# Selinexor with dexamethasone for treating relapsed or refractory multiple myeloma after four or more treatments

For projector – contains no confidential information

**Highly Specialised Technology appraisal committee**

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**External assessment group:** BMJ-TAG

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**Company:** Menarini-Stemline

# Selinexor with dexamethasone for treating relapsed or refractory multiple myeloma after four or more treatments

- ✓ **Background and key issues**
- ❑ Decision problem
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Summary

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# Background on multiple myeloma

**Causes**

- Multiple myeloma (MM) is an incurable blood cancer that arises from plasma cells in the bone marrow

**Epidemiology**

- There are around 5,000 new cases of MM per year, with approximately 350 suitable for 5L treatment[1]

**Diagnosis and classification**

- Refractory MM: disease that is not responsive to treatment or progresses within 60 days of last treatment
- Relapsed MM: previously treated myeloma that progresses and requires the initiation of new treatment

**Symptoms and prognosis**

- People with MM can experience bone pain, bone fractures, tiredness (due to anaemia), infections, hypercalcaemia (too much calcium in the blood) and kidney problems
- Median survival for MM is 5 to 7 years, with 1 in 3 patients surviving 10 years or more; survival at 5L+ is typically shorter

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[1]NHS England estimates.
Abbreviations: 5L, fifth-line; MM, multiple myeloma.

# Patient and clinical perspectives

## Substantial unmet need for people with MM on 5L+ treatment

**Submission from Myeloma UK**

- People with RRMM experience a more significant disease burden due to the progressive nature of the disease and the cumulative side effects of treatment
- Limited treatment options at 5L+ cause worry for people with RRMM
- Treatments which can be taken at home are advantageous, especially for people who live further away from the hospital

*"Myeloma has had a major impact on my quality of life … you can wake up in chronic pain and be unable to do anything."*

**Submission from UK Myeloma Society (formerly UK Myeloma Forum)**

Representing physicians, nursing staff and healthcare professionals

- Treatment of myeloma aims to control symptoms and prolong life
- Partial response (PR), very good partial response (VGPR), or complete response (CR) are considered clinically significant treatment outcomes. This depth of response is associated with length of response
- Most disease responds to therapies early on, but only a minority respond from 5L+

*"Limited options available at 5L+. Other than PomDex and PanoBorDex, the only option would be access to clinical trials."*

See appendix – Patient perspectives and Clinical perspectives

Abbreviations: 5L, fifth-line; RRMM, relapsed or refractory multiple myeloma; CR, complete response; PR, partial response; VGPR, very good partial response.

# Equality considerations

**Multiple myeloma risk is higher in:**

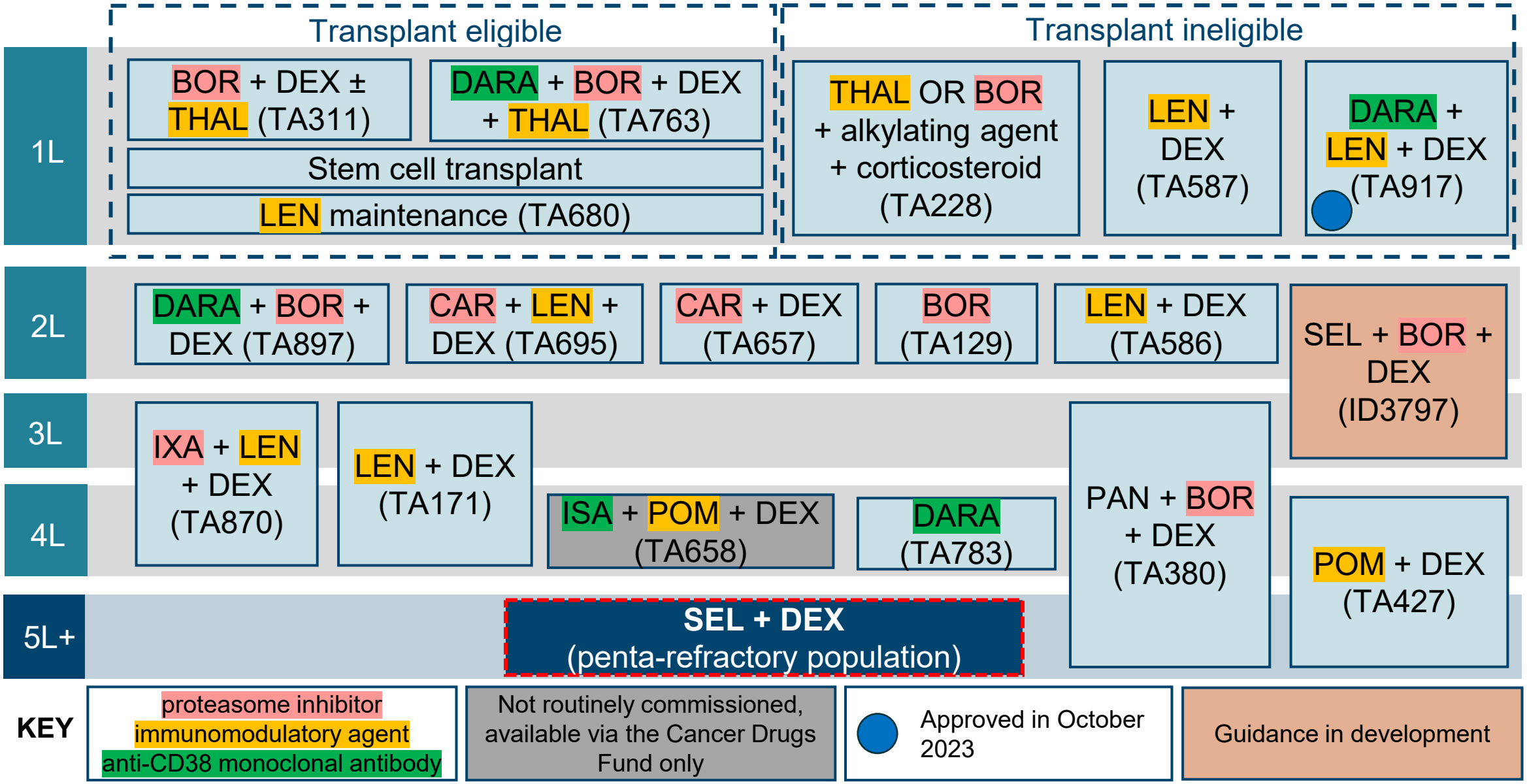
- Men than in women
- Older people (43% of new cases of multiple myeloma in England are in people aged ≥75 years)
- People of African and Caribbean family backgrounds

# Selinexor (Nexpovio®, Menarini-Stemline)

| | |
|---|---|
| **Marketing authorisation** | Selinexor, in combination with dexamethasone (Sd) is indicated for the treatment of multiple myeloma in adult patients who have received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors, two immunomodulatory agents and an anti-CD38 monoclonal antibody (penta-refractory), and who have demonstrated disease progression on the last therapy. |
| **Mechanism of action** | • Selinexor inhibits exportin 1 which causes tumour suppressor proteins to accumulate in the nucleus. This causes cell cycle arrest, reductions in oncoproteins such as c-Myc and cyclin D1, and apoptosis of cancer cells<br>• Selinexor and dexamethasone have synergistic cytotoxic effects in multiple myeloma |
| **Administration** | • Selinexor 80mg taken orally on Days 1 and 3 of each week with 20mg dexamethasone<br>• Treatment should be continued until disease progression or unacceptable toxicity |
| **Price** | • Proposed selinexor list price per pack:<br>  • £3,680 per 8x20mg (£460 per tablet)<br>• A confidential simple patient access scheme is in place |

NICE Abbreviations: Sd, selinexor with dexamethasone.

# Treatment pathway for multiple myeloma




Abbreviations: BOR, bortezomib; CAR, carfilzomib; DARA, daratumumab; DEX, dexamethasone; ISA, isatuximab; IXA, ixazomib; LEN, lenalidomide; PAN, panobinostat; POM, pomalidomide; SEL, selinexor; THAL, thalidomide

# Key issues

| Key issues | Resolved? | ICER impact |
|---|---|---|
| 1. Omission of clinical and cost-effectiveness analyses for PanoVd | No | **Unknown** |
| 2. Generalisability of the clinical data to the population eligible for Sd in clinical practice in England | No | **Unknown** |
| 3. Uncertainty in the results of the company ITC of Sd versus SoC and subsequent overall survival modelling | No | **Large** |

Abbreviations: ICER, incremental cost-effectiveness ratio; ITC, indirect treatment comparison; PanoVd, panobinostat with bortezomib and dexamethasone; Sd, selinexor with dexamethasone; SoC, standard of care.

