NICE National Institute for Health and Care Excellence

# Single Technology Appraisal

# Daratumumab monotherapy for treating relapsed and refractory multiple myeloma (CDF review of TA510) [ID3881]

# Committee Papers

NICE National Institute for Health and Care Excellence

**NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE**

**SINGLE TECHNOLOGY APPRAISAL**

# Daratumumab monotherapy for treating relapsed and refractory multiple myeloma (CDF review of TA510) [ID3881]

**Contents:**

The following documents are made available to consultees and commentators:

The **final scope** and **final stakeholder list** are available on the NICE website.

1. **Company submission summary** 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. **Evidence Review Group report** prepared by BMJ Group
5. **Evidence Review Group report – factual accuracy check**
6. **Public Health England Study Report**
7. **Technical engagement response from company**
8. **Technical engagement responses from consultees and commentators:**
   a. Myeloma UK
   b. UK Myeloma Forum
9. **Evidence Review Group critique of company response to technical engagement** prepared by BMJ Group

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

# Company NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

# Cancer Drugs Fund Review of TA510

# Daratumumab monotherapy for treating relapsed and refractory multiple myeloma [ID933]

# Company evidence submission for committee

**October 2021**

| File name | Version | Contains confidential information | Date |
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| TA510_ID933_daratumumab CDF review | – | Yes | 13th October 2021 |

## Contents

## List of tables

## List of figures

## Abbreviations

| Acronym | Definition |
|---|---|
| ACD | Appraisal consultation document |
| AE | Adverse event |
| ASCT | Autologous stem cell transplantation |
| CDF | Cancer Drugs Fund |
| CEAC | Cost-effectiveness acceptability curve |
| CEP | Cost-effectiveness plane |
| CI | Confidence interval |
| CSR | Clinical study report |
| ECOG | Eastern Cooperative Oncology Group |
| EoL | End of life |
| ESS | Effective sample sizes |
| HR | Hazard ratio |
| ICER | Incremental cost-effectiveness ratio |
| IMiD | Immunomodulator |
| KM | Kaplan-Meier |
| MAIC | Match-adjusted indirect comparison |
| NE | Not estimable |
| NHS | National Health Service |
| NICE | National Institute for Health and Care Excellence |
| NMB | Net monetary benefit |
| OS | Overall survival |
| PANO+BORT+DEX | Panobinostat plus bortezomib and dexamethasone |
| PAS | Patient Access Scheme |
| PFS | Progression-free survival |
| PHE | Public Health England |
| PI | Proteasome inhibitor |
| POM+DEX | Pomalidomide plus dexamethasone |
| PSA | Probabilistic sensitivity analysis |
| QALY | Quality-adjusted life year |
| rrMM | Relapsed and refractory multiple myeloma |
| SACT | Systemic Anti-Cancer Therapy |
| SmPC | Summary of product characteristics |
| TEAE | Treatment-emergent adverse event |
| TTD | Time-to-discontinuation |
| UK | United Kingdom |
| WTP | Willingness-to-pay |

# Cancer Drugs Fund review submission

## A.1 Background

Daratumumab monotherapy is recommended for use within the Cancer Drugs Fund (CDF) under the managed access agreement for the treatment of adult patients with relapsed and refractory multiple myeloma (rrMM) after three previous therapies (including a proteasome inhibitor [PI] and an immunomodulator [IMiD]), and whose disease has progressed on last therapy.

Incremental cost-effectiveness ratios (ICERs) presented to the committee included a patient access scheme (PAS) [redacted]

Despite uncertainties in the evidence at time of initial appraisal, the committee concluded that daratumumab had the potential to be cost effective versus its two comparators, pomalidomide plus dexamethasone (POM+DEX) and panobinostat plus bortezomib plus dexamethasone (PANO+BORT+DEX). [redacted]

As outlined in the Terms of Engagement (ToE) (1), the committee's key uncertainties were around whether daratumumab was more effective than current options within the NHS. This was due to single arm trials, the patient numbers on the licensed dose of daratumumab, immature overall survival (OS) data, differences in populations between and generalisability of MMY2002 and GEN501 trials, and uncertainty in the match-adjusted indirect comparison (MAIC).

Single arm trials are used in areas of highest unmet clinical need where there is no efficacious standard of care available to patients. Where there is a lack of clinical equipoise, it is unethical to randomise patients to suboptimal care, and thus single arm trials are necessary to assess the benefit of promising therapies. Whilst single arm trials do pose a challenge in terms of deriving robust comparative effectiveness estimates, this uncertainty is inherent and often unresolvable in end-of-life cancers with small patient numbers, such as at fourth line in rrMM.

As noted in the ToE (1), the committee acknowledged that uncertainty would remain about the relative effectiveness of daratumumab but felt that data collected through the Systemic Anti-Cancer Therapy (SACT) dataset would enhance the evidence for daratumumab and could resolve the key uncertainties. Indeed, SACT data (2) have been able to validate the generalisability of MMY2002 to UK clinical practice. However, no further data are collected or available for comparator treatments through the SACT dataset meaning comparative effectiveness must still rely on MAICs, now updated with more mature trial evidence. Residual uncertainty in the analyses must therefore be managed through appropriate scenario and sensitivity analysis to aid decision-making.

Of note, PANO+BORT+DEX is no longer a relevant comparator in this setting in the UK, as corroborated by expert clinical opinion (3), and confirmed through recent committee conclusions in TA658 and ID1510 (4, 5). Nevertheless, analyses versus PANO+BORT+DEX have still been presented in this CDF review to adhere to the NICE scope.

In this setting, daratumumab monotherapy meets NICE's end-of-life criteria. The life expectancy for patients with rrMM who have progressive disease despite prior treatment with a PI and an IMiD does not exceed 12 months, as demonstrated through RWE (6-11). Additionally, survival models presented herein, based on the updated MAICs, have shown that daratumumab prolongs survival by [redacted] months versus POM+DEX and by [redacted] months versus PANO+BORT+DEX.

The updated analyses presented in this CDF review demonstrate that daratumumab is a highly cost-effective use of NHS resources. [redacted] and therefore would be considered cost-effective at any willingness-to-pay (WTP) threshold. Janssen recognises that pomalidomide and panobinostat have confidential PASs in place in the UK, however additional threshold analyses have shown that even when these therapies are discounted by 100%, daratumumab monotherapy remains a cost-effective use of NHS resources at a WTP of £50,000 per QALY.

## A.2 Key committee assumptions

The company submission is generally consistent with committee-preferred assumptions as set out in the terms of engagement (1), with differences outlined in Table 1.

***Table 1: Key committee assumptions set out in the terms of engagement***

| Area | Committee-preferred assumptions | Rationale if different from committee-preferred assumptions |
|---|---|---|
| Population | Adults with relapsed or refractory multiple myeloma who have had three previous treatments including a proteasome inhibitor and an immunomodulator | As per committee-preferred assumption |
| Comparators | The company should present clinical and cost-effective evidence for daratumumab compared to pomalidomide plus dexamethasone and panobinostat plus bortezomib plus dexamethasone | As per committee-preferred assumption<br>• PANO+BORT+DEX is not used at fourth line in NHS clinical practice for patients with heavily pre-treated and highly refractory multiple myeloma. This has been validated by UK clinicians and confirmed in Committee conclusions within TA658 and ID1510 (4, 5); however, Janssen have maintained PANO+BORT+DEX as a comparator to meet committee-preferred assumptions in this CDF review |
| Generalisability of the trials | The company should use the data collected by SACT to test the generalisability of the trial data | As per committee-preferred assumption |
| Subsequent treatments | The company should use data collected via SACT to assess whether subsequent therapies are used in practice | As per committee-preferred assumption |
| Relative effectiveness | The company should use SACT data to inform the matching in the MAIC and the generalisability of the results | As per committee-preferred assumption:<br>• Janssen has conducted a MAIC of SACT data versus MMY2002, adjusting for the differences in available baseline characteristics, to validate the comparability of real-world and trial outcomes<br>• The new company base case utilises updated MAICs based on the MMY2002 trial only, as MMY2002 is considered reflective of UK clinical practice and closely matches the marketing authorisation (2) |

| Area | Committee-preferred assumptions | Rationale if different from committee-preferred assumptions |
|---|---|---|
| | | • Janssen has leveraged SACT data to validate generalisability of the new company base case; however, SACT data cannot be used to inform a MAIC in the absence of individual patient data |
| Proportional hazards | The company should demonstrate whether the proportional hazards assumption holds | As per committee-preferred assumption |
| Modelling of OS and PFS | The company should use the SACT data to validate the long-term survival extrapolations as well as data collected through the Early Access Programme | As per committee-preferred assumption:<br>• SACT data are utilised to validate the long-term survival extrapolations in this CDF review<br>• As discussed with NICE and the ERG, OS data are not available from the EAP (MMY3010) |
| Utility values | The company should use the utility values presented during the original appraisal | As per committee-preferred assumption |
| Costs of treatment in the model | The company should use SACT to explore the most appropriate previous and subsequent therapies and adjust the treatment effect and costs appropriately | As per committee-preferred assumption<br>• SACT data have been used to inform subsequent therapy costs. No adjustment to effectiveness in the new company base case is warranted given the comparability of SACT and MMY2002 OS outcomes (Section A.8.1 ). |
| Most plausible ICER | The committee agreed that daratumumab demonstrated plausible potential to be cost-effective if its clinical benefit was as the company suggested | As per committee-preferred assumption |
| End of life | Committee could not conclude on whether daratumumab met the end-of-life criteria | • Daratumumab monotherapy, used at fourth-line for patients with rrMM, meets NICE's end-of-life criteria. The life expectancy for patients with rrMM who have progressive disease despite prior treatment with a PI and an IMiD does not exceed 12 months, based on RWE (6-11), and updated analyses have shown that daratumumab prolongs survival by [redacted] months versus POM+DEX and by [redacted] months versus PANO+BORT+DEX (Section A.13 ). |

Source: NICE (2021) (1)

Abbreviations: EAP, Early Access Programme; EoL, end-of-life; ICER, incremental cost-effectiveness ratio; IMiD, immunomodulator; MAIC, matching-adjusted indirect comparison; OS, overall survival; PANO+BORT+DEX, panobinostat plus bortezomib plus dexamethasone; PFS, progression-free survival; PI, proteasome inhibitor; POM+DEX, pomalidomide plus dexamethasone; rrMM, relapsed and refractory multiple myeloma; SACT, Systemic Anti-Cancer Therapy.

## A.3 Other agreed changes

In addition to the changes outlined in Table 1, the following updates have been made to the model:

- Progression-free survival (PFS) and time-to-discontinuation (TTD) have been updated in line with the updated sources of daratumumab data for overall survival (OS) (see Section A.8.1 ).
- The updated summary of product characteristics (SmPC) includes daratumumab as an 1,800 mg subcutaneous injection, therefore daratumumab administration, dose, and adverse events (AEs) have been updated to reflect this change in clinical practice (see Sections A.8.2 and A.8.3 ).
- All analyses conducted include the current PAS [redacted]
- Costs have been updated in the model to reflect the latest data available or by inflating costs to 2021 prices (see Appendix J).
- An adjustment to the OS curve has been added to prevent the probability of death from falling below that of the general population (Section A.8.1 ).

## A.4 The technology

A summary of daratumumab is provided in Table 2. The only changes to the SmPC of relevance to this indication are the method of administration and dosage.

***Table 2: Technology being reviewed***

| | |
|---|---|
| **UK approved name and brand name** | Daratumumab (Darzalex®) |
| **Mechanism of action** | Daratumumab is a monoclonal antibody that binds to CD38, a cell-surface protein, resulting in tumour cell death by immune-mediated actions and apoptosis |
| **Marketing authorisation/CE mark status** | Marketing authorisation was granted by the EMA on the 20th of May 2016 (13) |
| **Indications and any restriction(s) as described in the SmPC** | The licensed indication for daratumumab monotherapy is for the treatment of adult patients with rrMM, whose prior therapy included a PI and an IMiD and who have demonstrated disease progression on the last therapy (13) |
| **Method of administration and dosage** | • Daratumumab monotherapy is recommended at a dose of 1,800 mg (15 ml, 120 mg per ml) via subcutaneous injection administered over approximately 3–5 minutes (13)<br>• Daratumumab monotherapy is also available via intravenous infusion at a dose of 16 mg/kg (focus of original submission (14))<br><br>Both doses/methods of administration are administered according to the following dosing schedule (13):<br>• Weeks 1–8: weekly<br>• Weeks 9–24: every two weeks<br>• Weeks 25 onward until disease progression: every four weeks<br><br>Subcutaneous injection is widely used in the UK due to its convenience and favourable tolerability profile (15), [redacted] |
| **Additional tests or investigations** | An additional resource usage unique to daratumumab is a requirement for a blood test to be carried out before initiation of therapy in order to type and screen patients for antibodies, since daratumumab is known to interfere with the indirect antiglobulin test (13) |
| **List price and average cost of a course of treatment** | List price (12): £4,320 per 1,800 mg solution for injection<br>• Cost per cycle: £2,246.40<br>• Cost per course: £32,724† |
| **Commercial arrangement (if applicable)** | [redacted] |
| **Date technology was recommended for use in the CDF** | March 2018 |
| **Data collection end date** | 16th November 2020 (SACT) (2) |

Source: EMA (2021) (13) and NICE (2018) (14)
†Cost per course assuming time to discontinuation as in the cost-effectiveness model.
Abbreviations: CDR, Cancer Drugs Fund; EMA, European Medicines Agency; IMiD, immunomodulator; NHS, National Health Service; PAS, patient access scheme; PI, proteasome inhibitor; rrMM, relapsed and refractory multiple myeloma; SACT, Systemic Anti-Cancer Therapy; SmPC, summary of product characteristics; UK, United Kingdom.

## A.5 Clinical effectiveness evidence

The MMY2002 trial (16) is the primary source of clinical effectiveness evidence for this CDF review, with supportive evidence provided by the GEN501 trial (17, 18) and the SACT real-world data (2). A summary of primary and supportive clinical effectiveness evidence is presented in Table 3.

At the time of the final appraisal document (FAD), integrated data from the MMY2002 and GEN501 trials were available for a median follow-up of 31.3 months (data cut-off of 18th November 2016). Details of the MMY2002 study can be found in Document B (ID933), Section 4.3.1 (pages 65–67). Details of the GEN501 study can be found in Document B (ID933), Section 4.3.2 (pages 68–69).

Final analyses are now available for both MMY2002 (data cut-off of 30th May 2017) and GEN501 (data cut-off of 31st March 2017) and results are provided in Section A.6.1 and Appendix E (16) and Section A.6.2 and Appendix F **Error! R eference source not found.** (18), respectively.

Consistent with the original submission, data presented from MMY2002 and GEN501 in this CDF review are focused on the licensed dose for intravenous daratumumab of 16 mg/kg. As mentioned in Table 2, daratumumab monotherapy is now licensed and available via subcutaneous injection at a dose of 1,800 mg (15 ml, 120 mg per ml) and use of this formulation now represents NHS clinical practice (13). Non-inferiority has been demonstrated between subcutaneous and intravenous daratumumab in an ongoing, multi-centre, open-label, non-inferiority, randomised, Phase 3 trial (COLUMBA) (15). As agreed with NICE and the ERG, the new company base case utilised subcutaneous daratumumab to ensure analyses are reflective of current UK practice. The COLUMBA trial was also used to inform AE data in the economic model, but not OS as the data were immature at time of CDF review (15). Data from the Early Access Programme (EAP) support the acceptable safety profile of daratumumab monotherapy (11) and do not warrant inclusion within the updated economic model.

During the period of managed access between 17th January 2018 and 16th November 2020, observational data were collected for daratumumab via the SACT dataset (2) to support generalisability of results from the MMY2002 trial, since this trial was considered most reflective of UK practice at time of the FAD. A snapshot of SACT data

was taken on 1st May 2021 and made available for analysis on 7th May 2021; this includes SACT activity up to 31st January 2021. Public Health England (PHE) has provided a summary of the SACT data collected, which includes treatment duration and OS for patients treated with daratumumab (Section A.6.3 and Appendix G**Error! R eference source not found.**) (2).

***Table 3: Sources of clinical effectiveness evidence***

| Study title | MMY2002 (primary evidence)† (16) | GEN501 (supportive evidence)‡ (18) | SACT data cohort study (2) (supportive evidence) |
|---|---|---|---|
| **Study design** | Phase 2, multicentre, open-label, single arm, two-part study | Phase 1/2, multicentre, open-label, single arm, two-part study¶ | Real-world evidence collection via the SACT database§ |
| **Population** | Patients with relapsed and refractory multiple myeloma that have previously been treated with a proteasome inhibitor and an immunomodulatory agent, and who have demonstrated disease progression on the last therapy. | Part 2: Patients with relapsed and refractory multiple myeloma whose disease was relapsed and refractory to two prior lines of cytoreductive therapies and without further established treatment options. | Patients who were eligible for Cancer Drugs Fund funding of daratumumab for previously treated MM from 17th January 2018 to 16th November 2020 in NHS England's Blueteq® database |
| **Intervention(s)** | • Group A: Daratumumab 16 mg/kg††,‡‡ Cycles 1 and 2: Days 1, 8, 15, and 22 (weekly), Cycle 3 to 6: Days 1 and 15 (every other week), and Cycles 7+: Day 1 (every 4 weeks)<br>• Group B: Daratumumab 8 mg/kg††,‡‡,¶¶ Cycle 1+: Day 1 (every 4 weeks) | • Part 1: 10 dose levels of daratumumab were sequentially evaluated: 0.005, 0.05, 0.10, 0.50, 1, 2, 4, 8, 16, and 24 mg/kg<br>• Part 2: based on the dose levels established in Part 1†,‡‡ | Daratumumab at licensed dose (16 mg/kg or 1,800 mg solution for injection) |
| **Comparator(s)** | Not applicable | Not applicable | Not applicable |
| **Outcomes collected that address committee's key uncertainties** | • **Overall survival**<br>• Progression-free survival<br>• Safety | • Overall survival<br>• Safety | • Overall survival<br>• Treatment duration |

| Study title | MMY2002 (primary evidence)† (16) | GEN501 (supportive evidence)‡ (18) | SACT data cohort study (2) (supportive evidence) |
|---|---|---|---|
| **Reference to section in appendix** | Appendix E | Appendix F | Appendix G |

Source: Janssen (2017) (16, 18) PHE (2021) (2)
**Bold** denotes the outcomes that are incorporated into the model's base-case results.
†Details of the MMY2002 study design can be found in Document B [ID933], Section 4.3.1 (pages 65–67) (19, 20); ‡Details of the GEN501 study design can be found in Document B [ID933], Section 4.3.2 (pages 68–69) (17, 20); ¶Data presented in this appraisal are from Part 2 of the study; §SACT data is supplemented by Blueteq data presented in the PHE SACT 3-year report.; ††Per kg of body weight; ‡‡Both MMY2002 and GEN501 trials evaluated daratumumab monotherapy at two doses: 8 mg/kg and 16 mg/kg. As mentioned in Table 2, daratumumab monotherapy is now recommended at a dose of 1,800 mg (15 ml, 120 mg per ml) via subcutaneous injection. For the purpose of this CDF review, data are provided from MMY2002 and GEN501 for daratumumab at the higher dose (16 mg/kg); ¶¶ During the study, 3 of the 18 patients in the 8 mg/kg group crossed over to the 16 mg/kg group; results for these three patients are included in the 8 mg/kg treatment group and therefore not presented here.
Abbreviations: CDF, Cancer Drugs Fund; DOR, duration of response; ECG, echocardiogram; ECOG, Eastern Cooperative Oncology Group; IMiD, immunomodulatory agent; MM, multiple myeloma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PI, proteasome inhibitor; PS, performance status; SACT, Systemic Anti-Cancer Therapy; TEAE, treatment emergent adverse event; TTP, time to disease progression; TTR, time to response.

## A.6 Key results of the data collection

As agreed with NICE and the ERG, updated data from MMY2002 have been adopted in the new company base case (16). Scenario analyses have also been conducted using SACT data (2) and the pooled MMY2002/GEN501 data set (updated data cuts) (11).

### A.6.1 *MMY2002 data*

At final analysis, after a median follow-up of 36.7 months (range: 0.5–42.3 months), [redacted] patients treated with daratumumab 16 mg/kg had discontinued treatment. The majority of treatment discontinuations ([redacted]) were due to progressive disease. [redacted] patients ([redacted]) discontinued from treatment due to a treatment-emergent adverse event (TEAE). [redacted] patients [redacted] withdrew consent, and [redacted] patients [redacted] discontinued for unspecified reasons (Appendix E**Error! Reference source not f ound.**) (16). Median duration of treatment for patients treated with daratumumab 16 mg/kg was [redacted](range: [redacted]) (16).

**Overall survival**

After a median follow-up of 36.7 months, [redacted] treated with daratumumab 16 mg/kg were still alive. Median OS for these patients [redacted]; however 95% confidence intervals (CI) are now available (final data-cut: 95% CI: [redacted]) (16). The 24-month OS rate was [redacted] (95% CI: [redacted]) and Figure 1 presents the Kaplan-Meier (KM) plot of OS from MMY2002. Detailed results are presented in Appendix E **Error! Reference source not found.** (16).

***Figure 1: Kaplan-Meier curve for overall survival from MMY2002; all treated, 16 mg/kg arm***

Source: Janssen (2017) (16)

### Progression-free survival

Median duration of follow-up was 36.7 months (range: 0.5–42.3 months) in the daratumumab 16 mg/kg group in the MMY2002 trial (21). At the time of the final analysis (30th May 2017), median PFS was [redacted] (95% CI [redacted]) (21) (Table 4).

***Table 4: Progression-free survival from MMY2002 (30th May 2017 final data cut-off)***

| Parameter | Daratumumab 16 mg/kg MMY2002 |
|---|---|
| Analysis set: all treated | [redacted] |
| Number of events (%) | [redacted] |
| Number of censored (%) | [redacted] |
| Median PFS, months (95% CI) | [redacted] |

Source: (22)
Abbreviations: CI, confidence interval; PFS, profession-free survival.

### Safety

No notable differences in the overall AE profile have been observed with increasing durations of follow-up from MMY2002 (Appendix E **Error! Reference source not found.**) (16).

### A.6.2 *GEN501 data*

At final analysis (18), after a median follow-up of 35.3 months (range:1.2–41.8 months) [redacted] of the [redacted] patients ([redacted]) treated with daratumumab 16 mg/kg arm had discontinued treatment. Of these, [redacted] patients discontinued treatment due to progressive disease, [redacted] patients due to physician decision, and [redacted] because of an AE (18). Median duration of treatment for patients treated with daratumumab 16 mg/kg was [redacted] (range: [redacted]) (Appendix F) (18).

**Overall survival**

After a median follow-up of 35.3 months, [redacted] treated with daratumumab 16 mg/kg were still alive. Median OS for these patients was [redacted] (95% CI: [redacted]) and the 24-month OS rate was [redacted] (95% CI: [redacted]). Figure 2 presents a KM plot of OS and detailed results are presented in Appendix F **Error! Reference source not found.** (18).

***Figure 2: Kaplan-Meier curve from GEN501 Part 2 study, all treated, 8mg/kg and 16mg/kg arms†***

[redacted]

Source: Janssen (2017) (18)
†Daratumumab 8 mg/kg is presented alongside the 16 mg/kg dose; however, the focus of this review is daratumumab 16 mg/kg.

**Safety**

No notable differences in the overall AE profile have been observed with increasing durations of follow-up from GEN501; no patients have died due to a daratumumab-

related TEAEs, and no additional safety signals have been identified with long-term follow up (Appendix F) (18).

### A.6.3 *Systemic Anti-Cancer Therapy database*

Observational data have been collected during the period of managed access via the SACT database. The SACT data set provides a large cohort of patients (n=2,301) representative of clinical practice in England, with 2,301 patients being treated with daratumumab via the CDF over 34 months. SACT data demonstrate the real-world efficacy of daratumumab; however, since individual patient data (IPD) are not available from SACT, it is only possible to conduct a naïve comparison between SACT and the relevant comparator trials (2). Thus, as agreed with NICE and the ERG, MMY2002 has been adopted in the new company base case and scenario analyses have been conducted using SACT data.

Analysis of SACT data includes patients with a CDF application from 17th January 2018 to 16th November 2020 and includes SACT activity up to 31st January 2021. In total, 2,503 applications for daratumumab were identified in NHS England and NHS Improvement's Blueteq system (2). Following the exclusion of duplicate applications (n=97), patients who had received daratumumab prior to CDF (n=24), patients who died prior to treatment (n=62), patients who did not receive treatment (n=16), and patients not in SACT (n=3), 2,301 patients were included in the SACT analysis (2). A summary of the key baseline characteristics and treatment status among included patients treated with daratumumab in the SACT dataset compared with MMY2002 is presented in Table 5 (2, 19). Patients included in the SACT analysis were slightly older than those in MMY2002 (median: [redacted] years versus [redacted] years, respectively) and included patients with higher Eastern Cooperative Oncology Group (ECOG) performance status scores than in MMY2002 (2, 19).

***Table 5: Baseline characteristics – SACT database versus MMY2002***

| Characteristic | SACT (2) (N=2,301) | MMY2002 (19) 16 mg/kg arm (N=106) |
|---|---|---|
| Age (years) | | |
| Median (range) | [redacted] | [redacted] |
| Sex | | |
| Female, n (%) | [redacted] | [redacted] |
| ECOG performance status | | |
| 0, n (%) | [redacted] | [redacted] |
| 1, n (%) | [redacted] | [redacted] |
| 2, n (%) | [redacted] | [redacted] |
| 3, n (%) | [redacted] | [redacted] |
| 4, n (%) | [redacted] | [redacted] |
| Missing, n (%) | [redacted] | [redacted] |
| Treatment response | | |
| Relapsed, n (%) | [redacted] | [redacted] |
| Refractory, n (%) | [redacted] | [redacted] |
| Previous stem cell transplant | | |
| No, n (%) | [redacted] | [redacted] |
| Yes, n (%) | [redacted] | [redacted] |

Source: Janssen (2015) (19) PHE (2021) (2)
Abbreviations: ECOG, Eastern Cooperative Oncology Group; NR, not reported; SACT, Systemic Anti-Cancer.

**Subsequent therapies**

In total, [redacted] out of [redacted] patients who discontinued from daratumumab went on to receive a subsequent therapy (Appendix G **Error! Reference source not found.**). M edian time from a patient's last daratumumab cycle to their next treatment was [redacted] (range:[redacted]) (2). The most commonly used subsequent therapies reported by MMY2002 patients compared with the SACT cohort is presented in Table 6.

***Table 6: Subsequent therapies for patients receiving daratumumab 16 mg/kg – SACT database versus MMY2002†***

| Therapy | SACT (2) (N=1,877)‡ n (%) | MMY2002 (20) (N=106) n (%) |
|---|---|---|
| Total number of patients who received subsequent therapy | [redacted] | [redacted] |
| Dexamethasone | [redacted] | [redacted] |
| Pomalidomide | [redacted] | [redacted] |
| Cyclophosphamide | [redacted] | [redacted] |
| Carfilzomib | [redacted] | [redacted] |
| Bortezomib | [redacted] | [redacted] |
| Lenalidomide | [redacted] | [redacted] |

Source: PHE (2021) (2) MMY2002 (20)
†SACT data presents first subsequent therapies and the full data set includes combination therapies, MMY2002 presents components of therapies; ‡Patients who have since ceased treatment with daratumumab.
Abbreviations: SACT, Systemic Anti-Cancer Therapy.

Expert clinical opinion has confirmed that the difference in total subsequent therapy usage between SACT and MMY2002 is expected given real-world patients are slightly older with poorer performance status (3), however these differences have not impacted the comparability of overall outcomes. The clinicians also commented on lenalidomide as a subsequent treatment in the SACT dataset, noting that there were funding restrictions and that it would often have been used prior to daratumumab (3).

**Treatment duration**

Of the 2,301 patients with CDF applications, [redacted] were identified as having "completed" treatment by 31st January 2021 (latest follow up in SACT dataset) (2).[a] Median follow-up time in SACT was 4.3 months (130 days) (2).[b] Median treatment duration for all patients was [redacted](95% CI: [redacted]) ([redacted]) (N=2,300) (2). Table 7 presents treatment duration at 6-, 12-, 18- and 24-month intervals.

A sensitivity analysis was carried out on treatment duration to evaluate a cohort for which all patients had a minimum follow-up of 6 months. Results for treatment duration

[a] Patients are assumed to have completed treatment if they have died, have an outcome summary recorded in the SACT dataset or they have not received treatment with daratumumab in at least 3 months.

[b] Median follow-up time was patients' median observed time from the start of their treatment to their last treatment date in SACT + prescription length.

showed a difference of [redacted](full cohort: [redacted]; sensitivity analysis cohort: [redacted]).

***Table 7: Treatment duration at 6-, 12-, 18- and 24-month intervals – SACT database***

| Time period | Treatment duration, % (95% CI) |
|---|---|
| 6-months | [redacted] |
| 12-months | [redacted] |
| 18-months | [redacted] |
| 24-months | [redacted] |

Source: PHE (2021) (2)
Abbreviations: CI, confidence interval; SACT, Systemic Anti-Cancer Therapy.

***Figure 3: Kaplan-Meier treatment duration (N=2,300) – SACT database***

[redacted]

Source: PHE (2021) (2)
Abbreviations: SACT, Systemic Anti-Cancer Therapy

**Overall survival**

Of the 2,301 patients with a treatment record in SACT, the minimum follow-up was 6.5 months (197 days) from the last CDF application. Median OS was [redacted](95% CI: [redacted]) ([redacted]) (2nd June 2021). Table 8 presents OS at 6-, 12-, 18- and 24-month intervals, and Figure 4 provides the KM curve for OS, censored on 2nd June 2021.

***Table 8: Overall survival at 6-, 12-, 18-, and 24-month intervals - SACT database***

| Time period | OS, % (95% CI) |
|---|---|
| 6-months | [redacted] |
| 12-months | [redacted] |
| 18-months | [redacted] |
| 24-months | [redacted] |

Source: PHE (2021) (2)
Abbreviations: CI, confidence interval; OS, overall survival; SACT, Systemic Anti-Cancer Therapy.

***Figure 4: Kaplan-Meier survival plot (N=2,300) - SACT database***

Source: PHE (2021) (2)
Abbreviations: CI, confidence interval; OS, overall survival; SACT, Systemic Anti-Cancer Therapy

Upon visual inspection, observed OS data from SACT is highly consistent with the observed OS data from MMY2002 (Figure 5). However, in order to validate the comparability of real-world outcomes from SACT and trial outcomes from MMY2002, an MAIC was conducted by adjusting the MMY2002 OS and PFS data[c] for ECOG status, prior autologous stem cell transplantation (ASCT), age and gender (i.e., characteristics available from the SACT 3-year report). Given that PFS data are not available from SACT, treatment duration data were assumed to be a reasonable proxy for PFS (see Section A.8.1 ). Results showed no significant difference between the

[c] Using MAIC methodology; see Section A.7

two data sets for OS (hazard ratio [HR]: [redacted]) and PFS/treatment duration (HR: [redacted]) confirming MMY2002 is generalisable to UK clinical practice. The unadjusted and adjusted MMY2002 OS KMs and the SACT OS KM are presented in Figure 5; the unadjusted and adjusted MMY2002 PFS KMs and the SACT treatment duration KM are presented in Figure 5.

***Figure 5: Daratumumab overall survival data from MMY2002 versus SACT***

Abbreviations: HR, hazard ratio; OS, overall survival; SACT, Systemic Anti-Cancer Therapy.

***Figure 6:Daratumumab treatment duration data from MMY2002 versus SACT***

This analysis therefore validates the appropriateness of maintaining the MMY2002 data within the new company base case, since no IPD are available from SACT to inform an MAIC versus POM+DEX and PANO+BORT+DEX.

## A.7 Evidence synthesis

The MAIC analyses presented in the original appraisal were updated to reflect:

- Additional follow-up data from MMY2002 (Section A.6.1 ) and GEN501 (Section A.6.2 )
- Restriction to MMY2002 only in the base case, with a scenario considering the pooled data set (MMY2002 and GEN501)
- Matching for the most important factors in the base case, with a scenario in which all possible factors are matched for.

Whilst Janssen acknowledges the ERG and Committee feedback at time of the FAD, updated fully adjusted MAICs resulted in effective sample sizes (ESS) of [redacted] (i.e., a [redacted] % reduction in sample size) versus POM+DEX and [redacted] (i.e. a [redacted] % reduction in sample size) versus PANO+BORT+DEX.

As noted in NICE DSU Technical Support Document 18, “when the ESS is markedly reduced, or equivalently the weights are highly variable, estimates become unstable and inferences depend heavily on just a small number of individuals” (23).

Expert clinical opinion was sought to confirm the ranking of key prognostic factors, as well as determining which prognostic factors were essential to adjust for within the analyses (3). Clinical experts confirmed that it was essential to adjust for refractory status to lenalidomide, to bortezomib, and to both therapies. Given that these factors were not available for the comparison versus PANO+BORT+DEX, the number of prior treatments (mean/median, received >2/3) and ISS staging were also considered.

Weighing up the necessity to adjust for as many prognostic factors as possible, whilst managing uncertainty and maintaining a suitably robust ESS, the decision was made to use MAICs adjusted for the key prognostic factors in the new company base case (refractory status, number of prior treatments, ISS staging), and fully matched MAICs were retained for scenario analyses.

The results section from the original appraisal (Document B [ID933], Section 4.10.3.3, pages 125–139) has been replicated and updated in Appendix H; a summary of the hazard ratios from the updated analysis is presented in Table 9. However, independent curves were used in the cost-effectiveness analysis, in line with Committee preferences at the time of the FAD (Section A.8.1 ).

***Table 9: Results of MAIC analyses***

| Comparator | Outcome | Hazard ratio | | |
|---|---|---|---|---|
| | | **Base case: MMY2002 only, matched on key factors** | **Scenario: MMY2002 only, fully matched** | **Scenario: pooled data set, matched on key factors** |
| POM+DEX | OS | [redacted] | [redacted] | [redacted] |
| | PFS | [redacted] | [redacted] | [redacted] |
| PANO+BORT+DEX | OS | [redacted] | [redacted] | [redacted] |
| | PFS | [redacted] | [redacted] | [redacted] |

Abbreviations: OS, overall survival, PANO+BORT+DEX, panobinostat plus bortezomib plus dexamethasone; PFS, progression-free survival; POM+DEX, pomalidomide plus dexamethasone.

## A.8 Incorporating collected data into the model

The starting point for the updated analysis was the '(ID933) Janssen_ Daratumumab_CEM_16122016 (CIC) _SA corrections_base case corrected' model, referred to as the 'original model' throughout this document.

Updates have been made to the following components of the model:

- OS, PFS and TTD curves for daratumumab (Section A.8.1 )
- AE rates for daratumumab (Section A.8.2 )
- Acquisition costs for daratumumab (Section A.8.3 )
- Subsequent therapy costs (Section A.8.4 )

All costs have been updated from the original appraisal to reflect the latest available sources or inflated to 2021 prices (Appendix J**Error! Reference source not found.**). F unctionality is included in the updated model to replicate the base-case results presented in the original model.

### A.8.1 *Survival curves*

Following the CDF review period, three alternative sources were available to inform the OS, PFS and TTD curves for daratumumab:

- Pooled MMY2002/GEN501 data set (updated data cut) (11)
- MMY2002 (updated data cut) (16)
- SACT data (2).

Whilst the pooled data set was used to inform daratumumab OS, PFS and TTD in the original submission, at the time of FAD, the committee concluded that MMY2002 was the more appropriate source of data. This was because it was not considered appropriate to pool two studies with differing baseline characteristics, and MMY2002 was deemed more reflective of the daratumumab marketing authorisation. The committee did however question the generalisability of MMY2002 to UK clinical practice.

As such, as agreed with NICE and the ERG, MMY2002 only has been adopted in the new company base case and SACT data has been used to validate generalisability to UK clinical practice. Indeed, OS data from MMY2002 and SACT are similarly mature and highly consistent, as shown in Section, A.6.3 .

Furthermore, since IPD are not available from SACT, it is only possible to conduct a naïve comparison between digitised SACT data and the relevant comparator trials.

This approach has significant limitations and is associated with greater uncertainty than updating the MAICs. Nevertheless, scenario analyses have been conducted in which the daratumumab OS, PFS and TTD is based on digitised SACT data and the pooled data set, respectively.

**Updated match-adjusted indirect comparison**

In the new company base case, the model used MAICs based on MMY2002 only, matching on only the most important factors to model OS and PFS (Section A.7 ). Scenario analyses are presented that use pooled MMY2002/GEN501 data[d], and MAICs adjusting for all possible characteristics. Given that some uncertainty remains in the appropriateness of the proportional hazards assumption, independent curves have been modelled for daratumumab and the comparators; this is aligned with the Committee preferences at the time of FAD (see Appendix H).

Model diagnostics for daratumumab OS and PFS versus POM+DEX and PANO+BORT+DEX, and resultant survival curve extrapolations, are presented in Appendix I. The choice of survival curve extrapolations was validated by UK clinical experts in September 2021 (3). The base-case survival distributions and the rationale for each decision are presented in Table 10. To align with the updated MAICs, daratumumab TTD was also modelled using updated data from MMY2002 only. Model diagnostics for daratumumab TTD are presented in Appendix I**Error! Reference source not found.**.

[d] In the scenario in which the pooled data set is used, TTD was also modelled using the pooled data set.

***Table 10: Base-case survival distributions***

| Outcome | Selected distribution | Rationale |
|---|---|---|
| OS | Weibull | All 6 survival curves were presented to three clinicians during clinical insight meetings in September and October 2021. One clinical expert considered the Weibull curve to be the most clinically plausible in the comparison vs PANO+BORT+DEX, one clinician considered the exponential the most plausible, and one clinician considered them both to be plausible. All clinicians considered the Weibull to be the most plausible in the comparison vs POM+DEX (3).<br><br>The Weibull curve was therefore selected for the model base case. All other distributions are considered in scenario analyses. |
| PFS | Log-normal | The log-normal curve was considered to produce clinically plausible outcomes by two clinicians in the comparison vs PANO+BORT+DEX, and by two clinicians in the comparison vs POM+DEX.<br><br>The log-normal curve was therefore selected for the model base case. All other distributions are considered in scenario analyses. |
| TTD | Log-logistic | All considered TTD curves resulted in similar extrapolations; the distribution from the original submission was therefore retained. |

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival; PFS, progression-free survival; TTD, time-to-discontinuation.

The base-case curves for daratumumab OS and PFS do not cross for each comparison, further supporting the face validity of the survival extrapolations (Figure 7).

***Figure 7: OS and PFS, daratumumab***

Abbreviations: KM, Kaplan Meier; OS, overall survival; PANO+BORT+DEX, panobinostat plus bortezomib and dexamethasone; POM+DEX, pomalidomide plus dexamethasone.

**Systemic Anti-Cancer Therapy data**

Acknowledging that the SACT dataset contributes 2,301 daratumumab-treated patients to the evidence base, a scenario analysis was presented that used digitised SACT KM data to model daratumumab OS and treatment duration. The definition of the treatment duration survival curve in SACT is equivalent to how the TTD survival curve is defined in MMY2002; treatment duration data from SACT are therefore referred to as TTD going forward.

As PFS data were not available from SACT, and PFS is required for the economic model, it was necessary to assume that PFS was equal to TTD. Figure 8 presents a comparison between PFS and TTD in MMY2002; as the KM curves are very similar, it was considered appropriate to also assume equivalence between PFS and TTD in SACT.

***Figure 8: Daratumumab progression-free survival and time to treatment discontinuation data from MMY2002***

Model diagnostics and resultant extrapolations for the survival curves based on digitised daratumumab OS and TD from SACT are presented in Appendix I**Error! R eference source not found.**.

**General population mortality**

The original model has been updated to include an adjustment whereby long-term OS estimates are constrained by general population mortality informed by life tables for England and Wales (24). To ensure face validity of model outcomes, the probability of death in the model is prevented from falling below that of the general population.

### A.8.2 *Adverse events*

The daratumumab SmPC has now been updated to include the option to receive treatment via a subcutaneous injection at a recommended dose of 1,800 mg weekly for Weeks 0–9, every two weeks from Weeks 9–24, then every four weeks thereafter until disease progression. Administration of daratumumab via subcutaneous injection is now most representative of UK clinical practice and therefore acquisition costs (Section A.8.3 ) and AEs have been updated to reflect this change in the new company base case.

As reported by Mateos et al, the AE profile of daratumumab via subcutaneous injection is improved when compared with daratumumab via an intravenous injection (15). As in the original submission, grade ≥3 AEs that occurred in ≥5% of patients in all comparator trials were included in the analyses. In the new company base case, AEs in the daratumumab arm were taken from the subcutaneous injection arm of the COLUMBA trial and are presented in Table 11 (15).

***Table 11: Daratumumab adverse events***

| Adverse event | Proportion of patients |
|---|---|
| Anaemia | 13.1% |
| Neutropenia | 13.1% |
| Thrombocytopenia | 13.8% |
| Lymphopenia | 5.0% |
| Leukopenia | 3.8% |
| Pneumonia | 2.7% |
| Nausea (all grades) | 8.1% |
| Diarrhoea | 0.8% |
| Fatigue | 0.8% |
| Dyspnoea | 0.4% |
| Back pain | 1.5% |
| Hypokalaemia | 0.4% |

Source: Mateos et al (2020) (15)

### A.8.3 *Acquisition costs*

All analyses conducted include the PAS for daratumumab. Drug acquisition costs for daratumumab via subcutaneous injection used in the model are presented in Table 12.

***Table 12: Daratumumab acquisition cost***

| Drug | Dose per unit | Units per pack | Price per pack |
|---|---|---|---|
| Daratumumab (list price) | 1,800mg | 1 | £4,320.00 |
| Daratumumab (PAS price) | | | [redacted] |

Source: BNF (12)
Abbreviations: PAS, patient access scheme.

### A.8.4 *Subsequent therapy costs*

Data from SACT were also used to update subsequent therapy costs in the model as agreed with NICE and the ERG. A total of [redacted]% of patients who had discontinued treatment with daratumumab in the SACT data set received a subsequent therapy in

the SACT dataset, therefore it was also assumed that [redacted]% of patients in each arm of the model received a subsequent therapy.

Only treatments that were used in ≥1% of patients in SACT (N=1,111) were included in the model. In the SACT data set, 30 patients received 'Trial' subsequent therapy; this was not included in the calculations. In the POM+DEX arm, pomalidomide and pomalidomide + cyclophosphamide use was set to 0% as it was assumed that pomalidomide would not follow treatment with POM+DEX. In the PANO+BORT+DEX arm, bortezomib + panobinostat and bortezomib + panobinostat + thalidomide use was set to 0% as it was assumed that panobinostat would not be used following treatment with PANO+BORT+DEX. The remaining subsequent therapies in each arm were re-weighted to sum to 100%. Subsequent therapy proportions used in the model are presented in Table 13.

As discussed in the original submission and validated by clinical expert opinion, treatment with daratumumab may improve the patient's underlying state (given its mechanism of action of utilising the body's own immune system by reducing immunosuppression caused by the malignant cells), meaning they may be more likely to receive subsequent therapies compared to those treated with other agents such as pomalidomide or panobinostat. To capture this differentiation, a scenario was considered in which [redacted]% (i.e. a 20% reduction compared with daratumumab) of patients in the POM+DEX and PANO+BORT+DEX arms receive subsequent therapies.

***Table 13: Subsequent therapy proportions – SACT database***

| Model | Daratumumab | PANO+BORT+DEX | POM+DEX |
|---|---|---|---|
| Pomalidomide | [redacted] | [redacted] | [redacted] |
| Cyclophosphamide | [redacted] | [redacted] | [redacted] |
| Cyclophosphamide + pomalidomide | [redacted] | [redacted] | [redacted] |
| Bortezomib + panobinostat | [redacted] | [redacted] | [redacted] |
| Melphalan | [redacted] | [redacted] | [redacted] |
| Bortezomib + panobinostat + thalidomide | [redacted] | [redacted] | [redacted] |
| Bendamustine | [redacted] | [redacted] | [redacted] |
| Lenalidomide | [redacted] | [redacted] | [redacted] |

Source: PHE (2021) (2)
Abbreviations: PANO+BORT+DEX, panobinostat plus bortezomib and dexamethasone; PFS, progression-free survival; POM+DEX, pomalidomide plus dexamethasone.

Of note, while the new company base case is based on MMY2002, and the distribution of subsequent therapies is informed by the SACT data, adjustment to effectiveness was not warranted given the comparability of SACT and MMY2002 OS outcomes despite differences in subsequent therapies.

## A.9 Key model assumptions and inputs

The key model assumptions and inputs that have been changed in the new company base case following the CDF data collection period are detailed in Table 14**.** All other parameters and assumptions remain unchanged from that submitted to NICE as part of the appraisal consultation document (ACD) response for TA510.

***Table 14: Key model assumptions and inputs***

| Model input and cross reference | Original parameter /assumption | Updated parameter /assumption | Source/Justification |
|---|---|---|---|
| **Source of daratumumab OS, PFS and TTD** | Pooled data from MMY2002 and GEN501 were used to inform MAICs versus POM+DEX and PANO+BORT+DEX for OS and PFS. Fully adjusted curves post-MAIC were used for the daratumumab arm. | MMY2002 trial data only were used to inform the updated MAICs versus POM+DEX and PANO+BORT+DEX.<br>MAICs adjusted for the top 5 prognostic factors.<br>Scenarios are considered using fully adjusted MAICs, data from SACT and the pooled MMY2002/GEN501 data set (Section A.12 ). | As outlined in the FAD, the committee considered MMY2002 to be a more appropriate source of data than the pooled data set.<br><br>OS data from MMY2002 and SACT are similarly mature (Section A.6.3 ) and MMY2002 had significantly longer follow-up than available at the time of the original appraisal (36.7 months compared with 20.7 months, respectively).<br><br>OS data from MMY2002 and SACT are highly consistent (Section A.6.3 ) and therefore data from MMY2002 is considered generalisable to UK clinical practice<br><br>Individual patient data were not available from SACT therefore it is only possible to conduct a naïve comparison between SACT and the relevant comparator trials, which is associated with significant limitations and greater uncertainty than MAICs.<br><br>MAICs adjusted for the top prognostic factors (refractoriness, prior therapies, and ISS) were used in order to balance the necessity to adjust for as many key prognostic factors as possible, whilst managing uncertainty and maintaining suitably robust ESSs. |
| **Survival distributions** | The parametric distributions for OS, PFS and TTD were selected based on a consideration of statistical fit | Distributions were selected for the updated survival curves based on consideration of statistical fit using AIC/BIC, | Virtual clinical insight meetings with UK clinical experts were used to choose the survival extrapolations that produced the most clinically |

| Model input and cross reference | Original parameter /assumption | Updated parameter /assumption | Source/Justification |
|---|---|---|---|
| | using AIC/BIC, visual inspection and clinical plausibility, as informed by expert clinical opinion (3).<br>• OS: Weibull<br>• PFS: Log-normal<br>• TTD: Log-logistic | visual inspection and clinical plausibility as informed by expert clinical opinion in September 2021 (3).<br>• OS: Weibull<br>• PFS: Log-normal<br>• TTD: Log-logistic | plausible survival, considering projected outcomes, visual inspection and statistical fit (3).<br>Other survival curves are considered in scenario analysis (Section A.12 ); all survival curves are presented in Appendix H**Error! Reference source not found.**. |
| **Subsequent therapy costs** | 100% of patients received a subsequent therapy in the daratumumab arm and 55% and 100% of patients received a subsequent therapy in the PANO+BORT+DEX and POM+DEX arms, respectively.<br>The proportions of therapies received were informed by a combination of pooled MMY2002/GEN501 data and clinical opinion. | Subsequent therapies for all comparators are informed by the SACT data set (2).<br>[redacted]% of patients receive a subsequent therapy in all arms.<br>Subsequent therapies from the SACT data set that accounted for ≥1% of all subsequent therapies used (N=1,111) are included in the model.<br>In the POM+DEX arm, pomalidomide use is assumed to be 0, given that pomalidomide would not be expected to be used following POM+DEX.<br>In all treatment arms, bendamustine use is set to 0 given that bendamustine is no longer available on the CDF. | The final 3-year SACT report provided real world data on subsequent therapy use following daratumumab treatment. Data were collected through the NHS England and NHS Improvement Blueteq system on all patients with an application for daratumumab for multiple myeloma in the CDF. These data were therefore considered a more accurate reflection of subsequent therapy use in UK clinical practice than data used in the ACD response model.<br>While the new company base case is based on MMY2002, and the distribution of subsequent therapies is informed by the SACT data, adjustment to effectiveness was not warranted given the comparability of SACT and MMY2002 OS, outcomes despite differences in subsequent therapies. |
| **Daratumumab administration** | 16 mg/kg via IV infusion weekly from Weeks 0–8, | 1,800 mg via subcutaneous injection weekly from Weeks | Daratumumab is now available as an 1,800 mg subcutaneous injection. The new company base case |

| Model input and cross reference | Original parameter /assumption | Updated parameter /assumption | Source/Justification |
|---|---|---|---|
| | every two weeks from Week 9–24, then every four weeks thereafter until disease progression | 0–8, every two weeks from Week 9–24, then every four weeks thereafter until disease progression | has been updated to reflect this change in UK clinical practice (13). |
| **Daratumumab AEs** | Grade ≥3 AEs occurring in ≥5% of patients for treatment comparators were included in the model. Daratumumab AEs were taken from a weighted average of pooled MMY2002/GEN501 data. | Daratumumab AEs were taken from the subcutaneous arm of COLUMBA trial (15). | Data from COLUMBA, as presented by Mateos et al, shows that the AE profile of daratumumab when administered via subcutaneous injection is improved when compared with daratumumab via IV. AE data for daratumumab was updated in the model to align with the method of administration now used in UK clinical practice. |
| **Daratumumab price** | [redacted] | [redacted] | An updated PAS is available for daratumumab. |
| **General population mortality adjustment** | No adjustment was made for general population mortality. | Functionality was added such that the per cycle probability of death could not fall below that of the general population. General population mortality is informed by the latest available England and Wales life tables (24). | When using MMY2002 data to inform the daratumumab survival curves, some distributions result in the probability of death per cycle being below that of the general population.<br><br>This update improves the face validity of model outcomes. |

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; CDF, Cancer Drugs Fund; IV, intravenous; MAIC, matching-adjusted indirect comparison; NHS, National Health Service; OS, overall survival; PANO+BORT+DEX, panobinostat plus bortezomib and dexamethasone; PAS, patient access scheme; PFS, progression-free survival; POM+DEX, pomalidomide plus dexamethasone; RWE, Real world evidence; SACT, Systemic Anti-Cancer Therapy; UK, United Kingdom.

## A.10 Cost-effectiveness results (deterministic)

The results of the updated economic analysis versus POM+DEX and PANO+BORT+DEX are presented in Table 15 and Table 16, respectively. Cost-effectiveness analysis 1 replicates the results that were presented in the final ACD as part of TA510, using MAICs versus each comparator based on pooled MMY2002/GEN501 data. Cost-effectiveness analysis 2 presents results using updated MAICs versus each comparator using only data from MMY2002 to inform the comparison. Cost-effectiveness analysis 3 presents the new company base case, including all other updates.

