Targeted Oncology (2023) 18:77–93
https://doi.org/10.1007/s11523-022-00930-w

REVIEW ARTICLE

Recent Evidence-Based Clinical Guide for the Use of Dinutuximab Beta in Pediatric Patients with Neuroblastoma

Julia Balaguer[1] · Laura García Hidalgo[2] · Raquel Hladun[3] · Catalina Márquez Vega[4] · Vanesa Pérez Alonso[5]

Accepted: 31 October 2022 / Published online: 12 December 2022

Abstract

The anti-GD2 antibody dinutuximab beta (Qarziba®) has been added to the present standard of care for patients with high-risk neuroblastoma in Europe based on the positive results obtained in different studies. In both the first-line and relapsed/refractory settings, treatment with dinutuximab beta attains objective clinical responses in children with high-risk neuroblastoma. Its incorporation has changed the outcome for these patients and optimized management should be guaranteed to minimize possible adverse effects. Most prevalent adverse events include pain, allergic reactions, fever and capillary leak syndrome. There are still no evidence-based clinical guidelines that include the latest published evidence to optimize its use, as it depends on the experience gained in each referral center. Topics such as the mode of preparation and administration, the concomitant use of interleukin-2, the recommended pediatric age and dose for its use, or the adequate management of possible toxicities are important aspects to review. The objective of this article was to update the clinical guide to management with dinutuximab beta of children with neuroblastoma based on the most recent published evidence and our own experience in clinical practice.

Key Summary Points

This review describes the current evidence supporting clinical management guidelines with the anti-GD2 antibody dinutuximab beta in the treatment of children with high-risk neuroblastoma (NB). Dinutuximab beta has been added to the current standard of care for patients with high-risk NB in Europe based on positive results from several studies.

The efficacy and safety of dinutuximab beta in children with NB has been demonstrated in several trials and its use has changed the outcome of patients with high-risk NB, both at diagnosis and at relapse.

Appropriate management of potential drug-associated toxicities of the patient, following recent evidence-based guidelines and clinical practice experience, reduces treatment-associated adverse effects and ensures better tolerability.

Extended author information available on the last page of the article

1 Introduction

Neuroblastoma (NB) is an aggressive malignant tumor of the sympathetic nervous system that predominantly occurs in children aged < 5 years, accounting for 10% of all pediatric cancers and 15% of all childhood cancer deaths [1, 2]. The treatment of NB is risk-based [3]. Risk is stratified into low, intermediate and high, based on distinct clinical and biological features, such as age at time of diagnosis, extent of the disease, tumor histology, molecular profile and presence of metastasis [3].

Children with high-risk NB (mostly metastatic and/or MYCN-amplified) comprise 50% of cases and have poor prognosis (survival rates < 50%) despite several approaches to treatment (induction chemotherapy, surgery, high-dose chemotherapy with autologous hematopoietic stem cell transplant, radiotherapy and differentiation therapy) [4]. Furthermore, half of the children with high-risk NB still relapse or do not respond to upfront therapy, and after relapse, survival options are minimal, with 4-year progression-free survival and overall survival (OS) rates of 6% and 20%, respectively, and even less in cases with amplification of MYCN [5].

As the disialoganglioside (GD2) is present on the majority of NB cells and in regular tissues, it is only expressed in melanocytes, neurons and fibers of the central and peripheral sensory and motor nervous system, it was proposed as a suitable target for immunotherapy [6]. The human/mouse chimeric anti-GD2 antibody ch14.18 (dinutuximab) produced in SP2/0 cells was developed and investigated in clinical trials [7], showing a significant increase in the survival of patients who received this drug. In Europe, ch14.18 was re-cloned in Chinese hamster ovarian (CHO) cells (dinutuximab beta [DB]) [8]. Other anti-GD2 molecules such as naxitamab or hu14.18K322A have also been developed, and athough in Europe currently only dinutuximab beta is authorized, there are many ongoing trials analyzing the role of immunotherapy with anti-GD2 monoclonal antibodies in different settings and using different strategies (NCT02258815, NCT01701479, NCT01767194, NCT02308527, NCT03794349, NCT01717554, NCT02914405).

The European Medicines Agency (EMA) has approved dinutuximab beta (Qarziba®) for the treatment of high-risk NB in patients aged ≥ 12 months who have previously received induction chemotherapy and achieved at least a partial response, followed by myeloablative therapy and stem cell transplantation, as well as patients with a history of relapsed or refractory NB, with or without residual disease [9]. This anti-GD2 antibody has been added to the present standard of care for patients with high-risk NB in Europe based on the positive outcomes obtained in different studies [9–12]. Its incorporation has altered the outcome for those with high-risk NB, but optimized management should be guaranteed in these patients to minimize possible adverse effects. Nevertheless, there are still no evidence-based clinical guidelines that include the latest published evidence to optimize its use, as it depends on the experience gained in each referral center.

The purpose of this work was to update the clinical management guide with dinutuximab beta of children with NB based on the most recent published evidence and our own experience in clinical practice.

2 Methods

We conducted a PubMed search on 10 April 2022 using the search terms ‘dinutuximab’ and ‘beta’ and ‘neuroblastoma’. Potentially relevant articles were chosen based on the title and abstract. Additional references were accessed as needed. The group of experts who wrote this clinical guideline present extensive experience in the use of the drug, and their institutions have participated in the SIOPEN studies.

3 Dinutuximab Beta

Dinutuximab beta is a chimeric monoclonal immunoglobulin (Ig) G1 antibody that is specifically targeted against the carbohydrate moiety of GD2, which is present on the suface of NB cells [13]. The complex antigen GD2 antibody activates the antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity, which cause apoptosis of NB cells [14]. In the presence of human effector cells, including peripheral blood nuclear cells and granulocytes from healthy human donors, dinutuximab beta was found to mediate the lysis of human NB and melanoma cell lines in a dose-dependent manner (Fig. 1) [15, 16].

Pharmacokinetic data were accessible from three clinical studies: APN311-101, -202 and -303 (see Table 1) [9, 17, 18]. In these studies [9, 18], maximum levels were generally attained at the end of the 10-day infusion, and the approximated half-life ($t_{½}$) was around 190 h [9, 18]. Given its target and elimination profile, dinutuximab beta is considered to have a reduced potential for drug–drug interactions [9, 18].

3.1 Dinutuximab Beta Clinical Trial Program

Efficacy and safety have been determined in five clinical trials (Table 1). The clinical data show evidence across different infusion regimens, different disease scenarios (first-line, relapse, and refractory), and as a single agent or in combination with aldesleukin (interleukin [IL]-2) and/or isotretinoin (13-*cis*-retinoic acid [13-*cis*-RA]).

Available data from these studies with dinutuximab beta show increases in event-free survival (EFS) and OS in patients with high-risk NB, with an increase in EFS of 20% and OS of 9%. Of note, the SIOPEN HRNBL1 clinical trial, which assessed the use of dinutuximab beta in the first-line setting, has been open to recruitment from 2002 to 2017. In this clinical trial, historical data with the same patient population showed a 5-year OS of 50% without dinutuximab beta versus 65% with dinutuximab beta ($p < 0.0001$) [12].

Most recent studies analyse the use of alternative schedules, strategies and combinations of dinutuximab beta. Recently, a phase I/II trial (NCT02258815) has shown that dinutuximab beta infusions after haploidentical stem cell transplantation in children with relapsed metastatic NBs appear to be acceptable without increased risk of inducing graft-versus-host disease. This study included 68 patients with 1st to 5th metastatic relapse. The success of treatment, defined as stable disease or improvement after the last treatment cycle, was shown in 58.8% of patients. OS at 2 and 3 years was 68.6% and 58%, respectively, and EFS at 2 and 3 years was 51.2% and 46.9%, respectively (median follow-up 2.5 years) [21]. Thus, the combinatorial therapy

