Chugai Oncology Media Seminar

September 2, 2008

Overview of Avastin® and Assessment of its Proper Use in Japan

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- Chugai Pharmaceutical Co., Ltd.

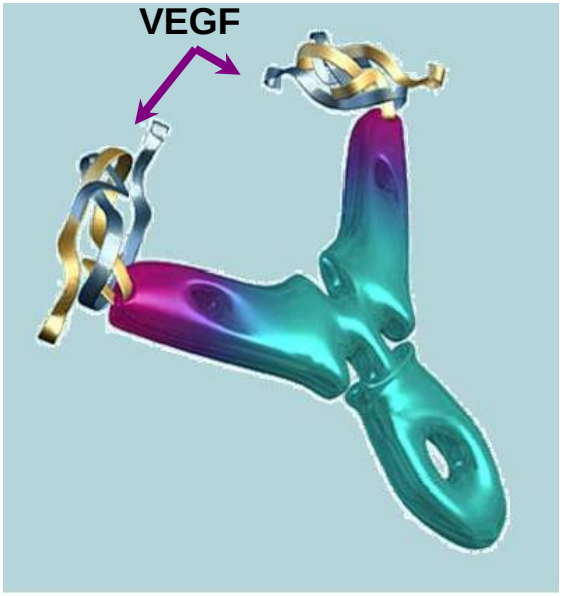
Overview (1)

Generic name

- Bevacizumab (genetical recombination)

Anti-VEGF humanized monoclonal antibody:

- 93% derived from human IgG1, 7% from murine antibody
- A protein composed of two light chains, each consisting of 214 amino acids, and two heavy chains, each consisting of 453 amino acids (molecular weight: 149 KDa)

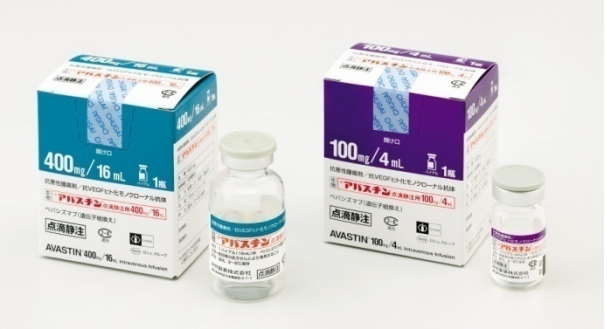


Target

- Inhibits VEGF-induced angiogenesis by binding to human VEGF (VEGF-A).

Formulation: injection (vial)

- Avastin® for intravenous infusion 100mg/4mL: single vial
- Avastin® for intravenous infusion 400mg/16mL: single vial



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Turn down angiogenesis

Vascular Endothelial Growth Factor (VEGF)

