FDA Briefing Document

Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee (ODAC)

May 12, 2022

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office.

We have brought the following issues to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package will not include issues relevant to any final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee.

The subcommittee will consider and discuss the potential utility and steps to validation of an intermediate clinical endpoint, response to induction therapy, in the development of new drugs for the first-line treatment of patients with high-risk neuroblastoma.

The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

Memorandum

Date: April 22, 2022

To: Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee (ODAC) Members, Consultants, and Guests

From: Gregory Reaman, MD
Associate Director for Pediatric Oncology, Oncology Center of Excellence, Office of the Commissioner, FDA

Subject: FDA Background Package for May 12, 2022 Meeting

Thank you for agreeing to participate in the upcoming Pediatric Oncology Subcommittee of the ODAC meeting. The Subcommittee will discuss the potential utility and steps to validation of an early clinical endpoint, response to induction therapy, for the development of new drugs for the first-line treatment of patients with high-risk neuroblastoma.

The Pediatric Oncology Subcommittee of the ODAC will address how response at the end of the induction phase of treatment is used in clinical decision-making and the implications for clinical trial conduct. The Subcommittee will also discuss the need, potential benefits, and limitations to using early clinical endpoints to assess the antitumor activity of investigational drugs used to treat patients with high-risk neuroblastoma in the front-line setting, and the strength of evidence for use of end-induction response for this purpose. Finally, the Subcommittee will discuss potential ways to use end-induction response to facilitate development of new drugs for the treatment of newly diagnosed patients with high-risk neuroblastoma, including the feasibility and potential ways to validate end-induction response as an endpoint that may be used for regulatory decision-making.

As always, we appreciate your time and commitment and look forward to an informative meeting on May 12, 2022.

Use of End-of-Induction Response for Clinical Decision-Making and as a Clinical Endpoint for Development of New Drugs for the First-Line Treatment of Patients with High-Risk Neuroblastoma

Neuroblastomas represent a heterogeneous group of neuroblastic tumors that originate from primitive sympathetic ganglion cells and can arise in locations throughout the sympathetic nervous system. One hallmark of neuroblastoma is its diversity; the clinical presentation and prognosis of patients with neuroblastoma are influenced by several factors, including patient age, tumor location and stage, tumor histology, and tumor molecular characteristics.

With approximately 650 new cases diagnosed each year in the United States[1,2], neuroblastoma is the most common extracranial solid tumor occurring in pediatric patients. Although neuroblastoma rarely occurs in adults[3], it primarily affects young children. The median age at diagnosis is 19 months, and 90% of patients with neuroblastoma are diagnosed at less than 5 years of age[4].

The prognosis for patients with neuroblastoma is highly variable and the risk of relapse can be predicted based on clinical factors and biological features of the tumor at the time of diagnosis. Children of any age with localized neuroblastoma and infants 18 months of age and younger with advanced neuroblastoma with favorable histology and molecular characteristics have a high likelihood of long-term survival. However, older children with advanced-stage disease have a much lower chance of being cured despite treatment with intensive multimodality therapy. Approximately half of patients diagnosed with neuroblastoma have disease that is categorized as high-risk. Patients with high-risk neuroblastoma, including patients greater than 18 months of age with metastases or unresectable disease with high-risk genetic features (e.g. segmental chromosomal aberrations, amplification of the MYCN oncogene, and FOXR2 activation) have a 40% to 50% chance of long-term survival[5].