# Selinexor with dexamethasone for treating relapsed or refractory multiple myeloma after four or more treatments

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# Key issue 1: Omission of PanoVd (panobinostat with bortezomib and dexamethasone) as a comparator

**Company**

- Consider the only relevant comparator is BSC
- Clinical advice → limited use of PanoVd → penta-refractory status dependent on being refractory to 2 PIs, unlikely that treatment with bortezomib containing regimen would be attempted

**EAG**

- Clinical advice to the EAG → PanoVd is a potentially relevant comparator as it is a treatment option at 5L+
- Would prefer to see a comparison to PanoVd in addition to a comparison with BSC.

**Recent appraisals: ID2701 Belantamab mafodotin for treating RRMM after 4 or more therapies**

Draft guidance (April 2023):

- *"The committee understood that there was no established standard care for people whose disease relapses after 5L treatment"*
- *"[The clinical experts] highlighted that panobinostat plus bortezomib and dexamethasone is rarely used and not appropriate when the disease is refractory to a proteasome inhibitor"*

Is PanoVd a relevant comparator?

See treatment pathway and appendix – comparators summary

Abbreviations: 5L, fifth-line; BSC, best supportive care; EAG, external assessment group; PanoVd, panobinostat with bortezomib and dexamethasone; PI, proteasome inhibitor; RRMM, relapsed or refractory multiple myeloma.

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# Key clinical trials: STORM Part 2 and MAMMOTH

| | **STORM** (selinexor) | **MAMMOTH** (SoC) |
|---|---|---|
| **Design** | Phase 2b, single-arm, 2-part, open-label, multicentre study | Multicentre, retrospective, cohort study |
| **Intervention** | Selinexor plus low-dose dexamethasone | SoC, including PIs, IMiDs, anti-CD38 monoclonal antibodies, chemotherapy drugs |
| **Relevant population** | **Part 2, penta-refractory population** (n=83)<br>Refractory* to bortezomib, carfilzomib, lenalidomide, pomalidomide, and daratumumab (BCLPD-refractory) | **Penta-refractory population** (n=70)<br>Refractory to 1 CD38 monoclonal antibody, 2 PIs, and 2 IMiDs |
| **Comparator** | N/A | N/A |
| **Outcomes** | Primary: ORR<br>Secondary: OS, PFS, AEs, HRQOL | OS, ORR |
| **Locations** | US, Austria, Belgium, France, Germany, Greece | US |
| **Used in model?** | Yes | Yes |

*Where refractory was defined as ≤25% response to treatment or progression during or within 60 days after completion of treatment
Abbreviations: AE, adverse event; HRQOL, health-related quality of life; IMiD, immunomodulatory imide drug; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PI, proteasome inhibitor; SoC, standard of care.

# Key issue 2: Generalisability of the clinical data

| | STORM Part 2 | MAMMOTH |
|---|---|---|
| **Age** | Median 65.3 years | Median 58.5 years |
| **Time from diagnosis** | Median 7.05 years (range 1.2 to 23.4) | Median 5.7 years (range 0.6 to 14.4) |
| **ECOG** | • 0, 32.5%<br>• 1, 56.6%<br>• 2, 8.4%<br>• Missing, 2.4% | NR |
| **Prior SCT** | 80.7% | 67.1% |
| **Prior treatments** | Median 8 (range 4 to 18) | Median 5 (range 2 to 16) |
| **Subsequent treatments** | [redacted]<br>• [redacted]<br>• [redacted]<br>• [redacted] | 90% |

## EAG

Concerns about the generalisability of STORM Part 2 and MAMMOTH to the NHS population:

- Median age younger than expected
- Prior SCT higher than expected
- More prior treatments than expected
- ECOG better than expected (STORM)
- Subsequent active treatments [redacted]
  - STORM – [redacted]
  - MAMMOTH – 90% used further active treatments, including IMiDs, PIs, and mAbs

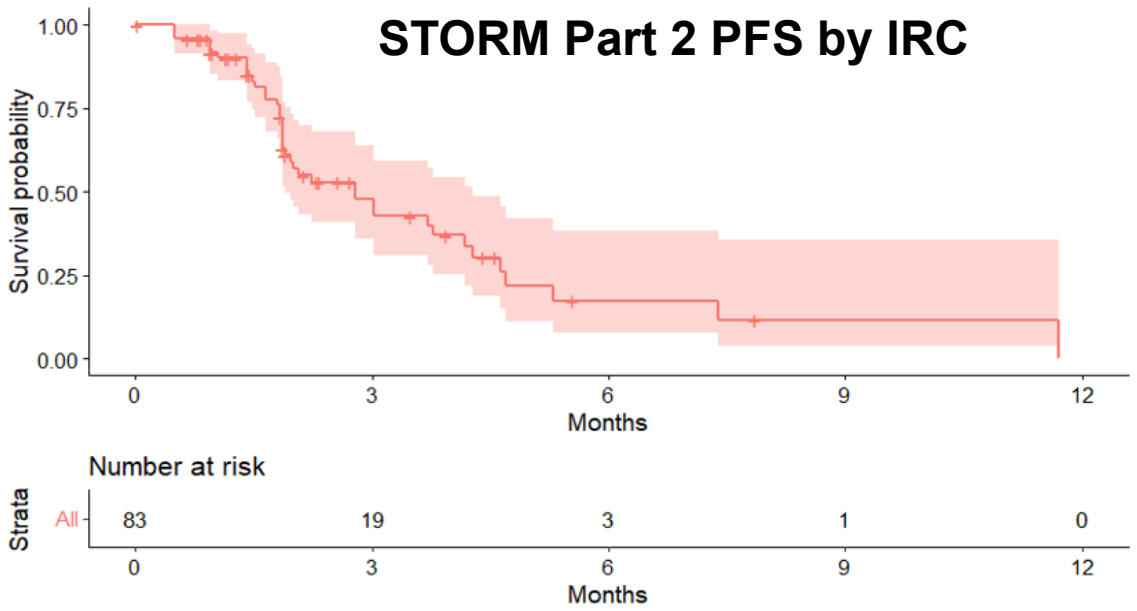
## Company

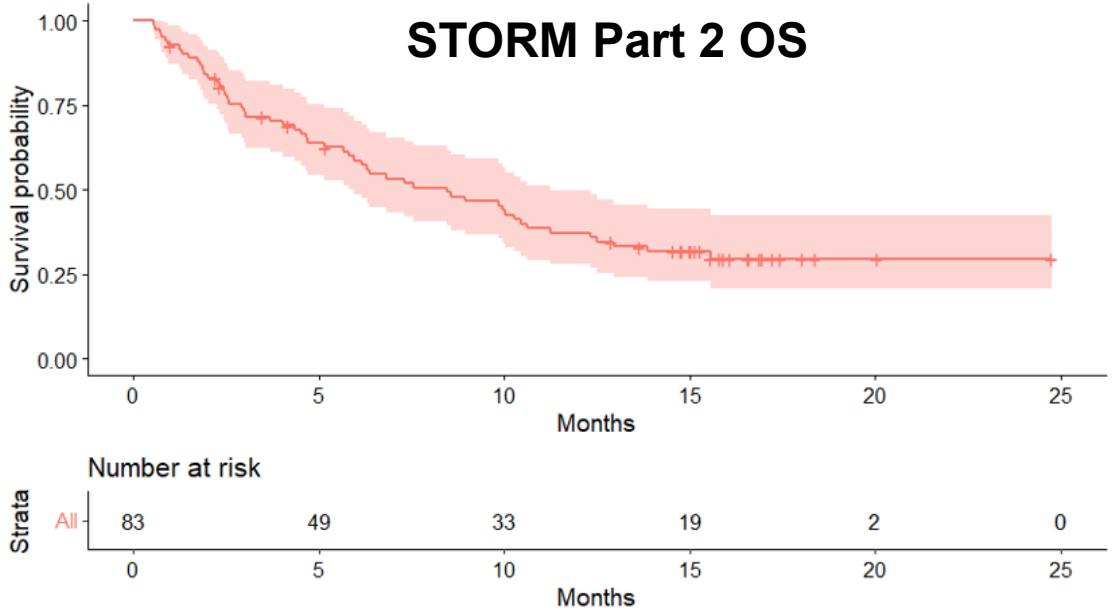
- Clinical advice → MAMMOTH is best available source of evidence for SoC

At what age would you expect patients to have selinexor?
What proportion of patients would you expect to have had SCT?

