CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Dinutuximab (Unituxin) for Neuroblastoma

March 26, 2019

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TABLE OF CONTENTS

1 GUIDANCE IN BRIEF

This Clinical Guidance Report was prepared to assist the pCODR Expert Review Committee (pERC) in making recommendations to guide funding decisions made by the provincial and territorial Ministries of Health and provincial cancer agencies regarding dinutuximab for neuroblastoma. The Clinical Guidance Report is one source of information that is considered in the *pERC Deliberative Framework*. The *pERC Deliberative Framework* is available on the CADTH website (www.cadth.ca/pcodr).

This Clinical Guidance is based on: a systematic review of the literature regarding dinutuximab for neuroblastoma conducted by the Neurological Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group; input from Registered Clinicians; and supplemental issues relevant to the implementation of a funding decision.

The systematic review and supplemental issues are fully reported in Sections 6 and 7. A background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input on dinutuximab for neuroblastoma, a summary of submitted Provincial Advisory Group Input on dinutuximab for neuroblastoma, and a summary of submitted Registered Clinician Input on dinutuximab for neuroblastoma, and are provided in Sections 2, 3, 4, and 5 respectively. Of note, 13 cis-retinoic acid, retinoic acid, RA, isotretinoin are used interchangeably in this report.

1.1 Introduction

According to the Health Canada product monograph, dinutuximab binds to cell surface GD2 and induces cell lysis of GD2-expressing cells through antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC).

Dinutuximab is indicated, in combination with granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-2 (IL-2), and 13 cis-retinoic acid (RA), for the treatment of high-risk neuroblastoma in pediatric patients who achieve at least a partial response to prior first-line multi-agent, multimodality therapy.[1] The Notice of Compliance was received on November 28, 2018. The reimbursement request is consistent with the Health Canada approved indication.

As noted in the Serious Warnings and Precautions of the dinutuximab Health Canada Product Monograph, serious and potentially life-threatening infusion reactions occurred in 26% of patients treated with dinutuximab and dinutuximab causes severe neuropathic pain.[1]

The recommended dose of dinutuximab is 17.5 mg/m^2/day administered as an intravenous infusion over 10 to 20 hours for 4 consecutive days for a maximum of 5 cycles (note of, for the RA component, patients also receive RA each cycle, and for a sixth cycle as monotherapy). According to the Health Canada Product Monograph, dinutuximab is to be initiated at an infusion rate of 0.875 mg/m2/hour for 30 minute; the infusion rate can be gradually increased as tolerated to a maximum rate of 1.75 mg/m^2/hour. [1]

The objective of this review is to evaluate the clinical efficacy and safety of dinutuximab (Unituxin) in combination with GM-CSF, IL-2, and RA against appropriate comparators for the treatment of pediatric patients with high-risk neuroblastoma who achieve at least a partial response to prior first-line multi-agent, multimodal therapy.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence [2]

One randomized controlled trial (RCT) was included in the systematic review, Study DIV-NB-301 (N = 226; referred to here as "Study 301").[2,3] Study 301 was a phase III, parallel-group, open-label RCT conducted by the Children's Oncology Group (COG). The objective of this study was to determine whether dinutuximab immunotherapy (dinutuximab, GM-CSF, and IL-2) with RA improved event-free survival (EFS) after myeloablative therapy and autologous stem cell therapy (ASCT) compared with RA alone in patients with high-risk neuroblastoma who achieved a pre-ASCT tumour response of complete response, very good partial response, or partial response.

Patients at 90 centres in the US, Canada, and Australia were randomized in a 1:1 ratio to dinutuximab immunotherapy with RA or RA alone. High-risk neuroblastoma was defined using the COG system[4] and tumour response to previous induction therapy at pre-ASCT evaluation was defined using the International Neuroblastoma Response Criteria (INRC).[5] Patients could not have progressive disease and had to have completed induction therapy, ASCT, and radiotherapy with study enrolment between day 50 and day 100 after final ASCT. Patient also had a Lansky or Karnofsky Performance Scale score of at least 50% and life expectancy of at least two months. Patients with biopsy-proven residual disease following ASCT could enrol in the study, but were non-randomly assigned to receive dinutuximab immunotherapy with RA and included in the safety population only.

Both treatment arms consisted of six consecutive 4-week treatment cycles. Each therapy was administered as follows:

- Dinutuximab i.v. over 5.75 to 20 hours at 25 mg/m^2 body surface area (BSA)/day for 4 consecutive days during cycles 1 to 5
- GM-CSF s.c. (preferred) or i.v. over two hours at 250 µg/m^2 BSA /day for 14 days starting 3 days before dinutuximab was started in cycles 1, 3, and 5
- IL-2 i.v. continuously at 3.0 × 10^6 international units (IU) / m^2 BSA /day for 4 days (96 hours) during week 1 and 4.5 × 10^6 IU/m^2/day for 4 days during week 2 in cycles 2 and 4
- RA p.o. 160 mg/ m^2 BSA /day (or 5.33 mg/kg/day divided twice daily for patients weighing 12 kg or less) during the last 2 weeks of cycles 1 to 6

Patients were required to discontinue dinutuximab treatment if they experienced dose limiting toxicities, used corticosteroids (unless required for a life-threatening condition), had recurrent or progressive disease, or used other anti-cancer agents.

The primary efficacy end point, EFS, was defined as the time from enrolment to the first occurrence of relapse, progressive disease, secondary malignancy, death, or date of last contact (if no event occurred). The definition of progressive disease used for the determination of EFS was the same as the one used in determining pre-ASCT response, with the addition of cases with an increase from 10% or less tumour in marrow to over 10%. Tumours were assessed with imaging and bone marrow biopsy prior to the start of study treatment and within two weeks following the last dose of RA in cycle 6. Imaging assessments were also performed every three months after the end of treatment for one year and subsequently every six months for another two years. Bone marrow biopsy was also collected three months after end of treatment and at relapse. Assessments performed as part of the standard of care regimen were also recorded.

Overall survival (OS) was defined as the time from study enrolment to death or time of last contact in the absence of death. Adverse events (AEs) of Grade 3 or higher were to be reported from the start of study treatment to 30 days following the last dose of study treatment.

Randomization was halted on January 13, 2009 as it was judged that the early stopping criteria for EFS had been met. All randomized patients enrolled up to this date were included in the intention-to-treat (ITT) analysis set. The results from the January 13, 2009 dataset were published[3] and used for the main analysis of the primary end point. Due to corruption of that dataset, the closest dataset available (June 30, 2009) was used for confirmatory analyses. Follow-up analyses were conducted with data cut-offs of June 30, 2012 and July 1, 2016.

The difference in EFS distributions between the treatment groups was to be tested with a two-sided log-rank test at a significance level of 0.05. The planned sample size was based on the assumption of a 3-year EFS of 50% in the RA alone group and 65% in the immunotherapy with RA group and a loss of 10% of patients to follow-up.

In the ITT population, most patients were male (range of 56.6% to 62.8%), white (79.6% to 84.1%), at least two years old (83.2% to 85.8%), had INSS stage 4 neuroblastoma (78.8% to 81.4%), had unfavourable tumour histological features (60.2% to 71.7%), and had received one previous ASCT (90% to 95%). MYCN status was amplified in 31.9% to 39.8%, tumour ploidy was hyperdiploid in 42.5% to 43.4%, and stem cell infusions were purged in at least one ASCT in 24.8% to 25.7% of patients. Response to induction therapy before ASCT was categorized as complete response in 33.6% to 35.4%, very good partial response in 41.6% to 43.4%, and partial response in 23.0%.

The following limitations of the RCT should be taken into account when interpreting the results:

- The study was open-label due to the complexity of the interventions. There was no risk of assessment bias for OS since it is an objective measure. Definitions of events and time points for follow-up assessments of disease status were pre-specified such that there was low risk of bias in EFS assessment.
- Imbalances in MYCN status, DNA ploidy, and tumour histology are likely to have favoured dinutuximab and the planned analysis did not adjust for any prognostic factors. However, post hoc EFS analyses performed for regulatory reviews[2,6] adjusting for prognostic factors confirmed the primary analysis.
- The study ended before the efficacy stopping criteria were met. The confirmatory EFS analysis in the June 30, 2009 dataset was less favourable than the January 13, 2009 analysis, though still statistically significant. There were also two separate amendments to the early stopping criteria for efficacy. Given the less than ideal circumstances surrounding the primary end point analysis, the follow-up analyses and the OS analyses are important for confirming the results of the primary analysis.
- Statistical testing and sample size calculations were based solely on EFS. There was no control for multiplicity of outcomes.
- Since dinutuximab was administered with IL-2 and GM-CSF and these two therapies were not included in the control arm, the results can only inform the efficacy and safety of the combination of dinutuximab, IL-2, and GM-CSF.
- Patients with residual disease following ASCT were not randomized and were all assigned to immunotherapy. Efficacy of dinutuximab in this group was not formally compared against a control arm.

Results for key efficacy and harms outcomes are summarized in Table 1.

Event-Free Survival[2]

Superiority of dinutuximab immunotherapy with RA over RA alone was demonstrated in the primary end point analysis in the January 13, 2009 data set and in the confirmatory analysis in the June 30, 2009 data set (Table 1). Analyses performed following the January 13, 2009 analysis are descriptive as the efficacy stopping criteria were considered to have been met at the 2009 cut-off. Follow-up analyses demonstrated a continued trend of improved EFS with the addition of dinutuximab therapy, though the between-group differences in EFS tended to decrease over time. This suggests that the effect of dinutuximab on EFS may not have been maintained at longer follow-up times. Post hoc analyses adjusting for prognostic factors yielded results consistent with the primary EFS analysis.

In the non-randomized group with residual disease, 2-year EFS was 32.3% (95% CI, 11.4% to 53.2%) in the June 30, 2009 data set (N = 25), 3-year EFS was 33.3% (95% CI, 15.6% to 51.1%) in the June 30, 2012 data set (N = 27), and 5-year EFS was 32.0% (standard error of 10.0%) in the July 1, 2016 data set (N = 25).

Overall Survival[2]

OS was greater in the dinutuximab group compared with the RA alone group in the January 13, 2009 data set (Table 1), though there was no adjustment for multiple outcomes. The results from the follow-up analyses strongly suggested that the OS benefit with dinutuximab was maintained over time. Post hoc analyses in the June 30, 2009 data set adjusting for prognostic factors yielded results consistent with the unadjusted analysis.

While OS was not a pre-specified outcome for the non-randomized group with residual disease, an OS estimate was provided for this group at the July 1, 2016 cut-off (5-year OS of 51.4% with a standard error of 10.4%).

Adverse Events[2]

AEs reported in at least 10% of patients in both treatment groups were as follows: lymphocyte count decreased, platelet count decreased, anemia, neutrophil count decreased, and device related infection (ranging from 17.0% to 56.0% in the dinutuximab group and ranging from 11.0% to 23.9% in the RA alone group). All other AEs occurred in no more than 8.3% of patients in the RA alone group. In addition, the following AEs occurred in at least 20% of patients in the dinutuximab group: pyrexia, hypokalemia, pain, abdominal pain, white blood cell count decreased, anaphylactic reaction, hyponatremia, alanine aminotransferase increased, and capillary leak syndrome (ranging from 22.0% to 40.4% of patients).

The only SAE occurring in more than one patient in the RA alone group was catheter related infection (1.8%). The most common SAEs in the dinutuximab group were catheter related infection, hypotension, anaphylaxis, hypokalemia, fever, and capillary leak syndrome, which occurred in 6.4% to 8.5% of patients.

AEs related to infusion reaction and capillary leak syndrome occurred almost exclusively in the dinutuximab group and were as follows: anaphylactic reaction (26.2% versus 0.9%), capillary leak syndrome (22.0% versus none), hypotension (19.9% versus none), serum sickness (0.7% versus 0.9%), and cytokine release syndrome (0.7% versus none). SAEs related to infusion reaction or capillary leak syndrome occurred in the dinutuximab group alone: hypotension (8.5%), anaphylaxis (7.8%), capillary leak syndrome (6.4%), allergic reaction (1.4%), cytokine release syndrome (1.4%), and bronchospasm (0.7%).

The most common pain-related AEs were pain (28.4% in the dinutuximab group versus 2.8% in the RA alone group), abdominal pain (29.8% versus none), pain in extremity (8.5% versus 1.8%), back pain (7.1% versus none), and neuralgia (6.4% versus none). Pain-related SAEs occurred exclusively in the dinutuximab group, the most common being pain (3.5%), abdominal pain (2.8%), arthralgia (2.1%), and pain in extremity (2.1%). AEs and SAEs potentially related to neurotoxicity occurred in 2.1% or less in each group.

Table 1: Highlights of Key Outcomes in Study 301

Efficacy outcomes in the ITT set	RA alone	Immunotherapy + RA
Primary		
EFS primary analysis (January 13, 2009 cut-off)	N = 113	N = 113
Number of events	49 (43.4)	33 (29.2)
2-year EFS, % (95% CI)	46.4 (35.8, 57.1)	66.3 (56.2, 76.3)
HR, immunotherapy+ RA vs. RA alone (95% CI)	0.57 (0.37, 0.89)	
P value for log-rank test	0.0115	
EFS (June 30, 2012 cut-off)	N = 114	N = 114
Number of events, n (%)	58 (50.9)	49 (43.0)
3-year EFS, % (95% CI)	50.9 (41.6, 60.2)	62.8 (53.9, 71.7)
HR, immunotherapy+ RA vs. RA alone (95% CI)	0.73 (0.5, 1.06)	
P value for log-rank test	0.0990	
EFS (July 1, 2016 cut-off)	N = 110	N = 113
5-year EFS, % (SE)	46.1 (5.2)	56.3 (4.7)
P value for log-rank test	0.1136	
Secondary		
OS (January 13, 2009 cut-off)	N = 113	N = 113
Number of events, n (%)	27 (23.9)	16 (14.2)
2-year OS % (95% CI)	74.5 (65.2, 83.9)	86.2 (78.8, 93.6)
HR, immunotherapy+ RA vs. RA alone (95% CI)	0.52 (0.30, 0.92)	
P value for log-rank test	0.0223	
OS (June 30, 2012 cut-off)	N = 114	N = 114
Number of events, n (%)	48 (42.1)[a]	31 (27.2)[a]
3-year OS % (95% CI)	67.3 (58.5, 76.1)	79.5 (72.1, 87.0)
HR, immunotherapy+RA vs. RA alone (95% CI)	0.57 (0.36, 0.92)[a]	
P value for log-rank test	0.0165	
OS (July 1, 2016 cut-off)	N = 110	N = 113
5-year OS % (SE)	56.4 (5.2)	73.2 (4.2)
P value for log-rank test	0.0543	
Harms outcomes in the safety set June 30, 2012 cut-off	**RA alone N = 109**	**Immunotherapy + RA N = 141**
Patients with ≥ 1 AE of grade 3 or higher, n (%)	70 (64.2)	136 (96.5)
Patients with ≥ 1 SAE, n (%)	4 (3.7)	72 (51.1)
Treatment discontinuations due to toxicity, n (%)	0	6 (4.3)
Deaths, n (%)	43 (39.4)	39 (28.5)
Disease-related	39 (35.8)	35 (24.8)
Infection	0	1 (0.7)
Multi-organ failure	2 (1.8)	1 (0.7)
Cytokine release syndrome due to IL-2 overdose	0	1 (0.7)
Hypoxia of unknown origin	0	1 (0.7)
Unspecified	2 (1.8)	0

Source: pCODR submission.[2]
Abbreviations: AE = adverse event; CI = confidence interval; EFS = event-free survival; HR = hazard ratio; ITT = intention-to-treat; NA = not applicable; NR = not reported; OS = overall survival; RA = 13 cis-retinoic acid; SAE = serious adverse event; SE = standard error.
Note: Hazard ratios are from unstratified Cox proportional hazards regression.

[a]These values are consistent with the original analysis of OS from the June 2012 data cut-off in which seven patients were erroneously censored at time of death. Updated values for the corrected analysis were not available, but are expected to be nearly identical to the original value.

1.2.2 Additional Evidence

See Section 3, Section 4, and Section 5 for a complete summary of patient advocacy group input, Provincial Advisory Group (PAG) Input, and Registered Clinician Input, respectively.

Patient Advocacy Group Input

A single joint submission was prepared by: Advocacy for Canadian Childhood Oncology Research Network (Ac2orn), Canadian Organization for Rare Disorders (CORD), and Ontario Parents Advocating for Children with Cancer (OPACC). See Section 3 for more information.

Provincial Advisory Group (PAG) Input

Input was obtained from all nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. See Section 4 for more information.

Registered Clinician Input

Four clinician input submissions were received, representing a total of thirteen clinicians: eleven practising oncologists or physicians who treat cancer patients, one nurse practitioner, and one oncology pharmacist

See section 5 for more information.

Summary of Supplemental Questions

There were no supplemental questions identified for this review.

Comparison with Other Literature

The pCODR Clinical Guidance Panel and the pCODR Methods Team did not identify other relevant literature providing supporting information for this review.

1.2.3 Factors Related to Generalizability of the Evidence

Table 2 addresses the generalizability of the evidence and an assessment of the limitations and sources of bias can be found in Sections 6.

Table 2: Assessment of generalizability of evidence for dinutuximab for neuroblastoma

Domain	Factor	Evidence from Study 301	Generalizability Question	CGP Assessment of Generalizability
Population	Relapsed/refractory neuroblastoma	PAG is seeking guidance on whether trial results are generalizable to patients in the relapsed/refractory neuroblastoma setting. Patients with relapsed/refracto	Can the trial results be generalized to patients with relapsed/refractory neuroblastoma?	The clinical trial evidence from the original submission (Study 301) addresses only the use of dinutuximab in the front-up setting for high-risk neuroblastoma and is not therefore generalizable to the relapsed/refractory setting.