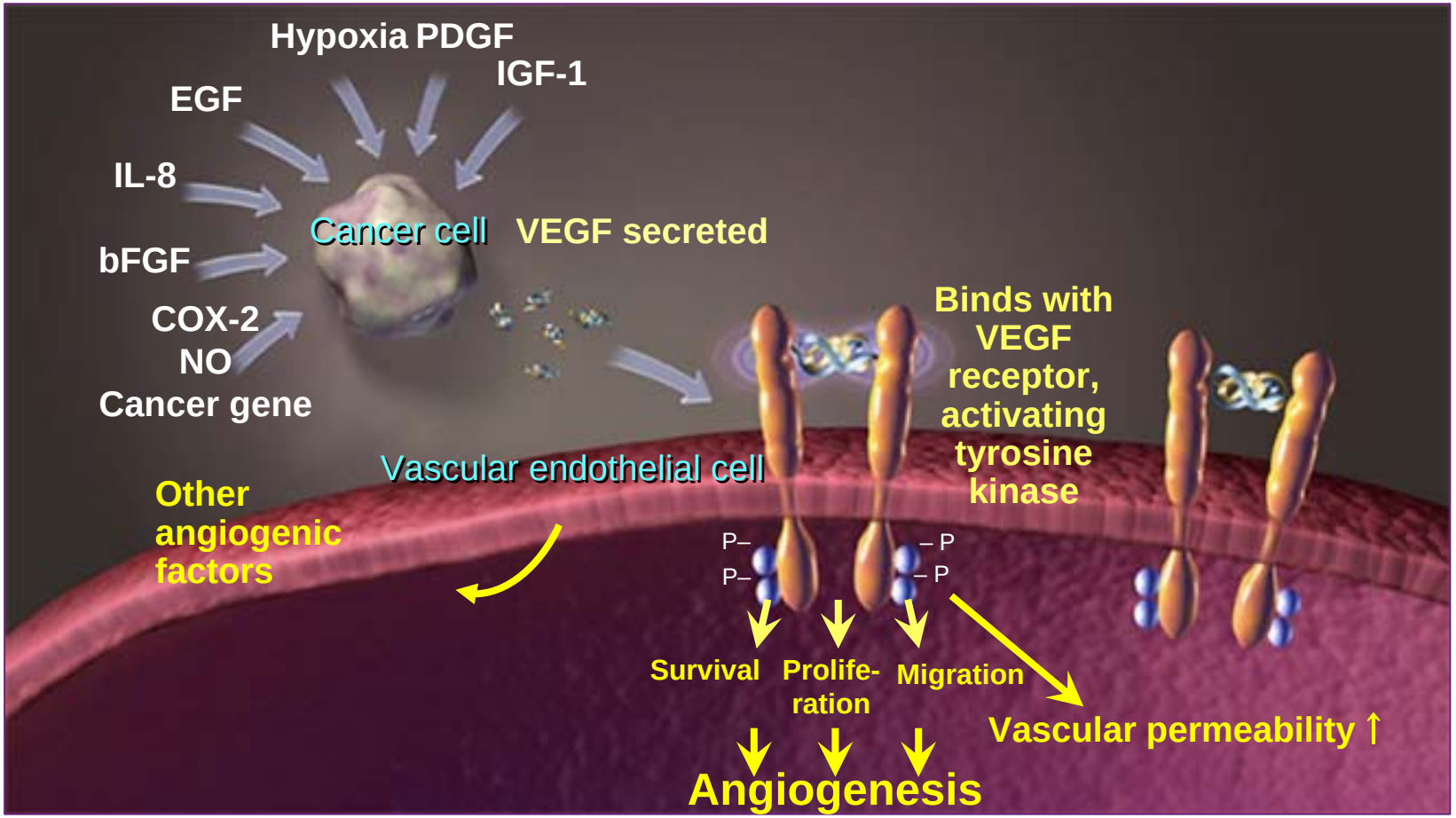
VEGF: Vascular Endothelial Growth Factor

- **Factors necessary for angiogenesis**
  - (1) Migration of vascular endothelial cells
  - (2) Proliferation of vascular endothelial cells
  - (3) Survival of immature vascular endothelial cells (inhibition of apoptosis)
  - (4) Increased vascular permeability

- Vascular endothelial growth factor receptor-1 (VEGFR-1) and VEGFR-2 are specifically expressed on vascular endothelial cells. The above factors bind to these receptors as a ligand, thus exerting their effects.

