3 An FDA Oncology Perspective of Juvenile Toxicity Studies to Support Pediatric Drug Development

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3.1 Introduction

In 2016, the FDA Office of Oncologic Diseases (formerly the Office of Hematology and Oncology Products) published their view of the utility of juvenile animal studies (JAS) to support clinical development in pediatric patients for the treatment of cancer (Leighton et al. 2016). After reviewing the available data in our files and considering how clinical trials are conducted in pediatric populations, FDA Oncology concluded that JAS were generally not warranted, consistent with the position described in the ICH S9 Guidance for Industry: Nonclinical Evaluation for Anticancer Pharmaceuticals (FDA 2010). The reasons for both the Office's conclusion and the original basis for the statement in the guidance were that available clinical data in adult patients could be used to inform on monitoring and to set a start dose; that the life expectancy of pediatric patients in phase 1 or 2 trials was relatively short; that there was adequate monitoring for potential adverse events in this patient population; and that there were benefits to not delaying the clinical development of potentially promising drugs for pediatric patients with advanced cancer. They concluded that a JAS initiated or completed after a clinical trial in pediatric patients was ongoing or complete was of little

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to no value unless there was a specific question to be asked and the data to answer this question could not be obtained through clinical studies. It is usually the scenario in the oncology setting that clinical trials in adults are ongoing or complete prior to the initiation of clinical trials in pediatric patients, with the rare exception of the monoclonal antibodies to treat patients with neuroblastoma (dinutuximab and naxitamab). These drugs are discussed in more detail below. Also discussed in more detail below are the NTRK inhibitors; one of the drugs, larotrectinib, is approved for pediatric patients 28 days and older. Both drugs in this class are also approved for use in adults.

Since 2016 two new comprehensive reviews were published expressing contrasting opinions. In November 2017 EMA (2017) published a final document titled "Results of juvenile animal studies (JAS) and the impact on anti-cancer medicine development and use in children." Included among the benefits of JAS articulated in this paper were the need for more information, deferring inclusion of the youngest pediatric patients, waiver of additional pediatric studies in children less than 2 years of age, and recommendations on clinical trial design. Contrarily, Visalli et al. (2018) published a review titled "Lack of value of juvenile animal toxicity studies for supporting the safety of pediatric oncology phase 1 studies" looking at a dataset similar to that in the EMA paper that included 25 molecularly targeted drugs and 4 biologics. These authors concluded that the first pediatric dose was safe for all 29 drugs, that no life-threatening adverse events occurred in the first cohort, that the maximum tolerated dose (MTD) in pediatrics compared to the MTD in adults was close to 1, and that standard JAS would not have predicted the serious adverse events that did occur but were not picked up in standard clinical monitoring plans. The differing conclusions may be partly due to differences in the analysis: the EMA focused on differences in juvenile vs. adult animals, whereas Visalli et al. focused on dose setting and clinical monitoring when considering the value of JAS. A search of the PubMed database did not reveal any more recent reviews of JAS from 2016.

Now is perhaps an opportune time to reexamine the utility of JAS in oncology drug development. Have we learned anything in the studies that have been conducted? Since the 2016 publication by Leighton et al., ICH published a Question and Answers document for ICH S9 (FDA 2018b) that does not address JAS, and the ICH S11 (FDA 2021). This paper will briefly summarize the positions described in the S9 Q&A and S11 Guidance documents regarding JAS and oncology drugs as well as FDA Oncology's analysis of JAS conducted over the last few years, with particular focus on the approved anti-GD2 antibodies and the NTRK inhibitors due to the available data and the roles of both of these targets in the CNS. JAS conducted for other products will not be discussed in this paper as FDA Oncology has not routinely requested JAS to support pediatric drug development. Note that presence of JAS data in a product label should not be taken as an indication that the study was specifically requested or of the added benefit of the study, as labeling practices call for the inclusion of information from a JAS in Section 8.4 of a product label regardless of the impact of the nonclinical study on the clinical trial.

