Medical Services Advisory Committee (MSAC) Public Summary Document

Application No. 1791 – Dinutuximab beta for primary relapse and refractory high-risk neuroblastoma

Applicant: **Recordati Rare Diseases Australia**

Date of MSAC consideration: **3-4 April 2025**

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, visit the MSAC website

1. Purpose of application

An application requesting public funding through the National Health Reform Agreement (NHRA) Addendum, high cost, highly specialised therapies (HST) program of dinutuximab beta (DB) (Qarziba®) for primary relapse or refractory high-risk neuroblastoma (RRHRNBL) was received from Recordati Rare Diseases Australia by the Department of Health and Aged Care.

2. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness, cost-effectiveness and total cost, MSAC supported the public funding of dinutuximab beta (DB; Qarziba®) as a Highly Specialised Therapy (HST) through the National Health Reform Agreement (NHRA) Addendum for primary relapsed or refractory (RR) high-risk neuroblastoma (HRNBL).

MSAC recognised the clinical need for access to new therapies in the RRHRNBL population and noted that DB is already funded as an HST through the NHRA for some patients with HRNBL. MSAC noted that there were uncertainties in the available clinical evidence, largely due to the rarity of the condition; however, MSAC considered that, overall, DB appeared to have clinical benefit with a clinically important response rate in the RRHNRBL population. MSAC further noted that DB was considered standard of care for RRHRNBL.

MSAC noted that the NHRA Addendum requires, by definition, that HSTs are Therapeutic Goods Administration (TGA) approved, and that the average annual treatment cost at the commencement of funding exceeds $200,000 per patient, including ancillary services. MSAC considered that DB treatment (including ancillary costs) is expected to cost more than $200,000 per patient. MSAC considered advice from the TGA that provided a treating physician considered that RR patients had achieved at least a partial response to induction chemotherapy, by any measure considered clinically appropriate, they would be within the existing indication. MSAC considered that DB treatment for the requested RRHRNBL population is covered by the intention of the current TGA indication for DB. MSAC therefore considered DB for the proposed population met this NHRA Addendum criterion for HST funding. MSAC noted that the extension of DB funding to this population would still be within the agreed financial caps for DB treatment for HRNBL.

Consumer summary

This application from Recordati Rare Diseases Australia requested joint Commonwealth and State/Territory public funding through the National Health Reform Agreement Addendum, high cost, highly specialised therapies program of dinutuximab beta (DB) for patients with high-risk neuroblastoma who either had recurrent (relapsed) disease after initial treatment (called induction treatment), or did not respond (refractory) to initial treatment.

Neuroblastoma is a rare type of cancer that affects the sympathetic nervous system. It mainly affects young children, and is the most frequently diagnosed cancer in children less than one year old (around 55 cases per year in Australia). Children diagnosed with neuroblastoma have a poor long-term outlook, and about half are classified as having high-risk (aggressive) disease.

DB is an immune protein (antibody) therapy designed to attack neuroblastoma cells that is given into a vein as treatment. DB treatment is currently funded for patients who achieve at least a partial response to induction chemotherapy. This application sought to extend funding to patients who experience primary relapse or are refractory to induction treatment. It is proposed to be used alongside combination chemotherapy (using 2 or more medications) in these patients.

MSAC acknowledged that DB is already considered standard of care in Australia for the small number of patients in the proposed population, who have a high level of need and for whom there is no alternative treatment. There is also reasonable clinical evidence to support the use of DB in this expanded group of patients, although the amount of evidence is limited because the condition is rare. It also appears to be relatively safe, and although pain is the major side effect, it can be managed with medication. Finally, MSAC considered that, although the treatment is expensive, the cost is acceptable for a highly specialised treatment.

MSAC's advice to the Commonwealth Minister for Health and Aged Care

MSAC supported public funding of DB for patients with primary relapse or refractory high-risk neuroblastoma. The population is small and has a high need, with no alternative treatment. The treatment appears to be effective and relatively safe and has an acceptable cost for a highly specialised treatment.

3. Summary of consideration and rationale for MSAC's advice

MSAC noted that this was an application from Recordati Rare Diseases Australia requesting public funding through the National Health Reform Agreement (NHRA) Addendum, high cost, highly specialised therapies (HST) program of dinutuximab beta (DB) (Qarziba®) for primary relapse or refractory high-risk neuroblastoma (RRHRNBL). MSAC noted that DB is already funded for high-risk neuroblastoma (HRNBL) in patients who have received induction chemotherapy and achieved at least a 'partial response' (MSAC Application 1625, supported July 2020). The current application was seeking to extend the existing funding of DB to include patients with RRHRNBL. MSAC noted that this application bypassed PASC. MSAC noted that New South Wales, Queensland, Victoria and Western Australia provided input on this application.

The applicant was granted a hearing, during which the applicant representatives presented information relating to the role of chemoimmunotherapy in the RRHRNBL population. The applicant representatives stated that chemoimmunotherapy is currently standard practice for all children with RRHRNBL, and aims to induce a response and increase the duration of survival for these children. The applicant representatives also stated that, while dinutuximab therapies are considered standard of care in this population, access to both is limited; DB is not currently funded for those with RRHRNBL, while dinutuximab alpha (DA) is only available through

compassionate access programs via the United States (US) and is not Therapeutic Goods Administration (TGA) approved. The applicant representatives stated that there are neuroblastoma-specific clinical response criteria to determine whether children respond to chemoimmuntherapy, but that these may exclude a small number of patients who improve to some degree, but do not meet the criteria to be considered to have achieved a partial response. The applicant representatives noted that current funding access criteria through the NHRA could permit treatment of patients with relapsed HRNBL but excludes refractory patients, despite evidence that these patients respond to chemoimmunotherapy with similar survival to refractory patients. The applicant representatives stated that it would therefore be disappointing to exclude the very small number of refractory patients from receiving funded treatment.

MSAC noted that, for a therapy to be considered an HST under the NHRA Addendum criteria, it must be TGA approved. MSAC noted the applicant's concerns around the TGA indication for DB, and also that ESC had considered that the TGA indication for DB may not be aligned with the proposed listing. MSAC further noted concerns from some states and territories that funding non-TGA-registered indications would set a precedent for future HST applications, and that it could undermine the public's perceptions of the TGA and confidence in the safety and efficacy of DB. MSAC noted that the TGA indication for DB is for 'high-risk neuroblastoma in patients who have previously received induction chemotherapy and achieved at least a partial response', which appears to exclude refractory HRNBL patients. MSAC noted that the applicant had stated in its pre-MSAC response that due to limited data, it was unlikely any application to change the TGA indication would occur. MSAC also noted from the pre-MSAC response, and further reiterated by the applicant representatives during the hearing, that approximately redacted refractory patients per year would be excluded by the current indication (i.e. those who do not achieve a response to induction chemotherapy).

MSAC noted advice from the TGA confirmed that both relapsed and refractory patients could be considered within the scope of the TGA indication as long as the patient 'has experienced what was considered by the treating physician to be at least a partial response by any measure', and that refractory patients were not intended to be excluded by the indication. Based on this advice, MSAC considered that the proposed population was sufficiently aligned with the TGA indication, and that DB therefore met the TGA approval criteria for HSTs. MSAC also noted that this was aligned with the use of DB overseas; for example, the European Medicines Agency (EMA) indication explicitly includes those with relapsed or refractory neuroblastoma, with or without residual disease[1].

MSAC noted that an additional criteria for HST funding is that the total cost of treatment exceeds $200,000 per patient per year. While the financials presented in the application did not exceed this cost, MSAC agreed with ESC that, if all ancillary costs were included (e.g. cost of hospitalisation and management of adverse events), and given that DB is already funded as an HST for a similar patient group, it is very likely that the proposed extension of DB use will exceed $200,000 per patient per year. This was also in line from advice from states and territories, which indicated that actual costs for delivery of DB were higher than what was proposed in the economic analysis, due to rates of neurotoxicity and ongoing costs for patients who respond to treatment. Based on the expected total cost of treatment, and the clarification from the TGA around the indication, MSAC considered that DB in this population met the requirements for HST funding under the NHRA.

[1] Qarziba, INN-Dinutuximab beta

MSAC noted and welcomed consumer input from 3 organisations, 9 individuals (parents or carers) and 2 health professionals, who were all supportive of public funding of DB those with RRHRNBL. MSAC acknowledged in particular the feedback received from families of children who had died from HRNBL, and recognised the impact that this disease had on families. MSAC noted feedback stated that DB resulted in improved outcomes and quality of life for patients, and that public funding would help to reduce financial stress for patients and their families, noting that costs can be substantial particularly for some families who travel overseas for treatment. MSAC also noted that, while feedback acknowledged there are side effects, including pain, these were likely to be outweighed by increased survival if well managed, and were considered to be comparable to existing treatments. MSAC advised that the views and experiences of children who have received the treatment would also be informative, particularly regarding the impact of adverse events. MSAC also noted feedback that equity of access, particularly for rural and remote patients, was important. MSAC noted that, currently, access to DA on a compassionate use basis is restricted to 8 paediatric centres and is not available in some hospitals, requiring some children to relocate to receive treatment, resulting in equity of access issues. MSAC considered that this may be reduced by public funding of DB, but acknowledged that equity of access is to some extent an unavoidable concern due to the highly specialised nature of the treatment requiring certain services and facilities during treatment.

MSAC noted feedback received from state and territory health authorities. The jurisdictions acknowledged the high need for treatment in the proposed population, but raised concerns around if DB in this population met the HST criteria. Some jurisdictions also noted that the cost of treatment had been underestimated in the application, and that treatment duration can be highly variable, and may require more than the 5 cycles costed within the application.

MSAC noted that the proposed clinical management algorithm was adapted from National Comprehensive Cancer Network (NCCN) guidelines. Although refractory disease was not explicitly included in the algorithm, MSAC noted that the use of DB for refractory disease was supported by the text in the guidelines.

MSAC noted the clinical claim that DB + chemotherapy has superior effectiveness and inferior safety compared with chemotherapy (standard of care) alone. MSAC considered the claim of inferior safety to be reasonable, noting that DB + chemotherapy is associated with higher rates of neurotoxicity, especially pain, compared with chemotherapy alone. MSAC considered that this was expected, due to the mechanism of action of DB, which targets neuroblastoma cells and because adding other drugs to chemotherapy typically increases side effects. MSAC noted that pain is typically considered manageable with current prophylactic analgesia protocols (morphine, gabapentin, and paracetamol or ibuprofen). At the hearing, representatives of the applicant stated that long-term adverse events do also occur and are typically an aggregate effect of the initial treatment, and subsequent salvage and relapse therapy.

Regarding the claim of superior effectiveness, MSAC agreed with ESC that clinical effectiveness was uncertain, but that the claim was likely supported by the evidence presented. The evidence was based on 2 randomised clinical trials (RCTs) (BEACON-Immuno, which used DB [N = 65]; ANBL 1221, which used DA [N = 35]) and one meta-analysis, with the main outcomes being overall response rate (ORR), progression-free survival (PFS) and overall survival (OS). MSAC noted that there were a number of issues with the evidence, contributing to overall uncertainty: sample sizes were small, due to the rarity of the disease; there was an assumption that DA and DB were therapeutically equivalent, and the BEACON-Immuno trial was not designed or powered for testing differences in efficacy between DB + chemotherapy and chemotherapy alone, limiting the interpretation and internal validity of the results. Despite these issues, based on the evidence presented, MSAC noted that DB treatment resulted in a higher ORR than the comparator, with

refractory patients appearing to have a higher response than relapsed patients. MSAC noted that DB treatment also appeared to result in higher PFS compared to no DB, although noted that this was based on very small numbers. Further, at the hearing, representatives of the applicant showed data from the ANBL 1221 trial that indicated that PFS was similar for relapsed and refractory patients. MSAC noted that the OS benefits from DB treatment were less convincing, but the Kaplan–Meier curve from the BEACON-Immuno trial was difficult to fully interpret due to 12 patients in the 'no DB' arm receiving crossover treatment. MSAC noted that the applicant representatives advised that DB and DA are used interchangeably in clinical practice and are considered equivalent, which was aligned with advice from the Australian and New Zealand Children's Haematology/Oncology Group (ANZCHOG) that clinicians consider the DA and DB to be similar and, in practice, will use whichever is readily available. Overall, MSAC considered that, based on the available data and noting that it was unlikely higher quality data would be available in future due to disease rarity, the claim of superior effectiveness appeared to be reasonable.

MSAC noted ESC had queried whether the appropriate dosing schedule was clear, as they differed between the key trials and from the TGA-approved dosing schedule. At the hearing, representatives of the applicant advised that the standard dosing schedule was a 21-day cycle for DB + temozolomide + irinotecan (TEMIRI) or a 28-day cycle for DB + temozolomide + topotecan (TOTEM). The applicant's representatives stated that clinicians are very familiar with these dosing schedules. The pre-MSAC response proposed that these be made available via eviQ for easy access by clinical staff.

MSAC noted that the economic evaluation included both a cost-effectiveness analysis and cost-utility analysis. MSAC agreed with ESC and considered that the economic evaluation was highly uncertain due to a number of issues.

MSAC noted that the calculations did not include costs associated with hospitalisation or adverse events, which the applicant considered were driven by chemotherapy. MSAC considered that this did not align with the claim of inferior safety, with the potential for Grade 3–5 adverse events (including liver injury, metabolic disturbances and electrolyte abnormalities) as highlighted by state and territory feedback.

MSAC noted that the applicant stated in its pre-MSAC response that clinicians consider life expectancy of 10-20 years to be reasonable based on follow-up; however, MSAC considered that the time horizon of 20 years may still be optimistic given the prognosis of RRHRNBL. MSAC noted that sensitivity analyses were presented in the pre-MSAC response, demonstrating that the base case incremental cost-effectiveness ratio (ICER) increased from $redacted per quality adjusted life year (QALY) to $redacted/QALY at a time horizon of 10 years, and to $redacted/QALY at a time horizon of 5 years.

MSAC noted that ESC had considered that the base case specifications were not well justified, and that it may have been more appropriate to use the BEACON-Immuno data alone for PFS, and present other scenarios as sensitivity analyses. MSAC noted that the applicant argued in the pre-MSAC response that due to the high proportion of crossover in BEACON-Immuno, this would have been inappropriate.