Abbreviations: ECOG, Eastern Cooperative Oncology Group; IMiD, immunomodulatory imide drug; mAb, monoclonal antibody; NR, not reported; PI, proteasome inhibitor; SCT, stem cell transplant.

# Key clinical trials: Results




| | STORM Part 2 (n=83) | MAMMOTH penta-refractory (n=70) |
|---|---|---|
| **Median OS, months (95% CI)** | 8.4 (5.9, 11.2) | 5.6 (3.5, 7.8) |
| **Est. 6-month survival, %** | 58.6 | NR |
| **Est. 12-month survival, %** | 37.3 | NR |
| **Median PFS, months (95% CI)** | 2.8 (1.9, 4.3) | NR |
| **ORR, n (%) [95% CI]** | 21 (25.3) [16.4, 36.0] | NR |
| **Median ToT, months** | 1.9 | NR |

Does committee accept the clinical evidence in light of the generalisability issues?

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Abbreviations: CI, confidence interval; IRC, independent review committee; NR, not reported; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; Sd, selinexor with dexamethasone, ToT, time on treatment.

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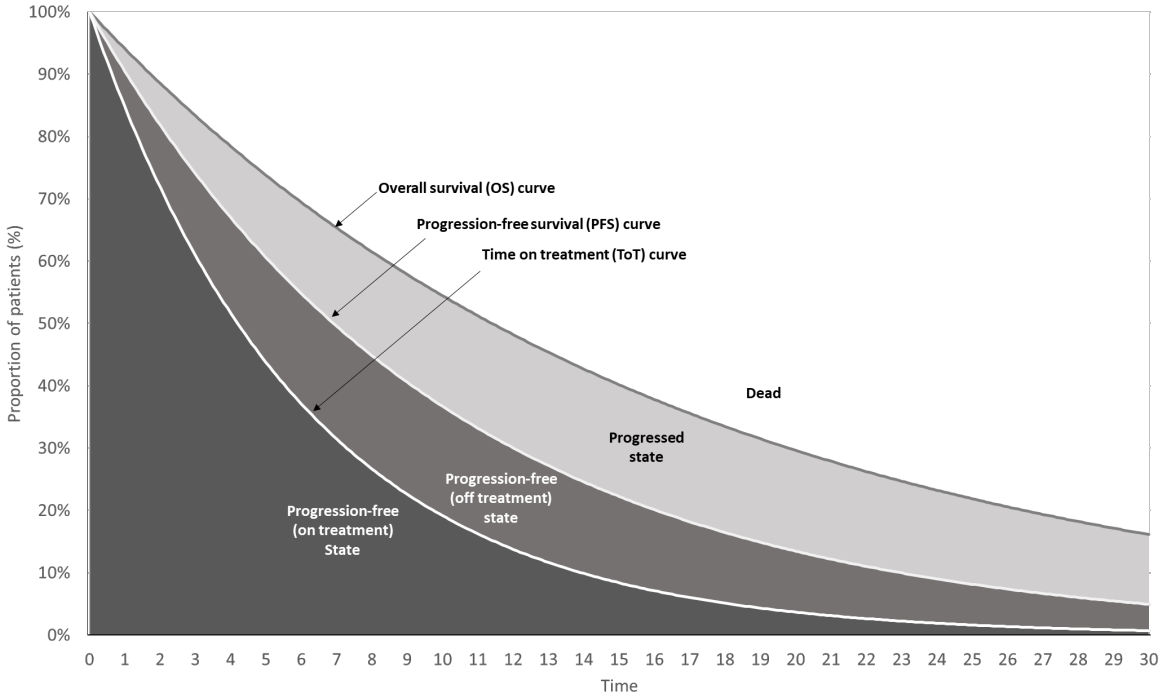
# Company's model overview

## Model structure

Partitioned survival model of 3 health states: PFS (on/off treatment), PD, and dead




Technology affects **costs** by:

- Higher treatment acquisition costs than currently available treatments for penta-refractory patients
- Management of AEs related to treatment*

Technology affects **QALYs** by:

- Increasing OS for all patients
- AEs experienced by patients receiving Sd*

Assumptions with greatest ICER effect:

- The estimation of OS for Sd and SoC
- Other assumptions have small effect on the ICER

See appendix – how company incorporated evidence into model

*As a conservative assumption, no adverse events have been assumed in the base case for patients receiving BSC. Although the expectation is that BSC would present AEs (especially where chemotherapy is received), the assumption is that Sd would more likely delay than displace alternative forms of therapy, and associated event rates would be similar.
Abbreviations: AE, adverse event; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; OS, overall survival; PD, progressed disease; PFS, progression-free survival; Sd, selinexor with dexamethasone; SoC, standard of care.

# Key issue 3: Indirect treatment comparison (1) – MAIC

## Company

- Conducted 3 MAICs using data from STORM Part 2 and MAMMOTH to generate HRs
- Each MAIC based on inclusion of various prognostic factors and effect modifiers

### Prognostic factors and effect modifiers in each MAIC

| Set of factors | Must Have | Full | Must Have + Nice to Have* | MAMMOTH |
|---|---|---|---|---|
| Age | ✓ | ✓ | ✓ | ✓ |
| Sex | ✓ | ✓ | ✓ | ✓ |
| ECOG | ✓ | ✓ | ✓ | × |
| R-ISS | ✓ | ✓ | ✓ | ✓ |
| High cytogenetic risk | ✓ | ✓ | ✓ | ✓ |
| No. prior regimens | ✓ | ✓ | ✓ | ✓ |
| Prior SCT | ✓ | | ✓ | ✓ |
| Duration of last therapy | | | ✓ | ✓ |
| Time since diagnosis | | ✓ | ✓ | ✓ |
| Creatinine clearance | | ✓ | ✓ | × |
| Haemoglobin | | ✓ | ✓ | × |

### MAIC results*

| | Must Have | Full |
|---|---|---|
| Original sample size | 80 | 80 |
| ESS, n (%) | 13.5 (17) | 10.4 (13) |
| HR naïve | 0.627 | 0.627 |
| HR weighted | 0.757 | 0.681 |

## Company

- Both MAICs exclude important factors
- MAIC ESS only 17% (n=13.5) and 13% (n=10.4) of the original sample size – too low to draw robust conclusions
- MAIC further adds to generalisability issues by adjusting the STORM Part 2 population to approximate MAMMOTH

See appendix – summary of chronology of ITC and OS

*Populations for the 'must have + nice to have' set could not be matched due to low ESS and therefore no results are available.
Abbreviations: ECOG, Eastern Cooperative Oncology Group; ESS, effective sample size; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; R-ISS, Revised International Staging System; SCT, stem cell transplant.

# Key issue 3: Indirect treatment comparison (2) – STC

## Company

- The company performed an STC to mitigate the loss of ESS in the MAICs
- Parametric survival models including all prognostic factors and effect modifiers in the 'Must have + Nice to have' covariate set were fit to the STORM Part 2 IPD
- Covariate values from the penta-refractory subgroup of MAMMOTH were inputted into the resulting survival model, and survival probabilities simulated from this model
- HR calculated between MAMMOTH KM data and the simulated Sd data
- Then, HR applied to Sd OS extrapolation to estimate SoC

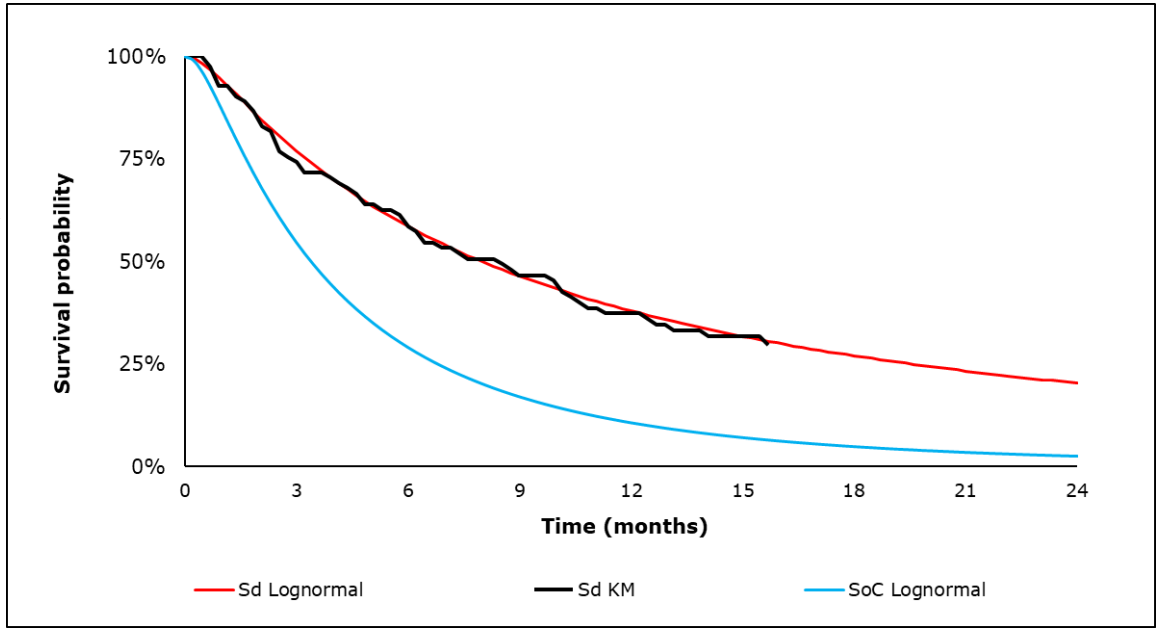
**HR calculated by each survival model**