Domain	Factor	Evidence from Study 301	Generalizability Question	CGP Assessment of Generalizability
		ry neuroblastoma were not included in Study 301		
	Definition of high-risk neuroblastoma	PAG is seeking clarity on whether dinutuximab would be limited to patients with high risk neuroblastoma. PAG is also seeking guidance on the definition of high risk as this would be an enabler to implementation. The 2007 COG criteria[4] were used to define high-risk neuroblastoma in Study 301.	Can the trial results be generalized to patients that fall outside of the 2007 COG criteria for the definition of high-risk neuroblastoma? Can the trial results be generalized to patients with non-high-risk neuroblastoma? Does the use of the 2007 COG criteria for the definition of high-risk neuroblastoma limit the interpretation of the trial results with respect to the target population?	The following were considered criteria for high-risk neuroblastoma in context of Study 301: 1. Metastatic disease in patients aged ≥547 days 2. All patients with *MYCN*-amplified tumours (except for those with INSS stage 1) 3. Metastatic disease in patients aged 365-547 days with unfavourable biological characteristics (e.g. histology, ploidy) 4. Localised disease in patients aged ≥547 days with unfavourable histology Broadly, the same criteria continue to be used in the current clinical management of neuroblastoma. There have been some changes in details, such as the move away from the INSS staging system towards INRGSS, although the principles remain the same. For patients aged 365-547 days with non-*MYCN*-amplified metastatic disease, consideration of unfavourable biological characteristics is likely now to take into account presence of segmental chromosomal abnormalities as well as other characteristics list in 2007 COG criteria. In practical terms, the decision about whether to treat a patient as high-risk

Domain	Factor	Evidence from Study 301	Generalizability Question	CGP Assessment of Generalizability
				is made early in treatment and is independent of a decision as to whether or not to administer dinutuximab-based immunotherapy. In practice, regardless of the precise definition of high-risk neuroblastoma (which may change slightly over time), those patients for whom dinutuximab should be considered are those treated as high-risk; i.e. with induction chemotherapy, consideration of surgical resection and high-dose chemotherapy with autologous stem-cell rescue (+/- radiotherapy) prior to immunotherapy. As acknowledged within Study 301 inclusion criteria, the other relevant patient population is those patients initially diagnosed as non-high-risk who later progressed or relapsed to high-risk neuroblastoma. These patients should be considered suitable for dinutuximab. Of note (with the above exception) there is currently no role for dinutuximab in the non-high-risk neuroblastoma population.
	Previous therapy	Patients in Study 301 had to complete induction therapy with one of several COG protocols, ASCT, and radiotherapy prior to randomization.	Do the requirements for previous therapy limit the interpretation of the trial results with respect to the target population?	Patients should have completed (at a minimum) induction chemotherapy and high-dose chemotherapy with autologous stem cell rescue (ASCT). In some patients (such as young infants) it may be preferable to defer radiotherapy until after the

Domain	Factor	Evidence from Study 301	Generalizability Question	CGP Assessment of Generalizability
		ASCT had to be performed within 9 months of initiation of induction therapy. Enrolment occurred between day 50 and day 100 after final ASCT, when combined neutrophils and monocytes ≥ 1000/μL and ≥ 7 days post-radiotherapy.		completion of immunotherapy and this would be a reasonable approach. In terms of the timing of initiation of immunotherapy following completion of ASCT, there are no data to support a particular cut-off. Patients should have achieved count recovery and in most cases will have completed radiotherapy. It would be reasonable to assume that consolidation with immunotherapy would be of benefit to patients even if initiated beyond the 100-day window mandated in Study 301 and a specific time-frame is probably not required in terms of clinical implementation of dinutuximab. In practice, clinicians will aim to move ahead with all components of therapy as quickly as possible, albeit accommodating individual patient toxicities, etc. In most cases, disease re-evaluation would be undertaken prior to initiating immunotherapy in order to detect patients with progressive disease (who would not then proceed to standard immunotherapy, but who might instead be considered for combined chemotherapy/immunotherapy as detailed above).
	Definition of tumour response to previous therapy	Tumour response for the eligibility criteria were based on the INRC from 1993.[5]	Does the eligibility criterion of partial response or better to	Patients were required to have at least a PR following induction chemotherapy/surgery. Per INRC criteria at the time

Domain	Factor	Evidence from Study 301	Generalizability Question	CGP Assessment of Generalizability
		The INRC were most recently revised in 2017[7] and the criteria for partial response or better are now different.	previous therapy based on the 1993 INRC limit the interpretation of the trial results with respect to the target population?	(Brodeur 1993), PR requires decrease in primary tumour size by >50%, reduction in metastatic disease by >50% and no more than 1 positive bone marrow site. The protocol also specified additional criteria in terms of requiring ≤10% tumor seen on any bone marrow specimen. The recently revised INRC criteria (Park 2017) are broadly similar in terms of defining PR, but with a ≥30% decrease in longest diameter of primary site and stable, improved or resolved MIBG or FDG-PET uptake at primary. Similarly, in terms of metastatic soft tissue lesions, a ≥30% decrease in sum of diameters or ≥50% reduction in MIBG or FDG-PET bone score is required for PR. Bone marrow requirement is required to have at least minimal disease (MD). Ultimately, the details of these differences are unlikely to have a significant practical impact since in reality, disease response to induction chemotherapy will be assessed in order to make a decision about proceeding (or otherwise) to high-dose chemotherapy and autologous stem cell rescue (ASCT). Of note, in the current COG high-risk neuroblastoma study (ANBL1531), patients are permitted to proceed to ASCT provided they have at least stable disease following induction/surgery. Patients will subsequently be eligible for immunotherapy

Domain	Factor	Evidence from Study 301	Generalizability Question	CGP Assessment of Generalizability
				consolidation provided there is no evidence of progressive disease on complete disease re-evaluation post-ASCT and prior to immunotherapy. In practice, therefore, immunotherapy would be considered standard of care for high-risk neuroblastoma patients who have a sufficient response that they are able to proceed to ASCT (based on either clinical trial or local practice criteria) and who have no evidence of progressive disease when reassessed prior to immunotherapy.
	Biopsy-proven residual disease	Patients with biopsy-proven residual disease following ASCT were included in the safety analyses and excluded from the efficacy comparison.	Does the exclusion of patients with residual disease following ASCT limit the interpretation of the trial efficacy results with respect to the target population?	The consort diagram for Study 301 shows that of 252 patients assessed for eligibility, 25 (10%) were non-randomly assigned to immunotherapy on the basis that they had evidence of (biopsy-proven) persistent residual disease following ASCT. These patients have an inferior outcome to compared to the randomised cohort. Although the benefit of dinutuximab-based immunotherapy has not been specifically demonstrated in this group, given their poorer prognosis and the benefit of immunotherapy in the randomised group, it would be unreasonable to exclude this population from treatment with dinutuximab. However, immunotherapy consolidation would not be appropriate for patients with evidence of

Domain	Factor	Evidence from Study 301	Generalizability Question	CGP Assessment of Generalizability
				progressive (as distinct from residual) disease.
	Neuroblastoma initially diagnosed as non-high-risk and later converted to high-risk neuroblastoma	Patients initially diagnosed with non-high-risk neuroblastoma were not eligible for Study 301.	Does the exclusion of patients initially diagnosed with non-high-risk neuroblastoma limit the interpretation of the trial results with respect to the target population?	As outlined above, patients who initially have non-high-risk neuroblastoma that then progress or relapse to have high-risk disease should then be considered eligible for dinutuximab-based immunotherapy as part of their overall management.
	Patent age	Patients up to the age of 31 years were eligible for Study 301. However, the Health Canada approval and pCODR submission reference 'paediatic patients'	Is there an upper age limit for which dinutuximab can be recommended?	Neuroblastoma is typically a cancer of young children and disease in adults is exceedingly rare. Given the mechanism of action of dinutuximab it is reasonable to assume that efficacy does not depend on patient age, and therefore dinutuximab-based immunotherapy should also be available for these very rare adult patients with high-risk neuroblastoma who are treated according to paediatric protocols. Given the very small number of such patients globally it will never be feasible to obtain definitive data in this subpopulation.
Outcomes	Definition of progressive disease for event-free survival	Progressive disease as an event was defined using the INRC from 1993.[5] The revised INRC from Park et al. 2017[7] use different criteria to define	Is the definition of event-free survival in Study 301 similar to what would be commonly considered to be event-free survival in	Progressive disease (PD) as per INRC from 1993 was defined as any new lesion; increase of any measurable lesion by >25%; or previous negative bone marrow positive for tumour. In the 2017 revision (Park 2017), PD was defined as a >20% increase in longest diameter (and at least 5mm increase) of soft tissue

Domain	Factor	Evidence from Study 301	Generalizability Question	CGP Assessment of Generalizability
		progressive disease.	Canadian clinical practice?	lesions; any new lesion or >20% increase in sum of diameters of metastatic soft tissue disease or relative MIBG score ≥1.2; or previous negative bone marrow positive for tumour, or >2x increase and >20% tumour infiltration in marrow. In clinical practice, these changes are unlikely to have a significant impact on event-free survival since the changes in definitions are relatively subtle and in the majority of cases, relapse or progressive disease is clearly apparent.

Abbreviations: ASCT = autologous stem cell transplantation; COG = Children's Oncology Group; GM-CSF = granulocyte macrophage colony stimulating factor; IL-2 = interleukin 2; INRC = International Neuroblastoma Response Criteria; RA = retinoic acid.

1.2.4 Interpretation

Burden of Illness

Despite its relative rarity compared to adult cancers, cancer in children is a significant cause of morbidity and mortality. Neuroblastoma is one of the most common types of childhood solid tumour and disproportionately affects young children and infants. Approximately half of patients have high-risk disease at presentation and have a poor overall survival rate despite very intensive multi-modal therapy including chemotherapy, surgery, high-dose chemotherapy with autologous stem cell rescue (also called autologous stem cell transplant, ASCT), radiotherapy and differentiation therapy with isotretinoin (also called cis-retinoic acid). Given the poor prognosis, there is therefore a clear need for additional therapeutic options in order to achieve better disease control and reduce the risk of relapse. Since 2010, and the release of the promising results of the randomised Children's Oncology Group study, [3] upfront therapy in Canada for high-risk neuroblastoma has included dinutuximab-based immunotherapy as part of standard of care.

Current Practice Patterns in Canada and Clinical Need

In Canada, children with suspected cancer are typically referred to a limited number of specialist paediatric centres for further work-up, diagnosis and treatment. Initial treatment approaches are according to established standards of care or, when available, via participation in an upfront clinical trial. For neuroblastoma, the definitions of high-risk

disease are well-established and there is near universal consensus within the US and Canada about the standard treatment approach for newly-diagnosed patients. As outlined above, this would include induction multi-agent chemotherapy, surgical resection of the primary tumour, high-dose chemotherapy with autologous stem cell rescue (as either a single or tandem procedure), external beam radiotherapy and combination immunotherapy with dinutuximab, IL-2 and GM-CSF, together with isotretinoin. Disease response is assessed sequentially during therapy and the minority of patients who progress, fail to respond or relapse while on treatment would be directed to alternative treatment approaches at that point.

There are approximately 70 new cases of neuroblastoma annually in Canada, [8] of which 35-40 would be expected to have high-risk disease. Consequently, 25-35 patients might be expected to receive dinutuximab-based immunotherapy as part of upfront treatment each year. Given the poor overall prognosis, there is a clear need for effective treatment options to be incorporated into upfront therapy.

Efficacy

The best evidence for the clinical efficacy of dinutuximab comes from a single randomised phase III trial undertaken by the Children's Oncology Group. This study compared a combination immunotherapy approach (dinutuximab, IL-2 and GM-CSF, together with isotretinoin) against the pre-existing standard of care (isotretinoin alone) following standard upfront therapy. The primary efficacy endpoint was an intention-to-treat analysis of event-free survival in the two treatment groups. Initial results (data cut-off 13 January 2009) were published in 2010[3]) at which time there was a significant improvement in 2-year EFS in the immunotherapy arm compared to standard (66.3% vs 46.4%, p=0.0115). Overall survival at 2-years was also significantly better in the immunotherapy arm (86.2% vs 74.5%, p=0.0223).

In view of evidence of clinical benefit for immunotherapy, randomisation was stopped early and thus randomised data are available from a total of 226 patients (compared to originally anticipated enrollment of 386). This may have an impact on the statistical power of this randomised cohort to demonstrate improved survival outcomes at later timepoints. Most recent survival data (1 July 2016, unpublished) suggest that the difference in EFS is no longer statistically significant (5-yr EFS 56.3% vs 46.1%, p=0.1136), while benefit in terms of OS may be maintained (5-yr OS 73.2% vs 56.4%, p=0.0543). Thus, it is possible that the clinical benefit of dinutuximab-based immunotherapy is in delaying early recurrence rather than contributing to additional long-term cure. Nevertheless, even if this were the only therapeutic benefit, it would still be of significant clinical importance to the patient population given the additional period of remission and avoidance of/delay to the need for toxic relapse therapies.

Of note (and as highlighted in Table 2 assessment of generalizability), the population selected for the randomised study was representative of, but not entirely inclusive of all, patients with high-risk neuroblastoma. Specifically, patients with residual disease following ASCT were assigned to immunotherapy and therefore formal demonstration of an improvement in outcomes with immunotherapy is not available in this cohort. Similarly, there were protocol-specific criteria in terms of the definition of tumour response to previous therapy and timing from completion of ASCT to initiation of immunotherapy that may not be met in the clinical practice setting. Nevertheless, despite these limitations,

the Clinical Guidance Panel believes that it is reasonable to generalize the results to include all patients with high-risk neuroblastoma who successfully complete ASCT and whose post-ASCT/pre-immunotherapy disease re-evaluation shows no evidence of disease progression.

Finally, since the randomised comparison was between combination immunotherapy (dinutuximab, IL-2 and GM-CSF, plus isotretinoin) versus isotretinoin alone, it is not possible to separate out the potential benefit (or otherwise) of each of these components and consequently dinutuximab can only be recommended when the intention is to administer in combination with IL-2 and GM-CSF cytokines (acknowledging that in some instances it may not be possible to continue to administer these cytokines due to toxicity). It is of concern that GM-CSF does not have marketing approval in Canada and thus is currently only available via Health Canada Special Access Program.

In terms of treatment-related quality of life, these data were not collected in the randomised study and therefore it is difficult to provide detailed comments. Dinutuximab-based immunotherapy clearly has the potential for significant acute toxicities, although many of these (especially pain) can be ameliorated by careful supportive care. Of note, with regards patient input to this appraisal half of survey respondents strongly agreed or agreed that dinutuximab improved quality of life while the other half were neutral. Ultimately, achieving a better overall outcome and sustained remission from high-risk neuroblastoma is of critical importance to quality of life and the toxicities of this therapy need to be seen in the context of a very intensive and lengthy overall treatment schedule.

Harms, Safety and Tolerability

The toxicities of dinutuximab (and associated cytokines) are significant and the therapy can only be safely administered in an experienced centre with an appropriately trained medical and nursing team. Management of expected neuropathic pain is a vital consideration and often requires the involvement of hospital acute pain/anaesthetic services given the high doses of opiate analgesia required. Treating teams also need to be conversant with management of acute toxicities such as capillary leak, hypotension and respiratory distress. Availability of paediatric intensive care facilities is an important consideration in the rare circumstances in which this is required for management of immunotherapy-related toxicities.

Despite these acute toxicities, dinutuximab-based immunotherapy has been used as part of standard of care for many years and consequently treating teams are already familiar with the management of side effects. With appropriate supportive care (such as pre-emptive use of opioid analgesia) these toxicities can be managed and, in many cases, controlled. Consequently, it is felt that the overall clinical benefit outweighs the justified concerns about toxicity and tolerability.

1.3 Conclusions

The Clinical Guidance Panel concluded that there is a net overall clinical benefit with the use of dinutuximab as part of the first-line treatment of patients with high-risk neuroblastoma. This conclusion is based on the evidence of the randomised Children's Oncology Group study (referred to as "Study 301" in this document) that demonstrated a statistically significant and clinically meaningful improvement in 2-year EFS and OS. It is also clear from patient advocacy group and registered clinician input that the use of dinutuximab in the treatment of high-risk neuroblastoma is fully supported by these groups and recognised as standard of care. Ongoing access to dinutuximab for this patient population is clearly of great concern.

The panel notes that the application specifically relates to the 'treatment of pediatric patients with high-risk neuroblastoma who achieve at least a partial response to prior first-line multi-agent, multimodal therapy'. As detailed in the generalizability table, the panel recommends that careful consideration is given to reimbursement criteria so that patients who could potentially benefit from dinutuximab are not arbitrarily excluded. Specifically, the panel concludes that it would reasonable to provide reimbursement for dinutuximab for the treatment of patients [regardless of age] with high-risk neuroblastoma who have completed treatment with induction chemotherapy and high-dose chemotherapy (excluding those with progressive disease) [i.e. not explicitly requiring a partial response].

The Clinical Guidance Panel notes that:

- Comparisons of EFS and OS at longer follow-up times beyond 2-years are of uncertain statistical significance, but the study was designed with a primary endpoint of early EFS and randomisation was stopped early due to evidence of benefit such that the total number of randomised patients for whom data are available is limited. The longer-term potential benefits of dinutuximab are therefore uncertain; nevertheless, given the context of a disease with poor prognosis, even an improvement in shorter term outcomes alone is of significant clinical value.
- The evidence for the use of dinutuximab only relates to its use in combination with the cytokines IL-2 and GM-CSF (plus retinoic acid administered between immunotherapy cycles). Consequently, it is not possible to determine the relative contributions of these individual agents to the clinical benefit. Since GM-CSF does not have marketing approval in Canada, continued access to GM-CSF via Health Canada Special Access Program (SAP) is an important consideration for the future use of dinutuximab in clinical practice.
- Administration of dinutuximab-based immunotherapy is associated with significant acute toxicity (particularly infusion reactions and severe neuropathic pain). Nevertheless, the CGP considers that the clinical benefit outweighs these risks and notes that since dinutuximab-based immunotherapy has already been part of standard of care for treatment of patients with high-risk neuroblastoma for several years, centres administering this therapy are already well-experienced in management of toxicities and methods to ameliorate immunotherapy-associated symptoms.
- At present, there are no data to support the use of additional treatment options following completion of treatment with dinutuximab-based immunotherapy in this setting.

Finally, the CGP recognises that dinutuximab is increasingly used in the setting of relapsed/refractory high-risk neuroblastoma. However, the scope of the requested reimbursement criteria and consequently of the CGP review do not permit the panel to provide a formal recommendation on the use of dinutuximab in this setting. The panel, however, notes the encouraging data for dinutuximab in combination with temozolomide/irinotecan in the relapsed/refractory setting[9,10] and, furthermore that this strategy has become one of the standard approaches to managing relapsed/refractory disease both in Canada and the US. The panel therefore strongly encourages the relevant stakeholders to consider ways to ensure that access to dinutuximab in the setting of relapsed/refractory disease is maintained so that Canadian patients are not disadvantaged.

2 BACKGROUND CLINICAL INFORMATION

This section was prepared by the pCODR Neurological Clinical Guidance Panel. It is not based on a systematic review of the relevant literature.

2.1 Description of the Condition

While rare overall, cancer in children has a disproportionate impact and represents the most common cause of disease-related mortality among Canadian children. Neuroblastoma is the most common extra-cranial solid tumour in childhood with an estimated 71 new cases annually in Canada. [8] Neuroblastoma is a malignancy with remarkably diverse clinical behaviour and although patients with low- or intermediate- risk disease generally have a good outcome with minimal chemotherapy, surgery alone or observation, those with high-risk disease (which represents approximately half of newly diagnosed patients) have a poor overall survival rate (5-year OS approximately 50%) despite intensive multi-modal therapy. [4 11]

The clinical heterogeneity of neuroblastoma means that upfront risk stratification is critical to guiding therapy. Contemporary risk stratification incorporates age at diagnosis, disease stage, and tumour characteristics such as presence or absence of *MYCN* gene amplification, histology, ploidy and presence of segmental chromosomal aberrations to determine risk group. The initial risk stratification was published using data from the International Neuroblastoma Risk Group (INRG) consortium which compiled data from multiple international cooperative groups. [12] Since then the risk stratification has been adapted by individual cooperative groups to meet the needs of their respective clinical trials and some differences between cooperative groups have arisen. The initial INRG risk stratification incorporated the International Neuroblastoma Staging System (INSS) [13 5] which was reliant on surgical intervention. This has subsequently been replaced by the imaging-based INRG Staging System (INRGSS). [14] Overall, there is consensus that patients aged ≥18 months at diagnosis with metastatic disease and those with *MYCN*-amplified disease (with the exception of very rare completely resected INSS stage 1 or INRGSS stage L1) should be treated as high-risk. In addition, there are other groups that are generally considered to have high-risk disease, but for whom a decision of risk-stratification and hence therapy may need to be made on an individual patient basis. These include: 1) patients with metastatic disease aged 12-18 months at diagnosis and without *MYCN*-amplification, who are generally considered to have high-risk disease unless their tumour has completely favourable biological characteristics (i.e. favourable histology as determined by International Neuroblastoma Pathology Classification[15] and absence of segmental chromosomal abnormalities); and 2) patients aged ≥18 months at diagnosis with L2, non-*MYCN*-amplified disease with unfavourable histology, who are also usually treated as high-risk according to protocols used in North America. In addition, patients who are initially characterised as having low- or intermediate-risk disease whose disease then progresses or relapses to become high-risk should also be treated as having high-risk disease.

2.2 Accepted Clinical Practice

Since the current 5-year overall survival for high-risk neuroblastoma is only ~50%,[11] there is considerable ongoing research effort to improve outcomes. For most patients in Canada enrolment on the currently open phase III clinical trial of the Children's Oncology Group (COG) or treatment according to the results of the most recent COG trial would be considered standard of care. Broadly, for high-risk neuroblastoma, treatment comprises five sequential components: 1) multi-agent induction chemotherapy, usually given as 5 cycles including cyclophosphamide, topotecan, cisplatin, etoposide, doxorubicin and vincristine; 2) surgical resection of the primary tumour; 3) high-dose chemotherapy with autologous stem cell rescue (ASCT); 4) external beam radiotherapy to the primary tumour site; and 5) immunotherapy with dinutuximab, GM-CSF, IL-2 and cis-retinoic acid. Following the publication of the results of COG ANBL0032[16] demonstrating the benefit of combination immunotherapy with dinutuximab, its use has become a standard part of upfront therapy for neuroblastoma in most of North America (the only exception being Memorial Sloan Kettering Cancer Center that has developed, and routinely uses, a different GD2-directed monoclonal antibody therapy). Recent results from COG

ANBL0532[17] have demonstrated an advantage of tandem over single high-dose chemotherapy (also called 'myeloablative therapy' or ASCT) and therefore, at least for patients with metastatic high-risk disease, this has also now been incorporated as standard-of-care.