***Table 15: Cost-effectiveness results (deterministic) versus pomalidomide plus dexamethasone***

| Technologies | Total costs (£) | Total LYG | Total QALYs | Incremental. costs (£) | Incremental LYG | Incremental QALYs | ICER versus baseline (£/QALY) | Incremental ICER (£/QALY) |
|---|---|---|---|---|---|---|---|---|
| **Cost-effectiveness analysis 1:** Replication of analysis that demonstrated plausible potential for cost-effectiveness at CDF entry | | | | | | | | |
| POM+DEX | [redacted] | 1.49 | [redacted] | – | – | – | – | – |
| Daratumumab | [redacted] | 2.74 | [redacted] | [redacted] | 1.24 | [redacted] | £15,772 | £15,772 |
| **Cost-effectiveness analysis 2:** Analysis that demonstrated plausible potential for cost-effectiveness at CDF entry – incorporating updated clinical data | | | | | | | | |
| POM+DEX | [redacted] | 1.49 | [redacted] | - | - | - | – | – |
| Daratumumab | [redacted] | 2.71 | [redacted] | [redacted] | 1.22 | [redacted] | Daratumumab Dominates | Daratumumab Dominates |
| **Cost-effectiveness analysis 3:** New company base-case | | | | | | | | |
| POM+DEX | [redacted] | 1.49 | 0.75 | - | - | - | | |
| Daratumumab | [redacted] | 2.71 | 1.41 | [redacted] | 1.22 | [redacted] | Daratumumab Dominates | Daratumumab Dominates |

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

***Table 16: Cost-effectiveness results (deterministic) versus panobinostat plus bortezomib and dexamethasone***

| Technologies | Total costs (£) | Total LYG | Total QALYs | Incremental. costs (£) | Incremental LYG | Incremental QALYs | ICER versus baseline (£/QALY) | Incremental ICER (£/QALY) |
|---|---|---|---|---|---|---|---|---|
| Cost-effectiveness analysis 1: Replication of analysis that demonstrated plausible potential for cost-effectiveness at CDF entry | | | | | | | | |
| PANO+BORT+DEX | [redacted] | 1.80 | [redacted] | – | – | – | – | – |
| Daratumumab | [redacted] | 2.28 | [redacted] | [redacted] | 0.48 | [redacted] | Daratumumab Dominates | Daratumumab Dominates |
| Cost-effectiveness analysis 2: Analysis that demonstrated plausible potential for cost-effectiveness at CDF entry – incorporating updated clinical evidence | | | | | | | | |
| PANO+BORT+DEX | [redacted] | 1.80 | [redacted] | - | - | - | – | – |
| Daratumumab | [redacted] | 2.97 | [redacted] | [redacted] | 1.17 | [redacted] | Daratumumab Dominates | Daratumumab Dominates |
| Cost-effectiveness analysis 3: New company base-case | | | | | | | | |
| PANO+BORT+DEX | [redacted] | 1.80 | [redacted] | - | - | - | – | – |
| Daratumumab | [redacted] | 2.97 | [redacted] | [redacted] | 1.17 | [redacted] | Daratumumab Dominates | Daratumumab Dominates |

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

## A.11 Probabilistic sensitivity analysis

Joint parameter uncertainty was explored through probabilistic sensitivity analysis (PSA), in which all parameters are assigned distributions and varied jointly. A total of 10,000 Monte Carlo simulations were recorded. Where the covariance structure between parameters was known, correlated random draws were sampled from a multivariate normal distribution. Results were plotted on a cost-effectiveness plane (CEP) and a cost-effectiveness acceptability curve (CEAC) was generated.

The updated probabilistic results for daratumumab versus POM+DEX and PANO+BORT+DEX are presented in Table 17 and Table 18, respectively. The CEPs are presented in Figure 9 and Figure 10. Daratumumab has a 100% probability of being cost-effective at considered willingness-to-pay thresholds up to £100,000 per QALY.

***Table 17: Updated base-case results (probabilistic) versus pomalidomide plus dexamethasone***

| Technologies | Total costs (£) | Total LYG | Total QALYs | Incremental. costs (£) | Incremental LYG | Incremental QALYs | ICER versus baseline (£/QALY) | Incremental ICER (£/QALY) |
|---|---|---|---|---|---|---|---|---|
| POM+DEX | [redacted] | 1.50 | [redacted] | – | – | – | – | – |
| Daratumumab | [redacted] | 2.74 | [redacted] | [redacted] | 1.24 | [redacted] | Daratumumab Dominates | Daratumumab Dominates |

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

***Table 18: Updated base-case results (probabilistic) versus panobinostat plus bortezomib and dexamethasone***

| Technologies | Total costs (£) | Total LYG | Total QALYs | Incremental. costs (£) | Incremental LYG | Incremental QALYs | ICER versus baseline (£/QALY) | Incremental ICER (£/QALY) |
|---|---|---|---|---|---|---|---|---|
| PANO+BORT+DEX | [redacted] | 1.83 | [redacted] | – | – | – | – | – |
| Daratumumab | [redacted] | 2.99 | [redacted] | [redacted] | 0.90 | [redacted] | Daratumumab Dominates | Daratumumab Dominates |

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

***Figure 9: Scatterplot of probabilistic results versus pomalidomide plus dexamethasone***

Abbreviations: QALY, quality-adjusted life year.

***Figure 10: Scatterplot of probabilistic results versus panobinostat plus bortezomib and dexamethasone***

Abbreviations: QALY, quality-adjusted life year.

## A.12 Key sensitivity and scenario analyses

Parameter uncertainty was tested using univariate sensitivity analysis, in which all model parameters were systematically and independently varied over a plausible

range determined by either the 95% CI, or ±20% where no estimates of precision were available. The ICER was recorded at the upper and lower values to produce a tornado diagram.

Results for the 10 most influential parameters are presented for the comparison versus POM+DEX and PANO+BORT+DEX in Figure 11 and Figure 12, respectively. As daratumumab dominates both comparators, net monetary benefit (NMB) is used in both tornado diagrams. In both comparisons, the most influential parameters are daratumumab survival model parameters.

***Figure 11: Tornado diagram versus pomalidomide plus dexamethasone***

Abbreviations: DARA, daratumumab; OS, overall survival; PFS, progression-free survival; POM+DEX, pomalidomide plus dexamethasone; PPS, post-progression survival SQ, sequential; SubsTx, subsequent treatment; TTD, time-to-discontinuation.

***Figure 12: Tornado diagram versus panobinostat plus bortezomib and dexamethasone***

Abbreviations: DARA, daratumumab; OS, overall survival, PANO+BORT+DEX, panobinostat plus bortezomib and dexamethasone; PFS, progression-free survival; SQ, sequential; SubsTx, subsequent treatment; TTD, time-to-discontinuation.

The most influential scenarios that were considered clinically plausible for each comparison are presented in Table 19. For each analysis, the scenarios that change the NMB by at least 10% or scenarios that were considered clinically relevant are presented. Daratumumab dominates POM+DEX and PANO+BORT+DEX in all scenarios.

***Table 19: Key scenario analyses***

| Scenario and cross reference | Scenario detail | Brief rationale | Impact on base-case ICER versus POM+DEX | Impact on base-case NMB versus POM+DEX | Impact on base-case ICER versus PANO+ BORT+DEX | Impact on base-case NMB versus PANO+ BORT+DEX |
|---|---|---|---|---|---|---|
| **Base case** | | | **Dominant** | [redacted] | **Dominant** | [redacted] |
| OS distributions | Gompertz OS distribution for all comparators | Scenarios were conducted varying the distribution of the OS curve to estimate the uncertainty in the survival extrapolations. | Dominant | [redacted] | Dominant | [redacted] |
| | Exponential OS distribution for all comparators | | Dominant | [redacted] | Dominant | [redacted] |
| MAIC | Fully matched MAIC, Weibull distribution for OS | Scenarios are presented using fully matched MAICs to model daratumumab OS and PFS. The exponential distribution is presented as the lower bound of daratumumab OS identified by clinicians. | Dominant | [redacted] | Dominant | [redacted] |
| | Fully matched MAIC, exponential distribution for OS | | Dominant | [redacted] | Dominant | [redacted] |
| Daratumumab clinical data source: SACT | OS distribution: Weibull<br>PFS/TTD distribution: log-logistic | RWE data from SACT was used in scenario analysis to test the generalisability of the base case results to UK clinical practice. In the absence of individual patient data, only a naïve comparison between SACT and comparator data was possible. An MAIC conducted comparing MMY2002 versus SACT showed that after adjusting for baseline | Dominant | [redacted] | Dominant | [redacted] |

| Scenario and cross reference | Scenario detail | Brief rationale | Impact on base-case ICER versus POM+DEX | Impact on base-case NMB versus POM+DEX | Impact on base-case ICER versus PANO+ BORT+DEX | Impact on base-case NMB versus PANO+ BORT+DEX |
|---|---|---|---|---|---|---|
| | | characteristics, the data was comparable (HR 1.07). | | | | |
| Daratumumab clinical data source: pooled MMY2002/GEN501 data | OS distribution: Weibull<br>PFS distribution: log-normal<br>TTD distribution: log-logistic | A scenario using the pooled data set was conducted to align with the analysis presented in the original company base-case in TA510. | Dominant | [redacted] | Dominant | [redacted] |
| Subsequent therapies | [redacted]% of patients in POM+DEX and PANO+BORT+DEX arms receive a subsequent therapy. | Due to the unique mechanism of action and favourable safety profile, patients are more able to receive subsequent therapies after treatment with daratumumab. Therefore, a scenario is considered that models a 25% reduction in subsequent therapy use in the comparator arms. | Dominant | [redacted] | Dominant | [redacted] |

Abbreviations: DARA, daratumumab; OS, overall survival, PANO+BORT+DEX, panobinostat plus bortezomib and dexamethasone; PFS, progression-free survival; POM+DEX, pomalidomide plus dexamethasone; SQ, sequential; SubsTx, subsequent treatment; TTD, time-to-discontinuation

## A.13 End of life criteria

***Table 20: End of life criteria – Document B [ID933] B.2.13 (pages 42-43)***

| Criterion | Data available |
|---|---|
| **The treatment is indicated for patients with a short life expectancy, normally less than 24 months** | Median survival<br>The life expectancy for patients with rrMM who have progressive disease despite prior treatment with a PI and an IMiD does not exceed 12 months, based on RWE (6-11). For patients who are refractory to both a PI and an IMiD, life expectancy is further reduced to 8–9 months, and for patients who are refractory to three or four of the common PIs and IMiDs, life expectancy decreases to only 3–5 months (11).<br><br>Mean survival<br>In the model base case mean OS is [redacted]months and [redacted] months in the POM+DEX and PANO+BORT+DEX arms, respectively. |
| **There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment** | Median survival<br>Median survival in MMY2002, which most closely aligns with the daratumumab marketing authorisation, was 18.6 months (CI: 13.7, 25.0). As life expectancy in this patient population is expected to be <12 months, daratumumab offers a life extension of greater than 3 months.<br><br>Mean survival<br>In the model base case, mean OS in the daratumumab arm is [redacted] and [redacted] months, extending life by [redacted] and [redacted] months versus POM+DEX and PANO+BORT+DEX, respectively. In all model scenarios, daratumumab extends life by >3 months. |

Abbreviations: CI, confidence interval; HR, hazard ratio; IMiD, immunomodulatory drugs; OS, overall survival; PANO+BORT+DEX, panobinostat plus bortezomib and dexamethasone; PI, proteasome inhibitor; POM+DEX, pomalidomide plus dexamethasone; rrMM, relapsed refractory multiple myeloma; RWE, real-world evidence.

## A.14 Key issues and conclusions based on the data collected during the CDF review period

Patients with rrMM who have previously received a PI and an IMiD agent, and who have demonstrated disease progression on the last therapy, have limited remaining treatment options, a poor prognosis, and live with the anxiety of their disease returning (6-11, 25). The original submission demonstrated that fourth-line treatment with daratumumab monotherapy was associated with a deep and durable response, an unprecedented survival benefit at this stage in the disease pathway, and was well tolerated in adult patients with rrMM (20). Additional data collected in the CDF period via updated MMY2002 and GEN501 data cuts and SACT further corroborate such conclusions and these data seek to address the committee's key uncertainties outlined in the ToE (1).

**Uncertainty in relative effectiveness**

No further data is collected or available for comparator treatments through the SACT dataset, meaning estimates for comparative effectiveness must still rely on MAICs, now updated with more mature trial evidence. Since time of the FAD, final analyses have been completed for MMY2002 and GEN501; an additional 5.6 months of follow-up is available from MMY2002. These data have been utilised in an updated MAIC within the new company base case to reduce the uncertainty surrounding the benefit of daratumumab compared with POM+DEX and PANO+BORT+DEX. At final analysis of MMY2002, after a median follow-up of 36.7 months, median OS [redacted] (95% CI: [redacted]) and [redacted] patients had died, reducing uncertainty in the OS extrapolations. Acknowledging that SACT contributes 2,301 daratumumab-treated patients to the clinical evidence base, a naïve comparison was also explored to leverage SACT data directly in the model. Daratumumab remains dominant versus both comparators and thus results are consistent with the new company base case, further supporting overall results.

**Generalisability of MMY2002 to UK clinical practice**

Data collected from the SACT cohort has validated the generalisability of outcomes from the MMY2002 study to UK clinical practice. When controlling for the differences in baseline characteristics presented in the SACT report, there was no significant difference in the OS KM data between MMY2002 and SACT (HR: [redacted]). Adjusted median OS in MMY2002 was [redacted] compared with [redacted] in the SACT cohort. Expert clinical opinion confirmed that the difference in total subsequent therapy usage between SACT and MMY2002 is expected given that real-world patients are slightly older with poorer performance status (3), however these differences have not impacted the comparability of overall outcomes. This analysis addresses a key uncertainty for the committee and supports the appropriateness of utilising the MMY2002 data within the new company base case. Indeed, comparison with SACT data has confirmed that model projections based on MMY2002 are reflective of UK clinical practice.

**End of life**

Patients with rrMM treated with daratumumab monotherapy at fourth line in their disease pathway have short life expectancy; for those refractory to both a PI and an IMiD, life expectancy is 8–9 months, and for those who are refractory to three or four

of the common PIs and IMiDs, it further decreases to only 3–5 months (20). Since median OS in MMY2002 was [redacted], daratumumab clearly extends median survival by greater than 3 months for these patients and this is further validated by mean modelled outcomes presented in this CDF review. In the model base case, daratumumab prolongs survival by [redacted] months versus POM+DEX and by [redacted] months versus PANO+BORT+DEX. As such, daratumumab monotherapy clearly meets NICE's end of life criteria for consideration alongside cost-effectiveness estimates and residual uncertainty.

**Cost-effectiveness of daratumumab monotherapy**

In the new company base case, using the committee's preferred assumptions outlined in the FAD and subsequent ToE (1), daratumumab monotherapy dominates POM+DEX and PANO+BORT+DEX, showing daratumumab to be a highly cost-effective use of NHS resources at any WTP versus both comparators. The results of sensitivity analyses demonstrate that the base-case results are robust to parameter uncertainty, and in all cases the daratumumab is less costly than both comparators and provides significant quality-adjusted life year (QALY) gain.

Results of probabilistic analysis were highly congruent with the base case results. Daratumumab dominated both comparators, with a NMB of [redacted] and [redacted] versus POM+DEX and PANO+BORT+DEX, respectively. Deterministic analyses showed that the survival model parameters had an impact on the results, but the impact of varying other parameters in the model was small. Scenario analyses showed that the parameters with the most influence on the ICER were the data source and distribution chosen to model daratumumab OS. However, in all scenarios daratumumab dominates both comparators. Janssen recognises that pomalidomide and panobinostat have confidential PASs in place in UK, however additional threshold analyses have shown that even when comparator therapies are discounted by 100%, daratumumab monotherapy remains a cost-effective use of NHS resources at a WTP of £50,000 per QALY.

**Residual uncertainty in the decision-problem**

As noted in the ToE (1), the committee have acknowledged that uncertainty would remain about the relative effectiveness of daratumumab. Clinical data are still from single arm sources which is reflective of the severity and stage of disease, as well as

the paucity of suitable therapies in rrMM at fourth line. Where there is a lack of clinical equipoise, it is unethical to randomise patients to sub-optimal care meaning uncertainty is inherent and often unresolvable in such settings. The updated MAIC analyses however have been aligned with committee preferred assumptions, balancing the necessity to adjust for key prognostic factors while managing uncertainty and maintaining suitably robust effective sample sizes. Residual uncertainty has been managed through extensive scenario and sensitivity analysis and should not preclude the reimbursement of daratumumab monotherapy within UK clinical practice.

**Remaining unmet need and clinical demand**

Daratumumab is an innovative first-in-class monoclonal antibody and its proven efficacy among patients with rrMM supports its continued use in the fourth-line treatment setting. The fact that 2,301 patients were treated with daratumumab via the CDF and captured within the SACT dataset between 17th January 2018 and 16th November 2020 clearly shows there is still a substantial need and clinical demand for daratumumab monotherapy at fourth line in the NHS (5). The uncertainties identified at the time of FAD in TA510 have been considerably reduced with the additional data collected in the CDF period via updated MMY2002/GEN501 data cuts and real-world data from SACT. Updated analyses presented in this CDF review confirm that daratumumab monotherapy is a cost-effective use of NHS resources for the treatment of rrMM and thus supports national reimbursement in England.

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## A.16 Appendices

All appendices are provided as separate documents:

- Appendix A: company guide to taking part in a CDF review
- Appendix B: participation and confidentiality agreement form (company consultee)
- Appendix C: expert nomination form (company consultee)
- Appendix D: confidential information checklist
- Appendix E: MMY2002 – final data cut-off (30th May 2017)
- Appendix F: GEN501 Part 2 – final data cut-off (31st March 2017)
- Appendix G: Systemic Anti-Cancer Therapy database outcomes – 31st January 2021
- Appendix H: Updated Match-adjusted indirect comparison
- Appendix I: Survival models
- Appendix J: Model inputs

# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Cancer Drugs Fund review

# Daratumumab monotherapy for treating relapsed and refractory multiple myeloma (CDF review of TA510) [ID3881]

## Clarification questions

**October 2021**

| File name | Version | Contains confidential information | Date |
|---|---|---|---|
| **[ID3881] Daratumumab – rrMM_clarification letter_tocompany – company response (AIC&CIC)** | **1** | **Yes** | **1st November 2021** |

## Abbreviations

| Abbreviation | Definition |
|---|---|
| CDF | Cancer Drugs Fund |
| CI | Confidence interval |
| EAP | Early Access Program |
| Effective sample size | ESS |
| ERG | Evidence review group |
| EQ-5D-5L | European Quality of Life Five Dimensions Questionnaire |
| HR | Hazard ratio |
| IMWG | International Myeloma Working Group |
| ISS | International Staging System |
| IV | Intravenous |
| K-M | Kaplan-Meier |
| MAIC | Matching-adjusted indirect comparison |
| NMB | Net monetary benefit |
| OS | Overall survival |
| PANO+BORT+DEX | Panobinostat plus bortezomib and dexamethasone |
| PFS | Progression-free survival |
| POM+DEX | Pomalidomide plus dexamethasone |
| SACT | Systemic Anti-Cancer Therapy |
| SC | Subcutaneous |
| TEAE | Treatment-emergent adverse event |
| TTD | Time to discontinuation |
| UK | United Kingdom |

## Section A: Clarification on effectiveness data

### *MAICs*

**A1. Priority question. The ERG notes that the NICE DSU Technical Support Document 18 (TSD18) states that for an unanchored MAIC all effect modifiers and prognostic variables should be adjusted for. Please can the company explain their rationale for only using a subgroup of prognostic factors in their MAICs that are used to inform the base case as TSD18 explicitly states this is only appropriate for an anchored MAIC.**

Although TSD18 states that all prognostic factors should be adjusted for, it also acknowledges that *"when the ESS[a] is markedly reduced, or equivalently the weights are highly variable, estimates become unstable, and inferences depend heavily on just a small number of individuals"*. The fully adjusted MAICs resulted in an ESS of [redacted] vs POM+DEX and [redacted] vs PANO+BORT+DEX, a [redacted]% and [redacted]% reduction in ESS, respectively. As described in Section A.7 of the company submission for the Cancer Drugs Fund (CDF) review, Janssen took the decision to adjust only for key prognostic factors that clinical experts deemed most relevant to maintain a sufficient ESS and ensure a robust analysis (1).

The results of the fully matched matching-adjusted indirect comparisons (MAICs) are presented in Table 1; matching for all prognostic factors results in improved hazard ratios (HRs) versus the key comparator of pomalidomide plus dexamethasone (POM+DEX).

**Table 1 Hazard ratios, key characteristics versus fully matched MAICs**

| Endpoint | MMY2002 – matching on key characteristics | | MMY2002 – fully matched | |
|---|---|---|---|---|
| | versus POM+DEX | versus PANO+BORT+DEX | versus POM+DEX | versus PANO+BORT+DEX |
| OS (95% CI) | [redacted] | [redacted] | [redacted] | [redacted] |
| PFS, IRC (95% CI) | [redacted] | [redacted] | [redacted] | [redacted] |

Abbreviations; CI, confidence interval; IRC, independent review committee; MAIC, matching-adjusted indirect comparison; OS, overall survival; PANO+BORT+DEX, panobinostat plus bortezomib and dexamethasone; PFS, progression-free survival; POM+DEX, pomalidomide plus dexamethasone.

The results of scenario analysis showed that when the fully adjusted MAICs are used, daratumumab remains dominant with the net monetary benefit (NMB) increasing by

[a] Effective sampling size

[redacted] versus POM+DEX and [redacted] versus panobinostat plus bortezomib and dexamethasone (PANO+BORT+DEX); therefore, the base-case analysis using MAICs adjusting for key prognostic factors can be considered a conservative approach.

**A2. Priority question. Please provide Kaplan-Meier plots for the fully adjusted MAICs of MMY2002 (final data cut) with POM+DEX and PANO+BORT+DEX and also include the daratumumab observed data on the plots.**

The Kaplan-Meier (K-M) plots for the fully adjusted MAICs of MMY2002 (final data cut) compared with POM+DEX and PANO+BORT+DEX are presented in Figure 1 to Figure 4.

**Figure 1 Adjusted K-M plot for OS, daratumumab versus POM+DEX (fully adjusted MAIC)**

Abbreviations: HR, hazard ratio; K-M, Kaplan-Meier; MAIC, matching-adjusted indirect comparison; OS, overall survival; POM+DEX, pomalidomide plus dexamethasone.

### Figure 2 Adjusted K-M plot for PFS, daratumumab versus POM+DEX (fully adjusted MAIC)

Abbreviations: HR, hazard ratio; K-M, Kaplan-Meier; MAIC, matching-adjusted indirect comparison; PFS, progression-free survival; POM+DEX, pomalidomide plus dexamethasone.

### Figure 3 Adjusted K-M plot for OS, daratumumab versus PANO+BORT+DEX (fully adjusted MAIC)

Abbreviations: HR, hazard ratio; K-M, Kaplan-Meier; MAIC, matching-adjusted indirect comparison; OS, overall survival; PANO+BORT+DEX, panobinostat plus bortezomib and dexamethasone.

**Figure 4 Adjusted K-M plot for PFS, daratumumab versus PANO+BORT+DEX (fully adjusted MAIC)**

Abbreviations: HR, hazard ratio; K-M, Kaplan-Meier; MAIC, matching-adjusted indirect comparison; PFS, progression-free survival; PANO+BORT+DEX, panobinostat plus bortezomib and dexamethasone.

**A3. Priority Question: Please provide hazard ratios, 95% confidence intervals, p values and Kaplan-Meier plots for the MAIC of MMY2002 (final data cut) compared to SACT for each adjustment factor (ECOG status, prior autologous stem cell transplantation (ASCT), age and sex) when applied independently.**

The HRs for the MAIC of MMY2002 compared with Systematic Anti-Cancer Therapy (SACT) data for each adjustment factor applied independently are presented in Table 2.

**Table 2 Univariate MAIC adjustment HR, MMY2002 versus SACT**

| Adjustment | HR | Lower CI | Upper CI | p-value |
|---|---|---|---|---|
| **OS** | | | | |
| ECOG status | [redacted] | [redacted] | [redacted] | [redacted] |
| Prior ASCT | [redacted] | [redacted] | [redacted] | [redacted] |
| Age | [redacted] | [redacted] | [redacted] | [redacted] |
| Sex | [redacted] | [redacted] | [redacted] | [redacted] |
| **PFS** | | | | |
| ECOG status | [redacted] | [redacted] | [redacted] | [redacted] |
| Prior ASCT | [redacted] | [redacted] | [redacted] | [redacted] |
| Age | [redacted] | [redacted] | [redacted] | [redacted] |
| Sex | [redacted] | [redacted] | [redacted] | [redacted] |

Abbreviations: ASCT, autologous stem cell transplant; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; OS, overall survival; PFS, progression-free survival; SACT, Systemic Anti-Cancer Therapy.

The OS Kaplan-Meier plots for each analysis are presented in Figure 5 to Figure 8.

The PFS K–M plots for each analysis are presented in Figure 9 to Figure 12.

**Figure 5 Adjusted K-M plot for OS, MMY2002 versus SACT (adjusted for ECOG status)**

Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; K-M, Kaplan-Meier; MAIC, matching-adjusted indirect comparison; OS, overall survival; SACT, Systemic Anti-Cancer Therapy.

### Figure 6 Adjusted K-M plot for OS, MMY2002 versus SACT (adjusted for prior ASCT)

Abbreviations: ASCT, autologous stem cell transplant; CI, confidence interval; HR, hazard ratio; K-M, Kaplan-Meier; MAIC, matching-adjusted indirect comparison; OS, overall survival; SACT, Systemic Anti-Cancer Therapy.

### Figure 7 Adjusted K-M plot for OS, MMY2002 versus SACT (adjusted for age)

Abbreviations: CI, confidence interval; HR, hazard ratio; K-M, Kaplan-Meier; MAIC, matching-adjusted indirect comparison; OS, overall survival; SACT, Systemic Anti-Cancer Therapy.

### Figure 8 Adjusted K-M plot for OS, MMY2002 versus SACT (adjusted for sex)

Abbreviations: CI, confidence interval; HR, hazard ratio; K-M, Kaplan-Meier; MAIC, matching-adjusted indirect comparison; OS, overall survival; SACT, Systemic Anti-Cancer Therapy.

### Figure 9 Adjusted K-M plot for PFS, MMY2002 versus SACT (adjusted for ECOG status)

Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; K-M, Kaplan-Meier; MAIC, matching-adjusted indirect comparison; PFS, progression-free survival; SACT, Systemic Anti-Cancer Therapy.

### Figure 10 Adjusted K-M plot for PFS, MMY2002 versus SACT (adjusted for prior ASCT)

Abbreviations: ASCT, autologous stem cell transplant; CI, confidence interval; HR, hazard ratio; K-M, Kaplan-Meier; MAIC, matching-adjusted indirect comparison; PFS, progression-free survival; SACT, Systemic Anti-Cancer Therapy.

### Figure 11 Adjusted K-M plot for PFS, MMY2002 versus SACT (adjusted for age)

Abbreviations: CI, confidence interval; HR, hazard ratio; K-M, Kaplan-Meier; MAIC, matching-adjusted indirect comparison; PFS, progression-free survival; SACT, Systemic Anti-Cancer Therapy.

**Figure 12 Adjusted K-M plot for PFS, MMY2002 versus SACT (adjusted for sex)**

Abbreviations: CI, confidence interval; HR, hazard ratio; K-M, Kaplan-Meier; MAIC, matching-adjusted indirect comparison; PFS, progression-free survival; SACT, Systemic Anti-Cancer Therapy

**A4. With regards to age, please explain how lack of convergence was determined plus any steps that were taken to improve convergence when this characteristic was added.**

As described by Signorovitch et al (2), the MAIC process attempts to find a weight for each patient such that the average weighted baseline characteristics are the same as those of the comparator. However, when too many variables are included in the algorithm, it is not always possible to find a perfect solution to these equations. The Newton-Raphson optimisation algorithm is used to solve the equations to match the included baseline characteristics. Janssen aimed to optimise this algorithm by running it with many different initial values. However, in certain settings (i.e., where there are too many characteristics that must be matched) it is not possible to find a mathematical solution.

This is demonstrated in Figure 13 below, which tries to match MMY2002 to MM-003, using one characteristic (match 1; values in grey are not matched) to using 15 characteristics (match 15).

When including 13 variables (match 13), the effective sample size (ESS) dropped to [redacted]. When age is also included, the ESS drops to [redacted] and the variables in the column labelled “match 14” are no longer identical to the ones of MM-003 (e.g., % International Staging System [ISS]=1 or 2 should be 68% but is 69%). This indicates that the algorithm is not able to find a proper solution, is very unstable (extreme weighting is needed), and produces unreliable results.

**Figure 13 Example of convergence issues when including age as a matching factor**

Abbreviations: ECOG, Eastern Cooperative Oncology Group; ISS, International Staging System; IgA, immunoglobulin A; IgD, immunoglobulin D; IgG, immunoglobulin G; IgM, immunoglobulin M; POM+DEX, pomalidomide plus dexamethasone.

**A5. Please explain why sex was not included in the adjustments for the POM+DEX and PANO+BORT+DEX MAICs and yet it was included in the MAIC for MMY2002 (final data cut) versus SACT.**

Sex was not selected as a relevant factor for the MAIC analyses versus POM+DEX and PANO+BORT+DEX based on clinician feedback. Given that a full match was not possible even with the other characteristics that are deemed more important (see Question A4), it was not included in the analysis versus MM-003 and PANORAMA 2.

However, for the comparison with SACT, fewer characteristics are available to be included in the MAIC analysis. Therefore, as many characteristics as possible presented in the SACT report, including sex, were used in the analysis.

**A6. Please provide a fully adjusted MAIC including sex as an adjustment factor for the comparisons of MMY2002 (final data cut) with POM+DEX and PANO+BORT+DEX for OS and PFS.**

The results of the fully adjusted MAICs including sex as an adjustment factor are presented in Table 3 and Figure 14 to Figure 17. The resultant ESS was [redacted] (a [redacted]% reduction) vs POM+DEX and [redacted] (a [redacted]% reduction) vs PANO+BORT+DEX. The results are shown to be highly consistent with the fully adjusted MAICs presented in the company submission for the Cancer Drugs Fund (CDF) review.

**Table 3 Results of fully adjusted MAICs (including sex as an adjustment factor)**

| Comparator | Outcome | Hazard ratio | |
|---|---|---|---|
| | | Point estimate | 95% confidence interval |
| POM+DEX | OS | [redacted] | [redacted] |
| | PFS | [redacted] | [redacted] |
| PANO+BORT+DEX | OS | [redacted] | [redacted] |
| | PFS | [redacted] | [redacted] |

Abbreviations: OS, overall survival; PANO+BORT+DEX, panobinostat plus bortezomib and dexamethasone; PFS, progression-free survival; POM+DEX, pomalidomide plus dexamethasone.

### Figure 14 Adjusted K-M plot for OS, daratumumab versus POM+DEX

Abbreviations: CI, confidence interval; HR, hazard ratio; K-M, Kaplan-Meier; OS, overall survival; POM+DEX, pomalidomide plus dexamethasone.

### Figure 15 Adjusted K-M plot for PFS, daratumumab versus POM+DEX

Abbreviations: CI, confidence interval; HR, hazard ratio; K-M, Kaplan-Meier; PFS, progression-free survival; POM+DEX, pomalidomide plus dexamethasone.

### Figure 16 Adjusted K-M plot for OS, daratumumab versus PANO+BORT+DEX

Abbreviations: CI, confidence interval; HR, hazard ratio; K-M, Kaplan-Meier; OS, overall survival; PANO+BORT+DEX, panobinostat plus bortezomib and dexamethasone.

### Figure 17 Adjusted K-M plot for PFS, daratumumab versus PANO+BORT+DEX

Abbreviations: CI, confidence interval; HR, hazard ratio; K-M, Kaplan-Meier; PFS, progression-free survival; PANO+BORT+DEX, panobinostat plus bortezomib and dexamethasone.

**A7. For the MAIC versus SACT, the ERG notes that the company has not adjusted for refractory status to lenalidomide, refractory status to bortezomib, and refractory status to both therapies, number of prior treatments, and ISS staging identified by the company as key prognostic factors in their MAICs versus POM+DEX and PANO+BORT+DEX. Please can the company comment on the reliability of the MAIC versus SACT given the lack of adjustment for these factors?**

As noted in Section A.1 of the company submission for the CDF review, the Committee felt that data collected through the SACT dataset would enhance the evidence for daratumumab and could resolve the key uncertainties. In particular, at the time of developing the data collection agreement for daratumumab, the Committee considered that should SACT data collection show that outcomes for daratumumab in the real world were consistent with that observed in MMY2002, this would resolve the fundamental uncertainty of this appraisal pertaining to the generalisability of MMY2002.

Given the limitations in data collection via SACT, a perfectly matched comparison of SACT and MMY2002 was never the aim of the CDF data collection agreement. Indeed, the data collection agreement states that *"where possible, treatments received subsequent to daratumumab and baseline characteristics will be collected to* ***contextualise*** [emphasis added] *these data against the observed OS from the daratumumab trials"* and *"it is anticipated that the refractoriness data in relation to the previous line of therapy may be available from the Blueteq preauthorisation form. However, the quality and completeness of such data is unknown. If the information should prove available and to be of sufficient quality and robustness, this will also be provided."* (3).

Although it was not possible to adjust for some prognostic factors identified by clinical experts (refractory status, number of prior treatments, ISS), the available evidence suggests that MMY2002 is broadly reflective of UK clinical practice. The unadjusted OS curves for daratumumab from SACT and MMY2002 are highly consistent (Figure 18), despite some differences in baseline characteristics and subsequent therapy use; adjustment for available baseline characteristics results in even greater concordance between the two data sources. As such, Janssen consider that the generalisability of MMY2002 has been demonstrated meaning MMY2002 can be used as the basis for decision making.

**Figure 18 K-M curves for daratumumab overall survival from SACT and MMY2002**

Abbreviations: HR, hazard ratio; K-M, Kaplan-Meier; MAIC, matching-adjusted indirect comparison; OS, overall survival; SACT, Systemic Anti-Cancer Therapy.

### *Unadjusted analyses*

**A8. Priority question. Please provide the results of the naive comparison using the MMY2002 data (final data cut) compared with POM+DEX from MM-003 for OS and PFS. Please provide:**

a) **the resulting hazard ratio, 95% confidence interval and p value;**
b) **the number of events and the number of patients at risk;**
c) **Kaplan-Meier plots.**

The HRs and 95% confidence intervals (CIs) for the naïve comparison of MMY2002 compared with POM+DEX for both OS and PFS are presented in Table 31 (Appendix H) of the company submission for the CDF review. The associated p-values, Kaplan-Meier plots, and number of patients at risk are presented in Figure 13 and Figure 14 of the CDF review company submission for OS and PFS, respectively.

Kaplan-Meier curves for the naïve comparison only (i.e. excluding the adjusted curves) are presented in Figure 19 and Figure 20 below for OS and PFS, respectively.

### Figure 19 Unadjusted OS K-M curves for MMY2002 (daratumumab) and MM-003 (POM+DEX)

Abbreviations: CI, confidence interval; HR, hazard ratio; K-M, Kaplan-Meier; OS, overall survival; POM+DEX, pomalidomide plus dexamethasone.

### Figure 20 Unadjusted PFS K-M curves for MMY2002 (daratumumab) and MM-003 (POM+DEX)

Abbreviations: CI, confidence interval; HR, hazard ratio; K-M, Kaplan-Meier; PFS, progression-free survival; POM+DEX, pomalidomide plus dexamethasone.

**A9. Priority question. Please provide the results of the naive comparison using the MMY2002 data (final data cut) compared with PANO+BORT+DEX from PANORAMA-2 for OS and PFS. Please provide:**

a) **the resulting hazard ratio, 95% confidence interval and p value;**
b) **the number of events and number of patients at risk;**
c) **Kaplan-Meier plots.**

The HRs and 95% CIs for the naïve comparison of MMY2002 compared with PANO+BORT+DEX for both OS and PFS were presented in Table 32 (Appendix H) of the company submission for the CDF review. The associated p-values, Kaplan-Meier plots, and number of patients at risk were presented in Figure 19 and Figure 20 of the CDF review company submission for OS and PFS, respectively.

Kaplan-Meier curves for the naïve comparison only (i.e. excluding the adjusted curves) are presented in Figure 21 and Figure 22 below for OS and PFS, respectively.

**Figure 21 Unadjusted OS K-M curves for MMY2002 (daratumumab) and PANORAMA 2 (PANO+BORT+DEX)**

Abbreviations: CI, confidence interval; HR, hazard ratio; K-M, Kaplan-Meier; OS, overall survival; PANO+BORT+DEX, panobinostat plus bortezomib and dexamethasone.

**Figure 22 Unadjusted PFS K-M curves for MMY2002 (daratumumab) and PANORAMA 2 (PANO+BORT+DEX)**

Abbreviations: CI, confidence interval; HR, hazard ratio; K-M, Kaplan-Meier; PFS, overall survival; PANO+BORT+DEX, panobinostat plus bortezomib and dexamethasone.

### *SACT analyses*

**A10. Priority question. Please provide the results of the naive comparison using the SACT data to inform daratumumab compared with POM+DEX from MM-003 for OS and PFS (using SACT TTD data due to the absence of PFS data from SACT). Please provide:**

a) **the resulting hazard ratio, 95% confidence interval and p value;**
b) **the number of events and number of patients at risk;**
c) **Kaplan-Meier plots.**

Hazard ratios and event numbers for the naïve comparison between SACT (daratumumab) and MM-003 (POM+DEX) are presented in Table 4. The Kaplan-Meier curves (including numbers of patients at risk) for OS and PFS/TTD are presented in Figure 23 and Figure 24, respectively.

As noted in Section A.8.1 of the company submission for the CDF review, naïve comparison is associated with significant uncertainty, given that no adjustment is made for differences in patient characteristics between the two data sources. In addition, the comparison between SACT and MM-003 compares real-world evidence with trial data; although SACT has confirmed that real-world outcomes for daratumumab match those observed in MMY2002, no such data exists for POM+DEX or PANO+BORT+DEX. In general, real-world outcomes are poorer than those

observed in clinical trials. Therefore, to avoid introducing bias of unknown magnitude, trial-based comparisons should be used to determine relative effectiveness of daratumumab versus POM+DEX.

**Table 4 Hazard ratios and event numbers for comparison between SACT and MM-003**

| | | Daratumumab OS (SACT) versus POM+DEX OS (MM-003) | Daratumumab TTD (SACT) versus POM+DEX PFS (MM-003) |
|---|---|---|---|
| Hazard ratio | Point estimate | [redacted] | [redacted] |
| | 95% CI | [redacted] | [redacted] |
| | P-value | [redacted] | [redacted] |
| Number of events (SACT) | | [redacted] | [redacted] |
| Number of events (MM-003) | | 171 | 237 |

Abbreviations: CI, confidence interval; OS, overall survival; PFS, progression-free survival; POM+DEX, pomalidomide plus dexamethasone; SACT, Systemic Anti-Cancer Therapy; TTD, time to discontinuation.

**Figure 23 K-M plot for daratumumab OS (SACT) versus POM+DEX OS (MM-003)**

Abbreviations: CI, confidence interval; HR, hazard ratio; K-M, Kaplan-Meier; OS, overall survival; POM+DEX, pomalidomide plus dexamethasone; SACT, Systemic Anti-Cancer Therapy.

**Figure 24 K-M plot for daratumumab TTD (SACT) versus POM+DEX OS (MM-003)**

Abbreviations: CI, confidence interval; HR, hazard ratio; K-M, Kaplan-Meier; PFS, progression-free survival; POM+DEX, pomalidomide plus dexamethasone; SACT, Systemic Anti-Cancer Therapy; TTD, time to discontinuation.

**A11. Priority question. Please provide the results of the naive comparison using the SACT data to inform daratumumab compared with PANO+BORT+DEX from PANORAMA-2 for OS and PFS (using SACT TTD data due to the absence of PFS data from SACT). Please provide:**

a) **the resulting hazard ratio, 95% confidence interval and p value;**
b) **the number of events and number of patients at risk;**
c) **Kaplan-Meier plots.**

Event numbers and HRs for the naïve comparison between SACT (daratumumab) and PANORAMA 2 (PANO+BORT+DEX) are presented in Table 5. The Kaplan-Meier curves (including numbers of patients at risk) for OS and PFS/TTD are presented in Figure **25** and Figure 26, respectively.

As noted in Section A.8.1 of the company submission for the CDF review, naïve comparison is associated with significant uncertainty, given that no adjustment is made for differences in patient characteristics between the two data sources. In addition, the comparison between SACT and MM-003 compares real-world evidence with trial data; although SACT has confirmed that real-world outcomes for daratumumab match those observed in MMY2002, no such data exists for POM+DEX or PANO+BORT+DEX. In general, real-world outcomes are poorer than those observed in clinical trials. Therefore, to avoid introducing bias of unknown magnitude, trial-based

comparisons should be used to determine relative effectiveness of daratumumab versus PANO+BORT+DEX.

**Table 5 Hazard ratios and event numbers for comparison between SACT and PANORAMA 2**

| | | Daratumumab OS (SACT) versus PANO+BORT+DEX OS (PANORAMA 2) | Daratumumab TTD (SACT) versus PANO+BORT+DEX PFS (PANORAMA 2) |
|---|---|---|---|
| Hazard ratio | Point estimate | [redacted] | [redacted] |
| | 95% CI | [redacted] | [redacted] |
| | P-value | [redacted] | [redacted] |
| Number of events (SACT) | | [redacted] | [redacted] |
| Number of events (PANORAMA 2) | | 27 | 39 |

Abbreviations: CI, confidence interval; OS, overall survival; PFS, progression-free survival; POM+DEX, pomalidomide plus dexamethasone; SACT, Systemic Anti-Cancer Therapy; TTD, time to discontinuation.

**Figure 25 K-M plot for daratumumab OS (SACT) versus PANO+BORT+DEX OS (PANORAMA 2)**

Abbreviations: CI, confidence interval; HR, hazard ratio; K-M, Kaplan-Meier; OS, overall survival; PANO+BORT+DEX, panobinostat plus bortezomib and dexamethasone; SACT, Systemic Anti-Cancer Therapy.

**Figure 26 K-M plot for daratumumab TTD (SACT) versus PANO+BORT+DEX PFS (PANORAMA 2)**

Abbreviations: CI, confidence interval; HR, hazard ratio; K-M, Kaplan-Meier; PFS, progression-free survival; PANO+BORT+DEX, panobinostat plus bortezomib and dexamethasone; SACT, Systemic Anti-Cancer Therapy; TTD, time to discontinuation.

### *MMY2002 final data cut*

***A12. Priority question. Please provide the MMY2002 (final data cut) daratumumab unadjusted OS KM (with KM data provided in an Excel sheet) data and median and mean OS with 95% confidence intervals based on subsequent post-daratumumab treatment received, more specifically for:***

a) **Patients receiving daratumumab with no subsequent treatment received;**
b) **Patients receiving bortezomib as a subsequent treatment after daratumumab;**
c) **Patients receiving carfilzomib as a subsequent treatment after daratumumab;**
d) **Patients receiving lenalidomide as a subsequent treatment after daratumumab;**
e) **Patients receiving pomalidomide as a subsequent treatment after daratumumab;**
f) **Patients receiving any subsequent treatment after daratumumab.**

Janssen does not consider it statistically robust or appropriate to provide the requested OS data on the following basis:

- These analyses are subject to a high level of selection bias because of indirectly selecting patients based on their outcome.
    - Patients need to survive longer to receive subsequent treatment and as such these subgroups are selecting patients based on survival outcomes.

    - In addition, patients are being indirectly selected based on fitness, as fitter patients will receive the more effective and more toxic treatments resulting in better outcomes.
- The number of patients receiving bortezomib, carfilzomib, lenalidomide and pomalidomide as a first subsequent therapy is [redacted], [redacted], [redacted], and [redacted], respectively; this is not considered sufficient to inform robust Kaplan-Meier curves.

As noted in response to question A7, the purpose of CDF data collection was to resolve outstanding questions on the generalisability of the daratumumab clinical trial programme to UK clinical practice, particularly in relation to the impact of subsequent therapy use on OS.

Janssen consider this question to be resolved on the basis that:

- The OS curves for MMY2002 and SACT are highly consistent (Figure 27).
- Towards the end of the observed follow-up, the OS curves from MMY2002 and SACT are observed to converge; if subsequent therapy use was driving increased OS in MMY2002, the curves would diverge at later time points (i.e., as more patients begin subsequent therapies).

**Figure 27 K-M curves for daratumumab OS from MMY2002 and SACT**

Abbreviations: CI, confidence interval; HR, hazard ratio; K-M, Kaplan-Meier; SACT, Systemic Anti-Cancer Therapy.

**A13. Priority Question. Please provide the mean and 95% confidence interval for the MMY2002 final data-cut for the following outcomes:**

a) **length of follow-up;**
b) **OS;**
c) **PFS; and**
d) **TTD.**

The mean length of follow-up, OS, PFS and TTD from the final data cut of MMY2002 is presented in Table 6. Please note that a restricted mean is presented for OS, PFS and TTD, given that the event of interest was not observed for all patients in MMY2002; the 95% confidence interval was generated from the standard error under the assumption of normality.

**Table 6 Mean outcomes from MMY2002 (final data cut)**

| Outcome | Mean (months) | 95% CI |
|---|---|---|
| Length of follow-up | [redacted] | [redacted] |
| OS | [redacted] | [redacted] |
| PFS (IRC) | [redacted] | [redacted] |
| PFS (INV) | [redacted] | [redacted] |
| TTD | [redacted] | [redacted] |

Abbreviations: CI, confidence interval; INV, investigator; IRC, independent review committee; OS, overall survival; PFS, progression-free survival; TTD, time to discontinuation.

### *MMY3010 study*

**A14. Priority question. Please provide details of the MMY3010 study including baseline characteristics and results for all primary and secondary outcomes.**

All available details on the MMY3010 study are presented by Cook et al (4). The authors of the publication stated the following that may be worth highlighting:

*''Efficacy was not formally evaluated in this study. Investigator-assessed disease response (e.g., disease progression or lack of clinical benefit) was used to determine whether continued treatment with daratumumab was warranted, and investigator-assessed best disease response according to IMWG[b] criteria was reported''.*

As previously discussed in the Company's CDF review engagement form, the objective of the Early Access Program (EAP) MM3010 study was to provide early access to daratumumab monotherapy and collect additional safety and patient reported outcomes data for 293 patients with heavily pre-treated relapsed and refractory multiple myeloma between the 10th of February

[b] International Myeloma Working Group.

2016 and the 2nd of August 2018. In this cohort, 98 patients were from the UK. A summary of patient characteristics is presented in Table 7.

The only survival outcome reported was PFS as follows: median PFS was 4.63 months (95% confidence interval [CI]: 3.75, 5.75) (4). These data are comparable to PFS from MMY2002 (3.7 months [95% CI: 2.8, 4.6]). Additionally, the median duration of treatment in the EAP was 4.2 months (95% CI: 0.0, 24.1) (4).

EAP safety results are reported in Table 8 as follows: 176 (60.1%) patients had Grade 3 and 4 treatment-emergent adverse events (TEAEs). Frequently reported Grade 3 or 4 TEAEs (occurring in >10% of patients) were thrombocytopenia (18.8%), anaemia (11.9%), and neutropenia (11.6%).

In MMY3010, 61 patients (20.8%) discontinued treatment due to TEAEs, of which 11 (3.8%) patients discontinued treatment due to drug-related TEAEs, and 11 patients (3.8%) discontinued because of daratumumab therapy.

Key baseline characteristics for MMY3010 study are presented in Table 7.

**Table 7 Baseline characteristics (MMY3010 study)**

| Characteristic | MMY3010<br>Daratumumab 16 mg/kg<br>(N=293) |
|---|---|
| Age (years), n (%) | |
| 18 to <65 | 150 (51.2) |
| 65 to <75 | 103 (35.2) |
| ≥75 | 40 (13.7) |
| Median (range) | 64 (32–85) |
| Mean (SD) | 63.5 (9.4) |
| Sex, n (%) | |
| Male | 166 (56.7) |
| Female | 127 (43.3) |
| Race, n (%) | |
| White | 274 (93.5) |
| Other | 19 (6.5) |
| ECOG performance status, n (%) | |
| 0 | 112 (38.2) |
| 1 | 148 (50.5) |
| 2 | 33 (11.3) |

| Characteristic | MMY3010<br>Daratumumab 16 mg/kg<br>(N=293) |
|---|---|
| Number of previous lines of therapy, n (%) | |
| ≥ 3 | 293 (100) |
| Creatinine clearance, mL/min[a], n (%) (n = 292) | |
| ≥90 | 81 (27.7) |
| 60 to <90 | 108 (37.0) |
| 30 to <60 | 89 (30.5) |
| 15 to <30 | 14 (4.8) |
| <15 | 0 |
| Median (range) | 70.8 (18.2–242.3) |
| Mean (SD) | 76.1 (34.6) |
| Haemoglobin, g/L, n (%) | |
| <80 | 18 (6.1) |
| 80–100 | 105 (35.8) |
| <100 | 170 (58.0) |
| Median (range) | 105.0 (71.0–156.0) |
| Mean (SD) | 106.1 (17.2) |
| Platelet count, $10^9$/L, n (%) | |
| <75 | 42 (14.3) |
| ≥75 | 251 (85.7) |
| Median (range) | 150.0 (17.0–483.0) |
| Mean (SD) | 154.1 (72.7) |

Source: Cook, G. et al. 2020 (4)
Abbreviations: ECOG: Eastern Cooperative Oncology Group, SD: standard deviation
Note: Percentages may not add to 100% due to rounding ECOG performance status, SD
[a] Creatinine clearance was estimated using the Cockcroft and Gault formula based on laboratory tests

**Table 8 Most common (>3% of patients) grade 3–4 treatment-emergent adverse events**

| TEAEs | MMY3010 Daratumumab 16mg/kg (N=293) |
|---|---|
| Patients with grade 3–4, n (%) | 176 (60.1) |
| Hematologic, n (%) | |
| Thrombocytopenia | 55 (18.8) |
| Anaemia | 35 (11.9) |
| Neutropenia | 34 (11.6) |
| Lymphopenia | 23 (7.8) |
| Leukopenia | 16 (5.5) |
| Non-hematologic, n (%) | |
| Lower respiratory tract infection | 13 (4.4) |
| Pneumonia | 11 (3.8) |
| Pyrexia | 10 (3.4) |
| Hypercalcemia | 10 (3.4) |
| Back pain | 9 (3.1) |

Source: Cook, G. et al. 2020 (4)
Abbreviations: TEAEs, treatment-emergent adverse events

Table 9 provides a summary of the European Quality of Life Five Dimensions Questionnaire (EQ-5D–5L) change from baseline, by visit.

