0.13, 0.51; p<0.001). As noted in Section B.2.6.2.10 (Document B), for the DLd group, the MRD negativity rate was approximately three times higher at the 10^{-5} threshold, and approximately four times higher at the higher sensitivity threshold of 10^{-6} . Patients in the DLd group demonstrated significantly higher 'durable MRD negativity' at the sensitivity threshold of 10^{-5}, defined as having MRD negativity for at least one year without a positive result, compared with the Ld group (DLd: [redacted]). Indeed, the current MAIA DLd mortality rate for those patients who achieve MRD negativity is tracking outcomes resembling that seen in the UK general population after five years of follow-up (Figure 23, Document B). As such, an OS waning of treatment effect for DLd is be inconsistent with substantial clinical evidence that deeper responses change the trajectory of the disease course, translate into improved long term outcomes. Studies investigating daratumumab in the relapse setting (POLLUX and CASTOR) provide further evidence of a substantial survival benefit driven by deeper responses after more than 6-years of follow-up, with no indication of an OS waning effect. Indeed, the POLLUX study (Figure 2) provides consistent evidence that the statistically significant and clinically meaningful OS benefit for DLd is driven by deeper responses that can be attributed to daratumumab's unique mechanism of action and synergy with lenalidomide. Specifically, daratumumab's combination of direct and immunomodulatory effects harness the body's own immune system to target and eliminate malignant plasma cells.	results since it is the **difference** between the curves that drive results. In terms of the timing and length of treatment waning, the EAG acknowledges that there is no data on which to base these assumptions. The PFS curve meets the OS curve due to the waning assumptions, but of course the extrapolation of the PFS curve is also uncertain. Similarly for the TTD curves. The EAG has provided scenarios with different waning assumptions to facilitate the committees discussion of the impact of the uncertainty in the long-term relative treatment effect on OS.

