NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Premeeting briefing

Dinutuximab for treating high-risk neuroblastoma

This premeeting briefing presents:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal.

Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies.

Key issues for consideration

Clinical effectiveness

- How is high-risk neuroblastoma defined in clinical practice?
- The clinical effectiveness data is from a single trial (ANBL0032). The ERG expressed concern about methodological errors and discrepancies in the analyses which may have overestimated the treatment effect of dinutuximab in combination with Granulocyte macrophage colony-stimulating factor (GMC-SF), interleukin-2 (IL-2) and isotretinoin. The company acknowledged that there may have been errors in the 2009 data cut. Which data cut (2009 or 2014) is the most reliable?
- The company presented data at 2 and 4 years after randomisation, but the ERG considered this timescale too short to determine efficacy. While analyses up to 5 years after randomisation showed higher event-free survival rates for dinutuximab

therapy compared to isotretinoin, longer-term follow-up (up to 10 years) suggested that approximately 50% of patients will either have a cancer-related event or be cured, regardless of treatment received. What is the estimated size of the treatment effect and the strength of supporting evidence?

- The company presented clinical evidence for the subgroup of people with refractory disease (specifically people with biopsy-proven disease following autologous stem cell transplant). Survival rates with immunotherapy were poor but no patients received standard therapy so no direct comparison could be made. Immunotherapy appeared ineffective in patients with a Curie score above zero and was no better than standard therapy in other subgroups. Is it possible to make any conclusions about clinical effectiveness in this subgroup?
- The marketing authorisation for dinutuximab requires that it is administered together with GMC-SF, however this technology is not currently licensed for any indication or commercially available in the UK. Is the arrangement in place to procure GMC-SF sufficient to ensure that it will be made available to the NHS if the dinutuximab is approved?

Cost effectiveness

- The economic model is very sensitive to which data cut is used. Which data cut is considered the most robust and appropriate for use in the economic analysis?
- The company's cost effectiveness results rely on the assumption that the event-free cohort is 'cured' at 5 years (cure threshold). The use of the 5-year cure assumption leads to survival gains beyond year 5 which are extrapolated over a lifetime horizon. However, the ERG considers this to be inappropriate since events occur after 5 years in the immunotherapy arm and the survival curves appear to converge between years 6.5 and 11 years suggesting that immunotherapy prolongs time to relapse rather than 'curing' neuroblastoma. Is the 5-year (company) or 10 year (ERG) cure assumption appropriate?
- The company applied an exponential model to the overall survival curve to calculate a monthly probability of death of 5.1% which it applied to the failure health state after year 5 in the model. The company also assumed that in the stable health state (event-free) after 5 years there was no further risk of relapse and that the monthly probability of death is equivalent to that of the general

population. However, the ERG found evidence of a higher mortality rate in survivors of neuroblastoma of 5.6% from the Childhood Cancer Survivor study. Are the company's mortality assumptions for the failure and stable health states appropriate?

- The company applied the same administration costs for dinutuximab and interleukin-2. The ERG considered that this while this captured the procurement cost of the treatment it did not capture the full cost of treatment administration. The ERG considered that this should have been explored further by the company by, for example, taking into account the length of stay in hospital for each treatment. What is the most appropriate approach regarding the administration costs of dinutuximab and interleukin-2?
- In the absence of EQ-5D data for the ANBL0032 study, the company used Health Utility Index data from a small Canadian study whose population consisted of children who had completed treatment for tumours of the central nervous system. However, the ERG identified a study by Nathan et al. 2007, described by the company in its submission, which reported SF-36 scores in long-term survivors of neuroblastoma. The ERG noted that these could have been an alternative source for utility values. What is the most appropriate source of utility values for people who have had neuroblastoma?
- The company's base case ICER was £37,423 per QALY gained using the 2009 data cut from ANBL0032. The ERG's preferred exploratory analyses resulted in an ERG base case ICER of £99,699 per QALY gained, which increased to £128,378 per QALY gained in alternative scenarios and up to £155,915 per QALY gained when all scenarios were combined. Which of the analyses is most representative of the cost-effectiveness of dinutuximab therapy?
- The company presented a scenario in which outcomes were discounted at a rate of 1.5% because the health benefits of leading a relatively healthy life compared to the general population may be sustained over the course of patients' lifetime with immunotherapy. Is it appropriate to apply the lower outcome discount rate of 1.5%?
- The company presented some evidence to support dinutuximab being considered by the Committee as a life-extending treatment at the end of life. Does

dinutuximab therapy for treating high-risk neuroblastoma following myeloablative therapy and autologous stem cell transplant meet the end of life criteria?

1 Remit and decision problems

1.1 The remit from the Department of Health for this appraisal was: To appraise the clinical and cost effectiveness of dinutuximab in combination with sargramostim, aldesleukin and isotretinoin within its marketing authorisation for treating high-risk neuroblastoma following myeloablative therapy and autologous stem cell transplant..

Table 1 Decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Comments from the company	Comments from the ERG
Pop.	People with high-risk neuroblastoma who have received myeloablative therapy and autologous stem cell transplant			The population described in the marketing authorisation is more restrictive than in the NICE scope (patients 12 months to 17 years who have previously received induction chemotherapy and achieved at least a partial response, followed by myeloablative therapy and autologous stem cell transplant). The population of the main study (ANBL0032) included patients aged 3 months to 14.5 years old. The ERG also noted that patients with biopsy-proven disease were non-randomly assigned to be given dinutuximab.
Int.	Dinutuximab in combination with sargramostim, aldesleukin, and isotretinoin			The ERG commented that the marketing authorisation for dinutuximab does not clearly specifically whether sargramostim should be used in combination with dinutuximab or whether other GMC-SF products such as morgramostim can be used as well. No GMC-SF products currently have a marketing authorisation for use in England.
Com.	Isotretinoin			The dosing used in the main clinical trial reflects current clinical practice in England.

	Final scope issued by NICE	Decision problem addressed in the submission	Comments from the company	Comments from the ERG
Out.	Overall survival Progression-free survival Adverse effects of treatment Health-related quality of life	Overall survival **Event-free survival** Adverse effects of treatment Health-related quality of life	Event-free survival was defined as the time to an event from study enrolment until the first occurrence of: • Relapse • Progressive disease • Secondary cancer • Death • Or, if none of these events occurred, until the last contact with the patient In the phase 3 trial, all patients experienced progressive disease, relapse, or death. As a result, the event-free survival outcome is similar to the progression-free survival outcome Health-related quality of life was not assessed in the pivotal trials, as the majority of the children treated were too young for an appropriate	None.

	Final scope issued by NICE	Decision problem addressed in the submission	Comments from the company	Comments from the ERG
Subgroups	If evidence allows: people with relapsed disease and people with refractory disease			Clinical evidence was presented for the subgroup of people with refractory disease (specifically people with biopsy-proven disease following autologous stem cell transplant). This subgroup was not included in the economic modelling. No evidence was presented for the subgroup of people with relapsed disease. Other subgroups considered include: • analysis by Curie score (a score predicting the extent and severity of disease based on a full body scan using radioactive isotopes) • age • International Neuroblastoma Staging system stage • the number of copies (amplification) of the MYCN oncogene (a gene which when overexpressed can lead to the development of cancerous tumours and which is associated with prognosis in neuroblastoma) • the amount of DNA (ploidy) before autologous stem cell transplant • histology (the microscopic structure analysis of tissue samples), and • stem cell type.

2 The technology and the treatment pathway

2.1 Dinutuximab (Unituxin, United Therapeutics) is a chimeric human/mouse monoclonal antibody produced in a murine myeloma cell line (SP2/0) by recombinant DNA technology. It has a marketing authorisation in England for treating high risk neuroblastoma in patients aged 12 months to 17 years who have previously received induction chemotherapy and achieved at least a partial response, followed by myeloablative therapy and autologous stem cell transplantation (ASCT). It is administered intravenously in combination with granulocyte-macrophage colony-stimulating factor (GMC-SF), interleukin-2 (known as aldesleukin in Europe) and isotretinoin. It is restricted to hospital use only. See table 2 below for the complete dosing regimen for dinutuximab.

Table 2 Complete dosing regimen for dinutuximab therapy based on the marketing authorisation (see table 6, page 34 of ERG report)

Dosing schedule with GM-CSF (Courses 1, 3,5)															
Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15-24
GM-CSF	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Dinutuximab[2]				X	X	X	X								
Isotrentinoin[3]											X	X	X	X	X
Dosing schedule with IL-2 (Courses 2 and 4) and Isotretinoin (Course 6)															
Day	1	2	3	4	5	6	7	8	9	10	11	12-14			15-28
IL-2[4]	X	X	X	X				X	X	X	X				
Dinutuximab[2]								X	X	X	X				
Isotrentinoin[3]															X

1 GM-CSF: (Granulocyte macrophage colony-stimulating factor) 250 micrograms/m2 /day, administered by either subcutaneous injection or intravenous infusion over 2 hours.

2. Dinutuximab: 17.5 mg/m2 /day, administered by intravenous infusion over 10–20 hours.

3. Isotretinoin: for body weight greater than 12 kg: 80 mg/m2 administered orally twice daily for a total dose of 160 mg/m2 /day; for body weight up to 12 kg: 2.67 mg/kg administered orally twice daily for a total daily dose of 5.33 mg/kg/day (round dose up to nearest 10 mg).

4. Interleukin-2 (IL-2): 3 milli-international units/m2/day administered by continuous intravenous infusion over 96 hours on Days 1-4 and4.5 milli-international units /m2 /day on Days 8-11.

2.2 Neuroblastoma is a cancer of immature nerve cells that usually affects infants and children aged 5 years and younger, and 90% of cases are

diagnosed by the age of 5 years. It often starts in the adrenal glands located above each kidney or in the abdomen, chest, or spinal cord. By the time neuroblastoma is diagnosed, the cancer has usually spread. It spreads most often to the lymph nodes, bones, bone marrow, liver, and in infants, the skin.

2.3 Neuroblastomas are classified into 3 different risk groups: low, intermediate, and high. Neuroblastoma are categorised based on the following characteristics:

- age
- stage of disease spread (see table 3 for a description of the stages of disease included in the International Neuroblastoma Staging System)
- the number of copies (amplification) of the MYCN oncogene (a specific gene which when overexpressed in cells can lead to the development of cancerous tumours and which is associated with prognosis in neuroblastoma)
- the amount of DNA (ploidy) in the neuroblastoma cells before autologous stem cell transplant (tumours with increased amounts of DNA predict a more favourable prognosis than normal diploid cells), and
- unfavourable tumour histopathology findings (tumour tissues which look abnormal).

Table 4 summarises the Children's Oncology Group's neuroblastoma risk group categorisation. Between 40% and 50% of neuroblastomas are classified as high risk. The company estimates the 5–year survival rate for children with high-risk neuroblastoma to be between 30% and 50%.

Table 3 International Neuroblastoma Staging System (company submission, table 11, page 31-32)

Stage	Description
1	Localised tumour with complete gross excision, with or without microscopic residual disease; representative ipsilateral lymph nodes negative for tumour microscopically (nodes attached to and removed with the primary tumour may be positive)
2A	Localised tumour with incomplete gross excision; representative ipsilateral nonadherent

Stage	Description
	lymph nodes negative for tumour microscopically
2B	Localised tumour with or without complete gross excision, with ipsilateral nonadherent lymph nodes positive for tumour. Enlarged contralateral lymph nodes must be negative microscopically
3	Unresectable unilateral tumour infiltrating across the midline, with or without regional lymph node involvement; or localised unilateral tumour with contralateral regional lymph node involvement; or midline tumour with bilateral extension by infiltration (unresectable) or by lymph node involvement
4	Any primary tumour with dissemination to distant lymph nodes, bone, bone marrow, liver, skin and/or other organs (except as defined for stage 4S)
4S	Localised primary tumour (as defined for stage 1, 2A, or 2B), with dissemination limited to skin, liver, and/or bone marrow (limited to infants <1 year of age). Marrow involvement should be minimal (ie, <10% of total nucleated cells identified as malignant on bone marrow biopsy or on marrow aspirate); more extensive marrow involvement would be considered to be stage 4

Table 4 Children's Oncology Group neuroblastoma risk group categorisation (company's submission table 12, page 32-33

Risk Group	INSS Stage	Age	MYCN Status	Histopathology (INPC Classification)	DNA Ploidy
Low	1	0-–21 years	Any	Any	Any
Low	2A/2B	<365 days	Any	Any	Any
Low		≥365 days – 21 years	Nonamplified	Any	-
Low		≥365 days – 21 years	Amplified	Favourable	-
High		≥365 days – 21 years	Amplified	Unfavourable	-
Intermediate	3	<365 days	Nonamplified	Any	Any
High		<365 days	Amplified	Any	Any
Intermediate		≥365 days – 21 years	Nonamplified	Favourable	-
High		≥365 days – 21 years	Nonamplified	Unfavourable	-
High		≥365 days – 21 years	Amplified	Any	-
Intermediate	4	<548 days	Nonamplified	Any	Any
High		<365 days	Amplified	Any	Any
High		≥548 days – 21 years	Any	Any	-
Low	4S	<365 days	Nonamplified	Favourable	>1
Intermediate		<365 days	Nonamplified	Any	=1
Intermediate		<365 days	Nonamplified	Unfavourable	Any
High		<365 days	Amplified	Any	Any
DNA ploidy > 1 is favourable, = 1 is unfavourable. INPC – International Neuroblastoma Pathologic Classification; INSS – International Neuroblastoma Staging System					

2.4 Treatment for high-risk disease is generally divided into 3 phases; induction, consolidation and maintenance (see figure 1below). Isotretinoin is considered to be the standard of care for maintenance therapy of high-risk neuroblastoma in England. However, the vast majority of people with high-risk neuroblastoma in England have been enrolled in an ongoing clinical trial of APN311 produced by Apeiron Biologics. APN311 is a monoclonal antibody made with the same ch14.18 anti-GD2 gene used to produce dinutuximab, but it is produced in a Chinese hamster ovary (CHO) hybridoma cell line, whereas dinutuximab is produced in a murine cell line (SP2/0). Producing the same antibody in different cell lines might result in different glycosylation patterns which can affect how the antibodies function, and these differences can lead to different clinical effects. There are no clinical trials comparing dinutuximab with APN311.

Figure 1 Treatment pathway for high risk neuroblastoma with expected position of dinutuximab

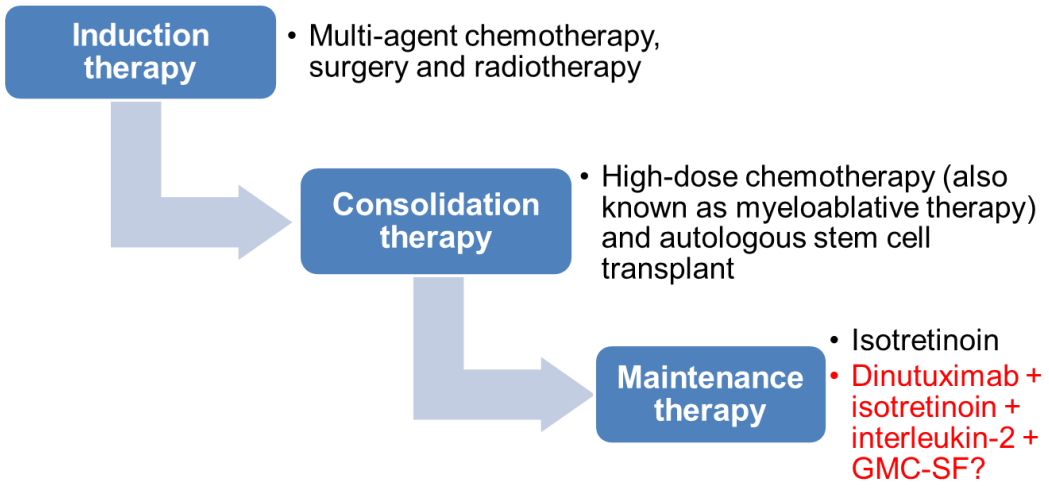


Table 5 Technologies

	Intervention	Comparator
Marketing authorisation	Dinutuximab is indicated for the treatment of high-risk neuroblastoma in patients aged 12 months to 17 years, who have previously received induction chemotherapy and achieved at least a partial response, followed by myeloablative therapy and autologous stem cell	Isotretinoin does not have a specific marketing authorisation for treating high-risk neuroblastoma in England.

	Intervention	Comparator
	transplantation	
Administration method	It is administered by intravenous infusion over 10-20 hours in combination with granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-2 (IL-2), and isotretinoin	It is self-administered orally.
Cost	£6390 per single infusion (17.5 mg dinutuximab) Per Cycle £25,560 (dinutuximab, cycles 1-5 only) £56.28 (isotretinoin, cycles 1-6) £2272.90 (GMC-SF, cycles 1, 3 and 5 only) £224 (interleukin-2, cycles 2, 4 only) Full course £127,800 (dinutuximab only) £7604.38 (isotretinoin, GMC-SF and interleukin-2) Total - £135,404.38	Per Cycle £56.28 per cycle (cycles 1-6) Full course £337.68

See summary of product characteristics for details on adverse reactions and contraindications.

3 Comments from consultees

3.1 Comments were received from the Children's Cancer and Leukaemia Group and 2 patient experts and 2 clinicians.

3.2 One patient group representative and clinical expert stated that approximately 100 infants, children and young people are diagnosed with neuroblastoma each year in the UK. Of these, more than half will be classified as having high-risk neuroblastoma on the basis of internationally agreed risk factors (International Neuroblastoma Risk Group classification). These children and young people require intensive treatment and are all treated within tertiary specialist oncology units. With standard isotretinoin therapy, long-term survival rates of approximately 30 to 40% were achieved, with treatment related mortality of approximately 3 to 5%.

3.3 The patient group representative and clinical expert explained that the vast majority of patients in the UK are enrolled in the European SIOPEN HR-NBL-1 or SIOPEN LTI study using a similar intervention (APN311) which is produced in a different cell line (Chinese hamster ovary) in combination with interleukin-2 alone. However, these clinical trials are planned to end in 2016 and 2017. Therefore, treatment with APN311 cannot be considered standard clinical practice in England. There will be some parents / patients who either choose not to take part in these trials or who are not eligible. These patients would potentially receive the new technology. This would include:

- Patients with high risk neuroblastoma, who would receive dinutuximab therapy as maintenance therapy after myeloablative chemotherapy and PBSCT.
- Patients with relapsed or refractory neuroblastoma, who do not have high risk disease at initial presentation but are considered to have 'high risk' disease on the basis of relapsed or refractory disease.

3.4 One patient expert stated that there is widespread support for immunotherapy treatments in England, with some variation in views about the specific types of antibody used and the way that existing clinical trials and treatment protocols are organised.

3.5 Another patient expert described how her family had to seek out treatment outside the UK after receiving standard therapy with isotretinoin. The patient expert explained that being cured of neuroblastoma is the single most important outcome; and that this is not the same as 5-year survival (event free or overall) "which serves merely as a convenient metric for assessing improvements in treatment, or comparing effectiveness between different therapies". Additionally, minimisation of serious and long-term damage and side-effects is of the utmost importance. The patient expert explained that children suffer a multitude of side-effects as a result of all the cytotoxic drugs they receive. Short-term effects include; nausea, vomiting, constipation, hair-loss, malnutrition, mucositis, and

diarrhoea. They are prone to febrile neutropenia, which requires in-patient hospital stays for supportive care. Immune suppression makes them vulnerable to infection, requiring treatment with strong antibiotics. Ultimately, some children die in treatment, as a result of drug toxicity, or severe infections. Long-term problems include hearing loss, organ dysfunction, sterility, growth issues, early onset puberty, permanent disability, and secondary malignancies.

4 Clinical-effectiveness evidence

Overview of the clinical trials

4.1 The U.S. National Cancer Institute (NCI) originally led the development of dinutuximab starting in 1995. In 2010, United Therapeutics (the company) began collaborating with the NCI to commercialise dinutuximab. As a result, the clinical trial evidence available for dinutuximab is based on 1 trial evaluating the clinical efficacy of dinutuximab (ANBL0032) and 3 additional trials reporting safety and adverse events which were conducted by the NCI. Due to the limited evidence base, the company was not able to conduct meta-analyses or indirect treatment comparisons.

4.2 ANBL0032 was a multicentre (U.S., Canada, Australia and New Zealand) randomised controlled trial (n=226) in which the clinical efficacy of dinutuximab in combination with interleukin-2, GMC-SF and isotretinoin was evaluated compared to isotretinoin alone in people with high risk neuroblastoma. Patients were randomised 1:1 to immunotherapy with dinutuximab or standard therapy with isotretinoin. In that same study, patients who had biopsy-proven disease (n=25) were not randomised and instead were assigned to receive dinutuximab immunotherapy; their results were excluded from the primary efficacy analysis. Table 6 summarises the baseline demographics and characteristics of the patients randomised in ANBL0032.

Table 6 Baseline demographics and characteristics of patients randomised in ANBL0032

Characteristic	**Standard Therapy** (n=113), n (%)	**Immunotherapy** (n=113), n (%)
Age		
<18 months	4 (4)	4 (4)
≥18 months	109 (96)	109 (96)
INSS stage[†]		
2	0 (0)	4 (4)
3	16 (15)	10 (10)
4S[‡]	0 (0)	2 (2)
4	92 (85)	89 (85)
Unknown	5	8
Tumour *MYCN* status		
Not amplified	51 (53)	52 (59)
Amplified	45 (47)	36 (41)
Unknown[§]	17	25
Tumour histologic features		
Favourable	5 (6)	4 (6)
Unfavourable	81 (94)	68 (94)
Unknown	27	41
Tumour ploidy		
Hyperdiploid	48 (51)	49 (58)
Diploid	46 (49)	35 (42)
Unknown	19	29
Response before ASCT[¶]		
Complete response	38 (34)	40 (35)
Very good partial response	49 (43)	47 (42)
Partial response	26 (23)	26 (23)
Number of ASCTs		
1	102 (90)	107 (95)
2	11 (10)	6 (5)
Number of purged infusions		
≥1	29 (33)	28 (31)
0	58 (67)	61 (69)
Unknown	26	24

4.3 Although it was originally designed to run 4 years, the trial was terminated early in 2009 (after 110 days) based on the safety monitoring committee's opinion that immunotherapy had met the pre-defined criteria for superiority over standard therapy as measured by event-free-survival.

Clinical trial results

4.4 The primary outcome of ANBL0032 was event-free survival (defined as the time from study enrolment until first occurrence of relapse, progressive disease, secondary cancer or death or the last contact with the patient) and the secondary outcome measure was overall survival (defined as time from study enrolment until death or last contact with patient). The trial did not measure health-related quality of life. The inclusion criteria for the study were: patients with high-risk neuroblastoma, age 30 or younger (although no patient older than 15 was recruited), who had completed induction therapy, autologous stem cell transplant and radiotherapy and had at least a partial response to treatment before autologous stem cell transplant. Enrolment also required that patients did not have progressive disease, had a life expectancy equal or greater than 2 months and adequate renal, liver, cardiac, pulmonary and central nervous system function.

4.5 The investigators sequentially monitored the primary outcome (that is, the statistical analyses were planned to take place at certain times) to detect a relative risk of event-free survival at 3 years between standard therapy and immunotherapy of 1.6, with the potential for early study termination if a statistically significant difference between groups was detected before the 3-year time point or if the conditional power fell below 20%. Interim analysis of data in clinical trials is an established practice for ethical, safety and practical reasons. However, testing interim data can lead to positive error rates if not appropriately approached. In order to account for this, the investigators used the method developed by Lan and DeMets et al. in which the alpha error is calculated at each interim analysis using a function (the alpha spending function) which is reduced as the trial approaches completion. Overall survival was not estimated until a statistically significant difference was detected in event-free survival.

4.6 The results from ANBL0032 for the overall intention-to-treat population are presented in table 7. The company provided Kaplan-Meier curves and

survival estimates from the original interim 2009 analysis (Yu et al. 2010) and 2012 (Yu et al 2014) in its submission. During clarification the company also provided the results from March 2014. The 2009 analysis results suggested that patients receiving dinutuximab therapy had a higher event-free survival at 2 years (66.3% compared with 46.4%, p=0.01) and overall survival (86.2% compared with 74.5%, p=0,02) compared to those receiving standard therapy. The 2012 results suggested that patients receiving dinutuximab had a relatively smaller event-free survival advantage at 4 years (62.8% compared with 50.9%, p=0.11) but the difference was no longer statistically signficant. The 2014 results were broadly similar to the 2012 results.

Table 7 Clinical trial outcomes for the ongoing ANBL0032 study (adapted from tables 7 and 8 in ERG report)

Outcome	Data used	Trial year	Dinutuximab therapy (n=113)	Isotretinoin (n=113)
			Survival probability (95% CI)	
Event-free survival (ITT analysis),	**Jan 09** HR 0.57 (0.37, 0.89)	Year 1	81.9% *	69.6%*
		Year 2	**66.3% (56.2,76.3)**	**46.4% (35.8,57.1)**
		Year 3	62.9%*	46.0%*
		Year 4	60.3%*	43.4%*
		Year 5	60.3%*	43.4%*
	Jun 12 HR 0.69 (0.47,1.01)	Year 1	79.9%*	69.0%*
		Year 2	69.7%*	54.9%*
		Year 3	**62.8% (53.9,71.7)**	**50.9% (41.6,60.2)**
		Year 4	57.8%*	48.7%*
		Year 5	56.2%*	46.8%*
	Mar 14 HR 0.759 (0.53, 1.11)	Year 1	79.8% (72.4,87.2)	68.1% (59.5,76.7)
		Year 2	67.4% (58.7,76.0)	52.3% (43.0,61.6)
		Year 3	62.9% (54.0,71.8)	51.3% (42.0,60.7)
		Year 4	59.3% (50.3,68.4)	48.3% (38.9,57.7)
		Year 5	56.5% (47.3,65.7)	48.3% (38.9,57.7)
Overall survival (ITT analysis),	**Jan 09** HR 0.52 (0.30 , 0.92)	Year 1	93.0%*	90.1%*
		Year 2	**86.2% (78.8,93.6)**	**74.5% (65.2,83.9)**
		Year 3	79.5%*	62.8%*
		Year 4	73.5%*	48.9%*
		Year 5	68.9%*	48.9%*
	Jun 12 HR 0.57 (0.36 ,	Year 1	91.8%*	90.3%*
		Year 2	83.9%*	76.1%*

Outcome	Data used	Trial year	Dinutuximab therapy (n=113)	Isotretinoin (n=113)
			Survival probability (95% CI)	
	0.89)	Year 3	**79.5% (72.1,87.0)**	**67.3% (58.4,76.1)**
		Year 4	74.3%*	59.2%*
		Year 5	72.7%*	54.4%*
	Mar 14 HR 0.621 (0.402 , 0.959)	Year 1	92.1% (87.1,97.0)	90.3% (84.8,95.7)
		Year 2	84.1% (77.3,90.8)	77.4% (69.5,85.2)
		Year 3	79.6% (72.1,87.0)	67.9% (59.1,76.7)
		Year 4	75.1% (67.1,83.1)	61.0% (51.8,70.3)
		Year 5	74.2% (66.1,82.3)	57.0% (47.5,66.4)

HR- hazard ratio

The probabilities in **bold** were calculated by the company.

* These probabilities are based on data reconstructed and extrapolated by the ERG from survival curves provided by the company

ERG comments

4.7 The ERG commented that the sequential monitoring process used by the company, including the use of the Lans-Demets alpha spending method, appeared appropriate. The ERG queried why the stopping boundary for the ANBL0032 trial was based on a relative risk of 1.6 and a 3-year outcome. Although the company explained in its clarification response that the relative risk of 1.6 had been calculated as control:experimental using the planning parameters for 3-year event-free survival. The ERG noted that in the Committee for Medicinal Products for Human Use report on dinutuximab, the committee was aware that the stopping boundary for the trial had not been crossed at the time that recruitment ceased. The company explained in its response to NICE's clarification questions that based on the stopping criteria initially established, the trial should not have been stopped as the alpha required for stopping the study for efficacy at the interim analysis was 0.0108, but the observed alpha was 0.0115. The ERG expressed concern that the boundary had not been crossed and commented that if recruitment had continued, the boundary may not have been crossed and efficacy results may have been different. The ERG also commented that the analyses presented by the company may have overestimated the treatment effect and the results were not adjusted for the early stopping. Although the company explained in its factual accuracy check of the ERG report that each sequential interim

analysis was adjusted according to protocol for ANBL0032, it did not clarify whether the final analysis was adjusted for early stopping once recruitment is stopped.

4.8 The ERG commented that the main analysis presented by the company was based on the data available after trial recruitment was stopped (January 2009, as reported in Yu 2010), for which Kaplan-Meier curves and survival estimates 2 years after randomisation were reported. The ERG reviewed the evidence provided by the company of the data points available after 2009. The ERG also reviewed the company's updated analysis from March 2014. Although the earlier data cut represented the primary analysis of the pivotal trial, the ERG noted that the Clinical Oncology Group and National Cancer Institute amended the protocol to include a later analysis because the OS data in the primary analysis were not considered mature enough. The ERG also noted that its clinical advisors also considered a 5-year outcome to be more appropriate, therefore the 2014 analyses would be most important results for the Committee to consider. Therefore, the ERG considered that as the analysis from March 2014 was the longest and most complete follow-up data for ANBL0032, it should have been the basis of the analysis for the company's submission even taking into account that this data was analysed after randomisation was broken and that due to stopping recruitment, the trial was not fully powered to detect the desired treatment effect.

4.9 The ERG used the Kaplan-Meier survival curves for the 2009, 2012 and 2014 data from the ANBL0032 study presented by the company to reconstruct the hazard ratios for event free survival and overall survival at years 1 to 5 using methods proposed by Guyot et al. These results are reported above in table 7. The ERG noted that the survival curves for event-free and overall survival for ANBL0032 suggest that approximately 50% of patients are disease free regardless of the treatment received. The ERG fitted various parametric models to the Kaplan-Meier curves for event-free survival and overall survival, with the Weibull cure model

representing the best fit for both (see figures 9 and 10, page 60 in the ERG report). The results of the ERG's exploratory analysis suggested that for event-free survival, 47% of patients were cured in both arms of the study, suggesting that dinutuximab does not prevent disease progression. However, for overall survival, 66% of patients were cured in the dinutuximab arm compared with 48.8% in the isotretinoin arm of the study, suggesting that dinutuximab delays and possibly prevents mortality (see table 19 of the ERG report).

Subgroup analysis

4.10 The company presented a subgroup analysis of patients over the age of 1 year with stage 4 disease (in which the cancer has spread to the lymph nodes, bone, liver skin, bone marrow or other organs). This subgroup represented 79% (197/226) of the patients recruited to the study. Of these patients, 89 received dinutuximab therapy and 90 received isotretinoin. The 2009 analysis results suggested that patients in this subgroup receiving dinutuximab therapy had a statistically significant event-free survival advantage at 2 years (63% compared with 42%, p=0.02) compared to those receiving standard therapy. The overall survival estimates at 2 years were not statistically significant but favoured dinutuximab therapy (84%) compared with isotretinoin (76%, p=0,10).

4.11 The company also presented a post-hoc subgroup analysis based on Curie score which is a score predicting the extent and severity of disease based on a full body scan using radioactive isotopes. A score greater than 0 indicates the presence of neuroblastoma tumours, while a score of 0 indicates that no tumours appear on the scan. The Curie scores of 197 patients enrolled in ANBL0032 were known: 167 patients had a Curie score = 0 and 30 patients had a score greater than 0. The company evaluated the outcomes following treatment with dinutuximab therapy (n=100) compared with isotretinoin (n=97). Event-free survival was higher in both treatment arms in patients with a Curie score =0 compared to patients with a Curie score greater than 0. Event-free survival at 3 years

for patients randomised to dinutuximab therapy was higher among patients with a Curie score of 0 compared with patient with a Curie score greater than 0 (70.5% vs 26.7%; p<0.001), while patients randomised to isotretinoin was similar in both Curie score subgroups (47.5% vs 40.0%; p=0.22). Dinutuximab therapy appeared to be more effective in people with a Curie score of 0 than isotretinoin, but appeared to be less effective than isotretinoin in people with a Curie score greater than 0. The company noted that the sample size in patients with a Curie score greater than 0 was small (n=30) and therefore the results should be interpreted with caution.

ERG comments

4.12 The ERG agreed with the company's interpretation that the evidence in this subgroup was very limited.

Adverse effects of treatment

4.13 The most common adverse effects of treatment reported in the dinutuximab arm of the ANBL0032 study were neuropathic pain (52%), infection (39%), fever without neutropenia (39%), low potassium blood concentration (35%), hypersensitivity reaction (25%), low sodium blood concentration (23%), abnormal alanine aminotransferase (23%), acute capillary leak syndrome (23%), and hypotension (18%). The most common adverse effect of treatment with isotretinoin maintenance therapy (standard therapy) was infection (22%). According to the company, most adverse reactions were self-limited and resolved after the cessation of treatment. The ERG commented that the adverse effects reported in the trial were serious, but generally acute and quickly resolved unless death occurred.

4.14 The company identified 3 single arm clinical studies which reported the rate of adverse reactions among high-risk neuroblastoma patients treated with dinutuximab: ANBL0931 (n=105), CCG-0935 (n=22) and CCG-0935A (n=25). The company stated that the results of these studies show a similar pattern of adverse effects in terms of pain which declines over

treatment courses. In the CCG-035A trial , which was a dose finding study, patients receiving the higher dose of dinutuximab had reported more neuropathic pain and peripheral capillary leak.

5 Cost-effectiveness evidence

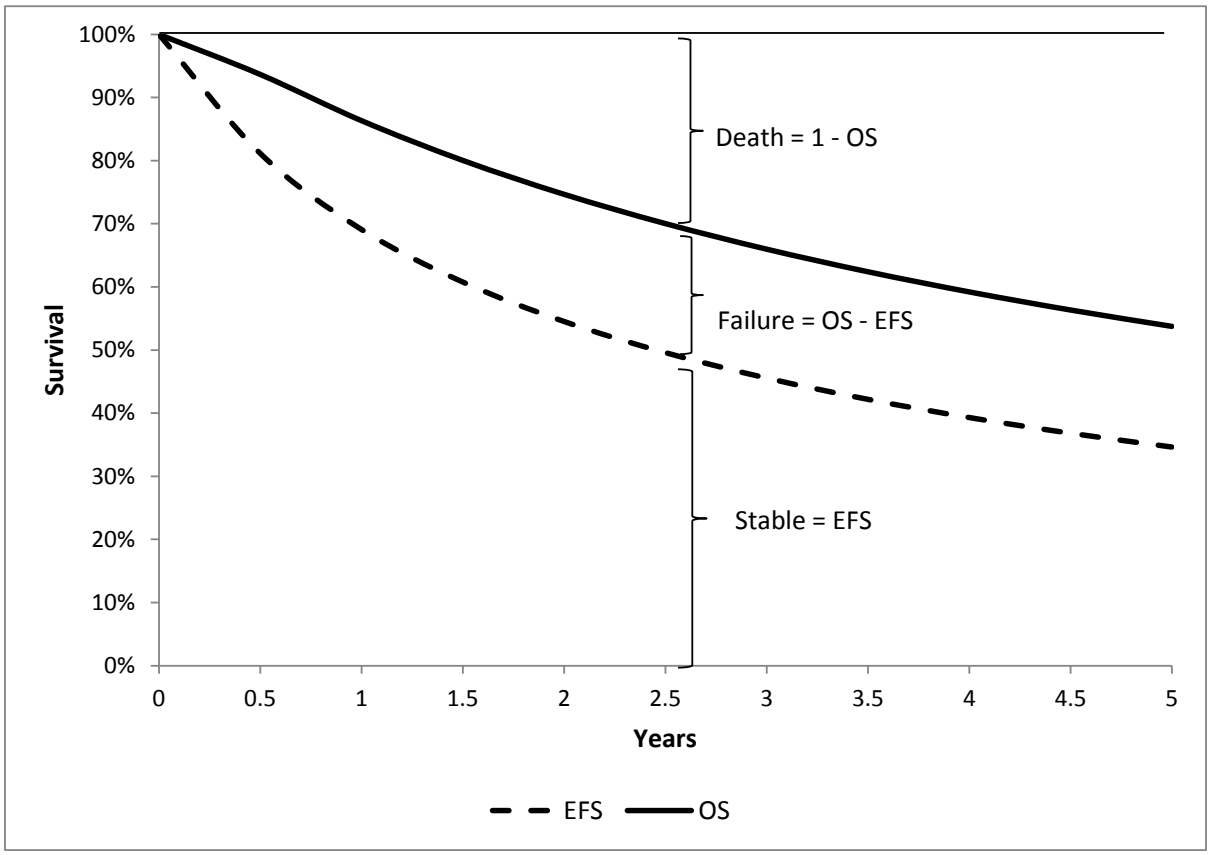
Model structure

5.1 The company created a partitioned survival model comparing the dinutuximab regimen with isotretinoin alone. The model has 3 exclusive health states:

- the ‘stable’ health state in which patients are alive and whose disease has not progressed
- the ‘failure’ health state in which patients are alive and whose disease has relapsed, progressed or which has developed into a secondary cancer; and
- death.

5.2 Unlike a Markov model, which models transitions between health states explicitly using transition probabilities, a partitioned survival model calculates the proportion of patients in each treatment arm at any time after starting treatment, using parametric survival curves fitted to empirical data on overall survival and progression free survival over time. The proportion of patients in the ‘stable’ health state is calculated based on event-free survival while the ‘failure’ health state was calculated as the difference between overall survival and event-free survival. Figure 2 is a graphical representation of the company’s partitioned survival model.

Figure 2 The company's partitioned survival model (based on figure 14 in the company's submission)



5.3 For the first 5 years, the model calculates the proportion of patients in each health state at monthly intervals with half-cycle correction using parametric survival curves fitted to data on overall survival and event-free survival. After 5 years, people in the 'stable' health state are assumed to be cured and their characteristics (such as mortality) begin following those of the general population for the lifetime of the modelled patients, taking into account the potential morbidities affecting the quality of life and resource use observed in patients who have survived neuroblastoma. The company used QALYs to capture health effects from an NHS/PSS perspective and discounted benefits and costs by 3.5% in its base case analysis. It used the lower discount rate of 1.5% in a scenario analysis.

ERG comments

5.4 The ERG noted that overall the company's model structure was appropriate. However, the ERG stated that the use of a single post-

progression health state oversimplified the treatment pathway for neuroblastoma as it does not make the distinction between patients whose disease does not progress following the first relapse or recurrence of the disease from those who do have subsequent further relapses.

5.5 The ERG commented that the patient population included in the model did not include patients with evidence of biopsy-proven persistent disease after autologous stem cell transplant and radiotherapy. The ERG noted that people with persistent disease after autologous stem cell transplant and radiotherapy benefit less from dinutuximab therapy than those who do not have persistent disease. The ERG stated that excluding this group could lead to a treatment effect skewed in favour of dinutuximab therapy, which in turn increased the uncertainty of the economic results.

5.6 The ERG commented on the time horizon chosen by the company which assumes that dinutuximab therapy compared with isotretinoin will result in event-free and overall survival differences which will persist for the remainder of the patient's lifetime. The ERG noted that the use of a lifetime horizon is only reasonable if the differences in survival are expected to be maintained over a lifetime.

5.7 The ERG also commented on the alternative discount rate of 1.5% used by the company in its scenario analysis. The ERG noted that the NICE Guide to the Methods of Technology Appraisal (2013) states that a discount rate of 1.5% for costs and benefits may be considered in cases when the treatment restores individuals who would otherwise die or have a very severely impaired life to full or near full health, and when this is sustained over a very long period (normally at least 30 years) and cost-effectiveness analyses are very sensitive to the discount rate used. The ERG stated that the evidence from ANBL0032 suggests that dinutuximab therapy delays rather than prevents cancer-related events according to the longer term event-free survival evidence presented by the company. Therefore, it was questionable whether this exception applied to dinutuximab.

Model details

5.8 The company chose isotretinoin as the comparator in the model, in line with the final scope. The full course is administered over 6 cycles in 6 months. Patients start the model in stable state at the age of 4 and 60% of the patients are males (dinutuximab pivotal phase 3 clinical trial, Yu 2010). Upon failure, patients receive topotecan combination treatment on a monthly basis until death.

5.9 The company used the results of the ANBL0032 analyses from 2009 to inform its base case. The 2 year event-free survival (66% for dinutuximab therapy; 46% for isotretinoin) and overall survival rates (86% for dinutuximab therapy; 75% for isotretinoin) were used. The company used this time point because it represented the period before randomisation was broken and therefore was less prone to bias as later time points when randomisation had been broken after the trial had been stopped early.

5.10 The company fitted parametric survival curves to the Kaplan-Meier event-free and overall survival data from ANBL0032 for the first 5 years of the model. These were used to identify the number of patients in each health state. In its base case, the company fitted a Gompertz survival model to the event free survival Kaplan-Meier curve (figure 3) and an exponential function for the overall survival Kaplan-Meier curve (figure 4).

Figure 3 Event-free survival parametric fit to the observed Kaplan-Meier data up to 5 years (2009 data) (taken from figure 14 in ERG report)

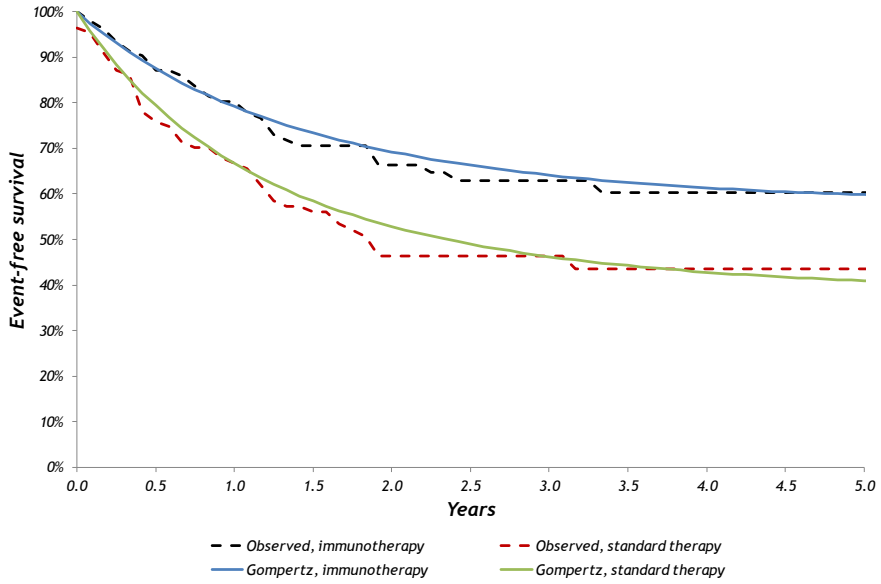
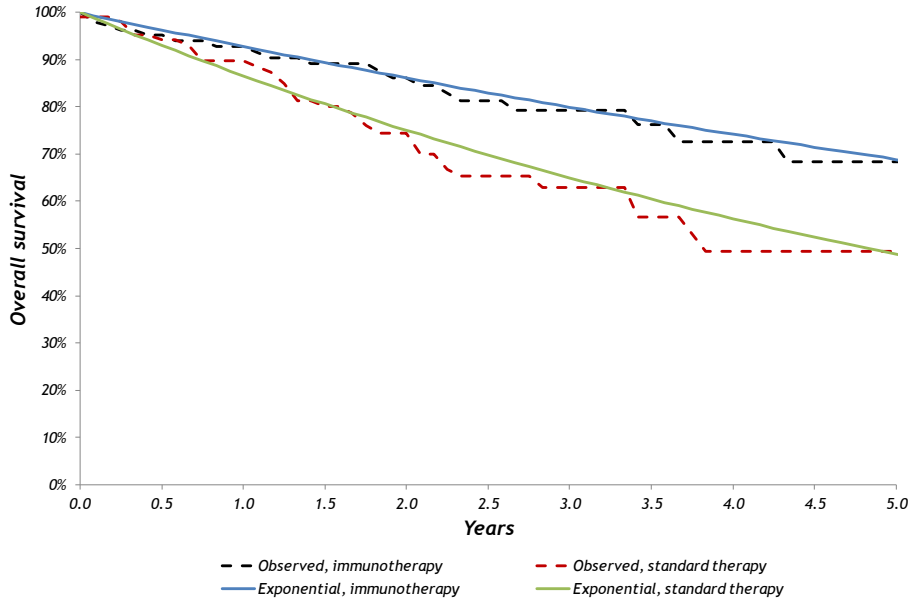
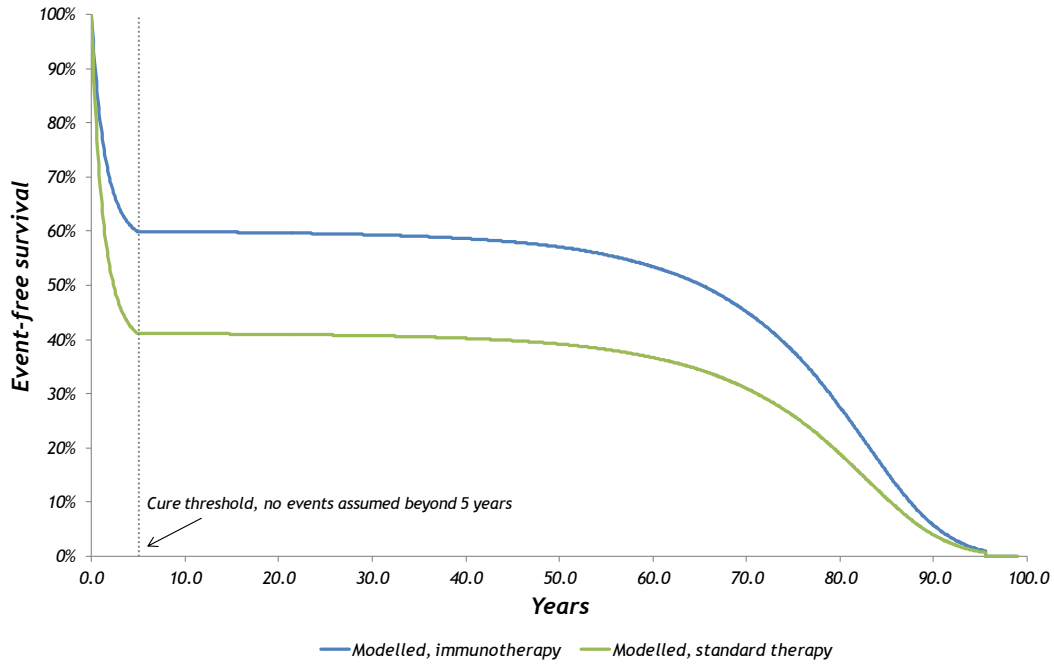


Figure 4 Overall survival parametric fit to the observed Kaplan-Meier data up to 5 years (2009 data) (taken from figure 15 in ERG report)



5.11 The company assumed that after 5 years, people who remain event-free are assumed to be cured. The company did not apply a parametric model to this period beyond 5 years. Instead, the company assumed that that these people's mortality, quality of life, and relapse rates become similar to the general population, while still accounting for potential morbidities affecting quality of life and resource use among neuroblastoma survivors.

Figure 5 Event-free survival over lifetime horizon (Company's base case using 2009 data) based on figure 16 from the ERG report



5.12 The company incorporated different parametric functions to fit to the Kaplan-Meier curves for event free survival and overall survival in the economic model for structural sensitivity analyses and different time points can be considered for when the “cure effect” starts to apply.

5.13 Monthly rates of adverse events were calculated based on follow-up time until 6 cycles (immunotherapy: 612 months; standard therapy: 626 months) and the number of patients with Grade 3/4 events. Table 38 of the company’s submission details the monthly adverse events rates applied in the model.

5.14 As health-related quality of life was not collected or assessed in ANBL0032, because the majority of the children treated were too young for an appropriate quality of life metric, the company searched for relevant studies which included health-related quality of life data for people with neuroblastoma. The company did not identify any studies which reported health state-specific utilities in patients with neuroblastoma, but they identified a study which measured the health-related quality of life of

patients who had tumours of the central nervous system. In the absence of any other health state-specific health-related quality of life evidence for people with neuroblastoma, the ERG stated that this assumption could be considered reasonable.

5.15 Utility values from Barr et al. (1999) were assigned to the stable (0.81) and failure (0.56) health states in the model for the first 5 years in the model. After 5 years, patients in the failure state continue to experience a health utility of 0.56 while patients in the stable state are assumed to follow similar characteristics to that of the general population (based on Ara et al. 2000) but using a 13% reduction in utility (based on Portwine et al. 2014) to account for potential morbidities among neuroblastoma survivors.

5.16 The company applied no administration cost in the model for isotretinoin, as it is self-administered. The administration cost per cycle of GMC-SF is estimated to be £142.50, which is based on an assumption of 75% self-administered and 25% administered by a nurse, where nurse costs are based on Personal Social Services Research Unit 2014. For dinutuximab and interleukin-2, the administration costs are based on NHS Reference Costs for procurement inpatient chemotherapy drugs for regimens in Band 10 (code SB10Z) of £1,908. The company used the same procurement cost to represent the administration costs for topotecan, received after disease progression in the model. The drug costs used in the model are based on the vials required for an average body surface area of 0.65 m^2. All patients are assumed to die by the age of 100.

ERG comments

5.17 The ERG noted that the company's base-case cost-effectiveness analysis was based on evidence from the ANBL0032 clinical trial using the primary 2-year efficacy analysis (June 2009) data cut although later data cuts were available. The ERG considers that the updated survival data from the pivotal trial (March 2014 data cut) provide the most relevant estimates

of event-free and overall survival for informing the assessment of cost-effectiveness (see section 4.8).

5.18 The ERG expressed concern that the company's cost effectiveness results are contingent on the assumption that the event free cohort is 'cured' at 5 years (cure threshold). The ERG noted that the company's justification for this assumption was based on information from the Children's Oncology Group (COG) neuroblastoma website which states that relapses occurring more than 5 years after the completion of therapy are rare. However, the ERG's clinical advisors the long-term benefits of immunotherapy are uncertain. Additionally, the ERG noted that the 2014 analysis of ANBL0032 suggested that further events would occur in the dinutuximab arm of the trial beyond 5 years as the observed data for immunotherapy and standard therapy appear to converge between 6.5 and 11 years for both event-free and overall survival in the updated analysis. Therefore the ERG considered that a longer cure threshold 10 years would be more appropriate.

5.19 The ERG noted that the company tried to apply parametric models to the Kaplan-Meier survival curves from the 2009 analyses of ANBL0032 to reflect what it expected the long-term survival of patients in the study would be over a lifetime horizon. Because the parametric model predictions were lower than the company expected, it did not use parametric models to reflect the period after the cure threshold of 5 years. The ERG noted that the updated 2014 analysis of ANBL0032 provided Kaplan-Meier curves for a further 5 years. Therefore, the ERG considered it unnecessary to apply parametric modelling since the data was not extrapolated beyond the trial period.

5.20 The ERG noted that the company assumed that patients in the event-free health-state at 5 years subsequently have the same survival rate as the general population. The ERG identified evidence from the Childhood Cancer Survivor Study which found a higher standardised mortality rate of 5.6 (95% confidence interval of 4.4 to 6.9) among neuroblastoma

survivors compared to low-risk siblings without cancer. In addition, the ERG found it unlikely that patients who had undergone chemotherapy and significant radiotherapy would return to the same mortality risk as the general population.

5.21 The ERG also noted that the mortality risk applied within the model for relapse in the failure state after the 5 year 'cure' was a monthly probability of death of 5.1% which seemed high. The ERG expressed concern that applying this monthly probability only to the failure state creates an inconsistency in how the mortality following relapse is captured within the model. This effect persists after the cure point due to a different proportion of patients being in the failure state at 5 years for dinutuximab therapy compared with isotretinoin.

5.22 The ERG noted that the company used evidence from Portwine et al. 2014 to incorporate a decrement in health-related quality of life of 13% compared to the general population for patients in the event-free health state at the point of the cure threshold. The ERG considered this to be an underestimate considering the exposure to radiation and chemotherapy that children with high-risk neuroblastoma have undergone. The ERG noted that an alternative decrement of 31.5% could be calculated from Nathan et al. 2007, a study identified by the company by mapping the SF-36 values from that study to EQ-5D. The ERG noted that mapping SF-36 values to EQ-5D has some limitations in that the models tend to overpredict for more severe health states. As a result, the ERG stated that it had no strong preference for the value derived from Nathan et al. and that the most likely value would lie between 13% and 31.5%.

5.23 The ERG noted that the company used the same procurement cost to represent the administration costs for dinutuximab, interleukin-2 and topotecan. The ERG considered there should be a distinction between procurement costing bands and delivery of treatment regimens. The ERG also expected that the administration costs of dinutuximab and interleukin-2 to be more than the administration costs for topotecan due to

the additional number of days that patients are required to be hospitalised during immunotherapy. The ERG estimated the total cost of administration for dinutuximab and interleukin-2 to be £28,399, an increase from the company's estimate of £13,356.

Company's base-case results and sensitivity analysis

5.24 In the base case, patients gained 4.71 (14.02, undiscounted) additional life-years (LYs) and 3.71 (10.57, undiscounted) additional QALYs with dinutuximab compared to isotretinoin at an incremental cost of £139,022, resulting in an ICER £37,423 per QALY gained (Table 8).

Table 8. The company's base-case economic results (based on the 2009 analysis of ANBL0032) (table 4, page 12 of company's submission)

Technologies	Total Costs (£)	Total LYs	Total QALYs	Incremental Costs (£)	Incremental LYs	Incremental QALYs	ICER (£) vs Baseline (QALYs)
Isotretinoin	46,573	12.46	9.73	-	-	-	-
Dinutuximab therapy	185,595	17.16	13.44	139,022	4.71	3.71	37,423

Company scenarios

5.25 The company used the updated analysis of March 2014 to provide an estimate of the cost-effectiveness of dinutuximab in a scenario analysis. Figure 6 and figure 7 show a comparison of the observed event-free survival and overall survival data, respectively, for the 2014 updated 4-year analysis and original 2012 analysis. When the company used parametric survival models based on the 2014 updated 4-year analysis data, the ICER increased to £66,344 per QALY gained, although the company reiterated that the trial was not powered to detect differences at year 4.

Figure 6 Observed EFS data for updated 4-year (March 2014) and primary 2-year (June 2009) data analysis (figure 19, page 86 ERG report)

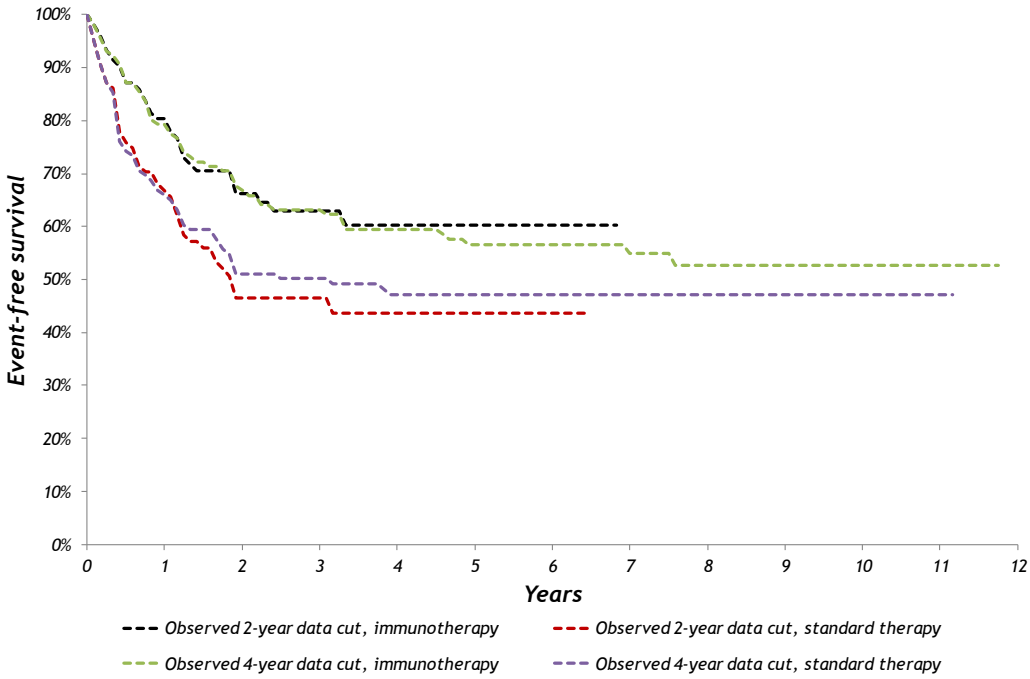
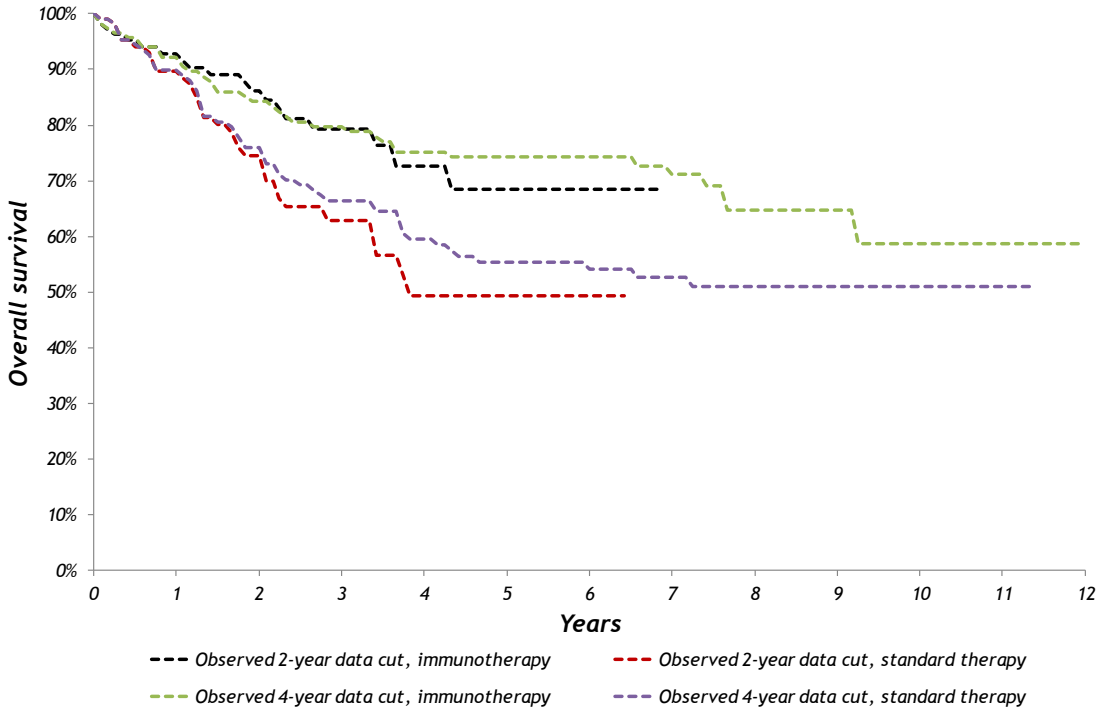
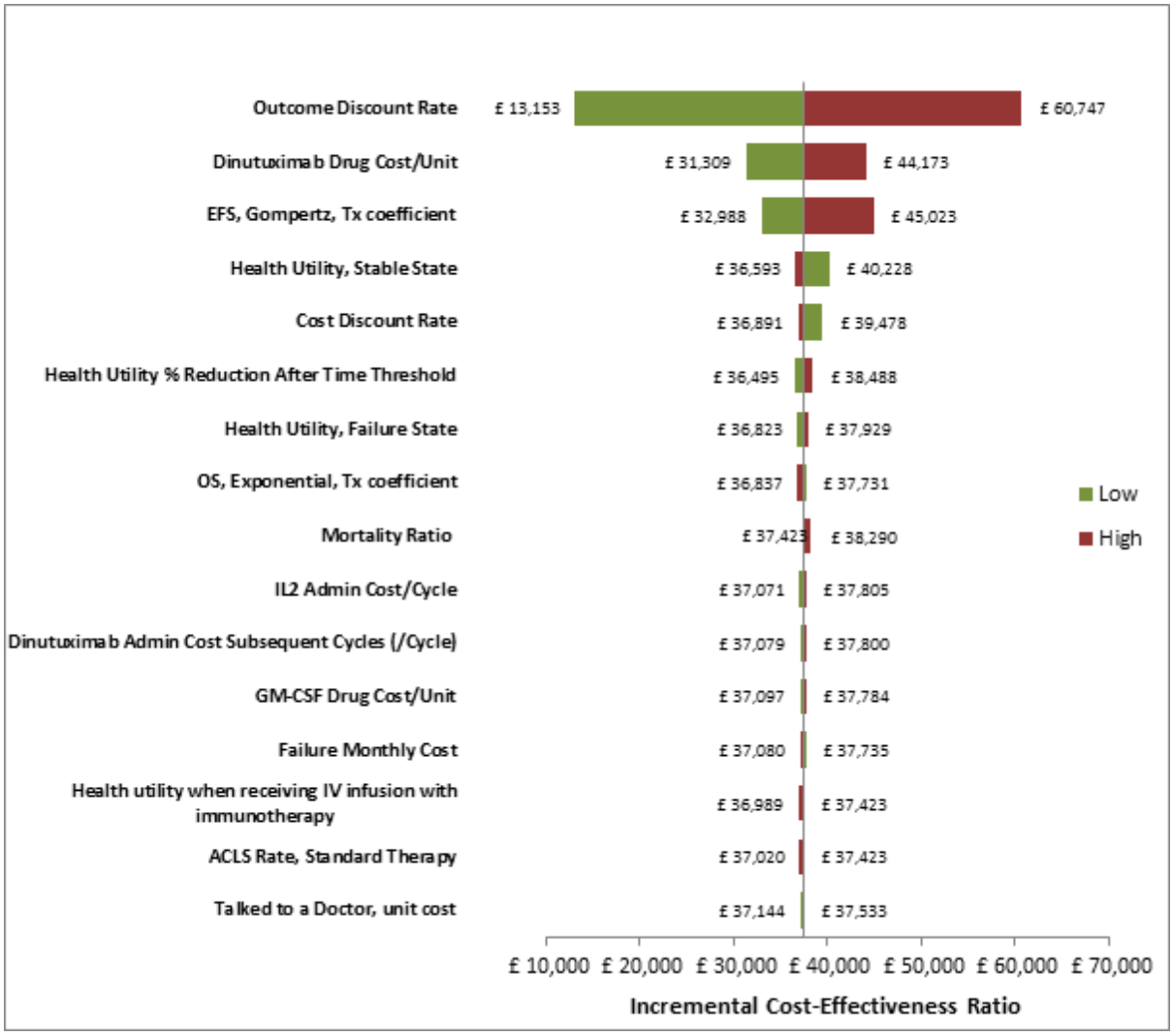


Figure 7 Observed OS data for updated 4-year (March 2014) and primary 2-year (June 2009) data analysis



5.26 The company conducted several one-way deterministic sensitivity analyses. The scenario that had the greatest impact on the ICER was varying the outcome discount rate from 0% (£13,153 per QALY gained) to 6% (£60,747 per QALY gained) for dinutuximab therapy compared with isotretinoin. (see figure 8 below).

Figure 8 Tornado diagram for one way deterministic sensitivity analysis (Figure 25, page 136 of the company's submission)



5.27 The company presented a scenario in which an outcome discount rate of 1.5% was used (see page 140 of the company submission). The company stated that this could be considered because of the health benefits of leading a relatively healthy life compared to the general population may be sustained over the course of patients' lifetime with immunotherapy. This approach was based on two things:

1) immunotherapy was shown to be superior compared to standard therapy with regard to EFS (66% vs. 46%) and OS (86% vs. 75%) at 2 years (Yu 2010)

2) given the external data, the majority of the disease-free patients are likely to experience sustained benefits approximately after 5 years.

The ICER using the 1.5% outcome discount rate was £22,017 per QALY gained for dinutuximab compared with isotretinoin.

5.28 The company did not include any subgroup in the economic analyses due to the small sample sizes.

ERG exploratory analyses

5.29 The ERG explored how a reduction in the time horizon of the extrapolated benefits would affect the cost effectiveness of dinutuximab therapy compared with isotretinoin. The ERG expressed concern at the use of a 100 year lifetime horizon considering the uncertainty of the benefits extrapolated from the data. The results of this scenario analysis showed that with a shorter the time horizon, a higher the ICER could be expected. See 9 below.

Table 9 ERG's exploratory scenario analyses for shorter time horizons using the company's base case assumptions (table 36, page 111 of ERG report)

	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY gained)
Company's base case – Lifetime horizon (best case scenario)					
Standard therapy	£46,573	9.73	-	-	-
Immunotherapy	£185,595	13.44	£139,022	3.71	£37,423
ERG scenario – Time horizon of 5 years (worst case scenario)					
Standard therapy	£35,681	2.49	-	-	-
Immunotherapy	£171,149	2.91	£135,468	0.41	£326,844
ERG scenario – Time horizon of 10 years					
Standard therapy	£41,069	3.86	-	-	-
Immunotherapy	£177,620	4.89	£136,551	1.03	£133,016
ERG scenario – Time horizon of 15 years					
Standard therapy	£42,179	4.97	-	-	-

Immunotherapy	£179,188	6.50	£137,009	1.53	£89,392
ERG scenario – Time horizon of 20 years					
Standard therapy	£42,987	5.89	-	-	-
Immunotherapy	£180,366	7.84	£137,378	1.95	£70,288

5.30 As stated previously (see section 5.17), the ERG expressed concern that the company had used the 2009 analysis of the ANLB0032 study rather than the 2014 analyses, which the ERG considered more mature. Therefore, the ERG used the 2014 data cut in its preferred exploratory analyses. The ERG also used the 2014 Kaplan-Meier data without parametric modelling and a cure threshold of 10 years (see figure 9 and figure 10 below), as it observed that the evidence for event-free and overall survival suggested that the survival curves for dinutuximab therapy and isotretinoin converge between 6.5 and 11 years. When the Kaplan-Meier survival curve data from the 2014 analysis of ANBL0032 is used with a cure point of 5 years, the resulting ICER is £70,296 per QALY gained. When the cure threshold is increased from 5 to 10 years, the ICER increases to £99,699 per QALY gained for dinutuximab therapy compared with isotretinoin. See table 10 below.

Figure 9 Modelled March 2014 (4-year) EFS data in the company's scenario analysis relative to the modelled June 2009 (2-year) data in the base case analysis and the observed March 2014 (4-year) Kaplan-Meier data (figure 23, page 113 ERG report)

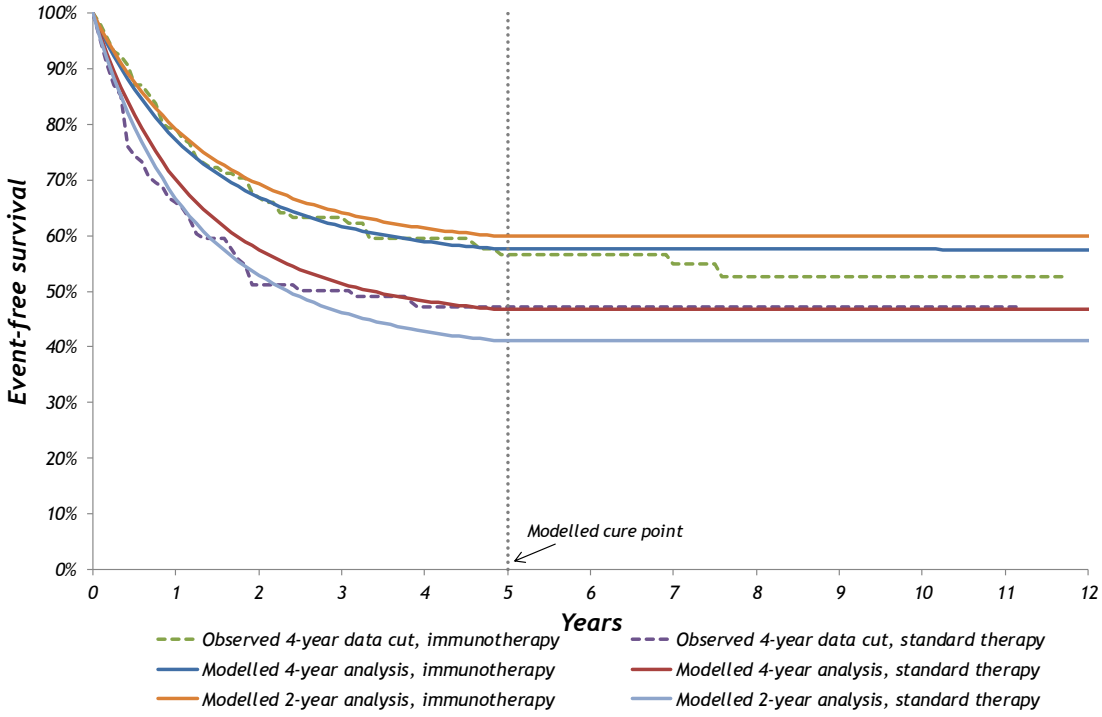
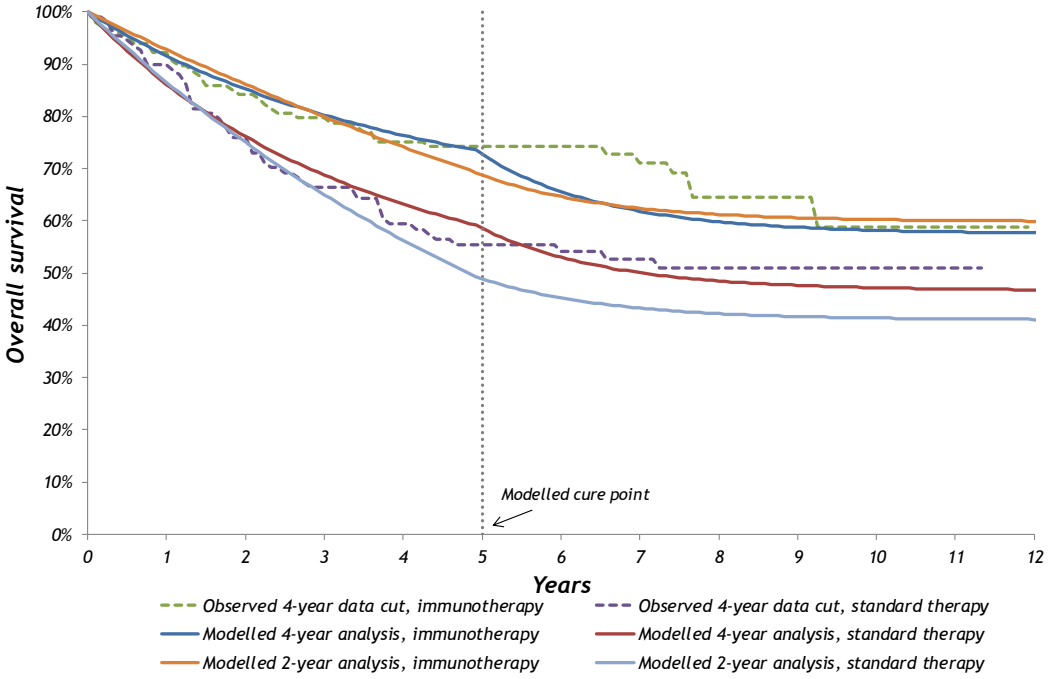


Figure 10 Modelled March 2014 (4-year) OS data in the company's scenario analysis relative to the modelled June 2009 (2-year) data in the base case analysis and the observed March 2014 (4-year) Kaplan-Meier data (figure 24, page 113 ERG report)



5.31 The ERG explored the implications of an adjustment to the general population mortality for neuroblastoma survivors. The higher standardised mortality rate of 5.6 from the Childhood Cancer Survivor Study increased the ERG's base case ICER from £99,699 to £105,160 per QALY gained.

5.32 Although the company included a scenario analysis which doubled the reduction to 26%, the ERG used evidence from Nathan et al 2007 suggesting that a 31.5% reduction in health-related quality of life might be appropriate for people in the event-free health state following high-risk neuroblastoma. When the ERG applied the 31.5% reduction to the ERG's preferred exploratory base case (using the 2014 analysis and a cure threshold of 10 years), the ICER for dinutuximab compared to isotretinoin increased from £99,699 to £112,051 per QALY gained (scenario 4 in table 7 below).

5.33 When the ERG applied the increased costed of administration for dinutuximab and interleukin-2 to the company's base case, the ICER for dinutuximab compared with isotretinoin increased from £37,423 to £41,959 per QALY gained. Applying the higher administration costs for dinutuximab and interleukin-2 to the ERG's preferred exploratory base case (using the 2014 analysis and a cure threshold of 10 years, the ICER increased from £99,699 to £128,378 per QALY gained (scenario 5 in table 7 below).

5.34 The ERG noted that the drug costs used by the company in the model are based on the vials required for an average body surface area of 0.65 m^2. The ERG noted that 4.8% of patients in the pivotal trial had a body surface area greater than 1 m^2. The ERG calculated there to be greater vial wastage and additional costs associated with patients with a body surface area greater than 1 m^2. When the ERG applied a weighted average of body surface area to its preferred assumptions, the ICER increased to £103,667 per QALY gained (scenario 6 in table 7 below).

Table 10 ERG exploratory analyses (dinutuximab compared with isotretinoin) based on tables 34-45 of the ERG report

ERG Scenarios	Total cost	Total QALY	Inc. cost	Inc. QALY	ICER
Company's base case	£185,595	13.44	£139,022	3.71	£37,423
Scenario 1 Using Kaplan-Meier data in the company's base case	£185,642	13.47	£141,059	3.39	£41,671
ERG exploratory base case (cure-threshold of 5 years)	£192,165	12.90	£144,086	2.05	£70,296
ERG preferred exploratory base case (cure-threshold of 10 years)	£208,435	12.44	£153,765	1.54	£99,699
Scenario 2 fixed treatment effect on mortality after 10 years	£254,276	13.02	£169,930	1.75	£97,265
Scenario 3 standardised mortality rate of 5.6% per year for event-free survivors	£207,658	11.68	£153,683	1.46	£105,160
Scenario 4 reduction of 31.5% in health-related quality of life	£208,435	11.31	£153,765	1.42	£112,051
Scenario 5 ERG's assumptions about the administration cost of dinutuximab	£252,666	12.44	£197,995	1.54	£128,378
Scenario 6 ERG's assumptions about the effect of body surface area on vial wastage	£214,562	12.44	£159,884	1.54	£103,667

5.35 For the alternative assumptions, the ERG's base case ICER ranges from £99,699 to £128,378 per QALY gained. However, if the alternative assumptions are taken together as follows:

- Standardised mortality rate of 5.6 for event-free survivors;
- 31.5% reduction in health-related quality of life ;
- Adjustment to the administration cost of dinutuximab;
- Weighted average of BSA above and below $1m^2$;

the ERG's ICER increases to £155,915 per QALY gained.

Innovation

5.36 The company presented the following justifications for the Committee to consider whether dinutuximab is innovative:

- The health-related benefits from improved treatments for high-risk neuroblastoma are unlikely to be fully captured in QALY
- Dinutuximab improves survival in a disease associated with high mortality in a paediatric population, therefore meeting a need that has been identified as being important by the NHS.
- There is a robust evidence base demonstrating that dinutuximab is effective.
- Dinutuximab represents a change in the treatment paradigm for children with high-risk neuroblastoma and may result in improved health-related quality of life for patients and their families.
- Dinutuximab immunotherapy will be the first European Medicines Agency (EMA)-approved maintenance therapy for patients with high-risk neuroblastoma and may become the new standard of care for these patients

6 End-of-life considerations

6.1 In its submission the company stated that population-based survival curves created using the most recent data available for patients aged 1 to 14 with neuroblastoma in Great Britain (December 2002 to December 2005) show a median survival of approximately 4 years following treatment with isotretinoin. The company referred to its 2009 results from ANBL0032 which suggested that It calculated the number of people in England and Wales for whom dinutuximab is being appraised (aged 12 months to 17 years who have previously received induction chemotherapy and achieved at least a partial response, followed by myeloablative therapy and ASCT) as 54 patients.

6.2 The company stated that in study ANBL0032, approximately 50% of patients randomised to isotretinoin were alive at 4 years after randomisation, but commented that that this likely overestimates life expectancy, as participants were required to have at a life expectancy of at least 2 months or more to be included in the study.

6.3 The ERG noted that the results from the ANBL0032 trial suggest that around half of all children with high-risk neuroblastoma who are eligible for dinutuximab treatment will survive long-term (at least 10 years) regardless of whether they receive dinutuximab or only isotretinoin. According to calculations made by the ERG, approximately 75% of patients receiving isotretinoin will have a life expectancy of 24 months or more. The ERG also noted that patients who may experience a relapse would have a shorter life expectancy (less than 23 months).

7 Equality issues

7.1 No equality issues have been identified during scoping or in the evidence submitted for this appraisal.

8 Authors

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Appendix A: Clinical efficacy section of the draft European public assessment report

EPAR - http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002800/WC500192794.pdf

SPC - http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002800/WC500192791.pdf

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Dinutuximab for treating high-risk neuroblastoma

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of dinutuximab in combination with sargramostim, aldesleukin and isotretinoin within its marketing authorisation for treating high-risk neuroblastoma following myeloablative therapy and autologous stem cell transplant.

Background

Neuroblastoma is a cancer of embryonic nerve cells called neural crest cells. It commonly occurs either in the adrenal glands located above each kidney or in any nerve tissue of the sympathetic nervous system, which runs alongside the spinal cord, from the neck through the chest and the abdomen to the pelvis. Neuroblastoma usually affects children under the age of 5 years.

The initial symptoms are usually vague, such as tiredness, fever and loss of appetite. Specific symptoms depend on the location of the tumour. Because neuroblastoma usually develops in the abdomen, the most common symptom is an abdominal lump and children may also experience constipation or difficulty in passing urine. The tumour may affect the chest or neck region and may cause breathlessness and difficulty in swallowing or a visible lump in the neck. Occasionally it can press the spinal cord causing numbness, weakness and loss of movement in the lower part of the body. Neuroblastoma often spreads to other parts of the body before any symptoms are apparent; therefore, more than half of all patients present with metastases. It commonly spreads to the bones and can cause pain and difficulty in walking. If it spreads to bone marrow it may cause anaemia, bruising, bleeding and infections. It may also spread to the liver or the skin causing small blue-coloured lumps.

Based on various prognostic factors and international staging systems children are classified into different risk groups. High-risk neuroblastoma can be characterised by age (>18 months), metastatic disease, and MYCN oncogene amplification and overexpression. However, ‘high risk’ is not rigidly defined in clinical practice because the definition tends to be driven by the criteria used for including participants in clinical trials for high-risk neuroblastoma.

Around 90 children are diagnosed with neuroblastoma each year in the UK. Approximately 40% of children with neuroblastoma are classified as high-risk. High-risk neuroblastoma is associated with a 5-year survival rate of 30–50%.

Treatment for high-risk disease is generally divided into 3 phases; induction, consolidation and maintenance. Children in the high-risk category are initially

treated with multi-agent chemotherapy, surgery and radiotherapy, followed by consolidation therapy with high-dose chemotherapy (which may cause severe or complete depletion of bone marrow cells; also known as myeloablative therapy) and autologous stem cell transplant. Radiotherapy may also be given after stem cell transplant. In the maintenance phase, standard of care is to treat the child for minimal residual disease with an immunotherapy-based regimen as part of a clinical trial. Children who are ineligible to participate in a trial, or who participate but subsequently withdraw, are normally treated with isotretinoin alone.

The technology

Dinutuximab (Unituxin, United Therapeutics) is a chimeric monoclonal antibody that targets GD2, a glycolipid overexpressed in certain tumours such as neuroblastoma. It induces antibody-dependent cell-mediated cytotoxicity and complement-dependent cytotoxicity against tumour cells. It is administered intravenously.

Dinutuximab does not currently have a marketing authorisation in the UK for treating neuroblastoma. It has been studied in clinical trials in combination with isotretinoin, aldesleukin (also known as interleukin -2, as referred to in clinical trials), and sargramostim (also known as granulocyte macrophage colony-stimulating factor, as referred to in clinical trials) compared with isotretinoin in people less than 30 years of age with high-risk neuroblastoma who had received myeloablative therapy and autologous stem cell transplant.

Intervention(s)	Dinutuximab in combination with sargramostim, aldesleukin, and isotretinoin
Population(s)	People with high-risk neuroblastoma who have received myeloablative therapy and autologous stem cell transplant
Comparators	Isotretinoin
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • adverse effects of treatment • health-related quality of life.

Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. Consideration should be given to alternative standardised and validated preference-based measures of health-related quality of life that have been designed specifically for use in children. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.
Other considerations	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator. If the evidence allows the following subgroups will be considered. These include: • people with relapsed disease • people with refractory disease. If no evidence is available for these subgroups, this should be stated, and the Appraisal Committee would then decide if the available evidence could be extrapolated to people with relapsed or refractory disease.
Related NICE recommendations and NICE Pathways	Related Guidelines: Cancer Service Guideline, 'Improving outcomes in children and young people with cancer', August 2005, Review proposal date: June 2016 Related Quality Standards: Quality Standard No. 55, February 2014, 'Children and young people with cancer'. Review proposal date TBC http://www.nice.org.uk/guidance/qualitystandards/qualitystandards.jsp

Related National Policy	Department of Health (2013): NHS Outcomes Framework 2014–2015 Specialist cancer services for children and young people, Chapter 106, 'Manual for prescribed services'. November 2012. http://www.england.nhs.uk/wp-content/uploads/2012/12/pss-manual.pdf

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Dinutuximab for the maintenance treatment of high risk neuroblastoma in infants, children and young people aged 11 months to 17 years [ID799]

Company evidence submission

July 2015

File name	Version	Contains confidential information	Date
United Therapeutics Dinutuximab STA_8-7-15	**1**	**Yes**	**8/7/15**

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Abbreviations

ABMT – autologous purged bone marrow transplantation

ACCIS – Automated Childhood Cancer Information System

ACS – American Cancer Society

ADA – antidrug antibody

AIC – Akaike's information criterion

ALT – alanine aminotransferase

APC – activated protein C

ASCT – autologous stem-cell transplantation

AST – aspartate aminotransferase

BIC – Bayesian information criterion

BNF – British National Formulary

BuMel – busulphan and melphalan

CEM – carboplatin, etoposide, melphalan

CHMP – Committee for Medicinal Products for Human Use

CI – confidence interval

CNS – central nervous system

COG – Children's Oncology Group

COJEC – cisplatin, vincristine, carboplatin, etoposide, and cyclophosphamide

CRADA – Cooperative Research and Development Agreement

CRD – Centre for Reviews and Dissemination

CS – Curie score

CTCAE – Common Terminology Criteria for Adverse Events

d – day

DNA – deoxyribonucleic acid

EFS – event-free survival

EMA – European Medicines Agency

EU – European Union

FDA – Food and Drug Administration

GD2 – disialoganglioside

GM-CSF – granulocyte macrophage colony-stimulating factor

HRQOL – health-related quality of life

IL-2 – interleukin-2

INPC – International Neuroblastoma Pathologic Classification

INSS – International Neuroblastoma Staging System

ITT – intention-to-treat

LY – life-year

m^2 – meters squared

MIBG – meta-iodobenzylguanidine

MIU – million international units

MTD – maximum tolerated dose

MYCN – v-myc avian myelocytomatosis viral oncogene neuroblastoma derived homolog

NCI – National Cancer Institute

NHS – National Health Service

NICE – National Institute for Health and Care Excellence

ONS – Office for National Statistics

OR – odds ratio

OS – overall survival

PEDsQL – Pediatric Quality of Life Inventory 4.0

PK – pharmacokinetics

QALY – quality-adjusted life-year

RA – retinoic acid

RCT – randomised controlled trial

RR – risk ratio

SE – standard error

SF-36 – 36-item Short Form Health Survey

SIGN – Scottish Intercollegiate Network

SmPC – summary of product characteristics

UK – United Kingdom

US – United States

UTC – United Therapeutics Corporation

WBC – white blood cell

yr – year

µg – microgram

1.0 Executive Summary

1.1 Statement of decision problem

The decision problem as outlined by the National Institute for Health and Care Excellence (NICE) final scoping document is presented in Table 1.

Table 1. The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with high-risk neuroblastoma who have received myeloablative therapy and autologous stem cell transplant	As defined	N/A
Intervention	Dinutuximab in combination with sargramostim, aldesleukin, and isotretinoin	As defined	N/A
Comparator(s)	Isotretinoin	As defined	N/A
Outcomes	• Overall survival • Progression-free survival • Adverse effects of treatment • Health-related quality of life	• Overall survival • Event-free survival • Adverse effects of treatment • Health-related quality of life* *Health-related quality of life was not assessed in the pivotal trials, as the majority of the children treated were too young for an appropriate quality of life metric	Outcomes were as defined in the scope with the exception of event-free survival. Event-free survival was defined as the time to an event from study enrollment until the first occurrence of: • Relapse • Progressive disease • Secondary cancer • Death • Or, if none of these events occurred, until the last contact with the patient In the phase 3 trial, all patients experienced progressive disease, relapse, or death. As a result, the event-free survival outcome is similar to the progression-free survival outcome
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. Consideration should be given to alternative standardised and validated preference-based measures of health-related quality of life that have been designed specifically for use in	As defined	N/A

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	children. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.		
Subgroups to be considered	If the evidence allows, the following subgroups will be considered. These include: • People with relapsed disease • People with refractory disease If no evidence is available for these subgroups, this should be stated, and the Appraisal Committee would then decide if the available evidence could be extrapolated to people with relapsed or refractory disease.	As defined	N/A
Special considerations including issues related to equity or equality	No comment	As defined	N/A

1.2 Description of the technology being appraised

Dinutuximab (ch14.18) is a monoclonal antibody targeting the tumour-associated disialoganglioside (GD2) and is currently under review for marketing authorization in the United Kingdom (UK). The ch14.18 monoclonal antibody used for the dinutuximab pivotal phase 3 clinical trial was manufactured at the National Cancer Institute (NCI). Comparability has been sufficiently demonstrated between the NCI molecule used in clinical studies and the United Therapeutics Corporation (UTC) molecule (dinutuximab) (DIV-NB-201); therefore, the name dinutuximab will be used throughout the evidence submission.

Table 2. Technology being appraised

UK-approved name and brand name	Unituxin (dinutuximab) 3.5 mg/mL concentrate for solution for infusion
Marketing authorisation/CE mark status	Under review
Indications and any restriction(s) as described in the summary of product characteristics	Unituxin is indicated for the treatment of high-risk neuroblastoma in patients aged 12 months to 17 years who have previously received induction chemotherapy and achieved at least a partial response, followed by myeloablative therapy and autologous stem cell transplantation (ASCT). It is administered in combination with granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-2 (IL-2), and isotretinoin.
Method of administration and dosage	Dinutuximab is administered by intravenous infusion over 5 courses at a daily dosage of 17.5 mg/m^2. Dinutuximab is administered on Days 4–7 during courses 1, 3, and 5 (each course lasting approximately 24 days) and on Days 8–11 during courses 2 and 4 (each course lasting approximately 28 days). A more detailed diagram of the dinutuximab, GM-CSF, IL-2, and isotretinoin dosing regimen is presented in Table 7 and Table 8.

1.3 Summary of the clinical effectiveness analysis

The clinical evidence for dinutuximab for the treatment of patients with high-risk neuroblastoma aged 12 months to 17 years who have previously received induction chemotherapy and achieved at least a partial response, followed by myeloablative therapy and autologous stem cell transplantation (ASCT) is based on 4 studies, listed in Table 3.

Table 3. Studies providing primary clinical evidence for dinutuximab

Study Number	Study Design	Intervention	Outcomes
ANBL0032	Phase 3, multicentre, prospective, partially randomised, active-controlled trial	Dinutuximab, GM-CSF, IL-2, and isotretinoin vs isotretinoin	Efficacy, safety
ANBL0931	Phase 3, single-arm, open-label study	Dinutuximab, GM-CSF, IL-2, and isotretinoin	Safety
CCG-A0935A	Phase 1, single arm, dose-finding study	Dinutuximab, GM-CSF, IL-2, and isotretinoin	Safety
CCG-0935	Phase 1, single-arm, open-label study	Dinutuximab and GM-CSF	Safety

Key: GM-CSF – granulocyte-macrophage colony-stimulating factor; IL-2 – interleukin 2.

Clinical efficacy

Study ANBL0032 was a phase 3, multicentre, prospective, partially randomised, active-controlled trial comparing immunotherapy (dinutuximab in combination with granulocyte-macrophage colony-stimulating factor [GM-CSF], interleukin-2 [IL-2], and isotretinoin) to standard therapy (isotretinoin) in patients with high-risk

neuroblastoma less than 31 years of age who had previously received induction chemotherapy and achieved at least a partial response, followed by myeloablative therapy and ASCT.

Although originally designed with a duration of 4 years, randomization for study ANBL0032 was terminated early based on the opinion of the safety monitoring committee that immunotherapy had met pre-defined criteria for superiority over standard therapy as measured by event-free-survival (EFS). Overall, 226 patients were randomized: 113 to immunotherapy and 113 to standard therapy. EFS at 2 years was higher among patients treated with immunotherapy (66% ± 5%) compared to standard therapy (46% ± 5%) (*P*=0.01) (Yu 2010). Immunotherapy also demonstrated superior efficacy for the secondary endpoint of overall survival (OS) at 2 years compared to standard therapy (86% ± 4% vs 75% ± 5%, respectively; *P*=0.02) (Yu 2010).

Clinical safety

In the 3 studies that investigated dinutuximab in combination with GM-CSF, IL-2, and isotretinoin, the most commonly reported grade 3 and 4 adverse reactions were hypotension (67%), pain (66%), hypersensitivity (56%), pyrexia (53%), capillary leak syndrome (45%), anaemia (34%), hypokalaemia (41%), decreased platelet count (40%), hyponatremia (37%), alanine aminotransferase increased (35%), decreased lymphocyte count (34%), and decreased neutrophil count (31%) (Appendix 1: Draft UNITUXIN (dinutuximab) SmPC). The frequency of adverse reactions tended to be higher in the first course of therapy and decreased over subsequent courses.

1.4 Summary of the cost-effectiveness analysis

The model consists of 3 health states (stable, failure, and death) to evaluate the cost-effectiveness of immunotherapy (dinutuximab in combination with GM-CSF, IL-2, and isotretinoin) compared to standard therapy with isotretinoin alone for the treatment of high-risk neuroblastoma in patients aged 12 months to 17 years who have previously received induction chemotherapy and achieved at least a partial response, followed by myeloablative therapy and ASCT.

Within the first 5 years, a partitioned survival approach is implemented based on parametric EFS and OS curves fit to dinutuximab clinical trial data. After 5 years, the event-free cohort is assumed to be cured and enters a phase when they are considered survivors and start to follow similar characteristics (ie, mortality, quality of life, relapse rates) to that of the general population, while still accounting for potential morbidities affecting quality of life and resource use among neuroblastoma survivors.

The model was informed by a well-designed randomised controlled study, which demonstrated immunotherapy's superiority over standard therapy with respect to EFS and OS. The main outcome (quality-adjusted life-years [QALYs]) and costs were mainly driven by health utility and survival estimates.

The incremental cost per QALY gained with immunotherapy vs standard therapy was £37,423 with a 3.5% outcome discount rate and £22,017 with a 1.5% outcome discount rate. An outcome discount rate of 1.5% was also considered because the substantial health benefits of leading a relatively healthy life compared to the general population may be sustained over the course of patients' lifetime with immunotherapy.

Due to the rarity of the disease (high-risk neuroblastoma), identifying data to inform model inputs was somewhat challenging. Key data constraints were around (1) the extrapolation of outcomes beyond the trial due to lack of data for similar populations and small sample sizes and (2) lack of neuroblastoma state-specific health-related quality of life (HRQOL) data. Nevertheless, the impact of these data constraints on model outcomes was tested to the extent possible via deterministic and probabilistic sensitivity analyses. Similarly, appropriate sources were used and the currently available data were utilized to reflect outcomes applicable to England's healthcare system. To our knowledge, this economic model is the first to address the cost-effectiveness of an intervention in patients with high-risk neuroblastoma by modelling the course of the disease over the long term and is hoped to edify future evaluations.

Table 4. Base-case results

Technologies	Total Costs (£)	Total LYs	Total QALYs	Incremental Costs (£)	Incremental LYs	Incremental QALYs	ICER (£) vs baseline (QALYs)
Standard therapy	46,573	12.46	9.73	-	-	-	-
Immunotherapy	185,595	17.16	13.44	139,022	4.71	3.71	37,423

Key: ICER – incremental cost-effectiveness ratio; LY – life-year; QALY – quality-adjusted life year.

2.0 The technology

2.1 Description of the technology

2.1.1 Give the brand name, UK approved name, therapeutic class, and a brief overview of the mechanism of action. For devices, provide details of any different versions of the same device.

Brand name: Unituxin™

UK approved name: Dinutuximab 3.5 mg/mL concentrate for solution for infusion

Therapeutic class: Monoclonal antibodies, ATC code: L01XC16

Mechanism of action: Dinutuximab is a monoclonal chimeric antibody composed of murine variable heavy and light chain regions and the human constant region for the heavy chain IgG1 and light chain kappa. Dinutuximab reacts specifically with the ganglioside GD2, which is highly expressed on the surface of neuroblastoma cells and minimally expressed on the surface of normal human neurons, peripheral pain fibres, and skin melanocytes.

2.2 Marketing authorisation/CE marking and health technology assessment

2.2.1 Indicate whether the technology has a UK marketing authorisation/CE marking for the indications detailed in this submission. If so, give the date on which this was received. If not, state the current UK regulatory status, with relevant dates.

Dinutuximab is a designated orphan drug in the European Union (EU) and United States (US). The company submitted a Marketing Authorisation Application to the EU in Q4 2013.

2.2.2 Give the (anticipated) indication(s) in the UK. For devices, provide the date of (anticipated) CE marking, including the indication for use. If a submission is based on the company's proposed or anticipated marketing authorisation, the company must advise NICE immediately of any variation between the anticipated and the final marketing authorisation approved by the regulatory authorities.

The anticipated indication for use within the UK for dinutuximab is for the treatment of high-risk neuroblastoma in patients aged 12 months to 17 years who have

previously received induction chemotherapy and achieved at least a partial response, followed by myeloablative therapy and ASCT. It is administered in combination with GM-CSF, IL-2, and isotretinoin.

2.2.3 Summarise any (anticipated) restrictions or contraindications that are likely to be included in the (draft) summary of product characteristics (SmPC).

The indicated use is restricted to high-risk neuroblastoma patients described above (those who have previously received induction chemotherapy and achieved at least a partial response, followed by myeloablative therapy and ASCT). Dinutuximab is restricted for use within a hospital setting under the supervision of a physician experienced in oncologic therapies.

There is no relevant use of dinutuximab in children aged 0 to 11 months. It has not been determined whether they respond differently than children aged 12 months or older. In addition, dinutuximab is contraindicated in patients with Grade 4 hypersensitivity to dinutuximab or excipients (histidine, polysorbate 20 [E 432], sodium chloride, or water for injection).

2.2.4 Include the (draft) SmPC for pharmaceuticals or information for use (IFU) for devices in an appendix.

A copy of the draft SmPC is included in Appendix 1: Draft UNITUXIN (dinutuximab) SmPC.

2.2.5 Provide the (draft) assessment report produced by the regulatory authorities (that is, the European public assessment report for pharmaceuticals).

A copy of the draft European Public Assessment Report for Pharmaceuticals is included in Appendix 2: Draft UNITUXIN (dinutuximab) European Public Assessment Report for Pharmaceuticals.

2.2.6 Summarise the main issues discussed by the regulatory authorities (preferably by referring to the [draft] assessment report [for example, the European Public Assessment Report]). State any special conditions attached to the marketing authorisation (for example, if it is a conditional marketing authorisation).

Quality:

A major concern was raised by the Committee for Medicinal Products for Human Use (CHMP) regarding the comparability between the UTC commercial product

(administered at a dose of 17.5 mg/m^2/day) and the NCI product (administered at a dose of 25 mg/m^2/day) that was used in the clinical trials. However, the population pharmacokinetic (PK) study and analyses of data from Study DIV-NB-201 demonstrate that there is not a significant difference in exposure between the two products. Based on all data provided by UTC to date, the issue of comparability has been satisfactorily addressed and the issue is considered resolved (Appendix 3: Committee for Medicinal Products for Human Use (CHMP) Assessment Report for Unituxin (EMA/CHMP/278656/2015)).

The CHMP noted that the source and history of cell substrate used to generate the cell line is no longer available due to the length of time since generation; however, characterisation tests, the coding sequence, and the determination of the copy number were acceptable. The manufacturing control strategy for the active substance was considered satisfactory; process validation studies demonstrated that upstream and downstream manufacturing processes were well controlled. While genetic stability at a commercial scale is expected to be maintained, the CHMP recommended that UTC make an end-of-production cell bank and characterise the genetic stability of both the white blood cell count and end-of-production cell bank. The use of the new white blood cell count will have to be authorised with a variation (Appendix 3: Committee for Medicinal Products for Human Use (CHMP) Assessment Report for Unituxin (EMA/CHMP/278656/2015)).

Validation and analytical methods were raised as issues by the CHMP that are considered resolved with review of additional data provided by UTC, with a recommendation that UTC provide for the product- and process-specific assay for host cell protein when available. UTC was also recommended to include an antibody-dependent cellular cytotoxicity assay and oxidation assay into the stability protocol and the ongoing stability studies in order to inform appropriate shelf life and in-use stability of the finished product (Appendix 3: Committee for Medicinal Products for Human Use (CHMP) Assessment Report for Unituxin (EMA/CHMP/278656/2015)).

Non-clinical:

The CHMP noted that the potential for peripheral neuropathy may warrant additional research. Although the administration of dinutuximab was not associated with peripheral neuropathy in non-clinical studies, it is noted that these studies involved the administration of a single dose only (Appendix 3: Committee for Medicinal Products for Human Use (CHMP) Assessment Report for Unituxin (EMA/CHMP/278656/2015)).

Although data suggest that dinutuximab does not cross the blood-brain barrier in appreciable amounts, during immunohistochemistry studies, 14.G2a was found to bind to the granular layer of the cerebellum, to the vagus nerves, and to many of the sciatic nerve fibres. Single doses of dinutuximab have also been associated with significant reduction in distal motor amplitude, possibly due to binding of 14.G2a to GD2 in the axon, disrupting normal axonal function. It has also been postulated that the observed effect could be a result of cytokine production and that the corresponding hyperplastic lymph nodes are indicative of a robust immune response to a mouse antibody. The release of cytokines has been described as a potential mechanism for the pain experienced in man (Appendix 3: Committee for Medicinal Products for Human Use (CHMP) Assessment Report for Unituxin (EMA/CHMP/278656/2015)).

The CHMP was of the view that the peripheral neuropathy following repeated administration observed in the repeated-dose study, the underlying pathophysiology, and the potential for reversibility would benefit from further investigation. UTC will conduct further non-clinical investigations post-authorisation in order to fully characterise the effects of dinutuximab on peripheral nerves. UTC has suggested that a juvenile toxicity study in monkeys of 5 months duration will be performed in order to evaluate the effects of dinutuximab on the central and peripheral nervous system. However, the CHMP are of the view that studies in non-human primates are not necessary to fulfil this request. Non-clinical data generated in a single study using one species, along with additional monitoring in patients, should provide additional information that would lead to improved information and advice for the prescriber (Appendix 3: Committee for Medicinal Products for Human Use (CHMP) Assessment Report for Unituxin (EMA/CHMP/278656/2015)).

GLP tissue cross-reactivity studies were conducted with rat, rabbit, and human tissues: staining with ch14.18 was generally consistent with reported sites of GD2 expression. Expression of GD2 by endothelium or perithelium, cardiac muscle, chondrocytes, or reproductive elements of the ovary, placenta, or testis has not been evaluated. UTC's rationale for not performing genotoxicity studies was deemed to be acceptable by the CHMP (Appendix 3: Committee for Medicinal Products for Human Use (CHMP) Assessment Report for Unituxin (EMA/CHMP/278656/2015)).

Although no direct evidence exists to suggest that dinutuximab does not have the potential to stimulate cell proliferation of healthy/normal cells, the potential for dinutuximab to cause carcinogenicity is low based on the mechanism of action and documented suppression of neuroblastomas, small cell lung cancer cells, and melanoma cells. Based on these data, the CHMP considered that the absence of carcinogenicity studies is justified (Appendix 3: Committee for Medicinal Products for Human Use (CHMP) Assessment Report for Unituxin (EMA/CHMP/278656/2015)).

Studies are also lacking for the evaluation of the effect of dinutuximab on fertility and embryofoetal development. In the repeat-dose toxicity studies, administration of dinutuximab in male and female rats resulted in no adverse effects on reproductive organs at exposures that were at least 60-fold higher than those observed clinically. However, in light of the potential expression of GD2 in the reproductive tract and the fact that the proposed product could be administered to patients up to the age of 17, at the request of the CHMP, UTC has discussed the effects (or lack thereof) on male and female fertility as observed during the repeated-dose studies and the level of information available has been included within the SmPC (see sections 4.6 and 5.3 of the SmPC). In addition, because of the limited reproductive toxicity data, dinutuximab is not recommended during pregnancy and in women of childbearing potential not using contraception. It is also recommended that women of childbearing potential use contraception for 6 months after discontinuation of treatment with dinutuximab (Appendix 3: Committee for Medicinal Products for Human Use (CHMP) Assessment Report for Unituxin (EMA/CHMP/278656/2015)).

Clinical:

The CHMP noted that the role of neutralising antibodies is currently unclear, as the number of subjects affected in a population PK analysis was too small to draw any conclusion. Therefore, UTC plans to develop and validate an assay for the detection of neutralising antibodies in the presence of dinutuximab and conduct a study to assess the neutralising antidrug antibody (ADA) response to dinutuximab (Appendix 3: Committee for Medicinal Products for Human Use (CHMP) Assessment Report for Unituxin (EMA/CHMP/278656/2015)).

No interaction studies have been performed. A risk for interactions with concomitantly used medicinal products (other than IL-2, GM-GSF, and isotretinoin) cannot be excluded (Appendix 3: Committee for Medicinal Products for Human Use (CHMP) Assessment Report for Unituxin (EMA/CHMP/278656/2015)).

In the pivotal randomised trial, most subjects (96%) exposed to the combination therapy experienced at least 1 severe (Grade ≥3) adverse reaction compared to 64% in the control arm treated with isotretinoin alone, and nearly all were considered treatment-related. The proportion of subjects experiencing adverse reactions and severe adverse reactions, as well as some specific adverse reactions, was higher in the randomised arm than in the overall exposed population. This could not be fully explained by UTC, although part of the differences might have been related to differences in data collection and variable intervals after ASCT. More than half the subjects (61%) exposed to the combination therapy experienced severe adverse reactions. As dinutuximab is used in combination with GM-CSF, IL-2, and isotretinoin, it is difficult to ascertain the causal relationship of each adverse reaction to a particular medicinal product. Although most patients received prophylactic analgesics as required in the study protocols, two-thirds of the patients experienced pain and 41% experienced severe pain. The incidence of pain decreased over the first 3 treatment courses, but about one-third of patients were still suffering in the last dinutuximab courses (Appendix 3: Committee for Medicinal Products for Human Use (CHMP) Assessment Report for Unituxin (EMA/CHMP/278656/2015)).

UTC will analyse laboratory data from patients with documented Grade 4 allergic reactions to allow for improved characterisation of these reactions. UTC also plans to conduct a safety study to better characterise the immunogenicity of dinutuximab. Based on the data currently available, 17% of the patients exposed developed

human anti-chimeric antibodies, which were persistent in 12% and neutralising in 3%. These antibodies did not seem to be associated with allergic reactions, but the detection of specific IgE against non-human glycans (galactose alpha-1,3-galactose and N-glycolylneuraminic acid) has not been performed. UTC will collect data on antibodies against non-human glycans from the ANBL0032 study and assess their impact on safety and efficacy (Appendix 3: Committee for Medicinal Products for Human Use (CHMP) Assessment Report for Unituxin (EMA/CHMP/278656/2015)).

Because of the lack of data on long-term effects of dinutuximab on the central and peripheral nervous system, the prevalence of organ dysfunction on growth and endocrine development, hearing loss, cardiac toxicity, and survival data, UTC will conduct a registry to collect more information on these adverse reactions (Appendix 3: Committee for Medicinal Products for Human Use (CHMP) Assessment Report for Unituxin (EMA/CHMP/278656/2015)).

Conditions or restrictions regarding supply and use:

Medicinal product subject to restricted medical prescription (Appendix 1: Draft UNITUXIN (dinutuximab) SmPC, section 4.2).

Conditions and requirements of the Marketing Authorisation:

UTC is required to submit periodic safety update reports as a condition of marketing authorisation, with the first periodic safety update report for dinutuximab due within 6 months following authorization (Appendix 3: Committee for Medicinal Products for Human Use (CHMP) Assessment Report for Unituxin (EMA/CHMP/278656/2015)).

Conditions or restrictions with regard to the safe and effective use of the medicinal product:

UTC will perform pharmacovigilance activities and interventions detailed in the agreed risk management plan presented in Module 1.8.2 of the Marketing Authorisation for dinutuximab and any agreed subsequent updates of the risk management plan (Appendix 3: Committee for Medicinal Products for Human Use (CHMP) Assessment Report for Unituxin (EMA/CHMP/278656/2015)).

Obligation to complete post-authorisation measures:

UTC is obligated to complete post-authorisation measures presented in Table 5.

Table 5. Post-authorisation measures required by the CHMP

Description
Non-interventional post-authorisation safety study (PASS): In order to evaluate the long-term safety outcomes of dinutuximab in patients with high-risk neuroblastoma (including central and peripheral nervous system, prevalence of organ dysfunction, long-term effects on growth and endocrine development, hearing loss, cardiac toxicity, and survival data) the applicant should conduct and submit the results of a safety registry. The final study report should be submitted by 06/2029.
PASS: In order to better characterise the safety and immunogenicity of dinutuximab and its impact on drug exposure, the applicant should conduct and submit the results of a safety study. The final study report should be submitted by 12/2018.

2.2.7 If the technology has not been launched, supply the anticipated date of availability in the UK.

It is anticipated that given approval, dinutuximab will be commercially available for use within the UK in 1Q16.

2.2.8 State whether the technology has regulatory approval outside the UK. If so, please provide details.

Dinutuximab was approved by the US Food and Drug Administration (FDA) on March 10, 2015, in combination with GM-CSF, IL-2, and 13-cis-retinoic acid (RA), for the treatment of paediatric patients with high-risk neuroblastoma who achieve at least a partial response to prior first-line multiagent, multimodality therapy.

2.2.9 State whether the technology is subject to any other health technology assessment in the UK. If so, give the timescale for completion.

Dinutuximab is subject to assessment by the Scottish Medicines Consortium (SMC); United Therapeutics intends to submit the New Product Assessment Form for dinutuximab by September 7, 2015.

2.3 Administration of costs of the technology

2.3.1 For pharmaceuticals, complete the table "Costs of the technology being appraised" in the company evidence submission template, including details of the treatment regimen and method of administration. Indicate whether the acquisition cost is list price or includes a patient access scheme and the anticipated care setting. Specify the sources of information and data used to complete the table (eg, SmPC or trial data).

Details of dinutuximab in combination with GM-CSF, IL-2, and isotretinoin treatment regimen are presented in Table 6, Table 7, Table 8, and Table 9.

Table 6. Costs of the technology being appraised

	Cost	Source
Pharmaceutical formulation	Dinutuximab is supplied as a 5 mL vial containing 17.5 mg of dinutuximab	Unituxin (dinutuximab) draft SmPC
Acquisition cost (excluding VAT)* **All prices represent UK list price without consideration of patient access schemes*	Dinutuximab: £6,390.00 per 17.5 mg vial	United Therapeutics
Method of administration	Intravenous infusion	Unituxin (dinutuximab) draft SmPC
Doses	The recommended dose of dinutuximab is 17.5 mg/m^2/day administered over 10–20 hours	Unituxin (dinutuximab) draft SmPC
Dosing frequency	The recommended dosing frequency for dinutuximab is once daily on days 4–7 during courses 1, 3, and 5 (each course lasting approximately 24 days) and on days 8–11 during courses 2 and 4 (each course lasting approximately 28 days) A more detailed diagram of the dinutuximab, GM-CSF, IL-2, and isotretinoin dosing regimen is presented in Table 7 and Table 8	Unituxin (dinutuximab) draft SmPC
Average length of a cycle of treatment	Courses 1, 3, and 5 last 24 days each and Courses 2, 4, and 6 last 28 days each, for a total of 156 days per cycle	Unituxin (dinutuximab) draft SmPC
Average cost of a cycle of treatment* **Includes dinutuximab drug cost only*	£127,800	Dinutuximab cost-effectiveness analysis (Section 5.0)
Anticipated average interval between cycles of treatments	Only one cycle of dinutuximab should be administered	
Anticipated number of repeat cycles of treatments	0 (only 1 cycle of dinutuximab should be administered)	
Dose adjustments	Dose modifications may be made in response to several potential adverse events, presented in Table 9	Unituxin (dinutuximab) draft SmPC
Anticipated care setting	Dinutuximab use is restricted to administration in a hospital setting only	Unituxin (dinutuximab) draft SmPC

Key: GM-CSF – granulocyte macrophage colony-stimulating factor – IL-2 interleukin 2; mg – milligram; m – meter; SmPC – summary of product characteristics.

Table 7. Courses 1, 3, and 5 dosing schedule for dinutuximab, GM-CSF, and isotretinoin

Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15-24
GM-CSF[1]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Dinutuximab[2]				X	X	X	X								
Isotrentinoin[3]											X	X	X	X	X

1. GM-CSF 250 µg/m^2/day, administered by either subcutaneous injection (strongly recommended) or intravenous infusion over 2 hours.
2. Dinutuximab 17.5 mg/m^2/day, administered by intravenous infusion over 10–20 hours.
3. Isotretinoin: for body weight greater than 12 kg administer 80 mg/m^2 orally twice daily for a total dose of 160 mg/m^2/day; for body weight up to 12 kg administer 2.67 mg/kg orally twice daily for a total daily dose of 5.33 mg/kg/day (round dose to nearest 10 mg).

Key: µg – microgram; GM-CSF – granulocyte macrophage colony-stimulating factor; kg – kilogram; m – meter; mg – milligram.

Table 8. Courses 2 and 4 dosing schedule for dinutuximab and IL-2; courses 2, 4, and 6 dosing schedule for isotretinoin

Day	1	2	3	4	5	6	7	8	9	10	11	12-14	15-28
IL-2[1]	X	X	X	X				X	X	X	X		
Dinutuximab[2]								X	X	X	X		
Isotrentinoin[3]													X

1. IL-2: 3 MIU/m^2/day administered by continuous intravenous infusion over 96 hours on Days 1–4 and 4.5 MIU/m^2 on Days 8–11.
2. Dinutuximab 17.5 mg/m^2/day, administered by intravenous infusion over 10-20 hours.
3. Isotretinoin: for body weight greater than 12 kg. administer 80 mg/m^2 orally twice daily for a total dose of 160 mg/m^2/day; for body weight up to 12 kg, administer 2.67 mg/kg orally twice daily for a total daily dose of 5.33 mg/kg/day (round dose to nearest 10 mg).

Key: IL-2 – interleukin-2; m – meter; mg – milligrams; MIU – million international unit.

Table 9. Dose modification guidance for the management of treatment-emergent adverse reactions during administration of dinutuximab in combination with GM-CSF, IL-2, and isotretinoin

Event	Dose modification
Grade 1 or 2 allergic conditions	*On symptom onset*: Reduce rate of infusion to 0.875 mg/m^2/hour and administer supportive measures (see section 4.4 of SmPC) *On resolution:* Resume infusion at the original rate. If not tolerated, reduce rate to 0.875 mg/m^2/hour
Grade 3 or 4 allergic conditions	*On symptom onset*: Immediately discontinue dinutuximab and intravenous GM-CSF or IL-2 and administer supportive measures (see section 4.4 of SmPC) *On resolution*: Resume dinutuximab at a rate of 0.875 mg/m^2/hour. Do not resume GM-CSF or IL-2 until the following day. For GM-CSF courses, administer GM-CSF at 50% of the dose starting the next day, and if tolerated, GM-CSF may be given at full dose after completing dinutuximab dosing for that course. For IL-2 courses, administer IL-2 at 50% of the dose starting the next day and continue for the remainder of the course. If symptoms recur with the addition of GM-CSF or IL-2, discontinue GM-CSF or IL-2 and dinutuximab. If symptoms resolve the following day, resume dinutuximab at tolerated rate without GM-CSF or IL-2 *On symptom recurrence*: Discontinue dinutuximab and GM-CSF or IL-2 for that day. If symptoms resolve that day, resume the next day with premedication in the intensive care setting *Subsequent courses*: Maintain tolerated dinutuximab infusion rate for all

Event	Dose modification
	subsequent courses with GM-CSF or IL-2
Grade 3 or 4 anaphylaxis	Permanently discontinue dinutuximab and GM-CSF or IL-2
Grade 3 capillary leak syndrome	*On symptom onset*: Discontinue dinutuximab and intravenous GM-CSF or IL-2 and administer supportive measures (see section 4.4 of SmPC) *On resolution*: Resume dinutuximab infusion at 0.875 mg/m^2/hour. Resume GM-CSF or IL-2 the following day at 50% of the dose until the last dose of dinutuximab for that course *Subsequent courses*: If patient tolerated 50% dose of GM-CSF or IL-2, start at this dose and dinutuximab rate of 0.875 mg/m^2/hour. If tolerated, increase GM-CSF or IL-2 to full dose the next day. If GM-CSF is not tolerated at 50% of the dose, administer dinutuximab alone for the remainder of the GM-CSF courses. If IL-2 is not tolerated at 50% of the dose, substitute with GM-CSF for the remainder of the IL-2 courses
Grade 4 capillary leak syndrome	*On symptom onset*: Discontinue dinutuximab and GM-CSF or IL-2 for that course and administer supportive measures (see section 4.4 of SmPC) *Subsequent courses*: If capillary leak syndrome occurred during IL-2 course, substitute GM-CSF for the remainder of IL-2 courses. If capillary leak syndrome occurred during GM-CSF course, administer dinutuximab alone for subsequent GM-CSF courses
Grade 4 hyponatremia	Permanently discontinue dinutuximab and GM-CSF or IL-2
Hypotension (symptomatic and/or systolic blood pressure (BP) less than 70 mmHg or a decrease that is more than 15% below baseline)	*On symptom onset*: Discontinue dinutuximab and intravenous GM-CSF or IL-2 and administer supportive measures (see section 4.4 of SmPC) *On resolution*: Resume dinutuximab infusion at 0.875 mg/m^2/hour. If BP remains stable for at least 2 hours, resume GM-CSF or IL-2. If BP remains stable for at least 2 hours after resuming GM-CSF or IL-2, increase the dinutuximab infusion to 1.75 mg/m^2/hour *On symptom recurrence*: Discontinue dinutuximab and GM-CSF or IL-2. Resume dinutuximab at 0.875 mg/m^2/hour once BP is stable *On resolution*: Resume GM-CSF or IL-2 the following day at 50% of the dose if BP remains stable. Start GM-CSF or IL-2 at 50% of the dose when administered with dinutuximab. Then increase to full dose if tolerated for the remainder of the course. If GM-CSF is not tolerated at 50% of the dose, administer dinutuximab alone for the remainder of the course. If IL-2 is not tolerated at 50% of the dose, administer dinutuximab alone for the remainder of the course. *Subsequent courses*: Start GM-CSF or IL-2 at 50% of the dose, increase to full dose if tolerated the next day. If GM-CSF is not tolerated at 50% of the dose, administer dinutuximab alone for the remainder of the GM-CSF courses. If IL-2 is not tolerated at 50% of the dose, substitute with GM-CSF for remainder of the IL-2 courses
Dilated pupil with sluggish light reflex	*On symptom onset*: Discontinue dinutuximab and GM-CSF or IL-2 *On resolution*: Administer dinutuximab at 0.875 mg/m^2/hour and resume GM-CSF or IL-2 *On symptom recurrence*: Discontinue all dinutuximab immunotherapy for remaining courses *Subsequent courses*: If abnormalities remain stable or improve before the next course, administer dinutuximab at 0.875 mg/m^2/hour and the full dose of GM-CSF or IL-2. If tolerated without worsening symptoms, administer dinutuximab at 1.75 mg/m^2/hour for subsequent courses. If symptoms recur, discontinue all dinutuximab immunotherapy for remaining courses
Grade 3 or 4 serum sickness	Permanently discontinue dinutuximab and GM-CSF or IL-2
Grade 3 or 4 systemic infection or sepsis	*On symptom onset*: Discontinue dinutuximab and GM-CSF or IL-2 for remainder of course *On resolution*: Proceed with subsequent planned dinutuximab and GM-CSF or IL-2 courses
Grade 4 pain	Discontinue dinutuximab and GM-CSF or IL-2

Event	Dose modification
Grade 2 peripheral neuropathy	Discontinue dinutuximab and GM-CSF or IL-2
Grade 3 peripheral neuropathy (sensory changes for more than 2 weeks, objective motor weakness) or Grade 4 peripheral neuropathy	Permanently discontinue dinutuximab and GM-CSF or IL-2
Atypical haemolytic uraemic syndrome	Permanently discontinue dinutuximab and GM-CSF or IL-2

Key: BP – blood pressure; GM-CSF – granulocyte macrophage colony-stimulating factor; IL-2 – interleukin-2; kg – kilogram; m – meter; mg – milligram; SmPC – summary of product characteristics.

