J Cell Signal. 2026;7(1):21–36.

Journal of Cellular Signaling Review

# Harnessing the Immune Arsenal against Neuroblastoma

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**Received date:** January 10, 2026, **Accepted date:** March 05, 2026

**Citation:** Han RY, Buhay BR, Chin JD, Marrah AJ, Wakefield MR, Fang Y. Harnessing the Immune Arsenal against Neuroblastoma. J Cell Signal. 2026;7(1):21–36.



## Abstract

Neuroblastoma (NB) is one of the most common causes of pediatric cancer mortality. Cancer is well known for its complexity and wide variety of presentations. At its worst, NB presents with early metastasis and resistance to therapies. It contains complex molecular and genetic features and has an immunosuppressive microenvironment that forms a complex case that is fatal in around 50% of affected patients, even with the current multimodal treatment standard for high-risk neuroblastoma (HR-NB). This has highlighted a need for comprehensive molecular understanding of the tumor, as well as multi-targeted therapeutic approaches. Current targets that remain a focus for NB include GD2 Disialoganglioside (GD2), v-myc avian myelocytomatosis viral oncogene neuroblastoma-derived homolog (MYCN), glypican 2 (GPC2), B7 Homolog 3 (B7-H3) also known as CD276, and Anaplastic Lymphoma Kinase (ALK). Recent advances covered in this review include further developments in anti-GD2 immunotherapy, targeted therapy for ALK-driven tumors, Chimeric Antigen Receptor T-cell therapy (CAR-T), combination therapies, and other immunotherapies. This review aims to compile the most up-to-date information on the recent advances in the molecular landscape of immunotherapy in a comprehensive manner to understand and identify the shortcomings and future directions for treatment targets of HR-NB.

**Keywords**: Immunotherapy, Neuroblastoma, Molecular pathogenesis, Precision oncology

## Introduction

NBs are part of a spectrum of neuroblastic pediatric tumors that originate from primitive sympathetic ganglion cells, also known as neural crest cells [1–3]. It is the most common extracranial solid tumor in children and is responsible for approximately 11–15% of all pediatric cancer deaths [4–6]. NBs are well known for their diversity in progression and presentation, whether it is on a clinical or cellular level [3,7,8]. Clinical presentation varies widely with tumor location, although the most common clinical presentation of neuroblastoma is an abdominal mass [5,9]. Other possible presentations include hypertension, opsoclonus-myoclonus syndrome, and symptoms based on areas of compression [5,9]. Due to their complex makeup, NBs are classified based on multiple prognostic factors including age at diagnosis, tumor staging, histopathology, MYCN amplification status, segmental chromosomal aberrations, and DNA ploidy [10,11].

Progression spans from spontaneous regression to aggressive disease with metastatic dissemination that can be fatal. NBs are staged, and their risk levels are assessed using the International Neuroblastoma Risk Group Staging System (INRGSS) as summarized in **Table 1**, which defines risk based on image-defined risk factors (IDRF) as validated by the Children's Oncology Group [10,11]. Most NBs with serious morbidity and mortality are high-risk (HR-NB). This "high-risk" designation is primarily assigned to patients who either have tumors with MYCN amplification or patients older than 18 months with metastatic disease per the INRGSS [10,11]. NBs account for approximately 15% of all pediatric cancer mortality in 2025 as the most common pediatric extracranial solid tumor [12–14]. Survival is dependent on the age at diagnosis, with a 5-year OS at 91% in infants that drops to an event-free survival of 48% in toddlers older than 18 months [4]. The National Comprehensive Cancer Network (NCCN) states that long-term survival for high-risk neuroblastomas remains at approximately 50%, and

**Table 1.** Staging criteria from INRGSS staging system [11].

| Stage | Age | Key Tumor Features | Risk Group | Notes |
|---|---|---|---|---|
| L1 | Any | Localized tumor, no IDRFs, favorable biology | Low | May spontaneously regress. Usually amenable to surgical resection only; minimal risk of metastasis |
| L2 | Any | Locoregional tumor, ≥1 IDRF, may have unfavorable biology | Intermediate / High (dependent on biology/age) | Often requires chemotherapy before surgery; higher surgical risk |
| M | <18 months | Distant metastasis, favorable biology (non-amplified MYCN) | Intermediate | Infants with limited metastasis may respond well to chemo |
| | ≥18 months | Distant metastasis, unfavorable biology (MYCN amplification, segmental chromosomal alterations) | High | Requires intensive multimodal therapy (chemo, surgery, radiation, immunotherapy) |
| MS | <18 months | Metastasis limited to liver, skin, minimal bone marrow involvement; favorable biology | Low / Intermediate | Often resolves with minimal therapy or observation; excellent prognosis |

relapse rates are high [15,16]. Prognosis is strongly affected by tumor biology; the most notable MYCN amplification, which is strongly associated with negative outcomes. Metaiodobenzylguanidine (mIBG) is a norepinephrine analog that is highly sensitive and specific for detecting NB. It is taken up by over 90% of NB cells, which makes it a radiotracer for the disease. The Curie score standardizes the interpretation of mIBG scintigraphy and is used in NB management for prognostic stratification, especially after induction. It allows tracking of NBs over time to assess response and residual disease or relapse. The prognostic relevance of this scoring system was demonstrated in the Children's Oncology Group A3973 study, where a post-induction Curie score greater than 2 was independently associated with significantly inferior event-free survival in patients with stage 4 disease. Additional prognostic and therapeutic determinants to be discussed in this review include segmental chromosomal aberrations, ALK alterations, and GD2 expression [17,18].

