Slides for public- contains no ACiC

Lead team presentation

Dinutuximab beta EUSA (dinutuximab beta) for high-risk neuroblastoma [ID910]

1st Appraisal Committee meeting

Committee D

Lead team: William Turner, Peter Hall and Malcolm Oswald

Chair: Gary McVeigh

ERG: BMJ-TAG

NICE team: Orsolya Balogh, Fay McCracken, Helen Knight

Company: EUSA Pharma (UK)

23 November 2017

Key issues: Clinical effectiveness

Overarching issues:

- Robustness of APN311-302 and the naive comparison for estimating treatment effect in the high-risk population
  - suitability for decision making
- No Match Adjusted Indirect Comparison (MAIC) or Simulated Treatment Comparison (STC) provided in company submission for the high risk population
  - preferred method for estimating treatment effect
- Robustness of APN311-303 and APN311-202 and the naïve comparison to estimate treatment effect in the relapsed and refractory (R&R) population
  - suitability for decision making given all patients in NHS practice receive dinutuximab beta first line & company does not support retreatment

Other issues:

- Generalisability of results from APN311-303 and APN311-202 for the R&R population to the NHS in England?
- Dosing schedule in APN311-302 (five daily infusions) does not reflect what is expected in NHS clinical practice
- Will IL-2 be used in UK practice in line with the marketing authorisation?
- More than half of the people experienced a Grade 3 or Grade 4 level infections

Disease background

- Neuroblastoma is a cancer of embryonic nerve cells called neural crest cells and has a diverse clinical presentation and prognosis depending on the tumour biology and cytogenetics
- Commonly occurs in adrenal glands (located above kidneys) or any nerve tissue of the sympathetic nervous system which runs alongside the spinal cord (neck, chest, abdomen and pelvis)
- Neuroblastoma usually affects children 5 years of age and under
- 90% of neuroblastoma cases are diagnosed by 5 years of age

High-risk and relapsed/refractory neuroblastoma

- Based on clinical stage of tumour; other prognostic factors, a person can be at very low, low, intermediate or high risk of relapse
- High-risk neuroblastoma: Consensus definition (International Neuroblastoma Risk Group):
    - age 1 year old or older
    - disease spread
    - the number of copies (amplification) of the MYCN oncogene
    - the amount of DNA (ploidy) in the neuroblastoma cells before autologous stem cell transplant, and
    - unfavourable tumour histopathology (tumour tissues which look abnormal)
- Relapsed or refractory neuroblastoma: disease does not necessarily need to be diagnosed as high-risk neuroblastoma initially
- Very-low, low, and intermediate risk patients without MYCN amplification can experience relapse or suffer from refractory disease
- Relapse occurs in 50% of high-risk cases (long-term survival from relapsed, high-risk neuroblastoma is currently <10%)

Dinutuximab beta EUSA

Marketing authorisation (MA) granted May 2017	• 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 EUSA should be combined with interleukin-2 (IL-2) • MA granted under exceptional circumstances (when applicant can't provide comprehensive data on the efficacy and safety; approval on the basis that more data be obtained and submitted for regular review)
Mechanism of action	Immunotherapy - a monoclonal, chimeric antibody that targets GD2, a glycolipid in neuroblastoma cells
Administration	Intravenous infusion
Dosing frequency	• Continuous infusion over the first 10 days of each course at the daily dose of 10 mg/m^2 ***[used in the company's model]*** • Five daily infusions of 20 mg/m^2 administered over 8 hours, on the first 5 days of each course ***[used in the main study APN311-302]***
List price (excluding VAT)	• Acquisition cost: £7,610 per vial • Average cost of a course of treatment: BSA of 0.63m^2; age 3: £152,200 • No patient access scheme

Relevant NICE Technology Appraisals

ID799 – Dinutuximab alpha

- Dinutuximab alpha (Unituxin - United Therapeutics Corporation): NICE STA (GID-TAG507) for treating high-risk neuroblastoma following myeloablative therapy and autologous stem cell transplant → *not recommended*
- Appealed by Solving Kids Cancer
  - Appeal ground 1(b): In making the assessment that preceded the recommendation, NICE has exceeded its powers
    - There has been a breach of Section 11 of the Children Act 2004, Article 3 of the UN Convention on the Rights of the Child and human rights legislation
  - Appeal Ground 2: The recommendation is unreasonable in the light of the evidence submitted to NICE
    - It was unreasonable for the Institute to use a 10-year cure point, given the evidence before it

→ Appeal Panel upheld both appeal points

- Appraisal was suspended in February 2017 when the European marketing authorisation was withdrawn at the request of the holder - cited production issues and a decision to supply only the US market as reasons for the request

Potential place of dinutuximab beta in current treatment pathway

High-risk neuroblastoma: 3 distinct phases of treatment

- Multi-agent chemotherapy, surgery

- High-dose chemotherapy (also known as myeloablative therapy) and autologous stem cell transplant, radiotherapy

- Isotretinoin [Dinutuximab beta + isotretinoin + interleukin-2?*]

Source: Figure 1 of the company submission

***IL-2 be given to only those not achieving complete response to induction therapy**

Relapsed/Refractory (R/R) neuroblastoma:

No defined NHS pathway for treating relapsed neuroblastoma, treatment usually comprises chemotherapy, radiotherapy and surgery. All patients would be treated through a clinical trial [**Dinutuximab beta+ isotretinoin + interleukin-2?**]

Decision problem (final scope)

	Final scope issued by NICE	Decision problem addressed in the company submission	ERG comment
Population	People with high-risk neuroblastoma who have had myeloablative therapy (MAT) and autologous stem cell transplant (ASCT)	Patients with high-risk neuroblastoma, 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	APN311-302 enrolled patients who achieved at least a partial response to induction therapy and represents a narrower population than scope and marketing authorisation
Intervention	Dinutuximab beta EUSA	As per scope	-
Comparators	Isotretinoin Dinutuximab (subject to NICE guidance)	Isotretinoin alone Dinutuximab not relevant because of withdrawal of marketing authorisation (MA)	ERG agrees with company
Outcomes	• Overall survival (OS) • Progression-free survival (PFS) • Adverse effects of treatment • Health-related quality of life	• Overall survival (OS) • Event-free survival (EFS) • Adverse effects of treatment • Tumour response rate • Health-related quality of life	-
Subgroups	• People with relapsed disease • People with refractory disease ➢ ID799 (Dinutuximab alpha, Unituxin) considered only high-risk population	Company suggested simplifying the technology evaluation and focus on high-risk neuroblastoma patients who have not previously received Dinutuximab beta EUSA	ERG questions the relevance of the R/R population with regard to the comparability of patients in clinical trials and patients seen in UK

Patient Perspectives

- Submissions from: Solving Kids Cancer, Neuroblastoma UK
- Living with neuroblastoma:
  - “it puts a high degree of strain on the family trying to balance the visits to hospital, clinic appointments, work, childcare and the needs of siblings...often means a parent giving up work...financial uncertainty”
  - “Paucity of treatments...clear unmet need in a very vulnerable patient population of children most whom are under the age of 5“
  - “Communication & explanation of activity and treatments can be hit and miss”
- Dinutuximab beta:
  - “extends periods of remission for some children, leading to an improved long-term survival rate with more children being cured”
  - “particularly when given in combination with IL-2, can make children seriously unwell... however, the side-effects (generally) resolve themselves once each cycle of treatment has been completed”
  - “certain patients may be more receptive to the treatment than others”
  - “if NICE issues a negative guidance...between 20 and 30 families per year will seek to fundraise...the £250,000-£500,000” for treatment

Clinician perspectives

- Submissions from: Children's Cancer and Leukaemia Group (CCLG)
- High-risk neuroblastoma and relapsed/refractory are different
- "Outcome for children with high risk neuroblastoma has lagged behind, and it accounts for a disproportionately high number of childhood cancer deaths"
- "Since 2010 almost all patients within the UK with high risk neuroblastoma have received anti-GD2 (Dinutuximab or dinutuximab beta)"
  - "so trials are reflective of the whole population"
  - "anti-GD2 now considered a standard of care...in the UK, across Europe and the US"
- "Dinutuximab beta is an innovative treatment modality to complement other modalities used"
- "in patients with relapsed/refractory disease, 40-50% objective response rates seen"
- Implementation:
  - "Well defined pathway, with little variation across UK, or indeed across Europe"
  - "ordinarily delivered over 5 cycles" unless progression of disease or unacceptable toxicity
  - "Specialist paediatric oncology treatment centres only"
  - "would not require any new investment, training etc."

Clinical evidence

- **One randomised controlled trial (RCT) in high-risk population:**
  APN311-302 (one phase of the HR-NBL-1 trial) - phase 3, open label, multinational trial designed to assess the efficacy and safety of adding interleukin-2 to a maintenance treatment regimen of dinutuximab beta and isotretinoin
- Everyone in the study received dinutuximab beta, there is **no direct evidence for dinutuximab beta versus isotretinoin alone**
  - Company carried out a naïve comparison using historical controls from an earlier phase of APN311-302
  - ➢ ID799: ANBL0032 Phase 3, multicentre, prospective, partially randomised, active-controlled trial (n=226) only in high-risk neuroblastoma; immunotherapy (n=113) and standard therapy (n=113)

- **Two observational studies in relapsed or refractory population:**
  APN311-202 (prospective design) and APN11-303 (retrospective design):
  Aim of both studies: to identify a tolerable treatment schedule of dinutuximab beta that reduced pain-toxicity profile yet maintained immunomodulatory effect
  - [redacted] in APN311-202 or APN311-303 had previously received dinutuximab beta – evidence on retreatment not available
  - Company does not support re-treatment with dinutuximab beta in R/R population (no ongoing studies and none planned)