Ferrara N, et al. Endocr Rev 1997;18:4–25

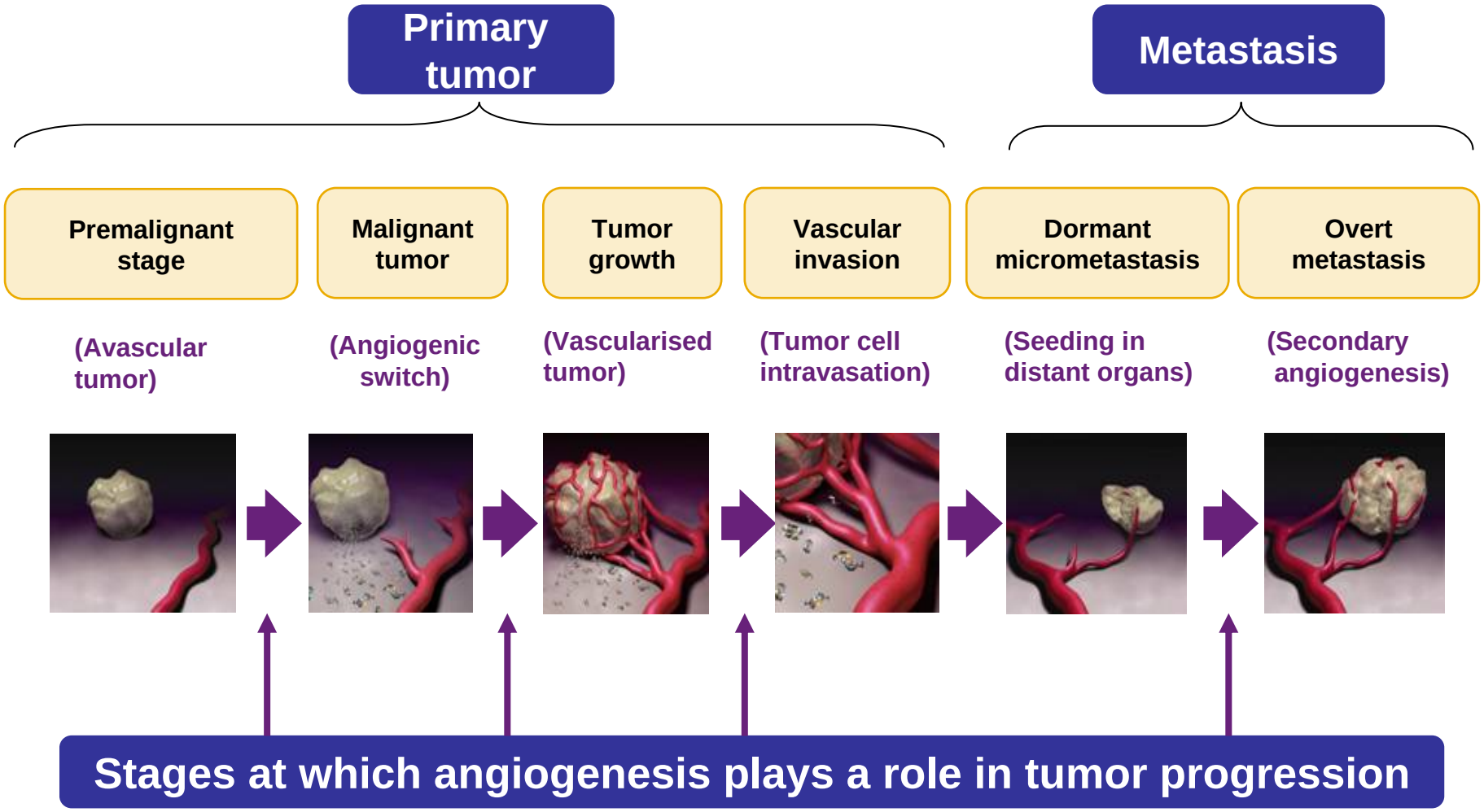
VEGF and VEGF Receptors



IGF = insulin-like growth factor
PDGF = platelet-derived growth factor
EGF = epidermal growth factor
bFGF = basic fibroblast growth factor

