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CADTH Reimbursement Review

Dinutuximab (Unituxin)

Sponsor: United Therapeutics Corp.

Therapeutic area: Neuroblastoma

Clinical Review

Pharmacoeconomic Review

CADTH

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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Abbreviations

AdEERS	Adverse Event Expedited Reporting System
AE	adverse event
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
ASCT	autologous stem cell transplantation
CI	confidence interval
CSR	Clinical Study Report
COG	Children's Oncology Group
CORD	Canadian Organization for Rare Disorders
CR	complete response
DOR	duration of response
FDG-PET	fluorodeoxyglucose-positron emission tomography
GM-CSF	granulocyte-macrophage colony-stimulating factor
HR	hazard ratio
HRQoL	health-related quality of life
IL	interleukin
I-MIBG	I-metaiodobenzylguanidine
INRC	International Neuroblastoma Response Criteria
INSS	International Neuroblastoma Staging System
ITT	intention to treat
OPACC	Ontario Parents Advocating for Children with Cancer
ORR	objective response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PO	orally
POGO	Pediatric Oncology Group of Ontario
PR	partial response
RCT	randomized controlled trial
R/R	relapsed or refractory
SAE	serious adverse event
SD	standard deviation

Executive Summary

An overview of the submission details for the drug under review is provided in Table 1.

Introduction

Neuroblastoma is an ultra-orphan condition that occurs almost exclusively in the pediatric population. Despite its rarity, neuroblastoma is the most common and most deadly extracranial solid tumour in the pediatric population.[2] Signs and symptoms can be non-specific, and include pain, persistent fever, uncharacteristic behaviours, low energy levels, weight loss or gain, constipation, and loss of appetite. At the time of diagnosis, tumours can be stratified into low-, intermediate-, and high-risk groups based on multiple factors.[3] High-risk disease has a poor prognosis, with 5-year survival around 50%.[4] Approximately 76 patients are diagnosed with neuroblastoma each year in Canada.[5] Of these, half (approximately 40 patients per year) have high-risk disease.[3]

Approximately 10% to 20% of patients (approximately 6 cases per year in Canada) have inadequate responses to upfront therapy and are deemed refractory to treatment, while 50% to 60% (approximately 18 cases per year in Canada) of patients who complete upfront therapy successfully will eventually relapse.[6] Prognosis is uncertain among patients with relapsed or refractory (R/R) high-risk neuroblastoma, and true cure is extremely difficult, with 1-year progression-free survival (PFS) and overall survival (OS) estimated at 21% and 57%, respectively.[7] There are currently no approved therapies for patients with R/R high-risk neuroblastoma in Canada. Treatment is often empirical, and there is no single approach supported by clear evidence from comparative randomized controlled trials (RCTs), recommendations, or guidelines.[8] Combination chemotherapy regimens that differ from those used in upfront therapy are often used, but have limited efficacy.

Table 1: Submitted for Review

Item	Description
Drug product	Dinutuximab (Unituxin) 17.5 mg/m^2 per day, administered as an IV infusion over 10 hours to 20 hours for 4 consecutive days per treatment cycle
Indication under review[a]	For the treatment of high-risk neuroblastoma patients in their first relapse or determination of refractory disease in combination with irinotecan, temozolomide, and GM-CSF
Reimbursement request	As per indication under review
Health Canada approval status	NA[a]
Health Canada review pathway	NA[a]
NOC date	NA[a]
Sponsor	United Therapeutics Corp.

GM-CSF = granulocyte-macrophage colony-stimulating factor; NA = not applicable; NOC = Notice of Compliance.

[a]No Health Canada review is planned for the indication under review. Dinutuximab (Unituxin) received a NOC from Health Canada on November 28, 2018, in combination with GM-CSF, interleukin-2, and 13 cis-retinoic acid for the treatment of high-risk neuroblastoma in pediatric patients who achieve at least a partial response to prior first-line, multi-drug, multimodality therapy.

Source: CADTH Review submission for dinutuximab.[1]

According to the clinicians consulted by CADTH for the purpose of this review, the most important goals of treatment in patients with R/R high-risk neuroblastoma are to control disease and delay progression in the short-term, with the aim of prolonging long-term disease-free survival and potentially providing a route to cure. The clinical experts also stated that the combination of dinutuximab with granulocyte-macrophage colony-stimulating factor (GM-CSF) and chemotherapy (irinotecan plus temozolomide) is usually preferred over other options in most patients. However, access is currently limited to trials and compassionate access through the sponsor. Dinutuximab with irinotecan plus temozolomide and GM-CSF is considered the standard approach by many clinicians, except in patients who have had severe adverse reactions to dinutuximab and possibly in patients who progressed while receiving dinutuximab during upfront therapy.

Dinutuximab is a monoclonal antibody that binds to the glycolipid GD2. GD2 is expressed on neuroblastoma cells and on normal cells of neuroectodermal origin, including in the central nervous system and peripheral nerves. Dinutuximab binding induces lysis of GD2-expressing cells through antibody-dependent, cell-mediated cytotoxicity and complement-dependent cytotoxicity.[9] Dinutuximab is indicated, in combination with GM-CSF, interleukin-2 (IL-2), and retinoic acid, for the treatment of pediatric patients with high-risk neuroblastoma who achieve at least a partial response (PR) to prior first-line, multi-drug, multimodality therapy (upfront setting).[9] The drug received a Notice of Compliance from Health Canada on November 28, 2018, for this indication. CADTH conducted a prior review of dinutuximab (in 2019) for the approved indication (upfront setting), which resulted in a provisional recommendation for funding. The focus of the current review is as follows: "For the treatment of high-risk neuroblastoma patients in their first relapse or determination of refractory disease, in combination with irinotecan, temozolomide, and GM-CSF." No regulatory submission to Health Canada for this indication is planned by the sponsor at this time. Dinutuximab is administered at a recommended dose of 17.5 mg/m^2 per day by IV infusion over 10 hours to 20 hours for 4 consecutive days per treatment cycle. Pre-treatment with hydrazine or diphenhydramine plus acetaminophen is recommended before dinutuximab infusion. Recommended pain management is through a morphine loading dose before dinutuximab infusion followed by continued morphine drip or other narcotic (hydromorphone or fentanyl). Gabapentin is used as an adjunct to dinutuximab in patients who need additional pain control.

The objective of this report was to perform a systematic review of the beneficial and harmful effects of dinutuximab IV infusion for the treatment of pediatric patients with high-risk neuroblastoma in their first relapse or determination of refractory disease, in combination with irinotecan, temozolomide, and GM-CSF.

Stakeholder Perspectives

The information in this section is a summary of the input provided by the patient groups who responded to CADTH's call for patient input and from the clinical experts consulted by CADTH for the purpose of this review.

Patient Input

Neuroblastoma Canada, the Canadian Organization for Rare Disorders (CORD), and Ontario Parents Advocating for Children with Cancer (OPACC) submitted a joint patient input for this review. Information for this input was gathered through an online survey made available to respondents through various social media channels and directly by email in October and November 2020. There were 20 responses to the survey. Most respondents (18 of 20) were

parents or caregivers of patients. Of these, 11 had direct experience with dinutuximab in combination with irinotecan and temozolomide (2 in front-line therapy and 9 in relapse). Five 1-on-one telephone interviews were also conducted with patients and families who had direct experience with dinutuximab in combination with irinotecan and temozolomide.

Patient groups highlighted the delayed diagnosis of high-risk neuroblastoma and the many adverse effects of disease on quality of life, including pain, persistent fevers, uncharacteristic behaviours, constipation, low energy levels, weight loss or gain, and loss of appetite. In the relapsed setting, most of the reported side effects from the combination immunotherapy (i.e., dinutuximab, GM-CSF, irinotecan, and temozolomide) were manageable and comparable to those experienced in front-line therapy. Pain, fever, nausea and vomiting, allergic reactions, breathing issues, headache, low platelet count, low red blood cell count, low white blood cell count, low or high blood pressure, fluid retention, dehydration, fatigue, vision changes, sleepiness, allergic reaction to GM-CSF, reaction to IL-2, diarrhea, and constipation were reported side effects.

Caregivers clearly stated that they selected a treatment with their child's health-related quality of life (HRQoL) in mind. Two caregivers noted that recovery from dinutuximab with irinotecan and temozolomide was different from traditional therapies in terms of HRQoL between treatment cycles. They felt that treatment with dinutuximab, irinotecan, and temozolomide did not come with the long-term side effects of traditional therapies, such as autologous stem cell transplantation (ASCT), harsher chemotherapies, and radiation. Most respondents stated that therapies were selected based on their possible disease impact, and that their utmost desire was to find an effective treatment for their child. There was reported frustration that more advanced or experimental therapies were not available to them. Respondents reported more challenges accessing dinutuximab with irinotecan and temozolomide for treatment during relapses compared with the upfront setting. Four respondents accessed immunotherapy through clinical trials and 2 accessed it through special access; for 3 respondents, the method of access was unreported. Three respondents (27%) stated that it was difficult or extremely difficult to access immunotherapy. The remaining respondents (73%) said it was not difficult to access. Ten respondents were able to access immunotherapy at their home hospital, with only 1 having to travel for treatment within their state or province. For 1 refractory patient, the option to access dinutuximab with irinotecan and temozolomide was due to the efforts of their oncologist, who made a request for compassionate access.

Overall, respondents were willing to tolerate the challenges with access and the side effects associated with dinutuximab, especially if this treatment could address the disease burden, help deter relapse, and potentially be lifesaving. For the most part, respondents noted that the side effects were temporary, and that although they were challenging at times, they could be managed through the use of supportive medications.

Clinician Input

Input From the Clinical Experts Consulted by CADTH

The clinical experts consulted by CADTH for this review indicated that there are significant unmet needs for the treatment of patients with R/R high-risk neuroblastoma. Not all patients respond to the available treatments (such as combination chemotherapy), and these have limited efficacy. Clinicians are currently accessing dinutuximab for patients with R/R high-risk neuroblastoma through clinical trials and/or through temporary arrangements for compassionate access from the sponsor.

Clinicians noted that patients with R/R high-risk neuroblastoma should be offered treatment with dinutuximab combined with chemotherapy if tolerable and safe. Both relapsed and refractory patients with high-risk neuroblastoma can be expected to benefit from this intervention. It would not generally be appropriate to recommend that patients with R/R high-risk neuroblastoma try other treatments before dinutuximab based on the currently available evidence on the efficacy of other treatment options. At present, there are no markers that are sufficiently robust for clinical decision-making in identifying which patients with R/R high-risk neuroblastoma will or will not benefit from dinutuximab immunotherapy. The only exceptions might be patients who progressed while receiving dinutuximab during upfront therapy or who previously experienced severe reactions to dinutuximab therapy. However, the clinical experts acknowledged that it is not known conclusively whether progression during upfront dinutuximab treatment precludes future response to dinutuximab combined with chemotherapy. Patients best suited for dinutuximab therapy would be identified by pediatric oncologists and multidisciplinary teams in tertiary pediatric oncology units. Identification of eligible patients is not challenging in routine clinical practice. It is based on clinical assessment, imaging results, and biopsy results confirming R/R disease. Patients unsuitable for dinutuximab treatment are generally those with organ failure who require palliative care as well as those who previously had severe allergic reactions to the drug because they may not tolerate therapy.

The outcome of dinutuximab treatment in patients with R/R high-risk neuroblastoma is assessed by synthesizing clinical, radiological, and bone marrow responses. Clinically meaningful responses to treatment could be manifested through disease control or significant reduction of disease burden on re-staging evaluations during and after treatment, with the eventual goal of cure; improved survival; stabilization or improvement of symptoms (e.g., bone pain); and/or improvement in HRQoL. Responses to dinutuximab plus chemotherapy tend to occur early rather than late; thus, continued therapy (e.g., beyond 6 cycles) in the absence of any objective response may not be justified. In any individual patient, the decision to continue therapy should be based on evidence of response (either objective improvement seen on imaging and/or bone marrow assessment, or symptomatic benefit) versus toxicity and burden of therapy. Clinicians agreed that dinutuximab should be discontinued when there is evidence of progression during treatment, when adverse events (AEs) or toxicities become difficult to manage, or when treatment does not result in further decrease in disease burden or improvement in response, despite being well-tolerated. The frequency of response assessment will vary depending on symptoms, but should generally be approximately every 3 months, or after the first 2 cycles of therapy, and then every 3 to 4 cycles, or if there is any clinical suspicion of relapse or progression during treatment.

The combination of dinutuximab with chemotherapy and GM-CSF should be administered in an inpatient setting in a hospital with relevant experience, usually a tertiary pediatric oncology unit. The diagnosis, treatment, and monitoring of patients with R/R high-risk neuroblastoma receiving dinutuximab would be managed by a pediatric oncologist (or an oncologist with relevant experience). The clinical experts emphasized that dinutuximab (in combination with irinotecan, temozolomide, and GM-CSF) is already in widespread use in pediatric oncology units and is generally considered the treatment of choice for patients with R/R high-risk neuroblastoma.

Clinician Group Input

Two registered joint clinician inputs were provided on behalf of 9 clinicians from the Pediatric Oncology Group of Ontario (POGO) and 10 clinicians from the Pediatric Oncology Department

of BC Children's Hospital. There were no significant differences in views between the input provided by the clinical experts consulted by CADTH (see previous section) and the clinician group input. Both groups agreed that there are no approved efficacious therapies for R/R high-risk neuroblastoma, and that access to dinutuximab as potentially the most effective targeted therapy was critical to offering patients the best chance of optimal outcomes. Clinicians from BC Children's Hospital stated that, due to evidence of efficacy and tolerability, they would support this regimen as a first-line "salvage" approach for children with R/R high-risk neuroblastoma. Both clinician groups agreed that disease should be assessed regularly by cross-sectional imaging at minimum at least every 2 cycles (every 3 months), or sooner if clinically indicated. All clinicians and clinician groups consulted for this review agreed that the combination of dinutuximab, GM-CSF, and irinotecan plus temozolomide was already considered the de facto treatment of choice for R/R high-risk neuroblastoma in North America and worldwide, taking advantage of compassionate access to dinutuximab from the sponsor.

Drug Program Input

Drug programs identified several key issues related to implementation. First, drug programs requested clarification of the specific definitions of relapsed versus refractory neuroblastoma. The clinical experts consulted by CADTH for this review explained that although there is some degree of overlap between these terms, the major distinction is response to induction chemotherapy allowing patients to proceed to high-dose chemotherapy (refractory: no; relapsed: yes). This comes down to a case-by-case clinical decision based on response. Second, drug programs asked whether there were differences in treatment strategies for patients with relapsed versus refractory neuroblastoma. The clinical experts answered that there are substantial differences. For patients with refractory neuroblastoma, the goal is to move to second-line treatment options and obtain a response, then return to and complete the original treatment protocol, including high-dose chemotherapy with ASCT rescue, radiotherapy, immunotherapy, and so on. Patients with relapsed neuroblastoma have most likely already received high-dose chemotherapy and would not receive it again. Third, drug programs inquired whether there was evidence to support dinutuximab treatment beyond 17 cycles in patients with R/R high-risk neuroblastoma. The clinical experts stated that the only available evidence is based on a trial that used an arbitrary maximum of 17 cycles. However, there is no clear evidence that treatment with dinutuximab beyond 17 cycles would not be an approach to consider; this is a risk-benefit balance aimed for by the treating physician. Finally, drug programs inquired whether there was evidence on re-treatment with the same drug in the R/R setting for patients who received prior dinutuximab. The clinical experts responded that there is evidence for the efficacy of combination therapy with dinutuximab and irinotecan plus temozolomide and GM-CSF in patients with R/R high-risk neuroblastoma even if dinutuximab was used in upfront therapy. There is also anecdotal evidence that patients can respond again to the same combination after relapse.

Clinical Evidence

Key Studies and Protocol Selected Studies

Description of Studies

A single study was included the systematic review. The ANBL1221 trial was a phase II, prospective, multi-centre, open-label RCT with a "pick the winner" design.[10,11] The initial primary objective of the study was to determine whether temsirolimus (regimen A) or dinutuximab (regimen B) was the optimal drug to move forward to a phase III trial in

patients with R/R high-risk neuroblastoma. A second primary objective — to determine the response rate more accurately for regimen B (dinutuximab with GM-CSF and irinotecan plus temozolomide) in an expanded cohort — was added through a protocol amendment to enable comparison with historical response rates to irinotecan and temozolomide alone (e.g., from the ANBL0421 trial).[12] The study enrolled patients of any age with histologic or bone marrow biopsy (with elevated urinary catecholamines) evidence of high-risk neuroblastoma at their first designation of relapse or refractory disease. Patients had to have adequate organ function, Karnofsky/Lansky scores of 50% or greater, and recovered from the toxic effects of prior therapies. Patients who had previously received treatment for high-risk R/R neuroblastoma, as well as those who had experienced severe reactions or progressive disease (PD) during upfront anti-GD2 immunotherapy, were excluded.

In the first stage of the study, patients (N = 35) were randomized 1:1 to receive either temsirolimus (regimen A) or dinutuximab and GM-CSF (regimen B), both with standard chemotherapy (irinotecan and temozolomide). Dinutuximab was dosed at 17.5 mg/m^2 per day on 4 consecutive days (days 2 to 5) per 3-week treatment cycle, while temsirolimus was dosed at 35 mg/m^2 on day 1 and day 8. Randomization was stratified by disease status at baseline (relapsed versus refractory), prior anti-GD2 immunotherapy, and *MYCN* status. No concomitant systemic anti-cancer therapies were permitted while on protocol therapy. Patients were evaluated after 2 cycles, then at cycles 4 and 6, and every 4 cycles thereafter to a maximum of 17 cycles. Response was assessed using the International Neuroblastoma Response Criteria (INRC).[13,14] The primary efficacy end point was the proportion of patients achieving at least a PR as their best overall response by the completion of 6 cycles; patients with PD at evaluation were taken off protocol therapy and classified as treatment failures. Exploratory objectives of interest to this review included a comparison of the objective response rates (ORRs) of the dinutuximab and temsirolimus regimens as well as duration of response (DOR), PFS, and OS. Following completion of the randomized stage, there was insufficient evidence for a treatment effect of regimen A (temsirolimus) based on pre-specified selection criteria; therefore, this arm was closed to accrual. Enrolment was expanded to permit accrual of 36 non-randomized patients treated with regimen B (dinutuximab with GM-CSF and irinotecan plus temozolomide) to determine the ORR more accurately. The mean duration of follow-up for patients in the study was 773.2 days (standard deviation [SD] 499.4 days).

The study was conducted at 49 sites in Canada, the US, Australia, and New Zealand. Patients were enrolled from 2013 to 2017, and the data cut-off was September 30, 2019. The patients enrolled in the ANBL1221 trial were primarily male (62.0%), White (67.6%), not of Hispanic ethnicity (77.5%), and from the US (81.7%). The mean age at enrolment was 6.4 years (SD = 3.6 years). Most patients (88.7%) had International Neuroblastoma Staging System (INSS)[15] stage 4 tumours. The study included patients with both relapsed (43.7%) and refractory (56.3%) disease, patients whose tumours were measurable (69.0%) and not measurable (31.0%) by CT or MRI, and patients with *MYCN*-amplified (26.8%) and *MYCN*-nonamplified (69.0%) tumours. Overall, baseline demographic and clinical characteristics were generally well balanced between the randomized arms and the non-randomized expansion cohort. However, patients treated with regimen A were slightly older at enrolment (median = 7.0 years) than those treated with regimen B (median = 5.1 years), and a subset of patients receiving regimen B (17%) were diagnosed before 2 years of age. Unlike patients receiving regimen A, a subgroup of patients treated with regimen B had INSS stage 3 or stage 4S tumours (11.3%).

Efficacy Results

ORR was assessed as a descriptive statistic as part of the "pick the winner" design of the ANBL1221 study[10,11]; no inferential statistical analysis was planned or required. In the randomized study, regimen A (temsirolimus) did not meet the pre-specified minimum standards for efficacy. As an exploratory analysis, ORR was compared between the randomized trial arms (Table 2). The ORR in patients treated with regimen B was 52.9% (9 of 17 patients had a PR or better; 95% confidence interval [CI], 27.7% to 77.0%) and was 5.9% in patients treated with regimen A (1 of 18 patients had a PR or better; 95% CI, 0.1% to 27.3%; P = 0.0027). Based on these results, patients were recruited into an expansion cohort and directly assigned to receive regimen B. The ORRs of patients in the expansion cohort and all regimen B–treated patients in the study were consistent with those of patients treated with regimen B in the randomized study (expansion cohort: 13 of 36 [36.1%] patients had a PR or better; 95% CI, 20.8% to 53.8%; P = 0.0205 versus regimen A; all regimen B–treated patients: 22 of 53 [41.5%] patients had a PR or better; 95% CI, 28.1% to 55.9%; P = 0.004 versus regimen A). The limitations associated with this result included the small sample size of the trial, the exploratory nature of the outcome and lack of multiplicity control, uncertain comparability of the randomized cohort with a non-randomized cohort that was added post hoc, and the potential for biased outcome assessment in the open-label study design. Despite these caveats, the clinical experts consulted by CADTH for this review stressed that the single-arm response data (ORR) from the ANBL1221 study suggest a benefit for the addition of dinutuximab,[10,11] and that the evidence has been sufficient to trigger a shift in the current treatment paradigm: dinutuximab with temozolomide, irinotecan, and GM-CSF has become the de facto standard of care for most patients.

DOR, PFS, and OS were also analyzed as exploratory outcomes. Median DOR was 35.1 weeks in the single responding patient treated with regimen A and 33.0 weeks (range = 2.4 weeks to 76.1 weeks) among all patients treated with regimen B. Median DOR based on Kaplan–Meier analysis was 76.1 weeks (95% CI not calculable) among all patients treated with regimen B. Median PFS was 7.7 weeks (range = 5.9 weeks to 66.0 weeks) in patients treated with regimen A and 57.0 weeks (range = 3.3 weeks to 196.9 weeks) in all patients treated with regimen B. Median PFS based on Kaplan–Meier estimates was 12.9 weeks (95% CI, 6.9 weeks to 47.3 weeks) in patients treated with regimen A and 97.9 weeks (95% CI, 60.3 weeks to 110.6 weeks) in all patients treated with regimen B (hazard ratio [HR] = 0.41; 95% CI, 0.22 to 0.77; P = 0.0054). Median OS was 54.8 weeks (range: 13.1 weeks to 165.9 weeks) in patients treated with regimen A and 72.8 weeks (range = 6.0 weeks to 219.4 weeks) in all patients treated with regimen B. Median OS, based on Kaplan–Meier estimates, was 117.3 weeks (95% CI, 23.6 weeks to 165.9 weeks) in patients treated with regimen A and 219.4 weeks (95% CI not calculable) in patients treated with regimen B (HR = 0.50; 95% CI, 0.2 to 1.04, P = 0.0636). The limitations associated with these results included the small sample size of the trial, wide CIs of effect estimates, the exploratory nature of the outcomes, lack of multiplicity control, limited power to evaluate survival end points, difficulty in accurately assessing DOR and PFS due to the low number of patients responding to therapy, variable follow-up times, the potential effects of other anti-cancer therapies administered following ANBL1221 trial protocol therapy on survival outcomes, and the potential for high variation in survival outcomes, even in the absence of treatment because of the clinical heterogeneity of the disease. Despite these caveats, DOR, PFS, and OS among patients treated with regimen B in the ANBL1221 trial were interpreted by the clinical experts consulted for this review as potentially clinically meaningful. In addition, subgroup analyses of all efficacy outcomes by relapsed versus refractory disease and *MYCN* status were underpowered to detect differences in efficacy.

Harms Results

The percentages of patients treated with regimen A and regimen B who experienced AEs were similar (88.9% and 94.1%, respectively) (Table 2). Some AEs were common in patients receiving both regimens (e.g., myelosuppression, anemia, hypokalemia, and diarrhea) while pain (33.3%), pyrexia (33.3%), hypoxia (21.6%), hypotension (11.8%), and dyspnea (5.9%) occurred more often in patients treated with regimen B. Serious AEs (SAEs) reportable in the Adverse Event Expedited Reporting System (AdEERS) occurred in a higher percentage of patients treated with regimen B (68.8% randomized cohort, 52.9% overall) than in those treated with regimen A (38.9%). The most common AdEERS-reportable events in all patients treated with regimen B were decreased neutrophil count (9.8%), death (7.8%), disease progression (5.9%), and hypoxia (5.9%). Very few patients treated with either regimen A (1 of 18; 5.9%) or regimen B (1 of 53; 2.0%) had AEs requiring withdrawal from protocol therapy; withdrawals due to adverse events included 1 patient treated with regimen A who experienced a severe infusion reaction and 1 patient treated with regimen B who developed grade 4 hypoxia. As expected for patients with high-risk R/R neuroblastoma, many deaths occurred over the study period (regimen A: 12 of 18; 66.7%; regimen B: 19 of 51; 37.3%); however, only 2 occurred during the treatment period. Both were in the non-randomized regimen B expansion cohort.

Of the notable harms identified in the CADTH review protocol, pain was the most frequent among patients treated with regimen B (17 of 51, 33.3%). AEs associated with infusion reactions — such as capillary leak syndrome (2 of 51; 4.0%), hypotension (5 of 51; 9.8%), dyspnea (3 of 51; 5.9%), and respiratory failure (3 of 51; 5.8%) — also occurred in patients treated with regimen B, but not in any patients treated with regimen A. Peripheral motor neuropathy occurred in 1 patient (2.0%) receiving regimen B. AEs requiring hospitalization or prolonged hospitalization occurred with similar frequency in patients receiving regimen A (44.4%) and regimen B (47.1%).

Critical Appraisal

The ANBL1221 study was a phase II, multi-centre, randomized, open-label RCT.[10,11] The major limitations of the trial included its small sample size, with only 18 patients treated with regimen A, and the fact that all comparisons of efficacy outcomes of interest to this review were exploratory in nature. Moreover, there was some concern regarding the number of protocol violations (e.g., incorrect doses) in the conduct of the trial. Another fundamental limitation was the questionable comparability of data from the randomized (regimen A versus regimen B) and non-randomized (regimen B) cohorts: without the power of randomization to balance confounding factors, the potential for selection bias and systematic differences between these groups of patients could have affected response rates. Because of the open-label design of the study and the complex criteria for assessing response, bias in outcome assessment may have influenced the results. The study was not powered to evaluate longer-term efficacy outcomes (DOR, PFS, OS), and the interpretation of these outcomes is complicated by variable follow-up times and the effects of other anti-cancer therapies received by patients after they discontinued the ANBL1221 trial protocol therapy. Subgroup analyses of efficacy outcomes (e.g., by relapsed versus refractory disease and *MYCN* status) were underpowered to detect any differences.

The characteristics of patients treated in this study were broadly similar to the Canadian context. However, the ANBL1221 trial excluded patients whose disease progressed during dinutuximab immunotherapy in upfront therapy as well as patients in their second or subsequent relapses. Therefore, the results cannot be extended to these patients. However,

Table 2: Summary of Results From Key and Protocol Selected Studies — ANBL1221 Trial

Result	Regimen A randomized	Regimen B randomized	Regimen B non-randomized	Regimen B total
ITT population				
N	18	17	36	53
ORR				
N (%)[a]	1 (5.6)	9 (52.9)	13 (36.1)	22 (41.5)
95% CI[b]	0.1 to 27.3	27.8 to 77.0	20.8 to 53.8	28.1 to 55.9
P value[c]	—	0.0027	0.0205	0.004
DOR (weeks)				
Median (range)	35.1 (35.1 to 35.1)	31.0 (24.3 to 37.7)	32.95 (2.4 to 76.1)	32.95 (2.4 to 76.1)
Kaplan–Meier estimated median (95% CI)[d]	35.1 (NC to NC)	NC (24.3 to NC)	35.0 (2.4 to NC)	76.1 (30.9 to NC)
P value[e]	—	0.1768	0.8858	0.4278
PFS (weeks)				
Median (range)	7.7 (5.9 to 66.0)	92.3 (5.1 to 196.9)	48.75 (3.3 to 121.3)	57.0 (3.3 to 196.9)
Kaplan–Meier estimated median (95% CI)	12.9 (6.9 to 47.3)	101.0 (30.1 to NC)	81.4 (42.4 to 110.6)	97.9 (60.3 to 110.6)
Hazard ratio (95% CI)[f]	—	0.39 (0.17 to 0.88)	(0.22 to 0.83)	0.41 (0.22 to 0.77)
P value[f]	—	0.024	0.012	0.0054
OS (weeks)				
Median (range)	54.75 (13.1 to 165.9)	120.1 (6.0 to 219.4)	62.4 (10.9 to 143.7)	72.75 (6.0 to 219.4)
Kaplan–Meier estimated median (95% CI)[d]	117.3 (23.6 to 165.9)	NC (120.1 to NC)	143.7 (105.9 to NC)	219.4 (120.1 to NC)
Hazard ratio (95% CI)[f]	—	0.37 (0.14 to 0.99)	0.65 (0.28 to 1.52)	0.50 (0.24 to 1.04)
P value[f]	—	0.0479	0.3186	0.0636
Safety population				
N	18	16	35	51
Harms, n (%)				
AEs	16 (88.9)	16 (100.0)	32 (91.4)	48 (94.1)
SAEs	7 (38.9)	11 (68.8)	16 (45.7)	27 (52.9)
WDAEs (from study treatment)	1 (5.6)	1 (6.3)	0	1 (2.0)
Deaths	12 (66.7)	7 (43.8)	12 (34.3)	19 (37.3)
Notable harms, n (%)				
Infusion reactions	1 (5.6)	0	0	0
Capillary leak syndrome	0	1 (6.3)	1 (2.9)	2 (3.9)

Result	Regimen A randomized	Regimen B randomized	Regimen B non-randomized	Regimen B total
Anaphylaxis	0	0	1 (2.9)	1 (2.0)
Hypersensitivity	1 (5.6)	1 (6.3)	0	1 (2.0)
Hypotension	0	3 (18.8)	3 (8.6)	6 (11.8)
Dyspnea	0	3 (18.8)	0	3 (5.9)
Respiratory failure	0	1 (6.3)	2 (5.7)	3 (5.9)
Pain	0	4 (25.0)	13 (37.1)	17 (33.3)
Peripheral motor neuropathy	0	1 (6.3)	0	1 (2.0)
AEs requiring hospitalization or prolonged hospitalization	8 (44.4)	12 (75.0)	12 (34.3)	24 (47.1)

AE = adverse event; CI = confidence interval; DOR = duration of response; ITT = intention to treat; NC = not calculable; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

[a]ORR was assessed up to cycle 6.

[b]Calculated using the Clopper-Pearson exact method.

[c]From Fisher's exact test. No adjustment for multiplicity was performed.

[d]Median not calculable because < 50% of patients experienced an event.

[e]From log-rank test. No adjustment for multiplicity was performed.

[f]From unadjusted Cox proportional hazards model. No adjustment for multiplicity was performed.

[f]Median values were not calculable because < 50% of patients in the analysis group experienced an event.

Source: Clinical Study Report for ANBL1221.[16]

the clinical experts consulted by CADTH for this review stated that in the R/R setting, dinutuximab with chemotherapy would be unlikely to be the treatment of choice for the former group of patients. In addition, the results may not be generalizable to patients treated in hospitals without significant experience with R/R high-risk neuroblastoma and/or dinutuximab administration. However, according to the clinicians consulted by CADTH for this review, in practice this is not a concern given that, in Canada, dinutuximab is routinely administered only in experienced centres.

Indirect Comparisons

No indirect evidence was identified for this review.

Other Relevant Evidence

No other evidence was identified for this review.

Conclusions

Data from the ANBL1221 trial suggested that the dinutuximab with GM-CSF and irinotecan plus temozolomide combination may be efficacious in inducing objective responses in patients with R/R high-risk neuroblastoma. Confidence in comparisons of these efficacy outcomes with other therapies was limited by the small number of participants, the challenges inherent in comparisons between regimen A and regimen B, the exploratory nature of the efficacy outcomes, and the absence of multiplicity control. Together, these factors contribute substantial uncertainty regarding the magnitude of the observed treatment effects. This regimen was tolerable and manageable in most patients, with a toxicity profile as expected based on prior studies of dinutuximab. Despite uncertainty in the effect size

for efficacy outcomes, these results are potentially clinically relevant for patients with R/R high-risk neuroblastoma.

Introduction

Disease Background

Cancer is rare in children, but it has a disproportionate impact on them, and is the most common cause of pediatric disease-related mortality in Canada.[17] Despite its status as an ultra-orphan condition, neuroblastoma is the most common and most deadly extracranial solid tumour in the pediatric population and the most common tumour diagnosed in the first year of life.[2] The etiology of neuroblastoma is poorly understood, and the sporadic occurrence of this disease has made it difficult to study. Primary tumours occur most frequently in abdominal or thoracic locations, while lymph nodes, bone, bone marrow, and liver are common sites of metastasis.[18] Signs and symptoms can include pain, persistent fever, uncharacteristic behaviours, low energy levels, weight loss or gain, constipation, and loss of appetite. Both the disease itself and its treatment (among the most intensive therapy for any form of cancer) severely affect HRQoL.[19] Because initial symptoms can be non-specific, diagnosis can take time, requiring multiple visits with primary care providers and significant advocacy from parents or guardians.

At the time of diagnosis by a pediatric oncologist (based on clinical evaluation, imaging results, and bone marrow biopsy), most patients already have distant metastases. At diagnosis, neuroblastoma tumours can be categorized into low, intermediate, or high-risk groups based on several factors, including patient age at diagnosis, *MYCN* status, histopathological classification, tumour DNA index, and stage of tumour.[3] While patients with low- or intermediate-risk disease generally have good outcomes following minimal chemotherapy or surgery, the clinical experts consulted by CADTH for this review noted that high-risk disease carries a poor prognosis, with 5-year survival around 50% despite intensive multi-drug, multimodality therapy.[4] There are approximately 76 cases of neuroblastoma diagnosed each year in Canada and 14 attributable deaths.[5] Roughly half of neuroblastoma cases are diagnosed with high-risk disease (approximately 40 incident cases per year).[3]

Approximately 10% to 20% of patients (6 cases per year) do not achieve remission during upfront therapy and are deemed refractory to treatment, and 50% to 60% of patients (approximately 18 cases per year) who complete upfront therapy successfully will eventually relapse.[6] Thus, the total number of patients with R/R high-risk neuroblastoma in Canada considered in this review is estimated at 24 per year. Outcomes among patients with R/R high-risk neuroblastoma are uncertain; prognosis is poor, and cure is extremely difficult. A meta-analysis of patients with R/R high-risk neuroblastoma treated in the modern era in Children's Oncology Group (COG) early-phase trials showed that 1-year and 4-year PFS rates were 21% and 6%, respectively; 1-year and 4-year OS rates were 57% and 20%, respectively; and the median time to progression was 58 days.[7] However, according to the clinicians consulted by CADTH for this review, it should be noted that many of these patients would have entered early-phase trials in the setting of multiply relapsed disease.

Standards of Therapy

Upfront treatment of high-risk neuroblastoma consists of 5 sequential components: multi-drug induction chemotherapy, including cyclophosphamide, topotecan, cisplatin, etoposide, doxorubicin, and vincristine; surgical resection of the primary tumour; high-dose chemotherapy with tandem ASCT[20]; external beam radiotherapy to the primary tumour site; and immunotherapy with dinutuximab, GM-CSF, IL-2, and retinoic acid.[21] In this setting, dinutuximab is considered part of the standard of care, based in part on the results of the DIV-NB-301 (COG ANBL-0032) study.[22]

There are currently no approved therapies for patients with R/R high-risk neuroblastoma in Canada. Typically, systemic combination chemotherapy regimens are used that differ from those used in upfront therapy. Systemic molecular radiotherapy (e.g., ^{131}I-metaiodobenzylguanidine [^{131}I-MIBG]) has shown some efficacy, although clinical benefit is often temporary.[23] According to the sponsor, ^{131}I-MIBG therapy is not routinely funded in Canada, and access often relies on charitable fundraising. A variety of immunotherapies and molecularly targeted therapies are under investigation, as are combinations of chemotherapies, radiotherapies, and/or immunotherapies.[24]

According to the clinicians consulted by CADTH for the purpose of this review, efficacious therapies are lacking. Treatment is often empirical, and there is no single approach supported by clear evidence from randomized comparative trials, recommendations, or guidelines.[8] Treatment options also vary because of the heterogeneity of this population in terms of extent and site of disease, previous therapy, toxicities, organ function, and patient or family priorities. The clinical experts noted that current treatment options include: combination chemotherapy (irinotecan with temozolomide, topotecan with cyclophosphamide, or ifosfamide, carboplatin, and etoposide); chemotherapy and immunotherapy (temozolomide plus irinotecan with dinutuximab and GM-CSF); ^{131}I-MIBG therapy with or without stem cell transplant; anaplastic lymphoma kinase (ALK) inhibitors (for patients whose tumours show ALK aberrations); and investigational therapies available through COG protocols or neuroblastoma investigational trials. Less often, patients with an isolated metastatic recurrence might receive only external beam radiotherapy as an initial treatment approach. In the setting of multiply relapsed or rapidly PD, it may be that no further treatment is appropriate, but this would be unusual in the setting of refractory disease or initial relapse. The clinical experts consulted by CADTH stated that the combination of dinutuximab with GM-CSF and chemotherapy (irinotecan plus temozolomide) is often preferred over other options, but access is currently limited to trials and compassionate access through the sponsor. Dinutuximab combined with irinotecan plus temozolomide and GM-CSF is considered the standard approach by many clinicians, except in patients who have had severe adverse reactions to dinutuximab and possibly in patients who progressed while receiving dinutuximab during upfront therapy. The clinical experts consulted by CADTH for this review felt it was important to clarify that adverse reactions are to be expected following dinutuximab therapy and are manageable. Enrolment in clinical trials would be considered the first option for most eligible patients. Clinicians stated that GM-CSF is not approved in Canada but can be accessed through Health Canada's Special Access Program.