**Table 9 Summary of EQ-5D–5L change from baseline, by visit**

| | Baseline | Change from baseline | | | |
|---|---|---|---|---|---|
| | | Cycle 2, Day 1 | Cycle 3, Day 1 | Cycle 6, Day 1 | Cycle 8, Day 1 |
| Utility score[a] | | | | | |
| N[b] | 279 | 202 | 170 | 109 | 85 |
| Mean | 0.66 | 0.00 | 0.00 | 0.01 | 0.03 |
| SD | 0.27 | 0.20 | 0.20 | 0.23 | 0.20 |
| Median | 0.70 | 0.00 | 0.00 | 0.00 | 0.02 |
| Visual analogue score[c] | | | | | |
| N[b] | 279 | 202 | 170 | 109 | 84 |
| Mean | 57.59 | 0.19 | 1.87 | 2.43 | 3.74 |
| SD | 19.41 | 16.78 | 16.00 | 18.21 | 20.65 |
| Median | 59.00 | 0.00 | 1.00 | 3.00 | 3.00 |

Abbreviations: EQ-5D–5L, European Quality of Life Five Dimensions Questionnaire
[a]The EQ-5D–5L utility score ranges from 0 to 1 and represents the general, self-evaluated health status of each patient. A higher score indicates a high level of utility. All scores were collected electronically at baseline and on day 1 of each cycle.
[b]The number of patients shown are those who completed the assessment at both baseline and each respective time point.
[c]The EQ-5D–5L visual analogue score ranges from 0 to 100, with a high score indicating a high level of self-evaluated health. status. All scores were collected electronically at baseline and on day 1 of each cycle.

### *Systematic literature review*

**A15. Please provide an updated systematic literature review for clinical effectiveness studies of relevance to the decision problem in the NICE final scope.**

As agreed with the ERG, a systematic literature review restricted to POM+DEX and PANO+BORT+DEX will be provided alongside the technical engagement response.

### *Licensed dose*

**A16. Please confirm when the new subcutaneous dose of daratumumab was approved for use in the UK.**

A licence extension for a subcutaneous (SC) formulation of daratumumab was received in June 2020. [redacted]. The SC formulation is used by most patients, currently at a [redacted] conversion rate. Non-inferiority between the weight-based intravenous (IV) formulation of daratumumab and the SC formulation of daratumumab has been demonstrated as part of the COLUMBA (MMY3012) trial (5).

A summary of conversion rate volume percentages for daratumumab by formulation are presented in Figure 28 and Table 10 below.

**Figure 28 Daratumumab IV/SC monthly volume share ([redacted])**

Abbreviations: IV, intravenous; SC, subcutaneous.

**Table 10 Daratumumab conversation rate volume percentages by monthly split between formulation ([redacted])**

| Formulation | [redacted] | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| SC | [redacted] | | | | | | | | |
| IV | [redacted] | | | | | | | | |
| Formulation | [redacted] | | | | | | | | |
| SC | [redacted] | | | | | | | | |
| IV | [redacted] | | | | | | | | |

Abbreviations: IV, intravenous; SC, subcutaneous.

### *Additional question*

**A17. Please confirm when the new subcutaneous dose of daratumumab was approved for use in the UK.**

**Given the company's statement in the original CS that *"For the POM+DEX arm of MM-003, only mean and median TTD could be obtained from the literature (mean TTD: 4.656; median TTD: 2.854), therefore, the TTD curves for daratumumab were calibrated to match the observed mean and median from MM-003.",* can the company please clarify:**

**a) How the TTD survival curves for POM+DEX were derived.**

The TTD survival curves for POM+DEX were derived by goal seeking the parametric curve parameters to minimise the sum of squared differences between the predicted mean and median values and those of the data source.

**b) If any calibration exercise was undertaken in the TTD analysis in the CDF submission.**

No additional calibration exercise was conducted to inform the CDF submission. Given that no additional data on treatment duration were available from MM-003, the TTD curves for POM+DEX from the original submission (i.e. those matching the observed mean and median TTD from MM-003) were retained.

## Section B: Clarification on cost-effectiveness data

**For any scenarios requested in Section B, please ensure these are implemented as user-selectable options in the economic model so that these can be combined. Furthermore, if the company chooses to update its base case results, please ensure that cost-effectiveness results, sensitivity and scenario analyses incorporating the revised base case assumptions are provided with the response along with a log of changes made to the company base case.**

**B1. Priority question. Please provide the updated MMY2002 data (final data cut) on the first subsequent line (i.e. 5th line) of treatment received after daratumumab by filling the table below with the updated data (and adding any additional treatments if necessary).**

Treatment regimens used as the first subsequent treatment following daratumumab in MMY2002 are presented in Table 11. Regimens requested by the ERG are indicated in bold.

**Table 11 First subsequent treatment used following daratumumab in MMY2002**

| First subsequent treatment[α] | MMY2002 patients (N=106) |
|---|---|
| Patients undergoing subsequent treatment after daratumumab | [redacted] |
| Bortezomib, carfilzomib, pomalidomide, chemotherapy, dexamethasone and other | [redacted] |
| Bortezomib, chemotherapy and dexamethasone | [redacted] |
| Bortezomib, chemotherapy, dexamethasone and other | [redacted] |
| Bortezomib, chemotherapy and other | [redacted] |
| Bortezomib, panobinostat and dexamethasone | [redacted] |
| Bortezomib, pomalidomide and dexamethasone | [redacted] |
| Bortezomib, thalidomide, chemotherapy, and dexamethasone | [redacted] |
| Bortezomib, thalidomide, daratumumab, chemotherapy, dexamethasone and other | [redacted] |
| Carfilzomib and chemotherapy | [redacted] |
| Carfilzomib, chemotherapy, and dexamethasone | [redacted] |
| Carfilzomib, chemotherapy, and prednisone | [redacted] |
| Carfilzomib, daratumumab, chemotherapy, dexamethasone and other | [redacted] |
| Carfilzomib and dexamethasone | [redacted] |
| Carfilzomib, panobinostat and dexamethasone | [redacted] |
| Carfilzomib, pomalidomide and chemotherapy | [redacted] |
| Carfilzomib, pomalidomide and dexamethasone | [redacted] |
| Chemotherapy | [redacted] |
| Chemotherapy and dexamethasone | [redacted] |
| Chemotherapy, dexamethasone, and prednisone | [redacted] |
| Chemotherapy and other | [redacted] |
| Dexamethasone | [redacted] |
| Elotuzumab and other | [redacted] |
| Ixazomib, pomalidomide and dexamethasone | [redacted] |
| Lenalidomide and chemotherapy | [redacted] |
| Lenalidomide, chemotherapy and dexamethasone | [redacted] |
| Pomalidomide | [redacted] |
| Pomalidomide, chemotherapy and dexamethasone | [redacted] |
| Pomalidomide, chemotherapy, dexamethasone, and prednisone | [redacted] |
| Pomalidomide and dexamethasone | [redacted] |
| Prednisone | [redacted] |

[α]Chemotherapy includes: melphalan, doxorubicin, bendamustine, vincristine, cisplatin, cyclophosphamide, etoposide, fludarabine, and carmustine.

**B2. Priority question. Please provide a table reporting the proportion of patients and respective therapies received in the updated MMY2002 data (final data cut) who received further treatment lines (i.e. 6th+) after daratumumab.**

Treatment regimens used as second and later subsequent therapies following daratumumab in MMY2002 are presented in Table 12.

**Table 12 Second and later subsequent treatments used following daratumumab in MMY2002 (N=106)**

| Subsequent treatment | Line of subsequent treatment | | | | | | |
|---|---|---|---|---|---|---|---|
| | 2nd | 3rd | 4th | 5th | 6th | 7th | 8th |
| Patients undergoing subsequent therapy after daratumumab | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Bortezomib | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Bortezomib and chemotherapy | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Bortezomib, chemotherapy and dexamethasone | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Bortezomib, chemotherapy, dexamethasone and other | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Bortezomib, chemotherapy and other | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Bortezomib, lenalidomide, daratumumab, chemotherapy, dexamethasone and other | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Bortezomib, panobinostat and dexamethasone | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Bortezomib, pomalidomide and dexamethasone | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Bortezomib, thalidomide, chemotherapy, dexamethasone and other | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Bortezomib, thalidomide, panobinostat, chemotherapy and dexamethasone | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Carfilzomib | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Carfilzomib and chemotherapy | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Carfilzomib, chemotherapy, and dexamethasone | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Carfilzomib and dexamethasone | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Carfilzomib, lenalidomide and dexamethasone | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Carfilzomib, panobinostat and dexamethasone | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

| Subsequent treatment | Line of subsequent treatment | | | | | | |
|---|---|---|---|---|---|---|---|
| | 2nd | 3rd | 4th | 5th | 6th | 7th | 8th |
| Carfilzomib, pomalidomide, chemotherapy and dexamethasone | [redacted] | | | | | | |
| Carfilzomib, pomalidomide and dexamethasone | [redacted] | | | | | | |
| Carfilzomib, thalidomide, and dexamethasone | [redacted] | | | | | | |
| Carfilzomib, thalidomide, panobinostat, chemotherapy and dexamethasone | [redacted] | | | | | | |
| Chemotherapy | [redacted] | | | | | | |
| Chemotherapy and dexamethasone | [redacted] | | | | | | |
| Chemotherapy and other | [redacted] | | | | | | |
| Chemotherapy and prednisone | [redacted] | | | | | | |
| Daratumumab and other | [redacted] | | | | | | |
| Dexamethasone | [redacted] | | | | | | |
| Elotuzumab and other | [redacted] | | | | | | |
| Ixazomib, pomalidomide and dexamethasone | [redacted] | | | | | | |
| Lenalidomide, dexamethasone and other | [redacted] | | | | | | |
| Lenalidomide, elotuzumab, dexamethasone and other | [redacted] | | | | | | |
| Lenalidomide, panobinostat and dexamethasone | [redacted] | | | | | | |
| Other | [redacted] | | | | | | |
| Pomalidomide | [redacted] | | | | | | |
| Pomalidomide, chemotherapy and prednisone | [redacted] | | | | | | |
| Pomalidomide and dexamethasone | [redacted] | | | | | | |

| Subsequent treatment | Line of subsequent treatment | | | | | | |
|---|---|---|---|---|---|---|---|
| | 2nd | 3rd | 4th | 5th | 6th | 7th | 8th |
| Pomalidomide, panobinostat and dexamethasone | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Pomalidomide and prednisone | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Thalidomide, chemotherapy, and dexamethasone | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Thalidomide and dexamethasone | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

Note: chemotherapy includes: melphalan, doxorubicin, bendamustine, vincristine, cisplatin, cyclophosphamide, etoposide, fludarabine, and carmustine.

**B3. Priority question. Please include a scenario in the economic model where the subsequent treatments received after daratumumab (and respective costs and other relevant outcomes in the model) are those received by patients in the MMY2002 final data cut (as per the company's answer to question B1).**

The results of the scenario that models subsequent therapy costs as per question B1 versus POM+DEX and PANO+BORT+DEX are presented in Table 13 and Table 14, respectively. Chemotherapy was costed assuming the costs of cyclophosphamide, and the costs of 'other' therapies were not included. A dropdown menu to select this scenario is included in cell E10 on the 'Subs Tx' sheet of the cost-effectiveness model.

**Table 13 Cost-effectiveness results versus POM+DEX based on subsequent therapy data from MMY2002 (as per company's answer to question B1)**

| Technologies | Total costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER versus baseline (£/QALY) |
|---|---|---|---|---|---|
| POM+DEX | [redacted] | [redacted] | - | - | - |
| Daratumumab | [redacted] | [redacted] | [redacted] | [redacted] | Daratumumab dominates |

Abbreviations: ICER, incremental cost-effectiveness ratio; POM+DEX, pomalidomide plus dexamethasone; QALY, quality-adjusted life year.

**Table 14 Cost-effectiveness results versus PANO+BORT+DEX based on subsequent therapy data from MMY2002 (as per company's answer to question B1)**

| Technologies | Total costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER versus baseline (£/QALY) |
|---|---|---|---|---|---|
| PANO+BORT+DEX | [redacted] | [redacted] | - | - | - |
| Daratumumab | [redacted] | [redacted] | [redacted] | [redacted] | Daratumumab dominates |

Abbreviations: ICER, incremental cost-effectiveness ratio; PANO+BORT+DEX, panobinostat plus bortezomib and dexamethasone; QALY, quality-adjusted life year.

**B4. Priority question. Please include a scenario in the economic model where the subsequent treatments received after POM+DEX (and respective costs and other relevant outcomes in the model) are those received by patients in the MM-003 trial (i.e. where 44% of patients received subsequent treatments, and each subsequent treatment received is modelled according to the table below). If there is a more recent data cut available for subsequent therapies received in MM-003, please use that data instead.**

**Table 15 Subsequent treatments received after POM+DEX (MM-003)**

| Subsequent treatment | Proportion of MM-003 patients |
|---|---|
| Dexamethasone | 29% |
| Pomalidomide | 0% |
| Cyclophosphamide | 21% |
| Carfilzomib | **2%** |
| Bortezomib | 18% |
| Lenalidomide | **5%** |
| Melphalan | **8%** |
| Etoposide | **3%** |
| Bendamustine | 11% |
| Thalidomide | **7%** |
| Values in bold are from a cut-off date of March 2013 while the other values are from a more up to date cut-off point of September 2013 | |

The results of the scenario that models POM+DEX subsequent therapies based on the therapies received in the MM-003 trial are presented in Table 16. A dropdown menu to select this scenario is included in cell E10 on the 'Subs Tx' sheet of the cost-effectiveness model.

**Table 16 Cost-effectiveness results versus POM+DEX modelling subsequent therapies in the POM+DEX arm based on MM-003**

| Technologies | Total costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER versus baseline (£/QALY) |
|---|---|---|---|---|---|
| POM+DEX | [redacted] | [redacted] | - | - | - |
| Daratumumab | [redacted] | [redacted] | [redacted] | [redacted] | Daratumumab Dominates |

Abbreviations: ICER, incremental cost-effectiveness ratio; POM+DEX, pomalidomide plus dexamethasone; QALY, quality-adjusted life year.

**B5. Priority question. Please include a scenario in the economic model where the survival outcomes for daratumumab (i.e. OS and PFS) are based on the data below (please conduct survival analysis according to TSD 14 in order to extrapolate the relevant KM data):**

a) **naive comparison of MMY2002 data (latest data cut) versus POM+DEX (as per question A8).**
b) **naive comparison of MMY2002 data (latest data cut) versus PANO+BORT+DEX (as per question A9).**

The results of the scenario that models daratumumab OS and PFS based on a naïve comparison of MMY2002 versus POM+DEX and PANO+BORT+DEX are presented in Table 17 and Table 18, respectively. This scenario can be generated in the cost-effectiveness model by selecting 'Naïve comparison' in Cells G83 and G85 on the 'Controls' sheet.

**Table 17 Cost-effectiveness results versus POM+DEX based on naïve comparison of MMY2002 versus POM+DEX (as per company's answer to question A8)**

| Technologies | Total costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER versus baseline (£/QALY) |
|---|---|---|---|---|---|
| POM+DEX | [redacted] | [redacted] | – | – | – |
| Daratumumab | [redacted] | [redacted] | [redacted] | [redacted] | Daratumumab dominates |

Abbreviations: ICER, incremental cost-effectiveness ratio; POM+DEX, pomalidomide plus dexamethasone; QALY, quality-adjusted life year.

**Table 18 Cost-effectiveness results versus PANO+BORT+DEX on naïve comparison of MMY2002 versus PANO+BORT+DEX (as per company's answer to question A9)**

| Technologies | Total costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER versus baseline (£/QALY) |
|---|---|---|---|---|---|
| PANO+BORT+DEX | [redacted] | [redacted] | – | – | – |
| Daratumumab | [redacted] | [redacted] | [redacted] | [redacted] | Daratumumab dominates |

Abbreviations: ICER, incremental cost-effectiveness ratio; PANO+BORT+DEX, panobinostat plus bortezomib and dexamethasone; QALY, quality-adjusted life year.

**B6. Priority question. Please include a scenario in the economic model where the survival outcomes for daratumumab (i.e. OS and PFS) are based on the naive comparison of the SACT data versus POM+DEX and PANO+BORT+DEX (as per questions A10 and A11). Please conduct survival analysis according to TSD 14 in order to extrapolate the relevant KM data.**

A scenario is presented in the company submission for the CDF review in which unadjusted SACT data are used to inform OS, PFS, and TTD for daratumumab

(resulting in a naïve comparison versus POM+DEX and PANO+BORT+DEX). Survival analysis was performed in line with NICE DSU TSD 14.

This approach is described in Section A.8.1 of the company submission. Please note that the results for this scenario presented in the company submission are incorrectly reported. Corrected results for this scenario are presented in Table 19 and Table 20 below. All other scenario analysis results were checked and confirmed to be correct.

In the Microsoft® Excel-based cost-effectiveness model, the option to use either trial data or SACT data for daratumumab is provided in Cell G78 on the 'Controls' sheet.

**Table 19 Cost-effectiveness results based on naïve comparison between daratumumab (SACT data) and POM+DEX**

| Technologies | Total costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER versus baseline (£/QALY) |
|---|---|---|---|---|---|
| POM+DEX | [redacted] | [redacted] | – | – | – |
| Daratumumab | [redacted] | [redacted] | [redacted] | [redacted] | Daratumumab dominates |

Abbreviations: ICER, incremental cost-effectiveness ratio; POM+DEX, pomalidomide plus dexamethasone; QALY, quality-adjusted life year.

**Table 20 Cost-effectiveness results based on naïve comparison between daratumumab (SACT data) and PANO+BORT+DEX**

| Technologies | Total costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER versus baseline (£/QALY) |
|---|---|---|---|---|---|
| PANO+BORT+DEX | [redacted] | [redacted] | – | – | – |
| Daratumumab | [redacted] | [redacted] | [redacted] | [redacted] | Daratumumab dominates |

Abbreviations: ICER, incremental cost-effectiveness ratio; POM+DEX, pomalidomide plus dexamethasone; QALY, quality-adjusted life year.

**B7. Please explain why patients' characteristics (age, weight, and height) have changed in the model submitted for this CDF review.**

In the original submission, patient age, weight, and height were taken from the pooled data set (MMY2002 and GEN501) to align with the efficacy data used in the base case. In the company submission for the CDF review, the new base case uses efficacy data from MMY2002 only, as it is considered more reflective of UK clinical practice and closely matches the marketing authorisation. On the same basis, patient characteristics in the new base case are taken from MMY2002 only.

**B8. Please justify the choice of a 20% decrease applied in the scenario analysis to estimate the reduction of patients receiving subsequent treatments in the comparator arms.**

In the company submission for the CDF review, the proportion of patients receiving subsequent therapies ([redacted]) was taken from SACT and assumed to be the same across all comparators. However, as discussed in the original submission and validated by clinical expert opinion, treatment with daratumumab may improve the patient's underlying state (given its mechanism of action of utilising the body's own immune system by reducing immunosuppression caused by the malignant cells), meaning they may be more likely to receive subsequent therapies compared with those treated with other agents, such as pomalidomide or panobinostat.

To explore uncertainty related to the proportion of patients receiving subsequent therapy, a hypothetical scenario was performed in which the proportion of patients receiving subsequent therapies was reduced by an arbitrary 20% in both the POM+DEX and PANO+BORT+DEX arms of the model. In this scenario, daratumumab remained dominant versus both POM+DEX and PANO+BORT+DEX, further demonstrating overall robustness of the cost-effectiveness results.

## Section C: Textual clarification and additional points

**C1. Please clarify if the date for the data presented in Table 25 for the column labelled 'Daratumumab 16 mg/kg 31st December 2017' should read 9th January 2015 rather than 31st December 2017**

In Table 25 (Appendix F), the second column (labelled 'Daratumumab 16 mg/kg 31st December 2017') should read 'Daratumumab 16 mg/kg 31st December 2015', as per the original submission.

## References

1. Janssen. Data on File - Daratumumab Clinical Insights Meeting Minutes: Cancer Drug Fund review of TA510 Daratumumab monotherapy. 2021.
2. Signorovitch JE, Sikirica V, Erder MH, Xie J, Lu M, Hodgkins PS, et al. Matching-adjusted indirect comparisons: a new tool for timely comparative effectiveness research. Value Health. 2012;15(6):940-7.
3. National Institute for Health and Care Excellence (NICE). Cancer Drugs Fund - Managed Access Agreement - Daratumumab monotherapy for treating relapsed and refractory multiple myeloma. Available at: https://www.nice.org.uk/guidance/ta510/documents/committee-papers-5 (last accessed 1st November 2021). 2017.
4. Cook G, Corso A, Streetly M, Mendeleeva LP, Ptushkin VV, Chan E, et al. Daratumumab Monotherapy for Relapsed or Refractory Multiple Myeloma: Results of an Early Access Treatment Protocol in Europe and Russia. Oncol Ther. 2021;9(1):139-51.
5. Mateos M, Nahi H, Legiec W, Grosicki S, Vorobyev V, Spicka I, et al. Efficacy and safety of the randomized, open-label, non-inferiority, phase 3 study of subcutaneous (SC) versus intravenous (IV) daratumumab (DARA) administration in patients (pts) with relapsed or refractory multiple myeloma (RRMM): COLUMBA. American Society of Clinical Oncology. 2019.

NICE National Institute for Health and Care Excellence

# Patient organisation submission

## Daratumumab monotherapy for treating relapsed and refractory multiple myeloma (CDF review of TA510) [ID3881]

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. 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 receive no government funding 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. We are not a membership organisation.</td></tr>
<tr><td>4b. 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.]</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>110,000</td><td>12,337</td><td>122,337</td></tr>
<tr><td>Janssen-Cilag</td><td>20,000</td><td>327</td><td>20,327</td></tr>
</table>
The table above shows the audited 2019 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>
</table>

| | |
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| If so, please state the name of manufacturer, amount, and purpose of funding. | |
| 4c. Do you have any direct or indirect links with, or funding from, the tobacco industry? | No |
| 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:<br>- Structured telephone interviews with relapsed myeloma patients about living with myeloma, their experience and expectations of treatment, and their thoughts on the myeloma treatment pathway.<br>- A multi-criteria decision analysis study of 560 myeloma patients, 70% of whom had received at least two prior lines of treatment. 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.<br>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 | **What is it like to live with myeloma?**<br>*"The uncertainty of not knowing when it will come back but the certainty of knowing it will is particularly difficult."* |

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| experience when caring for someone with the condition? | 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.<br><br>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.<br><br>*"The problem with myeloma is that you can set a goal, work towards it but then suddenly when you relapse it's dragged away again." Patient on 3rd line of treatment*<br><br>Multiply relapsed patients, the patient population covered in this appraisal, often experience an even more significant disease burden. They not only face a worse prognosis but also a greater symptomatic burden, due to the progressive nature of the disease and the cumulative effects of treatment which can result in reduced quality of life. 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.<br><br>*"The most difficult thing is not being able to plan things. I can't predict when I will have a bad night or feel fatigued. That is really hard." Patient with high risk myeloma on 5th line treatment*<br><br>*"That uncertainty and thinking you might have come to the end of the road that is so worrying." Patient on 5th line treatment*<br><br>Treatment related adverse events also generally increase with number of lines of therapy; the proportion of patients with one or more toxicity or comorbidity at the end of treatment increases with lines of treatment. |

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| | That said, patients often see symptoms and side effects as something to be expected and accept it as part of their disease and/or treatment, with many patients developing self-care strategies.<br><br>*"I have had a lot of treatment but I'm still up and about, walking and doing what I want to do. Overall, I would rate my quality of life highly." Patient at 5th line of treatment*<br><br>**What do carers experience?**<br><br>*"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".*<br><br>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:<br><br>- 94% of carers are emotionally impacted and found the uncertainty of myeloma a major factor.<br>- 25% of those in work had been unable to work or had to retire early to care for the person with myeloma.<br>- 84% always put the needs of their relative or friend with myeloma before their own.<br>- Only 42%of carers were not given enough information at diagnosis about how myeloma may affect them.<br><br>Living with myeloma is therefore often extremely challenging physically and emotionally for patients, carers, and family members.<br><br>*"I had to think of my husband. You are in this as a team, it is not an individual battle."* |

| Current treatment of the condition in the NHS | |
|---|---|
| 7. What do patients or carers think of current treatments and care available on the NHS? | Patients and carers appreciate the wider range of effective treatments that are now available for treating relapsed and refractory myeloma which has delivered significant improvements in survival in myeloma over the past decade. However, myeloma remains a challenging cancer to treat, often particularly so for multiply relapsed patients.<br><br>Myeloma is a relapsing and remitting cancer which evolves over time and becomes resistant to treatment; a range of treatment options with different mechanisms of action at each stage of the pathway is therefore vital for myeloma patients.<br><br>Current treatments available at 4th line through routine commissioning include Pomalidomide (Imnovid®) and dexamethasone (which is also available beyond 4th line) and Panobinostat (Farydak®) in combination with bortezomib and dexamethasone. There is also the CDF approved triplet available in Isatuximab (Sarclisa®) in combination with pomalidomide and dexamethasone.<br><br>Myeloma patients and their carers place a very high value on treatments that:<br><br>• **Prolong their life.**<br>• **Put their myeloma into remission for as long as possible.**<br>• **Allow them to enjoy normal day-to-day life.**<br><br>The Myeloma UK, EMA and the University of Groningen study showed that, achieving a lasting remission from treatment was the most important factor for most (75%) participants. This was true across all patient groups regardless of demographic and clinical characteristics.<br><br>Treatments with minimal negative impact on quality of life are very important, particularly those with as few side effects as possible and of low severity. 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. |

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| | Finally, due to its relapsing and remitting nature, patients see gains in survival as a "bridge" to further treatments coming down the line<br><br>*"The longer you stay well the better chance that another good treatment will come along." Patient on 4th line of treatment*<br><br>*"Only one benefit for this new treatment for me and that is staying alive for six months… if I could get maybe another drug trial, this and the panobinostat and pomalidomide then that is an extra two years instead of one year. Then maybe by that time something such as the CAR-T cells treatment will have progressed. However long I can extend my life then that is a positive, it is all about staying alive." Patient with high risk myeloma on 5th line treatment* |
| 8. Is there an unmet need for patients with this condition? | Yes. Multiply relapsed patients face particular treatment challenges and currently there are too few options, especially for patients at fourth line and beyond.[1]<br><br>Proteasome inhibitors (PI) and immunomodulatory (IMiD) drugs are the most commonly used in treating relapsed myeloma patients. Therefore, treatment options for patients previously treated with or refractory to proteasome inhibitors and immunomodulatory drugs are limited.<br><br>Data has shown that the life expectancy for multiply relapsed myeloma patients with prior treatment with a PI and an IMiD is typically less than 12 months. For patients who are refractory to both a PI and an IMid, median life expectancy is 8-9 months, and for patients who are refractory to three or four of the common PIs and IMiDs median life expectancy decreases to only 3-5 months.[2]<br><br>Due to the complex and fast-moving treatment pathway there is a considerable number of patients who will be at 2nd or 3rd line of treatment who have not yet had the opportunity to be treated with a CD38 |

[1] Most patients can be successfully treated at relapse, however, each remission is usually associated with diminishing duration and depth of response over time. If possible combinations of drugs are used compared with initial therapy (Bird, S.A. and Boyd, K., (2019). Multiple myeloma: an overview of management. Palliative Care and Social Practice, 13, p.1178224219868235.)

[2] Gooding S, Lau IJ, Sjeikh M et al, Double Relapsed and/or Refractory Multiple Myeloma: Clinical Outcomes and Real World Healthcare Costs. PLoS ONE. 2015. 10 (9): *e0136207*)

| | |
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| | monoclonal antibody. This also includes patients who cannot access the CDF approved Daratumumab in combination with bortezomib (Velcade®) and dexamethasone at 2nd line due to peripheral neuropathy caused by the Velcade.<br><br>This is especially significant as more new treatments are going to potentially become available for multiple relapsed patients that require them to be exposed to an IMid, a proteasome inhibitor and a CD38 monoclonal antibody. If this option were to be removed from the pathway these patients may not be able to access further treatments down the line.<br><br>*"The longer remissions are probably what is most important to me. A longer remission means it is more likely new drugs become available. This gives us who are multiply relapsed more options." Patient on 4th line of treatment* |
| **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.<br><br>In the original 2017 appraisal data for this treatment was submitted from two clinical trials MMY2002 and GEN501. An integrated analysis of the efficacy and safety of Daratumumab Monotherapy in both clinical trials produced results which are highly valued by patients.[3]<br><br>**Response:** Combined data from Study MMY2002 and Part 2 of Study GEN501 resulted in an Overall Response rate of 31% and a duration of response of 7.6 months. A depth of response (VGPR or better) of 11% was observed which is significant for a patient population that have gone through a number of treatments and relapses.[4] |

[3] Petrucci, Maria T., and Federico Vozella. 2019. "The Anti-CD38 Antibody Therapy in Multiple Myeloma" *Cells* 8, no. 12: 1629. https://doi.org/10.3390/cells8121629
[4] Ibid

| | |
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| | **Progression free survival (PFS) and Overall Survival (OS):** The combined clinical trial data shows a PFS gain of 4 months (95% CI: 3.0–5.6) and OS was measured at 19.9 months at 14.8-month follow-up; (95% CI: 15.1–NE).[5]<br><br>**Quality of life:** Importantly, daratumumab monotherapy demonstrated a highly favourable safety profile. The treatment was well tolerated with manageable side effects, and no patient discontinued treatment because of a drug-related treatment related side effects or an infusion-related reaction.<br><br>Overall, the data from both clinical trials demonstrated that daratumumab monotherapy has a highly favourable benefit/risk profile in heavily pre-treated patients with multiple myeloma who otherwise have very limited treatment options.<br><br>**Treatment Administration:** The ability to have daratumumab subcutaneously is now highly valued by patients. This is especially significant for patients who are receiving Daratumumab and want to reduce their risk of being exposed to infection such as COVID-19.<br><br>*"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."* |

[5] Ibid

| Disadvantages of the technology | |
|---|---|
| 10. What do patients or carers think are the disadvantages of the technology? | **Side Effects**<br><br>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.<br><br>Data from MMY2002 shows the most common (≥20%) side effects included fatigue (39.6%), anemia (33.0%), nausea (29.2%), thrombocytopenia (25.5%), neutropenia (22.6%), back pain (21.7%), and cough (20.8%). The most common Grade 3 or 4 side effects (>10%) were anemia (23.6%), thrombocytopenia (18.9%), and neutropenia (12.3%). The most frequently reported serious side effects (≥3%) were general physical health deterioration (4.7%), pneumonia (3.8%), and hypercalcemia (3.8%).[6]<br><br>Infusion-related reactions occurred in 42.5% of subjects. The vast majority (>90%) of these reactions were Grade 1 or 2 in severity and occurred during the first two infusions.[7]<br><br>There is strong evidence to show that patients will tolerate fairly severe side effects as long as the treatment is delivering in terms of efficacy, although there is of course some variation on an individual basis in terms of what this means in practice. Despite the increasing symptom burden, only 3% of patients at 4th or 5th line choose to discontinue treatment. [8]<br><br>*"I have never yet had a time where I have thought seriously about stopping a treatment because of side effects and I find it hard to imagine that I would." – Patient on 5th line treatment*<br><br>**Treatment Administrations -** Giving the treatment by IV infusion 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 have to accompany the patient to hospital. Oral treatments are often valued by patients, particularly those who are working and have dependents. That said, our patient engagement has shown that there are also patients who welcome their treatment being delivery in the safety of a hospital environment and the opportunity to interact with clinical staff and other patients. |

[6] Ibid
[7] Ibid
[8] Yong, K. et al 2016, Multiple myeloma: patient outcomes in real-world practice. British Journal of Haematology, 175(2), pp. 252-264.

| | |
|---|---|
| | Overwhelmingly, clinical efficacy and the opportunity of a good remission outweighs any disadvantages in the method of administration.<br>*"Going to the hospital for an infusion is not a problem for me. I'm used to it and my husband is able to drive me." Patient on 5th line of treatment* |
| **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. | Daratumumab can be described as a significant innovation in the treatment of multiple myeloma and many patients experience long periods in remission while receiving a highly tolerable treatment. As stated above there is a considerable number of patients who will not have been able to access the CDF approved daratumumab combination at second line due to peripheral neuropathy caused by bortezomib (Velcade®). Many of these patients will be at 2nd or 3rd line of treatment and deserve the opportunity to be treated with this effective and highly tolerable treatment for multiple myeloma. |
| **Equality** | |
| 12. Are there any potential equality issues that should be taken into account when considering this condition and the technology? | No |

| Other issues | |
|---|---|
| 13. Are there any other issues that you would like the committee to consider? | We would strongly advocate for access to this treatment to be made available for patients from 4th line and beyond. This would bring the recommendation into line with the EMA Marketing Authorisation which stats that Daratumumab can be used "*on its own when the disease has come back after treatment with cancer medicines (including proteasome inhibitors) and immunomodulatory medicines (that act on the immune system), or when the disease has not improved with these medicines."*<br><br>In the clinical trial setting the treatment has been shown to be effective for multiply relapsed patients. Data from MMY2002 and GEN501 focused on patients who had received a median of 5 prior lines of treatment.<br><br>Our Patient engagement has shown that some patients who are beyond 5th line can have a good treatment period while receiving Daratumumab: *"It has brought my paraprotein levels down to zero. All my other treatments never did that, and this has kept them at zero for two years. The side effects have been absolutely zero, all my other treatments had something uncomfortable associated with them. From day one, daratumumab has been absolutely fine. My treatment started as an infusion which involved going to hospital for a few hours. Now that I am getting it subcutaneously it is much speedier and quicker. I think it should be emphasised that Daratumumab should be available as widely as possible as it is an effective treatment for people who have had multiple lines of treatment."* Patient on 6th line of treatment<br><br>As more patients are living to 5th line and beyond, they need more options to be treated with.<br><br>*"What is concerning is I am running out of drugs and treatments. When I was first diagnosed I was given three years and that was fifteen years ago. I have had fantastic treatment but as I go through the lines we are running out of options. It's not clear when and why we can receive certain treatments at certain lines. This is a big bug bear of mine, people who have gone through many relapses are being forgotten about." Patient on fourth line of treatment*<br><br>We understand that this must be backed up by data and we would ask that company are able to submit data for patients who may benefit from this treatment from 4th line and beyond, including patients who may have accessed this privately through insurance or self-funding. |

| | |
|---|---|
| 14. Is the combination of panobinostat plus bortezomib and dexamethasone used to treat patients with heavily pre-treated and highly refractory multiple myeloma at third or fourth line in NHS clinical practice? | In our experience and engagement with myeloma patients there are not many patients who are treated with Panobinostat in combination with pomalidomide and dexamethasone at 3rd or 4th line of therapy. However, this still remains a vital option for patients who have are intolerant of other treatments in the myeloma pathway. |

**Key messages**

15. In up to 5 bullet points, please summarise the key messages of your submission:

- Daratumumab monotherapy delivers on patients preferences as it can put their myeloma into remission for as long as possible, prolong their life and allow them to enjoy a normal day to day life.
- Daratumumab monotherapy is a well-tolerated treatment which can provide clear clinical benefits in heavily pre-treated multiply relapsed patients with multiple myeloma who otherwise have very limited treatment options.
- As a monotherapy it is particularly important for patients to access a CD38 monoclonal antibody who are intolerant to other treatments due to severe peripheral neuropathy.
- The ability to give the treatment subcutaneously is highly valued by patients as this reduces the amount of time spent in hospital.
- The clear benefits of daratumumab in multiply relapsed patients shows that access to this treatment should be widened to patients from 4th line of treatment and beyond.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

## Professional organisation submission

# Daratumumab monotherapy for treating relapsed and refractory multiple myeloma (CDF review of TA510) [ID3881]

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 tick all that apply): | ☒ an employee or representative of a healthcare professional organisation that represents clinicians?<br>☒ a specialist in the treatment of people with this condition?<br>☒ a specialist in the clinical evidence base for this condition or technology?<br>☐ other (please specify): |
| 5a. Brief description of the organisation (including who funds it). | The UK Myeloma Forum (UKMF) is a charity for healthcare professionals that works to provide education and support for doctors, nurses, physiotherapists, pharmacists, scientists and researchers (including trial practitioners), as well as support for clinical research activities, working closely alongside the Myeloma Research Academy, a subgroup of the NCRI haematological oncology clinical studies group. Importantly the UKMF has a major advocacy role, working alongside Myeloma UK, the patient and carer support charity, to provide a voice for patients with regard to the access and approval of newly licensed treatments. In this regard, the UKMF works alongside NICE and NHSE in evaluating trial evidence with regard to the benefit for patients, the likely cost, both to the payer and to the patient in terms of quality of life, treatment and disease burden. |
| 4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant | UKMF has received an unrestricted grant from and Janssen-Cilag (£12,000) per annum). UKMF has also received unrestricted educational grants from other pharmaceutical companies. |

| | |
|---|---|
| manufacturers are listed in the appraisal matrix.]<br><br>If so, please state the name of manufacturer, amount, and purpose of funding. | |
| 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.) | Treatment is aimed at (1) controlling symptoms and treating complications, for example, alleviating bone pain, treating infections and reversing renal failure (2) halting disease activity and progression by eliminating the cancerous plasma cells, and (3) maintaining disease in a quiescent state, although this is strictly speaking not remission, as cure is rare. The majority of patients respond well to initial therapy and achieve disease stability, where the quality of the response to treatment is often measured by the reduction in the secreted paraprotein, thus ranging from complete response (CR) to stable disease (SD). During periods of disease control, patients may be off treatment or may continue on some treatment, but most will enjoy a return to reasonable quality life with good social and economic functioning. |
| 7. What do you consider a clinically significant treatment response? (For example, a | A clinically significant treatment response is any response that is accompanied by the disappearance of the signs and symptoms of active disease (including plasmacytomas) causing organ damage and/or symptoms, and is durable, i.e. lasts for at least 2-3 years in the case of newly diagnosed patients being treated for the first time, or at least 6 months in the case of patients being treated for relapse. Clinically |

| | |
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| reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.) | significant treatment responses are often measured as a complete response (disappearance of the paraprotein). Disease response is also assessed using CT or MRI scans, where the resolution of areas of active disease are also indicative of a complete response. Prospective published studies indicate that patients who achieve complete response and/or minimal residual disease negativity have longer disease free survival and usually longer overall survival compared to those who do not. |
| 8. In your view, is there an unmet need for patients and healthcare professionals in this condition? | Because this is an incurable cancer, and all patients will die of their myeloma, unless they perish from another cause, there is indeed an unmet need in the condition. In particular, those individuals who have received three prior therapies or more have a high unmet need as their condition has progressed despite having received the major currently available therapies. |
| **What is the expected place of the technology in current practice?** | |
| 9. How is the condition currently treated in the NHS? | The condition is currently treated with multi-drug regimens (including bortezomib or thalidomide or lenalidomide), and for patients who are sufficiently young and fit, the treatment paradigm includes high dose melphalan and autologous stem cell transplantation. Older and less medically fit patients receive only chemotherapy (same drugs). With subsequent relapse, patients are treated with chemotherapy again, often with different class of agents, in order to avoid drug resistance. Following development of drug resistance next therapy choices are based on exposure and response to previous treatments. |
| • Are any clinical guidelines used in the treatment of the condition, and if so, which? | UKMF/British Society for Haematology guidelines have recently been updated and published (Sive et al. (2021) *British Journal of Haematology* 193:245-268).<br>The choice of treatment is guided by NICE and NHSE/CDF approvals as outline in the scoping document. Pertinent to this appraisal are the Technology appraisals as described in the scope for this appraisal (TA171, TA380, TA505 for those who have had at least 2 prior therapies; TA427, TA510 and TA568 for those who have had at least 3 prior therapies). It should be noted that use of panobinostat / bortezomib / dexamethasone (TA380) is more often used after 4 – 5 lines of therapy. Other treatments such as |

| | |
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| | bendamustine or conventional chemotherapies (melphalan, cyclophosphamide) are infrequently used for active therapy due to low response rates and poor tolerability. |
| • 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.) | The pathway of care is well defined for newly diagnosed patients (see above), and at first relapse, regimens available include lenalidomide (with dexamethasone), daratumumab (with bortezomib) and carfilzomib (with dexamethasone). At second and subsequent relapse, the choice of treatment depends on previous therapies, and how well the patient has responded to those, as well as patient fitness and choice. In general, professionals across the NHS have similar approaches to treatment of this condition, the only exception being the availability of clinical trials in some centres. Following the CDF approval for daratumumab monotherapy a large number of patients accessed this preferentially as a 4$^{th}$ line therapy due to its excellent tolerability and good efficacy. The approval of daratumumab / bortezomib / dexamethasone (DVd; TA573) at 2$^{nd}$ line for patients who are not refractory to bortezomib has subsequently reduced the proportion and absolute numbers of patients eligible to receive daratumumab monotherapy at 4$^{th}$ line. However, ~25% of patients will be refractory to 1$^{st}$ line bortezomib and thereby ineligible for DVd. The NICE approval of TA658 (Isatuximab in combination with pomalidomide / dexamethasone) has led to this being used in preference for many patients at 4$^{th}$ line – in particular if cytopenia / thrombosis are not of concern. However, a significant proportion of patients will still elect or be more suitable for daratumumab monotherapy at 4$^{th}$ line despite TA658. |
| • What impact would the technology have on the current pathway of care? | The treatment is already approved via CDF. It will allow the continued flexibility to offer a single treatment that is well tolerated and in many cases an efficacious therapy. Administration is straightforward (subcutaneous) |
| 10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? | Yes – its is already used at 4$^{th}$ line |
| • How does healthcare resource use differ | No difference |

| | |
|---|---|
| between the technology and current care? | |
| • In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.) | Secondary care – specialist chemotherapy delivery units |
| • What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.) | None – already exists / being administered |
| 11. Do you expect the technology to provide clinically meaningful benefits compared with current care? | Clinical benefits have already been observed since approval via CDF. Response rates and duration are at least as good as reported in registration clinical trials. Since the marketing of a subcutaneous preparation the tolerability is excellent (superior to intravenous) for the vast majority of patients. It has the potential to be administered via Home Delivery services which enhances patient experience. |
| • Do you expect the technology to increase length of life more than current care? | Currently being given - with resulting improvements in length and quality of life. |
| • Do you expect the technology to increase health-related quality of | |

| | |
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| life more than current care? | |
| 12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population? | No – there are no predictive markers for response or non-response. |
| **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 | The technology is currently in use and presents no challenges. |

| | |
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| or ease of use or additional tests or monitoring needed.) | |
| 14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing? | Patients on therapy will have disease response assessment every 1 – 2 cycles of therapy. Each cycle is 28 days long. Treatment is discontinued if there is evidence of progressive disease, poor tolerance or withdrawal of patient consent. |
| 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? | This is an effective and simple to administer therapy that in clinical practice via the CDF has resulted in significant benefits in quality of life. Key among these is the low intensity / low toxicity nature of the treatment whilst maintaining disease stability. |
| 16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related | This is an established therapy that has demonstrated benefit when used as a monotherapy for patients who have not had prior exposure to anti-CD38 targeting treatment. |

| | |
|---|---|
| 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? | Daratumumab was the first approved monoclonal antibody for myeloma and is viewed as a step change in treatment. |
| • Does the use of the technology address any particular unmet need of the patient population? | It is associated with excellent responses and duration of response in a significant proportion of heavily pre-treated patients |
| 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? | The main side effect is 1st dose infusion related reaction. Pre-medication can limit the likelihood of this and almost all patients are able to proceed to subsequent treatments without problems. It is otherwise extremely well tolerated. |
| **Sources of evidence** | |
| 18. Do the clinical trials on the technology reflect current UK clinical practice? | The initial clinical trials reflected UK practice. Treatment approaches have moved forward since these trials and daratumumab monotherapy has not been further studied in clinical trials. |

| | |
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| • 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? | Overall response rates, depth of response, progression free survivial and overall survivial |
| • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? | Depth of response and progression free survival when viewed according to depth of response are excellent surrogates for long term outcomes |
| • 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 | No |

| | |
|---|---|
| treatment(s) since the publication of NICE technology appraisal guidance [TA510]? | |
| 21. How do data on real-world experience compare with the trial data? | Real world experience would suggest treatment is at least as efficacious and well tolerated as reported despite being extended to a less fit and older patient population. A published Real World Review of daratumumab monotherapy from a UK treatment centre (Sanchez I et al. BSH 2021-PO-177 *British Journal Of Haematology 2021:***193:** Suppl 1; page 168) observed overall response rates of ~40% and median progression free survival 5.5 months. This is at least as good as the reported outcomes in clinical trials. |
| **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. | Not applicable |
| **Topic-specific questions** | |

| | |
|---|---|
| 23 Is the combination of panobinostat plus bortezomib and dexamethasone used to treat patients with heavily pre-treated and highly refractory multiple myeloma at third or fourth line in NHS clinical practice? | This treatment combination is infrequently used and most often offered to patients at 4th or 5th line therapy. It would rarely be offered in preference to daratumumab monotherapy. |

**Key messages**

24. In up to 5 bullet points, please summarise the key messages of your submission.

- Daratumumab monotherapy via CDF has been associated with excellent responses and durations of response.
- Daratumumab is extremely well tolerated even when given to heavily pre-treated patients with fragile bone marrow
- Despite the access to daratumumab earlier in the treatment pathway and an alternative anti-CD38 monoclonal antibody at a similar time point in the pathway there remains a place for daratumumab monotherapy for less fit patients who are unable to tolerate immunomodulatory therapy (low blood counts or tendency to drop blood counts, prior class hypersensitivity, significant thrombosis, unable to take large capsules)
- Daratumumab monotherapy should continue to be an option for patients at 4th line and beyond to ensure therapy decisions are patients focused.
-

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# Daratumumab monotherapy for treating relapsed and refractory multiple myeloma (CDF review of TA510)

Cancer Drugs Fund Review

**Source of funding**

This report was commissioned by the NIHR Evidence Synthesis Programme as project number 13/52/68T.

| | |
|---|---|
| Title: | Daratumumab monotherapy for treating relapsed and refractory multiple myeloma (CDF review of TA510) |
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## Contribution of authors:

| | |
|---|---|
| Steve Edwards | Critical appraisal of the company's submission; validated the statistical analyses; provided feedback on all versions of the report. Guarantor of the report |
| Victoria Wakefield | Critical appraisal of the company's submission; critical appraisal of the clinical evidence; and drafted the summary, background and clinical results sections |

| | |
|---|---|
| Samantha Barton | Critical appraisal of the company's submission; critical appraisal of the clinical evidence; and assisted with drafting the clinical results sections |
| Mariana Bacelar | Critical appraisal of the company's submission; critical appraisal of the economic model; cross checking of company's search strategies; critical appraisal of the economic evidence; carried out the economic analyses; and drafted the economic sections |

All authors read and commented on draft versions of the ERG report.

# Table of Contents

# List of Tables

# List of Figures

# List of Abbreviations

| | |
|---|---|
| ACD | Appraisal consultation document |
| AE | Adverse event |
| ASCT | Autologous stem cell transplantation |
| CDF | Cancer Drugs Fund |
| CEAC | Cost-effectiveness acceptability curve |
| CEP | Cost-effectiveness plane |
| CI | Confidence interval |
| CSR | Clinical study report |
| ECOG | Eastern Cooperative Oncology Group |
| EoL | End of life |
| ERG | Evidence review group |
| ESS | Effective sample sizes |
| HR | Hazard ratio |
| ICER | Incremental cost-effectiveness ratio |
| IMiD | Immunomodulator |
| KM | Kaplan-Meier |
| MAIC | Match-adjusted indirect comparison |
| NE | Not estimable |
| NHS | National Health Service |
| NICE | National Institute for Health and Care Excellence |
| NMB | Net monetary benefit |
| OS | Overall survival |
| PANO+BORT+DEX | Panobinostat plus bortezomib and dexamethasone |
| PAS | Patient Access Scheme |
| PFS | Progression-free survival |
| PHE | Public Health England |
| PI | Proteasome inhibitor |
| POM+DEX | Pomalidomide plus dexamethasone |
| PSA | Probabilistic sensitivity analysis |
| QALY | Quality-adjusted life year |
| rrMM | Relapsed and refractory multiple myeloma |
| SACT | Systemic Anti-Cancer Therapy |
| SmPC | Summary of product characteristics |
| TEAE | Treatment-emergent adverse event |
| TTD | Time-to-discontinuation |

| | |
|---|---|
| UK | United Kingdom |
| WTP | Willingness-to-pay |

# 1 Executive summary

This summary provides a brief overview of the key issues identified by the evidence review group (ERG) as being potentially important for decision making. It also includes the ERG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides a critique of the adherence to committee's preferred assumptions from the Terms of Engagement (ToE) in the company's submission. Section 1.2 provides an overview of the key issues. Section 1.3 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.4 and 1.5 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main ERG report.

All issues identified represent the ERG's view, not the opinion of NICE.

## 1.1 Critique of the adherence to committees preferred assumptions from the Terms of Engagement in the company's submission

In general, the ERG considers that the company has adhered to the committee's preferred assumptions from the Terms of Engagement (ToE).

## 1.2 Overview of the ERG's key issues

Table 1 provides a summary of the ERG's key issues.

Table 1. Summary of key issues

| ID xxx | Summary of issue | Report sections |
|---|---|---|
| Issue 1 | Absence of an updated systematic literature review for the review of clinical effectiveness | 3.2 |
| Issue 2 | Uncertainty in the clinical-effectiveness estimates for daratumumab compared with POM+DEX and PANO+BORT+DEX | 3.1.4.3, 3.2 and 3.3 |
| Issue 3 | Source of treatment effectiveness in the model | 4.2.1 |
| Issue 4 | Impact of subsequent treatments received after daratumumab on overall survival | 4.2.3 |
| Issue 5 | Subsequent treatments modelled | 4.2.3 |

Abbreviations: ERG, evidence review group; MAIC, match-adjusted indirect comparison; PANO+BORT+DEX, panobinostat plus bortezomib and dexamethasone; POM+DEX, pomalidomide plus dexamethasone; and SLR, systematic literature review.

The key differences between the company's preferred assumptions and the ERG's preferred assumptions are the source of treatment effectiveness for daratumumab; and the subsequent treatments modelled after daratumumab and after POM+DEX.

## 1.3 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 extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Generating a survival benefit compared to POM+DEX and PANO+BORT+DEX;

Overall, the technology is modelled to affect costs by:

- Its lower unit cost compared with POM+DEX and PANO+BORT+DEX (when the PAS for daratumumab is included and the comparator list prices are used);
- Being better tolerated by patients than POM+DEX, therefore prolonging the time on treatment and possible number of subsequent treatments received;
- Being administered by subcutaneous injection.

The modelling assumptions that have the greatest effect on the ICER are:

- The source of treatment effectiveness used for daratumumab in the model (i.e., SACT vs MAIC data);
- The subsequent treatments modelled for POM+DEX.

## 1.4 The clinical effectiveness evidence: summary of the ERG's key issues

Table 2 and Table 3 present the key issues of the company's clinical effectiveness evidence.

Table 2. Issue 1: Absence of an updated systematic literature review for the review of clinical effectiveness

| Report section | 3.2 |
|---|---|
| Description of issue and | The ERG notes that the company has not updated the SLR for clinical |

| | |
|---|---|
| **why the ERG has identified it as important** | effectiveness evidence on daratumumab or the comparators of relevance to this appraisal (POM+DEX and PANO+BORT+DEX). The ERG is thus concerned that there may be new data available, in particular for the comparators POM+DEX and PANO+BORT+DEX that would be of relevance and may be more suitable than the current sources of data used in the MAICs in the company submission. |
| **What alternative approach has the ERG suggested?** | An updated systematic literature review to identify evidence for daratumumab, POM+DEX and PANO+BORT+DEX that has been published since the original submission is recommended to ensure there is no new data of relevance. In the event that new studies or data of relevance are identified then the company should consider their suitability for use in analyses and provide updated results for both clinical and cost-effectiveness incorporating these data if deemed appropriate. |
| **What is the expected effect on the cost-effectiveness estimates?** | Unknown. |
| **What additional evidence or analyses might help to resolve this key issue?** | An updated systematic literature review as detailed above. |

Abbreviations: ERG, evidence review group; MAIC, match-adjusted indirect comparison; PANO+BORT+DEX, panobinostat plus bortezomib and dexamethasone; POM+DEX, pomalidomide plus dexamethasone; and SLR, systematic literature review.