Of note, since the randomised evidence for the benefit of dinutuximab relates to its use in combination with GM-CSF and IL-2, the use of these cytokines would also be considered standard-of-care. Access to GM-CSF (sargramostim) is complex for patients in Canada since it does not have marketing approval from Health Canada and at present requires an application to the Special Access Program for each individual patient. It is not certain from available evidence the extent to which GM-CSF and IL-2 cytokines contribute to the effectiveness of dinutuximab-based immunotherapy and therefore, at least at present, it would not be considered standard-of-care to administer dinutuximab in isolation (although this is sometimes necessary in individual patients if toxicity of GM-CSF and/or IL-2 is deemed unacceptable).

Dinutuximab is administered in pediatric tertiary care inpatient settings. It is run as an IV infusion over 10 to 20 hours daily over four consecutive days in each of five planned maintenance cycles. Anticipated potential toxicities include neuropathic pain, acute vascular leak syndrome causing hypotension and hypersensitivity reactions. As per ANBL0032[16], patients routinely receive pre-medications to prevent reactions and pre-emptively start analgesic infusions prior to dinutuximab initiation, often in consultation with pediatric anesthesia, to manage neuropathic pain. Patients receive dinutuximab in combination with cytokines; GM-CSF in cycles 1,3 and 5 or IL2, which is run as a 96 hour continuous infusion twice per cycle, in cycles 2 and 4. Patients also receive isotretinoin in each cycle, and for a sixth cycle as monotherapy.

2.3 Evidence-Based Considerations for a Funding Population

The funding population for treatment with dinutuximab in the upfront setting may be defined in one of two, related manners: first, those defined *a priori* as having high-risk disease; or second, those treated according to a high-risk neuroblastoma protocol. For most practical purposes, these populations will be identical, but it is important to recognise that the details of risk stratification of neuroblastoma do change over time and therefore specific definitions of high-risk disease established now may not precisely apply in the future.

In the context of the available evidence for the benefit of dinutuximab, [16] the following criteria were used to define high-risk neuroblastoma: metastatic disease in patients aged ≥547 days; patients with *MYCN*-amplified tumours (except for those with INSS stage 1); metastatic disease in patients aged 365-547 days with unfavourable biological characteristics (e.g. histology, ploidy); and localised disease in patients aged ≥547 days with unfavourable histology. Broadly, the same criteria continue to be used in the current clinical management of neuroblastoma. There have been some changes in details, such as the move away from the INSS staging system towards INRGSS, although the principles remain the same. For patients aged 365-547 days with non-*MYCN*-amplified metastatic disease, consideration of unfavourable biological characteristics is likely now to consider presence of segmental chromosomal abnormalities as well as other characteristics listed in the 2007 COG criteria.

In practical terms, the decision about whether to treat a patient as high-risk is made early in treatment and is independent of a decision as to whether or not to administer dinutuximab-based immunotherapy. In practice, regardless of the precise definition of high-risk neuroblastoma those patients for whom dinutuximab should be considered are those treated as high-risk; i.e. with induction chemotherapy, consideration of surgical resection and high-dose chemotherapy with autologous stem-cell rescue (+/- radiotherapy) prior to immunotherapy. Patients initially diagnosed as non-high-risk who later progressed or relapsed to high-risk neuroblastoma should also be considered suitable for dinutuximab. Of note (with the above exception) there is currently no role for dinutuximab in the non-high-risk neuroblastoma population.

With regards other criteria for defining a funding population, although the randomised clinical trial demonstrating the effectiveness of dinutuximab[16] required immunotherapy to start within a defined

period for high-dose chemotherapy, it is recommended that such a timeframe not be mandated in defining the funding population. In practice, clinicians will aim to proceed with immunotherapy as quickly as possible following high-dose chemotherapy and/or radiotherapy; albeit accommodating individual patient toxicities, etc. In most cases, disease re-evaluation would be undertaken prior to initiating immunotherapy in order to detect patients with progressive disease (who would not then proceed to standard immunotherapy, but who might instead be considered for combined chemotherapy/immunotherapy). Similarly, it is recommended that the funding population should not be defined on the basis of a specific response to induction chemotherapy, but rather on the basis of treatment given; i.e. patients should be deemed eligible for dinutuximab-based immunotherapy if they have completed prior treatment with high-dose chemotherapy and autologous stem cell rescue (ASCT). Although, it is clear that patients with better responses to induction chemotherapy have a better long-term outcome, [18,19] there remains controversy about the degree of induction response required to justify a decision to proceed to high-dose chemotherapy (and by implication to immunotherapy). Recent evidence from COG ANBL0532[17] indicate that even patients with stable disease (rather than PR or better) following induction benefit from tandem ASCT – and therefore are also likely to benefit from immunotherapy thereafter.[17]

2.4 Other Patient Populations in Whom the Drug May Be Used

The clinical trial evidence[16] from the original submission addresses only the use of dinutuximab in the front-up setting for high-risk neuroblastoma and is not therefore generalizable to the relapsed/refractory setting. Nevertheless, there are additional published and unpublished data that support the use of dinutuximab in combination with GM-CSF and chemotherapy (temozolomide and irinotecan) in this relapsed/refractory setting. The COG trial ANBL1221 was a randomized phase II comparing the combinations of temozolomide/irinotecan chemotherapy with either temsirolimus or dinutuximab/GM-CSF. Initial results of the randomized cohort showed an impressive response rate (ORR) of >50% (9 of 17) in those receiving the combination with dinutuximab. [9]Although there was no randomization against chemotherapy alone, the ORR was dramatically better than that previously seen with temozolomide/irinotecan alone (ANBL0421) which achieved only a 15% ORR. [20] On the basis of the very encouraging results, the ANBL1221 study was expanded to treat an additional cohort of patients with the chemotherapy/dinutuximab combination. These data have not yet been publicly released but are sufficiently encouraging that the next COG study for relapsed/refractory neuroblastoma will build on the combination of temozolomide/irinotecan plus dinutuximab/GM-CSF.

Clinically, there is no single standard approach to the management of relapsed/refractory neuroblastoma and multiple therapeutic strategies may be considered by treating clinicians. [21] Nevertheless, the responses seen to the combination of temozolomide/irinotecan plus dinutuximab/GM-CSF mean that in recent years it has been used routinely in clinical practice in this setting throughout most of the United States and Canada. Access to dinutuximab for patients with relapsed/refractory neuroblastoma will be of major concern for paediatric oncologists in Canada given the impressive (and unprecedented) response rates seem with this chemo-immunotherapy combination.

3 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

The following patient advocacy groups provided input in a joint submission on dinutuximab for neuroblastoma and their input is summarized below: Advocacy for Canadian Childhood Oncology Research Network (Ac2orn), Canadian Organization For Rare Disorders (CORD), and Ontario Parents Advocating for Children with Cancer (OPACC).

Information was gathered through an online survey (25 respondents in total who were parents of patients) and five interviews with families. The online survey was distributed by the three patient advocacy groups through social media and email and the survey solicited input from patients and families of patients treated for high-risk neuroblastoma regardless of experience with dinutuximab. Of the 19 survey respondents who identified the location of their primary residence, 16 were from Ontario, one was from British Columbia, one was from the US, and one was international. Of the five interviewed families, three were from Ontario and two were from British Columbia.

There is a wide range of symptoms of neuroblastoma and in many cases, these were "nonspecific" or "general" symptoms . The symptoms include: pain, stomach ache, lethargy, weight loss or gain, fevers, bruising (particularly bruising around the eyes), limping, palpable mass, skin changes, and other infectious-like symptoms. Neuroblastoma may initially be misdiagnosed due to the non-specific nature of the symptoms and patients may not receive a correct diagnosis until their symptoms are very severe. Front-line treatment of high-risk neuroblastoma involves intensive multi-modal therapy and can include all or some of the following: induction chemotherapy, surgical resection, radiation therapy, and high-dose chemotherapy with autologous stem cell transplant (ASCT). Almost all of the treatment is administered on an in-patient basis and families spend most of their time in the hospital for almost 18 months. Current therapy for high-risk neuroblastoma has immense negative physical, psychological, and emotional impacts on patients and caregivers. There is a long list of side effects from treatment that can have a large or extremely large impact on patients, including neutropenia, fevers, nausea, vomiting, pain, hair loss, and hearing loss. Serious complications from current treatments including intestinal perforation can occur. The response to treatment varies widely between patients. Barriers to accessing treatment include: limitations of local care centres, the lack of assistance from social workers, the inadequacy of employment insurance compared with the duration of treatment, and the financial burden of transportation to and from hospitals.

The current standard of care for patients with high-risk neuroblastoma includes dinutuximab therapy with GM-CSF, Il-2, and retinoic acid. This treatment is also associated with a long list of potentially serious side effects, including fluid retention, pain, high or low blood pressure, fever, respiratory issues, fatigue, sleepiness, nausea, vomiting, allergic reactions, and vision changes. In particular, pain management was a commonly cited concern. Some parents found that the side effects of dinutuximab therapy more tolerable and manageable compared to those of the preceding therapies. Due to the frequency of drug administrations and time spent in the hospital, dinutuximab therapy imposes a substantial financial burden. A total of 23 respondents had direct experience with dinutuximab and all of the families interviewed had experience with dinutuximab. A total of 16 people in the survey were identified as having experience with dinutuximab in front-line therapy. The overall experience of parents whose children received dinutuximab therapy for high-risk neuroblastoma is that the side effects, though challenging to manage, are worth suffering through for a chance to eliminate their child's cancer and give them the best chance at survival.

Please see below for a summary of specific input received from the patient advocacy groups. 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 as is according to the submission, without modification.

3.1 Condition and Current Therapy Information

3.1.1 Experiences Patients have with High-Risk Neuroblastoma

Of the 24 survey respondents who provided the patient's age at the time of diagnosis, 90% reported an age of less than six years. Of these, the patient input submission stated that 8% were less than one year old, 25% were between one and two years of age, 46% were between two and three years of age, 13% were between four and five years old; and 8% were between six and 10 years of age. In one of the interviewed families, the patient was 15 years old at time of diagnosis. In the other four families interviewed, patients were diagnosed between ages 2 and 4, and all 4 received immunotherapy a year after diagnosis.

Most of the respondents indicated that by the time the patients received a diagnosis of neuroblastoma, the cancer was advanced which was considered common for high-risk neuroblastoma. Patients experienced a myriad of symptoms, including pain, stomach ache, lethargy, weight loss or gain, fevers, bruising (particularly bruising around the eyes), limping, palpable mass, skin changes, and other infectious-like symptoms. Experiences with obtaining a diagnosis of neuroblastoma varied, with some patients obtaining a fairly quick diagnosis following testing and other patients experiencing "challenge and trauma" before being diagnosed. Due to the non-specific nature of some symptoms, parents tended to dismiss symptoms as other common childhood ailments and in some cases healthcare professionals downplayed the symptoms or initially misdiagnosed patients. Patients underwent blood tests, urine tests, biopsy, and/or imaging tests with x-ray, ultrasound, or nuclear medicine prior to being diagnosed. The submission also noted that "escalation from 'routine' problems to severe and frightening symptoms was often rapid and intense". The following are quotations from parents of patients regarding experiences leading up to the diagnosis of neuroblastoma:

- *"My son … getting sick (from virus', ear infections, very tired, continuous fevers, and not breathing well). […] I asked about his extended belly and [doctor] said we could send him for an ultrasound. That afternoon my son woke up […] screaming in discomfort, so I look him to the local ER where they did an x-ray and ultrasound. The large mass in his abdomen […] was pushing a lot of his organs (his kidney was destroyed) and it was pushing his lungs up which was causing the breathing problems. […] Right after we were told he has some form of cancerous tumour (which eventually confirmed as Neuroblastoma that had started in his adrenal gland)."*
- *"Multiple trips to the doctor for months with incurable rash, stomach aches fatigue and fevers. When he started daycare, he would be sent home every day with fevers so we would miss work multiple times a week. Finally […] we were sent to the hospital for blood work, X-rays and urine samples. The next day after an ultrasound, we were sent to Sick Kids where he was finally diagnosed."*
- *"I saw the tumour to his neck. [...] GP [general practitioner] sent us to ENT [ear, nose, and throat]. […] They gave him antibiotics and misdiagnosed it as lymphadenitis. Discharged […] saying review in 6 weeks. Took him to my brother (worked in paediatric oncology). […] He immediately […] organised for an ent [sic] consultant to review. MRI scan the following day and emergency biopsy the day after. Results confirmed NB [neuroblastoma] the following Monday."*

3.1.2 Patients' Experiences with Current Therapy for High-Risk Neuroblastoma

The patient input submission noted that treatment for high-risk neuroblastoma is long and challenging, comprising almost every modality of cancer treatment: chemotherapy, surgery, high-dose chemotherapy with stem cell transplant, radiation, immunotherapy, and maintenance therapy. Of the patients represented by survey respondents and interviewed families, 84% had received surgery, 80% had received chemotherapy, 80% had received high dose chemotherapy, 76% had received both chemotherapy and high-dose chemotherapy, 76% had received radiation therapy, 76% had received stem cell transplant, and 72% had received all four therapies. The submission also noted that almost all of the treatment is administered on an in-patient basis and families spend most of their time in the hospital for almost 18 months. A total of 23 respondents had direct experience with dinutuximab and all of the families interviewed had experience with dinutuximab. A total of 16 people in the survey were identified as having experience with dinutuximab in front-line therapy. Of the 18 surveyed respondents who reported receiving all four therapies, 16 subsequently received dinutuximab due to participation in a Children's Oncology Group (COG) clinical trial.

The patient input submission detailed the immense negative physical, psychological, and emotional impacts that current therapy for high-risk neuroblastoma has on patients. As one parent stated, *"There are no words to actually describe what these kids have to go through. All of it is absolutely horrendous. We need better treatment. We need a cure."* Most parents rated the following symptoms as having an "extremely large" or "large" impact on their child's quality of life: neutropenia, fevers, nausea, vomiting, pain, and hair loss. About half of the respondents rated the following as having an "extremely large" or "large" impact on their child: changes to physical activity, eating challenges, and mental health and overall happiness. There was little impact in terms of education, possibly due to the majority of patients being under the age of six years at diagnosis. About two-fifths of respondents rated the following as having an "extremely large" or "large" impact on their child: weight loss, infection, neuropathy, and social development. The percentage of respondents indicating a "large" impact in terms of constipation, eyesight, and mobility was 10% to 20%. The following are quotations from parents of patients regarding the impacts of current therapy for high-risk neuroblastoma:

- *"She responded well and quickly to treatment. Chemo significantly shrunk the tumour and the visible traces of metastasized disease. Surgery removed all of the tumour so minimal radiation was needed. Hard time with cisplatin, including prolonged vomiting and electrolyte imbalances. Hearing Loss developed as a result of chemotherapy. Drug allergy (Tylenol) developed near the end of Immunotherapy."*
- *"Day of stem cell transplant after high dose chemo therapy she went into severe septic shock. Large intestine was completely perforated from chemo. They had to remove it entirely and a portion of small intestine. Created an illiostomy [sic]. One month on life support in icu. Followed by two month as inpatient for her recovery."*
- *"Initial surgery was followed by scans, then 18 months of chemotherapy, which was very harsh. The chemo did almost nothing to stop the cancer and was followed by two bone marrow transplants, then radiation, then another transplant. So the discussion was, do we stop? What is the point? When we were offered this clinical trial for immunotherapy, ch14.18 [Unituxin] we almost refused. I thought seriously about refusing."*

Aside from the physical side effects, treatment was considered a traumatic experience and older children retained the trauma. One parent stated, *"My daughter has developed extreme anxiety with going to doctors and medical procedures. She has been in therapy for the last few months trying to learn to cope."*

3.1.3 Impact of High Risk Neuroblastoma and Current Therapy on Caregivers

Caregivers, namely parents of children with neuroblastoma, experienced difficulty in obtaining the correct diagnosis for their child and the initial symptoms mentioned above mean disruption for the family (e.g., having to make multiple trips to the doctor and miss work). Parents reported feeling terrified, angry, and guilty for initially dismissing their child's symptoms and not seeking a diagnosis sooner.

With regards to therapy, parents acknowledged the benefits of therapy while also revealing that they were profoundly affected by the negative impacts of therapy on their children. In one case where chemotherapy was not successful, the parent questioned the value of the following procedures (multiple bone marrow transplants and radiation therapy) and almost refused participation in the clinical trial for dinutuximab (see the third quotation in the previous section).

Out of the survey respondents, most rated as "extremely large" or "large" the impacts in terms of "work or employment", "mental health or happiness", "participation in activities with family or friends", and "parenting other siblings" on the family. About two-thirds indicated that managing the disease and/or treatments had an "extremely large" or "large" impact on the ability to manage "financial responsibilities" and "home responsibilities". In contrast, 10% or fewer respondents indicated that they experienced little or no impact on family life in any of the surveyed areas.

Most respondents described their experiences with treatment and their primary care hospital as very positive. While most respondents had no issues accessing treatment, some barriers were identified. The following are quotations from parents of patients regarding their experiences in accessing treatment for high-risk neuroblastoma:

- *"Once our care was assumed by Kingston General we had difficulty accessing the best care available at bigger specialized hospitals for surgery […] and trials (fertility preservation trial)."*
- *"No social workers to help had to figure everything out on our own. EI [employment insurance] for Parent of critically Ill children is ridiculous 35 weeks is all you qualify for our daughter was in treatment for 2 years! Proton Radiation is not offered as an option in Canada unless you question the Dr. and only then do they get consults from Proton Centers in the US in our daughter's case it was recommended to avoid organ damage. If I had not asked the question she would have received photon. DFMO [*difluoromethylornithine] *was not available in Canada has to pay out of pocket for trip to Michigan now it is available in Canada, but we still have to cover travelling costs as it is not yet available in BC."*
- *"If I have warning, I can book with Wheels Of Hope thru the Cancer Society. But for spur of the moment hospital trips, I have had to take taxis which financially is a challenge."*

3.2 Information about the Drug Being Reviewed

3.2.1 Patient and Caregiver Expectations for and Experiences To Date with Dinutuximab

The patient input submission noted that parents were willing to make trade-offs and tolerate what is necessary to provide their child with effective treatments. Out of a list of factors in making a decision about a new cancer treatment, the factors that were meaningful to survey respondents were "possible impact on the disease" (76%), "quality of life" (68%), and "physician recommendation" (60%). The following are quotations from parents on how they would make a decision about a new cancer treatment:

- *"The increase to the odds of survival...the additional 20% is huge!"*
- *"The side effects are trivial when it saves my daughters life."*
- *"We were willing to tolerate the side effects because the results from studies showed positive outcomes."*
- *"..the most important thing is to be rescued from the disease."*

A total of 23 respondents had experience with dinutuximab. The submission stated that 67% of patients received dinutuximab through a clinical trials, 19% received it through a special access program, and 14% did not receive dinutuximab treatment. Two respondents noted challenges in accessing dinutuximab treatment due to the study eligibility criteria. One parent stated, *"My son's kidney function was in question which led to a two month delay. He barely made the cut-off. GFR of 60 or better. He was a 60 after a two month break off of toxic treatments."* Another parent stated, *"An ejection fraction value of his heart measured low on his echocardiogram […] [and] was repeated three times until the threshold value was met for inclusion […] My son was only two days away from not being accepted"*. Another barrier to accessing dinutuximab was transportation as some families had to travel long distances by car.

