Isatuximab with pomalidomide and dexamethasone for treating relapsed and refractory multiple myeloma [Review of TA658] [ID4067]

For Zoom [noACIC]
Version: Final 140324

March 14th 2024

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External assessment group: Sheffield Centre for Health and Related Research (SCHARR)

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Company: Sanofi

Isatuximab with pomalidomide and dexamethasone for treating relapsed and refractory multiple myeloma

- ✓ **Recap from ACM1**
- ❑ Consultation comments
- ❑ Company response and EAG critique
- ❑ Other considerations
- ❑ Summary

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Draft guidance: preliminary recommendation

ISA+POM+DEX was not recommended, within its marketing authorisation, for treating relapsed and refractory multiple myeloma in adults who have had LEN and a proteasome inhibitor, and whose disease has progressed on their last treatment.

Reason the committee made this decision:

The cost-effectiveness estimates are higher than what NICE considers an acceptable use of NHS resources, even when considering the condition's severity and effect on quality and length of life.

The economic evidence for ISA+POM+DEX is uncertain because there are uncertainties around how well it works in the long-term and some of the assumptions used to estimate its cost effectiveness

Consultation responses received from:
The company (Sanofi), Myeloma UK, UK Myeloma Society and 1 web comment

NICE

Abbreviations: DEX, Dexamethasone; ISA, Isatuximab; LEN, Lenalidomide; POM, Pomalidomide;

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Isatuximab (SARCLISA, Sanofi)

Marketing authorisation	• Isatuximab is indicated in combination with pomalidomide and dexamethasone, for the treatment of adult patients with RRMM who have received at least 2 prior therapies including lenalidomide and a proteasome inhibitor (PI) and have demonstrated disease progression on the last therapy • **Population considered in this CDF review** • Adults with RRMM who have had 3 prior therapies, including lenalidomide and a PI, and whose disease progressed on the last therapy (4th line treatment)
Mechanism of action	• Isatuximab is an IgG1-derived humanised monoclonal antibody, which binds to a specific extracellular epitope of cell surface glycoprotein CD38 that is highly expressed on myeloma cells
Administration	• 10 mg/kg IV infusion, weekly for 4 weeks (cycle 1: days 1, 8, 15, and 22), then every 2 weeks for cycle 2 and beyond (days 1, 15) • IV infusion costs: IV first dose: £258.56, IV subsequent doses £438.38
Price	• Isatuximab list price: • £506.94 (100 mg vial), £2,534.69 (500 mg vial) • A confidential PAS discount has been agreed

Abbreviations: CDF, Cancer Drugs Fund; PAS, Patient Access Scheme; PI, proteasome inhibitor; RRMM, Relapsed and refractory multiple myeloma;

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Consultation responses to draft guidance (1/2)

Consultation response: Myeloma UK (patient group)

- ISA+POM+DEX is a well-used and well-tolerated treatment a negative recommendation would have a significant impact on patient outcomes
- The committee should use any flexibility they have when evaluating the future cost of POM and determining the decision-making ICER threshold

Commented on the committee's assumptions relating to:

- The comparison with POM+DEX
- Modelling OS for DARA using SACT data
- Preferred utility values

Concerned that the committee did not fully consider:

- The heterogeneity of myeloma and the complex and evolving nature of the myeloma treatment pathway when evaluating the unmet need
- The significant benefit of receiving 1 treatment with a long PFS rather than sequential treatments
- The significant benefit of receiving a triplet rather than a doublet or a monotherapy

Abbreviations: DARA, Daratumumab; DEX, Dexamethasone; ICER, Incremental cost effectiveness ratio; ISA, Isatuximab; OS, Overall survival; PFS, Progression-free survival; POM, Pomalidomide; SACT, Systemic anti-cancer treatment;

Consultation responses to draft guidance (2/2)

Consultation response: UK Myeloma Society (professional group)

- ISA+POM+DEX provides improved clinical outcomes and is received by most patients at 4th line
  ↳ Patients and clinicians would be concerned if it was not recommended
- Both POM+DEX and DARA are comparators but in clinical practice most people receive POM+DEX as it is more effective than DARA at 4th line.
- The SACT data that has been presented does not reflect clinical experience
  ↳ It under-estimates OS for POM+DEX and over-estimates OS for DARA, due to sequential application

Commented on the committee's assumptions relating to:

- Waning of relative effect
- Preferred utility values

Consultation response: Web comment

- A negative recommendation would be concerning for patients and clinicians as the alternative would be less clinically effective therapies
- All relevant evidences has been considered

Abbreviations: DARA, Daratumumab; DEX, Dexamethasone; ISA, Isatuximab; OS, Overall survival; PFS, Progression-free survival; POM, Pomalidomide; SACT, Systemic anti-cancer treatment;

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Company response overview re key issues at ACM1 (1/3)

Key Issue	Committee conclusion	Company base case at ACM1	Company draft guidance response
Efficacy data ISA+POM+DEX vs POM+DEX	• Agreed with EAG's concerns about the naive comparison • Data from ICARIA-MM more appropriate • OS data should be adjusted for subsequent treatments not used in NHS, such as DARA and CARF • Requested analyses that explored: ↳ Applying the relative effect from ICARIA-MM to the SACT data ↳ Waning of treatment effect	• SACT data (naïve comparison)	• **Base case unchanged** **Scenario analysis** • Used TSE method to adjust for subsequent treatments and applied the relative effect from ICARIA-MM to SACT data • Used HRs from the adjusted ICARIA-MM OS applied to the SACT ISA+POM+DEX OS curve to generate a "time-varying HR simulated POM+DEX SACT OS curve"
Efficacy data ISA+POM+DEX vs DARA	• In the absence of additional data, a naive comparison provided the best estimates of relative effectiveness ↳ Result would be associated with high uncertainty	• SACT data (naïve comparison)	• **Base case unchanged** • DARA is less relevant than POM+DEX due to limited use

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Abbreviations: CARF, Carfilzomib; DARA, Daratumumab; DEX, Dexamethasone; EAG, External assessment group; ISA, Isatuximab; OS, Overall survival; POM, Pomalidomide; SACT, Systemic anti-cancer treatment; TSE, Two-stage estimation;

Company response overview re key issues at ACM1 (2/3)

Key Issue	Committee conclusion	Company base case at ACM1	Company draft guidance response
OS using ICARIA-MM: ISA+POM+DEX and POM+DEX	• EAG's extrapolation using independent log-normal distributions was most appropriate, adjusted so risk of death with ISA+POM+DEX was never higher than for POM+DEX	• Restricted log-normal distribution - both arms of the trial	• **Was not discussed**
PFS using ICARIA-MM: ISA+POM+DEX and POM+DEX	• Both RCS Weibull (company) and independently fitted log-normal distributions (EAG) were plausible	• RCS Weibull distribution	• **Was not discussed**
OS using SACT : ISA+POM+DEX	• EAG's RCS Weibull 3-knot extrapolation approach was most appropriate	• Log-normal distribution	• **Base case unchanged**
OS using SACT : DARA	• EAG's RCS log-normal 2-knot distribution approach was most appropriate	• Weibull distribution	• **Base case unchanged**

Abbreviations: Abbreviations: DARA, Daratumumab; DEX, Dexamethasone; EAG, External assessment group; ISA, Isatuximab; POM, Pomalidomide; RCS, Restricted cubic spline; SACT, Systemic anti-cancer treatment;

Company response overview re key issues at ACM1 (3/3)

Key Issue	Committee conclusion	Company base case at ACM1	Company draft guidance response
Utility values - differential utility values for ISA+POM+DEX and POM+DEX	• Not convinced that people who are progression-free and on ISA+POM+DEX would have a higher utility than people on POM+DEX	• Higher utility for people who are progression-free and on ISA+POM+DEX	• **Base case unchanged**
Costing of subsequent therapies	• Cost of subsequent treatments should be aligned with the source of the clinical evidence	• Used SACT data as the source of clinical evidence and SACT data to calculate the cost of subsequent therapies	• **Was not discussed**
Subcutaneous injection administration costs	• Company's administration cost assumptions were broadly appropriate	• Assumed that the cost per administration of DARA was £281.11	• **Base case unchanged – no further discussion required**

Abbreviations: DARA, Daratumumab; DEX, Dexamethasone; ISA, Isatuximab; POM, Pomalidomide; SACT, Systemic anti-cancer treatment;