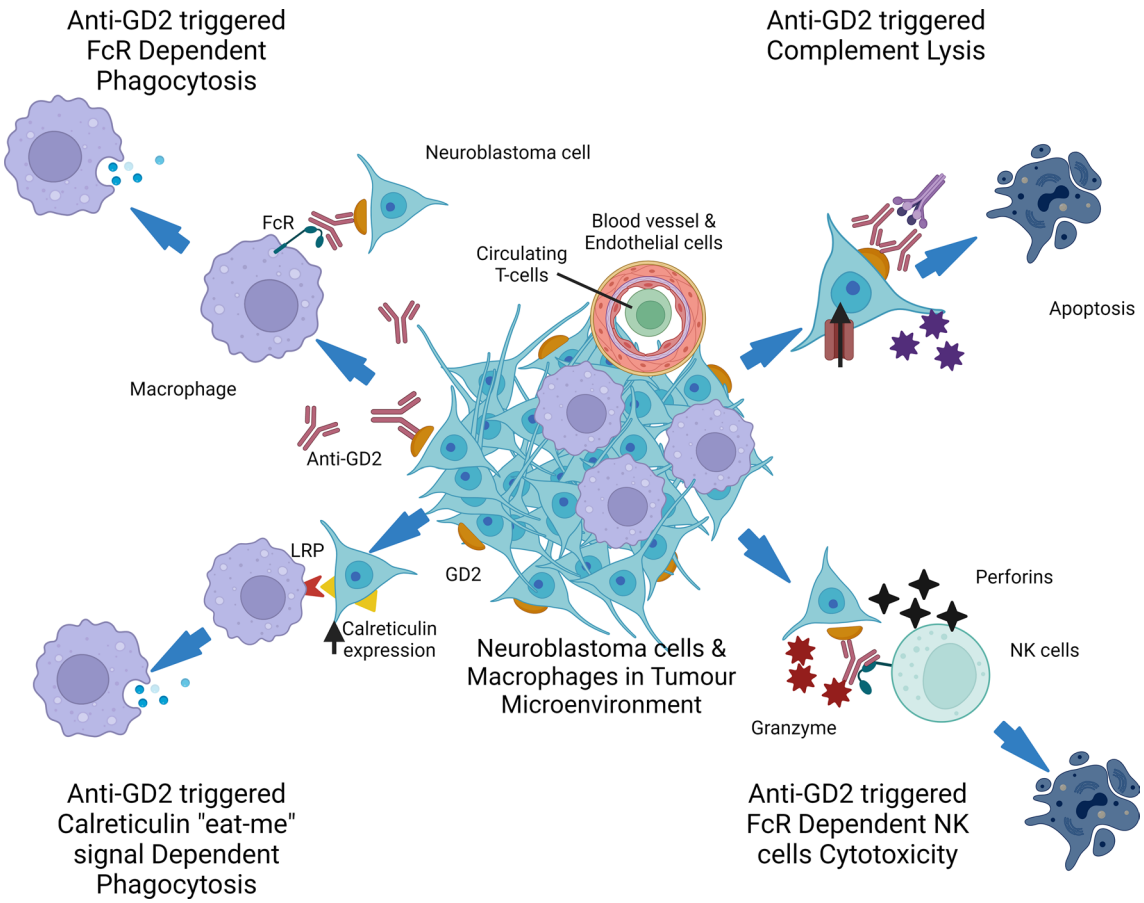

Fig. 1 Neuroblastoma tumor microenvironment and cytotoxic action induced by anti-GD2. (1) Anti-GD2 can trigger complementary activation by C1q–antibody interaction, leading to complement lysis of neuroblastoma cells (CDC). (2) Anti-GD2 activates NK cells via Fc RIIIA (CD16a), leading to the release of perforins and granzymes that can kill neuroblastoma cells (ADCC). (3) Anti-GD2 can activate macrophages via Fc RI (CD64) and Fc RIIA (CD32), leading to initiation of phagocytosis of neuroblastoma cells (ADP). (4) Monoclonal antibodies such as anti-GD2 can induce calreticulin ('eat me' molecule) expression on neuroblastoma cells and enhance phagocytosis by macrophages. The figure was created using Biorender.com, and was adapted from Chan and Chan [16]. *CDC* complement-dependent cytotoxicity, *NK* natural killer, *ADCC* antibody-dependent cellular cytotoxicity, *ADP* antibody-dependent phagocytosis

of haplo-SCT and dinutuximab beta seem to increase the efficacy of immunotherapy [22].

Early use of dinutuximab beta, post-induction chemotherapy, has been proposed as a promising strategy to improve responses. Administering at least one cycle of dinutuximab beta post-induction and prior to surgery in three children with high-risk NB who did not demonstrate a complete response to induction chemotherapy allowed them to achieve complete remission in one series [23].

In relapsed/refractory NB, the SIOPEN BEACON trial (NCT02308527) [24] has been amended to evaluate whether the incorporation of dinutuximab beta to temozolomide or temozolomide and topotecan enhances the efficacy of backbone chemotherapy, with results pending.

There is also an ongoing clinical trial to analyze a schedule of dinutuximab beta of 10–21 days, in combination with subcutaneous IL-2 and oral isotretinoin, to children and young people with primary refractory or relapsed NB without intravenous morphine (NCT01701479).

Opportunities to improve the activity of immunotherapy include targeting different mechanisms or increasing immune modulation (radiation can enhance immune responses). The MiNivAN study ($n = 36$) [NCT02914405] is looking at the efficacy, safety and tolerability of the combination dinutuximab beta, nivolumab and metaiodobenzylguanidine (mIBG) in pediatric patients with relapsed and refractory high-risk NB. Similarly, a previous case report analyzing the efficacy of the combination of dinutuximab beta with the checkpoint inhibitor nivolumab showed a complete and very good partial response in two patients with relapsed/refractory NB [25].

Table 1 Clinical studies

Study code phase	Neuroblastoma setting	Design	Treatment regimen	EFS (3 years)	OS (3 years)
APN311-101[17] Phase I EMA/263814/2017	R/R	Open-label, uncontrolled, multicentre	None	NA	NA
APN311-201[9] Phase II EMA/263814/2017	R/R	Open-label, uncontrolled, multicentre	Cycles 1–3: None Cycles 4–9: IL-2	40% (R/R together)	55% (R/R together)
APN311-202[9] Phase I/II NCT01701479	R/R	Open-label, uncontrolled, randomized, multicentre	IL-2, 13-cis-RA	37%/45% (R/R)	42%/62% (R/R)
APN311-303[18,19] (compassionate use) EMA/263814/2017	R/R	Open-label, uncontrolled, single-centre	IL-2, 13-cis-RA	24%/29% (R/R)	55%/70% (R/R)
APN311-304[20] Phase II NCT02743429 [20]	R/R	Open-label, uncontrolled, multicentre	None	31.5% (R/R together)	65.5% (R/R together)
APN311-302/HR-NBL1/SIOPEN[10,11,12] Phase III NCT01704716	First-line	Open-label, controlled, randomized, multicentre	With/without IL-2 13-cis-RA as maintenance therapy	STI[12] 57%/42%[a] (with/without DB) LTI[11] 63%/64%[b] (with/without IL-2)	STI[12] 57%/42%[a] (with/without DB) LTI[11] 74%/83%[b] (with/without IL-2)

EMA-/263814/2017: European Medicines Agency (Dinutuximab Beta Assessment Report) [available at: https://www.ema.europa.eu/en/documents/assessment-report/dinutuximab-beta-apeiron-epar-public-assessment-report_en.pdf]

ClinicalTrials.gov identifier NCT01701479: Long Term Continuous Infusion ch14.18/CHO Plus s.c. Aldesleukin (IL-2) (LTI) [available at: https://clinicaltrials.gov/ct2/show/NCT01701479]

ClinicalTrials.gov identifier NCT01704716: High Risk Neuroblastoma Study 1.8 of SIOP-Europe (SIOPEN) [available at: https://clinicaltrials.gov/ct2/show/NCT01704716]

DB dinutuximab beta, *EFS* event-free survival, *IL* interleukin, *LTI* long-term infusion, *OS* overall survival, *R/R* relapsed/refractory, *STI* short-term infusion, *13-cis-RA* 13-cis-retinoic acid

[a] 5 years

[b] 2 years

4 Treatment Schedules of Dinutuximab Beta

4.1 Short-Term versus Long-Term Infusion

In 2016, Siebert et al. [26] analyzed the pharmacokinetics and pharmacodynamics of long-term infusion (LTI; 100 mg/m^2 administered over 10 days as a continuous infusion) of dinutuximab beta in relapsed/refractory high-risk NB patients. LTI of dinutuximab beta demonstrated to induce effector mechanisms over the entire treatment period and the authors concluded that may therefore emerge as the preferred delivery method of anti-GD2 immunotherapy to NB patients [26]. They showed that extension of the treatment time of dinutuximab beta by the LTI resulted not only in effective immune modulation but also lowered pain toxicity, which is known to be a limiting factor after short-term infusions (STIs) of anti-GD2 Ab [27].

Later, the SIOPEN group tested the two different treatment schedules of dinutuximab beta in the first-line setting: STI (100 mg/m^2 administered over 5 days as a continuous infusion) and LTI (100 mg/m^2 administered over 10 days as a continuous infusion) [10, 11]. Dinutuximab beta administered as an LTI was linked with an improved toxicity profile compared with the STI schedule [11]. The most common grade 3/4 adverse events (AEs; according to the National Cancer Institute Common Toxicity Criteria [NCI-CTCAE]) described in the SIOPEN studies included pain, fever, hypersensitivity reactions/allergy, capillary leak syndrome, diarrhea and elevated liver enzymes. All of these AEs were experienced by patients receiving either treatment regimen,

but the incidence of some of the AEs, such as immunotherapy-related pain, hypersensitivity reactions and hypotension, was significantly lower with the LTI regimen compared with the STI regimen in patients receiving dinutuximab beta alone [10, 11]. Therefore, the use of the LTI schedule was considered to provide an improved toxicity profile (Fig. 2).

