

Chair's presentation Dinutuximab beta for neuroblastoma [ID910]

2nd Appraisal Committee meeting

Committee D

Lead team: William Turner, Peter Hall and Malcolm Oswald

ERG: BMJ-TAG; NICE Decision Support Unit

NICE technical team: Anna Brett, Nwamaka Umeweni

Company: EUSA Pharma (UK)

11 April 2018

Background

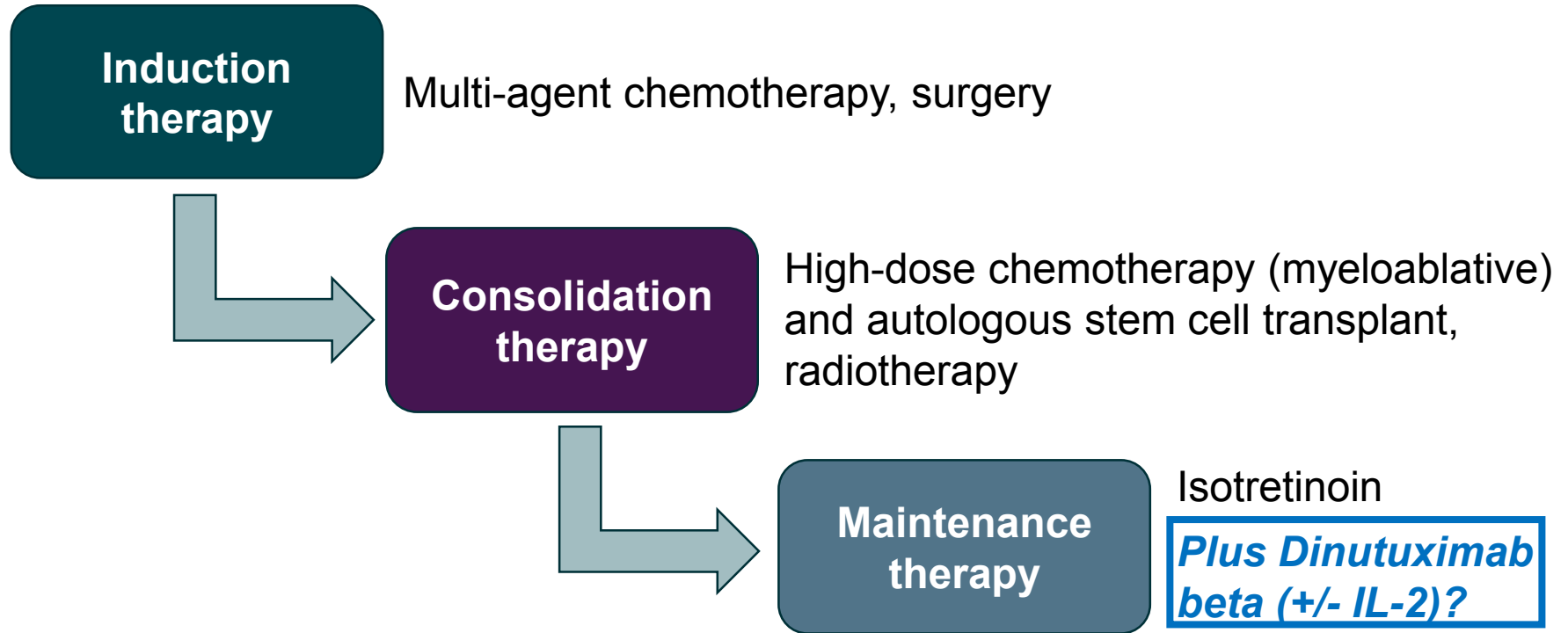
- Dinutuximab beta considered November 2017
- Committee unable to make recommendation because clinical effectiveness results highly uncertain
 - Further clarification and analyses requested from company (no ACD issued)
- NICE Decision Support Unit (DSU) asked to critique the new analyses

Dinutuximab beta (Qarziba, EUSA)

| | |
|---------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Marketing authorisation granted May 2017 under exceptional circumstances | <ul style="list-style-type: none">• Treatment of high-risk neuroblastoma in patients aged 12 months and above, who have previously received induction chemotherapy and achieved at least a partial response, followed by MAT and ASCT, as well as patients with a history of relapsed or refractory neuroblastoma, with or without residual disease• In patients with a history of relapsed/refractory disease and in patients who have not achieved a complete response after first line therapy, dinutuximab beta should be combined with IL-2 |
| Mechanism of action | Immunotherapy – a monoclonal, chimeric antibody that targets GD2, a glycolipid in neuroblastoma cells |
| Administration | Intravenous infusion |
| Dosing frequency | <ul style="list-style-type: none">• Continuous infusion over the first 10 days of each course at the daily dose of 10 mg/m² <i>or</i>• Five daily infusions of 20 mg/m² administered over 8 hours, on the first 5 days of each course |
| List price excluding VAT | Acquisition cost: £7,610 per vial; average cost of a course of treatment: £152,200 (no patient access scheme) |

Current treatment

High risk population



Dinutuximab beta currently used in research setting; since 2009 almost all patients in the UK who previously had induction chemotherapy with at least a partial response followed by myeloablative therapy and autologous stem cell transplant, were enrolled in the APN311-302 trial

Committee's ACM1 conclusions

Clinical effectiveness: high risk population

- APN311-302 trial
 - Open label, phase 3, dinutuximab beta plus isotretinoin vs. dinutuximab beta plus isotretinoin plus IL-2
 - Concomitant IL-2 did not improve event-free or overall survival
 - Data immature, no primary cut-off date specified, no time period for follow-up
 - Dosing schedule of continuous infusion for 5 days does not reflect current UK practice (10 day schedule has become standard across EU)
- No evidence directly comparing dinutuximab beta with isotretinoin
- Company's naïve ITC does not produce a robust treatment effect estimate
 - Data immature; at risk of bias from lack of randomisation and confounding
 - Historical cohort (from a trial phase used to compare different consolidation myeloablative therapies) used for control – and did not include EFS data

Committee concluded an ITC using matched-adjusted or simulated approach was needed for a more robust estimate of treatment effect

Committee's ACM1 conclusions

Economic model: Treatment effect estimates

- Structure of model appropriate; ERG's corrections accepted
- Estimates of treatment effect used in model not robust
 - Based on the company's naïve ITC
- Dinutuximab **alpha** appraisal (ID799) recalled – data more mature and after 5 years event-free and overall survival curves began to converge
 - Committee considered a similar effect may be seen in dinutuximab beta trial after longer follow-up, given similarity between the immunotherapies

Committee requested a MAIC or STC using data from dinutuximab alpha trial to estimate relative treatment effect for the model

- Clinical expert advice suggests adding IL-2 increases toxicity but tends not to improve efficacy and that standard practice does not include concomitant IL-2 in majority of patients (further chemotherapy used instead)

Committee requested scenario analyses exploring different proportions of patients having concomitant IL-2

Committee's ACM1 conclusions

Economic model: Cost assumptions

- Company's drug cost for dinutuximab beta
 - Based on the number of vials needed for an average body surface area of 0.63m^2

Committee requested weighted average costs, taking into account proportion of patients in different BSA categories in trial

- Failure state
 - Drug wastage not accounted for
 - Administration cost based on chemotherapy procurement cost
 - Chemotherapy costs applied for life