MSAC noted that because data was limited, data from different studies were used to model different outcomes (PFS and OS), resulting in health state probabilities exceeding 1 (which was arithmetically corrected).

MSAC noted that the base case ICER was high, albeit uncertain due to the issues noted with the model, but overall considered it to be acceptable for a HST in this context. MSAC considered that

addressing these issues in sensitivity analyses would likely not significantly improve the cost-effectiveness of the treatment.

MSAC noted that the eligible patient population was estimated to be redacted patients per year, with uptake starting at redacted% in Year 1 and increasing to redacted% by Year 6, which MSAC considered to be reasonable. Each patient was estimated to receive redacted vials, resulting in an estimated net financial impact to the NHRA HST program of $redacted (redacted vials) in Year 1 to $redacted million (redacted vials) in each of Years 5 and 6. MSAC considered that the net financial impact was underestimated due to the absence of hospitalisation costs. MSAC noted that, with these assumptions, the application estimated that the total number of patients receiving DB would not exceed the caps set out in the current deed of agreement between the Commonwealth and Sponsor for DB from March 2025 to February 2026. MSAC advised that a post-market evaluation would be valuable to obtain real-world data.

Overall, MSAC supported public funding of DB for RRHRNBL as an HST through the NHRA Addendum and advised that it would be appropriate for the existing DB access criteria to be expanded consistent with the TGA indication.

4. Background

This is the first submission to MSAC for consideration of DB for RRHRNBL.

At the July 2020 meeting, MSAC previously considered and supported joint Commonwealth and State/Territory funding of DB for high-risk neuroblastoma (HRNBL) in patients who have previously received induction chemotherapy and achieved at least a partial response (MSAC application 1625), subject to the applicant agreeing a price reduction for DB (MSAC 1625 Public Summary Document (PSD), p1). MSAC considered access criteria for DB should be consistent with the TGA indication and noted use of DB that may be outside of the access criteria (i.e. in patients with relapsed or refractory HRNBL) could appropriately be managed with a risk sharing arrangement.

In August 2024, the Joint Chairs (as defined in the Framework for the assessment, funding and implementation of high cost, highly specialised therapies and services) supported consideration of DB for relapsed or refractory HRNBL by MSAC as a HST.

5. Prerequisites to implementation of any funding advice

DB is not TGA approved specifically for the RRHRNBL indication, and the sponsoring pharmaceutical company (the Sponsor) has stated it will not seek an extension to the current TGA approval for DB. The ADAR explained there are several challenges in obtaining specific RRHRNBL registration. The key challenge is that it is unlikely that registration for the indication under consideration will occur in a timely manner, and the availability of a registration package is unpredictable. There are several reasons claimed for this, one of which is that the Sponsor does not have access to all the data to enable the production of a timely clinical study report (CSR) for submission to the TGA, as the DB studies were designed and run by the International Society of Paediatric Oncology Europe Neuroblastoma Group (SIOPEN).

DB is currently TGA-approved for the treatment of high-risk neuroblastoma in patients who have previously received induction chemotherapy and achieved at least a partial response. The ADAR states that “[t]he MSAC Executive supported the consideration of an application by MSAC for the extension of public funding of DB for the treatment of patients with relapsed or refractory HRNBL, noting the current TGA indication appears to only explicitly exclude those with relapsed disease”.

The commentary considered that, given patients are required to have at least a partial response to front-line therapy under the current indication, it would appear that the current TGA indication only explicitly excludes those with chemotherapy refractory disease. The current TGA indication for HRNBL does not specifically mention relapsed disease.

The TGA-approved dose regimen for DB in HRNBL consists of five consecutive courses, each course comprising 35 days:

- For patients weighing >12 kg, the individual dose is determined based on the body surface area and should be a total of 100 mg/m^2 per course.
- For patients weighing >5 kg and ≤12 kg, the individual dose is determined based on body weight and should be a total of 3.3 mg/kg per course.

Two modes of administration are possible:

- A continuous infusion over the first 10 days of each course (a total of 240 hours) at the daily dose of 10 mg/m^2 (for patients weighing >12 kg) or 0.33 mg/kg (for patients weighing >5 kg and ≤12 kg), or
- Five daily infusions of 20 mg/m^2 (for patients weighing >12 kg) or 0.66 mg/kg (for patients weighing >5 kg and ≤12 kg) administered over 8 hours, on the first 5 days of each course.

Of the DB studies presented in the ADAR, none used these dosage regimens for RRHRNBL. The dosage regimens used in the DB studies are provided in Table 1.

Table 1 Dosage regimens used in the DB RRHRNBL trial and studies

Study	DB regimen
BEACON-Immuno (RCT)[2]	10 mg/m^2/day per day IV on days 1-7 of each 28 day cycle for maximum of 6 cycles
Olgun 2022[3] (single arm)	10mg/m^2 per day IV on days 1-10 of each 28-day cycle, for 2-14 cycles
Wieczorek 2023[4] (single arm)	10 mg/m2/day IV on days 2–6 of each 21-day cycle for a maximum of 5 cycles (although if well tolerated, at least two further treatment cycles were given to patients with complete response (CR) or stable disease (SD))
Raiser 2024[5] (single arm)	10mg/m^2/day continuous IV on days 1-10 of each 28 day cycle for maximum of 6 cycles

Notably, the dosage regimens for DB differed between studies and it is not clear which regimen(s) will be used in Australian practice. The ADAR suggested that the dosing schedule would be a 7-day continuous infusion (10 mg/m^2/day), given in a 28-day cycle (with the cycle length determined by the relevant chemotherapy protocol). The applicant is requested to clarify "cycle length determined by relevant chemotherapy protocol" in its pre-pre-MSAC response as the concomitant chemotherapies intended for use with DB are (i) temozolomide + topotecan (TOTEM), which appears to consistently have a 28 day cycle in the studies or (ii) temozolomide and irinotecan (TEMIRI) which had either 21- or 28-day cycles in the studies.

[2] Gray, J. 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. *J Clin Oncol* 40(16 Supplement 1).

[3] Igun, N. et al. (2022). Dinutuximab beta + conventional chemotherapy for relapsed/refractory high-risk neuroblastoma: A single-center experience. *Front Oncol* 12: 1041443.

[4] Wieczorek, A. et al. (2023). Dinutuximab beta combined with chemotherapy in patients with relapsed or refractory neuroblastoma. *Front Oncol*.

[5] Raiser, P. et al. (2024). Chemoimmunotherapy with dinutuximab beta in patients with relapsed/progressive high-risk neuroblastoma: does chemotherapy backbone matter?. *Eur J Cancer* 202: 114001.

As DB is intended to be funded through the NHRA HST program and its use is likely to be limited to the eight specialist treatment centres that currently administer dinutuximab therapies for HRNBL (three in NSW, two in Victoria and one each in Queensland, South Australia and Western Australia), consideration is required of whether coordination of dosing regimens may be possible without a specific TGA approved dosing schedule.

The ADAR, in its economic evaluation, assumed a dose of 10 mg/m^2/day for seven days in each cycle to the maximum of six cycles, estimating an average usage of redactedmg equating to a mean of redacted (undiscounted) or redacted (discounted) vials per patient based on usage data from 42 patients in the BEACON-Immuno trial, adjusting for PFS. The base case of the modelled economic evaluation and the financial estimates assumed redacted vials per patient.

The application requests public funding of DB for primary RRHRNBL through the NHRA HST program. The NHRA defines HSTs as "TGA approved medicines and biologicals delivered in public hospitals where the therapy and its conditions of use are recommended by MSAC or PBAC; and the average annual treatment cost at the commencement of funding exceeds $200,000 per patient (including ancillary services) as determined by the MSAC or PBAC with input from the IHACPA; and where the therapy is not otherwise funded through an Australian Government program or the costs of the therapy would be appropriately funded through a component of an existing pricing classification". The commentary estimated that the total cost of treatment per patient was $redacted including all DB-associated costs but excluding drug administration costs

6. Proposal for public funding

The proposed eligibility criteria for treatment of RRHRNBL with DB are:

- Patient must have high risk neuroblastoma, AND
- Patient must have primary relapsed disease, OR
- Patient must have disease refractory to standard treatment.

The ADAR also suggested that, according to the TGA approved product information[6], DB must be administered under the direction of a physician experienced in the use of oncological therapies. The infusion must be initiated by a healthcare professional prepared to manage severe allergic reactions, including anaphylaxis, in an environment where full resuscitation services are immediately available.

The solution should be administered via a peripheral or central intravenous line. Other intravenously co-administered agents should be delivered via a separate infusion line.

For continuous infusions, the solution is administered at a rate of 2 mL per hour (48 mL per day) using an infusion pump.

For 8-hour daily infusions (i.e. dis-continuous), the solution is administered at a rate of approximately 13 mL per hour.

Pre-medication should always be considered before starting each infusion.

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).

[6] Therapeutic Goods Administration (2020). Australian Public Assessment Report (AusPAR): dinutuximab beta. Attachment: Product Information. https://www.tga.gov.au/sites/default/files/auspar-dinutuximab-beta-200630-pi.pdf

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

In the meeting (of April 2024) at which the MSAC Executive supported the consideration of an application by MSAC for the extension of public funding of DB for the treatment of patients with relapsed or refractory HRNBL, it noted from a letter from the Australian and New Zealand Children's Haematology/Oncology Group (ANZCHOG) that anti-GD2 immunotherapy (which includes DB) can have several clinical uses including as a bridging therapy for consolidation, as a maintenance therapy, and as a consolidation therapy after the initial chemotherapy. The MSAC Executive advised that if DB treatment was only extended to the relapsed and refractory HRNBL population, PASC consideration would not be required, but if the sponsor wanted to seek a broader listing which might raise multiple treatment pathways, PASC consideration would be required.

Per the ADAR the applicant accepted the conditions for bypassing PASC but a question which arises is whether the proposed funding conditions are specific enough to extend only to the relapse and refractory HRNBL population and avoids raising other treatment pathways. The wording of the relevant condition line "*Patient must have disease refractory to standard treatment"* may not be specific enough to patients with primary refractory HRNBL *as* within the scope and intent of the ADAR. This lack of specificity should also be considered in relation to the interaction of this proposal with the existing TGA indication and current NHRA funding for maintenance DB (as discussed above).

7. Population

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 categorises tumours as very low risk, low risk, intermediate risk or high risk based on the following prognostic factors: age at diagnosis (two cut-offs: 12 and 18 months), INRG tumour stage (two stages of localised disease, L1 and L2, and two stages of metastatic disease, M and 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 has an incidence of 10.6 children per million (Cancer Council Queensland 2014[7]), based on 46 new cases per annum reported on average between 2000-2014 and as stated in the ADAR for previous MSAC application 1625. This incidence was considered reasonable, given it is within the range of estimated incidences in the literature (i.e. 9.5 per million (reported by Youlden 2020[8]) and 11.6 per million (+10.5% incidence difference from 10.5 cases/million children)

[7] Cancer Council Queensland (2014). A summary of Childhood Cancer Statistics in Australia, 1983-2014. Retrieved September 2024, from https://cancerqld.blob.core.windows.net/site/content/uploads/2017/12/A-summary-of-childhood-cancer-in-Australia-1983-2014.pdf

[8] Youlden, D. R. et al. (2020). Incidence and outcomes of neuroblastoma in Australian children: A population-based study (1983–2015*). J Paediatr Child Health* 56(7): 1046-1052.

(reported by Heerden 2021[9]), and suggests that there are approximately 55 children diagnosed with NBL in Australia annually. Of these, about half have HRNBL (DuBois 2022, Krystal 2023); these results are in line with those reported in the Australian Childhood Cancer Registry, where 51% of children are diagnosed as stage 4 (Youlden 2019[10]).

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. A distribution of 1/3 of RRHRNBL being refractory and 2/3 relapsed is supported in the literature.

8. Comparator

The proposed comparator for primary RRHRNBL patients is chemotherapy that includes topotecan or irinotecan in addition to temozolomide (TOTEM or TEMIRI, respectively).

The ADAR provided results of a clinician survey of treatment options for patients with refractory or relapsing disease in the absence of chemoimmunotherapy (i.e., DB + chemotherapy). The survey included six respondents, one from each of the single treatment centres in Queensland, Western Australia and South Australia; one from one of the two treatment centres in Victoria; and two from the three treatment centres in New South Wales (NSW). For the NSW responses, it is not clear whether this represents one respondent from two centres or multiple responses from a single centre (although it is assumed to be the former as eight clinicians were approached, likely one from each centre).

The clinician survey results support the contention that TOTEM and TEMIRI are the most commonly used regimens in Australia, and that the topotecan + cyclophosphamide (TopoCyclo) regimen is less commonly used, with one of six clinicians reporting use of the TopoCyclo combination 90% of the time while another respondent reported its use 45% of the time for refractory, induction, consolidation, maintenance or post-maintenance treatment.

9. Summary of public consultation input

Consultation input was received from 3 consumer organisations, 2 individual health professionals (paediatric oncologists) and 9 individual parents who cared for children with the health condition that this health technology is for. The organisations that provided input were:

- Neuroblastoma Australia
- Rare Cancers Australia (RCA)
- National Paediatric Medicines Forum (NPMF).

Level of support for public funding

All organisations and individuals were supportive of public funding.

Perceived Advantages

Advantages of the service noted in the input included:

[9] Heerden, J. v., N. et al. (2021). Reporting Incidences of Neuroblastoma in Various Resource Settings. *JCO Global Oncology* (7): 947-964.

[10] Youlden, D. R. et al. (2019). Stage at diagnosis for childhood solid cancers in Australia: A population-based study. *Cancer Epidemiol* 59: 208-214.

