MSAC Application 1781

Dinutuximab beta for the treatment of primary relapsed and refractory high-risk neuroblastoma

PICO Set

REDACTED

Population

Patients with high-risk neuroblastoma (HRNBL) who are refractory during induction or have had a primary (first) relapse during or after one of the 3 treatment stages: induction, consolidation or post-consolidation/maintenance.

Intervention

Dinutuximab beta (dB, Qarziba®) used in conjunction with combination chemotherapy.

Comparator

Combination chemotherapy.

Outcomes

The relevant outcomes are overall response rate (ORR) that consists of complete response (CR) or partial response (PR), progression free survival (PFS) or event free survival (EFS) as well as overall survival (OS).

Population

Describe the population in which the proposed health technology is intended to be used:

Patients with high-risk neuroblastoma (HRNBL) who are refractory during induction or have had a primary (first) relapse during or after one of the 3 treatment stages: induction, consolidation or post-consolidation/maintenance.

Disease overview

Neuroblastoma (NBL) is an embryonal tumour of the autonomic nervous system. It usually occurs in very young children. The tumours are found in sympathetic nervous system tissues, typically in the adrenal medulla or paraspinal ganglia and can present as mass lesions in the neck, chest, abdomen, or pelvis.

Current practice for the staging and risk classification of NBL is through the International Neuroblastoma Risk Group (INRG) staging system. The INRG staging system categorises tumours as very low risk, low risk, intermediate risk or high risk (HR) based on the following prognostic factors: age at diagnosis (two cut-offs: 12 and 18 months), INRG tumour stage (L1, L2, M, MS), histologic category, grade of tumour differentiation, DNA ploidy (hyperploidy/diploidy), v-myc myelocytomatosis viral related oncogene (MYCN) oncogene status (amplified or not) and aberrations at chromosome 11q (presence/absence).

NBL accounts for 13% of all cancer deaths in Australian children and is the 3rd highest cause of cancer deaths (following central nervous system tumours and leukaemia) (Cancer Council Queensland 2020). With an incidence of 10.6 children per million (Cancer Queensland 2020), there are approximately 55 children diagnosed with NBL in Australia annually. Of these, 56% (31 per annum) have HRNBL (NCCN v2.2024, Meany 2019). Data from an Australian clinical survey undertaken that included REDACTED paediatric specialist centers estimated that REDACTED HRNBL children were treated over the past 2 years. These numbers confirm the estimate of 31 children per annum.

The likelihood of survival is dependent on several prognostic variables including age at diagnosis, tumour stage and biological characteristics of the disease (e.g. MYCN oncogene status, tumour ploidy, and chromosomal aberrations) (NCCN v2.2024). Age at diagnosis is highly prognostic, since patients under 18 months have better OS than those diagnosed after 18

months (Youlden 2020).

The 5-year survival rate for children with low-risk NBL is higher than 95%, intermediate-risk NBL is 90% to 95% (NCCN v2.2024). Over the years and with the introduction of immunotherapy and other treatments, OS and EFS have improved substantially. Long-term survival for children with HRNBL remains poor at about 62.5% (NCCN v2.2024). Of HRNBL patients, approximately half are expected to relapse within 5 years of diagnosis (DuBois 2022). Those who relapse following front-line therapy or are refractory to initial therapy often respond to additional interventions, but have a high rate of subsequent relapse, generally 80–90% within 2 years; less than 10% of patients whose disease recurs will survive (Sholler 2018). Australian data indicate that more than half of patients are diagnosed with metastatic disease and the 5-year cause-specific survival for these patients was 49.5% (Youlden 2020), similar to international data.

Outcomes remain poor in patients with HRNBL who have progressive disease or who after front-line therapy do not respond (refractory), with 4-year PFS and OS of 6% and 20%, respectively (London 2017).

Patient group of interest

Of HRNBL patients, approximately half are expected to relapse within 5 years of diagnosis. Those who are refractory to initial induction therapy, or experience a first relapse, are the group of interest in this application:

Primary Relapsed NBL: Patients who have initially responded to treatment but have since had their first relapse or progression. This group represents REDACTED% of patients with HRNBL according to the Australian clinical survey that was conducted.

Refractory NBL: Patients who are HRNBL but did not respond to induction treatment. This group of patients represents REDACTED% of patients with HRNBL according to the Australian clinical survey that was conducted.

These Australian clinical survey results are consistent with published literature reporting around half of HRNBL patients are expected to relapse within 5 years of diagnosis or fail to respond to therapy (DuBois 2022).

Specify any characteristics of patients with the medical condition, or suspected of, who are proposed to be eligible for the proposed health technology, describing how a patient would be investigated, managed and referred within the Australian health care system in the lead up to being considered eligible for the technology:

Treatment for HRNBL usually includes induction, consolidation and post-consolidation or maintenance therapy (Figure 2), with patients treated in specialised units in public children's hospitals once diagnosed. Post-consolidation/maintenance therapy usually includes immunotherapy with dinutuximab beta (dB, Qarziba®) which is currently funded under the NHRA HST program.

Patients with relapsed or refractory HRNBL continue to be treated by the same specialist public hospital clinicians and centres as during the initial treatment phase following diagnosis. Gaining funding for chemoimmunotherapy will ensure that any specialist centre in Australian public hospitals will have access to dB. REDACTED. Funding dB will ensure equitable and sustainable access to treatment for children irrespective of location.

Provide a rationale for the specifics of the eligible population:

The eligible population is based on the key population that has been studied in clinical trials. REDACTED. This population is clearly identifiable and has also been identified by Australian clinicians (Letter to MSAC November 2023) to be that which has a high clinical need.