Table 3. Issue 2: Uncertainty in the clinical-effectiveness estimates for daratumumab compared with POM+DEX and PANO+BORT+DEX

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|---|---|
| **Report section** | 3.1.4.3, 3.2 and 3.3 |
| **Description of issue and why the ERG has identified it as important** | The ERG considers there to be substantial uncertainty in the estimates of clinical effectiveness for the comparisons of daratumumab with POM+DEX and PANO+BORT+DEX. Unfortunately, there is an absence of head-to-head trial data for daratumumab with either of the comparators and the non-comparative nature of the daratumumab MMY2002 trial and the SACT dataset means any indirect analyses are unanchored. The analyses for daratumumab with POM+DEX are further hampered by implausible tails in the OS curves (i.e., the fully adjusted MAIC KM curve and any extrapolations based on it).<br>The ERG also has concerns about the impact and lack of relevance of subsequent therapies in the MMY2002 trial to UK clinical practice and thus would prefer the use of the SACT data in analyses. However, the absence of IPD from the SACT dataset or comparator studies limits analyses using the SACT data to naïve comparisons. |
| **What alternative approach has the ERG suggested?** | The absence of head-to-head data or IPD data for the SACT or comparator trials means that the company is limited in what further analyses can be performed. The ERG considers the current analyses presented by the company are comprehensive and the ERG is unable to recommend any alternative approaches using the current data in the company submission. |
| **What is the expected effect on the cost-effectiveness estimates?** | Unknown. |
| **What additional evidence or analyses might help to** | The ERG considers this to be an unresolvable uncertainty given the data currently available, although if the SLR recommended in Issue 1 yields new |

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| **resolve this key issue?** | sources of data, updated clinical and cost-effectiveness analyses using the new data may potentially help to resolve some of the uncertainty in the estimates of clinical effectiveness. |

Abbreviations: ERG, evidence review group; IPD, individual patient data; KM, Kaplan-Meier; MAIC, match-adjusted indirect comparison; OS, overall survival; PANO+BORT+DEX, panobinostat plus bortezomib and dexamethasone; POM+DEX, pomalidomide plus dexamethasone; SACT, Systemic Anti-Cancer Therapy; and SLR, systematic literature review.

## 1.5 The cost-effectiveness evidence: summary of the ERG's key issues

Table 4,Table 5, and Table 6 present the key issues identified by the ERG in the company's cost-effectiveness analysis.

Table 4. Issue 3: Source of treatment effectiveness in the model

| | |
|---|---|
| **Report section** | 4.2.1 |
| **Description of issue and why the ERG has identified it as important** | As discussed in Issue 2, from a methodological point of view, the ERG considers the fully adjusted MAIC more appropriate than the partially adjusted MAIC used by the company. Nonetheless, and even though the fully adjusted MAIC is methodologically superior to the partially adjusted one, the former produced clinically implausible OS curves for the comparison of daratumumab vs POM+DEX.<br><br>Even though a naïve comparison is also flawed from a methodological point of view, the ERG considers that in the absence of clinically plausible fully adjusted MAIC results, the naïve comparison of real-life daratumumab (i.e., the SACT data) with POM+DEX is of relevance to the committee, particularly given the subsequent treatments included in the SACT data and the more clinically plausible OS predictions for daratumumab.<br><br>With regards to the comparison of daratumumab with PANO+BORT+DEX the ERG considers that the fully adjusted MAIC might be the most methodologically robust source for estimating relative treatment effectiveness given that the fully adjusted OS MAIC curve for daratumumab produces clinically plausible survival tails. |
| **What alternative approach has the ERG suggested?** | The ERG presented a range of results, where using the SACT data for daratumumab reflects the most conservative source of treatment effectiveness for the drug, albeit based on a naïve comparison method. At the more optimistic end of the scale, the ERG used the fully adjusted MAIC results, which are based on a more robust method for analysis of treatment effectiveness (albeit producing clinically implausibly optimistic survival for daratumumab vs POM+DEX). |
| **What is the expected effect on the cost-effectiveness estimates?** | The results of the ERG's analysis produced ICERs which ranged from £3,060 per QALY gained to dominant vs POM+DEX and consistently dominant ICERs in favour of daratumumab vs PANO+BORT+DEX. |
| **What additional evidence or analyses might help to resolve this key issue?** | None. The company has already provided all the additional scenarios in the model. |

Abbreviations: Abbreviations: Abbreviations: ICER, incremental cost-effectiveness ratio

Table 5. Issue 4: Impact of subsequent treatments received after daratumumab on overall survival

| Report section | 4.2.3 |
|---|---|
| **Description of issue and why the ERG has identified it as important** | The ERG was originally concerned with the possibility of OS outcomes for daratumumab being confounded by the impact of subsequent therapies received in MMY2002 (and not available in the UK NHS). During the clarification stage of the CDF review, the ERG requested that the company provided the updated MMY2002 data on subsequent treatments, together with OS data by subsequent treatment received.<br><br>As a response to clarification, the company provided the updated MMY2002 data on subsequent therapies, showing that most patients in MMY2002 received either a regimen containing carfilzomib ([redacted]); or chemotherapy with or without dexamethasone ([redacted]) as first subsequent therapies after daratumumab. The company, however, did not provide the more mature OS data by subsequent treatment received, as it did not, "*consider it statistically robust or appropriate to provide the requested OS data on* [the basis that] *these analyses are subject to a high level of selection bias because of indirectly selecting patients based on their outcome*." The company also that "*there were insufficient patients receiving each of bortezomib, carfilzomib, lenalidomide, and pomalidomide ([redacted], [redacted], [redacted], and [redacted], respectively) to inform robust Kaplan-Meier curves*". The company added that the OS reported in SACT is similar to the MMY2002 OS, hence the impact of subsequent treatments on OS should not be an issue in MMY2002.<br><br>The ERG disagrees with the company's assessment that the OS curves in the SACT and in MMY2002 are similar and notes a considerable separation of the curves between month 3 and month 21.<br><br>The ERG notes that the subsequent treatments received in the SACT dataset do not include carfilzomib, and that the majority of patients received either pomalidomide (64%) or bortezomib in combination with panobinostat (13%). The ERG notes that the proportion of patients receiving lenalidomide in MMY2002 and SACT was [redacted]<br><br>The ERG concludes that the difference in OS curves seen in SACT and in MMY2002 is likely due to treatment with carfilzomib after daratumumab (and possibly re-treatment with bortezomib) in MMY2002. The ERG also notes that bias referred to by the company around patients being fitter to receive the more effective and toxic subsequent treatments (such as carfilzomib) is irrelevant as these patients (despite being potentially fitter) would not have the opportunity to receive such drugs in the UK. Finally, the ERG notes that in MM-003 patients received carfilzomib in much smaller numbers (2%) than in MMY2002. |
| **What alternative approach has the ERG suggested?** | The ERG considers that it would have been helpful to see OS KM curves by subsequent treatment received in MMY2002 to help mitigate some of these concerns. |
| **What is the expected effect on the cost-effectiveness estimates?** | It is likely that the OS curves will show that patients receiving carfilzomib after daratumumab have longer survival than patients receiving other treatments. |

| | |
|---|---|
| **What additional evidence or analyses might help to resolve this key issue?** | The company could provide the see OS KM curves by subsequent treatment received in MMY2002. |

Abbreviations: Abbreviations: Abbreviations: ICER, incremental cost-effectiveness ratio

Table 6. Issue 5: Subsequent treatments modelled

| | |
|---|---|
| **Report section** | 4.2.3 |
| **Description of issue and why the ERG has identified it as important** | The company's updated model assumed that 58% of patients who had discontinued treatment with daratumumab; POM+DEX; or PANO+BORT+DEX received a subsequent treatment in the model. This was based on the SACT dataset.<br>The company also noted that while the effectiveness data in the model is based on MMY2002, the distribution of subsequent therapies was informed by the SACT data. The company concluded that there was no need to conduct any adjustment to effectiveness given the comparability of SACT and MMY2002 OS outcomes despite differences in subsequent therapies.<br>As discussed in Issue 4 the ERG disagrees with the company's assessment of similar OS outcomes in MMY2002 and the SACT data.<br><br>Furthermore, the ERG is unclear why the subsequent treatment data for POM+DEX from MM-003 trial was not used to estimate subsequent treatments in the POM+DEX arm.<br><br>Similarly, the ERG considers that the source of subsequent treatments post daratumumab in the model should ideally match the source of clinical effectiveness for daratumumab in the analysis. |
| **What alternative approach has the ERG suggested?** | During clarification, the ERG asked that the company included a scenario in the economic model where the subsequent treatments received after POM+DEX were those received by patients in the MM-003 trial, and another scenario where the subsequent treatments received after daratumumab in the MMY2002 final data cut were also included in the model. |
| **What is the expected effect on the cost-effectiveness estimates?** | In all the ERG's analyses, the subsequent treatments received after POM+DEX were based on those received in MM-003.<br><br>For the scenario where the MAIC results are used to estimate treatment effectiveness in the model, the ERG has used the subsequent treatments received by patients in MMY2002. The dominance of daratumumab did not change in this analysis, however, the costs associated with subsequent treatment after daratumumab and after POM+DEX decreased (with the decrease in subsequent costs after POM+DEX being higher than that observed for daratumumab).<br><br>For the scenario where SACT data are used to estimate treatment effectiveness in the model, the ERG has used the subsequent treatments received in SACT. The ICER for POM+DEX increased from £2,659 to £12,546 per QALY gained, due to the decrease in subsequent treatment costs associated with POM+DEX. |
| **What additional evidence or analyses might help to** | None. The company has already provided all the additional scenarios in the model. |

| resolve this key issue? | |
|---|---|

Abbreviations: Abbreviations: Abbreviations: ICER, incremental cost-effectiveness ratio; KM, Kaplan Meier; TTD, time to treatment discontinuation

## 1.6 Summary of ERG's preferred assumptions and resulting ICER

The ERG presented a range of results, where using the SACT data for daratumumab reflects the most conservative source of treatment effectiveness for the drug, albeit based on a naïve comparison. At the more optimistic end of the scale, the ERG used the fully adjusted MAIC results, nonetheless, the ERG notes that even though these analyses are based on a more robust method for analysis of relative treatment effectiveness, the OS curves for daratumumab vs POM+DEX produce clinically implausible results.

For the naïve comparison of SACT daratumumab data with the relevant comparator studies, the ERG's preferred assumptions consist of the following:

a. Using a gamma distribution to estimate TTD (as a proxy for PFS) for daratumumab, and to estimate PFS for POM+DEX and PANO+BORT+DEX.
b. Modelling the subsequent treatments received after POM+DEX based on those received by patients in the MM-003 trial.

Results for the ERG's analysis for the comparison of daratumumab vs POM+DEX are provided in Table 7 and for PANO+BORT+DEX in Table 8.

For the fully adjusted MAIC scenario, the additional ERG's assumptions consist of the following:

c. Modelling the subsequent treatments received after POM+DEX based on those received by patients in the MM-003 trial.
d. Modelling the subsequent treatments received after daratumumab based on those received by patients in the MMY2002 trial.

Results for the ERG's analysis for the comparison of daratumumab vs POM+DEX are provided in Table 9 and for PANO+BORT+DEX in Table 10.

Table 7. ERG's preferred ICER for daratumumab vs POM+DEX (corrected)

| Interventions | Total Costs (£) | Total QALYs | Total LYG | Incremental costs (£) | Incremental QALYs | Incremental LYG | ICER (£/QALY) |
|---|---|---|---|---|---|---|---|
| POM+DEX | [redacted] | [redacted] | 1.49 | - | - | - | - |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Daratumumab | [redacted] | [redacted] | 2.26 | [redacted] | [redacted] | 0.77 | £3,060 |

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 8. ERG's preferred ICER for daratumumab vs PANO+BORT+DEX (corrected)

| Interventions | Total Costs (£) | Total QALYs | Total LYG | Incremental costs (£) | Incremental QALYs | Incremental LYG | ICER (£/QALY) |
|---|---|---|---|---|---|---|---|
| PANO+BORT+DEX | [redacted] | [redacted] | 1.80 | - | - | - | - |
| Daratumumab | [redacted] | [redacted] | 2.26 | [redacted] | [redacted] | 0.46 | Daratumumab Dominates |

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 9. ERG's ICER for daratumumab vs POM+DEX using fully adjusted MAIC

| Interventions | Total Costs (£) | Total QALYs | Total LYG | Incremental costs (£) | Incremental QALYs | Incremental LYG | ICER (£/QALY) |
|---|---|---|---|---|---|---|---|
| POM+DEX | [redacted] | [redacted] | 1.49 | - | - | - | - |
| Daratumumab | [redacted] | [redacted] | 5.25 | [redacted] | [redacted] | 3.75 | Daratumumab dominates |

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 10. ERG's ICER for daratumumab vs PANO+BORT+DEX using fully adjusted MAIC

| Interventions | Total Costs (£) | Total QALYs | Total LYG | Incremental costs (£) | Incremental QALYs | Incremental LYG | ICER (£/QALY) |
|---|---|---|---|---|---|---|---|
| PANO+BORT+DEX | [redacted] | [redacted] | 1.80 | - | - | - | - |
| Daratumumab | [redacted] | [redacted] | 3.33 | [redacted] | [redacted] | 1.53 | Daratumumab Dominates |

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Modelling errors identified and corrected by the ERG are described in Section 6.1. For further details of the exploratory and sensitivity analyses done by the ERG, see Section 6.2.

# 2 Introduction and background

## 2.1 Introduction

This report provides a critique of the evidence submitted by Janssen to the National Institute for Health and Care Excellence (NICE) Cancer Drugs Fund (CDF) review of TA510 in support of the clinical and cost effectiveness of daratumumab (Darzalex®) monotherapy for treating adults with relapsed and refractory multiple myeloma (rrMM) that has previously been treated with 3 treatments including a proteasome inhibitor (PI) and an immunomodulatory agent (IMiD) and who have demonstrated disease progression on the last therapy. The primary sources of clinical data for daratumumab are from the final analyses of the MMY2002 and GEN501 studies and real-world data that was collected within the CDF by Public Health England (the Systemic Anti-Cancer Therapy [SACT] dataset).

## 2.2 Background

Multiple myeloma (MM) is a type of blood cancer that arises from white blood cells known as plasma cells, which are made in the bone marrow.[1] In MM abnormal plasma cells are produced and these in turn produce abnormal antibodies known as paraproteins.

The aims of treatment in MM are generally to achieve disease control, improve quality of life and prolong survival.[2] Daratumumab (Darzalex®) is a monoclonal antibody that binds to CD38, a cell-surface protein, resulting in tumour cell death by immune-mediated actions and apoptosis. Marketing authorisation for the use of daratumumab monotherapy in the treatment of adult patients with rrMM, whose prior therapy included a PI and an IMiD and who have demonstrated disease progression on the last therapy, was granted by the European Medicines Agency (EMA) on the 20 May 2016.[3]

A licence extension for a subcutaneous (SC) formulation of daratumumab was granted in June 2020 and [redacted]. The ERG notes that the recommended dosing of daratumumab monotherapy for this indication is 1,800 mg (15 ml, 120 mg per ml) via subcutaneous injection administered over approximately 3–5 minutes, whereas for the intravenous infusion the recommended dose is 16 mg/kg.[4] The company reported that the new SC formulation is now used by most patients rather than the IV formulation and the company submitted data demonstrating a [redacted] conversion rate. Additionally, the company reported

that non-inferiority between the weight-based IV formulation of daratumumab and the fixed dose SC formulation of daratumumab was demonstrated as part of the COLUMBA (MMY3012) trial.[5] The ERG's clinical experts also reported that the vast majority of their patients are now given the SC formulation of daratumumab. The ERG notes that the primary source of clinical evidence for daratumumab used by the company in their submission and base case is the MMY2002 study which utilises the IV formulation of daratumumab rather than the SC regimen. However, the ERG also acknowledges that the company has provided data on the adverse event (AE) profile with the SC regimen, and this is used to inform the AEs in the economic model, although efficacy data relates to the IV formulation of daratumumab.

The ERG's clinical experts also reported that since the review of daratumumab in TA510, the treatment pathway for rrMM has changed substantially with the approval of further new treatments for rrMM for use within the CDF, in addition to access to other drugs through new clinical trials and expanded access programmes. However, the clinical experts reported that in terms of drugs approved for routine commissioning in the National Health Service (NHS), the treatment pathway remains largely unchanged.

The ERG notes that the daratumumab combination therapy comprising daratumumab plus bortezomib plus dexamethasone is now recommended by NICE (TA573)[6] for use within the CDF as an option for treating relapsed multiple myeloma in people who have had 1 previous treatment, i.e. as a second line therapy for multiple myeloma. The ERG's clinical experts reported that the second line availability of daratumumab has led to reduced usage of daratumumab monotherapy in the fourth line setting in their clinical practice but that it is still a valuable treatment option for patients who have not previously received daratumumab.

The ERG's clinical experts agreed with the company's view that pomalidomide plus dexamethasone (hereafter referred to as POM+DEX) is the primary comparator for fourth line daratumumab monotherapy. The ERG's clinical experts also consider panobinostat plus bortezomib plus dexamethasone (hereafter referred to as PANO+BORT+DEX) to still remain an important comparator, although they reported it is used much less frequently compared to POM+DEX in their clinical practice. The ERG thus disagrees with the company's assertion that analyses of daratumumab versus PANO+BORT+DEX are no longer of interest and the ERG thus critiques these analyses in this report.

The clinical-effectiveness evidence for daratumumab in the original company submission (CS) for TA510[7] was derived from two single-arm clinical trials, MMY2002 and GEN501. There was only a small subgroup of patients receiving the licensed dose of daratumumab in each of the studies, but these subgroups are used to inform the data in this review. Additionally, the ERG noted in TA510 that there were differences in the populations included in MMY2002 and GEN501 and therefore the ERG did not consider the company's pooled analysis appropriate, and the ERG maintains this view.

There are no head-to-head data for daratumumab with the comparators and therefore the company has conducted matched adjusted indirect comparisons (MAICs) to compare daratumumab with POM+DEX and PANO+BORT+DEX. As discussed in the ERG report for TA510, the ERG prefers the use of MMY2002 over GEN501 due to the availability of more characteristics for inclusion in the MAICs. The ERG notes that there is now also data available from the SACT dataset and the ERG considers the SACT data along with the MMY2002 updated analyses to be the key sources of clinical efficacy data on daratumumab for this appraisal.

Key uncertainties during the original appraisal included the impact of the subsequent therapies received after daratumumab (because those used in the clinical trials were not reflective of UK clinical practice) and the overall survival estimates, which were immature. This report provides a critique of the updated evidence and analyses the company has provided in an attempt to address these uncertainties.

## 2.3 Critique of company's adherence to committees preferred assumptions from the Terms of Engagement

In general, the ERG considers that the company has adhered to the committee's preferred assumptions from the Terms of Engagement. The ERG's critique of the company's adherence to the committee's preferred assumptions from the Terms of Engagement is provided in Table 11.

Table 11. Preferred assumptions from Terms of Engagement (Adapted from CS table 1)

| Area | Committee-preferred assumptions | Rationale if different from committee-preferred assumptions | ERG comment |
|---|---|---|---|
| Population | Adults with relapsed or refractory multiple myeloma who have had three previous treatments including a proteasome inhibitor and an immunomodulator | As per committee-preferred assumption | The company has used MMY2002 as the primary source of clinical efficacy data for daratumumab. As noted in TA510, the ERG is concerned that patients in MMY2002 had received a median of five lines of prior therapy and so |

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| | | | the population is likely to be more heavily pre-treated than those who would be eligible for treatment with daratumumab in the UK.<br>Additionally, the ERG notes that daratumumab is now more frequently administered subcutaneously and the data from MMY2002 relate to the IV administration of daratumumab. |
| Comparators | The company should present clinical and cost-effective evidence for daratumumab compared to pomalidomide plus dexamethasone and panobinostat plus bortezomib plus dexamethasone | As per committee-preferred assumption:<br>• PANO+BORT+DEX is not used at fourth line in NHS clinical practice for patients with heavily pre-treated and highly refractory multiple myeloma. This has been validated by UK clinicians and confirmed in Committee conclusions within TA658 and ID1510[8, 9]; however, Janssen have maintained PANO+BORT+DEX as a comparator to meet committee-preferred assumptions in this CDF review | The ERG's clinical experts still consider PANO+BORT+DEX to be an important comparator, although they agree with the company that POM+DEX is the main comparator. The company has conducted analyses (unadjusted and MAICs) for both treatment regimens and both are critiqued by the ERG. |
| Generalisability of the trials | The company should use the data collected by SACT to test the generalisability of the trial data | As per committee-preferred assumption | Data from the SACT have been collected and included in the company submission. |
| Subsequent treatments | The company should use data collected via SACT to assess whether subsequent therapies are used in practice | As per committee-preferred assumption | The subsequent treatment data from the SACT are presented and discussed alongside the updated data from MMY2002. |
| Relative effectiveness | The company should use SACT data to inform the matching in the MAIC and the generalisability of the results | As per committee-preferred assumption:<br>• Janssen has conducted a MAIC of SACT data versus MMY2002, adjusting for the differences in available baseline characteristics, to validate the comparability of real-world and trial outcomes<br>• The new company base case utilises updated MAICs based on the MMY2002 trial only, as MMY2002 is considered reflective of UK clinical practice and closely | The ERG does not consider the MAIC of MMY2002 versus SACT to be suitable for drawing conclusions on the generalisability of MMY2002 to the UK population (Section 3.1.4.1). The ERG therefore considers the naïve comparison of SACT with POM+DEX and with PANO+BORT+DEX should be considered in addition to the fully adjusted MAICs of MMY2002 versus |

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| | | matches the marketing authorisation (2)<br>• Janssen has leveraged SACT data to validate generalisability of the new company base case; however, SACT data cannot be used to inform a MAIC in the absence of individual patient data | POM+DEX and PANO+BORT+DEX.<br>The ERG also considers that the fully adjusted MAIC should include adjustment for sex and that the fully adjusted MAIC should be used in the economic base case rather than the partially adjusted MAIC which is currently used by the company. Please see Section 3.2 for further details on the ERG's view. |
| Proportional hazards | The company should demonstrate whether the proportional hazards assumption holds | As per committee-preferred assumption | The company fitted independent curves to each treatment arm in the model, which the ERG agrees with. |
| Modelling of OS and PFS | The company should use the SACT data to validate the long-term survival extrapolations as well as data collected through the Early Access Programme | As per committee-preferred assumption:<br>• SACT data are utilised to validate the long-term survival extrapolations in this CDF review<br>• As discussed with NICE and the ERG, OS data are not available from the EAP (MMY3010) | The company has included the SACT data as an option to estimate treatment effectiveness with daratumumab in the model, which the ERG agrees with. |
| Utility values | The company should use the utility values presented during the original appraisal | As per committee-preferred assumption | As per committee-preferred assumption. |
| Costs of treatment in the model | The company should use SACT to explore the most appropriate previous and subsequent therapies and adjust the treatment effect and costs appropriately | As per committee-preferred assumption:<br>• SACT data have been used to inform subsequent therapy costs. No adjustment to effectiveness in the new company base case is warranted given the comparability of SACT and MMY2002 OS outcomes | The company has included the SACT; MMY2002; and MM-003 data as options to estimate the costs of subsequent treatments in the model, which the ERG agrees with. |
| Most plausible ICER | The committee agreed that daratumumab demonstrated plausible potential to be cost-effective if its clinical benefit was as the company suggested | As per committee-preferred assumption | The ranges provided by the ERG's analyses lead to the conclusion that daratumumab is likely to produce ICERs well below the £30,000 threshold when the comparator list prices are used. The ERG has provided a confidential appendix including the results when the comparator treatment PAS discounts are used in the model. |

| | | | |
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| End of life | Committee could not conclude on whether daratumumab met the end-of-life criteria | Daratumumab monotherapy, used at fourth-line for patients with rrMM, meets NICE's end-of-life criteria. The life expectancy for patients with rrMM who have progressive disease despite prior treatment with a PI and an IMiD does not exceed 12 months, based on RWE[10-15], and updated analyses have shown that daratumumab prolongs survival by [redacted] months versus POM+DEX and by [redacted] months versus PANO+BORT+DEX. | Both the company's and the ERG's assessments suggest that life expectancy with the comparators POM+DEX and PANO+BORT+DEX is predicted to be less than 24 months. Additionally, both the ERG's and company's assessments suggest daratumumab is associated with a minimum extension to life of 0.46 years thus meeting the criterion of prolonging life by at least an additional 3 months. However, the ERG considers the clinical effectiveness evidence underpinning this assessment to be extremely uncertain as discussed in Section 3, and therefore the ERG recommends caution in drawing conclusions on the end of life criteria from only these findings. |

Source: NICE (2021) (1)

Abbreviations: EAP, Early Access Programme; EoL, end-of-life; ICER, incremental cost-effectiveness ratio; IMiD, immunomodulator; MAIC, matching-adjusted indirect comparison; OS, overall survival; PANO+BORT+DEX, panobinostat plus bortezomib plus dexamethasone; PFS, progression-free survival; PI, proteasome inhibitor; POM+DEX, pomalidomide plus dexamethasone; rrMM, relapsed and refractory multiple myeloma; SACT, Systemic Anti-Cancer Therapy.

# 3 Clinical effectiveness

## 3.1 Critique of new clinical evidence

As discussed in Section 2, the ERG considers the new clinical evidence from MMY2002[16] and the SACT[17] database to be of the most relevance to this CDF review. The ERG notes that updated analyses are also now available from the GEN501 trial[18] and results are available from MMY3010;[19] the ERG therefore also critiques these briefly below. Additionally, the ERG discusses the adverse events of the new subcutaneous formulation of daratumumab based on the findings of the COLUMBA study.[20]

As discussed in Section 2 and the ERG report for TA510,[21] the ERG does not consider it appropriate to pool the results from MMY2002 and GEN501 and therefore the ERG does not present or discuss the results of the company's pooled analysis.[15] However, the ERG notes that the data from MMY2002 are used in the company's base case and the SACT and pooled data were used in scenario analyses.

The new data available from MMY2002 (data cut-off of 30 May 2017) and GEN501 (data cut-off of 31 March 2017) are both from the final planned study analyses. As discussed in Section 2, these studies are both focussed on the intravenous (IV) licensed dose for daratumumab of 16 mg/kg rather than the now licensed SC dose of 1,800 mg (15 ml, 120 mg per ml), which is more commonly used in the NHS (according to the ERG's clinical experts).[4] The company reported that "non-inferiority has been demonstrated between subcutaneous and intravenous daratumumab in an ongoing, multi-centre, open-label, non-inferiority, randomised, Phase 3 trial (COLUMBA)".[20]

The ERG notes that the new company base case uses SC daratumumab to reflect current UK practice and the safety data from the COLUMBA trial were used to inform AE data in the economic model. However, the ERG notes that the overall survival (OS) data from COLUMBA are immature and thus the company has used the mature MMY2002 efficacy data in the model which relate to the IV dosing of daratumumab. The ERG considers this discrepancy in sources of data on efficacy and safety to be reasonable given the limitations in the data available at the time of the company submission, nevertheless the ERG would prefer to see a consistent source of efficacy and safety data.

Table 12 provides a summary of the key sources of efficacy data for daratumumab.

Table 12. Sources of clinical effectiveness evidence (Reproduced from CS table 3)

| Study title | MMY2002 (primary evidence)† [16] | GEN501 (supportive evidence)‡ [18] | SACT data cohort study [17] (supportive evidence) |
|---|---|---|---|
| **Study design** | Phase 2, multicentre, open-label, single arm, two-part study | Phase 1/2, multicentre, open-label, single arm, two-part study ¶ | Real-world evidence collection via the SACT database§ |
| **Population** | Patients with relapsed and refractory multiple myeloma that have previously been treated with a proteasome inhibitor and an immunomodulatory agent, and who have demonstrated disease progression on the last therapy. | Part 2: Patients with relapsed and refractory multiple myeloma whose disease was relapsed and refractory to two prior lines of cytoreductive therapies and without further established treatment options. | Patients who were eligible for Cancer Drugs Fund funding of daratumumab for previously treated MM from 17th January 2018 to 16th November 2020 in NHS England's Blueteq® database |
| **Intervention(s)** | • Group A: Daratumumab 16 mg/kg††,‡‡ Cycles 1 and 2: Days 1, 8, 15, and 22 (weekly), Cycle 3 to 6: Days 1 and 15 (every other week), and Cycles 7+: Day 1 (every 4 weeks)<br>• Group B: Daratumumab 8 mg/kg††,‡‡,¶¶ Cycle 1+: Day 1 (every 4 weeks) | • Part 1: 10 dose levels of daratumumab were sequentially evaluated: 0.005, 0.05, 0.10, 0.50, 1, 2, 4, 8, 16, and 24 mg/kg<br>• Part 2: based on the dose levels established in Part 1†,‡‡ | Daratumumab at licensed dose (16 mg/kg or 1,800 mg solution for injection) |
| **Comparator(s)** | Not applicable | Not applicable | Not applicable |
| **Outcomes collected that address committee's key uncertainties** | • **Overall survival**<br>• Progression-free survival<br>• Safety | • Overall survival<br>• Safety | • Overall survival<br>• Treatment duration |

Source: Janssen (2017) [16, 18] PHE (2021) [17]
**Bold** denotes the outcomes that are incorporated into the model's base-case results.

Note references in the footnotes below relate to the company submission and not this report.
†Details of the MMY2002 study design can be found in Document B [ID933], Section 4.3.1 (pages 65–67) [21, 22]; ‡Details of the GEN501 study design can be found in Document B [ID933], Section 4.3.2 (pages 68–69) [21, 23]; Data presented in this appraisal are from Part 2 of the study; §SACT data is supplemented by Blueteq data presented in the PHE SACT 3-year report.; ††Per kg of body weight; ‡‡Both MMY2002 and GEN501 trials evaluated daratumumab monotherapy at two doses: 8 mg/kg and 16 mg/kg. As mentioned in Table 2, daratumumab monotherapy is now recommended at a dose of 1,800 mg (15 ml, 120 mg per ml) via subcutaneous injection. For the purpose of this CDF review, data are provided from MMY2002 and GEN501 for daratumumab at the higher dose (16 mg/kg); ¶¶ During the study, 3 of the 18 patients in the 8 mg/kg group crossed over to the 16 mg/kg group; results for these three patients are included in the 8 mg/kg treatment group and therefore not presented here.

Abbreviations: CDF, Cancer Drugs Fund; DOR, duration of response; ECG, echocardiogram; ECOG, Eastern Cooperative Oncology Group; IMiD, immunomodulatory agent; MM, multiple myeloma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PI, proteasome inhibitor; PS, performance status; SACT, Systemic Anti-Cancer Therapy; TEAE, treatment emergent adverse event; TTP, time to disease progression; TTR, time to response

### *3.1.1 MMY2002*

The final analysis of MMY2002 used a data cut-off of 30 May 2017 and comprised a median follow-up of 36.7 months (range: 0.5–42.3 months). The ERG notes that at the final data cut-off, [redacted] patients treated with daratumumab 16 mg/kg in MMY2002 had discontinued treatment with most of these treatment discontinuations being a result of progressive disease ([redacted]

[Table 13]).[16] The resulting median duration of treatment for patients treated with daratumumab 16 mg/kg was [redacted] (range: [redacted]).[16]

Table 13. Patient disposition; 16mg/kg all treated analysis set– MMY2002 final data cut-off (30 May 2017) (Reproduced from CS table 21)

| | Daratumumab 16 mg/kg |
|---|---|
| Analysis set: all treated | [redacted] |
| Still on treatment | [redacted] |
| Discontinued from treatment, n (%) | [redacted] |
| Progressive disease, n (%) | [redacted] |
| Adverse event, n (%) | [redacted] |
| Other, n (%) | [redacted] |
| Withdrawal of consent, n (%) | [redacted] |
| Discontinued from study, n (%) | [redacted] |
| Death, n (%) | [redacted] |
| Study terminated by sponsor, n (%) | [redacted] |
| Withdrawal of consent, n (%) | [redacted] |
| Lost to follow-up, n (%) | [redacted] |
| Source: Janssen (2017)[16] | |

#### *3.1.1.1 Overall survival*

After a median follow-up of 36.7 months (range: 0.5–42.3 months),[24] [redacted] treated with daratumumab 16 mg/kg were still alive. Median OS for the patients treated with daratumumab 16 mg/kg [redacted] (Table 14); with 95% confidence intervals (CI) also now available (95% CI: [redacted] months).[16] In response to clarification, the company reported that the mean length of follow-up was [redacted] months (95% CI: [redacted]) and the restricted mean OS was [redacted] months (95% CI: [redacted]).

The 12-month OS rate was [redacted] (95% CI: [redacted]) and the 24-month OS rate was [redacted] (95% CI: [redacted]). Figure 1 presents the Kaplan-Meier (KM) plot of OS from the final data cut for MMY2002.

Figure 1. Kaplan-Meier curve for overall survival from MMY2002; all treated, 16 mg/kg arm (Reproduced from CS figure 1)

.Source: Janssen (2017) [16]

Table 14. Overall survival; MMY2002 31 December 2015 and 30 May 2017 (Reproduced from CS table 22)

| | Daratumumab 16 mg/kg 31 December 2015 | Daratumumab 16 mg/kg 30 May 2017 |
|---|---|---|
| Analysis set: all treated | | |
| Overall survival | | |
| Number of events, n (%) | | |
| Number of censored, n (%) | | |
| Kaplan-Meier estimate (months) | | |
| 25% quantile (95% CI) | | |
| Median (95% CI) | | |
| 75% quantile (95% CI) | | |
| 6-month OS rate % (95% CI) | | |
| 12-month OS rate % (95% CI) | | |
| 18-month OS rate % (95% CI) | | |
| 24-month OS rate % (95% CI) | | |
| 36-month OS rate % (95% CI) | | |

Source: NICE (2017)[21] Janssen (2017)[16]

Abbreviations: CI, confidence interval; NE, not estimable; NR, not reached; OS, overall survival

#### 3.1.1.2 *Progression-free survival and time to treatment discontinuation*

The ERG notes that independent review committee (IRC) assessed progression-free survival (PFS) was used in the base case for the original company submission and formed the primary analyses of PFS, although investigator (INV) assessed PFS was also analysed. The assessment used for the PFS data supplied in the company submission for this CDF review was not specified and so the ERG is unclear whether it is IRC or INV data (with the exception of the restricted mean data).

The median PFS for the daratumumab 16 mg/kg arm of MMY2002 was [redacted] (95% CI: [redacted]) at the final data cut-off with [redacted] of patients experiencing an event (Table 15). Median TTD was not reported, although the restricted mean TTD was supplied in the company response to clarification. The ERG notes that the restricted mean PFS and restricted mean TTD are similar (Table 15) and the KM plots of PFS and TTD suggest similar trends for both outcomes (Figure 2).

Table 15. Progression-free survival from MMY2002 (30 May 2017 final data cut-off) (Reproduced from CS table 4)

| Parameter | Daratumumab 16 mg/kg MMY2002 |
|---|---|
| Analysis set: all treated | [redacted] |
| Number of events (%) | [redacted] |
| Number of censored (%) | [redacted] |
| Median PFS, months (95% CI) | [redacted] |
| Restricted mean PFS (IRC) (95% CI) | [redacted] |
| Restricted mean PFS (INV) (95% CI) | [redacted] |
| Restricted mean TTD (95% CI) | [redacted] |

Abbreviations: CI, confidence interval; INV, investigator; IRC, independent review committee; PFS, profession-free survival; and TTD, time to treatment discontinuation.

Figure 2. Daratumumab progression-free survival and time to treatment discontinuation data from MMY2002 (Reproduced from CS figure 8)

[redacted]

### *3.1.1.3 Safety*

The company reported that there were no notable differences in the overall AE profile with daratumumab at the final analysis compared to the interim analysis previously reported. The ERG notes that the AE rate is [redacted] and that [redacted]% of patients experienced a serious AE (Table 16). However, as discussed in Section 2, the IV route of administration for daratumumab is now much less commonly used compared to the SC route and the AEs from the COLUMBA trial are used in the company's economic model base case.

Table 16. Overview of treatment-emergent adverse events; all treated analysis set – MMY2002 final data cut-off (Reproduced from CS table 23)

| | Daratumumab 8 mg/kg | Daratumumab 16 mg/kg | | | Total |
|---|---|---|---|---|---|
| | | Part I | Part 2 | Total | |
| Analysis set: all treated, n | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Any TEAE, n (%) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Drug-related, n (%) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Any serious TEAE, n (%) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Drug-related, n (%) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Maximum severity of any TEAE | | | | | |
| Grade 1, n (%) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Grade 2, n (%) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Grade 3, n (%) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Grade 4, n (%) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Grade 5, n (%) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Treatment discontinuation due to TEAE†, n (%) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Drug-related, n (%) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Death due to TEAE‡, n (%) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Drug-related, n (%) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

Source: Janssen (2017)[16]

†Treatment discontinuation due to adverse event on the end of treatment CRF page; ‡death due to adverse event on the death CRF page.

Abbreviations: TEAE, treatment-emergent adverse event.

### 3.1.2 GEN501

The final analysis of GEN501[18] comprised a median follow-up of 35.3 months (range: 1.2 to 41.8 months). At the final data cut-off, [redacted] of the [redacted] patients ([redacted]) treated with daratumumab 16 mg/kg arm had discontinued treatment with [redacted] patients discontinuing treatment due to progressive disease. The median duration of treatment for patients treated with daratumumab 16 mg/kg was [redacted] (range: [redacted]). Median follow-up in GEN501 and MMY2002 was thus similar (35.3 months and 36.7 months, respectively). However, the ERG notes that

[redacted]

#### 3.1.2.1 Overall survival

At the final data cut-off, [redacted] treated with daratumumab 16 mg/kg were still alive. The median OS was [redacted] (95% CI: [redacted]) and the 24-month OS rate was [redacted] (95% CI: [redacted]). Detailed results and a KM plot of OS are available in the company submission Appendix F and Figure 2. The ERG notes that median OS and the 24-month OS rate for GEN501 were [redacted] compared to in MMY2002 (please see Section 3.1.1.1 for MMY2002 results).

#### 3.1.2.2 Safety

Similar to MMY2002, the company reported that there were no notable differences in the overall AE profile for daratumumab in GEN501 with increasing durations of follow-up. AE data from the final data analysis of GEN501 are available in appendix F of the company submission but are not discussed further here as they do not inform the company base case.

### 3.1.3 EAP (MMY3010) study

The Early Access Program (EAP) MM3010 study[19] was designed to provide early access to daratumumab monotherapy and collect additional safety and patient-reported outcomes (PRO) data including health-related quality of life. All patients in MMY3010 received IV daratumumab at a dose of 16mg/kg and the ERG notes that efficacy was not formally evaluated in the study, although investigator-assessed best disease response was reported.

MMY3010 comprised 293 patients who had previously received at least 3 prior lines of therapy, including a proteasome inhibitor (PI) and an immunomodulatory drug (IMiD), or who were double refractory to both a PI and an IMiD. Patients were recruited to MMY3010 between February 2016 and August 2018 and a total of 98 patients were recruited from the UK. Baseline characteristics for the full study population are available in the company response to clarification along with detailed results but no subgroup data were reported for the UK patients.

The ERG notes that the treatment duration data from the EAP is limited to that relating to the EAP study supply of daratumumab and 49 (16.7%) patients went on to receive commercial stock. The ERG thus considers the EAP data for TTD likely to be an underestimate. The median duration of

treatment in the EAP was 4.2 months (95% CI: 0.0 to 24.1) and median PFS was also reported in the study publication by Cook *et al.*[19] PFS was only investigator assessed but the median PFS of 4.63 months (95% CI: 3.75 to 5.75)

[redacted]

Overall response rate, EQ-5D-5L and other PRO data along with safety results are also available for the EAP study in the Cook *et al.* publication but given that they relate to the IV dosing of daratumumab and do not inform the economic model they are not discussed in this report.

### *3.1.4 SACT*

Observational data on OS and subsequent treatments were collected during the period of managed access to daratumumab via the SACT database.[6] The SACT data analyses comprise 2,301 patients with a CDF application between 17 January 2018 to 16 November 2020 and includes SACT activity up to 31 January 2021.

Baseline characteristics for patients treated with daratumumab in the SACT dataset compared with MMY2002 show patients in the SACT were older (median: 71 years versus [redacted] years, respectively) and had higher Eastern Cooperative Oncology Group (ECOG) performance status scores (Table 17). The ERG's clinical experts reported that the baseline characteristics of patients in the SACT dataset were representative of the patients they would expect to use daratumumab monotherapy in clinical practice in England, although the ERG notes that over 20% of patients in the SACT had missing ECOG data.

Table 17. Baseline characteristics – SACT database versus MMY2002 (Reproduced from CS table 5)

| Characteristic | SACT [17] (N=2,301) | MMY2002 [22] 16 mg/kg arm (N=106) |
|---|---|---|
| Age (years) | | |
| Median (range) | 71 (NR, NR) | [redacted] |
| Sex | | |
| Female, n (%) | 959 (42) | [redacted] |
| ECOG performance status | | |
| 0, n (%) | 467 (20.3) | [redacted] |
| 1, n (%) | 936 (40.7) | [redacted] |
| 2, n (%) | 341 (14.8) | [redacted] |
| 3, n (%) | 36 (1.6) | [redacted] |
| 4, n (%) | 1 (0.04) | [redacted] |
| Missing, n (%) | 520 (22.6) | [redacted] |
| Treatment response | | |
| Relapsed, n (%) | 1,862 (81) | [redacted] |
| Refractory, n (%) | 439 (19) | [redacted] |
| Previous stem cell transplant | | |
| No, n (%) | 1,296 (56) | [redacted] |
| Yes, n (%) | 1,005 (44) | [redacted] |

Source: Janssen (2015) [22] PHE (2021) [17]
Abbreviations: ECOG, Eastern Cooperative Oncology Group; NR, not reported; SACT, Systemic Anti-Cancer.

#### *3.1.4.1 Treatment duration*

A total of 1,877 (82%) of patients in the SACT had "completed" treatment (defined as died, had an outcome summary recorded in the SACT dataset or not received treatment with daratumumab in at least 3 months) by the date of analysis (31 January 2021). The median length of follow-up for patients in SACT (N=2,300) was 4.3 months and median treatment duration was 4.5 months (95% CI: 4.3 to 4.9). A sensitivity analysis of patients with a minimum follow-up duration of 6 months showed consistent results for median treatment duration (4.4 months). The ERG notes that only 41% of patients had a treatment duration of 6 months or longer (**Error! Not a valid bookmark self-reference.**).

Table 18. Treatment duration at 6-, 12-, 18- and 24-month intervals – SACT database (Reproduced from CS table 7)

| Time period | Treatment duration, % (95% CI) |
|---|---|
| 6-months | 41 (39% to 43%) |
| 12-months | 25 (23% to 26%) |
| 18-months | 17 (15% to 19%) |
| 24-months | 12 (11% to 14%) |

Source: PHE (2021) [17]
Abbreviations: CI, confidence interval; SACT, Systemic Anti-Cancer Therapy.

The ERG notes that the company reported that the definition of the treatment duration survival curve in SACT was similar to how the TTD survival curve was defined in MMY2002. Additionally, as discussed in Section 3.1.1.2, the TTD and PFS KM curves in MMY2002 were similar. The company has therefore conducted a scenario analysis in the model where the SACT treatment duration data are assumed to be equivalent to PFS as PFS data were not available from the SACT. The ERG considers this to be a reasonable assumption but notes the absence of IPD data for the SACT and comparator studies limits the analyses to naïve comparisons. The results of the naïve comparison of the SACT data with each of the comparators (POM+DEX and PANO+BORT+DEX) are discussed in Section 3.3.

The ERG notes that naïve comparison of the MMY2002 daratumumab PFS data with the daratumumab SACT treatment duration data (hereon referred to as SACT TTD) showed [redacted] in outcomes with daratumumab suggesting [redacted] (HR [redacted]; 95% CI: [redacted] [Figure 3]). [redacted] the company has also conducted an MAIC using the same data (SACT treatment duration data and PFS data from MMY2002) which shows [redacted] (HR [redacted] [Figure 3]). The covariates included in the MAIC were restricted by the limited data on baseline characteristics for the SACT dataset but adjustments to the MMY2002 data were made to match the studies baseline ECOG status, prior autologous stem cell transplantation (ASCT), age and gender. The ERG is therefore concerned that the MAIC is not fully adjusted for all important prognostic characteristics. The ERG notes that the mean estimated HR is [redacted]) and the ERG does not consider [redacted] results of the MAIC to be suitable for drawing conclusions about the generalisability of the MMY2002 results to the UK population.

Figure 3. Daratumumab treatment duration data from MMY2002 versus SACT (Reproduced from CS figure 6)

[redacted]

### *3.1.4.2 Overall survival*

The minimum follow-up for patients in the SACT analysis of OS (N= 2,301) was 6.5 months from the last CDF application and median OS using data collected up until 2 June 2021 was 15.5 months (95% CI: 14.5, 16.7). The ERG notes that 913 patients (39.7%) were still alive and censored in the SACT analysis for OS at the date of last follow-up and OS rates at 12- and 24-months were 57% and 37%, respectively (**Error! Not a valid bookmark self-reference.**). The equivalent OS rates from MMY2002 were [redacted] (12-month OS [redacted]% and 24-month OS [redacted]%) compared to those seen in the SACT dataset and median OS was [redacted] in SACT (15.5 months) compared to in MMY2002 ([redacted]).

Table 19. Overall survival at 6-, 12-, 18-, and 24-month intervals - SACT database (Reproduced from CS table 8)

| Time period | OS, % (95% CI) |
|---|---|
| 6-months | 71 (69%, 73%) |
| 12-months | 57 (54%, 59%) |
| 18-months | 46 (44%, 48%) |
| 24-months | 37 (35%, 40%) |

Source: PHE (2021) [17]
Abbreviations: CI, confidence interval; OS, overall survival; SACT, Systemic Anti-Cancer Therapy.

Naïve comparison of the MMY2002 OS and SACT OS data suggested [redacted] in OS with daratumumab between the studies (HR [redacted]; 95% CI: [redacted] [Figure 4]). The company also conducted an MAIC for OS and similar to the MAIC for PFS, they adjusted the MMY2002 OS data for ECOG status, prior autologous stem cell transplantation (ASCT), age and gender.

The MAIC results for OS showed [redacted] between MMY2002 and SACT for OS ([HR [redacted] [Figure 4]), although the ERG does not consider the results of this analysis to be suitable for drawing conclusions on the generalisability of MMY2002 to UK clinical practice.

Figure 4. Daratumumab overall survival data from MMY2002 versus SACT (Reproduced from CS figure 5)

Abbreviations: HR, hazard ratio; OS, overall survival; SACT, Systemic Anti-Cancer Therapy.

As discussed for TTD in Section 3.1.4.1, the company included the SACT data for OS in a scenario analysis in the economic model. Results of the naïve comparison of the SACT data for OS with the comparator study data for POM+DEX and PANO+BORT+DEX is discussed in Section 3.3.

### *3.1.4.3 Subsequent therapies*

A total of 1,877 out of the 2,301 patients in the SACT (82%) had discontinued daratumumab at the final data analysis and 58% of these patients (N=1,111/1,877) had gone on to receive a subsequent

treatment. The median time from last daratumumab cycle to start of a subsequent treatment was 28 days (range:1–742 days). The most commonly used first subsequent therapy following daratumumab in the SACT was pomalidomide (N=709) and the second most common regimen was bortezomib + panobinostat (N=147) (Table 20). Some patients in the SACT had more than one subsequent therapy and the ERG notes that the subsequent lines of therapies beyond the first line post-daratumumab are aggregated and reported separately to the first line post-daratumumab (company submission Table 28).

[redacted] patients in MMY2002 had discontinued treatment at final data analysis, and a larger proportion went on to receive a subsequent therapy compared to in SACT ([redacted] versus 58%). First subsequent therapy is summarised in Table 20. The ERG notes that [redacted] either alone or in combination for the patients in SACT, although the ERG's clinical experts reported that it may be used in clinical practice. The ERG also notes that the first subsequent therapy data for MMY2002 were aggregated by single component, although [redacted].

The ERG considers the distribution of first subsequent therapies is markedly different between MMY2002 and SACT and that this is likely to be partly due to the lack of availability of some of the drug regimens in the UK and due to the difference in age and performance status of patients in the two studies. Additionally, the ERG notes that follow-up in MMY2002 was longer and data beyond first subsequent therapy are more limited for patients in the SACT compared to in MMY2002.

Table 20. Subsequent therapies for patients receiving daratumumab 16 mg/kg – SACT database versus MMY2002[†] (Reproduced from CS table 6)

| Therapy | SACT [17] (N=1,877)‡ n (%) | MMY2002 [21] (N=106) n (%) |
|---|---|---|
| Total number of patients who received subsequent therapy | 1,111 (59.2) | [redacted] |
| [redacted] | – | [redacted]† |
| Pomalidomide | 709 (37.8) | [redacted]† |
| Cyclophosphamide | 12 (0.6) | [redacted]† |
| [redacted] | – | [redacted]† |
| Bortezomib | 7 (0.4) | [redacted]† |
| Lenalidomide | 30 (1.6) | [redacted]† |
| Bortezomib + Panobinostat | 147 (7.8) | [redacted] |
| Cyclophosphamide + pomalidomide | 55 (2.9) | [redacted] |
| Trial | 30 (1.6) | [redacted] |
| Melphalan | 19 (1.0) | [redacted] |
| Bendamustine | 16 (0.9) | [redacted] |
| Bortezomib + panobinostat + thalidomide | 15 (0.8) | [redacted] |
| Bendamustine + thalidomide | 10 (0.5) | [redacted] |

Source: PHE (2021) [17] MMY2002 [21]
†SACT data presents first subsequent therapies and the full data set includes combination therapies, MMY2002 presents components of therapies; ‡Patients who have since ceased treatment with daratumumab.
Abbreviations: SACT, Systemic Anti-Cancer Therapy.

## 3.2 MAIC

The company provided MAICs using MMY2002 to provide efficacy estimates for daratumumab compared to POM+DEX and PANO+BORT+DEX for use in their base case. The ERG notes that the company used the comparator studies identified in the original appraisal and no updated systematic literature review (SLR) was provided for this CDF review. However, the ERG notes that the company reported in their response to clarification that a restricted SLR will be provided alongside their technical engagement response. The comparator studies used in the MAICs thus reflect the studies used in the MAICs in the company's original submission. The comparator study used for the analysis of daratumumab versus POM+DEX was MM-003 and for the analysis of daratumumab versus PANO+BORT+DEX the PANORAMA-2 study was used.