Company response: adjusted analyses from ICARIA-MM (1/3)

Background

- Committee requested that the relative effect from ICARIA-MM be adjusted to account for non-NHS subsequent treatments

Company:

- Adjusted analyses introduce additional uncertainty and require strong assumptions
- Analyses provided using IPCW and TSE methods to adjust OS in ICARIA-MM for both arms
  - ↳ Analysis presented adjusting for post progression DARA only or post progression DARA and CARF
- IPCW analysis lacked clinical validity, was highly uncertain and did not reach statistical significance
  - ↳ IPCW method can become less stable when using a small data set and can be unsuitable if key predictors of treatment switching were not collected
- Factors such as if DARA or CARF was given alone or in a combination could not be accounted for
- TSE analysis provided more plausible results, so scenarios presented that:
  - ↳ Use log-normal curves fitted independently to both TSE adjusted treatment arms
  - ↳ Use TSE adjusted HRs applied directly to the ISA+POM+DEX SACT arm to derive a POM+DEX arm

EAG

- Agrees with company that results from the IPCW analysis lack face validity
- TSE analysis lacks face validity → survival increased when CARF was removed as well as DARA

Abbreviations: CARF, Carfilzomib; DARA, Daratumumab; DEX, Dexamethasone; HR, Hazard ratio; IPCW, Inverse probability of censoring weights; ISA, Isatuximab; OS, Overall survival; POM, Pomalidomide; SACT, Systemic anti-cancer treatment; TSE, Two-stage estimation;

Company response: adjusted analyses from ICARIA-MM (2/3)

Table: Overall survival estimates for ISA+POM+DEX vs. POM+DEX: adjustment methods for removing impact of subsequent treatments not available in NHS

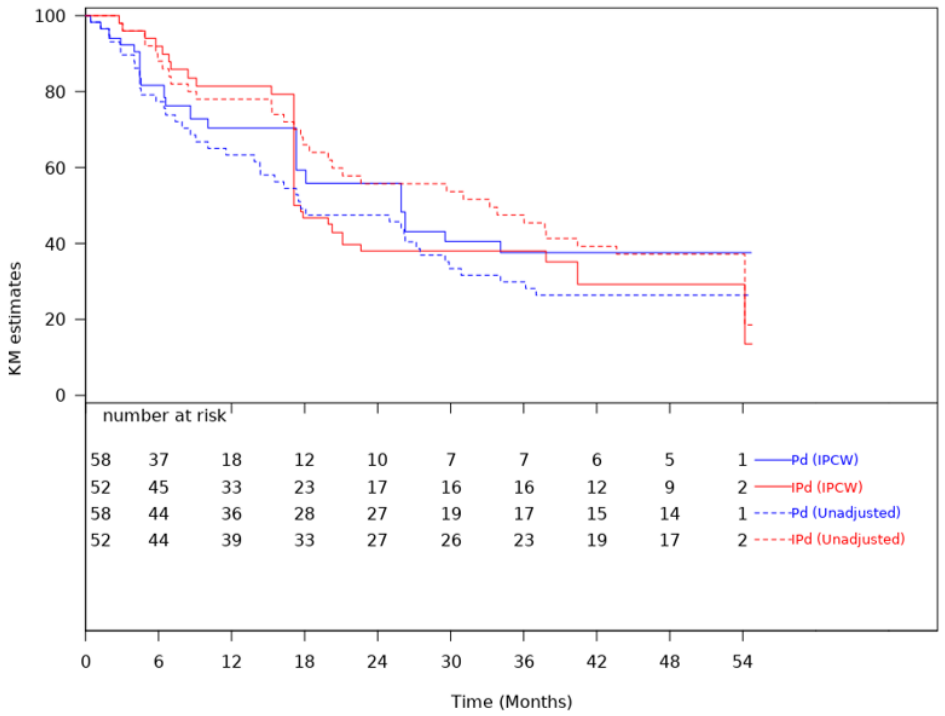
Cohort	Treatment arm	Median OS (months), [95% CI]	HR [95% CI]	p value
Unadjusted 4L OS	ISA+POM+DEX	33.3 [18.4; 54.3]	0.657 [0.409; 1.055]	0.08
	POM+DEX	17.7 [11.6; 27.5]		
IPCW adjusted – DARA only	ISA+POM+DEX	37.8 [21.1; NC]	0.567 [0.326; 0.987]	0.0447
	POM+DEX	17.3 [11.5; 37.0]		
IPCW adjusted – DARA or CARF	ISA+POM+DEX	17.7 [17.7; NC]	0.960 [0.537; 1.716]	0.8899
	POM+DEX	25.9 [17.3; NC]		
TSE adjusted – DARA only	ISA+POM+DEX	22.7 [17.9; NC]	0.618 [0.378; 1.009]	0.055
	POM+DEX	13.9 [8.2; 26.0]		
TSE adjusted – DARA or CARF	ISA+POM+DEX	25.18 [19.89; NC]	0.613 [0.372; 1.010]	0.055
	POM+DEX	15.76 [8.59; 26.0]		

Abbreviations: CARF, Carfilzomib; DARA, Daratumumab; DEX, Dexamethasone; HR, Hazard ratio; IPCW, Inverse probability of censoring weights; ISA, Isatuximab; OS, Overall survival; POM, Pomalidomide; TSE, Two-stage estimation;

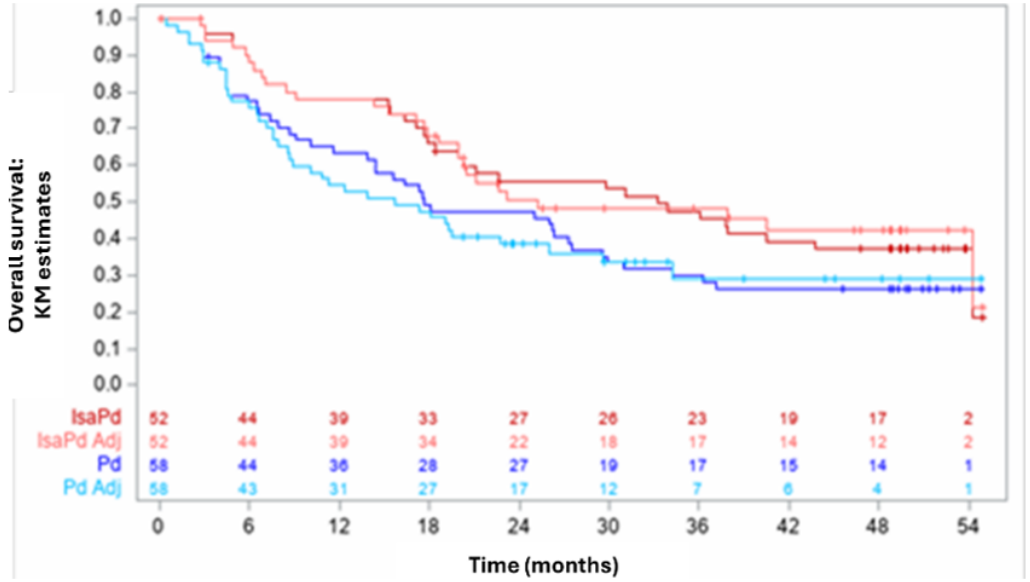
Company response: adjusted analyses from ICARIA-MM (3/3)

Figure: Kaplan Meier OS for ISA+POM+DEX and POM+DEX for scenario assuming no use of DARA or CARF post-progression

IPCW adjustment for subsequent therapy with daratumumab or carfilzomib – Adjusted vs unadjusted KM



TSE adjustment for subsequent therapy with daratumumab or carfilzomib – Adjusted vs unadjusted KM



Do the adjusted results represent a better estimate of relative effect than the unadjusted ICARIA-MM data?

