Report on the Deliberation Results

May 16, 2016

Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau

Ministry of Health, Labour and Welfare

Brand Name	Avastin 100 mg/4 mL Intravenous Infusion
	Avastin 400 mg/16 mL Intravenous Infusion
Non-proprietary Name	Bevacizumab (Genetical Recombination) (JAN*)
Applicant	Chugai Pharmaceutical Co., Ltd.
Date of Application	September 17, 2015

Results of Deliberation

In its meeting held on April 25, 2016, the Second Committee on New Drugs concluded that the partial change application for the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The re-examination period is 10 years.

Condition of Approval

The applicant is required to develop and appropriately implement a risk management plan.

**Japanese Accepted Name (modified INN)*

Review Report

April 12, 2016
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name	Avastin 100 mg/4 mL Intravenous Infusion Avastin 400 mg/16 mL Intravenous Infusion
Non-proprietary Name	Bevacizumab (Genetical Recombination)
Applicant	Chugai Pharmaceutical Co., Ltd.
Date of Application	September 17, 2015
Dosage Form/Strength	Injection: each vial contains 100 or 400 mg of Bevacizumab (Genetical Recombination).
Application Classification	Prescription drug, (4) Drug with a new indication
Items Warranting Special Mention	Orphan drug (Drug Designation No. 364 of 2015 [*27 yaku*]; PFSB/ELD Notification No. 0914-1 dated September 14, 2015, by the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare)
Reviewing Office	Office of New Drug V

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of advanced or recurrent cervical cancer, and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indications and dosage and administration shown below, with the following condition. The applicant should further investigate pelvic fistula occurring in patients receiving the product via post-marketing surveillance.

Indications

1. Unresectable advanced or recurrent colorectal cancer
2. Unresectable advanced or recurrent, non-squamous non-small cell lung cancer
3. Inoperable or recurrent breast cancer
4. Malignant glioma
5. Ovarian cancer

6. Advanced or recurrent cervical cancer

(Underline denotes additions.)

Dosage and Administration

1. Unresectable advanced or recurrent colorectal cancer
   - The usual adult dosage is 5 mg/kg (body weight) or 10 mg/kg (body weight) of Bevacizumab (Genetical Recombination) given as an intravenous infusion in combination with chemotherapy. The dosing interval should be ≥2 weeks.
   - The usual adult dosage is 7.5 mg/kg (body weight) of Bevacizumab (Genetical Recombination) given as an intravenous infusion in combination with chemotherapy. The dosing interval should be ≥3 weeks.
2. Unresectable advanced or recurrent, non-squamous non-small cell lung cancer

   The usual adult dosage is 15 mg/kg (body weight) of Bevacizumab (Genetical Recombination) given as an intravenous infusion in combination with chemotherapy. The dosing interval should be ≥3 weeks.
3. Inoperable or recurrent breast cancer

   The usual adult dosage is 10 mg/kg (body weight) of Bevacizumab (Genetical Recombination) given as an intravenous infusion in combination with paclitaxel. The dosing interval should be ≥2 weeks.
4. Malignant glioma

   The usual adult dosage is Bevacizumab (Genetical Recombination) at 10 mg/kg (body weight) every 2 weeks or 15 mg/kg (body weight) every 3 weeks, given as an intravenous infusion. The dosing interval may be prolonged according to the patient's condition.
5. Ovarian cancer

   The usual adult dosage is 15 mg/kg (body weight) of Bevacizumab (Genetical Recombination) given as an intravenous infusion in combination with chemotherapy. The dosing interval should be ≥3 weeks.
6. Advanced or recurrent cervical cancer

   The usual adult dosage is 15 mg/kg (body weight) of Bevacizumab (Genetical Recombination) given as an intravenous infusion in combination with chemotherapy. The dosing interval should be ≥3 weeks.

(Underline denotes additions.)

Condition of Approval The applicant is required to develop and appropriately implement a risk management plan.

Attachment

Review Report (1)

February 29, 2016

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency.

Product Submitted for Approval

Brand Name	Avastin 100 mg/4 mL Intravenous Infusion Avastin 400 mg/16 mL Intravenous Infusion
Non-proprietary Name	Bevacizumab (Genetical Recombination)
Applicant	Chugai Pharmaceutical Co., Ltd.
Date of Application	September 17, 2015
Dosage Form/Strength	Injection: each vial contains 100 or 400 mg of Bevacizumab (Genetical Recombination).
Proposed Indications	1. Unresectable advanced or recurrent colorectal cancer 2. Unresectable advanced or recurrent, non-squamous non-small cell lung cancer 3. Inoperable or recurrent breast cancer 4. Malignant glioma 5. Ovarian cancer 6. <u>Advanced or recurrent cervical cancer</u> (Underline denotes additions.)

Proposed Dosage and Administration

1. Unresectable advanced or recurrent colorectal cancer
   - The usual adult dosage is 5 mg/kg (body weight) or 10 mg/kg (body weight) of Bevacizumab (Genetical Recombination) given as an intravenous infusion in combination with chemotherapy. The dosing interval should be ≥2 weeks.
   - The usual adult dosage is 7.5 mg/kg (body weight) of Bevacizumab (Genetical Recombination) given as an intravenous infusion in combination with chemotherapy. The dosing interval should be ≥3 weeks.
2. Unresectable advanced or recurrent, non-squamous non-small cell lung cancer
   The usual adult dosage is 15 mg/kg (body weight) of Bevacizumab (Genetical Recombination) given as an intravenous infusion in combination with chemotherapy. The dosing interval should be ≥3 weeks.
3. Inoperable or recurrent breast cancer
   The usual adult dosage is 10 mg/kg (body weight) of Bevacizumab (Genetical Recombination)

given as an intravenous infusion in combination with paclitaxel. The dosing interval should be ≥2 weeks.

4. Malignant glioma

   The usual adult dosage is Bevacizumab (Genetical Recombination) at 10 mg/kg (body weight) every 2 weeks or 15 mg/kg (body weight) every 3 weeks, given as an intravenous infusion. The dosing interval may be prolonged according to the patient's condition.

5. Ovarian cancer

   The usual adult dosage is 15 mg/kg (body weight) of Bevacizumab (Genetical Recombination) given as an intravenous infusion in combination with chemotherapy. The dosing interval should be ≥3 weeks.

6. Advanced or recurrent cervical cancer

   The usual adult dosage is 15 mg/kg (body weight) of Bevacizumab (Genetical Recombination) given as an intravenous infusion in combination with chemotherapy. The dosing interval should be ≥3 weeks.

(Underline denotes additions.)

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List of Abbreviations

Bevacizumab	bevacizumab (genetical recombination)
Bevacizumab + PTX + CDDP	Combination therapy with bevacizumab (genetical recombination), paclitaxel, and cisplatin
Bevacizumab + PTX + nogitecan	Combination therapy with bevacizumab (genetical recombination), paclitaxel, and nogitecan hydrochloride
CBDCA	Carboplatin
CDDP	Cisplatin
CI	Confidence interval
DMC	Data Monitoring Committee
FIGO	International Federation of Gynecology and Obstetrics
GOG	Gynecologic Oncology Group
ITT	intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
MedDRA/J	Medical Dictionary for Regulatory Activities Japanese version
NCCN Guidelines	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Cervical Cancer
NCI-PDQ	National Cancer Institute Physician Data Query
Nogitecan	Nogitecan hydrochloride
OS	Overall survival
Partial change application	Partial change approval application
PMDA	Pharmaceuticals and Medical Devices Agency
PS	Performance Status
PTX	Paclitaxel
PTX + CBDCA	Combination therapy with paclitaxel and carboplatin
PTX + CDDP	Combination therapy with paclitaxel and cisplatin
PTX + nogitecan	Combination therapy with paclitaxel and nogitecan hydrochloride
RECIST	Response Evaluation Criteria in Solid Tumors
VEGF	Vascular endothelial growth factor

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

1.1 Outline of the proposed product

Bevacizumab (Genetical Recombination) (hereinafter, bevacizumab), developed by Genentech, Inc. (in the US), is a humanized monoclonal antibody targeting vascular endothelial growth factor (VEGF). Bevacizumab binds to VEGF and blocks the binding of VEGF to its receptors, thereby inhibiting angiogenesis and tumor growth.

In Japan, bevacizumab was approved for the indications of unresectable advanced or recurrent colorectal cancer in April 2007, unresectable advanced or recurrent, non-squamous non-small cell lung cancer in November 2009, inoperable or recurrent breast cancer in September 2011, malignant glioma in June 2013, and ovarian cancer in November 2013.

1.2 Development history etc.

The clinical development of bevacizumab for cervical cancer was started with a phase III study (Study GOG-0240) initiated in April 2009 by the Gynecologic Oncology Group (GOG) outside Japan. The study was conducted in patients with advanced or recurrent cervical cancer who were ineligible for surgery or radiotherapy. Based primarily on the results of the study, a supplemental new drug application was filed in the US in April 2014, and was approved in August 2014 for the following indication: "Avastin (bevacizumab), in combination with paclitaxel and cisplatin or paclitaxel and topotecan, is indicated for the treatment of persistent, recurrent, or metastatic carcinoma of the cervix." In Europe, an application was filed based primarily on the results of Study GOG-0240 in June 2014 and was approved in March 2015 for the following indication: "Avastin (bevacizumab), in combination with paclitaxel and cisplatin or, alternatively, paclitaxel and topotecan in patients who cannot receive platinum therapy, is indicated for the treatment of adult patients with persistent, recurrent, or metastatic carcinoma of the cervix."

As of January 2016, bevacizumab had been approved for the indication of cervical cancer in 67 countries or regions.

In Japan, the applicant started a phase II study in patients with advanced or recurrent cervical cancer who were ineligible for surgery or radiotherapy (Study JO29569) in [redacted].

The applicant has filed a partial change application for bevacizumab for the additional indication of cervical cancer, based mainly on the results of Studies GOG-0240 and JO29569.

In September 2015, bevacizumab was designated as an orphan drug for the intended indication of cervical cancer (Drug Designation No. 364 of 2015 [*27 yaku*]).

2. Data Relating to Quality and Outline of the Review Conducted by PMDA

The present application is for a new indication. No new data relating to quality were submitted.

3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

The present application is for a new indication. No new study data on non-clinical pharmacokinetics were submitted because the non-clinical pharmacokinetics of bevacizumab had been evaluated at the initial application.

3.R Outline of the review by PMDA

The applicant explained the efficacy of bevacizumab in the treatment of cervical cancer, based on the application data submitted for the initial approval of bevacizumab and other sources.

The applicant's explanation:

Bevacizumab blocks the binding of VEGF to its receptors, thereby inhibiting angiogenesis and tumor growth. Some reports suggested increased VEGF expression in the cervical cancer tissue (e.g., *Gynecol Oncol*, 1998;68:38-44; *Br J Cancer*, 2000;83:620-625); this suggests that VEGF-mediated angiogenesis is involved in tumor growth in cervical cancer. Bevacizumab is thus expected to be effective in the treatment of cervical cancer.

PMDA accepted the applicant's explanation.

4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA

The present application is for a new indication. No new study data on non-clinical pharmacokinetics were submitted because the non-clinical pharmacokinetics of bevacizumab had been evaluated at the initial application.

