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Review

Paediatric Strategy Forum for medicinal product development of agents targeting GD2 ganglioside in children and adolescents with cancer☆

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ABSTRACT

GD2 is a ganglioside expressed on the cell surface of a wide range of paediatric cancers. Expression is most consistently seen at a high level in neuroblastoma, though sarcomas and central nervous system (CNS) cancers may express variable levels of GD2. GD2 has been successfully leveraged therapeutically for patients with high-risk neuroblastoma, for which GD2 monoclonal antibodies have regulatory approvals in the post-consolidation frontline and relapsed neuroblastoma settings. Not all patients benefit, and first-generation antibodies are associated with dose-limiting on-target / off-tumour neuropathic pain. More recently, anti-GD2 antibodies have been combined with chemotherapy for neuroblastoma, though none of these combinations has regulatory approval to date. The potential for targeting GD2 in paediatric cancers beyond neuroblastoma remains relatively unexplored. The 14th ACCELERATE multi-stakeholder Paediatric Strategy Forum was convened to define a strategy for further development of these antibodies, but also for emerging novel approaches leveraging GD2 as a tumour-associated antigen, including antibody-drug conjugates (ADC), radiopharmaceuticals, chimeric antigen receptor engineered T-cells (CAR-T), bispecific T-cell engagers, and vaccines. Seven products being developed by industry were reviewed along with GD2-directed CAR-Ts being developed by academia. Key conclusions included 1) the critical importance of standardisation in quantifying GD2 tumour expression; 2) need for ongoing innovation and comparative effectiveness research with monoclonal antibodies already used in the neuroblastoma frontline setting; 3) urgent need to rapidly screen compounds that may improve the efficacy of chemo-immunotherapy; 4) importance of integrating frontline therapy for neuroblastoma and other tumour types in overall development plans for novel products; 5) mitigation of neuropathic pain and other off-tumour toxicities remains a critical need; and 6) the value of early patient advocate and regulatory interactions during development.

1. Introduction

Ganglioside GD2 is a glycolipid antigen expressed on the cell surface of a wide range of paediatric cancers, including tumour types that have a significant unmet need for novel therapies. Expression is most consistently seen at a high level in neuroblastoma. Sarcomas, central nervous system (CNS) cancers, and other tumours have also been reported to express variable levels of GD2, including osteosarcoma, Ewing sarcoma, H3K27-mutated gliomas, medulloblastoma, and adult cancers such as melanoma, small cell lung cancer, and breast cancer [1]. There has been tremendous interest in targeting GD2 therapeutically since the 1980s, initially with murine and chimeric monoclonal antibodies. The randomised ANBL0032 trial conducted by the National Cancer Institute-funded Children's Oncology Group (COG) demonstrated significant improvement in outcomes for children with high-risk neuroblastoma treated with dinutuximab during the frontline post-consolidation phase [2], paving the way for initial regulatory approval in the United States in 2015. Therefore, GD2 targeting monoclonal antibodies are noteworthy for being among the first immunotherapies approved for a paediatric solid tumour indication (neuroblastoma), but also for being one of a small number of anticancer products with an initial regulatory approval that was primarily focused on a paediatric population [3]. Despite this progress, not all paediatric patients benefit from current therapies, and first-generation antibodies are associated with dose-limiting, on-target/off-tumour neuropathic pain. Over the past decade, anti-GD2 antibodies have been combined with chemotherapy in neuroblastoma, but none of these regimens has yet achieved regulatory approval. Moreover, the therapeutic potential of GD2 targeting in paediatric cancers beyond neuroblastoma remains largely unexplored.

With GD2 credentialed as a tractable immunotherapy target in neuroblastoma, a number of new approaches and products targeting GD2 have been subsequently developed. Given the rarity of paediatric tumours that express GD2, a rational, coordinated strategy to develop newer GD2-targeting products is needed to advance the field most expeditiously for the greatest benefit of children and adolescents with these diseases. Therefore, the fourteenth multi-stakeholder Paediatric Strategy Forum organised by ACCELERATE in collaboration with the European Medicines Agency (EMA) and with the participation of the US Food and Drug Administration (FDA) focused on targeting GD2 in paediatric and adolescent cancers.

The meeting was held at the EMA, Amsterdam on 24 and 25 October 2024. There were 184 participants, 110 in person, and 74 virtual from 27 different countries. Participants included 111 international clinical paediatric oncology and biology experts from Europe, the United States (US), Canada, Japan, Australia, United Kingdom, Africa and Asia; 39 representatives from 6 pharmaceutical companies (Invenra, Merck Healthcare KGaA, Recordati Pharma, Renaissance – Essential Pharma, United Therapeutics, YmAbs Therapeutics); 11 patient advocates from Europe, the US, United Kingdom, Africa, Japan and Canada; 9 regulators from the EMA (including the Paediatric Committee [PDCO]) and national competent authorities within the EU regulatory network and US FDA as observers; and 14 organisers. To provide a basis for discussion, academic experts presented an overview of the biology of GD2, strategies for quantifying tumour GD2 expression, role of GD2-directed monoclonal antibodies in neuroblastoma, and overviews of non-antibody-based approaches including chimeric antigen receptor modified T cells (CAR-T) and radiopharmaceuticals. Details of seven products targeting GD2 were presented. The Forum included patient advocates' perspectives and multi-stakeholder strategic discussions of antibody and newer strategies for targeting GD2.

2. Biology and expression of GD2 across paediatric tumors

GD2 is a ganglioside consisting of a ceramide (lipid) portion that anchors the molecule in the plasma membrane and an extracellular oligosaccharide component containing two sialic acid residues [4]. GD2 is thought to have several biological roles in normal tissues and in malignancy. A cardinal role appears to be the interaction between GD2 and a number of extracellular matrix proteins, including integrins, to modulate cell adhesion and motility [5]. GD2 may create a more suppressive immune microenvironment by reducing recruitment of cytotoxic T cells [6]. GD2 also binds to Siglec-7, thereby serving as an immune checkpoint mainly suppressing macrophage activity [7].

GD2 is synthesised by a complex set of enzymes that determine the composition of the oligosaccharide component that ultimately differentiates GD2 from myriad related gangliosides such as GD3, GD1b, GM2, and GT2. Expression of these enzymes, particularly GD3 synthase, is epigenetically controlled, providing potential opportunities for modulating GD2 expression [4]. For example, EZH2 inhibition or HDAC inhibition have separately been shown to increase GD2 expression in paediatric cancers [8–10]. This epigenetic regulation results in GD2 expression that varies based upon tissue and developmental stage. Expression in normal postnatal tissues is largely restricted to CNS,

peripheral nervous system, skin (melanocytes), and prostate [4]. Expression in normal brain appears to be higher during development before decreasing to mature levels [11].