4.2 Dinutuximab Beta with or Without Interleukin-2

The APN311-302 study carried out by the SIOPEN group investigated the function of the addition of subcutaneous IL-2 to the STI of dinutuximab beta (20 mg/m^2/day as an 8 h infusion for 5 consecutive days) in association with 13-*cis*-RA, and randomized patients to dinutuximab beta plus 13-*cis*-RA versus dinutuximab beta plus subcutaneous IL-2 and 13-*cis*-RA. The trial showed that the addition of subcutaneous IL-2 to immunotherapy with dinutuximab beta and 13-*cis*-RA did not improve outcomes (3-year EFS was 56% without IL-2 and 60% with IL-2; $p = 0.76$) but increased toxicity [10]. The most frequent grade 3–4 AEs were hypersensitivity reactions (10% in the group without IL-2 vs. 20% in the subcutaneous IL-2 group), capillary leak (4% vs. 15%), fever (14% vs. 40%), infection (25% vs. 33%), immunotherapy-related pain (16% vs. 26%) and impaired general condition (16% vs. 41%).

Comparable with the STI study, the potential of IL-2 to improve patient outcomes was also evaluated in another randomization using dinutuximab beta-LTI [11]. The inclusion of IL-2 did not improve outcomes (2-year EFS and OS for dinutuximab beta-LTI vs. dinutuximab beta-LTI and subcutaneous IL-2 was 64% versus 63% [$p = 0.844$] and 83% versus 74%, respectively [$p = 0.337$]). Grade 3 and 4 toxicity was lower in the dinutuximab beta group versus dinutuximab beta and subcutaneous IL-2 for fever (14% vs. 31%; $p < 0.001$) and pain (7% vs. 18%; $p = 0.005$), and no significant difference was seen for general condition (17% vs. 22%; non-significant), allergy (3% vs. 3%; non-significant), capillary leak (4% vs. 8%, non-significant), liver enzyme elevation (20% vs. 27%; non-significant) and neurological toxicities (2% vs. 2%; non-significant). Therefore, the incorporation of IL-2 to dinutuximab beta-LTI did not improve survival in children with high-risk NB but substantially increased toxicity. Based on all these findings, dinutuximab beta-LTI without IL-2 is the standard of care for patients with high-risk NB receiving immunotherapy as part of maintenance therapy [10–12, 26, 27].

5 Therapeutic Indications

Expert Opinion

We recommend the use of dinutuximab beta:

1. Associated with 13-*cis*-RA as first-line maintenance to eliminate MRD after cytotoxic treatment in patients aged 12 months and above with high-risk neuroblastoma, defined as either International Neuroblastoma Risk Group Staging System (INRGSS) stage L2, M or MS with MYCN amplification, any age, or stage M, aged ≥ 12 months at diagnosis, and stage MS, 12–18 months of age, any MYCN status [28, 29].

   Although the current drug label contains the indication for concomitant use with IL-2, currently, following the recommendations of the SIOPEN group, there is no evidence of increased survival when associating IL-2, and it was related with more toxicity [10, 11]. Therefore, our recommendation is not to associate IL-2.

   Likewise, although the recommendation, according to the Summary of Product Characteristics, is for patients older than 12 months of age, the HR-NBL1/SIOPEN trial has shown that its use is well tolerated in younger patients, adjusting the dose according to weight in patients < 12 kg [30]. Nevertheless, our experience is that in children under 12 months of age, immunotherapy is not usually prescribed because the prognosis of high-

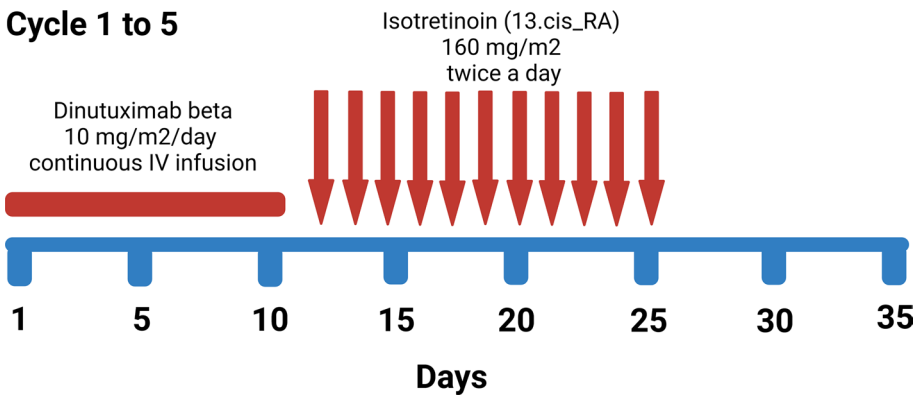

Fig. 2 Treatment schema of SIOPEN maintenance immunotherapy (dinutuximab beta). The figure was created using Biorender.com. *IV* intravenous, *13.cis-RA* 13-cis-retinoic acid

risk NB is more favorable at this age and therefore, it is not usually included in the SIOPEN protocols.
2. Association with Cytostatic Treatment for the Management of Relapsed/Refractory Disease [23].

Early-phase clinical trials with different anti-GD2 monoclonal antibodies in combination with different schemas of chemotherapy have shown positive results (NCT01576692, NCT01857934, NCT01767194). In addition, the BEACON phase II trial, the European trial for relapsed/refractory NB patients, has recently demonstrated the activity of dinutuximab beta in addition to chemotherapy with temozolomide and topotecan. The ORR was 18% with chemotherapy alone and 35% for patients receiving chemotherapy with dinutuximab beta. The 1-year PFS was also encouraging, with a rate of 27% for chemotherapy alone and 57% for chemotherapy with dinutuximab beta [31].

Based on these results, and considering fewer than 8% of children with relapsed high-risk NB achieve long-term survival, we recommend to include dinutiximab beta in the treatment strategy (ideally within a clinical trial), in refractory and first relapsed patients.

6 Posology

In the first-line setting, treatment with Qarziba consists of five consecutive courses, each comprising 35 days. The individual dose is established based on the body surface area and should be a total of 100 mg/m^2 per course (Fig. 2).

In the relapse setting, different schedules are being tested. For example, the BEACON trial (NCT02308527) proposes treatment with Qarziba within six consecutive courses. The total dose per course is 70 mg/m^2, administered in a continuous infusion over 7 days at the daily dose of 10 mg/m^2 (each course comprising 28 days) [32]. There is also an ongoing clinical trial (NCT01701479) to analyze a schedule of 10–21 days with dinutuximab beta in combination with subcutaneous IL-2 and oral isotretinoin in children and young patients with primary refractory or relapsed NB. Three dose levels will be considered with respect to daily dose (7, 10 and 15 mg/m^2), which relate to total doses of 100, 150 and 210 mg/m^2.

Expert Opinion

Two modes of administration are possible: a continuous infusion or a daily infusion administered over 8 h. We recommend continuous infusion in all scenarios due to a better toxicity profile and, in particular, less pain [10, 11]. In first-line treatment and R/R patients, the drug label indicates the dosage by body surface but the experts consider that in children between 5 and 12 kg, a dosage of 0.33 mg/kg/day, total dose per cycle of 3.3 mg/kg, is recommended. In children under 5 kg, 0.22 mg/kg/day is recommended, a total dose per cycle of 2.2 mg/kg.

7 Method of Administration

Dinutuximab beta is administered by intravenous infusion. In children, we recommend that the treatment should be administered through a central intravenous line, avoiding leakage and extravasation and facilitating children to have greater arm mobility. We strongly recommend to place a double lumen catheter, or, if not possible, a peripheral line (at least in the first administration), to be able to use it in case of secondary effects (such as anaphylaxia, hypotension, etc.) and also to be used for the other drugs administered concomitantly intravenously. For dinutuximab beta, the solution is administered at a rate of 2 mL per hour (48 mL per day) using an infusion pump.

8 Interaction with Other Medicinal Products and Other Forms of Interaction

Although no interaction studies have been carried out, a risk for indirect reduction of cytochrome P450 activity due to higher tumor necrosis factor (TNF)-α and IL-6 levels and therefore interactions with concomitantly used medicinal products, cannot be excluded (Table 2) [19, 33].

9 Practical Administration Guide

9.1 Preparation of Dinutuximab Beta

Dinutuximab beta is diluted in a solution of sodium chloride and albumin. The solution for infusion should be prepared under aseptic conditions and should not be exposed to heat or direct sunlight. Under usual conditions, the drug must be prepared and purged from the pharmacy service. The patient's daily dose is calculated based on body surface area, except in patients < 12 kg. The vials of the drug are diluted to a concentration of 4.5 mg/mL; it must be diluted to the patient's specific dose with a solution for infusion of chloride sodium 9 mg/mL (0.9%) containing human albumin. Solution for infusion can be prepared daily or in sufficient quantity for a maximum of 5 days of continuous infusion. The amount of solution to be perfused daily should be 48 mL (infusion rate 2–2.1 mL/h), for a total of 240 mL for a 5-day dose. It is recommended to prepare 50 mL of solution in a 50 mL syringe, or 250 mL in an infusion bag suitable for the infusion pump used, i.e. a surplus amount of 2 mL (syringe) or 10 mL (infusion bag), taking into account the residual volumes of the infusion systems. Purging is performed using

Table 2 Possible interactions with other medicinal products

Corticosteroids
Corticosteroids are likely to interfere with immunotherapy due to their immunosuppressant activity and are not recommended during the administration of dinutuximab beta treatment, from 2 weeks before the first dose in the first cycle to 1 week after the last dose in the previous process, except for life-threatening conditions, although studies to prove such an interaction have not been performed (Qarziba Summary of Product Characteristics, 2020) [9]
Vaccinations
During the administration of dinutuximab beta until 10 weeks after the last treatment course, vaccinations should be avoided due to immune stimulation through dinutuximab beta and the possible risk for rare neurological toxicities
Intravenous immunoglobulin
Concomitant use of intravenous immunoglobulins is not recommended as they may interfere with dinutuximab beta-dependent cellular cytotoxicity

the same preparation of the antibody and at the same rate, and is administered directly purged to the patient (infusion rate 2.1 mL/h prepared at 50 cc/day); at discharge, 2.1 mL/h (finished in 24–25 h). No washing is performed.