According to the clinicians consulted by CADTH for the purpose of this review, the most important goal of treatment in patients with R/R high-risk neuroblastoma is to control disease and delay progression in the short-term, with the aim of prolonging long-term disease-free survival and potentially providing a route to cure. Other goals include reducing symptom severity and improving HRQoL. Given the high risk of mortality associated with R/R high-risk

neuroblastoma, considerations regarding the toxicity and intensity of therapy are important but are secondary to the goal of obtaining disease response. Treatment for high-risk neuroblastoma is among the most intensive therapies used for cancer treatment; the clinical experts consulted by CADTH for this review emphasized that the toxicity of therapies for R/R disease should be viewed in that context.

Clinicians emphasized that for refractory patients who have inadequate responses to induction chemotherapy, the goal is to improve the extent of metastatic disease and resume the initial treatment plan, including high-dose chemotherapy with ASCT rescue, radiotherapy, and immunotherapy. These patients have worse prognoses than patients who respond to induction chemotherapy, but treatment intent is still curative. For relapsed patients, the goal is to achieve cure or at least prolong survival and improve symptoms. In the immediate term, the goal is to reduce the disease burden and, if possible, return the patient to a state of clinical complete response (CR) with the hope of improving survival time. For patients who are symptomatic at the time of recurrence (e.g., from bone involvement), improvement in disease extent is likely to lead to an improvement in symptoms; in some cases, symptomatic improvement may occur without significant changes in imaging appearance.

Drug

Dinutuximab is a monoclonal antibody that binds to the glycolipid GD2. GD2 is expressed on neuroblastoma cells and on normal cells of neuroectodermal origin, including in the central nervous system and peripheral nerves. Dinutuximab binding induces lysis of GD2-expressing cells through antibody-dependent cell-mediated cytotoxicity and complement-dependent cytotoxicity (Table 3).[9]

Dinutuximab is indicated — in combination with GM-CSF, IL-2, and retinoic acid — for the treatment of pediatric patients with high-risk neuroblastoma who achieve at least a PR to prior first-line, multi-drug, multimodality therapy (upfront setting).[9] The drug received a Notice of Compliance from Health Canada on November 28, 2018 for this indication. CADTH conducted a review of dinutuximab in 2019 for the approved indication (upfront setting), which resulted in a provisional recommendation for funding. The focus of the current review is as follows: "For the treatment of high-risk neuroblastoma patients in their first relapse or determination of refractory disease, in combination with irinotecan, temozolomide, and GM-CSF." No regulatory submission to Health Canada for this indication is planned by the sponsor at this time. Dinutuximab is administered at a recommended dose of 17.5 mg/m^2 per day by IV infusion over 10 hours to 20 hours for 4 consecutive days per treatment cycle. Pre-treatment is recommended before dinutuximab infusion, including hydroxyzine or diphenhydramine and acetaminophen. Recommended pain management is with a morphine loading dose before dinutuximab infusion followed by continued morphine drip or other narcotic (hydromorphone or fentanyl). Gabapentin is used as an adjunct to dinutuximab in patients needing additional pain control.

Stakeholder Perspectives

Patient Group Input

This section was prepared by CADTH staff based on the input provided by patient groups. Of note, quotes are reproduced as they appeared in the survey, with no modifications made for spelling, punctuation, or grammar. The statistical data that are reported have also been reproduced according to the submission, without modification.

About the Patient Groups and Information Gathered

Neuroblastoma Canada, CORD, and OPACC submitted a joint patient input for this review. Neuroblastoma Canada is a national, community-based organization dedicated to uniting Canadian neuroblastoma families. CORD is Canada's national network for organizations representing all those with rare disorders and provides a strong common voice to advocate for health policy and a health care system that works for those with rare disorders. It works with governments, researchers, clinicians, and industry to promote research, diagnosis, treatment, and services for rare disorders in Canada. OPACC is the leading voice and expert resource for families and organizations navigating the childhood cancer journey.

Table 3: Key Characteristics of Therapies for Relapsed or Refractory High-Risk Neuroblastoma

Characteristic	Dinutuximab	Systemic chemotherapy[a]	Systemic molecular radiotherapy[b]
Mechanism of action	Binding to cell-surface GD2 on neuroblastoma cells followed by ADCC and/or CDC	Topoisomerase inhibition/DNA alkylation	Delivery of ^{131}I-MIBG to tumours using radiolabelled benzylguanidine analogues to target the norepinephrine transporter
Route of administration	IV	IV (irinotecan), p.o. (temozolomide)	IV
Recommended dose	17.5 mg/m^2 per day over 10 hours to 20 hours for 4 consecutive days per treatment cycle	50 mg/m^2 over 90 minutes for 5 consecutive days per treatment cycle (irinotecan); 100 mg/m^2 for 5 consecutive days per treatment cycle (temozolomide)	18 mCi/kg
Serious adverse effects or safety issues	Serious and potentially life-threatening infusion reactions; capillary leak syndrome; neuropathic pain; severe neurologic toxicities	Diarrhea; infection; liver injury; myelosuppression	Infection; myelosuppression
Other	Dinutuximab is used in combination therapy regimens that include GM-CSF, which is not approved in Canada and is accessed through HC SAP	NA	NA

ADCC = antibody-dependent cellular cytotoxicity; CDC = complement-dependent cytotoxicity; GM-CSF = granulocyte-macrophage colony-stimulating factor; HC SAP = Health Canada Special Access Programs; ^{131}I-MIBG = ^{131}I-metaiodobenzylguanidine; NA = not applicable; p.o. = orally.

[a]For example, irinotecan plus temozolomide.

[b]For example, ^{131}I-MIBG.

Sources: Product monographs for dinutuximab (Unituxin),[9] irinotecan,[25] and temozolomide[26]; dose of ^{131}I-MIBG therapy provided by the clinical experts consulted by CADTH for this review.

Information for this input was gathered through 1 survey created jointly by Advocacy for Canadian Childhood Oncology Research Network, CORD, and OPACC. The survey was made available to respondents in October and November 2020. The online survey was distributed through various social media channels and directly by email. The survey asked for input from patients and families who were treated for high-risk R/R neuroblastoma and who may or may not have had experience with dinutuximab in combination with irinotecan and temozolomide for R/R neuroblastoma. There were 20 responses to the survey. Of these, 11 respondents had direct experience with dinutuximab in combination with irinotecan and temozolomide (2 in front-line treatment and 9 in relapse). Of respondents who identified the location of their primary residence (n = 11), 3 were from Ontario, 1 was from British Columbia, 5 were from the US, and 2 were international. Most survey respondents (n = 18) were parents and caregivers of patients.

Five 1-on-one telephone interviews were also conducted with patients and families who had direct experience with dinutuximab in combination with irinotecan and temozolomide. Two of these respondents were from Ontario, 2 were from British Columbia, and 1 was from the US. Most interviews (n = 4) were conducted with families of patients 10 years of age or older (10 years, 16 years, 17 years, and 17 years). The ages at time of diagnosis for the children in the survey and interviews were representative of the diagnosis age profile for high-risk neuroblastoma. The average reported age at diagnosis was 4 years. Most patients (80%) were aged 5 years or under at the time of diagnosis. Most patients (n = 24) were diagnosed with high-risk neuroblastoma. Only 1 was diagnosed with intermediate-risk neuroblastoma.

Disease Experience

Many respondents said that before diagnosis, their child experienced pain, persistent fevers, and uncharacteristic behaviours. Constipation, low energy levels, pain, weight loss or gain, and loss of appetite were other common issues reported before diagnosis.

For many respondents, a diagnosis of cancer took time and often required multiple visits to family doctors, emergency rooms, and specialists. Respondents said symptoms were downplayed by clinicians and classified as transitory or not serious (e.g., constipation). Four respondents stated that their child was initially diagnosed with juvenile arthritis, and that specialists identified the cancer through scans trying to locate the persistent joint and bone pain. When symptoms returned or persisted, caregivers advocated for their child until appropriate tests were ordered that ultimately identified the illness as neuroblastoma. Only in a few cases were diagnoses made directly.

- A parent of a 2-year-old patient said, “My son was finally diagnosed with NB [neuroblastoma] after I continually asked questions and brought my son back in to pediatrician. Saw a different pediatrician who felt mass and sent us to ER where X-ray confirmed a mass, and we were admitted.”
- A parent of a 5-year-old patient shared:

  She started with intermittent fevers and leg pain. Occasional stomach pain, fatigue, and loss of interest in playing. The fevers became more frequent over the course of 2 months until she ran a consistent 101 fever even on antipyretics. She stopped being able to walk more than a few steps and was experiencing constant leg pain. She was seen by infectious disease [doctors] for 2 months, we asked and was told it wouldn't be cancer because it was too rare and because her bloodwork didn't show any sign of leukemia. Weekly blood tests only showed mild and then progressively worse anemia, negative for every pathogen she was tested for. When she completely stopped eating and drinking, we

were referred to hematology, as opposed to waiting 6 weeks to get into rheumatology. A bone marrow biopsy revealed 99% bone marrow involvement, she needed an immediate blood transfusion. Three days later we had confirmation that it was neuroblastoma, she was admitted to the hospital, and we watched as a tumour grew on her skull in a matter of hours.

In many cases, respondents shared details about the escalation of symptoms until they reached severe levels before a diagnosis was finally made. Respondents revealed that it is not uncommon for neuroblastoma to masquerade as other common childhood conditions, or for high-risk neuroblastoma to be metastatic and advanced at the time of diagnosis.

Experiences With Currently Available Treatments

Experiences With Front-Line Therapy

The standard of care for front-line therapy includes multiple cycles of chemotherapy, surgery, mega-dose chemotherapy with ASCT, radiation, and immunotherapy. For almost all respondents, accessing front-line treatment was not an issue.

Of the 19 respondents who shared information about their child's front-line treatment, 68% received chemotherapy, 58% received radiation therapy, 63% underwent surgery, 53% received mega-dose chemotherapy, 9% underwent ASCT, 8% received immunotherapy or dinutuximab, and 32% experienced maintenance therapy (e.g., Accutane, retinoic acid). Two respondents stated that their child received dinutuximab with irinotecan and temozolomide in front-line therapy, and 3 respondents shared that their child received difluoromethylornithine after completing front-line therapy. One respondent shared that their child also received ^{131}I-MIBG therapy as part of their front-line treatment. One respondent noted that their child received naxitamab (also known as 3F8), an immunotherapy similar to dinutuximab.

Twelve respondents provided comments on their child's experience with front-line therapy. Three shared that they felt their child's cancer responded well to front-line therapy, with no major complications. Three other respondents shared that front-line treatment was difficult, but that they were able to manage through the expected complications. The remaining 5 respondents who provided details found various aspects of front-line treatment to be difficult and often overwhelming. The following are some quotes from caregivers explaining their children's experiences with front-line treatment:

- A caregiver whose child was diagnosed at 9 years of age shared, "My daughter's experience with front-line therapy was difficult, she suffered severe nausea and diarrhea through every admission for chemotherapy. My daughter[s] neuroblastoma did not respond very well to front-line treatment we did not see much response until she reached immunotherapy."
- A caregiver of a child who was diagnosed at 3 years of age said, "Front-line chemo was hard, but we took it one day at a time and made it through. She got infections between every round and spent the majority of her time inpatient. Stem cell was tough but easier than expected for us. She engrafted quickly and spent just 5 weeks in hospital. Radiation was relatively easy she was tired and nauseous every 3 to 4 days but tolerated it well. Immunotherapy was awful for her as we had a difficult time staying ahead of the pain. By round 4 we had a good routine set to tolerate it as well as possible."
- "After 2 years of chemotherapy which was very difficult, he received surgery followed by radiation was really brutal because we had to travel to Calgary and stay there. He was 12 years old and missed his school and friends."

- "For us, immunotherapy was the easiest part of the whole front-line treatment and was most effective at cleaning up residual disease. We didn't experience too many issues during immunotherapy, and it was nice to be predictable on when we would get to go home, unlike with chemo where we had to wait for puking to stop which was always an unknown."

Overall, neutropenia, nausea, vomiting, hair loss, fatigue, and weight loss were the most significant side effects faced in front-line therapies. Caregivers reported that the following side effects affected their children's HRQoL: eating challenges (46%), changes in physical activity (46%), social development (69%), and educational development (54%). There were also significant changes in mental health and overall happiness (39%) for children undergoing treatment for high-risk neuroblastoma. Respondents stated that front-line therapy had a large or extremely large impact in all categories of mental health and overall happiness (62%) of the family and on parenting other children (46%), ability to participate in activities with family and friends (77%), ability to work (85%), ability to manage financial responsibilities (69%), and ability to manage responsibilities at home (62%).

- One caregiver of a 2-year-old child noted, "The trauma my son carries as a result of us having to hold him down for dressing changes and procedures negatively impacted his relationship with us, where there is trust issues that result in him trying to control everything all the time."
- Another respondent shared, "My daughter was unable to continue with gymnastics and horseback riding due to compression fractures in her spine from treatments of chemotherapy, still to this day she is no longer able to do gymnastics because of weakened spinal cord."

Experiences With Therapy for R/R Neuroblastoma

Five respondents shared that their child relapsed during front-line therapy. Patients received a variety of therapies for R/R neuroblastoma, including chemotherapy (n = 7), radiation (n = 9), surgery (n = 3), high-dose chemotherapy (n = 1), immunotherapy (n = 3), maintenance therapy (n = 1), dinutuximab with irinotecan and temozolomide (n = 9), and difluoromethylornithine (n = 2).

- A caregiver of a 2-year-old patient shared, "He had a MIBG scan after surgery and 5 cycles of front-line treatment. We were told that while his condition had improved, he had not responded well enough to the chemotherapy to continue to bone marrow transplant. He was then put on a study ANBL1221."
- A caregiver of a 9-year-old said, "My daughter had progression during front-line therapy, she had a neuroblastoma tumour grow just weeks after having her tumour removal surgery. Once my daughter completed front-line therapy and was declared NED [no evidence of disease] she remained NED for 3 years before relapsing."

Other respondents shared that their child's relapse was identified during routine follow-up scans, with some children relapsing multiple times. Two sets of parents reported that their children had been refractory to all treatments. One father stated that his 10-year-old son did not respond to any of the traditional chemotherapies, surgery, or radiation: "We asked about clinical trials but were told there was nothing available here. We researched the option of going to the states where there were experimental therapies. That's when the oncologist came back and said we were approved for compassionate access to immune therapy. That was our first break in 2 years."

Improved Outcomes

When determining what therapies to access, all caregivers stated that they selected a treatment with their child's HRQoL in mind. Eighty-two percent stated that therapies were selected based on their possible disease impact. Other factors included physician recommendation (36%), proximity to home (27%), treatment in the outpatient setting (27%), and religious considerations (8%).

Respondents stated that their utmost desire was to find an effective treatment for their child. There was reported frustration that more advanced or experimental therapies were not available to them, even as options. "I can't say that we would have agreed to all of the experimental treatments that we were hearing about, and we knew from other parents that there was no guarantee, but we felt we should at least have the chance."

Experience With Drug Under Review

Accessing Dinutuximab for Front-Line Therapy and/or During Relapse

Many hospitals do not see patients with high-risk neuroblastoma as frequently as they see patients with other pediatric cancers; therefore, specialized treatments such as immunotherapy can be difficult to administer and because every child has a different experience to the therapy. One respondent stated, "Unituxin was difficult for my daughter, she was in a great deal of pain and suffered a few episodes of very low blood pressure. But once we added pre-meds prior to starting immunotherapy things were much better and more tolerable." If a hospital does not have a great deal of experience with dinutuximab, the steep learning curve can be challenging, as 1 respondent shared: "Our experience with Unituxin was very hard on our son, this was the first time our hospital had administer this medicine, gauging his pain and treating it was difficult, side effects after treatment were very hard."

Accessing Dinutuximab During Relapse

For relapsed therapy, respondents reported more challenges accessing dinutuximab with irinotecan and temozolomide for treatment. Four respondents accessed immunotherapy through clinical trials and 2 accessed it through special access; for 3 respondents, the method of access was unreported. Three respondents (27%) stated that it was difficult or extremely difficult to access immunotherapy. The remaining respondents (73%) reported that it had not been difficult to access. Ten respondents were able to access immunotherapy at their home hospital, with only 1 having to travel for treatment within their state or province. For 1 refractory patient, the option to access dinutuximab with irinotecan and temozolomide was due to the efforts of their oncologist, who made a request for compassionate access. "We were considering something else when she came back and suggested the immunotherapy combination [with Unituxin] with maybe a 50-50 chance of success. We thought these were good odds." Another parent said, "We initially refused. Another 17 weeks seemed too much."

Impact on Cancer

Respondents were unsure about the degree to which dinutuximab, irinotecan, and temozolomide affected their child's cancer because it was too soon post-therapy to assess the long-term success of the treatment. One caregiver shared that "It cleared residual disease in combination with the previous treatment with naxitamab with irinotecan/temozolomide." Another noted that even though her child's cancer has continued to progress through treatment, it may be progressing at a slower rate because of the combination immunotherapy. The parents of both patients with refractory neuroblastoma reported that their children's

scans were clear 3 months after the completion of the cycles and that their children remain in remission.

Side Effects From Combination Immunotherapy

Overall, most of the reported side effects from combination immunotherapy were manageable and comparable to those experienced in front-line therapy. Pain, fever, nausea and vomiting, allergic reactions, breathing issues, headache, low platelet count, low red blood cell count, low white blood cell count, low or high blood pressure, fluid retention, dehydration, fatigue, vision changes, sleepiness, allergic reaction to GM-CSF, reaction to IL-2, diarrhea, and constipation were reported side effects. The following are some comments provided by caregivers:

- "Once pre-meds were figured out and nausea diarrhea vomiting, and pain were under control this treatment was extremely tolerable."
- "My daughter had fevers, pain, neuropathy, blurred vision, diarrhea, and itchy feet. Her hair did grow back, and she wasn't neutropenic, and didn't have any organ damage. She did not get IL-2."
- "The first cycle was the hardest due to hospital protocols on getting to the right pain dosage. Once we got to the right level, pain was manageable but hard to see child so "doped up" all day. He had periodic allergic reactions but managed this by pausing/ slowing infusion."

One respondent felt that treatment with dinutuximab, irinotecan, and temozolomide had not been the right therapy for her daughter, and that if she had received a different therapy, such as ^{131}I-MIBG, she would not have died.

Caregivers noted that it took time to figure out how to manage the side effects of the immunotherapy and chemotherapy combination. However, they were able to figure out the right combination of medications to help their child and ease the side effect burden:

- "First round is hard but once you have the pain under control it's fairly smooth sailing. Beware of fluid retention and diarrhea causing dehydration."
- "Getting in front of the symptoms is much easier than trying to catch up from behind them. Advocate for your children ask questions keep trying different pre-meds so that your child is as comfortable as possible during their treatment."
- "It is a very effective treatment. The standard supportive medications do need to be adjusted for the specific patient, so the first few days can be rough. Pre-treatment with gabapentin (neurontin) for neuropathic pain, with antiemetics, and pro-biotics (for irinotecan induced diarrhea) made a big difference in controlling side effects."

Comparison to Previous Therapies

During an interview, 1 caregiver shared that her daughter did not have a great response to any of the chemotherapies in front-line treatment and that immunotherapy was the only treatment that significantly addressed the disease during 2 different relapses, resulting in CRs. She felt that the immunotherapy was "really tailored and really works." In a different interview with a caregiver, she shared that when her son relapsed during front-line therapy, and they were able to access dinutuximab with irinotecan and temozolomide, the response was "miraculous," leaving her son's oncologist stunned. She felt that the "quality of life was way better than the harder chemotherapies and very effective overall." She felt that ASCT "was hands down the worst" and that "all of the long-term side effects are because of transplant" (e.g., compression

fractures, growth issues). She did not feel that there were similar long-term side effects from the immunotherapy and chemotherapy combination. In between treatments, her son had good energy, went to school, and felt well overall.

One parent whose son had been refractory to previous treatments felt that dinutuximab with irinotecan and temozolomide should be first-line therapy. Like others, chemotherapy was not only harsh during treatment, but had long-term effects. This parent's opinion was that the short-term side effects of combination immunotherapy were worth the long-term benefits. Two caregivers noted that recovery from dinutuximab with irinotecan and temozolomide is different from recovery from traditional therapies in terms of HRQoL in between treatment cycles.

- "It seems overwhelming treatment to get your head around but it's really effective in treating disease, doesn't have long-term side effects like chemo and offers good quality of life in between cycles."
- "This treatment provides better quality of life between treatments. The side effects are unpredictable though."

Caregivers felt that treatment with dinutuximab, irinotecan, and temozolomide did not come with the long-term side effects of traditional therapies, such as ASCT, harsher chemotherapies, and radiation.

- "My daughter does not suffer any long-term side effects of this treatment."
- "Unituxin with irinotecan and temozolomide made her feel sicker for longer than naxitamab with irinotecan and temozolomide. But it was not any worse than side effects from front-line chemotherapy, and less severe than side effects from cisplatin and etoposide chemo rounds. Also, there were no long-term side effects, like the organ damage often suffered from transplant."
- "I think Unituxin IT combo changed trajectory of our journey with Neuroblastoma — we finally found treatment that worked, allowed better quality of life while on it and caused fewer long-term issues."
- "The side effects were not long term (unlike hearing loss and organ damage from chemo) and there were options to manage them. Her team worked at finding the best supportive medications for her. She did not get neutropenic which is very comforting given the risk of serious or fatal infections with regular chemo. And the treatment worked well, clearing soft-tissue disease. We would do almost anything to save her life, it's not a pleasant treatment but it's worth it to do something difficult in order to see her grow up, and without this treatment the OS for relapsed neuroblastoma is abysmal."
- "I strongly believe that chemotherapy in combination with immunotherapy is what cured my daughter's neuroblastoma. My daughter was a unique case she did not respond well to front-line therapy she had progression during front-line therapy, she went into bone marrow transplant with 50% of her disease. I am a strong and firm believer that irinotecan and temozolomide in combination with immunotherapy is what cured my daughter's cancer. And if she were to suffer another relapse that would be her third relapse, I would again choose to do this therapy."
- "High-dose chemo and stem cell transplant should be re-evaluated as a standard for all patients, especially stage III high-risk, given that patients still relapse and can suffer severe long-term side effects or death. Immunotherapy with low dose chemo is an excellent and effective treatment for relapsed neuroblastoma and will possibly be even more effective if it is preceded by regular chemo, radiation/surgery as necessary."

One caregiver believed that her child had a specific mutation that caused immunotherapy to provoke a "florid relapse." She commented that children with certain cancer mutations should not receive this therapy.

Overall Feelings Toward Dinutuximab

Overall, respondents were willing to tolerate the challenges with access and the side effects associated with dinutuximab, especially if this treatment could address disease burden, help to deter relapse, and potentially be lifesaving. For the most part, respondents noted that the side effects were temporary, and although they were challenging at the time, they could be managed by supportive medications. In an interview, a caregiver said she is "willing to accept that risk. It is an evolution. I want there to be data but if there is something promising in the long term, I will take it. It is all relative to your other choices." She felt that immunotherapy is "a path to less toxic treatments" and "ground-breaking," and that "relapsed neuroblastoma is no longer a death sentence." In an interview with another patient and her mother, the patient said that "pain is an acceptable side effect" and that the immunotherapy plus chemotherapy combination "gave me 33 months that I might not have had." She said that "none of the treatments have been pleasant but it is necessary. I have friends who have passed away who haven't had access to treatment. We need more treatments to be cancer-free." This patient was diagnosed with high-risk neuroblastoma at 5 years of age and has been fighting the cancer for almost 13 years.

Additional Information

The patient groups wanted to highlight that treatment for high-risk neuroblastoma is long, intensive, and full of challenges because almost every type of treatment is attempted to address the disease. For relapsed neuroblastoma, the pathway is less clear; however, therapies like dinutuximab with irinotecan and temozolomide are changing the stories for children. The once-held belief that a neuroblastoma relapse is incurable is changing quickly.

Clinician Input

Input From the Clinical Experts Consulted by CADTH

All CADTH review teams include at least 1 clinical specialist who has expertise in diagnosing and managing the condition for which the drug is indicated. Clinical experts are a critical part of the review team and are involved in all phases of the review process (e.g., providing guidance on the development of the review protocol; assisting in the critical appraisal of clinical evidence; interpreting the clinical relevance of the results; and providing guidance on the potential place in therapy). The following input was provided by 3 clinical specialists with expertise in the diagnosis and management of R/R high-risk neuroblastoma.

Unmet Needs

The clinical experts consulted by CADTH for this review stated that there are significant unmet needs for the treatment of patients with R/R high-risk neuroblastoma. Not all patients respond to available treatments that have limited efficacy (such as combination chemotherapy), and patients can become refractory to current treatment options. None of the treatments currently available can reverse the course of the disease. Treatments are needed that are better tolerated and can improve survival with limited side effects; parents expect such treatments.

There are currently barriers to the availability of immunotherapy, and many targeted therapies are investigational. There has not been a randomized study comparing temozolomide plus

irinotecan versus dinutuximab plus GM-CSF with chemotherapy. In Canada, the combination of chemotherapy and dinutuximab (with GM-CSF) is available for patients with R/R high-risk neuroblastoma only through clinical trials and/or temporary arrangements for compassionate access from the sponsor. The experts agreed that loss of access to dinutuximab in this setting would have significant consequences for Canadian patients with R/R high-risk neuroblastoma: not only will they potentially lose access to a combination therapy that has shown the best response rate in R/R high-risk disease, but they will also not be able to participate in the ongoing COG relapse study; most clinicians would consider participation as standard of care. The clinical experts believe that without dinutuximab, patients would have to pursue alternative treatment strategies that, in many cases, are likely to have inferior efficacy in terms of disease control, leading to shorter survival times and poorer control of symptoms (especially pain from bone metastases). The clinical experts emphasized that this review has implications for the continued availability of an existing therapy that is already considered standard of care in the setting of R/R high-risk neuroblastoma.

The clinical experts consulted by CADTH anticipate that, given the success of the combination of dinutuximab with temozolomide plus irinotecan, it is likely that dinutuximab will increasingly be used as part of other treatment strategies for patients with R/R high-risk neuroblastoma. They believe it is important to recognize that many of these novel treatment strategies will be part of multi-institutional clinical trials. Thus, establishing a mechanism for funding access to dinutuximab in the R/R setting is likely to have important implications for the ability of Canadian patients to participate in current and future studies.

Place in Therapy

Clinicians noted that immunotherapy with dinutuximab is complementary to other available treatments and administered as part of combination therapy. Dinutuximab is used as part of an aggressive, upfront, multimodality, multi-drug therapy (high-dose chemotherapy, ASCT, radiotherapy, and immunotherapy) for high-risk neuroblastoma in combination with GM-CSF, IL-2, and retinoic acid. In the R/R high-risk setting, the regimen consisting of dinutuximab with temozolomide, irinotecan, and GM-CSF has shown efficacy in inducing responses and is the treatment of choice in these patients. There is reason to expect that dinutuximab will increasingly be used to treat patients with R/R high-risk neuroblastoma in combination with chemotherapies other than temozolomide plus irinotecan (e.g., dinutuximab with cyclophosphamide plus topotecan), and there is growing interest in how to incorporate dinutuximab into other components of therapy (e.g., induction chemotherapy) and how to use it in combination with other modalities in the R/R setting (e.g., in combination with ^{131}I-MIBG therapy).

Clinicians indicated that dinutuximab would address the underlying disease process of R/R high-risk neuroblastoma rather than merely addressing symptoms. The clinical experts believed that dinutuximab with chemotherapy offers the best chance of improving survival and achieving disease control. Dinutuximab in combination with chemotherapy is primarily intended to achieve objective disease response rather than symptom control, although the latter often follows from the former. The clinical experts anticipated that dinutuximab use would not be restricted to patients who cannot tolerate other treatments or in whom other treatments are contraindicated. Rather, it would generally be offered to most patients at relapse or disease progression. They also agreed that it would generally not be appropriate to recommend that patients with R/R high-risk neuroblastoma try other treatments before dinutuximab with chemotherapy, based on the currently available evidence on the efficacy of other treatment options. However, the situation is less clear for patients who experience PD

during upfront immunotherapy with dinutuximab; for these patients, alternative strategies may be considered. One possibility is ^{131}I-MIBG therapy, which has shown some evidence of efficacy in R/R neuroblastoma. Patients who previously experienced severe anaphylaxis or other serious reaction during dinutuximab treatment are also unlikely to be suitable for re-treatment.

Patient Population

The clinical experts consulted by CADTH believed that patients with R/R high-risk neuroblastoma should be offered treatment with dinutuximab combined with chemotherapy if tolerable and safe. Both relapsed and refractory patients with high-risk neuroblastoma can be expected to benefit from this intervention. There is currently no place for dinutuximab in the treatment of low- or intermediate-risk neuroblastoma unless such patients experience relapse with high-risk features.

Experts revealed that considerable research efforts are being made to identify which patients will and will not benefit from dinutuximab-based therapy; however, at present, there are no markers that are sufficiently robust for use in clinical decision-making. The only exceptions might be patients who progressed while receiving dinutuximab during upfront therapy (for whom the benefit of re-treatment with dinutuximab with chemotherapy is less certain) or patients who previously experienced severe adverse reactions to dinutuximab therapy. However, it is not known conclusively whether progression during dinutuximab treatment precludes future response to the dinutuximab plus chemotherapy combination. It is likely that treatment with dinutuximab plus chemotherapy will be suitable for most patients with relapsed disease. For those with refractory disease, the precise definition of *refractory* — in terms of the extent of residual disease and change since baseline — is less well-established. For example, the decision for any individual patient about whether to proceed to high-dose chemotherapy or consider their disease "refractory" and consider dinutuximab plus chemotherapy can be complex.

Clinicians agreed that patients best suited for dinutuximab therapy would be identified by pediatric oncologists in tertiary pediatric oncology units. Treatment of high-risk R/R neuroblastoma is complex and needs to be managed by a multidisciplinary team with relevant experience. In Canada, children with cancer are routinely treated at 1 of 16 specialist centres. Identification of eligible patients is not challenging in routine clinical practice; misdiagnosis and underdiagnosis are not major issues. Patients suitable for combination treatment with dinutuximab and chemotherapy would be identified by pediatric oncologists based on the results of clinical assessment, imaging results, and biopsy results confirming R/R disease, and after review with a multidisciplinary pediatric oncology team. Staging investigations (including bone marrow evaluation, ^{123}I-MIBG, and fluorodeoxyglucose-PET [FDG-PET]) are routinely available and critical for accurate disease evaluation. There remains some controversy over the role of ongoing routine surveillance imaging following completion of upfront therapy for high-risk neuroblastoma, but in most institutions, it would not be considered routine to continue ^{123}I-MIBG scans for disease surveillance in patients with no evidence of residual ^{123}I-MIBG-avid metastatic sites. Thus, evidence of relapse will typically come from imaging prompted by the onset of new symptoms. However, regardless of symptoms, pre-symptomatic patients with evidence of R/R disease should be considered for dinutuximab treatment to obtain the best chance of extending survival and achieving disease control.

The clinical experts agreed that patients unsuitable for dinutuximab treatment are generally those with organ failure who require palliative care as well as those who previously had severe adverse reactions to the drug, given that they may not tolerate therapy. The experts noted that patients who experienced prior progression during dinutuximab therapy may show less benefit, although this is not known with any certainty. Because there are no predictive biomarkers for response to dinutuximab, all patients who have not previously been exposed to the drug and developed adverse reactions are good candidates. Evidence suggests that responses to dinutuximab plus chemotherapy tend to occur early rather than late; thus, continued therapy (e.g., beyond 6 cycles) in the absence of any objective response may not be justified.

Assessing Response to Treatment

The outcome of dinutuximab treatment in patients with R/R high-risk neuroblastoma is assessed by synthesizing clinical, radiological, and bone marrow responses. The outcomes used in clinical practice are the same as those used in clinical trials. Clinically meaningful responses to treatment could be manifested via disease control or significant reduction of disease burden on re-staging evaluations during and after treatment, with the eventual goal of cure; improved survival; stabilization or improvement of symptoms (e.g., bone pain); and/or improvement of HRQoL. Interpretation of pain improvement is challenging and may vary among treating physicians. In some patients, achieving symptom or HRQoL improvement in the absence of an objective reduction of disease would still be considered a meaningful response to treatment. In any individual patient, continuation of therapy should be a decision balanced on evidence of response (either objective improvement on imaging and/or bone marrow assessment, or symptomatic benefit) versus toxicity and burden of therapy. The clinical experts consulted by CADTH believed that it would be unreasonable to stop therapy for a patient with symptomatic benefit who is tolerating therapy well but has no objective response on imaging, but equally it would not be appropriate to continue therapy in the face of objective evidence of progression. The frequency of response assessment will vary depending on symptoms but should be performed at least after the proposed initial course of therapy. In practice, response to dinutuximab treatment should be assessed approximately every 3 months, or after the first 2 cycles of therapy and then every 3 or 4 cycles (or sooner, if there is any clinical suspicion of relapse or progression during treatment). The clinical experts consulted by CADTH for this review emphasized that guidelines for response assessment timelines have been developed (e.g., by POGO).

Discontinuing Treatment

Clinicians agreed that given its cost and potential toxicities, dinutuximab should be discontinued when there is evidence of progression during treatment, when AEs or toxicities become difficult to manage, or when treatment does not result in further decrease in disease burden or improvement in response, despite being well-tolerated. Unfortunately, despite response to therapy, the long-term survival of patients with R/R high-risk neuroblastoma is uncertain, and it is important to consider quality of life in this population. Treatment may also be discontinued when it does not result in further decrease in disease burden or improvement in response despite being well-tolerated. Guidelines for the discontinuation of dinutuximab in responding patients have been developed (e.g., by POGO). These suggest that when a CR is achieved, treatment with a potentially toxic regimen should not continue indefinitely, but it is reasonable to continue for several cycles beyond CR with the aim of treating residual disease that may not be apparent on imaging assessment, and that when a PR is achieved, treatment could be continued if evidence of disease response continues to be present, but discontinued if there is no further improvement in disease response. Because of the challenges of

determining overall response in neuroblastoma due to the specific definitions of PR and CR, these decisions should be left to the discretion of treating physicians and teams.

Prescribing Conditions

Clinicians agreed that the combination of dinutuximab with chemotherapy and GM-CSF should be administered in an inpatient setting in a hospital with a tertiary pediatric oncology unit or oncology unit with relevant experience because of the risk of potential life-threatening AEs during administration. The diagnosis, treatment, and monitoring of patients with R/R high-risk neuroblastoma receiving dinutuximab would be managed by a pediatric oncologist or an oncologist with relevant experience. Although no specific companion diagnostic tests exist for dinutuximab, assessment of treatment response (e.g., CT or MRI, ^{123}I-MIBG scan, bone marrow evaluation) can only be performed in this setting.

Additional Considerations

The clinical experts reiterated that dinutuximab (in combination with irinotecan, temozolomide, and GM-CSF) is already in widespread use in pediatric oncology units and is generally considered the treatment of choice for patients with relapsed or refractory high-risk neuroblastoma. They also emphasized the importance of framing this review as a reimbursement request for a drug that is already the standard of care, rather than a novel therapy.

Clinician Group Input

This section was prepared by CADTH staff based on the input provided by clinician groups.

Two registered joint clinician group inputs were provided on behalf of 9 clinicians from POGO and 10 clinicians from the Pediatric Oncology Department of BC Children's Hospital. These inputs were submitted for the review of dinutuximab for the treatment of pediatric patients with R/R high-risk neuroblastoma in combination with irinotecan, temozolomide, and GM-CSF. POGO, a collaboration of Ontario's 5 specialized childhood cancer centres, is the official advisor to the Ontario Ministry of Health and Long-Term Care on pediatric cancer care and control. Its input represents a collaboration of pediatric cancer clinicians from across the province with membership informed by its Therapeutic and Technology Advisory Committee. The clinicians from BC Children's Hospital were a group of pediatric oncologists caring for children with high-risk neuroblastoma.