Neuroblastoma treatment is dependent on the risk categorization, varying from observation or tumor resection in patients with low-risk disease to intensive multimodality therapy in patients with high-risk neuroblastoma. In the United States, the standard treatment regimen for patients with high-risk neuroblastoma consists of the following phases of treatment: induction (chemotherapy and surgical resection), consolidation (tandem cycles of myeloablative chemotherapy and autologous stem cell transplantation, and radiation to the primary and metastatic sites), and post-consolidation "maintenance" treatment for those who achieve an adequate response to the prior phases of treatment (anti-GD2 therapy [dinutuximab in the United

1 Howlader N, Noone AM, Krapcho M, et al., eds: SEER Cancer Statistics Review 1975-2009 (Vintage 2009 Populations). Bethesda, MD: National Cancer Institute, 2012.
2 Gurney JG, Ross JA, Wall DA, et al. *J Pediatr Hematol Oncol.* 1997; 19(5):428-32.
3 Esiashvili N, G. M. *Pediatr Blood Cancer*. 2007; 49, 41-46.
4 London WB, Castleberry RP, Matthay KK, et al. *J Clin Oncol*. 2005; 23(27):6459-65.
5 Gustafson WC and Matthay KK. *Expert Rev Neurother.* 2011;11(10):1411-23.

States] combined with granulocyte-macrophage colony-stimulating factor [GM-CSF] and isotretinoin).[6.]

Enrollment in a clinical trial can also be considered. In the United States, patients with high-risk neuroblastoma may be eligible to enroll in Children's Oncology Group (COG) studies ANBL1531 (NCT03126916) or ANBL19P1 (NCT04385277). Study ANBL1531 includes a randomized component to evaluate whether 131I-metaiodobenzylguanidine (131I-MIBG) added to induction therapy for patients with metaiodobenzylguanidine-avid neuroblastoma that lacks a detectable ALK alteration improves event-free survival. Patients with tumors with an ALK mutation or ALK amplification will enroll in a single-arm cohort to receive lorlatinib in additional to standard induction therapy. Study ANBL19P1 is a single-arm pilot study evaluating whether dinutuximab, GM-CSF, and isotretinoin in combination with irinotecan and temozolomide can be safely given to patients with high-risk neuroblastoma after the consolidation phase of treatment.

There are a limited number of drugs approved for the treatment of neuroblastoma, with the majority being older cytotoxic drugs that may be used in the front-line setting (e.g., cyclophosphamide, doxorubicin, vincristine). In March 2015, after decades of clinical development, the FDA approved dinutuximab, in combination with GM-CSF, IL-2, and 13-cis-retinoic acid, for the treatment of pediatric patients with high-risk neuroblastoma in the front-line maintenance setting who achieve at least a partial response to prior first-line multiagent, multimodality therapy. More recently, the FDA approved naxitamab-gqgk in combination with GM-CSF for the treatment of pediatric patients with relapsed/refractory neuroblastoma in the bone or bone marrow who have demonstrated a partial response, minor response, or stable disease following prior therapy.

The endpoints traditionally used to evaluate effectiveness of drugs for the first-line treatment of patients with high-risk neuroblastoma are event-free survival (EFS, typically defined as the time from randomization to the first occurrence of relapse, progressive disease, secondary malignancy or death) and overall survival. The approval of dinutuximab for the maintenance treatment of patients with high-risk neuroblastoma was based on the results of a trial conducted by the COG (Study ANBL0032), which demonstrated a clinically meaningful improvement in EFS as assessed by the investigator in patients randomized post-consolidation to receive dinutuximab in combination with IL-2, GM-CSF and 13-cis retinoic acid compared to those receiving 13-cis retinoic acid alone. The EFS results were supported by a trend toward improvement in Overall Survival.[7] The primary outcome measure in the ongoing ANBL1531 trial is also EFS, with overall survival and end-induction response rate (the percentage of patients who achieve at least a partial response per the revised International Neuroblastoma Response Criteria [INRC)] at the end of induction) as secondary objectives.

6 Neuroblastoma Treatment (PDQ®), "Treatment Option Overview for Neuroblastoma" at http://www.cancer.gov/cancertopics/pdq/treatment/neuroblastoma/HealthProfessional/page4#Reference4.8 accessed April 13, 2022.
7 Package insert for Unituxin, available at Drugs@FDA, accessed on April 13, 2022 https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/125516s000lbl.pdf.