Among paediatric cancers, the available data demonstrate a range of GD2 expression according to underlying histology, both in terms of percent of patients with detectable GD2 expression on tumour cells and density of expression. Neuroblastoma appears to be the best example of a GD2-expressing tumour. Most studies report that 90–100 % of neuroblastomas express GD2, with a very high density of GD2 on the tumour cell surface [12]. Expression appears to be highest in neuroblastoma, compared to other neuroblastic tumours such as ganglioneuroblastoma and ganglioneuroma [12]. GD2 expression may be lower in samples from patients at time of relapse [13], though additional work is needed to understand the impact of prior therapies on tumour GD2 expression.

Beyond neuroblastoma, primary CNS tumours and a range of paediatric sarcomas have also been shown to express GD2. In CNS tumours, GD2 appears to be highly expressed on most H3K27-mutated gliomas [14] and glioblastomas [15]. GD2 expression has also been assessed in medulloblastoma where expression is seen in a high proportion of patients, but intensity of expression varies based on medulloblastoma subtype [16]. Osteosarcoma and Ewing sarcoma have been the sarcoma histologies most likely to express GD2, though this expression can be heterogeneous and at lower antigen density than neuroblastoma. In one study utilizing an immunofluorescence assay, approximately 50 % of Ewing sarcoma cell lines expressed GD2 and approximately 60 % of Ewing sarcoma tissue samples expressed GD2 [17]. In this same study, approximately 75 % of osteosarcoma cell lines expressed GD2 by flow cytometry, but fewer tissue samples expressed GD2 by immunofluorescence.

Table 1
Investigational strategies for quantifying tumour GD2 expression.

Strategy	Advantages	Disadvantages
Flow cytometry	• Quantitative • Well-suited to liquid samples (e.g., bone marrow) • Detects co-expression of other antigens	• Cannot be applied to paraffin-embedded tissue • Does not allow visualisation of distribution of expression within tumour
Immunofluorescence	• Can be used on paraffin-embedded tissue • Published protocol can be adopted by multiple labs	• Semi-quantitative
Mass spectrometry	• Rapid readout • Inexpensive • Quantitative	• Cannot be applied to paraffin-embedded tissue • Does not allow visualisation of distribution of expression within tumour
Circulating GD2	• Rapid readout • Inexpensive • Quantitative • Blood test, so can be used just prior to GD2-directed therapy	• Association with tissue expression not yet defined
Nuclear medicine imaging	• Can be used just prior to GD2-directed therapy • Provides information about intra-patient heterogeneity in GD2 expression	• Requires administration of an imaging agent • Radiation exposure • Potential need for sedation in young children • Cost

3. Strategies for quantifying GD2 tumour expression

A wide variety of approaches have been evaluated to determine level of GD2 expression, acknowledging that there have been technical barriers to performing immunohistochemistry for GD2 on paraffin-embedded tissue samples. The five main strategies highlighted at the forum included three tumour tissue-based assays (flow cytometry, immunofluorescence, and mass spectrometry), assessment of circulating GD2, and nuclear medicine imaging approaches (Table 1).

Three tumour tissue-based assays were discussed. First, multiparameter flow cytometry assays to quantify GD2 expression in tissue and in bone marrow material have been developed by several groups. In one neuroblastoma-specific assay, negative selection for CD45 and positive selection based upon staining with an antibody directed against the HSAN antigen allowed bone marrow neuroblastoma cells to be detected [18]. The addition of an anti-GD2 antibody to the panel then allowed GD2 co-expression to be determined, with both the percentage of positive cells and the density of expression quantified. This assay has been extended to use on tissue samples as well. More recently, an immunofluorescence assay that can be applied to paraffin-embedded samples has been reported, providing the potential to study archival clinical samples for patients without available frozen material [19]. The results of this assay were validated against results obtained with flow cytometry in neuroblastoma and Ewing sarcoma. Mass spectrometry has also been used to quantify GD2 expression on tissues. This approach appears to be rapid, inexpensive, and quantitative, though requires availability of frozen tumour material and can only provide a pooled result for a whole sample, rather than assessment of expression at a cellular level. Using this approach, one group demonstrated the feasibility of quantifying GD2 expression in both neuroblastoma and medulloblastoma human tumour samples [20].

Circulating GD2 can be detected and quantified from plasma or serum by mass spectrometry. In one study, this approach was applied retrospectively to blood samples from a large cohort of patients with neuroblastoma along with both healthy controls and controls with other types of paediatric cancers [21]. Circulating GD2 levels were similar to controls in patients with ganglioneuroma or ganglioneuroblastoma-intermixed, but all baseline samples from patients with high-risk neuroblastoma had GD2 levels above the upper limit seen in healthy controls. Samples from patients with other paediatric cancers had circulating GD2 levels more in line with those seen in healthy controls.

Finally, an active area of research has been the use of radiolabelled anti-GD2 antibodies to determine GD2 expression *in vivo*. The feasibility of this approach has been demonstrated preclinically in neuroblastoma and osteosarcoma [22–24]. More recently, proof-of-concept imaging studies have shown that this approach is also feasible in patients with a range of paediatric cancers, including Ewing sarcoma, neuroblastoma, and osteosarcoma [25–27]. Importantly, these studies have highlighted both inter- and intra-patient heterogeneity in extent of GD2 expression, including identification of some patients with GD2-negative neuroblastoma. These approaches therefore have the potential to provide evidence of GD2 expression immediately prior to planned GD2-directed therapies and to also evaluate all sites of disease rather than a single biopsied lesion. As of now, these imaging approaches are not widely available and require further study.

Some of these assays are already being tested prospectively in frontline trials for patients with neuroblastoma and Ewing sarcoma, with the potential to be used as selection biomarkers for future trials of GD2-directed therapies. Determining which assay performs best and which cut points best define positive expression remains an area of high interest.

4. Development of anti-GD2 antibodies in children

Given the high level of GD2 expression in neuroblastoma, much of the clinical development of antibodies directed against GD2 has focused on children with neuroblastoma. In the laboratory, GD2 antibodies result in antibody-dependent cellular cytotoxicity (ADCC), an effect which is augmented by the addition of granulocyte-macrophage colony stimulating factor (GM-CSF) or interleukin-2 (IL2) [28–31]. Other antitumour mechanisms of GD2-directed antibodies include

antibody-dependent cellular phagocytosis (ADCP), complement-dependent cytotoxicity [32], and inhibition of the Siglec-7 immune checkpoint that mainly suppresses macrophage activity [7].