This paper will not discuss the role of pharmacology studies in assessing whether a clinical trial in pediatric patients is appropriate. Arguably, these proof-of-concept and mechanistic studies are more important than juvenile toxicity studies in that they lay the foundation for the initial Pediatric Study Plan and the study; without an adequate mechanistic understanding of the drug in the context of the disease, patients may be enrolling in a study which will be of little value, if any, for their treatment. For example, in vitro or in vivo nonclinical data (including in silico data, mechanism-based in vitro data, and appropriate tumor models) can inform the potential response to a treatment, and thus provide support for the inclusion of children from 2 to under 12 (see the final FDA Guidance on Cancer Clinical Trial Eligibility, March 2020a).

3.2 Should a JAS Be Considered?

A juvenile animal study (JAS) to support an oncology indication in a pediatric population is often not needed. But on rare occasions, a JAS may be considered, such as when there are no

data in adults (product to be developed in children only) and a long life expectancy is anticipated for the study participants. While ICH S11 is mainly for non-oncology indications, the weight of evidence (WoE) approach described in this guidance may be consulted when considering a JAS. Given the nature of the disease and the monitoring usually in place for clinical trials for oncology drugs, the available clinical data and nonclinical studies in adult animals are usually considered sufficient to initiate a pediatric trial, and, thus, a JAS is not usually warranted. This principle was outlined in ICH S9. The rationale for FDA Oncology's position that JAS are generally not warranted was further articulated by Leighton et al. (2016) and need not be repeated here. If there are age-dependent safety concerns regarding the conduct of a clinical trial in pediatric population, then a staggered age enrollment may be considered.

3.2.1 ICH S11: Nonclinical Safety Testing in Support of Development of Pediatric Medicines

The ICH S11 Guidance, finalized in 2020, does not replace the recommendations in ICH S9 but can be consulted as needed, e.g., for JAS design when a study is warranted. The objective of the S11 Guidance, like most ICH guidances, is to promote harmonization and to apply the principles of the 3Rs; reduce, refine, and replace the use of animals where appropriate. Consistent with ICH S9, the S11 Guidance states that nonclinical studies should be undertaken only when available nonclinical and clinical data are judged to be inadequate to support the safety of a clinical trial in pediatric patients. The S11 Guidance provides key factors to consider in a weight of evidence determination to assess whether additional nonclinical studies are needed, and information on the design of nonclinical studies to support a pediatric development program. The guidance also discusses that for severely debilitating and life-threatening diseases, the information obtained should be weighed against the potential delay in clinical development, a consideration that would generally encompass anticancer drugs proposed for use in pediatric patients.

3.2.2 ICH S9: Nonclinical Evaluation for Anticancer Pharmaceuticals Questions and Answers

The main ICH S9 Guidance on nonclinical development for anticancer pharmaceuticals was published in 2010 and stated that in general JAS were not warranted to support the development of drugs intended for the treatment of patients with cancer; however, even after publication of the guidance, the Agency noted that developers were still often conducting JAS and submitting these studies to INDs or to marketing applications. The reason for the continued frequency of JAS conducted to support the safety of oncology drugs was not obvious; it could have been a timing issue with studies initiated prior to finalizing the guidance, or perhaps regulatory agencies in other regions were requesting these studies. To provide additional clarity around this and other topics discussed in ICH S9, a Concept Paper (CP; available at ich.org) was proposed to the ICH Steering Committee and endorsed on 23 October 2014. The CP did not specifically mention juvenile toxicity studies. Nevertheless, in response to feedback received from various stakeholders in developing the Q&A, the S9 Implementation Working Group (IWG) formed after adoption of the CP received questions for clarification on this topic. A draft Q&A was published on 8 June 2016 at Regulations.gov (docket # FDA 2016-D-2569) that included the following juvenile animal discussion:

Q: The guideline states that juvenile animal studies should be considered only when human safety data and previous animal data are insufficient. Under what situations would a juvenile animal study be warranted? What should be the goal of a juvenile animal study to support development in paediatric patients with cancer?