Chemical and physical stability during use has been demonstrated for a period of up to 48 h at 25 °C (50 mL syringe) and for up to 7 days at 37 °C (infusion bag of 250 mL), after continuous storage in a refrigerator (between 2 and 8 °C) for 72 h (EMA, 2017) [18]. Any suitable medical device for infusion can be used at a rate of 2 mL/h, e.g. infusers/syringe infusion pumps or electronic pumps for outpatient infusions. If an infusion syringe is used, it is undoubtedly much more accurate but is not usually suitable for the home setting.

The container should be visually inspected for the presence of solid particles before administration. The use of a 0.22 µm inline filter during infusion, except in the case of elastomeric pumps, is recommended as the infusion rhythm may be altered. Once the filter and system are connected to the syringe or bag with the infusion solution, it is recommended that the system is purged with the drug in order to start the infusion at the corresponding rate, i.e. 2–2.1 mL/h. It is advisable to start with the purged antibody.

In the case of infusers, it is important to control their positioning (when the child sleeps or if the infuser bends) since the rhythm of the infusion must be constant and varies with gravity, and therefore depends on the arrangement of the infuser's backpack and whether the line bends. Therefore, during the use of these systems, caution is recommended at the beginning, both by professionals and in-home use, and to make it more flexible depending on the response and specific circumstances of each patient and the experience of the service itself to adapt to each specific case.

9.2 Home-Based Administration

Home-based administration has to be very carefully chosen, depending on the experience of the center; time to get to the hospital in case of risk; 24 hours, 7 days a week assessment by trained professionals; and parents' social profile. Home administration may be considered in centers with experience in handling the drug and once adequate patient tolerance has been guaranteed. The group of experts considers home administration when the distance from home to the center is < 30–60 min and always from the second cycle onwards. In successive cycles, home-based administration can be considered if no toxicity is observed and once the patient does not require concomitant intravenous medication. For adequate home administration, it is important to properly train the family in the use of the pumps/infusors, and the centers must have a set of tools at the disposal of the families (where to call, where to go, what to do in each case) (Fig. 3).

9.3 Types of Pumps Used at Home

Both elastomeric and home infusion pumps can be used at home. Elastomeric infusion pumps have a single infusion rate (2.1 mL/h), and their handling is ON/OFF. The advantage of these pumps is that they do not need manipulation, purging, or knowledge about electronic devices. The main disadvantage is that if any adverse effects appear, the infusion rate cannot be slowed down. Elastomeric pumps can be used at recommended administrations of 2–5 days. Specific instructions should be given to parents and they should be helped in the process, especially during the first cycle.

Home pumps include several models. It would be advisable to use stable systems such as household pumps that warn quickly when the system is bent and do not have a drip chamber so that air does not enter. Purging should be performed with SSF, not medication. The home pump system usually employed in most services only requires 5 cc. The purging is performed quickly but always by introducing a slightly lower amount into the system to avoid the administration of a bolus. The most rigorous method of employing the system is to use a closed purging system on the laminar flow hood: a serum system is placed in the bag with a three-step wrench at the end, and the air is removed from the empty system with a syringe so that it is filled little by little (if a small amount of air enters it can be returned to the bag without exposure to spills, in the same way that volume is not lost). At the end of the

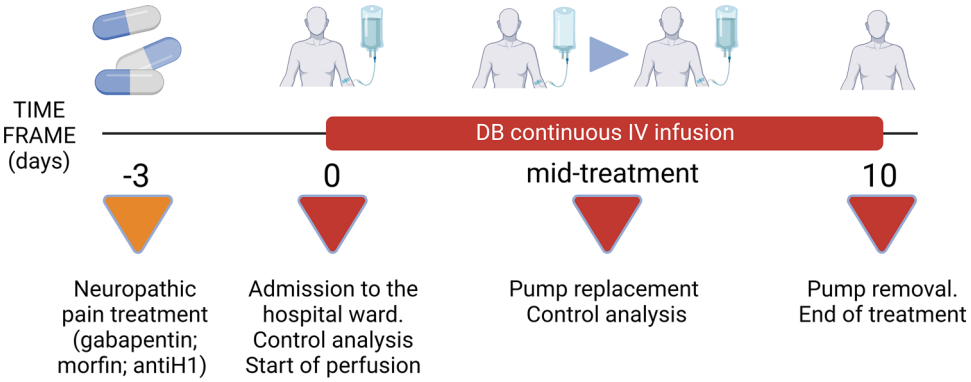

Fig. 3 General timeline, adjustable according to the characteristics of each patient. All cycles are started in hospital. The patient goes to the clinic on day −3 of treatment for clinical assessment, hemogram in the clinic, and initiation of prophylactic gabapentin. On day +3, when it is expected that the patient will not require intravenous medication, he/she will be able to go home. Halfway through treatment, the patient goes to the pediatric oncology outpatient clinic for a clinical check-up, and goes to the hospital for a change of medication pump. After the pump change, the patient goes home until day +10 of the cycle, when he/she will return to the oncology consultation and the infusion pump will be removed in the day hospital, ending the treatment cycle. The figure was created using Biorender.com. *DB* dinutuximab beta, *IV* intravenous

infusion, the serum is connected so that the system enters at the same speed as the infusion.

It is recommended that centers starting treatment with dinutuximab beta contact an experienced referral center to share experiences and logistical issues.

9.4 Patient Preparation

According to the Summary of Product Characteristics, before the initiation of each treatment course, the following clinical parameters should be assessed and treatment should be delayed until these values are reached: (1) pulse oximetry > 94% on room air; (2) adequate bone marrow function: absolute neutrophil count ≥ 500/µL, platelet count ≥ 20,000/µL, hemoglobin > 8.0 g/dL; (3) adequate liver function: alanine aminotransferase (ALT)/aspartate aminotransferase (AST) < 5 times the upper limit of normal (ULN); and (4) adequate renal function: creatinine clearance or glomerular filtration rate (GFR) > 60 mL/min/1.73 m^2 [9].

In the case of dinutuximab beta in combination with chemotherapy, adequate bone marrow function must also be ensured in the relapse setting.

Initiation of the infusion should be carried out under the supervision of a specialist in pediatric oncology, in a place equipped with the necessary means in case of a severe or potentially serious adverse reaction.

Expert Opinion

Prior to each cycle, the following are recommended. (1) Thorough history and detailed physical examination, including pupils and pupillary reflexes. (2) Vital constants measurements, i.e. temperature, heart rate (HR), respiratory rate (RR), oxygen saturation and blood pressure. During the infusion, on the first day of the cycle or until the patient is stable, it is recommended to repeat these determinations every 30 min for the first 4 h and then on an hourly basis. (3) A central line for dinutuximab beta should be ensured and, during the first cycles, a second venous access should be guaranteed only when other drugs are administered intravenously concomitantly.

If the patient does not meet all the criteria, the cycle will be delayed until basic requirements are met. However, if the patient meets all the requirements except minimum values of neutrophils and/or platelets, apart from patients receiving dinutuximab beta and chemotherapy, treatment could be initiated in individual cases by evaluating the risk/benefit in each case.

9.5 Premedication

9.5.1 Prevention of Neuropathic Pain

During treatment with dinutuximab beta, the occurrence of neuropathic pain is very common, mainly at the beginning of the infusion in the first cycle. That is why patients should begin prophylactic treatment with gabapentin 3 days prior to the start of each cycle (Day-3: 10 mg/kg/day [once]; Day-2: 20 mg/kg/day [twice daily]; Day-1: 30 mg/kg/day [three times daily]; with a maximum of 300 mg/dose) and is continued until the end of dinutuximab beta infusion.

Before starting dinutuximab beta (mainly in the first cycles), premedication with morphine is recommended. Based on our experience, different strategies can be used (see Table 3). It should be borne in mind that tolerance to dinutuximab beta evolves in each cycle, and our experience is that approximately 80% of patients are without intravenous morphine on the fifth day of treatment during the first

course of treatment. Thus, depending on the AEs of the previous cycle, the dose of morphine can be reduced in the next cycles, oral morphine can be used in some cases, or there is even no need for morphine.