- A superior response and survival rate for immuno-chemotherapy treatments compared to pure chemotherapy combinations, based on clinical trials that have occurred to date.
- Often this treatment option enables a patient to get into remission, which can provide time to access a clinical trial specifically for relapsed neuroblastoma if this is required (e.g. CAR-T, Vaccine trial USA). Access to these clinical trials may increase prospects to potentially also help maintain remission and improve chances of survival.
- Improved outcomes, quality and quantity of life for patients.
- A manageable side effect profile compared to some existing treatments, potentially improving the patient's quality of life during treatment.
- Improved equity of access as there is potential for the treatment to be given outside of hospital, which could be helpful to parents and families, especially from rural and remote locations, noting this would be dependent on there being suitably qualified staff and support.
- Potential for reduced care-related trauma and anxiety, for both children and their families or carers.
- Reduced financial stress for patients and families, which can be significant and is further increased by the need for long periods of travel and accommodation, as extended hospital stays are currently typically required.
- Availability of this treatment within Australia would reduce the need for overseas travel, decreasing the overall financial burden on families.

Perceived Disadvantages

Disadvantages of the service noted in the input included:

- While the side effect profile is manageable, adverse effects include pain. While the negative impacts of side effects are considered to be outweighed by the improvements in survival and reduced likelihood of disease recurrence, careful management of side effects and regular monitoring through follow-up care are required.
- Barriers include geographic access challenges for rural and remote populations and the need for specialised training for healthcare providers.

Support for Implementation /issues

- Health professional respondents were positive that their places of practice can accommodate delivery of this service to patients, if implemented for public funding.
- There should be clear guidelines and qualified support in place. Decisions around treatment approach should be made in consultation with the parents to ensure they feel comfortable (e.g. if a continuous infusion pump used).
- The proposed delivery approach needs to ensure equitable access across Australia, including rural and remote areas.
- Treatment delivery should be integrated with existing paediatric oncology services and local pathology services.
- Additional support services including comprehensive pain management, psychological support, nutritional guidance, and regular monitoring should be readily available and integrated into the treatment protocol to address the complex needs of patients.

10. Characteristics of the evidence base

Although the ADAR is specifically seeking extension of the listing for DB (as DB + chemotherapy), the literature search was broader and included dinutuximab alpha (DA) (specifically studies assessing DB + chemotherapy or DA + chemotherapy). The ADAR has assumed that DB and DA

are interchangeable for the purpose of evaluating treatment efficacy, without demonstrating at least non-inferiority of DB to DA and despite noting the differences between the two therapies.

The ADAR included a total of 11 studies:

- Four DB studies: one randomised controlled trial (RCT; BEACON-Immuno) and three single arm studies (Olgun 2022, Raiser 2024, Wieczorek 2023);
- Three DA studies: one RCT and its extension study (ANBL 1221[11]), one comparative cohort study (Sydney Children's Hospital [SCH] 2024[12]) and one single arm study (Lerman 2023[13]); and
- Four chemotherapy alone studies: one RCT (BEACON-1) and three single arm studies (Bagatell 2011[14], DiGiannatale 2014[15], DuBois 2018[16]).

Details of the included trials and studies are provided in Table 2.

[11] Mody, R. 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.

[12] SCH (2024). Outcome of patients with relapsed or refractory high-risk neuroblastoma (R/R HR-NB) at Sydney Children's Hospital (patients diagnosed from 1st January 2010 to 31st December 2021).

[13] Lerman, B. et al. (2023). Progression-Free Survival and Patterns of Response in Patients with Relapsed High-Risk Neuroblastoma Treated with Irinotecan/Temozolomide/Dinutuximab/Granulocyte-Macrophage Colony-Stimulating Factor. *J Clin Oncol* 41(3): 508-516.

[14] Bagatell, R. et al. (2011). Phase II study of irinotecan and temozolomide in children with relapsed or refractory neuroblastoma: a Children's Oncology Group study. *J Clin Oncol* 29(2): 208-213.

[15] Di Giannatale, A. et al. (2014). Phase II study of temozolomide in combination with topotecan (TOTEM) in relapsed or refractory neuroblastoma: a European Innovative Therapies for Children with Cancer-SIOP-European Neuroblastoma study. *Eur J Cancer* 50(1): 170-177.

[16] DuBois, S.G. et al. (2018). Phase II Trial of Alisertib in Combination with Irinotecan and Temozolomide for Patients with Relapsed or Refractory Neuroblastoma. *Clin Cancer Res* 24(24): 6142-6149.

Table 2 Summary of trial and study characteristics

	N	Design	Intervention (n)	Comparator (n)	Relapsed: Refractory (%)
DB studies					
BEACON-Immuno	65	RCT, OL	DB + TOTEM (43)	TOTEM (22)	55:45
Olgun 2022	19	SA	DB + TEMIRI (most common, although other chemotherapy regimens allowed)	-	47:53
Raiser 2024	39	SA	DB + TOTEM/TEMIRI (15)/ DB + topo + cyclo (24)	-	100:0
Wieczorek 2023	25	SA	DB + TEMIRI	-	80:20
DA studies					
ANBL 1221	35	RCT, OL	DA + TEMIRI + GM-CSF (17)	TEMIRI + temsirolimus (18)	54:46 (100% 1st relapse)
ANBL 1221	36	Extension, SA	DA + TEMIRI + GM-CSF	-	64:36
SCH 2024	20	Cohort	DA + Chemotherapy[1] (12)	Chemotherapy[1] (5), palliation (3)	60:40
Lerman 2023	146	SA	DA + TEMIRI + GM-CSF	-	100:0
Chemotherapy studies					
BEACON-1 (Moreno 2024[17])	80	RCT, OL	-	Temozolomide (36)/ TEMIRI (30)/ TOTEM (14)	59:41 (100% 1st relapse)
Bagatell 2011	55	SA	-	TEMIRI	73:27
Di Giannatale 2014	38	SA	-	TOTEM	66:34
DuBois 2018	32	SA	-	TEMIRI + alisertib	NR

cyclo = cyclophosphamide; DA = dinutuximab alpha; DB = dinutuximab beta; GM-CSF = granulocyte macrophage colony stimulating factor; NR = not reported; OL = open-label; RCT = randomised controlled trial; SA = single arm; SCH = Sydney Children's Hospital; TEMIRI = temozolomide + irinotecan; topo = topotecan; TOTEM = topotecan + temozolomide

[1] nature of chemotherapy not reported

The BEACON-Immuno trial is the most relevant evidence to this application and was therefore focussed on in the commentary.

BEACON-Immuno was a phase II, open-label, multicentre trial of TEMIRI or TOTEM, with or without bevacizumab or DB, for the treatment of patients with relapsed or refractory neuroblastoma. Patients were initially randomised to bevacizumab or not, to irinotecan or topotecan or neither, with a backbone of temozolomide into six treatment arms: (i) temozolomide only; (ii) bevacizumab + temozolomide; (iii) TEMIRI; (iv) bevacizumab + TEMIRI; (v) TOTEM; or (vi) bevacizumab + TOTEM.

The trial protocol was subsequently amended, wherein following completion of the bevacizumab randomisation, a planned 64 additional patients were enrolled and randomised to one of the following four arms, with patients randomised in a 2:1 ratio favouring the two DB arms:

1. Temozolomide alone

[17] Moreno, L. 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* 42(10): 1135-1145

2. DB + temozolomide
3. TOTEM
4. DB + TOTEM.

Following review by the trial management group of the PFS and OS results of the bevacizumab randomisation, evidence indicated that temozolomide alone was inferior and therefore the temozolomide alone (n=3) and DB + temozolomide (n=6) arms were closed partway through the accrual period (2019-2021) from 28 January 2020. The temozolomide alone patients (n=3) were merged into the TOTEM (n=19) arm; and the DB + temozolomide patients (n=6) were merged into the DB + TOTEM arm (n=37); however, it is not clear whether these patients actually received TOTEM versus temozolomide alone as this information is not available from the trial abstract/presentation reported by Gray 2022. This resulted in a final two arms for which results were presented: TOTEM (n=22) and DB + TOTEM (n=43).

It is unclear what impact the merging of arms and changes in chemotherapy regimen would have on the comparative efficacy results, given the small sample sizes. Crossover to DB + topotecan + cyclophosphamide was also allowed for patients randomised to chemotherapy alone who experienced disease progression. There were 12 patients (54.5%) in the no DB arm that received crossover treatment. Overall response rate (ORR) was measured prior to crossover. However, OS was not censored prior to crossover, and therefore may have been impacted by crossover treatment, in an unknown direction.

Regarding statistical planning for the DB amendment, the trial protocol stated (p108) that assuming a control arm response rate of 25% and experimental arm response rate of 45%, with 64 patients in total there will be 80% power with a one-sided p=0.23 for ORR. The statistical analysis plan was not available, and there was no evidence of controlling for multiplicity, though it was stated in the protocol that the DB question would not be taken any further if at the final analysis p>0.23. Other analyses were to be conducted per the bevacizumab randomisation.

Best response was defined as complete (CR) or partial (PR) response at any time during the first six cycles of trial therapy, with response evaluated every two cycles. Responses were locally evaluated using the Response Evaluation Criteria in Solid Tumours (RECIST Criteria 1.1) for those patients with measurable disease on cross-sectional imaging. Response was determined for patients with evaluable disease (only metaiodobenzylguanidine [MIBG] avid disease) using a semiquantitative score (CURIE & SIOPEN) and the new International Neuroblastoma Response Criteria. An independent blinded radiologist and nuclear medicine physician was to review all computed tomography (CT)/magnetic resonance imaging (MRI) and MIBG scans of patients who respond (CR or PR), along with a random sample of at least 20% of the non-responders.

Overall, the exploratory nature of the trial and the fact that BEACON-Immuno was not designed nor powered for testing differences in efficacy between DB + chemotherapy and chemotherapy alone limits the interpretation and internal validity of the results of this phase II, open-label trial.

All of the included trials and studies were relatively small with respect to sample size, likely reflecting the rarity of the condition. Most had a mixture of relapsed and refractory patients; among relapsed patients, only two studies (ANBL 1221 and BEACON-1) restricted enrolment to only those with first (primary) relapse, as per the intended treatment population.

The ADAR provided a summary of the prognostic factors of importance specific to the RRHRNBL indication. Differences in these adverse prognostic factors (proportion relapsed, older age at diagnosis, metastatic disease, measurable disease, *MYCN* oncogene amplification, shorter time from diagnosis to relapse, prior progressive disease, no prior anti-disialoganglioside 2 [GD2] treatment [DB or DA] and earlier treatment era) were observed between treatment arms of the BEACON-Immuno and ANBL 1221 trials, as well as between the trials and studies.

11. Comparative safety

The ADAR only reported safety outcomes for the RCTs (BEACON-Immuno and ANBL 1221).

The ADAR stated that DB showed a tolerable toxicity profile in RRHRNBL, with the majority of adverse events (AEs) of grade 1 or 2 intensity in both treatment arms. A higher rate of Grade 1 and 2 neurotoxicity was seen in the DB + TOTEM arm (63%) compared with the TOTEM arm (14%). In patients receiving DB, there was no increase in myelotoxicity or infection (Gray 2022). Grade 2 neurotoxic AEs reported were headache (one patient), neuralgia (five patients), nystagmus (one patient), paraesthesia (one patient) and peripheral motor neuropathy (one patient). The only grade 3 neurotoxicity reported was myelitis (one patient) (Gray 2022).

The commentary noted the evaluation of safety data is limited and not able to be verified given the absence of a CSR. Data provided from Gray 2022 showed that patients treated with DB + TOTEM were observed to have had a comparable rate of all AEs. As noted by the ADAR above, neurotoxicity appeared to be more common in the DB + TOTEM arm compared to the TOTEM arm.

12. Comparative effectiveness

The ADAR presented results for ORR, OS and PFS, where reported in the trials and studies.

Overall response rate (ORR)

ORR was reported for the individual trials, a meta-analysis of the BEACON-Immuno and ANBL 1221 trials and meta-analyses of the (i) DB/DA + chemotherapy and (ii) chemotherapy alone arms of all trials and studies, and provided a comparison of the meta-analysed single arm results, see Table 3.

Table 3 Results for ORR reported in the trials and studies

Study	Intervention n/N (%, [95% CI])	Comparator n/N (%, [95% CI])	Risk difference (95% CI)
BEACON-Immuno (DB)	15/43 (35, [21, 51])	4/22 (18 [5, 40])	0.17 (-0.05, 0.38)
ANBL 1221 RCT (DA)	9/17 (53 [28, 77])	1/18 (6 [0, 27])	0.47 (0.21, 0.73)
Meta-analysis of BEACON-Immuno and ANBL 1221			0.31 (0.01, 0.61); I^2 = 69%
BEACON-Immuno (DB)	15/43 (35, [21, 51])	-	-
ANBL 1221 RCT (DA)	9/17 (53 [28, 77])	-	-
ANBL 1221 ext (DA)	13/36 (36 [21, 54])	-	-
Lerman 2023 (DA)	57/146 (39 [31, 47])	-	-
Olgun 2022 (DB)	12/19 (63 [38, 84])	-	-
Wieczorek 2023 (DB)	13/17 (76 [50, 93])	-	-
Raiser 2024 (DB)	6/15 (40 [16, 68])	-	-
Meta-analysis of single-arm intervention	48 (36, 59); I^2 = 66%		
BEACON-Immuno	-	4/22 (18 [5, 40])	-
ANBL 1221 RCT	-	1/18 (6 [0, 27])	-
BEACON-1	-	14/80 (17 [10, 28])	-
Bagatell 2011	-	8/55 (15 [6, 27])	-
DiGiannatale 2014	-	9/38 (24 [11, 40])	-
DuBois 2018	-	5/32 (16 [5, 33])	-
Meta-analysis of single-arm comparator		15 (11, 20); I^2 = 3%	
Comparison of single arm intervention versus single arm comparator meta-analysis estimates			0.33 (0.26, 0.40)

CI = confidence interval; DA = dinutuximab alpha; DB = dinutuximab beta; ext = extension; I^2 = ratio of the (estimated) between-study variability of the treatment effect to the sum of the (estimated) between-study variability and the (estimated) within-study variability; n = number with event; N = total number of patients; ORR = overall response rate
Source: Figure 2-1, p46; Figure 2-2, p47 and Figure 2-3, p48 of the ADAR

No statistically significant differences were observed between treatment arms of the BEACON-Immuno trial. The ORR was 18% with chemotherapy alone and 35% for patients receiving chemotherapy with DB.