Intervention

Name of the proposed health technology:

Dinutuximab beta (dB, Qarziba®) is a mouse-human chimeric monoclonal IgG1 antibody produced in a mammalian cell line (CHO) by recombinant DNA technology. dB is specifically directed against the carbohydrate moiety of disialoganglioside 2 (GD2), which is overexpressed on NBL cells.

Describe the key components and clinical steps involved in delivering the proposed health technology:

The dosing schedule for chemoimmunotherapy involves administering dB in conjunction with combination chemotherapy as a 7-day continuous infusion (10 mg/m^2/24hr), usually given in a 28-day cycle (with the cycle length determined by the relevant combination chemotherapy protocol). The schedule is presented in Table 1

Table 1: Cycle schedule for combination chemotherapy and chemoimmunotherapy

	Dosing	Schedule
Combination Chemotherapy: Temozolomide + topotecan		
Days 1-5	Temozolomide 200mg/m^2/day PO	Every 4 weeks
Days 1-5	Topotecan 0.75 mg/m^2/day IV	Every 4 weeks
Chemoimmunotherapy: Temozolomide + Topotecan + dB		
Days 1-5	Temozolomide 200mg/m^2/day PO	Every 4 weeks
Days 1-5	Topotecan 0.75 mg/m^2/day IV	Every 4 weeks
Days 1-7	dB 10mg/m^2/day 24-hour iv infusion	Every 4 weeks

Note: Irinotecan may be used instead of topotecan at some centres.
Source: BEACON Immunotherapy dosing (BEACON Immuno 2022)

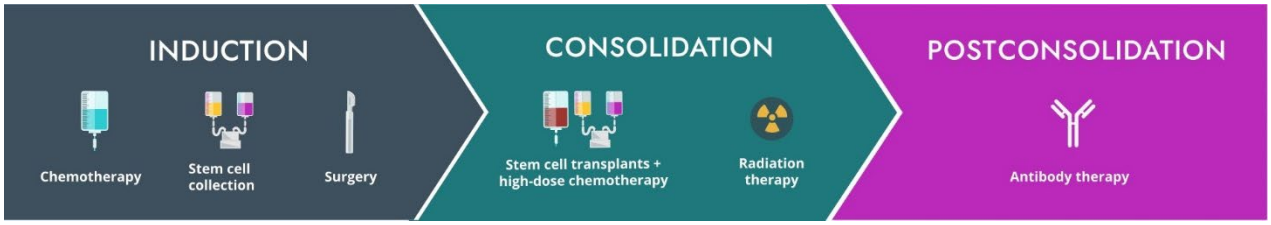
Prior to starting each treatment course, pulse oximetry, bone marrow function, liver function and renal function should be measured, and treatment delayed until adequate function is demonstrated (refer to Product Information for details).

Patients should receive concomitant treatment with morphine, gabapentin and paracetamol/ ibuprofen for pain management and antihistamine to prevent hypersensitivity reactions.

Long-term infusion (LTI) of dB (10 mg/m^2 IV continuously infused over 10 days) was shown to have a tolerable pain profile in relapsed and refractory NBL, with the use of IV morphine required by <10% of patients after cycle 2, reducing to 0% during cycles 4 and 5 (Lode 2023). Hence the pain profile of dB administered via LTI in this study was found to be improved compared with an earlier study of dB in maintenance therapy where patients received dB via the short term infusion (STI) protocol (20 mg/m^2 IV over 8 hours for 5 days) (Ladenstein 2018). In this earlier study, morphine was necessary in all 5 cycles when STI protocol dB (plus IL-2) was administered.

The standard clinical pathway for treating children with HRNBL is presented in Figure 1.

Figure 1: Clinical pathway for the treatment of HRNBL



During induction, which includes combination chemotherapy, stem cell collection and surgical resection of primary tumour some children will not have achieved at least a partial response. These patients are refractory. For refractory children, the standard of treatment has become chemoimmunotherapy as per the schedule in Table 1.

During induction, at the end of consolidation (transplantation and radiotherapy) and during maintenance (immunotherapy) or after maintenance, children who initially achieved at least a partial response may also experience a first relapse. For first relapse, the standard of treatment has become chemoimmunotherapy as per the schedule in Table 1.

Identify how the proposed technology achieves the intended patient outcomes:

dB has been shown *in vitro* to bind to NBL cell lines known to express GD2 and to induce both complement dependent cytotoxicity (CDC) and antibody dependent cell-mediated cytotoxicity (ADCC). The antitumor mechanism of action of dB in treating neuroblastoma is relevant for any line of therapy (newly diagnosed, relapsed, and refractory) since regardless of the line of therapy, neuroblastoma cells consistently express GD2 (Schumacher-Kuckelkorn 2017). In the presence of human effector cells, including peripheral blood nuclear cells and granulocytes from normal human donors, dB was found to mediate the lysis of human NBL and melanoma cell lines in a dose-dependent manner. Additionally, *in vivo* studies demonstrated that dB could suppress liver metastasis in a syngeneic liver metastasis mouse model.

There are multiple examples of successful combination of monoclonal antibodies with combination chemotherapy showing enhanced results, for example rituximab (anti-CD20) in combination with chemotherapy, in mature B-Non-Hodgkin Lymphomas (e.g., Meinhardt 2010).

Furthermore, preclinical evaluation of the combination of dinutuximab with combination chemotherapy has shown that neutrophils have significant anti-tumor effects against neuroblastomas *in vitro* but only in the presence of dinutuximab. Moreover, combination chemotherapy in combination with dinutuximab and GM-CSF achieved significant activity *in vitro* and *in vivo*, doubling median survival time and led to progression-free survival in a high-tumour burden metastatic xenogeneic neuroblastoma model.