Initial phase 1 testing of murine (3F8) or chimeric (ch14.18) antibodies demonstrated the feasibility of administering these antibodies as single agents to children with advanced neuroblastoma [33–35]. Similar toxicities were seen, including pain, fever, a wide range of allergic reactions, capillary leak syndrome, blood pressure alterations, and electrolyte abnormalities. Proof-of-concept activity was seen, with several patients with objective responses when treated on these initial monotherapy trials. These early trials led to the next generation of trials that combined GD2 antibodies with cytokines (GM-CSF or IL2), with a focus on patients with high-risk neuroblastoma in the post-autologous transplant setting [36,37]. These trials demonstrated the feasibility of this approach and provided the necessary safety data to conduct the landmark ANBL0032 phase 3 trial that randomised patients post-transplant to isotretinoin alone or to isotretinoin in combination with ch14.18 and GM-CSF (cycles 1, 3, 5) or intravenous IL2 (cycles 2 and 4). Patients on ANBL0032 who were randomised to the ch14.18 arm of the trial demonstrated a 2-year event-free survival (EFS) rate of 66 % vs. 46 % with isotretinoin alone [2]. These results contributed to EMA and US FDA approval in 2015 of ch14.18 (then named dinutuximab) as post-consolidation therapy, though the EMA marketing authorization was subsequently withdrawn due to drug supply issues.

Subsequent to the approval of dinutuximab, a similar antibody named dinutuximab beta was developed in Europe. In a historically controlled trial, patients with high-risk neuroblastoma treated with dinutuximab beta (without GM-CSF) in the post-consolidation setting had superior 5-year EFS and overall survival (OS) compared to patients treated without dinutuximab beta [38]. This finding contributed to central regulatory authorization of dinutuximab beta in Europe in 2017. In addition, a randomised trial conducted by the European neuroblastoma cooperative group (SIOPEN) helped to clarify the role of IL2 in the frontline post-consolidation setting. Patients in this trial were randomised to receive dinutuximab beta with or without subcutaneous IL2 [39]. The addition of IL2 did not improve EFS and was associated with additional toxicity, resulting in removal of IL2 from frontline post-consolidation in Europe and North America. More recently, use of a prolonged 10-day infusion of dinutuximab beta was shown to be tolerable and active [40], providing an outpatient option for anti-GD2 antibody therapy.

A humanised form of 3F8 known as hu3F8 or naxitamab has shown activity in patients with relapsed/refractory neuroblastoma. A phase 1 single institution trial in combination with GM-CSF reported the feasibility of administering naxitamab as outpatient therapy. Moreover, patients with relapsed neuroblastoma treated with this therapy had a 45 % partial or complete response rate [41]. A follow-up multicentre phase 2 trial reported a 50 % objective response rate in the setting of residual disease limited to bone or bone marrow and in the absence of active disease progressions [42]. The FDA provided accelerated approval of naxitamab in 2020 for patients with relapsed or refractory high-risk neuroblastoma with disease involving bone or bone marrow who had partial response, minor response, or stable disease to prior therapy.

Further work in the relapsed/refractory neuroblastoma setting has focused on the combination of anti-GD2 antibodies with chemotherapy. In the COG, the use of dinutuximab combined with chemotherapy (irinotecan and temozolomide, known as the DIT regimen) was evaluated in patients with first recurrent/refractory high-risk neuroblastoma in a randomised phase 2 trial [43]. Compared to patients randomised to temsirolimus, irinotecan, and temozolomide, patients randomised to the DIT arm had a significantly higher response rate (53 % vs. 6 %). This high level of activity for DIT was confirmed in an expansion phase of the trial and in a real-world evidence study [44,45], making the DIT regimen one of the most active reported for first recurrent/refractory high-risk neuroblastoma. Antitumour activity has also been observed following administration of other GD2 antibodies and other chemotherapy backbones [46–48]. These seminal findings with DIT chemoimmunotherapy in the relapsed/refractory neuroblastoma setting have in turn stimulated interest in evaluating chemoimmunotherapy earlier in the course of the disease. A single institution trial of a humanised 14.18 antibody (hu14.18K322A) in combination with high-risk neuroblastoma induction therapy demonstrated high response, EFS, and OS rates [49]. The results of that trial have led to an ongoing COG randomised phase 3 trial evaluating the role of early dinutuximab during induction (COG ANBL2131; NCT06172296).

While there is significant enthusiasm for chemoimmunotherapy, substantial challenges remain in improving outomes. For example, approximately 40–60 % of patients with relapsed/refractory neuroblastoma do not respond to chemoimmunotherapy and those who respond are still at high risk for subsequent progression [45]. It is also not yet clear why combining a GD2 antibody with chemotherapy leads to such robust activity. Potential mechanisms include increasing penetration of antibody into the tumour, effects on suppressive immune cells in the tumour microenvironment, increasing local cytokines that might recruit additional immune effector cells, or some combination of these hypothesised mechanisms. To build upon these potential mechanisms, other novel combinations with GD2 antibodies (with or without chemotherapy) have been studied or are being studied, with results pending at the time of the forum. These include combinations with lenalidomide, ^{131}I-MIBG, cytokines beyond GM-CSF and IL2, immune checkpoint inhibitors, NK cells, and eflornithine. Of note, following the forum, the results of a randomised trial evaluating eflornithine added to chemoimmunotherapy were reported and showed no improvement in response rate with the addition of eflornithine [50].

Beyond neuroblastoma, there has been limited evaluation of anti-GD2 monoclonal antibodies in other paediatric malignancies. The most substantial experience to date has been in patients with relapsed osteosarcoma, including a phase 2 trial of 39 patients with relapsed pulmonary metastatic osteosarcoma back in surgical remission and treated with adjuvant dinutuximab and GM-CSF [51]. The 12-month disease control rate was 28.2 %, which was not statistically different from historic benchmark.

5. Lessons learnt from successful development of GD2 antibodies in neuroblastoma

With three GD2 antibodies with marketing authorization, there have been substantial lessons learnt. First, the overall drug development timelines have been protracted. As an example, the first-in-child trial of ch14.18 immunotherapy was published in 1995 [34], yet dinutuximab did not receive EMA and FDA approval until 2015, two decades later. The development of these agents was largely driven by the academic community, underscoring the role academic trials can play in an overall drug development strategy. However, academic trials have not always planned for the next steps that might follow a successful outcome, including the potential for subsequent regulatory filings [52]. For example, after the positive results of the randomized COG ANBL0032 study were published in 2010, an industry partner willing to take responsibility for commercial manufacture of dinutuximab needed to be identified and additional clinical trials to characterize the safety and pharmacokinetics of dinutuximab were required to support the marketing application. These factors collectively contributed to the extended product development timeframe.