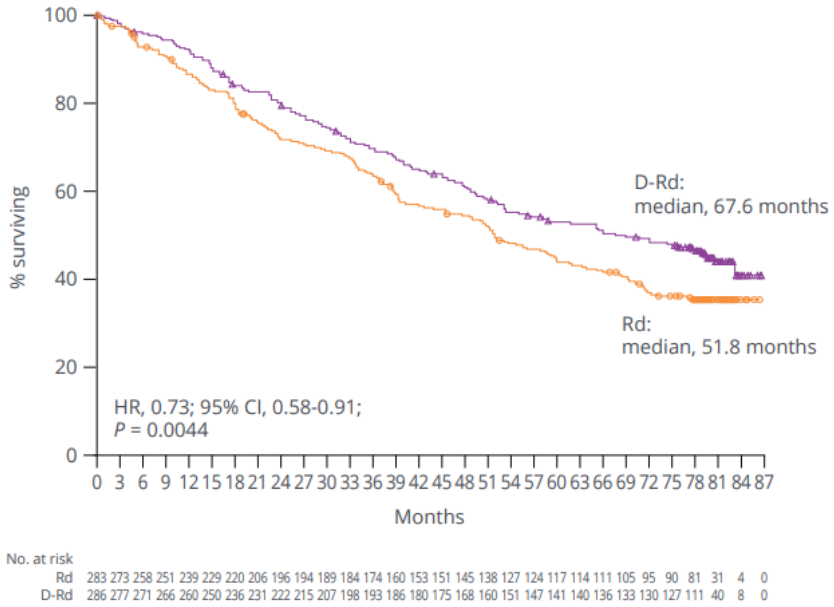
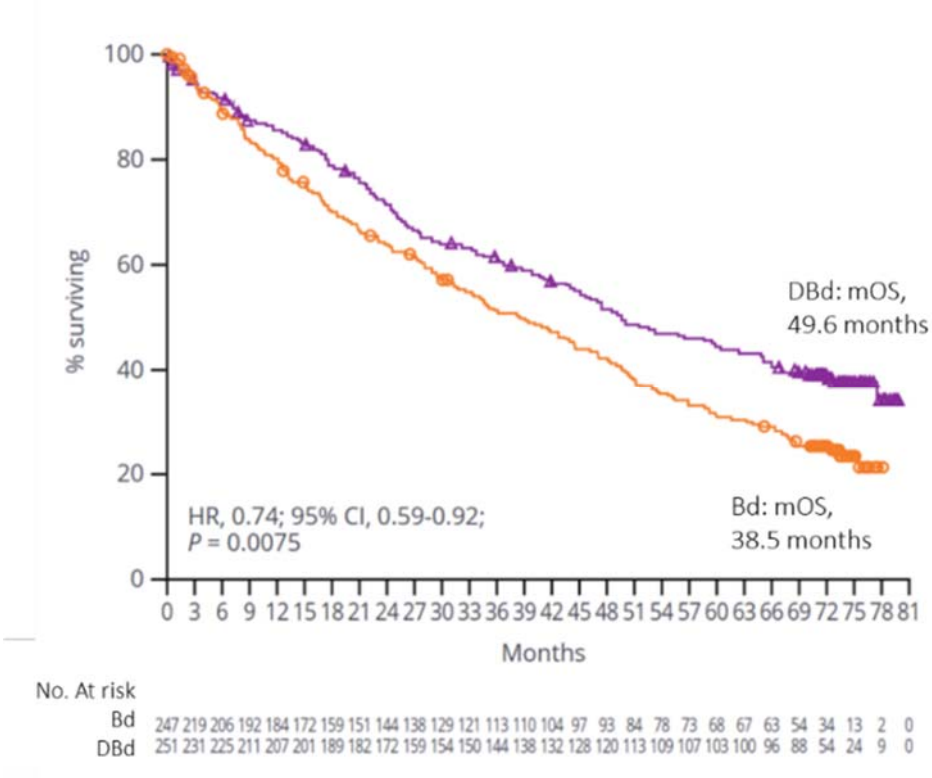
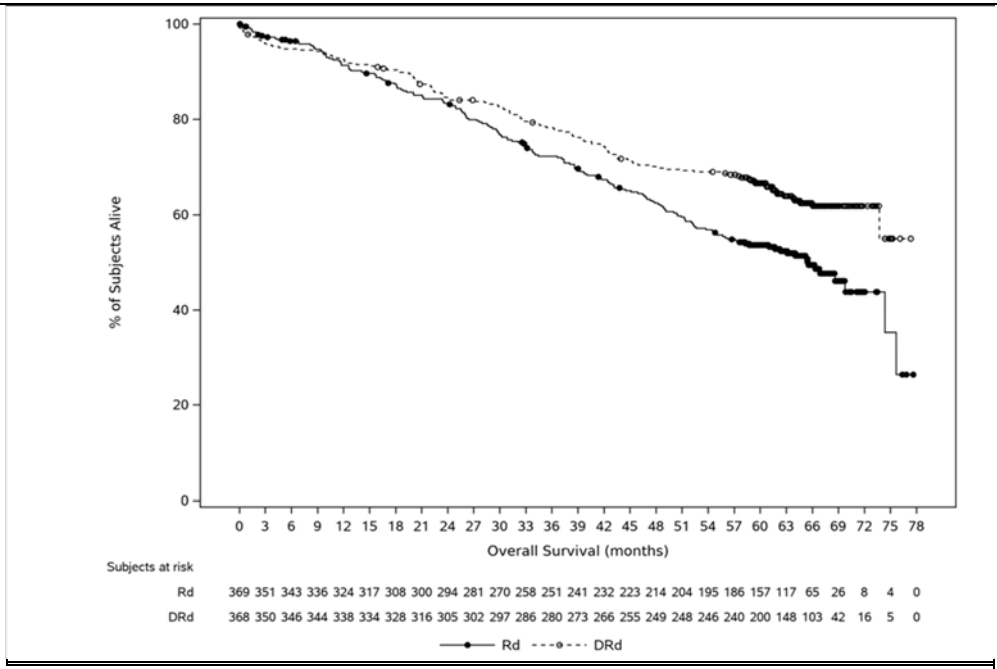
		Figure 2: Kaplan–Meier estimates of OS in the POLLUX trial (ITT population); median follow up 79.7 months (Dimopolous, 2022) **FIGURE 3. OS in the ITT population.**  OS, overall survival; ITT, intent-to-treat; D-Rd, daratumumab plus lenalidomide/dexamethasone; Rd, lenalidomide/dexamethasone; HR, hazard ratio; CI, confidence interval. This is also observed in longer follow up from the CASTOR trial, which demonstrated the efficacy of DBd versus bortezomib with dexamethasone (Bd) in patients with relapsed or refractory multiple myeloma (Figure 3).	