2.3.2 Provide details of any patient access scheme that has been referred to NICE for inclusion in the technology appraisal by ministers and formally agreed by the company with the Department of Health before the date of evidence submission to NICE for the technology.

At present, no patient access scheme has been proposed for dinutuximab.

2.4 Changes in service provision and management

2.4.1 State whether additional tests or investigations are needed (for example, diagnostic tests to identify the population for whom the technology is indicated in the marketing authorisation) or whether there are particular administration requirements for the technology.

Eligibility for dinutuximab therapy is primarily based upon clinical history and health status. No specific companion diagnostic tests are available to identify the target patient population. However, several clinical criteria must be met before administering each treatment course of dinutuximab. These evaluations include assessment of central nervous system toxicity, hepatic function, platelet function, respiratory function, renal function, cardiovascular function, and assessment for the presence of infection or leukopaenia. Dinutuximab is restricted to hospital use only and must be administered under the supervision of a physician experienced in the use of oncological therapies. Dinutuximab must be administered by a healthcare professional prepared to manage severe allergic reactions including anaphylaxis in an environment where full resuscitation services are immediately available.

2.4.2 Identify the main resource use to the NHS associated with the technology being appraised. Describe the location or setting of care (that is, primary and/or secondary care, commissioned by NHS England specialised services and/or clinical

commissioning groups), staff costs, administration costs, monitoring, and tests. Provide details of data sources used to inform resource estimates and values.

Dinutuximab administration is best commissioned by NHS England specialized services, as administration of dinutuximab is to be performed in a secondary care hospital setting only and must be administered under the supervision of a physician experienced in the use of oncological therapies. As such, the main resource use associated with the technology are drug costs, cost of administration, cost of monitoring, and cost of treating adverse reactions in a hospital setting. These costs are described in detail in section 5.0 (cost-effectiveness modelling report).

2.4.3 Specify if the technology requires additional infrastructure in the NHS to be put in place.

Patients with high-risk neuroblastoma are typically treated with a multimodal therapeutic approach, including intensive induction chemotherapy, autologous stem cell harvesting to enable bone marrow rescue following myeloablative consolidation chemotherapy, and subsequent surgical resection and radiation at the primary site to optimize local control (Ganeshan 2011). Currently, the standard approach for residual disease in patients with high-risk neuroblastoma includes retinoids and immunotherapy (NCI 2012). It is anticipated that the existing infrastructure for intravenous oncologic treatments in the UK will be leveraged for drug infusion and monitoring of patients treated with dinutuximab, with no additional infrastructure needed.

2.4.4 State if and to what extent the technology will affect patient monitoring compared with established clinical practice in England.

The addition of dinutuximab, GM-CSF, and IL-2 to standard isotretinoin therapy was associated with a greater risk of adverse reactions such as pain, hypersensitivity, and capillary leak syndrome compared to isotretinoin alone. While on dinutuximab treatment, appropriate patient monitoring includes hepatic function, visual changes, and monitoring for potential adverse reactions.

2.4.5 State whether there are any concomitant therapies specified in the Marketing Authorisation or used in the key clinical trials (for example, for managing adverse reactions) administered with the technology.

Dinutuximab is approved for use in combination with GM-CSF, IL-2, and isotretinoin.

Severe allergic reactions are more likely when dinutuximab is co-administered with IL-2. Antihistamine premedication (eg, hydroxyzine or diphenhydramine) must be administered by intravenous injection approximately 20 minutes before starting each dinutuximab infusion. It is recommended that antihistamine medication be repeated every 4 to 6 hours as required during infusion of this treatment.

Epinephrine (adrenaline) and hydrocortisone for intravenous administration must be immediately available at the bedside during administration of dinutuximab to manage life-threatening allergic reactions.

Capillary leak syndrome is more likely when dinutuximab is co-administered with IL-2. Administer oral metolazone or intravenous furosemide every 6 to 12 hours as required. Administer supplemental oxygen, respiratory support, and albumin replacement therapy as necessary according to clinical response.

Administer intravenous sodium chloride 9 mg/mL (0.9%) solution for injection (10 mL/kg) over 1 hour just prior to the dinutuximab infusion. If hypotension occurs, repeat sodium chloride 9 mg/mL (0.9%) solution for injection, or administer intravenous albumin or packed red blood cells as clinically indicated. It is recommended that vasopressor therapy be also administered if necessary to restore an adequate perfusion pressure.

Severe pain (Grade 3 or 4) occurs most frequently during the first 4-day course of dinutuximab, often subsiding over time with subsequent courses. Paracetamol should be administered orally 20 minutes prior to starting each dinutuximab infusion and repeated every 4 to 6 hours as needed. Regular dosing every 4 to 6 hours is recommended when IL-2 is coadministered with this medicinal product. If required for persistent pain, ibuprofen should be administered orally every 6 hours between doses of paracetamol. Ibuprofen must not be administered if there is evidence of thrombocytopenia, bleeding, or renal dysfunction.

An opioid such as morphine sulphate is recommended to be administered by intravenous infusion prior to each dinutuximab infusion and continued as an intravenous infusion during administration of dinutuximab until 2 hours after completion of the treatment. It is recommended that additional intravenous bolus doses of an opioid be administered as needed for treatment of pain up to once every 2 hours during the dinutuximab infusion. If morphine is not tolerated, then fentanyl or hydromorphone may be utilized.

Lidocaine may be administered as an intravenous infusion (2 mg/kg in 50 mL of 0.9% sodium chloride) over 30 minutes prior to the start of each dinutuximab infusion and continued via intravenous infusion at 1 mg/kg/h up to 2 hours after completion of the treatment. Lidocaine infusion must be discontinued if the patient develops dizziness, perioral numbness, or tinnitus.

Gabapentin may be administered at the time of starting morphine premedication, at an oral dose of 10 mg/kg/day. The dose may be subsequently increased (up to a maximum of 60 mg/kg/day or 3600 mg/day) as needed for pain management.

2.5 Innovation

2.5.1 If you consider the technology to be innovative with potential to make a substantial impact on health-related benefits that are unlikely to be included in the QALY calculation, state whether and how the technology is a "step-change" in the management of the condition and provide a rationale to support innovation, identifying and presenting the data you have used.

Neuroblastoma has a substantial negative impact on quality of life, including physical performance and activities of daily living (Ness 2005), academic performance (Gurney 2007), and psychosocial functioning (Barrera 2005). As neuroblastoma affects children who are very young at the time of diagnosis, the disease affects the entire family; typical family concerns include financial stresses, transportation to the cancer centre, the potential loss of a job, and the possible need for home schooling (ACS 2013). For these reasons, health-related benefits from improved treatments for high-risk neuroblastoma are unlikely to be fully captured in QALYs alone.

Maintenance therapy for high-risk neuroblastoma is designed to eliminate the minimal residual disease that remains after consolidation and induction therapy

(Ganeshan 2011). Historically, isotretinoin has been considered the standard of care for maintenance therapy after demonstrating improved survival following high-dose chemotherapy and ASCT (Matthay 1999). Despite use of isotretinoin, approximately 50% to 60% of patients with high-risk neuroblastoma are likely to have a relapse (Matthay 1999, Matthay 2009).

As maintenance therapy in high-risk neuroblastoma, dinutuximab meets the 5 criteria for a step-change innovation as laid out in the Kennedy Report: (Kennedy 2009):

- Dinutuximab significantly and substantially improves the way that a current need is met: *Dinutuximab improves survival in a disease associated with high mortality in a paediatric population.*

- Dinutuximab meets a need that the NHS has identified as being important: *The recent 2014–2015 NHS Outcomes Framework reflects the government's commitment to improving survival from cancer (NHS 2013). By providing a significant improvement in EFS and OS, dinutuximab has the potential to prevent patients from dying prematurely.*

- Dinutuximab has a robust evidence base providing research on the populations in which the product is effective: *The dinutuximab pivotal phase 3 clinical trial was conducted by the NCI over more than 8 years and includes 226 patients with high-risk neuroblastoma (high-risk neuroblastoma is a very rare orphan condition).*

- Dinutuximab has been shown to have an appropriate level of effectiveness: *Dinutuximab's pivotal phase 3 trial demonstrated significantly improved survival in patients with high-risk neuroblastoma assigned to immunotherapy (isotretinoin and dinutuximab in combination with alternating GM-CSF and IL-2) vs standard therapy (isotretinoin) in terms of EFS (66% ± 5% vs 46% ± 5% at 2 years, respectively; P=0.01) and OS (86% ± 4% vs 75% ± 5% at 2 years, respectively; P=0.02) (Yu 2010).*

- Dinutuximab has marketing authorisation for the particular indication: *Dinutuximab is indicated for the treatment of high-risk neuroblastoma in patients aged 12 months to 17 years who have previously received induction*

chemotherapy and achieved at least a partial response, followed by myeloablative therapy and ASCT. It is administered in combination with GM-CSF, IL-2, and isotretinoin.

These statistically significant improvements in survival represent a change in the treatment paradigm for children with high-risk neuroblastoma and may result in improved HRQOL for patients and their families. Dinutuximab immunotherapy will be the first European Medicines Agency (EMA)-approved maintenance therapy for patients with high-risk neuroblastoma and may become the new standard of care for these patients.

3.0 Health condition and position of the technology in the treatment pathway

3.1 Disease overview

3.1.1 Provide a brief overview of the disease or condition for which the technology is being used. Include details of the underlying cycle of the disease.

Neuroblastoma is primarily a tumour of early childhood, with nearly 90% of cases diagnosed by the age of 5 (ACS 2013). It is the most common cancer in infants (<1 year of age) (ACS 2013). Approximately 100 new cases of neuroblastoma are diagnosed each year in the UK (Neuroblastoma Alliance UK 2011), accounting for approximately 6% of childhood cancers (Powell 1998). Data from the Automated Childhood Cancer Information System (ACCIS) reported an age-standardized incidence rate for both sexes of 9.1 cases per million in the British Isles during 1988 to 1997 (Spix 2006). Incidence by age groups (both sexes) in this region was as follows: 34.4 per million (<1 year), 17.1 per million (1–4 years), 3.1 per million (5 to 9 years), and 0.6 per million (10 to 14 years) (Spix 2006).

There can be considerable variability in the signs and symptoms of neuroblastoma, depending on the size and location of the tumour, the extent of spread to other parts of the body, and whether or not the tumour cells secrete hormones (Table 10) (ACS 2013). While most primary neuroblastoma tumours occur in the abdomen (65%), most often in the adrenal medulla, other sites may include the paraspinal sympathetic ganglia of the chest (20%), pelvis (5%), and neck (5%) (Janoueix-Lerosey 2010). The most common presentation is an abdominal mass (NCI 2012). The child may complain of a feeling of fullness and may not want to eat, which can lead to weight loss (ACS 2013). With more advanced disease, symptoms may be related to the mass effect of the tumour or bone pain from metastases (NCI 2012).

Table 10. Clinical Presentation of Neuroblastoma

Potential Signs and Symptoms	
• Abdominal mass	• Weight loss
• Abdominal distention	• Feeling of fullness
• Swelling	• Diarrhea
• Problems with urination	• Constipation
• Headache	• Dizziness

Potential Signs and Symptoms	
• Coughing	• Difficulty breathing or swallowing
• Drooping eyelid	• Periorbital ecchymosis
• Bone pain	• Paralysis
• Excess bruising or bleeding	• Numbness or weakness
• High blood pressure	• Fatigue
• Sweating	• Reddening (flushing) of the skin

The aetiology of neuroblastoma is not completely understood. Neuroblastoma is an embryonal tumour of the autonomic nervous system derived from neural crest tissue (Graham 2012; ACS 2013). Both nerve cells and cells of the medulla of the adrenal gland develop from neuroblasts in the foetus. If these cells fail to mature normally into nerve cells or adrenal medulla cells, they may continue to grow and divide and develop into neuroblastomas (ACS 2013). Researchers have frequently observed chromosome changes associated with neuroblastoma cells, such as too many or too few chromosomes or missing a part of a chromosome (Janoueix-Lerosey 2010). While neuroblastomas may occur in other contexts, namely familial and syndromic, the disease most often occurs sporadically (Janoueix-Lerosey 2010). Several genes have been implicated in neuroblastoma, including ALK, PHOX2B, and MYCN (Janoueix-Lerosey 2010).

Based on various prognostic factors and International Neuroblastoma Staging System (INSS) stage of disease, children diagnosed with neuroblastoma are classified into 3 different risk groups: low, intermediate, and high (NCI 2012). High-risk neuroblastoma is characterized by age (>1 year), disseminated disease, MYCN oncogene amplification, and unfavourable histopathologic findings; 40% to 50% of children with neuroblastoma are classified as high risk (Ganeshan 2011; Maris 2007). An internationally accepted staging system for neuroblastoma, known as the INSS, is listed in Table 11 (Brodeur 1993).

Table 11. International Neuroblastoma Staging System

Stage	Description
1	Localised tumour with complete gross excision, with or without microscopic residual disease; representative ipsilateral lymph nodes negative for tumour microscopically (nodes attached to and removed with the primary tumour may be positive)
2A	Localised tumour with incomplete gross excision; representative ipsilateral nonadherent lymph nodes negative for tumour microscopically
2B	Localised tumour with or without complete gross excision, with ipsilateral nonadherent lymph nodes positive for tumour. Enlarged contralateral lymph nodes must be negative microscopically

Stage	Description
3	Unresectable unilateral tumour infiltrating across the midline, with or without regional lymph node involvement; or localised unilateral tumour with contralateral regional lymph node involvement; or midline tumour with bilateral extension by infiltration (unresectable) or by lymph node involvement
4	Any primary tumour with dissemination to distant lymph nodes, bone, bone marrow, liver, skin and/or other organs (except as defined for stage 4S)
4S	Localised primary tumour (as defined for stage 1, 2A, or 2B), with dissemination limited to skin, liver, and/or bone marrow (limited to infants <1 year of age). Marrow involvement should be minimal (ie, <10% of total nucleated cells identified as malignant on bone marrow biopsy or on marrow aspirate); more extensive marrow involvement would be considered to be stage 4

The Children's Oncology Group (COG), an NCI-supported clinical trials group, established a neuroblastoma risk grouping profile divided into low-, intermediate-, and high-risk groups based on age, INSS stage, and tumour biology (Table 12) (NCI 2012). The relevant biological attributes of the tumour include the following: MYCN gene expression, International Neuroblastoma Pathologic Classification (INPC) histopathology classification, and tumour DNA index. The risk group assignment was used to assign treatment in prior COG clinical studies (COG-9641 and COG-A3961) (NCI 2012).

Table 12. Children's Oncology Group neuroblastoma low-, intermediate-, and high-risk group assignment schema

INSS Stage	Age	*MYCN* Status	INPC Classification	DNA Ploidy[a]	Risk Group
1	0-–21 yr	Any	Any	Any	Low
2A/2B	<365 d	Any	Any	Any	Low
	≥365 d–21 yr	Nonamplified	Any	-	Low
	≥365 d–21 yr	Amplified	Favourable	-	Low
	≥365 d–21 yr	Amplified	Unfavourable	-	High
3	<365 d	Nonamplified	Any	Any	Intermediate
	<365 d	Amplified	Any	Any	High
	≥365 d–21 yr	Nonamplified	Favourable	-	Intermediate
	≥365 d–21 yr	Nonamplified	Unfavourable	-	High
	≥365 d–21 yr	Amplified	Any	-	High
4	<548 d	Nonamplified	Any	Any	Intermediate
	<365 d	Amplified	Any	Any	High
	≥548 d–21 yr	Any	Any	-	High

INSS Stage	Age	*MYCN* Status	INPC Classification	DNA Ploidy[a]	Risk Group
4S	<365 d	Nonamplified	Favourable	>1	Low
	<365 d	Nonamplified	Any	=1	Intermediate
	<365 d	Nonamplified	Unfavourable	Any	Intermediate
	<365 d	Amplified	Any	Any	High

[a] DNA Ploidy: DI >1 is favourable; DI=1 is unfavourable.

Key: d – days; DI – DNA index; DNA – deoxyribonucleic acid; INPC – International Neuroblastoma Pathologic Classification; INSS – International Neuroblastoma Staging System; yr – years.

The prognosis for neuroblastoma is related to age at diagnosis, clinical stage of disease, site of the primary tumour, tumour histology, and, in patients older than 1 year of age, regional lymph node involvement (NCI 2012). Children less than 1 year of age at diagnosis have a more favourable prognosis compared to children older than 1 year of age (Goodman 1999). Approximately 70% of patients with neuroblastoma present with metastatic disease at diagnosis (NCI 2012). The 5-year survival rate for children with high-risk neuroblastoma is about 30% to 50% (ACS 2013).

3.1.2 Describe the effects of the disease or condition on patients, carers and society.

Neuroblastoma has a significant impact on morbidity, mortality, and quality of life of patients and their caregivers. The ACCIS data for the British Isles reported a 5-year survival probability (95% confidence interval [CI]) of 49% (45, 52) for all ages (ie, 0 to 14 years) during 1988 to 1997 (Spix 2006). The 5-year survival (95% CI) dropped to 30% (26, 35) for ages 2 to 14 years (Spix 2006). Five-year survival probability (95% CI) by age groups in this region was as follows: 80% (74, 85) for <1 year, 37% (33, 42) for 1 to 4 years, 34% (24, 44) for 5 to 9 years, and 26% (10, 47) for 10 to 14 years (Spix 2006).

Both the effect of the disease itself and its treatment may result in long-term complications associated with neuroblastoma. In rare cases, the child's immune system may attack the healthy nerve tissue. This can lead to learning disabilities, delays in muscle development, language problems, and behavioural problems (ACS 2013). While neuroblastoma survivors are at risk for potential treatment-related complications (resulting particularly from chemotherapy and radiation),

immunotherapy was not identified as a risk factor for any late effect, except for hypothyroidism after receiving I-3F8 (Laverdière 2005). Specific treatment-related complications are dependent on factors such as the treatments received, doses of treatment, and age when treatment was received. Some of the potential long-term effects of exposure to intensive, multimodality therapy include the following (Laverdière 2005; ACS 2013):

- Hearing loss
- Heart or lung problems
- Slowed or decreased growth and development
- Bone damage or thinning of bones
- Changes in sexual development and ability to have children
- Changes in intellectual function with learning problems
- Development of other cancers (eg, leukaemia)

Neuroblastoma has been shown to have a negative impact on physical performance and activities of daily living (Ness 2005), academic performance (Gurney 2007), and psychosocial functioning (Barrera 2005) among patients with active disease and survivors. A survey was conducted to assess quality of life among long-term (≥10 years post-diagnosis) neuroblastoma survivors (N=137) using the Pediatric Quality of Life Inventory 4.0 (PedsQL) and an outcomes questionnaire for parents (Gurney 2007). Hearing loss, which is a potential treatment-related effect of high doses of platinum chemotherapy, was generally associated with increased parent-reported academic problems: neuroblastoma survivors with hearing loss had at least twice the risk of a problem with reading skills, math skills, poor attention, general learning disability, and/or special education needs than neuroblastoma survivors without hearing loss (Gurney 2007). Consistent with this finding, hearing loss was associated with a 10-point lower mean score in the PedsQL school-functioning scale (71.6 vs 81.6; *P*=0.02 for those with hearing loss vs those without hearing loss, respectively), and lower summary scores for psychosocial functioning (76.4 vs 82.8, respectively; *P*=0.03) and total quality of life (79.5 vs 84.6, respectively; *P*=0.05) (Gurney 2007).

Similarly, a retrospective study to assess educational and social late effects for young survivors of childhood cancer, including neuroblastoma, demonstrated that these individuals were more likely to experience educational and social difficulties

compared with population controls of the same age and gender (Barrera 2005). Compared to parents of controls, parents of neuroblastoma survivors were more likely to report that their child had no close friends (adjusted odds ratio [OR]: 4.1; 99% CI: 1.2, 13.8; *P*<0.01) and had academic or other school problems (adjusted OR: 2.5; 99% CI: 1.3, 4.8; *P*<0.001) (Barrera 2005).

Another study was conducted to assess health-related quality of life among long-term survivors of either childhood neuroblastoma or Wilms tumour, as measured by the 36-item Short Form Health Survey (SF-36) (Nathan 2007). Among adult survivors of neuroblastoma (N=432), there was no significant difference in scores compared to population norms on the Physical Component Summary scale; however, the neuroblastoma group scored significantly below the population mean score (50) on the Mental Component Summary scale (mean [standard error (SE)]: 42.41 [2.23]; *P*<0.0001), indicating decreased emotional health (Nathan 2007). Independent risk factors for lower scores on this scale included the following: female gender, Native American race, and household income below $20,000 US dollars (Nathan 2007).

An epidemiologic survey, the Childhood Cancer Survivor Study, evaluated long-term survivors, defined as those surviving at least 5 years after initial diagnosis of childhood cancer (N=11,481), including neuroblastoma, across 26 institutions in the US (Ness 2005). Compared with siblings with no cancer, neuroblastoma survivors were at increased risk for functional limitations in physical performance and activities of daily living (Table 13) (Ness 2005).

Table 13. Performance limitations and participation restrictions among siblings and survivors of neuroblastoma

	Control (siblings with no cancer) (N=3,839)		Neuroblastoma survivors (N=802)	
Limitation	**Participants, n (%)**	**RR[a] (95% CI)**	**Participants, n (%)**	**RR[a] (95% CI)**
Performance limitation	455 (11.8)	Reference	136 (16.9)	1.7 (1.4, 2.1)
Restricted personal care skills	21 (0.5)	Reference	25 (3.1)	3.8 (2.2, 6.8)
Restricted routine activities	53 (1.4)	Reference	45 (5.6)	3.6 (2.5, 5.4)
Health prevents school or work attendance	57 (1.5)	Reference	42 (5.2)	5.1 (3.4, 7.6)

[a] RRs were standardized for age, sex, and intrafamily correlation and refer to the RR performance limitations in cancer survivors relative to the risk in the sibling group.

Key: CI – confidence interval; RR – risk ratio.

Although a rare condition, neuroblastoma can pose a substantial economic burden on patients/caregivers, healthcare providers, and payers; however, very few economic studies have been conducted in neuroblastoma and no studies have been conducted to assess the economic burden of neuroblastoma in the UK.

Access to new drugs for the treatment of neuroblastoma is an issue on a global scale. Many experimental agents are only available within clinical trials, prompting parents to travel abroad for their children to receive these new drugs (Gains 2012). This can have a major financial impact on a family. As an example, after the demonstration that immunotherapy improved outcomes in high-risk neuroblastoma, UK families of children not eligible for immunotherapy within current European trials pursued assistance from the National Health Service (NHS) to fund the treatment abroad (Gains 2012). This is an ongoing issue that has generated Parliamentary debates in the UK (Gains 2012).

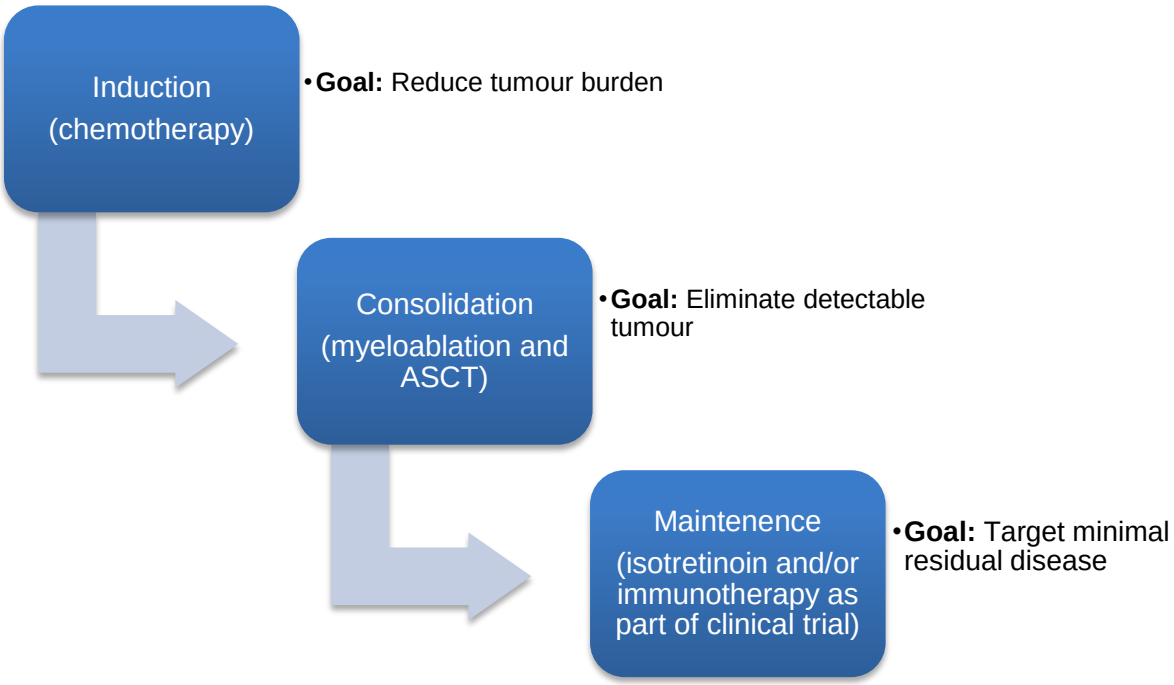
3.1.3 Present the clinical pathway of care that shows the context of the proposed use of the technology. This information may be presented in a diagram. Explain how the new technology may change the existing pathway. If a relevant NICE clinical guideline has been published, the response to this point should be consistent with the guideline and any differences should be explained.

This section focuses specifically on the treatment of patients with high-risk neuroblastoma in line with the proposed use of dinutuximab. Patients with high-risk neuroblastoma are typically treated with a multimodal therapeutic approach, including intensive induction chemotherapy, autologous stem cell harvesting to enable bone marrow rescue following myeloablative consolidation chemotherapy, and subsequent surgical resection and radiation at the primary site to optimize local control (Ganeshan 2011). Additionally, maintenance therapy intended to eliminate minimal residual disease and prevent relapse is provided using retinoids and immunotherapy (Ganeshan 2011).

For tumours with unfavourable prognostic features, the trend has shifted over the past 2 decades toward intensifying chemoradiotherapy (Maris 2010). Also, research groups are working to develop therapies that will exploit the key oncogenic features found in the tumour cells and/or the tumour microenvironment (Maris 2010).

Treatment for high-risk neuroblastoma can be categorized into 3 phases (Figure 1) (Maris 2010).

Figure 1. Phases of treatment for high-risk neuroblastoma



The primary aims of induction therapy are to improve surgical resectability by reducing the tumour size and/or to induce apparent remission before myeloablative consolidation chemotherapy followed by stem cell transplantation (Ganeshan 2011). The most frequently used induction chemotherapeutic regimen in Europe consists of dose-intensive cisplatin, vincristine, carboplatin, etoposide, and cyclophosphamide (COJEC). A randomised trial demonstrated that an increase in dose intensity of induction chemotherapy by rapid drug scheduling of COJEC improved outcomes compared to the standard of care at the time, consisting of courses of vincristine, cisplatin, etoposide, and cyclophosphamide alternating with vincristine, carboplatin, etoposide, and cyclophosphamide administered at 21-day intervals (Pearson 2008). Three-year (31.0% vs 24.2%), 5-year (30.2% vs 18.2%), and 10-year (27.1% vs 18.2%) EFS were better in patients given rapid treatment vs those given standard treatment, respectively, although this was statistically significant only in the 5-year data (*P*=0.022) (Pearson 2008). Furthermore, a review of available data reported improvements in response rates and OS rates associated with increasing the intensity of induction chemotherapy (Cheung 1991). Studies have demonstrated that evaluation of early response by meta-iodobenzylguanidine (MIBG) scan was highly

correlated with outcomes, indicating its potential prognostic value for identifying poor responders at risk for disease relapse (Yanik 2013; Matthay 2003; Katzenstein 2004; Schmidt 2008).

The primary aim of consolidation therapy is to produce myeloablation prior to stem cell transplantation (Ganeshan 2011). Improvements in EFS have been demonstrated in randomised clinical trials with myeloablative chemotherapy administered after induction therapy and followed rapidly by rescue with ASCT (Berthold 2005; Matthay 1999; Pritchard 2005; Landestein 2011). Early studies included either multi-agent regimens (including carboplatin, etoposide, and melphalan [CEM]) or single-agent melphalan, with or without total-body irradiation (Berthold 2005; Matthay 1999; Pritchard 2005). More recently, the combination of busulphan and melphalan (BuMel) demonstrated superior outcomes compared with CEM, with significant differences at 3 years in favour of BuMel observed for EFS (49% vs 33%; *P*=0.004) and OS (60% vs 48%; *P*=0.004) (Landestein 2011). The superiority of BuMel was confirmed in follow-up analyses, demonstrating significantly greater 3-year EFS and OS over CEM (50% vs 38% and 61% vs 52%, respectively; *P*<0.001 for both) (Landestein 2014). Additionally, there is evidence indicating that rapid-sequence tandem high-dose myeloablative treatments with ASCT may improve outcomes (George 2006; Seif 2013). The optimal chemotherapeutic regimen for myeloablation, however, remains to be determined and is still under investigation (Maris 2010).

Maintenance therapy is designed to target minimal residual disease and prevent relapse (Ganeshan 2011). Matthay et al established the benefit of maintenance therapy based on the observation that nearly 50% of patients who appeared to be in complete remission after treatment with conventional chemotherapeutics relapsed with progressive disease (Matthay 1993). Research has demonstrated differentiating and tumour growth-inhibiting effects of retinoic acid (Sidell 1982). As a result, 13-cis-retinoic acid (isotretinoin) has become part of the standard maintenance therapy regimen in patients with high-risk neuroblastoma (Maris 2010). A randomised clinical trial first demonstrated the benefit of using 13-cis-retinoic acid following recovery from high-dose chemotherapy, radiotherapy, and stem cell transplantation (Matthay 1999). Three-year mean ± SE EFS was significantly better for those who received

subsequent therapy with 13-cis-retinoic acid vs those assigned no further therapy (46% ± 6% vs 29% ± 5%, respectively; *P*=0.027) (Matthay 1999).

Targeted immunotherapy is also used in the setting of minimal residual disease; this approach involves programming immune cells to act against cancer cells by labelling antigens on cancer cells with monoclonal antibodies (Ganeshan 2011). Gangliosides are glycolipids found on outer cell membranes. The ganglioside GD2 has been discovered to be both ubiquitous and abundant on neuroblastoma cells, which makes it an ideal target for immunotherapy (Wu 1986). The effects of anti-GD2 antibodies can be intensified by cytokines, such as GM-CSF or IL-2 (Maris 2010). A randomised clinical trial demonstrated significantly improved mean ± SE EFS (66% ± 5% vs 46% ± 5% at 2 years, respectively; *P*=0.01) and OS (86% ± 4% vs 75% ± 5% at 2 years, respectively; *P*=0.02) in patients with high-risk neuroblastoma assigned to immunotherapy (isotretinoin and chimeric human-murine anti-GD2 monoclonal antibody [dinutuximab] in combination with alternating GM-CSF and IL-2) vs standard therapy (isotretinoin) (Yu 2010).

3.1.4 Provide information about the life expectancy of people with the disease or condition in England and the source of the data. Please provide information on the number of people with the particular therapeutic indication for which the technology is being appraised. If the Marketing Authorisation also includes other therapeutic indications for the technology, provide information about the numbers of people with these diseases or conditions in England and provide the source of the data. This is to assess whether the technology may be suitable for consideration as a "life-extending treatment at the end of life" as described in section 6.2.10 of the NICE guide to the methods of technology appraisal.

Data from the ACCIS, consisting of 80 population-based registries across 35 European countries including the UK, estimates the age-standardized incidence of neuroblastoma at 9.1 per million children over 10 years (0.91 per million per year) (Spix 2006). Approximately 40% to 50% of these patients are expected to have high-risk neuroblastoma (Ganeshan 2011; Maris 2007). Of these patients with high-risk neuroblastoma, 52% are expected to have prior response to induction therapy, stem-cell therapy, and transplantation and be eligible for maintenance therapy (Matthay 2009). Population-based survival curves created using the most recent data available for patients aged 1 to 14 with neuroblastoma in Great Britain (December

2002 to December 2005) show a median survival of approximately 4 years (Stiller 2012).

Given a population size of 57,408,700 in England and Wales, an incidence of 0.91 per million per year, and median survival time of 4 years, the prevalent number of people in England and Wales for whom dinutuximab is being appraised (aged 12 months to 17 years who have previously received induction chemotherapy and achieved at least a partial response, followed by myeloablative therapy and ASCT) is a total of only 54 patients (Table 14).

Table 14. Estimation of the prevalent number of people indicated for dinutuximab treatment in England and Wales

Epidemiological Parameter	Value	Source / Explanation	Resulting Number of Patients
England and Wales population size	57,408,700	ONS (mid 2014 estimate)	**57,408,700**
Incidence / million / year	9.1 / 10 = 0.91	Spix 2006 Standardized incidence for ages 0-14 (9.1) (Table 3, last column for British Isles) divided by 10 to obtain an annual rate	-
Median survival time for neuroblastoma patients (years)	4	Stiller 2012 Figure 2, survival curve Dec02-05	-
Estimated prevalence (per year, per million)	9.1 / 10 x 4 = ~4	Since prevalence data are not published, it was estimated based on incidence and median survival time	9.1 / 10 x 4 x 57,408,700 / 1,000,000 = **209**
% high risk	50%	Maris 2007	233 x 50% = **104**
% with response to induction therapy, stem-cell transplantation, and radiotherapy	52%	Matthay 1999	117 x 52% = **54**

Key: ONS – Office for National Statistics; UK – United Kingdom

As such, dinutuximab meets criteria set forth by NICE and may be considered as a life-extending treatment at the end of life. Dinutuximab in combination with a GM-CSF, IL-2, and isotretinoin compared to isotretinoin alone has been shown to statistically significantly improve EFS at 2 years (63% vs 42%, respectively; *P*=0.01) and OS at 2 years (86% vs 75%, respectively; *P*=0.02) (Yu 2010). This survival benefit was maintained in an updated analysis of 225 patients randomised in the original phase 3 trial with a median follow up of 5.5 years. In this analysis, 1 patient was ineligible and 4 patients crossed over to immunotherapy after completing

isotretinoin and were censored at the start of immunotherapy (Yu 2014). At 4 years, between-group differences favouring dinutuximab were maintained for OS (74% vs 59%; *P*=0.02). Numerical differences for EFS at 4 years favoured dinutuximab (59% vs 48%) but did not reach statistical significance (*P*<0.10) (Yu 2014). It is important to note that the 4-year data presented at the 2014 Advances in Neuroblastoma Research (ANR) Congress were not powered to examine data over 4 years, as there were too few patients to adequately detect a statistical difference between immunotherapy and standard therapy over this time period.

These survival gains translate into a meaningful benefit to a small patient population (54 children in England and Wales) that would otherwise have limited life expectancy.

3.1.5 Provide details of any relevant NICE guidance, pathways, or commissioning guides related to the condition for which the technology is being used. Specify whether any subgroups were explicitly addressed.

Two NICE guidance documents are relevant to the treatment of neuroblastoma: (1) NICE cancer service guideline children and young people: Improving outcomes in children and young people with cancer. August 2005; and (2) NICE quality standards. Children and young people with cancer (QS55). February 2014. Both present a broad scope of goals for the delivery of cancer care to children with cancer in the UK. Neither specially addresses treatment or recommendations for management of neuroblastoma or specific subgroups of neuroblastoma patients.

3.1.6 Provide details of other clinical guidelines (for example, UK guidance from the royal societies or European guidance) and national policies.

The Scottish Intercollegiate Network guidelines for the long-term follow-up of survivors of childhood cancer (SIGN 132; March 2013) outline potential long-term complications and monitoring for survivors of childhood cancers. The guidelines cite the need for ongoing thyroid management for patients previously treated with MIBG high-dose radiation to the neck. In addition, survivors of neuroblastoma have been reported to have diminished bone mineral density, with bone mineral density scores of the lumbar spine correlated to overall quality of life. No specific guidance is provided for the maintenance treatment of neuroblastoma in patients who have

previously received induction chemotherapy and achieved at least a partial response followed by myeloablative therapy and ASCT.

3.1.7 Describe any issues relating to current clinical practice, including any variations or uncertainty about established practice.

Standard therapy for maintenance phase treatment of high-risk neuroblastoma following chemotherapy, myeloablative therapy, and ASCT primary consists of isotretinoin. Currently, no immunotherapy is approved by the EMA, but immunotherapy may be given as maintenance treatment through clinical trials alongside differentiation therapy (isotretinoin).

3.1.8 Provide an assessment of whether the use of this technology is likely to raise any equality issues.

There are no equality issues surrounding the use of dinutuximab for the indicated patient population.

4.0 Clinical effectiveness

4.1 Identification and selection of relevant studies

4.1.1 Assessment of need for systematic literature review

The NCI has led the development of dinutuximab for more than 20 years. In July 2010, UTC entered into a Cooperative Research and Development Agreement (CRADA) with the NCI to collaborate on the late-stage development and commercialization of dinutuximab. As such, under the CRADA, UTC has exclusive rights to the clinical study data from all NCI-sponsored dinutuximab studies, including the pivotal phase 3 study and the technical information needed to manufacture comparable dinutuximab. No additional relevant studies have been performed outside the organization and all data necessary to address the remit and scope of the technology appraisal is presented herein. In the instance that UTC is unwilling or unable to accommodate requests for supplementary information, UTC offers consent for the NICE Appraisal Committee to seek this information directly from European Economic Area regulatory authorities.

In order to ensure that all relevant literature pertaining to the NICE decision problem was contained in the submission, a systematic literature review was conducted to retrieve safety and efficacy data for dinutuximab as outlined in the scope. This was supplemented by hand-searching the bibliographies of relevant review articles, conference proceedings, and trial databases.

Section 8.2 (Appendix 4: Search strategy for section 4.1 (Identification and selection of relevant studies)) provides details regarding the search methodology.

4.1.2 Search strategy

Studies retrieved from the systematic literature review were initially assessed based on abstract and title. The full text was reviewed if eligibility could not be ascertained from the abstract and title. Key inclusion criteria were: prospective clinical trial; conducted in a population of high-risk neuroblastoma patients aged 12 months to 17 years; investigating dinutuximab (ch14.18); collected safety and/or efficacy data; published in English language. Key exclusion criteria were: neuroblastoma patients aged <1 year or >17 years and those studies not reporting the outcomes listed in the

dinutuximab scope. Published literature also exists for ch14.18 monoclonal antibodies that are not bioequivalent to dinutuximab. These molecules are created by differing production processes and no evidence is available to suggest interchangeability. Therefore, these studies were excluded from the review of evidence for dinutuximab.

A full list of inclusion and exclusion criteria is presented in section 4.1.3.

4.1.3 Inclusion and exclusion selection criteria, language restrictions, and the study selection process

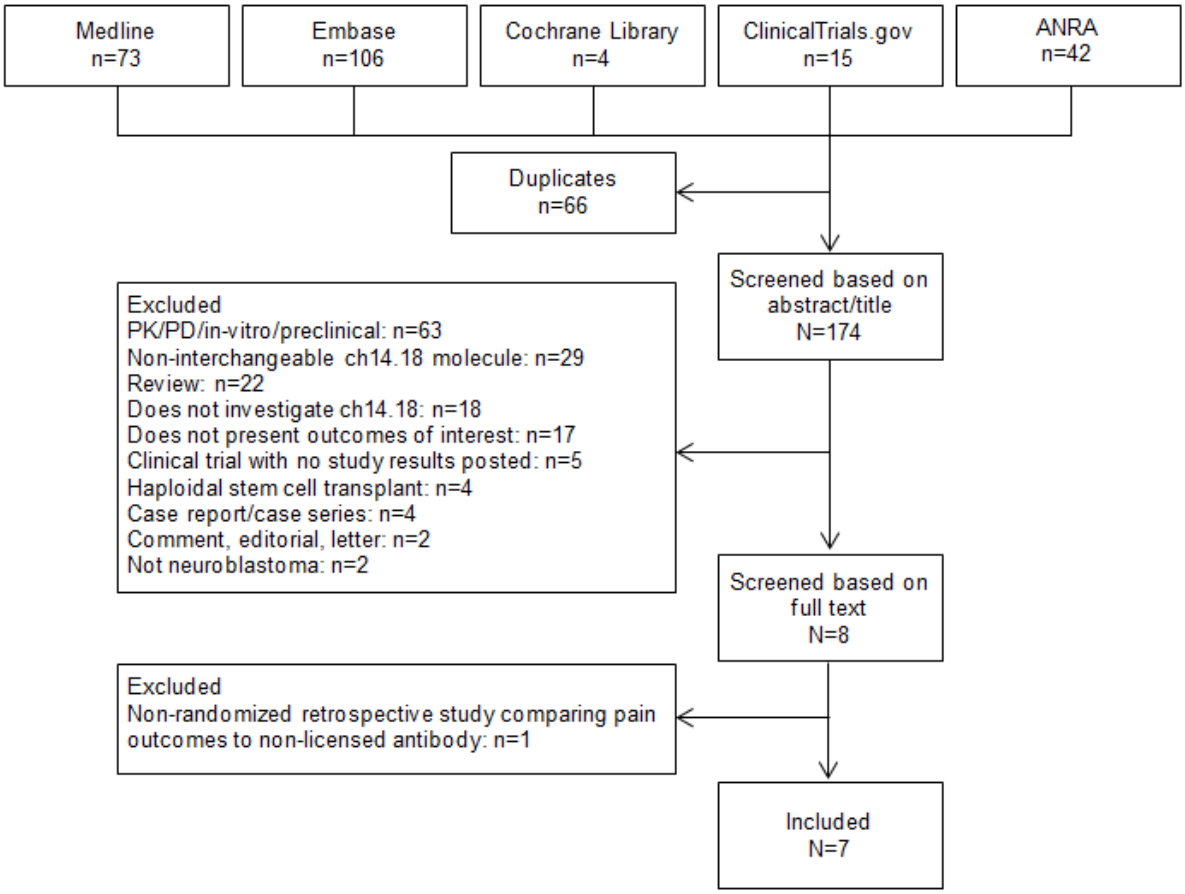
Table 15. Systematic literature review study inclusion and exclusion criteria

PICOS Category	**Description**	**Justification**
Inclusion criteria		
Population	High-risk neuroblastoma patients aged 12 months to 17 years	As specified by final scope
Intervention	Dinutuximab (ch14.18 antibody)	As specified by final scope
Outcomes	OS PFS (ie, EFS) Response rate HRQOL Adverse reactions	As specified by final scope
Study design	Prospective studies	All relevant clinical studies of dinutuximab will be included
Language restrictions	English language	-
Exclusion criteria		
Population	Patients without neuroblastoma Patients aged <1 year or >17 years	As specified by final scope
Intervention	Studies not investigating dinutuximab or studies utilising ch14.18 antibody derived from alternative cell lines	Ch14.18 antibodies derived from alternative CHO cell lines are created by differing production processes and no evidence is available to suggest interchangeability
Outcomes	Studies not reporting the outcomes listed in the final scope	As specified by final scope
Study design	Letters, comments, editorials, reviews, pharmacokinetic studies, pharmacodynamic studies, *in vitro* studies	-
Language restrictions	Non-English publications	-

Key: CHO – Chinese hamster ovaries; EFS – event-free survival; HRQOL – health-related quality of life; OS – overall survival; PFS – progression-free survival.

4.1.4 Flow diagram of the numbers of studies included and excluded

Figure 2. Flow diagram for systematic literature review



Key: ANRA – Advances in Neuroblastoma Research Association; PK – pharmacokinetic; PD – pharmacodynamic.

4.1.5 Search results

All duplicate records were identified and removed. Titles and abstracts were screened independently by two reviewers to identify all of the citations that met the inclusion/exclusion criteria in Table 15. Abstracts and titles were assessed by two reviewers against the inclusion/exclusion criteria. Discrepancies were resolved by consensus. Full manuscripts of selected citations were then retrieved and assessed against the inclusion/exclusion criteria. Studies that did not meet the criteria were excluded and their bibliographic details were listed alongside reasons for their exclusion. The search yielded 174 articles, 7 of which met all inclusion and exclusion criteria and are included in the submission. These 7 articles pertain to 5 unique studies. One pharmacokinetic study was excluded due to study design; however, it

provides evidence of equivalence of dinutuximab to the NCI ch14.18 molecule for which early clinical development for dinutuximab is based upon (DIV-NB-201). This study is listed in Table 16 for reference but excluded from the remainder of the submission.

4.1.6 Excluded studies

A complete list of references for unique studies identified during the systematic literature review with reasons for exclusion is presented in section 8.2.8 (Appendix 4: Search strategy for section 4.1 (Identification and selection of relevant studies)).

4.2 List of relevant randomised clinical trials

4.2.1 Present the list of relevant RCTs comparing the intervention with other therapies (including placebo) in the relevant patient group.

Relevant RCTs for dinutuximab for the treatment of high-risk neuroblastoma are presented in Table 16.

Table 16. List of relevant RCTs

Trial number (acronym) **Primary Study Reference**	**Population**	**Intervention**
ANBL0032 (ongoing) Yu 2010 **Secondary references:** Yu 2014 Naranjo 2014 ***Population and comparators are directly related to the NICE decision problem***	• High-risk neuroblastoma, as defined by the COG (Table 12) • Age at diagnosis <31 years • Completion of induction therapy, ASCT, and radiotherapy • Achievement of at least a partial response at the time of evaluation before ASCT • ASCT performed within 12 months after the initiation of induction therapy, with study enrollment between day 50 and day 100 after the final ASCT • Absence of progressive disease • Adequate organ function • A life expectancy of ≥2 months • Enrolled in the COG biology study (ANBL00B1)	Patients were randomly assigned in a 1:1 ratio to receive: • Isotretinoin (160 mg/m^2 per day, divided into 2 daily doses, for 14 consecutive days within each of 6 consecutive 28-day courses) OR • Immunotherapy (consisting of 6 courses of isotretinoin and 5 concomitant courses of dinutuximab in combination with alternating GM-CSF and IL-2). The immunotherapy group received the following: ○ Dinutuximab (25 mg/m^2 per day for 4 consecutive days during each of 5 consecutive 28-day courses) ○ GM-CSF (250 µg/m^2 per day for 14 days during courses 1, 3, and 5, starting 3 days before dinutuximab was initiated) ○ IL-2 (during courses 2 and 4 via continuous infusion for 4 days during week 1 at a dose of 3.0 MIU/m^2 per day, and for 4 days during week 2 at a dose of 4.5

Trial number (acronym) Primary Study Reference	Population	Intervention
		MIU/m^2 per day, concurrent with dinutuximab) ○ Isotretinoin (160 mg/m^2 per day, divided into 2 daily doses, for 14 consecutive days during the last 2 weeks in each of the 5 dinutuximab courses and by itself during a final sixth course)
DIV-NB-201 ClinicalTrials.gov NCT01592045	• High-risk neuroblastoma, as defined by the COG (Table 12) • Age at diagnosis ≤8 years • Completion of intensive induction followed by ASCT and radiotherapy (radiotherapy may be waived for patients who either have small adrenal masses that are completely resected up front or who never have an identifiable primary tumour) • Achievement of at least a partial response at the time of evaluation before ASCT • ASCT performed within 12 months after the initiation of induction therapy • No progressive disease at time of registration • Adequate renal, liver, cardiac, pulmonary, and CNS function • CNS toxicity Grade <2	Randomised, open-label, 2-sequence, cross-over pharmacokinetic study to assess the comparability of ch14.18 manufactured with UTC drug product (dinutuximab) and ch14.18 manufactured with NCI drug product Subjects were randomly allocated to receive: • Dinutuximab for 2 courses and NCI ch14.18 for 3 courses ○ Dinutuximab (17.5 mg/m^2 per day for 4 consecutive days) ○ ch14.18–NCI (25 mg/m^2 per day for 4 consecutive days) OR • NCI ch14.18 for 2 courses and UTC ch14.18 for 3 courses ○ ch14.18–NCI (25 mg/m^2 per day for 4 consecutive days) ○ Dinutuximab (17.5 mg/m^2 per day for 4 consecutive days) In addition to: ○ GM-CSF (250 mcg/m^2 per day for 14 days during courses 1, 3, and 5) ○ IL-2 (3 MIU/m^2 per day for the first week and at a dose of 4.5 MIU/m^2 day for the second week during courses 2 and 4) ○ Isotretinoin: - If weight >12 kg: 160 mg/m^2 per day, divided twice daily - If weight ≤12 kg: 5.33 mg/kg per day, divided twice daily

Key: ASCT – autologous stem cell transplant; COG – Children's Oncology Group; GD-2 –disialoganglioside; GM-CSF – granulocyte-macrophage colony-stimulating factor; IL-2 – interleukin 2; IU – international units; kg – kilogram; m – meters; mg – milligrams; NCI – National Cancer Institute; UTC – United Therapeutics Corporation.

4.2.2 When the RCTs listed above have been excluded from further discussion, justification should be provided to ensure that the rationale for doing so is transparent. For example, when RCTs have been identified, but there is no access to the level of data required, this should be stated.

The pivotal phase 3 study ANBL0032 provides the primary evidence for the safety and efficacy of dinutuximab for the treatment of neuroblastoma (Yu 2010). An

additional open-label, randomised study evaluated the pharmacokinetic profile of dinutuximab compared to a chimeric ch14.18 monoclonal antibody developed by the NCI (DIV-NB-201). As noted previously, this study is provided for reference only and is excluded from further discussion.

4.3 Summary of development and methodology of the relevant randomised controlled trials

The feasibility of dinutuximab in combination with GM-CSF after high-dose chemotherapy and ASCT was evaluated in a phase 1 study (Study A0935A) to determine the maximum tolerated dose (MTD) and toxicities in this setting (Ozkaynak 2000; Gilman 2009). Part A (January 1995 to September 1997) of the A0935A study evaluated the MTD and safety of dinutuximab with GM-CSF immediately after high-dose chemotherapy and ASCT (Ozkaynak 2000). The MTD of dinutuximab was determined to be 40 mg/m^2 per day for 4 days when given in this setting with GM-CSF. Common toxicities were severe neuropathic pain, fever, nausea/vomiting, urticaria, hypotension, mild to moderate capillary leak syndrome, and neurotoxicity (Ozkaynak 2000). Following Part A, Part B (June 1997 to February 2002) of the A0935A study evaluated the MTD and safety of integrating IL-2 into a regimen of dinutuximab plus GM-CSF after high-dose chemotherapy and ASCT (Gilman 2009). The study design was amended to accommodate the new standard of care when Matthay et al demonstrated that 13-*cis*-retinioc acid was shown to improve survival after high-dose chemotherapy and ASCT (Gilman 2009; Matthay 1999). Additional changes were made in anticipation of the phase 3 trial. For example, in Part A of the A0935A study, dinutuximab 40 mg/m^2 per day for 4 days was tolerated with GM-CSF. However, in Part B, 2 of 6 assessable patients had toxicity meeting dose-limiting toxicity criteria (used for the IL-2 course) with this dinutuximab dose. Based on these findings and the desire to explore a dose feasible for a phase 3 trial, a dinutuximab dose of 25 mg/m^2 for 4 days was chosen for all courses in the final study design of Part B. The toxicity of dinutuximab given with IL-2 was considerable, but also manageable and reversible. Common toxicities included neuropathic pain, fever, nausea, emesis, diarrhea, urticaria, mild elevation of hepatic transaminases, capillary leak syndrome, and hypotension (Gilman 2009). Fever, hypotension, and capillary leak syndrome were slightly more severe in courses with

IL-2 vs courses with GM-CSF. No additional toxicity was observed when isotretinoin was given between courses of dinutuximab (Gilman 2009).

The preclinical and early phase clinical trials demonstrated that dinutuximab had activity against neuroblastoma that was enhanced when dinutuximab was combined with GM-CSF alone or in combination with GM-CSF and IL-2 in the early post-transplant period. These studies paved the way for the pivotal phase 3 trial, described in Table 17 (Yu 2010).

Table 17. Summary of methodology of ANBL0032 (Yu 2010)

Location	US, Canada, Australia, New Zealand
Trial design	ANBL0032 was a multicentre, prospective, partially randomised, active-controlled trial Randomisation was stratified according to prior response to ASCT ("complete" vs "very good partial" vs "partial"), stem cells received ("purged" vs "unpurged"), and frontline chemotherapy ("COG-A3973" vs "POG 9341/9342" vs "COG-ANBL02P1" vs "other therapy"). Patients were randomised 1:1 via stratified permuted blocks to receive standard therapy (6 courses of isotretinoin) or immunotherapy (6 courses of isotretinoin and 5 concomitant courses of dinutuximab in combination with alternating GM-CSF and IL-2) Patients with biopsy-proven residual disease after ASTC were non-randomly assigned to receive immunotherapy and were excluded from the primary efficacy analysis
Eligibility criteria	• High-risk neuroblastoma as defined by the COG (Table 12) • Age <31 years • Completion of induction therapy, ASCT, and radiotherapy • Achievement of at least partial response at time of evaluation before ASCT • ASCT performed within 9 months after the initiation of induction therapy • Study enrollment between day 50 and day 100 after the final ASCT • Absence of progressive disease • Adequate renal, liver, cardiac, pulmonary, and CNS function • Life expectancy ≥2 months • Enrollment in the COG study ANBL00B1, a study of biomarkers in tumour tissue samples from patients with newly diagnosed neuroblastoma or ganglioneuroblastoma
Settings and locations where the data were collected	The study was carried out in COG participating institutions in the US, Canada, Australia, and New Zealand. Study sites represent a secondary care setting.
Trial drugs and concomitant medications Immunotherapy (n=113) Standard therapy (n=113)	**<u>Dinutuximab (immunotherapy group)</u>** 6 courses of isotretinoin and 5 concomitant courses of dinutuximab in combination with alternating GM-CSF and IL-2. The immunotherapy group received the following: • Dinutuximab (25 mg/m^2 per day for 4 consecutive days during each of 5 consecutive 28-day courses) • GM-CSF (250 µg/m^2 per day for 14 days during courses 1, 3, and 5, starting 3 days before dinutuximab was initiated) • IL-2 (during courses 2 and 4 via continuous infusion for 4 days during week 1 at a dose of 3.0 MIU/m^2 per day and for 4 days during week 2 at a dose of 4.5 MIU/m^2 per day, concurrent with dinutuximab) • Isotretinoin (160 mg/m^2 per day, divided into 2 daily doses, for 14 consecutive days during the last 2 weeks in each of the 5 dinutuximab courses and by itself during a final sixth course)

	Isotretinoin monotherapy (standard therapy group) Isotretinoin 160 mg/m^2 per day, divided into 2 daily doses, for 14 consecutive days within each of 6 consecutive 28-day courses Concomitant medications were not restricted in either treatment group.
Primary outcomes	**Primary outcome measure** EFS (ITT analysis), defined as the time from study enrollment until the first occurrence of relapse, progressive disease, secondary cancer, or death or the last contact with the patient, if none of these events occurred
Secondary outcomes	**Secondary outcome measure** OS (ITT analysis), defined as the time from study enrollment until death or the last contact with the patient, if death did not occur during the study.
Pre-planned subgroups/analyses	EFS and OS for patients with evidence of residual disease non-randomly assigned to immunotherapy

Key: ASCT – autologous stem cell transplant; COG – Children's Oncology Group; CNS – central nervous system; GM-CSF – granulocyte-macrophage colony-stimulating factor; IL-2 – interleukin 2; ITT – intent-to-treat; IU – international units; kg – kilogram; m – meters; mg – milligrams; NCI – National Cancer Institute; UTC – United Therapeutics Corporation.

4.4 Statistical analysis and definition of study groups in the relevant randomised controlled trials

4.4.1 Sample size, interim analyses and stopping guidelines, and statistical methods used to compare group

A sample size of 386 was determined to produce statistical power of 80% with 2-sided log-rank test at a level of 0.05 to detect an absolute between-group difference in EFS of 15 percentage points at 3 years. Based on sample size and predicted EFS under the null hypothesis, a total of 137 events were expected to be reported. *P*-values were calculated using the log-rank test for the analyses of survival.

Sequential monitoring of the primary outcome was performed, with the potential for early study termination if a statistically significant difference between groups was detected before the 3-year time point or if the conditional power fell below 20%. The risk ratio (RR) of an event for standard therapy vs immunotherapy was compared with an alternative hypothesis of RR=1.6. The Lan-DeMets upper (efficacy) boundary was calculated with the spending function alpha × time^2 for a cumulative alpha level of 0.025.

All efficacy analyses were conducted on the intent-to-treat (ITT) population. Patients non-randomly assigned to immunotherapy (n=25) were excluded from the primary efficacy analysis.

A gate-keeping approach was undertaken whereby overall survival would not be estimated without detection of a statistically significant difference in the primary outcome measure.

4.4.2 Details of trial population included in the primary analysis and methods to account for missing data

All patients who underwent randomisation in the immunotherapy group (n=113) and in the standard therapy group (n=113) were evaluated for efficacy outcomes. All patients, regardless of randomisation, were included in the safety analysis (n=251). Missing data due to patient withdrawal or loss to follow-up was considered an event for the primary analysis of EFS and lack of survival for analysis of OS.

4.4.3 For each trial, provide details of the statistical tests used in the primary analysis. Also provide details of the primary hypothesis or hypotheses under consideration, the power of the trial, and a description of sample size calculation, including rationale and assumptions in a table. If the outcomes were adjusted for covariates, provide the rationale.

A summary of the primary hypothesis under consideration in study ANBL0032 and details for statistical tests and calculations are provided in Table 18.

Table 18. Summary of statistical analyses in ANBL0032 (Yu 2010)

Trial Number (acronym)	Hypothesis Objective	Statistical Analysis	Sample Size, Power Calculation	Data Management, Patient Withdrawals
ANBL0032	Test whether the addition of immunotherapy (dinutuximab with GM-CSF and IL-2) to isotretinoin improves survival compared to isotretinoin alone	• Statistical comparisons were made using 2-sided tests at the 0.05 significance level • Sequential monitoring based on the Lan-DeMets error spending function method; hypothesis testing was performed at cumulative alpha=0.025	• 386 evaluable patients would provide 80% power to detect a difference of 15 percentage points in EFS at a 2-sided significance level of 0.05	Patient withdrawal or loss to follow-up was considered an event or lack of survival for the primary and secondary outcomes analyses, respectively

Key: EFS – event-free survival; GM-CSF – granulocyte macrophage colony-stimulating factor; IL-2 – interleukin 2.

4.5 Participant flow in the relevant randomised controlled trials

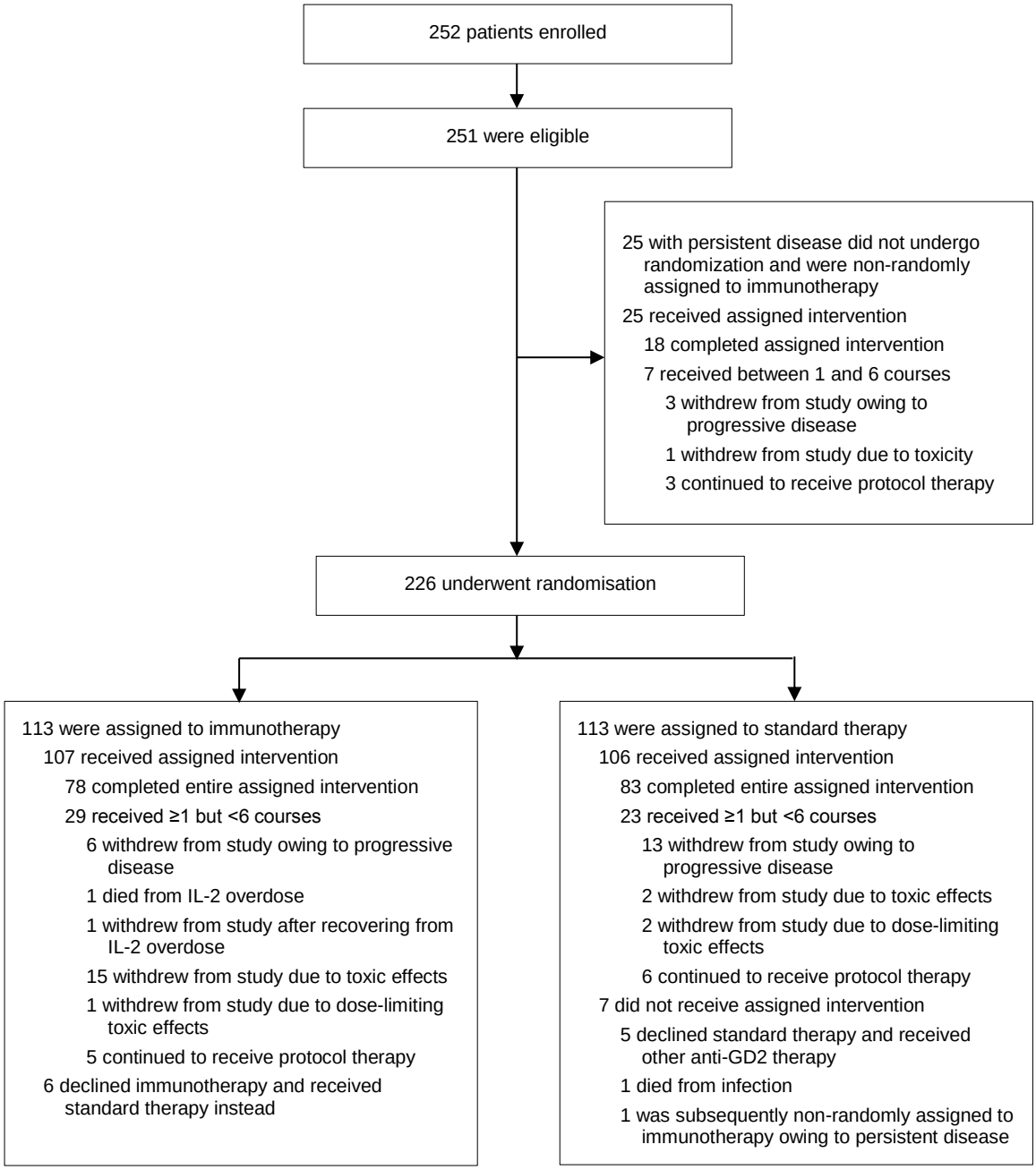
4.5.1 Provide details of the numbers of participants who were eligible to enter the trials. Include the number of participants randomised and allocated to each treatment. Provide details of and the rationale for participants who crossed over treatment groups, were lost to follow-up, or withdrew from the RCT. Provide a CONSORT diagram showing the flow of participants through each stage of each of the trials.

Among 252 enrolled patients, 1 patient was ineligible and 25 patients with biopsy-proven persistent disease after ASCT were non-randomly assigned to immunotherapy. The remaining 226 eligible patients were randomly assigned to a treatment group: 113 patients in the standard-therapy group and 113 patients in the immunotherapy group. All 251 eligible patients were analysed for toxic effects. There were no significant differences between the 2 groups for baseline characteristics. The median duration of follow-up after randomization for patients who were alive and had not had a study event was 2.1 years (range: 4 days to 6.9 years).

Among the 113 randomised patients assigned to immunotherapy, 107 received the assigned intervention, while 6 declined immunotherapy and received standard therapy (Yu 2010). Among the 107 who received immunotherapy, 78 completed the entire assigned intervention while 29 received between 1 and 5 courses (6 withdrew due to progressive disease, 1 died from IL-2 overdose, 1 withdrew after recovering from IL-2 overdose, 15 withdrew due to toxic effects, 1 withdrew due to dose-limiting toxic effects, and 5 continued to receive protocol therapy). Among the 113 randomised patients assigned to standard therapy, 106 received the assigned intervention while 7 did not receive the assigned intervention (5 declined standard therapy and received other anti-GD2, 1 died from infection, and 1 was subsequently nonrandomly assigned to immunotherapy due to persistent disease). Among the 106 who received standard therapy, 83 completed the entire assigned intervention while 23 received between 1 and 5 courses (13 withdrew due to progressive disease, 2 withdrew due to toxic effects, 2 withdrew due to dose-limiting toxic effects, and 6 continued to receive protocol therapy).

A CONSORT flow chart showing the number of patients who were eligible to enter the study, were randomised, and received each treatment is presented in Figure 3.

Figure 3. Patient flow for study ANBL0032 (Yu 2010)



Key: GD2 – disialoganglioside; IL-2 – interleukin-2.

4.5.2 In a table, describe the characteristics of the participants at baseline for each of the trials.

Baseline characteristics of the trial population included in the primary analysis are presented in Table 19. Patient demographics and clinical characteristics were similar between treatment groups. *P*-values for baseline differences in patient characteristics were calculated using a chi-square test.

Although study inclusion criteria allowed enrollment of all patients <31 at age of diagnosis, the average age at enrollment was 4.1 years (range 0.94 to 15.29 years). The majority of randomised patients (179/226; 79%) were aged ≥1 year with stage 4 disease; an analysis of EFS and OS in this subgroup is presented in section 4.8.1.

Table 19. Baseline demographics and characteristics of the 226 randomised patients of study ANBL0032 (Yu 2010)

Characteristic	Standard Therapy (n=113), n (%)	Immunotherapy (n=113), n (%)	*P*-value
Age			1.00
<18 months	4 (4)	4 (4)	
≥18 months	109 (96)	109 (96)	
INSS stage[†]			0.93
2	0 (0)	4 (4)	
3	16 (15)	10 (10)	
4S[‡]	0 (0)	2 (2)	
4	92 (85)	89 (85)	
Unknown	5	8	
Tumour *MYCN* status			0.42
Not amplified	51 (53)	52 (59)	
Amplified	45 (47)	36 (41)	
Unknown[§]	17	25	
Tumour histologic features			0.94
Favourable	5 (6)	4 (6)	
Unfavourable	81 (94)	68 (94)	
Unknown	27	41	
Tumour ploidy			0.33
Hyperdiploid	48 (51)	49 (58)	
Diploid	46 (49)	35 (42)	
Unknown	19	29	
Response before ASCT[¶]			0.96
Complete response	38 (34)	40 (35)	
Very good partial response	49 (43)	47 (42)	
Partial response	26 (23)	26 (23)	
Number of ASCTs			
1	102 (90)	107 (95)	0.31
2[‖]	11 (10)	6 (5)	
Number of purged infusions			0.79
≥1	29 (33)	28 (31)	
0	58 (67)	61 (69)	
Unknown	26	24	

[†] All *P*-values for INSS stage are reported for stage 4 versus stage 2, 3, or 4S.

[‡] The 2 patients with an INSS stage of 4S had neuroblastoma considered to be high risk because of *MYCN* amplification.

[§] Since obtaining a tumour specimen for purposes of ascertaining *MYCN* status was not an eligibility requirement, this information was unavailable for some patients.

[¶] All *P*-values for response before ACST are reported for complete response or very good partial response vs partial response.

[‖] For patients who underwent 2 ASCTs, the maximum duration of follow-up with regard to the rates of survival was 1.5 years.

Key: ASCT – autologous stem cell transplant; INSS – International Neuroblastoma Staging System; MYCN – v-myc avian myelocytomatosis viral oncogene neuroblastoma derived homolog.

4.6 Quality assessment of the relevant randomised controlled trials

4.6.1 The validity of the results of an individual RCT will depend on the robustness of its overall design and execution and its relevance to the decision problem. The quality of each RCT identified in section 4.2 should be appraised. Whenever possible, the criteria for assessing published studies should be used to assess the validity of unpublished and part-published studies. The quality assessment will be validated by the Evidence Review Group. Describe the methods used for assessing risk of bias and generalisability of individual RCTs (including whether this was done at the study or outcome level) and how this information is to be used in any data synthesis.

Was randomisation carried out appropriately?

Randomisation was carried out by block stratification according to prognostic factors thought to potentially affect the result in order to create adequately balanced treatment groups. These factors included response before ASCT, type of induction therapy, number of ASCTs, and purged vs nonpurged stem cell infusion. Comparability between groups at baseline was tested using chi-squared test with an alpha level of 0.05, with no statistically significant between-group differences detected at baseline (Section 4.5.2; Table 19).

Was the concealment of treatment allocation adequate?

Not applicable; the study was designed as a randomised, active-controlled, unblinded study, thus treatment allocation was not concealed.

Were the groups similar at the outset of the study in terms of prognostic factors?

Groups were similar at baseline in regards to prognostic factors thought to potentially affect the study outcome. Baseline characteristics for both treatment groups are presented in Section 4.5.2 (Table 19).

Were the care providers, participants, and outcome assessors blind to treatment allocation?

Neither patients nor providers were masked to treatment allocation. As a result, 6 patients assigned to immunotherapy declined treatment and received standard therapy instead and 5 patients who were assigned to standard therapy declined treatment and received other anti-GD2 therapy. In the context of an unblinded study design, potential sources of bias must be considered. Reporting bias may exist whereby detection and reporting of progression events is influenced by knowledge of the treatment received (eg, in the case of borderline results upon progression evaluation). The impact of this type of bias on the results of the phase 3 trial of dinutuximab is expected to be minimal due to the low frequency of borderline results (Freidlin 2007). As study subjects were made aware of randomisation to the standard therapy arm, subjects in this arm may be more likely to drop out of the study earlier and at higher rates in order to seek alternative treatment. Event-free survival was defined as the time to first recurrence of relapse, progressive disease, secondary cancer, death, or last contact with the patient. Thus, higher rates of early study withdrawal in the standard therapy arm could potentially bias the standard therapy arm toward a shorter EFS. The impact of this bias is expected to be minimal or favour immunotherapy in this study, as early study withdrawal rates were higher in the immunotherapy arm than in the standard therapy arm. A larger proportion of patients randomised to the standard therapy arm completed the entire assigned intervention (83/113; 73%) compared to the immunotherapy arm (78/113; 69%). Another potential concern with an unblinded study design is the potential for evaluation-time bias; that is, if 1 group was subject to more frequent evaluation for progression events than another or if investigators were more apt to request additional evaluations for progression in the standard therapy group compared to the immunotherapy group (Freidlin 2007). To ameliorate this potential bias, the study was designed to evaluate EFS at a fixed time point (ie, 3 years) rather than evaluate time to progression, a metric which would be more highly influenced by evaluation-time bias (Freidlin 2007). As this study met pre-defied criteria for early termination based upon demonstrated statistically significant EFS benefit for patients treated with immunotherapy, results for the primary endpoint are presented as EFS at 2 years rather than 3 years.

Were there any unexpected imbalances in drop-outs between groups?

Although reasons for drop-out differed between treatment groups, a similar proportion of patients in the immunotherapy group and standard therapy group completed the entire assigned intervention (69% vs 73%, respectively). In the immunotherapy group, the majority of patients who started but did not complete the entire assigned therapy withdrew due to toxic effects. The primary reason for early withdrawal among patients who started but did not complete the entire cycle of standard therapy was progressive disease. Complete reasons for early withdrawal are presented in the patient flow diagram in section 4.5.1 (Figure 3).

Is there any evidence to suggest that the authors measured more outcomes than they reported?

The authors reported the pre-specified primary and secondary outcomes. In addition, outcomes were analysed and presented for the subgroup of patients who were non-randomly assigned to immunotherapy due to the presence of progressive disease upon enrollment and were thus excluded from the primary efficacy analysis. Corresponding outcomes for all study measures that were described in the study design were presented as study results with no evidence of outcomes that were collected but not reported.

Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?

The primary and secondary efficacy analyses were conducted on the ITT population, with a safety analysis of the entire treated study sample. Missing data due to patient withdrawal or loss to follow-up was considered a progression event or lack of survival for the primary and secondary outcomes analyses, respectively.

4.6.2 Consider how closely the RCT(s) reflects routine clinical practice in England.

Routine clinical practice for the treatment of high-risk neuroblastoma in England in the context of maintenance treatment often involves investigational therapies (such as immunotherapy) given through clinical trials alongside differentiation therapy (isotretinoin). Therefore, the Yu 2010 RCT very closely reflects routine clinical practice in England.

4.6.3 Tabular summary of the responses applied to each of the quality assessment criteria.

Table 20. Quality assessment results for study ANBL0032

Trial Number (Reference)	ANBL0032 (Yu 2010)
Was randomisation carried out appropriately?	Yes
Was the concealment of treatment allocation adequate?	N/A*
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes
Were the care providers, participants, and outcome assessors blind to treatment allocation?	No*
Were there any unexpected imbalances in drop-outs between groups?	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No
Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes/Yes

*ANBL0032 was designed as an unblinded active comparator RCT.

4.6.4 The complete quality assessment for each RCT should be included in an appendix.

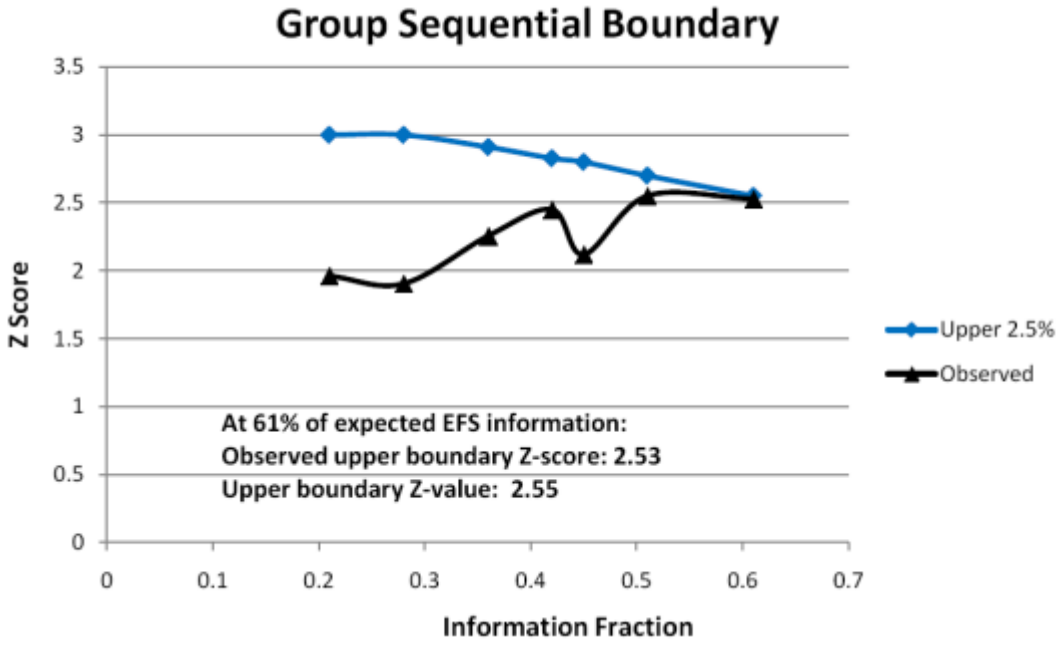
As only 1 RCT met criteria for inclusion, the complete quality assessment for study ANBL0032 is presented within section 4.6.

4.7 Clinical effectiveness results of the relevant randomised controlled trials

4.7.1 Efficacy

On January 9, 2009, the COG data and safety monitoring committee determined that the study met the pre-defined criteria for early stopping of the randomisation on the basis of the superiority of immunotherapy vs standard therapy as measured by EFS (defined as the time from study enrollment until the first occurrence of relapse, progressive disease, secondary cancer, or death or the last contact with the patient, if none of these events occurred). At the time of early stopping, 83 of the expected 137 events had been reported [61%]) (Figure 4). Analyses were carried out based on differences in EFS and OS at 2 years.

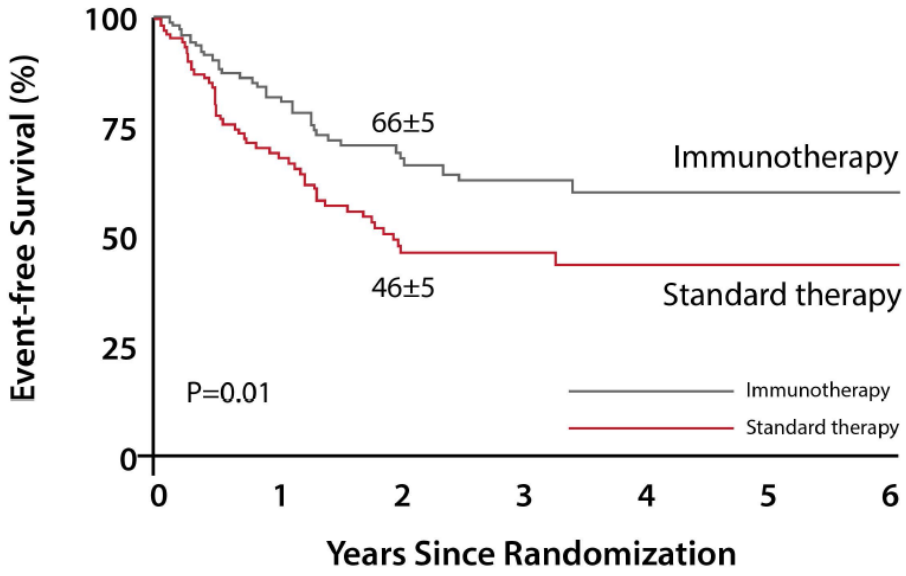
Figure 4. Group sequential Lan-DeMets upper monitoring boundaries



Key: EFS – event-free survival.

Figure 5 presents the Kaplan-Meier estimates of EFS for the overall randomised population (N=226). Patients randomised to immunotherapy (ITT population) had higher EFS at 2 years compared to those randomised to standard therapy (66% ± 5% for immunotherapy vs 46% ± 5% for standard therapy; *P*=0.01). Kaplan-Myer estimates for OS also demonstrated the superiority of immunotherapy compared to standard therapy for OS at 2 years (86% ± 4% vs 75% ± 5%, respectively; *P*=0.02) (Figure 6).

Figure 5. Kaplan-Meier estimates of EFS for the overall ANBL0032 study population (ITT analysis) (Yu 2010)

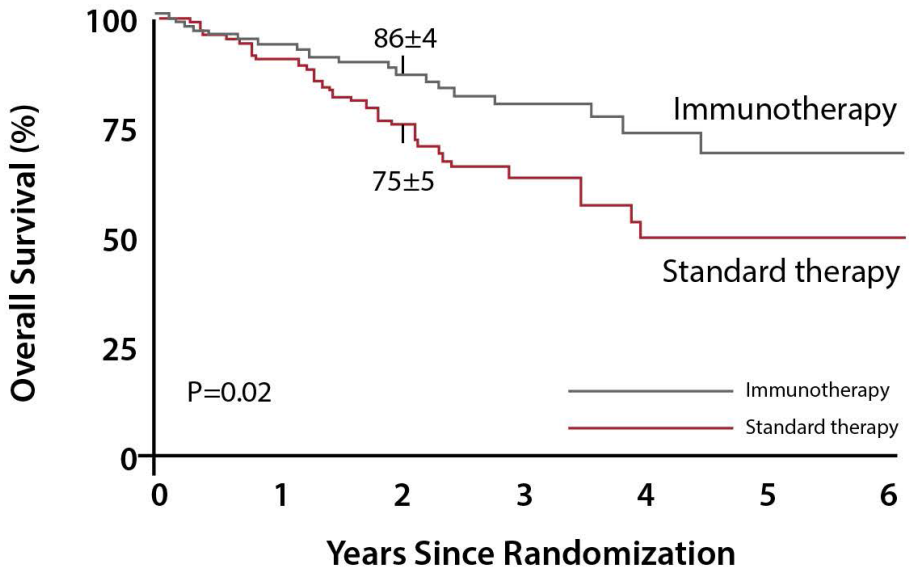


No. at Risk

Immunotherapy	113	69	47	29	15	9	3
Standard therapy	113	59	32	20	10	8	1

Key: EFS – event-free survival; ITT – intent-to-treat.

Figure 6. Kaplan-Meier estimates of OS for the overall ANBL0032 study population (ITT analysis) (Yu 2010)*



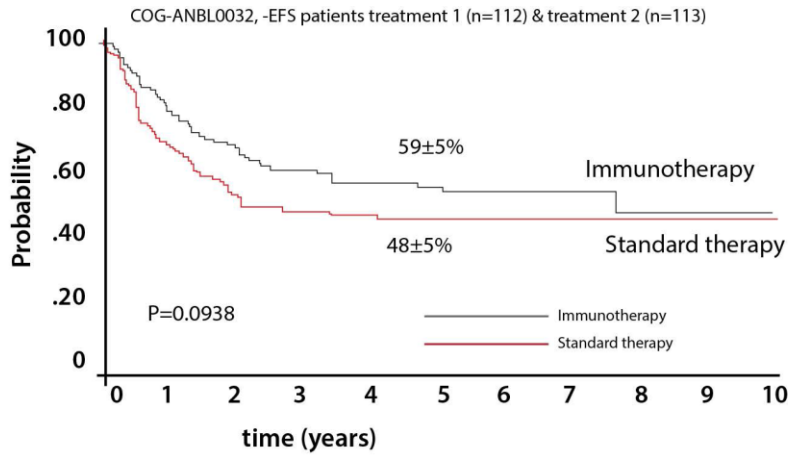
No. at Risk

Immunotherapy	113	77	59	37	20	10	3
Standard therapy	113	79	51	26	12	9	1

**P*-value calculated without adjustment for interim analyses.
Key: ITT – intent-to-treat; OS – overall survival.

An updated analysis for 225 patients with median follow-up time of 5.5 years was conducted for EFS and OS (Yu 2014). Of 226 original randomised patients, 1 was found to be ineligible after the publication of the primary analysis and 4 crossed over to receive immunotherapy after completing standard therapy treatment; these patients were censored at the start of immunotherapy. The ITT analysis evaluated EFS and OS at 4 years using a 2-sided log rank test to test for differences between treatment groups. Kaplan-Meier estimates of EFS at 4 years favoured immunotherapy 59% ± 5% compared to standard therapy 48 ± 5%, but the difference no longer reached statistical significance (P=0.11) (Figure 7). Note that the 4-year results on data presented at the 2014 ANR Congress were not powered to examine data over 4 years, as there were too few patients to adequately detect a statistical difference between immunotherapy and standard therapy over this time period. An OS benefit for immunotherapy was maintained in the follow-up analysis, with a 4-year OS of 74% ± 4% in the immunotherapy group and 59% ± 5% in the standard therapy group (*P*=0.021) (Figure 8).

Figure 7. Kaplan-Meier estimates of EFS at 4 years for the overall ANBL0032 study population (ITT analysis) (Yu 2014)

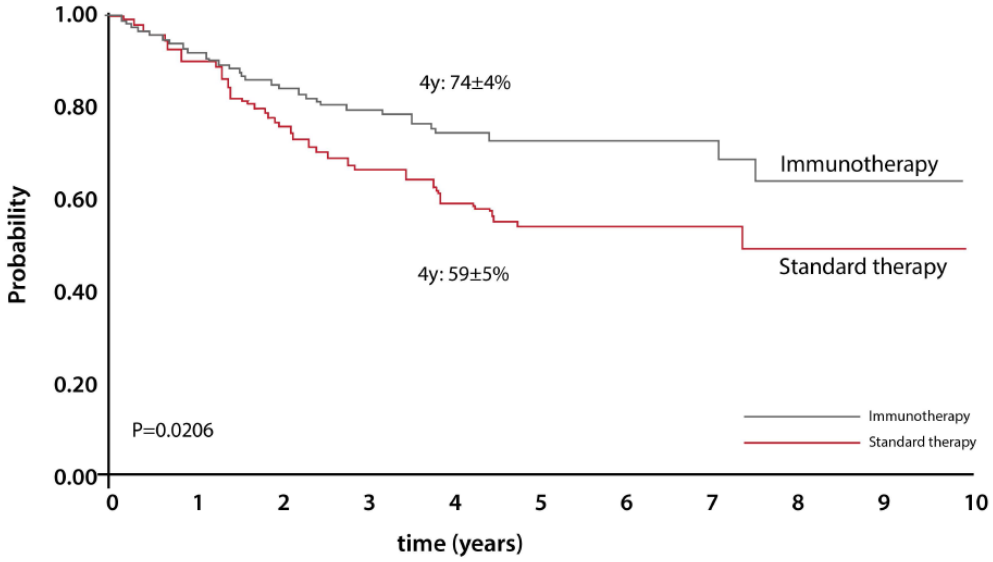


No. at Risk

Immunotherapy	112	73	53	50	42	33	20	11	8	6	0
Standard therapy	113	88	74	68	53	39	27	11	8	5	0

Key: EFS – event-free survival; ITT – intent to treat.

Figure 8. Kaplan-Meier estimates of OS at 4 years for the overall ANBL0032 study population (ITT analysis) (Yu 2014)



No. at Risk

Immunotherapy	112	98	80	68	52	35	22	13	9	6	0
Standard therapy	113	102	92	86	66	49	34	18	9	5	0

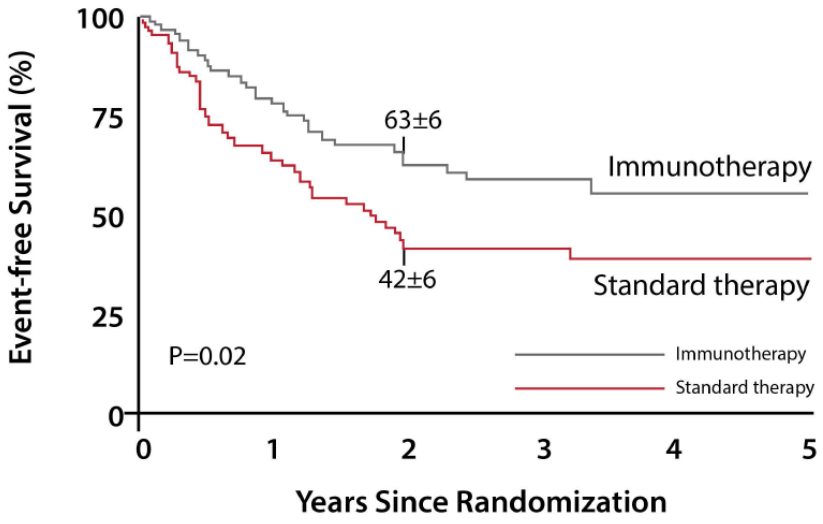
Key: ITT – intent to treat; OS – overall survival.

4.8 Subgroup analysis

4.8.1 Patients over the age of 1 with stage 4 disease

Patients over the age of 1 with stage 4 disease comprised the majority (79%) of the ANBL0032 study sample (179/226 randomised patients), and these patients are thought to represent the majority of high-risk neuroblastoma patients seen in clinical practice. A subgroup analysis was undertaken to assess the efficacy of immunotherapy in this group. Of 179 patients over the age of 1 with stage 4 disease, 89 were randomised to immunotherapy while 90 were randomised to standard therapy. EFS was significantly greater in the immunotherapy group (63% ± 6%) compared to the standard-therapy group (42% ± 6%) at 2 years (*P*=0.02) (Figure 9). Estimates of OS at 2 years favoured immunotherapy (84% ± 4% vs 76% ± 5%), but differences did not reach statistical significance (*P*=0.10) (Figure 10).

Figure 9. Kaplan-Meier estimates of EFS at 2 years for patients aged ≥1 with stage 4 disease (Yu 2010)

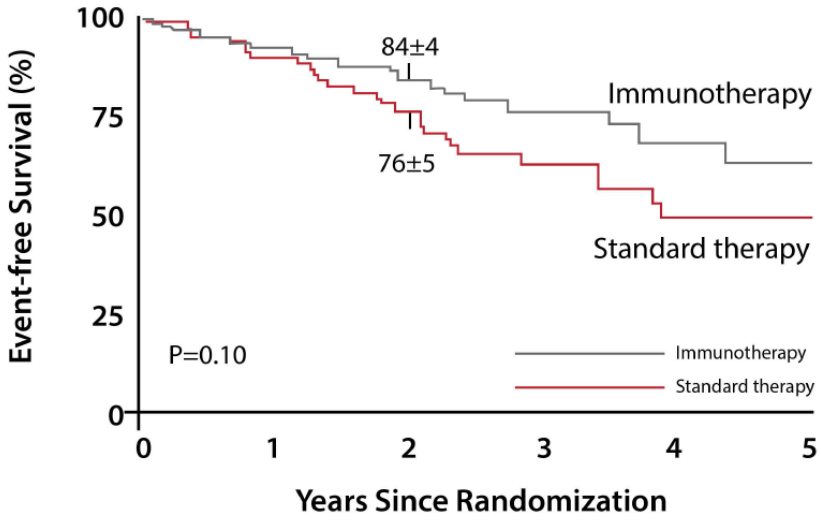


No. at Risk

Immunotherapy	89	56	37	22	11	7
Standard therapy	90	46	26	19	10	8

Key: EFS – event-free survival.

Figure 10. Kaplan-Meier estimates of OS at 2 years for patients aged ≥1 with stage 4 disease (Yu 2010)



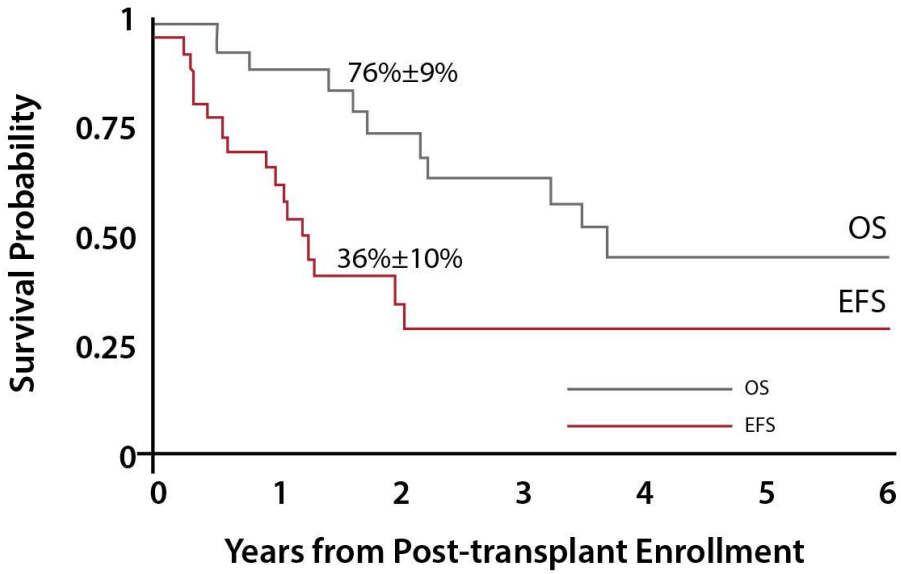
No. at Risk

Immunotherapy	89	64	49	30	16	8
Standard therapy	90	65	45	25	12	9

Key: OS – overall survival.

In addition, results were analysed for the 25 patients who were non-randomly assigned to immunotherapy due to evidence of biopsy-proven persistent disease after ASCT and radiotherapy and were subsequently excluded from the primary efficacy analysis. The median duration of follow-up among the patients without an event was 3.6 years (range: 1.0 to 6.7 years). All of these patients were >18 months of age at diagnosis, 23 patients had stage 4 disease, 6 tumours showed MYCN amplification, 16 tumours had unfavourable histologic features, and 12 tumours were diploid. A total of 21 of the 25 patients had a partial response before ASCT. In these patients, the Kaplan-Meier estimate of EFS and OS at 2 years was 36% ± 10% and 76% ± 9%, respectively (Figure 11). In the follow-up analysis of these patients, EFS and OS at 4 years were 32% ± 9% and 53% ± 11%, respectively (Figure 12). As noted previously, it is important to consider that the analysis at 4 years was inadequately powered to detect statistical difference between immunotherapy and standard therapy, as randomisation was terminated early according pre-defined criteria.

Figure 11. Kaplan-Meier estimates of EFS and OS at 2 years for non-randomised patients due to evidence of persistent disease (Yu 2010)

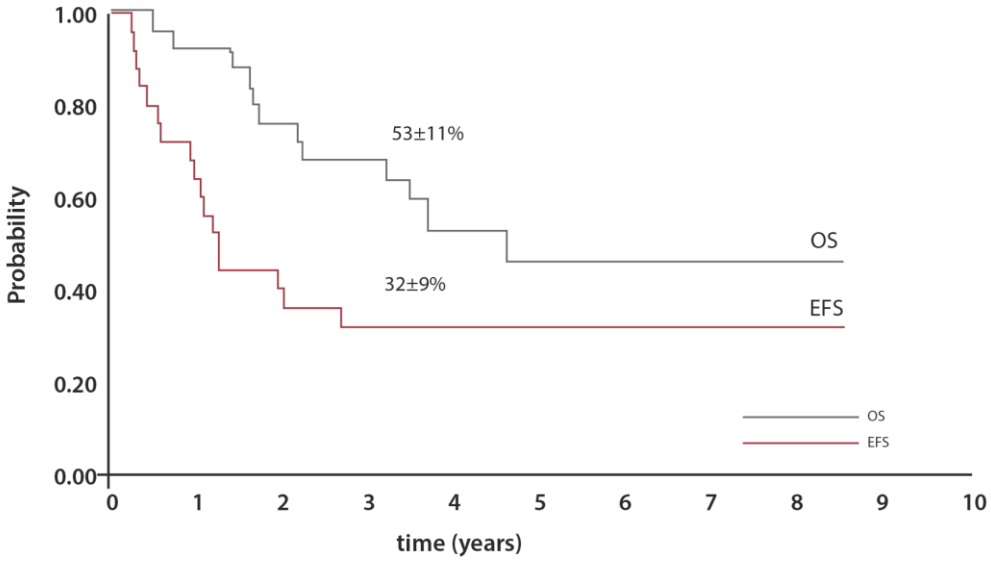


No. at Risk

Immunotherapy	25	16	6	5	4	2	1
Standard therapy	25	22	14	12	6	3	1

Key: ASCT – autologous stem cell transplant; EFS – event-free survival; OS – overall survival.

Figure 12. Kaplan-Meier estimates of OS at 4 years for non-randomised patients due to evidence of persistent disease (Yu 2014)



No. at Risk

Immunotherapy	25	23	19	17	8	7	6	3	2	0	0
Standard therapy	25	16	10	8	4	4	4	2	1	0	0

Key: COG – Children's Oncology Group; EFS – event-free survival; OS – overall survival.

4.8.2 Post-hoc analysis: Stratification by Curie score

Semiquantitative MIBG scores (Curie scores [CS]) have been identified as a potential prognostic marker in studies of neuroblastoma (Yanik 2013; Matthay 2003; Katzenstein 2004; Schmidt 2008). A post-hoc analysis of 197 patients enrolled in ANBL0032 was undertaken to evaluate the impact of baseline CS (0 [n=167] vs >0 [n=30]) on outcomes following treatment with immunotherapy (n=100) vs standard therapy (n=97) (Narajo 2014). Across both treatment groups, EFS at 3 years was higher among patients with CS=0 compared to those with CS>0 (59.2% vs 33.3%; *P*≤0.01) (Table 21). In patients randomised to immunotherapy, 3-year EFS remained higher among patients with CS=0 vs CS>0 (70.5% vs 26.7%; *P*<0.001), whereas no such relationship was observed in patients randomised to standard therapy (47.5% vs 40.0%; *P*=0.22). Patients with CS=0 treated with immunotherapy had a significantly greater EFS compared to those treated with standard therapy (70.5% vs 47.5%; *P*=0.02); however; this treatment benefit was not maintained in patients with CS>0 (26.7% vs 40.0%; *P*=0.93), suggesting that immunotherapy may be less effective in this subgroup of patients. However, the small sample size in patients with CS>0 may limit the ability to detect statistically significant differences between immunotherapy and standard therapy in this group.

Table 21. EFS by CS and Treatment Arm

	CS=0 n=167	**CS>0 n=30**	***P*-value (CS=0 vs CS>0)**
Overall	59.2% ± 3.9%	33.3% ± 8.6%	≤0.01
Immunotherapy	70.5% ± 5.0%	26.7% ± 11.4%	<0.001
Standard therapy	47.5% ± 5.6%	40.0% ± 12.6%	0.22
P-value (immunotherapy vs standard therapy)	0.02	0.93	

Key: CS – Curie score; EFS – event-free survival.

4.8.3 Other subgroups

Dinutuximab has not been evaluated in subgroups other than those listed above. There is no evidence for use of dinutuximab in the subgroups listed in the final scope (people with relapsed disease and people with refractory disease). These patient subgroups may have been studied in clinical studies of ch14.18; however, these studies utilise ch14.18 monoclonal antibodies that are not considered interchangeable with dinutuximab.

4.9 Meta-analysis

A meta-analysis is not possible at this time owing to the lack of comparable clinical trials.

4.10 Indirect and mixed treatment comparisons

Indirect and mixed treatment comparisons are not possible at this time owing to the lack of comparable clinical trials.

4.11 Non-randomised and non-controlled evidence

4.11.1 In a table, present the list of non-randomised and non-controlled evidence (for example, experimental and observational data) considered relevant to the decision problem and justify including each study.

Table 22 presents non-randomised and non-controlled evidence for dinutuximab.

Table 22. List of relevant non-randomised and non-controlled evidence for dinutuximab

Trial number (acronym) Primary Study Reference	Design	Population	Intervention	Justification for inclusion
ANBL0931 Ozkaynak 2014; ClinicalTrials.gov NCT01041638 ***Population and comparators are directly related to the NICE decision problem***	Single-arm phase 3 open-label safety study	• High-risk neuroblastoma • Achievement of at least a partial response at the time of evaluation before ASCT • Residual disease with absence of disease progression • ASCT performed within 100 days after the initiation of induction therapy • Life expectancy of ≥2 months • Lansky performance status (PS) 50%–100% (for patients ≤16 years of age) or Karnofsky PS 50%–100% (for patients >16 years of age) • Adequate renal, liver, cardiac, pulmonary, and CNS function	• Ch14.18 25 mg/m^2 on days 3–6 of courses 1, 3, and 5 and on days 7–10 of courses 2 and 4 • GM-CSF on days 0–13 of courses 1, 3, and 5 • IL-2 continuously on days 0–3 and on days 7–10 of courses 2 and 4 • Oral isotretinoin twice daily on days 11–24 of course 1, on days 14–27 of courses 2, 4, and 6, and on days 10–23 of courses 3 and 5 Treatment repeats every 24–32 days for 6 courses in the absence of disease progression or unacceptable toxicity	Includes safety data relevant to the NICE decision problem
CCG-A0935A Gilman 2009 ***Population and comparators are directly related to the NICE decision problem***	Single-arm phase 1 dose-finding study	• Diagnosis of neuroblastoma (based on tumour histology or bone marrow metastases and elevated urine catecholamine metabolites) • <21 years old • Recently completed high-dose chemotherapy followed by ASCT • Enrolled within 8 weeks after the total absolute phagocyte count reached more than 1,000/L after high-density chemotherapy/ASCT • Life expectancy ≥2 months • Adequate renal, liver, cardiac, pulmonary, and CNS function	Single-arm dose-finding study Regimen 1 (28-day courses): • Ch14.18 40 mg/m^2 per day for 4 consecutive days on courses 1, 3, and 5 • Ch14.18 20 mg/m^2 per day for 4 consecutive days on courses 2, 4, and 6 • GM-CSF (250 µg/m^2 per day for 14 days during courses 1, 3, and 5) • IL-2 (4.5 MIU/m^2 during courses 2, 4 and 6) Regimen 2 (21-day courses): • Ch14.18 40 mg/m^2 per day for 4 consecutive days on courses 1 and 3 • Ch14.18 20 mg/m^2 per day for 4 consecutive days on course 2 • GM-CSF (250 µg/m^2 per day for 14 days during courses 1, 2, and 3)	Includes safety data relevant to the NICE decision problem

Trial number (acronym) Primary Study Reference	Design	Population	Intervention	Justification for inclusion
			• IL-2 (4.5 MIU/m^2 during course 2) Regimen 3 (28-day courses): • Ch14.18 25 mg/m^2 per day for 4 consecutive days on courses 1, 3, 4, and 5 • GM-CSF (250 µg/m^2 per day for 14 days during courses 1, 3, and 5) • IL-2 (3 MIU/m^2 during courses 2 and 4)	
CCG-0935 Ozkaynak 2000 ***Population and comparators are directly related to the NICE decision problem***	Single-arm phase 1 open-label safety study	• Diagnosed neuroblastoma • <21 years old • Achievement of at least a partial response at the time of evaluation before ASCT • Recent myeloablative therapy followed by ASCT • Life expectancy of ≥2 months • PS of 0, 1, or 2 • Adequate renal, liver, cardiac, pulmonary, and CNS function	• Ch14.18 for 4 consecutive days dosed as 20, 30, 40, or 50 mg/m^2/d • GM-CSF 250 µg/m^2 per day for 4 consecutive days Up to six 4-day courses of therapy	Includes safety data relevant to the NICE decision problem

Key: ASCT – autologous stem cell transplant; CNS – central nervous system; COG – Children's Oncology Group; GD2 – anti-disialoganglioside; GM-CSF – granulocyte-macrophage colony-stimulating factor; IL-2 – interleukin 2; MIU – million international units; m – meters; mg – milligrams; NCI – National Cancer Institute; PK – pharmacokinetic.

4.11.2 If trials listed above have been excluded from further discussion, justification should be provided to ensure that the rationale for doing so is transparent. For example, when studies have been identified but there is no access to the level of data required, this should be stated.

Studies ANBL0931, CCG-0935, and CCG-0935A provide additional safety evidence for dinutuximab that is relevant to the NICE decision problem. The primary objective of study ANBL0931 was to collect safety and efficacy data for dinutuximab. Efficacy measures, 2-year EFS and OS, were collected as secondary outcomes. In the 105 treated patients, the 2-year EFS and OS were 74% ± 6% and 84% ± 5%, respectively. As this study was designed as a single-arm, open-label study with efficacy outcomes collected as a secondary measure, it is discussed along with CCG-0935 and CCG-0935A in section 4.124.12, *Adverse Reactions*.

4.12 Adverse reactions

4.12.1 Evidence from comparative RCTs and regulatory summaries is preferred, but findings from non-comparative trials may sometimes be relevant. For example, post-marketing surveillance data may demonstrate that the technology shows a relative lack of adverse reactions commonly associated with the comparator or that the occurrence of adverse reactions is not statistically significantly different to those associated with other treatments.

Four clinical studies report on the rate of adverse reactions among high-risk neuroblastoma patients treated with dinutuximab (ANBL0032, ANBL0931, CCG-0935 and CCG-0935A). Table 23 presents a tabular summary of adverse reactions reported for dinutuximab in combination with GM-CSF, IL-2, and isotretinoin taken from the dinutuximab SmPC (studies ANBL0032, ANBL0931, and CCG-0935A). Adverse reactions were coded using the Medical Dictionary for Regulatory Activities (MedDRA) system organ class and frequency. Frequency categories are defined as very common (≥1/10), common (≥1/100 to <1/10), and uncommon (≥1/1,000 to <1/100) and are presented in order of decreasing seriousness.

Table 23. Summary of adverse reactions reported for dinutuximab in combination with GM-CSF, IL-2, and isotretinoin in patients with high-risk neuroblastoma (Unituxin [dinutuximab] SmPC 2015)

System organ class	Very common	Common	Uncommon
Infections and	-	Device-related infection,	

System organ class	Very common	Common	Uncommon
infestations		infection susceptibility increased, bacteraemia, enterocolitis	
Blood and lymphatic system disorders	Anaemia	Febrile neutropenia	Atypical haemolytic uraemic syndrome
Immune system disorders	Anaphylactic reaction, hypersensitivity	Cytokine release syndrome	Serum sickness
Endocrine disorders	-	-	Hyperthyroidism
Metabolism and nutrition disorders	Hypokalaemia, hyponatraemia, hypocalcaemia, hypophosphataemia, hypoalbuminaemia hyperglycaemia decreased appetite	Hypomagnesaemia, acidosis, hypoglycaemia,	-
Nervous system disorders	-	Neuralgia, peripheral neuropathy, headache	Posterior reversible encephalopathy syndrome
Eye disorders	-	Vision blurred, photophobia, mydriasis	Unequal pupils
Cardiac disorders	Tachycardia (sinusal, atrial, ventricular)	-	Atrial fibrillation, ventricular arrhythmia
Vascular disorders	Capillary leak syndrome, hypotension, hypertension	-	-
Respiratory, thoracic and mediastinal disorders	Hypoxia, cough, dyspnoea	Bronchospasm, pulmonary oedema	Stridor, laryngeal oedema
Gastrointestinal disorders	Diarrhoea, vomiting, nausea	Constipation, lower gastrointestinal haemorrhage	-
Skin and subcutaneous tissue disorders	Urticaria, pruritus	Maculo-papular rash	-
Renal and urinary disorders	-	Urinary retention, proteinuria, haematuria	Renal failure
General disorders and administration site conditions	Pyrexia, pain,[a] face oedema	Peripheral oedema, chills, fatigue, irritability, injection site reaction	-
Investigations	Decreased platelet count, decreased lymphocyte count, decreased white blood cell count, decreased neutrophil count, increased aspartate aminotransferase, increased alanine aminotransferase	Increased gamma-glutamyltransferase, increased blood creatinine, increased weight	Blood culture positive

[a] Includes preferred terms abdominal pain, abdominal pain upper, arthralgia, back pain, bladder pain, bone pain, chest pain, facial pain, gingival pain, musculoskeletal chest pain, myalgia, neck pain, neuralgia, oropharyngeal pain, pain, pain in extremity, and proctalgia.

4.12.2 In a table, summarise adverse reactions reported in the studies listed in section 4.2. For each intervention group, give the number with the adverse reaction and the frequency, the number in the group, and the percentage with the reaction. Then present the relative risk and risk difference and associated 95% CIs for each adverse reaction.

The study ANBL0032 safety analysis set included all randomised and non-randomised patients exposed to treatment (immunotherapy, n=137; standard therapy, n=108), lending data for a total of 598 courses of immunotherapy. Six patients (1 in the immunotherapy group and 5 in the standard therapy group) initially assigned to therapy were excluded from the safety analysis due to withdrawal of consent (n=4) or absence of any data reported (n=2). Immunotherapy was associated with an increased risk of adverse reactions, notably pain, hypotension, capillary leak syndrome, and hypersensitivity. The observed rate of grade 3 and 4 adverse events by treatment group is presented in Table 24. Toxicities were graded according to the NCI Common Terminology Criteria for Adverse Events version 3.0 (CTCAE v3.0) (Cancer Therapy Evaluation Program 2006). One treatment-related death (a Grade 5 event) was reported during the study due to capillary leak syndrome as a result of an IL-2 overdose. All other adverse reactions were self-limiting and resolved after each course of therapy well before the next course of therapy was to be initiated.

Table 24. Grade 3 and 4 adverse events by treatment group in study ANBL0032 (Yu 2010)

Adverse Event	Immunotherapy (N=137), n (%)	Standard therapy (N=108), n (%)	Absolute Risk Difference	Relative Risk	95% Confidence Interval	
					Low	High
Neuropathic pain[a]	71 (52)	6 (6)	46.3%	9.3	4.2	20.6
Hypotension	24 (18)	0	17.5%	38.6[d]	2.4	628.0
Hypoxia	18 (13)	2 (2)	11.3%	7.1	1.7	29.9
Fever without neutropenia	53 (39)	6 (6)	33.1%	7.0	3.1	15.6
Acute capillary leak syndrome	31 (23)	0	22.6%	49.7[d]	3.1	802.4
Hypersensitivity reaction	34 (25)	1 (1)	23.9%	26.8	3.7	192.7
Urticaria	18 (13)	0	13.1%	29.2[d]	1.8	478.6
Infection, any	54 (39)	24 (22)	17.2%	1.8	1.2	2.7
Infection, catheter-related	18 (13)	7 (7)	6.7%	2.0	0.9	4.7

Adverse Event	Immunotherapy (N=137), n (%)	Standard therapy (N=108), n (%)	Absolute Risk Difference	Relative Risk	95% Confidence Interval	
					Low	High
Nausea	4 (3)	1 (1)	2.0%	3.2	0.4	27.8
Vomiting	8 (6)	3 (3)	3.1%	2.1	0.6	7.7
Diarrhea	18 (13)	1 (1)	12.2%	14.2	1.9	104.6
Hyponatremia	31 (23)	4 (4)	18.9%	6.1	2.2	16.8
Hypokalaemia	48 (35)	2 (2)	33.2%	18.9	4.7	76.1
Abnormal ALT[b]	31 (23)	3 (3)	19.8%	8.1	2.6	25.9
Abnormal AST[b]	14 (10)	0	10.2%	22.9[d]	1.4	378.9
Hypercalcemia	7 (5)	6 (6)	-0.4%	0.9	0.3	2.7
Serum sickness	1 (1)	0	0.7%	2.4[d]	0.1	57.5
Ocular symptoms	0	1 (1)	0.0%	0.8[d]	0.0	19.2
Seizure	1 (1)	1 (1)	-0.2%	0.8	0.0	12.5
Central nervous system cortical symptom[c]	5 (4)	0	3.6%	8.7[d]	0.5	155.1
None	8 (6)	40 (37)	-31.2%	0.2	0.1	0.3

[a] Grade 3 pain defined as pain or severe pain or the use of analgesics that severely interferes with activities of daily living; Grade 4 pain defined as disabling pain.

[b] Grade 3 ALT and AST elevation defined as levels 5 to 20 times the upper limit of the normal range; Grade 4 elevations defined as levels >20 times the upper limit of the normal range.

[c] Includes encephalopathy, confusion, and psychosis.

[d] A value of 0.5 was added to both treatment arms in order to calculate the risk ratio and corresponding confidence interval if zero events were reported.

Key: ALT – alanine aminotransferase; AST – aspartate aminotransferase.

Pain was the most frequently reported Grade 3 or 4 adverse event, reported by 52% of patients, or in 25% of immunotherapy courses; it was most commonly abdominal pain. The frequency of pain was highest in the first course (37%) and decreased over subsequent courses, with 14% of patients reporting Grade 3 or 4 pain in the fifth course (P<0.001 for trend) (Table 25). Capillary leak syndrome was reported by 23% of patients during 8% of immunotherapy courses. Capillary leak syndrome was more commonly observed during courses 2 (11%) and 4 (13%) (corresponding to those involving IL-2) compared to courses 1, 3, and 5 (corresponding to those involving GM-CSF), with rates of 7%, 7%, and 3%, respectively (P=0.06). Grade 3 or 4 hypersensitivity was reported by 25% of patients in 15% of immunotherapy courses. Hypersensitivity was also more frequent in courses involving IL-2 compared to courses involving GM-CSF (P=0.001).

Table 25. Grade 3 and 4 adverse events in the immunotherapy arm by treatment course in study ANBL0032 (Yu 2010)

	Course					
Adverse Event	**1 (n=137)**	**2 (n=127)**	**3 (n=121)**	**4 (n=114)**	**5 (n=107)**	**6 (n=104)**
Pain, n (%)	50 (37)	30 (24)	23 (19)	33 (29)	15 (14)	4 (4)
Hypersensitivity reaction, n (%)	14 (10)	33 (26)	6 (5)	29 (25)	13 (12)	3 (3)
Capillary leak syndrome, n (%)	9 (7)	14 (11)	8 (7)	15 (13)	3 (3)	0

4.12.3 Provide details of any studies that report additional adverse reactions to those reported in section 4.2.

Three additional non-randomised studies provide data for dinutuximab in combination with GM-CSF, IL-2, and isotretinoin and are summarized below.

4.12.3.1 Study methodology

A summary of the methodology for 3 uncontrolled safety studies for dinutuximab for the treatment of high-risk neuroblastoma is presented in Table 26.

Table 26. Summary of methodology of non-randomised safety studies

Trial Number	**ANBL0931**	**CCG-0935A**	**CCG-0935**
Primary Study Reference	Ozkaynak 2014; NCT01041638	Gilman 2009	Ozkaynak 2000
Location	US	US	US
Trial Design	Phase 3, multicentre, prospective, open-label, single-arm safety study	Phase 1, multicentre, prospective, open-label, single-arm safety study	Phase 1, multicentre, prospective, open-label, single-arm safety study
Eligibility Criteria	• High-risk neuroblastoma • Completion of induction therapy, ASCT, and radiotherapy • Achievement of at least partial response at time of evaluation before ASCT • Completed therapy that included intensive induction chemotherapy followed by ASCT and radiotherapy within the past 100 days • Absence of progressive disease • Lansky PS 50%–100% (for patients ≤16 years of age) **or** Karnofsky PS 50%–100% (for patients >16 years of age) • Adequate renal, liver,	• Neuroblastoma (based on tumour histology or bone marrow metastases and elevated urine catecholamine metabolites) • <21 years old • Recently completed high-dose chemotherapy followed by ASCT • Enrolled within 8 weeks after the total absolute phagocyte reached more than 1,000/L after high-density chemotherapy/ ASCT • Life expectancy ≥2 months • Adequate renal, liver, cardiac, pulmonary, and CNS function	• Neuroblastoma • <21 years old • Achievement of at least a partial response at the time of evaluation before ASCT • Recent myeloablative therapy followed by ASCT • A life expectancy of ≥2 months • PS of 0, 1, or 2 • Adequate renal, liver, cardiac, pulmonary, and CNS function

Trial Number	ANBL0931	CCG-0935A	CCG-0935
	cardiac, pulmonary, and CNS function • Life expectancy ≥2 months • No concurrent anticancer therapy, pentoxyfilline, immunosuppressive drugs, cytokines, or growth factors • No prior anti-GD-2 antibody therapy or vaccine therapy for neuroblastoma		
Settings and Locations Where Data Were Collected	The study was carried out in COG participating institutions in the US. Study sites represent a secondary care setting	The study was carried out in COG participating institutions in the US. Study sites represent a secondary care setting	The study was carried out in COG participating institutions in the US. Study sites represent a secondary care setting
Trial Drugs and Concomitant Medications	**Dinutuximab (immunotherapy group n=113)** 6 courses of isotretinoin and 5 concomitant courses of dinutuximab in combination with alternating GM-CSF and IL-2. The immunotherapy group received the following: • Dinutuximab (25 mg/m^2 on days 3–6 of course 1, 3, and 5 and on days 7–10 of courses 2 and 4) • Isotretinoin (twice daily on days 11–24 of course 1, on days 14–27 of course 2, 4, and 6, and on days 10–23 of course 3 and 5 (weight-based dosage: >12 kg: 80 mg/m^2/dose BID; total daily dose 160 mg/m^2/day, divided BID. ≤12 kg: 2.67 mg/kg/dose BID); total daily dose is 5.33 mg/kg/day, divided BID) • GM-CSF (250 µg/m^2 per day for 14 days during courses 1, 3, and 5) • IL-2 (during courses 2 and 4 via continuous infusion on days 0–3 and days 7–10 [dose dependent on body surface and course]) **Standard therapy (n=113)** • Isotretinoin 160 mg/m^2	Regimen 1 (28-day courses): • Dinutuximab 40 mg/m^2 per day for 4 consecutive days on courses 1, 3, and 5 • Dinutuximab 20 mg/m^2 per day for 4 consecutive days on courses 2, 4, and 6 • GM-CSF (250 µg/m^2 per day for 14 days during courses 1, 3, and 5) • IL-2 (4.5 MIU/m^2 during courses 2, 4 and 6) Regimen 2 (21-day courses): • Dinutuximab 40 mg/m^2 per day for 4 consecutive days on courses 1 and 3 • Dinutuximab 20 mg/m^2 per day for 4 consecutive days on course 2 • GM-CSF (250 µg/m^2 per day for 14 days during courses 1, 2, and 3) • IL-2 (4.5 MIU/m^2 during course 2) Regimen 3 (28-day courses): • Dinutuximab 25 mg/m^2 per day for 4 consecutive days on courses 1, 3, 4, and 5 • GM-CSF (250 µg/m^2 per day for 14 days during courses 1, 3, and 5) • IL-2 (3 MIU/m^2 during	• Dinutuximab for 4 consecutive days dosed as 20, 30, 40, or 50 mg/m^2/dose • GM-CSF 250 µg/m^2 per day for 4 consecutive days Up to six 4-day courses of therapy

Trial Number	ANBL0931	CCG-0935A	CCG-0935
	per day divided BID for 14 consecutive days Treatment repeats every 24–32 days for 6 courses in the absence of disease progression or unacceptable toxicity	courses 2 and 4) Trial drugs were modified to include isotretinoin and Dinutuximab dose 40 mg/m^2 per day changed to 25 mg/m^2 per day	
Primary Outcomes	Percentage of patients with Grade 3–5 pain, hypotension, allergic reactions, capillary leak syndrome, or fever	Determine the maximum tolerated dose and toxicity of dinutuximab given in combination with IL-2 soon after high-dose chemotherapy/stem cell rescue	Determine the maximum tolerated dose and toxicity of dinutuximab given in combination with GM-CSF
Secondary Outcomes	EFS, defined as time from enrollment until the first occurrence of relapse, progressive disease, secondary malignancy, death, or until last contact if no event occurred (up to 5 years) OS, defined as time from enrollment until death or until last contact with the patient (up to 5 years)	OS	Progression
Pre-planned Subgroups/Analyses	None	None	None

Key: ASCT – autologous stem cell transplant; BID – twice daily; COG – Children's Oncology Group; GD2 – anti-disialoganglioside; GM-CSF – granulocyte-macrophage colony-stimulating factor; IL-2 – interleukin 2; m – meters; mg – milligrams; OS – overall survival; US – United States.

4.12.3.2 Statistical analysis of the non-randomised and non-controlled evidence

No statistical analyses were undertaken.

4.12.3.3 Baseline characteristics

Baseline characteristics of the participants enrolled in the included non-controlled safety studies are presented in Table 27.