9.5.2 Prevention of Anaphylactic Reactions

Anaphylactic reactions can occur at any time during treatment but are more frequent within minutes after starting the infusion. Therefore, the administration of prophylactic medication at the beginning of each cycle is necessary.

Expert Opinion

The administration of intravenous antihistamines 20 min prior to infusion is recommended. The dose can be repeated every 4–6 h as needed.

The different antihistamine options include (1) dexchlorpheniramine 0.1–0.15 mg/kg/intravenous dose (daily maximum 20 mg) every 8 h; (2) diphenhydramine 1.25 mg/kg/dose (maximum 50 mg/dose) every 6 h; (3) cetirizine 5 mg every 24 h (children < 30 kg) or 5 mg every 12 h (children > 30 kg) orally; (4) hydroxyzine 1–2 mg/kg/day (divided into two to three doses) orally.

Administration of one dose of ondansetron (0.15 mg/kg/dose) is recommended prior to initiation of morphine therapy and premedication with omeprazole (1 mg/kg/day) in case of gastric pain is also recommended.

10 Toxicity Management

The incidence and severity of AEs have been widely reported and some instructions are available in the literature regarding the management of common AEs (pain, allergic reactions, fever, hypotension, capillary leak syndrome, neurotoxicity, hematological toxicity, liver toxicity, cardiac toxicity) in children receiving dinutuximab beta [33]. Educating clinicians and nurses on how to adequately identify and manage these AEs is very important to avoid unplanned dose and schedule modifications that may reduce efficacy and ensure safe immunotherapy administration [33]. Many of the adverse effects of dinutuximab beta may coincide with those of other NB treatments, but some, such as pain, allergic reactions or capillary leak syndrome, are quite specific. Therefore, whenever they appear in a patient receiving dinutuximab beta, this should be taken into account in the differential diagnosis, in order to ensure the best possible management of the drug.

Table 3 Summary of recommendations for the management of pain associated with dinutuximab beta treatment in patients with neuroblastoma

Drug	Management recommendation
Intravenous morphine	
Day 1	Premedication: Prior to dinutuximab beta (2 h before infusion), start a continuous intravenous morphine infusion (0.03 mg/kg/h) or administer bolus (0.03–0.06 mg/kg) with the possibility of increasing the dose up to 0.1 mg/kg Concomitantly to dinutuximab beta infusion: Intravenous morphine infusion at 0.03 mg/kg/h. This dose can be reduced from the first day depending on tolerance
Days 2–10[a]	If well-controlled pain: early morphine reduction is recommended as well as oral morphine as soon as possible (to allow outpatient infusion), with a progressive decrease in the rate of infusion until its suspension: · Day +2: Continous intravenous morphine infusion at a rate of 0.02 mg/kg/h · Day +3: Continous intravenous morphine infusion at a rate of 0.01 mg/kg/h · Day +4: Continous intravenous morphine infusion at a rate of 0.005 mg/kg/h · Day +5: Discontinue intravenous morphine and switch to oral morphine or fentanyl patches
Oral morphine	Dose between 0.2 and 0.4 mg/kg/dose, every 4–6 h, to be adapted to each patient according to evolution Conversion to oral morphine, depending on the intravenous dose being administered, and progressively decrease until withdrawal
Non-opioid analgesics	Administer scheduled paracetamol throughout the infusion. If necessary, for abdominal pain, fever, etc., prescribe metamizole,[b] ibuprofen, or other according to the usual practice of each center In the case of *abdominal cramping pain or visceral pain*, the treatment of choice is *metamizole* for its antispasmolytic effect In the case of *high fever,* consider the introduction of *indomethacin.* To be avoided in patients under 2 years of age *Recommended doses:* Paracetamol: 10–15 mg/kg/6 h orally, 15 mg/kg/6 h (7.5 mg/kg/6 h for patients < 10 kg) intravenously Ibuprofen: 7 mg/kg/dose orally, every 6–8 h Metamizole: 12.5 mg/kg/dose orally, 20 mg/kg/dose intravenously, and doses can be increased up to 40 mg/kg/dose according to patient characteristics Indomethacin: 0.5 mg/kg/6 h orally

[a]This recommendation of morphine reduction applies to cycle 1. For successive cycles, it can be adapted according to the needs of the patient and the medical criteria

[b]Metamizole is banned in some countries due to its potential for adverse events, including agranulocytosis

The degree of toxicity refers to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 published in November 2017 [34].

The most common AEs (Qarziba Summary of Product Characteristics, 2022) [29] are summarized in Table 4.

In the experience of experts, pain is the most frequent adverse effect reported. Other frequent adverse effects include fever and hypersensitivity reactions (mainly pruritus and mild skin lesions). Furthermore, it has been observed that irritative cough subsides with adrenaline sprays and does not usually require suspension of the treatment because it does not produce dyspnoea. Regarding capillary leakage syndrome, some mild forms are observed, such as fluid retention.

10.1 General Recommendations for the Management of Common Adverse Effects Associated with Dinutuximab Beta Treatment

Regarding the management of AEs, it should be noted that most occur during dinutuximab beta administration and resolve upon infusion finalization [10]. Therefore, it is recommended to momentarily discontinue the treatment to provide supportive therapy as it can prevent the progression of symptoms and does not appear to be detrimental. When symptoms improve, dinutuximab beta administration can resume, except in a few situations of severe toxicity that are specified below. Proper management of AEs with supportive therapy is critical before considering dose reduction or discontinuation of immunotherapy in successive cycles.

Significantly, the incidence and/or intensity of some AEs, such as pain, allergic reactions, urticaria or capillary leak syndrome, generally decreases beyond the first cycle of treatment with dinutuximab beta [10, 19]. It is also essential to differentiate when the symptoms are due to the treatment per se or may be a consequence of the NB itself (i.e. central nervous system [CNS] symptoms) or, as in the case of some symptoms such as fever, hypotension or capillary leak syndrome, are caused by other triggers such as possible infection or sepsis. Once an AE has occurred in a patient and is considered related to dinutuximab beta treatment, proactively preventing recurrence during the current cycle and subsequent treatment cycles is mandatory.

Finally, to optimize the management of these patients, educating parents/caregivers to identify possible AEs to support their children during treatment is essential.

Table 4 Most common adverse effects with dinutuximab beta

Fever	88%
Pain	77%
Hypersensitivity	74.1%
Vomiting	57%
Diarrhea	51%
Capillary leak syndrome	40%
Hypotension	42.2%

10.2 Pain

Systemic administration of dinutuximab beta may result in allodynia and severe neuropathic pain (localized most commonly in the extremities, abdomen, back, chest or joints (arthralgia) [9]. Neuropathic pain may appear due to the activation by dinutuximab beta of the complement cascade at the GD2-expressing peripheral sensory nerve fibers [35], since GD2 is not only expressed in NB but also in healthy nerve cells of the central and peripheral nervous systems [36]. Pain generally begins immediately, the first or second day after initiation of the infusion during the first cycle, and decreases with subsequent treatment cycles.

Expert Opinion

In the event that a patient presents pain despite the prophylaxis regimen described, the analgesic treatment with intravenous morphine should be adjusted (morphine bolus EV: 0.02 mg/kg and/or increase the rate of continuous infusion of morphine, according to the needs of each patient). If refractory pain occurs, assess continuous infusion with lidocaine (per protocol) or ketamine (usual analgesic doses). The appearance of tolerable G4 pain does not imply modifications in the administration of dinutuximab beta, as long as the pain can be controlled with the scheduled rescue analgesic treatment. Individually, if the pain persists, it may be considered to interrupt the infusion of the antibody for 30 min and then restart at half speed, and progressively increasing the rate up to 100%. An intolerable, refractory and/or unresponsive G4 pain despite the administration of continuous infusion of morphine, indicates discontinuing treatment with dinutuximab beta.

The administration of dinutuximab beta as LTI and the omission of IL-2 from the treatment regimen resulted in decreased morphine use [18], potentially allowing home-based treatment during the last days of infusion, once the pain is controlled with doses of stable oral morphine.

The recommendations of the morphine regimen will be determined by the patient's tolerance to pain and is mainly met in the first cycles. When patients have not had any pain during the first two cycles, many of the centers start the third cycle with the morphine bolus and administer oral morphine or simply usual analgesia; no incidences in these patients have been observed.

10.3 Allergic Reactions

Hypersensitivity reactions are a possible AE in patients undergoing treatment with dinutuximab beta [37] due to the immunotoxic effects associated with monoclonal antibodies [38]. These hypersensitivity reactions may produce severe (e.g. bronchospasm, angioedema or anaphylactic shock), moderate (e.g. hypotension) or mild (e.g. pruritus or skin lesions) symptoms [10] but the omission of IL-2, the administration of the drug by LTI, and the use of premedication in current clinical practice has resulted in most hypersensitivity reactions now being mild and mainly cutaneous (rash/pruritus). Severe reactions, such as anaphylaxis, are rare and if they occur exceptionally, it is within a few minutes of the administration of the first infusion of the drug. Thus, patients should be closely monitored for anaphylaxis/allergic reactions, particularly during the first and second treatment cycle [31].