| Distribution | HR | 95% CI | Mean (SD) |
|---|---|---|---|
| Exponential | 0.388 | 0.191 to 0.790 | 0.414 (0.153) |
| Weibull | 0.389 | 0.185 to 0.787 | 0.413 (0.154) |
| Lognormal | 0.433 | 0.229 to 0.795 | 0.455 (0.146) |
| Loglogistic | 0.420 | 0.208 to 0.789 | 0.442 (0.152) |
| Gompertz | 0.392 | 0.198 to 0.760 | 0.417 (0.151) |

See appendix – STC HRs

Abbreviations: CI, confidence interval; ESS, effective sample size; HR, hazard ratio; IPD, individual patient data; KM, Kaplan-Meier; MAIC, matching-adjusted indirect comparison; Sd, selinexor with dexamethasone; SD, standard deviation; SoC, standard of care; STC, simulated treatment comparison.

**Lognormal Sd extrapolation and SoC HR from the STC**



# Key issue 3: Indirect treatment comparison (3) – EAG concerns with the STC

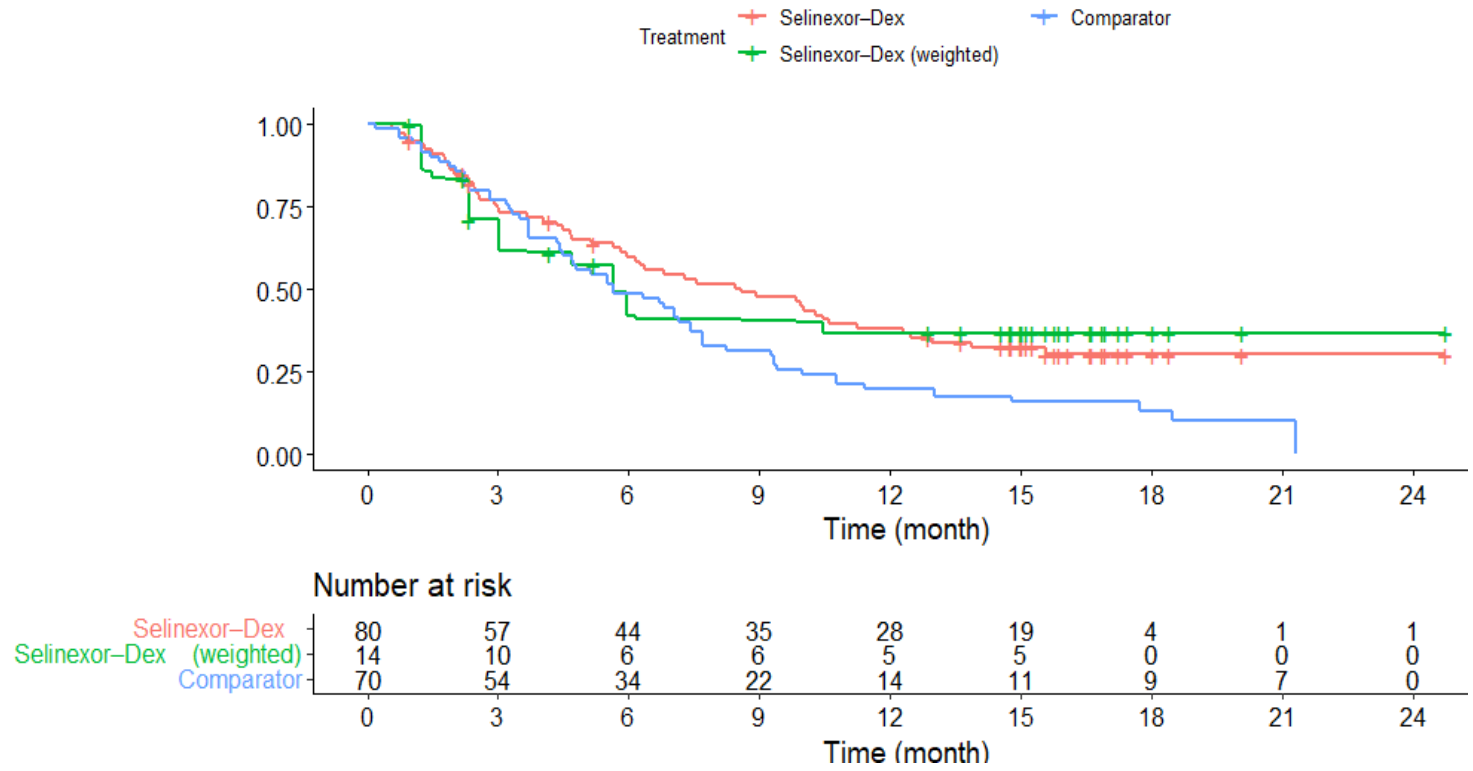
## EAG

Several concerns with the STC:

- Uncertainty in regression models mean HR estimate may change if study replicated
- Outcome regression may lack clinical plausibility
- No assessment of the overall model fit
- STC method assumes proportional hazards. Overlaps in the survival curves means that this is inappropriate:
  - Both naïve (~3.5 months) and 'full' MAIC (~7 months) Sd KM overlap with SoC
  - Overlaps occur early in the curves when number at risk and ESS are higher

EAG considers neither the MAIC or STC are robust for estimating comparative efficacy, but the 'full' MAIC is more reasonable

**Sd weighted by 'Full' MAIC**




## Company

- Does not agree that the initial overlapping curves are a meaningful representation of the treatment effect given the uncertainties and low ESS with the MAIC

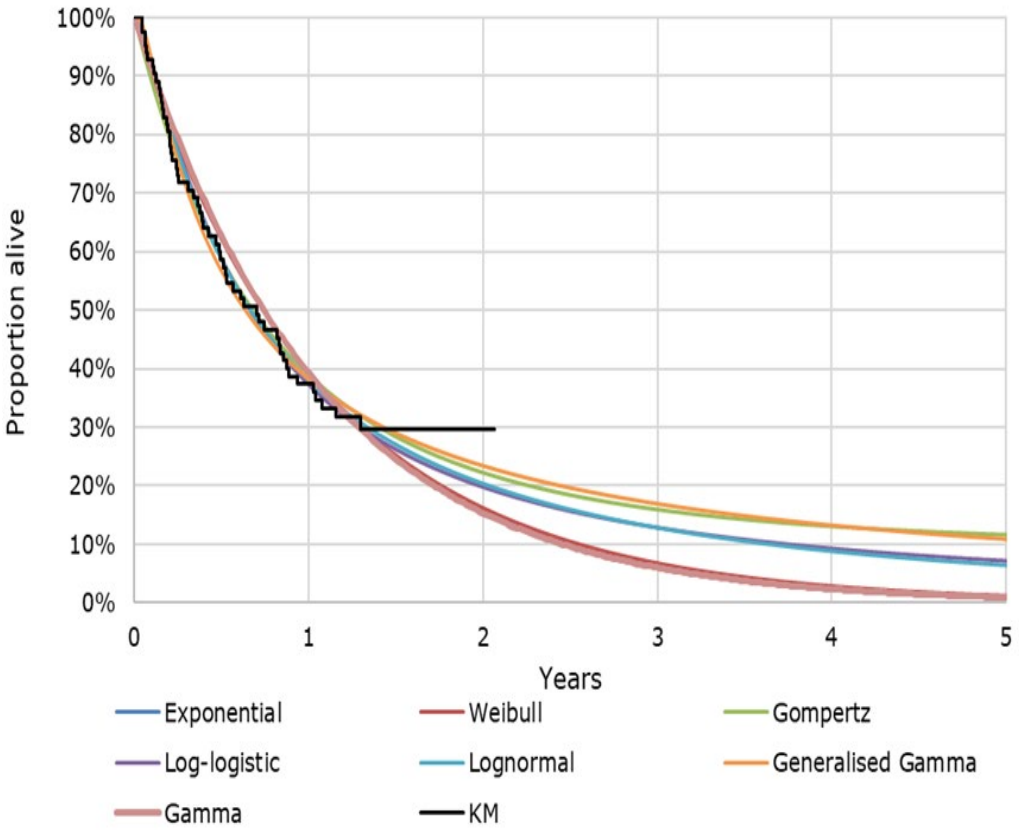
Abbreviations: EAG, external assessment group; ESS, effective sample size; HR, hazard ratio; KM, Kaplan-Meier; MAIC, matching-adjusted indirect comparison; Sd, selinexor with dexamethasone; STC, simulated treatment comparison.