Risk ratios were reported in Gray 2022, noting that BEACON-Immuno was not powered to show a difference in ORR:

- Unadjusted: 1.92 (80% confidence interval [CI] 1.01, 3.63, one-sided p=0.10).
- Adjusted for topotecan administration: 1.66 (80% CI 0.9 to 3.06, one-sided p = 0.19).

The unadjusted and adjusted risk ratios had wide CIs and should be interpreted in the context of the small sample size (N=65: control n=22, chemotherapy + DB n=43), differences in baseline characteristics (including limited ability to assess without the CSR), and potential for biased outcome assessment with an open-label design.

The ORR results for ANBL 1221 were potentially impacted by high rates of discontinuation in the control arm. The 18 patients assigned to chemotherapy alone received 98 total courses of treatment (median 3 [interquartile range 2–10]); the 17 patients assigned to DA + chemotherapy received 148 courses (median 6 [interquartile range 3–17]), potentially confounding response rates.

For the control group, one of 18 patients (6%, 95% CI 0.0–16.1) treated with chemotherapy alone, and 9 of 17 patients (53%, 95% CI 29.2–76.7) treated with DA + chemotherapy, achieved partial or complete response.

The included RCT evidence consisted of two exploratory open-label trials, which were not powered nor designed for testing hypotheses of differences in treatment efficacy between DB/DA + chemotherapy versus chemotherapy alone, and were at risk of assessment bias given response was locally assessed. Consequently, the validity of the pooled estimate for risk difference is uncertain, dependent on accepting that results for DA are interchangeable for DB (for which no evidence has been provided) and the results should be interpreted cautiously with limited conclusive value.

The following points were noted regarding studies included in the intervention arm meta-analysis:

- The pooled ORR estimate assumes DB and DA are interchangeable in terms of treatment efficacy, which may not be the case.
- The included studies are of small sample size, with highly heterogeneous patient populations and treatment regimens.

Overall, the pooled estimate of ORR is unlikely to be reliable.

The following points were noted regarding studies included in the control arm meta-analysis:

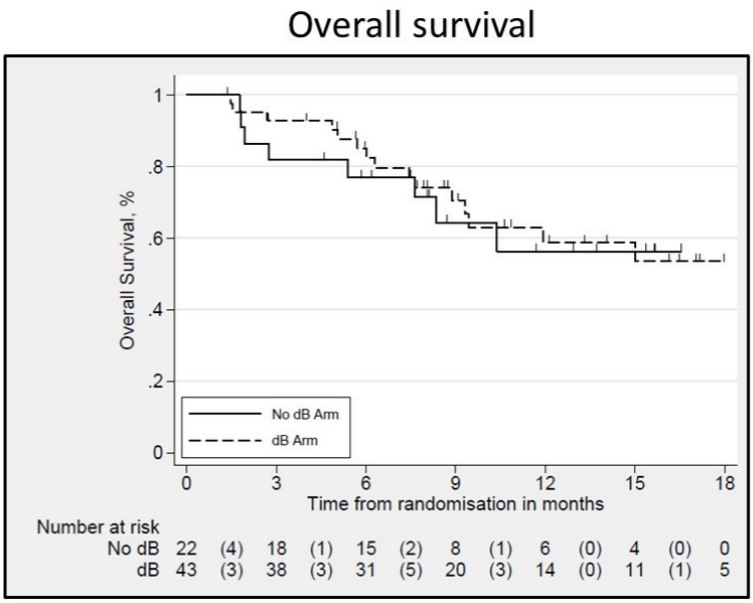
- Discontinuation rates for BEACON-Immuno were unable to be assessed from the abstract.
- In ANBL 1221 there was a higher discontinuation rate in the control arm, with 72% of patients discontinuing prior to cycle 5. This may explain the lower ORR in the control arm.
- In BEACON 1, nearly half of patients in the control arm received temozolomide alone (n=36, 45%), a regimen that was closed early in BEACON-Immuno due to evidence indicating that temozolomide alone was inferior to TOTEM. Therefore, this control arm may be lower than observed with current standard of care.
- In Bagatell 2011, patients were enrolled into the study between June 2006 and July 2008. Treatment protocols from over a decade ago may not be reflective of current standard of care, with trial enrolments prior to 2009 being associated with poorer OS outcomes (London 2017).

The ADAR stated that “an incremental benefit of including dinutuximab + chemotherapy of 33% (95% CI 26%, 40%) is shown in the [naive comparison of single arm meta-analyses] (i.e. 48% minus 15%, with 95% CIs calculated from the estimated standard error (SE)). This level of incremental benefit is very similar to the 31% benefit seen in the meta-analysis of RCTs, supporting a similar level of benefit for dinutuximab + chemotherapy when used outside of more rigorous study design protocols, i.e. in more real-world use.”

Overall survival (OS)

The Kaplan Meier (KM) curve for OS reported in the BEACON-Immuno trial is presented in Figure 2. No difference in OS was observed between groups. As noted by the ADAR, the extensive crossover of more than half (12 of 22) of the no DB group makes interpretation highly uncertain.

Figure 1 KM curve for OS in BEACON-Immuno



Unadjusted HR 0.89 (p=0.79)
Adjusted HR (topo. admin) 0.99 p=0.99
12 patients in 'no dB' arm received cross over treatment

Source: Slide 12 of Gray 2022 ASCO presentation

An overall OS comparison was provided for all the comparative and single-arm cohort studies reporting this outcome, based on median OS (months) and the percent of patients with OS at 1 year, as these were outcomes reported across some of the studies (see Table 4).

The DB + chemotherapy median OS in the studies ranged from median not reached in the ANBL 1221 randomised cohort (33 months in the extension cohort) to 10.3 months in Wieczorek 2023. Wieczorek 2023 included 80% relapsed patients (higher than all other studies that weren't specifically restricted to relapsed patients), including 40% with ≥2 relapses. Hence, the ADAR claimed it was likely that this study included a particularly difficult to treat population. One-year OS ranged from 47% to 88% with DB + chemotherapy treatment, compared with 58% to 65% in the control arms (Table 4), with limited studies reporting these data.

Table 4 Results for OS reported in the relevant trials and studies

Study ID	Dinutuximab+chemo		Control		Dinutuximab+chemo		Control	
	N	Median OS (95% CI), months	N	Median OS (95% CI), months	N	1-Year OS (95% CI), % patients	N	1-Year OS (95% CI), % patients
BEACON-Immuno	43	-	22	-	43	-	22	-
ANBL 1221 RCT	18	NC (27.7, NC)	17	27.1 (5.5, 38.3)	18	88 (72, 100)	17	65 (41, 89)
ANBL 1221 ext	36	33.2 (24.4, NC)	-	-	36	NR	-	-
Wieczorek 2023	25	10.3 (range 0.7, 43.0)	-	-	25	47	-	
BEACON 1	-	-	80	14.5	-	-	80	NR
Bagatell 2011	-	-	55	13.2	-	-	55	NR
Di Giannatale 2014	-	-	38	19.0	-	-	38	58 (42, 72)

Source: Table 2-13, p52 of the ADAR
chemo = chemotherapy; CI = confidence interval; N = number of total patients; NC = not calculable; NR = not reported; OS = overall survival

The ADAR also presented OS results from the SCH Cohort (2024), providing a comparison of 12 patients treated with DA + chemotherapy versus eight patients in the control arm (five treated with chemotherapy and three palliatively), reporting 30% and 0%, respectively remaining alive at four years. Median OS was 30.0 months in the DA group versus 9.5 months in the control group. The ADAR stated that the calculated HR of 0.30 (95% CI 0.11, 0.81) p=0.017 supports a statistically significant 70% reduction in the risk of death in the DA + chemotherapy versus control arm. The commentary noted that the SCH 2024 cohort data were not designed for measuring comparative treatment efficacy and, as such, the estimated HR for death is highly uncertain. The inclusion of palliative therapy in the control arm, which accounted for three of the eight patients, likely biased survival in favour of the chemoimmunotherapy group and is unlikely to reflect an accurate difference in risk of death.

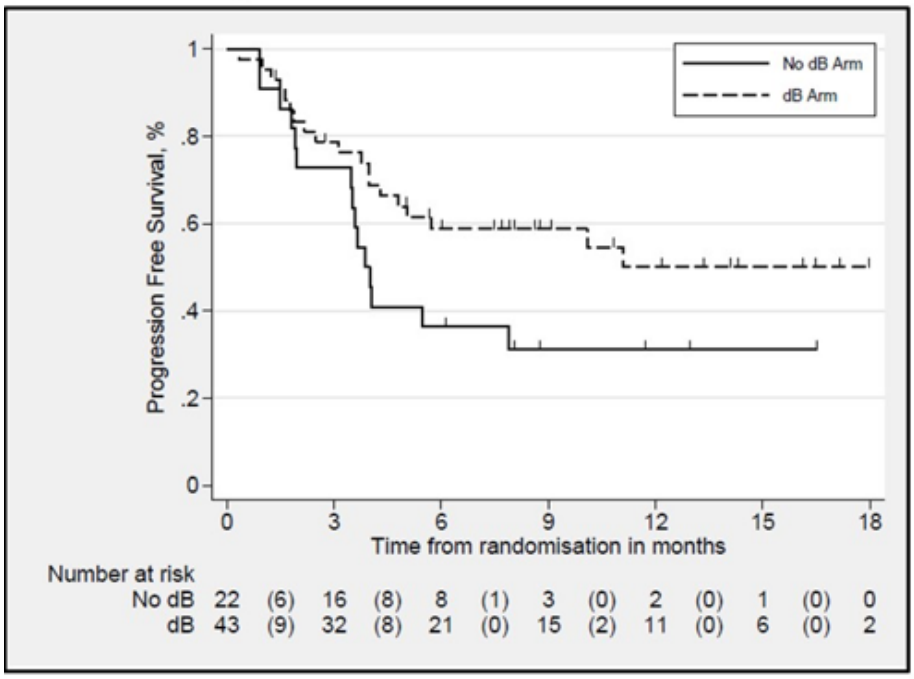
Progression-free survival (PFS)

The KM curve for PFS reported in the BEACON-Immuno trial is presented in Figure 2.

The PFS data should be considered in context of the 2:1 randomisation ratio, which can result in the smaller control group being more sensitive to individual variability, and therefore reduced reliability of results. PFS is additionally a composite outcome, which includes progression events which were not blinded and assessed locally and is therefore prone to bias.

An overall PFS comparison was provided for all the comparative and single-arm cohort studies reporting this outcome, based on median PFS (months) and the percent of patients with PFS at 1 year, as these were outcomes reported across some of the studies (see Table 5).

Figure 2 KM curve for PFS in BEACON-Immuno



Source: Figure 2-6, p53 of the ADAR

Table 5 Results for PFS reported in the trials and studies

Study ID	Dinutuximab+chemo		Control		Dinutuximab+chemo		Control	
	N	Median PFS (95% CI), months	N	Median PFS (95% CI), months	N	1-Year PFS (95% CI), % patients	N	1-Year PFS (95% CI), % patients
BEACON-Immuno	43	11.1	22	4.2	43	57	22	27
ANBL 1221 RCT	18	23.3 (6.9, NC)	17	3.0 (1.6, 10.9)	18	77 (56, 97)	17	25 (0.4, 49)
ANBL 1221 ext	36	18.8 (9.8, 25.5)	-	-	36	NR	-	-
Lerman 2023	146	13.1 (9.8, 16.5)	-	-	146	51 (43, 60)	-	-
Wieczorek 2023	25	6.3 (range 0.2–37.0)	-		25	48	-	-
BEACON 1	-	-	80	5.3	-	-	80	38 (27, 49)
Bagatell 2011	-	-	55	3.7	-	-	55	NR
Di Giannatale 2014	-	-	38	10.3 (6.4, 17.8)	-	-	38	45 (30, 60)
DuBois 2018	-	-	32	2.3	-	-	32	NR

Source: Table 2-15, p57 of the ADAR
chemo = chemotherapy; CI = confidence interval; N = number of total patients; NC = not calculable; NR = not reported; PFS = progression-free survival

Clinical claim

The ADAR claimed the use of DB + chemotherapy results in superior effectiveness compared with the comparator chemotherapy. Chemotherapy in both arms comprised the standard of care regimens TOTEM or TEMIRI. The claim is based on the key outcomes ORR, OS and PFS.

The use of DB + chemotherapy results in inferior (may be preventable and manageable) safety compared with the comparator chemotherapy.

Overall, the commentary considered that the key uncertainties with the comparative clinical evidence presented by the ADAR were:

- Open-label, exploratory randomised trials with small sample sizes provide an uncertain and unreliable basis for comparative survival data, with the primary outcome, ORR, being at greater risk of assessment bias. In addition, the BEACON-Immuno CSR or full publication was not available for verification.
- The most patient-relevant outcome of OS from BEACON-Immuno was not able to be reliably interpreted due to extensive cross-over of more than half of the control arm.
- The ADAR relied on DB and DA having interchangeable clinical efficacy, although they are not considered biosimilars. While the antibodies have similar specificity for GD2, they should be considered as distinct agents that potentially have different pharmacokinetics, efficacy and safety.
- Patient characteristics, including important prognostic variables such as relapsed versus refractory disease and *MYCN* oncogene amplification, varied significantly between studies, and between Australian cohort data and studies. The Australian cohort data by Padhye 2024 were also not provided and therefore could not be verified for validity. Overall, it is uncertain how generalisable the results of BEACON-Immuno and ANBL 1221 are to Australian patients with RRHRNBL.

However, the uncertainty surrounding the presented clinical evidence must also be balanced with consideration of equity of access issues, with patients currently reliant on clinical trials or compassionate access.

13. Economic evaluation

The ADAR presented cost-effectiveness and cost-utility analyses estimating the incremental cost per life-year (LY) gained and per quality-adjusted life year (QALY) gained, respectively. The ADAR argued that because of the conceptual and practical difficulties associated with Health-related Quality of Life (HRQoL) assessments in children and young people that MSAC consider the cost per LY gained as an important performance measure. However, the commentary considered that LYs are not a substitute for QALYs, which is a universally accepted outcome informing HTA decision making.