Early clinical trials conducted in the US, with two different anti-GD2 monoclonal antibodies (with dinutuximab alpha (Mody 2017) and hu14.18K322A (Federico 2017)), in combination with combination chemotherapy, as well as early experience with dinutuximab beta in Germany (Mueller 2018) have all shown unprecedented positive results.

Does the proposed health technology include a registered trademark component with characteristics that distinguishes it from other similar health components?

Yes.

Explain whether it is essential to have this trademark component or whether there would be other components that would be suitable:

dB (Qarziba®) has been previously recommended for funding via the NHRA HST program. It is important for the long-term sustainability of the treatment, being the only TGA-registered version of dinutuximab.

It is also important to distinguish this from dinutuximab alpha (dA; Unituxin®) REDACTED (as it is not TGA-registered).

Are there any proposed limitations on the provision of the proposed health technology delivered to the patient (For example: accessibility, dosage, quantity, duration or frequency):

No.

Provide details and explain:

Other than restriction of the population to primary relapsed and refractory NBL patients, there are no additional proposed limitations.

If applicable, advise which health professionals will be needed to provide the proposed health technology:

Paediatric oncologists and nurses in specialised centres.

If applicable, advise whether delivery of the proposed health technology can be delegated to another health professional:

It is not expected that it can be delegated to another health care professional.

If applicable, advise if there are any limitations on which health professionals might provide a referral for the proposed health technology:

There are none.

Is there specific training or qualifications required to provide or deliver the proposed service, and/or any accreditation requirements to support delivery of the health technology?

Yes.

Provide details and explain:

This is a highly specialised treatment, and few clinicians have experience. However, clinicians currently treating patients with refractory or relapsed NBL have experience with dB administration.

Indicate the proposed setting(s) in which the proposed health technology will be delivered:

- ☐ Consulting rooms
- ☐ Day surgery centre
- ☐ Emergency Department
- ☐ Inpatient private hospital
- ☒ Inpatient public hospital
- ☐ Laboratory
- ☐ Outpatient clinic
- ☒ Patient's home
- ☐ Point of care testing
- ☐ Residential aged care facility
- ☐ Other (please specify)

With chemoimmunotherapy it is likely that the delivery of dB is provided to inpatients, mainly as topotecan also requires an admission for its administration. However, there is the potential for some centres and children to be discharged for part of their treatment and have treatment delivered by a continuous infusion pump. This will be dependent on each child's condition.

Is the proposed health technology intended to be entirely rendered inside Australia?

Yes.

Provide additional details on the proposed health technology to be rendered outside of Australia:

Not relevant.

Comparator

Nominate the appropriate comparator(s) for the proposed medical service (i.e. how is the proposed population currently managed in the absence of the proposed medical service being available in the Australian health care system). This includes identifying health care resources that are needed to be delivered at the same time as the comparator service:

The proposed comparator for primary relapse and refractory HRNBL patients is combination chemotherapy. There is a minority use of radiotherapy (external beam radiotherapy) in 3 centres however, this will not form part of the base case.

Provide a name for your comparator:

Combination chemotherapy that includes topotecan or irinotecan in addition to temozolomide.

Provide an identifying number for your comparator (if applicable):

Not applicable.

Provide a rationale for why this is a comparator:

The choice of comparator is supported twofold.

Firstly, clinical practice has changed since the ANLB1221 study, so that the current National Comprehensive Cancer Network (NCCN) Guidelines for HRNBL (NCCN v2.2024; pdf copy supplied as login is required for access) recommend that for relapsing and refractory patients the standard of care is now chemoimmunotherapy (the focus of this application). Therefore, we refer to the older Children's Cancer and Leukaemia Group (CCLG) 2017 Guidelines (CCLG 2017) where the recommended treatment following primary relapse was an alternative combination chemotherapy regimen, with or without radiotherapy, or a clinical study. The guidelines recommended that patients be assessed every 2 cycles and no more than 12 cycles of combination chemotherapy be given. For refractory patients an alternative combination chemotherapy is also recommended.

The second confirmatory source of the choice of combination chemotherapy ± radiotherapy is a survey of Australian clinicians which is summarised in Table 2. Before chemoimmunotherapy became standard clinical practice, Australian clinicians would treat most patients with combination chemotherapy or enter them into a clinical trial. The most frequently utilised combination chemotherapy was topotecan/irinotecan + temozolomide (Table 2).

Table 2: Summary of Australian Clinician Survey – the most appropriate comparator for primary relapse and refractory HRNBL (weighted by number of children)

Comparator Treatment Options	Refractory	Induction	Consolidation	Maintenance	Post Maintenance
Topotecan/Irinotecan + temozolomide	REDACTED	REDACTED	REDACTED	REDACTED	REDACTED
Topotecan + cyclophosphamide	REDACTED	REDACTED	REDACTED	REDACTED	REDACTED
Topotecan/Irinotecan + temozolomide and radiotherapy	REDACTED	REDACTED	REDACTED	REDACTED	REDACTED
Other treatments such as iMBG±stem cell transplantation	REDACTED	REDACTED	REDACTED	REDACTED	REDACTED
Sent oversees for treatment	REDACTED	REDACTED	REDACTED	REDACTED	REDACTED
Clinical trials	REDACTED	REDACTED	REDACTED	REDACTED	REDACTED
Total	100%	100%	100%	100%	100%

NB: REDACTED.