Randomized trials appear to have a continued role in generating the evidence needed to improve treatment paradigms for patients with high-risk neuroblastoma, despite the challenges associated with enrolling sufficient numbers of patients in a timely fashion and the length of time needed to conduct the trials. Citing the occurrence of early disease progression reported in an estimated 7 to 15% of patients in prior studies, researchers have also emphasized the importance of identifying the most effective treatments to use during the induction phase of treatment in order to improve patient outcomes, and the role of end-of-induction response as a prognostic factor based on an identified association between end-of-induction response and event-free survival or overall survival[8, 9,10]. As such, further exploration of the potential utility of end-of-induction response as a clinical endpoint to support drug development for the first-line treatment of patients with high-risk neuroblastoma may be warranted.

Traditional approval of drugs and biologics by the FDA is based on demonstration of clinical benefit to patients (for example, by demonstrating an improvement in overall survival), or an effect on an established surrogate known to predict clinical benefit. Accelerated approval is based on "…a determination that the product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and availability or lack of alternative treatments."[11] In oncology, endpoints such as progression-free survival and overall response rate can serve different purposes depending on the context of use. The determination is based on the specific diseases and is highly dependent upon factors such as the effect size, effect duration, depth of response, available therapy, disease setting, location of diseases.[12] Aside from use as an endpoint to support drug approval, clinical endpoints can be used for multiple other purposes to optimize clinical trial design, inform drug development decisions, and guide patient care.

From a U.S. regulatory standpoint, surrogate endpoints and potential surrogate endpoints can be characterized by the level of clinical validation. The strength of evidence to support surrogacy depends on factors including (1) the biological plausibility of the relationship, (2) demonstration in epidemiological studies of the prognostic value of the surrogate endpoint for the clinical outcome, and (3) evidence from clinical trials that treatment effects on the surrogate endpoint correspond to effects on the clinical outcome.[13] Presence of a strong prognostic relationship

8 DuBois SG, Bagatell R. Improving Outcomes in Children With High-Risk Neuroblastoma: The Role of Randomized Trials. *J Clin Oncol*. 2021 Aug 10;39(23):2525-2527. doi: 10.1200/JCO.21.01066. Epub 2021 Jun 21. PMID: 34152837; PMCID: PMC8330963.

9 Pinto N, Naranjo A, Hibbitts E, Kreissman SG, Granger MM, Irwin MS, Bagatell R, London WB, Greengard EG, Park JR, DuBois SG. Predictors of differential response to induction therapy in high-risk neuroblastoma: A report from the Children's Oncology Group (COG). *Eur J Cancer*. 2019 May;112:66-79. doi: 10.1016/j.ejca.2019.02.003. Epub 2019 Apr 1. PMID: 30947024; PMCID: PMC6491235..

10 Barr EK, Laurie K, Wroblewski K, Applebaum MA, Cohn SL. Association between end-induction response according to the revised International Neuroblastoma Response Criteria (INRC) and outcome in high-risk neuroblastoma patients. *Pediatr Blood Cancer*. 2020 Oct;67(10):e28390. doi: 10.1002/pbc.28390. Epub 2020 Jul 25. PMID: 32710697; PMCID: PMC7722196..

11 Section 506(c) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 356(b), as amended by the Food and Drug Administration Safety and Innovation Act of 2012.

12 2018 FDA Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. https://www.fda.gov/media/71195/download.

13 ICH guidance for industry E9 Statistical Principles for Clinical Trials (September 1998).

between potential surrogate and clinical outcome does not guarantee correct inference based on a potential surrogate endpoint[14,15,16].

There are a variety of statistical approaches to explore the evidence of surrogacy of an early endpoint to clinical outcome from clinical trials. One approach is to show that an early endpoint fulfills the Prentice criteria that it is a correlate of the clinical outcome and fully captures the net effect of treatment on the clinical outcome.[17] This approach is theoretically appealing but likely to be impractical[18,19]. The other approaches include assessment of proportion of net treatment effect explained by the surrogate endpoint[20], assessment of the proportion of times the trials reached the same conclusion based on statistical significance testing for the two endpoints[19], and assessment of individual- and trial-level association between the proposed surrogate and the true endpoint[21.] In general, the FDA recommends that sponsors seek advice regarding a planned approach prior to committing resources to providing evidence of surrogacy for regulatory purposes.