The MAIC analyses presented and used in the company base case incorporated the data from the final analyses of MMY2002, although MAIC analyses using the pooled dataset were also provided. The ERG considers MMY2002 to be the most appropriate source of clinical effectiveness data on daratumumab for use in the MAICs with POM+DEX and PANO+BORT+DEX given the absence of IPD for the SACT dataset. The ERG notes that the company has chosen to use partially adjusted MAICs to inform their base case, matching on only the factors deemed by their clinical experts to be the most important for matching. The company's rationale for this was that "fully adjusted MAICs resulted in

effective sample sizes (ESS) of [redacted] (i.e., a [redacted]% reduction in sample size) versus POM+DEX and [redacted] (i.e. a [redacted]% reduction in sample size) versus PANO+BORT+DEX". The company cited text from NICE DSU Technical Support Document (TSD) 18 that states: "when the ESS is markedly reduced, or equivalently the weights are highly variable, estimates become unstable and inferences depend heavily on just a small number of individuals". [25] However, given that the MAICs are unanchored, the ERG considers all effect modifiers and prognostic variables should be adjusted for as recommended in TSD 18. The ERG is concerned that the company's use of the partially adjusted MAICs may be introducing bias into the results and the ERG therefore prefers the use of the fully adjusted MAICs compared to the partially adjusted MAICs.

The ERG notes that the company included a scenario analysis using the fully adjusted MAIC results. However, the ERG also notes that the fully adjusted MAICs did not include any adjustments for sex, although the MAIC for the MMY2002 versus SACT comparison presented by the company included sex as a covariate. The ERG sought clarification on this from the company and it was reported that the company's clinical experts did not consider it a relevant factor for adjustment in the analyses with POM+DEX or PANO+BORT+DEX, whereas for SACT due to the limited characteristics available it was included as an adjustment factor. The ERG considers sex should also be included in the fully adjusted MAICs of daratumumab versus POM+DEX and PANO+BORT+DEX and notes that the resultant ESS of MMY2002 for the POM+DEX MAIC was [redacted] (a [redacted]% reduction) and [redacted] (a [redacted]% reduction) for the PANO+BORT+DEX MAIC.

The key prognostic factors deemed to be essential to adjust for by the company's clinical experts were refractory status to lenalidomide, to bortezomib, and to both therapies. However, these factors were not available for the comparison versus PANO+BORT+DEX and so the number of prior treatments (mean/median, received >2/3) and ISS staging were adjusted for instead and the analyses with POM+DEX adjusted for all five factors (refractory status to lenalidomide, to bortezomib, and to both therapies, as well as number of prior treatments and ISS staging). These are the covariates adjusted for in the analyses referred to as the partially adjusted MAICs. The company's fully adjusted MAIC also included matching for creatinine clearance, ECOG, high cytogenetic risk, time from diagnosis, myeloma subtype, race, bone lesions and prior ASCT and the ERG's preferred fully adjusted MAIC also includes adjustment for sex.

The ERG notes that the company's fully adjusted MAICs were also planned to incorporate age as an adjustment factor but due to issues with convergence it was unable to be included. Additionally, in

the fully adjusted MAIC of MMY2002 with PANORAMA2, the company reported it was not possible to include myeloma subtype or prior ASCT either as the analysis did not converge.

The ERG notes that in the company fully adjusted MAIC the sample size from MMY2002 prior to matching reduces from [redacted] patients to [redacted] for the POM+DEX comparison and [redacted] for the PANO+BORT+DEX comparison due to patients with missing data. The company provided detailed baseline characteristics for patients in each of the studies including the MMY2002 characteristics before and after matching to MM-003 and PANORAMA2 in Table 29 and Table 30 of the company submission. The ERG notes that in the unmatched MMY2002 population there is [redacted]. Additionally, in MMY2002 there was [redacted] compared to in MM-003. However, MMY2002 and MM-003 were [redacted] compared to MMY2002 and PANORAMA 2. When compared to PANORAMA 2, MMY2002 patients have [redacted] suggesting MMY2002 patients had [redacted] compared to PANORAMA 2 prior to matching.

### *3.2.1 Daratumumab monotherapy versus POM+DEX*

The results of the unadjusted, partially adjusted, fully adjusted and fully adjusted including sex MAICs of daratumumab versus POM+DEX are presented in Table 21. The ERG notes that in the unadjusted and partially adjusted analyses of OS [redacted] For PFS, [redacted]

Table 21. Results of the comparisons of daratumumab with POM+DEX

| Endpoint | MMY2002 – unadjusted | MMY2002 – partially adjusted | MMY2002 – fully adjusted | MMY2002 – fully adjusted including sex |
|---|---|---|---|---|
| OS (95% CI) | [redacted] | [redacted] | [redacted] | [redacted] |
| PFS, IRC | [redacted] | [redacted] | [redacted] | [redacted] |

| | | | | |
|---|---|---|---|---|
| (95% CI) | | | | |

Abbreviations; CI, confidence interval; IRC, independent review committee; MAIC, matching-adjusted indirect comparison; OS, overall survival; PANO+BORT+DEX, panobinostat plus bortezomib and dexamethasone; PFS, progression-free survival; POM+DEX, pomalidomide plus dexamethasone.

The KM plots for the fully adjusted including age dataset are presented in Figure 5 and Figure 6 with KM plots for the other analyses provided in Appendix 9.1. The company reported that there was evidence suggesting that the proportional hazards assumption is violated for both PFS and OS and therefore independent curve fitting for daratumumab and POM+DEX was required in the economic model.

Figure 5. Fully adjusted including sex KM plot for OS, daratumumab versus POM+DEX (Reproduced from company response to clarification questions figure 14)

Abbreviations: CI, confidence interval; HR, hazard ratio; KM, Kaplan-Meier; OS, overall survival; POM+DEX, pomalidomide plus dexamethasone.

Figure 6. Fully adjusted including sex KM plot for PFS, daratumumab versus POM+DEX (Reproduced from company response to clarification questions figure 15)

[redacted]

Abbreviations: CI, confidence interval; HR, hazard ratio; KM, Kaplan-Meier; PFS, progression-free survival; POM+DEX, pomalidomide plus dexamethasone.

### *3.2.2 Daratumumab monotherapy versus PANO+BORT+DEX*

The results of the unadjusted, partially adjusted, fully adjusted and fully adjusted including sex MAICs of daratumumab versus PANO+BORT+DEX are presented in Table 22. The ERG notes that [redacted]

Additionally, the ERG notes that the company reported there were differences in the criteria used to assess PFS in MMY2002 and PANORAMA 2, which further add to the uncertainty in the results of the comparison of daratumumab and PANO+BORT+DEX for PFS.

Table 22. Results of the comparisons of daratumumab versus PANO+ BORT+DEX

| Endpoint | MMY2002 – unadjusted | MMY2002 – matching on key characteristics | MMY2002 – fully matched | MMY2002 – fully matched including sex |
|---|---|---|---|---|
| OS (95% CI) | [redacted] | [redacted] | [redacted] | [redacted] |
| PFS, IRC (95% CI) | [redacted] | [redacted] | [redacted] | [redacted] |

Abbreviations; CI, confidence interval; IRC, independent review committee; MAIC, matching-adjusted indirect comparison; OS, overall survival; PANO+BORT+DEX, panobinostat plus bortezomib and dexamethasone; PFS, progression-free survival; POM+DEX, pomalidomide plus dexamethasone.

The KM plots for the fully adjusted including sex dataset are presented in Figure 7 and

Figure 8 with KM plots for the other analyses provided in Appendix 9.2. The company reported that there was evidence suggesting that the proportional hazards assumption is violated for both PFS and OS and therefore independent curve fitting for daratumumab and PANO+BORT+DEX was also required in the economic model similar to the analyses for POM+DEX.

Figure 7. Adjusted KM plot for OS, daratumumab versus PANO+BORT+DEX (Reproduced from company response to clarification questions figure 16)

Abbreviations: CI, confidence interval; HR, hazard ratio; KM, Kaplan-Meier; OS, overall survival; PANO+BORT+DEX, panobinostat plus bortezomib and dexamethasone.

Figure 8. Adjusted KM plot for PFS, daratumumab versus PANO+BORT+DEX (Reproduced from company response to clarification questions figure 17)

Abbreviations: CI, confidence interval; HR, hazard ratio; KM, Kaplan-Meier; PFS, progression-free survival; PANO+BORT+DEX, panobinostat plus bortezomib and dexamethasone.

## 3.3 Naïve comparisons of SACT

Unfortunately, IPD is not available for the SACT data or the comparator studies (MM-003 and PANORAMA 2) and so MAICs could not be performed using the SACT data. However, naïve comparisons using the SACT data have been conducted by the company and the results of these are discussed below.

### *3.3.1 SACT vs POM+DEX*

The resulting hazard ratios for the naïve comparison between SACT (daratumumab) and MM-003 (POM+DEX) are presented in Table 23 and the KM curves (including numbers of patients at risk) for OS and PFS/TTD are presented in

Figure 9 and

Figure 10, respectively. The ERG considers it important to highlight that the results of these naïve comparisons should be interpreted with caution as no adjustment is made for the differences in patient characteristics between the two studies. However, given the differences in subsequent therapies seen between MMY2002 and patients in the UK, the ERG considers the SACT data an important data set, especially for OS. However, the ERG also notes that subsequent therapies from MM-003 and PANORAMA 2 may not be consistent with either MMY2002 or SACT.

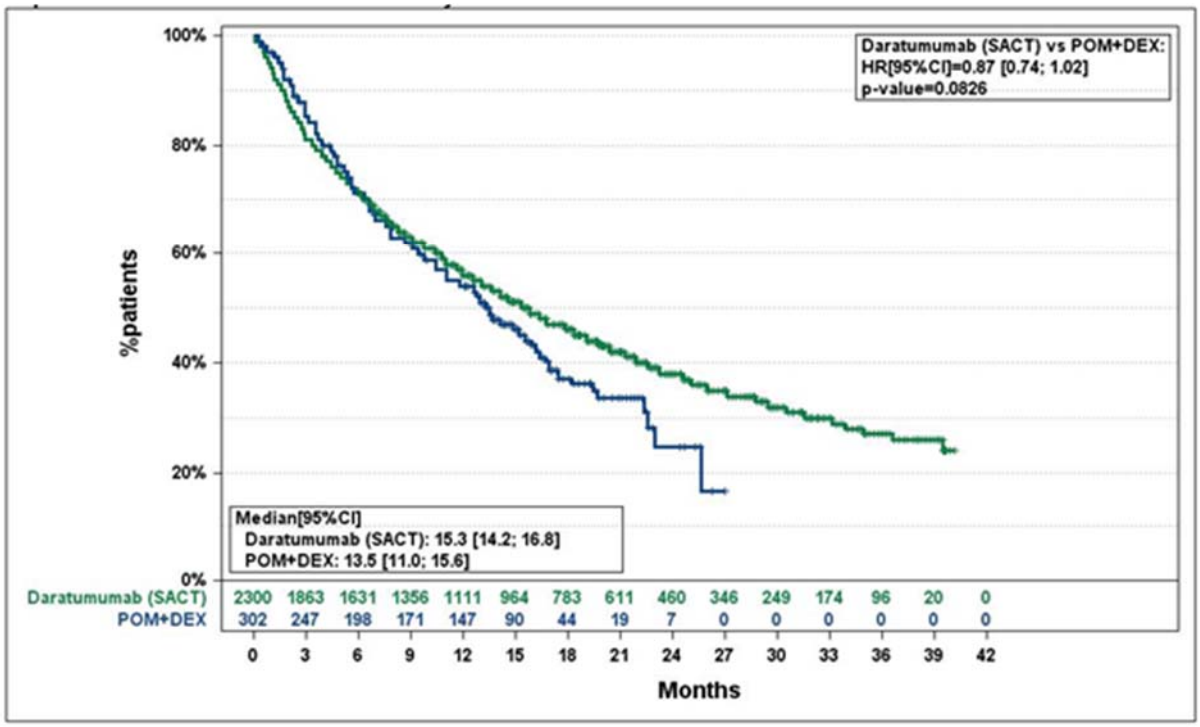
The HR for OS in the SACT naïve comparison of daratumumab with POM+DEX [redacted]. For the naïve analysis of PFS using the SACT treatment duration data, PFS is significantly longer with daratumumab compared to POM+DEX ($p<0.05$). The HR for the fully adjusted including sex MAIC using MMY2002 daratumumab data was [redacted] The ERG thus considers the data from the SACT [redacted]. However, the ERG considers the analyses for both OS and PFS are uncertain due to the limitations of using a naïve comparison for the SACT data, and the differences in subsequent therapies and the [redacted] in the fully adjusted MAICs using the MMY2002 data.

Table 23. Hazard ratios and event numbers for comparison between SACT and MM-003 (Reproduced from company response to clarification questions table 4)

| | | Daratumumab OS (SACT) versus POM+DEX OS (MM-003) | Daratumumab TTD (SACT) versus POM+DEX PFS (MM-003) |
|---|---|---|---|
| Hazard ratio | Point estimate | 0.87 | 0.79 |
| | 95% CI | 0.74 to 1.02 | 0.69 to 0.91 |
| | P-value | 0.0826 | 0.0009 |
| Number of events (SACT) | | 1,388 | 1,857 |
| Number of events (MM-003) | | 171 | 237 |

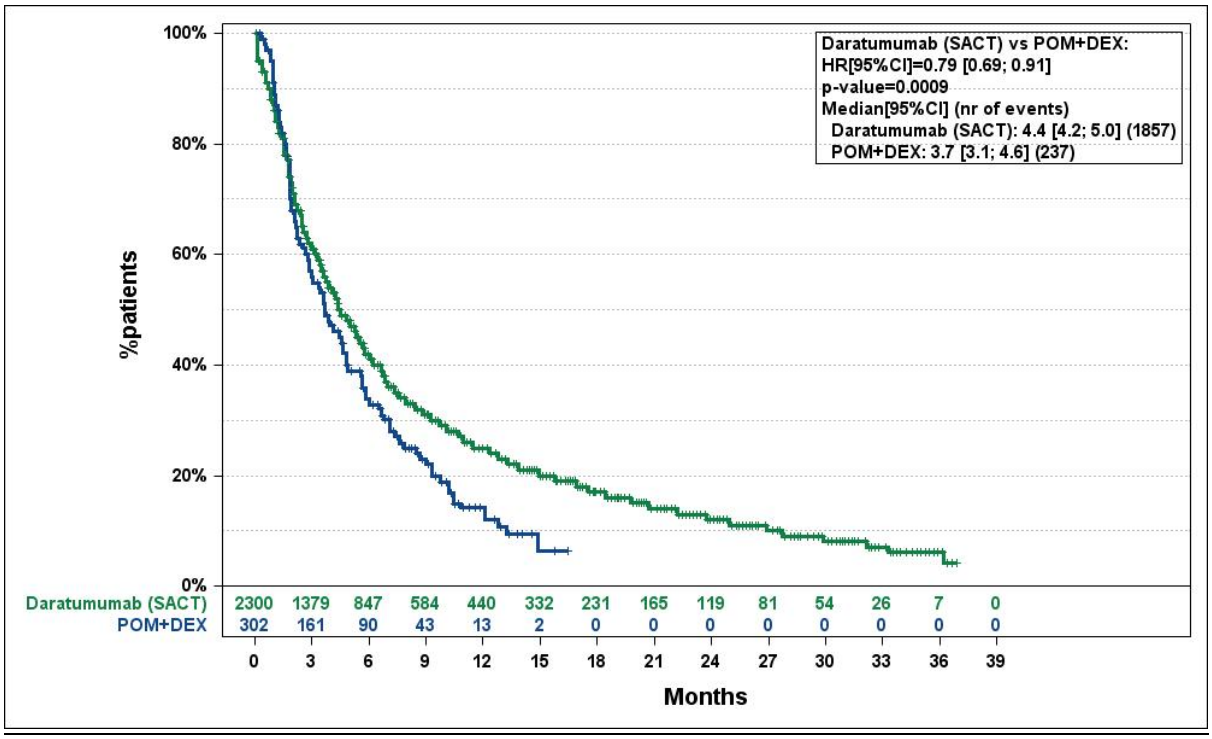
Abbreviations: CI, confidence interval; OS, overall survival; PFS, progression-free survival; POM+DEX, pomalidomide plus dexamethasone; SACT, Systemic Anti-Cancer Therapy; TTD, time to discontinuation.

Figure 9. KM plot for daratumumab OS (SACT) versus POM+DEX OS (MM-003) (Reproduced from company response to clarification questions figure 23)




Abbreviations: CI, confidence interval; HR, hazard ratio; KM, Kaplan-Meier; OS, overall survival; POM+DEX, pomalidomide plus dexamethasone; SACT, Systemic Anti-Cancer Therapy.

Figure 10. KM plot for daratumumab TTD (SACT) versus POM+DEX OS (MM-003) (Reproduced from company response to clarification questions figure 24)




Abbreviations: CI, confidence interval; HR, hazard ratio; KM, Kaplan-Meier; PFS, progression-free survival; POM+DEX, pomalidomide plus dexamethasone; SACT, Systemic Anti-Cancer Therapy; TTD, time to discontinuation.

### *3.3.2 SACT vs PANO+BORT+DEX*

The resulting hazard ratios for the naïve comparison between SACT (daratumumab) and PANORAMA 2 (PANO+BORT+DEX) are presented in Table 24 and the KM curves (including numbers of patients at risk) for OS and PFS/TTD are presented in

Figure 11 and Figure 12, respectively. The ERG considers it important to highlight that the results of these naïve comparisons should be interpreted with caution as no adjustment is made for the differences in patient characteristics between the two studies. However, given the differences in subsequent therapies seen between MMY2002 and patients in the UK, the ERG considers the SACT data an important data set, although the ERG also notes that it does not report on PFS and treatment duration is used instead as a proxy for PFS data as detailed in Section 3.1.4.1. Additionally, the ERG acknowledges that subsequent therapies from MM-003 and PANORAMA 2 may not be consistent with UK clinical practice either.

The HRs for the naïve comparison of daratumumab from the SACT with PANO+BORT+DEX did not reach statistical significance. The HR for OS suggested a trend towards longer OS with PANO+BORT+DEX whereas the HR for PFS showed a trend towards longer PFS with daratumumab.

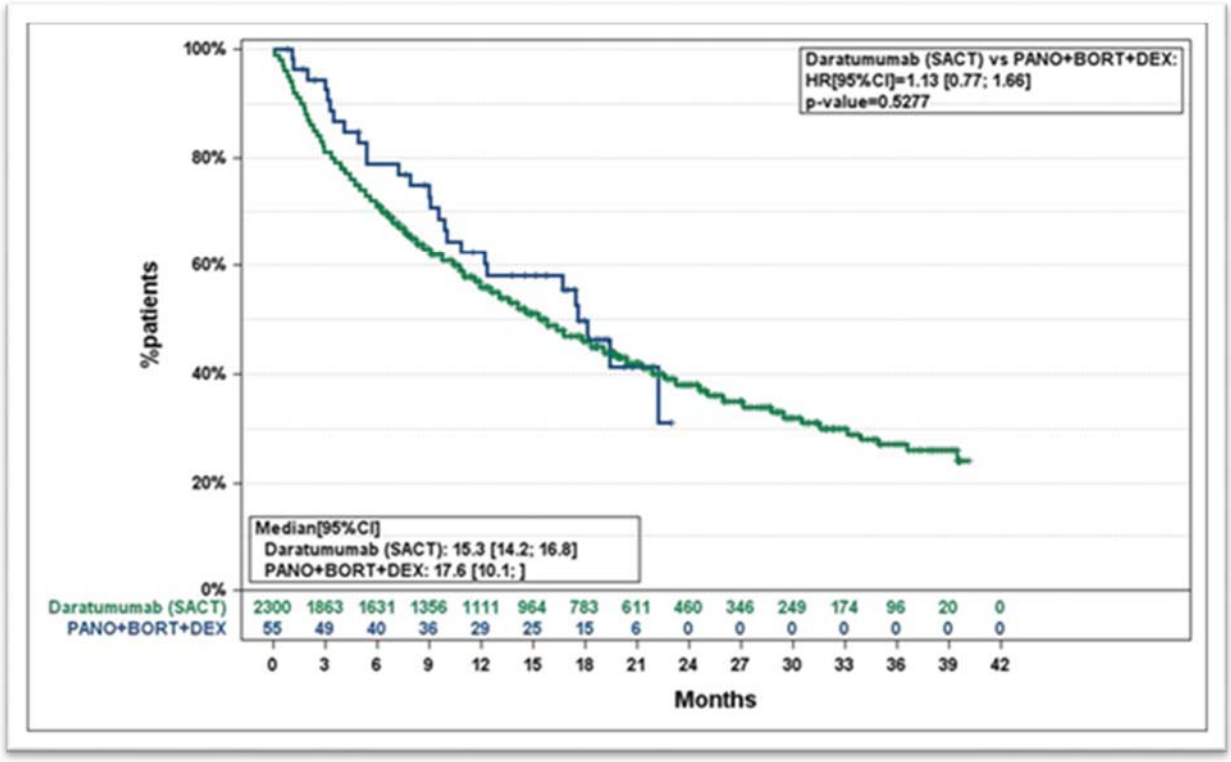
The ERG notes that the HRs for the fully adjusted including sex MAIC using daratumumab from MMY2002 showed [redacted] However, the ERG considers the results of the analyses for daratumumab versus PANO+BORT+DEX are extremely uncertain due to the [redacted]. In addition, as discussed earlier, the naïve comparison using the SACT data is not ideal due to the unaccounted for differences between the studies, and the fully adjusted MAICs using the MMY2002 data are impacted by differences in subsequent therapies and the [redacted]. The ERG thus recommends caution in drawing conclusions from the results of any of the analyses of daratumumab versus PANO+BORT+DEX.

Table 24. Hazard ratios and event numbers for comparison between SACT and PANORAMA 2 (Reproduced from company response to clarification questions table 5)

| | | Daratumumab OS (SACT) versus PANO+BORT+DEX OS (PANORAMA 2) | Daratumumab TTD (SACT) versus PANO+BORT+DEX PFS (PANORAMA 2) |
|---|---|---|---|
| Hazard ratio | Point estimate | 1.13 | 0.95 |
| | 95% CI | 0.77 to 1.66 | 0.69 to 1.31 |
| | P-value | 0.5277 | 0.7578 |
| Number of events (SACT) | | 1,388 | 1,857 |
| Number of events (PANORAMA 2) | | 27 | 39 |

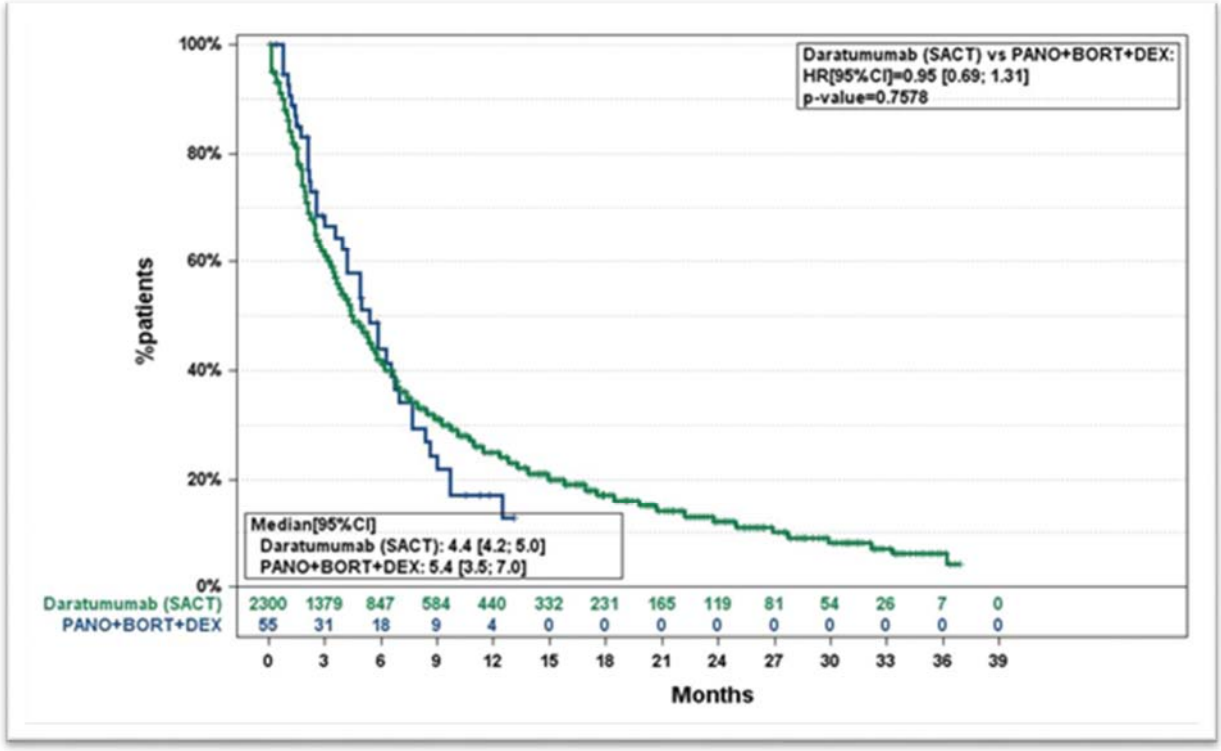
Abbreviations: CI, confidence interval; OS, overall survival; PFS, progression-free survival; POM+DEX, pomalidomide plus dexamethasone; SACT, Systemic Anti-Cancer Therapy; TTD, time to discontinuation.

Figure 11. KM plot for daratumumab OS (SACT) versus PANO+BORT+DEX OS (PANORAMA 2) (Reproduced from company response to clarification questions figure 25)




Abbreviations: CI, confidence interval; HR, hazard ratio; KM, Kaplan-Meier; OS, overall survival; PANO+BORT+DEX, panobinostat plus bortezomib and dexamethasone; SACT, Systemic Anti-Cancer Therapy.

Figure 12. KM plot for daratumumab TTD (SACT) versus PANO+BORT+DEX PFS (PANORAMA 2) (Reproduced from company response to clarification questions figure 26)




Abbreviations: CI, confidence interval; HR, hazard ratio; KM, Kaplan-Meier; PFS, progression-free survival; PANO+BORT+DEX, panobinostat plus bortezomib and dexamethasone; SACT, Systemic Anti-Cancer Therapy; TTD, time to discontinuation.

## 3.4 Adverse events

As discussed in Section 2.2, the daratumumab SmPC has now been updated to include the option to receive treatment via a subcutaneous (SC) injection at a recommended dose of 1,800 mg and the ERG notes that the recommended dosing schedule is weekly for Weeks 1 to 8, every two weeks from Weeks 9 to 24, and then every four weeks thereafter until disease progression. The ERG's clinical experts agreed with the company that administration of daratumumab via subcutaneous injection is now most representative of UK clinical practice. The ERG also notes that the company has updated the acquisition costs and AEs to reflect this change in practice in the new company base case.

The company has used the AEs reported in the COLUMBA trial to inform the SC AEs for daratumumab in the economic model and reported that all Grade ≥3 AEs that occurred in ≥5% of patients in all comparator trials were included in the analyses (Table 25).[20] The ERG notes that the COLUMBA trial reported that the safety profiles of SC and intravenous (IV) daratumumab were similar with 288 (88%) SC patients and 230 (89%) IV patients reporting at least one treatment-emergent adverse event (TEAE). However, Grade 3 or higher TEAEs were reported in slightly fewer patients in the SC trial arm compared to the IV arm (46% versus 49%, respectively).

Table 25. The Grade ≥3 AEs that occurred with SC daratumumab in the COLUMBA trial that were used in the new company base case (Reproduced from CS table 11)

| Adverse event | Proportion of patients |
|---|---|
| Anaemia | 13.1% |
| Neutropenia | 13.1% |
| Thrombocytopenia | 13.8% |
| Lymphopenia | 5.0% |
| Leukopenia | 3.8% |
| Pneumonia | 2.7% |
| Nausea (all grades) | 8.1% |
| Diarrhoea | 0.8% |
| Fatigue | 0.8% |
| Dyspnoea | 0.4% |
| Back pain | 1.5% |
| Hypokalaemia | 0.4% |
| Source: Mateos *et al.* 2020[20] | |

## 3.5 Conclusions of the clinical effectiveness section

In general, the ERG considers that the company has adhered to the committee's preferred assumptions from the ToE, although the ERG still considers there to be considerable uncertainty in the estimates of the efficacy of daratumumab compared to POM+DEX and PANO+BORT+DEX. Unfortunately, there is an absence of head-to-head trial data for daratumumab with either of the comparators, and the non-comparative nature of the daratumumab MMY2002 trial and the SACT dataset means any indirect analyses are unanchored and so contain the potential biases caused by non-randomised comparisons.

In terms of addressing the committee's concerns around the uncertainty in OS with daratumumab, the company has provided data from final analyses of MMY2002, GEN501 and reported on the OS data collected from the SACT cohort. The ERG notes that while there is now longer follow-up data from MMY2002 (median of 36.7 months follow-up for OS), [redacted] of patients were still alive at the final analysis. Additionally, the ERG notes that in the SACT cohort, 39.7% of patients were still alive at the final data collection timepoint for OS. The ERG therefore considers the long term effects of daratumumab on OS are still not fully known.

The ERG also has concerns about the impact and lack of relevance of subsequent therapies in the MMY2002 trial to UK clinical practice because, as highlighted by the SACT subsequent therapy data, the subsequent treatments used in UK clinical practice varied compared to those used in MMY2002. The ERG would therefore prefer the use of the SACT data in analyses. However, the absence of IPD from the SACT dataset or comparator studies limits analyses using the SACT data to naïve comparisons.

The ERG considers it important to flag that as discussed in the original ERG report for TA510; the MMY2002 patient population is not restricted to patients consistently receiving daratumumab at fourth line, instead patients had a range of prior therapies and the median number was five. The ERG therefore does not consider the use of daratumumab in MMY2002 to reflect how it would be used in clinical practice and is concerned about the impact both prior and subsequent therapies may have on the estimates of efficacy for daratumumab. Additionally, the ERG does not consider the company's MAIC of the daratumumab data from MMY2002 and the SACT dataset to be appropriate for drawing conclusions on the generalisability of MMY2002 to the UK population. However, the ERG does consider the use of the SACT data in naïve comparisons with POM+DEX and PANO+BORT+DEX likely to result in conservative estimates for the efficacy of daratumumab as they are based on a comparison of observational data (from SACT for daratumumab) to clinical trial data (for POM+DEX and PANO+BORT+DEX).

For the comparison of daratumumab with POM+DEX, the ERG considers there to be implausible "tails" in the fully adjusted MAIC KM OS curves for daratumumab, which has a direct impact on any extrapolations made to these curves. The ERG therefore considers the naïve SACT comparison of daratumumab with POM+DEX from MM-003 to be the most reliable source of data for the comparison of daratumumab with POM+DEX. However, the use of a naïve comparison is associated with an inherent risk of bias as differences in the patient populations in the studies are not accounted for and therefore caution must be taken in drawing any conclusions from the results.

For the comparison of daratumumab with PANO+BORT+DEX, the ERG considers both the fully adjusted including sex MAIC and the naïve SACT comparisons to have strengths and weaknesses associated with them. For the fully adjusted including sex MAIC, the main issues are around the smaller effective sample size and the difference in subsequent therapies received in MMY2002 compared to in UK clinical practice. For the SACT naïve comparison, there are issues around the lack of adjustment for differences in the population of the SACT and PANORAMA 2 study's because IPD is

not available for the SACT cohort. As it is not possible to assess the relative impact of these different issues, the ERG presents both as options for the committee to consider.

Finally, the ERG notes that the company did not conduct an updated systematic literature review (SLR) for clinical effectiveness evidence on daratumumab or the comparators of relevance to this appraisal (POM+DEX and PANO+BORT+DEX). The ERG is thus concerned that there may be new data available, in particular for the comparators POM+DEX and PANO+BORT+DEX that would be of relevance and may be more suitable than the current sources of data used in the MAICs in the company submission.

# 4 Cost effectiveness

This section presents a summary and critique of the company's updated model for this CDF review. Section 4.1 describes the company's changes to the economic analysis while Section 4.2 provides a detailed discussion of the changes made. Section 5 presents the results of the company's updated model and Section 6 presents the results of additional exploratory analyses undertaken by the ERG.

As discussed in Section 2.2, the use of PANO+BORT+DEX has reduced substantially in the NHS since the beginning of this appraisal. Both clinical experts advising the ERG agreed with the company that the most relevant comparator for daratumumab is now POM+DEX (with PANO+BORT+DEX being used by less than 5% of patients). Therefore, while the ERG provides details for the estimation of treatment effectiveness with PANO+BORT+DEX in the model, it does not provide the same level of detail in its discussions and additional analysis when compared to the cost-effectiveness of POM+DEX.

## 4.1 Summary of company's updated economic analysis

The starting point for the company's updated economic analysis was the model amended by the ERG – '(ID933) Janssen_ Daratumumab_CEM_16122016 (CIC) _SA corrections_base case corrected', hereafter referred to as the original model. The key features of the company's original model, the company's updated model, and the ERG summary comments are provided in Table 26. Overall, these amendments are in line with the terms of engagement for the CDF guidance review.

Table 26. Key model assumptions and inputs

| Model feature | Parameter/assumption in original model | Updated parameter /assumption | ERG comments |
|---|---|---|---|
| Data used to model daratumumab OS and PFS | Pooled data from MMY2002 and GEN501 were used to inform MAICs versus POM+DEX and PANO+BORT+DEX for OS and PFS. Fully adjusted curves post-MAIC were used for the daratumumab arm. | MMY2002 updated data were used to inform the updated MAICs versus POM+DEX and PANO+BORT+DEX - MAICs adjusted for the top 5 or top 2 prognostic factors, respectively.<br>Scenarios were considered using fully adjusted MAICs, data from SACT and the pooled MMY2002/GEN501 data set. | The ERG agrees with the use of the MMY2002 updated data instead of the pooled data from MMY2002 and GEN501.<br>Nonetheless, the ERG disagrees with the use of the partially adjusted MAIC for the estimation of OS and PFS for daratumumab (see Section 3.2 for more details). |

| | | | |
|---|---|---|---|
| Data used to model daratumumab TTD | For daratumumab the pooled MMY2002 and GEN501 TTD were used.<br>For POM+DEX only mean and median TTD could be obtained from MM-003, and the company reported that "TTD survival curves for POM+DEX were derived with a loglogistic curve by goal seeking the parametric curve parameters to minimise the sum of squared differences between the predicted mean and median values and those of [MM-003]." For PANO+BORT+DEX, the company could not find any TTD data, therefore patients were assumed to be treated until progression, or when the maximum number of treatment cycles was reached for the treatment. | TTD data for daratumumab from the MMY2002 latest data cut were used.<br>The company's approach to estimating TTD for POM+DEX and PANO+BORT+DEX did not change. | The ERG agrees with the use of the updated MMY2002 TTD data for daratumumab.<br>The ERG notes that even though the parametric loglogistic curve used for POM+DEX replicates the mean and median estimate observed in MM-003, it relies on a very strong assumption that the TTD KM data (not reported for MM-003) would follow a loglogistic distribution. |
| Survival distributions | OS: Exponential dependent fit<br>PFS: Log-normal dependent fit<br>TTD: Log-logistic | OS: Weibull independent fit<br>PFS: Log-normal independent fit<br>TTD: Log-logistic | The ERG agrees with the use of these distributions in the partially and fully adjusted MAIC scenarios. However, when the scenario for the naïve comparison of daratumumab (SACT) with POM+DEX and PANO+BORT+DEX, the ERG considers that a gamma distribution should be used to model PFS. |
| Daratumumab AEs | Daratumumab AEs were taken from a weighted average of pooled MMY2002/GEN501 data | Daratumumab AEs were taken from the subcutaneous arm of the COLUMBA trial | The ERG agrees with the company's updates. |
| Daratumumab administration and dose | 16 mg/kg via IV infusion weekly from Weeks 0–8, every two weeks from Week 9–24, then every four weeks thereafter until disease progression | 1,800 mg via subcutaneous injection weekly from Weeks 0–8, every two weeks from Week 9–24, then every four weeks thereafter until disease progression | The ERG agrees with the company's updates. |

| | | | |
|---|---|---|---|
| Daratumumab price | [redacted] | [redacted]. | The ERG agrees with the company's updates. |
| Subsequent therapy costs | 100% of patients received a subsequent therapy in the daratumumab arm and 55% and 100% of patients received a subsequent therapy in the PANO+BORT+DEX and POM+DEX arms, respectively.<br>The proportions of therapies received were informed by a combination of pooled MMY2002/GEN501 data and clinical opinion. | 58% of patients are assumed to receive a subsequent therapy in all arms. In all treatment arms, bendamustine use is set to 0 given that bendamustine is no longer available on the CDF. The proportions of therapies received<br>for all comparators are informed by the SACT data set. | The ERG considers that the source of subsequent treatments post daratumumab in the model should match the source of clinical effectiveness for daratumumab in the analysis. Given the ERG's preference for the SACT data (as it better reflects the subsequent treatments available to NHS patients after daratumumab), the ERG's preferred approach is to use the SACT data to estimate treatment effectiveness and subsequent treatments after daratumumab.<br><br>During clarification the ERG also asked that the company included a scenario in the economic model where the subsequent treatments received after daratumumab were those received by patients in the MMY2002 final data cut (to match the source of clinical effectiveness for daratumumab in the model when the MAIC results are used).<br><br>The ERG considers that the distribution of subsequent treatments received after POM+DEX should be based on the same source of effectiveness data for POM+DEX in the model (i.e., MM-003) therefore, the ERG presents the impact of using these data in the ERG's analysis in Section 6. |
| General population | No adjustment was made for general population mortality. | Functionality was added such that the per cycle probability of death could not | The ERG agrees with the company's updates. |

| | | | |
|---|---|---|---|
| mortality adjustment | | fall below that of the general population. General population mortality is informed by the latest available England and Wales life tables. | |

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; CDF, Cancer Drugs Fund; IV, intravenous; MAIC, matching-adjusted indirect comparison; NHS, National Health Service; OS, overall survival; PANO+BORT+DEX, panobinostat plus bortezomib and dexamethasone; PAS, patient access scheme; PFS, progression-free survival; POM+DEX, pomalidomide plus dexamethasone; RWE, Real world evidence; SACT, Systemic Anti-Cancer Therapy; UK, United Kingdom.

## 4.2 Detailed description of model amendments included in company's updated model

### *4.2.1 Treatment effectiveness*

Treatment effectiveness in the company's updated base case analysis for the CDF review was estimated using the following data sources:

- For daratumumab: the latest data cut from the MMY2002 study was used in the company's updated MAICs. The company explained that the IPD from SACT were not available, thus, it was only possible to conduct a naïve comparison between digitised SACT data and the relevant comparator trials. The company conducted scenario analyses in which the daratumumab OS and TTD curves (used as a proxy for PFS curves) were based on digitised SACT data.
- For POM+DEX: the source remained unchanged (MM-003 trial).
- For PANO+BORT+DEX: the source remained unchanged (PANORAMA 2 trial).

The company used the updated MAIC-derived OS and PFS curves based on MMY2002, matching on what the company considered to be the most important factors to model these survival outcomes. As discussed in Section 3.2, the ERG disagrees with the use of the partially adjusted MAIC. Therefore, in the following sections the ERG provides details of the company's base case as necessary, however, also describes the implementation of the fully adjusted MAIC and the naïve comparison using the SACT data in the model.

#### *4.2.1.1 Overall survival and progression-free survival*

*Partially adjusted MAIC*

The company modelled independent OS and PFS curves for all treatment arms, in alignment with the committee preferences at the FAD. The selected models to extrapolate the KM MAIC-adjusted OS

and PFS data did not change from the original submission, with the company finding the Weibull and the lognormal distributions the most appropriate fit to OS and PFS data, respectively, for all three treatments.

The company provided Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) for each distribution in Table 33- Table 36 of the CS (appendix 5). The ERG agrees with the choice of the Weibull and the lognormal models and with the independently fitted curves. However, the ERG found an error in the updated model where the curve selection for PFS was drawing from the OS curve selection. Therefore, the company's base case was using a Weibull (instead of a lognormal) curve to model PFS for daratumumab. The ERG changed this in the model and the ICERs remained dominant in favour of daratumumab.

*Fully adjusted MAIC*

As discussed in Section 3.2, from a methodological point of view, the ERG considers the fully adjusted MAIC more appropriate than the partially adjusted MAIC used by the company. The company chose the same distributions for the OS and PFS fully adjusted MAIC curves as those used for the partially adjusted MAIC (AIC and BIC statistics in Table 37 – Table 40 of the CS, appendix 5).

Even though the fully adjusted MAIC is methodologically superior to the partially adjusted MAIC, the former produced clinically implausible OS curves for the comparison of daratumumab vs POM+DEX. As can be seen in Figure 13, in the fully adjusted OS curves, there were [redacted]% of daratumumab patients alive at 10 years in the model. Clinical expert opinion provided to the ERG informed that less than 5% of patients on fourth line daratumumab are expected to survive for 10 years. Figure 14 shows the equivalent OS curves for the partially adjusted MAIC, which produces more clinically plausible results, albeit based on a methodologically flawed approach.

Even though a naïve comparison is also flawed from a methodological point of view, the ERG considers that in the absence of clinically plausible fully adjusted MAIC results, the naïve comparison of real-life daratumumab (i.e., the SACT data) with POM+DEX is of relevance to the committee, particularly given the subsequent treatments included in the SACT data and the more clinically plausible OS predictions for daratumumab (see discussion in the next subsection and in Section 4.2.3).

With regards to the comparison of daratumumab with PANO+BORT+DEX the ERG considers that the fully adjusted MAIC might be the most methodologically robust source for estimating relative treatment effectiveness given that the fully adjusted OS MAIC curve for daratumumab (Figure 15) produces clinically plausible survival tails. Nonetheless, the ERG notes that using the SACT data for daratumumab would provide a more conservative estimation for OS with daratumumab (see Section 4.2.3).

Figure 13. Fully adjusted OS curve for daratumumab vs POM+DEX

Figure 14. Partially adjusted OS curve for daratumumab vs POM+DEX

Figure 15. Fully adjusted OS curve for daratumumab vs PANO+BORT+DEX

*Naïve comparison using the SACT data*

The company acknowledged that the SACT dataset contributed with 2,301 daratumumab-treated patients to the evidence base, thus, conducted a scenario analysis which used digitised SACT OS KM data to model OS curves for daratumumab.

As PFS data were not available from SACT, the company had to assume that PFS was equal to TTD. Given the similarity between the TTD and the PFS curves in MMY2002 (Figure 8 of CS), the ERG agrees with the company's simplifying assumption.

The CS reports that model diagnostics and resultant extrapolations for the survival curves based on digitised daratumumab OS and TD from SACT were presented in appendix 5 of the CS, however, the ERG could not find these in the CS. The company's model, however, included the AIC and BIC statistics for the OS and TTD models chosen to fit the OS and TTD data from SACT.

- Overall survival

The company chose a Weibull curve to model OS KM data from SACT. Even though the Weibull curve had the second worst AIC and BIC statistics, it did visually provide the most clinically plausible tails (Figure 16). Given that the Weibull model did not (visually) provide a bad fit to the KM OS data, the ERG agrees with the use of this curve, as it provides the most plausible, and conservative long-term extrapolation of survival.

Figure 16. SACT OS curve for daratumumab

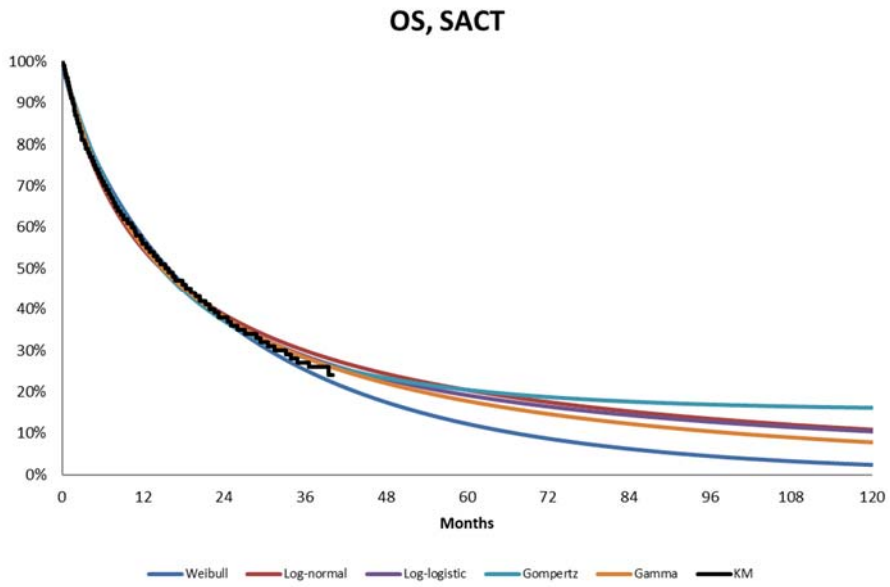
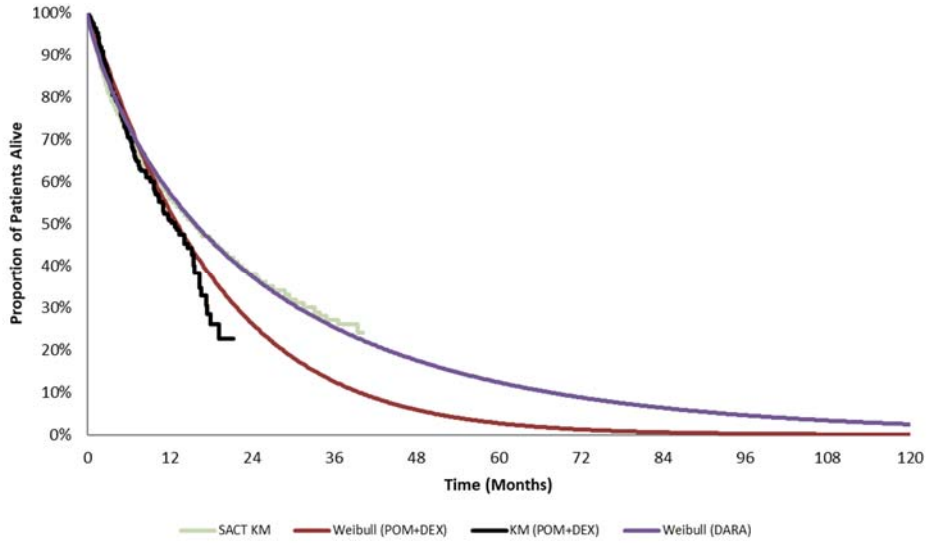



Figure 17 shows that the naïve comparison of OS estimates for daratumumab (SACT) and POM+DEX yields a survival benefit for daratumumab from about 12 months in the model.

Figure 17. Naïve comparison of OS curves (daratumumab SACT vs POM+DEX)




- Time to treatment discontinuation (as a proxy for PFS)

The ERG found an error where the exponential model (instead of the loglogistic) was being used to fit the TTD KM data from SACT. Correcting this to reflect the company's choice of the loglogistic curve, changed the ICER from dominant to £2,659 for daratumumab vs POM+DEX (while the ICER against PANO+BORT+DEX remained dominant). The AIC and BIC statistics included in the model

show that the loglogistic curve is the second best-fitting model, with the gamma providing the best fit. Furthermore, the company selected a lognormal curve to model PFS for POM+DEX and for PANO+BORT+DEX. According to the DSU TSD 14, the same type of parametric model should be chosen for the same clinical outcome across model arms, unless there is a strong clinical rationale to select different models.

Given the similarity in the long-term predictions of the Gamma and the lognormal curves for all three treatments (Figure 18, Figure 19 for daratumumab and for POM+DEX, respectively), the ERG considers that the gamma distribution should be used to model TTD (as a proxy for PFS) for daratumumab, and to estimate PFS for POM+DEX and PANO+BORT+DEX in this scenario. The ERG conducted this analysis and presents the results in Section 6.

Figure 20 shows that the naïve comparison of PFS estimates using a gamma distribution for daratumumab (SACT) vs POM+DEX yields a PFS benefit for daratumumab from about 6 months in the model.

Figure 18. SACT TTD (as a proxy for PFS) curve for daratumumab

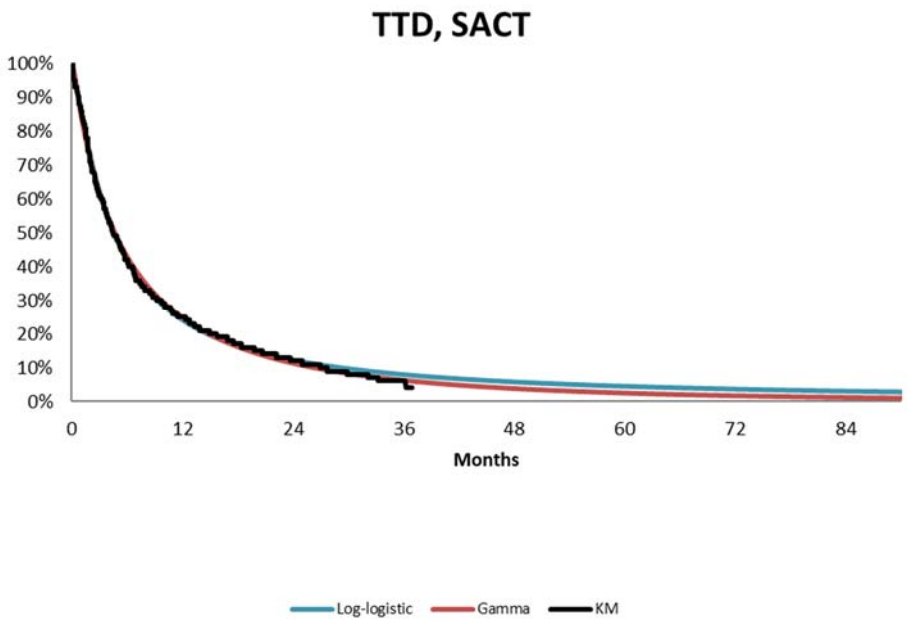



Figure 19. PFS curves for POM+DEX

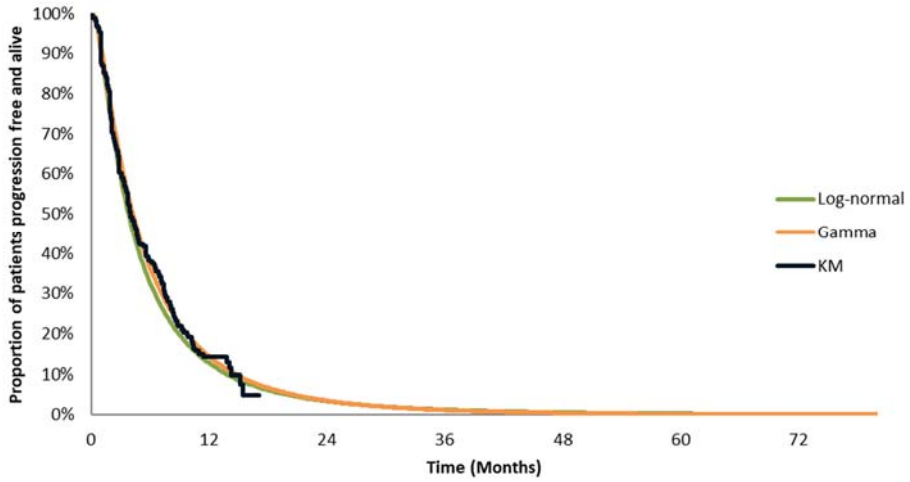
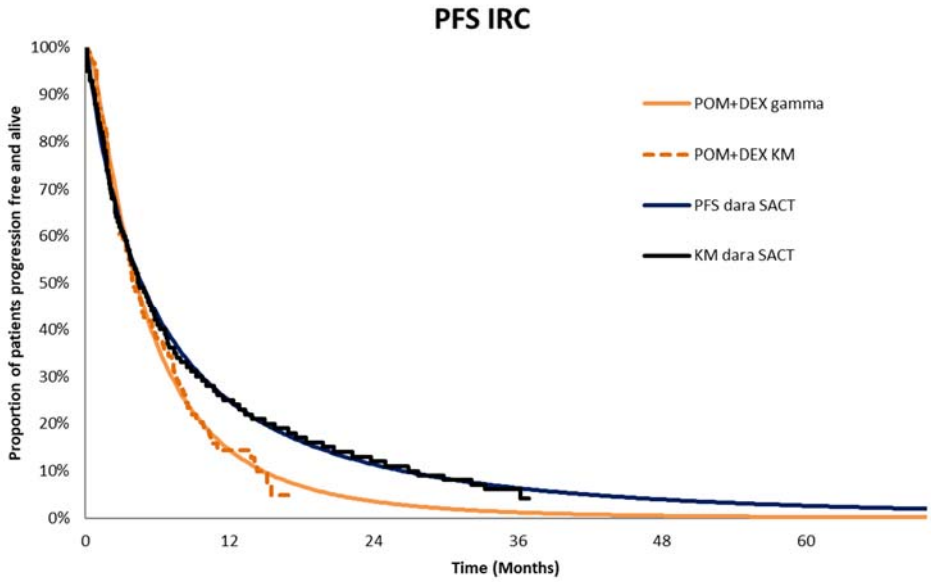



Figure 20. Naïve comparison of PFS curves (daratumumab SACT vs POM+DEX) using a gamma model




### *4.2.2 Time to treatment discontinuation*

The company estimated TTD curves for daratumumab using the latest data cut from MMY2002. For both POM+DEX and PANO+BORT+DEX, the TTD curves remained unchanged from the original model.