Second, approval of an agent does not always come with a global access strategy, resulting in significant disparities in availability across regions. This situation has resulted in one GD2 antibody mainly used in North America and another antibody mainly used in Europe. Representatives from SIOPEN and COG are leading a multistakeholder effort to develop strategies that obviate the need for similar trials of dinutuximab and dinutuximab-beta and enable coordinated conduct of complementary trials to address distinct clinically important questions. Moreover, to maximise the impact of therapeutic trials in rare diseases,

there is interest in trans-Atlantic collaboration particularly for combination studies of GD2 antibodies with novel agents that might augment the immune response. Different antibodies that are viewed as standard in each cooperative group or products not being available in large parts of the globe present additional hurdles beyond the usual complexities of international clinical research. While three products have achieved marketing authorisation, many countries remain without access to any GD2 antibody. The reasons for this limited access are multifactorial. For healthcare systems, there are substantial costs to procure and administer these products. There are also substantial operational and regulatory considerations needed to expand access by the relatively smaller companies who produce these antibodies.

Third, ongoing innovation often stalls after initial regulatory approval, highlighting the need for better post-authorization collaborative strategies. For example, although chemoimmunotherapy has become a widely used standard regimen for children with relapsed/refractory neuroblastoma, no chemoimmunotherapy regimen has yet received regulatory authorization [52]. This situation has the potential to limit access to a known active and clinically accepted treatment in regions in which a regulatory authorization and health technology assessment are required for prescribing.

Fourth, although numerous studies have investigated potential biomarkers of response or resistance to GD2 antibodies, none of these are yet used clinically in selecting patients for GD2 antibody therapies. For example, anti-drug antibodies were reported in approximately 10 % of patients treated with dinutuximab on the ANBL0032 trial, with no association with clinical outcomes [53]. There is also significant interest in the potential for lost or heterogeneous GD2 expression to potentially reduce the efficacy of GD2 antibodies, but clinical tools are not routinely available to evaluate tumour GD2 expression (see above). Finally, a range of germline markers associated with NK cell response (e.g., KIR/KIR ligand mismatch and Fc gamma receptor genotype) have been reported to be associated with clinical outcomes in patients with neuroblastoma treated with GD2 antibodies, although it is not yet clear how to integrate these findings into clinical practice [54–58].

As newer products are developed targeting GD2 in rare paediatric tumours, it will be critical to anticipate these four challenges, such that these innovative products can be accessed more quickly and by more children globally.

6. Other strategies for targeting GD2

With the success of anti-GD2 antibodies and validation of GD2 as a therapeutic target in neuroblastoma, a wide range of other approaches leveraging this target has been developed. Figure 1 provides a schematic overview of a range of therapeutic strategies for targeting GD2, highlighting newer approaches beyond naked antibodies. It was acknowledged that some of these approaches may be more appropriate in the context of bulk disease, while others may be more useful in the context of low disease burden.

6.1. Antibody drug conjugates (ADCs)

Several groups have studied strategies that link anti-GD2 antibodies with either a cytotoxic payload or with a cytokine payload. In preclinical studies, dinutuximab conjugated to the cytotoxin MMAE had activity against GD2-positive models but not against GD2-negative models [59]. Moreover, the concentration of the ADC needed for efficacy in these models was far below the concentrations of either MMAE or dinutuximab needed for efficacy, demonstrating the potential for this approach to improve the therapeutic window both of cytotoxic agents and also of GD2 targeting agents that have a known risk of dose-related neuropathic pain. A clinical compound (M3554, a GD2 ADC with the topisomerase 1 inhibitor exatecan as a payload) is now undergoing adult phase 1 testing

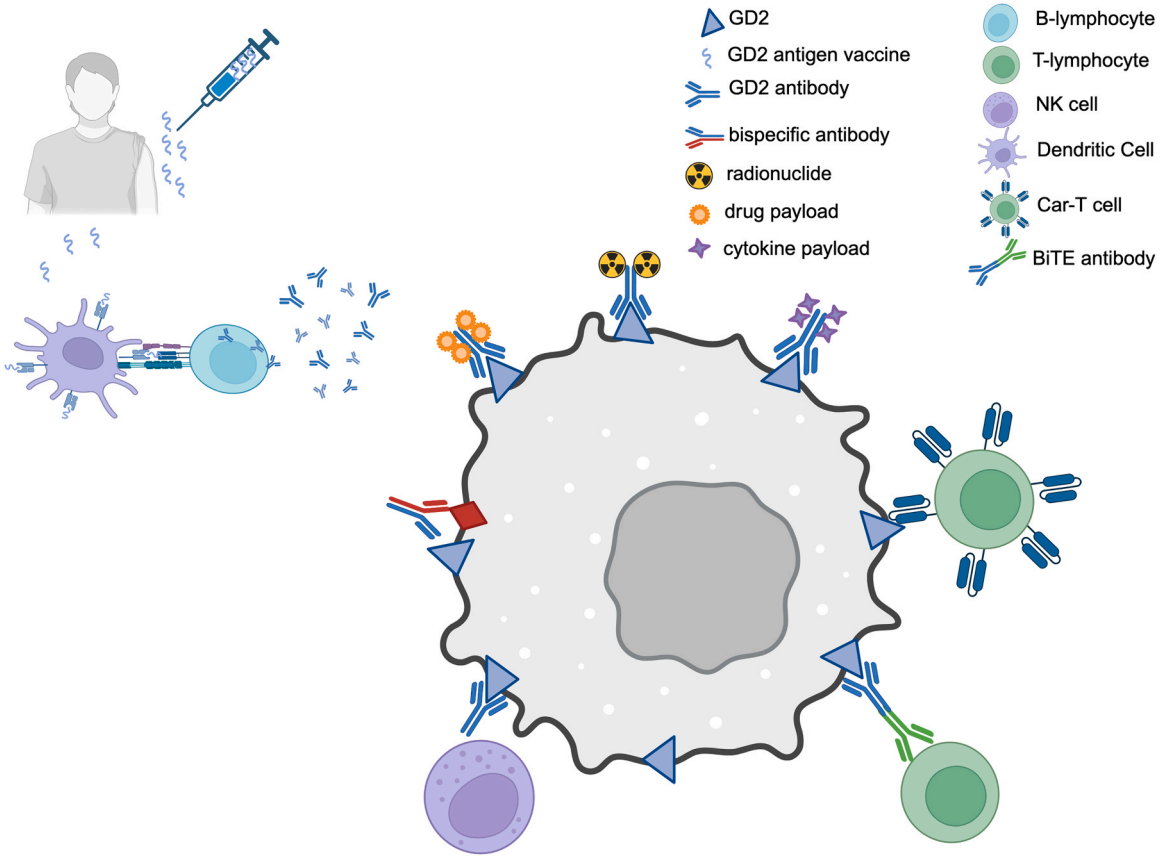

Fig. 1. Schematic overview of strategies for targeting GD2. Created with BioRender.

(NCT06641908).