The modelled economic evaluation was a partitioned survival model (PSM). The commentary considered there were structural problems with the model (as discussed below) that related to the choice of clinical evidence used and how the evidence was combined/transformed and subsequently used in the model which cast significant doubt on the validity of the incremental cost-effectiveness ratio (ICER) estimates generated by the model.

Table 6 Summary of the economic evaluation

Component	Description
Perspective	Australian health care system
Population	Relapsed and Refractory High Risk Neuroblastoma (RRHRNBL)
Prior testing	Test(s) to confirm the diagnosis of RRHRNBL
Comparator	Chemotherapy + BSC
Type(s) of analysis	Cost-effectiveness analysis, Cost-utility analysis
Outcomes	Progression free survival, overall survival, Life Years and QALYs gained.
Time horizon	20 years in the model base case
Computational method	Partitioned Survival Model (PSM)
Generation of the base case	Modelled economic evaluation
Health states	Stable disease (Progression Free Survival), failure state (Progressed disease) and Death.
HRQoL	Health state utility is based on HUI2 and HUI3 values from Portwine et al 2016 and Barr et al 1999 (as presented in the 2020 PBAC/MSAC submission).
Cycle length	28 days (reflective of the background chemotherapy cycles).
Transition probabilities	Transitions in the model are based on KM data (from various data sources) and extrapolated parametric functions. In scenarios where OS is not available, it is derived from PFS data and vice versa.
Costs	Estimated costs for treatment, administration, concomitant medications, monitoring, ongoing health state costs and the cost of death.
Discount rate	5% for both costs and outcomes
Software	Microsoft Excel

BSC=best supportive care; HRQoL= health-related quality of life; HUI = health utility index; KM = Kaplan-Meier; OS = overall survival; PFS = progression-free survival

There was paucity of clinical evidence for the comparative effectiveness and safety of DB + chemotherapy and the nominated comparator of TEMIRI or TOTEM. The ADAR acknowledged the lack of comparative data making it necessary "to either interpolate PFS from OS (or OS from PFS, depending on the data source), or alternatively to combine different sources of PFS and OS data". The ADAR described that OS data from the BEACON-Immuno trial are impacted by early crossover from the control arm to DB (allowed after 2 cycles of treatment), and 12 patients out of 22 in the control arm crossed over. The ADAR also stated that 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 versus non-crossover control patients.

To compensate for the paucity of comparative clinical evidence supporting the superiority claim of DB + chemotherapy, the ADAR complemented data from the key BEACON-Immuno trial with data from two comparative studies of DA + chemotherapy (ANBL 1221 and SCH 2024) and from observational cohorts. The rationale for selecting one study or the other to parameterise PFS or OS curves in either the DB/DA + chemotherapy arm or the comparator arm was not clearly explained; however, it seems to have been driven by statistical considerations (statistical significance of HR) rather than clinical, biological or data quality considerations. All ICER estimates in the ADAR were derived from numerous variations of the same PSM, by choosing a data source and the best-fitting parametric distribution via an Excel toggle option.

The ADAR presented two modelling methods:

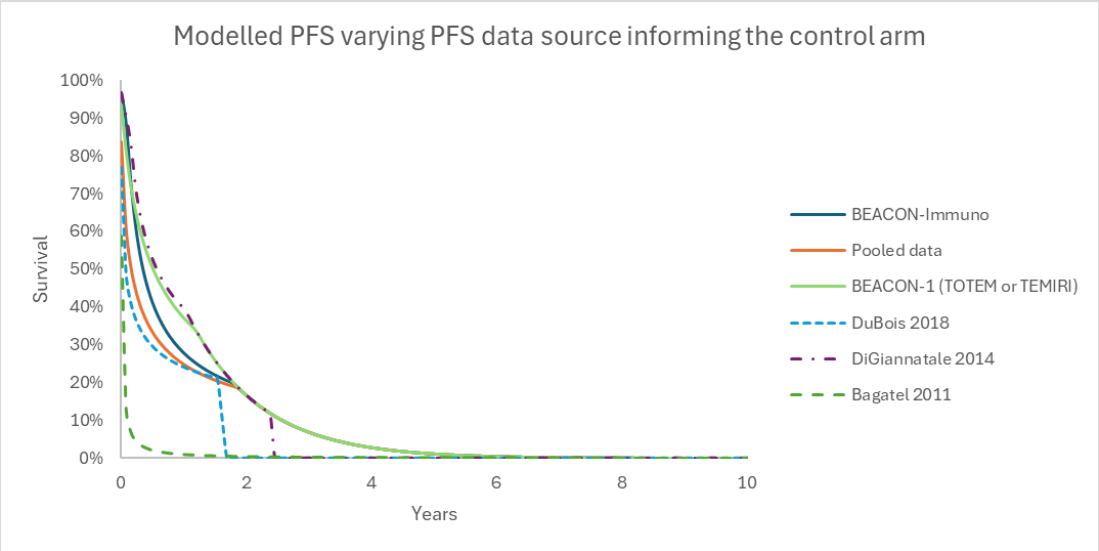
1. Aggregating digitalised individual patient observations across the selected studies to inform PFS and OS in both arms of the model.
2. Interpolating missing OS from PFS (or PFS from OS).

Method 1: combining different data sources to estimate PFS and OS.

The evidence that the ADAR considered relevant for the PSM consists of:

- BEACON-Immuno phase II RCT (Gray 2022, N=65); used to estimate parameters of PFS curves in both the intervention (N=43) and the comparator arms (N=22).
- Wieczorek (2023, N=25); used for PFS in the DB arm either on its own or in combination with BEACON-Immuno as in the base case.
- PFS in the comparator arm was informed by the entire dataset from the studies that used chemotherapy regimens, whether consisting solely of TOTEM and TEMIRI, as in the BEACON-Immuno comparator arm, or in combination with different drugs. In the base case, pooled PFS data from six studies were used: comparator arms from the ANBL 1221 (Mody 2017, N=18) and BEACON-Immuno (N=22); TOTEM and TEMIRI arms from BEACON-1 (Moreno 2024, N=80), and the single-arm studies by Bagatell (2011, N=55), Di Giannatale (2014, N=38) and DuBois (2018, N=32). In alternative versions of the model, each of these studies could be used on its own to inform PFS in the comparator arm. Figure 3 presents the modelled KM curves for PFS for the comparator arm across the various studies. The commentary considered that pooling these data in the base case analysis calls into question the study selection criteria (see heterogeneity concerns below) and challenges the validity of the parameter estimates used to model PFS based on these sources.

Figure 3 Modelled PFS in the control arm varying the data source informing PFS in the control arm.



Source: constructed during the evaluation

- The OS curves in both arms were informed by mortality data from the SCH Cohort 2024 (N=20). The data consisted of the intervention group of 12 patients who received chemoimmunotherapy (DA + chemotherapy) while the OS data in the comparator group of eight patients were collected retrospectively, with five (63%) patients from this group receiving chemotherapy and the rest receiving an alternative regimen without chemotherapy.

The following problems were identified in the commentary regarding the collection and aggregation of the data used to model patients' progression through the health states and calculate ICER estimates:

- The potential sources of heterogeneity relate to the differences in the administered therapies (drugs, doses, number of treatment cycles), characteristics of the populations at baseline (e.g. proportion of refractory to relapsed patients), duration of follow up, etc. The apparent heterogeneity in the clinical outcomes (ORR) in the dinutuximab trials was evident from values of I^2 statistics in the meta-analyses (e.g. Table 3). Although acknowledged, the heterogeneity was not accounted for when aggregating the data from individual studies. Instead, the ADAR claimed that it may promote a better representation of the natural variability of the RRHRNBL population. For example, by combining results of the relatively poorer prognostic patients in BEACON-Immuno with the results of the somewhat better prognostic group in ANLB 1221, the results become more generalisable.
- Breaking of randomisation outcomes has occurred in the base case analysis and in all other calculations, whenever PFS data for the chemotherapy arm were obtained from single-arm studies rather than from the BEACON-Immuno trial.
- Within the same arm of the model there is a disconnect between the data sources for the PFS and OS outcomes. PFS was estimated from digitalised individual patient data in one (or a set) of trials, and OS was estimated from the entirely different dataset, (the DA study in the SCH Cohort). Among other concerns, it implies that DB and DA are biologically and clinically equivalent. This assumption should hold for both modelling approaches, otherwise pooling the evidence in a single model is not justified. The ADAR raised the question of the similarity of DA and DB in clinical practice, claiming that though not "bio-similar", they could be considered ostensibly similar at a population level but not at an individual patient level.

The commentary considered the modelled outcomes may not be accepted as reliable since the fundamental rule of any probabilistic analysis, namely that a sum of probabilities in the mutually exclusive and exhaustive health states of PFS, progressed disease and death should equal one, is violated in every version of the model in both the intervention and the comparator arm. This occurs as the PFS observations are sourced from one trial (or from a combination of studies) and the OS observations are sourced from another (the SCH cohort).

The impact on the ICER using data from different studies to inform PFS and OS for DB + chemotherapy and for chemotherapy alone are presented in Table 10.

In the base case, the ADAR selected the following parametric distributions to model PFS and OS based on the best fitting Akaike Information Criterion (AIC).

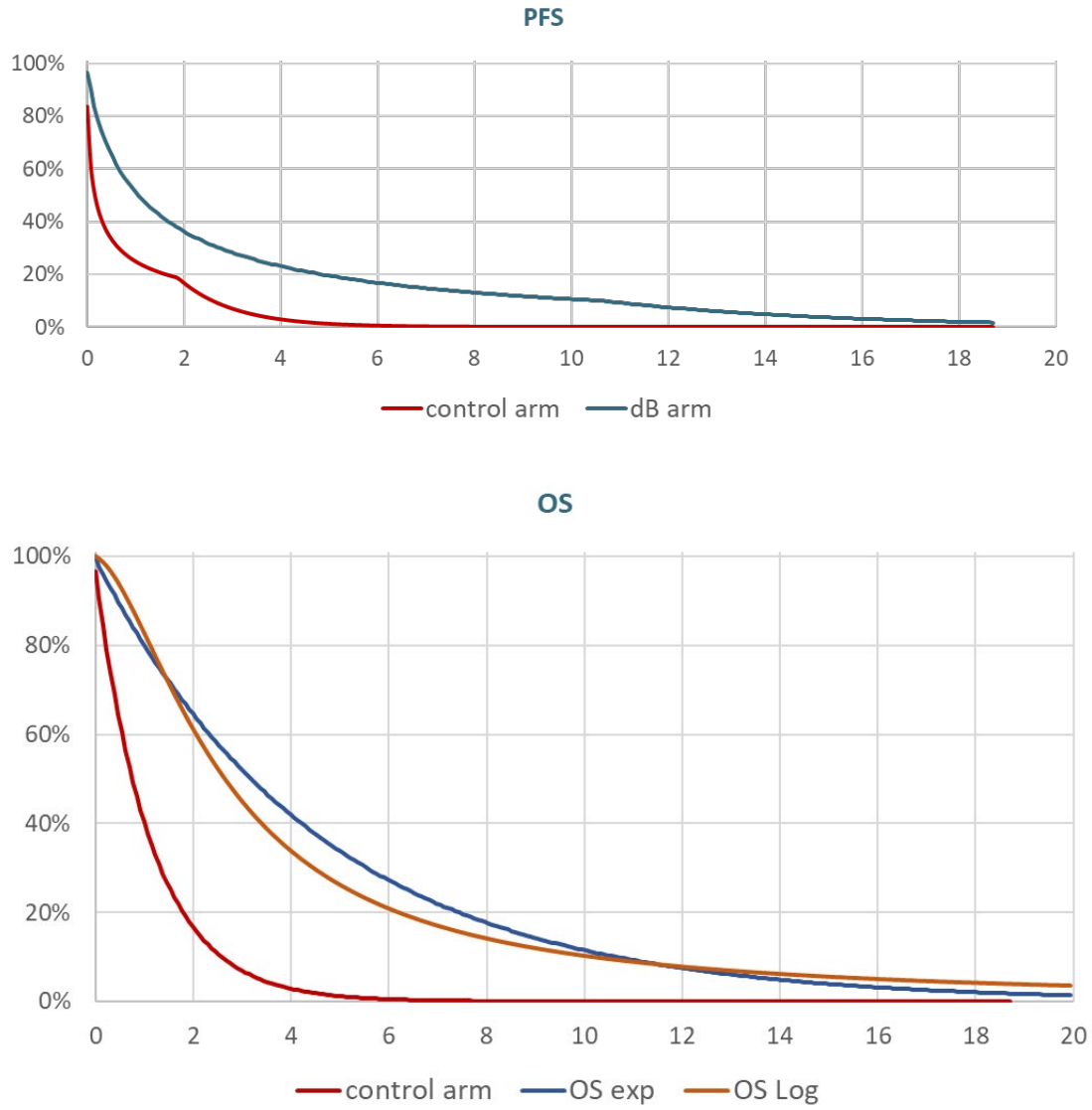
- PFS in DB arm: log normal function
- PFS in control arm: generalised gamma function
- OS in both arms: exponential function

In each case, the same parametric function was used for interpolations (of the extracted KM trial data) and for extrapolation over the 20-year time horizon, i.e. PFS and OS were incorporated into the model by using full parametric approximation. Other choices of a parametric distribution included Weibull (AFT), Gompertz and log logistic. The AIC criteria for each of the parametric functions were recalculated whenever an alternative data source for either PFS or OS in the intervention and/or comparator arm was made.

A further issue with the application of disparate sources of data for PFS and OS outcomes provides a good illustration of the structural problem with the model (which goes deeper than this particular example and affects every cycle in every arm of the model). In the base case analysis,

the probability of PFS exceeded the probability of OS in the control arm starting from cycle 25 (about two years in the 20 year time horizon). To correct for such an implausibility, the modelled PFS progression was arithmetically controlled in each cycle by setting the PFS value equal to the OS value if PFS>OS and this explains the 'kink' in PFS curves observed in the base case (Figure 4 below), indicating that starting from this point in time, the proportion of patients in the comparator arm (equal to the difference in proportions between OS and PFS) began experiencing a rate of disease progression above the probability determined by the fitted parametric function. In cycle 25 (second year), this proportion is 2% but quickly accelerated, reaching 78% by the fourth year. This biased the outcomes in favour of DB; however, even without this additional bias, the ICERs remain unreliable due to the violation of the basic principle of the probabilistic analysis, as explained above. The same phenomenon was observed in other versions of the model when the PFS in the control arm was modelled from individual chemotherapy studies.

