

Translation

Anti-Angiogenic Anti-Cancer Agent Avastin® Condition for Approval (All Patients Surveillance) Removed in Japan

September 8, 2010 (Tokyo) - Chugai Pharmaceutical Co., Ltd. [Head Office: Chuo-ku, Tokyo; President: Osamu Nagayama (hereafter, "Chugai")] today announced that it has received a notification from the Japanese Ministry of Health, Labour and Welfare (MHLW) that the condition for approval (surveillance of all patients^{*1}) has been removed for the humanized anti-VEGF monoclonal antibody Avastin® (brand name: Avastin® for intravenous infusion 100mg/4mL or 400mg/16mL). for the treatment of patients with "advanced or refractory colorectal cancer who is not the candidate for the curative operation." Avastin is marketed for the treatment of "advanced or refractory colorectal cancer who is not the candidate for the curative operation" and "unresectable advanced or recurrent non-squamous non-small cell lung cancer."

Avastin was originally approved for "advanced or refractory colorectal cancer who is not the candidate for the curative operation" in 2007. As part of the MHLW approval conditions an extensive post-marketing surveillance was undertaken in order to obtain safety information for patients in a large observational study. The original condition for approval stated that *"Because of a very limited number of the subjects treated in the domestic clinical trials, a post-marketing surveillance of all patients who received Avastin® after the launch of it should be conducted until the data of a certain number of patients are accumulated in order to identify the background of the patients and collect the safety and efficacy data of them early, and take necessary measures for proper use of Avastin®."*

Safety and efficacy data on 2,699 patients with "advanced or refractory colorectal cancer who is not the candidate for the curative operation" was submitted to the Japanese MHLW as the aggregate analysis results of the surveillance**. Based on the results, it has been determined that the post marketing surveillance, which was the condition for the approval of Avastin®, had been conducted properly, necessary measures for proper use of the drug are already in place and accordingly no further surveillance is required.

No conditions for approval are required for Avastin in unresectable advanced or recurrent non-squamous NSCLC.

Chugai, as a leading pharmaceutical company in the field of oncology, will continuously provide innovative and useful pharmaceutical products and information for "the realization of cancer care that brings about hope for patients in their coping with cancer" and will continue to make efforts to provide information on the proper use of our products while giving the highest priority to the safety of patients.

[References]

* Objective of all patients surveillance

The objective of the surveillance is to obtain information on the safety (adverse effects of the drug) of the drug and to ensure the safe use of the drug for those patients with "advanced or refractory colorectal cancer who is not the candidate for the curative operation," who receive treatment with AVASTIN[®]. The all patients surveillance started from June 11, 2007, and completed on December 31, 2008.

** Aggregate analysis results

Of 2,712 patients with "advanced or refractory colorectal cancer who is not the candidate for the curative operation" who were enrolled between June 11, 2007 and November 9, 2007, those subjected to data aggregation (background data aggregation: 2,699 patients, safety data aggregation: 2,696 patients, effective data aggregation: 2,695 patients) were included in this surveillance and data on these patients was evaluated.

In this surveillance, Avastin[®] was used for first line and second line treatments of "advanced or refractory colorectal cancer who is not the candidate for the curative operation" in 45.7% and 52.5% of patients, respectively. Major concomitant chemotherapies were FOLFOX therapy in 63.5% and FOLFIRI therapy in 28.9%.

The overall incidence of adverse drug reaction was 61.9%, in which the incidence of serious adverse drug reactions accounted for 15.3%. As adverse drug reactions characteristic of Avastin[®], hypertension (frequency: 13.5%) and hemorrhage (mostly epistaxis) (frequency: 11.8%) occurred most frequently, and serious adverse drug reactions such as gastrointestinal perforation and venous thromboembolism were reported although the frequency was low at approximately 1%. The safety profile was almost the same as in the clinical trials previously reported in other countries and clinical trials/safety assurance studies conducted in Japan during development of the drug.

The results of these surveillances have been presented at domestic and international meetings¹⁾
2) 3) 4) 5) and provided to healthcare professionals in various forms of information including package insert, interview form and guidance for proper use of the drug.

- 1) The 46th Annual Meeting of the Japan Society of Clinical Oncology (October 30-November 1, 2008, Nagoya) #S6-8
- 2) 2009 Gastrointestinal Cancers Symposium (ASCO GI, January 15-17, 2009, San Francisco) #485
- 3) The 7th Annual Meeting of Japanese Society of Medical Oncology (March 20-21, 2009, Nagoya) #O1-061
- 4) The 64th General Meeting of the Japanese Society of Gastroenterological Surgery (July 16-18, 2009, Osaka) #O-2-045
- 5) The joint 15th Congress of the European Cancer Organization and 34th Congress of the European Society for Medical Oncology (ECCO/ESMO, September 20-24, 2009, Berlin) #6.057