Of 105 participants enrolled in study ANBL0931, 78 completed and 27 did not complete the study. Reasons for attrition were toxicity (n=4), death (n=1), lack of efficacy (n=7), physician decision (n=4), and withdrawal (n=11). One participant did not receive treatment and was excluded from analyses.

Table 27. Characteristics of participants in non-randomized studies

Study (Primary reference)	ANBL0931 (Ozkaynak 2014; NCT01041638)	CCG-0935A (Gilman 2009)	CCG-0935 (Ozkaynak 2000)
Total sample size	105	25	22

Study (Primary reference)	ANBL0931 (Ozkaynak 2014; NCT01041638)	CCG-0935A (Gilman 2009)	CCG-0935 (Ozkaynak 2000)
Age (years), mean (SD)	4.1 (4.0)	NR	NR
Age (years), median (range)	NR	4 (1–14)	4.8 (2–15)
Age, *n*			
≤18 years	103	NR	NR
>18	2	NR	NR
Gender, n			
Female	46	10	6
Male	59	15	13
Race, n			
American Indian or Alaska Native	1	0	NR
Asian	2	2	NR
Native Hawaiian or Other Pacific Islander	0	1	NR
Black or African American	10	1	NR
White	82	20	NR
More than 1 race	0	0	NR
Unknown or not reported	10	0	NR
Ethnicity, n			
Hispanic or Latino	9	2	NR
Not Hispanic or Latino	87	0	NR
Unknown or not reported	9	23	NR
Disease stage at diagnosis			
4	NR	25	NR
Other	NR	0	NR
Measurable disease at study entry			
Yes	NR	16	NR
No	NR	9	NR
Prior radiation			
Yes	NR	20	NR
No	NR	5	NR
Bone marrow metastases at study entry			
Yes	NR	6	NR
No	NR	19	NR

Key: NR – not reported; SD – standard deviation.

4.12.3.4 Quality assessment of the relevant non-randomised and non-controlled evidence

A brief discussion of the quality of ANBL0931, CCG-0935A, and CCG-0935A is presented in the following sections.

4.12.3.5 Describe the methods used for assessing risk of bias of individual studies (including whether this was done at the study or outcome level) and how this information is to be used in any data synthesis.

No methods were employed to assess or remediate risk of bias.

4.12.3.6 If there is more than 1 non-randomised or non-controlled study, tabulate a summary of the responses applied to each of the quality assessment criteria.

A tabular summary for the comparative quality assessment for these 3 studies is presented in Table 28.

Table 28. Quality assessment results for study ANBL0931

Trial Number (Reference)	ANBL0931 (Ozkaynak 2014; NCT01041638)	CCG-0935A (Gilman 2009)	CCG-0935 (Ozkaynak 2000)
Was randomisation carried out appropriately?	N/A*	N/A*	N/A*
Was the concealment of treatment allocation adequate?	N/A*	N/A*	N/A*
Were the groups similar at the outset of the study in terms of prognostic factors?	N/A*	N/A*	N/A*
Were the care providers, participants, and outcome assessors blind to treatment allocation?	No	No	No
Were there any unexpected imbalances in drop-outs between groups?	N/A*	N/A*	N/A*
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Yes	No	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	No	No	No

*Designed as a single arm, open label, non-randomised safety study.

4.12.3.7 Adverse reactions reported in non-controlled studies

In study ANBL0931, a total of 104 participants were analysed for the primary analysis of Grade 3 to 5 non-haematological toxicities of interest (pain, hypotension, allergic reactions, capillary leak syndrome, or fever). The proportion of participants experiencing each adverse event by treatment course is presented in Table 29.

Table 29. Proportion of participants experiencing non-haematological Grade 3 to 5 adverse events by treatment course in study ANBL0931 (ClinicalTrials.gov NCT01041638)

	Course					
Type of Grade 3–5 Adverse Event	**1**	**2**	**3**	**4**	**5**	**6**
Abdominal pain	17%	5 %	6%	4%	6%	0%
Allergic reaction	2%	5%	3%	2%	1%	0%
Anal pain	0%	1%	0%	0%	0%	0%

	Course					
Type of Grade 3–5 Adverse Event	**1**	**2**	**3**	**4**	**5**	**6**
Anaphylaxis	1%	4%	1%	3%	1%	0%
Back pain	5%	5%	3%	3%	5%	0%
Capillary leak syndrome	1%	4%	0%	2%	0%	0%
Chest wall pain	0%	0%	1%	0%	1%	0%
Fever	21%	58%	6%	31%	5%	1%
Flank pain	1%	0%	0%	0%	0%	0%
Hypotension	10%	17%	4%	14%	8%	0%
Neck pain	1%	3%	0%	0%	1%	0%
Non-cardiac chest pain	1%	0%	0%	0%	0%	0%
Pain	23%	16%	13%	20%	11%	1%
Pain in extremity	5%	4%	3%	7%	2%	1%
Peripheral sensory neuropathy	1%	0%	1%	0%	0%	0%

In study CCG-035A, 25 patients were assessed for a total of 23 courses of dinutuximab at a dose of 20 mg/m^2/dose and 60 courses of dinutuximab at a dose of 25 mg/m^2/dose, both dosages in combination with IL-2 (Gilman 2009). The proportion of courses in which a Grade 3 or 4 adverse reaction was reported is presented in Table 30.

Table 30. Proportion of courses with Grade 3 or 4 adverse reaction in study CCG-035A (Gilman 2009)

Adverse Reaction	**Dinutuximab 20 mg/m^2 N=23 Courses, n (%)**	**Dinutuximab 25 mg/m^2 N=60 Courses, n (%)**
Neuropathic pain	7 (35.0)	55 (87.3)
Fever without infection	4 (20.0)	8 (12.7)
Renal		
Low systolic blood pressure	1 (5.0)	10 (15.9)
Low diastolic blood pressure	3 (15.0)	14 (22.2)
Cardiac		
Hypertension	1 (5.0)	2 (3.2)
Hypotension	3 (15.0)	2 (3.2)
Peripheral capillary leak	1 (5.0)	6 (9.5)
Diarrhea	0 (0.0)	1 (1.6)
Nausea	3 (15.0)	13 (20.6)
Vomiting	1 (5.0)	4 (6.3)
Hypoxia	1 (5.0)	3 (4.8)
Central nervous system cortical	2 (10.0)	2 (3.2)
Prolonged prothrombin time	1 (5.0)	4 (6.3)
Hypokalaemia	1 (5.0)	2 (3.2)
Infection	4 (20.0)	2 (3.2)
Decreased performance status	0 (0.0)	3 (4.8)

Adverse Reaction	Dinutuximab 20 mg/m^2 N=23 Courses, n (%)	Dinutuximab 25 mg/m^2 N=60 Courses, n (%)
Leukopenia	5 (25.0)	1 (1.6)
Neutropenia	6 (30.0)	9 (14.3)
Thrombocytopenia	7 (35)	12 (19.0)
Anemia	5 (25)	8 (12.7)
Lymphopenia	1 (5)	16 (25.4)
Elevated		
AST	2 (10)	1 (1.6)
ALT	3 (15)	1 (1.6)
Alkaline phosphatase	1 (5)	0 (0.0)
Bilirubin	2 (10)	0 (0.0)

Key: ALT – alanine aminotransferase; AST – aspartate aminotransferase.

In study CCG-035, 19 patients were included in the final analysis, for a total of 79 courses of dinutuximab in combination GM-CSF (Ozkynak 2000). The proportion of courses an adverse reaction (of any grade) was reported for the first course of therapy and in any course of therapy is presented in Table 31.

Table 31. Proportion of courses with adverse reaction in study CCG-035A (Ozkynak 2000)

	First Course N=19, n (%)	Any Course N=79, n (%)
Neuropathic pain	13 (68)	47 (59)
Fever, no source of infection	7 (37)	36 (46)
Nausea/vomiting	6 (32)	24 (30)
Urticarial eruption	7 (37)	21 (37)
Hypotension	4 (21)	12 (15)
AST/ALT elevations	2 (11)	9 (11)
Capillary leak syndrome	2 (11)	9 (11)
Dilated pupils	0 (0)	6 (8)
Paresthesias	0 (0)	5 (6)
Pulmonary toxicity (dyspnea)	1 (5)	4 (5)
Hyponatremia	0 (0)	4 (5)
Motor weakness	1 (5)	3 (4)
Decline in blood counts[a]	1 (5)	3 (4)
WBC	14 (74)	43 (56)[b]
APC	15 (79)	40 (56)[c]
Platelets (untransfused patients)	6 (86)[d]	44 (85)[e]
Haematocrit	12 (63)	52 (68)[b]

[a] Pre-therapy compared with the last day of therapy of each course.

[b] Out of 77 courses with sufficient data to determine change in WBC count.

[c] Out of 72 courses with sufficient data to determine change in APC.

[d] Out of 7 courses among untransfused patients.

[e] Out of 52 courses among untransfused patients with sufficient data to determine change in platelet count.

Key: ALT – alanine aminotransferase; APC – activated protein C; AST – aspartate aminotransferase; WBC – white blood cell.

4.12.4 *Provide a brief overview of the safety of the technology in relation to the decision problem.*

The most frequently occurring adverse reactions reported in studies of dinutuximab for the treatment of neuroblastoma (occurring in more than 30% of patients) were hypotension (67%), pain (66%), hypersensitivity (56%), pyrexia (53%), urticaria (49%), capillary leak syndrome (45%), anaemia (34%), hypokalaemia (41%), decreased platelet count (40%), hyponatraemia (37%), alanine aminotransferase increased (35%), decreased lymphocyte count (34%), and decreased neutrophil count (31%) (Unituxin [dinutuximab] SmPC). Hypersensitivity reactions were also reported, including anaphylactic reaction (17%) and bronchospasm (4%) (Unituxin [dinutuximab] SmPC).

4.13 Interpretation of clinical effectiveness and safety evidence

4.13.1 *Statement of principal (interim) findings from the clinical evidence highlighting the clinical benefits and harms of the technology*

Dinutuximab in combination with GM-CSF, IL-2, and isotretinoin is associated with improved EFS at 2 years compared to standard therapy consisting of isotretinoin alone (mean ± SE: 66% ± 5% vs 46% ± 5%, respectively, at 2 years; *P*=0.01). The most frequent toxic effects reported in the phase 3 trial in the immunotherapy arm were neuropathic pain (52%), infection (39%), fever without neutropenia (39%), hypokalaemia (35%), hypersensitivity reaction (25%), hyponatremia (23%), abnormal alanine aminotransferase (23%), acute capillary leak syndrome (23%), and hypotension (18%) compared to infection (22%) in the standard-therapy arm (Unituxin [dinutuximab] SmPC 2015). Most adverse reactions were self-limited and resolved after the cessation of treatment (Yu 2010).

4.13.2 *Discussion of the strengths and limitations of the clinical evidence base for the technology.*

The efficacy and safety of immunotherapy (dinutuximab in combination with GM-CSF, IL-2, and isotretinoin) for improving EFS and OS is demonstrated in 1 multicentre, randomised, phase 3 trial and 3 non-randomised safety studies. These studies represent the population and treatments that are relevant to the NICE decision problem and clinically meaningful outcomes to patients (ie, improvements in

survival). The chosen comparator, isotretinoin monotherapy, represents the only treatment used outside of clinical trials for the treatment of people with high-risk neuroblastoma who have received myeloablative therapy and ASCT in the NHS.

The 5-year survival rate for children with high-risk neuroblastoma is about 30% to 50% (ACS 2013). The prevention of relapse in patients with high-risk neuroblastoma with prior myeloablative therapy and ASCT is an important component of treatment. In patients with high-risk neuroblastoma who relapse, 5-year OS is only 8% for children with metastatic neuroblastoma and 4% for patients with MYCN amplification (Moreno 2013). Based on national estimates for the population size and prevalence of neuroblastoma in England and Wales presented in section 3.1.4, the prevalent population eligible for treatment with dinutuximab is expected to be 54 (Table 14). As such, dinutuximab may be considered by the Appraisal Committee as a life-extending treatment at the end of life (Table 32).

Table 32. End-of-life criteria

Criterion	Data Available
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	In participants enrolled in study ANBL0032, approximately 50% of those randomised to standard therapy were alive at 4 years after randomisation (Figure 6). Note that this likely overestimates life expectancy, as participants were required to have ≥2 months of life expectancy at baseline per study inclusion criteria (Table 19)
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	In the interim analysis, Kaplan-Meier estimates for OS at 2 years were 86% for the immunotherapy group and 75% for the standard therapy group; *P*=0.02 (Figure 6). At 4 years, OS was 74% for the immunotherapy group and 59% for the standard therapy group (Figure 8), representing significant extension of life compared to the current standard of care in the NHS
The treatment is licensed or otherwise indicated for small patient populations	The anticipated patient population is small, with 54 patients in England and Wales expected to be eligible for treatment with dinutuximab (Table 14).

Key: NHS – National Health Service; OS – overall survival; UK – United Kingdom.

4.14 Ongoing studies

Study ANBL0032 is ongoing and will provide additional evidence for the long-term impact of immunotherapy on OS and adverse reactions in patients with high-risk neuroblastoma (NCT00026312).

5.0 Cost effectiveness

5.1 Published cost-effectiveness studies

Search strategy

A systematic review of the published research evidence was conducted to inform the design and inputs of the cost-effectiveness model. Searches were undertaken to capture literature relating to costs, resource use, cost-effectiveness, and quality of life for neuroblastoma.

The review was conducted following the general principles published by the Centre for Reviews and Dissemination's (CRD's) guidance for undertaking reviews in health care (CRD guidance).

The following databases of published studies were searched in February 2015: MEDLINE (through PubMed), EMBASE, and the CRD databases of the National Health Service (NHS) Economic Evaluation Database (NHS EED) and the Health Technology Assessment (HTA) database. In addition, bibliographies of retrieved articles were hand-searched for further studies.

The search strategies were initially developed for MEDLINE and were adapted as appropriate for other databases. Details are provided in Appendix 6: Search strategies used for economic evaluation.

Inclusion and exclusion selection criteria, language restrictions, and study selection process

The inclusion and exclusion criteria are shown in Table 33.

Table 33. Inclusion and exclusion criteria

PICOS Category	Description
Inclusion criteria	
Population	Patients with neuroblastoma
Intervention	Due to the limited therapeutic options and studies in neuroblastoma, studies were included regardless of interventions and/or comparators used
Comparators	
Outcomes	Studies were included if they reported one or more of the following outcomes: • Costs reported from the perspective of the UK's NHS/PSS • Resource use (non-UK resource utilization acceptable)

PICOS Category	Description
	• Cost-effectiveness • Quality of life • For costs, resource use, or quality of life, studies reporting these outcomes based on disease health states or for neuroblastoma survivors
Study design	All study types (except those outlined under exclusion criteria)
Language restrictions	English language
Exclusion criteria	
Population	Patients without neuroblastoma No additional exclusion criteria were employed based on sub-population type (eg, high-risk or by age groups)
Intervention	Screening/diagnostic studies not reporting relevant outcomes for the treatment of neuroblastoma
Comparators	
Outcomes	• Screening/diagnostic studies not reporting costs, resource use, or quality of life specific to the treatment of neuroblastoma • Quality of life studies not reporting health utilities
Study design	Case reports, comments, editorials, or letters
Language restrictions	Non-English publications

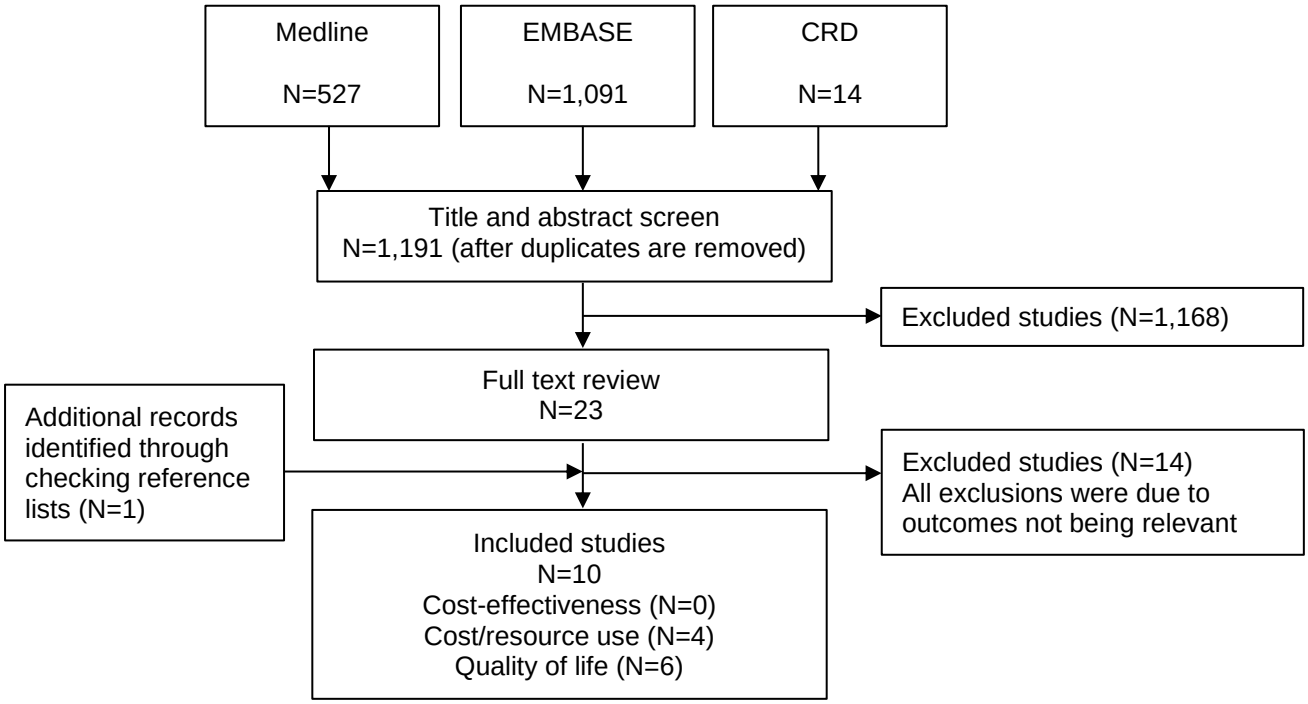
Key: NHS – National Health Service; PICOS – Population Intervention Comparators Outcomes Study; PSS – Personal Social Services; UK – United Kingdom.

All duplicate records were identified and removed. Titles and abstracts were screened independently by 2 reviewers to identify all of the citations that met the inclusion/exclusion criteria in Table 33. Full manuscripts of selected citations were then retrieved and assessed by one reviewer against the inclusion/exclusion criteria and checked independently by a second reviewer. Discrepancies were resolved by consensus. Studies that did not meet the criteria were excluded and their bibliographic details were listed alongside reasons for their exclusion. Reference lists of articles accepted for full text review were also checked for identification of additional relevant studies.

Flow diagram of the numbers of studies included and excluded

The study flow was documented using a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram (Figure 13).

Figure 13. PRISMA diagram for systematic literature review



Key: CRD – Centre for Reviews and Dissemination; PRISMA – Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Search results

The systematic searches did not identify any published studies relating to cost-effectiveness models assessing the course and treatment of neuroblastoma. Several studies assessed economic impact of screening for neuroblastoma (Scriver 1987, Soderstrom 2005, Nishi 1991, Nishi 1998, Sawada 1982, Berthold 1991); however, these were not deemed relevant since disease states and treatment effects were not captured. Four studies were identified as potentially useful to inform costs and resource use for the model. Six studies included health utility information relevant for the model. These 10 studies are discussed in the subsequent sections with respect to the appropriateness to be used for retrieving inputs for the economic evaluation.

5.2 De novo analysis

Patient population

Consistent with the scoping document, anticipated marketing authorization, and the dinutuximab pivotal phase 3 clinical trial (Yu 2010), the economic evaluation includes

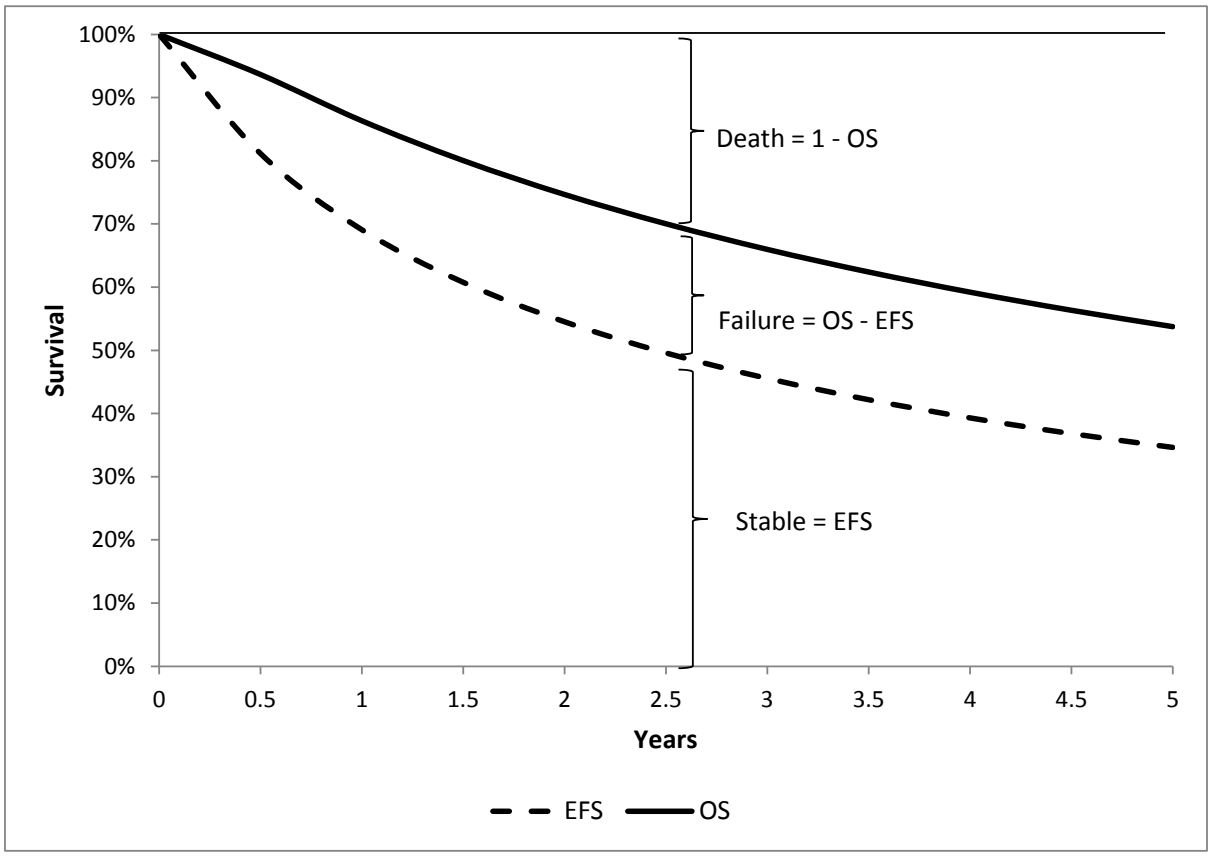
patients aged 12 months to 17 years who have previously received induction chemotherapy and achieved at least a partial response, followed by myeloablative therapy and ASCT.

Model structure

The model was constructed using a partitioned survival approach, a frequently used analytic framework for evaluating oncology therapies. By using parametric curves for relevant outcomes, this method enables ongoing risks that may vary over time to be addressed, as demonstrated by survival data in clinical trials.

The model consists of 3 mutually exclusive states: stable, failure, and death. The stable state represents patients alive without failure, where a failure event is defined as the occurrence of a relapse, progressive disease, or secondary cancer (but not death). Within the first 5 years, the model calculates the proportion of patients in each health state at monthly intervals with half-cycle correction using parametric survival curves fitted to data on OS and EFS over time (Figure 14). The proportion of patients in the stable state at any given time is calculated based on EFS, and the proportion of patients in the failure state is calculated as the difference between OS and EFS. The remaining proportion represents the death state (ie, 1-OS).The aforementioned health states, determined based on OS and EFS, capture key outcomes reflecting the health status and associated consequences in the target population and are therefore deemed appropriate for the evaluation.

Figure 14. Partitioned survival model



Key: EFS – event-free survival; OS – overall survival

After 5 years, the event-free cohort is assumed to be cured and enters a phase when they are considered survivors and start to follow similar characteristics (ie, mortality, quality of life, relapse rates) to that of the general population, while still accounting for potential morbidities affecting quality of life and resource use among neuroblastoma survivors (Portwine 2014, Rebholz 2011). This structure was considered based on the following:

- According to the COG, a relapse (if any) usually occurs within the first 2 years after the end of treatment and the likelihood continues to decline as more and more time passes after treatment is complete, and relapses occurring more than 5 years after the completion of therapy are rare (COG neuroblastoma website).
    - This was confirmed by two UK clinical experts, who had stated that if patients did not experience a relapse event within approximately 5 years after the start of a treatment, they would typically be considered

cured (with a slight possibility for a late relapse). This was consistent with information provided by other UK clinical experts that had been consulted.

  - Experts were selected based on their experience treating patients with high-risk neuroblastoma in the NHS. Five experts were approached and 2 provided clinical feedback. The information provided was related to long-term survival of patients with high-risk neuroblastoma treated with immunotherapy, and the evidence provided was consistent with what appears in this submission. Clinical opinions were obtained via direct in-person interviews and telephone interviews. While follow-up sessions were held to gain additional clarification, an iterative methodology was not used. Neither advisor reports a conflict of interest. A sample of the questions advisors were asked can be found in Appendix 5: Sample clinical advisor questions.

- Supplementary long-term data outside the dinutuximab pivotal phase 3 clinical trial (Yu 2010) matching the same characteristics of the Yu 2010 cohorts are limited. However, despite some excess morbidity, OS and EFS appear to reach a plateau between 5 and 10 years in recent long-term studies (Cheung 2012, Kubota 2010, Matthay 2009, Perwein 2011, Simon 2011).

After 5 years, the following were considered:

- Patients in the stable state follow general population mortality rates (instead of using parametric survival curves).

- Patients in the stable state observe the same HRQOL as the general population, with a reduction for neuroblastoma survivors suggested by the literature. Additionally, they continue with the resource use consumption specific to neuroblastoma survivors.

- No further failure events are observed; however, patients already in the failure state follow mortality rates that apply to the recurrent/relapsed population and continue with costs and HRQOL associated with the failure state.

The features of the de novo analysis are presented in Table 34.

Table 34. Features of the de novo analysis

Factor	Chosen values	Justification
Time horizon	Lifetime	The technology being evaluated (ie, immunotherapy) is expected to lead to differences in OS and EFS that persist for the remainder of the patient's lifetime
Were health effects measured in QALYs; if not, what was used?	QALYs	QALYs are appropriate to capture the key disease outcomes (OS and EFS) and the expected benefit with immunotherapy in terms of these outcomes
Discount of 3.5% for utilities and costs	3.5% for utilities and costs	Reference case as recommended by NICE (Guide to methods of TA)
Perspective	NHS/PSS	Reference case as recommended by NICE (Guide to methods of TA)

Key: EFS – event-free survival; NHS – National Health Service; OS – overall survival; PSS – Personal Social Services; QALY – quality-adjusted life-year; TA – technology appraisal.

Intervention technology and comparators

The model evaluates clinical and economic outcomes with the use of immunotherapy (consisting of dinutuximab, GM-CSF, IL-2, and isotretinoin) compared to standard therapy (isotretinoin). Isotretinoin was chosen as the appropriate comparator consistent with the final scope issued by NICE and, historically, isotretinoin has been considered the standard of care for maintenance therapy of high-risk neuroblastoma after demonstrating improved survival following high-dose chemotherapy and ASCT (Matthay 1999).

The treatment regimen details implemented in the model over the cycle of 6 courses (ie, 6 months) for immunotherapy and standard therapy are consistent with the final scope, anticipated marketing authorization, and the pivotal phase 3 clinical (Yu 2010). Please refer to Section 2.3.1 for regimen details.

5.3 Clinical parameters and variables

Survival parameters

Individual patient data from the dinutuximab pivotal phase 3 clinical trial (Yu 2010) were fit to parametric OS and EFS curves using StataMP 13 to identify the number of patients in each health state (as described in section 5.2) within the first 5 years of the model. As the model was constructed using a partitioned survival approach, the number of patients in each health state at each model cycle was calculated directly based on predicted EFS and OS rather than using transition probabilities during this time frame (section 5.2).

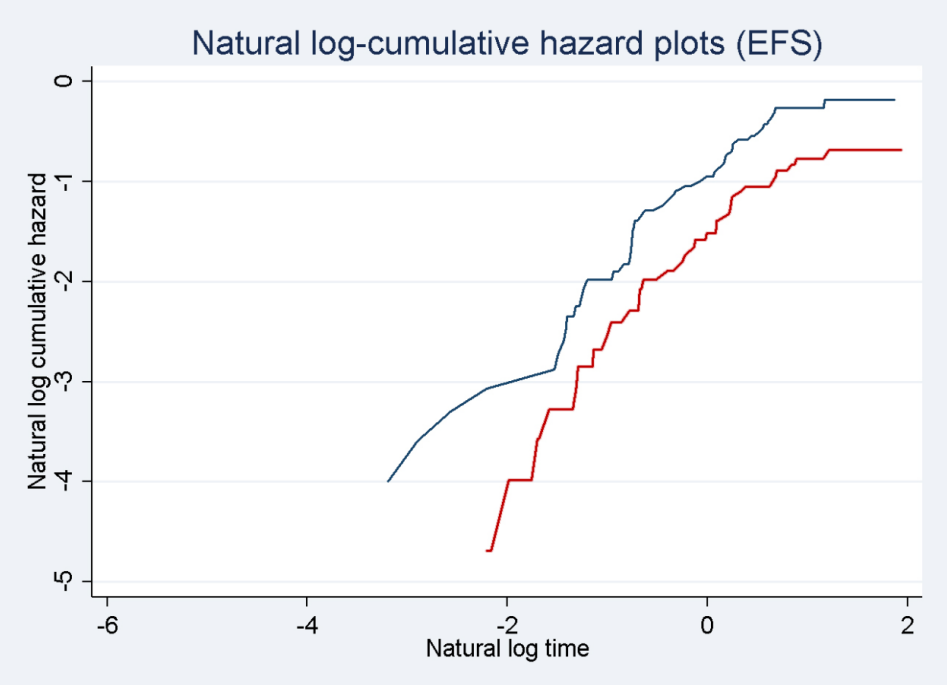
Per-patient QALYs, as the final outcome, for each treatment arm were calculated based on health state-specific utilities and the number of patients in each health state over the model time horizon.

A multi-step approach was taken to identify the most appropriate parametric model types as explained below:

1. Investigation of log-cumulative hazard plots

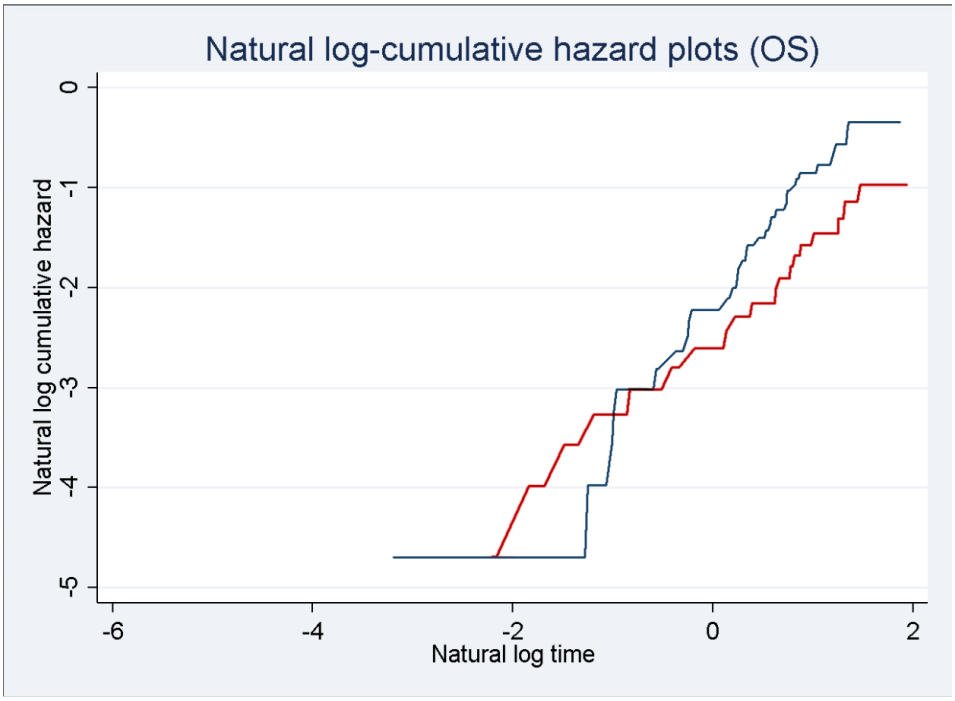
   The log-cumulative hazard plots were generated for EFS and OS for immunotherapy and standard therapy arms (Figure 15, Figure 16).

Figure 15. Log-cumulative hazard plot for EFS



Key: EFS – event-free survival. Blue line = standard therapy. Red line = immunotherapy. Time reported in years.

Figure 16. Log-cumulative hazard plot for OS



Key: OS – overall survival. Blue line = standard therapy. Red line = immunotherapy. Time reported in years.

2. Assessment of suitability of single parametric model use and proportional hazards assumption

   Since the plots were approximately straight and parallel, the use of a single type of parametric model with proportional hazards assumption was deemed appropriate for both EFS and OS. For OS, use of separate parametric functions for immunotherapy and standard therapy were tested in sensitivity analysis due to the shape of the plots before approximately 4.5 months (LN(4.5/12)~-1).

3. Visual inspection of different parametric models compared to observed data

   The individual patient data were fit to exponential, Weibull, Gompertz, log-logistic, and lognormal parametric models. The coefficients for these models along with Akaike's information criterion (AIC) and Bayesian information criterion (BIC) statistics are provided in Table 35 and Table 36.

Table 35. Coefficients for different parametric function fits for EFS

	Treatment[a]	Constant	Third Coefficient[b]	AIC Statistic	BIC Statistic
Exponential (PH model)	-0.6121	-0.6730	N/A	502	509
Weibull (PH model)	-0.5806	-0.5208	0.7785	496	506
Gompertz (PH model)	-0.5520	-0.0882	-0.5535	476	487
Log-logistic (AFT model)	0.7939	0.0449	1.0430	487	497
Lognormal (AFT model)	0.7849	0.1127	1.8010	481	491

Key: AFT – accelerated failure time; AIC – Akaike's information criterion; BIC – Bayesian information criterion; EFS – event-free survival; N/A – not applicable; PH – proportional hazards.

[a] 1, standard therapy; 2,immunotherapy

[b] Exponential: no third coefficient, Weibull: ρ (rho), Gompertz: ɣ (gamma), log-logistic: ɣ (gamma), lognormal: σ (sigma)

Table 36. Coefficients for different parametric function fits for OS

	Treatment[a]	Constant	Third coefficient[b]	AIC statistic	BIC statistic
Exponential (PH model)	-0.6547	-1.2861	N/A	319	326
Weibull (PH model)	-0.6652	-1.3590	1.0823	320	331
Gompertz (PH model)	-0.6517	-1.2643	-0.0156	321	331
Log-logistic (AFT model)	0.6195	0.9634	0.8210	320	330
Lognormal (AFT model)	0.5754	1.1851	1.6077	322	332

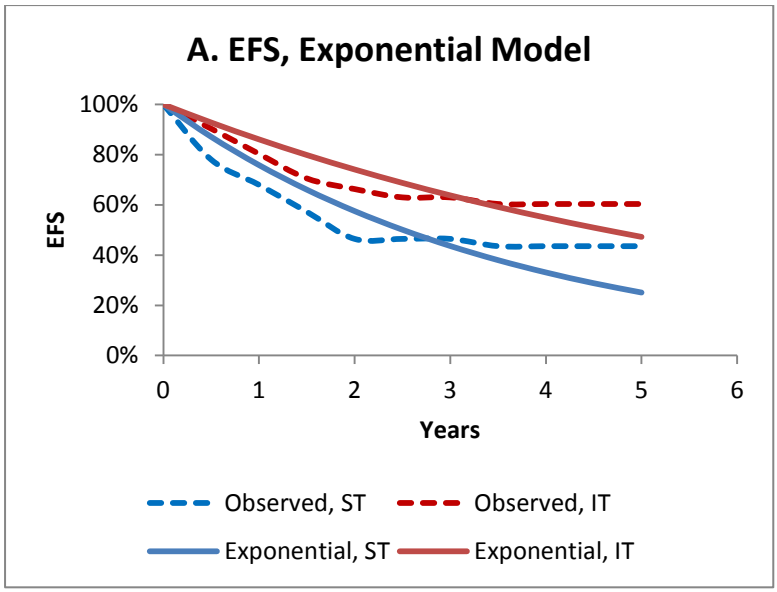
Key: AFT – accelerated failure time; AIC – Akaike's information criterion; BIC – Bayesian information criterion; N/A – not applicable; OS – overall survival; PH – proportional hazards.

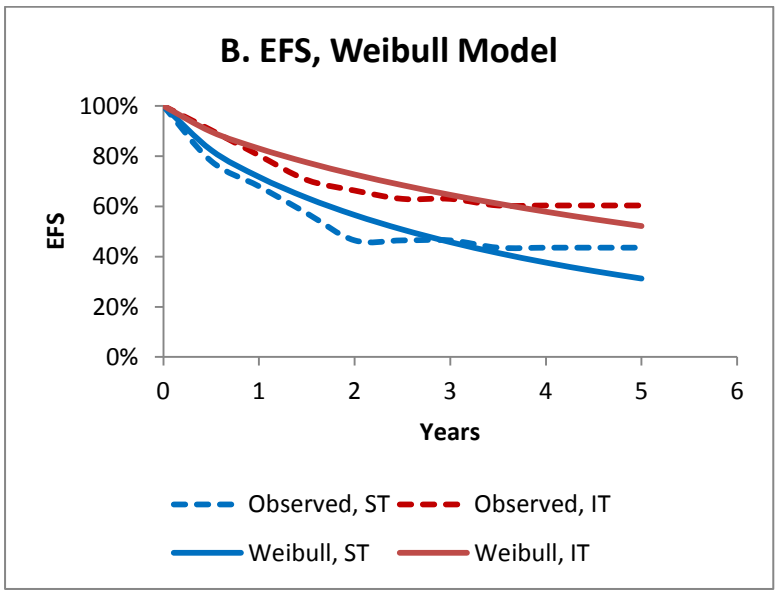
[a] 1, standard therapy; 2,immunotherapy

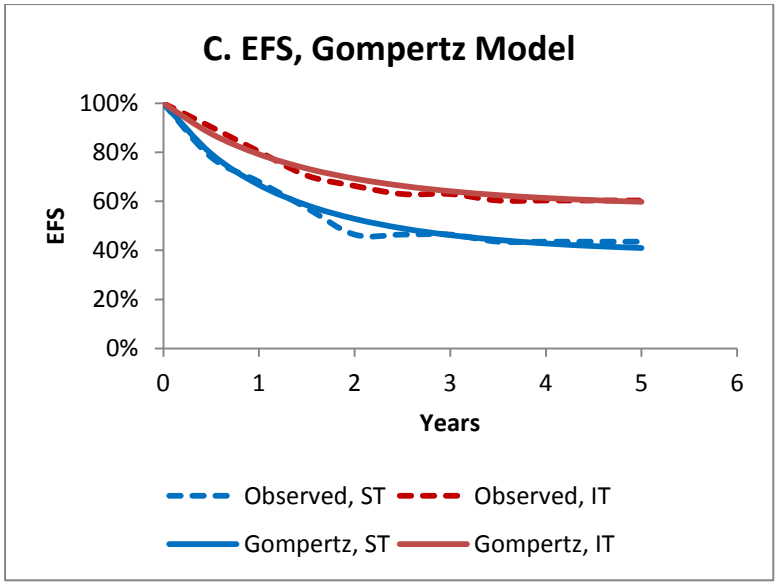
[b] Exponential: no third coefficient, Weibull: ρ (rho), Gompertz: ɣ (gamma), log-logistic: ɣ (gamma), lognormal: σ (sigma)

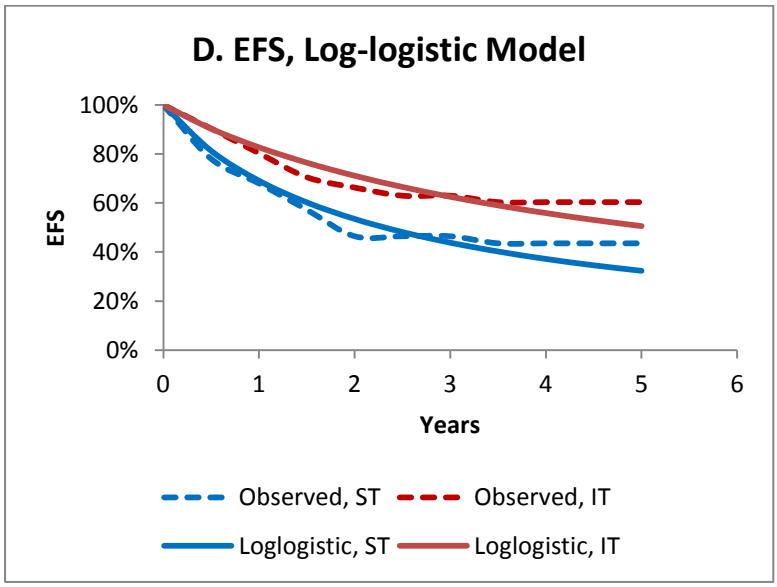
As shown in Figure 17, the Gompertz model provided a better visual fit for the EFS data. This was supported by the AIC and BIC statistics (Table 35).

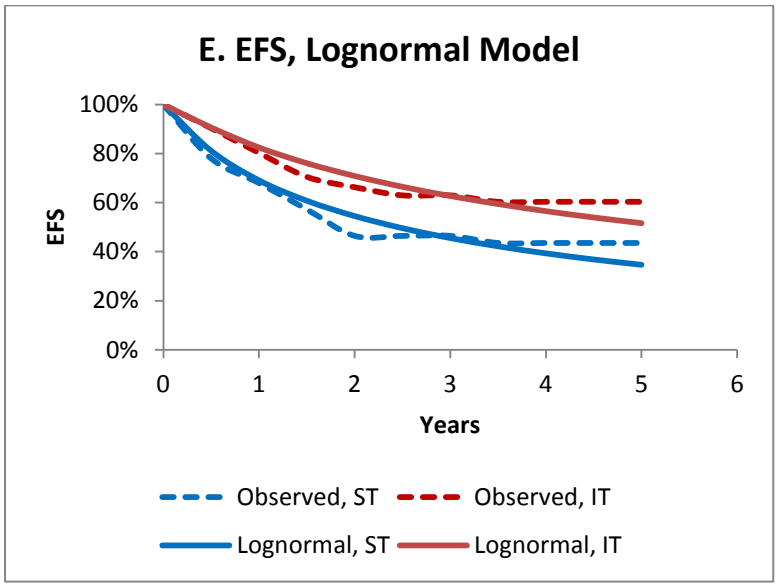
Figure 17. EFS parametric fits vs observed data






C. EFS, Gompertz Model
100%
80%
60%
40%
20%
0%
EFS
0
1
2
3
4
5
6
Years
Observed, ST
Observed, IT
Gompertz, ST
Gompertz, IT

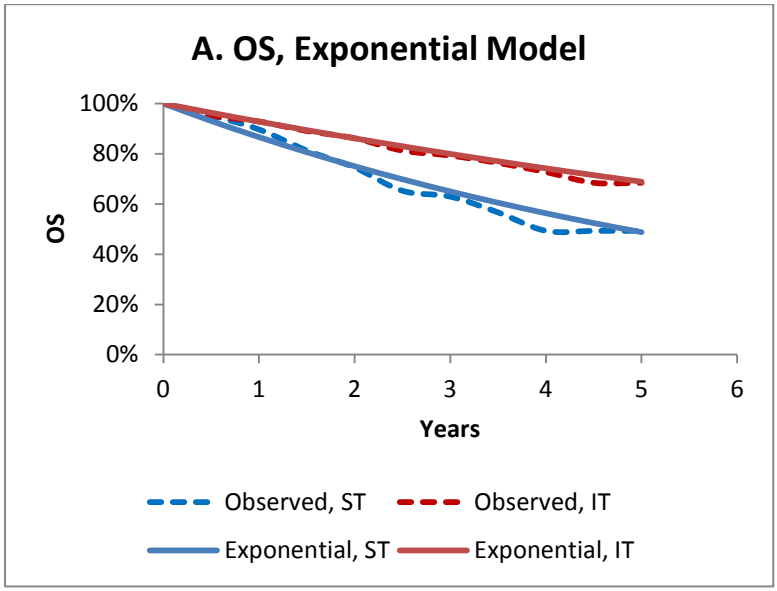

D. EFS, Log-logistic Model
100%
80%
60%
40%
20%
0%
EFS
0
1
2
3
4
5
6
Years
Observed, ST
Observed, IT
Loglogistic, ST
Loglogistic, IT

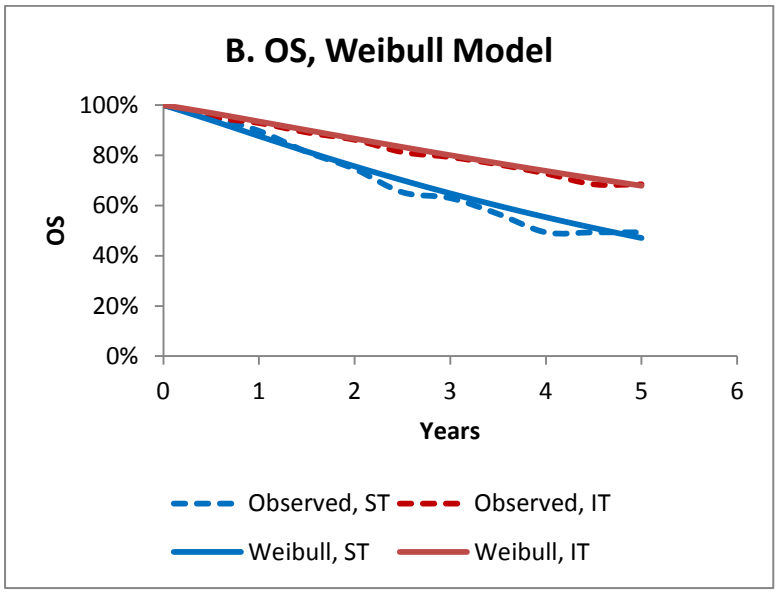

E. EFS, Lognormal Model
100%
80%
60%
40%
20%
0%
EFS
0
1
2
3
4
5
6
Years
Observed, ST
Observed, IT
Lognormal, ST
Lognormal, IT

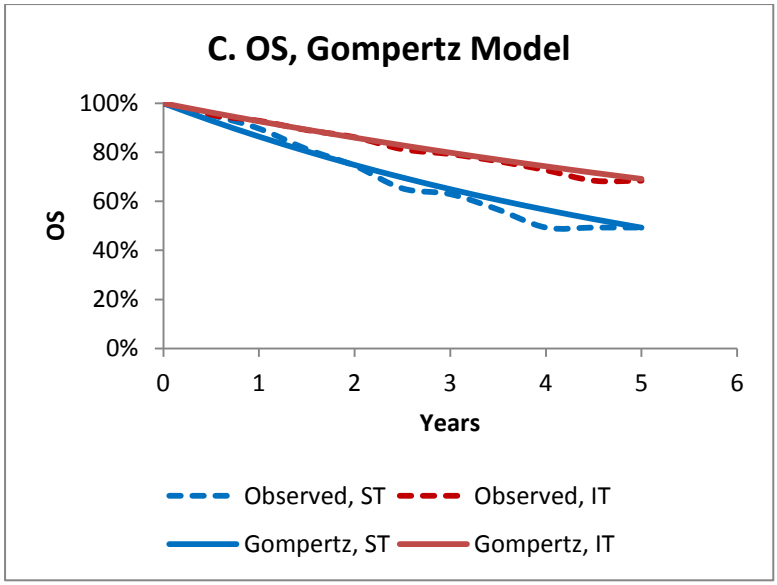
Key: EFS – event-free survival; IT – immunotherapy; ST – standard therapy.

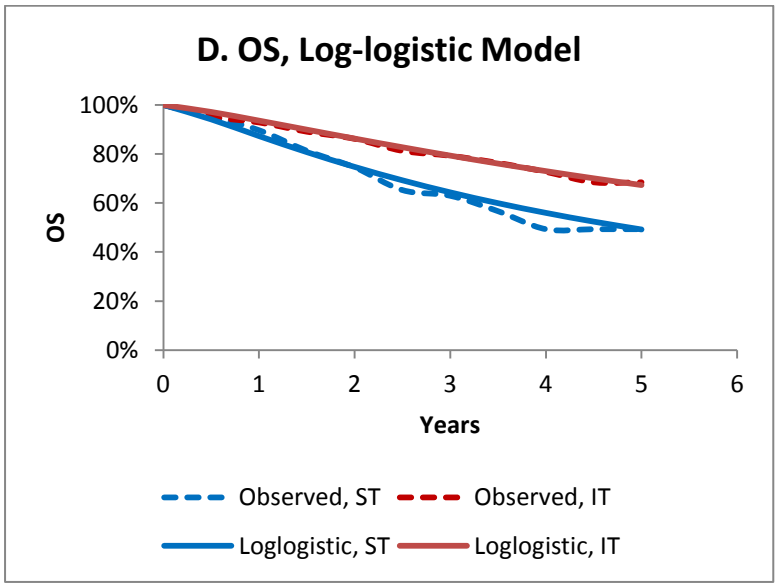
As shown in Figure 18 and Table 36, all functions investigated provided similar visual and statistical fits for the OS data, with the exponential model resulting in the best statistical fit.

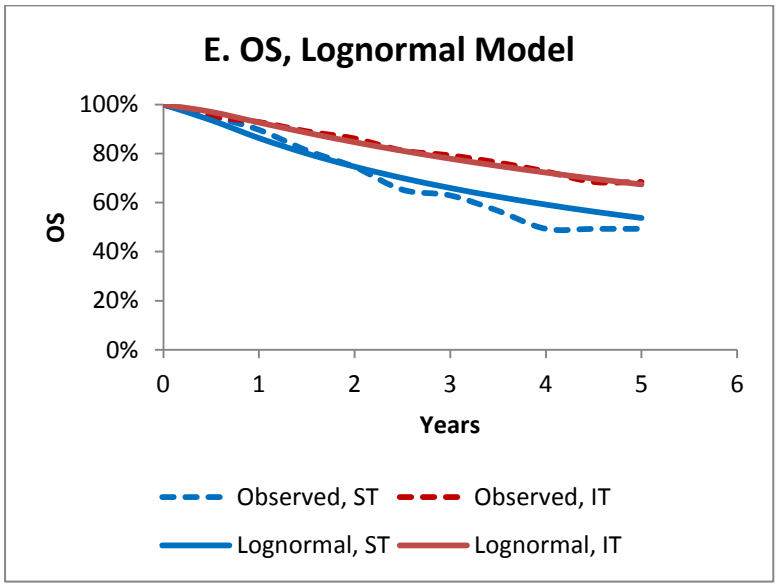
Figure 18. OS parametric fits vs observed data






C. OS, Gompertz Model
100%
80%
60%
40%
20%
0%
OS
0
1
2
3
4
5
6
Years
Observed, ST
Observed, IT
Gompertz, ST
Gompertz, IT


D. OS, Log-logistic Model
100%
80%
60%
40%
20%
0%
OS
0
1
2
3
4
5
6
Years
Observed, ST
Observed, IT
Loglogistic, ST
Loglogistic, IT


E. OS, Lognormal Model
100%
80%
60%
40%
20%
0%
OS
0
1
2
3
4
5
6
Years
Observed, ST
Observed, IT
Lognormal, ST
Lognormal, IT

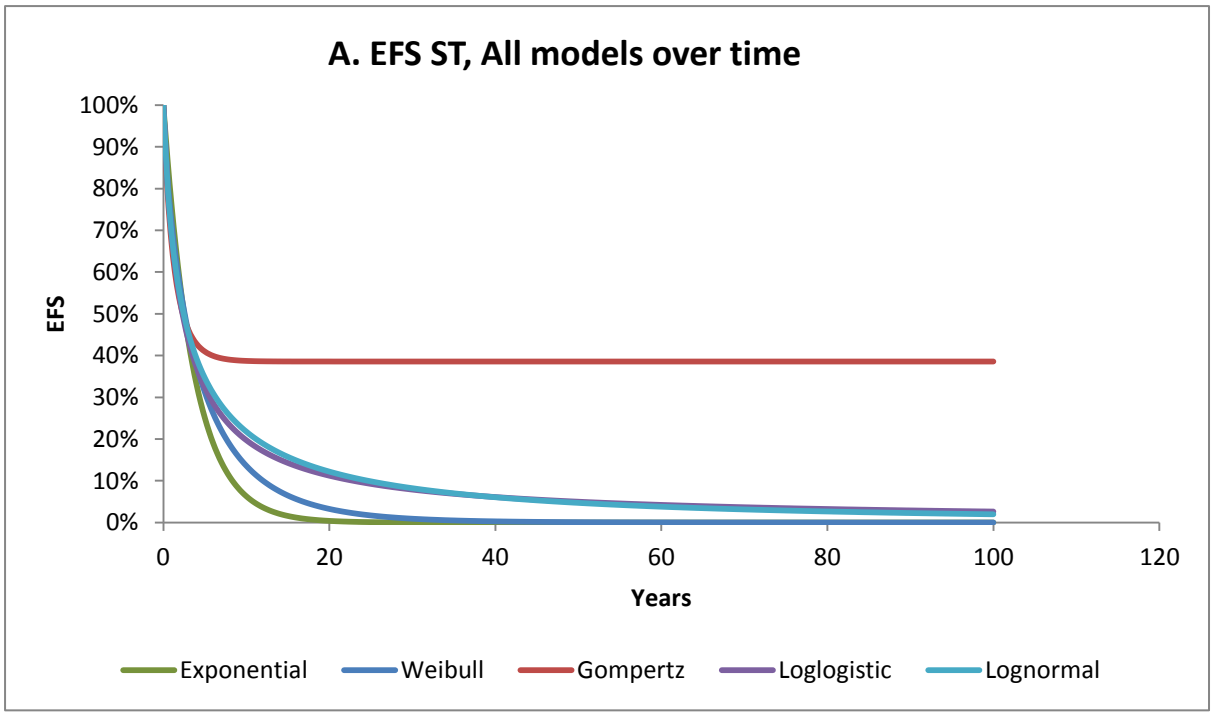
Key: IT – immunotherapy; OS – overall survival; ST – standard therapy.

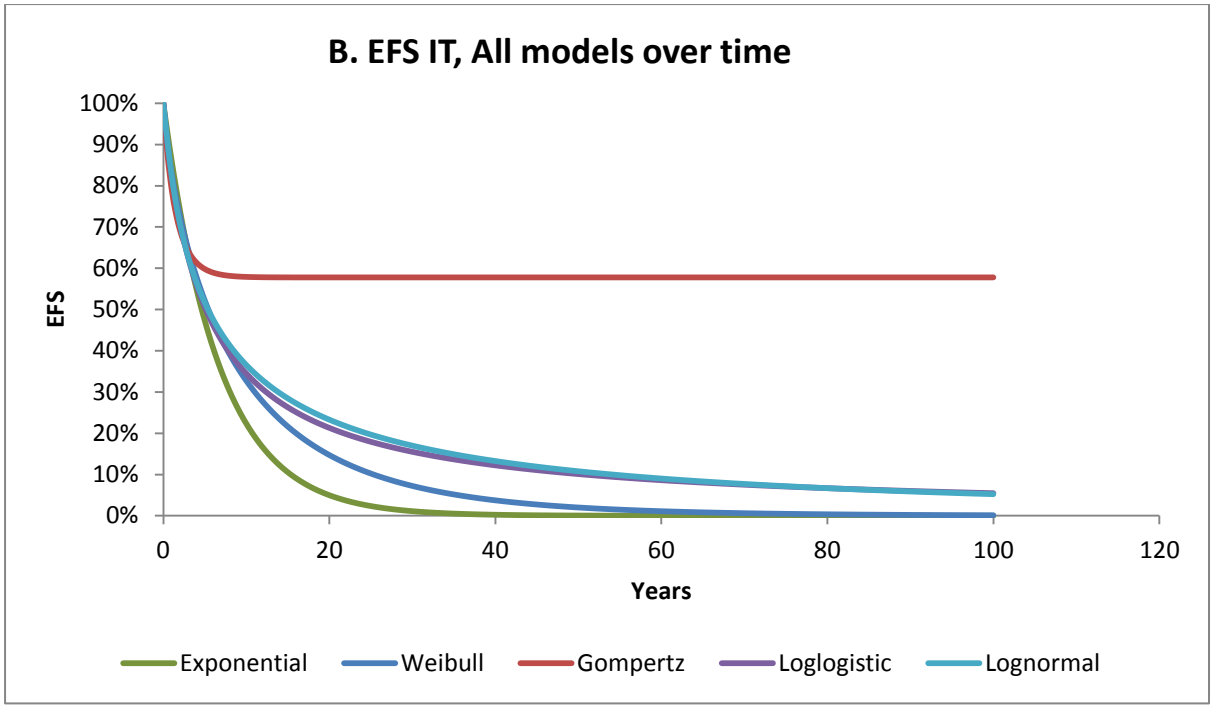
4. Consideration of extrapolation beyond trial period

a. Visual inspection of curves extended beyond trial period

The EFS models generally displayed a similar decline until 3 years: beyond that, the exponential and Weibull curves declined steeply followed by log-logistic and lognormal models. The Gompertz curve on the other hand, reached a plateau beyond year 3, which is consistent with the “curing” effect discussed in the **Model structure** section (section 5.2) (Figure 19).

Figure 19. Parametric function estimates beyond trial period for EFS

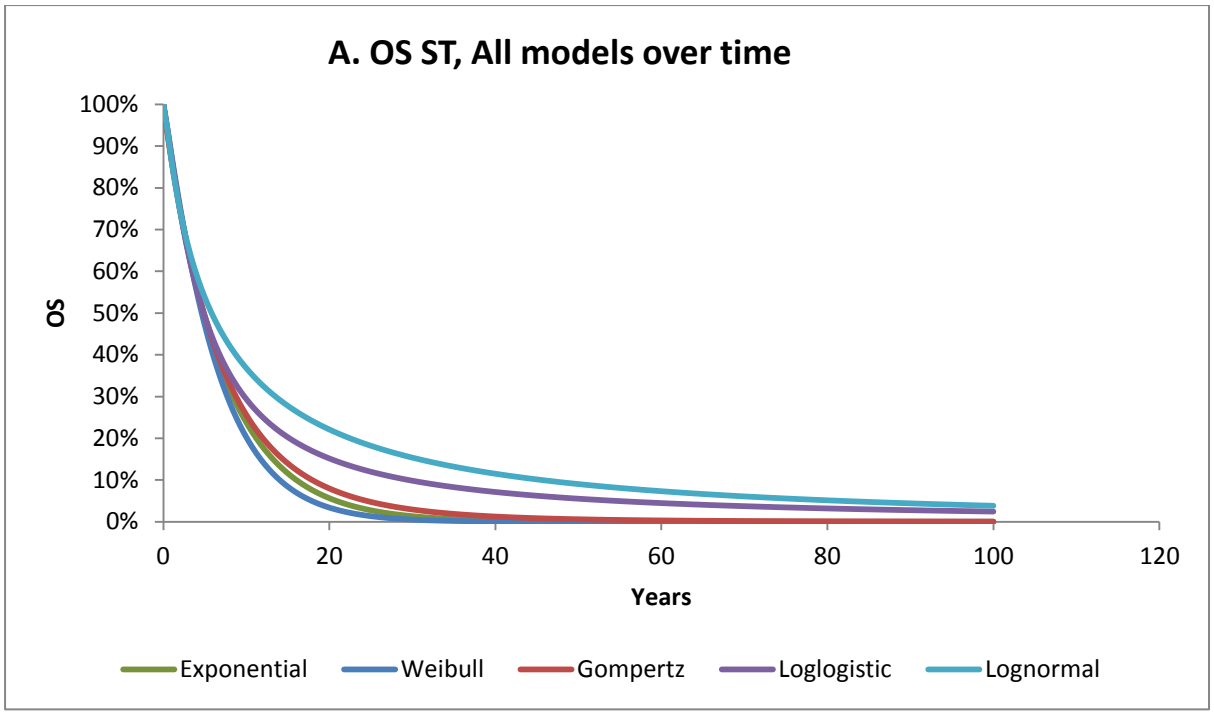


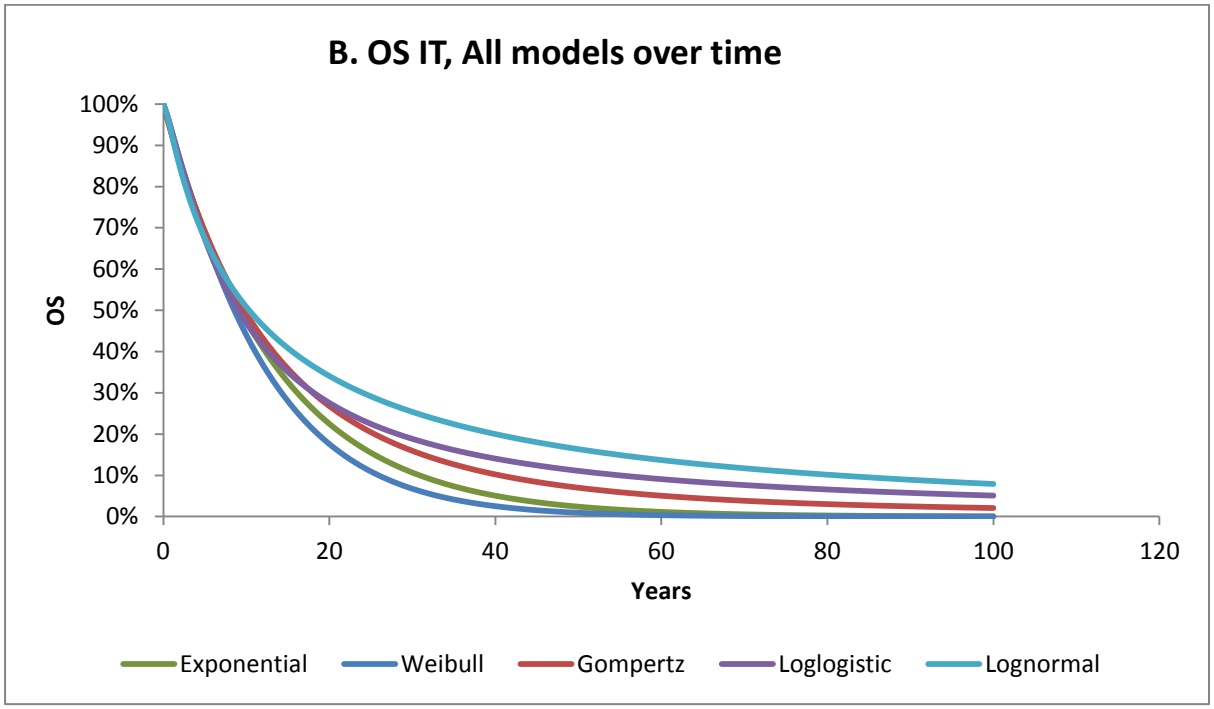


Key: EFS – event-free survival; IT – immunotherapy; ST – standard therapy.

The visual inpection of the extrapolated OS curves revealed that the exponential, Weibull, and Gompertz models present a generally steeper decline within the first 40 years, therefore potentially underestimating the OS beyond the trial period (Figure 20). Although higher than the other models, the OS was also somewhat low with log-logistic and lognormal models after 5 years given the “curing” effect discussed in the **Model structure** section (section 5.2). Additionally, log-logistic and log-normal models appear to overestimate survival towards the curve ends, as up to 10% of the population are observed to be alive around very late age segments.

Figure 20. Parametric function estimates beyond trial period for OS





Key: OS – overall survival; IT – immunotherapy; ST – standard therapy.

b. External data

Identifying external data for extrapolation of survival beyond the trial presented a challenge due to the rarity of the disease and the fact that immunotherapy or standard therapy with isotretinoin has not been studied (at

all or for extended time periods) for the population of interest[1] outside the dinutuximab pivotal phase 3 clinical trial. Two studies were identified as potentially relevant:

Matthay 2009: In this study, patients with high-risk neuroblastoma received the same induction chemotherapy, with random assignment to consolidation with myeloablative chemotherapy, total-body irradiation, and autologous purged bone marrow transplantation (ABMT) vs 3 cycles of intensive chemotherapy. Patients who completed consolidation without disease progression were randomly assigned to receive no further therapy or isotretinoin for 6 months. While this design had similarities with the isotretinoin arm of the dinutuximab pivotal phase 3 clinical trial (Yu 2010), the follow-up time was relatively short[2] for long-term extrapolation purposes and a plateau effect was observed between 6 and 8 years[3]. Five-year survival figures from Yu 2010, Matthay 2009, and parametric models are provided in Table 37. Parametric EFS model predictions were lower compared to clinical trials (Yu 2010, Matthay 2009), whereas OS predictions were generally close to the observed dinutuximab pivotal phase 3 clinical trial data (Yu 2010) but lower than that reported by Matthay et al (Matthay 2009).

Table 37. Five-year survival from Yu 2010, Matthay 2009 and parametric models (standard therapy arm)

	EFS	OS
Yu 2010 (observed data)	43.5%	49.3%
Matthay 2009[a] (observed data)	50.0%	59.0%
Exponential[b]	25.1%	48.8%
Weibull[b]	31.2%	47.0%
Gompertz[b]	41.0%	49.3%
Log-logistic[b]	32.3%	49.2%
Lognormal[b]	34.6%	53.7%

Key: ABMT – autologous purged bone marrow transplantation; EFS – event-free survival; OS – overall survival.

[a] Figure 4, ABMT with isotretinoin arm in Matthay 2009. Sample size was 50.

[b] 5-year predictions from parametric models.

[1] Patients aged 12 months to 17 years who have previously received induction chemotherapy and achieved at least a partial response, followed by myeloablative therapy and ASCT

[2] The median follow-up time of patients alive without an event was 7.7 years.

[3] Figure 4, ABMT with isotretinoin arm in Matthay 2009. Sample size was 50.

Simon 2011: In this study, high-risk neuroblastoma patients who successfully completed induction therapy were assigned to receive monoclonal anti-GD2-antibody (MAB) ch14.18 consolidation therapy in 6 cycles over 12 months. The information from this study was not deemed relevant or helpful to inform long-term extrapolation due to the following reasons: (1) the immunotherapy regimen was different than that studied in Yu 2010[4] and (2) survival data were presented since diagnosis, not from the start of consolidation therapy.

c. Expert opinion

As discussed in the **Model structure** section, information from the COG (COG neuroblastoma website), clinical expertise, and some published data (Cheung 2012, Kubota 2010, Matthay 2009, Perwein 2011, Simon 2011) suggest that patients who are event-free within approximately 5 years after treatment can typically be considered cured.

5. Choice of final parametric models and additional considerations

Given the evidence around the "curing effect" as discussed previously and the inability of the extrapolated EFS and OS curves to address this effect as well as issues regarding underestimating/overestimating the OS beyond the trial period, the model was structured so that survival was modelled based on curves providing the best fit to the trial data (EFS: Gompertz and OS: exponential) within the first 5 years, and assuming that after 5 years, the event-free cohort is cured and enters a phase when they are considered survivors and start to follow similar characteristics (ie, mortality, quality of life, relapse rates) to that of the general population (while still accounting for potential morbidities affecting quality of life and resource use among neuroblastoma survivors).

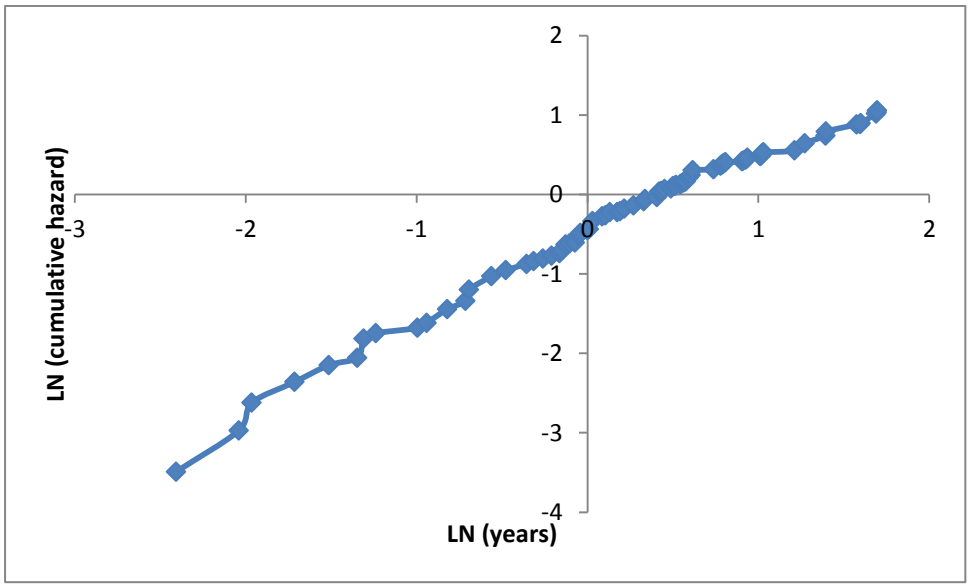
Despite the efforts to identify the parametric models that match the trial period closely, as well as provide a reasonable extrapolation beyond the trial period,

[4] The regimen consisted of an infusion of ch14.18 over 8-12 hours on five subsequent days. This cycle was repeated every 2 months for a total of six cycles.

selection of the optimal approach presents challenges due to data availability. Thus, structural sensitivity analyses were incorporated into the model so that different parametric models for OS and EFS could be selected until the "curing" point and different time points could be considered for when the "cure effect" started to apply. Details on these analyses are provided in the **Sensitivity analysis** section (Section 5.8).

In order to determine the deaths in the stable state after 5 years, UK life tables were used (ONS) (Office of National Statistics). The monthly probability of death for patients in the failure state was taken as 5.1%. This was calculated assuming an exponential survival function and using 3-year OS (1-EXP(LN(0.15)/(3*12))) from a study of children with recurrent or refractory neuroblastoma (Figure 21) (London 2010). Please refer to the **Health-state unit costs and resource use** section for the rationale for selecting this study.

Figure 21. Log-cumulative hazard plot of overall survival (London 2010)[a]



[a] Survival graph from the publication (London 2010) was scanned to obtain data points

Adverse events

Monthly rates of adverse events were calculated based on follow-up time until 6 cycles (immunotherapy: 612 months; standard therapy: 626 months) and the number of patients with Grade 3/4 events (Yu 2010). Resulting rates are shown in Table 38.

Table 38. Monthly adverse event rates

Event	Immunotherapy	Standard Therapy
Neuropathic pain	0.1160	0.0096
Hypoxia	0.0294	0.0032
Fever without neutropenia	0.0866	0.0096
Acute capillary leak syndrome	0.0506	0.0000
Hypersensitivity reaction	0.0555	0.0016
Urticaria	0.0294	0.0000
Infection	0.1176	0.0495
Nausea	0.0065	0.0016
Vomiting	0.0131	0.0048
Diarrhea	0.0294	0.0016
Hyponatremia	0.0506	0.0064
Hypokalaemia	0.0784	0.0032
Abnormal ALT/AST	0.0735	0.0048
CNS cortical symptom	0.0082	0.0000

Key: ALT – alanine transaminase; AST – aspartate transaminase; CNS – central nervous system.

5.4 Measurement and valuation of health effects

The health effects were expressed in QALYs.

Health-related quality of life data from clinical trials and mapping

HRQOL was not collected or assessed in the dinutuximab pivotal phase 3 clinical trial (Yu 2010), as the majority of the children treated were too young for an appropriate quality of life metric.

Health-related quality of life studies

The systematic search details for identifying HRQOL data for the cost-effectiveness model are provided in section 5.1. Consistent with the model structure (section 5.2), the search aimed to identify studies that reported health-state specific health utilities or health utilities for the survivors of neuroblastoma.

None of the studies identified by the systematic search reported health state-specific utilities for patients with neuroblastoma. The majority of the neuroblastoma studies addressed HRQOL among survivors of neuroblastoma, typically corresponding to a patient population alive around at least 5 years after the diagnosis of the disease. There was only 1 study (Barr 1999) that was identified through screening reference lists of the full text articles (appeared in the reference list of 4 articles out of 10

HRQOL articles identified as potentially relevant for full text review). Barr et al measured HRQOL in survivors of tumours of the central nervous system (CNS) in childhood in a cross-sectional study (Barr 1999). Portwine et al reported better HRQOL among advanced neuroblastoma survivors (0.86) than survivors of brain tumours (0.81) (Portwine 2014). Hence, the estimates from the Barr 1999 study may be an underestimate of the health status of the neuroblastoma patients. However, given the lack of health state-specific utility data for neuroblastoma, the estimates from this study were used to inform the cost-effectiveness model inputs. Study details are provided in Table 39.

Table 39. Details of the HRQOL study used to inform health-state specific utilities (Barr 1999)

	Study Detail
Population	Children who had completed therapy for tumours of the CNS and who were attending the neuro-oncology follow-up clinic in the Children's Hospital at Chedoke-McMaster (Hamilton, Ontario, Canada) during the interval from February 1993 to February 1995
Information on recruitment	A 15-item self-administered questionnaire was completed with respect to each child independently by the nurse, a parent, 1 of 4 physicians and, when possible, by the child
Intervention/comparator	N/A; patients already completed therapy
Sample size	41
Health states	The status of disease at the time of study was categorized as “none evident,” “residual,” or “recurrent”
Appropriateness of health states	The disease states are consistent with those captured in this de novo cost-effectiveness analysis
Method of elicitation and valuation	Information from the questionnaires was converted to health status classification system attribute levels of the HUI mark 2 (HUI2) and HUI mark 3 (HUI3)
Consistency with reference case	The study (Barr 1999) does not reflect health utilities based on EQ-5D as recommended by the reference case. However, given the lack of EQ-5D data[a] for the population in question, the findings from Barr 1999 were deemed appropriate to be used
Appropriateness for cost-effectiveness analysis	Although the population studied by Barr et all did not include neuroblastoma patients, it had several similarities with the population considered in this cost-effectiveness analysis • Paediatric patients had suffered from cancer • Patients completed therapy • Similar health states were studied (residual disease and recurrent disease) Given the lack of data specific to the neuroblastoma population, the findings from Barr 1999 were deemed appropriate to be used
Results by health state: HUI2 (mean, standard deviation)	None evident (0.89, 0.13) Residual (0.81, 0.19) Recurrent (0.56, 0.41)

Key: CNS – central nervous system; EQ-5D – European Quality of Life-5 Dimensions; HUI – health utilities index; N/A – not applicable.

	Study Detail

[a] Mapping was not carried out due to lack of access to patient-level data from Barr 1999.

The characteristics of studies that reported health utility data for neuroblastoma survivors (to be used after 5 years for patients in the stable state) are summarized in Table 40 (Alessi 2007, Barr 2000, Grant 2006, Portwine 2014, Shimoda 2008). None of the health utilities reported were based on the EQ-5D. The information from Portwine 2014 was selected to be most appropriate for the cost-effectiveness model for the following reasons:

- The study had the largest sample size
- The population was more consistent with that investigated in the dinutuximab phase 3 clinical trial (Yu 2010) in that advanced neuroblastoma patients who underwent intensive chemotherapy followed by myeloablative therapy with ASCT were studied
- The study provided a comparison of HRQOL between the neuroblastoma population and the general population

Table 40. Details of the neuroblastoma survivor studies reporting health utility

	Alessi 2007	Barr 2000	Grant 2006	Portwine 2014	Shimoda 2008
Population	5-year survivors (>15 years old), identified from the population-based Childhood Cancer Registry of Piedmont	Survivors of advanced neuroblastoma not receiving treatment and not in a relapse state who were treated in the Children's Hospital at Chedoke-McMaster in Hamilton and the Hospital for Sick Children in Toronto over a decade were considered suitable	Adolescent survivors of cancer in childhood who were younger than 15 years of age at diagnosis, whose management was undertaken at the McMaster Children's Hospital of the Hamilton Health Sciences Corporation, and who were 15–19 years of age in April 2002	Survivors of AN who underwent intensive chemotherapy followed by myeloablative therapy with ASCT	Survivors were eligible for the study if they had been diagnosed with cancer at less than 19 years of age, presented for an annual check-up at the GEPETTO clinic, were cancer-free, were literate in Brazilian Portuguese, and were 13 years of age or older
Country	Italy	Canada	Canada	Canada	Brazil
Time since diagnosis	At least 5 years (see Table 1 in article)	At least 5 years on average (see Table 1 in article)	At least 5 years on average (see Table 1 in article)	Unclear from abstract	Survivors who were at least 8 years beyond the end of active treatment
Information on recruitment	15-item HUI questionnaire (mailed) was completed by	One parent of each child was asked to complete a	A standard HUI self-complete questionnaire for self-assessed	Parents of survivors completed a proxy HUI	Health status measurements were collected using a Brazilian

	Alessi 2007	Barr 2000	Grant 2006	Portwine 2014	Shimoda 2008
	survivors	questionnaire, and children who had achieved at least a grade 3 education were asked to complete a similar questionnaire	"usual" health status was completed by each patient	questionnaire, scored on a scale of 0.00 to 1.00	Portuguese HUI questionnaire
Sample size[a]	35	26	5 (neuroblastoma) 84 (overall)	99	2 (neuroblastoma) 138 (overall)
Method of elicitation and valuation	HUI3	HUI2 and HUI3	HUI2 and HUI3	HUI	HUI2 and HUI3
Results (mean, standard deviation)	0.75 (0.1-1.0)[b]	HUI2 (0.90,0.13) HUI3 (0.87, 0.19)	Not reported separately for neuroblastoma patients	AN (0.84, 0.18) General population (0.96)[c]	Not reported separately for neuroblastoma patients

Key: AN – advanced neuroblastoma; HUI – health utilities index.

[a] Neuroblastoma patients unless otherwise indicated.

[b] 25th percentile and range.

[c] Standard deviation not reported for general population.

Adverse reactions

The dinutuximab phase 3 clinical trial and the HRQOL articles identified from the systematic review did not reveal any information with respect to the effects of adverse reactions on HRQOL. However, clinical experts have indicated that patients typically experience severe negative effects (eg, pain) with intravenous (IV) infusions of dinutuximab and IL-2 and that a patient's health utility could be considered to approach 0 while product is being administered.

Health-related quality of life data used in cost-effectiveness analysis

Patients in the stable state before 5 years experience a health utility of 0.810. This value is based on the residual health state utility reported by Barr et al (Barr 1999). Patients in the more disabled state of failure experience a lower health utility of 0.560, corresponding to the recurrent health state estimate reported by Barr et al (Barr 1999).

Based on expert opinion,[5] the worsening in HRQOL due to adverse events associated with immunotherapy is not permanent and only affects the patient while

[5] Experts were selected based on their experience treating patients with high-risk neuroblastoma in the NHS. Five experts were approached and 2 provided clinical feedback. The information provided was related to long-term survival of patients with high-risk neuroblastoma treated with immunotherapy, and the evidence provided was consistent with what appears in this submission. Clinical opinions were obtained via direct in-person interviews and telephone interviews. While follow-up sessions

dinutuximab and IL-2 are actively infused via IV. Therefore, the decrement to HRQOL attributed to adverse events associated with immunotherapy administration is captured within the first 5 cycles of the model while patients are receiving immunotherapy through IV infusion. As such, during cycles 1, 2, 3, 4, and 5, a health utility of 0 is applied to the immunotherapy cohort for a duration of 4, 8, 4, 8, and 4 days (consistent with the IV dosing schedule), respectively. It should be noted that assuming a utility of 0 is likely to be a conservative approach since the utility decrement due to dinutuximab and IL-2 administration has not been quantified in previous studies. Moreover, the pain that may be largely responsible for the utility decrement is expected to decrease after subsequent courses and can be managed with pain medication.

After 5 years, patients in the failure state still experience a health utility of 0.560 (Barr 1999); however, patients in the stable state follow general population health utilities predicted based on age and gender (Ara 2010):

EQ-5D = 0.9508566 + 0.0212126*male - 0.0002587*age - 0.0000332*age^2

Patients start the model in the stable state at the age of 4 and 60% of the patients are males (dinutuximab pivotal phase 3 clinical trial baseline characteristics) (Yu 2010). After 5 years, a reduction of 13% to the general population health utility estimates is applied to account for potential morbidities among neuroblastoma survivors (Portwine 2014). This was calculated based on the estimates for the neuroblastoma survivor population and the general population ((0.96-0.84)/0.96=13%) (Portwine 2014). At year 5 in the model (ie, when age is 9 years old), the general population estimates and the reduction applied leads to a health utility of 0.83, a value similar to that reported in Barr, et al (0.81) (Barr 1999). The health utility in the model then declines as the population ages.

The summary of health utility values used in the de novo analysis is provided in Table 41.

Table 41. Summary of utility values for cost-effectiveness analysis

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were held to gain additional clarification, an iterative methodology was not used. Neither advisor reports a conflict of interest. A sample of the questions advisors were asked can be found in Appendix 5.

State	Utility Value: Mean (Standard Error)	95% CI (Calculated)	Reference in Submission and Justification
Stable (Barr 1999)	0.810 (0.060[b])	0.692, 0.928	Section 5.4 (page)
Failure (Barr 1999)	0.560 (0.237[c])	0.096, 1.024	Section 5.4 (page)
Death	0	N/A	N/A
IV infusion of dinutuximab or IL-2[a] (expert opinion)	0	N/A	Section 5.4 (page)
% reduction in health utility due to neuroblastoma (compared to general population after 5 years)[d] (Portwine 2014)	13% (1.33%)[e]	0.104, 0.156	Section 5.4 (page)

Key: CI – confidence interval; IV – intravenous; N/A – not applicable; SQRT – square root.

[a] Applies to patients in the stable state while receiving IV infusion (for duration of 4, 8, 4, 8, and 4 days in cycles 1, 2, 3, 4, and 5, respectively).

[b] Calculated as 0.19/SQRT(10) based on Barr 1999.

[c] Calculated as 0.41/SQRT(3) based on Barr 1999.

[d] Applies after 5 years.

[e] Mean calculated as (0.96-0.84)/0.96. Standard error calculated assuming 95% CI half-width represents 20% of the mean given the lack of standard deviation/error estimate in the publication.

5.5 Cost and healthcare resource use identification, measurement, and valuation

Resource identification, measurement, and valuation studies

The systematic search details for identifying cost and/or resource use data for the cost-effectiveness model are provided in section 5.1. Four studies were identified as potentially useful to inform costs and resource use for the model. Details including reason for using or not using the outcomes from each study in the cost-effectiveness model are included in Table 42.

Table 42. Details of the neuroblastoma studies reporting costs and/or resource use

	Bagatell 2014 (poster)	Casillas 2011	Rebholz 2011	Soderstrom 2005
Population	Dinutuximab pivotal phase 3 clinical trial population (Yu 2010)	Adult survivors of childhood cancer	Long-term survivors of childhood cancer	Patients from the Quebec Neuroblastoma Screening Project
Country	United States	United States	United Kingdom	Canada
Date of study	2014	2011	2011	2005
Applicability to clinical practice in England	Possibly	Possibly	Yes	Possibly
Cost valuations or resource use reported in the	Hospital days, % receiving intensive care, intensive care	% of patients with cancer-related visits, cancer centre visits,	The following percentages were reported for “at least	The units of resources and costs avoided for particular types of

	Bagatell 2014 (poster)	Casillas 2011	Rebholz 2011	Soderstrom 2005
study	days, and drug utilization were reported	general physical exams, dental exams, breast exams, and pap smear tests were reported	once vs never" and "more than once vs once": • Talked to a doctor in the last 2 weeks • Attended hospital outpatient department in the last 3 months • Hospitalized as a day patient • Hospitalized as an inpatient	diagnosis, treatment, and follow-up services used were reported
Technology costs	Costs were not reported. Resource utilization for 2 study arms (Yu 2010) was reported	Costs were not reported. Resource use specific to the technology was not reported	Costs were not reported. Resource use specific to the technology was not reported	Resource use specific to the technology was not reported
Costs for use in the economic analysis	While the population and study is very relevant, the resource use was reported for a period of approximately 6 months and cannot be separated based on health states	The outcomes from this study were not deemed appropriate for the economic analysis as: • Data were not reported for neuroblastoma patients separately • Detailed resource use information were not reported to support model inputs	Resource utilization data from this study combined with UK-specific unit costs can be used in the economic analysis for patients in the stable state	The outcomes from this study were not deemed appropriate for the economic analysis since detailed resource use information and health state-specific data were not reported to support model inputs

Given the available information, the data from Rebholz 2011 were deemed most appropriate to be used in the economic model (Table 43). Since the specifics regarding what percentage of the population consisted of high-risk patients were not provided, sensitivity analyses were conducted around parameter estimates from this study.

Table 43. Resource utilization reported by Rebholz 2011

	% of Patients Using Resource	
	At Least Once vs Never	More Than Once Vs Once
Talked to a doctor in the last 2 weeks	14.2%	24.1%
Attended hospital outpatient department in the last 3 months	24.1%	33.3%
Hospitalized as a day patient (no overnight stay) in the last year	11.8%	38.8%
Hospitalized as an inpatient (overnight stay) in the last year	9.6%	35.0%

Other cost and resource-related data used in the model, including unit costs, are described in subsequent sections.

Intervention and comparators' costs and resource use

Patients follow the treatment regimens shown in Table 44 during the first 6 cycles of the model. Drug and administration cost details are provided in Table 45 and Table 46, respectively.

Table 44. Treatment regimens

	Agent	Route	Dose/Day	Time/ Administration	Courses Administered	Duration/ Cycle (Days)
Standard therapy	Isotretinoin	Oral	160 mg/m^2	-	1, 2, 3, 4, 5, 6	14
Immunotherapy	Isotretinoin	Oral	160 mg/m^2	-	1, 2, 3, 4, 5, 6	14
	Dinutuximab	IV infusion	17.5 mg/m^2	10–20 hours	1, 2, 3, 4, 5	4
	GM-CSF	SC or IV	250 mcg/m^2	-	1, 3, 5	14
	IL-2	IV infusion	3.0 x10 MIU/m^2	96 hours Week 1	2, 4	4
	IL-2	IV infusion	4.5 x10 MIU/m^2	96 hours Week 2	2, 4	4

Key: GM-CSF – granulocyte macrophage colony-stimulating factor; IL-2 – interleukin-2; MIU – million international units; IV – intravenous; SC – subcutaneous.

For determining appropriate dosing, the average body surface area was taken as 0.65 (average at baseline in the dinutuximab pivotal phase 3 clinical trial) (Yu 2010). Unit drug costs were obtained from the British National Formulary (BNF) (available through MedicinesComplete), except for dinutuximab and GM-CSF. Per-vial dinutuximab and GM-CSF costs were taken as £6,390.00 and £162.35,[6] respectively. Total drug costs for all model cycles were estimated as £135,404.38 and £337.68 (£56.28 x 6) for immunotherapy and standard therapy, respectively (Table 45).

[6] Currently, GM-CSF is not approved for marketing authorization by the EMA for any indication. . The US price ($248.39 converted to GBP using an exchange rate of 0.653632 on April 28, 2015). 250 mcg/ml, 1-ml vial cost of Leukine (Sargramostin). Variations on the conversion explored in the sensitivity analysis

Table 45. Drug costs

Model Cycle Number	Agent	Units	Cost/Vial or Tablet (£)	Vials/ Tablets Used	Cost/ Model Cycle (£)	Explanation
Immunotherapy						
1	Isotretinoin	20 mg tablet	0.67 (20.02/30)	84	56.28	0.65 m^2 x 160 mg/m^2 = 104 mg/day ~ 6 cycles x 14 20 mg tablets/cycle
	Dinutuximab	17.5 mg vial	6,390.00	4	25,560.00	0.65 m^2 x 17.5 mg/m^2 x 4 vials = 46 mg ~1x4 vials/cycle
	GM-CSF	250 mcg vial	162.35	14	2,272.90	0.65 m^2 x250 mcg/m^2 = 162.5 mcg/day ~1x14 vials/cycle
	TOTAL				27,889.18	
2	Isotretinoin	20 mg tablet	0.67 (20.02/30)	84	56.28	0.65 m^2 x 160 mg/m^2 = 104 mg/day ~ 6 cycles x 14 20 mg tablets/cycle
	Dinutuximab	17.5 mg vial	6,390.00	4	25,560.00	0.65 m^2 x 17.5 mg/m^2 x 4 vials = 46 mg ~1x4 vials/cycle
	IL-2	18x10^6 vial	112.00	2	224	0.65 m^2 x 3 MIU/m^2/day x 4 days = 7.8 units ~1 vial/cycle 0.65 m^2 x 4.5 MIU/m^2/day x 4 days = 11.7 units ~1 vial/cycle
	TOTAL				25,840.28	
3	TOTAL				27,889.18	Same as cycle 1
4	TOTAL				25,840.28	Same as cycle 2
5	TOTAL				27,889.18	Same as cycle 1
6	TOTAL				56.28	Isotretinoin cost only
All model cycles	TOTAL				135,404.38	
Standard therapy						
Each model cycle (1–6)	Isotretinoin	20 mg tablet	0.67 (20.02/30)	84	56.28	0.65 m^2 x 160 mg/m^2 = 104 mg/day ~ 6 cycles x 14 20 mg tablets/cycle
All model cycles	TOTAL				337.68	

Key: GM-CSF – granulocyte macrophage colony-stimulating factor; IL-2 – interleukin-2.

Table 46. Administration costs

Model Cycle Number	Agent	Administration Cost per Cycle (£)	Explanation
Immunotherapy			
1	Isotretinoin	0.00	Oral
	Dinutuximab	1,908.00	Source: NHS Reference Costs 2013–2014 Service code: IP, service description: inpatient, currency code: SB10Z, currency description: procure chemotherapy drugs for regimens in Band 10
	GM-CSF	14.25 x 10 = 142.50	Source: PSSRU 2014, Rogers 2012 Assumed 75% self-administered, 25% administered by nurse (Rogers 2012) Administration cost by the nurse based on PSSRU 2014 (10.1 Community nurse [includes district nursing sister, district nurse]). Assumes 1 hour of nurse time at £57 Resulting weighted average cost = £14.25/injection Applied for 10 days in the cycle, since 4 days of GM-CSF overlap with dinutuximab administration
	TOTAL	2,050.50	
2	Isotretinoin	0.00	Oral
	Dinutuximab[a]	1,908.00	Source: NHS Reference Costs 2013–2014 Service code: IP, service description: inpatient, currency code: SB10Z, currency description: procure chemotherapy drugs for regimens in Band 10
	IL-2[b]	1,908.00	
	TOTAL	3,816.00	
3	TOTAL	2,050.50	Same as cycle 1
4	TOTAL	3,816.00	Same as cycle 2
5	TOTAL	2,050.50	Same as cycle 1
6	TOTAL	0.00	Isotretinoin administration only
Standard therapy			
Each model cycle (1–6)	Isotretinoin	0	Oral

Key: GM-CSF – granulocyte macrophage colony-stimulating factor; IL-2– interleukin-2; PSSRU – Personal Social Services Research Unit.

[a] Second dose of IL-2 administered on the same days as dinutuximab, therefore the maximum cost of administration (for IL-2 and dinutuximab) is considered during this administration period.

[b] For first dose of IL-2.

In addition to the technology and administration costs, concomitant medication and monitoring costs indicated by the EMA label were also considered (Table 47). Note that costs for management of adverse events (eg, pain) were addressed separately (please see **Adverse reaction unit costs and resource use** section), and the concomitant medications and monitoring requirements reflect costs associated with preventive purposes.

Table 47. Concomitant medication and monitoring costs

Model Cycle Number	Concomitant Medication Costs per Cycle (£)	Monitoring Costs per Cycle (£)	Explanation
Immunotherapy			
1	34.00	12.00	Concomitant medications Sodium chloride 9 mg/mL to prevent hypotension. One litre bag assumed to be used on days when dinutuximab is administered. Cost per 1 litre sodium chloride: £0.80 (BNF) Paracetamol to prevent pain. 240 mg/day (BNF, ages 4–6) on days when dinutuximab is administered. Daily cost 0.66/100*240*5/120=£0.07 (BNF, oral suspension) Morphine to prevent pain. 100 mcg/kg every 4 hours (BNF, ages 6 months–12 years) on days when dinutuximab is administered, resulting in a daily dose of approximately 100*17.7*(24/4)/1000= 10.62 mg; assumed one 50 mL vial (1 mg/mL) per day at a cost of £5.25 (BNF) Lidocaine to prevent pain. 2 mg/kg over 30 minutes prior to dinutuximab infusion, continued at 1 mg/kg/hour up to 2 hours after treatment completion (approximately 17 hours), resulting in ~340 mg/day (average patient weight: 17.7) on days when dinutuximab is used (dosing per EMA label). Cost per day is £0.85, based on one 20 mL amp of injection 2% (BNF) Gabapentin to prevent pain. Oral dose of 10 mg/kg/day, administered with morphine (EMA label), resulting in approximately 17.7*10=177 mg/day. Cost per day is £1.53 (57.5/150*4, BNF) All treatments applied for 4 days/cycle when dinutuximab is administered (0.8[sodium chloride] + 0.07[paracetamol]+ 5.25[morphine] + 1.53[gabapentin] + 0.85[lidocaine])*4=£34.00 Monitoring One liver function test prior to each dinutuximab administration at a cost of £3 per test (NHS reference costs 2013/2014, directly accessed pathology services, currency code: DAPS05, currency description: haematology), £12 per cycle
2	34.89	12.00	In addition to cycle 1 costs, antihistamine medication to prevent allergic conditions. 50 mg/day Ucerax (BNF, ages 1–6) taken for 4 days during cycles 2 and 4 when dinutuximab is administered with IL-2. Ucerax syrup daily cost: 1.78/200*50*5/10 (BNF) Per-cycle cost= £34.00 + £0.22*4
3	34.00	12.00	Same as cycle 1
4	34.89	12.00	Same as cycle 2
5	34.00	12.00	Same as cycle 1
Standard therapy			
Each model cycle (1–6)	0	0	Concomitant medication and monitoring costs apply to immunotherapy only.

Key: BNF – British National Formulary; EMA – European Medicines Agency; IL-2 – interleukin-2; NHS – National Health Service.

The summary of costs associated with the technology is provided in Table 48. Note that CIs are not reported, as the variations around the components that make up the costs are provided in the **Summary of base-case de novo analysis inputs** section.

Table 48. Costs associated with the technology in the economic model

Items	Immunotherapy	Reference in Submission	Standard Therapy	Reference in Submission
Drug (£)[a]	135,404.38	Table 45	337.68	Table 45
Administration (£)[a]	13,783.50	Table 46	0.00	Table 46
Concomitant medication (£)[a]	171.78	Table 47	0.00	Table 47
Monitoring (£)[a]	60.00	Table 47	0.00	Table 47
Total (£)[a]	149,419.66	-	337.68	-

[a] 6 full cycles of treatment.

Health-state unit costs and resource use

The costs and resource use data for the stable and failure health states are shown in Table 49. The stable state costs were calculated based on resource use data for neuroblastoma survivors in the UK (Rebholz 2011) and unit costs from the NHS Reference Costs 2013 to 2014. Since Rebholz et al reported the percent of patients using a resource (rather than number of units), the following steps were implemented to determine resource frequency:

1. The distribution of level of use (never, once, and more than once) was calculated for each resource item using reported percentages of “at least once vs never” and “more than once vs once.”
2. Assuming that the “more than once” category consumed 2 units, the weighted average number of units was calculated for each resource item. While 2 units represent the lower end of the possible outcomes, the authors expressed that “the distribution of frequencies of healthcare events was highly skewed and comprised a limited number of discrete values” (Rebholz 2011). Therefore, the selection of the most representative value was not possible. Additionally, despite covering the 5-year survivors, the survey results for some patients may represent a phase when they had received chemotherapy or radiotherapy or were in a relapse or second neoplasm state. As these types of phases and their corresponding costs are already accounted for in the model separately, the resource use estimates from Rebholz 2011 may be slightly inflated for the health state in question. Taking this into account, the “2 units” argument above can be considered a reasonable assumption.
3. The number of units were converted into monthly amounts.

In order to determine costs for the failure state, NCI's cancer database was searched for information on the treatment of patients with high-risk, recurrent neuroblastoma (NCI Physician Data Query). The highest level of evidence was available for topotecan combinations. As such, it was assumed that the patients in the failure state followed the treatment regimen used in the phase 2 randomized trial of topotecan (London 2010). The use of topotecan regimens for relapsed patients in the UK setting was also confirmed by a UK expert.[7] Based on London 2010, the treatment regimen was as follows: intravenous topotecan 0.75 mg/m^2/day and cyclophosphamide 250 mg/m^2/day for 5 days; cycles were 21 days, and subcutaneous filgrastim 5 µg/kg/day was started on day 6.

Table 49. List of health states and associated costs in the economic model

	Item	Monthly Units of Resources Consumed	Unit Cost (£)	Reference in Submission
Stable state	Talk to a doctor	0.35	88[a]	Table 42
	Hospital outpatient visit	0.11	144[b]	
	Hospitalized as day patient	0.01	698[c]	
	Hospitalized for overnight stay	0.01	603[d]	
Failure state[e]	Drug costs			N/A
	Topotecan	~3 mg[f]	261.55[6]	
	Cyclophosphamide	~ 1000 mg[g]	17.06[7]	
	Filgrastim	~ 105 µg/day[h]	36/day, 576/cycle[8]	
	Administration cost	1[i]	1,908.00[9]	
	Total	-	2,762.61	

Key: BNF – British National Formulary; NHS – National Health Service; N/A – not applicable.

[a] Consultant-led outpatient attendances, currency code: WF01C, currency description: non-admitted non-face-to-face attendance follow-up, service code: 300, service description: general medicine.

[b] Consultant-led outpatient attendances, currency code: WF01A, currency description: non-admitted face-to-face attendance follow-up, service code: 300, service description: general medicine.

[c] National day-case hospital visit average

[d] National non-elective inpatient short stay average

[e] Per 21-day cycle

[f] 0.75 mg/m^2/day x 0.65 m^2 x 5 days = ~2.4 mg for 5 days (per cycle). Average surface area (0.65) based on average baseline value in the dinutuximab pivotal phase 3 clinical trial (Yu 2010). Cost per 21-day cycle is £261.55 (one 4 mL vial at 1 mg/mL) based on topotecan cost from BNF.

[g] 250 mg/m^2/day x 0.65 m^2 x 5 days = ~813 mg for 5 days (per cycle). Average surface area (0.65) based on average baseline value in the dinutuximab pivotal phase 3 clinical trial (Yu 2010). Cost per 21-day cycle is £17.06 (one 1 g vial) based on cyclophosphamide cost from BNF.

[h] 5 µg/kg/day x 17.7 kg = ~89 µg/day. Average weight (17.7 kg) based on average baseline value in the dinutuximab pivotal phase 3 clinical trial (Yu 2010). Use one 120 mcg syringe per day at the cost of £36. Per 21-

[7] Experts were selected based on their experience treating patients with high-risk neuroblastoma in the NHS. Five experts were approached and 2 provided clinical feedback. The information provided was related to long-term survival of patients with high-risk neuroblastoma treated with immunotherapy, and the evidence provided was consistent with what appears in this submission. Clinical opinions were obtained via direct in-person interviews and telephone interviews. While follow-up sessions were held to gain additional clarification, an iterative methodology was not used. Neither advisor reports a conflict of interest. A sample of the questions advisors were asked can be found in Appendix 5.

day cycle cost £576 (36 x 16).

[i] Source: NHS Reference Costs 2013–2014. Service code: IP, service description: inpatient, currency code: SB10Z, currency description: procure chemotherapy drugs for regimens in Band 10.

Based on these resource use and unit cost data, the monthly costs for stable and failure states were calculated as £59.65 and £3,683.48 (£2,762.61 adjusted to reflect an average 28-day cycle), respectively.

Adverse reaction unit costs and resource use

The costs per event experienced in the clinical trial (Yu 2010) by patients receiving immunotherapy or standard therapy were determined based on the corresponding appropriate unit costs from NHS Reference Costs 2013 to 2014 (Table 50).

Table 50. List of adverse reactions and summary of costs in the economic model

Adverse Event	Per-event Cost (£)	Explanation
Neuropathic pain	493	Consultant-led outpatient attendances, currency code: WF01A, currency description: non-admitted face-to-face attendance follow-up, service code: 241, service description: paediatric pain management
Hypoxia Hypersensitivity reaction Urticaria Hyponatremia Hypokalaemia CNS cortical symptom	265	Consultant-led outpatient attendances, currency code: WF01A, currency description: non-admitted face-to-face attendance follow-up, service code: 260, service description: paediatric medical oncology
Fever without neutropenia	478	Day cases, currency code: PW20A, currency description: paediatric fever unspecified with CC score 3+
Acute capillary leak syndrome	2,837	Average non-elective inpatient (long stay)
Nausea Vomiting Diarrhea	540	Day cases, currency code: PF26B, currency description: paediatric other gastrointestinal disorders with CC score 1–3
Infection	654	Day cases, currency code: PW18A, currency description: paediatric minor infections with CC score 2+
Abnormal ALT/AST	265	Day cases, currency code: GC01F, currency description: liver failure disorders without interventions, with CC score 0–4

Key: ALT – alanine transaminase; AST – aspartate transaminase; CNS – central nervous system.

The monthly costs due to adverse events (applies to patients on treatment) were calculated as £432 and £51 for immunotherapy and standard treatment, respectively, based on adverse event rates (Table 38) and unit cost of adverse events (Table 50).

Miscellaneous unit costs and resource use

No other costs and/or resource use were used in addition to those mentioned in the previous sections.

5.6 Summary of base-case de novo analysis inputs and assumptions

Summary of base-case de novo analysis inputs

Table 51. Summary of variables applied in the economic model

Variable	Value (Reference to Appropriate Table or Figure in Submission)	SE (Distribution)	Reference to Section in Submission
Event-free survival (Source: Analysis of dinutuximab pivotal phase 3 clinical trial, Yu 2010)	Gompertz l model coefficients (mean) Treatment: -0.5520 Constant: -0.0882 Sigma: -0.5535 (Table 35)	Gompertz model coefficients (SE) Treatment: 0.2245 Constant: 0.3460 Sigma: 0.1232 See Appendix 7. Covariance matrices for survival models for covariance matrix	Section **Clinical parameters and variables > Survival parameters**
Overall survival (Source: Analysis of dinutuximab pivotal phase 3 clinical trial, Yu 2010)	Exponential model coefficients (mean) Treatment: -0.6547 Constant: -1.2861 (Table 36)	Exponential model coefficients (SE) Treatment: 0.2880 Constant: 0.4169 See Appendix 7. Covariance matrices for survival models for covariance matrix	Section **Clinical parameters and variables > Survival parameters**
Time horizon (NICE reference case)	Lifetime	N/A	Section **De novo analysis > Model structure**
Discount rate, outcomes (NICE reference case)	3.5% (Table 34)	N/A	Section **De novo analysis > Model structure**
Discount rate, costs (NICE reference case)	3.5% (Table 34)	N/A	Section **De novo analysis > Model structure**
Neuropathic pain rate, IT[a] (Source: Dinutuximab pivotal phase 3 clinical trial, Yu 2010)	0.1160 (Table 38)	0.0118 (gamma)	Section **Clinical parameters and variables > Adverse events**
Hypoxia rate, IT[a] (Source: Dinutuximab pivotal phase 3 clinical trial, Yu 2010)	0.0294 (Table 38)	0.0030 (gamma)	Section **Clinical parameters and variables > Adverse events**
Fever without neutropenia rate, IT[a]	0.0866 (Table 38)	0.0088 (gamma)	Section **Clinical parameters and**

Variable	Value (Reference to Appropriate Table or Figure in Submission)	SE (Distribution)	Reference to Section in Submission
(Source: Dinutuximab pivotal phase 3 clinical trial, Yu 2010)			**variables > Adverse events**
ACLS rate, IT[a] (Source: Dinutuximab pivotal phase 3 clinical trial, Yu 2010)	0.0506 (Table 38)	0.0052 (gamma)	Section **Clinical parameters and variables > Adverse events**
Hypersensitivity reaction rate, IT[a] (Source: Dinutuximab pivotal phase 3 clinical, Yu 2010)	0.0555 (Table 38)	0.0057 (gamma)	Section **Clinical parameters and variables > Adverse events**
Urticaria rate, IT[a] (Source: Dinutuximab pivotal phase 3 clinical trial, Yu 2010)	0.0294 (Table 38)	0.0030 (gamma)	Section **Clinical parameters and variables > Adverse events**
Infection rate, IT[a] (Source: Dinutuximab pivotal phase 3 clinical trial, Yu 2010)	0.1176 (Table 38)	0.0120 (gamma)	Section **Clinical parameters and variables > Adverse events**
Nausea rate, IT[a] (Source: Dinutuximab pivotal phase 3 clinical trial, Yu 2010)	0.0065 (Table 38)	0.0007 (gamma)	Section **Clinical parameters and variables > Adverse events**
Vomiting rate, IT[a] (Source: Dinutuximab pivotal phase 3 clinical trial, Yu 2010)	0.0131 (Table 38)	0.0013 (gamma)	Section **Clinical parameters and variables > Adverse events**
Diarrhea rate, IT[a] (Source: Dinutuximab pivotal phase 3 clinical trial, Yu 2010)	0.0294 (Table 38)	0.0030 (gamma)	Section **Clinical parameters and variables > Adverse events**
Hyponatremia rate, IT[a] (Source: Dinutuximab pivotal phase 3 clinical trial, Yu 2010)	0.0506 (Table 38)	0.0052 (gamma)	Section **Clinical parameters and variables > Adverse events**
Hypokalemia rate, IT[a] (Source: Dinutuximab pivotal phase 3 clinical trial, Yu 2010)	0.0784 (Table 38)	0.0080 (gamma)	Section **Clinical parameters and variables > Adverse events**
Abnormal ALT/AST rate, IT[a] (Source: Dinutuximab pivotal phase 3 clinical trial, Yu 2010)	0.0735 (Table 38)	0.0075 (gamma)	Section **Clinical parameters and variables > Adverse events**
CNS cortical symptom rate, IT[a] (Source: Dinutuximab pivotal phase 3 clinical trial, Yu 2010)	0.0082 (Table 38)	0.0008 (gamma)	Section **Clinical parameters and variables > Adverse events**
Neuropathic pain rate, ST[a] (Source: Dinutuximab	0.0096 (Table 38)	0.0010 (gamma)	Section **Clinical parameters and**

Variable	Value (Reference to Appropriate Table or Figure in Submission)	SE (Distribution)	Reference to Section in Submission
pivotal phase 3 clinical trial, Yu 2010)			**variables > Adverse events**
Hypoxia rate, ST[a] (Source: Dinutuximab pivotal phase 3 clinical trial, Yu 2010)	0.0032 (Table 38)	0.0003 (gamma)	Section **Clinical parameters and variables > Adverse events**
Fever without neutropenia rate, ST[a] (Source: Dinutuximab pivotal phase 3 clinical trial, Yu 2010)	0.0096 (Table 38)	0.0010 (gamma)	Section **Clinical parameters and variables > Adverse events**
ACLS rate, ST[a] (Source: Dinutuximab pivotal phase 3 clinical trial, Yu 2010)	0.0000 (Table 38)	Not varied in PSA	Section **Clinical parameters and variables > Adverse events**
Hypersensitivity reaction rate, ST[a] (Source: Dinutuximab pivotal phase 3 clinical trial, Yu 2010)	0.0016 (Table 38)	0.0002 (gamma)	Section **Clinical parameters and variables > Adverse events**
Urticaria rate, ST[a] (Source: Dinutuximab pivotal phase 3 clinical trial, Yu 2010)	0.0000 (Table 38)	Not varied in PSA	Section **Clinical parameters and variables > Adverse events**
Infection rate, ST[a] (Source: Dinutuximab pivotal phase 3 clinical trial, Yu 2010)	0.0495 (Table 38)	0.0051 (gamma)	Section **Clinical parameters and variables > Adverse events**
Nausea rate, ST[a] (Source: Dinutuximab pivotal phase 3 clinical trial, Yu 2010)	0.0016 (Table 38)	0.0002 (gamma)	Section **Clinical parameters and variables > Adverse events**
Vomiting rate, ST[a] (Source: Dinutuximab pivotal phase 3 clinical trial, Yu 2010)	0.0048 (Table 38)	0.0005 (gamma)	Section **Clinical parameters and variables > Adverse events**
Diarrhea rate, ST[a] (Source: Dinutuximab pivotal phase 3 clinical trial, Yu 2010)	0.0016 (Table 38)	0.0002 (gamma)	Section **Clinical parameters and variables > Adverse events**
Hyponatremia rate, ST[a] (Source: Dinutuximab pivotal phase 3 clinical trial, Yu 2010)	0.0064 (Table 38)	0.0007 (gamma)	Section **Clinical parameters and variables > Adverse events**
Hypokalemia rate, ST[a] (Source: Dinutuximab pivotal phase 3 clinical trial, Yu 2010)	0.0032 (Table 38)	0.0003 (gamma)	Section **Clinical parameters and variables > Adverse events**
Abnormal ALT/AST rate, ST[a] (Source: Dinutuximab pivotal phase 3 clinical trial,	0.0048 (Table 38)	0.0005 (gamma)	Section **Clinical parameters and variables > Adverse events**

Variable	Value (Reference to Appropriate Table or Figure in Submission)	SE (Distribution)	Reference to Section in Submission
Yu 2010)			
CNS cortical symptom rate, ST[a] (Source: Dinutuximab pivotal phase 3 clinical trial, Yu 2010)	0.0000 (Table 38)	Not varied in PSA	Section **Clinical parameters and variables > Adverse events**
Health utility, stable state (Source: Barr 199)	0.810 (Table 41)	0.060 (beta)	Section **Measurement and valuation of health effects > Health-related quality-of-life data used in cost-effectiveness analysis**
Health utility, failure state (Source: Barr 199)	0.560 (Table 41)	0.237 (beta)	Section **Measurement and valuation of health effects > Health-related quality-of-life data used in cost-effectiveness analysis**
% reduction in health utility due to neuroblastoma (compared to general population) after 5 years[b] (Source: Portwine 2014)	13% (Table 41)	1.33% (beta)	Section **Measurement and valuation of health effects > Health-related quality-of-life data used in cost-effectiveness analysis**
Health utility when receiving IV infusion for immunotherapy (Source: Expert opinion)	0 (Table 41)	Uniform (0,0.560)[c]	Section **Measurement and valuation of health effects > Health-related quality-of-life data used in cost-effectiveness analysis**
Duration (days) at the health utility (above) when receiving IV infusion for immunotherapy (Source: Expert opinion, per dosing schedule)			
Cycles 1, 3, 5	4 (Table 41)	0.4 (normal)[d]	Section **Measurement and valuation of health effects > Health-related quality-of-life data used in cost-effectiveness analysis**
Cycles 2, 4	8 (Table 41)	0.8 (normal)[d]	Section **Measurement and valuation of health effects > Health-related quality-of-life data used in cost-effectiveness analysis**
Mortality ratio in the stable state (neuroblastoma vs general population, after 5 years)[b] (Source: ONS for UK life tables)	1 See Appendix 8. UK life tables (ONS) for general population life tables	0.1 (lognormal)[d]	Section **Clinical parameters and variables > Survival parameters**
Monthly probability of death in the failure state[b]	5.1%	1.4% (beta)[p]	Section **Clinical parameters and**

Variable	Value (Reference to Appropriate Table or Figure in Submission)	SE (Distribution)	Reference to Section in Submission
(Source: London 2010)			**variables > Survival parameters**
Isotretinoin cost per 20 mg tablet (Source: BNF)	0.67 (Table 45)	0.07 (gamma)[d]	Section **Cost and healthcare resource use identification, measurement and valuation > Intervention and comparators' costs and resource use**
Dinutuximab cost per 20 mg vial	£6,390.00 (Table 45)	652.04 (gamma)[d]	Section **Cost and healthcare resource use identification, measurement and valuation > Intervention and comparators' costs and resource use**
GM-CSF cost per 250 mcg vial	£162.35 (Table 45)	16.57 (gamma)[d]	Section **Cost and healthcare resource use identification, measurement and valuation > Intervention and comparators' costs and resource use**
IL-2 cost per $18x10^6$ units (Source: BNF)	£112.00 (Table 45)	11.43 (gamma)[d]	Section **Cost and healthcare resource use identification, measurement and valuation > Intervention and comparators' costs and resource use**
Dinutuximab cost per administration (Source: NHS Reference Costs)	£1,908.00 (Table 46)	£469.16 (gamma)[e]	Section **Cost and healthcare resource use identification, measurement and valuation > Intervention and comparators' costs and resource use**
GM-CSF cost per administration (Source: PSSRU, Rogers 2012)	£14.25 (Table 46)	£1.90 (gamma)[f]	Section **Cost and healthcare resource use identification, measurement and valuation > Intervention and comparators' costs and resource use**
IL-2 cost per administration (Source: NHS reference costs)	£1,908.00 (Table 46)	£469.16 (gamma)[e]	Section **Cost and healthcare resource use identification, measurement and valuation > Intervention and comparators' costs and resource use**
Concomitant medication cost per cycle for immunotherapy (cycles 1, 3, 5) (Source: BNF and EMA label)	£34.00 (Table 47)	£3.47 (gamma)[d]	Section **Cost and healthcare resource use identification, measurement and valuation > Intervention and comparators' costs and resource use**

Variable	Value (Reference to Appropriate Table or Figure in Submission)	SE (Distribution)	Reference to Section in Submission
Concomitant medication cost per cycle for immunotherapy (cycles 2, 4) (Source: BNF and EMA label)	£34.89 (Table 47)	£3.56 (gamma)[d]	Section **Cost and healthcare resource use identification, measurement and valuation > Intervention and comparators' costs and resource use**
Monitoring cost per cycle for immunotherapy (Source: NHS Reference Costs and EMA label)	£12.00 (Table 47)	£3.48(gamma)[o]	Section **Cost and healthcare resource use identification, measurement and valuation > Intervention and comparators' costs and resource use**
Neuropathic pain, cost per event (Source: NHS Reference Costs)	£493.00 (Table 50)	£105.13 (gamma)[g]	Section **Cost and healthcare resource use identification, measurement and valuation > Adverse reaction unit costs and resource use**
<u>Cost per event:</u> Hypoxia Hypersensitivity reaction Urticaria Hyponatremia Hypokalaemia CNS cortical symptom (Source: NHS Reference Costs)	£265.00 (Table 50)	£79.50 (gamma)[h]	Section **Cost and healthcare resource use identification, measurement and valuation > Adverse reaction unit costs and resource use**
Fever without neutropenia, cost per event (Source: NHS Reference Costs)	£478.00 (Table 50)	£88.62 (gamma)[i]	Section **Cost and healthcare resource use identification, measurement and valuation > Adverse reaction unit costs and resource use**
ACLS, cost per event (Source: NHS Reference Costs)	£2,837.00 (Table 50)	£289.49 (gamma)[d]	Section **Cost and healthcare resource use identification, measurement and valuation > Adverse reaction unit costs and resource use**
<u>Cost per event:</u> Nausea Vomiting Diarrhea (Source: NHS Reference Costs)	£540.00 (Table 50)	£139.88 (gamma)[j]	Section **Cost and healthcare resource use identification, measurement and valuation > Adverse reaction unit costs and resource use**
Infection, cost per event (Source: NHS Reference Costs)	£654.00 (Table 50)	£196.35 (gamma)[k]	Section **Cost and healthcare resource use identification, measurement and valuation > Adverse**

Variable	Value (Reference to Appropriate Table or Figure in Submission)	SE (Distribution)	Reference to Section in Submission
			reaction unit costs and resource use
Abnormal ALT/AST, cost per event (Source: NHS Reference Costs)	£265.00 (Table 50)	£177.24 (gamma)[l]	Section **Cost and healthcare resource use identification, measurement and valuation > Adverse reaction unit costs and resource use**
Failure state cost (per cycle) (Source: London 2010, NHS Reference Costs, BNF)	£3,683.48 (Table 49)	£375.87 (gamma)[d]	Section **Cost and healthcare resource use identification, measurement and valuation >Health-state unit costs and resource use**
Monthly talks to a doctor, stable state (Source: Rebholz 2011)	0.35 (Table 49)	0.036 (gamma)[d]	Section **Cost and healthcare resource use identification, measurement and valuation >Health-state unit costs and resource use**
Monthly hospital outpatient visits, stable state (Source: Rebholz 2011)	0.11 (Table 49)	0.011 (gamma)[d]	Section **Cost and healthcare resource use identification, measurement and valuation >Health-state unit costs and resource use**
Monthly hospitalizations as day patient, stable state (Source: Rebholz 2011)	0.01 (Table 49)	0.001 (gamma)[d]	Section **Cost and healthcare resource use identification, measurement and valuation >Health-state unit costs and resource use**
Monthly hospitalizations for overnight stay, stable state (Source: Rebholz 2011)	0.01 (Table 49)	0.001 (gamma)[d]	Section **Cost and healthcare resource use identification, measurement and valuation >Health-state unit costs and resource use**
Cost per talk to a doctor (Source: NHS Reference Costs)	£88.00 (Table 49)	£30.84 (gamma)[m]	Section **Cost and healthcare resource use identification, measurement and valuation >Health-state unit costs and resource use**
Cost per hospital outpatient visit (Source: NHS Reference Costs)	£144.00 (Table 49)	£28.67 (gamma)[n]	Section **Cost and healthcare resource use identification, measurement and valuation >Health-state unit costs and resource use**

Variable	Value (Reference to Appropriate Table or Figure in Submission)	SE (Distribution)	Reference to Section in Submission
Cost per hospitalization as day patient (Source: NHS Reference Costs)	£698.00 (Table 49)	£71.22 (gamma)[d]	Section **Cost and healthcare resource use identification, measurement and valuation >Health-state unit costs and resource use**
Cost per hospitalization for overnight stay (Source: NHS Reference Costs)	£603.00 (Table 49)	£61.53 (gamma)[d]	Section **Cost and healthcare resource use identification, measurement and valuation >Health-state unit costs and resource use**

Key: ACLS – acute capillary leak syndrome; ALT – alanine transaminase; AST – aspartate transaminase; CNS – central nervous system; EMA – European Medicines Agency; GM-CSF – granulocyte macrophage colony-stimulating factor; IL-2 – interleukin-2; IT – immunotherapy; IV – intravenous; N/A – not applicable; NHS – National Health Service; ONS – Office for National Statistics; PSA – probabilistic sensitivity analysis; SE – standard error; ST – standard therapy.