Figure 4 Fitted PFS and OS curves in the base case analysis



Source: Worksheet 'Results' corresponding to the base-case analysis with exponential and log-logistic OS curves

In the base case, the modelled OS in the DB arm was ~40% at four years, which is inconsistent with the Australian SCH data that reported OS of 30% at four years. The discrepancy was

lessened when the OS extrapolation was fitted with a loglogistic instead of an exponential function as in the base case (Figure 4). The loglogistic distribution corresponded to ~30% at 4-years, increasing the ICER by 28.5%.

Method 2: Exploring the PFS-OS relationship to derive the missing OS from PFS

The ADAR presented a second method of informing the anticipated OS gains available from DB by inferring these from the PFS clinical data. This approach "involves exploiting the inherent relationship between PFS and OS and using data from one trial (from which the PFS-OS relationship can be derived) and applying the derived HR to either OS data to derive a matched PFS KM curve, or from PFS data to derive a matched OS KM curve". That is, the application of a HR to either OS or PFS data to estimate a matched KM curve, or more precisely, its parametric approximation. Therefore, the task is essentially reduced to identifying the type of parametric distribution and its parameters to approximate the missing parametric OS curves for the intervention and comparator arms. The commentary was not aware of a precedent of this method for filling gaps in the evidence. Apparently, it had an element of indirect comparison of the survival outcomes from two different studies (a few pairs of studies were explored in the ADAR) together with the stated intention of translating an interim outcome (PFS) to the final outcome (OS). In this case, it was not clear how the reverse transformation of OS into PFS can be justified on the same grounds. The ADAR admitted that "the choice of method and relevant data source is somewhat subjective because it involves hierarchical ranking of the assumptions and data used". The meaning of "hierarchical ranking" and how it was factored into the mathematical algorithm for deriving OS or PFS parametric functions was not made clear.

The first step involved estimating hazards from the KM plots of the individual patient data (separately for PFS and OS) that were reported in ANBL 1221, the meta-analysis by Moreno (2017), and BEACON-1 (Moreno 2024, all arms). Secondly, for each study, and for each arm of ANBL 1221, the HRs comparing OS with PFS (or the other way around) were calculated using a simple Cox regression. Finally, the ADAR applied "the derived HR to either OS data to derive a matched PFS KM curve, or from PFS data to derive a matched OS KM curve". Normally, the HR is a measure of clinical effectiveness of the intervention versus a comparator. The commentary was not aware of any precedence of employing a HR derived from two survival functions (OS and PFS) from the same arm of one trial to estimate parameters of the survival functions in a different trial.

One particular study – BEACON-1 (Moreno 2024, all arms) - was selected as the source for OS coefficients (with covariances) that were then combined with parametric survival models for PFS to obtain full OS models. The ICER estimates based on BEACON-1 (all arms) are presented in Table 11. The data sources and extrapolations informing PFS was the same as in the Method 1.

Every study used to inform the OS extrapolation has a limited applicability to the RRHRNBL population since the subgroups of patients treated with the relevant intervention (DB) or comparator chemotherapy regimens (TOTEM or TEMIRI) were relatively small in every data source. More specifically, the applicability of BEACON-1 (N=160) data aggregated across all arms of the trial to the research question of comparative effectiveness of DB vs chemotherapy is questionable. BEACON-1 used 3x2 factorial design to allocate patients to temozolomide, TEMIRI, or TOTEM with or without bevacizumab. Concerns about selecting and mixing the data from various trials, including trials of medications other than DB/DA and the nominated comparators, TEMIRI and TOTEM, are presented above. There is no clinical justification for selecting the BEACON-1 trial other than its large sample size of 160 patients because the evidence relates to some arms involving bevacizumab while no chemoimmunotherapy (DB or DA) therapy regimen was featured in any arm of the trial, making it irrelevant to the purpose of the ADAR.

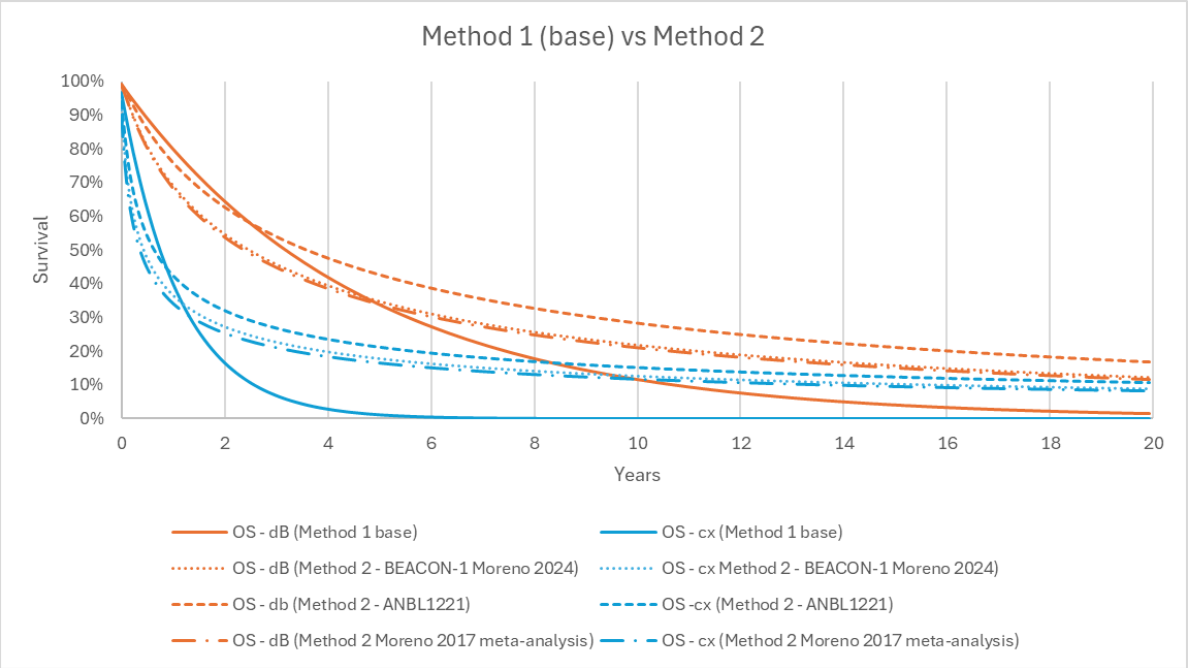
However, there were statistical considerations in favour of the BEACON-1 trial. The ADAR reasonably suggested that in relation to the BEACON-1 RCT, the assumption of proportionality of hazards in Cox regression should be confirmed, without which the parameter estimates that the ADAR employed to extrapolate OS (or PFS) in the "matched" study are unreliable. The HR of OS vs PFS in BEACON-1 trial was 0.67 with the p-value of 0.002 indicating that the rates of disease progression and mortality in patients receiving chemotherapy with or without bevacizumab are statistically different and constant over time. However, this conclusion is not consistent with graphical representation of the survival function versus the survival time and the graph of the log(-log(survival)) versus log of survival time. If hazard is proportional, the curves should be roughly parallel, but they seem to intersect at around the 2200 day mark (~6 years of the 20 year time horizon). However, given the larger scale of more serious deficiencies in the modelled economic evaluation, these appear to be minor. Suspending for a moment the reservations about the previously untested method of obtaining the missing survival data (no reference to the literature was provided), the ANBL-1221 (DA) trial seems to be more appropriate to inform the missing parameters of KM curves extrapolating OS (PFS) in the model. However, it appears that neither ANBL-1221 nor the meta-analysis of three chemotherapy trials Moreno (2017) meet the proportionality of hazard assumption and its constancy over time.

Other implications of using Method 2 to derive the missing OS from PFS include:

- applying a single coefficient from a simple Cox regression assumes a static relationship between PFS and OS from the same arm of ANBL-1221 or a single-arm study and does not capture time-dependent covariates. The clinical and modelling significance of this is unclear; and
- since OS is dependent on the parametric function of PFS, it is possible that the selected function is not the most appropriate fit for modelling OS.

Figure 5 presents model traces corresponding to the alternative data sources used to inform the OS parametric curves under Method 2. The impact of the use of these estimates on the ICER are presented in Table 11.

Figure 5 Comparison of the OS benefit in the dB and control arms using Method 1 and Method 2 based on BEACON-1, ANBL 1221, and Moreno 2017 as the data sources



Source: constructed during the evaluation
Cx = control; dB = dinutuximab beta; OS = overall survival

Health care resources in the model are summarised in Table 7. A cost of DB of $**redacted** per 20 mg/4.5 mL vial administered at a dose of 10 mg/m^2/day for 7 days in each cycle to the maximum of six cycles was applied. The cost was converted into a mean cost of DB per 28-day cycle from usage data in 42 patients in BEACON-Immuno (one patient did not receive treatment). Adjustment for the observed rates of progression was also applied to each of the six cycles and ranged from 83% in cycle 2 to 50% in cycle 6 (for comparison, 67% remained pre-progressed in the DB arm at cycle 6 in the base case). The ADAR estimated an average usage of **redacted**mg equating to a mean of **redacted** vials per patient. Wastage was assumed to be negligible since DB can be stored for several days. Excluded were hospitalisation cost (AR-DRG I65A, $25,523), AE costs and the cost of chemotherapy (TOTEM and TEMIRI) under the unsupported assumption that these costs are the same in both arms and cancel out in the ICER calculation. The ADAR included "arbitrary" health state-specific costs that applied to each model cycle depending on the health state: $500 in PFS, and $1,500 in OS. The nature of these costs was not described. Similarly, no justification was offered for the one-time costs "per event" including the cost at the start of the treatment (cycle 0) and when transitioning to "progressed" state of disease. The terminal-care cost was based on $28,091 cost of the last 6 months of life of Australian patients with cancer (Reeve, 2017[18]) in 2009/10, which was inflated to 2024 prices using the Australian Bureau of Statistics Health Price Index.

[18] Reeve R. et al. (2017). Health care use and costs at the end of life: a comparison of elderly Australian decedents with and without a cancer history. *BMC Palliative Care* 17(1): 1.

Table 7 Costs included in the model

Cost component	Timing/frequency	Value	Comments
DB (Qarziba)	Each cycle unless progressed	$**redacted**	per 20 mg/4.5 mL vial
Cost of adjunctive treatment	Each cycle unless progressed	$259.49	per 28-day cycle
Monitoring cost (tests)	Not reported	$205.95	per 28-day cycle
Cost by state (both arms)	Before progression (PFS)	$500.00	per 28-day cycle
	After progression	$1,500.00	per 28-day cycle
One-time cost (both arms)	Cycle 0	$25,523.00	per event
	New progression	$25,523.00	per event
	New death	$52,218.00	per event

Table 8 presents the disaggregated and incremental costs demonstrating that the largest cost component is the cost of DB treatment. There are also some incremental savings most likely explained by the structural deficiency in the model that biased the outcomes in favour of DB.

Table 8 Disaggregated Modelled Base Case Costs

	DB arm	Control arm	Incremental	% of incremental
Cost of DB treatment	$**redacted**	$0	$**redacted**	**redacted**%
DB-associated cost	$1,357	$0	$1,357	**redacted**%
PFS state cost	$16,442	$4,956	$11,487	**redacted**%
After-progression state cost	$24,478	$6,231	$18,248	**redacted**%
Death & progression onset costs	$89,491	$93,946	-$4,455	**redacted**%
Total cost	**$redacted**	**$105,133**	**$redacted**	**100%**

Utilities for the pre-progressed and progressed disease health states were identical to the utilities in MSAC 1625. The DB "maintenance" MSAC 1625 ADAR estimated the paediatric population norms based on EQ-5D-5L adult population norms reported in the literature (McCaffrey 2016)[19] and then applied a utility decrement for the stable disease state (-7.3%) and failure state (-41.7%) based on HUI2 and HUI3 values from Portwine (2016)[20] and Barr (1999[21]). The ADAR stated that it uses the same literature sources, however it could not be verified whether the same algorithm for estimating health state utilities was used in this ADAR and whether the reported values of 0.89 (pre-progression) and 0.56 (progressed disease) are the same as in the MSAC 1625 ADAR. Subject to this reservation, application of utilities was considered reasonable by the commentary. No cost or utility decrement associated with AEs were included.

Table 9 presents base case results as reported in the ADAR using Method 1. ICER in relation to the LY outcome was included for the sake of completeness; the problems with the modelled

[19] McCaffrey, N. et al. (2016). Health-related quality of life measured using the EQ-5D-5L: South Australian population norms. *Health Qual Life Outcomes* 14(1):133.

[20] Portwine, C. et al. (2016). Health-Related Quality of Life in Survivors of High-Risk Neuroblastoma After Stem Cell Transplant: A National Population-Based Perspective. *Pediatric Blood Cancer* 63(9): 1615-1621.

[21] Barr, R. D. et al. (1999). Health-related quality of life in survivors of tumours of the central nervous system in childhood - a preference-based approach to measurement in a cross-sectional study. *Eur J Cancer* 35(2): 248-255.

economic evaluation outlined above equally apply to the incremental cost per LY gained. Both ICER estimates should be interpreted with caution.

Table 9 Base Case results for the RRHRNBL population (using Method 1)

Therapies	Total			Incremental			ICER (discounted)	
	Cost	LYs	QALYs	Cost	LYs	QALYs	Cost per LYG	($/QALY)
Control	$105,133	1.08	redacted	$redacted	2.69	redacted	$redacted	$redacted
DB	$redacted	3.77	redacted					

LY = life year; QALY = quality adjusted life year

Serious structural, conceptual and evidence-related deficiencies in the modelled economic evaluation were outlined above. The biggest challenge of the ADAR was the absence of a data source to inform disease progression and mortality from a single comparative study. The commentary noted that the ADAR also argued that the result of a sensitivity analysis assuming a zero discount rate bringing the ICER down to $redacted was more appropriate for a young patient cohort. However, the commentary considered that as a plausible ICER could not be estimated, there is no value in conducting sensitivity analyses of the outcomes of a model that lacks face validity

Instead, a set of scenario analyses were undertaken to demonstrate the variability of the [unreliable] modelled outcomes to the choice of the sources of clinical evidence and assumptions about the best fitted parametric functions. Table 10 presents results of the model based on Method 1 and various data sources. Of particular note, there is considerable sensitivity of ICER estimates to the choice of parametric distribution to model the PFS populated from the DB study by Wieczorek (2023). This became even more pronounced in the Method 2 modelling approach (see Table 12). A version of the model solely based on the data from the BEACON-Immuno trial was not presented in the ADAR even for illustrative purposes and under a conservative assumption of the control group crossing over to DB, benefitting the comparator.