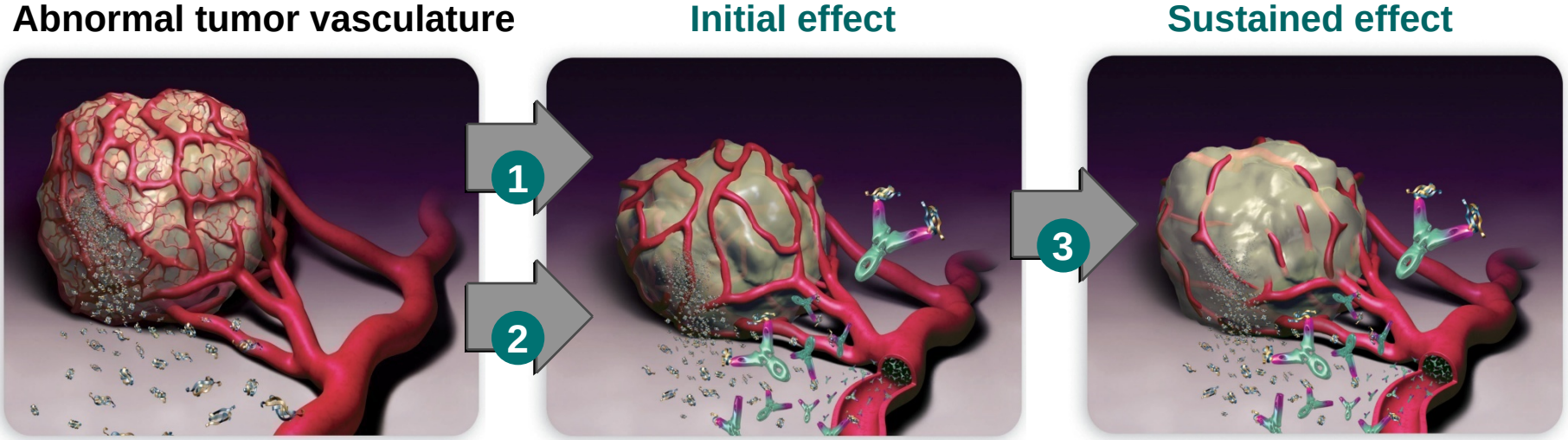
IL-8 = interleukin-8
COX-2 = cyclooxygenase
NO = nitric oxide

Angiogenesis and Progression of Cancer



Poon RT-P, et al. J Clin Oncol 2001;19:1207–25

Mode of Action and the Relation with Treatment Effects



- **Starvation**
- **Enhancement of combination therapy**

1 Regression of existing microvasculature
Additive effect for tumor shrinkage
(direct effect of Avastin®)

3 Inhibition of newly formed vessels
Prolonged overall survival and progression-free survival
(direct effect of Avastin®)

2 Normalization of existing vasculature
Maximizes effect of anticancer drugs used with Avastin®
(Enhancing effect of the combination therapy)

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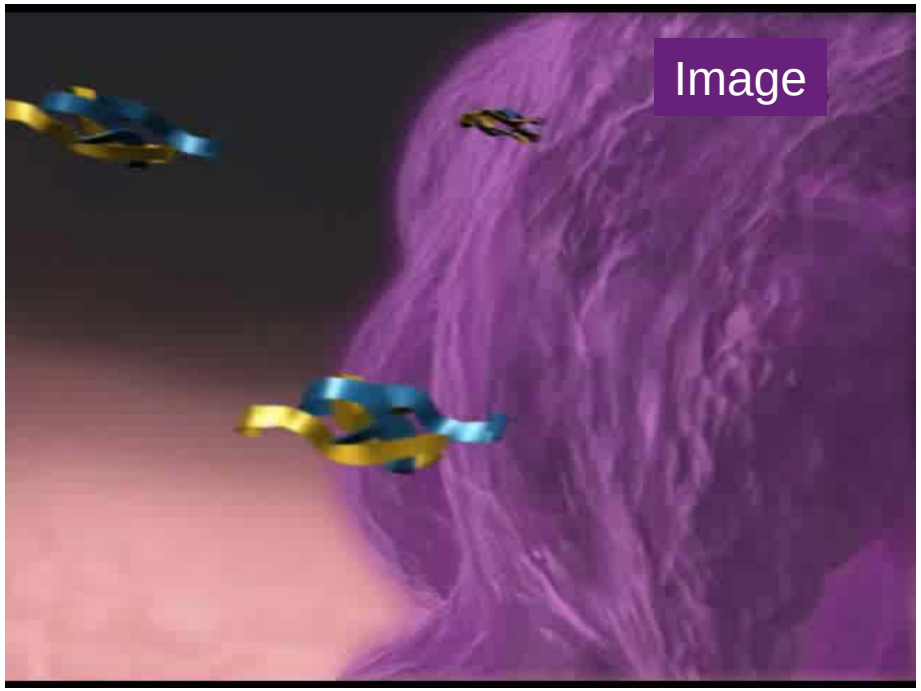
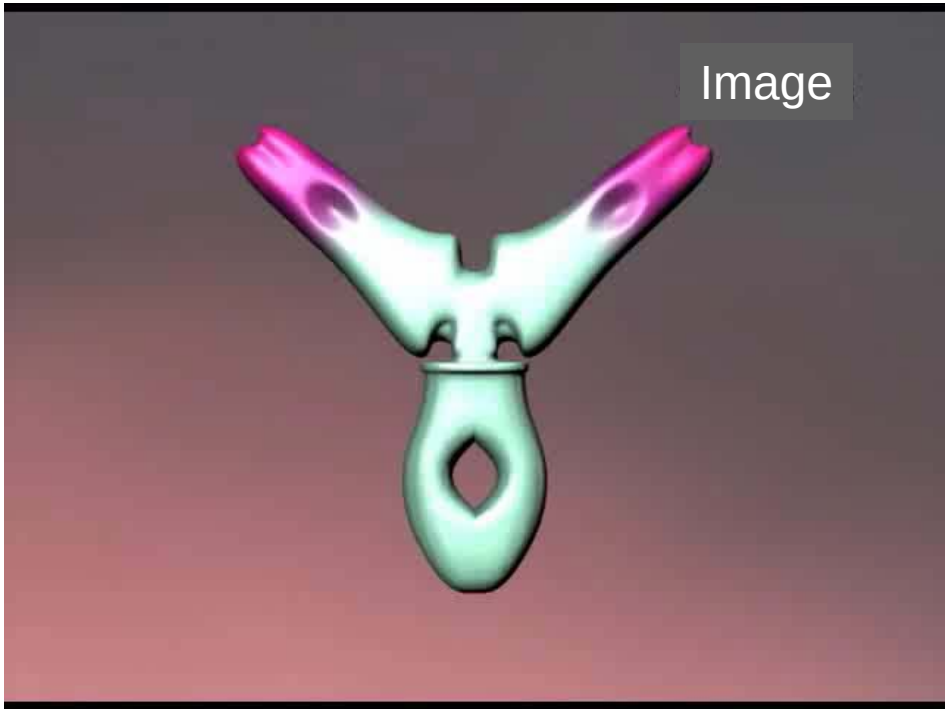
Mode of Action