Committee requested company account for wastage, use cost of hospital inpatient stay for administration costs per cycle and provide alternative assumptions for treatment duration and resource use in the failure state

- Infection-related hospitalisation

Committee requested company include costs for infections

Committee's ACM1 conclusions

Economic model: Utility values; discount rate

- Utility values
 - Health-related quality of life data not captured in APN311-302
 - Company applied a decrement to UK EQ-5D general population values to reflect that patients have neuroblastoma
 - Dinutuximab **alpha** appraisal reported a published algorithm (Ara et al. 2010) used to estimate mean EQ-5D health state utility values for general population
 - ERG considered Ara et al. more appropriate than logistic regression

Committee requested company use Ara et al. to estimate age-specific UK EQ-5D values in the modelling

- Discount rate
 - 1.5% discount rate appropriate
 - Consistent with dinutuximab alpha appraisal

Committee's ACM1 conclusions

Economic model: Cure thresholds

- Cure point in company's model was 10 years
- Dinutuximab **alpha** appraisal recalled – committee preferred 10 year cure point because although most relapses happened before 5 years, some relapses did occur after 5 years
 - Appeal panel noted there were a number of possible cure points other than 10 years that could have been explored
 - Appeal panel concluded that a reasonable approach might be to consider a range of plausible cure points and explore the strengths and weaknesses of each

Company should explore a range of cure points (between 5 and 10 years) and associated ICERs in scenario analyses

Committee's ACM1 conclusions

- Most plausible ICER could not be determined – further analyses needed
- End of life criteria not met
 - APN311-302 results showed median overall survival of 1,869 days (~5 years); mean 2,447 (~7 years), for patients having isotretinoin alone (historical control)
 - Data insufficiently robust to demonstrate survival gain for dinutuximab beta compared with isotretinoin
- Criteria for inclusion in Cancer Drugs Fund not met
 - Lack of robust estimates of treatment effect to include in modelling
 - Lack of any robust cost-effectiveness estimates
- Some health-related benefits not captured in model
 - Reduced quality of life because of stress and depression caused by the disease on young patients and their families
 - Effect of bereavement on families
- No equality issues identified

New analyses provided by company

| Requested | Provided |
|---------------------------------------------------------------------------|----------|
| Matched-adjusted indirect comparison (MAIC) with isotretinoin | ✓ |
| Weighted average costs | ✓ |
| Failure health state assumptions: treatment duration, resource-use | ✓ |
| Adjustment for wastage in chemotherapy costs in failure state | ✓ |
| Admin costs per cycle calculated using cost of a hospital day | ✓ |
| Adjustment for wastage of gabapentin in concomitant costs in stable state | ✓ |
| UK EQ-5D estimated using Ara et al. (2010) algorithm | ✓ |
| Scenario analyses exploring impact of concomitant IL-2 | ✓ |
| Scenarios reflecting hazard ratios varying over time* | ✗ |
| Scenarios for various cure time points between 5 and 10 years | ✓ |
| PSA incorporating impact of varying relative treatment effectiveness | ✓ |

*The company did not use hazard ratios in the model but fitted separate parametric curves to the MAIC adjusted data; the DSU explored the use of longer-term effectiveness data and its impact on the shape of the survival curves

Company's MAIC Methods

- Comparator data obtained from ANBL0032 trial reported by Yu et al. 2010
- Prognostic variables included in MAIC:
 - Age
 - INSS stage
 - Tumour MYCN status
 - Response before ASCT
- Weighting then applied to APN311-302 baseline characteristics to enable comparison with Yu et al. 2010
- Both arms of APN311-302 pooled because both arms received dinutuximab beta and no difference in OS or EFS was shown in the trial
- Patients from APN311-302 excluded if not eligible for Yu et al. 2010

INSS, International Neuroblastoma Risk Group Staging System; MYCN, V-Myc myelocytomatosis viral-related oncogene; ASCT, Autologous stem cell transplant

Company's MAIC Results

| Dinutuximab beta + isotretinoin +/-IL-2 vs. Isotretinoin alone | Hazard ratio | 95% Confidence interval |
|----------------------------------------------------------------|--------------|-------------------------|
| Event-free survival | | |
| At 24 months | 0.553 | 0.51 – 0.63 |
| At 48 months | 0.672 | 0.61 – 0.79 |
| At 70 months | 0.681 | 0.62 – 0.8 |
| Overall survival | | |
| At 24 months | 0.886 | 0.78 – 1.16 |
| At 48 months | 0.620 | 0.53 – 0.85 |
| At 70 months | 0.629 | 0.54 – 0.86 |