5. Toxicity and Outline of the Review Conducted by PMDA

The present application is for a new indication. No data relating to the toxicity of bevacizumab were submitted.

6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

The present application is for a new indication. No new data relating to biopharmaceutics or associated analytical methods or clinical pharmacology were submitted, because such data had been evaluated at the initial application.

7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

The applicant submitted data from 2 studies for efficacy and safety evaluation: a Japanese phase II study and a foreign phase III study (see Table 1).

Table 1. List of clinical studies to assess efficacy and safety

Data type	Region	Study identifier	Phase	Population	No. of enrolled patients	Dosage regimen	Main endpoints
Evaluation data	Japan	JO29569	II	Patients with advanced or recurrent cervical cancer who were ineligible for surgery or radiotherapy	8	Bevacizumab + PTX + CDDP	Tolerability Safety Efficacy
	Foreign	GOG-0240	III	Patients with advanced or recurrent cervical cancer who were ineligible for surgery or radiotherapy	452 (a) 114 (b) 115 (c) 111 (d) 112	(a) PTX + CDDP (b) Bevacizumab + PTX + CDDP (c) PTX + nogitecan (d) Bevacizumab + PTX + nogitecan	Efficacy Safety

A summary of each clinical study is shown below. Table 2 shows the dosage regimen of combination therapies used in the studies. Non-fatal adverse events reported in the studies are presented in Section "7.2 Adverse events in clinical studies."

Table 2. Dosage regimen of combination therapies

	Dosage regimen
PTX + CDDP	Investigators selected one of the following regimens for individual patients. (a) Intravenous PTX 135 mg/m^2 over 24 hours on Day 1 and intravenous CDDP 50 mg/m^2 on Day 2 in a 21-day cycle. (b) Intravenous PTX 175 mg/m^2 over 3 hours and intravenous CDDP 50 mg/m^2 on Day 1 in a 21-day cycle. (c) Intravenous PTX 175 mg/m^2 over 3 hours on Day 1 and intravenous CDDP 50 mg/m^2 on Day 2 in a 21-day cycle.
Bevacizumab + PTX + CDDP	Intravenous bevacizumab 15 mg/kg with PTX and CDDP, over 30 to 90 minutes on Day 1 or Day 2 in a 21-day cycle.
PTX + nogitecan	Intravenous PTX 175 mg/m^2 over 3 hours on Day 1 and intravenous nogitecan 0.75 mg/m^2 over 30 minutes on Days 1 to 3 in a 21-day cycle.
Bevacizumab + PTX + nogitecan	Intravenous bevacizumab 15 mg/kg with PTX and nogitecan, over 30 to 90 minutes on Day 1 in a 21-day cycle.

7.1 Evaluation data

7.1.1 Japanese clinical study

7.1.1.1 Japanese phase II study (CTD 5.3.5.2.1, Study JO29569 [ongoing since [redacted]; cut-off date, [redacted]])

An open-label, uncontrolled study was conducted in patients with advanced or recurrent[1)] cervical cancer who were ineligible for surgery or radiotherapy (target sample size, 6 subjects), at 8 study sites in Japan, to evaluate the tolerability, safety, and efficacy of bevacizumab in combination with paclitaxel (PTX) and cisplatin (CDDP).

Treatment was continued until disease progression or study discontinuation criteria were met.

1) In the present review report, "advanced or recurrent cervical cancer" includes FIGO stage IVB cervical cancer and refractory cervical cancer.

Of the 8 subjects enrolled, 1 was withdrawn before the beginning of treatment and 7 received treatment. The 7 subjects were included in the analysis populations for tolerability, safety, and efficacy.

The first 21 days of treatment were defined as the tolerability assessment period. The bevacizumab + PTX + CDDP therapy was considered tolerable if <34% of the enrolled subjects met the tolerability assessment criteria[2)] during this period. None of the subjects met the criteria.

Efficacy results:
One of the 7 subjects (14.3%) had a partial response (PR), as assessed by the investigator using the Response Evaluation Criteria In Solid Tumors (RECIST; version 1.1).

Safety results:
No deaths occurred during the treatment period or within 28 days after the last dose of study drug.

7.1.2 Foreign clinical study

7.1.2.1 Foreign phase III study (CTD 5.3.5.1.1, Study GOG-0240 [April 2009 to March 2014])

An open-label, randomized, comparative study with a 2-by-2 factorial design was conducted in patients with advanced or recurrent cervical cancer who were ineligible for surgery or radiotherapy (target sample size, 450 subjects) at 165 foreign study sites. The study had the following 2 primary objectives. (The study was designed to evaluate the 2 primary hypotheses.)

- To compare the efficacy and safety of chemotherapy alone (PTX + CDDP or PTX + nogitecan) and bevacizumab + chemotherapy (bevacizumab + PTX + CDDP or bevacizumab + PTX + nogitecan)
- To compare the efficacy and safety of platinum-based chemotherapy (PTX + CDDP or bevacizumab + PTX + CDDP) and non-platinum-based chemotherapy (PTX + nogitecan or bevacizumab + PTX + nogitecan)

Treatment was continued until disease progression or study discontinuation criteria were met.

In total, 452 subjects were enrolled, randomized to treatment, and included in the intent-to-treat (ITT) population, which was the efficacy analysis population. Of the 452 subjects, 225 were assigned to chemotherapy alone (114 in the PTX + CDDP group and 111 in the PTX + nogitecan group) and 227 to bevacizumab + chemotherapy (115 in the bevacizumab + PTX + CDDP group and 112 in the bevacizumab + PTX + nogitecan group). Of the ITT population, 12 subjects did not receive the study drug (5 in the chemotherapy alone arm [2 in the PTX + CDDP group and 3 in the PTX + nogitecan group]; 7 in the bevacizumab + chemotherapy arm [4 in the bevacizumab + PTX + CDDP group and 3 in the bevacizumab + PTX + nogitecan group]). Of the subjects assigned to bevacizumab + chemotherapy, 2 received only chemotherapy and were therefore included in the chemotherapy alone

[2)] (a) Grade 4 neutrophil count decreased persisting for ≥7 days; (b) febrile neutropenia; (c) Grade 4 platelet count decreased or Grade 3 platelet count decreased requiring platelet transfusion; (d) Grade ≥3 non-hematological toxicity excluding transient electrolyte abnormality, etc.; or (e) Unable to start Cycle 2 within 6 weeks from Day 1 of Cycle 1, due to adverse events.

arm (the PTX + CDDP group). Consequently, 440 subjects were included in the safety analysis population (222 in the chemotherapy alone arm [114 in the PTX + CDDP group and 108 in the PTX + nogitecan group]; 218 in the bevacizumab + chemotherapy arm [109 in the bevacizumab + PTX + CDDP group and 109 in the bevacizumab + PTX + nogitecan group]).

The primary endpoint was overall survival (OS). An interim analysis and the final analysis were to be conducted after the occurrence of 173 and 346 OS events, respectively, to evaluate the efficacy of treatment. The OS in the chemotherapy alone arm was compared with that in the bevacizumab + chemotherapy arm at a 1-sided significance level of 2.5%. The OS in the platinum-based chemotherapy arm was compared with that in the non-platinum-based chemotherapy arm at a 1-sided significance level of 2.5%. The probability of type 1 error in the interim analysis of OS was adjusted based on the Lan-DeMets alpha spending function (αt^2).

Efficacy results:
An interim analysis (cut-off date, February 6, 2012) was performed after the occurrence of 174 OS events. There was a significant difference in efficacy between bevacizumab + chemotherapy (PTX + CDDP or PTX + nogitecan) and chemotherapy alone, with a *P*-value being less than the predetermined significance level. The Data Monitoring Committee (DMC), however, recommended that the study be continued and the second interim analysis be conducted at the end of 2012.[3)] The efficacy of platinum-based chemotherapy (PTX + CDDP or bevacizumab + PTX + CDDP) and non-platinum-based chemotherapy (PTX + nogitecan or bevacizumab + PTX + nogitecan) was also compared. The hazard ratio for OS (non-platinum-based chemotherapy/platinum-based chemotherapy) was 1.2 (99% confidence interval [CI], 0.82, 1.76), showing that non-platinum-based chemotherapy was not superior in OS to platinum-based chemotherapy. On the basis of this result, the protocol was amended (dated June 25, 2012) to allow investigators to replace nogitecan with CDDP.

The second interim analysis was performed after the occurrence of 271 OS events (cut-off date, December 12, 2012). On the basis of the analysis results, DMC concluded that bevacizumab + chemotherapy resulted in a significant prolongation of OS compared with chemotherapy alone, and recommended the termination of study. The analysis results were published by GOG, and OS event data were transferred from GOG to Roche to be further analyzed for marketing application. The transferred data included additional 17 OS events collected between the cut-off date (December 12, 2012) and the data transfer. (These events occurred before the cut-off date but were collected after the date by GOG.) Thus, a total of 288 OS events were analyzed by Roche in the primary analysis.

[3)] It remains unknown why DMC recommended a second interim analysis instead of study termination when the first interim analysis results were obtained.

The primary OS analysis results and the Kaplan-Meier curves are shown in Table 3 and Figure 1, respectively. Non-platinum-based chemotherapy did not result in a significant prolongation of OS compared with platinum-based chemotherapy (stratified hazard ratio [95% CI], 1.15 [0.91, 1.46]).

Table 3. Primary OS analysis results
(ITT population; cut-off date, December 12, 2012)

	Bevacizumab + chemotherapy	Chemotherapy alone
N	227	225
Number of deaths (%)	141 (62.1)	147 (65.3)
Median [95% CI] (months)	16.8 [14.1, 19.0]	12.9 [10.9, 15.0]
Hazard ratio [95% CI]*1	0.74 [0.58, 0.94]	
P-value (1-sided)*2	0.0066	

*1, Cox regression hazards models stratified by disease status (FIGO stage IVB, refractory or recurrent), GOG PS (0, 1), prior platinum-based chemotherapy (yes, no), and assigned treatment (platinum-based chemotherapy, non-platinum-based chemotherapy)

*2, Log-rank test stratified by disease status (FIGO stage IVB, refractory or recurrent), GOG PS (0, 1), prior platinum-based chemotherapy (yes, no), and assigned treatment (platinum-based chemotherapy, non-platinum-based chemotherapy) with a 1-sided significance level of 0.0140