Tumor environment and VEGFR

Mode of action of Avastin®



Overview (2)

Effect/Efficacy

- Advanced or refractory colorectal cancer who is not the candidate for the curative operation

Dosage and administration

- The usual adult dosage of bevacizumab is 5 mg/kg or 10 mg/kg bodyweight per intravenous infusion in combination with other anticancer chemotherapy. The administration interval should be two weeks or longer.

Approval conditions

- Because of a very limited number of patients treated in the internal clinical trials, a post-marketing surveillance of all patients who received Avastin® after the launch of it should be conducted until the data of a certain number of patients are accumulated in order to identify the background of the patients and collect the safety and efficacy data of them early, and take necessary measures for proper use of Avastin®.

Safety Measures Implemented After Launch

1. Measures to promote proper use of Avastin®
   - Prior confirmation from relevant medical institutions and physicians
   - Confirmation upon first delivery of product
   - Prior enrollment and caution exercised to patients scheduled to receive Avastin®
   - Post-marketing surveillance (centralized monitoring of adverse drug reactions for all patients enrolled)
2. Conduct post-marketing surveillance study of all patients
   - Target number of cases: 2,500
   - Survey period: 18 months after launch (tentative)
3. Develop materials for physicians, pharmacists, nurses and patients to promote proper use
4. Establish the external peer review committee

Post Marketing Surveillance Study

Type of survey

- Post marketing surveillance study

Subjects:

- All colorectal cancer patients treated with Avastin®

Survey objectives:

(1) Confirm whether the incidence of adverse drug reactions typically associated with Avastin® such as gastrointestinal perforations and tumor-related hemorrhage are similar to those found in overseas clinical trials, and also investigate risk factors

(2) Investigate all adverse drug reactions for patients given dosages of 5mg/kg/2 weeks and 10mg/kg/2 weeks

Target number of cases:

- 2,500

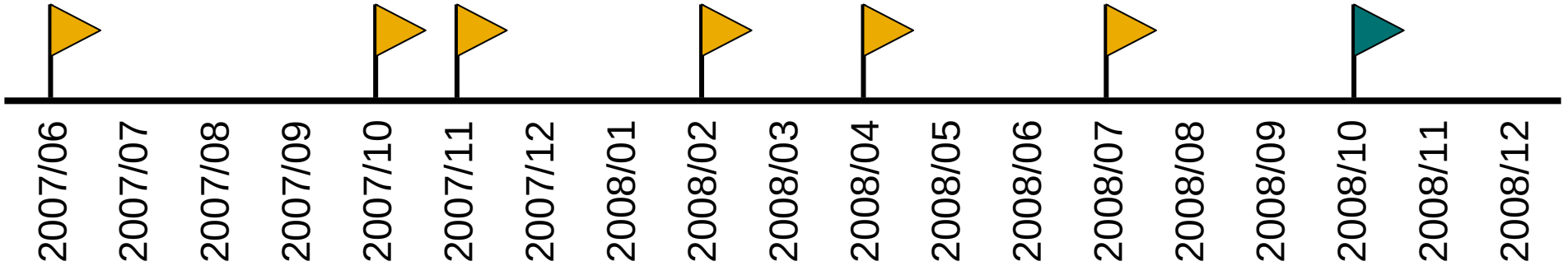
Length of survey:

- 18 months

Timeline of Events Since Launch

- 2,500 patients enrolled for PMS survey
- Start of enrollment for FOLFIRI+ BV clinical trial (after launch)
- Release the interim results of PMS survey (1,018 cases)

- Launch
- Start of PMS study of all patients
- Start of confirmation of eligibility (enrollment) with contact slips to be used
- Publication of safety confirmation study results (JO18158) at JSMO
- Revision of prescription information
- Final results of PMS Study (2,705 cases) to be presented at JSCO



JSMO: Japanese Society of Medical Oncology
JSCO: Japan Society of Clinical Oncology
BV: Bevacizumab

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Enrollment and Collection of ADR Reports

Number of patients treated with Avastin® (estimated)

- Number of patients treated since launch : 11,783
  - PMS survey
    - Cases enrolled 2,712* (June 11, 2007 to November 9, 2007)
  - Cases due to be treated with Avastin® (using contact slips)
    - Cases enrolled 9,071* (as of August 21, 2008)

ADR reports collected in PMS survey interim results

- Number of patients in interim report : 1,018
  - 626 patients experienced ADR (rate of incidence: 61.49%) ; total of 2,271 ADR reports
    - Severe ADR: 178 patients (incidence rate: 17.49%); total of 303 reports
    - Major ADR (SOC)
      - Abnormal clinical test values (decrease in leukocyte, neutrophil and platelet counts, etc.), gastrointestinal disorders (nausea, diarrhea, stomatitis, etc.), cardiovascular disorders (hypertension, etc.)