Note: hazard ratios not used in the model

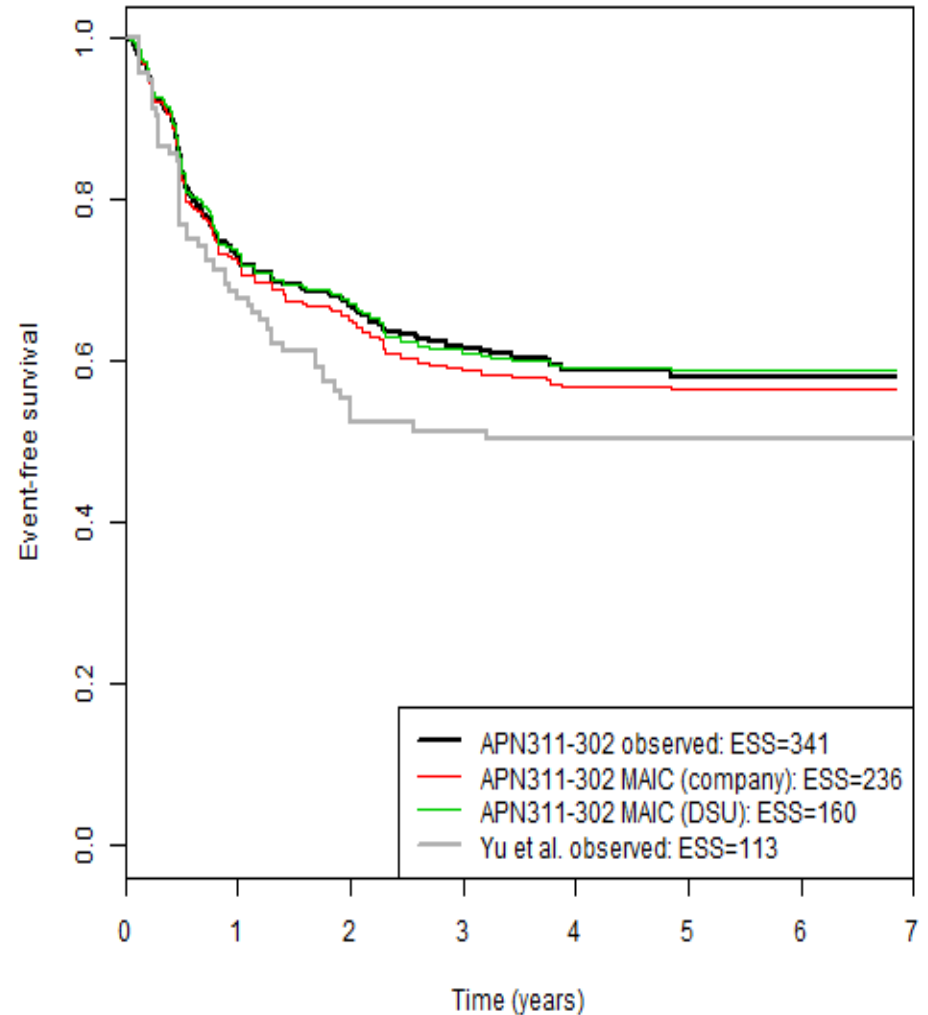
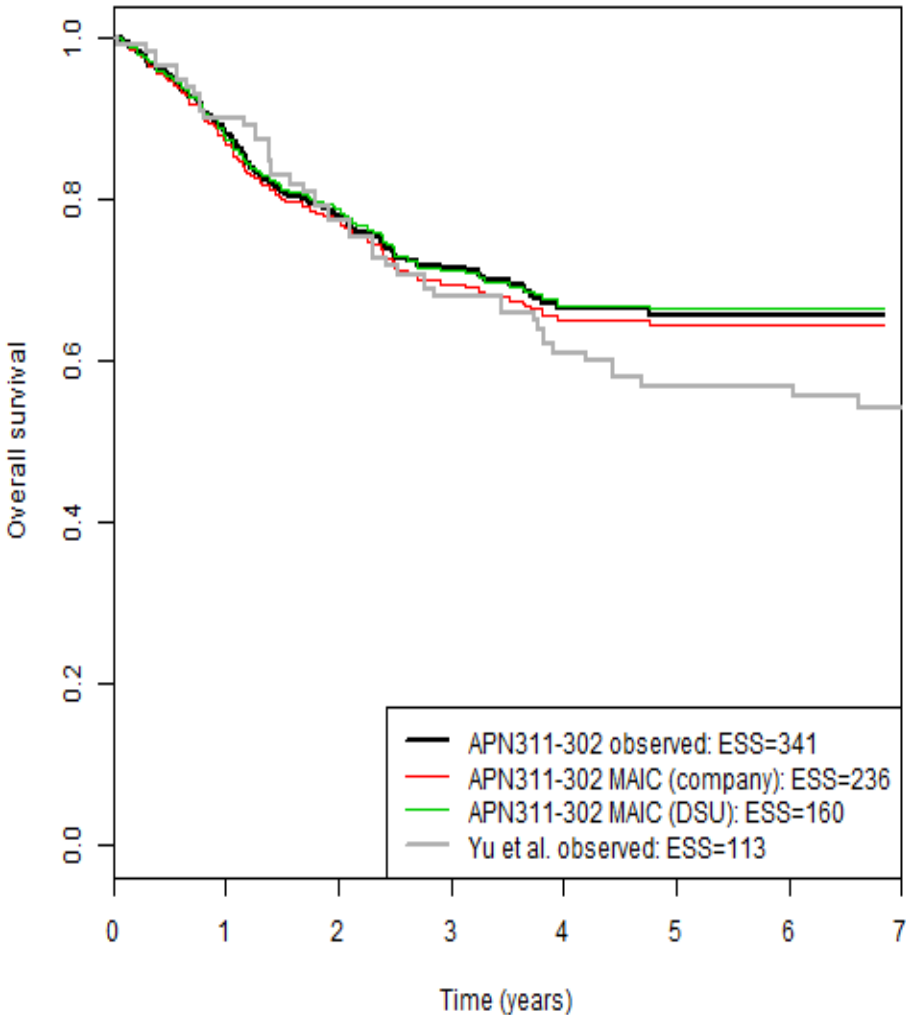
DSU's critique MAIC

- Appropriate to pool data from both arms of APN311-302
- Previous consolidation therapy not accounted for
 - Differed between APN311-302 (BuMel) and Yu et al. (CEM)
 - BuMel is now standard of care and CEM rarely used (clinical advice)
 - However, not appropriate to adjust MAIC for previous consolidation therapy for a number of reasons, including lack of population overlap, small sample size and required assumptions about relative effect of dinutuximab beta following different consolidation therapies
 - Direction or size of the potential bias therefore cannot be determined
- Hazard ratios (HRs) should be interpreted with caution because company assumes data follows exponential distribution, but HRs would vary according to how the interval is chosen
- DSU re-ran MAIC with minor errors corrected; results were similar to the company's MAIC results

BuMel, busulfan + melphalan hydrochloride; CEM, carboplatin, etoposide + melphalan

MAIC comparison

Observed data, company's and DSU's MAIC results



Company's new analyses

Survival analysis

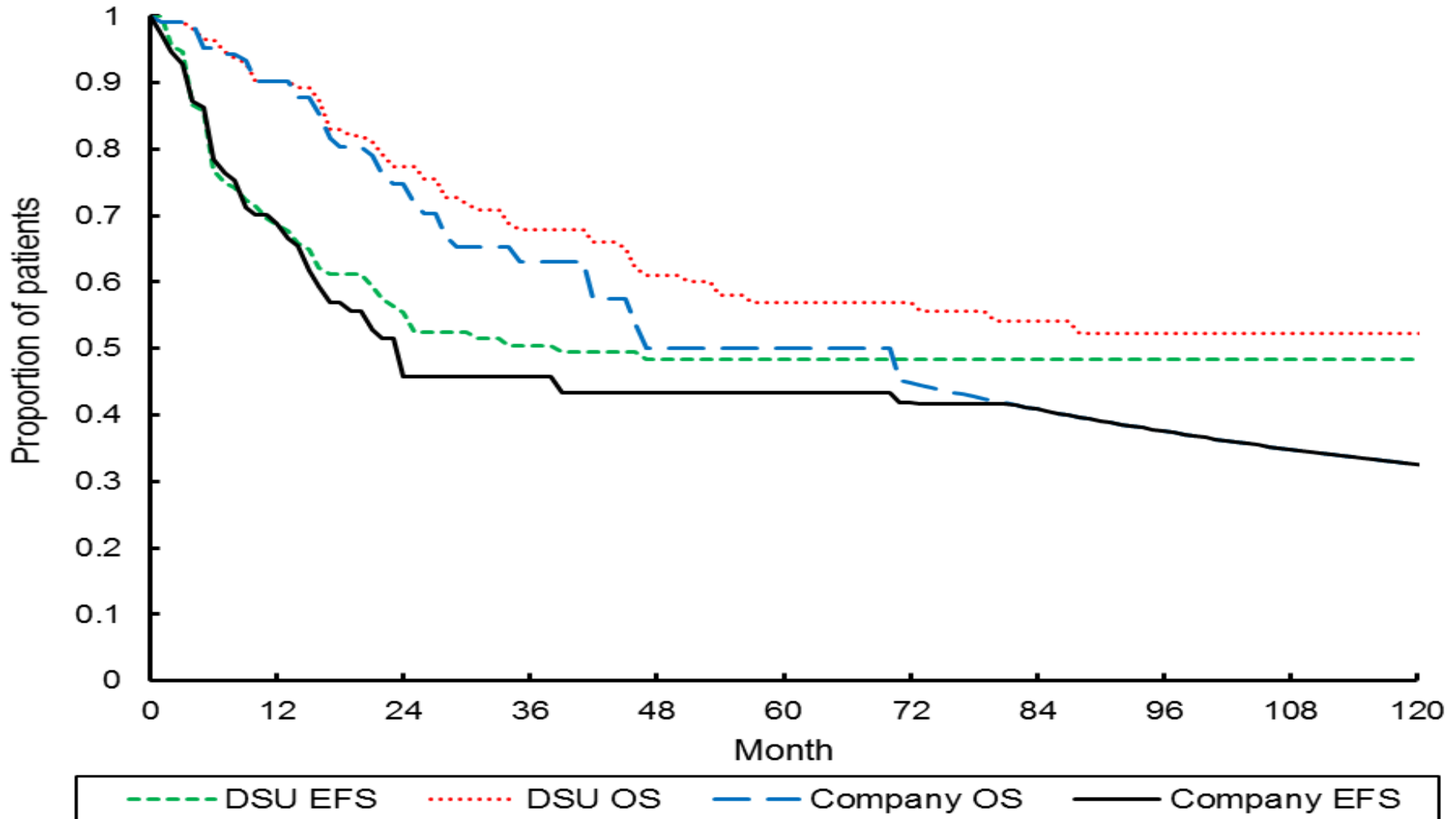
- MAIC-adjusted Kaplan-Meier (KM) curves considered similar to observed KM curves in APN311-302 for dinutuximab arm
- OS and EFS data from MAIC used to determine mortality and disease progression for each cycle of the model
- OS and EFS data used for the time period where data were available (70 months) and then extrapolated
- Gompertz parametric curves fitted to both OS and EFS data in both arms (considered best visual fit, supported by AIC/BIC criteria)
- In response to clarification the company provided a scenario analysis using the Yu et al. 2014 data for the isotretinoin arm