Pattern of substitution – Will the proposed health technology wholly replace the proposed comparator, partially replace the proposed comparator, displace the proposed comparator or be used in combination with the proposed comparator?

☒ None (used with the comparator)
☐ Displaced (comparator will likely be used following the proposed technology in some patients)
☐ Partial (in some cases, the proposed technology will replace the use of the comparator, but not all)
☐ Full (subjects who receive the proposed intervention will not receive the comparator)

Outline and explain the extent to which the current comparator is expected to be substituted:

While current standard of care has already become chemo-immunotherapy (NCCN v2.2024; pdf copy supplied as login is required for access), the clinical/economic comparator is proposed to be the same combination chemotherapy (without immunotherapy).

Outcomes

List the key health outcomes (major and minor – prioritising major key health outcomes first) that will need to be measured in assessing the clinical claim for the proposed medical service/technology (versus the comparator):

☒ Health benefits
☒ Health harms
☐ Resources

Major health outcomes:

- Overall response rates (ORR): complete response (CR) and partial response (PR)
- Progression free survival (PFF) or Event Free Survival (EFS)
- Overall Survival (OS)

Health Harms: Reporting of adverse events.

Outcome description – please include information about whether a change in patient management, or prognosis, occurs as a result of the test information:

Not relevant.

Claims

In terms of health outcomes (comparative benefits and harms), is the proposed technology claimed to be superior, non-inferior or inferior to the comparator(s)?

☒ Superior
☐ Non-inferior
☐ Inferior

Please state what the overall claim is, and provide a rationale:

dB used in conjunction with combination chemotherapy will improve the survival of children with primary relapse and refractory HRNBL, providing superior comparative benefits and non-inferior harms.

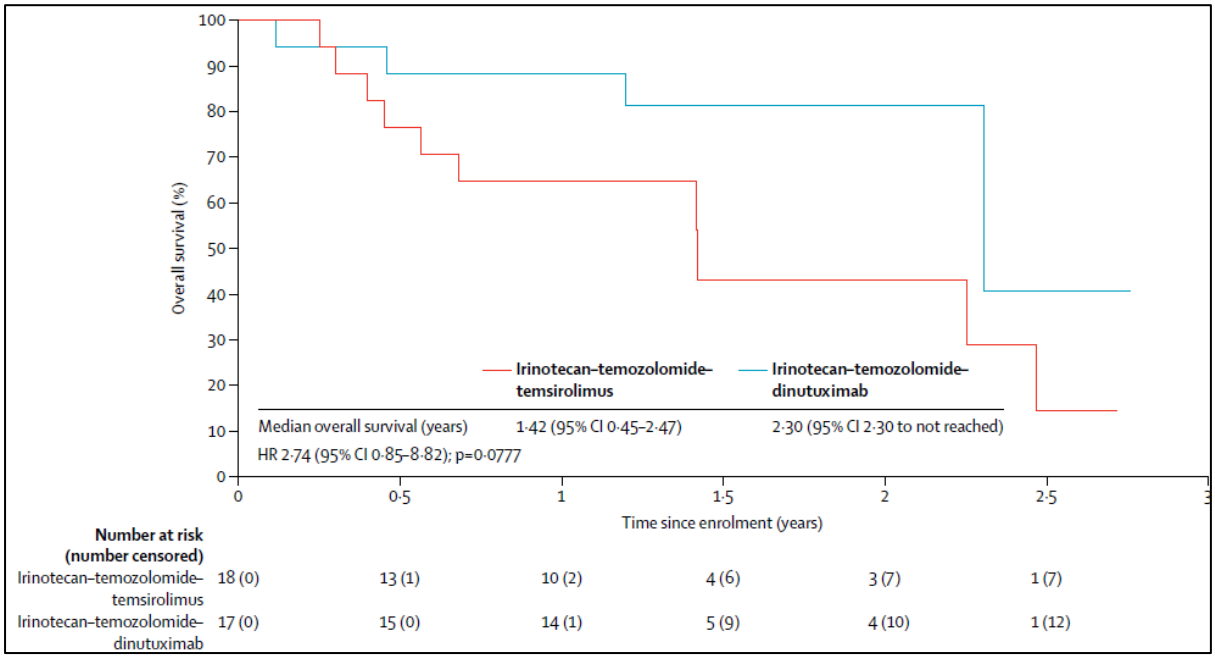
The data presented in the Application and in the ADAR includes data from dB as well as dA and data from Australian clinical practice. dA and dB are not biosimilars, and there are differences between the two agents. However, given the rarity of the disease and the limited clinical data the clinical trial results for both will be presented. Australian clinicians have stated publicly during the MSAC pre-application meeting that these agents are sufficient similar that the data is supportive of anti-GD2 treatment in general. Further, across the studies the patients represent the full spectrum of relapsed and refractory HRNBL patients. This is the approach taken during the initial MSAC July 2020 ADAR and was acceptable to MSAC, and therefore it is the approach taken for this application (and the proposed October 2024 ADAR).

Overall Survival (OS)

OS in the key dB randomised, controlled trial (RCT) BEACON Immuno is impacted by early crossover to active treatment in the control arm (i.e. crossover allowed after 2 cycles of treatment because of the clinical benefit for dinutuximab already demonstrated in ANBL1221). As there were only N=22 control patients and approximately half of the patients crossed over, it was not possible to analyse the impact of crossover using any accepted statistical means (e.g. inverse probability of censoring of weights (IPCW)) or by separately analysing the crossover vs. non-crossover control patients (as patients crossed over following progression, censoring of cross-over patients would introduce bias).