		Figure 3: Kaplan-Meier plot for overall survival among patients treated with DBd or Bd in the CASTOR trial (ITT population); median follow-up: 72.6 months (Sonneveld P, 2022)  Overall, there is significant evidence to support deeper, and more sustained responses with DLd versus Ld. Furthermore, additional follow up from CASTOR and POLLUX (DBd and DLd in the relapsed setting) does	

		not support any OS waning. The inclusion of an OS waning assumption for the DLd arm can therefore be considered a non-evidence based approach, and is in fact inconsistent with the evidence that deeper responses translate into improved long term outcomes. **2) <u>Analyses on the observed MAIA OS data indicates the OS benefit of DLd is improving over time</u>** With over 5 years of follow up available, visual inspection of the observed MAIA KM OS data (Figure 4) shows no evidence of any waning of the DLd OS treatment effect. In contrast to the inclusion of a OS waning assumption, the observed data suggest an improving OS benefit over time; at the end of follow up KM curves are continuing to separate. **<u>Figure 4: Kaplan–Meier estimates of OS in the MAIA trial (ITT population) (data cut-off 21st October 2021) (as per Section B.2.6.25 of Document B)</u>**	



This is supported by an exploratory analysis examining the MAIA OS HR over time, using additional MAIA follow up as it became available. The analysis below considers the estimated OS HR after partitioning the follow up from MAIA into increasing 6 month periods. The analysis shows that, with the inclusion of each additional 6 month follow up from MAIA, the overall OS HR is decreasing, indicating an improving OS benefit for DLd over time (Table 6).

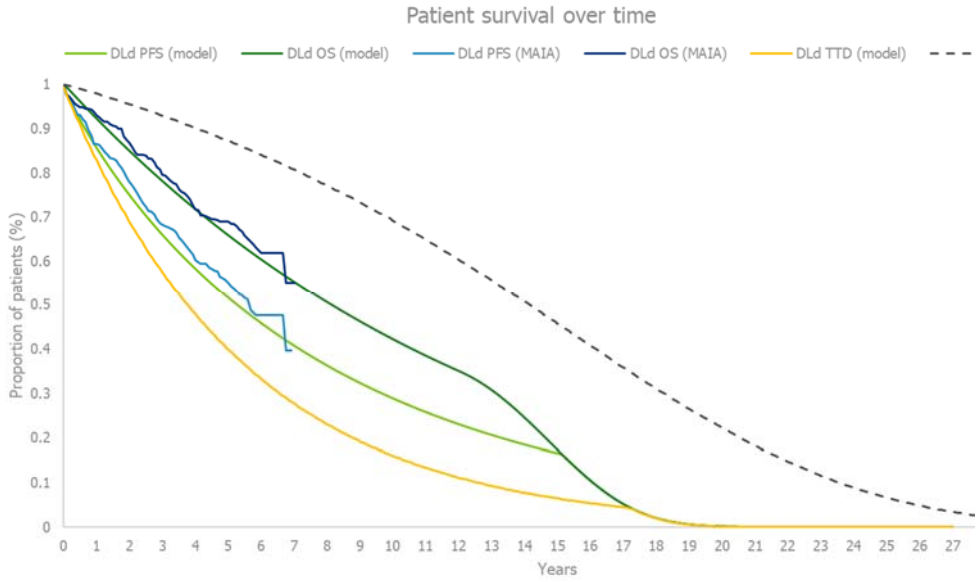
Table 6: Analysis of MAIA OS data: Piecewise Cox of MAIA OS over time

MAIA Follow up duration (months)	*OS HR*	*95% CI*	*P value*
≤6	[redacted]	[redacted]	[redacted]
≤12	[redacted]	[redacted]	[redacted]
≤18	[redacted]	[redacted]	[redacted]
≤24	[redacted]	[redacted]	[redacted]
≤30	[redacted]	[redacted]	[redacted]
≤36	[redacted]	[redacted]	[redacted]
≤42	[redacted]	[redacted]	[redacted]
≤48	[redacted]	[redacted]	[redacted]
≤54	[redacted]	[redacted]	[redacted]
≤60	[redacted]	[redacted]	[redacted]
≤66	[redacted]	[redacted]	[redacted]
≤72	[redacted]	[redacted]	[redacted]
≤78	[redacted]	[redacted]	[redacted]