DSU's critique

Survival analysis

- Company used KM data from MAIC up to month 70 then fitted separate parametric curves to extrapolate survival up to 10 years for both arms
- Limitation of analysis is that company use least squares to fit parametric models (an optimisation approach), which ignores that data are time-to-event and does not rely on any formal statistical methods for making inferences
- Dinutuximab **alpha** appraisal showed that hazard ratios increased when longer-term data was included, indicating that relative effectiveness of dinutuximab decreased over time
- Although longer-term data not available for dinutuximab beta, 12 years of data for isotretinoin was available (Yu et al. 2014)
- More appropriate to use longer-term data because it reduces uncertainty arising from extrapolation of the comparator arm
- In response to clarification the company provided a scenario analysis using Yu et al. 2014 but extrapolated data from month 70 for both arms (unnecessary for isotretinoin arm; data available for full 10 years)

EFS and OS curves for isotretinoin 2010 data (company) vs. 2014 data (DSU)



DSU's survival analysis

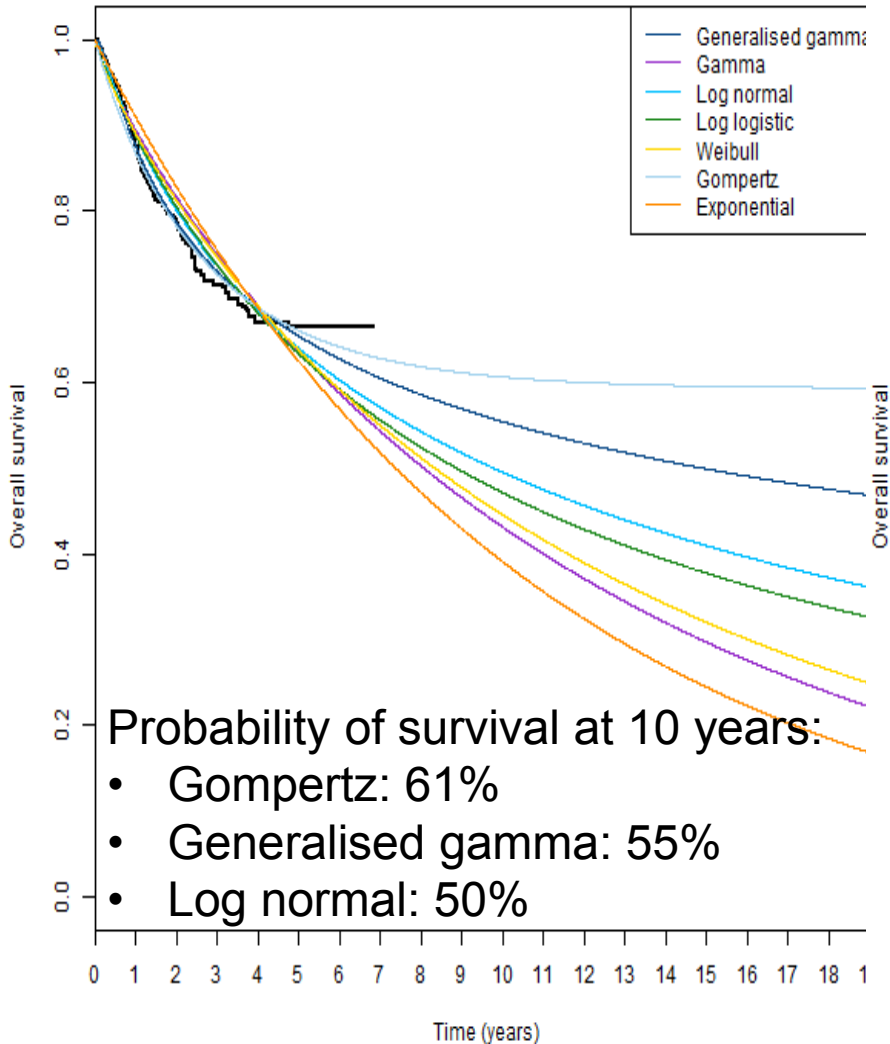
Overall survival

- Re-did survival analysis using 2014 data and explored alternative extrapolations that enabled modelling of more complex hazard functions:
 - Kaplan-Meier data used for isotretinoin
 - Dinutuximab beta data extrapolated beyond 70 months
- Extrapolations validated by visual fit and AIC/BIC criteria; clinical experts advised uncertainty in predicting long-term benefits of immunotherapy
- In addition, long term data for dinutuximab **alpha** used to inform potential relationship between dinutuximab beta and isotretinoin (exact relationship between alpha and beta unknown but both derived from same antibody and may therefore be expected to be similar)
- Dinutuximab **alpha** KM and best fitting curves indicate that overall survival higher with dinutuximab than isotretinoin over 12 years
- DSU considers gompertz or spline models to be plausible