An immunocytokine consisting of a GD2 antibody linked to IL2 has been evaluated in children with neuroblastoma in phase 1 and 2 clinical trials [60,61]. These trials have demonstrated the feasibility of this approach, but antitumour activity was only observed in patients with limited tumour burden rather than patients with bulk disease. Newer constructs with IL15 appear more active preclinically [62], but have not yet been evaluated in the paediatric clinic.

6.2. Radiopharmaceuticals

Given the radiosensitivity of several paediatric GD2-positive tumours, there is strong rationale for leveraging GD2 expression to deliver a therapeutic radioisotope to sites of tumour. This approach may also be beneficial for less radiosensitive histologies such as osteosarcoma. In one preclinical study, the alpha particle ^{225}Ac was conjugated to hu3F8 and tested in an *in vivo* model of osteosarcoma [63]. Treatment with the radiopharmaceutical led to significantly lower tumour burden compared to vehicle control.

This so-called "one-step" radiopharmaceutical involves administration of the GD2 targeting agent and the radioisotope simultaneously. With this approach, there is the risk of non-specific binding of the antibody as well as a long circulating half-life of the radiopharmaceutical, thereby exposing healthy tissues to radiation, increasing toxicity. Newer multi-step approaches are being developed which first administer the GD2 targeting agent, allow time for non-specific binding to dissipate and for clearance of the circulating anti-GD2, and only then administer the radioisotope to direct the radiation to sites of high-affinity GD2 binding. Preclinical proof-of-concept of this approach has been demonstrated with a GD2-directed self-assembling / disassembling (SADA) construct and ^{177}Lu-DOTA in neuroblastoma models [64]. The two-step SADA delivery resulted in lower tumour volumes and prolonged PFS compared to ^{177}Lu-DOTA alone without GD2 pre-targeting. This approach is now under investigation in the clinic (NCT05130255).

A key advantage of radiopharmaceuticals is their potential to be paired with an imaging agent and therefore provide real-time demonstration of GD2-positive tumour prior to proceeding with the therapeutic dose. This theranostic approach may be particularly important in evaluating tumour histologies with more heterogenous GD2 expression.

6.3. CAR-T cell therapy

GD2-directed CAR-T cell therapies have shown robust activity in multiple paediatric cancers. While first generation products had some activity in neuroblastoma [65,66] including long-term survival of some patients, subsequent generation products have shown more robust activity. Specifically, a second-generation construct (incorporating a co-stimulatory domain) led to some disease regression in 3 of 6 patients with neuroblastoma treated at the top dose levels of a phase 1 trial [67]. A third-generation product showed an objective response rate of 63 % and 3-year EFS of 36 % in a phase 1–2 trial in 27 children with relapsed or refractory neuroblastoma [68]. Multiple patients had prolonged disease control with this approach, with patients with lower disease burden noted to have superior EFS and overall survival compared to patients with higher disease burden. These findings suggest a potential future role for this product as a consolidation strategy in patients treated with prior cytoreductive approaches. Importantly, neuropathic pain has been an infrequent adverse event in these trials.

This work has been extended in several ways, including evaluation of novel CAR-T constructs and investigation in indications beyond neuroblastoma. One novel construct has evaluated CAR NK cells directed against GD2 and engineered to express IL15. This approach resulted in multiple objective responses in initial phase 1 testing in neuroblastoma [69]. Another approach in early trials with results not yet available is utilizing CAR-T cells that target GD2 while also secreting IL18 locally [17]. Beyond neuroblastoma, GD2 CAR-T cells have led to objective responses in patients with H3K27M midline gliomas, including spinal gliomas. In an initial report, several patients had proof-of-concept benefit with intravenous or intraventricular administration of this product [70]. A recent update from that trial reported additional responses with this approach [71]. Initial evidence suggests lower likelihood of benefit in patients with osteosarcoma treated with third-generation CAR-T cell therapy [72].

In parallel with development of these products by academia, the field has considered new models to expand access to GD2 CAR-T products. It was acknowledged that the predominant model currently involves centralised manufacturing and administration of cellular products at single centres, thereby necessitating that patients and families travel to access the therapy. A position paper has outlined other potential models that might be considered in the future, including a) centralised production by industry, academia, or public-private sponsor, with treatment of the patients at centres closer to home or b) decentralised manufacturing by multiple academic centres all adhering to the same production standards [73,74]. Given the activity observed in patients with neuroblastoma and H3K27M glioma, expanding access to these products through such models will be critical to ensuring equitable delivery of these emerging treatments.

6.4. Bispecific T-cell engagers

Given the success of GD2 antibodies and of GD2-directed CAR-T cells, the use of bispecific T-cell engagers is appealing and has the advantage of being an off-the-shelf approach. Interestingly, very little work with this approach has been reported. One trial evaluated autologous T cells that were expanded and preloaded with a GD2-directed bispecific T-cell engager [75]. The trial included patients with relapsed neuroblastoma and osteosarcoma. This approach was feasible with early suggestions of activity, though only 1 of 21 participants had an objective response, highlighting the need for further optimisation and investigation.

6.5. Vaccine approaches

While many of the approaches discussed thus far represent passive immune strategies, the use of GD2 as an antigen for active immunization has also been evaluated. In one phase 2 trial, 102 patients with relapsed neuroblastoma in second or greater remission were treated with a GD2/GD3 vaccine along with beta glucan as an adjuvant [76]. Patients mounted an anti-GD2 IgG response that persisted off vaccine and patients with higher titres had more favourable outcomes. The overall clinical outcomes from the trial were promising, though the lack of a randomised control or strong comparative data limited conclusions about the role of the vaccine in patients who had already responded to prior therapy.

There has also been interest in anti-idiotype vaccines in this space. In melanoma and neuroblastoma, the use of an anti-idiotype vaccine led to detectable anti-GD2 titres, some of which persisted over time [77,78]. The clinical impact of these anti-GD2 antibodies and ultimate role of anti-idiotype vaccines is not yet known.

7. Products discussed at the forum

Seven medicinal products were discussed (Table 2), including five monoclonal antibodies directed against GD2 (three with existing marketing authorisation: dinutuximab, dinutuximab beta and naxitamab; two that are currently in clinical development: hu14.18K322A and INV724) and two further novel agents [GD2 self-assembling / disassembling (SADA) radiopharmaceutical and M3554 ADC]. Development of GD2-directed CAR-T cells being developed in academia were discussed separately, including a discussion of strategies to expand development and access to this modality.

With five monoclonal antibodies currently in development or

Table 2
GD2 targeting therapies discussed at the Forum.