Draft response: Juvenile toxicity studies should only be performed when available animal models are believed to generate data relevant for paediatric safety, and there is a clear

value for such data for supporting clinical paediatric development. This is normally not the case for paediatric clinical trials in children with limited available therapeutic options and short life expectancy. Clinical data from adults is typically available prior to initiation of these paediatric trials; this data is used to set a starting dose and inform monitoring plans. In addition, these trials are usually done in a controlled setting with substantial safety monitoring. Pharmacology data and toxicology data from adult animals can also inform on safety.

When clinical development is pursued in children with longer life expectancy, the need for juvenile toxicity testing should be a case by case decision based on the available knowledge on pharmacology, nonclinical and clinical safety and the presence of safety concerns where a juvenile toxicity study could add important information. When studies are needed, ICH S11 should be consulted to address the design of the juvenile animal study. A dialogue with the regulatory agency is also encouraged.

To support the clinical development in a paediatric-only indication, the age of animals in the repeat-dose toxicity studies should be chosen to cover the age of the patient population in the initial clinical trials.

The FDA did not receive any comments to the docket regarding this question during the public comment period, but objections were raised in the deliberations of the IWG subsequent to the publication of the draft Step 2 guidance. The IWG explored various wordings to achieve harmonization, but could not reach consensus and, thus, decided that removing the reference to JAS entirely would allow sponsors more freedom to have discussions with regional regulators. For this reason, the Step 2 draft language was removed, and there is no reference to JAS in the final S9 Q&A guidance published in 2018.

3.3 Dinutuximab and Naxitamab

The anti-GD2 antibodies Unituxin (dinutuximab) (FDA 2015) and Danyelza (naxitamab-GQGK) (FDA 2020b) were approved in 2015 and 2020, respectively. Both products were follow-ons to murine antibodies against human GD2 originally developed in academic settings in the 1980s. As expected of a murine antibody, development of human anti-murine antibodies limited clinical utility leading developers to develop chimeric or fully humanized versions of the products as clinical development proceeded. The biology, chemistry, and nonclinical and clinical development of the anti-GD2 antibodies have been reviewed by Sait and Modak (2017). A major side effect noted in these trials is neuropathic pain, which was moderated in those patients developing an immunogenic response.

Dinutuximab (ch14.18), a chimeric IgG1 antibody produced in the murine SP2/0 cell line, is now a standard therapy for treatment of pediatric patients with high-risk neuroblastoma. It was also studied in adults at Memorial Sloan Kettering between 1979 and 2015 for the same indication (Suzuki et al. 2018). The major side effect of dinutuximab is neuropathic pain, probably related to the pharmacologic activity of the drug. There were no long-term toxicology studies conducted with dinutuximab, and the majority of the clinical experience was in combination with other therapies (IL-2 and/or GM-CSF). There was limited chronic toxicity data in either human adults or in animals, and questions related to recovery of neurotoxicity remained, particularly in still developing brains. For these reasons a post-marketing requirement (PMR) to conduct a JAS in cynomolgus monkeys of 5-month duration was requested for dinutuximab to further understand the potential neurotoxicity and potential for recovery. The PMR requested a detailed evaluation of the central and peripheral nervous systems, with 7–8 slices of the brain for histopathological assessment and long-term evaluation for potential effects on nociception and pain threshold at the end of an appropriate recovery period. Section 8.4 of the original label has since been updated to reflect the results of this JAS. The main findings of the study were degeneration in the dorsal root ganglia that persisted 6 months after cessation of dosing, although with lesser severity, and decreased nerve conduction velocity that also showed signs of slow reversibility after 6 months.