ANBL1221 did not include crossover in the control arm (since it was the first chemoimmunotherapy RCT in this population), with non-significantly improved OS in the dA vs. control arm (HR 2.74 (95% CI 0.85, 8.82; *p=0.077* for control vs dA-containing arm; Figure 2) reported in in the publication (Mody 2017). Note that when this HR is inverted to show outcomes for dA vs. control a HR of 0.36 (95% CI 0.11, 1.18) is obtained at median follow-up of all participants of 1.26 years (65.5 weeks). With more mature data (reported in CADTH 2021), statistically significant improvement in OS was seen with a HR for time to death of 0.37 (95% CI 0.14, 0.99) *p=0.0479* in the randomised phase. Median OS was 143.7 (95% CI 23.6, 165.9) weeks in the patients randomised to receive dA. Hence the OS benefit of dA was shown to be statistically significant, compared with control, with longer follow-up. Anecdotally Australian clinicians participating in ANBL1221 noted that the study showed that temsirolimus was not to be used in combination chemotherapy given the toxicity exhibited during the study. This in part may explain the low response rate seen in the combination chemotherapy + temsirolimus in ANBL1221 compared to the combination chemotherapy arm in BEACON-immuno.

Figure 2: OS outcomes in ANBL1221



HR: hazard ratio; OS: overall survival
Source: Figure 3**Error! Bookmark not defined.**

Why would the requestor seek to use the proposed investigative technology rather than the comparator(s)?

Because it improves the survival of the proposed population.

Identify how the proposed technology achieves the intended patient outcomes:

dB used with combination chemotherapy allows for more children to respond to treatment, thereby extending their progression free and overall survival.

For some people, compared with the comparator(s), does the test information result in:

A change in clinical management? Yes

A change in health outcome? Yes

Other benefits? Yes

Provide a rationale, and information on other benefits if relevant:

The other benefits are an improvement in the quality of life of the children.

While quality of life was not measured in the key dB or dA studies (BEACON Immuno or ANBL1221), in the CADTH economic evaluation of dA in relapsed and refractory NBL, improved response to treatment was assumed to provide better quality of life (CADTH 2021). The best quality of life (utility) was assumed in patients with non-evident disease (utility 0.78), with lower quality of life assumed in stable disease (utility 0.56) and in patients with recurrent disease (utility 0.32). This association of better quality of life with improved outcomes was based on published utility data in survivors of childhood central nervous system tumours, in the absence of NBL-specific data.

In terms of the immediate costs of the proposed technology (and immediate cost consequences, such as procedural costs, testing costs etc.), is the proposed technology claimed to be more costly, the same cost or less costly than the comparator?

☒ More costly
☐ Same cost
☐ Less costly

Provide a brief rationale for the claim:

The cost of dB is REDACTED more than $200,000 for the total cost of care.

Algorithms

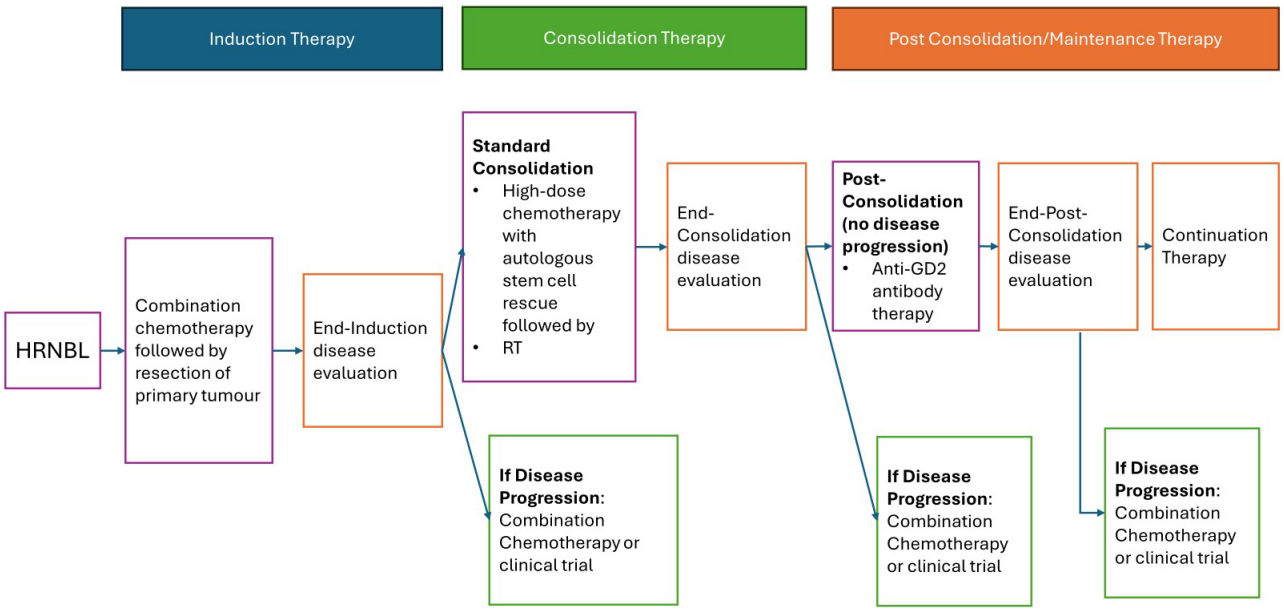
PREPARATION FOR USING THE HEALTH TECHNOLOGY

Define and summarise the clinical management algorithm, including any required tests or healthcare resources, before patients would be eligible for the proposed health technology:

Treatment for refractory or relapsed children has always been and will remain highly individualised. In recent years the major change in treatment is the standardisation of chemo-immunotherapy for this population.