Clinical trial evidence: High risk population

APN311-302

Trial	Population	Intervention	Outcomes
Randomised, phase III, open-label, multicentre study (intention-to-treat (ITT)=406; actual patients involved in analyses=370) [redacted]/370 people recruited from UK	- Established diagnosis of neuroblastoma according to the INSS - Age < 21 years - High-risk neuroblastoma - Achieved at least a partial response to induction therapy - No previous chemotherapy except for 1 cycle of etoposide and carboplatin - Tumour cell material available for determination of biological prognostic factors	- Dinutuximab beta + isotretinoin (N=180) - Dinutuximab beta + isotretinoin + IL-2 (N=190) Dinutuximab beta admin: five 28-day cycles of dinutuximab beta (20 mg/m²/day over 5 days) Isotretinoin admin: six 28-day cycles of oral isotretinoin (160 mg/m²/day over 14 days)	1° • 3-year EFS 2° • Overall survival • Incidence of relapse/refractory • Incidence of death, infection • Overall response • Toxicity • Relationship of survival, EFS, response rates

- ID799: administered at a daily dose of 17.5 mg/m^2 on days 4–7 during courses 1, 3 and 5 (each course lasting ~ 24 days) and on days 8–11 during courses 2 and 4 (each course lasting ~ 28 days). Course 6 includes treatment with isotretinoin alone

ERG critique of trial design & conduct: APN311-302 High-risk population

- Open-label design introduces bias
- Lack of pre-specified time point for assessment of disease status during or after treatment → for EFS, unclear whether the exact point of disease progression is captured
- Data presented do not use ITT principles
- Complete case analysis based on 370 people for whom an electronic case report form (eCRF) was available, instead of 406 randomised
  - Unclear why an eCRF was not available for all randomised patients
  - Some people did not receive any treatment
- Short-term dosing schedule (over 5 days) → not likely to be in line with UK clinical practice (suggested that it would be continuous over 10 days)
- No evidence on whether rate of infusions affects clinical outcomes
- Data from 302 is immature and length of follow up insufficient to determine clinical effectiveness
  - Not clear whether any benefit is maintained in the longer term

Clinical trial evidence: Relapsed and refractory populations

APN311-202 & -303

Trial name	Population	Intervention	Primary outcomes
APN311-202 **n= 44**	• Primary refractory or relapsed neuroblastoma • Aged 1-21 years • Neuroblastoma diagnosed according to INSS • Received at least 1 previous high-dose treatment	100mg/m^2 treatment course of dinutuximab beta, administered as one continuous 10-day infusion at 10mg/m^2/day, in cycles of 35 to 49 days	Determine tolerable treatment schedule that reduces pain-toxicity profile of dinutuximab beta
APN311-303 **n= 54**	• Patients with high-risk, relapsed or refractory neuroblastoma • Aged 1-45 • Estimated life expectancy of at least 12 weeks • Could not get adequate treatment through routine medical treatment/clinical trials	Dinutuximab beta given in combination with fixed doses of IL-2 and oral isotretinoin	Retrospectively evaluate safety and assess the pain-toxicity profile of a prolonged continuous infusion of dinutuximab beta

- APN311-202 is an ongoing prospective study, number of people recruited from the UK to date is unclear
- APN311-303 is a retrospective analysis administered at a single site in Germany

ERG critique of trial design and conduct: APN311-202 & 303 in relapsed/refractory population

- No formal statistical hypotheses, analyses methods or power calculation specified *a priori*, in 202 no clinical outcome was pre-specified
- Considerable disparity across APN311-202, APN311-303 and the published literature in the reported proportions of people with MYCN amplification → key prognostic factor in neuroblastoma
- In the UK since 2009 most patients with relapsed disease have received dinutuximab first-line through participation in the HR-NBL-1 / APN311-302 study
- [redacted] in 202 and 303 previously received dinutuximab beta
- There is considerable uncertainty in the extent to which the populations in the two studies are generalisable to those in England with R/R neuroblastoma

KM curve for EFS APN311-302 - High-risk population

Concomitant administration of IL-2 does not improve EFS

Source: Figure 4 of the company submission

EFS at 1 year (%)	**72.3%**	**72.3%**
EFS at 2 years (%)	**63.2%**	**66.3%**
EFS at 3 years (%)	**55.4%**	**61.2%**
Log-rank test	p = 0.3202*	
Last cut-off (August 2017)	[redacted]	[redacted]

*p-values refer to the analysis based on 3 years' follow-up (not latest data-cut)

KM curve for OS APN311-302 - High-risk population

Concomitant administration of IL-2 does not improve OS

Source: Figure 5 of the company submission

OS at 1 year (%)	**86.3%**	**87.9%**
OS at 2 years (%)	**76.0%**	**75.4%**
OS at 3 years (%)	**64.1%**	**69.1%**
Log-rank test	p = 0.6114*	
Last cut-off (August 2017)	[redacted]	[redacted]

*p-values refer to the analysis based on 3 years' follow-up (not latest data-cut)

Adjusted KM curves for EFS

APN311-202 and APN311-303 – R/R population

Source: Figure 5 of the ERG report

Adjusted KM curves for OS

APN311-202 and APN311-303 – R/R population

Source: Figure 8 of the ERG report

KM estimates of EFS and OS

APN311-202 and APN311-303 – R/R population

Time	Relapsed neuroblastoma				Refractory neuroblastoma			
	APN311-202 (N=19)		APN311-303 (N=29)		APN311-202 (N=25)		APN311-303 (N=15)	
	EPAR	CS	EPAR	CS	EPAR	CS	EPAR	CS
EFS 1 year	42.1%	[redacted]	44.8%	[redacted]	60.0%	[redacted]	58.2%	[redacted]
EFS 2 years	36.8%	[redacted]	31.0%	[redacted]	55.7%	[redacted]	29.1%	[redacted]
EFS 3 years	36.8%	[redacted]	24.1%	[redacted]	44.6%	[redacted]	29.1%	[redacted]
OS 1 year	73.7%	[redacted]	89.7%	[redacted]	100.0 %	[redacted]	92.9%	[redacted]
OS 2 years	42.1%	[redacted]	69.0%	[redacted]	78.3%	[redacted]	69.8%	[redacted]
OS 3 years	42.1%	[redacted]	54.7%	[redacted]	62.5%	[redacted]	69.8%	[redacted]

Source: Tables 19 and 22 of the ERG report

Key: EPAR: European public assessment report; CS: company submission, NR: not rated; NE: not estimable

ERG critique on EFS and OS trial results

APN311-302 (high risk population):

- Clinical data on the comparative clinical effectiveness of dinutuximab beta versus no dinutuximab beta are not available from a head-to-head study → APN311-302 represents the best available evidence, but does not inform the decision problem

- ERG notes [redacted] in the reported number of events at 3 years for EFS and OS in APN311-302 (August 2017 cut-off)
  - OS data presented at 5 years seems insufficient length of follow-up to assess clinical-effectiveness (mean follow-up in APN311-302 was [redacted], which equates to [redacted]: median follow up was [redacted] days)
  - Lack of long-term follow-up of events (i.e., limited to 5 years) potentially affects the applicability of the results for EFS and OS to the decision problem

ERG additional work for high risk population:

- Using the adjusted time-to-event data supplied by the company, carried out a Cox proportional hazard analysis to generate an effect estimate of IL-2 versus no IL-2 added to dinutuximab beta and differentiation therapy with isotretinoin

APN311-202 and 303 (relapsed and refractory population):

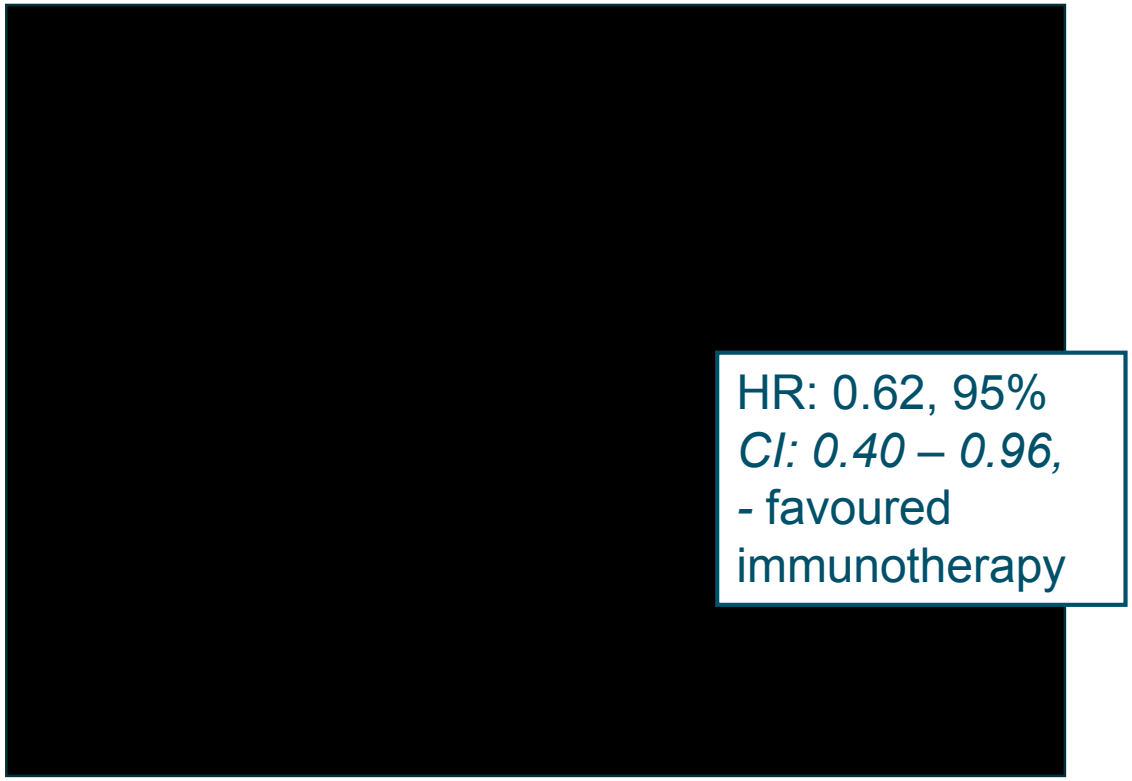
- Single-arm studies, not appropriate for capturing time-to-event data, such as EFS and OS

