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REVIEW

GM-CSF, G-CSF or no cytokine therapy with anti-GD2 immunotherapy for high-risk neuroblastoma

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Abstract

Colony-stimulating factors have been shown to improve anti-disialoganglioside 2 (anti-GD2) monoclonal antibody response in high-risk neuroblastoma by enhancing antibody-dependent cell-mediated cytotoxicity (ADCC). A substantial amount of research has focused on recombinant human granulocyte-macrophage colony-stimulating factor (GM-CSF) as an adjuvant to anti-GD2 monoclonal antibodies. There may be a disparity in care among patients as access to GM-CSF therapy and anti-GD2 monoclonal antibodies is not uniform. Only select countries have approved these agents for use, and even with regulatory approvals, access to these agents can be complex and cost prohibitive. This comprehensive review summarizes clinical data regarding efficacy and safety of GM-CSF, recombinant human granulocyte colony-stimulating factor (G-CSF) or no cytokine in combination with anti-GD2 monoclonal antibodies (ie, dinutuximab, dinutuximab beta or naxitamab) for immunotherapy of patients with high-risk neuroblastoma. A substantial body of clinical data support the immunotherapy combination of anti-GD2 monoclonal antibodies and GM-CSF. In contrast, clinical data supporting the use of G-CSF are limited. No formal comparison between GM-CSF, G-CSF and no cytokine has been identified. The treatment of high-risk neuroblastoma with anti-GD2 therapy plus GM-CSF is well established. Suboptimal efficacy outcomes with G-CSF raise concerns about its suitability as an alternative to GM-CSF as an adjuvant in immunotherapy for patients with high-risk neuroblastoma. While programs exist to facilitate obtaining GM-CSF and anti-GD2 monoclonal antibodies in regions where they are not commercially available, continued work is needed to ensure equitable therapeutic options are available globally.

KEYWORDS
anti-GD2 monoclonal antibody, cytokines, dinutuximab, dinutuximab beta, G-CSF, GM-CSF, immunotherapy, naxitamab, neuroblastoma, sargramostim

1 | INTRODUCTION

Neuroblastoma is the most common childhood extracranial solid tumor, accounting for ~10% of all cancer-related mortality in patients under 15 years old.[1,2] Approximately 90% of patients are diagnosed before 5 years of age, commonly between 1 and 2 years old.[1] While the overall 5-year relative survival rate has improved and is ~80%, prognosis varies widely based on risk classification.[1,3] Children with high-risk neuroblastoma (HR-NB) have a 5-year survival rate, at best, of ~60%.[1]

In HR-NB, anti-disialoganglioside 2 (anti-GD2) monoclonal antibodies (mAbs) have substantially improved outcomes such as preventing relapse for patients in remission and inducing responses in patients with relapsed disease.[4] Approvals and availability of these agents vary globally (Table 1). Anti-GD2 mAbs approved for clinical use include dinutuximab (Unituxin®), dinutuximab beta (Qarziba®) and naxitamab (Danyelza®).[5–7] Dinutuximab (ch14.18) and dinutuximab beta (ch14.18/CHO) are both human/mouse chimeric mAbs.[16] While dinutuximab is produced using mouse SP2/0 cells, dinutuximab beta is produced using Chinese hamster ovary cells.[16] Naxitamab (hu3F8) is a humanized mAb.

Exogenous cytokines, including recombinant human granulocyte-macrophage colony-stimulating factor (GM-CSF; sargramostim [Leukine®]) and interleukin-2 (IL-2), have been used extensively in clinical practice. GM-CSF accelerates bone marrow (BM) recovery after myelosuppression and BM-damaging exposures.[17] Both GM-CSF and IL-2 have been shown to improve antitumor response to anti-GD2 mAbs by stimulating neutrophils and natural killer (NK) cells, respectively, to enhance antibody-dependent cell-mediated cytotoxicity (ADCC).[18–26] The largest known cohort of patients ($n = 1183$) with HR-NB receiving post-consolidation/maintenance therapy with dinutuximab plus isotretinoin, IL-2 and GM-CSF (sargramostim) demonstrated a 5-year event-free survival (EFS) of 61% and overall survival (OS) of 72%.[27]

The United States Food and Drug Administration (FDA) granted approval for dinutuximab with IL-2, GM-CSF and isotretinoin for pediatric patients with HR-NB who achieve at least a partial response to prior first-line multiagent, multimodality therapy (ie, post-consolidation/maintenance setting).[5] The European Medicines Agency (EMA) approved dinutuximab beta in conjunction with IL-2 (without GM-CSF) for HR-NB patients for a similar indication, and for patients with relapsed/refractory neuroblastoma with or without residual disease.[7] Recent data showed less toxicity with similar survival when dinutuximab beta was used alone vs with IL-2.[1,28–30] These data resulted in removal of IL-2 as an adjuvant from International Society of Pediatric Oncology Europe Neuroblastoma (SIOPEN) and Children's Oncology Group (COG) protocols (Table 1).[1] Most recently, FDA granted approval for naxitamab in combination with GM-CSF for patients with relapsed/refractory HR-NB in the bone/BM compartment who have achieved at least stable disease with prior therapy.[6]

Due to limited GM-CSF availability outside the United States, recombinant human granulocyte colony-stimulating factor (G-CSF; filgrastim [Neupogen®], pegfilgrastim [Neulasta®] and their biosimilars) has been proposed as an alternative adjuvant to anti-GD2 mAb treatment.[31] While G-CSF is also a hematopoietic growth factor, there are limited data exploring efficacy and safety as an adjuvant to anti-GD2 mAbs. No neuroblastoma clinical studies comparing G-CSF and GM-CSF as adjuvants exist. Furthermore, there are considerable differences between G-CSF and GM-CSF with regard to structure, receptors/receptor distribution and biologic effects important in neuroblastoma tumorigenesis (Table 2).[17] For example, GM-CSF induces differentiation to anti-tumor proinflammatory Type 1 dendritic cells (DC1) while G-CSF induces differentiation to immunosuppressive Type 2 dendritic cells (DC2).[48,54] Although not in neuroblastoma, the few prospective studies specifically comparing GM-CSF (sargramostim) and G-CSF therapy showed similar toxicity profiles between the two products.[57–59] For dinutuximab beta, no cytokines are recommended for patients who achieved complete response after first-line therapy.[7] No formal comparison between GM-CSF and no cytokines has been identified. Limited and/or cost-prohibitive access to GM-CSF as well as anti-GD2 mAbs sets up a global disparity in neuroblastoma care that must be addressed without compromising patient outcomes. Herein, we summarize clinical data regarding efficacy and safety of GM-CSF, G-CSF or no cytokines with anti-GD2 mAbs in the treatment of HR-NB.

2 | METHODS

EMBASE was searched to identify clinical studies published in English (inception-December 14, 2022) evaluating efficacy and/or safety of anti-GD2 mAbs in combination with either GM-CSF or G-CSF in patients with HR-NB. A separate EMBASE search was performed to identify clinical studies evaluating efficacy and/or safety of dinutuximab beta without cytokine use. Search string details are available in Supplemental Methods in Data S1. Additional studies found during literature review were also considered. Studies of commercially available anti-GD2 mAbs listed as phase 2 or later or with at least 30 patients are detailed in this review. Table S2 summarizes phase 1 studies and/or studies that enrolled <30 patients.

In recognition that disease state and study outcome terms are defined per individual study methods, study summaries within this review strived to present terms as they appeared in the original source. For example, there are mentions of either EFS or PFS (progression-free survival) based on the original study data presentation. In addition, relapsed disease or refractory disease have specific definitions per individual study (see Table S1).

3 | ANTI-GD2 MONOCLONAL ANTIBODIES

Dinutuximab (ch14.18), the first marketed anti-GD2 mAb, was FDA approved in 2015.[5] It is used in the post-consolidation/maintenance phase in combination with isotretinoin and GM-CSF.[1,5] Naxitamab (hu3F8), combined with GM-CSF, received accelerated FDA-approval in 2020 for patients with relapsed/refractory HR-NB with osteomedullary disease.[6] As a humanized mAb, naxitamab was designed, in part, to have lower immunogenicity than chimeric mAb dinutuximab.[60]

TABLE 1 Characteristics of approved anti-GD2 monoclonal antibodies.

Characteristic	Dinutuximab (Unituxin®)[5]	Naxitamab-gqgk (Danyelza®)[6]	Dinutuximab beta (Qarziba®)[7]
Other name	ch14.18	hu3F8	ch14.18/CHO
mAb origin	Human/mouse chimeric	Humanized	Human/mouse chimeric produced in CHO
Initial market availability	2015 (US)	2020 (US)	2017 (Europe)
Markets where currently approved	Canada[8] Japan[9] US[5]	China[10] Israel[11] US[6]	Australia[12] Brazil[13] China[14] Europe[7] Israel[15]
Place in therapy studied in Registration Trial(s)	Post-consolidation/ maintenance phase of multimodal therapy for HR-NB	Treatment of relapsed/refractory HR-NB confined to bone/BM only	Post-consolidation/ maintenance phase of multimodal therapy for HR-NB Treatment of relapsed/ refractory neuroblastoma with or without residual disease
Concomitant agents in Registration Trials(s)	rhu GM-CSF, IL-2 and isotretinoin	rhu GM-CSF	Isotretinoin with or without IL-2
Most common adverse reactions per prescribing information (≥40%)[a,b,c]	Dinutuximab plus rhu GM-CSF, IL-2 and isotretinoin • Pain • Pyrexia • Thrombocytopenia • Lymphopenia • Infusion reactions • Hypotension • Hyponatremia • Increased alanine aminotransferase • Anemia • Vomiting • Diarrhea • Hypokalemia • Capillary leak syndrome	Naxitamab plus rhu GM-CSF • Infusion-related reaction • Pain • Tachycardia • Vomiting • Cough • Nausea • Diarrhea • Decreased appetite • Hypertension • Fatigue	Dinutuximab beta plus isotretinoin with or without IL-2 • Pyrexia • Pain despite analgesic treatment • Hypersensitivity • Vomiting • Diarrhea • Capillary leak syndrome • Anemia • Neutropenia • Thrombocytopenia • Hypotension
Inclusion in COG/SIOPEN Protocols	COG: part of immunotherapy during post-consolidation/ maintenance phase (eg, NCT04385277) COG: part of immunotherapy in combination with chemotherapy in relapsed/refractory treatment (eg, NCT03794349)	Not included to date	SIOPEN: part of immunotherapy during post-consolidation/ maintenance phase (eg, NCT04221035)
Other places in neuroblastoma therapy under investigation	Induction phase Relapsed/refractory	Consolidation phase	None identified

Abbreviations: BM, bone marrow; CHO, Chinese hamster ovary; COG, Children's Oncology Group; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; HR-NB, high-risk neuroblastoma; IL-2, interleukin-2; mAb, monoclonal antibody; rhu, recombinant human; SIOPEN, International Society of Pediatric Oncology Europe Neuroblastoma; US, the United States.