The results in Table 10 indicate that using only the BEACON-Immuno observations for the PFS analysis in both arms (Scenario 2), increased ICER from $redacted in the base case to $redacted, indicating the importance of the Wieczorek (2023) data for keeping ICER under a $redacted threshold (Scenario 3). The ADAR claimed a similarity between the BEACON-Immuno and Wieczorek (2023) studies, so in Scenario 5, where the DB arm was modelled solely from Wieczorek (2023), the ICER slightly decreased from $redacted to $redacted. However, in this scenario, the ICER was sensitive to the choice of a parametric function (next best fitted parametric function produced ICER of $redacted, a redacted% increase). In a set of analyses from Scenario 6, the PFS data for the DB arm was from the BEACON-Immuno trial, while the chemotherapy arm were populated with each of the individual studies in turn instead of using the entire combination of these studies as in the base case. After fitting the best parametric distribution (by the AIC criterion, if available, otherwise as in the base case), the corresponding ICER estimates ranged from $redacted (Bagatell, 2011) to $redacted (BEACON-1, TEMIRI or TOTEM data).

Table 10 Data sources used in Method 1: combining different sources of PFS and OS data

Scenario	PFS/OS	Intervention arm (drug dB or dA; N)	Comparator arm (chemotherapy)	ICER per QALY gained*
1. Based only on BEACON-Immuno data for both PFS and OS analyses (hypothetical)	PFS	BEACON-Immuno (DB; N=43)	BEACON-Immuno (TOTEM or TIMIRI; N=22)	Not reported Without the primary individual patient data, the ICER could not be estimated
	OS	BEACON-Immuno (DB; N=43)	BEACON-Immuno (TOTEM or TIMIRI; N=22)[1]	
2. Based on BEACON-Immuno data for PFS and on SCH (2024) data for OS	PFS	BEACON-Immuno (DB; N=43)	BEACON-Immuno (TOTEM or TIMIRI; N=22)	$**redacted**
	OS	Australian SCH Cohort (DA; N=12)	Australian SCH Cohort (Chemotherapy/palliation; N=8)	
3. Adding the Wieczorek (2023) data to BEACON-Immuno for PFS	PFS	BEACON-Immuno (DB; N=43) + Wieczorek (DB; N=25)	BEACON-Immuno (TOTEM or TIMIRI; N=22)	$**redacted**
	OS	Australian SCH Cohort (DA; N=12)	Australian SCH Cohort (Chemotherapy/palliation; N=8)	
4. **Base case**	PFS	BEACON-Immuno (DB; N=43) + Wieczorek (DB; N=25)	BEACON-Immuno (TOTEM or TIMIRI; N=22) + 1 comparator arm (ANBL 1221, N=18)[2] and 4 single arm studies[3] (chemotherapy; N=223)	**$redacted**
	OS	Australian SCH Cohort (DA; N=12)	Australian SCH Cohort (Chemotherapy/palliation; N=8)	
5. For completeness, Wieczorek (2023) DB data rather than BEACON-Immuno (N=43) was used for PFS analysis	PFS	Wieczorek (DB; N=25)	BEACON-Immuno (TOTEM or TIMIRI; N=22)	$**redacted** (AIC=23.2% - lognormal distribution for PFS in the dB arm from Wieczorek, 2023)
	OS	Australian SCH Cohort (DA; N=12)	Australian SCH Cohort (Chemotherapy/palliation; N=8)	$**redacted (**AIC=23.1% - exponential distribution in the dB arm from Wieczorek, 2023)
6. Five alternative analyses, where PFS in the control arm was informed by a single study from the collection of 6 studies in the base case	PFS	BEACON-Immuno (DB; N=43)	1.BEACON-1 (TOTEM and TEMIRI N=80) 2. ANBL 1221 (N=18) 3.Bagatell (N=52) 4.DuBois (N=32) 5.Di Giannatale (N=38)	$**redacted** $**redacted** $**redacted** $**redacted**[4] $**redacted**[4]
	OS	Australian SCH Cohort (DA; N=12)	Australian SCH Cohort (Chemotherapy/palliation; N=8)	

[1] 12 patients out of 22 in the chemotherapy arm crossed over to receive DB at progression.
[2] In ANBL 1221 the comparator arm was TEMIRI + temsirolimus
[3] In DuBois (2018) the comparator arm was TEMIRI + alisertib; the proportion in PFS were set to 0% from the 21st cycle
[4] Gen gamma distribution is left as a in the base case analysis, in the absence of AIC value for the best fit parametric function
* *Note*: Unless stated otherwise, a parametric function with the best fit was used (according to the AIC value if available, otherwise – as in the base case); other assumptions of the base case analysis (time horizon, cycle length, annual discount rate, utility values and DB price per 20 mg vial) also applied.

Table 11 provides results of the model utilising Method 2 and various data sources.

Table 11 Scenario analyses using Method 2 to model OS

	Inc cost	Inc LYG	Inc QALY	ICER ($/QALY)	% change
Base case Method 1 PFS in DB arm BEACON-Immuno + Wieczorek (2024) PFS in the comparator arm – 6 different data sources	**$redacted**	**2.69**	**2.09**	**$redacted**	**-**
OS extrapolation informed by PFS - Method 2 (PFS as in base case from Method 1)					
Method 2: BEACON-1 Moreno 2024, all arms	$**redacted**	1.83	1.37	$**redacted**	52.0%
Method 2: ANBL 1221, both arms	$**redacted**	2.28	1.61	$**redacted**	32.6%
Method 2: Moreno 2017 meta-analysis	$**redacted**	1.93	1.42	$**redacted**	48.0%

Generally, Method 2 led to more favourable survival estimates in the DB and control arms as observed by the upward shift in survival curves. As the increase in survival using Method 2 was more prominent in the control arm compared to the DB arm, there is a greater narrowing in the OS benefit under Method 2 compared with Method 1 (Figure 5). This is observed in the reduction in incremental LYG compared to the base case. Interpolating OS parametric functions using BEACON-1 (all arms) led to the most conservative ICER (+52%), followed by Moreno 2017[22] meta-analysis (+48%) and ANBL 1221 (+32.6%).

Table 12 presents additional scenario analyses corresponding to Method 2, that were not included in the ADAR. An error in the VBA code was identified in the formulae that modelled PFS and OS with a half-cycle correction, thus the ICER values are reported with and without a half-cycle correction. The BEACON-Immuno RCT was selected for both the intervention and comparator arm to prevent randomisation breakdown. This data source was combined with OS parametric functions from each of the three options included in Method 2. The ICER varied from $redacted to $redacted, an increase from the base case value of 155% and 216% respectively.

[22] Moreno, L. et al. (2017). Outcome of children with relapsed or refractory neuroblastoma: A meta-analysis of ITCC/SIOPEN European phase II clinical trials. *Pediatric Blood & Cancer* 64(1): 25-31.

Table 12 Additional scenario analyses corresponding to Method 2

Scenario name	PFS - DB	PFS - Control	OS	Incr. PFS (mean, years)	Incr. OS (mean, years)	QALY gained (discounted)	ICER
Base-case analysis	**All studies** BEACON-Immuno & Wieczorek 2023	**All studies** (2 control arms+ 4 single arm studies)	SCH 2024	**2.31**	**3.44**	**2.09**	**$redacted** ($**redacted**)*
Scenario 1 (AIC =N/A)	Derive PFS from OS (BEACON-1 Moreno 2024)	Derive PFS from OS (BEACON-1 Moreno 2024)	SCH 2024	2.28	3.44	2.14	$**redacted** ($**redacted**)*
Scenario 2	BEACON-Immuno	BEACON-Immuno	Deriving OS from PFS (BEACON-1 Moreno 2024)	0.31	1.06	0.61	$**redacted** ($**redacted**)*
Scenario 3	BEACON-Immuno	BEACON-Immuno	Deriving OS from PFS (Moreno 2017)	0.31	1.25	0.69	$**redacted** ($**redacted**)*
Scenario 4	BEACON-Immuno	BEACON-Immuno	Deriving OS from PFS (ANBL 1221 both arms)	0.31	1.56	0.77	$**redacted** ($**redacted**)*
Scenario 5	Wieczorek 2023 (lognormal; AIC=23.2%)	BEACON-Immuno	Deriving OS from PFS (ANBL 1221 both arms)	1.55 years	3.09 years	1.57	$**redacted** ($**redacted**)*
Scenario 6	Wieczorek 2023 (exponential; AIC=23.1%)	BEACON-Immuno	Deriving OS from PFS (ANBL 1221 both arms)	-0.51	-0.34	0.02	$**redacted** ($**redacted**)*
Scenario 7	Wieczorek 2023 (lognormal; AIC=23.2%)	BEACON-Immuno	Deriving OS from PFS (BEACON-1 Moreno 2024)	1.54	2.56	1.41	$**redacted** ($**redacted**)*
Scenario 8	Wieczorek 2023 (exponential; AIC=23.1%) The same as PFS distribution G45	BEACON-Immuno	Deriving OS from PFS (BEACON-1 Moreno 2024)	-0.51	-0.99	-0.27	DB is dominated

*Replication of the ICER value without a half-cycle correction

As was noted above, in Method 1 (Table 10), two different parametric distributions used to extrapolate PFS in the intervention arm with the data from Wieczorek (2023) produced significantly different ICERs. This effect is much more pronounced in Method 2. Depending on whether the exponential or lognormal parametric distribution was selected to extrapolate PFS in the DB arm, the ICER changed from $redacted to $redacted (when informed by ANBL 1221). When BEACON-1 (Moreno 2024, all arms) was selected to inform the PFS in both arms, the lognormal distribution in Wieczorek (2023) corresponded to an ICER of $redacted, while the exponential distribution resulted in the comparator dominating DB. In both cases AIC criteria of 23.2% suggested lognormal distribution was best fitting but differed very little from the AIC criteria of 23.1% for exponential distribution. This suggests the algorithm for interpolating PFS in one study from OS in an unrelated study can produce dramatically unstable outcomes.

14. Financial/budgetary impacts

The ADAR estimated the use and cost of DB as follows:

- conducting a survey of current Australian clinical centres treating patients with HRNBL and enquiring about how many patients have presented with RRHRNBL over the last two years. Responses suggested a total of **redacted** patients across all eight treatment centres in Australia, so the ADAR assumed **redacted** patients per year;
- assuming an initial uptake rate of **redacted**% in Year 1, increasing to **redacted**%, **redacted**%, **redacted**%, **redacted**% and **redacted%** in Years 2, 3, 4, 5 and 6, respectively. The ADAR anticipates an initial uptake rate of **redacted**% in the first year reflecting the expectation that some centres currently have access to DA at no cost (with the exception of two centres);
- assuming **redacted** vials of DB per patient. This differs to the assumed **redacted** vials in the economic evaluation and was tested in a sensitivity analysis, see below;
- a 20mg vial of DB costs $**redacted**; and
- assuming no change to chemotherapy use (as DB is intended to be used in combination with chemotherapy).

The financial implications to the NHRA HST program resulting from the proposed listing of DB are summarised in Table 13.

Table 13 Net financial implications of DB to the NHRA HST program

Parameter	Year 2025	Year 2026	Year 2027	Year 2028	Year 2029	Year 2030
Estimated use and cost of the proposed health technology						
Number of people eligible for DB	**redacted**	**redacted**	**redacted**	**redacted**	**redacted**	**redacted**
Number of people who receive DB	**redacted**	**redacted**	**redacted**	**redacted**	**redacted**	**redacted**
Number of services of DB (assume **redacted** vials per patient)	**redacted**	**redacted**	**redacted**	**redacted**	**redacted**	**redacted**
Cost to the NHRA HST program (with appropriate copayments excluded)	$**redacted**	$**redacted**	$**redacted**	$**redacted**	$**redacted**	$**redacted**
Change in use and cost of other health technologies						
Change in use of chemotherapy	N/A	N/A	N/A	N/A	N/A	N/A
Change in use of other affected health technologies	N/A	N/A	N/A	N/A	N/A	N/A
Net change in costs to the PBS (with appropriate copayments excluded)	$0	$0	$0	$0	$0	$0
Net financial impact to the NHRA HST program	$**redacted**	$**redacted**	$**redacted**	$**redacted**	$**redacted**	$**redacted**
Net financial impact to the NHRA HST program (assuming redacted vials per patient)	$**redacted**	$**redacted**	$**redacted**	$**redacted**	$**redacted**	$**redacted**

HST = Highly Specialised Therapies; N/A = not applicable; NHRA = National Health Reform Agreement, PBS = Pharmaceutical Benefits Scheme

The ADAR also noted that there is expected to be no increase in the current Government – Sponsor agreement to accommodate the use of DB for RRHRNBL for March 2025 to February 2026 as **redacted** vials were forecast for this period, whereas the ADAR estimates **redacted** vials for HRNBL and **redacted** vials for RRHRNBL over this time period (total of **redacted** vials).

15. Other relevant information

None.

16. Key issues from ESC to MSAC

Main issues for MSAC consideration

Clinical issues:

- The clinical trial evidence had a high risk of bias, but overall there was biological plausibility and a convincing signal of efficacy for dinutuximab beta (DB) in these patients.
- The applicant-developed assessment report (ADAR) assumed that DB and dinutuximab alpha (DA) are therapeutically equivalent but provided no evidence for this assumption. However, given that overseas regulatory agencies consider that there is no significant difference in safety or efficacy between DA and DB, ESC considered the assumption of therapeutic similarity may be acceptable.
- The dosing schedules in the key trials were different from one another and from the TGA-approved dosing schedule.