ERG additional work: Adjusted KM curve for EFS for APN311-302

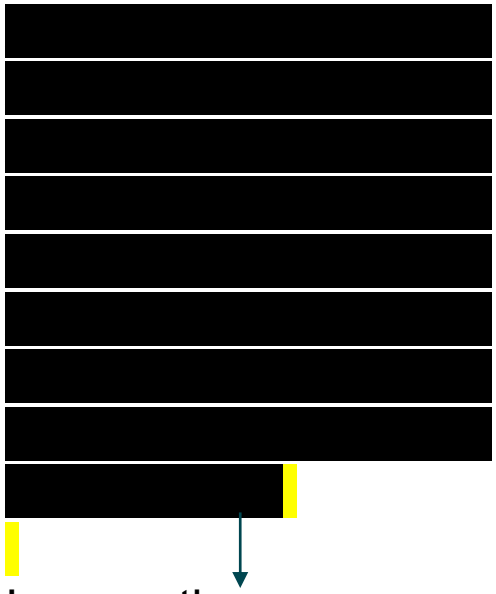
ERG:
Addition of [redacted]

Source: Figure 4 of the ERG report

ERG additional work: Adjusted KM curve for OS for APN311-302



ERG: Addition of



Immunotherapy can delay, and possibly prevent mortality

Source: Figure 7 of the ERG report

Key: HR: hazard ratio; CI: confidence interval

Adverse events in high risk population

APN311-302

- Dose reductions or premature discontinuations of dinutuximab beta or IL-2 [redacted] in patients receiving concomitant treatment with IL-2
- Mean [redacted] of dinutuximab beta was [redacted], as was the total amount of dinutuximab beta [redacted] of the study
- [redacted] of dinutuximab beta occurred [redacted] treatment ([redacted])
- Changes in dinutuximab beta treatment in both groups were because of toxicity - of those receiving IL-2, [redacted] had a [redacted]
- Exposure to [redacted] the two groups ([redacted])

- There were 238 instances of infection - 106 instances in patients not receiving IL-2 and 132 instances in patients receiving IL-2
  - No IL-2 group: [redacted] of the infections Grade 3 severity, and 2 Grade 4 severity
  - IL-2 group: [redacted] cases Grade 3, and 6 Grade 4

  Figures based on 5-day infusion schedule as per APN311-302, rather than 10 day continuous schedule used in UK practice and modelled

Adverse events in R/R population

Summary of adverse effects of special interest experienced by ≥20% of people and thought to be related to dinutuximab beta

Adverse effect of special warning or precaution of use	APN311-202 (N=44)	APN311-303 (N=54)
Pain	28 (63.6%)	35 (64.8%)
Hypersensitivity reactions		
Hypotension	22 (50.0%)	32 (59.3%)
Capillary leak syndrome	15 (34.1%)	45 (83.3%)
Eye disorders[a]	10 (22.7%)	13 (24.1%)
Peripheral neuropathy	Unclear	Unclear
Infections and infestations[b]	13 (29.5%)	3 (5.6%)
Haematologic toxicities	Unclear	Unclear
Laboratory abnormalities	Unclear	Unclear

[a] SmPC specifies neurological disorders of the eye as the adverse effect with special warning or precaution for use.

[b] SmPC specifies systemic infections as the adverse effect with special warning or precaution for use.

Abbreviation: SmPC, summary of product characteristics

Source: Table 26 of the ERG report

ERG critique on adverse events

High-risk population

- APN311-302: data on the AEs associated with the addition of IL-2 to dinutuximab beta and isotretinoin
- As anticipated (based on the known AE profile of IL-2), severe adverse effects occurred more frequently in people receiving IL-2 (46% with IL-2 vs 27% without IL-2; event rate not reported in CS)
- Capillary leak syndrome, platelet abnormalities, hypotension, infections, nausea or vomiting, fever, and pain related to dinutuximab beta were more common with concomitant administration of IL-2
- More than half of patients experienced Grade 3 or Grade 4 level infection

R/R population

- Each person in APN311-202 and APN311-303 experienced a treatment-emergent adverse event (TEAE)
- The proportion of people experiencing a TEAE remained high throughout the studies
- Pain and hypotension were each experienced by a similar proportion of people in APN311-202 compared with APN311-303
- Considerably larger proportion of people experienced capillary leak syndrome in APN311-303 (83.3%) compared with APN311-202 (34.1%)

No direct evidence comparing dinutuximab beta with comparator

Company performed naïve indirect comparisons for OS only
No MAIC or STC presented in CS (preferred method)

High-risk population
Dinutuximab beta + isotretinoin with/or without IL-2 vs. historical control

Historical controls from R1 phase of HR-NBL-1 (comparing busulfan and melphalan hydrochloride (BuMel) vs. carboplatin, etoposide and melphalan (CEM) as consolidation myeloablative therapy in high-risk neuroblastoma) n=450

Relapsed or refractory population
Dinutuximab beta plus IL-2 plus isotretinoin vs. no dinutuximab beta

2 historical controls:
a) R1 phase of HR-NBL-1 who experienced relapse n=52
b) Garavanta retrospective study comprised only those with a date of initial diagnosis of 1999 or later. Patients received tumour resection, chemotherapy and MAT followed by ASCT, but no immunotherapy used n=29

- Difference in OS evaluated using the log-rank test
- HRs and 95% confidence intervals (Cis) provided for the indirect comparisons of the relevant APN311 study versus historical control from R1
- HR adjusted for prior treatment (BuMel vs CEM, MYCN status, and age at diagnosis and INSS stage)

➢ ID799 STA used HRs directly from RCT data

Company's KM curves for OS of isotretinoin alone vs. dinutuximab beta-containing treatment

High-risk population

Source: Figure 10 of the ERG report

Relapsed/Refractory population: Company's KM curves for OS

KM curves for overall survival for APN311-303 versus Garaventa

KM curves for overall survival for APN311-202 plus APN311-303 versus Garaventa

Source: Figures 14, 15 of the ERG report

ERG's critique of company's naïve indirect comparisons to estimate OS between treatments

- Indirect treatment comparison involving dinutuximab beta was not possible → company carried out a naïve comparison
  - ERG requested a Match Adjusted Indirect Comparison (MAIC) at clarification, company did not provide it
- ERG disagrees with company: naïve indirect comparisons versus historical controls at risk from the same type of bias arising from lack of randomisation, also from confounding

High-risk population vs historical control:

- APN311-302 and the historical control R1 are comparable in terms of baseline characteristics – however, there is an imbalance between groups in number of residual disease → bias to results
- People in APN311-302 received BuMel as consolidation myeloablative therapy ←→ R1: half of the people received CEM as their consolidation therapy

Relapsed/Refractory population vs. historical controls

- People in APN311-202 and APN311-303 might not be representative of those in the UK with these stages of disease
- Garavanta: historical control of 29 people; 24% of patients had progressive disease – different outcome to those who are not at that stage of disease; broad range of treatment
- Baseline characteristics not reported for cohorts
- **Interpret results with extreme caution**

Key issues: Clinical effectiveness

Overarching issues:

- Robustness of APN311-302 and the naive comparison for estimating treatment effect in the high-risk population
  - suitability for decision making
- No Match Adjusted Indirect Comparison (MAIC) or Simulated Treatment Comparison (STC) provided in company submission for the high risk population
  - preferred method for estimating treatment effect
- Robustness of APN311-303 and APN311-202 and the naïve comparison to estimate treatment effect in the relapsed and refractory (R&R) population
  - suitability for decision making given all patients in NHS practice receive dinutuximab beta first line & company does not support retreatment

Other issues:

- Generalisability of results from APN311-303 and APN311-202 for the R&R population to the NHS in England?
- Dosing schedule in APN311-302 (five daily infusions) does not reflect what is expected in NHS clinical practice
- Will IL-2 be used in UK practice in line with the marketing authorisation?
- [redacted] people experienced a Grade 3 or Grade 4 level infections

Cost-effectiveness evidence

Key cost-effectiveness issues

- **Clinical inputs:**
  - Lack of robust clinical inputs - no MAIC/STC estimate of treatment effect for the high risk population
- **Modelling assumptions:**
  - Treatment administration – weighted average of costs using body surface area categories from APN311-302 should have been used *(key driver)*
  - Failure state resource use and treatment costs not appropriate
  - Impact of infections not captured in the modelling
  - Dosing schedule - continuous infusions over 10 days modelled in line with NHS practice, but no evidence demonstrating impact on efficacy and safety of this schedule (5 day infusions in trial)
  - Appropriateness of the 10-year cure assumption (*upheld appeal point in ID799*)
  - Utility values – Ara et al should have been used to adjust for age
  - 1.5% discount rate for costs and health effects may be appropriate in this case *(as concluded in ID799)*
- **Other issues:**
  - Lack of robust cost effectiveness estimates for decision making
  - Legal issues regarding paediatric patient group *(issue in ID799)*
  - End-of-life criteria not met (not met in ID799 either)
  - No evidence presented regarding health related benefits not captured by the QALY
  - No equalities issues raised

Company's model structure

Partitioned-survival (area-under-the-curve) model to assess cost-effectiveness of dinutuximab beta vs isotretinoin

Partitioned Survival Analysis with 3 states and starting age 3 years:

- **Event-free state** (EFS)
- **Failure state** (FS)
- **Death**

➢ ID799 model health states: stable, failure, and death

- Proportion of patients occupying the different health states from cycle 0 until the point of the cure threshold based on a cohort-based partitioned survival model
  - *Referred to as the 'short-term model'*
- Economic outcomes for the first 5 cycles (first 5 months) of the model are estimated in a decision-tree-based model
- The economic model after the cure threshold is also a cohort-based partitioned survival model
  - *Referred to as the 'long-term model'*
- Time: monthly cycles for the short-term model and yearly cycles for the long-term model
- Lifetime horizon of 90yrs, no half-cycle correction applied, NHS & PSS perspective
- Discount rate 1.5% [ID799: 1.5%]