Unmet Needs

Clinicians from POGO stated that the likelihood of a true cure in patients with relapsed neuroblastoma is very low. Patients who do not respond to initial front-line cytotoxic therapy are deemed refractory and have dismal outcomes. A small portion of these patients (8% to 10%) may harbour aberrations in genes, such as ALK, that allow for the use of a targeted drug. However, the majority have no curative options. Therefore, this population needs treatments that prolong lifespan with good symptom control and HRQoL.

Both clinician groups agreed that patients who are refractory to or relapse following upfront therapy are most in need of potentially efficacious therapies such as dinutuximab. Without it, patients would lack critical access to the most effective, targeted therapy that is available for this disease. While not all patients can be expected to respond, those who do should have continued access if there is meaningful impact and if the patient and family find the toxicities of therapy tolerable.

Clinicians at BC Children's Hospital stated that conventional salvage chemotherapy regimens (irinotecan plus temozolomide or cyclophosphamide plus topotecan) have poor response rates and significant toxicities and require inpatient stays. Salvage chemotherapy can result in subsequent febrile neutropenia episodes and a significant need for blood product support. It is often not possible to continue cyclophosphamide plus topotecan due to the profound bone marrow suppression that can result from the intensive therapy that these children have already received. High-dose ^{131}I-MIBG therapy may be offered to some patients, but it has lower response rates than chemoimmunotherapy, is only offered at 2 sites in eastern Canada, and comes with the toxicities of bone marrow suppression and need for ASCT.

Place in Therapy

Clinicians from POGO stated that current front-line therapy includes a wide variety of modalities, including traditionally dosed cytotoxic therapy, high-dose chemotherapy with ASCT rescue, radiation therapy, surgery, and immunotherapy with dinutuximab and cytokine stimulation. Despite relapses occurring in approximately 40% of patients with high-risk neuroblastoma, there is no clear standard of care at the time of relapse or in cases of refractory disease. Traditional cytotoxic drugs were generally considered the treatment of choice but have variable responses. Importantly, while the response rates to further cytotoxic therapy are less than ideal, relapsed patients who respond to therapy may have prolonged disease control. For a significant percentage of these patients, their relapse course may mirror a chronic disease, with their disease waxing and waning for many years before their death.

Clinicians from BC Children's Hospital have experience managing dinutuximab therapy and its side effects. In their clinical practices, many patients obtain sustained disease response. However, children whose disease does not respond to conventional upfront therapy may have a dramatic response to chemoimmunotherapy, facilitating a reduction in disease burden before standard consolidation therapy. In addition, children who relapse following upfront therapy — which typically includes dinutuximab-based maintenance — often respond to subsequent dinutuximab-based chemoimmunotherapy.

Both clinician groups indicated that the combination under review is currently used in front-line, high-risk neuroblastoma, where it is administered with cytokines but not concurrently with traditional cytotoxic therapy. The indication under review brings this therapy to R/R patients. Clinicians from BC Children's Hospital stated that based on evidence of efficacy and tolerability, they would support this regimen as a first-line salvage approach for children with R/R disease. Indeed, both groups of clinicians felt that the combination of dinutuximab with GM-CSF and irinotecan plus temozolomide was already considered the de facto treatment of choice for R/R neuroblastoma in North American and worldwide, taking advantage of compassionate access to dinutuximab from the sponsor.

Clinicians at POGO specified that patients who are deemed refractory to their initial therapy may proceed to this therapy without previously undergoing high-dose chemotherapy with ASCT or differentiation therapy with a retinoid. It is conceivable that those who achieve a CR or near CR to therapy may proceed to front-line therapy in ultimate hopes of a cure. Dinutuximab is part of the final phase of front-line neuroblastoma therapy. During relapse, multiple factors are considered when choosing the first-line relapse therapy, including the timing of relapse, extent of disease, tolerance of previous immunotherapy, and patient and family preference. For patients who have been in remission for months to years before

relapse, the therapy of choice is dinutuximab. In fact, new clinical trials for patients with relapsed neuroblastoma use the ANBL1221 trial regimen[10,11] as the standard of care.

Clinicians from POGO stated that for patients with relapsed disease, multiple factors must be considered when choosing relapse therapy. Subsequent lines of therapy are not clearly defined for patients whose disease progresses while receiving this therapy or after having completed it. For those with a history of severe or unacceptable toxicity in response to previous dinutuximab, it may not be advisable to proceed with further dinutuximab therapy. Similarly, relapses that occur soon after the last treatment with dinutuximab or while on front-line dinutuximab therapy would suggest the need for alternative therapy. For these patients, systemic therapy with ^{131}I-MIBG may be more appropriate, provided the patient has stem cells available to support such therapy. Others may warrant a trial of further cytotoxic or radiation therapy. Many of these patients and their families elect to participate in phase I or II clinical trials. Ultimately, palliative care (with or without antitumour therapy) will be the final therapy many of these patients receive. Importantly, exposure to dinutuximab combined with GM-CSF, and temozolomide plus irinotecan does not alter a patient's eligibility for any of these options.

Patient Population

As stated by clinicians, children with primary R/R high-risk neuroblastoma have poor survival outcomes. About 8 children per 1 million individuals (less than 15 years of age) are diagnosed annually with neuroblastoma, of whom 40% to 45% have high-risk disease. Approximately 15% of children with high-risk neuroblastoma have primary refractory disease.

Clinicians at BC Children's Hospital identified children with high-risk neuroblastoma (primary refractory or PD) following upfront conventional high-risk chemotherapy, or patients with high-risk neuroblastoma and confirmed relapsed disease, as the best suited patients for the treatment under review. Patients who experienced prior disease progression while receiving dinutuximab-based therapy may be less likely to benefit. In addition, POGO clinicians stated that although GD2 expression is generally considered ubiquitous in neuroblastoma, it is difficult to predict accurately which patients will and will not respond; studies to date have not identified clinical factors or biomarkers (e.g., *MYCN* gene status) that predict response. There are many ongoing research studies that aim to identify biomarkers for patients who will (and will not) respond to dinutuximab combined with GM-CSF, and irinotecan plus temozolomide. Given the potential toxicities of therapy, those with pre-existing hemodynamic instability or respiratory disease may be less likely to tolerate therapy.

BC Children's Hospital clinicians indicated that all patients with high-risk neuroblastoma in Canada are followed by tertiary-care pediatric oncology programs. In addition, clinicians from POGO stated that the patients best suited for treatment with dinutuximab-based therapy would be identified by the detection of increased size of existing tumours or new sites of metastatic disease found through cross-sectional imaging, ^{123}I-MIBG scan, or bone marrow examination. Because most cases of neuroblastoma respond at least initially to induction cytotoxic therapy, designating refractory disease is normally not challenging. Relapsed disease may present with patient symptoms or be observed during routine follow-up. Recurrent disease may be suggested by elevated urine catecholamines and confirmed by cross-sectional imaging, ^{123}I-MIBG scan, FDG-PET scanning for ^{123}I-MIBG non-avid tumours, or confirmation of disease on bone marrow biopsy. In rare cases where relapse is not apparent through these modalities, a biopsy may be needed to confirm recurrence.

For patients whose relapses occur in the absence of symptoms, treatment with dinutuximab may still be warranted. Treating before a large burden of disease may result in therapy being

better tolerated. The decision to begin treatment in these situations should be made only after careful discussion with the patient and their family. For this patient population, keeping them free of symptoms of recurrent disease may be an important HRQoL issue.

Clinicians from POGO indicated that patients with significant cardiac or respiratory dysfunction are more likely to experience unacceptable toxicities from dinutuximab. Similarly, those who experienced PD while receiving front-line dinutuximab should be considered for alternative therapy. In addition, clinicians from BC Children's Hospital suggested that patients who do not have high-risk neuroblastoma, or do not have disease that is refractory or relapsed to standard therapy, would not be suitable for treatment. Patients require central venous access and must be willing to travel for inpatient care at a tertiary-care pediatric site.

Assessing Response to Treatment

Clinicians from POGO stated that in clinical practice, important tools to determine whether a patient is responding to treatment are regular clinical assessments of symptoms and radiologic assessment of disease. Clinically relevant outcomes include reduction of disease as shown by CT or MRI or by ^{123}I-MIBG scan. Symptomatic relief of disease-related pain is also considered important. Similarly, clinicians from BC Children's Hospital stated that eligible patients are routinely identified as part of tertiary-care pediatric oncology practice. Patients with both primary refractory and relapsed disease achieved response in the clinical trial, and it is not clear which factors predict response. BC clinicians supported a trial of therapy for up to 6 cycles to evaluate for evidence of disease response, in the absence of unacceptable toxicity or disease progression.

Clinicians from POGO indicated that while reduced disease burden is the preferred response, patients who obtain symptomatic relief from therapy in the setting of radiologic stable disease should be considered as having a clinically relevant response. BC clinicians stated that it is extremely clinically meaningful to achieve disease response that leads to additional time with greater HRQoL, improved or resolved clinical symptoms, and the ability to return to normal childhood activities, including school, play, and quality time with family.

Both clinician groups agreed that disease should be assessed regularly by cross-sectional imaging at least every 2 cycles (every 3 months) or sooner if clinically indicated. Consideration should also be given to monitoring ^{123}I-MIBG and bone marrow response. For patients who respond to therapy with PRs or stable disease, the frequency of disease assessment may be spaced out, particularly in settings when sedation or anesthetic are required.

Discontinuing Treatment

Clinicians from POGO indicated that patients with PD on therapy should discontinue further dinutuximab therapy. Both clinician groups agreed that therapy should be discontinued if there is documented disease progression or absence of disease response by the completion of 6 cycles of therapy. Clinicians expect patients to have objective evidence of benefit by the completion of 6 cycles of therapy. For patients with PRs or stable disease, therapy may be continued for a prolonged time (up to 17 cycles, according to the ANBL1221 study),[10,11] provided there is no worsening of the patient's clinical condition. BC clinicians supported continuing therapy in patients who achieve PRs or CRs for up to 6 cycles beyond best response by INRC criteria.[13,14] For all patients, therapy should be discontinued if treatment toxicities and patient HRQoL are unacceptable. Intolerable toxicity, including capillary leak syndrome or neuropathic pain, may also require therapy discontinuation.

Prescribing Conditions

Both clinician groups agreed that the drug under review should only be delivered in a specialized childhood cancer centre under the care of health professionals with experience and knowledge of managing neuroblastoma and the toxicities of therapy. Inpatient admission is required for each cycle. Pediatric anesthesiology is typically involved in the pre-emptive management of neuropathic pain associated with this therapy.

Additional Considerations

Clinicians at BC Children's Hospital stated that R/R high-risk neuroblastoma is a rare subgroup of a rare disease. It is essential that CADTH reviewers recognize that the level of evidence provided by a randomized, pediatric phase II clinical trial has changed the landscape of therapy for this subgroup.

Drug Program Input

The drug programs provide input on each drug being reviewed through CADTH's reimbursement review processes by identifying issues that may affect their ability to implement a recommendation. The implementation questions and corresponding responses from the clinical experts consulted by CADTH are summarized in Table 4.

Clinical Evidence

The clinical evidence included in the review of dinutuximab is presented in the Systematic Review section, which includes key studies provided in the sponsor's submission to CADTH as well as those studies that were selected according to an a priori protocol. No indirect evidence met the inclusion criteria for this review. No additional relevant studies were identified that were considered to address important gaps in the evidence included in the systematic review.

Systematic Review (Key and Protocol Selected Studies)

Objectives

To perform a systematic review of the beneficial and harmful effects of dinutuximab IV infusion in combination with irinotecan plus temozolomide and GM-CSF for the treatment of pediatric patients with high-risk neuroblastoma in their first relapse or determination of refractory disease.

Methods

Studies selected for inclusion in the systematic review included key studies provided in the sponsor's submission to CADTH as well as those meeting the selection criteria presented in Table 5. Outcomes included in the CADTH review protocol reflect outcomes considered to be important to patients, clinicians, and drug plans.

The literature search for clinical studies was performed by an information specialist using a peer-reviewed search strategy according to the *PRESS Peer Review of Electronic Search Strategies* checklist (https://www.cadth.ca/resources/finding-evidence/press).[27] Published literature was identified by searching the following bibliographic databases: MEDLINE All

(1946–) through Ovid and Embase (1974–) through Ovid. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical

Table 4: Summary of Drug Plan Input and Clinical Expert Response

Drug program implementation questions	Clinical expert response
To help define the eligible patient population, what are the specific definitions for relapsed vs. refractory neuroblastoma?	Patients with relapsed neuroblastoma had a response to upfront therapy, and the disease has recurred or progressed. Patients with refractory neuroblastoma have responses to induction chemotherapy that the treating physician feels are inadequate to proceed to high-dose chemotherapy. These patients need additional treatment to achieve a response before consolidation. If patients achieve PR or CR, they can proceed to high-dose chemotherapy and consolidation. Patients with stable disease encompass both those with no change in disease status and those whose responses do not meet the threshold for PR. Clinically, this would come down to a case-by-case decision of whether the patient has responded sufficiently to proceed to high-dose chemotherapy. A patient whose bone marrow disease responds well to treatment but still has primary site disease would be considered a good candidate. There is some overlap between these terms. A relapsed patient who is treated with second-line therapy and does not respond would also be considered to have refractory disease.
Are there any differences in treatment strategies for patients who have relapsed neuroblastoma vs. refractory neuroblastoma? For example, if a patient has a late relapse following previous treatment for high-risk disease, would they be eligible to repeat the same high-risk treatment protocol vs. moving on to the regimen requested in this submission?	Yes, there are substantial differences. In general, treating physicians would not administer the same high-risk treatment protocol again. However, it is theoretically possible to have a patient who was treated for high-risk disease so long ago that they could be treated again with the upfront regimen. Typically, a patient is defined as having refractory neuroblastoma because of an inadequate response to induction therapy before high-dose chemotherapy. For patients with refractory neuroblastoma, the goal is to move to second-line treatment options and obtain a response, then return to and complete the original treatment protocol, including high-dose chemotherapy, radiotherapy, immunotherapy, and so on. If disease can be brought under control, the patient can return to the original treatment plan. However, there is no definitive proof that this is the correct approach. Patients with relapsed neuroblastoma have most likely already received high-dose chemotherapy and would not receive it again. In patients with relapsed neuroblastoma, good control and induction of remission does not change the high probability of relapse.
If patients are tolerating therapy and have not progressed, is there evidence to support providing treatment beyond 17 cycles?	The only available evidence comes from the ANBL1221 study.[10,11] In this trial, the maximum of 17 cycles was arbitrary (equivalent to a treatment duration of 2 years) and was selected based on reasonable expectations of treatment duration in the chemotherapy arm. However, there is no clear evidence that treatment with dinutuximab beyond 17 cycles would not be an approach to consider. There is a balance of risk-benefit considered by the treating physician. Further treatment is given in the hope of consolidating a response, but it is not carried on indefinitely.
For patients who received prior dinutuximab, is there evidence on re-treatment with the same drug in the R/R setting?	Yes, there is evidence from the ANBL1221 study showing that responses to dinutuximab occurred in R/R patients who had received dinutuximab previously as well as in dinutuximab-naive patients.[10,11] There is evidence for the efficacy of combination therapy with dinutuximab combined with irinotecan plus temozolomide and GM-CSF even if dinutuximab was used in upfront therapy. There is also anecdotal evidence that patients can respond again to the same combination after relapse.

CR = complete response; GM-CSF = granulocyte-macrophage colony-stimulating factor; PR = partial response; R/R = relapsed or refractory.

Subject Headings), and keywords. The main search concepts were Unituxin or dinutuximab. Clinical trials registries were searched: the US National Institutes of Health's clinicaltrials.gov, WHO's International Clinical Trials Registry Platform search portal, Health Canada's Clinical Trials Database, and the European Union Clinical Trials Register. No filters were applied to limit retrieval by study type. Retrieval was not limited by publication date or by language. Conference abstracts were excluded from the search results. The detailed search strategy is provided in Appendix 1. The initial search was completed on January 7, 2021. Regular alerts updated the search until the meeting of the CADTH pan-Canadian Oncology Drug Review Expert Committee on May 13, 2021.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the CADTH *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* checklist (https://www.cadth.ca/grey-matters).[28] Included in this search were the websites of regulatory agencies (US FDA and European Medicines Agency). Google was

Table 5: Inclusion Criteria for the Systematic Review

Item	Criteria
Patient population	Pediatric patients with high-risk neuroblastoma in their first relapse or determination of refractory disease Subgroups: • Relapsed vs. refractory disease • *MYCN* amplification • Age • INSS stage[15]
Intervention	Dinutuximab (17.5 mg/m^2 per day, administered as an IV infusion over 10 hours to 20 hours for 4 consecutive days per treatment cycle) in combination with irinotecan, temozolomide, and GM-CSF
Comparators	• Chemotherapy (with or without ASCT) • Systemic molecular radiotherapy • Best supportive therapy
Outcomes	**Efficacy:** • ORR (PR, VGPR, CR) • DOR • PFS • EFS • OS • HRQoL • Symptom relief **Safety:** • AEs, SAEs, WDAEs • Notable harms (infusion reactions, capillary leak syndrome, neuropathic pain, severe neurologic toxicities, inpatient hospitalizations, ICU admissions)
Study design	Published and unpublished phase II, III, and IV RCTs

AE = adverse events; ASCT = autologous stem cell transplantation; CR = complete response; DOR = duration of response; EFS = event-free survival; GM-CSF = granulocyte-macrophage colony-stimulating factor; HRQoL = health-related quality of life; ICU = intensive care unit; INSS = International Neuroblastoma Staging System; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; RCT = randomized controlled trial; SAE = serious adverse events; VGPR = very good partial response; WDAE = withdrawal due to adverse events.

used to search for additional internet-based materials. See Appendix 1 for more information on the grey literature search strategy.

These searches were supplemented by reviewing bibliographies of key papers and through contacts with appropriate experts. In addition, the drug sponsor was contacted for information regarding unpublished studies. Two CADTH clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least 1 reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion.

Findings From the Literature

One study was identified from the literature for inclusion in the systematic review (Figure 1). The included study is summarized in Table 6.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

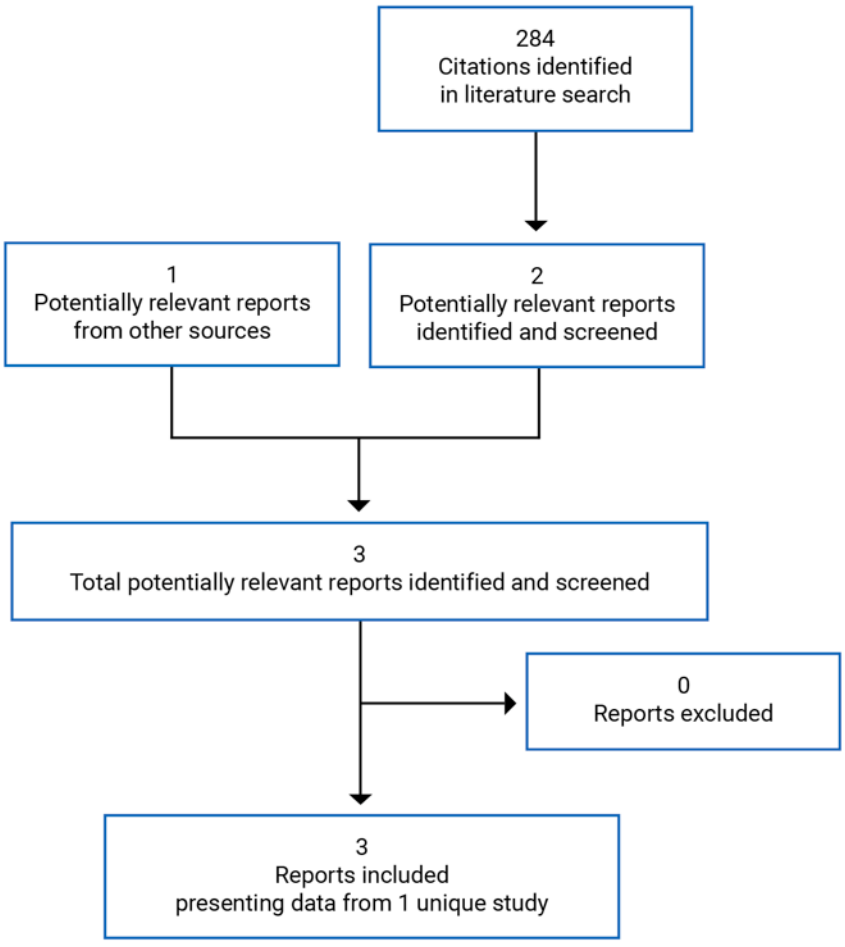


Table 6: Details of the Included Study

Detail	ANBL1221 trial
Design and population	
Study design	Phase II, prospective, multi-centre, open-label RCT
Locations	49 sites in Canada, the US, Australia, and New Zealand
Patient enrolment dates	February 22, 2013, to March 23, 2015 (randomized) August 26, 2016, to May 18, 2017 (non-randomized)
Data cut-off	September 30, 2019
Randomized (N)	36 enrolled, 35 randomized
Non-randomized assignment (N)	37
Inclusion criteria	• No age limitations • Histologic or bone marrow biopsy (+ elevated urinary catecholamines ≥ 2 × ULN) demonstration of neuroblastoma • Documentation of disease by 1 of CT or MRI + ^{123}I-MIBG scan or FDG-PET, . ^{123}I-MIBG scan alone, or biopsy + catecholamine evaluation • First episode of recurrent disease following aggressive front-line multi-drug therapy (surgery, chemotherapy, ASCT ± ^{131}I-MIBG, immunotherapy, radiotherapy, and retinoids), first episode of PD during front-line therapy, or refractory disease (< PR) following ≥ 4 cycles of front-line therapy • Recovery from acute toxicities associated with prior therapies (1 week since biologic therapy, 2 weeks since chemotherapy, 4 weeks since radiotherapy, 6 weeks since ^{131}I-MIBG or stem cell transplant) • ECOG performance status 0, 1, or 2 (Karnofsky/Lansky scores ≥ 50%) • Adequate organ function: bone marrow (neutrophils ≥ 750/μL, platelets ≥ 75,000/μL), renal (creatinine clearance ≥ 70 mL/min), liver (total bilirubin ≤ 1.5 × ULN for age, ALT ≤ 5.0 × ULN for age), CNS (no clinical or radiological evidence of disease or toxicity), cardiac (shortening fraction ≥ 27% or ejection fraction ≥ 50%), coagulation (prothrombin time ≤ 1.2 × ULN), pulmonary (no evidence of dyspnea at rest, no exercise intolerance, no chronic oxygen requirement, and room air pulse oximetry > 94%)
Exclusion criteria	• Prior treatment of R/R high-risk neuroblastoma (e.g., second-line chemotherapy, such as irinotecan plus temozolomide; mTOR inhibitors and chemotherapy) • History of grade 4 allergic reactions to anti-GD2 immunotherapy, reactions requiring discontinuation of anti-GD2 immunotherapy, or PD during prior anti-GD2 therapy • Bone marrow disease only or elevated catecholamines only • Enzyme-inducing anticonvulsants, myeloid growth factors, or pharmacologic doses of systemic corticosteroids • Myelodysplastic syndrome, non-neuroblastoma malignancy, congestive heart failure, grade ≥ 2 diarrhea, or any significant intercurrent illness • Pregnancy

Detail	ANBL1221 trial
Drugs	
Intervention	• Dinutuximab (17.5 mg/m^2 per day IV days 2 to 5) in combination with irinotecan (50 mg/m^2 IV days 1 to 5), temozolomide (100 mg/m^2 p.o. days 1 to 5), and GM-CSF (250 mcg/m^2 IV or SC days 6 to 12); cycles were 21 days; treatment was administered to a maximum of 17 cycles
Comparator(s)	• Temsirolimus (35 mg/m^2 IV on day 1 and day 8) in combination with irinotecan (50 mg/m^2 IV days 1 to 5) and temozolomide (100 mg/m^2 p.o. days 1 to 5); cycles were 21 days, and treatment was administered to a maximum of 17 cycles
Duration	
Randomized phase	Treatment: 17 cycles (51 weeks) for both regimens; follow-up maximum 5 years
Non-randomized phase	Treatment: 17 cycles (51 weeks); follow-up maximum 5 years
Outcomes	
Primary end point	Proportion of patients who achieved PR or better using INRC criteria[13,14] as their best overall response after up to 6 cycles of therapy
Secondary and exploratory end points	Exploratory: • difference in ORR between interventions • DOR • OS • PFS
Notes	
Publications[a]	Mody et al. (2017)[10] Mody et al. (2020)[11]

ALT = alanine aminotransferase; ASCT = autologous stem cell transplantation; CNS = central nervous system; ECOG = Eastern Cooperative Oncology Group; FDG-PET = fludeoxyglucose-PET; GM-CSF; granulocyte-macrophage colony-stimulating factor; INRC = International Neuroblastoma Response Criteria; ^{123}I-MIBG = ^{123}I-metaiodobenzylguanidine; ^{131}I-MIBG = ^{131}I-metaiodobenzylguanidine; OS = overall survival; PFS = progression-free survival; PD = progressive disease; p.o. = orally; PR = partial response; RCT = randomized controlled trial; R/R = relapsed or refractory; SC = subcutaneous; ULN = upper limit of normal.

[a]One additional source of information was included (ANBL1221 Clinical Study Report).[16]

Description of Studies

COG study ANBL1221 was a phase II, prospective, open-label, multi-centre trial with a 2-stage planned sequential and selection ("pick the winner") design (see Figure 2; for details of the design, see Statistical Analysis).[10,11] The study was funded by the National Cancer Institute. The study was conducted at 49 sites, including 5 sites in Canada: 2 in Montreal, 1 in Toronto, 1 in London, and 1 in Vancouver. The study enrolled patients of any age with histologic or bone marrow biopsy (with elevated urinary catecholamines) demonstration of high-risk neuroblastoma at their first designation of relapse or refractory disease.

The initial primary objective of the study was to determine whether temsirolimus (regimen A) or dinutuximab (regimen B) was the optimal drug to move forward to a phase III trial in patients with R/R high-risk neuroblastoma. In the first stage, patients (N = 35) were randomized 1:1 to receive either temsirolimus (regimen A) or dinutuximab and GM-CSF (regimen B), both with standard chemotherapy (irinotecan and temozolomide). Computed block permutation (block size 2) was conducted using the COG RandoNode web service and the Cancer Trials Support Unit Oncology Patient Enrollment Network with coding such that the allocation sequence was not known at the site when assignment occurred.

Randomization was stratified by disease status at baseline (relapsed versus refractory), prior anti-GD2 immunotherapy (yes or no), and *MYCN* status (amplified, nonamplified, or unknown), yielding 12 strata. The study began with a safety phase in which 6 patients were treated with each of regimen A and B and monitored for safety and feasibility. This was followed by a 2-stage activity evaluation; a 3-stage stopping rule for unacceptable toxicity or feasibility was applied. Patients were evaluated after 2 cycles, then at cycles 4 and 6 and every 4 cycles thereafter to a maximum of 17 cycles. The primary efficacy end point was best overall response (at least a PR) achieved by the completion of 6 cycles; patients with PD at evaluation were taken off protocol therapy and classified as treatment failures.

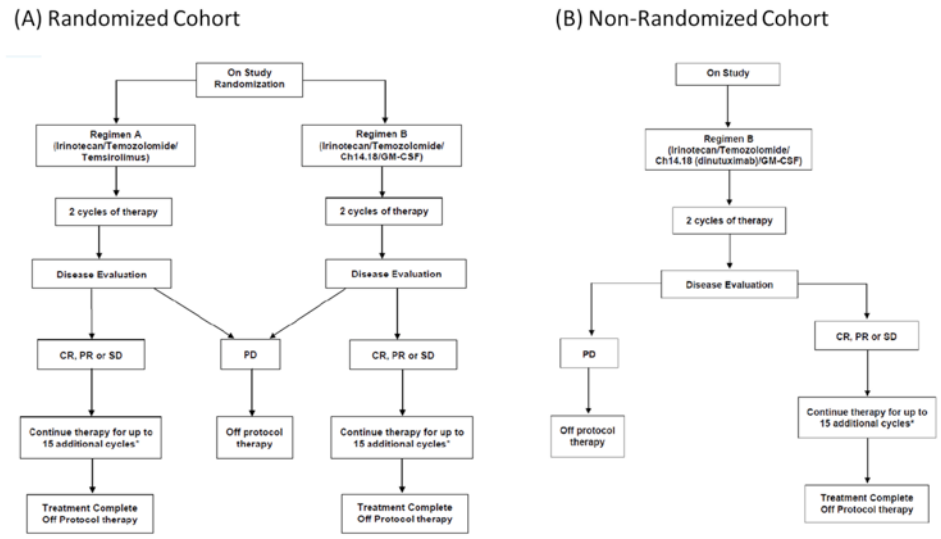
Following completion of the randomized stage, there was insufficient evidence based on pre-specified selection criteria for a treatment effect of regimen A (temozolomide; 1 of 18 patients with at least a PR), and this arm was closed to accrual. Enrolment was expanded to permit the accrual of 36 non-randomized patients treated with regimen B (dinutuximab). A single-stage toxicity stopping rule was applied in the expanded cohort. The primary objective of the non-randomized cohort was to accurately determine the response rate to dinutuximab with GM-CSF, irinotecan, and temozolomide and compare this with historical response rates to irinotecan and temozolomide alone (e.g., the ANBL0421 trial).[12] Both regimens were tolerated, and the stopping rules for the safety phase were not triggered. The data cut-off for both the randomized and non-randomized cohorts was September 30, 2019.

Populations

Inclusion and Exclusion Criteria

Inclusion and exclusion criteria for the ANBL1221 study are summarized in Table 6. Patients of any age with high-risk neuroblastoma documented by imaging and/or bone marrow biopsy

Figure 2: Study Design of the ANBL1221 Trial



ch14.18 = dinutuximab; CR = complete response; GM-CSF = granulocyte-macrophage colony-stimulating factor; PD = progressive disease; PR = partial response; SD = stable disease.

* Disease was re-evaluated after cycles 4 and 6 and every 4 cycles thereafter. Therapy may have continued up to a maximum of 17 cycles in total in the absence of PD or intolerance to therapy. The primary outcome was the proportion of patients who achieved at least a PR as their best overall response after up to 6 cycles of therapy.

Source: Clinical Study Report for ANBL1221.[16]

plus urinary catecholamine evaluation were included at their first relapse following aggressive front-line therapy (defined as chemotherapy with ≥ 2 drugs that must include an alkylating agent and a platinum-containing compound) or their first episode of refractory disease (defined as PD during front-line therapy or stable disease following at least 4 cycles of front-line therapy). Disease must have been documented within 3 weeks before study entry through demonstration of a measurable tumour by CT or MRI that was ^{123}I-MIBG–avid or showed FDG uptake on PET, through ^{123}I-MIBG scan with positive uptake at a minimum of 1 site, or through biopsy showing viable neuroblastoma. Recovery from the acute toxicities associated with prior therapies and adequate organ function were required. Patients had to have adequate organ function and performance status. Patients who had previously been treated for R/R high-risk neuroblastoma were excluded. Patients who had developed PD during prior anti-GD2 immunotherapy or who had experienced severe allergic reactions during prior anti-GD2 immunotherapy were excluded, as were patients with any significant intercurrent illness and patients who were pregnant or breastfeeding. Patients must have not have recently received myeloid growth factors and must have discontinued pharmacologic doses of systemic steroids; patients who required pharmacologic doses of systemic steroids were excluded.

Baseline Characteristics

The mean age at enrolment was 6.4 years (SD = 3.5 years) (Table 7). Patients were predominately male (62.0%), White (67.6%), not of Hispanic ethnicity (77.5%), and from the US (81.7%). Approximately 90% of patients had INSS stage 4 disease, 26.8% patients had *MYCN*-amplified tumours, and 69.0% had disease that was measurable by CT or MRI. Approximately half of patients had relapsed versus refractory disease. Patients had received a variety of prior treatments, including GD2 immunotherapy (25.4%), ASCT (46.5%), and radiotherapy (40.8%). The most common sites of disease were bone marrow, bone, and soft tissue, while the most common disease anatomic site classifications were adrenal gland and retroperitoneum or peritoneum.

Baseline demographic and clinical characteristics were generally well balanced between study arms. In the randomized cohort, there were slight imbalances between patients treated with regimen A (temsirolimus) and regimen B (dinutuximab) in terms of age at enrolment (median = 7.0 years versus 4.7 years), prior radiotherapy (44.4% versus 58.8%), and prior anti-GD2 immunotherapy (22.2% versus 35.3%). In addition, a higher proportion of patients treated with regimen A versus regimen B had retroperitonea or peritoneal tumours (22.2% versus 5.9%), and a smaller proportion had soft tissue disease (38.9% versus 70.6%). There were also slight imbalances between the randomized cohort and the non-randomized expansion cohort. Patients assigned to receive regimen B in the non-randomized expansion cohort were predominantly male (66.7%) with refractory disease (66.7%) that was present in soft tissue (80.6%) and detectable by CT or MRI (75.0%). Compared with those in the randomized cohort, fewer patients in the expansion cohort had received prior radiotherapy (30.6%) or undergone ASCT (36.1%). Unlike those in the randomized cohort, a subset of patients in the expansion cohort (16.7%) had INSS stage 3 or 4S tumours. Patients who received regimen B in the expansion cohort were also younger at enrolment (median = 3.5 years) than patients randomized to receive regimen A (median = 7.0 years).

Interventions

In the randomized cohort, patients were randomized 1:1 to receive either temsirolimus (regimen A) or dinutuximab and GM-CSF (regimen B), both with irinotecan and temozolomide. In the expansion cohort, all patients received regimen B. Treatment cycles were 21 days (Table 8 and Table 9). Regimen A consisted of temsirolimus (35 mg/m^2 IV infusion on day 1

Table 7: Summary of Baseline Characteristics — Intention-to-Treat Population

Characteristic	ANBL1221 trial			
	Regimen A randomized (N = 18)	Regimen B randomized (N = 17)	Regimen B non-randomized (N = 36)	Regimen B total (N = 53)
Age at enrolment (years)				
Mean (SD)	7.6 (3.5)	6.1 (3.8)	5.9 (3.5)	5.9 (3.6)
Median (range)	7.0 (2.9 to 16.2)	4.7 (2.0 to 15.6)	5.7 (1.3 to 15.9)	5.1 (1.3 to 15.9)
Age at enrolment category, n (%)				
Infant/toddler (< 2 years)	0	0	4 (11.1)	4 (7.5)
Child (2 years to 12 years)	16 (88.9)	15 (88.2)	29 (80.6)	44 (83.0)
Adolescent (12 years to 18 years)	2 (11.1)	2 (11.8)	3 (8.3)	5 (9.4)
Sex, n (%)				
Male	11 (61.1)	9 (52.9)	24 (66.7)	33 (62.3)
Female	7 (38.9)	8 (47.1)	12 (33.3)	20 (37.7)
Ethnicity, n (%)				
Hispanic or Latino	4 (22.2)	2 (11.8)	7 (19.4)	9 (17.0)
Not Hispanic or Latino	14 (77.8)	13 (76.5)	28 (77.8)	41 (77.4)
Unknown	0	2 (11.8)	1 (2.8)	3 (5.7)
Race, n (%)				
Black	3 (16.7)	4 (23.5)	4 (11.1)	8 (15.1)
Pacific Islander	2 (11.1)	2 (11.8)	6 (16.7)	8 (15.1)
White	13 (72.2)	11 (64.7)	24 (66.7)	35 (66.0)
Native Hawaiian or other	0	0	2 (5.6)	2 (3.8)
Baseline weight (kg)				
Mean (SD)	26.856 (15.533)	22.408 (12.017)	21.431 (10.640)	21.738 (10.978)
Median (range)	22.350 (12.10 to 65.45)	18.800 (10.03 to 51.90)	17.100 (9.30 to 59.50)	18.800 (9.30 to 59.50)
Baseline BSA (m^2)				
Mean (SD)	0.946 (0.346)	0.832 (0.286)	0.813 (0.276)	0.819 (0.276)
Median (range)	0.875 (0.56 to 1.77)	0.760 (0.50 to 1.46)	0.720 (0.43 to 1.72)	0.740 (0.43 to 1.72)
Age at diagnosis				
< 18 months	0	0	5 (13.9)	5 (9.4)
≥ 18 months	18 (100.0)	17 (100.0)	31 (86.1)	48 (90.6)
Age at diagnosis category, n (%)				
Infant or toddler (28 days to < 2 years)	0	1 (5.9)	8 (22.2)	9 (17.0)

Characteristic	ANBL1221 trial			
	Regimen A randomized (N = 18)	Regimen B randomized (N = 17)	Regimen B non-randomized (N = 36)	Regimen B total (N = 53)
Child (2 years to 12 years)	16 (88.9)	16 (94.1)	26 (72.2)	42 (79.2)
Adolescent (12 years to 18 years)	2 (11.1)	0	2 (5.6)	2 (3.8)
INSS stage, n (%)				
Stage 1	1 (5.6)	0	0	0
Stage 3	0	0	4 (11.1)	4 (7.5)
Stage 4	17 (94.4)	17 (100.0)	30 (83.3)	47 (88.7)
Stage 4S	0	0	2 (5.6)	2 (3.8)
Relapsed or refractory, n (%)				
Relapsed	10 (55.6)	9 (52.9)	12 (33.3)	21 (39.6)
Refractory	8 (44.4)	8 (47.1)	24 (66.7)	32 (60.4)
Disease measurable by CT or MRI, n (%)				
Yes	12 (66.7)	10 (58.8)	27 (75.0)	37 (69.8)
No	6 (33.3)	7 (41.2)	9 (25.0)	16 (30.2)
Prior anti-GD2 immunotherapy, n (%)				
Yes	4 (22.2)	6 (35.3)	8 (22.2)	14 (26.4)
No	14 (77.8)	11 (64.7)	28 (77.8)	39 (73.6)
Prior ASCT, n (%)				
Yes	10 (55.6)	10 (58.8)	13 (36.1)	23 (43.4)
No	8 (44.4)	7 (41.2)	23 (63.9)	30 (56.6)
Prior radiotherapy, n (%)				
Yes	8 (44.4)	10 (58.8)	11 (30.6)	21 (39.6)
No	10 (55.6)	7 (41.2)	25 (69.4)	32 (60.4)
***MYCN* status, n (%)**				
Amplified	5 (27.8)	3 (17.6)	11 (30.6)	14 (26.4)
Nonamplified	12 (66.7)	13 (76.5)	24 (66.7)	37 (69.8)
Unknown	1 (5.6)	1 (5.9)	1 (2.8)	2 (3.8)
Site of disease, n (%)				
Bone	10 (55.6)	11 (64.7)	25 (69.4)	36 (67.9)
Bone marrow	14 (77.8)	13 (88.2)	28 (77.8)	43 (81.1)
Liver	0	1 (5.9)	6 (16.7)	7 (13.2)
Lung	2 (11.1)	1 (5.9)	0	1 (1.9)
Soft tissue	7 (38.9)	12 (70.6)	29 (80.6)	41 (77.4)
Other	7 (38.9)	4 (23.5)	12 (33.3)	16 (30.2)

Characteristic	ANBL1221 trial			
	Regimen A randomized (N = 18)	Regimen B randomized (N = 17)	Regimen B non-randomized (N = 36)	Regimen B total (N = 53)
Disease anatomic site classification, n (%)				
Posterior mediastinum	0	3 (17.6)	1 (2.8)	4 (7.5)
Peripheral nerves and autonomic nervous system	0	0	1 (2.8)	1 (1.9)
Retroperitoneum or peritoneum	4 (22.2)	1 (5.9)	11 (30.6)	12 (22.6)
Kidney	0	0	1 (2.8)	1 (1.9)
Spinal cord, cranial nerves, other parts of CNS[a]	0	0	1 (2.8)	1 (1.9)
Adrenal gland	11 (61.1)	10 (58.8)	15 (41.7)	25 (47.2)
Head, face, or neck, NOS	0	0	1 (2.8)	1 (1.9)
Thorax, NOS	0	1 (5.9)	0	1 (1.9)
Abdomen, NOS	3 (16.7)	2 (11.8)	5 (13.9)	7 (13.2)

ASCT = autologous stem cell transplant; BSA = body surface area; CNS = central nervous system; INSS = International Neuroblastoma Staging System; NOS = not otherwise specified; SD = standard deviation.