Abbreviations: CARF, Carfilzomib; DARA, Daratumumab; DEX, Dexamethasone; IPCW, Inverse probability of censoring weights; ISA, Isatuximab; KM, Kaplan-Meier; POM, Pomalidomide; TSE, Two-stage estimation;

Company response: Efficacy data for POM+DEX comparison (1/3)

Background

- Committee requested analyses that apply the relative effect from ICARIA-MM to the absolute event rates from SACT data for ISA+POM+DEX. Requested for OS and PFS using time on treatment as a proxy

Company

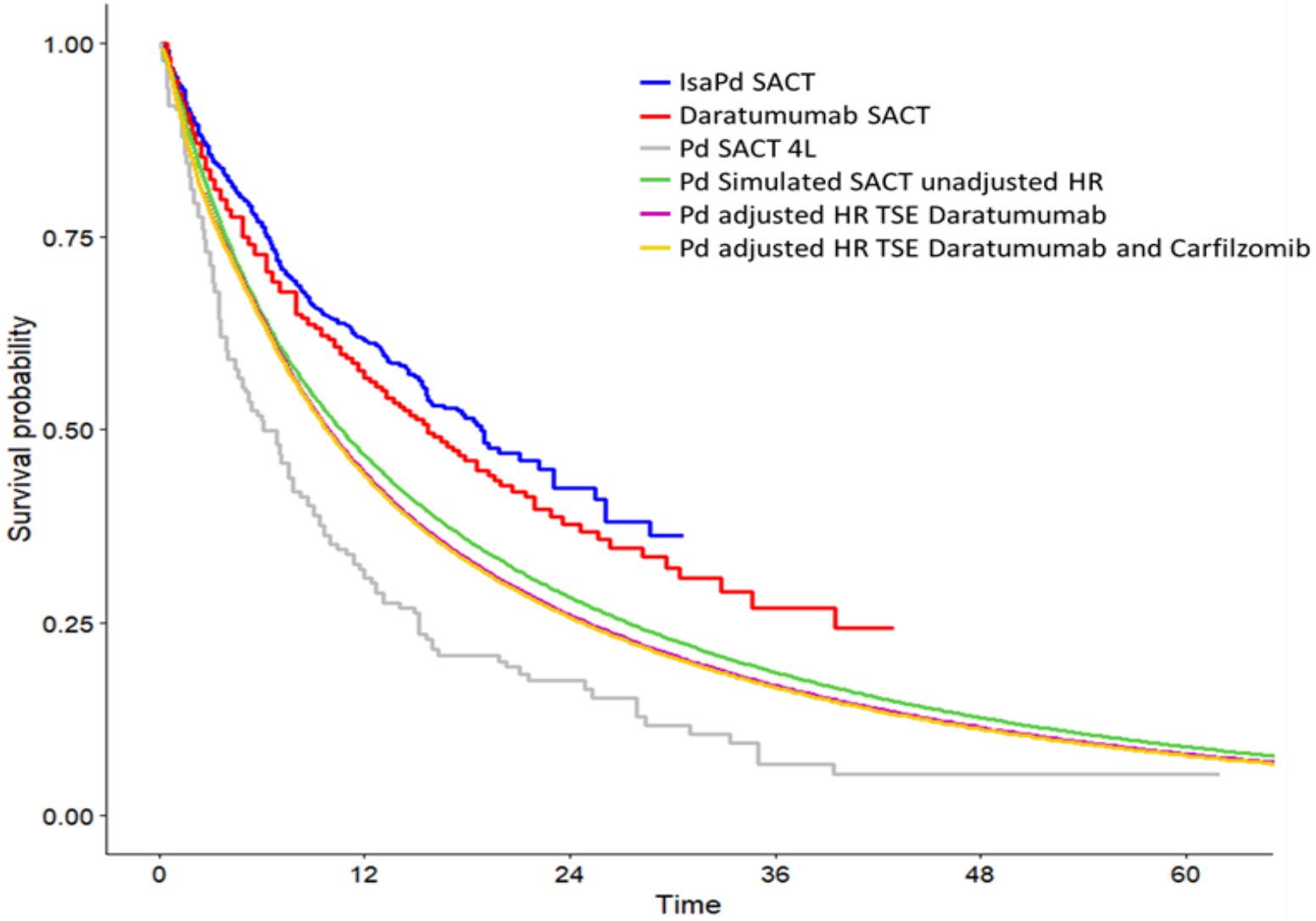
Base case retained a naïve comparison using SACT data but scenario analyses presented

- ICARIA-MM data and adjusted analysis are associated with significant uncertainty
- SACT data reflects treatment patterns, patient demographics and outcomes in a real-world setting
- People at 4L in the POM+DEX SACT data identified based on a line of therapy algorithm and consultation with experts to minimise misclassifications
- ISA+POM+DEX, POM+DEX and DARA SACT cohorts had similar demographics & clinical characteristics
- Early separation of survival curves observed for ISA+POM+DEX SACT vs POM+DEX SACT is not unexpected, and the same trend was observed in ICARIA-MM
  - ↳ Higher early deaths in the POM+DEX arm may be driven by people with less than a partial response
- RWE relevant to the UK reports a median OS post POM+DEX of at most 10.9 months
  - ↳ Suggests outcomes in ICARIA-MM (POM+DEX median OS: 17.71 months) are higher than what is expected in a real-world setting
- Using the HR from ICARIA-MM to estimate OS for POM+DEX may produce conservative results
- Re-iterates that SACT data has been accepted as appropriate in TA783 (note, no comparative data)

Abbreviations: DEX, Dexamethasone; HR, Hazard ratio; ISA, Isatuximab; OS, Overall survival; PFS, Progression-free survival; POM, Pomalidomide; RWE, Real world evidence; SACT, Systemic anti-cancer treatment; VAS, Visual analogue scale;

Company response: Efficacy data for POM+DEX comparison (2/3)

Figure: Overlay of SACTs with adjusted and unadjusted HR 'Simulated POM+DEX SACT'- Overall survival



Abbreviations: DEX, Dexamethasone; HR, Hazard ratio; POM, Pomalidomide; SACT, Systemic anti-cancer treatment;

Company response: Efficacy data for POM+DEX comparison (3/3)

EAG

- SACT data provides a good insight into the efficacy of ISA+POM+DEX in a real-world setting
  - ↳ However, it does not allow for a robust estimate of relative efficacy which is best captured in an RCT
- Possible that the percentage of people in the POM+DEX SACT data at later than 4L is small, but it cannot be guaranteed to be zero
- Populations included in the ISA+POM+DEX, POM+DEX and DARA may not be equivalent because:
  - ↳ Prognostic variables and treatment effect modifiers may not been captured within the datasets
  - ↳ ECOG scores have a non-trivial number of missing/unknown data (approx. 20% for POM+DEX; 27% for ISA+POM+DEX) → observed data signals that ISA+POM+DEX may be used less in patients with ECOG scores of 2 or more and used more in patients with ECOG scores of 0 vs POM+DEX
  - ↳ Exclusion of people from the POM+DEX SACT that had treatments in the CDF data would be expected to exclude the fittest people.
  - ↳ Clinical advice is that people would need to be fitter to have ISA+POM+DEX than POM+DEX.

Myeloma UK

- No evidence that the population in the POM+DEX SACT data set were frailer or less healthy than the population in the ISA+POM+DEX SACT data or that the exclusion of people who had received treatments in the CDF leads to a significant age difference between data sets

What is the most robust data for the comparison with POM+DEX?

Abbreviations: CDF, Cancer Drugs Fund; DEX, Dexamethasone; ISA, Isatuximab; POM, Pomalidomide; RCT, Randomised controlled trial; SACT, Systemic anti-cancer treatment;

Company response: Extrapolating OS using SACT: ISA+POM+DEX

Background

- Committee considered EAG's extrapolation using RCS Weibull 3-knot distribution was most appropriate
  - ↳ Company's use of log-normal could be plausible but appeared to overestimate tail end of KM curve

Company - Maintains preference for the log-normal distribution

- RCS Weibull 3-knot could be cautious in its predicted survival benefits
- Choice of extrapolation supported by clinical expert opinion
  - ↳ Clinical experts took into consideration that the SACT data collection period overlapped with the COVID-19 pandemic and the possibility of people bridging onto effective subsequent therapy
- Data on MRD status from ICARIA-MM supports using the log-normal distribution*
  - ↳ In the ITT and 4L populations only people in the ISA+POM+DEX arm achieved MRD-ve status
- MRD is a more sensitive measure of disease burden than complete response, reasonable to anticipate that the improved treatment duration would result in prolonged OS after ISA+POM+DEX in the long-term
- Evidence on tumour shrinkage / regrowth for elotuzumab+LEN+DEX may be generable to ISA+POM+DEX

EAG - Maintains preference for the RCS Weibull 3-knot distribution

- ↳ It has a similar statistical fit to the log-normal which appears to overestimate the tail of the KM curve
- Data provided by company are all from analyses marked exploratory
- Only provided qualitative discussions on the relationship between achieving MRD-ve status and improved OS outcomes, and the impact of monoclonal antibody therapies on the immune system

Following consultation, has the committee's view on extrapolating OS using SACT data changed?