Focus of economic analyses

High risk population, R/R not considered further

- Company provided 2 models
  - high-risk population
  - R/R population
- ERG has focussed its review on the high-risk population
- It **did not consider the R/R population further** due to:
  - Evidence base for the relapsed model being extremely poor and unfit for purpose, hence it is not robust enough to inform decision making
  - Company's clarification response showed that the fully adjusted HRs produced a HR below 1 (when using APN311-202 study), therefore the results and the model results lack clinical meaningfulness
  - Dinutuximab beta is always given first line in the UK and clinicians would not retreat patients unless there was evidence supporting this (there are no ongoing or planned studies)
  - The company doesn't support retreatment with dinutuximab beta

Company's modelling assumptions

Element	ID910 Company assumption & ERG response	ID799 committee conclusions
Dosage	Continuous infusion over the first 10 days ERG: 10 day continuous infusions reflects UK practice (clinical trial 5 days) → unclear if the method of admin impacts treatment effectiveness and the safety profile of the drug	Daily dose of 17.5 mg/m^2 on days 4–7 during courses 1, 3 and 5 (lasting ~ 24 days) and on days 8–11 during courses 2 and 4 (lasting ~ 28 days) Course 6 includes treatment with isotretinoin alone
Cure threshold	a) patients in EFS state for 5yrs are cured b) after 10yrs in EFS a patient assumed cured (Base case) ERG: 10yrs	10yrs (but appealed)
Mortality rate in cured state	5.6 factor applied to the age and gender matched mortality in the UK general population ERG: agrees, but points out that difficult to estimate the increase	Annual standardised mortality ratio of 5.6 from the childhood cancer survivor study for stable health state
Costs and resource use in Failure state	Administration cost for FS based on procurement cost for chemotherapy drugs (£2,620.54) ERG: Cost of a hospital day (£934/day) should be used to calculate the admin costs per cycle (total of £4,670 for 10 days in the hospital). Should be adjusted for wastage Assumption that patients entering FS receive chemotherapy for life. ERG: need assumptions for treatment duration & for the resource use to manage relapsed patients who have gone off chemotherapy and are still alive in the FS	Cost of a hospital day should be used to calculate the admin costs per cycle

*assumptions used in ID799 dinutuximab alpha are included for reference

Element	ID910 Company assumption & ERG response	ID799 committee conclusions
HRQOL	12.5% decrement associated with having the disease compared with the general population based on Portwine et al ERG: agrees with having a constant utility decrement applied after the cure threshold, but a few concerns remain about plausibility	13% reduction in general population utility estimate based on Portwine et al – committee agreed reasonable but uncertain
Adverse events	Assumed that utility values for each health state do not differ by treatment arm. Company did not identify any studies from the literature review that estimated the impact of adverse events on patients' QOL, therefore did not include utility values or decrements in the analysis. ERG: unclear if the administration method bears any effect on dinutuximab beta's safety profile → conducted scenario analysis	Adverse reactions during treatment were severe (as reflected in the utility values of 0), and the effects stopped when treatment ended
Admin – Body surface area	Median BSA from APN311-302 (0.63m^2, 4 vials) used for most of the cost calculations. For patients with a BSA greater than 0.83m^2, 6 vials may be required to achieve the recommended dose. Company assessed impact in a scenario analysis ERG: Company did not provide the BSA categories for APN311-302, but from the maximum height and weight provided in the CSR, the ERG estimated a maximum BSA of 1.66m^2 in the trial. Remains uncertain what percentage of patients would have a BSA greater than 0.83m^2 and thus require 6 vials of treatments	4.8% of patients included in ANBL0032 had a body surface area over 1 $metre^2$ Weighted average to account for additional vials needed for BSA>1m^2
Hospitalisations	APN311-302 study: mean hospitalisation days not reported Model: total of 54 days most due to receiving IL-2, 15 days without IL-2. Hospitalisations for infections not included ERG: Most of the hospitalisations were due to receive IL-2 with dinutuximab	Mean of 35 hospital days based on hospitalisation data from ANBL0032

Element	ID910 Company assumption & ERG response	ID799 committee conclusions
Treatment effectiveness	Dinutuximab arm: KM curves from the 302 study for the 7yrs that KM data were available, then parametric curves (Gompertz) to extrapolate for the 3yr horizon of the short term model Isotretinoin arm: unadjusted KM data from the historical control R1 used to estimate OS Hence naïve comparison of KM (and fitted data) from unadjusted 302 data, with unadjusted R1 data was carried out ERG: Severe concerns with the estimation of treatment effect in the economic analysis (disagrees with the approach of using OS and EFS KM data for dinutuximab beta for 7 years, and then using estimated survival data for 3 years; lack of appropriate: methods; PH assumptions; expert opinion; uncertain use of piecewise approach; log-cumulative hazard plots)	ANBL0032 trial (n=226; International, multicentre, partly randomised, event-driven trial of dinutuximab alpha, GM-CSF, IL-2, and isotretinoin vs isotretinoin)
Discount rate	1.5% ERG: 3.5% should be used in additional scenario analysis	1.5%
EOL	Company does not explicitly state that they are requesting that dinutuximab beta be considered in the end of life setting, but they provide a rationale for end of life considerations ERG: end-of-life criteria not met (life expectancy is uncertain; life extension not available, data immature)	Life expectancy: median 4yrs (doesn't meet criterion) Life extension: 33.7mo (2.81 LYs), (meets this criterion) EOL not met overall

ERG's comment on company's model structure and comparators used in the model

- Modelling approach and structure unnecessarily burdensome; removes transparency → higher probability of errors in formulae, lower probability of all errors being identified
- Quantification of the survival benefit of dinutuximab beta highly uncertain
- Treatment and comparator arms include IL-2 as a treatment (not reported in CS)
- Patients in the trial received 6 cycles of isotretinoin treatment, people in the model received only 5 cycles
- 10 day continuous infusions of dinutuximab beta reflects current practice in the UK, unclear if the method of administration would have had any impact in terms of treatment effectiveness and the safety profile
- Clinical outcomes for R1 patients are negatively biased due to half of the patients receiving CEM instead of BuMel as consolidation therapy, before receiving isotretinoin → likely to be a poor reflection of the maintenance treatment for neuroblastoma patients in the UK
    - Baseline health of the population receiving isotretinoin is likely to be poorer than population receiving dinutuximab beta plus isotretinoin
    - Needs to be adjusted for the type of consolidation therapy to have a valid estimate of relative effectiveness of dinutuximab beta plus isotretinoin compared with isotretinoin

Company's estimation of treatment effect: high-risk population

OS

- ***Dinutuximab arm:***
  - Used KM curves from APN311-302 for approximately 7 years, then used parametric curve to extrapolate clinical data for rest of the short-term model's time horizon (3 years)
  - Final OS and EFS curves based on the respective KM curves available, followed by a parametric tail fitted with Gompertz models for both clinical outcomes
- ***Isotretinoin arm:***
  - Unadjusted KM data from the historical control R1 to estimate OS

➡ Treatment effect in the model based on a **naïve comparison** of KM (and fitted) data from unadjusted APN311-302 data with unadjusted R1 data

EFS

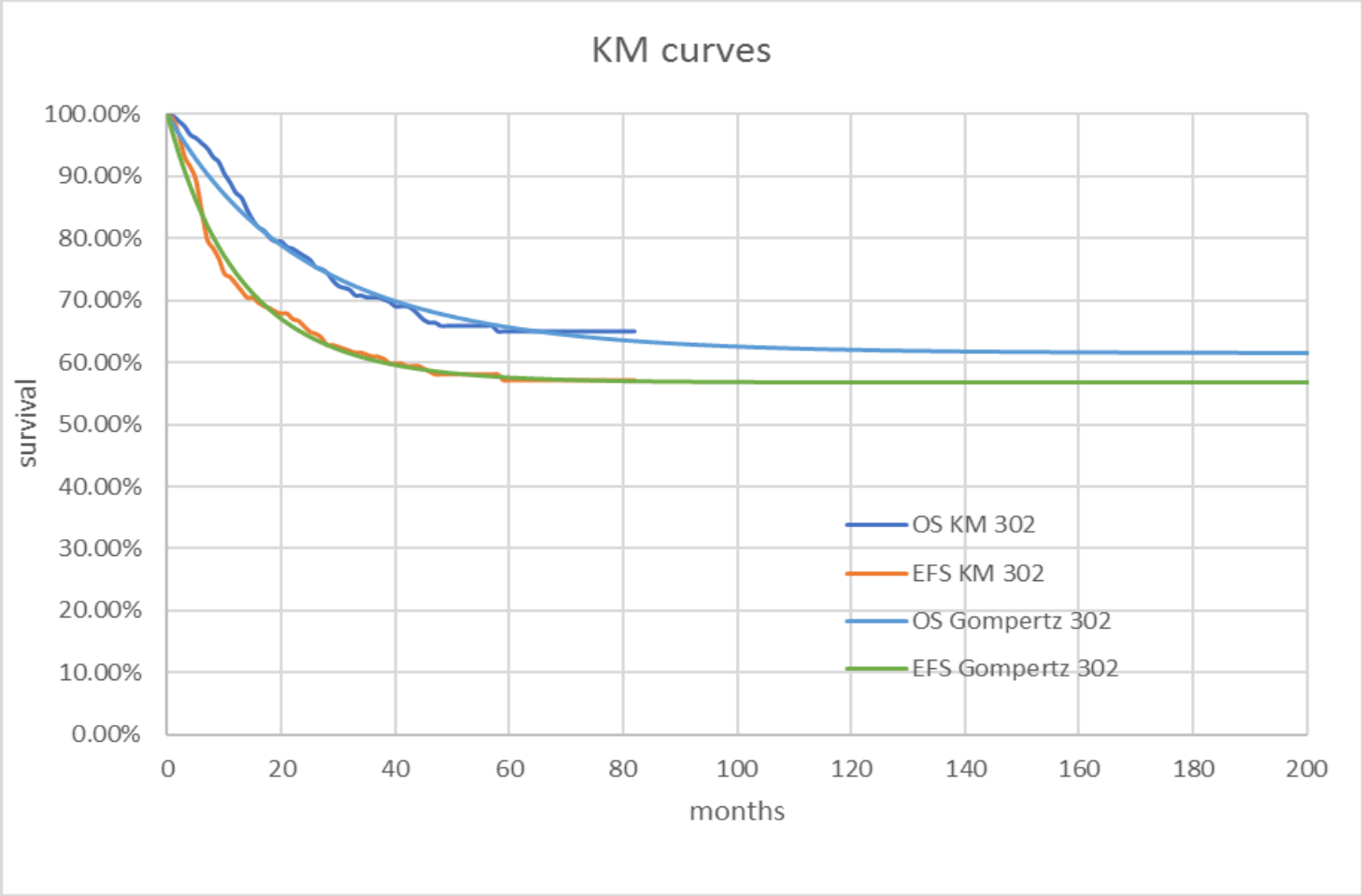
- Absolute separation between OS and EFS is estimated in every cycle - [OSisotretinoin – (OSdinutuximab – EFSisotretinoin)]