3) **Applying the OS waning assumption solely to the DLd arm lacks face validity**

The EAG include an OS waning effect only for the DLd OS curve in their preferred assumptions. From a face validity perspective, given that both DLd and Ld are treat-to-progression treatments, any 'waning' of treatment effect would be expected to be similar across arms with the relative

		treatment effect maintained. In addition, we note that no waning of OS benefit was included in the Committee's decision making assumptions in the appraisal of Ld (TA587), which was conducted in the same patient population. As such, including an OS waning effect solely for DLd is inconsistent with this approach in previous NICE decision making. Given that the EAG has not applied any waning to the Ld OS benefit, it would be inappropriate to decrease the OS benefit for DLd in isolation. Reviewing the overall coherency of solely including an OS waning assumption for DLd, we also note the relatively sharp decrease to the DLd OS curve at the time that waning is included. There is also a significant impact on DLd PFS and TTD outcomes, as a result of increasing the HR to 1 over a relatively short duration of 7 years (Figure 5). Intuitively, a longer TTD would correlative to a longer OS. Relative to the company base case, however, the EAG prefer a longer TTD for DLd (exponential), in addition to a shorter OS curve, by including an OS waning assumption. The overall consistency of this logic does not make sense. **Figure 5: EAG base case (OS waning between 12-19 years): DLd patient survival over time (OS: Gompertz, PFS: Weibull, TTD: exponential)**	

			
Key Issue 10 Are the MAIA or ALCYONE health-state utilities	No	The EAG consider the MAIA utilities, as used in the company base case, to have better face validity. Similarly, Janssen also consider the MAIA utilities to be most appropriate and to have better face validity. This is because the MAIA utilities reflect the primary treatments of interest for this appraisal (DLd and Ld), and are also aligned with the efficacy data used for the decision problem. In contrast, utilities from the ALCYONE study were derived from BMP and DBMP treatment arms. The inclusion of DBMP reduces the relevance of the utilities from the ALCYONE trial for the current appraisal, as utility	As stated the EAG agree that the MAIA utilities are more appropriate.

more appropriate?		estimates derived from DBMP (as a quadruplet treatment) would may not be as representative of treatments used in UK clinical practice.	
Key Issue 11 Should costs for dose-reductions using RDIs be included in the model?	No	Janssen consider that RDIs to reflect dose-reductions should be included in the model for decision making. This is aligned with the EAG's perspective, as well as the perspective of the EAG's clinical advisor. In addition, Janssen note that, based on the feedback received from clinical advisors in the EAG report, the current ICER can be considered a conservative upper estimate. This because the EAG's clinical advisors 'felt the proportions dropping dexamethasone and lenalidomide seen in MAIA are likely to be an underestimate compared with clinical practice' (p87 of EAG report). Relative to Ld, if more patients in clinical practice discontinue dexamethasone and lenalidomide, then the total costs for DLd would be expected to decrease, resulting in a decrease to the DLd ICER.	As stated, the EAG and Janssen agree on this point.
Key Issue 12 What is the most appropriate market share of treatme	Yes	Related to Key Issue 7, Janssen consider it is most appropriate to include modelled treatments at 2nd and 3rd line which reflect MM treatments used in the UK treatment pathway conditional to these treatments being routinely commissioned. The EAG agree that the current methodology (using an average across the clinicians elicited distributions) to estimate the % market share for subsequent treatments is as good approach as any. Whilst the EAG state there may be high variation in subsequent treatments used, it is clear from the clinical feedback received (Table 17 of clinical advisory board minutes, Data on File) that almost all patients will receive	We thank Janssen for providing the functionality to explore the impact of the outcome of the CDF reviews on the cost-effectiveness results. However, note that at this point in time we do not know the outcome of the CDF reviews for DBd at 2L or IxaLd at 3L, neither in terms of recommendation nor price.

nts used at 2nd and 3rd line in England?		DBd at 2L following receipt of Ld at frontline. Over half (n=4/7) of the responses indicated that 100% of patients would receive DBd at 2L (average market share of 88%), and thus DBd should be included in the pathway for efficient decision making once routinely commissioned. Given the significance of DBd on the cost effectiveness of DLd, we have therefore provided sensitivity analyses for: 1) Excluding treatments currently on CDF 2) Including DBd (2L), and excluding IxaLd (3L) 3) Including DBd (2L), and including IxaLd (3L) The market shares of 2L and 3L treatments in each of these scenarios are included in the economic model (subsequent treatments tab).	

