

## **Avastin** **Establishing new standards of care**

*Stefan Frings, dLCL Avastin*



**Genentech**

## **Avastin - An unprecedented potential**

- **Proven survival benefit in multiple tumor types**
- **Strongest launch of any oncology product**
  - Global sales of CHF 1.7bn in 2005 after less than 2 years on the market
- **Extensive development program unique in breadth and scope**
  - Ongoing projects in 8 tumor types, in different settings
  - > 25,000 patients (excluding collaborative trials) to be recruited over next years globally

**Avastin-based regimens on track to become  
backbone therapies in oncology**



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## Avastin today

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## Avastin tomorrow

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## Avastin today

*Over 92,000 patients treated and 3 major filings*

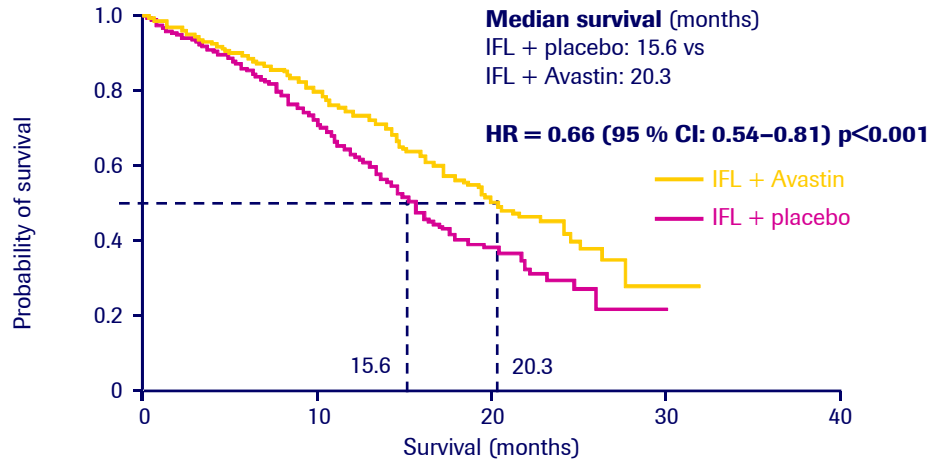
- **Indicated in metastatic colorectal cancer (CRC)**
  - 1<sup>st</sup> line treatment in combination with IV 5-FU/FA or IV 5-FU/FA/irinotecan (EU)
  - Filing to include oxaliplatin and Xeloda combinations on course for H2 '06
- **Filings in non small cell lung cancer (NSCLC) and breast cancer (BC)**
  - Advanced/metastatic NSCLC
    - US: 11 April 06
    - EU: H2 '06
  - Advanced/metastatic BC
    - US: 25 May 06
    - EU: H2 '06

FA = folinic acid

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### 1<sup>st</sup> line mCRC: Largest improvement in overall survival in phase III when adding a targeted agent to chemotherapy (+ 4.7 months)

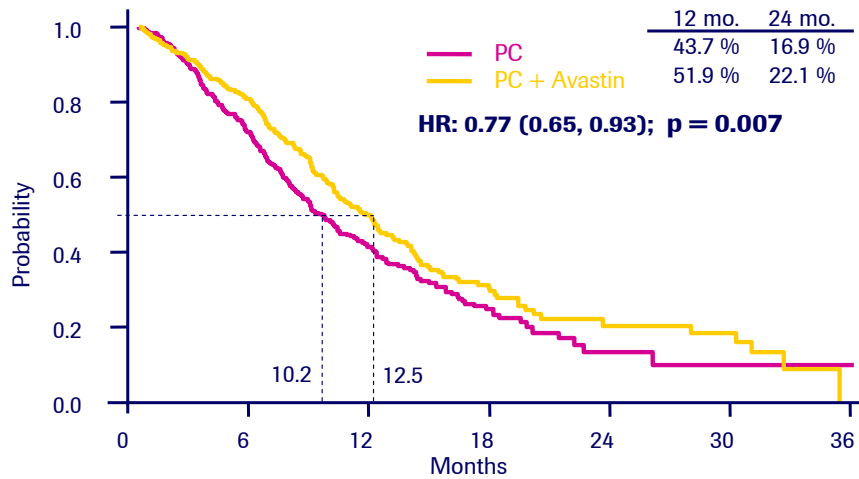


CI = confidence interval; IFL = irinotecan, bolus 5-FU/FA  
Hurwitz H, et al. N Engl J Med 2004;350:2335-42