[a]Most common adverse reactions in dinutuximab and naxitamab product information included those occurring in ≥25% of patients, while dinutuximab beta listed most common/frequent adverse reactions occurring ≥40% of patients. Accordingly, most common adverse reactions in this table were limited to those occurring in ≥40% of patients based on available information in each respective product information.

[b]Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials for a drug cannot be directly compared to rates in clinical trials for another drug and may not reflect the rates observed in practice.

[c]For naxitamab, the adverse reaction was listed if it occurred in ≥40% in either registration trial (Trial 201 or Trial 12-230).

Dinutuximab beta (ch14.18/CHO), was first approved in 2017 in Europe.[7] Current protocols for dinutuximab beta do not include concomitant cytokines.[1] Despite available evidence showing improved outcomes with GM-CSF as an adjuvant with dinutuximab,[19] registration trials for dinutuximab beta did not include GM-CSF due to unavailability in Europe.[7,29] To date, there are no data available in which dinutuximab beta was given with GM-CSF. Table 1 compares characteristics of dinutuximab, dinutuximab beta and naxitamab.

TABLE 2 Comparison of biological properties GM-CSF and G-CSF.

Characteristic	GM-CSF	G-CSF
Structure	Single soluble isoform of 127 amino acids weighing 22 kDa with two intrachain disulfide bonds and two potential N-linked glycosylation sites[32]	Expressed in two isoforms (177 and 174 amino acids) weighing 21 kDa, with two interchain disulfide bonds and one O-linked glycosylation site[32]
Receptor	CD116[32]	CD114[32]
Receptor distribution	Neutrophils, basophils, eosinophils, monocytes/macrophages, dendritic cells[32,33]	Neutrophils, myeloid BM precursor cells[33,34]
Stimulates growth and differentiation	Neutrophils and macrophages[32]	Neutrophils[32]
Summary of biological effects on each cell type	Neutrophils* • Improves neutrophil survival[33] • Induces neutrophil cytokine production[33] • Regulates or inhibits neutrophil chemotaxis[35–37] • Inhibits neutrophil transendothelial migration[38–40] • Induces neutrophil degranulation[33] • Regulates neutrophil surface phenotypic expression[33] • Modulates neutrophil reaction to secondary stimuli[33] Macrophages* • Maintains macrophage survival[33] • Stimulates phagocytosis by macrophages[41] • Regulates macrophage cytokine release (appropriate immune response)[33,42] • Maintains pulmonary homeostasis via alveolar macrophage immune functions[43] • Regulates intestinal macrophages[44] Eosinophils* • Promotes eosinophil development[33] • Improves eosinophil survival[33] • Augments eosinophil phagocytosis[33] • Primes eosinophils for chemotaxis and degranulation[33] Basophils* • Improves basophil survival[45] Dendritic cells* • Promotes dendritic cell development[33] • Increases MHC-II expression[46,47] • Promotes differentiation of antitumor proinflammatory Type I dendritic cells[48,49] T cells • Stimulates CD8+ T cell anti-tumor immunity[50] *Contributes to host defense against bacterial, viral, fungal and parasitic infections via all these cell types[32,51]	Neutrophils • Stimulates phagocytosis by neutrophils[32] • Stimulates neutrophil chemotaxis[32] • Promotes neutrophil transendothelial migration[38] • Regulates neutrophil ADCC against tumor cells[32] • Increases neutrophil production of reactive oxygen intermediates[32] • Increases neutrophil expression of C3b receptor[32] • Promotes neutrophil release of arachidonic acid and myeloperoxidase[32] • Primes neutrophils for NETosis[52] Dendritic cells • Impairs dendritic cell development[53] • Decreases expression of HLA-DR[53] • Promotes differentiation of immunosuppressive Type 2 dendritic cell differentiation[49,54] T cells • Impairs CD8+ T cell functionality[55]
Synergism with anti-GD2 monoclonal antibodies	• In vitro rhu GM-CSF increased 3F8-mediated ADCC by >93%[21] • 3F8-mediated ADCC was augmented when assay performed in presence of rhu GM-CSF[22] • In vitro rhu GM-CSF enhancement of 3F8-mediated ADCC correlated with increased CD11/CD18 expression[24] • In vitro rhu GM-CSF enhanced ch14.18-mediated ADCC[20] • 14.18 mediated cytotoxicity enhanced with rhu GM-CSF pretreatment[23]	• In vivo rhu G-CSF enhanced tumor growth suppression with 220-551[56] • In vitro and in vivo rhu G-CSF enhanced neutrophil mediated ADCC with dinutuximab[31]

Abbreviations: ADCC, antibody-dependent cell-mediated cytotoxicity; BM, bone marrow; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; HLA, human leukocyte antigen; MHC, major histocompatibility complex; NETosis, formation of neutrophil extracellular traps; rhu, recombinant human.

3.1 | Mechanism of action

Targeting GD2, the major disialoganglioside expressed on neuroblastoma cells, was the foundation for one of the most significant advancements in immunotherapy for neuroblastoma.[4] Anti-GD2 mAbs promote neuroblastoma cell cytotoxicity via several pathways (Figure 1). ADCC involves immune effector cells, such as neutrophils, macrophages and NK cells.[20,63,69,70] In vitro, neutrophils did not

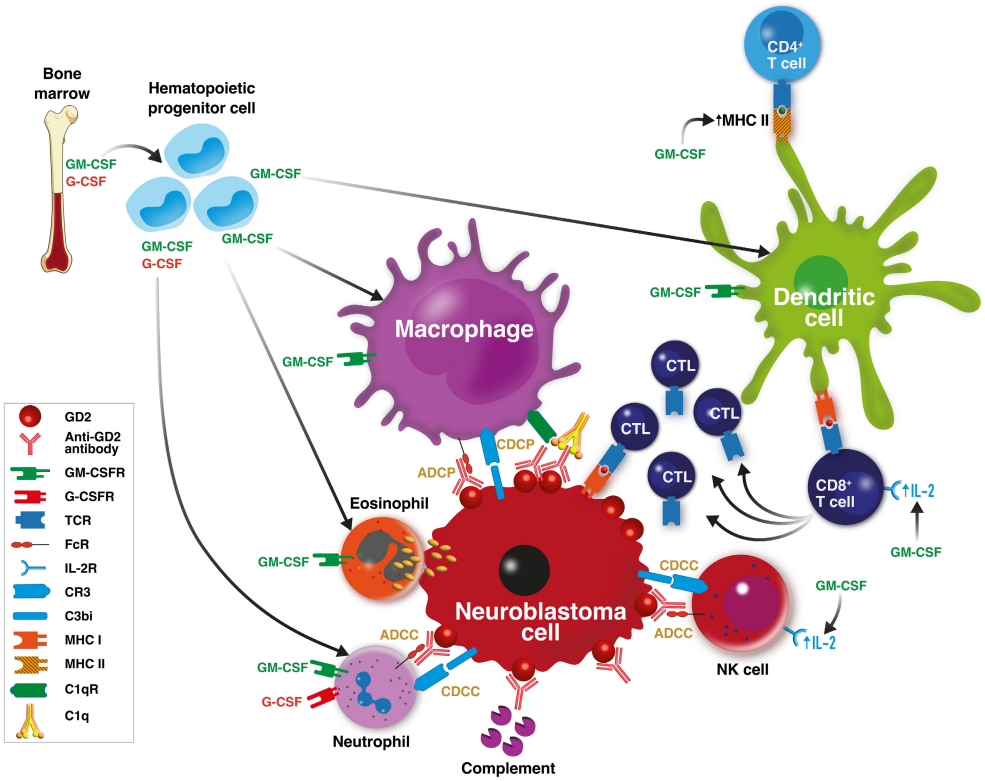

FIGURE 1 GM-CSF, G-CSF and anti-GD2 immunotherapy exerting effects via "cell-mediated killing" on neuroblastoma cells. Anti-GD2 monoclonal antibodies promote neuroblastoma cell cytotoxicity via neutrophil-mediated antibody-dependent cell-mediated cytotoxicity (ADCC), natural killer (NK) cell-mediated ADCC, macrophage-mediated antibody-dependent cell-mediated phagocytosis (ADCP), complement-mediated cytotoxicity and direct interaction with the neuroblastoma cell.[5–7,18,61,62] Complement-dependent cell-mediated cytotoxicity (CDCC) or phagocytosis (CDCP) are additional pathways potentially enhanced by anti-GD2 monoclonal antibodies.[62] Granulocyte-macrophage colony-stimulating factor (GM-CSF) stimulates neutrophils and macrophages directly through GM-CSF receptors (GM-CSFR), enhancing neutrophil-mediated ADCC and macrophage-mediated ADCP.[17,18,46,62–64] GM-CSF is required in multiple differentiation steps of the hematopoietic cascade to increase numbers of myeloid-derived cells in circulation and tissues, including neutrophils, macrophages, dendritic cells and eosinophils.[17] In addition, GM-CSF stimulates increases in major histocompatibility complex class II (MHC II) expression which could lead to enhanced tumor antigen presentation on dendritic cells and T cell-mediated anti-tumor effects.[46,47] There is also evidence GM-CSF increases soluble IL-2 receptor levels, which could possibly enhance T cell and NK cell pathways.[65] Finally, GM-CSF stimulates eosinophils, and some eosinophils have been found to enhance anti-tumor immune response,[66–68] although this effect has not been observed specifically in neuroblastoma. In contrast, granulocyte colony-stimulating factor (G-CSF) acts primarily via neutrophil effects and does not increase dendritic cell numbers or enhance NK- or T cell-mediated cytotoxicity effects.[17] There are additional activating accessory receptors (eg, CD11b/CD18, NKG2 receptors, etc) involved in these interactions not represented in the figure. ADCC, antibody-dependent cell-mediated cytotoxicity; ADCP, antibody-dependent cell-mediated phagocytosis; CDCC, complement-dependent cell-mediated cytotoxicity; CDCP, complement-dependent cell-mediated phagocytosis; CTL, cytotoxic T lymphocyte; FcR, Fc receptor; GD2, disialoganglioside 2; G-CSF, granulocyte colony-stimulating factor; G-CSFR, granulocyte colony-stimulating factor receptor; GM-CSF, granulocyte-macrophage colony-stimulating factor; GM-CSFR, granulocyte-macrophage colony-stimulating factor receptor; IL-2, interleukin 2; IL-2R, interleukin 2 receptor; MHC, major histocompatibility complex; NK, natural killer; TCR, T cell receptor.