# Key issue 3: Overall survival modelling (1)

See appendix – OS extrapolations

## Company

- Fit parametric survival curves to Sd KM data from STORM Part 2, selected lognormal based on clinical advice that around 5% of people treated with Sd expected to be alive at 5 years
- Applied HR of 0.43 derived from the STC to model the SoC curve




| Year | 5-year OS |
|---|---|
| **Exponential** | 0.94% |
| **Weibull** | 1.22% |
| **Gompertz** | 11.63% |
| **Log-logistic** | 7.17% |
| **Lognormal** | 6.43% |
| **Gen.Gamma** | 10.88% |
| **Gamma** | 0.89% |

| Year | Sd (lognorm) | SoC (HR) |
|---|---|---|
| **1** | 37.99% | 11.70% |
| **2** | 20.37% | 2.54% |
| **3** | 12.83% | 0.87% |
| **5** | 6.43% | 0.18% |
| **10** | 2.06% | 0.01% |
| **20** | 0.52% | 0.00% |

## EAG

- Clinical advice: expect all patients would die at 5 years; 6% alive unlikely given treatment duration in model is 2.5 months, and PFS is 3.83 months
- Exponential or Weibull curves provide better tail for this assumption, but worse fit to KM
- Inappropriate to apply HR to lognormal
- Requested company to fit piecewise model (company did this but it did not resolve uncertainty – see appendix)
- Prefers independent curve fitting to 'Full' MAIC-adjusted Sd and unadjusted SoC

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# Key issue 3: Overall survival modelling (2)

See appendix – OS extrapolations

**Company**

- At EAG request, fit independent curves to 'Full' MAIC-adjusted Sd KM and to the MAMMOTH SoC KM

**EAG**

- Chose Weibull curve for both arms – based on survival estimates and because the curves cross at 3.5 months, similar to naïve KM
- Notes that with this method, survival is likely overpredicted, therefore ICER estimate optimistic
- Additionally conducted a 'pessimistic' scenario analysis – Weibull to extrapolate Sd, no treatment effect until 7 months, MAIC "Full" HR for SoC extrapolation

**The EAG considers that there is unresolvable uncertainty in the overall survival modelling and therefore did not produce a base case ICER**

**Company**

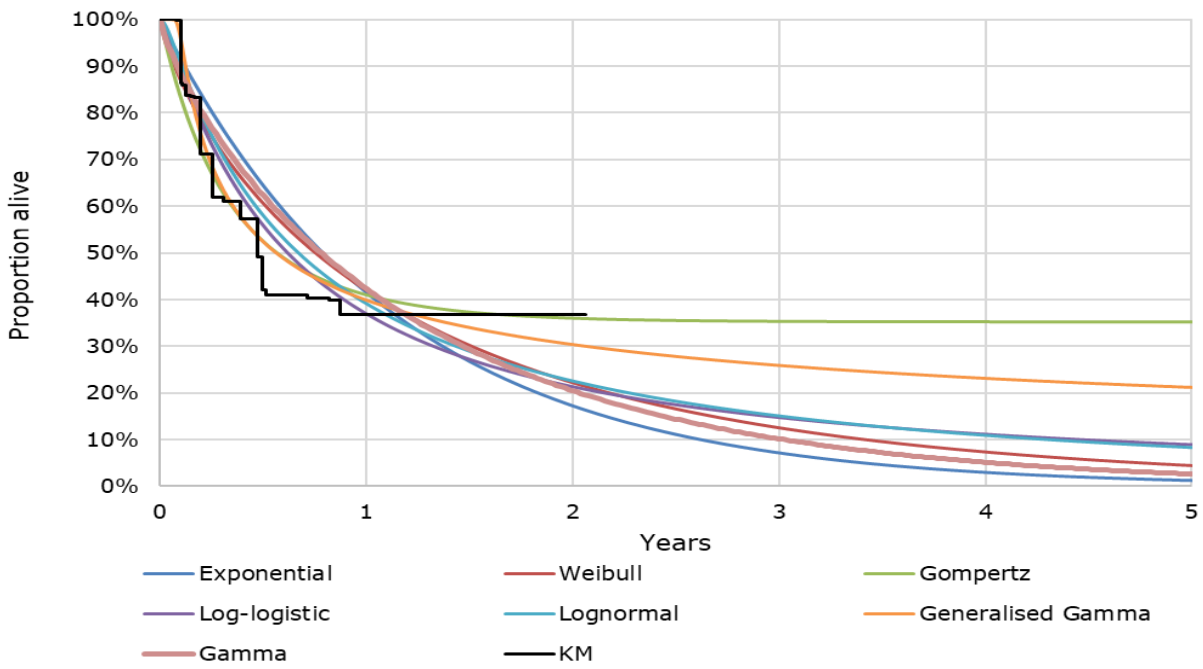
- Reiterate issues with using the 'Full' MAIC to estimate comparative efficacy – low ESS, important prognostic factors and effect modifiers are missing (such as prior SCT and duration of last therapy), and adds to generalisability issue by adjusting the STORM population to be more similar to MAMMOTH



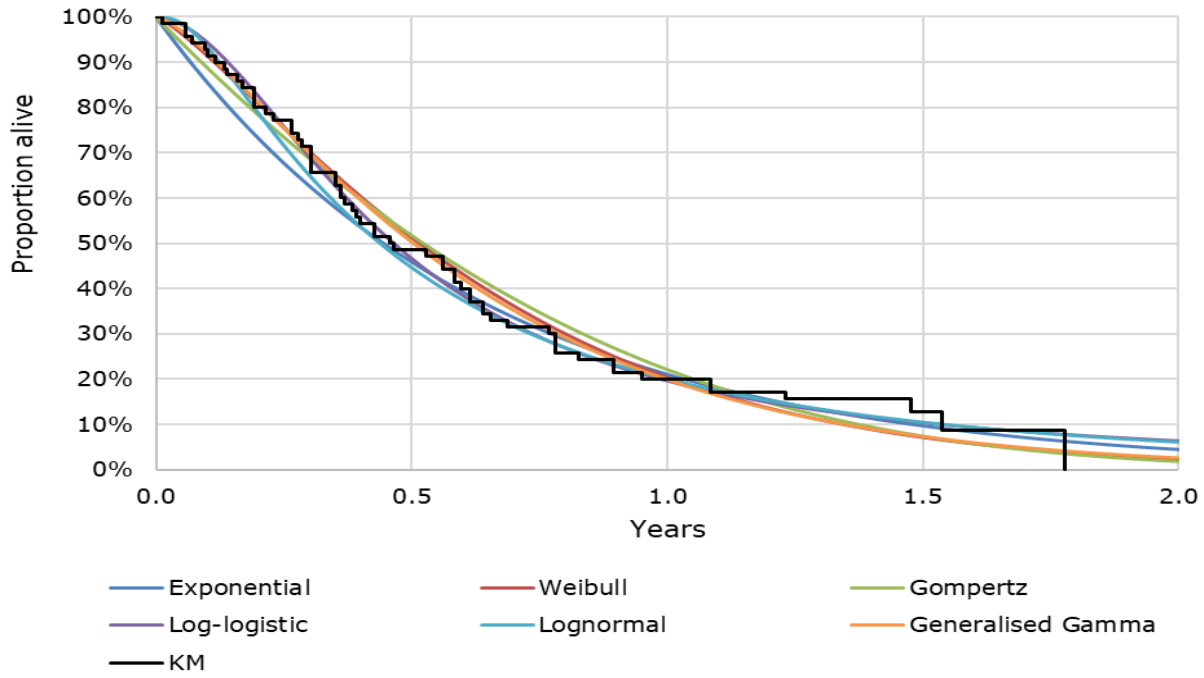
Abbreviations: EAG, external assessment group; ESS, effective sample size; HR, hazard ratio; KM, Kaplan-Meier; MAIC, matching-adjusted indirect comparison; OS, overall survival; Sd, selinexor with dexamethasone; STC, simulated treatment comparison; SoC, standard of care.