The treatment algorithm prior to the advent of chemoimmunotherapy (the proposed health technology), is presented in Figure 3. Once patients were refractory or relapsed, they would either be treated with an alternative combination chemotherapy or they would be entered into a clinical study, irrespective of the stage at which the relapse occurred.

Figure 3: Treatment algorithm before chemo-immunotherapy



Chemoimmuno: chemo-immunotherapy; HRNBL: high risk neuroblastoma; RT: radiation therapy

Adapted from: NCCN v2.2024 (pdf copy supplied as login is required for access)

The National Comprehensive Cancer Network have issued new guidelines for patients that are relapsed and these have been adapted for Australia (NCCN v2.2024; pdf copy supplied as login is required for access) in Figure 4. In the case of relapse, patients have the option of being

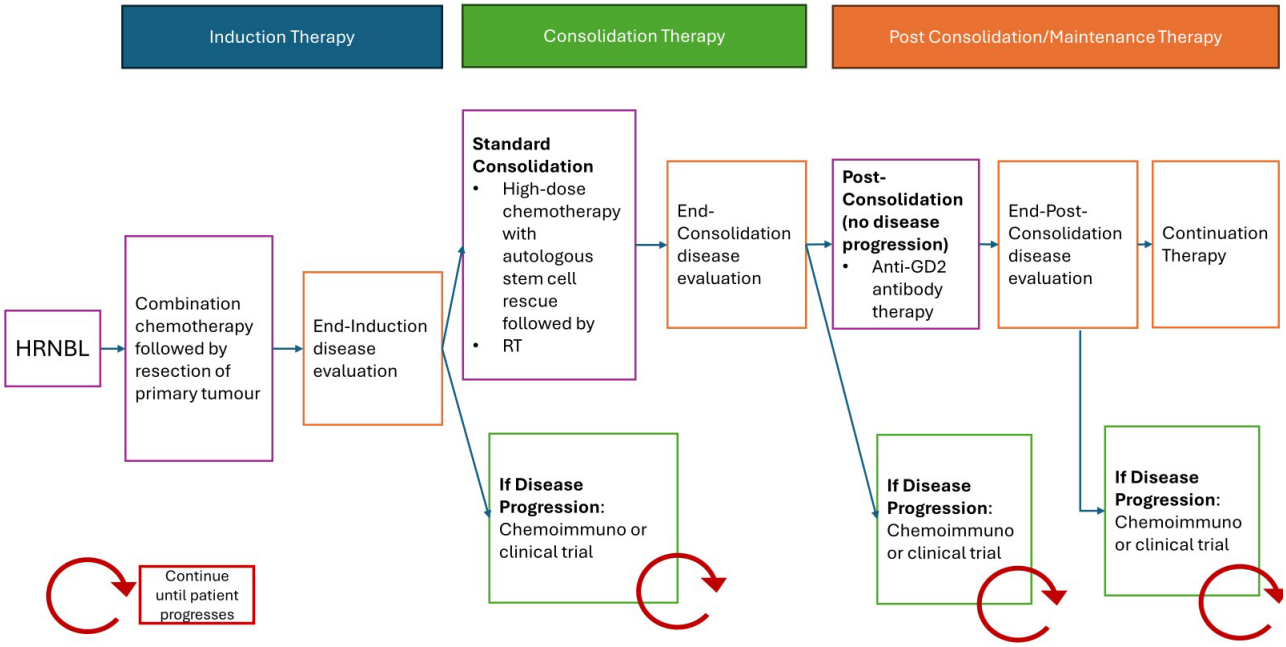
treated with combination chemotherapy or chemo-immunotherapy.

For refractory disease the NCCN guidelines recommend:

> *"For patients with end-Induction minor response or stable disease not proceeding to consolidation therapy, the panel recommends a chemoimmunotherapy regimen combining anti-GD2 monoclonal antibody with chemotherapy or participation in clinical trials for patients with refractory disease."*

Patients, whether they are refractory or have had a first relapse, will continue on chemo-immunotherapy for a median of 6 cycles (BEACON Immuno 2022). .

Figure 4: Overview of treatment for high-risk neuroblastoma relapsing or refractory disease with chemoimmunotherapy



Chemoimmuno: chemo-immunotherapy; HRNBL: high risk neuroblastoma; RT: radiation therapy

Source: Adapted from NCCN Guidelines v2, 2024
Refractory patients are those experiencing disease progression at the end-induction disease evaluation step.

Is there any expectation that the clinical management algorithm *before* the health technology is used will change due to the introduction of the proposed health technology?

No

Describe and explain any differences in the clinical management algorithm prior to the use of the proposed health technology vs. the comparator health technology:

Not applicable.

USE OF THE HEALTH TECHNOLOGY

Explain what other healthcare resources are used in conjunction with delivering the proposed health technology:

The healthcare resources used in conjunction with dB are generally the same as those used in conjunction with the comparator. Both the dB and comparator group receive combination chemotherapy, initiated and delivered largely as an inpatient.

Prior to starting each dB treatment course, the following clinical parameters should be evaluated and treatment should be delayed until these values are reached (Qarziba Product Information):

- pulse oximetry > 94% on room air.
- adequate bone marrow function: absolute neutrophil count ≥ 500/μL, platelet count ≥ 20,000/μL, haemoglobin > 8.0 g/dL.
- adequate liver function: alanine aminotransferase (ALT)/ aspartate aminotransferase (AST) < 5 times upper limit of normal (ULN).
- adequate renal function: creatinine clearance or glomerular filtration rate (GRF).
- 60 mL/min/1.73 m^2.