In 2010, the identification of GD2's high expression on nearly all NB cells provided the first major breakthrough in NB immunotherapy [22]. The ANBL0032 trial demonstrated that anti-GD2 monoclonal antibody dinutuximab, in combination with cytokines and isotretinoin, improved the 2-year event-free survival from 46% to 66% when compared to isotretinoin alone [19,20]. Since the success of anti-GD2 monoclonal antibodies, the field has seen an explosion of novel immunotherapeutic approaches over the past several years. CAR-T targeting GD2 has shown to be particularly promising, with third-generation GD2-CAR T cells incorporating dual costimulatory domains and inducible safety switches that demonstrate a 63–66% overall response rate and 68% 5-year overall survival (OS) in relapsed/refractory patients that had been pretreated [21–23]. Other antigens are also being targeted by CAR T-cell platforms to address NB heterogeneity [26]. Rational combination strategies have become a central focus of contemporary NB immunotherapy development. Clinical trials are currently underway for combinations of anti-GD2 antibodies with checkpoint inhibitors such as nivolumab (anti-PD-1), cytokines (IL-15, IL-21), epigenetic modulators (EZH2 inhibitors), and metabolic modulators [24–27]. Additionally, biomarker-guided treatments that check ALK mutation status, immune infiltration profiles, cytokine signatures, and GD2 expression levels for individual tumors are being utilized more frequently to guide therapy [24–26]. Platforms like armored CAR T-cells, bispecific antibodies, antibody-drug conjugates, among others, are some of the more novel therapeutic options in development for NB [25,27].

Even with the developing therapies, there are still several roadblocks for HR-NB treatments that prevent long-term survivability. HR-NB's immunosuppression and molecular complexity continue to create challenges in its therapeutic approach, with 5-year event-free survival still only reaching 50% of affected pediatric individuals [4,5,24]. HR-NB's infiltration of myeloid cells, downregulation of MHC class I expression, secretion of immunosuppressive mediators such as galectin-1, and low mutational burden create the tumor's immunosuppressive microenvironment [28–31]. This behavior limits therapeutic efficacy. For instance, CAR-T is restricted by antigen loss following CAR-T, T-cell exhaustion, decreased CAR-T persistence, and immunosuppressive myeloid populations continue to limit long-standing responses to treatment [20,21,28]. HR-NBs additionally have extensive redundancy and multiple interconnected pathways that require a rational combination of therapies to overcome resistance [28]. The toxicity of many of these therapies, such as neuropathic pain, also limit treatment due to tolerability [27,32]. Socioeconomic limitations to necessary agents and resources for research and clinical trials require coordinated international effort and early regulatory engagement [3,14,25,27].

This review aims to synthesize the current evidence on the most recent developments in immunotherapeutic strategies for NB with an emphasis on GD2-targeted therapies, CAR

T-cell platforms, combination approaches, and biomarker-driven personalization. By achieving this, we hope to facilitate current understanding of NB, so that further advancements may be made to improve the outcomes for the affected pediatric population.

## Molecular/Genetic Features

Given the high level of differentiation required by these multipotent embryonic cells, the cellular process of differentiation is very complex and consists of a multitude of genes [3,6,7]. The alteration of a gene implicated in these differentiating pathways can then lead to the formation of neuroblasts [33]. With the wide variety of genes involved neural crest development, no genetic marker has been singled out to drive the formation of NB [34]. Instead, multiple molecular biomarkers, pathways and therapeutic targets such as ALK, MYCN, GPC2, mTOR, GD2, and B7-H3 have been implicated in NB and its treatment [2,35–42]. **Figure 1** illustrates the tumor biology and receptor targets relevant for this review. These biomarkers have a range of expression frequencies in NBs that make them choice targets for therapy. ALK is altered in around 14–21.5% of HR-NBs, with higher percentages of ALK alteration on relapsed patients. MYCN is amplified in about 36–38% of HR-NBs [35,43,44], and GPC2 is expressed in 50–90% of all NBs [38,45]. B7-H3 is expressed in 74–96% of NBs with limited expression in normal tissues [46–48]. GD2 is expressed in about 96–100% of all NBs and is considered a hallmark target for immunotherapy [37,49,50]. There is currently limited published data on the precise percentages of overlap between the mentioned biomarkers (ALK, MYCN, GD2, GPC2, B7-H3) in NB. However, there is high overlap and regulation between their roles for the development of NB [38,42,44,49,51,52]. These biomarkers, the mechanisms by which they are involved in HR-NB development, and some of their relationships with each other are discussed further to develop an understanding of the mechanisms behind the developing therapies for NB.

ALK is a gene encoding a tyrosine kinase receptor and is typically expressed during nervous system development. It is a current developing target for immunotherapy as the most mutated single gene in primary NB [30,51,53]. ALK-activating mutations have recently been found in up to 21.5% of HR-NB tumors, a percentage higher than the normally attributed 9–10% [51–53]. ALK is overactivated outside its usual expression in the context of specific development, leading to downstream signals being amplified to cause abnormal proliferation and blockage of cell differentiation [34,53]. Heritable mutations in ALK following this pathway have been found to cause the majority of hereditary NB cases [36]. In a genomic analysis completed by the Children's Oncology Group in September, clonal and subclonal ALK mutations, as well as ALK amplification, were found to independently predict inferior outcomes for patient, with a 5-year survival that drops from the 66.3% of ALK wild-type tumors to a 37.7% in ALK-mutated tumors, and even lower to 25% for ALK-amplified tumors [51].