# Key issue 3: Overall survival modelling (3)

### Sd 'Full' MAIC OS extrapolation




### SoC unadjusted OS extrapolation



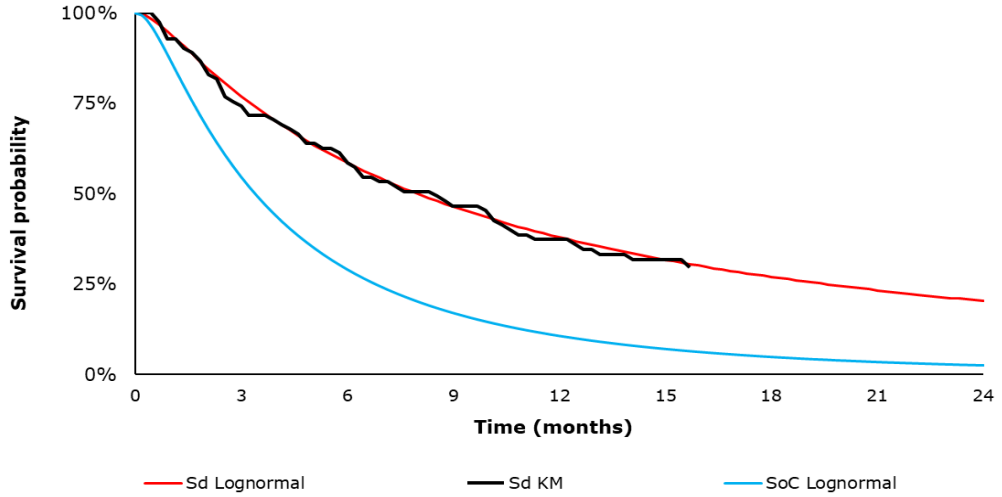

**Landmark survival estimates for independent curves**

| | STORM ('full' MAIC-adjusted) | | MAMMOTH (unadjusted) | |
|---|---|---|---|---|
| | 3-year OS | 5-year OS | 3-year OS | 5-year OS |
| Exponential | 7.15% | 1.21% | 0.93% | 0.04% |
| Weibull | 12.53% | 4.39% | 0.18% | 0.00% |
| Gompertz | 35.28% | 35.22% | 0.03% | 0.00% |
| Log-logistic | 14.73% | 8.88% | 3.14% | 1.25% |
| Log-normal | 15.08% | 8.26% | 2.49% | 0.65% |
| Generalised Gamma | 25.89% | 21.15% | 0.30% | 0.00% |
| Gamma | 10.15% | 2.55% | 0.32% | 0.00% |

# Key issue 3: Summary of approaches

## Company

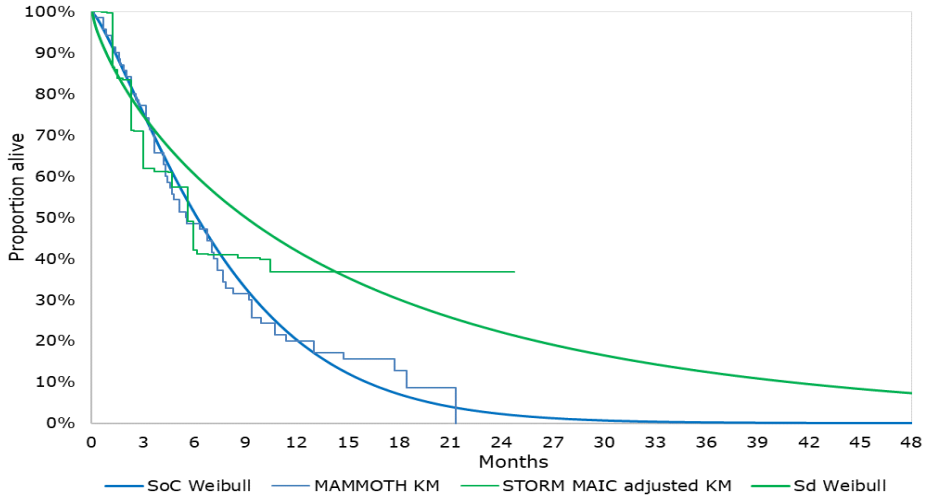
- STC to derive HR
- Lognormal fit to Sd KM, HR applied for SoC




| Year | Sd lognormal | SoC with STC HR |
|---|---|---|
| 1 | 37.99% | 11.70% |
| 2 | 20.37% | 2.54% |
| 3 | 12.83% | 0.87% |
| 5 | 6.43% | 0.18% |
| 10 | 2.06% | 0.01% |
| 20 | 0.52% | 0.00% |

## EAG

- ‘Full’ MAIC to adjust Sd KM
- Weibull fit to both adjusted Sd and SoC



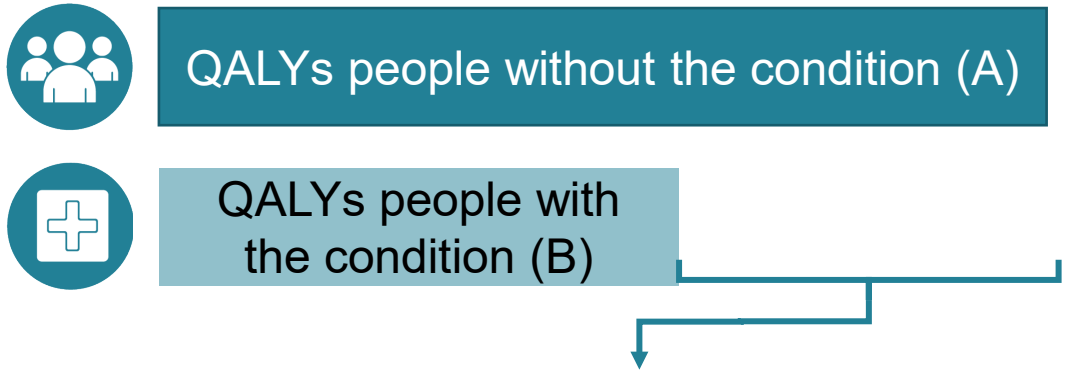

| Year | Sd (‘full’ MAIC) Weibull | SoC Weibull |
|---|---|---|
| 1 | 41.97% | 20.39% |
| 2 | 22.19% | 2.26% |
| 3 | 12.53% | 0.18% |
| 5 | 4.39% | 0.0% |
| 10 | 0.44% | 0.0% |
| 20 | 0.01% | 0.0% |

Which ITC method (STC or MAIC) is most appropriate for modelling relative treatment effect? Are the landmark estimations of survival with the chosen model clinically plausible?

Abbreviations: EAG, external assessment group; HR, hazard ratio; KM, Kaplan-Meier; MAIC, matching-adjusted indirect comparison; Sd, selinexor with dexamethasone; STC, simulated treatment comparison; SoC, standard of care.

# QALY weightings for severity (1)

**New severity modifier calculations and components:**




Health lost by people with the condition:

- Absolute shortfall: total = A – B
- Proportional shortfall: fraction = ( A – B ) / A
- *Note: The QALY weightings for severity are applied based on **whichever of absolute or proportional shortfall implies the greater severity**. If either the proportional or absolute QALY shortfall calculated falls on the cut-off between severity levels, the higher severity level will apply

| QALY weight | Absolute shortfall | Proportional shortfall |
|---|---|---|
| 1 | Less than 12 | Less than 0.85 |
| X 1.2 | 12 to 18 | 0.85 to 0.95 |
| X 1.7 | At least 18 | At least 0.95 |

Abbreviations: QALY, quality-adjusted life year.

# QALY weightings for severity (2)

**Background**

- Company calculated the QALY shortfall using the following assumptions:
  - Sex distribution: 61.5% male (STORM Part 2)
  - Starting age: 64.5 years (STORM Part 2)
  - Expected QALYs for general population: 11.14 (Schneider et al. 2021)
  - Discount rate: 3.5%

| | Expected total QALYs for the general population | Expected total QALYs that people living with the condition would be expected to have on SoC | Absolute QALY shortfall | Proportional QALY shortfall | Severity modifier |
|---|---|---|---|---|---|
| **Company base case** | 11.14 | [redacted] | [redacted] | [redacted] | 1.7 |
| **EAG scenarios 1–6** | 11.14 | [redacted] | [redacted] | [redacted] | 1.7 |
| **EAG scenarios 1–6 + starting age of 72*** | 8.24 | [redacted] | [redacted] | [redacted] | 1.2 |

Which severity modifier should be applied?