Many parents were unsure of the long-term impact of dinutuximab on their child's cancer due to the short length of time since the dinutuximab therapy. None of the parents reported that dinutuximab did not work for their child's cancer and all of the interviewed parents and 25% of the survey respondents noted that dinutuximab therapy eliminated their child's cancer with no relapse or some time prior to relapse. One parent reported that dinutuximab therapy kept their child's disease stable. Some parents reported that dinutuximab therapy was effective after other first-line therapies were not effective. One interviewed patient was 15 years old at the time of diagnosis and had cancer that did not respond well to surgery, chemotherapy, radiation, and IL-2 therapy. After six cycles of dinutuximab therapy, the patient was "cancer-free" on scans and biopsy and remained so in all subsequent tests. The patient was able to return to high school without further scheduled treatment. The following are quotations from parents regarding the outcomes of dinutuximab therapy:

- "*It gave us our first clear scan. Essentially it gave us hope that he might beat NB [neuroblastoma]."*
- *"We were pretty close to stopping all treatment and almost refused clinical trial ch14.18 (Unituxin) when it was offered. To our amazement, the results from the very scans were 'stunning.'"*
- *"After three months of trials, he exhibited a 90% response. Now, more than one year later, his scans are still clear and he is a 'normal and perfectly healthy' five-year-old."*

- "*Glad he got to get it and hope it stops relapse. He is 2 years since treatment has stop and still NED [no evidence of disease].*"

On the other hand, there were many side effects experienced during dinutuximab therapy that were considered by respondents to be "very serious" or "serious": fluid retention (70% of respondents); pain (53% of respondents); high or low blood pressure (half of respondents), fever, respiratory issues, fatigue, and sleepiness (one third of respondents); and nausea and vomiting, allergic reactions, and vision changes (one quarter of respondents). Most (60% to 70%) considered headache and blood cell count to be "minor" or did not experience these side effects. The following are quotations from parents regarding the side effects of dinutuximab, GM-CSF and IL-2 therapy:

- *"[X] had a few episodes of bronchospasms, which were controlled. Her pain and nausea could be controlled."*
- *"After the initial infusion we were admitted for an additional 9 days to manage diarrhea, fever, and dehydration. Urticaria was one of the most challenging side effects as there wasn't a medication which seems to alleviate these symptoms."*
- *"Painful - he could not even find comfort in cuddling with us. Stiff as a board due to the pain. Lack of sleep until the drip was completed. High fever."*
- *"At first she could tolerate treatment well. After she finished second cycle, more and more issues happened, like infection, she had a minor surgery to replace CVL [central venous line] and experienced one time no responding. Due to she had fluids in her lungs and around heart during treatment, doctors stopped GM-CSF and IL2."*
- *"It is a very hard part of the treatment physically and emotionally, because it causes them pain. Chasing the pain with the pain meds was extremely challenging at the beginning, but it got better as we knew where to start the pain meds at. It was also very challenging as certain pain meds caused low blood pressures in our daughter so we had to stop them in order for her to be able to get ch14.18 [dinutuximab]."*

The most frequently mentioned side effect in the provided quotations was pain. Parents mentioned that managing pain with pain medications was initially challenging, but that as they gained more experience with administering pain medications, the pain became more tolerable. Parents also observed that patients tended to recover after each treatment cycle; for example: *"He definitely had pain, discomfort, and all the medications made him tired and not playful during the high doses but he bounced back right after."* According to another parent, *"It is relatively tolerable treatment. Do not rush into each round of treatment. Make sure the child is physically well enough to handle each round of treatment."* Overall, the respondents noted that the side effects were mostly temporary and manageable with supportive medications.

With regards to quality of life, half of the survey respondents strongly agreed or agreed that dinutuximab improved quality of life while the other half were neutral. The following are quotations from parents regarding the side effects of dinutuximab, GM-CSF and IL-2 therapy relative to previous first-line therapy and in balance with the potential benefits of dinutuximab therapy:

- *"Considering all of the intense treatments that come ahead of immunotherapy, this really did feel much easier and more manageable."*

- *"We are past it now and I hope to never have to go through it again, but I would not skip it. I know that for a lot of children this is what cleared the cancer so it does have effects on it."*
- *"It is hard, but it is so worth it! Our son would not be here if it were not for his immunotherapy treatment."*

The severity of the side effects and the intensive nature of dinutuximab therapy also affect parents of patients. Parents find it difficult to witness their children suffering the side effects of treatment, with one parent noting, *"I hope to one day forget the side effects and the worry attributed with this treatment"*. The financial burden of dinutuximab therapy is substantial due to the frequency of drug administrations and time spent in the hospital. Sources of financial burden include loss of income, childcare expenses for patients' siblings, supportive care costs, and transportation, parking, and meal costs. One parent noted that the cost of GM-CSF would have been burdensome if it hadn't been covered by workplace insurance.

The patient input noted that despite the challenges and side effects associated with dinutuximab therapy, parents of patients were willing to endure the treatment for the chance that it will address disease burden, prevent relapse, and improve survival. The following are quotations from parents regarding their overall feelings toward dinutuximab therapy for high-risk neuroblastoma:

- *"Definitely worth tolerating the side effects. Chemo side effects were actually more difficult to manage."*
- *"The side effects are most temporary. The outlook for the treatment is just too positive to miss out."*
- *"The potential benefit of this treatment for long-term outcome was a challenge our family was willing to accept. Until evidence says otherwise, I would still consider this treatment."*

3.3 Additional Information

Lastly, the patient input noted the importance of immunotherapy: "*families see and experience the importance of immunotherapy. They are encouraged by treatments like Unituxin. 'The days in-patient are long and at times difficult/busy but overall it was a positive experience.' 'We need more new drugs like immunotherapy.'*"

4 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

The Provincial Advisory Group includes representatives from provincial cancer agencies and provincial and territorial Ministries of Health participating in pCODR. The complete list of PAG members is available on the pCODR website (www.cadth.ca/pcodr). PAG identifies factors that could affect the feasibility of implementing a funding recommendation.

Overall Summary

Input was obtained from all nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation:

Clinical factors:

- Eligibility for patients with non-high-risk neuroblastoma

Economic factors:

- Significant wastage due to single use vial, one vial size, and small number of patients

Please see below for more details.

4.1 Currently Funded Treatments

PAG identified that up-to-date COG chemotherapy protocols or active COG clinical trials could be considered standard of care. Treatment options include multi-agent chemotherapy regimens (and autologous stem cell transplant if eligible) or isotretinoin. Patients are enrolled into clinical trials and in some jurisdictions, treated out of province at pediatric hematology/oncology transplant centres.

4.2 Eligible Patient Population

PAG noted that the COG trial included patients with neuroblastoma categorized as high risk at the time of diagnosis or those who are converted and/or relapsed to high risk neuroblastoma. PAG is seeking clarity on whether dinutuximab would be limited to patients with high risk neuroblastoma. PAG is also seeking guidance on the definition of high risk as this would be an enabler to implementation.

If recommended for reimbursement, PAG noted that patients currently receiving other treatment (e.g., isotretinoin alone) for high risk neuroblastoma would need to be addressed on a time-limited basis.

PAG noted that patients with relapsed or refractory disease are currently covered under the Special Access Programme and are seeking guidance on whether trial results are generalizable to these patients.

4.3 Implementation Factors

Dinutuximab is administered over 10 to 20 hours for four consecutive days for a maximum of five cycles. PAG noted the long infusion would be a barrier to implementation as patients would need to be in hospital for delivery of treatment. PAG also noted as treatment would be administered primarily in hospital, coverage and funding of inpatient oncology treatment differs by province; this would require collaboration with hospitals for implementation of reimbursement of dinutuximab.

Additional nursing and pharmacy resources will be required for pre-medication, drug

preparation, administration time and monitoring for multiple severe adverse effects including infusion reactions and severe neurotoxicity (i.e., severe neuropathic pain and peripheral neuropathy). PAG noted that the significantly increased chair time compared to current treatment is a barrier to implementation, given the additional resources needed as well as slower infusion time to reduce the risk of infusion reactions with dinutuximab.

Dinutuximab is to be used in combination with GM-CSF, IL-2, and retinoic acid. PAG noted that additional resources and costs will also be required for GM-CSF, IL-2, and retinoic acid. It was also noted that GM-CSF is not available in Canada; GM-CSF requires Health Canada Special Access Programme approval and some provinces do not fund Health Canada Special Access Programme drugs, these are barriers to implementation. PAG also noted limited bed spaces in hospitals would be a barrier to implementation.

Dinutuximab is available in a single-use 17.5 mg vial. PAG noted there would be significant wastage as there is only one strength available in a single use vial which limits dose adjustments and vial sharing would be unlikely due to the small number of pediatric patients with high-risk neuroblastoma who would be eligible for dinutuximab. Dinutuximab vials require refrigeration, diluted drugs also must be refrigerated and utilized within 24 hours of preparation, and this is also a barrier to implementation.

4.4 Sequencing and Priority of Treatments

PAG is seeking guidance on the appropriate treatment options following treatment with dinutuximab in this setting.

4.5 Companion Diagnostic Testing

None identified.

4.6 Additional Information

None provided.

5 SUMMARY OF REGISTERED CLINICIAN INPUT

The registered clinicians provided input on dinutuximab (Unituxin), used in combination with GM-CSF, IL-2, and retinoic acid (RA) for the treatment of pediatric patients with high-risk neuroblastoma who achieve at least a partial response to prior first-line multi-agent, multimodal therapy, their input is summarized below. Four clinician input submissions were received, representing a total of thirteen clinicians: eleven practising oncologists or physicians who treat cancer patients, one nurse practitioner, and one oncology pharmacist:

- One joint submission from the Pediatric Oncology Group of Ontario (POGO) from a total of seven clinicians (five pediatric oncologists, one oncology nurse practitioner, and one oncology pharmacist)
- One joint submission from four pediatric oncologists at CancerCare Manitoba (CCM)
  One submission from a pediatric oncologist from the Division of Pediatric Hematology/Oncology at Montreal Children's Hospital (MCH)
  One submission from a specialist in pediatric hematology-oncology from Centre hospitalier universitaire (CHU) Sainte-Justine

All four clinical input submissions stated that dinutuximab in combination with GM-CSF and IL-2 is part of the current standard of care (SOC) for the front-line treatment of patients with high-risk neuroblastoma. The addition of dinutuximab therapy to the previous standard of care has led to improvements in event-free survival and overall survival of patients with high-risk neuroblastoma. However, there are serious side effects that require intense medical and nursing management, including pain, hypotension, fluid retention, capillary leak syndrome, and risk of infection.

The four submissions agreed that the patient population of the reimbursement request reflects the patients who would be treated with dinutuximab therapy in clinical practice. However, the definitions of high-risk neuroblastoma differed slightly between the submissions. Three of the submissions noted that patients with relapsed neuroblastoma (one submission specified relapsed or refractory neuroblastoma) are not part of the reimbursement request and that these patients would potentially benefit from dinutuximab and GM-CSF therapy in combination with irinotecan and temozolomide.

Dinutuximab would be an add-on therapy to the previous standard of care for front-line treatment of high-risk neuroblastoma. Dinutuximab therapy with GM-CSF, IL-2, and RA would follow induction chemotherapy, autologous stem cell transplant (ASCT) and possibly surgery and radiation therapy. Dinutuximab would only be administered to patients with high-risk neuroblastoma and the diagnosis of high-risk neuroblastoma uses a combination of imaging modalities and/or tumour features from biopsy samples. Three submissions (two group and one individual) agreed that the effectiveness of dinutuximab therapy would be compromised if GM-CSF was unavailable while one individual submission considered the administration of dinutuximab without GM-CSF to be a reasonable option with proven effectiveness.

Please see below for a summary of specific input received from the registered clinicians.

5.1 Current Treatments for Pediatric High-Risk Neuroblastoma

All four clinician input submissions indicated that front-line treatment of high-risk neuroblastoma involves a combination of treatment modalities. According to the CCM submission, the SOC consists of five to six cycles of multi-agent chemotherapy, surgical resection, tandem ASCT, and radiation therapy. The POGO submission indicated that the SOC consists of five to six cycles of induction chemotherapy, one to two courses of high dose chemotherapy with ASCT rescue, radiation therapy, and multiple cycles of RA therapy. The POGO submission also stated that

there is no current provincially funded treatment for high-risk neuroblastoma and that dinutuximab has been available in Ontario through the COG trial and subsequently on a compassionate access basis. The MCH submission indicated that the SOC consists of a few cycles of intensive neoadjuvant chemotherapy, surgical resection, one to two ASCTs, radiation therapy, and RA therapy. The CHU submission stated that the current SOC is induction chemotherapy and surgical resection followed by ASCT and radiation therapy.

In addition, all four submissions noted that dinutuximab (or more generally, anti-GD2 antibody) therapy administered with GM-CSF and IL-2 is already considered to be part of the SOC for the front-line treatment of high-risk neuroblastoma. Both the CCM and MCH submissions stated that allogeneic transplant is not a part of the SOC for high-risk neuroblastoma. The POGO submission noted that the most appropriate comparator for dinutuximab therapy would be the. SOC based on the Children's Oncology Group's (COG) approach including 5-6 courses of induction chemotherapy followed 1-2 courses of high dose chemotherapy with autologous stem cell rescue, radiation therapy and multiple cycles of isotretinoin (i.e., the same treatment without dinutuximab therapy).

5.2 Eligible Patient Population

The clinicians providing input for the two joint submissions indicated that dinutuximab with GM-CSF and IL-2 would be used to treat all patients with high-risk neuroblastoma who have at least a partial response to prior therapy (specified by POGO as induction chemotherapy and high dose chemotherapy with ASCT). The submission from MCH indicated that dinutuximab therapy would be part of the front-line treatment of high-risk neuroblastoma unless the patient had a medical contraindication. The joint submission from POGO noted that severe renal or cardiac dysfunction may be regarded as relative contraindications for dinutuximab therapy. The clinician input from CHU stated that the only absolute contraindication is documented acute allergic reaction to previous administration of dinutuximab.

The POGO and CHU submissions noted that the eligibility criteria described in the submitted study[3] are compatible with clinical practice while MCH provided a definition of high-risk neuroblastoma in their input submission: INRG Stage M with N-myc amplification, age >547 days regardless of biologic features, stage MS or L2 with N-myc amplification (i.e., the inclusion criteria of current COG trial ANBL 1531).

The POGO, MCH, and CHU submissions noted that patients with relapsed neuroblastoma (relapse or refractory in the case of the CHU submission) are not included in the reimbursement request. The submissions stated that dinutuximab and GM-CSF therapy in combination with irinotecan and temozolomide can be effective in this population. The CHU submission described benefits in progression free survival and overall survival with dinutuximab and GM-CSF in this population (with the eligibility criteria for COG trial ANBL 1221 being appropriate for identifying this population).

The POGO submission estimated that on an annual basis in Ontario, 10 to 15 patients would be eligible for dinutuximab as per the reimbursement request, with another five to seven patients with relapsed neuroblastoma potentially benefitting from dinutuximab and GM-CSF therapy in combination with irinotecan and temozolomide.

5.3 Relevance to Clinical Practice

All of the submissions indicated that the clinicians had experience using dinutuximab since it is now part of the SOC for high-risk neuroblastoma patients. The MCH submission also indicated experience with dinutuximab therapy from the clinical trial setting. The submission from POGO

and CHU highlighted the improvements to event-free survival (EFS) and overall survival (OS) with dinutuximab therapy in patients with high-risk neuroblastoma.

The submission from POGO outlined the harms associated with dinutuximab therapy and the supportive care required. Common harms included pain, hypotension, fluid retention, and capillary leak syndrome. Dinutuximab must be administered in an in-patient setting with intense medical and nursing management, the clinicians indicated that they have developed their own standard protocols to manage the side effects of dinutuximab. Patients must also be closely followed after discharge due to the significant risk of infection and bacteremia. GM-CSF therapy must be obtained through the Special Access Program at considerable expense and the submission stated that funding schemes for dinutuximab therapy should include a method of reimbursing institutions for GM-CSF therapy to ensure equitable care.

Similarly, the submission from CHU noted that dinutuximab with GM-CSF, IL-2, and RA therapy is highly toxic and should be prescribed and managed by a team with prior experience with this treatment protocol. The submission also stated the less toxic combination of dinutuximab, temozolomide, irinotecan, and GM-CSF (used in the relapsed or refractory setting) should also be prescribed by a team with experience with dinutuximab in combination with GM-CSF, IL-2, and RA.

5.4 Sequencing and Priority of Treatments with Dinutuximab

All of the inputs received from clinicians indicated that dinutuximab therapy is to be used as an additional front-line therapy. It was noted that dinutuximab would not replace any other therapy but rather would be an add on to the end of a treatment regimen. As well, it was noted that dinutuximab therapy is already part of the current SOC in Canada.

5.5 Companion Diagnostic Testing

The submission from POGO stated that the diagnosis of high-risk neuroblastoma uses a combination of imaging modalities (i.e., computed tomography, magnetic resonance imaging, and metaiodobenzylguanidine scan) and/or tumour features (i.e., MYCN amplification and unfavourable histology) from biopsy samples. The MCH submission noted that routine testing can determine whether patients have adequate organ function prior to dinutuximab therapy. The submission from CHU stated that no companion diagnostic testing was required, aside from the diagnosis of high-risk neuroblastoma.

5.6 Additional Information

None.

5.7 Implementation Questions

5.7.1 In clinical practice, what definition of high-risk neuroblastoma is used?

The POGO submission referred to the International Neuroblastoma Risk Group (INRG) Consensus Pretreatment Classification (published in Cohn et al. 2009[12]) for its definition of high-risk

neuroblastoma. In this system, any of the following sets of characteristics would be classified as high-risk neuroblastoma:

- INRG stage L1 with MYCN amplification and any histologic category except for ganglioneuroma maturing or ganglioneuroblastoma intermixed; or
- INRG stage 2 with MYCN amplification, at least 18 months of age, and histologic category of ganglioneuroblastoma nodular or neuroblastoma; or
- INRG stage M and at least 18 months of age; or
- INRG stage M or MS, less than 18 months of age, and MYCN amplification.

The POGO submission also noted that patients initially diagnosed with low- or intermediate-risk neuroblastoma and then subsequently reclassified to high-risk neuroblastoma (due to genetic testing or disease progression) are also included in the definition of high-risk neuroblastoma.

The MCH submission considered the following inclusion criteria for the current COG trial (ANBL 1531) in patients with newly diagnosed high-risk neuroblastoma to be appropriate for defining high-risk neuroblastoma:

- INRG stage M with MYCN amplification; or
- INRG stage M and older than 547 days; or
- INRG stage MS or L2, with MYCN amplification.

The CCM submission stated that there are standard definitions of high-risk neuroblastoma used by pediatric oncologists but did not specify a particular definition. Instead, the submission stated that patients with International Neuroblastoma Staging System (INSS) stage 4 and over the age of 18 months would be considered to have high-risk neuroblastoma.

The CHU submission stated that high-risk neuroblastoma includes children older than 18 months with metastatic neuroblastoma, children younger than 18 months with MYCN amplification, or metastatic relapse of initially low or intermediate risk neuroblastoma.

5.7.2 In clinical practice, would you want to extend the use of dinutuximab to patients with non-high-risk neuroblastoma? If so, are you aware of any evidence of dinutuximab in patients with non-high-risk neuroblastoma?

All of the submissions indicated that dinutuximab would not be used to treat patients with non high-risk neuroblastoma. The POGO submission noted that this is due to the toxicity associated with dinutuximab and the generally favourable prognosis of patients with low- and intermediate risk neuroblastoma. None of the inputs from clinicians indicated that there was any evidence for the use of dinutuximab in patients with non-high-risk neuroblastoma.

5.7.3 Currently GM-CSF requires Health Canada Special Access Programme (SAP) approval and access to drugs on SAP varies by province. In clinical practice, if dinutuximab was reimbursed, but you could not access GM-CSF through SAP, how would you manage?

The input from CCM noted that access to GM-CSF has not been an issue in Manitoba. The inputs from POGO and MCH emphasized that GM-CSF is an important part of dinutuximab therapy and that administration of dinutuximab without GM-CSF could compromise the efficacy of dinutuximab therapy. The submission from POGO stated that dinutuximab with IL 2 alone would

be considered if GM-CSF was unavailable, but that it would be "far from optimal". In contrast, according to the input from CHUin Europe where GM-CSF is not available, dinutuximab is used and is considered effective alone or in association with IL2, and therefore would be a reasonable option.

6 SYSTEMATIC REVIEW

6.1 Objectives

The objective of this review is to evaluate the clinical efficacy and safety of dinutuximab (Unituxin) used in combination with granulocyte macrophage colony-stimulating factor (GM-CSF), interleukin-2 (IL-2), and retinoic acid against appropriate comparators for the treatment of pediatric patients with high-risk neuroblastoma who achieve at least a partial response to prior first-line multi-agent, multimodal therapy.