directly kill neuroblastoma cells and required ch14.18 antibody binding.[23] Dinutuximab, dinutuximab beta and naxitamab bind to cell surface GD2 and regulate complement-mediated cytotoxicity and neutrophil- and NK-cell-mediated ADCC of neuroblastoma cells.[5–7,18,20–22,60,71] Recent data show interaction of GD2 with Siglec-7 (sialic acid-binding immunoglobulin-like lectin 7), which is expressed on human macrophages and NK cells, resulting in suppression of immune cell activity (eg, "don't eat me" signal).[61,72] Anti-GD2 mAbs interrupt the GD2:siglec-7 interaction and, when combined with CD47 blockade, shift toward an "eat me" signal and recruit tumor-associated macrophages (TAMs) of the immunostimulatory M1 type to increase neuroblastoma cell susceptibility to macrophage-mediated antibody-dependent cellular phagocytosis (ADCP).[18,61,62] Anti-GD2 mAbs may also induce neuroblastoma cell death through direct killing.[61,71] There are known differences in the killing potency via ADCC, ADCP and complement-mediated cytotoxicity among different anti-GD2 mAbs.[62]

Enhancing effector cell populations increases anti-GD2 mAb cytotoxicity.[18,71] IL-2 and GM-CSF have been widely used to increase number and function of effector cells.[73] IL-2 was historically a common component of HR-NB immunotherapy to modulate NK cell-mediated cytotoxicity[1,25,26]; however, more recent clinical data

showing increased toxicity with no efficacy difference led to removal of IL-2 from protocols.[1,28–30] Of note, GM-CSF induces a sustained and sufficient activation of the endogenous IL-2 system in patients with HR-NB,[65] potentially enhancing NK cell-mediated neuroblastoma cytotoxicity without the added toxicity of exogenous IL-2. Because of its pleiotropic effects on NK cells and T cells, IL-15 is being investigated as a substitute for IL-2.[62,74] Significant in vitro and in vivo (mice) neuroblastoma tumor regression has been observed with IL-15, but to our knowledge to date there are no clinical data using IL-15 with anti-GD2 mAbs in pediatric high-risk neuroblastoma.

4 | GM-CSF IN COMBINATION WITH ANTI-GD2 MONOCLONAL ANTIBODIES

4.1 | Preclinical/translational GM-CSF data

GM-CSF promotes neuroblastoma cell cytotoxicity via several pathways (Figure 1). By stimulating neutrophil production and activation, GM-CSF enhances anti-GD2 mAb-mediated ADCC of neuroblastoma cells (Table 2).[17] GM-CSF signaling is required in several hematopoietic differentiation steps to increase numbers of myeloid-derived cells, including neutrophils, macrophages, dendritic cells and eosinophils.[17] Neuroblastoma cells are efficiently phagocytosed by activated monocyte-macrophages,[63] and GM-CSF increases macrophage numbers and induces the immunostimulatory M1 TAMs enhancing macrophage-mediated ADCP.[17,46,62,64] GM-CSF has been shown to increase adhesion molecules on polymorphonuclear neutrophils to enhance ADCC when added to anti-GD2 mAbs.[24,75] GM-CSF also stimulates increases in major histocompatibility complex class II (MHC II) expression, potentially enhancing tumor antigen presentation on dendritic cells and T cell-mediated antitumor effects.[46] Some evidence shows GM-CSF increases soluble IL-2 receptor levels,[65] which could possibly boost T cell and NK cell pathways. GM-CSF signaling activates anti-tumor response of some eosinophils in mice, although this effect has not been specifically observed with neuroblastoma.[66–68] Notably for neuroblastoma tumorigenesis, DC1 induction[48,49] and CD8+ T cell antitumor immunity promotion[50] by GM-CSF (Table 2) may be especially important because neuroblastoma cells potently inhibit dendritic cell generation, migration and function,[76–78] and a higher risk of progression and death has been correlated to low CD8+ and other T cell numbers in patients with neuroblastoma.[79]

4.2 | Clinical data

Early data with murine anti-GD2 mAb 3F8 (predecessor to hu3F8, ie, naxitamab) demonstrated improved patient outcomes with GM-CSF as an adjuvant. This effect was attributed to increased granulocyte activation as measured by expression of CBRM1/5 (activation epitope of granulocyte activation marker CD11b).[69,80] In this study, increased expression of CBRM1/5 was found to be greater with subcutaneous administration vs intravenous.[69] Since then, GM-CSF has been studied extensively in combination with anti-GD2 mAbs in patients with neuroblastoma (Tables 3, 4, S2 and S3). Although other GM-CSF products have been developed (eg, molgramostim, regramostim), sargramostim is currently the only GM-CSF product commercially available (FDA-approved in the United States) with global availability via a named patient program.[95,96] Sargramostim was used in all registration trials supporting FDA-approval of dinutuximab and naxitamab, and accordingly, both are indicated in combination with GM-CSF.[19,88,90] Moreover, current COG standard immunotherapy for HR-NB recommends the combination of dinutuximab with GM-CSF 250 mcg/m^2.[1,19,65] Based on preclinical findings demonstrating greater anti-tumor efficacy using higher GM-CSF doses,[21] Memorial Sloan Kettering Cancer Center uniquely employs GM-CSF at 500 mcg/m^2 in the clinical setting when used with dinutuximab and naxitamab.

In addition to its standard use in post-consolidation/maintenance phase therapy, dinutuximab combined with GM-CSF has been studied in various HR-NB treatment phases (Table 3). Five-year EFS was 57% for patients who received post-consolidation/maintenance therapy with dinutuximab plus sargramostim, IL-2 and isotretinoin in the long-term follow-up of the registration trial,[19,65] compared to 46% for patients randomized to isotretinoin only ($P = .042$). Data from the non-randomized extension of the registration trial demonstrated lower grade 3–4 hematologic adverse events in sargramostim cycles vs IL-2 cycles.[27] Other studies demonstrated the benefit of adding dinutuximab plus sargramostim to chemotherapy for relapsed/refractory HR-NB,[82,84,85] including patients previously treated with anti-GD2 therapy.[84,85] A more recent study explored earlier use of dinutuximab with GM-CSF as part of induction therapy in HR-NB and showed promising end-of-induction objective response rates of up to 87%.[87] Additional dinutuximab studies are summarized in Table S2.

Initial approval for naxitamab combined with GM-CSF was based on preliminary data showing overall response rate (ORR; 34%–45%) and duration of response (>6 months for 23%–30% of patients) from two ongoing, single-arm studies conducted in patients with relapsed/refractory HR-NB confined to bone/BM, Trial 201 and Trial 12-230 (Table 4).[6] The most recent data from these two trials continue to demonstrate ORR of 40%–50%, with reported ORR as high as 84% in the subgroup of patients with primary refractory neuroblastoma.[88,89] In another study (HITS protocol; hu3F8, irinotecan, temozolomide, sargramostim), resistant, heavily pretreated patients experienced promising objective responses to naxitamab plus sargramostim combined with chemotherapy (Table 4).[91] Recently, early salvage therapy with the HITS protocol led to significantly longer survival than late salvage with HITS in primary refractory HR-NB (3-year OS 85% vs 29%; $P = .0037$) (Table 4).[92] Although it is not currently approved as part of the initial multimodality regimen for HR-NB, data from a compassionate use, expanded access program demonstrated a 5-year EFS of 58% with adding naxitamab plus sargramostim into the consolidation phase for patients with HR-NB in first complete response after chemotherapy induction (Table 4).[93]

Additionally, GM-CSF is an integral part of widely used combination chemotherapy and anti-GD2 mAb regimens.[84,85,91,92] Furthermore,

TABLE 3 GM-CSF in combination with dinutuximab (ch14.18) for neuroblastoma.