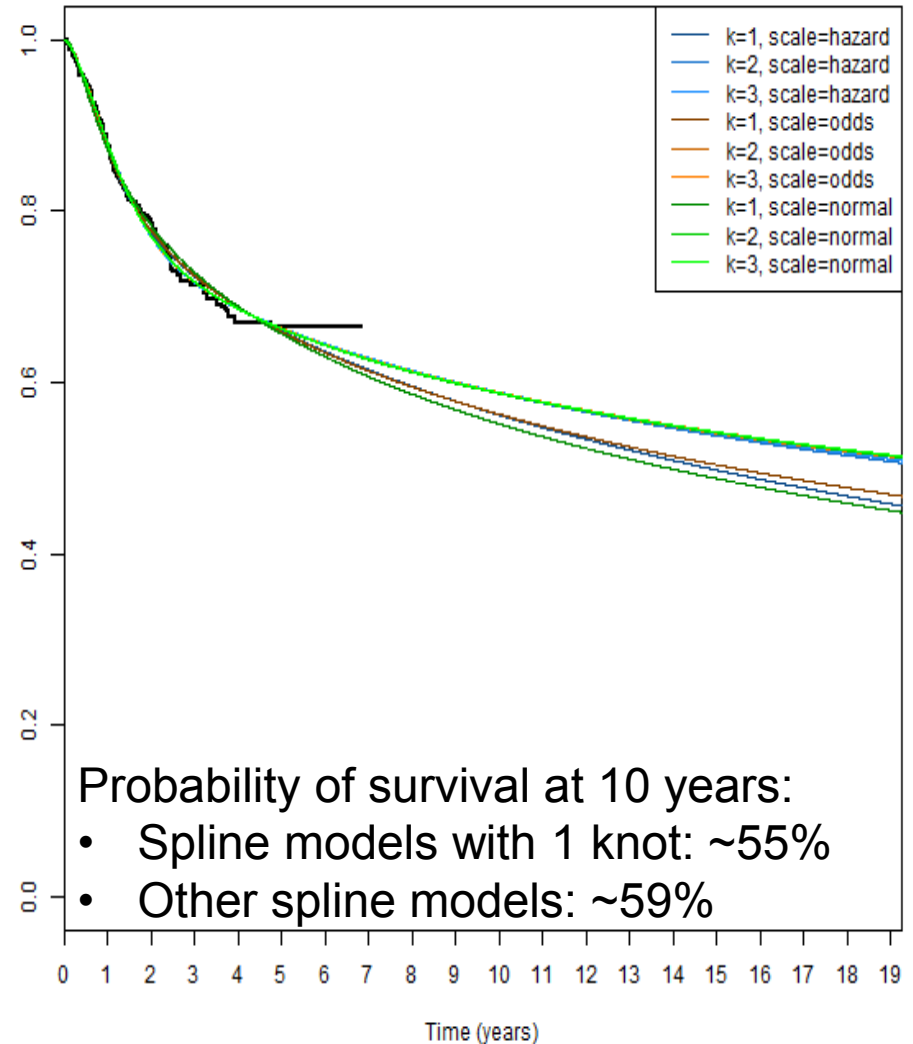
DSU's extrapolation for dinutuximab beta