[a] Rate per cycle (ie, 4 weeks).

[b] Applies after 5 years.

[c] Given the lack of data for this input, the value was varied according to a uniform distribution between 0 and 0.560 (ie, health utility corresponding to the failure state).

[d] Standard error calculated assuming 95% confidence interval half width represents 20% of the mean given the lack of standard deviation/error estimate (SE=0.2*mean/1.96).

[e] SE calculated based on lower quartile (1,207) and upper quartile (2,287) estimates from NHS Reference costs (2013–2014), SE=(2287-1207)/2/1.151.

[f] From PSSRU: “the mean average cost for a face-to-face contact in district nursing services for 2013/2014 was £39, with an interquartile range of £31 to £43.” Estimated SE=(43-31)/2/1.151 is 13.4% of the mean (ie,£39). Therefore, this is applied to the mean in the model resulting in 1.90 (14.25*13.4%).

[g] SE calculated based on lower quartile (160) and upper quartile (402) estimates from NHS Reference costs (2013–2014), SE=(402-160)/2/1.151.

[h] SE calculated based on lower quartile (166) and upper quartile (349) estimates from NHS Reference costs (2013–2014), SE=(349-166)/2/1.151.

[i] SE calculated based on lower quartile (312) and upper quartile (516) estimates from NHS Reference costs (2013–2014), SE=(516-312)/2/1.151.

[j] SE calculated based on lower quartile (328) and upper quartile (650) estimates from NHS Reference costs (2013–2014), SE=(650-328)/2/1.151.

[k] SE calculated based on lower quartile (362) and upper quartile (814) estimates from NHS Reference costs (2013–2014), SE=(814-362)/2/1.151.

[l] SE calculated based on lower quartile (104) and upper quartile (512) estimates from NHS Reference costs (2013–2014), SE=(512-104)/2/1.151.

[m] SE calculated based on lower quartile (37) and upper quartile (108) estimates from NHS Reference costs (2013–2014), SE=(108-37)/2/1.151.

[n] SE calculated based on lower quartile (114) and upper quartile (180) estimates from NHS Reference costs (2013–2014), SE=(180-114)/2/1.151.

[o] Unit cost (£3) SE calculated based on lower quartile (2) and upper quartile (4) estimates from NHS Reference costs (2013–2014), SE=(4-2)/2/1.151. This represents 29% of the mean. 29% is applied to per cycle cost (£12) to estimate per cycle SE.

[p] The ratio of SE to reported 3-year OS from London 2010 (4%/15%) applied to monthly probability (ie, 5.1%*(4%/15%)).

5.6.1 Assumptions

- Patients start the model in stable state at the age of 4 and 60% of the patients are males (dinutuximab pivotal phase 3 clinical trial, Yu 2010).

- Average body surface area and weight is 0.65 m^2 and 17.7 kg, respectively (dinutuximab pivotal phase 3 clinical trial, Yu 2010).

- Upon failure, patients receive topotecan combination treatment on a monthly basis until death.

  The information from NCI's cancer database indicated that the highest level of evidence was available for topotecan combinations for patients with high-risk, recurrent neuroblastoma. Additionally, the use of topotecan regimens for relapse patients in the UK setting was also confirmed by a UK expert (see section **Health-state unit costs and resource use** for details).

- After 5 years, the event-free cohort is assumed to be cured and enters a phase when they are considered survivors and start to follow similar characteristics (ie, mortality, quality of life, relapse rates) to that of the general population, while still accounting for potential morbidities affecting quality of life and resource use among neuroblastoma survivors.

- All patients die by the age of 100.

5.7 Base-case results

Base-case incremental cost effectiveness analysis results

In the base case, patients gained 4.71 (14.02, undiscounted) additional life-years (LYs) and 3.71 (10.57, undiscounted) additional QALYs with immunotherapy compared to standard therapy at an incremental cost of £139,022, resulting in an incremental cost per QALY gain of £37,423 (Table 52).

Table 52. Base-case results

Technologies	Total Costs (£)	Total LYs	Total QALYs	Incremental Costs (£)	Incremental LYs	Incremental QALYs	ICER (£) vs Baseline (QALYs)
Standard therapy	46,573	12.46	9.73	-	-	-	-
Immunotherapy	185,595	17.16	13.44	139,022	4.71	3.71	37,423

Key: ICER – incremental cost-effectiveness ratio; LY – life-year; QALY – quality-adjusted life-year.

Clinical outcomes from the model

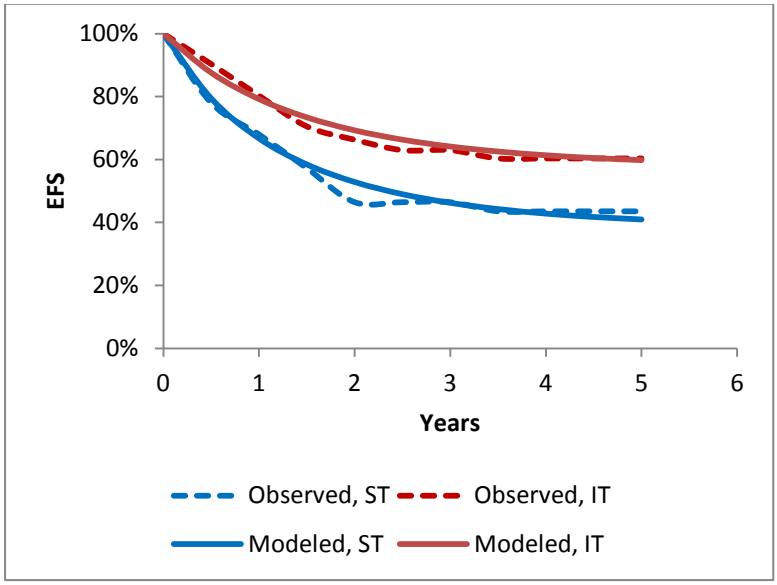
EFS and OS at year 2 from the clinical trial (dinutuximab clinical trial, Yu 2010) were generally similar to the model results (Table 53). Actual vs modelled survival over 5 years is presented in Figure 22.

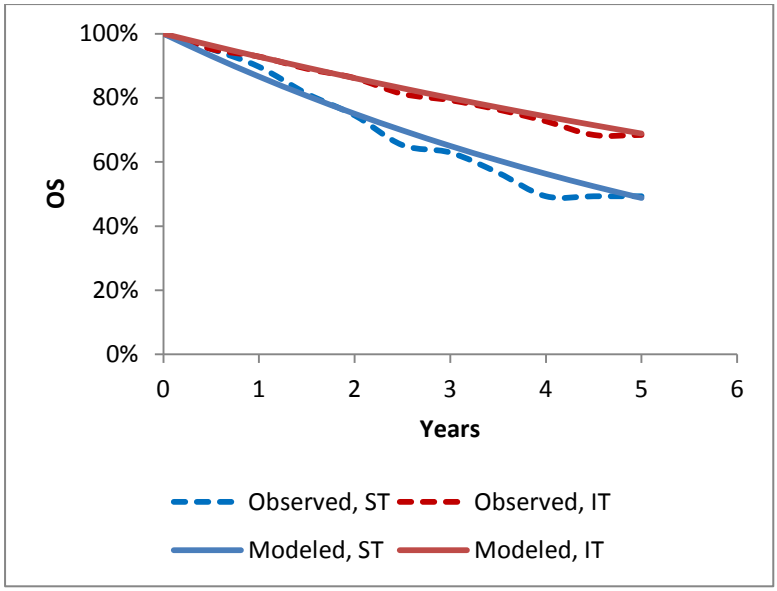
Table 53. Summary of model results compared with clinical trial results

Outcome*	Immunotherapy		Standard Therapy	
	Clinical trial result	Model result	Clinical trial result	Model result
EFS at year 2	66%	69%	46%	53%
OS at year 2	86%	86%	75%	75%

Key: EFS – event-free survival; OS – overall survival.

Figure 22. Actual vs modelled survival





Key: EFS – event-free survival; IT – immunotherapy; OS – overall survival; ST – standard therapy.

The proportion of the cohort and QALYs in each health state over time are shown in Table 54 and Table 55, respectively.

Table 54. Proportion of the cohort in each health state over time

Years	Immunotherapy			Standard therapy		
	Stable	Failure	Dead	Stable	Failure	Dead
1	79%	14%	7%	67%	20%	13%
2	69%	17%	14%	53%	22%	25%
3	64%	16%	20%	46%	19%	35%
4	61%	13%	26%	43%	13%	44%
5	60%	9%	31%	41%	8%	51%
10	60%	0%	40%	41%	0%	59%
15	60%	0%	40%	41%	0%	59%
20	60%	0%	40%	41%	0%	59%
25	60%	0%	40%	41%	0%	59%
30	59%	0%	41%	41%	0%	59%
35	59%	0%	41%	40%	0%	60%
40	59%	0%	41%	40%	0%	60%
45	58%	0%	42%	40%	0%	60%
50	57%	0%	43%	39%	0%	61%
55	56%	0%	44%	38%	0%	62%
60	53%	0%	47%	37%	0%	63%
65	50%	0%	50%	34%	0%	66%
70	45%	0%	55%	31%	0%	69%
75	38%	0%	62%	26%	0%	74%

Years	Immunotherapy			Standard therapy		
	Stable	Failure	Dead	Stable	Failure	Dead
80	27%	0%	73%	19%	0%	81%
85	15%	0%	85%	11%	0%	89%
90	6%	0%	94%	4%	0%	96%
95	1%	0%	99%	1%	0%	99%
100	0%	0%	100%	0%	0%	100%

Table 55. QALYs in each health state over time

Years	Immunotherapy			Standard therapy		
	Stable	Failure	Dead	Stable	Failure	Dead
1	0.052	0.006	0.000	0.044	0.009	0.000
2	0.044	0.007	0.000	0.034	0.010	0.000
3	0.039	0.007	0.000	0.028	0.008	0.000
4	0.036	0.005	0.000	0.025	0.006	0.000
5	0.035	0.004	0.000	0.024	0.003	0.000
10	0.029	0.000	0.000	0.020	0.000	0.000
15	0.025	0.000	0.000	0.017	0.000	0.000
20	0.020	0.000	0.000	0.014	0.000	0.000
25	0.017	0.000	0.000	0.012	0.000	0.000
30	0.014	0.000	0.000	0.010	0.000	0.000
35	0.012	0.000	0.000	0.008	0.000	0.000
40	0.010	0.000	0.000	0.007	0.000	0.000
45	0.008	0.000	0.000	0.005	0.000	0.000
50	0.006	0.000	0.000	0.004	0.000	0.000
55	0.005	0.000	0.000	0.003	0.000	0.000
60	0.004	0.000	0.000	0.003	0.000	0.000
65	0.003	0.000	0.000	0.002	0.000	0.000
70	0.002	0.000	0.000	0.002	0.000	0.000
75	0.002	0.000	0.000	0.001	0.000	0.000
80	0.001	0.000	0.000	0.001	0.000	0.000
85	0.000	0.000	0.000	0.000	0.000	0.000
90	0.000	0.000	0.000	0.000	0.000	0.000
95	0.000	0.000	0.000	0.000	0.000	0.000
100	0.000	0.000	0.000	0.000	0.000	0.000

Disaggregated results of the base case incremental cost-effectiveness analysis

QALY gains (3.79) with immunotherapy compared to standard therapy occurred in the Stable state, while slightly higher gains (0.08) were predicted with standard

therapy in the Failure state, resulting in an overall net gain of 3.71 QALYs with immunotherapy (Table 56). Immunotherapy was associated with an incremental cost of £145,105 in the Stable state, £6,083 of which was offset by the additional costs with standard therapy in the Failure state, resulting in an overall incremental cost of £139,022 with immunotherapy (Table 57). Drug and administration costs constituted most of the incremental costs with immunotherapy, with a relatively small offset due to savings in the Failure state (

Table 58).

Table 56. Summary of QALY gain by health state

Health State	QALY, Immunotherapy	QALY, Standard Therapy	Increment	Absolute Increment	% Absolute Increment
Stable	13.04	9.25	3.79	3.79	102%
Failure	0.40	0.48	-0.08	0.08	2%
Dead	0	0	0	0	0%
Total	13.44	9.73	3.71	Total absolute increment	100%

Key: QALY – quality-adjusted life-year.

Table 57. Summary of costs by health state

Health state	Cost (£), Immunotherapy	Cost (£), Standard Therapy	Increment	Absolute Increment	% Absolute Increment
Stable	153,978	8,873	145,105	145,105	104%
Failure	31,617	37,700	-6,083	6,083	4%
Dead	0	0	0	0	0%
Total	185,595	46,573	139,022	Total absolute increment	100%

Table 58. Summary of predicted resource use by category of cost

Item	Cost (£), Immunotherapy	Cost (£), Standard Therapy	Increment	Absolute Increment	% Absolute Increment
Drug cost[a]	126,698	297	126,401	126,401	91%
Administration cost	12,895	0	12,895	12,895	9%
Concomitant medication cost	161	0	161	161	0%
Monitoring cost	56	0	56	56	0%
Adverse event cost	2,395	270	2,125	2,125	2%
Failure cost	31,617	37,700	-6,083	6,083	4%
Ongoing healthcare cost[b]	11,773	8,306	3,467	3,467	2%
Total	185,595	46,573	139,022	Total absolute increment	100%

[a] Drug costs for immunotherapy (dinutuximab, IL-2, GM-CSF, and isotretinoin).

[b] Occurs in stable state.

5.8 Sensitivity analyses

Probabilistic sensitivity analysis

In the probabilistic sensitivity analysis (PSA), parameters were sampled probabilistically from appropriate distributions using mean and standard error estimates as outlined in Table 51.

Parameters that represent a probability were sampled using beta distributions since the beta distribution is constrained on the interval 0-1. Gamma distribution was used for costs, rates, and resource use frequencies, a function constrained on the interval 0 to positive infinity. Parametric survival parameters were sampled using Cholesky matrices to ensure correlated sampling. Health utility when receiving IV infusion for immunotherapy was sampled using a uniform distribution given that the mean value was 0 (based on expert opinion) and the amount of uncertainty surrounding this input. Lastly, durations for applying the decreased health utility (when receiving IV infusion of immunotherapy) were varied using normal distributions. Only adverse events that did not occur in the standard therapy arm were not varied in the PSA for that technology.

Variation around mean values was generally quantified based on standard errors reported by sources used for each variable. When a standard error was not reported, it was calculated based on available information from the source. For parameters

without sufficient information to identify the estimate, the standard error was calculated assuming 95% confidence interval half width representing 20% of the mean. One thousand simulations were run.

The PSA results are presented in Table 59 and show similar results to the deterministic analyses presented in Table 52. The scatter plots for cost and health outcomes are shown in Figure 23. The cost-effectiveness acceptability curve (CEAC) is shown in Figure 24, and indicates that at the £30,000 willingness-to-pay (WTP) threshold, immunotherapy has 0.27 probability of being cost-effective. After around the £40,000 WTP threshold, the likelihood that immunotherapy is cost-effective compared to standard therapy is more than 0.5.

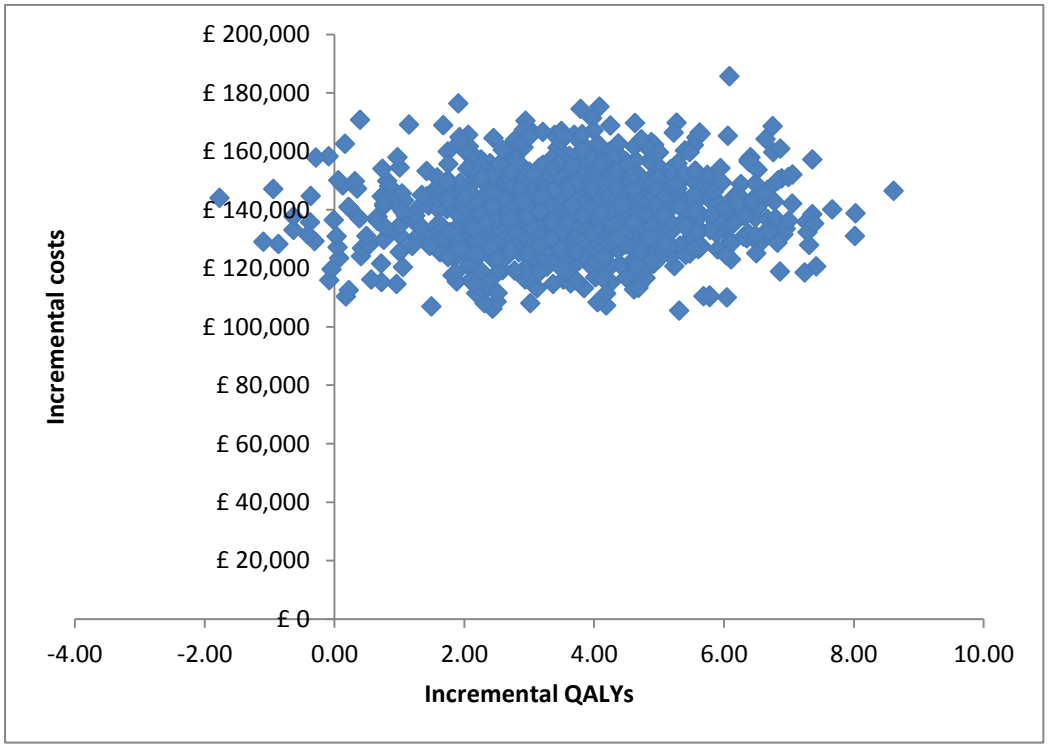
Table 59. PSA results

	Immunotherapy				Standard Therapy			
	Mean	**Median**	**Lower 95% CI**	**Upper 95% CI**	**Mean**	**Median**	**Lower 95% CI**	**Upper 95% CI**
Cost (£)	186,410	185,971	185,496	187,324	47,252	46,869	46,682	47,823
QALY	13.30	13.33	13.23	13.37	9.65	9.63	9.58	9.73
Mean ICER[a] (£)	38,128							

Key: CI – confidence interval; ICER – incremental cost-effectiveness ratio; PSA – probabilistic sensitivity analysis; QALY – quality-adjusted life-year.

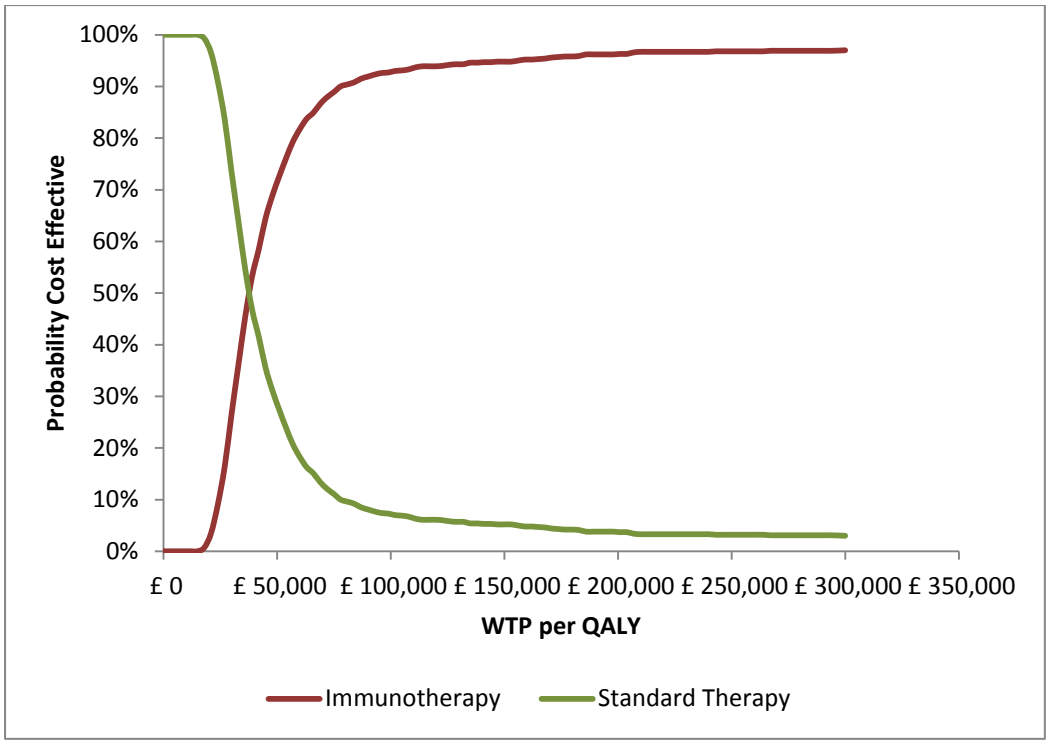
[a] Incremental cost per QALY gained.

Figure 23. PSA scatterplot



Key: QALY – quality-adjusted life-year.

Figure 24. Cost-effectiveness acceptability curve



Key: QALY – quality-adjusted life-year; WTP – willingness to pay.

Deterministic sensitivity analysis

One-way deterministic analyses were conducted using ranges outlined in Table 60. The results are presented in a Tornado diagram in Figure 25.

Table 60. One-way deterministic sensitivity analysis ranges

Parameter	Mean	Low value	High value	Explanation
Outcome and cost discount rates	3.5%	0%	6%	Ranges considered in previous economic evaluations
Event-free survival parameters	See Table 51	-0.6642	-0.4397	Only treatment coefficients were varied by half a SE. Additional considerations investigated in scenario analyses
Overall survival parameters	See Table 51	-0.7987	-0.5107	Only treatment coefficients were varied by half a SE. Additional considerations investigated in scenario analyses
Adverse event rates	See Table 51	Fifth percentile of GAMMA function	Ninety-fifth percentile of GAMMA function	Fifth and ninety-fifth percentiles of the GAMMA functions were estimated using alpha and beta parameters which were calculated based on mean and SE
Health utility, stable state	0.810	0.380	0.950	Low and high values were set based on minimum and maximum values from Barr 1999, respectively
Health utility, failure state	0.560	0.120	0.920	Low and high values were set based on minimum and maximum values from Barr 1999, respectively
% reduction in health utility due	13.00%	10.51%	15.71%	Fifth and ninety-fifth percentiles of the BETA function were estimated using alpha and beta

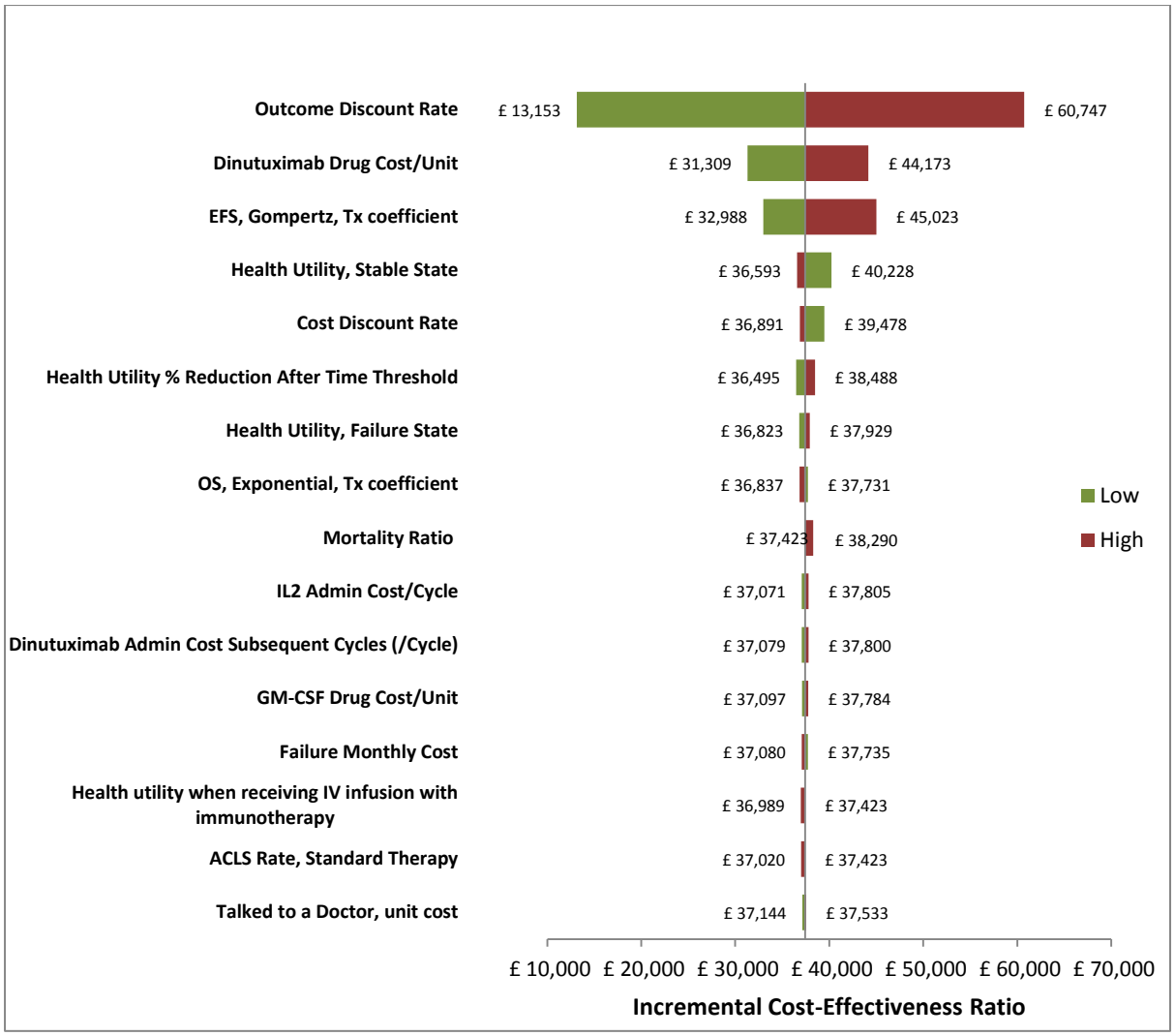
Parameter	Mean	Low value	High value	Explanation
to neuroblastoma (compared to general population) after 5 years[a]				parameters which were calculated based on mean and SE
Health utility when receiving IV infusion for immunotherapy	0	0	0.560	Upper range was based on mean utility for patients in the Failure state
Duration (days) at the health utility (above) when receiving IV infusion for immunotherapy	4 (cycles 1, 3, 5) 8 (cycles 2, 4)	2 (cycles 1, 3, 5) 4 (cycles 2, 4)	8 (cycles 1, 3, 5) 16 (cycles 2, 4)	Mean was divided by 2 and multiplied by 2 for low and high ranges, respectively
Mortality ratio in the stable state (neuroblastoma vs general population, after 5 years)[a]	1	1	2	Twice of the general population mortality was assumed for the upper range
Monthly probability of death in the failure state[a]	5.1%	2.7%	8.2%	Fifth and ninety-fifth percentiles of the BETA function were estimated using alpha and beta parameters which were calculated based on mean and SE
Unit drug costs and per cycle concomitant medication costs	See Table 51	Fifth percentile of GAMMA function	Ninety-fifth percentile of GAMMA function	Fifth and ninety-fifth percentiles of the GAMMA functions were estimated using alpha and beta parameters which were calculated based on mean and SE, to account for potential dosing differences
Dinutuximab cost per administration	£1,908	£1,207	£2,287	Upper and lower quartiles from NHS reference costs
IL-2 cost per administration	£1,908	£1,207	£2,287	Upper and lower quartiles from NHS reference costs
GM-CSF cost per administration	£14.25	£10.77	£18.21	Fifth and ninety-fifth percentiles of the GAMMA functions were estimated using alpha and beta parameters which were calculated based on mean and SE
Monitoring cost per cycle for immunotherapy	£12.00	£8.00	£16.00	Upper and lower quartiles from NHS reference costs
Neuropathic pain, cost per event	£493.00	£160.00	£402.00	Upper and lower quartiles from NHS reference costs
<u>Cost per event:</u> Hypoxia Hypersensitivity reaction Urticaria Hyponatremia Hypokalaemia CNS cortical symptom	£265.00	£166.00	£349.00	Upper and lower quartiles from NHS reference costs
Fever without neutropenia, cost per event	£478.00	£312.00	£516.00	Upper and lower quartiles from NHS reference costs
ACLS, cost per event	£2,837.00	£2,298.08	£3,431.83	Fifth and ninety-fifth percentiles of the GAMMA functions were estimated using alpha and beta parameters which were calculated based on mean and SE

Parameter	Mean	Low value	High value	Explanation
Cost per event: Nausea Vomiting Diarrhea	£540.00	£328.00	£650.00	Upper and lower quartiles from NHS reference costs
Infection, cost per event	£654.00	£362.00	£814.00	Upper and lower quartiles from NHS reference costs
Abnormal ALT/AST, cost per event	£265.00	£104.00	£512.00	Upper and lower quartiles from NHS reference costs
Failure state cost (per cycle)	£3,683.48	£2983.76	£4,455.80	Fifth and ninety-fifth percentiles of the GAMMA functions were estimated using alpha and beta parameters which were calculated based on mean and SE
Monthly talks to a doctor, Stable state	0.35	0.2835	0.4234	Fifth and ninety-fifth percentiles of the GAMMA functions were estimated using alpha and beta parameters which were calculated based on mean and SE
Monthly hospital outpatient visits, Stable state	0.11	0.0891	0.1331	Fifth and ninety-fifth percentiles of the GAMMA functions were estimated using alpha and beta parameters which were calculated based on mean and SE
Monthly hospitalizations as day patient, Stable state	0.01	0.0081	0.0121	Fifth and ninety-fifth percentiles of the GAMMA functions were estimated using alpha and beta parameters which were calculated based on mean and SE
Monthly hospitalizations for overnight stay, Stable state	0.01	0.0081	0.0121	Fifth and ninety-fifth percentiles of the GAMMA functions were estimated using alpha and beta parameters which were calculated based on mean and SE
Cost per talk to a doctor	£88.00	£37.00	£108.00	Upper and lower quartiles from NHS reference costs
Cost per hospital outpatient visit	£144.00	£114.00	£180.00	Upper and lower quartiles from NHS reference costs
Cost per hospitalization as day patient	£698.00	£565.42	£844.34	Fifth and ninety-fifth percentiles of the GAMMA functions were estimated using alpha and beta parameters which were calculated based on mean and SE
Cost per hospitalization for overnight stay	£603.00	£488.46	£729.43	Fifth and ninety-fifth percentiles of the GAMMA functions were estimated using alpha and beta parameters which were calculated based on mean and SE

Key: ACLS – acute capillary leak syndrome; ALT – alanine transaminase; AST – aspartate transaminase; CNS – central nervous system; GM-CSF – granulocyte macrophage colony-stimulating factor; IL-2 – interleukin-2; IV – intravenous; NHS – National Health Service; SE – standard error; ST – standard therapy.

[a] Applies after 5 years.

Figure 25. Tornado diagram for one-way deterministic sensitivity analysis[a]



Key: ACLS – acute capillary leak syndrome; EFS – event-free survival; GM-CSF – granulocyte macrophage colony-stimulating factor; IL-2 – interleukin-2; IV – intravenous; OS – overall survival.

[a] The results obtained by varying less influential parameters not shown.

Scenario analysis

Additional sensitivity analyses were conducted in the form of scenario analyses involving survival, health utility, resource use, outcome discount rate and GM-CSF cost inputs.

Survival analyses

- The effect of changing combination of different parametric function types are shown in Table 61.

- For OS, immunotherapy and standard therapy log-cumulative hazard plots generally looked straight and parallel, resulting in selection of a single parametric model with a treatment effect for the base case (Figure 16). Due to the shape of plots before approximately 4.5 months, the use of separate models for each treatment arm was investigated in scenario analysis (Table 62). Parametric model coefficients are provided in Appendix 9. Coefficients for separate OS models for immunotherapy and standard therapy.

- The “cure” point (5 years in the reference case) was set to 2 and 6.5 years. The lower end was based on the information from the COG that relapses typically occur within the first 2 years after treatment (COG neuroblastoma website). The upper end was based on the fact that the selected best-fitting curves (EFS-Gompertz and OS-exponential) resulted in infeasible estimates after 6.5 years (ie, EFS>OS), suggesting that this point could potentially represent a clinically feasible alternative. Additionally, given that the studied population has already received treatment (ie, induction chemotherapy followed by myeloablative therapy and ASCT) before the start of the dinutuximab study, the patients are already past the start of therapy mentioned by the experts, suggesting a cure point closer to 5 years rather than 10. The incremental cost per QALY gain was £42,707 and £37,421 for the selected thresholds of 2 and 6.5 years, respectively.

- Using a different set of survival parameters derived from a 4-year data cut was also explored. It is important to note that the 4-year data presented at the 2014 ANR Congress were not powered to examine data over 4 years, as there were too few patients to adequately detect a statistical difference between immunotherapy and standard therapy over this time period. Analysis specifics are included in Appendix 10. 4-year data cut analyses. Using the parametric survival models based on 4-year data, the incremental cost per QALY gain was £66,344.

Table 61. Combination of different parametric function types and corresponding ICERs

EFS model	OS Model	ICER[a]
Exponential	Exponential	32,712
Exponential	Weibull	32,790

EFS model	OS Model	ICER[a]
Exponential	Gompertz	32,690
Exponential	Log-logistic	32,509
Exponential	Lognormal	31,596
Weibull	Exponential	34,054
Weibull	Weibull	34,134
Weibull	Gompertz	34,032
Weibull	Log-logistic	33,847
Weibull	Lognormal	32,911
Gompertz	Exponential	37,423[b]
Gompertz	Weibull	37,505
Gompertz	Gompertz	37,401
Gompertz	Log-logistic	37,214
Gompertz	Lognormal	36,264
Log-logistic	Exponential	38,525
Log-logistic	Weibull	38,606
Log-logistic	Gompertz	38,502
Log-logistic	Log-logistic	38,316
Log-logistic	Lognormal	37,369
Lognormal	Exponential	42,091
Lognormal	Weibull	42,170
Lognormal	Gompertz	42,070
Lognormal	Log-logistic	41,888
Lognormal	Lognormal	40,966

Key: EFS – event-free survival; ICER – incremental cost-effectiveness ratio; OS – overall survival.

[a] Incremental cost (£) per quality adjusted life year gained.

[b] Base case scenario.

Table 62. Combination of different parametric function types and corresponding ICERs, with separate OS functions used for immunotherapy and standard therapy

EFS model	OS Model	ICER[a]
Exponential	Exponential	32,712
Exponential	Weibull	32,954
Exponential	Gompertz	32,775
Exponential	Log-logistic	33,021
Exponential	Lognormal	32,681
Weibull	Exponential	34,054
Weibull	Weibull	34,302
Weibull	Gompertz	34,119
Weibull	Log-logistic	34,370

EFS model	OS Model	ICER[a]
Weibull	Lognormal	34,022
Gompertz	Exponential	37,423
Gompertz	Weibull	37,674
Gompertz	Gompertz	37,489
Gompertz	Log-logistic	37,743
Gompertz	Lognormal	37,391
Log-logistic	Exponential	38,525
Log-logistic	Weibull	38,775
Log-logistic	Gompertz	38,590
Log-logistic	Log-logistic	38,843
Log-logistic	Lognormal	38,493
Lognormal	Exponential	42,091
Lognormal	Weibull	42,334
Lognormal	Gompertz	42,155
Lognormal	Log-logistic	42,401
Lognormal	Lognormal	42,060

Key: EFS – event-free survival; ICER – incremental cost-effectiveness ratio; OS – overall survival.

[a] Incremental cost (£) per quality adjusted life year gained.

Health utility analyses

- The results based on using different health utility estimates from Barr 1999 are shown in Table 63.
- A more aggressive reduction in health utility (26% vs 13%) compared to the general population was applied to the survivors in the Stable state. This resulted in an ICER of £43,159 per QALY gained.
- Applying a health utility of 0 for the full duration of 6 cycles of immunotherapy lead to an ICER of £40,155 per QALY gained.

Table 63. ICERs predicted using different health utility estimates from Barr 1999

	ICER[a]
Use HUI3 (stable state: 0.56; failure: 0.32)	38,647
Use “none evident” HUI2 for stable state (0.89)	36,944
Use HUI3 and “none evident” for stable state (stable state: 0.78; failure: 0.32)	37,273
Apply 6% increase[b] to base case estimates from Barr 1999 (stable state: 0.859; failure:	37,175

0.594)	

Key: HUI – health utility index; ICER – incremental cost-effectiveness ratio.

[a] Incremental cost (£) per QALY gained.

[b] Based on information from Portwine 2014 that better HRQOL was reported among advanced neuroblastoma survivors (0.86) than survivors of brain tumours (0.81), corresponding to 6% increase.

Resource use analyses

Given that the Stable state resource use estimates were taken from a study with overall neuroblastoma population (not only high risk patients[8]), twice the resource use frequencies for all resource items was tested in a multi-way analysis. This resulted in an ICER of £38,357 per QALY gained.

Outcomes discount rate analyses

An annual outcome discount rate of 1.5%, resulting in an ICER of £22,017 per QALY gained was explored because with immunotherapy, the substantial health benefits of leading a relatively healthy life compared to the general population may be sustained over the course of patients' lifetime. This consideration is based on two aspects: 1) immunotherapy was shown to be superior compared to standard therapy with regard to EFS (66% vs. 46%) and OS (86% vs. 75%) at 2 years (Yu 2010) 2) given the external data, the majority of the disease-free patients are likely to experience sustained benefits approximately after 5 years. Several economic evaluations have followed this approach, including one in a similar population (Johal 2013, NICE HST 1 [Eculizumab guidance], and NICE TA 235 [Mifamurtide guidance; paediatric oncology population]), basing it on the NICE's recommendations for interventions with treatment effects that are both substantial in restoring health and are sustained over a long period.[9]

GM-CSF cost analysis

When a fluctuation in exchange rate of US dollars to British pound was considered, using 0.55 resulted (per vial cost: £136.61) in an ICER of £37,151, and using 0.7 (per vial cost: £173.87) resulted in an ICER of £37,545.

[8] Specifics regarding the risk levels were not provided in Rebholz 2011.
[9] NICE document was no longer available at the cited web page in Johal 2013.

5.8.1 Summary of sensitivity analyses results

Survival parameters and the outcome discount rate had the greatest impact on cost-effectiveness.

Combination of different parametric survival curves resulted in an ICER range of £31,596 to £42,170 per QALY gained. Similar results were predicted when separate OS curves were fit to immunotherapy and standard therapy, and when different "cure" point thresholds were used. When parametric survival models based on 4-year OS data were used, the ICER increased to £66,344, although it should be mentioned that the trial was not powered to detect differences at year 4.

Changing health utility estimates did not have a substantial impact on the results.

When discount rates were varied between 0%-6%, the predicted ICER range was £13,153-£60,747 (1.5% outcome discount rate ICER: £22,017).

Changes in other parameters, with the exception of dinutuximab cost, had little impact on the results.

5.9 Subgroup analysis

Given the small sample sizes and the narrow target population definition (ie, patients aged 12 months to 17 years, who have previously received induction chemotherapy and achieved at least a partial response, followed by myeloablative therapy and ASCT), subgroup analyses were not performed.

5.10 Validation

5.10.1 Validation of de novo cost-effectiveness analysis

The de novo cost-effectiveness model was validated by checking the model structure, calculations and predictive validity. The structure and assumptions were reviewed by an external health economic expert and a clinical expert for appropriateness for the disease and its treatment. Technical accuracy was checked by going through the calculations and inputs, and running sensitivity analyses to ensure that any changes to the input values produced changes to the results of the expected direction and magnitude; this was carried out by the main programmer as well as a second independent internal programmer. The predictive validity was

addressed as discussed in sections **Clinical parameters and variables > Survival parameters** and **Base-case results > Clinical outcomes from the model.** In general, assessment of predictive validity especially beyond the trial has been challenging due to lack of long-term data for the population in question. Therefore, attempts were made to combine data from the literature with expert opinion to inform assumptions beyond the trial period.

5.11 Interpretation and conclusions of economic evidence

This economic evaluation aimed to evaluate the cost-effectiveness of immunotherapy compared to standard therapy for the treatment of high-risk neuroblastoma in patients aged 12 months to 17 years, who have previously received induction chemotherapy and achieved at least a partial response, followed by myeloablative therapy and ASCT. This population reflects a small group of patients (see section 3.1.1), suggesting an ultra-orphan indication for immunotherapy. The model was informed by a well-designed randomized controlled study, which demonstrated immunotherapy's superiority over standard therapy, with respect to OS and EFS.

The incremental cost per QALY gained with immunotherapy vs standard therapy was £37,423 with 3.5% outcomes discount rate (£22,017 with 1.5% outcome discount rate). Similar outcomes were observed in probabilistic sensitivity analyses. In deterministic sensitivity analyses, survival parameters and the outcome discount rate had the greatest impact on cost-effectiveness.

As other published cost-effectiveness evaluations for the treatment of neuroblastoma were not identified in the literature, comparison of results, structure, and inputs could not be made. However, while the range of predicted ICERs are beyond the threshold of £20,000-£30,000 per QALY gain accepted by NICE, they generally appear to be lower than ICERs for other ultra-orphan indications (Table 64).

Table 64. Some ultra-orphan drugs in current use (adapted from Johal 2013)[10]

Product	Condition	Prevalence	Preliminary estimated ICER (£ per QALY)
Agalsidase beta (Fabrazyme)	Fabry's	200	203,009
Imiglucerase (Ceredase)	Gaucher's (types I and III)	270	391,244
Laronidase (Aldurazyme)	Mucopolysaccharidosis (type 1)	130	334,880
Miglustat (Zavesca)	Gaucher's (type I)	270	116,800
Nonacog alfa (BeneFIX)	Haemophilia B	350	172,500
Iloprost (Ventavis)	Primary pulmonary hypertension	100	23,324
Mifamurtide	Mifamurtide for the treatment of osteosarcoma	58	68,734 (reference case), 41,933 (using 1.5% outcomes discount rate) based on Johal 2013 109,296 (reference case), 54,334 (using 1.5% outcomes discount rate) (ERG assessment for mifamurtide, NICE TA 235)

Key: ERG – Evidence Review Group; ICER – incremental cost-effectiveness ratio; QALY – quality-adjusted life year.

Due to the rarity of the disease, identification of data to inform model inputs was somewhat challenging. Key data constraints were around: 1) the extrapolation of outcomes beyond the trial due to lack of data for similar populations and small sample sizes 2) lack of neuroblastoma state-specific HRQOL data. Nevertheless, the impact of these on model outcomes was tested to the extent possible via deterministic and probabilistic sensitivity analyses. Similarly, appropriate sources were used and the currently available data were utilized to reflect outcomes applicable to England's health care system. As more information becomes available regarding these aspects, it would be beneficial to update this analysis to provide more up-to-date and reliable estimates for the decision problem.

[10] Note that the original reference (NICE document) was no longer available at the cited web page.

To our knowledge, this economic model is the first to address the cost-effectiveness of an intervention in patients with neuroblastoma, modelling the course of the disease over long term and is hoped to edify future evaluations.

6.0 Assessment of factors relevant to the NHS and other parties

As with other oncology indications, the cost of treating a neuroblastoma patient is expected to be high; however, given the low incidence rates associated with the disease, the total number of patients affected is very small. As the impact on NHS budgets must be evaluated given these considerations, a separate model was created to assess the budgetary impact to the NHS due to adopting immunotherapy.

The estimated incident population of high-risk neuroblastoma patients eligible for immunotherapy is approximately 14 per annum using epidemiological estimates (population size, incidence, percentage that are high risk, and percentage with response to induction therapy, stem-cell transplantation, and radiotherapy). Details of the calculation used to derive the high-risk neuroblastoma population eligible for immunotherapy is provided in Table 65. Assuming a population growth of 0.8% per annum, the incident population of high-risk neuroblastoma patients eligible for immunotherapy remains at 14 until well after 2020.

Table 65. Population size for the budget impact analysis

Epidemiological Parameter	Value	Source / Explanation	Resulting Number of Patients
England and Wales population size	57,408,700	ONS (mid 2014 estimate)	**57,408,700**
Incidence / million / year	9.1 / 10 = 0.91	Spix 2006 Standardized incidence for ages 0-14 (9.1) (Table 3, last column for British Isles) divided by 10 to obtain an annual rate	57,408,700 * (1/1,000,000) **= 52**
% high risk	50%	Maris 2007	52 x 50% = **26**
% with response to induction therapy, stem-cell transplantation, and radiotherapy	52%	Matthay 1999	26 x 52% = **14**

Key: ONS – Office for National Statistics

Treatment costs are derived from the economic model and are provided in Table 66. The cost inputs are described in detail in Section 5.5.

Table 66. Costs derived from the economic model and used in the budget impact model calculations

Product	Standard Therapy	Immunotherapy
Drug Cost	£338	£135,404
Administration Cost	£0	£13,784
Concomitant Medication Cost	£0	£172
Monitoring Cost	£0	£60
Adverse Event Cost	£306	£2,590
Total Cost	**£644.12**	**£152,009.89**

The annual budget impact was calculated as the difference in total costs between the future practice (ie, post-immunotherapy) and the current practice (ie, pre-immunotherapy). Table 67 below describes the anticipated 5-year budget impact to the NHS of introducing dinutuximab, assuming positive NICE guidance. The five-year budget impact was calculated as the difference in total costs between future practice (ie, post-immunotherapy) and current practice (ie, pre-immunotherapy). It was assumed that, due to immunotherapy's significant survival benefits above standard therapy, immunotherapy would become standard of care and would quickly (Year 2017) reach 100% market share.

Table 67. Anticipated budget impact of introducing dinutuximab

	2016	2017	2018	2019	2020
Current practice					
Standard therapy market share	100%	100%	100%	100%	100%
Standard therapy patients	14	14	14	14	14
Total current practice cost	£9,018	£9,018	£9,018	£9,018	£9,018
Future practice					
Standard therapy market share	20%	0%	0%	0%	0%
Standard therapy patients	3	0	0	0	0
Standard therapy cost	£1,932	£0	£0	£0	£0
Dinutuximab market share	80%	100%	100%	100%	100%
Dinutuximab patients	11	14	14	14	14
Dinutuximab cost	£1,672,109	£2,128,138	£2,128,138	£2,128,138	£2,128,138
Total future practice cost	£1,674,041	£2,128,138	£2,128,138	£2,128,138	£2,128,138
Budget impact	**£1,665,023**	**£2,119,121**	**£2,119,121**	**£2,119,121**	**£2,119,121**

Based on the patient population eligible to receive immunotherapy for high-risk neuroblastoma treatment, it is predicted that there will be a budget increase of between £1,665,023 and £2,119,121 between 2016 and 2020.

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Single Technology Appraisal (STA)
Dinutuximab for treating high-risk neuroblastoma [ID799]

Dear [redacted],

The Evidence Review Group, Centre for Reviews and Dissemination and Centre for Health Economics – York, and the technical team at NICE have now had an opportunity to take a look at the submission received on the 6 July 2015 by United Therapeutics Corporation. In general terms they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification relating to the clinical and cost effectiveness data.

Both the ERG and the technical team at NICE will be addressing these issues in their reports.

We request you to provide a written response to this letter to the Institute by **5pm** on 11 August 2015. Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, and all information submitted under 'academic in confidence' in yellow.

If you present data that is not already referenced in the main body of your submission and that data is seen to be academic/commercial in confidence information, please complete the attached checklist for in confidence information.

Please do not 'embed' documents (i.e. PDFs, spreadsheets) within your response as this may result in your information being displaced or unreadable. Any supporting documents should be uploaded to NICE Docs/Appraisals via this link: <<Insert NICE DOCS LINK>>.

If you have any further queries on the technical issues raised in this letter then please contact Richard Diaz, Technical Lead (Richard.Diaz@nice.org.uk). Any procedural questions should be addressed to Kate Moore, Project Manager (Kate.Moore@nice.org.uk) in the first instance.

Yours sincerely

Helen Knight
Associate Director – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for in confidence information

Section A: Clarification on effectiveness data

Ch14.18 antibody United Technologies Corp. (UTC) and National Cancer Institute (NCI) bioequivalence

A1. **Priority question:** The draft CHMP opinion provided refers to DIV-NB-201 a bioequivalence study of the UTC and NCI ch14.18 antibodies. Please provide a copy of any published report of this study. If no published report is available for this study, please provide a more detailed summary of the results of the study.

A2. **Priority question:** On page 45 it is stated that: "Published literature exists for ch14.18 monoclonal antibodies that are not bioequivalent to dinutuximab". Please provide the following:

a. a summary of these trials including a summary of the results on event-free survival (EFS) and overall survival (OS), or similar outcomes.

b. A reason these studies were excluded from the submission

c. Any evidence demonstrating that the antibodies are not bioequivalent;

d. Any evidence that the antibodies are likely to have different treatment efficacy.

GM-CSF

A3. **Priority question**: In the company submission (page 110 footnote) it states that GM-CSF does not have a marketing authorisation in England for any indication:

a. Please clarify whether GM-CSF is commercially available in England and current procurement arrangements.

b. Please state whether GM-CSF is used routinely in English clinical practice and clarify potential implications for the submission.

A4. **Priority Question:** Please provide any published literature and clinical study data to establish the contribution of each therapeutic component (dinutuximab, IL-2, and GM-CSF) to the overall efficacy of dinutuximab in combination with IL-2 and GM-CSF. In particular, is there any evidence for the efficacy of dinutuximab + IL-2 without GM-CSF?

Efficacy results

A5. **Priority question:** The CHMP assessment of dinutuximab indicates that analyses of EFS and OS were available from the ANBL0032 trial at a number of different data cut-off points: 13 January 2009, 30 June 2009, 30 June 2012 and March 2014 (Tables 25 and 26 of the CHMP assessment report, pages 84-86).

Please clarify the following:

a. Whether the CHMP report on this trial presents the more complete and/or up-to-date analyses.

b. Please clarify the differences in data and analyses at the various dates presented.

c. Please specify what the correction errors are that are referred to in the CHMP assessment report (footnote to Tables 25 and 26), which were addressed in the 30 June 2009 data cut-off point.

A6. **Priority question**: Please provide additional results of the survival analyses for the ANBL0032 trial as follows:

a. Please provide the Kaplan-Meier curves (with the number of patients at risk at each time point and the total number of events over the observed period) for EFS and OS for each treatment arm in the same format as presented in Figures 7 and 8 of the company submission for the following data cut-off points:

Date of analyses	Data cut-off point	EFS	OS
30 June 2009	2-year	√	√
30 June 2012	3-year	√	√
March 2014	5-year	√	√

b. For the most recent data cut-off point, please provide estimated survival probabilities with 95% confidence intervals for each of 1, 2, 3, 4, and 5 years survival:

i. for both immunotherapy and standard therapy

ii. for both EFS and OS

iii. please provide p-values for these comparisons at each of 1 to 5 years.

c. Please provide hazard ratios assuming proportional hazards comparing the 2 arms for both EFS and OS.

Subgroup analyses

A7. **Priority question**: For the subgroup analysis of Curie score (CS) please provide the following for both EFS and OS, using the most recent data cut-off point as noted in A4:

a. The Kaplan-Meier curves (with the number of patients at risk at each time point and the total number of events over the observed period) for each treatment arm for the separate subgroup populations with a CS=0 and CS>0 (in the same format as presented in Figures 7 and 8 in the submission).

b. The hazard ratios and 95% confidence intervals for immunotherapy compared with standard therapy for both CS=0 and CS>0 subgroup populations.

A8. Figures 14 and 15 of the CHMP assessment report (pages 89-90) present forest plots of EFS and OS by a number of prognostic factors. Not all of the prognostic factors included in the forest plots are included in section 4.8 of the company submission. Please provide justification for the choice of subgroups presented.

The ANBL0032 trial

A9. Please provide a copy of the full trial report for the ANBL0032 study, including reports of all analyses of EFS and OS data.

A10. The ANBL0032 trial is described as being "partially randomised" (page 9 and Table 17 of the submission). Please clarify whether this is solely because patients with biopsy-proven residual disease were not randomised? If so, please clarify why these patients could not be randomised.

A11. The eligibility criterion for age of entry into the ANBL0032 trial was anyone under the age of 31 years, but the final scope specifies children only.

a. Please provide details of the age distribution across the trial, that is numbers of patients in each category: aged 18 months to 5 years, 5 to 11 years, and 11 to 17 years.

b. In order to better understand the risk profile of the trial population please provide the same breakdown by age category for age at diagnosis.

A12. The stopping boundary for the ANBL0032 trial was based on a relative risk of 1.6 (page 50 of the submission).

a. Please clarify to what outcome this relative risk refers

b. Please explain why a relative risk was used rather than a hazard ratio, given that the primary outcome was survival.

A13. In the CHMP assessment report it states that the stopping boundary for the trial was not crossed (page 94 of the CHMP report). Please confirm whether the boundary was or was not crossed, if necessary, by providing full results of the sequential analysis process.

A14. What were the dates of recruitment for the ANBL0032 trial?

A15. Please report the mean (and standard error) number of treatment courses received in each arm of the ANBL0032 trial.

A16. Given that the ANBL0032 trial was stopped early, was any statistical adjustment made in any analyses to account for early stopping? If it was, please provide details of the methods and results.

A17. Please confirm whether the p-values presented in figures 5 and 6 (pages 60 and 61 of the submission, respectively) are based on a log-rank analysis of the survival data.

The ANBL0931 trial

A18. Please provide Kaplan-Meier curves for EFS and OS for the ANBL0931 trial.

Section B: Clarification on cost-effectiveness data

Model

B1. **Priority Question:** Please provide a revised version of the Excel model with the flexibility to allow switching between observed Kaplan-Meier data and parametric analyses of the Kaplan-Meier data in the estimate of cost-effectiveness.

B2. **Priority Question:** In order to allow validation of the cost-effectiveness results for the scenarios, please provide a revised version of the model which includes the results of the 4-year data cut (Appendix 10 of the submission). Please provide the observed Kaplan-Meier data, the full set of parametric estimates (Exponential, Weibull, Gompertz, Log-Logistic and Lognormal), AIC and BIC criteria for each distribution, a visual inspection of the fitted parametric curves (equivalent to Figures 17 and 18, pages 93-96 of the submission), and the variance-covariance and Cholesky decomposition matrices for the scenario analysis.

Long-term outcomes

B3. **Priority Question:** Please provide additional clinical evidence to support the "cure point" of 5-years used in the model (page 137 of submission).

a. A study of long-term outcomes in 5-year survivors of neuroblastoma based on the Childhood Cancer Survivor Study (Laverdière C et al 2009, J Natl Cancer Inst) reported a standardised mortality ratio of 5.6 due to recurrence and secondary malignant neoplasms. Please discuss the generalisability of this study to the population of England.

b. Please clarify whether evidence of longer term mortality was systematically considered within any of the reviews (page 33 of submission).

c. Please provide the rationale for the range applied to the mortality ratio in the sensitivity analysis (SMR between 1 and 2) (see table 60 of submission).

B4. **Priority Question:** What is the basis for the assumption that patients in the failure health state receive topotecan in combination with cyclophosphamide and filgrastim monthly for the rest of their life? Please provide evidence supporting the use of this combination in UK clinical practice.

Costs

B5. **Priority Question:** Please provide justification for using the same administration cost for topotecan therapies as dinutuximab and IL-2 (£1908) from the NHS Reference Costs. Are there any potential differences in hospital length of stay between these therapies?

B6. **Priority Question:** Please provide the proportion of patients at baseline with a body surface area greater than 1 m^2 in the ANBL0032 trial.

Adverse events

B7. **Priority Question:** Please provide details showing how the monthly adverse event rates presented in Table 38 of the company submission (pages 102-103) are derived. Please provide the duration of the adverse events.

End-of-life criteria

B8. **Priority Question:** Please provide justification for the applicability of NICE end-of-life criteria. The company submission states that the life expectancy of patients with neuroblastoma on standard maintenance therapy is greater than 24 months (OS at 2 years from the ANBL0032 trial: Immunotherapy, 86±4%; standard therapy, 75±5%, Figure 6, page 61 of company submission).

Section C: Textual clarifications and additional points

C1. On page 53 of the company submission, please clarify if there is any distinction between, "withdrew due to toxic effects" and "withdrew due to dose-limiting toxic effects"? What is meant by "continued to receive protocol therapy"?

C2. Do the definitions of event-free survival as used in the ANBL0032 trial, and progression-free survival, as specified in the scope differ (table 1 of submission)?

C3. The following references are missing from the reference pack that was provided:

- Latimer NR, Abrams KR, Lambert PC, Crowther MJ, Morden JP. Assessing methods for dealing with treatment crossover in clinical trials: a follow-up simulation study. University of Sheffield Health Economics and Decision Science Discussion Paper No. 14/01. 2014.

- Maris JM, Hogarty MD, Bagatell R, Cohn SL. Neuroblastoma. *Lancet*. 2007;369:2106-2120.

- Matthay KK, Reynolds CP, Seeger RC, et al. Long-term results for children with high-risk neuroblastoma treated on a randomised trial of myeloablative therapy followed by 13-*cis*-retinoic acid: a Children's Oncology Group study. *J Clin Oncol*. 2009;27(7):1007-1013.

- Spix C, Pastore G, Sankila R, et al. Neuroblastoma incidence and survival in European children (1978-1997): report from the Automated Childhood Cancer Information System project. *Eur J Cancer*. 2006;42:2081-2091.

- Stiller CA, Kroll ME, Pritchard-Jones K. Population survival from childhood cancer in Britain during 1978-2005 by eras of entry to clinical trials. *Ann Oncol*. 2012 Sep;23(9):2464-2469.

Additionally, 1 reference is mentioned in the submission, but not listed in the references section. Please confirm whether the following is the correct citation, and please provide a copy of the reference with those listed above in the manner as those previously provided.

- Yu AL, Gilman AL, Ozkaynak MF, Fevzi, M, Sondel, PM, London WB, Cretella, S, Diccianni, M, Cohn SL, Maris JM, Smith, M, Park, Julie on behalf of Children's Oncology Group. Update of Outcome for High-Risk Neuroblastoma Treated on a Randomized Trial of chimeric anti-GD2 antibody (ch14.18) + GM-CSF / IL2 immunotherapy in 1st response: A Children's Oncology Group Study. Advances in Neuroblastoma Research, 2014.

Literature searches

Note: These questions refer to searches in company submission appendix 1.4.4 pages 1-3.

C4. In the MEDLINE search the text word term neuroblastoma is used but not the MeSH term neuroblastoma. Please comment on whether this will increase the likelihood of relevant papers not having been identified.

C5. Which service provider was used to conduct the MEDLINE & Embase search.

C6. Describe the search strategy used to search Clinicaltrials.gov at http://clinicaltrials.gov/ .

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Single Technology Appraisal (STA)
Dinutuximab for treating high-risk neuroblastoma [ID799]

Dear [redacted],

The Evidence Review Group, Centre for Reviews and Dissemination and Centre for Health Economics – York, and the technical team at NICE have now had an opportunity to take a look at the submission received on the 6 July 2015 by UTC. In general terms they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification relating to the clinical and cost effectiveness data.

Both the ERG and the technical team at NICE will be addressing these issues in their reports.

We request you to provide a written response to this letter to the Institute by **5pm** on 11 August 2015. Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, and all information submitted under 'academic in confidence' in yellow.

If you present data that is not already referenced in the main body of your submission and that data is seen to be academic/commercial in confidence information, please complete the attached checklist for in confidence information.

Please do not 'embed' documents (i.e. PDFs, spreadsheets) within your response as this may result in your information being displaced or unreadable. Any supporting documents should be uploaded to NICE Docs/Appraisals via this link: <<Insert NICE DOCS LINK>>.

If you have any further queries on the technical issues raised in this letter then please contact Richard Diaz, Technical Lead (Richard.Diaz@nice.org.uk). Any procedural questions should be addressed to Kate Moore, Project Manager (Kate.Moore@nice.org.uk) in the first instance.

Yours sincerely

Helen Knight
Associate Director – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for in confidence information

Section A: Clarification on effectiveness data

Ch14.18 antibody United Therapeutics Corp. (UTC) and National Cancer Institute (NCI) bioequivalence

A1. **Priority question:** The draft CHMP opinion provided refers to DIV-NB-201 a bioequivalence study of the UTC and NCI ch14.18 antibodies. Please provide a copy of any published report of this study. If no published report is available for this study, please provide a more detailed summary of the results of the study.

DIV-NB-201 has not yet been published in a peer-reviewed journal; however, data were presented at the 2014 Advances in Neuroblastoma Research Congress. Poster presentation and meeting abstract are enclosed.

DIV-NB-201 Study Summary

Source: Data on file, UTC clinical study report for study DIV-NB-201

Design: A Phase 2, multi-center, open-label, randomized, 2-sequence, cross-over comparative pharmacokinetic (PK) and safety study

Study Objective: Compare the PK profiles of UTC-manufactured ch14.18, dinutuximab, and NCI-manufactured ch14.18. Criteria evaluated were PK, immunogenicity, and safety.

Sample Size: 28 subjects with high-risk neuroblastoma

Treatment: Subjects were randomly allocated to receive UTC-ch14.18 or NCI-ch14.18 during Courses 1 and 2 followed by ch14.18 by the alternate manufacturer during Courses 3, 4, and 5. Subjects received ch14.18 with GM-CSF in Courses 1, 3, and 5 and ch14.18 with IL-2 in Courses 2 and 4. The NCI-ch14.18 was administered intravenously (IV) at a dose of 25 mg/m^2/day for 4 days in each course. The UTC-ch14.18 was administered at a dose of 17.5 mg/m^2/day for 4 consecutive days (this dose is equivalent to 25 mg/m^2/day of NCI-manufactured ch14.18; concentrations differ as a result of the manufacturing process). GM-CSF was administered IV or subcutaneously (SC) at a dose of 250 mcg/m^2/day for 14 days during Courses 1, 3, and 5. IL-2 was administered IV at a dose of 3 MIU/m^2/day for 4 days during the 1st week followed by 4 days at 4.5 MIU/m^2/day for the 2nd week during Courses 2 and 4. isotretinoin was administered by mouth for 14 days during all 6 courses. Isotretinoin dosing was based on weight.

Inclusion criteria: Appropriate written informed consent; <8 years old at diagnosis; high-risk neuroblastoma at diagnosis; completed intensive induction followed by autologous stem cell transplantation (ASCT) and radiotherapy therapies; at pre-ASCT evaluation, must have met the International Neuroblastoma Response Criteria (INRC) for complete response (CR), good partial response (GPR), or partial response (PR) for primary site, soft tissue metastases, and bone metastases; had a determination of residual disease performed prior to enrolment in the study; no more than 12 months from date of starting the 1st induction chemotherapy after diagnosis to the date of ASCT; Lansky performance status score of >50%; adequate organ function (criteria specified); life expectancy of >2 months.

Exclusion: Received prior anti-disialoganglioside antibody therapy; received prior vaccine therapy specifically administered as treatment for neuroblastoma; received or

planned to receive anti-cancer therapies no included in the prescribed protocol therapy during the study; received or planned to receive immunosuppressive drugs (as specified) during the study; received or planned to receive cytokines or growth factors not included in the prescribed protocol therapy list during the study.

Pharmacokinetics: Data from 27/28 patients were analyzed for PK; one subject was excluded from analysis due to development of a human anti-chimeric antibody (HACA) response that inhibited the PK assay. Summary statistics from the primary analyses of the PK parameters for ch14.18 are summarized in the table below

ID	C_{max} (ng/mL)			AUC_{inf} (mcg*h/mL)			Vss (L)		$t^{1}/_{2}$, λ_2(h)	
	UTC	NCI	Ratio (UTC/NCI)	UTC	NCI	Ratio (UTC/NCI)	UTC	NCI	UTC	NCI
Mean	6468	6689	0.963	518	470	1.051	5.37	5.13	240	197
SD	719	853	0.054	418	376	0.048	1.47	1.50	135	116

Results of the statistical analysis (ANCOVA) of pharmacokinetic parameters are presented in the table below.

PK Parameter	Geometric Mean UTC (Comparator)	Geometric Mean NCI (Reference)	Ratio	90% CI of Ratio	
				Lower	Upper
AUC_{inf} (mcg*h/mL)	431.2	413.5	1.04	0.98	1.11
C_{max} (ng/mL)	6568.2	6876.9	0.96	0.88	1.04

As necessitated when treating a pediatric oncology population, this study was associated with limited PK sampling, variable absolute doses (due to differences in body surface area), differences in infusion duration, and interruption/re-initiation of infusions in certain subjects based on safety/tolerability considerations that limited the feasibility of a traditional comparability analysis based on noncompartmental PK techniques. To address these issues, a model-based approach was employed to account for the complexities of this study while providing a quantitative assessment of comparability for ch14.18 manufactured by NCI and UTC.

The current analysis indicates that ch14.18 is well-described by a two-compartment PK model with first-order distributional and elimination clearance. Results from the model-based assessment of comparability indicate that UTC-ch14.18 and NCI-ch14.18 provide comparable systemic exposure with the 90% confidence intervals for exposure ratios contained within the standard bioequivalence bounds (0.80 – 1.25).

A small number of subjects in the primary analysis had pre-dose concentrations greater than 5% of the subsequent C_{max}. Given the potential for outlying values to alter the interpretation of model-based analyses, a secondary analysis was performed to assess the impact of these subjects on the conclusion of comparability. Following exclusion of these subjects, the 90% confidence intervals of exposure ratios remained within the standard bioequivalence bounds.

Safety: All 28 subjects randomized in the study had at least one treatment-emergent adverse event (TEAE). There were a total of 1945 events reported in the study and all subjects had at least one AE considered by the investigator to be attributable to ch14.18. The majority of the AEs were ≤ Grade 3. Overall, the most commonly

reported TEAEs included: pyrexia (100%), hypoalbuminaemia (96%), hypokalemia (96%), hyponatremia (82%), cough (75%), ALT increased (68%), anemia (68%), hypocalcemia (68%), pain (68%), pruritus (68%), AST increased (64%), hypertriglyceridemia (64%), and abdominal pain (61%). A summary of AEs occurring in at least 10% of subjects overall is presented below:

MedDRA Preferred Term	UTC-manufactured ch14.18 (N=27) n (%) [# of events]	NCI-manufactured ch14.18 (N=27) n (%) [# of events]	Overall (N=28) n (%)% [# of events]
No. of Subjects with at least one Adverse Event	27 (100.0%)	27 (100.0%)	28 (100.0%)
PYREXIA	27 (100.0%) [71]	27 (100.0%) [64]	28 (100.0%) [135]
HYPOALBUMINAEMIA	25 (92.6%) [60]	26 (96.3%) [59]	27 (96.4%) [119]
HYPOKALAEMIA	25 (92.6%) [65]	23 (85.2%) [55]	27 (96.4%) [120]
HYPONATRAEMIA	21 (77.8%) [48]	20 (74.1%) [43]	23 (82.1%) [91]
COUGH	13 (48.1%) [16]	13 (48.1%) [21]	21 (75.0%) [37]
ALANINE AMINOTRANSFERASE INCREASED	18 (66.7%) [27]	9 (33.3%) [15]	19 (67.9%) [42]
ANAEMIA	15 (55.6%) [22]	13 (48.1%) [15]	19 (67.9%) [37]
HYPOCALCAEMIA	15 (55.6%) [30]	15 (55.6%) [26]	19 (67.9%) [56]
PAIN	16 (59.3%) [28]	12 (44.4%) [22]	19 (67.9%) [50]
PRURITUS	17 (63.0%) [21]	14 (51.9%) [18]	19 (67.9%) [39]
ASPARTATE AMINOTRANSFERASE INCREASED	14 (51.9%) [27]	14 (51.9%) [27]	18 (64.3%) [54]
HYPERTRIGLYCERIDAEMIA	12 (44.4%) [14]	10 (37.0%) [10]	18 (64.3%) [24]
ABDOMINAL PAIN	13 (48.1%) [22]	11 (40.7%) [21]	17 (60.7%) [43]
DIARRHOEA	10 (37.0%) [13]	13 (48.1%) [17]	16 (57.1%) [30]
HYPOTENSION	12 (44.4%) [18]	9 (33.3%) [13]	16 (57.1%) [31]
PLATELET COUNT DECREASED	12 (44.4%) [18]	12 (44.4%) [17]	16 (57.1%) [35]
FACE OEDEMA	10 (37.0%) [13]	8 (29.6%) [9]	15 (53.6%) [22]
PAIN IN EXTREMITY	9 (33.3%) [14]	11 (40.7%) [18]	15 (53.6%) [32]
VOMITING	10 (37.0%) [11]	12 (44.4%) [21]	15 (53.6%) [32]
NAUSEA	9 (33.3%) [11]	6 (22.2%) [10]	14 (50.0%) [21]
NEUTROPHIL COUNT DECREASED	11 (40.7%) [19]	9 (33.3%) [11]	13 (46.4%) [30]
DECREASED APPETITE	6 (22.2%) [9]	7 (25.9%) [8]	12 (42.9%) [17]
HYPERGLYCAEMIA	10 (37.0%) [15]	8 (29.6%) [14]	12 (42.9%) [29]
TACHYCARDIA	11 (40.7%) [18]	10 (37.0%) [15]	12 (42.9%) [33]
DRY SKIN	6 (22.2%) [6]	6 (22.2%) [6]	11 (39.3%) [12]
WHITE BLOOD CELL COUNT DECREASED	6 (22.2%) [8]	8 (29.6%) [12]	11 (39.3%) [20]
RASH	7 (25.9%) [10]	7 (25.9%) [7]	10 (35.7%) [17]
URTICARIA	8 (29.6%) [9]	7 (25.9%) [10]	10 (35.7%) [19]
CAPILLARY LEAK SYNDROME	6 (22.2%) [10]	6 (22.2%) [9]	9 (32.1%) [19]
HYPERCALCAEMIA	6 (22.2%) [8]	4 (14.8%) [6]	9 (32.1%) [14]
HYPERTENSION	7 (25.9%) [15]	7 (25.9%) [17]	9 (32.1%) [32]
HYPOGLYCAEMIA	5 (18.5%) [5]	8 (29.6%) [10]	9 (32.1%) [15]
HYPOMAGNESAEMIA	8 (29.6%) [18]	7 (25.9%) [15]	9 (32.1%) [33]
SINUS TACHYCARDIA	7 (25.9%) [14]	7 (25.9%) [13]	9 (32.1%) [27]
FATIGUE	5 (18.5%) [6]	5 (18.5%) [10]	8 (28.6%) [16]
HYPOPHOSPHATAEMIA	5 (18.5%) [5]	6 (22.2%) [6]	8 (28.6%) [11]
HYPOXIA	5 (18.5%) [7]	5 (18.5%) [9]	8 (28.6%) [16]

URINARY RETENTION	7 (25.9%) [7]	4 (14.8%) [7]	8 (28.6%) [14]
BLOOD CREATININE INCREASED	3 (11.1%) [8]	6 (22.2%) [6]	7 (25.0%) [14]
HYPERKALAEMIA	4 (14.8%) [4]	4 (14.8%) [7]	7 (25.0%) [11]
IRRITABILITY	5 (18.5%) [8]	4 (14.8%) [9]	7 (25.0%) [17]
AGITATION	4 (14.8%) [7]	4 (14.8%) [4]	6 (21.4%) [11]
BLOOD ALKALINE PHOSPHATASE INCREASED	2 (7.4%) [4]	5 (18.5%) [5]	6 (21.4%) [9]
BLOOD BILIRUBIN INCREASED	6 (22.2%) [8]	3 (11.1%) [6]	6 (21.4%) [14]
CONSTIPATION	4 (14.8%) [7]	3 (11.1%) [4]	6 (21.4%) [11]
DEVICE RELATED INFECTION	4 (14.8%) [5]	2 (7.4%) [2]	6 (21.4%) [7]
HAEMATURIA	2 (7.4%) [3]	4 (14.8%) [5]	6 (21.4%) [8]
LYMPHOCYTE COUNT DECREASED	2 (7.4%) [3]	4 (14.8%) [6]	6 (21.4%) [9]
MALAISE	3 (11.1%) [5]	3 (11.1%) [5]	6 (21.4%) [10]
PROTEINURIA	3 (11.1%) [5]	5 (18.5%) [10]	6 (21.4%) [15]
URINE OUTPUT DECREASED	5 (18.5%) [11]	4 (14.8%) [5]	6 (21.4%) [16]
BACK PAIN	4 (14.8%) [5]	2 (7.4%) [3]	5 (17.9%) [8]
CHEILITIS	2 (7.4%) [2]	3 (11.1%) [3]	5 (17.9%) [5]
CHILLS	3 (11.1%) [3]	2 (7.4%) [2]	5 (17.9%) [5]
HEADACHE	4 (14.8%) [5]	1 (3.7%) [1]	5 (17.9%) [6]
HYPERSENSITIVITY	2 (7.4%) [3]	3 (11.1%) [4]	5 (17.9%) [7]
OEDEMA	3 (11.1%) [4]	3 (11.1%) [4]	5 (17.9%) [8]
OEDEMA PERIPHERAL	4 (14.8%) [5]	3 (11.1%) [3]	5 (17.9%) [8]
RHINORRHOEA	2 (7.4%) [3]	3 (11.1%) [4]	5 (17.9%) [7]
ANXIETY	2 (7.4%) [2]	3 (11.1%) [4]	4 (14.3%) [6]
CONTUSION	4 (14.8%) [4]	0	4 (14.3%) [4]
FLUID RETENTION	3 (11.1%) [3]	2 (7.4%) [2]	4 (14.3%) [5]
FLUSHING	2 (7.4%) [2]	3 (11.1%) [3]	4 (14.3%) [5]
HYPERBILIRUBINAEMIA	3 (11.1%) [4]	2 (7.4%) [3]	4 (14.3%) [7]
INJECTION SITE REACTION	3 (11.1%) [3]	1 (3.7%) [1]	4 (14.3%) [4]
INTERNATIONAL NORMALISED RATIO INCREASED	4 (14.8%) [6]	3 (11.1%) [4]	4 (14.3%) [10]
NASAL CONGESTION	1 (3.7%) [1]	3 (11.1%) [3]	4 (14.3%) [4]
PERIORBITAL OEDEMA	4 (14.8%) [4]	0	4 (14.3%) [4]
RASH MACULO-PAPULAR	3 (11.1%) [4]	2 (7.4%) [3]	4 (14.3%) [7]
TACHYPNOEA	3 (11.1%) [3]	1 (3.7%) [1]	4 (14.3%) [4]
UPPER RESPIRATORY TRACT INFECTION	1 (3.7%) [1]	3 (11.1%) [3]	4 (14.3%) [4]
WEIGHT DECREASED	2 (7.4%) [2]	3 (11.1%) [3]	4 (14.3%) [5]
WEIGHT INCREASED	3 (11.1%) [5]	4 (14.8%) [5]	4 (14.3%) [10]
ABDOMINAL DISTENSION	2 (7.4%) [2]	2 (7.4%) [2]	3 (10.7%) [4]
ABNORMAL BEHAVIOUR	2 (7.4%) [2]	1 (3.7%) [1]	3 (10.7%) [3]
ACTIVATED PARTIAL THROMBOPLASTIN TIME PROLONGED	3 (11.1%) [4]	3 (11.1%) [5]	3 (10.7%) [9]
ASTHENIA	2 (7.4%) [2]	1 (3.7%) [1]	3 (10.7%) [3]
ELECTROCARDIOGRAM QT PROLONGED	2 (7.4%) [2]	1 (3.7%) [1]	3 (10.7%) [3]
GASTROENTERITIS VIRAL	2 (7.4%) [2]	1 (3.7%) [1]	3 (10.7%) [3]
INSOMNIA	1 (3.7%) [1]	2 (7.4%) [2]	3 (10.7%) [3]
LETHARGY	1 (3.7%) [2]	2 (7.4%) [2]	3 (10.7%) [4]
MYDRIASIS	1 (3.7%) [1]	2 (7.4%) [2]	3 (10.7%) [3]
NECK PAIN	2 (7.4%) [2]	1 (3.7%) [1]	3 (10.7%) [3]
OROPHARYNGEAL PAIN	2 (7.4%) [2]	1 (3.7%) [2]	3 (10.7%) [4]
RESTLESSNESS	1 (3.7%) [1]	2 (7.4%) [2]	3 (10.7%) [3]

In this study there were 22 subjects overall that reported a serious adverse event (SAE), including 17 subjects (63%) that reported an SAE when treated with UTC-

ch14.18 and 12 subjects (44%) receiving NCI-ch14.18. By manufacturer, there were seven subjects (26%) in the UTC-ch14.18 group that had at least one SAE attributed to study drug and five subjects (19%) in the NCI- ch14.18 group. The most commonly reported SAEs regardless of manufacturer were pyrexia (25%), device related infection (14%), gastroenteritis viral (11%), and hypokalemia (11%).

A2. **Priority question:** On page 45 it is stated that: "Published literature exists for ch14.18 monoclonal antibodies that are not bioequivalent to dinutuximab". Please provide the following:

a. a summary of these trials including a summary of the results on event-free survival (EFS) and overall survival (OS), or similar outcomes.

A total of 29 articles were excluded from the STA submission for dinutuximab due to non-interchangeability of the ch14.18 molecule under investigation. Several of these articles summarize the same study. Of these 29 articles, 12 investigated the efficacy of ch14.18 and present efficacy outcomes in terms of EFS, OS, or similar (Table 20). An additional 2 studies assessed risk factors on outcomes among high-risk neuroblastoma patients, some of whom were treated with ch14.18 as maintenance therapy as part of the trial (Ladenstein 2014a; Ladenstein 2014b). Neither of these publications analysed risk factors related to clinical outcomes specifically of the patients treated with ch14.18, nor provided any assessment of treatment benefit. A summary of all 29 articles identified during the systematic literature review that were excluded from the STA submission due to non-interchangeability with dinutuximab is presented in Table 21.

b. A reason these studies were excluded from the submission

Dinutuximab is a monoclonal antibody which is manufactured in a specific, controlled, and validated process. Study DIV-NB-201 established the equivalence of the UTC ch14.18 molecule to the ch14.18 molecule used in earlier studies by the NCI. A second ch14.18 molecule has been studied in neuroblastoma (APN311). The APN311 molecule originated from the same original hybridoma clone, and maintains the same amino acid sequence as dinutuximab; however, the APN311 molecule is manufactured in a CHO cell line rather than the murine myeloma cell line (SP2/0 hybridoma cells), and as such, the APN311 molecule is not considered equivalent (Committee for Medicinal Products for Human Use (CHMP) Assessment Report for Unituxin (EMA/CHMP/278656/2015). Studies which evaluate the APN311 molecule were not considered relevant to the NICE decision problem regarding dinutuximab.
In order to satisfy the request of the ERG, studies excluded for this reason were reviewed and efficacy results reported in Table 20 and Table 21. Of note, none of the studies with treatment arms utilising non-interchangeable ch14.18 molecules employed the treatment regimen for dinutuximab as proposed by the NICE final scope (ch14.18 in combination with sargramostim [GM-CSF], aldesleukin [IL-2], and isotretinoin).
Due to the (1) non-equivalence of the ch14.18 molecule used in these studies and (2) differing treatment regimen than that proposed for dinutuximab, these studies were deemed to have limited applicability to the evidence submission for dinutuximab and were excluded from the submission.

c. Any evidence demonstrating that the antibodies are not bioequivalent;

At present, no clinical studies directly compare dinutuximab (manufactured from SP2/0 murine cell line) and APN311 (manufactured from CHO cell line). Monoclonal antibodies such as ch14.18 inherit posttranslational modification profiles (most notably glycosylation) that are characteristic of the specific host cell line used. Significant heterogeneity in glycosylation profiles have been demonstrated for monoclonal antibodies produced from SP2/0 and CHO cell lines (Geist 2013). Due to the difference in cell lines, dinutuximab and APN311 are likely to have different glycosylation patterns, which may lead to differences between the two molecules in regards to effector function and clinical efficacy (Horizon Scanning Research & Intelligence Centre. APN311 for high risk neuroblastoma in children and adolescents – first line. NIHR HSRIC ID: 8394. May 2015).

d. Any evidence that the antibodies are likely to have different treatment efficacy.

At present, no clinical studies directly compare the treatment efficacy of dinutuximab and APN311. However, differences in posttranslational modification owing to differing cell lines (as described in the response to A2.c.), may lead to differences between the two molecules in regards to effector function and clinical efficacy (Costa 2014 ; Horizon Scanning Research & Intelligence Centre. APN311 for high risk neuroblastoma in children and adolescents – first line. NIHR HSRIC ID: 8394. May 2015).

GM-CSF

A3. **Priority question**: In the company submission (page 110 footnote) it states that GM-CSF does not have a marketing authorisation in England for any indication:

a. Please clarify whether GM-CSF is commercially available in England and current procurement arrangements.

Dinutuximab is intended to be administered as indicated according to the marketing authorisation, in combination with GM-CSF, IL-2, and isotretinoin. Currently, GM-CSF is not approved for marketing authorization by the EMA for any indication, and therefore is not commercially available in England. UTC does not manufacture this molecule and has no relationship with the manufacturer. However, UTC has arranged for access to GM-CSF through a third party distributor, available through a bona fide request from the treating physician independent of UTC. Additionally, the treating physician would also be able to procure the GM-CSF through their institution's standard operating procedures from a different distributor, if the distributor can provide access to GM-CSF in England.

b. Please state whether GM-CSF is used routinely in English clinical practice and clarify potential implications for the submission.

Although GM-CSF is not routinely used in English clinical practice, the dinutuximab SmPC provides sufficient instructions on using the product in immunotherapy. Additional information regarding GM-CSF can be found in the GM-CSF (Leukine®) Prescribing Information.

A4. **Priority Question:** Please provide any published literature and clinical study data to establish the contribution of each therapeutic component (dinutuximab, IL-2, and GM-CSF) to the overall efficacy of dinutuximab in combination with IL-2 and GM-CSF. In particular, is there any evidence for the efficacy of dinutuximab + IL-2 without GM-CSF?

ch14.18 is a monoclonal antibody composed of the variable region heavy and light chain genes of the murine mAb 14.18 (Mujoo 1987) and the human constant region genes for heavy chain IgG1 and light chain kappa (Gillies 1989). ch14.18 reacts specifically with disialoganglioside (GD2) which is highly expressed on human tumors of neuroectodermal origin such as neuroblastoma and melanoma (Schulz 1984). The mechanism of action for ch14.18 is through antibody dependent cell-mediated cytotoxicity (ADCC) and complement dependent cytotoxicity (CDC) (Mujoo 1987; Mueller 1990).

In vitro studies have demonstrated that anti-GD2 antibodies effectively lyse tumor cells through ADCC (Mujoo 1987, Mueller 1990) and CDC (Mujoo 1987). In particular, Mujoo and colleagues conducted a series of studies with murine antibody 14.G2a which demonstrated ADCC and CDC mediated tumor lysis. In addition, 14.G2a was shown to suppress neuroblastoma tumor growth nude mice. Following the results of this study, Mueller and colleagues demonstrated that ch14.18 was 50- to 100-fold more efficient at inducing ADCC against GD2 positive melanoma cells as compared to the murine antibody 14.G2a.

In clinical studies investigating the safety and efficacy of ch14.18 monotherapy, results are mixed. Handgretinger and colleagues (Handgretinger 1995) investigated escalating doses of ch14.18 in nine refractory or relapsed neuroblastoma subjects. Doses ranged from 30- 50 mg/m^2 dosed over five days (up to a total of four courses for some subjects). A treatment course was five days and the time between courses ranged from 8 to 12 weeks. In this study, two subjects had a complete response (CR) (one subject had a CR in the first course and relapsed in the second course), two subjects had a partial response (PR), one subject had stable disease (SD), and one subject had a minor response. The last three subjects had progressive disease (PD). The adverse reactions associated with ch14.18 monotherapy included pain, fever, and urticaria. Yu and colleagues (Yu 1998) also investigated dose escalation of ch14.18 in one osteosarcoma subject and 10 subjects with refractory high-risk neuroblastoma. In this study, doses of ch14.18 were escalated from 10 to 200 mg/m^2. In the 10 subjects evaluable for disease, there was one PR, four mixed responses (MR), and one SD. The remaining four subjects had PD. The most common toxicities included pain, tachycardia, hypertension, and hypotension.

Simon and colleagues (Simon 2004) conducted a retrospective analysis of subjects enrolled in one of two clinical studies; NB90 (a non-randomized trial that included some patients treated with ch14.18 in consolidation after induction therapy) and in NB97 (a study where all high risk subjects received ch14.18) to evaluate outcomes in subjects who received ch14.18 with those subjects who underwent a 12-month low-dose chemotherapeutic maintenance therapy or who had no additional therapy. Multivariate analysis of the results obtained from this retrospective analysis revealed no advantage in EFS or OS for subjects who were older than one year and received

ch14.18 antibody therapy. Safety analysis revealed similar adverse events to other monotherapy studies with ch14.18. Similar results in the same study were observed when subjects who were less than one year of age with stage 4 neuroblastoma without disease following chemotherapy followed by either low dose oral chemotherapy or high dose chemotherapy plus ASCT were treated with either six courses of ch14.18 or 12 months of oral maintenance chemotherapy (Simon 2005). The authors concluded there was no advantage associated with ch14.18 therapy for improving EFS or OS compared to maintenance chemotherapy. Interestingly, a multivariate analysis of the same study performed 11 years later, found that maintenance treatment with ch14.18 significantly improved EFS and OS outcomes in subjects with stage 4 neuroblastoma as compared to no maintenance therapy (EFS: $p = 0.021$; OS: $p = 0.011$); however, no difference was observed in EFS and OS outcomes between maintenance treatment with ch14.18 as compared to low-dose chemotherapy (EFS: $p = 0.688$; OS: $p = 0.182$). The authors concluded that ch14.18 may prevent late relapses in subjects with MRD which may explain why the survival benefit was observed at nine years and not at the initial three-year follow-up (Simon 2011).

Given the less than optimal responses for subjects treated with ch14.18 monotherapy, investigators posited whether the addition of GM-CSF to ch14.18 could improve outcomes in patients with high-risk neuroblastoma. The rationale for including GM-CSF is multifold. GM-CSF is known to promote antitumor immunity through the activation of monocytes, macrophages, and dendritic cells, thereby enhancing ADCC which is a known mechanism for ch14.18 (Mujoo 1987). In addition, peripheral blood mononuclear cells (PBMC), T cells, and antigen presenting cells cultured with GM-CSF exhibit increased production of Type-1cytokines (i.e., IL-12, interferon-γ, and tumor necrosis factor-α) which stimulate inflammatory and cellular responses. PBMCs cultured with GM-CSF have been associated with a decreased production of Type-2 cytokines (IL-10 and IL-4) which are mediators of immune suppression (Eksioglu 2007). In fact, APCs treated with GM-CSF induced higher proliferation of allogeneic T cells which supports immune stimulatory effects of GM-CSF (Eksioglu 2007).

Given the antitumor nature of GM-CSF, its use has been investigated in several clinical studies. These studies have been reviewed by Arellano and Lonial (Arellano 2008). Of particular interest, rituximab which is typically used alone or in combination with chemotherapy was combined with GM-CSF and chemotherapy (cyclophosphamide, hydroxy doxorubicine, vincristine, and prednisone [CHOP]) in patients with non-Hodgkin's lymphoma (NHL) relapsing after ASCT. GM-CSF was included in this study because it is known to augment the expression of the CD20 antigen on tumor cells and may increase the cell killing and effectiveness of rituximab (Olivieri 2005). This study demonstrated a 75% overall response rate in these patients and supported the further study of the addition of GM-CSF in combination therapy.

The amplification of cell-mediated effector mechanisms against residual tumor/leukemic cells is another potential use of GM-CSF to reduce relapse rates in MRD setting (Toren 1998). Recombinant human GM-CSF has been administered to 20 patients with acute myeloid leukemia (AML) undergoing autologous bone marrow transplant (ABMT) (Richard 1995).

After a median follow-up of 24 months, the actuarial risk of relapse was 37.4% in GM-CSF treated patients compared with 49.5% in historical controls. GM-CSF dependent ADCC was studied in 34 patients with a variety of tumors post-ABMT including three with neuroblastoma (Nagler 1996). A significant increase in monocyte-mediated ADCC following GM-CSF therapy was documented in comparison to pretreatment values and controls. A higher rate of CR and a trend towards better disease-free survival has been reported in patients with acute leukemia or Hodgkin's/non-Hodgkin's lymphoma post-transplant (Gulati 1992; De Witte 1993; Gerhartz 1993). No difference in OS was seen after one year of follow-up in any of these studies; however, this may be due to the short follow-up time. Additionally, GM-CSF has been combined with chemotherapy or other cytokines in renal cell carcinoma, melanoma, and ovarian cancer and has been tested as a vaccine in other solid tumors, including but not limited to breast, pancreas, non-small cell lung, and prostate carcinomas with mixed results (Arellano and Lonial 2008).

As described, ch14.18 is able to kill neuroblastoma cells via ADCC. It has been consistently demonstrated in vitro that granulocytes are more efficient at inducing ADCC to neuroblastoma cells when combined with GM-CSF and anti-GD2 antibodies including: 220- 51 (Fukuda 1998), 3F8 (Kushner 1989, Kushner 1991, Kushner 1992), mAb14.18 (Bruchelt 1989), and ch14.18 (Barker 1991, Barker 1993, Chen 2000). The mechanism behind this enhanced lysis has been linked to a GM-CSF induced up regulation of CD11 and CD18 expression on granulocytes which are thought to be critical adhesion molecules for the development of an anti-GD2 mediated granulocyte ADCC response (Kushner 1992, Cheung 2012). Importantly, GM-CSF has not been shown to induce the proliferation of neuroblastoma cells nor does it appear on its own to kill neuroblastoma cells (Dedhar 1988).

The synergistic effect of GM-CSF in combination with anti-GD2 antibodies has been further demonstrated in the clinic with 3F8 and ch14.18 (Yu 1997, Ozkaynak 2000). Furthermore, a recent publication by Cheung and colleagues (Cheung 2012) provides evidence that granulocyte activation by GM-CSF in neuroblastoma patients as measured by the CD11b activation neoepitope CBRM1/5 may be an independent prognostic factor on outcome. This finding was observed for patients who were in first and second CR/very good partial response (VGPR) as well as those who had primary refractory neuroblastoma. There was a correlation between the amount of CBRM1/5-postive granulocytes and progression-free survival among 147 patients treated with the anti-GD2 antibody 3F8 and GM-CSF (administered subcutaneously [SC]).

The clinical benefit of ch14.18 and GM-CSF has been demonstrated in two clinical trials in patients with neuroblastoma (Yu 1997, Ozkaynak 2000). Specifically, Yu et al. (Yu 1997) conducted the POG-9347 Phase II clinical study to determine the efficacy and toxicity of a combined ch14.18 and GM-CSF treatment regimen in children with recurrent neuroblastoma. ch14.18 was administered intravenously (IV) as a five hour infusion at a dose of 50 mg/m^2/day for four days. GM-CSF was administered SC at a dose of 10 mcg/kg/day for 14 days. This combination was given at three week intervals, for a total duration of six weeks or two courses. Of 28 subjects evaluable for tumor response, one subject experienced a CR, three subjects had PRs, and two subjects had a MR. The rest of the study subjects had PD.

Following the POG-9347 study, Ozkaynak and colleagues (Ozkaynak 2000), conducted a Phase I study (CCG-0935) with ch14.18 in combination with GM-CSF in subjects with neuroblastoma and other GD2 positive childhood tumors following intensive marrow-ablative therapy and ABMT or peripheral blood stem cell (PBSC) transfer. In this study, subjects received ch14.18 infused over five hours for four consecutive days at the following dose levels: 20, 30, 40, and 50 mg/m^2/day. Subjects only received a single dose level for the duration of the study. Subjects who did not have PD may have received a second four-day course of ch14.18. If tumor measurements showed a response after the first two courses, subjects may have received additional courses of ch14.18 treatment at the same dose. During the second and subsequent courses, GM-CSF was administered for seven days (Days 0 through 6) and ch14.18 for four days (Days 0 through 3). Twenty-three subjects were enrolled in this study following the completion of high-dose chemotherapy and stem cell rescue. The majority of subjects received either four (n = 8) or six (n = 8) courses of therapy. The remaining subjects received either one (n = 2), two (n = 1), or three (n = 3) courses of therapy. Ten of 22 subjects had PD at their last assessment. Two of the 10 subjects stopped treatment prematurely due to PD (one of whom also died on study due to PD). Eleven subjects had no change in their disease status and one subject had SD at the time of last assessment. No subjects showed any lasting positive tumor responses.

Ultimately, in vitro (Bruchelt 1989, Kushner 1989, Barker 1991, Kushner 1991, Kushner 1992, Barker 1993, Fukuda 1998, Chen 2000) and clinical data (Yu 1997, Ozkaynak 2000, Kushner 2001, Kushner 2007, Cheung 2012, Cheung 2012) support the addition of GM-CSF to anti-GD2 therapy in patients with neuroblastoma.

Clinical responses observed in high-risk neuroblastoma following ch14.18 plus GM-CSF remained suboptimal, so investigators decided to include IL-2 in the combination. The reason for including IL-2 is multifold. IL-2 causes activation of natural killer (NK) cells, generation of lymphokine-activated killer (LAK) cells, and augments ADCC, a mechanism of action for ch14.18 (Lotze 1981; Grimm 1982; Hank 1988; Hank 1990). IL-2 has been effective at inducing measurable antitumor responses in patients with renal cell carcinoma and melanoma (Rosenberg 1985; Fisher 1988). In a Children's Cancer Group (CCG) Phase II clinical trial, IL-2 was administered to children with refractory solid tumors (Bauer 1995). No antitumor effects were observed in children with sarcomas or neuroblastomas, whereas one of five children with renal cell carcinoma had a CR. Two prospective randomized trials in adult patients with metastatic melanoma failed to show any benefit of IL-2 administered with interferon following standard chemotherapy (Johnston 1998; Rosenberg 1999). IL-2 has been administered post-ABMT in a variety of diseases such as AML, lymphoma, breast cancer and neuroblastoma to eradicate the residual malignant cells via immune activation (Michon 1994; Marti 1995; Valteau-Couanet 1995; Fefer 1997; Meehan 1997; Nagler 1997). All of the trials in patients with neuroblastoma were feasibility and toxicity studies in the post-ABMT setting and were not designed to evaluate antitumor efficacy (Michon 1994; Marti 1995; Valteau-Couanet 1995). Therefore, it is not possible to know the exact antitumor efficacy of IL-2 alone in neuroblastoma patients with MRD

following ASCT; however, the aforementioned studies suggest its effect would be minimal.

In vitro studies with anti-GD2 antibodies and IL-2 demonstrate that in the presence of IL-2, anti-GD2 antibodies are able to enhance the lysis of GD2-expressing cells (Honsik 1986, Munn 1987) as compared to antibody alone. In particular, Munn and colleagues (Munn 1987) demonstrated a 100 to 330% increase in 3F8 mediated ADCC against human neuroblastoma and melanoma cell lines following pre-incubation with IL-2. Honsik and colleagues (Honsik 1986) also demonstrated increased natural killer and ADCC induced tumor lysis when murine 14.18 was administered with PBMC cells incubated with recombinant IL-2.

In vivo experiments also demonstrate enhanced tumor lysis with anti-GD2 antibodies and IL-2 (Honsik 1986, Hank 1990, Kendra 1999). In particular, peripheral blood mononuclear cells incubated with recombinant IL-2 were found to significantly suppress tumor growth in a xenotransplant nude mouse model (Honsik 1986). In addition, Hank and colleagues (Hank 1990) reported a notable increase in 3F8 and 14.G2a mediated ADCC when PMBCs were obtained from cancer patients following treatment with *in vivo* IL-2. Finally, Kendra and colleagues demonstrate that the addition of IL-2 to ch14.18 resulted in no detectable tumor growth in a melanoma xenograft mouse model (Kendra 1999). In this model, IL-2 alone had no effect on tumor growth, indicating that the combination of both ch14.18 and IL-2 was most effective at eradicating tumors.

Early clinical studies with the murine antibody 14.G2a and IL-2 demonstrated the combination was well tolerated and induced ADCC-mediated tumor lysis (Hank 1994, Frost 1997). Specifically, the use of 14.G2a in combination with IL-2 was evaluated in a Phase I/IB study conducted in 33 pediatric patients with GD2 positive tumors (Frost 1997). This study evaluated three different dosing regimens including 14.G2a in combination with IL-2 (Regimen A), 14.G2a alone (Regimen B), and 14.G2a in combination with IL-2 and GM-CSF (Regimen C). This study reported similar AEs when 14.G2a was administered with and without IL-2. In addition, when serial blood samples from two refractory neuroblastoma patients treated with IL-2 and 14.G2a were evaluated, Hank and colleagues (Hank 1994) were able to demonstrate effective ADCC-mediated tumor lysis.

A Phase IB study was subsequently conducted with ch14.18 and IL-2 in patients with melanoma. In this study, 24 adult melanoma patients were treated with ch14.18 (2- 10 mg/m^2/day) for five days prior to, during, or after initial IL-2 administration (1.5 MIU/m^2/day). The maximum tolerated dose of ch14.18 in combination with IL-2 was 7.5 mg/m^2/day. Immune activation was confirmed following ch14.18 and IL-2 administration through the induction of LAK cells and ADCC (Albertini 1997). Notably, patients who received IL-2 one week after initiating ch14.18 alone were more likely to develop a HACA response as compared to those patients who received IL-2 before and/or during ch14.18 administration supporting the administration of IL-2 prior to and during ch14.18 administration (Albertini 1996).

Based on the results of early in vitro and early clinical data with anti-GD2 antibodies and IL-2, IL-2 was added to the ch14.18 regimen included in the CCG-0935A study. The CCG-0935A study was the second part of the CCG-0935 study which was amended to evaluate the tolerability of two dose levels of ch14.18 (20 and 40 mg/m^2/day) in combination with GM-CSF (250 mcg/m^2/day) administered during Courses 1, 3, and 5 alternated with IL-2 (4.5 MIU/m^2/day) administered during Courses 2, 4, and 6 (Gilman 2009). Specifically, this was an open-label, uncontrolled, Phase I study of subjects with neuroblastoma and other GD2 positive childhood tumors that had undergone high-dose chemotherapy and subsequently completed ASCT. Subjects who had undergone high-dose chemotherapy with ASCT were eligible to receive ch14.18 with GM-CSF (250 mcg/m^2/day from Days 0- 9 [for three days before the ch14.18 infusion, during the ch14.18 infusion, and for three days after the ch14.18 infusion]) during Courses 1, 3 and 5 and ch14.18 with IL-2 (4.5 MIU/m^2/day for 96 hours on Days 0-3 and 7-10) during Courses 2, 4 and 6. ch14.18 was given every 28 to 56 days (i.e., ch14.18 treatment courses may have been delayed for justified clinical reasons at the discretion of the responsible physician). The initial dose of ch14.18 with IL-2 was 20 mg/m^2/day for four days for the first cohort. If this dose was tolerated, the next cohort received a dose of 40 mg/m^2/day for four days (regimen 1). The ch14.18 dose with GM-CSF was 40 mg/m^2/day was the maximum tolerated dose (MTD) of ch14.18 when given with GM-CSF as determined in the CCG-0935 study. The study design was later amended to include isotretinoin for six courses based on data from Matthay and colleagues which demonstrated improved EFS with isotretinoin (Matthay 1999). The number of ch14.18 courses (40 mg/m^2/day for four days) was decreased to three and the interval between courses was shortened from 28 days to 21 days (regimen 2) to complete immunotherapy before starting isotretinoin; however, after dose limiting toxicities (DLT) were observed during this treatment regimen, the study was amended again such that ch14.18 was given at a dose of 25 mg/m^2/day for all courses for a total of five courses, and the interval between ch14.18 courses returned to every 28 days. The IL-2 dose was also reduced such that it was given at 3 MIU/m^2/day for 96 hours during the week before ch14.18 and 4.5 MIU/m^2/day for 96 hours concomitantly with ch14.18 regimen 3). Of the 23 subjects who received at least one dose of ch14.18, 14 subjects had no change in their disease status at their last assessment, five had PD, and data on disease status were not available for four subjects. Two subjects showed a CR following treatment, but had relapsed by their last assessment.

The CCG-0935 and CCG-0935A studies were the precursor studies to determine the dosing schedule for use in the randomized, controlled Phase III (ANBL0032, DIV-NB-301) study conducted by the Children's Oncology Group (COG) to determine the effect of ch14.18 in combination with GM-CSF, IL-2, and isotretinoin compared to isotretinoin alone in subjects with high-risk neuroblastoma following successful completion of myeloablative chemotherapy, ASCT, and radiotherapy. In brief, this study showed that there was a statistically significant improvement ($p = 0.0115$) in EFS in the ch14.18 immunotherapy and isotretinoin treated subjects compared to the isotretinoin treated subjects. The two-year point estimate of EFS (95% confidence interval [CI]) for the ch14.18 immunotherapy and isotretinoin group was 66% (56%, 75%) versus 46% (36%, 57%) for the isotretinoin alone group. Additionally, a clinically and statistically significant improvement in OS among those subjects exposed to ch14.18

immunotherapy and isotretinoin compared with isotretinoin alone was observed in the post-ASCT setting (p = 0.0223). The two-year point estimate of OS (95% CI) with the ch14.18 immunotherapy and isotretinoin group was 86% (79%, 94%) as compared to the isotretinoin alone group's two-year estimate of OS of which was 75% (65%, 84%). These findings were further upheld with data from 105 patients participating in the ANBL0931 study which demonstrated two-year EFS and OS of 74 ±6% and 84 ± 5%, respectively (Ozkaynak 2014).

The use of ch14.18 and IL-2 (without GM-CSF) has been reexamined in more recent studies with ch14.18/CHO. The International Society of Paediatric Oncology Europe Neuroblastoma (SIOPEN) recently evaluated the use of ch14.18/CHO plus SC IL-2 versus ch14.18 alone in the post-ASCT setting in the R2 arm of the HR-NBL1 study (Ladenstein 2014). Preliminary results from this study demonstrated two-year event free survival rates of 63% and 67% among patients treated with ch14.18/CHO, IL-2, and isotretinoin versus ch14.18/CHO and isotretinoin, respectively. These results were similar to the 66% two-year EFS rate observed in the ch14.18 immunotherapy arm of the ANBL0032 study (Yu 2010); however, the patients included in the HR-NBL1 study were considered to be more clinically stable with a lower disease burden than the patients included in the ANBL0032 study which makes a direct comparison of the study results difficult. In particular, patients included in the ANBL0032 study could have limited evidence of bone marrow disease whereas patients included in the HR-NBL1 study could not have bone marrow disease at pre-ASCT evaluation. In addition, the HR-NBL1 study reported a relatively low number of patients completing ch14.18/CHO and IL-2 therapy (51%) as compared to those patients receiving ch14.18/CHO alone (84%) which may have impacted the study results. Although the authors concluded that therapy with ch14.18/CHO alone may be as effective as combinations with cytokines, they continue to randomize patients to receive a continuous infusion of ch14.18/CHO ± IL-2 demonstrating the evaluation of IL-2 in combination with ch14.18/CHO still ongoing and subsequently the potential benefit of this combination therapy cannot be discounted.

Ultimately, pre-clinical and clinical data support the concomitant administration of anti-GD2 antibodies such as ch14.18 and cytokines.

Efficacy results

A5. **Priority question:** The CHMP assessment of dinutuximab indicates that analyses of EFS and OS were available from the ANBL0032 trial at a number of different data cut-off points: 13 January 2009, 30 June 2009, 30 June 2012 and March 2014 (Tables 25 and 26 of the CHMP assessment report, pages 84-86).

Please clarify the following:

a. Whether the CHMP report on this trial presents the more complete and/or up-to-date analyses.

The data presented in the submission is the most up-to-date information (March 2014).

b. Please clarify the differences in data and analyses at the various dates presented.

Several different data cut-off points were submitted for regulatory approval. A summary of these data cuts are as follows:

13 January 2009: Primary data analysis (Yu 2010)

Randomized enrolment into ANBL0032 ended on 13 January 2009, after a planned interim analysis demonstrated improved two-year EFS and OS rates in the immunotherapy arm as compared to standard therapy. Data from the 13 January 2009 close of randomized enrolment were the basis for the safety and primary efficacy analyses reported by Yu et al. on behalf of the COG (Yu, 2010).

30 June 2009: Confirmatory data analysis

While the analyses performed by the COG with data collected up to 13 January 2009 is the definitive analysis for EFS, the raw data used to create the analytical data sets by the COG were unavailable to UTC. Therefore, UTC utilized a 30 June 2009 data cut to create analytical data sets, provide data traceability, and produce the safety and confirmatory efficacy analyses that were reviewed by the FDA as part of the process for US regulatory approval. Data in the EMA prescribing information are based on the 30 June 2009 data cut performed by UTC.

30 June 2012: Follow-up data analysis

The follow up data analysis was provided because at the time of the original analysis for OS, the OS data were not considered mature enough and the COG and NCI amended the protocol to include a later analysis for OS at 2-years post the close to randomization. This analysis was also performed on EFS.

March 2014: Overall survival efficacy analysis per request of EMA as part of DIV-NB-301 Clinical Study Report addendum

As stated above, this efficacy analysis was performed at the request of the EMA. It is not UTC's practice to continue to re-analyze the efficacy data unless requested to do so by the regulatory authorities.

c. Please specify what the correction errors are that are referred to in the CHMP assessment report (footnote to Tables 25 and 26), which were addressed in the 30 June 2009 data cut-off point.

The results of the interim analysis of the 13 January 2009 raw dataset lead to the cessation of randomization into the study as the analysis met the criteria for early stopping of randomization, on the basis of the superiority of ch14.18 immunotherapy and isotretinoin over isotretinoin alone with regards to event-free survival. The study and its interim results of efficacy which showed the clinical benefits of chl4.18 immunotherapy and isotretinoin in this difficult-to-treat condition were subsequently published in the New England Journal of Medicine in September 2010 (Yu 2010).

[redacted]

[redacted]

A6. **Priority question**: Please provide additional results of the survival analyses for the ANBL0032 trial as follows:

a. Please provide the Kaplan-Meier curves (with the number of patients at risk at each time point and the total number of events over the observed period) for EFS and OS for each treatment arm in the same format as presented in Figures 7 and 8 of the company submission for the following data cut-off points:

Date of analyses	Data cut-off point	EFS	OS
30 June 2009	2-year	√	√
30 June 2012	3-year	√	√
March 2014	5-year	√	√

Kaplan Meier curves, including the number of patients at risk at each time point, have been provided for EFS and OS utilizing each of the data cuts noted above. The total number of events per treatment group have been noted in the table above for each requested data cut. Note that the number of events is calculated as the difference between the total number of subjects per treatment group and the total number of censored observations over the full survival curve per treatment group.

Please see attached Kaplan Meier curves for 30 June 2009, 30 June 2012, and March 2014 for both EFS and OS.

b. For the most recent data cut-off point, please provide estimated survival probabilities with 95% confidence intervals for each of 1, 2, 3, 4, and 5 years survival:

i. for both immunotherapy and standard therapy

ii. for both EFS and OS

iii. please provide p-values for these comparisons at each of 1 to 5 years.

From the March 2014 data-cut, the estimated survival probabilities with 95% CIs have been provided for each of the 1-5 years of survival. Note that no inferential testing was performed at specific years of survival, but rather a log-rank test was utilized to test the difference in survival distributions between the two treatment arms. It should be noted that the p-values for EFS and OS presented in the company submission reflect the associated log-rank test and not a comparison at the specified survival time point. The survival estimates at 4 years were solely provided to descriptively characterize the differences between the two treatment groups. Therefore, the log-rank test from the March 2014 data analysis is also provided in the attached references.

Table 1. Ad hoc summary of EFS Analysis

United Therapeutics Corporation
Protocol: ANBL0032 (Data as of 31-MAR-2014)

Adhoc Table
Summary of Event-Free Survival Analysis
Randomized ITT Population

	Immunotherapy + RA (n=114)	RA Alone (n=113)	P-value (log-rank test)	Hazard Ratio	95% Hazard Ratio Confidence Limits
1 year EFS rate	79.8%	68.1%			
95% CI	(72.4,87.2)	(59.5,76.7)			
2 year EFS rate	67.4%	52.3%			
95% CI	(58.7,76.0)	(43.0,61.6)			
3 year EFS rate	62.9%	51.3%			
95% CI	(54.0,71.8)	(42.0,60.7)			
4 year EFS rate	59.3%	48.3%			
95% CI	(50.3,68.4)	(38.9,57.7)			
5 year EFS rate	56.5%	48.3%			
95% CI	(47.3,65.7)	(38.9,57.7)			
Log-Rank Test			0.1531		
Hazard Ratios				0.759	(0.520, 1.108)

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Table 2. Ad hoc summary of OS Analysis.

United Therapeutics Corporation
Protocol: ANBL0032 (Data as of 31-MAR-2014)

Adhoc Table
Summary of Overall Survival Analysis
Randomized ITT Population

	Immunotherapy + RA (n=114)	RA Alone (n=113)	P-value (log-rank test)	Hazard Ratio	95% Hazard Ratio Confidence Limits
1 year OS rate	92.1%	90.3%			
95% CI	(87.1,97.0)	(84.8,95.7)			
2 year OS rate	84.1%	77.4%			
95% CI	(77.3,90.8)	(69.5,85.2)			
3 year OS rate	79.6%	67.9%			
95% CI	(72.1,87.0)	(59.1,76.7)			
4 year OS rate	75.1%	61.0%			
95% CI	(67.1,83.1)	(51.8,70.3)			
5 year OS rate	74.2%	57.0%			
95% CI	(66.1,82.3)	(47.5,66.4)			
Log-Rank Test			0.0301		
Hazard Ratios				0.621	(0.402, 0.959)

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c. Please provide hazard ratios assuming proportional hazards comparing the 2 arms for both EFS and OS.

The hazard ratio and 95% CI is provided for both EFS and OS utilizing the March 2014 data cut, See Table 1 and Table 2.

Subgroup analyses

A7. **Priority question**: For the subgroup analysis of Curie score (CS) please provide the following for both EFS and OS, using the most recent data cut-off point as noted in A4:

a. The Kaplan-Meier curves (with the number of patients at risk at each time point and the total number of events over the observed period) for each treatment arm for the separate subgroup populations with a CS=0 and CS>0 (in the same format as presented in Figures 7 and 8 in the submission).

b. The hazard ratios and 95% confidence intervals for immunotherapy compared with standard therapy for both CS=0 and CS>0 subgroup populations.

These analyses were requested from the COG Statistics & Data Center as the patient level data for these analyses is not available in-house at UTC. The new analyses can be performed using a March 2014 data freeze, but unfortunately the COG has indicated they will need at least 1 month to complete the additional investigations.

A8. Figures 14 and 15 of the CHMP assessment report (pages 89-90) present forest plots of EFS and OS by a number of prognostic factors. Not all of the prognostic factors included in the forest plots are included in section 4.8 of the company submission. Please provide justification for the choice of subgroups presented.

Page 66 (Section 4.8.3) of the submission stating that “Dinutuximab has not been evaluated in subgroups other than those listed above” refers to subgroup analyses which were available in the published studies identified during the systematic literature review. Secondary analyses of the ANBL0032 dataset were, however, conducted to support the EMA submission. EFS and OS outcomes by prognostic factors are presented below in Table 3 and Table 4 (CSR Data on File). A forest plot of these prognostic factors is also available from the CHMP Assessment Report in Figure 1 and Figure 2.

An analysis of EFS by prognostic factors across the overall randomized ITT population (regardless of treatment arm) was conducted using the 13 January 2009 data cut (Table 3). Across the overall randomized ITT population, age at diagnosis, age at enrolment, INSS stage, and pre-ASCT response were found to be statistically significantly different on EFS outcomes. Improved EFS at 2 years was seen in age category infant/toddler and adolescent vs child at age of diagnosis (P=0.0194), in age category infant/toddler and adolescent vs child at age of enrolment (P=0.0066), INSS

stages 2a, 3, 4S vs stage 4 (P= 0.0029), and pre-ASCT responses of CR and VGPR vs PR (P= 0.0439) (CSR Data on File).

Table 3. EFS by Prognostic Factors for the Overall Randomized ITT Population (30 June 2009) (CSR Data on File).

Prognostic Factor	Number of Patients (N=226) n(%)	2-Year EFS % (95% CI)	*P*-Value[1]
Age at Enrolment	-	-	0.3355
<18 months	8 (3.5%)	72.9% (40.6, 105)	-
≥18 months	218 (96.5%)	55.5% (47.8, 63.1)	-
Age at Diagnosis (category)	-	-	0.0194[2]
Adolescent (12-18 years)	5 (2.2%)	-	-
Child (2-12 years)	150 (66.4%)	48.2% (38.7, 57.7)	-
Infant/Toddler (28 days-2 years)	63 (27.9%)	70.5% (58.9, 82.1)	-
Unknown	8 (3.5%)	-	-
Age at Enrolment (category)	-	-	0.0066[2]
Adolescent (12-18 years)	5 (2.2%)	-	-
Child (2-12 years)	191 (85.5%)	51.0% (42.6, 59.4)	-
Infant/Toddler (28 days-2 years)	30 (13.3%)	78.9% (65.0, 92.9)	-
INSS Stage	-	-	0.0029[3]
Stage 2a	4 (1.8%)	86.6%	-
Stage 3	26 (11.5%)	-	-
Stage 4s	2 (0.9%)	-	-
Stage 4	181 (80.1%)	52.3%	-
Unknown	13 (5.8%)	-	-
MYCN Amplification	-	-	0.2898
Amplified	81 (35.8%)	53.1% (41.0, 65.2)	-
Non-amplified	103 (45.6%)	62.8% (52.0, 73.6)	-
Unknown	42 (18.6%)	-	-
DNA Ploidy	-	-	0.1589
Diploid	81 (35.8%)	48.5% (36.4, 60.5)	-
Hyperdiploid	97 (42.9%)	62.1% (50.7, 73.5)	-
Unknown	48 (21.2%)	-	-
Histology	-	-	0.0957
Favourable	9 (4.0%)	88.9% (68.4, 109)	-
Unfavourable	149 (65.9%)	55.7% (46.6, 64.9)	-
Unknown	68 (30.1%)	-	-
Pre-ASCT Response	-	-	0.0439[4]
CR	78 (34.5%)	59.8% (51.4, 68.3)	-
VGPR	96 (42.5%)	-	-
PR	52 (23.0%)	45.1% (29.9, 60.3)	-

Stem Cell Type	-	-	0.3397
Purged	57 (25.2%)	64.7% (51.8, 77.5)	-
Unpurged	119 (52.7%)	55.7% (45.6, 65.7)	-
Unknown	50 (22.1%)	-	-

1 *P*-values were calculated with the use of logrank test for the analyses of survival (with subjects with 'Unknown' status excluded from analysis).

2 *P*-values for age categories were reported for child versus infant/toddler and adolescent.

3 The *P*-value for INSS stage was reported for Stage 4 versus Stages 2a, 3, or 4s.

4 The *P*-value for pre-ASCT response was reported for CR and VGPR combined versus PR.

Key: ASCT – autologous stem cell transplant; CI – confidence interval; CR – complete response; EFS – event-free survival; INSS – International Neuroblastoma Staging System; MYCN - v-myc avian myelocytomatosis viral oncogene neuroblastoma derived homolog; PR – partial response; VGPR – very good partial response.

An analysis of OS by prognostic factors across the overall randomized ITT population (regardless of treatment arm) was also conducted using the 13 January 2009 data cut. Across the overall randomized ITT population DNA ploidy and pre-ASCT response were found to be statistically significantly different on OS outcomes. Improved OS at 2 years was seen in hyperdiploid vs diploid DNA ploidy (P=0.0068) and pre-ASCT responses of CR and VGPR vs PR (P=0.0175) (CSR Data on File).

Table 4. Overall Survival by Prognostic Factors for the Overall Randomized ITT Population (30 June 2009) (CSR Data on File).