ERG - overarching concerns

1. **Lack of maturity of OS data and non-existence of EFS data in historical control R1**
2. **Naïve (unadjusted) analysis of the relative treatment effectiveness of dinutuximab beta compared with isotretinoin**
   - Sampling error; systematic error due to imbalance in prognostic factors and effect modifiers
   - Clinical outcomes for R1 patients are negatively biased due to half the patients receiving CEM instead of BuMeL as consolidation before receiving isotretinoin
   - ERG requested a MAIC of the full 302 population vs. isotretinoin alone in the Yu et al RCT to provide a better comparison than using R1

Company's modelling of treatment-effectiveness

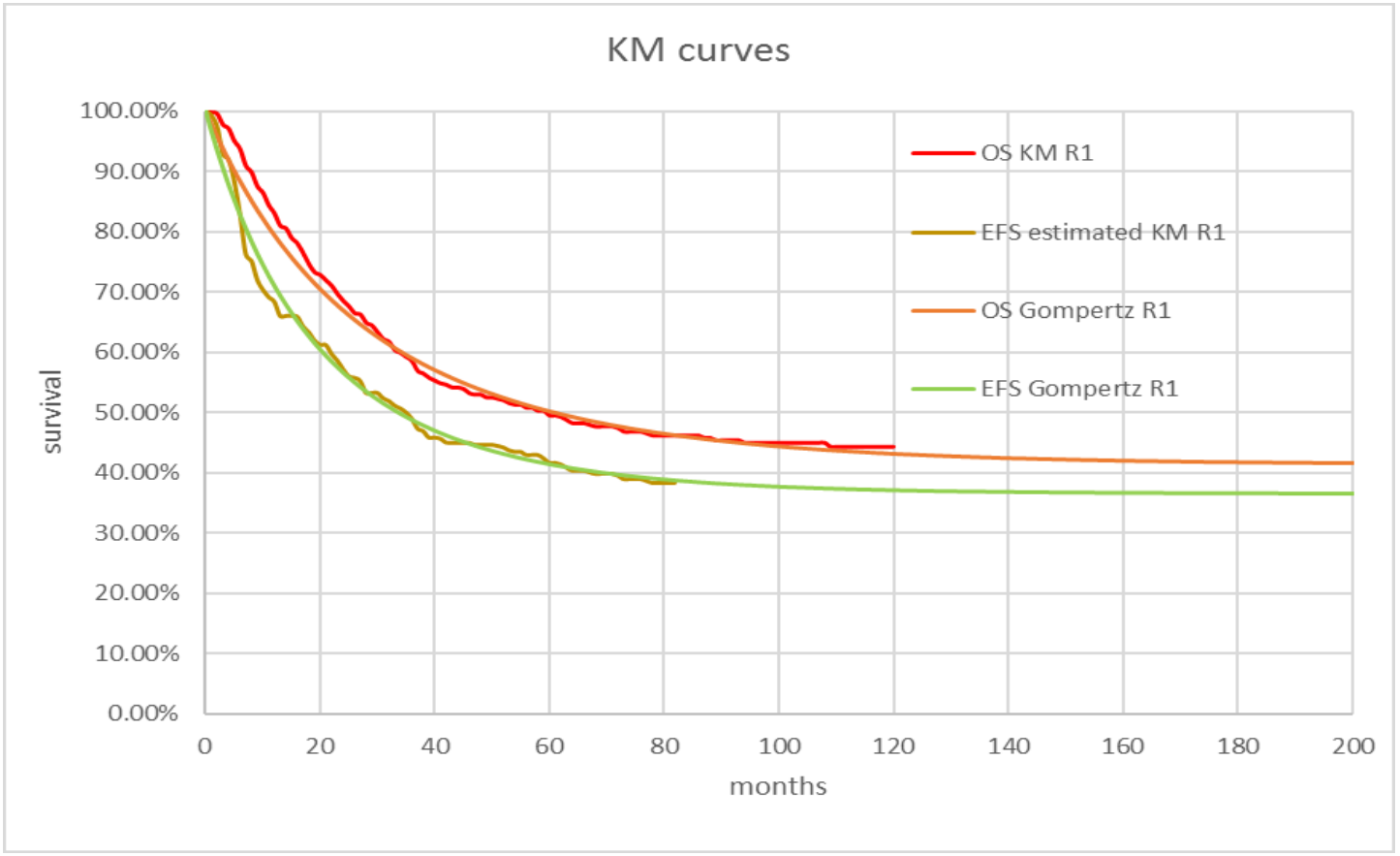
Kaplan-Meier data for OS and EFS for APN311-302 along with the fitted Gompertz curves



Source: Figure 20 of the ERG report

Company's modelling of treatment-effectiveness

KM data for OS for isotretinoin from R1 and estimated KM data for EFS for isotretinoin from R1 along with the fitted Gompertz curves



Source: Figure 21 of the ERG report

Company's adjusted HRs for indirect comparison of OS in APN311-302 vs. historical control R1

At clarification, company provided HRs and 95% CIs for the indirect comparisons of OS, adjusting for prior treatment (BuMel vs CEM), MYCN status, and age and INSS stage at diagnosis

- **ERG concerned about the process for estimating adjusted OS HR, unclear if it included all covariates**

ERG used the OS HR for exploratory analysis

Factors adjusted for	HR[a]	95% CI
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		

Source: Table 36 of the ERG report

HRQOL in the model

- HRQOL not captured in APN311-302 study
  - Health state utility values estimated by applying utility decrements to age-specific UK EQ-5D general population norms
  - EQ-5D norms only available for 18-75yrs+ → used a logistic regression to estimate interpolated utility values for age 0 onward
  - To estimate utilities for EFS and FS, a decrement was applied for the UK EQ-5D general population values to reflect that patients have neuroblastoma

Health states	Dinutuximab beta EUSA	Dinutuximab alpha (ID799)
Stable (0-5 years)	•12.5% decrement • Survivors of high-risk neuroblastoma (0.84); general population (0.96) - from Portwine et al. 2016 and HUI3	0.81 based on patients with residual disease from Barr et al. 1999
Stable (5+ years)		•12.5% decrement • Survivors of high risk neuroblastoma (0.84); general population (0.96) - from Portwine et al. 2014 and HUI
Failure	•41.7% decrement applied to age-specific UK EQ-5D general population norms •Decrement calculated using HUI2 utility value for patients with recurrent disease (0.56) from Barr et al. 2016; HUI3 utility value for general population (0.96) from Portwine et al. 2016	• 0.56 utility value based on patients with recurrent disease from Barr et al.,2016

Key: HUI, health utility index; EQ-5D, euroqol-5 dimensions

ERG critique of HRQOL in the model

- **ERG cannot draw final conclusions on which values should be used to estimate quality of life in the model**
  - Seems more appropriate to account for the impact of age for the entire model, for both the EFS and the FS health states
  - Decrements applied to the UK EQ-5D general population values remain a source of uncertainty
  - Disagree with methodology used to adjust for age, the published algorithm by Ara et al. 2010 should have been used instead
  - Cannot anticipate the impact of using a different methodology for adjusting for age in the final ICER
- **Company assumed that utility value for each health state do not differ by treatment arm**
  - No studies identified from the literature review estimating the impact of AEs on patients' QOL → did not include utility values or decrements associated with AEs
  - AEs are substantially worse for patients on dinutuximab beta than on isotretinoin. The analysis potentially overestimates the quality-adjusted life year (QALY) gain associated with dinutuximab beta, as the impact of its AEs are not being captured on patients' QOL

Failure health state costs and resource use

- **In CS, administration cost used for the FS was based on a procurement cost for chemotherapy drugs rather than delivery of the therapy**
  - ➢ ID799 dinutuximab alpha: ERG concluded that given the FS treatment regimen will be delivered as inpatient care over 5 days (topotecan/cyclophosphamide is given intravenously for 5 days), an inpatient hospital cost would have been more appropriate
  - – ERG agrees with conclusion in ID799, cost of a hospital day (£934 per day) should used to calculate the administration costs per cycle (total of £4,670 for 10 days in the hospital). Chemotherapy procurement cost used in the model originally £2,620.54)
  - – FS costs should also be adjusted for wastage
- **In the CS, once patients enter the failure health state, they accrue the costs associated with the failure state until death**
  - – ERG: treatment regimen associated with FS should only be given until further disease progression or up to one year without progression
  - – More appropriate to calculate the proportion of newly relapsed patients entering the FS in each cycle and track disease progression for these patients
  - – Likely that the FS treatment costs are being overestimated in the analysis

Company's base case results: High-risk population

Clinical inputs into the modelling are not robust, interpret model estimates with caution

Therapy	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Isotretinoin	£190,521	13.97	-	-	£22,338
Dinutuximab beta + isotretinoin	£311,569	19.39	£121,048	5.42	

Abbreviations in table: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life-years

Source: Table 53 of ERG report

ERG **does not consider that a naïve comparison of APN311-302 and R1 data is a reliable method for estimating treatment effectiveness** for use in the company base case

- In response to factual error check, company provided a revised ICER calculated using an MAIC approach
  - No supporting documentation was provided, the ERG has not had an opportunity to critique these results