Overall survival

Parametric curves

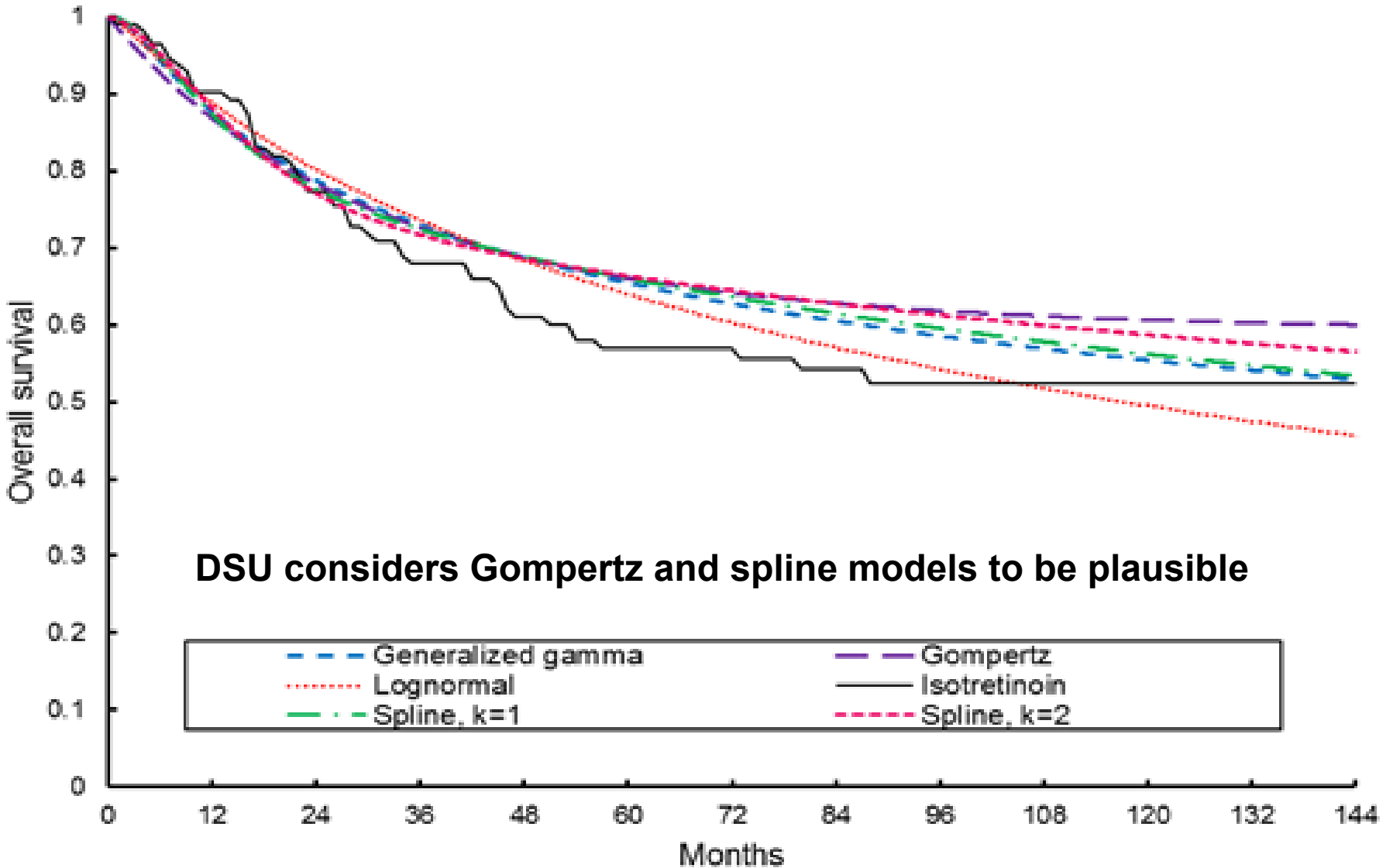


Spline models



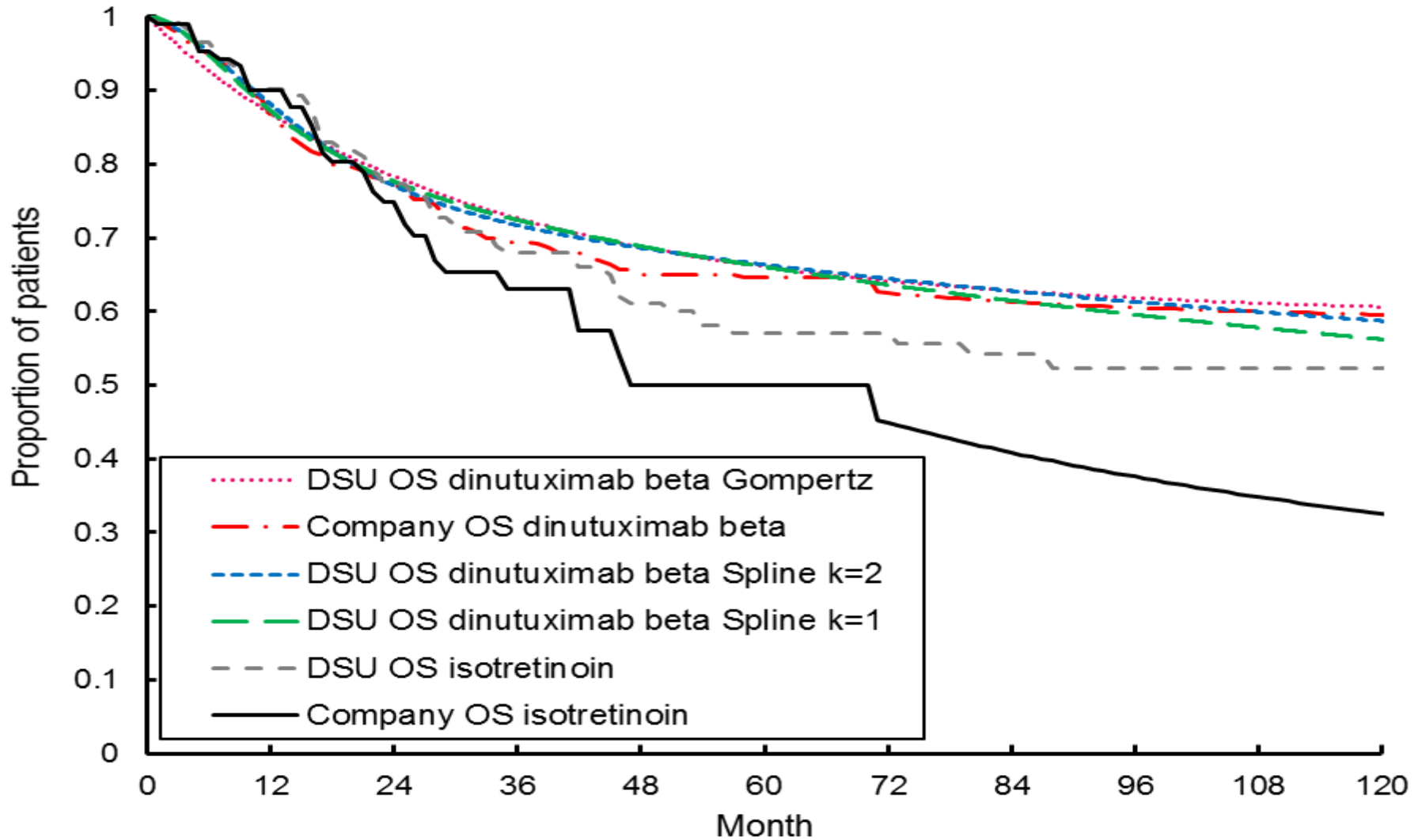
Overall survival

Extrapolated dinutuximab beta vs. KM isotretinoin



Overall Survival

DSU's preferred extrapolations vs. Company's



DSU's survival analysis

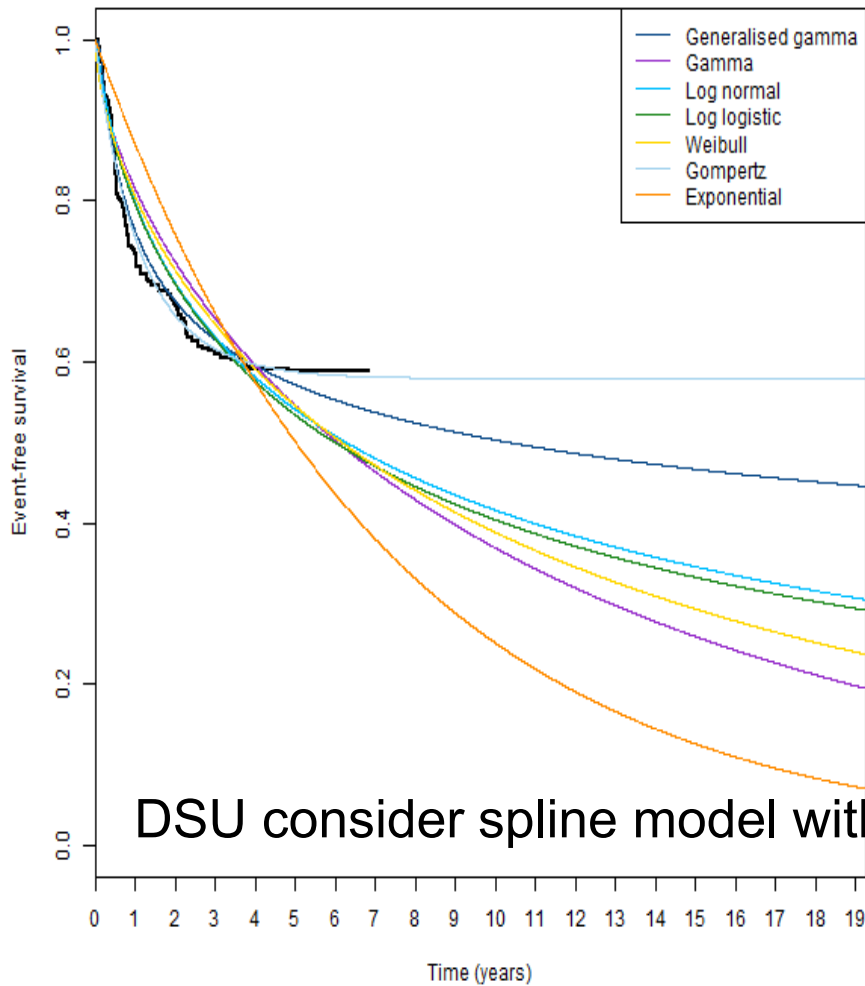
Event-free survival

- Clinical experts advised that the rate at which treatment fails is not constant over time
- Most people who relapse do so in the first 1-3 years, and then the rate of relapse decreases and relapse after 5 years is rare
- Would expect that the most appropriate model has a steep decline in the first few years and a more gradual decline (but not completely flat) for years 5-10
- Spline models fit this description and are best fitting according to AIC/BIC
- Validation against longer-term data from dinutuximab **alpha** indicates that this shape is likely to be appropriate (also ERG considered spline model to be a good fit)
- DSU consider spline model with $k=1$ and $\text{scale}=\text{odds}$ most plausible
- Generalised gamma used in a scenario analysis, although considered less realistic