Note: Regimen A: temsirolimus plus irinotecan/temozolomide; regimen B: dinutuximab with GM-CSF and irinotecan plus temozolomide.

[a]Excludes peripheral nerves, sympathetic and parasympathetic nerves, and ganglia c47.

Source: ANBL1221 Clinical Study Report.[16]

and day 8) in combination with irinotecan (50 mg/m^2 IV on days 1 to 5) and temozolomide (100 mg/m^2 orally on days 1 to 5). Temsirolimus was administered by infusion twice per 3-week treatment cycle until disease progression or unacceptable toxicity to a maximum of 17 cycles. Regimen B consisted of dinutuximab (17.5 mg/m^2 per day IV infusion on days 2 to 5) in combination with irinotecan (50 mg/m^2 IV on days 1 to 5), temozolomide (100 mg/m^2 orally on days 1 to 5), and GM-CSF (250 mcg/m^2 IV or subcutaneous on days 6 to 12). Dinutuximab was administered as an infusion over 10 hours to 20 hours for 4 consecutive days per 3-week treatment cycle until disease progression or unacceptable toxicity to a maximum of 17 cycles. Drug doses were adjusted based on body surface area and calculated within 1 week of the start of each treatment cycle. Dose modifications of dinutuximab due to toxicity were permitted for diarrhea, elevated liver enzymes, hypotension, anaphylaxis or allergic reactions, capillary leak syndrome, renal insufficiency, visual changes, or neurotoxicity. Common dose modifications involved holding dinutuximab, then restarting infusion at a 50% reduced rate or dose reductions of 25% to 50%. Dinutuximab infusion was administered in an inpatient setting, while other components of therapy were administered in both inpatient and outpatient settings.

The randomized study protocol included a 3-stage stopping rule for unacceptable toxicity and to assess feasibility during the first 2 cycles of treatment. The stopping rules for safety and tolerability were at least 3 of 6 patients with at least 1 unacceptable toxicity during the safety phase; at least 4 of 17 patients during stage 1 of the efficacy phase; and at least 6 of 25 patients during stage 2 of the efficacy phase. The expansion cohort included a single-stage stopping rule. If 7 or fewer patients (of a maximum anticipated enrolment of 50) experienced a protocol-defined unacceptable toxicity during the first 2 cycles of treatment, the regimen was defined as tolerable. If 20 or fewer patients required a greater than 25%

dose modification or were taken off protocol therapy during the first 2 cycles, the regimen was deemed feasible. Stopping rules also included toxic death or requirement for ventilator support. The stopping rule was not met for either regimen.

Protocol therapy was administered until PD or withdrawal from therapy to a maximum of 17 cycles. Criteria for discontinuation of therapy included: PD, intolerance of protocol therapy, patient or family refusal, physician decision, second malignant neoplasm, and failure to meet repeat eligibility requirements for starting the next cycle. Patients were evaluated after 2 cycles, then at cycle 4, cycle 6, and every 4 cycles thereafter. Cycles were repeated every 21 days if patients had stable disease or better and had laboratory parameters meeting eligibility requirements.

In terms of concomitant treatments permitted while on protocol therapy, patients received cefixime or equivalent cephalosporin for diarrhea prophylaxis as well as pneumocystis prophylaxis. Pharmacological doses of systemic corticosteroids were used only for life-threatening conditions. Low-dose corticosteroids as premedication for transfusion were permitted. Dexamethasone as an anti-emetic was not permitted. Appropriate antibiotics, antiemetics, blood products, fluids, electrolytes, and general supportive care were provided as necessary. Recommended premedications (for administration before dinutuximab infusion) included hydroxyzine orally or diphenhydramine IV and acetaminophen. Recommended pain management was with a morphine loading dose before dinutuximab infusion followed by continued morphine drip. Other narcotic use (hydromorphone or fentanyl) was permitted. Use of gabapentin as an adjunct to dinutuximab in patients needing additional pain control was permitted. Use of additional medications (lidocaine, ketamine) in extenuating circumstances was undertaken in consultation with pediatric pain management specialists.

While on protocol therapy, no other systemic anti-cancer therapy was permitted. Radiotherapy to painful localized lesions was permitted as long as at least 1 lesion measurable by CT or MRI or evaluable by ^{123}I-MIBG was not irradiated. The irradiated lesion was not used to judge tumour response. After protocol therapy was discontinued, patients went on to be

Table 8: Treatment Schedule for Regimen A

Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8
TEMO	TEMO	TEMO	TEMO	TEMO	—	—	—
IRIN	IRIN	IRIN	IRIN	IRIN	—	—	—
TORI	—	—	—	—	—	—	TORI

IRIN = irinotecan 50 mg/m^2 IV daily on days 1 to 5; TEMO = temozolomide 100 mg/m^2 orally daily on days 1 to 5; TORI = temsirolimus 35 mg/m^2 IV on day 1 and day 8.
Source: Clinical Study Report for ANBL1221.[16]

Table 9: Treatment Schedule for Regimen B

Day 1	Day 2	Day 3	Day 4	Day 5	Days 6 to 12
TEMO	TEMO	TEMO	TEMO	TEMO	—
IRIN	IRIN	IRIN	IRIN	IRIN	—
—	DINU	DINU	DINU	DINU	GM-CSF

DINU = dinutuximab 17.5 mg/m^2 IV on days 2 to 5; GM-CSF = granulocyte-macrophage colony-stimulating factor 250 mcg/m^2 SC on days 6 to 12; IRIN = irinotecan 50 mg/m^2 IV daily on days 1 to 5; TEMO = temozolomide 100 mg/m^2 orally daily on days 1 to 5.
Source: Clinical Study Report for ANBL1221.[16]

treated with other systemic anti-cancer therapies at the discretion of the treating physician. Information about additional anti-cancer therapies received was not provided.

Outcomes

A list of efficacy end points identified in the CADTH review protocol that were assessed in the clinical trials included in this review is provided in Table 10. These end points are summarized and discussed in the text.

The primary outcome (best overall response of at least a PR as per INRC criteria[13,14] up to 6 cycles of protocol therapy; binary responder or nonresponder) was assessed as defined as in Table 11. The maximum duration of treatment over which a patient's response was to be assessed for determination of response was after the completion of the first 6 cycles. This limit was applied to both the randomized and non-randomized cohorts. If a patient became a responder and later had PD or went off protocol therapy, they were counted as a responder. By contrast, patients with PD before attaining a PR or better were considered to have failed treatment and went off protocol therapy. Patients who had stable disease at cycles 2, 4, and 6 but achieved a PR or better thereafter were counted as non-responders. Patients with stable disease continued protocol therapy. Patients could also be removed from therapy for other reasons (e.g., toxicity, patient or family refusal, or physician decision); if this occurred before achieving a PR or better, then these patients were counted as non-responders.

The INRC criteria[13,14] were used to define the primary outcome (ORR). These criteria integrate responses at all sites during disease evaluation. The response of lesions detectable by CT or MRI was assessed using the Response Evaluation Criteria in Solid Tumours Version 1.1. Responses of ^{123}I-MIBG–avid lesions were assessed using Curie scoring. Bone marrow response was assessed by bilateral biopsy and staining. CR was defined as no evidence of tumour and normal catecholamine levels. PR of soft tissue disease was defined as at least a 50% reduction in Curie score (if ^{123}I-MIBG–avid lesions were present at study entry) and resolution of bone marrow disease (if present at study entry). Patients with stable disease in any site category were classified as having stable disease. PD was defined as any of development of a new lesion, a doubling of the percentage of tumour cells in bone marrow

Table 10: Summary of Outcomes of Interest Identified in the CADTH Review Protocol

Outcome measure	ANBL1221 Trial
Best overall response (PR or better) after 6 cycles of therapy	Primary
Differences in ORRs between study arms	Exploratory
DOR	Exploratory
OS	Exploratory
PFS	Exploratory
EFS	NR
HRQoL	NR
Symptom relief	NR

DOR = duration of response; EFS = event-free survival; HRQoL = health-related quality of life; NR = not reported; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PR = partial response.

Source: Clinical Study Report for ANBL1221.[16]

(minimum 25% marrow involvement), or an increase of 20% or more in the longest dimension of a soft tissue mass.

The process for determining ORR began at the treating institution, where patients, families, and treating physicians were not blinded to group assignment after randomization. Bone marrow, CT, or MRI and ^{123}I-MIBG scans were first evaluated by the treating institution, and response was designated locally. Subsequently, ^{123}I-MIBG and CT or MRI scans were evaluated through COG central review by the study chair without information about group assignment. Any patient who was scored by their local institution as showing long-term PR or better based on improvement in CT, MRI, or ^{123}I-MIBG scanning (or FDG-PET if their tumour was not ^{123}I-MIBG–avid) had scans evaluated centrally to confirm response status. These reviews were performed retrospectively. Scans for patients designated as having prolonged stable disease (> 6 cycles) were also centrally reviewed. The study chair cross-checked the institutional data (imaging and marrow studies) and integrated local response data with information on central review forms for patients whose imaging results met the criteria for central review. The central review designation of response was used for formal statistical evaluation of ORR.

Exploratory end points included DOR, PFS, and OS. For patients with at least PRs, DOR was calculated from the time of initial response until documented tumour or disease progression. DOR was calculated separately, based on local investigator and central review designations of OR; DOR based on central review is presented in this report. The DOR was censored at the date of last assessment if there was no documented tumour or disease progression and no additional anti-cancer therapy use. If additional anti-cancer therapy use was reported, the DOR was censored at the start date of the follow-up period during which the patients received additional anti-cancer therapy. DOR was also presented as n (%) of patents with responses of greater than or equal to 6 months.

PFS was assessed in the same manner as DOR among all patients by calculating time from enrolment to an event (first relapse, PD, or death attributable to tumour or treatment) or to time of last patient contact if no event occurred. For patients who died from causes other than disease or treatment, PFS was censored at the time of death. For OS, time from enrolment to death from any cause, or time to last contact if the patient was alive, was calculated. In PFS and OS calculations, patients with unknown cause of death were counted as death attributable to disease or treatment. Neither PFS nor OS took into account the effects of additional anti-cancer therapies received following protocol therapy.

Harms outcomes included treatment-emergent AEs (i.e., AEs with onset dates equal to or after the start date of the study drug). AEs were graded as per version 4.0 of the Common Terminology Criteria for Adverse Events toxicity grading scale. The toxicity end point for the safety phase was the occurrence of the following protocol-defined unacceptable toxicities: grade 4 capillary leak syndrome, grade 4 anaphylaxis or allergic reaction, and grade 3 or 4 hypotension; grade 4 respiratory toxicity, including acute respiratory distress syndrome, bronchospasm, dyspnea, hypoxia, or respiratory failure; grade 3 or 4 peripheral neuropathy; grade 3 or 4 sensory motor neuropathy; grade 4 cytokine release syndrome or acute infusion reaction; and toxic death. Safety analyses were performed in the safety population.

Statistical Analysis

The randomized portion of the study used a Simon's 2-stage activity design to assess whether each regimen met pre-specified minimum requirements for clinical activity (≥ 4

patients among 17 with PRs or better or ≥ 7 patients among 25 with PRs or better). The study began with a safety phase in which 6 patients were treated with each of regimen A and B and monitored for safety and feasibility. Both regimens were tolerated, and the stopping rule for the safety phase (≥ 3 of 6 patients with unacceptability toxicities during the first 2 cycles of treatment) was not triggered. In stage 1 of the efficacy phase, 17 patients were to be randomized to each regimen (including the 6 patients from the safety phase) to permit evaluation of activity. If the protocol-defined minimum number of responses (≥ 4 patients with PRs or better) was observed for both regimens, additional patients would be recruited in stage 2 of the efficacy phase, up to 25 patients per randomized arm. Regimens that did not meet these minimum criteria were eliminated; if both regimens met the minimum activity, the selection design would be applied (i.e., the winning regimen would have ≥ 3 additional patients with PRs or better compared with the losing 1). In the event of a tie, other criteria (toxicity, feasibility, and PFS) would be used to select the winner. Recruitment of up to 37 patients per treatment arm was planned to achieve the 25 evaluable participants needed for stage 2 of the activity design. Safety and feasibility rules were also applied to stage 1 and stage 2 of the efficacy phase (≥ 4 of 17 patients with unacceptable toxicities during stage 1; ≥ 6 of 25 patients during stage 2). However, they were not triggered because the minimum criterion for efficacy was met in stage 1 for regimen B.

The non-randomized expansion cohort was recruited because the results of the randomized study were considered promising by the investigators. There were no pre-specified criteria for efficacy. The expansion cohort included a single-stage stopping rule for safety and feasibility. If 7 or fewer patients (out of a maximum anticipated enrolment of 50) experienced protocol-defined unacceptable toxicity during the first 2 cycles, the regimen was defined as

Table 11: Measurement of Overall Response in the ANBL1221 Trial

Response by individual site				Overall response
CT or MRI lesions	^{123}I-MIBG lesions	Bone marrow	Catechols	
PD	Any	Any	Any	PD
Any	PD	Any	Any	PD
Any	Any	PD	Any	PD
CR	CR	CR	Normal	CR
VGPR	CR in bone lesions; may have stable disease or CR in soft tissue sites corresponding to lesions on CT or MRI	CR	Normal	VGPR
PR	PR/CR in bone lesions; may have stable disease or CR in soft tissue sites corresponding to lesions on CT or MRI	CR	Any	PR
Stable disease	Stable disease, PR, or CR	Stable disease or CR	Any	Stable disease
Stable disease, PR, VGPR, or CR	Stable disease	Stable disease or CR	Any	Stable disease
Stable disease, PR, VGPR, or CR	Stable disease, PR, or CR	Stable disease	Any	Stable disease

CR = complete response; ^{123}I-MIBG = ^{123}I-metaiodobenzylguanidine; PD = progressive disease; PR = partial response; VGPR = very good partial response.
Source: Clinical Study Report for ANBL1221.[16]

tolerable. If 20 or fewer patients required a greater than 25% dose modification, or were taken off protocol therapy during the first 2 cycles, the regimen was deemed feasible. Amendment 4 was added to permit statistical analysis of data from the randomized and non-randomized cohort together. Amendment 5A added the primary objective of more accurately determining the response rate to regimen B (dinutuximab) in an expanded cohort, enabling comparison with historical response rates to irinotecan and temozolomide alone.

All efficacy analyses were based on the intention-to-treat (ITT) set. The initial primary objective — to choose either dinutuximab or temsirolimus to move forward to a phase III trial — was accomplished using pre-specified activity thresholds without formal statistical analysis. Differences in the proportion of patients treated with dinutuximab versus temsirolimus (plus irinotecan and temozolomide) who achieved at least a PR as their best overall response were assessed as an exploratory objective using Fisher's exact test (Table 12). This was a pre-specified analysis. The overall design had a 91.1% power to detect a 25% difference (15% under the null hypothesis and 40% under the alternative hypothesis) in ORR with a type I error of 0.064. In the non-randomized expansion cohort, the primary objective was to accurately determine the response rate to dinutuximab and compare it with historical response rates to irinotecan plus temozolomide alone. The expansion permitted accrual of up to 50 eligible patients (40 additional patients to yield 33 eligible patients). This sample size would allow the estimation of ORR with a standard error of 0.07. Losses to follow-up were not accounted for in the analysis of differences in ORR between treatment arms.

DOR, PFS, and OS were evaluated in an exploratory fashion using Kaplan–Meier analysis and Cox proportional hazards models (for PFS and OS only). Differences in median DOR, PFS, and OS from the Kaplan–Meier analyses were assessed using the log-rank test; P values for the null hypothesis of HR equals 1 were derived from Cox proportional hazards models. Changes in the statistical analysis plan based on protocol amendments were not provided. The study was not powered to permit definitive evaluation of survival outcomes, and no power calculations were applied for time-to-event analyses. Time-to-event analyses accounted for losses to follow-up by censoring at the date of last patient contact (see Outcomes). For PFS and OS, additional anti-cancer therapies received following protocol therapy were not accounted for. The percentage of patients with DOR 6 months or longer was calculated, and OS was evaluated at pre-specified time points (26 weeks, 52 weeks, 78 weeks, and 104 weeks).

Subgroup analyses of interest to this review that were pre-specified in the study protocol included assessments of the efficacy outcomes (ORR, DOR, PFS, and OS) according to relapsed versus refractory disease and *MYCN* amplification status. The study was not powered to evaluate each stratum separately. All subgroup analyses were performed as described previously for comparisons of efficacy outcomes between patients treated with regimen A versus regimen B.

Analysis Populations

The ITT population was defined as all eligible patients who were randomized into the randomized cohort of the study or enrolled into the non-randomized cohort of the study. The safety population was defined as all eligible patients in the ITT population who received at least 1 dose of temsirolimus or dinutuximab.

Results

Patient Disposition

In the randomized cohort, 36 patients were enrolled (19 randomized to regimen A and 17 to regimen B). One patient randomized to regimen A (temsirolimus) was deemed ineligible; thus, the ITT population included a total of 35 patients (18 randomized to receive regimen A and 17 randomized to receive regimen B). One patient randomized to receive regimen B did not receive study therapy; thus, only 16 patients were part of the safety population for evaluation of safety and feasibility. In the non-randomized regimen B expansion cohort, 37 patients were enrolled. One patient was deemed ineligible before treatment assignment; thus, the ITT population included 36 patients. One patient refused study therapy after randomization; thus, only 35 patients were included in the safety population.

One patient (5.3%) randomized to regimen A and 3 patients (17.6%) randomized to regimen B — as well as 2 patients (5.4%) in the regimen B expansion cohort — withdrew from protocol therapy and follow-up (Table 13). Overall, 17 of 19 patients (94.4%) randomized to receive regimen A, 14 of 17 patients (82.4%) randomized to receive regimen B, and 35 of 37 patients (94.6%) in the regimen B expansion cohort discontinued protocol therapy. Patients who discontinued study therapy prematurely (i.e., before 17 cycles) remained in the study and were followed until the criteria were met for study discontinuation. The most common reason for prematurely discontinuing therapy in the randomized regimen A arm was PD (n = 12; 63.2%). Among the 53 patients in the total regimen B ITT set, the most common reasons for premature discontinuation of study therapy included physician decision (n = 21; 38.9%), completion of maximum allowable number of cycles of therapy (n = 11; 20.4%), and PD (n = 10; 18.5%).

Table 12: Statistical Analysis of Efficacy End Points

End point	Statistical model
Best overall response (PR or better) after 6 cycles of therapy	The ORRs for regimens A and B were determined and their 95% CIs calculated using the Clopper-Pearson exact method.
Difference in ORR between study arms	Fisher's exact tests were used to compare ORRs among patients treated with regimen A (randomized cohort) vs. regimen B (randomized cohort, expansion cohort, and all regimen B–treated patients).
DOR	The Kaplan–Meier method was used to estimate median DOR and 95% CIs. P values for differences in DOR were calculated using a 2-sided log-rank test.
OS	The Kaplan–Meier method was used to estimate median survival and 95% CIs. Standard error was calculated according to Peto. P values were calculated using a 2-sided log-rank test. For OS, survival and its 95% CI were calculated at pre-specified time intervals (26 weeks, 52 weeks, 78 weeks, and 104 weeks). HRs, 95% CIs, and P values for the differences between treatment groups (null hypothesis: HR = 1) were derived using Cox proportional hazards models.
PFS	The Kaplan–Meier method was used to estimate median PFS and 95% CIs. Standard error was calculated according to Peto. P values were calculated using a 2-sided log-rank test. HRs, 95% CIs, and P values for the differences between treatment groups (null hypothesis: HR = 1) were derived using Cox proportional hazards models.

CI = confidence interval; DOR = duration of response; HR = hazard ratio; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PR = partial response.

Source: Clinical Study Report for ANBL1221.[16]

Exposure to Study Treatments

Individual patients were administered IV dinutuximab in an inpatient settings. Consequently, appropriate inpatient clinical staff observed the dinutuximab administration and recorded the actual dosage information. Because a larger proportion of patients randomized to regimen A had PD at cycle 2 (n = 8; 42.1%), exposure in this group was roughly half that of patients in the regimen B arm in the randomized study (Table 14). In the randomized stage, the mean duration of exposure was 5.4 cycles (SD = 4.8 cycles) for regimen A and 9.3 cycles (SD = 6.3

Table 13: Patient Disposition in the ANBL1221 Trial

Disposition	Regimen A randomized	Regimen B randomized	Regimen B non-randomized	Regimen B total
Screened	NR	NR	NR	NR
Enrolled, N	19	17	37	54
Randomized or assigned, n (%)	18 (94.7)	17	37 (97.3)	53 (98.1)
Received study drug, n (%)	18 (94.7)	16 (94.1)	35 (94.6)[a]	52 (96.3)
Discontinued from study and follow-up, n (%)	1 (5.3)	3 (17.6)	2 (5.4)	5 (9.3)
Reason for discontinuation from study and follow-up, n (%)				
Disease progression	0	1 (5.9)	0	1 (1.9)
Physician decision	0	0	2 (5.4)	2 (3.7)
Patient or family refusal	1 (5.3)	0	0	0
Death	0	1 (5.9)	0	1 (1.9)
Withdrawal of consent	0	1 (5.9)	0	1 (1.9)
Discontinued study therapy, n (%)	17 (94.4)	14 (82.4)	35 (94.6)	49 (90.7)
Reason for discontinuation of therapy, n (%)				
Intolerance of therapy	1 (5.3)	1 (5.9)	0	1 (1.9)
Disease progression	12 (63.2)	1 (5.9)	9 (24.3)	10 (18.9)
Physician decision	2 (10.5)	5 (29.4)	16 (43.2)	21 (38.9)
Patient or family refusal	1 (5.3)	2 (11.8)	3 (8.1)	5 (9.3)
Did not meet criteria to start next treatment cycle	0	0	1 (2.7)	1 (1.9)
Completion of 17 cycles	1 (5.3)	5 (29.4)	6 (16.2)	11 (20.4)
ITT, n (%)	18 (94.7)	17	36 (97.3)	53 (98.1)
Safety, n (%)	18 (94.7)	16 (94.1)	35 (94.6)	51 (94.4)

NR = not reported; GM-CSF = granulocyte-macrophage colony-stimulating factor; ITT = intention to treat.

Note: Regimen A: temsirolimus plus irinotecan plus temozolomide; regimen B: dinutuximab combined with GM-CSF and irinotecan plus temozolomide.

[a]There was a discrepancy between study records as to whether all 36 patients received study treatment or whether 1 patient refused treatment and was thus excluded from the safety population.

Source: Clinical Study Report for ANBL1221.[16]

cycles) for regimen B. In the non-randomized stage, the mean duration of exposure was 7.1 cycles (SD = 5.7 cycles) for patients receiving regimen B. Among all patients receiving regimen B, the mean duration of exposure was 7.8 cycles (SD = 5.9 cycles). The mean duration of follow-up was shorter among patients randomized to receive regimen A (643.7 days) compared with patients randomized to receive regimen B (1,155.8 days) or patients assigned to receive regimen B in the expansion cohort (663.9 days).

Table 14: Exposure to Study Therapy in the ANBL1221 Trial

Exposure	Regimen A randomized	Regimen B randomized	Regimen B non-randomized	Regimen B total
Overall study population				
N	19	17	37	54
Duration of follow-up (days)				
Mean (SD)	643.7 (547.5)	1,155.8 (639.3)	663.9 (277.4)	818.8 (478.4)
Median (range)	517 (6 to 1,518)	1,440 (1 to 1,946)	755 (44 to 1,041)	782 (1 to 1,946)
Discontinued therapy, n (%)				
Missing	2 (10.5)	3 (17.6)	2 (5.4)	5 (9.3)
Cycle 1	0	1 (5.9)	1 (2.7)	2 (3.7)
Cycle 2	8 (42.1)	1 (5.9)	9 (24.3)	10 (18.5)
Cycle 3	2 (10.5)	1 (5.9)	2 (5.4)	3 (5.6)
Cycle 4	1 (5.3)	0	4 (10.8)	4 (7.4)
Cycle 5	0	1 (5.9)	2 (5.4)	3 (5.6)
Cycle 6	1 (5.3)	3 (17.6)	4 (10.8)	7 (13.0)
Cycle 8	0	1 (5.9)	1 (2.7)	2 (3.7)
Cycle 9	0	0	1 (2.7)	1 (1.9)
Cycle 10	2 (10.5)	1 (5.9)	3 (8.1)	4 (7.4)
Cycle 11	1 (5.3)	0	0	0
Cycle 13	0	0	1 (2.7)	1 (1.9)
Cycle 14	1 (5.3)	0	0	0
Cycle 15	0	0	1 (2.7)	1 (1.9)
Cycle 17	1 (5.3)	5 (29.4)	6 (16.2)	11 (20.4)
Safety population				
N	**18**	**16**	**35**	**51**
Duration of exposure (cycles)				
Mean (SD)	5.4 (4.8)	9.3 (6.3)	7.1 (5.7)	7.8 (5.9)
Median (range)	3 (2 to 17)	7 (1 to 17)	5 (1 to 17)	6 (1 to 17)

GM-CSF = granulocyte-macrophage colony-stimulating factor; SD = standard deviation.

Note: Regimen A: temsirolimus plus irinotecan plus temozolomide; regimen B: dinutuximab combined with GM-CSF and irinotecan plus temozolomide.

Source: Clinical Study Report for ANBL1221.[16]

A majority of patients in the overall ITT population (n = 58, 81.7%, irrespective of treatment assignment) had at least 1 protocol deviation (Table 15). Major deviations (i.e., those reportable to the Clinical Study Report [CSR]) were defined as those related to the inclusion or exclusion criteria, the overall conduct of the trial, patient management, or patient assessment that could have affected the safety of the patients or jeopardized the quality of the study data. In the randomized regimen A arm, 2 of 18 patients (11.1%) had a major CSR-reportable protocol deviation due to incorrect dose. In the regimen B arm,6 of 17 patients (35.5%) had this. In the non-randomized regimen B expansion cohort, 7 of 36 patients (19.4%) had CSR-reportable protocol deviations for incorrect dose.

Additional Anti-Cancer Therapies Received

Patients who discontinued protocol therapy (50% to 94%, depending on treatment arm) could go on to receive other systemic anti-cancer therapies. Some of the patients with refractory disease who responded to the dinutuximab-containing regimen went on to receive additional components of standard front-line therapy, such as surgery and/or high-dose chemotherapy with ASCT. Details were not provided on additional anti-cancer therapies received.

Efficacy

Only those efficacy outcomes and analyses of subgroups identified in the review protocol are reported here.

Objective Response Rate

In the randomized cohort, after 6 cycles of therapy, the ORR among patients randomized to receive regimen A was 5.6% (1 of 18; 95% CI, 0.1% to 27.3%); the ORR among those randomized to receive regimen B was 52.9% (9 of 17; 95% CI, 27.8% to 77.0%) (P = 0.0027) (Table 16). The ORR among patients assigned to receive regimen B in the expansion cohort

Table 15: Protocol Deviations in the ANBL1221 Trial — Intention-to-Treat Population

Protocol deviations	Regimen A randomized (N = 18)	Regimen B randomized (N = 17)	Regimen B non-randomized (N = 36)	Regimen B total (N = 53)
≥ 1 protocol deviation, n (%)	14 (77.8)	14 (82.4)	30 (83.3)	44 (83.0)
Concomitant medications	1 (5.6)	1 (5.9)	0	1 (1.9)
Incorrect dose	2 (11.1)	6 (35.3)	7 (19.4)	13 (24.5)
Informed consent	3 (16.7)	4 (23.5)	11 (30.6)	15 (28.3)
Investigational product	8 (44.4)	12 (70.6)	17 (47.2)	29 (54.7)
Not withdrawn, but developed withdrawal criteria	1 (5.6)	0	1 (2.8)	1 (1.9)
≥ 1 major (CSR-reportable) protocol deviation, n (%)	3 (16.7)	6 (35.5)	8 (22.2)	14 (26.4)
Incorrect dose	2 (11.1)	6 (35.5)	7 (19.4)	13 (24.5)
Not withdrawn, but developed withdrawal criteria	1 (5.6)	0	1 (2.8)	1 (1.9)

CSR = Clinical Study Report; GM-CSF = granulocyte-macrophage colony-stimulating factor.

Note: Regimen A consisted of temsirolimus, irinotecan, and temozolomide; regimen B consisted of dinutuximab, GM-CSF, irinotecan, and temozolomide.

Source: Clinical Study Report for ANBL1221.[16]

was 36.1% (13 of 36; 95% CI, 20.8% to 53.8%; P = 0.0205 versus regimen A), and the ORR among all patients who received regimen B was 41.5% (22 of 53; 95% CI, 28.1% to 55.9%; P = 0.004 versus regimen A). Similar numbers of patients who responded to regimen B (n = 22) achieved PRs (n = 11; 50.0%) versus CRs (n = 11; 50.0%). No patient with stable disease by cycle 6 subsequently achieved at least a PR.

A subgroup analysis of ORR was conducted among patients with relapsed versus refractory disease (Table 17). In the total group of relapsed patients treated with regimen B, the ORR was 52.4% (95% CI, 29.8% to 74.3%; P = 0.0464). ORRs among relapsed patients treated with regimen B were 55.6% (5 of 9) in the randomized cohort and 50.0% (6 of 12) in the expansion cohort. In the total group of refractory patients treated with regimen B, the ORR was 34.4% (95% CI, 18.6% to 53.2%; P = 0.0803). The ORRs among refractory patients treated with regimen B were 50.0% (4 of 8) in the randomized cohort and 29.2% (7 of 24) in the expansion cohort.

A subgroup analysis of ORR was conducted based on tumour *MYCN* amplification status (Table 18). In the total group of patients with *MYCN*-amplified tumours treated with regimen B, the ORR was 28.6% (95% CI, 8.4% to 58.1%; P = 0.5304). ORRs among patients with *MYCN*-amplified tumours treated with regimen B were 66.7% (2 of 3) in the randomized cohort and 18.2% (2 of 11) in the expansion cohort. In the total group of patients with *MYCN*-

Table 16: Objective Response Rate in the ANBL1221 Trial — Intention-to-Treat Population

Response	Regimen A randomized (N = 18)	Regimen B randomized (N = 17)	Regimen B non-randomized (N = 36)	Regimen B total (N = 53)
Patients with response (PR or better)				
n (%)	1 (5.6)	9 (52.9)	13 (36.1)	22 (41.5)
95% CI[a]	0.1 to 27.3	27.8 to 77.0	20.8 to 53.8	28.1 to 55.9
P value[b]	—	0.0027	0.0205	0.004
Type of response				
CR, n (%)	0	5 (29.4)	6 (16.7)	11 (20.8)
VGPR, n (%)	0	0	0	0
PR, n (%)	1 (5.6)	4 (23.5)	7 (19.4)	11 (20.8)
No response				
n (%)	17 (94.4)	8 (47.1)	23 (63.9)	31 (58.5)
Outcome in non-responders				
Stable disease, n (%)	10 (55.6)	4 (23.5)	18 (50.0)	22 (41.5)
Progressive disease, n (%)	7 (38.9)	3 (17.6)	4 (11.1)	7 (13.2)
Not evaluated, n (%)[c]	0	1 (5.9)	1 (2.8)	2 (3.8)

CI = confidence interval; CR = complete response; GM-CSF = granulocyte-macrophage colony-stimulating factor; PR = partial response; VGPR = very good partial response.
Note: Regimen A: temsirolimus plus irinotecan plus temozolomide; regimen B: dinutuximab combined with GM-CSF and irinotecan plus temozolomide
[a]Calculated using the Clopper-Pearson exact method.
[b]From Fisher's exact test. No adjustment for multiplicity was performed.
[c]Not evaluated because of refusal to receive therapy after randomization.
Source: Clinical Study Report for ANBL1221.[16]

Table 17: Subgroup Analysis of ORRs in ANBL1221 Trial Patients With Relapsed and Refractory Disease

Response	Regimen A randomized	Regimen B randomized	Regimen B non-randomized	Regimen B total
ANBL-1221 trial (relapsed)				
N	10	9	12	21
Patients with response (PR or better)				
n (%)	1 (10.0)	5 (55.6)	6 (50.0)	11 (52.4)
95% CI[a]	0.3 to 44.5	21.2 to 86.3	21.1 to 78.9	29.8 to 74.3
P value[b]	—	0.0573	0.0743	0.0464
Type of response				
CR, n (%)	0	2 (22.2)	3 (25.0)	5 (23.8)
VGPR, n (%)	0	0	0	0
PR, n (%)	1 (10.0)	3 (33.3)	3 (25.0)	6 (28.6)
No response				
n (%)	9 (90.0)	4 (44.4)	6 (50.0)	10 (47.6)
Outcome in non-responders				
Stable disease, n (%)	4 (40.0)	1 (11.1)	4 (33.3)	5 (23.8)
Progressive disease, n (%)	5 (50.0)	2 (22.2)	2 (16.7)	4 (19.0)
Not evaluated, n (%)[c]	0	1 (11.1)	0	1 (4.8)
ANBL-1221 trial (refractory)				
N	8	8	24	32
Patients with response (PR or better)				
n (%)	0	4 (50.0)	7 (29.2)	11 (34.4)
95% CI[a]	0 to 36.9	15.7 to 84.3	12.6 to 51.1	18.6 to 53.2
P value[b]	—	0.0769	0.1497	0.0803
Type of response				
CR, n (%)	0	3 (37.5)	3 (12.5)	6 (18.8)
VGPR, n (%)	0	0	0	0
PR, n (%)	0	1 (12.5)	4 (16.7)	5 (15.6)
No response				
n (%)	8 (100.0)	4 (50.0)	17 (70.8)	21 (65.6)
Outcome in non-responders				
Stable disease, n (%)	6 (75.0)	3 (37.5)	14 (58.3)	17 (53.1)
Progressive disease, n (%)	2 (25.0)	1 (12.5)	2 (8.3)	3 (9.4)
Not evaluated, n (%)[c]	0	0	1 (4.2)	1 (3.1)

CI = confidence interval; CR = complete response; GM-CSF = granulocyte-macrophage colony-stimulating factor; ORR = objective response rate; PR = partial response; VGPR = very good partial response.

