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CHUGAI
Roche Group

Translation

Anti-Cancer Agent "Avastin®," Obtained Approval for Additional Indication and Dosage and Administration of Malignant Glioma

June 14, 2013 (Tokyo) - Chugai Pharmaceutical Co., Ltd. [Main Office: Chuo-ku, Tokyo. Chairman & CEO: Osamu Nagayama (hereafter, "Chugai")] announced today that it obtained approval by the Japanese Ministry of Health, Labour and Welfare (MHLW) on June 14, 2013, for the additional indication and dosage and administration of "Malignant glioma," for the anti-cancer agent / anti-VEGF humanized monoclonal antibody, "AVASTIN® I.V. Infusion 100mg/4mL and 400mg/16mL" [generic name: bevacizumab (recombinant) for Infusion] (hereafter, Avastin®). In Japan, Avastin® is currently marketed for the indications of "unresectable advanced or recurrent colorectal cancer," "unresectable advanced or recurrent non-squamous non-small cell lung cancer," and "inoperable or recurrent breast cancer."

On April 6, 2012, Chugai received a request from the MHLW to develop "Avastin®" for the treatment of recurrent glioblastoma, as a result of the evaluation by the "11th Review Committee on Unapproved Drugs and Indications with High Medical Needs" held on March 23, 2012. Chugai filed an application for approval on September 19, 2012. On May 13, 2013, "Avastin®" for malignant glioma has been designated as orphan drug.

This approval was obtained based on the data of the US phase II clinical study (The BRAIN study) in patients with glioblastoma that recurred after treatment with temozolomide and radiotherapy, the Japanese phase II clinical study (JO22506 study) in which a single agent of Avastin® was administered in patients with recurrent malignant glioma, and the phase III global, randomized, placebo-controlled comparative study (The AVAglio study) in which Avastin® was combined with standard radiotherapy and temozolomide in patients with newly diagnosed glioblastoma. The BRAIN study demonstrated a progression-free survival at 6 months of 42.6% and an objective response rate of 28.2%. The JO22506 study demonstrated a progression free survival at 6 months of 33.9% and an objective response rate of 27.6% in patients with glioblastoma. These efficacy data exceed those reported in the previous studies with recurrent glioblastoma patients.
Furthermore, in the AVAglio study, both progression-free survival and overall survival were set to be the co-primary endpoints and it was stipulated that the study would be successful if either of the endpoints was achieved. As a result, the median progression-free survival was 10.6 months in the Avastin® group, indicating a statistically significant extension compared to 6.2 months in the control group (hazard ratio 0.64, 95% confidence interval 0.55-0.74, $p<0.0001$). On the other hand, the median overall survival was 16.8 months in the Avastin® group and 16.7 months in the control group (hazard ratio 0.88, 95% confidence interval 0.76-1.02, $p=0.0987$).

Avastin® was well tolerated and its safety profile was consistent with the previously reported data of Avastin®.

Avastin® is approved in Europe for the treatment of advanced stages of breast cancer, colorectal cancer, non-small cell lung cancer, kidney cancer and ovarian cancer, and is available in the US for the treatment of colorectal cancer, non-small cell lung cancer and kidney cancer. In addition, Avastin® is approved in over 60 other countries worldwide for the treatment of patients with progressive glioblastoma following prior therapy.
Avastin® will be now available for patients with malignant glioma including glioblastoma in Japan, in addition to the current indications of advanced stages of colorectal, non-small cell lung cancer and breast cancer. This approval of the indications including the treatment for patients with newly diagnosed glioblastoma based on the data of the AVAglio study is the world's first approval in Japan.

As the top pharmaceutical company in the field of oncology, Chugai is convinced that Avastin® can contribute to the treatment of patients with "malignant glioma," a disease with extremely high-grade malignancy and with high unmet medical need, by providing a new therapeutic option.

About "Avastin®"

"Avastin®" is an antibody drug that binds specifically to VEGF, which plays an important role in the vascularization needed for the growth and metastatis of tumors, and impedes its activity. "Avastin®" received approval for the treatment of metastatic colorectal cancer in the U.S. in February 2004 and is recommended as one of the standard treatments in several guidelines. In Japan, it received approval for "unresectable advanced or recurrent colorectal cancer" in April 2007, "unresectable advanced or recurrent non-squamous non-small cell lung cancer" in November 2009 and "inoperable or recurrent breast cancer" in September 2011.

About the "Review Committee on Unapproved Drugs and Indications with High Medical Needs"

The "Review Committee on Unapproved Drugs and Indications with High Medical Needs" was established for the purpose of "enhancing development by the pharmaceutical companies of drugs and indications that have been approved for use in western countries but not yet approved in Japan, through activities such as evaluating medical needs and confirming the applicability of "application based on evidence in the public domain" and investigating the need for studies that should be additionally conducted."

About malignant glioma and glioblastoma

Among gliomas which are brain tumors that grow from glial cells, those with highly malignant tumors are called malignant glioma. Gliobastoma is the most aggressive malignant glioma with poor prognosis.

Drug Information

The underlined descriptions are newly added.

Brand name: Avastin® for intravenous infusion 100 mg/4 mL
Avastin® for intravenous infusion 400 mg/16 mL

Generic name: bevacizumab (genetic recombination)

Indications, dosage and administration:

Indications	Dosage and Administration
Unresectable advanced or recurrent colorectal cancer	The usual adult dosage is 5 mg/kg (body weight) or 10 mg/kg (body weight) of bevacizumab (recombinant) per intravenous infusion in combination with other antineoplastic agents. The administration interval of AVASTIN should be 2 weeks or longer.
	The usual adult dosage is 7.5 mg/kg (body weight) of bevacizumab (recombinant) per intravenous infusion in combination with other antineoplastic agents. The administration interval of AVASTIN should be 3 weeks or longer.
Unresectable advanced or recurrent non-squamous non-small cell lung cancer	The usual adult dosage is 15 mg/kg (body weight) of bevacizumab (recombinant) per intravenous infusion in combination with other antineoplastic agents. The administration interval of AVASTIN should be 3 weeks or longer.
Inoperable or recurrent breast cancer	The usual adult dosage is 10 mg/kg (body weight) of bevacizumab (recombinant) per intravenous infusion in combination with paclitaxel. The administration interval of AVASTIN should be 2 weeks or longer.
<u>Malignant glioma</u>	<u>The usual adult dosage per intravenous infusion of bevacizumab (recombinant) is 10 mg/kg (body weight) every 2 weeks or 15 mg/kg (body weight) every 3 weeks. The administration interval of AVASTIN should be appropriately extended on the basis of patient condition.</u>

Drug prices: Avastin® for intravenous infusion 100 mg/4 mL JPY 45,563/vial
Avastin® for intravenous infusion 400 mg/16 mL JPY 173,511/vial