*Average age of stem cell transplant ineligible patients in the STORM trial
Abbreviations: QALY, quality-adjusted life year; SoC, standard of care.

# Company base case results

## Deterministic incremental base case results

| Technology | Total costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER (£/QALY) | ICER (£/QALY) severity modifier (1.7) applied |
|---|---|---|---|---|---|---|
| Sd | [redacted] | [redacted] | - | - | - | - |
| SoC | [redacted] | [redacted] | [redacted] | [redacted] | £39,285 | £23,109 |

## Probabilistic incremental base case results

| Technology | Total costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER (£/QALY) | ICER (£/QALY) severity modifier (1.7) applied |
|---|---|---|---|---|---|---|
| Sd | [redacted] | [redacted] | - | - | - | - |
| SoC | [redacted] | [redacted] | [redacted] | [redacted] | £40,816 | £24,009 |

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Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; Sd, selinexor with dexamethasone; SoC, standard of care.

# Company deterministic scenario analysis

| No. | Scenario (applied to company base case) | Incremental costs (£) versus SoC | Incremental QALYs versus SoC | ICER (£/QALY) versus SoC (1.7 severity modifier) |
|---|---|---|---|---|
| **1** | **Company base case** | [redacted] | [redacted] | £23,109 |
| **2** | SoC OS HR: MAMMOTH MAIC (full) | [redacted] | [redacted] | £36,454 |
| **3** | OS extrapolation: Weibull | [redacted] | [redacted] | £35,824 |
| | OS extrapolation: Exponential | [redacted] | [redacted] | £37,221 |
| | OS extrapolation: Gen. Gamma | [redacted] | [redacted] | £15,951 |
| | OS extrapolation: Log Logistic | [redacted] | [redacted] | £20,923 |
| | OS extrapolation: Gompertz | [redacted] | [redacted] | £13,039 |
| | OS extrapolation: Gamma | [redacted] | [redacted] | £37,402 |
| **4** | Flexible modelling*: Piecewise curves, Lognormal from baseline, Weibull from 63 weeks, STC HR to extrapolate SoC | [redacted] | [redacted] | £35,823 |

*see appendix – flexible piecewise modelling

Abbreviations: HR, hazard ratio; ICER, incremental cost-effectiveness ratio; MAIC, matching-adjusted indirect comparison; OS, overall survival; QALY, quality-adjusted life year; Sd, selinexor with dexamethasone; SoC, standard of care; STC, simulated treatment comparison

# EAG additional scenario analysis

**The EAG did not produce a base case due to OS modelling uncertainty**

| No. | Scenario | Incremental costs (£) versus SoC | Incremental QALYs versus SoC | ICER (£/QALY) versus SoC (1.7 severity modifier) |
|---|---|---|---|---|
| | **Company base case** | [redacted] | [redacted] | £23,109 |
| 1 | Resource use assumptions | [redacted] | [redacted] | £23,471 |
| 2 | Admin cost for oral chemotherapy | [redacted] | [redacted] | £23,409 |
| 3 | Cyclophosphamide 500mg dose | [redacted] | [redacted] | £23,145 |
| 4 | Updated adverse event costs | [redacted] | [redacted] | £22,088 |
| 5 | PSSRU end of life care cost | [redacted] | [redacted] | £22,840 |
| 6 | OS illustrative example* | [redacted] | [redacted] | £73,469 |
| 7 | Independent curves fit to Sd + SoC | [redacted] | [redacted] | £33,122 |
| | EAG scenarios 1–5, probabilistic | [redacted] | [redacted] | £22,929 |
| | **EAG scenarios 1–5+7, probabilistic (optimistic)** | [redacted] | [redacted] | **£31,701** |
| | **EAG scenarios 1–6, probabilistic (pessimistic)** | [redacted] | [redacted] | **£73,206** |

*Weibull to extrapolate Sd, no treatment effect until 7 months (by visual inspection, the MAIC KM curves overlap for the first 7 months), MAIC "Full" HR for SoC extrapolation

Abbreviations: EAG, external assessment group; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; MAIC, matching-adjusted indirect comparison; OS, overall survival; PSSRU, Personal Social Services Research Unit; QALY, quality-adjusted life year; SoC, standard of care.

# Selinexor with dexamethasone for treating relapsed or refractory multiple myeloma after four or more treatments

- ❑ Background and key issues
- ❑ Decision problem
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ✓ **Summary**

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# Key issues

| Key issues | Resolved? | ICER impact |
|---|---|---|
| 1. Omission of clinical and cost-effectiveness analyses for PanoVd | No | **Unknown** |
| 2. Generalisability of the clinical data to the population eligible for Sd in clinical practice in England | No | **Unknown** |
| 3. Uncertainty in the results of the company ITC of Sd versus SoC and subsequent overall survival modelling | No | **Large** |

Abbreviations: ITC, indirect treatment comparison; PanoVd, panobinostat with bortezomib and dexamethasone; Sd, selinexor with dexamethasone; SoC, standard of care.

# Committee decision making slide

## What are the committee's preferred assumptions?

| Assumption | Question for committee |
|---|---|
| **Comparator choice** | Is PanoVd a relevant comparator? |
| **Clinical evidence** | At what age would the committee expect patients to be eligible for selinexor?<br>What proportion of patients would the committee expect to have had SCT? |
| | Does committee accept the clinical evidence in light of the generalisability issues? |
| **ITC and OS modelling** | Which ITC method (STC or MAIC) is most appropriate for modelling relative treatment effect?<br>Are the landmark estimations of survival with the chosen model clinically plausible? |
| **Other issues** | Should the EAG's additional scenarios be included? If so, which scenarios? |
| **Severity/threshold modifiers** | Which severity modifier should be applied?<br>Are there any benefits of selinexor which are not captured in the QALY calculations? |
| **ICER threshold** | What is the committee's preferred ICER threshold? |
| **Preferred ICER** | What is the committee's preferred ICER? |

Abbreviations: EAG, external assessment group; ICER, incremental cost-effectiveness ratio; ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparison; OS, overall survival; PanoVd, panobinostat with bortezomib and dexamethasone; QALY, quality-adjusted life year; SCT, stem-cell transplant; Sd, selinexor with dexamethasone; STC, simulated treatment comparison.

# Selinexor with dexamethasone for treating relapsed or refractory multiple myeloma after four or more treatments

# Supplementary appendix

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# Patient perspectives

## Substantial unmet need for people with MM on 5L+ treatment

**Submission from Myeloma UK**

Myeloma is a highly individual and complex cancer with no cure

People with relapsed/refractory disease experience a more significant disease burden due to the progressive nature of the disease and the cumulative effects of treatment

Limited treatment options at 5L+ cause worry for people with myeloma, their carers and family members

Treatments which can be taken at home are seen as an advantage, especially for people who live further away from the hospital

People with relapsed/refractory MM would welcome a new treatment with a novel mechanism of action

*"Myeloma has had a major impact on my quality of life. No day is the same as you can wake up and find you are in chronic pain and unable to do anything for yourself and have to rely on your carers."*

*"My consultant told me I was on the last thing... Hopefully there's a couple of other treatments in the pipeline."*

*"Tablet form or even injections you can take at home are hugely preferable. Getting to the hospital is an absolute nightmare."*



Abbreviations: 5L, fifth-line; MM, multiple myeloma.

Link back to patient and clinical perspectives

# Clinical perspectives

## Selinexor would easily fit into the care pathway for MM

**Submission from UK Myeloma Society (formerly UK Myeloma Forum)**

Representing physicians, nursing staff and healthcare professionals

Treatment of myeloma aims to control symptoms and prolong life

A partial response (PR), very good partial response (VGPR), or complete response (CR) are generally considered clinically significant treatment outcomes. This depth of response is associated with length of response

Though most patients respond to therapies early on, only a minority of patients will respond from 5L+

Only limited treatments available at 5L+, including:

- Pomalidomide with dexamethasone (PomDex, TA427)
- Panobinostat with bortezomib and dexamethasone (PanoBorDex, PanoVd, TA380)
- Best supportive care

*"Limited options available to clinicians to treat patients at 5L+. Other than PomDex and PanoBorDex, the only option would be access to clinical trials."*

*"Selinexor is an oral therapy with manageable toxicities. It would easily fit into the current treatment algorithm and would be easily delivered."*

NICE

Abbreviations: 5L, fifth-line; MM, multiple myeloma.