Authors/study identifier	Design/patient population	Treatment	Efficacy outcomes	Safety	Comments
Post-consolidation/maintenance phase – FDA-approved indication					
Yu et al (2010)[19] Yu et al (2021)[65] NCT00026312[a]	Phase 3, prospective, RCT HR-NB, $N = 226$ Patients with biopsy-proven persistent disease were ineligible for randomization	*Post consolidation* Isotretinoin alone ($n = 113$) vs isotretinoin plus dinutuximab with alternating cycles of sargramostim and IL-2 ($n = 113$) 28-day cycles × 6 cycles Sargramostim dose 250 mcg/m^2/day[b]	*Dinutuximab + sargramostim/IL-2 with isotretinoin vs isotretinoin* Survival • 5-year EFS 57% ± 5% with din + sargramostim/IL-2 vs 46% ± 5% without din + sargramostim/IL-2 ($P = .042$) • 5-year OS 73% ± 4% with din + sargramostim/IL-2 vs 57% ± 5% without din + sargramostim/IL-2 ($P = .045$)	*Dinutuximab + sargramostim/IL-2 with isotretinoin vs isotretinoin* Grade 3–4 AEs (≥10% in either group) • Neuropathic pain (52% vs 6%) • Infection, any (39% vs 22%) • Fever without neutropenia (39% vs 6%) • Hypokalemia (35% vs 2%) • Hypersensitivity reaction (25% vs 1%) • Hyponatremia (23% vs 4%) • Abnormal ALT (23% vs 3%) • Acute capillary leak syndrome (23% vs 0%) • Hypotension (18% vs 0%) • Infection, catheter-related (13% vs 7%) • Hypoxia (13% vs 2%) • Diarrhea (13% vs 1%) • Urticaria (13% vs 0%) • Abnormal AST (10% vs 0%) One grade 5 event occurred (capillary leak syndrome due to IL-2 overdose)	Dinutuximab + sargramostim/IL-2 with isotretinoin as post-consolidation provided superior EFS and OS which was sustained through 5-year follow-up Incidence of grade 3–4 AE was greater with dinutuximab + sargramostim/IL-2
Desai et al (2022)[27] Non-randomized expansion of NCT00026312	Phase 3, nonrandomized, prospective, single-arm study HR-NB, $N = 1183$	*Post-consolidation* Isotretinoin plus dinutuximab with alternating cycles of sargramostim and IL-2 28-day cycles × 6 cycles Sargramostim dose 250 mcg/m^2/day[b]	*Dinutuximab + sargramostim/IL-2 with isotretinoin* Survival • 5-year EFS 61% ± 2% • 5-year OS 72% ± 2%	*Sargramostim vs IL-2 cycles* Grade 3–4 AEs different between cytokine cycles ($P < .05$) • Pain (28% vs 18%) • Anemia (19% vs 22%) • Fever (16% vs 34%) • Platelet count decreased (14% vs 17%) • Hypokalemia (13% vs 25%) • Allergic/hypersensitivity reaction (12% vs 21%) • Lymphocyte count decreased (12% vs 16%) • Hypotension (9% vs 14%)	Other than pain, grade 3–4 toxicities including hematologic AEs occurred more often during IL-2 cycles than sargramostim cycles

TABLE 3 (Continued)

Authors/study identifier	Design/patient population	Treatment	Efficacy outcomes	Safety	Comments
				• Neutrophil count decreased (7% vs 16%) • Capillary leak syndrome (5% vs 11%) • Creatinine increased (0.3% vs 1.3%) • Eye disorders (0.2% vs 0.7%)	
Ozkaynak et al (2018)[81] NCT01041638[c]	Phase 3 single-arm, safety trial HR-NB, $N = 105$	*Post-consolidation* Isotretinoin plus dinutuximab with alternating cycles of sargramostim and IL-2 28-day cycles × 6 cycles Sargramostim dose 250 mcg/m^2/day SQ (strongly recommended) or IV	*Dinutuximab + sargramostim/IL-2 with isotretinoin* Survival • 3-year EFS 68% ± 5% • 3-year OS 79% ± 4%	*Sargramostim (c1/3/5) vs IL-2 (c2/4) cycles* Grade 3–4 AEs by cytokine cycle (c1/3/5 vs c2/4, respectively) • Pain (41%/22%/24% vs 28%/31%) • Fever (21%/6%/5% vs 59%/32%) • Hypotension (10%/4%/8% vs 17%/14%) • Allergic reactions (3%/5%/2% vs 10%/7%) • Capillary leak syndrome (1%/0%/0% vs 4%/2%) One grade 5 event occurred (cardiac arrest)	Other than pain in c1 (sargramostim-containing cycle), grade 3–4 clinical toxicities were observed more frequently in IL-2-containing cycles than sargramostim-containing cycles, although these differences were not statistically significant
Relapsed/refractory[d] *treatment – Investigational regimens*					
Mody et al (2017)[82] NCT01767194	Phase 2, prospective, open-label, randomized trial RR-NB[d] (no prior treatment for RR), $N = 35$ • Refractory, $n = 16$ • Relapsed, $n = 19$ Patients with BM only disease were ineligible	*First-line relapsed/refractory*: Temozolomide/irinotecan plus either temsirolimus ($n = 18$) or dinutuximab + sargramostim ($n = 17$) 21-day cycles for up to 17 cycles Sargramostim dose 250 mcg/m^2/day SQ	*Dinutuximab + sargramostim vs temsirolimus arm* Overall objective response (INRC v1993[83]) • CR 29% for din/sargramostim vs 0% for temsir • PR 24% for din/sargramostim vs 6% for temsir Refractory ($n = 8$ vs $n = 8$) • CR 38% for din/sargramostim vs 0% for temsir • PR 13% for din/sargramostim vs 0% for temsir Relapsed ($n = 9$ vs $n = 10$) • CR 22% for din/sargramostim vs 0% for temsir	*Dinutuximab + sargramostim vs temsirolimus arm* Grade 3–4 TRAE (≥10% in either group) • Pain (44% vs 6%) • Hypokalemia (38% vs 22%) • Neutropenia (25% vs 44%) • Anemia (25% vs 33%) • Thrombocytopenia (25% vs 28%) • Fever/infection (25%[e] vs 11%) • Hypoxia (25% vs 0%) • Dehydration (19% vs 17%) • Vomiting (19% vs 11%) • Hyponatremia (19% vs 0%) • Hypotension (13% vs 0%)	In relapsed/refractory setting, temozolomide/irinotecan plus dinutuximab + sargramostim showed notable antitumor activity per the authors In the dinutuximab + sargramostim group, objective responses were observed in patients with MYCN amplified disease, previous HCT and previous treatment with anti-GD2 mAb Capillary leak syndrome was not reported in any patients

(Continues)

TABLE 3 (Continued)

Authors/study identifier	Design/patient population	Treatment	Efficacy outcomes	Safety	Comments
			• PR 33% for din/sargramostim vs 10% for temsir Survival • 1-year PFS 77% (95% CI: 56%–97%) for din/sargramostim vs 25% (95% CI: 0.4%–49%) for temsir • 1-year OS 88% (95% CI: 72%–100%) for din/sargramostim vs 65% (95% CI: 41%–87%) for temsir	• ALT increased (6% vs 28%) • Diarrhea (6% vs 11%) • Febrile neutropenia (0% vs 17%) • Mucositis (0% vs 11%)	
Mody et al (2020)[84] Nonrandomized expansion of NCT01767194	Nonrandomized expansion of dinutuximab/sargramostim arm of phase 2 randomized trial RR-NB[d] (no prior treatment for RR), $N = 36$ • Refractory, $n = 23$ • Relapsed, $n = 13$ Patients with BM only disease were ineligible	*First-line relapsed/refractory*: Temozolomide/irinotecan plus dinutuximab/sargramostim 21-day cycles for up to 17 cycles Sargramostim dose 250 mcg/m^2/day SQ	*Dinutuximab + sargramostim with chemotherapy* Overall objective response (INRC v1993[83]) in nonrandomized expansion ($n = 36$) • CR 17% • PR 19% Refractory ($n = 23$) • ORR 26% Relapsed ($n = 13$) • ORR 54% Survival in combined patients from randomized trial[82] and nonrandomized expansion ($N = 53$) • 1-year PFS 68 ± 6% • 1-year OS 85 ± 5%	*Dinutuximab + sargramostim with chemotherapy* Grade 3–4 TRAE in combined patients from randomized trial and nonrandomized expansion ($N = 53$) • Fever/infection (35%[e]) • Neutropenia (33%) • Pain (29%) • Diarrhea (20%) • Thrombocytopenia (10%) • Vomiting (8%)	In relapsed/refractory setting, dinutuximab + sargramostim with chemotherapy resulted in an ORR >40% in ITT analysis of randomized trial + nonrandomized expansion patients Objective responses observed in 61% patients who had previous AHCT and 64% with prior anti-GD2 therapy
Lerman et al (2022)[85]	Retrospective, multicenter study of off-study temozolomide/irinotecan + dinutuximab/GM-CSF treatment Relapsed[d] HR-NB, $N = 146$ (primary refractory disease excluded)	*Relapsed or progressive HR-NB after standard frontline therapy*: Temozolomide/irinotecan plus dinutuximab/GM-CSF Received at least one 21-day cycle GM-CSF dose 250 mcg/m^2/day SQ	*Dinutuximab + GM-CSF with chemotherapy* Overall objective response (INRC v2017[86]) • ORR 49% • CR 29% • PR 15% • MR 5% Survival • 1-year PFS 51% • 2-year PFS 28%	*Dinutuximab + GM-CSF with chemotherapy* Discontinuation due to acute or chronic toxicity 13% Patients received a median of 3 cycles (range, 1–15 cycles) before discontinuing due to toxicity	Acknowledging evolution of INRC, objective responses in this real-world setting still appear consistent with prior prospective studies Patients with objective responses more likely to have prior anti-GD2 therapy (65% vs 47%, $P = .03$) in a univariate analysis

TABLE 3 (Continued)

Authors/study identifier	Design/patient population	Treatment	Efficacy outcomes	Safety	Comments
Induction phase – Investigational regimen					
Federico et al (2022)[87] NCT03786783	Prospective, single-arm, pilot study Newly diagnosed HR-NB, $N = 42$	*Induction*: COG induction chemotherapy[f] plus dinutuximab/ sargramostim Sargramostim dose 250 mcg/m^2/ day SQ	*Dinutuximab + sargramostim with standard induction chemotherapy* EOI objective response (revised INRC; $n = 38$ completed EOI evaluation) • EOI objective response 87% • EOI CR 29% • EOI PR 58% • EOI MR 0%	*Dinutuximab + sargramostim with standard induction chemotherapy* Grade >3 TRAE • Fever (31%) • Pain (10%)	Induction with chemotherapy plus dinutuximab/ sargramostim was deemed tolerable and feasible with promising EOI objective response rate Induction regimen being investigated in phase 3 trial

Abbreviations: AE, adverse event; AHCT, autologous hematopoietic cell transplant; ALT, alanine aminotransferase; AST, aspartate aminotransferase; c, cycle; COG, Children's Oncology Group; CR, complete response; din, dinutuximab; EFS, event-free survival; EOI, end of induction; GM-CSF, recombinant human granulocyte-macrophage colony-stimulating factor; HCT, hematopoietic cell transplant; HR, high-risk; IL, interleukin; INRC, International Neuroblastoma Response Classification; ITT, intention-to-treat; IV, intravenous; mo, month; mAb, monoclonal antibody; MR, minor response; NB, neuroblastoma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; RCT, randomized controlled trial; RR, relapsed/refractory; SQ, subcutaneous; temsir, temsirolimus; TRAE, treatment-related adverse event.