Abbreviations: MRD, minimal residual disease

* See appendix – Data on MRD status

* See appendix – Extrapolation curves

Company response: Extrapolating OS using SACT: DARA (1/2)

Background

- Committee said that EAG's extrapolation using RCS log-normal 2-knot distribution was most plausible
  - ↳ Company's use of Weibull distribution appeared to underestimate the tail end of the KM curve

Company

Maintained preference for the Weibull distribution

- RCS log-normal 2-knot distribution may underestimate true OS benefit of ISA+POM+DEX
- There is no new evidence for DARA beyond what was used to recommend it in TA783
  - ↳ EAG in TA783 described the Weibull distribution as the "most plausible, and conservative long-term extrapolation of survival"
  - ↳ Not using the same distribution would introduce inconsistency and disadvantage this appraisal
- Survival estimates from the Weibull distribution were considered clinically plausible during the appraisal of TA783 and were validated by clinical experts
- ISA+POM+DEX SACT data was collected during the COVID-19 pandemic so the observed OS difference may be an underestimate, this would be exacerbated if the RCS log-normal 2-knot distribution is used.

EAG comments

Maintains preference for the RCS lognormal 2-knot distribution

- The Weibull distribution
  - ↳ Provided much higher AIC and BIC scores that the RCS log-normal 2-knot
  - ↳ Appears to underestimate the tail end of the KM curve

Abbreviations: AIC: Akaike Information Criterion; BIC, Bayesian Information Criterion; DARA, Daratumumab; DEX, Dexamethasone; EAG, External assessment group; ISA, Isatuximab; KM, Kaplan-Meier; OS, Overall survival; POM, Pomalidomide; RCS, Restricted cubic spline; SACT, Systemic anti-cancer treatment;

Company response: Extrapolating OS using SACT: DARA (2/2)

EAG comments

- In TA783 the Weibull distribution was described as conservative → Because DARA was being appraised it may have been appropriate to be conservative as there was the risk of recommending a non-cost-effective treatment → In this appraisal DARA is a comparator so that risk does not exist and the best fitting distribution should be chosen (RCS lognormal 2 knots (BIC))

Myeloma UK

- NICE should assess the cost-effectiveness of treatments consistently across all appraisals
  ↳ DARA may have been undervalued in TA783 and may be overvalued in the current appraisal

Following consultation, has committee's view on extrapolating OS for DARA changed?

* See appendix – Extrapolation curves

Abbreviations: DARA, Daratumumab; EAG, External assessment group; RCS, Restricted cubic spline; SACT, Systemic anti-cancer treatment;

Company response: Waning of the treatment effect (1/2)

Background

- Committee requested additional analyses that explore waning of treatment effect

Company

Base case does not include a waning effect and 1 additional scenario provided

- The current approach to addressing waning is arbitrary and unsubstantiated
- Waning was not requested by the EAG or committee in other MM appraisals (TA783, TA380 & TA427)
- In TA870, committee concluded that the waning effect was almost completely included in the trial follow up
- Potential decline in treatment benefit over time is accounted for in the survival projections by
  - ↳ The choice of extrapolation method and inclusion of a general population mortality constraint
- The independently fitted curves in the naïve comparison create the opportunity for treatment effect waning
  - ↳ Imposing additional waning assumptions could unnecessarily restrict projected efficacy
- More people achieved MRD-ve status in the ISA+POM+DEX arm which could drive the tails of the survival curve & support an argument that the survival benefit does not diminish instantly after progression
- ISA+POM+DEX exerts immunomodulatory effects that may persist post treatment

Scenario presented that:

- Used cycle-based HRs generated from independent log-normal distributions fitted to the ICARIA-MM OS curve (capped so risk of death with ISA+POM+DEX was never higher than for POM+DEX) applied to the SACT ISA+POM+DEX OS curve to generate a “time-varying HR simulated POM+DEX SACT OS curve”
  - ↳ Scenario supports the use of the unadjusted POM+DEX SACT curve because the “time-varying HR simulated” and “unadjusted” POM+DEX SACT OS curves are close

Abbreviations: DEX, Dexamethasone; EAG, External assessment group; ISA, Isatuximab; MM; Multiple myeloma; MRD-ve: Minimal residual disease negative; OS, Overall survival; POM, Pomalidomide; SACT, Systemic anti-cancer treatment;

Company response: Waning of the treatment effect (2/2)

EAG

- Generating a "time-varying HR simulated POM+DEX SACT OS curve" using the adjusted independent lognormal distributions used for the ICARIA-MM OS data captures potential waning of treatment effect
- SACT data supports the use of time-variant HRs, rather than the other way around as there are known limitations within the SACT dataset
- Neither the extrapolations using constant HR nor the time-variant HR fits the SACT data particularly well

UK Myeloma Society

- There is no evidence of a treatment waning effect in those with RRMM where treatment is given until progression or in the currently published ICARIA-MM trial data
- ISA is likely to change and improve response to subsequent treatments.

Is the committee satisfied that waning of treatment effect has been explored?

* See appendix – Extrapolation curves "time-varying HR simulated" and "unadjusted" POM+DEX SACT OS

Abbreviations: DEX, Dexamethasone; HR, Hazard ratio; ISA, Isatuximab; OS, Overall survival; POM, Pomalidomide; RRMM, Relapsed and refractory multiple myeloma; SACT, Systemic anti-cancer treatment;

Company response: Utility values (1/2)

Background

- Committee was not convinced that people who are progression-free and on ISA+POM+DEX would have a higher utility than people on POM+DEX. Differential utilities by treatment were accepted in TA658.

Company

- Contradictory for committee to reach a different conclusion in this appraisal compared to TA658
- Higher baseline utility for ISA+POM+DEX in ICARIA-MM is not driving the difference it utility values
- The larger difference in utility values than in TA658 is influenced by changes in the NICE recommended EQ-5D-5L to 3L mapping function
- People reported higher EQ-5D VAS scores while on treatment with ISA+POM+DEX than with POM+DEX
- Maintenance of HRQoL is partially attributed to improvements in pain management and the delay in physical functioning decline seen in the ISA+POM+DEX arm
- Despite a higher rate of AEs in the ISA+POM+DEX arm treatment discontinuation due to TEAEs occurred at a lower rate in the ISA+POM+DEX arm
  - ↳ Highlights the tolerability of ISA+POM+DEX and manageable natures of associated AEs
- POM+DEX's oral delivery is more convenient but the impact of ISA+POM+DEX on daily life compensates

EAG

- No new data have been submitted by the company
- EAG provides scenarios with and without differential utilities by treatment in the PFS state

Abbreviations: AE, Adverse events; DEX, Dexamethasone; HRQoL, Health related quality of life; ISA, Isatuximab; PFS, Progression-free survival; POM, Pomalidomide; TEAE; Treatment Emergent Adverse Events; VAS, Visual analogue scale;

Company response: Utility values (2/2)

Myeloma UK

- Reaching a complete response has a significant impact on QoL
- The QoL impact of achieving complete response would not be captured by the anxiety and depression domain of the EQ-5D
- The utility values do not take into account the anxiety partners and children experience

UK Myeloma Society

- As patients remain progression free for longer with preserved quality of life, this will translate into patients having a higher health utility

Following consultation, has the committee's view on the utility values changed?

* See appendix – Utility values

Abbreviations: QoL, Quality of life

Company response: benefits not captured in the QALY

Background

- Committee concluded at ACM1 that it had not seen any evidence that ISA+POM+DEX provides additional benefits that had not already been taken into account

Company

- Being progression-free and having symptoms under control enables a fulfilling life: patient expert at ACM1 was able to enjoy a “full family life”, including holidays, leisure activities and volunteer work - these speak to the wider societal benefits not captured in generic QoL instruments
- Psychological impact of accessing effective treatment after multiple relapses should not be underestimated
  - loss of positive attitude can impact adversely on life expectancy
  - significant psychological burden from not knowing if there is another line of treatment
- Improved disease management, enhanced symptom control and potentially extended periods of stability can lead to decreased stress and anxiety and improved QoL for patients and their families/caregivers

EAG

- Unclear why the benefits would not be shown in the anxiety/depression and usual activity domains of the EQ-5D - should be accounted for in the utility values
- Unknown if gains for families/caregivers are greater/less than for treatments that would no longer be funded

Have the consultation comments altered the committee’s view on additional benefits not already captured?