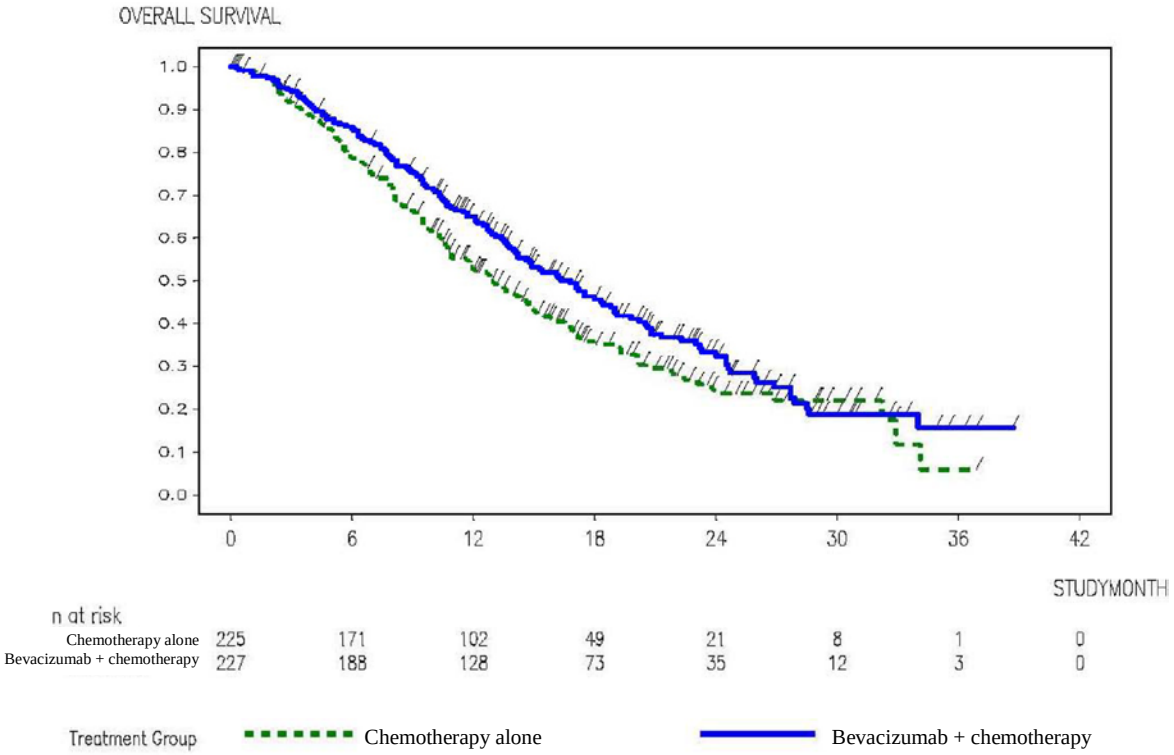

Figure 1. Kaplan-Meier curves for OS results of the primary analysis
(ITT population; cut-off date, December 12, 2012)

Safety results:

Deaths occurred during the treatment period or within 30 days after the last dose of study drugs: 9 subjects in the bevacizumab + chemotherapy arm (4 in the bevacizumab + PTX + CDDP group and 5 in the bevacizumab + PTX + nogitecan group) and 5 in the chemotherapy alone arm (5 in the PTX + nogitecan group). Of these subjects, 1 died of disease progression (in the bevacizumab + PTX + CDDP group). Other causes of deaths: ileal perforation, dyspnea, and multi-organ failure (1 subject each) in the bevacizumab + PTX + CDDP group; neutropenia (2 subjects) and acute respiratory distress

syndrome, large intestine perforation, sudden death, pneumonia, and cellulitis (1 subject each) in the bevacizumab + PTX + nogitecan group (a single subject may have more than one cause of death); and pelvic infection, death, lung disorder, febrile neutropenia, and epistaxis (1 subject each) in the PTX + nogitecan group. A causal relationship with study drug could not be ruled out for the following: ileal perforation (1 subject) in the bevacizumab + PTX + CDDP group; neutropenia (2 subjects) and acute respiratory distress syndrome, large intestine perforation, pneumonia, and cellulitis (1 subject each) in the bevacizumab + PTX + nogitecan group (a single subject may have more than one cause of death); and pelvic infection and febrile neutropenia (1 subject each) in the PTX + nogitecan group.

7.R Outline of the review by PMDA

7.R.1 Review policy

PMDA decided to focus on data from the foreign phase III study (Study GOG-0240), to evaluate the efficacy and safety of bevacizumab in patients with advanced or recurrent cervical cancer who are ineligible for surgery or radiotherapy.

PMDA decided to focus on data from the Japanese phase II study (Study JO29569), to evaluate the safety of bevacizumab in Japanese patients with advanced or recurrent cervical cancer who are ineligible for surgery or radiotherapy.

7.R.2 Efficacy

On the basis of the following review, PMDA concluded that the efficacy of bevacizumab has been demonstrated in patients with advanced or recurrent cervical cancer who are ineligible for surgery or radiotherapy.

7.R.2.1 Comparators

The applicant explained the reason Study GOG-0240 used PTX + CDDP and PTX + nogitecan as comparator regimens.

The applicant's explanation:

The National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Cervical Cancer (NCCN Guidelines) (ver.1.2008), available before the beginning of Study GOG-0240, recommended PTX + CDDP for patients with advanced or recurrent cervical cancer who were ineligible for surgery or radiotherapy. This patient population was enrolled in Study GOG-0240, and therefore PTX + CDDP was used as a comparator regimen.

PTX + nogitecan, though not recommended by the NCCN Guidelines (ver.1.2008), was also used as a comparator regimen, because a purpose of Study GOG-0240 was to compare the efficacy and safety of platinum-based chemotherapy and non-platinum-based chemotherapy [see Section 7.1.2.1], and because

clinical study data suggested the efficacy of PTX + nogitecan in patients with cervical cancer (*Gynecol Oncol*, 2004;92:635-638).

PMDA accepted the applicant's explanation.

7.R.2.2 Endpoints and the results of evaluation

The primary analysis performed by Roche demonstrated that bevacizumab + chemotherapy was superior in OS to chemotherapy alone [see Section 7.1.2.1]. Table 4 shows the efficacy results of bevacizumab by concomitant chemotherapy in Study GOG-0240. The efficacy of bevacizumab was not affected by concomitant chemotherapy regimen (i.e., no difference between bevacizumab + PTX + CDDP and bevacizumab + PTX + nogitecan).

Table 4. Efficacy of bevacizumab by concomitant chemotherapy (ITT population; cut-off date, December 12, 2012)

Treatment	n	OS		
		Median [95% CI] (months)	Hazard ratio* [95% CI]	Interaction *P*-value
Bevacizumab + PTX + CDDP	115	17.5 [14.2, 23.0]	0.72 [0.51, 1.02]	0.9286
PTX + CDDP	114	14.3 [10.9, 16.9]		
Bevacizumab + PTX + nogitecan	112	14.9 [12.7, 18.4]	0.76 [0.55, 1.06]	
PTX + nogitecan	111	11.9 [10.2, 14.7]		

*, Cox regression hazards models stratified by disease status (FIGO stage IVB, refractory or recurrent), GOG PS (0, 1), and prior platinum-based chemotherapy (yes, no)

Study GOG-0240 had 2 main hypotheses (the superiority of bevacizumab + chemotherapy to chemotherapy alone in OS; and the superiority of non-platinum-based chemotherapy to platinum-based chemotherapy in OS). Since both hypotheses were tested at a 1-sided significance level of 2.5%, PMDA asked the applicant to explain the appropriateness of the study results.

The applicant's response:

The statistical analysis plan (dated [redacted]) prepared by Roche included a plan for sensitivity analysis of the 2 primary hypotheses at a 1-sided significance level of 1.25%. The sensitivity analysis showed the significance levels in the second interim analysis and the primary analysis conducted by Roche (see Table 5). The *P*-value (0.0066) in the primary analysis of Study GOG-0240 by Roche satisfied the significance level shown in Table 5, suggesting the robustness of the efficacy data of bevacizumab. Because the same cut-off date was used in the second interim analysis and the primary analysis by Roche, their significance levels were calculated on the assumption that these analyses were equal to each other.

Table 5. *P*-values and significance levels of OS analyses (ITT population)

	Protocol		
	P-value (1-sided)	Significance level (1-sided)	
		2.5%	1.25%
First interim analysis (174 events*)	0.0013	0.0063	0.0032
Second interim analysis (271 events*)	0.0035	0.0122	0.0059
Roche's primary analysis (288 events*)	0.0066	0.0140	0.0068

*, Number of OS events

An additional analysis of OS (cut-off date, March 7, 2014) was performed after collecting the target number of OS events (346 events). The results showed a similar tendency to the primary analysis results (Table 6).

Table 6. Results of the additional analysis of OS (ITT population; cut-off date, March 7, 2014)

	Bevacizumab + chemotherapy	Chemotherapy alone
N	227	225
Number of deaths (%)	170 (74.9)	180 (80.0)
Median [95% CI] (months)	16.8 [14.8, 19.0]	13.3 [10.9, 15.8]
Hazard ratio [95% CI]*1	0.76 [0.62, 0.94]	
P-value (1-sided)*2	0.0063	

*1, Cox regression hazards models stratified by disease status (FIGO stage IVB, refractory or recurrent), GOG PS (0, 1), prior platinum-based chemotherapy (yes, no), and assigned treatment (platinum-based chemotherapy, non-platinum-based chemotherapy)

*2, Log-rank test stratified by disease status (FIGO stage IVB, refractory or recurrent), GOG PS (0, 1), prior platinum-based chemotherapy (yes, no), and assigned treatment (platinum-based chemotherapy, non-platinum-based chemotherapy)

PMDA's view:

Study GOG-0240 used OS as the primary endpoint. This is appropriate because the purpose of treatment for patients with advanced or recurrent cervical cancer who are ineligible for surgery or radiotherapy is to extend their lives.

Since 2 primary hypotheses were to be tested [see Section 7.1.2.1], multiplicity adjustment should have been included in the analysis plan for Study GOG-0240. However, in view of the following points, PMDA has concluded that the results of Study GOG-0240 demonstrated the efficacy of bevacizumab in the study patients.

- The DMC concluded that the second interim analysis demonstrated a significant prolongation of OS in the bevacizumab + chemotherapy arm, compared with the chemotherapy alone arm. Both the second interim analysis and the primary analysis performed by Roche attained a P-value lower than the predetermined 1-sided significance level of 1.25% (two-sided 2.5%).
- The efficacy of bevacizumab was also demonstrated in the additional analysis of the protocol-specified target number of events (346 OS events).

7.R.3 Safety [for adverse events, see Section "7.2 Adverse events in clinical studies."]

PMDA's conclusion:

On the basis of its review presented in Sections 7.R.3.1 and 7.R.3.2, PMDA has concluded that attention should be paid to the following adverse events when bevacizumab + chemotherapy are administered to patients with advanced or recurrent cervical cancer who are ineligible for surgery or radiotherapy:

- The events identified as requiring attention at the regulatory reviews for the previously approved indications: gastrointestinal perforation, fistula, wound healing delayed, hypertension, proteinuria, arterial/venous thromboembolism, haemorrhage (including cerebral haemorrhage), cardiotoxicity (cardiac failure congestive), infusion reaction, posterior reversible encephalopathy syndrome, interstitial lung disease, bone marrow depression, and infection (see Review Report of Avastin for intravenous infusion 100 mg/4 mL and 400 mg/16 mL, dated May 17, 2013)
- Thrombotic microangiopathy. This event was added to the list of adverse reactions in the package insert based on post-marketing case reports collected in Japan (PFSB/SD Notification No. 1022-1 dated October 22, 2013, by the Safety Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare)
- Gastrointestinal vaginal fistula, vesicovaginal fistula, etc.

These adverse events require careful attention in the use of bevacizumab. Nevertheless, bevacizumab is tolerable in patients with cervical cancer as long as they are followed up by physicians with sufficient knowledge and experience in cancer chemotherapy, through monitoring of adverse events, interruption or discontinuation of bevacizumab or concomitant chemotherapy, or other appropriate actions.