For POM+DEX only mean and median TTD could be obtained from MM-003, and the company reported that, "*TTD survival curves for POM+DEX were derived by goal seeking the parametric curve parameters to minimise the sum of squared differences between the predicted mean and median*

*values and those of* [MM-003].” A mean and median TTD of 4.7 months and 2.9 months was observed for POM+DEX in the MM-003 trial, respectively.

For PANO+BORT+DEX, the company could not find any TTD data, therefore patients were assumed to be treated until progression, or when the maximum number of treatment cycles was reached for the treatment.

The company fitted a loglogistic curve to the updated MMY2002 TTD data, and presented AIC and BIC criteria in Table 45 of appendix 5 of the CDF review report. The ERG agrees with the use of the loglogistic curve (Figure 21).

For POM+DEX, the company also used a loglogistic curve to try and replicate the mean and median estimate observed in MM-003. The ERG notes that even though the model estimates by the company replicates the observed mean and median TTD in MM-003 it relies on a very strong assumption that the TTD KM data (not reported for MM-003) would follow a loglogistic distribution.

Figure 21. TTD curves for daratumumab and POM+DEX

### 4.2.3 Subsequent treatments

*Impact of subsequent treatments received in MMY2002 and in SACT on survival*

The ERG was originally concerned with the possibility of OS outcomes for daratumumab being confounded by the impact of subsequent therapies received in MMY2002 (and not available in the UK NHS). The ERG was particularly concerned with the use of carfilzomib, lenalidomide and bortezomib as subsequent treatments, given that the proportion of patients receiving these treatments in MM-003 was much smaller than those observed in MMY2002. As discussed in the ERG's original report, treatment with carfilzomib and retreatment with lenalidomide and bortezomib are not available in the UK and are likely to considerably increase overall survival as subsequent therapies for rrMM patients. As a response to an ERG's request, the company provided OS KM data by subsequent treatment received. These data (originally provided in Figure 44 of the ERG report and reproduced in Figure 22**Error! Reference source not found.** below) suggest that patients receiving carfilzomib and lenalidomide [redacted] compared with patients receiving other treatments. The ERG caveats this observation by the fact that the OS KM curves reported below are for the MMY2002 and GEN501 studies integrated data, however, notes that with the exception of lenalidomide, the proportion of patients receiving carfilzomib and bortezomib as a subsequent treatment were broadly similar in MMY2002 and GEN501.

Figure 22. Overall survival for patients receiving subsequent treatment (earlier data cut from MMY2002 and GEN501)

During the clarification stage of the CDF review, the ERG requested that the company provided the updated MMY2002 data on subsequent treatments, together with OS data by subsequent treatment received.

As a response to clarification, the company provided the updated MMY2002 data on subsequent therapies. Table 27 shows that [redacted] in MMY2002 received either a regimen containing carfilzomib ([redacted]); or chemotherapy with or without dexamethasone [redacted] as first subsequent therapy after daratumumab. The [redacted] received treatment was a regimen containing pomalidomide with or without dexamethasone ([redacted]), followed by regimens containing bortezomib ([redacted]).

Table 27. First subsequent treatment used following daratumumab in MMY2002

| First subsequent treatment[α] | MMY2002 patients (N=106) | Proportion of patients |
|---|---|---|
| Patients undergoing subsequent treatment after daratumumab | [redacted] | [redacted] |
| Bortezomib, carfilzomib, pomalidomide, chemotherapy, dexamethasone and other | [redacted] | [redacted] |
| Bortezomib, chemotherapy and dexamethasone | [redacted] | [redacted] |
| Bortezomib, chemotherapy, dexamethasone and other | [redacted] | [redacted] |
| Bortezomib, chemotherapy and other | [redacted] | [redacted] |
| Bortezomib, panobinostat and dexamethasone | [redacted] | [redacted] |
| Bortezomib, pomalidomide and dexamethasone | [redacted] | [redacted] |
| Bortezomib, thalidomide, chemotherapy, and dexamethasone | [redacted] | [redacted] |
| Bortezomib, thalidomide, daratumumab, chemotherapy, dexamethasone and other | [redacted] | [redacted] |
| Carfilzomib and chemotherapy | [redacted] | [redacted] |
| Carfilzomib, chemotherapy, and dexamethasone | [redacted] | [redacted] |
| Carfilzomib, chemotherapy, and prednisone | [redacted] | [redacted] |
| Carfilzomib, daratumumab, chemotherapy, dexamethasone and other | [redacted] | [redacted] |
| Carfilzomib and dexamethasone | [redacted] | [redacted] |
| Carfilzomib, panobinostat and dexamethasone | [redacted] | [redacted] |
| Carfilzomib, pomalidomide and chemotherapy | [redacted] | [redacted] |
| Carfilzomib, pomalidomide and dexamethasone | [redacted] | [redacted] |
| Chemotherapy | [redacted] | [redacted] |
| Chemotherapy and dexamethasone | [redacted] | [redacted] |
| Chemotherapy, dexamethasone, and prednisone | [redacted] | [redacted] |
| Chemotherapy and other | [redacted] | [redacted] |
| Dexamethasone | [redacted] | [redacted] |
| Elotuzumab and other | [redacted] | [redacted] |
| Ixazomib, pomalidomide and dexamethasone | [redacted] | [redacted] |
| Lenalidomide and chemotherapy | [redacted] | [redacted] |
| Lenalidomide, chemotherapy and dexamethasone | [redacted] | [redacted] |
| Pomalidomide | [redacted] | [redacted] |

| | | |
|---|---|---|
| Pomalidomide, chemotherapy and dexamethasone | [redacted] | [redacted] |
| Pomalidomide, chemotherapy, dexamethasone, and prednisone | [redacted] | [redacted] |
| Pomalidomide and dexamethasone | [redacted] | [redacted] |
| Prednisone | [redacted] | [redacted] |
| [α]Chemotherapy includes: melphalan, doxorubicin, bendamustine, vincristine, cisplatin, cyclophosphamide, etoposide, fludarabine, and carmustine. | | |

The company, however, did not provide the more mature OS data by subsequent treatment received, as it did not, "*consider it statistically robust or appropriate to provide the requested OS data on* [the basis that] *these analyses are subject to a high level of selection bias because of indirectly selecting patients based on their outcome*." The company added that patients had to survive longer to have received subsequent treatment and had to be fitter to receive the more effective and more toxic treatments which led to better survival outcomes.

The company also added that the OS reported in SACT is similar to the MMY2002 OS, hence the impact of subsequent treatments on OS should not be an issue in MMY2002 (

Figure 23). The company noted that towards the end of the observed follow-up period, the OS curves from MMY2002 and SACT converge and if subsequent therapy use was driving increased OS in MMY2002, the curves would diverge at later time points (i.e., as more patients begin subsequent therapies).

Figure 23. KM curves for daratumumab OS from MMY2002 and SACT

*ERG critique*

As discussed in Section 2.2 of the report, clinical practice has evolved since daratumumab was first assessed as a fourth line treatment, nonetheless, the subsequent treatments included in SACT are more reflective of UK's clinical practice than those included in MMY2002 (especially with regards to the use of carfilzomib). The ERG notes that the subsequent treatments received in the SACT dataset (Table 28) do not include carfilzomib, and that the majority of patients received either pomalidomide (64%) or bortezomib in combination with panobinostat (13%). The ERG notes that the proportion of patients receiving lenalidomide in MMY2002 and SACT was [redacted].

The ERG disagrees with the company's assessment that the OS curves in the SACT and in MMY2002 are similar and notes a considerable separation of the curves between month 3 and month 21. The ERG notes that in MMY2002, about [redacted] of patients had discontinued daratumumab at month 3, and therefore, were already receiving a subsequent treatment. At 3 months, only 39% of patients had discontinued daratumumab in the SACT study.

At 12 months, [redacted] of MMY2002 had discontinued treatment with daratumumab, while 75% of SACT patients had discontinued treatment. Thus, the ERG also disagrees with the company's assessment that a separation at the end of the KM curves (instead of a separation in earlier time points) would be indicative of the impact of subsequent treatments in OS. Furthermore, the KM curves include very few patients at risk at the end of the follow-up period, therefore, making the interpretation of the KM curves uncertain.

The ERG concludes that the difference in OS curves seen in SACT and in MMY2002 is likely due to treatment with carfilzomib after daratumumab (and possibly re-treatment with bortezomib) in MMY2002. The ERG notes that it would have been helpful to see OS KM curves by subsequent treatment received in MMY2002 to help mitigate some of the concerns discussed here. The ERG also notes that bias referred by the company around patients being fitter to receive the more effective and toxic subsequent treatments (such as carfilzomib) is irrelevant as these patients (despite being potentially fitter) would not have the opportunity to receive such drugs in the UK. Finally, the ERG notes that in MM-003 patients received carfilzomib in much smaller numbers (2%) than in MMY2002.

Table 28. Subsequent treatments observed in the SACT population

| Regimen | Number of subsequent | Proportion |
|---|---|---|

| | treatments | |
|---|---|---|
| Pomalidomide | 709 | 63.8% |
| Bortezomib + panobinostat | 147 | 13.2% |
| Cyclophosphamide + pomalidomide | 55 | 5.0% |
| Lenalidomide | 30 | 2.7% |
| Trial | 30 | 2.7% |
| Melphalan | 19 | 1.7% |
| Bendamustine | 16 | 1.4% |
| Bortezomib + panobinostat + thalidomide | 15 | 1.4% |
| Cyclophosphamide | 12 | 1.1% |
| Bendamustine + thalidomide | 10 | 0.9% |
| Bortezomib + cyclophosphamide | 8 | 0.7% |
| Cisplatin + cyclophosphamide + doxorubicin + etoposide + thalidomide | 8 | 0.7% |
| Bortezomib | 7 | 0.6% |
| Cyclophosphamide + lenalidomide | 5 | 0.5% |
| Cyclophosphamide + thalidomide | 5 | 0.5% |
| Melphalan + thalidomide | 5 | 0.5% |
| Bortezomib + pomalidomide | 4 | 0.4% |
| Azacitidine | 3 | 0.3% |
| Panobinostat | 3 | 0.3% |
| Bortezomib + thalidomide | 2 | 0.2% |
| Fluorouracil + irinotecan + panitumumab | 2 | 0.2% |
| Ixazomib + lenalidomide | 2 | 0.2% |
| Rituximab | 2 | 0.2% |
| Thalidomide | 2 | 0.2% |
| Bortezomib + cisplatin + cyclophosphamide + doxorubicin + etoposide + lenalidomide | 1 | 0.1% |
| Bortezomib + cisplatin + cyclophosphamide + doxorubicin + etoposide + thalidomide | 1 | 0.1% |
| Capecitabine + oxaliplatin | 1 | 0.1% |
| Cisplatin + gemcitabine | 1 | 0.1% |
| Cyclophosphamide + doxorubicin + vincristine | 1 | 0.1% |
| Cyclophosphamide + doxorubicin + vincristine + pomalidomide | 1 | 0.1% |
| Cytarabine + daunorubicin | 1 | 0.1% |
| Cytarabine + fludarabine | 1 | 0.1% |
| Etoposide + idarubicin + thalidomide | 1 | 0.1% |
| Liposomal daunorubicin + liposomal cytarabine | 1 | 0.1% |
| **Total number** | **1,111** | 100.0% |

*Subsequent treatments modelled*

The company's updated model assumed that [redacted]% of patients who had discontinued treatment with daratumumab; POM+DEX; or PANO+BORT+DEX received a subsequent treatment in the model. This was based on the SACT dataset. Only treatments that were used in ≥1% of patients in SACT were included in the model. The company excluded 30 patients who received 'trial' subsequent therapy in the SACT data. In the POM+DEX arm of the model, the company assumed that patients would not be retreated with pomalidomide and similarly, in the PANO+BORT+DEX arm, it was assumed that panobinostat would not be used following treatment with PANO+BORT+DEX. The remaining subsequent therapies in each arm were re-weighted to sum to 100% (Table 13 in the CS).

The company included a scenario analysis where the proportion of patients receiving subsequent treatment after POM+DEX or PANO+BORT+DEX was [redacted] (i.e., an arbitrary 20% reduction compared with daratumumab) received subsequent therapies. The company explained that this hypothetical scenario was meant to reflect clinical expert opinion that treatment with daratumumab may improve patient's underlying health state, thus making patients more likely to receive subsequent therapies compared to those treated with other agents such as pomalidomide or panobinostat.

The company also noted that while the effectiveness data in the model is based on MMY2002, the distribution of subsequent therapies was informed by the SACT data. The company concluded that there was no need to conduct any adjustment to effectiveness given the comparability of SACT and MMY2002 OS outcomes despite differences in subsequent therapies.

*ERG critique*

As discussed by the ERG in the previous section, the ERG disagrees with the company's assessment of similar OS outcomes in MMY2002 and the SACT data. Furthermore, the ERG is unclear why the subsequent treatment data for POM+DEX from MM-003 trial was not used to estimate subsequent treatments in the POM+DEX arm. During clarification, the ERG asked that the company included a scenario in the economic model where the subsequent treatments received after POM+DEX were those received by patients in the MM-003 trial (i.e., where 44% of patients received subsequent treatments, and each subsequent treatment received was modelled according to Table 29). The results of the company's scenario analysis did not change the dominance of daratumumab vs POM+DEX.

The ERG considers that the distribution of subsequent treatments received after POM+DEX should be based on the same source of effectiveness data for POM+DEX in the model, therefore, the ERG presents the impact of using these data in the ERG's analysis in Section 6.

Table 29. Subsequent treatments received after POM+DEX (MM-003)

| Subsequent treatment | Proportion of MM-003 patients |
|---|---|
| Dexamethasone | 29% |
| Pomalidomide | 0% |
| Cyclophosphamide | 21% |
| Carfilzomib | **2%** |
| Bortezomib | 18% |
| Lenalidomide | **5%** |
| Melphalan | **8%** |
| Etoposide | **3%** |
| Bendamustine | 11% |
| Thalidomide | **7%** |

Values in bold are from a cut-off date of March 2013 while the other values are from a more up to date cut-off point of September 2013

Similarly, the ERG considers that the source of subsequent treatments post daratumumab in the model should ideally match the source of clinical effectiveness for daratumumab in the analysis. Given the ERG's preference for the SACT data (as it better reflects the subsequent treatments available to NHS patients after daratumumab), the ERG's preferred approach is to use the SACT data to estimate treatment effectiveness (discussed in Section 4.2.1) and subsequent treatments after daratumumab.

During clarification the ERG also asked that the company included a scenario in the economic model where the subsequent treatments received after were those received by patients in the MMY2002 final data cut (to match the source of clinical effectiveness for daratumumab in the model). The company undertook the requested analysis and concluded that the dominance of daratumumab over POM+DEX and PANO+BORT+DEX did not change.

Finally, the ERG notes that when the MM-003 and the SACT data are used to estimate subsequent treatments in the model for POM+DEX and daratumumab, respectively, the proportion of patients receiving a fifth line of therapy are [redacted] for daratumumab patients and 44% for POM+DEX patients.

### 4.2.4 Adverse events

Administration of daratumumab via subcutaneous injection is now most representative of UK clinical practice as discussed in Section 3.1. Therefore, the company updated the acquisition costs and AEs in the model to reflect this change. The company presented the AEs used in the updated model in Table 11 of the CS. The ERG agrees with the company's update.

### 4.2.5 Resource use and costs

The company updated analysis included a new PAS ([redacted] discount) for daratumumab and reflected the change in mode of administration and in dose. Drug acquisition costs for daratumumab via subcutaneous injection used in the model are presented in Table 30. All costs have been updated from the original appraisal to reflect the latest available sources or inflated to 2021 prices.

Table 30. Daratumumab acquisition cost

| Drug | Dose per unit | Units per pack | Price per pack |
|---|---|---|---|
| Daratumumab (list price) | 1,800mg | 1 | £4,320.00 |
| Daratumumab (PAS price) | | | [redacted] |

The company's updated analysis also incorporated a change in the cost of subsequent treatments received, which have been discussed in Section 4.2.3.

## 5 Cost effectiveness results

The deterministic results of the pair-wise comparison of daratumumab with POM+DEX and PANO+BORT DEX are presented in Table 31 and Table 32, respectively. The equivalent probabilistic results are provided in Table 33 and Table 34.

According to the company's analysis daratumumab is expected to increase patients' life expectancy by 1.22 years and 1.17 years compared with POM+DEX and PANO+BORT+DEX, respectively, at a lower cost and incremental QALYs, resulting in the dominance of daratumumab. The company's probabilistic results also show dominance.

Table 31. Company's base case deterministic results vs POM+DEX

| Interventions | Total Costs (£) | Total LYG | Total QALYs | Incremental costs (£) | Incremental LYG | Incremental QALYs | ICER (£/QALY) |
|---|---|---|---|---|---|---|---|
| POM+DEX | [redacted] | 1.49 | [redacted] | - | - | - | |
| Daratumumab | [redacted] | 2.71 | [redacted] | [redacted] | 1.22 | [redacted] | Daratumumab Dominates |

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 32. Company's base case deterministic results vs PANO+BORT+DEX

| Interventions | Total Costs (£) | Total LYG | Total QALYs | Incremental costs (£) | Incremental LYG | Incremental QALYs | ICER (£/QALY) |
|---|---|---|---|---|---|---|---|
| PANO+BORT+DEX | [redacted] | 1.80 | [redacted] | - | - | - | |
| Daratumumab | [redacted] | 2.97 | [redacted] | [redacted] | 1.17 | [redacted] | Daratumumab Dominates |

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 33. Company's base case probabilistic results vs POM+DEX

| Interventions | Total Costs (£) | Total LYG | Total QALYs | Incremental costs (£) | Incremental LYG | Incremental QALYs | ICER (£/QALY) |
|---|---|---|---|---|---|---|---|
| POM+DEX | [redacted] | 1.50 | [redacted] | – | – | – | |
| Daratumumab | [redacted] | 2.74 | [redacted] | [redacted] | 1.24 | [redacted] | Daratumumab Dominates |

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 34. Company's base case probabilistic results vs PANO+BORT+DEX

| Interventions | Total Costs (£) | Total LYG | Total QALYs | Incremental costs (£) | Incremental LYG | Incremental QALYs | ICER (£/QALY) |
|---|---|---|---|---|---|---|---|
| PANO+BORT+DEX | [redacted] | 1.83 | [redacted] | – | – | – | |
| Daratumumab | [redacted] | 2.99 | [redacted] | [redacted] | 1.16 | [redacted] | Daratumumab Dominates |

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

The company provided a range of scenario analyses (Table 19 of CS), where all the ICERs remained dominant in favour of daratumumab.

# 6 Additional economic analysis undertaken by the ERG

## 6.1 Model corrections

As described in Section 4, the ERG corrected two errors in the model:

1. The company's base case was using a Weibull (instead of a lognormal) curve to model PFS for daratumumab. The ERG changed this in the model and the ICERs remained dominant in favour of daratumumab (Table 35 and Table 36);
2. The ERG found an error where the exponential model (instead of the loglogistic) was being used to fit the TTD KM data from SACT in the company's scenario analysis including the naïve comparison of the SACT data. Therefore, this correction only changed the company's results for the ICER for daratumumab vs POM+DEX, where it changed from dominant to £2,659 (while the ICER against PANO+BORT+DEX remained dominant).

The ERG's corrections had a negligible impact on the company's base case results.

Table 35. Company's base case deterministic results vs POM+DEX (corrected)

| Interventions | Total Costs (£) | Total QALYs | Total LYG | Incremental costs (£) | Incremental QALYs | Incremental LYG | ICER (£/QALY) |
|---|---|---|---|---|---|---|---|
| POM+DEX | [redacted] | [redacted] | 1.49 | - | - | - | - |
| Daratumumab | [redacted] | [redacted] | 2.71 | [redacted] | [redacted] | 1.22 | Daratumumab Dominates |

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 36. Company's base case deterministic results vs PANO+BORT+DEX (corrected)

| Interventions | Total Costs (£) | Total QALYs | Total LYG | Incremental costs (£) | Incremental QALYs | Incremental LYG | ICER (£/QALY) |
|---|---|---|---|---|---|---|---|
| PANO+BORT+DEX | [redacted] | [redacted] | 1.80 | - | - | - | - |
| Daratumumab | [redacted] | [redacted] | 2.97 | [redacted] | [redacted] | 1.17 | Daratumumab Dominates |

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

## 6.2 ERG scenario analysis

The scenario analyses undertaken by the ERG are explained throughout Section 4 of the report. The ERG conducted the analyses using the naïve comparison of SACT daratumumab data with the relevant comparator studies as it considered this to be the more conservative source to estimate treatment effectiveness with daratumumab (see Section 4.2.1). For this scenario, the additional ERG's assumptions consist of the following:

e. Using a gamma distribution to estimate TTD (as a proxy for PFS) for daratumumab, and to estimate PFS for POM+DEX and PANO+BORT+DEX.

f. Modelling the subsequent treatments received after POM+DEX based on those received by patients in the MM-003 trial.

The ERG notes that all the scenarios reported in Table 37 include the subsequent treatments received after daratumumab based on those received by patients in SACT (as this was the company's base case assumption). The key driver of the model results is the source of data used to model subsequent treatments after POM+DEX, where the ICER for POM+DEX increased from £2,659 to £12,546 per QALY gained.

Table 37. Results of the ERG's scenario analyses

| | Results per patient | Daratumumab (1) | POM+DEX (2) | PANO+BORT DEX (3) | Incremental value (1-2) | Incremental value (1-3) |
|---|---|---|---|---|---|---|
| 1 | Using the naïve comparison of SACT daratumumab data | | | | | |
| | Total costs | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| | QALYs | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| | ICER (£/QALY) | - | - | - | £2,659 | Daratumumab dominates |
| 1a | Using the naïve comparison of SACT daratumumab data and using a gamma distribution to estimate TTD (as a proxy for PFS) for daratumumab, and to estimate PFS for POM+DEX and PANO+BORT+DEX | | | | | |
| | Total costs | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| | QALYs | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| | ICER (£/QALY) | - | - | - | Daratumumab dominates | Daratumumab dominates |
| 1b | Using the naïve comparison of SACT daratumumab data and modelling the subsequent treatments received after POM+DEX based on those received by patients in the MM-003 trial. | | | | | |
| | Total costs | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| | QALYs | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| | ICER (£/QALY) | - | - | - | £12,546 | Daratumumab dominates |

Abbreviations: ICER, incremental cost-effectiveness ratio; HR, hazard ratio; PAIC, population adjusted indirect comparison; PFS, progression free survival; PPS, post-progression survival; QALY, quality adjusted life year

## 6.3 ERG preferred assumptions

The ERG's preferred assumptions have been reported in Section 6.2. The cumulative ICER resulting from combining all the assumptions results in an ICER of £3,060 per QALY gained for POM+DEX and a dominant ICER in favour of daratumumab vs PANO+BORT+DEX (Table 38 and Table 39).

The ERG also presents the results for the fully adjusted MAIC, which provides extremely optimistic (albeit clinically implausible) long-term survival with daratumumab (see Section 4.2.1). For this scenario, the additional ERG's assumptions consist of the following:

g. Modelling the subsequent treatments received after POM+DEX based on those received by patients in the MM-003 trial.
h. Modelling the subsequent treatments received after daratumumab based on those received by patients in the MMY2002 trial.

The ERG's results (Table 40 and Table 41) show that daratumumab dominates both POM+DEX and PANO+BORT+DEX.

Table 38. ERG's preferred ICER for daratumumab vs POM+DEX (corrected)

| Interventions | Total Costs (£) | Total QALYs | Total LYG | Incremental costs (£) | Incremental QALYs | Incremental LYG | ICER (£/QALY) |
|---|---|---|---|---|---|---|---|
| POM+DEX | [redacted] | [redacted] | 1.49 | - | - | - | - |
| Daratumumab | [redacted] | [redacted] | 2.26 | [redacted] | [redacted] | 0.77 | £3,060 |

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 39. ERG's preferred ICER for daratumumab vs PANO+BORT+DEX (corrected)

| Interventions | Total Costs (£) | Total QALYs | Total LYG | Incremental costs (£) | Incremental QALYs | Incremental LYG | ICER (£/QALY) |
|---|---|---|---|---|---|---|---|
| PANO+BORT+DEX | [redacted] | [redacted] | 1.80 | - | - | - | - |
| Daratumumab | [redacted] | [redacted] | 2.26 | [redacted] | [redacted] | 0.46 | Daratumumab Dominates |

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 40. ERG's ICER for daratumumab vs POM+DEX using fully adjusted MAIC

| Interventions | Total Costs (£) | Total QALYs | Total LYG | Incremental costs (£) | Incremental QALYs | Incremental LYG | ICER (£/QALY) |
|---|---|---|---|---|---|---|---|
| POM+DEX | [redacted] | [redacted] | 1.49 | - | - | - | - |
| Daratumumab | [redacted] | [redacted] | 5.25 | [redacted] | [redacted] | 3.75 | Daratumumab dominates |

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 41. ERG's ICER for daratumumab vs PANO+BORT+DEX using fully adjusted MAIC

| Interventions | Total Costs (£) | Total QALYs | Total LYG | Incremental costs (£) | Incremental QALYs | Incremental LYG | ICER (£/QALY) |
|---|---|---|---|---|---|---|---|
| PANO+BORT+DEX | [redacted] | [redacted] | 1.80 | - | - | - | - |
| Daratumumab | [redacted] | [redacted] | 3.33 | [redacted] | [redacted] | 1.53 | Daratumumab Dominates |

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

## 6.4 Conclusions of the cost effectiveness sections

The ERG presented a range of results, where using the SACT data for daratumumab reflects the most conservative source of treatment effectiveness for the drug, albeit based on a naïve comparison. The results of the ERG's analysis produced an ICER of £3,060 vs POM+DEX and a dominant ICER in favour of daratumumab for PANO+BORT+DEX.

At the more optimistic end of the scale, the ERG used the fully adjusted MAIC results, which only produced dominant ICER's in favour daratumumab. Nonetheless, the ERG notes that even though these analyses are based on a more robust method for analysis of treatment effectiveness, the OS curves for daratumumab vs POM+DEX produce clinically implausible results.

The company's partially adjusted MAIC (with the same ERG's preferred options as those reported in the previous section for the fully adjusted MAIC) also produce dominant ICERs in favour of daratumumab for both comparator treatments, albeit with less incremental life years than those reported for the fully adjusted MAIC in Table 40 and Table 41 (1.22 life years gained for daratumumab vs POM+DEX and 1.17 for daratumumab vs PANO+BORT+DEX).

The ranges provided by the ERG lead to the conclusion that daratumumab is likely to produce ICERs well below the £30,000 threshold when the comparator list prices are used. The ERG has provided a confidential appendix including the results when the comparator treatment PAS discounts are used in the model.

# 7 End of Life

The company has submitted daratumumab for end of life consideration; the company and ERG assessments are summarised in Table 42. The ERG notes that both the company and ERG assessments suggest life expectancy with the comparators POM+DEX and PANO+BORT+DEX is predicted to be less than 24 months. Additionally, both the ERG and company assessments suggest daratumumab is associated with a minimum extension to life of 0.46 years thus meeting the criterion of prolonging life by at least an additional 3 months. However, the ERG considers the clinical effectiveness evidence underpinning this assessment to be extremely uncertain as discussed in Section 3, and therefore the ERG recommends caution in drawing conclusions on the end of life criteria from only these findings.

Table 42. End of life considerations

| NICE criterion | Company assessment | ERG assessment |
|---|---|---|
| The treatment is indicated for patients with a short life expectancy, normally less than 24 months | Median life expectancy: less than 24 months, and closer to 12 months. | The corrected model for the company's analysis of the MMY2002 population shows the following mean undiscounted total life-years for each treatment:<br>Daratumumab monotherapy: [redacted] years<br>Pano+bort+dex: [redacted] years<br>Pom+dex: [redacted] years |
| There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment | Mean OS estimates in company's base case analysis:<br>Daratumumab monotherapy: [redacted] years vs pom+dex<br>Pom+dex: [redacted] years<br>Daratumumab monotherapy: [redacted] years vs pano+bort+dex<br>Pano+bort+dex: [redacted] | |
| The treatment is licensed or otherwise indicated, for small patient populations | In 2013, the Committee for Orphan Medicinal Products (COMP) granted daratumumab orphan drug status due to the classification of MM as a rare disease: COMP defines a rare disease as one that affects fewer than 5 in 10,000 people across the European Union | n/a |

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# 9 Appendices

## 9.1 KM plots for POM+DEX

Figure 24. Partially adjusted KM plot for OS, daratumumab monotherapy versus POM+DEX (company base-case MAIC) (Reproduced from company submission figure 13)

Abbreviations: MAIC, matching-adjusted indirect comparison; OS, overall survival; POM+DEX, pomalidomide plus dexamethasone.

Figure 25. Partially adjusted KM plot for PFS, daratumumab monotherapy versus POM+DEX (company base-case MAIC) (Reproduced from company submission figure 14)

Abbreviations: MAIC, matching-adjusted indirect comparison; PFS, progression-free survival; POM+DEX, pomalidomide plus dexamethasone.

Figure 26. Fully adjusted KM plot for OS, daratumumab versus POM+DEX (Reproduced from company response to clarification questions figure 1)

Abbreviations: HR, hazard ratio; KM, Kaplan-Meier; MAIC, matching-adjusted indirect comparison; OS, overall survival; POM+DEX, pomalidomide plus dexamethasone.

Figure 27. Fully adjusted KM plot for PFS, daratumumab versus POM+DEX (Reproduced from company response to clarification questions figure 2)

Abbreviations: HR, hazard ratio; KM, Kaplan-Meier; MAIC, matching-adjusted indirect comparison; PFS, progression-free survival; POM+DEX, pomalidomide plus dexamethasone.

## 9.2 KM plots for PANO+BORT+DEX

Figure 28. Partially adjusted KM plot for OS, daratumumab monotherapy versus PANO+ BORT+DEX (company base-case MAIC) (Reproduced from company submission figure 19)

Abbreviations: BORT+DEX, bortezomib plus dexamethasone; MAIC, matching-adjusted indirect comparison; OS, overall survival; PANO+BORT+DEX, panobinostat plus bortezomib and dexamethasone.

Figure 29. Partially adjusted KM plot for PFS, daratumumab monotherapy versus PANO+ BORT+DEX (company base-case MAIC) (Reproduced from company submission figure 20)

Abbreviations: BORT+DEX, bortezomib plus dexamethasone; MAIC, matching-adjusted indirect comparison; PANO+BORT+DEX, panobinostat plus bortezomib and dexamethasone; PFS, progression-free survival.

Figure 30. Fully adjusted KM plot for OS, daratumumab versus PANO+BORT+DEX (Reproduced from company response to clarification questions figure 3)

Abbreviations: HR, hazard ratio; KM, Kaplan-Meier; MAIC, matching-adjusted indirect comparison; OS, overall survival; PANO+BORT+DEX, panobinostat plus bortezomib and dexamethasone.

Figure 31. Fully adjusted MAIC KM plot for PFS, daratumumab versus PANO+BORT+DEX (Reproduced from company response to clarification questions figure 4)

Abbreviations: HR, hazard ratio; KM, Kaplan-Meier; MAIC, matching-adjusted indirect comparison; PFS, progression-free survival; PANO+BORT+DEX, panobinostat plus bortezomib and dexamethasone.

# National Institute for Health and Care Excellence

# Centre for Health Technology Evaluation

## ERG report – factual accuracy check and confidential information check

**Daratumumab monotherapy for treating relapsed and refractory multiple myeloma (CDF review of TA510) [ID3881]**

'*Data owners will be asked to check that confidential information is correctly marked in documents created by others in the technology appraisal process before release; for example, the technical report and ERG report.*' (Section 3.1.29, Guide to the processes of technology appraisals).

You are asked to check the ERG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **12pm on 25 November** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as '[redacted]' in turquoise, all information submitted as '[redacted]' in yellow, and all information submitted as '[redacted]' in pink.

**Issue 1** **Reporting errors**

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
|---|---|---|---|
| Page 45, Table 21 (row 3, column 4) | Please change from: "[redacted]"<br>To: "[redacted]" | The point estimate is reported on page 27 of the company submission as [redacted] | The ERG has made the amendment proposed by the company. |
| Page 47 | Please change from: "The results of the unadjusted, partially adjusted, fully adjusted and fully adjusted including sex MAICs of daratumumab versus **PM+DEX** are presented in **Error! Reference source not found.**"<br>To: "The results of the unadjusted, partially adjusted, fully adjusted and fully adjusted including sex MAICs of daratumumab versus **PANO+BORT+DEX** are presented in **Error! Reference source not found.**" | The results presented in Table 22 of the ERG report are for PANO+BORT+DEX | The ERG has made the amendment proposed by the company. |
| Page 48 | Please change from: "The KM plots for the fully adjusted including **age** dataset are presented in Figure 7 and Figure 8"<br>To: "The KM plots for the fully adjusted including **sex** dataset are presented in Figure 7 and Figure 8" | The results presented in Figure 7 and Figure 8 of the ERG report reflect the fully adjusted MAIC including sex as a matching factor | The ERG has made the amendment as proposed by the company. |
| Page 58, Table 26 (row 2, column 3) | Please change from: "MAICs adjusted for the top 5 or top **3** prognostic factors" | The MAIC for POM+DEX used the top 5 factors, while the MAIC for PANO+BORT+DEX used the top 2 | The ERG has made the amendment as proposed by the company. |

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
|---|---|---|---|
| | To: "MAICs adjusted for the top 5 or top **2** prognostic factors" | factors (see page 27 of the company submission) | |
| Page 62 | Please change from: "the company finding the Weibull and the **loglogistic** distributions the most appropriate fit to OS and PFS data"<br>To: "the company finding the Weibull and the **lognormal** distributions the most appropriate fit to OS and PFS data" | The lognormal distribution was selected for PFS in the company submission (see page 30 of the company submission) | The ERG has made the amendment as proposed by the company. |
| Page 62 | Please change from: "there were [redacted]**%** of daratumumab patients alive at 10 years in the model"<br>To: "there were [redacted]**%** of daratumumab patients alive at 10 years in the model" | There were [redacted]**%** of daratumumab patients alive at 10 years in the Excel model ('OS_fulladjuMAICvsPOM', Cell S543) | The ERG has made the amendment as proposed by the company. |
| Page 70, Table 27 | Please update Table 27 to reflect Janssen's revised response to ERG clarification question B1. | A corrected version of this table including 75 patients receiving subsequent therapies was submitted at clarification stage | The ERG has made the amendment as proposed by the company. |
| Page 72 | Please change from: "while [redacted] of SACT patients had discontinued treatment"<br>To: "while [redacted] of SACT patients had discontinued treatment" | [redacted] of SACT patients discontinued treatment at 12 months (Excel model, 'KM Data', Cell DB548) | The ERG has made the amendment as proposed by the company. |

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
|---|---|---|---|
| Page 76 | Please change from "the proportion of patients receiving a fifth line of therapy are [redacted] for daratumumab patients"<br><br>To: "the proportion of patients receiving a fifth line of therapy are [redacted] for daratumumab patients" | On page 21 of the company submission, [redacted] of daratumumab patients received a fifth-line therapy in the SACT data set. | The ERG has made the amendment as proposed by the company. |

**Issue 2 Clarity of statements**

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
|---|---|---|---|
| Page 17 | Please change from: "**The** analyses for daratumumab with POM+DEX are further hampered by implausible tails in the OS curves (i.e., the fully adjusted MAIC KM curve and any extrapolations based on it)."<br><br>To: "**Some** analyses for daratumumab **compared** with POM+DEX are further hampered by implausible tails in the OS curves (i.e., the fully adjusted MAIC KM curve and any extrapolations based on it)." | The original ERG report text suggests that the fully adjusted MAIC was presented in the company base case | Not a factual inaccuracy; no change required. The current text does not mention the company base case. |

| | | | |
|---|---|---|---|
| Page 19, Table 5 (row 2, column 2, paragraph 2) | Please include the statement: “The company also noted that there were insufficient patients receiving each of bortezomib, carfilzomib, lenalidomide, and pomalidomide ([redacted], [redacted], [redacted], and [redacted], respectively) to inform robust Kaplan-Meier curves”. | The original ERG report text does not include a key additional reason why the company was not able to provide the requested analyses | The ERG has made the amendment as proposed by the company. |
| Page 19, Table 5 (row 2, column 2, paragraph 3) | Please include the statement: “However, the OS curves were closer following adjustment for baseline characteristics” | The original ERG report text does not acknowledge that any differences in the OS curves from SACT and MMY2002 are largely explained by differences in baseline characteristics | Not a factual inaccuracy; no change required. |
| Page 21 | Please change from: “a more robust method for analysis of treatment effectiveness”<br>To: “a more robust method for analysis of **relative** effectiveness” | This wording better reflects the analysis performed | The ERG has made the amendment as proposed by the company. |

| | | | |
|---|---|---|---|
| Page 43 | Please change from: “Although MAIC analyses using **GEN501 and** the pooled data set were also provided”<br><br>To: “Although MAIC analyses using the pooled data set were also provided” | MAIC analyses using the GEN501 data were available in the Excel model; however, these analyses were not presented in the company submission dossier | The ERG has made the amendment proposed by the company. |
| Page 45 | Please change from: “The ERG notes that in the company fully adjusted MAIC the sample size from MMY2002 reduces from106 patients to [redacted] for the POM+DEX comparison and [redacted] for the PANO+BORT+DEX comparison due to patients with missing data”<br><br>To: “The ERG notes that in the company fully adjusted MAIC the sample size from MMY2002 **prior to matching** reduces from 106 patients to [redacted] for the POM+DEX comparison and [redacted] for the PANO+BORT+DEX comparison due to patients with missing data” | The original text in the ERG report could be misinterpreted as the *effective* sample sizes for the fully adjusted MAIC being [redacted] and [redacted] for the comparisons versus POM+DEX and PANO+BORT+DEX, respectively | The ERG has made the amendment proposed by the company. |
| Page 52 | Please change from: “treatment duration is used instead as a **surrogate** for PFS data”<br><br>To: “treatment duration is used instead as a **proxy** for PFS data” | The original text in the ERG report implies that additional data is used to link the treatment duration and PFS data (as is typical of surrogate outcomes) rather than using the treatment duration data directly as a proxy for PFS | The ERG has made the amendment proposed by the company. |

| | | | |
|---|---|---|---|
| Page 68 | Please change from: “The ERG notes that even though the model estimates by the company replicates the observed mean and median TTD in MM-003 it relies on **a very strong** assumption that the TTD KM data (not reported for MM-003) would follow a loglogistic distribution”<br><br>To: “The ERG notes that even though the model estimates by the company replicates the observed mean and median TTD in MM-003 it relies on **the** assumption that the TTD KM data (not reported for MM-003) would follow a loglogistic distribution” | The original text in the ERG report states that the assumption is very strong; however, if the mean is correct (as original text implies), the impact on cost-effectiveness should be minimal | Not a factual inaccuracy; no change required. |

| | | | |
|---|---|---|---|
| Page 70 | Please add clarification of how values in the below text were calculated:<br><br>Table 27 shows that [redacted] in MMY2002 received either a regimen containing carfilzomib ([redacted]); or chemotherapy with or without dexamethasone (also [redacted]) as first subsequent therapy after daratumumab. The [redacted] received treatment was a regimen containing pomalidomide with or without dexamethasone ([redacted]), followed by regimens containing bortezomib ([redacted]). | We were not able to replicate all values (for example, where bortezomib and carfilzomib are included in same regimen) | The calculations come from adding the proportion of patients receiving the treatments indicated in the model (tab Subs Tx, column E56:E86). The ERG found a discrepancy in the estimation of patients receiving bortezomib and carfilzomib and/or thalidomide, as said patients were not added in the proportion of patients receiving subsequent bortezomib. The ERG has changed this and as a result it has replaced the sentence "followed by regimens containing bortezomib ([redacted]%)" by "followed by regimens containing bortezomib ([redacted])." |
| Page 72 | Please clarify the source of the following statement:<br><br>"The ERG notes that in MMY2002, about [redacted]% of patients had discontinued daratumumab at month 3" | We were unable to match this value in the Excel model | In the Excel model, tab "KM Data", cell DD103 shows that [redacted]% of patients had discontinued daratumumab at month 3. |

**Issue 3 Errors in company submission**

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
|---|---|---|---|
| Page 55 | Please change: "the recommended dosing schedule is weekly for **Weeks 0 to 9**"<br>To: "the recommended dosing schedule is weekly for **Weeks 1 to 8**" | The latest version of the Summary of Product Characteristics refers to the dosing schedule as Weeks 1 to 8. We apologise for any inconsistencies within the original submission. | The ERG has made the amendment proposed by the company. |
| Page 77 | Please remove the following statement: "however, the probabilistic incremental QALY gain for PANO+BORT+DEX is considerably lower than the deterministic estimate." | Please see the correction to the probabilistic results in the row below | The ERG has made the amendment proposed by the company. |
| Page 78, Table 34 (row 2) | Please change:<br>• Incremental costs: [redacted] to [redacted]<br>• Incremental LYG: **0.90** to **1.16**<br>• Incremental QALYs: [redacted] to [redacted] | The probabilistic results for PANO+BORT+DEX were incorrectly reported in the company submission. This is because incremental values in the Excel model were incorrectly linked to the daratumumab results for the comparison versus POM+DEX. We apologise for this error. | The ERG has made the amendment proposed by the company. |

**Issue 4 Typographic errors**

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
|---|---|---|---|
| Page 21 | Please change from: "the ERG's **prefer** assumptions"<br>To: "the ERG's **preferred** assumptions" | Typographic error | The ERG has made the amendment proposed by the company. |
| Page 22 | Please change from: "Section **61**"<br>To: "Section **6.1**" | Typographic error | The ERG has made the amendment proposed by the company. |
| Page 29 | Please change from: "which is **the** more commonly used in the NHS"<br>To: "which is more commonly used in the NHS" | Typographic error | The ERG has made the amendment proposed by the company. |
| Page 31 | Please change from: "30**t** May 2017"<br>To: "30**th** May 2017" | Typographic error | The ERG has deleted the 't' for consistency with the reporting of dates throughout the ERG report. |
| Page 34 | Please change from: "**COLUMA**"<br>To: "**COLUMBA**" | Typographic error | The ERG has made the amendment proposed by the company. |
| Pages 36, 37 | Please change from: "**Cooke** et al"<br>To: "**Cook** et al" | Typographic error | The ERG has made the two amendments proposed by the company. |

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
|---|---|---|---|
| Page 37 | Please change from: "EQ-5D-**L**"<br>To: "EQ-5D-**5L**" | Typographic error | The ERG has made the amendment proposed by the company. |
| Page 39 | Please change from: "The results of the naïve comparison of the SACT data with **the** each of the comparators"<br>To: "The results of the naïve comparison of the SACT data with each of the comparators" | Typographic error | The ERG has made the amendment proposed by the company. |
| Page 42 | Please change from: "the second most common **was** regimen was bortezomib + panobinostat"<br>To: "the second most common regimen was bortezomib + panobinostat" | Typographic error | The ERG has made the amendment proposed by the company. |
| Page 42 | Please change from: "the **firsnict** line"<br>To: "the **first** line" | Typographic error | The ERG was unable to locate this potential error. |
| Pages 45 (two instances), 47, 49 (two instances), 52 | Please change from: "**PANORMA**"<br>To: "**PANORAMA**" | Typographic error | The ERG has made the six amendments proposed by the company. |
| Page 47 | Please change from: "longer PFS with PANO+BORT+DEX compared **to with** daratumumab" | Typographic error | The ERG has made the amendment proposed by the company. |

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
|---|---|---|---|
| | To: “longer PFS with PANO+BORT+DEX compared **with** daratumumab” | | |
| Page 47 | Please change from: “**PAN**+BORT+DEX”<br>To: “**PANO**+BORT+DEX” | Typographic error | The ERG has made the amendment proposed by the company. |
| Page 48 | Please change from: “independent curve fitting for daratumumab and PANO+BORT+DEX was also required in the economic model similar to for POM+DEX”<br>To: “independent curve fitting for daratumumab and PANO+BORT+DEX was also required in the economic model similar to **the analyses** for POM+DEX” | Typographic error | The ERG has made the amendment proposed by the company. |
| Page 52 | Please remove the carriage return between “presented in” and “Figure 11” | Typographic error | The ERG has made the amendment proposed by the company. |
| Page 56 | Please remove the double space between “in” and “conservative” | Typographic error | The ERG has made the amendment proposed by the company. |
| Page 57 | Please remove the double space between “is” and “associated” | Typographic error | The ERG has made the amendment proposed by the company. |

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
|---|---|---|---|
| Page 58 | Please change from: "The starting point for company's updated economic analysis"<br>To: "The starting point for **the** company's updated economic analysis" | Typographic error | The ERG has made the amendment proposed by the company. |
| Page 82 | Please change from: "in favour daratumumab"<br>To: "in favour **of** daratumumab" | Typographic error | The ERG has made the amendment proposed by the company. |

**Issue 5 Incorrect marking up**

| Location of incorrect marking | Description of incorrect marking | Amended marking | ERG response |
|---|---|---|---|
| Page 72 | Please change from: "The ERG notes that in MMY2002, about [redacted]% of patients had discontinued daratumumab at month 3, and therefore, were already receiving a subsequent treatment. At 3 months, only 39% of patients had discontinued daratumumab in the SACT study."<br>To: "The ERG notes that in MMY2002, about [redacted] of patients had discontinued daratumumab at month 3, and therefore, were already receiving a subsequent treatment. At 3 months, only [redacted] of patients | Unpublished data from SACT dataset is considered Academic in Confidence | The ERG has made the amendment proposed by the company. |

| | | | |
|---|---|---|---|
| | had discontinued daratumumab in the SACT study.” | | |
| Page 72 | Please change from: At 12 months, [redacted]% of MMY2002 had discontinued treatment with daratumumab, while 80% of SACT patients had discontinued treatment.<br>To: At 12 months, [redacted] of MMY2002 had discontinued treatment with daratumumab, while [redacted] of SACT patients had discontinued treatment. | Unpublished data from SACT dataset is considered Academic in Confidence | The ERG has made the amendment proposed by the company. |
| Pages 73, 74 | The number and proportion of subsequent treatments observed in SACT (reported in Table 28) should be marked as Academic in Confidence | Unpublished data from SACT dataset is considered Academic in Confidence | The ERG has made the amendment proposed by the company. |

Public Health England

Protecting and improving the nation's health

# Daratumumab for treating multiple myeloma – data review

Commissioned by NHS England and NHS Improvement

# Contents

# Executive summary

## Introduction

The National Institute for Health and Care Excellence (NICE) appraised the clinical and cost effectiveness of daratumumab for multiple myeloma. The appraisal committee highlighted clinical uncertainty around estimates of overall survival (OS) and duration of treatment in the evidence submission. As a result, they recommended the commissioning of daratumumab through the Cancer Drugs Fund (CDF) to allow a period of managed access, supported by additional data collection to answer the clinical uncertainty.

NHS England and NHS Improvement commissioned Public Health England (PHE) to evaluate the real-world treatment effectiveness of daratumumab in the CDF population, during the managed access period. This report presents the results of the use of daratumumab in clinical practice in England, using the routinely collected Systemic Anti-Cancer Therapy (SACT) dataset.

This report, and the data presented, demonstrate the potential within the English health system to collect real-world data to inform decision-making about patient access to cancer treatments via the CDF. The opportunity to collect real-world data enables patients to access promising new treatments much earlier than might otherwise be the case, whilst further evidence is collected to address clinical uncertainty.

The NHS England and NHS Improvement and PHE partnership for collecting and following up real-world SACT data for patients treated through the CDF in England has resulted in analysis being carried out on 99.9% of patients and 82% of patient outcomes reported in the SACT dataset. PHE and NHS England and NHS Improvement are committed to providing world first, high-quality real-world data on CDF cancer treatments to be appraised alongside the outcome data from the relevant clinical trials.

## Methods

NHS England and NHS Improvement's Blueteq® system was used to provide a reference list of all patients with an application for daratumumab for multiple myeloma in the CDF. Patient NHS numbers were used to link Blueteq applications to PHE's routinely collected SACT data to provide SACT treatment history.

Between 17 January 2018 and 16 November 2020, 2,503 applications for daratumumab were identified in NHS England and NHS Improvement's Blueteq system. Following appropriate exclusions (see Figure 1 and Figure 2), 2,301 unique patients who received treatment were

included in these analyses. All patients were traced to obtain their vital status using the personal demographics service (PDS) (1).

# Results

2,301 (99.9%) unique patients with CDF applications were reported in the SACT dataset and were included in the final cohort.

Median treatment duration was 4.5 months [95% CI: 4.3, 4.9] (136 days). 41% of patients were still receiving treatment at 6 months [95% CI: 39%,43%], 25% of patients were still receiving treatment at 12 months [95% CI: 23%, 26%], 17% of patients were still receiving treatment at 18 months [95% CI: 15%, 19%] and 12% of patients were still receiving treatment at 24 months [95% CI: 11%, 14%].

At data cut off, 82% (N=1,877) of patients were identified as no longer being on treatment. Of these 1,877 patients, 56% (N=1,052) of patients stopped treatment due to progression, 3% (N=53) of patients stopped treatment due to acute toxicity, 2% (N=36) of patients chose to end their treatment, 26% (N=481) of patients died not on treatment, 3% (N=55) of patients died on treatment, 2% (N=37) of patients completed treatment as prescribed, less than 1% (N=2) of patients stopped treatment due to COVID and 9% (N=161) of patients did not have a treatment record in SACT in at least 3 months and are assumed to have completed treatment.

The median OS was 15.5 months [95% CI: 14.5, 16.7] (471 days). OS at 6 months was 71% [95% CI: 69%, 73%], 12 months OS was 57% [95% CI: 54%, 59%], OS at 18 months was 46% [95% CI: 44%, 48%] and OS at 24 months was 37% [95% CI: 35%, 40%].