[a]Registration trial.

[b]Route not specified.

[c]FDA required safety data in follow up to NCT00026312.

[d]In general, relapsed disease refers to recurrence after initial response to treatment while refractory disease refers to inadequate response to treatment, but individual study definitions for these subgroups vary. When data for relapsed and refractory subgroups were available, they were included in the table. Individual study definitions for relapsed neuroblastoma and refractory neuroblastoma are described in Table S1 as available.

[e]In Mody et al (2017), fever/infection was reported in 4 of 16 (25%) patients in the dinutuximab + sargramostim arm. In the subsequent study publication (Mody et al, 2020) including the same group of patients, fever/infection was reported in 6 of 16 (37.5%) in this same arm.

[f]Details of induction chemotherapy regimen not specified.

TABLE 4 GM-CSF in combination with naxitamab (hu3F8) for neuroblastoma.

Authors/study identifier(s)	Design/patient population	Treatment	Efficacy outcomes	Safety	Comments
Relapsed/refractory[a] *treatment – FDA-approved indication*					
Mora et al (2022)[88] NCT03363373 Study 201[b]	Phase 2, multicenter, single-arm trial (ongoing) RR-NB[a] with residual disease in bone/BM Interim analysis • Efficacy, $n = 52$ ○ Primary refractory, $n = 26$ ○ Incomplete response to salvage therapy (Relapsed), $n = 26$ • Safety, $n = 74$ Data cut-off December 31, 2021	*Relapsed/refractory NB*: Naxitamab plus sargramostim 4-week cycles until CR/PR followed by 5 more cycles; Subsequent 8-week cycles per investigator discretion through 101 weeks Sargramostim dose 250 mcg/m^2/day SQ × 5 days, then 500 mcg/m^2/day SQ × 5 days of each cycle	*Naxitamab + sargramostim (Data cut-off December 31, 2021)* Overall objective response (INRC v2017[86]) in patients with evaluable disease in bone/BM per radiology ($n = 52$) • ORR 50% (95% CI: 36%–64%) • CR 39% (95% CI: 25%–53%) Primary refractory ($n = 26$) • ORR 58% • CR 46% Incomplete response to salvage therapy (Relapsed, $n = 26$) • ORR 42% • CR 31%	*Naxitamab + sargramostim (Data cut-off December 31, 2021)* Grade 3–4 TRAE (≥10%; $n = 74$) • Hypotension (60%) • Pain (54%) • Urticaria (19%) • Bronchospasm (18%) • Abdominal pain (16%) • Hypoxia (11%) • Neutropenia (11%)	In RR-NB with residual disease in bone/BM, naxitamab + sargramostim resulted in ORR of 50% Registration trial met primary endpoint for the prespecified analysis (ORR lower 95% CI >20%) AE profile similar to prior reports, with most being infusion-related reactions
Kushner et al (2020)[89] NCT01757626 Study 12-230[b] Phase 2 interim data	Phase 2, single-arm, expansion phase of Study 12-230 RR-NB[a] confined to bone/BM • Primary refractory NB, $n = 29$ • Secondary refractory NB (persistent disease post treatment for progression), $n = 51$	*Relapsed/refractory NB*: Naxitamab plus sargramostim Initial cycles were monthly Sargramostim dose 250 mcg/m^2/day SQ × 5 days, then 500 mcg/m^2/day SQ × 5 days of each cycle Outpatient treatment	*Naxitamab + sargramostim (Interim results of 80 patients)* Objective response (INRC v2017[86]) in patients with disease confined to bone/BM Primary refractory, evaluable ($n = 25$) • CR 44% • PR 40% Secondary refractory, evaluable ($n = 41$) • CR 24% • PR 15%	Safety not reported	Outpatient treatment with naxitamab + sargramostim resulted in CR + PR of 84% in primary refractory NB confined to bone/BM This study is being supplanted by NCT02502786 in osteosarcoma for full FDA-approval
Kushner et al (2018)[90] NCT01757626 Study 12-230[b] Phase 1 data	Phase 1, single-arm, prospective, 3 + 3 dose escalation trial RR-NB[a] (no limit on prior number of treatments), $N = 57$ • Primary refractory NB, $n = 10$ • Secondary refractory NB (incomplete response to salvage therapy), $n = 15$ • Progressive disease, $n = 6$ • Second or later complete remission but no evaluable disease, $n = 26$	*Relapsed/refractory NB*: Naxitamab plus sargramostim Weekly × 4 weeks; if no progression, could continue treatment at intervals of ≤8 weeks between cycles Sargramostim dose 250 mcg/m^2/day SQ × 5 days, then 500 mcg/m^2/day SQ × 5 days of each weekly cycle Outpatient treatment	*Naxitamab + sargramostim* Best response (INRC v2017[86]) in analyzed[c] patients with evaluable disease ($n = 30$) • CR 20% • PR 27% Primary refractory, evaluable ($n = 10$) • CR 40% • PR 30% Secondary refractory, evaluable ($n = 14$)[c] • CR 14% • PR 36%	*Naxitamab + sargramostim* Grade 3–4 AEs in cycle 1 ($n = 57$) • ALT toxicity (9%) • Hypokalemia (7%) • AST toxicity (4%) • Respiratory (encompasses hypoxia, stridor or wheezing; 4%) • Diarrhea (2%) DLTs • Grade 4 anaphylaxis ($n = 2$, 4%)	In relapsed/refractory NB, outpatient treatment with naxitamab + sargramostim resulted in CR + PR of 47%, with modest toxicity profile

TABLE 4 (Continued)

Authors/study identifier(s)	Design/patient population	Treatment	Efficacy outcomes	Safety	Comments
			Progressive disease, evaluable ($n = 6$) • No responses Survival • In 8 patients evaluable for response who remained progression-free, median PFS was >37 months from start of treatment • Among patients with no evaluable disease, 5 patients achieved PFS for median >50 months from the start of treatment	• Acute transient renal failure ($n = 1$, 2%) • Transient grade 3–4 hypertension ($n = 1$, 2%)	
Relapsed/refractory[a] treatment – Investigational regimen					
Modak 2022[91] NCT03189706 HITS protocol	Phase 2, prospective trial Resistant/heavily pretreated RR-NB[a], $N = 90$ • Refractory to induction, $n = 8$ • Relapsed NB, $n = 82$	*Relapsed/refractory NB*: Temozolomide/irinotecan with naxitamab plus sargramostim 3- to 5-week cycles × 4 cycles Sargramostim dose 250 mcg/m^2/day SQ Outpatient treatment	*Naxitamab + sargramostim with chemotherapy* INRC response 31% Best response (INRC) • CR 26% • PR 11% • Mixed response 9% Refractory ($n = 8$) • Objective response 100% Relapsed ($n = 82$) • Objective response 61%	*Naxitamab + sargramostim with chemotherapy* Toxicities • Pain and hypertension as expected with naxitamab • Febrile neutropenia (4%)	In resistant/heavily pretreated HR-NB, naxitamab + sargramostim with chemotherapy provided best response of CR + PR in 47% with expected toxicities Objective responses noted in MYCN-amplified (25%), temozolomide/irinotecan pretreated (64%) and naxitamab pretreated (68%)
Munoz et al (2023)[92] HITS protocol	Retrospective analysis of prospectively collected data from a compassionate use program Non-progressive, primary refractory[a] HR-NB, $N = 34$ • No prior post-induction therapy (early HITS salvage), $n = 17$ • Prior post-induction therapy (late HITS salvage), $n = 17$	*Relapsed/refractory NB*: Temozolomide/irinotecan with naxitamab plus sargramostim 4-week cycles for up to 12 cycles Sargramostim dose 250 mcg/m^2/day SQ Outpatient treatment	*Naxitamab + sargramostim with chemotherapy* Best response at any time (INRC v2017[86]) in evaluable patients ($n = 30$) • CR 29% • PR 3% Early HITS salvage, evaluable ($n = 17$) • CR 47% • PR 0% Late HITS salvage, evaluable ($n = 13$) • CR 12% • PR 6%	*Naxitamab + sargramostim with chemotherapy* Grade 3–4 toxicities (≥10%; $N = 34$) • Myelosuppression (including anemia, low neutrophil or low platelet count) ($n = 24$, 71%) • Hypotension ($n = 6$, 18%) • Pain ($n = 6$, 18%) One discontinuation due to grade 4 anaphylaxis day 1 of naxitamab	In patients who failed to achieve complete remission after standard induction, early salvage therapy with HITS protocol led to greater objective responses and survival than HITS protocol administered after prior lines of salvage therapy

(Continues)

TABLE 4 (Continued)

Authors/study identifier(s)	Design/patient population	Treatment	Efficacy outcomes	Safety	Comments
			Survival ($N = 34$) • 3-year EFS 34% (95% CI: 20%–58%) • 3-year OS 56% (95% CI: 40%–78%) Early ($n = 17$) vs late ($n = 17$) salvage with HITS • 3-year EFS 54% (95% CI: 32%–92%) for early vs 16% (95% CI: 5%–51%) for late ($P = .0041$) • 3-year OS 85% (95% CI: 67%–100%) for early vs 29% (95% CI: 13%–68%) for late ($P = .0037$)		
Consolidation phase – Investigational regimen					
Mora et al (2023)[93,94]	Compassionate use expanded access program HR-NB in 1st CR, $N = 82$	*Consolidation*: Naxitamab plus sargramostim 4-week cycles × 5 cycles Sargramostim dose 250 mcg/m^2/day SQ × 5 days, then 500 mcg/m^2/day SQ × 5 days of each cycle Outpatient treatment Consolidation included radiation; AHCT not required	*Naxitamab + sargramostim* Survival ($n = 82$) • 5-year EFS 58% (95% CI: 47%–71%) • 5-year OS 79% (95% CI: 69%–90%) MYCN-amplified ($n = 21$) • 5-year EFS 71% (95% CI: 55%–94%) • 5-year OS 81% (95% CI: 66%–100%)	*Naxitamab + sargramostim* Grade 4 toxicities leading to treatment discontinuation • Apnea ($n = 2$, 2%) • Opioid-related chest rigidity ($n = 1$, 1%) • Stroke, unrelated to naxitamab ($n = 1$, 1%)	In this consolidation phase study, naxitamab + sargramostim administered with radiation therapy resulted in reassuring survival rates in patient in 1st CR without high-dose chemotherapy

Abbreviations: AE, adverse event; AHCT, autologous hematopoietic cell transplant; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BM, bone marrow; CR, complete response; DLT, dose-limiting toxicity; EFS, event-free survival; GM-CSF, recombinant human granulocyte-macrophage colony-stimulating factor; HITS, *H*umanized anti-GD2 monoclonal antibody naxitamab (Hu3F8), *I*rinotecan, *T*emozolomide and *S*argramostim; HR, high-risk; mo, month; NB, neuroblastoma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; RR, relapsed/refractory; SQ, subcutaneous; TRAE, treatment-related adverse event.