Note: Regimen A: temsirolimus plus irinotecan plus temozolomide; regimen B: dinutuximab combined with GM-CSF and irinotecan plus temozolomide.

[a]Calculated using the Clopper-Pearson exact method.

[b]From Fisher's exact test. No adjustment for multiplicity was performed.

[c]Not evaluated because of refusal to receive therapy after randomization.

Source: Clinical Study Report for ANBL1221.[16]

nonamplified tumours treated with regimen B, the ORR was 45.9% (95% CI, 29.5% to 63.1%; P = 0.0356). ORRs among patients with *MYCN*-nonamplified tumours treated with regimen B were 46.2% (6 of 13) in the randomized cohort and 45.8% (11 of 24) in the expansion cohort.

No subgroup analyses of ORR were conducted by age or INSS stage.

Duration of Response

For time-to-event analyses (DOR, PFS, and OS), numbers of events and censored observations varied. One patient randomized to receive regimen A achieved a PR or greater and responded for 35.1 weeks (Table 19 and Figure 3). For analysis of DOR among the 22 patients in total who responded to regimen B, events (relapse, progression, or death) occurred for 6 patients (27.3%); the remainder of observations were censored when patients started other anti-cancer therapies or at the last time of contact. The median DOR was 31.0 weeks (range = 24.3 weeks to 37.7 weeks), 33.0 weeks (range = 2.4 weeks to 76.1 weeks), and 33.0 weeks (range = 2.4 weeks to 76.1 weeks) in the randomized regimen B arm, the regimen B expansion cohort, and all regimen B–treated patients. The median DOR based on Kaplan–Meier analysis was not calculable for the randomized regimen B arm based on the data available. The median DORs among patients treated with regimen B based on Kaplan–Meier analysis in the expansion cohort alone and the pooled randomized and expansion cohort were 35.0 weeks and 76.1 weeks, respectively. Boundaries of 95% CIs for median DOR based on Kaplan–Meier analysis could not be calculated because of the rarity of events.

A subgroup analysis of DOR was conducted among patients with relapsed versus refractory disease (Table 20). In the total group of relapsed patients treated with regimen B, 4 of 11 patients (36.4%) with responses experienced relapse, PD, or death, while the remaining observations were censored. The median DOR was 34.3 weeks (range = 2.4 weeks to 76.1 weeks) among all regimen B–treated relapsed patients. The median DOR from Kaplan–Meier analysis was 76.1 weeks (randomized cohort = not calculable; expansion cohort = 76.1 weeks). In the total group of refractory patients treated with regimen B, 2 of 11 patients (18.2%) with responses experienced relapse, PD, or death, while the remaining observations were censored. The median DOR was 29.7 weeks (range = 24.3 weeks to 35.0 weeks) among all regimen B–treated refractory patients. The median DOR from Kaplan–Meier analysis was not calculable (randomized cohort: not calculable; expansion cohort: 35.0 weeks). Boundaries of 95% CIs for median DOR based on Kaplan–Meier analysis could not be calculated in this subgroup analysis because of the rarity of events.

A subgroup analysis of DOR was conducted based on tumour *MYCN* amplification status (Table 21). In the total group of patients with *MYCN*-amplified tumours treated with regimen B, 1 of 4 responding patients (25.0%) experienced relapse, PD, and/or death while the remaining observations were censored. The median DOR in the single patient with a *MYCN*-amplified tumour treated with regimen B was 2.4 weeks. The median DOR from Kaplan–Meier analysis was not calculable based on the available data. In the total group of patients with *MYCN*-nonamplified tumours treated with regimen B, 5 of 17 responding patients (29.4%)

Table 18: Subgroup Analysis of ORR in ANBL1221 Trial Patients With *MYCN*-Amplified and *MYCN*-Nonamplified Tumours

Response	Regimen A randomized	Regimen B randomized	Regimen B non-randomized	Regimen B total
ANBL-1221 trial (*MYCN*-amplified)				
N	5	3	11	14
Patients with response (PR or better)				
n (%)	0	2 (66.7)	2 (18.2)	4 (28.6)
95% CI[a]	0 to 52.2	9.4 to 99.2	2.3 to 51.8	8.4 to 58.1
P value[b]	—	0.1071	1	0.5304
Type of response				
CR, n (%)	0	1 (33.3)	1 (9.1)	2 (14.3)
VGPR, n (%)	0	0	0	0
PR, n (%)	0	1 (33.3)	1 (9.1)	2 (14.3)
No response				
n (%)	5 (100.0)	1 (33.3)	9 (81.8)	10 (71.4)
Outcome in non-responders				
Stable disease, n (%)	2 (40.0)	0	5 (45.5)	5 (35.7)
Progressive disease, n (%)	3 (60.0)	1 (33.3)	3 (27.3)	4 (28.6)
Not evaluated, n (%)[c]	0	0	1 (9.1)	1 (7.1)
ANBL-1221 trial (*MYCN*-nonamplified)				
N	12	13	24	37
Patients with response (PR or better)				
n (%)	1 (8.3)	6 (46.2)	11 (45.8)	17 (45.9)
95% CI[a]	0.2 to 38.5	19.2 to 74.9	25.6 to 67.2	29.5 to 63.1
P value[b]	—	0.0730	0.0307	0.0356
Type of response				
CR, n (%)	0	3 (23.1)	5 (20.8)	8 (21.6)
VGPR, n (%)	0	0	0	0
PR, n (%)	1 (8.3)	3 (23.1)	6 (25.0)	9 (24.3)
No response				
n (%)	11 (91.7)	7 (53.8)	13 (54.2)	20 (54.1)
Outcome in non-responders				
Stable disease, n (%)	7 (58.3)	4 (30.8)	12 (50.0)	16 (43.2)
Progressive disease, n (%)	4 (33.3)	2 (15.4)	1 (4.2)	3 (8.1)
Not evaluated, n (%)[c]	0	1 (7.7)	0	1 (2.7)

Response	Regimen A randomized	Regimen B randomized	Regimen B non-randomized	Regimen B total
ANBL-1221 (*MYCN* status unknown)				
N	1	1	1	2
Patients with response (PR or better)				
n (%)	0	1 (100.0)	0	1 (50.0)
95% CI[a]	0 to 97.5	2.5 to 100.0	0 to 97.5	1.3 to 98.7
P value[b]	—	1	—	1
Type of response				
CR, n (%)	0	1 (100.0)	0	1 (50.0)
VGPR, n (%)	0	0	0	0
PR, n (%)	0	0	0	0
No response				
n (%)	1 (100.0)	0	1 (100.0)	1 (50.0)
Outcome in non-responders				
Stable disease, n (%)	1 (100.0)	0	1 (100.0)	1 (50.0)
Progressive disease, n (%)	0	0	0	0
Not evaluated, n (%)[c]	0	0	0	0

CI = confidence interval; CR = complete response; GM-CSF = granulocyte-macrophage colony-stimulating factor; ORR = objective response rate; PR = partial response; VGPR = very good partial response.

Note: Regimen A consisted of temsirolimus, irinotecan, and temozolomide; regimen B consisted of dinutuximab, GM-CSF, irinotecan, and temozolomide.

[a]Calculated using the Clopper-Pearson exact method.

[b]From Fisher's exact test. No adjustment for multiplicity was performed.

[c]Not evaluated because of refusal to receive therapy after randomization.

Source: Clinical Study Report for ANBL1221.[16]

experienced relapse, PD, or death, while the remaining observations were censored. The median DOR among all patients with *MYCN*-nonamplified tumours treated with regimen B was 35.0 weeks (range = 24.3 to 76.1 weeks). The median DOR from Kaplan–Meier analysis was 56.9 weeks (randomized cohort: not calculable; expansion cohort, 55.6 weeks). Boundaries of 95% CIs for median DOR based on Kaplan–Meier analysis could not be calculated in this subgroup analysis because of the rarity of events.

No subgroup analyses of DOR were conducted by age or INSS stage.

Progression-Free Survival

In the randomized portion of the study, 15 of 18 patients (83.3%) treated with regimen A and 11 of 17 (64.7%) of patients treated with regimen B experienced relapse, PD, or death during the follow-up period. The median PFS was 7.7 weeks (range = 5.9 weeks to 66.0 weeks) in patients randomized to receive regimen A and 92.3 weeks (range = 5.1 weeks to 196.9 weeks) in patients randomized to receive regimen B. The median PFS of patients based on Kaplan–Meier estimates (Table 22 and Figure 4) was 12.9 weeks (95% CI, 6.9 weeks to 47.3 weeks) in patients randomized to receive regimen A and 101.0 weeks (95% CI, not calculable) in patients randomized to receive regimen B (HR = 0.39; 95% CI, 0.17 to 0.88, P = 0.0240).

In the non-randomized portion of the study, 24 of 36 patients (66.7%) treated with regimen B experienced relapse, PD, or death during the follow-up period. The median PFS in these patients was 48.8 weeks (range = 3.3 weeks to 121.3 weeks), and the median PFS based on Kaplan–Meier estimates was 81.4 weeks (95% CI, 42.4 weeks to 110.6 weeks; HR = 0.43; 95% CI, 0.22 to 0.83, P = 0.0120 versus regimen A). Among all patients treated with regimen B, 35 out of 53 (66.0%) experienced relapse, PD, or death during the follow-up period. The median PFS was 57.0 weeks (range = 3.3 weeks to 196.9 weeks) in these patients, and the median PFS based on Kaplan–Meier estimates was 97.9 weeks (95% CI, 60.3 weeks to 110.6 weeks; HR = 0.41; 95% CI, 0.22 to 0.77, P = 0.0054 versus regimen A).

A subgroup analysis of PFS was conducted among patients with relapsed versus refractory disease treated with regimen B. Data tables were not provided for this analysis. The Kaplan–Meier survival curve is presented in Figure 5.

Event-Free Survival

Data on event-free survival were not reported in the ANBL1221 study.

Table 19: Duration of Response in the ANBL1221 Trial — Intention-to-Treat Population

Response	Regimen A randomized (N = 18)	Regimen B randomized (N = 17)	Regimen B non-randomized (N = 36)	Regimen B total (N = 53)
Patients with response (PR or better)				
n	1	9	13	22
End of response				
Relapse, progression, or death, n (%)	1 (100.0)	2 (22.2)	4 (30.8)	6 (27.3)
Censored[a]	0	7 (77.8)	9 (69.2)	16 (72.7)
Duration of response (weeks)				
Mean (SD)	35.1 (NA)	31.0 (9.5)	36.1 (30.4)	34.4 (24.0)
Median (range)	35.1 (35.1 to 35.1)	31.0 (24.3 to 37.7)	33.0 (2.4 to 76.1)	33.0 (2.4 to 76.1)
Response > 6 months, n (%)[b]	1 (100.0)	1 (50.0)	3 (75.0)	4 (66.7)
Kaplan-Meier estimates for duration of response (weeks)				
Median (95% CI)[c]	35.1 (NC to NC)	NC (24.3 to NC)	35.0 (2.4 to NC)	76.1 (30.9 to NC)
P value[d]	—	0.1768	0.8858	0.4278
Response > 6 months, n (%)[e]	1 (100.0)	5 (55.6)	4 (30.8)	9 (40.9)

CI = confidence interval; GM-CSF = granulocyte-macrophage colony-stimulating factor; NA = not applicable; NC = not calculable; PR = partial response; SD = standard deviation.

Note: Regimen A: temsirolimus plus irinotecan plus temozolomide; regimen B: dinutuximab combined with GM-CSF and irinotecan plus temozolomide.

[a]Patients without progression or relapse had DOR censored when they received additional anti-cancer therapy or at the date of last assessment.

[b]The denominator is the number of patients with initial response and with relapse or progression (i.e., censored events ignored).

[c]The median was not calculable because less than 50% of patients experienced events.

[d]From log-rank test.

[e]The denominator is the number of patients with initial response (i.e., censored events included).

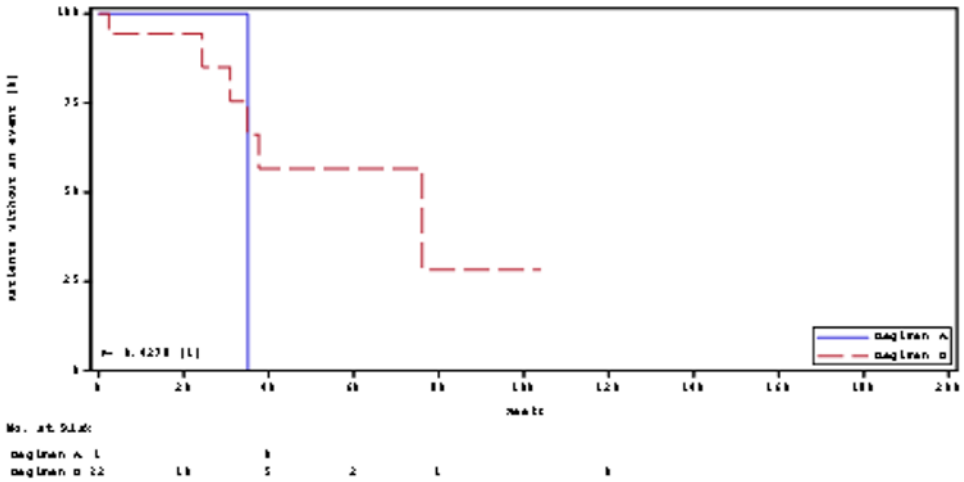
Source: Clinical Study Report for ANBL1221.[16]

Overall Survival

In the randomized portion of the study, 12 of 18 patients (66.7%) treated with regimen A and 7 of 17 patients (41.2%) treated with regimen B died during the follow-up period. Median OS was 54.8 weeks (range = 13.1 weeks to 165.9 weeks) in patients randomized to receive regimen A and 120.1 weeks (range = 6.0 weeks to 219.4 weeks) in patients randomized to receive regimen B. Median OS based on Kaplan–Meier estimates (Table 23 and Figure 6) was 117.3 weeks (95% CI, 23.6 weeks to 165.9 weeks) for patients randomized to receive regimen A and was not calculable for patients randomized to receive regimen B (HR = 0.37; 95% CI, 0.14 to 0.99; P = 0.0479). In the non-randomized portion of the study, 13 of 36 patients (36.1%) treated with regimen B died during the follow-up period. Median OS in these patients was 62.4 weeks (range = 10.9 weeks to 143.7 weeks) and median OS based on Kaplan–Meier estimates was 143.7 weeks (95% CI, not calculable; HR = 0.65; 95% CI, 0.28 to 1.52, P = 0.3186 versus regimen A). Among all patients receiving regimen B, 20 of 53 (37.7%) died during the follow-up period. Median OS in these patients was 72.8 weeks (range = 6.0 weeks to 219.4 weeks) and median OS based on Kaplan–Meier estimates was 219.4 weeks (95% CI, not calculable; HR = 0.50; 95% CI, 0.24 to 1.04; P = 0.0636 versus regimen A).

In the randomized portion of the study, the proportion of patients surviving ranged from 77.1% at 26 weeks to 52.8% at 104 weeks for regimen A compared to 87.9% at 26 weeks and 81.6% at 104 weeks for regimen B. In the non-randomized portion of the study, the proportion of surviving patients treated with regimen B ranged from 88.7% at 26 weeks to 70.7% at 104 weeks. For the total group of patients treated with regimen B, the proportion of surviving patients ranged from 88.5% at 26 weeks to 74.3% at 104 weeks.

Figure 3: Kaplan–Meier Analysis of Duration of Response in the ANBL1221 Trial



GM-CSF = granulocyte-macrophage colony-stimulating factor.

Note: Duration of response was calculated using central assessment of response and was censored when patients began to receive other anti-cancer therapies. Regimen A: temsirolimus plus irinotecan plus temozolomide; Regimen B: dinutuximab combined with GM-CSF and irinotecan plus temozolomide.

[1] P value from log-rank test.

Source: Clinical Study Report for ANBL1221.[16]

Table 20: Subgroup Analysis of DOR in ANBL1221 Trial Patients With Relapsed Versus Refractory Disease

Response	Regimen A randomized	Regimen B randomized	Regimen B non-randomized	Regimen B total
ANBL-1221 trial (relapsed)				
N	10	9	12	21
Patients with response (PR or better)				
n	1	5	6	11
End of response				
Relapse, progression, or death, n (%)	1 (100.0)	1 (20.0)	3 (50.0)	4 (36.4)
Censored[a]	0	4 (80.0)	3 (50.0)	6 (63.6)
Duration of response (weeks)				
Mean (SD)	35.1 (NA)	37.7 (NA)	36.5 (37.2)	36.8 (30.4)
Median (range)	35.1 (35.1 to 35.1)	37.7 (37.7 to 37.7)	30.9 (2.4 to 76.1)	34.3 (2.4 to 76.1)
Response > 6 months, n (%)[b]	1 (100.0)	1 (100.0)	2 (66.7)	3 (75.0)
Kaplan–Meier estimates for duration of response (weeks)				
Median (95% CI)[c]	35.1 (NC to NC)	NC (37.7 to NC)	76.1 (2.4 to NC)	76.1 (2.4 to NC)
P value[d]	—	0.0833	0.7357	0.3066
Response > 6 months, n (%)[e]	1 (100.0)	3 (60.0)	3 (50.0)	6 (54.5)
ANBL-1221 trial (refractory)				
N	8	8	24	32
Patients with response (PR or better)				
n	0	4	7	11
End of response				
Relapse, progression, or death, n (%)	0	1 (25.0)	1 (14.3)	2 (18.2)
Censored[a]	0	3 (75.0)	6 (85.7)	9 (81.8)
Duration of response (weeks)				
Mean (SD)	NA	24.3 (NA)	35.0 (NA)	29.7 (7.6)
Median (range)	NA	24.3 (24.3 to 24.3)	35.0 (35.0 to 35.0)	29.7 (24.3 to 35.0)
Response > 6 months, n (%)[b]	0	0	1 (100.0)	1 (50.0)
Kaplan–Meier estimates for duration of response (weeks)				
Median (95% CI)[c]	NA	NC (24.3 to NC)	35.0 (NC to NC)	NC (24.3 to NC)
P value[d]	—	NA	NA	NA
Response > 6 months, n (%)[e]	0	2 (50.0)	1 (14.3)	3 (27.3)

CI = confidence interval; DOR = duration of response; GM-CSF = granulocyte-macrophage colony-stimulating factor; NA = not applicable; NC = not calculable; PR = partial

response; SD = standard deviation.

Note: Regimen A: temsirolimus plus irinotecan plus temozolomide; regimen B: dinutuximab combined with GM-CSF and irinotecan plus temozolomide.

[a]Patients without progression or relapse had DOR censored when they received additional anti-cancer therapy or at the date of last assessment.

[b]Denominator is the number of patients with initial response and with relapse or progression (i.e., censored events ignored).

[c]Median was not calculable because less than 50% of patients experienced events.

[d]From log-rank test.

[e]Denominator is the number of patients with initial response (i.e., censored events included).

Source: Clinical Study Report for ANBL1221.[16]

A subgroup analysis of OS was conducted among patients with relapsed versus refractory disease treated with regimen B. Data tables were not provided for this analysis. The Kaplan–Meier survival curve is presented in Figure 7.

Health-Related Quality of Life

Data on HRQoL were not reported in the ANBL1221 study.

Symptom Relief

Data on symptom relief were not reported in the ANBL1221 study.

Harms

Only those harms identified in the review protocol are reported in this review. AE summary tables were limited to include only treatment-emergent AEs in each treatment group.

Unacceptable Toxicities

See Table 24 for summaries of protocol-defined unacceptable toxicities. During the study treatment period, 9 of 51 patients (17.6%) in the total regimen B group (randomized cohort: 6 of 16; 37.5%; expansion cohort: 3 of 35; 8.6%) reported at least 1 protocol-defined unacceptable toxicity. No patients treated with regimen A had an unacceptable toxicity.

Adverse Events

Overall, 16 of 18 patients (88.9%) treated with regimen A and 48 of all 51 patients (94.1%) treated with regimen B (randomized cohort: 16 of 16 [100.0%]; expansion cohort: 32 of 35 [91.4%]) experienced at least 1 AE (Table 25). Common AEs in patients treated with both regimens were decreased neutrophil counts (regimen A: 44.4%; regimen B: 39.2%), decreased white blood cell counts (regimen A: 33.3%; regimen B: 33.3%), decreased lymphocyte counts (regimen A: 22.2%; regimen B: 37.3%), anemia (regimen A: 38.9%; regimen B: 31.4%), hypokalemia (regimen A: 27.8%; regimen B: 23.5%), increased ALT (regimen A: 27.8%; regimen B: 19.6%) and diarrhea (regimen A: 16.7%; regimen B: 25.5%). Pain (33.3%), pyrexia (33.3%), hypoxia (21.6%), hypotension (11.8%), and dyspnea (5.9%) occurred more often in patients treated with regimen B.

Serious (AdEERS-Reportable) Adverse Events

Serious adverse events (SAEs) occurred more frequently in patients treated with regimen B. Overall, 7 of 18 patients (38.9%) in the randomized regimen A group and 11 of 16 patients (68.8%) in the randomized regimen B group experienced at least 1 SAE that was AdEERS-reportable. In the expansion cohort, 16 of 35 patients (45.7%) treated with regimen B experienced at least 1 SAE, and SAEs occurred in 27 (52.9%) of the total regimen B patients. The most common AdEERS-reportable events in the total regimen B group were decreased neutrophil count (5 of 51; 9.8%), death (4 of 51; 7.8%), disease progression (3 of 51; 5.9%), and hypoxia (3 of 51; 5.9%). All other SAEs occurred in 1 or 2 patients each.

Table 21: Subgroup analysis of DOR in ANBL1221 Trial Patients With *MYCN*-Amplified and *MYCN*-Nonamplified Tumours

Response	Regimen A randomized	Regimen B randomized	Regimen B non-randomized	Regimen B total
ANBL-1221 trial (*MYCN*-amplified tumour)				
N	5	3	11	14
Patients with response (PR or better)				
n	0	2	2	4
End of response				
Relapse, progression, or death, n (%)	0	0	1 (50.0)	1 (25.0)
Censored[a]	0	2 (100.0)	1 (50.0)	3 (75.0)
Duration of response (weeks)				
Mean (SD)	NA	NA	2.4 (NA)	2.4 (NA)
Median (range)	NA	NA	2.4 (2.4 to 2.4)	2.4 (2.4 to 2.4)
Response > 6 months, n (%)[b]	0	0	0	0
Kaplan–Meier estimates for duration of response (weeks)				
Median (95% CI)[c]	NA	NA	NC (2.4 to NC)	NC (2.4 to NC)
P value[d]	—	NA	NA	NA
Response > 6 months, n (%)[e]	0	1 (50.0)	0	1 (25.0)
ANBL-1221 trial (*MYCN*-nonamplified tumour)				
N	12	13	24	37
Patients with response (PR or better)				
n	1	6	11	17
End of response				
Relapse, progression, or death, n (%)	1 (100.0)	2 (33.3)	3 (27.3)	5 (29.4)
Censored[a]	0	4 (66.7)	8 (72.7)	12 (70.6)
Duration of response (weeks)				
Mean (SD)	35.1 (NA)	31.0 (9.5)	47.3 (25.0)	40.8 (20.4)
Median (range)	35.1 (35.1 to 35.1)	31.0 (24.3 to 37.7)	35.0 (30.9 to 76.1)	35.0 (24.3 to 76.1)
Response > 6 months, n (%)[b]	1 (100.0)	1 (50.0)	3 (100.0)	4 (80.0)
Kaplan–Meier estimates for duration of response (weeks)				
Median (95% CI)[c]	35.1 (NC to NC)	NC (24.3 to NC)	55.6 (30.9 to NC)	56.9 (24.3 to NC)
P value[d]	—	0.3508	0.7741	0.5072
Response > 6 months, n (%)[e]	1 (100.0)	3 (50.0)	4 (36.4)	7 (41.2)

Response	Regimen A randomized	Regimen B randomized	Regimen B non-randomized	Regimen B total
ANBL-1221 trial (*MYCN* status unknown)				
N	1	1	1	2
Patients with response (PR or better)				
n	0	1	0	1
End of response				
Relapse, progression, or death, n (%)	0	0	0	0
Censored[a]	0	1 (100.0)	0	1 (100.0)
Duration of response (weeks)				
Mean (SD)	NA	NA	NA	NA
Median (range)	NA	NA	NA	NA
Response > 6 months, n (%)[b]	0	0	0	0
Kaplan–Meier estimates for duration of response (weeks)				
Median (95% CI)[c]	NA	NC (NC to NC)	NA	NC (NC to NC)
P value[d]	—	NA	NA	NA
Response > 6 months, n (%)[e]	0	1 (100.0)	0	1 (100.0)

CI = confidence interval; DOR = duration of response; GM-CSF = granulocyte-macrophage colony-stimulating factor; NA = not applicable; NC = not calculable; PR = partial response; SD = standard deviation.

Note: Regimen A: temsirolimus plus irinotecan plus temozolomide; Regimen B: dinutuximab combined with GM-CSF and irinotecan plus temozolomide.

[a]Patients without progression or relapse had DOR censored when they received additional anti-cancer therapy or at the date of last assessment.

[b]Denominator is the number of patients with initial response and with relapse/progression (i.e., censored events ignored).

[c]Median not calculable because < 50% of patients experienced events.

[d]From log-rank test.

[e]Denominator is the number of patients with initial response (i.e., censored events included).

Source: Clinical Study Report for ANBL1221.[16]

Withdrawals Due to Adverse Events

Only 2 patients discontinued protocol therapy due to intolerance of the study therapy: 1 patient receiving regimen A (1 of 18; 5.6%) and 1 patient receiving regimen B (1 of 16; 6.3%) in the randomized portion of the study (Table 11). The patient treated with regimen A developed a severe infusion reaction at the third cycle but did not require hospitalization. The patient treated with regimen B experienced life-threatening dyspnea and/or hypoxia during the first cycle and was hospitalized.

Mortality

Overall, 32 patients died during treatment and follow-up: 12 of 18 patients (66.7%) treated with regimen A and 20 of 51 patients (39.2%) treated with regimen B (randomized cohort: 7 of 16; 43.8%; expansion cohort: 12 of 35; 34.3%). Of the 31 patients included in the safety population, the primary cause of death was underlying disease (for all deaths among patients treated with regimen A and for 18 of 19 deaths among patients treated with regimen B). The primary cause of death was unknown for 1 patient in the randomized regimen B group. Nearly all the deaths (30 of 32) occurred during the follow-up period and were attributable to

PD. Two deaths occurred during protocol therapy, both in the randomized regimen B group.

Table 22: Progression-Free Survival in the ANBL1221 Trial — Intention-to-Treat Population

Relapse	Regimen A randomized (N = 18)	Regimen B randomized (N = 17)	Regimen B non-randomized (N = 36)	Regimen B total (N = 53)
Patients with relapse, progression, or death				
n (%)	15 (83.3)	11 (64.7)	24 (66.7)	35 (66.0)
Time to relapse, progression, or death (weeks)				
Mean (SD)	20.9 (21.2)	73.7 (59.1)	53.2 (39.4)	59.6 (46.6)
Median (range)	7.7 (5.9 to 66.0)	92.3 (5.1 to 196.9)	48.8 (3.3 to 121.3)	57.0 (3.3 to 196.9)
Kaplan–Meier estimates for time to relapse, progression, or death (weeks)				
Median (95% CI)	12.9 (6.9 to 47.3)	101.0 (30.1 to NC)	81.4 (42.4 to 110.6)	97.9 (60.3 to 110.6)
Hazard ratio (95% CI)[a]	—	0.39 (0.17 to 0.88)	0.43 (0.22 to 0.83)	0.41 (0.22 to 0.77)
P value[a]	—	0.024	0.012	0.0054

CI = confidence interval; GM-CSF = granulocyte-macrophage colony-stimulating factor; NC = not calculable; SD = standard deviation.

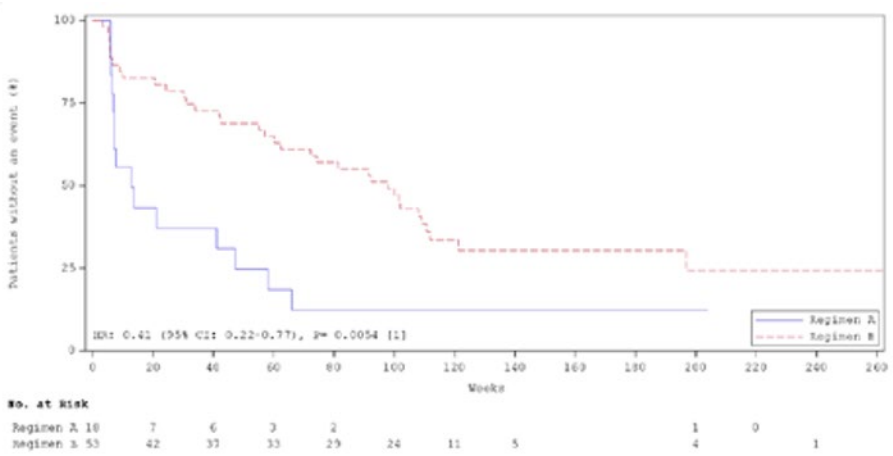
Note: Regimen A: temsirolimus plus irinotecan plus temozolomide; Regimen B: dinutuximab combined with GM-CSF and irinotecan plus temozolomide.

[a]From unadjusted Cox proportional hazards model.

Note: Patients who did not have relapse, progression, or death had their time to relapse, progression, or death censored at the date of the last assessment.

Source: Clinical Study Report for ANBL1221.[16]

Figure 4: Kaplan–Meier Analysis of Progression-Free Survival in the ANBL1221 Trial



CI = confidence interval; GM-CSF = granulocyte-macrophage colony-stimulating factor; HR = hazard ratio.

Note: Regimen A: temsirolimus plus irinotecan plus temozolomide; Regimen B: dinutuximab combined with GM-CSF and irinotecan plus temozolomide.

[1] There was a conflict in the Clinical Study Report as to whether this P value was from the log-rank test or unadjusted Cox proportional hazard model.

Source: Clinical Study Report for ANBL1221.[16]

One patient died of hypoxia secondary to PD, while a second died unexpectedly. One patient assigned to the non-randomized regimen B cohort who died did not receive study therapy.

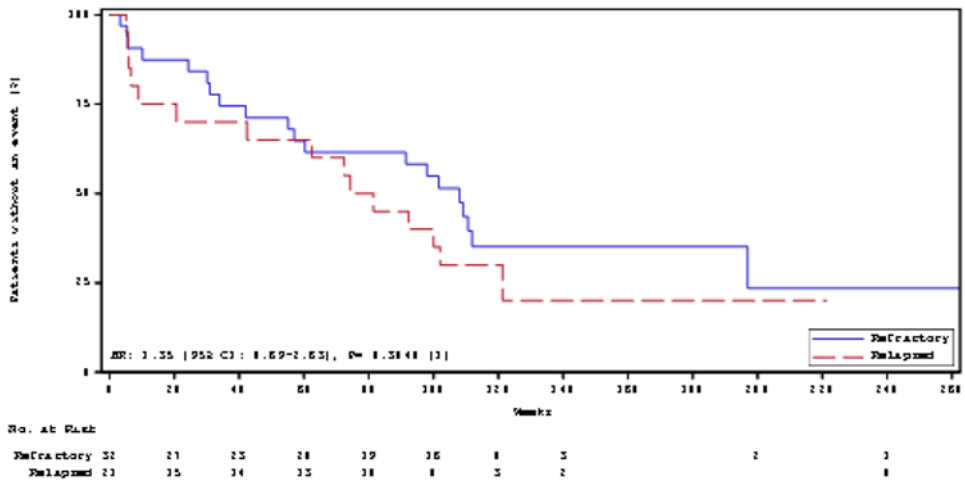
Notable Harms

Notable harms identified in the protocol fell into 4 categories: infusion reactions and/or capillary leak syndrome, neuropathic pain, neurologic toxicities, and inpatient hospitalization and/or intensive care unit admission. One patient had an infusion reaction and was treated with regimen A (1 of 18; 5.6%). Capillary leak syndrome was reported in 2 of 51 patients (3.9%) treated with regimen B. Hypotension was reported in 6 of 51 patients (11.8%) treated with regimen B; 5 of 6 cases were hypotension of grade 3 or higher. Dyspnea and respiratory failure each occurred in 3 of 51 patients (5.9%) treated with regimen B. Bronchospasm occurred in 1 patient (2.0%) treated with regimen B.

The AE reporting did not distinguish neuropathic pain from other types of pain. Generic AE pain was not reported in any patients treated with regimen A, although 1 patient treated with regimen A (1 of 18; 5.6%) reported oral pain. In contrast, 17 of 51 patients (33.3%) receiving regimen B experienced pain as well as a variety of more specific pain types. In terms of neurologic toxicities, 1 patient treated with regimen B (1 of 51; 2.0%) experienced each of the following: peripheral motor neuropathy, loss of consciousness, loss of vision, and loss of smell.

Those AEs requiring inpatient hospitalization, including prolonged hospitalization, were slightly more common among patients receiving regimen B versus regimen A in the randomized cohort (12 of 16; 75.0% versus 8 of 18; 44.4%); 12 of 35 patients (34.3%) in the

Figure 5: Subgroup Kaplan–Meier Analysis of Progression-Free Survival in ANBL1221 Trial Patients With Relapsed Versus Refractory Disease



CI = confidence interval; GM-CSF = granulocyte-macrophage colony-stimulating factor; HR = hazard ratio.

Regimen A: temsirolimus plus irinotecan plus temozolomide; Regimen B: dinutuximab combined with GM-CSF and irinotecan plus temozolomide.

[1] There was a conflict in the Clinical Study Report as to whether this P value was from the log-rank test or unadjusted Cox proportional hazard model.

Source: Clinical Study Report for ANBL1221.[16]

expansion regimen B cohort had AEs requiring hospitalization. AEs requiring hospitalization occurred at similar frequency in the overall groups of patients treated with regimen A versus regimen B (44.4% versus 47.1%). Intensive care unit admission was not reported in the ANBL1221 study.

Critical Appraisal

Internal Validity

ANBL1221 was a multi-centre, open-label, phase II trial (N = 71).[10,11] The study consisted of an initial randomized cohort with a "pick the winner" design followed by a subsequent non-randomized expansion cohort. The initial primary objective of the trial was to explore the efficacy of 2 different drugs (regimen A and regimen B: temsirolimus and dinutuximab, respectively, both with irinotecan plus temozolomide) in patients with R/R high-risk neuroblastoma and determine which was the optimal drug to consider for testing in a future phase III trial. A second primary objective — to determine the response rate more accurately to regimen B (dinutuximab with GM-CSF, irinotecan, and temozolomide) in an expanded cohort — was added by means of a protocol amendment to enable comparison with historical response rates to irinotecan and temozolomide alone (e.g., from the ANBL0421 trial).[12] Overall, this was an exploratory trial with a stepwise approach to assessing the efficacy and

Table 23: Overall Survival in the ANBL1221 Trial — Intention-to-Treat Population

Survival	Regimen A randomized (N = 18)	Regimen B randomized (N = 17)	Regimen B non-randomized (N = 36)	Regimen B total (N = 53)
Deaths				
n (%)	12 (66.7)	7 (41.2)	13 (36.1)	20 (37.7)
Time to death (weeks)				
Mean (SD)	70.8 (56.5)	103.3 (76.2)	66.3 (45.2)	79.25 (58.8)
Median (range)	54.8 (13.1 to 165.9)	120.1 (6.0 to 219.4)	62.4 (10.9 to 143.7)	72.8 (6.0 to 219.4)
% surviving for at least				
26 weeks (95% CI)	77.1 (50.0 to 90.7)	87.9 (59.6 to 96.8)	88.7 (72.7 to 95.6)	88.5 (76.1 to 94.6)
52 weeks (95% CI)	65.3 (38.4 to 82.7)	87.9 (59.6 to 96.8)	83.0 (66.0 to 92.0)	84.5 (71.4 to 91.9)
78 weeks (95% CI)	52.8 (27.3 to 73.1)	81.6 (53.1 to 93.7)	80.1 (62.8 to 90.0)	80.6 (66.9 to 89.1)
104 weeks (95% CI)	52.8 (27.3 to 73.1)	81.6 (53.1 to 93.7)	70.7 (52.3 to 83.1)	74.3 (59.9 to 84.2)
Kaplan–Meier estimates for time to death (weeks)				
Median (95% CI)[a]	117.3 (23.6 to 165.9)	NC (120.1, NC)	143.7 (105.9 to NC)	219.4 (120.1 to NC)
Hazard Ratio (95% CI)[b]	—	0.37 (0.14 to 0.99)	0.65 (0.28 to 1.52)	0.50 (0.24 to 1.04)
P value[b]	—	0.0479	0.3186	0.0636

CI = confidence interval; GM-CSF = granulocyte-macrophage colony-stimulating factor; NC = not calculable; SD = standard deviation.