ALK's role in NB development comes from its function as an oncogene. Point mutations (usually R1275Q and F1174L) or genomic amplification cause ligand-independent

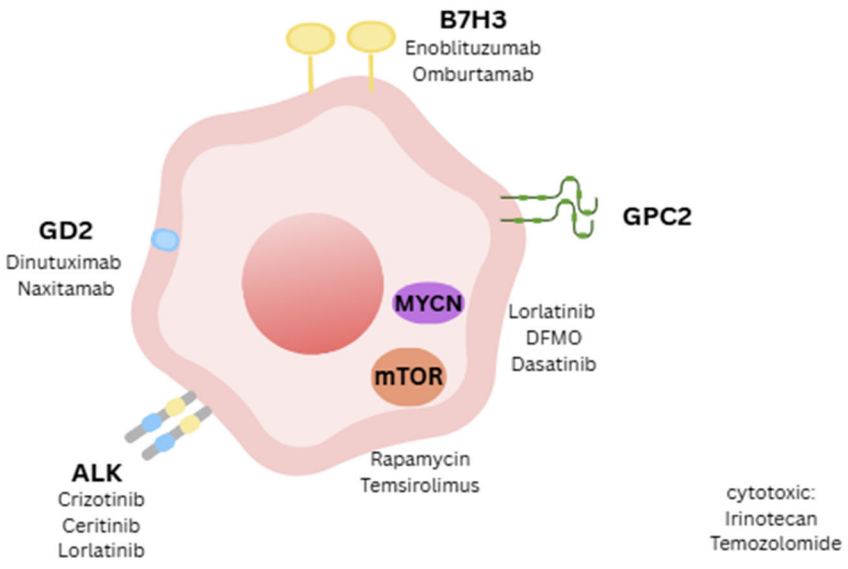


**Figure 1.** Molecular targets in Neuroblastomas [42,148].

dimerization to constitutively activate ALK [52,54]. Activated ALK then autophosphorylates specific tyrosine residues in its intracellular domain to create docking sites for adaptor proteins with SH2 domains [55–57]. This then initiates multiple parallel signaling cascades including ERK-ETV5-RET, PI3K/AKT/mTOR, STAT3, and JAK/STAT pathways, among others, to create a critical oncogenic axis [54] and promote differentiation and cell-cycle arrest [29,34,53]. ALK mutations additionally upregulates POSTN (periostin) and WNT signaling in a feedforward loop that increases focal adhesion and extracellular matrix (ECM) genes and promotes tumor growth and maintenance [58].

It is important to note that a large majority of the pathways and signals can be activated and promoted through multiple mechanisms and can involve several biomarkers. For example, B7-H3 (CD276) is an immune checkpoint protein that is highly expressed in NBs with limited expression in normal tissue [46,48]. It activates STAT3 through the JAK2/STAT3 pathway, which integrates with ALK-driven STAT3 activation, and contributes to chemoresistance in NB [46,48,59]. Another example is MYCN, which directly targets GPC2 transcription, which then also activates the WNT B-catenin pathway [38,45]. ALK mutations cooperate with MYCN in a bidirectional positive feedback loop through several interconnected pathways to mutually promote their expression [29,54]. Their coexpression works to upregulate S-phase kinase-associated protein 2 (SKP2), an E3 ubiquitin ligase that targets the CDK inhibitor p27 for degradation, maintaining neuroblast proliferation [55,60,61]. This then decreases ECM integrity and enhances cell invasion to cause complete penetrance of NB in mouse models [29,54,62]. Outcomes were more inferior with simultaneous ALK and MYCN amplification in HR-NB, with specific ALK F1174L mutation showing to have a synergistic effect with worse outcomes when present with concurrent amplification of MYCN [51,52,63].

As briefly mentioned previously, MYCN status is considered one of the more important features of NB tumors due to its association with poor prognosis, especially in HR-NB [64]. MYCN amplification is found in around 25% of all NB cases [65]. MYCN is an oncogene that encodes for the transcription factor N-Myc, a basic helix-loop-helix leucine zipper transcription factor that forms heterodimers with myc-associated factor X (MAX) to regulate gene expression [66,67]. The MYCN-MAX heterodimer binds to DNA at enhancer boxes sequences that are both canonical and non-canonical. This regulates transcription and activation of an extensive list of genes, proteins, and pathways, including GPC2 and mTOR pathway components, that influence cellular processes through numerous mechanisms including cell cycle progression, metabolic reprogramming, differentiation, angiogenesis, tumor invasion, apoptosis, and metastasis in the context of NB development [68–70]. More specifically N-Myc is involved with spliceosome machinery and increasing RNA and protein production [71]. MYCN amplification also causes cellular undifferentiation and increased mitotic and karyorrhectic activities [72,73]. It is worth mentioning that MYCN is stabilized by mTOR signaling, creating a bidirectional regulatory loop [74,75]. This creates therapeutic vulnerability in MYCN-amplified NBs as mTOR kinase activity must be completely blocked to effectively destabilize MYCN [74–77]. Overall, those with an unfavorable histology designation and an amplified MYCN status showed the poorest clinical outcomes [72].