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

Table 3: Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Published and unpublished RCTs In the absence of RCT data, non-randomized clinical trials investigating the safety and efficacy of dinutuximab will be included.	Pediatric patients with high-risk neuroblastoma who achieve at least a partial response to prior first-line multi-agent, multimodal therapy Subgroups: • Age • INSS stage • Tumour MYCN amplification	Dinutuximab in combination with retinoic acid, GM-CSF, and IL-2	Retinoic acid	Efficacy: • OS • EFS • PFS • DFS • MRD burden • HRQoL Safety: • AEs, SAEs, WDAEs • Notable harms (infusion reaction, capillary leak syndrome, neuropathic pain, and severe neurologic toxicity)

Note: The unit mg/m^2/day refers to mg per m^2 of body surface area per day.
Abbreviations: ACST = autologous stem cell transplant; AE = adverse event; BSA = body-surface area; DFS = disease-free survival; EFS = event-free survival; GM-CSF = granulocyte macrophage colony-stimulating factor; HRQoL = health-related quality of life; IL-2 = interleukin-2; INSS = International Neuroblastoma Staging System; MRD = minimal residual disease; OS = overall survival; PFS = progression-free survival; RCT = randomized controlled trial; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

** Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions)*

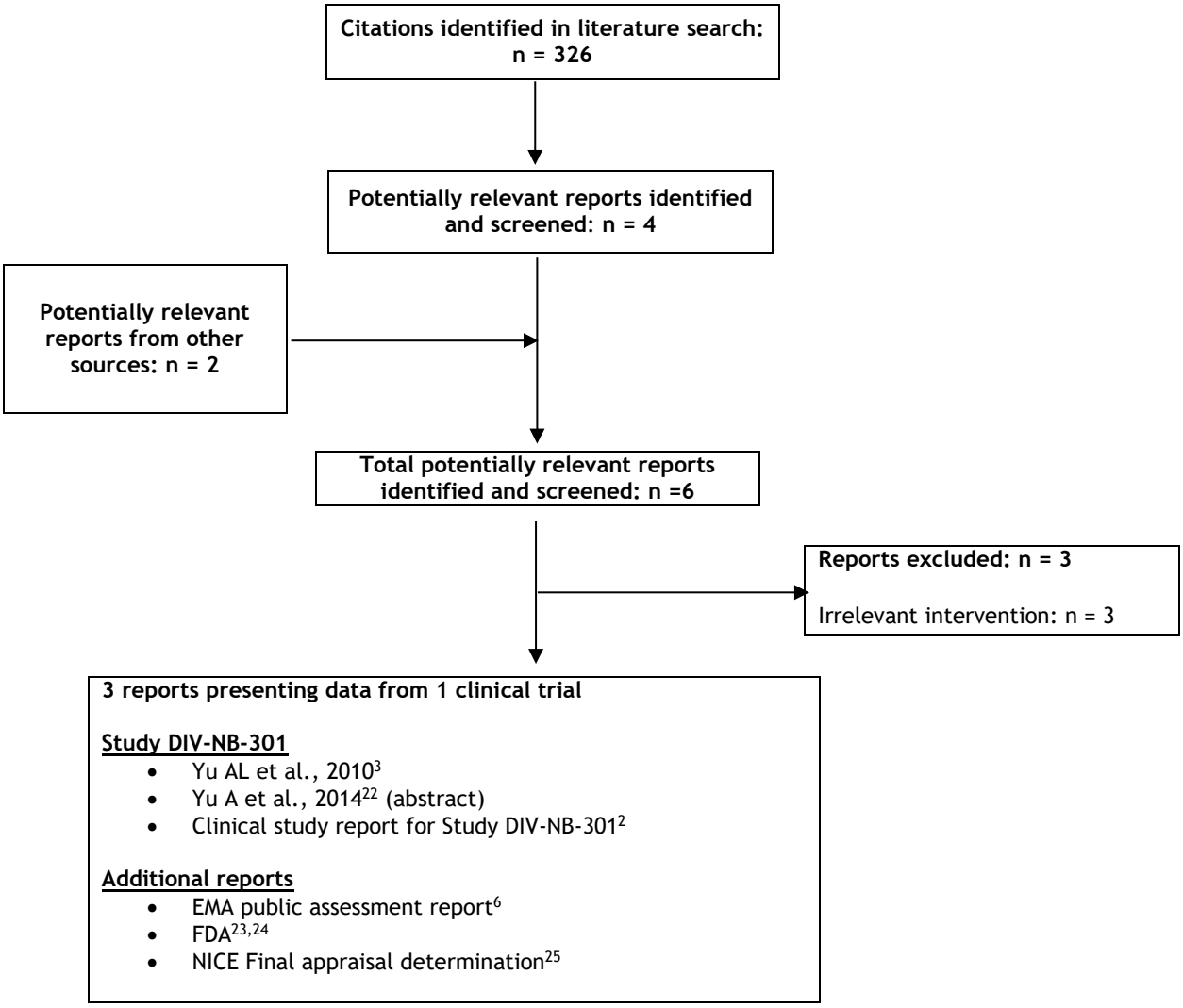
The systematic review protocol was developed jointly by the CGP and the pCODR Methods Team. Studies were chosen for inclusion in the review based on the criteria in the table below. Outcomes considered most relevant to patients, based on input from patient advocacy groups are those in bold. The literature search strategy and detailed methodology used by the pCODR Methods Team are provided in Appendix A.

6.3 Results

6.3.1 Literature Search Results

Of the six potentially relevant reports identified, one study was included in the pCODR systematic review and three reports of two studies were excluded. The studies were excluded because they were retrospective analyses and the studies used an irrelevant intervention.

Figure 1. QUOROM Flow Diagram for Inclusion and Exclusion of studies



Note: Additional data related to Study DIV-NB-301 were also obtained through requests to the Submitter by pCODR[2]

6.3.2 Summary of Included Studies

One RCT was included in the systematic review, Study DIV-NB-301 (N = 226).[2,3]

6.3.2.1 Detailed Trial Characteristics

Table 4: Summary of Trial Characteristics of the Included Studies

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
Study DIV-NB-301 Yu et al. 2010 Phase III, parallel-group, open-label RCT Patients randomized 1:1 with stratification on response before ASCT ("complete", "very good partial, or "partial"), induction therapy protocol, number of ASCTs, and stem cells received ("purged" vs. "non-purged") N randomized = 226 n treated = 213 (out of the randomized patients) 90 sites in the US, Canada, and Australia Patient enrolment dates: October 18, 2001 to January 13, 2009 Data cut-off for primary efficacy analysis: January 13, 2009 Confirmatory analysis date: June 30, 2009 Follow-up analysis dates: June 30, 2012; March 2014; July 1, 2016 Funded by grants from the US National Institutes of Health and the Food and Drug Administration	<u>Key Inclusion Criteria:</u> • High-risk neuroblastoma defined by the COG[4] • Age at diagnosis < 31 years • Completion of induction therapy, ASCT, and radiotherapy • Complete response, very good partial response, or partial response at pre-ASCT evaluation (defined in Brodeur 1993[5]) • ASCT performed within 9 months after initiation of induction therapy • Enrolment between day 50 and day 100 after final ASCT, when combined neutrophils and monocytes ≥ 1000/μL and ≥ 7 days post-radiotherapy • Absence of progressive disease • Lansky or Karnofsky Performance Scale score of ≥ 50% • Life expectancy ≥ 2 months • Adequate renal, hepatic, cardiac, pulmonary, and central nervous system function <u>Key Exclusion Criterion:</u> • Patients with biopsy-proven residual disease after ASCT could be enrolled, but were not randomized (all were assigned to receive dinutuximab)	Both arms received treatment for 6 consecutive 4-week cycles <u>Intervention:</u> Combination of dinutuximab (i.v. 25 mg/m^2/day[a] for 4 consecutive days during cycles 1 to 5, GM-CSF (s.c. or i.v. 250 μg/m^2/day for 14 days starting 3 days before dinutuximab was started in cycles 1, 3, and 5), IL-2 (i.v. during cycles 2 and 4 of 3.0 × 10^6 IU/m^2/day for 4 days during week 1 and 4.5 × 10^6 IU/m^2/day for 4 days during week 2), and retinoic acid (p.o. 160 mg/m^2/day during the last 2 weeks of cycles 1 to 6) <u>Comparator:</u> Retinoic acid (p.o. 160 mg/m^2/day divided in 2 daily doses for 14 consecutive days within each of cycles 1 to 6	<u>Primary:</u> • Event-free survival <u>Secondary:</u> • Overall survival • Disease status • MRD • AEs, SAEs
Source: pCODR submission[2] **Abbreviations:** AE = adverse event; ASCT = autologous stem cell transplantation; COG = Children's Oncology Group; GM-CSF = granulocyte macrophage colony-stimulating factor; IL-2			

= interleukin-2; IU = international units; MRD = minimal residual disease; RCT = randomized controlled trial; SAE = serious adverse event.
Note: The unit m^2 refers to body surface area.
[a] The dosage 25 mg/m^2/day applies to dinutuximab that was produced by the National Cancer Institute and it is equivalent to 17.5 mg/m^2/day of dinutuximab produced by the United Therapeutics Corporation. Only the National Cancer Institute dinutuximab was administered in the study.

a) Trial[2]

Details on Study DIV-NB-301 (referred to here as "Study 301") are presented in Table 4. Study 301 was a phase III, parallel-group, multi-centre, open-label RCT conducted by the Children's Oncology Group (COG). The objective of this study was to determine whether dinutuximab immunotherapy (dinutuximab, granulocyte macrophage colony-stimulating factor [GM-CSF], and interleukin-2 [IL-2]) with retinoic acid (RA) improved event-free survival (EFS) after myeloablative therapy and autologous stem cell therapy (ASCT) compared with RA alone in patients with high-risk neuroblastoma who achieve a pre-ASCT tumour response of complete response, very good partial response, or partial response.

Eligibility Criteria[2]

A total of 226 patients with high-risk neuroblastoma at 90 centres in the US, Canada, and Australia were randomized in a 1:1 ratio to dinutuximab immunotherapy with RA or RA alone. High-risk neuroblastoma was defined using the COG system,[4] in which patients must meet one of the following sets of criteria to be considered as having high-risk neuroblastoma:

- INSS stage 2A/2B or 3 and MYCN status of "amplified"
- INSS stage 4, age of less than 1 year, and MYCN status of "amplified"
- INSS stage 4, age of 1 year to 1.5 years, and one of the following: MYCN status of "amplified", DNA index of 1, or unfavourable histology
- INSS stage 4 and age of at least 1.5 years
- INSS stage 4S, age of less than 1 year, and MYCN status of "amplified"

Tumour response to previous induction therapy at pre-ASCT evaluation was based on the INRC[5] which classifies response as one of the following:

- Complete response: No evidence of primary tumour or metastases; and urine catecholamines normal
- Very good partial response: Greater than 90% reduction in primary tumour; no evidence of metastatic disease; and catecholamines normal (residual bone scan changes attributable to incomplete healing of the bone allowed)
- Partial response: Greater than 50% reduction of primary tumour; greater than 50% reduction in measurable sites of metastases; no more than one positive bone marrow site; and number of positive bone sites decreased by greater than 50%
- Mixed response: No new lesions; greater than 50% reduction of any measurable lesion with less than 50% reduction in any other site; and less than 25% increase in any existing lesions
- No response: No new lesions; less than 50% reduction and less than 25% increase in any existing lesions
- Progressive disease: Any new lesion or increase of any measurable lesion by more than 25%; or previously negative marrow positive for tumour

Patients with more than one myeloablative consolidation and stem cell transplantation were excluded (as of protocol amendment 4 on March 12, 2004), though this did not apply to patients who received tandem transplants per one of the specified precursor study protocols.

Informed consent was obtained within the three weeks prior to ASCT. The eligibility criteria are listed in Table 4.

Randomization[2]

Randomization was stratified according to the pre-ASCT chemotherapy protocol, whether stem cells were purged or not, the number of ASCTs, and response to chemotherapy (complete, very good partial, or partial). In total, there were 24 randomized strata as well as one stratum of patients with post-ASCT persistent disease who were allocated to the immunotherapy arm. The CGP noted that having persistent disease does not exclude patients from the population of the reimbursement request.

Randomization was done by the COG Remote Data Entry system using stratified permuted blocks with a block size of 2 within each stratum. Assignment to treatment groups was random unless a margin within a stratum was exceeded. At that point, treatment assignment became deterministic. Once a patient was assigned to a treatment group, their assignment did not change.

Assessment of Outcomes[2]

The primary efficacy end point, EFS, was defined as the time from enrolment to the first occurrence of relapse, progressive disease, secondary malignancy, death, or date of last contact (if no event occurred). The definition of progressive disease used for the determination of EFS was the same as the one used in determining pre-ASCT response, with the addition of cases with an increase from 10% or less tumour in marrow to over 10% tumour in marrow.

Tumours were assessed prior to the start of study treatment and within two weeks following the last dose of RA in cycle 6. The following assessments were performed: metaiodobenzylguanidine (MIBG) scan (with bone or fluorodeoxyglucose [FDG] positron emission tomography [PET] allowed for patients without MIBG avid tumours), computed tomography (CT) scan, magnetic resonance imaging (MRI) scan, and bone marrow biopsy/aspiration. In addition to the aforementioned time points, imaging assessments were performed every three months after the end of treatment for one year and subsequently every six months for another two years. Bone marrow biopsy/aspiration was also collected three months after end of treatment and at relapse. Assessments performed as part of the standard of care regimen were also recorded. Tumour measurements were determined by the product of the longest and widest perpendicular diameters, with a third dimension added when possible.

Overall survival (OS) was defined as the time from study enrolment to death or time of last contact in the absence of death.

Minimal residual disease (MRD) was assessed up to four weeks prior to the start of study treatment and within two weeks following the last dose of RA. Category of change in MRD (no evidence of disease, improved, no change, or progression/new lesions) from the pre-treatment time point to the end to treatment time point was reported for MIBG scans of the primary tumour, bone marrow, and bone. Immunocytology of blood and bone marrow sample was also to be performed for MRD assessment, but these results were not reported (likely due to the issues with compliance in collecting immunocytology samples outlined below).

Adverse events (AEs) of Grade 3 or higher were to be reported from the start of study treatment to 30 days following the last dose of study treatment. The following AEs were to be reported regardless of severity: drug hypersensitivity, capillary leak syndrome, and peripheral neuropathy for the 2009 analysis and hypotension, hypersensitivity, urticaria, capillary leak syndrome, anaphylactic reaction, dyspnea, cytokine release syndrome, and acute respiratory distress syndrome for the 2012 follow-up analysis. AEs that were reported according to the National Cancer Institute's (NCI) Adverse Event Expedited Reporting System (AdEERS) reporting criteria were considered to be serious AEs (SAEs).

Data Cut-offs[2]

Randomization was halted on January 13, 2009 as it was judged that the early stopping criteria for EFS had been met. All randomized patients enrolled up to this date were included in the intention-to-treat (ITT) analysis set. The results from the January 13, 2009 data cut-off were published in Yu et al., 2010[3] and were used for the main analysis of the primary end point. Since that data set became corrupted and was not archived, the closest data set available (June 30, 2009) was used for confirmatory analyses. Follow-up analyses were conducted with a data cut-off of June 30, 2012. The European Medicines Agency reported results from analyses using data from 2014.[6] A final study progress report was also prepared by the Submitter using a data cut-off of July 1, 2016.

The study continued after randomization was closed and all subsequently enrolled patients received dinutuximab immunotherapy with RA. The results for patients who enrolled after the close of randomization were presented as a separate study (Study DIV-NB-302) that is outside the scope of this review.

Statistical Analysis[2]

The difference in EFS distributions between the treatment groups was to be tested with a two-sided log-rank test at a significance level of 0.05. EFS was to be analyzed by comparing 2-year survival point estimates, plotting the Kaplan-Meier curves using product-limit estimates, and comparing incidence of events using Fisher's exact test. While EFS and OS were both primary endpoints in the original protocol, OS became a secondary endpoint in amendment 4 (March 12, 2004).

The planned sample size was based on the following assumptions: 3-year EFS of 50% in the RA alone group and 65% in the immunotherapy with RA group, proportional hazards with average post- versus pre- 3-year hazard ratio of 0.25, loss of 10% of patients to follow-up, and a percentage of about 85% of patients with INSS Stage 4 neuroblastoma. A sample size of 386 was planned to provide 80% power to detect a 15% difference in 3-year EFS between the treatment groups at a significance level of 0.05 for a two-sided test. The originally planned sample size was 322 based on a one-sided test at a significance level of 0.05 and this was revised in amendment 4. The revised sample size estimate corresponded to at least 85% power to detect a difference using a one-sided 0.05 test in the INSS Stage 4 subgroup.

Interim analyses were performed every six months by the Data Safety Monitoring Committee (DSMC), starting after 20% of the planned events occurred. The DSMC consisted of a minimum of nine voting members, including one consumer representative, two statisticians from outside the COG, two COG members (DSMC Chair and Vice-Chair), and four to five other members. The majority of voting members were not affiliated with COG.

Boundaries for efficacy and non-significance for the first three interim analyses were calculated using the Fleming-Harrington-O'Brien method with a cumulative alpha level

of 0.05. The following three interim analyses used the same method with a cumulative one-sided alpha level of 0.025 (the FDA stated they would consider the antibody for licensure if a significance level of 0.025 was reached). For the seventh and last interim analysis, the more conservative Lan-DeMets method with a cumulative alpha level of 0.025 was used. The upper boundary for efficacy (EFS) was determined for the Lan DeMets method using a spending function of $\alpha \times t^2$ for a cumulative alpha level of 0.025 and the lower boundary for non-significance was determined based on repeated testing of the alternative hypothesis that relative risk (RA alone versus immunotherapy with RA) was 1.6 at a *P* value of 0.005.

The study was temporarily closed on January 13, 2009 over concern about the increased incidence of allergic reactions in the dinutuximab group. However, the stopping rule on unacceptable toxicities was not met. Using the amended rule for stopping based on interim efficacy analyses (Lan-DeMets method with a cumulative alpha level of 0.025) on the January 13, 2009 data set, the observed upper boundary z-value (2.528) was very close to the upper Lan-DeMets boundary z-value (2.55). While the stopping rule for efficacy was not met, the statistician considered the evidence to be sufficient for stopping the study as it was very likely the significance level of 0.025 proposed by the FDA would be met should the study reach full accrual.

All other outcomes besides EFS were secondary outcomes with no adjustment for multiplicity. The same statistical analyses performed for EFS were to be performed for OS, provided the 0.05 significance level for the two-sided log rank test of EFS was met. Subgroup analyses for EFS and OS were pre-specified for patients diagnosed with INSS Stage 4 neuroblastoma.

Immunocytology specimens for MRD assessment were to be submitted at three time points: the end of induction and before ASCT, prior to treatment cycle 4, and after completion of treatment cycle 6. In all of the DSMC reports compliance in the submission of immunocytology data was well below the 80% compliance goal and the stopping rule for compliance was met at every interim assessment from November 30, 2006 onwards. The study proceeded despite the stopping rule being met and the middle MRD assessment became optional after protocol amendment 8.

Although formal comparisons of change in MRD between the treatment groups were planned, MIBG data was presented descriptively according to category in each treatment cycle and data from biopsy samples were not presented in the clinical study report.

Protocol Amendments[2]

There were nine major protocol amendments, including the one that ended randomization into the study. Neither the EMA's Assessment Report on dinutuximab[6] nor the pCODR CGP identified any amendments that would have had a significant impact on the study.

b) Populations[2]

Detailed baseline characteristics in the ITT population at the June 30, 2009 data cut-off (identical to the January 13, 2009 ITT population) are presented in Table 5. In the ITT population, most patients were male (range of 56.6% to 62.8%), white (79.6% to 84.1%), at least two years old (84.1% to 89.3%), had INSS stage 4 neuroblastoma (78.8% to 81.4%), had unfavourable tumour histological features (60.2% to 71.7%), and had received one previous ASCT (90% to 95%). MYCN status was amplified in 31.9% to 39.8%, tumour ploidy was hyperdiploid in 42.5% to 43.4%, and stem cell infusions were purged in at least one ASCT in 24.8% to 25.7% of patients. Categorization of response to induction therapy before ASCT was similar between groups with 33.6% to 35.4% of

patients achieving complete response, 41.6% to 43.4% achieving very good partial response, and 23.0% achieving partial response. There were higher percentages of patients in the RA alone group with INSS stage 3 neuroblastoma (14.2% versus 8.8%), amplified MYCN status (39.8% versus 31.9%), diploid DNA (40.7% versus 31.0%), and unfavourable tumour histology (71.7% versus 60.2%).