[a]In general, relapsed disease refers to recurrence after initial response to treatment while refractory disease refers to inadequate response to treatment but individual study definitions for these subgroups vary. When data for relapsed and refractory subgroups were available, they were included in the table. Individual study definitions for relapsed neuroblastoma and refractory neuroblastoma are described in the Table S1 as available.

[b]Registration trial.

[c]One additional patient with evaluable disease had DLT after initial treatment and was not analyzed for response.

several investigational anti-GD2 based approaches have included concomitant GM-CSF treatment (Table S3).

5 | G-CSF IN COMBINATION WITH ANTI-GD2 MONOCLONAL ANTIBODIES

5.1 | Preclinical/translational G-CSF data

As G-CSF acts primarily via neutrophil effects, only one mechanism of neuroblastoma cytotoxicity is augmented with G-CSF (Figure 1 and Table 2).[17] In vitro data show G-CSF receptor expression in five different neuroblastoma cell lines, with increased tumor cell proliferation observed in three lines after exposure to exogenous G-CSF.[97] Another preclinical study identified a novel, distinct subpopulation of neuroblastoma cells expressing CSF3R which encodes the G-CSF receptor (CD114).[98] These G-CSF receptor-positive cells were observed to have stem cell characteristics, and were found to be tumorigenic and capable of self-renewal and differentiation to progeny cells. Additional in vitro data show G-CSF selectively activated STAT3 within neuroblastoma cancer stem cell populations.[99] Subsequently, enhanced tumor growth and metastasis in human xenograft and murine neuroblastoma models was observed with G-CSF 250 mcg/kg/day for 21 days. Notably, the G-CSF dose used in this study was higher than recommended for patients receiving myelosuppressive chemotherapy (5 mcg/kg/day for 2 weeks).[100] In contrast to these first three studies, more recent preclinical data from Martinez-Sans et al show no alteration of neuroblastoma cell phenotype by G-CSF as well as no difference in proliferation of tumor cell cultures between G-CSF-exposed cells and control neutrophils.[31]

Limited preclinical efficacy data exist supporting G-CSF as an adjuvant with anti-GD2 mAbs. Two preclinical studies examined anti-tumor effects with this combination and found varied results. In the first study, no significant ADCC augmentation was observed in vitro with G-CSF and anti-GD2 mouse mAb 220-51 compared to mAb alone.[56] Of note, neutrophil ADCC was enhanced with GM-CSF plus 220-51 ($P < .05$). Interestingly, in vivo data from the same study found G-CSF plus 220-551 resulted in enhanced tumor growth suppression over 220-551 alone in tumor-bearing nude mice ($P < .05$). The authors speculate in vivo G-CSF increased circulating neutrophils which increased the ratio of effector cells to tumor cells. A second, more recent study compared neutrophil-mediated ADCC potentiation with the addition of either G-CSF or GM-CSF to dinutuximab.[31] Although no significant difference was found, G-CSF plus dinutuximab produced less in vitro cytotoxicity of GD2-positive neuroblastoma cell lines and GD2-positive primary patient tumor material compared to GM-CSF plus dinutuximab. Of concern, and which effects would not be revealed from these in vitro studies, is that increased circulating neutrophils correspond to a high neutrophil-lymphocyte ratio (NLR), an independent negative prognostic factor for patients with HR-NB, that is, linked to worse clinical characteristics and survival rate.[101] Furthermore, the most prominent immune-suppressive infiltrating cells found in neuroblastoma are immature neutrophil/granulocytic myeloid-derived suppressor-like cells (G-MDSC).[102] While G-CSF increases circulating neutrophils and promotes their transendothelial migration putatively contributing to increased NLR and intratumoral G-MDSCs, GM-CSF regulates neutrophil chemotaxis and inhibits neutrophil extravasation into tissues, thereby potentially counteracting these neuroblastoma-associated hallmarks (Table 2).[35,36,38–40] Also in contrast to GM-CSF, G-CSF induces DC2 (immunosuppressive type) differentiation,[54] reduces anti-tumor cytokine production,[53] reduces expression of human leukocyte antigen (HLA)-DR and other co-stimulators (ie, CD86),[53] inhibits dendritic cell production,[53] and impairs cytotoxic CD8+ T cell function and activation.[55]

5.2 | Clinical data

G-CSF is a standard supportive care measure during induction chemotherapy protocols for HR-NB and other solid tumors.[103] It is also used for hematopoietic stem cell mobilization in patients with HR-NB.[100] G-CSF given in the rapid COJEC (cisplatin, vincristine, carboplatin, etoposide, cyclophosphamide) induction regimen reduced febrile neutropenic episodes, days with fever, hospital days and antibiotic days when compared to symptom-triggered G-CSF administration.[104] No difference in severe infection or mortality was observed. In general, G-CSF has a good safety profile, although anecdotal adverse effects including acute respiratory failure[105,106] and subretinal hemorrhage[107] have been reported when G-CSF has been used for neutrophil recovery/mobilization in neuroblastoma (Table S4).

In contrast to numerous clinical studies evaluating GM-CSF with anti-GD2 mAbs, to date there is only one small, published study from Japan examining use of G-CSF as an adjuvant with anti-GD2 mAbs for post-consolidation/maintenance immunotherapy in patients with HR-NB.[108] This phase 1-2a study focused on tolerability and safety of dinutuximab plus IL-2 combined with either recombinant human macrophage colony-stimulating factor (M-CSF; $n = 11$) or G-CSF ($n = 14$). The authors thought both combinations to be "feasible options" in Japanese patients; however, the small sample size limits safety confirmation. After a median observation of 350 days, the G-CSF group had cumulative OS and PFS rates of 93% and 67%, respectively. These results must be considered cautiously in the context of a study not designed to evaluate efficacy.

6 | ANTI-GD2 MONOCLONAL ANTIBODIES WITHOUT EXOGENOUS CYTOKINES

6.1 | Clinical data

Dinutuximab beta is used for treatment of patients with HR-NB who have achieved at least a partial response to prior first-line multiagent, multimodality therapy (ie, post-consolidation/maintenance phase) and for patients with relapsed/refractory neuroblastoma with or without residual disease.[7] These indications do not include concomitant

TABLE 5 Dinutuximab beta (ch14.18/CHO) ± IL-2 (without GM-CSF) for neuroblastoma.

Authors or source/study identifier(s)	Design/patient population	Treatment	Efficacy outcomes	Safety	Comments
Post-consolidation/maintenance phase – EMA-approved indication					
Ladenstein et al (2018)[29] HR-NBL1/SIOPEN[a] NCT01704716 EudraCT 2006-001489-17	Phase 3, prospective, open-label RCT HR-NB, $N = 406$ Patients with BM involvement were ineligible for randomization	*Post-consolidation* Isotretinoin plus dinutuximab beta STI with ($n = 206$) or without IL-2 ($n = 200$) 35-day cycles × 5 cycles	*Dinutuximab beta STI + IL-2 with isotretinoin vs dinutuximab beta STI alone with isotretinoin* Survival • 3-year EFS 60% (95% CI: 53%–66%) for din beta/IL-2 vs 56% (95% CI: 49%–63%) for din beta alone ($P = .76$) • 5-year OS 62% (95% CI: 55%–69%) for din beta/IL-2 vs 63% (95% CI: 55%–69%) for din beta alone ($P = .968$) Additional objective response to immunotherapy (INRC v1993[83]) in patients with evaluable disease before immunotherapy ($n = 134$) • CR to immunotherapy 46% for din beta/IL-2 vs 32% for din beta alone • PR to immunotherapy 7% for din beta/IL-2 vs 12% for din beta alone	*Dinutuximab beta STI + IL-2 with isotretinoin vs dinutuximab beta STI alone with isotretinoin* Grade 3–4 AEs (≥10% in either group) • Hemoglobin toxicity (anemia; 67% vs 42%) • Platelet toxicity (thrombocytopenia; 61% vs 34%) • Granulocyte toxicity (neutropenia; 58% vs 33%) • Impaired general condition (41% vs 16%) • Fever (40% vs 14%) • WBC toxicity (leukopenia; 36% vs 26%) • Infection (33% vs 25%) • Immunotherapy-related pain (26% vs 16%) • Increased liver enzymes (23% vs 17%) • Hypersensitivity reactions (20% vs 10%) • Diarrhea (21% vs 7%) • Hypotension (17% vs 7%) • Capillary leak (15% vs 4%) • Urticaria (10% vs 5%) Two grade 5 events occurred: capillary leak syndrome (IL-2 group; $n = 1$) and ARDS with infection (dinutuximab beta alone; $n = 1$)	Post-consolidation immunotherapy with dinutuximab beta STI without IL-2 produced similar efficacy outcomes and a better safety profile than dinutuximab beta STI with IL-2 Additional randomization arm[30] investigating dinutuximab beta LTI ± low dose IL-2 achieved similar response rate to STI results, no additional efficacy observed in IL-2 group Led to removal of IL-2 as an adjuvant from SIOPEN and COG post-consolidation/ maintenance immunotherapy protocols
Relapsed/refractory[b] treatment – EMA-approved indication					
Mueller et al (2018),[109] Qarziba SmPC,[7] EMA EPAR[110] APN311-303[a]	Open-label, non-controlled, single-center, compassionate use program RR-NB[b], $N = 54$ • Primary refractory, $n = 19$	*Relapsed/refractory NB*: Dinutuximab beta LTI with IL-2 followed by isotretinoin 35-day cycles × 5–6 cycles	*Dinutuximab beta LTI + IL-2 with isotretinoin* Overall objective response (INRC) in patients with measurable disease ($n = 37$)	*Dinutuximab beta LTI + IL-2 with isotretinoin* Grade 3–4 TRAEs (≥10%) • Neuropathic pain (38%)	LTI administration resulted in ORR of 41% and was associated with an improved pain toxicity profile compared to prior data with STI