GD2 ganglioside is a glycosphingolipid found on a broad spectrum of human cancers, both pediatric and adult [78] but limited to peripheral pain fibers (C-fibers), melanocytes, and some central nervous system structures in normal tissue [32,79]. GD2 biosynthesis begins with ceramides then becomes glucosylceramide (via GCS). It then consecutively becomes lactosylceramide, then GM3 (via GM3 synthase/ST3GAL5), then GD3 (via GD3 synthase/ST8SIA1), and finally becomes GD2 (via GD2 synthase/B4GALNT1 [80,81]. Its expression on normal tissue surfaces is associated with the more severe side effects of anti-GD2 immunotherapy, such as neuropathic pain [32]. Gangliosides are sphingolipids that physiologically function in cell recognition and the regulation of signaling proteins including epidermal growth factor (EGF) receptor and vascular endothelial growth factor (VEGF) receptor [37,82]. The exact function of GD2 itself in normal tissue is not yet completely understood, but it is known to function in cell signaling [78]. In a wide spectrum of cancers, including NB, GD2 is believed to escalate progression by increasing tumor cell proliferation, motility, migration, and invasion [37,83]. In NBs, the expression patterns of GD2 can vary and higher tumor derived GD2 levels have been linked to accelerated progression and lower survival rates in patients [84].

Nevertheless, 98–100% of NB tumors have been found to express GD2 at some level [37,50,85]. Since GD2 is highly sensitive to NB tissue and is only expressed in a small amount of normal tissue, it is an ideal target antigen for immunotherapy [37,50,85]. The biosynthesis of GD2 biosynthesis includes sialylation by GM3 synthase (ST3GAL5) and GD3 synthase (ST8SIA1), which is why GD2 expression can be modulated by sialic acid availability and histone deacetylase activity [86]. GD2 acts as a signaling modulator within lipid rafts in the plasma membrane of NB cells [37,80]. In the lipid rafts, it interacts with tyrosine kinases and signal transducers to enhance phosphorylation and induces SRC-dependent activation of signaling cascades that go on to promote tumor progression and maintenance [85,87–89]. This pathway is mechanistically different from growth-factor-induced signaling [37,83]. GD2 additionally contributes to immune evasion by functioning as an immune checkpoint that induces T-cell dysfunction [80].

## Histologic Classification

Under the microscope, neuroblastomas present as uniform, small round blue tumor cells [90]. Another popular diagnostic feature includes "Homer-Wright rosettes". This name represents the neural fibrils and bundles of cells seen in neuroblastomas described by James Wright in his landmark paper in 1910 [91]. In the present day, neuroblastomas have a range of histopathologic diversity that can impact the prognosis and course of treatment of the disease. The International Neuroblastoma Pathology Classification (INPC) system is recommended by National Comprehensive Cancer Network® (NCCN®) guidelines to predict outcomes and guide treatment intensity. NCCN advises that histologic classification based on INPC should be made before initiation of therapy [92]. The classification can be seen broken down in **Figure 2**. Histologically, the diagnosis of neuroblastoma is completed by distinguishing it from peripheral neuroblastic tumors including ganglioneuroblastoma (intermixed), ganglioneuroblastoma (nodular), and ganglioneuroma [93]. NBs are identified as Schwannian stroma poor, then further classified as favorable or unfavorable depending on the grade of neuroblastic differentiation, mitosis-kayorrhexis index (MKI), and age at diagnosis [94]. Neuroblastic differentiation of NB cells includes undifferentiated, poorly differentiated, or differentiating while the MKI is the estimated mitotic and karyorrhectic nuclei per 5,000 neuroblastoma cells. Below 100 is considered low, intermediate between 100–200, and over 200 is high [95]. NB tumors fall under the Favorable Histology category if they fall into one of two groups. The first group includes poorly differentiated or differentiating subtypes with low or intermediate MKI and less than or equal to 547 days of age at diagnosis [95]. The first group includes poorly differentiated or differentiating subtypes with low or intermediate MKI and less than or equal to 547 days of age at diagnosis [94]. The second group includes tumors with the differentiating subtype with low MKI and less than or equal to 1,824 days of age at diagnosis [95]. The Unfavorable Histology tumors can fall within 5 groups; 1) undifferentiated subtype at any age, 2) high MKI at any age, 3) poorly differentiated subtype with any MKI with more than or equal to 548 days of age at time of diagnosis, 4) differentiating subtype with intermediate MKI with mora than or equal to 548 days of age at diagnosis, and 5) differentiating subtype with any MKI with more than or equal to 1,825 days of age at diagnosis [94]. All of these factors must be considered and determined of NB tumor before treatment can begin, thus contributing to the complexity of NB management and course of treatment.