Abbreviations: DEX, Dexamethasone; ISA, Isatuximab; POM, Pomalidomide; QALY, Quality-adjusted life year, QoL, Quality of life;

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Company response: exceptional circumstances of appraisal

Company

- Concerned that patients could lose access to this clinically effective and clinically preferred treatment as highly likely it will not be cost-effective even if ISA has zero cost - a strong case to apply flexibility
- Company internal analyses suggest that POM+DEX and DARA would not necessarily be cost-effective if reappraised today
- Would be perverse for NICE to issue final negative guidance on this basis and urges the committee to:
  - Apply a QALY weighting equivalent to the EoL weighting
  - Ensure non-reference case analyses (including removal of backbone costs) can be considered in line with the NICE manual
  - Consider value attribution methods to specifically assess the value afforded by ISA discounts)

NICE response

- CDF entry requires that the cost-effectiveness of the treatment must be established upon exit
- The isatuximab data collection agreement stated that the methods and processes in place ***at the time of the CDF exit*** would be the ones used for the CDF review
- QALY weighting is based on present treatments in pathway
- Allowing a weighting equivalent to EOL would represent significant deviation from 2022 methods
- people with other conditions if the methods are dismissed in the way suggested.
- Removal of background costs as a scenario are for independent committee to consider
- No mechanism for value attribution to be taken into consideration in methods – largely a commercial issue

Abbreviations: CDF, Cancer Drugs Fund; DARA, Daratumumab; DEX, Dexamethasone; EOL, End of life; ISA, Isatuximab; POM, Pomalidomide; QALYs, Quality-adjusted life year;

QALY weightings for severity (1/2)*

* See appendix– QALY weightings for severity

Background

- For the comparison with POM+DEX, QALY shortfall estimates were only high enough for a severity weight to be applied if using SACT data
- Committee concluded it would review the weightings for both comparators after considering the additional analyses requested at ACM1
  - ↳ Analyses using unadjusted HR from ICARIA-MM, TSE adjusted HR and Time-variant HR for the comparison with POM+DEX results in QALY shortfall estimates that correspond with a disease severity modifier of 1.2
- Using age and sex distribution data from the SACT data and the committee's preferred distribution at ACM1 (RCS lognormal 2-knot distribution) to extrapolate OS using DARA SACT, produces QALY shortfall estimate not high enough for a severity weight to be applied
  - ↳ Using the company's preferred distribution (Weibull distribution) to extrapolate OS using DARA SACT, produces a QALY shortfall estimate high enough for a severity weight of 1.2 to be applied

Abbreviations: DARA, Daratumumab; DEX, Dexamethasone; HR, Hazard ratio; OS, Overall survival; POM, Pomalidomide; QALY, Quality-adjusted life year; RCS, Restricted cubic spline; SACT, Systemic anti-cancer treatment; TSE, Two-stage estimation;

QALY weightings for severity (2/2)

Table: Disease severity modifiers – Each analysis – Absolute and Proportional QALY shortfall

	Utilities	Absolute QALY shortfall	Proportional QALY shortfall, %
Naïve comparison of SACT data – POM+DEX	Differential	[redacted]	[redacted]
	Non differential	[redacted]	[redacted]
Naïve comparison of SACT data – DARA monotherapy	Differential	[redacted]	[redacted]
	Non differential	[redacted]	[redacted]
Unadjusted HR from ICARIA-MM applied to ISA+POM+DEX SACT PFS and OS	Differential	[redacted]	[redacted]
	Non differential	[redacted]	[redacted]
TSE HR adjusted for DARA only applied to ISA+POM+DEX SACT OS	Differential	[redacted]	[redacted]
	Non differential	[redacted]	[redacted]
TSE HR adjusted for DARA and CARF applied to ISA+POM+DEX SACT OS	Differential	[redacted]	[redacted]
	Non differential	[redacted]	[redacted]
Time-variant HR applied to ISA+POM+DEX SACT PFS and OS	Differential	[redacted]	[redacted]
	Non differential	[redacted]	[redacted]

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Is it appropriate to apply a QALY weighting for severity?

Abbreviations: CARF, Carfilzomib; DARA, Daratumumab; DEX, Dexamethasone; EAG, External assessment group; HR, Hazard ratio; ISA, Isatuximab; OS, Overall survival; PFS, Progression-free survival; POM, Pomalidomide; SACT, Systemic anti-cancer treatment;

Isatuximab with pomalidomide and dexamethasone for treating relapsed and refractory multiple myeloma

- ❑ Recap from ACM1
- ❑ Consultation comments
- ❑ **Company response and EAG critique**
- ❑ Other considerations
- ✓ **Summary**

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Cost-effectiveness results

All ICERs are reported in PART 2 slides

because they include confidential

comparator prices

- When the company and EAG base case ICERs are calculated using confidential prices both are substantially above what NICE considers an acceptable use of NHS resources (regardless of whether a 1.2 severity modifier is applied)
- Scenario analyses consider potential generic POM prices

Abbreviations:

Key issues for decision making

Key issue	Committee's preferred assumption
Do the adjusted ICARIA-MM results represent a better estimate of efficacy than the unadjusted results?	
What data should be used for estimating the relative effect of ISA+POM+DEX vs POM+DEX?	
Has the committee's view on extrapolating OS using SACT data changed: - for ISA+POM+DEX? - for DARA?	
What is the committee's conclusion about waning of treatment effect?	
Has the committee's view on the utility values changed?	
Are there additional benefits that have not been captured?	
Is it appropriate to apply a QALY weighting for severity?	
What is the preferred decision-making threshold?	

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Abbreviations: DARA, Daratumumab; DEX, Dexamethasone; ISA, Isatuximab; OS, Overall survival; POM, Pomalidomide; QALY, Quality-adjusted life year; SACT, Systemic anti-cancer treatment;

Isatuximab with pomalidomide and dexamethasone for treating relapsed and refractory multiple myeloma [Review of TA658] [ID4067]

Supplementary appendix

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ICARIA-MM trial of ISA+POM+DEX vs POM+DEX: results – PFS

Figure: Kaplan-Meier plot of PFS (Final data cut (March 2022) in 4th line patients)

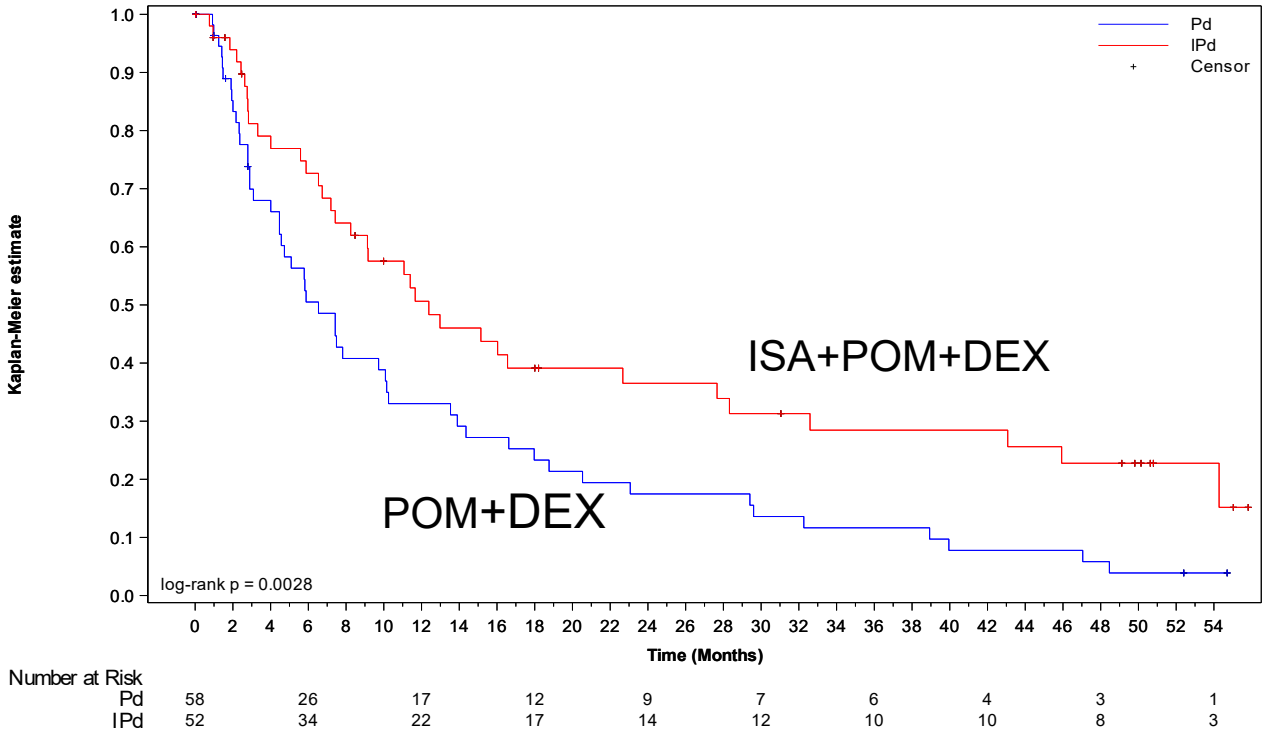


Table: Summary of PFS in ICARIA-MM trial (Final data cut (March 2022) in 4th line patients)