Intravenous antihistamine, epinephrine and methylprednisone should be ready for administration at the bedside in case of a severe allergic reaction during dinutuximab beta treatment. Antihistamines (e.g. diphenhydramine, chlorphenamine) should be administered approximately 20 min before starting each dinutuximab beta infusion and repeated every 4–6 h as required. Regular administration of oral antihistamines from the day before starting the dinutuximab beta infusion, depending on the symptoms presented during the previous cycles, should also be considered (see Table 5).

Expert Opinion

In the management of hypersensitivity reactions, it is essential to make a good differential diagnosis and to rule out other possible causes (i.e. hypotension can be the symptom of an infectious process or the administration of morphine, etc.). The use of corticosteroids should be restricted as much as possible.

10.4 Fever

Fever, which is considered to be an axillary temperature of ≥ 38 °C, is the most common AE associated with dinutuximab beta treatment, occurring in more than 80% of treated patients. A temperature above 37–38 °C accompanied by constitutional symptoms should be treated with usual antipyretics: metamizole, paracetamol or ibuprofen if the platelet count is normal. The management of grade 3–4 fever is summarized in Table 6.

Analytical modifications of commonly used acute-phase reactants (C-reactive protein and procalcitonin) related to the administration of dinutuximab beta have been described. At the physician's discretion and individually in each patient, infectious causes should be excluded in cases of febrile processes in these patients, with the extraction of blood cultures and initiation of empirical antibiotic therapy until the resolution of fever and negative cultures. In general, empirical antibiotic therapy is not recommended when there is only fever (even with elevated C-reactive protein). However,

Table 5 Management of allergic reactions

Mild symptoms
Reduce the rate of infusion of the antibody to 50% until recovery of symptoms
Dexchlorpheniramine 0.1–0.15 mg/kg every 6–8 h intravenously (maximum 20 mg)
If tolerance is adequate, the rate can continue to be increased up to 100%. Complete the infusion as planned
Avoid the use of corticosteroids
Moderate symptoms
Discontinue infusion of the antibody
Supportive treatment depending on the clinical situation, which may include:
» Volume infusion in the form of physiological saline serum (20 mL/kg intravenously)
» Administration of antihistamines (dexchlorpheniramine 0.1–0.15 mg/kg intravenously)
» Administration of adrenaline (0.01 mg/kg/dose intramuscularly)
» Administration of corticosteroids (methylprednisone 1–2 mg/kg)
Clinical surveillance and monitoring of the patient until the resolution of symptoms
After complete resolution of symptoms (hypotension), 50% antibody infusion may be restarted. If tolerance is adequate, the rate can continue to be increased up to 100%
Severe symptoms
Discontinue infusion of the antibody
Supportive treatment depending on the clinical situation, which may include:
» Volume infusion in physiological saline serum (20 mL/kg intravenously)
» Administration of antihistamines (dexchlorpheniramine 0.1–0.15 mg/kg intravenously)
» Administration of adrenaline (0.01 mg/kg/dose intramuscularly)
» Administration of corticosteroids (methylprednisone 1–2 mg/kg)
» Administration of salbutamol ± ipratropium bromure
Clinical surveillance and monitoring of the patient until the resolution of symptoms for at least 24 h
DO NOT restart the antibody infusion in the same cycle. It could be restarted in subsequent cycles at a slower rate, except for grade 3 bronchospasm and grade 4 anaphylaxis, which would be definitively discontinued

empirical antibiotic therapy would be recommended if there is associated neutropenia or clinical suspicion of an infectious process. If symptoms are resolved and cultures are negative after 72 h, antibiotics can be withdrawn.

10.5 Hypotension

Hypotension can be a symptom of a cytokine release syndrome, characterized by systemic symptoms such as fever, hypotension and urticaria that appears after the start of the first infusion. In case the patient presents hypotension, despite all the measures described above, follow the recommendations summarized in Table 7.

10.6 Capillary Leak Syndrome (CLS)

CLS consists of the massive leakage of fluids and proteins from the intravascular space to the interstitial space, giving rise to a situation of shock due to volume depletion and anasarca (severe hypotension, hypoalbuminemia and hemoconcentration). Complications include pulmonary edema, multiorgan failure related to hypoperfusion, hypercoagulability due to hemoconcentration and increased serum viscosity and anasarca (see Table 8).

Management consists of intravenous hydration and early use of vasopressors (see Table 9).

10.7 Neurological Toxicity

Sensory and motor neuropathies have been reported in 9% of patients [9]. Although most adverse reactions were grade 1–2 (and resolved), cases of neuropathy lasting > 4 days should be assessed and non-inflammatory causes (infections, disease progression, metabolic syndromes or concomitant medication) should be ruled out. Treatment should be interrupted for patients with grade 2 neuropathy (motor with or without sensory) and may be resumed at a rate of 50% after neurologic symptoms resolve. Increase to the initial infusion rate if the adverse effect disappears. It is recommended to discontinue the dinutuximab beta infusion in case of persistent peripheral motor neuropathy grade 2; peripheral neuropathy grade 3; ocular toxicity grade 3; and objective prolonged weakness. In the case of recurrence, the infusion will be discontinued and re-evaluated individually. Recent publications have shown that if severe neurotoxicity

Table 6 Management of fever

• *Fever grade 3*
Dose modifications not required, except in individual cases at the discretion of the physician
• *Fever grade 4*
Stop the antibody if fever (> 40 °C) is present for ≥ 6 h, despite the use of antipyretics
In subsequent cycles, the dose of dinutuximab beta should be reduced to 50%

Table 7 Management of hypotension

• *Hypotension grade 1–2*
Interrupt the infusion and initiate support measures: fluid administration (e.g. 20 mL/kg of SSF intravenously)
Once the symptoms have subsided, restart the infusion at the same rate
• *Hypotension grade 3–4*
Immediately interrupt the cycle with dinutuximab beta and initiate support measures. Treatment with dinutuximab beta will be restarted in the next cycle if it has resolved
In the case of a decrease in diuresis associated with hypotension, ensure a good renal perfusion with fluids prior to the use of a diuretic. If required, the oral route is advised, which has a more progressive and slow effect

Table 8 Capillary leak syndrome complications

Prodromes	Hemoconcentration phase	Leak phase	Post-leak phase
Asthenia Myalgia Fever Abdominal pain	Presyncope Oliguria Hypotension Hypoperfusion	Hypoalbuminemia Generalized edema	Restoration of intravascular volume
Complications			
• Deep vein thrombosis	• Shock • Multiorgan failure	• Compartment syndrome • Rhabdomyolysis	• Cardiopulmonary failure

Table 9 Management of capillary leak syndrome

Capillary leak syndrome grade 3:
Stop dinutuximab beta perfusion
If resolved or improved to grade 2 with supportive measures, the infusion is resumed on the hour, at 50% of the dose until the prescribed dose is completed. In subsequent courses, the dose can be increased depending on tolerance
Capillary leak syndrome grade 4, or recurrence:
If capillary leak syndrome recurs or occurs in grade 4, including ventilatory support, treatment is definitively discontinued

Table 10 Treatment of ocular toxicity

Mydriasis with slow photomotor reflex ± photophobia
The infusion should be discontinued, resuming it at a rate of 50% if resolved. In this case, the use of sunglasses and photoprotection is recommended to continue the treatment, and immediately refer patients to an ophthalmologist
Persistent mydriasis
Weigh the risks and benefits of discontinuing therapy
Vision-related grade 3 adverse reaction (subtotal loss of vision)
Administration should be discontinued

is developed, the use of corticosteroids, gamma globulins and plasmapheresis can help with resolution of the situation [39, 40].

10.8 Ocular Toxicity

There is a lack of information in the literature regarding visual disturbances in association with dinutuximab beta therapy [41]. Ocular toxicity may occur in the form of mydriasis and alteration of visual accommodation that is correctable with glasses (13%), blurred vision (3%), photophobia (3%), paralysis of the eye muscles, ophthalmoplegia (2%) and optic atrophy. The treatment of ocular toxicity is summarized in Table 10.

The experts recommend a complete ophthalmological examination before starting the first cycle, as well as regular monitoring of patients.

10.9 Hematological Toxicity

In patients who have undergone stem cell transplant, low-grade hematological toxicities such as thrombocytopenia, leucopenia and anemia are often observed and are usually self-limiting. In general, these hematological toxicities resolve with time and do not require specific management or modifications of dinutuximab beta administration. In the case of delay, the dose will be reduced by 50% in the following course.

10.10 Hepatotoxicity

In patients treated with dinutuximab beta, particularly those who experienced veno-occlusive disease or previously received busulfan/melphalan, increased levels of liver transaminases have also been described [10, 11]. Generally, these events are transient, not severe and are considered related to concomitant hepatotoxic medications (see Table 11). Therefore, hepatotoxicity does not require specific management if no other symptoms are observed. However, if transaminase levels are < 20 times the normal upper limit, the patient should be monitored closely without reducing or interrupting dinutuximab beta, and hepatotoxic drugs should be avoided.