Product	Drug Class	Paediatric clinical trials (recruiting)	Regulatory status (as of March 2025)	Company
Dinutuximab	Anti-GD2 antibody	Yes	Paediatric approval (FDA)	United Therapeutics
Dinutuximab beta	Anti-GD2 antibody	Yes	Paediatric approval (EMA)	Recordati Pharma
Naxitamab	Anti-GD2 antibody	Yes	Paediatric Approval (FDA)	YmAbs
hu14.18K322A	Anti-GD2 antibody	No	No regulatory approval	Renaissance – Essential Pharma
INV724	Bispecific GD2 / B7H3 antibody	No	No regulatory approval	Invenra
M3554	GD2 antibody drug conjugate	No	No regulatory approval	Merck Healthcare KGaA
GD2-SADA*	GD2-directed radiopharmaceutical	No	No regulatory approval	YmAbs

*SADA = self-assembling / disassembling construct

approved, the group discussed differentiating features of these products (Table 3). It was noted that no comparative effectiveness studies have been performed to understand differential efficacy or toxicity between products. Two of the products hu14.18K322A and INV724 were specifically developed with the intent to cause less neuropathic pain by either modification of the Fc domain (hu14.18K322A) or a requirement for dual expression of both GD2 and B7H3 (INV724), though the field lacks agreed-upon tools or validated endpoints for assessing this potential safety advantage.

Details of ongoing paediatric trials of agents targeting GD2 are shown in Table 4 (listed as recruiting on clinicaltrials.gov as of a search performed on November 17, 2024). Eleven trials are evaluating a range of non-cellular products, with few comparative trials. Sixteen trials are evaluating a variety of cell-based therapies. Six of 11 non-cellular trials are multicentre and 3 are intercontinental. Only 3 of 16 cell-based therapy trials are multicentre and none are intercontinental trials, highlighting the challenges in expanding access to these products.

8. Discussion

8.1. Patient advocates' perspectives

Patient advocates emphasised key lessons learned from the development of anti-GD2 drugs for children with neuroblastoma, particularly noting the fragmented nature of their initial commercialization. They observed that while academic initiatives in Europe and North America were pivotal in driving these advances, the lack of collective strategic planning or coordination hindered broader and more cohesive progress [51]. Moving forward, advocates stressed that the successful development of new anti-GD2 therapies must require active engagement of all stakeholders, and cooperative groups must work together for the maximum benefit of children with cancer. They recommended early and inclusive discussions between pharmaceutical companies, academia, patient advocates and regulators to establish strategic development plans that anticipate and address roadblocks, conflicts, delays, or regulatory challenges. This coordinated approach can help streamline the development process and minimise inefficiencies. Advocates underscored the critical need for pharmaceutical companies to work closely with academic researchers to prioritise the best interests of children where a clear rationale for using their drugs exists. All stakeholders must work together to seek the timely evaluation of drugs with a strong preclinical rationale in clinical trials. The involvement of patient advocates was highlighted as indispensable in ensuring that development efforts remain patient-centred, incorporating outcomes and approaches that matter most to children and families facing cancer.

In addition to these strategic considerations, advocates called for increased focus on accessibility and inclusivity in trial designs. They underscored the pressing need for mechanisms to ensure access during the gap between trial completion and regulatory approvals, a period which remains a significant source of distress for families seeking better treatment options. As anti-GD2 therapies are explored in paediatric sarcomas, the need for routine testing for GD2 expression is clear. Advocates urged that the design of clinical trials reduce barriers to participation and improve equity, including approaches that address geographical, socioeconomic, age-related, and disease-specific barriers, particularly for ultra-rare sarcomas.

By fostering open communication, embracing innovative and inclusive trial design, and prioritising equitable access, the development process can be accelerated. Such measures will not only reduce unnecessary delays and duplicative parallel efforts, but will also ensure that promising therapies reach the children and families who need them most.

9. Strategic recommendations

9.1. Biomarker development

The field has evolved with multiple independent assays for detecting

Table 3
Differentiating features of five monoclonal antibodies directed against GD2.

Product	Species	Regulatory Status	Administration	Other Features
Dinutuximab	Chimeric	Marketing authorisation in US, Canada, and Japan as post-consolidation therapy for high-risk neuroblastoma*	IV over 10–20 h daily for 4 days per cycle (inpatient)	Extensive experience by COG centres
Dinutuximab beta	Chimeric	Marketing authorization in Europe, UK, and other regions as post-consolidation therapy for high-risk neuroblastoma and for relapsed/refractory disease	IV long-term infusion over 10 days (potential for outpatient therapy) or once daily over 8 h for 5 days	Extensive experience by SIOPEN centres
hu14.18K322A	Humanised	No marketing authorization	No approved schedule, but phase II testing utilised 4-hour infusions daily x 4 doses	Preclinical increased ADCC activity due to afucosylation; K322 mutation reduces complement dependent toxicity, so designed to lead to less neuropathic pain
INV724	Human	No marketing authorisation	Not defined	Bispecifc antibody directed against GD2 and B7H3 to reduce off-tumour binding to nerves; afucosylated to augment ADCC
Naxitamab	Humanised	Marketing authorisation in US, China, Macau, Hong Kong, Brazil, Israel, and Mexico for relapsed/refractory neuroblastoma**	IV over 30–60 min on days 1, 3, and 5 per cycle (potential for outpatient therapy)	Not based upon a 14.18 antibody

*Approved in combination with GM-CSF and IL2.
**Patients with disease in bone or bone marrow disease who have had a partial response, minor response, or stable disease. Approved in combination with GMCSF.

Table 4
Actively recruiting clinical trials focused on targeting GD2 as a primary objective and include patients < 18 years of age*.

