September 24th, 2020
Ohara Pharmaceutical Co., Ltd.

Recombinant Chimeric Monoclonal Antibody "Dinutuximab (OP-08)": Application Filed for Marketing Authorization for Neuroblastoma

Ohara Pharmaceutical Co., Ltd. (head office: Koga City, Shiga Prefecture; president: Seiji Ohara) has filed an application for marketing authorization to the Ministry of Health, Labour and Welfare for Dinutuximab (hereinafter referred to as "OP-08"), a recombinant chimeric monoclonal antibody as a therapeutic agent for neuroblastoma.

This application has been filed based on the outcome of the two clinical studies below conducted in Japan (Study GD2-PI and Study GD2-PII). These studies demonstrated the efficacy and safety of three-drug combination therapy (with filgrastim and teceleukin).

OP-08 acquired Orphan Drug Designation from the Ministry of Health, Labour and Welfare on August 17th, 2020.

[Study GD2-PI]

The phase I/IIa study in Japan was conducted as an investigator-initiated study. This study was conducted in patients with relapsed neuroblastoma or high-risk neuroblastoma in remission with treatment, and demonstrated the tolerability for three-drug combination therapy.

[Study GD2-PII]

The phase IIb study in Japan was conducted as an investigator-initiated study. This study was conducted in patients with high-risk neuroblastoma in remission with treatment, for the purpose of demonstrating non-inferiority to the U.S. regimen of three-drug combination therapy (a regimen approved in the U.S. that combines sargramostim as a GM-CSF preparation and aldesleukin and isotretinoin as IL-2 preparations), with two-year EFS (event-free survival) as the primary end point. The two-year EFS as the primary end point was demonstrating the non-inferiority of the three-drug combination therapy to the US regimen. There was no substantial difference in safety between the three-drug combination therapy and the US regimen.

We will continue to further endeavor to deliver OP-08 to patients with neuroblastoma as fast as possible.

[About Neuroblastoma]

Neuroblastoma refers to a type of childhood solid tumor where cells become cancerous, originating in neural crest cells in the fetal period. This is the third most frequently observed tumor among childhood cancers, after leukemia and brain tumor. The peak age of onset is 0 and 3 years.[1)] This disease is difficult to detect in the early stage, because it remains asymptomatic while the tumor is small. In most patients, it is detected after the tumor has progressed and become metastatic, marked by symptoms such as a head bump, swollen eyes, pain in the limbs, anemia and/or bruise. [2)]

It is estimated that about up to 160 patients are diagnosed with neuroblastoma every year in Japan, with about up to 3,300 patients in total.

Neuroblastoma is classified into three risk groups (Low, Intermediate and High), based on the five prognostic factors: staging, age, extra copies of the *MYCN* gene in the tumor cells, International Neuroblastoma Pathology Classification, and the number of chromosomes in the tumor cells.[3)] While the cure rate of patients in the Low to Intermediate risk groups exceed 90%, about 60% of all patients are classified in the High risk group with the five-year survival rate 50% or lower. This is why neuroblastoma is considered to have the poorest prognosis among other childhood solid tumors.[2)]

[What are orphan drugs?]

Orphan drugs refer to drugs designated by the Minister of Health, Labour and Welfare for diseases with less than 50,000 patients in Japan, considered to be of particularly high medical needs through the relevant review.

【参考文献】

1） 日本小児血液・がん学会作成　小児がん診療ガイドライン 2016 年版

2） 七野 他. 神経芽腫に対する集学的治療法：化学療法を中心に. 小児がん. 2010, Vol. 47, No.1, p. 046-052.

3） Cohn SL., et al. The International Neuroblastoma Risk Group (INRG) Classification System:An INRG Task Force Report. J Clin Oncol. 2009, Vol. 27, No. 2, p. 289-297.

[About OP-08]

OP-08 is a recombinant chimeric monoclonal antibody, and is a glycoprotein with the molecular weight of approx. 150,000 Daltons, consisting of the variable region (mouse anti-Ganglioside-GD2 monoclonal antibody) and the constant region (human IgG1).

This drug specifically interacts with the antigen GD2 that frequently expresses in human neuroectodermal tumor (such as neuroblastoma), and provokes the cytolysis of neuroblastoma cells through the antibody-dependent cell-mediated cytotoxicity (ADCC) effect and the complement-dependent cytotoxicity (CDC) effect.

In the U.S. and Canada, OP-08 was approved for the following indication and marketed as Unituxin® by United Therapeutics Corporation of the U.S: "Unituxin (dinutuximab) is indicated, in combination with granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-2 (IL-2) and 13-cis-retinoic acid (RA), for the treatment of pediatric patients with high-risk neuroblastoma who achieve at least a partial response to prior first-line multiagent, multimodality therapy."

[About Ohara Pharmaceutical Co., Ltd.]

Ohara Pharmaceutical Co., Ltd. is a pharmaceutical company that discovers and develops orphan drugs and generic drugs as its mainstay business. The company particularly focuses on the development and marketing of orphan drugs for pediatric cancer and other areas, and on the development, manufacturing and marketing of generic drugs that feature the prevention of medical accidents. Ohara Pharmaceutical aims to become a company that provides total healthcare solution by promoting innovations not only in treatment, but also for prevention, diagnosis and aftercare that affect the quality of healthcare, in the substantially changing healthcare environment and improving treatment outcome.