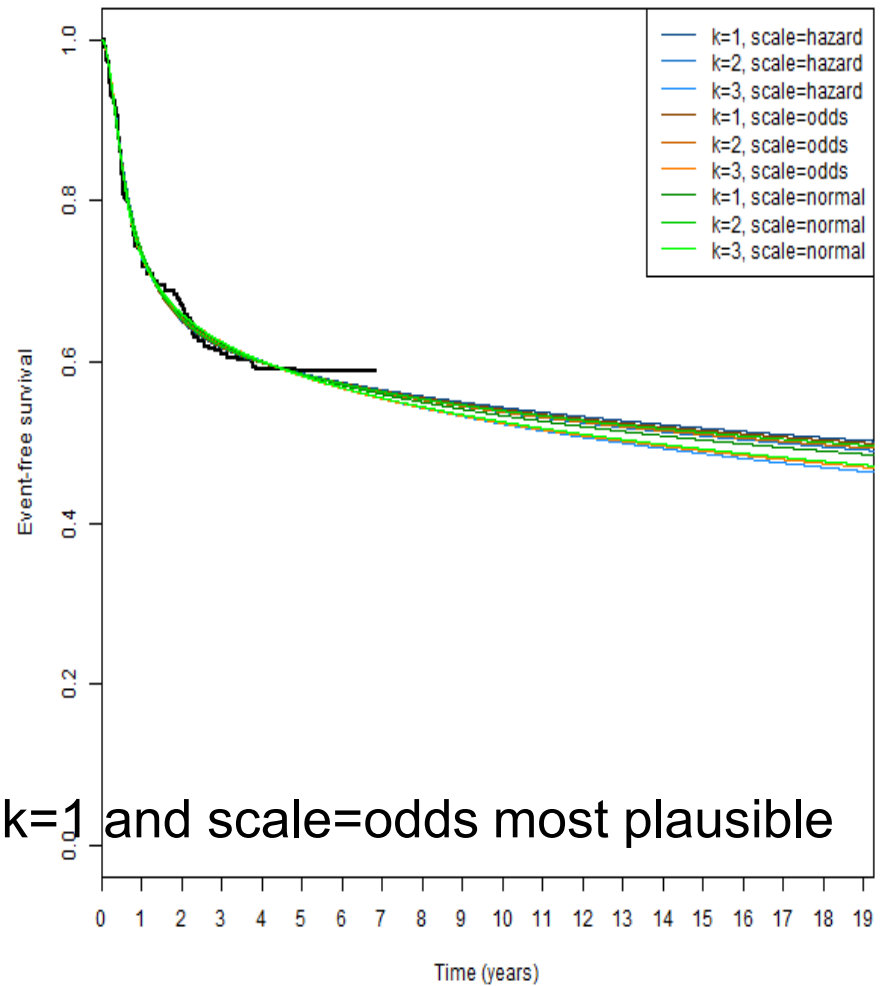
DSU's extrapolation for dinutuximab beta

Event free survival

Parametric curves

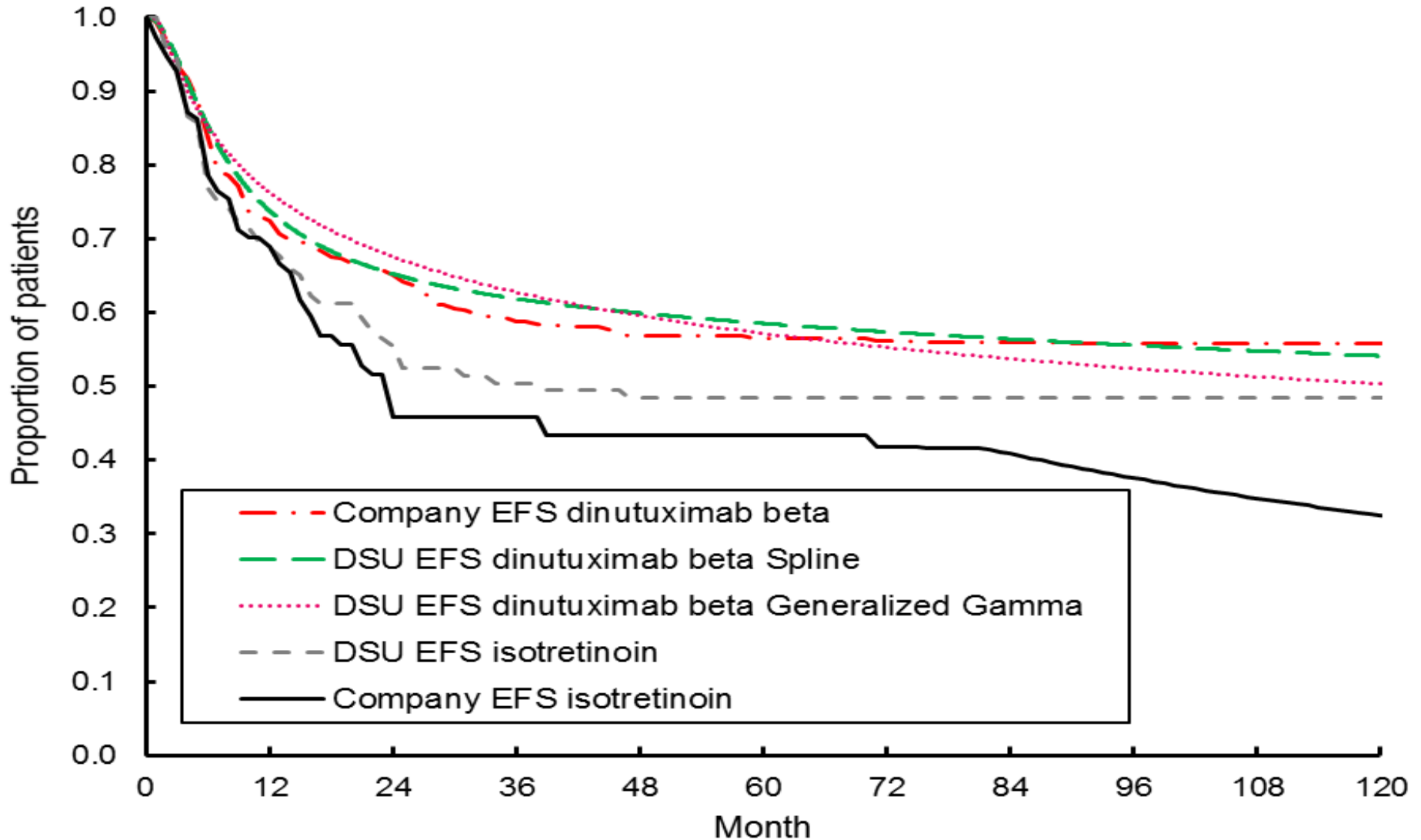


Spline models



Event-free survival

DSU's preferred extrapolations vs. Company's



Company's new analyses

Costs and utilities

- Weighted average costs taking into account the proportion of people in different BSA categories in trial APN311-302
- Assumptions in failure health state:
 - Proportion of newly progressed patients having chemotherapy: derived from APN311-302; assumed the same for isotretinoin arm
 - Chemotherapy treatment duration: 1 year
 - Resource use for people who complete chemotherapy: £76.50 per month
- Adjustment for including wastage in cost estimates for chemotherapy
- Administration costs: cost of a 5 day hospital stay per cycle
- Adjustment for including wastage of gabapentin
- Multiple regression by Ara et al. (2010) to estimate age-specific EQ-5D values
- Infection costs included in scenarios including IL-2 (£3,980 per event) based on:
 - Paediatric major infections with complication and comorbidity score 2-4 for each grade 3/4 infection
 - Comprises cost for non-elective long-stay inpatient (average stay of 5 days)
 - Validated by expert opinion

DSU's critique

Costs and utilities

- Adjustment for including wastage in cost estimates for chemotherapy:
 - May overestimate costs for topotecan: DSU corrected (no impact on ICER)
- Failure state assumptions:
 - Approach to determining proportion of newly progressed patients having chemotherapy is reasonable
 - 1 year duration of chemotherapy considered reasonable; 2 and 3 years explored in scenario analyses because some patients may have later lines of treatment
 - Resource use estimate for patients who have completed chemotherapy is reasonable
- Probabilities of grade 3 to 4 infection (according to whether or not having concomitant IL-2) included in model; attached costs considered appropriate by clinical experts
- All other amendments considered to have been implemented correctly by the company