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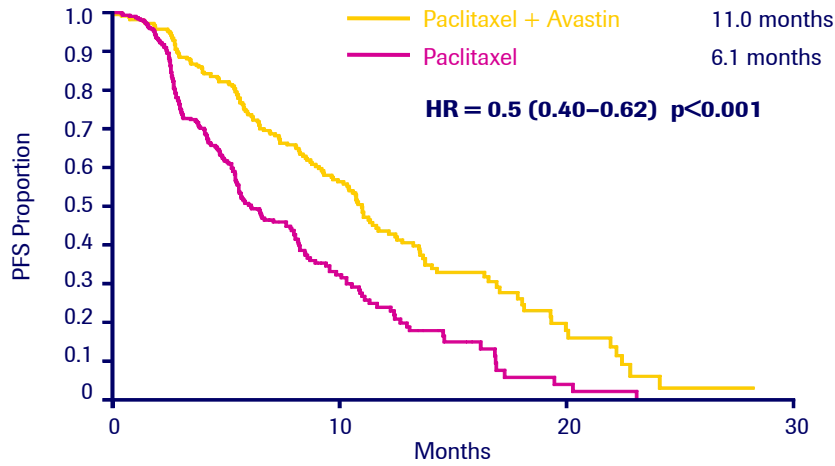
### 1<sup>st</sup> line NSCLC: First medicine in a decade to show an overall survival benefit (30 %)



Sandler AL, et al. J Clin Oncol 2005;23 (June 1 Suppl): Abstract LBA4 (E4599) \*PC= paclitaxel/carboplatin

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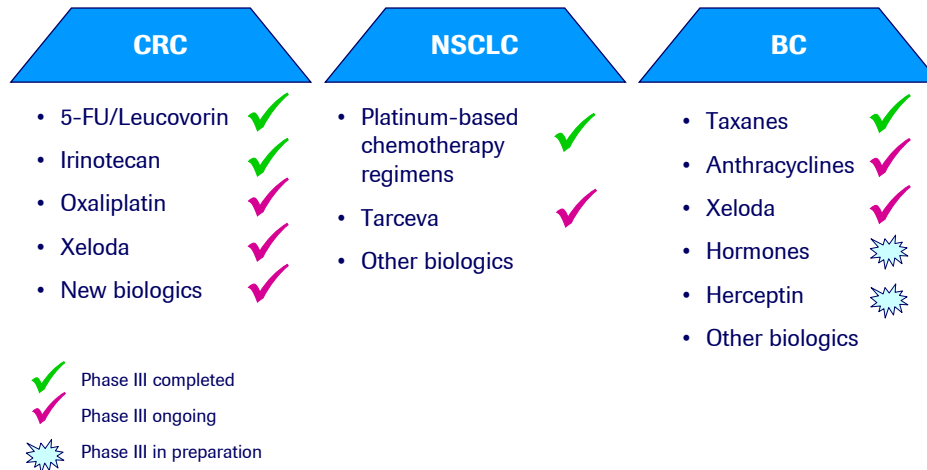
## 1<sup>st</sup> line mBC: First medicine to double PFS in HER2-negative BC



K. Miller, San Antonio Breast Cancer conference 2005

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## A combination partner to current standards



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## A well established safety profile

- Around 75,000 patients treated with marketed drug and 17,000 in clinical trials
- **Large safety data base** from randomized clinical trials in combination with multiple chemotherapy agents, different tumor types, and different settings
- In general,
  - Avastin **does not add to chemotherapy related toxicities**
  - Most **common side effects** (hypertension and nose bleeds) are **well manageable**

### Grade 3-5 toxicities associated with Avastin

### Frequency

Grade 3-5 toxicities associated with Avastin	Frequency
Gastrointestinal perforation	1-2 %
Arterial thromboembolic events	2-5 %
Bleeding in CRC/ BC	3.1/ 1.4 %
Pulmonary hemorrhage in NSCLC	2.3 %