Drug / Agent	Combination Partner	NCT Identifier	Phase	Indication	Frontline vs. Relapse	Sponsor	Multicentre?	Intercontinental?
Non-Cellular Therapies								
BCD−245	None	NCT05782959	1	Neuroblastoma	Relapse	Industry	Yes	No
Dinutuximab	Chemotherapy	NCT06172296	3	Neuroblastoma	Frontline	Government	Yes	Yes
Dinutuximab beta	Chemotherapy	NCT06669013	3	Ewing sarcoma, osteosarcoma, and rhabdomyosarcoma	Relapse	Government	No	No
Dinutuximab beta	Chemotherapy	NCT05272371	1	Neuroblastoma	Relapse	Academic	No	No
Dinutuximab beta	Chemotherapy	NCT06071897	3	Neuroblastoma	Frontline	Government	No	No
Dinutuximab beta	^{131}I-MIBG and nivolumab	NCT02914405	1	Neuroblastoma	Relapse	Academic	Yes	Yes
GD2-SADA:^{177}Lu-DOTA Complex	None	NCT05130255	1	Small cell lung; neuroblastoma**; sarcoma**; melanoma	Relapse	Industry	Yes	No
GD2/GD3 vaccine	Beta glucan	NCT06057948	2	Neuroblastoma	Both	Academic	No	No
GD2/GD3 vaccine	Beta glucan and sargramostim	NCT04936529	2	Neuroblastoma	Both	Academic	No	No
Naxitamab	Chemotherapy	NCT05489887	1	Neuroblastoma	Frontline	Academic	Yes	No
Naxitamab	Sargramostim	NCT03363373	2	Neuroblastoma	Relpase	Industry	Yes	Yes
Cell-Based Therapies								
GD2 CAR-T	None	NCT03373097	1 / 2	Neuroblastoma and GD2-positive tumours	Relapse	Academic	No	No
GD2 CAR-T	None	NCT04099797	1	GD2-positive CNS tumours	Newly diagnosed and relapsed	Academic	No	No
GD2 CAR-T	None	NCT05298995	1	CNS tumours	Relapse	Academic	No	No
GD2 CAR-T	None	NCT05544526	1	Diffuse midline glioma	Frontline post-radiotherapy	Academic	No	No
GD2 CAR-T	None	NCT05990751	1	Neuroblastoma	Relapse	Academic	No	No
GD2 CAR-T	None	NCT06684639	1	Neuroblastoma	Relapse	Government	No	No
GD2 CAR-T	None	NCT04539366	1	Neuroblastoma and osteosarcoma	Relapse	Government	Yes	No
GD2 CAR-T	None	NCT04196413	1	Diffuse midline glioma	Frontline after radiotherapy	Academic	No	No
IL15 expressing GD2 CAR-T	None	NCT03721068	1	Neuroblastoma and osteosarcoma	Relapse	Academic	Yes	No
IL15 expressing GD2 CAR-NK Cells	None	NCT03294954	1	Neuroblastoma	Relapse	Academic	No	No
GD2/PSMA Bispecific CAR-T	None	NCT05437315	1 / 2	GD2 and PSMA-positive tumours	Relapse	Government	No	No
GD2/CD70 Bispecific CAR-T	None	NCT05438368	1 / 2	GD2 and CD70-positive tumours	Relapse	Government	No	No
GD2/CD56 Bispecific CAR-T	None	NCT05437328	1 / 2	GD2 and CD56-positive tumours	Relapse	Government	No	No
Gamma delta T cells	Dinutuximab, chemotherapy, zolendronic acid	NCT05400603	1	Neuroblastoma and osteosarcoma	Relapse	Academic	No	No
NK cells	Dinutuximab and chemotherapy	NCT06450041	2	Neuroblastoma	Relapse	Academic	Yes	No
NK cells	Dinutuximab or naxitamab, sargramostim, IL−2, spironolactone	NCT05754684	2	Neuroblastoma	Relapse	Academic	No	No

*Search completed in clinicaltrials.gov on November 17, 2024. Search term was "GD2" and filters were "Actively recruiting", "Interventional", and "Child."
**Age $\geq$ 16 years for neuroblastoma and sarcoma.

tissue expression of GD2. There is no standardisation in these approaches, nor are critical thresholds of GD2 expression for efficacy defined. Despite the use of GD2 monoclonal antibodies for decades, there is no standardised testing approach widely accepted by the field. This situation has major consequences, including 1) inability to use GD2 expression as a predictive biomarker for patients with neuroblastoma treated with frontline antibodies or chemoimmunotherapy; 2) lack of selection biomarkers to determine eligibility of patients with other tumour types who might be candidates for trials of GD2-directed therapies, raising additional concern that negative results to date may be due to enrolment of children with low GD2-expressing tumours; and 3) inability to compare results between studies since GD2 expression has been evaluated differently across trials.

In this context, the group identified an urgent need for potential biomarkers currently being studied in academic research laboratories to be developed into robust, validated, standardised diagnostics to quantify GD2 tissue expression. The tumour tissue-based assays (flow cytometry, mass spectrometry, and immunofluorescence) have different tissue

requirements and the testing results only reflect the single site that was biopsied. It was acknowledged that predictive biomarker development can be challenging without outcome data and biomarker data from a comparator population of patients treated without GD2-directed therapy. In this context, evaluation of tissue samples from second look surgical resections may be useful during frontline neuroblastoma trials of randomised trials with and without frontline chemoimmunotherapy. The role of measures of circulating GD2 and nuclear medicine imaging techniques need to be considered as well. A working group was recommended to compare the available assays and develop a consensus statement for standardising the approaches used.

9.2. Continued innovation with monoclonal antibodies

Given the inadequate frontline outcomes and difficulties associated with the patient experience during post-consolidation therapy for high-risk neuroblastoma, there is a need to continue to innovate in this space. Innovation here might take the form of optimising schedules of administration for existing antibodies, development of more effective antibodies, novel immunomodulators that enhance the efficacy of GD2 antibodies, and/or antibodies with more favourable toxicity profiles. From a toxicity perspective, two of the products discussed (hu14.18K322A and INV724) were viewed as potentially advantageous in this regard and merit further study. The challenges of comparing antibodies head-to-head were acknowledged and therefore the field requires comparative effectiveness studies that leverage a standard approach for reporting preclinical drug properties but also clinical outcomes including toxicity, patient-reported outcomes, particularly pain, and opiate usage. Early interaction with regulatory authorities was encouraged when considering a development pathway centred around improved patient experience.

9.3. Strategies to enhance the efficacy of chemoimmunotherapy

Strategies to build upon the success of chemoimmunotherapy in neuroblastoma and to ensure access to chemoimmunotherapy for these patients are top priorities. Moreover, it is strongly preferred to enrol patients on a chemoimmunotherapy trial rather than treating them off trial. The preferred trial design is an "add-on" strategy with randomisation to isolate the contribution of the novel combination partner. In the setting of multiple potential immunomodulatory agents, the ideal context for rapidly screening agents that may enhance chemoimmunotherapy in children with relapsed/refractory neuroblastoma would be an international platform trial for patients in first relapse that includes a common comparator arm in which patients receive standard chemoimmunotherapy, including the GD2 antibody available in each region. Such a design has the potential to enhance access to innovation, accelerate the pace at which new agents can be screened, and facilitate generation of fit-for-filing data suitable in multiple regions.

Given the major impact that GD2 chemoimmunotherapy has had for children with neuroblastoma and the paucity of studies of chemoimmunotherapy in other GD2-positive diseases, testing chemoimmunotherapy in these other diseases is a priority. However, it was agreed that evaluation of chemoimmunotherapy in other disease contexts should be based upon tissue testing to demonstrate target expression.

9.4. Development of novel products

Given that GD2 is a validated target, there was broad consensus that the development of novel products leveraging this target remains a high priority. Specifically, while naked antibodies have significantly advanced the treatment of children with neuroblastoma, there is a need for ongoing innovation given the narrow therapeutic index of these products. Regulatory bodies now have substantial expertise in this space, having granted marketing authorisation to multiple GD2 antibodies. Therefore, early engagement between sponsors developing novel products in this space and regulatory agencies is encouraged, with patient advocate participation.