7.R.3.1 Differences in the safety profile of bevacizumab between Japanese and non-Japanese patients

The applicant's explanation about the differences in the safety profile of bevacizumab:

The safety results in the bevacizumab + chemotherapy arm and the chemotherapy alone arm in Study GOG-0240 are summarized in Table 7. Data on adverse events leading to dose reduction or treatment interruption were not collected in the study.

Table 7. Summary of safety results

	n (%)	
	Bevacizumab + chemotherapy N = 218	Chemotherapy alone N = 222
Adverse events	216 (99.1)	219 (98.6)
Grade ≥3 adverse events	165 (75.7)	127 (57.2)
Adverse events resulting in death	9 (4.1)	5 (2.3)
Serious adverse events	111 (50.9)	81 (36.5)
Adverse events leading to treatment discontinuation	56 (25.7)	40 (18.0)

All-grade adverse events with a ≥10% higher incidence in the bevacizumab + chemotherapy arm than in the chemotherapy alone arm were hypertension (bevacizumab + chemotherapy, 28.9%; chemotherapy alone, 6.3%), epistaxis (17.0%, 1.8%), and weight decreased (20.6%, 6.8%). Grade ≥3 adverse events with a ≥3% higher incidence in the bevacizumab + chemotherapy arm than in the chemotherapy alone arm were hypertension (11.5%, 0.5%), thrombosis (8.3%, 2.7%), infection (6.4%, 1.8%), fatigue (14.2%,

9.9%), pelvic pain (5.5%, 1.4%), anal fistula (3.7%,[4] 0%), neutropenia (7.8%, 4.1%), and dehydration (4.1%, 0.5%). Serious adverse events with a ≥3% higher incidence in the bevacizumab + chemotherapy arm than in the chemotherapy alone arm were fatigue (7.8%, 0.9%), anal fistula (4.6%,[5] 0%), infection (6.0%, 1.4%), thrombosis (7.3%, 2.7%), abdominal pain (9.6%, 5.9%), nausea (8.3%, 5.0%), vomiting (8.3%, 5.0%), constipation (5.5%, 2.3%), and dehydration (4.1%, 0.9%). There were no adverse events leading to treatment discontinuation with a ≥3% higher incidence in the bevacizumab + chemotherapy arm than in the chemotherapy alone arm.

The applicant's explanation about differences in the safety of bevacizumab between Japanese and non-Japanese patients:
The safety of bevacizumab in Japanese and non-Japanese patients receiving bevacizumab + PTX + CDDP was compared (Study JO29569 [Japanese] vs Study GOG-0240 [non-Japanese]). The results are summarized in Table 8.

Table 8. Safety results in Japanese and non-Japanese populations

	n (%)	
	Study JO29569	Study GOG-0240 (Bevacizumab + PTX + CDDP)
	N = 7	N = 109
Adverse events	7 (100)	109 (100)
Grade ≥3 adverse events	5 (71.4)	85 (78.0)
Adverse events resulting in death	0	4 (3.7)
Serious adverse events	2 (28.6)	50 (45.9)
Adverse events leading to treatment discontinuation	1 (14.3)	36 (33.0)

All-grade adverse events with a ≥20% higher incidence in Study JO29569 than in Study GOG-0240 were neutrophil count decreased (Study JO29569, 42.9%; Study GOG-0240, 0%), alopecia (100%, 59.6%), malaise (28.6%, 0%), anaemia (28.6%, 0%), and upper respiratory tract infection (28.6%, 5.5%). Grade ≥3 adverse events with a ≥10% higher incidence in Study JO29569 than in Study GOG-0240 were neutrophil count decreased (28.6%, 0%), hypertension (28.6%, 12.8%), gingivitis (14.3%, 0%), pyelonephritis (14.3%, 0%), anaemia (14.3%, 0%), febrile neutropenia (14.3%, 2.8%), and dehydration (14.3%, 3.7%). Serious adverse events with a ≥10% higher incidence in Study JO29569 than in Study GOG-0240 were febrile neutropenia (14.3%, 1.8%) and pyelonephritis (14.3%, 0%). Adverse events leading to treatment discontinuation with a ≥10% higher incidence in Study JO29569 than in Study GOG-0240 were peripheral sensory neuropathy (14.3%, 2.8%) and blood creatinine increased (14.3%, 0%).

Some adverse events occurred in patients with advanced or recurrent cervical cancer, but have not been reported in those receiving bevacizumab for the approved indications.

[4] Anal fistula in 8 subjects (3.7%) comprised rectovaginal fistula in 7 subjects and rectal fistula in 1 subject.
[5] Anal fistula in 10 subjects (4.6%) comprised rectovaginal fistula in 8 subjects and rectal fistula and colovaginal fistula in 1 subject each.

The applicant's explanation about the events:

The following adverse events were not listed in the Company Core Data Sheet prepared based on the clinical study data for the approved indications, but occurred more frequently in the bevacizumab + chemotherapy arm than in the chemotherapy alone arm in Study GOG-0240:

- All-grade adverse events with a ≥10% higher incidence in the bevacizumab + chemotherapy arm than in the chemotherapy alone arm: weight decreased (20.6%)
- Grade ≥3 adverse events with a ≥2% higher incidence in the bevacizumab + chemotherapy arm than in the chemotherapy alone arm: lymphopenia (6.0%), back pain (5.5%), pelvic pain (5.5%), anal fistula (3.7%), cellulitis (3.2%), and proctalgia (2.8%).

The following adverse events occurred in Study JO29569, but have not been reported in the Japanese clinical studies[6)] of the approved indications or in Japanese patients enrolled in the multiregional clinical studies[7)]: rash maculo-papular, infusion site phlebitis, and infusion site oedema in 1 subject each.

PMDA's view:

Attention should be paid to adverse events that occurred more frequently in the bevacizumab + chemotherapy arm than in the chemotherapy alone arm in Study GOG-0240, and healthcare professionals should be appropriately informed of the incidence and severity of the events. Attention should also be paid to adverse events that occurred more frequently in Japanese patients, though not many, who received bevacizumab + PTX + CDDP than in non-Japanese patients receiving the combination therapy. However, all these adverse events are known events of monotherapy with bevacizumab, PTX, or CDDP, and were all successfully controlled by treatment discontinuation or other appropriate measures. Therefore, PMDA concluded that Japanese patients with cervical cancer can tolerate bevacizumab in combination with chemotherapy as long as they are followed up by physicians with sufficient knowledge and experience in cancer chemotherapy who fully understand the safety profile of bevacizumab, through monitoring of adverse events, interruption or discontinuation of bevacizumab or concomitant chemotherapy, or other appropriate actions.

Gastrointestinal vaginal fistula, vesicovaginal fistula, etc., occurring in Study GOG-0240, are specific to patients with cervical cancer. PMDA's review on these events is presented in the following section.

7.R.3.2 Gastrointestinal vaginal fistula, vesicovaginal fistula, and other similar events

The applicant's explanation about gastrointestinal-vaginal fistula, vesicovaginal fistula, etc.:

With respect to gastrointestinal-vaginal fistula, vesicovaginal fistula, etc., events classified as fistula/abscess (excluding gastrointestinal events) or as "gastrointestinal perforation" according to the Standardised MedDRA Queries were medically re-evaluated and re-summarized based on case reports.

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6) Studies JO18157, JO18158 and JO19380 in patients with colorectal cancer, Study JO19907 in patients with non-small cell lung cancer, Study JO19901 in patients with breast cancer, and Study JO22506 in patients with malignant glioma

7) Study BO21990 in patients with glioblastoma and Study AV03390 (GOG-0218) in patients with ovarian cancer

Table 9 summarizes the gastrointestinal-vaginal fistula, vesicovaginal fistula, etc. reported in Study GOG-0240.

Table 9. Gastrointestinal vaginal fistula, vesicovaginal fistula, and other similar events

	n (%)			
	Bevacizumab + chemotherapy N = 218		Chemotherapy alone N = 222	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Gastrointestinal vaginal fistula, vesicovaginal fistula, etc.	23 (10.6)	16 (7.3)	5 (2.3)	5 (2.3)
Rectovaginal fistula	13 (6.0)	8 (3.7)	1 (0.5)	1 (0.5)
Vesicovaginal fistula	3 (1.4)	2 (0.9)	3 (1.4)	3 (1.4)
Enterovaginal fistula	2 (0.9)	2 (0.9)	0	0
Vesicorectal vaginal fistula	1 (0.5)	1 (0.5)	1 (0.5)	1 (0.5)
Vaginal fistula	1 (0.5)	1 (0.5)	0	0
Rectal fistula	1 (0.5)	1 (0.5)	0	0
Ileorectal vaginal fistula	1 (0.5)	1 (0.5)	0	0
Colovaginal fistula	1 (0.5)	0	0	0

There were no events of gastrointestinal-vaginal fistula, vesicovaginal fistula, etc. resulting in death. Serious gastrointestinal-vaginal fistula, vesicovaginal fistula, etc. occurred in 19 subjects (8.7%) in the bevacizumab + chemotherapy arm (rectovaginal fistula in 10 subjects; vesicovaginal fistula and enterovaginal fistula in 2 subjects each; and vesicorectal vaginal fistula, vaginal fistula, rectal fistula, ileorectal vaginal fistula, and colovaginal fistula in 1 subject each) and 4 subjects (1.8%) in the chemotherapy alone arm (vesicovaginal fistula in 2 subjects, rectovaginal fistula and vesicorectal vaginal fistula in 1 subject each). A causal relationship to study treatment could not be ruled out for events in 17 subjects in the bevacizumab + chemotherapy arm (rectovaginal fistula in 9 subjects; vesicovaginal fistula and enterovaginal fistula in 2 subjects each; and vaginal fistula, rectal fistula, ileorectal vaginal fistula, and colovaginal fistula in 1 subject each). Gastrointestinal vaginal fistula, vesicovaginal fistula, etc. led to treatment discontinuation in 7 subjects (3.2%) in the bevacizumab + chemotherapy arm and 1 subject (0.5%) in the chemotherapy alone arm.

In Study JO29569, no patients experienced adverse events classified as gastrointestinal vaginal fistula, vesicovaginal fistula, etc.

PMDA asked the applicant to explain the time of onset and risk factors of gastrointestinal-vaginal fistula, vesicovaginal fistula, etc.

The applicant's response:
The median time of onset of gastrointestinal-vaginal fistula, vesicovaginal fistula, etc. was 4.5 cycles (range, 1-12 cycles) in the bevacizumab + chemotherapy arm and 3 cycles (range, 1-4 cycles) in the chemotherapy alone arm, showing no specific tendency in the common time of onset.

Five of 5 subjects in the chemotherapy alone arm and 22 of 23 subjects in the bevacizumab + chemotherapy arm had received prior radiotherapy to the pelvic region where gastrointestinal-vaginal fistula, vesicovaginal fistula, etc. occurred. In patients without gastrointestinal-vaginal fistula, vesicovaginal fistula, etc., the applicant collected information only on the presence or absence of prior radiotherapy with no information on irradiated areas. Therefore, the applicant evaluated the relationship between "the presence or absence of prior radiotherapy" and "gastrointestinal-vaginal fistula, vesicovaginal fistula, etc." Among patients without prior radiotherapy, gastrointestinal-vaginal fistula, vesicovaginal fistula, etc. occurred in 0 of 43 patients (0%) receiving chemotherapy alone and 1 of 46 patients (2.2%) receiving bevacizumab + chemotherapy. Among patients with prior radiotherapy, gastrointestinal-vaginal fistula, vesicovaginal fistula, etc. occurred in 5 of 179 patients (2.8%) receiving chemotherapy alone and 22 of 172 patients (12.8%) receiving bevacizumab + chemotherapy.