For irinotecan/temozolomide combination chemotherapy in neuroblastoma the following monitoring is required:

- Irinotecan and temozolomide to be given when absolute neutrophil count >0.75 x 10^9/L and platelets >75x10^9/L, or ANC ≥ 0.5x10^9/L and platelets ≥ 50x10^9/L if bone marrow involved.
- Prophylactic G-CSF not to be routinely administered. It can be used in case of delayed count recovery.
- Prophylactic co-trimoxazole to be administered.
- If the patient develops irinotecan induced diarrhoea, in the absence of any contraindications such as allergies, treatment with cefixime 8 mg/kg once a day (max daily dose 400 mg) could be considered and started 2 days before combination chemotherapy and continued daily until day 7, following local policies for the management of irinotecan-related diarrhoea.
- For delayed onset diarrhoea occurring >8 hours after irinotecan administration, children should receive loperamide. Loperamide should continue until a normal pattern of bowel movements returns. Oral hydration with large volumes of water and electrolytes should be prescribed during whole diarrhea episode. If the delayed diarrhoea recurs, then cefixime should be given with the following courses.

Evaluation should be carried out every 2 courses.

(Source: CCLG Relapse/Refractory HRNBL Treatment Options v 2.0 2015)

Explain what other healthcare resources are used in conjunction with the comparator health technology:

As with the intervention the following monitoring is required with use of comparator combination chemotherapy with irinotecan and temozolomide:

- Irinotecan and temozolomide to be given when absolute neutrophil count >0.75 x 10^9/L and platelets >75x10^9/L, or ANC ≥ 0.5x10^9/L and platelets ≥ 50x10^9/L if bone marrow involved.
- Prophylactic G-CSF not to be routinely administered. It can be used in case of delayed count recovery.
- Prophylactic co-trimoxazole to be administered.

- If the patient develops irinotecan induced diarrhoea, in the absence of any contraindications such as allergies, treatment with cefixime 8 mg/kg once a day (max daily dose 400 mg) could be considered and started 2 days before combination chemotherapy and continued daily until day 7, following local policies for the management of irinotecan-related diarrhoea.
- For delayed onset diarrhoea occurring >8 hours after irinotecan administration, children should receive loperamide. Loperamide should continue until a normal pattern of bowel movements returns. Oral hydration with large volumes of water and electrolytes should be prescribed during whole diarrhea episode. If the delayed diarrhoea recurs, then cefixime should be given with the following courses.

Evaluation should be carried out every 2 courses.

(Source: CCLG Relapse/Refractory HRNBL Treatment Options v 2.0 2015)

Describe and explain any differences in the healthcare resources used in conjunction with the proposed health technology vs. the comparator health technology:

Similar healthcare resources are used in conjunction with dB (plus combination chemotherapy) vs. the comparator (combination chemotherapy). Patients require haematological, liver function, and renal function tests to be conducted prior to administration of each cycle or every second cycle.

CLINICAL MANAGEMENT AFTER THE USE OF HEALTH TECHNOLOGY

Define and summarise the clinical management algorithm, including any required tests or healthcare resources, *after* the use of the proposed health technology:

See healthcare resource used in conjunction with the intervention above.

Define and summarise the clinical management algorithm, including any required tests or healthcare resources, after the use of the comparator health technology:

See healthcare resource used in conjunction with the comparator above.

Describe and explain any differences in the healthcare resources used *after* the proposed health technology vs. the comparator health technology:

No differences in healthcare resource use after each cycle is expected for dB vs. the comparator, with patients receiving combination chemotherapy in each arm and hence requiring monitoring related to this combination chemotherapy.

Insert diagrams demonstrating the clinical management algorithm with and without the proposed health technology:

Note:

There is no difference in the expected algorithms, except that dB is used in association with combination chemotherapy in the intervention arm vs. the same combination chemotherapy alone in the comparator arm. See clinical management algorithm in Figure 4.

Summary of Evidence

Provide one or more recent (published) high quality clinical studies that support use of the proposed health service/technology. At 'Application Form lodgement',

	Type of study design	Title of journal article or research project	Short description of research	Website link to article	Date of publication
RCTs: dinutuximab beta (dB; Qarziba) or dinutuximab (dA; Unituxin) + combination chemotherapy vs. control (combination chemotherapy)					
1.	Phase 2 RCT, open-label, multicentre	Gray, J., Moreno, R., Weston, G. et al. (2022). "BEACON-Immuno: Results of the dinutuximab beta (dB) randomization of the BEACON-Neuroblastoma phase 2 trial-A European Innovative Therapies for Children with Cancer (ITCC-International Society of Paediatric Oncology Europe Neuroblastoma Group (SIOPEN) trial." Journal of Clinical Oncology 40(16 Supplement 1). ITCC-032; ClinicalTrials.gov identifier: NCT02308527; EudraCT 2012-000072-42	Relapsed, progressed or refractory HRNBL dB N=43, Control N=22, crossover allowed in control arm following progression. Key results: ORR: dB 15 (35%), Control 4 (18%) 1-year PFS: dB 57%, Control 27%: HR= 0.56 (p=0.09)	BEACON Immuno 2022	2022
2	Phase 2 RCT, open-label, multicentre	Mody, R., Naranjo, C. Van Ryn, A, et al. (2017). "Irinotecan-temozolomide with temsirolimus or dinutuximab in children with refractory or relapsed neuroblastoma (COG ANBL1221): an open-label, randomised, phase 2 trial." The Lancet Oncology 18(7): 946-957. COG ANBL1221 study; ClinicalTrials.gov identifier: NCT01767194	First relapse or refractory disease/progression HRNBL. dA N=17, Control (with temsirolimus) N=18 Key results: ORR, n (%): dA 9 (53%), Control 1 (6%) Median PFS (years): dA 2.14, Control 0.25, HR (control vs. dA) 6.86 (95% CI 2.15, 21.96) p=0.0003 Median OS (years): dA 2.30 (95% CI 2.30, NR), Control 1.42 (95% CI 0.45, 2.47), HR (control vs. dA) 2.74 (95% CI 0.85, 8.82) p=0.0777	Mody 2017	2017
Non-comparative dinutuximab beta (dB; Qarziba) or dinutuximab (dA; Unituxin) studies					
3	Retrospective single-arm cohort, MC	Lerman, B., Li, Y., Carlowicz, C., et al. (2022). "Progression-Free Survival and Patterns of Response in Patients with Relapsed High-Risk Neuroblastoma Treated with Irinotecan/Temozolomide/Dinutuximab/Granulocyte-Macrophage Colony-Stimulating Factor." Journal of Clinical Oncology 41(3): 508-516.	Relapsed HRNBL. dA N=146. Key results: ORR, n (%): 57 (39%) Median 2-year PFS 28% median DOR 13.1 months.	Lerman 2022	2022