➢ ID799 for reference:
- Company base-case ICER: £49,000 (without PAS)
- Committee's most plausible ICER: £88,100 (without PAS)

Impact of body surface area on company base case ICER

When maximum BSA is considered, impact on the final ICER is considerable

- BSA: one of main cost effectiveness drivers
- Median BSA from APN311-302 (0.63m^2) used for most of the cost calculations in model
  - Data seem reasonably reflective of what would be seen in UK clinical practice, but estimates used are based on median values instead of mean BSA values
  - In patients with an average BSA of 0.63m^2 → 4 vials of dinutuximab beta are required
  - In patients with a BSA greater than 0.83m^2 → 6 vials may be required to achieve the recommended dose for dinutuximab beta
- Company did not provide BSA categories for APN311-302
  - From maximum height and weight provided in CSR → ERG estimated a maximum BSA of 1.66m^2 in the trial
  - Remains uncertain what percentage of patients would have a BSA greater than 0.83m^2
- Company assessed the impact of changing the BSA estimate used in the economic model on the final ICER (lower BSA ICER: £9,083; upper BSA ICER: £61,576)

ERG corrections to company model

Company's approach	ERG's corrections
Long-term model has annual cycles	Applied a half-cycle correction in the long-term model
5.6 increase in mortality factor applied to only female mortality	Applied to weighted male and female mortality in the UK population
Company included cost of treatment with IL-2 in the isotretinoin arm of the model	ERG does not see a clinical justification for this→ removed the costs of IL-2
Used 7.5 hospital days for the 1st cycle and 2.5 days for the 2nd cycle	Included 10 days for hospitalisation
100% of patients in the dinutuximab arm assumed to receive IL-2	Changed the 100% assumption to 51% of patients (based on proportion in 302)
Not included the administration costs associated with treatment with IL-2	Included it
Undiscounted total costs for the stable and FS of the short-term model	Replaced these with discounted costs
First row of costs and QALYs in the Excel model wasn't included	Included it in the model
Discounting factor estimated on a monthly basis instead of an annual basis	Corrected this to reflect annual discounting in the analysis

Impact of ERG's model corrections on company base case ICER

Clinical inputs into the modelling are not robust, interpret model estimates with caution

Therapy	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Isotretinoin	£172,236	13.61	—	—	£31,366
Dinutuximab beta + isotretinoin	£336,172	18.83	£163,808	5.22	

Abbreviations in table: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life-years.

Source: Table 56 of ERG report

Interpret with caution:

ERG does not consider that a naïve comparison of APN311-302 and R1 data is a reliable method for estimating treatment effectiveness for use in the company base case

- The ERG used the only available evidence to explore two alternative approaches summarised in the following slides

➢ ID799: Total cost of isotretinoin is between £46,573 to £54,671 depending on the assumptions

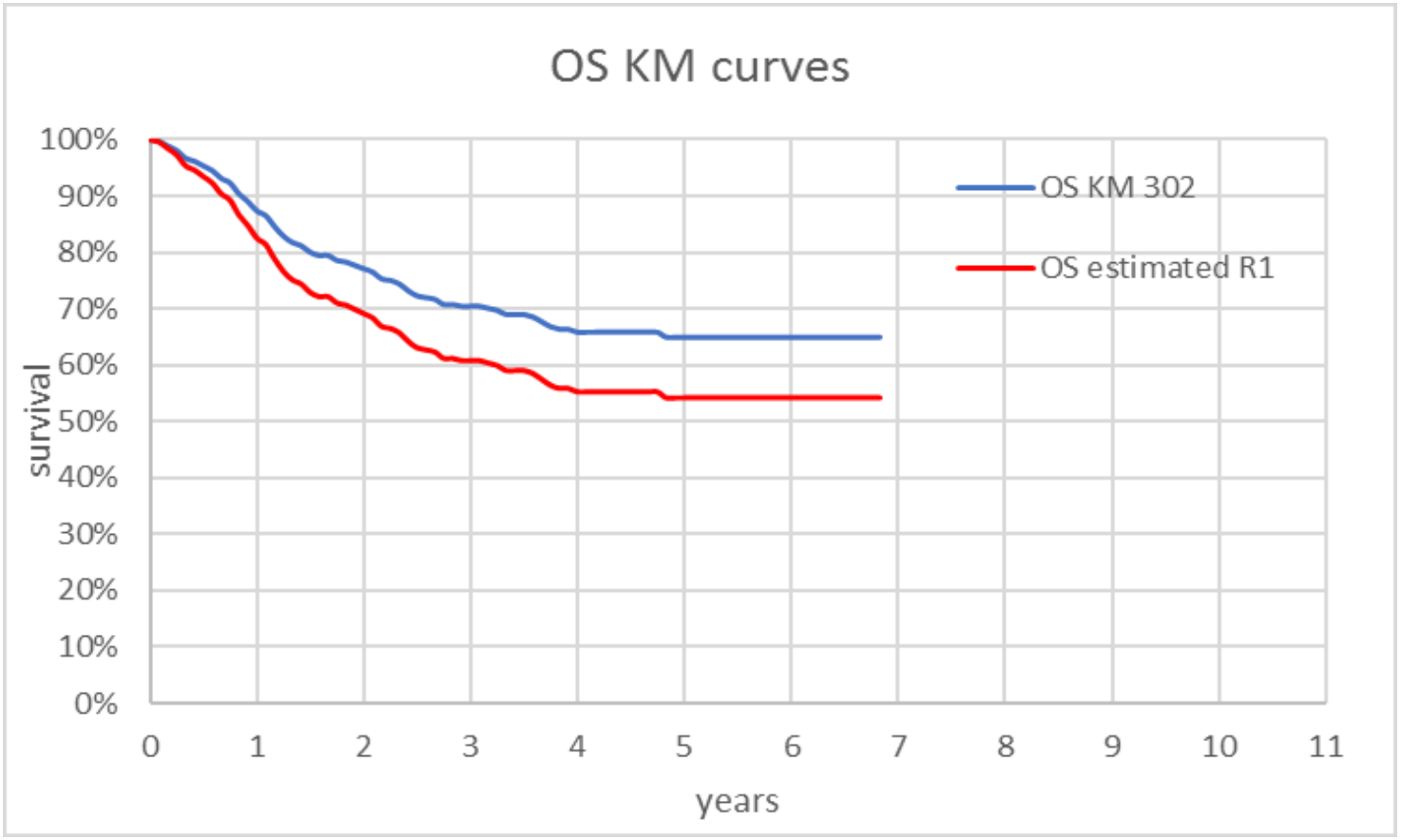
Summary of ERG's exploratory analyses

Problem in CS	ERG amendment	Level of mitigation	Proposed approach
Naïve comparison of OS data	1. Restructuring the high-risk economic model to incorporate the use of the OS HR ([redacted]) to estimate OS for isotretinoin	**Problem partially mitigated** • Some adjustment for patients' characteristics and previous treatments was applied • HR estimation method is flawed and unlikely that the use of HRs is an appropriate method of analysis	An **indirect comparison using MAIC and/or STC** of dinutuximab beta versus isotretinoin and versus dinutuximab alpha should be undertaken
Naïve comparison of EFS data + lack of EFS data for isotretinoin in historical control R1	2. Taking the relative difference between the OS HR and the EFS HR (from ID799 dinutuximab alpha compared with isotretinoin) and applying it to the adjusted OS HR estimated for dinutuximab beta of [redacted] ERG's estimated EFS HR for dinutuximab beta vs. isotretinoin 1.656/1.319*[redacted]	**Problem partially mitigated** • Some level of adjustment for patients' characteristics and previous treatments was applied in the analysis, through the adjusted OS HR • EFS HR carries the same flaws as the OS HR • It relies on the naïve comparison of the relative treatment effectiveness of dinutuximab alpha vs isotretinoin and isotretinoin beta vs isotretinoin	

Robustness of the final analysis			
Economic analysis **unfit for purpose**. Resulting ICERs are meaningless	Economic analysis **unfit for purpose**	Problem **partially mitigated**	**MAIC or STC required** for dinutuximab beta vs. iso and vs dinutuximab alpha

ERG's exploratory analysis for OS (I)

Unadjusted OS curve for dinutuximab beta and estimated isotretinoin OS curve with adjusted HR