Additional issues

Table 3 Additional issues from the EAR

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response	EAG Response
Additional issue 1: Pricing of lenalidomide generics	N/A	No	[redacted]	[redacted]

Additional issue 2: EAG's methodology for costing of subsequent treatments	Section 6.1, EAG report (post FAC: P96	No	In the original model submitted by Janssen (May 2022), the costs for subsequent treatments were derived by calculating the weighted costs and weighted time on treatment per line and 1L treatment received separately, and then multiplying these figures together to give the total costs by line of treatment. Time on treatment (ToT) was based on median TTP or PFS reported from clinical trials for each regimen. This can be summarised using the formula: $\sum weights * cost + \sum weights * time$. During the clarification questions process, the EAG requested this formula was updated to calculate the weighted costs and time on treatment line per line simultaneously, using the formula $\sum weights * costs * time$. Janssen agree with the EAGs preferred approach and updated the CEM accordingly in the 22nd July version shared with the EAG. In these calculations, the company first calculates a cost per model cycle for subsequent treatments with a fixed regimen by dividing the total cost for the whole treatment regimen by the median TTP/PFS. This approach spreads the costs of the subsequent treatments with fixed regimens over the TTP/PFS, thus accounting for the fact some subsequent	We thank the company for explaining their formula for the subsequent treatment costs, as it had not been clear to us why different treatment durations were used from the ToT estimates. We agree that time on treatment should not exceed the fixed treatment period and have re-run our base-case correcting for this. We have provided the updated Excel model for our base-case and the results in an Addendum to our report.

			treatment regimens are shorter than the corresponding PFS. The cost per model cycle is then used to inform the costs in the EAGs preferred formula by multiplying the market share, calculated cost per model cycle and ToT for each regimen. However, in their own model version (post FAC), the EAG have implemented a different approach which multiplies the market share, acquisition costs per cycle and ToT for each regimen. Janssen disagrees with this approach because it overestimates the cost per cycle for subsequent treatment regimens with a fixed duration that is shorter than the corresponding median PFS/PD, given this approach applies the cost per cycle for each regimen for the full time spent on treatment. As such, Janssen maintain the updated methodology, as per the model submitted on 22nd July.	

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Key Issue 8	• DLd PFS: exponential • DLd OS: exponential	As per EAG's preferred assumptions: • DLd PFS: Weibull • DLd OS: Gompertz	ICER vs Ld: • Base case before TE: [redacted] • Base case after TE: [redacted] = [redacted]
Key Issue 5	Comparison vs BMP using unanchored indirect comparison	Comparison vs BMP using parametric NMA, excluding CTD (OS: Gompertz, PFS: Gamma)	N/A- no impact on ICER vs Ld
Company's base case following technical engagement (or revised base case) (excluding CDF treatments)	Incremental QALYs vs Ld: [redacted]	Incremental costs vs Ld: [redacted]	Revised base-case ICER (excluding CDF treatments) with PAS = [redacted]

Sensitivity analyses around revised base case

As noted above in Key Issue 7, Janssen have provided the below sensitivity analyses around the revised base case:

Company's base case following technical engagement (or revised base case)	Incremental QALYs vs Ld: [redacted]	Incremental costs vs Ld: [redacted]	ICER vs Ld: Revised base-case ICER with PAS = [redacted]
Scenario including CDF treatments: DBd (2L)	Incremental QALYs vs Ld: [redacted]	Incremental costs vs Ld: [redacted]	ICER vs Ld (with PAS) [redacted]
Scenario including CDF treatments: DBD (2L) and IxaLd (3L)	Incremental QALYs vs Ld: [redacted]	Incremental costs vs Ld: [redacted]	ICER vs Ld (with PAS) [redacted]

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