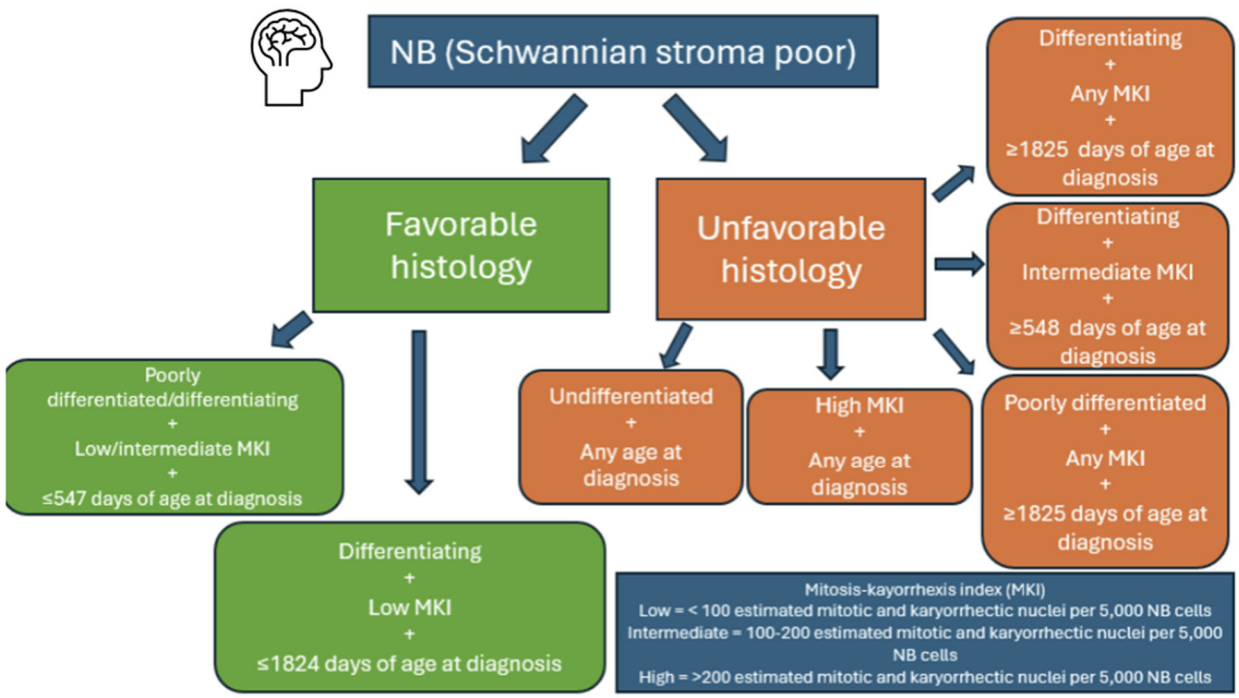


**Figure 2.** Favorable and unfavorable histology groups based on INPC system [72,94].

## Current and Ongoing Therapies

The extensive crosstalk and redundancy in signaling networks, as discussed above, explains why single-agent therapies often fail in NB [96]. The current consensus treatment regimen for high-risk neuroblastoma can be found in **Table 2**. It consists of intensive multimodal therapy divided into three sequential phases, achieving an estimated 5-year event-free survival rate of 51% [15]. Induction therapy involves 5–6 cycles of multiagent chemotherapy (preferably ANBL12P1 [97] or ANBL1531 [98] regimens per the Children's Oncology Group), followed by surgical resection of the primary tumor with a goal of gross total resection, yielding approximately 80% partial response or better [15,97]. Consolidation therapy includes tandem autologous stem cell transplantation with thiotepa/cyclophosphamide followed by dose-reduced carboplatin/etoposide/melphalan (demonstrating superior 3-year event-free survival of 61.6% versus 48.4% for single transplant), along with consolidative radiotherapy at 21.6 Gy to the primary site and residual metastatic disease [99–101]. Post-consolidation therapy consists of immunotherapy, often an anti-GD2 monoclonal antibody (dinutuximab) combined with sargramostim, and a retinol, generally isotretinoin, for six 28-day cycles, which significantly improved 2-year event-free survival to 66% compared to 46% with isotretinoin alone [19,102], with interleukin-2 no longer recommended based on recent data showing no benefit and increased toxicity [20,49,103,104]. For eligible patients achieving partial response or better following immunotherapy, continuation therapy with eflornithine (also known as DFMO) for up to 2 years is an additional treatment option (category 2B recommendation) that has recently become FDA approved [105] and is supported by non-randomized data demonstrating improved event-free survival (hazard ratio 0.48) and overall survival (hazard ratio 0.32) compared to historical controls [106–108].

The majority of novel therapeutics seek to either improve outcomes, decrease toxicity, or address treatment resistance [109]. Based on current literature, targeted therapies can be split into two categories based on their mechanism of action. One category includes agents centered around tumor destruction through the enhancement of the immune system. These agents recruit and activate the immune system to destroy tumor cells. This category would include anti-GD2 antibodies, immune checkpoint inhibitors, CAR-T, cytokine therapies, and other cellular immunotherapies [15,24]. The other category includes agents centered around inhibition of oncogenic signaling activity. These agents include ALK and mTOR pathway inhibitors, multi-kinase inhibitors, MYCN-targeted therapies, cell cycle inhibitors, epigenetic modulators, and metabolic modulators, among others [15,31,40]. Chemoimmunotherapy regimens currently utilize the differing mechanisms to target HR-NB from both sides, and the different approaches are part of the consideration of ongoing approaches towards combination therapies [26]. As previously discussed, recent advances include anti-GD2 immunotherapy, targeted therapy for ALK-driven tumors, and GD2-targeted CAR-T, among other immunotherapies [25]. These and other novel therapies will now be discussed in further detail.

### Immunotherapy with anti-GD2 monoclonal antibodies

Currently, anti-GD2 monoclonal antibodies (dinutuximab, dinutuximab beta) are the standard of care for HR-NB maintenance and relapse treatment [104,110,111]. Anti-GD2 antibodies function by decreasing phosphorylation to downregulate multiple signaling pathways including the PI3K/AKT/mTOR pathway [88,112]. Dinutuximab and dinutuximab-beta are the main anti-GD2 antibodies utilized clinically at this time, but naxitamab has also become more popular and has gained FDA approval in 2023 [113] for relapsed or refractory high-risk neuroblastoma in bone or bone marrow, when combined with GM-CSF [114,115]. Clinical trials based around naxitamab have increased, and show higher response rates compared to the general treatment regime for HR-NB. A phase 2 trial demonstrated a 50% overall response rate in