While patients with relapsed/refractory neuroblastoma were identified as a population of interest by PAG, these patients were excluded from Study 301. Patients non-randomly assigned to immunotherapy and RA were included in the safety population but not the ITT population.

Table 5: Baseline patient characteristics in Study DIV-NB-301

June 30, 2009 cut-off	RA alone ITT Set N = 113	Immunotherapy + RA ITT Set N = 113
Age at enrolment		
Mean in years (SD)	4 (2.13)	4.3 (2.49)
Age category, n (%)		
28 days to 2 years	18 (15.9)	12 (10.6)
2 to 12 years	94 (83.2)	97 (85.8)
12 to 18 years	1 (0.9)	4 (3.5)
Age category at diagnosis, n (%)		
28 days to 2 years	35 (31.0)	28 (24.8)
2 to 12 years	71 (62.8)	79 (69.9)
12 to 18 years	1 (0.9)	4 (3.5)
Unknown	6 (5.3)	2 (1.8)
Sex, n (%)		
Male	64 (56.6)	71 (62.8)
Female	49 (43.4)	42 (37.2)
Ethnicity, n (%)		
Hispanic or Latino	11 (10)	11 (10)
Not Hispanic or Latino	96 (85)	100 (89)
Unknown	6 (5)	2 (2)
Race, n (%)		
White	90 (79.6)	95 (84.1)
Black or African American	8 (7.1)	8 (7.1)
Asian	4 (3.5)	2 (1.8)
Native Hawaiian or Other Pacific Islander	2 (1.8)	0
Multiple	2 (1.8)	1 (0.9)
Other	0	1 (0.9)
Unknown	7 (6.2)	6 (5.3)
Pre-ASCT response, n (%)		
Complete	38 (33.6)	40 (35.4)
Very good partial	49 (43.4)	47 (41.6)
Partial	26 (23.0)	26 (23.0)
Number of ASCTs, n (%)		
1	102 (90)	107 (95)
2	11 (10)	6 (5)
Stem cell type, n (%)		
Purged	29 (25.7)	28 (24.8)
Unpurged	58 (51.3)	61 (54.0)
Unknown	26 (23.0)	24 (21.2)
Mean days since final ASCT (SD)	77 (12.0)	75 (8.7)
INSS stage, n (%)		
Stage 2a	0	4 (3.5)
Stage 3	16 (14.2)	10 (8.8)
Stage 4	92 (81.4)	89 (78.8)
Stage 4S	0	2 (1.8)

June 30, 2009 cut-off	RA alone ITT Set N = 113	Immunotherapy + RA ITT Set N = 113
Missing	5 (4.4)	8 (7.1)
MYCN status, n (%)		
Amplified	45 (39.8)	36 (31.9)
Non-amplified	51 (45.1)	52 (46.0)
Missing	17 (15.0)	25 (22.1)
DNA ploidy, n (%)		
Diploid	46 (40.7)	35 (31.0)
Hyperdiploid	48 (42.5)	49 (43.4)
Missing	19 (16.8)	29 (25.7)
Tumour histology, n (%)		
Favourable	5 (4.4)	4 (3.5)
Unfavourable	81 (71.7)	68 (60.2)
Missing	27 (23.9)	41 (36.3)
Mean absolute phagocyte count /μL (SD)	17153 (74215)	11767 (50411)

Source: pCODR submission,[2] Yu et al., 2010.[3]
Abbreviations: ASCT = autologous stem cell transplant; DNA = deoxyribonucleic acid; INSS = International Neuroblastoma Staging System; ITT = intention-to-treat; RA = retinoic acid; SD = standard deviation.

c) Interventions[2]

Dinutuximab was administered in combination with GM-CSF, IL-2, and RA. Both treatment arms consisted of six consecutive 4-week treatment cycles. The dinutuximab group received dinutuximab during cycles 1 to 5, RA during cycles 1 to 6, GM-CSF during cycles 1, 3, and 5, and IL-2 during cycles 2 and 4. The control group received RA alone for six cycles.

Each therapy was administered as follows:

- Dinutuximab i.v. over 5.75 to 20 hours at 25 mg/m^2 body surface area (BSA)/day for 4 consecutive days during cycles 1 to 5
- GM-CSF s.c. (preferred) or i.v. over two hours at 250 μg/m^2 BSA /day for 14 days starting 3 days before dinutuximab was started in cycles 1, 3, and 5
- IL-2 i.v. continuously at 3.0 × 10^6 international units (IU) / m^2 BSA /day for 4 days (96 hours) during week 1 and 4.5 × 10^6 IU/m^2/day for 4 days during week 2 in cycles 2 and 4
- RA p.o. 160 mg/ m^2 BSA /day (or 5.33 mg/kg/day divided twice daily for patients weighing 12 kg or less) during the last 2 weeks of cycles 1 to 6

Dinutuximab in Study 301 was produced by the NCI. The 25 mg/m^2/day dosage of this product is equivalent to the 17.5 mg/m^2/day dosage of dinutuximab produced by the United Therapeutics Corporation.

Each cycle of dinutuximab was only started if criteria related to liver enzymes, skin toxicity, infection status, serum creatinine, and platelet count were met. Each cycle of RA was only started if patients met criteria related to liver enzymes, skin toxicity, serum triglycerides, proteinuria, hematuria, serum creatinine, and serum calcium. Pre-specified dose modifications were implemented if certain toxicities were observed.

Patients were required to discontinue dinutuximab treatment if they experienced dose limiting toxicities (Grade 3 and 4 allergic reaction, Grade 3 serum sickness, Grade 4 severe, unrelenting neuropathic pain unresponsive to narcotics and other

measures, neurotoxicity, Grade 4 hyponatremia, Grade 4 capillary leak syndrome, or Grade 4 skin toxicity), used corticosteroids (unless required for a life-threatening condition), had recurrent or progressive disease, or used other anti-cancer agents.

During study treatment, other anti-cancer therapies and immunosuppressive drugs were prohibited. Antibiotics, blood products, anti-emetics, fluids, electrolytes, and general supportive care measures were allowed. The following pre-medications were administered during the dinutuximab treatment cycles: hydroxyzine or diphenhydramine, acetaminophen, morphine sulfate (or other narcotics), and lidocaine and/or gabapentin if needed. The following pre-medications were administered during the first four days of each IL-2 treatment cycle: acetaminophen, ibuprofen, and hydroxyzine or diphenhydramine, meperidine, anti-emetics, and/or furosemide as needed. The CGP noted that supportive care and pre-medications in Canadian clinical practice match those that were used in the study.

Concomitant medications were not recorded in the study. Steroid use was reported, though the reason for steroid use was not recorded.

Protocol Deviations[2]

The Study Data Review Committee (SDRC) reviewed study data according to a review plan on a regular basis and comprised of the study chair, COG study statistician, and COG research coordinator. The data reviewed included data delinquencies, data validations, patient eligibility data, patient safety data, and regulatory compliance data. The COG reviewed at least 10% of accrued study patients at each site every 36 months in accordance with NCI guidelines.

Protocol deviations were classified as patient case, pharmacy, institutional review board, or informed consent form deviations. There were many protocol deviations recorded for the latter three categories; however, these were site-specific as opposed to patient-specific. Patient case deviations are summarized in Table 6 by treatment group. The most frequent categories of protocol deviation were dosing deviation, missing documentation, and procedural deviation. The most common dosing deviations were: "treatment doses incorrectly administered, calculated or documented" and "dose deviation, modification, or calculations incorrect (error greater than +/- 10%)". The most common deviation for missing documentation was "documentation missing; unable to confirm eligibility". The most common deviations for procedural deviation were "tumor measurements/evaluation of status or disease not performed according to protocol" and "follow-up studies necessary to assess AEs not performed". There were no notable imbalances in protocol deviations between the treatment groups and no more than 10% of patients were affected per group in each category of deviation.

Table 6: Protocol deviations in Study DIV-NB-301

	RA alone ITT Set N = 113	Immunotherapy + RA ITT Set N = 113
Protocol deviations by category, n (%)		
Data entry error	5 (4)	5 (4)
Deviation from COG policy	2 (2)	2 (2)
Dosing deviation	7 (6)	11 (10)
Dosing deviation and missing documentation	0	1 (< 1)
Entry criteria deviation	1 (< 1)	0
Missing documentation	9 (8)	5 (4)

	RA alone ITT Set N = 113	Immunotherapy + RA ITT Set N = 113
Procedural deviation	5 (4)	9 (8)
Unapproved medication	0	1 (< 1)

Source: pCODR submission.[2]
Abbreviations: COG = Children's Oncology Group; ITT = intention-to-treat; RA = retinoic acid.

d) Patient Disposition[2]

The intention-to-treat (ITT) population was defined as all eligible patients who were randomized and patients were analyzed according to the group to which they were randomized. All efficacy analyses were performed in the ITT population. The safety population was defined as all patients who enrolled and started study treatment and patients were analyzed according to the actual treatment received. All safety analyses were performed in the safety population. The CGP did not expect there to be any differences in harms outcomes related to the presence of residual disease and considered the combining of randomized and non-randomized patients in the safety population acceptable.

In this report, results from both the January 13, 2009 and June 30, 2009 data sets are presented for EFS and OS and results from the June 30, 2012 data set are presented for the safety results and MRD results. Follow-up EFS and OS analyses from June 30, 2012, a 2014 data set in the EMA's Assessment Report, and a progress report from Fall 2016 (July 1, 2016 data cut-off) are also presented in this report.

One patient in the 2009 ITT sets was excluded from subsequent ITT analyses as they were found to be ineligible for the study in a COG audit. Two patients assigned to the non-randomized group and included in the 2012 data set were not included in the 2009 data set due to a lack of data in the database.

Four patients who initially received RA alone (full six cycles) crossed over to receive a full course (six cycles) of dinutuximab with RA. For the efficacy outcomes, these patients were censored at the time of crossover. For the safety analyses, these patients were each counted under both treatment groups.

Seven patients in the ITT population were originally censored with date of last contact in the June 30, 2012 data set, though it was later found that date of last contact was in fact date of death for these patients. A corrected OS analysis was performed using the updated information. Since events had occurred prior to death in these patients, EFS was not affected.

Safety results are presented for a revised June 30, 2012 safety set. The revisions involved three randomized patients who were originally analyzed in the incorrect group and nine randomized patients who were originally included despite not receiving study therapy.

The ITT set in the Fall 2016 progress report used the same population as in the Janurary 13, 2009 ITT set aside from the exclusion of three patients in the RA alone group who were retrospectively found to have been ineligible for the study.

There was no imputation of missing data and patients were censored at the last point of contact at the time of data cut-off for EFS and OS. Patients who discontinued the intervention were followed until death, loss to follow-up, enrolment in another study for tumour treatment, withdrawal of consent, or 10 years after enrolment.

Patient disposition is described for the 2009 ITT sets and the 2012 safety set in Table 7. In both of the 2009 data sets, notably more patients discontinued intervention due to progressive disease in the RA alone group compared with the dinutuximab group (15.9% versus 6.2% in the June 30, 2009 data set and 11.5% versus 5.3% in the January 13, 2009 data set). Discontinuations due to toxic effects in the January 13, 2009 data set were also different between the groups (1.8% in the RA alone group and 13.3% in the dinutuximab group). In the June 30, 2009 data set, there were higher percentages of patients discontinuing due to withdrawal of consent and toxicity in the dinutuximab group versus the RA alone group (12.4% versus 8.0% and 4.4% versus 0%). Similar trends were observed in the June 30, 2012 safety set. Differences between the two 2009 data sets in terms of categories of discontinuation of intervention and percentages of patients in each category could not be explained by the Submitter because patient-level data from the January 13, 2009 data set was not available. The Submitter noted that the reasons for discontinuation could have been updated after the January 13, 2009 cut-off due to data reconciliation.

Table 7: Patient disposition in Study DIV-NB-301

June 30, 2009 cut-off	RA alone ITT set	Imm + RA ITT set	Imm + RA (non-randomized)
Enrolled, N	251 (includes 25 assigned to Imm + RA)		
Randomized, N	**113**	**113**	**25 assigned**
Discontinued intervention, n (% of randomized or assigned)	29 (25.6)	34 (30.1)	7 (28.0)
Progressive disease	18 (15.9)	7 (6.2)	5 (20.0)
Death	1 (0.9)	1 (0.9)	0
Consent	9 (8.0)	14 (12.4)	0
Toxicity	0	5 (4.4)	1 (4.0)
Corticosteroid use	0	2 (1.8)	0
Missing	0	5 (4.4)	1 (4.0)
Other	1 (0.9)	0	0
Discontinued study, n (% of randomized or non-randomized)	40 (35.4)	32 (28.3)	4 (16.0)
No data	20 (17.7)	15 (13.3)	2 (8.0)
Consent	5 (4.4)	6 (5.3)	0
Enrolled in another study	8 (7.1)	6 (5.3)	1 (4.0)
Death	7 (6.2)	5 (4.4)	1 (4.0)
January 13, 2009 cut-off	**RA alone ITT set**	**Imm + RA ITT set**	**Imm + RA (non-randomized)**
Enrolled, N	252 (includes 25 assigned to Imm + RA)		
Randomized, N	**113**	**113**	**25 assigned**
Received allocated/assigned intervention, N	106	107	25
Did not receive allocated/assigned intervention, N	7	6	0
Declined immunotherapy and received standard therapy	0	6	0
Declined immunotherapy and received other anti-GD2 therapy	5	0	0
Died from infection	1	0	0
Subsequently non-randomly assigned to immunotherapy owing to persistent disease	1	0	0
Discontinued intervention, n (% of randomized or assigned)	17 (15.0)	24 (21.2)	4 (16)
Progressive disease	13 (11.5)	6 (5.3)	3 (12.0)
Died from IL-2 overdose	0	1 (0.9)	0

Recovered from IL-2 overdose	0	1 (0.9)	0
Toxic effects	2 (1.8)	15 (13.3)	1 (4.0)
Dose-limiting toxic effects	2 (1.8)	1 (0.9)	0
Were continuing to receive protocol therapy, n (%)	6 (5.3)	5 (4.4)	3 (12.0)
June 2012 cut-off	**RA alone Safety set**	**Imm + RA (all) Safety set**	
Enrolled, N	114	141	
Randomized, N	114	114 (+ 27 assigned)	
Safety population, N	**109**	**141**	
Completed treatment, N	85	110	
Discontinued treatment, n (% of safety population)	24 (22.0)	31 (22.0)	
Cycle 1	7 (6.4)	7 (5.0)	
Cycle 2	1 (0.9)	6 (4.3)	
Cycle 3	7 (6.4)	7 (5.0)	
Cycle 4	5 (4.6)	7 (5.0)	
Cycle 5	1 (0.9)	2 (1.4)	
Cycle 6	3 (2.8)	2 (1.4)	
Reason for discontinuing treatment, n (% of safety population)			
Progressive disease	18 (16.5)	12 (8.5)	
Patient withdrawal	5 (4.6)	10 (7.1)	
Toxicity	0	6 (4.3)	
Corticosteroid use	0	2 (1.4)	
Death	0	1 (0.7)	
Physician decision	1 (0.9)	0	
Discontinued study, n (% of safety population)	39 (35.8)	47 (33.3)	
Death	26 (23.9)	26 (18.4)	
Enrolment in another therapeutic study for tumour	8 (7.3)	12 (8.5)	
No data entered	2 (1.8)	2 (1.4)	
Withdrawal of consent for further data submission	1 (0.9)	3 (2.1)	
Lost to follow-up	2 (1.8)	4 (2.8)	
Days of follow-up			
Mean (SD)	1485 (865.58)	1614.2 (852.04)	
Median (range)	1414 (100, 3514)	1595 (40, 3614)	

Sources: pCODR submission[2] and Yu et al., 2010.[3]
Abbreviations: IL-2 = interleukin-2; Imm = immunotherapy; ITT = intention-to-treat; NA = not applicable; RA = retinoic acid; SD = standard deviation.

Treatment Exposure[2]

Most patients completed six treatment cycles. Treatment exposure was similar between the treatment groups in the ITT set (Table 8). There was steroid use in 6.8% or less of each treatment group during each cycle with no notable differences between groups.

Table 8: Treatment exposure in Study DIV-NB-301

	RA alone ITT Set N = 113	Immunotherapy + RA ITT Set N = 113
Number of treatment cycles completed, n (%)		
0	2 (1.8)	0
1	111 (98.2)	113 (100)

	RA alone ITT Set N = 113	Immunotherapy + RA ITT Set N = 113
2	99 (87.6)	102 (90.3)
3	98 (86.7)	95 (84.1)
4	91 (80.5)	89 (78.8)
5	86 (76.1)	84 (74.3)

Source: pCODR submission.[2]
Abbreviations: ITT = intention-to-treat; RA = retinoic acid.
Note: RA was administered for a six cycles while immunotherapy was administered for five cycles.

e) Limitations/Sources of Bias[2]

Overall, the design of the RCT was appropriate for testing the efficacy of dinutuximab, IL-2, and GM-CSF in high-risk neuroblastoma patients with at least a partial response to first-line, multimodal therapy. Randomization and allocation methods were appropriate, as were the outcome measures and statistical analyses. The study was open-label and there were no efforts to blind patients and study personnel to treatment allocation due to the complexity of the interventions. There was no risk of assessment bias for OS since it is an objective measure. Definitions of events and time points for follow-up assessments of disease status were pre-specified such that there was only a low risk of bias in EFS assessment.

The following limitations of the RCT should be taken into account when interpreting the results:

- There were higher percentages of patients in the RA alone group with INSS stage 3 neuroblastoma (14.2% versus 8.8%), amplified MYCN status (39.8% versus 31.9%), diploid DNA (40.7% versus 31.0%), and unfavourable tumour histology (71.7% versus 60.2%). The imbalances in MYCN status, DNA ploidy, and tumour histology are likely to have favoured dinutuximab and the planned analysis did not adjust for prognostic factors.
- There were imbalances in treatment discontinuation, with higher percentages of the dinutuximab group discontinuing due to toxicity or withdrawal of consent in the ITT set. However, treatment exposure was similar between the treatment groups in the ITT set and the CGP did not expect toxicity reactions to be related to prognosis or treatment efficacy. Therefore, there is a low risk of bias from these imbalances.
- The study technically ended before the efficacy stopping criteria were met. The confirmatory EFS analysis in the June 30, 2009 was less favourable than the January 13, 2009 analysis, though still statistically significant. There were also two separate amendments to the early stopping criteria for efficacy. Given the less than ideal circumstances surrounding the primary end point analysis, the follow-up analyses and the OS analyses are important for confirming the results of the primary analysis.
- Statistical testing and sample size calculations were based solely on EFS. There was no control for multiplicity of outcomes.
- MRD burden is a surrogate outcome. While it may be a prognostic factor for EFS and OS, it is less informative than these outcomes. Only MIBG results were reported for MRD burden and these had substantial amounts of missing data.

- It is not possible to rule out bias in the reporting of AEs due to the open-label nature of the study.
- Health-related quality of life data was not collected.
- The results can only inform the efficacy and safety of the combination of dinutuximab, IL-2, and GM-CSF and not the individual components.
- Patients with residual disease following ASCT were not randomized and were non-randomly assigned to the immunotherapy arm. Efficacy of dinutuximab in this group was not formally compared against a control arm.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

Efficacy Outcomes

Event-Free Survival[2]

Superiority of dinutuximab immunotherapy with RA over RA alone was demonstrated in the primary end point analysis in the January 13, 2009 data set (Table 9). EFS at two years was greater in the dinutuximab group than in the RA alone group (66.3% versus 46.4%), with a hazard ratio (HR) of 0.57 (95% confidence interval [CI], 0.37 to 0.89) in favour of dinutuximab and a statistically significant log-rank test (*P* = 0.0115; see Figure 2 for the Kaplan-Meier curves). The confirmatory analysis in the June 30, 2009 data set was consistent with these results, with 2-year EFS for the dinutuximab and RA alone groups similar to those in the primary analysis (65.6% versus 48.1%; HR = 0.64 [95% CI, 0.43 to 0.97]; *P* = 0.0330).