To date, only a small number of patients have experienced gastrointestinal-vaginal fistula, vesicovaginal fistula, etc. Therefore no firm conclusions can be drawn on the risk factors of these events, but prior radiotherapy may become a risk factor.

PMDA's view:
In Study GOG-0240, the incidence of gastrointestinal-vaginal fistula, vesicovaginal fistula, etc. was higher in the bevacizumab + chemotherapy arm than in the chemotherapy alone arm, and a causal relationship to bevacizumab could not be ruled out for some of serious gastrointestinal-vaginal fistula, vesicovaginal fistula, etc. Attention should therefore be paid to these events in patients receiving bevacizumab. Most of the subjects experiencing these events had received prior radiotherapy to the pelvic region; special attention should be paid to the events when administering bevacizumab to patients with prior radiotherapy to the pelvic region. Using the package insert and other relevant documents, the applicant should provide healthcare professionals with information regarding (a) gastrointestinal-vaginal fistula, vesicovaginal fistula, and other similar events reported in clinical studies and (b) prior radiotherapy to the pelvic region in patients with the events.

7.R.4 Clinical positioning and indication

The proposed indication of bevacizumab is "advanced or recurrent cervical cancer." The following statement is included in the proposed Precautions for Indications section:

- Eligible patients must be selected based on a full understanding of the information in "CLINICAL STUDIES" and of the efficacy and safety of bevacizumab.

PMDA's conclusion based on its review of the efficacy and safety of bevacizumab [see Sections 7.R.2 and 7.R.3] and the review presented in Section 7.R.4.1:
The additional indication of bevacizumab should be "advanced or recurrent cervical cancer." The "CLINICAL STUDIES" section of the package insert should state that Study GOG-0240 enrolled

patients with advanced or recurrent cervical cancer who were ineligible for surgery or radiotherapy. The "Precautions for Indications" section should include the following precautionary statement:

- Eligible patients must be selected based on a full understanding of the information in "CLINICAL STUDIES" and of the efficacy and safety of bevacizumab.

7.R.4.1 Clinical positioning of bevacizumab and eligible patients

Japanese and foreign clinical practice guidelines and representative oncology textbooks mention bevacizumab therapy for advanced or recurrent cervical cancer (see below for details):

Clinical practice guidelines

- NCCN Guidelines (ver.1. 2016):
  Based on the results of Study GOG-0240, bevacizumab + PTX + CDDP or bevacizumab + PTX + nogitecan is strongly recommended as a first-line therapy of advanced or recurrent cervical cancer. Bevacizumab + PTX +carboplatin (CBDCA) is also recommended. Bevacizumab monotherapy is a second-line treatment option for advanced or recurrent cervical cancer.
- The US National Cancer Institute Physician Data Query (NCI-PDQ) (April 21, 2015):
  Bevacizumab + PTX + CDDP is a standard treatment option for advanced or recurrent cervical cancer.
- The Japan Society of Gynecologic Oncology guidelines for the treatment of cervical cancer (Kanehara & Co., Ltd.; 2011):
  A randomized comparative study of bevacizumab in combination with chemotherapy has been planned.

Textbooks

- *Clinical Oncology Version 4 (*Nankodo, 2015):
  Study GOG-0240 demonstrated that bevacizumab + chemotherapy was superior to chemotherapy alone in response rate, progression-free survival, and OS. Bevacizumab monotherapy was also effective in treating patients with cervical cancer.
- *DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology 10th edition* (Lippincott Williams & Wilkins, 2015, USA):
  In Study GOG-0240 in patients with advanced or recurrent cervical cancer, bevacizumab + chemotherapy resulted in a prolongation of OS, compared with chemotherapy alone.

The applicant's explanation about the clinical position of bevacizumab and eligible patients.

In Study GOG-0240, bevacizumab + chemotherapy was superior in efficacy to chemotherapy alone in patients with advanced or recurrent cervical cancer who were ineligible for surgery or radiotherapy. Bevacizumab in combination with chemotherapy thus offers a treatment option for this patient population. Therefore, the additional indication of bevacizumab should be "advanced or recurrent cervical cancer," and the package insert should include (a) detailed information on patients enrolled in

Study GOG-0240 (in "CLINICAL STUDIES") and (b) the following precautionary statement (in the "Precautions for Indications" section):

- Eligible patients must be selected based on a full understanding of the information in "CLINICAL STUDIES" and of the efficacy and safety of bevacizumab.

PMDA's view:

In Study JO29569, the investigator-assessed response rate was 14.3% (1 of 7 subjects) [see Section 7.1.1.1]. The sample size (7 subjects) was too small to fully evaluate the efficacy of bevacizumab in Japanese patients with advanced or recurrent cervical cancer. Meanwhile, no differences have been reported in the efficacy of bevacizumab between Japanese and non-Japanese patients treated for the approved indications. This suggests that, based on the results of the foreign Study GOG-0240, bevacizumab may be positioned as a treatment option for Japanese patients with advanced or recurrent cervical cancer. PMDA therefore accepted the applicant's explanation.

7.R.5 Dosage and administration

The proposed dosage and administration of bevacizumab are as follows:

"The usual adult dosage is 15 mg/kg (body weight) of Bevacizumab (Genetical Recombination) given as an intravenous infusion in combination with chemotherapy. The dosing interval should be ≥3 weeks."

The following precautionary statements are included in the proposed "Precautions for Dosage and Administration":

- Treatment with bevacizumab should be initiated in combination with chemotherapy. Concomitant chemotherapeutic agents should be selected based on a full understanding of the information in "CLINICAL STUDIES."
- The package inserts for concomitant chemotherapeutic agents should be read carefully.
- The efficacy and safety of bevacizumab monotherapy have not been established.

PMDA's conclusion based on its review presented in Sections 7.R.5.1 to 7.R.5.3:

As proposed by the applicant, the additional dosage and administration of bevacizumab should be as follows: "The usual adult dosage is 15 mg/kg (body weight) of Bevacizumab (Genetical Recombination) given as an intravenous infusion in combination with chemotherapy. The dosing interval should be ≥3 weeks." The following precautionary statements should be included in the "Precautions for Dosage and Administration":

- Treatment with bevacizumab should be initiated in combination with PTX-based chemotherapy. Concomitant chemotherapeutic agents should be selected based on a full understanding of the information in "CLINICAL STUDIES."
- The package inserts for concomitant chemotherapeutic agents should be read carefully.
- There is no clinical experience with bevacizumab in combination with PTX and nogitecan in Japanese patients with cervical cancer.
- The efficacy and safety of bevacizumab monotherapy have not been established.

7.R.5.1 Dosage and administration of bevacizumab

The applicant's explanation about the dosage and administration of bevacizumab in patients with advanced or recurrent cervical cancer:

In a foreign phase II study (GOG-0227C), bevacizumab 15 mg/kg was administered every 3 weeks to patients with advanced or recurrent cervical cancer who had received prior chemotherapy, to evaluate the efficacy, safety, and other aspects of bevacizumab. In total, 11 of 46 subjects (23.9%) achieved progression-free survival for ≥6 months and bevacizumab showed a tolerable safety profile (*J Clin Oncol*, 2009;27:1069-1074).

On the basis of the above results, Study GOG-0240 used the same dosage (bevacizumab 15 mg/kg every 3 weeks) and demonstrated its efficacy and safety in patients with advanced or recurrent cervical cancer. The applicant therefore proposed the dosage (15 mg/kg every 3 weeks) in the present application.

PMDA accepted the applicant's explanation.

7.R.5.2 Chemotherapy in combination with bevacizumab

Study GOG-0240 in patients with advanced or recurrent cervical cancer demonstrated the clinical usefulness of bevacizumab in combination with PTX + CDDP or PTX + nogitecan. However, according to the proposed "Precautions for Dosage and Administration," recommended concomitant chemotherapies are not limited to PTX + CDDP or PTX + nogitecan. PMDA asked the applicant to discuss whether the section should include a statement restricting concomitant chemotherapies to PTX + CDDP or PTX + nogitecan in patients with advanced or recurrent cervical cancer.

The applicant's response:

The clinical usefulness of bevacizumab in combination with chemotherapies other than PTX + CDDP or PTX + nogitecan has not been demonstrated in patients with advanced or recurrent cervical cancer. Therefore, bevacizumab in combination with chemotherapy other than PTX + CDDP or PTX + nogitecan is not strongly recommended for this patient population.

However, for the reasons presented below, concomitant chemotherapeutic agents should be selected at the discretion of the physician based on the clinical study results in patients with cervical cancer, the patient's prior treatments, and other factors. Therefore, limiting concomitant chemotherapy to PTX + CDDP or PTX + nogitecan is unnecessary, provided that the "CLINICAL STUDIES" section of the package insert states that bevacizumab was used in combination with PTX + CDDP or PTX + nogitecan in Study GOG-0240, and that the "Precautions for Dosage and Administration" section states that chemotherapeutic agents used in combination with bevacizumab should be selected based on a full understanding of the information in "CLINICAL STUDIES."

- In Study GOG-0240, bevacizumab showed add-on effects in combination with either PTX + CDDP or PTX + nogitecan [see Section 7.R.2.2], and non-platinum-based chemotherapy (PTX + nogitecan

or bevacizumab + PTX + nogitecan) was not markedly inferior in efficacy to platinum-based chemotherapy (PTX + CDDP or bevacizumab + PTX + CDDP) [see Section 7.1.2.1].

- No clinical studies have been conducted in patients with advanced or recurrent cervical cancer to investigate the efficacy and safety of bevacizumab in combination with PTX/CBDCA. However, in a Japanese phase III study (JCOG0505) conducted in the same patient population, the clinical usefulness of PTX/CBDCA was similar to that of PTX + CDDP (*J Clin Oncol*, 2015;33:2129-2135). Based on this study results and other factors, the NCCN Guidelines (ver.1, 2016) recommend bevacizumab in combination with PTX + CBDCA.
- A subgroup analysis of Study JCOG0505 suggested the superiority of PTX + CBDCA in efficacy to PTX + CDDP particularly in patients with prior CDDP therapy. This result suggests that many patients with advanced or recurrent cervical cancer receive CDDP-based concurrent chemoradiotherapy before bevacizumab therapy. It this patient population, therefore, PTX + CBDCA is more likely to be selected than PTX + CDDP as chemotherapy in combination with bevacizumab.
- The safety of bevacizumab + PTX + CBDCA has been confirmed in patients with advanced or recurrent non-small cell lung cancer, an approved indication of bevacizumab.

PMDA's view:

Study GOG-0240 demonstrated the clinical usefulness of bevacizumab in combination with PTX + CDDP or PTX + nogitecan. Therefore PTX should always be used in combination with bevacizumab in patients with advanced or recurrent cervical cancer.

