ACCELERATE
INNOVATION FOR CHILDREN AND ADOLESCENTS WITH CANCER

Paediatric Strategy Forum for Medicinal Product Development of Anti-GD2 Therapies in Children and Adolescents

ACCELERATE in collaboration with the European Medicines Agency and with participation of the Food and Drug Administration

The fourteenth multi-stakeholder Paediatric Strategy Forum focused on products targeting the cell surface ganglioside GD2. GD2 is known to be highly expressed in a variety of paediatric and adult malignancies, particularly in neuroblastoma and three monoclonal antibodies have been granted marketing authorization for this particular indication. However, targeting GD2 with monoclonal antibodies is associated with risk of significant neuropathic pain and other toxicities and resistance remains a challenge, as a proportion of patients continue to relapse after anti-GD2 therapy. In this context, newer products that target GD2 have been developed. Clinical trials of these products and new combinations are either ongoing or planned to evaluate these approaches in neuroblastoma and other GD2-expressing paediatric cancers, including sarcomas and CNS tumours.

The meeting was held at the European Medicines Agency, Amsterdam on 24 and 25 October 2024. There were 184 participants, 110 in person, and 74 virtual attendees.These participants represented a diverse group from 27 different countries, including the USA, Netherlands, United Kingdom, Spain, France, Germany, Belgium, Denmark, Italy, Czechia, Croatia, Canada, Japan, Switzerland, Australia, Greece, Turkey, Ireland, Sweden, Poland, Bénin, Nigeria, Finland, Slovakia, Austria, Singapore, and Norway. The in-person attendees made up approximately 59.8% of the total, while the virtual attendees accounted for 40.2%. This blend of in-person and virtual participation highlights the forum's broad reach and the importance of our discussions on a global scale." The first part of the meeting included foundational background material from academic investigators focused on the biology of GD2, range of expression of GD2 in paediatric cancers, methods for quantifying GD2, and strategies to upregulate GD2 expression. Next, lessons learnt from the experience with monoclonal antibodies in neuroblastoma were presented, including the use of approved agents in the frontline post-consolidation setting and in patients with relapsed/refractory disease. Key challenges highlighted were the need to shorten timelines for clinical development of newer products and avoiding the duplication of clinical trials when different backbone therapies are used in Europe and North America. More recently, chemoimmunotherapy (combination of chemotherapy plus an anti-GD2 monoclonal antibody) has shown transformational activity in patients with relapsed/refractory neuroblastoma and this experience was reviewed. Potential predictive biomarkers of response were summarized, acknowledging that much remains to be learnt in this regard.

Next, a broad range of strategies to target GD2 beyond monoclonal antibodies were discussed, including antibody-drug conjugates, radiopharmaceuticals, chimeric antigen receptor engineered T cells (CAR-T), bispecific T cell engagers, and vaccine approaches. The published experience was reviewed, including the high level of activity seen in patients with relapsed/refractory neuroblastoma treated with third generation CAR-T directed against GD2.

Prepared by Steven DuBois and Lucas Moreno.

Dedicated time was spent discussing the challenges and opportunities of academic development of GD2 CAR-T, along with the need to advance this therapy to multicenter trials earlier in the course of the disease.

Representatives from six pharmaceutical companies presented seven products. These included four monoclonal antibodies specific for GD2 (dinutuximab, dinutuximab beta, hu14.18K322A, and naxitamab), a bispecific antibody directed against GD2 and B7H3 (INV724), an antibody-drug conjugate (M3554), and a GD2-directed self-assembling / disassembling radiopharmaceutical.

Patient advocates provided their perspectives, including lack of clarity on which specific antibodies and antibody combinations are best for children with neuroblastoma. There was further concern about the potential need to repeat studies with one antibody, even after another antibody had been shown to be active in a similar context. There was a strong desire to move novel products into the frontline neuroblastoma space as expeditiously as possible, while also ensuring that innovation continues for children with other GD2-positive cancers who might also benefit from these approaches.

Strategic discussions and conclusions initially focused on general considerations for the field, including the need for early engagement between sponsors and regulatory agencies, with patient advocate participation. Development plans for novel products in neuroblastoma should include a strategy that includes future evaluation in the frontline setting. Likewise, development plans for novel products should consider other tumour types beyond neuroblastoma, including a role for basket trials and prospective GD2 testing to qualify for trial participation.

Additional conclusions centred around four main themes: GD2 testing; improving anti-GD2 therapy in neuroblastoma post-consolidation; improving chemoimmunotherapy; and strategies for novel products beyond GD2-specific monoclonal antibodies.

1) For **testing**, an urgent need was identified for development of standardized tests to enable quantification of GD2 expression for incorporation into routine practice in a homogeneous and comparable manner. A working group was encouraged to review different tissue-based assays, including flow cytometry, immunofluorescence and mass spectrometry,
2) In the **post-consolidation** neuroblastoma space, it was recognized that frontline outcomes and the patient experience are both inadequate and there is a need to continue to innovate in this space by evaluating antibodies that may be associated with less toxicity. With multiple antibodies, it will be important to develop a common framework to better evaluate and compare clinical outcomes with monoclonal antibodies, including toxicities, patient-reported outcomes, and opiate usage.
3) For **chemoimmunotherapy**, strategies to build upon success of chemoimmunotherapy in neuroblastoma are a top priority. The ideal context for rapidly screening agents that may enhance chemoimmunotherapy in neuroblastoma would be a transatlantic platform trial that includes a common comparator arm receiving standard chemoimmunotherapy, with early and parallel engagement with regulators to ensure the trial data can be used for regulatory purposes
4) For **novel products**, it was acknowledged that other disease contexts other than neuroblastoma should be considered for clinical development. For neuroblastoma, the optimal role of novel products in development must be considered: cytotoxic agents (e.g., antibody drug conjugates and radiopharmaceuticals) to reduce bulk disease used

earlier in therapy and CAR-T and bispecific T cell engagers to consolidate responses in low disease burden disease settings. GD2 CAR-T cells urgently warrant evaluation in first relapse, refractory or frontline setting in neuroblastoma in multicenter studies, facilitating development by academia. Randomized trials of vaccine approaches are needed to understand their role in context of patients without evidence of disease.

Prepared by Steven DuBois and Lucas Moreno.