A treatment duration sensitivity analysis was conducted for a cohort with at least 6 months' data follow-up in the SACT dataset. Results were consistent with the full analysis cohort.

# Conclusion

This report analysed SACT real-world data for patients treated with daratumumab for multiple myeloma in the CDF. It evaluates treatment duration, OS and treatment outcomes for all patients treated with daratumumab for this indication.

# Introduction

Multiple myeloma (ICD-10: C90) accounts for 2% of all cancer diagnoses in England. In 2018, 5,063 patients were diagnosed with multiple myeloma (males 2,972, females 2,091) (2).

Daratumumab is recommended for use within the Cancer Drugs Fund as an option for treating relapsed and refractory multiple myeloma in adults whose previous therapy included a proteasome inhibitor and an immunomodulator, and whose disease progressed on the last therapy, only if:

- they have daratumumab after 3 previous therapies, and
- the conditions in the managed access agreement are followed (3)

# Background to this report

## The Public Health England and NHS England and NHS Improvement partnership on cancer data – using routinely collected data to support effective patient care

High quality and timely cancer data underpin NHS England and NHS Improvement and Public Health England's (PHE's) ambitions of monitoring cancer care and outcomes across the patient pathway. The objective of the PHE and NHS England and NHS Improvement partnership on cancer data is to address mutually beneficial questions using Systemic Anti-Cancer Therapy (SACT) data collected by PHE. This includes NHS England and NHS Improvement commissioning PHE to produce routine outcome reports on patients receiving treatments funded through the Cancer Drugs Fund (CDF) during a period of managed access.

The CDF is a source of funding for cancer drugs in England (4). From 29 July 2016 NHS England implemented a new approach to the appraisal of drugs funded by the CDF. The new CDF operates as a managed access scheme that provides patients with earlier access to new and promising treatments where there is uncertainty as to their clinical effectiveness. During this period of managed access, ongoing data collection is used to answer the clinical uncertainties raised by the NICE committee and inform drug reappraisal at the end of the CDF funding period (5).

PHE analyse data derived from patient-level information collected in the NHS, as part of the care and support of cancer patients. The data is collated, maintained, quality-assured and analysed by the National Cancer Registration and Analysis Service, which is part of PHE.

## NICE Appraisal Committee review of daratumumab for treating relapsed and refractory multiple myeloma [TA510].

The NICE Appraisal Committee reviewed the clinical and cost effectiveness of daratumumab (Janssen) in treating relapsed and refractory multiple myeloma [TA510] and published guidance for this indication in March 2018 (6).

Due to the clinical uncertainties identified by the committee and outlined below, the committee recommended the commissioning of daratumumab through the CDF for a period of 34 months, from January 2018 to November 2020.

For this indication, SACT is the primary source of data and will be used to answer clinical uncertainties raised by the NICE committee.

Analysis of the SACT dataset provides information on real-world treatment patterns and outcomes for daratumumab treating multiple myeloma in England, during the CDF funding period.

The committee identified the key areas of uncertainty below for re-appraisal at the end of the CDF data collection;

- **Treatment duration** for the use of daratumumab
- **Overall survival** from the start of a patient's first treatment with daratumumab
- **Subsequent therapies** following daratumumab

### Approach

Upon entry to the CDF, representatives from NHS England and NHS Improvement, NICE, PHE and the company (Janssen) formed a working group to agree the Data Collection Agreement (DCA) (6). The DCA set out the real-world data to be collected and analysed to support the NICE re-appraisal of daratumumab. It also detailed the eligibility criteria for patient access to daratumumab through the CDF, and CDF entry and exit dates.

This report includes patients with approved CDF applications for daratumumab, approved through Blueteq® and followed up in the SACT dataset collected by PHE.

# Methods

## CDF applications – identification of the cohort of interest

NHS England and NHS Improvement collects applications for CDF treatments through their online prior approval system (Blueteq®). The Blueteq application form captures essential baseline demographic and clinical characteristics of patients needed for CDF evaluation purposes. Where appropriate, Blueteq data are included in this report.

Consultants must complete a Blueteq application form for every patient receiving a CDF funded treatment. As part of the application form, consultants must confirm that a patient satisfies all clinical eligibility criteria to commence treatment. PHE has access to the Blueteq database and key data items such as NHS number, primary diagnosis and drug information of all patients with an approved CDF application (which therefore met the treatment eligibility criteria).

The lawfulness of this processing is covered under Article 6(1)(e) of the United Kingdom (UK) General Data Protection Regulations (GDPR) (processing is necessary for the performance of a task carried out in the public interest or in the exercise of official authority vested in the

controller). The processing of special categories of personal data is also covered under article 9(2)(h) of UK GDPR (processing is necessary for the purposes of preventive or occupational medicine). As NHS England and NHS Improvement do not have an exemption to the Common Law Duty of Confidentiality, NHS England and NHS Improvement cannot access the identifiable data directly. PHE, through the National Cancer Registration and Analysis Service have permission to process confidential patient information though Regulation 2 of The Health Service (Control of Patient Information) Regulations 2002.

PHE collates data on all SACT prescribed drugs by NHS organisations in England, irrespective of the funding mechanism. The Blueteq extract is therefore essential to identify the cohort of patients whose treatment was funded by the CDF.

# Daratumumab clinical treatment criteria

Daratumumab clinical treatment criteria include:

- confirmed diagnosis of multiple myeloma
- documented relapse of disease after initial response or refractory to immediately preceding line of systemic therapy
- patient has received 3 prior lines of treatment only (induction chemotherapy and stem cell transplant is considered to be 1 line of therapy)
- patient has responded to at least 1 of these 3 lines of treatment
- patient has either relapsed after initial response to the immediately previous line of systemic therapy, or has refractory disease
- patient has previously been treated with a proteasome inhibitor
- patient has been previously treated with an immunomodulatory agent
- any previous treatment with a stem cell transplant has been recorded
- patient has not previously been treated with daratumumab (unless this was subcutaneous daratumumab during COVID19) or an anti-CD38 antibody
- daratumumab is only to be used as a single agent
- daratumumab is to be continued until disease progression or unacceptable toxicity or patient choice to stop treatment
- no treatment breaks of more than 6 weeks beyond the expected cycle length are allowed (treatment breaks of up to 6 weeks are allowed for any toxicity of current therapy to settle or intercurrent comorbidities to improve)
- patient has a performance status of 0, 1 or 2
- daratumumab to be otherwise used as set out in its summary of product characteristics

# CDF applications - de-duplication criteria

Before conducting any analysis on CDF treatments, the Blueteq data is examined to identify duplicate applications. The following de-duplication rules are applied:

1. If 2 trusts apply for daratumumab for the treatment of relapsed and refractory multiple myeloma for the same patient (identified using the patient's NHS number), and both applications have the same approval date, then the record where the CDF trust (the trust applying for CDF treatment) matches the SACT treating trust is selected.

2. If 2 trusts apply for daratumumab for the treatment of relapsed and refractory multiple myeloma for the same patient, and the application dates are different, then the record where the approval date in the CDF is closest to the regimen start date in SACT is selected, even if the CDF trust did not match the SACT treating trust.

3. If 2 applications are submitted for daratumumab for the treatment of relapsed and refractory multiple myeloma and the patient has no regimen start date in SACT capturing when the specific drug was delivered, then the earliest application in the CDF is selected.

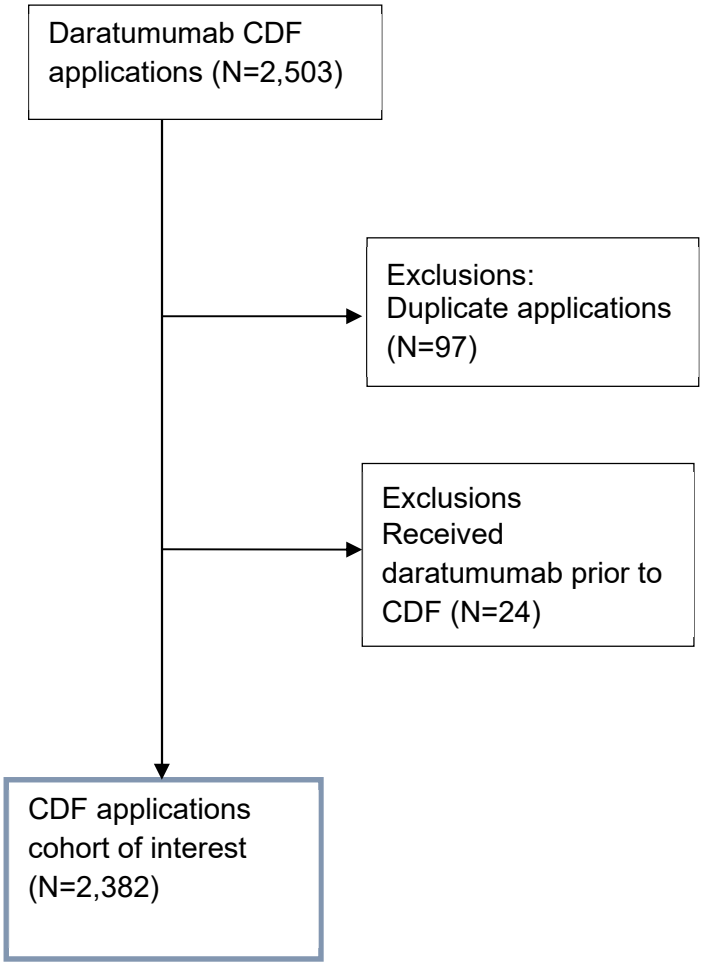
# Initial CDF cohorts

The analysis cohort is limited to the date daratumumab entered the CDF for this indication, onwards. Any treatments delivered before the CDF entry date are excluded as they are likely to be patients receiving treatment via an Early Access to Medicines Scheme (EAMS) or a compassionate access scheme run by the company. These schemes may have different eligibility criteria compared to the clinical treatment criteria detailed in the CDF managed access agreement for this indication.

The CDF applications included in these analyses are from 17 January 2018 to16 November 2020. A snapshot of SACT data was taken on 1 May 2021 and made available for analysis on 7 May 2021 and includes SACT activity up to the 31 January 2021. Tracing the patients' vital status was carried out on 2 June 2021 using the Personal Demographics Service (PDS) (1).

There were 2,503 applications for CDF funding for daratumumab for the treatment of relapsed and refractory multiple myeloma between 17 January 2018 and 16 November 2020 in the NHS England and NHS Improvement Blueteq database. Following de-duplication this relates to 2,406 unique patients. Twenty-four patients were excluded as they received daratumumab prior to the drug being available through the CDF.

**Figure 1. Derivation of the cohort of interest from all CDF (Blueteq) applications made for daratumumab for the treatment of relapsed and refractory multiple myeloma between 17 January 2018 and 16 November 2020**




## Linking CDF cohort to SACT

NHS numbers were used to link SACT records to CDF applications for daratumumab in NHS England and NHS Improvement's Blueteq system. Information on treatments in SACT were examined to ensure the correct SACT treatment records were matched to the CDF application; this includes information on treatment dates (regimen, cycle and administration dates) and primary diagnosis codes in SACT.

# Addressing clinical uncertainties

## Treatment duration

Treatment duration is calculated from the start of a patient's treatment to their last known treatment date in SACT.

Treatment start date is defined as the date the patient started their CDF treatment. This date is identified as the patient's earliest treatment date in the SACT dataset for the treatment of interest. Data items (7) used to determine a patient's earliest treatment date are:

- start date of regimen – SACT data item #22
- start date of cycle – SACT data item #27
- administration date – SACT data item #34

The earliest of these dates is used as the treatment start date.

The same SACT data items (#22, #27, #34) are used to identify a patient's final treatment date (7). The latest of these 3 dates is used as the patient's final treatment date.

Additional explanation of these dates is provided below:

### Start date of regimen

A regimen defines the drugs used, their dosage and frequency of treatment. A regimen may contain many cycles. This date is generally only used if cycle or administration dates are missing.

### Start date of cycle

A cycle is a period of time over which treatment is delivered. A cycle may contain several administrations of treatment, after each treatment administration, separated by an appropriate time delay. For example; a patient may be on a 3-weekly cycle with treatment being administered on the first and eighth day, but nothing on days 2 to 7 and days 9 to 20. The first day would be recorded as the 'start day of cycle'. The patient's next cycle would start on the 21st day.

### Administration date

An administration is the date a patient is administered the treatment, which should coincide with when they receive treatment. Using the above example, the administrations for a single 3-week cycle would be on the first and eighth day. The next administration would be on the 21st day, which would be the start of their next cycle.

The interval between treatment start date and final treatment date is the patient's time on treatment.

All patients are then allocated a 'prescription length', which is a set number of days added to the final treatment date to allow for the fact that they are effectively still 'on treatment' between administrations. The prescription length should correspond to the typical interval between treatment administrations.

If a patient dies between administrations, then their censor date is their date of death and these patients are deemed to have died on treatment unless an outcome summary is submitted to the SACT database confirming that the patient ended treatment due to disease progression or toxicity before death.

Daratumumab is administered intravenously. As such, treatment is generally administered in a healthcare facility and healthcare professionals can confirm that treatment administration has taken place on a specified date. A duration of 6, 7 or 14 days has been added to the final treatment date for all patients, depending on the prescribing schedule they are on; this represents the duration from a patient's last cycle to their next (8).

Treatment duration is calculated for each patient as:
Treatment duration (days) = (Final treatment date – Treatment start date) + prescription length (days). This date would be the patients censored date, unless a patient dies in between their last treatment and the prescription length added, in this case, the censored date would be the patients date of death.

Once a patient's treatment duration has been calculated, the patient's treatment status is identified as one of the following:

No longer receiving treatment (event), if:

- the patient has died.
- the outcome summary, detailing the reason for stopping treatment has been completed:
    - SACT v2.0 data item #41
    - SACT v3.0 data item #58 to #61
- there is no further SACT records for the patient following a 3-month period.

If none of the above apply, the patient is assumed to still be on treatment and is censored.

## Overall survival (OS)

OS is calculated from the CDF treatment start date, not the date of a patient's cancer diagnosis. Survival from the treatment start date is calculated using the patient's earliest treatment date, as described above, and the patient's date of death or the date the patient was traced for their vital status.

All patients in the cohort of interest are submitted to the PDS to check their vital status (dead or alive). Patients are traced before any analysis takes place. The date of tracing is used as the date of follow-up (censoring) for patients who have not died.

OS is calculated for each patient as the interval between the earliest treatment date where a specific drug was given to the date of death or date of follow-up (censoring).

OS (days) = Date of death (or follow up) - treatment start date

The patient is flagged as either:

Dead (event):
At the date of death recorded on the PDS.

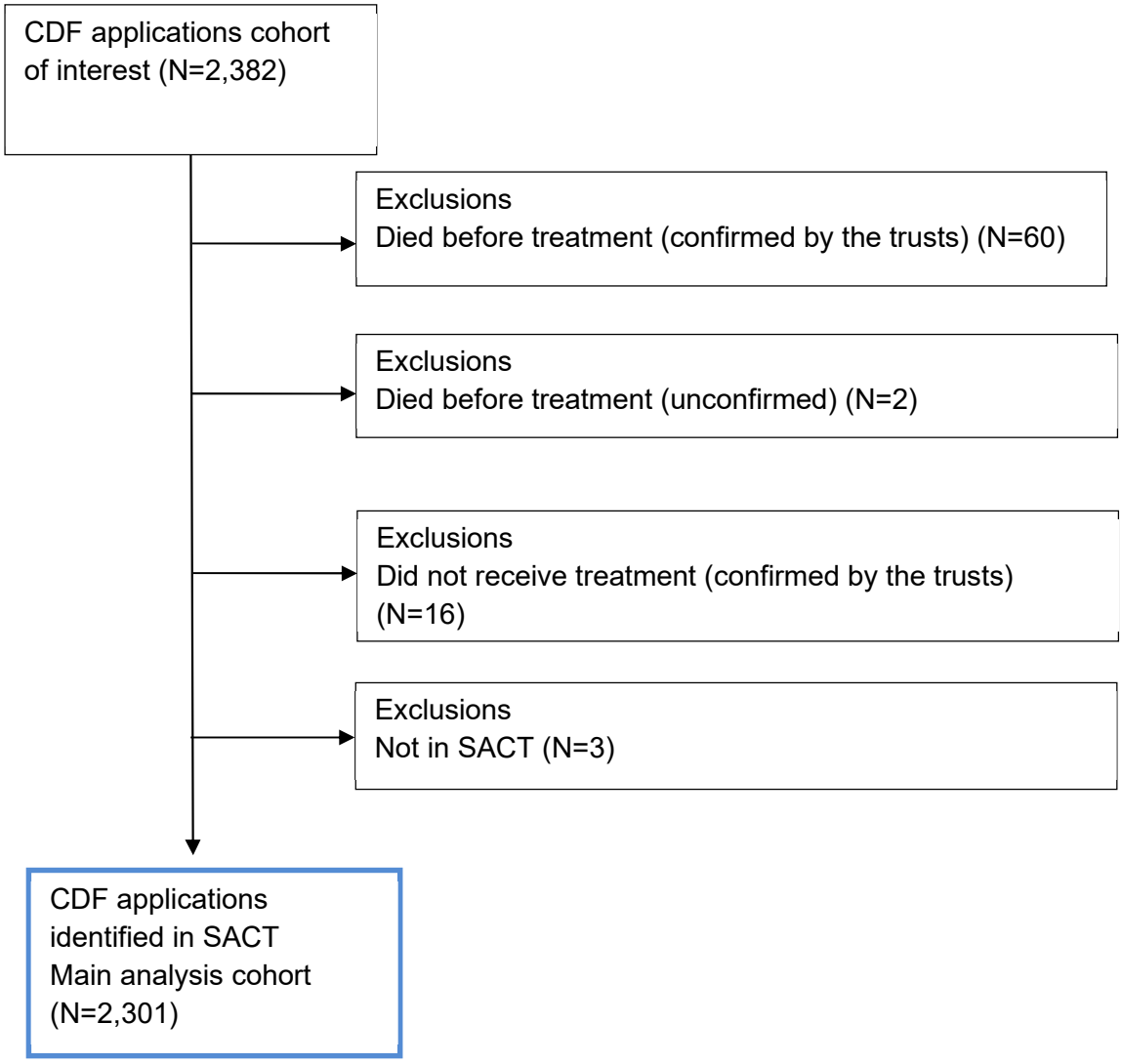
Alive (censored):
At the date patients were traced for their vital status as patients are confirmed as alive on this date.

# Results

## Cohort of interest

Of the 2,382 applications for CDF funding for daratumumab for the treatment of relapsed and refractory multiple myeloma, 16 patients did not receive treatment, 62 patients died before treatment and 3 patients were missing from SACT[a] (see Figure 2).

**Figure 2. Matched cohort - SACT data to CDF (Blueteq®) applications for daratumumab for the treatment of relapsed and refractory multiple myeloma between 17 January 2018 and 16 November 2020**




[a] Of the 16 patients that did not receive treatment, all were confirmed by the relevant trust by the PHE data liaison team. Of the 62 patients that died before treatment, 60 have been confirmed by the relevant trusts by the PHE data liaison team, 2 patients were followed up by the data liaison team but the relevant trust did not confirm if the patient died before treatment.

A maximum of 2,304 daratumumab records are expected in SACT for patients who were alive, eligible and confirmed to have commenced treatment (Figure 2). 99.9% (2,301 out of 2,304) of these applicants for CDF funding have a treatment record in SACT.

# Completeness of SACT key variables

Table 1 presents the completeness of key data items required from SACT. Completeness is 100% for primary diagnosis, date of birth, gender and treatment dates. Performance status at the start of regimen is 77% complete.

**Table 1. Completeness of key SACT data items for the daratumumab cohort (N=2,301)**

| Variable | Completeness (%) |
|---|---|
| Primary diagnosis | 100% |
| Date of birth (used to calculate age) | 100% |
| Sex | 100% |
| Start date of regimen | 100% |
| Start date of cycle | 100% |
| Administration date | 100% |
| Performance status at start of regimen | 77% |

Table 2 presents the completeness of regimen outcome summary. A patient's outcome summary, detailing the reason why treatment was stopped, is only captured once a patient has completed their treatment. Therefore, the percentage completeness provided for outcome summary is for records where we assume treatment has stopped and an outcome is expected. Outcomes are expected if a patient has died, has an outcome in SACT stating why treatment has ended or has not received treatment with daratumumab in at least 3 months (8). These criteria are designed to identify all cases where a patient is likely to have finished treatment. Based on these criteria, outcomes are expected for 1,877 patients. Of these, 1,533 (82%) have an outcome summary recorded in the SACT dataset.

**Table 2. Completeness of outcome summary for patients that have ended treatment (N=1,877)**

| Variable | Completeness (%) |
|---|---|
| Outcome summary of why treatment was stopped | 82% |

# Completeness of Blueteq key variables

Table 3 presents the completeness of key data items required from Blueteq, all of which are 100% complete.

**Table 3. Completeness of key Blueteq data items for the daratumumab cohort (N=2,301)**

| Variable | Completeness (%) |
|---|---|
| Treatment response | 100% |
| Previous stem cell transplant | 100% |

# Patient characteristics

The median age of the 2,301 patients receiving daratumumab for treating multiple myeloma was 71 years. The median age in males and females was 71 and 72 years respectively.

**Table 4. Patient characteristics (N=2,301)**

| Patient characteristics[b] | | | |
|---|---|---|---|
| | | N | % |
| Sex | Male | 1,342 | 58% |
| | Female | 959 | 42% |
| Age | Less than 40 | 4 | Less than 1% |
| | 40 to 49 | 64 | 3% |
| | 50 to 59 | 305 | 13% |
| | 60 to 69 | 571 | 25% |
| | 70 to 79 | 967 | 42% |
| | 80 plus | 390 | 17% |
| Performance status | 0 | 467 | 20% |
| | 1 | 936 | 41% |
| | 2 | 341 | 15% |
| | 3 | 36 | 2% |
| | 4 | 1 | Less than 1% |
| | Missing | 520 | 23% |

[b] Figures may not sum to 100% due to rounding.

# Blueteq data items

Table 5 shows the distribution of Blueteq data items with 81% (N=1,862) of patients being treated for relapsed disease and 19% (N=449) of patients being treated for refractory disease.

**Table 5. Distribution of key Blueteq data items (N=2,301)**

**Blueteq data items**[c]

| | | N | % |
|---|---|---|---|
| Treatment response | Relapsed | 1,862 | 81% |
| | Refractory | 439 | 19% |
| Previous stem cell transplant | No | 1,296 | 56% |
| | Yes | 1,005 | 44% |

# Time to subsequent treatments in SACT

1,111 out of 2,301 (48%) unique patients treated with daratumumab in the CDF have subsequent therapies recorded in the SACT dataset, received after the patient's last daratumumab cycle. This includes all patients regardless of whether they have completed treatment or not.

1,111 out of 1,877 (58%) unique patients who have since completed treatment with daratumumab went on to receive a subsequent therapy.

Table 6 reports regimens prescribed after daratumumab, as recorded in the SACT dataset, some patients have more than one subsequent therapy, these regimens are shown in Table 7.

The median time from a patient's last daratumumab cycle in SACT to their next treatment was 28 days, the range was between 1 and 742 days[d].

The median time from a patient's first daratumumab cycle in SACT to their next treatment was 144 days.

[c] Figures may not add to 100% due to rounding.
[d] If a patient has more than 1 subsequent regimen recorded in SACT, time to next treatment only includes regimen immediately after daratumumab.

# Distribution of subsequent treatments in SACT

**Table 6. Distribution of first treatments prescribed after a patient's last daratumumab cycle (N(Patients)=1,111)** [e,f]

| Regimen | Number of subsequent treatments |
|---|---|
| Pomalidomide | 709 |
| Bortezomib + panobinostat | 147 |
| Cyclophosphamide + pomalidomide | 55 |
| Lenalidomide | 30 |
| Trial | 30 |
| Melphalan | 19 |
| Bendamustine | 16 |
| Bortezomib + panobinostat + thalidomide | 15 |
| Cyclophosphamide | 12 |
| Bendamustine + thalidomide | 10 |
| Bortezomib + cyclophosphamide | 8 |
| Cisplatin + cyclophosphamide + doxorubicin + etoposide + thalidomide | 8 |
| Bortezomib | 7 |
| Cyclophosphamide + lenalidomide | 5 |
| Cyclophosphamide + thalidomide | 5 |
| Melphalan + thalidomide | 5 |
| Bortezomib + pomalidomide | 4 |
| Azacitidine | 3 |
| Panobinostat | 3 |
| Bortezomib + thalidomide | 2 |
| Fluorouracil + irinotecan + panitumumab | 2 |
| Ixazomib + lenalidomide | 2 |
| Rituximab | 2 |
| Thalidomide | 2 |
| Bortezomib + cisplatin + cyclophosphamide + doxorubicin + etoposide + lenalidomide | 1 |
| Bortezomib + cisplatin + cyclophosphamide + doxorubicin + etoposide + thalidomide | 1 |

[e] Some patients will have received more than one subsequent therapy. Table 6 lists therapies prescribed immediately after a patient's last daratumumab cycle. Subsequent therapies could be related to a second primary tumour.
[f] These data have not been validated/confirmed with trusts or by the PHE data liaison team.

| Regimen | Number of subsequent treatments |
|---|---|
| Capecitabine + oxaliplatin | 1 |
| Cisplatin + gemcitabine | 1 |
| Cyclophosphamide + doxorubicin + vincristine | 1 |
| Cyclophosphamide + doxorubicin + vincristine + pomalidomide | 1 |
| Cytarabine + daunorubicin | 1 |
| Cytarabine + fludarabine | 1 |
| Etoposide + idarubicin + thalidomide | 1 |
| Liposomal daunorubicin + liposomal cytarabine | 1 |
| **Total number of subsequent treatments** | **1,111** |

**Table 7. Distribution of further lines of therapy following a patient's daratumumab cycle (N(Patients)=1,111) [g,h]**

| Regimen | Number of subsequent treatments |
|---|---|
| Bortezomib + panobinostat | 120 |
| Pomalidomide | 88 |
| Cyclophosphamide | 33 |
| Cyclophosphamide + pomalidomide | 18 |
| Bendamustine | 17 |
| Melphalan | 17 |
| Trial | 16 |
| Melphalan + thalidomide | 14 |
| Cyclophosphamide + thalidomide | 12 |
| Belantamab mafodotin | 9 |
| Bendamustine + thalidomide | 9 |
| Cisplatin + cyclophosphamide + doxorubicin + etoposide + thalidomide | 9 |
| Thalidomide | 9 |
| Bortezomib + panobinostat + thalidomide | 7 |
| Bortezomib | 5 |
| Bortezomib + cyclophosphamide | 5 |
| Idarubicin | 5 |

[g] Some patients will have received more than one subsequent therapy. Table 7 lists further lines of therapies prescribed after a patient's last daratumumab cycle in SACT. Subsequent therapies could be related to a second primary tumour.
[h] These data have not been validated/confirmed with trusts or by the PHE data liaison team.

| Regimen | Number of subsequent treatments |
|---|---|
| Bortezomib + cisplatin + cyclophosphamide + doxorubicin + etoposide + thalidomide | 3 |
| Panobinostat | 3 |
| Selinexor | 3 |
| Cyclophosphamide + doxorubicin + rituximab + vincristine | 2 |
| Hydroxycarbamide | 2 |
| Azacitidine | 1 |
| Bortezomib + melphalan | 1 |
| Bortezomib + thalidomide | 1 |
| Capecitabine | 1 |
| Carboplatin | 1 |
| Carboplatin + cyclophosphamide + doxorubicin + etoposide + thalidomide | 1 |
| Carfilzomib | 1 |
| Carfilzomib + pomalidomide | 1 |
| Clodronic acid | 1 |
| Cyclophosphamide + doxorubicin + vincristine | 1 |
| Cyclophosphamide + lenalidomide | 1 |
| Cyclophosphamide + rituximab + vincristine | 1 |
| Cytarabine | 1 |
| Doxorubicin | 1 |
| Etoposide + idarubicin + thalidomide | 1 |
| Fludarabine | 1 |
| Lenalidomide | 1 |
| Methotrexate | 1 |
| Transplant alemtuzumab + fludarabine + melphalan | 1 |
| **Total number of subsequent treatments** | **425** |

# Treatment duration

Of the 2,301 patients with CDF applications, 1,877 (82%) were identified as having completed treatment by 31 January 2021 (latest follow up in SACT dataset). Patients are assumed to have completed treatment if they have died, have an outcome summary recorded in the SACT dataset or they have not received treatment with daratumumab in at least 3 months (see Table 12). The median follow-up time in SACT was 4.3 months (130 days). The median follow-up time in SACT is the patients' median observed time from the start of their treatment to their last treatment date in SACT + prescription length.

Presently, 94% (N=132) of trusts submit their SACT return to the submission portal 2 months after the month's treatment activity has ended; this provides a maximum follow-up period of 36 months. 6% (N=9) of trusts submit their SACT return to the submission portal one month after the month's treatment activity has ended; this provides a maximum follow-up period of 37 months. SACT follow-up ends 31 January 2021.

**Table 8. Breakdown by patients' treatment status[i,j,k]**

| Patient status | Frequency (N) | Percentage (%) |
|---|---|---|
| Patient died – not on treatment | 1,333 | 58% |
| Patient died – on treatment | 55 | 2% |
| Treatment stopped | 489 | 21% |
| Treatment ongoing | 424 | 18% |
| **Total** | **2,301** | **100%** |

**Table 9. Treatment duration at 6, 12, 18 and 24-month intervals**

| Time period | Treatment duration (%) |
|---|---|
| 6 months | 41% [95% CI: 39%, 43%] |
| 12 months | 25% [95% CI: 23%, 26%] |
| 18 months | 17% [95% CI: 15%, 19%] |
| 24 months | 12% [95% CI: 11%, 14%] |

[i] Figures may not sum to 100% due to rounding.
[j] Table 12 presents the outcome summary data reported by trusts. This includes patients from Table 8 who 'died on treatment', 'died not on treatment' and 'stopped treatment'.
[k] 'Deaths on treatment' and 'deaths not on treatment' are explained in the methodology paper available on the SACT website.

The Kaplan-Meier curve for ongoing treatment is shown in Figure 3. The median treatment duration for all patients was 4.5 months [95% CI: 4.3, 4.9] (136 days) (N=2,300).

**Figure 3. Kaplan-Meier treatment duration (N=2,300)** [I]

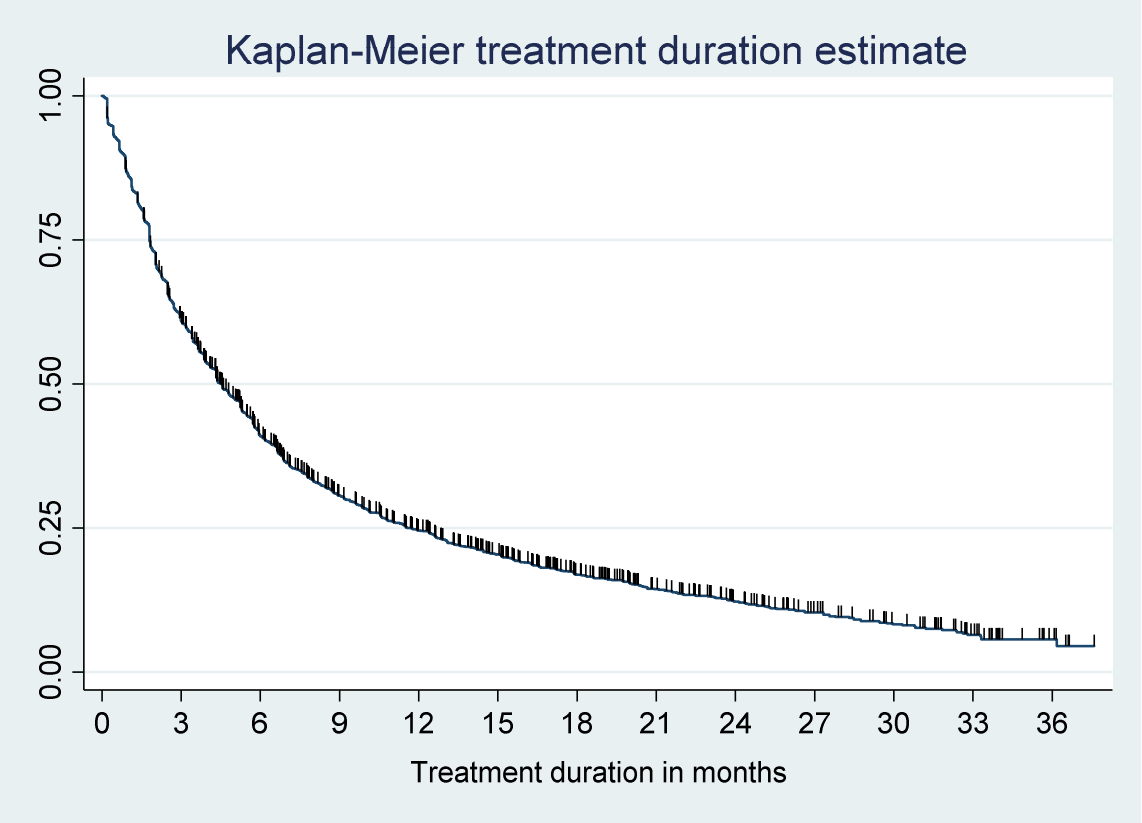



Table 10 and Table 11 show the number of patients at risk, the number of patients that were censored and the number of patients that ended treatment (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for all patients for treatment duration was 36 months (1,095 days). SACT contains more follow-up for some patients.

[I] One patient died on the same day they started treatment, and as such, they were excluded from the model as their treatment duration was zero days.

**Table 10. Number of patients at risk, by quarterly breakpoints**

| Time intervals (months) | 0 to 36 | 3 to 36 | 6 to 36 | 9 to 36 | 12 to 36 | 15 to 36 | 18 to 36 | 21 to 36 | 24 to 36 | 27 to 36 | 30 to 36 | 33 to 36 | 36 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Number at risk | 2,300 | 1,379 | 847 | 584 | 440 | 332 | 231 | 165 | 119 | 81 | 54 | 26 | 7 |

Table 11 shows that for all patients who received treatment, 424 were still on treatment (censored) at the date of follow-up and 1,876 had ended treatment (events).

**Table 11. Number of patients at risk, by quarterly breakpoints split between patients that have ended treatment (events) and patients that are still on treatment (censored)**

| Time intervals (months) | 0 to 36 | 3 to 36 | 6 to 36 | 9 to 36 | 12 to 36 | 15 to 36 | 18 to 36 | 21 to 36 | 24 to 36 | 27 to 36 | 30 to 36 | 33 to 36 | 36 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Censored | 424 | 398 | 302 | 246 | 215 | 179 | 131 | 96 | 73 | 52 | 40 | 22 | 6 |
| Events | 1,876 | 981 | 545 | 338 | 225 | 153 | 100 | 69 | 46 | 29 | 14 | 4 | 1 |

Table 12 gives a breakdown of a patient's treatment outcome recorded in SACT when a patient's treatment has come to an end. 82% (N=1,877) of patients had ended treatment at 31 January 2021.

**Table 12. Treatment outcomes for patients that have ended treatment (N=1,877)[m],[n]**

| Outcome | Frequency (N) | Percentage (%) |
|---|---|---|
| Stopped treatment – progression of disease | 1,052 | 56% |
| Stopped treatment – acute toxicity | 53 | 3% |
| Stopped treatment – patient choice | 36 | 2% |
| Stopped treatment – died not on treatment[o] | 481 | 26% |
| Stopped treatment – died on treatment | 55 | 3% |
| Stopped treatment – completed as prescribed[p] | 37 | 2% |
| Stopped treatment – COVID | 2 | Less than 1% |
| Stopped treatment – no treatment in at least 3 months | 161 | 9% |
| **Total** | **1,877** | **100%** |

[m] Figures may not sum to 100% due to rounding.
[n] Table 12 presents the outcome summary data reported by trusts. This includes patients from Table 8 who 'died on treatment', 'died not on treatment' and 'stopped treatment'.
[o] 'Deaths on treatment' and 'deaths not on treatment are explained in the methodology paper available on the SACT website.
[p] Of the patients with an outcome of 'stopped treatment - completed as prescribed', reasons ranged from patient proceeded to a stem cell transplant or changing regimen/treatment plan.

**Table 13. Treatment outcomes and treatment status for patients that have ended treatment (N=1,877)**

| Outcome[q] | Patient died [r] not on treatment | Treatment stopped | Patient died on treatment |
|---|---|---|---|
| Stopped treatment – progression of disease | 768 | 284 | |
| Stopped treatment – acute toxicity | 39 | 14 | |
| Stopped treatment – patient choice | 29 | 7 | |
| Stopped treatment – died not on treatment | 481 | | |
| Stopped treatment – died on treatment | | | 55 |
| Stopped treatment – completed as prescribed | 15 | 22 | |
| Stopped treatment – COVID | 1 | 1 | |
| Stopped treatment – no treatment in at least 3 months | | 161 | |
| **Total** | **1,333** | **489** | **55** |

[q] Relates to outcomes submitted by the trust in Table 12.
[r] Relates to treatment status in Table 8 for those that have ended treatment.

# Overall survival (OS)

Of the 2,301 patients with a treatment record in SACT, the minimum follow-up was 6.5 months (197 days) from the last CDF application. Patients were traced for their vital status on 2 June 2021. This date was used as the follow-up date (censored date) if a patient is still alive. The median follow-up time in SACT was 11.6 months (353 days). The median follow-up is the patients' median observed time from the start of their treatment to death or censored date.

**Table 14. OS at 6, 12, 18 and 24-month intervals**

| Time period | OS (%) |
|---|---|
| 6 months | 71% [95% CI: 69%, 73%] |
| 12 months | 57% [95% CI: 54%, 59%] |
| 18 months | 46% [95% CI: 44%, 48%] |
| 24 months | 37% [95% CI: 35%, 40%] |

Figure 4 provides the Kaplan-Meier curve for OS, censored at 2 June 2021. The median OS was 15.5 months [95% CI: 14.5, 16.7] (471 days).

**Figure 4. Kaplan-Meier survival plot (N=2,300)[s]**

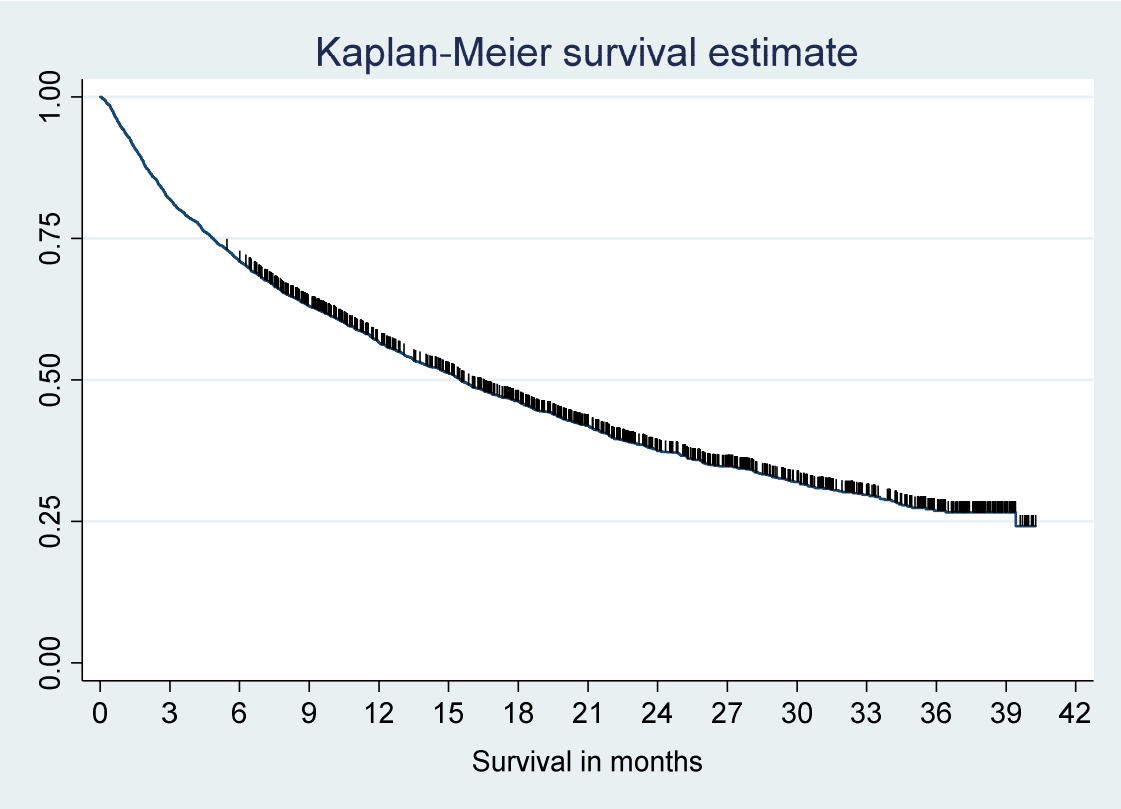



Table 15 and Table 16 show the number of patients at risk, the number of patients that were censored and the number of patients that died (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for survival was 40.5 months (1,232 days), all patients were traced on 2 June 2021.

[s] One patient died on the same day they started treatment, and as such, they were excluded from the model as their treatment duration was zero days.

**Table 15. Includes the number of patients at risk, by quarterly breakpoints**

| Time intervals (months) | 0 to 42 | 3 to 42 | 6 to 42 | 9 to 42 | 12 to 42 | 15 to 42 | 18 to 42 | 21 to 42 | 24 to 42 | 27 to 42 | 30 to 42 | 33 to 42 | 36 to 42 | 39 to 42 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Number at risk | 2,300 | 1,884 | 1,631 | 1,356 | 1,111 | 964 | 783 | 611 | 460 | 346 | 249 | 174 | 96 | 20 |

Table 16 shows that for all patients who received treatment, 913 were still alive (censored) at the date of follow-up and 1,387 had died (events).

**Table 16. Number of patients at risk, those that have died (events) and those that are still alive (censored) by quarterly breakpoints**

| Time intervals (months) | 0 to 42 | 3 to 42 | 6 to 42 | 9 to 42 | 12 to 42 | 15 to 42 | 18 to 42 | 21 to 42 | 24 to 42 | 27 to 42 | 30 to 42 | 33 to 42 | 36 to 42 | 39 to 42 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Censored | 913 | 913 | 912 | 813 | 702 | 657 | 566 | 463 | 373 | 290 | 217 | 158 | 94 | 19 |
| Events | 1,387 | 971 | 719 | 543 | 409 | 307 | 217 | 148 | 87 | 56 | 32 | 16 | 2 | 1 |

# Sensitivity analysis

## 6-month SACT follow up

## Treatment duration

Sensitivity analyses were carried out on a cohort with at least 6 months follow-up in SACT. To identify the treatment duration cohort, CDF applications were limited from 17 January 2018 to 31 July 2021 and SACT activity was followed up to the 31 January 2021.

Following the exclusions above, 2,088 patients (91%) were identified for inclusion. One patient died on the same day they received treatment, and as such, they were excluded from the model as their treatment duration was zero days. Included in these analyses was 2,087 patients. The median follow-up time in SACT was 4.4 months (133 days). The median follow-up time in SACT is the patients' median observed time from the start of their treatment to their last treatment date in SACT + prescription length.

The Kaplan-Meier curve for ongoing treatment is shown in Figure 5. The median treatment duration for patients in this cohort was 4.4 months [95% CI: 4.3, 4.8] (133 days) (N=2,087).

**Figure 5. Kaplan-Meier treatment duration plot (N=2,087)**

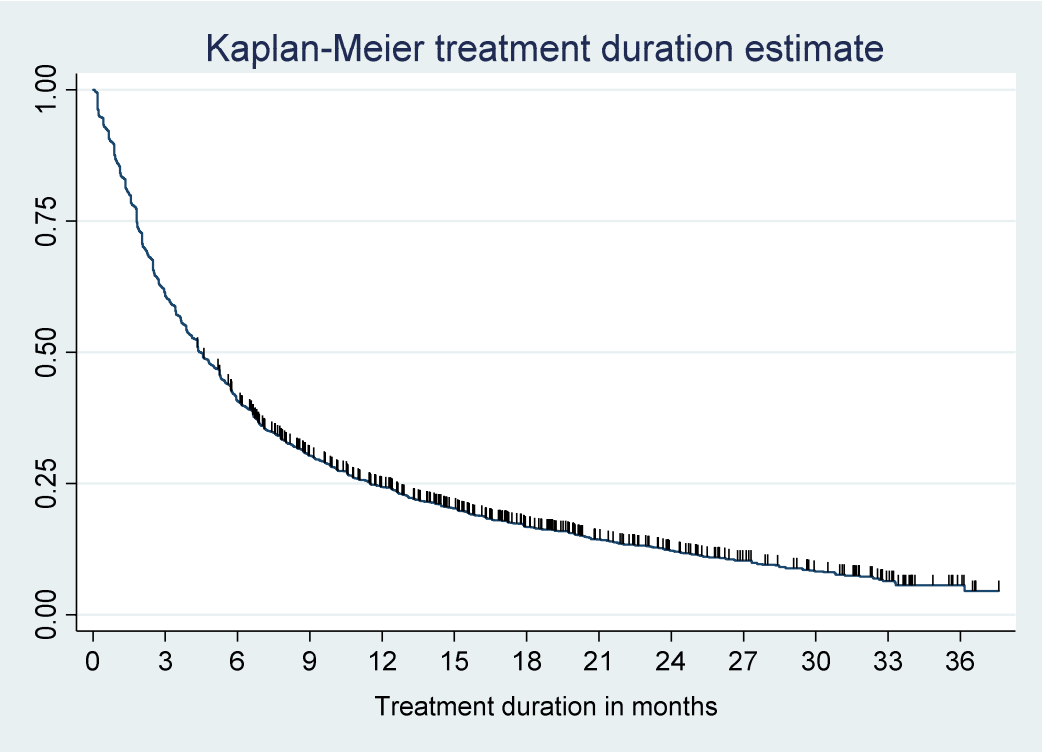


Table 17 and Table 18 show the number of patients at risk, the number of patients that were censored and the number of patients that ended treatment (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for all patients for treatment duration was 36 months (1,095 days).

**Table 17. Includes the number of patients at risk, by quarterly breakpoints**

| Time intervals (months) | 0 to 36 | 3 to 36 | 6 to 36 | 9 to 36 | 12 to 36 | 15 to 36 | 18 to 36 | 21 to 36 | 24 to 36 | 27 to 36 | 30 to 36 | 33 to 36 | 36 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Number at risk | 2,087 | 1,268 | 836 | 582 | 438 | 331 | 230 | 165 | 119 | 81 | 54 | 26 | 7 |

Table 18 shows that for all patients who received treatment, 307 were still on treatment (censored) at the date of follow-up and 1,780 had ended treatment (events).

**Table 18. Number of patients at risk, by quarterly breakpoints split between patients that have ended treatment (events) and patients that are still on treatment (censored)**

| Time intervals (months) | 0 to 36 | 3 to 36 | 6 to 36 | 9 to 36 | 12 to 36 | 15 to 36 | 18 to 36 | 21 to 36 | 24 to 36 | 27 to 36 | 30 to 36 | 33 to 36 | 36 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Censored | 307 | 307 | 293 | 246 | 215 | 179 | 131 | 96 | 73 | 52 | 40 | 22 | 6 |
| Events | 1,780 | 961 | 543 | 336 | 223 | 152 | 99 | 69 | 46 | 29 | 14 | 4 | 1 |

**Table 19. Median treatment duration and OS, full cohort and sensitivity analysis[t]**

| Metric | Standard analysis: Full cohort | Sensitivity analysis: 6 months follow-up cohort: treatment duration |
|---|---|---|
| **N** | 2,300 | 2,087 |
| **Median treatment duration** | 4.5 months [95% CI: 4.3, 4.9] (136 days) | 4.4 months [95% CI: 4.3, 4.8] (136 days) |
| **OS** | 15.5 months [95% CI: 14.5, 16.7] (471) | |

[t] One patient died on the same day they started treatment, and as such, they were excluded from the model as their treatment duration was zero days.

# Conclusions

2,304 patients received daratumumab for the treatment of multiple myeloma [TA510] through the CDF in the reporting period (17 January 2018 and 16 November 2020). 2,301 patients were reported to the SACT dataset, giving a SACT dataset ascertainment of 99.9%. An additional 16 patients with a CDF application did not receive treatment and 62 patients died before treatment. Not all were confirmed by the trust responsible for the CDF application by the team at PHE.

Patient characteristics from the SACT dataset show that 58% (N=1,342) of patients that received daratumumab for multiple myeloma were male, 42% (N=959) of patients were female. Most of the cohort were aged 50 years and over 97%, (N=2,233) and 76% (N=1,744) of patients had a performance status between 0 and 2 at the start of their regimen.

At data cut off, 82% (N=1,877) of patients were identified as no longer being on treatment. Of these 1,877 patients, 56% (N=1,052) of patients stopped treatment due to progression, 3% (N=53) of patients stopped treatment due to acute toxicity, 2% (N=36) of patients chose to end their treatment, 26% (N=481) of patients died not on treatment, 3% (N=55) of patients died on treatment, 2% (N=37) of patients completed treatment as prescribed, less than 1% (N=2) of patients stopped treatment due to COVID and 9% (N=161) of patients did not have a treatment record in SACT in at least 3 months and are assumed to have completed treatment.

Median treatment duration was 4.5 months [95% CI: 4.3, 4.9] (136 days). 41% of patients were still receiving treatment at 6 months [95% CI: 39%,43%], 25% of patients were still receiving treatment at 12 months [95% CI: 23%, 26%], 17% of patients were still receiving treatment at 18 months [95% CI: 15%, 19%] and 12% of patients were still receiving treatment at 24 months [95% CI: 11%, 14%].

The median OS was 15.5 months [95% CI: 14.5, 16.7] (471 days). OS at 6 months was 71% [95% CI: 69%, 73%], 12 months OS was 57% [95% CI: 54%, 59%], OS at 18 months was 46% [95% CI: 44%, 48%] and OS at 24 months was 37% [95% CI: 35%, 40%].

Sensitivity analysis was carried out on treatment duration to evaluate a cohort for which all patients had a minimum follow-up of 6 months. Results for treatment duration showed a difference of 0.1 month (full cohort = 4.5 months; sensitivity analysis cohort = 4.4 months).

# References


1. The Personal Demographics Service (PDS). NHS Digital: 2020 (cited 2021 June)
2. National Statistics. 'Cancer Registration Statistics, England: 2018.' 2020 (cited 2021 June)
3. 'National Institute for Health and Care Excellence: 2018' (cited 2021 June)
4. Cancer Drugs Fund. 'NHS England and NHS Improvement: 2017' (cited 2021 June)
5. 'Appraisal and funding of cancer drugs.' NHS England and NHS Improvement: 2016 (cited 2021 June)
6. 'National Institute for Health and Care Excellence: 2018' (cited 2021 June)
7. 'Systemic Anti-Cancer Therapy.' SACT: 2019 (cited 2021 June)
8. 'CDF analytical methods.' PHE: 2019 (cited 2021 June)

# About Public Health England

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# Technical engagement response form

## Daratumumab monotherapy for treating relapsed and refractory multiple myeloma (CDF review of TA510) [ID3881]

As a stakeholder you have been invited to comment on the evidence review group (ERG) report for this appraisal.