The tolerability and safety of bevacizumab + PTX + nogitecan are unknown in Japanese patients because no clinical study data are available on the combination therapy in the population. Bevacizumab + PTX + nogitecan thus cannot be recommended for Japanese patients.

On the basis of the above, the proposed dosage and administration of bevacizumab in patients with advanced or recurrent cervical cancer are acceptable. The "CLINICAL STUDIES" section of the package insert should state that bevacizumab was administered in combination with PTX + CDDP or PTX + nogitecan in Study GOG-0240. The "Precautions for Dosage and Administration" section should include the following precautionary statements:

- Treatment with bevacizumab should be initiated in combination with PTX-based chemotherapy. Concomitant chemotherapeutic agents should be selected based on a full understanding of the information in "CLINICAL STUDIES."
- The package inserts for concomitant chemotherapeutic agents should be read carefully.
- There is no clinical experience with bevacizumab in combination with PTX and nogitecan in Japanese patients with cervical cancer.

7.R.5.3 Bevacizumab monotherapy

The applicant's explanation about bevacizumab monotherapy:
A foreign phase II study (GOG-0227C) suggested the efficacy and safety of bevacizumab monotherapy (15 mg/kg) in patients with advanced or recurrent cervical cancer (*J Clin Oncol*, 2009;27:1069-1074). However, Study GOG-0240 showed the clinical usefulness of bevacizumab in combination with PTX + CDDP or PTX + nogitecan. Therefore, the "Precautions for Dosage and Administration" section states that treatment with bevacizumab should be initiated in combination with chemotherapy, and that the efficacy and safety of bevacizumab monotherapy have not been established.

PMDA accepted the applicant's explanation.

7.R.6 Post-marketing investigations

The applicant's explanation about the proposed post-marketing surveillance plan:
The applicant plans to conduct post-marketing surveillance to investigate exclusively the occurrence of gastrointestinal-vaginal fistula in patients with advanced or recurrent cervical cancer who receive bevacizumab in clinical practice, for the following reasons.

- In Study GOG-0240, gastrointestinal-vaginal fistula occurred more frequently in the bevacizumab + chemotherapy arm than in the chemotherapy alone arm [see Section 7.R.3.2].
- The safety profile of bevacizumab is similar irrespective of cancer type, except for safety in terms of gastrointestinal-vaginal fistula.

No key survey items will be defined because the surveillance will collect information only on gastrointestinal-vaginal fistula. The planned sample size is 130 based on the incidence of gastrointestinal-vaginal fistula in Study GOG-0240.

In Study GOG-0240, most events of gastrointestinal-vaginal fistula occurred within the first 8 cycles of bevacizumab therapy, and 176 days (median) were required to complete 8 cycles of treatment. The proposed observation period is therefore 6 months.

PMDA's view:
Since only a small number of Japanese patients were enrolled in Study JO29569, the applicant should conduct post-marketing surveillance to investigate the safety and other aspects of bevacizumab in clinical practice in Japan.

In Study GOG-0240, vesicovaginal fistula etc. occurred in addition to gastrointestinal-vaginal fistula, and radiotherapy to the pelvic region was suspected of causing these events [see Section 7.R.3.2]; therefore, the surveillance should collect information on the occurrence of fistula in the pelvis. Because the surveillance will collect information only on specific events, fistula in the pelvis should be classified as a key survey item.

The sample size and the observation period should be reconsidered based on the key survey item.

7.2 Adverse events in clinical studies

Among the clinical study data submitted for safety evaluation, fatal events are presented in Section "7.1 Evaluation data." Other adverse events are shown in Sections 7.2.1 and 7.2.2.

7.2.1 Japanese phase II study (Study JO29569)

All subjects experienced adverse events. All subjects also experienced adverse events for which a causal relationship to study drug could not be ruled out. Table 10 lists adverse events occurring in ≥3 subjects.

Table 10. Adverse events occurring in ≥3 subjects

System Organ Class Preferred Term (MedDRA/J ver.17.1)	n (%) N = 7	
	All Grades	Grade ≥3
All adverse events	7 (100)	5 (71.4)
Gastrointestinal disorders		
Nausea	4 (57.1)	0
Constipation	3 (42.9)	0
Nervous system disorders		
Peripheral sensory neuropathy	3 (42.9)	0
Vascular disorders		
Hypertension	3 (42.9)	2 (28.6)
Skin and subcutaneous tissue disorders		
Alopecia	7 (100)	0
Investigations		
Neutrophil count decreased	3 (42.9)	2 (28.6)

Serious adverse events occurred in 2 of 7 subjects (28.6%): pyelonephritis and febrile neutropenia in 1 subject (14.3%) each. A causal relationship to study treatment could not be ruled out for the febrile neutropenia.

Adverse events led to treatment discontinuation in 1 of 7 subjects (14.3%): peripheral sensory neuropathy and blood creatinine increased in 1 subject (14.3%) each. A causal relationship to study treatment could not be ruled out for both events.

7.2.2 Foreign phase III study (Study GOG-0240)

Adverse events occurred in 216 of 218 subjects (99.1%) in the bevacizumab + chemotherapy arm and 219 of 222 subjects (98.6%) in the chemotherapy alone arm. Adverse events for which a causal relationship to study treatment could not be ruled out occurred in 214 of 218 subjects (98.2%) in the bevacizumab + chemotherapy arm and 216 of 222 subjects (97.3%) in the chemotherapy alone arm. The adverse events with an incidence of ≥20% in either group are shown in Table 11.

Table 11. Adverse events with an incidence of ≥20% in either group

System Organ Class Preferred Term (MedDRA/J ver.16.0)	n (%)			
	Bevacizumab + chemotherapy arm N = 218		Chemotherapy alone arm N = 222	
	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	216 (99.1)	165 (75.7)	219 (98.6)	127 (57.2)
Gastrointestinal disorders				
Nausea	137 (62.8)	11 (5.0)	135 (60.8)	15 (6.8)
Constipation	106 (48.6)	6 (2.8)	110 (49.5)	4 (1.8)
Diarrhoea	81 (37.2)	12 (5.5)	79 (35.6)	6 (2.7)
Abdominal pain	75 (34.4)	26 (11.9)	72 (32.4)	22 (9.9)
Vomiting	74 (33.9)	10 (4.6)	71 (32.0)	9 (4.1)
Infections and infestations				
Urinary tract infection	48 (22.0)	18 (8.3)	32 (14.4)	14 (6.3)
Metabolism and nutrition disorders				
Decreased appetite	75 (34.4)	6 (2.8)	57 (25.7)	4 (1.8)
Hyperglycaemia	56 (25.7)	9 (4.1)	43 (19.4)	5 (2.3)
Hypomagnesaemia	53 (24.3)	2 (0.9)	34 (15.3)	2 (0.9)
Nervous system disorders				
Peripheral sensory neuropathy	134 (61.5)	14 (6.4)	140 (63.1)	11 (5.0)
Headache	47 (21.6)	3 (1.4)	29 (13.1)	2 (0.9)
Vascular disorders				
Hypertension	63 (28.9)	25 (11.5)	14 (6.3)	1 (0.5)
Respiratory, thoracic and mediastinal disorders				
Dyspnoea	50 (22.9)	7 (3.2)	53 (23.9)	3 (1.4)
General disorders and administration site conditions				
Fatigue	174 (79.8)	31 (14.2)	166 (74.8)	22 (9.9)
Oedema peripheral	33 (15.1)	2 (0.9)	49 (22.1)	4 (1.8)
Musculoskeletal and connective tissue disorders				
Back pain	46 (21.1)	12 (5.5)	42 (18.9)	7 (3.2)
Arthralgia	48 (22.0)	3 (1.4)	39 (17.6)	2 (0.9)
Skin and subcutaneous tissue disorders				
Alopecia	136 (62.4)	0	138 (62.2)	0
Investigations				
Weight decreased	45 (20.6)	3 (1.4)	15 (6.8)	0

Serious adverse events occurred in 111 of 218 subjects (50.9%) in the bevacizumab + chemotherapy arm and 81 of 222 subjects (36.5%) in the chemotherapy alone arm. The following serious adverse events occurred in ≥3 subjects:

The bevacizumab + chemotherapy arm:

Abdominal pain in 21 subjects (9.6%), nausea and vomiting in 18 subjects (8.3%) each, urinary tract infection and fatigue in 17 subjects (7.8%) each, thrombosis in 16 subjects (7.3%), neutropenia in 14 subjects (6.4%), diarrhea and infection in 13 subjects (6.0%) each, constipation in 12 subjects (5.5%), anal fistula in 10 subjects (4.6%), febrile neutropenia and dehydration in 9 subjects (4.1%) each, hypokalaemia, hypertension, and pelvic pain in 7 subjects (3.2%) each, pyrexia, dyspnoea, haemorrhage urinary tract, cellulitis, and vaginal haemorrhage in 6 subjects (2.8%) each, embolism, blood creatinine increased, intestinal obstruction, decreased appetite, cystitis, and proctalgia in 5 subjects (2.3%) each, ureteric obstruction, pain in extremity, back pain, rectal haemorrhage, vaginal fistula, proctitis, pneumonia, and syncope in 4 subjects (1.8%) each, and hypoalbuminaemia,

hypotension, lymphopenia, hyponatraemia, dizziness, and urinary bladder haemorrhage in 3 subjects (1.4%) each.

The chemotherapy alone arm:

Urinary tract infection in 14 subjects (6.3%), abdominal pain in 13 subjects (5.9%), nausea, vomiting, and febrile neutropenia in 11 subjects (5.0%) each, neutropenia in 9 subjects (4.1%), diarrhea in 7 subjects (3.2%), thrombosis, pyrexia, embolism, and ureteric obstruction in 6 subjects (2.7%) each, constipation in 5 subjects (2.3%), dyspnea, small intestinal obstruction, and renal failure in 4 subjects (1.8%) each, and infection, hypokalaemia, haemorrhage urinary tract, blood creatinine increased, pain in extremity, back pain, hypoxia, supraventricular tachycardia, lung disorder, and pain in 3 subjects (1.4%) each.

Among these serious adverse events, a causal relationship to study treatment could not be ruled out for the following:

The bevacizumab + chemotherapy arm:

Vomiting in 17 subjects, nausea and fatigue in 16 subjects each, thrombosis in 14 subjects, urinary tract infection, neutropenia, and diarrhea in 13 subjects each, abdominal pain in 11 subjects, febrile neutropenia and anal fistula in 9 subjects each, constipation and dehydration in 8 subjects each, infection, hypokalaemia, and hypertension in 7 subjects each, pyrexia and cellulitis in 6 subjects each, decreased appetite and cystitis in 5 subjects each, blood creatinine increased, vaginal haemorrhage, and vaginal fistula in 4 subjects each, embolism, haemorrhage urinary tract, rectal haemorrhage, proctitis, pneumonia, lymphopenia, dizziness, and urinary bladder haemorrhage in 3 subjects each, dyspnea, pelvic pain, intestinal obstruction, proctalgia, hypoalbuminaemia, hypotension, and hyponatraemia in 2 subjects each, and pain in extremity and syncope in 1 subject each.