Link back to patient and clinical perspectives

# Summary of comparators in scope

| Comparators in NICE scope | Company considerations | |
|---|---|---|
| | ***Relevant?*** | ***Rationale*** |
| Pomalidomide with dexamethasone (PomDex) | No | • Would not be used for patients refractory to IMiDs |
| Panobinostat with bortezomib and dexamethasone (PanoVd) | No | • Limited use<br>• Would not be used for patients refractory to PIs |
| Belantamab mafodotin (subject to NICE appraisal) | No | • NICE draft guidance – not recommended |
| Conventional chemotherapy regimens | No | • Limited use<br>• Would class under BSC |
| Best supportive care (BSC) | Yes | • Most appropriate comparator |

Link back to Key issue 1: Omission of PanoVd

Abbreviations: BSC, best supportive care; IMiD, immunomodulatory imide drug; PI, proteasome inhibitor; PanoVd, panobinostat with bortezomib and dexamethasone; PomDex, pomalidomide with dexamethasone.

# How company incorporated evidence into model

## Input and evidence sources

| Input | Assumption and evidence source |
|---|---|
| **Baseline characteristics** | STORM Part 2 BCPLD-refractory subpopulation |
| **Intervention efficacy** | Log-normal distribution fit to STORM Part 2 BCPLD-refractory subpopulation |
| **Comparator efficacy** | HR estimated from the STC |
| **Utilities** | FACT-G utilities from STORM mapped to the EQ-5D-3L |
| **Adverse events** | STORM Part 2 |
| **Costs** | Selinexor acquisition – PAS price; dexamethasone – eMIT; SoC costs (cyclophosphamide) – eMIT; disease management – NHS Reference Costs 2021/22; adverse events – NHS Reference Costs 2021/22; End of life costs – literature source (Round et al. 2015) |
| **Resource use** | Physician visits, blood count tests and biochemistry tests – differing between PFS and PD, based on TA897 |

Link back to company's model overview

Abbreviations: BCPLD, bortezomib, carfilzomib, lenalidomide, pomalidomide, and daratumumab; eMIT, electronic market information tool; EQ-5D, EuroQoL 5-dimensions; FACT-G, Functional Assessment of Cancer Therapy – General; HR, hazard ratio; PD, progressed disease; PFS, progression-free survival; SoC, standard of care; STC, simulated treatment comparison.

# Summary of chronology of ITC and OS modelling

**Indirect treatment comparison**

**OS modelling**

| Conduct MAICs | Conduct STC | Apply STC HR to Sd KM | Fit flexible curves | Fit independent curves |
|---|---|---|---|---|
| Company conducted 3 MAICs (based on various prognostic factors and effect modifiers)<br>Company chose to not use due to low ESS | To mitigate loss of ESS, company conducted STC to generate HRs<br>EAG note several concerns with STC, requested independent curves fit to MAIC | Company fit parametric survival curves to Sd KM data, used STC HR for SoC<br>EAG clinical advice suggests survival is unrealistic. Note poor fit of curves, proportional hazards violation, and request piecewise fitting | At EAG request, company fit flexible curves<br>EAG concerned company did not fit flexible curves correctly, acknowledge that complex curves may not be appropriate due to lack of data. Preferred MAIC to STC | At EAG request, company fit independent curves to MAIC-adjusted Sd and unadjusted SoC<br>EAG selected distribution based on survival estimates, AIC/BIC, and curves crossing point |



Link back to indirect treatment comparison – MAIC

# STC HRs

**Key:** Chosen distribution

**HR calculated by each survival model**

| Distribution | HR | 95% CI | Mean (SD) |
|---|---|---|---|
| Exponential | 0.388 | 0.191 to 0.790 | 0.414 (0.153) |
| Weibull | 0.389 | 0.185 to 0.787 | 0.413 (0.154) |
| Lognormal | 0.433 | 0.229 to 0.795 | 0.455 (0.146) |
| Loglogistic | 0.420 | 0.208 to 0.789 | 0.442 (0.152) |
| Gompertz | 0.392 | 0.198 to 0.760 | 0.417 (0.151) |

**AIC/BIC ranking of each STC survival model**

| Distribution | AIC | BIC | AIC+BIC | Ranking |
|---|---|---|---|---|
| Lognormal | 368.99 | 395.05 | 764.04 | 1 |
| Exponential | 371.53 | 395.23 | 766.76 | 2 |
| Loglogistic | 371.11 | 397.17 | 768.28 | 3 |
| Weibull | 372.87 | 398.93 | 771.80 | 4 |
| Gompertz | 373.38 | 399.44 | 772.82 | 5 |

Link back to indirect treatment comparison – STC

# OS extrapolations

**Key:** Chosen distribution

Link back to overall survival modelling 1 and 2

## AIC/BIC statistics for each model fit to naïve Sd KM

| Function | AIC | BIC |
|---|---|---|
| Exponential | 385.39 | 387.81 |
| Weibull | 387.30 | 392.14 |
| Gompertz | 385.23 | 390.07 |
| Log-logistic | 382.97 | 387.81 |
| Lognormal | 380.84 | 385.68 |
| Gen. gamma | 381.77 | 389.03 |
| Gamma | 387.39 | 392.22 |

## Landmark survival estimates for naïve Sd extrapolations

| Year | Exponential | Weibull | Gompertz | Log-logistic | Lognormal | Gen. Gamma | Gamma |
|---|---|---|---|---|---|---|---|
| 1 | 39.30% | 39.40% | 38.96% | 37.26% | 37.99% | 38.21% | 39.27% |
| 2 | 15.44% | 16.21% | 22.25% | 19.79% | 20.37% | 23.41% | 15.34% |
| 5 | 0.94% | 1.22% | 11.63% | 7.17% | 6.43% | 10.88% | 0.89% |
| 10 | 0.01% | 0.02% | 9.91% | 3.11% | 2.06% | 5.69% | 0.01% |
| 20 | 0.00% | 0.00% | 9.79% | 1.32% | 0.52% | 2.84% | 0.00% |
| 30 | 0.00% | 0.00% | 9.79% | 0.79% | 0.21% | 1.87% | 0.00% |

## AIC/BIC statistics and 3-year survival for MAIC-adjusted Sd and unadjusted SoC

| | STORM ('full' MAIC-adjusted) | | | MAMMOTH (unadjusted) | | |
|---|---|---|---|---|---|---|
| | AIC | BIC | 3-year OS | AIC | BIC | 3-year OS |
| Exponential | 66.8 | 71.5 | 7.15% | 424.1 | 428.6 | 0.93% |
| Weibull | 65.5 | 67.9 | 12.53% | 427.3 | 429.6 | 0.18% |
| Gompertz | 63.5 | 68.3 | 35.28% | 425.2 | 429.7 | 0.03% |
| Log-logistic | 64.8 | 69.6 | 14.73% | 430.0 | 434.5 | 3.14% |
| Log-normal | 64.1 | 68.9 | 15.08% | 431.8 | 436.3 | 2.49% |
| Gen. Gamma | 61.3 | 68.5 | 25.89% | 425.9 | 432.6 | 0.30% |
| Gamma | 67.2 | 71.9 | 10.15% | 423.9 | 428.4 | 0.32% |

# Flexible piecewise modelling

Link back to overall survival modelling 1

## Company

- As a scenario, fit flexible piecewise modelling approach
- Lognormal curve from baseline; then Weibull curve at user-specified point (week 63 selected – point where Lognormal and Weibull curves cross); HR from the STC used to estimate SoC survival
- Produces results similar to applying Weibull curve throughout

| Year | Company base case | | Flexible modelling approach | |
|---|---|---|---|---|
| | Sd survival | SoC survival | Sd survival | SoC survival |
| 1 | 37.99% | 11.70% | 37.99% | 10.70% |
| 2 | 20.37% | 2.54% | 16.21% | 1.50% |
| 3 | 12.83% | 0.87% | 1.22% | 0.00% |
| 5 | 6.43% | 0.18% | 0.02% | 0.00% |
| 10 | 2.06% | 0.01% | 0.00% | 0.00% |
| 20 | 0.52% | 0.00% | 0.00% | 0.00% |

## EAG

- Piecewise approach leads to estimates of survival for Sd more like the EAG clinical experts' opinions
- Concerned that company did not do piecewise modelling according to NICE DSU 21 → parametric curves fit to each piece of the KM; choice of the cut point determined by evaluating the underlying hazards
- Acknowledge that complex curve fitting may not be appropriate due to lack of data

Abbreviations: DSU, decision support unit; EAG, external assessment group; HR, hazard ratio; KM, Kaplan-Meier; Sd, selinexor with dexamethasone; STC, simulated treatment comparison; SoC, standard of care.