There are challenges to the validation and use of surrogate endpoints. A major challenge in using meta-analytic methods for surrogate validation is that these methods often require patient-level data from multiple randomized controlled trials. This challenge may be particularly difficult to address in rare diseases such as neuroblastoma, where only a limited number of randomized controlled trials is feasible. A recent commentary authored by several patient advocates who work to promote development and access to new treatments for patients with neuroblastoma highlighted the importance of early and extensive planning and coordination among global stakeholders. Such collaborations may help to address the challenges associated with development of new treatments for patients with high-risk neuroblastoma and facilitate the design and conduct of clinical trials that can satisfy regulatory requirements for approval and applicable requirements for drug reimbursement and access, in addition achieving other scientific objectives to best serve patients.[22] The FDA is committed to early and sustained multistakeholder collaboration to facilitate drug development for patients with high-risk neuroblastoma, who have continue to have a substantial unmet medical need.

14 DeMets DL, Psaty BM, Fleming TR. When Can Intermediate Outcomes Be Used as Surrogate Outcomes? *JAMA*. 2020;323(12):1184–1185. doi:10.1001/jama.2020.117.
15 McShane LM, Smith MA. Prospects for Minimal Residual Disease as a Surrogate Endpoint in Pediatric Acute Lymphoblastic Leukemia Clinical Trials. *JNCI Cancer Spectr*. 2018 Dec 19;2(4):pky070. doi: 10.1093/jncics/pky070. PMID: 31360885; PMCID: PMC6649735.
16 Baker SG, Kramer BS. A perfect correlate does not a surrogate make. *BMC Med Res Methodol*. 2003 Sep 9;3:16
17 Prentice RL. Surrogate endpoints in clinical trials: definitions and operational criteria. *Statistics in Medicine.* 1989; 8: 431–440.
18 Berger VW. Does the Prentice criterion validate surrogate endpoints? *Statistics in Medicine*. 2004 May 30;23(10):1571-8.
19 Begg CB, Leung DHY. On the use of surrogate end points in randomized trials. *Journal of the Royal Statistical Society (Series A).* 2000; 163: 15–24.
20 Freedman LS, Graubard BI, Schatzkin A. Statistical validation of intermediate endpoints for chronic diseases. *Statistics in Medicine.* 1992; 11: 167–178.
21 Burzykowski T, Molenberghs G, Buyse M, Geys H, Renard D. Validation of surrogate end points in multiple randomized clinical trials with failure time end points. *Applied Statistics.* 2001; 50: 405–22.
22 Bird, N., Knox, L., Palmer, A., Heenen, D., Blanc, P., Scobie, N., & Ludwinski, D. (2022). When Innovation and Commercialization Collide: A Patient Advocate View in Neuroblastoma. *Journal of Clinical Oncology*. 40(2), 120–126. https://doi.org/10.1200/JCO.21.01916.

Discussion Topics Relating to the End of Induction Response in High-Risk Neuroblastoma

1. Please discuss the potential benefits and limitations to use of an intermediate clinical endpoint in the evaluation of new drugs under development for the first-line treatment of patients with high-risk neuroblastoma.

2. Please discuss the strength of the evidence for use of end-of-induction response as a prognostic factor and to assess antitumor activity of investigational treatments during the induction phase of treatment.

3. Please discuss how end-of-induction response is used in clinical decision-making and the implications of its use to the design and conduct of clinical trials investigating new treatments during the induction phase of treatment of patients with high-risk neuroblastoma.

4. Given the current strength of evidence for use response at the end-of-induction to predict patient outcome and assess antitumor activity, consider the appropriate use of this endpoint in clinical trials.

5. If there is sufficient evidence to support future efforts, please provide recommendations regarding interest, feasibility and future steps to validation of end-of-induction response as a clinical endpoint in front line treatment of patients with high-risk neuroblastoma.