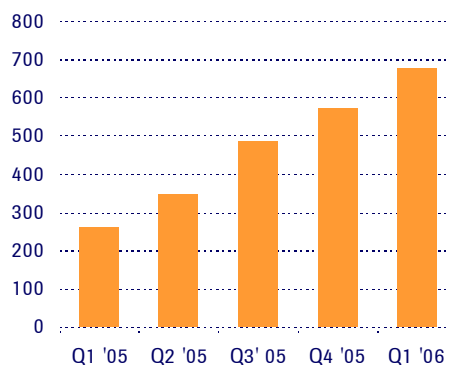
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## Strongest launch of an oncology product

*Roll-out completed in all major markets*

### Quarterly Group sales (CHF m)



- Fast market penetration in the US
- 82 countries approved ex-US
- Reimbursement in all major markets
  - earlier than anticipated in some
- NICE: discussions continue
- US, Germany, France currently biggest sales contributors
- Sales force in place to cover key indications

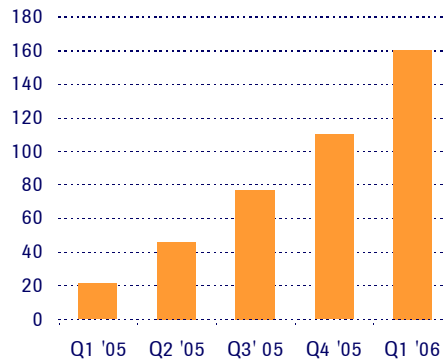
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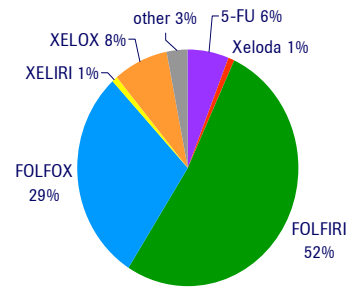
## Combination regimens with Avastin in mCRC

*Dominated by FOLFIRI; oxaliplatin use already substantial*

Quarterly Roche sales (CHF m)



EU major markets



Based on early market research interviews with 216 physicians

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**Avastin today**

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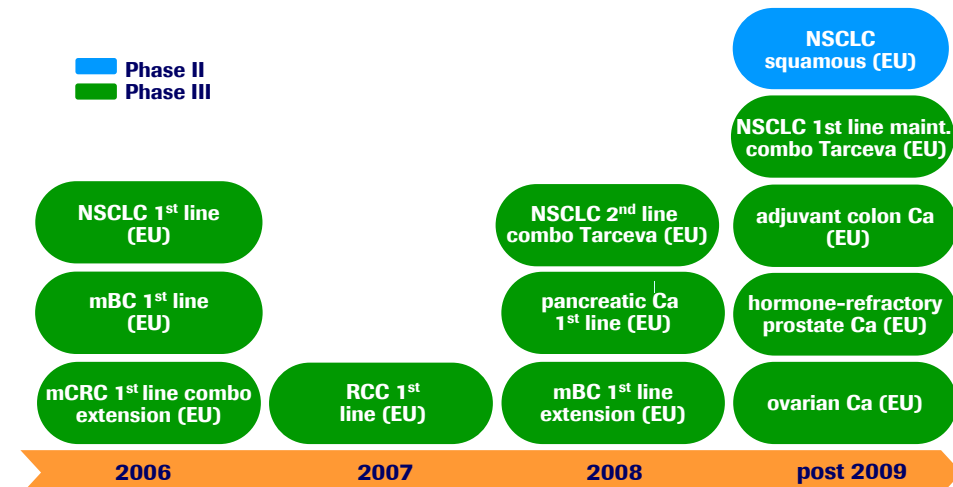
**Avastin tomorrow**

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## Avastin tomorrow

*Numerous submissions in the next few years*

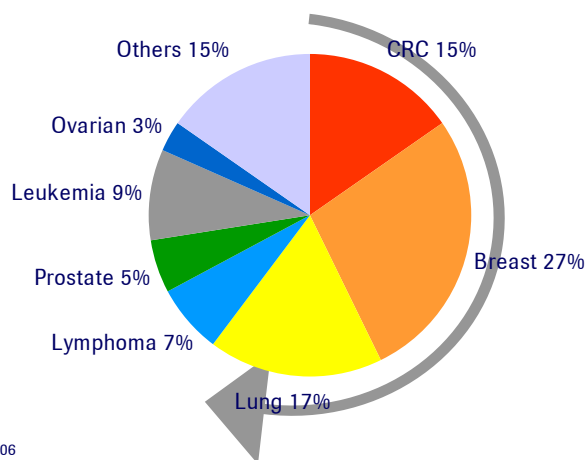


Status as of March 31, 2006

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## In oncology, sales in BC, CRC and NSCLC are estimated to have a market share of 60 % in 2015