An isolated elevation of alkaline phosphatase is not a good indicator of liver toxicity. Therefore, in such a circumstance, it is unnecessary to modify doses or interrupt treatment. However, if bilirubin triples its normal value, dinutuximab beta should be started when it has returned to normal. In such a case, the dose can be restarted at 100%.

10.11 Nephrotoxicity

Adequate kidney function (based on GFR or serum creatinine clearance) is necessary to be able to administer treatment. If kidney function is impaired but lower than grade 3, avoid other nephrotoxic drugs.

10.12 Cardiac Toxicity

Any evidence of cardiac impairment requires immediate electrocardiogram evaluation, and if ischemia occurs, discontinue immediately. Patients with asymptomatic atrial

Table 11 Management of hepatotoxicity

Liver toxicity grade 3:
If < 3 days or returning to grade 1 before the next course, dose modification of dinutuximab beta is not needed, provided that these toxicities are considered tolerable by the doctor in charge, as well as by the family and the patient

Table 12 Recommended dose modifications for dinutuximab beta according to adverse reaction

Adverse reaction	Severity	Treatment modification
Any	*Grade 1–2*	Decrease infusion rate to 50% After resolution, resume infusion at the original rate
Hypersensitivity reaction	For example, hypotension	Interrupt infusion and administer supportive measures After resolution, resume infusion at the original rate
Dilated pupils with sluggish light reflex ± photophobia		Interrupt infusion After resolution, resume infusion at 50% rate
Any	*Grade ≥ 3*	Interrupt infusion and administer supportive measures Resume infusion at 50% rate if adverse reaction resolves or improves to Grade 1–2 After resolution, increase to the original rate
	Recurrent	Discontinue infusion Resume the next day if adverse reaction resolves
Hypersensitivity reaction	For example, bronchospasm, angioedema	Interrupt infusion immediately and treat appropriately (see Sect. 4.4) Resume treatment for subsequent courses
Capillary leak syndrome		Interrupt infusion and administer supportive measures depending on the grade, Resume at 50% rate if adverse reaction resolves or improves to grade 1–2

tachycardia, related to temperature elevation, but without evidence of ischemia or clinical hypotension, will be monitored but treatment may continue. Only in patients with cardiac toxicity higher than grade 3 should treatment with dinutuximab beta be discontinued definitively.

Patients with clinical problems of volume overload may receive diuretics (furosemide) to lower systolic blood pressure (SBP), and infusion of dinutuximab beta should be stopped if SBP < 80 mmHg or drops at least 20 mmHg from its baseline blood pressure and does not recover after passing fluids or seroalbumin (e.g. 20 mL/kg of SSF). Treatment can be resumed once baseline SBP is recovered, but always at 50% of the dose.

10.13 Hyponatremia

Hyponatremia may occur in patients treated with dinutuximab beta. Dinutuximab beta should be discontinued in those patients with either symptomatic hyponatremia, persistent (> 48 h) sodium < 125 mmol/L, or severe hyponatremia without symptoms (sodium < 120 mmol/L). Grade 3 electrolyte imbalance (especially hyponatremia < 124 mEq/L in the absence of CNS symptoms and sequelae) that improve with treatment within 24 h will not require dose modification when observed, provided that such toxicity is considered tolerable at the discretion of the responsible clinician.

10.14 Vomiting and Diarrhea

According to the experts, prophylaxis of vomiting with serotonin 5-HT_3 receptor antagonists is recommended and patients with mild diarrhea may only require fluid support.

11 Recommended Dose Modifications [19]

Treatment with dinutuximab beta should be permanently discontinued if the following toxicities occur:

- Intolerable, refractory and/or unresponsive G4 pain despite administration of a continuous infusion of morphine ± lidocaine.
- Grade 3 or 4 anaphylaxis.
- Prolonged grade 2 peripheral motor neuropathy and objective prolonged weakness.
- Grade 3 peripheral neuropathy.
- Grade 3 vision eye toxicity.
- Grade 4 hyponatremia (< 120 mEq/L) despite appropriate fluid management.
- Recurrent or grade 4 capillary leak syndrome (requires ventilator support).
- Grade 4 cardiac toxicity.

11.1 Pediatric Population

The safety and efficacy of Qarziba in children aged < 12 months has not yet been established and no data are available (Table 12).

12 Conclusions

The efficacy and safety of dinutuximab beta in children with NB has been demonstrated in several trials, and its use has changed the outcome of patients with high-risk

NB, both at diagnosis and at relapse. The experience of experts corroborates these findings, and in those patients in whom the use of dinutuximab beta is indicated, the benefits in their clinical practice are evident. Nevertheless, these patients should be guaranteed optimized management to minimize the possible adverse effects. Continuous infusion of the drug during 10 days (LTI) and without IL-2 is recommended. Dinutuximab beta administered as an LTI provides the same efficacy but a significantly lower toxicity profile than the STI schedule, allowing the possibility of home administration. Adequate patient management of the potential drug-associated toxicities following recent evidence-based guidelines and clinical practice experience could reduce potential treatment-associated adverse effects and ensure a better tolerance. For the management of adverse reactions, it is recommended to reduce the rate or suspend the infusion of dinutuximab beta, manage the symptoms with supportive care, and once resolved, restart the drug progressively according to the patient's tolerance and the data sheet, except in severe and life-threatening situations, where it should be definitively suspended.

To optimize the use of dinutuximab beta, management should be carried out in centers where the personnel (nurses, clinicians and pharmacists) are specifically trained and have experience in ensuring proper preparation and administration of the drug and in early detection of possible adverse effects. To date, there is increasing experience with the use of dinutuximab beta, which favors home-based management that should be very carefully indicated in selected patients according to individualized criteria.

Acknowledgments The authors would like to thank Ana Ortega of Springer Healthcare Communications who wrote the first and second drafts of this manuscript.

Declarations

Author contributions All authors contributed equally to the conception, writing and critical revision of this manuscript, and have read and agreed on the final version.

Funding Medical writing assistance was funded by EUSA Pharma Iberia S.L. EUSA Pharma had the opportunity to provide a courtesy review of the manuscript but the final content is the responsibility of the authors alone.

Conflicts of interest Julia Balaguer, Laura García Hidalgo and Catalina Marquez Vega report advisory fees and support for travel to meetings from EUSA Pharma. Vanesa Pérez Alonso reports advisory fees from EUSA Pharma. Raquel Hladun reports advisory fees and support for lectures and travel to meetings from EUSA Pharma.

References

1. Swift CC, Eklund MJ, Kraveka JM, Alazraki AL. Updates in diagnosis, management, and treatment of neuroblastoma. Radiographics. 2018;38:566–80.
2. Steliarova-Foucher E, Colombet M, Ries LAG, Moreno F, Dolya A, Bray F, et al. International incidence of childhood cancer, 2001–10: a population-based registry study. Lancet Oncol. 2017;18:719–31.
3. Pinto NR, Applebaum MA, Volchenboum SL, Matthay KK, London WB, Ambros PF, et al. Advances in risk classification and treatment strategies for neuroblastoma. J Clin Oncol. 2015;33:3008–17.
4. Smith V, Foster J. High-risk neuroblastoma treatment review. Children. 2018;5:1–7.
5. London WB, Bagatell R, Weigel BJ, Fox E, Guo D, Van Ryn C, et al. Historical time to disease progression and progression-free survival in patients with recurrent/refractory neuroblastoma treated in the modern era on Children's Oncology Group early-phase trials. Cancer. 2017;123(24):4914–23.
6. Nazha B, Inal C, Owonikoko TK. Disialoganglioside GD2 expression in solid tumors and role as a target for cancer therapy. Front Oncol. 2020;10:1000.
7. Cheung NK, Dyer MA. Neuroblastoma: developmental biology, cancer genomics and immunotherapy. Nat Rev Cancer. 2013;13:397–411.
8. Zeng Y, Fest S, Kunert R, Katinger H, Pistoia V, Michon J, et al. Anti-neuroblastoma effect of ch14.18 antibody produced in CHO cells is mediated by NK-cells in mice. Mol Immunol. 2005;42:1311–9.
9. Qarziba (dinutuximab beta) Summary of Product Characteristics (28/01/2020). Available at: https://www.ema.europa.eu/en/documents/product-information/qarziba-epar-product-information_en.pdf. Accessed Dec 2021
10. Ladenstein RL, Poetschger U, Valteau-Couanet D, Luksch R, Castel V, Yaniv I, et al. Interleukin 2 with anti-GD2 antibody ch14.18/CHO (dinutuximab beta) in patients with high-risk neuroblastoma (HR-NBL1/SIOPEN): a multicentre, randomised, phase 3 trial. Lancet Oncol. 2018;19:1617–29.
11. Ladenstein RL, Poetschger U, Valteau-Couanet D, Gray J, Luksch R, Balwierz W, et al. Randomization of dose-reduced subcutaneous interleukin-2 (scIL2) in maintenance immunotherapy (IT) with anti-GD2 antibody dinutuximab beta (DB) long-term infusion (LTI) in front–line high-risk neuroblastoma patients: early results from the HR-NBL1/SIOPEN trial. J Clin Oncol. 2019;37:10013.
12. Ladenstein R, Pötschger U, Valteau-Couanet D, Luksch R, Castel V, Ash S, et al. Investigation of the role of dinutuximab beta-based immunotherapy in the SIOPEN high-risk neuroblastoma 1 trial (HR-NBL1). Cancers (Basel). 2020;12(2):309.
13. Hoy SM. Dinutuximab: a review in high-risk neuroblastoma. Target Oncol. 2016;11(2):247–53.
14. Mastrangelo S, Rivetti S, Triarico S, Romano A, Attinà G, Maurizi P, et al. Mechanisms, characteristics, and treatment of neuropathic