**Table 2.** Current management recommended for HR-NB therapy per Children's Oncology Group and NCCN guidelines [15].

| Phase | Treatment / Modalities | Typical Agents |
|---|---|---|
| Induction | Intensive multi-agent chemotherapy (5-6 rounds) | Platinum agents (cisplatin, carboplatin), alkylators (cyclophosphamide, ifosfamide), topoisomerase inhibitors (etoposide, topotecan), anthracyclines (doxorubicin) |
| | Surgical resection of primary tumor | Or locoregional disease |
| Consolidation | High-dose myeloablative chemotherapy + autologous stem cell transplant (ASCT/HSCT) | Bu-Mel (busulfan + melphalan) or CEM (carboplatin, etoposide, melphalan) + stem-cell rescue post-myeloablative chemo |
| | Radiation therapy | External-beam RT to primary site ± sites of residual disease. |
| Maintenance / Post-consolidation | Anti-GD2 immunotherapy | Dinutuximab, dinutuximab beta, naxitamab ± sargramostim (GM-CSF) |
| | Differentiation therapy | Isotretinoin / 13-cis-retinoic acid |

heavily pretreated patients with residual disease, including 38% complete responses and 58% bone compartment responses, with manageable toxicities mainly consisting of grade 3 hypotension and pain [114,116]. Naxitamab-based chemoimmunotherapy regimens have achieved response rates of 64–85% in patients with refractory or progressive neuroblastoma [117]. In another phase I/II trial with a small cohort, complete response was noted in 75%, with five-year progression-free and overall survival rates being 38% and 64% respectively [118].

The anti-GD2 antibodies' antitumor mechanism of action works mainly through the activation of the antibody-dependent cell-mediated cytotoxicity (ADCC) pathway. This is often enhanced using granulocyte-macrophage colony-stimulating factor (GM-CSF) and is a part of the current consensus treatment [119]. GM-CSF, known as the drug sargramostim, enhances the sensitivity of the response by activating and expanding myeloid effector populations and is a common adjuvant in HR-NB treatment to anti-GD2 antibodies [120,121]. However, due to the downsides of GM-CSF, such as its high levels of toxicity, cost, and its ability to blunt some anti-tumor immunity, researchers have consistently searched for alternative cytokines to utilize [122]. While G-CSF had previously been offered as a suitable alternative to GM-CSF [123], clinical data has sufficiently found that there is a clinically significant difference between using the two cytokines, and a worse outcome when no cytokine is used at all [120].

There have additionally been studies centered around immunocytokines and engineered cytokine fusions linking anti-GD2 antibodies to IL-15 or IL-21, among others, that demonstrate superior preclinical activity compared to the IL-2-based constructs previously mentioned, with complete tumor regressions in immunocompetent mouse models using enhanced CD8+ T cell responses and favorable modulation of the tumor microenvironment [124–130]. One study studied trifunctional antibody-cytokine fusion protein formats by combining two interleukins, either IL-15 and IL-7 or IL-17 and IL-21, and saw improved potency in inducing JAK-STAT pathway activation, providing a promising candidate for future drug development [130]. Another ongoing area of investigation focuses on other fusion antibodies, such as the combination of anti-GD2 antibodies with SIRPα domains to block CD47-mediated signal to overcome innate immune checkpoint resistance, demonstrating enhanced phagocytosis and NK cell-mediated killing in preclinical models [24,131–133].

## CAR-T therapies

Recent phase 1/2 clinical trials of GD2-targeted chimeric antigen receptor T cells (GD2-CART01) have shown encouraging results in pediatric patients with refractory and high-risk metastatic NBs. GD2-direced CAR T cells are patient derived T-lymphocytes that are chemically engineered to express a CAR recognizing the neuroblastoma-associated antigen GD2, enabling for the targeted destruction of GD2-positive tumor cells [21]. As GD2 is abundantly expression on NB with limited expression on normal tissues, it serves as an ideal immunotherapeutic target [21,35]. Initial findings from the trial found an overall response rate of 63% among the 27 patients studied, including 9 complete remissions, as well as detectable CAR T-cell among patients for up to 30 months. From the patients who received the recommended doses, the 5-year OS and event free survival were found to be 68% and 53%, respectively [22,23].

Based on the high response rates and sustained CAR T-cell persistence observed in the initial cohort, investigators broadened the study with 19 additional participants and continued follow-up, enabling a more extensive long-term evaluation. GD2-CART01 continued significant clinical activity, with an overall response of ~66% and complete remission in up to 40% of patients [22]. Notably, GD2-CART01 persistence was detectable in ~64% of patients for at least 12 months, suggesting sustained immunological surveillance. The study concluded that in patients with refractory or relapsing NB after conventional treatments, immunotherapy targeting GD2-CART01 can induce clinically significant and durable remissions while maintaining a favorable safety profile [21,22].

Current CAR-T related preclinical focus is on armored CAR T-cells with targets outside of GD2, bicistronic CARs, and synthetic extracellular vesicles (SyntEVs), GD2IL18CART, which has added IL18 to GD2 CAR T-cells, has demonstrated higher levels of IFN-γ and TNF-α release in comparison to GD2CART01, and it is now being prepared for clinical investigation [134]. CXCR2-armored GPC2 CAR-T is also under investigation. The CXCR2 cytokine armor has been found to simultaneously enhance trafficking and reduce myeloid-derived suppressor cells (MDSCs), providing the T cells with improved infiltration and targeting of the tumors [109]. GPC2-targeted CAR T cells with NFAT-inducible IL-15/IL-21 have also been found to prolong survival without inducing hypercytokinemia-related mortality in mouse models [135,136].