Note: patients who survived had their time to death censored at the date of last contact. Regimen A: temsirolimus plus irinotecan plus temozolomide; Regimen B: dinutuximab combined with GM-CSF and irinotecan plus temozolomide.

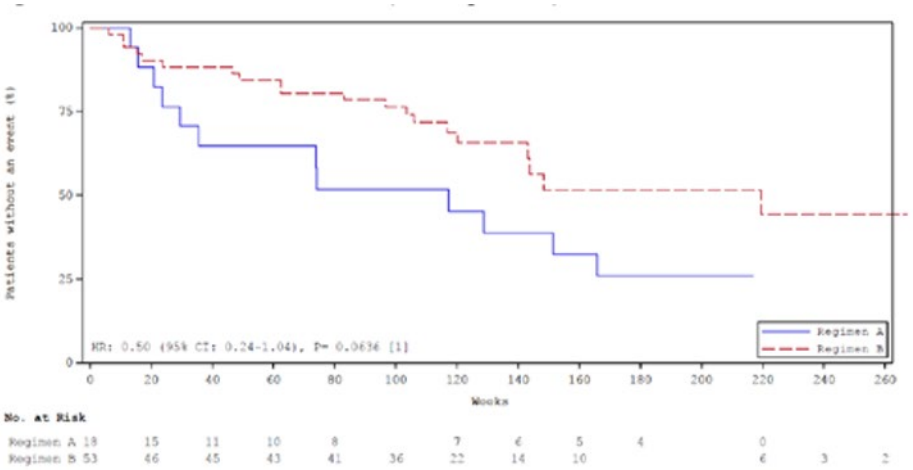
[a]The median values were not calculable because less than 50% of patients in the analysis group experienced an event.

[b]From unadjusted Cox proportional hazards model.

Source: Clinical Study Report for ANBL1221.[16]

safety of dinutuximab in combination with GM-CSF, irinotecan, and temozolomide. This was a small phase II trial, and its findings must be considered in this context.

Figure 6: Kaplan–Meier Analysis of Overall Survival in the ANBL1221 Trial



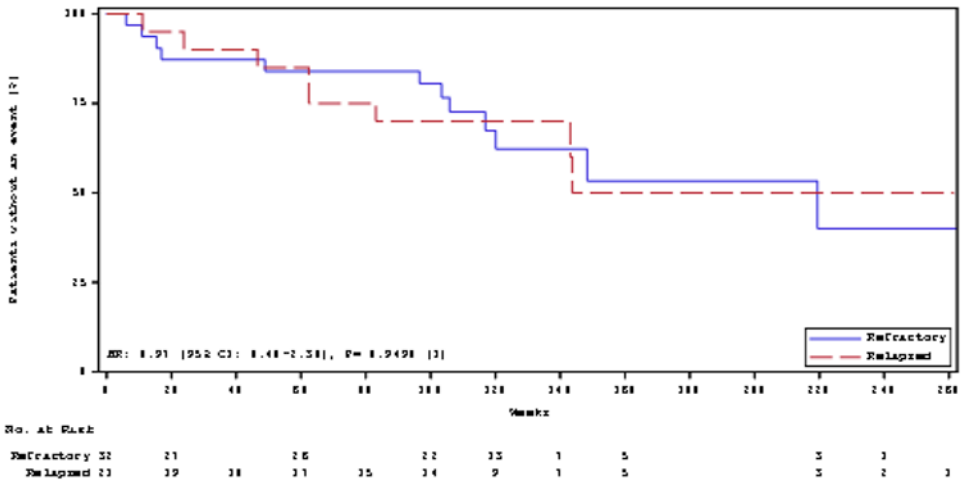
CI = confidence interval; GM-CSF = granulocyte-macrophage colony-stimulating factor; HR = hazard ratio.

Note: Regimen A: temsirolimus plus irinotecan plus temozolomide; Regimen B: dinutuximab combined with GM-CSF and irinotecan plus temozolomide.

[1] There was a conflict in the Clinical Study Report as to whether this P value was from the log-rank test or unadjusted Cox proportional hazard model.

Source: Clinical Study Report for ANBL1221.[16]

Figure 7: Subgroup Kaplan–Meier Analysis of Overall Survival in ANBL1221 Trial Patients With Relapsed Versus Refractory Disease



CI = confidence interval; GM-CSF = granulocyte-macrophage colony-stimulating factor; HR = hazard ratio.

Note: Regimen A: temsirolimus plus irinotecan plus temozolomide; Regimen B: dinutuximab combined with GM-CSF and irinotecan plus temozolomide.

[1] There was a conflict in the Clinical Study Report as to whether this P value was from the log-rank test or unadjusted Cox proportional hazard model.

Source: Clinical Study Report for ANBL1221.[16]

Several basic features of the study design and the conduct of the trial may have affected the interpretation and the internal validity of the results. The study was not primarily designed and powered to test pre-specified hypotheses regarding differences in efficacy outcomes such as ORR, DOR, PFS, or OS in patients treated with regimen A versus regimen B. Without controlling the potential for inflated type I error rate, this design is generally not aimed at making direct comparisons, especially of multiple outcomes, among treatment arms. As such, all comparisons of efficacy outcomes between trial arms in the ANBL1221 study were exploratory (see further discussion). The clinical experts consulted by CADTH for this review indicated that the data from the ANBL1221 study are perhaps best interpreted in the context of a single-arm trial of patients treated with regimen B. In addition, protocol deviations were common in the ANBL1221 study; overall, 81.7% of patients had at least 1 protocol deviation. Among patients treated with regimen A, 11.1% received an incorrect dose. Among all patients treated with regimen B, 24.5% received an incorrect dose (randomized cohort: 35.3%; expansion cohort: 19.4%). The impact of major protocol violations on efficacy outcomes, particularly changes in dosing, is unknown.

While the baseline characteristics of patients in the ANBL1221 study treated with regimen A versus regimen B were generally well balanced, several slight imbalances were present that the clinical experts considered as unlikely to be of prognostic importance. First, patients treated with regimen A were slightly older than those treated with regimen B at enrolment (regimen A: median 7.0 years; regimen B: median 5.1 years), and a subset of patients receiving regimen B (17%) had been diagnosed before 2 years of age. Second, a subset of patients treated with regimen B in the expansion cohort (16.7%) had INSS stage 3 or 4S tumours. Third, a majority of patients receiving regimen B in the expansion cohort had refractory disease (66.7% versus 44.4% of patients randomized to receive regimen A and 47.1% of patients randomized to receive regimen B), and comparatively fewer had received prior ASCT (36.1% versus 55.6% of patients randomized to receive regimen A and 58.8% of patients randomized to receive regimen B) or radiotherapy (30.1% versus 44.4% of patients randomized to receive regimen A and 58.8% of patients randomized to receive regimen B).

Table 24: Summary of Unacceptable Toxicities in ANBL1221 Trial — Safety Population

Toxicities	Regimen A randomized (N = 18)	Regimen B randomized (N = 16)	Regimen B non-randomized (N = 35)	Regimen B total (N = 51)
Total number of patients with unacceptable toxicities				
n (%)	0	6 (37.5)	3 (8.6)	9 (17.6)
Number of patients with unacceptable toxicities by type, n (%)				
Death	0	1 (6.3)	0	1 (2.0)
Hypotension	0	2 (12.5)	3 (8.6)	5 (9.8)
Hypoxia	0	2 (12.5)	0	2 (3.9)
Peripheral motor neuropathy	0	1 (6.3)	0	1 (2.0)
Respiratory failure	0	1 (6.3)	0	1 (2.0)

GM-CSF = granulocyte-macrophage colony-stimulating factor.

Note: Regimen A: temsirolimus plus irinotecan plus temozolomide; Regimen B: dinutuximab combined with GM-CSF and irinotecan plus temozolomide.

Source: Clinical Study Report for ANBL1221.[16]

Table 25: Summary of Harms — Safety Population

Harms	ANBL1221 Trial			
	Regimen A randomized (N = 18)	Regimen B randomized (N = 16)	Regimen B non-randomized (N = 35)	Regimen B total (N = 51)
Patients with ≥ 1 AE				
n (%)	16 (88.9)	16 (100.0)	32 (91.4)	48 (94.1)
Common AEs, n (%)[a]				
Neutrophil count decreased	8 (44.4)	7 (43.8)	13 (37.1)	20 (39.2)
White blood cell count decreased	6 (33.3)	5 (31.3)	12 (34.3)	17 (33.3)
Lymphocyte count decreased	4 (22.2)	6 (37.5)	13 (37.1)	19 (37.3)
Anemia	7 (38.9)	8 (50.0)	8 (22.9)	16 (31.4)
Hypokalemia	5 (27.8)	6 (37.5)	6 (17.1)	12 (23.5)
Diarrhea	3 (16.7)	2 (12.5)	11 (31.4)	13 (25.5)
ALT increased	5 (27.8)	1 (6.3)	9 (25.7)	10 (19.6)
Pain	0	4 (25.0)	13 (37.1)	17 (33.3)
Pyrexia	1 (5.6)	4 (25.0)	13 (37.1)	17 (33.3)
Hypoxia	0	5 (31.3)	6 (17.1)	11 (21.6)
Hypotension	0	3 (18.8)	3 (8.6)	6 (11.8)
Dyspnea	0	3 (18.8)	0	3 (5.9)
Patients with ≥ 1 AdEERS-reportable event				
n (%)	7 (38.9)	11 (68.8)	16 (45.7)	27 (52.9)
Common AdEERs-reportable events, n (%)[b]				
Neutrophil count decreased	1 (5.6)	3 (18.8)	2 (5.7)	5 (9.8)
Death	0	2 (12.5)	2 (5.7)	4 (7.8)
Disease progression	2 (11.1)	1 (6.3)	2 (5.7)	3 (5.9)
Hypoxia	0	3 (18.8)	0	3 (5.9)
Patients with ≥ 1 WDAE				
n (%)	1 (5.6)	1 (6.3)	0	1 (2.0)
Common WDAEs, n (%)				
Severe infusion reaction	1 (5.6)	0	0	0
Dyspnea/hypoxia	0	1 (6.3)	0	1 (2.0)
Deaths				
n (%)	12 (66.7)	7 (43.8)	12 (34.3)	19 (37.3)
Primary cause of death, n (%)				
Disease	12 (66.7)	6 (37.5)	11 (31.4)	17 (33.3)
Protocol treatment	0	0	0	0

Harms	ANBL1221 Trial			
	Regimen A randomized (N = 18)	Regimen B randomized (N = 16)	Regimen B non-randomized (N = 35)	Regimen B total (N = 51)
Unknown	0	1 (6.3)	0	1 (2.0)
Cardiac arrest	0	0	1 (2.9)	1 (2.0)
Notable harms, n (%)				
Infusion reactions/capillary leak syndrome				
Infusion reactions	1 (5.6)	0	0	0
Capillary leak syndrome	0	1 (6.3)	1 (2.9)	2 (3.9)
Anaphylaxis	0	0	1 (2.9)	1 (2.0)
Hypersensitivity	1 (5.6)	1 (6.3)	0	1 (2.0)
Hypotension	0	3 (18.8)	3 (8.6)	6 (11.8)
Dyspnea	0	3 (18.8)	0	3 (5.9)
Respiratory failure	0	1 (6.3)	2 (5.7)	3 (5.9)
Bronchospasm	0	1 (6.3)	0	1 (2.0)
Neuropathic pain				
Pain	0	4 (25.0)	13 (37.1)	17 (33.3)
Pain in extremity	0	2 (12.5)	0	2 (3.9)
Oral pain	1 (5.6)	0	0	0
Tumour pain	0	1 (6.3)	0	1 (2.0)
Back pain	0	1 (6.3)	0	1 (2.0)
Abdominal pain	0	0	2 (5.7)	2 (3.9)
Headache	0	1 (6.3)	1 (2.9)	2 (3.9)
Non-cardiac chest pain	0	1 (6.3)	1 (2.9)	2 (3.9)
Severe neurologic toxicities				
Peripheral motor neuropathy	0	1 (6.3)	0	1 (2.0)
Loss of consciousness	0	0	1 (2.9)	1 (2.0)
Loss of vision	0	0	1 (2.9)	1 (2.0)
Hearing loss	0	1 (6.3)	0	1 (2.0)
AEs requiring hospitalization or prolonged hospitalization	8 (44.4)	12 (75.0)	12 (34.3)	24 (47.1)
ICU admission	NR	NR	NR	NR

AE = adverse event; AdEERS: Adverse Event Expedited Reporting System; ALT = alanine transaminase; GM-CSF = granulocyte-macrophage colony-stimulating factor; ICU = intensive care unit; NR = not reported; WDAE = withdrawal due to adverse event.

Note: Regimen A: temsirolimus plus irinotecan plus temozolomide; Regimen B: dinutuximab combined with GM-CSF and irinotecan plus temozolomide.

[a]Frequency greater than 10% of patients in any treatment group.

[b]Frequency greater than 2 patients in any treatment group.

Source: Clinical Study Report for ANBL1221.[16]

Finally, fewer patients treated with regimen A had soft tissue disease (38.9%) compared with patients receiving regimen B (77.4%). Systematic differences in anatomic site of disease might have contributed to bias in response outcome assessment, especially in an open-label trial (as discussed later in this review).

In addition to the potential for selection bias during recruitment of a non-randomized expansion cohort, other sources of bias could have affected the study results. Dropout before treatment and discontinuation from study and follow-up was not a major source of bias, occurring in approximately 5% to 10% of patients treated with both regimens A and B. Other potential sources of bias primarily related to outcome assessment in an open-label trial. The primary outcome was ORR, defined using INRC criteria,[13,14] which are widely used and accepted. Although the most recently revised criteria (2017)[29] have some slight differences compared with the 1993 criteria, these differences are unlikely to make a major difference to treatment strategies in clinical practice, according to the clinical experts consulted by CADTH for this review. However, these experts indicated that assessment of OR in neuroblastoma is complex — requiring the integration of multiple readouts — and arbitrary, to some degree; distinguishing stable disease from PR can be challenging, especially for tumours not measurable by CT or MRI because these techniques classify tumours with no change in Curie score and changes of less than 50% as stable disease and changes of greater than 50% as PR. Although OR assessment was partially blinded by central review of imaging results by the study chair, who was unaware of group assignments, this was problematic in several ways. Because response was first designated locally by unblinded investigators and then reviewed centrally, some potential for biased outcome assessment remains. Blinding was not possible in the non-randomized expansion cohort.

The interpretation of the primary outcome (ORR) was complicated by several factors and statistical issues that should be considered. First and critically, the comparison of ORR between patients treated with regimen A and regimen B, even in the randomized cohort alone, was pre-specified but exploratory. There was no control for multiplicity, and the study sample size could not accommodate effective multivariate adjustment. The small sample size of the randomized portion of the trial resulted in very wide CIs for estimates of ORR. While a slightly higher number of patients were enrolled in the expansion cohort, the ORRs from this group of patients have uncertain comparability with those of patients in the randomized cohort or with historical controls. The comparison between patients treated with regimen B in the non-randomized cohort and patients randomized to receive regimen A was a naive, indirect comparison. As outlined earlier, the potential for biased outcome assessment in the open-label study design applies to the interpretation of ORR, especially because dinutuximab came to be viewed as the standard of care over the study period. Subgroup analyses were pre-specified, and for 2 of the subgroups of interest considered in this report (relapsed versus refractory disease and *MYCN* status), were based on stratification variables to maintain randomization. However, as noted in the CSR, the study was not designed to evaluate each stratum separately.

The interpretation of time-to-event outcomes (DOR, PFS, and OS) was also complicated by several factors. All 3 outcomes are valid and commonly used in oncology trials. However, as with the primary analysis of ORR, all of these outcomes were exploratory, and none of the analyses were controlled for multiplicity. Although the comparisons of DOR, PFS, and OS between trial arms using Kaplan–Meier analysis and proportional hazards models were pre-specified, the study was not powered to evaluate differences in these outcomes. The estimates of median DOR, PFS, and OS calculated using these methods were very uncertain, and in many cases diverged significantly from non-censored observations only; for DOR

and OS, the Kaplan–Meier estimator selected the longest uncensored observation as the median. Potential bias in outcome assessment (as noted previously) extends to DOR and PFS as well as ORR. The follow-up period was longer in the randomized cohort than in the non-randomized expansion cohort, allowing more time for events to accumulate. Importantly, while concomitant systemic anti-cancer therapies were not allowed while on protocol therapy, DOR was censored when patients discontinued protocol therapy and began other anti-cancer therapies. Among the 22 patients treated with regimen B who achieved a PR or better, 16 (72.7%) went onto other anti-cancer therapies before the end of response. PFS and OS were not censored when patients discontinued protocol therapy and began other anti-cancer therapies; thus, these analyses do not account for the effects of these therapies, which may have significantly biased the results in an unpredictable direction because of the relatively short duration of treatment in most patients compared with follow-up. The discontinuation of more than half of patients randomized to receive regimen A after 2 to 3 cycles meant that these patients may have received other treatments for the majority of the follow-up period. Information about additional anti-cancer therapies that may have been received following the protocol therapy was not available. The Kaplan–Meier survival curves suggested that, at least for PFS, the proportional hazard assumption may not be met.

External Validity

By necessity, studies of patients with neuroblastoma are typically conducted in many different sites (49 sites in the ANBL1221 trial)[10,11] to recruit adequate numbers of participants. However, most sites were in the US (81.7%). As a result, it is conceivable that the additional therapies received following ANBL1221 protocol therapy discontinuation may not have been aligned with the standard of care in Canada. Despite this, the ANBL1221 study population was generally reflective of the Canadian population with R/R high-risk neuroblastoma, and the clinical experts consulted by CADTH for this review confirmed that the baseline characteristics of the study population were representative of the patients they usually see in Canadian clinical practice. The inclusion and exclusion criteria would be expected to recruit a population similar to that treated with dinutuximab in clinical practice. Although 25% of the enrolled patients had previously tolerated and responded to anti-GD2 immunotherapy, the clinical experts stated that this situation reflects both current clinical practice and the important place of dinutuximab in upfront therapy. However, the study excluded patients who progressed during anti-GD2 immunotherapy in upfront therapy as well as patients in their second or subsequent relapses; as a result, it provided no information on re-treatment in these patients. However, the clinical experts stated that in the R/R setting, dinutuximab with chemotherapy would be unlikely to be the treatment of choice for the former group of patients. Similarly, extended treatment beyond 17 cycles could not be evaluated.

All drugs were dosed as they would be in clinical practice and in line with Health Canada–approved dosing. Since dinutuximab and many other therapies for R/R high-risk neuroblastoma are administered through trial enrolment, patients participating in ANBL1221 likely received similar background care while receiving protocol therapy as patients treated in clinical practice. Notably, many hospitals do not see high-risk neuroblastoma patients frequently, and administration of dinutuximab, including the management of toxicities, was acknowledged by patient groups to have a steep learning curve. Thus, the findings of the ANBL1221 study may not be generalizable to patients treated in smaller centres with limited experience of administering dinutuximab. However, the clinical experts consulted by CADTH for this review noted that in Canada, most children with R/R high-risk neuroblastoma would be treated in 1 of 16 specialist centres with relevant experience.

All efficacy outcomes (ORR, DOR, PFS, OS) were clinically relevant, used in routine clinical practice, and identified by patients and their families as important to them. According to the clinical experts consulted by CADTH for this review, the duration of follow-up (2 to 3 years on average) was sufficient for the evaluation of efficacy outcomes in this population, with the possible exception of OS. Importantly, information about additional anti-cancer therapies received after discontinuation of protocol therapy, which may have influenced all efficacy outcomes other than ORR, was not provided; thus, we could not evaluate the generalizability of the overall care received by ANBL1221 patients to routine clinical practice.

Indirect Evidence

No indirect evidence was identified for this review.

Other Relevant Evidence

No other evidence was identified for this review.

Discussion

Summary of Available Evidence

Only 1 study (ANBL1221, a phase II, multi-centre, open-label RCT)[10,11] met the inclusion criteria for this review. The COG protocol ANBL1221 was a multi-centre clinical trial involving several Canadian centres. The initial goal of this study was to "pick the winner" between 2 regimens (dinutuximab and GM-CSF versus temsirolimus, both with irinotecan and temozolomide) used to treat patients with R/R high-risk neuroblastoma (N = 73) and move the successful regimen forward to phase III trials. The primary outcome was the proportion of patients responding to treatment (PR or better) after up to 6 cycles of treatment. The comparison of all efficacy outcomes (ORR, DOR, PFS, OS) across treatment arms was exploratory.

The baseline characteristics of the ANBL1221 study population were typical of patients with R/R high-risk neuroblastoma. Participants were children (mean = 6.4 years old at enrolment) with high-grade metastatic tumours (88.7% INSS stage 4 tumours). The study included patients with both relapsed (43.7%) and refractory (56.3%) disease, patients whose tumours were measurable (69.0%) and not measurable (31.0%) by CT or MRI, patients whose tumours were *MYCN*-amplified (26.8%) and *MYCN*-nonamplified (69.0%), and patients who had received a variety of prior treatments, including GD2 immunotherapy (25.4%), ASCT (46.5%), and radiotherapy (40.8%). The study population captured the clinical heterogeneity of R/R high-risk neuroblastoma. The key limitations were the exploratory nature of all efficacy outcomes in the study, none of which were controlled for multiplicity; the potential for bias in outcome assessment (ORR, DOR, PFS) in an open-label trial; potential imbalances of prognostic importance in the baseline characteristics between trial arms; weakness of the naive indirect comparison between patients treated with regimen B in the non-randomized expansion cohort and patients randomized to receive regimen A; and the potential effects of additional anti-cancer therapies received following protocol therapy discontinuation on PFS and OS, which could not be accounted for.

Interpretation of Results

Efficacy

The effect sizes of dinutuximab (regimen B) treatment on exploratory efficacy outcomes (including the primary outcome, ORR, as well as DOR, PFS, and OS) should be interpreted with caution. All these outcomes were exploratory. For the primary outcome, ORR, 1 of 18 patients treated with regimen A (5.9%; 95% CI, 0.1% to 27.3%) and 22 of 53 patients treated with regimen B (41.5% overall; 95% CI, 28.1% to 55.9%) achieved a PR or better as their best overall response after 6 cycles. However, these estimates had wide CIs and should be interpreted in light of the following important caveats: the small size of the randomized portion of the trial (N = 35), uncertain comparability of the randomized cohort with a non-randomized cohort added post hoc, and the potential for biased outcome assessment in the open-label study design. The clinical experts consulted by CADTH for this review stressed that the single-arm response data (ORR) from the ANBL1221 study strongly suggest a benefit for the addition of dinutuximab,[10,11] and that the evidence is sufficient to alter clinical practice: there has been a shift in the current treatment paradigm, and dinutuximab with temozolomide, irinotecan, and GM-CSF has become the de facto standard of care for most patients, based on the results of the ANBL1221 study.[10,11] According to clinicians, access to dinutuximab for patients with R/R high-risk neuroblastoma needs to be facilitated because loss of access would mandate a paradigm shift back to the therapies that were previously available; the current alternative is enrolment in another trial for this cohort of patients.

Patient group input received for this review indicated that the most important outcomes were treatment efficacy in inducing responses, decreasing the burden of disease, extending survival, and, hopefully, offering a path to cure. HRQoL was also an important consideration. In this light, both the ORR (41.5% overall; 95% CI, 28.1% to 55.9%), the DOR (median = 33.0 weeks; range = 2.4 to 76.1 weeks; Kaplan–Meier estimated median = 76.1 weeks; 95% CI, not calculable), PFS (median = 57.0 weeks; range = 3.3 to 196.9 weeks; Kaplan–Meier estimated median = 97.9 weeks; 95% CI, 60.3 weeks to 110.6 weeks), and OS (median = 72.8 weeks; range = 6.0 to 219.4 weeks; Kaplan–Meier estimated median = 219.4 weeks; 95% CI, not calculable) among patients treated with regimen B were interpreted by the clinical experts consulted for this review as potentially clinically meaningful. DOR was difficult to assess accurately due to the low number of responders. The wide CIs of the effect estimates signalled the high uncertainty in the results of such a small study. These analyses were exploratory, not controlled for multiplicity, and must be considered with the potential for type I error. This study was not specifically powered to evaluate survival end points. Thus, survival data should be interpreted in light of the limited sample size, variable follow-up time, the fact that event-free survival in children with neuroblastoma may vary considerably because of the clinical heterogeneity of this disease, and the potential impact of other anti-cancer therapies administered following ANBL1221 protocol therapy. It was unclear whether the high number of protocol deviations, especially related to incorrect dosing, might have biased the efficacy outcomes, although this situation may reflect how dinutuximab is used in clinical practice.

The clinicians consulted by CADTH for this review, as well as other clinician groups, were unequivocal that however imperfect, the level of evidence provided by the study has already changed the landscape of therapy for patients with R/R high-risk neuroblastoma. This is a rare subgroup of an ultra-rare disease that has no effective therapies. The data from ANBL1221 suggest that dinutuximab offers patients the best chance at effective treatment.

Harms

As per the clinical experts consulted by CADTH, the toxicity profile of dinutuximab in the ANBL1221 study[10,11] was as expected based on previous experience with this drug and consistent with the Health Canada product monograph. Clinician groups stated that this study was completed at a time when most centres already had experience administering dinutuximab in the upfront setting; as a result, the centres had the skills to administer the drug and minimize toxicity. Pain as well as pyrexia, hypotension, dyspnea, and hypoxia occurred more frequently in patients treated with regimen B in the ANBL1221 study. This was consistent with the safety profile of dinutuximab established in prior studies. When considering all grade 3 or higher AEs, the most frequent AEs occurred consistently in both groups. Events representing the myelosuppressive activity of chemotherapy drugs — such as decreased neutrophil counts, decreased white blood cell counts, anemia, and decreased platelet counts — were reported with similar frequency in patients treated with regimen A and regimen B. Very few patients treated with either regimen A or regimen B had AEs requiring withdrawal from protocol therapy, and study therapy did not result in the death of any patients in either treatment arm.

Patients were able to tolerate the dinutuximab regimen with AEs that were manageable overall; approximately 29% of patients treated with dinutuximab required dose modification, and the median number of cycles completed by all patients treated with dinutuximab was 6. The clinical experts felt that these data were consistent with their previous experience with dinutuximab in the upfront high-risk neuroblastoma indication. This demonstrates that, while the safety profile of dinutuximab-containing regimen is not benign, years of experience administering the antibody have created a depth of knowledge that has led to appropriate management strategies for these patients. The toxicities associated with dinutuximab treatment are mitigated by premedication and pain management, as outlined in the product monograph. Patient groups have clearly indicated their willingness to accept the toxicities associated with dinutuximab, which have been acknowledged to be manageable and no worse than those of prior intensive therapies received; the toxicity profile of dinutuximab should be viewed in that context. Longer-term safety, and safety outcomes in patients who did not participate in the ANBl1221 study, remain unknown.

Other Considerations

The clinicians consulted by CADTH for this review felt that additional consideration should be given to regulatory and access issues. Dinutuximab is currently the standard of care for patients with R/R high-risk neuroblastoma. Access is through clinical trials or compassionate access from the sponsor. Although the data from ANBL1221 addressed the combination of dinutuximab with GM-CSF, temozolomide, and irinotecan, the clinical experts consulted for this review anticipated that dinutuximab will be increasingly combined with other chemotherapy regimens. In addition, although the ANBL1221 study enrolled patients in their first relapse or designation of refractory disease, dinutuximab with chemotherapy is the standard of care for other patients as well; clinicians expressed concern that restricting funding to the former group of patients could be limiting in clinical practice, where this combination would potentially be used either later in disease course or for re-treatment of further progression.

Conclusions

Data from the ANBL1221 study suggested that dinutuximab combined with GM-CSF and irinotecan plus temozolomide may be efficacious in inducing objective responses in patients with R/R high-risk neuroblastoma. Confidence in the comparisons of these efficacy outcomes with other therapies was limited by the small number of study participants, challenges inherent in comparisons between regimen A and regimen B, the exploratory nature of efficacy outcomes, and the absence of multiplicity control. Together, these factors contribute substantial uncertainty to the magnitude of the observed treatment effects. This regimen was tolerable and manageable in most patients, with a toxicity profile as expected based on prior studies of dinutuximab. Despite uncertainty in the effect size for efficacy outcomes, these results are potentially clinically relevant for patients with R/R high-risk neuroblastoma.

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Appendix 1: Literature Search Strategy

Note that this appendix has been formatted for accessibility but has not been copy-edited.

Clinical Literature Search

Overview

Interface: Ovid

Databases

- MEDLINE All (1946 to present)
- Embase (1974 to present)
- Note: Subject headings and search fields have been customized for each database. Duplicates between databases were removed in Ovid.

Date of search: January 7, 2021

Alerts: Bi-weekly search updates until project completion

Study types: All study types

Limits: Conference abstracts excluded

Table 26: Syntax Guide

Syntax	Description
/	At the end of a phrase, searches the phrase as a subject heading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
.ti	Title
.ab	Abstract
.dq.	Candidate term word
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.nm.	Name of substance word
.ot.	Original title
.pt	Publication type
.rn	Registry number
medall	Ovid database code: MEDLINE All, 1946 to present, updated daily
oemezd	Ovid database code; Embase, 1974 to present, updated daily

Multi-Database Strategy

Database(s): Embase 1974 to 2021 January 06, Ovid MEDLINE(R) ALL 1946 to January 06, 2021

Search Strategy

1. (dinutuximab* or unituxin* or Qarziba* or Isquette* or APN-311 or APN311 or HSDB8407 or HSDB 8407 or 7SQY4ZUD30).ti,ab,ot,kf,hw,nm,rn.
2. (ch1418* or ch 1418* or ch14 18* or ch 14 18*).ti,ab,ot,kf,hw,nm,rn.
3. 1 or 2
4. 3 use medall
5. *dinutuximab/ or (dinutuximab* or unituxin* or Qarziba* or Isquette* or APN-311 or APN311 or HSDB8407 or HSDB 8407).ti,ab,kw,dq.
6. (ch1418* or ch 1418* or ch14 18* or ch 14 18*).ti,ab,kw,dq.
7. 5 or 6
8. 7 use oemezd
9. 8 not (conference abstract or conference review).pt.
10. 4 or 9
11. remove duplicates from 10

Clinical Trials Registries

ClinicalTrials.gov

Produced by the US National Library of Medicine. Targeted search used to capture registered clinical trials.

[Search -- Studies with results | Unituxin, dinutuximab AND neuroblastoma]

WHO ICTRP

International Clinical Trials Registry Platform, produced by the WHO. Targeted search used to capture registered clinical trials.

[Search terms – Unituxin, dinutuximab AND neuroblastoma]

Health Canada's Clinical Trials Database

Produced by Health Canada. Targeted search used to capture registered clinical trials.

[Search terms – Unituxin or dinutuximab]

EU Clinical Trials Register

European Union Clinical Trials Register, produced by the European Union. Targeted search used to capture registered clinical trials.

[Search terms – Unituxin, dinutuximab AND neuroblastoma]

Canadian Cancer Trials

Produced by the Canadian Partnership Against Cancer Corporation. Targeted search used to capture registered clinical trials.

[Search terms – Unituxin or dinutuximab]

Grey Literature

Search dates: December 18 to 23, 2020

Keywords: Unituximab, dinutuximab, neuroblastoma

Limits: None

Updated: Search updated before the completion of stakeholder feedback period

Relevant websites from the following sections of the CADTH grey literature checklist *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* (https://www.cadth.ca/grey-matters) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Clinical Trials Registries
- Databases (free)

CADTH

Pharmacoeconomic Review

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Abbreviations

BIA	budget impact analysis
GM-CSF	granulocyte-macrophage colony-stimulating factor
HUI 3	Health Utilities Index 3
ICER	incremental cost-effectiveness ratio
OS	overall survival
PFS	progression-free survival
QALY	quality-adjusted life-year
WTP	willingness to pay

Executive Summary

The executive summary comprises 2 tables (Table 1 and Table 2) and a conclusion.

Conclusions

The CADTH reanalysis addressed several limitations in the sponsor's model. Key changes in the CADTH base-case reanalysis included changes to the "cure" threshold assumption, consistent with other reviews[1,2]; changes to the progression-free survival (PFS) curves for refractory patients receiving the standard treatment regimen; removal of temsirolimus to better reflect care in Canada; consideration of drug wastage; and the addition of costs associated with inpatient hospital stay during treatment.

In the CADTH base-case reanalysis for relapsed patients, dinutuximab-based immunotherapy had incremental costs of $826,899 and incremental quality-adjusted life-years (QALYs) of 1.67 compared to standard chemotherapy alone, resulting in an incremental cost-effectiveness ratio (ICER) of $495,696 per QALY gained. For refractory patients, dinutuximab-based immunotherapy had an incremental cost of $593,337 and an incremental QALY of 1.291, translating to an ICER of $459,747 per QALY gained. In both populations, compared to standard chemotherapy, dinutuximab-based immunotherapy had a 0% probability of cost-effectiveness at conventional willingness-to-pay (WTP) thresholds. Even with price reductions approaching 100%, the cost-effectiveness of dinutuximab is not within conventionally

Table 1: Submitted for Review

Item	Description
Drug product	Dinutuximab (Unituxin), IV infusion
Submitted price	Dinutuximab, 17.5 mg/5 mL, vial: $12,850
Indication	For the treatment of high-risk neuroblastoma patients in their first relapse or determination of refractory disease, in combination with irinotecan, temozolomide, and GM-CSF
Health Canada approval status	NA[a]
Health Canada review pathway	NA[a]
NOC date	NA[a]
Reimbursement request	As per indication
Sponsor	United Therapeutics Canada Corp.
Submission history	Previously reviewed: Yes Indication: Pediatric patients with high-risk neuroblastoma who achieve at least a partial response to prior first-line, multi-drug, multimodal therapy Recommendation date: March 26, 2019 Recommendation: Reimburse with clinical condition and/or condition cost-effectiveness improved to acceptable level.

GM-CSF = granulocyte-macrophage colony-stimulating factor; NA = not applicable; NOC = Notice of Compliance.

[a]No Health Canada review is planned for the indication under review. Dinutuximab (Unituxin) received a NOC from Health Canada on November 28, 2018, in combination with GM-CSF, interleukin-2, and 13 cis-retinoic acid for the treatment of high-risk neuroblastoma in pediatric patients who achieve at least a partial response to prior first-line, multi-drug, multimodality therapy.

Table 2: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Partitioned survival model
Target population(s)	High-risk neuroblastoma patients who have relapsed after a complete course of therapy, or patients who have been unable to achieve a response to induction therapy and are deemed refractory
Treatment	Dinutuximab in combination with GM-CSF added onto a chemotherapy regimen of irinotecan and temozolomide
Comparator	Temsirolimus added to standard chemotherapy of irinotecan and temozolomide
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs and LYs
Time horizon	Relapsed: 25 years Refractory: lifetime (75 years)
Key data source	ANBL1221 trial
Submitted results	**Relapsed patients** ICER = $450,370 per QALY (incremental costs: $888,923; incremental QALYs: 1.717) **Refractory patients** ICER = $170,015 per QALY (incremental costs: $722,378; incremental QALYs: 3.354)
Key limitations	• The sponsor's assumption that all patients who are event-free after 5 years would be cured for the remainder of their lifetime, with no possibility of progression and significantly lower mortality, was deemed to be optimistic by clinical experts given the paucity of data in this patient population. • Model was informed by limited data on clinical effectiveness and survival in this population, given the small number of patients in the ANBL1221 trial (N = 35) and limited long-term data (5-year trial data are extrapolated to 25 years and 75 years for relapsed and refractory patients, respectively). This makes interpolating and extrapolating OS and PFS highly uncertain. PFS interpolation around standard chemotherapy for refractory patients was deemed inappropriate. • The clinical experts consulted for this review indicated that temsirolimus is not used alongside standard chemotherapy (irinotecan and temozolomide) because it does not provide additional clinical benefit. Therefore, in Canadian practice, only irinotecan and temozolomide are used as part of standard care. • Cost of hospital stay was not considered during the administration of dinutuximab. • Wastage was not considered in the calculation of drug costs for GM-CSF and irinotecan.