Development plans for these novel products should acknowledge the disease context in which patients are most likely to benefit. For example, GD2 targeting agents linked to a cytotoxic or radioisotope payload may be most impactful in the setting of bulk disease, while the available data suggest that GD2 CAR-T and GD2 vaccines may be most effective in low disease burden states. As GD2-directed therapies are already in the frontline space in neuroblastoma, development plans for novel products should include the potential for evaluation in the frontline setting, taking into account whether the agent will be best suited to treat bulk vs. low burden disease.

The degree of clinical testing of novel products in diseases beyond neuroblastoma likely depends upon preclinical evidence, but also on the status of clinical testing in neuroblastoma. In general, development plans for novel products should consider other tumour types beyond neuroblastoma. The use of prospective GD2 testing to qualify for trial participation in tumour types with less consistent GD2 expression was advocated, along with the use of basket trial designs to evaluate novel products in multiple GD2-positive tumour types simultaneously. If a development program for a novel product has started with neuroblastoma as the model GD2-positive tumour and that initial clinical testing has shown limited activity, then development in other indications would generally be of lower priority unless compelling evidence suggests differential efficacy in tumours with lower or heterogeneous GD2 expression.

In terms of specific novel approaches, early development of GD2 ADCs is encouraged, particularly given the long and successful track record of anti-GD2 antibodies in paediatrics and the multiple successes of ADCs in medical oncology. In addition, many paediatric tumours are sensitive to topoisomerase 1 inhibitors and/or tubulin-targeting agents, which are common mechanisms of action of ADC payloads. With this experience and the high unmet need faced by children with relapsed solid tumours, a development plan that starts initial paediatric enrolment before a final dose has been defined in adults is considered appropriate and encouraged. Likewise, multi-step GD2-directed radiopharmaceuticals are a priority and should be advanced quickly to paediatric testing once adult testing has established optimal dosing. GD2 CAR-T cells urgently warrant evaluation earlier in the treatment of patients with high-risk neuroblastoma in a multicentre academia-led setting. Given the data that current GD2 CAR-T cells may be most beneficial in the setting of low burden disease, the role of GD2 CAR-T as a consolidation strategy for patients in first or subsequent remission should be evaluated. Likewise, with proof-of-concept activity of GD2 CAR-T already demonstrated in patients with primary CNS tumours, concerted efforts are warranted to further investigate this approach in children with primary CNS tumours or CNS metastatic disease. The field needs additional development of GD2 bispecific T-cell engagers, which may address some of the issues of access, cost, and complexity associated with CAR-T. For vaccine approaches, randomised trials are needed to understand their role in context of patients without evidence of disease.

10. Conclusions

The Text Box shows the key conclusions from the meeting. As seen, the GD2 drug development space is very active in neuroblastoma and expanding to other GD2-positive paediatric tumours. The strategies discussed have the potential to improve upon the current standard of care for frontline disease in neuroblastoma by developing antibodies predicted to have a more favourable therapeutic window. Likewise, some newer approaches in development (e.g., CAR-T) are showing promise against relapsed GD2-positive paediatric cancers and comprehensive development plans are needed to expand both the indications for and access to these innovative approaches.

Text Box
Key conclusions of the GD2 Paediatric Strategy Forum.

- Need a plan for a standardised diagnostic development to enable quantification of GD2 expression as a selection biomarker.
- Need to continue to innovate in the post-consolidation space with monoclonal antibodies in neuroblastoma.
- Chemoimmunotherapy strategic recommendations include:
  - Ensure access in neuroblastoma
  - Intercontinental platform trial proposed to screen novel agents added to chemoimmunotherapy in neuroblastoma
  - Evaluation of chemoimmunotherapy in other diseases (e.g., bone sarcoma) should be based upon tissue testing to demonstrate target expression.
- Development of novel products leveraging GD2 as a target (e.g., CAR-T, antibody drug conjugates, bispecific T-cell engagers, and radiopharmaceuticals) is a high priority.
- Consider optimal role for novel products as part of modern therapy, including as cytoreduction and/or as strategies to consolidate responses in low disease burden disease settings.
- Development plan for novel products should include:
  - Strategy that includes future evaluation in the frontline setting.
  - Consideration of other tumour types beyond neuroblastoma.
  - Acknowledgement that novel products already shown to be unsuccessful in neuroblastoma would have lower priority for development in other indications.
  - Patient advocate input to ensure that development efforts remain patient-centred.
- GD2 CAR-T cells urgently warrant evaluation earlier in the course of the disease in neuroblastoma with a multicentre approach.
- Development of novel products in children with primary CNS tumours and CNS metastatic disease requires special consideration.
- Randomised trials of vaccine approaches are needed to understand their role in context of patients without evidence of disease.

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grants from Y-mabs Therapeutics and Abpro-Labs Inc. NKC was named as inventor on multiple patents filed by MSK, including those licensed to Ymabs Therapeutics, Biotec Pharmacon, and Abpro-Labs. Steven DuBois reports advisory fees from Amgen, Bayer, EMD Serono, InhibRx, Jazz, and Merck. Juliet Gray has had consulting roles with EUSA Pharma, YmAbs Therapeutics and Norgine and has received institutional grant funding from BMS, Celgene and EUSA Pharma. Bonnie Hammer is an employee of Invenra. Danelle Meager is an employee of United Therapeutics. Lucas Moreno reports membership of Data Monitoring Committees (DMC) for clinical trials sponsored by the University of Southampton, Karolinska University Hospital and the Royal Marsden NHS Foundation Trust; consulting role for Novartis, Bayer, BMS, Merck, Norgine and Gilead, travel expenses from Recordati Rare Diseases, participation in educational activities organized by Recordati, Beigene, Y-mAbs and Bayer and is the President of the SIOPEN (European neuroblastoma research cooperative group), organization which receives royalties for the sales of dinutuximab beta. His institution receives funding for educational activities, advisory role or conducting industry-sponsored clinical trials. Daniel Morgenstern reports consultancy for Abbvie, Clarity Therapeutics and US World Meds; travel expenses from Abbvie and Lilly and speaker fees from YmAbs Therapeutics and Takeda Israel Ltd. Vanessa Pons Sanz is an employee of Merck Healthcare KGaA. Claudia Rossig has received honoraria for presentations and participation in advisory boards by Novartis and Amgen. Paul Sondel is a co-inventor of INV724; Through his role at the University of Wisconsin, he is a co-inventor/co-patent holder, with Invenra of this agent. Joen Sveistrup is an employee of YmAbs. The remaining authors have declared no conflicts of interest.

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