## Other immunotherapies

A portion of HR-NB's therapeutic resistance has recently been attributed to tumor-derived extracellular vesicles that remodel the tumor microenvironment by simultaneously inhibiting natural killer cell (NK) maturation and suppressing macrophages [137]. This diminishes ADCC and decreases the efficacy of medications focused on tumor destruction and immune system upregulation. In November 2025, nontumor-derived GPC2+ SyntEVs were developed as enhancers for CAR-T with GD2 or albumin-binding domains [138]. Serial infusions of these after GPC2 CAR-T boosted peripheral CAR T-cell persistence in patient-derived xenografts, and the GD2-targeting SyntEVs showed decreased levels of

antigen downregulation [138]. Bicistronic CARs that target both GPC2 and B7-H3 have also been under development and aim to address GD2 resistant therapies overcome [139]. Currently, these CARs have shown prolonged resistance to exhaustion compared to single-antigen CARs and hold further implications for combination therapies [139].

Other possible therapies that aim to address GD2-resistant HR-NB by modulating GD2 expression, synthesis, and signaling pathways are being investigated. EZH2 inhibitors, which are epigenetic modulators, are about to undergo clinical testing in combination with anti -GD2 antibodies [140]. NB cells become resistant to anti-GD2 therapy by reducing expression of GD3 synthase (ST8SIA1) and downregulating GD2 expression by transitioning from adrenergic to mesenchymal NB cells [140]. Inhibiting EZH2 rewires these mesenchymal NB cells and restores GD3 synthase and GD2 surface expression [141]. This resensitizes cells to anti-GD2 antibody therapy [140]. Another study has found that combining histone deacetylase (HDAC) inhibitors (i.e. vorinostat) with sialic acid supplementation upregulates GD2 and could be utilized to boost anti-GD2 immunotherapy in NB tumors with less GD2 expression [86]. The shift towards prioritization of GPC2 and B7-H3 also highlights alternative treatment to GD2-centered treatments and has with both targets demonstrating great preclinical validation. The ongoing clinical development of these platforms will be highly important in determining the potential of these alternative targets in comparison to GD2-centered treatments [25,26,47,48,136].

## Pathway-directed therapies for HR-NB

ALK inhibitors have become a good alternative for the subset of HR-NB patients with ALK positive disease. Combined with the ANBL0532 trial, discussed in the genetics section previously, an argument is building for the early integration of ALK inhibitors in patients with ALK mutation, although safety and efficacy data for ALK inhibitors is still not sufficient enough for adoption outside of its current utilization in clinical trials during induction therapy [15,26,141]. The current ALK inhibitors include crizotinib, ceretinib, ensartinib, alectinib, and loratinib. Lorlatinib is a relatively newer drug as a third-generation ALK/ROS1 inhibitor currently in clinical trials. It has been designed for high penetration of the blood brain barrier and is effective against resistance mutations compared to previous generations [142].

Lorlatinib's mechanism of action works mainly by downregulating the G2/M cell cycle kinases and repressing MYCN expression [142]. Phase 1 testing of lorlatinib with relapsed/refractory ALK-driven NB was completed in the NANT2015-02 trial and established recommended phase 2 dosing of 115 mg/m$^2$ in children and 150 mg in adults, with the majority of its toxicity profiles being metabolic effects (hypertriglyceridemia 90%, hypercholesterolemia 79%, weight gain 87%) [143]. Notably, single-agent response rates reached 30% in pediatric patients and 67% in adults, with 48% of responders achieving complete MIBG responses [143]. Further research found that when combined with topotecan/cyclophosphamide, the response rate for lorlatinib increased to 63% in children, supporting synergistic activity [144]. The drug is now in phase 3 testing by the Children's Oncology Group for integration into frontline therapy.

Despite initial sensitivity to ALK inhibition, ALK-mutant tumors can develop resistance through kinase mutations and oncogenic cooperation with MYCN. This resistance mechanism enables cooperative signaling between ALK and MYCN, further amplifying resistance to maintain oncogenic mechanisms despite ALK inhibition [61]. These adaptive mechanisms sustain proliferative and survival pathways despite ALK inhibition, highlighting that ALK-targeted therapy fails as a single therapy measure and can only benefit a subset of patients.

Combinations with ALK inhibitors are currently considered a possible alternative for tumors with resistance against ALK inhibitors due to their synergistic effects [145]. The NANT consortium phase 1/2 trial found that combining lorlatinib with topotecan and cyclophosphamide, two chemotherapy drugs, achieved a 50% response rate in pretreated patients [145]. Studies combining lorlatinib with the MDM2 inhibitor idasanutlin have demonstrated improved effects, inducing complete tumor regression and significantly delayed regrowth in ALK-amplified models [145]. Other newer ALK inhibitors, such as ESK 440, are also under development as possible alternatives for HR-NBs resistant to treatments currently available. ESK440 is a dual ALK/FAK inhibitor that has shown either equal or enhanced efficacy compared to loratinib alone and retained activity against loratinib-resistant cell lines in preclinical models [29]. A dual ALK/ATR inhibition combination has also developed, utilizing the high levels of replication stress induced by ALK signaling and removing the defense ATR signaling would normally provide to reduce tumors [146,147]. The preclinical trial demonstrated that 14-day ALK/ATR inhibition achieved complete tumor regression and promoted differentiation to neuronal/Schwann cell lineages [146].