Economic issues:

- The economic model was impeded by very limited data, leading to highly uncertain results because the two alternative methodologies that were used to fill evidence gaps either led to significant errors in the partition survival model (the sum of proportions in each health state did not equal 100%) or involved an unvalidated method of using hazard ratios to derive one health outcome from another in the same treatment group.
- The selection of base-case specifications was not well justified. ESC considered that it may be more justifiable to use the BEACON Immuno study alone for progression-free survival (PFS) in the base case, with evidence from other studies included in sensitivity analyses. ESC also considered that the base-case time horizon of 20 years was too long and that a shorter time horizon was more clinically plausible.
- The costs of hospitalisation, managing adverse events, and chemotherapy were excluded from the economic model under the unsupported assumption that adverse events (and associated hospitalisation for these events) are driven by chemotherapy only and that all these costs cancel out in the ICER calculation. However given the clinical claim of inferior safety of DB compared with chemotherapy, there may be additional hospital costs for pain management in young children due to more adverse events in the intervention arm compared to the chemotherapy arm. Therefore ESC advised that it was appropriate to include the costs of hospitalisation (inclusive of the cost of managing adverse events) in the model.

Implementation issues

- Dinutuximab beta (DB) is already approved for funding as a highly specialised therapy for high-risk neuroblastoma in patients who have previously received induction chemotherapy and achieved at least a partial response (refer to MSAC application 1625). The proposed population for the current application is patients with high-risk neuroblastoma 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.
- TGA registration is required for eligibility as a highly specialised therapy (HST) under the National Health Reform Agreement (NHRA). The TGA registration for DB includes relapsed patients, but not all patients who are refractory: only refractory patients with a partial response to therapy are included.

ESC discussion

ESC noted that this application sought public funding for dinutuximab beta (DB) for primary relapsed and refractory high-risk neuroblastoma. As a high cost, highly specialised therapy (HST), DB would be delivered through public hospitals under the National Health Reform Agreement (NHRA) Addendum 2020–2025. ESC noted that this application had bypassed PASC on the advice of the MSAC Executive.

ESC noted that eligibility for HST funding is limited to Therapeutic Goods Administration (TGA)-approved indications and treatments that cost more than $200,000 per patient per year. The department advised that the HST criterion for cost includes treatment and ancillary costs.

ESC noted that the current TGA indication for DB is for 'high-risk neuroblastoma in patients who have previously received induction chemotherapy and achieved at least a partial response'. ESC considered that while this explicitly excludes patients with primary refractory neuroblastoma, it may include those patients with primary relapsed neuroblastoma. ESC noted advice from the department that the applicant previously advised they do not intend to apply to the TGA to amend the registered indication to include primary relapsed or refractory disease. ESC noted that, because eligibility for HST funding is limited to TGA-approved medicines and biologicals delivered in public hospitals, DB may not meet the HST criteria for the entirety of the proposed population. The department advised that it would further clarify the HST criteria before MSAC considers this application.

ESC noted and welcomed the consultation feedback received from 3 organisations, 7 individuals (including 3 parents or carers of a person with neuroblastoma) and 1 health professional. The feedback was supportive of funding DB as it would provide another option for a group with high clinical need, provide hope for families, and is already used as standard of care. Some feedback highlighted that access to DB is currently inequitable across different hospitals. ESC noted that it had received supportive consultation feedback from families whose children had died from neuroblastoma and acknowledged their willingness to provide input.

ESC noted and welcomed the consultation feedback from Queensland, New South Wales, Victoria and Western Australia. All submissions noted failure to meet the eligibility criteria for HST, notably the lack of TGA approval for the proposed indication. The submissions also raised concerns that there is potential to undermine the public perception of the TGA and confidence in the safety and efficacy of DB, if treatment of a population outside the TGA approved indication is supported. ESC noted that a number of the states also raised that, while dinutuximab alpha (DA), which is not TGA-registered, can be provided on compassionate grounds for treatment of the refractory population, it is only available at some but not all treatment centres, and therefore relying on DA alone would lead to inequity in access. Concerns were also raised regarding the longer-term availability of DA.

ESC noted that neuroblastoma is a rare sympathetic nervous system cancer that predominantly affects children under 4 years of age. Of the approximately 40–60 cases in Australia each year, around half of these are high-risk neuroblastoma (HRNBL). HRNBL has a 5-year event-free survival of 51%, and around one third of patients may be refractory to chemotherapy (around 10 patients per year).

ESC noted the proposed population is patients with 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.

The proposed intervention is DB, a monoclonal antibody targeting cell surface disialoganglioside 2 (GD2), administered in conjunction with chemotherapy. ESC noted that the proposed eligibility criteria state that patients must have high-risk neuroblastoma, AND primary

relapsed disease OR disease refractory to standard treatment. ESC queried whether the meaning of refractory in the criterion 'disease refractory to standard treatment' could be clarified to specify 'end induction' (in line with National Comprehensive Cancer Network [NCCN] guidelines, which state 'for patients with end-induction minor response or stable disease not proceeding to consolidation therapy') or 'disease refractory to frontline therapy'. ESC noted that in its pre-ESC response the applicant indicated its willingness to work with the Department to make the item descriptors more specific as needed.

ESC noted that the comparator is chemotherapy – either temozolomide + irinotecan (TEMIRI) or temozolomide + topotecan (TOTEM). ESC noted that, per the current clinical management algorithm without the use of DB, chemotherapy is used at each stage of disease if progression occurs. ESC noted that, in the proposed clinical management algorithm, DB would be used at any stage of disease in conjunction with chemotherapy, and that this is in line with international (NCCN) clinical guidelines for the proposed population. ESC considered the clinical management algorithms to be appropriate.

ESC noted the clinical evidence base in the application consisted of 11 studies, of which 4 were studies of DB (comprising one RCT and 3 single arm studies), 3 were studies of DA (comprising one RCT, one single arm and one cohort study) and 4 investigated use of chemotherapy alone (comprising one RCT and 3 single arm studies). ESC noted that the applicant-developed assessment report (ADAR) assumed that DB and DA are therapeutically equivalent, despite providing no evidence for this assumption. ESC noted that the applicant's pre-ESC response stated that other agencies consider that there is no significant difference in safety or efficacy between DA and DB. ESC acknowledged the pre-ESC response's argument that it may not be possible to ever provide directly comparative RCT evidence to investigate therapeutic equivalence between DA and DB given current treatment practices and the regulatory status of DB and DA internationally. ESC also noted the pre-ESC response's observation that trial design and conduct changes were ethically required in the two pivotal trials of DB because of the accepted clinical interchangeability of DB and DA. ESC therefore considered the assumption of therapeutic similarity may be acceptable.

ESC noted that the two pivotal randomised controlled trials (RCTs) included in the application were open-label Phase II trials with small numbers of participants, and did not provide specific comparative evidence on patients with refractory disease, and that for one of these trials (the BEACON Immuno trial) only the conference abstract and presentation were available. The BEACON Immuno trial had 55% cross-over (with outcomes not censored at cross-over) and an imbalance in previous use of anti-GD2 therapy. The ANBL trial had notable discontinuation in the control arm. ESC therefore considered both these trials to have a high risk of bias. ESC noted that the dosing schedule differed from the TGA-approved schedule and differed between studies, but acknowledged the applicant's comments in the pre-ESC response that dose per day was consistent across the studies (10 mg/m^2/day). ESC noted that the pooled risk difference in ORR was 31% after 6 cycles between the DB/DA + chemotherapy group compared to chemotherapy alone. ESC noted that, while the validity of this estimate was uncertain due to the high risk of bias, there was a suggestion of benefit. ESC also noted that the refractory group typically has a very poor prognosis, yet they comprised 4 out of the 9 responders in the DA group. ESC noted that this evidence has been accepted in international guidelines. ESC also noted that, while the magnitude of effect was uncertain, there appeared to be some benefit in terms of both PFS and OS in these trials. Overall, ESC considered that the evidence suggested a consistent signal of benefit in a rare disease where there is a high unmet clinical need.

Regarding comparative safety, ESC noted that DB is associated with higher incidence of neurotoxicity, particularly pain, compared to chemotherapy alone. ESC considered that clinicians

are likely to be familiar with managing adverse events following DB treatment from its current TGA-approved use, and noted that feedback from states and territories supported this.

ESC noted that the clinical claim presented in the application was that the use of DB in conjunction with chemotherapy in patients with relapsed or refractory HRNBL results in superior effectiveness (based on the key outcomes of ORR, OS and PFS) and inferior but manageable safety compared with chemotherapy alone (TOTEM or TEMIRI). ESC considered that the evidence was limited, due to the high risk of bias and the variation between studies. ESC acknowledged that given the condition is so rare, meaningful comparisons are very difficult to undertake but there was unlikely to be major variations in baseline characteristics of trial populations and the results of these trials are likely generalisable to Australian patients. Therefore ESC considered that overall there was a suggestion of benefit, and therefore that the claim of superior effectiveness was likely reasonable. ESC considered that the claim of inferior safety was reasonable, noting the increase in adverse events associated with DB, but agreed with the ADAR and the feedback from states and territories that this was likely to be manageable.

ESC noted the economic evaluation presented a cost-utility analysis and cost-effectiveness analysis based on a partitioned survival model (PSM). The limitations in clinical data meant that the PSM relied on data from different studies to estimate proportions in PFS and OS over time. In particular, PFS data were derived from 2 studies for the intervention and 6 studies for the comparator, and OS data were derived from an observational study where it was noted that data for 3 patients in the comparator arm should be excluded as they received palliative care rather than the comparator (chemotherapy) while the OS data derived for the intervention arm were for DA rather than DB. The studies showed heterogeneity in treatment regimens, selection criteria, other treatments, baseline characteristics, and the proportion of patients who were relapsed or refractory. Much of this data were from non-randomised and retrospective studies with potential for biases. Heterogeneity was not accounted for, but simply pooled, and then used to generate parametric functions that estimated long-term survival.

ESC noted that the basic principle of a PSM was violated in the economic model as the sum of proportions in each state does not sum to 100% (because of the use of different data sources) and the PFS was greater than OS in the base case from about 2 years into the model. To correct for this, the modelled PFS progression was arithmetically controlled in each cycle by setting the PFS value equal to the OS value if PFS>OS. In the base case which used an exponential function to fit the data, this approach meant that the modelled OS in the DB arm was ~40% at four years, which is inconsistent with the Australian Sydney Children's Hospital data that reported OS of 30% at four years, though this discrepancy was reduced when the OS extrapolation was fitted with a loglogistic instead of an exponential function.

The base case incremental cost-effectiveness ratio (ICER) was $redacted per quality-adjusted life year (QALY) gained. ESC agreed with the commentary that the model was impeded by very limited data and the selection of base case specifications was not well justified, leading to highly uncertain results and uncertain model validity. An alternate method was also presented in the ADAR where OS was inferred from PFS assuming that there are proportional hazards between PFS and OS to generate a parametric estimate of an OS Kaplan Meier curve. However, ESC considered that there was no precedent for this approach of employing a hazard ratio (HR) to derive one outcome from another in the same group in order to fill in gaps in the evidence, as the HR is usually used to estimate differences in survival between different treatment groups. ESC also noted that the alternate method assumed that the HR from one trial could be applied to the other, despite their heterogeneity and that the assumption of proportional hazards always applies. ESC therefore considered that the first method was more useful than the second, alternate method. ESC considered that it may be more justifiable to use the BEACON Immuno

study alone for PFS in the base case, and the use of data from other studies could be included in sensitivity analyses.

ESC considered that the base-case time horizon of 20 years was optimistic based on the survival data showing poor long-term survival, and that it was neither appropriate nor justified. ESC noted that the model was sensitive to changes in the time horizon. ESC therefore advised that the time horizon in the base case be reduced, and that multiple time horizons be explored in sensitivity analyses.

ESC noted that the model does not separate patients according to relapsed or refractory status but acknowledged that given the small sample sizes in the studies considered, splitting the populations into subgroups would not be reliable. ESC noted that there was a half cycle correction error in the model, but this only had a small impact on results.

ESC noted that the ADAR argued that cost per life years (LY) should be a preferred measure of ICER for this population because the patient population is primarily children and there are conceptual and practical difficulties associated with Health-related Quality of Life (HRQoL) assessments in children. However, ESC considered this to be an exaggerated concern and that QALYs generated from parent-reported QoL instruments are widely used as a proxy for the child's QoL.

ESC noted that the cost of hospitalisation, managing adverse events and chemotherapy were excluded from the economic model under the unsupported assumption that adverse events (and associated hospitalisation for these events) are driven by chemotherapy only and cancel out in the ICER calculation (though the costs of hospitalisation were included in cycle 0 for both arms, they were excluded in subsequent cycles). However, ESC considered that given the clinical claim of inferior safety of DB compared with chemotherapy, there may be additional hospital costs for pain management in young children due to more adverse events in the intervention arm compared to the chemotherapy arm. Therefore, ESC advised that its strong preference was for the costs of hospitalisation (inclusive of the cost of managing adverse events) to be included in the model unless the applicant could provide further evidence or justification that hospitalisation costs are equivalent across both arms (including beyond the first cycle of treatment).

ESC noted the estimated net financial impact to the NHRA HST program totalled $redacted (redacted vials) in year 1 and increased to $redacted (redacted vials) in each of years 5 and 6. ESC noted that this assumed the number of eligible patients did not change over time, and assumed that uptake would start at redacted% in year 1 and increase to redacted% by year 6. With these assumptions, it was noted by ESC that the application estimates there would be no expected increase in the current Government–Sponsor agreement for DB from March 2025 to February 2026. The current agreement has a forecasted use of redacted vials for that period, which would accommodate the ADAR estimates of redacted vials for HRNBL and redacted vials for RRHRNBL over this time period (total of redacted vials).

17. Applicant comments on MSAC's Public Summary Document

Recordati Rare Diseases welcomes the decision from the Medical Services Advisory Committee to recommend to the Minister dinutuximab beta, a Highly Specialised Therapy (HST) through the National Health Reform Agreement (NHRA) Addendum for primary relapsed or refractory (RR) high-risk neuroblastoma (HRNBL), acknowledging the high clinical need for this patient population.

18. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website: visit the MSAC website