Prognostic Factor	Number of Patients (N=226) n(%)	2-Year OS % (95% CI)	*P*-Value[1]
Age at Enrolment	-		0.8850
<18 months	8 (3.5%)	72.9% (40.6, 105)	-
≥18 months	218 (96.5%)	80.6% (74.4,86.7)	-
Age at Diagnosis (category)	-	-	-
Adolescent (12-18 years)	5 (2.2%)	-	0.8453[2]
Child (2-12 years)	150 (66.4%)	82.2% (74.8, 89.6)	-
Infant/Toddler (28 days-2 years)	63 (27.9%)	74.9% (63.8, 86.0)	-
Unknown	8 (3.5%)	-	-
Age at Enrolment (category)	-	-	-
Adolescent (12-18 years)	5 (2.2%)	-	0.2560[2]
Child (2-12 years)	191 (85.5%)	79.8% (73.0, 86.6)	-
Infant/Toddler (28 days-2 years)	30 (13.3%)	81.7% (68.3, 95.0)	-
INSS Stage	-	-	0.1218[3]
Stage 2a	4 (1.8%)	85.4% (70.1, 101)	-
Stage 3	26 (11.5%)	-	-
Stage 4s	2 (0.9%)	-	-
Stage 4	181 (80.1%)	79.9% (73.3, 86.6)	-
Unknown	13 (5.8%)	-	-
MYCN Amplification	-	-	0.1934
Amplified	81 (35.8%)	72.8% (62.0, 83.7)	-
Non-amplified	103 (45.6%)	85.9% (77.7, 94.1)	-

Unknown	42 (18.6%)	-	-
DNA Ploidy	-	-	0.0068
Diploid	81 (35.8%)	72.2% (61.4, 82.9)	-
Hyperdiploid	97 (42.9%)	85.4% (76.8, 94.0)	-
Unknown	48 (21.2%)	-	-
Histology	-	-	0.1311
Favourable	9 (4.0%)	100% (100, 100)	-
Unfavourable	149 (65.9%)	81.0% (73.6, 88.4)	-
Unknown	68 (30.1%)	-	-
Pre-ASCT Response	-	-	-
CR	78 (34.5%)	84.8% (87.7, 90.9)	0.0175[4]
VGPR	96 (42.5%)	-	-
PR	52 (23.0%)	66.6% (51.5, 81.6)	-
Stem Cell Type	-	-	0.9046
Purged	57 (25.2%)	83.3% (73.4, 93.3)	-
Unpurged	119 (52.7%)	81.2% (73.2, 89.1)	-
Unknown	50 (22.1%)	-	-

1 *P*-values were calculated with the use of logrank test for the analyses of survival (with subjects with 'Unknown' status excluded from analysis).

2 *P*-values for age categories were reported for child versus infant/toddler and adolescent.

3 The *P*-value for INSS stage was reported for Stage 4 versus Stages 2a, 3, or 4s.

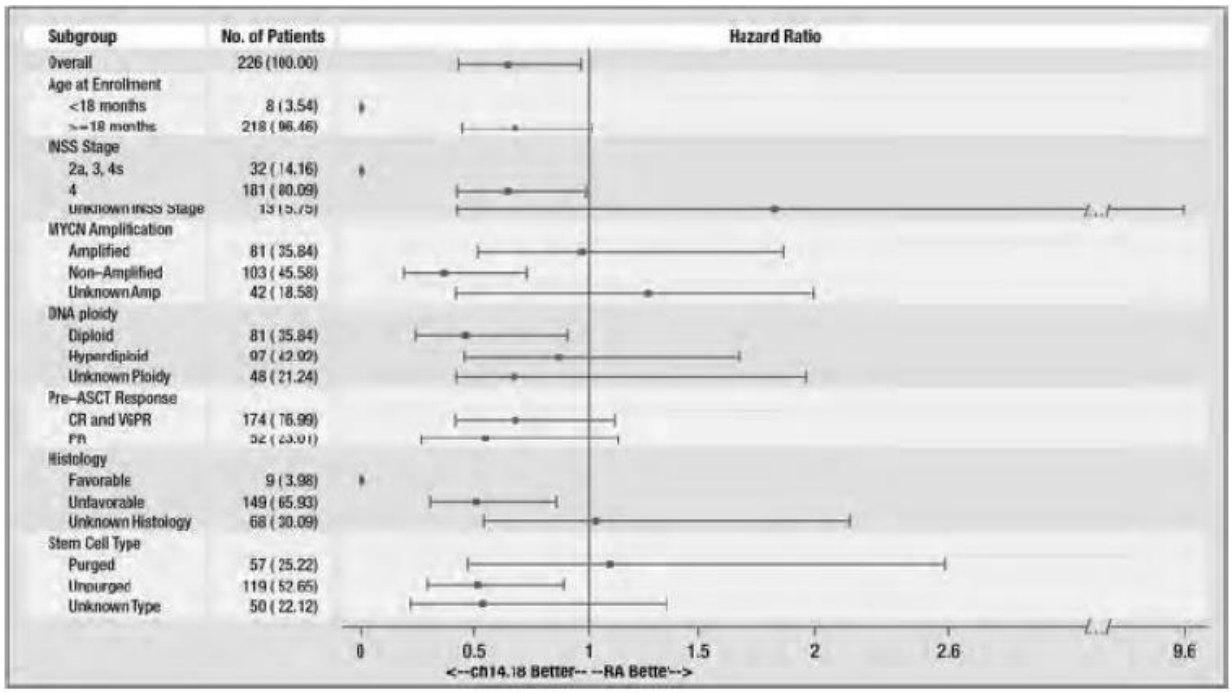
4 The *P*-value for pre-ASCT response was reported for CR and VGPR combined versus PR.

Key: ASCT – autologous stem cell transplant; CI – confidence interval; CR – complete response; INSS – International Neuroblastoma Staging System; MYCN - v-myc avian myelocytomatosis viral oncogene neuroblastoma derived homolog; OS – overall survival; PR – partial response; VGPR – very good partial response.

As these prognostic factors were shown to impact EFS and OS outcomes, forest plots were created to compare immunotherapy to standard therapy across the main prognostic factors listed in Table 3 and Table 4. The forest plots of EFS and OS for the main prognostic factors are presented in Figure 1 and Figure 2.

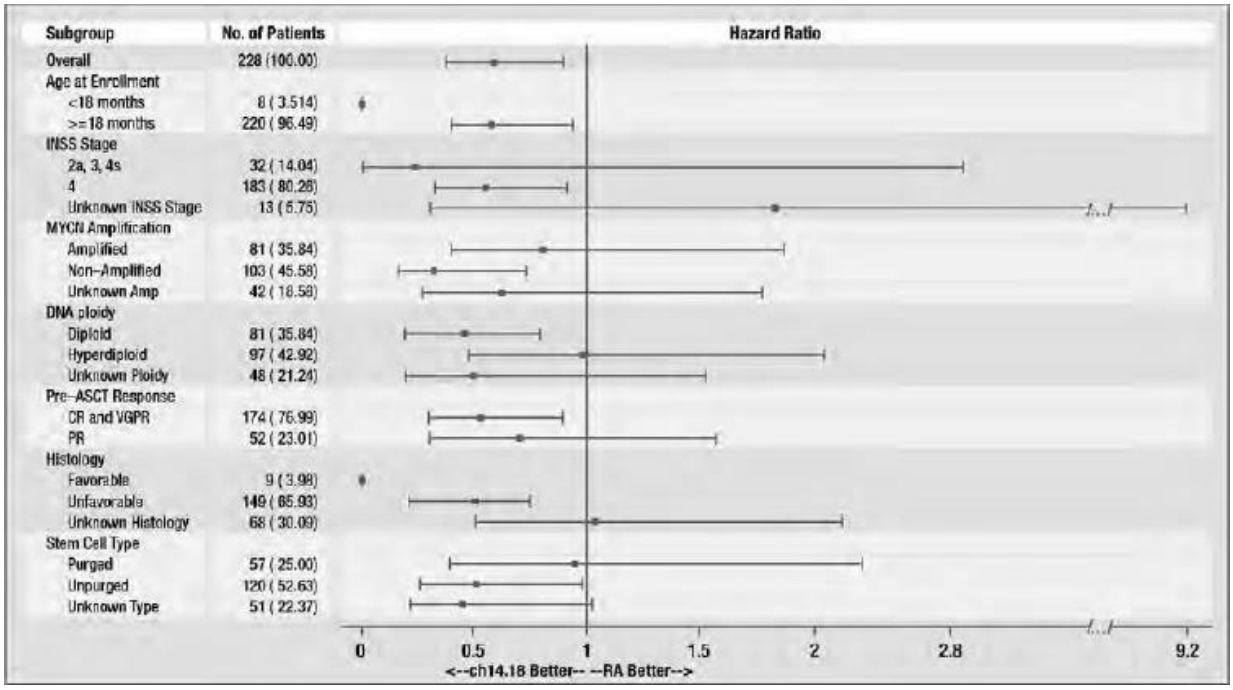
The forest plots show that standard therapy was not statistically superior to immunotherapy for either outcome for any subgroup. For the outcome of EFS at 2 years, results favoured immunotherapy for all prognostic groups except unknown INSS stage, unknown MYCN amplification status, unknown histology, and purged stem cell type (results not statistically significant). For OS at 2 years, results favoured immunotherapy for all prognostic groups except unknown INSS stage and unknown histology (results not statistically significant). Prognostic subgroups were not adequately powered to detect treatment differences and overall demonstrate the superiority of immunotherapy over standard therapy.

Figure 1. Forest Plot of 2-Year EFS Results by Prognostic Factors (30 June 2009) (CSR Data on File).



Key: ASCT – autologous stem cell transplant; CR – complete response; EFS – event-free survival; INSS – International Neuroblastoma Staging System; MYCN - v-myc avian myelocytomatosis viral oncogene neuroblastoma derived homolog; No – number; PR – partial response; VGPR – very good partial response.

Figure 2. Forest Plot of 2-Year OS Results by Prognostic Factors (30 June 2012).



Key: ASCT – autologous stem cell transplant; CR – complete response; INSS – International Neuroblastoma Staging System; MYCN - v-myc avian myelocytomatosis viral oncogene neuroblastoma derived homolog; No – number; OS – overall survival; PR – partial response; VGPR – very good partial response.

The ANBL0032 trial

A9. Please provide a copy of the full trial report for the ANBL0032 study, including reports of all analyses of EFS and OS data.

These reports have been provided in a separate file.

A10. The ANBL0032 trial is described as being "partially randomised" (page 9 and Table 17 of the submission). Please clarify whether this is solely because patients with biopsy-proven residual disease were not randomised? If so, please clarify why these patients could not be randomised.

ANBL0032 is described as a "partially randomised" study as it consisted of both randomized (Part A) and non-randomized (Part B) portions. Randomized enrolment into ANBL0032 Part A ended on 13 January 2009, after a planned interim analysis demonstrated improved two-year EFS and OS rates in the immunotherapy arm as compared to standard therapy. Data from the 13 January 2009 close of randomized enrolment were the basis for the safety and primary efficacy analyses reported by Yu et al. on behalf of the COG. [Yu, 2010] After randomized enrolment stopped into ANBL0032 Part A, all additional patients were enrolled into ANBL0032 Part B, a single arm, multi-center expanded access trial. All patients enrolled in ANBL0032 Part B received the immunotherapy regimen utilized in ANBL0032 Part A.

In addition, subjects with biopsy proven residual disease following ASCT (Stratum 07) were eligible for enrolment in the study but not for randomization. These subjects were non-randomly assigned to treatment in the ch14.18 and isotretinoin group for both Parts A and B, and were excluded from the primary efficacy analysis, but included in the safety analyses.

A11. The eligibility criterion for age of entry into the ANBL0032 trial was anyone under the age of 31 years, but the final scope specifies children only.

a. Please provide details of the age distribution across the trial, that is numbers of patients in each category: aged 18 months to 5 years, 5 to 11 years, and 11 to 17 years.

Please see Table 5 and Table 6.

Table 5. Age at enrolment (years) for the overall ANBL0032 population

Age at enrolment (years)	Overall population N=246
Mean (SD)	4.3 (2.48)
Median	3.85
Min, max	0.95, 15.29

Table 6. Categorical age breakdown based on the March 2014 data cut of the ANBL0032 trial

	Control group from ANBL0032 (Randomized) (N=108)	ch14.18 group from ANBL0032 (Randomized) (N=141)
Age at Enrollment (Years)		
N	108	141
Mean (SD)	4 (2.15)	4.5 (2.67)
Median	3.67	3.96
Min, Max	0.95, 13.29	0.95, 15.29
Categorical Age at Enrollment (Years)		
Age 1 year or less	1 (0.9%)	1 (0.7%)
Age > 1 to 3 years	39 (36.1%)	39 (27.7%)
Age > 3 to 5 years	39 (36.1%)	62 (44.0%)
Age > 5 to 8 years	23 (21.3%)	30 (21.3%)
Age > 8 to 12 years	5 (4.6%)	3 (2.1%)
Age > 12 to 15 years	1 (0.9%)	4 (2.8%)
Age > 15 to 17 years	0	2 (1.4%)
Age > 17 years	0	0
Missing	0	0

b. In order to better understand the risk profile of the trial population please provide the same breakdown by age category for age at diagnosis.

Please see Table 7Table 7

Table 7. Age category for age at diagnosis in the ANBL0032 trial.

	Control group from ANBL0032 (Randomized) (N=108)	ch14.18 group from ANBL0032 (Randomized) (N=141)
Age at Diagnosis (Years)		
N	108	141
Mean (SD)	3.3 (2.15)	3.8 (2.66)
Median	2.9	3.2
Min, Max	0.2, 12.6	0.3, 14.5
Categorical Age at Diagnosis (Years)		
Age 1 year or less	8 (7.4%)	5 (3.5%)
Age > 1 to 3 years	51 (47.2%)	56 (39.7%)
Age > 3 to 5 years	30 (27.8%)	57 (40.4%)
Age > 5 to 8 years	14 (13.0%)	14 (9.9%)
Age > 8 to 12 years	4 (3.7%)	3 (2.1%)
Age > 12 to 15 years	1 (0.9%)	6 (4.3%)

A12. The stopping boundary for the ANBL0032 trial was based on a relative risk of 1.6 (page 50 of the submission).

a. Please clarify to what outcome this relative risk refers

The relative risk of 1.6 was calculated as control:experimental using the planning parameters for 3-year EFS.

b. Please explain why a relative risk was used rather than a hazard ratio, given that the primary outcome was survival.

The ANBL0032 protocol was developed by the COG and the National Cancer Institute with no input from UTC. As a reminder, UTC became involved in the program after the ANBL0032 study results were published in the NEJM. The COG confirmed that HR was used for the calculations, and had intended for the text to refer to HR but RR was erroneously stated.

A13. In the CHMP assessment report it states that the stopping boundary for the trial was not crossed (page 94 of the CHMP report). Please confirm whether the boundary was or was not crossed, if necessary, by providing full results of the sequential analysis process.

Based on the stopping criteria initially established, the trial should not have been stopped. As detailed in Table 8 below, the nominal alpha required for stopping the study for efficacy at the Nov 2008 interim analysis was 0.0108. The observed alpha from this interim analysis was 0.0115. Thus the stopping boundary had not been crossed.

[redacted]

A14. What were the dates of recruitment for the ANBL0032 trial?

26 Oct 2001 (first subject enrolled)

03 Nov 2008 (last subject enrolled during the randomized portion of the study)

Open-label, non-randomized portion still ongoing

A15. Please report the mean (and standard error) number of treatment courses received in each arm of the ANBL0032 trial.

Table 9. Mean (and standard error) number of treatment courses received in each arm of the ANBL0032 trial.

	Treatment	
	RA Alone	Immunotherapy + RA
Courses Completed		
n	109	141
Mean (SD)	5.3 (1.46)	5.3 (1.46)
Median	6	6
Min, Max	1, 6	1, 6

RA – retinoic acid (ie, isotretinoin); SD – standard deviation

A16. Given that the ANBL0032 trial was stopped early, was any statistical adjustment made in any analyses to account for early stopping? If it was, please provide details of the methods and results.

The data were analysed as specified in the protocol, with the exception of the 4 patients who crossed over from isotretinoin alone to immunotherapy + isotretinoin after

the study randomization was halted in 2009. These patients were censored at the date of crossover for all efficacy analyses in the 30 June 2012 and March 2014 data cuts.

A17. Please confirm whether the p-values presented in figures 5 and 6 (pages 60 and 61 of the submission, respectively) are based on a log-rank analysis of the survival data.

Yes, the p-values presented are from a log-rank analysis.

The ANBL0931 trial

A18. Please provide Kaplan-Meier curves for EFS and OS for the ANBL0931 trial.

According to the protocol, efficacy data collected in the ANBL0931 study will be analysed after 2 years of follow-up on all subjects. As of the last data cut received from the COG, efficacy data were not mature enough to analyse and therefore Kaplan Meier curves are unavailable.
Survival estimates, however, were presented at the 2014 ANR Congress (Ozkaynak 2014):

> One of the 226 randomized patients was subsequently deemed ineligible, leaving 225 analysed herein. Four patients crossed over from the isotretinoin arm to receive immunotherapy after randomization was halted, and were censored at the start of antibody therapy. The median follow-up time for patients alive without an event is 5.5 years. The updated EFS (± standard error) for immunotherapy was 67±4% (2-year) and 59±5% (4-year) versus 51±5% (2-year) and 48±5% (4-year) for isotretinoin alone (p= 0.11). The updated OS was significantly better for immunotherapy (2-year: 83±4%; 4-year: 74±4%) than isotretinoin alone (2-year: 76±4%; 4-year: 59±5%) (p=0.02). For stage 4 patients (N=180), EFS was 64±5% (2-year)/54±5% (4-year) versus 45±5% (2-year)/44±5% (4-year) (p=0.1); OS was 83±4% (2-year)/72±5% (4-year) versus 75±5% (2-year)/56±5% (4-year) (p=0.02) for immunotherapy and for isotretinoin, respectively. For 25 patients who were non-randomly assigned to immunotherapy for biopsy-proven residual disease, 4-year EFS and OS were 32±9% and 53±11%. Peak anti-α-Gal antibody levels were higher for patients with allergic reactions than those without (p=0.03 one-sided).

Section B: Clarification on cost-effectiveness data

Model

B1. **Priority Question:** Please provide a revised version of the Excel model with the flexibility to allow switching between observed Kaplan-Meier data and parametric analyses of the Kaplan-Meier data in the estimate of cost-effectiveness.

See attached model titled “Dinutuximab Economic Model 31-07-2015 2-year data (with observed data option)” which includes an option to select the observed Kaplan-Meier data or parametric analyses.

B2. **Priority Question:** In order to allow validation of the cost-effectiveness results for the scenarios, please provide a revised version of the model which includes the results of the 4-year data cut (Appendix 10 of the submission). Please provide the observed Kaplan-Meier data, the full set of parametric estimates (Exponential, Weibull, Gompertz, Log-Logistic and Lognormal), AIC and BIC criteria for each distribution, a visual inspection of the fitted parametric curves (equivalent to Figures 17 and 18, pages 93-96 of the submission), and the variance-covariance and Cholesky decomposition matrices for the scenario analysis.

See attached model titled "Dinutuximab Economic Model 31-07-2015 4-year data (with observed data option)", which includes an option to select the observed Kaplan-Meier data or parametric analyses. This version includes the full set of updated parametric estimates (Exponential, Weibull, Gompertz, Log-Logistic and Lognormal). The full set of estimates, including Akaike's information criterion (AIC) and Bayesian information criterion (BIC), are shown in the tables below, along with tables for the variance-covariance matrices.

Table 10. Coefficients for different parametric function fits for EFS (4-year data)

	Treatment[a]	Constant	Third Coefficient[b]	AIC Statistic	BIC Statistic
Exponential (PH model)	-0.3362	-1.6803		738	745
Weibull (PH model)	-0.3120	-0.9715	0.5627	682	693
Gompertz (PH model)	-0.3208	-0.4400	-0.5782	630	641
Log-logistic (AFT model)	0.7252	0.6751	1.4141	667	678
Lognormal (AFT model)	0.7069	0.7682	2.3288	658	668

Key: AFT – accelerated failure time; AIC – Akaike's information criterion; BIC – Bayesian information criterion; EFS – event-free survival; PH – proportional hazards.

[a] 1, standard therapy; 2,immunotherapy

[b] Exponential: no third coefficient, Weibull: ρ (rho), Gompertz: ɣ (gamma), log-logistic: ɣ (gamma), lognormal: σ (sigma)

Table 11. Coefficients for different parametric function fits for OS (4-year data)

	Treatment[a]	Constant	Third Coefficient[b]	AIC Statistic	BIC Statistic
Exponential (PH model)	-0.5705	-1.7874		525	532
Weibull (PH model)	-0.5492	-1.4448	0.7950	521	531
Gompertz (PH model)	-0.5328	-1.2792	-0.1883	512	522
Log-logistic (AFT model)	0.7406	1.2950	1.0791	517	527
Lognormal (AFT model)	0.6839	1.4570	1.9260	514	524

Key: AFT – accelerated failure time; AIC – Akaike's information criterion; BIC – Bayesian information criterion; EFS – event-free survival; PH – proportional hazards.

[a] 1, standard therapy; 2,immunotherapy

[b] Exponential: no third coefficient, Weibull: ρ (rho), Gompertz: ɣ (gamma), log-logistic: ɣ (gamma), lognormal: σ (sigma)

Table 12. Covariance matrices for survival models (4-year data)

Model type		EFS			OS		
		Treatment	Constant	Third coefficient*	Treatment	Constant	Third coefficient*
Exponential	Treatment	0.0371517		N/A	0.0485714		N/A
	Constant	-0.0546956	0.0897833	N/A	-0.0685714	0.1085714	N/A
Weibull	Treatment	0.03717814			0.04865078		
	Constant	-0.05434998	0.09429995		-0.06744014	0.12469645	
	Third coefficient*	-0.0004397	-0.00574672	0.00731176	-0.00087606	-0.01248733	0.00967026
Gompertz	Treatment	0.03716872			0.04866539		
	Constant	-0.05433303	0.09750733		-0.06744334	0.12211384	
	Third coefficient*	-0.00029667	-0.00632072	0.00517235	-0.00050219	-0.00602873	0.00268383
Log-logistic	Treatment	0.12792823			0.08704557		
	Constant	-0.1907569	0.32120247		-0.12287585	0.20142706	
	Third coefficient*	0.00170672	0.00319635	0.00676835	0.00379813	0.00244597	0.00909995
Lognormal	Treatment	0.11958279			0.09397386		
	Constant	-0.1768055	0.29950269		-0.1334544	0.22463075	
	Third coefficient*	0.00175389	0.00442022	0.00593186	0.00380125	0.00408229	0.00754123

EFS, event-free survival; OS, overall survival; N/A – not applicable

* Weibull: ρ (rho), Gompertz: ɣ (gamma), log-logistic: ɣ (gamma), lognormal: σ (sigma)

Obtained from analysis of individual patient data from dinutuximab by using 4 year data from the pivotal phase 3 clinical trial

Long-term outcomes

B3. **Priority Question:** Please provide additional clinical evidence to support the "cure point" of 5-years used in the model (page 137 of submission).

a. A study of long-term outcomes in 5-year survivors of neuroblastoma based on the Childhood Cancer Survivor Study (Laverdière C et al 2009, J Natl Cancer Inst) reported a standardised mortality ratio of 5.6 due to recurrence and secondary malignant neoplasms. Please discuss the generalisability of this study to the population of England.

The Childhood Cancer Survivor Study was a 27-site survey of 954 neuroblastoma survivors (defined as alive 5 years after diagnosis) compared to low-risk siblings without cancer in the United States and Canada followed over 30 years. This study found a higher mortality rate among neuroblastoma survivors compared to non-cancer controls (standardised mortality rate of 5.6 [95% confidence interval of 4.4 to 6.9]). Neuroblastoma survivors were at a higher risk of cancer recurrence, secondary malignant neoplasm, chronic health problems, musculoskeletal and neurological complications, many of which may be attributable to the treatment received. Generalisability of the study is limited by both geography and time of data collection, as the study population represents a group of patients treated in the 1970s and 1980s. The treatment paradigm at this time differs significantly from current practice and does not include the treatment of interest evaluated within the model (ie, dinutuximab).

Nevertheless, Childhood Cancer Survivor Study was identified as the best available source of data for long-term survivorship in neuroblastoma. The authors cite that the findings are similar to those reported from smaller population-based European studies, for example, a standardized mortality ratio (SMR) of 10.8 was found in a population-based study of 5 Nordic countries for 5-year survivors of childhood cancer, in general (not specific to neuroblastoma) (Möller 2001). Patients eligible for dinutuximab have already received induction chemotherapy, myeloablative therapy, and ASCT. As mentioned in the submission, patients are well past the initiation of therapy, suggesting a cure point closer to 5 years rather than 10. Due to the uncertainty in this "cure point", a sensitivity analysis was undertaken whereby the cure rate was set at 2 years and 6.5 years, with a resulting incremental cost per QALY gain of £42,707 and £37,421, respectively.

b. Please clarify whether evidence of longer term mortality was systematically considered within any of the reviews (page 33 of submission).

Longer-term mortality was not explicitly considered within the clinical or economic review of the literature; however, mortality rates were a topic of interest. Due to the lack of long-term data for dinutuximab in combination with GM-CSF, IL-2, and isotretinoin in this patient population and uncertainty regarding the long-term impact of treatment (positive or negative), the model was structured based upon the observation that OS and EFS appear to reach a plateau between 5 and 10 years in recent long-term studies (Cheung 2012, Kubota 2010, Matthay 2009, Perwein 2011, Simon 2011).

c. Please provide the rationale for the range applied to the mortality ratio in the sensitivity analysis (SMR between 1 and 2) (see Table 60 of submission).

For patients who achieve stable state (ie, 5-year survivors), the base-case analysis assumes no difference in mortality. In the sensitivity analysis, the mortality rate was increased to twice that of the general population (a high value of 2). This range was chosen due to the uncertainty surrounding long-term mortality for high risk neuroblastoma patients treated with currently available therapies and the observation that OS and EFS appear to plateau between 5 and 10 years (Cheung 2012, Kubota 2010, Matthay 2009, Perwein 2011, Simon 2011). As discussed in the response to question B3.a., The Childhood Cancer Survivor Study long-term study of neuroblastoma survivors who were diagnosed from 1970 to 1986 found a higher mortality rate (SMR of 5.6). An additional scenario analysis was conducted using an SMR of 5.6, resulting in only a modest impact on the model results (ICER of £40,374 per QALY gained vs £37,423 per QALY gained in the base-case analysis which assumes no difference in long-term mortality).

Table 13. Model Outcomes Using a Mortality Ratio of 5.6

Outcome	Immunotherapy	Standard Therapy	Difference
LYs per Patient (Discounted)	15.91	11.60	4.31
QALYs per Patient (Discounted)	12.56	9.12	3.44
TOTAL	£ 184,696	£ 45,957	£ 138,740
Incremental Cost per LY Gained (Discounted)	£ 32,180		
Incremental Cost per QALY Gained (Discounted)	£ 40,374		

Key: LY – life-years; QALY – quality-adjusted life-years.

B4. **Priority Question:** What is the basis for the assumption that patients in the failure health state receive topotecan in combination with cyclophosphamide and filgrastim monthly for the rest of their life? Please provide evidence supporting the use of this combination in UK clinical practice.

According to expert opinion, patients in the failure state were assumed to receive topotecan in combination with cyclophosphamide and filgrastim because this is how patients would typically be treated for a relapse. A clinical trial (London, J Clin Oncol 2010;28:3808-3815) compared topotecan alone (with subcutaneous filgrastim) versus topotecan plus cyclophosphamide in relapsed/refractory neuroblastoma and found that topotecan plus cyclophosphamide had improved PFS (but no difference in OS). The protocol in this study called for continued treatment until disease progression or up to 1-year in patients without progression. In the analytic model, patients in the failure state die at a rate of 5.1% per month and therefore survive on average 14 months. Consequently, it was considered that this assumption is sufficiently close to the maximum duration of treatment to assume that patients in the failure state continue treatment until death as the cohort design of the analytic model does not allow tracking patient history to implement treatment until progression or a maximum of 12 months. Additionally, in the one-way sensitivity analysis, the cost of treatment in the failure state was found to have a very small impact on the ICER (eg, modifying the cost of the failure state by +/-20% resulted in a change of approximately +/- £300 in the ICER).

Costs

B5. **Priority Question:** Please provide justification for using the same administration cost for topotecan therapies as dinutuximab and IL-2 (£1,908) from the NHS Reference Costs. Are there any potential differences in hospital length of stay between these therapies?

The administration cost associated with topotecan and dinutuximab were based on assumptions derived from NHS Reference Costs (SB10Z; procure chemotherapy drugs for regimens in Band 10). Length of stay may differ between the two regimens as dinutuximab is administered over 4 consecutive days. However, two different scenarios were investigated to test the robustness of model results to uncertainty surrounding hospital length of stay: 1) that dinutuximab is associated with longer length of hospital stay than assumed under base-case model assumptions and 2) that topotecan is associated with shorter length of hospital stay than assumed under base-case model assumptions.

The mean number of hospitalized days by course for the safety population of study ANBL0032 ranged from 10 to 14 (Table 14**Error! Reference source not found.**) (Clinical Study Report DIV-NB-301 [COG Protocol ANBL0032]). As such, dinutuximab was assumed to be in the highest cost band for chemotherapeutic regimens (Band 10). The cost of dinutuximab administration was varied in sensitivity analysis by the lower and upper quartile range of cost listed in the NHS reference costs (£1,207 and £2,287,

respectively). Results showed that the cost of dinutuximab administration was not a major driver of model results, with an ICER of £37,079 per QALY assuming an administration cost of £1,207 and an ICER of £37,800 assuming an administration cost of £2,287.

Table 14. Mean Days of Hospitalization in the Immunotherapy + Isotretinoin Arm of ANBL0032 (Clinical Study Report DIV-NB-301 [COG Protocol ANBL0032])

Course	Mean (SD) days of hospitalization
1	10 ± 5.0
2	14 ± 6.8
3	10 ± 3.3
4	14 ± 6.2
5	11 ± 6.9
6	10 ± 5.7

To further evaluate the potential cost of administration for dinutuximab, an additional analysis was conducted based on the mean days of hospitalisation per course of immunotherapy observed in study ANBL0032 (10 days for course 1 and an average of 11.8 for courses 2 through 6). Table 15 presents NHS reference costs for the delivery of complex chemotherapy (£370.84), mean cost per hospitalised stay (£7,743.11), and mean length of stay (17.21 days) for an elective inpatient stay for the treatment of brain tumours or cerebral cysts with the highest complication and comorbidity level. The cost per hospitalised day was taken to be £7743.11 divided by 17.21 (£449.87 per day using values reported in the NHS National Schedule of Reference Costs, without rounding). For dinutuximab, cycle 1, assuming 10 day duration of hospitalisation, total cost of administration was estimated at £4,869.58. For subsequent cycles of 11.8-day length of stay, total cost of administration was estimated at £5,679.35

Table 15. Unit Costs for Delivery Fee and Cost per Hospitalised Day

Code	Description	Unit Cost
SB14Z	Deliver complex chemotherapy, including prolonged infusional treatment, at first attendance	£370.84
AA24C	Brain tumours or cerebral cysts, with CC Score 11+	£7743.11 per average 17.21-day LOS

Key: CC – complication and comorbidity; LOS – length of stay.

Source: Department of Health. NHS Reference Costs 2013-14. URL: https://www.gov.uk/government/publications/nhs-reference-costs-2013-to-2014. Accessed 07 August 2015.

The higher cost of dinutuximab administration results in an increase in the incremental cost per QALY gained relative to the base-case analysis (£41,959 per QALY vs £37,423 per QALY for the base-case), further confirming the robustness of the model results to uncertainty in cost of dinutuximab administration (Table 16).

Table 16. Model Outcomes Using Administration Costs Based on Mean LOS per Course of Immunotherapy in Study ANBL0032

Outcome	Immunotherapy	Standard Therapy	Difference
LYs per Patient (Discounted)	17.16	12.46	4.71
QALYs per Patient (Discounted)	13.44	9.73	3.71

TOTAL	£ 202,442	£ 46,573	£ 155,869
Incremental Cost per LY Gained (Discounted)	£ 32,120		
Incremental Cost per QALY Gained (Discounted)	£ 41,959		

Key: LY – life-years; QALY – quality-adjusted life-years.

Each course of topotecan is administered over 5 consecutive days and was also assumed to be in the highest cost band for chemotherapeutic regimens (Band 10). However, uncertainty does exist surrounding the number of days patients remain hospitalized for each course of topotecan therapy in the UK. A retrospective Canadian study of neuroblastoma patients with first relapse or progression who were treated with topotecan and cyclophosphamide on an outpatient basis found the mean number of hospitalized days to be less than 1 day per course (Ashraf 2013), suggesting the possibility of a shorter hospital stay than assumed in the base-case model. The monthly cost of treatment failure (cost of drug and administration; base-case £3,683.48) was varied in sensitivity analysis from £2,983.76 to £4,455.80 and this parameter was not found to substantially impact the model results, with an ICER of £37,080 per QALY assuming the higher estimate and £37,735 assuming the lower estimate.

In order to fully investigate the possibility of lower treatment administration costs with topotecan, the monthly cost of failure was recalculated to exclude any cost of administration. This new value of £1,139.48 produces an ICER of £41,596 per QALY gained compared to £37,423 for the base-case analysis.

B6. **Priority Question:** Please provide the proportion of patients at baseline with a body surface area greater than 1 m^2 in the ANBL0032 trial.

BSA was calculated via the Mosteller equation (BSA = sqrt([ht*wt]/3600)).

From the March 2014 dataset for the ANBL0032 study, the Table 17 details the subjects with a baseline BSA > 1 m^2 for both the randomized and non-randomized populations.

Table 17. Number (percent) of subjects with a baseline BSA > 1m^2.

	Randomized (N=249)		Non-randomized (N=834)
	IMM (N=141)	Isotretinoin alone (N=108)	IMM (N=834)
BSA > 1 m^2	8 (5.7%)	4 (3.7%)	52 (6.2%)

Adverse events

B7. **Priority Question:** Please provide details showing how the monthly adverse event rates presented in Table 38 of the company submission (pages 102-103) are derived. Please provide the duration of the adverse events.

The monthly adverse event rates were derived from the number of events per arm reported in the pivotal trial (Yu 2010) divided by the number of person months during the treatment period (6 months) from each arm of the trial. The number of person months calculated from the trial data was 612 and 626, respectively, for the immunotherapy and standard therapy arms. The cost of adverse events in the model is based on the rate (per month of treatment) and the average cost per event. Therefore, the duration of adverse events is not necessary, nor considered, within the analytic model.

End-of-life criteria

B8. **Priority Question:** Please provide justification for the applicability of NICE end-of-life criteria. The company submission states that the life expectancy of patients with neuroblastoma on standard maintenance therapy is greater than 24 months (OS at 2 years from the ANBL0032 trial: Immunotherapy, 86±4%; standard therapy, 75±5%, Figure 6, page 61 of company submission).

As stated, the overall survival (OS) at 2 years for all randomized patients in the ANBL0032 trial was 86% in the immunotherapy arm and 75% in the standard therapy arm. While more than half of patients remain alive at 2 years after treatment with immunotherapy or standard therapy, the fact that 25% of children have died at this point is not insignificant to patients or families of patients with neuroblastoma. Additionally, there are 3 phases of treatment for high-risk neuroblastoma - induction, consolidation, and maintenance (dinutuximab is intended for use as maintenance therapy). In order to be eligible for treatment with dinutuximab according to the EMA label, patients must achieve at least a partial response to induction chemotherapy and undergo myeloablative therapy and autologous stem cell transplantation (ASCT). Only 52% of patients with high-risk neuroblastoma have a response to induction therapy, stem-cell transplantation, and radiotherapy and are therefore eligible for dinutuximab treatment. For those patients receiving standard therapy (isotretinoin alone), 75% survive to 24 months, therefore, only 39% of all high-risk neuroblastoma patients respond to induction / consolidation therapy and survive up to 24 months. Moreover, the inclusion criteria of the ANBL0032 trial may have selected for a group of patients with longer life expectancy than the entire cohort of patients with high-risk neuroblastoma who are candidates for maintenance therapy. For example, the inclusion requirement of life expectancy ≥2 months and the non-random assignment of 27 patients with biopsy-proven residual disease to immunotherapy because of known poor prognosis on standard therapy may have selected for a study sample with longer life expectancy than those observed in clinical practice (Matthay 2009). It is also important to consider that some patients who are eligible for maintenance therapy with dinutuximab have a worse prognosis than others, depending on stage and tumour characteristics. In an analysis of prognostic factors in the HR-NBL1/SIOPEN trial, the 5-year OS of all patients was 41% from time of induction, with a lower rate amongst

patients with stage 4 disease (38%), especially amongst patients with stage 4 disease who are greater than 5 years of age (28%) (Landestein 2014). In context of significant risk of mortality in children and the potential use in patient subgroups with OS as low as 28% at 5 years from the start of induction therapy, the NICE end-of-life criteria may be applicable when considering dinutuximab for this indication.

Section C: Textual clarifications and additional points

C1. On page 53 of the company submission, please clarify if there is any distinction between, "withdrew due to toxic effects" and "withdrew due to dose-limiting toxic effects"? What is meant by "continued to receive protocol therapy"?

There is no difference between withdrew due to toxic effects or withdrew due to dose-limiting toxic effect; this is just how they were reported. "Continued to receive protocol therapy" indicates that they continued to receive protocol therapy at the time of the data cut off. Protocol therapy would have been either isotretinoin or immunotherapy.

C2. Do the definitions of event-free survival as used in the ANBL0032 trial, and progression-free survival, as specified in the scope differ (Table 1 of submission)?

The ANBL0032 trial as reported in Yu 2010 and Yu 2014 used the following definition of event-free survival: the time from study enrolment until the first occurrence of relapse, progressive disease, secondary cancer, or death or, if none of these events occurred, until the last contact with the patient. Event-free survival is differentiated from progression-free survival (as defined in the scope) as the latter only includes progressive disease or death (not relapse and/or secondary cancer, as in event-free survival).

C3. The following references are missing from the reference pack that was provided:

These resources have been noted and sent to NICE via post on 29 July 2015.

- Latimer NR, Abrams KR, Lambert PC, Crowther MJ, Morden JP. Assessing methods for dealing with treatment crossover in clinical trials: a follow-up simulation study. University of Sheffield Health Economics and Decision Science Discussion Paper No. 14/01. 2014.
- Maris JM, Hogarty MD, Bagatell R, Cohn SL. Neuroblastoma. *Lancet*. 2007;369:2106-2120.
- Matthay KK, Reynolds CP, Seeger RC, et al. Long-term results for children with high-risk neuroblastoma treated on a randomised trial of myeloablative therapy followed by 13-*cis*-retinoic acid: a Children's Oncology Group study. *J Clin Oncol*. 2009;27(7):1007-1013.
- Spix C, Pastore G, Sankila R, et al. Neuroblastoma incidence and survival in European children (1978-1997): report from the Automated Childhood Cancer Information System project. *Eur J Cancer*. 2006;42:2081-2091.

- Stiller CA, Kroll ME, Pritchard-Jones K. Population survival from childhood cancer in Britain during 1978-2005 by eras of entry to clinical trials. *Ann Oncol*. 2012 Sep;23(9):2464-2469.

Additionally, 1 reference is mentioned in the submission, but not listed in the references section. Please confirm whether the following is the correct citation, and please provide a copy of the reference with those listed above in the manner as those previously provided.

This resource has been noted and sent to NICE via post on 29 July 2015.

- Yu AL, Gilman AL, Ozkaynak MF, Fevzi, M, Sondel, PM, London WB, Cretella, S, Diccianni, M, Cohn SL, Maris JM, Smith, M, Park, Julie on behalf of Children's Oncology Group. Update of Outcome for High-Risk Neuroblastoma Treated on a Randomized Trial of chimeric anti-GD2 antibody (ch14.18) + GM-CSF / IL2 immunotherapy in 1st response: A Children's Oncology Group Study. Advances in Neuroblastoma Research, 2014.

Literature searches

Note: These questions refer to searches in company submission appendix 1.4.4 pages 1-3.

C4. In the MEDLINE search the text word term neuroblastoma is used but not the MeSH term neuroblastoma. Please comment on whether this will increase the likelihood of relevant papers not having been identified.

To assess whether relevant articles were excluded, an additional MEDLINE search was conducted on August 4, 2015 using the MeSH term “neuroblastoma” (Table 18). This search yielded 65 articles, 62 of which were published prior to the original search date on April 14, 2015. A total of 73 articles were identified on the original search.

Table 18. MEDLINE® 1990 to Present; Searched on August 4, 2015

Search Number	Terms	Results
#4	Search **((#1) AND #2) OR #3**	65
#3	Search **dinutuximab[Text Word]**	5
#2	Search **ch14.18[Text Word]**	94
#1	Search **neuroblastoma[MeSH]**	25,143

A side-by side comparison of the search results using the PubMed ID number as a unique identifier confirmed that no studies were identified using the MeSH term that were not captured by the original search using the text word; 11 studies were identified in the original search which were not captured using the MeSH term (Table 19).

Table 19. Comparison of April 15, 2015 MEDLINE Search and August 4, 2015 MEDLINE Search, by PubMed ID Number

Original Search using neuroblastoma[TextWord]	August 4, 2015 search using neuroblastoma[MeSH]
1988079	1988079
7656271	7656271
7718335	7718335
7937818	7937818

7954465	7954465
8417829	8417829
8620525	8620525
8635190	8635190
9060025	excluded
9329622	9329622
9362156	9362156
9457407	9457407
9626218	9626218
9816154	excluded
9849423	9849423
10188730	excluded
10411920	10411920
10632368	10632368
10655443	10655443
10663607	10663607
10852128	excluded
11107135	11107135
11118469	11118469
11878578	11878578
11904735	11904735
12393580	12393580
15337804	15337804
15589320	15589320
15800908	15800908
15858706	15858706
15950727	15950727
15953676	15953676
16568495	16568495
16751426	16751426
17079481	17079481
17332365	17332365
17954911	17954911
19047298	19047298
19492317	19492317
19715061	19715061
20171010	excluded
20879881	20879881
21244693	21244693
21247330	21247330
21595822	21595822
22095188	22095188
22327432	22327432
22589483	22589483

23052481	23052481
23295797	23295797
23378384	23378384
23386066	23386066
23534082	excluded
23591980	23591980
23924804	23924804
23982484	23982484
24055592	24055592
24520328	24520328
24535934	24535934
24711551	24711551
24727144	24727144
24846335	24846335
24893631	24893631
24904828	excluded
25212536	25212536
25226154	25226154
25263424	25263424
25382742	excluded
25484055	25484055
25711293	excluded
25719414	excluded
25730142	excluded
25851859	25851859

C5. Which service provider was used to conduct the MEDLINE & Embase search.

Xcenda, LLC conducted the systematic literature search for both the clinical and cost-effectiveness sections. MEDLINE was searched using the National Center for Biotechnology Information, U.S. National Library of Medicine PubMed.gov. Embase was searched via Elsevier subscription.

C6. Describe the search strategy used to search Clinicaltrials.gov at http://clinicaltrials.gov/.

Clinicaltrials.gov was searched using the single term “ch14.18”.

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ClinicalTrials.gov. ch14.18/CHO bridging study. http://ClinicalTrials.gov/show/NCT01704872. Accessed April 14, 2015.

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Table 20. Summary of EFS and OS Outcomes for Studies Excluded due to Investigation of Non-interchangeable ch14.18 Molecule

Citation	Treatment Arm							*P*-value
	Ch14.18	Ch14.18 + G-CSF	Ch14.18 + IL-2	Isotretinoin	Ch14.18 (long-term infusion) + IL-2 + Isotretinoin	Maintenance Chemotherapy	No Treatment	
Handgretinger 1995	CR: n=2 PR: n=2 MR: n=1 SD: n=1 Progression: n=3							
Klingebiel 1998		19mo PFS: 70%±15%						
Landestein 2014d (CR prior to immunotherapy) (Residual disease prior to immunotherapy)	1y EFS: 75% 2y EFS: 67% 3y EFS: 64% 1y EFS: 63% 2y EFS: 56% 3y EFS: 52%		1y EFS: 71% 2y EFS: 63% 3y EFS 63% 1y EFS: 72% 2y EFS: 58% 3y EFS: 48%					
Lode 2014a; Lode 2014c; Lode 2014d; Lode 2014e					1.6y EFS: 32.4% 3.1y OS: 66.8%			
Simon 2011a (ASCT subset)	5y EFS: 50.5% 5y OS: 58.3% 9y EFS: 44.5% 9y OS: 47.0%						5y EFS: 31.8% 5y OS: 45.2% 9y EFS: 38.1% 9y OS: 40.5%	*P*=0.241 *P*=0.152 *P*=0.241 *P*=0.152
Simon 2011b	5y EFS: 50.5% 5y OS: 60%			5y EFS: 37% 5y OS: 50%				*P*=0.237 *P*=0.244

Simon 2004	3y EFS: 46.5% 3y OS: 68.5%					3y EFS: 44.4% 3y OS: 56.6%	3y EFS: 37.1% 3y OS: 46.8%	*P*=0.314 *P*=0.018
Simon 2005 (aged <1 year)	3y EFS: 80.5% 3y OS: 90.1%					3y EFS: 87.5% 3y OS: 93.8%	3y EFS 75.0% 3y OS: 91.7%	*P*=0.433 *P*=0.931

Key: CR – complete response; EFS – Event-free survival; G-CSF – granulocyte-colony stimulating factor; MR – minor response; mo – month; OS – overall survival; PFS – progression-free survival; PR – partial response; SD – stable disease; y – year.

Table 21. Summary of all Studies Excluded due to Investigation of Non-interchangeable ch14.18 Molecule

Reference	Summary	Outcomes	Relevant to the NICE Decision Problem?
ClinicalTrials.gov. CH14.18 1021 antibody and IL2 after haplo SCT in children with relapsed neuroblastoma. http://ClinicalTrials.gov/show/NCT02258815. Accessed April 14, 2015.	**Design/Description:** Phase 2, single arm **Population:** Post-haploidentical stem cell transplantation in children with relapsed neuroblastoma **Sample size**: unknown **Intervention:** • ch14.18 • IL-2	None posted	**No** (different population and treatment regimen)
ClinicalTrials.gov. Long term continuous infusion ch14.18/CHO plus s.c. aldesleukin (IL-2). http://ClinicalTrials.gov/show/NCT01701479. Accessed April 14, 2015.	**Design/Description:** Phase 1/2 dose schedule finding study **Population:** Primary refractory or relapsed neuroblastoma **Sample size**: unknown **Intervention:** • ch14.18 • IL-2 • isotretinoin	None posted	**No** (different population)
ClinicalTrials.gov. Combination chemotherapy with or without filgrastim before surgery, high-dose chemotherapy, and radiation therapy followed by isotretinoin with or without monoclonal antibody in treating patients with neuroblastoma. http://ClinicalTrials.gov/show/NCT00030719. Accessed April 14, 2015.	**Design/Description:** Phase 3 **Population:** Stage 2 or 3 (MycN amplification) or stage 4 neuroblastoma **Sample size**: unknown **Intervention:** • Randomized into 8 treatment arms, 5 of which contain ch14.18 • Combinations of ch14.18, G-CSF, and procedures (no IL-2)	None posted	**No** (different treatment regimen)
ClinicalTrials.gov. High risk neuroblastoma study 1.7 of SIOP-Europe (SIOPEN). http://ClinicalTrials.gov/show/NCT01704716. Accessed April 14, 2015.	**Design/Description:** Phase 3 **Population:** High-risk neuroblastoma **Sample size**: Recruitment is ongoing **Intervention:** • Randomized into 10 treatment arms, 2 of which contain ch14.18 • ch14.18 ± IL-2 (no G-CSF)	None posted	**No** (different treatment regimen)
ClinicalTrials.gov. ch14.18/CHO bridging study. http://ClinicalTrials.gov/show/NCT01704872. Accessed April 14, 2015.	**Design/Description:** Phase 1, single arm **Population:** Refractory neuroblastoma **Sample size**: unknown **Intervention:** • ch14.18	None posted	**No** (different population and treatment regimen)

Reference	Summary	Outcomes	Relevant to the NICE Decision Problem?
Handgretinger R, Anderson K, Lang P, et al. A phase I study of human/mouse chimeric antiganglioside GD2 antibody ch14.18 in patients with neuroblastoma. *Eur J Cancer.* 1995;31A(2):261-267.	**Design/Description:** Phase 1, single arm **Population:** Stage 4 neuroblastoma **Sample size**: 9 **Intervention:** • ch14.18	**CR:** n=2 **PR:** n=2 **MR:** n=1 **SD:** n=1 **Progression:** n=3	**No** (different treatment regimen)
Kawamoto H, Yoshimura K, Kimura T, Nitani C, Hara J. Phase I/IIa multicenter trial for high-risk and recurrent neuroblastoma: Anti-GD(2) antibody (ch14.18) immunotherapies using M-CSF or G-CSF. *J Clin Oncol.* 2014;32(suppl1):15.	**Design/Description:** Phase 1/2a dose-finding study **Population:** Aged 2-45 years with refractory or relapsed (phase I and phase IIa) and high risk (phase IIa) neuroblastoma **Sample size**: 9 **Intervention:** • ch14.18 + G-CSF or M-CSF • ch14.18 + IL-2	Dose-limiting toxicity	**No** (different treatment regimen; no efficacy data reported)
Klingebiel T, Bader P, Bares R, et al. Treatment of neuroblastoma stage 4 with 131I-meta-iodo-benzylguanidine, high-dose chemotherapy and immunotherapy. A pilot study. *Eur J Cancer.* 1998;34(9):1398-1402.	**Design/Description:** Pilot study to test treatment with ([131I-m]IBG **Population:** Stage 4 neuroblastoma **Sample size**: 11 **Intervention:** • ([131I-m]IBG • High-dose chemotherapy • G-CSF • ch14.18	**19 mo PFS:** 70% ± 15%	**No** (different treatment regimen)
Kremens B, Hero B, Esser J, et al. Ocular symptoms in children treated with human-mouse chimeric anti-GD2 mAb ch14.18 for neuroblastoma. *Cancer Immunol Immunother.* 2002;51(2):107-110.	**Design/Description:** Subanalysis of German Collaborative Neuroblastoma Study NB97 **Population:** High risk neuroblastoma **Sample size**: 85 **Intervention:** • ch14.18	No efficacy data reported	No efficacy data reported
Ladenstein R, Poetschger U, Luksch R, et al. Influence of age and stage on outcome in the high risk neuroblastoma HR-NBL1/SIOPEN Trial. Advances in Neuroblastoma Research Congress, Cologne. May 2014a. Poster presentation.	**Design/Description:** HR-NBL1/SIOPEN Trial **Population:** High risk neuroblastoma **Sample size**: 2,242 **Intervention:** • isotretinoin (2002-2007) • ch14.18 (after 2007)	EFS and OS stratified by age and stage, not by intervention (ie, EFS and OS were presented for all patients in the aggregate)	**No** (cannot assess treatment effect)

Reference	Summary	Outcomes	Relevant to the NICE Decision Problem?
	• IL-2 (after 2009)		
Ladenstein R, Weixler S, Baykan B, et al. Ch14.18 antibody produced in CHO cells in relapsed or refractory Stage 4 neuroblastoma patients: a SIOPEN Phase 1 study. *MAbs.* 2013;5(5):801-9.	**Design/Description:** Phase 1, dose-finding study **Population:** Recurrent/refractory neuroblastoma **Sample size**: 16 **Intervention:** • ch14.18	No efficacy data reported	No efficacy data reported
Ladenstein R, Poetschger U, Luksch R, et al. Major results from the HR-NBl1/siopen trial for high risk neuroblastoma. *Pediatr Blood Cancer.* 2012;59(6):988-989.	**Design/Description:** HR-NBL1/SIOPEN randomized trial **Population:** High risk neuroblastoma **Sample size**: not stated **Intervention:** • ch14.18 ± IL-2	No efficacy data reported	No efficacy data reported
Ladenstein R, Poetschger U, Luksch R, et al. Myeloablative therapy (MAT) and immunotherapy (IT) with CH14.18/CHO for high risk neuroblastoma: Update and news of randomised results from the HR-NBL1/SIOPEN trial. *Pediatr Blood Cancer.* 2014b;61(suppl2):S122-S123.	**Design/Description:** HR-NBL1/SIOPEN randomized trial **Population:** High risk neuroblastoma **Sample size**: not stated **Intervention:** • ch14.18 ± IL-2	No efficacy data reported	No efficacy data reported
Ladenstein R, Poetschger U, Luksch R, et al. Risk factors within the European high risk neuroblastoma HR-NBL1/SIOPEN trial. *Pediatr Blood Cancer.* 2014c;61(suppl2):S119.	**Design/Description:** HR-NBL1/SIOPEN randomized trial **Population:** High risk neuroblastoma **Sample size**: 2,242 **Intervention:** • ch14.18 + IL-2 (after 2009)	EFS and OS stratified by age and stage, not by intervention (ie, EFS and OS were presented for all patients in the aggregate)	**No** (cannot assess treatment effect)
Ladenstein RL, Poetschger U, Luksch R, et al. Immunotherapy (IT) with ch14.18/CHO for high-risk neuroblastoma: First results from the randomised HR-NBL1/SIOPEN trial. J *Clin Oncol*. 2014d:32(suppl1):15. Results taken from: Horizon Scanning Research & Intelligence Centre. APN311 for high risk neuroblastoma in children and adolescents – first line. NIHR HSRIC ID: 8394. May 2015.	**Design/Description:** HR-NBL1/SIOPEN randomized trial **Population:** High risk neuroblastoma **Sample size**: not stated **Intervention:** • ch14.18 ± IL-2	CR prior to immunotherapy: **1y EFS:** 75% vs 71% **2y EFS:** 67% vs 63% **3y EFS:** 64% vs 63% Residual disease: **1y EFS:** 63% vs 72% **2y EFS:** 56% vs 58% **3y EFS:** 52% vs 48%	**No** (different treatment regimen)

Reference	Summary	Outcomes	Relevant to the NICE Decision Problem?
Levy G, Bonnevalle M, Rocourt N, Sudour H, Defachelles AS. Necrotizing enterocolitis as an adverse effect of recombinant interleukin-2 and ch14.18 in maintenance therapy for high-risk neuroblastoma. *J Pediatr Hematol Oncol.* 2015;37(4):e250-252.	**Design/Description:** Case study **Population:** Localized MYCN amplified neuroblastoma **Sample size**: 1 **Intervention:** • ch14.18 • IL-2	No efficacy data reported	No efficacy data reported
Lode H. Evaluation of clinical response and survival following long-term infusion of anti-GD2 antibody ch14.18/CHO in combination with subcutaneous interleukin-2 in a single center treatment program in high-risk neuroblastom. Advances in Neuroblastoma Research Congress, Cologne. May 2014a. Poster presentation.	**Design/Description:** Single arm, single institution study **Population:** High risk neuroblastoma **Sample size**: 53 **Intervention:** • Long-term infusion of ch14.18 • IL-2 • Isotretinoin	**Mean 1.6y EFS:** 32.4% **Mean 3.1y OS:** 66.8%	**No** (different treatment regimen)
Lode H. Long-Term Infusion of ch14.18/CHO combined with s.c. interleukin-2 applied in a single center treatment program effectively stimulates anti-neuroblastoma activity with reduced pain in high-risk neuroblastoma patients. Advances in Neuroblastoma Research Congress, Cologne. May 2014b. Poster presentation.	**Design/Description:** Single arm, single institution study **Population:** High risk neuroblastoma **Sample size**: 53 **Intervention:** • Long-term infusion of ch14.18 • IL-2 • Isotretinoin	Pain outcomes	**No** (different treatment regimen and outcome)
Lode H, Jensen C, Siebert N, et al. Immune activation, clinical response and survival following long-term infusion of anti-GD2 antibody ch14.18/CHO in combination with interleukin-2 in high-risk neuroblastoma patients. *Cancer Res.* 2014c;74(suppl1):19.	**Design/Description:** Single arm, single institution study **Population:** High risk neuroblastoma **Sample size**: 53 **Intervention:** • Long-term infusion of ch14.18 • IL-2 • Isotretinoin	**Mean 1.6y EFS:** 32.4% **Mean 3.1y OS:** 66.8%	**No** (different treatment regimen)
Lode H, Siebert N. Disialoganglioside GD2 directed immunotherapy of neuroblastoma. *Eur J Cancer*. 2013;49(suppl2):S75.	**Design/Description:** Review **Population:** High risk neuroblastoma **Sample size**: not stated **Intervention:**	No efficacy data reported	No efficacy data reported

Reference	Summary	Outcomes	Relevant to the NICE Decision Problem?
	• ch14.18		
Lode H, Weixler S, Garaventa A, Ladenstein R. Characterization of ch14.18 antibody produced in CHO cells (ch14.18/CHO) for neuroblastoma immunotherapy. *Monatsschrift fur Kinderheilkunde* 2010;158(10):1009.	**Design/Description:** Preclinical and Phase 1 bridging study **Population:** Relapsed/refractory neuroblastoma **Sample size**: 16 **Intervention:** • ch14.18	Pharmacokinetics	No efficacy data reported
Lode HN, Eger C, Seidel D, Brackrock D, Siebert N. Characterization and activity of a new anti-idiotype antibody in neuroblastoma. *Eur J Cancer.* 2013;49(suppl2):S350.	**Design/Description:** Preclinical study **Population:** non-human (murine) **Sample size**: N/A **Intervention:** N/A	Preclinical	No efficacy data reported
Lode HN, Jensen C, Endres S, et al. Survival following long-term infusion of anti-GD2 antibody CH14.18/CHO in combination with interleukin-2 in a pilot cohort of high-risk neuroblastoma patients correlates with FC-gamma receptor polymorphisms. *Pediatr Blood Cancer.* 2014d;61(suppl2):S122.	**Design/Description:** Single arm, single institution study **Population:** High risk neuroblastoma **Sample size**: 53 **Intervention:** • Long-term infusion of ch14.18 • IL-2 • Isotretinoin	**Mean 1.6y EFS:** 32.4% **Mean 3.1y OS:** 66.8% Patients with high affinity FCGR alleles had longer EFS; *P*=0.025 (data not shown)	**No** (different treatment regimen)
Lode HN, Jensen C, Endres S, et al. Immune activation and clinical responses following long-term infusion of anti-GD(2) antibody ch14.18/CHO in combination with interleukin-2 in high-risk neuroblastoma patients. *J Clin Oncol.* 2014e;32(suppl1):15.	**Design/Description:** Single arm, single institution study **Population:** High risk neuroblastoma **Sample size**: 53 **Intervention:** • Long-term infusion of ch14.18 • IL-2 • Isotretinoin	**Mean 1.6y EFS:** 32.4% **Mean 3.1y OS:** 66.8% Patients with high affinity FCGR alleles had longer EFS; *P*=0.025 (data not shown)	**No** (different treatment regimen)
Simon T, Hero B, Faldum A, et al. Long term outcome of high-risk neuroblastoma patients after immunotherapy with antibody ch14.18 or oral metronomic chemotherapy. *BMC Cancer.* 2011a;11:21.	**Design/Description:** German Collaborative Neuroblastoma Study NB97 **Population:** High risk neuroblastoma **Sample size**: 334 (145 with ASCT) **Intervention:** • ch14.18 vs no therapy	**5y EFS:** 50.5% vs 31.8%; *P*=0.241 **5y OS:** 58.3% vs 45.2%; *P*=0.152 **9y EFS:** 44.5% vs 38.1%; *P*=0.241 **9y OS:** 47.0% vs 40.5%; *P*=0.152	**No** (different treatment regimen)

Reference	Summary	Outcomes	Relevant to the NICE Decision Problem?
Simon T, Hero B, Handgretinger R, et al. Anti-GD2-antibody CH14.18 or retinoic acid as consolidation therapy in high-risk neuroblastoma. *Pediatr Blood Cancer.* 2011b;57(5):789.	**Design/Description:** Retrospective analysis **Population:** High risk neuroblastoma **Sample size**: 149 **Intervention:** • ch14.18 vs isotretinoin	**5y EFS:** 50.5% vs 37% *P*=0.237 **5y OS:** 60% vs 50%; *P*=0.244 Multivariate analysis demonstrated no impact of consolidation therapy on EFS and OS	**No** (different treatment regimen)
Simon T, Hero B, Faldum A, et al. Consolidation treatment with chimeric anti-GD2-antibody ch14.18 in children older than 1 year with metastatic neuroblastoma. *J Clin Oncol.* 2004;22(17):3549-3557.	**Design/Description:** Subanalysis of German Collaborative Neuroblastoma Study NB90 and NB97 **Population:** High risk neuroblastoma **Sample size**: 334 **Intervention:** • ch14.18 vs maintenance chemotherapy vs no therapy	**3y EFS:** 46.5% vs 44.4% vs 37.1%; *P*=0.314 **3y OS:** 68.5% vs 56.6% vs 46.8%; *P*=0.018 Analysis of patients with ASCT and multivariate analysis revealed no advantage with ch14.18	**No** (different treatment regimen)
Simon T, Hero B, Faldum A, et al. Infants with stage 4 neuroblastoma: the impact of the chimeric anti-GD2-antibody ch14.18 consolidation therapy. Klin Padiatr. 2005;217(3):147-152.	**Design/Description:** Observational study based on clinical data **Population:** Infants aged <1 year with neuroblastoma **Sample size**: 59 **Intervention:** • ch14.18 vs maintenance chemotherapy vs no therapy	**3y EFS:** 80.5% vs 87.5% vs 75.0% *P*=0.433 **3y OS:** 90.1% vs 93.8% vs 91.7% *P*=0.931 Multivariate analysis revealed no advantage with ch14.18	**No** (different treatment regimen)
Thorsten S, Hero B, Handgretinger R, et al. Comparison of anti-GD2-antibody ch14.18 and 13-cis-retinoic acid as consolidation therapy for high-risk neuroblastoma. Results of the German NB97 trial. Advances in Neuroblastoma Research Congress. Stockholm, Sweden. June 2010. Poster presentation.	**Design/Description:** Retrospective analysis of German Collaborative Neuroblastoma Study NB97 **Population:** High risk neuroblastoma **Sample size**: 149 **Intervention:** • ch14.18 vs isotretinoin	**3y EFS:** 52.7% vs 50.5±5.8%; *P*=0.209 **3y OS:** 68.9% vs 65.0%; *P*=0.228	**No** (different treatment regimen)

Key: [131I-m]IBG – 131I-meta-iodobenzylguanidine; CR – complete response; FGCR – Fgc receptor; G-CSF – granulocyte-colony stimulating factor; IL-2 – interleukin-2; MR – minor response; M-CSF – macrophage colony-stimulating factor; mo – month; MycN – Myc Avian Myelocytomatosis Viral Oncogene Neuroblastoma Derived Homolog; N/A – not applicable; OS – overall survival; PFS – progression-free survival; PR – partial response; SD – stable disease; S.C. – subcutaneous; y – year.

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Dinutuximab for the maintenance treatment of high risk neuroblastoma in infants, children and young people aged 11 months to 17 years [ID799]

Thank you for agreeing to make a submission on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your submission, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: *Children's Cancer and Leukaemia Group (CCLG)*

Name of your organisation:
Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology?
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)?
- other? (please specify); *Children's Cancer and Leukaemia Group is a children's cancer charity and the UK and Ireland's professional association for those involved in the treatment and care of children with cancer.*

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Dinutuximab for the maintenance treatment of high risk neuroblastoma in infants, children and young people aged 11 months to 17 years [ID799]

Background

Approximately 100 infants, children and young people are diagnosed with neuroblastoma each year in the UK. Of these, more than half will be classified as having 'High Risk' Neuroblastoma on the basis of internationally agreed risk factors (International Neuroblastoma Risk Group (INRG) classification). These children and young people require intensive multi-modal treatment and are all treated within tertiary specialist oncology units. Until 2009, the standard treatment for these patients across Europe (and in US) was considered to be:

i) A period of induction chemotherapy (e.g. Rapid COJEC)
ii) Surgical excision of the primary tumour
iii) Myeloablative chemotherapy (e.g Busuphan / Melphalan) with peripheral blood stem cell rescue
iv) Radiotherapy to tumour bed
v) Cis-retinoic acid as differentiation therapy

With this therapy, long-term survival rates of approximately 30-40% were achieved, with treatment related mortality in the order of 3-5% (1-3).

In 2009 a study run by US Children's Oncology Group (ABL0032) was terminated early because of a significant improvement in 2 year event free and overall survival (66±5% vs. 46±5% (P=0.01) and 86±4% vs. 75±5% (P=0.02) respectively) in patients with high risk neuroblastoma receiving Dinutuximab (ch14.18/SP2/0) in combination with IL-2 and GM-CSF, as compared to patients receiving standard high risk neuroblastoma therapy (4). These preliminary results represented a significant improvement in outcome for this population, and anti-GD2 monoclonal antibody has since been considered (in the US and Europe) an important component of high risk neuroblastoma therapy. As all patients within the immunotherapy arm of the ABL0032 trial received IL-2 and GM-SCF as well as Dinutuximab, it was not possible to attribute the relative contributions of each agent to the observed therapeutic benefit. Patients eligible for this trial had to have shown a good response to the previous treatment modalities. The two year survival data is from start of the immunotherapy randomisation treatment, which is many months after the initial diagnosis of neuroblastoma. It does not therefore represent accurately the two year survival of all patients diagnosed with high-risk neuroblastoma, which is appreciably lower because of early mortality.

Since 2010, the majority of patients in the UK with high risk neuroblastoma have received ch14.18/CHO as part of either the European SIOPEN HR-NBL-1 or SIOPEN LTI study. Ch14.18/CHO (Apeiron Biologics) is from the same original hybridoma clone as ch14.18/SP2/0 (Dinutuximab) and has an identical amino acid sequence, but has been grown in a different producer cell lines (CHO rather than SP2/0). There are no clinical studies directly comparing the two agents, but as they are grown in different cell lines they are likely to have different glycosylation patterns which might significantly affect effector function. The two antibodies should therefore be considered as separate agents, and should not be assumed to have clinically identical effects. In Europe the SIOPEN HR NBL-1 study is a phase III study, open to patients with newly diagnosed high risk neuroblastoma. This study has compared maintenance therapy with ch14.18/CHO alone with ch14.18/CHO given with subcutaneous IL-2. Preliminary outcome data from this study has suggested significantly more toxicity when the ch14.18/CHO is given with IL-2 (such that a large proportion of patients do not complete the full scheduled dose) but 2 year Event Free Survival appears similar between the 2 arms (5). The 2 year EFS from the start of immunotherapy (+/- IL-2)

appears to be very similar to that observed within the ABL0032 study (see Appendix i, abstract submitted for presentation at SIOP 2015). The SIOPEN Long Term Infusion (LTI) study is a phase II study, open to patients with relapsed, refractory or slowly responding high risk neuroblastoma. This study has investigated if toxicity of the antibody can be reduced by delivering the antibody more slowly. The study has demonstrated that tolerance of slow continuous infusion (240 hours compared to 5 x 8 hour infusions) is significantly better, with reduced intravenous opioid requirement, such that a proportion of patients can receive the treatment on an ambulatory basis, reducing time spent in hospital (6). The LTI study is now re-addressing the potential therapeutic benefit of additional subcutaneous IL-2, in the context of a more tolerable antibody delivery. The SIOPEN HR-1 has recently been amended to include a new randomisation, which will also investigate the benefit of IL-2 with long term infusion of antibody, but in the context of up front high risk neuroblastoma treatment.

What is the expected place of the technology in current practice?

The vast majority of patients in the UK with high risk neuroblastoma are currently recruited to the above SIOPEN trials. In the immediate term, it is envisaged that this would continue and the majority of patients would continue to receive ch14.18 /CHO +/- IL-2. There will however be some parents / patients who either choose not to take part in these trials or who are not eligible. These patients would potentially receive the new technology. This would include:

i) Patients with high risk neuroblastoma, as maintenance therapy after myeloablative chemotherapy and PBSCT.

ii) Patients with relapsed or refractory neuroblastoma, who do not have high risk disease at initial presentation but are considered to have 'high risk' disease on the basis of relapsed or refractory disease.

How is the condition currently treated in the NHS?

See above.
Virtually all UK patients with high risk neuroblastoma patients, who are eligible, have received ch14.18/CHO (+/- IL-2) as part of the SIOPEN HR-NBL-1 or LTI study. 2 UK patients have received ch14.18/CHO via the IDIS compassionate access programme.

Is there significant geographical variation in current practice?

No significant variation across UK. All UK paediatric oncology centres recruit or refer to the above trials, and follow the same recommendations for patients with relapsed and refractory patients (CCLG "Options for the treatment of patients with relapsed or progressive high risk neuroblastoma March 2015") .

As the SIOPEN trial is European then practice in UK is identical to other participating European centres, Elements of treatment differ with that delivered in the US, but the general structure and intensity of treatment is very similar. In the US maintenance immunotherapy with ch14.18/SP2/0 with IL-2 and GM-CSF in alternating cycles would generally be considered standard of care for patients with high risk neuroblastoma. In the UK and most of Europe, there is an unusual situation in that although most paediatric oncologists would consider that treatment for high risk neuroblastoma should now include some form of anti-GD2 immunotherapy, this has only been available in the context of the clinical trials mentioned above. In the absence of these clinical trials, cis-retinoic acid maintenance therapy would be considered the 'standard of care' for these patients. However, since it was not felt to

be acceptable to include cis-retinoic acid as the 'standard' arm of the of the SIOPEN HR NBL-1 R2 randomisation, in practice almost all children in the UK with high risk neuroblastoma have received ch14.18/CHO based immunotherapy in addition to this over the last 4-5 years. In view of the results of the SIOPEN LTI study, showing improved tolerance and reduced toxicity with slower delivery, the practice within the UK and Europe has moved towards this, and the new R4 randomisation of the SIOPEN HR NBL-1 trial will include all ch14.18/CHO delivered as a 240 hour infusion. This differs from the proposed delivery speed of ch14.18/SP2/0 in the proposed technology – the faster delivery of ch14.18/SP2/0 may be associated with more toxicity than current ch14.18/CHO as a slow infusion.

Are there differences of opinion between professionals as to what current practice should be?

There is general consensus by paediatric oncology clinicians that anti-GD2 based immunotherapy should be a component of current high risk neuroblastoma therapy. There is no clinical evidence comparing ch14.18/CHO and ch14.18/SP2/0 and there is absence of evidence that observation in laboratory studies will be predictive of clinical behaviour. Therefore it is not possible to predict whether ch14.18/CHO provides equivalent clinical effects as ch14.18/Sp2/0. Some experts however might be more willing to extrapolate data from one antibody to the other.

There is no definite evidence of the role of cytokines (GM-CSF and IL-2) in augmenting ch14.18 therapy, and opinion as to the likely role these play is probably divided. Moreover, the respective roles of the cytokines could be markedly different between the two antibodies.

What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Ch14.18/CHO is the main current alternative to ch14.18/SP2/0. As discussed above there is no clinical evidence available to compare either the toxicity or therapeutic efficacy of these agents.

The proposed technology includes delivery of IL-2 and GM-CSF with ch14.18/SP2/0. The therapeutic advantage of giving these cytokines is at present unclear, but is likely to significantly increase toxicity compared to giving the antibody alone.

Practice in the US (and in the FDA approval) is to deliver ch14.18/SP2/0 over 4 days. There may be advantage (extrapolating from the SIOPEN LTI study) to delivering this as a slower infusion to reduce toxicity and improve pharmacokinetics.

Other immunotherapy approaches (e.g. GD2 targeting CAR therapies) are in clinical development, but all are experimental, and none are yet available outside the context of a clinical trial.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient?

There is a population of patients with metastatic disease that is slow or resistant to clearance with induction chemotherapy, and may be considered to have 'ultra high risk' disease. There is no evidence to guide whether these patients benefit more or less from immunotherapy than standard 'high' risk patients. Anti-GD2 based immunotherapy would be considered an

important component of these children's care providing that some degree of disease control can be achieved prior to immunotherapy.

The definition of 'high risk' neuroblastoma is debated, and there is a subgroup of patients previously considered to have 'intermediate risk' disease, who may have a worse prognosis and warrant high risk treatment. This may for example include older children (> 5 years) with localised unresectable tumours, with adverse cytogenetics, If these children are considered to have high risk disease then they may benefit form anti-GD2 based immunotherapy, but there is currently no evidence for this.

Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

See above.

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics?

This technology should only be delivered in tertiary paediatric oncology centres.

Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

All UK paediatric oncology centres already have experience of delivering ch14.18/CHO and have all the necessary infrastructure to deliver the new technology.

If the technology is already available, is there variation in how it is being used in the NHS?

This technology is not currently available in UK. As discussed above ch14.18/CHO (+/-IL-2) has been widely used in UK since 2010. This differs from the proposed technology in the source of antibody, the speed of delivery of antibody and the inclusion of both GM-CSF and IL-2 with the antibody.

Is it always used within its licensed indications? If not, under what circumstances does this occur?

As above. The new technology would be considered for relapsed neuroblastoma as well as first line treatment of high risk disease.

Please tell us about any relevant clinical guidelines and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

Guidelines for clinical use of ch14.18/CHO are included within the protocols of the SIOPEN HR-1 and LTI studies. There are no UK or European guidelines that relate to the use of ch14.18/SP2/0

The advantages and disadvantages of the technology

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Dinutuximab for the maintenance treatment of high risk neuroblastoma in infants, children and young people aged 11 months to 17 years [ID799]

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

As discussed above, the technology differs from current standard practice in the UK and there is no clinical evidence to guide whether the proposed technology is superior or inferior to current ch14.18/CHO based immunotherapy used in the UK.

The new technology is likely to be similar in complexity of delivery and expected toxicity to currently delivered ch14.18/CHO +/- IL-2. Concomitant therapies and supportive care is likely to be similar.

Patients / families are likely to accept the new technology, and may opt for this in preference to receiving ch14.18/CHO within SIOPEN trial – as the combination of CH14.18/SP2/0, IL-2 and GM-CSF has been viewed by some as the 'gold standard' as this was the treatment in the seminal COG ABL0032 study.

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

We have not reviewed specific guidance for starting and stopping the technology, but would expect these to be broadly similar to those currently sued for ch14.18/CHO therapy. Patients would ordinarily receive 5 cycles of treatment, but this may be stopped earlier in the face of significant toxicity or if there is evidence of disease progression.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

The proposed technology could be delivered in conditions similar to that in which the APL0032 trial was conducted. The only element of the technology which could not be currently delivered with the UK is GM-CSF, which we understand is not currently clinically available in Europe. The delivery and toxicity of current ch14.18/CHO therapy within the UK is otherwise likely to be broadly similar to that of the proposed technology, and incorporation of the technology into standard clinical practice in UK paediatric oncology centres would be achievable.

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

Side effects and adverse reactions of the proposed technology are likely to be significant, requiring in patient delivery and intravenous opioid analgesia. Although this represents a considerable treatment burden on children and their families, this is generally considered

warranted considering the poor prognosis of high risk neuroblastoma, and the potential therapeutic benefits of this therapy. The side effects are likely to be broadly similar to those of ch14.18/CHO, with which UK paediatric oncologists are very familiar with managing. It is possible that more long term side effects of the technology will become evident with time.

Any additional sources of evidence

See references and abstract i)

Implementation issues

The NHS is required by the Department of Health to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

The majority of paediatric oncology doctors, nurses and pharmacists are already very experienced with the delivery of ch14.18/CHO, and would therefore need little training to implement the new technology. No extra equipment would be needed. Supply of GM-CSF would need to be ascertained.

Equality
NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

We do not believe there are any issues of equality – and the technology should be available to all patients with high risk neuroblastoma. As this is a very high cost technology, access

may not be equitable if NICE approval was not granted and other funding sources had to be found.

References

1. Zage, P. E. et 2008. *Outcomes of the POG 9340/9341/9342 trials for children with high-risk neuroblastoma: A report from the Children's Oncology Group*. *Pediatr Blood Cancer*.

2. Pearson, A. D. et *al High-dose rapid and standard induction chemotherapy for patients aged over 1 year with stage 4 neuroblastoma: a randomised trial. Lancet Oncol* 9:247-256.

3**.** R. L. Ladenstein et al. *Busulphan-melphalan as a myeloablative therapy (MAT) for high-risk neuroblastoma: Results from the HR-NBL1/SIOPEN trial.* Journal of Clinical Oncology, 2011 ASCO Annual Meeting Abstracts Part 2. Vol 29, No 18_suppl (June 20 Supplement), 2011: 2

4. Yu AL et al. *Anti-GD2 antibody with GM-CSF, interleukin-2, and isotretinoin for neuroblastoma*. N Engl J Med. 2010 Sep 30;363(14):1324-34

5. Ladenstein R et al. *Immunotherapy (IT) with ch14.18/CHO for high-risk neuroblastoma: First results from the randomised HR-NBL1/SIOPEN trial.*

6. Lode H et al. *Long-term infusion of anti-GD2 antibody ch14.18/CHO in combination with interleukin-2 (IL2) activity and efficacy in high-risk relapsed/refractory neuroblastoma patients* J. Clinical Oncology 33, 2015 (suppl abstr TPS10080)

Appendix i) Abstract submitted to SIOP 2015 by SIOPEN (Confidential until presented at conference)

Short (STI) and Long Term Infusion (LTI) of ch14.18/CHOmAB Immunotherapy: Toxicity Profiles and Outcomes in 530 High Risk Neuroblastoma (HR-NBL) patients of two SIOPEN trials

Ruth Ladenstein*, Ulrike Pötschger*, Juliet Gray, Dominique Valteau-Couanet, Roberto Luksch, Victoria Castel, Isaac Yaniv, Geneviève Laureys, Martin Elliot, Jean Michon, Cormac Owens, Toby Trahair, Godfrey Chan, Ellen Ruud, Henrik Schroeder, Maja Beck- Popovic, Evgenia Glogova*, Günter Schreier**, Hans Loibner***, Holger N. Lode

* St. Anna Children‘s Hospital and Research Institute, Vienna, Austria
for the SIOP Europe Neuroblastoma Group
** Austrian Institute of Technology
*** APEIRON Biologics AG

Objectives
Design of a tolerable and efficacious immunotherapy based on the European ch14.18/CHO monoclonal antibody immunotherapy (IT) ± subcutaneous interleukin 2 (scIL2).

Methods
The HR-NBL1/SIOPEN Phase III trial (APN311-302)(EudraCT:2006-001489-17) randomized 406 high risk first-line neuroblastoma patients (HR-pts) in consolidation phase to receive either ch14.18/CHOmAB alone as 8-hour STI with 100mg/m² (d 8-12) and 160 mg/m^2 oral 13-cis-RA (d19-32) (STIA) alone or combined with 6x10^6 IU/m^2 scIL2 (d1-5; 8-12) (STIB). This

schedule required intravenous (iv) high-dose morphine (MO) to control for neuropathic pain. In the SIOPEN Phase II study (APN311-202)(EudraCT:2009-018077-31) 124 high risk relapsed/refractory neuroblastoma pts (VHR-pts) received LTI of 100 mg/m^2 ch14.18/CHO (d8-17) and scIL2 and 13-cis-RA as outlined above. The latter trial aimed to reduce pain and use ivMO based on the LTI schedule. Both trials planned a total of 5 IT cycles. Median follow-up was 2.1 years (0-4.5) for the STI and 0.8 years (0-3) for the LTI trial.

Results

In LTI a significantly better general tolerance by Lansky score (<0.001:10% (LTI)- 39%(STIB)-17%(STIA)) and reduced allergic reactions (<0.001:10%(LTI)-20%(STIB)-9%(STIA)) were observed. Capillary leak (9%(LTI)–9%(STIB)-1%(STIA)) remained associated with scIL2. Fever was significantly lower without scIL2. Clinical experience shows markedly reduced pain and ivMO in the LTI setting.

Using STI, the HR-NBL1/SIOPEN trial showed no EFS benefit for HR-pts with scIL2. 2-year EFS rates of pts in CR (or VGPR/PR) with and without scIL2 are 65%±5% (58%±6%) and 67%±5% (59%±6%), and 50%±7% for VHR-pts with LTI. In STIA 18% did not complete MRD-therapy. In STIB, major toxicities and progressions prevented full delivery of IT in 44% (36% toxicity-related, 8% progressions). In LTI 42% (21% toxicity-related, 21% progressions) stopped early

Conclusion: Although disease risk-profiles differ between trials reduced toxicities were observed with LTI. Ongoing randomised SIOPEN trials will clarify the role of scIL2

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer organisation submission (STA)

Dinutuximab for the maintenance treatment of high risk neuroblastoma in infants, children and young people aged 11 months to 17 years [ID799]

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, and including health-related quality of life)
- the acceptability of different treatments and how they are given
- expectations about the risks and benefits of the treatment.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The length of your response should not normally exceed 10 pages.

1. About you and your organisation

Your name: [redacted]

Name of your organisation: Neuroblastoma UK

Your position in the organisation: [redacted]

Brief description of the organisation: Neuroblastoma UK (formerly the Neuroblastoma Society) is a registered charity formed and run by voluntary supporters. It funds clinical research projects into the causes and treatments of neuroblastoma, organises and supports clinical research meetings, and provides information and support to families and others affected by the disease. Annual revenues from fundraising are in the range £250-400K.

We are asking for your collective view as an organisation and will be asking patient experts for their individual input separately. If you have the condition, or care for someone with the condition, you may wish to complete a patient expert questionnaire to give your individual views as well.

2. Living with the condition

What is it like to live with the condition or what do carers experience when caring for someone with the condition?

Infants and children with neuroblastoma experience a range of symptoms including discomfort and pain, and in addition experience side effects and consequences of some of the treatments (such as nausea, hair loss, los of appetites, and recurring infections), as well as anxiety and fears about their illness and its treatment. Their daily lives are also affected and disrupted for example though long breaks from schooling.

As well as the obvious anxiety and distress resulting from seeing a child's illness and treatment, parents and other carers experience disruption to working life (and hence often income) and other aspects of life, including relationships.

3. Current practice in treating the condition

Which treatment outcomes are important to patients or carers? (That is, what would patients or carers like treatment to achieve?) Which of these are most important? If possible, please explain why.

Extended event-free survival, improved or new primary treatments, effective alternative treatments where primary treatment is ineffective or not tolerated, better treatment for refractory or relapsed disease, prevention or relapse.

What is your organisation's experience of currently available NHS care and of specific treatments for the condition? How acceptable are these treatments and which are preferred and why?

Standard treatment regime of chemotherapy, surgery and radiotherapy is effective (if aggressive) for a proportion of patients once neuroblastoma has been diagnosed (not always achieved as early as it needs to be), but far less so for those with high risk disease. Options are limited for these cases and for those who do not tolerate or respond to standard treatments, and for relapsed patients.

Parents almost always report that their child has been ill or displaying symptoms for some time (often months) before a diagnosis is made, which obviously has an impact on the treatment challenge. Hence greater awareness and knowledge is desirable, especially among GPs.

As neuroblastoma becomes better understood, it should be more and more possible to gauge accurately the appropriate treatment for an individual patient and avoid unnecessary levels of therapy and other interventions.

4. What do patients or carers consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)

- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that patients or carers expect to gain from using the treatment being appraised.

Impact on refractory disease and on prevention/avoidance of relapse.

Extended EFS.

Please explain any advantages that patients or carers think this treatment has over other NHS treatments in England.

Complementary to the standard currently available treatments (this statement applies to all similar immunotherapy treatments, including the SIOP-EN protocol currently offered to the majority of UK patients).

If you know of any differences in opinion between patients or carers about the benefits of the treatment being appraised, please tell us about them.

There is widespread support for immunotherapy treatments, with some variation in views about the specific types of antibody used and that ways that existing clinical trials and treatment protocols are organised. Some parents choose to access treatments available outside the UK, including immunotherapy. Some of these cases are referrals from NHS specialists and sometimes funded by the NHS, while in other cases charitable organisations provide financial and other support. Neuroblastoma UK funds research projects rather than supporting individual patients, but this does not imply any view about the decisions that are made about treatment options, and we advocate on behalf of patients and families where the NHS appears reluctant to fund treatments recommended by NHS clinicians

5. What do patients and/or carers consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse

- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns patients or carers have about current NHS treatments in England.

Limited options where standard treatment is ineffective or not well tolerated, and for cases of relapse.

Please list any concerns patients or carers have about the treatment being appraised.

The treatment can be difficult for patients (for example pain) and requires careful assessment and management by clinical teams.

The treatment being appraised has been developed and trialled in the US. As we understand it is not clear whether the US antibody and protocol is more effective than analogous antibody treatment developed and trialled in Europe including the UK). Hence there could be a concern that approval would result in UK patients receiving treatment which is not demonstrably belter that the existing European treatment, and of the development and trailing of the latter being impaired.

If you know of any differences in opinion between patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

There are inevitably different views about how to balance the impact of therapies in terms of side effects against the potential benefits, but this is more about the decisions in an individual case than about the benefits and downsides of the treatment in general.

6. Patient population

Are there any groups of patients who might benefit more from the treatment than others? If so, please describe them and explain why.

Patients with high risk disease, and those at risk of relapse.

Are there any groups of patients who might benefit less from the treatment than others? If so, please describe them and explain why.

May not be appropriate or required for patients with lower risk variations of neuroblastoma

7. Research evidence on patient or carer views of the treatment

Is your organisation familiar with the published research literature for the treatment?

x Yes ☐ No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether patients' experience of using the treatment as part of their routine NHS care reflects the experiences of patients in the clinical trials.

Currently this treatment is provided as clinical trials

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

Yes re important outcomes. Collection, assessment and appraisal of data has been thorough and rigorously examined.

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

As per earlier comment, treatment is currently provided as part of clinical trials.

Are you aware of any relevant research on patient or carer views of the condition or existing treatments (for example, qualitative studies, surveys and polls)?

☐ Yes x No

If yes, please provide references to the relevant studies.

8. Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Protected characteristics are: age; being or becoming a transsexual person; being married or in a civil partnership; being pregnant or having a child; disability; race including colour, nationality, ethnic or national origin; religion, belief or lack of religion/belief; sex; sexual orientation.

Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, such as:

- excluding from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment is/will be licensed;
- having a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the treatment;
- any adverse impact on people with a particular disability or disabilities.

Please let us know if you think that there are any potential equality issues that should be considered in this appraisal.

Are there groups of patients who would have difficulties using the treatment or currently available treatments? Please tell us what evidence you think would help the Committee to identify and consider such impacts.

Nothing beyond the outcomes and side effects identified in trials.

9. Other issues

Do you consider the treatment to be innovative?

x Yes ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition.

Very few options currently available to treat or reduce risk of relapse

Are there any other issues that you would like the Appraisal Committee to consider?

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- There is widespread interest in immunotherapy treatments for childhood cancer including neuroblastoma
- Clinical trials have been running for some time and there have been some positive indicaitons, although the full picure is not yet clear
- Care is needed to avoid closing down other promising potential treatment options (immunotherapy or other) as a result of approval
- There are presently limited options for treating relapsed patients or those who don't respond to the current mainstream treatment
- The treatment does have significant side effects and this has to be balanced against effectiveness

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer organisation submission (STA)

Dinutuximab for the maintenance treatment of high risk neuroblastoma in infants, children and young people aged 11 months to 17 years [ID799]

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, and including health-related quality of life)
- the acceptability of different treatments and how they are given
- expectations about the risks and benefits of the treatment.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The length of your response should not normally exceed 10 pages.

1. About you and your organisation

Your name: [redacted]

Name of your organisation: Solving Kids' Cancer (Europe)

Your position in the organisation: [redacted]

Brief description of the organisation:

Solving Kids' Cancer (Europe) supports families affected by aggressive forms of childhood cancer. We exist to increase access to the best possible treatments, fund research which will help develop improved treatments and raise awareness about the condition. We also offer a range of family support services to help inform and support families faced with childhood cancer.

The organisation is currently merging with a US-based charity of the same name to strengthen international ties as well as improving access to clinical trials for families in the UK. We currently have around 14 members of staff in the UK and Ireland and around 9 in the USA with many partners in the field.

2. Living with the condition

What is it like to live with the condition or what do carers experience when caring for someone with the condition?

High risk neuroblastoma has a devastating impact on the individuals and families it affects. The treatment for high risk neuroblastoma is characterised by the intensity of the treatment and the length of time it usually continues for.

For most sufferers frontline treatment will consist of several rounds of chemotherapy, complex surgery, stem cell transplant, radio-therapy and maintenance low dose therapy. This will last the best part of a year and can sometimes last much longer, during which time there will typically be many hospital stays and visits as a result of side effects from the treatment.

For those sufferers that suffer a relapse of the disease or primary disease is considered refractory, the treatment can be continuous and open ended. Whereas the expected 'long term' survival rate is considered to be between 30 and 50% for a primary diagnosis of high risk neuroblastoma, a disease

considered relapsed or refractory is expected to be incurable. This is quickly understood by families.

3. Current practice in treating the condition

Which treatment outcomes are important to patients or carers? (That is, what would patients or carers like treatment to achieve?) Which of these are most important? If possible, please explain why.

Achieving a long term survival is the most important outcome for patients and carers. As the sufferers are typically young children, the possibility of a 'cure' has obvious merit as a goal. Further to this, minimising the long term effects of the treatment to achieve a 'cure' is a secondary goal. Thirdly, maintaining a good quality of life for those who cannot be cured is a goal.

What is your organisation's experience of currently available NHS care and of specific treatments for the condition? How acceptable are these treatments and which are preferred and why?

The treatment under evaluation is the only one that is internationally recognised as being of benefit, but is not available in the UK.

4. What do patients or carers consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that patients or carers expect to gain from using the treatment being appraised.

The primary benefit is the potential for a cure. A secondary potential benefit is treatment free survival.

Please explain any advantages that patients or carers think this treatment has over other NHS treatments in England.

Currently a similar treatment is under trial in Europe. This European trial does not have a standard control arm and therefore determining benefit is close to impossible.

As the treatment under evaluation was compared with standard treatment as part of a randomised control trial, it is clear that this has benefit.

The treatment under evaluation has to be considered in the context of the other treatments given as part of neuroblastoma. These treatments have significant long term effects for the survivors that can be life threatening. The immunotherapy treatment has no known long term effects.

If you know of any differences in opinion between patients or carers about the benefits of the treatment being appraised, please tell us about them.

none

5. What do patients and/or carers consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)

- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns patients or carers have about current NHS treatments in England.

Current treatment for high risk neuroblastoma does not include the treatment under evaluation, the benefit of which has been widely communicated. This is a concern for patients and their families regarding the prevention of relapse.

Please list any concerns patients or carers have about the treatment being appraised.

Management of the administration of the treatment is a concern. The treatment needs to be carefully administered with supporting narcotics for pain relief as well as close monitoring for reactions.

If you know of any differences in opinion between patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

We are not aware of any disputing of the fact regarding the treatment, that those having the treatment have less chance of relapse in the first two years after treatment.

6. Patient population

Are there any groups of patients who might benefit more from the treatment than others? If so, please describe them and explain why.

Those patients that respond well to the first phases of treatment and who enter the treatment under evaluation in a state of no, or minimal disease burden are thought to benefit more from the treatment.

Are there any groups of patients who might benefit less from the treatment than others? If so, please describe them and explain why.

Those patients who have a significant disease burden would not be thought to benefit as much from the treatment.

7. Research evidence on patient or carer views of the treatment

Is your organisation familiar with the published research literature for the treatment?

x Yes ☐ No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether patients' experience of using the treatment as part of their routine NHS care reflects the experiences of patients in the clinical trials.

Patients experience of the treatment concurs with published evidence, that of severe but manageable side effects.

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

Overall and event free survival is the key outcome and these have been assessed.

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

no

Are you aware of any relevant research on patient or carer views of the condition or existing treatments (for example, qualitative studies, surveys and polls)?

x Yes ☐ No

If yes, please provide references to the relevant studies.

Anti-GD2 Antibody with GM-CSF, Interleukin-2, and Isotretinoin for Neuroblastoma, Yu et al. N Engl J Med 2010; 363:1324-1334 September 30, 2010.

Review article:

Recent Advances in Neuroblastoma

John M. Maris, M.D.

N Engl J Med 2010; 362:2202-2211June 10, 2010

8. Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Protected characteristics are: age; being or becoming a transsexual person; being married or in a civil partnership; being pregnant or having a child; disability; race including colour, nationality, ethnic or national origin; religion, belief or lack of religion/belief; sex; sexual orientation.

Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, such as:

- excluding from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment is/will be licensed;
- having a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the treatment;
- any adverse impact on people with a particular disability or disabilities.

Please let us know if you think that there are any potential equality issues that should be considered in this appraisal.

N/A

Are there groups of patients who would have difficulties using the treatment or currently available treatments? Please tell us what evidence you think would help the Committee to identify and consider such impacts.

Not aware of any.

9. Other issues

Do you consider the treatment to be innovative?

x Yes ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition.

This is the first immunotherapy treatment that we are aware of, that has been developed specifically for a childhood cancer.

Are there any other issues that you would like the Appraisal Committee to consider?

We are aware of several cases of families attempting to access this treatment since 2009. This has included successful court action against a PCT regarding access to this treatment and on another occasion funding applications (supported by NHS centres of excellence) to a PCT to access this treatment. In both these cases the children concerned were eventually treated in the United States with charity support.

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- There is an urgent need for this drug to gain a UK marketing authorisation. There are currently no other treatments that are licenced in the UK that act to prevent relapse of neuroblastoma by immunotherapy. Patients urgently need access to this drug which has been effectively standard treatment in the US since 2009.
- Patients will benefit hugely from the approval of dinutuximab as there are very few other options for them.
- The immunotherapy has no known significant long term side effects, in contrast to current treatments.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Dinutuximab for the maintenance treatment of high-risk neuroblastoma after myeloablative therapy and autologous stem cell transplant [ID799]

Thank you for agreeing to give us a statement on your view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: Martin Elliott

Name of your organisation:

Leeds Teaching Hospitals NHS Trust - employer
Member of the Neuroblastoma subgroup of the NCRI Children's Cancer and Leukaemia CSG
Member of the NCRI Children's Cancer and Leukaemia CSG
UK Chief investigator of the SIOPEN HR-NB1 trial

Are you (tick all that apply):

- **a specialist in the treatment of people with the condition for which NICE is considering this technology?**
- **a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?**
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)?
- other? (please specify)

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Single Technology Appraisal (STA)

What is the expected place of the technology in current practice?

Current immunotherapy in UK for high risk neuroblastoma patients

Currently patients with high risk neuroblastoma (approximately 50 per annum in UK,) are treated with multi-modality therapy which includes:

1. Induction chemotherapy
2. Surgery to primary site
3. Myeloablative chemotherapy and peripheral blood stem cell rescue
4. Radiotherapy to primary site
5. Differentiation therapy - *cis* -retinoic acid
6. Immunotherapy - currently only available in clinical trial.

The majority of UK patients diagnosed with high risk neuroblastoma are registered and treated according to a European international clinical trial protocol. The European clinical trials in neuroblastoma are hosted by SIOPEN (International Society of Paediatric Oncology - Europe Neuroblastoma).

There are two SIOPEN neuroblastoma trials which include immunotherapy within the protocol and currently these trials are the only route to access immunotherapy for high risk neuroblastoma in UK.

The two trials are:

<u>1. High Risk Neuroblastoma Study 1 (HR-NB-1)</u>
This trial has been open since 2002 and in that time has included 5 treatment randomisations. Only patients with newly diagnosed high risk neuroblastoma are eligible for this trial. Currently the trial has 2 randomisations (induction chemotherapy randomisation and the final immunotherapy randomisation is about to open in UK). Since 2010 patients have been able to receive immunotherapy on the trial, subject to satisfactory responses within appropriate time frames.

<u>2. A phase I/II dose finding study of ch14.18/CHO continuous infusion combined with subcutaneous aldesleukin (IL-2) in patients with primary refractory or relapsed neuroblastoma</u>
This is known as long term infusion (LTI) trial and patients are eligible for this trial if they are not able to access immunotherapy on the HR-NB-1 trial as they failed to meet the appropriate time frames or for patients who have relapsed disease.

The immunotherapy in both trials uses the SIOPEN antibody ch14.18/CHO produced by Apeiron Biologics for clinical research in SIOPEN trials. ch14.18/CHO and dinutuximab (ch14.18/SP2/0) have the same amino acid sequence but have been

grown in different cell lines and therefore may have different glycosylation patterns and hence it cannot be assumed that they are of equivalent efficacy.

Immunotherapy is not available to UK patients unless they are registered on HR-NB-1 or LTI trials. In practice virtually all UK patients with high risk neuroblastoma are registered on HR-NB-1 and if they become ineligible to receive immunotherapy on HR-NB-1 they are offered immunotherapy on the LTI trial. HR-NB-1 is open in all tertiary paediatric oncology centres in UK but LTI is only open in limited centres and many patients need to travel to alternative centres. Currently there is an "incentive" for parents to register their children on HR-NB-1 at initial diagnosis to ensure that they can access immunotherapy in UK.

For any patient not registered on these clinical trials then they would receive the other five treatment modalities as listed above but they would not be able to receive immunotherapy in the UK. The only current option to access immunotherapy would be travelling to USA at their own expense to receive dinutuximab by registering on the US Children's Oncology Group (COG) expansion cohort part of their clinical trial, pending dinutuximab being commercially available in US now that it has FDA approval.

Dinutuximab

Data regarding the efficacy of dinutuximab is primarily the COG publication (1) from 2009 of the trial ABL0032. This trial randomised patients with high risk neuroblastoma who had responded well to previous treatment modalities to two arms. One arm received *cis*-retinoic acid (differentiation therapy) only and the other arm received *cis*-retinoic acid in conjunction with immunotherapy. The immunotherapy consisted of dinutuximab and the cytokines GM-CSF and IL-2. The results showed a 2 year EFS of 66±5% vs 46±5% (p=0.01) and 2 year OS of 86±4% vs 75±5% (p=0.02) in favour of those receiving immunotherapy compared to those receiving *cis*-retinoic acid only. As all patients receiving immunotherapy received dinutuximab, GM-CSF and IL-2 then the relative contribution of each component to the improved outcome is not known. The trial was only designed to show 2 year EFS and OS, but the updates 2 and 4 year data has been presented in abstract form (2). This updated data showed 2 year EFS 67±4% vs 51±5% and the 4 year EFS of 59±5% vs 48±5% in favour of the immunotherapy arm which is not significant (p=0.01). The updated OS data remains significant at 4 years, showing 2 year OS 83%±4% vs 75±2% and 4 year OS 72±5% vs 56±5% (p=0.02) in favour of the immunotherapy arm.

SIOPEN immunotherapy clinical trial strategy

Since 2010 the SIOPEN immunotherapy trials all using ch14.18/CHO antibody have been designed to investigate:
i) Whether the addition of the cytokine (IL-2) to antibody treatment with ch14.18/CHO improves EFS in high risk neuroblastoma patients.

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Single Technology Appraisal (STA)

ii) Whether immunotherapy (ch14.18/CHO ± IL-2) can be administered with less toxicity by administering ch14.18/CHO as a slow continuous infusion, rather than 8h infusions.
iii)Whether the toxicity of immunotherapy is increased by the addition of the cytokine (IL-2).

Preliminary data (3,4) from the European trials shows that:

i) The addition of the IL-2 to ch14.18/CHO increases toxicity associated with administration of immunotherapy and in particular myelosuppression, diarrhoea, allergy and hypotension.
ii) Patients allocated to receive ch14.18/CHO and IL-2 receive less immunotherapy than those allocated ch14.18/CHO alone as the toxicity results in more patients failing to complete individual courses or having to stop immunotherapy treatment early.
iii) Initial analysis of HR-NB-1 data, analysed by intention to treat, shows no difference in 2 year EFS between the ch14.18/CHO only and ch14.18/CHO + IL-2 randomised arms.
iv) Patients who receive the antibody as a 10 day continuous infusion compared to the 8h x 5 day infusion show significantly less toxicity and in particular less pain and a lesser need for IV opiate infusion.
v) Patients receiving immunotherapy on the HR-NB-1 trial have a similar outcome (2 year EFS) compared to those treated with immunotherapy on the COG ABL0032 trial - this comparison needs to be taken in context of different trials, time periods, etc. There has been no trial directly comparing dinutuximab and ch14.18/CHO.

Current immunotherapy in UK for high risk neuroblastoma patients

Currently UK high risk neuroblastoma patients on the HR-NB1 receive immunotherapy as:

<u>ch14.18/CHO</u>
On the HR-NB-1 trial this is currently administered as 8 hour infusion for 5 consecutive days - five courses. However there is a current protocol amendment awaiting regulatory (MHRA and ethics) approval and subject to approval the protocol will be changed such that patients receive:
Ch14.18/CHO as a 24 hour infusion for 10 consecutive days - five courses. The cumulative dose per course is identical (100 mg/m^2).

Patients on LTI receive ch14.18/CHO as a 10 day continuous infusion.

<u>Aldesleukin (IL-2)</u>
Currently patients on HR-NB-1 do not receive IL-2. The above amendment includes the re-introduction of Il-2 into the protocol as a 1:1 randomisation to further explore the effectiveness and toxicity of Il-2 but in the context of long term ch14.18/CHO infusion. Those allocated Il-2 receive 3 IU/m^2 x 10 doses per course.

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Patients on LTI currently receive IL-2 as a 1:1 randomisation at a dose of 6 IU/m^2 x 10 doses.

It is anticipated that HR-NB1 will continue to recruit patients until May 2017 and that LTI will continue until early 2016. Discussions within SIOPEN have commenced regarding the next high risk neuroblastoma trial to follow closure of HR-NB-1. It is likely that there will be a period of time between closure of HR-NB1 and opening of the next trial. Similarly there are plans to open a UK only trial to follow closure of LTI but this will be dependent on successful funding and regulatory authority applications etc.

References:

1. Yu AL et al. Anti-GD2 antibody with GM-CSF, interleukin-2, and isotretinoin for neuroblastoma. N Engl J Med. 2010 Sep 30;363(14):1324-34

2. Yu AL et al, Update of Outcome for High-Risk Neuroblastoma Treated on a Randomised Trial of chimeric Anti GD2 Antibody (ch14.18) + GM-CSF / IL2 Immunotherapy in 1st Response: A Children's Oncology Group Study. Advances in Neuroblastoma Research, Cologne 2014

3 Ladenstein R et al. Immunotherapy (IT) with ch14.18/CHO for high-risk neuroblastoma: First results from the randomised HR-NBL1/SIOPEN trial. J Clin Oncol 2014 32:5(s) (ASCO meeting 2014)

4. Abstract - accepted for presentation at SIOP Oct 2015

Short (STI) and Long Term Infusion (LTI) of ch14.18/CHOmAB Immunotherapy: Toxicity Profiles and Outcomes in 530 High Risk Neuroblastoma (HR-NBL) patients of two SIOPEN trials

Ruth Ladenstein*, Ulrike Pötschger*, Juliet Gray, Dominique Valteau-Couanet, Roberto Luksch, Victoria Castel, Isaac Yaniv, Geneviève Laureys, Martin Elliot, Jean Michon, Cormac Owens, Toby Trahair, Godfrey Chan, Ellen Ruud, Henrik Schroeder, Maja Beck- Popovic, Evgenia Glogova*, Günter Schreier**, Hans Loibner***, Holger N. Lode

* St. Anna Children's Hospital and Research Institute, Vienna, Austria
for the SIOP Europe Neuroblastoma Group
** Austrian Institute of Technology
*** APEIRON Biologics AG

Objectives

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Single Technology Appraisal (STA)

Design of a tolerable and efficacious immunotherapy based on the European ch14.18/CHO monoclonal antibody immunotherapy (IT) ± subcutaneous interleukin 2 (scIL2).

Methods
The HR-NBL1/SIOPEN Phase III trial (APN311-302)(EudraCT:2006-001489-17) randomized 406 high risk first-line neuroblastoma patients (HR-pts) in consolidation phase to receive either ch14.18/CHOmAB alone as 8-hour STI with 100mg/m² (d 8-12) and 160 mg/m2 oral 13-cis-RA (d19-32) (STIA) alone or combined with 6x106 IU/m2 scIL2 (d1-5; 8-12) (STIB). This schedule required intravenous (iv) high-dose morphine (MO) to control for neuropathic pain. In the SIOPEN Phase II study (APN311-202)(EudraCT:2009-018077-31) 124 high risk relapsed/refractory neuroblastoma pts (VHR-pts) received LTI of 100 mg/m2 ch14.18/CHO (d8-17) and scIL2 and 13-cis-RA as outlined above. The latter trial aimed to reduce pain and use ivMO based on the LTI schedule. Both trials planned a total of 5 IT cycles. Median follow-up was 2.1 years (0-4.5) for the STI and 0.8 years (0-3) for the LTI trial.

Results
In LTI a significantly better general tolerance by Lansky score (<0.001:10% (LTI)-39%(STIB)-17%(STIA)) and reduced allergic reactions (<0.001:10%(LTI)-20%(STIB)-9%(STIA)) were observed. Capillary leak (9%(LTI)–9%(STIB)-1%(STIA)) remained associated with scIL2. Fever was significantly lower without scIL2. Clinical experience shows markedly reduced pain and ivMO in the LTI setting.
Using STI, the HR-NBL1/SIOPEN trial showed no EFS benefit for HR-pts with scIL2. 2-year EFS rates of pts in CR (or VGPR/PR) with and without scIL2 are 65%±5% (58%±6%) and 67%±5% (59%±6%), and 50%±7% for VHR-pts with LTI. In STIA 18% did not complete MRD-therapy. In STIB, major toxicities and progressions prevented full delivery of IT in 44% (36% toxicity-related, 8% progressions). In LTI 42% (21% toxicity-related, 21% progressions) stopped early

Conclusion: Although disease risk-profiles differ between trials reduced toxicities were observed with LTI. Ongoing randomised SIOPEN trials will clarify the role of scIL2

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Single Technology Appraisal (STA)

The advantages and disadvantages of the technology

All centres treating children and adults with high risk neuroblastoma now have the skills and expertise to deliver immunotherapy to this patient group.
Currently GM-CSF is not readily available in UK and the availability of this needs to be secured to enable the delivery of dinutuximab, GM-CSF and IL-2 as a package.

Patients treated with the new technology (dinutuximab, GM-CSF and IL-2) administered according to the 10 hour schedule are likely to suffer more toxicity compared to those treated on HR-NB-1 and LTI in which ch14.18/CHO is delivered as a 10 day infusion and only 50% of patients will be randomised to receive IL-2. The new technology (dinutuximab) and the SIOPEN ch14.18/CHO have never been directly compared in clinical trials and therefore it is not known whether there is any difference in efficacy between the new technology (dinutuximab, GM-CSF and IL-2) and the current available immunotherapy on SIOPEN trials.

There is general agreement amongst UK paediatric oncologists that high risk neuroblastoma patients should receive immunotherapy based on the data detailed above and accept this as “standard of care” but acknowledge that this is currently only available in UK within the context of a clinical trial. There is therefore a degree of pressure for parents to consent for their children to enter a clinical trial to enable them to receive a treatment for which there is data to suggest improved survival outcomes using a similar (but different) treatment. If this new technology becomes available then some parents are likely to decline consent for the clinical trial and opt for their child to receive dinutuximab, GM-CSF and IL-2.

We cannot rely on availability of clinical trials as a route to allow access to immunotherapy for this patient group because of no guarantee regarding availability of trials, patient eligibility etc.

Apart from the SIOPEN clinical trials there is no alternative route to access immunotherapy for high risk neuroblastoma patients within the UK. If patients did not receive immunotherapy, they would still receive *cis*-retinoic acid as differentiation therapy but given the current data most clinicians would view this as less than optimal, particularly given the relative poor prognosis of this disease.

Patients on immunotherapy need regular (often daily) blood tests and other investigations as clinically indicated, particularly if they develop side effects. It is likely that the frequency of investigations in clinical practice will differ significantly compared to those within the current SIOPEN trial protocols. Levels of supportive care, PICU admission rates may be higher when treating patients with the new technology compared to the current clinical trial related immunotherapy because of the quicker antibody infusion rate and all rather than 50% of patients would receive cytokines in addition to antibody

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Single Technology Appraisal (STA)

Equality and Diversity

Currently all children (and occasional adult patient) with high risk neuroblastoma can access immunotherapy if eligible for one of the SIOPEN clinical trials if their parents / legal guardian consent to their participation in clinical research.

There are some patients with intermediate risk neuroblastoma (>5 yrs, unresectable with adverse cytogenetic features) who have a poor outcome and should be considered for high risk neuroblastoma treatment - currently there is no evidence to suggest that they would benefit from this more intensive approach.

Patients who have standard risk disease and then relapse are currently eligible for the LTI trial if their relapse treatment includes MAT. This group should be considered regarding for eligibility for dinutuximab but this would depend on the licensed indication of the new technology.

If the new technology is not available to NHS patients and they do not receive immunotherapy on current clinical trials for whatever reason then the only option to access immunotherapy would be to self-fund which would restrict the treatment to a very limited proportion of patients. Patients who have travelled to USA in previous years have done so by fund raising thorough one of the national neuroblastoma charities and if this technology is not approved and the SIOPEN immunotherapy is not available then there is likely to be a significant increase in families fund-raising, re-mortgaging homes etc. to fund treatment either in private health providers in UK or overseas.

Any additional sources of evidence

Above

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Single Technology Appraisal (STA)

Implementation issues

All patients would be treated with the new technology in tertiary paediatric oncology centres, all of which are already experienced in administering immunotherapy to this group of patients within the context of the SIOPEN clinical trials. There would be no need for any new equipment or facilities and staff (medical, nursing, pharmacy) would need to familiarise themselves with dinutuximab and GM-CSF but would not require any significant re-training or support.

As above a supply of GM-CSF for clinical use in UK would need to be secured.

I can see no reason why the provision would not be possible within 3 months from publication of any guidance, subject to GM-CSF supply.

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Single Technology Appraisal (STA)

Dinutuximab for the maintenance treatment of high-risk neuroblastoma after myeloablative therapy and autologous stem cell transplant [ID799]

Thank you for agreeing to give us a statement on your view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: Dr Juliet Gray

Name of your organisation ; University of Southampton / Southampton University NHS Foundation Trust

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? Yes
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? Yes
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)?
- other? (please specify) Academic clinician with research interest in neuroblastoma immunotherapy

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Single Technology Appraisal (STA)

Background

Approximately 100 infants, children and young people are diagnosed with neuroblastoma each year in the UK. Of these, more than half will be classified as having 'High Risk' Neuroblastoma on the basis of internationally agreed risk factors (International Neuroblastoma Risk Group (INRG) classification). These children and young people require intensive multi-modal treatment and are all treated within tertiary specialist oncology units. Until 2009, the standard treatment for these patients across Europe (and in US) was considered to be:

i) A period of induction chemotherapy (e.g. Rapid COJEC)
ii) Surgical excision of the primary tumour
iii) Myeloablative chemotherapy (e.g Busuphan / Melphalan) with peripheral blood stem cell rescue
iv) Radiotherapy to tumour bed
v) Cis-retinoic acid as differentiation therapy

With this therapy, long-term survival rates of approximately 30-40% were achieved, with treatment related mortality in the order of 3-5% (1-3).

In 2009 a study run by US Children's Oncology Group (ABL0032) was terminated early because of a significant improvement in 2 year event free and overall survival (66±5% vs. 46±5% (P=0.01) and 86±4% vs. 75±5% (P=0.02) respectively) in patients with high risk neuroblastoma receiving Dinutuximab (ch14.18/SP2/0) in combination with IL-2 and GM-CSF, as compared to patients receiving standard high risk neuroblastoma therapy (4). These preliminary results represented a significant improvement in outcome for this population, and anti-GD2 monoclonal antibody has since been considered (in the US and Europe) an important component of high risk neuroblastoma therapy. As all patients within the immunotherapy arm of the ABL0032 trial received IL-2 and GM-SCF as well as Dinutuximab, it was not possible to attribute the relative contributions of each agent to the observed therapeutic benefit. Patients eligible for this trial had to have shown a good response to the previous treatment modalities. The two year survival data is from start of the immunotherapy randomisation treatment, which is many months after the initial diagnosis of neuroblastoma. It does not therefore represent accurately the two year survival of all patients diagnosed with high-risk neuroblastoma, which is appreciably lower because of early mortality.

Since 2010, the majority of patients in the UK with high risk neuroblastoma have received ch14.18/CHO as part of either the European SIOPEN HR-NBL-1 or SIOPEN LTI study. Ch14.18/CHO (Apeiron Biologics) is from the same original hybridoma clone as ch14.18/SP2/0 (Dinutuximab) and has an identical amino acid sequence, but has been grown in a different producer cell lines (CHO rather than SP2/0). There are no clinical studies directly comparing the two agents, but as they are grown in different cell lines they are likely to have different glycosylation patterns which might significantly affect effector function. The two antibodies should therefore be considered as separate agents, and should not be assumed to have clinically

identical effects. In Europe the SIOPEN HR NBL-1 study is a phase III study, open to patients with newly diagnosed high risk neuroblastoma. This study has compared maintenance therapy with ch14.18/CHO alone with ch14.18/CHO given with subcutaneous IL-2. Preliminary outcome data from this study has suggested significantly more toxicity when the ch14.18/CHO is given with IL-2 (such that a large proportion of patients do not complete the full scheduled dose) but 2 year Event Free Survival appears similar between the 2 arms (5). The 2 year EFS from the start of immunotherapy (+/- IL-2) appears to be very similar to that observed within the ABL0032 study (see Appendix i, abstract submitted for presentation at SIOP 2015). The SIOPEN Long Term Infusion (LTI) study is a phase II study, open to patients with relapsed, refractory or slowly responding high risk neuroblastoma. This study has investigated if toxicity of the antibody can be reduced by delivering the antibody more slowly. The study has demonstrated that tolerance of slow continuous infusion (240 hours compared to 5 x 8 hour infusions) is significantly better, with reduced intravenous opioid requirement, such that a proportion of patients can receive the treatment on an ambulatory basis, reducing time spent in hospital (6). The LTI study is now re-addressing the potential therapeutic benefit of additional subcutaneous IL-2, in the context of a more tolerable antibody delivery. The SIOPEN HR-1 has recently been amended to include a new randomisation, which will also investigate the benefit of IL-2 with long term infusion of antibody, but in the context of up front high risk neuroblastoma treatment.

What is the expected place of the technology in current practice?

The vast majority of patients in the UK with high risk neuroblastoma are currently recruited to the above SIOPEN trials. In the immediate term, it is envisaged that this would continue and the majority of patients would continue to receive ch14.18 /CHO +/- IL-2. There will however be some parents / patients who either choose not to take part in these trials or who are not eligible. These patients would potentially receive the new technology. This would include:

i) Patients with high risk neuroblastoma, as maintenance therapy after myeloablative chemotherapy and PBSCT.

ii) Patients with relapsed or refractory neuroblastoma, who do not have high risk disease at initial presentation but are considered to have ‘high risk’ disease on the basis of relapsed or refractory disease.

How is the condition currently treated in the NHS?

See above.

Virtually all UK patients with high risk neuroblastoma patients, who are eligible, have received ch14.18/CHO (+/- IL-2) as part of the SIOPEN HR-NBL-1 or LTI study. 2 UK patients have received ch14.18/CHO via the IDIS compassionate access programme.

Is there significant geographical variation in current practice?

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Single Technology Appraisal (STA)

No significant variation across UK. All UK paediatric oncology centres recruit or refer to the above trials, and follow the same recommendations for patients with relapsed and refractory patients (CCLG "Options for the treatment of patients with relapsed or progressive high risk neuroblastoma March 2015") .

As the SIOPEN trial is European then practice in UK is identical to other participating European centres, Elements of treatment differ with that delivered in the US, but the general structure and intensity of treatment is very similar. In the US maintenance immunotherapy with ch14.18/SP2/0 with IL-2 and GM-CSF in alternating cycles would generally be considered standard of care for patients with high risk neuroblastoma. In the UK and most of Europe, there is an unusual situation in that although most paediatric oncologists would consider that treatment for high risk neuroblastoma should now include some form of anti-GD2 immunotherapy, this has only been available in the context of the clinical trials mentioned above. In the absence of these clinical trials, cis-retinoic acid maintenance therapy would be considered the 'standard of care' for these patients. However, since it was not felt to be acceptable to include cis-retinoic acid as the 'standard' arm of the of the SIOPEN HR NBL-1 R2 randomisation, in practice almost all children in the UK with high risk neuroblastoma have received ch14.18/CHO based immunotherapy in addition to this over the last 4-5 years. In view of the results of the SIOPEN LTI study, showing improved tolerance and reduced toxicity with slower delivery, the practice within the UK and Europe has moved towards this, and the new R4 randomisation of the SIOPEN HR NBL-1 trial will include all ch14.18/CHO delivered as a 240 hour infusion. This differs from the proposed delivery speed of ch14.18/SP2/0 in the proposed technology – the faster delivery of ch14.18/SP2/0 may be associated with more toxicity than current ch14.18/CHO as a slow infusion.

Are there differences of opinion between professionals as to what current practice should be?

There is general consensus by paediatric oncology clinicians that anti-GD2 based immunotherapy should be a component of current high risk neuroblastoma therapy. There is no clinical evidence comparing ch14.18/CHO and ch14.18/SP2/0 and there is absence of evidence that observation in laboratory studies will be predictive of clinical behaviour. Therefore it is not possible to predict whether ch14.18/CHO provides equivalent clinical effects as ch14.18/Sp2/0. Some experts however might be more willing to extrapolate data from one antibody to the other.