Your comments and feedback on the key issues below are really valued. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal 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 ERG report that are likely to be discussed by the committee. The key issues in the ERG report 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 ERG report.

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 ERG report 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 appraisal, 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.

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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 replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Deadline for comments by **5pm** on **Thursday 16th December**. 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.**

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# About you

**Table 1 About you**

| | |
|---|---|
| **Your name** | **Renelle Tarnowska** |
| **Organisation name: stakeholder or respondent**<br>(if you are responding as an individual rather than a registered stakeholder, please leave blank) | **Janssen-Cilag Ltd** |
| **Disclosure**<br>Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry. | **N/A** |

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# Key issues for engagement

**All**: Please use the table below to respond to the key issues raised in the ERG report.

**An updated patient access scheme (PAS) for daratumumab has been approved by NHS England. A discount of [CiC information removed] is now applied to the list price of daratumumab. All analysis conducted as part of the technical engagement response below includes the updated PAS price for daratumumab.**

**Table 1: Key issues**

| Key issue | Does this response contain new evidence, data or analyses? | Response |
|---|---|---|
| **Issue 1 – Absence of an updated systematic literature review for the review of clinical effectiveness** | **Yes** | • In response to the ERG's concern that there may be more recent data sources to inform comparative effectiveness, a systematic literature review (SLR) update was conducted on 29th October 2021. Specifically, this update sought to identify efficacy and safety data for pomalidomide and dexamethasone (POM+DEX) and panobinostat plus bortezomib and dexamethasone (PANO+BORT+DEX) published following the searches conducted for the original SLR in July 2016. This update included a review of Embase, Medline and Cochrane library (Central & Cochrane Database of Systematic Reviews) databases, in addition to a hand search of relevant conference websites (American Society of Clinical Oncology, American Society of Hematology, European Hematology Association, European Society for Medical Oncology, and British Society for Haematology) held in the last 3 years, to ensure that all relevant material were identified.<br>• It was not necessary to search for additional efficacy and safety data for daratumumab. As the manufacturer of this technology, Janssen is aware of the relevant published trials evaluating daratumumab, and patient-level data (PLD) |

| | | |
|---|---|---|
| | | from the pivotal clinical trial MMY2002 remains the most relevant efficacy source to inform this Cancer Drugs Fund (CDF) review.<br>• In summary, the SLR update identified 35 additional studies presenting efficacy and safety data for either POM+DEX or PANO+BORT+DEX. Of these, Janssen considered five studies relevant for consideration to conduct additional matching adjusted indirect comparison (MAIC) analysis (refer to Key Issue 2). The reasons for exclusion of the remaining 30 studies, and full details of the SLR update, are provided in Appendix A. |
| **Issue 2 – Uncertainty in the clinical-effectiveness estimates for daratumumab compared with Pomalidomide plus dexamethasone and Panobinostat plus bortezomib and dexamethasone** | **No** | • Janssen acknowledge the inherent uncertainty assessing comparative effectiveness due to the single-arm study design of MMY2002, and lack of head-to-head data available for daratumumab versus POM+DEX or PANO+BORT+DEX.<br>• CDF data collection aimed to address the fundamental uncertainty on the generalisability of daratumumab trial data to UK clinical practice. Uncertainty in the comparative effectiveness of daratumumab, although reduced by addressing uncertainty around generalisability of daratumumab trial data, was not an aim of the CDF data collection. Indeed, it is not possible to collect evidence on comparative effectiveness via SACT.<br>• As demonstrated in Section A.6.3 of the Company CDF re-submission, the Systemic Anti-Cancer Therapy (SACT) data supports the generalisability of MMY2002 to UK clinical practice with non-statistically significant differences observed for overall survival (OS); assessed both as a naïve comparison, and after conducting MAIC. Generalisability of the trial data is further supported by post-hoc exploratory analysis investigating the impact of subsequent therapies not available in England on OS (refer to Key Issue 4 for further details).<br>• Janssen acknowledge the known limitations of unanchored MAICs, including the assumption that all effect modifiers and prognostic factors are accounted for. In the absence of direct head-to-head evidence; however, Janssen consider an unanchored MAIC of daratumumab and POM+DEX/PANO+BORT+DEX trial data preferable to a naïve comparison using RWE (SACT) data for daratumumab and |

trial data for POM+DEX/PANO+BORT+DEX. While unanchored MAIC **may** have residual bias if important effect modifiers and prognostic factors are not accounted for, a naive comparison **will** be biased; particularly when comparing RWE data with trial data.

- Following the SLR update referred to in Key Issue 1, five studies were assessed for feasibility to perform an additional MAIC of daratumumab versus POM+DEX or PANO+BORT+DEX. None of the identified studies were considered appropriate to perform an additional MAIC that would reduce the uncertainty in the comparative efficacy estimates. A summary of the studies is provided in Table 2. Full details of study baseline characteristics are provided in Appendix B.

**Table 2: MAIC feasibility assessment**

| Author, year | Comparator | MAIC feasibility |
|---|---|---|
| Richardson, 2019 (1) | POM+DEX | • Patients in the ICARIA-MM study received a median of 3 prior therapies compared with 5 in MMY2002.<br>• When attempting to match on the number of prior lines of therapy, ESS drops from [redacted] to [redacted]; therefore, a suitable ESS cannot be retained.<br>• The population is therefore fundamentally different to MMY2002, and the Richardson study was not considered suitable for a MAIC. |
| Dimopoulos, 2018 (2) | POM+DEX | • In the MM-013 study, 0% of patients were ISS=1 compared with [redacted] % of patients in MMY2002; therefore the studies are not comparable.<br>• The MM-013 study requires significant weighting to match the populations and a suitable ESS cannot be retained, |

| | | | | |
|---|---|---|---|---|
| | | | | therefore the Dimopoulos study was not considered suitable for a MAIC. |
| | | Maciocia, 2017 (3) | POM+DEX | • In the Maciocia study, 27% of patients were refractory to bortezomib compared with [redacted] % in MMY2002.<br>• After matching on this characteristic, the ESS is [redacted], and matching any further reduces the ESS below [redacted].<br>• Refractory to previous treatments was identified by clinicians as the most important prognostic factor for patients at this line of therapy<br>• The median number of prior therapies received in the study was three compared with five in MMY2002.<br>• The population presented by Maciocia is fundamentally different to MMY2002 and therefore was not considered suitable for a MAIC. |
| | | Parisi, 2019 (5) | POM+DEX | • It is not possible to retain ESS when including prior lines of therapy as a prognostic factor.<br>• The population presented received three lines of prior therapy compared with five in MMY2002; therefore, the Parisi study was not considered suitable for a MAIC. |
| | | Maouche, 2020 (4) | PANO+BORT+DEX | • There were no clear markings of the months on the KM curves presented in the Maouche paper, producing significant uncertainty when estimating |

| | | |
|---|---|---|
| | | <table><tr><td></td><td></td><td>the time points associated with the KM when scanning the curves.<br>• The KM images are not clear enough to provide reliable estimates for the analysis, therefore the Maouche study was not considered suitable for a MAIC.</td></tr></table><br>Abbreviations: KM, Kaplan Meier; ESS, effective sample size; ISS, International Staging System; MAIC, matching-adjusted indirect comparison; PANO+BORT+DEX, panobinostat plus bortezomib and dexamethasone; POM+DEX; pomalidomide plus dexamethasone; SACT, systemic anti-cancer therapy.<br><br>• As stated by the ERG *"the SACT data for daratumumab reflects the most conservative source of treatment effectiveness for the drug".* By contrast, the fully adjusted MAIC vs POM+DEX produced the most optimistic estimates of treatment effectiveness for daratumumab. In addition, the fully adjusted MAIC resulted in a significant reduction in effective sample size (ESS). Janssen, therefore, considers the partially adjusted MAIC to be an appropriate middle ground between the most conservative and optimistic survival estimates for daratumumab whilst maintaining a reasonable ESS ([redacted] vs POM+DEX, and [redacted] vs PANO+BORT+DEX). |
| **Issue 3 – Source of treatment effectiveness in the model (Report sections 4.2.1)** | **No** | • Janssen considers that the partially adjusted MAIC represents the most robust source of daratumumab data for the comparison with POM+DEX and PANO+BORT+DEX.<br>o PLD were not available from SACT and therefore any comparison with POM+DEX/PANO+BORT+DEX is naïve, and conclusions based on these data are biased and highly uncertain. This comparison also involves comparing RWE (daratumumab) with trial data (POM+DEX and PANO+BORT+DEX). Although trial outcomes are similar between SACT and MMY2002, RWE data is often worse than trial data, and there is no available comparison between RWE and trial data for the comparators; therefore conclusions based on comparing SACT with trial data for the comparators are uncertain and likely subject to bias against daratumumab. |

- Although it is preferable to adjust for as many prognostic factors as possible in a MAIC, this results in a low ESS that produces overly optimistic and highly uncertain estimates of comparative efficacy. As noted in NICE decision support units (DSU) Technical Support Document 18 (6), *"when the ESS is markedly reduced, or equivalently the weights are highly variable, estimates become unstable and inferences depend heavily on just a small number of individuals"*.
- Therefore, partially adjusted MAICs (matched on the most important prognostic factors based on clinical expert opinion) were considered to provide an approach that balanced the need to adjust for key prognostic factors and retain a suitable ESS.
- Clinical experts advised Janssen that refractoriness to previous treatments were the only key prognostic factors for patients at this line of therapy.

- As discussed in Key Issue 2, data collected in SACT are highly consistent with MMY2002, and the model base case represents an appropriate middle ground between the most conservative and optimistic comparative efficacy estimates.
- Furthermore, in all three methods presented to estimate comparative effectiveness, daratumumab is dominant versus both POM+DEX and PANO+BORT+DEX Table 3) Moreover, in all but the pessimistic SACT data scenario, daratumumab remains cost-effective at a 100% discount for POM.

**Table 3: Daratumumab clinical efficacy scenario results**

| Daratumumab clinical efficacy scenario | Result vs POM+DEX | Result vs PANO+BORT+DEX |
|---|---|---|
| Partially adjusted MAIC (base case) | Dominant | Dominant |
| Fully adjusted MAIC | Dominant | Dominant |
| SACT data | Dominant | Dominant |

Abbreviations: MAIC, matching-adjusted indirect comparison; PANO+BORT+DEX, panobinostat plus bortezomib and dexamethasone; POM+DEX; pomalidomide plus dexamethasone; SACT, Systemic Anti-Cancer Therapy.

| | | |
|---|---|---|
| **Issue 4 – Impact of subsequent treatments received after daratumumab on overall survival (Report sections 4.2.3)** | **Yes** | • Janssen does not consider it appropriate to conduct analysis on MMY2002 OS by subsequent therapy received<br>o These analyses are subject to high levels of selection bias by selecting patients based on their outcome.<br>o The number of patients that received subsequent bortezomib (N=[redacted]) or carfilzomib (N=[redacted]) is low, and not considered sufficient to inform robust Kaplan Meier (KM) curves.<br>**However, to address the concern raised by the ERG on the impact of subsequent therapies on OS, an exploratory post-hoc analysis has been conducted on OS by subsequent therapy in MMY2002. Analysis was conducted for all lines of subsequent therapy received (Figure 1) and first-line after daratumumab only (**<br>o Figure 2).<br>o Although results should be interpreted with substantial caution, and the KM curves cross, patients who received subsequent carfilzomib or bortezomib did not have improved OS when compared with patients who received |

other subsequent therapies, or when compared with all patients who received a subsequent therapy, further supporting the generalisability of MMY2002 to UK clinical practice

- A summary of key prognostic factors between groups is presented in
- 

**Table 4 and**

- Table 5. The characteristics are generally well-balanced between subgroups; however, patients in the carfilzomib subgroup have a higher proportion classed as ISS III (despite lower ECOG), while patients in the bortezomib subgroup have a higher cytogenic risk than other subgroups. A full description of baseline characteristics is presented in Appendix C.
- As the patient numbers in each group are small, and limited information was collected in MMY2002 regarding time-varying covariates, Janssen did not consider it statistically robust or appropriate to conduct analysis adjusting for baseline characteristics.

**Figure 1: OS by subsequent therapy received (all lines), MMY2002†‡**

CiC information removed

| | | |
|---|---|---|
| | | †Note, there is overlap in subsequent therapy subgroups when assessed across all lines with some patients treated with either bortezomib or carfilzomib subsequently treated with carfilzomib or bortezomib respectively at later lines<br>‡Subseq therapy refers to all patients who received a subsequent therapy<br>Abbreviations: BORT, bortezomib; CARF, carfilzomib; subseq, subsequent.<br><br>**Figure 2: OS by subsequent therapy received (first-line only), MMY2002†** |

CiC information removed

†Subseq therapy refers to all patients who received a subsequent therapy
Abbreviations: 1L, first-line; BORT, bortezomib; CARF, carfilzomib; subseq, subsequent.

**Table 4: Key prognostic factors, MMY2002 subsequent therapy subgroups (all lines)**

| | All MMY2002 | All subsequent | Other | Bortezomib | Carfilzomib |
|---|---|---|---|---|---|

| | patients | therapies | | | |
|---|---|---|---|---|---|
| Age | CiC information removed | CiC information removed | CiC information removed | CiC information removed | CiC information removed |
| Refractory to lenalidomide | CiC information removed | CiC information removed | CiC information removed | CiC information removed | CiC information removed |
| Refractory to bortezomib | CiC information removed | CiC information removed | CiC information removed | CiC information removed | CiC information removed |
| Refractory to lenalidomide and bortezomib | CiC information removed | CiC information removed | CiC information removed | CiC information removed | CiC information removed |
| ISS = 1 or 2 | CiC information removed | CiC information removed | CiC information removed | CiC information removed | CiC information removed |
| ISS = 3 | CiC information removed | CiC information removed | CiC information removed | CiC information removed | CiC information removed |
| ECOG = 0 | CiC information removed | CiC information removed | CiC information removed | CiC information removed | CiC information removed |
| ECOG = 1 | CiC information removed | CiC information removed | CiC information removed | CiC information removed | CiC information removed |
| ECOG = 2 | CiC information removed | CiC information removed | CiC information removed | CiC information removed | CiC information removed |
| High cytogenetic risk | CiC information removed | CiC information removed | CiC information removed | CiC information removed | CiC information removed |

Abbreviations: ECOG, Eastern Cooperative Oncology Group; ISS, International Staging System.

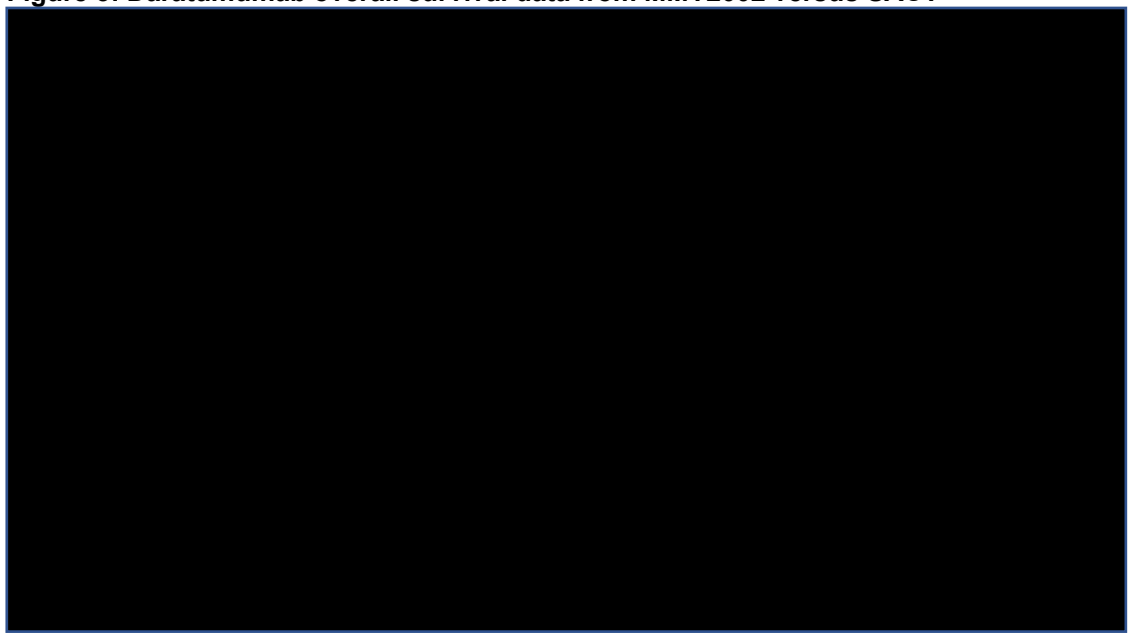
**Table 5: Key prognostic factors, MMY2002 subsequent therapy subgroups (first-line only)**

| | All MMY2002 patients | All subsequent therapies | Other | Bortezomib | Carfilzomib |
|---|---|---|---|---|---|

| | | | | | | |
|---|---|---|---|---|---|---|
| Age | CiC information removed | CiC information removed | CiC information removed | CiC information removed | CiC information removed |
| Refractory to lenalidomide | CiC information removed | CiC information removed | CiC information removed | CiC information removed | CiC information removed |
| Refractory to bortezomib | CiC information removed | CiC information removed | CiC information removed | CiC information removed | CiC information removed |
| Refractory to lenalidomide and bortezomib | CiC information removed | CiC information removed | CiC information removed | CiC information removed | CiC information removed |
| ISS = 1 or 2 | CiC information removed | CiC information removed | CiC information removed | CiC information removed | CiC information removed |
| ISS = 3 | CiC information removed | CiC information removed | CiC information removed | CiC information removed | CiC information removed |
| ECOG = 0 | CiC information removed | CiC information removed | CiC information removed | CiC information removed | CiC information removed |
| ECOG = 1 | CiC information removed | CiC information removed | CiC information removed | CiC information removed | CiC information removed |
| ECOG = 2 | CiC information removed | CiC information removed | CiC information removed | CiC information removed | CiC information removed |
| High cytogenetic risk | CiC information removed | CiC information removed | CiC information removed | CiC information removed | CiC information removed |

Abbreviations: ECOG, Eastern Cooperative Oncology Group; ISS, International Staging System.

- These findings are consistent with a study that reported that single agent carfilzomib failed to show an OS benefit over low-dose dexamethasone with or without cyclophosphamide in heavily pre-treated patients with relapsed or refractory multiple myeloma (rrMM) (7).
- As discussed in Key Issue 2, the company disagrees with the ERG's statement that the OS curves from SACT and MMY2002 are not similar.
    - There is a small difference between the unadjusted MMY2002 and SACT OS curves between Months 3 and 21.

| | | |
|---|---|---|
| | | o After adjustment for baseline characteristics, this difference is no longer observed, suggesting that the impact of any differences in subsequent therapy use is negligible (Figure 3).<br>**Figure 3: Daratumumab overall survival data from MMY2002 versus SACT**<br>  <br>Abbreviations: HR, hazard ratio; OS, overall survival; SACT, Systemic Anti-Cancer Therapy. |
| **Issue 5 – Subsequent treatments modelled (Report sections 4.2.3)** | **No** | • Subsequent therapy proportions from SACT data are considered the most suitable to inform the modelled costs as they are the most up to date, real-world estimates of subsequent therapy use in UK clinical practice.<br>• However, scenario analyses were conducted that used a consistent source of efficacy and cost data between comparators. When data from MMY2002 and MM- |

| | | |
|---|---|---|
| | | 003 are used to cost subsequent therapies in the daratumumab and POM+DEX arms of the model, daratumumab remains dominant versus each comparator.<br>o A further scenario analysis was conducted that models subsequent therapy use in the daratumumab arm using SACT data and in the POM+DEX arm using MM-003 data. In this analysis, daratumumab remains dominant versus each comparator. |

## Additional issues

**All:** Please use the table below to respond to additional issues in the ERG report 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 appraisal (for example, at the clarification stage).

**Table 6: Additional issues from the ERG report**

| Issue from the ERG report | Relevant section(s) and/or page(s) | Does this response contain new evidence, data or analyses? | Response |
|---|---|---|---|
| Additional issue 1: *'the ERG notes that daratumumab is now more frequently administered subcutaneously and the data from MMY2002 relate to the IV administration of daratumumab'* | Section 2.3, page 26 | No | • Non-inferiority has been demonstrated between subcutaneous and intravenous daratumumab in the COLUMBA trial, an ongoing, multi-centre, open-label, non-inferiority, randomised, Phase 3 trial.<br>• The COLUMBA trial demonstrated that the safety profile of subcutaneous daratumumab was improved compared with IV daratumumab (8). |
| Additional issue 2: *'ERG recommends caution in drawing conclusions on the end-of-life criteria from only these findings'* | Section 2.3, page 28 | No | • In the model base-case, mean OS is [redacted] months and [redacted] months in the POM+DEX and PANO+BORT+DEX arms, respectively.<br>• In each of the methods presented to estimate comparative effectiveness of daratumumab vs POM+DEX and PANO+BORT+DEX, daratumumab is associated with a greater than 3-month survival gain compared with both comparators (Table 7). |

**Table 7: Daratumumab mean OS gain**

| Daratumumab clinical efficacy scenario | Mean OS gain vs POM+DEX | Mean OS gain vs PANO+BORT+DEX |
|---|---|---|
| Partially adjusted MAIC (base case) | [redacted] | [redacted] |
| Fully adjusted MAIC | [redacted] | [redacted] |
| SACT data | 9.19 | 5.54 |

Abbreviations: MAIC, matching-adjusted indirect comparison; OS, overall survival; PANO+BORT+DEX, panobinostat plus bortezomib and dexamethasone; POM+DEX; pomalidomide plus dexamethasone; SACT, systemic anti-cancer therapy.

# 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 8: Changes to the company's cost-effectiveness estimate**

| Key issue(s) in the ERG report 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) |
|---|---|---|---|
| – | A simple PAS discount of [CiC information removed] was applied to the list price of daratumumab. | An updated PAS for daratumumab has been approved by NHS England. A discount of [CiC information removed] is now applied to the list price of daratumumab. | ICER vs POM+DEX:<br>Daratumumab dominates<br><br>ICER vs PANO+BORT+DEX:<br>Daratumumab dominates |
| **Company's base case following technical engagement** | **Incremental quality adjusted life years (QALYs) vs POM+DEX:** [CiC information removed]<br><br>**Incremental QALYs vs PANO+BORT+DEX:** [CiC information removed] | **Incremental costs vs POM+DEX: [**CiC information removed]<br><br>**Incremental costs vs PANO+BORT+DEX: [**CiC information removed] | **ICER vs POM+DEX:**<br>**Daratumumab dominates**<br><br>**ICER vs PANO+BORT+DEX:**<br>**Daratumumab dominates**<br><br>Full model results are provided in Appendix D |

**Sensitivity analyses around revised base case**

Daratumumab remains cost-effective in all sensitivity analyses conducted and therefore the conclusions of the analysis remain consistent with the Company CDF re-submission. Full details of sensitivity analyses conducted, and results of the analyses, are presented in Appendix D.

# References

1. Attal M, Richardson PG, Rajkumar SV, San-Miguel J, Beksac M, Spicka I, et al. Isatuximab plus pomalidomide and low-dose dexamethasone versus pomalidomide and low-dose dexamethasone in patients with relapsed and refractory multiple myeloma (ICARIA-MM): a randomised, multicentre, open-label, phase 3 study. Lancet. 2019;394(10214):2096-107.
2. Dimopoulos M, Weisel K, van de Donk N, Ramasamy K, Gamberi B, Streetly M, et al. Pomalidomide Plus Low-Dose Dexamethasone in Patients With Relapsed/Refractory Multiple Myeloma and Renal Impairment: Results From a Phase II Trial. J Clin Oncol. 2018;36(20):2035-43.
3. Maciocia N, Melville A, Cheesman S, Sharpley F, Ramasamy K, Streetly M, et al. Real-world use of pomalidomide and dexamethasone in double refractory multiple myeloma suggests benefit in renal impairment and adverse genetics: a multi-centre UK experience. Br J Haematol. 2017;176(6):908-17.
4. Maouche N, Kishore B, Bhatti Z, Supratik B, Karim F, Sundararaman S, et al. Panobinostat in combination with bortezomib and dexamethasone for heavily pre-treated myeloma: a UK real-world multi-centre cohort. Br J Haematol. 2020.
5. Parisi MS, Leotta S, Romano A, Del Fabro V, Martino EA, Calafiore V, et al. Clinical Benefit of Long-Term Disease Control with Pomalidomide and Dexamethasone in Relapsed/Refractory Multiple Myeloma Patients. J Clin Med. 2019;8(10).
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7. Hájek R, Masszi T, Petrucci M, Palumbo A, Rosiñol L, Nagler A, et al. A randomized phase III study of carfilzomib vs low-dose corticosteroids with optional cyclophosphamide in relapsed and refractory multiple myeloma (FOCUS). Leukemia. 2017;31(1):107-14.
8. Mateos MV, Nahi H, Legiec W, Grosicki S, Vorobyev V, Spicka I, et al. Subcutaneous versus intravenous daratumumab in patients with relapsed or refractory multiple myeloma (COLUMBA): a multicentre, open-label, non-inferiority, randomised, phase 3 trial. Lancet Haematol. 2020;7(5):e370-e80.

# Appendices

## Appendix A: Systematic literature review update

## Appendix B: MAIC feasibility – baseline characteristics

## Appendix C: MMY2002 subsequent therapy analysis, baseline characteristics

## Appendix D: Updated model results

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# Technical engagement response form

## Daratumumab monotherapy for treating relapsed and refractory multiple myeloma (CDF review of TA510) [ID3881]

As a stakeholder you have been invited to comment on the evidence review group (ERG) report for this appraisal.

Your comments and feedback on the key issues below are really valued. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal 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 ERG report that are likely to be discussed by the committee. The key issues in the ERG report 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 ERG report.

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 ERG report 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 appraisal, 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 replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Deadline for comments by **5pm** on **16 December 2021** 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.**

Technical engagement response form

Daratumumab monotherapy for treating relapsed and refractory multiple myeloma (CDF review of TA510) [ID3881]

NICE National Institute for Health and Care Excellence

# About you

### Table 1 About you

| | |
|---|---|
| **Your name** | [redacted] |
| **Organisation name: stakeholder or respondent**<br>(if you are responding as an individual rather than a registered stakeholder, please leave blank) | Myeloma UK |
| **Disclosure**<br>Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry. | **No** |

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# Key issues for engagement

**All**: Please use the table below to respond to the key issues raised in the ERG report.

**Table 2 Key issues**

| Key issue | Does this response contain new evidence, data or analyses? | Response |
|---|---|---|
| Issue 1 – Absence of an updated systematic literature review for the review of clinical effectiveness (Report sections 3.2) | No | No comment |
| Issue 2 – Uncertainty in the clinical-effectiveness estimates for daratumumab compared with Pomalidomide plus dexamethasone and Panobinostat plus bortezomib and dexamethasone (Report sections 3.1.4.3, 3.2 and 3.3) | No | No comment |
| Issue 3 – Source of treatment effectiveness in the model (Report sections 4.2.1) | No | No Comment |
| Issue 4 – Impact of subsequent treatments received after | No | The treatments listed in section 4.2.3 capture the main treatments approved on the NHS which patients would receive. Some patients may choose to join a clinical trial |

| | | |
|---|---|---|
| daratumumab on overall survival (Report sections 4.2.3) | | at this point in the treatment pathway. Patients at this point of their disease are likely to be multiply relapsed with a high disease impact and associated side effects burden from continued treatment toxicities. |
| Issue 5 – Subsequent treatments modelled (Report sections 4.2.3) | No | No comment |

# Additional issues

**All:** Please use the table below to respond to additional issues in the ERG report 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 appraisal (for example, at the clarification stage).

**Table 3 Additional issues from the ERG report**

| Issue from the ERG report | 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 ERG report 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 ERG report 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] |

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# 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 ERG report 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 ERG report | Briefly describe the company's original preferred assumption or analysis | Briefly describe the change(s) made in response to the ERG report | 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 ERG report | … | … | [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

# Technical engagement response form

## Daratumumab monotherapy for treating relapsed and refractory multiple myeloma (CDF review of TA510) [ID3881]

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If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.

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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.

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**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.**

Technical engagement response form

Daratumumab monotherapy for treating relapsed and refractory multiple myeloma (CDF review of TA510) [ID3881]

NICE National Institute for Health and Care Excellence

# About you

**Table 1 About you**

| | |
|---|---|
| **Your name** | [redacted] |
| **Organisation name: stakeholder or respondent**<br>(if you are responding as an individual rather than a registered stakeholder, please leave blank) | UK Myeloma Forum |
| **Disclosure**<br>Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry. | **No links – nil to disclose** |

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# Key issues for engagement

**All**: Please use the table below to respond to the key issues raised in the ERG report.

**Table 2 Key issues**

| Key issue | Does this response contain new evidence, data or analyses? | Response |
|---|---|---|
| Issue 1 – Absence of an updated systematic literature review for the review of clinical effectiveness (Report sections 3.2) | No | Agree with ERG that updated SLR should be presented. |
| Issue 2 – Uncertainty in the clinical-effectiveness estimates for daratumumab compared with Pomalidomide plus dexamethasone and Panobinostat plus bortezomib and dexamethasone (Report sections 3.1.4.3, 3.2 and 3.3) | No | Agree with the ERG |
| Issue 3 – Source of treatment effectiveness in the model (Report sections 4.2.1) | No | Agree with the ERG. It is noted that daratumumab is either dominant or ICER within acceptable limits with each presented analysis |
| Issue 4 – Impact of subsequent treatments received after | No | Agree with ERG. It would be preferred for to exclude subsequent treatments not routine available in England in particular carfizlomib |

| | | |
|---|---|---|
| daratumumab on overall survival (Report sections 4.2.3) | | |
| Issue 5 – Subsequent treatments modelled (Report sections 4.2.3) | No | Agree with the ERG |

# Additional issues

**All:** Please use the table below to respond to additional issues in the ERG report 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 appraisal (for example, at the clarification stage).

**Table 3 Additional issues from the ERG report**

| Issue from the ERG report | Relevant section(s) and/or page(s) | Does this response contain new evidence, data or analyses? | Response |
|---|---|---|---|
| Additional issue 1: | Please indicate the section(s) of the ERG report 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 ERG report 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] |

NICE National Institute for Health and Care Excellence

# 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 ERG report 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 ERG report | Briefly describe the company's original preferred assumption or analysis | Briefly describe the change(s) made in response to the ERG report | 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 ERG report | … | … | [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]

# Daratumumab monotherapy for treating relapsed and refractory multiple myeloma (CDF review of TA510)

ERG review of company's response to the TE

January 2022

**Source of funding**

This report was commissioned by the NIHR Evidence Synthesis Programme as project number 13/52/68T.

# 1 Introduction

This document provides the evidence review group's (ERG's) response in relation to the company's comments and additional data presented as a response to the technical engagement document (TE).

# 2 ERG review of comments

## 2.1 Issue 1: Absence of an updated systematic literature review for the review of clinical effectiveness

The company conducted an updated systematic literature review (SLR) on 29 October 2021 to identify efficacy and safety data for pomalidomide and dexamethasone (POM+DEX) and panobinostat plus bortezomib and dexamethasone (PANO+BORT+DEX) published following the searches conducted for the original SLR in July 2016. The company's updated SLR included searches of Embase, Medline and Cochrane library (Central & Cochrane Database of Systematic Reviews) databases, in addition to a hand search of conference websites deemed to be relevant by the company (American Society of Clinical Oncology, American Society of Hematology, European Hematology Association, European Society for Medical Oncology, and British Society for Haematology) for conferences held in the last 3 years. The company reported that it was not necessary to search for additional efficacy and safety data for daratumumab explaining that as they are the manufacturer of daratumumab they are aware of the relevant published trials, and they consider the patient-level data (PLD) from the clinical trial MMY2002 remains the most relevant efficacy source to inform this Cancer Drugs Fund (CDF) review.

The ERG considers the company's approach to the updated SLR to be appropriate and considers the searches to be comprehensive, although the ERG notes that non-English language publications were excluded. The ERG notes that the SLR update identified 35 additional studies presenting efficacy and safety data for either POM+DEX or PANO+BORT+DEX and that the company considered five studies relevant for consideration to conduct additional matching adjusted indirect comparison (MAIC) analysis (see Issue 2, Section 2.2 for further details). The reasons for exclusion of the remaining 30 studies, and full details of the SLR update, were provided in the company response to technical engagement (TE) Appendix A. The ERG notes that the reason for the majority of the 30 studies not being considered further for MAIC was due to the absence of Kaplan-Meier (KM) data in the publications.

## 2.2 Issue 2: Uncertainty in the clinical effectiveness estimates for daratumumab compared with Pomalidomide plus dexamethasone and Panobinostat plus bortezomib and dexamethasone

The company acknowledge the inherent uncertainty assessing the comparative effectiveness of daratumumab due to the single-arm study design of the key MMY2002 clinical study, and lack of head-to-head data available for daratumumab versus POM+DEX or PANO+BORT+DEX. The company also highlight that the purpose of the CDF data collection was to address the uncertainty on the generalisability of daratumumab trial data to UK clinical practice and not to address the uncertainty in the comparative effectiveness of daratumumab. The ERG and company both acknowledge that it was not possible to collect evidence on comparative effectiveness via SACT.

The company also report how they consider an unanchored MAIC of daratumumab and POM+DEX/PANO+BORT+DEX trial data to be preferable to a naïve comparison using the real world evidence (RWE) from SACT for daratumumab and trial data for POM+DEX/PANO+BORT+DEX. The company acknowledge that an unanchored MAIC may have residual bias if important effect modifiers and prognostic factors are not accounted for, but they consider a naïve comparison to also be biased; flagging particular concerns with the use of the SACT RWE data in the comparisons with POM+DEX and PANO+BORT+DEX where the comparator data are from clinical trials. This issue is discussed further in Section 2.3 along with the ERG's view.

As discussed in response to Key Issue 1 (Section 2.2), five studies were identified in the updated SLR and assessed for feasibility to perform an additional MAIC of daratumumab versus POM+DEX (four studies) or PANO+BORT+DEX (one study). The company reported that following feasibility assessment it was deemed that none of the newly identified studies were appropriate to perform an additional MAIC that would reduce the uncertainty in the comparative efficacy estimates. The sources of clinical data for the comparators thus remain as in the original company submission.

The company provided a summary of the five studies assessed for feasibility (Table 1) and baseline characteristics for the studies were provided in the company response to TE Appendix B. Due to time constraints the ERG has been unable to fully assess the studies but the ERG notes that the company's rationale for not conducting MAICs using any of the four new POM+DEX studies is related to a low effective sample size (ESS) after matching, although the ESS is not explicitly reported for the Dimopoulos *et al.* [1] or Parisi *et al.*[2] studies. The ERG also notes that for the new PANO+BORT+DEX study the company has flagged concerns around the quality of the KM data.

Table 1. MAIC feasibility assessment (reproduced from company response to TE, table 2)

| Author, year | Comparator | MAIC feasibility |
|---|---|---|
| Richardson, 2019 [3] | POM+DEX | • Patients in the ICARIA-MM study received a median of 3 prior therapies compared with 5 in MMY2002.<br>• When attempting to match on the number of prior lines of therapy, ESS drops from [redacted] to [redacted]; therefore, a suitable ESS cannot be retained.<br>• The population is therefore fundamentally different to MMY2002, and the Richardson study was not considered suitable for a MAIC. |
| Dimopoulos, 2018 [1] | POM+DEX | • In the MM-013 study, 0% of patients were ISS=1 compared with [redacted]% of patients in MMY2002; therefore the studies are not comparable.<br>• The MM-013 study requires significant weighting to match the populations and a suitable ESS cannot be retained, therefore the Dimopoulos study was not considered suitable for a MAIC. |
| Maciocia, 2017 [4] | POM+DEX | • In the Maciocia study, 27% of patients were refractory to bortezomib compared with [redacted]% in MMY2002.<br>• After matching on this characteristic, the ESS is [redacted], and matching any further reduces the ESS below [redacted].<br>• Refractory to previous treatments was identified by clinicians as the most important prognostic factor for patients at this line of therapy<br>• The median number of prior therapies received in the study was three compared with five in MMY2002.<br>• The population presented by Maciocia is fundamentally different to MMY2002 and therefore was not considered suitable for a MAIC. |
| Parisi, 2019 [2] | POM+DEX | • It is not possible to retain ESS when including prior lines of therapy as a prognostic factor.<br>• The population presented received three lines of prior therapy compared with |

| | | |
|---|---|---|
| | | five in MMY2002; therefore, the Parisi study was not considered suitable for a MAIC. |
| Maouche, 2020 [5] | PANO+BORT+DEX | • There were no clear markings of the months on the KM curves presented in the Maouche paper, producing significant uncertainty when estimating the time points associated with the KM when scanning the curves.<br>• The KM images are not clear enough to provide reliable estimates for the analysis, therefore the Maouche study was not considered suitable for a MAIC. |

Abbreviations: KM, Kaplan Meier; ESS, effective sample size; ISS, International Staging System; MAIC, matching-adjusted indirect comparison; PANO+BORT+DEX, panobinostat plus bortezomib and dexamethasone; POM+DEX; pomalidomide plus dexamethasone; SACT, systemic anti-cancer therapy.

## 2.3 Issue 3: Source of treatment effectiveness in the model

In their response to technical engagement the company reiterates their view that they consider the partially adjusted MAIC represents the most robust source of daratumumab data for the comparison with POM+DEX and PANO+BORT+DEX. The company reported concerns that the results of the naïve comparisons with POM+DEX and PANO+BORT+DEX are likely subject to bias against daratumumab and they are highly uncertain. The company highlights that the comparison involves comparing real world evidence (RWE) for daratumumab with trial data for POM+DEX and PANO+BORT+DEX and argue that although trial outcomes are similar between SACT and MMY2002, RWE data is often worse than trial data, and there is no available comparison between RWE and trial data for the comparators.

The company also argues that their use of partially adjusted MAICs provides an approach that balances the need to adjust for key prognostic factors and retain a suitable ESS and cites the following text from the NICE decision support units (DSU) Technical Support Document 18[6] again: *"when the ESS is markedly reduced, or equivalently the weights are highly variable, estimates become unstable and inferences depend heavily on just a small number of individuals"*. The company report that their clinical experts considered refractoriness to previous treatments were the only key prognostic factors for patients at this line of therapy and thus these were the only factors included in the partially adjusted MAICs. As discussed in the ERG report, given that the MAICs are unanchored, the ERG considers all effect modifiers and prognostic variables should be adjusted for as recommended in TSD 18 and the ERG remains concerned that the company's use of the partially adjusted MAICs may be introducing bias into the results.

The ERG maintains its view that the fully adjusted MAIC is more appropriate from a methodological point of view compared with the partially adjusted MAIC used by the company. Nonetheless, and even though the fully adjusted MAIC is methodologically superior to the partially adjusted one, the former produced clinically implausible OS curves for the comparison of daratumumab vs POM+DEX. The ERG acknowledges that a naïve comparison is also flawed from a methodological point of view, but in the absence of clinically plausible fully adjusted MAIC results, the ERG considers the naïve comparison of real-life daratumumab (i.e., the SACT data) with POM+DEX is of relevance to the committee, particularly given that the patient population included and the subsequent treatments received reflect patients treated in UK clinical practice, along with the more clinically plausible OS predictions for daratumumab.

With regards to the comparison of daratumumab with PANO+BORT+DEX the ERG considers that the fully adjusted MAIC might be the most methodologically robust source for estimating relative treatment effectiveness given that the fully adjusted OS MAIC curve for daratumumab produces clinically plausible survival tails.

## 2.4 Issue 4: Impact of subsequent treatments received after daratumumab on overall survival

The ERG was originally concerned with the possibility of OS outcomes for daratumumab being confounded by the impact of subsequent therapies received in MMY2002 (and not available in the UK NHS). The updated MMY2002 data on subsequent therapies reported that most patients in MMY2002 received either a regimen containing carfilzomib ([redacted]); or chemotherapy with or without dexamethasone ([redacted]) as first subsequent therapies after daratumumab.

The company did not provide the more mature OS data by subsequent treatment received as originally requested by the ERG, as it did not, "*consider it statistically robust or appropriate to provide the requested OS data on* [the basis that] *these analyses are subject to a high level of selection bias because of indirectly selecting patients based on their outcome*." The company also added that the OS reported in SACT is similar to the MMY2002 OS, hence the impact of subsequent treatments on OS should not be an issue in MMY2002.

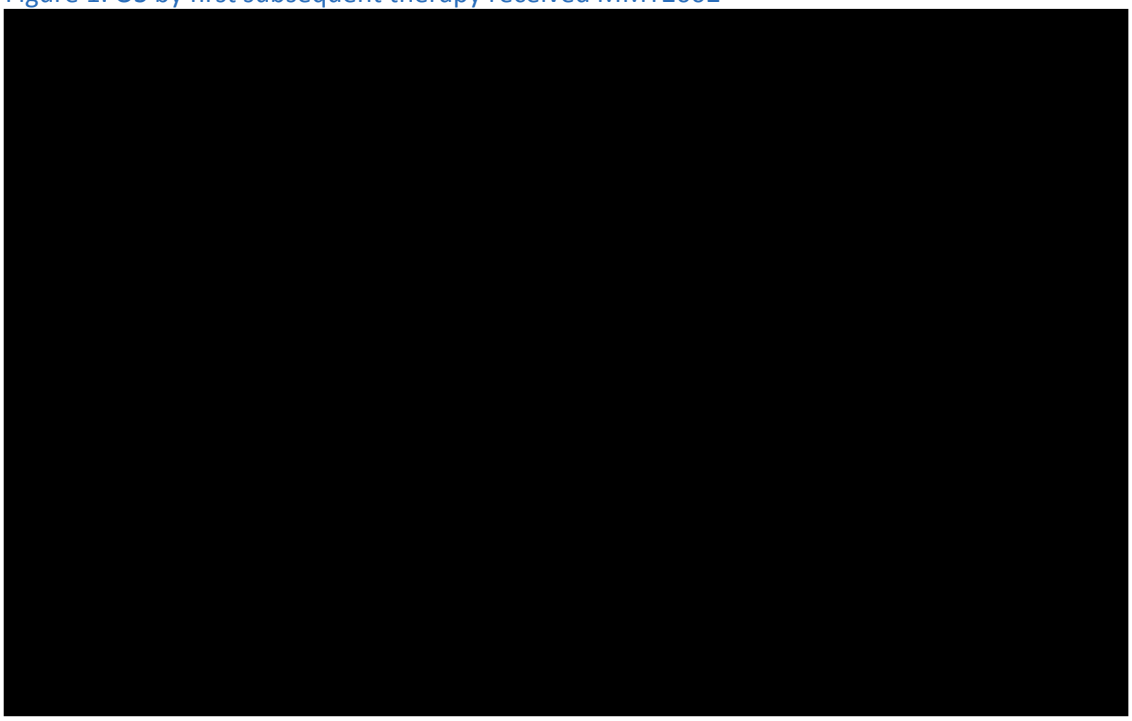
The ERG disagreed with the company's assessment that the OS curves in the SACT and in MMY2002 are similar and noted a considerable separation of the curves between month 3 and month 21. The ERG also noted that the subsequent treatments received in the SACT dataset do not include

carfilzomib, and that the majority of patients received either pomalidomide (64%) or bortezomib in combination with panobinostat (13%).

As a response to TE, the company provided an exploratory *post-hoc* analysis on OS by subsequent therapy in MMY2002 (Figure 1).

The company concluded that patients who received subsequent carfilzomib or bortezomib did not have improved OS when compared with patients who received other subsequent therapies, or when compared with all patients who received a subsequent therapy, further supporting the generalisability of MMY2002 to UK clinical practice, although noted that number of patients who received subsequent bortezomib ([redacted]) or carfilzomib ([redacted]) was low, and thus the OS curves should be interpreted with caution.

Figure 1. OS by first subsequent therapy received MMY2002



The ERG maintains its view that the OS curves in the SACT and in MMY2002 are not similar and notes a considerable separation of the curves between month 3 and month 21 (Figure 2). According to Figure 1, patient receiving carfilzomib had a survival advantage compared to patients receiving any other subsequent treatment between approximately month 3 and month 19 in MMY2002. This corresponds to the separation in the MMY2002 and SACT OS curves seen curves between month 3 and month 21 (Figure 2).

Figure 2. KM curves for daratumumab OS from MMY2002 and SACT

Therefore, the ERG maintains its original conclusion that the difference in OS curves seen in SACT and in MMY2002 is likely due to treatment with carfilzomib after in MMY2002, and therefore reinforces the use of the SACT data as its preferred source of clinical effectiveness for daratumumab in the model.

## 2.5 Issue 5: Subsequent treatments modelled

The company's model assumed that 58% of patients who had discontinued treatment with daratumumab; POM+DEX; or PANO+BORT+DEX received a subsequent treatment in the model. This was based on the SACT dataset. The company also noted that while the effectiveness data in the model is based on MMY2002, the distribution of subsequent therapies was informed by the SACT data. The company concluded that there was no need to conduct any adjustment to effectiveness given the comparability of SACT and MMY2002 OS outcomes despite differences in subsequent therapies.

As discussed in Section 2.4 and in the ERG report, the ERG disagrees with the company's assessment of similar OS outcomes in MMY2002 and the SACT data. Furthermore, the ERG was unclear why the subsequent treatment data for POM+DEX from MM-003 trial had not been used to estimate subsequent treatments in the POM+DEX arm. Similarly, the ERG considered that the source of

subsequent treatments post daratumumab in the model should ideally match the source of clinical effectiveness for daratumumab in the analysis.

Therefore, for all the scenario analyses conducted by the ERG before TE, the subsequent treatments received after POM+DEX were based on those received by patients in the MM-003 trial. Furthermore, for the scenario where the MAIC results were used to estimate treatment effectiveness in the model, the ERG used the subsequent treatments received by patients in MMY2002; and for the scenario where SACT data are used to estimate treatment effectiveness in the model, the ERG used the subsequent treatments received in SACT.

The dominance of daratumumab did not change in the MAIC analysis; however, the costs associated with subsequent treatment after daratumumab and after POM+DEX decreased (with the decrease in subsequent costs after POM+DEX being higher than that observed for daratumumab).

As a response to TE, the company maintained its view that the subsequent therapy proportions from SACT data are the most suitable to inform the modelled costs as they are the most up to date, real-world estimates of subsequent therapy use in UK clinical practice. The company added that regardless of the source of data used to model subsequent treatments, daratumumab remained dominant against its comparators.

The ERG maintains its view that the subsequent treatments received after POM+DEX in the model should be based on those received by patients in the MM-003 trial, but agrees with the company that the choice of subsequent treatments has a negligible impact on the final ICERs.

## 2.6 Additional issues

The ERG notes that both the company and ERG assessments suggest life expectancy with the comparators POM+DEX and PANO+BORT+DEX is predicted to be less than 24 months. Additionally, both the ERG and company assessments suggest daratumumab is associated with a minimum extension to life of 0.46 years thus meeting the criterion of prolonging life by at least an additional 3 months. However, the ERG considers the clinical effectiveness evidence underpinning this assessment to be extremely uncertain and as discussed in Section 2.2, no new data have been identified from the updated SLR to help address the uncertainty in the clinical effectiveness estimates for daratumumab compared with POM+DEX and PANO+BORT+DEX. The ERG therefore recommends caution in drawing conclusions on the end of life criteria from only these findings.

## 2.7 Company's updated cost-effectiveness results

During TE, the company updated their patients access scheme (PAS) discount from [redacted]. Consequently, the company provided a new set of results, which remained dominant in favour of daratumumab vs POM+DEX and vs PANO+BORT+DEX. The company's updated results are provided in Appendix D of the company's response to TE.

## 2.8 ERG scenario analysis

The scenario analyses originally undertaken by the ERG are explained throughout Section 4 of the ERG report (CDF review). The ERG conducted the analyses using the naïve comparison of SACT daratumumab data with the relevant comparator studies and the subsequent treatments received after daratumumab in SACT. For this scenario, the additional ERG's assumptions consist of the following:

a. Using a gamma distribution to estimate TTD (as a proxy for PFS) for daratumumab, and to estimate PFS for POM+DEX and PANO+BORT+DEX.
b. Modelling the subsequent treatments received after POM+DEX based on those received by patients in the MM-003 trial.

With the updated PAS included, all of the individual scenarios ran by the ERG remained dominant in favour of daratumumab vs PANO+BORT+DEX; and for daratumumab vs POM+DEX, with the exception of scenario b (i.e., using the subsequent treatments received in MM-003 to inform the subsequent treatments after POM+DEX in the model), where the ICER increased to £1,173 per QALY gained. The cumulative ICER resulting from combining all the assumptions results in dominant ICERs in favour of daratumumab vs POM+DEX and vs PANO+BORT+DEX (Table 2 and Table 3, respectively).

Table 2. ERG's preferred cumulative ICER for daratumumab vs POM+DEX

| Interventions | Total Costs (£) | Total QALYs | Total LYG | Incremental costs (£) | Incremental QALYs | Incremental LYG | ICER (£/QALY) |
|---|---|---|---|---|---|---|---|
| POM+DEX | [redacted] | [redacted] | 1.49 | - | - | - | - |
| Daratumumab | [redacted] | [redacted] | 2.26 | [redacted] | [redacted] | 0.77 | Daratumumab Dominates |

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 3. ERG's preferred cumulative ICER for daratumumab vs PANO+BORT+DEX

| Interventions | Total Costs (£) | Total QALYs | Total LYG | Incremental costs (£) | Incremental QALYs | Incremental LYG | ICER (£/QALY) |
|---|---|---|---|---|---|---|---|
| PANO+BORT +DEX | [redacted] | [redacted] | 1.80 | - | - | - | - |
| Daratumumab | [redacted] | [redacted] | 2.26 | [redacted] | [redacted] | 0.46 | Daratumumab Dominates |

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

The ERG also presents the results for the fully adjusted MAIC, which provides extremely optimistic (albeit clinically implausible) long-term survival with daratumumab (see Section 2.3 for the ERG's view on the most appropriate source of clinical data for the comparison with POM+DEX). For this scenario, the additional ERG's assumptions consist of the following:

a. Modelling the subsequent treatments received after POM+DEX based on those received by patients in the MM-003 trial.
b. Modelling the subsequent treatments received after daratumumab based on those received by patients in the MMY2002 trial.

The ERG's results (Table 4 and Table 5) show that daratumumab dominates both POM+DEX and PANO+BORT+DEX.

Results of all the ERG's scenario analyses using the comparator's PASs are provided in a confidential appendix.

Table 4. ERG's ICER for daratumumab vs POM+DEX using fully adjusted MAIC

| Interventions | Total Costs (£) | Total QALYs | Total LYG | Incremental costs (£) | Incremental QALYs | Incremental LYG | ICER (£/QALY) |
|---|---|---|---|---|---|---|---|
| POM+DEX | [redacted] | [redacted] | 1.49 | - | - | - | - |
| Daratumumab | [redacted] | [redacted] | 5.25 | [redacted] | [redacted] | 3.75 | Daratumumab dominates |

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 5. ERG's ICER for daratumumab vs PANO+BORT+DEX using fully adjusted MAIC

| Interventions | Total Costs (£) | Total QALYs | Total LYG | Incremental costs (£) | Incremental QALYs | Incremental LYG | ICER (£/QALY) |
|---|---|---|---|---|---|---|---|
| PANO+BORT+DEX | [redacted] | [redacted] | 1.80 | - | - | - | - |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Daratumumab | [redacted] | [redacted] | 3.33 | [redacted] | [redacted] | 1.53 | Daratumumab Dominates |

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

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