pain and peripheral neuropathy associated with dinutuximab in neuroblastoma patients. Int J Mol Sci. 2021;22(23):12648.
15. Ladenstein R, Weixler S, Baykan B, Bleeke M, Kunert R, Katinger D, et al. Ch14.18 antibody produced in CHO cells in relapsed or refractory Stage 4 neuroblastoma patients:a SIOPEN Phase 1 study. MAbs. 2013;5:801–9.
16. Chan GC, Chan CM. Anti-GD2 directed immunotherapy for high-risk and metastatic neuroblastoma. Biomolecules. 2022;12(3):358.
17. McKeage K, Lyseng-Williamson KA. Dinutuximab beta in high-risk neuroblastoma: a profile of its use. Drugs Ther Perspect. 2018;34:281–7.
18. Mueller I, Ehlert K, Endres S, Pill L, Siebert N, Kietz S, et al. Tolerability, response and outcome of high-risk neuroblastoma patients treated with long-term infusion of anti-GD2 antibody ch14.18/CHO. MAbs. 2018;10(1):55–61. https://doi.org/10.1080/19420862.2017.1402997.
19. European Medicines Agency (EMA). European Public Assessment Report (EPAR) for dinutuximab beta (Apeiron): EMA/263814/2017, first published 15 May 2017.
20. Lode HN. Single agent activity of the anti-GD2 antibody dinutuximab beta long-term infusion in high-risk neuroblastoma patients with relapsed and refractory disease. a multicenter phase II trial [SIOP 2022 Abstract 0147/#1343]. Pediatr Blood Cancer. 2022;69 Suppl. 5:e29952.
21. Flaadt T, Lang P, Ebinger M, Schumm M, Ebinger M, Koscielniak E, et al. Haploidentical Stem Cell Transplantation and Subsequent Immunotherapy With antiGD2 Antibody for Patients With Relapsed Metastatic Neuroblastoma. SIOP ABSTRACTS 0059/#1479 H.
22. Seitz CM, Flaadt T, Mezger M, Lang AM, Michaelis S, Katz M, et al. Immunomonitoring of Stage IV Relapsed Neuroblastoma Patients Undergoing Haploidentical Hematopoietic Stem Cell Transplantation and Subsequent GD2 (ch14.18/CHO) Antibody Treatment. Front Immunol. 2021;12:690467.
23. Spasov N, Spasova M. Early use of dinutuximab beta in patients with high-risk neuroblastoma. Case Rep Pediatr. 2021;2021:6610955.
24. Wheatley K, Holt G, Owens C, LaidlerLaidler J, Valteau-Couanet D, GambartValteau-CouanetGambart M, et al. Randomized comparisons of bevacizumab (B) and irinotecan (I), added to temozolomide (T), in children with relapsed or refractory high-risk neuroblastoma (RR-HRNB): first survival results of the ITCC-SIOPEN BEACON-Neuroblastoma phase II trial. J Clin Oncol. 2020;38:10501.
25. Ehlert K, Hansjuergens I, Zinke A, Otto S, Siebert N, Henze G, et al. Nivolumab and dinutuximab beta in two patients with refractory neuroblastoma. J Immunother Cancer. 2020;8(1): e000540.
26. Siebert N, Eger C, Seidel D, Jüttner M, Zumpe M, Wegner D, et al. Pharmacokinetics and pharmacodynamics of ch14.18/CHO in relapsed/refractory high-risk neuroblastoma patients treated by long-term infusion in combination with IL-2. MAbs. 2016;8(3):604–16.
27. Siebert N, Troschke-Meurer S, Marx M, Zumpe M, Ehlert K, Gray J, et al. Impact of HACA on immunomodulation and treatment toxicity following ch14.18/CHO long-term infusion with interleukin-2: results from a SIOPEN phase 2 trial. Cancers (Basel). 2018;10(10):387.
28. Monclair T, Brodeur GM, Ambros PF, Brisse HJ, Cecchetto G, Holmes K, et al. INRG task force. The international neuroblastoma risk group (INRG) staging system: an INRG Task force report. J Clin Oncol. 2009;27(2):298–303.
29. Qarziba (Dinutuximab beta): Summary of Product Characteristics (SmPC) [emc] (medicines.org.uk) [18/07/2022]. Available at: https://www.medicines.org.uk/emc/product/9441/smpc#UNDESIRABLE_EFFECTS. Accessed Oct 2022
30. HR-NBL-1.8 / SIOPEN (EudraCT number 2006-001489-17) Protocol. High Risk Neuroblastoma Study 1.8 of SIOP-Europe (SIOPEN). Available at: http://www.gruponeuroblastoma.es/que-hacemos_protocolos-de-diagnostico-y-tratamiento2
31. Gray J, Moreno L, Weston R, Barone G, Rubio A, Makin G, et al. 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. 2022;40(16 Suppl):10002.
32. Moreno L, Laidler J, Moroz V, Owens C, Rubié H, Berlanga P, et al. A randomised phase IIb trial of BEvACizumab added to Temozolomide ± IrinOtecan for children with refractory/relapsed Neuroblastoma—BEACON-neuroblastoma, a European Innovative Therapies for Children with Cancer (ITCC) - International Society of Paediatric Oncology Europe Neuroblastoma Group (SIOPEN) trial. J Clin Oncol. 2015;33(15):10082.
33. Barone G, Barry A, Bautista F, Brichard B, Defachelles AS, Herd F, et al. Managing adverse events associated with dinutuximab beta treatment in patients with high-risk neuroblastoma: practical guidance. Paediatr Drugs. 2021;23(6):537–48.
34. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 Published: 27 November 2017. U.S. Department of Health and Human Services, National Institutes of Health National Cancer Institute. Available at: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf
35. Keyel ME, Reynolds CP. Spotlight on dinutuximab in the treatment of high-risk neuroblastoma: development and place in therapy. Biologics. 2018;13:1–12.
36. Lammie G, Cheung N, Gerald W, Rosenblum M, Cordoncardo C. Ganglioside GD(2) expression in the human nervous-system and in neuroblastomas: an immunohistochemical study. Int J Oncol. 1993;3:909–15.
37. Lode H, Valteau-Couanet D, Gray J, Luksch R, Wieczorek A, Castel V, et al. Randomised use of Anti-GD2 antibody dinutuximab beta (DB) long-term infusion with and without subcutaneous interleukin-2 (scIL-2) in high-risk neuroblastoma patients with relapsed and refractory disease: results from the SIOPEN LTI trial. J Clin Oncol. 2019;37(15 Suppl):10014. https://doi.org/10.1200/JCO.2019.37.15_suppl.10014.
38. Brennan FR, Morton LD, Spindeldreher S, Kiessling A, Allenspach R, Hey A, et al. Safety and immunotoxicity assessment of immunomodulatory monoclonal antibodies. MAbs. 2010;2(3):233–55.
39. Papadakis V, Kelaidi C, Zisaki K, Antoniadi K. Dinutuximab beta-related severe neurotoxicity: resolution with the use of plasmapheresis. Pediatr Blood Cancer. 2022;69(4): e29465.
40. Wieczorek A, Manzitti C, Garaventa A, Gray J, Papadakis V, Valteau-Couanet D, et al. Clinical phenotype and management of severe neurotoxicity observed in patients with neuroblastoma treated with dinutuximab beta in clinical trials. Cancers (Basel). 2022;14(8):1919.
41. Blom T, Lurvink R, Aleven L, Mensink M, Wolfs T, Dierselhuis M, et al. Treatment-related toxicities during anti-GD2 immunotherapy in high-risk neuroblastoma patients. Front Oncol Patch. 2021;10: 601076.

Authors and Affiliations

Julia Balaguer[1] · Laura García Hidalgo[2] · Raquel Hladun[3] · Catalina Márquez Vega[4] · Vanesa Pérez Alonso[5]

✉ Vanesa Pérez Alonso
vperezah12o@outlook.es

[1] Pediatric Oncology and Hematology Unit, La Fe University Hospital, Valencia, Spain

[2] Pediatric Oncology Unit, Regional University Hospital of Malaga, Málaga, Spain

[3] Pediatric Oncology and Hematology Department, Vall d'Hebron University Hospital, Barcelona, Spain

[4] Pediatric Oncology Unit, Virgen del Rocío University Hospital, Sevilla, Spain

[5] Pediatric Oncology and Hematology Department, University Hospital 12 de Octubre, Madrid, Spain