There is no definite evidence of the role of cytokines (GM-CSF and IL-2) in augmenting ch14.18 therapy, and opinion as to the likely role these play is probably divided. Moreover, the respective roles of the cytokines could be markedly different between the two antibodies.

What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Ch14.18/CHO is the main current alternative to ch14.18/SP2/0. As discussed above there is no clinical evidence available to compare either the toxicity or therapeutic efficacy of these agents.

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Single Technology Appraisal (STA)

The proposed technology includes delivery of IL-2 and GM-CSF with ch14.18/SP2/0. The therapeutic advantage of giving these cytokines is at present unclear, but is likely to significantly increase toxicity compared to giving the antibody alone.

Practice in the US (and in the FDA approval) is to deliver ch14.18/SP2/0 over 4 days. There may be advantage (extrapolating from the SIOPEN LTI study) to delivering this as a slower infusion to reduce toxicity and improve pharmacokinetics.

Other immunotherapy approaches (e.g. GD2 targeting CAR therapies) are in clinical development, but all are experimental, and none are yet available outside the context of a clinical trial.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient?

There is a population of patients with metastatic disease that is slow or resistant to clearance with induction chemotherapy, and may be considered to have 'ultra high risk' disease. There is no evidence to guide whether these patients benefit more or less from immunotherapy than standard 'high' risk patients. Anti-GD2 based immunotherapy would be considered an important component of these children's care providing that some degree of disease control can be achieved prior to immunotherapy.

The definition of 'high risk' neuroblastoma is debated, and there is a subgroup of patients previously considered to have 'intermediate risk' disease, who may have a worse prognosis and warrant high risk treatment. This may for example include older children (> 5 years) with localised unresectable tumours, with adverse cytogenetics, If these children are considered to have high risk disease then they may benefit form anti-GD2 based immunotherapy, but there is currently no evidence for this.

Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

See above.

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics?

This technology should only be delivered in tertiary paediatric oncology centres**.**

Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

All UK paediatric oncology centres already have experience of delivering ch14.18/CHO and have all the necessary infrastructure to deliver the new technology**.**

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Single Technology Appraisal (STA)

If the technology is already available, is there variation in how it is being used in the NHS?

This technology is not currently available in UK. As discussed above ch14.18/CHO (+/-IL-2) has been widely used in UK since 2010. This differs from the proposed technology in the source of antibody, the speed of delivery of antibody and the inclusion of both GM-CSF and IL-2 with the antibody.

Is it always used within its licensed indications? If not, under what circumstances does this occur?

As above. The new technology would be considered for relapsed neuroblastoma as well as first line treatment of high risk disease.

Please tell us about any relevant clinical guidelines and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

Guidelines for clinical use of ch14.18/CHO are included within the protocols of the SIOPEN HR-1 and LTI studies. There are no UK or European guidelines that relate to the use of ch14.18/SP2/0

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

As discussed above, the technology differs from current standard practice in the UK and there is no clinical evidence to guide whether the proposed technology is superior or inferior to current ch14.18/CHO based immunotherapy used in the UK.

The new technology is likely to be similar in complexity of delivery and expected toxicity to currently delivered ch14.18/CHO +/- IL-2. Concomitant therapies and supportive care is likely to be similar.

Patients / families are likely to accept the new technology, and may opt for this in preference to receiving ch14.18/CHO within SIOPEN trial – as the combination of CH14.18/SP2/0, IL-2 and GM-CSF has been viewed by some as the ‘gold standard’ as this was the treatment in the seminal COG ABL0032 study.

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

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Single Technology Appraisal (STA)

I have not reviewed specific guidance for starting and stopping the technology, but would expect these to be broadly similar to those currently sued for ch14.18/CHO therapy. Patients would ordinarily receive 5 cycles of treatment, but this may be stopped earlier in the face of significant toxicity or if there is evidence of disease progression.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

The proposed technology could be delivered in conditions similar to that in which the APL0032 trial was conducted. The only element of the technology which could not be currently delivered with the UK is GM-CSF, which we understand is not currently clinically available in Europe. The delivery and toxicity of current ch14.18/CHO therapy within the UK is otherwise likely to be broadly similar to that of the proposed technology, and incorporation of the technology into standard clinical practice in UK paediatric oncology centres would be achievable.

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

Side effects and adverse reactions of the proposed technology are likely to be significant, requiring in patient delivery and intravenous opioid analgesia. Although this represents a considerable treatment burden on children and their families, this is generally considered warranted considering the poor prognosis of high risk neuroblastoma, and the potential therapeutic benefits of this therapy. The side effects are likely to be broadly similar to those of ch14.18/CHO, with which UK paediatric oncologists are very familiar with managing. It is possible that more long term side effects of the technology will become evident with time.

Any additional sources of evidence

See references and abstract i)

Implementation issues

The NHS is required by the Department of Health to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

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Single Technology Appraisal (STA)

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within
3 months, NICE may advise the Department of Health to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

The majority of paediatric oncology doctors, nurses and pharmacists are already very experienced with the delivery of ch14.18/CHO, and would therefore need little training to implement the new technology. No extra equipment would be needed. Supply of GM-CSF would need to be ascertained.

Equality
NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

I do not believe there are any issues of equality – and the technology should be available to all patients with high risk neuroblastoma. As this is a very high cost technology, access may not be equitable if NICE approval was not granted and other funding sources had to be found.

References

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Single Technology Appraisal (STA)

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3. R. L. Ladenstein et al. Busulphan-melphalan as a myeloablative therapy (MAT) for high-risk neuroblastoma: Results from the HR-NBL1/SIOPEN trial. Journal of Clinical Oncology, 2011 ASCO Annual Meeting Abstracts Part 2. Vol 29, No 18_suppl (June 20 Supplement), 2011: 2

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Appendix i) Abstract submitted to SIOP 2015 by SIOPEN (Confidential until presented at conference)

Short (STI) and Long Term Infusion (LTI) of ch14.18/CHOmAB Immunotherapy: Toxicity Profiles and Outcomes in 530 High Risk Neuroblastoma (HR-NBL) patients of two SIOPEN trials

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*** St. Anna Children's Hospital and Research Institute, Vienna, Austria**
for the SIOP Europe Neuroblastoma Group
**** Austrian Institute of Technology**
***** APEIRON Biologics AG**

Objectives
Design of a tolerable and efficacious immunotherapy based on the European ch14.18/CHO monoclonal antibody immunotherapy (IT) ± subcutaneous interleukin 2 (scIL2).

Methods
The HR-NBL1/SIOPEN Phase III trial (APN311-302)(EudraCT:2006-001489-17) randomized 406 high risk first-line neuroblastoma patients (HR-pts) in consolidation phase to receive either ch14.18/CHOmAB alone as 8-hour STI with 100mg/m² (d 8-12) and 160 mg/m2 oral 13-cis-RA (d19-32) (STIA) alone or

combined with 6x106 IU/m2 scIL2 (d1-5; 8-12) (STIB). This schedule required intravenous (iv) high-dose morphine (MO) to control for neuropathic pain. In the SIOPEN Phase II study (APN311-202)(EudraCT:2009-018077-31) 124 high risk relapsed/refractory neuroblastoma pts (VHR-pts) received LTI of 100 mg/m2 ch14.18/CHO (d8-17) and scIL2 and 13-cis-RA as outlined above. The latter trial aimed to reduce pain and use ivMO based on the LTI schedule. Both trials planned a total of 5 IT cycles. Median follow-up was 2.1 years (0-4.5) for the STI and 0.8 years (0-3) for the LTI trial.

Results
In LTI a significantly better general tolerance by Lansky score (<0.001:10% (LTI)- 39%(STIB)-17%(STIA)) and reduced allergic reactions (<0.001:10%(LTI)-20%(STIB)-9%(STIA)) were observed. Capillary leak (9%(LTI)–9%(STIB)-1%(STIA)) remained associated with scIL2. Fever was significantly lower without scIL2. Clinical experience shows markedly reduced pain and ivMO in the LTI setting.
Using STI, the HR-NBL1/SIOPEN trial showed no EFS benefit for HR-pts with scIL2. 2-year EFS rates of pts in CR (or VGPR/PR) with and without scIL2 are 65%±5% (58%±6%) and 67%±5% (59%±6%), and 50%±7% for VHR-pts with LTI. In STIA 18% did not complete MRD-therapy. In STIB, major toxicities and progressions prevented full delivery of IT in 44% (36% toxicity-related, 8% progressions). In LTI 42% (21% toxicity-related, 21% progressions) stopped early

Conclusion: Although disease risk-profiles differ between trials reduced toxicities were observed with LTI. Ongoing randomised SIOPEN trials will clarify the role of scIL2What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

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Single Technology Appraisal (STA)

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

Equality and Diversity

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts

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Single Technology Appraisal (STA)

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer expert statement (STA)

Dinutuximab for the maintenance treatment of high-risk neuroblastoma after myeloablative therapy and autologous stem cell transplant [ID799]

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, including health-related quality of life)
- preferences for different treatments and how they are given
- expectations about the risks and benefits of the treatment.

We have already asked your nominating organisation to provide an organisation's view. We are asking you to give your views as an individual whether you are:

- a patient
- a carer (who may be voicing views for a patient who is unable to) or
- somebody who works or volunteers for a patient organisation.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The response area will expand as you type. The length of your response should not normally exceed 10 pages.

1. About you

Your name: Nicholas James Bird
Name of your nominating organisation: NCCA UK
Do you know if your nominating organisation has submitted a statement?

■ Yes ☐ No

Do you wish to agree with your nominating organisation's statement?

■ Yes ☐ No

(We would encourage you to complete this form even if you agree with your nominating organisation's statement.)

Are you:

- a patient with the condition?

☐ Yes ■ No

- a carer of a patient with the condition?

■ Yes ☐ No

- a patient organisation employee or volunteer?

■ Yes ☐ No

Do you have experience of the treatment being appraised?

■ Yes ☐ No

If you wrote the organisation submission and do not have anything to add, tick here ☐ (If you tick this box, the rest of this form will be deleted after submission.)

2. Living with the condition

What is your experience of living with the condition as a patient or carer?

My son, [redacted], was diagnosed with high-risk neuroblastoma in 2009, at age 5. He had a primary adrenal tumour, and metastatic disease to lymph nodes, bones, and bone marrow. As is common, initial signs were vague; loss of appetite, difficulty sleeping, and he was not diagnosed until more severe symptoms presented.

Our primary treatment centre was [redacted].

Induction therapy was 80 days during which regular chemotherapy cycles were administered, followed by supportive care at home, and frequent in-patient stays at our local hospital for episodes of febrile neutropenia.

Insufficient response to induction meant [redacted] had 6 further rounds of stronger chemotherapy, and then 4 rounds of yet another combination. By which time he was classed as 'refractory', and off protocol.

Following resolution of his bone marrow disease, [redacted] underwent several stem cell harvests, and then underwent major surgery to resect his primary tumour at [redacted].

After surgery he underwent 2 x I-131 MIBG (internal radiation) therapy at [redacted], followed by myeloablative chemotherapy with Autologous Stem Cell Transplant at [redacted], and differentiation therapy with 13-cis-retinoic acid.

In the second half of 2011, we took [redacted] to Germany for 6 months of immunotherapy under the care of Prof. [redacted]. There he received ch14.18/CHO (APN311) anti-GD2 antibody as a continuous infusion, together with sub-cutaneous interleukin 2 (IL-2).

Despite all this intensive treatment, spanning two-and-a-half years, [redacted] remained with extensive skeletal disease, as shown by imaging scans.

In 2012 his disease, which had been stable, began to progress for the first time since start of treatment. After two rounds of salvage chemotherapy at

[redacted] failed to halt the progression, we travelled with [redacted] to Michigan, USA, to enrol on an FDA approved molecular guided therapy phase 1 clinical trial.

We travelled back-and-forth to Michigan between August 2012 and April 2013, during which time [redacted] received a number of different therapy combinations.

In July 2013, at age 9, [redacted] died at home of his disease.

3. Current practice in treating the condition

Which treatment outcomes are important to you? (That is, what would you like treatment to achieve?) Which of these are most important? If possible, please explain why.

Being cured of neuroblastoma is the single most important outcome; which for the avoidance of doubt means it being completely eradicated, and never coming back. This is *not* the same as 5-year survival (event-free or overall), which serves merely as a convenient metric for assessing improvements in treatment, or comparing effectiveness between different therapies.

Within the goal of curative treatment, minimization of serious and long-term damage and side-effects, is of utmost importance.

For those children who do not achieve remission, or for whom curative therapy is no longer a realistic aim, prolonged disease-control, and quality of life, is of prime importance.

What is your experience of currently available NHS care and of specific treatments? How acceptable are these treatments – which did you prefer and why?

Current standard-of-care treatment on NHS comprises an intensive induction regimen of chemotherapy, primary tumour resection, myeloablative chemotherapy with autologous stem cell transplant (ASCT), radiotherapy to the primary tumour bed, and differentiation therapy using isotretinoin (13-cis-retinoic acid). The UK is currently participating in a SIOPEN clinical trial of immunotherapy following ASCT, comprising ch14.18/CHO (Apeiron APN311) ± s/c IL-2, given alongside isotretinoin.

Children suffer a multitude of side-effects as a result of all the cytotoxic drugs they receive. Short-term effects include; nausea, vomiting, constipation, hair-loss, malnutrition, mucositis, and diarrhoea. They are prone to febrile neutropenia, which necessitates in-patient hospital stays for supportive care. Immune suppression makes them vulnerable to infection, requiring treatment with strong antibiotics. Ultimately, some children die in treatment, as a result of drug toxicity, or severe infections. Long-term problems include hearing loss, organ dysfunction, sterility, growth issues, early onset puberty, permanent disability, and secondary malignancies. Tumour surgery is also usually highly complex, as neuroblastomas wrap around organs, become indistinguishable from blood vessels, and respond to treatment by calcifying and becoming difficult to deal with. Total resection cannot always be achieved.

The treatment that was most tolerable, apart from the necessary period of isolation, was I131-MIBG high-dose internal radiation therapy; and even then the long-term side-effects of this type of therapy are not well known yet.

There was absolutely nothing about the NHS treatment of neuroblastoma that I preferred. It's completely horrendous. As is the disease that it's used to treat.

4. What do you consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that you expect to gain from using the treatment

being appraised.

Reduced rate of relapse. Improvement in long-term survival, hopefully equating to an increased cure rate for high-risk neuroblastoma. Delayed relapse for some children, giving them additional years of life, disease free and off treatment, with good quality of life.

Please explain any advantages that you think this treatment has over other NHS treatments in England.

Immunotherapy is not currently available on the NHS as standard-of-care. There is no proven treatment, only an on-going clinical trial (R2 of HR-NBL-1/SIOPEN), the design of which is not randomized against any control (ch14.18/CHO Active Comparator vs. ch14.18/CHO + s/c IL-2 Experimental). Because of the high dropout rate amongst those patients receiving ch14.18/CHO + IL-2 the study is currently asking another question (R4) using a completely different dosing schedule for both ch14.18/CHO and IL-2. Currently neither of the treatment arms in the R2 study, which has initial results presented at Advances in Neuroblastoma (ANR) conference in 2014, are available to patients at all!

An important component of the treatment regimen being considered by this appraisal process, GM-CSF (sargramostim), is not currently available in any form. This immunostimulator is believed to be an integral part of the treatment, and there is scientific evidence to support this from both early phase clinical trials conducted with ch14.18/SP/2, and from papers published by Memorial Sloan Kettering Cancer Center (MSKCC) where it is used in combination with their 3F8 anti-GD2 monoclonal antibody. The reason for it not being included in the SIOPEN studies was that no commercial supply was available, rather than any scientific rationale. Of course dinutuximab was also not available at that time – it was manufactured in limited supply for COG-ANBL0032 by the U.S. National Cancer Institute.

Parents want to see their children receive the best possible treatment. Dinutuximab + sargramostim + interleukin 2 + isotretinoin is the only maintenance therapy that has been proven, by way of a randomized control trial, to improve survival in children with high-risk neuroblastoma. It is FDA

approved, and has been standard of care in America for some time. It has gone through a lengthy process, both in terms safety and efficacy, to reach this point, and is now commercially available in the UK.

If you know of any differences in opinion between you and other patients or carers about the benefits of the treatment being appraised, please tell us about them.

I do not know of any such differences of opinion. Some parents may be ignorant of the facts, or indifferent, and others have had no other alternative but to enrol on the SIOPEN trial using ch14.18/CHO. It is important to keep in mind that every parent wants to believe they are doing the best for their child. However, I have not heard an opinion that immunotherapy options available on the current SIOPEN clinical trial are *better* than the combination of dinutuximab, sargramostim, interleukin 2 and isotretinoin, that is being appraised here.

5. What do you consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Immunotherapy treatment requires the child to be hospitalized during administration. Current standard of care (13-cis-RA) does not. This would extend regular inpatient-based treatment by 5-6 months. The main observable

side-effects are; neuropathic pain that must be controlled with strong medication such as IV morphine, and capillary/vascular leak syndrome where fluid accumulates inside the body - if this occurs at the site of major organs, such as heart or lungs, it can become dangerous.

Please list any concerns you have about current NHS treatments in England.

As parents of children newly diagnosed with cancer we become introduced to this concept of evidence-based medicine. Most, like myself, have no prior knowledge of how this works, and are plunged into a world of clinical trials that they hitherto knew absolutely nothing about.

And then, when what seems to us to be compelling evidence comes along, it is not acted upon. It appears that different sets of rules are being selectively applied. This gives to rise to the situation where parents have a hard time understanding how some of these decisions are made, and are frankly sceptical about what might be going on behind the scenes.

It is hard for me to understand the rationale for the R2, and now on-going R4 randomizations on HR-NBL-1/SIOPEN when a treatment with proven efficacy *and* safety already exists, and is now available commercially. I understand the rationale for trying to ameliorate the side-effects, but the starting point for this should be the proven treatment *then compared against something else.*

Please list any concerns you have about the treatment being appraised.

The only concern I have is that this particular treatment combination has never been given to a child in the UK. This is always a concern where there is no prior experience of administering a particular treatment, and managing its side effects. However, the experience with ch14.18/CHO + IL-2 would be very similar I expect, except for the administration of IL-2 (*sc* versus *iv*). It is my understanding that the most severe side-effects present during the cycles where dinutuximab and interleukin 2 are used in combination, rather than dinutuximab and sargramostim.

If you know of any differences in opinion between you and other patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

I do not know of any such differences of opinion.

6. Patient population

Do you think some patients might benefit more from the treatment than others? If so, please describe them and explain why.

Patients in complete first remission, or those with only small amounts of disease remaining - so-called minimal residual disease (MRD), after ASCT, would benefit most. This type of immunological treatment cannot deal with heavy disease burden.

There is also some evidence that exists to suggest that anti-GD2 monoclonal antibody therapy in children reaching remission after relapse can also lead to long-term survival.

There is also some evidence that exists to suggest that anti-GD2 monoclonal antibody therapy is effective at treatment of disease in the bone marrow, or with small amounts of skeletal disease.

Do you think some patients might benefit less from the treatment than others? If so, please describe them and explain why.

Those who fall outset the category of patients described above.

7. Research evidence on patient or carer views of the treatment

Are you familiar with the published research literature for the treatment?

■ Yes ☐ No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether your experience of using the treatment as part of routine NHS care reflects the experience of patients in the clinical trials.

This is not applicable. I have not had access to this precise treatment, nor has it ever been available on the NHS.

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

I think the clinical trials have captured the most important measurable outcome to patients and parents/carers. A randomized control trial, using event free survival as the primary end point, is the gold standard in clinical research of rare orphan diseases and COG-ANBL0032 showed clear survival advantage (and randomization was ended early for ethical reasons) when a statistically significant difference was established in 2-year event-free survival. Relapsed neuroblastoma has always been considered to ultimately result in death. Whilst this attitude is not so universally held nowadays in some places, it remains the prevailing view in the UK. Prevention of relapse is therefore critical to improving long-term survival rate for high-risk neuroblastoma

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

It is not currently available in the NHS.

Are you aware of any relevant research on patient or carer views of the condition or existing treatments?

☐ Yes ■ No

If yes, please provide references to the relevant studies.

8. Equality

NICE is committed to promoting equality of opportunity and eliminating discrimination. Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, who they are and why.

I do not believe there would be any such adverse affect.

9. Other issues

Do you consider the treatment to be innovative?

■ Yes ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition.

It was the first time the therapeutic power of a patient's own immune system had to been used to treat neuroblastoma. When the results of COG-ANBL0032 were first published they represented the single biggest advance in high-risk neuroblastoma treatment in decades.

Before immunotherapy the improvements in survival for high-risk neuroblastoma came from intensifying the treatment regimen. Giving higher doses of induction chemotherapy. Shortening the time between cycles of induction chemotherapy, adding radiotherapy after surgery, introducing myeloablative chemotherapy with autologous stem cell transplant. The trade off was improvements in long-term survival, but also greater toxicities, both in the near and longer term.

Immunotherapy with ch14.18 + GM-CSF + IL-2 has not only made the biggest single improvement of *any* additive therapy, but it has done so with no additional long-term side-effects.

Is there anything else that you would like the Appraisal Committee to consider?

Outside of the cost implications and considerations, this appraisal comes down to a choice between either; giving children access to a treatment combination that has been proven to be both safe and efficacious, or leaving parents with the options of enrolling them on the SIOPEN immunotherapy research study, or travelling to America where this treatment is available.

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- Proven to improve survival in a large Phase III randomized control trial.
- Currently neuroblastoma relapse is almost always fatal in the UK.
- There are no long-term toxicities.
- It is currently standard-of-care in United States, approved by FDA.
- Parents in the UK want, expect, and deserve, the best treatments for their children, offering them the best chance to beat this disease.

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Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

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- the experience of receiving NHS care for the condition
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- preferences for different treatments and how they are given
- expectations about the risks and benefits of the treatment.

We have already asked your nominating organisation to provide an organisation's view. We are asking you to give your views as an individual whether you are:

- a patient
- a carer (who may be voicing views for a patient who is unable to) or
- somebody who works or volunteers for a patient organisation.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The response area will expand as you type. The length of your response should not normally exceed 10 pages.

1. About you

Your name: Stephen Smith
Name of your nominating organisation: Neuroblastoma UK
Do you know if your nominating organisation has submitted a statement?

☐ Yes x No

Do you wish to agree with your nominating organisation's statement?

x Yes ☐ No

(We would encourage you to complete this form even if you agree with your nominating organisation's statement.)

Are you:

- a patient with the condition?

☐ Yes x No

- a carer of a patient with the condition?

☐ Yes x No

- a patient organisation employee or volunteer?
-

x Yes ☐ No

Do you have experience of the treatment being appraised?

☐ Yes x No

If you wrote the organisation submission and do not have anything to add, tick here ☐ (If you tick this box, the rest of this form will be deleted after submission.)

2. Living with the condition

What is your experience of living with the condition as a patient or carer?

My daughter was diagnosed with neuroblastoma at the age of 11 months and treated for the next 9-10 months.

3. Current practice in treating the condition

Which treatment outcomes are important to you? (That is, what would you like treatment to achieve?) Which of these are most important? If possible, please explain why.

Extended event-free survival, improved or new primary treatments, effective alternative treatments where primary treatment is ineffective or not tolerated, better treatment for refractory or relapsed disease, prevention or relapse.

What is your experience of currently available NHS care and of specific treatments? How acceptable are these treatments – which did you prefer and why?

Standard treatment regime of chemotherapy, surgery and radiotherapy is effective (if aggressive) for a proportion of patients once neuroblastoma has been diagnosed (not always achieved as early as it needs to be), but far less so for those with high risk disease. Options are limited for these cases or for relapsed patients.

4. What do you consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)

- any other issues not listed above

Please list the benefits that you expect to gain from using the treatment being appraised.

Impact on refractory disease and on prevention/avoidance of relapse.

Extended EFS.

Please explain any advantages that you think this treatment has over other NHS treatments in England.

Complementary to the standard currently available treatments

If you know of any differences in opinion between you and other patients or carers about the benefits of the treatment being appraised, please tell us about them.

There is widespread support for immunotherapy treatments, with some variation in views about the specific types of antibody used and that ways that existing clinical trials and treatment protocols are organised.

5. What do you consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns you have about current NHS treatments in England.

Limited options where standard treatment is ineffective or not well tolerated, and for cases of relapse.

Please list any concerns you have about the treatment being appraised.
The treatment can be difficult for patients and requires careful management by clinical teams.

The treatment being appraised has been developed and trialled in the US. As I understand it is not clear whether the US antibody and protocol is more effective than analogous antibody treatment developed and trialled in Europe including the UK). Hence there could be a concern that approval would result in UK patients receiving treatment which is not demonstrably belter that the existing European treatment, and of the development and trailing of the latter being impaired.

If you know of any differences in opinion between you and other patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

6. Patient population

Do you think some patients might benefit more from the treatment than others? If so, please describe them and explain why.
Patients with high risk disease, and those at risk of relapse.

Do you think some patients might benefit less from the treatment than others? If so, please describe them and explain why.
May not be appropriate or required for patients with lower risk variations of neuroblastoma.

7. Research evidence on patient or carer views of the treatment

Are you familiar with the published research literature for the treatment?

☐ Yes x No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether your experience of using the treatment as part of routine NHS care reflects the experience of patients in the clinical trials.

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

Are you aware of any relevant research on patient or carer views of the condition or existing treatments?

☐ Yes ☐ No

If yes, please provide references to the relevant studies.

8. Equality

NICE is committed to promoting equality of opportunity and eliminating discrimination. Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, who they are and why.

9. Other issues

Do you consider the treatment to be innovative?

x Yes ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition.

Very few options currently available to treat or reduce risk of relapse

Is there anything else that you would like the Appraisal Committee to consider?

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- There is widespread interest in immunotherapy treatments for childhood cancer including neuroblastoma
- Clinical trials have been running for some time and there have been some positive indicaitons, although the full picure is not yet clear
- Care is needed to avoid closing down other promising potential treatment options (immunotherapy or other) as a result of approval
- There are presently limited options for treating relapsed patients or those who don't respond to the current mainstream treatment
- The treatment does have significant side effects and this has to be balanced against effectiveness

CONFIDENTIAL UNTIL PUBLISHED
Evidence Review Group's Report
Dinutuximab for treating high-risk neuroblastoma

Produced by CRD and CHE Technology Assessment Group, University of York, Heslington, York YO10 5DD

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Declared competing interests of the authors
None

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Rider on responsibility for report
The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Pedro Saramago wrote the cost-effectiveness sections of the report and conducted the economic analyses. Claire Rothery wrote the cost effectiveness sections of the report, assisted with the economic analyses and took overall responsibility for the cost effectiveness sections of the report. Mark Simmonds and Mousumi Biswas wrote the clinical sections of the report. Kath Wright provided literature searching support. Nerys Woolacott wrote chapters 2 and 3 and took overall responsibility for the report.

Note on the text

All commercial-in-confidence (CIC) data have been highlighted in blue and underlined, all adademic-in-confidence (AIC) data are highlighted in yellow and underlined.

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List of abbreviations

ABMT	Autologous purged bone marrow transplantation
ACST	Autologous stem-cell transplantation
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
COG	Children's Oncology Group
CS	Company evidence submission
EFS	Event-free survival
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
GM-CSF	Granulocyte macrophage colony-stimulating factor
HR	Hazard ratio
HRQOL	Health-related quality of life
IL-2	Interleukin-2
INSS	International Neuroblastoma Staging System
ITT	Intention-to-treat
MYCN	v-myc avian myelocytomatosis viral oncogene neuroblastoma derived homolog
NCI	National Cancer Institute
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
OR	Odds ratio
OS	Overall survival
RR	Risk ratio
SE	Standard error
UTC	United Therapeutics Corporation

1 Summary

Neuroblastoma is primarily a tumour of early childhood, with nearly 90% of cases diagnosed by the age of 5 years. Children diagnosed with neuroblastoma are classified into three different risk groups: low, intermediate, and high. In UK clinical practice a patient with neuroblastoma, aged over 1 year, with INSS Stage 4, or INSS Stage 3 plus abnormalities, would be classified as high-risk. In particular the disease is very different in infants under age 1 in whom it often presents with localised disease and spontaneously regresses, and is easier to treat. Neuroblastoma has a significant impact on morbidity, mortality, and quality of life of patients and their caregivers. Five year mortality in patients diagnosed aged >1 year is estimated at around 30 or 40%. However those who do survive five years may well be cancer survivors, though due to both the effect of the disease itself and its treatment, survivors are at significant risk of long-term complications associated with neuroblastoma, including increased risk of secondary malignancy and mortality.

High-risk neuroblastoma is typically treated with a multimodal therapeutic approach, including intensive induction chemotherapy, autologous stem cell transplantation (SCT), with maintenance therapy intended to eliminate minimal residual disease and prevent relapse provided using retinoids and immunotherapy; radiotherapy and surgery may also be included.

1.1 Critique of the decision problem in the manufacturer's submission

The CS statement of the decision problems matches the population specified in the NICE scope: people with high-risk neuroblastoma who have received myeloablative therapy and autologous stem cell transplant. However, the anticipated marketing authorisation dictates a more restricted population than that in the NICE scope,

"Patients aged 12 months to 17 years who have previously received induction chemotherapy and achieved at least a partial response, followed by myeloablative therapy and ASCT."

The main RCT providing the evidence for the efficacy of dinutuximab included patients mean age at diagnosis of 3.5 years (range 0.2 to 14.5 years); the vast majority of patients recruited (around 78%) were aged 1 to 5 years.

Furthermore, in this main RCT, only those patients without MRD following autologous-SCT were randomised. Hence the population supported by the CS is only a sub-set of the licenced population.

The two subgroup populations listed in the final scope issued by NICE of (i) people with relapsed disease and (ii) people with refractory disease were not considered by the company due to a lack of evidence for the use of dinutuximab in these subpopulations. Whilst some clinical evidence is provided for a refractory subgroup (patients with persistent disease (MRD- positive) after autologous-

SCT) this subgroup is not analysed in the economic model. Other sub-groups are considered but not included in the economic modelling: by Curie score (=0 and > 0); and following ERG request, age, INSS stage, MYCN amplification, DNA ploidy, pre-autologous-SCT response, histology, and stem cell type. _

The CS statement of the decision problems claims to adhere to the intervention specified in the NICE scope: dinutuximab in combination with sargramostim, aldesleukin, and isotretinoin. No dose was specified in the NICE scope. The licenced use of dinutuximab (as specified in the SmPC (see Appendix of CS)) is as part of a specified combination therapy including isotretinoin and inter-leukin-2 (IL-2) and GM-CSF. Sargramostim is a GM-CSF marketed by Genzyme; there are also other GM-CSF products such as Morgramostim (Leukomax). Aldesleukin is another name for IL-2. Both IL-2 and GM-CSF contribute to the efficacy of dinutuximab based immunotherapy.

The authorised posology for dinutuximab is for it to be administered by intravenous infusion over five courses at a daily dose of 17.5 mg/m^2. This dose has been demonstrated to have bioequivalence with the 25 mg/m^2 dose of the NCI ch14.18 product that was used in the clinical trials used to support the product licensing and this NICE appraisal for dinutuximab.

Dinutuximab is intended to be administered as indicated according to the marketing authorisation, in combination with GM-CSF, IL-2, and isotretinoin. Currently, GM-CSF is not approved for marketing authorization by the EMA for any indication, and therefore is not commercially available in England. The company has stated,

"_UTC does not manufacture this molecule and has no relationship with the manufacturer. However, UTC has arranged for access to GM-CSF through a third party distributor, available through a bona fide request from the treating physician independent of UTC. Additionally, the treating physician would also be able to procure the GM-CSF through their institution's standard operating procedures from a different distributor, if the distributor can provide access to GM-CSF in England."

The Company has also stated,

"Although GM-CSF is not routinely used in English clinical practice, the dinutuximab SmPC provides sufficient instructions on using the product in immunotherapy. Additional information regarding GM-CSF can be found in the GM-CSF (Leukine®) Prescribing Information.

The comparators described in the CS match the comparators described in the final NICE scope: isotretinoin. No dose was specified in the NICE scope. The dosing used in the main clinical trial reflects that currently used in UK clinical practice.

The outcomes described in the final NICE scope were: overall survival; progression-free survival; adverse effects of treatment; and health-related quality of life. In the CS the outcomes addressed in the decision problem were similar but progression-free survival was replaced with event-free-survival, defined as the time to an event from study enrolment until the first occurrence of: relapse; progressive disease; secondary cancer; death; or, if none of these events occurred, until the last contact with the patient. The CS states that in the phase 3 trial, all patients experienced progressive disease, relapse, or death, and consequently, the event-free survival outcome is similar to the progression-free survival outcome.

1.2 Summary of clinical effectiveness evidence submitted by the manufacturer

1.2.1 Event-free and overall survival

The CS identified one randomised controlled trial (ANBL0032) which evaluated the clinical efficacy of dinutuximab, in combination with IL-2 and GM-CSF, compared to standard therapy with isotretinoin alone. This trial recruited 226 children with high risk neuroblastoma. The trial was stopped early as evidence of superiority, based on a formal sequential monitoring process, was identified.

The CS reported results from both a 2009 and a 2012 analysis of the trial, but the ERG requested results from the most recent data follow-up analysis from 2014.The manufacturers provided analyses of the March 2014 data on request, with analyses of both overall and event-free survival. Summary Kaplan-Meier curves are presented for event-free survival in Figure 1and for overall survival in Figure 2.

Figure 1: Event-free survival in ANBL0032 trial (March 2014 data)

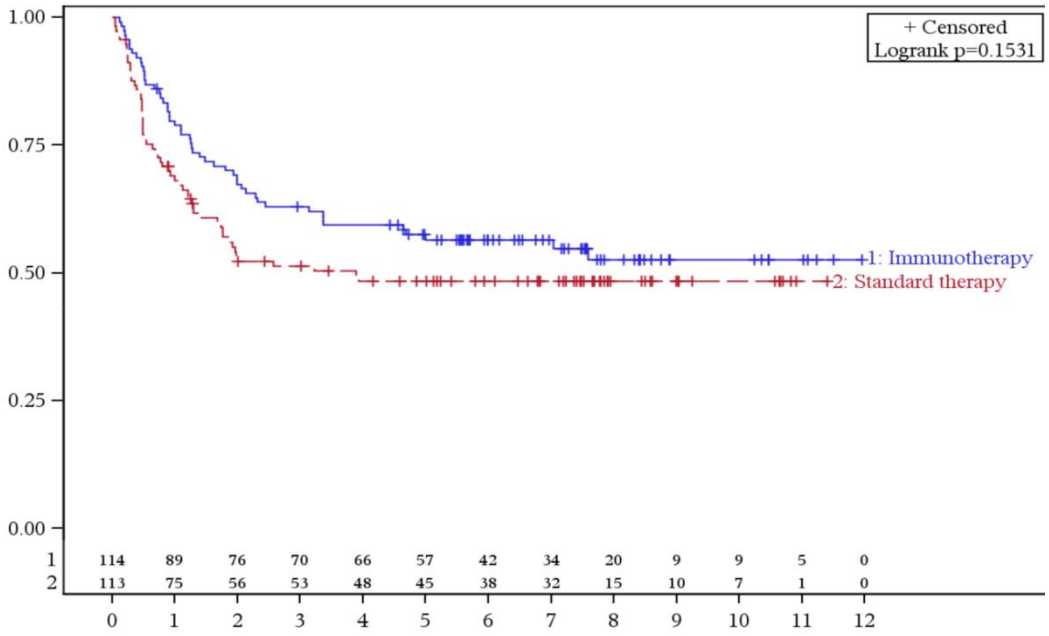
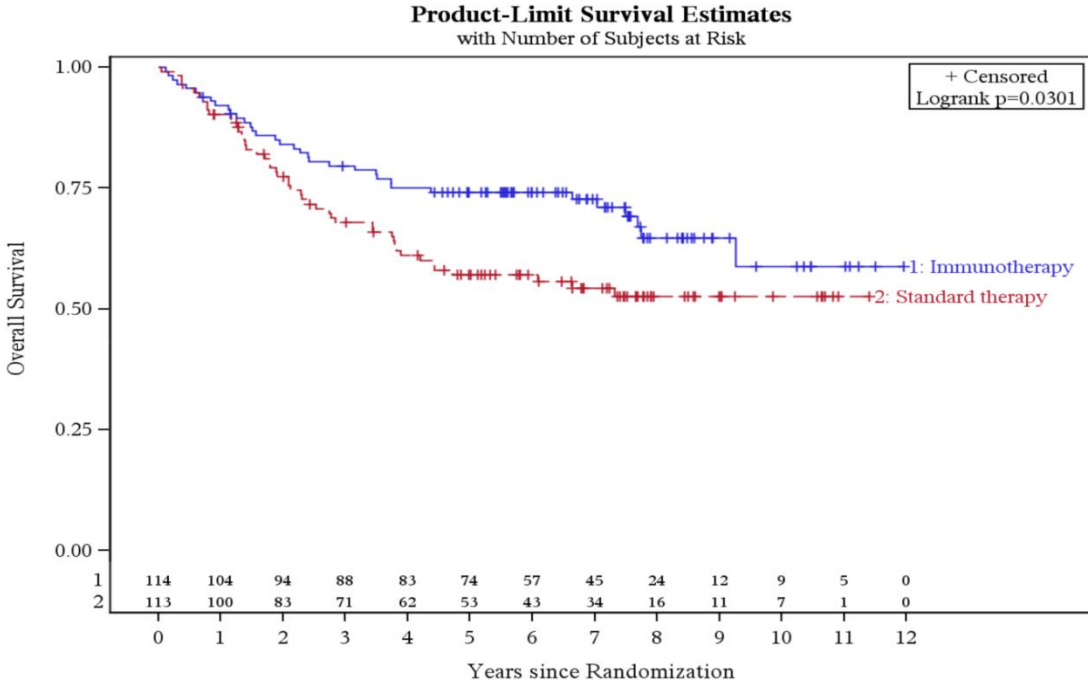


Figure 2: Overall survival in ANBL0032 trial (March 2014 data)



Survival probabilities for both outcomes were higher with immunotherapy than standard therapy at all times up to five years after randomisation. Longer-term follow-up for event-free survival suggested that survival curves for both arms converged at around a 50% long-term (beyond 10 years) survival rate. This suggests that immunotherapy does not permanently prevent cancer-related events. A proportional hazards model found that, although the hazard was lower with immunotherapy, the

difference was not statistically significant (HR 0.759, 95% CI 0.53 to 1.11). For overall survival the survival curves also appeared to be converging to long-term survival rates of just over 50%, although the longer survival times mean this is less certain. The hazard of mortality was significantly lower for immunotherapy (HR 0.621, 95% CI 0.402 to 0.959), suggesting that immunotherapy can delay, and possibly prevent, mortality.

Only one further trial (ANBL0931) collected efficacy data for dinutuximab. The final analysis of this trial has yet to be performed, but interim results, provided by the manufacturer, support the findings of the ANBL0032 trial.

1.2.2 Adverse events

The ANBL0032 trial also reported the incidence of adverse events. A summary of these adverse event results is presented inTable 1.

Table 1: Example adverse event rates in ANBL0032 trial

Adverse Event	Immunotherapy (N=137) %	Standard therapy (N=108) %	Relative Risk	95% Confidence Interval	
				Low	High
Neuropathic pain	52	6	9.3	4.2	20.6
Hypotension	18	0	38.6	2.4	628.0
Fever without neutropenia	39	6	7.0	3.1	15.6
Acute capillary leak syndrome	23	0	49.7	3.1	802.4
Hypersensitivity reaction	25	1	26.8	3.7	192.7
Hyponatremia	23	4	6.1	2.2	16.8
Hypokalaemia	35	2	18.9	4.7	76.1
Abnormal ALT	23	3	8.1	2.6	25.9
None	6	37	0.2	0.1	0.3

ALT – alanine aminotransferase

There were a number of adverse events that were substantial more common among immunotherapy patients than patients receiving standard care, including, neuropathic pain, acute capillary leak syndrome, fever without neutropenia, hypokalaemia and hypersensitivity reaction.. Only 6% of immunotherapy patients had no adverse events, compared to 37% of standard therapy patients.. The incidence of pain appeared to decline over successive courses of treatment, and acute capillary leak syndrome and hypersensitivity were more common in IL-2 treatment courses than in GM-CSF courses. Three single-arm trials which reported adverse events were described (ANBL0931 (104

patients), CCG-035A (25 patients) and CCG-035 (19 patients)). These results generally concurred with those of the ANBL0032 trial.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

1.3.1 Early stopping of trial ANBL0032

All the evidence on efficacy for dinutuximab-based immunotherapy, and much of the evidence on safety, is drawn from the ANBL0032 trial. This trial whilst randomised and controlled was not double-blind. Furthermore, it was stopped early after recruiting 226 patients who subsequently experienced only 83 cancer related events. It appears that the sequential monitoring used to terminate recruitment was not performed correctly as the monitoring boundary had not been crossed at the time the trial was stopped. This is of concern, because, had the trial continued recruitment, the observed benefit might not have persisted and, because the trial was stopped because was favourable result was achieved; any analysis of the results may overestimate the benefit of dinutuximab.

The CS based much of the clinical analysis on the data at the time the trial was stopped (2009). However, it was acknowledged that there were some errors in the data at that time, and checks by the ERG confirmed that the analysis results based on this 2009 data were inconsistent with later analyses. The ERG therefore considers the analysis based on the 2009 data to be unreliable and analyses should instead use the most up-to-date follow-up data (March 2014).

1.3.2 Long-term survival

The CS presented data only at two and four years after randomisation, which the ERG considers to be too short a timescale to determine efficacy. While analyses up to five years after randomisation for event-free survival showed higher rates for immunotherapy, longer-term follow-up (up to ten years) suggests that around half of patients will have a cancer-related event, regardless of treatment received. A similar pattern was observed for overall survival, with around half of patients surviving for ten years or more. Further analyses performed by the ERG suggest that immunotherapy delays events, and hence lengthens overall survival times, but does not prevent cancer recurrence.

The ERG used data reconstructed from the 2014 Kaplan-Meier curves to fit a parametric cure model to the data, which assumes a proportion of patients are "cured" and at no risk of cancer events or death. This model was found to fit the data well, suggesting that some patients are cured regardless of therapy received. For event-free survival the cured fraction was 47% in both arms, so immunotherapy did not prevent events from occurring, but it did reduce the hazard of events. This suggests that immunotherapy delays rather than prevents events. For overall survival, the cured fraction was 48.8% in the standard therapy arm, but is higher (around 66%) in the immunotherapy arm, with lower hazard

in the immunotherapy arm. This suggests that immunotherapy delays and possibly prevents some mortality.

1.3.3 Patient subgroups

Subgroup analyses presented in the CS and on request for clarification suggested that survival rates with immunotherapy were poor for patients with persistent disease following autologous-SCT (i.e. refractory patients), although no such patients received standard therapy, so no comparison could be made. Immunotherapy appeared to be ineffective in patients with a Curie score above zero, and may be no better than standard therapy in some other subgroups (patients who are MYCN amplified or whose amplification is unknown, patients with unknown histology, patients with purged stem cell type), but evidence in these groups was limited.

1.3.4 Other forms of ch14.18

As only one trial of dinutuximab was presented the ERG requested data on trial of other forms of ch14.18 antibody that had been excluded from consideration. These antibodies may not be bioequivalent to dinutuximab, and the trials did not combine ch14.18 with IL-2 or GM-CSF, so they are not directly comparable. In general, these trials found little or no evidence of any benefit of ch14.18 over other forms of treatment, and in particular, in one trial, no evidence that ch14.18 was superior to isotretinoin. This may be because other trials did not combine ch14.18 with IL-2 and/or GM-CSF.

1.3.5 Summary

The manufacturer's conclusions in the CS are largely based on a single trial, which may have had methodological errors in its analysis and conduct.

Evidence from the ANBL0032 trial suggests that around half of all patients with high-risk neuroblastoma will never have any cancer recurrence, regardless of treatment, and so will survive long-term (beyond ten years). Among those who will have a cancer recurrence, immunotherapy comprising dinutuximab+IL-2+GM-CSF may delay the event, with a consequent lengthening of life. This must be balanced against the substantial increased incidence of potentially serious adverse events and significant toxicity with immunotherapy. Ideally, further trials of dinutuximab are required to reach firm conclusions on its efficacy.

1.4 Summary of cost effectiveness submitted evidence by the manufacturer

No previously published cost-effectiveness studies of dinutuximab for the maintenance treatment of high-risk neuroblastoma were identified by the company. Therefore, the company submitted a *de novo* analysis to estimate the cost-effectiveness of immunotherapy (dinutuximab in combination with

GM-CSF, IL-2 and isotretinoin) compared with standard therapy (isotretinoin) within the licensed population for use of dinutuximab. The assessment of cost-effectiveness was based on evidence from the ANBL0032 clinical trial using the primary 2-year efficacy analysis (July 2009) data cut although later data cuts were available.

The decision model was based on a partitioned survival approach, which uses EFS and OS estimates over time to inform three mutually exclusive health states of stable (event-free cohort), failure (difference between OS and EFS) and death (1-OS). The company used parametric survival curves fitted to empirical Kaplan-Meier data on EFS and OS up to a pre-defined time point of 5 years. The company assumed that survival gains are extrapolated over a lifetime horizon. At 5 years, the event-free cohort was assumed to be cured, i.e. patients who have survived to 5 years without an event were considered survivors and entered a phase where they followed similar characteristics to that of the general population (same mortality risk), while still accounting for potential morbidities affecting quality of life and resource use among neuroblastoma survivors. At 5 years, patients in the failure health state were assumed to have a monthly probability of death of 5.1% and incurred monthly costs associated with a topotecan-based combination of therapies until death. Health-related quality of life (HRQoL) was quantified by applying utility weights to the health states derived from the Health Utility Index questionnaire from a small Canadian study of children treated for tumours of the central nervous system. A reduction in HRQoL of 13% was applied to the event-free cohort at 5 years to account for potential morbidities associated with neuroblastoma survival. Costs were assessed from an NHS and personal and social services perspective and incorporated drug acquisition, administration, concomitant medication and monitoring costs, costs associated with adverse events and health state costs. The outcomes of the cost-effectiveness analysis were total costs and quality-adjusted life years (QALYs).

The company presented an incremental cost per additional QALY gained for immunotherapy compared with standard therapy of £37,423 based on the primary July 2009 data cut of trial ANBL0032. The company presented a series of one-way deterministic sensitivity and scenario analyses to assess the impact of uncertainty around key model input parameters on the estimate of the ICER. The results of these indicated that the base case ICER was most sensitive to the maturity of the survival data used in the analysis and the outcome discount rate: the most favourable ICER obtained was £22,017 per QALY gained for an outcome discount rate of 1.5% per annum, while the least favourable ICER obtained was £66,344 per QALY gained using the most mature (March 2014) survival data. The company's probabilistic sensitivity analysis concluded that the probability that immunotherapy is cost-effective at a threshold value of £30,000 per additional QALY was 27% compared with standard therapy.

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The ERG considers that the updated survival data from the pivotal trial (March 2014 data cut) provide the most relevant estimates of EFS and OS in this patient population for informing the assessment of cost-effectiveness. Although the earlier data cut represented the primary analysis of the pivotal trial, the COG and NCI amended the protocol to include a later analysis because the OS data in the primary analysis were not considered mature enough.

The cost-effectiveness results are contingent on the assumption that the event-free cohort is 'cured' at 5 years (cure threshold). The ERG considers this assumption of a 'cure' threshold at 5 years to be inappropriate since the updated evidence from the trial shows that further events did occur in the immunotherapy arm of the trial after 5 years. Furthermore, both the EFS and OS curves for immunotherapy and standard therapy appear to converge between 6.5 and 11 years suggesting that immunotherapy prolongs the time to relapse rather than 'cures' neuroblastoma.

The two assumptions in the company's model of, (i) cured at 5 years and (ii) extrapolation of survival gains over a lifetime horizon, mean that the cost-effectiveness results are very sensitive to the proportion of patients in each health state at 5 years for immunotherapy and standard therapy. As a consequence, the model results are also sensitive to the parametric functions used to fit the observed Kaplan-Meier data since any small difference between treatments in the proportion of individuals in the health states at the cure point are extrapolated over a lifetime.

The company assumed that patients event-free at 5 years have the same survival rate as the general population. However, evidence from the Childhood Cancer Survivor Study [1] found a higher standardised mortality rate of 5.6 (95% confidence interval of 4.4 to 6.9) among neuroblastoma survivors compared to low-risk siblings without cancer.

The ERG also considers there to be an inconsistency in how the mortality of the failure health state is modelled. The mortality risk for patients who fail treatment within the trial period is captured within the OS curves but this differs from the mortality risk for patients who fail after the threshold of 5 years (monthly probability of death of 5.1% after 5 years). This leads to a perverse effect that there is a differential treatment effect on mortality that persists after the cure point due to a different proportion of patients in the failure state at 5 years for immunotherapy compared with standard therapy.

The ERG identified a number of issues associated with the costs in the model. The most significant of these was the use of the same administration cost for dinutuximab and IL-2 as the topotecan combination of therapies for relapse. The ERG believes that the administration cost of dinutuximab

and IL-2 should be much higher than the administration cost for topotecan due to the additional number of days that patients are hospitalised for immunotherapy.

1.6 ERG commentary on the robustness of evidence submitted by the manufacturer

1.6.1 Strengths

Clinical

The clinical evidence was identified through a good quality systematic review process and it is likely that all relevant clinical trials reporting efficacy or safety data have been identified. The primary trial (ANBL0032) appears to have been a generally well-conducted RCT, although it could not be blinded.

Cost effectiveness

The ERG considers the company's economic submission to meet the requirements of the NICE reference case. The partitioned survival model structure is generally appropriate since it enables ongoing risks to vary over time and is typical of that used for evaluating oncology therapies. Although the ERG does not consider the use of a cure threshold of 5 years to be appropriate, the model structure does allow the possibility of 'altering' the cure threshold to a different point in time in order to assess the implications on the results of the cost-effectiveness analysis.

1.7 Weaknesses and areas of uncertainty

Clinical

The efficacy evidence, and much of the safety evidence, was derived from a single trial (ANBL0032) of 226 children. Hence the evidence base for dinutuximab is very limited, and is not supported by results from trials of other forms of ch14.18 antibody. Furthermore the trial was stopped early, before an appropriate stopping boundary was crossed. This both reduces the size of the evidence base, and increases the risk that any benefit of dinutuximab is overestimated. Consequently the ERG considers that the true efficacy of dinutuximab remains uncertain.

Data on survival beyond 12 years after randomisation was not available, and data beyond ten years was very limited. Hence there is uncertainty around the long-term survival of neuroblastoma patients. In particular there is uncertainty around whether patients who received immunotherapy but have a cancer recurrence survive long-term, and what happens in the long term to neuroblastoma "survivors" generally. No health-related quality of life data were available, so the quality of life of neuroblastoma patients, particularly for cancer survivors, is uncertain.

Cost effectiveness

The ERG's primary concern with the company's base case estimate of cost-effectiveness is the fact that the evidence used to inform the key parameters of EFS and OS is based on the earliest data cut of the pivotal trial. The ERG considers the updated data from the trial to be fundamental to the assessment of cost-effectiveness of immunotherapy compared with standard therapy since this data provides the longest follow-up evidence. A second concern relates to the use of a cure threshold at 5 years in the model. This threshold means that the survival gains observed at 5 years are extrapolated over a lifetime horizon. The ERG considers this a strong assumption since the long-term consequences of therapy in this patient population are unknown. Furthermore, it means that in the model patients event-free at 5 years do not experience any further risk of relapse and return to the same survival rates as that of the general population. The extrapolation of survival benefits over a lifetime horizon also means that greater weight is given to the survival benefits of treatment observed at the time point of 5 years in the estimate of cost-effectiveness than the survival benefits observed at any other time point within the trial period.

In the absence of EQ-5D utility data for the target population, the company used Health Utility Index data from a small Canadian study of children that completed treatment for tumours of the central nervous system. While no other evidence was identified to inform HRQoL in the target population, the ERG considers there to be considerable uncertainty surrounding the utility values used in the model for the stable and failure health states, which are based on a sample size of 10 and 3 patients, respectively.

1.8 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG undertook a range of exploratory analyses to assess the uncertainties raised in the review and critique of the company's clinical and cost-effectiveness evidence. The company's assumption that survival gains at 5 years are maintained over a lifetime horizon has a major impact on the cost-effectiveness results: the company's base case ICER increases from £37,423 (lifetime horizon – best case scenario) to between £70,288 (20-year horizon) and £326,844 (5-year horizon – worst case scenario) per additional QALY. The use of the updated data March 2014 from the pivotal trial also had a major impact on the cost-effectiveness results. The ERG used the observed Kaplan-Meier data from the trial to inform the assessment of cost-effectiveness (instead of parametric modelling, which was unnecessary and relies on assumptions about proportional hazards). The use of the observed Kaplan-Meier data increased the company's scenario analysis ICER from £66,344 to £70,296 per additional QALY. This increase was driven by the extrapolation of a smaller difference between treatments in EFS at 5 years in the observed data compared with the parametric fit over a lifetime horizon.

The ERG used the March 2014 data in all additional analyses. The ERG considered the use of an alternative cure point of 10 years in the model to reflect the fact that further relapses did occur in the immunotherapy arm of the trial after 5 years. A cure threshold of 10 years increased the ICER to £99,699 per additional QALY. This ICER represents the ERG's base case analysis.

The ERG explored the implications of an adjustment to the general population mortality for neuroblastoma survivors. The higher standardised mortality rate of 5.6 from the Childhood Cancer Survivor Study increased the ERG's base case ICER from £99,699 to £105,160 per additional QALY. An increased reduction in the HRQoL of neuroblastoma survivors relative to the general population from 13% (in the company's base case analysis) to 31.5% (based on a study by Nathan 2007) increased the ICER to £112,051 per additional QALY. In separate scenarios, the ERG considered alternative assumptions for the administration costs of dinutuximab and potential drug vial wastage; these increased the ICER from £99,699 to £128,378 and £103,667 per additional QALY, respectively.

1.9 Conclusions from the ERG analyses

The ERG's base case analysis suggests that the ICER for immunotherapy compared with standard therapy is around £100,000 per QALY gained. The results from the ERG's additional exploratory analyses using a range of alternative assumptions indicate that this ICER is likely to represent a lower bound. For example, the ERG considers it very unlikely that the event-free cohort at the point of cure would return to the same mortality risk as that of the general population.

2 Background

2.1 Critique of company's description of the technology

The company submission includes a description of the technology:

Brand name: Unituxin™

UK approved name: Dinutuximab 3.5 mg/mL concentrate for solution for infusion

Therapeutic class: Monoclonal antibodies, ATC code: L01XC16

The mechanism of action is described briefly: Dinutuximab is a monoclonal chimeric antibody composed of murine variable heavy and light chain regions and the human constant region for the heavy chain IgG1 and light chain kappa. Dinutuximab reacts specifically with the ganglioside GD2, which is highly expressed on the surface of neuroblastoma cells and minimally expressed on the surface of normal human neurons, peripheral pain fibres, and skin melanocytes.

The company submission addressed the issues of the comparability of the licenced UTC product (dinutuximab) and the National Cancer Institute (NCI) ch14.18 product; the latter having been used in the key clinical trials. The company submission reports that based on all data provided by, the issue of comparability has been satisfactorily addressed and the issue is considered resolved (Appendix 3: Committee for Medicinal Products for Human Use (CHMP) Assessment Report for Unituxin™ (EMA/CHMP/278656/2015)).

For completeness the ERG points out the existence of another ch14.18 product, not referred to in the company submission: ch14.18/CHO (APN311, Apeiron Biologics). As part of the scoping exercise for this appraisal comments were received by NICE from National Cancer Research Institute & Children's Cancer and Leukaemia. These comments stated that,

"There are two forms of ch14.18 anti-GD2 monoclonal antibody that have been widely used clinically: ch14.18/ SP2/0 (Dinutuximab, United Therapeutics) and ch14.18/CHO (Apeiron Biologics). These two antibodies are from the same original hybridoma clone, and have identical amino acid sequences, but have been grown in different producer cell lines (SP2/0 and CHO respectively). There are no clinical studies directly comparing the two agents, but as they are grown in different cell lines they are likely to have different glycosylation patterns which might significantly affect effector function. ch14.18 SP/20 (Dinutuximab) has been used in the North American Children's Oncology Group (COG) clinical trials, and ch14.18 /CHO has been used in the several European SIOPEN trials. In view of the potential functional differences between these agents, it should not be assumed that the clinical effects are the same, or that the benefit (if any) of combining

antibody with cytokines (e.g. IL-2 and GM-CSF) is equivalent. In view of the fact that ch14.18 SP2/0 and ch14.18/CHO have been used in clinical trials for the same indications (high risk and relapsed neuroblastoma) in US and Europe respectively, and are both likely to receive marketing authorisation within the next 12-24 months, we strongly recommend that both are considered in the same NICE appraisal. However it is essential that the consultation recognises the potential biological differences between these agents."

This comment makes clear that ch14.18/ SP2/0 (Dinutuximab, United Therapeutics) and ch14.18/CHO (APN311, Apeiron Biologics) should not be considered as the same technology and that data relevant to APN311 is not directly relevant to the appraisal of dinutuximab. The ERG also requested that the company provide justification for the exclusion of ch14.18/CHO data from their submission.

NICE noted the comment above and stated that ch14.18/CHO; Apeiron Biologics will be considered through NICE's topic selection function.

Marketing authorisation

The anticipated indication for use within the UK for dinutuximab is for the treatment of high-risk neuroblastoma in patients aged 12 months to 17 years who have previously received induction chemotherapy and achieved at least a partial response, followed by myeloablative therapy and ASCT. It is administered in combination with GM-CSF, IL-2, and isotretinoin.

A similar approved indication was granted by the US FDA in March 2015.

The CHMP indicated use is restricted to high-risk neuroblastoma patients (those who have previously received induction chemotherapy and achieved at least a partial response, followed by myeloablative therapy and ASCT). Dinutuximab is restricted for use within a hospital setting under the supervision of a physician experienced in oncologic therapies.

Dinutuximab is contraindicated in patients with Grade 4 hypersensitivity to dinutuximab or excipients (histidine, polysorbate 20 [E 432], sodium chloride, or water for injection).

A summary of non-clinical and clinical issues raised by CHMP is provided in the company submission (section 2.2.6, pages 14 to 20). Post-authorisation measures required by the CHMP were reported in the CS: the company is required to submit periodic safety update reports as a condition of marketing authorisation, with the first periodic safety update report for dinutuximab due within 6 months following authorization; and the company will perform pharmacovigilance activities and interventions detailed in the agreed (and future agreed) risk management plan. The company were

also required to conduct two post-authorisation safety studies (PASS). A non-interventional study in the form of a safety registry was required in order to evaluate the long-term safety outcomes of dinutuximab in patients with high-risk neuroblastoma (including central and peripheral nervous system, prevalence of organ dysfunction, long-term effects on growth and endocrine development, hearing loss, cardiac toxicity, and survival data) the report of the results to be submitted by 06/2029. A safety study was also required in order to better characterise the safety and immunogenicity of dinutuximab and its impact on drug exposure. The final study report should be submitted by 12/2018.

The company submission included as appendices to the CS a copy of the draft SmPC and the draft European Public Assessment Report for Pharmaceuticals.

2.2 Critique of company's description of underlying health problem.

The description of underlying health problem provided in the CS is generally appropriate, drawing on reliable sources (ACS 2013[2, 3] and NCI 2012[4, 5] amongst others), providing a brief overview of neuroblastoma and then focussing on the more relevant for this appraisal, high-risk neuroblastoma.

Neuroblastoma is primarily a tumour of early childhood, with nearly 90% of cases diagnosed by the age of 5 (ACS 2013).[2, 3] The CS states that children diagnosed with neuroblastoma are classified into three different risk groups: low, intermediate, and high (NCI 2012).[4, 5] Specifically the CS details the Children's Oncology Group (COG) classification of low-, intermediate and high-risk neuroblastoma based on age, INSS stage (Table 2 (Table 11 in CS)), and tumour biology. This COG classification is given in Table 3 (Table 12 in CS) (NCI 2012). This classification was used in the key clinical trial of dinutuximab for high risk neuroblastoma. The clinical advisor to the ERG advised that in UK clinical practice a patient with neuroblastoma, aged over 1 year, with INSS Stage 4, or INSS Stage 3 plus abnormalities (e.g. MYCN amplification), would be classified as high-risk. In particular he emphasised that the disease is very different in infants under age 1 in whom it often presents with localised disease and spontaneously regresses, and is easier to treat.

Table 2. International Neuroblastoma Staging System

Stage	Description
1	Localised tumour with complete gross excision, with or without microscopic residual disease; representative ipsilateral lymph nodes negative for tumour microscopically (nodes attached to and removed with the primary tumour may be positive)
2A	Localised tumour with incomplete gross excision; representative ipsilateral nonadherent lymph nodes negative for tumour microscopically
2B	Localised tumour with or without complete gross excision, with ipsilateral nonadherent lymph nodes positive for tumour. Enlarged contralateral lymph nodes must be negative microscopically
3	Unresectable unilateral tumour infiltrating across the midline, with or without regional lymph node involvement; or localised unilateral tumour with contralateral regional lymph node involvement; or midline tumour with bilateral extension by infiltration (unresectable) or by lymph node involvement
4	Any primary tumour with dissemination to distant lymph nodes, bone, bone marrow, liver, skin and/or other organs (except as defined for stage 4S)
4S	Localised primary tumour (as defined for stage 1, 2A, or 2B), with dissemination limited to skin, liver, and/or bone marrow (limited to infants <1 year of age). Marrow involvement should be minimal (ie, <10% of total nucleated cells identified as malignant on bone marrow biopsy or on marrow aspirate); more extensive marrow involvement would be considered to be stage 4

Table 3. Children's Oncology Group neuroblastoma low-, intermediate-, and high-risk group assignment schema

INSS Stage	Age	*MYCN* Status	INPC Classification	DNA Ploidy[a]	Risk Group
1	0–-21 yr	Any	Any	Any	Low
2A/2B	<365 d	Any	Any	Any	Low
	≥365 d–21 yr	Nonamplified	Any	-	Low
	≥365 d–21 yr	Amplified	Favourable	-	Low
	≥365 d–21 yr	Amplified	Unfavourable	-	High
3	<365 d	Nonamplified	Any	Any	Intermediate
	<365 d	Amplified	Any	Any	High
	≥365 d–21 yr	Nonamplified	Favourable	-	Intermediate
	≥365 d–21 yr	Nonamplified	Unfavourable	-	High
	≥365 d–21 yr	Amplified	Any	-	High
4	<548 d	Nonamplified	Any	Any	Intermediate
	<365 d	Amplified	Any	Any	High
	≥548 d–21 yr	Any	Any	-	High
4S	<365 d	Nonamplified	Favourable	>1	Low
	<365 d	Nonamplified	Any	=1	Intermediate
	<365 d	Nonamplified	Unfavourable	Any	Intermediate
	<365 d	Amplified	Any	Any	High

[a] DNA Ploidy: DI >1 is favourable; DI=1 is unfavourable.

Key: d – days; DI – DNA index; DNA – deoxyribonucleic acid; INPC – International Neuroblastoma Pathologic Classification; INSS – International Neuroblastoma Staging System; yr – years.

The prognosis for neuroblastoma is related to age at diagnosis, clinical stage of disease, site of the primary tumour, tumour histology, and, in patients older than 1 year of age, regional lymph node involvement (NCI 2012). The 5-year survival rate for children with high-risk neuroblastoma reported in the CS is about 30% to 50% (ACS 2013). The clinical advisor to the ERG felt that in the UK the lower estimate of 30% was perhaps more realistic.

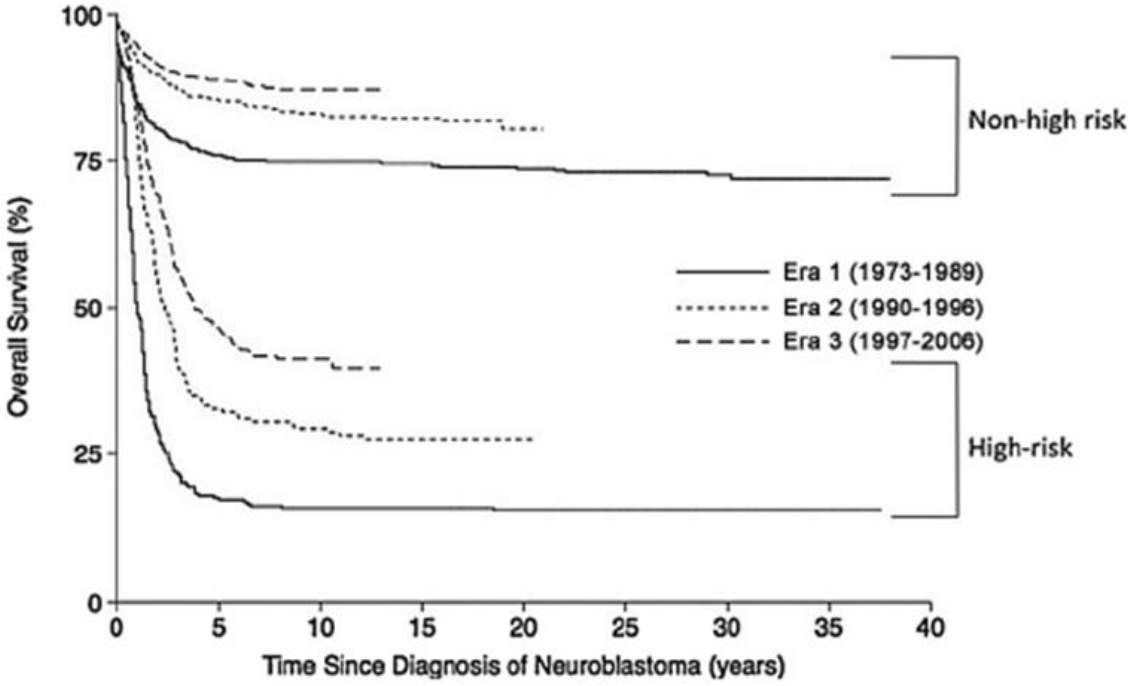
UK data reported in the CS find that approximately 100 new cases of neuroblastoma are diagnosed each year in the UK (Neuroblastoma Alliance UK 2011. Data from the Automated Childhood Cancer Information System (ACCIS) reported an age-standardized incidence rate for both sexes of 9.1 cases per million in the British Isles during 1988 to 1997 (Spix 2006).[6] Incidence by age groups (both sexes) in this region was as follows: 34.4 per million (<1 year), 17.1 per million (1–4 years), 3.1 per million (5 to 9 years), and 0.6 per million (10 to 14 years) (Note these Spix statistics are based on old data ((1988-1997)). The CS estimate for the number of patients who would be eligible for dinutuximab is 54. The clinical advisor to the ERG suggested that this figure was an underestimate: the Children's cancer registry suggests 94 neuroblastoma cases per year, of which 24 are high risk; this contrasts with the 14 per annum quoted in the budget impact analysis (p146 of submission).

Impact of high-risk neuroblastoma

The CS provides information on the impact of neuroblastoma, stating that neuroblastoma has a significant impact on morbidity, mortality, and quality of life of patients and their caregivers. The CS also provides UK survival probabilities. Impact in terms of survival is cited as five-year survival probability (95% CI) by age groups in this region: 80% (74, 85) for <1 year, 37% (33, 42) for 1 to 4 years, 34% (24, 44) for 5 to 9 years, and 26% (10, 47) for 10 to 14 years (Spix 2006),[6] though these figures are not specific to high-risk patients and also are based on old data (cohort followed 1988 to 1997).

The ERG identified further information on long-term mortality. One study used data sourced the SEER cancer database (US).[7] The investigators identified all individuals with non-CNS neuroblastoma or ganglioneuroblastoma diagnosed between 1973 and 2006. To account for changes in therapy over this very long period the data analysed by era (date of diagnosis): 1973-1989; 1990-1996; and 1997-2006. Median follow-up of whole sample was 74 months. For era 3 (most relevant to current practice) it was 67 months (maximum 155 months) (7560 patient years). Five year OS for high risk Era 3 patients is estimated to be 46.2% (95% CI 41.9-50.9%), and this was statistically significantly better than that for Era 1 (17.1% (95% CI 13.2-22.2%). Note the Kaplan-Meier plot for OS high risk Era 3 patients does not plateau at 5 years (Figure 3).

Figure 3: Estimated survival according to neuroblastoma risk group and treatment era



The long-term impact of neuroblastoma is described in some detail in the CS, although again not specific to high-risk patients. In summary, the CS reports that both the effect of the disease itself and its treatment may result in long-term complications associated with neuroblastoma. Specific treatment-related complications are dependent on factors such as the treatments received, doses of treatment, and age when treatment was received. Some of the potential long-term effects of exposure to intensive, multimodality therapy: hearing loss; heart or lung problems; slowed or decreased growth and development; bone damage or thinning of bones; changes in sexual development and ability to have children; changes in intellectual function with learning problems; development of other cancers (e.g. leukaemia).[3, 8] Also, neuroblastoma has been shown to have a negative impact on physical performance and activities of daily living [9], academic performance,[10] and psychosocial functioning [11] among patients with active disease and survivors. A survey was conducted to assess quality of life among long-term (≥10 years post-diagnosis) neuroblastoma survivors (N=137) using the Pediatric Quality of Life Inventory 4.0 (PedsQL) and an outcomes questionnaire for parents.[10] Hearing loss, was associated with increased parent-reported academic problems (reading skills, math skills, poor attention, general learning disability, and/or special education needs); a 10-point lower mean score in the PedsQL school-functioning scale; lower summary scores for psychosocial functioning (76.4 vs 82.8, respectively; *P*=0.03); and total quality of life (79.5 vs 84.6, respectively; *P*=0.05).[10] Another study of health-related quality of life among long-term survivors of either childhood neuroblastoma or

Wilms tumour, as measured by the 36-item Short Form Health Survey (SF-36) found that adult survivors of neuroblastoma scored significantly below the population mean score on the Mental Component Summary scale, indicating decreased emotional health.[12] An epidemiologic survey, the Childhood Cancer Survivor Study, evaluated long-term survivors, defined as those surviving at least 5 years after initial diagnosis of childhood cancer (N=11,481), including neuroblastoma, across 26 institutions in the US [9]. Compared with siblings with no cancer, neuroblastoma survivors were at increased risk for functional limitations in physical performance and activities of daily living.[9]

Table 4. Performance limitations and participation restrictions among siblings and survivors of neuroblastoma

	Control (siblings with no cancer) (N=3,839)		Neuroblastoma survivors (N=802)	
Limitation	**Participants, n (%)**	**RR[a] (95% CI)**	**Participants, n (%)**	**RR[a] (95% CI)**
Performance limitation	455 (11.8)	Reference	136 (16.9)	1.7 (1.4, 2.1)
Restricted personal care skills	21 (0.5)	Reference	25 (3.1)	3.8 (2.2, 6.8)
Restricted routine activities	53 (1.4)	Reference	45 (5.6)	3.6 (2.5, 5.4)
Health prevents school or work attendance	57 (1.5)	Reference	42 (5.2)	5.1 (3.4, 7.6)

[a] RRs were standardized for age, sex, and intrafamily correlation and refer to the RR performance limitations in cancer survivors relative to the risk in the sibling group.

Key: CI – confidence interval; RR – risk ratio.

Finally, compared to parents of controls, parents of neuroblastoma survivors were more likely to report that their child had no close friends (adjusted odds ratio [OR]: 4.1; 99% CI: 1.2, 13.8; $P<0.01$) and had academic or other school problems (adjusted OR: 2.5; 99% CI: 1.3, 4.8; $P<0.001$).[11]

The Clinical advisors to the ERG have commented that this is a fair summary and reflection of the long-term impact of neuroblastoma and its treatments. The CS does not provide equivalent information specifically for high-risk patients. As the studies summarised include (are probably dominated by) low-risk patients the ERG would suggest that survivors of high-risk neuroblastoma, whose therapy on average will have been more intensive will be at higher than average risk of these adverse long-term consequences.

Late Mortality in cancer survivors

The ERG identified some additional relevant publications relevant to the long-term outcomes of neuroblastoma survivors. The Childhood Cancer Survivor study, is a US based study of 20304 5 year Cancer survivors and approximately 4000 non-cancer siblings.[13] Using 20.227 5-year survivors, 2030 deaths had been recorded representing a 10.8-fold excess mortality (SMR 10.8 (96% CI 0.3-11.3)).[13]

A separate analysis of only neuroblastoma survivors included all neuroblastoma patients in the cohort, excluding only those whose death was not recorded in data from US national death Index (NDI)[1]. . Out of the 1358 neuroblastoma survivors there were 84 deaths giving a 25-year cumulative mortality of 6%. The SMR for all cause death was 5.6 (95% CI 4.4 to 6.9). Cumulative mortality was associated with higher age at diagnosis. Figures are not given in the publication but it is clear that SMR for high-risk neuroblastoma survivors (diagnosed over age 1) would be higher.

The study also investigated the age adjusted rate ratios for some chronic health conditions and found the cumulative 20 year incidence was 41.1%, with a relative risk compared to siblings cohort of 8.3 (9%% CI 7.1-9.7). These data would suggest that it is unlikely that on average, survivors of neuroblastoma will have the same HrQoL as the general population.

Another study of cancer survivors (not specifically neuroblastoma) based on the British Childhood Cancer Survivor Study found that consumption of healthcare resource (particularly hospital resource) was increased in survivors of neuroblastoma.[14]

Studies have been made of the risk of secondary malignancies in neuroblastoma survivors (SMN). One study used data sourced the SEER cancer database (US).[7] The investigators identified all individuals with non-CNS neuroblastoma or ganglioneuroblastoma diagnosed between 1973 and 2006. To account for changes in therapy over this very long period the data analysed by era (date of diagnosis): 1973-1989; 1990-1996; and 1997-2006. Median follow-up of whole sample was 74 months. For era 3 (most relevant to current practice) it was 67 months (maximum 155 months) (7560 patient years).

Overall there were 34 SMNs recorded (1.2%). Of high risk patients (defined as aged >1 at diagnosis) alive at 5 years post-diagnosis (n=1848) the cumulative incidence of SMN at 30 years was 10.44% (95% CI 3.98%-20.52%). Most of the data in this analysis are from Era 1 patients.

Standardised incidence ratios (SIR) were calculated as a measure of the incidence of SMN in these patients relative to the general US population using age and sex matched comparison rates from the SEER database. The SIR for all SMN was 5.6 (95% CI 3.9-7.9) and for Era 3 patients only it was 7.6 (95% CI 3.6-13.9), indicating that the increased risk of SMN was not lower with more modern therapy. The data presented also indicate that the risk for SMN does not plateau.

A second study of SMN analysed data from patients with high-risk neuroblastoma only.[15] This paper presents a retrospective review of 87 patients with high-risk neuroblastoma (US) treated 1992-2009. The study investigated OS and SMN: 15 year OS was 34.3% (95% CI 23.4-45.5%); and 15 year SMN was 34.2% (95% CI 18.6-63.1%), with no evidence of plateauing at 15 years. Although after 5 years

of follow-up patients were transferred to the survivors clinics, results for survivors only were not presented.

2.3 Critique of company's overview of current service provision

The CS description of current service provision (clinical pathway of care) appropriately focuses specifically on the treatment of patients with high-risk neuroblastoma in line with the proposed use of dinutuximab. The CS states that patients with high-risk neuroblastoma are typically treated with a multimodal therapeutic approach, including intensive induction chemotherapy, autologous stem cell harvesting to enable bone marrow rescue following myeloablative consolidation chemotherapy, and subsequent surgical resection and radiation at the primary site to optimize local control.[16] Additionally, maintenance therapy intended to eliminate minimal residual disease and prevent relapse is provided using retinoids and immunotherapy.[16] The source cited is a non-systematic commissioned review, but the clinical advisor to the ERG confirms that the treatment described reflects UK clinical practice. Further details are provided in the CS (Section 3.1.3).

The use of isotretinoin as maintenance therapy to target MRD and prevent relapse following SCT was established following a demonstration of efficacy in a RCT.[17] Following recovery from high-dose chemotherapy, radiotherapy, and stem cell transplantation, three-year mean EFS was significantly better for those who received subsequent therapy with 13-cis-retinoic acid vs those assigned no further therapy (46% vs 29% , respectively; P=0.027).[17]

The addition of targeted immunotherapy in the setting of minimal residual disease can theoretically further improve outcomes. This approach involves programming immune cells to act against cancer cells by labelling antigens on cancer cells with monoclonal antibodies.[16] The ganglioside GD2 (a glycolipid found on outer cell membranes) is both ubiquitous and abundant on neuroblastoma cells, which makes it an ideal target for immunotherapy. Dinutuximab is an anti-GD2 antibody.

3 Critique of company's definition of decision problem

The decision problem issued by NICE and that addressed in the CS are detailed in Table 5 below.

Table 5. The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with high-risk neuroblastoma who have received myeloablative therapy and autologous stem cell transplant	As defined	N/A
Intervention	Dinutuximab in combination with sargramostim, aldesleukin, and isotretinoin	As defined	N/A
Comparator(s)	Isotretinoin	As defined	N/A
Outcomes	• Overall survival • Progression-free survival • Adverse effects of treatment • Health-related quality of life	• Overall survival • Event-free survival • Adverse effects of treatment • Health-related quality of life* *Health-related quality of life was not assessed in the pivotal trials, as the majority of the children treated were too young for an appropriate quality of life metric	Outcomes were as defined in the scope with the exception of event-free survival. Event-free survival was defined as the time to an event from study enrollment until the first occurrence of: • Relapse • Progressive disease • Secondary cancer • Death • Or, if none of these events occurred, until the last contact with the patient In the phase 3 trial, all patients experienced progressive disease, relapse, or death. As a result, the event-free survival outcome is similar to the progression-free survival outcome
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. Consideration should be given to alternative standardised and validated preference-based measures of health-related quality of life that have been designed specifically for use in children. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social	As defined	N/A

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	Services perspective.		
Subgroups to be considered	If the evidence allows, the following subgroups will be considered. These include: • People with relapsed disease • People with refractory disease If no evidence is available for these subgroups, this should be stated, and the Appraisal Committee would then decide if the available evidence could be extrapolated to people with relapsed or refractory disease.	As defined	N/A
Special considerations including issues related to equity or equality	No comment	As defined	N/A

3.1 Population

The CS statement of the decision problems claims to adhere to the population specified in the NICE scope. However, the anticipated marketing authorisation dictates a more restricted population than that in the NICE scope,

"patients aged 12 months to 17 years who have previously received induction chemotherapy and achieved at least a partial response, followed by myeloablative therapy and ASCT."

The main RCT providing the evidence for the efficacy of dinutuximab included patients mean age at diagnosis of 3.5 years (range 0.2 to 14.5 years); the vast majority of patients recruited (around 78%) were aged 1 to 5 years.

Furthermore, in this main RCT, only those patients without MRD following ASCT were randomised. Hence the population supported by the CS is only a sub-set of the licenced population.

3.2 Intervention

The CS statement of the decision problems claims to adhere to the population specified in the NICE scope: dinutuximab in combination with sargramostim, aldesleukin, and isotretinoin. No dose was specified in the NICE scope. The licenced use of dinutuximab (as specified in the SmPC (see Appendix of CS)) is as part of a specified combination therapy including isotretin and inter-leukin-2 (IL-2) and GM-CSF. Aldesleukin is another name for IL-2. Sargramostim (Leukine) is a GM-CSF marketed by Genzyme. It is not clear to the ERG whether the marketing authorisation for dinutuximab

requires specifically sargramostim or whether other GM-CSF products (such as Morgramostim (Leukomax)) can be used. To our knowledge, no forms of GM-CSF are currently in regular use in the UK. Within its licenced indication dinutuximab is restricted to hospital-use only and must be administered under the supervision of a physician experienced in the use of oncological therapies. It must be administered by a healthcare professional prepared to manage severe allergic reactions including anaphylaxis in an environment where full resuscitation services are immediately available. This environment for its administration is reflected in the main clinical trial.

The authorised posology for dinutuximab is for it to be administered by intravenous infusion over five courses at a daily dose of 17.5 mg/m2. It is administered on Days 4–7 during Courses 1, 3, and 5 (each course lasting approximately 24 days) and on Days 8–11 during Courses 2 and 4 (each course lasting approximately 28 days). The treatment regimen consists of dinutuximab, GM-CSF, IL-2, and isotretinoin, administered over six consecutive courses. The complete dosing regimen is outlined in Table 6 (SPC Table 1 and Table 2)

Table 6: Complete dosing regimen for dinutuximab-based immunotherapy in marketing authorisation

Dosing schedule with GM-CSF (Courses 1, 3,5)															
Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15-24
GM-CSF[1]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Dinutuximab[2]				X	X	X	X								
Isotrentinoin[3]											X	X	X	X	X
Dosing schedule with IL-2 (Courses 2 and 4) and Isotretinoin (Course 6)															
Day	1	2	3	4	5	6	7	8	9	10	11		12-14		15-28
IL-2[1]	X	X	X	X				X	X	X	X				
Dinutuximab[2]								X	X	X	X				
Isotrentinoin[3]															X

3.2.1 Immunotherapy regimen: dinutuximab, GM-CSF, IL-2, and isotretinoin

The ERG requested that the company provide evidence of the contribution of each therapeutic component (dinutuximab, IL-2, and GM-CSF) to the overall efficacy of dinutuximab in combination with IL-2 and GM-CSF. The company provided a comprehensive response in their clarification response document which is summarized here.

Clinical studies of ch14.18 alone provide equivocal evidence of any clinical activity. In particular a multivariate analysis of the results obtained from a retrospective analysis revealed no advantage in EFS or OS for subjects who were older than one year and received ch14.18 antibody therapy.[18] Given the less than optimal responses for subjects treated with ch14.18 monotherapy, investigators posited

whether the addition of GM-CSF to ch14.18 could improve outcomes in patients with high-risk neuroblastoma. The rationale for including GM-CSF is multifold: GM-CSF is known to promote antitumor immunity, stimulate inflammatory and cellular responses, and promote mediators of immune suppression. Given the antitumor nature of GM-CSF, its use has been investigated in combination with a number of other agents, e.g. rituximab, several clinical studies. GM-CSF has not been shown to induce the proliferation of neuroblastoma cells nor does it appear on its own to kill neuroblastoma cells.

Clinical responses observed in high-risk neuroblastoma following ch14.18 plus GM-CSF remained suboptimal, so investigators decided to include IL-2 in the combination. The reason for including IL-2 is again multifold: IL-2 causes activation of natural killer (NK) cells, generation of lymphokine-activated killer (LAK) cells, and augments ADCC, a mechanism of action for ch14.18. Based on the results of early in vitro and early clinical data with anti-GD2 antibodies and IL-2, IL-2 was added to the ch14.18 regimen included in the CCG-0935A study (see section 4.2.2.3).

In brief Il-2 and GM-CSF contribute to the efficacy of dinutuximab based immunotherapy.

3.3 Comparators

The comparators described in the CS match the comparators described in the final NICE scope: isotretinoin. No dose was specified in the NICE scope. The dosing used in the main clinical trial reflects that currently used in UK clinical practice. The ERG considers this comparator the appropriate standard of care for maintenance therapy of high-risk neuroblastoma.[17]

3.4 Outcomes

The outcomes described in the final NICE scope were: overall survival; progression-free survival; adverse effects of treatment; and health-related quality of life. In the CS the outcomes addressed in the decision problem were similar. Overall survival, adverse effects of treatment and health-related quality of life were addressed but progression-free survival was replaced with event-free-survival. Event-free survival was defined as the time to an event from study enrolment until the first occurrence of: relapse; progressive disease; secondary cancer; death; or, if none of these events occurred, until the last contact with the patient. The CS states that in the phase 3 trial, all patients experienced progressive disease, relapse, or death, and consequently, the event-free survival outcome is similar to the progression-free survival outcome.

3.5 Sub-groups

The NICE final scope specified two subgroups should evidence allow: people with relapsed disease; and people with refractory disease. The CS decision problem statement claims to include these

subgroups. However, whilst some clinical evidence is provided for a refractory subgroup (patients with persistent disease (MRD- positive) after autologous-SCT) this subgroup is not analysed in the economic model. No consideration is given to the treatment of relapsed patients in the submission. Other sub-groups are considered (see Sections 4.2.1.3).

3.6 Other relevant factors

GM-CSF

In the company submission (page 110 footnote) it states that GM-CSF does not have a marketing authorisation in England for any indication. The ERG asked the Company to clarify whether GM-CSF is commercially available in England and current procurement arrangements. The Company's response stated,

"Dinutuximab is intended to be administered as indicated according to the marketing authorisation, in combination with GM-CSF, IL-2, and isotretinoin. Currently, GM-CSF is not approved for marketing authorization by the EMA for any indication, and therefore is not commercially available in England. UTC does not manufacture this molecule and has no relationship with the manufacturer. However, UTC has arranged for access to GM-CSF through a third party distributor, available through a bona fide request from the treating physician independent of UTC. Additionally, the treating physician would also be able to procure the GM-CSF through their institution's standard operating procedures from a different distributor, if the distributor can provide access to GM-CSF in England."

The Company's response also stated,

"Although GM-CSF is not routinely used in English clinical practice, the dinutuximab SmPC provides sufficient instructions on using the product in immunotherapy. Additional information regarding GM-CSF can be found in the GM-CSF (Leukine®) Prescribing Information."

PAS

No patient access scheme has been proposed for dinutuximab.

4 Clinical Effectiveness

This section considers the clinical evidence submitted by the company. It covers four areas: clinical efficacy of dinutuximab, safety of dinutuximab, pharmacokinetics, and trials of different forms of ch14.18 antibody. Only one trial of efficacy and four trials reporting safety and adverse events were identified, so no meta-analyses or indirect treatment comparisons were performed. Therefore, this section discusses only the results of each trial.

4.1 Critique of the methods of review(s)

4.1.1 Searches

The company performed a systematic search for trials of dinutuximab (or ch14.18 antibody) in high-risk neuroblastoma patients aged 1 to 17 years. MEDLINE, EMBASE, the Cochrane library, Conference proceedings from the Advances in Neuroblastoma Research Association Meetings (ANRA) and Clinicaltrials.gov.

Details of the searches were presented in Appendix 1.4. Search terms were limited to: "neuroblastoma", "ch14.18" and "dinutuximab". This search was not particularly sensitive, and did not include key word terms or any alternative names for ch14.18 antibodies or dinutuximab. It is therefore possible that relevant papers were not identified, particularly those relating to APN311, the other ch14.18 product, though the direct relevance of those studies is questionable and discussed in Sections 2.1 and 4.2.4.

4.1.2 Inclusion criteria

Full inclusion criteria were presented in Table 15 of the CS. Briefly; they were any study of dinutuximab in high-risk neuroblastoma patients aged 12 months to 17 years. "High-risk" was not defined in the inclusion criteria, but is presumed to be similar to that given in Table 12 of the report (and discussed in Section 2.2 above). Studies had to present data on at least one of: overall survival progression-free or event-free survival, response rate, adverse events or quality of life.

Studies not published in English were excluded, and so some relevant material may not have been included in the submission.

The key exclusion from consideration was all trials of ch14.18 antibodies derived from alternative cell lines from those of dinutuximab. The CS justified their exclusion because these alternative cell lines have different production processes and there is no evidence to suggest interchangeability. Whilst the ERG accepts that trials of alternative products are not of direct relevance to the appraisal of dinutuximab, it considered that information on these alternative products could be supportive and therefore, the ERG requested that evidence be provided to support the assertion of no

interchangeability, and that a summary of any trials of other cell lines be provided. These are discussed in Section 4.2.4.

Apart from this key exclusion, the ERG considers that the inclusion criteria were reasonable.

4.1.3 Critique of data extraction

The CS did not discuss any data extraction plan, so it was not clear whether all relevant data was extracted from trial reports.

For the efficacy trial baseline demographic data were extracted, as were data on overall and event-free survival (as Kaplan-Meier curves, survival probabilities and hazard ratios). For safety trials numbers of various types of adverse events were reported. Numbers of adverse events in each treatment course were reported, where available.

The ERG notes that, while a data extraction plan should have been provided, the data reported is appropriate and matches the scope.

4.1.4 Quality assessment

The CS presented a quality assessment of the single efficacy trial (ANBL0032) based on the Cochrane risk-of-bias approach, with assessments of: randomisation, allocation concealment, blinding, drop-out rates and selective reporting.

This assessment concluded that the trial was suitably randomised, and that groups were similar in terms of baseline characteristics. There was no evidence of selective reporting biases and an ITT analysis was used. Although reasons for drop-out differed between arms, drop-out rates were similar in the two arms, suggesting that bias due to differential drop-out was unlikely.

The nature of the intervention meant that the trial was not blinded. The CS noted that this could lead to potential bias, including: reporting bias due to differing interpretations of outcomes in the two arms; bias due to early withdrawal before events occurred, with early withdrawal being more common in the immunotherapy arm; and bias due to differing frequency of evaluation in the two arms. The ERG is of the opinion that bias due to early withdrawal is of some concern, but the other biases are likely to be minimal.

Overall, the ERG agrees with the quality assessment presented in the CS for the ANBL0032 trial, and concludes that this trial is likely to be at moderate risk of bias as a consequence of the lack of blinding.

The CS also presented a Cochrane risk-of-bias assessment for the three included safety trials. However, all three trials were single-arm unblinded safety trials, so the ERG considers that a bias assessment designed for randomised trials was not appropriate. Instead the fact that these are uncontrolled, unblinded trials, with the consequent risk of bias and misinterpretation due to awareness of the treatment received and lack of a comparator group should be borne in mind when interpreting results from these trials. The CS noted that one trial (ANBL0931) may not have reported all outcomes measured, and so be at risk of reporting bias, but the CS did not expand further on this point.

4.1.5 Evidence synthesis

Only one trial examining the efficacy of dinutuximab was identified, so no synthesis or meta-analysis was possible for efficacy.

Only four trials with evidence of the safety of dinutuximab were identified. Results of each trial were presented separately and no meta-analysis was attempted. As three of these trials were single-arm trials with no comparator, and because results were presented differently across trials, the ERG considers that no statistical synthesis of these data would have been feasible.

No indirect comparison with any other therapies for neuroblastoma was presented, apparently because there are no immediate alternatives to dinutuximab / ch14.18 therapy, other than standard therapy as used in trial ANBL0032, i.e. isotretinoin given at a dose of 160 mg per square meter of body-surface area per day, divided into two daily doses, for 14 consecutive days within each of six consecutive 28-day cycles.

4.2 Critique of trials of the technology of interest, their analysis and interpretation

Seven publications relating to five studies were identified by the search process described in Section 4.1.1. One RCT reporting the efficacy and safety of dinutuximab and three uncontrolled safety trials of dinutuximab were identified and were reported in detail in the CS.

One pharmacokinetic study comparing the NCI and UTC forms of dinutuximab (ch14.18) was identified but not reported in detail. The ERG requested further details on this study, and this is discussed in Section 4.2.3. Studies of ch14.18 antibodies considered not to be bioequivalent to dinutuximab were excluded. The ERG requested a summary of these studies, and these are discussed in Section 4.2.4.

4.2.1 Efficacy trials (ANBL0032)

The ANBL0032 trial was the only trial identified that reported on the efficacy (in terms of event-free and overall survival) of dinutuximab compared to standard therapy. One further trial (ANBL0931) also reported event-free and overall survival for dinutuximab use. These were not reported in the CS,

but some survival probability data were provided on request. The sections below discuss the ANBL0032 trial.

4.2.1.1 Trial methodology

The trial was conducted in the USA, Canada, Australia and New Zealand, so the ERG considers that recruited patients are likely to be broadly similar to the UK population. Patients had to have high-risk neuroblastoma as set out in Table 3. Any patient aged 30 or under was eligible, so some adult patients outside the NICE scope might have been included, however, on clarification, the manufacturer confirmed that no persons aged over 15 were recruited. Patients had to have completed induction therapy, autologous SCT, and radiotherapy.

Patients were randomised 1:1 to immunotherapy or standard therapy, except for patients with biopsy-proven residual disease after autologous-SCT, who all received immunotherapy and were excluded from primary analyses. Patients in the immunotherapy arm received five 28-day cycles of dinutuximab (25mg/m^2). In cycles 1, 3 and 5 they also received GM-CSF (250μg/m^2), and in cycles 2 and 4 they received IL-2 (3.0MIU/m^2 rising to 4.5MIU/m^2). Patients received isotretinoin (160mg/m^2) in all cycles and in an additional sixth cycle. Patients in the standard therapy arm received only the six cycles of isotretinoin.

Further details of the trial methodology are presented in Table 17 of the CS. The ERG notes that GM-CSF is not currently in regular use for neuroblastoma treatment in the UK, and it is unclear what additional benefit this has over and above the use of dinutuximab. In their clarification response the Company provided further details and these are summarised in Section 3.2.The trial was designed to recruit 386 patients in order to achieve 80% power to detect an event-free survival difference of 15% after three years. The ERG notes that this three-year outcome was not reported in the CS and recruitment was stopped early after 226 randomisations, so the trial was not fully powered to detect the desired treatment effect.

The trial was sequentially monitored to detect a relative risk of event-free survival at three years between arms of 1.6. It was not clear why this relative risk was chosen, nor why a three-year outcome was chosen. Clinical advice given to the ERG suggested that a five-year time horizon is more appropriate, in case dinutuximab delays rather than prevents progression. The ERG therefore considers that this choice of stopping criterion may have been inappropriate. The sequential monitoring process used appeared appropriate, including the use of a suitable Lans-DeMets alpha-spending boundary.

The CS reported that the stopping boundary was crossed after randomisation of 226 patients and 83 events (61% of the expected number), but there appears to have been some disagreement, with the Committee for Medicinal Products for Human Use (CHMP) Assessment Repoort (2014) questioning whether the stopping boundary was crossed.[19] On request for clarification, the manufacturer confirmed that the stopping boundary had not been crossed when recruitment ceased, and so the trial should have continued recruitment. This is of concern because had recruitment continued, the boundary may not have been crossed and efficacy results, particularly at or before three years, may have been different.

In any sequentially monitored trial, if the trial is stopped early because there is evidence of benefit a naïve statistical analysis is likely to overestimate the size of the beneficial effect [20]. The analyses presented in the CS did not appear to adjust for this early stopping, so the efficacy of dinutuximab, particularly at two and three years, may be overestimated.

4.2.1.2 Trial results: survival analyses

The analysis presented in the CS reported event-free and overall survival using two distinct data sets. The main analysis was based on the data available after trial recruitment was stopped (January 2009, as reported in Yu 2010)[21], for which Kaplan-Meier curves and survival estimates two years after randomisation were reported. Kaplan-Meier curves and survival estimates were also presented at four years after randomisation, based on a longer-term follow-up of the data (June 2012).

On request for clarification the manufacturer confirmed that data were available at four follow-up points as follows:

13 January 2009: Original analysis after close of randomisation performed by Yu et al.

30 June 2009: Updated confirmatory analysis by the COG. The manufacturer confirmed that, due to data entry errors, there were some differences between this and the January 2009 analysis.
30 June 2012: Follow-up analysis to consider more mature data on overall survival, performed by Yu et al.
March 2014: Further analysis requested by the EMA.

The ERG considers that the longest and most complete follow-up data (March 2014) should be the basis of analysis for this report, and so requested details of the analysis of these latest follow-up data, which were provided. Although we consider the latest follow-up data to be most relevant, for completeness, we also consider the analyses presented in the CS (January 2009 and June 2012) in this report.

Based on clinical advice, the ERG also considered it important to consider survival estimates up to five years after randomisation, as cancer recurrence most commonly occurs up to five years after treatment, and longer follow-up is needed to investigate whether dinutuximab prevents, or merely delays, recurrence. The ERG requested that survival probabilities be presented at each year for one to five years after randomisation, and also that hazard ratios comparing the dinutuximab and standard therapy arms should be provided; these were provided by the company.

Event-free survival

Figure 4 presents the Kaplan-Meier survival curves for event-free survival based on the March 2014 data (as provided on request for clarification). Immunotherapy appears to delay the onset of events. Despite the apparent difference between the two curves, this was not found to be statistically significant (p-value for log rank test: 0.153). This appears to be because immunotherapy delays rather than prevents events. In both arms around 50% of patients will eventually have an event, however nearly all events happen within two years on standard therapy, while a substantial proportion of events happen between three and seven years on immunotherapy.

Figure 4: Kaplan-Meier survival curves for event-free survival in trial ANBL0032 (March 2014 data)

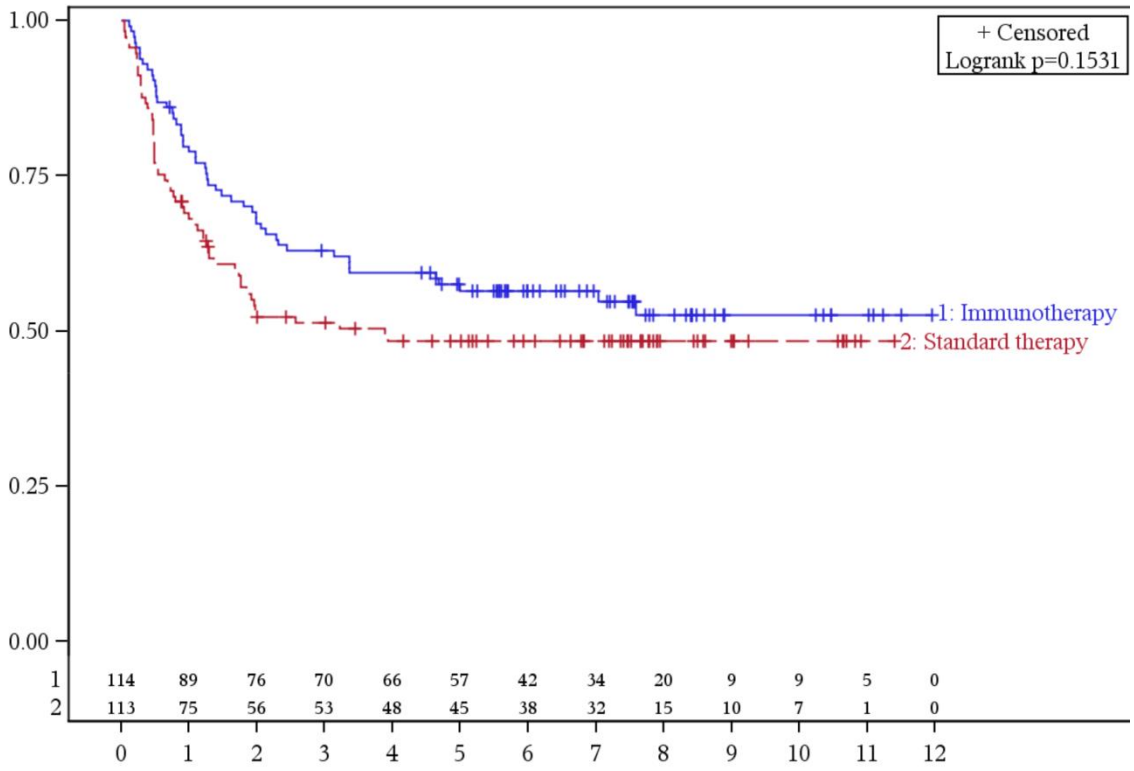


Table 7 summarises the survival probabilities in each trial arm for event-free survival, for each year from one to five, and for all three follow-up data sets under consideration. Results shown in italics are estimates based on reconstructions by the ERG of the Kaplan-Meier curves, because these data for the

2009 and 2012 data sets were not provided in the CS or in clarifications. For the March 2014 data (which were provided in full), the hazard for events is lower in the immunotherapy arm, but this results is not statistically significant (HR 0.759, 95% CI 0.53 to 1.11). This hazard ratio is closer to unity than was found in the two earlier data sets, suggesting that the two survival curves converge over longer follow-up times, as seen in Figure 4.

While the results from the 2014 and 2012 data sets are broadly consistent, the results for standard therapy in the 2009 analysis are different, with considerably poorer outcomes in this arm. Either there were some data errors in this 2009 analysis, or the initial group of recruited standard therapy arms performed particularly poorly compared with those recruited later (who had no reached two or three years of follow-up by 2009). This suggests that conclusions based on the two-year survival results from the 2009 data, which are the key results in the CS, are overestimating the benefit of immunotherapy.

Also, because the trial was stopped on the basis of the results available in 2009, it may be that the trial was stopped inappropriately, either because of incorrect analysis, or because of the chance recruitment of standard therapy patients of particularly poor prognosis. Had the trial continued to recruit results may have been different.

Overall there is no conclusive evidence that immunotherapy improves event-free survival, although it may delay onset of cancer recurrence.

Table 7: Event-free survival probabilities in ANBL0032

Data source	Treatment	Survival probability (95% confidence interval)				
		Year 1	Year 2	Year 3	Year 4	Year 5
January 2009	Immunotherapy	*81.9% **	66.3% (56.2,76.3)	*62.9%**	*60.3%**	*60.3%**
	Standard	*69.6%**	46.4% (35.8,57.1)	*46.0%**	*43.4%**	*43.4%**
	Hazard ratio	0.57 (0.37, 0.89)				
June 2012	Immunotherapy	*79.9%**	*69.7%**	62.8% (53.9,71.7)	*57.8%**	*56.2%**
	Standard	*69.0%**	*54.9%**	50.9% (41.6,60.2)	*48.7%**	*46.8%**
	Hazard ratio	0.69 (0.47,1.01)				
March 2014	Immunotherapy	79.80% (72.4,87.2)	67.40% (58.7,76.0)	62.90% (54.0,71.8)	59.30% (50.3,68.4)	56.50% (47.3,65.7)
	Standard	68.10% (59.5,76.7)	52.30% (43.0,61.6)	51.30% (42.0,60.7)	48.30% (38.9,57.7)	48.30% (38.9,57.7)
	Hazard ratio	0.759 (0.53, 1.11)				

* Numbers in italics are based on data reconstructed from supplied survival curves

Overall survival

Figure 5 presents the Kaplan-Meier survival curves for overall survival based on the March 2014 data (as provided on request for clarification). Immunotherapy appears to improve overall survival, and there was a statistically significant difference between the two arms (p-value for log rank test: 0.030). As with event-free survival the curves appear to converge at around ten years after randomisation, and long term survival is only slightly better among immunotherapy patients (approximately 59% vs 52% at ten years). The data for such long term follow-up were too sparse to determine whether this difference is meaningful. Comparing these results with those for event-free survival suggests that most long-term survival is among the approximately 50% of patients with no cancer recurrence, regardless of treatment. Most patients in whom the cancer recurs will die within ten years. The improvement in overall survival observed with immunotherapy appears to arise because it delays recurrence by five to six years (based on Figure 4) and hence delays mortality by a similar amount (Figure 5).

Figure 5 : Kaplan-Meier survival curves for overall survival in trial ANBL0032 (March 2014 data)

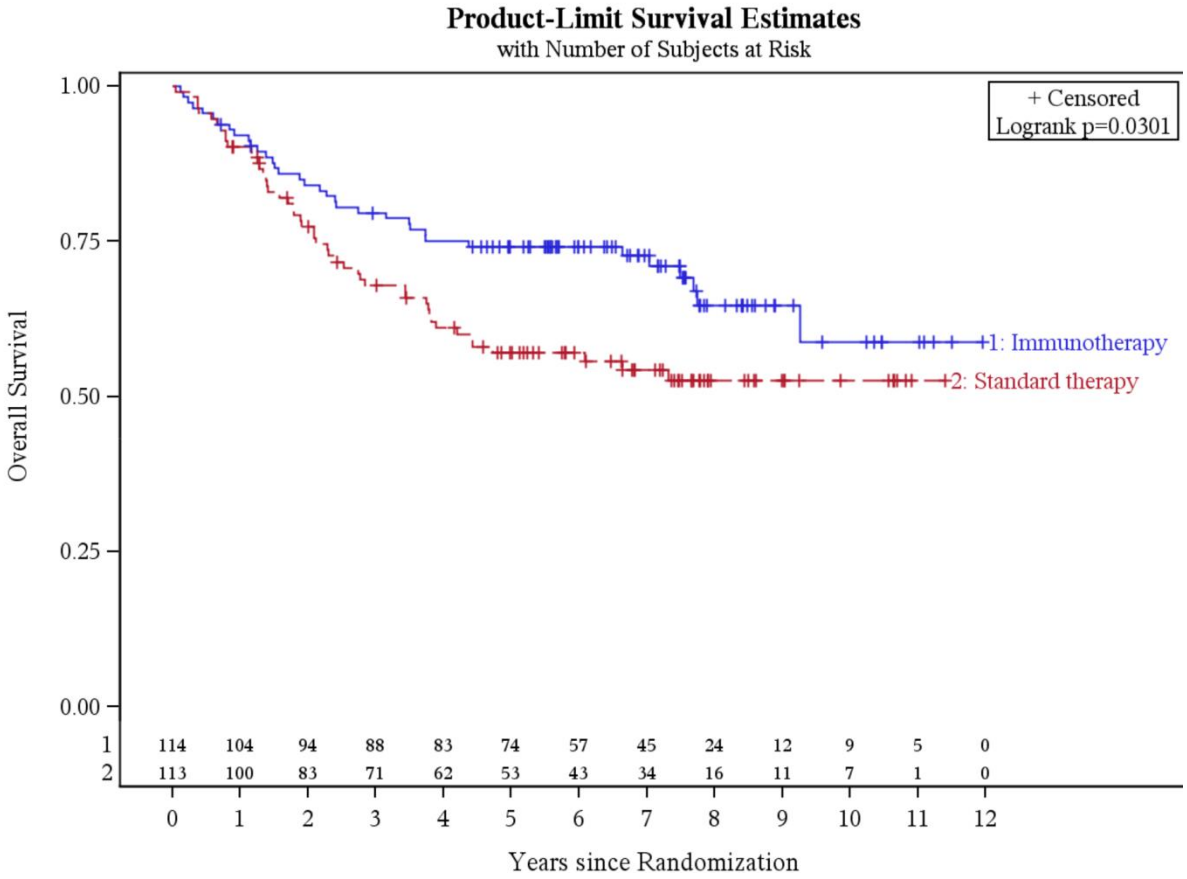


Table 8 summarises the survival probabilities in each trial arm for overall survival, for each year from one to five, and for all three follow-up data sets under consideration. Results shown in italics are estimates based on reconstructions of the Kaplan-Meier curves, because these data for the 2009 and 2012 data sets were not provided in the CS or in clarifications. The hazard for events is lower in the immunotherapy arm and is statistically significant (HR 0.621, 95% CI 0.40 to 0.96). As with event-free survival, this hazard ratio is slightly closer to unity than was found in the two earlier data sets, suggesting that there is some convergence of survival curves over longer follow-up times, as seen in Figure 5.

Survival probabilities at five years are substantially higher in the immunotherapy arm. This appears to be because immunotherapy delays mortality, so many patients on immunotherapy are still alive after five years, even though many will subsequently die. As for event-free survival, the results from the 2014 and 2012 data sets are broadly consistent, but the results for standard therapy in the 2009 analysis are different, with poorer outcomes in this arm at later times.

The results of the ANBL0032 suggest that immunotherapy has a beneficial effect on overall survival, because it delays cancer recurrence and hence subsequent mortality by several years.

Table 8: Overall survival probabilities in ANBL0032

Data source	Treatment	Survival probability (95% confidence interval)				
		Year 1	Year 2	Year 3	Year 4	Year 5
January 2009	Immunotherapy	*93.0%**	86.2% (78.8,93.6)	*79.5%**	*73.5%**	*68.9%**
	Standard	90.1%*	74.5% (65.2,83.9)	*62.8%**	*48.9%**	*48.9%**
	Hazard ratio	0.52 (0.30 , 0.92)				
June 2012	Immunotherapy	*91.8%**	*83.9%**	79.5% (72.1,87.0)	*74.3%**	*72.7%**
	Standard	*90.3%**	*76.1%**	67.3% (58.4,76.1)	*59.2%**	*54.4%**
	Hazard ratio	0.57 (0.36 , 0.89)				
March 2014	Immunotherapy	92.10% (87.1,97.0)	84.10% (77.3,90.8)	79.60% (72.1,87.0)	75.10% (67.1,83.1)	74.20% (66.1,82.3)
	Standard	90.30% (84.8,95.7)	77.40% (69.5,85.2)	67.90% (59.1,76.7)	61.00% (51.8,70.3)	57.00% (47.5,66.4)
	Hazard ratio	0.621 (0.402 , 0.959)				

4.2.1.3 Subgroup analyses

The ANBL0032 trial included 25 patients with evidence of persistent disease after autologous-SCT who were not randomised but all assigned to immunotherapy. Survival rates for these patients were poor (see CS Figure 12), with event-free survival rate at four years of 32% and an overall survival rate of 53%. This is substantially poorer than for patients without persistent disease, and also poorer than for patients on standard therapy. As no patients with persistent disease received standard therapy it is no possible to determine if immunotherapy is effective in these patients, however their poor prognosis suggests that immunotherapy cannot be recommended for these patients without further randomised evidence.

A subgroup analysis by Curie score was presented in the CS. Results were presented only for event-free survival at three years, apparently based on the 2009 data. As discussed earlier, a three year analysis using these data may not be the most appropriate analysis. The ERG requested further subgroup analyses by Curie score, but these were not available. The results are summarised in Table 9. Treatment efficacy was substantially poorer in both arms in patients with a Curie score above zero, although numbers of patients in that group were few. There was no statistically significant evidence of

any difference in event-free survival rates between arms in patients with non-zero Cure score, and survival probabilities were poorer in the immunotherapy arm. This suggests that immunotherapy cannot be recommended in patients with a Curie score above zero.

Table 9: Three year event-free survival probabilities by Curie score

	Curie score = 0 (167 patients)	Curie score > 0 (30 patients)
Immunotherapy	70.5% ± 5.0%	26.7% ± 11.4%
Standard therapy	47.5% ± 5.6%	40.0% ±12.5%
P-value	0.02	0.93

On request, the manufacturer's also presented results of further subgroup analyses of the ANBL0032 trial: age, INSS stage, MYCN amplification, DNA ploidy pre-autologous-SCT response, histology, and stem cell type. These are presented here in Figure 6 for event-free survival and in Figure 7 for overall survival. These analyses are based on the June 2009 data, which, as observed in Table 7 and Table 8, appears to produce hazard ratios that are too favourable to immunotherapy. Numbers in most subgroups are small, leading to wide confidence intervals, so drawing any firm conclusions is not possible.

There are a few small groups where immunotherapy appears particularly effective: the very young (under 18 months), those with favourable histology, and those with INSS stage below 4. Numbers in all these groups are too small to reach any firm conclusions. Conversely there appear to be some subgroups where immunotherapy is no more effective than standard therapy: patients who are MYCN amplified or whose amplification is unknown, patients with unknown histology, and patients with purged stem cell type. Confidence intervals are too wide to determine if these apparent differences between subgroups are genuine.

Figure 6: Forest Plot of 2-Year EFS Results by Prognostic Factors (June 2009 data)

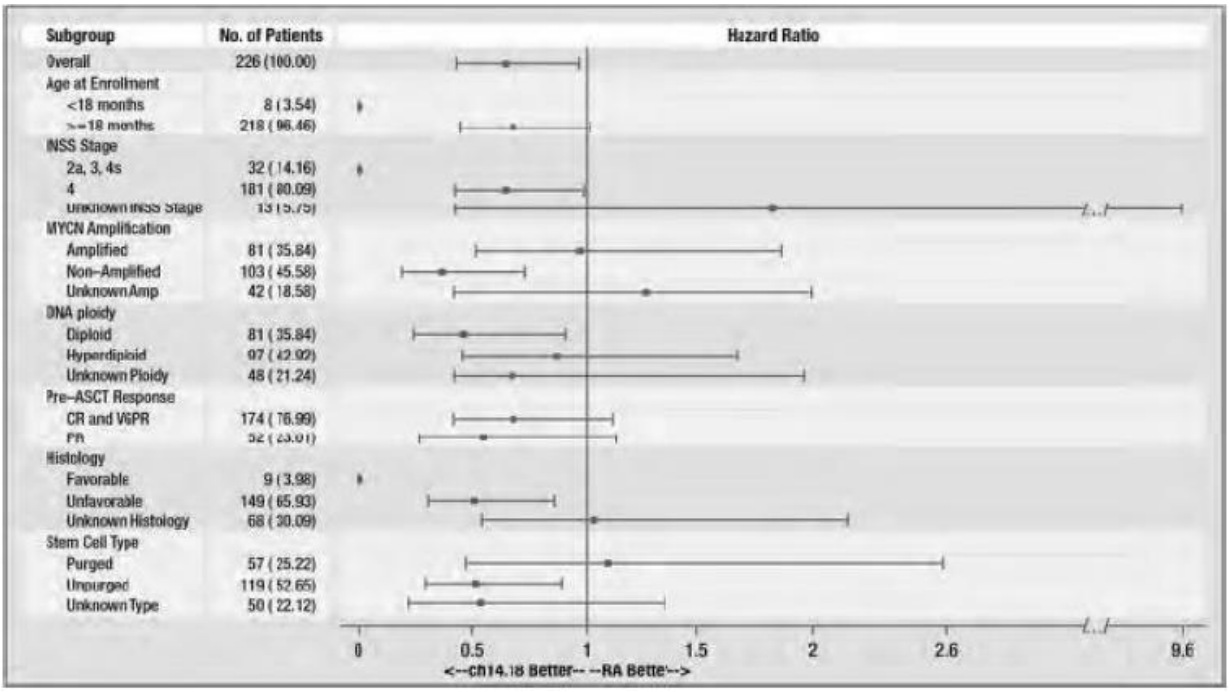
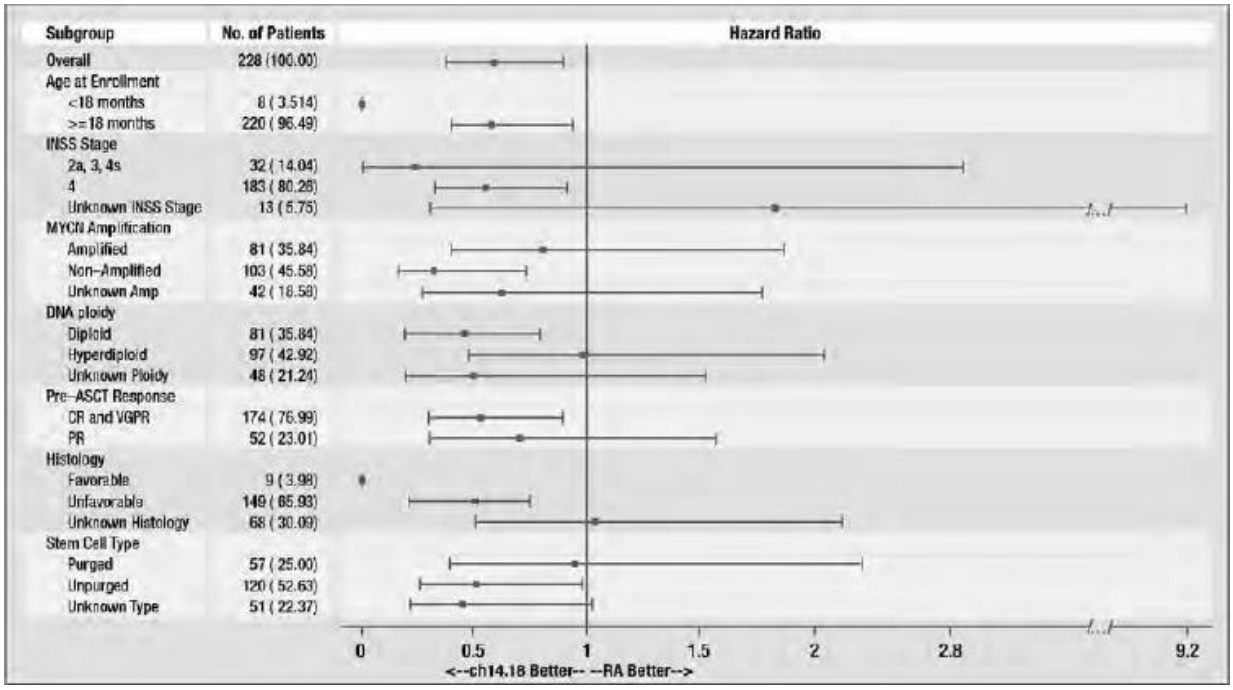


Figure 7: Forest Plot of 2-Year OS Results by Prognostic Factors (June 2009 data)



4.2.1.4 The ANBL0931 trial

The CS reported this trial as a single-arm trial of immunotherapy designed as a safety trial[22]. This was confirmed by the ERG against the record on the ClinicalTrials.gov website. The treatment received was similar to the immunotherapy arm of the ANBL0032 trial. This trial recorded event-free and overall survival, but these were not reported in the CS. The ERG requested relevant survival data for this trial. The manufacturers reported that a full analysis his yet to be performed, but provided some preliminary results. Results were presented both for immunotherapy and isotretinoin arms, suggesting that this trial was comparative and possibly randomised, which is inconsistent with the reporting in the CS and the ClinicalTrials.gov website. It is unclear to the ERG what the isotretinoin arm for which results are presented comprises.

The preliminary survival data for this trial is summarised in Table 10. These results are almost identical to those of the ANBL0032 trial. There was a statistically significant difference in overall survival between arms, but not for event-free survival, and the results appear consistent with immunotherapy delaying, rather than preventing, cancer recurrence and mortality.