	ISA+POM+DEX (n=52)	POM+DEX (n=58)
Number of Events (%)	35 (67.3)	50 (86.2)
Median Months (95% CI)	12.39 (7.43 - 27.66)	6.54 (4.47 – 10.09)
Stratified HR (95% CI)	0.536 (0.343 – 0.840)	
p-value	0.0057	

Abbreviations: DEX, Dexamethasone; HR, Hazard ratio; ISA, Isatuximab; PFS, Progression-free survival; POM, Pomalidomide;

ICARIA-MM trial: results – OS

Figure: Kaplan-Meier plot of OS
(Cut-off date 27th Jan 2022 - in 4th line patients)

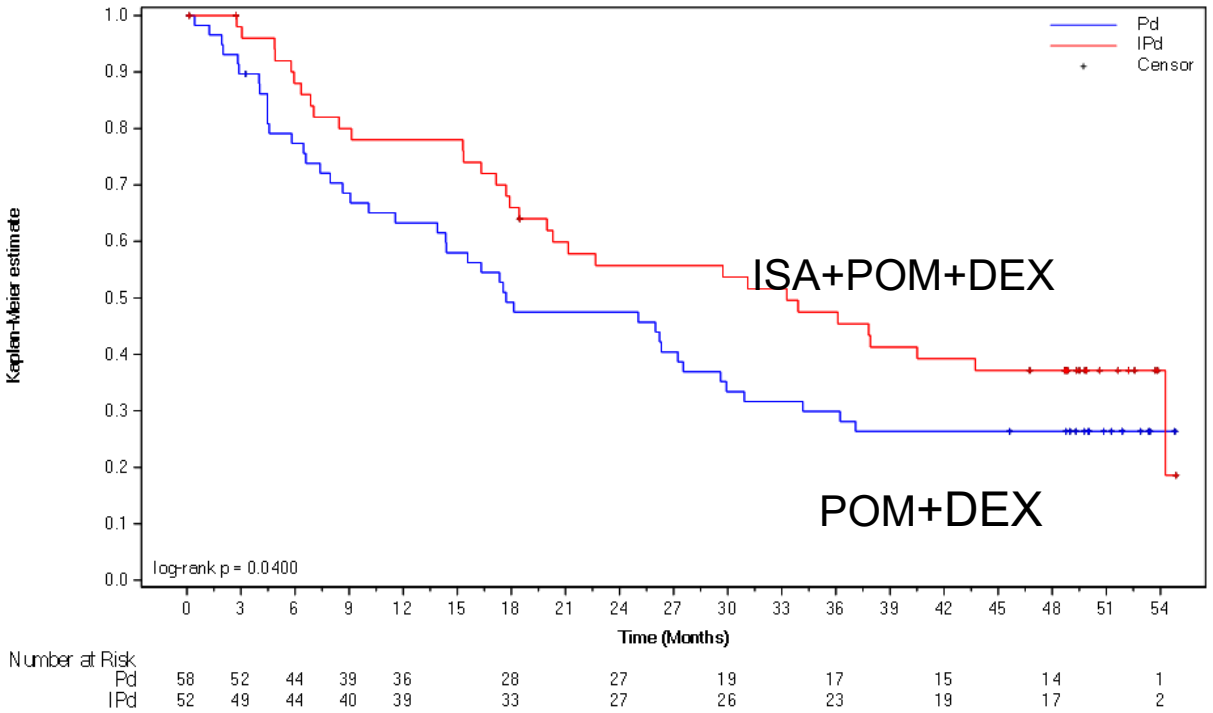


Table: Summary of OS in ICARIA-MM trial.
Median follow-up, 52.4 months in 4th line patients

	ISA+POM+DEX (n=52)	POM+DEX (n=58)
Number of Events (%)	32 (61.5)	42 (72.4)
Median Months (95% CI)	33.28 (18.43 – 54.28)	17.71 (11.56 – 27.53)
Stratified HR (95% CI)	0.657 (0.409 - 1.055)	
p-value	0.080	

NICE Abbreviations: Abbreviations: DEX, Dexamethasone; HR, Hazard ratio; ISA, Isatuximab; OS, Overall survival; POM, Pomalidomide;

SACT results – Time to discontinuation (TTD)*

Figure: Reconstructed SACT Treatment duration – Kaplan-Meier curves by treatment group

Table: Median treatment duration in the SACT-treated cohort at 4th line (proxy for PFS)

Cohort	Median TD, months (95% CI)	Number of patients
ISA+POM+DEX	8.9 (7.3, 10.8)	736
POM+DEX	3.2 (2.7, 4.1)	175
DARA	4.5 (4.3-4.9)	2300

Background

- The SACT datasets did not use the same data sources and collected data over different time periods
  - ↳ ISA+POM+DEX: CDF and EAMS cohorts *(2nd December 2019 to 31st March 2022)*
  - ↳ DARA: CDF cohort *(17th January 2018 to 16th November 2020)*
  - ↳ POM+DEX: Retrospective study of SACT, COSD and other linked datasets (1 January 2014 to 31 August 2021) – LoT identified using a novel algorithm - CDF treated patients excluded

Abbreviations: COSD, Cancer Outcomes and Services Dataset; DARA, Daratumumab; DEX, Dexamethasone; ISA, Isatuximab; KM, Kaplan-Meier; LoT, Line of therapy; PFS, Progression-free survival; POM, Pomalidomide; SACT, Systemic anti-cancer treatment; TD, Treatment duration; TTD, Time to discontinuation;