	Type of study design	Title of journal article or research project	Short description of research	Website link to article	Date of publication
4	Retrospective chart review, multicentre	Lode, H., Ladenstein, S. Troschke-Meurer, L. et al. (2023). "Effect and Tolerance of N5 and N6 Chemotherapy Cycles in Combination with Dinutuximab Beta in Relapsed High-Risk Neuroblastoma Patients Who Failed at Least One Second-Line Therapy." Cancers 15(13): 3364	Relapsed or refractory HRNBL, Failed ≥1 2nd line therapy. dB N=25. Key results: ORR, n (%): 9 (36%); minor response, n (%) 3 (12%) 1 year EFS 27% (95% CI 8%, 47%); 1 year OS 44% (95% CI 24%, 65%)	Lode 2023	2022 (online)
5	Open-label, multicentre, non-comparative extension phase	Mody, R., Yu, A. Naranjo, F. et al. (2020). "Irinotecan, temozolomide, and dinutuximab with GM-CSF in children with refractory or relapsed neuroblastoma: A report from the children's Oncology group." Journal of Clinical Oncology 38(19): 2160-2169. ANBL1221 extension phase	First relapse or refractory disease/progression HRNBL. N=17 dA arm patients from RCT phase; N=36 non-randomly assigned dA patients. ORR non-randomised dA arm, n (%): 13 (36%); Results for combined dA patients (N=53): ORR, n (%): 22 (42%): 1-year PFS 67.9% (95% CI 55.4%, 80.5%) 1-year OS 84.9% (95% CI 75.3%, 94.6%)	Mody 2020	2020 Extended non-comparative data for dA arm of Mody 2017, plus additional dA treated arm.
6	Prospective cohort, single arm	Olgun, N., Cecen, E., Ince, D. et al. (2022). "Dinutuximab beta plus conventional chemotherapy for relapsed/refractory high-risk neuroblastoma: A single-center experience." Frontiers in Oncology 12: 1041443.	Relapsed or refractory ± progressive HRNBL following salvage treatment. dB N=19 Key result: ORR, n (%): 12 (63%)	Olgun 2022	
7	Prospective cohort, multicentre	Raiser, P., Schleiermacher, G., Gambart, M., et al. (2024). "Chemo-immunotherapy with dinutuximab beta in patients with relapsed/progressive high-risk neuroblastoma: does chemotherapy backbone matter?" Eur J Cancer 202: 114001.	Relapsed/progressive HRNBL. dB N=39. Key results: ORR, n (%): 14 (39%) 9-month PFS: 32% 9-month OS: 53%	Raiser 2024	2024
8	Retrospective single arm cohort, multicentre	Wieczorek, A., Zebrowska, M., Ussowicz, A. et al. (2023). "Dinutuximab Beta Maintenance Therapy in Patients with High-Risk Neuroblastoma in First-Line and Refractory/Relapsed Settings-Real-World Data." Journal of Clinical Medicine 12(16): 5252.	Relapsed or refractory HRNBL. dB N=17 Key results: ORR, n (%): 13 (76%) 3-year PFS 63% 3-year OS 80%	Wieczorek 2023	2023

	Type of study design	Title of journal article or research project	Short description of research	Website link to article	Date of publication
Control data: contemporary chemotherapy					
9	RCT of multiple chemotherapies	Moreno, L., Weston, R., Owens, C., et al. (2024). "Bevacizumab, Irinotecan, or Topotecan Added to Temozolomide for Children With Relapsed and Refractory Neuroblastoma: Results of the ITCC-SIOPEN BEACON-Neuroblastoma Trial." J Clin Oncol: Jco2300458.	Relapsed, progressed or refractory HRNBL. N=160, Randomised to 6 different chemotherapy (without immunotherapy) arms Key results for N=80 (excluding bevacizumab arms, as not used in HRNBL in Australia): ORR, n (%): 14 (17%)	Moreno 2024	2024

Abbreviations: CI: confidence interval; COG: Children's Oncology Group; CR: complete response; DOR: duration of response; EFS: event-free survival; HR: Hazard ratio; N: number of study patients; ORR: overall response rate (including CR + PR); PFS: progression-free survival; PR: partial response; RCT: randomised controlled trial

Identify yet-to-be-published research that may have results available in the near future (that could be relevant to your application).

There are no registered studies or studies currently underway.