Component	Description
CADTH reanalysis results	The CADTH reanalyses included: • The assumption that all patients who are event-free after 5 years would be cured was adjusted to 7 years, in line with previous reviews (CADTH and NICE). • Changes to PFS were made for the standard chemotherapy arm for refractory patients. • Temsirolimus was removed from the comparator regimen. • Wastage for GM-CSF and irinotecan was considered, assuming no vial sharing in this population. • Cost associated with 5-day hospital stay at every cycle was added. CADTH base-case reanalysis results: • Relapsed patients: ICER = $495,696 per QALY vs. standard chemotherapy alone (incremental costs: $826,869; incremental QALYs: 1.668) • Refractory patients: ICER = $459,747 per QALY vs. standard chemotherapy alone (incremental costs: $593,337; incremental QALYs: 1.291) • For both groups, 0% of iterations below a $50,000 per QALY threshold • There is no reduction in the price of dinutuximab that could achieve an ICER of $50,000 per QALY

GM-CSF = granulocyte-macrophage colony-stimulating factor; ICER = incremental cost-effectiveness ratio; LY = life-year; NICE = National Institute for Health and Care Excellence; QALY = quality-adjusted life-year; HRQoL = health-related quality of life; OS = overall survival; PFS = progression-free survival.

accepted levels, largely because of considerable non-drug health care costs that contribute to the cost of care and because there is uncertainty regarding the magnitude of benefit associated with dinutuximab.

The estimates of cost-effectiveness are mostly driven by the substantial drug cost of dinutuximab ($68,533 per 28 days) relative to standard chemotherapy ($3,246 per 28 days). There is also considerable uncertainty around overall survival (OS) and PFS derived from the ANBL1221 trial. The small number of patients in each cohort in the ANBL1221 trial and the lack of long-term data in this patient population make survival extrapolations highly uncertain. Therefore, there is certainty of high incremental costs and considerable uncertainty regarding the size of incremental benefit. Furthermore, the model relied on several assumptions around when patients may be considered "cured" and the benefits realized after this point. Crucially, due to the sponsor's model design, the difference in PFS at the point of cure is fundamental to the cost-effectiveness results, but there are no reliable data to inform what this difference may be. Various scenario analyses that explore the impact of these assumptions show that the CADTH base case may overestimate the benefits associated with dinutuximab, and that the true ICER could be more than $1.4 million per QALY in the refractory cohort and $800,000 per QALY in the relapsed cohort.

Based on the CADTH base case, the budget impact of introducing dinutuximab is expected to be $12,496,315 in year 1, $12,630,026 in year 2, and $12,765,167 in year 3, for a 3-year total of $37,891,509. This is slightly higher than the sponsor's estimate of $35,810,289 over 3 years.

Stakeholder Input Relevant to the Economic Review

This section is a summary of the feedback received from the patient groups, registered clinicians, and drug plans that participated in the CADTH review process.

Patient group input was provided jointly for this review by Neuroblastoma Canada, the Canadian Organization for Rare Disorders (CORD), and Ontario Parents Advocating for Children with Cancer (OPACC). Neuroblastoma Canada provides support to Canadian neuroblastoma families, CORD represents and advocates for those with rare disorders, and OPACC supports families and other organizations involved in childhood cancer. Patient information was gathered through online surveys or telephone interviews of parents and caregivers of patients, of whom 4 identified their place of residence as Canada. Eleven of 19 respondents had received chemotherapy, radiation therapy, and/or surgery; among them, 25% of respondents with children who had received front-line chemotherapy noted an improved response to treatment and manageable complications; 42% reported their child experiencing a relapse following front-line therapy, after which treatment options were primarily limited to chemotherapy, radiation, and surgery. Several patients had received dinutuximab but reported that few hospitals were experienced with the drug, and that its administration may be challenging due to individual patient experiences with the drug. As a result, it was difficult to monitor patients' pain levels, and some patients were unable to tolerate the therapy due to pain and/or low blood pressure. Adverse events (AEs) were similar between immunotherapy and previous chemotherapies; key events included pain, fever, nausea, fatigue, and allergic reactions.

Two registered joint clinician inputs were received from pediatric oncology groups in Ontario and British Columbia, representing a total of 19 oncologists. Clinicians stated that the likelihood of a cure in patients with relapsed neuroblastoma is low, and that there remains an unmet need for therapies with improved efficacy, such as dinutuximab. Conventional salvage chemotherapy regimens (irinotecan plus temozolomide or cyclophosphamide plus topotecan) have poor response rates, significant toxicities, and require an inpatient stay for treatment administration. Clinicians indicated that the combination therapy of dinutuximab with GM-CSF and irinotecan plus temozolomide would be considered first-line salvage therapy for children with relapsed or refractory disease, the final phase of front-line neuroblastoma therapy. Treatment with dinutuximab should be discontinued following disease progression or absence of disease response after 6 cycles of therapy.

The drug plans identified the following considerations for the implementation of dinutuximab as relevant to the economic analysis: uncertainty in the effectiveness of dinutuximab after 17 cycles of therapy (maximum follow-up in the ANBL1221 trial); patients with previous radiation therapy, stem cell transplant, or dinutuximab pre-treatment; or the potential for indication creep in the first-line setting. The drug plans noted that the extended time on dinutuximab (i.e., 17 cycles) compared with conventional salvage chemotherapy (i.e., 5 cycles) currently used for high-risk disease would incur additional health care resource use. It was further noted that the single vial of dinutuximab (i.e., 17.5 mg) may lead to drug wastage because vial sharing would be unlikely to occur in clinical practice. The plans noted that GM-CSF is not currently marketed in Canada and can only be obtained through special access programs, which would be a barrier to implementation in some provinces. Additional resources (e.g., nursing and clinic visits) would be required to monitor and treat infusion-related reactions and AEs.

Several of these concerns were addressed in the sponsor's model:

- Drug wastage for dinutuximab was considered, but wastage for other drugs (granulocyte-macrophage colony-stimulating factor [GM-CSF] and irinotecan) was not.
- The submission did not consider the cost of inpatient hospital stay associated with chemotherapy.

In addition, CADTH addressed some of these concerns as follows:

- Drug wastage for dinutuximab, GM-CSF, and irinotecan were included, assuming no vial sharing.
- The cost of inpatient hospital stays associated with chemotherapy administration was included in the CADTH reanalysis.

Economic Review

The current review is for dinutuximab (Unituxin) for the treatment of high-risk neuroblastoma pediatric patients in their first relapse or determination of refractory disease.

Economic Evaluation

Summary of Sponsor's Economic Evaluation

Overview

The sponsor submitted a cost-utility analysis of dinutuximab-based immunotherapy compared with the standard chemotherapy regimen of irinotecan plus temozolomide combined with temsirolimus.[3] The model population comprised high-risk neuroblastoma patients (pediatric) who had relapsed after a complete course of therapy or were unable to achieve a response to induction therapy and had been deemed refractory. In the analysis, the refractory and relapsed cohorts were evaluated separately.

The recommended dose of dinutuximab is 17.5 mg/m^2 per day administered as an IV infusion for 4 consecutive days per 21-day cycle until failure (i.e., progressive disease) or unacceptable toxicity (up to a maximum of 17 cycles) in combination with GM-CSF (213 mcg/m^2 per day injected subcutaneously or through IV infusion for 7 days per cycle), temozolomide (85.2 mg/m^2 per day taken orally 5 days per cycle), and irinotecan (42.6 mg/m^2 per day through IV infusion 5 days per cycle).[3] Dosing was based on a body surface area of 0.852 m^2 observed in the ANBL1221 trial. The total cost of dinutuximab-based therapy, including the cost of administration, was $69,272 per cycle (dinutuximab: $66,748; GM-CSF: $1,937; temozolomide: $332; irinotecan: $106; administration: $148 per cycle), based on a unit price of $12,850 per 17.5 mg vial of dinutuximab.[3] The sponsor did not consider wastage for GM-CSF or irinotecan.

The comparator evaluated in the sponsor's analysis is a standard chemotherapy regimen of temsirolimus, irinotecan, and temozolomide, administered per 21-day cycle until failure or unacceptable toxicity up to maximum of 17 cycles. Temsirolimus (29.8 mcg/m^2 per day through IV infusion 2 days per cycle) is administered in combination with temozolomide (85.2 mg/m^2 per day taken orally over 5 days per cycle) and irinotecan (42.6 mg/m^2 per day through IV infusion 5 days per cycle).The total cost of standard chemotherapy, including the cost of administration, was $3,908 per 21-day cycle (temsirolimus: $3,322; temozolomide: $332; irinotecan: $106; administration: $148 per cycle).[3]

The clinical outcomes modelled were QALYs and life-years. The economic analysis was undertaken over 25-year and lifetime (75 years) time horizons for relapse and refractory patients, respectively, using 4-week cycles from the perspective of a public health care payer. Discounting (1.5% per annum) was applied to both costs and effectiveness outcomes.

Model Structure

The sponsor submitted a partitioned survival model with 3 mutually exclusive health states: "stable" (patients who remain alive without failure), "failed" (occurrence of a relapse or progressive disease), and dead. Time spent in each state was derived using OS and PFS curves, with the proportion of stable patients calculated as the area under the PFS curve and the proportion of failed patients calculated as the difference between OS and PFS curves. Individual patient data from the ANBL1221 trial were used to derive the PFS and OS curves for both the relapsed and refractory populations.[4]

After a period of 5 years, the cohort who remain in the stable phase are assumed to be cured. Therefore, after this time point, the "cured" cohort and the "failed" cohort no longer follow trial-based extrapolations with respect to OS or PFS, such that the failed cohort dies more rapidly, whereas the cured cohort realizes a substantial improvement in survival for the remainder of their lifetime. Figure 1 (Appendix 3) illustrates the residency in each health state by month, showing the effect of the cure time assumption after 5 years.

Model Inputs

The baseline characteristics in the model were aligned with those of the ANBL1221 trial patient population, which included high-risk pediatric neuroblastoma patients who had relapsed after a complete course of therapy or were unable to achieve a response to induction therapy and had been deemed refractory.[3] The dosing of dinutuximab-based immunotherapy and the standard chemotherapy regimen in the model were consistent with the dosing described in the Overview section of this report.

The clinical efficacy (i.e., OS and PFS) of dinutuximab-based immunotherapy and standard chemotherapy for both refractory and relapsed patients were obtained from the ANBL1221 trial.[4,5] Exponential parametric functions were fitted to the individual patient-level data in the ANBL1221 trial to model OS and PFS up to the clinical cure time point (assumed to be 5 years). The sponsor assumed patients who remained stable up to this cure threshold would be considered cured, while those who had progressed by this time point would be considered failed. The suitability of the parametric models was determined by mathematical fit (Akaike or Bayesian information criterion) and clinical playability.[3] Parametric survival functions are provided in Figures 2 to 9 (Appendix 3).

Following the cure time point, the sponsor made several assumptions about OS and PFS. First, it was assumed that the cured cohort would not relapse thereafter.[6] Second, it was assumed that the cured cohort realized a considerably lower mortality (i.e., mortality for this group is estimated to be 9.3 times higher than the general Canadian population, based on standardized mortality ratio estimates of childhood neuroblastoma survivors).[7] Finally, it was assumed the failed cohort (i.e., those who experienced a relapse or progressive disease) died more rapidly at this time point, with a mortality rate of 5% per month until the end of the model time horizon, from a study of children with recurrent or refractory neuroblastoma by London et al.[8] Thus, the treatment effect was assumed to be maintained over the model time horizon.

Health-state utility values were not assessed as part of the ANBL1221 trial; therefore, the sponsor used the cross-sectional study by Barr et al. (1999),[9] which reported health-related quality of life (i.e., Health Utilities Index 3 [HUI 3]) in survivors of childhood central nervous system tumours. Specifically, the sponsor assumed that patients with stable disease were representative of residual disease (HUI 3 = 0.56) as defined in Barr et al., that failure was

represented by recurrent disease (HUI 3 = 0.32), and that cured patients were represented by non-evident disease (0.78).[9] The sponsor also assumed that AE utility decrements were similar for both chemotherapy options because these were transient.

Costs included drug acquisition and administration costs, AE costs, consolidation treatment costs (stem cell transplantation, radiation, and chemotherapy with carboplatin, etoposide, and melphalan),[10] post-consolidation treatment costs (dinutuximab, GM-CSF, interleukin-2, and isotretinoin), health state–specific costs, and terminal-care costs. Drug acquisition costs for dinutuximab were obtained from the sponsor, and all other treatment costs were sourced from published literature or databases.[11-13] Chemotherapy administration costs were based on a Quebec study.[14] Treatment-associated AE rates (grade 3 or 4) were derived from the ANBL1221 trial.[4] Costs for AEs were collected from the Ontario Case Costing Initiative based on adult patients. Health-state costs for the stable cohort were derived using the health care resource utilization data reported by Rebholz et al. (2011) for neuroblastoma survivors.[15] For those in the failed state, the sponsor applied subsequent chemotherapy costs for patients with high-risk, recurrent neuroblastoma as per the protocol for topotecan reported by London et al.[8] Refractory patients who achieve a response proceed to consolidation and post-consolidation care, incurring the costs associated with those therapies. Given that patients with relapsed neuroblastoma do not undergo further consolidation and post-consolidation treatment, no additional consolidation or post-consolidation costs were applied to this patient cohort. Consolidation costs for surgical recession were collected from the Alberta Interactive Health Database (73), and chemotherapy costs were based on the Ontario Drug Benefit formulary and CADTH pan-Canadian Oncology Drug Review recommendations.[16,17] Terminal-care costs were collected from an international survey.[18]

Summary of Sponsor's Economic Evaluation Results

All analyses were run probabilistically (5,000 iterations for the base-case and scenario analyses). The deterministic and probabilistic results were similar. The probabilistic findings are presented below.

Base-Case Results

In the sponsor's base case for relapsed patients, dinutuximab-based immunotherapy was associated with an expected cost of $888,923 and 2.539 QALYs. When compared with standard chemotherapy, dinutuximab-based immunotherapy had an incremental cost of $773,360 and was associated with 1.71 incremental QALYs, resulting in an ICER of $450,370 per QALY gained (Table 3). Dinutuximab-based immunotherapy had a 0% probability of being considered cost-effective at a $50,000 per QALY gained.

For refractory patients, dinutuximab-based immunotherapy was associated with an expected cost of $722,378 and 5.828 QALYs. When compared to standard chemotherapy, the incremental cost of dinutuximab-based immunotherapy was $570,305, and the incremental QALYs were 3.35. In this population, the ICER was $170,015 per QALY gained. The cost-effectiveness acceptability curve indicated that dinutuximab-based immunotherapy has a 0% chance of generating a higher net monetary benefit versus chemotherapy at a WTP threshold of $50,000 per QALY.

Additional results from the sponsor's submitted base-case economic evaluation are presented in Appendix 3.

Sensitivity and Scenario Analysis Results

- The sponsor undertook scenario analyses varying several parameters, including discount rate, time horizon (5 years for relapse and 25 years for refractory), cure time (7 years), and exclusion of costs associated with consolidation and post-consolidation treatment.
- For the relapsed cohort, the ICER ranged from $417,911 to $803,408 in the sensitivity analyses. The undiscounted scenario led to the to the lowest ICER, and the use of a shorter time horizon (to 5 years) led to the highest ICER in this group.
- For the refractory cohort, the ICER ranged from $117,791 to $280,896 in the sensitivity analyses. The undiscounted scenario led to the lowest ICER, and the use of a shorter time horizon (to 25 years) led to the highest ICER in this group.

CADTH Appraisal of the Sponsor's Economic Evaluation

CADTH identified several key limitations in the sponsor's analysis that have notable implications for the economic analysis:

- **Cure threshold:** The sponsor assumed that patients who are stable after 5 years are cured for the remainder of their lifetimes (i.e., they are no longer at risk of progression and have substantial improvement in OS). However, due to a lack of reliable data, there is a high degree of uncertainty as to when patients, particularly those who are relapsed or refractory, will achieve these outcomes. Previous reviews from the National Institute for Health and Care Excellence and CADTH have assumed longer cure thresholds (ranging from 6.5 years to 10 years).[1,2] There is also considerable uncertainty around long-term survival in this population.
  - CADTH assumed that patients who remain stable for 7 years would be considered cured in the base case, consistent with previous reviews.[1,2] To explore this further, CADTH conducted scenario analyses that increased the time to cure to 10 years and also removed this threshold entirely under the assumption that the impact of cure is captured within the OS and PFS curves.
- **OS and PFS extrapolations were based on highly uncertain clinical data:** The OS and PFS curves were estimated by fitting an exponential parametric survival function to

Table 3: Summary of the Sponsor's Economic Evaluation Results

Drug	Total costs ($)	Incremental costs ($)	Total QALYs	Incremental QALYs	ICER vs. standard chemotherapy ($/QALY)
Relapsed					
Standard chemotherapy	115,563	–	0.822	–	–
Dinutuximab-based immunotherapy	888,923	773,360	2.539	1.717	450,370
Refractory					
Standard chemotherapy	152,073	–	2.474	–	–
Dinutuximab-based immunotherapy	722,378	570,305	5.828	3.414	170,015

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; vs. = versus .

Source: Sponsor's pharmacoeconomic submission.[3]

observed trial data until the specified cure threshold, which in the sponsor's base case coincides with the trial follow-up period (5 years). Parametric curves are primarily used to interpolate trial data, meaning their suitability to predict long-term outcomes beyond the trial is less relevant because long-term survival is determined by a separate set of assumptions regarding cure. In most cases, the exponential functional form was used because it displayed the best mathematical fit (Akaike or Bayesian information criterion). However, with respect to the PFS curve for refractory patients on standard chemotherapy, the exponential curve chosen displayed the poorest mathematical fit (see Appendix 3, Figure 9). In this case, the exponential function chosen by the sponsor assumes that more patients have progressed at the time of cure than all other functions available. Given the small size of the trial (N = 35) used to estimate these survival curves, there is a considerable amount of uncertainty as to the extent of clinical benefit from dinutuximab, particularly in the long-term.

    - CADTH assumed a log-normal parametric form for PFS for refractory patients on standard chemotherapy, which has a better mathematical fit to trial data compared to the exponential form and a better face validity relative to the Gompertz distribution. A scenario analysis was also conducted that assumed there would be no incremental benefit beyond 5 years for those starting on dinutuximab versus standard chemotherapy.

- **Inappropriate comparator:** In discussion with clinical experts, it was believed that temsirolimus is not used in Canadian clinical practice because it does not provide additional clinical benefit.
    - CADTH addressed this by removing the cost of temsirolimus from the analysis to reflect the current cost of treatment more accurately. The clinical effects of the temsirolimus-based regimen used in the ANBL1221 trial are assumed to be representative of traditional standard care, given that temsirolimus is not believed to provide additional clinical benefit.
- **Inpatient stay costs**: The sponsor did not consider the costs associated with inpatient stay for the administration of therapy in this patient population. Given that patients would spend 5 days in hospital to receive the infusion therapy, this was considered an important and relevant cost associated with dinutuximab therapy.
    - This was addressed by applying an inpatient stay cost of $1,822.89 per hospital bed day. This figure was sourced from a previous CADTH review of dinutuximab, which was calculated using the Patient Cost Estimator from the Canadian Institute for Health Information for patients aged 1 to 7 years across Canada.[2]
- **Drug wastage:** The sponsor did not consider drug wastage for GM-CSF and irinotecan. The clinical experts consulted by CADTH believed that, due to small patient sizes, it is likely that there would be vial wastage in the context of dosing based on pediatric body surface area, especially where vial sharing may not be common.
    - CADTH addressed this by assuming that there is no vial sharing for these drugs.
- **Inaccurate price of irinotecan:** The sponsor assumed a cost of $20.00 per 40 mg vial of irinotecan as per the CADTH review of cetuximab[12]; however, CADTH noted the price to be out of date and underestimated. CADTH updated the price of irinotecan according to the IQVIA Pharmastat database, which reported a unit price of $208.35 per 40 mg vial.[19]
    - CADTH updated the price of irinotecan as part of the base case.

CADTH Reanalyses of the Economic Evaluation

Base-Case Results

The CADTH reanalysis was derived by making changes in model parameter values and assumptions in consultation with clinical experts (see Table 5). The following changes were made in the CADTH base-case reanalysis (1) a longer, 7-year time frame for was assumed for patients to be considered as "cured"; (2) the cost of temsirolimus was removed from the standard therapy arm; (3) cost associated with a 5-day hospital stay at every cycle as added for dinutuximab; (4) drug costs were adjusted to account for wastage; and (5) a log-normal parametric form was used to model PFS for refractory patients on standard chemotherapy.

In the CADTH base-case reanalysis for relapsed patients, dinutuximab-based immunotherapy was associated with an expected cost of $939,177 and 2.491 QALYs over a 25-year time horizon. When compared with standard chemotherapy, dinutuximab-based immunotherapy had an incremental cost of $826,899 and was associated with 1.67 incremental QALYs, resulting in an ICER of $495,696 per QALY gained (Table 6). In relapsed patients, dinutuximab-based immunotherapy had a 0% probability of being cost-effective at a WTP threshold of $50,000 per QALY.

In the CADTH base-case reanalysis for refractory patients, dinutuximab-based immunotherapy was associated with an expected cost of $753,207 and 3.995 QALYs over a 75-year time horizon. When compared to standard chemotherapy, the incremental cost of dinutuximab-based immunotherapy was $593,337, and the incremental QALYs were 1.291. In this population, the ICER was $465,466 per QALY gained (Table 7). In refractory patients, dinutuximab-based immunotherapy had a 0% probability of being cost-effective at a WTP threshold of $50,000 per QALY.

Scenario Analysis Results

Price reduction analyses of the drug acquisition cost suggest that no price reduction for dinutuximab could achieve an ICER that is below the conventional $50,000 per QALY threshold, considering the CADTH base-case analyses (Table 8 and Table 9).

Additional scenario analyses were undertaken on the CADTH base-case reanalysis by (1) assuming there would be no incremental benefit or cost beyond the 5-year trial, (2) using a longer 10-year cure threshold (versus 7 years) for both cohorts, (3) using a longer 10-year cure threshold and fitting an exponential (versus log-normal) functional form to model PFS for standard care in the refractory cohort, (4) removing the cure thresholds (i.e., assuming that

Table 4: Key Assumptions of the Submitted Economic Evaluation (Not Noted as Limitations to the Submission)

Sponsor's key assumption	CADTH comment
The quality of life for patients with central nervous system tumours was assumed to be representative of neuroblastoma patients due to limited data on HRQoL. In addition, the impact of treatment-related adverse events on HRQoL was assumed to be the same for dinutuximab-treated and standard chemotherapy. Also, the magnitude of improvement in quality of life between the "stable," "failed," and "cure" health states was assumed to be the same for both refractory and relapse patients.	Due to the lack of data CADTH recognizes the need to make assumptions; however, the utilities used in the model have substantial uncertainty around them.

HRQoL = health-related quality of life.

stable patients remain at risk of progression throughout their lifetimes) for both cohorts, (5) removing the cure thresholds and fitting an exponential (versus log-normal) functional form to model PFS for standard care in the refractory cohort, and (6) removing the cure thresholds and fitting a log-normal functional form to model PFS for both dinutuximab and standard care in the refractory cohort.

For the relapse cohort, the ICERs in the scenario analyses were $871,382 per QALY assuming no benefit or cost after 5 years, $495,233 per QALY with a 10-year cure threshold, and $500,199 per QALY when assuming no cure threshold. For the refractory cohort, the ICER was $1,455,105 per QALY assuming no benefit or costs occurring after 5 years. The ICER varied between $481,052 and $866,031 per QALY when a 10-year cure threshold was considered and between $565,384 and $790,767 when assuming no cure threshold, depending on the use of an exponential versus log-normal extrapolation of PFS curves (Table 14 and Table 15, Appendix 4). Given the lack of clinical data, all of these scenario analyses are highly plausible, demonstrating that the CADTH base case may be a significant underestimation.

Table 5: CADTH Revisions to the Submitted Economic Evaluation

Stepped analysis	Sponsor's value or assumption	CADTH value or assumption
Corrections to sponsor's base case		
Drug costs	Cost of irinotecan was valued at $107 per cycle.	Cost of irinotecan was amended to $2,604.25 per cycle.
Changes to derive the CADTH base case		
1. Cure threshold	Assumption that patients who are stable after 5 years are cured for the remainder of their lifetime.	Assumption that patients who are stable after 7 years are cured for the remainder of their lifetime.
2. Inappropriate comparator	Inclusion of temsirolimus as a relevant comparator.	Remove the cost of temsirolimus from the analysis; assume that the effectiveness of the temsirolimus-based regimen used in the ANBL1221 trial was equivalent to standard care without temsirolimus.
3. Cost of inpatient stay	The cost of inpatient stay for treatment was not included.	A cost of inpatient hospital stay of $1,822.89 per hospital bed day added for the duration of treatment administration.
4. Drug wastage	No drug wastage considered for GM-CSF. No drug wastage considered for irinotecan (corrected cost of irinotecan without wastage was $1,109 per cycle based on correction 1 above).	GSM-CSF cost including wastage (no vial sharing) is estimated as $2,953.14. Irinotecan cost, including wastage (no vial sharing), is estimated as $2,604.25.
5. Determination of PFS curve for standard care (refractory cohort)	Exponential parametric form used to model PFS for refractory patients on standard chemotherapy.	A log-normal parametric form is used to model PFS for refractory patients on standard chemotherapy.
CADTH base case	—	Reanalysis 1 + 2 + 3 + 4 (for relapse) Reanalysis 1 + 2 + 3 + 4 + 5 (for refractory)

GM-CSF = granulocyte-macrophage colony-stimulating factor; PFS = progression-free survival.

Issues for Consideration

This submission was reviewed for an indication that the sponsor chose not to pursue for a regulatory submission.

Overall Conclusions

Based on the clinical review, data from the ANBL1221 study indicate that dinutuximab may be efficacious at prolonging PFS and OS. However, due to limitations with the trial data, such as small sample sizes and issues with trial design, the magnitude of this benefit is highly uncertain. This generates a significant amount of uncertainty regarding the cost-effectiveness of dinutuximab.

Table 6: Summary of the Stepped Analysis of the CADTH Reanalysis Results — Relapse

Stepped analysis	Drug	Total costs ($)	Total QALYs	ICER ($/QALY)
Sponsor's base case	Standard chemotherapy	115,563	0.822	Reference
	Dinutuximab-based immunotherapy	888,923	2.539	450,370
Sponsor's corrected base case	Standard chemotherapy	120,212	0.822	Reference
	Dinutuximab-based immunotherapy	898,646	2.520	458,339
CADTH reanalysis 1 (cure threshold = 7 years)	Standard chemotherapy	119,286	0.817	Reference
	Dinutuximab-based immunotherapy	896,891	2.502	461,504
CADTH reanalysis 2 (inappropriate comparator)	Standard chemotherapy	105,490	0.812	Reference
	Dinutuximab-based immunotherapy	899,320	2.524	463,783
CADTH reanalysis 3 (cost of inpatient stay)	Standard chemotherapy	119,418	0.821	Reference
	Dinutuximab-based immunotherapy	913,764	2.521	467,310
CADTH reanalysis 4 (drug wastage)	Standard chemotherapy	124,826	0.820	Reference
	Dinutuximab-based immunotherapy	921,721	2.534	464,726
CADTH base case (reanalysis 1 + 2 + 3 + 4)	Standard chemotherapy	112,278	0.822	Reference
	Dinutuximab-based immunotherapy	939,177	2.491	495,696

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

Note: Reanalysis is based on publicly available prices of the comparator.

As part of its reanalyses, CADTH corrected the sponsor's model for the costs for irinotecan, redefined the cure threshold to 7 years, considered more appropriate models for PFS for refractory patients on standard chemotherapy, modified the comparator to reflect the standard treatment option in Canada (removing the cost of temsirolimus from the analysis), added the cost of a 5-day inpatient stay associated with therapy, and considered drug wastage for GM-CSF and irinotecan, assuming no vial sharing in this patient population.

In the CADTH base-case reanalysis for relapsed patients, dinutuximab-based immunotherapy had an ICER of $495,696 per QALY gained compared to standard chemotherapy. For refractory patients, dinutuximab-based immunotherapy had an ICER of $459,747 per QALY gained compared to standard chemotherapy. In both populations, dinutuximab-based immunotherapy had a 0% probability of cost-effectiveness at a WTP threshold of $50,000 per QALY. Even with price reductions approaching 100%, the cost-effectiveness of dinutuximab is not within conventionally accepted levels, largely because of considerable non-drug health care costs contributing to the cost of care and uncertainty regarding the magnitude of benefit associated with dinutuximab.

Table 7: Summary of the Stepped Analysis of the CADTH Reanalysis Results — Refractory

Stepped analysis	Drug	Total costs ($)	Total QALYs	ICER ($/QALY)
Sponsor's base case	Standard chemotherapy	152,073	2.474	Reference
	Dinutuximab-based immunotherapy	722,378	5.828	170,015
CADTH reanalysis 1 (cure threshold = 7 years)	Standard chemotherapy	158,961	1.896	Reference
	Dinutuximab-based immunotherapy	724,028	3.975	271,702
CADTH reanalysis 2 (inappropriate comparator)	Standard chemotherapy	137,501	2.458	Reference
	Dinutuximab-based immunotherapy	728,358	5.895	171,926
CADTH reanalysis 3 (cost of inpatient stay)	Standard chemotherapy	158,832	2.457	Reference
	Dinutuximab-based immunotherapy	739,873	5.823	172,593
CADTH reanalysis 4 (drug wastage)	Standard chemotherapy	169,204	2.467	Reference
	Dinutuximab-based immunotherapy	744,522	5.853	169,920
CADTH reanalysis 5 (adjustments to PFS curve for standard care for refractory group)	Standard chemotherapy	177,632	3.317	Reference
	Dinutuximab-based immunotherapy	730,532	5.803	222,387
CADTH base case (reanalysis 1 + 2 + 3 + 4 + 5)	Standard chemotherapy	159,871	2.704	Reference
	Dinutuximab-based immunotherapy	753,207	3.995	459,747

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.
Note: Reanalysis is based on publicly available prices of the comparator.

The estimates of cost-effectiveness are mostly driven by the substantial drug cost of dinutuximab ($68,533 per 28 days) relative to standard chemotherapy ($3,246 per 28 days). There is also considerable uncertainty around OS and PFS derived from the ANBL1221 trial. The small number of patients in each cohort in the ANBL1221 trial and the lack of long-term data in this patient population make survival extrapolations highly uncertain. Therefore, there is certainty of high incremental costs and considerable uncertainty regarding the size of incremental benefit. Furthermore, the model relied on several assumptions around when

Table 8: CADTH Price Reduction Analyses — Relapse

Price reduction	ICERs for dinutuximab vs. standard chemotherapy ($)	
	Sponsor's base case (corrected)	CADTH reanalysis
No price reduction	458,339	495,696
10%	446,370	483,515
20%	406,422	443,228
30%	366,475	402,702
40%	326,528	362,177
50%	286,581	321,651
60%	246,633	281,126
70%	206,686	240,601
80%	166,739	200,075
90%	126,792	159,312
100%	86,844	115,413

ICER = incremental cost-effectiveness ratio.

Table 9: CADTH Price Reduction Analyses — Refractory

Price reduction	ICERs for dinutuximab vs. standard chemotherapy ($)	
	Sponsor's base case (corrected)	CADTH reanalysis
No price reduction	168,823	459,747
10%	155,266	435,003
20%	142,588	399,366
30%	129,808	362,907
40%	117,028	313,807
50%	104,248	297,661
60%	91,468	264,150
70%	78,688	229,210
80%	65,908	185,733
90%	53,127	159,006
100%	40,347	127,940

ICER = incremental cost-effectiveness ratio.

patients may be considered cured and the benefits realized after this point. Crucially, due to the sponsor's model design, the difference in PFS at the point of cure is fundamental to the cost-effectiveness results, but there are no reliable data to inform what this difference may be.

To evaluate these uncertainties, scenario analyses explored a set of more conservative assumptions, mainly by assuming no benefit or costs beyond 5 years (corresponding to the observed trial period) and by increasing and removing the cure threshold assumption. In the scenario analyses for the relapse cohort, the ICERs ranged from $495,233 per QALY when assuming a 10-year cure threshold to $871,382 per QALY when considering no incremental benefits or costs beyond 5 years. For the refractory cohort, the ICERs range from $481,052 per QALY (assuming a 10-year cure threshold) to $1,455,105 per QALY with no incremental changes beyond 5 years. Given that the key clinical inputs are informed by small sample sizes and the uncertainty around long-term outcomes in this population, the CADTH base case could be a considerable underestimation of the ICER.

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Appendix 1: Cost Comparison Table

Note that this appendix has not been copy-edited.

The comparators presented in the following table have been deemed to be appropriate based on feedback from clinical experts. Comparators may be recommended (appropriate) practice or actual practice. Existing Product Listing Agreements are not reflected in the table. As such, the table may not represent the actual costs to public drug plans.

Table 10: CADTH Cost Comparison Table for Relapsed and Refractory Neuroblastoma

Treatment	Strength	Form (size if single use)	Price ($)	Recommended dosage[a]	Daily cost ($)[b]	28-day cycle cost ($)
Dinutuximab	3 mg/mL	IV infusion 5 mL	12,850.0000[c]	17.5 mg/m^2 per day 4 times per 3 weeks	2,447.62	68,533
GM-CSF	250 mcg	SC injection	324.87[c]	250 mcg/m^2 per day 7 times per 3 weeks	108.29	3,032
Irinotecan	20 mg/mL	IV infusion 2 mL	208.3500[d]	50 mg/m^2 per day 5 times per 3 weeks	99.21	2,778
Temozolomide	5 mg 20 mg 100 mg 140 mg 250 mg	Capsules	3.9000 15.6000 78.0030 109.2050 195.0020	100 mg/m^2 per day 5 times per 3 weeks	16.71	468
Dinutuximab + GM-CSF + temozolomide + irinotecan	NA	NA	NA	NA	2,671.84	74,811
Chemotherapy						
Cyclophosphamide	500 mg 1,000 mg	Powder for IV infusion	91.3100[d] 165.5200[d]	250 mg/m^2 per day 5 times per 3 weeks	21.74	609
Irinotecan	20 mg/mL	IV infusion 2 mL	208.3500[d]	50 mg/m^2 per day 5 times per 3 weeks	99.21	2,778
Temsirolimus	25 mg/mL	IV infusion	1,091.3330[d]	35 mg/m^2/day twice per 3 weeks	123.98	3,471
Temozolomide	5 mg 20 mg 100 mg 140 mg 250 mg	Capsules	3.9000 15.6000 78.0030 109.2050 195.0020	100 mg/m^2 per day 5 times per 3 weeks	16.71	468
Topotecan	1 mg/mL	IV infusion 4 mL	567.0000[d]	0.75 mg/m^2 per day 5 times per 3 weeks	135.00	3,780

Treatment	Strength	Form (size if single use)	Price ($)	Recommended dosage[a]	Daily cost ($)[b]	28-day cycle cost ($)
Regimens						
Temsirolimus + temozolomide + irinotecan	NA	NA	NA	NA	239.90	6,717
Temozolomide + irinotecan	NA	NA	NA	NA	115.93	3,246
Cyclophosphamide + topotecan	NA	NA	NA	NA	156.74	4,389

GM-CSF = granulocyte-macrophage colony-stimulating factor; NA = not applicable; SC = subcutaneous.

Note: All prices are from the Ontario Drug Benefit Formulary (accessed January 2021)[20] unless otherwise indicated, and do not include dispensing fees. Wastage was assumed to occur in the cases where the product monograph explicitly stated that the vial was for single use.

[a]Recommended dosages are based on the ANBL1221 trial[4] for all comparators except cyclophosphamide and topotecan, for which recommended dosages are from the respective published clinical trials.[8,21,22]

[b]Where applicable, daily and cycle costs are based on a mean body surface area of 0.852 m^2 at baseline in the ANBL1221 trial.[4]

[c]Sponsor's submitted price.[3]

[d]Price obtained from IQVIA Delta PA database (accessed January 2021).[19]

Appendix 2: Submission Quality

Note that this appendix has not been copy-edited.