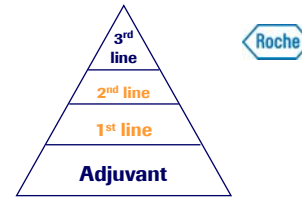
Est. market sales split by indication in 2015



Wood Mackenzie, Jan 2006  
includes cytotoxic, hormonal and biologics & novel agents

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**Focus on 3 major tumor types**  
*A closer look at Colorectal Cancer*



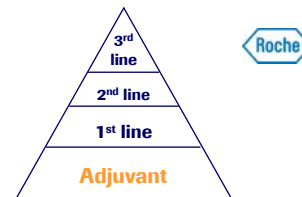
Trial	N	Treatment	Status
<b>NO16966C</b> (1 <sup>st</sup> line)	1,920	FOLFOX ± Avastin vs. XELOX ± Avastin	Recruitment completed, final data in H2 '06
<b>E3200</b> (pretreated)	829	FOLFOX ± Avastin vs. Avastin	Phase III completed – superior PFS and OS for FOLFOX plus Avastin

**Trials with oxaliplatin and Xeloda to expand usage in 1<sup>st</sup> line in EU**  
**Filing (NO16966C + E3200 ) H2 '06**

FOLFOX = infused 5-FU/LV + oxaliplatin, XELOX = Xeloda + oxaliplatin, bFOL = bolus 5-FU + oxaliplatin

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**Focus on 3 major tumor types**  
*A closer look at Colon Cancer*



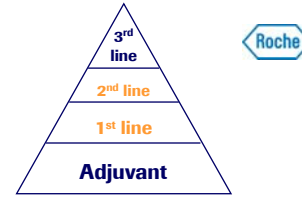
Trial	n	Treatment	Status
<b>AVANT</b>	3,450	FOLFOX-4 ± Avastin vs. XELOX + Avastin	Started Q4 '04, already more than 2,200 patients randomized
<b>NSABP C-08</b>	2,714	FOLFOX-6 ± Avastin	Started Q3 '04, recruitment on track

**EU filing post 2009**

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## Focus on 3 major tumor types

### A closer look at Breast Cancer (1)



#### HER-2 negative

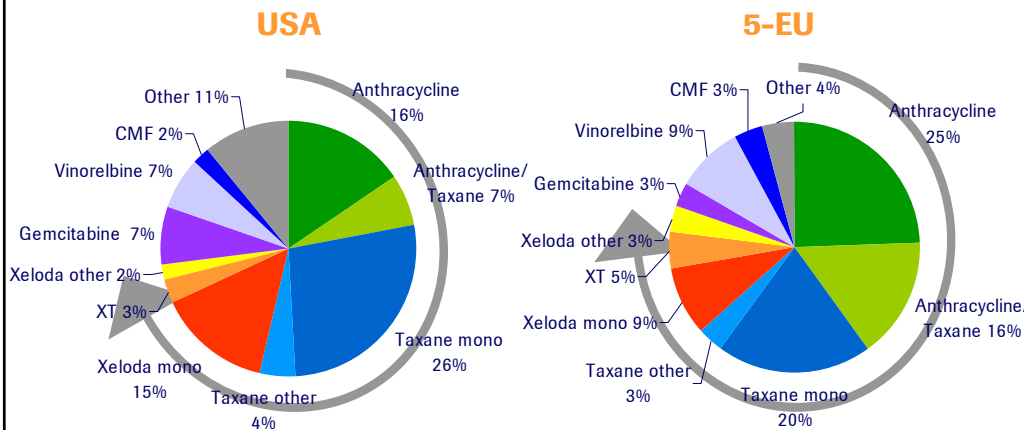
Trial	n	Treatment	Status
<b>E2100</b> (1 <sup>st</sup> line)	722	Paclitaxel ± Avastin	Phase III completed – superior PFS and improved OS with addition of Avastin
<b>AVADO</b> (1 <sup>st</sup> line)	705	Docetaxel ± Avastin	Ex-US, initiated Q1 '06
<b>RIBBON-1</b> (1 <sup>st</sup> line)	900	Standard CT (taxanes or anthracycline combinations or Xeloda) ± Avastin	Global, initiated Q4 '05
<b>RIBBON-2</b> (2 <sup>nd</sup> line)	630	Xeloda or vinorelbine or gemcitabine ± Avastin	US, initiated Q1 '06