Another combination addressing the increasing resistance in HR-NB therapy is based on disrupting the PI3K/Akt/mTOR pathway, a common focus for NB pathogenesis [12,148]. The clinical trial ITCC-053 focuses on the combination of crizotinib with temsirolimus, an mTOR inhibitor, for ALK/MET-aberrated relapsed/refractory NBs. It has currently completed phase 1b and has established a recommended phase 2 dose as crizotinib 150 mg/m$^2$ twice daily with temsirolimus 40 mg/m$^2$/week. However, the grade 3 toxicities, as well as the need for dose reductions due to CYP3A4 interactions, have raised concerns for the tolerability and utility of the combination

[149–151]. Preclinical data investigating mTOR inhibition in combination with chemotherapy in NB and in other pediatric tumors implies that mTOR inhibition may overcome relative resistance to ALK inhibitors, but trials are ongoing, and clinical validation is still required for HR-NB at this time [149,151–153].

### Treatments for MYCN-amplified relapsed/refractory neuroblastoma

Given the central role that MYCN amplification has in driving aggressive tumor behavior, targeted immunotherapies have increasingly advanced to improve outcomes in relapsed or refractory NB. MYCN-amplified tumors are increasingly dependent on the mTOR signaling complex for cell proliferation, a serine-threonine protein kinase composed of mTORC1 and mTORC2 subunits. mTORC1 has been largely studied for its ability to promote anabolic processes through the signaling conduction of nutrient availability and cellular energy status, while mTORC2 focuses on the insulin/IGF-1 pathway to increase cell proliferation and regulate survival [154,155]. Rapamycin, under the generic name of sirolimus, is an mTOR inhibitor that has shown extensive inhibition in the proliferation of NB cells through the initiation of G1 cell-cycle arrest [156].

NB cells are particularly subjected to the pro-oncogenic effects of autophagy, a mechanism that can allow NBs to sustain survival under metabolic stress, including the recycling of damaged organelles to support energy homeostasis to avoid cell death despite a nutrient or oxygen-limited environment [157]. mTOR is a negative regulator of autophagy, where activated mTOR promotes anabolic metabolism and inhibits autophagy initiation [158]. Rapamycin mediated inhibition of mTORC1 functions to reduce anabolic signaling and shift to catabolic survival pathways, ultimately reducing proliferative capacity. When metabolic stress becomes excessive, autophagy can no longer sustain survival and rendering NB cells become largely vulnerable to growth inhibition by the mTORC1 blockade. While prolonged rapamycin treatment has shown to induce insulin resistance, impair glucose homeostasis, and even block T-cell activation, such effects reflect the spectrum of mTOR's influence in cellular physiology and highlights why this pathway remains a compelling candidate for approaching MYCN-amplified NB [159].

Further advancements in treating MYCN amplified tumors have been made with the combination of dasatinib plus rapamycin alongside traditional therapies of irinotecan plus temozolomide (RIST). The clinical trial evaluated 124 patients to randomly receive either RIST or standalone therapy of irinotecan plus temozolomide. Specifically, among MYCN amplified-tumors, the median progression-free survival was 6 months in the RIST group while only 2 months in the control group. The trial also demonstrated acceptable and comparable toxicity profiles between the two groups, primarily consisting of hematological adverse events such as thrombocytopenia and anemia [96].

## Conclusion: Challenges and Further Investigation

Over the past two decades, HR-NB immunotherapy has seen substantial developments, improving life expectancy from 10–20% in the 1990s to over 50% currently. However, HR-NB still lacks long-standing curative treatment. Current research is centered around addressing the ongoing therapeutic challenges investigating high variability in NB and HR-NB expression and the complex interconnected relationships of the factors and pathways in these tumors [109]. Ongoing challenges in current HR-NB therapy include dose-limiting toxicities such as neuropathic pain, the varying levels of biomarker expression and immunosuppression within NBs that cause resistance to its treatment, and the emergence of late relapses and central nervous system metastases [27,117,160]. Collectively, these resistance mechanisms highlight the limitations of the standard therapy for NBs and emphasize the need to overcome conventional treatment modalities. Multi-targeting approaches are currently considered the most promising in addressing the resistance mechanisms that NB has developed and are highlighted as high priority for investigation in the Third Neuroblastoma Drug Development Strategy Forum [26]. Studies such as the one on CXCR2-armored GPC2 CAR T-cells have shown the importance of studying both therapeutic efficacy as well as the resistance mechanisms of NB [127]. Epigenetic reprogramming of tumor microenvironment through chromatin-modifying agents such as EZH2 inhibition, SyntEVs, and other approaches to enhance or alter anti-GD2 antibody efficacy, have shown potential for clinical translation as well [25]. Moving forward, improvements in HR-NB outcomes depend on further addressing the key gaps in the current knowledge and clinical approaches. The major areas that require investigation and prioritization can be sorted as either further understanding of the disease itself or further development of novel treatments. Due to the heterogeneity of NB, precision-based therapies utilizing the biomarkers discussed (GD2, GPC2, B7-H3, MYCN, ALK, etc.) is a major focus for HR-NB treatment. It would simultaneously reduce major toxicities and allow for a more focused dismantling of HR-NBs. To have more precise therapies, an understanding of the whole picture of NB is required. The molecular and genetic complexity of HR-NB, with the numerous signaling pathways, oncogenic cooperation, chemokines such as CXCR2, the feedback loops and axis, and the synergistic relationships between all these factors, among others, are all areas that still need further investigation at this time. Future progress will depend on improving overall survival and highlights the necessity of continued international collaboration to also address progress that has alternatively been slowed due to cost and access to resources. From the approval of dinutuximab to the identification of novel targets

and checkpoints, the consistent progress of the past decades provides the confidence that continued investigation of HR-NB, and its therapeutic interventions will lead towards a world where the treatment of HR-NB will be curative and long-standing, instead of being palliative and short-lived.

## Author Disclosure Statement

The authors have no disclosures or conflicts.

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