TABLE 5 (Continued)

Authors or source/study identifier(s)	Design/patient population	Treatment	Efficacy outcomes	Safety	Comments
	• Relapsed, $n = 29$ • Front-line patients treated after completion of AHCT, $n = 5$		• CR 14% • PR 27% Survival in refractory ($n = 15$) • 3-year EFS 29% • 3-year OS 70% Survival in relapsed ($n = 29$) • 3-year EFS 24% • 3-year OS 55%	• Pruritus (15%) • Cough (15%) • Capillary leak syndrome (13%)	Dinutuximab beta LTI + IL-2 led to higher 1-year and 4-year PFS and OS rates compared to historical data in patients with RR-NB
Qarziba SmPC,[7] EMA EPAR[110] APN311-202[a] NCT01701479 EudraCT 2009-018077-31	Phase 1–2, open-label, uncontrolled study RR-NB[b], $N = 44$ • Refractory, $n = 25$ • Relapsed, $n = 19$	*Relapsed/refractory NB*: Dinutuximab beta LTI with IL-2 followed by isotretinoin 35-day cycles × 5–6 cycles	*Dinutuximab beta LTI + IL-2 with isotretinoin* Treatment response in patients with detectable disease ($n = 33$) • No evidence of disease 26% • Improved disease 29% Survival in refractory ($n = 25$) • 3-year EFS 45% • 3-year OS 63% Survival in relapsed ($n = 19$) • 3-year EFS 37% • 3-year OS 42%	*Dinutuximab beta LTI + IL-2 with isotretinoin* Grade 3–4 TEAEs (≥10%) • Anemia (41%) • Pyrexia (34%) • Device-related infection (25%) • Neutropenia (23%) • Hypotension (21%) • Hypoxia (18%) • Pain (16%) • Febrile neutropenia (14%) • Sepsis (11%)	Patients with refractory disease experienced greater survival rates than patients with relapsed disease
Lode et al (2019)[28] SIOPEN/LTI trial Expansion of NCT01701479 EudraCT 2009-018077-31	Phase 2, open-label, randomized study RR-NB[b], $N = 160$	*Relapsed/refractory NB*: Dinutuximab beta LTI followed by isotretinoin with ($n = 81$) or without IL-2 ($n = 79$) 35-day cycles for up to 5 cycles	*Dinutuximab beta LTI + IL-2 with isotretinoin* vs *dinutuximab beta LTI alone with isotretinoin* Response in patients with evaluable disease ($n = 97$) • Response rate 52% for din beta/IL-2 vs 49% for din beta alone • CR 26% for din beta/IL-2 vs 9% for din beta alone • PR 26% for din beta/IL-2 vs 40% for din beta alone Survival • 2-year EFS 65% ± 6% for din beta/IL-2 vs 59% ± 6% ($P = .721$) for din beta alone • 2-year OS 84% ± 4% for din beta/IL-2 vs 79% ± 5% for din beta alone ($P = .904$)	*Dinutuximab beta LTI + IL-2 with isotretinoin* vs *dinutuximab beta LTI alone with isotretinoin* Grade 3–4 AEs different between groups ($P < .05$) • Hematologic toxicity (66% vs 46%) • Fever (46% vs 16%) • Allergic reaction (14% vs 1%) • Neurotoxicity (8% vs 0%)	In relapsed/refractory setting, dinutuximab beta LTI alone produced similar efficacy outcomes and a better safety profile than dinutuximab beta LTI + IL-2

(Continues)

TABLE 5 (Continued)

Authors or source/study identifier(s)	Design/patient population	Treatment	Efficacy outcomes	Safety	Comments
Relapsed/refractory[b] *treatment – Investigational regimens*					
Lode et al (2022)[111] NCT02743429 EudraCT 2014-000588-42	Phase 2, open-label, uncontrolled study RR-NB[b], $N = 40$	*Relapsed/refractory NB*: Dinutuximab beta LTI monotherapy 35-day cycles × 5 cycles	*Dinutuximab beta LTI monotherapy* Overall objective response (INRC) in patients in full analysis set ($n = 38$) • CR 11% • PR 26% • MR 13% Patients with BM involvement ($n = 14$) • CR 86% • PR 7% Survival • 3-year PFS 32% ± 8% • 3-year OS 66% ± 8%	*Dinutuximab beta LTI monotherapy* Grade 3–4 AEs (≥10%) • Inflammation (20%) • GI disorders (13%) • Pyrexia (10%)	Dinutuximab beta LTI monotherapy was considered highly tolerable with clinically meaningful response rates in patients with RR-NB Per authors, survival rates were significantly higher in patients with refractory NB than in patients with relapsed NB (data not provided)
Gray et al (2022)[112] BEACON-Immuno Trial NCT02308527 EudraCT 2012-000072-42	Phase 2, open-label, randomized study RR-NB[b], $N = 65$	*Relapsed/refractory NB*: Chemotherapy (either temozolomide alone or temozolomide/topotecan) with ($n = 43$) or without ($n = 22$) dinutuximab beta 28-day cycles × 6 cycles	*Dinutuximab beta with chemotherapy* vs *chemotherapy alone* Best response (RECIST or INRC) in patients with measurable ($n = 48$) or evaluable ($n = 17$) disease (overall $n = 65$) • Objective response rate 35% with din beta vs 18% without din beta (risk ratio 1.66, 80% CI: 0.9–3.06, 1-sided $P = .19$) Survival • 1-year PFS 57% with din beta vs 27% without din beta (hazard ratio, 0.63; 95% CI: 0.32–1.25; $P = .19$) • OS hazard ratio 0.99 (95% CI: 0.42–2.36; $P = .99$)	*Dinutuximab beta with chemotherapy* vs *chemotherapy alone* • Grade ≥3 AE (30% vs 41%) • Neurotoxicity grade 1–2 (67% vs 14%) • Neurotoxicity grade 3 (9% vs 0%)	Objective response rate success criteria met for proceeding to phase 3 trial of dinutuximab beta added to temozolomide or temozolomide/topotecan in relapsed/refractory setting Higher neurotoxicity was observed in the chemotherapy + dinutuximab beta group
Flaadt et al 2020[113]	Phase 1–2 study Relapsed[b] metastatic NB, $N = 68$	*Relapsed metastatic NB*: Haploidentical HCT followed by dinutuximab beta plus IL-2 6 cycles starting day 60–180 post-transplant	*Post-transplant dinutuximab beta + IL-2* Disease status evaluated by MRI, MIBG and BM-aspirates • Of patients achieving CR prior to dinutuximab beta ($n = 24$), 54% maintained CR after dinutuximab beta • Of patients achieving PR prior to dinutuximab beta ($n = 36$),	*Post-transplant dinutuximab beta + IL-2* • Frequent side effects of dinutuximab beta therapy were pain, fever and CRP elevation (% not reported) • Induction of late onset GvHD (during dinutuximab beta therapy) occurred in 2 patients	Anti-tumor effect was observed with dinutuximab beta + IL-2 after haploidentical HCT; no apparent increased risk of GvHD

TABLE 5 (Continued)

Authors or source/study identifier(s)	Design/patient population	Treatment	Efficacy outcomes	Safety	Comments
			55% achieved CR or reduced tumor load after dinutuximab beta Survival • 3-year EFS 47% • 3-year OS 58%		

Abbreviations: AE, adverse event; ARDS, acute respiratory distress; BM, bone marrow; COG, Children's Oncology Group; CRP, c-reactive protein; din beta, dinutuximab beta; EFS, event-free survival; EMA, European Medicines Agency; EPAR, European public assessment report; GvHD, graft vs host disease; HR, high-risk; IL, interleukin; LTI, long-term infusion; MIBG, metaiodobenzylguanidine; MRI, magnetic resonance imaging, NB, neuroblastoma; ORR, objective response rate; OS, overall survival; RCT, randomized, controlled trial; RR, relapsed/refractory; SIOPEN, International Society of Pediatric Oncology Europe Neuroblastoma; SmPC, Summary of Product Characteristics; STI, short-term infusion; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

[a]Registration trial.

[b]In general, relapsed disease refers to recurrence after initial response to treatment while refractory disease refers to inadequate response to treatment but individual study definitions for these subgroups vary. When data for relapsed and refractory subgroups were available, they were included in the table. Individual study definitions for relapsed neuroblastoma and refractory neuroblastoma are described in the Table S1 as available.

GM-CSF/G-CSF therapy. Dinutuximab beta prescribing information includes three registration trials supporting the EMA-approved indications, one in post-consolidation/maintenance and two in relapsed/refractory treatment (Table 5).[7,29,30,109,110] The highly complex, multiple-randomization, phase 3 HR-NBL1/SIOPEN trial is the registration trial for post-consolidation/maintenance phase treatment.[29,30] This trial led to removal of IL-2 from SIOPEN and COG protocols.[1] In one randomization arm of this trial, patients received short-term infusion dinutuximab beta plus isotretinoin either with or without IL-2. No differences were observed with or without IL-2, respectively, in 3-year EFS (60% vs 56%; $P = .76$) or 5-year OS (62% vs 63%; $P = .968$).[29] However, IL-2 was associated with more grade 3–4 hypersensitivity reactions, capillary leak, fever, infection, immunotherapy-related pain and impaired general condition. A separate HR-NBL1/SIOPEN randomization arm found a reduced toxicity profile with dinutuximab beta long-term infusion and dose-reduced IL-2.[30]

The two registration trials listed in the dinutuximab beta prescribing information for relapsed/refractory neuroblastoma included concomitant isotretinoin and IL-2 (Table 5).[7,109,110] In pooled data from these studies in the prescribing information, ORR was 36% in patients with evidence of disease at baseline.[7] Patients with relapsed neuroblastoma experienced 3-year EFS of 24%–37% and OS of 42%–55%, and patients with refractory neuroblastoma had 3-year EFS of 29%–45% and OS of 62%–70%.[110] More recent data have also shown decreased tolerability and no difference in efficacy with IL-2 compared to without (Table 5).[28] The recent BEACON-Immuno trial in relapsed/refractory neuroblastoma reported best objective response rate of 35% in patients receiving chemotherapy (either temozolomide/topotecan or temozolomide alone) plus dinutuximab beta vs 18% in patients receiving chemotherapy alone (risk ratio 1.66; 80% CI: 0.9–3.06; 1-sided $P = .19$) (Table 5).[112] Finally, another recent trial[111] exploring single-agent dinutuximab beta (without cytokines as adjuvants) in the relapsed/refractory setting (ORR 37%, 3-year PFS 32%, OS 66%) found comparable response and survival rates to the registration trials[7,109,110] which included concomitant isotretinoin and IL-2 (Table 5). Of note, single-agent dinutuximab beta led to objective responses in BM in 13 of 14 patients.[111] Additional non-registration dinutuximab beta studies are summarized in Table S2.