**E2100 data filed in US, filing in EU H2 '06**

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## Metastatic breast cancer (HER2-negative)

### Highly segmented market

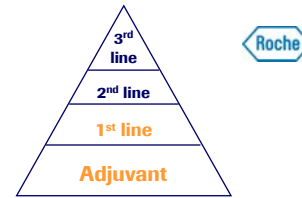


USA Tandem Breast Cancer Supplemental Study MAT Q3 2005  
Genactis MBC study, 5-EU Q4 2005

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## Focus on 3 major tumor types

### *A closer look at Breast Cancer (2)*

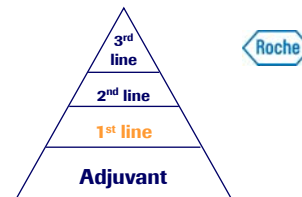


- **1<sup>st</sup> line HER2-positive**
  - Two phase III trials in preparation of Avastin in combination with Herceptin
    - Ex-US: docetaxel + Herceptin ± Avastin
    - US: Planned weekly paclitaxel + carboplatin + Herceptin ± Avastin
- **Adjuvant HER2-negative setting**
  - Pilot recruiting in US E2104: AC + Avastin followed by paclitaxel + Avastin vs. AC followed by paclitaxel + Avastin
  - Phase III trials planned in US and ex-US
- **Adjuvant HER2-positive setting**
  - Under discussion

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## Focus on 3 major tumor types

### *A closer look at NSCLC (1)*



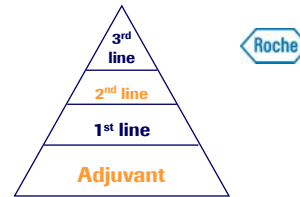
- **1<sup>st</sup> line**
  - Phase III trial E4599: carboplatin/ paclitaxel ± Avastin
    - Results available (PFS and OS superior with the addition of Avastin)
  - Phase III AVAiL: cisplatin/ gemcitabine (CG) vs. CG + Avastin 7.5 mg/kg q3 weeks vs. CG + Avastin 15 mg/kg q3 weeks
    - Trial ongoing
    - Interim data to be submitted H2 '06 for filing purposes only with final E4599 data
  - Phase III chemotherapy + Avastin for 4 cycles followed by Avastin ± Tarceva (maintenance) ATLAS - recruiting in US
  - Predominant squamous cell histology: Safety trials exploring Avastin + chemotherapy ongoing/ about to start
  - Treated brain metastases: Safety trial exploring Avastin + chemotx ongoing in US

**Filed in US, first filing in EU H2 '06**

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## Focus on 3 major tumor types

### *A closer look at NSCLC (2)*



- **Adjuvant setting**

- Phase III trial allowing different chemotherapies for 4 cycles  $\pm$  Avastin (for up to one year)
  - Global trial led by ECOG with ex US participation coordinated by EORTC
  - 'First-patient-in' planned in H2 '06

- **2<sup>nd</sup> line**

- Randomized phase II trial Avastin + Tarceva vs. Avastin + chemotherapy (permetrexed or docetaxel) vs. chemotherapy alone
  - Data presented at ASCO '06
- Phase III Tarceva  $\pm$  Avastin **BETA Lung**: ongoing

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## Development trials in other indications