Table 11: Submission Quality

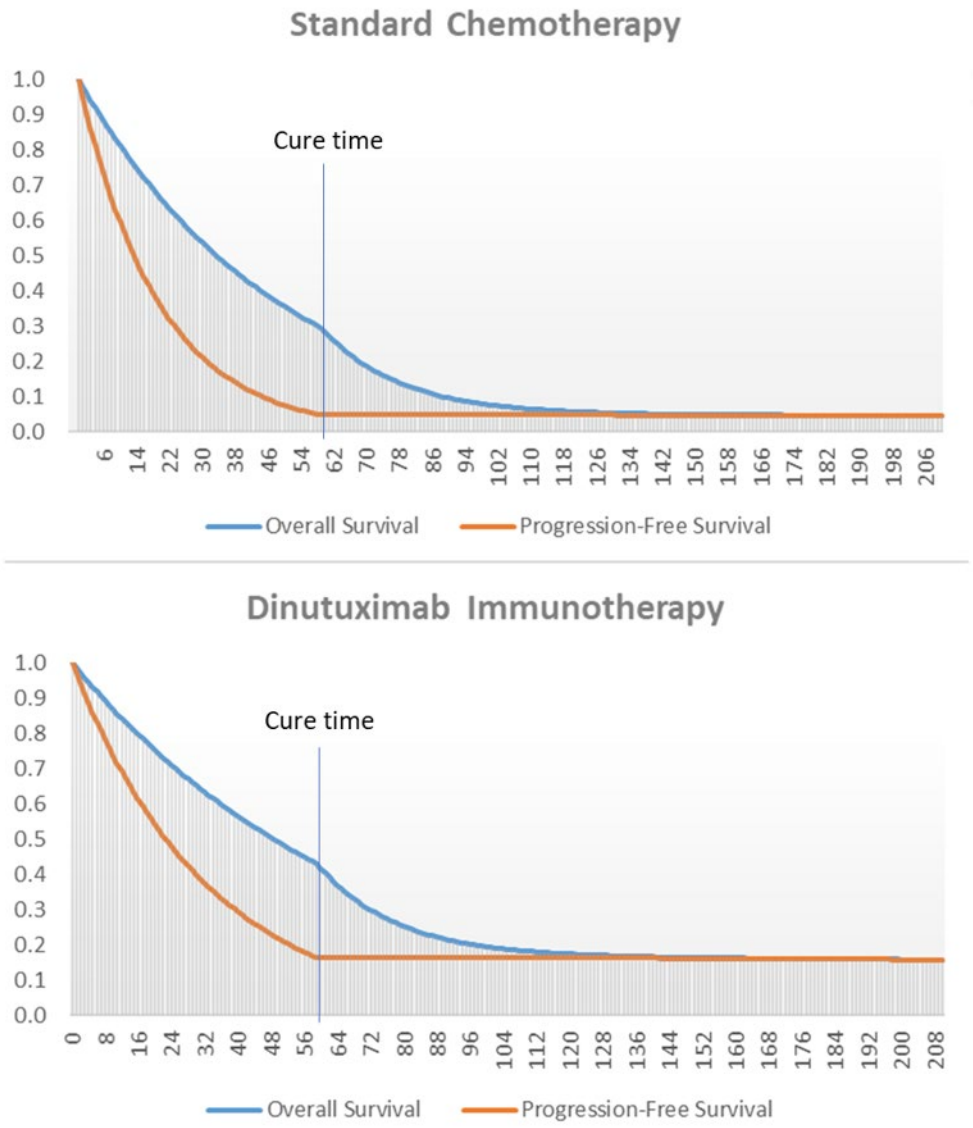
Description	Yes/no	Comments
Population is relevant, with no critical intervention missing, and no relevant outcome missing	Yes	None
Model has been adequately programmed and has sufficient face validity	Yes	Face validity is reasonable but uncertain over the long-term extrapolations/projections.
Model structure is adequate for the decision problem	No	Model made important structural assumptions after the cure threshold, and the submitted model was not flexible enough to assess the impact of these structural assumptions in detail.
Data incorporation into the model has been done adequately (e.g., parameters for probabilistic analysis)	Yes	None
Parameter and structural uncertainty were adequately assessed; analyses were adequate to inform the decision problem	No	Parameter and structural uncertainty could have been assessed in more detail. There was limited sensitivity analysis around model inputs. The impact of parameter uncertainty around HRQoL, cost components, and other assumptions was not fully explored or reported.
The submission was well-organized and complete; the information was easy to locate (clear and transparent reporting; technical documentation available in enough details)	No	The report should explicitly list all assumptions and test them in a more explicit way.

HRQoL = health-related quality of life.

Appendix 3: Additional Information on the Submitted Economic Evaluation

Note that this appendix has not been copy-edited.

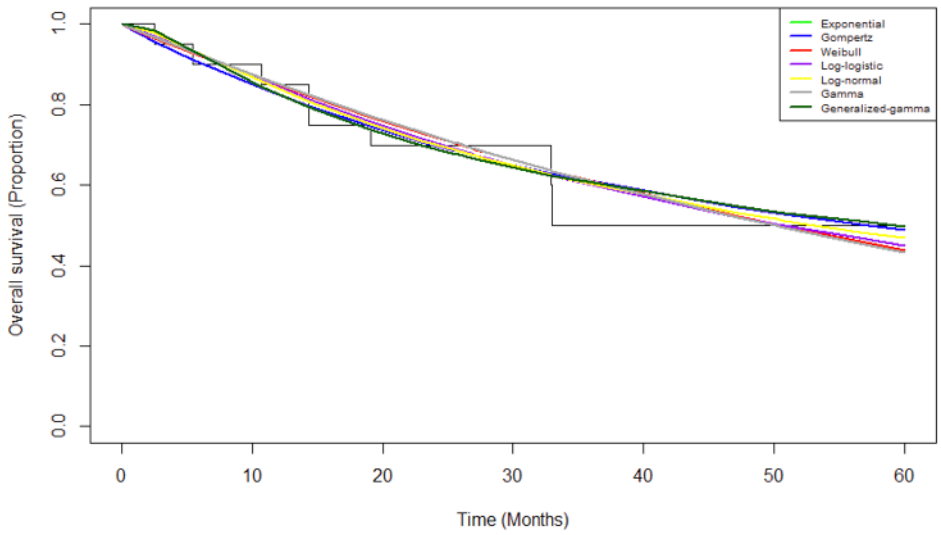
Figure 1: Submitted Partitional Survival Model Outputs



Detailed Results of the Sponsor's Base Case

Source: Sponsor's submission.

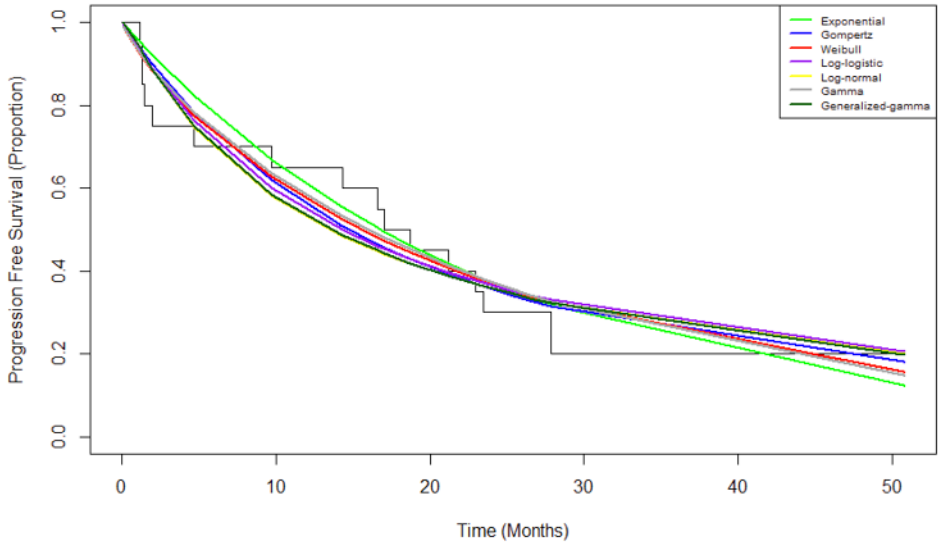
Figure 2: Parametric Fits Versus Trial Data for OS — Relapsed Dinutuximab-Treated Patients



OS = overall survival.

Source: Sponsor's submission

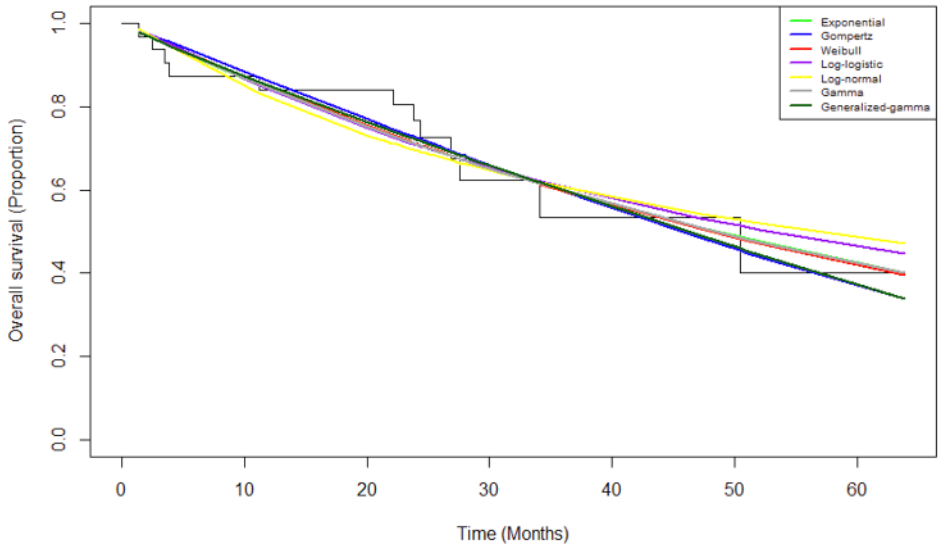
Figure 3: Parametric Fits Versus Trial Data for PFS — Relapsed Dinutuximab-Treated Patients



PFS = progression-free survival.

Source: Sponsor's submission.

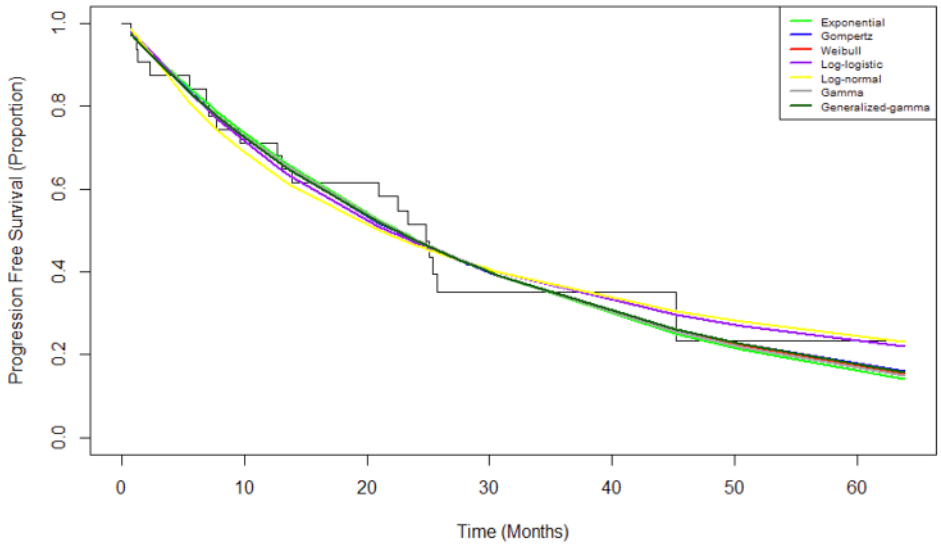
Figure 4: Parametric Fits Versus Trial Data for OS — Refractory Dinutuximab-Treated Patients



OS = overall survival.

Source: Sponsor's submission.

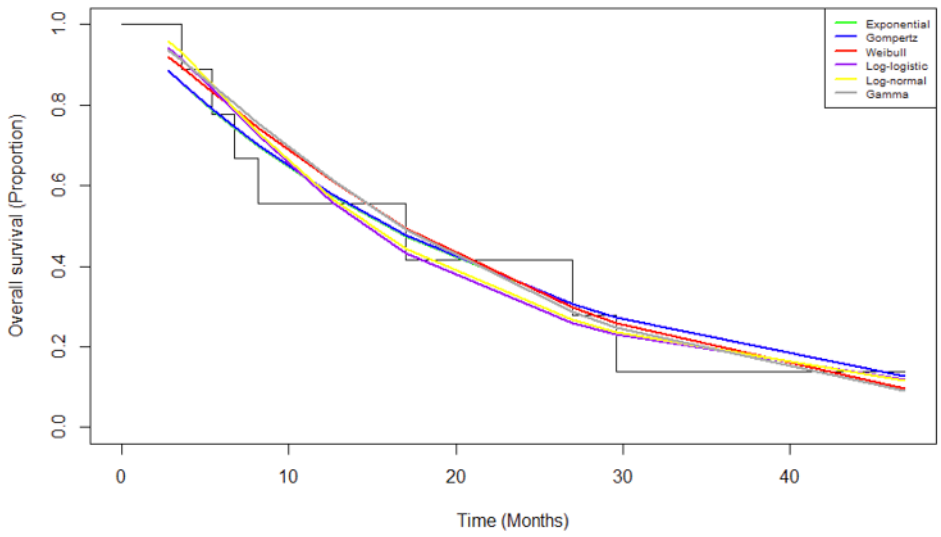
Figure 5: Parametric Fits Versus Trial Data for PFS — Refractory Dinutuximab-Treated Patients



PFS = progression-free survival.

Source: Sponsor's submission.

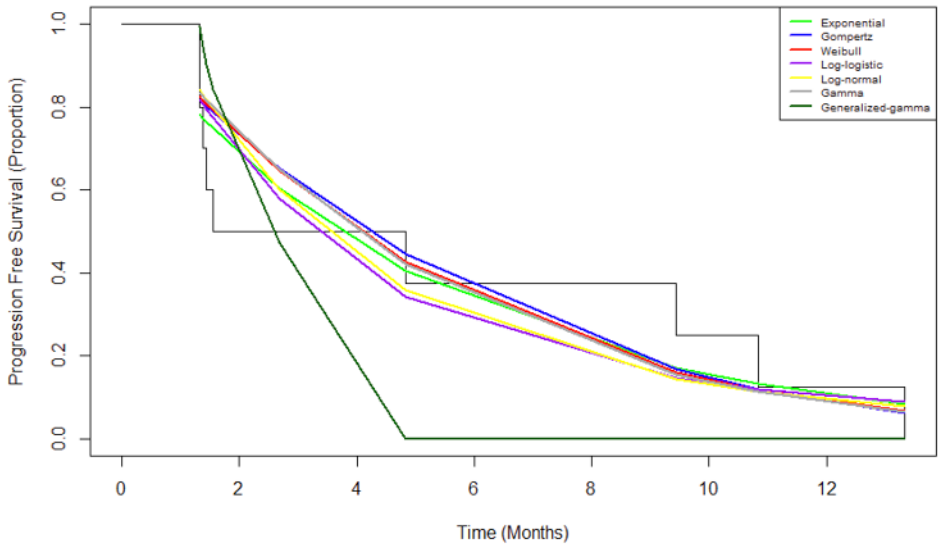
Figure 6: Parametric Fits Versus Trial Data for OS — Relapsed Chemotherapy-Treated Patients



OS = overall survival.

Source: Sponsor's submission.

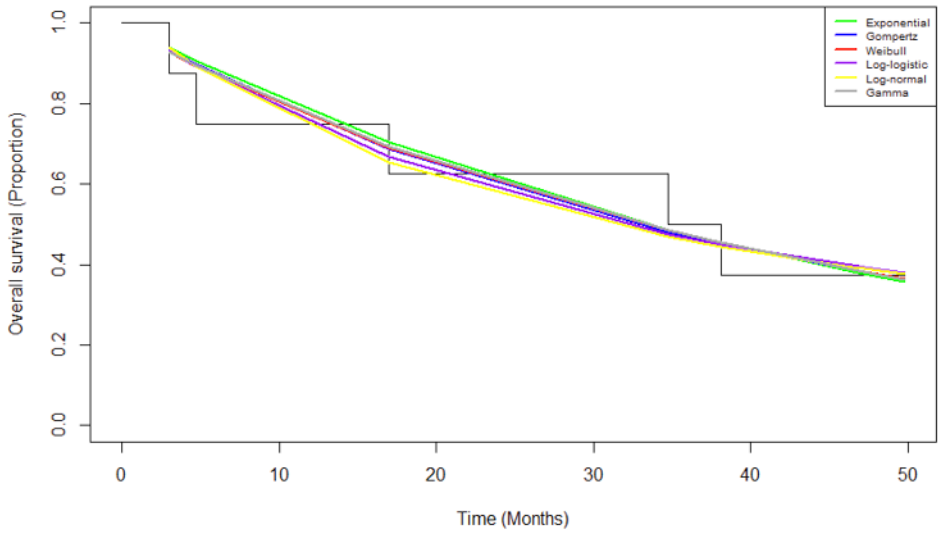
Figure 7: Parametric Fits Versus Trial Data for PFS — Relapsed Chemotherapy-Treated Patients



PFS = progression-free survival.

Source: Sponsor's submission.

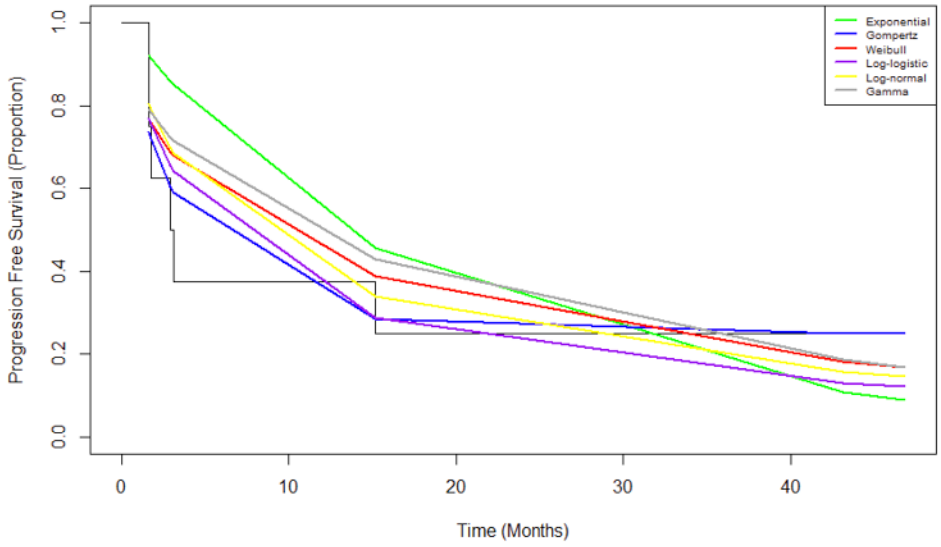
Figure 8: Parametric Fits Versus Trial Data for OS — Refractory Chemotherapy-Treated Patients



OS = overall survival.

Source: Sponsor's submission.

Figure 9: Parametric Fits Versus Trial Data for PFS — Refractory Chemotherapy-Treated Patients



PFS = progression-free survival.

Source: Sponsor's submission.

Appendix 4: Additional Details on the CADTH Reanalyses and Sensitivity Analyses of the Economic Evaluation

Note that this appendix has not been copy-edited.

Table 12: Disaggregated Summary of CADTH's Economic Evaluation Results — Relapse

Parameter	Dinutuximab-based therapy	Standard chemotherapy	Incremental
Discounted LYs			
Stable	2.118	0.523	1.595
Failed	3.997	1.655	2.342
Total	6.115	2.177	3.988
Discounted QALYs			
Stable	1.209	0.292	0.917
Failed	1.281	0.530	0.751
Total	2.491	0.822	1.668
Discounted costs ($)			
Total	939,177	112,278	826,899
Primary drug and administration	707,643	12,152	695,491
Consolidation	0	0	0
Ongoing health care	204,673	81,322	123,351
Adverse events	13,688	4,295	9,394
Terminal care	13,173	14,509	−1,337
ICER ($/QALY)	495,696		

ICER = incremental cost-effectiveness ratio; LY = life-year; QALY = quality-adjusted life-year.

Table 13: Disaggregated Summary of CADTH's Economic Evaluation Results — Refractory

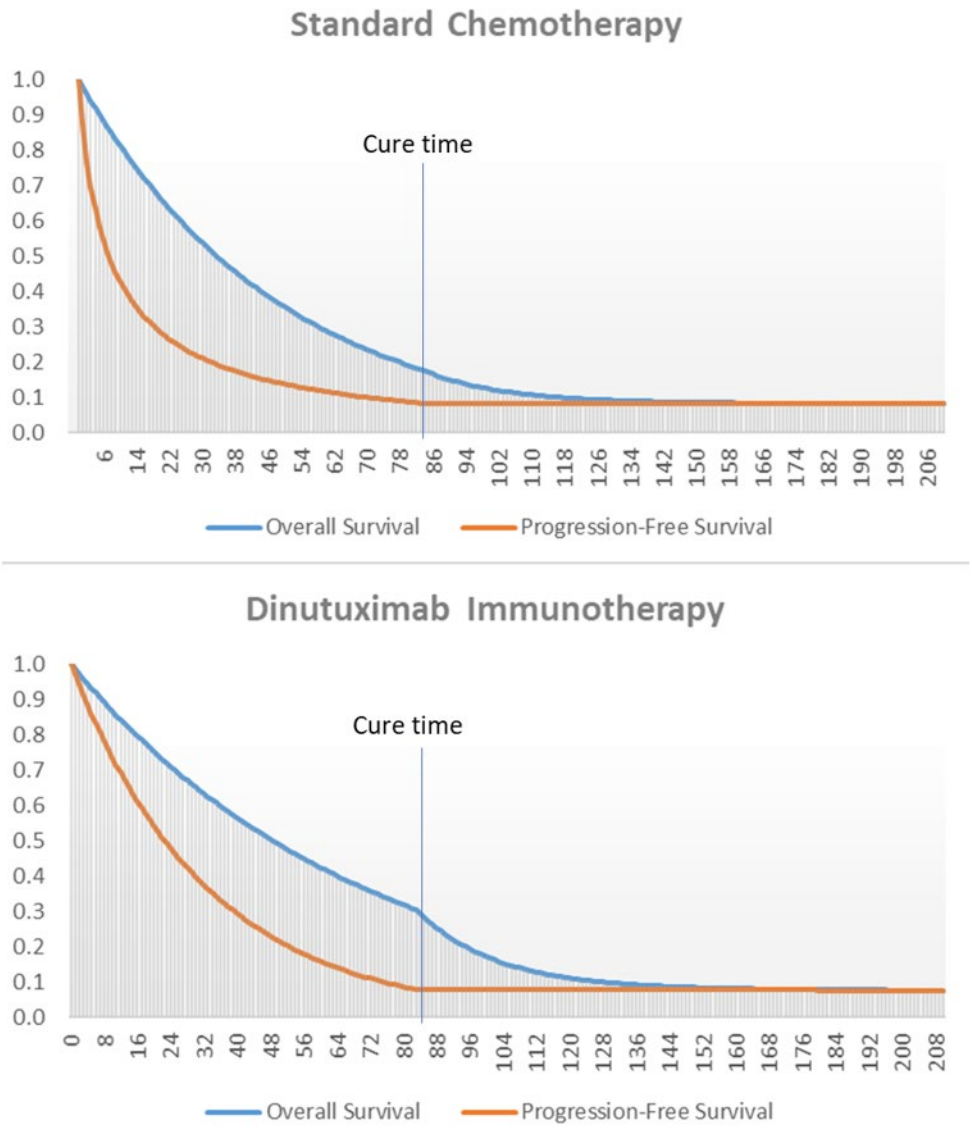
Parameter	Dinutuximab-based therapy	Standard chemotherapy	Incremental
Discounted Lys			
Stable	5.086	3.825	1.261
Failed	1.820	1.758	0.062
Total	6.906	5.583	1.323
Discounted QALYs			
Stable	3.411	2.142	1.270
Failed	0.582	0.562	0.021
Total	3.995	2.704	1.291

Parameter	Dinutuximab-based therapy	Standard chemotherapy	Incremental
Discounted costs ($)			
Total	753,207	159,871	593,337
Primary drug and administration	482,568	19,635	462,933
Consolidation	112,741	0	112,741
Ongoing health care	135,061	119,492	15,569
Adverse events	9,354	6,956	2,398
Terminal care	13,484	13,788	−304
ICER ($/QALY)	459,747		

ICER = incremental cost-effectiveness ratio; LY = life-year; QALY = quality-adjusted life-year.

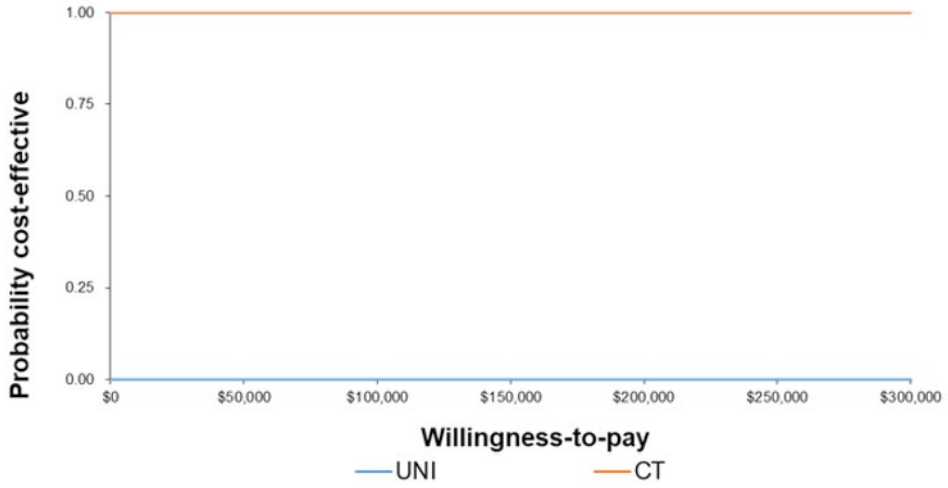
Detailed Results of CADTH Base Case

Figure 10: Model Structure — CADTH Base-Case Model



Source: Sponsor's submission

Figure 11: CADTH Base-Case Cost-Effectiveness Acceptability Curve for Relapse Cohort



CT = chemotherapy; UNI = dinutuximab.
Source: Sponsor's submission.

Scenario Analyses

Table 14: Summary of the Scenario Analyses — Relapse

Drug	Total costs ($)	Total QALYs	ICER vs. standard chemotherapy ($)	Sequential ICER
CADTH base-case analysis				
Standard chemotherapy	112,278	0.822	—	—
Dinutuximab-based immunotherapy	939,177	2.491	495,696	—
CADTH scenario analysis 1 (assume no incremental benefit or cost after 5 years)				
Standard chemotherapy	96,434	0.715	—	—
Dinutuximab-based immunotherapy	815,992	1.541	871,382	—
CADTH scenario analysis 2 (10-year cure threshold)				
Standard chemotherapy	112,404	0.820	—	—
Dinutuximab-based immunotherapy	936,763	2.484	495,233	—
CADTH scenario analysis 3 (no cure threshold)				
Standard chemotherapy	111,498	0.812	—	—
Dinutuximab-based immunotherapy	937,590	2.464	500,199	—

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; vs. = versus .

Table 15: Summary of the Scenario Analyses — Refractory

Drug	Total costs ($)	Total QALYs	ICER vs. standard chemotherapy ($)	Sequential ICER
CADTH base-case analysis				
Standard chemotherapy	159,871	2.704	—	159,871
Dinutuximab-based immunotherapy	753,207	3.995	459,747	753,207
CADTH scenario analysis 1 (assume no incremental benefit or cost after 5 years)				
Standard chemotherapy	114,424	1.225	—	—
Dinutuximab-based immunotherapy	680,932	1.614	1,455,105	—
CADTH scenario analysis 2 (10-year cure threshold)				
Standard chemotherapy	158,024	2.239	—	—
Dinutuximab-based immunotherapy	757,242	2.931	866,031	—
CADTH scenario analysis 3 (10-year cure threshold plus exponential extrapolation of PFS curves)				
Standard chemotherapy	151,478	1.679	—	—
Dinutuximab-based immunotherapy	755,634	2.935	481,052	—
CADTH scenario analysis 4 (no cure threshold)				
Standard chemotherapy	152,414	1.729	—	—
Dinutuximab-based immunotherapy	787,962	2.532	790,767	—
CADTH scenario analysis 5 (no cure threshold, exponential extrapolation of PFS curves)				
Standard chemotherapy	162,052	1.669	—	—
Dinutuximab-based immunotherapy	787,653	2.543	715,526	—
CADTH scenario analysis 6 (no cure threshold + log-normal extrapolation of PFS curves)				
Standard chemotherapy	152,882	1.735	—	—
Dinutuximab-based immunotherapy	744,940	2.788	562,384	—

ICER = incremental cost-effectiveness ratio; PFS = progression-free survival; QALY = quality-adjusted life-year; vs. = versus .

Appendix 5: Submitted Business Impact Analysis and CADTH Appraisal

Note that this appendix has not been copy-edited.

Table 16: CADTH Summary of Findings From the Sponsor's Business Impact Analysis

Key take-aways of the business impact analysis
• CADTH identified the following key limitations with the sponsor's analysis: • The price of irinotecan did not reflect current drug costs and underestimated the budget impact of dinutuximab. • Temsirolimus in combination with irinotecan and temozolomide was not reflective of clinical practice. Its inclusion overestimates total drug costs and underestimates the budget impact of dinutuximab. • Administration costs should not be included in a budget impact analysis conducted from a drug program perspective. • The CADTH reanalysis updated the price of irinotecan, removed temsirolimus as a comparator, and excluded administration costs. Based on the CADTH base case, the budget impact is expected to be $12,496,315 in year 1, $12,630,026 in year 2, and $12,765,167 in year 3, for a 3-year total of $37,891,509. • The 3-year budget impact is expected to be $8,119,609 and $29,771,900 in relapsed and refractory patients, respectively.

Summary of the Sponsor's Business Impact Analysis

The submitted budget impact analysis (BIA) assessed the introduction of dinutuximab for the treatment of relapsed and refractory neuroblastoma. The analysis was conducted from the perspective of Canadian public drug plans using an epidemiology-based approach and included drug acquisition and administration costs as part of the base case. A 3-year time horizon was used, from 2021 to 2024, with 2020 as a base year.

Comparators for this analysis aligned with the ANBL1221 trial[4] and included temsirolimus in combination with temozolomide and irinotecan for the reference case scenario. The new drug scenario included dinutuximab in combination with GM-CSF, temsirolimus, irinotecan, and temozolomide compared to temsirolimus in combination with irinotecan and temozolomide. The mean number of treatment cycles with dinutuximab and chemotherapy for relapsed and refractory patients was 9.65 and 6.55, respectively, and the mean number of treatment cycles with chemotherapy alone was 4.30 and 6.88, respectively. Key inputs to the BIA are documented in Table 17 below.

Table 17: Summary of Key Model Parameters

Parameter	Sponsor's estimate (reported as year 1 / year 2 / year 3, if appropriate)
Target population	
Neuroblastoma annual incidence	76[23]
Proportion high-risk neuroblastoma	50%[24,25]
Proportion relapsed	15%[26]
Proportion refractory	55%[26]
Population growth rate	1.07%[27]
Number of total patients eligible for dinutuximab	27 / 27 / 27
Number of relapsed patients eligible for dinutuximab	6 / 6 / 6
Number of refractory patients eligible for dinutuximab	21 / 21 / 22

Parameter	Sponsor's estimate (reported as year 1 / year 2 / year 3, if appropriate)
Market uptake (3 years)	
Uptake (reference scenario)	
Dinutuximab + chemotherapy	0% / 0% / 0%
Temsirolimus + chemotherapy[a]	100% / 100% / 100%
Uptake (new drug scenario)	
Dinutuximab + chemotherapy	90% / 90% / 90%
Temsirolimus + chemotherapy [a]	10% / 10% / 10%
Cost of treatment (per patient)	
Cost of treatment over 21-day cycle	
Dinutuximab	$66,748.10
GM-CSF	$1,937.52
Temozolomide	$332.28
Irinotecan	$106.50
Temsirolimus	$3,321.59

GM-CSF = granulocyte-macrophage colony-stimulating factor.

[a]Chemotherapy consists of temozolomide and irinotecan.

Summary of the Sponsor's BIA Results

The estimated budget impact of funding dinutuximab for the treatment of relapsed and refractory neuroblastoma was $11,809,946 in year 1, $11,936,312 in year 2, and $12,064,031 in year 3, for a 3-year total of $35,810,289. In the relapsed population only, the budget impact was $2,530,703 in year 1, $2,557,781 in year 2, and $2,585,149 in year 3, for a 3-year total of $7,673,633. In the refractory population only, the budget impact was $9,279,243 in year 1, $9,378,531 in year 2, and $9,478,881 in year 3, for a 3-year total of $28,136,655.

CADTH Appraisal of the Sponsor's BIA

CADTH identified several key limitations to the sponsor's analysis that have notable implications for the results of the BIA.

- **Price of irinotecan is inaccurate:** The sponsor assumed a cost of $20.00 per 40 mg vial of irinotecan as per the CADTH review of cetuximab[12]; however, CADTH noted the price to be out of date and underestimated. CADTH updated the price of irinotecan according to the IQVIA Pharmastat database, which reported a unit price of $208.35 per 40 mg vial.[19]
  - CADTH updated the price of irinotecan as part of the base case.
- **Temsirolimus is not a relevant comparator:** The sponsor's main comparator in the analysis was temsirolimus, given in combination with chemotherapy (temozolomide and irinotecan), which aligned with the comparator arm of the ANBL1221 trial.[4] However, the clinical experts consulted by CADTH stated that temsirolimus is not a relevant comparator and is neither currently included nor funded as part of standard chemotherapy regimens because it does not provide additional clinical benefit compared to the doublet therapy of temozolomide and irinotecan, which is considered standard of care in this population by clinical experts.
  - CADTH removed the cost of temsirolimus as part of the base case.
- **Inclusion of administration costs:** The sponsor included administration costs (e.g., physician services, equipment, and operational costs) of dinutuximab and chemotherapy as part of the base-case analysis. As per the CADTH Procedures for Reimbursement

Reviews, the budget impact base case must be undertaken from a drug program perspective, which focuses on drug costs and may include wholesale or pharmacy mark-ups and dispensing fees.[28]

- CADTH excluded administration costs as part of the base case.

- **Wastage of GM-CSF, irinotecan, and temozolomide:** The sponsor included wastage for dinutuximab, but not for any of the other drugs in its base case. Because vial sharing is unlikely to occur with IV formulations, CADTH felt that wastage should be considered for all drugs. The sponsor's base case also included perfect capsule sharing of temozolomide, which was thought to be inappropriate.
  - CADTH considered drug wastage of GM-CSF, irinotecan, and temozolomide as part of the base case.

CADTH Reanalyses of the BIA

CADTH corrected the price of irinotecan as part of the base case; further revisions included the removal of temsirolimus costs as part of the comparator arm, the exclusion of administration costs for all therapies, and consideration of drug wastage.

Table 18: CADTH Revisions to the Submitted BIA

Stepped analysis	Sponsor's value or assumption	CADTH value or assumption
Corrections to sponsor's base case		
1. Corrected price of irinotecan	21-day cycle cost: $106.50	21-day cycle cost: $1,109.46
Changes to derive the CADTH base case		
1. Remove temsirolimus costs as part of the comparator arm	Main comparator: temsirolimus, irinotecan, and temozolomide	Main comparator: irinotecan and temozolomide
2. Exclude administration costs for therapies	Included administration costs	Excluded administration costs
3. Drug wastage for temozolomide, irinotecan, and GM-CSF	Not considered	**21-day cycle costs** Temozolomide: $351.00 Irinotecan: $2,604.25 GM-CSF: $2,953.14
CADTH base case		Reanalysis 1 + 2 + 3

GM-CSF = granulocyte-macrophage colony-stimulating factor.

The results of the CADTH step-wise reanalyses are presented in summary format in Table 19, and a more detailed breakdown is presented in Table 20. Based on the CADTH base case, the budget impact of the reimbursement of dinutuximab for the treatment of relapsed and refractory neuroblastoma is expected to be $12,496,315 in year 1, $12,630,026 in year 2, and $12,765,167 in year 3, for a 3-year total of $37,891,509. By subgroup, the 3-year budget impact in relapsed patients only is expected to be $2,677,782 in year 1, $2,706,434 in year 2, and $2,735,393 in year 3, for a 3-year total of $8,119,609; in refractory patients, it is expected to be $9,818,534 in year 1, $9,923,592 in year 2, and $10,029,774 in year 3, for a 3-year total of $29,771,900.

Table 19: Summary of the CADTH Reanalyses of the BIA

Stepped analysis	3-year total
Submitted base case	$35,810,289
Submitted base case (corrected)	$36,054,290
CADTH reanalysis 1: Removed temsirolimus as a comparator	$37,017,657
CADTH reanalysis 2: Excluded administration costs	$36,018,294

Stepped analysis	3-year total
CADTH reanalysis 3: Drug wastage considered	$36,964,137
CADTH base case	**$37,891,509**

BIA = budget impact analysis.

Table 20: Detailed Breakdown of the CADTH Reanalyses of the BIA

Stepped analysis	Scenario	Year 0 (current situation)	Year 1	Year 2	Year 3	3-year total
Submitted base case	Reference	$411,014	$415,412	$419,857	$424,349	$1,670,631
	New drug	$411,014	$12,225,357	$12,356,169	$12,488,380	$37,480,919
	Budget impact	**$0**	**$11,809,946**	**$11,936,312**	**$12,064,031**	**$35,810,289**
Submitted base case (corrected)	Reference	$516,478	$522,005	$527,590	$533,235	$2,099,309
	New drug	$516,478	$12,412,420	$12,545,233	$12,679,467	$38,153,599
	Budget impact	**$0**	**$11,890,415**	**$12,017,643**	**$12,146,232**	**$36,054,290**
CADTH base case	Reference	$310,795	$314,120	$317,481	$320,878	$1,263,275
	New drug	$310,795	$12,810,436	$12,947,507	$13,086,046	$39,154,784
	Budget impact	**$0**	**$12,496,315**	**$12,630,026**	**$12,765,167**	**$37,891,509**

BIA = budget impact analysis.