Follow-up analyses demonstrated a continued trend of improved EFS with the addition of dinutuximab therapy, though the between-group differences in EFS tended to decrease over time. Analyses performed following the January 13, 2009 analysis were descriptive as the efficacy stopping criteria were considered to have been met at the 2009 cut-off. In the June 30, 2012 data set, 3-year EFS was 62.8% in the dinutuximab group and 50.9% in the RA alone group. In the July 1, 2016 data set, 5-year EFS was 56.3% in the dinutuximab group compared with 46.1% in the RA alone group. The EFS curves from that data set almost converged after 10 years of follow-up, though the low numbers of patients at risk confer a substantial amount of uncertainty at that time point (Figure 4). Overall, the follow-up analyses of EFS suggest that the effect of dinutuximab on EFS may not have been maintained at longer follow-up times.

The EMA Assessment Report noted that adjustment for each individual prognostic factor related to tumour biology in Cox proportional hazards regression analyses yielded results consistent with the primary EFS analysis, though details were not provided.[6] The Submitter also performed post hoc analyses for inclusion in the Health Canada-approved product monograph.[2] Adjusting for age at diagnosis, age at enrolment, INSS stage, and pre-ASCT response in the analysis of EFS at June 30, 2009 yielded results consistent with the primary analysis.

In the non-randomized group with residual disease, 2-year EFS was 32.3% (95% CI, 11.4% to 53.2%) in the June 30, 2009 data set (N = 25), 3-year EFS was 33.3% (95% CI, 15.6% to 51.1%) in the June 30, 2012 data set (N = 27), and 5-year EFS was 32.0% (standard error of 10.0%) in the July 1, 2016 data set (N = 25). As an informal comparison, 3-year EFS in patients with residual disease from another COG study (Study CCG-3891) was estimated to be 12% (SE of 6%).[26]

Among patients with INSS Stage 4 neuroblastoma, EFS in both treatment groups tended to be about 3% to 4% lower than in the overall ITT population. Similar between-group differences in 2-year and 3-year EFS were observed in the January 13, 2009, June 30, 2009, and June 30, 2012 data sets in this subgroup as in the overall ITT population (Table 9). The log-rank test yielded *P* values of less than 0.05 in the 2009 data sets.

Overall Survival[2]

OS was also greater in the dinutuximab group compared with the RA alone group (Table 9), though there was no adjustment for multiple outcomes. In the January 13, 2009 data set, 2-year OS in the dinutuximab versus the RA alone group was 86.2% versus 74.5% with an HR of 0.52 (95% CI, 0.30 to 0.92; see Figure 3 for the Kaplan-Meier curves). The results from the June 30, 2009 data set confirmed these findings with a 2-year OS of 85.4% in the dinutuximab group and 75.3% in the RA alone group and an HR of 0.54 (95% CI, 0.32 to 0.92) in favour of dinutuximab.

Follow-up analyses strongly suggested that the OS benefit with dinutuximab was maintained over time. In the June 30, 2012 data set, 3-year EFS was 79.5% in the dinutuximab group and 67.3% in the RA alone group and the HR was provided by the Submitter as 0.57 (95% CI, 0.36 to 0.92). While updated 3-year OS and *P* values were provided for the corrected 2012 OS analysis (refer to Patient Disposition for details), updated numbers of events and HR were not provided by the Submitter upon request. However, the updated HR and confidence interval would have been nearly identical to the original values.

The post hoc analysis for Health Canada, adjusting for DNA ploidy and pre-ASCT response, was consistent with the results of the unadjusted analysis. The March 2014 results reported in the EMA Assessment Report (5-year OS of 74.2% versus 57.0%) and the July 1, 2016 results (5-year OS of 73.2% versus 56.4%; see Figure 5 for the Kaplan-Meier curves) showed consistently greater OS in the dinutuximab group with follow-up of up to 14 years.

OS values in the subgroup of patients with INSS Stage 4 neuroblastoma were similar to those in the overall ITT population (Table 9). A *P* value of less than 0.05 for the log-rank test was observed in the 2012 data set, but not in the 2009 data sets.

While OS was not a pre-specified outcome for the non-randomized group with residual disease, an OS estimate was provided for this group at the July 1, 2016 cut-off (5-year OS of 51.4% with a standard error of 10.4%).

Table 9: Efficacy outcomes in Study 301 evaluating dinutuximab in pediatric patients with high-risk neuroblastoma.

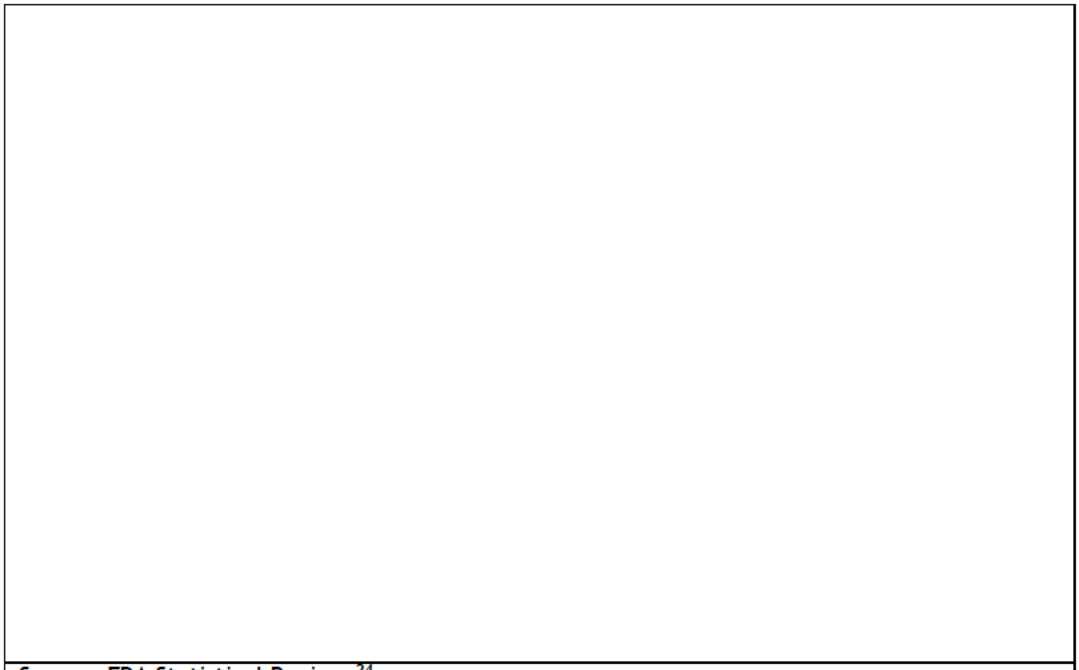
Efficacy outcomes	RA alone ITT set	Immunotherapy + RA ITT set
Primary		
EFS primary analysis (January 13, 2009 cut-off)	N = 113	N = 113
Number of events	49 (43.4)	33 (29.2)
2-year EFS, % (95% CI)	46.4 (35.8, 57.1)	66.3 (56.2, 76.3)
HR, immunotherapy vs. RA alone (95% CI)	0.57 (0.37, 0.89)	
P value for log-rank test	0.0115	
EFS confirmatory analysis (June 30, 2009 cut-off)	N = 113	N = 113
Number of events, n (%)	54 (47.8)	40 (35.4)
2-year EFS, % (95% CI)	48.1 (38.0, 58.2)	65.6 (56.1, 75.2)

Efficacy outcomes	RA alone ITT set	Immunotherapy + RA ITT set
HR, immunotherapy vs. RA alone (95% CI)	0.64 (0.43, 0.97)	
P value for log-rank test	0.0330	
EFS follow-up analysis (June 30, 2012 cut-off)	N = 114	N = 114
Number of events, n (%)	58 (50.9)	49 (43.0)
3-year EFS, % (95% CI)	50.9 (41.6, 60.2)	62.8 (53.9, 71.7)
HR, immunotherapy vs. RA alone (95% CI)	0.73 (0.50, 1.06)	
P value for log-rank test	0.0990	
EFS follow-up analysis (July 1, 2016 cut-off)	N = 110	N = 113
5-year EFS, % (SE)	46.1 (5.2)	56.3 (4.7)
P value for log-rank test	0.1136	
Secondary		
OS (January 13, 2009 cut-off)	N = 113	N = 113
Number of events, n (%)	27 (23.9)	16 (14.2)
2-year OS % (95% CI)	74.5 (65.2, 83.9)	86.2 (78.8, 93.6)
HR, immunotherapy vs. RA alone (95% CI)	0.52 (0.30, 0.92)	
P value for log-rank test	0.0223	
OS (June 30, 2009 cut-off)	N = 113	N = 113
Number of events, n (%)	36 (31.9)	22 (19.5)
2-year OS % (95% CI)	75.3 (66.4, 84.2)	85.4 (78.2, 92.6)
HR, immunotherapy vs. RA alone (95% CI)	0.54 (0.32, 0.92)	
P value for log-rank test	0.0213	
OS (June 30, 2012 cut-off)	N = 114	N = 114
Number of events, n (%)	44 (42.1)[a]	28 (27.2)[a]
3-year OS % (95% CI)	67.3 (58.5, 76.1)	79.5 (72.1, 87.0)
HR, immunotherapy vs. RA alone (95% CI)	0.57 (0.36, 0.92)[a]	
P value for log-rank test	0.0165	
OS (March 2014 cut-off[b])	N = 114	N = 114
5-year OS % (95% CI)	57.0 (47.5, 66.4)	74.2 (66.1, 82.3)
P value for log-rank test	0.0301	
OS (July 1, 2016 cut-off)	N = 110	N = 113
5-year OS % (SE)	56.4 (5.2)	73.2 (4.2)
P value for log-rank test	0.0543	
Efficacy outcomes in INSS Stage 4 subgroup	**RA alone ITT set**	**Immunotherapy + RA ITT set**
EFS (January 13, 2009 cut-off)	N = 92	N = 89
2-year EFS % (95% CI)	42.3 (31.0, 53.6)	62.9 (51.5, 74.2)
P value for log-rank test	0.0150	
EFS (June 30, 2009 cut-off)	N = 92	N = 89
2-year EFS % (95% CI)	43.7 (32.8, 54.7)	62.6 (51.8, 73.4)
HR, immunotherapy vs. RA alone (95% CI)[b]	0.64 (0.42, 0.99)	
P value for log-rank test	0.0422	
EFS (June 30, 2012 cut-off)	N = 93	N = 90
3-year EFS % (95% CI)	46.5 (36.3, 56.8)	59.5 (49.3, 69.7)
P value for log-rank test	0.0971	
HR, immunotherapy vs. RA alone (95% CI)[b]	0.71 (0.47, 1.07)	
OS (January 13, 2009 cut-off)	N = 92	N = 89
2-year OS % (95% CI)	75.7 (65.9, 85.6)	84.5 (75.9, 93.0)
P value for log-rank test	0.0866	

Efficacy outcomes	RA alone ITT set	Immunotherapy + RA ITT set
OS (June 30, 2009 data cut-off)	N = 92	N = 89
2-year OS % (95% CI)	75.8 (66.2, 85.4)	83.3 (74.9, 91.7)
HR, immunotherapy vs. RA alone (95% CI)[b]	0.62 (0.36, 1.07)	
P value for log-rank test	0.0813	
OS (June 30, 2012 cut-off)	N = 93	N = 90
3-year OS % (95% CI)	64.3 (54.3, 74.2)	81.7 (73.6, 89.8)
HR, immunotherapy vs. RA alone (95% CI)[b]	0.55 (0.34, 0.90)	
P value for log-rank test	0.0186	

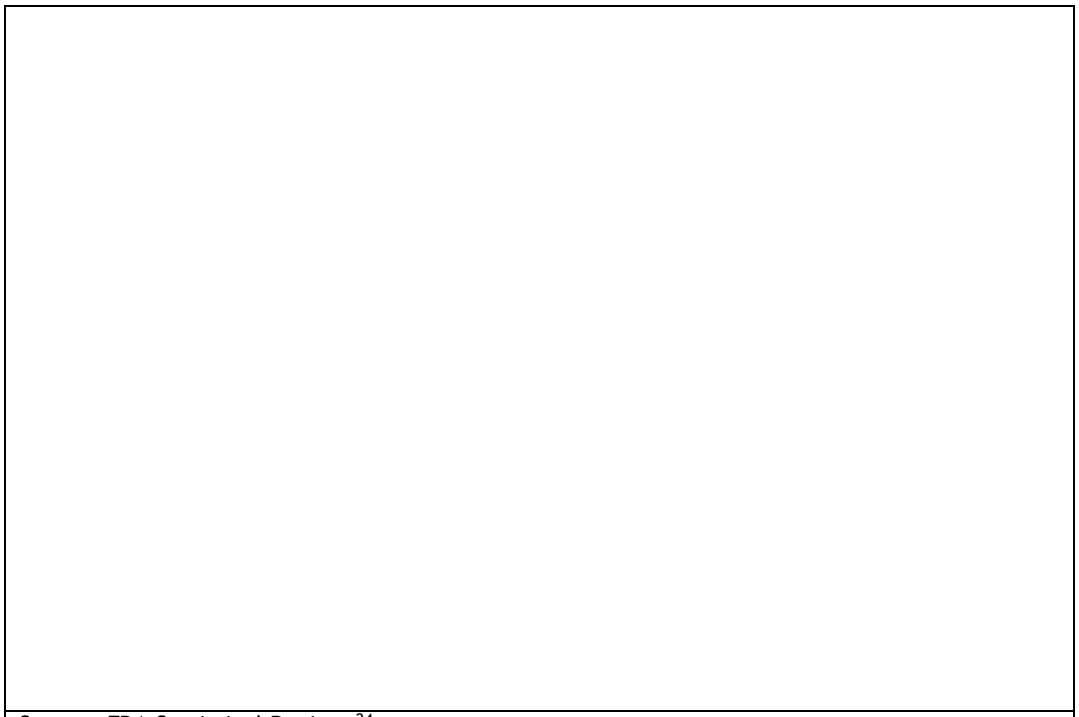
Source: pCODR submission,[2] and EMA assessment report.[6]
Abbreviations: CI = confidence interval; EFS = event-free survival; HR = hazard ratio; ITT = intention-to-treat; NA = not applicable; NR = not reported; OS = overall survival; RA = retinoic acid; SE = standard error.
Note: Hazard ratios are from unstratified Cox proportional hazards regression.
[a] These values are consistent with the original analysis of OS from the June 2012 data cut-off in which four patients in the RA alone group and three patients in the immunotherapy + RA group were erroneously censored at time of death.
[b] From analyses in the EMA Assessment Report.[6]

Figure 2: Kaplan-Meier curves of event-free survival for the January 13, 2009 data set



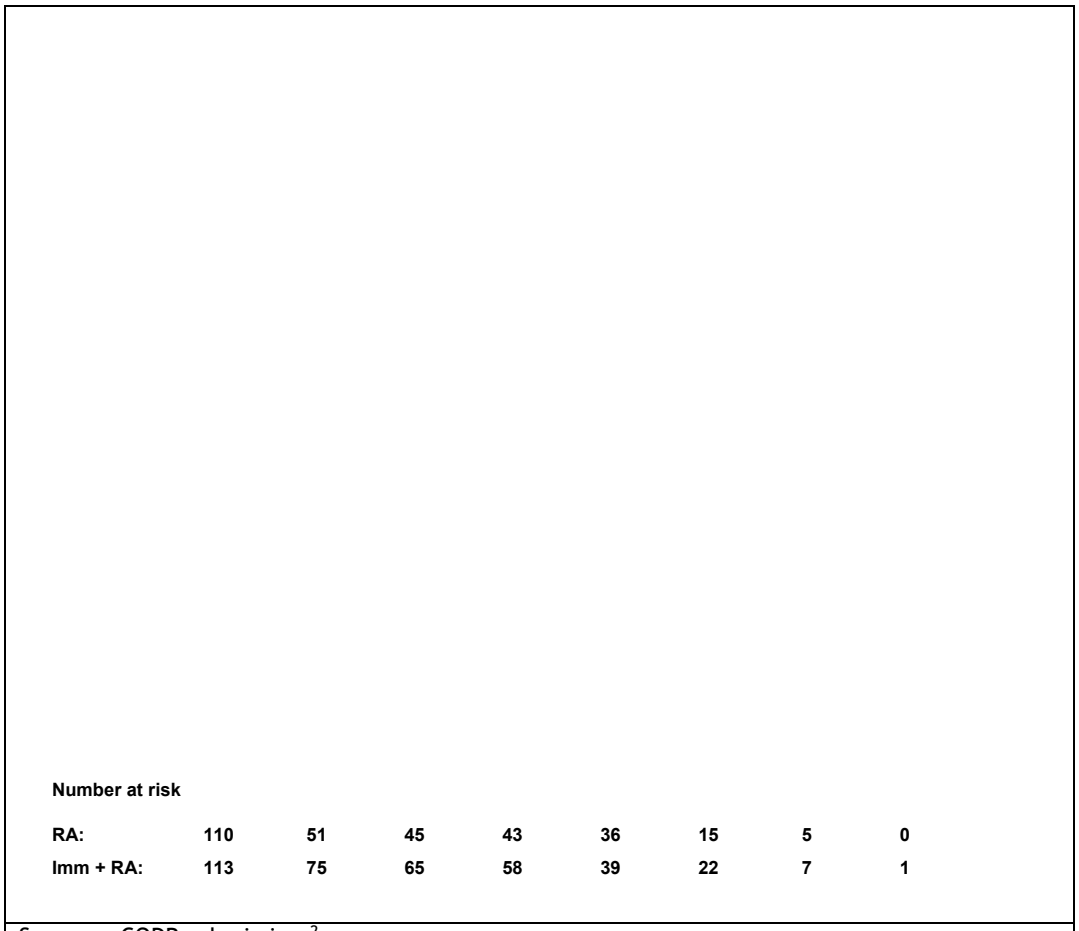
Source: FDA Statistical Review.[24]
Abbreviation: Immuno = immunotherapy; RA = retinoic acid.
Note: Numbers above the horizontal axis represent the number at risk at the beginning of each time period.

Figure 3: Kaplan-Meier curves of overall survival for the January 13, 2009 data set



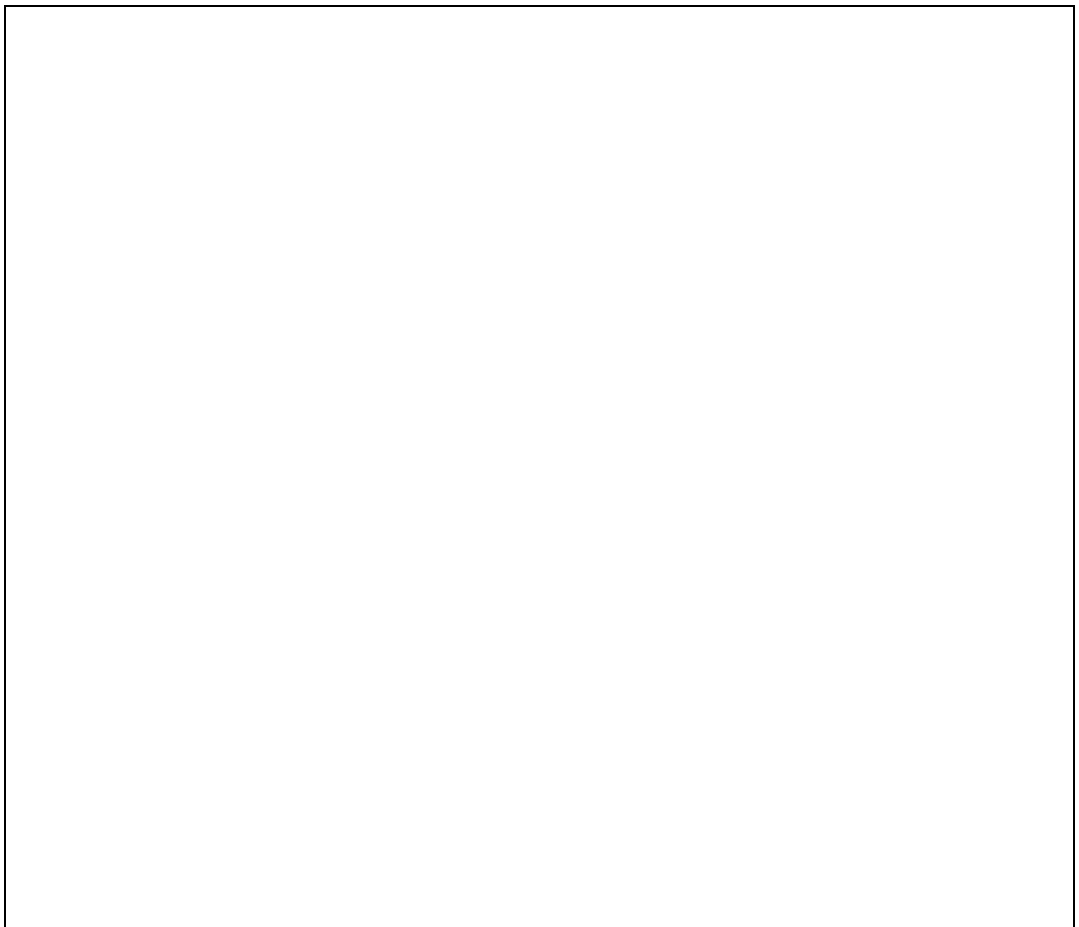
Source: FDA Statistical Review.[24]
Abbreviation: Immuno = immunotherapy; RA = retinoic acid.
Note: Numbers above the horizontal axis represent the number at risk at the beginning of each time period.