Company's new base case

- Treatment effectiveness estimates from MAIC (using 2010 data for isotretinoin)
- Updated costs and utility assumptions
- 10 year cure threshold
- Assumption of no concomitant IL-2

| | Total | | Incremental | | ICER |
|---------------------------------|----------|-------|-------------|-------|----------------|
| | Cost | QALYs | Cost | QALYs | |
| Deterministic | | | | | |
| Isotretinoin alone | £55,923 | 11.65 | | | |
| Dinutuximab beta + isotretinoin | £225,373 | 18.52 | £169,450 | 6.87 | £24,661 |
| Probabilistic | | | | | |
| Isotretinoin alone | £55,590 | 11.68 | | | |
| Dinutuximab beta + isotretinoin | £224,192 | 18.57 | £168,602 | 6.89 | £24,684 |

Company's scenario analyses

| Scenario | ICER |
|--------------------------------------------------------------------------|---------|
| Proportion of patients having concomitant IL-2 in dinutuximab arm | |
| 0% (base case) | £24,661 |
| 41% (marketing authorisation) | £27,924 |
| 51% (trial) | £28,755 |
| Cure thresholds | |
| 10 years (base case) | £24,661 |
| 9 years | £26,451 |
| 8 years | £28,968 |
| 7 years | £32,699 |
| 6 years | £36,133 |
| 5 years | £41,286 |
| Using Yu et al. 2014 data for isotretinoin arm (up to month 70) | £43,308 |

The company also explored scenarios with different combinations of prognostic factors included in the MAIC

Impact of DSU's changes on ICER

| DSU change (all other assumptions the same as the company's) | Deterministic ICER (probabilistic) |
|--------------------------------------------------------------------------------------|------------------------------------|
| Corrected topotecan wastage (no change to company b-c) | £24,661 |
| Using longer-term isotretinoin data (Yu et al. 2014) | £79,811 |
| Change to dinutuximab survival extrapolation (KM data used for isotretinoin): | |
| OS extrapolation: gompertz | £72,839 |
| OS extrapolation: spline k=1, scale=hazards | £101,723 |
| OS extrapolation: spline k=2, scale=hazards | £83,131 |
| EFS extrapolation: spline k=1, scale=odds (OS: gompertz) | £75,831 (£79,493) |
| EFS extrapolation: spline k=1, scale=odds (OS: spline k=1) | £108,301 (£121,563) |
| EFS extrapolation: spline k=1, scale=odds (OS: spline k=2) | £87,164 |
| EFS extrapolation: generalised gamma (OS: gompertz) | £89,351 (£95,903) |
| EFS extrapolation: generalised gamma (OS: spline k=1) | £140,073 (£158,708) |
| EFS extrapolation: generalised gamma (OS: spline k=2) | £105,899 |

DSU's preferred range of ICERs

| | Total | | Incremental | | Deterministic ICER (probabilistic) |
|--|-------|-------|-------------|-------|---------------------------------------|
| | Costs | QALYs | Costs | QALYs | |

OS extrapolation: gompertz; EFS: spline k=1 scale=odds

| | | | | | |
|---------------------------------|----------|-------|----------|------|------------------------------------|
| Isotretinoin alone | £60,459 | 16.45 | | | |
| Dinutuximab beta + isotretinoin | £224,234 | 18.61 | £163,775 | 2.16 | £75,831 (£79,493) |

OS extrapolation: spline k=1 scale=hazards; EFS: spline k=1 scale=odds

| | | | | | |
|---------------------------------|----------|-------|----------|------|--------------------------------------|
| Isotretinoin alone | £60,459 | 16.45 | | | |
| Dinutuximab beta + isotretinoin | £224,192 | 17.96 | £163,733 | 1.51 | £108,301 (£121,563) |

OS extrapolation: spline k=2 scale=hazards; EFS: spline k=1 scale=odds

| | | | | | |
|---------------------------------|----------|-------|----------|------|----------------|
| Isotretinoin alone | £60,459 | 16.45 | | | |
| Dinutuximab beta + isotretinoin | £224,898 | 18.34 | £164,439 | 1.89 | £87,164 |

DSU's scenario analyses

| | EFS: spline OS: gompertz | EFS: spline OS: spline k=1 | EFS: gen. gam. OS: gompertz | EFS: gen. gam. OS: spline k=1 |
|---------------------------------|-----------------------------|-------------------------------|--------------------------------|----------------------------------|
| Cure points | | | | |
| 5 years | £60,824 | £61,222 | £62,329 | £62,747 |
| 6 years | £71,709 | £74,818 | £76,854 | £80,492 |
| 7 years | £68,100 | £74,701 | £74,553 | £82,715 |
| 8 years | £66,700 | £77,795 | £74,343 | £88,771 |
| 9 years | £71,564 | £91,432 | £82,090 | £110,224 |
| Concomitant IL-2 | | | | |
| 41% | £86,215 | £123,135 | £101,888 | £159,732 |
| 51% | £88,858 | £126,911 | £105,079 | £164,735 |
| Duration of chemotherapy | | | | |
| 2 years | £69,657 | £99,162 | £80,554 | £125,855 |
| 3 years | £61,330 | £86,806 | £68,720 | £106,689 |

Summary: Preferred assumptions

Company and DSU

| | Company | DSU |
|--------------------------------------------------------|----------------|------------------------------------|
| MAIC | As requested | Corrected for minor errors |
| <u>Survival analysis</u> | | |
| Isotretinoin data | Yu et al. 2010 | Yu et al. 2014 |
| Isotretinoin extrapolation: | | |
| • Overall survival | Gompertz | N/A; used Kaplan-Meier data |
| • Event-free survival | Gompertz | N/A; used Kaplan-Meier data |
| Dinutuximab extrapolation: | | |
| • Overall survival | Gompertz | Gompertz, spline k=1 or spline k=2 |
| • Event-free survival | Gompertz | Spline k=1 |
| Costs | As requested | Correction to topotecan |
| Utilities | | As requested: Ara et al. (2010) |
| Duration of chemotherapy post treatment failure | 1 year | 1 year |
| Concomitant IL-2 | 0% | 0% |
| Cure threshold | 10 years | 10 years |

End of life

| NICE criteria | DSU modelled estimates |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------|
| Treatment indicated for patients with a short life expectancy, normally less than 24 months | Life expectancy with isotretinoin only: 379 months (31.5 years) |
| 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 | Incremental gain with dinutuximab beta ranges from 30 to 53 months , across the range of ICERs considered to be most plausible |

Key issues

- Most appropriate data for isotretinoin: 2010 or 2014 analysis
 - 2014 data considered more appropriate in dinutuximab alpha appraisal
 - If using 2014 analysis, is it more appropriate to extrapolate survival with isotretinoin beyond 70 months (company's approach) or use the direct Kaplan-Meier data (DSU's approach)?
- Most appropriate extrapolations in the dinutuximab arm:
 - EFS (gompertz [Company], spline k=1 scale=odds or generalised gamma [DSU])
 - OS (gompertz [Company and DSU], spline k=1 scale=hazards or spline k=2 scale=hazards [DSU])?
- Likely duration of chemotherapy after treatment failure
- Proportion of concomitant IL-2 use that best reflects UK practice
- Most appropriate cure threshold
- End of life considerations
- Most plausible ICER
- Any uncaptured benefits or equalities issues