The chemotherapy alone arm:

Febrile neutropenia in 11 subjects, nausea and vomiting in 10 subjects each, urinary tract infection and neutropenia in 9 subjects each, diarrhea in 6 subjects, abdominal pain in 4 subjects, constipation, pyrexia, hypokalaemia, blood creatinine increased, and renal failure in 3 subjects each, infection and embolism in 2 subjects each, and thrombosis, pain in extremity, and supraventricular tachycardia in 1 subject each.

Adverse events led to treatment discontinuation in 56 of 218 subjects (25.7%) in the bevacizumab + chemotherapy arm and 40 of 222 subjects (18.0%) in the chemotherapy alone arm. The following adverse events led to treatment discontinuation in ≥2 subjects:

The bevacizumab + chemotherapy arm:

Unevaluable event in 9 subjects (4.1%), neuropathy peripheral in 6 subjects (2.8%), performance status decreased and fatigue in 4 subjects (1.8%) each, peripheral sensory neuropathy and female genital tract fistula in 3 subjects (1.4%) each, and toxicity to various agents, nausea, thrombocytopenia, febrile neutropenia, vomiting, and fistula in 2 subjects (0.9%) each.

The chemotherapy alone arm:

Neuropathy peripheral in 9 subjects (4.1%), drug hypersensitivity in 6 subjects (2.7%), unevaluable event in 4 subjects (1.8%), and peripheral sensory neuropathy and toxicity to various agents in 3 subjects (1.4%) each.

Among these adverse events leading to treatment discontinuation, a causal relationship to study treatment could not be ruled out for the following:

The bevacizumab + chemotherapy arm:

Unevaluable event in 9 subjects, neuropathy peripheral in 6 subjects, performance status decreased and fatigue in 4 subjects each, female genital tract fistula in 3 subjects, and peripheral sensory neuropathy, toxicity to various agents, nausea, thrombocytopenia, febrile neutropenia, vomiting, and fistula in 2 subjects each.

The chemotherapy alone arm:

Neuropathy peripheral in 9 subjects, drug hypersensitivity in 6 subjects, unevaluable event in 4 subjects, and peripheral sensory neuropathy and toxicity to various agents in 3 subjects each.

8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

8.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The new drug application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

8.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The new drug application data (CTD 5.3.5.2-1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

9. Overall Evaluation during Preparation of the Review Report (1)

On the basis of the data submitted, PMDA has concluded that bevacizumab has efficacy in the treatment of advanced or recurrent cervical cancer, and that bevacizumab has acceptable safety in view of its benefits. Bevacizumab is clinically meaningful because it offers a treatment option for patients with advanced or recurrent cervical cancer. The dosage and administration, post-marketing investigation items, and other issues should be further discussed in the Expert Discussion.

PMDA has concluded that bevacizumab may be approved if bevacizumab is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

April 11, 2016

Product Submitted for Approval

Brand Name	Avastin 100 mg/4 mL Intravenous Infusion Avastin 400 mg/16 mL Intravenous Infusion
Non-proprietary Name	Bevacizumab (Genetical Recombination)
Applicant	Chugai Pharmaceutical Co., Ltd.
Date of Application	September 17, 2015

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized in the following. The expert advisors present during the Expert Discussion were nominated based on their declarations etc., concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions etc., by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

1.1 Efficacy

PMDA's conclusion based on its review presented in Section "7.R.2 Efficacy" of Review Report (1):
In a foreign phase III study in patients with advanced or recurrent cervical cancer who were ineligible for surgery or radiotherapy (Study GOG-0240), Bevacizumab (Genetical Recombination) (hereinafter, bevacizumab) in combination with chemotherapy ([a] bevacizumab + paclitaxel [PTX] + cisplatin [CDDP], or [b] bevacizumab + PTX + nogitecan hydrochloride [hereinafter, nogitecan]) was superior in overall survival (OS; the primary endpoint) to chemotherapy alone ([a] PTX + CDDP, or [b] PTX + nogitecan). Thus, the efficacy of bevacizumab has been demonstrated in the population of Study GOG-0240.

This conclusion was supported by the expert advisors at the Expert Discussion.

1.2 Safety

PMDA's conclusion based on its review presented in Section "7.R.3 Safety" of Review Report (1):
In patients with advanced or recurrent cervical cancer who were ineligible for surgery or radiotherapy, most adverse events occurring during treatment with bevacizumab + PTX + CDDP or bevacizumab + PTX + nogitecan were characteristic events known to occur during monotherapy with each drug. Special attention should be paid to gastrointestinal-vaginal fistula, vesicovaginal fistula, etc. in patients receiving bevacizumab for the proposed indication.

Bevacizumab in combination with chemotherapy is tolerable as long as patients are followed up by physicians with sufficient knowledge and experience in cancer chemotherapy, through monitoring of adverse events, interruption or discontinuation of bevacizumab or concomitant chemotherapy, or other appropriate actions.

During the Expert Discussion, the expert advisors supported this conclusion and made the following comments:

- The applicant should investigate whether the incidence or severity of gastrointestinal-vaginal fistula, vesicovaginal fistula, etc. differed according to chemotherapy used in combination with bevacizumab.

PMDA asked the applicant to show the incidence and severity of gastrointestinal-vaginal fistula, vesicovaginal fistula, etc. by concomitant chemotherapy in Study GOG-0240.

The applicant's response:
Table 12 shows the incidence and severity of gastrointestinal-vaginal fistula, vesicovaginal fistula, etc. by concomitant chemotherapy in Study GOG-0240.

Table 12. Incidence and severity of gastrointestinal-vaginal fistula, vesicovaginal fistula, etc. by concomitant chemotherapy

	n (%)			
	Bevacizumab + PTX + CDDP N = 109		Bevacizumab + PTX + nogitecan N = 109	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Gastrointestinal vaginal fistula, vesicovaginal fistula, etc.	11 (10.1)	8 (7.3)	12 (11.0)	8 (7.3)
Rectovaginal fistula	7 (6.4)	5 (4.6)	6 (5.5)	3 (2.8)
Vesicovaginal fistula	2 (1.8)	1 (0.9)	1 (0.9)	1 (0.9)
Enterovaginal fistula	1 (0.9)	1 (0.9)	1 (0.9)	1 (0.9)
Vesicorectal vaginal fistula	0	0	1 (0.9)	1 (0.9)
Vaginal fistula	1 (0.9)	1 (0.9)	0	0
Rectal fistula	0	0	1 (0.9)	1 (0.9)
Ileorectal vaginal fistula	0	0	1 (0.9)	1 (0.9)
Colovaginal fistula	0	0	1 (0.9)	0

PMDA's view:
No marked differences were noted in the incidence or severity of gastrointestinal-vaginal fistula, vesicovaginal fistula, etc. between the 2 chemotherapy regimens used in combination with bevacizumab. However, the applicant should appropriately inform healthcare professionals of the incidence and severity by disseminating information materials, because such data are important in deciding whether to administer bevacizumab to a patient.

1.3 Clinical positioning and indication

PMDA's conclusion based on its review presented in Section "7.R.4 Clinical positioning and indication" of Review Report (1):

The additional indication for bevacizumab should be “advanced or recurrent cervical cancer.” The “CLINICAL STUDIES” section of the package insert should include detailed information regarding patients enrolled in Study GOG-0240, and the “Precautions for Indications” section should include the following precautionary statement:

Precautions for Indications
Eligible patients must be selected based on a full understanding of the information in “CLINICAL STUDIES” and of the efficacy and safety of bevacizumab.

This conclusion was supported by the expert advisors at the Expert Discussion.

PMDA instructed the applicant to include the above indication and the precautions for indications in the package insert. The applicant agreed.

1.4 Dosage and administration

PMDA’s conclusion based on its review presented in Section “7.R.5 Dosage and administration” of Review Report (1):
The dosage and administration should be as follows: “The usual adult dosage is 15 mg/kg (body weight) of bevacizumab (genetical recombination) given as an intravenous infusion in combination with chemotherapy. The dosing interval should be ≥3 weeks.” The “CLINICAL STUDIES” section of the package insert should state that bevacizumab was administered in combination with PTX + CDDP or PTX + nogitecan in Study GOG-0240. The “Precautions for Dosage and Administration” section should include the following precautionary statements.

Precautions for Dosage and Administration

- Treatment with bevacizumab should be initiated in combination with PTX-based chemotherapy. Concomitant chemotherapeutic agents should be selected based on a full understanding of the information in “CLINICAL STUDIES.”
- The package inserts for concomitant chemotherapeutic agents should be read carefully.
- There is no clinical experience with bevacizumab in combination with PTX and nogitecan in Japanese patients with cervical cancer.
- The efficacy and safety of bevacizumab monotherapy have not been established.

During the Expert Discussion, the expert advisors supported this conclusion and made the following comments:

- In Japanese clinical practice, the combination of PTX and carboplatin (CBDCA) has been widely used in patients with cervical cancer. This suggests that physicians may administer bevacizumab in combination with PTX + CBDCA to Japanese patients in the Japanese post-marketing settings. Precautionary measures should therefore be discussed and developed.

PMDA's view:
As stated in PMDA's conclusion in Review Report (1), the packaged insert should state that Study GOG-0240 showed the clinical usefulness of bevacizumab only in combination with PTX + CDDP or PTX + nogitecan. Further, using information materials, the applicant should inform healthcare professionals that no clinical study data have demonstrated the clinical usefulness of bevacizumab + PTX + CBDCA in patients with cervical cancer.

PMDA instructed the applicant to take actions accordingly, and to use the above wording for Dosage and Administration and the Precautions for Dosage and Administration in the package insert. The applicant agreed.

1.5 Risk management plan (draft)

The applicant plans to conduct post-marketing surveillance (target sample size, 130; observation period, 6 months) to investigate the incidence of gastrointestinal-vaginal fistula in patients with advanced or recurrent cervical cancer receiving bevacizumab in clinical practice.

PMDA's conclusion based on its review presented in Section "7.R.6 Post-marketing investigations" of Review Report (1):
The applicant should conduct surveillance to investigate the safety and other aspects of bevacizumab in clinical practice. The following are PMDA's view on the post-marketing surveillance plan:

- Fistula in the pelvis should be classified as the key survey item, because gastrointestinal-vaginal fistula, vesicovaginal fistula, etc. occurred in Study GOG-0240, and because radiotherapy to the pelvic region may cause these events.
- The planned sample size and the observation period should be reconsidered according to the incidence, severity, and time of onset of fistula in the pelvis, the key survey item.

During the Expert Discussion, the expert advisors supported this conclusion and made the following comments:

- The surveillance should collect information on the relationship between cervical cancer lesions and the onset of fistula.
- The surveillance should also collect information on the safety of bevacizumab in combination with chemotherapy (e.g., PTX + CBDCA) other than PTX + CDDP.

On the basis of the above, PMDA instructed the applicant to reconsider the post-marketing surveillance plan.
The applicant's response:

- Fistula in the pelvis is classified as the key survey item.
- The target sample size is 130 based on the incidence of fistula in the pelvis in Study GOG-0240.

- The observation period is 6 months based on the time of onset of fistula in the pelvis in Study GOG-0240.

PMDA accepted the applicant's response.

In view of the discussion above, PMDA has concluded that the risk management plan (draft) for bevacizumab should include the safety specification presented in Table 13, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 14.