Naxitamab (hu3F8-IgG1) is a humanized version of m3F8 (a murine version of the antibody).

It is reported to be associated with much less immunogenicity than its murine precursor, and higher doses are tolerated (Sait and Modak 2017). Due to concerns regarding the relevance of the model chosen to assess the toxicity of this product (the nude rat) and the age of the only indicated patient population, a JAS in a relevant species similar in design to that requested for dinutuximab was also requested as a PMR for naxitamab. According to the PMR timelines, a final report is expected in July 2023.

3.4 TRK Inhibitors

Trk proteins have an established role in neuronal development (Smeyne et al. 1994; Tucker et al. 2001). Published reports of congenital somatic mutations in TRK proteins or their ligands suggest a relationship between deficient Trk signaling and development of schizophrenia, mood disorders, obesity, and peripheral sensory and motor disorders (Indo et al. 1996; Knable 1999; Kranz et al. 2015; Lewis et al. 2005; Otnaess et al. 2009; Yeo et al. 2004). An awareness of the link between deficiencies in these pathways and CNS effects in humans might raise the value JAS for drugs targeting these pathways, particularly as other studies typically conducted to support clinical development of oncology drugs may not fully capture these endpoints. For example, while embryo-fetal development studies can detect malformations in brain structure, they are not designed to assess motor development or psychiatric function, and while a pre- and postnatal development study may be capable of evaluating some endpoints of concern, these studies are not typically recommended for a drug intended to treat patients with advanced cancer.

Vitrakvi (larotrectinib sulfate) (FDA 2018a) was approved in 2018 for used in adult and pediatric patients with solid tumors that have the neurotrophic tyrosine receptor kinase (NTRK) gene fusion. The results of a JAS submitted with the original application are described in Section 8.4 of the label and in more detail in the nonclinical review. As part of the administrative record for NDA 210861, the Applicant, Loxo, described the design of a JAS that was requested by the European Medicines Agency and the Pediatric Subcommittee of the Oncology Drugs Advisory Committee. In two separate studies, juvenile animals were dosed from day 7 to 27, and from day 28 to 70; the main findings were transient central nervous system-related signs, including head flick, tremor, and circling in both sexes. These studies also demonstrated potential effects on learning and memory, consistent with known effects of TrkA signaling deficiencies in humans associated with the rare recessive disorder, congenital insensitivity to pain, and anhidrosis (CIPA; Indo et al. 1996).

Rozlytrek (entrectinib) (FDA 2019) was approved in 2019 with a similar indication regarding the NTRK gene fusion. JAS data are described in Section 8.4 of the product label. In a 13-week JAS where animals were dosed from the neonatal stage to adulthood (day 7–97), the main findings were decreased body weight gain and delayed sexual maturation, neurobehavioral deficits, and decreased femur length. Both JAS did show evidence of neurobehavioral changes compared to untreated controls; nevertheless, toxicity to the central nervous system is an expected finding based on expression of TRKs and their known roles on neural development and behavior, and there were similar signs in adult animals. While the JAS did suggest a potential for increased effects or effects at lower doses in pediatric patient populations compared to adults, findings of increased severity are not uncommon in JAS for other targets either and do not represent new toxicities compared to those identified in adult studies.

3.5 Conclusion

FDA Oncology's general approach to use of JAS to support pediatric oncology indications has been well articulated by ICH S9 and by Leighton et al. (2016). There has been no significant new data to suggest that the current approach needs to be reconsidered at this time. FDA Oncology has requested JAS on a rare basis, to address specific questions and concerns. This approach is consistent with the principles outlined by the FDA Roadmap regarding reducing, refining, and replacing the

use of animals for nonclinical studies when warranted. Not routinely requesting JAS to support the development of drugs to treat pediatric patients with cancer clearly reduces animal use, especially use of nonhuman primates, often the only pharmacologically relevant model for biotherapeutics including immune-oncology drugs and antibody-drug conjugates.

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