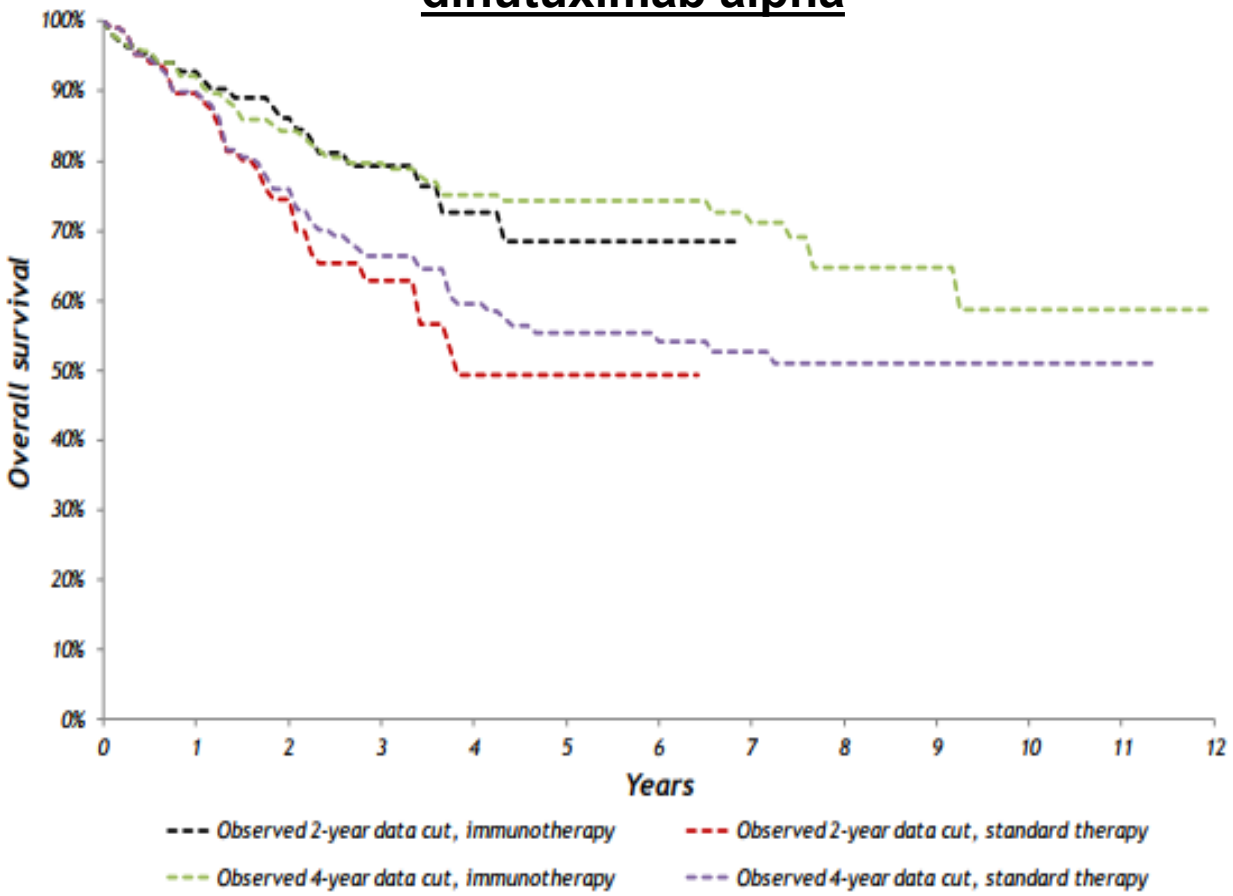


Source: Figure 24 of the ERG report

Dinutuximab beta in combination with isotretinoin with or without IL-2 [redacted] compared with isotretinoin alone [redacted]

ERG's exploratory analysis for OS (II)

Observed OS data for updated 4-year (March 2014) and primary 2-year (June 2009) data analysis – **dinutuximab alpha**



Source: Figure 25 in ERG report

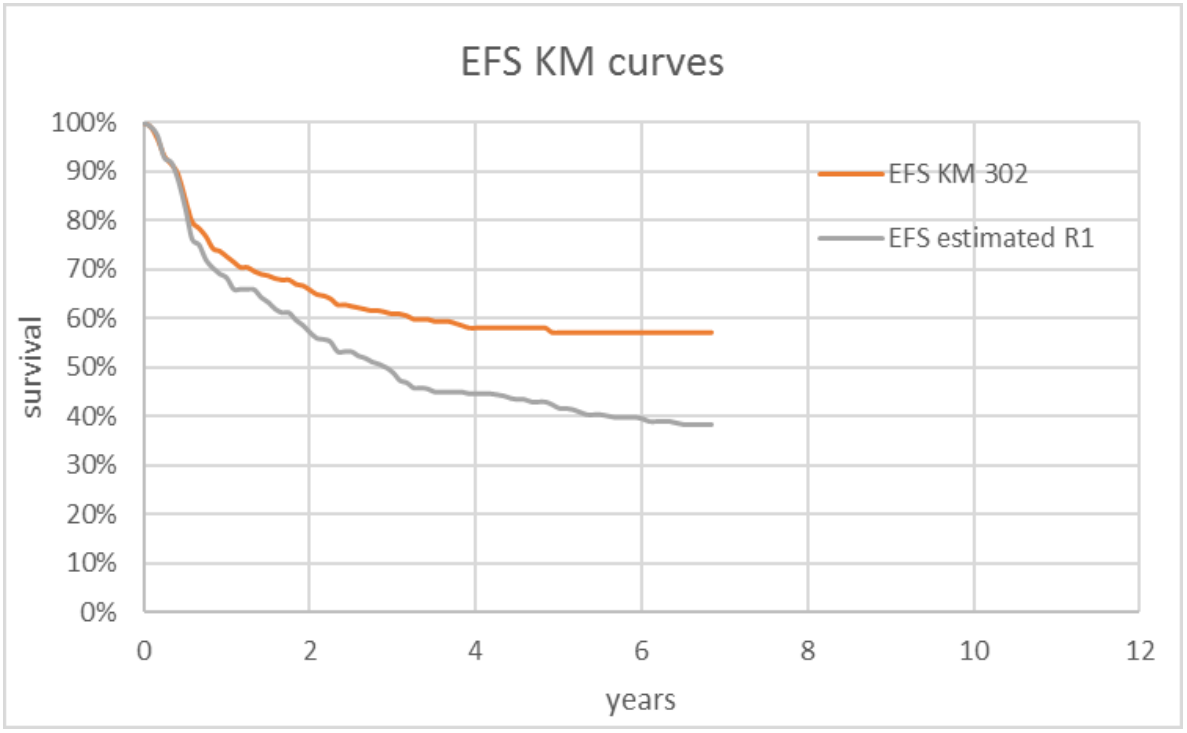
- Observed data for immunotherapy and standard therapy appear to converge between 6.5 and 11 years in the updated analysis
- At 5 years, there were still 65% of patients at risk in the dinutuximab alpha arm and 47% of patients in the isotretinoin arm

↓

- Seems plausible that the relative effectiveness of dinutuximab beta might decrease over time

ERG's exploratory analysis for EFS (I)

Unadjusted EFS curve for dinutuximab beta and estimated unadjusted EFS curve for isotretinoin

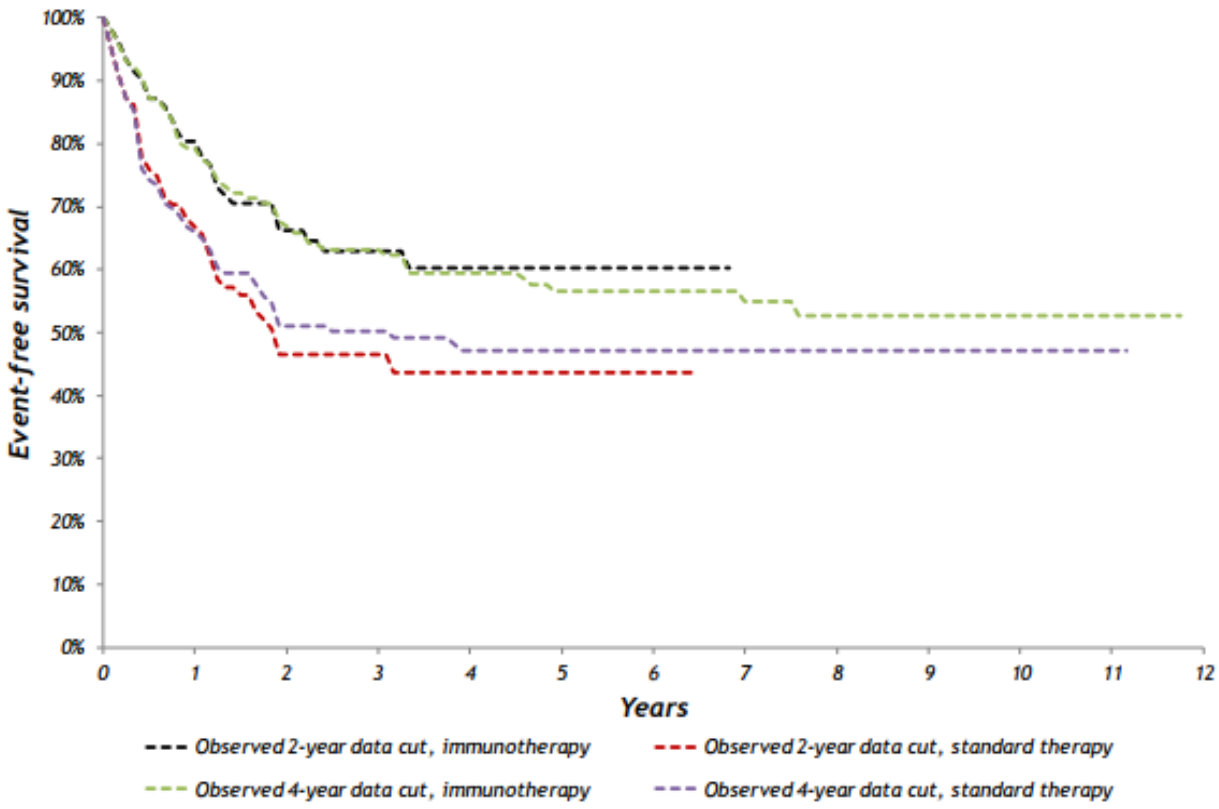


Source: Figure 26 in ERG report

- Unadjusted analysis of dinutuximab beta shows a substantial separation of EFS curves at around year 7 (approximately 57% vs 38%)
- It is based on a naïve comparison and is very likely to represent an overestimation of the effect of dinutuximab beta in terms of preventing disease progression

ERG's exploratory analysis for EFS (II)

Observed EFS data for updated 4-year (March 2014) and primary 2-year (June 2009) data analysis – **dinutuximab alpha**