Table 13. Safety and efficacy specifications in risk management plan (draft)

Safety specification		
Important identified risk	Important potential risk	Important missing information
• Haemorrhage • Arterial thromboembolism • Hypertension, hypertensive crisis • Cardiac failure congestive • Proteinuria, nephrotic syndrome • Wound healing delayed • Gastrointestinal perforation • Posterior reversible encephalopathy syndrome (PRES) • Bone marrow depression • Venous thromboembolism • Fistula • Shock, anaphylaxis, hypersensitivity reaction, infusion reaction • Interstitial pneumonia • Thrombotic microangiopathy (TMA) • Necrotising fasciitis • Effects on embryo-fetal development • Osteonecrosis in children (excluding osteonecrosis of jaw) • Adverse events occurring after intravitreal administration of bevacizumab for off-label indications	• Pulmonary hypertension • Osteonecrosis of jaw • Cardiac disorder (excluding cardiac failure congestive and arterial thromboembolism) • Gallbladder perforation • Infection	• None
Efficacy specification (relating to the present partial change application)		
• None		

Table 14. Summary of additional pharmacovigilance activities and risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
• <u>Specified use-results survey of patients with advanced or recurrent cervical cancer</u> • Post-marketing clinical study in patients with non-squamous non-small cell lung cancer (MO22097 [the AvaALL study]) • Use-results survey of patients with malignant glioma (AVA1301)	• <u>Preparation and distribution of information materials for healthcare professionals</u>

The activities underlined will be implemented for the additional indication proposed in the present application.

Table 15. Outline of use-result survey (draft)

Objective	To investigate the occurrence of fistula in the pelvis in patients receiving bevacizumab in clinical practice
Survey method	Central registration method
Population	Patients with advanced or recurrent cervical cancer
Observation period	6 months
Planned sample size	130 patients
Main survey items	Key survey item: fistula in the pelvis Other main survey items: patient characteristics (e.g., prior radiotherapy to the pelvic region, lesion areas), exposure to bevacizumab, concomitant drugs and therapies, and other relevant items

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the additional indication and dosage and administration statements, with the condition of approval shown below, provided that necessary precautionary statements are included in the package insert and information on the proper use of the product is properly disseminated after the market launch, and provided that the product is used under the supervision of physicians with sufficient knowledge and experience in cancer chemotherapy at medical institutions that can provide emergency medical care. Since the product has been designated as an orphan drug for the intended indication, "cervical cancer," the re-examination period should be 10 years for the proposed indication.

Indications (Underline denotes additions.)

1. Unresectable advanced or recurrent colorectal cancer
2. Unresectable advanced or recurrent, non-squamous non-small cell lung cancer
3. Inoperable or recurrent breast cancer
4. Malignant glioma
5. Ovarian cancer
6. Advanced or recurrent cervical cancer

Dosage and Administration (Underline denotes additions.)

1. Unresectable advanced or recurrent colorectal cancer
   - The usual adult dosage is 5 mg/kg (body weight) or 10 mg/kg (body weight) of Bevacizumab (Genetical Recombination) given as an intravenous infusion in combination with chemotherapy. The dosing interval should be ≥2 weeks.
   - The usual adult dosage is 7.5 mg/kg (body weight) of Bevacizumab (Genetical Recombination) given as an intravenous infusion in combination with chemotherapy. The dosing interval should be ≥3 weeks.
2. Unresectable advanced or recurrent, non-squamous non-small cell lung cancer

   The usual adult dosage is 15 mg/kg (body weight) of Bevacizumab (Genetical Recombination) given as an intravenous infusion in combination with chemotherapy. The dosing interval should be ≥3 weeks.

3. Inoperable or recurrent breast cancer

   The usual adult dosage is 10 mg/kg (body weight) of Bevacizumab (Genetical Recombination) given as an intravenous infusion in combination with paclitaxel. The dosing interval should be ≥2 weeks.

4. Malignant glioma

   The usual adult dosage is Bevacizumab (Genetical Recombination) at 10 mg/kg (body weight) every 2 weeks or 15 mg/kg (body weight) every 3 weeks, given as an intravenous infusion. The dosing interval may be prolonged according to the patient's condition.

5. Ovarian cancer

   The usual adult dosage is 15 mg/kg (body weight) of Bevacizumab (Genetical Recombination) given as an intravenous infusion in combination with chemotherapy. The dosing interval should be ≥3 weeks.

6. Advanced or recurrent cervical cancer

   The usual adult dosage is 15 mg/kg (body weight) of Bevacizumab (Genetical Recombination) given as an intravenous infusion in combination with chemotherapy. The dosing interval should be ≥3 weeks.

Condition of Approval

The applicant is required to develop and appropriately implement a risk management plan.

Warnings (No change)

1. Avastin in combination with chemotherapy should be administered only to patients eligible for the treatment under the supervision of physicians with sufficient knowledge and experience in cancer chemotherapy at medical institutions that can provide adequate emergency medical care. Eligible patients must be carefully selected after reading the package inserts for Avastin and concomitant chemotherapeutic agents. Treatment should be started only after obtaining informed consent from patients or their families who are fully informed of the efficacy and risk of treatment.
2. Gastrointestinal perforations, including fatal cases, have been reported. Discontinue Avastin and take appropriate measures in patients given a diagnosis of gastrointestinal perforation during Avastin therapy. The patients should not be re-exposed to Avastin.
3. Wound healing complications (e.g., wound dehiscence, post-operative haemorrhage) may occur.
   (1) Examine the surgical wound in postoperative patients to determine whether they can receive Avastin. Do not administer Avastin to patients with unhealed wound after major surgery, except in situations where the therapeutic benefits are expected to outweigh the risk of wound healing complications.
   (2) In patients experiencing wound healing complications during treatment, Avastin should be interrupted until the wound is fully healed and appropriate measures should be taken.
   (3) An adequate interval should be allowed between the termination of Avastin and subsequent elective surgery.

4. Avastin may increase the risk of tumor-associated haemorrhage. Avastin therapy may result in cerebral haemorrhage in patients with brain tumor (including brain metastases). Discontinue Avastin and take appropriate measures in patients experiencing severe hemorrhage during treatment. The patients should not be re-exposed to Avastin.
5. Pulmonary hemorrhages (hemoptysis) associated with Avastin, including fatal cases, have been reported. Patients should be carefully monitored for these events. Discontinue Avastin and take appropriate measures in patients experiencing pulmonary hemorrhage (hemoptysis) during treatment. The patients should not be re-exposed to Avastin.
6. Arterial thromboembolic events (e.g., cerebrovascular accident, transient ischemic attack, myocardial infarction, angina pectoris, cerebral ischemia, and cerebral infarction), including fatal cases, have been reported. Patients should be carefully monitored for these events. Discontinue Avastin and take appropriate measures in patients presenting with any abnormal findings. Patients who experience arterial thromboembolic events should not be re-exposed to Avastin.
7. Hypertensive encephalopathy or hypertensive crisis, including fatal cases, has been reported. Discontinue Avastin and take appropriate measures in patients experiencing these events. The patients should not be re-exposed to Avastin. Blood pressure should be monitored periodically during Avastin therapy.
8. Reversible posterior leukoencephalopathy syndrome may occur. Discontinue Avastin and take appropriate measures in patients suspected to have reversible posterior leukoencephalopathy syndrome.

Contraindications (No change)

1. Patients with a history of hypersensitivity to any of the ingredients of Avastin
2. Patients with a history of hemoptysis (fresh blood of ≥2.5 mL) (Pulmonary hemorrhage [hemoptysis] may occur, which may result in death.]

Precautions for Indications (Underline denotes additions.)

(1) Unresectable advanced or recurrent colorectal cancer, or unresectable advanced or recurrent, non-squamous non-small cell lung cancer
   (a) The efficacy and safety of Avastin in combination with adjuvant chemotherapy have not been established.
   (b) Eligible patients must be selected based on a full understanding of the information in “CLINICAL STUDIES” and of the efficacy and safety of Avastin.

(2) Inoperable or recurrent breast cancer
   (a) The efficacy and safety of Avastin in combination with adjuvant chemotherapy have not been established.
   (b) Avastin has not been shown to prolong survival.
   (c) Eligible patients must be selected after investigating the necessity of Avastin therapy in each patient according to the expression status of HER2 and hormone receptors, based on a full

understanding of the information in “CLINICAL STUDIES” and of the efficacy and safety of Avastin.

(3) Malignant glioma

Eligible patients must be selected based on a full understanding of the information in “CLINICAL STUDIES” and of the efficacy and safety of Avastin, and based on medical history, histopathological type, and other patient characteristics.

(4) Ovarian cancer

(a) Administer Avastin to patients with FIGO Stage III or IV ovarian cancer.

(b) Eligible patients must be selected based on a full understanding of the information in “CLINICAL STUDIES” and of the efficacy and safety of Avastin.

(5) Advanced or recurrent cervical cancer

Eligible patients must be selected based on a full understanding of the information in “CLINICAL STUDIES” and of the efficacy and safety of Avastin.

Precautions for Dosage and Administration (Underline denotes additions, and strikethrough denotes deletions.)

(1) Avastin should be used in combination with fluoropyrimidine-based chemotherapy in patients with unresectable advanced or recurrent colorectal cancer.

Treatment with Avastin should be initiated in combination with platinum-based chemotherapy in patients with unresectable advanced or recurrent, non-squamous non-small cell lung cancer; with paclitaxel-based chemotherapy in patients with inoperable or recurrent breast cancer; with radiotherapy and temozolomide in patients with primary malignant glioma; with carboplatin and paclitaxel in patients with ovarian cancer; and with paclitaxel-based chemotherapy in patients with advanced or recurrent cervical cancer.

The chemotherapeutic agents used in combination with Avastin must be selected based on a full understanding of the information in “CLINICAL STUDIES.”

(2) Read carefully the package inserts for concomitant chemotherapeutic agents.

(3) The efficacy and safety of Avastin monotherapy have not been established for any conditions other than recurrent malignant glioma.

(4) The dosage of Avastin in patients with unresectable advanced or recurrent colorectal cancer should be selected according to concomitant chemotherapeutic agents and prior chemotherapy regimens, based on a full understanding of the information in “CLINICAL STUDIES.”

(5) The dosage of Avastin in patients with malignant glioma should be selected according to prior chemotherapy regimens, based on a full understanding of the information in “CLINICAL STUDIES.”

(6) Patients with ovarian cancer should continue to receive Avastin as monotherapy after the completion of combination therapy with Avastin and chemotherapy. (The efficacy of Avastin has not been established in patients who do not receive Avastin monotherapy after the combination therapy [see “CLINICAL STUDIES”].)

(~~6~~7) There is no clinical experience with Avastin in combination with paclitaxel and nogitecan in Japanese patients with advanced or recurrent cervical cancer.

(~~7~~8) Preparation of infusion solution and infusion duration

(a) Withdraw the necessary volume of Avastin with a syringe and dilute in a total volume of approximately 100 mL isotonic sodium chloride solution (JP). The initial dose should be administered over 90 minutes as an intravenous infusion.

(b) If the first infusion is well tolerated, the second infusion may be administered over 60 minutes. If the 60-minute infusion is well tolerated, all subsequent infusions may be administered over 30 minutes.