Figure 4: Kaplan-Meier curves of event-free survival for the 2016 Progress Report data set



Source: pCODR submission.[2]
Abbreviation: GD2 = dinutuximab; Imm = immunotherapy; RA = retinoic acid.
Note: The numbers at risk at the bottom of the figure were added to the figure from the pCODR submission.

Figure 5: Kaplan-Meier curves of overall survival for the 2016 Progress Report data set



Source: pCODR submission.[2]
Abbreviation: GD2 = dinutuximab; Imm = immunotherapy; RA = retinoic acid.
Note: The numbers at risk at the bottom of the figure were added to the figure from the pCODR submission.

Minimal Residual Disease[2]

Although MRD burden based on MIBG scans was categorized according to change in disease, it was not clear what time point was used as a baseline. Since MRD assessment were only required at pre-randomization and following treatment cycle 6, it is likely that changes were relative to the pre-randomization time point. The MIBG scan results from treatment cycle 6 in the June 20, 2012 data set are presented in Table 10. MIBG results were only available for 88 patients in the RA alone group and 87 patients in the dinutuximab group of the ITT set. In a separate report analyzing survival according to baseline Curie score, it was noted that 28 patients were excluded from this analysis due to the absence of a baseline MIBG scan or a baseline MIBG scan outside the pre-specified time window. However, this does not account for all of the missing data in the CSR. The percentage of patients with evidence of progression or new lesions was numerically greater in the RA alone group for the primary tumour (4.5% versus 2.3%), bone marrow (1.1% versus

none), and bone (6.8% versus 3.4%). However, percentages of patients with progression or new lesions were small overall.

Table 10: Minimal residual disease results in Study 301

MRD measured by MIBG imaging June 30, 2012 cut-off	RA alone ITT set N = 114	Immunotherapy + RA ITT set N = 114
Treatment cycle 6	N = 88	N = 87
MRD primary tumour, n (%)		
No evidence of disease	68 (77.3)	74 (85.1)
Improved	2 (2.3)	3 (3.4)
No change	4 (4.5)	4 (4.6)
Progression/new lesions	4 (4.5)	2 (2.3)
Not done	10 (11.4)	4 (4.6)
MRD bone marrow, n (%)		
No evidence of disease	74 (84.1)	79 (90.8)
Improved	0	0
No change	0	0
Progression/new lesions	1 (1.1)	0
Not done	13 (14.8)	8 (9.2)
MRD bone, n (%)		
No evidence of disease	69 (78.4)	71 (81.6)
Improved	0	3 (3.4)
No change	1 (1.1)	3 (3.4)
Progression/new lesions	6 (6.8)	3 (3.4)
Not done	12 (13.6)	7 (8.0)

Source: pCODR submission.[2]
Abbreviations: ITT = intention-to-treat; MIBG = metaiodobenzylguanidine; MRD = minimal residual disease; RA = retinoic acid.

Harms Outcomes

Adverse Events[2]

Although AEs of grade 3 or higher were to be collected, AEs of all grades were reported for Study 301. Since the completeness of AE reporting for all grades is unknown, a summary of AEs of grade 3 or higher in the June 30, 2012 safety population was requested from the Submitter and is included in this report. The June 30, 2012 data set was used to ensure the most complete reporting.

AEs of grade 3 or higher were reported in 96.5% of patients in the dinutuximab group and 64.2% of patients in the RA alone group (Table 11). AEs occurring in at least 10% of patients in both groups were as follows: lymphocyte count decreased, platelet count decreased, anemia, neutrophil count decreased, and device related infection (ranging from 17.0% to 56.0% in the dinutuximab group and ranging from 11.0% to 23.9% in the RA alone group). All other AEs occurred in no more than 8.3% of patients in the RA alone group. In addition, the following AEs occurred in at least 20% of patients in the dinutuximab group: pyrexia, hypokalemia, pain, abdominal pain, white blood cell count decreased, anaphylactic reaction, hyponatremia, alanine aminotransferase increased, and capillary leak syndrome (ranging from 22.0% to 40.4% of patients).

Serious Adverse Events[2]

SAEs occurred in 51.1% of patients in the dinutuximab group compared with 3.7% of patients in the RA alone group (Table 11). The only SAE occurring in

more than one patient in the RA alone group was catheter related infection (1.8%). The most common SAEs were catheter related infection, hypotension, anaphylaxis, hypokalemia, fever, and capillary leak syndrome, which occurred in 6.4% to 8.5% of patients in the dinutuximab group and no patients in the RA alone group (aside from catheter related infection).

Notable Harms[2]

AEs and SAEs related to infusion reaction, capillary leak syndrome, neuropathic pain, and severe neurologic toxicity were identified as being of particular interest in the systematic review protocol. However, each of these harms was associated with multiple AEs. The CGP identified the AEs of interest for the purposes of this review corresponding to each notable harm.

In terms of infusion reaction and capillary leak syndrome AEs in the dinutuximab versus RA alone groups, anaphylactic reaction (26.2% versus 0.9%), capillary leak syndrome (22.0% versus none), hypotension (19.9% versus none), serum sickness (0.7% versus 0.9%), and cytokine release syndrome (0.7% versus none) occurred almost exclusively in the dinutuximab group (Table 11). SAEs related to infusion reaction or capillary leak syndrome occurred in the dinutuximab group alone: hypotension (8.5%), anaphylaxis (7.8%), capillary leak syndrome (6.4%), allergic reaction (1.4%), cytokine release syndrome (1.4%), and bronchospasm (0.7%).

According to the CGP, pain with a neuropathic etiology could have been reported as any type of pain; therefore, all AEs containing "pain" or words ending in "algia" were included as notable harms in this report. The most common pain-related AEs were pain (28.4% in the dinutuximab group versus 2.8% in the RA alone group), abdominal pain (29.8% versus none), pain in extremity (8.5% versus 1.8%), back pain (7.1% versus none), and neuralgia (6.4% versus none). Pain-related SAEs occurred exclusively in the dinutuximab group, the most common being pain (3.5%), abdominal pain (2.8%), arthralgia (2.1%), and pain in extremity (2.1%).

AEs potentially related to severe neurotoxicity were included in this report, though they were not necessarily specific to neurotoxicity. AEs and SAEs considered by the CGP to be potentially related to neurotoxicity occurred in 2.1% or less in each group. Aside from psychotic disorder (2.1% versus none), all AEs and SAEs potentially related to neurotoxicity occurred in only one or two patients per group. Also, most of the AEs and all of the SAEs occurred in the dinutuximab group and not in the RA alone group.

Deaths[2]

Most deaths that occurred during the study were due to disease progression (28.5% of those who received dinutuximab and 39.4% of the RA alone group in the safety set, see Table 11). Aside from disease progression, four patients who received dinutuximab died from the following causes: infection, multi-organ failure, cytokine release syndrome due to IL-2 overdose, and hypoxia of unknown origin. Four patients died in the RA alone group from causes other than disease progression – two from multi-organ failure and two from unspecified causes.

Table 11: Adverse events in the Study 301 data set

Adverse events	Safety Set	
June 30, 2012 cut-off	RA alone N = 109	Immunotherapy + RA N = 141
Patients with ≥ 1 AE of grade 3 or higher, n (%)	70 (64.2)	136 (96.5)
AEs of Grade 3 or higher occurring in ≥5% of any treatment group, n (%)		
Lymphocyte count decreased	21 (19.3)	79 (56.0)
Platelet count decreased	26 (23.9)	55 (39.0)
Anemia	17 (15.6)	51 (36.2)
Neutrophil count decreased	14 (12.8)	51 (36.2)
Pyrexia	6 (5.5)	57 (40.4)
Hypokalemia	3 (2.8)	49 (34.8)
Pain[a]	3 (2.8)	40 (28.4)
Abdominal pain[a]	0	42 (29.8)
White blood cell count decreased	9 (8.3)	32 (22.7)
Anaphylactic reaction[a]	1 (0.9)	37 (26.2)
Hyponatremia	4 (3.7)	33 (23.4)
Device related infection	12 (11.0)	24 (17.0)
Alanine aminotransferase increased	3 (2.8)	31 (22.0)
Capillary leak syndrome[a]	0	31 (22.0)
Hypotension[a]	0	28 (19.9)
Urticaria	0	20 (14.2)
Diarrhea	1 (0.9)	18 (12.8)
Hypoxia	1 (0.9)	18 (12.8)
Decreased appetite	4 (3.7)	14 (9.9)
Staphylococcal bacteremia	3 (2.8)	15 (10.6)
Infection susceptibility increased	5 (4.6)	11 (7.8)
Aspartate aminotransferase increased	0	14 (9.9)
Pain in extremity[a]	2 (1.8)	12 (8.5)
Hypercalcemia	6 (5.5)	6 (4.3)
Hearing impaired	4 (3.7)	7 (5.0)
Vomiting	3 (2.8)	8 (5.7)
Back pain[a]	0	10 (7.1)
Hypoalbuminemia	0	10 (7.1)
Hypocalcemia	0	10 (7.1)
Hypophosphatemia	0	10 (7.1)
Hyperglycemia	1 (0.9)	8 (5.7)
Neuralgia[a]	0	9 (6.4)
Other notable AEs, n (%)		
Arthralgia	2 (1.8)	5 (3.5)
Headache	1 (0.9)	5 (3.5)
Musculoskeletal chest pain	0	6 (4.3)
Non-cardiac chest pain	0	5 (3.5)
Bone pain	1 (0.9)	3 (2.1)
Myalgia	0	4 (2.8)
Abdominal pain upper	0	3 (2.1)
Proctalgia	1 (0.9)	2 (1.4)
Psychotic disorder	0	3 (2.1)
Convulsion	1 (0.9)	1 (0.7)
Death	0	2 (1.4)
Irritability	0	2 (1.4)
Oropharyngeal pain	0	2 (1.4)
Peripheral motor neuropathy	0	2 (1.4)
Peripheral sensory neuropathy	0	2 (1.4)
Personality change	2 (1.8)	0
Serum sickness	1 (0.9)	1 (0.7)

Adverse events	Safety Set	
Blindness	1 (0.9)	0
Confusional state	0	1 (0.7)
Cytokine release syndrome	0	1 (0.7)
Depression	0	1 (0.7)
Euphoric mood	0	1 (0.7)
Facial pain	1 (0.9)	0
Hypersensitivity	0	1 (0.7)
Neck pain	0	1 (0.7)
Urinary tract pain	0	1 (0.7)
Vulvovaginal pain	0	1 (0.7)
Patients with ≥ 1 SAE, n (%)	4 (3.7)	72 (51.1)
SAEs occurring in ≥1% of any treatment group, n (%)		
Infections and infestations - Other, specify	0	17 (12.1)
Catheter related infection	2 (1.8)	10 (7.1)
Hypotension[a]	0	12 (8.5)
Anaphylaxis[a]	0	11 (7.8)
Hypokalemia	0	11 (7.8)
Fever	0	10 (7.1)
Capillary leak syndrome[a]	0	9 (6.4)
Hypercalcemia	0	5 (3.5)
Hypoalbuminemia	0	5 (3.5)
Hypocalcemia	0	5 (3.5)
Pain[a]	0	5 (3.5)
Abdominal pain[a]	0	4 (2.8)
Diarrhea	0	4 (2.8)
Hypoxia	0	4 (2.8)
Lymphocyte count decreased	0	4 (2.8)
Arthralgia[a]	0	3 (2.1)
General disorders and administration site conditions - Other, specify	0	3 (2.1)
Pain in extremity[a]	0	3 (2.1)
Respiratory, thoracic and mediastinal disorders - Other, specify	0	3 (2.1)
Acute kidney injury	0	2 (1.4)
Alanine aminotransferase increased	0	2 (1.4)
Allergic reaction[a]	0	2 (1.4)
Anemia	0	2 (1.4)
Anorexia	0	2 (1.4)
Aspartate aminotransferase increased	0	2 (1.4)
Bone pain[a]	0	2 (1.4)
Cardiac disorders - Other, specify	0	2 (1.4)
Creatinine increased	0	2 (1.4)
Cytokine release syndrome[a]	0	2 (1.4)
Edema face	0	2 (1.4)
Hyperglycemia	0	2 (1.4)
Myalgia[a]	0	2 (1.4)
Neuralgia[a]	0	2 (1.4)
Platelet count decreased	0	2 (1.4)
Rash maculo-papular	0	2 (1.4)
Sinus tachycardia	0	2 (1.4)
Urticaria	0	2 (1.4)
Other notable SAEs, n (%)		
Back pain	0	1 (0.7)
Bronchospasm	0	1 (0.7)
Ear pain	0	1 (0.7)
Headache	0	1 (0.7)

Adverse events	Safety Set	
Non-cardiac chest pain	0	1 (0.7)
Psychosis	0	1 (0.7)
Seizure	0	1 (0.7)
Deaths, n (%)	43 (39.4)	39 (28.5)
Disease-related	39 (35.8)	35 (24.8)
Infection	0	1 (0.7)
Multi-organ failure	2 (1.8)	1 (0.7)
Cytokine release syndrome due to IL-2 overdose	0	1 (0.7)
Hypoxia of unknown origin	0	1 (0.7)
Unspecified	2 (1.8)	0

Source: pCODR submission.[2]
Note: SAEs were AEs reported in the AdEERS database as of September 30, 2012. AEs and SAEs are listed in descending order of overall frequency.
[a] Notable harm identified in the systematic review protocol.
Abbreviations: AE = adverse event; SAE = serious adverse event.

6.4 Ongoing Trials

There were no ongoing trials identified for this review.

7 SUPPLEMENTAL QUESTIONS

There were no supplemental questions identified for this review.

8 COMPARISON WITH OTHER LITERATURE

The pCODR Clinical Guidance Panel and the pCODR Methods Team did not identify other relevant literature providing supporting information for this review.

9 ABOUT THIS DOCUMENT

This Clinical Guidance Report was prepared by the pCODR Neurological Clinical Guidance Panel and supported by the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding the clinical evidence available on dinutuximab for neuroblastoma. Issues regarding resource implications are beyond the scope of this report and are addressed by the relevant pCODR Economic Guidance Report. Details of the pCODR review process can be found on the CADTH website (www.cadth.ca/pcodr).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Clinical Guidance Report was handled in accordance with the pCODR Disclosure of Information Guidelines. There was no non-disclosable information in the Clinical Guidance Report provided to pERC for their deliberations.

This Final Clinical Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Clinical Guidance Report supersedes the Initial Clinical Guidance Report. Note that no revision was made in between posting of the Initial and Final Clinical Guidance Reports.

The Neurological Clinical Guidance Panel is comprised of three medical oncologists. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package, which is available on the CADTH website (www.cadth.ca/pcodr). Final selection of the Clinical Guidance Panels was made by the pERC Chair in consultation with the pCODR Executive Director. The Panel and the pCODR Methods Team are editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

APPENDIX A: LITERATURE SEARCH STRATEGY AND DETAILED METHODOLOGY

1. Literature search via OVID platform

Database(s): EBM Reviews - Cochrane Central Register of Controlled Trials September 2018, Embase 1974 to 2018 October 08, Ovid MEDLINE(R) ALL 1946 to October 08, 2018

#	Searches	Results
1	(dinutuximab* or Unituxin* or "Ch 14.18" or "Ch 14.18UTC" or "Ch14.18" or "Ch14.18UTC" or 7SQY4ZUD30).ti,ab,ot,kf,kw,hw,nm.	569
2	1 use medall	153
3	1 use cctr	26
4	2 or 3	179
5	*dinutuximab/	75
6	(dinutuximab* or Unituxin* or "Ch 14.18" or "Ch 14.18UTC" or "Ch14.18" or "Ch14.18UTC").ti,ab,kw,dq.	469
7	5 or 6	473
8	7 use oemezd	308
9	8 not (conference review or conference abstract).pt.	182
10	4 or 9	361
11	remove duplicates from 10	233
12	8 and (conference review or conference abstract).pt.	126
13	limit 12 to yr="2013 -Current"	96
14	11 or 13	329
15	limit 14 to english language	324

2. Literature search via PubMed

A limited PubMed search was performed to capture records not found in MEDLINE.

Search	Query	Items found
3	Search #1 and #2	6
2	Search publisher[sb]	529908
1	Search ch14.18 monoclonal antibody [Supplementary Concept] OR dinutuximab*[tiab] OR Unituxin*[tiab] OR "Ch 14.18"[tiab] OR "Ch 14.18UTC"[tiab] OR "Ch14.18"[tiab] OR "Ch14.18UTC"[tiab] OR 7SQY4ZUD30[rn]	152

3. Cochrane Central Register of Controlled Trials (Central)

Searched via Ovid

4. Grey Literature search via:

Clinical Trial Registries:

U.S. NIH ClinicalTrials. gov
http://www.clinicaltrials.gov/

Canadian Partnership Against Cancer Corporation. Canadian Cancer Trials
http://www.canadiancancertrials.ca/

Search: Unituxin/dinutuximab

Select international agencies including:

Food and Drug Administration (FDA):
http://www.fda.gov/

European Medicines Agency (EMA):
http://www.ema.europa.eu/

Search: Unituxin/dinutuximab, neuroblastoma

Conference abstracts:

American Society of Clinical Oncology (ASCO)
http://www.asco.org/

ESMO
https://oncologypro.esmo.org/Meeting-Resources

Search: Unituxin/dinutuximab – last 5 years

Detailed Methodology

The literature search was performed by the pCODR Methods Team using the search strategy above.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-) with in-process records & daily updates via Ovid; Embase (1974-) via Ovid; The Cochrane Central Register of Controlled Trials (Sep 2018) via Ovid; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept was dinutuximab/Unituxin.

No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English-language documents, but not limited by publication year.

The search is considered up to date as of Feb 6, 2019.

Grey literature (literature that is not commercially published) was identified by searching the websites of regulatory agencies (Food and Drug Administration and European Medicines Agency), clinical trial registries (U.S. National Institutes of Health – clinicaltrials.gov and Canadian Partnership Against Cancer Corporation - Canadian Cancer Trials), and relevant conference abstracts. Conference abstracts were retrieved through a search of the Embase database limited

to the last five years. Abstracts from the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) were searched manually for conference years not available in Embase. Searches were supplemented by reviewing the bibliographies of key papers and through contacts with the Clinical Guidance Panel. In addition, the manufacturer of the drug was contacted for additional information as required by the pCODR Review Team.

Study Selection

One member of the pCODR Methods Team selected studies for inclusion in the review according to the predetermined protocol. All articles considered potentially relevant were acquired from library sources. Two members of the pCODR Methods Team independently made the final selection of studies to be included in the review and differences were resolved through discussion.

Included and excluded studies (with reasons for exclusion) are identified in section 6.

Quality Assessment

Assessment of study bias was performed by one member of the pCODR Methods Team with input provided by the Clinical Guidance Panel and other members of the pCODR Review Team. SIGN-50 Checklists were applied as a minimum standard. Additional limitations and sources of bias were identified by the pCODR Review Team.

Data Analysis

No additional data analyses were conducted as part of the pCODR review.

Writing of the Review Report

This report was written by the Methods Team, the Clinical Guidance Panel and the pCODR Secretariat:

- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental questions.
- The pCODR Clinical Guidance Panel wrote a summary of background clinical information and the interpretation of the systematic review. The Panel provided guidance and developed conclusions on the net clinical benefit of the drug.
- The pCODR Secretariat wrote summaries of the input provided by patient advocacy groups, by the Provincial Advisory Group (PAG), and by Registered Clinicians.

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