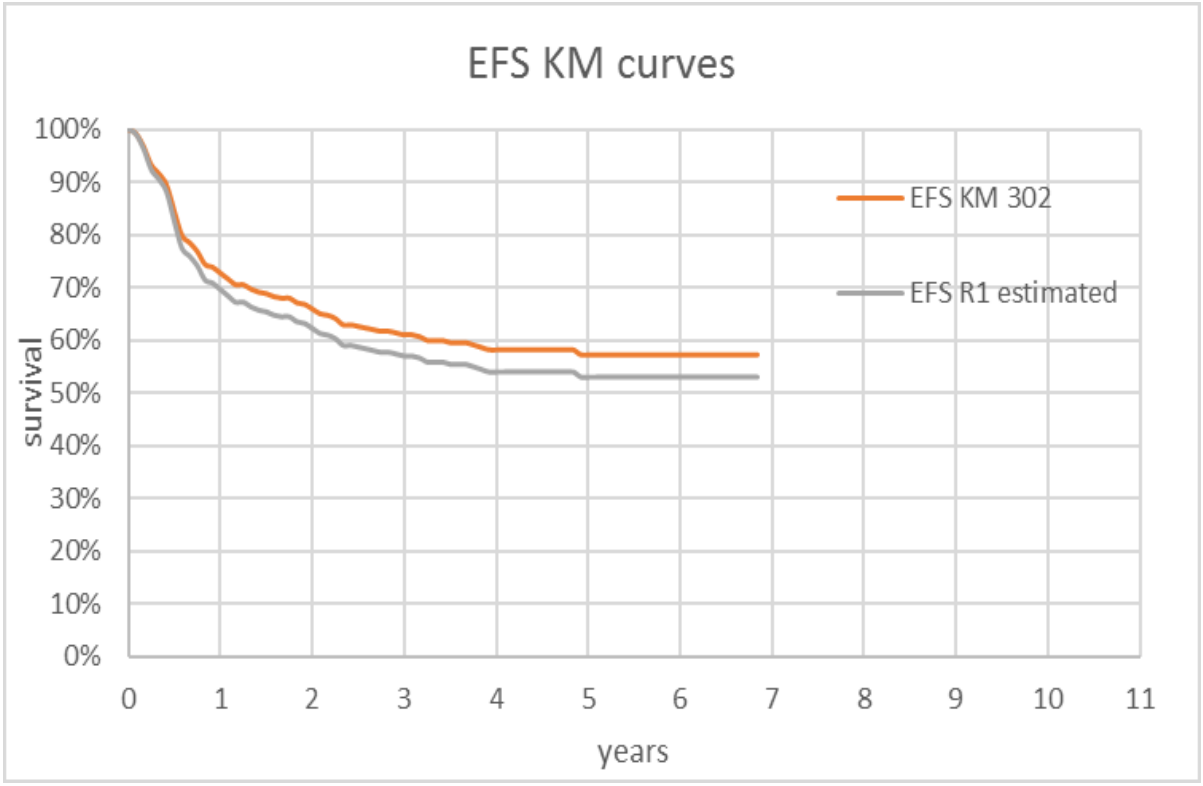


Source: Figure 27 in ERG report

- Observed data for immunotherapy and standard therapy appear to converge between 4.5 and 11 years in the updated analysis
- From year 7.5, dinutuximab alpha is associated with a gain in EFS by 7%
- Dinutuximab alpha curve seems similar to the shape of the EFS KM curves for dinutuximab beta (Figure 26) from APN311-302 when the longer follow-up data is considered
- Seems plausible that the relative effectiveness of dinutuximab beta might decrease over time

ERG's exploratory analysis for EFS (III)

Unadjusted EFS curve for dinutuximab beta and estimated isotretinoin EFS curve with adjusted HR



Source: Figure 28 in ERG report

- Direct comparison between the dinutuximab alpha and beta curves is flawed
- ERG took the relative difference between the OS HR and the EFS HR in the dinutuximab alpha submission and applied it to the adjusted OS HR estimated for dinutuximab beta
- 1.656/1.319* [redacted]
- At year 7, the EFS curves seem to be separated by approximately 4%
- Dinutuximab beta is expected to delay events, rather than prevent them

ERG conclusions on the exploratory analysis

Clinical inputs into the modelling are not robust, interpret model estimates with caution

Therapy	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Isotretinoin	£29,898	16.12	—	—	£111,858
Dinutuximab beta + isotretinoin	£331,939	18.82	£302,041	2.70	

Abbreviations in table: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life-years.

Source: Table 57 of ERG report

Interpret with caution:

The **ERG does not consider that the changes made to the company's model are robust enough to provide results suitable for decision-making**

A **more robust estimate of the treatment effect is required before a meaningful ICER can be produced**

- ERG identified issues relating to the estimation of utility values and costs in the economic analyses, however these will only become relevant to consider once the fundamental issues around treatment effectiveness have been addressed

ERG: Further analyses required for decision-making

1. Changing the assumption that patients entering the FS of the economic model receive chemotherapy for the rest of their lives
   - Once newly progressed patients are estimated, an assumption needs to be made for treatment duration + assumption should be made for the resource use required to manage relapsed patients who have gone off chemotherapy and still alive in the FS
2. Cost estimations regarding the chemotherapy regimens used in the FS should include wastage
3. Cost of treatment administration in the FS should use the cost of an inpatient stay (£4,670 for 5 days)
4. Concomitant medication costs in the stable state should include wastage for gabapentin
5. Proportion of patients receiving IL-2 in the dinutuximab beta arm should be explored (using 41% to reflect 41% of children in 302 had residual disease at baseline and would require IL-2 as a concomitant medication)
6. Published multiple regression to estimate age-specific UK EQ-5D in the model by Ara *et al.* should be used to estimate mean EQ-5D HSUVs for general population
7. A weighted analysis of costs taking into consideration the proportion of patients falling into different BSA categories
8. A discount rate of 3.5% (instead of 1.5%) for costs and benefits should be used to explore structural uncertainty in the analysis
9. Probabilistic sensitivity analysis should be undertaken to incorporate the impact of varying relative treatment effectiveness estimates on the final ICER

End-of-life

Criteria not met

NICE criterion	Company assessment	ERG assessment
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	Survival in both relapsing and high-risk patients is expected to be shorter than 2 years Median survival for relapsing patients (Garaventa control) was 318 days High-risk patients included in HRNBL1 study and; who did not receive immunotherapy (R1 control) → median survival 629 days	Median survival of 629 days is uncertain It is unclear whether the data cited are post-relapse Company reports median OS of 1,869 days and a mean OS of 2,447.1 days for historical control R1 End of life criterion of life expectancy of has not been met for high-risk neuroblastoma
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	Immunotherapy with dinutuximab beta and isotretinoin with or without IL-2 showed statistically significantly better OS for patients with high-risk neuroblastoma Median OS time was longer in APN311-202 + APN311-303 patients compared with the historical control patients (1254 days vs. 318 days, respectively)	Log rank test indicated there is a statistically significant difference between dinutuximab beta vs. isotretinoin in OS in high-risk neuroblastoma ($p < 0.0001$), but an estimate of the additional survival is not yet available ERG considers that OS data for APN311-302 are immature For relapsed neuroblastoma ERG considers that the populations of APN311-202 and APN311-303 are not representative of relapse in the UK

Innovation

Company state:

- Dinutuximab beta EUSA's main benefit stands in its continuous infusion scheme, which shows major improvements of the safety profile by reducing pain and associated i.v. morphine use
- Together with the possibility of receiving the treatment in outpatient setting, will facilitate patients remaining on therapy and receiving the full cycle of treatment, optimizing the possibility of long-term benefits

Equalities issues

- Company: There are no equality issues surrounding the use of Dinutuximab beta EUSA for the indicated patient population
- ERG & experts: No equalities issues identified

Key cost-effectiveness issues

- **Clinical inputs:**
  - Lack of robust clinical inputs - no MAIC/STC estimate of treatment effect for the high risk population
- **Modelling assumptions:**
  - Treatment administration – weighted average of costs using body surface area categories from APN311-302 should have been used *(key driver)*
  - Failure state resource use and treatment costs not appropriate
  - Impact of infections not captured in the modelling
  - Dosing schedule - continuous infusions over 10 days modelled in line with NHS practice, but no evidence demonstrating impact on efficacy and safety of this schedule (5 day infusions in trial)
  - Appropriateness of the 10-year cure assumption (*upheld appeal point in ID799*)
  - Utility values – Ara et should have been used to adjust for age
  - 1.5% discount rate for costs and health effects may be appropriate in this case *(as concluded in ID799)*
- **Other issues:**
  - Lack of robust cost effectiveness estimates for decision making
  - Legal issues regarding paediatric patient group *(issue in ID799)*
  - End-of-life criteria not met (not met in ID799 either)
  - No evidence presented regarding health related benefits not captured in the QALY
  - No equalities issues raised

Additional slides

Main baseline characteristics for APN311-302 versus historical Control R1

Parameter	Isotretinoin alone (N=450)	Dinutuximab beta plus isotretinoin with or without IL-2 (N=370)	Total (N=820)
Gender, n (%)			
Male	275 (61.1)	236 (63.8)	511 (62.3)
Female	175 (38.9)	134 (36.2)	309 (37.7)
Age at initial diagnosis (years)			
Mean (SD)	3.24 (2.18)	2.46 (2.60)	3.34 (2.38)
Median	2.65	2.90	2.70
Min, Max	0.1, 16.8	0.0, 19.5	0.0, 19.5
Missing	0	1	1
Age groups (years), n (%)			
<1	5 (1.1)	28 (7.6)	33 (4.0)
≥1.5[b] to <1.5	56 (12.4)	25 (6.8)	81 (9.9)
>1.5 to ≤5	322 (71.6)	249 (67.3)	571 (69.6)
>5	67 (14.9)	67 (18.1)	134 (16.3)
Missing	0	1 (0.3)	1 (0.1)
MYCN status, n (%)			
Amplified	215 (47.8)	152 (41.1)	367 (44.8)
Not amplified	204 (45.3)	181 (48.9)	385 (47.0)
Missing	31 (6.9)	37 (10.0)	68 (8.3)
INSS stage at initial diagnosis			
Local	59 (13.1)	35 (9.5)	94 (11.5)
4	391 (86.9)	328 (88.6)	719 (87.7)
4S	0	7 (1.9)	7 (0.9)

Cancer Drugs Fund

Decision points

Starting point: drug not recommended for routine use

Proceed down if answer to each question is yes

1. Why is drug not recommended? Is it due to clinical uncertainty?

2. Does drug have plausible potential to be cost-effective at the current price, taking into account end of life criteria?

3. Could data collection reduce uncertainty

4. Will ongoing studies provide useful data?

and

5. Is CDF data collection feasible?

Recommend enter CDF

Define the nature of clinical uncertainty and the level of it. Indicate research question, required analyses, and number of patients in NHS in England needed to collect data