- **1<sup>st</sup> line renal cell cancer**: two phase III trials using interferon as backbone  $\pm$  Avastin
  - Recruitment completed
- **1<sup>st</sup> line pancreatic cancer**: two phase III trials using either gemcitabine or gemcitabine + Tarceva as backbone  $\pm$  Avastin
  - US enrollment completed Q2 '06/ EU recruitment on track
- **1<sup>st</sup> line ovarian cancer**: two phase III trials using carboplatin/paclitaxel as backbone  $\pm$  Avastin
  - US trial ongoing/ ex-US trial expected to start H2 '06
- **Hormone-refractory prostate cancer**: one phase III trial ongoing using docetaxel + prednisone  $\pm$  Avastin
  - Recruitment on track
- **Further indications** are planned

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## Competitive landscape

*... Avastin is leading the pack*

- **Avastin will be 1<sup>st</sup> to market in at least three major indications by several years**
  - Establish new standard of care
  - Raise hurdles for competition
  - Likely used in combination rather than replaced
- **Multiple anti-angiogenic agents currently under development**
  - In CRC, BC and NSCLC only limited data of competitor molecules available
  - Limited data in combination with cytotoxics
  - Renal Cell cancer becoming crowded
- **Up-coming targeted agents using other modes of actions provide combination opportunities for Avastin**

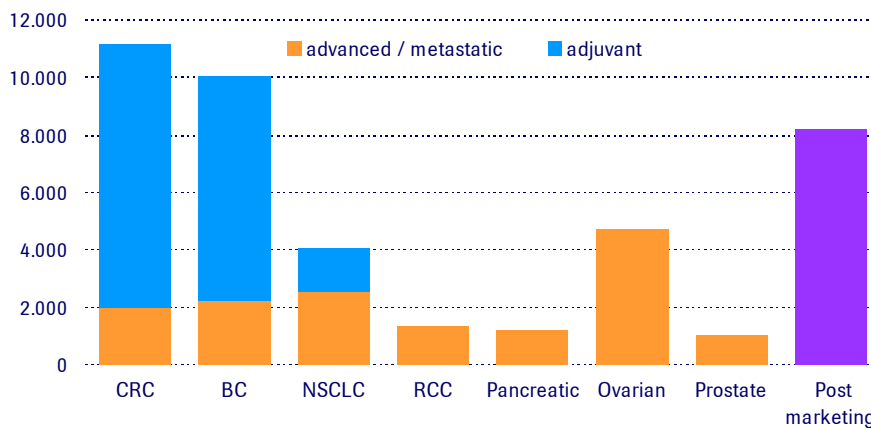
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## Global development program for Avastin

*Targeting 40,000 patients in over 3,000 sites*

### Total number of patients to be enrolled



Targeted patient and sites numbers in major ongoing and prepared phase III trials and post-marketing initiatives

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## **Avastin product strategy**

### *In summary*

- **Where to go**
  - Establish Avastin as fifth treatment modality in oncology and thus as backbone therapy for all major malignancies
- **How to get there**
  - Unprecedented clinical benefit
  - Broad clinical development program
  - Huge commitment
- **What are the challenges**
  - Manage a “portfolio in a portfolio”
  - Continuously remain ahead of competition

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## **Appendix**



## Product profile

### *Avastin*

<b>Indication</b>	Metastatic colorectal cancer
<b>Exclusion criteria</b>	Patients with: a history of arterial thromboembolic events, symptomatic CNS metastasis
<b>Dosing</b>	5mg/kg once every two weeks until progression
<b>Adverse reactions</b>	Hypertension, proteinuria, arterial thromboembolic events, GI perforations, Bleeding, Pulmonary hemorrhage
<b>Incidence mCRC</b>	~29,000 (US), ~95,000 (5-EU);
<b>Current sales</b>	CHF 1,665 m
<b>Further development</b>	Combination with Xeloda, oxaliplatin, mBC, NSCLC, RCC, pancreatic Ca, ovarian Ca; adjuvant use in CC, BC, NSCLC



## Approval status

### *Avastin in colorectal cancer*

#### EU

Avastin in combination with intravenous 5-fluorouracil/folinic acid or intravenous 5-fluorouracil/folinic acid/irinotecan is indicated for 1<sup>st</sup> line treatment of patients with metastatic carcinoma of the colon or rectum

#### US

Avastin, used in combination with intravenous 5-fluorouracil-based chemotherapy, is indicated for 1<sup>st</sup> line treatment of patients with metastatic carcinoma of the colon or rectum