Table 10: Preliminary results from the ANBL0931 trial

Outcome	Arm	Two-year survival	Four-year survival	p-value
EFS	Immunotherapy	67% ± 4%	59% ± 5%	0.11
	Isotretinoin	51% ± 5%	48% ± 5%	
OS	Immunotherapy	83% ± 4%	74% ± 4%	0.02
	Isotretinoin	76% ± 4%	59% ± 5%	

4.2.2 Safety trials

The CS identified four clinical studies which reported the rate of adverse reactions among high-risk neuroblastoma patients treated with dinutuximab. These were: the randomised trial of efficacy ANBL0032 discussed in Section 4.2.1; the ANBL0931 trial discussed in Section 4.2.1.4above,and two single-arm non-randomised studies CCG-0935[23] and CCG-0935A[24].

4.2.2.1 The ANBL0032 trial

Only the ANBL0032 trial compared adverse events when using immunotherapy (dose of dinutuximab 25 mg/m^2, which is equivalent to the licensed dose) with those using isotretinoin alone. The CS presented the observed rate of grade 3 and 4 adverse reaction events by treatment group for the ANBL0032 study, reproduced in simplified form here as Table 11, with adverse events occurring in fewer than 10 patients removed. Immunotherapy was associated with a statistically significant increased risk of adverse reactions compared to standard therapy across a range of adverse reactions.

Only 6% of immunotherapy patients had no adverse events, compared to 37% of standard therapy patients. The most common adverse events (at least 25% of immunotherapy patients) with higher incidence in the immunotherapy arm were: neuropathic pain (RR 9.3), infection (RR 1.8), fever without neutropenia (RR 7.0), hypokalaemia (RR 18.9), and hypersensitivity reaction (RR 26.8). There were a number of adverse reactions that were common with immunotherapy but almost absent from standard therapy patients, most notably: acute capillary leak syndrome (RR 49.7), hyponatremia (RR6.1), abnormal ALT (RR 8.1) and aspartate aminotransferase (RR 22.9), and urticaria (RR 29.2).

The CS stated that most adverse reactions were self-limited and resolved after the cessation of each course of treatment and well before the initiation of the next course. The ERG points out that these are potentially dangerous and serious adverse events, but generally acute and quickly resolved unless fatal.

Table 11: Grade 3 and 4 adverse events by treatment group in study ANBL0032

Adverse Event	Immunotherapy (N=137) %	Standard therapy (N=108) %	Absolute Risk Difference	Relative Risk	95% Confidence Interval	
					Low	High
Neuropathic pain	52	6	46.3%	9.3	4.2	20.6
Hypotension	18	0	17.5%	38.6	2.4	628.0
Hypoxia	13	2	11.3%	7.1	1.7	29.9
Fever without neutropenia	39	6	33.1%	7.0	3.1	15.6
Acute capillary leak syndrome	23	0	22.6%	49.7	3.1	802.4
Hypersensitivity reaction	25	1	23.9%	26.8	3.7	192.7
Urticaria	13	0	13.1%	29.2	1.8	478.6
Infection, any	39	22	17.2%	1.8	1.2	2.7
Infection, catheter-related	18	7	6.7%	2.0	0.9	4.7
Diarrhea	13	1	12.2%	14.2	1.9	104.6
Hyponatremia	23	4	18.9%	6.1	2.2	16.8
Hypokalaemia	35	2	33.2%	18.9	4.7	76.1
Abnormal ALT	23	3	19.8%	8.1	2.6	25.9
Abnormal AST	10	0	10.2%	22.9	1.4	378.9
None	6	37	-31.2%	0.2	0.1	0.3

ALT – alanine aminotransferase; AST – aspartate aminotransferase.

The CS reported that the incidence of key adverse events declined over successive treatment courses. This could suggest improved tolerability and/or pain management over the time. Adverse event rates by treatment course among immunotherapy patients are summarised in Table 12. Further logistic regression analysis of pain incidence against treatment course and therapy received in each course by the ERG suggests that there is statistically significant evidence that incidence of pain declines over the treatment courses ($p = 0.001$), and also that pain is less common in course 6 (where neither GM-CSF nor IL-2 were used; $p = 0.023$). This observed decline could be a genuine decline in adverse pain over time, or because patients particularly susceptible to pain have already withdrawn from treatment.

Capillary leak syndrome appeared to be more common during courses 2 and 4 (corresponding to those involving IL-2) compared to courses 1, 3, and 5 (corresponding to those involving GM-CSF). Further regression analysis by the ERG confirmed that this adverse event was significantly more common in courses using IL-2 ($p = 0.004$), and did not otherwise decline over time. One treatment-related death was reported due to capillary leak syndrome as a result of an IL-2 overdose.

Hypersensitivity also appeared to be more frequent in courses involving IL-2 compared to courses involving GM-CSF. Further regression analysis by the ERG confirmed that this adverse event was significantly more common in courses using IL-2 ($p < 0.001$), and did not otherwise decline over time. No other adverse events were presented over the course of treatment from study ANBL0032 in this submission.

Table 12: Grade 3 and 4 adverse events in the immunotherapy arm by treatment course in trial ANBL0032

	Course					
Adverse Event	**1 (n=137)**	**2 (n=127)**	**3 (n=121)**	**4 (n=114)**	**5 (n=107)**	**6 (n=104)**
Pain, n (%)	50 (37)	30 (24)	23 (19)	33 (29)	15 (14)	4 (4)
Hypersensitivity reaction, n (%)	14 (10)	33 (26)	6 (5)	29 (25)	13 (12)	3 (3)
Capillary leak syndrome, n (%)	9 (7)	14 (11)	8 (7)	15 (13)	3 (3)	0

4.2.2.2 The ANBL0931 trial

A total of 105 patients were recruited in the immunotherapy group which was a combination of dinutuximab (25 mg/m^2), isotretinoin, GM-CSF and IL-2. Among the 105 participants, 78 completed the study. Reasons for attrition were toxicity (four patients), death (one patient), lack of efficacy (seven patients), physician decision (four patients), and withdrawal (11 patients). A total of 104 participants were analysed for the primary analysis of Grade 3 to 5 non-haematological toxicities of interest (pain, hypotension, allergic reactions, capillary leak syndrome, or fever). Table 13 shows the proportion of participants experiencing each adverse event by treatment course. The results show

similar pattern with the ANBL0032 study in terms of the pain which declines over the treatment courses, and also that pain is less common in course 6 (where neither GM-CSF nor IL-2 were used).

Table 13: Non-haematological Grade 3 to 5 adverse events by treatment course in the ANBL0931 trial (adapted from CS Table 29)

	Course					
Type of Grade 3–5 Adverse Event	**1**	**2**	**3**	**4**	**5**	**6**
All pain	54%	34%	27%	34%	26%	2%
Allergic reaction	2%	5%	3%	2%	1%	0%
Anaphylaxis	1%	4%	1%	3%	1%	0%
Capillary leak syndrome	1%	4%	0%	2%	0%	0%
Fever	21%	58%	6%	31%	5%	1%
Hypotension	10%	17%	4%	14%	8%	0%

4.2.2.3 The CCG-035A trial

The CCG-035A trial was designed to determine the maximum tolerated dose and toxicity of dinutuximab given in combination with IL-2 and GM-CSF. A total of 25 neuroblastoma patients were assessed for a total of 23 courses of dinutuximab at a dose of 20 mg/m^2 and 60 courses of dinutuximab at a dose of 25 mg/m^2, both dosages in combination with IL-2 and GM-CSF. The most common non-haematological adverse events were neuropathic pain, fever, hypotension, peripheral capillary leak, infection and nausea. Neuropathic pain and peripheral capillary leak were reported more with the higher dose of therapy. The number of courses in which a Grade 3 or 4 adverse events was reported. The ERG has recalculated the percentages of patients with adverse events and these are presented in Table 14.

Table 14: Proportion of courses with Grade 3 or 4 adverse events in the CCG-035A trial

Adverse events	**Dinutuximab 20 mg/m^2, N=23 Courses**	**Dinutuximab 25 mg/m^2, N=60 Courses**
Neuropathic pain	30%	92%
Fever without infection	17%	13%
Renal		
Low systolic blood pressure	4%	17%
Low diastolic blood pressure	13%	23%
Cardiac		
Hypotension	13%	3%
Peripheral capillary leak	4%	10%
Infection	17%	3%
Nausea	13%	22%
Leukopenia	22%	2%
Neutropenia	26%	15%
Thrombocytopenia	30%	20%
Anaemia	22%	13%
Lymphopenia	4%	27%
Elevated		
AST	9%	2%
ALT	13%	2%

Key: ALT – alanine aminotransferase; AST – aspartate aminotransferase.

4.2.2.4 The CCG-035 trial

The CS presented data from another phase one single-arm safety study (CCG-0935) which evaluated the maximum tolerated dose and toxicity of dinutuximab given in combination with GM-CSF (but without IL-2). In a total of 22 neuroblastoma patients were recruited in the study. Among the 22 patients, 19 patients were included in the final analysis, for a total of 79 courses of dinutuximab in combination GM-CSF. Table 15shows proportion of courses an adverse event (of any grade) was reported for the first course of therapy and in any course of therapy. The proportions were more or less similar comparing the first course of therapy with the any course of therapy.

Table 15: Proportion of courses with adverse events in the CCG-035 trial

Adverse events	First Course (N=19)	Any Course (N=79)
Neuropathic pain	68%	59%
Fever, no source of infection	37%	46%
Urticarial eruption	37%	37%
Hypotension	21%	15%
Capillary leak syndrome	11%	11%
Nausea/vomiting	32%	30%
AST/ALT elevations	11%	11%
Decline in blood counts	5%	4%
WBC	74%	56%
APC	79%	56%
Platelets (untransfused patients)	86%	85%
Haematocrit	63%	68%

ALT – alanine aminotransferase; APC – activated protein C; AST – aspartate aminotransferase; WBC – white blood cell.

4.2.2.5 Summary of evidence from safety trials

The toxicity related to immunotherapy is clearly significant and needs prophylactic medications for the management of the adverse events over the course of treatment. Pain is the adverse event most clearly associated with dinutuximab, whilst acute capillary leak syndrome may be most associated with IL-2 and hypersensitivity with GM-CSF.

4.2.3 Pharmacokinetics

The form of dinutuximab used in the trials (NCI) is not that produced by the manufacturer (UTC). The CS identified a pharmacokinetic trial comparing these two forms of dinutuximab (DIV-NB-201), but results were not presented. The ERG requested the results of this trial. The manufacturers reported that the trial has not been published, but provided a summary of the trial.

The trial recruited 28 patients randomised to UTC or NCI products: the NCI-ch14.18 was administered intravenously (IV) at a dose of 25 mg/m^2/day for 4 days in each course. The UTC-ch14.18 was administered at a dose of 17.5 mg/m^2/day for 4 consecutive days. The report of the trial stated that these doses of product are equivalent: concentrations differ as a result of the manufacturing process. Note that the licensed dose of dinutuximab is 17.5 mg/m^2/day. All patients received GM-CSF, IL-2 and isotretinoin, in a similar fashion to the ANBL0032 trial. One patient could not be analysed. Standard pharmacokinetic data were recorded, as were adverse events. The pharmacokinetic data found no statistically significant differences between the two products, and differences were within standard bioequivalence bounds (0.8 to 1.25) (see Table 16). Adverse event rates were similar between the two products (see submitted clarifications from manufacturer).

Based on this evidence it is reasonable to assume bioequivalence of the UTC and NCI products. The CS reported that the EMA Committee for Medicinal Products for Human Use (CHMP) has accepted their bioequivalence.

Table 16: Key results of DIV-NB-201 pharmacokinetic trial

PK Parameter	Geometric Mean UTC (Comparator)	Geometric Mean NCI (Reference)	Ratio	90% CI of Ratio	
				Lower	Upper
AUC_{inf} (mcg*h/mL)	431.2	413.5	1.04	0.98	1.11
C_{max} (ng/mL)	6568.2	6876.9	0.96	0.88	1.04

4.2.4 Other trials of ch14.18 antibodies

The CS reported that its search identified 29 publications relating to forms of the ch14.18 antibody that were not interchangeable with dinutuximab, and so were excluded from further consideration. The ERG is of the opinion that these trials may provide useful supporting evidence, and requested clarification on a) what evidence was available to demonstrate non-bioequivalence with dinutuximab and b) whether any evidence was available to show that non-bioequivalence might lead to different efficacy of these antibodies.

The manufacturers confirmed that it was generally accepted (for example, by the EMA CHMP) that the different cell lines used to produce the different antibodies meant that the resulting molecules may differ, that they have different glycosylation profiles, and hence are not bioequivalent. However no clinical studies have compared dinutuximab to other ch14.18 antibodies to test this. No clinical studies have compared dinutuximab to any other forms of ch14.18 to investigate efficacy, so it is unclear whether a lack of bioequivalence of necessity means a different in efficacy, although the ERG accepts that the differences could potentially affect efficacy.

The ERG considers that as all trials are of broadly the same ch14.18 antibody it is reasonable to assume a priori that they might have comparable (if not identical) efficacy, and so other trials of ch14.18 antibodies should be considered in this report as supporting evidence. The ERG therefore requested that a summary of the trials of other ch14.18 antibodies be provided.

The manufacturers provided summary details of all the 29 excluded publications, noting that most were multiple publications of the same trials. The manufacturer provided a summary table of results from those trials that reported event-free or overall survival rates. This is reproduced as Table 17 below (the study in infants aged under one year has been removed). The ERG has confirmed the accuracy of this summary table, based on published results, for all trials except Landenstein.

Table 17: Results from trials of other ch14.18 antibodies

Citation	Treatment Arm							*P*-value
	Ch14.18	**Ch14.18 + G-CSF**	**Ch14.18 + IL-2**	**Isotretinoin**	**Ch14.18 (long-term infusion) + IL-2 + Isotretinoin**	**Maintenance Chemotherapy**	**No Treatment**	
Handgretinger 1995	CR: n=2 PR: n=2 MR: n=1 SD: n=1 Progression: n=3							
Klingebiel 1998		19mo PFS: 70%±15%						
Landenstein 2014d (CR prior to immunotherapy) (Residual disease prior to immunotherapy)	1y EFS: 75% 2y EFS: 67% 3y EFS: 64% 1y EFS: 63% 2y EFS: 56% 3y EFS: 52%		1y EFS: 71% 2y EFS: 63% 3y EFS 63% 1y EFS: 72% 2y EFS: 58% 3y EFS: 48%					
Lode 2014a; Lode 2014c; Lode 2014d; Lode 2014e					1.6y EFS: 32.4% 3.1y OS: 66.8%			
Simon 2011a (ASCT subset)	5y EFS: 50.5% 5y OS: 58.3% 9y EFS: 44.5% 9y OS: 47.0%						5y EFS: 31.8% 5y OS: 45.2% 9y EFS: 38.1% 9y OS: 40.5%	*P*=0.241 *P*=0.152 *P*=0.241 *P*=0.152
Simon 2011b	5y EFS: 50.5% 5y OS: 60%			5y EFS: 37% 5y OS: 50%				*P*=0.237 *P*=0.244
Simon 2004	3y EFS: 46.5% 3y OS: 68.5%					3y EFS: 44.4% 3y OS: 56.6%	3y EFS: 37.1% 3y OS: 46.8%	*P*=0.314 *P*=0.018

Key: CR – complete response; EFS – Event-free survival; G-CSF – granulocyte-colony stimulating factor; MR – minor response; mo – month; OS – overall survival; PFS – progression-free survival; PR – partial response; SD – stable disease; y – year.

None of these trials combined ch14.18 with both GM-CSF and IL-2, and most used ch14.18 without either of the additional medications. As the company noted, this restricts comparison with the ANBL0032 trial. Absolute event rates in the Klingebiel and Landenstein trials for event-free (or progression-free) survival rates were similar to the immunotherapy arm of the ANBL0032 trial. Survival rates in the Lode and Simon trials are somewhat lower than in ANBL0032. The Landenstein trial appears to show no difference between ch14.18 alone and ch14.18 combined with IL-2.

Only the three analyses of Simon et al. compared ch14.18 to other treatment options. Although ch14.18 had higher survival rates that other treatments, in only one case was a statistically significant effect found (for ch14.18 vs no treatment for overall survival rates). In the single trial comparing ch14.18 to isotretinoin (and hence most similar to ANBL0032) found no statistically significant differences between the treatments, although survival rates were higher with ch14.18, based on 149 patients.

Consequently there is no good supporting evidence to suggest ch14.18 antibodies (and hence dinutuximab) are more effective that alterative treatment approaches. This may be because dinutuximab is genuinely more effective than other strains of ch14.18, although this cannot be assumed on the basis of results from a single trial. It may be because dinutuximab is only fully effective in combination with IL-2 and GM-CSF, which is of concern because GM-CSF is not in current use in the NHS. The possibility that ANBL0032 showed a positive result purely by chance cannot be ruled out, as if enough trials of an ineffective treatment are performed, one will eventually produce a favourable result.

4.3 Meta-analyses and indirect comparisons

As noted in Section 4.1.5, only one trial examining the efficacy of dinutuximab was identified, so no synthesis or meta-analysis was possible for efficacy. Only four trials with evidence of the safety of dinutuximab were identified; the ERG considers that no statistical synthesis of these data would have been feasible.

No indirect comparison with any other therapies for neuroblastoma was presented, apparently because there are no immediate alternatives to dinutuximab / ch14.18 therapy, other than standard therapy as used in trial ANBL0032.

4.4 Additional work on clinical effectiveness undertaken by the ERG

The ERG used the Kaplan-Meier survival curves for the 2009 data (Figures 5 and 6 of CS), the 2012 data (Figures 7 and 8), and for the 2014 data (supplied after request) to reconstruct individual participant level data for the ANBL0032 trial, for both treatment arms and for both event-free and

overall survival. This reconstruction was performed using the methods proposed by Guyot et al [25] using R code adapted from that produced by Guyot.

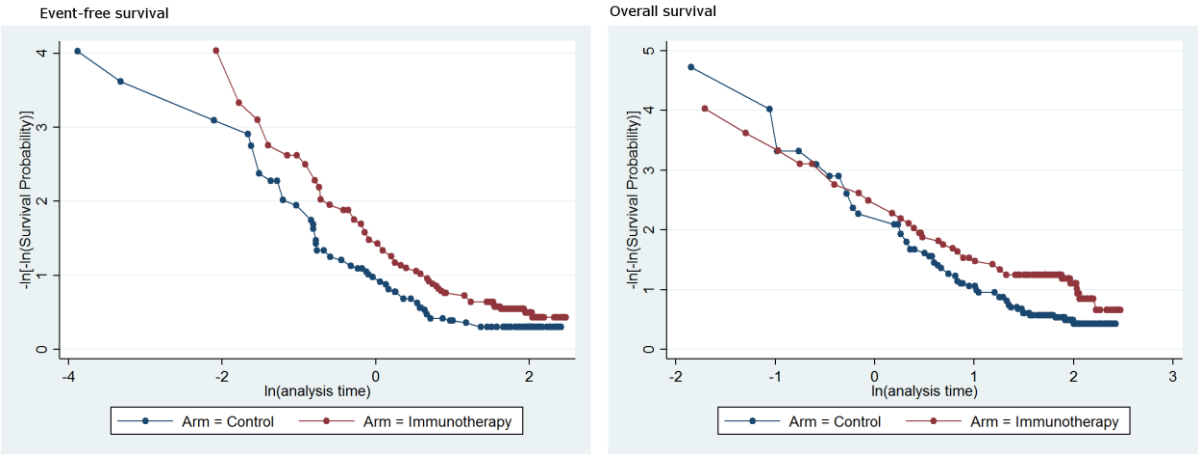
These reconstructed data were checked for robustness by comparing survival probabilities at one to five years with reported results, and by calculating hazards ratios based on a Cox proportional hazards model. Hazard ratios for the March 2014 data are summarised in Table 18. The results are very similar, although not identical, suggesting that the reconstruction process was robust. Estimated survival probabilities not reported in the CS were calculated for comparison with reported results (see Table 7 and Table 8).

Table 18: Reported and reconstructed hazard ratios for the March 2014 data of ANBL0032 trial

Hazard ratio (95% CI)	Event-free survival	Overall survival
Reported by manufacturer	0.759 (0.53, 1.11)	0.621 (0.40 , 0.96)
From reconstructed data	0.758 (0.52 , 1.10)	0.604 (0.39 , 0.94)

The reconstructed data from March 2014 was used to check the proportional hazards assumption. Log cumulative hazard for event-free survival (on left) and overall survival (on right) are shown in Figure 8. For event-free survival the curves are approximately parallel, suggest proportional hazards is a reasonable assumption. The curved lines suggest that hazard changes over time. For overall survival the lines are approximately parallel, but do cross, so proportional hazards is plausible, but less certain.

Figure 8: Log-cumulative hazard plots for trial ANBL0032



The ERG fitted a range of parametric survival models to the reconstructed March 2014 data, following the models used in the CS (see pages 93-98), namely exponential, Weibull, log-logistic, lognormal and Gompertz models.

The ERG notes that the Kaplan-Meer curves for event-free and overall survival in trial ANBL0032 (see Figure 4and Figure 5) show a levelling off in event-free survival in both arms after around eight years for event-free and after around ten years for overall survival. This suggests that a proportion (around 50% in this trial) of children are "cured" of cancer regardless of treatment received, will never experience any further events, and so will survival long-term. This is consistent with a cure model in survival analysis, so the ERG fitted a parametric Weibull cure model[26], which assumes that a proportion of children (to be estimated) are "cured" and are never at risk of events or mortality and the "uncured" fraction have a Weibull distributed survival times.

Figure 9 presents a comparison of some of the fitted parametric models with the Kaplan-Meier curve for event-free survival, and Figure 10 likewise for overall survival. For event-free the log-logistic model was a poor fit to the data, as were exponential, Weibull and lognormal models. The Gompertz model and the cure model both fit well, with the cure model fitting better for long-term survival in the standard therapy arm. For overall survival the fit for all models was more similar, although it appears that the Gompertz and cure models better represent the longer-term survival, although all models suggested there is continued mortality in both arms after 12 years.

Table 19 shows the numerical results for the Weibull cure model. For event-free survival the cured fraction is 47% in both arms, so immunotherapy does not prevent events from occurring, but the scale parameter is statistically significant, so immunotherapy reduces the hazard of events. This suggests that immunotherapy delays rather than prevents events. For overall survival, the cured fraction is 48.8% in the standard therapy arm, but is higher (around 66%) in the immunotherapy arm. The scale factor is also statistically significant. This suggests that immunotherapy delays and possibly prevents some mortality. The good fit of this cure model suggests that assuming some patients are cured regardless of therapy received is reasonable.

Figure 9: Predicted event-free survival

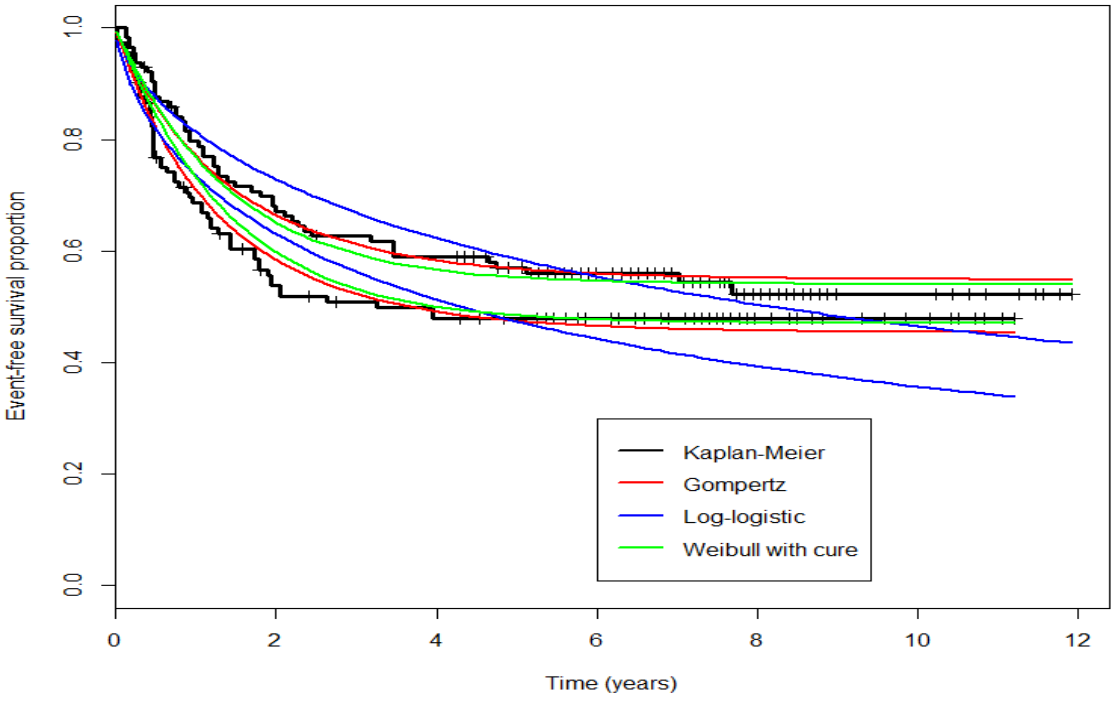


Figure 10: predicted overall survival

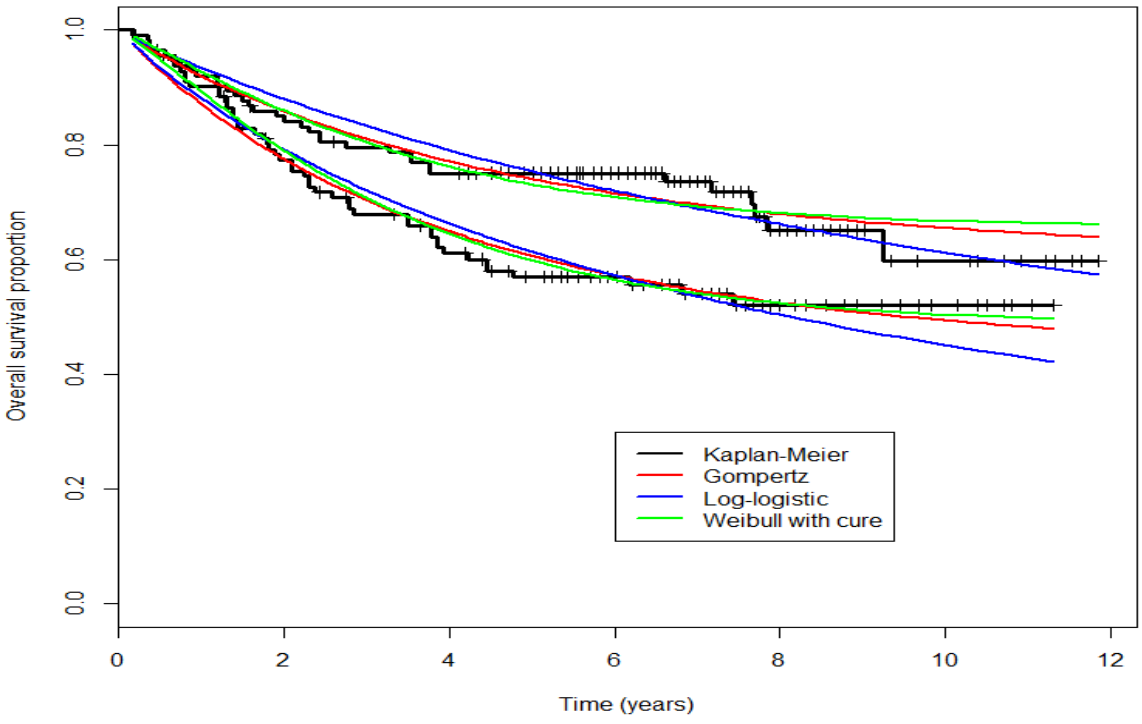


Table 19: Results of the cure model

Outcome	Cured fraction in standard therapy	Excess cured fraction on immunotherapy	Scale parameter in uncured fraction *(approx. hazard ratio)*
Event-free survival	47.0% (37.4 , 56.6)	0.7% (−6.3, 20.3)	0.701 (0.56 , 0.88)
Overall survival	48.8% (36.8 , 60.8)	16.9% (2.6 , 31.2)	0.235 (0.16 , 0.35)

4.5 Conclusions of the clinical effectiveness section

The CS submitted one trial (ANBL0032) which evaluated the clinical efficacy of dinutuximab, in combination with IL-2 and GM-CSF (the regimen and doses matching the marketing authorisation), compared to standard therapy with isotretinoin alone. This trial recruited 226 children with high risk neuroblastoma.

The trial was stopped early as evidence of superiority, based on a formal sequential monitoring process, was identified. However it appears that this sequential monitoring was not performed correctly as the monitoring boundary had not been crossed at the time the trial was stopped. This is of concern, because, had the trial continued recruitment, the observed benefit might not have persisted and, because the trial was stopped because was favourable result was achieved; any analysis of the results may overestimate the benefit of dinutuximab.

The CS based much of the clinical analysis on the data at the time the trial was stopped (2009). However, it was acknowledged that there were some errors in the data at that time, and checks by the ERG confirmed that the analysis results based on this 2009 data were inconsistent with later analyses. The ERG therefore considers the analysis based on the 2009 data to be unreliable and analyses should instead use the most up-to-date follow-up data (March 2014).

The manufacturers provided analyses of the March 2014 data on request, with analyses of both overall and event-free survival. Survival probabilities for both outcomes were higher with immunotherapy than standard therapy at all times up to five years after randomisation. Longer-term follow-up for event-free survival suggested that survival curves for both arms converged at around a 50% long-term (beyond 10 years) survival rate. This suggests that immunotherapy does not permanently prevent cancer-related events. A proportional hazards model found that, although the hazard was lower with immunotherapy, the difference was not statistically significant (HR 0.759, 95% CI 0.53 to 1.11). For overall survival the survival curves also appeared to be converging to long-term survival rates of just over 50%, although the longer survival times mean this is less certain. The hazard of mortality was

significantly lower for immunotherapy (HR 0.621, 95% CI 0.402 to 0.959), suggesting that immunotherapy can delay, and possibly prevent, premature mortality.

Subgroup analyses presented in the CS and on request for clarification suggested that survival rates with immunotherapy were poor for patients with persistent disease following autologous-SCT (refractory patients), although no such patients received standard therapy, so no comparison could be made. Immunotherapy appeared to be ineffective in patients with a Curie score above zero, and may be no better than standard therapy in some other subgroups (patients who are MYCN amplified or whose amplification is unknown, patients with unknown histology, patients with purged stem cell type), but evidence in these groups was limited.

Only one further trial (ANBL0931) collected efficacy data for dinutuximab. The final analysis of this trial has yet to be performed, but interim results, provided by the manufacturer, support the findings of the ANBL0032 trial.

As only one trial of dinutuximab was presented the ERG requested data on trial of other forms of ch14.18 antibody that had been excluded from consideration. These antibodies may not be bioequivalent to dinutuximab, and the trials did not combine ch14.18 with IL-2 or GM-CSF, so they are not directly comparable. In general, these trials found little or no evidence of any benefit of ch14.18 over other forms of treatment, and in particular, in one trial (Simon 2011), no evidence that ch14.18 was superior to isotretinoin. This raises some concerns as to whether ch14.18 is effective in general, and whether combining it with IL-2 and/or GM-CSF is necessary to produce a treatment benefit.

The ANBL0032 trial also reported the incidence of adverse events. There were a number of adverse events that were substantially more common among immunotherapy patients that patients receiving standard care, including, neuropathic pain, acute capillary leak syndrome, fever without neutropenia, hypokalaemia and hypersensitivity reaction. Only 6% of immunotherapy patients had no adverse events, compared to 37% of standard therapy patients. The incidence of pain appeared to decline over successive courses of treatment, and acute capillary leak syndrome and hypersensitivity were more common in IL-2 treatment courses than in GM-CSF courses. Three other single-arm trials which reported adverse events were described. These results generally concurred with those of the ANBL0032 trial.

In conclusion, evidence form the ANBL0032 trial suggests that around half of all patients with high-risk neuroblastoma will never have any cancer recurrence, regardless of treatment, and so will survive long-term (beyond ten years). Among those who will have a cancer recurrence, immunotherapy may

delay the event, with a consequent lengthening of life. This must be balanced against the substantial increased incidence of serious adverse events and significant toxicity with immunotherapy. These conclusions are based on a single trial, which may have had methodological errors in its analysis and conduct, and are not supported by results from other trials of albeit different ch141.18 antibodies. Ideally, further trials of dinutuximab are required to reach firm conclusions on its efficacy.

5 Cost Effectiveness

This section focuses on the economic evidence submitted by the company and the additional information provided in response to the ERG's points for clarification. The submission was subject to a critical review on the basis of the company's report and by direct examination of the electronic version of the economic model. The critical appraisal was conducted with the aid of a checklist to assess the quality of economic evaluations [27] and a narrative review to highlight key assumptions and possible limitations. Section 6 presents additional work undertaken by the ERG to further explore these uncertainties.

The company's economic submission included:

- A description of the systematic literature review conducted to identify published evidence on the cost-effectiveness of dinutaximab for the maintenance treatment of high risk neuroblastoma (CS, Section 5.1) with further details in a separate appendix (CS, Appendix 6).
- A report on the de novo economic evaluation conducted by the company. The report included a description of the patient population and the model structure (CS, Section 5.2); the clinical parameters used in the economic model (CS, Section 5.3); the measurement and valuation of health effects and quality-of-life data used in the cost-effectiveness analysis (CS, Section 5.4); the cost and healthcare resource use identification, measurement, and valuation, together with the parameters used in the model (CS, Section 5.5); a summary of the inputs and assumptions used in the model (CS, Section 5.6); and the cost-effectiveness results for the base-case (CS, Section 5.7) and sensitivity analyses (CS, Section 5.8).
- An electronic copy of the company's economic model developed in Microsoft Excel®.

In response to a number of points for clarification raised by the ERG, the company further submitted:

- A descriptive reply to the ERG's points for clarification, as well as appendices with additional data requested by the ERG.
- An updated Excel-based model, which incorporated the data and results from the updated 4-year data cut (CS, Appendix 10) of the dinutuximab pivotal trial. The updated model also included an option to select either observed Kaplan-Meier data or parametric analyses in the assessment of cost-effectiveness.

5.1 ERG comment on company's review of cost-effectiveness evidence

5.1.1 Searches

The company undertook a systematic literature review of published research evidence to identify literature relating to costs, resource use, cost-effectiveness studies and health-related quality of life relevant to this appraisal of dinutuximab for the maintenance treatment of high risk neuroblastoma. The search strategies were described in the main body of the submission, and full details were provided in Appendix 6 of the CS.

The electronic databases MEDLINE (through PubMed), EMBASE, and the CRD databases of the National Health Service Economic Evaluation Database (NHS EED) and the Health Technology Assessment (HTA) database were searched. In addition to the formal electronic searches, reference lists of included cost-effectiveness and quality-of-life studies were hand searched for additional relevant studies. Searches for each database were reported in Appendix 6 of the CS.

The searches were performed in February 2015 and no time restrictions were imposed, although searches were limited to the English language.

Generally, the search strategies were well reported in the CS. The exact search strategies used along with the databases searched, the database service provider and dates of searches were all clearly reported. The Embase interface was not reported and a date span for the searches was not included. The rationale for restricting the search results from both MEDLINE and Embase to English language only studies is not presented.

Due to the anticipated lack of studies in neuroblastoma, no restrictions were imposed with respect to interventions and/or comparators used. Boolean operators, truncation and field searches have been used appropriately.

5.1.2 Inclusion/exclusion criteria used for study selection

The inclusion/exclusion criteria used for study selection can be found on page 83, Table 33, of the CS followed the usual PICOS framework and are reproduced below:

- Population: patients with neuroblastoma;
- Intervention/Comparators: Due to the limited therapeutic options and studies in neuroblastoma, studies were included regardless of interventions and/or comparators used. Screening/diagnostic studies not reporting relevant outcomes for the treatment of neuroblastoma were excluded;

- Outcomes: results from costs reported from the perspective of the UK's NHS and PSS, healthcare resource use from the UK and abroad, and health-related quality of life based on disease health states or for neuroblastoma survivors, together with results from cost-effectiveness evaluations. Screening/diagnostic studies not reporting costs, resource use, or quality of life specific to the treatment of neuroblastoma and health related quality of life studies not reporting health utilities were excluded;
- Study designs: all study types except for case reports, comments, editorials and letters.

Duplicate results were eliminated and the remainder was screened by 2 reviewers and checked against the inclusion/exclusion criteria.

The ERG considers these criteria to be reasonable for identifying existing published evidence specifically on the cost-effectiveness of dinutaximab for the maintenance treatment of high risk neuroblastoma. The restriction to English language only studies is not discussed.

5.1.3 Studies included and excluded in the cost effectiveness review

A total of 1,191 studies were initially identified. According to the company a large majority of the studies (1,168 of the 1,191) were excluded during primary filtering. No summary description of the exclusions was provided. Of the 23 studies remaining for secondary filtering, 14 were further excluded due to outcomes not being relevant. Nonetheless, an additional record was included when checking reference lists. From the final ten included studies, four were identified as potentially useful to inform the decision model's costs and healthcare resource use. While the remaining six studies included health utility information relevant for the model.

5.1.4 Conclusions of the systematic review

The company's search did not identify any relevant economic assessments of dinutuximab for the maintenance treatment of high risk neuroblastoma. Therefore, the ERG considers the cost-effectiveness analysis reported in the current submission to be the most relevant source of evidence to inform the decision problem.

5.2 ERG's summary and critique of the company's submitted economic evaluation

An overall summary of the company's approach and signposts to the relevant sections in the CS are reported in Table 20 below:

Table 20 Summary of the company's economic evaluation (and signposts to company's submission)

	Approach	Source / Justification	Location in CS
Model	Decision model with 100 year time horizon and monthly cycles. Within the first 5 years, the model makes use of the AUC survival (or partitioned survival) approach, common in the clinical area of cancer. After this, the event-free cohort is assumed to be cured and patients start to follow similar characteristics (ie, mortality, quality of life, relapse rates) to that of the general population, while still accounting for potential morbidities affecting quality of life and resource use among neuroblastoma survivors	The model evaluates the clinical and economic outcomes of two alternative technologies for high-risk neuroblastoma in children who have previously received induction chemotherapy and achieved at least a partial response, followed by myeloablative therapy and ASCT. It reflects the final phase of the treatment pathway (i.e. maintenance) with the goal of achieving minimal residual disease	Section 5.2; p85-89
States and events	Using a partitioned survival approach, the model consists of 3 mutually exclusive health states: stable, failure, and an absorbing health state death. Response to treatments was evaluated using EFS and OS. At a given time the proportion of patients in each health state are based on EFS and OS calculations. Adverse events, with corresponding HRQoL and related costs, were modelled.	Treatment response criteria was defined in the pivotal trial Yu 2010 and used within the survival modelling which informed the decision model. Adverse events, based on the Grade 3/4, were also based on the Yu 2010.	Section 5.2; p85-89
Comparators	The appraisal compares immunotherapy (consisting of dinutuximab in combination with sargramostim, aldesleukin, and isotretinoin) with standard therapy (isotretinoin).	The decision problem was addressed by comparing the two interventions in question. The choice of isotretinoin as comparator is consistent with the final scope by NICE.	Sections 1.1 and 5.2; p7 and p85-89
Natural History	The health states were defined as described above with occurrence of relevant events used as a proxy for movement between them.	Patients' transitions between stable and failure health states, and consequently, movement from one treatment to the following one (i.e. topotecan combination), were based on EFS and OS as reported in the pivotal clinical trial Yu 2010.	Section 5.2; p85-89
Treatment effectiveness	EFS and OS for immunotherapy and isotretinoin were modelled using a 2 part curve fit.	The 2-part curve fit consisted of: i) a fitted parametric curve up to 5 years (base case time threshold of 'cure'). Differences in EFS and OS at this cut-off point persist for the remainder of the patient's lifetime; and ii) patients in the stable health state are assumed to follow the long-term survival of the general population and patients in the failure health state follow mortality rates that apply to the recurrent/relapsed population.	Section 5.2; p85-89
Adverse events	Inclusion criteria for adverse events in the model were any Grade 3 or 4 event. Toxicity level was graded according to the NCI CTCAE v3.0.	Adverse event monthly rates used were based on the record events in the pivotal clinical trial Yu 2010. Decrements to HRQoL attributed to adverse events associated with immunotherapy administration are	Section 4.12; p70-81 Section 5.3; p102-103 Section 5.4;

	Approach	Source / Justification	Location in CS
		captured within the first 5 cycles of the model. Costs for adverse events were applied at the start and for 6 cycles. Per-event unit costs for each adverse event item was obtained from NHS Reference Costs 2013/2014	p106-107 Section 5.5; p116
Mortality	General population all-cause mortality rates for England and Wales (ONS 2015) were used for patients in the stable state after 5 years. Also a monthly probability of death of 5.1% was used for patients in the failure health state.	All-cause mortality rates were obtained from the UK life tables (ONS 2015). The monthly probability of death of 5.1% for patients in the failure state was calculated assuming an exponential survival function and using 3-year OS from a study of children with recurrent or refractory neuroblastoma (London 2010)	Section 5.3; p102
Health-related quality of life	As no HRQoL was collected in dinutuximab pivotal clinical trial (Yu 2010), HRQoL utility estimates were obtained from external data.	HRQoL utility estimates were obtained from a small cross-sectional study (Barr 1999). Health utilities from this study populated the first 5 years of the model. After five years, patients in the stable state follow general population health utilities linear prediction based on age and gender (Ara 2010) adjusted by a reduction of 13% to account for potential morbidities among neuroblastoma survivors (Portwine 2014)	Section 5.4; p106-108
Resource utilisation and costs	Costs included were: drug acquisition costs; drug administration costs; concomitant medication and monitoring costs; and health-state-related costs which include health resource use and other drug acquisition and administration costs	Resource use associated with drug administration, physician visits, monitoring and hospitalisation was based on Rebholz 2011. Unit costs were obtained from Consultant-led outpatient attendances and national averages. Unit drug costs were obtained from the BNF, 2015. Administration unit costs of immunotherapy and comparator were obtained from the NHS Reference Costs 2013-2014 and PSSRU 2014 Concomitant unit costs were obtained from BNF and monitoring costs were obtained from NHS Reference Costs 2013-2014	Section 5.5; p108-116
Discount rates	3.5% for utilities and costs	NICE reference case	Section 5.6; p117
Population and Subgroups	The final scope defined the population as: people with high-risk neuroblastoma who have received myeloablative therapy and autologous stem cell transplant. The subgroups of people with relapsed and refractory disease were identified as important sub-populations for assessment.	The target population for the base case analysis was as defined in the final scope from NICE. Subgroup-analysis over the effectiveness of the modelled interventions was performed for patients over the age of 1 with stage 4 disease and by Curie score.	Section 1.1; p7 Section 4.8; p63-66 Section 5.9; p141

	Approach	Source / Justification	Location in CS
	Cost-effectiveness subgroup analysis was not performed.	Cost-effectiveness subgroup analysis was not performed given the small sample sizes and the narrow target population definition.	
Sensitivity analysis	Deterministic sensitivity analysis was performed on a series of model parameters. Probabilistic sensitivity analysis and scenario analyses were also performed.	NICE reference case	Section 5.8; p130-141
AUC – Area under the curve; ASCT – autologous stem-cell transplantation; EFS – event-free survival; OS – overall survival; HRQoL – health-related quality of life; NICE – National Institute for Health and Care Excellence; NCI – National Cancer Institute; CTCAE – Common Terminology Criteria for Adverse Events; NHS – National Health Service; ONS – Office for National Statistics; UK – United Kingdom; BNF – British National Formulary; PSSRU - Personal Social Services Research Unit			

5.2.1 The company's economic evaluation compared with the NICE reference case checklist

Table 21 summarises the economic submission and the ERG's assessment of whether the *de novo* evaluation meets NICE's reference case and other methodological recommendations.

Table 21 NICE reference case

Attribute	Reference Case	Included in CS	Comment on whether *de novo* evaluation meets requirements of NICE reference case
Comparator(s)	Isotretinoin	Yes	Isotretinoin was chosen as the comparator. This choice is consistent with the final scope issued by NICE. Isotretinoin has been considered the standard of care for maintenance therapy of high-risk neuroblastoma.
Type of economic evaluation	Cost-effectiveness analysis	Yes	Yes. The de novo model produced in CS Excel considers a pairwise comparison only.
Perspective - costs	NHS and PSS	Yes	NHS and PSS costs were taken into account, as recommended by NICE (Guide to methods of TA)
Perspective - benefits	All health effects on individuals	Yes	QALY benefits to treated individuals were considered.
Time horizon	Sufficient to capture differences in costs and outcomes	Yes	The economic model followed a life-time horizon (100 years). Less than 0.01% of patients were expected to be alive beyond this period. However, long-term time horizons rely on assumptions, due to the lack of long-term data.
Synthesis of evidence on outcomes	Systematic review	Partially	A systematic review on clinical effectiveness was conducted. No synthesis of evidence was implemented due to the lack of comparable clinical trials.
Outcome measure	QALYs	Yes	
Health states for QALY measurement	Described using a standardised and validated instrument	Yes	HRQoL data from Barr 1999 study, based on the HUI mark 2 (HUI2) and HUI mark 3 (HUI3) instruments, was available for each health state being considered in the cost-effectiveness modelling.
Benefit valuation	Time Trade Off or Standard Gamble	Yes	HUI intrinsically uses the Standard Gamble approach to measure preferences
Source of preference data	Representative sample of the public	Yes	The study (Barr 1999) does not reflect health utilities based on EQ-5D as recommended by the reference case. However, valuations from the HUI were considered appropriate for this population.
Discount rate	3.5% on costs and health benefits	Yes	Costs and benefits have been discounted at 3.5% per annum.
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes	
Sensitivity analysis	Probabilistic sensitivity analysis	Yes	Probabilistic sensitivity analysis was conducted as well as deterministic and structural sensitivity analyses. Mean increment results for the probabilistic sensitivity analysis were presented as well as graphical results using scatter plots, cost-effectiveness acceptability curves and tornado diagrams

NHS - National Health Service; PSS - personal social services; QALY - quality-adjusted life years; HRQoL - health-related quality of life; NICE - National Institute for Health and Care Excellence; TA – Technology appraisal;

5.2.2 Population

The patient population considered within the company's decision problem is in line with the licensed population. No additional patient subgroup populations were considered within the CS. The two subgroup populations listed in the final scope issued by NICE of (i) people with relapsed disease and (ii) people with refractory disease were not considered by the company due to a lack of evidence for the use of dinutuximab in these subpopulations.

As stated in Section 3, the ERG considers the patient population to be appropriate but it represents a more restricted population. In particular, the ERG has concerns that the evidence used to inform the cost-effectiveness of dinutuximab in this patient population has excluded patients with evidence of biopsy-proven persistent disease after ASCT and radiotherapy. As discussed in Section 4.2.1.3 the survival benefit of immunotherapy is less good in patients with biopsy-proven persistent disease (than in patients without persistent disease. The exclusion of this high risk group of patients is likely to have created a more favourable treatment effect for immunotherapy compared with standard therapy in the primary efficacy analysis. This creates uncertainty since patients presenting for treatment within the licensed population in the NHS is likely to also include those patients with evidence of biopsy-proven persistent disease.

Comparative efficacy estimates for a subgroup of patients over the age of 1 year with stage 4 disease in the ANBL0032 study population was presented in the CS (Section 4.8.1 of CS) but this subpopulation was not considered in the economic analysis. Furthermore, the company presented a post-hoc analysis of EFS in patients stratified by Curie score (=0 or >0), which has been identified as a potential prognostic marker for neuroblastoma and treatment efficacy was substantially poorer in both arms in patients with a Curie score above zero (see Section 4.2.1.3). However, this subpopulation was not considered in the economic analysis.

5.2.3 Intervention and comparators

As discussed in Section 3, the ERG considers the treatment regimen of dinutuximab in combination with GM-CSF, IL-2 and isotretinoin to be comparable with the marketing authorization for the use of dinutuximab, the pivotal phase 3 clinical trial, and the final scope issued by NICE. The comparator included in the company decision problem is isotretinoin. As described in Section 3, the ERG considers this comparator the appropriate standard of care for maintenance therapy of high-risk neuroblastoma and is consistent with the final scope issued by NICE.

5.2.4 Perspective, time horizon and discounting

The perspective of the company's analysis was the NHS and Personal Social Services. The time horizon used in the model was 100 years, which represents a lifetime horizon for the patient

population. This time horizon was chosen as the company assumes that immunotherapy compared with standard therapy leads to a difference in EFS and OS at 5 years which persists for the remainder of the patient's lifetime. The ERG considers the use of a lifetime horizon to only be reasonable if the differences in survival are expected to be maintained over a lifetime. For example, if the survival curves for immunotherapy and standard therapy converge at some time point before a lifetime horizon then a shorter time horizon may be sufficient to capture the relevant differences in costs and outcomes. Therefore, the appropriate time horizon depends on the assumptions about the extrapolation of benefits over the long-term for immunotherapy compared with standard therapy.

A discount rate of 3.5% per annum was applied to both costs and outcomes in the company's base case analysis, which is in line with NICE guidance. However, in a separate scenario analysis the company also applied an annual discount rate of 1.5% to outcomes (and 3.5% to costs) under the assumption that patients who are event-free at 5 years are cured and follow similar characteristics to that of the general population. The NICE Guide to the Methods of Technology Appraisal (2013) states that a discount rate of 1.5% for costs and benefits may be considered in cases when the treatment restores individuals who would otherwise die or have a very severely impaired life to full or near full health, and when this is sustained over a very long period (normally at least 30 years) and cost-effectiveness analyses are very sensitive to the discount rate used. As discussed in Section 4, the evidence from the dinutuximab pivotal trial suggests that immunotherapy delays rather than permanently prevents cancer-related events. Longer-term follow-up data for EFS suggested that the survival curves for immunotherapy and standard therapy converged at around a 50% long-term (beyond 10 years) survival rate. For OS the survival curves also appeared to be converging to long-term survival rates of just over 50%, although the longer survival times are less certain.

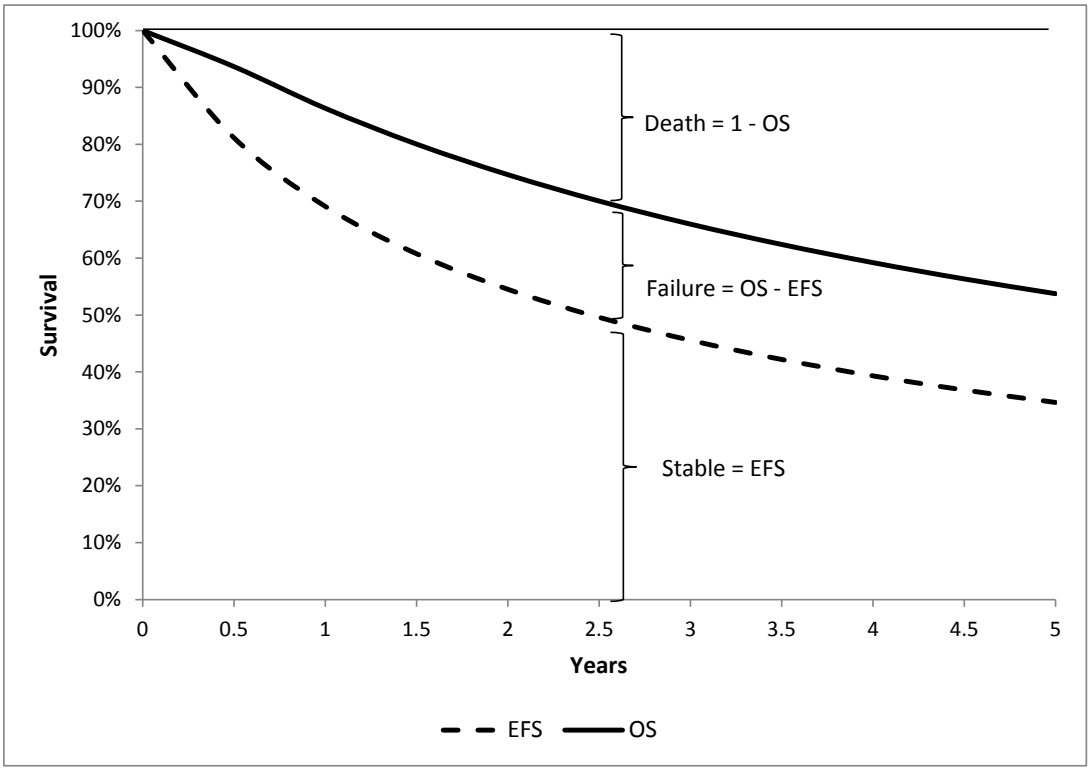
5.2.5 Model structure

In the absence of previously published cost-effectiveness analyses of dinutuximab in the defined patient population, the company undertook a *de novo* economic evaluation. The CS presented a decision model which was based on a partitioned survival approach, which used survival data from the main clinical trial for the outcomes of EFS and OS.

The model consisted of 3 mutually exclusive health states: stable, failure, and death. The stable health state represents patients alive without a failure event. The failure state represents patients with a failure event, which is defined as the occurrence of relapse, progressive disease or secondary cancer. The remaining proportion of patients is represented by the death state. Patients started the model in the stable health state at the age of 4 years and 60% of patients are males based on the baseline characteristics of the ANBL0032 study population.

Unlike a Markov model, which explicitly incorporates transitions between health states using probabilities, the partitioned survival model calculates the proportion of patients in each health state at each point in time using estimates of survival over time. The proportion of patients in the stable state at any given time is based on estimates of EFS, while the proportion of patients in the death state is 1 minus the estimate of OS (i.e. 1-OS). The proportion of patients in the failure state is calculated as the difference between OS and EFS. Figure 11 represents a schematic diagram of a partitioned survival model.

Figure 11 Schematic diagram of a partitioned survival model (Figure 14 of CS)



Given the nature of the survival data in the main clinical trial, the ERG considers the model structure to be generally appropriate as it enables ongoing risks that vary over time to be addressed and is typical of that used for evaluating oncology therapies. However, the use of a single post-progression health state (failure state) is a simplification of the treatment pathway as it doesn't allow a distinction to be made between patients who remain progression-free following first relapse/ recurrence of disease from those who have subsequent further relapses (and where differences in further treatment may exist).

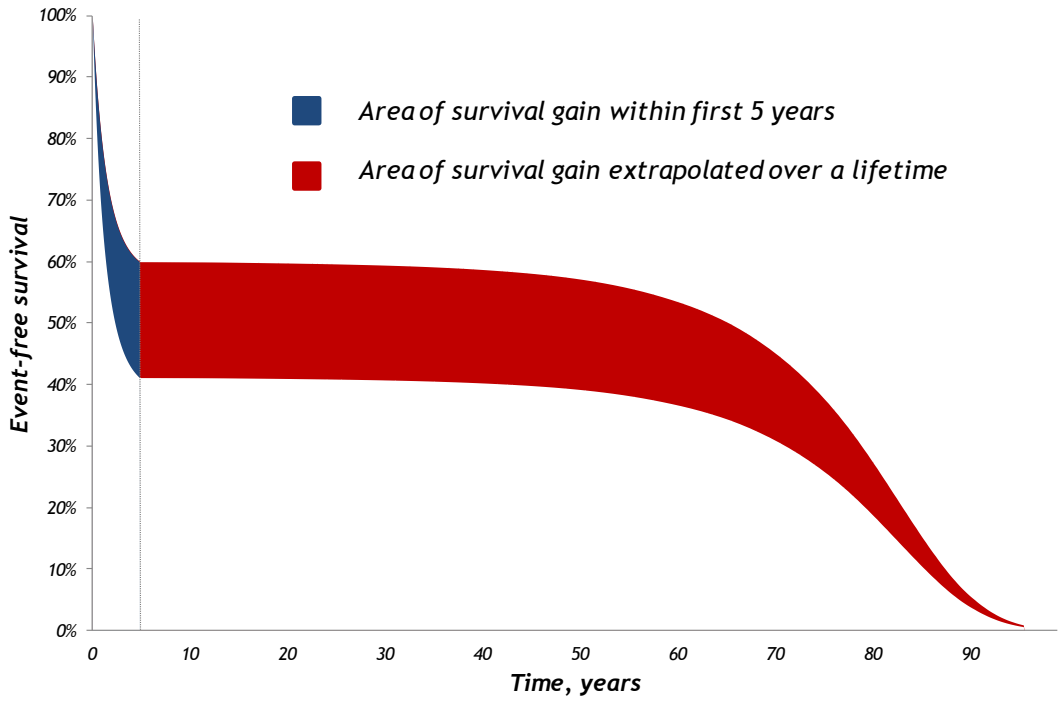
5.2.5.1 Cure threshold of 5 years

The company used the survival estimates from the main clinical trial up to a pre-defined time threshold of 5 years. Within the first 5 years, the model calculated the proportion of patients in each

health state by treatment at monthly intervals (with half-cycle correction) using parametric curves fitted to empirical Kaplan-Meier data on EFS and OS over time. Importantly, at 5 years the event-free cohort in the stable health state was assumed to be cured, i.e. patients who have survived to 5 years without an event are considered survivors who will not relapse at any time point in the future. Therefore, after 5 years the company assumed that the event-free cohort enters a phase where they follow similar characteristics to that of the general population (same mortality risk), while still accounting for potential morbidities affecting quality of life and resource use among neuroblastoma survivors.

The ERG has a number of significant concerns regarding the use of cure threshold of 5 years. Firstly, this assumption inevitably means that the survival gains observed at 5 years are effectively extrapolated over a lifetime. This will have a significant impact on the resulting estimates of cost-effectiveness. This is illustrated in Figure 12 which shows the area of survival gain within the observed time period of 5 years (represented by the blue area between the treatment curves) and the area of survival gain extrapolated over a lifetime (represented by the red area between the curves) with patients assumed to follow similar characteristics to that of the general population after 5 years. This means that the difference in survival between immunotherapy and standard therapy that is observed at the time point of 5 years is maintained over a lifetime horizon. The ERG considers this a strong assumption since the long-term consequences of therapy in this patient population are unknown.

Figure 12 Area of survival gain within the observed and extrapolated time periods



Secondly, and more importantly, the evidence from the ANBL0032 study population does not support the assumption that patients event-free at 5 years do not experience further risk of relapse. The most up-to date and complete analysis of the ANBL0032 trial (March 2014) shows that the Kaplan-Meier curves for EFS for immunotherapy and standard therapy converge between 5 and 10 years (see Figure 4 (Figure 7 of the CS); EFS at 7.5 years is approximately 50% and 48% for immunotherapy and standard therapy, respectively).

The company justified the assumption of a cure threshold of 5 years based on information from the Children's Oncology Group (COG) neuroblastoma website which states that relapses occurring more than 5 years after the completion of therapy are rare. This was confirmed to the company by two UK clinical experts. The company also stated that supplementary long-term data outside of the ANBL0032 study population is limited but further justified the assumption on the basis that some recent long-term studies show that OS and EFS appear to reach a plateau between 5 and 10 years [28-31].

The clinical advisor to the ERG emphasised that the long-term benefits of immunotherapy in this patient population are unknown and that immunotherapy might simply prolong the time to relapse. The ERG's clinical advisor also stated that although conventional trial results using cytotoxic chemotherapy would generally assume that patients event-free at 5 years are unlikely to experience disease occurrence at a later point in time, this would be a strong assumption for immunotherapy since the treatment works in a very different way from conventional chemotherapy. Furthermore, the clinical advisor did not support the assertion that this patient population event-free at 5 years would have the same survival as that of the general population since prior to commencing immunotherapy this patient population have already received intensive chemotherapy and radiotherapy (see Section 2.2).

Therefore the ERG does not consider the use of a cure threshold of 5 years as appropriate. The evidence from the updated analysis of the ANBL0032 study population suggests that the cure threshold should be at least 10 years since patients on immunotherapy did experience relapse between 5 and 10 years.

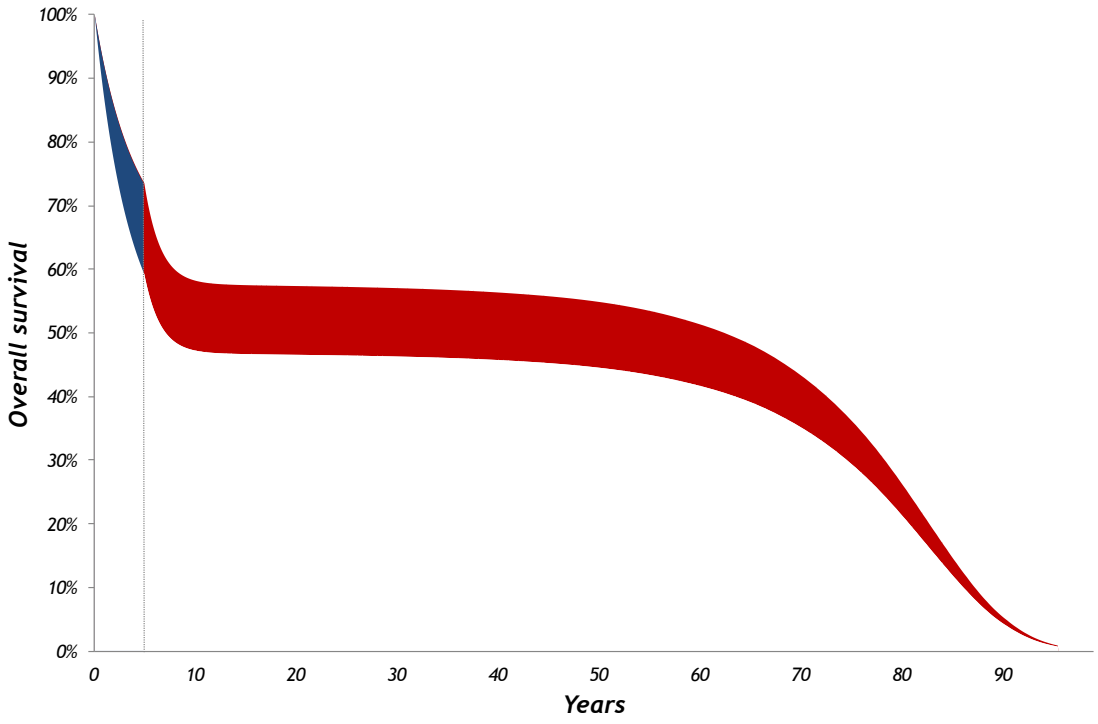
5.2.5.2 Failure health state

An important structural concern identified by the ERG is the assumption that there is a differential treatment effect on mortality that persists after the cure point of 5 years. The company assumed that patients who experience a failure event (failure health state) have a monthly probability of death of 5.1%, while those in the stable health state (event-free) after 5 years have a monthly probability of death equivalent to that of the general population. This means that effectively a differential treatment effect persists after the cure point due to a different proportion of patients in the failure health state on

immunotherapy compared with standard therapy at 5 years. This is illustrated in Figure 13, which shows the effect of assuming a differential treatment effect on survival beyond the cure point of 5 years. The implications for lifetime survival gains in the company's base case analysis are minimal because there is only a 1% difference between immunotherapy and standard therapy in the proportion of patients in the failure state at 5 years. However, this assumption will have a much more marked effect if there is a greater difference between treatments in the proportion of patients in the failure state at the cure time point. It means that the treatment effect observed within the trial period is not only extrapolated over a lifetime horizon but it also increases or decreases in the extrapolated period depending on the differential proportion of patients in the failure state by treatment at the time point of the cure threshold.

The implication of the company's assumption on the results of the cost-effectiveness analysis depends on the resource use, unit costs and health-related quality of life associated with the failure health state. The company assumes that upon treatment failure, patients in the model receive a topotecan combination of therapies on a monthly basis until death. Therefore the assessment of cost-effectiveness depends on the balance between costs and effects for survival gains in the failure health state and cumulative long-term treatment costs associated with receiving topotecan therapies over a lifetime.

Figure 13 Differential treatment effect on survival in the extrapolated period



5.2.6 Treatment effectiveness and extrapolation

To establish the cost-effectiveness of immunotherapy compared with standard therapy, the company used the ANBL0032 trial to provide a direct comparison of EFS and OS in each treatment arm up to a threshold of 5 years. The trial has been described in detail in Section 4.2.1. The company used the data of June 2009 [21] for the primary efficacy analyses to inform the base case analysis in the assessment of cost-effectiveness. These data represent the point at which randomisation in the trial was stopped early, and an interim analysis demonstrated improved 2-year EFS and OS rates for immunotherapy compared with standard therapy (EFS: 66% ± 5% for immunotherapy, 46% ± 5% for standard therapy; OS: 86% ± 4% for immunotherapy, 75% ± 5% for standard therapy). After randomisation was terminated patients assigned to standard therapy had the option of switching to immunotherapy provided that they had not experienced disease progression since trial enrolment or received further anti-neuroblastoma therapy following completion of isotretinoin.

Parametric survival curves were fitted to the empirical Kaplan-Meier data on EFS and OS within the first 5 years of the model and the number of patients in each health state at each monthly cycle was calculated directly based on predicted EFS and OS for each treatment. A single parametric model was fitted to the survival data, with treatment group included as a covariate in the analysis and assuming proportional hazards. The company justified the use of a single curve and the assumption of proportional hazards based on an inspection of the log-cumulative hazard plots, which show where any significant changes in the observed hazard occur. In the June 2009 data used in the company's base case analysis, the hazards for EFS were reasonably proportional between the two treatment groups (Figure 15 of the CS), whereas for OS there was an important change in the hazard at approximately 4.5 months and some evidence for partial violation of the proportional hazards assumption (Figure 16 of the CS). The company, however, considered that a single parametric model with proportional hazards was appropriate for both EFS and OS in the base case analysis and the use of separate parametric functions on each treatment arm was examined in a sensitivity analysis. The company considered several different survival models for the curve fit: exponential, Weibull, Gompertz, log-logistic and log-normal (Figures 17 and 18 of the CS). Of these, a Gompertz survival function was fitted to the Kaplan-Meier data on EFS and an exponential function fitted to OS data up to 5 years, based on the best fitting curve as determined by Akaike information criterion (AIC) and Bayesian information criterion (BIC). Figure 14 shows the parametric fit to the observed EFS data used in the company's model for the first 5 years, while Figure 15 shows the parametric fit to the OS data.

The ERG considers the general approach used by the company for fitting parametric curves to the survival data to be appropriate but it is important to note that the population under assessment is

heterogeneous and a 'purely' statistical approach to parametric fitting of trial data may not be sufficient to represent unobserved heterogeneity in the patient population. Furthermore the choice of parametric model can lead to different results so it may be appropriate to place more weight on the clinical plausibility of the curves than on the statistical goodness of fit.

Figure 14 EFS parametric fit to the observed Kaplan-Meier data up to 5 years

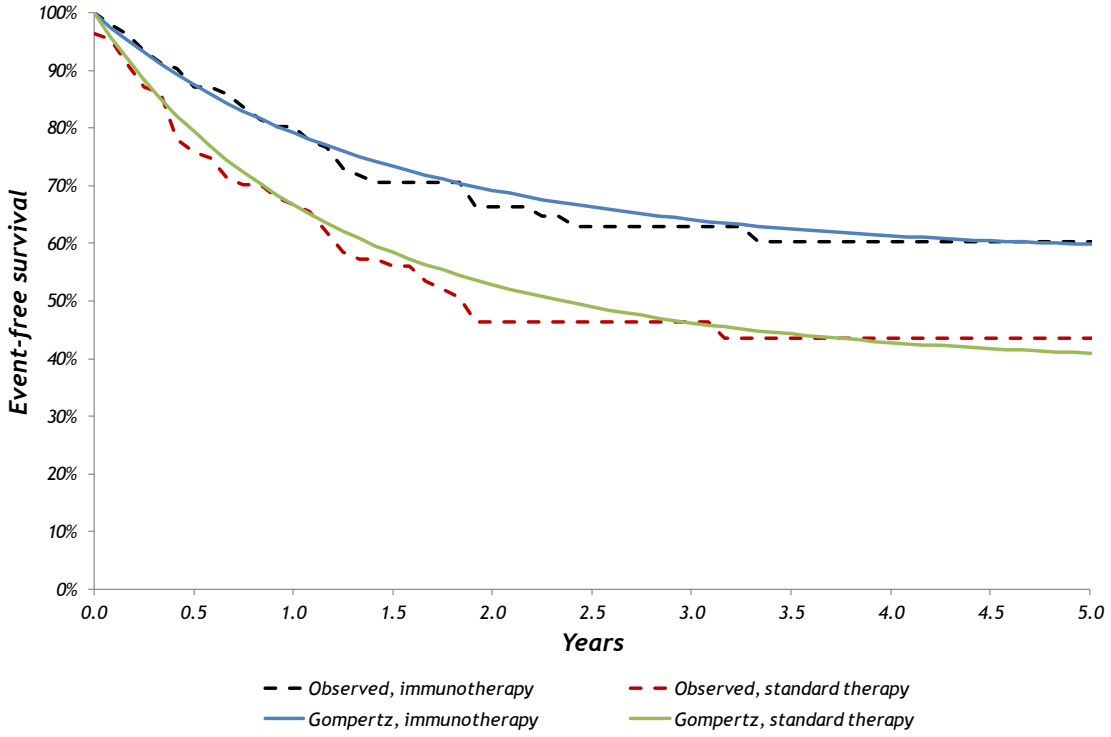
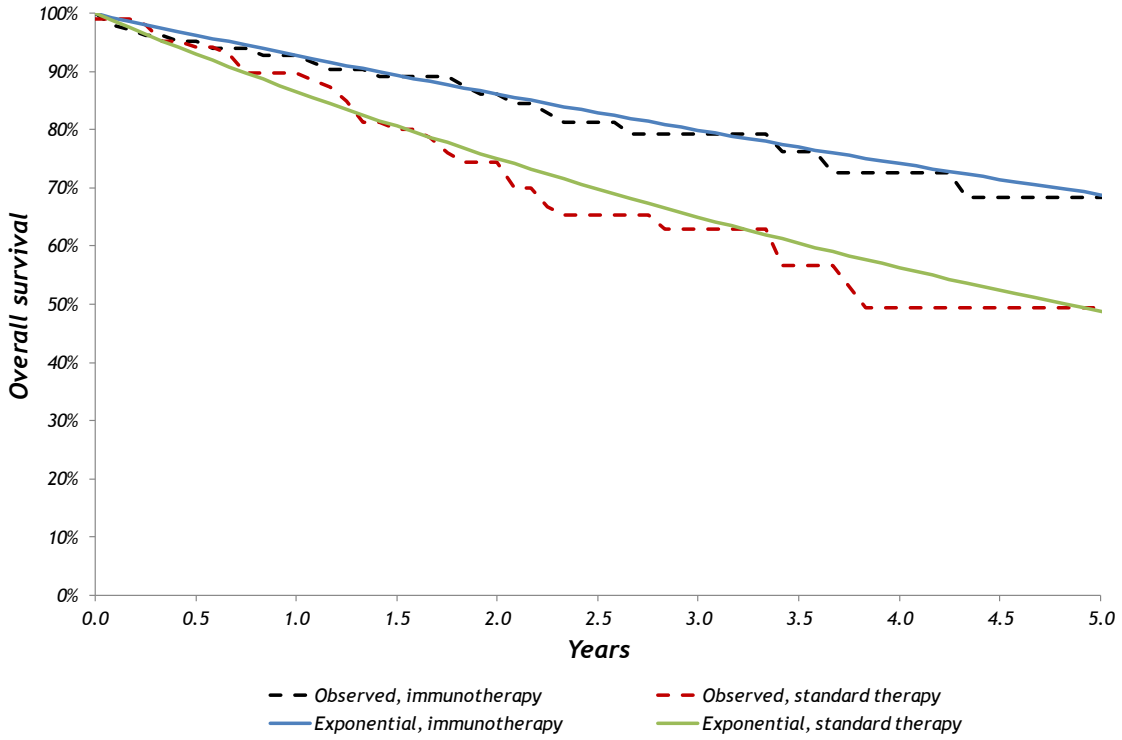


Figure 15 OS parametric fit to the observed Kaplan-Meier data up to 5 years



5.2.6.1 Extrapolation beyond the trial follow-up

For the period beyond 5 years, a visual inspection of the parametric curves extrapolated over a lifetime horizon was considered by the company (Figures 19 and 20 of CS). The company concluded that the Gompertz function was the only curve that reached a plateau in EFS, which is consistent with the 'curing' effect introduced into the model structure at 5 years, but that none of the extrapolated OS curves were consistent with this curing effect and therefore potentially underestimated survival beyond the trial period. The company also tried to identify external data to inform the extrapolation beyond the trial period but only identified one relevant study of Matthay 2009.[32] In this study a plateau effect in OS was observed between 6 and 8 years for treatment with isotretinoin in a population of patients who completed consolidation (with myeloablative chemotherapy, total-body radiation and ABMT) without disease progression. Table 22 shows a comparison of 5-year EFS and OS estimates from the pivotal trial, Matthay 2009 and the parametric models (standard therapy arm). The company concluded that the parametric EFS model predictions were lower compared to the clinical trials (Yu 2010 and Matthay 2009), while OS predictions were generally close to the observed 2-year data cut from the pivotal trial (Yu 2010) but lower than that reported by Matthay 2009. For these reasons, the company discarded the use of parametric models in the extrapolated period since none of the curves were able to address the curing effect.

Table 22 Five-year survival estimates from Yu 2010, Matthay 2009 and parametric models for standard therapy arm (Table 37 of CS)

	EFS	OS
Yu 2010 (observed data)	43.5%	49.3%
Matthay 2009[a] (observed data)	50.0%	59.0%
Exponential[b]	25.1%	48.8%
Weibull[b]	31.2%	47.0%
Gompertz[b]	41.0%	49.3%
Log-logistic[b]	32.3%	49.2%
Lognormal[b]	34.6%	53.7%

Key: ABMT – autologous purged bone marrow transplantation; EFS – event-free survival; OS – overall survival.

[a] Figure 4, ABMT with isotretinoin arm in Matthay 2009. Sample size was 50.

[b] 5-year predictions from parametric models.

The company assumed that after 5 years, the event-free cohort in the model is cured and enters a phase where they are considered survivors and start to follow similar characteristics (i.e. mortality, quality of life, relapse rates) to that of the general population (while still accounting for potential morbidities affecting quality of life and resource use among neuroblastoma survivors). Figure 16 shows the modelled EFS curves used for a lifetime horizon, while Figure 17 shows the modelled OS curves.

Figure 16 Modelled EFS over the lifetime horizon

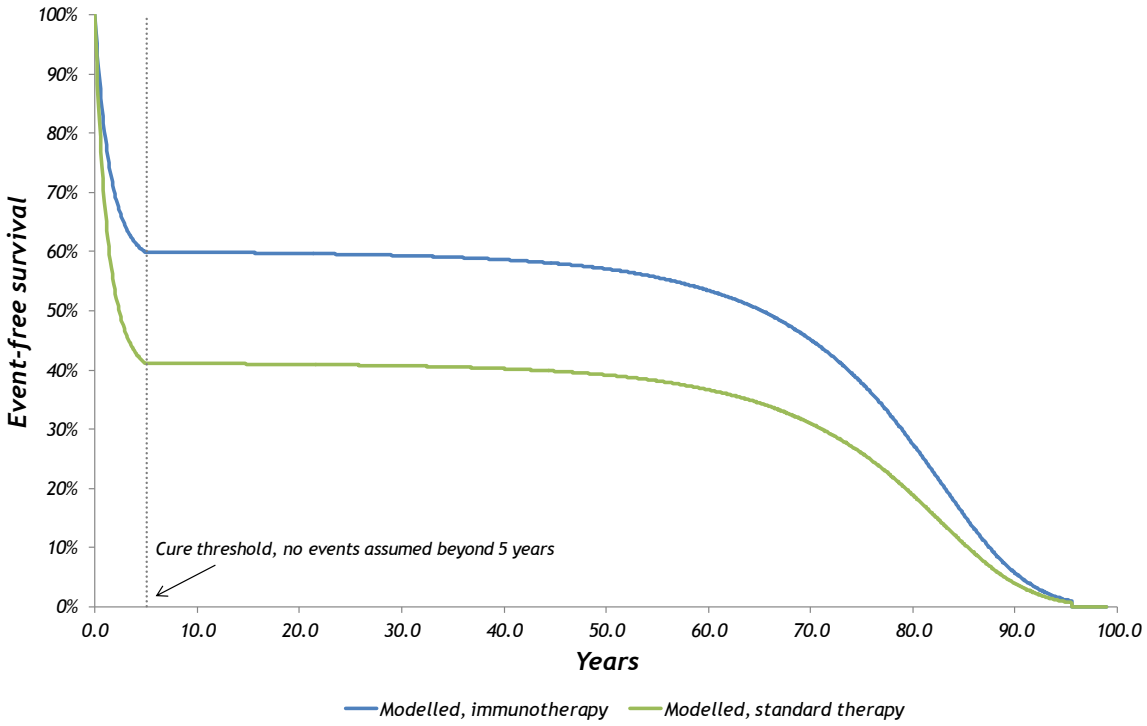
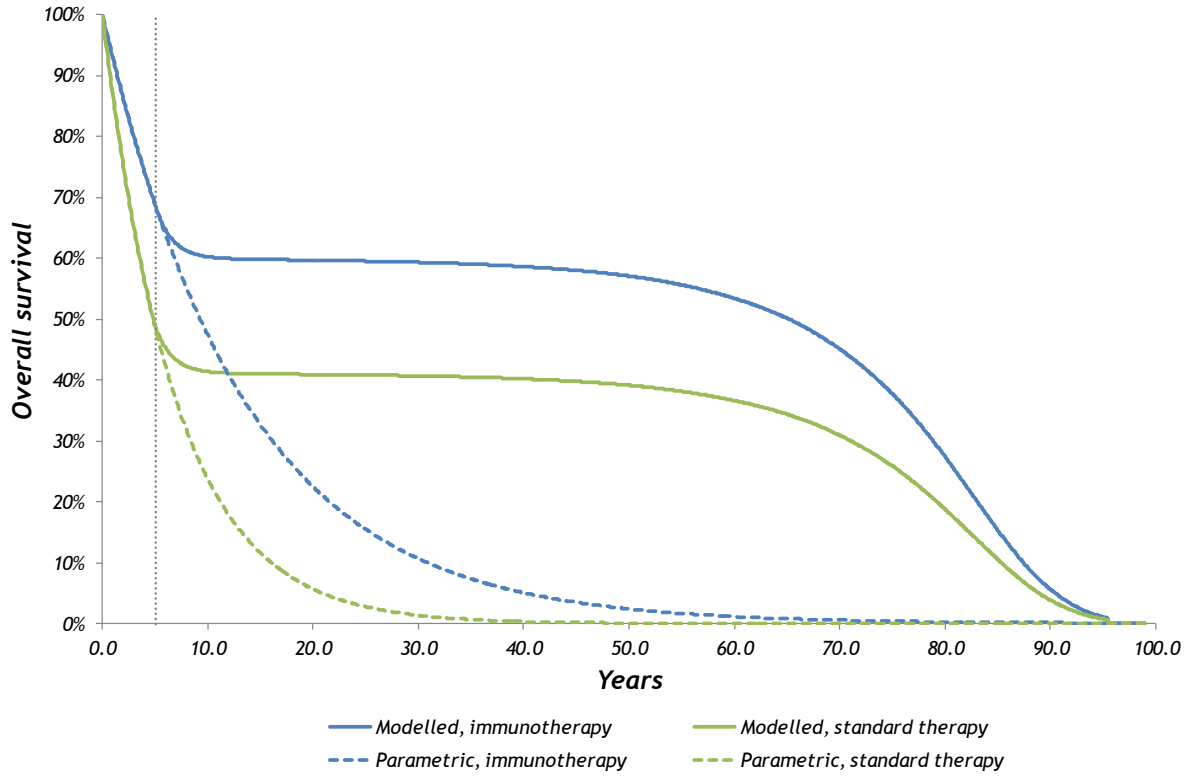


Figure 17 Modelled OS over the lifetime horizon compared with a parametric extrapolation of the trial data



The ERG has a number of concerns about the approach used by the company. Firstly, the assumption that the surviving event-free cohort at 5 years is cured appears to be founded on weak evidence. Secondly, the justification for not extrapolating the data beyond the trial follow-up using parametric curves is not supported by any evidence. Table 22 above does not provide any long-term (beyond 5 years) evidence that the parametric curves under- or over-estimate survival in the long-term (it only presents a comparison of 5-year survival estimates). Thirdly, the assumption that the event-free cohort follows similar characteristics to the general population at 5 years makes the need for parametric modelling within the first 5 years redundant. The ERG considers that the use of the observed Kaplan-Meier data for each treatment arm within the trial period to be more appropriate since the empirical data provides the full distribution of survival within the first 5 years of the model. The use of observed Kaplan-Meier data also avoids the need to make any assumptions about the data, e.g. proportional hazards, and reflects the actual treatment effect observed in the trial.

5.2.6.2 Mortality beyond the trial follow-up

A general population age-specific mortality rate based on Interim Life Tables for England and Wales (2011-2013) using a weighted average of male and female mortality risks (derived from the gender distribution of participants in the ANBL0032 study population) was used to determine the deaths in the stable state after 5 years.

The mortality rate in the failure state after 5 years was based on a constant monthly probability of death of 5.1% based on the study by London 2010.[33] This study examined the effects of further therapies (single-agent topotecan and combination topotecan and cyclophosphamide) in a clinical trial of children with refractory/recurrent neuroblastoma. The results showed a 3-year OS rate of 13.8% for topotecan alone and 17.3% for topotecan combination therapy. In order to derive the modelled mortality risk, the company assumed an exponential survival function and an average 3-year OS rate of 15% to give a monthly probability of death of 5.1% (=1-EXP(LN(0.15)/(3*12))) in the failure state.

The ERG has a number of significant concerns with the approach used to model mortality risk in the failure state after 5 years. Firstly, outcomes in the population of the study by London 2010 in relapsed/ refractory neuroblastoma may be dissimilar to outcomes in the ANBL0032 study population following relapse, progressive disease or secondary cancer (definition of the failure state) due to differences in the stage of treatment in the pathway of care. In the study by London 2010,[33] eligibility criteria included neuroblastoma patients in first recurrence or progression after treatment with aggressive multidrug therapy (two or more agents, including an alkylator and a platinum-containing compound) or at second recurrence after a single regimen of aggressive chemotherapy at first

recurrence. Patients in the study were also permitted to pursue ASCT or alternative therapy at any time. Of the 119 eligible patients, 60% previously underwent high-dose chemotherapy with ASCT as initial treatment and 40% had not. This is in contrast to the ANBL0032 study population where all patients had previously received induction chemotherapy followed by myeloablative therapy and ASCT. Secondly, and more importantly, it means that the mortality risk applied to the failure state differs within the trial period (which is captured within the OS estimates for immunotherapy and standard therapy) from the mortality risk that is applied after the trial period (beyond 5 years). This creates an inconsistency in how the mortality of the failure state is captured within the model; it means that outcomes for patients who fail treatment within the first 5 years differ from outcomes for those patients who fail treatment after 5 years. Patients who fail treatment after 5 years face a very low survival rate compared with patients who fail treatment within the first 5 years. This is shown in Figure 18, which shows the modelled proportion of patients in the failure health state over time. Within the observed trial period the proportion of patients in the failure state is given by the difference between OS and EFS in the ANBL0032 study population for each treatment arm. However, after 5 years the proportion of patients in the failure state (regardless of treatment arm) is determined by the very high monthly mortality risk of 5.1% (patients in the stable state are assumed to be cured at this point and follow a low background mortality risk of the general population). Furthermore, this leads to a perverse effect that there is an additional differential treatment effect on mortality that extends beyond the trial period. Although patients in the failure health state face the same mortality risk after 5 years regardless of previous treatment received, the fact that there is a different proportion of patients in the failure state at 5 years for immunotherapy compared with standard therapy means that this difference is extrapolated over the long-term. The implications on the company's base case analysis is minimal because there is only a 1% difference between immunotherapy and standard therapy in the proportion of patients in the failure state at 5 years, as shown in Table 23. However, it will lead to a much more marked effect if there is a greater difference between treatments in the proportion of patients in the failure state at 5 years. The effect favours immunotherapy in the company's base case analysis because even though there is a greater proportion of patients in the failure state at 5 years for immunotherapy compared with standard therapy, the very high mortality rate after 5 years reduces the time that costs and health-related quality of life decrements associated with the failure health state are incurred within the model.

Figure 18 Modelled proportion of patients in the failure health state over time

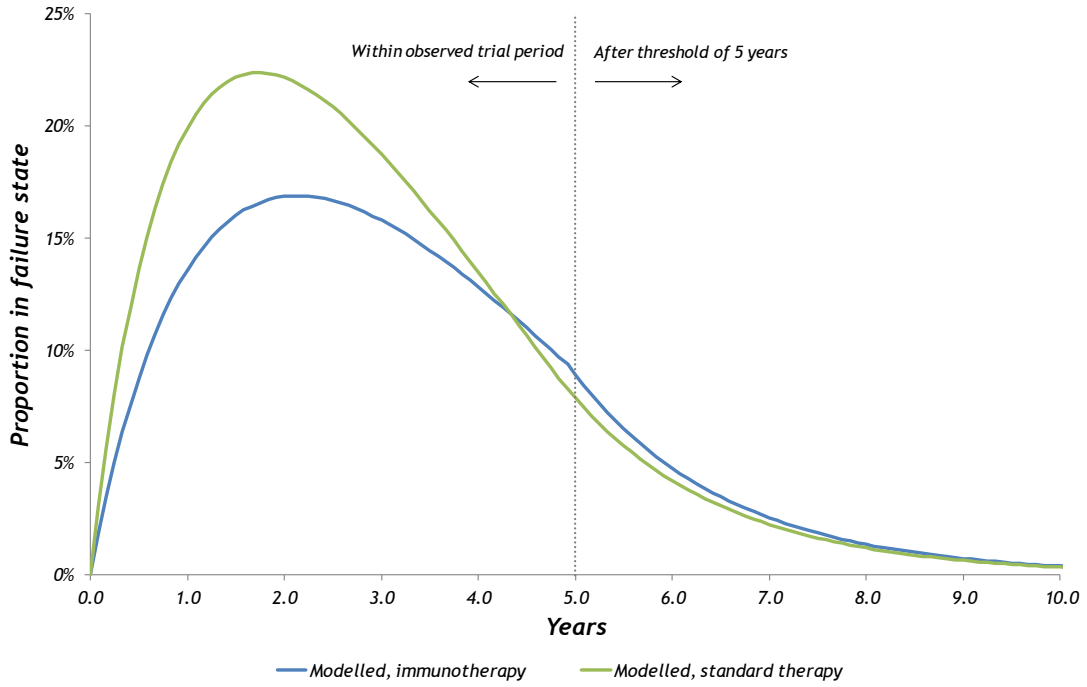


Table 23 Proportion of patients in each health state by treatment at 5 years in the company's base case analysis

Health state	Proportion of patients in health state at 5 years		
	Immunotherapy	Standard therapy	Difference
Stable	59.9%	41.0%	18.9%
Failure	8.9%	7.9%	1.0%
Death	31.2%	51.1%	19.9%

The ERG considers the use of parametric survival curves extrapolated over the long-term (beyond 5 years) would remove this concern. The extrapolation of the parametric curves would ensure that the mortality risk associated with the failure state within the trial period is consistent with the mortality risk applied beyond the observed period. This would remove the perverse change in mortality at the point of the cure threshold. Alternatively, it would seem appropriate to remove the differential treatment effect on mortality that persists beyond 5 years. This would involve applying the same fixed assumption for mortality at 5 years for patients who are event-free (stable state) and those who have had an event (failure state). This means that any differences between treatments in terms of

mortality following relapse/progressive disease is captured within the first 5 years and only the difference observed at 5 years is maintained over the long-term.

Finally, the approach used by the company to incorporate the evidence from London 2010 into the model is a simplification of the evidence presented. In the study by London 2010, progression-free survival (PFS) and OS Kaplan-Meier estimates for relapse are available over a follow-up period of 5 years. The company did not attempt to incorporate this observed time to event data into the model or reflect outcomes associated with further relapses. The ERG recognises that the incorporation of the time-dependent OS and PFS curves into the current model structure would have been difficult to implement since patients progressed to the failure state at different time points. However, this highlights the limitations of the current model structure since it only considers a single post-progression health state (failure state), which is a simplification of the treatment pathway. The model does not allow a distinction to be made between patients who remain progression-free following first relapse/ recurrence of disease from those who have subsequent further relapses (and where differences in further treatment may exist).

5.2.6.3 Updated analysis of the ANBL0032 study population

An updated analysis for 225 of the original 226 patients in the pivotal clinical trial was conducted for EFS and OS using longer-term follow-up data, analysed at 4 years after randomisation (March 2014 data cut). Of the 225 patients, only 4 crossed over to receive immunotherapy after completing standard therapy and these patients were censored at the start of immunotherapy. However, the updated analysis was only used by the company to inform a scenario analysis in the assessment of cost-effectiveness. The reason given by the company for excluding this data from the base case analysis was because the March 2014 had too few patients at 4 years follow-up to adequately detect a statistically significant difference between treatments. The ERG does not consider this a valid reason. Firstly, the number of patients at risk at 4 years in the updated analysis is comparable to the number of patients at risk at 2 years in the primary analysis. For example, in the updated analysis (March 2014) there were 66 and 48 patients at risk of EFS at 4 years for immunotherapy and standard therapy, respectively (OS: 83 and 62 patients at risk at 4 years for immunotherapy and standard therapy, respectively), while in the 2-year data analysis there were 47 and 32 patients at risk of EFS at 2 years for immunotherapy and standard therapy, respectively (OS: 59 and 51 for immunotherapy and standard therapy, respectively). Secondly, in the company's response to the ERG's points for clarification it was stated that the OS data in the primary 2-year analysis was not considered mature enough and therefore the COG and NCI amended the protocol to include a later analysis for OS post the close of randomisation. For these reasons, the ERG considers the updated March 2014 analysis of

EFS and OS as fundamental to informing the long-term survival of immunotherapy compared with standard therapy.

The company used the updated analysis of March 2014 to provide an estimate of the cost-effectiveness of dinutuximab in a scenario analysis. The implications of using the updated analysis are explored in Section 6. Figure 19 shows a comparison of the observed EFS data for the updated 4-year analysis and primary 2-year analysis, while Figure 20 shows the same comparison for the OS data. The results suggest that a cure point of 5 years is unlikely to hold since the observed data for immunotherapy and standard therapy appear to converge between 6.5 and 11 years for both EFS and OS in the updated analysis.

Figure 19 Observed EFS data for updated 4-year (March 2014) and primary 2-year (June 2009) data analysis

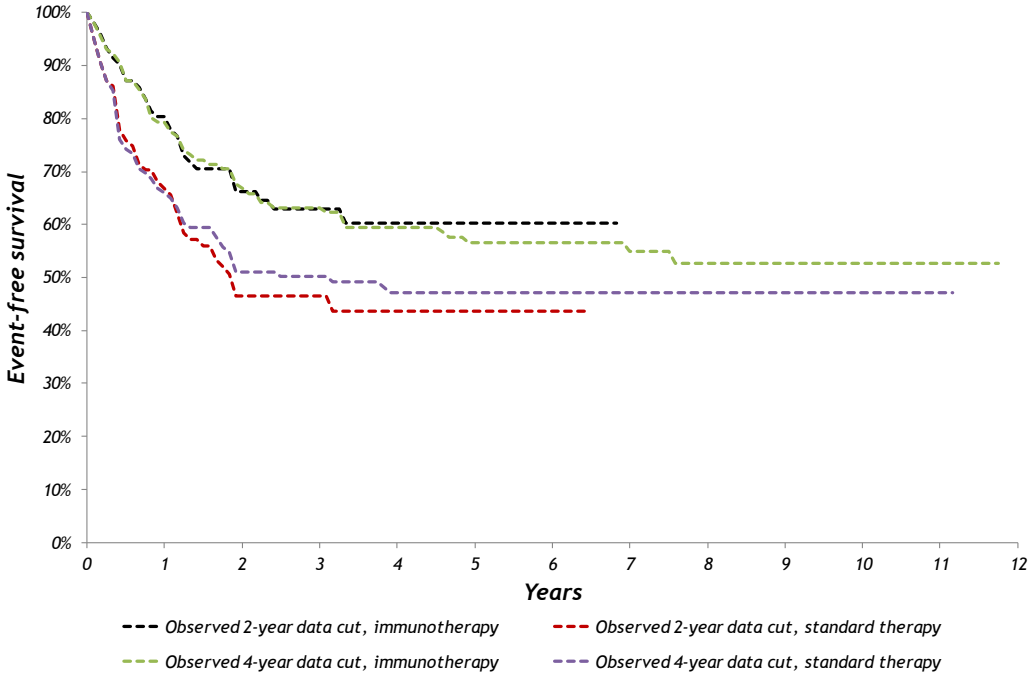
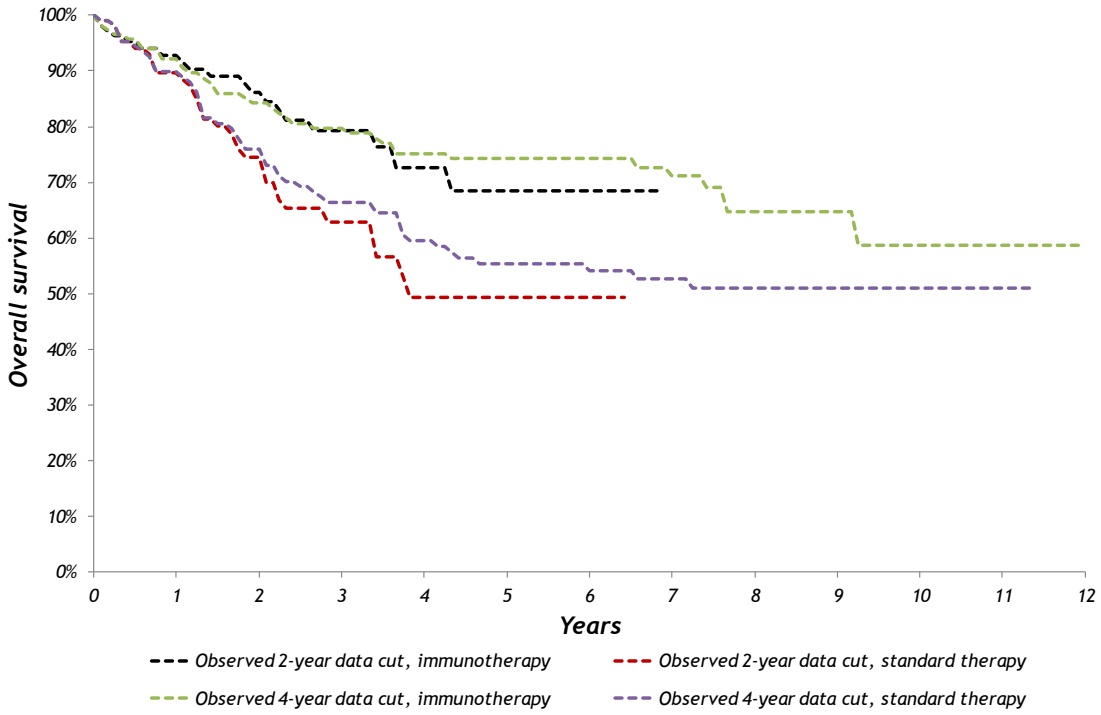


Figure 20 Observed OS data for updated 4-year (March 2014) and primary 2-year (June 2009) data analysis



5.2.7 Health-related quality of life

5.2.7.1 Source of health-related quality of life data

The pivotal clinical trial of dinutuximab [21] did not collect health-related quality of life (HRQoL) evidence from the trial participants. A systematic search of the literature was performed by the company to identify HRQoL data to inform the assessment of cost-effectiveness of dinutuximab. The search criteria involved identifying studies which reported health state-specific utilities or health utilities for survivors of neuroblastoma. The aim was to populate the stable and failure health states of the decision model with utility values and to also reflect potential differences in HRQoL of neuroblastoma survivors relative to the general population.

The systematic search undertaken by the company did not identify any studies which reported health state-specific utilities for the target population. However, by screening reference lists of full text articles, a cross-sectional study was identified [34], which measured HRQoL in survivors of tumours of the central nervous system (CNS) in childhood. Barr 1999 was a small Canadian study (sample size = 41) whose population consisted of children who had completed treatment for tumours of the CNS and who were being medically monitored by attending neuro-oncology follow-up hospital appointments. Although the study by Barr 1999 did not include neuroblastoma patients, the company considered the

study to be applicable to the target population of high-risk neuroblastoma in children and young adults. The company highlighted similarities between the populations, including: (i) study patients were children who had suffered from cancer; (ii) study patients had completed therapy; and (iii) similar health states were studied (residual disease and recurrent disease) to the ones considered in the cost-effectiveness analysis (stable and failure states). In the absence of any other health state-specific HRQoL evidence for the target population, the ERG considers these assumptions to be reasonable.

The study by Barr 1999 did not provide health utilities based on the EQ-5D as recommended by the NICE Reference Case. However, both the Guide to the Methods of Technology Appraisal [35] and the NICE Decision Support Unit Technical Support Document 8 [36] recommend the use of metrics and measures that are specifically developed for children when examining a target population of children. In Barr 1999, a 15-item self-administered questionnaire was completed with respect to each child either by a parent, healthcare professional or the child itself. The information collected from the questionnaires was converted to health status classification system attribute levels of the Health Utility Index mark 2 (HUI2) and HUI mark 3 (HUI3). The HUI [37] belongs to a family of generic preference-based systems for measuring comprehensive health status and HRQoL. By considering vision, hearing, speech, ambulation/mobility, pain, dexterity, self-care, emotion and cognition, this instrument is able to provide scores for each of these dimensions and an overall HRQoL utility value. HUI2 describes 24,000 unique health states, while HUI3 describes 972,000 unique health states. The use of HUI2 is recommended by NICE [35] as it has been developed specifically for use in children and a value set has been developed based on general population values in the UK. Additionally, the HUI2 questionnaire can be (self-) completed by children aged 8 years and over. Two other instruments exist that are suitable for use in children approximately aged 7 to 12 years, the EQ-5D-Y (Y for Youth) [38] and the Child Health Utility 9 dimension (CHU-9D) [39]. However, further empirical research is needed to assess the suitability of these latter instruments more widely. Given that Barr 1999 provided HRQoL utility values based on HUI2 and is the only available evidence, the ERG considers the health utilities estimated from this study to be suitable for the target population in the CS.

The status of the disease in Barr 1999 was categorised as "none evident", "residual" or "recurrent". The disease states of residual with a utility value of 0.81 (SE, 0.060) and recurrent with a utility value of 0.56 (SE, 0.237) were considered by the company to be representative of the stable and failure health states of the model, respectively. While no other evidence was found, the ERG considers there to be considerable uncertainty surrounding the use of these values in the model since the sample sizes from which they are derived are very small; the residual utility value was based on a sample of 10 patients and the recurrent utility value was based on a sample of 3 patients.

The systematic search undertaken by the company to identify HRQoL utility values for neuroblastoma survivors returned 5 studies [40-44]. Alessi 2007 was a small Italian study (sample size = 35), which examined HRQoL using the HUI3 questionnaire in 5-year survivors (>15 years old) from a variety of different cancers, including neuroblastoma, based on an Italian Childhood Cancer Registry. Shimoda 2008 considered HRQoL using the HUI2 and HUI3 questionnaires in cancer survivors (>13 years of age) who were at least 8 years beyond the end of active treatment, but it only recruited 2 neuroblastoma patients and was therefore excluded from the company's analysis. Three Canadian studies were identified [41-43]. All these studies considered neuroblastoma survivors, with Portwine 2014 being the one with the largest sample size (sample size = 99). Grant 2006 did not report HRQoL findings separately for neuroblastoma patients and, therefore, was excluded. Barr 2000 collected HRQoL evidence for neuroblastoma survivors using the HUI2 and HUI3 questionnaires. The company considered the Portwine 2014 population to be most relevant to the population in the dinutuximab clinical trial [21]. In addition, it represented the largest sample of neuroblastoma survivors and HRQoL estimates were collected using the HUI questionnaire (although it is not clear which version was implemented) for survivors and compared with the general population.

It is not clear to the ERG why the study by Nathan 2007[12], which was described in Section 3.1.2 of the CS to substantiate the argument that neuroblastoma has a significant impact on HRQoL of patients and their caregivers, was not considered by the company in the assessment of cost-effectiveness. Nathan 2007 assessed the HRQoL of long-term survivors of childhood neuroblastoma (sample size = 432) and Wilms tumour using the US Childhood Cancer Survivor Study registry. HRQoL estimates were obtained using the Short Form 36 Health Survey (SF-36) [45] generic instrument. Nathan 2007 present SF-36 adjusted mean dimension-level (i.e., physical functioning, role limitations due to physical health, bodily pain, general health, vitality, social functioning, role limitations due to emotional health and general mental health) scores and summary-level (i.e., physical component and mental component) scores. Using the algorithm of Rowen 2009 the dimension-level SF-36 information can be mapped onto EQ-5D index scores. The ERG performed this mapping to derive EQ-5D scores based on Nathan 2007. The ERG also used another mapping algorithm [46], which also maps SF-36 onto EQ-5D but using the SF-36 physical and mental component summary scores. Using these mapping algorithms, EQ-5D estimates of 0.658 and 0.792 were derived based on Rowen 2009 and Maund 2012, respectively. As these EQ-5D estimates are based on mapping algorithms, they have, inherently, some limitations. Nevertheless, they do provide an alternative source of utility values.

Table 24 summarises the details of the studies reporting HRQoL for neuroblastoma survivors.

Table 24 Details of the neuroblastoma survivor studies reporting health utility evidence

	Alessi 2007	Shimoda 2008	Barr 2000	Grant 2006	Portwine 2014	Nathan 2007
Country	Italy	Brazil	Canada	Canada	Canada	US
Sample size (neuroblastoma patients)	35	2	26	5	99	432
Method of elicitation and valuation	HUI3	HUI2 and HUI3	HUI2 and HUI3	HUI2 and HUI3	HUI	SF-36
Results (mean, standard deviation (sd))	0.75 (0.1-1.0) – 25th percentile and range	Not reported separately for neuroblastoma patients	HUI2 (0.90,0.13) HUI3 (0.87, 0.19)	Not reported separately for neuroblastoma patients	(0.84, 0.18)	mapped EQ-5D estimates: 0.658 (Rowen 2009, dimension-level score mapping); 0.792 (Maund 2012, summary-level score mapping)
General population (mean, sd)	N/A	N/A	Assumption: same as in Portwine 2014	Assumption: same as in Portwine 2014	General population (0.96, sd not reported)	Assumption: general population health utilities (Ara 2010) with mean age of 4 and 60% of male patients (Yu 2010)
Health utility reduction (%)	N/A	N/A	(0.96-0.90) / 0.96 = 6.25%	N/A	(0.96-0.84) / 0.96 = 12.5% (used in CS)	(0.96-0.658) / 0.96 = 31.5%; (0.96-0.792) / 0.96 = 17.5%

5.2.7.2 HRQoL values used in cost-effectiveness analysis

HRQoL utility values were assigned to the stable (pre-event) and failure (post-event) health states in the model. The health state utility estimates from Barr 1999 of 0.81 and 0.56 were used to inform the utility for the stable and failure health state, respectively, for the first 5 years in the model, i.e. up until the point of the cure threshold. After 5 years, patients in the failure state continue to experience a health utility of 0.56 [34], while patients in the stable state are assumed to follow similar characteristics to that of the general population but accounting for potential morbidities among neuroblastoma survivors.

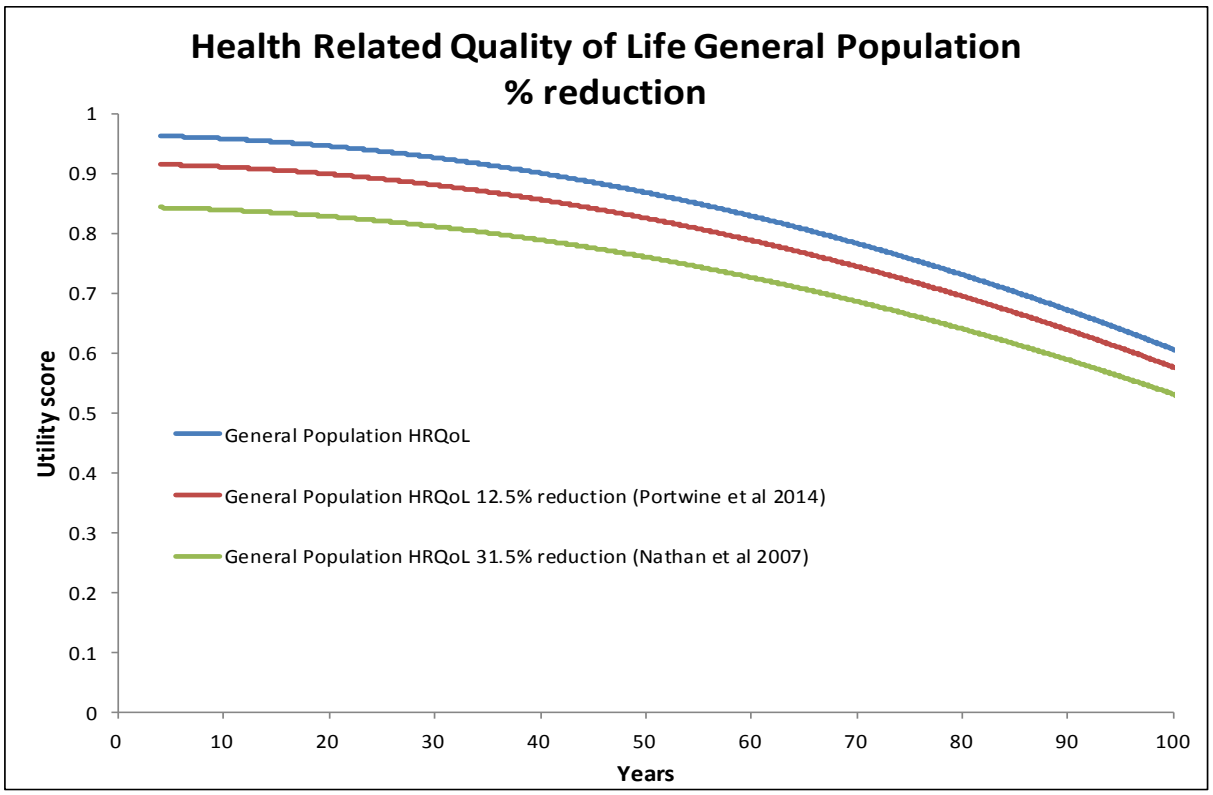
General population health utilities were calculated based on age and gender EQ-5D predicted from the model of Ara 2010:

EQ-5D = 0.9508566 + 0.0212126*male – 0.0002587*age – 0.0000332*age^2

where age and gender was based on the starting age of 4 years and 60% male in Yu 2010. To reflect potential morbidities in the stable state after 5 years, a reduction to the general population health utility estimate was applied. The company estimated a reduction of 13% ((0.96-0.84)/0.96=12.5%), based on the study of Portwine 2014.

The ERG considers this reduction in utility (relative to the general population estimate) to be potentially underestimated given the impact of neuroblastoma disease and the intense treatments received by the target population (as discussed in Section 3.1.2 of the CS). The ERG used the same approach as the company to derive an alternative estimate based on the study by Nathan 2007. By assuming that the general population average utility score of 0.96 in Portwine 2014 is generalizable to the Nathan 2007 population, a reduction of 31.5% ((0.96-0.658)/0.96=31.5%) relative to the general population is estimated. Figure 21 shows the general population HRQoL utility for different ages and a 12.5% and 31.5% reduction based on Portwine 2014 and Nathan 2007, respectively. The implication on the cost-effectiveness results of the reductions in HRQoL for neuroblastoma survivors is examined in Section 6.

Figure 21 HRQoL of the general population and % reductions for neuroblastoma survivors over time



5.2.7.3 HRQoL associated with adverse events

The impact of adverse events on HRQoL was not reported in the dinutuximab trial.[21, 47] Also, no studies were identified in the literature which reported information on the effects of adverse events on patients with neuroblastoma and their HRQoL. In the absence of information, the company used expert opinion to quantify a decrement in HRQoL attributed to adverse events associated with the administration of dinutuximab and IL-2 (mostly pain). The company assumed a utility value of 0 during the drug administration period, i.e. during cycles 1, 2, 3, 4 and 5, a health utility value of 0 was applied to the immunotherapy cohort for a duration of 4, 8, 4, 8, and 4 days (consistent with the intravenous dosing schedule), respectively. The company assumed that pain is largely responsible for the utility decrement and this is expected to decrease after subsequent courses and can be managed with pain medication. The ERG considers this utility decrement to have minimal impact on the cost-effectiveness results due to the short duration of application within the model.

5.2.8 Resource use and costs

The CS gave a detailed description of resource use and costs incurred over time. These included: drug acquisition costs, drug administration costs, concomitant medication and monitoring costs, and costs related to the health states, which include health resource use and other drug acquisition and administration costs. The company's model adopted an NHS and PSS cost perspective. To identify cost and resource use data to inform the assessment of cost-effectiveness, the company performed a systematic review of the literature for neuroblastoma patients, as described in section 5.1 of the CS. Four studies met the inclusion criteria of this review reporting a variety of cost valuations or health resource use consumption, which are presented in Table 42 of the CS.

5.2.8.1 Drug acquisition costs

Both immunotherapy and standard therapy are administered to patients over 6 cycles, which are represented in the first 6 months of the cost-effectiveness model. Table 25 presents the drug costs used in the model per monthly cycle. The dosage of each drug was determined based on the average baseline body surface area (BSA) of 0.65 m^2 obtained from the dinutuximab pivotal clinical trial (Yu 2010). Unit drug costs were obtained from the British National Formulary (BNF) with the exception of dinutuximab and GM-CSF. The per-vial cost of IL-2 was found to be £112.00, while the per-tablet cost of isotretinoin (20 mg tablet) was £0.67. The cost per-vial of dinutuximab was taken as £6,390.00, while the cost per-vial of GM-CSF was taken as £162.35. GM-CSF is not approved for marketing authorization by the EMA for any indication and is therefore not commercially available in England and Wales. The company performed a direct conversion of the GM-CSF US price of US$248.39 for a 250mcg/ml vial to GBP using an exchange rate of 0.653632 as of April 28, 2015. The ERG requested further clarification from the company on the procurement arrangements for GM-

CSF in England and Wales; the company stated that no relationship exists between them and the manufacturer of GM-CSF. However, UTC has arranged for access to GM-CSF through a third-party distributor, available through a bona fide request from the treating physician independent of UTC. Additionally, the treating physician would also be able to procure GM-CSF through their own institution's standard operating procedures from a different distributor who can provide access to the drug in England. The ERG is unable to confirm the US price of this drug or any arrangements put in place to obtain access to GM-CSF. Therefore there is a degree of uncertainty surrounding this drug price, which is used as part of the immunotherapy combination. The company performed a scenario analysis over the per-unit cost of GM-CSF and the impact on the ICER was marginal (£37,097/QALY and £37,784/QALY, assuming low and high value estimates, respectively, compared to £37,423/QALY in the company's base case results).

Table 25 Drug cost and vial/tablet used per cycle in the base case analysis

Drug	Cost per vial or tablet (£)	Vials or tablets used per cycle (calculation assumption) *	Drug cost per cycle (£)	
			Immunotherapy	Standard therapy
Isotretinoin (20 mg)	0.67	84 (round up to nearest tablet)	56.28 (cycles 1 to 6)	56.28 (cycles 1 to 6)
Dinutuximab (17.5 mg vial)	6,390.00	4 (round up to nearest full vial)	25,560.00 (cycles 1 to 5)	N/A
GM-CSF (250 mcg vial)	162.35**	14 (round up to nearest full vial)	2,272.90 (cycles 1, 3 and 5)	N/A
IL-2 ($18x10^6$ U vial)	112.00	2 (round up to nearest full vial)	224.00 (cycles 2 and 4)	N/A

* based on baseline average BSA of 0.65 (Yu 2010);

** conversion of US price to GBP

Table 26 presents the total drug costs, as well as the administration, concomitant medication and monitoring costs, per cycle in the model. The total drug cost of immunotherapy over 6 cycles is £135,404.38, of which £127,800.00 (94.4%) comes from the cost dinutuximab. In comparison, the total drug cost of standard therapy is £337.68, i.e. approximately 400 times less than the total drug cost of immunotherapy.

Table 26 Total drug, administration, concomitant medication and monitoring costs per cycle

Cycle	Total drug cost (£)		Total administration cost (£)		Total concomitant medication cost (£)		Total monitoring cost (£)	
	Immun	ST	Immun	ST	Immun	ST	Immun	ST
1	27,889.18	56.28	2,050.50	0.00	34.00	0.00	12.00	0.00
2	25,840.28	56.28	3,816.00	0.00	34.89	0.00	12.00	0.00
3	27,889.18	56.28	2,050.50	0.00	34.00	0.00	12.00	0.00
4	25,840.28	56.28	3,816.00	0.00	34.89	0.00	12.00	0.00
5	27,889.18	56.28	2,050.50	0.00	34.00	0.00	12.00	0.00
6	56.28	56.28	0.00	0.00	0.00	0.00	0.00	0.00
Total	**135,404.38**	**337.68**	**13,783.50**	**0.00**	**171.78**	**0.00**	**60.00**	**0.00**

The ERG considers the modelled drug costs as appropriate as long as all patients have a BSA below $1m^2$. The ERG requested from the company the number (percentage) of patients with a baseline BSA > $1m^2$ in the ANBL0032 study population. The company stated that 12 patients out of 249 randomised, i.e. 4.8%, had a baseline BSA > $1m^2$. Using the same rationale as the company, the ERG calculated the per-cycle number of vials or tablets needed if patients had a baseline BSA over $1m^2$ – these are presented in Table 27. The ERG then calculated a weighted average cost per cycle for each drug based on baseline BSA of patients under and above $1m^2$ (see Table 27). The updated estimate of drug costs for immunotherapy is £141,910.96 (approximately £6,500 higher than the company's base case estimate), of which £133,959.04 comes from the cost of dinutuximab. The updated total drug cost of standard therapy is £345.82 (approximately £8 higher than the company's base case estimate). The implications on the cost-effectiveness results are explored in Section 6.

Table 27 Drug cost and vial/tablet used per cycle – accounting for patients with BSA over $1m^2$

Drug	Vials or tablets used per cycle if patients ≤ $1m^2$ (calculation assumption)	Vials or tablets used per cycle if patients > $1m^2$ (calculation assumption)	Drug cost per cycle (£)	
			Immunotherapy	Standard therapy
Isotretinoin (20 mg)	84 (round up to nearest tablet)	>160mg; 9*14= 126 (round up to nearest tablet)	57.64 (cycles 1 to 6)	57.64 (cycles 1 to 6)
Dinutuximab (17.5 mg vial)	4 (round up to nearest full vial)	2*4= 8 (round up to nearest full vial)	26,791.81 (cycles 1 to 5)	N/A
GM-CSF (250 mcg vial)	14 (round up to nearest full vial)	>250mcg/day; 2*14= 28 (round up to nearest full vial)	2,382.44 (cycles 1, 3 and 5)	N/A
IL-2 ($18x10^6$ U vial)	2 (round up to nearest full vial)	>12 units= 1vial; >18 units= 2vial; 3 vials (round up to nearest full vial)	229.40 (cycles 2 and 4)	N/A

5.2.8.2 Administration, monitoring and concomitant medication costs

Isotretinoin is self-administered orally and therefore there are no administration costs associated with standard therapy in the model. The administration cost per cycle of GM-CSF is estimated to be £142.50, which is based on an assumption of 75% self-administered and 25% administered by a nurse, where nurse costs are based on PSSRU 2014. For dinutuximab and IL-2, the administration costs are based on NHS Reference Costs for procurement inpatient chemotherapy drugs for regimens in Band 10 (code SB10Z) of £1,908.00.

The ERG has an important concern that these procurement costs are not appropriate for representing administration costs for dinutuximab and IL-2. Procurement costs refer to costs associated with the drug itself. In contrast, administration costs refer to the delivery of treatment regimens, which in this case are delivered as an inpatient stay as patients are hospitalised for treatment with dinutuximab. This means that there is an important distinction between procurement costing bands and delivery of treatment regimens, which has not been recognised by the company. For chemotherapies delivered as an outpatient or day patient there are specific codes which capture the costs associated with different regimens. However, for treatments which are administered as an inpatient there is no separate delivery code. Therefore an assumption relating to the cost of an inpatient episode is required. In the absence of a delivery code for inpatient stay, the ERG considers that the best way to capture the administration cost of these drugs is to consider how long patients are hospitalised (i.e. costs associated with length of stay) rather than by using an inappropriate procurement cost as used in the company's model. Following the ERG's request for further clarification, the company provided the average number of days of hospitalisation per treatment course in the immunotherapy arm of the ANBL0032 study population (see Table 28). In addition, the company presented a scenario in response to the points for clarification, which used the number of days hospitalised to evaluate the potential cost of administration for dinutuximab. This scenario used the NHS reference costs for the delivery of complex chemotherapy (£370.84, code SB14Z), the mean cost per hospital stay (£7,743.11) and the mean length of stay (17.21 days) for an elective inpatient stay for the treatment of brain tumours or cerebral cysts with the highest complication and comorbidity level (code AA24C). The cost per hospitalised day was taken to be £7,743.11/17.21 days = £449.87. Using the average number of days hospitalised for each treatment course in Table 28, the total cost of administration for dinutuximab and IL-2 was estimated to be approximately £28,399 (now described as Scenario 1), compared to £13,356.00 used in the company's base case analysis. This higher cost of administration results in an increase in the company's base-case ICER from £37,423 to £41,959 per QALY (Scenario 1).