7 | DISCUSSION

Clinical data supporting anti-GD2 mAbs with GM-CSF therapy are substantial. The body of evidence demonstrates safety and effectiveness of GM-CSF (sargramostim) with anti-GD2 mAbs in neuroblastoma patients in both the post-consolidation/maintenance phase and relapsed/refractory disease setting (see Tables 3 and 4). When given with anti-GD2 mAbs, GM-CSF enhances neutrophil-mediated ADCC as well as other neuroblastoma cell cytotoxicity pathways (Figure 1).[17,18,20–24,46,61,62,65–68] All the trials supporting FDA-approval of dinutuximab and naxitamab included sargramostim as the GM-CSF adjuvant, and, accordingly, the indicated uses include

concomitant GM-CSF.[19,88–90] Additionally, recent studies examining earlier use of immunotherapy in the overall HR-NB treatment plan (eg, during induction) as well as studies with investigational anti-GD2 compounds (Table S3) include concomitant GM-CSF.[87,114]

FDA approved for over 30 years, sargramostim has an established safety profile.[95] Sargramostim is proven to be safe and effective in patients with cancer receiving BM-suppressive drugs and/or radiation, and post-hematopoietic cell transplant (HCT) graft-failure, as evidenced by indications in these settings.[95] Additionally, many investigational studies exploring sargramostim use in other cancers such as melanoma, colorectal, ovarian, prostate and pancreatic continue to demonstrate safety and tolerability in a variety of settings.[115–119] Historical concerns that GM-CSF leads to more adverse events than G-CSF may, in part, be explained by the different products and expression systems of GM-CSF (eg, sargramostim, molgramostim, regramostim). Studies have shown glycosylated, yeast-derived GM-CSF (sargramostim) is associated with a lower frequency and severity of adverse events when compared to *Escherichia coli*-derived, non-glycosylated GM-CSF (molgramostim).[120] Unfortunately, study publications do not always clearly identify the GM-CSF formulation being used, and a general perception of higher toxicity with all GM-CSF forms developed. Furthermore, the few prospective studies specifically comparing GM-CSF (sargramostim) and G-CSF therapy showed similar toxicity profiles between the two products.[57–59] Of note, toxicities of concern (eg, hypotension, capillary leak syndrome, hypersensitivity reactions and fever) occurred more frequently in IL-2-containing cycles compared to sargramostim-containing cycles in two studies with dinutuximab in HR-NB (cycles alternated IL-2 and sargramostim use; see Table 3).[27,81]

GM-CSF (sargramostim) in combination with anti-GD2 mAbs has been studied in thousands of patients and has been in routine clinical use for neuroblastoma since 2015.[5] In contrast, there is only a single phase 1-2a clinical study evaluating G-CSF combined with anti-GD2 mAbs ($n = 14$).[108] While preclinical data suggest a theoretical risk of enhanced tumorigenicity with G-CSF use in neuroblastoma,[97–99] Martinez-sans et al found no unfavorable effects of in vitro G-CSF on neuroblastoma cell growth.[31] Clinical data support G-CSF use as a supportive care measure for patients with neuroblastoma receiving high-dose chemotherapy during induction therapy[104]; however, the fact remains that only one clinical study has evaluated G-CSF as an adjuvant with anti-GD2 mAb.[108] Given the lack of supportive data on the efficacy of G-CSF, widespread substitution of GM-CSF with G-CSF as an adjuvant to neuroblastoma immunotherapy would be imprudent. Furthermore, numerous undesirable G-CSF effects including DC2 induction, DC1 inhibition, cytotoxic CD8+ T cell impairment and potential G-MDSC and prognostic NLR level increases, warrant concern that these effects might outweigh any potential ADCC benefit with anti-GD2 therapy and instead exacerbate neuroblastoma progression.

In some geographic regions, standard practice omits use of cytokines. Dinutuximab beta was approved in Europe without including GM-CSF in registration trials likely due to lack of an approved product. Notably, dinutuximab beta alone has demonstrated improved outcomes over prior standards of care.[29,121] However, existing clinical evidence with other anti-GD2 mAbs, in addition to its multiple mechanisms for enhancing neuroblastoma cytotoxicity (Figure 1), predict concomitant GM-CSF could lead to even greater outcomes with dinutuximab beta. For example, 5-year OS was 63% for patients who received dinutuximab beta without cytokines in the post-consolidation/maintenance registration trial,[29] while the recently reported 5-year OS was 72% in patients who received dinutuximab plus alternating cycles of IL-2 and sargramostim.[27] Additionally, the dinutuximab beta alone study had higher incidence of hematologic adverse events than the dinutuximab study which included alternating cycles of IL-2 and sargramostim.[27,29] It is unknown if these benefits come from the addition of GM-CSF or the choice of anti-GD2 monoclonal antibody (Table 3 and Table 5). Considering cross-trial comparison limitations, it is also possible these differences in survival and hematologic adverse events are due to other variations between the trials, such as induction/consolidation regimens, IL-2 effects and cycle lengths. In a poor prognosis disease such as HR-NB, every known advantage should be explored. A formal comparison of outcomes and safety with dinutuximab beta (or other anti-GD2 mAbs) with or without GM-CSF is warranted.

Ongoing research is further evaluating using anti-GD2 mAbs plus GM-CSF as part of HR-NB induction regimens.[87,122] Efforts are also underway to improve management of anti-GD2-based immunotherapy-related toxicities,[123–125] and newer anti-GD2 mAb generations are being designed to improve upon toxicity profiles of their predecessors.[126,127] Other data have shown similar survival rates for patients receiving post-induction immunotherapy with anti-GD2 mAbs and GM-CSF regardless of whether the patients underwent autologous HCT or not.[128–131] These data suggest that in the future autologous HCT may not be needed to improve outcomes when anti-GD2 mAbs with GM-CSF are used. Phase 2 data indicate that GD2/GD3 vaccine plus β-glucan elicits anti-GD2 antibody responses in patients with HR-NB,[132,133] and an ongoing trial (NCT04936529) is investigating whether addition of GM-CSF as a vaccine adjuvant will enhance seroconversion rates.[134] Another investigational strategy seeks to exploit the anti-idiotypic response to anti-GD2 mAbs whereby anti-GD2 anti-idiotype antibodies are being developed and investigated for use as anti-neuroblastoma vaccines.[135–138] Some investigational anti-GD2-based therapies have also shown promise in neuroblastoma when used in combination with GM-CSF (Table S3). Anti-GD2 therapies with or without GM-CSF are being explored in other disease states such as osteosarcoma[139–141] and breast cancer.[142]

This review is hampered by the lack of direct comparisons between GM-CSF, G-CSF and/or no cytokine use in neuroblastoma. However, the depth of evidence supporting GM-CSF as an adjuvant to anti-GD2 mAbs supports its continued use in HR-NB. Achieving access to affordable quality care is a worldwide problem that extends to all areas of oncology.[143] Efforts should be made to continue to facilitate GM-CSF, dinutuximab, dinutuximab beta and naxitamab availability globally, including programs by which these agents can be obtained on a case-by-case basis where they are not commercially available.[96,144–146]

8 | CONCLUSIONS

Even with the success of anti-GD2 mAbs, the survival rate of patients with HR-NB is, at best, ~60%. Given the poor prognosis of this high-risk population, patients should be afforded the best chance for positive outcomes whenever possible. GM-CSF (sargramostim) has been shown to be a safe and effective adjuvant to anti-GD2 mAbs (dinutuximab and naxitamab) in patients with HR-NB in the post-consolidation/maintenance phase of treatment and in the relapsed/refractory disease setting. The lack of G-CSF efficacy data raises concerns about its suitability as an alternative to GM-CSF. Existing clinical data suggest concomitant GM-CSF could lead to longer survival than dinutuximab beta monotherapy (without cytokines). Work must continue toward achieving global equitable access to the best therapeutic options.

AUTHOR CONTRIBUTIONS

Jaume Mora: Conceptualization, supervision, writing-reviewing and editing. **Shakeel Modak:** Conceptualization, supervision, writing-reviewing and editing. **Joyce Kinsey:** Conceptualization, methodology, supervision, writing – original draft, writing – reviewing and editing. **Carolyn E. Ragsdale:** Conceptualization, methodology, supervision, writing – original draft, writing – reviewing and editing. **Hillard M. Lazarus:** Conceptualization, methodology, supervision, writing – original draft, writing – reviewing and editing. All authors contributed to the article and approved the submitted version. The work reported in the article has been performed by the authors, unless clearly specified in the text.

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HML is a paid consultant and has stock options for Partner Therapeutics, Inc. JK and CER are employees of and have stock options for Partner Therapeutics, Inc. Outside the current work, JM has received consulting fees from Y-mAbs Therapeutics, Inc. Outside the current work, SM has been a consultant for Y-mAbs Therapeutics, Inc, EUSA Pharma (UK) Limited (a Recordati Group Company), Kymera Therapeutics and Innervate Radiopharmaceuticals LLC.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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