SACT results – OS*

Figure: Reconstructed SACT OS – Kaplan-Meier curves by treatment group

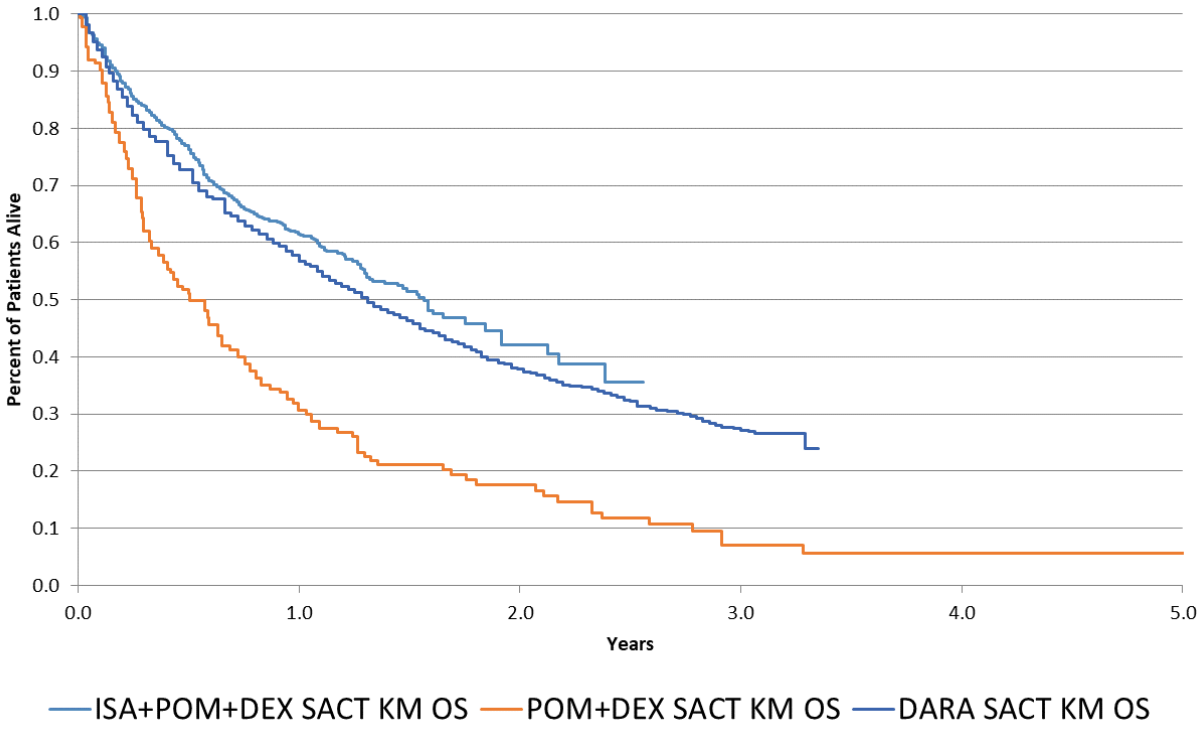


Table: Median OS in the SACT-treated cohort at 4th line

Cohort	Median OS, months (95% CI)	Number of patients
ISA+POM+DEX	18.8 (15.7, 22.9)	736
POM+DEX	6.3 (4.6, 7.8)	175
DARA	15.5 (14.5, 16.7)	2300

* See appendix – Summary of SACT data

Abbreviations: Abbreviations: DARA, Daratumumab; DEX, Dexamethasone; ISA, Isatuximab; KM, Kaplan-Meier; OS, Overall survival; POM, Pomalidomide; SACT, Systemic anti-cancer treatment;

Company response: Extrapolating OS using SACT: ISA+POM+DEX (Supplementary slide)

Table: ICARIA-MM MRD-ve status by arm and cohort

Cohort	Treatment arm	MRD-ve status
ITT Population	ISA+POM+DEX	10*
	POM+DEX	0
4L Subgroup	ISA+POM+DEX	4*
	POM+DEX	0

*minimum sensitivity of one in 10^5 nucleated cells

Table: ICARIA-MM ISA+POM+DEX arm - median PFS2, OS prob at 4 years, % alive March 2022 cut-off

ISA+POM+DEX Depth of response	Median PFS2, months	OS probability at 4 years, %	Alive at median follow up 52.4 months (March 2022 cut-off)
MRD−ve (n=4)	NC (54,275; NC)	100%	75%
≥ VGPR and MRD+ve (n=17)	NC (15.014; NC)	51.2%	-
PR (n=10)	21.03 (8.54; NC)	30%	-
Less than PR (n=20)	8.44 (5.947; 16.92)	<15.8%	-

Link to – Extrapolating OS using SACT: ISA+POM+DEX

Abbreviations: DEX, Dexamethasone; ISA, Isatuximab; MRD+ve, Minimal residual disease positive; MRD-ve: Minimal residual disease negative; NC, not calculable; OS, Overall survival; POM, Pomalidomide; PR, Partial response; SACT, Systemic anti-cancer treatment; VGPR, Very good partial response;

Company response: Extrapolating OS using SACT: ISA+POM+DEX & DARA (Supplementary slide)