Table 28 Average number of days of hospitalization in the immunotherapy arm in the ANBL0032 clinical trial for each course of treatment

Course	Mean (SD) days of hospitalization
1	10 ± 5.0
2	14 ± 6.8
3	10 ± 3.3
4	14 ± 6.2
5	11 ± 6.9
6	10 ± 5.7

The ERG considers the above scenario based on hospital length of stay to be more appropriate for the administration costs of dinutuximab and IL-2 than using the inappropriate procurement costs from the CS. However, the ERG considers the NHS reference cost for the corresponding paediatric population to be more relevant to the target population. The NHS reference costs provide the cost per hospital stay (£3,169.17) and mean length of stay (3.20 days) for an elective inpatient stay for the treatment of paediatric brain tumours (with length of stay 1 day or more, CC score 1+, code PM42A), which corresponds to the company's scenario but for the paediatric population instead. Under this code, the cost per hospitalised day is estimated to be £991.92. Using the average number of days hospitalised for each treatment course in Table 28, the total cost of administration for dinutuximab and IL-2 is estimated to be approximately £60,377.2 (now described as Scenario 2). This higher cost of administration results in an increase in the company's base-case ICER from £37,423 to £49,254 per QALY gained (Scenario 2).

Table 29 summarises the administration costs for dinutuximab and IL-2 based on mean number of days hospitalised for Scenarios 1 and 2 above.

Table 29 Cost of dinutuximab and IL-2 administration

Course	Cost of administration per cycle (£) – scenario 1	Cost of administration per cycle (£) – scenario 2
1	4,870.0 (=449.87 * 10 + 370.84)	10,290.0 (=991.92 * 10 + 370.84)
2	6,669.7 (=449.87 * 14 + 370.84)	14,257.7 (=991.92 * 14 + 370.84)
3	4,870.0 (=449.87 * 10 + 370.84)	10,290.0 (=991.92 * 10 + 370.84)
4	6,669.7 (=449.87 * 14 + 370.84)	14,257.7 (=991.92 * 14 + 370.84)
5	5,320.0 (=449.87 * 11 + 370.84)	11,281.9 (=449.87 * 11 + 370.84)
Total cost	**28,399.4**	**60,377.2**

Concomitant medication was mainly used to prevent or manage pain episodes during dinutuximab administration. The total cost of concomitant medication used in the company's model was £171.78 for all 6 treatment courses, while the total cost of monitoring was £60.00. No concomitant medication or monitoring costs were considered for the standard therapy arm.

5.2.8.3 Health-state costs

The company conducted a systematic review of the literature to identify resource use and costs associated with the stable and failure health states in the model. Four studies were identified as potentially relevant. Two of the studies [48, 49] were based on data from the United States. Casillas 2011 did not report cost and resource use information specific to a neuroblastoma population and therefore was excluded. Bagatell 2014 provides preliminary results of resource use in the dinutuximab pivotal clinical trial population [21] but with limited information available only in abstract form and no health state-specific resource consumption provided. For the same reason, another study was excluded [50] due to the limited information available to inform the economic analysis. The review identified a UK study by Rebholz 2011,[14] which provides health care resource use information from the British Childhood Cancer Survivor study. This study reports neuroblastoma specific resource utilisation (i.e. visits to the doctor in the last 2 weeks, visits to the hospital as an outpatient in the last 3 months, visits to the hospital as a day patient in the last year, and visits to the hospital as an inpatient in the last year), which can be applied to patients in the stable state of the model. Monthly units of resources consumed were obtained and unit costs attached. The monthly total cost of ongoing

healthcare in the stable state was estimated to be of £59.65 (see Table 30). These ongoing costs of the stable health state were applied for the entire time horizon of the model. It is not clear to the ERG whether these ongoing costs are applicable to a lifetime horizon.

Table 30 Total monthly costs associated with the health states in the model

	Item	Monthly Units of Resources Consumed	Monthly cost (£) per item (28 day cycle)	Total monthly cost (£) (28 day cycle)
Stable state	Doctor visit	0.35	30.8	**59.65**
	Hospital visit (outpatient)	0.11	15.84	
	Hospitalised as day patient	0.01	6.98	
	Hospitalised for overnight stay	0.01	6.03	
Failure state	Drug costs			**3,683.48**
	Topotecan	~3 mg	348.73	
	Cyclophosphamide	~ 1000 mg	22.75	
	Filgrastim	~ 105 µg/day	768	
	Administration cost	-	2,544	

For the failure health state, the company used the study by London 2010 to infer that patients receive a topotecan combination of therapies following relapse in high-risk neuroblastoma. The company assumed that neuroblastoma patients in the failure health state followed the same treatment regimen used in the topotecan randomised trial, which consisted of a 21-day cycle treatment regimen of intravenous topotecan 0.75 mg/m^2/day, cyclophosphamide 250 mg/m^2/day for 5 days and filgrastim 5 µg/kg/day starting on day 6. Monthly units of resources consumed were estimated by using the average BSA and weight (i.e. 0.65m^2 and 17.7kg, respectively) from the dinutuximab pivotal clinical trial. The administration cost for the topotecan combination of therapies was assumed to be £1,908, i.e. the same as the NHS Reference Costs for procurement inpatient chemotherapy drugs for regimens in Band 10 (code SB10Z). The total monthly cost (28-day cycle) of being in the failure state was estimated to be £3,683.48 (see Table 30). In the model this cost was incurred in each monthly cycle in the failure state until death.

The ERG has a number of concerns relating to the costs associated with the failure state in the model. Firstly, it does not seem plausible that patients in the failure state receive the topotecan combination of therapies on a monthly basis for the rest of their life. The ERG requested further clarification from the company on the justification for assuming that this combination of therapies is given for the remainder of the patient's lifetime. The company stated that the protocol in the study by London 2010 called for continued treatment until disease progression or up to 1 year in patients without progression. The company added that patients in the failure state die at a rate of 5.1% per month and

therefore survive on average 14 months, which was considered sufficiently close to the maximum duration of treatment of 12 months to assume that patients in the failure state continue treatment until death. However, the ERG notes that the monthly mortality risk of 5.1% is only applied after the cure point of 5 years; therefore, patients who enter the failure state before the cure point have a different mortality rate and therefore a different average survival from 14 months. Secondly, the calculations of the monthly drug vials consumed for the topotecan combination of therapies are based on baseline BSA and weight from Yu 2010, which does not account for any growth in BSA and weight over time for a lifetime duration of treatment costs. Thirdly, the ERG does not consider the procurement cost for the administration of topotecan to be appropriate for the same reasons discussed above for dinutuximab and IL-2 administration costs. In addition, it does not reflect the monthly length of hospital stay (i.e., 5 days) required for this treatment regimen.

5.2.8.4 Costs associated with adverse events

Costs associated with adverse events were considered in the model. The list of adverse reactions was based on the toxic effects of Grade 3 or 4 events experienced by patients in the pivotal trial [21] and shown in Table 31 below. However, the ERG notes that a number of adverse events listed in Table 2 of Yu 2010 were not considered in the model; for example 18% of patients in the immunotherapy arm experienced hypotension compared with 0% in the standard therapy arm, which was not considered in the model. It is not clear to the ERG why these particular adverse events were excluded from the analysis.

The unit costs associated with the adverse events considered in the model were based on NHS Reference costs (see Table 31). The ERG has some concerns that the costs associated with particular adverse events may be underestimated. For example, the unit cost of £654 (relating to day case paediatric minor infections with CC score 2+, code PW18A, NHS Reference cost 2013/14) for an infection may be underestimated given the potential heterogeneity in the type of infection that patients may experience once hospitalised for immunotherapy. However, the ERG considers these costs to have minimal impact on the cost-effectiveness outcomes for immunotherapy.

The company estimated the total cost per cycle for adverse events to be £431.70 and £51.07 in the immunotherapy and standard therapy arms, respectively (see Table 31).

Table 31 Per-cycle cost by adverse events and per-cycle total cost of adverse events per treatment arm

Adverse events	Unit cost (£)	Reference	Cost per cycle (£) in the stable health state	
			Immunotherapy	Standard therapy
Neuropathic pain	493	NHS Ref. Cost 13/14, Consultant led outpatient attendances, WF01A, 241	57.17	4.72
Hypoxia	265	NHS Ref. Cost 13/14, Consultant led outpatient attendances, WF01A, 260	7.79	0.85
Fever without neutropenia	478	NHS Ref. Cost 13/14, Day cases, PW20A	41.38	4.58
Acute capillary leak syndrome	2,837	NHS Ref. Cost 13/14, average non-elective inpatient (long stay)	143.65	0.00
Hypersensitivity reaction	265	NHS Ref. Cost 13/14, Consultant led outpatient attendances, WF01A, 260	14.72	0.42
Urticaria	265	NHS Ref. Cost 13/14, Consultant led outpatient attendances, WF01A, 260	7.79	0.00
Infection	654	NHS Ref. Cost 13/14, Day cases, PW18A	76.91	32.38
Nausea	540	NHS Ref. Cost 13/14, Day cases, PF26B	3.53	0.86
Vomiting	540	NHS Ref. Cost 13/14, Day cases, PF26B	7.06	2.59
Diarrhea	540	NHS Ref. Cost 13/14, Day cases, PF26B	15.88	0.86
Hyponatremia	265	NHS Ref. Cost 13/14, Consultant led outpatient attendances, WF01A, 260	13.42	1.69
Hypokalaemia	265	NHS Ref. Cost 13/14, Consultant led outpatient attendances, WF01A, 260	20.78	0.85
Abnormal ALT/AST	265	NHS Ref. Cost 13/14, Day cases, GC01F	19.48	1.27
CNS cortical symptom	265	NHS Ref. Cost 13/14, Consultant led outpatient attendances, WF01A, 260	2.16	0.00
Total cost per cycle			**431.70**	**51.07**

5.2.9 Cost effectiveness results

5.2.9.1 Base case results

The company presented results for the base case analysis based on the June 2009 data cut of the ANBL0032 trial [21]. These results are presented in Table 32. The company found dinutuximab to be more costly (£139,022) but also more beneficial (gain of 3.71 QALYs) compared with standard therapy for the treatment of high-risk neuroblastoma in patients aged 12 months to 17 years who have previously received induction chemotherapy and achieved at least a partial response, followed by myeloablative therapy and ASCT. The resulting incremental cost-effectiveness ratio (ICER) is £37,423 per QALY gained.

Table 32 Company's base case results (Table 52 of the CS)

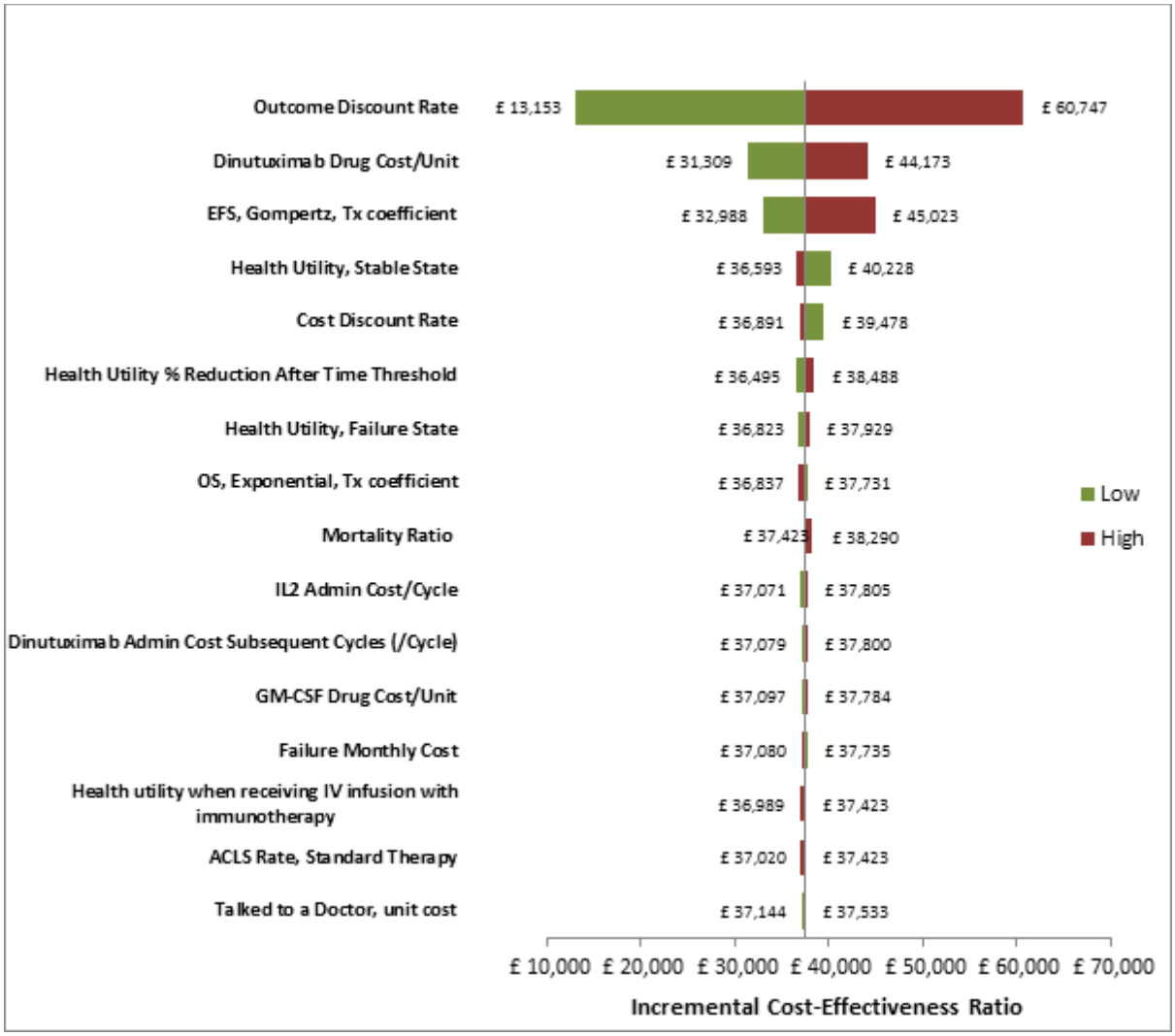
Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£) *vs* baseline (QALYs)
Standard therapy	£46,573	12.46	9.73	---	---	---	---
Immunotherapy	£185,595	17.16	13.44	£139,022	4.71	3.71	£37,423

5.2.9.2 Sensitivity analyses

Deterministic sensitivity analysis

The company presented a series of one-way deterministic sensitivity analysis to assess the impact of varying key model input parameters on the ICER. Figure 22 shows a tornado diagram of the model parameters which the company considered to have the most influence on the assessment of cost-effectiveness of immunotherapy compared with standard therapy. The model parameters were varied between upper and lower bounds presented in Table 60 of the CS. From this analysis, three model parameters were found to have the most influence: the outcome discount rate (varied from 0.0% to 6.0%; base case rate: 3.5%), the dinutuximab drug cost per vial (varied from £5,176.16 to £7,729.78; base case value: £ 6,390.00) and the EFS Gompertz parametric treatment estimates (varied from -0.664 to -0.440; base case estimate: -0.552).

Figure 22 Tornado diagram for one way deterministic sensitivity analysis (Figure 25 of the CS)



Key: ACLS – acute capillary leak syndrome; EFS – event-free survival; GM-CSF – granulocyte macrophage colony-stimulating factor; IL-2 – interleukin-2; IV – intravenous; OS – overall survival.

Probabilistic sensitivity analysis

The company performed a probabilistic sensitivity analysis (PSA) where parameters were sampled probabilistically from distributions using mean and standard error estimates outlined in Table 51 of the CS and using 1,000 simulations. The cost-effectiveness plane and acceptability curves were presented in the CS. The results from the PSA were similar to those of the deterministic analysis, as shown in Table 33. The probability that immunotherapy is cost-effective at a threshold value of £30,000 per additional QALY is 0.27 compared with standard therapy.

Table 33 Results of the company's probabilistic sensitivity analysis (Table 59 of the CS)

PSA results	Immunotherapy				Standard Therapy			
	Mean	Median	Lower 95% CI	Upper 95% CI	Mean	Median	Lower 95% CI	Upper 95% CI
Cost (£)	186,410	185,971	185,496	187,324	47,252	46,869	46,682	47,823
QALY	13.30	13.33	13.23	13.37	9.65	9.63	9.58	9.73
Mean ICER (£/QALY)	38,128							

CI – confidence interval; ICER – incremental cost-effectiveness ratio; PSA – probabilistic sensitivity analysis; QALY – quality-adjusted life-year.

5.2.9.3 Scenario analyses

The CS also included a series of scenario analyses which were performed by the company to check the robustness of the model results to uncertainty relating to survival data and structural assumptions. For example, survival data from the updated March 2014 data cut of the ANBL0032 trial were used to inform EFS and OS, alternative parametric functions for survival data, a higher reduction in health utility compared to the general population for patients in the stable state, an annual outcome discount rate of 1.5% and variations on the drug costs of GM-CSF. The results of these analyses are reported in Tables 61 to 63 (pages 136 to 140) of the CS. The large majority of the company's scenario analyses showed that the cost-effectiveness of immunotherapy compared with standard therapy is relatively insensitive to changes in the structural assumptions, with the ICERs varying from approximately £32,000 to £43,000 per QALY gained. The most favourable ICER obtained was £22,017 per QALY gained when an outcome discount rate of 1.5% was applied. The least favourable ICER obtained was £66,344 per QALY gained when the March 2014 data analysis from the pivotal trial was used to inform the EFS and OS estimates in the model (with the base case discount rate of 3.5% per annum).

From the list of scenarios undertaken by the company, the ERG considers the scenario using the March 2014 data to be the most important. This is considered further in Section 6.

5.2.10 Model validation

The company states that the cost-effectiveness model was validated with respect to its structure, calculations and predictive validity. The model structure and assumptions were reviewed by an external health economics expert. The technical accuracy of the calculations within the model was verified by the company's internal quality control processes, which entailed detailed checking of calculations and inputs, and running sensitivity analyses to ensure that any changes to the input values produced changes to the results in the expected direction and magnitude.

The company stated that a clinical expert reviewed the model with respect to its appropriateness for the disease and its treatment. Clinical experts were also consulted in relation to specific topics; for example, experts were consulted to provide their assessment about the short and long-term survival of patients with high-risk neuroblastoma (a sample of the questions presented to the clinical experts is presented in Appendix 5 of the CS). The ERG would like to have seen more validation of the structural assumptions, e.g. cure point of 5 years, by a larger group of clinical experts. The ERG would also like to have seen more validation surrounding the assumptions for the topotecan combination of therapies in the failure health state.

5.3 Summary of uncertainties and issues from the cost-effectiveness analysis

The ERG considered the company's economic submission to meet the requirements of the NICE reference case. However, the ERG identified a number of key uncertainties. The main concerns expressed by the ERG relate to the following issues:

1. *Use of earlier data (June 2009) from the pivotal trial instead of mature data (March 2014)*

   Although the earlier data cut represented the primary analysis of the pivotal trial, the COG and NCI amended the protocol to include a later analysis because the OS data in the primary analysis was not considered mature enough. The ERG considers the updated analysis to be fundamental to the assessment of clinical efficacy and cost-effectiveness of immunotherapy compared with standard therapy since it represents the most up-to-date information and provides longer follow-up evidence.

2. *Use of a cure threshold of 5 years*

   The company assumed that patients event-free at 5 years are cured and do not experience relapse at any time point in the future after 5 years. The ERG considers this a strong assumption since the updated evidence (March 2014) from the pivotal clinical trial clearly shows that further events did occur in the immunotherapy arm of the trial after 5 years. In fact, both the EFS and OS curves for immunotherapy and standard therapy appear to converge between 6.5 and 11 years suggesting that immunotherapy prolongs the time to relapse.

3. *Use of parametric modelling*

   The company used parametric modelling to inform the EFS and OS estimates used in the cost-effectiveness model. However, these parametric curves were not extrapolated beyond the trial follow-up period due to the company's use of a cure threshold at 5 years. Therefore, the ERG considers the parametric modelling within the first 5 years of the model as unnecessary.

4. General population mortality

The company assumed that patients event-free at 5 years have the same survival rate as the general population. Evidence from the Childhood Cancer Survivor Study [1] found a higher standardised mortality rate of 5.6 (95% confidence interval of 4.4 to 6.9) among neuroblastoma survivors compared to low-risk siblings without cancer. In addition, the ERG considers it unlikely that these patients would return to the same mortality risk as the general population since prior to commencing immunotherapy this patient population have already received a significant amount of chemotherapy and radiotherapy.

5. Modelling of relapse in the failure health state

The mortality risk applied within the model for relapse in the failure state within the trial period (captured within the OS curves) differs from the mortality risk that is applied after the cure threshold of 5 years (a very high monthly probability of death of 5.1% is applied after 5 years). This creates an inconsistency in how the mortality following relapse is captured within the model. It also leads to a perverse effect that there is an additional differential treatment effect on mortality that persists after the cure point due to a different proportion of patients in the failure state at 5 years for immunotherapy compared with standard therapy.

6. Health-related quality of life for the stable and failure health states

In the absence of EQ-5D data for the target population, the company used Health Utility Index data from a small Canadian study whose population consisted of children who had completed treatment for tumours of the central nervous system. While no other evidence to inform HRQoL in the target population was identified, the ERG considers there to be considerable uncertainty surrounding the utility values used in the model for the stable and failure health states, which are based on a sample size of 10 and 3 patients, respectively.

7. Reduction in health-related quality of life for survivors

The company assumed that patients event-free at 5 years follow similar characteristics to the general population, while accounting for potential morbidities through a reduction in HRQoL relative to the general population. The ERG considers the reduction in utility of 13% to be potentially underestimated given the impact of neuroblastoma disease and the intense treatments received by the target population.

8. Administration costs associated with dinutuximab, IL-2 and topotecan therapies

The company used the same procurement cost to represent the administration costs for dinutuximab, IL-2 and topotecan combination of therapies. The ERG considers there to be a distinction between procurement costing bands and delivery of treatment regimens. More

importantly, the ERG considers the administration costs of dinutuximab and IL-2 to be much higher than the administration costs for topotecan due to the additional number of days that patients are hospitalised for immunotherapy.

9. *Drug vial wastage for patients with body surface area greater than 1m^2*

The drug costs used in the model are based on the vials required for an average BSA of 0.65m^2. However, 4.8% of patients in the pivotal trial had a BSA greater than 1m^2. The ERG considers there to be greater vial wastage and therefore additional costs associated with patients with a BSA > 1m^2.

Given the importance of a number of these issues, additional analyses undertaken by the ERG are presented in Section 6, which consider the potential impact of the remaining uncertainties on the cost-effectiveness results.

6 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

6.1 Overview

This section details the ERG's further exploration of the issues and uncertainties raised in the review and critique of the company's cost-effectiveness analysis presented in Section 5. The additional work undertaken by the ERG has three main elements:

- Exploratory work by the ERG to identify the key assumptions underpinning the company's cost-effectiveness results;
- Presentation of the ERG's base case analysis;
- More detailed work exploring the robustness of the cost-effectiveness results to specific assumptions and additional uncertainties identified by the ERG.

The exploratory analysis in this section focuses on the following key issues and uncertainties:

1. Use of parametric survival curves instead of observed Kaplan-Meier data in the company's base case analysis;
2. Extrapolation of treatment benefits over a lifetime horizon;
3. Use of primary 2009 data versus updated 2014 data from the dinutuximab pivotal trial;
4. Alternative time points for the cure threshold;
5. Differential treatment effect on mortality after the cure threshold;
6. Adjustment of general population mortality;
7. Reduction in health-related quality of life;
8. Administration cost for dinutuximab;
9. Drug vial wastage for patients with body surface area $>1m^2$.

After demonstrating the uncertainty that surrounds the company's base-case results, the impact of these various assumptions on the ICER is presented.

6.2 Exploratory work by the ERG to identify the key assumptions underpinning the company's cost-effectiveness results

Although the company undertook a detailed series of univariate sensitivity and scenario analyses, the ERG considered that it was difficult to establish the impact of particular assumptions (e.g. cured at 5 years for patients event-free) based on the evidence submitted by the company. Therefore, the ERG first undertook exploratory work to identify the key assumptions underpinning the company's cost-

effectiveness results. These assumptions were then subject to additional scrutiny and further re-analysis by the ERG. The results are outlined below.

6.2.1 Use of parametric survival curves in the company's base case analysis

As discussed in Section 5.2.6, the company fitted parametric survival curves to observed Kaplan-Meier data on EFS and OS to estimate the number of patients in each health state within the first 5 years of the model, i.e. within the observed period of trial follow-up for the 2-year data cut of the ANBL0032 study population. However, these parametric survival curves were not extrapolated to the period after 5 years since the company assumed that the event-free cohort in the model is cured and starts to follow similar characteristics to that of the general population. Under the assumption of a cure point of 5 years, the ERG considers the use of parametric modelling within the observed trial period as redundant. The ERG believes that the use of the observed Kaplan-Meier data within the trial period would be more appropriate since the empirical data for each treatment arm provides the full distribution of survival within the first 5 years of the model and reflects the actual treatment effect that is observed in the trial. The use of observed Kaplan-Meier data also avoids the need to make the assumption of proportional hazards between the two treatment arms and overcomes the issue of choosing between alternative parametric models (e.g. exponential, Weibull, Gompertz, log-logistic and log-normal), which can lead to different estimates of the ICER. A comparison of the company's parametric fit to the observed Kaplan-Meier data up to 5 years is presented in Figure 14 and Figure 15 of Section 5.2.6 for EFS and OS, respectively.

Table 34 shows the implications of using the observed Kaplan-Meier data rather than the parametric survival curves on the estimate of cost-effectiveness (with all other assumptions the same as the company's base case analysis). The resulting impact on the ICER is to increase it from £37,423 to £41,671 per QALY gained. This difference in the ICER is driven by both a reduction in the costs of standard therapy and by an increase in the total QALYs associated with standard therapy. In order to understand this difference further, the ERG examined the fit of the parametric curves to the observed data within the trial period and the proportion of patients in each health state at the cure point of 5 years. The parametric fit to the observed data appears reasonable for both EFS and OS.

Table 34 Cost-effectiveness results for the use of observed Kaplan-Meier data in the company's base case analysis

	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Company's base case – use of parametric survival curves					
Standard therapy	£46,573	9.73	-	-	-
Immunotherapy	£185,595	13.44	£139,022	3.71	£37,423
ERG scenario – use of observed Kaplan-Meier data					
Standard therapy	£44,583	10.08	-	-	-
Immunotherapy	£185,642	13.47	£141,059	3.39	£41,671

Table 35 shows the proportion of patients in each health state at 5 years for the company's base case analysis and the ERG's scenario using observed Kaplan-Meier data. It shows that the difference between treatments in terms of event-free survival at 5 years is smaller for the observed Kaplan-Meier data (16.8%) compared with the parametric modelling (18.8%). This small difference is extrapolated over a lifetime horizon (due to the cure assumption at 5 years) which results in lower lifetime benefits for immunotherapy compared with standard therapy, i.e. the greater proportion of patients in the stable health state for standard therapy is extrapolated over a lifetime and is largely responsible for the decrease in incremental QALYs of 0.32 (=3.71-3.39) QALYs in Table 34. The OS for standard therapy is also slightly higher for the observed data compared with the parametric modelling which (together with EFS) means that there is a higher difference between treatments in the proportion of patients in the failure state at 5 years for the observed data (2.3% for Kaplan-Meier data versus 1% for parametric modelling). This results in higher incremental costs over a lifetime for immunotherapy compared with standard therapy since patients who fail treatment are assumed to receive topotecan combination of therapy for the rest of their lifetime; however, these patients are also assumed to have a higher monthly mortality rate of 5.1% compared with the mortality rate of the general population, which means that the additional costs associated with topotecan are not accrued for very long in the model.

The results highlight how sensitive the cost-effectiveness of immunotherapy is to the differences in survival between treatments at the point of the cure threshold. This reflects the fact that these differences are extrapolated over a lifetime horizon (i.e. maintained for the remainder of the child's lifetime), which means that the survival benefits of treatment observed at the time point of 5 years are given much greater weight in the estimate of cost-effectiveness than the survival benefits observed at any other time point within the trial period. In the next section, the ERG considers the implications of a reduction in the time horizon of the extrapolated benefits.

Table 35 Proportion of patients in each health state at 5 years for the company's base case analysis and the ERG's scenario using observed Kaplan-Meier data

Health state	Company base case – parametric curves			ERG scenario – Kaplan-Meier data		
	Immuno-therapy	Standard therapy	Difference	Immuno-therapy	Standard therapy	Difference
Stable	59.9%	41.0%	18.9%	60.3%	43.5%	16.8%
Failure	8.9%	7.9%	1.0%	8.1%	5.8%	2.3%
Death	31.2%	51.1%	19.9%	31.6%	50.7%	19.0%

6.2.2 Extrapolation of treatment benefits over a lifetime horizon

The previous section highlighted how sensitive the cost-effectiveness results are to the survival observed at the cure point of 5 years and to the extrapolation of differences between treatments over a lifetime horizon. In this section, the ERG considers a reduction in the time horizon of the extrapolated benefits. A worst case scenario is presented where the survival observed within the trial period is only maintained for the duration of the trial follow-up, i.e. 5 years. Time horizons of 10, 15 and 20 years are then presented where the shorter time horizons are assumed to be sufficient to capture the relevant differences in costs and outcomes between immunotherapy and standard therapy.

Table 36 shows the implications on the cost-effectiveness results of using a shorter time horizon. In all scenarios the reduction in time horizon is applied to the company's base case analysis which uses parametric modelling for survival. The results show the substantial gain in incremental QALYs for immunotherapy relative to standard therapy when the benefits are maintained over a lifetime (3.71 QALYs) compared with the benefits maintained for a shorter duration of 20 years (1.95 QALYs), 15 years (1.53 QALYs), 10 years (1.03 QALYs) or 5 years (0.41 QALYs).

Table 36 Cost-effectiveness results for shorter time horizons in the company's base case analysis

	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Company's base case – Lifetime horizon (best case scenario)					
Standard therapy	£46,573	9.73	-	-	-
Immunotherapy	£185,595	13.44	£139,022	3.71	£37,423
ERG scenario – Time horizon of 5 years (worst case scenario)					
Standard therapy	£35,681	2.49	-	-	-
Immunotherapy	£171,149	2.91	£135,468	0.41	£326,844
ERG scenario – Time horizon of 10 years					
Standard therapy	£41,069	3.86	-	-	-
Immunotherapy	£177,620	4.89	£136,551	1.03	£133,016
ERG scenario – Time horizon of 15 years					
Standard therapy	£42,179	4.97	-	-	-
Immunotherapy	£179,188	6.50	£137,009	1.53	£89,392
ERG scenario – Time horizon of 20 years					
Standard therapy	£42,987	5.89	-	-	-
Immunotherapy	£180,366	7.84	£137,378	1.95	£70,288

6.2.3 Use of primary 2009 versus updated 2014 data from trial ANBL0032

The company used the June 2009 data cut of the ANBL0032 clinical trial to inform EFS and OS in the base case analysis. The updated analysis from March 2014 was only used to inform a scenario analysis. The ERG considers the March 2014 data cut as providing the most relevant and up-to-date estimates of EFS and OS in this patient population. In particular, in the company's response to the ERG's points for clarification it states that the COG and NCI amended the protocol of the trial to include a later analysis for OS post the close of randomisation since the OS data in the original 2009 analysis was not considered mature enough. Therefore the ERG considers the company's scenario analysis to be a more accurate reflection of the cost-effectiveness of immunotherapy rather than the base case analysis.

Figure 19 and Figure 20 of Section 5.2.6.3 shows a comparison of EFS and OS for the updated 2014 analysis compared with the 2009 data analysis, respectively. Table 37 shows the corresponding implications on the estimates of cost-effectiveness for the 2009 and 2014 analysis, with the same model assumptions, e.g. cure threshold of 5 years. The impact on the ICER of using the updated

analysis (company's scenario analysis) is to increase it from £37,423 to £66,344 per QALY gained. The CS provides limited details (Appendix 10) about the assumptions underpinning this difference in cost-effectiveness. Therefore the ERG explored this further by examining a comparison of the modelled 2014 analysis with the modelled 2009 analysis and the observed March 2014 Kaplan-Meier data.

Table 37 Cost-effectiveness results for the June 2009 and March 2014 analysis in the company's base case and scenario analysis, respectively

	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Company's base case – June 2009 data					
Standard therapy	£46,573	9.73	-	-	-
Immunotherapy	£185,595	13.44	£139,022	3.71	£37,423
Company's scenario – March 2014 data					
Standard therapy	£47,213	10.87	-	-	-
Immunotherapy	£192,744	13.06	£145,531	2.19	£66,344

Figure 23 shows the EFS estimates for the treatment arms under the three comparisons and

Figure 24 shows the same for the OS estimates. It is clear from the figures that the difference in the ICER is driven by a much smaller difference between treatments in EFS and OS at the cure point of 5 years in the modelled March 2014 analysis (EFS, 10.9%; OS, 14.3%) compared with the modelled June 2009 analysis (EFS, 18.9%; OS, 19.9%). This difference is then extrapolated over a lifetime horizon and results in a reduction in total incremental QALYs for immunotherapy compared with standard therapy of 1.52 QALYs for the March 2014 data cut compared with the June 2009 data cut.

Figure 23 Modelled March 2014 (4-year) EFS data in the company's scenario analysis relative to the modelled June 2009 (2-year) data in the base case analysis and the observed March 2014 (4-year) Kaplan-Meier data

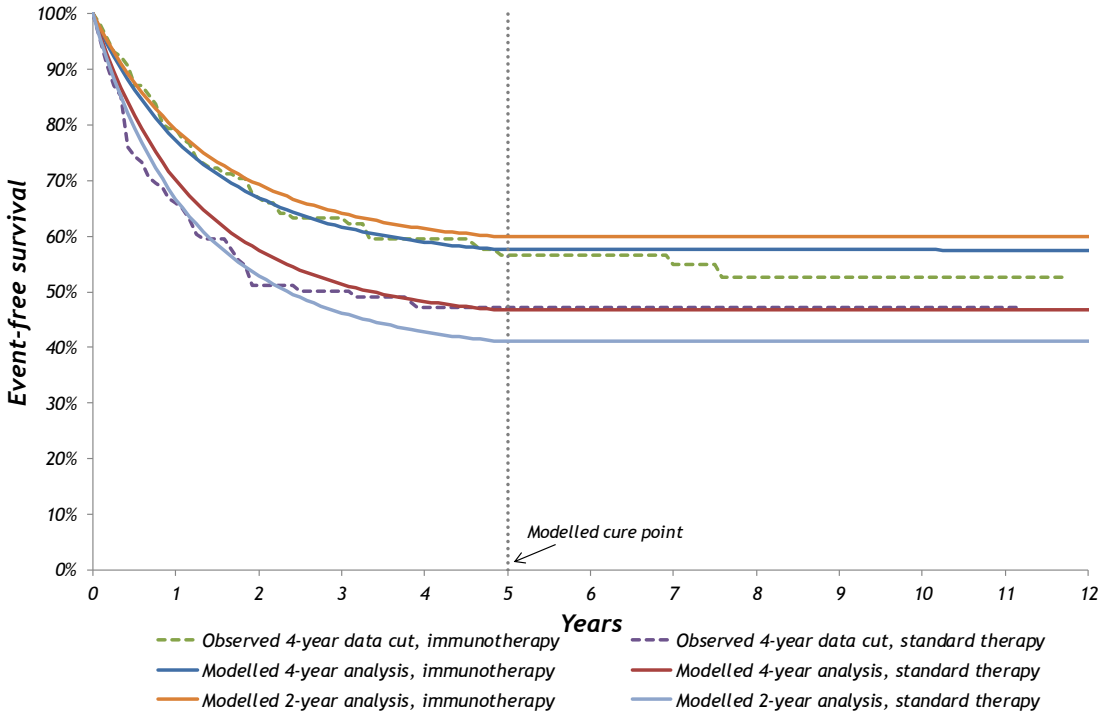


Figure 24 Modelled March 2014 (4-year) OS data in the company's scenario analysis relative to the modelled June 2009 (2-year) data in the base case analysis and the observed March 2014 (4-year) Kaplan-Meier data

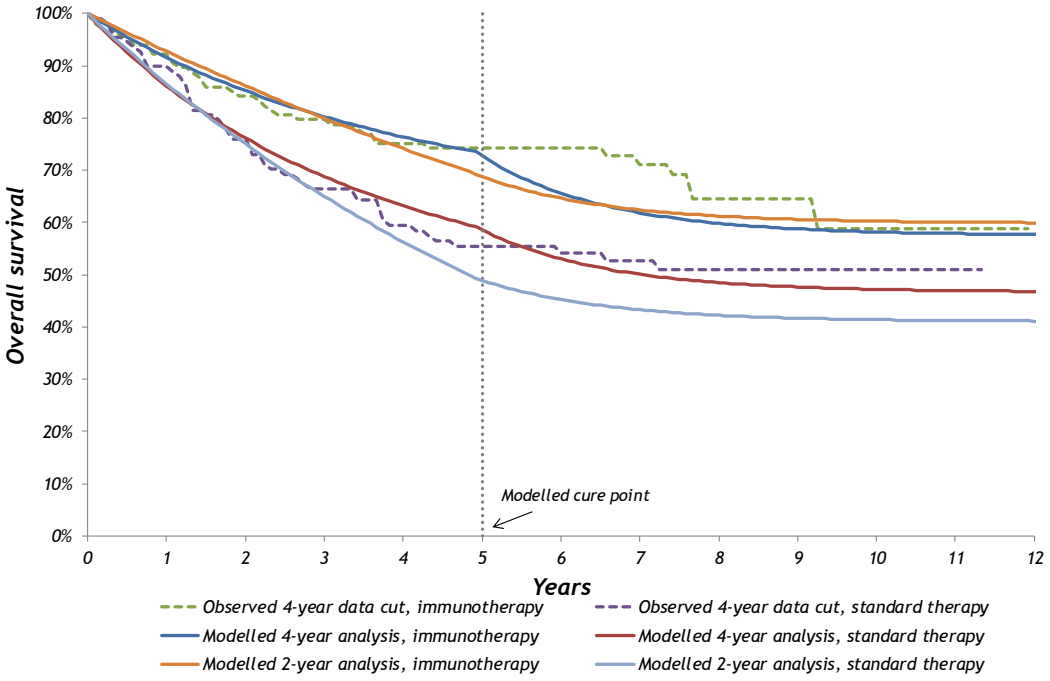


Figure 23 and

Figure **24** highlight two further issues with the company's analyses. Firstly, the company's modelling of the observed 2014 Kaplan-Meier data is a poor fit over the entire follow-up period. The company fitted a single parametric function (Gompertz) to the 2014 data assuming proportional hazards but with a cure threshold of 5 years. Secondly, the observed Kaplan-Meier curves for immunotherapy and standard therapy appear to converge for both EFS and OS between 6.5 and 11 years. Therefore the assumption of a cure threshold of 5 years does not hold in the 2014 analysis. The implications of this assumption is that the treatment differences observed in the parametric modelling at the 5 year time point (i.e. EFS, 10.9%; OS, 14.3%) are maintained over a lifetime horizon when it is clear from the figures that these differences neither match the observed differences at 5 years (EFS, 9.5%; OS, 18.8%) nor take account of the observed follow-up data that extends beyond 10 years (EFS at 10 years, 5.6%; OS at 10 years, 7.7%).

In Section 6.3, the ERG presents their preferred base case analysis which uses the observed March 2014 Kaplan-Meier data with a cure threshold of 10 years.

6.2.4 Summary of the key assumptions underpinning the company's cost-effectiveness results

Based on the evidence submitted by the company, the key assumptions underpinning the results of the cost-effectiveness analysis can be summarised as follows:

- Parametric survival functions fitted to observed Kaplan-Meier data that are not subsequently used to extrapolate benefits beyond the trial follow-up period. The ERG notes that very small differences in the parametric modelling at the time point of 5 years leads to significant differences in total QALYs between treatments because the small differences are maintained over a lifetime horizon.
- Extrapolation of treatment benefits over a lifetime. A shorter time horizon leads to a significant reduction in the total incremental QALYs for immunotherapy compared with standard therapy.
- Analysis based on the latest March 2014 data cut of the pivotal trial. OS data in the original June 2009 analysis was not considered mature by the COG and NCI.
- Cure threshold of 5 years. The observed Kaplan-Meier data for immunotherapy and standard therapy appears to converge for both EFS and OS between 6.5 and 11 years. Therefore a cure threshold of 5 years misrepresents the survival associated with immunotherapy and standard therapy.

6.3 ERG's base case analysis

In this section, the ERG presents their preferred base case analysis. The ERG believes that the March 2014 data cut of the pivotal trial represents the most relevant estimates of EFS and OS. The ERG does not consider the argument that the March 2014 data cut had too few patients to adequately detect a statistically significant difference between treatments as a sufficient basis for excluding the longer follow-up data. As discussed in Section 5.2.6.3, the updated analysis had equally as many patients at risk of an event at 4 years as the analysis from the 2-year data cut at 2 years. Furthermore, the COG and NCI amended the protocol to include this later data analysis since OS in the primary June 2009 analysis was not mature enough. Furthermore, the latest data analysis was presented to the EMA for obtaining regulatory approval for dinutuximab. Therefore, the March 2014 data cut is used in the ERG's base case analysis.

The ERG's base case uses the observed Kaplan-Meier data for the assessment of cost-effectiveness since it avoids the need to make the proportional hazards assumption and reflects the actual treatment effect observed in the trial. A cure threshold of 10 years is also used in the ERG's base case analysis since the observed evidence for EFS and OS suggests that the immunotherapy and standard therapy curves converge between 6.5 and 11 years. In the next section, the results of the ERG's base case analysis are presented and the implications of the alternative cure time point is discussed.

6.3.1 ERG's base case results for a cure threshold of 10 years

Table 38 presents the ERG's base case results using the March 2014 Kaplan-Meier data and a cure threshold of 10 years. The table also presents a scenario which uses a cure threshold of 5 years in order to explore the implications of the company's assumption of 5 years. The use of the Kaplan-Meier data increases the ICER from £66,344 per additional QALY in the company's scenario analysis which uses parametric modelling to £70,296 per additional QALY in the ERG's scenario with the same cure point of 5 years. Of more interest is the change in the ICER from £70,296 to £99,699 per additional QALY for an increase in the cure threshold from 5 to10 years. This difference results from a reduction in the total incremental QALYs for immunotherapy compared with standard therapy and an increase in the incremental costs. The largest proportion of the ICER is driven by the extrapolation of survival that is reached at the cure point over a lifetime horizon.

Table 39 shows the proportion of patients in each health state at the cure points of 5 and 10 years. The difference between treatments in EFS at 10 years (5.6%) is much smaller than the difference observed at 5 years (9.6%). The same is also true for OS, where the difference between treatments in

the proportion of patients in the death state is 7.7% at 10 years and 18.8% at 5 years. These differences give rise to a smaller difference between treatments in the proportion of patients in the failure state at 10 years. It should be noted that although there is a higher proportion of patients in the failure state at 5 years for immunotherapy compared with standard therapy, this higher proportion has limited effect on the ICER because patients in the failure state are assumed to have a high monthly mortality rate of 5.1%, which means that any additional costs associated with topotecan combination of therapy are not accrued for very long in the model.

Table 38 ERG's base case results

	Total costs	**Total QALYs**	**Incremental costs**	**Incremental QALYs**	**ICER (£/QALY)**
ERG's base case – Cure threshold of 10 years					
Standard therapy	£54,671	10.90	-	-	-
Immunotherapy	£208,435	12.44	£153,765	1.54	£99,699
ERG's scenario – Cure threshold of 5 years					
Standard therapy	£48,079	10.85	-	-	-
Immunotherapy	£192,165	12.90	£144,086	2.05	£70,296

Table 39 Proportion of patients in each health state at a cure threshold of 5 and 10 years for the ERG's base case analysis

Health state	Cure threshold at 5 years			Cure threshold at 10 years		
	Immuno-therapy	Standard therapy	Difference	Immuno-therapy	Standard therapy	Difference
Stable	56.7%	47.1%	9.6%	52.7%	47.1%	5.6%
Failure	17.5%	8.3%	9.2%	6.0%	3.9%	2.1%
Death	25.8%	44.6%	18.8%	41.3%	49.0%	7.7%

6.3.2 Parametric models

The ERG considers the Kaplan-Meier data to be most relevant to the assessment of cost-effectiveness since it avoids the need to make the proportional hazards assumption and reflects the actual treatment effect observed in the trial. Moreover, since the estimates of survival are not extrapolated beyond the trial follow-up period the use of parametric modelling seems redundant. However, the ERG has examined parametric survival models assuming proportional hazards (see Section 4.4). The parametric model that represented the best fit to the data was the Weibull cure fraction model, which

assumes that there are a proportion of individuals who are "cured" (i.e. never experience the event and thus the survival curve will eventually reach a plateau for these individuals) and an "uncured" fraction of individuals who have survival times that are described by a Weibull distribution. The ERG also considered a more weakly structured, flexible model of Royston and Parmar. The Royston-Parmar spline based model [51] splits the data at different time points into a series of piecewise polynomials which is less restrictive than applying a single parametric function over time. The ERG fitted the Royston-Parmar spline based function to each treatment arm separately, removing the assumption of proportional hazards.

Figure 25 and Figure 26 show the visual fit of the Weibull cure fraction and Royston-Parmar models to EFS and OS, respectively. Table 40 shows the corresponding impact on the cost-effectiveness results. Both the Weibull cure fraction model and the Royston-Parmar fitted to each treatment arm separately produce similar results to the ERG's base case analysis.

Table 40 ERG scenarios using parametric modelling up to a cure threshold of 10 years

	Total costs	**Total QALYs**	**Incremental costs**	**Incremental QALYs**	**ICER (£/QALY)**
ERG's base case – Observed Kaplan-Meier data (cure threshold, 10 years)					
Standard therapy	£54,671	10.90	-	-	-
Immunotherapy	£208,435	12.44	£153,765	1.54	£99,699
ERG's scenario – Weibull cure fraction model (cure threshold, 10 years)					
Standard therapy	£52,914	11.08	-	-	-
Immunotherapy	£217,392	12.72	£164,478	1.64	£100,250
ERG's scenario – Royston-Parmar fitted to treatment arms separately (cure threshold, 10 years)					
Standard therapy	£53,717	10.90	-	-	-
Immunotherapy	£216,180	12.54	£162,463	1.64	£99,083

Figure 25 Weibull cure fraction and Royston-Parmar models of EFS

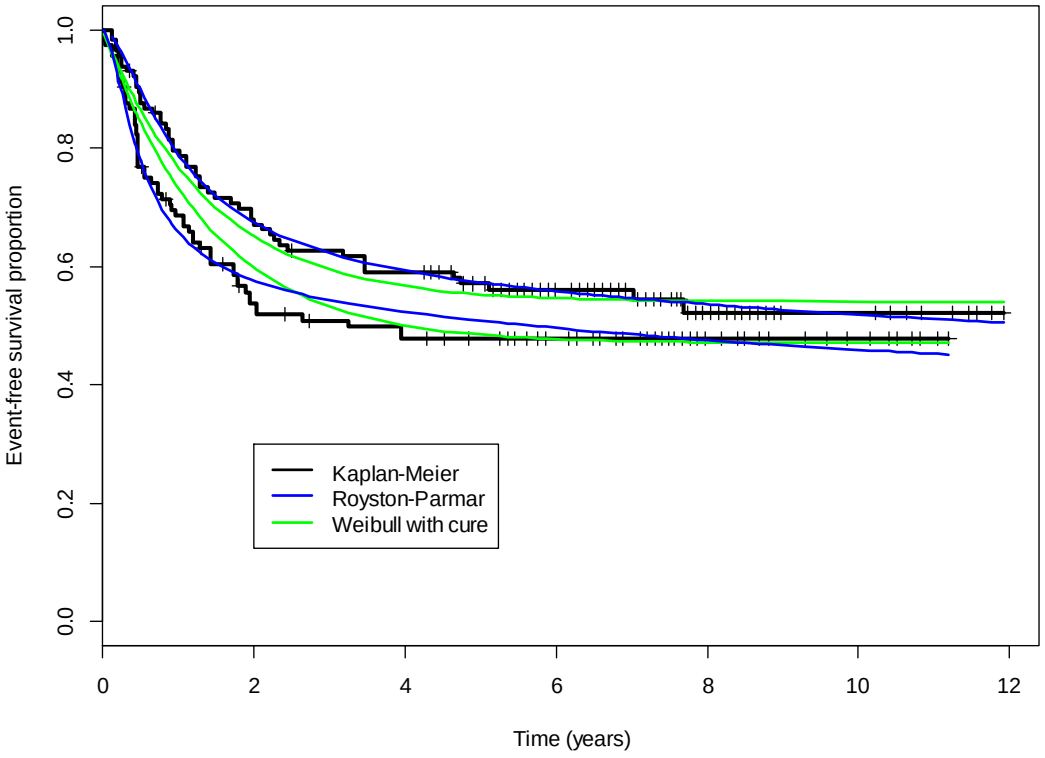
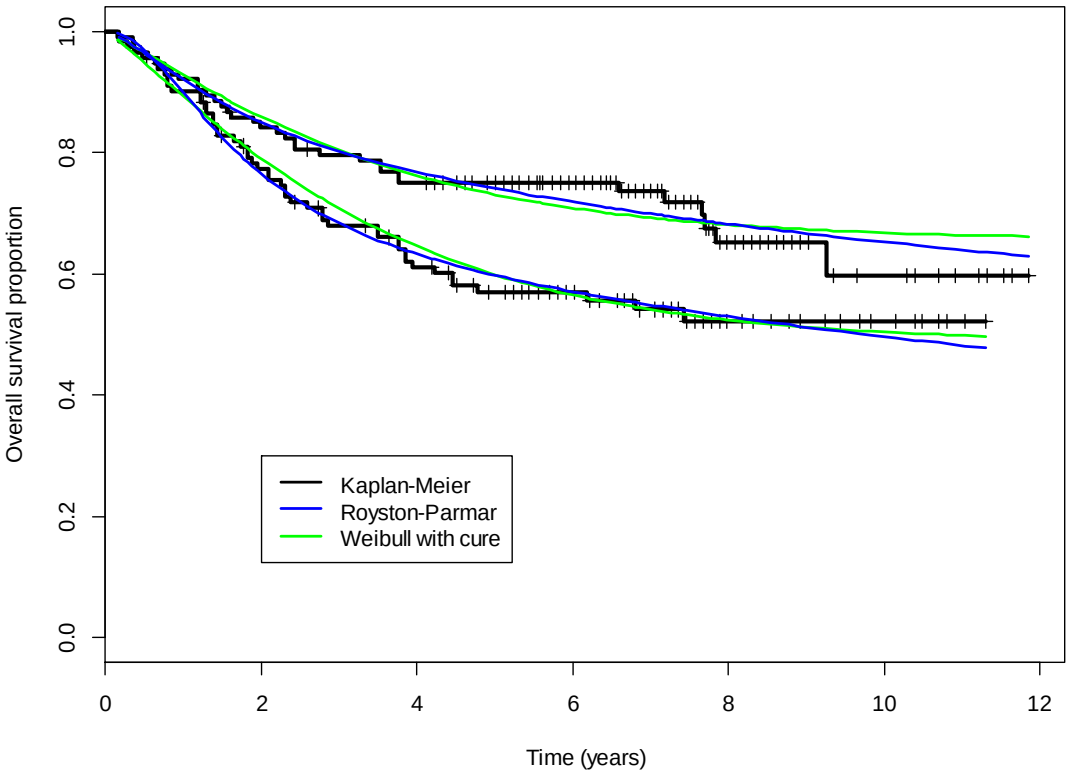


Figure 26 Weibull cure fraction and Royston-Parmar models of OS



6.4 More detailed work exploring the robustness of the cost-effectiveness results to specific assumptions and additional uncertainties identified by the ERG

During the critique of the CS in Section 5, the ERG identified a number of specific assumptions applied within the model that gives rise to additional uncertainty in the estimate of cost-effectiveness. These are explored below with application to the ERG's base case analysis.

6.4.1 Differential treatment effect on mortality after the cure threshold

In Section 5.2.5.2 the ERG identified an important structural concern with the company's model where an additional differential treatment effect on mortality is assumed beyond the cure threshold. The company assumes that patients who experience a failure event after the cure point have a very high monthly probability of death of 5.1%, while the mortality of those who experience a failure event within the trial follow-up period is captured within the OS estimates for immunotherapy and standard therapy. This creates an inconsistency in how the mortality of the failure state is captured within the model. One way to remove this concern would be to extrapolate the parametric survival curves over the long-term (beyond the cure threshold) in order to ensure that the mortality risk associated with the failure state within the trial period is consistent with the mortality risk applied beyond the observed period. However, all of the parametric curves extrapolated beyond the cure threshold require a switch to the general population mortality at some point in time due to the flattening of both the immunotherapy and standard therapy curves for EFS and OS at about 10 years (otherwise the extrapolation implies that patients live forever). In addition, the extrapolation beyond the cure threshold eventually leads to infeasible values in the model where EFS becomes greater than OS. Therefore, the ERG was unable to extrapolate the parametric curves without the need to incorporate a cure threshold at some point in time.

A second way to remove the concern that there is an additional differential treatment effect on mortality beyond the trial period is to apply the same fixed mortality assumption at the point of the cure threshold for patients who are event-free (stable state) and those who have had an event (failure state). This means that any difference between treatments in terms of mortality after relapse/progressive disease is captured within the trial follow-up period and only the difference observed at the point of the cure threshold is maintained over the long-term. Therefore, the ERG examined a scenario where all survivors (patients in the stable and failure health states) are assumed to have the same fixed mortality equivalent to that of the general population beyond the cure threshold of 10 years.

Table 41 shows the implications on the cost-effectiveness results of assuming the same fixed mortality for all survivors after the cure point of 10 years. The impact on the ICER is minimal by reducing it from £99,699 to £97,265 per additional QALY. However, the impact of this assumption

on total costs and QALYs is significant. The company assumes that upon treatment failure patients in the model receive topotecan combination of therapies on a monthly basis until death. Therefore the assessment of cost-effectiveness depends on the balance between costs and effects for survival gains in the failure health state and cumulative long-term treatment costs associated with receiving topotecan therapies over a lifetime. Under the fixed mortality assumption, patients in the failure health state at 10 years are now assumed to live considerably longer (i.e. the mortality rate of 5.1% is not applied), but as a consequence of living longer these patients now incur considerably more costs associated with topotecan therapies over a lifetime. The ERG does not consider this scenario a very realistic assumption (i.e. that patients in the failure health state have the same mortality as patients in the stable state) but it is used to highlight an important structural concern within the company's model.

Table 41 ERG scenario using the same fixed mortality for all survivors beyond the cure threshold of 10 years

	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
ERG's base case – Company's assumption of differential effect on mortality after 10 years					
Standard therapy	£54,671	10.90	-	-	-
Immunotherapy	£208,435	12.44	£153,765	1.54	£99,699
ERG's scenario – Fixed treatment effect on mortality after 10 years					
Standard therapy	£84,346	11.27	-	-	-
Immunotherapy	£254,276	13.02	£169,930	1.75	£97,265

6.4.2 Adjustment of general population mortality

The company assumes that patients event-free at the point of the cure threshold do not experience further risk of relapse and start to follow similar characteristics to that of the general population. Therefore, a general population age-specific mortality rate is applied to patients in the stable state at the point of the cure threshold. In Section 2.2 the ERG identified a number of studies which suggest that the mortality risk for survivors of high-risk neuroblastoma is much greater than that of the general population. For example, the Childhood Cancer Survivor Study [1] found a higher standardised mortality rate of 5.6 (95% confidence interval of 4.4 to 6.9) among neuroblastoma survivors compared to low-risk siblings without cancer. Therefore, the ERG examined a scenario where the mortality risk was increased to 5.6 times that of the general population and a second scenario where a 10-fold excess mortality risk was applied.

Table 42 shows the impact on the cost-effectiveness results of an adjustment to the general population mortality for patients event-free in the model. A standardised mortality rate (SMR) of 5.6 increases the ICER from £99,699 to £105,160 per additional QALY, while a SMR of 10.0 increases the ICER to £108,378 per additional QALY. The increase in the ICER is driven by a reduction in the life years gained over a lifetime horizon for patients event-free on immunotherapy compared with standard therapy at the cure point of 10 years.

Table 42 ERG scenarios for a general population mortality adjustment for event-free survivors

	Total costs	**Total QALYs**	**Incremental costs**	**Incremental QALYs**	**ICER (£/QALY)**
ERG's base case – Company's assumption of same mortality as the general population					
Standard therapy	£54,671	10.90	-	-	-
Immunotherapy	£208,435	12.44	£153,765	1.54	£99,699
ERG's scenario – Standardised mortality rate of 5.6 for event-free survivors					
Standard therapy	£53,976	10.21	-	-	-
Immunotherapy	£207,658	11.68	£153,683	1.46	£105,160
ERG's scenario – Standardised mortality rate of 10.0 for event-free survivors					
Standard therapy	£53,618	9.84	-	-	-
Immunotherapy	£207,258	11.26	£153,640	1.42	£108,378

6.4.3 Reduction in health-related quality of life

As discussed in Section 5.2.7.2, the company used evidence from Portwine 2014 to incorporate a decrement in HRQoL of 13% compared to the general population for patients event-free at the point of the cure threshold. The ERG considers this reduction in utility to be potentially underestimated as survivors from childhood neuroblastoma are likely to have been exposed to intensive and aggressive treatment regimens [8] with clear long-term effects on morbidity and quality of life (as described in Section 3.1.2 of the CS).

The company performed a scenario analysis where the impact of a more aggressive reduction in health utility was evaluated by doubling the reduction to 26%. The ERG used evidence from Nathan 2007 to obtain a more substantiated alternative estimate of the reduction in HRQoL relative to the general population. This resulted in a 31.5% reduction for neuroblastoma survivors. Figure 21 in Section 5.2.7.2 shows the impact of these reductions relative to the general population values.

Table 43 shows the implications on the estimate of cost-effectiveness of reductions of 26% and 31.5% in HRQoL values relative to the general population for event-free survivors (with all other assumptions the same as the ERG's base case analysis). The resulting impact on the ICER is an increase from £99,699 to £108,070 per QALY gained for a 26% reduction and to £112,051 per QALY gained for a 31.5% reduction. The increase in the ICER is driven by a reduction in total QALYs for both treatments but the incremental QALY gains for immunotherapy compared with standard therapy are smaller with a larger reduction in utility relative to the general population. As expected, the total cost estimates for both treatments remain unchanged.

Table 43 Cost-effectiveness results for different reductions in HRQoL relative to the general population

	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
ERG's base case – Company's assumption of 13% reduction in HRQoL					
Standard therapy	£54,671	10.90	-	-	-
Immunotherapy	£208,435	12.44	£153,765	1.54	£99,699
ERG's base case – Company's scenario of 26% reduction in HRQoL					
Standard therapy	£54,671	9.89	-	-	-
Immunotherapy	£208,435	11.31	£153,765	1.42	£108,070
ERG's scenario – ERG's assumption of 31.5% reduction in HRQoL					
Standard therapy	£54,671	9.46	-	-	-
Immunotherapy	£208,435	10.83	£153,765	1.37	£112,051

6.4.4 Administration cost for dinutuximab

Section 5.2.8.2 describes the assumptions made by the company relating to the administration cost of dinutuximab. The company assumed a procurement cost of £1,908 (NHS Reference Costs procure inpatient chemotherapy drugs for regimens in Band 10, code SB10Z) for the administration of dinutuximab in each cycle. The same cost was also assumed for the administration cost of IL-2. The ERG considers it inappropriate to use procurement costs to represent administration costs since procurement costs are very different from delivery costs. In addition, the costs do not reflect the length of hospital stay required by patients receiving immunotherapy. Following the ERG's request for clarification, the company provided the average number of days of hospitalisation per treatment course in the immunotherapy arm of the ANBL0032 study population (see Table 28). Using this information, the company performed a scenario (described as Scenario 1) where the total cost of administration was adjusted from £13,783.5 to £28,399.43 based on average number of hospitalised

days, NHS reference costs for the delivery of complex chemotherapy (code SB14Z) and mean cost per hospital stay for an elective inpatient stay for the treatment of brain tumours or cerebral cysts with CC Score 11+ (code AA24C). Table 44 shows the impact on the cost-effectiveness estimates of Scenario 1 on the ERG's base case analysis. The resulting impact on the ICER is to increase it from £99,699 to £108,872 per QALY gained.

Using the additional information provided by the company relating to hospital length of stay, the ERG performed a second scenario (described as Scenario 2) using administration costs based on average number of hospitalised days, NHS reference costs for the delivery of complex chemotherapy (code SB14Z) and mean cost per hospital stay for an elective inpatient stay for the treatment of paediatric brain tumours with length of stay 1 day or more, with CC score 1+ (code PM42A). Table 44shows the impact on the cost-effectiveness estimates of Scenario 2 on the ERG's base case analysis, which increases it from £99,699 to £128,378 per QALY gained.

Table 44 Cost-effectiveness results for different assumptions about the administration cost of dinutuximab

	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
ERG's base case – Company's assumption of administration cost of dinutuximab fixed at £1,908					
Standard therapy	£54,671	10.90	-	-	-
Immunotherapy	£208,435	12.44	£153,765	1.54	£99,699
ERG's base case – Company's scenario for administration cost of dinutuximab (Scenario 1)					
Standard therapy	£54,671	10.90	-	-	-
Immunotherapy	£222,582	12.44	£167,911	1.54	£108,872
ERG's scenario – ERG scenario for the administration cost of dinutuximab (Scenario 2)					
Standard therapy	£54,671	10.90	-	-	-
Immunotherapy	£252,666	12.44	£197,995	1.54	£128,378

6.4.5 Drug vial wastage for patients with body surface area > 1m2

The drug costs used in the company's model were derived from the dosage of each drug required for an average baseline BSA of 0.65m^2. The ERG requested from the company the percentage of patients (4.8%) with a baseline BSA > 1m^2 in the ANBL0032 study population. A greater BSA (> 1m^2) increases the number of vials required. The ERG calculated the per-cycle number of vials or tablets needed if patients had a baseline BSA over 1m^2 and estimated a weighted average cost per cycle for each drug based on the percentage of BSA under and over 1m^2 (see Table 27). Table 45 shows the

corresponding implications on the estimate of cost-effectiveness. The total costs for immunotherapy increased from £208,435 to £214,562, which resulted in an increase in the ICER from £99,699 to £103,667 per QALY gained.

Table 45 Cost-effectiveness results for different assumptions about BSA on drug vial wastage

	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
ERG's base case – Company's assumption using average BSA of 0.65m^2					
Standard therapy	£54,671	10.90	-	-	-
Immunotherapy	£208,435	12.44	£153,765	1.54	£99,699
ERG's scenario – ERG scenario using a weighted average of BSA above and below 1m^2					
Standard therapy	£54,678	10.90	-	-	-
Immunotherapy	£214,562	12.44	£159,884	1.54	£103,667

6.5 Conclusions from ERG analyses

The ERG's exploratory analyses have demonstrated that a number of significant uncertainties exist in relation to several key assumptions which underpin the company's base case results. The results from these analyses highlight that the assessment of cost-effectiveness of immunotherapy is greatly dependent on which data cut of the pivotal trial is used to inform the EFS and OS estimates. The results are also contingent on the assumption that the event-free cohort is 'cured' at a particular point in time (cure threshold). The two assumptions: (i) cured at a particular pre-defined point in time and (ii) extrapolation of survival gains over a lifetime horizon means that the cost-effectiveness results are highly sensitive to the proportion of individuals in each health state at the cure threshold. As a consequence, the model results are also sensitive to the parametric functions used to fit the observed Kaplan-Meier data since any small difference between treatments in the proportion of individuals in the health states at the cure point are extrapolated over a lifetime horizon.

The ERG's base case analysis suggests that the ICER for immunotherapy compared with standard therapy is around £100,000 per QALY gained. The results from the ERG's additional exploratory analyses using a range of alternative assumptions indicate that this ICER is likely to represent a lower bound. For example, the ERG considers it unlikely that the event-free cohort at the point of cure would return to the same mortality risk as that of the general population since prior to commencing immunotherapy this patient population have already received intensive treatments. Furthermore, the ERG believes that the company have underestimated the costs associated with dinutuximab. For the

alternative assumptions, the ERG's base case ICER ranges from £99,699 to £128,378 per QALY gained. However, if the alternative assumptions are taken together as follows:

- Standardised mortality rate of 5.6 for event-free survivors;
- 31.5% reduction in HRQoL;
- Adjustment to the administration cost of dinutuximab (Scenario 2) ;
- Weighted average of BSA above and below $1m^2$;

the ERG's ICER increases to £155,915 per QALY gained.

7 End of life

NICE end of life criteria are as follows: that the treatment is indicated for patients with a short life expectancy, normally less than 24 months; there is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment; and that the treatment is licensed or otherwise indicated, for small patient populations.

The ERG notes that whether dinutuximab (with IL-2 and GM-CSF) meets NICE end-of life criteria is unclear. The results from the ANBL0032 trial suggest that around half of all children with high-risk neuroblastoma who are eligible for dinutuximab treatment will survive long-term (at least ten years) regardless of whether they receive dinutuximab or only isotretinoin. Also around 75% of patients on standard therapy will survive for 24 months or more. So, in general, the first criterion is not met.

However, if we exclude the half of patients who will survive indefinitely without cancer recurrence, and consider only the half who will have a further cancer event, then among these patients the median survival time on isotretinoin is around 23 months (based on reconstructed data, see Section 4.4. Hence dinutuximab can meet the NICE end-of life criteria for short life expectancy among this small group of at-risk patients.

Again considering only the half of high-risk neuroblastoma patients who will have a further cancer event, then the median survival time on isotretinoin is around 23 months, compared to 33 months on immunotherapy. Hence dinutuximab can meet the criterion for an extension to life of at least an additional 3 months, among this small group of at-risk patients.

The size of the patient population is extremely small. The high-risk neuroblastoma population was is estimated at between 24 and 94 patients, making the estimate for the number who meet the end of life survival duration 12 and 50 patients

Hence the ERG considers that dinutuximab does comply with NICE end-of-life criteria, but only among the unidentified half of patients still at risk of cancer recurrence at the time of commencing treatment. The ERG notes that this conclusion is based on data from only one trial.

8 Overall conclusions

8.1 Clinical effectiveness

All the evidence on efficacy for dinutuximab-based immunotherapy, and much of the evidence on safety, is drawn from the ANBL0032 trial. The trial was stopped early. This is of concern, because, had the trial continued recruitment, the observed benefit might not have persisted and, because the trial was stopped because was favourable result was achieved, any analysis of the results may overestimate the benefit of dinutuximab.

Analyses up to five years after randomisation for event-free survival showed higher rates of survival with immunotherapy, but longer-term follow-up (up to ten years) suggests that around half of patients will have a cancer-related event, regardless of treatment received. A similar pattern was observed for overall survival. Further analyses performed by the ERG found that some patients are cured regardless of therapy received. For event-free survival the cured fraction was 47% in both arms, so immunotherapy did not prevent events from occurring, but it did reduce the hazard of events. For overall survival, the cured fraction was 48.8% in the standard therapy arm, but is higher (around 66%) in the immunotherapy arm, with lower hazard in the immunotherapy arm. These results suggest that immunotherapy delays events, and hence lengthens overall survival times, but does not prevent cancer recurrence.

In the ANBL0032 trial there were a number of adverse events that were substantial more common among immunotherapy patients than patients receiving standard care, including, neuropathic pain, acute capillary leak syndrome, fever without neutropenia, hypokalaemia and hypersensitivity reaction. Only 6% of immunotherapy patients had no adverse events, compared to 37% of standard therapy patients.

Overall, evidence from the ANBL0031 trial suggests that around half of all patients with high-risk neuroblastoma will never have any cancer recurrence, regardless of treatment, and so will survive long-term (beyond ten years). Among those who will have a cancer recurrence, immunotherapy comprising dinutuximab+IL-2+GM-CSF may delay the event, with a consequent lengthening of life. This must be balanced against the substantial increased incidence of potentially serious adverse events and significant toxicity with immunotherapy.

8.2 Cost-effectiveness

The company's economic analysis was used to estimate the cost-effectiveness of dinutuximab in combination with GM-CSF, IL-2 and isotretinoin in the licensed population. The cost-effectiveness was assessed by using evidence from the pivotal trial comparing dinutuximab (manufactured by the NCI and administered at a dose of 25 mg/m^2/day) with isotretinoin (standard therapy). The company's base case estimate of cost-effectiveness was based on the primary data analysis of EFS and OS from the trial (June 2009). The resulting ICER is £37,423 per QALY gained. The results of the company's scenario analyses indicated that the ICER estimate was most sensitive to the use of the primary data analysis from the trial: the resulting ICER using the updated data analysis of the trial (March 2014) is £66,344 per QALY gained. The ERG believes that this latter ICER using the most up-to-date estimates of EFS and OS should represent the company's base case estimate.

The ERG considers the company's assessment of cost-effectiveness of immunotherapy to be uncertain with respect to a number of assumptions used in the model. Two key assumptions of 'cured' at 5 years and extrapolation of survival gains at 5 years over a lifetime horizon are major drivers of the cost-effectiveness results. The ERG considers the use of a cure threshold at 5 years as inappropriate since the observed EFS evidence from the trial suggests that further relapses do occur in the immunotherapy arm after 5 years. Furthermore, the immunotherapy and standard therapy curves for EFS and OS appear to converge between 6.5 and 11 years. Therefore, the ERG considers a cure threshold of 10 years to be a better representation of the observed EFS data. The extrapolation of survival gains at 5 years over a lifetime horizon represents the most optimistic scenario for dinutuximab.

The ERG attempted to address some of the key issues and uncertainties by conducting separate analyses using the company's model. The ERG's exploratory analyses focused on the implications of using a cure threshold of 10 years and the updated observed data from the trial. The ERG's base case ICER is £99,699 per additional QALY. The ERG showed that this ICER is likely to represent a lower bound. The ERG considers that a number of assumptions in the company's model are unlikely to hold. For example, the ERG considers it unlikely that the event-free cohort at the point of cure would return to the same mortality risk as that of the general population since prior to commencing immunotherapy this patient population have already received intensive treatments. Furthermore, the ERG believes that the company have underestimated the costs associated with dinutuximab. For the alternative assumptions, the ERG's base case ICER ranges from £99,699 to £128,378 per QALY.

8.3 Implications for research

As only one trial reporting the efficacy of dinutuximab-based immunotherapy has been published to date there is a need for further high quality randomised controlled trials of dinutuximab therapy. Future trials should have long-term follow-up of all patients (for at least ten years) to fully investigate whether immunotherapy delays or prevents cancer recurrence and mortality. Trials should carefully record adverse events and, ideally, also investigate the quality of life in children with cancer recurrence and in long-term cancer survivors.

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National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Dinutuximab for treating high-risk neuroblastoma [ID799]

You are asked to check the ERG report from the Centre for reviews and Dissemination and Centre for Health Economics - York to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm** on **Thursday 17 September 2015** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Use of 4-year data vs 2-year data

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 19, Section 1.5: "The ERG considers that the updated survival data from the pivotal trial (March 2014 data cut) provide the most relevant estimates of EFS and OS in this patient population for informing the assessment of cost-effectiveness. Although the earlier data cut represented the primary analysis of the pivotal trial, the COG and NCI amended the protocol to include a later analysis because the OS data in the primary analysis were not considered mature enough."	Please consider revising the ERG's cost-effectiveness model results to utilise the January 2009 EFS data analysis.	United Therapeutics Corporation (UTC) acknowledges that study ANBL0032's interim efficacy analyses conducted from 2006 to 2009 were performed utilizing interim study data that had not been rigorously monitored and cleaned. However, these interim efficacy analyses were detailed *a priori* in the study protocol, including an accounting of the alpha spend for multiple looks. With respect to the January 2009 interim analysis that resulted in the cessation of randomization, UTC acknowledges that the interim efficacy stopping boundary was not met (observed *P*=0.0115 vs pre-specified *P* =0.0108); however, this analysis provides the most appropriate analysis of event-free survival (EFS). This analysis was performed while the study was ongoing, utilizing a prespecified analysis plan which included an alpha spend function to adjust for multiple interim analyses. The results of this analysis led the National Cancer Institute (NCI) and Children's Oncology Group (COG) to halt randomization upon the	This is not a factual inaccuracy. However, for completeness, the ERG has added an Appendix to the report (Appendix A) which presents results for the ERG's exploratory cost-effectiveness analysis in Section 6 using the 2009 data. Note this Appendix A is not referred to in the body of the report.

		recommendation of the data monitoring committee, given its proximity to the stopping boundary *P*-value and the ethics surrounding a paediatric study with a control group. Upon cessation of randomization, all subjects received immunotherapy and the successful results were published in the New England Journal of Medicine. Thus, any analyses of EFS after January 2009 were conducted under an inherent bias and not according to any prespecified analysis plan; thus with no alpha adjustment for previous interim analyses. Therefore, while UTC understands the ERG's perspective and reasoning, UTC strongly encourages the use of the January 2009 EFS analysis as the most unbiased and appropriate for the analysis of dinutuximab's effectiveness and cost-effectiveness. Conversely, UTC concurs with the ERG that the March 2014 overall survival (OS) analysis for the analysis of dinutuximab's cost-effectiveness is reasonable. With respect to OS, after the randomization was halted, the protocol was amended to note: "The definitive analysis of EFS in the randomized portion of the study was completed when the interim stopping	

		boundary for efficacy was met. The final analysis of EFS in the Stage 4 subset and OS (overall and in the Stage 4 subset) will be performed based on a data snapshot taken 2 years after the last randomized patient was enrolled (i.e., in early 2011)." The last randomized patient was enrolled on 31DEC2008. A data snapshot was taken per COG timelines on June 2012, at which time the data were deemed mature enough for an accurate assessment of OS.	

Issue 2 Calculation of dinutuximab patient population

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 27, Section 2.2: "The CS estimate for the number of patients who would be eligible for dinutuximab is 54. The clinical advisor to the ERG suggested that this figure was an underestimate: the Children's cancer registry suggests 94 neuroblastoma cases per year, of which 24 are high risk; this contrasts with the 14 per annum quoted in the budget impact analysis (p146 of submission)"	Please consider replacing with: "The clinical advisor to the ERG indicated that the Children's cancer registry suggests 94 neuroblastoma cases per year, of which 24 are high risk. Not all 24 patients are eligible for dinutuximab, however, as only those patients who have previously received induction chemotherapy, (and achieved at least a partial response), myeloablative therapy, and autologous stem cell transplantation (ASCT) would be indicated."	UTC's calculation of 26 high-risk neuroblastoma patients aligns with the ERG estimate of 24 high-risk neuroblastoma patients; however, not all patients with high-risk neuroblastoma will be eligible for dinutuximab. Matthay 1999 found that only 52% of patients responded to induction therapy, stem-cell transplantation, and radiotherapy. Therefore, if we apply this 52% to the 24 patients with high-risk neuroblastoma from the ERG estimate, we get ~13 patients with high-risk neuroblastoma who would be eligible for treatment with	We have modified Section 2.2 page 27, broadly in line with the proposed amendment: the following text has been added, "Not all the estimated 24 patients are eligible for dinutuximab, however, as only those patients who have previously received induction chemotherapy, (and achieved at least a partial response), myeloablative therapy, and autologous stem cell.

		dinutuximab. This aligns with the CS estimate of 14 patients (Table 65 of submission).	transplantation (ASCT) would be indicated.”

Issue 3 The mislabelling of ANBL0931 as a comparative and randomised trial

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>ERG Response</th></tr>
<tr>
<td>Page 49; Table 10:

“Results were presented both for immunotherapy and isotretinoin arms, suggesting that this trial was comparative and possibly randomised, which is inconsistent with the reporting in the CS and the ClinicalTrials.gov website. It is unclear to the ERG what the isotretinoin arm for which results are presented comprises.

The preliminary survival data for this trial is summarised in Table 10. These results are almost identical to those of the ANBL0032 trial. There was a statistically significant difference in overall survival between arms, but not for event-free survival, and the results appear consistent with immunotherapy delaying, rather than preventing, cancer recurrence and mortality.

Table 10
<table>
<tr><th>Outcome</th><th>Arm</th><th>Two-year survival</th><th>Four-year survival</th><th>p-value</th></tr>
<tr><td>EFS</td><td>Immunotherapy</td><td>67% ± 4%</td><td>59% ± 5%</td><td>0.11</td></tr>
</table>
</td>
<td>Please consider deletion of this section.</td>
<td>UTC acknowledges and apologises for an error in their Clarification letter to NICE in which the incorrect Ozkaynak 2014 abstract was quoted. ANBL0931 is a single arm trial that has no comparator.

The only data available are from Ozkaynak 2014. The correct abstract should read:

Of 105 patients enrolled (none ineligible), five patients developed protocol-defined unacceptable toxicities and came off study (four grade 4 allergic reaction/anaphylaxis, one sudden death -sudden onset of abdominal pain and arrest).The most common grade 3 or higher non-hematologic toxicities of ImmRx were neuropathic pain (cycles 1,2,3,4,5 were 30.9%,22%,13.3%,20%,17%, respectively), hypotension</td>
<td>We thank the manufacturers for correcting this error.

Section 4.2.1.4 on Page 49 has been modified to present the results of the correct abstract presented left.</td>
</tr>
</table>

	Isotretinoin	51% ± 5%	48% ± 5%	
OS	Immunotherapy	83% ± 4%	74% ± 4%	0.02
	Isotretinoin	76% ± 4%	59% ± 5%	

“

(9.6%,17%,3.1%,12.2%,5.7%), allergic reactions (2.9%,9%,3%,6.6%,2.2%), capillary leak syndrome (1%,4%,0,2.2%,0), fever (21%,58%, 6.1%, 31.1%,4.5%). Toxicities occurred more frequently during IL-2 cycles compared to GM-CSF cycles. Dose modifications were reported in 73 patients (69%) most of which are thought to be prolongation of the ch14.18 infusion time beyond 10 hrs. The 2-year EFS and OS were 74+/-6% and 84+/-5%, respectively (n=105).		

Issue 4 31.5% Reduction in HRQoL for neuroblastoma survivors

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 121, Section 6.4.3 “The ERG used evidence from Nathan 2007 to obtain a more substantiated alternative estimate of the reduction in HRQoL relative to the general population. This resulted in a 31.5% reduction for neuroblastoma survivors. Figure 21 in Section 5.2.7.2 shows the impact of these reductions relative to the general population values.”	Please consider revising the statement and/or modelling calculations in consideration of the article’s conclusions and results.	UTC would like to clarify that the conclusion of Nathan 2007 is “*Adult survivors of childhood Wilms tumor and neuroblastoma do not differ from population norms on most health-related quality of life (HRQL) measures*.” UTC acknowledges differences on certain social functioning/mental health scales, although UTC is not clear on how the ERG calculated the 31.5% reduction based on the conclusion of this publication. Because the SF-36 for neuroblastoma patients does not	The ERG has added an appendix to the report (Appendix B) which outlines the steps used to derive the 31.5% reduction in HRQoL for neuroblastoma survivors based on the study by Nathan 2007. In the study by Nathan 2007, the neuroblastoma group scored significantly below the population mean score on the Mental Component Summary

		differ substantially from population norms in Nathan 2007, the 31.5% lower utility compared to population norms as measured by the EQ-5D may be driven by limitations of the mapping algorithm rather than by a true difference in health utility.	Score of the SF-36. Reference to this Appendix has been inserted on page 89 of the report

Issue 5 The patient population randomised to the main RCT

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 11, Section 1.1: "Furthermore, in this main RCT, only those patients without MRD following autologous-SCT were randomised. Hence the population supported by the CS is only a sub-set of the licenced population."	Please consider removal of the statement, "Furthermore, in this main RCT, only those patients without MRD following autologous-SCT were randomised." Please consider revising the second sentence to state, "The population supported by the CS matches the licensed population."	UTC would like to clarify that biopsy-proven residual disease is not the same as minimal residual disease (MRD). To be enrolled and randomised in the main RCT, patients had to have at least a partial response (PR), very good partial response (VGPR), or complete response (CR) to induction chemotherapy prior to ASCT. By definition, CR is defined as no evidence of primary tumour, no evidence of metastases (chest, abdomen, liver, bone, bone marrow, nodes, etc.), and HVA/VMA normal. VGPR is defined as: greater than 90 reduction of primary tumour; no metastatic tumour (as above except bone); no new bone lesions, all pre-existing lesions improved on bone	The ERG accept that they have used the term MRD instead of 'biopsy-proven persistent disease' in error and misunderstood . On page 11 and on page 33 the first sentence has been removed and the second sentence has been amended to, "The randomised population in the main trial appears to reflect the licensed indication". It is still not clear to the ERG if the sub-group of patients with biopsy-proven persistent disease after ASCT who

		scan; HVA/VMA normal. and a partial response is defined as fifty-90% reduction of primary tumour; 50% or greater reduction in measurable sites of metastases; 0-1 bone marrow samples with tumour; number of positive bone sites decreased by > 50%.	were non-randomly assigned to immunotherapy are included or not in the licensed population. This has been clarified on page 36 of the ERG report

Issue 6 Errors Present in the 2009 Analysis of ANBL0032

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 16, Section 1.3.1 "The CS based much of the clinical analysis on the data at the time the trial was stopped (2009). However, it was acknowledged that there were some errors in the data at that time, and checks by the ERG confirmed that the analysis results based on this 2009 data were inconsistent with later analyses. The ERG therefore considers the analysis based on the 2009 data to be unreliable and analyses should instead use the most up-to-date follow-up data (March 2014)." Page 41, Section 4.2.1.2 "On request for clarification the	Please consider revising this section to state, "The CS based much of the clinical analysis on the data at the time the trial was stopped (2009). However, because the raw data from the January 2009 data cut were not recoverable, an additional data cut at June 2009 was requested to confirm earlier results. While there are differences in the data due to the use of two separate time points, all differences are documented and validated. Furthermore, the results from the June 2009 analysis were consistent with the results from the January 2009 analysis which both demonstrated improved event-free survival in the immunotherapy arm compared to the RA alone arm."	The 2009 data analysis was performed as part of a pre-specified interim analysis, utilizing an alpha spending function to account for multiple interim analyses of EFS. Data for interim analyses do not undergo the same "cleaning" as final data and therefore often contain errors/data discrepancies. The efficacy data in this data cut were reviewed and cleaned up to the extent feasible prior to analysis. The January 2009 efficacy data were further confirmed after receipt of the additional data cut in June 2009. Efficacy analyses from both data cuts were consistent in the conclusion of improved EFS in the immunotherapy arm compared to	The ERG does not consider these generally to be factual inaccuracies as the justification left states: "[the data] often contain errors/data discrepancies" We have amended some sections for the sake of clarity: Section 1.3.1 page 16 has been amended to discuss issues of data "cleaning". Section 4.2.1.2 Page 41. We have removed the sentence

manufacturer confirmed that data were available at four follow-up points as follows: 30 June 2009: Updated confirmatory analysis by the COG. The manufacturer confirmed that, due to data entry errors, there were some differences between this and the January 2009 analysis." Page 43, Section 4.2.1.2 "While the results from the 2014 and 2012 data sets are broadly consistent, the results for standard therapy in the 2009 analysis are different, with considerably poorer outcomes in this arm. Either there were some data errors in this 2009 analysis, or the initial group of recruited standard therapy arms performed particularly poorly compared with those recruited later (who had no reached two or three years of follow-up by 2009). This suggests that conclusions based on the two-year survival results from the 2009 data, which are the key results in the CS, are overestimating the benefit of immunotherapy."	Please consider removing the statement, "The manufacturer confirmed that, due to data entry errors, there were some differences between this and the January 2009 analysis." Please consider revising this section to state: "While the results from the 2014 and 2012 data sets are broadly consistent, the results for standard therapy in the 2009 analysis are different, with considerably poorer outcomes in this arm. This suggests that conclusions based on the early two-year survival results from the 2009 data, which are the key results in the CS, are potentially overestimating the benefit of immunotherapy."	the RA alone arm. The follow-up data from March is further biased by post-study therapies, which were not recorded, and this analysis did not follow the pre-specified interim analysis plan, thus does not include any alpha spending function to adjust for previous interim analyses of EFS data. The 2009 data most accurately reflects immunotherapy's impact on EFS. The June 2009 analysis was not performed due to data entry errors, but rather the raw data from the January 2009 data cut were not recoverable and UTC requested the June 2009 data cut at a later date to confirm the earlier results. Because the June 2009 data cut of this live database was six months after the final interim datacut in January 2009, there were data differences noted when compared to the earlier data cut, but all differences have been documented and validated. Data entry errors were not the reason for the later cut, but rather to demonstrate data traceability for the January 2009 data (for which no raw data were available). No additional patients were randomized after January 13, 2009, so the January 2009 and March 2014 datacuts represent the same	here as requested. Section 4.2.1.2, page 43. This is not a factual inaccuracy

		group of patients.	

Issue 7 Early Stopping of ANBL0032

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 41, Section 4.2.1.1: "In any sequentially monitored trial, if the trial is stopped early because there is evidence of benefit a naïve statistical analysis is likely to overestimate the size of the beneficial effect. The analyses presented in the CS did not appear to adjust for this early stopping, so the efficacy of dinutuximab, particularly at two and three years, may be overestimated."	Please revise the statement to read, "In any sequentially monitored trial, if the trial is stopped early because there is evidence of benefit, a naïve statistical analysis is likely to overestimate the size of the beneficial effect. The sequential interim analyses presented in the CS were adjusted for this early stopping."	UTC can confirm that each sequential interim analysis was adjusted for, as noted in the study protocol's early stopping rules (Section 11.6, Amendment 8) which details the interim monitoring boundary values for log-rank EFS comparison of treatment arms for each of the planned interim analyses.	Think this is a factual inaccuracy. Adjusting the sequential interim analyses for early stopping while the trial is ongoing is not the same as adjusting hazard ratios and other analyses once the trial has stopped to account for the fact that the trial was stopped early. As stated in the ERG report, the ERG considers that there is insufficient evidence in the CS to confirm that such adjustments to the overall analyses were made.

Evidence Review Group's Errata
Dinutuximab for treating high-risk neuroblastoma

CRD and CHE Technology Assessment Group, University of York,

Heslington, York YO10 5DD

24th September 2015

1 Summary

Neuroblastoma is primarily a tumour of early childhood, with nearly 90% of cases diagnosed by the age of 5 years. Children diagnosed with neuroblastoma are classified into three different risk groups: low, intermediate, and high. In UK clinical practice a patient with neuroblastoma, aged over 1 year, with INSS Stage 4, or INSS Stage 3 plus abnormalities, would be classified as high-risk. In particular the disease is very different in infants under age 1 in whom it often presents with localised disease and spontaneously regresses, and is easier to treat. Neuroblastoma has a significant impact on morbidity, mortality, and quality of life of patients and their caregivers. Five year mortality in patients diagnosed aged >1 year is estimated at around 30 or 40%. However those who do survive five years may well be cancer survivors, though due to both the effect of the disease itself and its treatment, survivors are at significant risk of long-term complications associated with neuroblastoma, including increased risk of secondary malignancy and mortality.

High-risk neuroblastoma is typically treated with a multimodal therapeutic approach, including intensive induction chemotherapy, autologous stem cell transplantation (SCT), with maintenance therapy intended to eliminate minimal residual disease and prevent relapse provided using retinoids and immunotherapy; radiotherapy and surgery may also be included.

1.1 Critique of the decision problem in the manufacturer's submission

The CS statement of the decision problems matches the population specified in the NICE scope: people with high-risk neuroblastoma who have received myeloablative therapy and autologous stem cell transplant. However, the anticipated marketing authorisation dictates a more restricted population than that in the NICE scope,

"Patients aged 12 months to 17 years who have previously received induction chemotherapy and achieved at least a partial response, followed by myeloablative therapy and ASCT."

The main RCT providing the evidence for the efficacy of dinutuximab included patients mean age at diagnosis of 3.5 years (range 0.2 to 14.5 years); the vast majority of patients recruited (around 78%) were aged 1 to 5 years.

The randomised population in the main trial appears to reflect the licensed indication.

The two subgroup populations listed in the final scope issued by NICE of (i) people with relapsed disease and (ii) people with refractory disease were not considered by the company due to a lack of evidence for the use of dinutuximab in these subpopulations. Whilst some clinical evidence is provided for a refractory subgroup (patients with persistent disease (MRD- positive) after autologous-

patients), CCG-035A (25 patients) and CCG-035 (19 patients)). These results generally concurred with those of the ANBL0032 trial.

1.2 Summary of the ERG's critique of clinical effectiveness evidence submitted

1.2.1 Early stopping of trial ANBL0032

All the evidence on efficacy for dinutuximab-based immunotherapy, and much of the evidence on safety, is drawn from the ANBL0032 trial. This trial whilst randomised and controlled was not double-blind. Furthermore, it was stopped early after recruiting 226 patients who subsequently experienced only 83 cancer related events. It appears that the sequential monitoring used to terminate recruitment was not performed correctly as the monitoring boundary had not been crossed at the time the trial was stopped. This is of concern, because, had the trial continued recruitment, the observed benefit might not have persisted and, because the trial was stopped because was favourable result was achieved; any analysis of the results may overestimate the benefit of dinutuximab.

The CS based much of the clinical analysis on the data at the time the trial was stopped (2009). However these data were from an interim analysis for which the data may not have been fully "cleaned", so may have contained some errors or data discrepancies. Additional data were also available at later time points. Checks by the ERG confirmed that the analysis results based on this 2009 data were inconsistent with later analyses. The ERG therefore considers the analysis based on the 2009 data to be unreliable and analyses should instead use the most up-to-date follow-up data (March 2014).

1.2.2 Long-term survival

The CS presented data only at two and four years after randomisation, which the ERG considers to be too short a timescale to determine efficacy. While analyses up to five years after randomisation for event-free survival showed higher rates for immunotherapy, longer-term follow-up (up to ten years) suggests that around half of patients will have a cancer-related event, regardless of treatment received. A similar pattern was observed for overall survival, with around half of patients surviving for ten years or more. Further analyses performed by the ERG suggest that immunotherapy delays events, and hence lengthens overall survival times, but does not prevent cancer recurrence.

The ERG used data reconstructed from the 2014 Kaplan-Meier curves to fit a parametric cure model to the data, which assumes a proportion of patients are "cured" and at no risk of cancer events or death. This model was found to fit the data well, suggesting that some patients are cured regardless of therapy received. For event-free survival the cured fraction was 47% in both arms, so immunotherapy did not prevent events from occurring, but it did reduce the hazard of events. This suggests that

immunotherapy delays rather than prevents events. For overall survival, the cured fraction was 48.8% in the standard therapy arm, but is higher (around 66%) in the immunotherapy arm, with lower hazard

The prognosis for neuroblastoma is related to age at diagnosis, clinical stage of disease, site of the primary tumour, tumour histology, and, in patients older than 1 year of age, regional lymph node involvement (NCI 2012). The 5-year survival rate for children with high-risk neuroblastoma reported in the CS is about 30% to 50% (ACS 2013). The clinical advisor to the ERG felt that in the UK the lower estimate of 30% was perhaps more realistic.

UK data reported in the CS find that approximately 100 new cases of neuroblastoma are diagnosed each year in the UK (Neuroblastoma Alliance UK 2011. Data from the Automated Childhood Cancer Information System (ACCIS) reported an age-standardized incidence rate for both sexes of 9.1 cases per million in the British Isles during 1988 to 1997 (Spix 2006).[6] Incidence by age groups (both sexes) in this region was as follows: 34.4 per million (<1 year), 17.1 per million (1–4 years), 3.1 per million (5 to 9 years), and 0.6 per million (10 to 14 years) (Note these Spix statistics are based on old data ((1988-1997)). The CS estimate for the number of patients who would be eligible for dinutuximab is 54. The clinical advisor to the ERG suggested that this figure was an underestimate: the Children's cancer registry suggests 94 neuroblastoma cases per year, of which 24 are high risk; this contrasts with the 14 per annum quoted in the budget impact analysis (p146 of submission). Not all the estimated 24 patients are eligible for dinutuximab, however, as only those patients who have previously received induction chemotherapy, (and achieved at least a partial response), myeloablative therapy, and autologous stem cell transplantation (ASCT) would be indicated.

Impact of high-risk neuroblastoma

The CS provides information on the impact of neuroblastoma, stating that neuroblastoma has a significant impact on morbidity, mortality, and quality of life of patients and their caregivers. The CS also provides UK survival probabilities. Impact in terms of survival is cited as five-year survival probability (95% CI) by age groups in this region: 80% (74, 85) for <1 year, 37% (33, 42) for 1 to 4 years, 34% (24, 44) for 5 to 9 years, and 26% (10, 47) for 10 to 14 years (Spix 2006),[6] though these figures are not specific to high-risk patients and also are based on old data (cohort followed 1988 to 1997).

The ERG identified further information on long-term mortality. One study used data sourced the SEER cancer database (US).[7] The investigators identified all individuals with non-CNS neuroblastoma or ganglioneuroblastoma diagnosed between 1973 and 2006. To account for changes in therapy over this very long period the data analysed by era (date of diagnosis): 1973-1989; 1990-1996; and 1997-2006. Median follow-up of whole sample was 74 months. For era 3 (most relevant to current practice) it was 67 months (maximum 155 months) (7560 patient years). Five year OS for high risk Era 3 patients is estimated to be 46.2% (95% CI 41.9-50.9%), and this was statistically

significantly better than that for Era 1 (17.1% (95% CI 13.2-22.2%). Note the Kaplan-Meier plot for OS high risk Era 3 patients does not plateau at 5 years (**Error! Reference source not found.**).

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	Services perspective		
Subgroups to be considered	If the evidence allows, the following subgroups will be considered. These include: • People with relapsed disease • People with refractory disease If no evidence is available for these subgroups, this should be stated, and the Appraisal Committee would then decide if the available evidence could be extrapolated to people with relapsed or refractory disease.	As defined	N/A
Special considerations including issues related to equity or equality	No comment	As defined	N/A

1.3 Population

The CS statement of the decision problems claims to adhere to the population specified in the NICE scope. However, the anticipated marketing authorisation dictates a more restricted population than that in the NICE scope,

"patients aged 12 months to 17 years who have previously received induction chemotherapy and achieved at least a partial response, followed by myeloablative therapy and ASCT."

The main RCT providing the evidence for the efficacy of dinutuximab included patients mean age at diagnosis of 3.5 years (range 0.2 to 14.5 years); the vast majority of patients recruited (around 78%) were aged 1 to 5 years.

The randomised population in the main trial appears to reflect the licensed indication

1.4 Intervention

The CS statement of the decision problems claims to adhere to the population specified in the NICE scope: dinutuximab in combination with sargramostim, aldesleukin, and isotretinoin. No dose was specified in the NICE scope. The licenced use of dinutuximab (as specified in the SmPC (see Appendix of CS)) is as part of a specified combination therapy including isotretin and inter-leukin-2 (IL-2) and GM-CSF. Aldesleukin is another name for IL-2. Sargramostim (Leukine) is a GM-CSF marketed by Genzyme. It is not clear to the ERG whether the marketing authorisation for dinutuximab

subgroups. However, whilst some clinical evidence is provided for a refractory subgroup (patients with persistent disease after autologous-SCT) this subgroup is not included in the licensed population, nor is it analysed in the economic model. No consideration is given to the treatment of relapsed patients in the submission. Other sub-groups are considered (see Sections 4.2.1.3).

1.5 Other relevant factors

GM-CSF

In the company submission (page 110 footnote) it states that GM-CSF does not have a marketing authorisation in England for any indication. The ERG asked the Company to clarify whether GM-CSF is commercially available in England and current procurement arrangements. The Company's response stated,

"Dinutuximab is intended to be administered as indicated according to the marketing authorisation, in combination with GM-CSF, IL-2, and isotretinoin. Currently, GM-CSF is not approved for marketing authorization by the EMA for any indication, and therefore is not commercially available in England. UTC does not manufacture this molecule and has no relationship with the manufacturer. However, UTC has arranged for access to GM-CSF through a third party distributor, available through a bona fide request from the treating physician independent of UTC. Additionally, the treating physician would also be able to procure the GM-CSF through their institution's standard operating procedures from a different distributor, if the distributor can provide access to GM-CSF in England."

The Company's response also stated,

"Although GM-CSF is not routinely used in English clinical practice, the dinutuximab SmPC provides sufficient instructions on using the product in immunotherapy. Additional information regarding GM-CSF can be found in the GM-CSF (Leukine®) Prescribing Information."

PAS

No patient access scheme has been proposed for dinutuximab.

The CS reported that the stopping boundary was crossed after randomisation of 226 patients and 83 events (61% of the expected number), but there appears to have been some disagreement, with the Committee for Medicinal Products for Human Use (CHMP) Assessment Repoort (2014) questioning whether the stopping boundary was crossed.[19] On request for clarification, the manufacturer confirmed that the stopping boundary had not been crossed when recruitment ceased, and so the trial should have continued recruitment. This is of concern because had recruitment continued, the boundary may not have been crossed and efficacy results, particularly at or before three years, may have been different.

In any sequentially monitored trial, if the trial is stopped early because there is evidence of benefit a naïve statistical analysis is likely to overestimate the size of the beneficial effect [20]. The analyses presented in the CS did not appear to adjust for this early stopping, so the efficacy of dinutuximab, particularly at two and three years, may be overestimated.

1.5.1.2 Trial results: survival analyses

The analysis presented in the CS reported event-free and overall survival using two distinct data sets. The main analysis was based on the data available after trial recruitment was stopped (January 2009, as reported in Yu 2010)[21], for which Kaplan-Meier curves and survival estimates two years after randomisation were reported. Kaplan-Meier curves and survival estimates were also presented at four years after randomisation, based on a longer-term follow-up of the data (June 2012).

On request for clarification the manufacturer confirmed that data were available at four follow-up points as follows:

13 January 2009: Original analysis after close of randomisation performed by Yu et al.

30 June 2009: Updated confirmatory analysis by the COG.
30 June 2012: Follow-up analysis to consider more mature data on overall survival, performed by Yu et al.
March 2014: Further analysis requested by the EMA.

The ERG considers that the longest and most complete follow-up data (March 2014) should be the basis of analysis for this report, and so requested details of the analysis of these latest follow-up data, which were provided. Although we consider the latest follow-up data to be most relevant, for completeness, we also consider the analyses presented in the CS (January 2009 and June 2012) in this report.

1.5.1.3 The ANBL0931 trial

The CS reported this trial as a single-arm trial of immunotherapy designed as a safety trial[22]. This was confirmed by the ERG against the record on the ClinicalTrials.gov website. The treatment received was similar to the immunotherapy arm of the ANBL0032 trial. This trial recorded event-free and overall survival, but these were not reported in the CS. The ERG requested relevant survival data for this trial. The manufacturers reported that a full analysis his yet to be performed, but provided some preliminary results.

The preliminary survival data for this trial, based on 105 patients, is summarised in Table 1. Event-free survival rates were somewhat higher than they were in the ANBL0032 trial (67.4%), but overall survival rates were almost identical.

Table 1: Preliminary results from the ANBL0931 trial

Outcome	Two-year survival
EFS	74% ± 6%
OS	84% ± 5%

1.5.2 Safety trials

The CS identified four clinical studies which reported the rate of adverse reactions among high-risk neuroblastoma patients treated with dinutuximab. These were: the randomised trial of efficacy ANBL0032 discussed in Section **Error! Reference source not found.**; the ANBL0931 trial discussed in Section 1.5.1.3above,and two single-arm non-randomised studies CCG-0935[23] and CCG-0935A[24].

1.5.2.1 The ANBL0032 trial

Only the ANBL0032 trial compared adverse events when using immunotherapy (dose of dinutuximab 25 mg/m^2, which is equivalent to the licensed dose) with those using isotretinoin alone. The CS presented the observed rate of grade 3 and 4 adverse reaction events by treatment group for the ANBL0032 study, reproduced in simplified form here as **Error! Reference source not found.**, with adverse events occurring in fewer than 10 patients removed. Immunotherapy was associated with a statistically significant increased risk of adverse reactions compared to standard therapy across a range of adverse reactions.

The systematic search undertaken by the company to identify HRQoL utility values for neuroblastoma survivors returned 5 studies [40-44]. Alessi 2007 was a small Italian study (sample size = 35), which examined HRQoL using the HUI3 questionnaire in 5-year survivors (>15 years old) from a variety of different cancers, including neuroblastoma, based on an Italian Childhood Cancer Registry. Shimoda 2008 considered HRQoL using the HUI2 and HUI3 questionnaires in cancer survivors (>13 years of age) who were at least 8 years beyond the end of active treatment, but it only recruited 2 neuroblastoma patients and was therefore excluded from the company's analysis. Three Canadian studies were identified [41-43]. All these studies considered neuroblastoma survivors, with Portwine 2014 being the one with the largest sample size (sample size = 99). Grant 2006 did not report HRQoL findings separately for neuroblastoma patients and, therefore, was excluded. Barr 2000 collected HRQoL evidence for neuroblastoma survivors using the HUI2 and HUI3 questionnaires. The company considered the Portwine 2014 population to be most relevant to the population in the dinutuximab clinical trial [21]. In addition, it represented the largest sample of neuroblastoma survivors and HRQoL estimates were collected using the HUI questionnaire (although it is not clear which version was implemented) for survivors and compared with the general population.

It is not clear to the ERG why the study by Nathan 2007[12], which was described in Section 3.1.2 of the CS to substantiate the argument that neuroblastoma has a significant impact on HRQoL of patients and their caregivers, was not considered by the company in the assessment of cost-effectiveness. Nathan 2007 assessed the HRQoL of long-term survivors of childhood neuroblastoma (sample size = 432) and Wilms tumour using the US Childhood Cancer Survivor Study registry. HRQoL estimates were obtained using the Short Form 36 Health Survey (SF-36) [45] generic instrument. Nathan 2007 present SF-36 adjusted mean dimension-level (i.e., physical functioning, role limitations due to physical health, bodily pain, general health, vitality, social functioning, role limitations due to emotional health and general mental health) scores and summary-level (i.e., physical component and mental component) scores. Using the algorithm of Rowen 2009 the dimension-level SF-36 information can be mapped onto EQ-5D index scores. The ERG performed this mapping to derive EQ-5D scores based on Nathan 2007 (see Appendix B). The ERG also used another mapping algorithm [46], which also maps SF-36 onto EQ-5D but using the SF-36 physical and mental component summary scores. Using these mapping algorithms, EQ-5D estimates of 0.658 and 0.792 were derived based on Rowen 2009 and Maund 2012, respectively. As these EQ-5D estimates are based on mapping algorithms, they have, inherently, some limitations. Nevertheless, they do provide an alternative source of utility values.

Error! Reference source not found. summarises the details of the studies reporting HRQoL for neuroblastoma survivors.

APPENDIX A: ERG's exploratory cost-effectiveness results using the 2009 data

This appendix details the results of the ERG's exploratory analyses as presented in Section 6 using the 2009 data instead of the updated March 2014 data from trial ANBL0032.

A.1 ERG's exploratory base case using the 2009 data and a cure threshold of 5 years

As discussed in Sections 5 and 6, the ERG considers the use of observed Kaplan-Meier data to be more appropriate than fitting of parametric functions to EFS and OS within the first 5 years of the model. The 2009 data has a maximum follow-up of 6.5 years. Therefore this exploratory analysis is based on a cure threshold of 5 years. Table A.1 presents the results of the ERG exploratory base case using the 2009 data and a cure threshold of 5 years.

Table A.1 ERG's exploratory cost-effectiveness results using the 2009 data

	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
ERG exploratory base case – observed Kaplan-Meier data and cure threshold of 5 years					
Standard therapy	£44,583	10.08	-	-	-
Immunotherapy	£185,642	13.47	£141,059	3.39	£41,671

A.2 ERG's exploratory scenarios using the 2009 data and a cure threshold of 5 years

This section presents the results of the ERG's exploratory scenarios in Section 6 using the 2009 data and a cure threshold of 5 years. The results for the following scenarios are presented:

- Extrapolation of treatment benefits for different durations (corresponding to Section 6.2.2) are presented in Table A.2;
- Adjustment of general population mortality (corresponding to Section 6.4.2) are presented in Table A.3;
- Reduction in health-related quality of life (corresponding to Section 6.4.3) are presented in Table A.4;
- Administration cost for dinutuximab (corresponding to Section 6.4.4) are presented in Table A.5; and
- Drug vial wastage for patients with body surface area > $1m^2$ (corresponding to Section 6.4.5) are presented in Table A.6.

Table A.2 ERG's exploratory results using the 2009 data for different model time horizons (corresponding to Table 36 in Section 6)

	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
ERG exploratory base case – Lifetime horizon (best case scenario)					
Standard therapy	£44,583	10.08	-	-	-
Immunotherapy	£185,642	13.47	£141,059	3.39	£41,671
ERG exploratory scenario – Time horizon of 5 years (worst case scenario)					
Standard therapy	£34,644	2.43	-	-	-
Immunotherapy	£171,817	2.86	£137,173	0.43	£317,488
ERG exploratory scenario – Time horizon of 10 years					
Standard therapy	£38,807	3.87	-	-	-
Immunotherapy	£177,635	4.85	£138,828	0.99	£140,688
ERG exploratory scenario – Time horizon of 15 years					
Standard therapy	£39,928	5.04	-	-	-
Immunotherapy	£179,190	6.48	£139,262	1.44	£96,807
ERG exploratory scenario – Time horizon of 20 years					
Standard therapy	£40,783	6.01	-	-	-
Immunotherapy	£180,375	7.83	£139,592	1.81	£76,917

Table A.3 ERG's exploratory results using the 2009 data for a general population mortality adjustment for event-free survivors (corresponding to Table 42 in Section 6)

	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
ERG exploratory base case – Company's assumption of same mortality as the general population					
Standard therapy	£44,583	10.08	-	-	-
Immunotherapy	£185,642	13.47	£141,059	3.39	£41,671
ERG exploratory scenario – Standardised mortality rate of 5.6 for event-free survivors					
Standard therapy	£43,930	9.44	-	-	-
Immunotherapy	£184,737	12.58	£140,807	3.14	£44,890
ERG exploratory scenario – Standardised mortality rate of 10.0 for event-free survivors					
Standard therapy	£43,590	9.09	-	-	-
Immunotherapy	£184,265	12.09	£140,675	3.00	£46,881

Table A.4 ERG's exploratory results using the 2009 data for different reductions in HRQoL relative to the general population (corresponding to Table 43 in Section 6)

	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
ERG exploratory base case – Company's assumption of 13% reduction in HRQoL					
Standard therapy	£44,583	10.08	-	-	-
Immunotherapy	£185,642	13.47	£141,059	3.39	£41,671

ERG exploratory scenario – Company's scenario of 26% reduction in HRQoL					
Standard therapy	£44,583	8.94	-	-	-
Immunotherapy	£185,642	11.89	£141,059	2.94	£47,903
ERG exploratory scenario – ERG's assumption of 31.5% reduction in HRQoL					
Standard therapy	£44,583	8.46	-	-	-
Immunotherapy	£185,642	11.22	£141,059	2.76	£51,138

Table A.5 ERG's exploratory results using the 2009 data for different assumptions about the administration cost of dinutuximab (corresponding to Table 44 in Section 6)

	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
ERG exploratory base case – Company's assumption of administration cost of dinutuximab fixed at £1,908					
Standard therapy	£44,583	10.08	-	-	-
Immunotherapy	£185,642	13.47	£141,059	3.39	£41,671
ERG exploratory scenario – Company's scenario for administration cost of dinutuximab (Scenario 1)					
Standard therapy	£44,583	10.08	-	-	-
Immunotherapy	£199,774	13.47	£155,190	3.39	£45,845
ERG exploratory scenario – ERG scenario for the administration cost of dinutuximab (Scenario 2)					
Standard therapy	£44,583	10.08	-	-	-
Immunotherapy	£229,828	13.47	£185,245	3.39	£54,724

Table A.6 ERG's exploratory results using the 2009 data for different assumptions about BSA on drug vial wastage (corresponding to Table 45 in Section 6)

	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
ERG exploratory base case – Company's assumption using average BSA of 0.65m^2					
Standard therapy	£44,583	10.08	-	-	-
Immunotherapy	£185,642	13.47	£141,059	3.39	£41,671
ERG exploratory scenario – ERG scenario using a weighted average of BSA above and below 1m^2					
Standard therapy	£44,590	10.08	-	-	-
Immunotherapy	£191,763	13.47	£147,173	3.39	£43,477

APPENDIX B: Reduction in health-related quality of life for neuroblastoma survivors

This appendix describes how the 31.5% reduction in HRQoL relative to the general population norms was estimated in the ERG's exploratory scenario analysis. Nathan 2007 present SF-36 adjusted mean dimension level (i.e., physical functioning, role limitations due to physical health, bodily pain, general health, vitality, social functioning, role limitations due to emotional health and general mental health) scores for long-term survivors of childhood neuroblastoma (sample size = 432) using the US Childhood Cancer Survivor Study registry (see Table B.1 below). These dimension scores were mapped onto the EQ-5D index to provide a summary EQ-5D utility score for neuroblastoma survivors using the algorithm of Rowen 2009.

The model specification used in Rowen 2009 was:

$$y_i = \alpha + \beta x_{ij} + \theta r_{ij} + \delta z_{ij} + \epsilon_{ij}$$

where i = 1,2,..., n represents individual respondents and j = 1,2,..., m represents the 8 different SF-36 dimensions. The dependent variable, y, represents the EQ-5D utility score, x represents the vector of SF-36 dimensions, r represents the vector of squared terms, z represents the vector of interaction terms and ϵ_{ij} represents the error term.

The predicted EQ-5D scores are based on the Generalised Least Squares (GLS) model using squared and interaction terms, which were shown to have the most accurate predictions as indicated by the mean absolute error (MAE) and mean squared error (MSE) compared to other models in Rowan 2009. Table B.1 shows how the SF-36 dimension scores are mapped onto the EQ-5D index using the specification of Rowan 2009.

Table B.1 Mapping of SF-36 dimension scores from Nathan 2007 to EQ-5D

Parameter	Rowen 2009 coefficient (GLS – Table 2)	Nathan 2007, neuroblastoma SF-36 scores sub-scales	EQ-5D score estimation
Dimensions (x)			
Physical functioning (PF)	0.559	52.02/100 = 0.520	0.291
Role physical (RP)	-0.146	52.09/100 = 0.521	-0.076
Bodily pain (BP)	0.715	52.84/100 = 0.528	0.378
General health (GH)	0.407	48.99/100 = 0.490	0.199
Vitality (VIT)	0.017	39.97/100 = 0.400	0.007
Social functioning (SF)	0.293	46.30/100 = 0.463	0.136
Role-emotional (RE)	0.067	42.41/100 = 0.424	0.028
Mental health (MH)	0.483	50.08/100 = 0.501	0.242
Dimensions squared (r)			
PF^2	-0.227	0.520^2 = 0.271	-0.061
RP^2	0.001	0.271	0.000

BP^2	-0.33	0.279	-0.092
GH^2	0.032	0.240	0.008
VIT^2	-0.012	0.160	-0.002
SF^2	-0.163	0.214	-0.035
RE^2	0.034	0.180	0.006
MH^2	-0.242	0.251	-0.061
Interaction terms (z)			
PFxRP	0.022	0.271	0.006
PFxBP	-0.032	0.275	-0.009
PFxGH	0.073	0.255	0.019
PFxVIT	-0.132	0.208	-0.027
PFxSF	-0.023	0.241	-0.006
PFxRE	0.047	0.221	0.010
PFxMH	-0.014	0.261	-0.004
RPxBP	0.019	0.275	0.005
RPxGH	0.068	0.255	0.017
RPxVIT	0.050	0.208	0.010
RPxSF	0.067	0.241	0.016
RPxRE	-0.012	0.221	-0.003
RPxMH	0.022	0.261	0.006
BPxGH	-0.217	0.259	-0.056
BPxVIT	-0.002	0.211	0.000
BPxSF	0.055	0.245	0.013
BPxRE	-0.038	0.224	-0.009
BPxMH	0.131	0.265	0.035
GHxVIT	-0.066	0.196	-0.013
GHxSF	-0.157	0.227	-0.036
GHxRE	-0.033	0.208	-0.007
GHxMH	-0.084	0.245	-0.021
PFxRP	0.143	0.185	0.026
PFxBP	-0.020	0.170	-0.003
PFxGH	0.023	0.200	0.005
PFxVIT	-0.023	0.196	-0.005
PFxSF	-0.065	0.232	-0.015
PFxRE	-0.048	0.212	-0.010
Constant	-0.256		-0.256
EQ-5D mapped score estimate			**0.658**

Using the same population norm health utility of 0.96 from Portwine 2014, the EQ-5D score of 0.658 corresponds to a reduction of 31.5% ((0.96-0.658)/0.96=31.5%) in HRQoL relative to the general population.

The use of this mapping algorithm has limitations:

i) The mapping algorithm used multiple correlated input dimensions. Only summary statistics for each SF-36 dimension score are available from Nathan 2007 and, therefore, no account of correlation between dimension scores was made.

ii) Uncertainty in the mapping process. This arises due to both the presence of unmeasured predictors (reflected in the residual error of the mapping algorithm) and the fact that the coefficients of the mapping algorithm are also random variables.

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Evidence Review Group's Addendum
Dinutuximab for treating high-risk neuroblastoma

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None

Table 1 presents the cost-effectiveness results for the ERG's base case (corresponding to Section 6.3.1) for a lower discount rate of 1.5% per annum for costs and outcomes.

Table 1: ERG's base case results for a lower discount rate of 1.5% per annum

	Total costs	**Total LYs**	**Total QALYs**	**Incre. costs**	**Incre. LYs**	**Incre. QALYs**	**ICER (£/QALY)**
ERG's base case – 3.5% discount rate							
Standard therapy	£54,671	14.03	10.90	-	-	-	-
Immunotherapy	£208,435	16.11	12.44	£153,765	2.08	1.54	£99,699
ERG's base case – 1.5% discount rate							
Standard therapy	£64,232	22.80	17.46	-	-	-	-
Immunotherapy	£221,887	26.00	19.82	£157,655	3.19	2.36	£66,690

LYs, life years; QALYs, quality-adjusted life years; incre., incremental; ICER, incremental cost-effectiveness ratio

Tables 2 and 3 present the cost-effectiveness results for the following assumptions:

Parameter	**Company's base case analysis using 2014 data**	**Committee's preferred assumptions**
Year of data	2014	2014
EFS and OS data	Company's base case parametric assumptions (Gompertz) up to cure threshold	Observed Kaplan-Meier data up to cure threshold
Cure threshold	5 years	10 years
Mortality	Same as general population for stable state after cure threshold	Standardised mortality rate of 5.6 applied to the general population mortality for stable state after cure threshold
Reduction in health-related quality of life (HRQoL)	13% relative to general population	13% relative to general population
Administration cost of dinutuximab	Company's base case assumption of £1,908 (without consideration of length of hospitalisation stay)	Adjustment to the administration cost of dinutuximab taking account of length of hospitalisation stay (Scenario 2 - based on hospital days, SB14Z and PM42A)
Body surface area (BSA)	Company's base case assumption based on an average BSA of 0.65m^2 from pivotal trial	Weighted average of BSA above and below 1m^2 from pivotal trial

Table 2: Cost-effectiveness results for company's base case analysis using 2014 data

	Total costs	Total LYs	Total QALYs	Incre. costs	Incre. LYs	Incre. QALYs	ICER (£/QALY)
Company's base case analysis using 2014 data - 3.5% discount rate							
Standard therapy	£47,213	13.89	10.87	-	-	-	-
Immunotherapy	£192,744	16.74	13.06	£145,531	2.85	2.19	£66,344
Company's base case analysis using 2014 data - 1.5% discount rate							
Standard therapy	£55,892	22.58	17.37	-	-	-	-
Immunotherapy	£203,932	27.44	21.07	£148,040	4.86	3.70	£40,042

LYs, life years; QALYs, quality-adjusted life years; incre., incremental; ICER, incremental cost-effectiveness ratio

Table 3: Cost-effectiveness results for committee's preferred assumptions

	Total costs	Total LYs	Total QALYs	Incre. costs	Incre. LYs	Incre. QALYs	ICER (£/QALY)
Committee's preferred assumptions - 3.5% discount rate							
Standard therapy	£53,983	13.06	10.21	-	-	-	-
Immunotherapy	£258,015	15.02	11.68	£204,032	1.97	1.46	£139,612
Committee's preferred assumptions - 1.5% discount rate							
Standard therapy	£61,955	19.61	15.27	-	-	-	-
Immunotherapy	£269,935	22.43	17.38	£207,980	2.81	2.11	£98,798

LYs, life years; QALYs, quality-adjusted life years; incre., incremental; ICER, incremental cost-effectiveness ratio

Table 4 presents the undiscounted life years for the company's base-case using 2014 data and the committee's preferred assumptions.

Table 4: Undiscounted life years for alternative assumptions

	Immunotherapy	Standard therapy	Incremental difference
Undiscounted life years			
Company's base-case using 2014 data	45.40	37.16	8.24
Committee's preferred assumptions	33.13	29.13	4.00