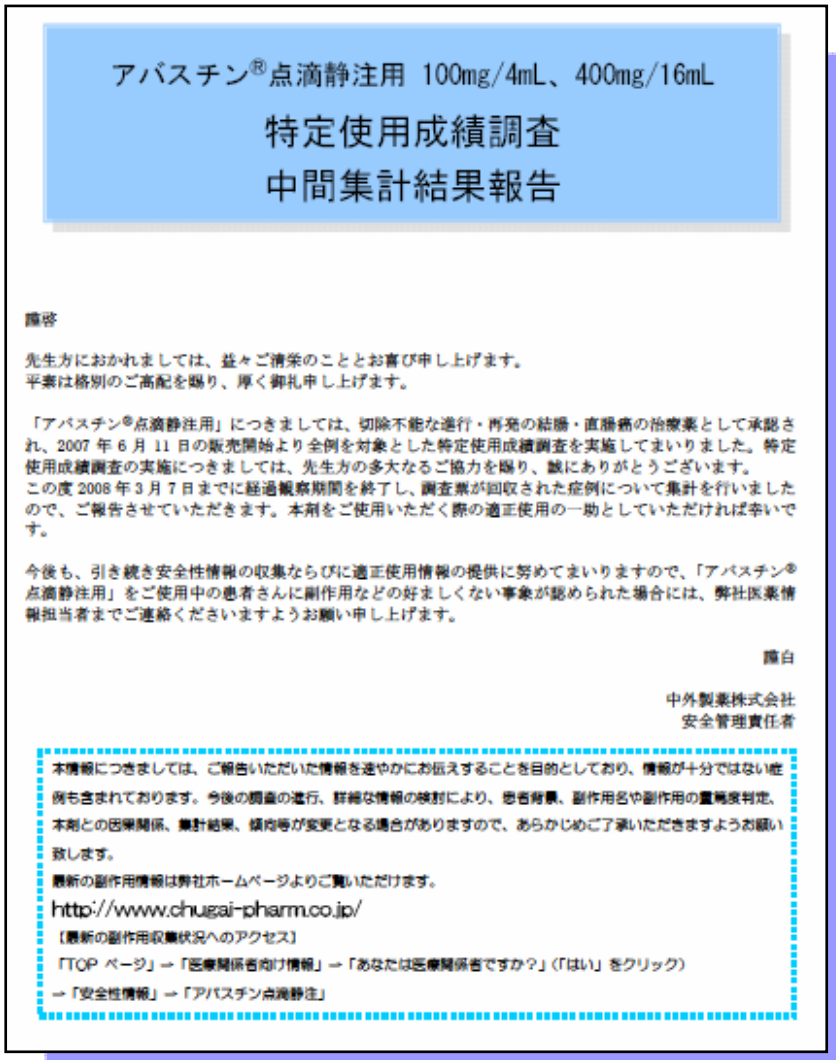
* Chugai Pharmaceutical website (updated on August 26, 2008) http://www.chugai-pharm.co.jp/

Assessment of Proper Use in Japan

- PMS study—total number of patients: 1,018
  - Rate of proper use: 97.15%

		Rate of proper use (%)	Cases other than proper use
Back-ground	Indications	100.0%	Patients with conditions other than colorectal cancer: 0
	Warning	99.9%	Patients with cerebral metastasis: 1 (continued from private import)
	Treatment line	97.8%	Third-line therapy: 22
	Complications that could be a risk factor for ADR of Avastin®	99.9%	Aftereffect of stroke: 1
	Performance status (P.S.)	100.0%	P.S. of 3 or greater: 0
Previous treatment	Major operation	99.6%	Operation within 28 days of beginning administration: 4
Therapy	Combination chemotherapy	99.8%	5-FU single agent therapy (due to allergic reaction to *I-LV*) Combination therapy with 5-FU and CPT-11: 1

PMS Study Interim Results



アバスチン®点滴静注用 100mg/4mL、400mg/16mL

特定使用成績調査

中間集計結果報告

謹啓

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「アバスチン®点滴静注用」につきましては、切除不能な進行・再発の結腸・直腸癌の治療薬として承認され、2007 年 6 月 11 日の販売開始より全例を対象とした特定使用成績調査を実施してまいりました。特定使用成績調査の実施につきましては、先生方の多大なるご協力を賜り、誠にありがとうございます。
この度 2008 年 3 月 7 日までに経過観察期間を終了し、調査票が回収された症例について集計を行いましたので、ご報告させていただきます。本剤をご使用いただく際の適正使用の一助としていただければ幸いです。

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最新の副作用情報は弊社ホームページよりご覧いただけます。
http://www.chugai-pharm.co.jp/
【最新の副作用収集状況へのアクセス】
「TOP ページ」→「医療関係者向け情報」→「あなたは医療関係者ですか？」(「はい」をクリック)
→「安全性情報」→「アバスチン点滴静注」

- This report can be downloaded in PDF format from the Chugai Pharmaceutical website (information released on August 6, 2008).
  - http://www.chugai-pharm.co.jp/ (Japanese Only)

- The final results of the PMS study (2,705 patients) are scheduled to be presented at the Japan Society of Clinical Oncology (JSCO) annual meeting this year.
  - **October 31, 2008**
    - **Symposium 6**
    - **"At the Front Line of Molecular Targeted Therapy (2) Clinical Research"**

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