Link to – Extrapolating OS using SACT: ISA+POM+DEX

Link to – Extrapolating OS using SACT: DARA

Figure: ISA+POM+DEX and DARA long-term OS projections based on distributions

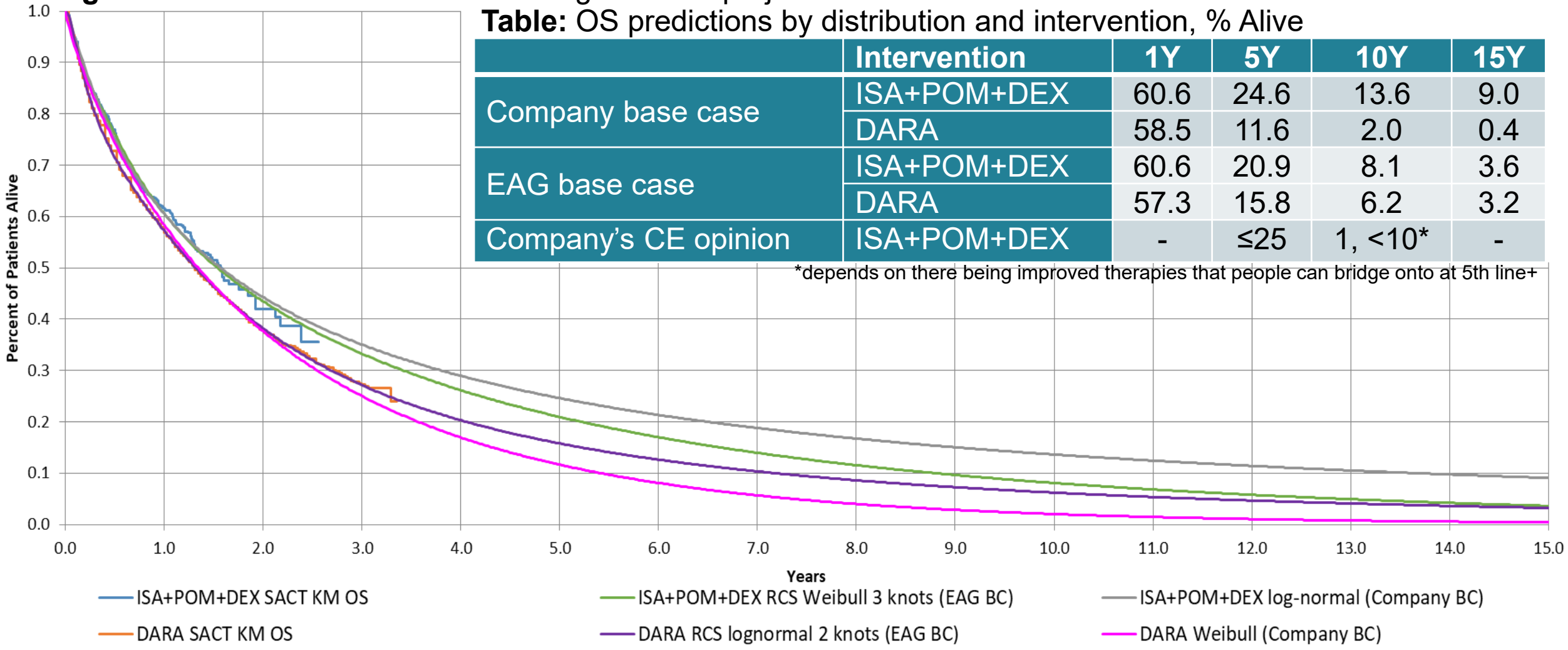


Table: OS predictions by distribution and intervention, % Alive

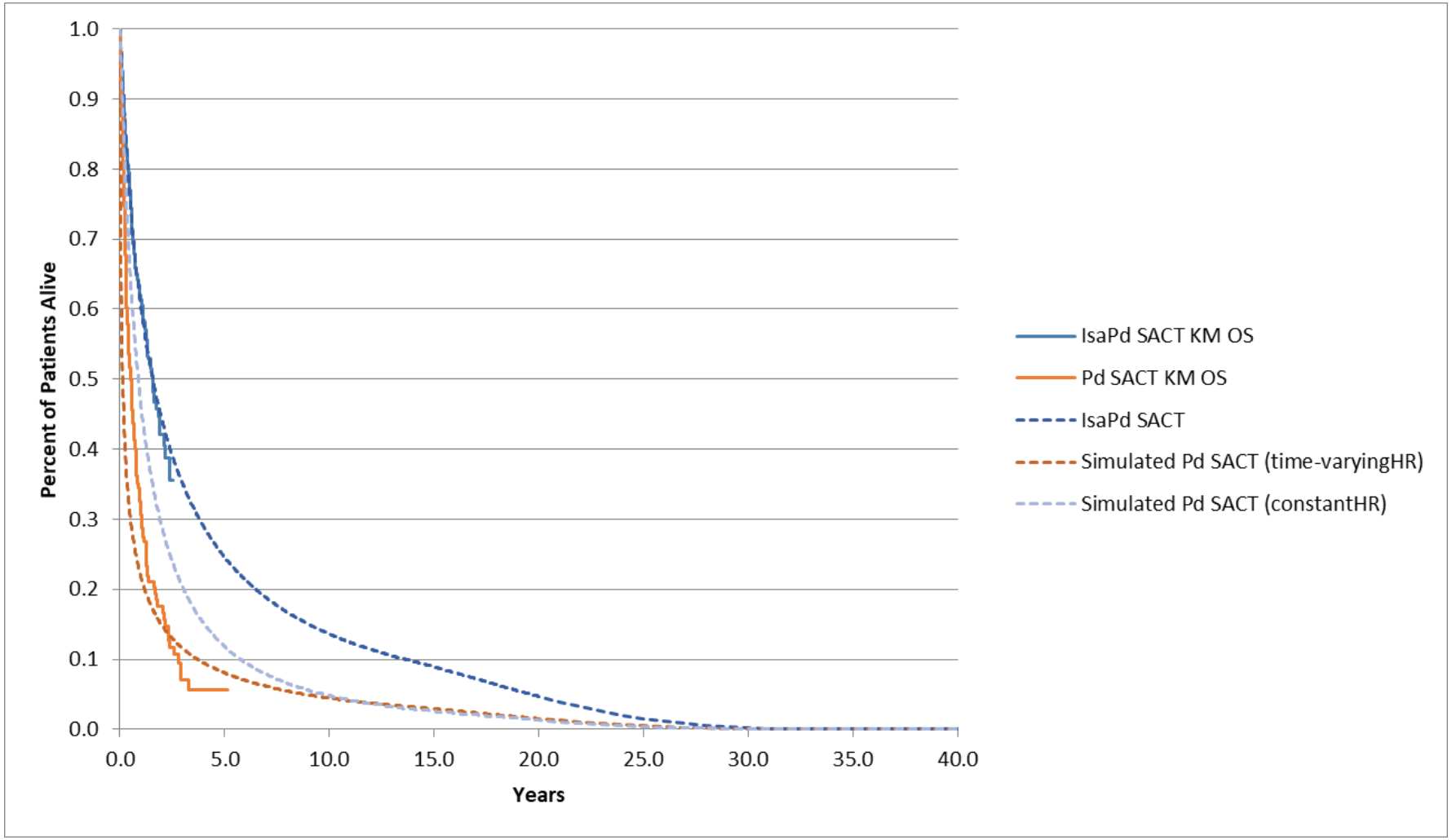
	Intervention	1Y	5Y	10Y	15Y
Company base case	ISA+POM+DEX	60.6	24.6	13.6	9.0
	DARA	58.5	11.6	2.0	0.4
EAG base case	ISA+POM+DEX	60.6	20.9	8.1	3.6
	DARA	57.3	15.8	6.2	3.2
Company's CE opinion	ISA+POM+DEX	-	≤25	1, <10*	-

*depends on there being improved therapies that people can bridge onto at 5th line+

Abbreviations: CE, Clinical expert; DARA, Daratumumab; DEX, Dexamethasone; ISA, Isatuximab; KM, Kaplan-Meier; OS, Overall survival; POM, Pomalidomide; RCS, Restricted cubic spline; SACT, Systemic anti-cancer treatment;

Company response: Waning of the treatment effect (Supplementary slide)

Figure: OS extrapolations using Simulated POM+DEX SACTs vs POM+DEX SACT



Link to – Waning of the treatment effect

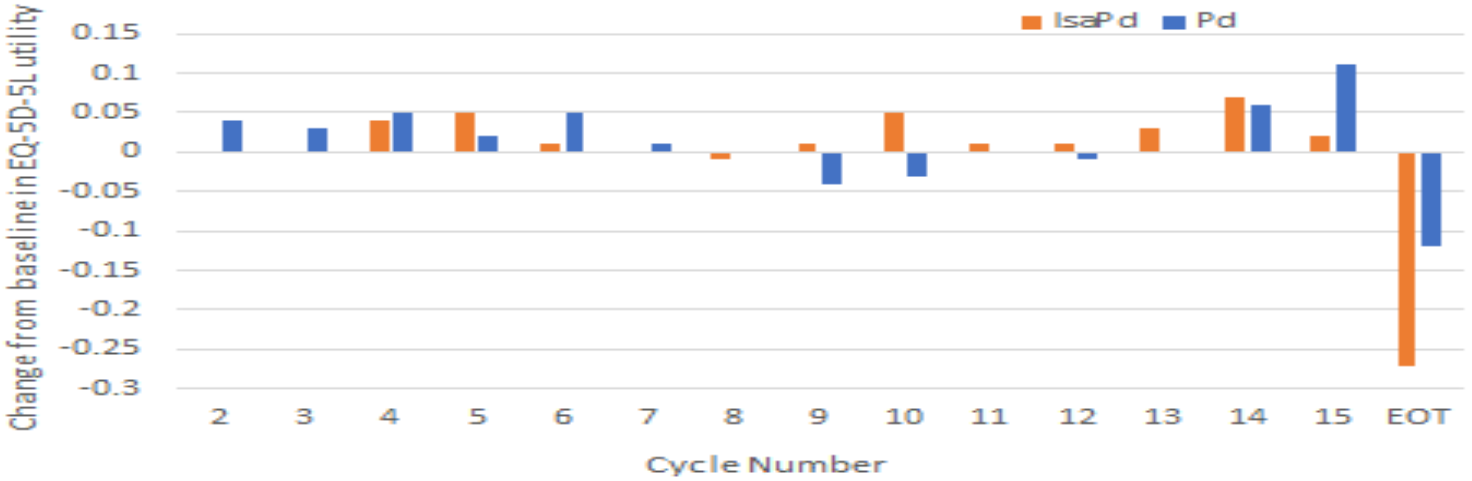
Abbreviations: DEX, Dexamethasone; OS, Overall survival; POM, Pomalidomide; SACT, Systemic anti-cancer treatment;

Company response: Utility values (Supplementary slide)

Table: Health-State Utility Values, by line and Treatment + EAG scenario analysis
(Company submission Doc B – Table 36, TA658 EAG report – Table 7)

	On-Therapy Progression -Free	Off-Therapy Progression -Free	On-Therapy Post Progression	Off-Therapy Post Progression	Terminal Decrement
ISA+POM+DEX – Current Appraisal (ISA+POM+DEX – TA658)	[redacted] (0.719)	[redacted] (0.719)	[redacted] (0.611)	[redacted] (0.611)	[redacted] (0.225)
POM+DEX (POM+DEX – TA658)	[redacted] (0.717)	[redacted] (0.717)	[redacted] (0.611)	[redacted] (0.611)	[redacted] (0.225)
EAG's same utility scenario	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

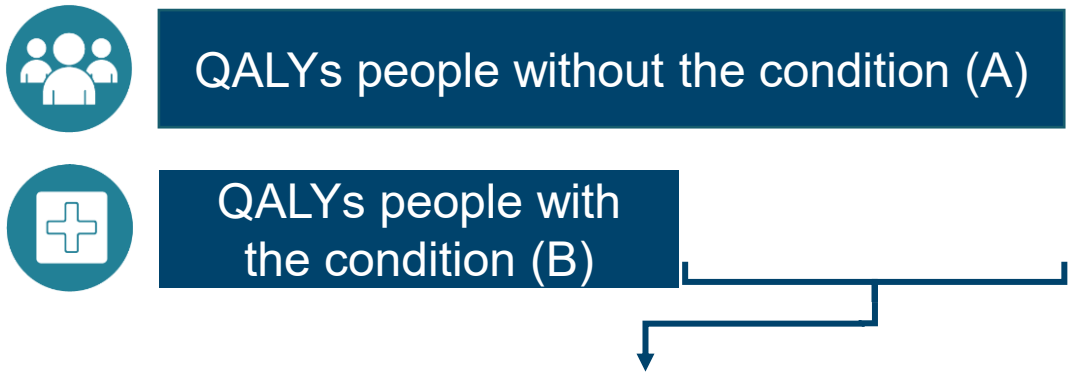
Figure: Change from baseline in EQ-5D-5L utility by treatment arm and cycle number or end of treatment



Link to –Utility values

QALY weightings for severity

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

Link to – QALY weightings for severity

Abbreviations: QALY, quality-adjusted life year